Supporting Information

Identification of small molecule positive modulators of calcitonin-like receptor-based receptors

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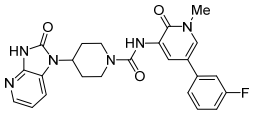
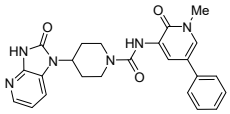
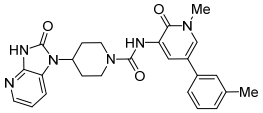
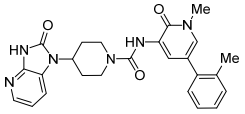
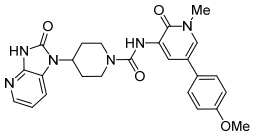
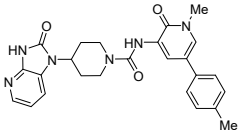
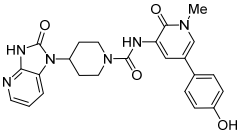
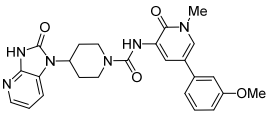
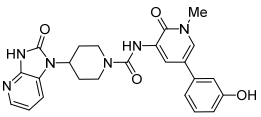
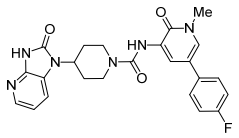
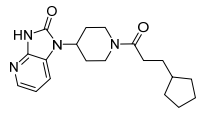
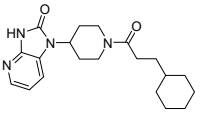
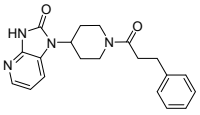
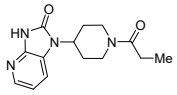
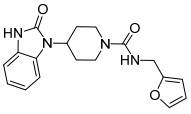
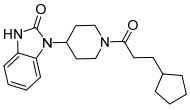
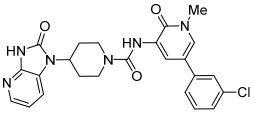
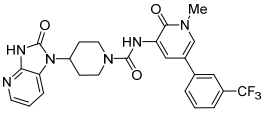
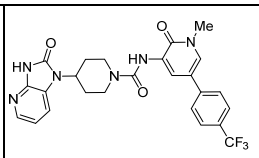
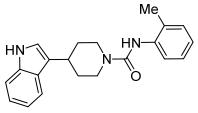
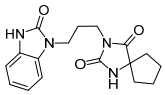
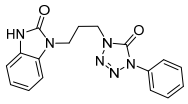
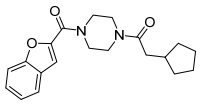
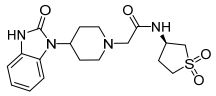
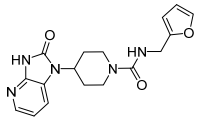
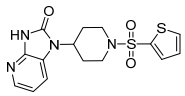
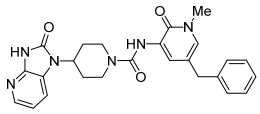
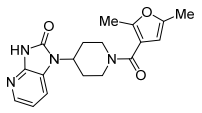
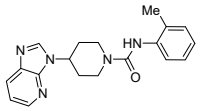
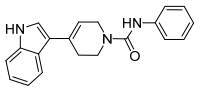
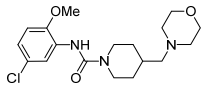
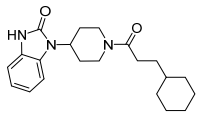
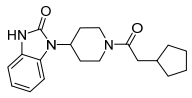
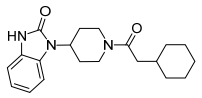
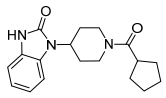
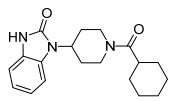
Table S1

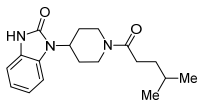
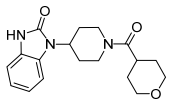
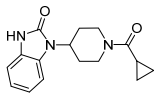
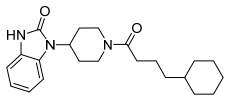
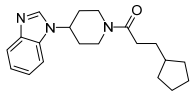
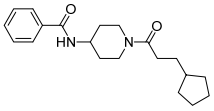
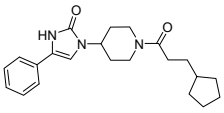
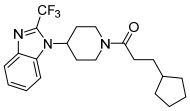
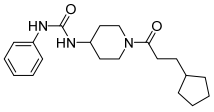
Compounds with aryl, heteroaryl, fused aryl, benzyl, benzyl ether and benzyl amine substituents on a pyridine or phenyl core (Compounds **S1**–**S118**).

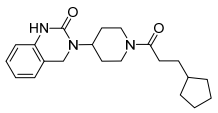
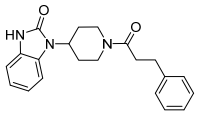
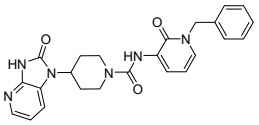
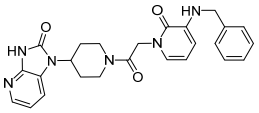
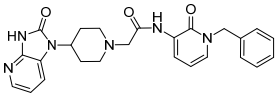
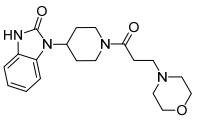
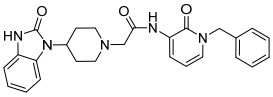
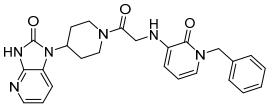
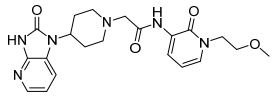
Compound number	SN	Structure	SMILES	HPLC Purity %
S1	34328		O=C1N(C2CCN(C(NC3=CC(C4=CC(F)=CC=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	99.3
S2	34395		O=C1N(C2CCN(C(NC3=CC(C4=CC=CC=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	99.5%
S3	34397		O=C1N(C2CCN(C(NC3=CC(C4=CC(C)=CC=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	99.4
S4	34422		O=C1N(C2CCN(C(NC3=CC(C4=C(C)C=CC=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	99.5
S5	34427		O=C1N(C2CCN(C(NC3=CC(C4=CC=C(OC)C=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	99.7
S6	34428		O=C1N(C2CCN(C(NC3=CC(C4=CC=C(C)C=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	99.2
S7	34434		O=C1N(C2CCN(C(NC3=CC(C4=CC=C(O)C=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	85.6
S8	34439		O=C1N(C2CCN(C(NC3=CC(C4=CC(OC)=CC=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	98.5
S9	34440		O=C1N(C2CCN(C(NC3=CC(C4=CC(OC)=CC=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	77.7

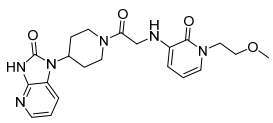
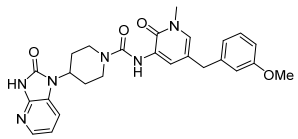
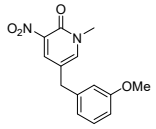
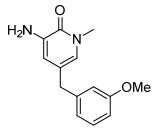
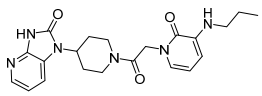
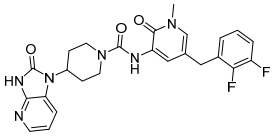
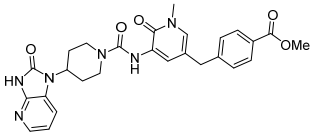
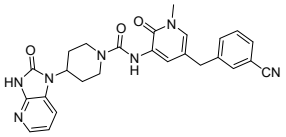
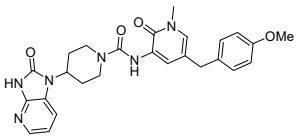
S10	34442		O=C1N(C2CCN(C(NC3=CC(C4=CC=C(F)C=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	99.4
S11	34491		O=C1NC2=NC=CC=C2N1C3CCN(C(CCC4CCCC4)=O)CC3	99.9
S12	34496		O=C1NC2=NC=CC=C2N1C3CCN(C(CCC4CCCCC4)=O)CC3	99.9
S13	34498		O=C1NC2=NC=CC=C2N1C3CCN(C(CCC4=CC=CC=C4)=O)CC3	99.5
S14	34499		O=C1NC2=NC=CC=C2N1C3CCN(C(CC)=O)CC3	88.8
S15	34807		O=C1N(C2CCN(C(NCC3=CC=CO3)=O)CC2)C4=CC=CC=C4N1	*
S16	34816		O=C(CCC1CCCC1)N(CC2)CCC2N3C4=CC=CC=C4NC3=O	100
S17	34817		O=C1N(C2CCN(C(NC3=CC(C4=CC(Cl)=CC=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	96.5
S18	34848		O=C1N(C2CCN(C(NC3=CC(C4=CC(C(F)(F)F)=CC=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	99.1

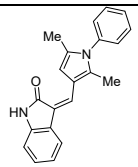
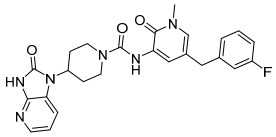
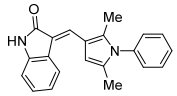
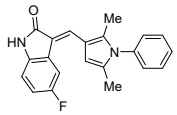
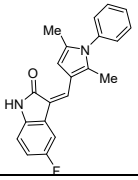
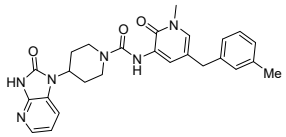
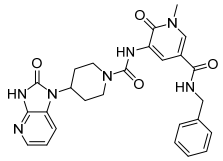
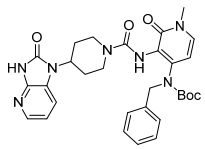
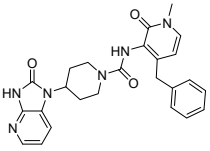
S19	34849		O=C1N(C2CCN(C(NC3=CC(C4=CC=C(C(F)(F)F)C=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	99.1
S20	34857		O=C(N(CC1)CCC1C2=CNC3=CC=CC=C32)NC4=CC=CC=C4C	*
S21	34860		O=C1N(CCCN2C(NC3(CCCC3)C2=O)=O)C4=CC=CC=C4N1	*
S22	34927		O=C1N(CCCN2N=NN(C3=CC=CC=C3)C2=O)C4=CC=CC=C4N1	*
S23	34929		O=C(N1CCN(C(CC2CCCC2)=O)CC1)C3=CC4=CC=CC=C4O3	*
S24	34931		O=C1N(C2CCN(CC(N[C@@H]3CCS(C3)(=O)=O)=O)CC2)C4=CC=CC=C4N1	*
S25	34964		O=C1N(C2CCN(C(NCC3=CC=CO3)=O)CC2)C4=CC=CN=C4N1	ND
S26	34983		O=C1N(C2CCN(S(=O)(C3=CC=CS3)=O)CC2)C4=CC=CN=C4N1	ND
S27	34988		O=C1N(C2CCN(C(NC3=CC(CC4=CC=CC=C4)=CN(C)C3=O)=O)CC2)C5=CC=CN=C5N1	99.6

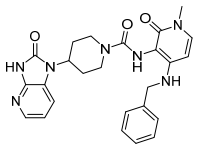
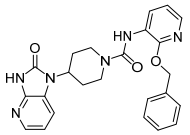
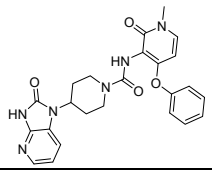
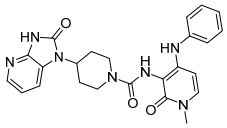
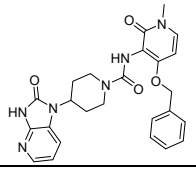
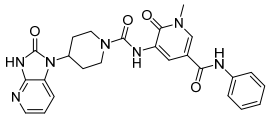
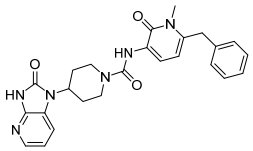
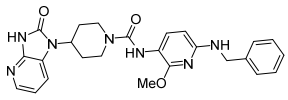
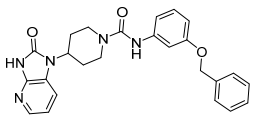
S28	34989		O=C1N(C2CCN(C(C3=C(C)OC(C)=C3)=O)CC2)C4=CC=CN=C4N1	99.2
S29	35136		O=C(NC1=CC=CC=C1C)N2CCC(CC2)N3C=NC4=CC=CN=C34	*
S30	35138		O=C(NC1=CC=CC=C1)N2CCC(C3=CNC4=CC=CC=C34)=CC2	*
S31	35139		ClC1=CC=C(OC)C(NC(N2CCC(CN3CCOCC3)CC2)=O)=C1	*
S32	35145		O=C1NC2=CC=CC=C2N1C3CCN(C(CCC4CCCCC4)=O)CC3	89.3
S33	35147		O=C1NC2=CC=CC=C2N1C3CCN(C(CC4CCCC4)=O)CC3	100
S34	35148		O=C1NC2=CC=CC=C2N1C3CCN(C(CC4CCCCC4)=O)CC3	100
S35	35149		O=C1NC2=CC=CC=C2N1C3CCN(C(C4CCCC4)=O)CC3	99.9
S36	35150		O=C1NC2=CC=CC=C2N1C3CCN(C(C4CCCCC4)=O)CC3	99.9

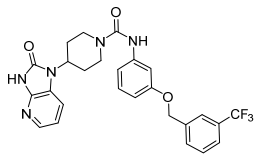
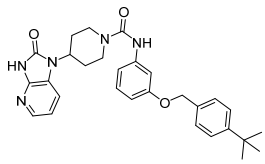
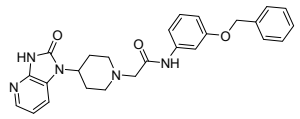
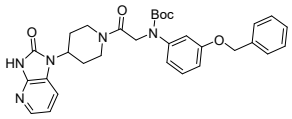
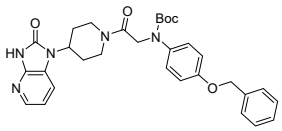
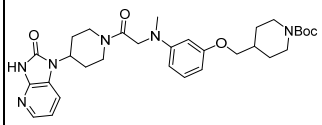
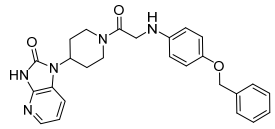
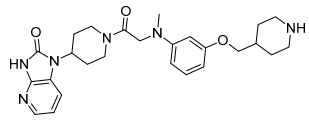
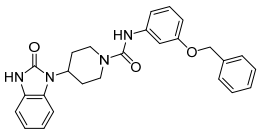
S37	35155		O=C1NC2=CC=CC=C2N1C3CCN(C(CCC(C)C)=O)CC3	99.8
S38	35156		O=C1NC2=CC=CC=C2N1C3CCN(C(C4CCOCC4)=O)CC3	98
S39	35157		O=C1NC2=CC=CC=C2N1C3CCN(C(C4CC4)=O)CC3	99.7
S40	35160		O=C1NC2=CC=CC=C2N1C3CCN(C(CCCC4CCCCC4)=O)CC3	99.9
S41	35174		O=C(CCC1CCCC1)N(CC2)CCC2N3C=NC4=CC=CC=C43	100
S42	35175		O=C(CCC1CCCC1)N(CC2)CCC2NC(C3=CC=CC=C3)=O	100
S43	35177		O=C1NC(C2=CC=CC=C2)=CN1C3CCN(C(CCC4CCCC4)=O)CC3	99.3
S44	35179		O=C(CCC1CCCC1)N(CC2)CCC2N3C(C(F)(F)F)=NC4=CC=CC=C43	100
S45	35190		O=C(CCC1CCCC1)N(CC2)CCC2NC(NC3=CC=CC=C3)=O	100

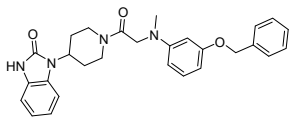
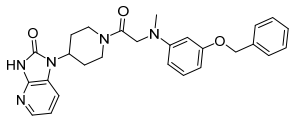
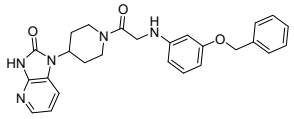
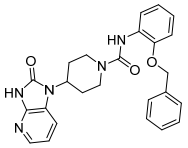
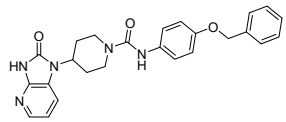
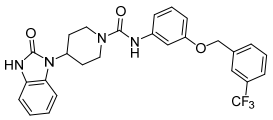
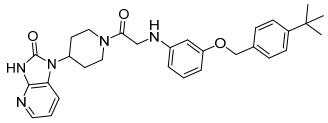
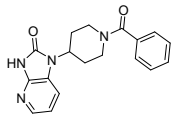
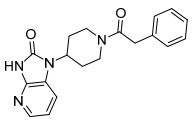
S46	35199		O=C(CCC1CCCC1)N(CC2)CCC2N3C(NC(C=CC=C4)=C4C3)=O	98.4
S47	35326		O=C1NC2=CC=CC=C2N1C3CCN(C(CCC4=CC=CC=C4)=O)CC3	100
S48	35352		O=C1N(C2CCN(C(NC3=CC=CN(CC4=CC=CC=C4)C3=O)=O)CC2)C5=CC=CN=C5N1	97.6
S49	35356		O=C1N(C2CCN(C(CN3C=CC=C(NCC4=CC=CC=C4)C3=O)=O)CC2)C5=CC=CN=C5N1	98.9
S50	35357		O=C1N(C2CCN(CC(NC3=CC=CN(CC4=CC=CC=C4)C3=O)=O)CC2)C5=CC=CN=C5N1	ND
S51	35362		O=C1NC2=CC=CC=C2N1C3CCN(C(CCN4CCOCC4)=O)CC3	90.3
S52	35385		O=C1N(C2CCN(CC(NC3=CC=CN(CC4=CC=CC=C4)C3=O)=O)CC2)C5=CC=CC=C5N1	ND
S53	35702		O=C1N(CC2=CC=CC=C2)C=CC=C1NCC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	94.0
S54	35737		O=C1NC2=NC=CC=C2N1C3CCN(CC(NC4=CC=CN(CCOC)C4=O)=O)CC3	99.0

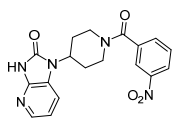
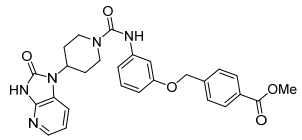
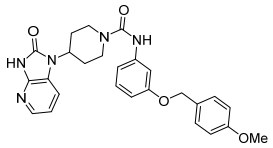
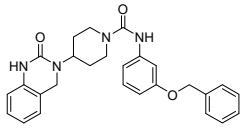
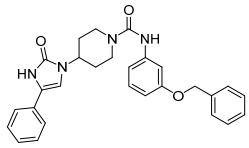
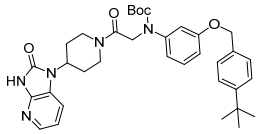
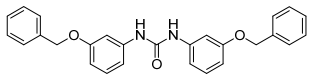
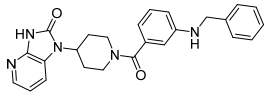
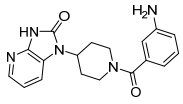
S55	35765		O=C(N(CC1)CCC1N2C3=CC=CN=C3NC2=O)CNC4=CC=CN(CCOC)C4=O	96.6
S56	35766		O=C1N(C)C=C(CC2=CC=CC(OC)=C2)C=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	95.3
S57	35767		O=C1N(C)C=C(CC2=CC=CC(OC)=C2)C=C1[N+]([O-])=O	100
S58	35768		O=C1N(C)C=C(CC2=CC=CC(OC)=C2)C=C1N	99.9
S59	35769		O=C1NC2=NC=CC=C2N1C3CCN(C(CN4C=CC=C(NCCC)C4=O)=O)CC3	98.1
S60	35770		O=C1N(C)C=C(CC2=CC=CC(F)=C2F)C=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	98.1
S61	35771		O=C1N(C)C=C(CC2=CC=C(C(OC)=O)C=C2)C=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	97.2
S62	35774		O=C1N(C)C=C(CC2=CC(C#N)=CC=C2)C=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	98.6
S63	35775		O=C1N(C)C=C(CC2=CC=C(OC)C=C2)C=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	98.7

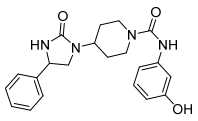
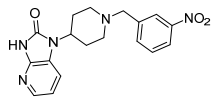
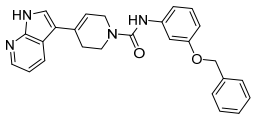
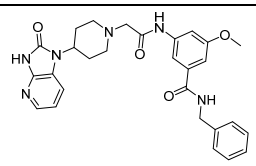
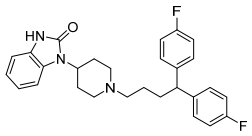
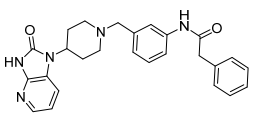
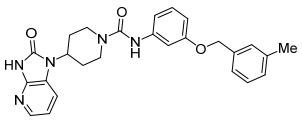
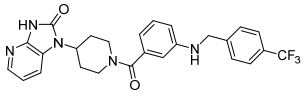
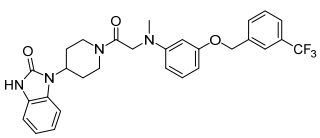
S64	36205		O=C(N1)/C(C2=C1C=CC=C2)=C\C3=C(C)N(C4=CC=CC=C4)C(C)=C3	ND
S65	36206		O=C1N(C)C=C(CC2=CC(F)=CC=C2)C=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	99.8
S66	36207		O=C(N1)/C(C2=C1C=CC=C2)=C/C3=C(C)N(C4=CC=CC=C4)C(C)=C3	ND
S67	36227		O=C(N1)/C(C2=C1C=CC(F)=C2)=C/C3=C(C)N(C4=CC=CC=C4)C(C)=C3	ND
S68	36228		O=C(N1)/C(C2=C1C=CC(F)=C2)=C\C3=C(C)N(C4=CC=CC=C4)C(C)=C3	ND
S69	36230		O=C1N(C)C=C(CC2=CC(C)=CC=C2)C=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	98.5
S70	36266		O=C1N(C)C=C(C(NCC2=CC=CC=C2)=O)C=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	96.1
S71	36317		O=C1N(C)C=CC(N(C(OC(C)(C)C)=O)CC2=CC=CC=C2)=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	99.6
S72	36318		O=C1NC2=NC=CC=C2N1C3CCN(C(NC4=C(CC5=CC=CC=C5)C=CN(C)C4=O)=O)CC3	97.3

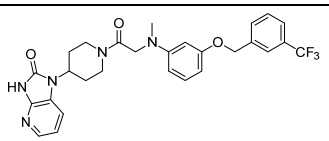
S73	36346		O=C1N(C)C=CC(NCC2=CC=CC=C2)=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	97.7
S74	36371		O=C1NC2=NC=CC=C2N1C3CCN(C(NC4=CC=CN=C4OCC5=CC=CC=C5)=O)CC3	99.6
S75	36527		O=C1NC2=NC=CC=C2N1C3CCN(C(NC4=C(OC5=CC=CC=C5)C=CN(C)C4=O)=O)CC3	98.4
S76	36528		O=C1N(C)C=CC(NC2=CC=CC=C2)=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	96.8
S77	36551		O=C1N(C)C=CC(OCC2=CC=CC=C2)=C1NC(N(CC3)CCC3N4C5=CC=CN=C5NC4=O)=O	99.9
S78	36556		O=C1NC2=NC=CC=C2N1C3CCN(C(NC4=CC(C(NC5=CC=CC=C5)=O)=CN(C)C4=O)=O)CC3	97.9
S79	36621		O=C1NC2=NC=CC=C2N1C3CCN(C(NC(C(N4C)=O)=CC=C4CC5=CC=CC=C5)=O)CC3	95.7
S80	36622		O=C1NC2=NC=CC=C2N1C3CCN(C(NC4=CC=C(NCC5=CC=CC=C5)N=C4OC)=O)CC3	87.3
S81	36707		O=C1NC(N=CC=C2)=C2N1C3CCN(C(NC4=CC=CC(OCC5=CC=CC=C5)=C4)=O)CC3	99.4

S82	36708		O=C1NC(N=CC=C2)=C2N1C3CCN(C(NC4=CC=CC(OCC5=CC=CC(C(F)(F)F)=C5)=C4)=O)CC3	99.4
S83	36709		O=C1NC(N=CC=C2)=C2N1C3CCN(C(NC4=CC=CC(OCC5=CC=C(C(C)(C)C)C=C5)=C4)=O)CC3	99.5
S84	36765		O=C(NC1=C2C=CC=N1)N2C3CCN(CC(NC4=CC(OCC5=CC=CC=C5)=CC=C4)=O)CC3	99.6
S85	36874		O=C1NC2=NC=CC=C2N1C3CCN(C(CN(C4=CC=CC(OCC5=CC=CC=C5)=C4)C(OC(C)(C)C)=O)=O)CC3	99.5
S86	36875		O=C(N1CCC(N2C(NC3=C2C=CC=N3)=O)CC1)CN(C(OC(C)(C)C)=O)C4=CC=C(OCC5=CC=CC=C5)C=C4	99.6
S87	36876		O=C1NC2=NC=CC=C2N1C3CCN(C(CN(C4=CC=CC(OCC5CCN(C(OC(C)(C)C)=O)CC5)=C4)C)=O)CC3	98.6
S88	36877		O=C1NC2=C(C=CC=N2)N1C3CCN(CC3)C(CNC4=CC=C(C=C4)OCC5=CC=CC=C5)=O	99.9
S89	36920		O=C(NC1=C2C=CC=N1)N2C3CCN(C(CN(C)C4=CC=CC(OCC5CCNCC5)=C4)=O)CC3	93.2
S90	36944		O=C1NC(C=CC=C2)=C2N1C3CCN(C(NC4=CC=CC(OCC5=CC=CC=C5)=C4)=O)CC3	99.4

S91	36962		O=C1NC(C=CC=C2)=C2N1C3CCN(C(CN(C)C4=CC=CC(OCC5=CC=CC=C5)=C4)=O)CC3	99.8
S92	36963		O=C1NC(N=CC=C2)=C2N1C3CCN(C(CN(C)C4=CC=CC(OCC5=CC=CC=C5)=C4)=O)CC3	99.9
S93	36972		O=C1NC2=NC=CC=C2N1C3CCN(C(CNC4=CC=CC(OCC5=CC=CC=C5)=C4)=O)CC3	92.5
S94	36973		O=C1NC2=NC=CC=C2N1C3CCN(C(NC4=CC=CC=C4OCC5=CC=CC=C5)=O)CC3	99.8
S95	36987		O=C1NC2=NC=CC=C2N1C3CCN(C(NC4=CC=C(OCC5=CC=CC=C5)C=C4)=O)CC3	99.9
S96	36988		O=C1NC(C=CC=C2)=C2N1C3CCN(C(NC4=CC=CC(OCC5=CC=CC(C(F)(F)F)=C5)=C4)=O)CC3	100
S97	37102		CC(C)(C1=CC=C(COC2=CC=CC(NCC(N3CCC(N4C(NC5=CC=CC=C45)=O)CC3)=O)=C2)C=C1)C	99.6
S98	37103		O=C(C1=CC=CC=C1)N2CCC(N3C(NC4=C3C=CC=N4)=O)CC2	99.9
S99	37104		O=C(CC1=CC=CC=C1)N2CCC(N3C(NC4=C3C=CC=N4)=O)CC2	99.7

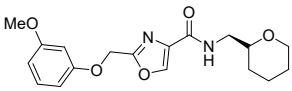
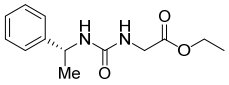
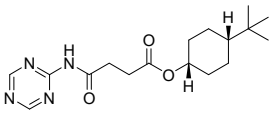
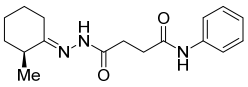
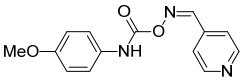
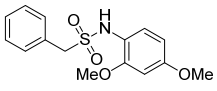
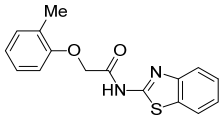
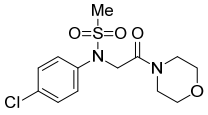
S100	37105		O=C1NC(N=CC=C2)=C2N1C3CCN(C(C4=CC=CC([N+]([O-])=O)=C4)=O)CC3	100
S101	37106		O=C(NC1=CC=CC(OCC2=CC=C(C(OC)=O)C=C2)=C1)N3CCC(N4C(NC5=C4C=CC=N5)=O)CC3	99.1
S102	37107		O=C1NC2=NC=CC=C2N1C3CCN(C(NC4=CC=CC(OCC5=CC=C(OC)C=C5)=C4)=O)CC3	98.3
S103	37130		O=C1NC2=NC=CC=C2CN1C3CCN(C(NC4=CC=CC(OCC5=CC=CC=C5)=C4)=O)CC3	97.5
S104	37131		O=C1NC(C2=CC=CC=C2)=CN1C3CCN(C(NC4=CC=CC(OCC5=CC=CC=C5)=C4)=O)CC3	98.5
S105	37134		O=C(NC1=C2C=CC=N1)N2C3CCN(C(CN(C(OC(C)(C)C)=O)C4=CC=CC(OCC5=CC=C(C(C)(C)C)C=C5)=C4)=O)CC3	98.9
S106	37135		O=C(NC1=CC(OCC2=CC=CC=C2)=CC=C1)NC3=CC=CC(OCC4=CC=CC=C4)=C3	99.4
S107	37163		O=C(C1=CC(NCC2=CC=CC=C2)=CC=C1)N3CCC(N4C(NC5=C4C=CC=N5)=O)CC3	96.5
S108	37164		O=C1NC(N=CC=C2)=C2N1C3CCN(C(C4=CC=CC(N)=C4)=O)CC3	96.6

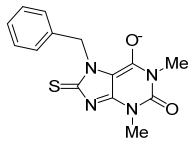
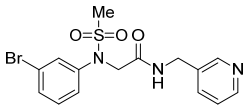
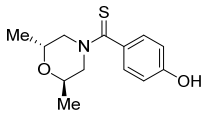
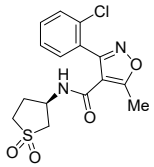
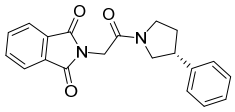
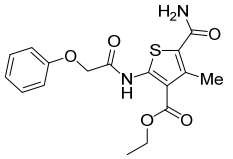
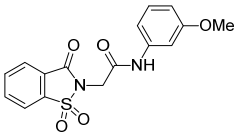
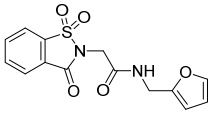
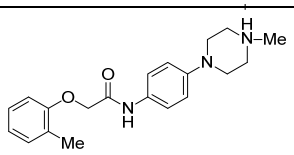
S109	37176		O=C1NC(C2=CC=CC=C2)CN1C3CCN(C(NC4=CC=CC(O)=C4)=O)CC3	98.5
S110	37177		O=C(NC1=C2C=CC=N1)N2C3CCN(CC4=CC=CC([N+]([O-])=O)=C4)CC3	99.8
S111	37178		O=C(N(CC1)CCC1C2=CNC3=NC=CC=C32)NC4=CC(OCC5=CC=CC=C5)=CC=C4	92.5
S112	37179		O=C1NC2=NC=CC=C2N1C3CCN(CC(NC4=CC(C(NCC5=CC=CC=C5)=O)=CC(OC)=C4)=O)CC3	98.9
S113	37180		O=C(NC1=C2C=CC=C1)N2C3CCN(CCCC(C4=CC=C(F)C=C4)C5=CC=C(F)C=C5)CC3	98.8
S114	37241		O=C(NC1=C2C=CC=N1)N2C3CCN(CC4=CC=CC(NC(CC5=CC=CC=C5)=O)=C4)CC3	97.0
S115	37242		O=C(N1CCC(N2C(NC3=C2C=CC=N3)=O)CC1)NC4=CC(OCC5=CC(C)=CC=C5)=CC=C4	99.7
S116	37243		O=C1NC(N=CC=C2)=C2N1C3CCN(C(C4=CC=CC(NCC5=CC=CC(C(F)(F)F)=C5)=C4)=O)CC3	97.5
S117	37244		O=C1NC(C=CC=C2)=C2N1C3CCN(C(CN(C)C4=CC=CC(OCC5=CC=CC(C(F)(F)F)=C5)=C4)=O)CC3	100

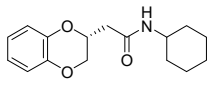
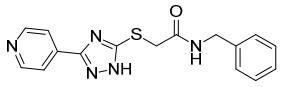
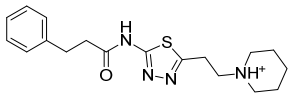
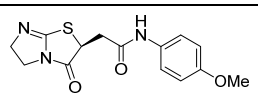
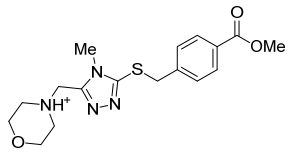
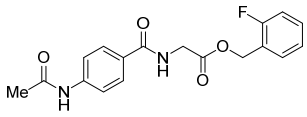
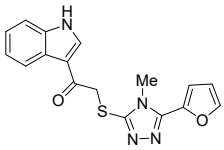
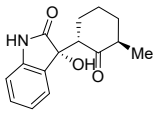
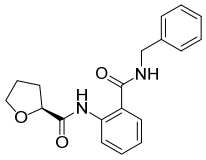
S118	37245		O=C1NC(N=CC=C2)=C2N1C3CCN(C(CN(C)C4=CC=CC(OCC5=CC=CC(C(F)(F)F)=C5)=C4)=O)CC3	99.6

*Compounds were purchased and tested as received from the vendor.

Table S2. Compounds selected for testing from the virtual screen using a model of the AM_1 receptor derived from 3AQF (Compounds S119–S153).

Compound number	Chembridge ID	Structure	SMILES
S119	14271319		O=C(NCC1OCCCC1)C2=COC(COC3=CC=CC(OC)=C3)=N2
S120	5100323		CCOC(CNC(N[C@H](C)C1=CC=CC=C1)=O)=O
S121	5106039		CC(C)(C1CCC(OC(CCC(NC2=NC=NC=N2)=O)=O)CC1)C
S122	5475655		O=C(CCC(NC1=CC=CC=C1)=O)N/N=C2[C@H](CCCC/2)C
S123	5545064		O=C(O/N=C\C1=CC=NC=C1)NC2=CC=C(C=C2)OC
S124	5569618		O=S(NC1=C(OC)C=C(C=C1)OC)(CC2=CC=CC=C2)=O
S125	5688261		O=C(NC(S1)=NC2=C1C=CC=C2)COC3=C(C)C=CC=C3
S126	6236278		O=S(N(C1=CC=C(Cl)C=C1)CC(N2CCOCC2)=O)(C)=O

S127	6267661		[O-]C(N(C)C1=O)=C(N2CC3=CC=CC=C3)C(N1C)=NC2=S
S128	6399732		O=S(N(C1=CC(Br)=CC=C1)CC(NCC2=CN=CC=C2)=O)(C)=O
S129	6625020		S=C(C1=CC=C(O)C=C1)N(C[C@H]2C)C[C@H](O2)C
S130	6717909		ClC1=C(C=CC=C1)C2=NOC(C)=C2C(N[C@H](CC3)CS3(=O)=O)=O
S131	6806958		O=C(CN(C(C1=C2C=CC=C1)=O)C2=O)N3CC[C@H](C4=CC=CC=C4)C3
S132	7258158		CCOC(C1=C(NC(COC2=CC=CC=C2)=O)SC(C(N)=O)=C1C)=O
S133	7380441		O=C(CN(C(C1=C2C=CC=C1)=O)S2(=O)=O)NC3=CC=CC(OC)=C3
S134	7457259		O=C(N(CC(NCC1=CC=CO1)=O)S2(=O)=O)C3=C2C=CC=C3
S135	7645530		O=C(NC1=CC=C(N2CC[NH+](C)CC2)C=C1)COC3=C(C=CC=C3)C

S136	7646371		O=C(NC1CCCCC1)C[C@@H]2COC3=C(O2)C=CC=C3
S137	7676715		O=C(CSC1=NC(C2=CC=NC=C2)=NN1)NCC3=CC=CC=C3
S138	7701549		O=C(NC1=NN=C(CC[NH+]2CCCCC2)S1)CCC3=CC=CC=C3
S139	7745171		O=C(C[C@@H]1SC2=NCCN2C1=O)NC3=CC=C(C=C3)OC
S140	7748258		O=C(OC)C1=CC=C(C=C1)CSC2=NN=C(C[NH+]3CCOCC3)N2C
S141	7933822		O=C(NC1=CC=C(C(NCC(OCC2=C(F)C=CC=C2)=O)=O)C=C1)C
S142	7952006		O=C(C1=CNC2=CC=CC=C12)CSC3=NN=C(C4=CC=CO4)N3C
S143	7984549		O=C1[C@@H](CCC[C@H]1[C@](C2=C(N3)C=CC=C2)(O)C3=O)C
S144	9000840		O=C(C1=C(NC([C@H]2OCCC2)=O)C=CC=C1)NCC3=CC=CC=C3

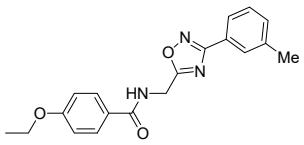
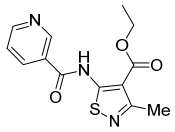
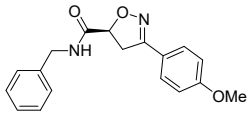
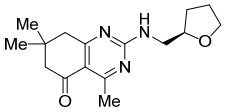
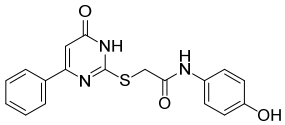
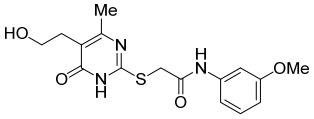
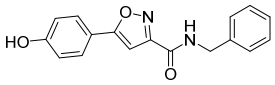
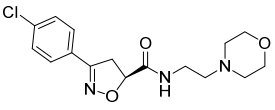
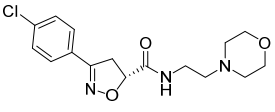
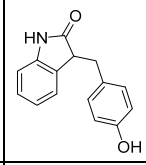
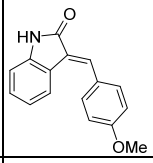
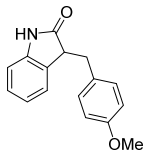
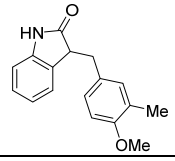
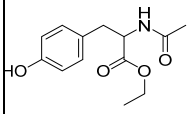
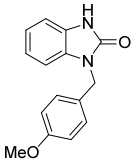
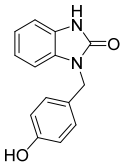
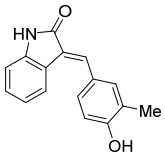
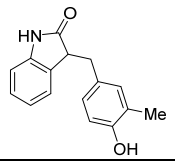
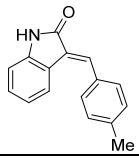
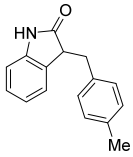
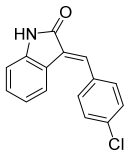
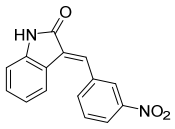
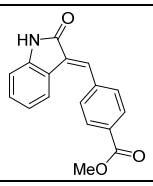
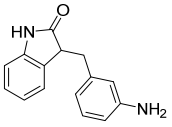
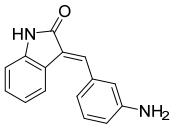
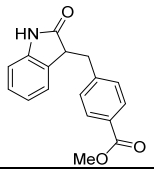
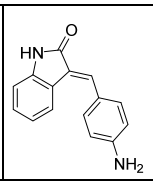
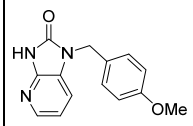
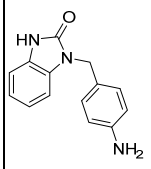
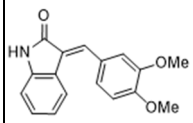
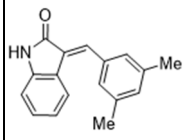
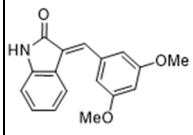
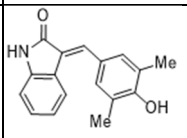
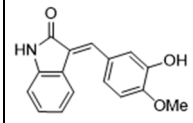
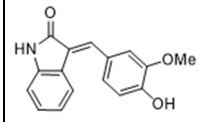
S145	9002015		CCOC1=CC=C(C(NCC2=NC(C3=CC(C)=CC=C3)=NO2)=O)C=C1
S146	9048476		CCOC(C1=C(NC(C2=CN=CC=C2)=O)SN=C1C)=O
S147	9061534		O=C(NCC1=CC=CC=C1)[C@H]2ON=C(C2)C3=CC=C(C=C3)OC
S148	9065389		O=C1CC(CC2=C1C(C)=NC(NC[C@H]3CCCO3)=N2)(C)C
S149	9123217		O=C(NC(SCC(NC1=CC=C(O)C=C1)=O)=N2)C=C2C3=CC=CC=C3
S150	9138048		O=C(NC(SCC(NC1=CC(OC)=CC=C1)=O)=N2)C(CCO)=C2C
S151	9235375		O=C(C1=NOC(C2=CC=C(O)C=C2)=C1)NCC3=CC=CC=C3
S152	9245673		O=C(NCCN1CCOCC1)[C@H]2ON=C(C2)C3=CC=C(Cl)C=C3
S153	9245673		O=C(NCCN1CCOCC1)[C@@H]2ON=C(C2)C3=CC=C(Cl)C=C3

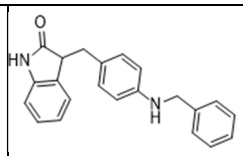
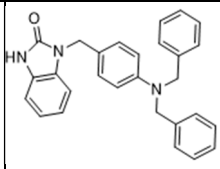
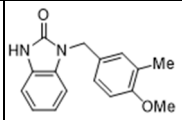
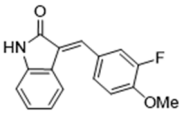
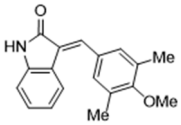
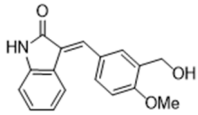
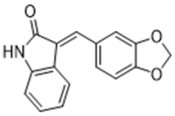
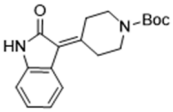
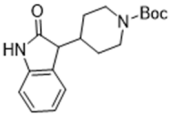
Table S3

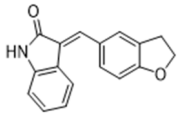
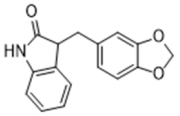
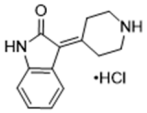
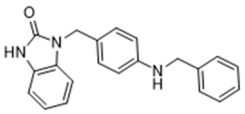
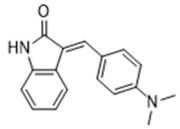
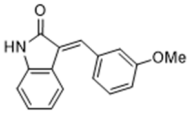
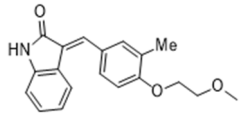
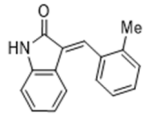
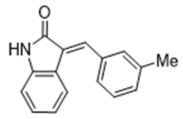
Compounds to mimic the binding of the N-terminal tyrosine (AM peptide) to the AM_1 receptor (**S154-S240**).

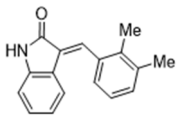
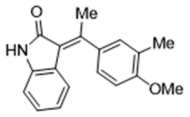
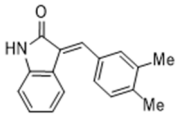
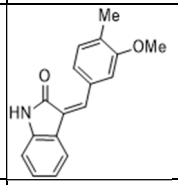
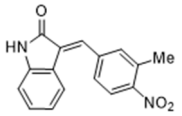
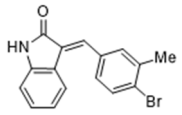
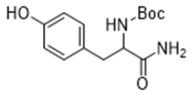
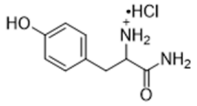
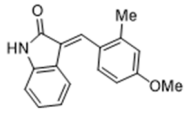
Compound number	SN	Structure	SMILES	HPLC Purity %
S154	37308		O=C(N1)C(CC2=CC=C(O)C=C2)C3=C1C=CC=C3	94.7
S155	37309		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(OC)C=C3	98.8
S156	37310		O=C(N1)C(CC2=CC=C(OC)C=C2)C3=C1C=CC=C3	100
S157	37312		O=C1C(CC2=CC=C(OC)C(C)=C2)C3=CC=CC=C3N1	99.2
S158	37321		OC1=CC=C(CC(C(OCC)=O)NC(C)=O)C=C1	*
S159	37322		O=C(N1)N(CC2=CC=C(OC)C=C2)C3=C1C=CC=C3	99.2
S160	37340		O=C(N1)N(CC2=CC=C(O)C=C2)C3=C1C=CC=C3	98.4
S161	37341		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(O)C(C)=C3	100

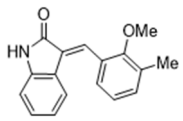
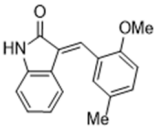
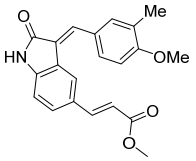
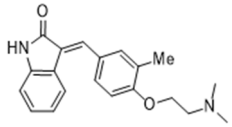
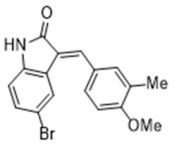
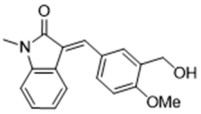
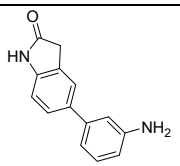
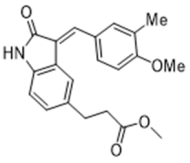
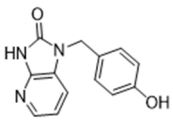
S162	37342		O=C1C(CC2=CC=C(O)C(C)=C2)C3=CC=CC=C3N1	100
S163	37343		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(C)C=C3	98.9
S164	37344		O=C(N1)C(CC2=CC=C(C)C=C2)C3=C1C=CC=C3	99.5
S165	37345		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(Cl)C=C3	100
S166	37365		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=CC([N+]([O-])=O)=C3	99.8
S167	37366		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(C(OC)=O)C=C3	99.1
S168	37367		O=C1C(CC2=CC=CC(N)=C2)C3=CC=CC=C3N1	96.4
S169	37368		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=CC(N)=C3	97.9
S170	37369		O=C(N1)C(CC2=CC=C(C(OC)=O)C=C2)C3=C1C=CC=C3	98.5

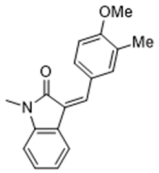
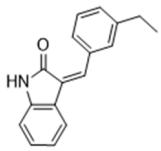
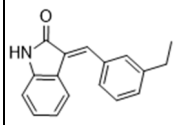
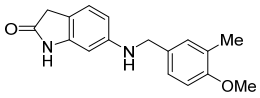
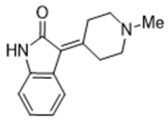
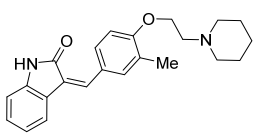
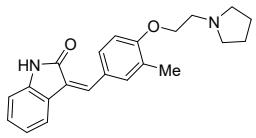
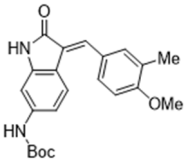
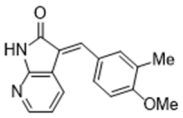
S171	37443		O=C1/C(C2=CC=CC=C2N1)=C\C3=CC=C(N)C=C3	99.7
S172	37444		O=C(N1)N(CC2=CC=C(OC)C=C2)C3=C1N=CC=C3	100
S173	37446		O=C1N(CC2=CC=C(N)C=C2)C3=CC=CC=C3N1	100
S174	37510		O=C1/C(C2=CC=CC=C2N1)=C\C3=CC=C(OC)C(OC)=C3	100
S175	37511		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC(C)=CC(C)=C3	100
S176	37513		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC(OC)=CC(OC)=C3	100
S177	37514		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC(C)=C(O)C(C)=C3	100
S178	37515		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(OC)C(O)=C3	100
S179	37516		O=C1/C(C2=CC=CC=C2N1)=C\C3=CC=C(O)C(OC)=C3	100

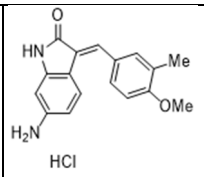
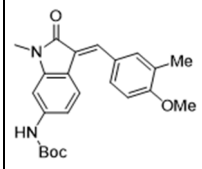
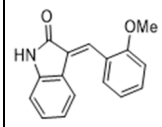
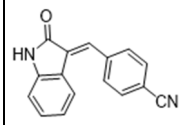
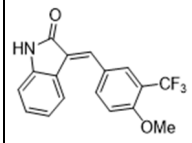
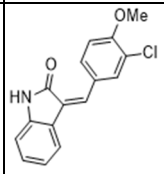
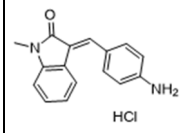
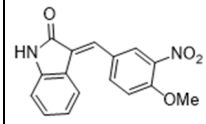
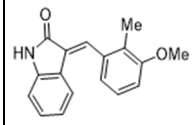
S180	37517		O=C1C(CC2=CC=C(NCC3=CC=CC=C3)C=C2)C4=CC=CC=C4N1	95.5
S181	37518		O=C1N(CC2=CC=C(N(CC3=CC=CC=C3)CC4=CC=CC=C4)C=C2)C5=CC=CC=C5N1	98.6
S182	37519		O=C(N1)N(CC2=CC=C(OC)C(C)=C2)C3=C1C=CC=C3	99.9
S183	37520		O=C1/C(C2=CC=CC=C2N1)=C\C3=CC=C(OC)C(F)=C3	99.9
S184	37562		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC(C)=C(OC)C(C)=C3	100
S185	37563		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(OC)C(CO)=C3	99.0
S186	37657		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C4C(OCO4)=C3	100
S187	37658		O=C1/C(C2=CC=CC=C2N1)=C3CCN(C(OC(C)(C)C)=O)CC/3	99.1
S188	37659		O=C1C(C2CCN(C(OC(C)(C)C)=O)CC2)C3=CC=CC=C3N1	97.4

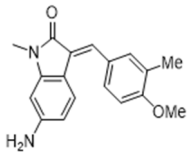
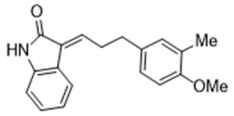
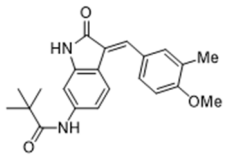
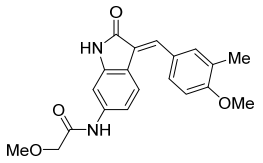
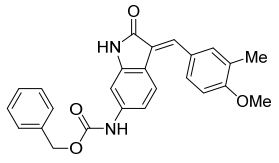
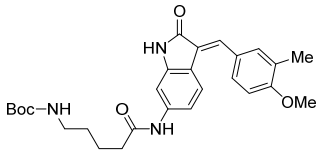
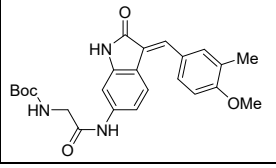
S189	37660		O=C1/C(C2=CC=CC=C2N1)=C\C3=CC=C(OCC4)C4=C3	99.8
S190	37673		O=C1C(CC2=CC=C3C(OCO3)=C2)C4=CC=CC=C4N1	97.0
S191	37674		O=C1/C(C2=CC=CC=C2N1)=C3CCNCC/3.Cl	ND
S192	37729		O=C1N(CC2=CC=C(NCC3=CC=CC=C3)C=C2)C4=CC=CC=C4N1	96.8
S193	37730		O=C1/C(C2=CC=CC=C2N1)=C\C3=CC=C(N(C)C)C=C3	99.7
S194	37731		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=CC(OC)=C3	100
S195	37732		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(OCCOC)C(C)=C3	100
S196	37769		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=CC=C3C	99.8
S197	37770		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=CC(C)=C3	99.8

S198	37771		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=CC(C)=C3C	99.7
S199	37797		O=C1/C(C2=CC=CC=C2N1)=C(C)/C3=CC=C(OC)C(C)=C3	99.8
S200	37798		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(C)C(C)=C3	99.9
S201	37799		O=C1/C(C2=CC=CC=C2N1)=C\C(C=C3OC)=CC=C3C	99.8
S202	37800		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C([N+]([O-])=O)C(C)=C3	99.2
S203	37801		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(Br)C(C)=C3	100
S204	37836		OC1=CC=C(CC(NC(OC(C)(C)C)=O)C(N)=O)C=C1	94.9
S205	37837		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=CC(C)=C3OC	ND
S206	37838		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(OC)C=C3C	99.0

S207	37839		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=CC(C)=C3OC	100
S208	37840		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC(C)=CC=C3OC	100
S209	37841		O=C1/C(C2=CC(/C=C/C(OC)=O)=CC=C2N1)=C/C3=CC=C(OC)C(C)=C3	96.4
S210	37847		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(OCCN(C)C)C(C)=C3	82.5
S211	37883		O=C1/C(C2=CC(Br)=CC=C2N1)=C/C3=CC=C(OC)C(C)=C3	99.0
S212	37884		O=C1/C(C2=CC=CC=C2N1C)=C/C3=CC=C(OC)C(CO)=C3	98.1
S213	37943		O=C1CC2=CC(C3=CC=CC(N)=C3)=CC=C2N1	99.3
S214	37944		O=C1/C(C2=CC(CCC(OC)=O)=CC=C2N1)=C/C3=CC=C(OC)C(C)=C3	97.8
S215	37988		O=C(N1)N(CC2=CC=C(O)C=C2)C3=C1N=CC=C3	99.8

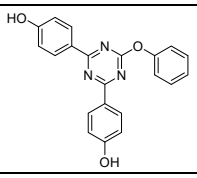
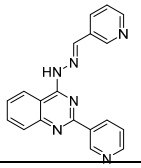
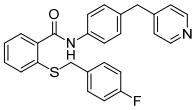
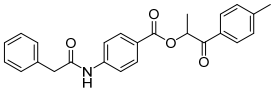
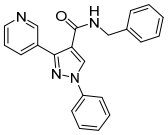
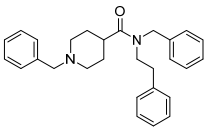
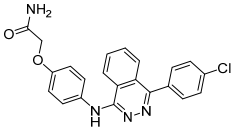
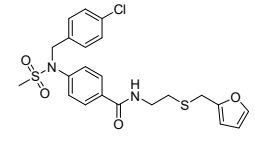
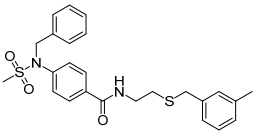
S216	37989		O=C(N1C)/C(C2=C1C=CC=C2)=C\C3=CC=C(OC)C(C)=C3	99.9
S217	37991		O=C(N1)/C(C2=C1C=CC=C2)=C\C3=CC=CC(CC)=C3	99.4
S218	37992		O=C(N1)/C(C2=C1C=CC=C2)=C/C3=CC=CC(CC)=C3	99.4
S219	37993		O=C1CC2=CC=C(NCC3=CC=C(OC)C(C)=C3)C=C2N1	90.7
S220	37994		O=C1/C(C2=CC=CC=C2N1)=C3CCN(C)CC/3	95.2
S221	38047		O=C1/C(C2=CC=CC=C2N1)=C\C3=CC=C(OCCN4CCCCC4)C(C)=C3	98.8
S222	38048		O=C1/C(C2=CC=CC=C2N1)=C\C3=CC=C(OCCN4CCCC4)C(C)=C3	99.3
S223	38049		O=C1/C(C2=CC=C(NC(OC(C)(C)C)=O)C=C2N1)=C/C3=CC=C(OC)C(C)=C3	97.9
S224	38050		O=C1/C(C2=CC=CN=C2N1)=C/C3=CC=C(OC)C(C)=C3	96.8

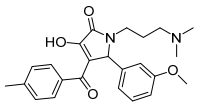
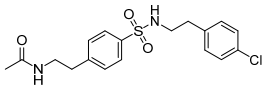
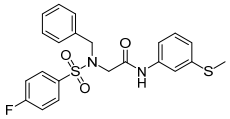
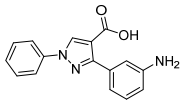
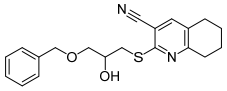
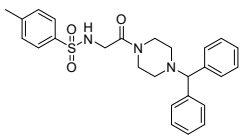
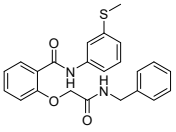
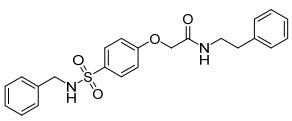
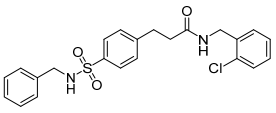
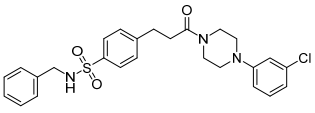
S225	38051		O=C1/C(C2=CC=C(N)C=C2N1)=C/C3=CC=C(OC)C(C)=C3	98.9
S226	38052		O=C1/C(C2=CC=C(NC(OC(C)(C)C)=O)C=C2N1C)=C/C3=CC=C(OC)C(C)=C3	98.9
S227	38053		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=CC=C3OC	98.8
S228	38054		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(C#N)C=C3	94.2
S229	38055		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=C(OC)C(C(F)(F)F)=C3	99.9
S230	38056		O=C1/C(C2=CC=CC=C2N1)=C\C3=CC=C(OC)C(Cl)=C3	98.2
S231	38078		O=C1/C(C2=CC=CC=C2N1C)=C\C3=CC=C(N)C=C3	92.6
S232	38079		O=C1/C(C2=CC=CC=C2N1)=C\C3=CC=C(OC)C([N+]([O-])=O)=C3	96.91
S233	38082		O=C1/C(C2=CC=CC=C2N1)=C/C3=CC=CC(OC)=C3C	99.3

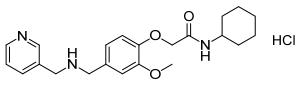
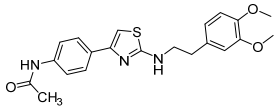
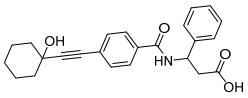
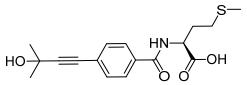
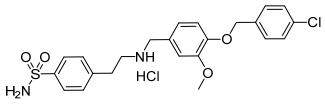
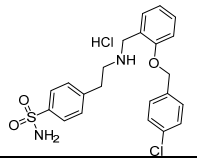
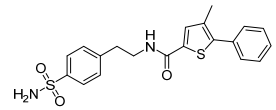
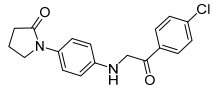
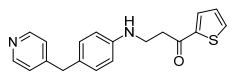
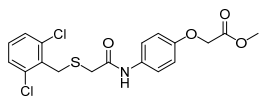
S234	38146		O=C1/C(C2=CC=C(N)C=C2N1C)=C/C3=CC=C(OC)C(C)=C3	99.0
S235	38147		O=C1/C(C2=CC=CC=C2N1)=C/CCC3=CC=C(OC)C(C)=C3	97.0
S236	38211		O=C1/C(C2=CC=C(NC(C(C)(C)C)=O)C=C2N1)=C/C3=CC=C(OC)C(C)=C3	99.9
S237	38212		O=C1/C(C2=CC=C(NC(COC)=O)C=C2N1)=C/C3=CC=C(OC)C(C)=C3	99.8
S238	38303		O=C1/C(C2=CC=C(NC(OCC3=CC=CC=C3)=O)C=C2N1)=C/C4=CC=C(OC)C(C)=C4	98.8
S239	38304		O=C1/C(C2=CC=C(NC(CCCCNC(OC(C)(C)C)=O)=O)C=C2N1)=C/C3=CC=C(OC)C(C)=C3	98.9
S240	38305		O=C1/C(C2=CC=C(NC(CNC(OC(C)(C)C)=O)=O)C=C2N1)=C/C3=CC=C(OC)C(C)=C3	87.2

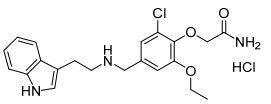
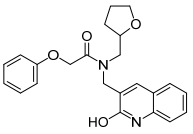
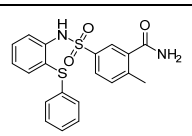
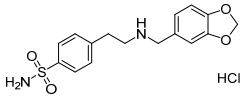
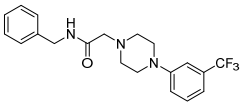
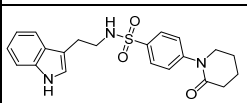
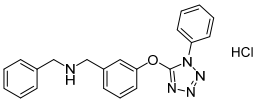
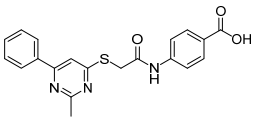
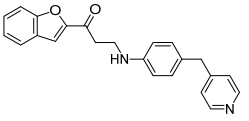
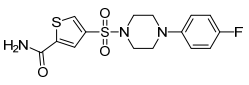
*Compounds were purchased and tested as received from the vendor.

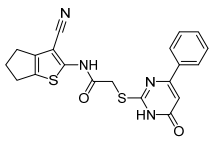
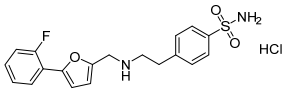
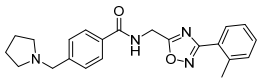
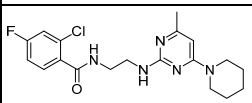
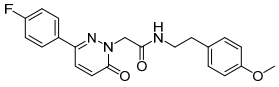
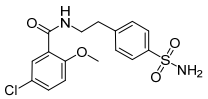
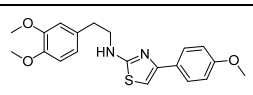
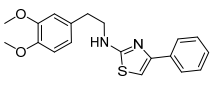
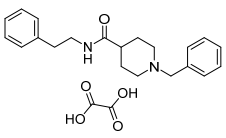
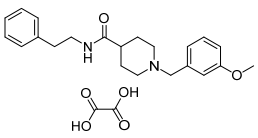
Table S4
Compounds selected for testing from the virtual screen using a model of the AM_1 receptor derived from 3AQF (**S241-S318**).

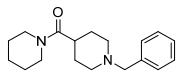
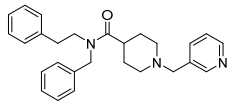
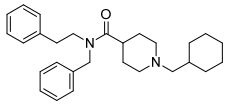
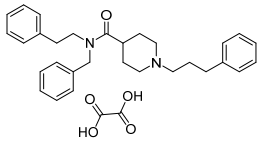
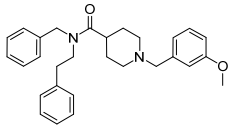
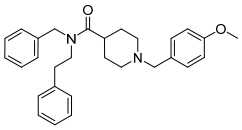
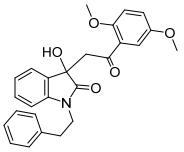
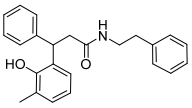
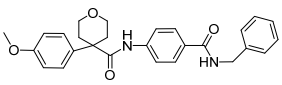
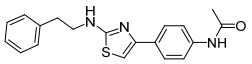
Compound number	Chembridge ID	Structure	SMILES
S241	5210142		OC1=CC=C(C2=NC(C3=CC=C(O)C=C3)=NC(OC4=CC=CC=C4)=N2)C=C1
S242	5580676		C1(/C=N/NC2=C3C=CC=CC3=NC(C4=CC=CN=C4)=N2)=CN=CC=C1
S243	6053535		O=C(NC1=CC=C(CC2=CC=NC=C2)C=C1)C3=CC=CC=C3SCC4=CC=C(F)C=C4
S244	6557648		O=C(OC(C)C(C1=CC=C(C)C=C1)=O)C2=CC=C(NC(CC3=CC=CC=C3)=O)C=C2
S245	6568730		O=C(NCC1=CC=CC=C1)C2=CN(C3=CC=CC=C3)N=C2C4=CC=CN=C4
S246	6578789		O=C(N(CC1=CC=CC=C1)CCC2=CC=CC=C2)C3CCN(CC4=CC=CC=C4)CC3
S247	6606435		O=C(N)COC1=CC=C(NC2=NN=C(C3=CC=C(Cl)C=C3)C4=C2C=CC=C4)C=C1
S248	6809216		O=C(NCCSCC1=CC=CO1)C2=CC=C(N(CC3=CC=C(Cl)C=C3)S(=O)(C)=O)C=C2
S249	6865940		O=C(NCCSCC1=CC=CC(C)=C1)C2=CC=C(N(CC3=CC=CC=C3)S(=O)(C)=O)C=C2

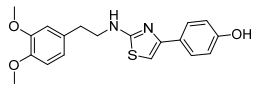
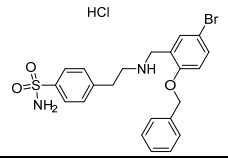
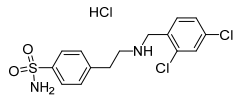
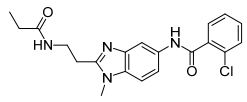
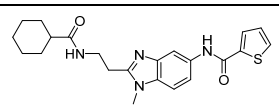
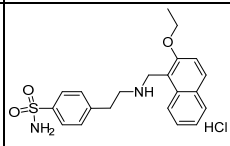
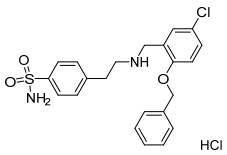
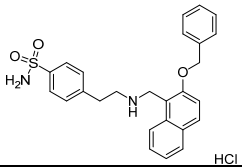
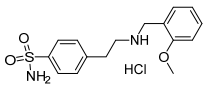
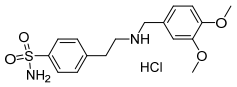
S250	6939665		O=C1N(CCCN(C)C)C(C2=CC=CC(OC)=C2)C(C(C3=CC=C(C)C=C3)=O)=C1O
S251	6968242		CC(NCCC1=CC=C(S(=O)(NCCC2=CC=C(Cl)C=C2)=O)C=C1)=O
S252	7030634		O=C(NC1=CC=CC(SC)=C1)CN(CC2=CC=CC=C2)S(=O)(C3=CC=C(F)C=C3)=O
S253	7141751		O=C(C1=CN(C2=CC=CC=C2)N=C1C3=CC=CC(N)=C3)O
S254	7591892		N#CC1=CC2=C(N=C1SCC(O)COCC3=CC=CC=C3)CCCC2
S255	7596514		CC1=CC=C(S(=O)(NCC(N2CCN(C(C3=CC=CC=C3)C4=CC=CC=C4)CC2)=O)=O)C=C1
S256	7639598		O=C(NC1=CC=CC(SC)=C1)C2=CC=CC=C2OCC(NCC3=CC=CC=C3)=O
S257	7722400		O=C(NCCC1=CC=CC=C1)COC2=CC=C(S(=O)(NCC3=CC=CC=C3)=O)C=C2
S258	7788404		O=C(NCC1=CC=CC=C1Cl)CCC2=CC=C(S(=O)(NCC3=CC=CC=C3)=O)C=C2
S259	7789506		O=S(C1=CC=C(CCC(N2CCN(C3=CC=CC(Cl)=C3)CC2)=O)C=C1)(NCC4=CC=CC=C4)=O

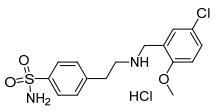
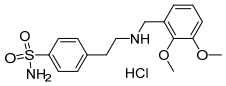
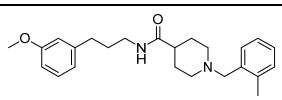
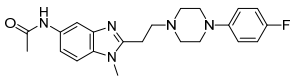
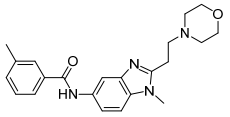
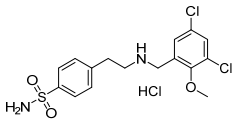
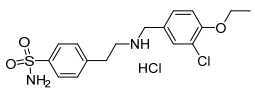
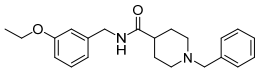
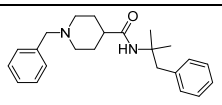
S260	7867889		O=C(NC1CCCCC1)COC2=CC=C(CNCC3=CC=CN=C3)C=C2OC.Cl
S261	7872017		CC(NC1=CC=C(C2=CSC(NCCC3=CC(OC)=C(OC)C=C3)=N2)C=C1)=O
S262	7921125		O=C(O)CC(NC(C1=CC=C(C#CC2(O)CCCCC2)C=C1)=O)C3=CC=CC=C3
S263	7921132		CSCC[C@@H](C(O)=O)NC(C1=CC=C(C#CC(C)(O)C)C=C1)=O
S264	7929934		O=S(C1=CC=C(CCNCC2=CC(OC)=C(OCC3=CC=C(Cl)C=C3)C=C2)C=C1)(N)=O.Cl
S265	7938921		ClC(C=C1)=CC=C1COC2=CC=CC=C2CNCCC3=CC=C(S(=O)(N)=O)C=C3.Cl
S266	7945479		O=C(C1=CC(C)=C(C2=CC=CC=C2)S1)NCCC3=CC=C(S(=O)(N)=O)C=C3
S267	7951332		O=C1N(C2=CC=C(NCC(C3=CC=C(Cl)C=C3)=O)C=C2)CCC1
S268	7959301		O=C(C1=CC=CS1)CCNC2=CC=C(CC3=CC=NC=C3)C=C2
S269	7961792		O=C(OC)COC1=CC=C(NC(CSCC2=C(Cl)C=CC=C2Cl)=O)C=C1

S270	7979845		O=C(N)COC1=C(OCC)C=C(CNCCC2=CNC3=C2C=CC=C3)C=C1Cl.Cl
S271	7997028		O=C(N(CC1=CC2=CC=CC=C2N=C1O)CC3OCCC3)COC4=CC=CC=C4
S272	9007761		O=C(N)C1=CC(S(=O)(NC2=CC=CC=C2SC3=CC=CC=C3)=O)=CC=C1C
S273	9018313		O=S(C1=CC=C(CCNCC2=CC=C(OCO3)C3=C2)C=C1)(N)=O.Cl
S274	9044198		O=C(CN1CCN(C2=CC=CC(C(F)(F)F)=C2)CC1)NCC3=CC=CC=C3
S275	9114960		O=S(C1=CC=C(N2C(CCCC2)=O)C=C1)(NCCC3=CNC4=C3C=CC=C4)=O
S276	9133243		C1(CNCC2=CC=CC=C2)=CC=CC(OC3=NN=NN3C4=CC=CC=C4)=C1.Cl
S277	9141148		O=C(O)C1=CC=C(NC(CSC2=NC(C)=NC(C3=CC=CC=C3)=C2)=O)C=C1
S278	9153159		O=C(C(O1)=CC2=C1C=CC=C2)CCNC3=CC=C(CC4=CC=NC=C4)C=C3
S279	9153611		O=C(C1=CC(S(=O)(N2CCN(C3=CC=C(F)C=C3)CC2)=O)=CS1)N

S280	9155005		O=C(NC1=C(C#N)C(CCC2)=C2S1)CSC3=NC(C4=CC=CC=C4)=CC(N3)=O
S281	9158511		O=S(C1=CC=C(CCNCC2=CC=C(C3=CC=CC=C3F)O2)C=C1)(N)=O.Cl
S282	9214149		O=C(NCC1=NC(C2=CC=CC=C2C)=NO1)C3=CC=C(CN4CCCC4)C=C3
S283	9231370		O=C(NCCNC1=NC(N2CCCCC2)=CC(C)=N1)C3=CC=C(F)C=C3Cl
S284	9302281		O=C(NCCC1=CC=C(OC)C=C1)CN2C(C=CC(C3=CC=C(F)C=C3)=N2)=O
S285	5232626		O=S(C1=CC=C(CCNC(C2=CC(Cl)=CC=C2OC)=O)C=C1)(N)=O
S286	5674182		COC1=C(OC)C=CC(CCNC2=NC(C3=CC=C(OC)C=C3)=CS2)=C1
S287	5674819		COC1=C(OC)C=CC(CCNC2=NC(C3=CC=CC=C3)=CS2)=C1
S288	6578109		O=C(O)C(O)=O.O=C(NCCC1=CC=CC=C1)C2CCN(CC3=CC=CC=C3)CC2
S289	6578132		O=C(O)C(O)=O.O=C(NCCC1=CC=CC=C1)C2CCN(CC3=CC=CC(OC)=C3)CC2

S290	6578487		O=C(C1CCN(CC2=CC=CC=C2)CC1)N3CCCCC3
S291	6578792		O=C(C1CCN(CC2=CN=CC=C2)CC1)N(CCC3=CC=CC=C3)CC4=CC=CC=C4
S292	6578796		O=C(C1CCN(CC2CCCCC2)CC1)N(CCC3=CC=CC=C3)CC4=CC=CC=C4
S293	6578807		O=C(C1CCN(CCCC2=CC=CC=C2)CC1)N(CCC3=CC=CC=C3)CC4=CC=CC=C4.O=C(O)C(O)=O
S294	6578810		O=C(C1CCN(CC2=CC=CC(OC)=C2)CC1)N(CCC3=CC=CC=C3)CC4=CC=CC=C4
S295	6578811		O=C(C1CCN(CC2=CC=C(OC)C=C2)CC1)N(CCC3=CC=CC=C3)CC4=CC=CC=C4
S296	7126098		O=C(C(CC(C1=C(OC)C=CC(OC)=C1)=O)(O)C2=C3C=CC=C2)N3CCC4=CC=CC=C4
S297	7422362		O=C(NCCC1=CC=CC=C1)CC(C2=CC=CC=C2)C3=CC=CC(C)=C3O
S298	7645439		O=C(NC1=CC=C(C=C1)C(NCC2=CC=CC=C2)=O)C3(CCOCC3)C4=CC=C(OC)C=C4
S299	7868949		O=C(C)NC1=CC=C(C=C1)C2=CSC(NCCC3=CC=CC=C3)=N2

S300	7877565		OC1=CC=C(C=C1)C2=CSC(NCCC3=CC(OC)=C(OC)C=C3)=N2
S301	7927320		O=S(C1=CC=C(CCNCC2=CC(Br)=CC=C2OCC3=CC=CC=C3)C=C1)(N)=O.Cl
S302	7928297		O=S(C1=CC=C(CCNCC2=C(Cl)C=C(Cl)C=C2)C=C1)(N)=O.Cl
S303	7949979		O=C(C(C=CC=C1)=C1Cl)NC2=CC(N=C(CCNC(CC)=O)N3C)=C3C=C2
S304	7960449		O=C(C1=CC=CS1)NC2=CC(N=C(CCNC(C3CCCCC3)=O)N4C)=C4C=C2
S305	7974219		O=S(C1=CC=C(CCNCC2=C(OCC)C=CC3=CC=CC=C23)C=C1)(N)=O.Cl
S306	7983219		O=S(C1=CC=C(CCNCC(C=C(Cl)C=C2)=C2OCC3=CC=CC=C3)C=C1)(N)=O.Cl
S307	7991851		O=S(C1=CC=C(CCNCC2=C(C=CC=C3)C3=CC=C2OCC4=CC=CC=C4)C=C1)(N)=O.Cl
S308	9019928		O=S(C1=CC=C(CCNCC2=CC=CC=C2OC)C=C1)(N)=O.Cl
S309	9029058		O=S(C1=CC=C(CCNCC2=CC=C(C(OC)=C2)OC)C=C1)(N)=O.Cl

S310	9037225		O=S(C1=CC=C(CCNCC2=CC(Cl)=CC=C2OC)C=C1)(N)=O.Cl
S311	9040374		O=S(C1=CC=C(CCNCC2=C(OC)C(OC)=CC=C2)C=C1)(N)=O.Cl
S312	9102814		O=C(NCCCC1=CC=CC(OC)=C1)C(CC2)CCN2CC3=CC=CC=C3C
S313	9105783		O=C(C)NC1=CC2=C(C=C1)N(C)C(CCN3CCN(C(C=C4)=CC=C4F)CC3)=N2
S314	9110752		O=C(C1=CC=CC(C)=C1)NC2=CC3=C(C=C2)N(C)C(CCN4CCOCC4)=N3
S315	9144907		O=S(C1=CC=C(CCNCC2=C(OC)C(Cl)=CC(Cl)=C2)C=C1)(N)=O.Cl
S316	9153200		O=S(C(C=C1)=CC=C1CCNCC2=CC(Cl)=C(OCC)C=C2)(N)=O.Cl
S317	9220392		O=C(C1CCN(CC2=CC=CC=C2)CC1)NCC3=CC(OCC)=CC=C3
S318	9286559		O=C(C1CCN(CC2=CC=CC=C2)CC1)NC(C)(C)CC3=CC=CC=C3

General procedures for chemical characterization and synthesis

All final products were analysed by reverse-phase HPLC, (ZORBAX Eclipse XDB C8 5 µm column, 4.6 × 150 mm; Agilent Technologies) using an Agilent Technologies 1260 Infinity equipped with a diode-array detector. Mobile phases were gradients of 80% acetonitrile/20% H_2O (v/v) in 45 mM ammonium formate at pH 3.5 and 0.8 mL/min. Final compound purity was determined by monitoring at 330 ± 50 nM and was >95%. Microanalytical analyses were carried out in the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined on an Electrothermal 2300 Melting Point Apparatus. NMR spectra were obtained on a Bruker Avance 400 spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C spectra. Spectra were obtained in $CDCl_3$ unless noted otherwise. Chemical shifts and coupling constants were recorded in units of ppm and Hz, respectively. Low resolution mass spectra were gathered by direct injection of methanolic solutions into an Agilent 6120 mass spectrometer using an atmospheric pressure chemical ionization (APCI) mode with a fragmentor voltage of 50 V and a drying gas temperature of 250 °C. High resolution mass spectra (HRMS) were measured on an Agilent Technologies 6530 Accurate-Mass Quadrupole Time of Flight (Q-TOF) LC / MS interfaced with an Agilent Jet Stream Electrospray Ionization (ESI) source allowing positive or negative ions detection.

Organic solutions were dried over $MgSO_4$ or Na_2SO_4 and solvents were evaporated under reduced pressure on a rotary evaporator. Thin-layer chromatography was carried out on aluminium-backed silica gel plates (Merck 60 F_{254}) with visualization of components by UV light (254 nm) or exposure to I_2. Column chromatography was carried out on silica gel (Merck 230–400 mesh). Abbreviations: DCM, dichloromethane; DIPEA, diisopropylethylamine; DMAP, 4-dimethylaminopyridine; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; EDCI, 1-ethyl-3-(dimethylaminopropyl)carbodiimide; Et_2O, diethyl ether; EtOAc, ethyl acetate, HATU, 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HBTU, (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; MeOH, methanol; pet. ether, petroleum ether boiling fraction 40–60 °C; THF, tetrahydrofuran; TFA, trifluoroacetic acid.

General Methods

Method A: Suzuki-Miyaura coupling

$PdCl_2$.dppf.DCM (0.05 eq.) was added to a stirred suspension of bromide (1.0 eq, 1 mmol), boronic acid (1.1 eq.) and Na_2CO_3 (2.2) in dioxane/water (1:1, 15 mL/mmol) and the mixture was stirred at 100 °C for 2 h. The mixture was cooled to 20 °C, diluted with water (50 mL/mmol) and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (2 × 30 mL) and brine (30 mL), dried and the solvent evaporated. The crude solid was purified by column chromatography to give product.

Method B: Nitro reduction

A mixture of nitroaryl compound (1.0 eq., 1 mmol) and Pd/C (50 mg) was stirred in EtOAc/EtOH (1:1, 80 mL) under H_2 (60 psi) for 2 h. The mixture was filtered through diatomaceous earth, washed with EtOAc (30 mL) and the solvent evaporated. The crude solid was purified by column chromatography to give aminoaryl compound.

Method C: Urea formation with triphosgene
iPr_2NEt (1.1 eq.) was added dropwise to a stirred suspension of aniline (1.0 eq., 0.5 mmol) and triphosgene (0.4 eq.) in dry THF (20 mL) at 0 °C and the mixture was stirred at 0 °C for 1 h. Amine (1.1 eq.) and iPr_2NEt (2.2 eq.) were added and the mixture was stirred at 20 °C for 16 h. The mixture was diluted with $CHCl_3$ (100 mL), washed sequentially with water (3 × 30 mL), brine (30 mL) and then dried and the solvent evaporated. The crude solid was purified by column chromatography to give urea.

Method D: Amide coupling with HBTU
iPr_2NEt (1.1 eq.) was added dropwise to a stirred solution of acid (1.0 eq. 1 mmol) and HBTU (1.1 eq.) in dry DMF (5 mL) at 20 °C and the mixture was stirred for 10 min. Amine (1.2 eq.) and iPr_2NEt (2.2 eq.) was added and the mixture was stirred at 20 °C for 16 h. The mixture was diluted with EtOAc (100 mL), washed sequentially with water (3 × 30 mL), 1 M HCl solution (2 × 30 mL), 1 M NaOH solution (30 mL), water (30 mL) and brine (30 mL), and then dried and the solvent evaporated. The crude solid was purified by column chromatography to give amide.

Method E: Alkylation with K_2CO_3 in DMF
A mixture of alkyl or aryl halide (1.0 eq., 10 mmol), amine or phenol (1.3 eq.) and K_2CO_3 (1.5 eq.) in dry DMF (50 mL) was stirred at 70 °C for 16 h. The solvent was evaporated and the residue was partitioned between EtOAc (150 mL) and water (150 mL). The organic fraction was washed sequentially with water (2 × 50 mL), brine (50 mL), then dried and the solvent evaporated. The residue was purified by column chromatography to give amine product.

Method F: Acid hydrolysis of carbamates
A solution of HCl in dioxane (4 M, 5 eq.) was added to a stirred solution of carbamate (1 eq., 5 mmol) in MeOH (50 mL) and the solution was stirred at 20 °C for 24 h. The solvent was evaporated to a small volume and chilled at 5 °C for 24 h. The precipitate was filtered and washed with ice-cold DCM (2 mL) and dried to give amine hydrochloride.

Method G: Tin (II) chloride reduction
$SnCl_2 \cdot 2H_2O$ (5 eq.) was added to a solution of nitroaryl compound (1.0 eq., 3 mmol) in EtOAc (30 mL) and the mixture was heated at 70 °C for 24 h. The resulting mixture was quenched with sat. $NaHCO_3$ (100 mL), and extracted with EtOAc (3 × 80 mL). The combined organic fractions were washed with water (100 mL) and brine (100 mL), dried and concentrated *in vacuo* to give amine.

Method H: Amide coupling with HATU
iPr_2NEt (5 eq.) was added dropwise to a stirred suspension of acid (1.0 eq., 0.2 mmol) and HATU (1 eq.) in dry DMF (5 mL) at 20 °C and the mixture was stirred at 20 °C for 10 min. Amine (1.1 eq.) was added and the mixture was stirred at 20 °C for 16 h. The mixture was diluted with EtOAc (50 mL), washed with water (3 × 30 mL) and brine (30 mL) and then dried and the solvent evaporated.

Method I: Alkylation with organic base in DCM
Alkyl halide (1.05 eq.) was added dropwise to a stirred suspension of amine (1.0 eq., 2 mmol) and iPr_2NEt (1.5 eq.) in dry DCM (20 mL) and the mixture was stirred at 20 °C for 3 h. The mixture was diluted with DCM (50 mL) and washed sequentially with ice/water (50 mL), cold sat. aqueous $KHCO_3$ (50 mL), dried and the solvent evaporated to give product.

Method J: Base hydrolysis
An aqueous solution of NaOH (1 M, 10 eq.) was added to a solution of ester (1.0 eq., 0.5 mmol) in MeOH (5 mL) and the mixture stirred at 20 °C for 24 h. The pH of the reaction mixture was adjusted to ~6 with HCl solution (1 M) and MeOH was removed under reduced pressure. The aqueous fraction was diluted with water (5 mL) and extracted with EtOAc (3 × 50 mL). The organic fractions were combined, dried and the solvent evaporated to give acid.

Method K: BOC formation
A solution of amine (1.0 eq., 2 mmol), di-*tert*-butyl dicarbonate (1.2 eq.) and DMAP (1.0 eq.) in dioxane (10 mL) was stirred at 20 °C for 20 h. The mixture was diluted with EtOAc (50 mL), washed with water (50 mL) and brine (50 mL), dried and the solvent evaporated to give carbamate.

Method L: Alkylation with NaH
NaH (60%, 1.5 eq.) was added to a solution of alcohol or amine (1.0 eq., 1 mmol) in dry DMF (10 mL) at 20 °C and the mixture stirred for 5 min. Halide (1.0 eq.) was added and the mixture was stirred at 20 °C for 24 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (2 × 30 mL) and brine (30 mL), dried and the solvent evaporated.

Method M: Alkene reduction
Alkene (1 eq., 1 mmol) and 10% Pd/C (10% w/w for alkene) were suspended in MeOH (10 mL). The reaction vessel was evacuated and filled with H_2 gas. The reaction mixture was stirred under H_2 (40 psi) at 20 °C for 2 d. The catalyst was removed by filtration over a pad of diatomaceous earth, washed with MeOH and concentrated under reduced pressure.

Method N: Oxindole condensation
A solution of oxindole (1 eq., 3.0 mmol), aldehyde (2 eq.) and piperidine (0.1 eq.) in EtOH (10 mL) was purged with N_2, sealed and heated at 80 °C for 3 h. The reaction mixture was cooled to 20 °C and concentrated under reduced pressure.

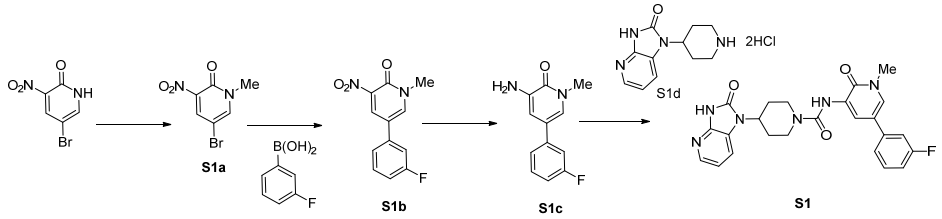
Method O: CDI condensation
CDI (3 eq.) was added to a solution of diamine (1.0 eq., 3 mmol) in MeCN (20 mL) and the reaction mixture was stirred at 20 °C for 18 h. The mixture was diluted with water (50 mL), and extracted with EtOAc (2 × 50 mL). The organic layer was washed with water (50 mL), then brine (50 mL), dried and concentrated under reduced pressure.

Method P: Reductive amination

TFA (2.2 eq.) was added to a solution of amine (1.0 eq., 1 mmol) and aldehyde (1.2 eq.) in EtOAc (10 mL) at 0 °C. The mixture was stirred for 10 minutes and $NaBH(OAc)_3$ (1.5 eq.) was added. The reaction mixture was allowed to warm to 20 °C and stirred for 20 h. The resulting mixture was quenched with 2M NaOH (10 mL) and diluted with water (50 mL). The product was extracted with EtOAc (2 × 50 mL) and the organic fraction was washed with brine (50 mL), dried and concentrated under reduced pressure.

Chemical synthesis of compounds S1-S118 (Table S1).

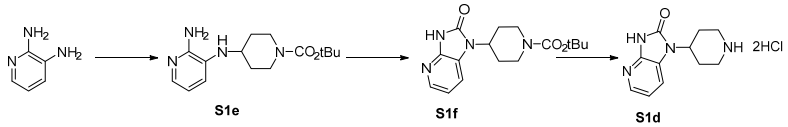
SN34328 *N*-[5-(3-Fluorophenyl)-1-methyl-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (**S1**).



5-Bromo-1-methyl-3-nitropyridin-2(1*H*)-one (S1a). Prepared using Method E from methyl iodide and 5-bromo-3-nitropyridin-2-ol at 20 °C. The crude residue was purified by silica gel column chromatography, eluting with 50% EtOAc/pet. ether to give **S1a** (0.93 g, 87%) as a yellow powder: mp 120–122°C; ^{1}H NMR δ 8.37 (d, *J* = 2.7 Hz, 1H, H-4), 7.81 (d, *J* = 2.7 Hz, 1H, H-6), 3.68 (s, 3H, Me); MS *m/z* 231.4 (MH^+, 100%).

5-(3-Fluorophenyl)-1-methyl-3-nitro-2(1*H*)-pyridinone (S1b). Prepared using Method A from bromide **S1a** and 3-fluorophenylboronic acid. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give nitropyridinone **S1b** (260 mg, 80%) as a yellow powder: mp (EtOAc/pet. ether) 173–175 °C; ^{1}H NMR δ 8.58 (d, *J* = 2.7 Hz, 1H, H-6), 7.92 (d, *J* = 2.7 Hz, 1H, H-4), 7.45 (dt, *J* = 8.0, 6.0 Hz, 1H, H-5′), 7.22 (ddd, *J* = 7.8, 1.7, 0.9 Hz, 1H, H-4′), 7.15 (ddd, *J* = 9.6, 2.2, 2.0 Hz, 1H, H-2′), 7.10 (ddd, *J* = 8.4, 2.5, 0.9 Hz, 1H, H-6′), 3.78 (s, 3H, NCH_3); MS *m/z* 249.4 (MH^+, 100%). Anal. calcd for $C_{12}H_9FN_2O_3$: C, 58.07; H, 3.65; N, 11.29. Found: C, 58.20; H, 3.47; N, 11.34%.

3-Amino-5-(3-fluorophenyl)-1-methyl-2(1*H*)-pyridinone (S1c). Prepared using Method B from nitropyridinone **S1b**. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give aminopyridinone **S1c** (127 mg, 62%) as a white powder: mp (EtOAc/pet. ether) 169–172 °C; ^{1}H NMR δ 7.35 (dt, *J* = 8.0, 6.1 Hz, 1H, H-5′), 7.17 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H, H-4′), 7.10 (dt, *J* = 10.2, 2.4 Hz, 1H, H-2′), 6.99 (ddt, *J* = 8.4, 2.5, 0.9 Hz, 1H, H-6′), 6.94 (d, *J* = 2.3 Hz, 1H, H-6), 6.78 (d, *J* = 2.3 Hz, 1H, H-4), 4.34 (br s, 2H, NH_2), 3.65 (s, 3H, NCH_3); MS *m/z* 219.5 (MH^+, 100%). Anal. calcd for $C_{12}H_{11}FN_2O$: C, 66.05; H, 5.08; N, 12.84. Found: C, 66.22; H, 5.06; N, 13.01%.



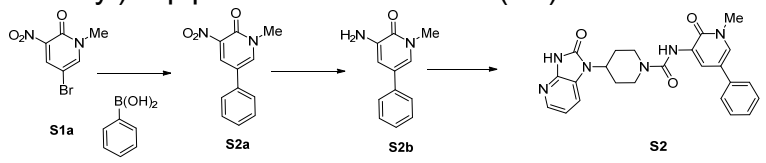
Piperidine·2HCl **S1d** was prepared as described previously (Burgey et al in WO 2004/092166).[1]

1-(4-Piperidinyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one Hydrochloride (S1d). $NaBH(OAc)_3$ (5.82 g, 27.45 mmol) was added in portions to a stirred solution of 2,3-diaminopyridone (2.00 g, 18.3 mmol) and *tert*-butyl 4-oxopiperidine-1-carboxylate (3.85 g, 19.24 mmol) in DCM (50 mL) at 20 °C. The mixture was stirred at 20 °C for 16 h and then quenched with aqueous NaOH solution (1 M, 20 mL). The mixture was extracted with DCM (100 mL) and the combined organic fraction was washed sequentially with

aqueous NaOH solution (1 M, 20 mL), water (2 × 20 mL), brine (20 mL) and dried and the solvent evaporated. The residue was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give *tert*-butyl 4-((2-aminopyridin-3-yl)amino)piperidine-1-carboxylate (**S1e**) (2.13 g, 40%) as a white solid: ^{1}H NMR δ 10.04 (br s, 1H, NH), 8.06 (dd, *J* = 5.3, 1.2 Hz, 1H, H-5′), 7.33 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7′), 7.00 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6′), 4.52 (tt, *J* = 12.4, 4.0 Hz, 1H, H-4), 4.32 (br s, 2H, H-2, H-6), 2.87 (br s, 2H, H-2, H-6), 2.20 (dq, *J* = 12.5, 4.4 Hz, 2H, H-3, H-5), 1.87 (br d, *J* = 10.6 Hz, 2H, H-3, H-5), 1.51 [s, 9H, OC(CH$_3$)$_3$]; MS *m/z* 493.2 (MH$^+$, 100%). CDI (1.09 g, 6.7 mmol) was added to a stirred solution of carboxylate (1.78 g, 6.1 mmol) in MeCN (150 mL) at 20 °C and the mixture was stirred for 24 h. The solvent was evaporated and the residue was partitioned between CHCl$_3$ (100 mL) and water (100 mL). The organic fraction was washed with sequentially water (2 × 50 mL), brine (50 mL) and dried. The solvent was evaporated and the residue purified by column chromatography, eluting with a gradient (0–3%) of MeOH/DCM, to give *tert*-butyl 4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate (**S1f**) (1.91 g, 98%) as a white powder which was used directly. A solution of HCl in dioxane (4 M, 8 mL) was added to a stirred solution of carboxylate (1.91 g, 6.08 mmol) and the mixture was stirred at 20 °C for 16 h before being chilled at 0 °C for 16 h. The resulting precipitate was filtered and washed with DCM (5 mL) and dried to give piperidine **S1d** (1.41 g, 81%) as the dihydrochloride salt: ^{1}H NMR [(CD$_3$)$_2$SO] δ 11.64 (br s, 1H), 9.11–9.13 (m, 1H), 8.90–8.92 (m, 1H), 7.93 (dd, *J* = 5.3, 1.1 Hz, 1H), 7.77 (dd, *J* = 7.9, 1.1Hz, 1 H), 7.04 (dd, *J* = 7.9, 5.3 Hz, 1H), 4.52–4.61 (m, 1H), 3.40 (br d, *J* = 12.4 Hz, 2H), 3.03–3.12 (m, 2H), 2.54–2.64 (m, 2H), 1.87 (br d, *J* = 12.4 Hz, 2H); MS *m/z* 219.5 (MH$^+$, 100%). The mother liquor was concentrated and chilled to give a second crop of dihydrochloride (0.23 g, 13%), spectroscopically identical to the first sample.

***N*-[5-(3-Fluorophenyl)-1-methyl-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (S1).** Prepared using Method C from amine **S1c** and piperidine **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give urea **S1** (62 mg, 33%) as a white powder: mp (MeOH/DCM) 279–282 °C; ^{1}H NMR [(CD$_3$)$_2$SO] δ 9.79 (br s, 1H, CONH), 8.53 (d, *J* = 2.4 Hz, 1H, H-6″), 8.07 (br s, 1H, CONH), 8.04 (dd, *J* = 5.3, 1.2 Hz, 1H, H-5′), 7.35 (dt, *J* = 8.0, 6.0 Hz, 1H, H-5‴), 7.32 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7′), 7.28 (ddd, *J* = 7.8, 1.6, 1.0 Hz, 1H, H-4‴), 7.17–7.22 (m, 2H, H-4″, H-2‴), 7.02 (ddt, *J* = 8.4, 2.5, 0.9 Hz, 1H, H-6‴), 6.98 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6′), 4.60 (tt, *J* = 12.5, 4.2 Hz, 1H, H-4), 4.38 (br d, *J* = 13.8 Hz, 2H, H-2, H-6), 3.70 (s, 3H, NCH$_3$), 3.10 (br t, *J* = 12.5 Hz, 2H, H-2, H-6), 2.30 (dq, *J* = 12.5, 4.2 Hz, 2H, H-3, H-5), 1.99 (br d, *J* = 12.5 Hz, 2H, H-3, H-5); MS *m/z* 463.6 (MH$^+$, 100%). Anal. calcd for C$_{24}$H$_{23}$FN$_6$O$_3$·¾CH$_3$OH: C, 61.10; H, 5.39; N, 17.27. Found: C, 61.21; H, 5.27; N, 17.07%.

SN34395 N-(1-Methyl-2-oxo-5-phenyl-1,2-dihydro-3-pyridinyl)-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidinecarboxamide (**S2**).

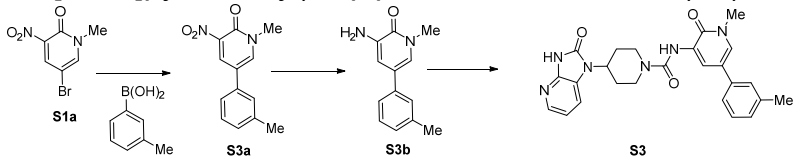


1-Methyl-3-nitro-5-phenyl-2(1*H*)-pyridinone (S2a). Prepared using Method A from **S1a** and phenylboronic acid. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give nitropyridinone **S2a** (346 mg, 81%) as a yellow powder: mp (EtOAc/pet. ether) 216–218 °C; ^{1}H NMR δ 8.60 (d, *J* = 2.7 Hz, 1H, H-6), 7.90 (d, *J* = 2.7 Hz, 1H, H-4), 7.38–7.50 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 3.77 (s, 3H, NCH_3); MS *m/z* 231.5 (MH^+, 100%). Anal. calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.51; H, 4.38; N, 12.22%.

3-Amino-1-methyl-5-phenyl-2(1*H*)-pyridinone (S2b). Prepared using Method B from **S2a**. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give aminopyridinone **S2b** (252 mg, 90%) as a white powder: mp (EtOAc/pet. ether) 161–162 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.45 (br dd, *J* = 8.1, 1.4 Hz, 1H, H-2′, H-6′), 7.39 (br dd, *J* = 8.1, 7.4 Hz, 1H, H-3′, H-5′), 7.31 (d, *J* = 2.4 Hz, 1H, H-6), 7.27 (tt, *J* = 7.3, 1.2 Hz, 1H, H-4′), 6.80 (d, *J* = 2.4 Hz, 1H, H-4), 5.22 (br s, 2H, NH_2), 3.52 (s, 3H, NCH_3); MS *m/z* 201.5 (MH^+, 100%). Anal. calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.23; H, 6.11; N, 14.08%.

***N*-(1-Methyl-2-oxo-5-phenyl-1,2-dihydro-3-pyridinyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (S2).** Prepared using Method C from **S2b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give urea **S2** (196 mg, 79%) as a white powder: mp (MeOH/DCM) 247–249 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.73 (br s, 1H, CONH), 8.55 (d, *J* = 2.4 Hz, 1H, H-6″), 8.07 (br s, 1H, CONH), 8.04 (dd, *J* = 5.3, 1.2 Hz, 1H, H-5′), 7.50 (br d, *J* = 7.0 Hz, 2H, H-2‴, H-6‴), 7.41 (br dd, *J* = 7.8, 7.0 Hz, 2H, H-3‴, H-5‴), 7.30–7.35 (m, 2H, H-7′, H-4‴), 7.17 (d, *J* = 2.4 Hz, 1H, H-4″), 6.98 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6′), 4.61 (tt, *J* = 12.5, 4.2 Hz, 1H, H-4), 4.38 (br d, *J* = 13.7 Hz, 2H, H-2, H-6), 3.70 (s, 3H, NCH_3), 3.09 (br t, *J* = 12.5 Hz, 2H, H-2, H-6), 2.30 (dq, *J* = 12.7, 4.2 Hz, 2H, H-3, H-5), 1.98 (br d, *J* = 12.7 Hz, 2H, H-3, H-5); MS *m/z* 445.7 (MH^+, 100%). Anal. calcd for $C_{24}H_{24}N_6O_3 \cdot ½CH_3OH$: C, 63.90; H, 5.69; N, 18.25. Found: C, 64.18; H, 5.64; N, 18.26%.

SN34397 N-[1-Methyl-5-(3-methylphenyl)-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidinecarboxamide (**S3**).

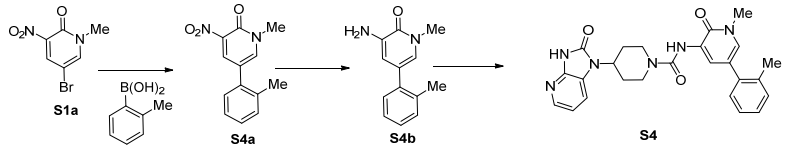


1-Methyl-5-(3-methylphenyl)-3-nitro-2(1*H*)-pyridinone (S3a). Prepared using Method A from **S1a** and 3-methylphenylboronic acid. The crude solid was purified by column chromatography, eluting with a gradient (60–80%) of EtOAc/pet. ether, to give nitropyridinone **S3a** (290 mg, 80%) as a yellow powder: mp (EtOAc/pet. ether) 171–173 °C; ^{1}H NMR δ 8.59 (d, *J* = 2.7 Hz, 1H, H-6), 7.89 (d, *J* = 2.7 Hz, 1H, H-4), 7.35 (br dd, *J* = 7.8, 7.5 Hz, 1H, H-5′), 7.20–7.25 (m, 3H, H-2′, H-4′, H-6′), 3.77 (s, 3H, NCH_3), 2.42 (s, 3H, 3′-CH_3); MS *m/z* 245.4 (MH^+, 100%). Anal. calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.06; H, 4.85; N, 11.50%.

3-Amino-5-(3-methylphenyl)-1-methyl-2(1*H*)-pyridinone (S3b). Prepared using Method B from **S3a**. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give aminopyridinone **S3b** (212 mg, 88%) as a white powder: mp (EtOAc/pet. ether) 111–113 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.24–7.31 (m, 4H, H-6, H-2′, H-4′, H-5′), 7.08 (br d, *J* = 6.3 Hz, 1H, H-6′), 6.78 (d, *J* = 2.3 Hz, 1H, H-4), 5.19 (br s, 2H, NH_2), 3.51 (s, 3H, NCH_3), 2.34 (s, 3H, 3′-CH_3); MS *m/z* 215.5 (MH^+, 100%). Anal. calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 73.04; H, 6.57; N, 12.92%.

***N*-[5-(3-Methylphenyl)-1-methyl-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (S3).** Prepared using Method C from **S3b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give urea **S3** (128 mg, 33%) as a white powder: mp (MeOH/EtOAc) 240–242 °C; ^{1}H NMR δ 9.89 (br s, 1H, CONH), 8.54 (d, *J* = 2.4 Hz, 1H, H-6″), 8.08 (br s, 1H, CONH), 8.05 (dd, *J* = 5.3, 1.2 Hz, 1H, H-5′), 7.27–7.35 (m, 4H, H-7′, H-2‴, H-4‴, H-5‴), 7.13–7.18 (m, 2H, H-4″, H-6‴), 6.98 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6′), 4.62 (tt, *J* = 12.4, 4.2 Hz, 1H, H-4), 4.39 (br d, *J* = 13.8 Hz, 2H, H-2, H-6), 3.70 (s, 3H, NCH_3), 3.10 (br t, *J* = 12.5 Hz, 2H, H-2, H-6), 2.36 (s, 3H, 3‴-CH_3), 2.30 (dq, *J* = 12.7, 4.2 Hz, 2H, H-3, H-5), 1.98 (br d, *J* = 12.2 Hz, 2H, H-3, H-5); MS *m/z* 459.6 (MH^+, 100%). Anal. calcd for $C_{25}H_{26}N_6O_3 \cdot ¼EtOAc$: C, 64.99; H, 5.87; N, 17.49. Found: C, 65.10; H, 5.98; N, 17.63%.

SN34422 N-[1-Methyl-5-(2-methylphenyl)-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)-1-piperidinecarboxamide (**S4**).

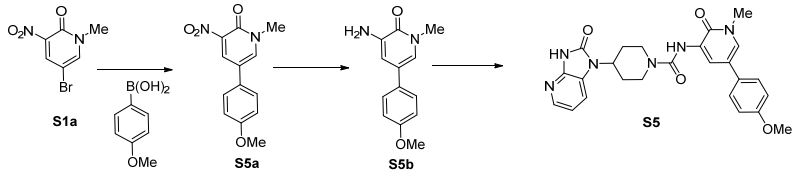


1-Methyl-5-(2-methylphenyl)-3-nitro-2(1*H*)-pyridinone (S4a). Prepared using Method A from **S1a** and 2-methylphenylboronic acid. The crude solid was purified by column chromatography, eluting with a gradient (50–80%) of EtOAc/pet. ether, to give nitropyridinone **S4a** (314 mg, 90%) as a yellow powder: mp (EtOAc/pet. ether) 197–199 °C; ^{1}H NMR δ 8.34 (d, *J* = 2.6 Hz, 1H, H-6), 7.65 (d, *J* = 2.6 Hz, 1H, H-4), 7.25–7.35 (m, 3H, H-4′, H-5′, H-6′), 7.17 (br dd, *J* = 7.4, 0.8 Hz, 1H, H-3′), 3.74 (s, 3H, NCH_3), 2.32 (s, 3H, 2′-CH_3); MS *m/z* 245.4 (MH^+, 100%). Anal. calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.72; H, 4.95; N, 11.44%.

3-Amino-5-(2-methylphenyl)-1-methyl-2(1*H*)-pyridinone (S4b). Prepared using Method B from **S4a**. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give aminopyridinone **S4b** (236 mg, 92%) as a white powder: mp (EtOAc/pet. ether) 122–125 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.14–7.26 (m, 4H, H-2′, H-4′, H-5′, H-6′), 6.89 (d, *J* = 2.3 Hz, 1H, H-6), 6.46 (d, *J* = 2.3 Hz, 1H, H-4), 5.15 (br s, 2H, NH_2), 3.48 (s, 3H, NCH_3), 2.26 (s, 3H, 2′-CH_3); MS *m/z* 215.5 (MH^+, 100%). Anal. calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.67; H, 6.76; N, 12.90%.

***N*-[5-(2-Methylphenyl)-1-methyl-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (S4).** Prepared using Method C from **S4c** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–6%) of MeOH/DCM, to give urea **S4** (109 mg, 25%) as a white powder: mp (MeOH/EtOAc) 262–264 °C; ^{1}H NMR δ 9.93 (br s, 1 H, CONH), 8.25 (d, *J* = 2.2 Hz, 1H, H-6″), 8.06 (br s, 1H, CONH), 8.04 (dd, *J* = 5.3, 1.2 Hz, 1H, H-5′), 7.31 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7′), 7.18–7.27 (m, 4H, H-3‴, H-4‴, H-5‴, H-6‴), 6.98 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6′), 6.90 (d, *J* = 2.2 Hz, 1H, H-4″), 4.60 (tt, *J* = 12.4, 4.2 Hz, 1H, H-4), 4.37 (br d, *J* = 13.8 Hz, 2H, H-2, H-6), 3.68 (s, 3H, NCH_3), 3.08 (br dd, *J* = 12.5, 11.7 Hz, 2H, H-2, H-6), 2.35 (s, 3H, 2‴-CH_3), 2.28 (dq, *J* = 12.7, 4.2 Hz, 2H, H-3, H-5), 1.97 (br d, *J* = 12.6 Hz, 2H, H-3, H-5); MS *m/z* 459.6 (MH^+, 100%). Anal. calcd for $C_{25}H_{26}N_6O_3 \cdot ¼CH_3OH$: C, 64.00; H, 5.83; N, 18.01. Found: C, 65.08; H, 5.83; N, 17.72%.

SN34427 *N*-[5-(4-Methoxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S5**).



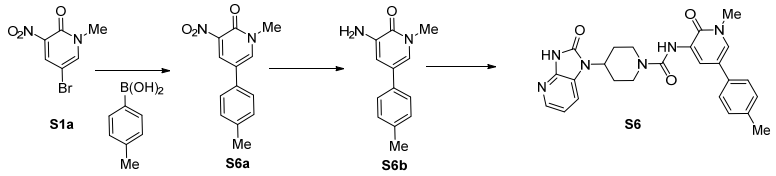
5-(4-Methoxyphenyl)-1-methyl-3-nitro-2(1*H*)-pyridinone (S5a). Prepared using Method A from **S1a** and 4-methoxyphenylboronic acid. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give nitropyridinone **S5a** (293 mg, 86%) as orange needles: mp (EtOAc/pet. ether) 191–192 °C; ^{1}H NMR δ 8.54 (d, *J* = 2.7 Hz, 1H, H-6), 7.83 (d, *J* = 2.7 Hz, 1H, H-4), 7.35 (ddd, *J* = 8.9, 3.1, 2.2 Hz, 2H, H-2′, H-6′), 6.99 (ddd, *J* = 8.9, 3.1, 2.2 Hz, 2H, H-3′, H-5′), 3.86 (s, 3H, 4′-OCH_3), 3.78 (s, 3H, NCH_3); MS *m/z* 261.4 (MH^+, 100%). Anal. calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 60.04; H, 4.63; N, 10.86%.

3-Amino-5-(4-methoxyphenyl)-1-methyl-2(1*H*)-pyridinone (S5b). Prepared using Method B from **S5a**. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give aminopyridinone **S5b** (215 mg, 86%) as a white powder: mp (EtOAc/pet. ether) 202–204 °C; ^{1}H NMR δ 7.39 (ddd, *J* = 8.8, 3.1, 2.1 Hz, 2H, H-2′, H-6′), 7.21 (d, *J* = 2.4 Hz, 1H, H-6), 6.96 (ddd, *J* = 8.8, 3.1, 2.2 Hz, 2H, H-3′, H-5′), 6.76 (d, *J* = 2.4 Hz, 1H, H-4), 5.18 (br s, 2H, NH_2), 3.76 (s, 3H, OCH_3), 3.50 (s, 3H, NCH_3); MS *m/z* 231.5 (MH^+, 100%). Anal. calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.73; H, 6.24; N, 12.22%.

***N*-[5-(4-Methoxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S5).** Prepared using Method C from **S5b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give urea **S5** (191 mg, 69%) as a white powder: mp (MeOH/DCM) 261–264 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.81 (br s, 1H, CONH), 8.52 (d, *J* = 2.3 Hz, 1H, H-6″), 8.09 (br s, 1H, CONH), 8.06 (dd, *J* = 5.3, 1.2 Hz, 1H, H-5′), 7.43 (ddd, *J* = 8.9, 3.0, 2.1 Hz, 2H, H-2‴, H-6‴), 7.33 (dd, *J* = 7.9, 1.3

Hz, 1H, H-7′), 7.12 (d, *J* = 2.3 Hz, 1H, H-4″), 7.00 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6′), 6.95 (ddd, *J* = 8.9, 3.0, 2.1 Hz, 2H, H-3‴, H-5‴), 4.60 (tt, *J* = 12.5, 4.2 Hz, 1H, H-4), 4.38 (br d, *J* = 13.8 Hz, 2H, H-2, H-6), 3.86, (s, 3H, 4‴-OCH_3), 3.70 (s, 3H, NCH_3), 3.10 (br dd, *J* = 12.5, 11.7 Hz, 2H, H-2, H-6), 2.31 (dq, *J* = 12.7, 4.2 Hz, 2H, H-3, H-5), 1.99 (br dd, *J* = 12.1, 2.2 Hz, 2H, H-3, H-5); MS *m/z* 475.5 (MH^+, 100%). Anal. calcd for $C_{25}H_{26}N_6O_4 \cdot ½CH_3OH$: C, 62.44; H, 5.75; N, 17.13. Found: C, 62.51; H, 5.60; N, 17.31%.

SN34428 *N*-[5-(4-Methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S6**).

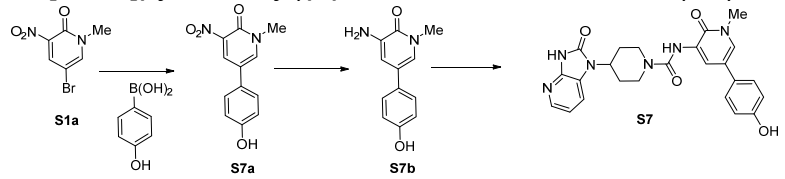


5-(4-Methylphenyl)-1-methyl-3-nitro-2(1*H*)-pyridinone (S6a). Prepared using Method A from **S1a** and 4-methylphenylboronic acid. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give nitropyridinone **S6a** (242 mg, 74%) as a yellow powder: mp (EtOAc/pet. ether) 250–252 °C; ^{1}H NMR δ 8.58 (d, *J* = 2.7 Hz, 1H, H-6), 7.86 (d, *J* = 2.7 Hz, 1H, H-4), 7.32 (br d, *J* = 8.3 Hz, 2H, H-2′, H-6′), 7.27 (br d, *J* = 8.3 Hz, 2H, H-3′, H-5′), 3.76 (s, 3H, NCH_3), 2.40 (s, 3H, 4′-CH_3); MS *m/z* 215.4 (MH^+, 100%). Anal. calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.06; H, 4.92; N, 11.41%.

3-Amino-5-(4-methylphenyl)-1-methyl-2(1*H*)-pyridinone (S6b). Prepared using Method B from **S6a**. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give aminopyridinone **S6b** (166 mg, 90%) as a purple oil: ^{1}H NMR [$(CD_3)_2SO$] δ 7.36 (br d, *J* = 8.0 Hz, 2H, H-2′, H-6′), 7.27 (d, *J* = 2.4 Hz, 1H, H-6), 7.20 (br d, *J* = 8.0 Hz, 2H, H-3′, H-5′), 6.78 (d, *J* = 2.4 Hz, 1H, H-4), 5.19 (br s, 2H, NH_2), 3.51 (s, 3H, NCH_3), 2.40 (s, 3H, 4′-CH_3); MS *m/z* 215.5 (MH^+, 100%).

***N*-[5-(4-Methylphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S6).** Prepared using Method C from **S6b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give urea **S6** (137 mg, 42%) as a white powder: mp (MeOH/DCM) 267–270 °C; ^{1}H NMR δ 9.41 (br s, 1H, CONH), 8.53 (d, *J* = 2.4 Hz, 1H, H-6″), 8.07 (br s, 1H, CONH), 8.04 (dd, *J* = 5.3, 1.2 Hz, 1H, H-5′), 7.39 (br d, *J* = 8.1 Hz, 2H, H-2‴, H-6‴), 7.32 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7′), 7.21 (br d, *J* = 8.0 Hz, 2H, H-3‴, H-5‴), 7.15 (d, *J* = 2.4 Hz, 1H, H-4″), 6.98 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6′), 4.61 (tt, *J* = 12.5, 4.2 Hz, 1H, H-4), 4.38 (br d, *J* = 12.9 Hz, 2H, H-2, H-6), 3.70 (s, 3H, NCH_3), 3.10 (br dd, *J* = 12.5, 11.6 Hz, 2H, H-2, H-6), 2.38 (s, 3H, 4‴-CH_3), 2.30 (dq, *J* = 12.6, 4.2 Hz, 2H, H-3, H-5), 1.98 (br d, *J* = 12.2 Hz, 2H, H-3, H-5); MS *m/z* 459.5 (MH^+, 100%). Anal. calcd for $C_{25}H_{26}N_6O_3$: C, 65.49; H, 5.72; N, 18.33. Found: C, 65.54; H, 5.75; N, 18.27%.

SN34434 *N*-[5-(4-Hydroxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S7**).

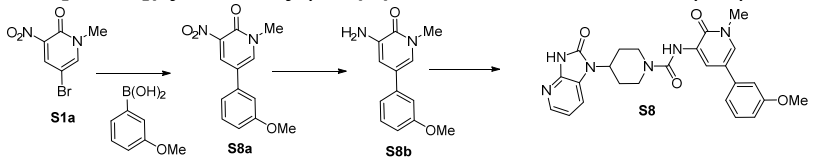


5-(4-Hydroxyphenyl)-1-methyl-3-nitro-2(1*H*)-pyridinone (S7a). Prepared using Method A from **S1a** and 4-hydroxyphenylboronic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give nitropyridinone **S7a** (266 mg, 82%) as an orange powder: mp (EtOAc/pet. ether) 256–257 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.62 (s, 1H, OH), 8.60 (d, *J* = 2.7 Hz, 1H, H-6), 8.54 (d, *J* = 2.7 Hz, 1H, H-4), 7.46 (ddd, *J* = 8.6, 3.0, 2.0 Hz, 2H, H-2′, H-6′), 6.84 (ddd, *J* = 8.6, 3.0, 2.0 Hz, 2H, H-3′, H-5′), 3.63 (s, 3H, NCH_3); MS *m/z* 247.4 (MH^+, 100%). Anal. calcd for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.79; H, 4.04; N, 11.26%.

3-Amino-5-(4-hydroxyphenyl)-1-methyl-2(1*H*)-pyridinone (S7b). Prepared using Method B from **S7a**. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give aminopyridinone **S7b** (217 mg, 98%) as a white powder: mp (MeOH/CH_2Cl_2) 231–232 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.41 (s, 1H, OH), 7.25 (ddd, *J* = 8.6, 3.0, 2.0 Hz, 2H, H-2′, H-6′), 7.15 (d, *J* = 2.4 Hz, 1H, H-6), 6.78 (ddd, *J* = 8.6, 3.0, 3.0 Hz, 2H, H-3′, H-5′), 6.72 (d, *J* = 2.4 Hz, 1H, H-4), 5.15 (br s, 2H, NH_2), 3.49 (s, 3H, NCH_3); MS *m/z* 217.5 (MH^+, 100%). Anal. calcd for $C_{12}H_{12}N_2O_2 \cdot 1/3CH_2Cl_2$: C, 61.26; H, 5.14; N, 11.29. Found: C, 61.16; H, 5.14; N, 11.88%.

***N*-[5-(4-Hydroxyphenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S7).** Prepared using Method C using **S7b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–6%) of MeOH/DCM, to give urea **S7** (206 mg, 83%) as a white powder: mp (MeOH/DCM) 234–238 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (br s, 1H, CONH), 9.50 (br s, 1H, OH), 8.31 (d, *J* = 2.4 Hz, 1H, H-6″), 8.07 (br s, 1H, CONH), 7.90 (dd, *J* = 5.2, 1.3 Hz, 1H, H-5′), 7.57–7.61 (m, 2H, H-7′, H-4″), 7.34 (ddd, *J* = 8.7, 2.9, 2.1 Hz, 2H, H-2‴, H-6‴), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 6.83 (ddd, *J* = 8.7, 2.9, 2.1 Hz, 2H, H-3‴, H-5‴), 4.43 (tt, *J* = 12.2, 4.0 Hz, 1H, H-4), 4.17 (br d, *J* = 13.3 Hz, 2H, H-2, H-6), 3.58 (s, 3H, NCH_3), 3.04 (br t, *J* = 12.1 Hz, 2H, H-2, H-6), 2.25 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3, H-5), 1.80 (br d, *J* = 12.5 Hz, 2H, H-3, H-5); MS *m/z* 461.5 (MH^+, 100%). HRMS calcd for $C_{24}H_{25}N_6O_4$ (MH^+) *m/z* 461.1932. Found 461.1943 (-2.5 ppm).

SN34439 *N*-[5-(3-Methoxyphenyl)-1-methyl-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (**S8**).



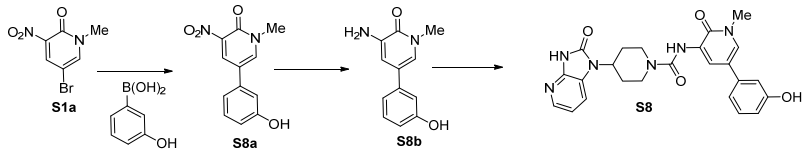
1-Methyl-5-(3-methoxyphenyl)-3-nitro-2(1*H*)-pyridinone (S8a). Prepared using Method A from **S1a** and 3-methoxyphenylboronic acid. The crude solid was purified by

column chromatography, eluting with 50% EtOAc/pet. ether, to give nitropyridinone **S8a** (386 mg, 86%) as a yellow powder: mp (EtOAc/pet. ether) 182–184 °C; ^{1}H NMR δ 8.59 (d, *J* = 2.7 Hz, 1H, H-6), 7.89 (d, *J* = 2.7 Hz, 1H, H-4), 7.38 (dd, *J* = 8.9, 7.7 Hz, 1H, H-5′), 7.00 (ddd, *J* = 7.6, 1.7, 0.8 Hz, 1H, H-6′), 6.92–6.96 (m, 2H, H-2′, H-4′), 3.87 (s, 3H, OCH_3), 3.77 (s, 3H, NCH_3); MS *m/z* 261.5 (MH^+, 100%). Anal. calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 60.26; H, 4.64; N, 10.79%.

3-Amino-1-methyl-5-(3-methoxyphenyl)-2(1*H*)-pyridinone (S8b). Prepared using Method B from **S8a**. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give aminopyridinone **S8b** (292 mg, 91%) as a gum: ^{1}H NMR [$(CD_3)_2SO$] δ 7.34 (d, *J* = 2.4 Hz, 1H, H-6), 7.30 (dd, *J* = 8.2, 7.7 Hz, 1H, H-5′), 7.04 (ddd, *J* = 7.7, 1.6, 1.0 Hz, 1H, H-6′), 7.01 (dd, *J* = 2.3, 1.6 Hz, 1H, H-2′), 6.84 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H, H-4′), 6.80 (d, *J* = 2.4 Hz, 1H, H-4), 5.19 (br s, 2H, NH_2), 3.79 (s, 3H, OCH_3), 3.51 (s, 3H, NCH_3); MS *m/z* 231.5 (MH^+, 100%). Anal. calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.92; H, 6.37; N, 12.03%.

***N*-[5-(3-Methoxyphenyl)-1-methyl-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (S8).** Prepared using Method C from **S8b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give urea **S8** (145 mg, 44%) as a white powder: mp (MeOH/DCM) 283–286 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.55 (br s, 1H, CONH), 8.37 (d, *J* = 2.4 Hz, 1H, H-6″), 8.08 (br s, 1H, CONH), 7.90 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.78 (d, *J* = 2.4 Hz, 1H, H-4″), 7.59 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7′), 7.36 (t, *J* = 8.0 Hz, 1H, H-5‴), 7.10 (br d, *J* = 7.7 Hz, 1H, H-6‴), 7.08 (dd, *J* = 2.4, 1.7 Hz, 1H, H-2‴), 6.98 (dd, *J* = 7.9, 5.2 Hz, 1H, H-6′), 6.90 (ddd, *J* = 8.2, 2.4, 1.6 Hz, 1H, H-4‴), 4.43 (tt, *J* = 12.5, 4.0 Hz, 1H, H-4), 4.18 (br d, *J* = 13.4 Hz, 2H, H-2, H-6), 3.82 (s, 3H, OCH_3), 3.61 (s, 3H, NCH_3), 3.05 (br t, *J* = 12.3 Hz, 2H, H-2, H-6), 2.25 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3, H-5), 1.81 (br d, *J* = 12.5 Hz, 2H, H-3, H-5); MS *m/z* 475.6 (MH^+, 100%). Anal. calcd for $C_{25}H_{26}N_6O_4 \cdot H_2O$: C, 60.97; H, 5.73; N, 17.06. Found: C, 61.06; H, 5.45; N, 16.92%.

SN34440 *N*-[5-(3-Hydroxyphenyl)-1-methyl-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (**S9**).

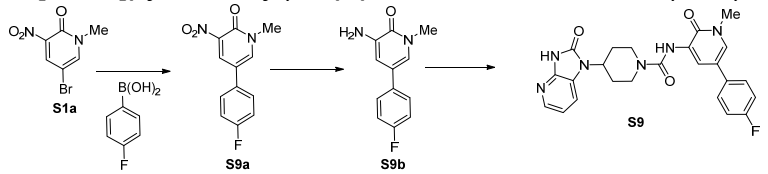


1-Methyl-5-(3-hydroxyphenyl)-3-nitro-2(1*H*)-pyridinone (S9a). Prepared using Method A from **S1a** and 3-hydroxyphenylboronic acid. The crude solid was purified by column chromatography, eluting with a gradient of 80–100% EtOAc/pet. ether, to give nitropyridinone **S9a** (244 mg, 64%) as an orange powder: mp (EtOAc/pet. ether) 272–275 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.60 (br s, 1H, OH), 8.61–8.63 (m, 2H, H-4, H-6), 7.25 (t, *J* = 7.9 Hz, 1H, H-5′), 7.06 (ddd, *J* = 7.7, 1.8, 0.9 Hz, 1H, H-4′), 7.00 (t, *J* = 2.0 Hz, 1H, H-2′), 6.77 (ddd, *J* = 8.0, 2.4, 0.8 Hz, 1H, H-6′), 3.65 (s, 3H, NCH_3); MS *m/z* 268.6 (MH^+, 100%). Anal. calcd for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.81; H, 4.79; N, 11.27%.

3-Amino-1-methyl-5-(3-hydroxyphenyl)-2(1*H*)-pyridinone (S9b). Prepared using Method B from **S9a**. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give aminopyridinone **S9b** (95 mg, 97%) as a gum: ^{1}H NMR [$(CD_3)_2SO$] δ 9.43 (s, 1H, OH), 7.24 (d, *J* = 2.4 Hz, 1H, H-6), 7.17 (d, *J* = 7.9 Hz, 1H, H-5′), 6.89 (ddd, *J* = 7.7, 1.6, 0.9 Hz, 1H, H-4′), 6.84 (d, *J* = 2.0 Hz, 1H, H-2′), 6.74 (d, *J* = 2.4 Hz, 1H, H-4), 6.67 (ddd, *J* = 8.0, 2.4, 0.9 Hz, 1H, H-6′), 5.21 (br s, 2H, NH_2), 3.50 (s, 3H, NCH_3); MS *m/z* 268.5 (MH^+, 100%). Anal. calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.42; H, 5.68; N, 12.87%.

***N*-[5-(3-Hydroxyphenyl)-1-methyl-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (S9).** Prepared using Method C from **S9b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–6%) of MeOH/DCM, to give urea **S9** (32 mg, 20%) as a pink powder: mp (MeOH/DCM) 189–192 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.58 (br s, 1H, CONH), 9.70 (s, 1H, OH), 8.36 (d, *J* = 2.4 Hz, 1H, H-6″), 8.09 (br s, 1H, CONH), 7.90 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.70 (d, *J* = 2.4 Hz, 1H, H-4″), 7.59 (dd, *J* = 7.9, 1.1 Hz, 1H, H-7′), 7.23 (t, *J* = 7.9 Hz, 1H, H-5‴), 6.95–7.00 (m, 2H, H-6′, H-4‴), 6.93 (t, *J* = 2.0 Hz, 1H, H-2‴), 6.70–6.74 (m, 1H, H-6‴), 4.44 (tt, *J* = 12.5, 4.0 Hz, 1H, H-4), 4.18 (br d, *J* = 13.3 Hz, 2H, H-2, H-6), 3.60 (s, 3H, NCH_3), 3.05 (br dd, *J* = 12.5, 12.0 Hz, 2H, H-2, H-6), 2.25 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3, H-5), 1.80 (br d, *J* = 12.5 Hz, 2H, H-3, H-5); MS *m/z* 461.6 (MH^+, 100%). Anal. calcd for $C_{24}H_{24}N_6O_4 \cdot ¼CH_3OH$: C, 60.96; H, 5.73; N, 17.06. Found: C, 60.69; H, 5.34; N, 16.65%.

SN34442 *N*-[5-(4-Fluorophenyl)-1-methyl-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (**S10**).

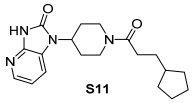


1-Methyl-5-(4-fluorophenyl)-3-nitro-2(1*H*)-pyridinone (S10a). Prepared using Method A from **S1a** and 4-fluorophenylboronic acid. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give nitropyridinone **S10a** (291 mg, 43%) as a yellow powder: mp (EtOAc/pet. ether) 280–282 °C; ^{1}H NMR δ 8.54 (d, *J* = 2.7 Hz, 1H, H-6), 7.84 (d, *J* = 2.7 Hz, 1H, H-4), 7.37–7.42 (m, 2H, H-2′, H-6′), 7.14–7.20 (m, 2H, H-3′, H-5′), 3.77 (s, 3H, NCH_3); MS *m/z* 249.5 (MH^+, 100%). Anal. calcd for $C_{12}H_9FN_2O_3$: C, 58.07; H, 3.65; N, 11.29. Found: C, 58.42; H, 3.47; N, 11.34%.

3-Amino-1-methyl-5-(4-fluorophenyl)-2(1*H*)-pyridinone (S10b). Prepared using Method B from **S10a**. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give aminopyridinone **S10b** (148 mg, 84%) as a tan powder: mp (EtOAc/pet. ether) 140–142 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.47–7.52 (m, 2H, H-2′, H-6′), 7.30 (d, *J* = 2.4 Hz, 1H, H-6), 7.20–7.26 (m, 2H, H-3′, H-5′), 6.76 (d, *J* = 2.4 Hz, 1H, H-4), 5.23 (br s, 2H, NH_2), 3.51 (s, 3H, NCH_3); MS *m/z* 219.5 (MH^+, 100%). Anal. calcd for $C_{12}H_{11}FN_2O$: C, 66.05; H, 5.08; N, 12.84. Found: C, 66.08; H, 4.95; N, 12.86%.

***N*-[5-(4-Fluorophenyl)-1-methyl-2-oxo-1,2-dihydro-3-pyridinyl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (S10).** Prepared using Method C using **S10b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give urea **S10** (77 mg, 26%) as a cream powder: mp (MeOH/DCM) 268–271 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (br s, 1H, CONH), 8.34 (d, *J* = 2.4 Hz, 1H, H-6″), 8.10 (s, 1H, CONH), 7.90 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.74 (d, *J* = 2.4 Hz, 1H, H-4″), 7.54–7.60 (m, 3H, H-7′, H-2‴, H-6‴), 7.28 (ddd, *J* = 8.8, 2.2, 2.0 Hz, 2H, H-3‴, H-5‴), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 4.44 (tt, *J* = 12.3, 4.0 Hz, 1H, H-4), 4.18 (br d, *J* = 13.1 Hz, 2H, H-2, H-6), 3.60 (s, 3H, NCH_3), 3.05 (br dd, *J* = 12.5, 11.8 Hz, 2H, H-2, H-6), 2.25 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3, H-5), 1.80 (br d, *J* = 12.5 Hz, 2H, H-3, H-5); MS *m/z* 463.6 (MH^+, 100%). Anal. calcd for $C_{24}H_{23}FN_6O_3 \cdot ¼EtOAc$: C, 61.98; H, 5.20; N, 17.34. Found: C, 61.88; H, 5.19; N, 17.16%.

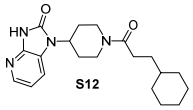
SN34491 1-(1-(3-Cyclopentylpropanoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S11**).



S11

1-(1-(3-Cyclopentylpropanoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S11). Prepared using Method D from 3-cyclopentylpropanoic acid and piperidine **S1d**. The crude solid was purified by column chromatography, eluting with EtOAc, to give amide **S11** (234 mg, 95%) as a white foam: mp 112–115 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.54 (s, 1H, CONH), 7.89 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H, H-7), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6), 4.58 (br d, *J* = 12.8 Hz, 1H, H-2′, H-6′), 4.41 (tt, *J* = 12.3, 4.0 Hz, 1H, H-4′), 4.01 (br d, *J* = 12.8 Hz, 1H, H-2′, H-6′), 3.15 (br dd, *J* = 12.6, 11.8 Hz, 1H, H-2′, H-6′), 2.62 (br dd, *J* = 12.6, 11.8 Hz, 1H, H-2′, H-6′), 2.37 (t, *J* = 7.9 Hz, 2H, $COCH_2$), 2.20 (dq, *J* = 12.5, 4.0 Hz, 1H, H-3′, H-5′), 2.04 (dq, *J* = 12.4, 4.0 Hz, 1H, H-3′, H-5′), 1.70–1.80 (m, 5H, H-3′, H-5′, CH, CH_2), 1.46–1.58 (m, 6H, 3 × CH_2), 1.05–1.12 (m, 2H, CH_2); MS *m/z* 343.4 (MH^+, 100%). Anal. calcd for $C_{19}H_{26}N_4O_2$: C, 66.64; H, 7.65; N, 16.36. Found: C, 66.24; H, 7.87; N, 16.04%.

SN34496 1-(1-(3-Cyclohexylpropanoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S12**).

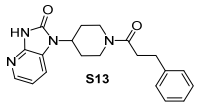


S12

1-(1-(3-Cyclohexylpropanoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (12). Prepared using Method D from **S1d** and 3-cyclohexylpropanoic acid. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give amide **S12** (286 mg, 95%) as a tan foam: mp 200–203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.60 (s, 1H, CONH), 7.89 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 7.55 (dd, *J* = 7.8, 1.2 Hz, 1H, H-7), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6), 4.57 (br d, *J* = 13.1 Hz, 1H, H-2′, H-6′), 4.41 (tt, *J* = 12.3, 4.0 Hz, 1H, H-4′), 4.02 (br d, *J* = 12.8 Hz, 1H, H-2′, H-6′), 3.15 (br dd, *J* = 12.6, 11.8 Hz, 1H, H-2′, H-6′), 2.62 (br dd, *J* = 12.6, 11.8 Hz, 1H, H-2′, H-6′), 2.37 (dd, *J* = 8.0, 7.7 Hz, 2H, $COCH_2$), 2.19 (dq, *J* = 12.5, 4.0 Hz, 1H, H-3′, H-5′), 2.04 (dq, *J* = 12.5, 4.0 Hz, 1H, H-3′, H-5′), 1.62–1.80 (m, 7H, H-3′, H-5′, CH, 2 × CH_2), 1.38–1.43 (m,

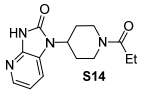
2H, CH_2), 1.10–1.28 (m, 4H, 2 × CH_2), 0.85–0.92 (m, 2H, CH_2); MS *m/z* 357.2 (MH^+, 100%). Anal. calcd for $C_{20}H_{28}N_4O_2$: C, 67.39; H, 7.92; N, 15.72. Found: C, 65.52; H, 8.07; N, 15.63%.

SN34498 1-(1-(3-Phenylpropanoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S13**).



1-(1-(3-Phenylpropanoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S13). Prepared using Method D from **S1d** and 3-phenylpropanoic acid. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give amide **S13** (286 mg, 95%) as a white powder: mp 257–260 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.50 (s, 1H, CONH), 7.90 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 7.50 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7), 7.25–7.30 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.16–7.21 (m, 1H, H-4″), 6.99 (dd, *J* = 7.9, 5.2 Hz, 1H, H-6), 4.59 (br d, *J* = 13.3 Hz, 1H, H-2′, H-6′), 4.41 (tt, *J* = 12.2, 4.0 Hz, 1H, H-4′), 4.02 (br d, *J* = 15.3 Hz, 1H, H-2′, H-6′), 3.10 (br t, *J* = 12.4 Hz, 1H, H-2′, H-6′), 2.86 (t, *J* = 7.4 Hz, 2H, CH_2), 2.60–2.75 (m, 3H, CH_2, H-2′, H-6′), 2.12 (dq, *J* = 12.4, 4.2 Hz, 1H, H-3′, H-5′), 2.02 (dq, *J* = 12.4, 4.2 Hz, 1H, H-3′, H-5′), 1.73 (br d, *J* = 11.8 Hz, 2H, H-3′, H-5′); MS *m/z* 351.2 (MH^+, 100%). Anal. calcd for $C_{20}H_{22}N_4O_2$: C, 68.55; H, 6.33; N, 15.99. Found: C, 68.20; H, 6.36; N, 15.88%.

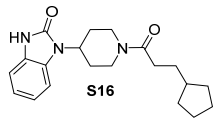
SN34499 1-(1-Propionylpiperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S14**).



1-(1-Propionylpiperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S14). Prepared using Method D from **S1d** and propionic acid. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give pyridinone **S14** (91 mg, 24%) as a cream powder: mp 187–190 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.55 (s, 1H, CONH), 7.89 (dd, *J* = 5.2, 1.3 Hz, 1H, H-5), 7.57 (dd, *J* = 7.9, 1.3 Hz, 1H, H-7), 6.98 (dd, *J* = 7.9, 5.2 Hz, 1H, H-6), 4.58 (br d, *J* = 13.1 Hz, 1H, H-2′, H-6′), 4.41 (tt, *J* = 12.2, 4.0 Hz, 1H, H-4′), 4.02 (br d, *J* = 15.3 Hz, 1H, H-2′, H-6′), 3.10 (br dd, *J* = 12.8, 11.7 Hz, 1H, H-2′, H-6′), 2.63 (br dd, *J* = 12.6, 11.5 Hz, 1H, H-2′, H-6′), 2.38 (dt, *J* = 7.4, 2.6 Hz, 2H, CH_2), 2.21 (dq, *J* = 12.5, 4.0 Hz, 1H, H-3′, H-5′), 2.05 (dq, *J* = 12.5, 4.2 Hz, 1H, H-3′, H-5′), 1.73 (br dd, *J* = 12.4, 11.7 Hz, 2H, H-3′, H-5′), 1.01 (t, *J* = 7.4 Hz, 3H, CH_3); MS *m/z* 275.2 (MH^+, 100%). Anal. calcd for $C_{14}H_{18}N_4O_2$: C, 61.30; H, 6.61; N, 20.42. Found: C, 61.61; H, 6.77; N, 20.19%.

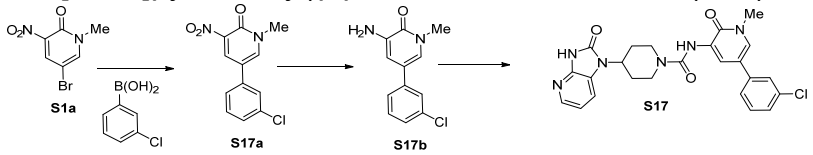
SN34807 *N*-(Furan-2-ylmethyl)-4-(2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)piperidine-1-carboxamide (**S15**) was obtained from Enamine.

SN34816 1-[1-(3-Cyclopentylpropanoyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**S16**).



1-[1-(3-Cyclopentylpropanoyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (S16). Prepared using Method D from 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one and 3-cyclopentylpropanoic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzimidazolone **S16** (633 mg, 89%) as a cream powder: mp (EtOAc/pet. ether) 166–168 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.23 (s, 1H, CONH), 7.05–7.12 (m, 4H, H-4, H-5, H-6, H-7), 4.90 (br d, *J* = 13.6 Hz, 1H, H-2′, H-6′), 4.55 (tt, *J* = 12.4, 4.2 Hz, 1H, H-4′), 4.07 (br d, *J* = 13.6 Hz, 1H, H-2′, H-6′), 3.20 (br dd, *J* = 12.9, 11.5 Hz, 1H, H-2′, H-6′), 2.68 (br dd, *J* = 12.9, 11.5 Hz, 1H, H-2′, H-6′), 2.43 (dd, *J* = 7.5, 6.3 Hz, 2H, $COCH_2$), 2.32 (dq, *J* = 12.6, 4.2 Hz, 2H, H-3′, H-5′), 1.80 (br dd, *J* = 12.9, 12.2 Hz, 2H, H-3′, H-5′), 1.76–1.85 (m, 3H, CH, CH_2), 1.60–1.73 (m, 2H, CH_2), 1.58–1.63 (m, 2H, CH_2), 1.48–1.56 (m, 2H, CH_2), 1.10–1.19 (m, 2H, CH_2); MS *m/z* 342.4 (MH^+, 100%). Anal. calcd for $C_{20}H_{27}N_3O_2$: C, 70.35; H, 7.97; N, 12.31. Found: C, 70.32; H, 7.71; N, 12.22%.

SN34817 *N*-(5-(3-Chlorophenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S17).



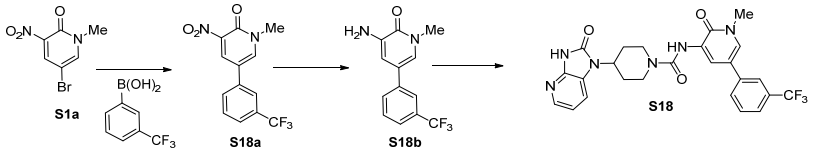
5-(3-Chlorophenyl)-1-methyl-3-nitropyridin-2(1*H*)-one (S17a). Prepared using Method A from **S1a** and 3-chlorophenylboronic acid. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give nitropyridinone **S17a** (351 mg, 72%) as a yellow powder: mp (EtOAc/pet. ether) 189–191 °C; ^{1}H NMR δ 8.77 (d, *J* = 2.8 Hz, 1H, H-6), 8.74 (d, *J* = 2.8 Hz, 1H, H-4), 7.80 (t, *J* = 1.9 Hz, 1H, H-2′), 7.65 (ddd, *J* = 7.8, 1.8, 1.1 Hz, 1H, H-4′), 7.49 (t, *J* = 7.9 Hz, 1H, H-5′), 7.42 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 1H, H-6′), 3.65 (s, 3H, NCH_3); MS *m/z* 265.2 (MH^+, 100%).

3-Amino-5-(3-chlorophenyl)-1-methylpyridin-2(1*H*)-one (S17b). Prepared using Method B from **S17a**. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give aminopyridinone **S17b** (223 mg, 74%) as a gum: ^{1}H NMR [$(CD_3)_2SO$] δ 7.53–7.56 (m, 1H, H-4), 7.41–7.45 (m, 3H, H-2′, H-4′, H-5′), 7.32 (dt, *J* = 7.1, 2.0 Hz, 1H, H-6′), 6.81 (d, *J* = 2.5 Hz, 1H, H-6), 5.23 (br s, 2H, NH_2), 3.51 (s, 3H, NCH_3); MS *m/z* 235.2 (MH^+, 100%).

***N*-(5-(3-Chlorophenyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S17).** Prepared using Method C from **S17b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give urea **S17** (96 mg, 48%) as a white powder: mp (MeOH/EtOAc) 271–274 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (br s, 1H, CONH), 8.37 (d, *J* = 2.5 Hz, 1H, H-6″), 8.10 (br s, 1H, CONH), 7.89 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.87 (d, *J* = 2.5 Hz, 1H, H-4″), 7.61 (d, *J* = 1.7 Hz, 1H, H-2‴), 7.58 (dd,

J = 7.9, 1.3 Hz, 1H, H-7′), 7.51 (dd, *J* = 7.8, 1.6 Hz, 1H, H-4‴), 7.47 (t, *J* = 7.8 Hz, 1H, H-5‴), 7.38 (dt, *J* = 7.5, 1.8 Hz, 1H, H-6‴), 6.69 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 4.43 (tt, *J* = 12.2, 4.0 Hz, 1H, H-4), 4.18 (br d, *J* = 13.4 Hz, 2H, H-2, H-6), 3.61 (s, 3H, NCH_3), 3.05 (br dd, *J* = 12.5, 11.7 Hz, 2H, H-2, H-6), 2.24 (dq, *J* = 12.4, 4.0 Hz, 2H, H-3, H-5), 1.80 (br d, *J* = 11.9 Hz, 2H, H-3, H-5); MS *m/z* 479.2 (MH^+, 100%). Anal. calcd for $C_{24}H_{23}ClN_6O_3 \cdot ¼EtOAc$: C, 59.94; H, 5.03; N, 16.78. Found: C, 59.96; H, 4.91; N, 17.10%.

SN34848 *N*-(1-Methyl-2-oxo-5-(3-(trifluoromethyl)phenyl)-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S18**).

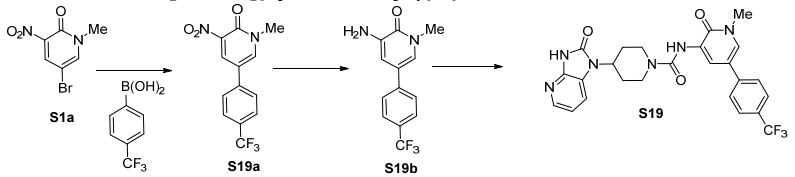


1-Methyl-3-nitro-5-(3-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (S18a). Prepared using Method A from **S1a** and 3-trifluoromethylphenylboronic acid. The crude solid was purified by column chromatography, eluting with 60% EtOAc/pet. ether, to give nitropyridinone **S18a** (473 mg, 86%) as a yellow solid: ^{1}H NMR [$(CD_3)_2SO$] δ 8.84 (d, *J* = 2.8 Hz, 1H, H-6), 8.80 (d, *J* = 2.8 Hz, 1H, H-4), 8.07 (br s, 1H, H-2′), 7.97–8.01 (m, 1H, H-4′), 7.67–7.73 (m, 2H, H-5′, H-6′), 3.65 (s, 3H, NCH_3); MS *m/z* 265.2 (MH^+, 100%).

3-Amino-1-methyl-5-(3-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (S18b). Prepared using Method B from **S18a**. The crude solid was purified by column chromatography, eluting with 60% EtOAc/pet. ether, to give aminopyridinone **S18b** (249 mg, 93%) as a gum: ^{1}H NMR [$(CD_3)_2SO$] δ 7.77–7.82 (m, 2H, H-2′, H-4′), 7.60–7.67 (m, 2H, H-5′, H-6′), 7.49 (d, *J* = 2.5 Hz, 1H, H-6), 6.85 (d, *J* = 2.5 Hz, 1H, H-4), 5.26 (br s, 2H, NH_2), 3.53 (s, 3H, NCH_3); MS *m/z* 269.2 (MH^+, 100%).

***N*-(1-Methyl-2-oxo-5-(3-(trifluoromethyl)phenyl)-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S18).** Prepared using Method C from **S18b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give urea **S18** (110 mg, 57%) as a white powder: mp (MeOH/EtOAc) 273–276 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (br s, 1H, CONH), 8.40 (d, *J* = 2.5 Hz, 1H, H-6″), 8.11 (br s, 1H, CONH), 7.95 (d, *J* = 2.5 Hz, 1H, H-4″), 7.90 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.82–7.86 (m, 2H, H-2‴, H-4‴), 7.65–7.72 (m, 2H, H-5‴, H-6‴), 7.58 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7′), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 4.43 (tt, *J* = 12.3, 4.0 Hz, 1H, H-4), 4.20 (br d, *J* = 13.1 Hz, 2H, H-2, H-6), 3.62 (s, 3H, NCH_3), 3.05 (br dd, *J* = 12.8, 11.5 Hz, 2H, H-2, H-6), 2.24 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3, H-5), 1.80 (br d, *J* = 10.2 Hz, 2H, H-3, H-5); MS *m/z* 513.2 (MH^+, 100%). Anal. calcd for $C_{25}H_{23}F_3N_6O_3$: C, 58.59; H, 4.52; N, 16.40. Found: C, 58.76; H, 4.63; N, 16.00%.

SN34849 *N*-(1-Methyl-2-oxo-5-(4-(trifluoromethyl)phenyl)-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S19**).



1-Methyl-3-nitro-5-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (S19a). Prepared using Method A from **S1a** and 4-trifluoromethylphenylboronic acid. The crude solid was purified by column chromatography, eluting with 60% EtOAc/pet. ether, to give nitropyridinone **S19a** (450 mg, 82%) as a yellow solid; ^{1}H NMR δ 8.81 (br s, 2H, H-4, H-6), 7.91 (br d, *J* = 8.2 Hz, 2H, H-3′, H-5′), 7.82 (br d, *J* = 8.2 Hz, 2H, H-2′, H-6′), 3.67 (s, 3H, NCH_3); MS *m/z* 299.2 (MH^+, 100%).

3-Amino-1-methyl-5-(4-(trifluoromethyl)phenyl)pyridin-2(1*H*)-one (S19b). Prepared using Method B from **S19a**. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give aminopyridinone **S19b** (277 mg, 85%) as a gum: ^{1}H NMR [$(CD_3)_2SO$] δ 7.74 (br d, *J* = 8.5 Hz, 2H, H-3′, H-5′), 7.70 (br d, *J* = 8.5 Hz, 2H, H-2′, H-6′), 7.49 (d, *J* = 2.4 Hz, 1H, H-6), 6.85 (d, *J* = 2.4 Hz, 1H, H-4), 5.29 (br s, 2H, NH_2), 3.53 (s, 3H, NCH_3); MS *m/z* 269.2 (MH^+, 100%).

***N*-(1-Methyl-2-oxo-5-(4-(trifluoromethyl)phenyl)-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S19).** Prepared using Method C from **S19b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/EtOAc, to give urea **S19** (101 mg, 52%) as a white powder: mp (EtOAc) 279–282 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (br s, 1H, CONH), 8.44 (d, *J* = 2.5 Hz, 1H, H-6″), 8.11 (br s, 1H, CONH), 7.93 (d, *J* = 2.5 Hz, 1H, H-4″), 7.89 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.81 (br d, *J* = 8.7 Hz, 2H, H-3‴, H-5‴), 7.77 (br d, *J* = 8.7 Hz, 2H, H-2‴, H-6‴), 7.58 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7′), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 4.45 (tt, *J* = 12.3, 4.0 Hz, 1H, H-4), 4.20 (br d, *J* = 13.5 Hz, 2H, H-2, H-6), 3.63 (s, 3H, NCH_3), 3.05 (br dd, *J* = 12.4, 11.8 Hz, 2H, H-2, H-6), 2.25 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3, H-5), 1.80 (br d, *J* = 11.3 Hz, 2H, H-3, H-5); MS *m/z* 513.3 (MH^+, 100%). Anal. calcd for $C_{25}H_{23}F_3N_6O_3 \cdot ¼EtOAc$: C, 58.42; H, 4.71; N, 15.72. Found: C, 58.50; H, 4.72; N, 15.72%.

SN34857 4-(1*H*-Indol-3-yl)-*N*-(2-methylphenyl)piperidine-1-carboxamide (**S20**) was obtained from Enamine.

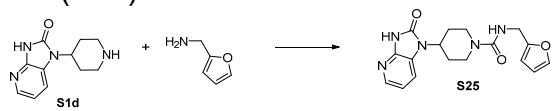
SN34860 3-(3-(2-Oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)propyl)-1,3-diazaspiro[4.4]nonane-2,4-dione (**S21**) was obtained from Enamine.

SN34927 1-(3-(5-Oxo-4-phenyl-4,5-dihydro-1*H*-tetrazol-1-yl)propyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (**S22**) was obtained from Enamine.

SN34929 1-(4-(Benzofuran-2-carbonyl)piperazin-1-yl)-2-cyclopentylethan-1-one (**S23**) was obtained from Enamine.

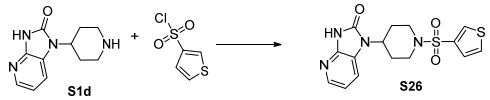
SN34931 (*R*)-*N*-(1,1-Dioxidotetrahydrothiophen-3-yl)-2-(4-(2-oxo-2,3-dihydro-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)acetamide (**S24**) was obtained from Enamine.

SN34964 *N*-(Furan-2-ylmethyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S25**).



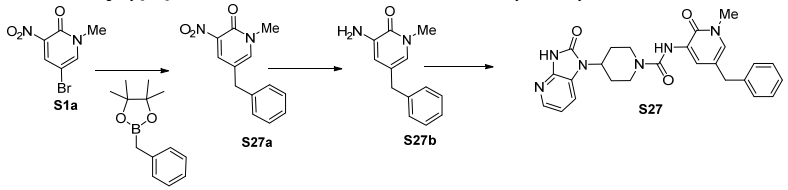
***N*-(Furan-2-ylmethyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S25).** Prepared using Method C from **S1d** and furan-2-ylmethanamine. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/EtOAc, to give urea **S25** (60 mg, 44%) as a white powder: mp (EtOAc) 242–245 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.50 (s, 1H, CONH), 7.89 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.54 (dd, *J* = 1.8, 0.8 Hz, 1H, H-5″), 7.44 (dd, *J* = 7.8, 1.3 Hz, 1H, H-7′), 7.08 (t, *J* = 5.6 Hz, 1H, CONH), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 6.38 (dd, *J* = 3.1, 1.8 Hz, 1H, H-4″), 6.20 (dd, *J* = 3.1, 0.7 Hz, 1H, H-3″), 4.36 (tt, *J* = 12.3, 4.0 Hz, 1H, H-4), 4.24 (d, *J* = 5.5 Hz, 2H, CH_2N), 4.13 (br d, *J* = 13.6 Hz, 2H, H-2, H-6), 2.82 (br dd, *J* = 12.5, 11.5 Hz, 2H, H-2, H-6), 2.10 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3, H-5), 1.68 (br d, *J* = 10.3 Hz, 2H, H-3, H-5); MS *m/z* 342.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{19}N_5O_3$: C, 59.81; H, 5.61; N, 20.52. Found: C, 59.79; H, 5.61; N, 20.39%.

SN34983 1-(1-(Thiophen-3-ylsulfonyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S26**).



1-(1-(Thiophen-3-ylsulfonyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S26). Thiophene-3-sulfonyl chloride (100 mg, 0.55 mmol) was added to a stirred solution of piperidine **S1d** (209 mg, 0.82 mmol) dry pyridine (10 mL) at 0 °C and the mixture was stirred at 20 °C for 16 h. The solvent was evaporated and the residue suspended in ice-cold water and stirred vigorously for 1 h. The resulting precipitate was filtered and washed with water (2 mL). The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/EtOAc, to give sulfonamide **S26** (68 mg, 34%) as a white powder: mp (EtOAc) 309–311 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.53 (s, 1H, CONH), 8.30 (dd, *J* = 3.0, 1.3 Hz, 1H, H-2″), 7.85–7.90 (m, 2H, H-5′, H-5″), 7.37–7.42 (m, 2H, H-7′, H-4″), 6.96 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 4.22 (tt, *J* = 12.2, 4.0 Hz, 1H, H-4), 3.82 (br d, *J* = 12.0 Hz, 2H, H-2, H-6), 2.54 (br dd, *J* = 12.4, 10.5 Hz, 2H, H-2, H-6), 2.30 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3, H-5), 1.77 (br d, *J* = 12.1 Hz, 2H, H-3, H-5); MS *m/z* 365.2 (MH^+, 100%). Anal. calcd for $C_{15}H_{16}N_4O_3S_2$: C, 49.43; H, 4.43; N, 15.37. Found: C, 49.43; H, 4.44; N, 15.37%.

SN34988 *N*-(5-Benzyl-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S27**).

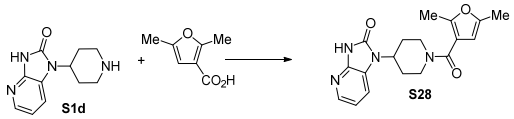


5-Benzyl-1-methyl-3-nitropyridin-2(1*H*)-one (S27a). Prepared using Method A from **S1a** and benzylboronic acid pinacol ester The crude solid was purified by column chromatography, eluting with 60% EtOAc/pet. ether, to give nitropyridinone **S27a** (85 mg, 19%) as a yellow solid: ^{1}H NMR [$(CD_3)_2SO$] δ 8.30 (d, *J* = 2.5 Hz, 1H, H-4), 8.23 (d, *J* = 2.5 Hz, 1H, H-6), 7.32 (br d, *J* = 8.2 Hz, 2H, H-2′, H-6′), 7.26–7.31 (m, 2H, H-3′, H-5′), 3.79 (s, 2H, CH_2), 3.55 (s, 3H, NCH_3); MS *m/z* 245.2 (MH^+, 100%).

3-Amino-5-benzyl-1-methylpyridin-2(1*H*)-one (S27b). Prepared using Method B from **S27a** The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give aminopyridinone **S27b** (108 mg, 82%) as a tan powder: mp (EtOAc/pet. ether) 160–162 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.28 (br dd, *J* = 7.5, 7.2 Hz, 2H, H-3′, H-5′), 7.16–7.22 (m, 3H, H-2′, H-4′, H-6′), 7.82 (d, *J* = 2.2 Hz, 1H, H-6), 6.23 (d, *J* = 2.2 Hz, 1H, H-4), 5.31 (br s, 2H, NH_2), 3.56 (s, 2H, CH_2), 3.41 (s, 3H, NCH_3); MS *m/z* 215.2 (MH^+, 100%).

***N*-(5-Benzyl-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S27).** Prepared using Method C using **S27b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/EtOAc, to give urea **S27** (139 mg, 98%) as a white powder: mp (EtOAc) 244–247 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.55 (s, 1H, CONH), 8.01 (s, 1H, CONH), 7.88 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.84 (d, *J* = 2.3 Hz, 1H, H-6″), 7.55 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7′), 7.31 (br dd, *J* = 7.5, 7.3 Hz, 2H, H-3‴, H-5‴), 7.27 (d, *J* = 2.3 Hz, 1H, H-4″), 7.18–7.25 (m, 3H, H-2‴, H-4‴, H-6‴), 6.96 (dd, *J* = 7.9, 5.2 Hz, 1H, H-6′), 4.00 (tt, *J* = 12.2, 4.0 Hz, 1H, H-4), 4.10 (br d, *J* = 13.6 Hz, 2H, H-2, H-6), 3.69 (s, 2H, CH_2), 3.50 (s, 3H, NCH_3), 3.00 (br dd, *J* = 12.5, 11.7 Hz, 2H, H-2, H-6), 2.19 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3, H-5), 1.75 (br d, *J* = 10.3 Hz, 2H, H-3, H-5); MS *m/z* 495.3 (MH^+, 100%); HRMS calcd for $C_{25}H_{27}N_6O_3$ (MH^+) *m/z* 459.2139. Found 459.2152 (-2.7 ppm).

SN34989 1-(1-(2,5-Dimethylfuran-3-carbonyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S28**).



1-(1-(2,5-Dimethylfuran-3-carbonyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S28). NEt_3 (0.80 mL, 5.71 mmol) was added dropwise to a stirred suspension of 2,5-dimethylfuran-3-carboxylic acid (200 mg, 1.43 mmol), EDCI (301 mg, 1.57 mmol), HOBT (212 mg, 1.57 mmol) and **S1d** (400 mg, 1.57 mmol) in dry DCM (50 mL) at 0 °C and the mixture was stirred at 20 °C for 16 h. The mixture was diluted with DCM (50 mL), washed with water (3 × 30 mL) and brine (30 mL) and then dried and the

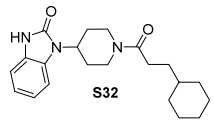
solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give carboxamide **S28** (261 mg, 54%) as a white powder: mp (EtOAc) 262–265 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.50 (s, 1H, CONH), 7.90 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 7.61 (dd, *J* = 7.8, 1.2 Hz, 1H, H-7), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6), 6.17 (s, 1H, H-4″), 4.50 (br s, 1H, H-2′, H-6′), 4.45 (tt, *J* = 12.2, 4.0 Hz, 1H, H-4′), 4.00 (br s, 1H, H-2′, H-6′), 3.13 (br s, 1H, H-2′, H-6′), 2.80 (br s, 1H, H-2′, H-6′), 2.29 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.17 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3′, H-5′), 1.77 (br d, *J* = 11.4 Hz, 2H, H-3′, H-5′); MS *m/z* 341.2 (MH^+, 100%); HRMS calcd for $C_{18}H_{20}N_4O_3$ (MH^+) *m/z* 341.1608. Found 341.1614 (-1.9 ppm).

SN35136 4-(3*H*-Imidazo[4,5-*b*]pyridin-3-yl)-*N*-(2-methylphenyl)piperidine-1-carboxamide (**S29**) was obtained from ChemDiv.

SN35138 4-(1*H*-Indol-3-yl)-*N*-phenyl-3,6-dihydropyridine-1(2*H*)-carboxamide (**S30**) was obtained from ChemDiv.

SN35139 *N*-(5-Chloro-2-methoxyphenyl)-4-(morpholinomethyl)piperidine-1-carboxamide (**S31**) was obtained from ChemDiv.

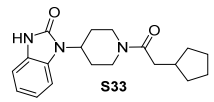
SN35145 1-[1-(3-Cyclohexylpropanoyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**S32**).



S32

1-[1-(3-Cyclohexylpropanoyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (S32). Prepared using Method D from 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one and cyclohexylpropionic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzimidazolone **S32** (460 mg, 90%) as a white foam: mp 77–80 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, CONH), 7.17–7.22 (m, 1H, H-7), 6.95–7.00 (m, 3H, H-4, H-5, H-6), 4.58 (br d, *J* = 12.8 Hz, 1H, H-2′, H-6′), 4.40 (tt, *J* = 12.2, 4.1 Hz, 1H, H-4′), 4.00 (br d, *J* = 12.9 Hz, 1H, H-2′, H-6′), 3.14 (br dd, *J* = 12.7, 11.7 Hz, 1H, H-2′, H-6′), 2.63 (br dd, *J* = 12.7, 11.7 Hz, 1H, H-2′, H-6′), 2.37 (dt, *J* = 7.5, 2.8 Hz, 2H, $COCH_2$), 2.25 (dq, *J* = 12.4, 4.1 Hz, 1H, H-3′, H-5′), 2.10 (dq, *J* = 12.4, 4.1 Hz, 1H, H-3′, H-5′), 1.58–1.74 (m, 7H, H-3′, H-5′, CH, 2 × CH_2), 1.42 (dt, *J* = 7.5, 7.4 Hz, 2 H, CH_2), 1.10–1.24 (m, 4H, 2 × CH_2), 0.84–0.92 (m, 2H, CH_2); MS *m/z* 356.4 (MH^+, 100%). Anal. calcd for $C_{21}H_{29}N_3O_2$: C, 70.95; H, 8.22; N, 11.82. Found: C, 70.70; H, 8.26; N, 11.53%.

SN35147 1-[1-(Cyclopentylacetyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**S33**).

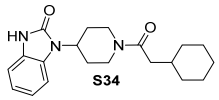


S33

1-[1-(3-Cyclopentylacetyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (S33). Prepared using Method D from 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one and cyclopentylacetic acid. The crude solid was purified by column chromatography, eluting

with EtOAc, to give benzimidazolone **S33** (502 mg, 74%) as a white powder: mp (EtOAc/pet. ether) 173–175 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, CONH), 7.17–7.22 (m, 1H, H-7), 6.92–6.98 (m, 3H, H-4, H-5, H-6), 4.57 (br d, *J* = 13.0 Hz, 1H, H-2′, H-6′), 4.39 (tt, *J* = 12.2, 4.1 Hz, 1H, H-4′), 4.02 (br d, *J* = 13.0 Hz, 1H, H-2′, H-6′), 3.14 (br dd, *J* = 12.8, 11.7 Hz, 1H, H-2′, H-6′), 2.63 (br dd, *J* = 12.9, 11.7 Hz, 1H, H-2′, H-6′), 2.39 (d, *J* = 7.1 Hz, 2 H, $COCH_2$), 2.06–2.31 (m, 3H, H-3′, H-5′, CH), 1.67–1.82 (m, 4 , H-3′, H-5′, CH_2), 1.56–1.63 (m, 2H, CH_2), 1.45–1.54 (m, 2H, CH_2), 1.08–1.20 (m, 2H, CH_2); MS *m/z* 328.4 (MH^+, 100%). Anal. calcd for $C_{19}H_{25}N_3O_2$: C, 69.70; H, 7.70; N, 12.83. Found: C, 69.76; H, 7.74; N, 12.71%.

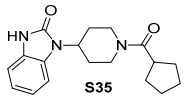
SN35148 1-[1-(Cyclohexylacetyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**S34**).



S34

1-[1-(3-Cyclohexylacetyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (S34). Prepared using Method D from 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one and cyclohexylacetic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzimidazolone **S34** (658 mg, 93%) as a white foam: mp (EtOAc/pet. ether) 85–88 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, CONH), 7.14–7.19 (m, 1H, H-7), 6.95–6.98 (m, 3H, H-4, H-5, H-6), 4.58 (br d, *J* = 13.2 Hz, 1H, H-2′, H-6′), 4.40 (tt, *J* = 12.2, 4.1 Hz, 1H, H-4′), 4.02 (br d, *J* = 13.2 Hz, 1H, H-2′, H-6′), 3.15 (br dd, *J* = 12.7, 11.7 Hz, 1H, H-2′, H-6′), 2.62 (br dd, *J* = 12.6, 11.0 Hz, 1H, H-2′, H-6′), 2.16–2.30 (m, 3H, H-3′, H-5′, $COCH_2$), 2.10 (dq, *J* = 12.2, 4.2 Hz, 1H, H-3′, H-5′), 1.57–1.75 (m, 7H, CH, 3 × CH_2), 1.10–1.24 (m, 4H, 2 × CH_2), 0.90–1.00 (m, 2H, CH_2); MS *m/z* 342.4 (MH^+, 100%). Anal. calcd for $C_{20}H_{27}N_3O_2 \cdot ¼EtOAc$: C, 69.39; H, 8.04; N, 11.56. Found: C, 69.50; H, 7.98; N, 11.93%.

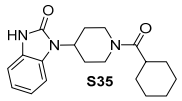
SN35149 1-[1-(Cyclopentylcarbonyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**S35**).



S35

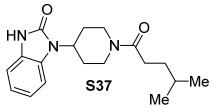
1-[1-(Cyclopentylcarbonyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (S35). Prepared using Method D from 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one and cyclopentanecarboxlic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzimidazolone **S35** (593 mg, 94%) as a white foam: mp (EtOAc/pet. ether) 91–94 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, CONH), 7.17–7.21 (m, 1H, H-7), 6.95–7.00 (m, 3H, H-4, H-5, H-6), 4.59 (br d, *J* = 13.3 Hz, 1H, H-2′, H-6′), 4.41 (tt, *J* = 12.2, 4.1 Hz, 1H, H-4′), 4.13 (br d, *J* = 13.9 Hz, 1H, H-2′, H-6′), 3.15 (br dd, *J* = 12.9, 12.2 Hz, 1H, H-2′, H-6′), 3.00–3.07 (m, 1H, COCH), 2.65 (br dd, *J* = 13.0, 11.0 Hz, 1H, H-2′, H-6′), 2.23 (dq, *J* = 12.5, 4.1 Hz, 1H, H-3′, H-5′), 2.11 (dq, *J* = 12.7, 4.1 Hz, 1H, H-3′, H-5′), 1.50–1.83 (m, 10H, H-3′, H-5′, 4 × CH_2); MS *m/z* 314.4 (MH^+, 100%). Anal. calcd for $C_{18}H_{23}N_3O_2 \cdot ⅛EtOAc$: C, 68.36; H, 7.47; N, 12.83. Found: C, 68.65; H, 7.70; N, 12.87%.

SN35150 1-[1-(Cyclohexylcarbonyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**S36**).



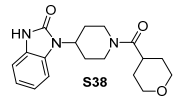
1-[1-(Cyclohexylcarbonyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (S36). Prepared using Method D from 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one and cyclohexylcarboxylic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzimidazolone **S36** (560 mg, 83%) as a white powder: mp (EtOAc/pet. ether) 200–203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, CONH), 7.16–7.20 (m, 1H, H-7), 6.95–7.00 (m, 3H, H-4, H-5, H-6), 4.58 (br d, *J* = 12.0 Hz, 1H, H-2′, H-6′), 4.40 (tt, *J* = 12.2, 4.1 Hz, 1H, H-4′), 4.09 (br d, *J* = 12.1 Hz, 1H, H-2′, H-6′), 3.15 (br dd, *J* = 12.8, 12.0 Hz, 1H, H-2′, H-6′), 2.57–2.67 (m, 2H, H-2′, H-6′, COCH), 2.23 (dq, *J* = 12.2, 4.1 Hz, 1H, H-3′, H-5′), 2.09 (dq, *J* = 12.2, 4.1 Hz, 1H, H-3′, H-5′), 1.60–1.79 (m, 8H, H-3′, H-5′, 3 × CH_2), 1.25–1.44 (m, 4H, 2 × CH_2); MS *m/z* 328.4 (MH^+, 100%). Anal. calcd for $C_{19}H_{25}N_3O_2$: C, 69.70; H, 7.70; N, 12.83. Found: C, 69.96; H, 7.71; N, 13.01%.

SN35155 1-[1-(4-Methylpentanoyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**S37**).



1-[1-(4-Methylpentanoyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (S37). Prepared using Method D from 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one and 4-methylpentanoic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzimidazolone **S37** (292 mg, 90%) as a white powder: mp (EtOAc/pet. ether) 168–170 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, CONH), 7.18–7.23 (m, 1H, H-7), 6.95–7.00 (m, 3H, H-4, H-5, H-6), 4.58 (br d, *J* = 13.3 Hz, 1H, H-2′, H-6′), 4.40 (tt, *J* = 12.2, 4.1 Hz, 1H, H-4′), 4.02 (br d, *J* = 13.3 Hz, 1H, H-2′, H-6′), 3.16 (br dd, *J* = 12.7, 11.6 Hz, 1H, H-2′, H-6′), 2.63 (br dd, *J* = 12.8, 11.0 Hz, 1H, H-2′, H-6′), 2.36 (dd, *J* = 8.0, 7.7 Hz, 2H, $COCH_2$), 2.27 (dq, *J* = 12.2, 4.1 Hz, 1H, H-3′, H-5′), 2.10 (dq, *J* = 12.2, 4.1 Hz, 1H, H-3′, H-5′), 1.64–1.74 (m, 2H, H-3′, H-5′), 1.56 (sept, *J* = 6.6 Hz, 1H, CH), 1.41 (dt, *J* = 7.7, 6.6 Hz, 2H, CH_2), 0.89 (d, *J* = 6.6 Hz, 6H, 2 × CH_3); MS *m/z* 316.5 (MH^+, 100%). Anal. calcd for $C_{18}H_{25}N_3O_2$: C, 68.54; H, 7.99; N, 13.32. Found: C, 68.67; H, 8.10; N, 13.38%.

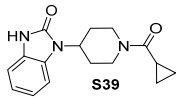
SN35156 1-[1-(Tetrahydro-2*H*-pyran-4-ylcarbonyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**S38**).



1-[1-(Tetrahydro-2*H*-pyran-4-ylcarbonyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (S38). Prepared using Method D from 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one and tetrahydropyrancarboxylic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzimidazolone **S38** (21 mg, 6%) as a tan gum: ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, CONH), 7.18–7.22 (m, 1H, H-7), 6.95–7.00 (m, 3H, H-4, H-5, H-6), 4.58 (br d, *J* = 13.0 Hz, 1H, H-2′, H-6′), 4.41 (tt, *J* =

12.2, 4.1 Hz, 1H, H-4′), 4.15 (br d, *J* = 13.0 Hz, 1H, H-2′, H-6′), 3.80–3.90 (m, 2H, CH_2O), 3.40 (br dd, *J* = 13.4, 11.6 Hz, 2H, CH_2O), 3.18 (br dd, *J* = 13.3, 11.3 Hz, 1H, H-2′, H-6′), 2.85–2.89 (m, 1H, COCH), 2.63 (br t, *J* = 12.4 Hz, 1H, H-2′, H-6′), 2.23 (dq, *J* = 12.2, 4.2 Hz, 1H, H-3′, H-5′), 2.10 (dq, *J* = 12.2, 4.2 Hz, 1H, H-3′, H-5′), 1.65–1.80 (m, 2H, H-3′, H-5′), 1.52–1.60 (m, 4H, 2 × CH_2); MS *m/z* 330.4 (MH^+, 100%).

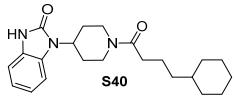
SN35157 1-[1-(Cyclopropylcarbonyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**S39**).



S39

1-[1-(Cyclopropylcarbonyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (S39). Cyclopropanecarbonyl chloride (100 μL 1.10 mmol) was added dropwise to a stirred solution of 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one (218 mg, 1.00 mmol) and iPr_2NEt (209 μL, 1.20 mmol) in dry DCM (10 mL) at 20 °C and the solution was stirred for 16 h. The mixture was diluted with DCM (50 mL), washed sequentially with saturated aqueous $KHCO_3$ solution (30 mL), 1 M HCl solution (30 mL), water (30 mL), and brine (30 mL) and then dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzimidazolone **S39** (203 mg, 71%) as a tan gum: mp (EtOAc/pet. ether) 207–209 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, CONH), 7.18–7.22 (m, 1H, H-7), 6.96–7.01 (m, 3H, H-4, H-5, H-6), 4.56 (br d, *J* = 13.0 Hz, 1H, H-2′, H-6′), 4.35–4.50 (m, 2H, H-2′, H-6′, H-4′), 3.17–3.25 (m, 1H, H-2′, H-6′), 2.65–2.70 (m, 1H, H-2′, H-6′), 2.25–2.35 (m, 1H, H-3′, H-5′), 2.10–2.20 (m, 1H, H-3′, H-5′), 2.04 (p, *J* = 6.3 Hz, 1H, COCH), 1.64–1.73 (m, 2H, H-3′, H-5′), 0.68–0.72 (m, 4H, 2 × CH_2); MS *m/z* 286.3 (MH^+, 100%). Anal. calcd for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.73. Found: C, 67.25; H, 6.74; N, 14.67%.

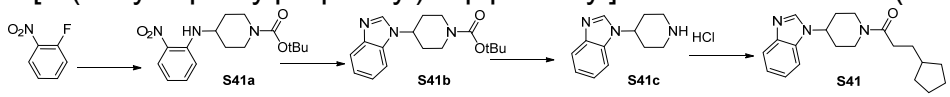
SN35160 1-[1-(4-Cyclohexylbutanoyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**S40**).



S40

1-[1-(4-Cyclohexylbutanoyl)-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (S40). Prepared using Method D from 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one and cyclohexylbutanoic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzimidazolone **S40** (467 mg, 97%) as a white foam: ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, CONH), 7.17–7.21 (m, 1H, H-7), 6.94–6.99 (m, 3H, H-4, H-5, H-6), 4.58 (d, *J* = 13.6 Hz, 1H, H-2′, H-6′), 4.40 (tt, *J* = 12.2, 4.1 Hz, 1H, H-4′), 4.00 (br d, *J* = 13.4 Hz, 1H, H-2′, H-6′), 3.15 (br dd, *J* = 12.8, 11.7 Hz, 1H, H-2′, H-6′), 2.63 (br dd, *J* = 12.7, 11.1 Hz, 1H, H-2′, H-6′), 2.33 (dt, *J* = 8.0, 7.4 Hz, 2H, $COCH_2$), 2.24 (dq, *J* = 12.4, 4.2 Hz, 1H, H-3′, H-5′), 2.10 (dq, *J* = 12.4, 4.2 Hz, 1H, H-3′, H-5′), 1.60–1.76 (m, 7H, H-3′, H-5′, CH, 2 × CH_2), 1.53 (br pent, *J* = 7.5 Hz, 2H, CH_2), 1.10–1.27 (m, 6H, 3 × CH_2), 0.81–0.90 (m, 2H, CH_2); MS *m/z* 370.6 (MH^+, 100%). Anal. calcd for $C_{22}H_{31}N_3O_2$: C, 71.51; H, 8.46; N, 11.37. Found: C, 71.36; H, 8.68; N, 11.20%.

SN35174 1-[1-(3-Cyclopentylpropanoyl)-4-piperidinyl]-1*H*-benzimidazole (**S41**).



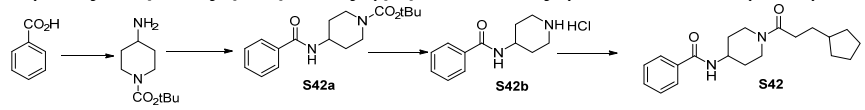
***tert*-Butyl 4-(2-Nitroanilino)-1-piperidinecarboxylate (S41a).** Prepared using Method E from 2-fluoronitrobenzene and *tert*-butyl 4-aminopiperidine-1-carboxylate. The residue was purified by column chromatography, eluting with 20% EtOAc/ pet. ether, to give carbamate **S41a** (9.10 g, 99%) as a white powder: mp (EtOAc/pet. ether) 75–77 °C (lit. [2] mp 88.5–89 °C); ^{1}H NMR δ 8.19 (dd, *J* = 8.6, 1.7 Hz, 1H, H-3′), 8.10 (br d, *J* = 7.3 Hz, 1H, NH), 7.40–7.57 (m, 1H, H-5′), 6.87 (d, *J* = 8.5 Hz, 1H, H-6′), 6.66 (ddd, *J* = 8.6, 7.0, 1.2 Hz, 1H, H-4′), 4.03 (br d, *J* = 11.2 Hz, 2H, H-2, H-6), 3.60–3.70 (m, 1H, H-4), 3.06 (br t, *J* = 11.2 Hz, 2H, H-2, H-6), 2.10–2.10 (m, 2H, H-3, H-5), 1.50–1.62 (m, 2H, H-3, H-5), 1.48 [s, 9H, C(CH_3)$_3$]; MS *m/z* 222.4 (MH^+-CO_2tBu, 100%).

***tert*-Butyl 4-(1*H*-Benzimidazol-1-yl)-1-piperidinecarboxylate (S41b).** A mixture of carbamate **S41a** (1.05 g, 3.27 mmol), Pd/C (50 mg), CH(OCH_3)$_3$ (3.6 mL, 32.7 mmol) and PPTS (82 mg, 0.33 mmol) in EtOAc (50 mL) was stirred under H_2 (50 psi) for 6 h. The mixture was filtered through a pad of diatomaceous earth and the pad was washed with EtOAc (50 mL). The solvent was evaporated and the residue was purified by column chromatography, eluting with 50% EtOAc/ pet. ether, to give carbamate **S41b** (0.47 g, 47%) as a colourless gum; ^{1}H NMR δ 7.97 (s, 1H, H-2′), 7.80–7.84 (m, 1H, H-5′), 7.40–7.43 (m, 1H, H-6′), 7.26–7.38 (m, 2H, H-4′, H-7′), 4.30–4.39 (m, 3H, H-2, H-4, H-6), 2.93 (br t, *J* = 12.4 Hz, 2H, H-2, H-6), 2.18 (br d, *J* = 12.4 Hz, 2H, H-3, H-5), 2.02 (dq, *J* = 14.4, 4.4 Hz, 2H, H-3, H-5), 1.50 [s, 9H, C(CH_3)$_3$]; MS *m/z* 302.4 (MH^+, 100%).

1-(4-Piperidinyl)-1*H*-benzimidazole Hydrochloride (S41c). Prepared using Method F from carbamate **S41b** to give piperidine hydrochloride **S41c** (370 mg, 100%) as a white powder: mp (MeOH) 295–298 °C; ^{1}H NMR [(CD_3)$_2$SO] δ 9.62 (s, 1H, H-2), 9.39–9.46 (m, 2H, NH·HCl), 8.20–8.24 (m, 1H, H-5), 7.86–7.90 (m, 1H, H-6), 7.58–7.64 (m, 2H, H-4, H-7), 5.03 (tt, *J* = 11.8, 4.0 Hz, 1H, H-4′), 3.48 (br d, *J* = 12.4 Hz, 2H, H-2′, H-6′), 3.01–3.10 (m, 2H, H-2′, H-6′), 2.44 (dq, *J* = 12.4, 4.4 Hz, 2H, H-3′, H-5′), 2.33 (br d, *J* = 11.4 Hz, 2H, H-3′, H-5′); MS *m/z* 202.4 (MH^+, 100%).

1-[1-(3-Cyclopentylpropanoyl)-4-piperidinyl]-1*H*-benzimidazole (S41). Prepared using Method D using **S41c** and 3-cyclopentylpropanoic acid. The crude solid was purified by column chromatography, eluting with a gradient (0–20%) of MeOH/EtOAc, to give benzimidazole **S41** (175 mg, 46%) as a white foam: ^{1}H NMR [(CD_3)$_2$SO] δ 8.34 (s, 1H, H-2), 7.63–7.69 (m, 2H, H-4, H-7), 7.26 (ddd, *J* = 7.8, 7.2, 1.2 Hz, 1H, H-5), 7.20 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H, H-6), 4.57–4.70 (m, 3H, H-2′, H-4′, H-6′), 4.05 (br d, *J* = 13.2 Hz, 2H, H-2′, H-6′), 3.23 (br dd, *J* = 12.2, 11.6 Hz, 1H, H-3′, H-5′), 2.73 (br dd, *J* = 12.5, 11.0 Hz, 1H, H-3′, H-5′), 2.35–2.39 (m, 2H, COCH), 1.92–2.10 (m, 3H, H-3′, H-5′, CH_2), 1.86 (dq, *J* = 12.2, 4.2 Hz, 1H, H-3′, H-5′), 1.70–1.79 (m, 3H, CH, CH_2), 1.45–1.60 (m, 6H, 3 × CH_2); MS *m/z* 326.4 (MH^+, 100%). Anal. calcd for $C_{20}H_{27}N_3O$·¼CH_3OH: C, 72.94; H, 8.46; N, 12.60. Found: C, 72.96; H, 8.53; N, 12.84%.

SN35175 *N*-(1-(3-Cyclopentylpropanoyl)piperidin-4-yl)benzamide (**S42**).

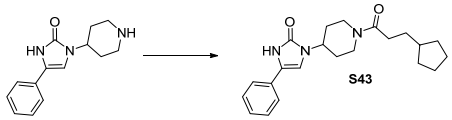


***tert*-Butyl 4-Benzamidopiperidine-1-carboxylate (S42a).** Prepared using Method D from benzoic acid and *tert*-butyl 4-aminopiperidine-1-carboxylate. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give carbamate **S42a** (175 mg, 46%) as a white powder: mp (EtOAc/pet. ether) 169–171 °C; ^{1}H NMR δ 7.75 (br d, *J* = 7.0 Hz, 2H, H-2′, H-6′), 7.50 (tt, *J* = 7.3, 1.3 Hz, 1H, H-4′), 7.44 (br dd, *J* = 7.6, 7.0 Hz, 2H, H-3′, H-5′), 5.98 (br d, *J* = 7.5 Hz, 1H, CONH), 4.05–4.19 (m, 3H, H-2, H-4, H-6), 2.92 (br t, *J* = 12.0 Hz, 2H, H-2, H-6), 2.00–2.07 (m, 2H, H-3, H-5), 1.48 [s, 9H, $C(CH_3)_3$], 1.40 (dq, *J* = 11.9, 3.5 Hz, 2H, H-3, H-5); MS *m/z* 305.2 (MH^+, 20%), 205.2 (MH^+-CO_2tBu, 100%). Anal. calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.25; H, 8.06; N, 9.27%.

***N*-(Piperidin-4-yl)benzamide Hydrochloride (S42b).** Prepared using Method F from carbamate **S42a** (2.69 g, 8.84 mmol) to give piperidine hydrochloride **S42b** (1.92 g, 90%) as a white powder: mp (MeOH) 281–283 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.62 (br s, 2H, NH·HCl), 8.52 (d, *J* = 7.4 Hz, 1H, CONH), 7.87 (br d, *J* = 7.0 Hz, 2H, H-2′, H-6′), 7.52 (tt, *J* = 7.3, 1.3 Hz, 1H, H-4′), 7.46 (br dd, *J* = 7.6, 7.0 Hz, 2H, H-3′, H-5′), 4.01–4.09 (m, 1H, H-4), 3.29 (br dt, *J* = 13.0, 3.6 Hz, 2H, H-2, H-6), 2.97 (ddd, *J* = 13.1, 12.3, 3.0 Hz, 2H, H-2, H-6), 1.96 (br dd, *J* = 13.6, 3.0 Hz, 2H, H-3, H-5), 1.74–1.86 (m, 2H, H-3, H-5); MS *m/z* 205.2 (MH^+, 100%). Anal. calcd for $C_{12}H_{17}ClN_2O$: C, 59.87; H, 7.12; N, 11.64. Found: C, 59.93; H, 7.17; N, 11.69%.

***N*-(1-(3-Cyclopentylpropanoyl)piperidin-4-yl)benzamide (S42).** Prepared using Method D using **S42b** and cyclopentylpropionic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzamide **S42** (461 mg, 97%) as a white powder: mp (EtOAc) 168–170 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.27 (br d, *J* = 7.8 Hz, 1H, CONH), 7.83 (br d, *J* = 7.0 Hz, 2H, H-2′, H-6′), 7.51 (tt, *J* = 7.3, 1.3 Hz, 1H, H-4′), 7.45 (br dd, *J* = 7.6, 7.0 Hz, 2H, H-3′, H-5′), 4.35 (br d, *J* = 13.3. Hz, 1H, H-2, H-6), 4.01 (ddt, *J* = 11.2, 7.8, 3.9 Hz, 1H, H-4), 3.87 (br d, *J* = 13.6 Hz, 2H, H-2, H-6), 3.10 (br t, *J* = 11.9 Hz, 1H, H-2, H-6), 2.66 (br dt, *J* = 12.3, 1.8 Hz, 1H, H-2, H-6), 2.31 (dt, *J* = 8.2, 2.0 Hz, 2H, $COCH_2$), 1.86 (br d, *J* = 12.0 Hz, 1H, H-3, H-5), 1.70–1.78 (m, 3H, CH, CH_2), 1.42–1.60 (m, 7H, 3 × CH_2, H-3, H-5), 1.36 (dq, *J* = 12.0, 3.9 Hz, 1H, H-3, H-5), 1.02–1.12 (m, 2H, CH_2); MS *m/z* 329.2 (MH^+, 100%). Anal. calcd for $C_{20}H_{28}N_2O_2$: C, 73.14; H, 8.59; N, 8.53. Found: C, 73.20; H, 8.84; N, 8.65%.

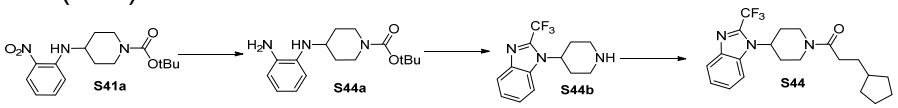
SN35177 1-(1-(3-Cyclopentylpropanoyl)piperidin-4-yl)-4-phenyl-1,3-dihydro-2*H*-imidazol-2-one (**S43**).



1-(1-(3-Cyclopentylpropanoyl)piperidin-4-yl)-4-phenyl-1,3-dihydro-2*H*-imidazol-2-one (S43). Prepared using Method D from 4-phenyl-1-(piperidin-4-yl)-1,3-dihydro-2*H*-imidazol-2-one and 3-cyclopentanecarboxylic acid. The crude solid was purified by

column chromatograhy, eluting with EtOAc, to give imidazolone **S43** (447 mg, 94%) as a white powder: mp (EtOAc) 191–194 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.69 (br s, 1H, CONH), 7.50 (br d, *J* = 8.1 Hz, 2H, H-2″, H-6″), 7.32 (br dd, *J* = 8.1, 7.6 Hz, 2H, H-3″, H-5″), 7.14–7.20 (m, 2H, H-5′, H-4″), 4.53 (br d, *J* = 13.2 Hz, 1H, H-2, H-6), 4.10 (tt, *J* = 11.9, 4.1 Hz, 1H, H-4), 3.98 (br d, *J* = 13.4 Hz, 1H, H-2, H-6), 3.12 (br dd, *J* = 12.6, 11.7 Hz, 1H, H-2, H-6), 2.60 (br dd, *J* = 12.6, 11.1 Hz, 1H, H-2, H-6), 2.33 (dt, *J* = 8.1, 7.1 Hz, 2H, $COCH_2$), 1.70–1.85 (m, 6H, 3 × CH_2), 1.45–1.62 (m, 7H, 3 × CH_2, CH), 1.03–1.13 (m, 2H, CH_2); MS *m/z* 368.2 (MH^+, 100%). Anal. calcd for $C_{22}H_{29}N_3O_2$: C, 71.90; H, 7.95; N, 11.43. Found: C, 71.80; H, 8.07; N, 11.47%.

SN35179 3-Cyclopentyl-1-(4-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)propan-1-one (**S44**).



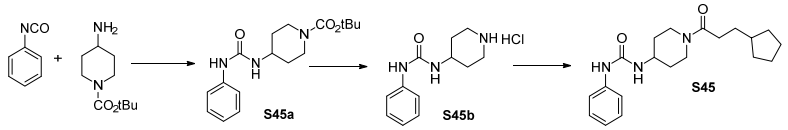
***tert*-Butyl 4-((2-Aminophenyl)amino)piperidine-1-carboxylate (S44a).** Prepared using Method B from **S41a**. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give aniline **S44a** (348 mg, 90%) as a white solid: ^{1}H NMR δ 6.80 (br ddd, *J* = 7.8, 7.4, 1.8 Hz, 1H, H-4′), 6.75 (br ddd, *J* = 7.8, 7.4, 1.6 Hz, 1H, H-5′), 6.65–6.68 (m, 2H, H-3′, H-6′), 3.90–4.06 (m, 2H, H-2, H-6), 3.20–3.43 (m, 4H, H-4, NH, NH_2), 2.95 (br t, *J* = 11.5 Hz, 2H, H-2, H-6), 1.99–2.08 (m, 2H, H-3, H-5), 1.47 [s, 9H, $C(CH_3)_3$], 1.33–1.43 (m, 2H, H-3, H-5), MS *m/z* 192.1 (MH^+-CO_2tBu, 100%).

1-(Piperidin-4-yl)-2-(trifluoromethyl)-1*H*-benzo[*d*]imidazole Trifluoroacetate (S44a). A mixture of *tert*-butyl 4-((2-aminophenyl)amino)piperidine-1-carboxylate (344 mg, 1.18 mmol) and trifluoroacetic acid (3 mL) in DCM (10 mL) was stirred at 20 °C for 16 h. The mixture was filtered through a pad of diatomaceous earth and the pad was washed with EtOAc (50 mL). The solvent was evaporated and the residue was triturated with Et_2O and filtered to give benzimidazole **S44a** (338 mg, 75%) as a colourless solid: mp (Et_2O) 265 °C (decomp.); ^{1}H NMR [$(CD_3)_2SO$] δ 8.71 (br s, 1H, NH), 8.56 (br s, 1H, NH), 8.07 (d, *J* = 8.4 Hz, 1H, H-4), 7.87 (d, *J* = 8.1 Hz, 1H, H-7), 7.50 (ddd, *J* = 8.3, 7.3, 1.0 Hz, 1H, H-5), 7.42 (ddd, *J* = 8.1, 7.3, 1.0 Hz, 1H, H-6), 4.88 (tt, *J* = 12.2, 4.4 Hz, 1H, H-4′), 3.50 (br d, *J* = 12.3 Hz, 2H, H-2′, H-6′), 2.36 (br dd, *J* = 12.0, 11.2 Hz, 2H, H-2′, H-6′), 2.70 (dq, *J* = 13.0, 3.9 Hz, 2H, H-3′, H-5′), 2.10 (br d, *J* = 11.2 Hz, 2H, H-3′, H-5′); MS *m/z* 265.2 (MH^+, 100%).

3-Cyclopentyl-1-(4-(2-(trifluoromethyl)-1*H*-benzo[*d*]imidazol-1-yl)piperidin-1-yl)propan-1-one (S44). Prepared using Method D from **S44a** and 3-cyclopentanecarboxylic acid. The crude solid was purified by column chromatography, eluting with a gradient (25–30%) of EtOAc/pet. ether, to give amide **S44** (318 mg, 80%) as a clear oil: ^{1}H NMR [$(CD_3)_2SO$] δ 7.81–7.86 (m, 2H, H-4″, H-7″), 7.42 (ddd, *J* = 8.0, 7.1, 1.2 Hz, 1H, H-5″), 7.36 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, H-6″), 4.60–4.73 (m, 2H, H-2′, H-4′, H-6′), 4.07 (br d, *J* = 13.8 Hz, 1H, H-2′, H-6′), 3.23 (br dd, *J* = 11.8 Hz, 1H, H-2′, H-6′), 2.70–2.78 (m, 1H, H-2′, H-6′), 2.40 (br dd, *J* = 7.4, 6.2 Hz, 2H, $COCH_2$), 2.21 (dq, *J* = 12.2, 4.2 Hz, 1H, H-3′, H-5′), 1.92 (br t, *J* = 12.7 Hz, 2H, H-3′, H-5′), 1.70–1.81 (m, 3H, H-3′, H-5′, CH_2), 1.50–1.60 (m, 5H, CH, 2 × CH_2), 1.44–1.48 (m, 2H, CH_2), 1.05–1.13 (m,

2H, CH_2); MS *m/z* 394.2 (MH^+, 100%). Anal. calcd for $C_{21}H_{26}F_3N_3O$: C, 64.11; H, 6.66; N, 10.68. Found: C, 64.38; H, 6.87; N, 10.56%.

SN35190 1-(1-(3-Cyclopentylpropanoyl)piperidin-4-yl)-3-phenylurea (**S45**).

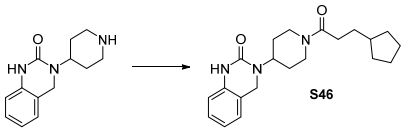


***tert*-Butyl 4-(3-phenylureido)piperidine-1-carboxylate (S45a).** Phenyl isocyanate (0.59 mL, 5.39 mmol) was added dropwise to a stirred solution of *tert*-butyl 4-aminopiperidine-1-carboxylate (1.08 g, 5.39 mmol) in dry THF (25 mL) at 20 °C and the mixture was stirred for 48 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and the mixture was diluted with EtOAc (100 mL), washed sequentially with dilute citric acid solution (2 × 50 mL), water (50 mL), and brine (50 mL) and then dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (30–50%) of EtOAc/pet. ether, to give carbamate **S45a** (1.635 g, 95%) as a white powder: mp (EtOAc/pet. ether) 184–186 °C; ^{1}H NMR δ 7.26–7.34 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.09 (tt, *J* = 7.0, 1.6 Hz, 1H, H-4′), 6.51 (s, 1H CONH), 4.78 (d, *J* = 7.8 Hz, 1H, CONH), 4.00 (br s, 2H, H-2, H-6), 3.84 (dq, *J* = 10.9, 4.0 Hz, 1H, H-4), 2.87 (br dd, *J* = 12.4, 11.9 Hz, 2H, H-2, H-6), 1.94 (br dd, *J* = 12.5, 2.6 Hz, 2H, H-3, H-5), 1.45 [s, 9H, $C(CH_3)_3$], 1.25 (dq, *J* = 11.9, 4.0 Hz, 2H, H-3, H-5); MS *m/z* 320.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{25}N_3O_3$: C, 63.93; H, 7.89; N, 13.16. Found: C, 64.18; H, 8.10; N, 13.24%.

1-Phenyl-3-(piperidin-4-yl)urea Hydrochloride (S45b). Prepared using Method F from carbamate **S45a** to give piperidine hydrochloride **S45b** (1.13 g, 100%) as a white foam: ^{1}H NMR [$(CD_3)_2SO$] δ 8.76 (br s, 2H, NH·HCl), 8.67 (s, 1H, CONH), 7.37 (br d, *J* = 8.0 Hz, 2H, H-2′, H-6′), 7.20 (br dd, *J* = 8.0, 7.6 Hz, 2H, H-3′, H-5′), 6.87 (br t, *J* = 7.3 Hz, 1H, H-4′), 6.78 (d, *J* = 7.5 Hz, 1H, CONH), 3.71–3.80 (m, 1H, H-4), 3.24 (br d, *J* = 12.6 Hz, 2H, H-2, H-6), 2.94–3.04 (m, 2H, H-2, H-6), 1.93–1.99 (m, 2H, H-3, H-5), 1.55–1.65 (m, 2H, H-3, H-5); MS *m/z* 220.2 (MH^+, 100%). Anal. calcd for $C_{12}H_{18}ClN_3O·CH_3OH$: C, 54.26; H, 7.71; N, 14.60. Found: C, 54.42; H, 7.26; N, 14.60%.

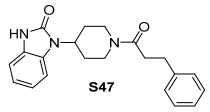
1-(1-(3-Cyclopentylpropanoyl)piperidin-4-yl)-3-phenylurea (S45). Prepared using Method D from **S45b** and 3-cyclopentanecarboxylic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give urea **S45** (386 mg, 66%) as white crystals: mp (EtOAc) 179–180 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.31 (s, 1H, CONH), 7.37 (dd, *J* = 8.6, 1.1 Hz, 2H, H-2, H-6), 7.20 (dd, *J* = 8.6, 7.4 Hz, 2H, H-3, H-5), 6.89 (tt, *J* = 7.3, 1.1 Hz, 1H, H-4), 6.16 (d, *J* = 7.6 Hz, 1H, CONH), 4.17 (br d, *J* = 13.6 Hz, 1H, H-2′, H-6′), 3.76 (br d, *J* = 14.1 Hz, 1H, H-2′, H-6′), 3.65–3.70 (m, 1H, H-4′), 3.14 (br t, *J* = 11.3 Hz, 1H, H-2′, H-6′), 2.76 (br t, *J* = 11.3 Hz, 1H, H-2′, H-6′), 2.30 (dd, *J* = 7.9, 7.6 Hz, 2H, $COCH_2$), 1.68–1.85 (m, 5H, H-3′, H-5′, CH, CH_2), 1.43–1.60 (m, 6H, 3 × CH_2), 1.28 (dq, *J* = 10.5, 4.0 Hz, 1H, H-3′, H-5′), 1.19 (br dq, *J* = 10.5, 4.0 Hz, 1H, H-3′, H-5′), 1.03–1.10 (m, 2H, CH_2); MS *m/z* 344.2 (MH^+, 100%). Anal. calcd for $C_{20}H_{29}N_3O_2$: C, 69.94; H, 8.51; N, 12.23. Found: C, 69.73; H, 8.70; N, 12.26%.

SN35199 3-(1-(3-Cyclopentylpropanoyl)piperidin-4-yl)-3,4-dihydroquinazolin-2(1*H*)-one (**S46**).



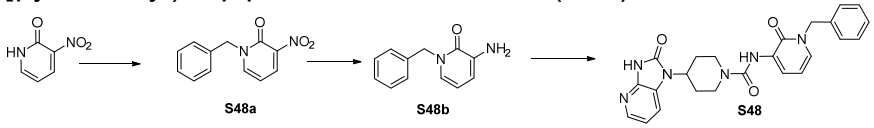
3-(1-(3-Cyclopentylpropanoyl)piperidin-4-yl)-3,4-dihydroquinazolin-2(1*H*)-one (S46). Prepared using Method D using 3-(piperidin-4-yl)-3,4-dihydroquinazolin-2(1*H*)-one and 3-cyclopentanecarboxylic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give amide **S46** (485 mg, 76%) as white powder: mp (EtOAc) 191–193 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.21 (s, 1H, CONH), 7.08–7.13 (m, 2H, H-7, H-8), 6.85 (dt, *J* = 7.4, 1.1 Hz, 1H, H-6), 6.76 (d, *J* = 7.5 Hz, 1H, H-5), 4.52 (br d, *J* = 12.7 Hz, 1H, H-2′, H-6′), 4.36 (tt, *J* = 11.4, 4.4 Hz, 1H, H-4′), 4.28 (s, 2H, H-4), 3.95 (br d, *J* = 13.8 Hz, 1H, H-2′, H-6′), 3.07 (br dd, *J* = 12.7, 11.4 Hz, 1H, H-2′, H-6′), 2.55 (br dd, *J* = 12.8, 3.7 Hz, 1H, H-2′, H-6′), 2.33 (br dt, *J* = 7.6, 4.2 Hz, 2H, $COCH_2$), 1.68–1.78 (m, 4H, 2 × CH_2), 1.44–1.64 (m, 9H, CH, 2 × CH_2, H-3′, H-5′), 1.02–1.12 (m, 2H, CH_2); MS *m/z* 356.2 (MH^+, 100%). Anal. calcd for $C_{21}H_{29}N_3O_2$: C, 70.95; H, 8.22; N, 11.82. Found: C, 70.85; H, 8.26; N, 11.90%.

SN35326 1-(1-(3-Phenylpropanoyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (**S47**).



1-(1-(3-Phenylpropanoyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (S47). Prepared using Method D using 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one and 3-phenylpropionic acid. The crude solid was purified by column chromatography, eluting with EtOAc, to give benzimidazolone **S47** (496 mg, 86%) as a white powder: mp 178–180 °C; ^{1}H NMR δ 10.84 (s, 1H, CONH), 7.32 (br t, *J* = 7.3 Hz, 2H, H-3″, H-5″), 7.20–7.28 (m, 3H, H-2″, H-4″, H-6″), 7.02–7.12 (m, 4H, H-4, H-5, H-6, H-7), 4.90 (br d, *J* = 13.2 Hz, 1H, H-2′, H-6′), 4.51 (tt, *J* = 12.2, 4.1 Hz, 1H, H-4′), 3.98 (br d, *J* = 13.7 Hz, 1H, H-2′, H-6′), 3.11 (br t, *J* = 12.5 Hz, 2H, CH_2), 2.99–3.06 (m, 1H, H-2′, H-6′), 2.63–2.78 (m, 3H, $COCH_2$, H-2′, H-6′), 2.27 (dq, *J* = 12.6, 4.3 Hz, 1H, H-3′, H-5′), 2.10 (dq, *J* = 12.5, 4.3 Hz, 1H, H-3′, H-5′), 1.87 (br dd, *J* = 13.2, 12.2 Hz, 2H, H-3′, H-5′); MS *m/z* 350.2 (MH^+, 100%). Anal. calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 71.93; H, 6.74; N, 11.95%.

SN35352 *N*-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (**S48**).



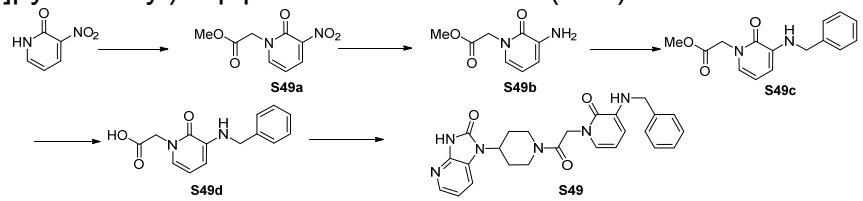
1-Benzyl-3-nitro-2(1*H*)-pyridinone (S48a). Prepared using Method E from benzyl bromide and 3-nitro-2(1*H*)-pyridinone. The crude solid was purified by column chromatography, eluting with 60% EtOAc/pet. ether, to give nitropyridinone **S48a** (1.69 g, 97%) as a yellow powder: mp (EtOAc/pet. ether) 96–99 °C (lit. [3] mp 86–88 °C); ^{1}H NMR δ 8.30 (dd, *J* = 7.6, 2.1 Hz, 1H, H-4), 7.66 (dd, *J* = 6.7, 2.1 Hz, 1H, H-6), 7.32–7.41 (m,

5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.28 (dd, *J* = 7.6, 6.7 Hz, 1H, H-5), 5.24 (s, 2H, CH_2); MS *m/z* 231.4 (MH^+, 100%).

3-Amino-1-benzyl-2(1*H*)-pyridinone (S48b). Prepared by Method G from nitropyridinone **S48a**. The crude solid was purified by column chromatography, eluting with 60% EtOAc/pet. ether, to give aminopyridinone **S48b** (1.33 g, 92%) as green crystals: mp (EtOAc/pet. ether) 124–125 °C; ^{1}H NMR δ 7.27–7.35 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.73 (dd, *J* = 6.9, 1.7 Hz, 1H, H-6), 6.05 (dd, *J* = 7.1, 1.7 Hz, 1H, H-4), 6.05 (d, *J* = 7.0 Hz, 1H, H-5), 4.24 (br s, 2H, NH_2), 5.17 (s, 2H, CH_2); MS *m/z* 201.4 (MH^+, 100%). Anal. calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.13; H, 6.16; N, 14.07%.

***N*-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (S48).** Prepared using Method C from **S48b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/EtOAc, to give urea **S48** (60 mg, 13%) as a white powder: mp (MeOH/EtOAc) 218–219 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.52 (br s, 1H, CONH), 8.16 (dd, *J* = 7.4, 1.7 Hz, 1H, H-6″), 8.07 (br s, 1H, CONH), 7.25–7.38 (m, 6H, H-7′, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴), 6.96–7.01 (m, 2H, H-6′, H-4″), 6.29 (t, *J* = 7.2 Hz, 1H, H-5″), 5.19 (s, 2H, CH_2), 4.58 (tt, *J* = 12.5, 4.2 Hz, 1H, H-4), 4.36 (br d, *J* = 13.9 Hz, 2H, H-2, H-6), 3.06 (br t, *J* = 12.5 Hz, 2H, H-2, H-6), 2.27 (dq, *J* = 12.7, 4.2 Hz, 2H, H-3, H-5), 1.95 (dd, *J* = 12.2, 2.2 Hz, 2H, H-3, H-5); MS *m/z* 445.7 (MH^+, 100%). Anal. calcd for $C_{24}H_{24}N_6O_3 \cdot ½CH_3OH$: C, 63.90; H, 5.69; N, 18.25. Found: C, 64.24; H, 5.63; N, 18.02%.

SN35356 *N*-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-1-piperidinecarboxamide (**S49**).



Methyl (3-Nitro-2-oxo-1(2*H*)-pyridinyl)acetate (S49a). Prepared using Method E from methyl bromoacetate and 3-nitro-2(1*H*)-pyridinone. The crude solid was purified by column chromatography, eluting with EtOAc, to give nitropyridinone **S49a** (0.56 g, 37%) as a tan powder: mp (EtOAc/pet. ether) 96–98 °C; ^{1}H NMR δ 8.40 (dd, *J* = 7.7, 2.1 Hz, 1 H, H-4′), 7.63 (dd, *J* = 6.6, 2.1 Hz, 1 H, H-6′), 6.37 (dd, *J* = 7.7, 6.6 Hz, 1 H, H-5′), 4.78 (s, 2 H, CH_2), 3.82 (s, 3 H, OCH_3); MS *m/z* 213.4 (MH^+, 100%). Anal. calcd for $C_8H_8N_2O_5$: C, 45.29; H, 3.80; N, 13.20. Found: C, 44.50; H, 3.78; N, 12.94%.

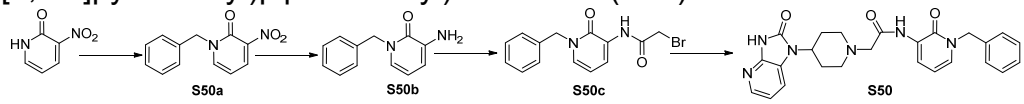
Methyl (3-Amino-2-oxo-1(2*H*)-pyridinyl)acetate (S49b). Prepared by Method B using **S49a**. The crude solid was purified by column chromatography, eluting with 70% EtOAc/pet. ether, to give aminopyridinone **S49b** (306 mg, 78%) as a green oil which was used directly: ^{1}H NMR δ 6.65 (dd, *J* = 6.8, 1.6 Hz, 1H, H-6), 6.54 (dd, *J* = 7.1, 1.6 Hz, 1H, H-4), 6.10 (t, *J* = 7.0 Hz, 1H, H-5), 4.67 (s, 2H, CH_2N), 3.78 (s, 3H, OCH_3); MS *m/z* 183.4 (MH^+, 100%).

Methyl (3-(Benzylamino)-2-oxo-1(2*H*)-pyridinyl)acetate (S49c). Prepared using Method E from benzyl bromide and 3-aminopyridinone **S49b**. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give benzylaminopyridinone **S49c** (238 mg, 53%) as a white powder: mp (EtOAc/pet. ether) 130–131 °C; ^{1}H NMR δ 7.32–7.36 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.24–7.28 (m, 1H, H-4′), 6.57 (dd, *J* = 6.6, 1.9 Hz, 1H, H-6), 6.16 (dd, *J* = 7.3, 1.9 Hz, 1H, H-4), 6.12 (dd, *J* = 7.3, 6.6 Hz, 1H, H-5), 5.44 (br s, 1H, NH), 4.67 (s, 2H, CH_2N), 4.32 (s, 2H, CH_2N), 3.79 (s, 3H, OCH_3); MS *m/z* 273.4 (MH^+, 100%). Anal. calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.32; H, 5.98; N, 10.38%.

(3-(Benzylamino)-2-oxo-1(2*H*)-pyridinyl)acetic Acid (S49d). Prepared using Method J from ester **S49c** to give acid **S49d** (171 mg, 83%) as a white powder: mp (H_2O) 190–191 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.92 (br s, 1H, CO_2H), 7.30–7.36 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.18–7.26 (m, 1H, H-4″), 6.84 (dd, *J* = 6.7, 1.8 Hz, 1H, H-6′), 6.00–6.08 (m, 3H, H-4′, H-5′, NH), 4.60 (s, 2H, H-2), 4.28 (d, *J* = 6.2 Hz, 2H, CH_2N); MS *m/z* 259.4 (MH^+, 100%). Anal. calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.95; H, 5.47; N, 10.65%.

1-{1-[(3-(Benzylamino)-2-oxo-1(2*H*)-pyridinyl)acetyl]-4-piperidinyl}-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S49). Prepared by Method D using **S49d** and **S1d**. The crude solid was recrystallised to give pyridinone **S49** (216 mg, 76%) as a pale blue powder: mp (EtOAc) 258–260 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.57 (br s, 1H, CONH), 7.89 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 7.61 (dd, *J* = 7.8, 1.2 Hz, 1H, H-7), 7.28–7.36 (m, 4H, H-2‴, H-3‴, H-5‴, H-6‴), 7.20–7.24 (m, 1H, H-4‴), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6), 6.81 (dd, *J* = 6.7, 1.8 Hz, 1H, H-6″), 6.10 (dd, *J* = 7.3, 1.7 Hz, 1H, H-4″), 6.05 (t, *J* = 7.0 Hz, 1H, H-5″), 5.94 (t, *J* = 6.2 Hz, 1H, CONH), 4.86 (2 × d, *J* = 15.8 Hz, 2H, CH_2CO), 4.44–4.53 (m, 2H, H-4′, H-2′, H-6′), 4.30 (d, *J* = 6.2 Hz, 2H, CH_2N), 4.10 (br d, *J* = 13.9 Hz, 1H, H-2′, H-6′), 3.28 (br t, *J* = 12.8 Hz, 2H, H-2′, H-6′), 2.75 (br t, *J* = 12.8 Hz, 2H, H-2′, H-6′), 2.35 (dq, *J* = 12.5, 3.9 Hz, 1H, H-3′, H-5′), 2.08 (dd, *J* = 12.3, 4.0 Hz, 1H, H-3′, H-5′), 1.73–1.85 (m, 2H, H-3′, H-5′); MS *m/z* 459.7 (MH^+, 100%). Anal. calcd for $C_{25}H_{26}N_6O_3$: C, 65.49; H, 5.72; N, 18.33. Found: C, 65.16; H, 5.69; N, 18.30%.

SN35357 *N*-(1-Benzyl-2-oxo-1,2-dihydropyridin-3-yl)-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)acetamide (**S50**).



1-Benzyl-3-nitropyridin-2(1*H*)-one (S50a). Prepared using Method E from benzyl bromide and 3-nitro-2(1*H*)-pyridinone. The crude solid was purified by column chromatography, eluting with 60% EtOAc/pet. ether, to give nitropyridinone **S50a** (1.69 g, 97%) as a yellow powder: mp (EtOAc/pet. ether) 96–99 °C (lit. [3] mp 86–88 °C); ^{1}H NMR δ 8.30 (dd, *J* = 7.6, 2.1 Hz, 1H, H-4), 7.66 (dd, *J* = 6.7, 2.1 Hz, 1H, H-6), 7.32–7.41 (m, 5H, H_{aryl}), 6.28 (dd, *J* = 7.6, 6.7 Hz, 1H, H-5), 5.24 (s, 2H, CH_2); MS *m/z* 231.2 (MH^+, 100%).

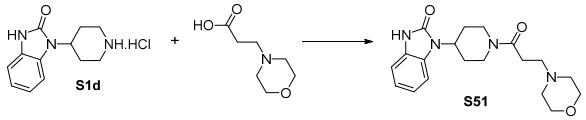
3-Amino-1-benzylpyridin-2(1*H*)-one (S50b). Prepared by Method G from nitropyridinone **S50a**. The crude solid was purified by column chromatography, eluting

with 70% EtOAc/pet. ether, to give aminopyridinone **S50b** (1.33 g, 92%) as green crystals: mp (EtOAc/pet. ether) 124–125 °C; ^{1}H NMR δ 7.27–7.35 (m, 5H, H_{aryl}), 6.73 (dd, *J* = 6.9, 1.7 Hz, 1H, H-6), 6.52 (dd, *J* = 7.1, 1.7 Hz, 1H, H-4), 6.05 (t, *J* = 7.0 Hz, 1H, H-5), 5.17 (s, 2H, CH_2N), 4.24 (s, 2H, NH_2); MS *m/z* 231.2 (MH^+, 100%). Anal. calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.13; H, 6.16; N, 14.07%.

***N*-(1-Benzyl-2-oxo-1,2-dihydropyridin-3-yl)-2-bromoacetamide (S50c).** Prepared using Method I from 2-bromoacetyl bromide and 3-aminopyridinone **S50b**. The crude solid was purified by column chromatography, eluting with a gradient (50–100%) of EtOAc/pet. ether, to give acetamide **S50c** (468 mg, 63%) as white plates: mp (EtOAc/pet. ether) 110–111 °C; ^{1}H NMR δ 9.29 (br s, 1H, CONH), 8.33 (dd, *J* = 7.4, 1.8 Hz, 1H, H-4′), 7.32–7.40 (m, 3H, H-3″, H-4″, H-5″), 7.27–7.30 (m, 2H, H-2″, H-6″), 6.07 (dd, *J* = 7.0, 1.8 Hz, 1H, H-6′), 6.25 (t, *J* = 7.2 Hz, 1H, H-5′), 5.19 (s, 2H, CH_2N), 3.99 (s, 2H, H-2); MS *m/z* 321.1 (MH^+, 100%), 323.1 (MH^+, 100%). Anal. calcd for $C_{14}H_{13}BrN_2O_2$: C, 52.36; H, 4.08; N, 8.72. Found: C, 52.99; H, 3.98; N, 8.72%.

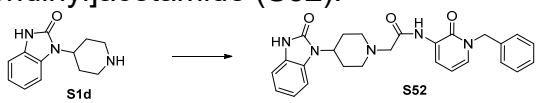
***N*-(1-Benzyl-2-oxo-1,2-dihydropyridin-3-yl)-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)acetamide (S50).** Prepared using Method E from bromide **S50c** and piperidine **S1d** with Cs_2CO_3. The crude solid was purified by column chromatography, eluting with EtOAc, to give acetamide **S50** (195 mg, 65%) as a white powder: mp (EtOAc) 231–234 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (br s, 1H, CONH), 10.24 (br s, 1H, CONH), 8.24 (dd, *J* = 7.4, 1.8 Hz, 1H, H-4‴), 7.92 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5″), 7.77 (dd, *J* = 7.8, 5.2 Hz, 1H, H-7″), 7.56 (dd, *J* = 6.8, 1.8 Hz, 1H, H-6‴), 7.26–7.38 (m, 5H, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-5″), 6.34 (t, *J* = 7.1 Hz, 1H, H-5‴), 5.24 (s, 2H, CH_2N), 4.22–4.29 (m, 1H, H-4′), 3.21 (s, 2H, H-2), 2.96 (br d, *J* = 9.7 Hz, 2H, H-2′, H-6′), 2.32–2.48 (m, 4H, H-2′, H-3′, H-5′, H-6′), 1.70–1.78 (m, 2H, H-3′, H-5′); MS *m/z* 459.3 (MH^+, 100%). Anal. calcd for $C_{25}H_{26}N_6O_3 \cdot ¼EtOAc$: C, 64.99; H, 5.87; N, 17.49. Found: C, 64.85; H, 5.86; N, 17.23%.

SN35362 1-{1-[3-(4-Morpholinyl)propanoyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one (**S51**).



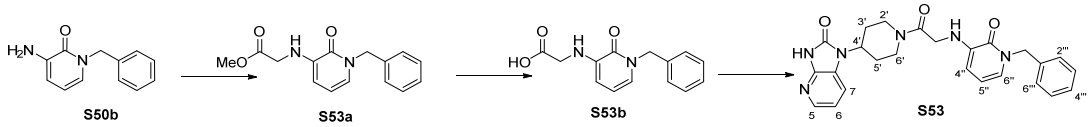
1-{1-[3-(4-Morpholinyl)propanoyl]-4-piperidinyl}-1,3-dihydro-2*H*-benzimidazol-2-one (S51). Prepared by Method D from 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one and 3-(4-morpholinyl)propanoic acid hydrochloride. The crude solid was purified by column chromatography, eluting with 5–10% MeOH/DCM, to give benzimidazolone **S51** (141 mg, 29%) as a tan powder: mp (EtOAc/pet. ether) 201–204 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, CONH), 7.19–7.23 (m, 1H, H-7), 6.95–6.99 (m, 3H, H-4, H-5, H-6), 4.57 (br d, *J* = 12.9 Hz, 1H, H-2′, H-6′), 4.41 (tt, *J* = 12.2, 4.2 Hz, 1H, H-4′), 4.03 (br d, *J* = 12.2 Hz, 1H, H-2′, H-6′), 3.57 (br s, 4H, 2 × CH_2O), 3.15 (br dd, *J* = 12.9, 11.4 Hz, 1H, H-2′, H-6′), 2.65 (br dd, *J* = 12.9, 11.1 Hz, 1H, H-2′, H-6′), 2.54–2.59 (m, 4H, H-2″, H-3″), 2.29 (dq, *J* = 12.3, 3.9 Hz, 2H, H-3′, H-5′), 2.11 (dq, *J* = 12.3, 4.0 Hz, 2H, H-3′, H-5′), 1.71 (br dd, *J* = 12.7, 12.1 Hz, H, H-3′, H-5′); MS *m/z* 359.5 (MH^+, 100%). Anal. calcd for $C_{19}H_{26}N_4O_3 \cdot {}^1/_3CH_2Cl_2$: C, 60.05; H, 6.95; N, 14.49. Found: C, 60.49; H, 7.19; N, 14.08%.

SN35385 *N*-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-2-[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl]acetamide (**S52**).



***N*-(1-Benzyl-2-oxo-1,2-dihydro-3-pyridinyl)-2-[4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1-piperidinyl]acetamide (S52).** Prepared by Method E from bromide **S50c** and piperidine **S1d** with Cs_2CO_3. The crude solid was purified by column chromatography, eluting with EtOAc, to give acetamide **S52** (275 mg, 94%) as a white powder: mp (EtOAc) 229–232 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (br s, 1H, CONH), 10.21 (br s, 1H, CONH), 8.25 (dd, *J* = 7.4, 1.8 Hz, 1H, H-4‴), 7.56 (dd, *J* = 6.9, 1.8 Hz, 1H, H-6‴), 7.44–7.48 (m, 1H, H-7‴), 7.32–7.39 (m, 4H, H-2‴, H-3‴, H-5‴, H-6‴), 7.27–7.31 (m, 1H, H-4‴), 6.96–7.03 (m, 3H, H-4″, H-5″, H-6″), 6.33 (t, *J* = 7.1 Hz, 1H, H-5‴), 5.23 (s, 2H, CH_2N), 4.20–4.25 (m, 1H, H-4′), 3.21 (s, 2H, CH_2N), 2.97 (br d, *J* = 7.8 Hz, 2H, H-2′, H-6′), 2.40–2.48 (m, 4H, H-2′, H-3′, H-5′, H-6′), 1.68 (br d, *J* = 7.8 Hz, 2H, H-3′, H-5′); MS *m/z* 458.3 (MH^+, 100%). Anal. calcd for $C_{26}H_{27}N_5O_3 \cdot ¾CH_3OH$: C, 66.72; H, 6.28; N, 14.54. Found: C, 66.51; H, 5.95; N, 14.73%.

SN35702 1-(1-(2-((1-Benzyl-2-oxo-1,2-dihydropyridin-3-yl)amino)acetyl)piperidin-4-yl)-1*H*-imidazo[4,5-b]pyridin-2(3*H*)-one (**S53**).



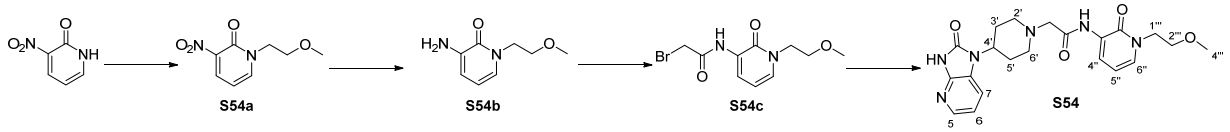
Methyl 2-((1-Benzyl-2-oxo-1,2-dihydropyridin-3-yl)amino)acetate (S53a). Prepared using Method I from methyl bromoacetate and amine **S50b**. The crude oil was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give methyl ester **S53a** (168 mg, 62%) as a blue solid: mp 71–73 °C; ^{1}H NMR δ 7.28–7.35 (m, 5H, H-2", H-3", H-4", H-5", H-6"), 6.67–6.71 (m, 1H, H-6'), 6.09–6.13 (m, 2H, H-4', H-5'), 5.56 (br t, *J* = 5.4 Hz, 1H, NH), 5.17 (s, 2H, CH_2N), 3.90 (d, *J* = 6.0 Hz, 2H, H_2-2), 3.77 (s, 3H, OCH_3); MS *m/z* 273.5 (MH^+, 100%).

2-((1-Benzyl-2-oxo-1,2-dihydropyridin-3-yl)amino)acetic acid (S53b). Prepared using Method J from acetate **S53a** to give the carboxylic acid **S53b** (226 mg, 67%) as a pale blue solid: mp 144–145°C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.79 (br s, 1H, COOH), 7.24–7.35 (m, 5H, H-2", H-3", H-4", H-5", H-6"), 7.00–7.04 (m, 1H, H-6'), 6.12–6.16 (m, 2H, H-4', H-5'), 5.63 (br s, 1H, NH), 5.12 (s, 2H, NCH_2), 3.78 (s, 2H, H_2-2); MS *m/z* 259.5 (MH^+, 100%). Anal. calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.89; H, 5.49; N, 10.93%

1-(1-(2-((1-Benzyl-2-oxo-1,2-dihydropyridin-3-yl)amino)acetyl)piperidin-4-yl)-1*H*-imidazo[4,5-b]pyridin-2(3*H*)-one (S53). Prepared using Method D from **S53b** and **S1d**. The residue was purified by column chromatography, eluting with 4% MeOH/DCM, followed by preparative HPLC [gradient (90–50–98%) ammonium formate pH 3.45/90% CH_3CN/H_2O] to give amide **S53** (82 mg, 31%) as a dark green powder: mp 143 °C (decomp.); ^{1}H NMR δ 8.03 (dd, *J* = 7.0, 1.2 Hz, 1H, H-5), 7.25–7.33 (m, 5H, H-2‴, H-3‴,

H-4‴, H-5‴, H-6‴), 7.23 (dd, *J* = 7.0, 1.2 Hz, 1H, H-7), 6.94 (dd, *J* = 7.0, 1.2 Hz, 1H, H-6), 6.71 (dd, *J* = 7.0, 1.7 Hz, 1H, H-6″), 6.21 (dd, *J* = 7.0, 1.7 Hz, 1H, H-4″), 6.14 (t, *J* = 7.0 Hz, 1H, H-5″), 5.96 (br s, 1H, NH), 5.14–5.20 (m, 2H, NCH_2), 4.89 (br d, *J* = 12.7 Hz, 1H, H-2' or H-6'), 4.58–4.66 (m, 1H, H-4'), 3.90–4.06 (m, 3H, H-2' or H-6', $COCH_2$), 3.25 (br t, *J* = 12.7 Hz, 1H, H_2-2' or H_2-6'), 2.76 (br t, *J* = 12.7 Hz, 1H, H_2-2' or H_2-6'), 2.17–2.27 (m, 2H, H_2-3' or H_2-5'), 1.96 (br t, *J* = 12.0 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR δ 167.0 ($COCH_2$), 157.7 (C-2″), 153.4 (C-2), 143.2 (C-3a), 140.3 (C-5), 138.6 (C-3″), 136.7 (C-1‴), 128.9 (C-3‴, C-5‴), 128.2 (C-2‴, C-6‴), 128.0 (C-4‴), 123.5 (C-6″), 123.3 (C-7a), 117.1 (C-6), 115.5 (C-7), 107.3 (C-5″), 107.0 (C-4″), 52.4 (NCH_2), 50.4 (C-4'), 45.6 ($COCH_2$), 44.4 (C-2' or C-6'), 42.0 (C-2' or C-6'), 30.0 (C-3' or C-5'), 29.3 (C-3' or C-5'); MS *m/z* 460.0 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 459.2144 (calcd for $C_{25}H_{27}N_6O_3$, 459.2139).

SN35737 *N*-(1-(2-Methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidin-1-yl)acetamide (**S54**).



1-(2-Methoxyethyl)-3-nitropyridin-2(1*H*)-one (S54a). [4] Prepared by Method E from 2-bromoethyl methyl ether and 2-hydroxy-3-nitropyridine with Cs_2CO_3. The crude residue was purified by column chromatography, eluting with 60% EtOAc/pet. ether, to give pyridone **S54a** (0.50 g, 71%) as yellow needles: mp 59–60 °C; ^{1}H NMR δ 8.34 (dd, *J* = 7.7, 2.2 Hz, H-4), 7.75 (dd, *J* = 6.6, 2.2 Hz, 1H, H-6), 6.27 (dd, *J* = 7.7, 6.6 Hz, 1H, H-5), 4.24–4.26 (m, 2H, CH_2-1'), 3.69–3.71 (m, 2H, CH_2-2'), 3.32 (s, 3H, OMe-4'); MS *m/z* 199.5 (MH^+, 100%).

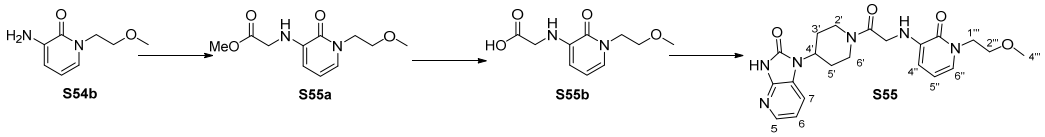
3-Amino-1-(2-methoxyethyl)pyridin-2(1*H*)-one (S54b). [4] Prepared using Method B from **S54a** to give the amine **S54b** (697 mg, 97%) as a clear yellow oil: ^{1}H NMR δ 6.78 (dd, *J* = 7.0, 1.7 Hz, 1H, H-6), 6.54 (dd, *J* = 7.0, 1.7 Hz, 1H, H-4), 6.03 (t, *J* = 7.0 Hz, 1H, H-5), 4.27 (br s, 2H, NH_2), 4.16 (t, *J* = 5.2 Hz, 2H, H_2-1'), 3.69 (t, *J* = 5.2 Hz, 2H, H_2-2'), 3.32 (s, 3H, OMe-4'); MS *m/z* 169.5 (MH^+, 100%).

2-Bromo-*N*-(1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)acetamide (S54c). Prepared using Method I from 2-bromoacetyl bromide and amine **S54b**. The residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether, give the amide **S54c** (276 mg, 86%) as an orange solid: mp 99–100 °C; ^{1}H NMR δ 9.26 (br s, 1H, NH), 8.34 (dd, *J* = 7.2, 1.8 Hz, 1H, H-4), 7.11 (dd, *J* = 7.2, 1.8 Hz, 1H, H-6), 6.23 (t, *J* = 7.2 Hz, 1H, H-5), 4.18 (t, *J* = 5.0 Hz, 2H, H_2-1'), 3.99 (s, 2H, CH_2), 3.69 (t, *J* = 5.0 Hz, 2H, H_2-2'), 3.32 (s, 3H, OMe-4'); MS *m/z* 291.5 (MH^+, 100%). Anal. calcd for $C_{10}H_{13}BrN_2O_3 \cdot 0.05H_2O$: C, 41.40; H, 4.86; N, 9.66. Found: C, 40.95; H, 4.44; N, 9.35%.

***N*-(1-(2-Methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidin-1-yl)acetamide (S54).** Prepared using Method E from bromide **S54c** and piperidine **S1d** with Cs_2CO_3 at 20 °C. The residue was purified by column chromatography, eluting with 75% acetone/EtOAc, to give a cream coloured precipitate. The precipitate was washed with EtOAc (2 × 5mL) and dried under vacuum

to give the amide **S54** (244 mg, 48%) as a white solid: mp 181–182 °C; ^{1}H NMR δ 10.33 (br s, 1H, NH), 9.20 (br s, 1H, NH-3), 8.39 (dd, *J* = 7.1, 1.8 Hz, 1H, H-4''), 8.05 (dd, *J* = 5.3, 1.2 Hz, 1H, H-5), 7.88 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7), 7.10 (dd, *J* = 7.1, 1.8 Hz, 1H, H-6''), 7.05 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6), 6.23 (t, *J* = 7.1 Hz, 1H, H-5''), 4.51–4.57 (m, 1H, H-4'), 4.22 (t, *J* = 5.2 Hz, 2H, H_2-1'''), 3.74 (t, *J* = 5.2 Hz, 2H, H_2-2'''), 3.35 (s, 3H, OMe-4'''), 3.24 (s, 2H, CH_2CO), 3.02–3.07 (m, 2H, H_2-2', H_2-6'), 2.47–2.59 (m, 4H, H-2', H-3', H-5', H-6'), 1.90–1.95 (m, 2H, H_2-3', H_2-5'); ^{13}C NMR δ 169.6 (CH_2CO), 157.6 (C-2''), 153.8 (C-2), 143.5 (C-3a), 140.1 (C-5), 131.8 (C-6''), 129.0 (C-3''), 123.4 (C-7a), 122.4 (C-4''), 117.1 (C-6), 117.0 (C-6), 106.1 (C-5''), 70.3 (C-2'''), 61.9 (CH_2CO), 59.2 (C-4'''), 53.4 (C-2', C-6'), 50.1 (C-1'''), 49.4 (C-4'), 29.7 (C-3', C-5'); MS *m/z* 427.9 (MH^+, 100%). Anal. calcd for $C_{21}H_{26}N_6O_4$: C, 59.14; H, 6.14; N, 19.71. Found: C, 58.97; H, 6.14; N, 19.82%.

SN35765 1-(1-(2-((1-(2-Methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)amino)acetyl)piperidin-4-yl)-1*H*-imidazo[4,5-b]pyridin-2(3*H*)-one (**S55**).



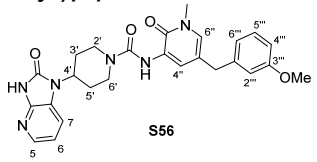
Methyl 2-((1-(2-Methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)amino)acetate (S55a). Prepared using Method I from methyl bromoacetate and amine **S54b**. The crude residue was purified by column chromatrography, eluting with 60–90% EtOAc/pet. ether, to give methyl ester **S55a** (187 mg, 25%) as a blue oil: ^{1}H NMR δ 6.75 (dd, *J* = 6.5, 2.0 Hz, 1H, H-6), 6.07–6.14 (m, 2H, H-5, H-4), 5.48 (br t, *J* = 5.9 Hz, 1H, NH), 4.14 (t, *J* = 5.2 Hz, 2H, H_2-1'), 3.90 (d, *J* = 5.9 Hz, 2H, CH_2NH), 3.77 (s, 3H, COOMe), 3.69 (t, *J* = 5.2 Hz, 2H, H_2-2'), 3.32 (s, 3H, OMe-4'); MS *m/z* 241.5 (MH^+, 100%).

2-((1-(2-Methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)amino)acetic Acid (S55b). Prepared using Method J from methyl ester **S55a** to give acid **S55b** (103 mg, 98%) as a blue solid: ^{1}H NMR δ 6.79 (dd, *J* = 7.0, 1.7 Hz, 1H, H-6), 6.22 (dd, *J* = 7.0, 1.7 Hz, 1H, H-4), 6.15 (t, *J* = 7.0 Hz, 1H, H-5), 4.16 (t, *J* = 5.1 Hz, 2H, H_2-1), 3.92 (s, 2H, CH_2NH), 3.69 (t, *J* = 5.1 Hz, 2H, H_2-2'), 3.32 (s, 3H, OMe-4'); MS *m/z* 227.5 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 227.1020 (calcd for $C_{10}H_{15}N_2O_4$, 227.1026).

1-(1-(2-((1-(2-Methoxyethyl)-2-oxo-1,2-dihydropyridin-3-yl)amino)acetyl)piperidin-4-yl)-1*H*-imidazo[4,5-b]pyridin-2(3*H*)-one (S55). Prepared using Method D from acid **S55b** and piperidine **S1d**. The resulting dark green residue was purified by column chromatography, eluting with 25% MeOH/EtOAc, to give a green residue, which was triturated with pet. ether to give the amide **S55** (27 mg, 9%) as a light green solid: mp 213–216 °C; ^{1}H NMR δ 9.32 (br s, 1H, NH-3), 8.04 (d, *J* = 5.3 Hz, 1H, H-5), 7.22 (d, *J* = 7.9 Hz, 1H, H-7), 6.97 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6), 6.77 (dd, *J* = 6.7, 1.2 Hz, 1H, H-6''), 6.22 (d, *J* = 6.7 Hz, 1H, H-4''), 6.12 (t, *J* = 6.7 Hz, 1H, H-5''), 5.86 (br t, *J* = 4.5 Hz, 1H, CH_2NH), 4.90 (br d, *J* = 13.0 Hz, 1H, H-2' or H-6'), 4.57–4.65 (m, 1H, H-4'), 4.15 (t, *J* = 4.8 Hz, 2H, H_2-1'''), 3.90–4.05 (m, 3H, H-2' or H-6', $COCH_2$), 3.70 (t, *J* = 4.8 Hz, 2H, H_2-2'''), 3.32 (s, 3H, OMe-4'''), 3.25 (br t, *J* = 14.3 Hz, 1H, H_2-2' or H_2-6'), 2.77 (br t, *J* = 12.7 Hz, 1H, H_2-2' or H_2-6'), 2.17–2.27 (m, 2H, H_2-3' or H_2-5'), 1.98 (br t, *J* = 11.4 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR δ 167.1 ($COCH_2$), 157.6 (C-2''), 153.1 (C-2), 143.0 (C-3a), 140.7

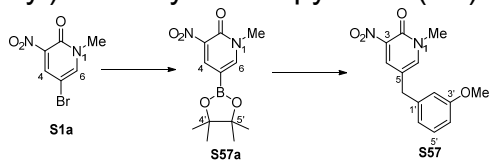
(C-5), 138.3 (C-3''), 125.3 (C-6''), 123.2 (C-7a), 117.2 (C-6), 115.4 (C-7), 107.3 (C-5''), 106.4 (C-4''), 70.7 (C-2'''), 59.1 (C-4'''), 50.4 (C-4'), 49.9 (C-1'''), 45.6 ($COCH_2$), 44.4 (C-2' or C-6'), 42.0 (C-2' or C-6'), 30.0 (C-3' or C-5'), 29.3 (C-3' or C-5'); (+)-HRESIMS *m/z* $[M+Na]^+$ 449.1912 (calcd for $C_{21}H_{276}N_6NaO_4$, 449.1921).

SN35766 *N*-(5-(3-Methoxybenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S56**).



***N*-(5-(3-Methoxybenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S56).** Prepared using Method C from **S1d** and **S58**. The crude residue was purified by column chromatography, eluting with 10–20% MeOH/EtOAc, to give urea **S56** (68 mg, 54%) as an off-white solid: mp 268–271 °C; ^{1}H NMR δ 9.62 (br s, 1H, NH-3), 8.10 (d, *J* = 2.1 Hz, H-4''), 8.03–8.04 (m, 2H, H-5, CONH), 7.31 (dd, *J* = 7.9, 1.0 Hz, 1H, H-7), 7.24 (t, *J* = 8.0 Hz, 1H, H-5'''), 6.97 (dd, *J* = 7.9, 5.1 Hz, 1H, H-6), 6.77–6.81 (m, 2H, H-4''', H-6'''), 6.74 (m, 1H, H-2'''), 6.67 (d, *J* = 2.1 Hz, 1H, H-6''), 5.60 (tt, *J* = 12.9, 4.1 Hz, 1H, H-4'), 4.34 (br d, *J* = 12.9 Hz, 2H, H_2-2' or H-6'), 3.80 (s, 3H, OMe-3'''), 3.72 (s, 2H, CH_2), 3.57 (s, 3H, Me-1''), 3.02–3.08 (m, 2H, H_2-2' or H_2-6'), 2.26 (qd, *J* = 12.9, 4.1 Hz, 2H, H_2-3' or H_2-5'), 1.94–1.97 (m, 2H, H_2-3' or H_2-5'); ^{13}C NMR δ 160.0 (C-3'''), 157.4 (C-2''), 154.1 (CONH), 153.2 (C-2), 143.1 (C-3a), 141.3 (C-1'''), 140.5 (C-5), 130.1 (C-3''), 129.8 (C-5'''), 127.2 (C-6''), 123.3 (C-7a), 121.7 (C-4''), 121.3 (C-6'''), 120.1 (C-5''), 117.1 (C-6), 115.6 (C-7), 114.9 (C-2'''), 111.8 (C-4'''), 55.4 (OMe-3'''), 50.5 (C-4'), 44.0 (C-2', C-6'), 38.7 (CH_2), 37.9 (Me-1''), 29.5 (C-3', C-5'); MS *m/z* 490.2 (MH^+, 100%). Anal. calcd for $C_{26}H_{28}N_6O_4 \cdot 0.5MeOH$: C, 63.08; H, 5.99; N, 16.66. Found: C, 63.25; H, 5.77; N, 16.45%.

SN35767 5-(3-Methoxybenzyl)-1-methyl-3-nitropyridin-2(1*H*)-one (**S57**).

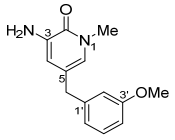


1-Ethyl-3-nitro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2(1*H*)-one (S57a). Bromide **S1a** (500 mg, 2.15 mmol), B_2Pin_2 (599 mg, 2.36 mmol) and KOAc (1.28 g, 13.09 mmol) were suspended in DMSO (25 mL). The reaction mixture was purged with dry N_2 (gas bubbling through solution) for 10 min before addition of $Pd(dppf)Cl_2$.DCM (88 mg, 0.11 mmol). The reaction mixture was heated at 90 °C for 1 h while being continuously purged with dry N_2. The resulting cooled mixture was diluted with EtOAc (100 mL) and partitioned with water (200 mL). The aqueous layer was extracted with more EtOAc (4 × 100mL). The organic fractions were dried and concentrated under vacuum to give a dark brown residue. The residue was triturated with 25% EtOAc/pet. ether and filtered through a pad of diatomaceous earth. The filtrate was concentrated and dried under vacuum to give the boronate ester **S57a** (577 mg) as a light brown solid, which was used in the next step without further purification: mp 211–214 °C; ^{1}H NMR δ 8.58 (d, *J* =

2.0 Hz, 1H, H-4), 8.07 (d, *J* = 2.0 Hz, 1H, H-6), 3.70 (s, 3H, Me-1), 1.34 (s, 12H, H_3-4', H_3-5').

5-(3-Methoxybenzyl)-1-methyl-3-nitropyridin-2(1*H*)-one (S57). Prepared using Method A from **S57a** and 3-methoxybenzyl bromide with $Pd(PPh_3)_4$. The crude material was purified by column chromatography, eluting with 10–20% EtOAc/DCM, to give the pyridone **S57** (130 mg, 23%) as a yellow solid: mp 88–89 °C; ^{1}H NMR δ 8.17 (d, *J* = 2.6 Hz, 1H, H-4), 7.43 (d, *J* = 2.6 Hz, 1H, H-6), 7.28 (t, *J* = 7.9 Hz, 1H, H-5'), 6.83 (dd, *J* = 7.9, 1.3 Hz, 1H, H-4'), 6.75 (dd, *J* = 7.9, 1.3 Hz, 1H, H-6'), 6.69 (m, 1H, H-2'), 3.81 (s, 3H, OMe-3'), 3.77 (s, 2H, CH_2), 3.64 (s, 3H, Me-1); ^{13}C NMR δ 160.3 (C-3'), 154.3 (C-2), 142.9 (C-6), 139.8 (C-4), 139.6 (C-1'), 138.5 (C-3), 130.4 (C-5'), 121.1 (C-6'), 116.6 (C-5), 115.0 (C-2'), 112.3 (C-4'), 55.4 (OMe-3'), 39.0 (Me-1), 37.4 (CH_2); MS *m/z* 275.5 (MH^+, 100%). Anal. calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.23; H, 5.29; N, 10.07%.

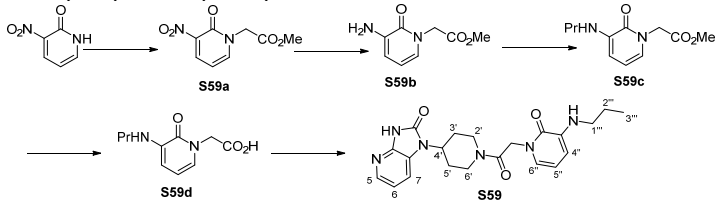
SN35768 3-Amino-5-(3-methoxybenzyl)-1-methylpyridin-2(1*H*)-one (**S58**).



S58

3-Amino-5-(3-methoxybenzyl)-1-methylpyridin-2(1*H*)-one (S58). Prepared using Method B from **S57**. The residue was triturated with diethyl ether to obtain the amine **S58** (92 mg, quant.) as a tan powder: mp 101–103 °C; ^{1}H NMR δ 7.22 (t, *J* = 8.1 Hz, 1H, H-5'), 6.77 (dd, *J* = 8.1, 2.2 Hz, 2H, H-4', H-6'), 6.71 (t, *J* = 2.2 Hz, 1H, H-2'), 6.52–6.53 (m, 1H, H-6), 6.36 (d, *J* = 2.2 Hz, H-4), 4.15 (s, 2H, NH_2), 3.79 (s, 3H, OMe-3'), 3.60 (s, 2H, CH_2), 3.54 (s, 3H, Me-1); ^{13}C NMR δ 159.9 (C-3'), 157.5 (C-2), 141.7 (C-1'), 137.4 (C-3), 129.6 (C-5'),124.1 (C-6), 121.2 (C-6'), 119.3 (C-5), 114.8 (C-2'), 114.0 (C-4), 111.6 (C-4'), 55.3 (OMe-3'), 38.3 (CH_2), 37.5 (Me-1); MS *m/z* 245.6 (MH^+, 100%). Anal. calcd for $C_{14}H_{16}N_2O_2 \cdot 0.5H_2O$: C, 66.38; H,6.76; N, 11.06. Found: C, 66.28; H, 6.36; N,10.95%.

SN35769 1-(1-(2-(2-Oxo-3-(propylamino)pyridin-1(2*H*)-yl)acetyl)piperidin-4-yl)-1*H*-imidazo[4,5-b]pyridin-2(3*H*)-one (**S59**).



S59a **S59b** **S59c** **S59d** **S59**

Methyl 2-(3-Nitro-2-oxopyridin-1(2*H*)-yl)acetate (S59a). Prepared using Method E from methylbromoacetate and 2-hydroxy-3-nitropyridine. The crude residue was purified by column chromatography, eluting with 60–100% EtOAc/pet. ether, to give ester **S59a** (1.15 g, 76%) as an orange solid: ^{1}H NMR δ 8.41 (dd, *J* = 7.6, 2.1 Hz, 1H), 7.64 (dd, *J* = 6.7, 2.1 Hz, 1H), 6.39 (dd, *J* = 7.6, 6.7 Hz, 1H), 4.79 (s, 2H), 3.84 (s, 3H); MS *m/z* 213.5 (MH^+, 100%).

Methyl 2-(3-Amino-2-oxopyridin-1(2*H*)-yl)acetate (S59b). Prepared using Method B from **S59a** to give amine **S59b** (383 mg, 88%) as a yellow-green oil: ^{1}H NMR δ 6.66 (dd,

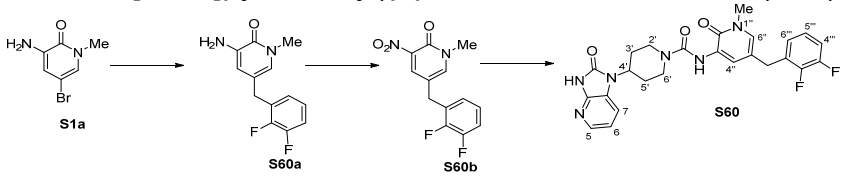
J = 7.0, 1.7 Hz, 1H), 6.55 (dd, *J* = 7.0, 1.7 Hz, 1H), 6.11 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.67 (s, 2H), 4.21 (br s, 2H), 3.78 (s, 3H); MS *m/z* 183.5 (MH^+, 100%).

Methyl 2-(2-Oxo-3-(propylamino)pyridin-1(2*H*)-yl)acetate (S59c). To a solution of the amine **S59b** (158 mg, 0.87 mmol) in DCM (10 mL) was added propionaldehyde (94 µL, 1.30 mmol). The resulting mixture was allowed to stir at 20 °C for 4 h under N_2 before addition of $NaBH(OAc)_3$ (202 mg, 0.95 mmol), which was left to stir 17 h at 20 °C under N_2. The reaction mixture was diluted with EtOAc (50 mL), washed with 5% K_2CO_3 (50 mL) and brine (50 mL), dried and concentrated under reduced pressure to give a crude blue oil. The crude residue was purified by column chromatography, eluting with 30–40% EtOAc/pet. ether, to give ester **S59c** (145 mg, 75%) as a blue solid: mp 60–61 °C; ^{1}H NMR δ 6.55 (m, 1H, H-6), 6.16 (m, 2H, H-4, H-5), 4.96 (br s, 1H, NH), 4.65 (s, 2H, CH_2CO), 3.76 (s, 3H, OMe), 3.02 (td, *J* = 7.1, 5.8 Hz, 2H, H_2-1'), 1.66 (qt, *J* = 7.4, 7.1 Hz, 2H, H_2-2'), 0.99 (t, *J* = 7.4 Hz, 3H, H_3-3'); MS *m/z* 225.5 (MH^+, 100%).

2-(2-Oxo-3-(propylamino)pyridin-1(2*H*)-yl)acetic Acid (S59d). Prepared using Method J from methyl ester **S59c** to give the acid **S59d** (105 mg, 92%) as a grey solid: mp 148–150 °C; ^{1}H NMR δ 6.62 (dd, *J* = 6.0, 2.2 Hz, 1H, H-6), 6.31 (m, 2H, H-4, H-5), 4.70 (s, 2H, CH_2CO), 3.05 (t, *J* = 7.1 Hz, 2H, H_2-1'), 1.68 (qt, *J* = 7.4, 7.1 Hz, 2H, H_2-2'), 1.01 (t, *J* = 7.4 Hz, 3H, H_2-3'); MS *m/z* 211.6 (MH^+, 100%). Anal. calcd for $C_{10}H_{14}N_2O_3 \cdot 0.08H_2O$: C, 56.74; H, 6.74; N, 13.23. Found: C, 57.21; H, 6.79; N, 12.73%.

1-(1-(2-(2-Oxo-3-(propylamino)pyridin-1(2*H*)-yl)acetyl)piperidin-4-yl)-1*H*-imidazo[4,5-b]pyridin-2(3*H*)-one (S59). Prepared using Method D from **S59d** and **S1d**. The crude green oil was purified by column chromatography, eluting with 6–10% MeOH/EtOAc, which was triturated with 10% EtOAc/pet. ether to give the amide **S59** (34 mg, 17%) as a light blue powder: mp 188–191 °C; ^{1}H NMR δ 8.15 (br s, 1H, NH-3), 8.02 (dd, *J* = 5.1, 1.1 Hz, 1H, H-5), 7.44 (dd, *J* = 7.7, 1.1 Hz, 1H, H-7), 6.98 (dd, *J* = 7.7, 5.1 Hz, 1H, H-6), 6.71 (dd, *J* = 6.2, 2.2 Hz, 1H, H-6''), 6.21–6.26 (m, 2H, H-4'', H-5''), 5.12 (d, *J* = 14.8 Hz, 1H, $COCH_2$), 4.93 (t, *J* = 5.3 Hz, $NHCH_2$), 4.82 (br d, *J* = 12.9 Hz, 1H, H_2-1' or H-6'), 4.59–4.66 (m, 1H, H-4'), 4.51 (d, *J* = 14.8 Hz, 1H, $COCH_2$), 4.20 (br d, *J* = 11.6 Hz, 1H, H_2-1' or H_2-6'), 3.30 (br t, *J* = 11.6 Hz, 1H, H_2-1' or H_2-6'), 3.04 (td, *J* = 7.4, 5.3 Hz, 2H, H_2-1'''), 2.76 (br t, *J* = 12.9 Hz, 1H, H_2-1' or H_2-6'), 2.34–2.42 (m, 1H, H_2-3' or H_2-5'), 2.17–2.26 (m, 1H, H_2-3' or H_2-5'), 1.90–1.98 (m, 2H, H_2-3' or H_2-5'), 1.68 (qt, *J* = 7.5, 7.1 Hz, 2H, H_2-2'''), 1.01 (t, *J* = 7.5 Hz, 3H, H-3'''); ^{13}C NMR δ 165.8 ($COCH_2$), 157.7 (C-2''), 153.3 (C-2), 143.1 (C-3a), 140.6 (C-5), 139.0 (C-3''), 123.2 (C-7a), 123.1 (C-6''), 117.1 (C-6), 116.0 (C-7), 107.9 (C-5''), 106.5 (C-4''), 50.1 (C-4'), 49.9 ($COCH_2$), 45.3 (C-2' or 6'), 45.2 (C-1'''), 42.4 (C-2' or 6'), 29.7 (C-3' or C-5'), 29.2 (C-3' or C-5'), 22.3 (C-2'''), 11.9 (C-3'''); MS *m/z* 411.9 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 411.2126 (calcd for $C_{21}H_{27}N_6O_3$, 411.2139).

SN35770 *N*-(5-(2,3-Difluorobenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S60**).

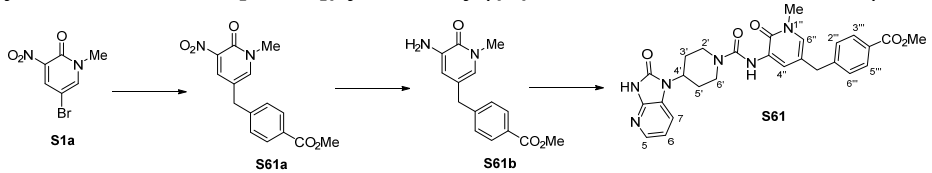


5-(2,3-Difluorobenzyl)-1-methyl-3-nitropyridin-2(1*H*)-one (60a). Prepared using Method A from **S1a** and 2,3-difluorophenylboronic acid. The crude mixture was purified by column chromatography, eluting with 10–20% EtOAc/DCM. Further column chromatography, eluting with EtOAc, gave **S60a** (0.022 g, 12%) as a yellow powder: mp 151–153 °C; ^{1}H NMR δ 8.19 (d, *J* = 2.3 Hz, 1H, H-4), 7.58 (d, *J* = 2.3 Hz, 1H, H-6), 7.06–7.15 (m, 2H, H-4', H-5'), 6.95–6.99 (m, 1H, H-6'), 3.85 (s, 2H, CH_2), 3.66 (s, 3H, Me-1); MS *m/z* 281.5 (MH^+, 100%). Anal. calcd for $C_{13}H_{10}F_2N_2O_3$: C, 55.72; H, 3.60; N, 10.00. Found: C, 55.98; H, 3.62; N, 9.73%.

3-Amino-5-(2,3-difluorobenzyl)-1-methylpyridin-2(1*H*)-one (S60b). Prepared using Method B from **S60a**. The crude product which was purified by column chromatography, eluting with EtOAc. Amine **S60b** (35 mg, quant.) was obtained as a tan powder: mp 130–134 °C (decomp.); ^{1}H NMR δ 6.98–7.08 (m, 2H, H-4', H-5'), 6.89–6.92 (m, 1H, H-6'), 6.56 (d, *J* = 2.1 Hz, 1H, H-6), 6.38 (d, *J* = 2.1 Hz, 1H, H-4), 4.19 (br s, 2H, NH_2), 3.67 (s, 2H, CH_2), 3.54 (s, 3H, Me-1); MS *m/z* 251.5 (MH^+, 100%). Anal. calcd for $C_{13}H_{12}F_2N_2O\cdot0.15EtOAc$: C, 54.88; H, 4.42; N, 9.62. Found: C, 55.28; H, 4.36; N, 9.62%.

***N*-(5-(2,3-Difluorobenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S60).** Prepared using Method C. The crude mixture was purified by column chromarography, eluting with 10% MeOH/EtOAc, to give urea **S60** (86 mg, 64%) an off-white solid: mp 241–243 °C; ^{1}H NMR δ 9.89 (br s, 1H, NH-3), 8.11 (d, *J* = 1.9 Hz, 1H, H-4"), 8.04–8.05 (m, 2H, H-5, CONH), 7.30 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7), 7.02–7.09 (m, 2H, H-4"', H-5"'), 6.96–7.00 (m, 2H, H-6, H-6"'), 6.75 (d, *J* = 1.9 Hz, 1H, H-6"), 4.59 (tt, *J* = 12.5, 4.1 Hz, 1H, H-4'), 4.34 (br d, *J* = 13.8 Hz, 2H, H_2-2' or H_2-6'), 3.79 (s, 2H, CH_2), 3.59 (s, 3H, Me-1"), 3.06 (br t, *J* = 12.7 Hz, 2H, H_2-2' or H_2-6'), 2.27 (qd, *J* = 12.7, 4.1 Hz, 2H, H_2-3' or H_2-5'), 1.96 (br dd, *J* = 12.7, 2.1 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR δ 157.3 (C-2"), 154.1 (CONH), 153.3 (C-2), 150.8 (dd, *J* = 248.4, 13.3 Hz, C-3"'), 149.1 (dd, *J* = 247.0, 12.8 Hz, C-2"'), 143.2 (C-3a), 140.5 (C-5), 130.3 (C-3"), 129.3 (C-1"'), 127.3 (C-6"), 125.5 (C-6"'), 124.4 (C-5"'), 123.3 (C-7a), 121.2 (C-4"), 118.2 (C-5"), 117.1 (C-6), 115.9 (C-4"'), 50.5 (C-4'), 44.0 (C-2', C-6'), 38.0 (Me-1"), 31.6 (CH_2), 29.5 (C-3', C-5'); MS *m/z* 496.1 (MH^+, 100%). Anal. calcd for $C_{25}H_{24}F_2N_6O_3$: C, 60.72; H, 4.89; N, 17.00. Found: C, 60.44; H, 4.90; N, 16.83%.

SN35771 *N*-(5-(4-Carbomethoxybenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S61**).

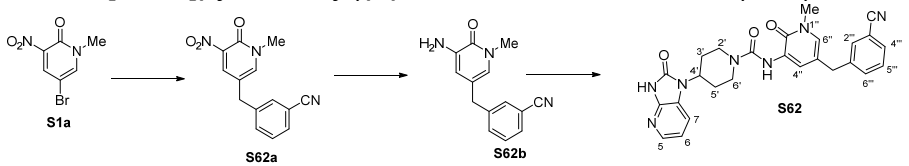


5-(4-Carbomethoxybenzyl)-1-methyl-3-nitropyridin-2(1*H*)-one (S61a). Prepared using Method A from **S1a** and (4-(methoxycarbonyl)benzyl)boronic acid. The crude mixture was purified by column chromatography, eluting with 10–20% EtOAc/DCM, to give a yellow residue which was purified by column chromatography, eluting with EtOAc, to give **S61a** (164 mg, 22%) as a yellow powder: mp 164–167 °C; ^{1}H NMR δ 8.15 (d, *J* = 2.6 Hz, 1H, H-4), 8.01–8.04 (m, 2H, H-3', H-5'), 7.45 (d, *J* = 2.6 Hz, 1H, H-6), 7.24 (obsc., 2H, H-2', H-6'), 3.93 (s, 3H, OMe), 3.86 (s, 2H, CH_2), 3.65 (s, 3H, Me-1); MS *m/z* 303.6 (MH^+, 100%). Anal. calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.75; H, 4.64; N, 9.20%.

3-Amino-5-(4-carbomethoxybenzyl)-1-methylpyridin-2(1*H*)-one (S61b). Prepared using Method B from **S61a**. The crude product which was purified by column chromatography, eluting with (0-2%) MeOH/EtOAc, to give amine **S61b** (111 mg, 87%) as an off-white solid: mp 170–172 °C; ^{1}H NMR δ 7.96–7.99 (m, 2H, H-3', H-5'), 7.24 (d, *J* = 8.4 Hz, 2H, H-2', H-6'), 6.51–6.52 (m, 1H, H-6), 6.32 (d, *J* = 2.2 Hz, 1H, H-4), 4.18 (br s, 2H, NH_2-3), 3.91 (s, 3H, OMe), 3.68 (s, 2H, CH_2), 3.54 (s, 3H, Me-1); MS *m/z* 273.5 (MH^+, 100%). Anal. calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.24; H, 5.91; N, 10.32%.

***N*-(5-(4-Carbomethoxybenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S61).** Prepared using Method C from **S61b** and **S1d**. The product was washed with EtOAc (2 × 3 mL) and dried under vacuum to give urea **S61** (144 mg, 84%) as an off-white solid: mp 245–248 °C; ^{1}H NMR δ 10.0 (br s, 1H, NH-3), 8.08 (d, *J* = 2.2 Hz, 1H, H-4''), 8.04–8.05 (m, 2H, H-5, CONH), 7.97–8.00 (m, 2H, H-3''', H-5'''), 7.27–7.31 (m, 3H, H-7, H-2''', H-6'''), 6.97 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6), 6.68 (d, *J* = 2.2 Hz, 1H, H-6''), 4.59 (tt, *J* = 12.7, 4.1 Hz, 1H, H-4'), 4.33 (br d, *J* = 12.7 Hz, 1H, H_2-2' or H_2-6'), 3.91 (s, 3H, OMe), 3.79 (s, 2H, CH_2), 3.58 (s, 3H, Me-1''), 3.05 (br t, *J* = 12.7 Hz, 2H, H_2-2' or H_2-6'), 2.26 (qd, *J* = 12.7, 4.1 Hz, 2H, H_2-3' or H_2-5'), 1.95 (dd, *J* = 12.7, 2.4 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR δ 167.1 (COOMe), 157.3 (C-2''), 154.0 (CONH), 153.4 (C-2), 145.0 (C-1'''), 143.2 (C-3a), 140.5 (C-5), 130.3 (C-3''), 130.2 (C-3''', C-5'''), 128.9 (C-2''', C-6'''), 128.7 (C-4'''), 127.2 (C-6''), 123.3 (C-7a), 121.4 (C-4''), 119.4 (C-5''), 117.1 (C-6), 115.5 (C-7), 52.2 (OMe), 50.5 (C-4'), 43.9 (C-2', C-6'), 38.6 (CH_2), 37.9 (Me-1''), 29.5 (C-3', C-5'); (+)-HRESIMS *m/z* $[M+Na]^+$ 539.2008 (calcd for $C_{27}H_{28}N_6NaO_5$, 539.2013). Anal. calcd for $C_{27}H_{28}N_6O_5 \cdot 0.55H_2O$: C, 62.78; H, 5.46; N, 16.27. Found: C, 61.51; H, 5.41; N, 15.82%.

SN35774 *N*-(5-(3-Cyanobenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S62**).



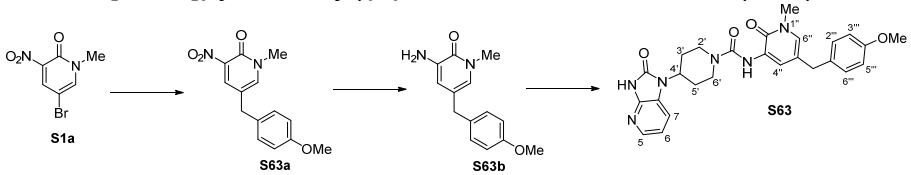
5-(3-Cyanobenzyl)-1-methyl-3-nitropyridin-2(1*H*)-one (S62a). Prepared using Method A from **S1a** and 3-cyanobenzylboronic acid. The crude mixture was purified by column chromatography, eluting with 10–12% EtOAc/DCM, to give **S62a** (41 mg, 6%) as a yellow powder: mp 187–190 °C; ^{1}H NMR δ 8.12 (d, *J* = 2.6 Hz, 1H, H-4), 7.60–7.62 (m, 1H, H-

4'), 7.47–7.52 (m, 3H, H-6, H-2', H-5'), 7.42–7.44 (m, 1H, H-6'), 3.85 (s, 2H, CH_2), 3.67 (3H, s, Me-1); MS *m/z* 270.5 (MH^+, 100%). Anal. calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.35; H, 4.19; N, 15.41%.

3-Amino-5-(3-cyanobenzyl)-1-methylpyridin-2(1*H*)-one (S62b). Prepared using Method B from **S62a**. The crude product which was purified by column chromatography, eluting with EtOAc, to give amine **S62b** (24 mg, 69%) as an off-white solid: mp 161–164 °C; ^{1}H NMR δ 7.51–7.54 (m, 1H, H-4'), 7.47 (d, *J* = 0.8 Hz, 1H, H-2'), 7.39–7.44 (m, 2H, H-5', H-6'), 6.53 (m, 1H, H-6), 6.27 (d, *J* = 2.2 Hz, 1H, H-4), 4.22 (br s, 2H, NH_2-3), 3.66 (s, 2H, CH_2), 3.56 (s, 3H, Me-1); MS *m/z* 240.6 (MH^+, 100%). Anal. calcd for $C_{14}H_{13}N_3O \cdot 0.6H_2O$: C, 67.24; H, 5.72; N, 16.80. Found: C, 66.84; H, 5.32; N, 16.75%.

***N*-(5-(3-Cyanobenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S62).** Prepared using Method C from **S62b** and **S1d**. The crude mixture was purified by column chromatography, eluting with 10% MeOH/EtOAc. The product was concentrated under reduced pressure, redissolved in DCM (1 mL), and triturated in diethyl ether (20 mL). The product was filtered and dried under vacuum to give urea **S62** (34 mg, 65%) as an off-white solid: mp 210–212 °C; ^{1}H NMR δ 11.03 (br s, 1H, NH-3), 8.05–8.07 (m, 3H, H-5, CONH, H-4''), 7.53 (ddd, *J* = 7.4, 1.5, 1.5 Hz, 1H, H-4'''), 7.40–7.48 (m, 3H, H-2''', H-5''', H-6'''), 7.30 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7), 6.97 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6), 6.74 (d, *J* = 2.2 Hz, 1H, H-6''), 4.60 (tt, *J* = 12.3, 4.4 Hz, 1H, H-4'), 4.34 (br d, *J* = 12.3, 2H, H_2-2' or H_2-6'), 3.78 (s, 2H, CH_2), 3.62 (s, 3H, Me-1''), 3.06 (br t, *J* = 12.3 Hz, 2H, H_2-2' or H_2-6'), 2.28 (qd, *J* = 12.3, 4.4 Hz, 2H, H_2-3' or H_2-5'), 1.96 (d, *J* = 12.3 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR δ 157.3 (C-2''), 154.0 (CONH), 153.7 (C-2), 143.5 (C-3a), 141.3 (C-1'''), 140.2 (C-5), 133.3 (C-2'''), 132.2 (C-6'''), 130.5 (C-3'', C-4'''), 129.6 (C-5'''), 127.3 (C-6''), 123.3 (C-7a), 121.0 (C-4''), 118.8 (CN-3'''), 118.5 (C-5''), 116.8 (C-6), 115.4 (C-7), 112.8 (C-3'''), 50.3 (C-4'), 43.9 (C-2', C-6'), 38.0 (Me-1'', CH_2), 29.4 (C-3', C-5'); MS *m/z* 485.2 (MH^+, 100%). Anal. calcd for $C_{26}H_{25}N_7O_3 \cdot 0.25H_2O$: C, 63.99; H, 5.27; N, 20.09. Found: C, 64.16; H, 5.19; N, 19.91%.

SN35775 *N*-(5-(4-Methoxybenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S63**).



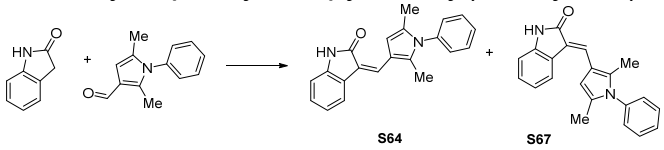
5-(4-Methoxy)-1-methyl-3-nitropyridin-2(1*H*)-one (S63a). Prepared using Method A from **S1a** and 4-methoxybenzylboronic acid. The crude mixture was purified by column chromatography, eluting with 5–10% EtOAc/DCM, to give pyridone **S63a** (22 mg, 4%) as a yellow powder: mp 169–171 °C; ^{1}H NMR δ 8.15 (d, *J* = 2.6 Hz, 1H, H-4), 7.44 (d, *J* = 2.6 Hz, 1H, H-6), 7.02–7.14 (m, 2H, H-2', H-6'), 6.86–6.90 (m, 2H, H-3', H-5'), 3.81 (s, 3H, OMe-4'), 3.75 (s, 2H, CH_2), 3.63 (s, 3H, Me-1); MS *m/z* 275.6 (MH^+, 100%). Anal. calcd for $C_{14}H_{14}N_2O_4$: C, 60.12; H, 5.26; N, 10.02. Found: C, 60.49; H, 5.18; N, 9.63%.

3-Amino-5-(4-methoxybenzyl)-1-methylpyridin-2(1*H*)-one (S63b). Prepared using Method B from **S63a**. The product was purified by column chromatography, eluting with 1%MeOH/EtOAc, to give amine **S63b** (52 mg, 85%) as an off-white solid: mp 130–131

°C; ^{1}H NMR δ 7.06–7.10 (m, 2H, H-2', H-6'), 6.82–6.86 (m, 2H, H-3', H-5'), 6.49 (m, 1H, H-6), 6.35 (d, *J* = 2.2 Hz, 1H, H-4), 4.15 (br s, NH_2-3), 3.79 (s, 3H, OMe-4'), 3.57 (s, 2H, CH_2), 3.53 (s, 3H, Me-1); MS *m/z* 245.6 (MH^+, 100%). Anal. calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.54; H, 6.73; N, 11.35%.

***N*-(5-(4-Methoxybenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S63).** Prepared using Method C from **S63a** and **S1d**. The crude mixture was purified by column chromatography, eluting with 10% MeOH/EtOAc, to give urea **S63** (39 mg, 45%) as an off-white solid: mp 234–237 °C; ^{1}H NMR δ 10.24 (s, 1H, NH-3), 8.09 (d, *J* = 2.2 Hz, 1H, H-4''), 8.05 (dd, *J* = 5.3, 1.3 Hz, 1H, H-5), 8.03 (s, 1H, CONH), 7.30 (dd, *J* = 7.9, 1.3 Hz, 1H, H-7), 7.11–7.14 (m, 2H, H-2''', H-6'''), 6.97 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6), 6.84–6.87 (m, 2H, H-3''', H-5'''), 6.64–6.65 (m, 1H, H-6''), 4.60 (tt, *J* = 12.6, 4.2 Hz, 1H, H-4'), 4.34 (d, *J* = 12.6 Hz, 2H, H_2-2' or H_2-6'), 3.80 (s, 3H, OMe-4'''), 3.68 (s, 2H, CH_2), 3.57 (s, 3H, Me-1''), 3.05 (t, *J* = 12.6 Hz, 2H, H_2-2' or H_2-6'), 2.26 (dq, *J* = 12.6, 4.2 Hz, 2H, H_2-3' or H_2-5'), 1.95 (dd, *J* = 12.07, 2.1 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR δ 158.4 (C-4'''), 157.3 (C-2''), 154.1 (CONH), 153.5 (C-2), 143.3 (C-3a), 140.4 (C-5), 131.7 (C-1'''), 130.1 (C-3''), 129.9 (C-2'''), 126.9 (C-6''), 123.3 (C-7a), 121.7 (C-4''), 120.8 (C-5''), 117.0 (C-6), 115.5 (C-7), 114.3 (C-3'''), 55.4 (OMe-4'''), 50.4 (C-4'), 44.0 (C-2', C-6'), 37.9 (CH_2), 37.8 (Me-1''), 29.5 (C-3', C-5'); MS *m/z* 490.2 (MH^+, 100%). Anal. calcd for $C_{26}H_{28}N_6O_4 \cdot 0.25H_2O$: C, 63.34; H, 5.83; N, 17.04. Found: C, 63.19; H, 5.63; N, 16.84%.

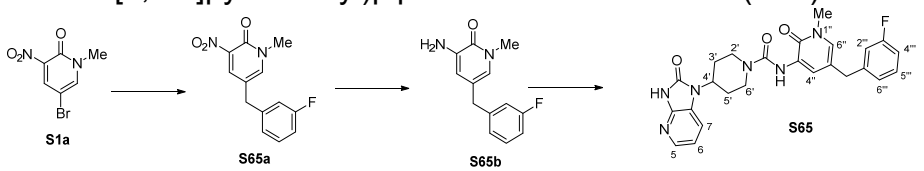
SN36205 (*Z*)-3-((2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)methylene)indolin-2-one (**S64**).



S64 S67

(*Z*)-3-((2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)methylene)indolin-2-one (S64). Prepared using Method N indolin-2-one and 2,5-dimethyl-1-phenyl-1*H*-pyrrole-3-carbaldehyde. The resulting crystals were filtered and dried to give indoline **S64** (295 mg, 62%) as yellow plates: mp (EtOH) 213–216 °C; ^{1}H NMR δ 8.08 (d, *J* = 7.7 Hz, 1 H, H-4), 7.89 (br s, 1 H, CONH), 7.82 (s, 1 H, H-4″), 7.45–7.55 (m, 3 H, H-2‴, H-4‴, H-6‴), 7.23–7.27 (m, 2 H, H-3‴, H-5‴), 7.18 (dt, *J* = 7.7, 1.1 Hz, 1 H, H-5), 7.03 (dt, *J* = 7.6, 1.1 Hz, 1 H, H-6), 6.90 (br d, *J* = 7.6 Hz, 1 H, H-7), 6.63 (s, 1 H, H-1′), 2.21 (s, 3 H, CH_3), 2.09 (s, 3 H, CH_3); MS *m/z* 315.2 (MH^+, 100%). Anal. calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.99. Found: C, 80.25; H, 5.92; N, 8.89%.

SN36206 *N*-(5-(3-Fluorobenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S65**).



S1a S65a S65b S65

5-(3-Fluorobenzyl)-1-methyl-3-nitropyridin-2(1*H*)-one (S65a). Prepared using Method A from **S1a** and 3-fluorobenzylboronic acid. The crude mixture was purified by column chromatography, eluting with 5–10% EtOAc/DCM, to give pyridone **S65a** (133 mg, 19%) as a yellow powder: mp 110–111 °C; ^{1}H NMR δ 8.15 (d, *J* = 2.6 Hz, 1H, H-4), 7.45 (d, *J*

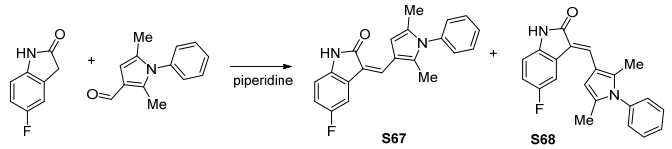
= 2.6 Hz, 1H, H-6), 7.30–7.36 (ddd, *J* = 6.0, 6.0, 6.0 Hz, 1H, H-5'), 6.95–7.02 (m, 2H, H-4', H-6'), 6.87 (ddd, *J* = 9.5, 2.0, 1.9 Hz, H-2'), 3.80 (s, 2H, CH_2), 3.65 (s, 3H, Me-1); ^{13}C NMR δ 163.3 (d, J_{CF} = 246.0 Hz, C-3'), 154.3 (C-2), 143.0 (C-6), 140.5 (d, J_{CF} = 7.1 Hz, C-1'), 139.7 (C-4), 138.6 (C-3), 130.9 (d, J_{CF} = 8.5 Hz, C-5'), 124.5 (d, J_{CF} = 2.6 Hz, C-6'), 115.9 (C-5), 115.8 (d, J_{CF} = 21.6 Hz, C-2'), 114.5 (d, J_{CF} = 20.9 Hz, C-4'), 39.0 (Me-1), 37.1 (d, J_{CF} = 1.3 Hz, CH_2); MS *m/z* 263.5 (MH^+, 100%). Anal. calcd for $C_{13}H_{11}FN_2O_3$: C, 59.54; H, 4.23; N, 10.68. Found: C, 59.77; H, 4.17; N, 10.72%.

3-Amino-5-(3-fluorobenzyl)-1-methylpyridin-2(1*H*)-one (S65b). Prepared using Method B from **S65a** to give the amine **S65b** (93 mg, quant.) as an off-white solid which was used without further purification: mp 113–115 °C; ^1H NMR δ 7.23–7.29 (m, 1H, H-5'), 6.85–6.96 (m, 3H, H-2', H-4', H-6'), 6.53 (m, 1H, H-6), 6.33 (d, *J* = 2.2 Hz, 1H, H-4), 4.20 (br s, 2H, NH_2-3), 3.62 (s, 2H, CH_2), 3.54 (s, 3H, Me-1); ^{13}C NMR δ 163.1 (d, J_{CF} = 244.7 Hz, C-3), 157.6 (C-2), 142.7 (d, J_{CF} = 7.1 Hz, C-1'), 137.6 (C-3), 130.1 (d, J_{CF} = 8.5 Hz, C-5'), 124.5 (d, J_{CF} = 2.9 Hz, C-6'), 124.2 (C-6), 118.8 (C-5), 115.7 (d, J_{CF} = 20.9 Hz, C-2'), 113.8 (C-4), 113.5 (d, J_{CF} = 20.8 Hz, C-4'), 38.1 (CH_2), 37.6 (Me-1); MS *m/z* 233.6 (MH^+, 100%). Anal. calcd for $C_{13}H_{13}FN_2O \cdot 0.45H_2O$: C, 64.96; H, 5.83; N, 11.65. Found: C, 64.74; H, 5.45; N, 11.43%.

***N*-(5-(3-Fluorobenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S65).** Prepared using Method C from **S65b** and **S1d**. The crude mixture was purified by column chromatography, eluting with 10% MeOH/EtOAc, to give urea **S65** (109 mg, 76%) as an off-white solid: mp 240–242 °C; ^1H NMR δ 10.77 (br s, 1H, NH-3), 8.08 (d, *J* = 2.2 Hz, 1H, H-4''), 8.05–8.06 (m, 2H, H-5, CONH), 7.25–7.32 (m, 2H, H-7, H-5'''), 6.88–7.01 (m, 4H, H-6, H-2''', H-4''', H-6'''), 6.70 (d, *J* = 2.2 Hz, 1H, H-6''), 4.61 (tt, *J* = 12.7, 4.1 Hz, 1H, H-4'), 4.34 (d, *J* = 12.7 Hz, 2H, H_2-2' or H_2-6'), 3.74 (s, 2H, CH_2), 3.59 (s, 3H, Me-1), 3.06 (t, *J* = 12.7 Hz, 2H, H_2-2' or H_2-6'), 2.27 (qd, *J* = 12.7, 4.1 Hz, 2H, H_2-3' or H_2-5'), 1.96 (dd, *J* = 12.7, 2.4 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR δ 163.1 (d, J_{CF} = 246.2 Hz, C-3'''), 157.3 (C-2''), 154.0 (CONH), 153.6 (C-2), 143.5 (C-3a), 142.2 (d, J_{CF} = 7.1 Hz, C-1'''), 140.3 (C-5), 130.3 (C-3''), 130.3 (d, J_{CF} = 6.5 Hz, C-5'''), 127.2 (C-6''), 124.5 (d, J_{CF} = 2.9 Hz, C-6'''), 123.3 (C-7a), 121.4 (C-4''), 119.5 (C-5''), 116.9 (C-6), 115.7 (d, J_{CF} = 21.4 Hz, C-2'''), 115.5 (C-7), 113.6 (d, J_{CF} = 21.2 Hz, C-4'''), 50.4 (C-4'), 43.9 (C-2', C-6'), 38.3 (d, J_{CF} = 1.2 Hz, CH_2), 37.9 (Me-1''), 29.5 (C-3', C-5'); MS *m/z* 478.1 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 477.2049 (calcd for $C_{25}H_{26}FN_6O_3$, 477.2045). Anal. calcd for $C_{25}H_{25}FN_6O_3 \cdot 0.5EtOAc \cdot 0.8H_2O$: C, 61.54; H, 5.85; N, 15.95. Found: C, 61.69; H, 5.66; N, 15.77%.

SN36207 (*E*)-3-((2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)methylene)indolin-2-one (**S66**). The mother liquor from **S64** was purified by chromatography, eluting with a gradient (30–50%) of EtOAc/pet. ether, to give the *E*-isomer **S66** (128 mg, 27%) as a tan gum: ^1H NMR δ 7.93 (br s, 1 H, CONH), 7.70 (s, 1 H, H-4′′), 7.58 (s, 1 H, H-1′), 7.45–7.54 (m, 4 H, H-4, H-2′′′, H-4′′′, H-6′′′), 7.20–7.24 (m, 2 H, H-3′′′, H-5′′′), 7.13 (dt, *J* = 7.6, 1.0 Hz, 1 H, H-5), 7.00 (dt, *J* = 7.6, 1.0 Hz, 1 H, H-6), 6.85 (d, *J* = 7.6 Hz, 1 H, H-7), 2.24 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3); MS *m/z* 315.2 (MH^+, 100%).

SN36227 (*Z*)-3-((2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)methylene)-5-fluoroindolin-2-one (**S67**).

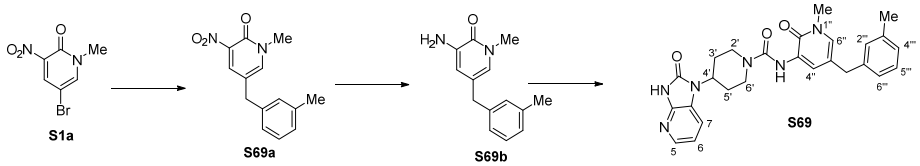


(*Z*)-3-((2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)methylene)-5-fluoroindolin-2-one (S67). Prepared using Method N 5-fluoroindolin-2-one and 2,5-dimethyl-1-phenyl-1*H*-pyrrole-3-carbaldehyde. The resulting crystals were filtered and dried to give indoline **S67** (57 mg, 10%) as a yellow solid: mp (EtOH) 238–241 °C; ^{1}H NMR δ 7.71 (s, 1H, H-1′), 7.67 (br s, 1H, CONH), 7.45–7.55 (m, 4H, H-4″, H-2‴, H-4‴, H-6‴), 7.21 (ddd, *J* = 6.8, 2.2, 1.6 Hz, 2H, H-3‴, H-5‴), 7.17 (dd, *J* = 8.8, 2.5 Hz, 1H, H-4), 6.82 (ddd, *J* = 8.8, 8.5, 2.4 Hz, 1H, H-6), 6.74 (dd, *J* = 8.4, 4.4 Hz, 1H, H-7), 2.251 (s, 3H, CH_3), 2.05 (s, 3H, CH_3); MS *m/z* 333.2 (MH^+, 100%).

SN36228 (*E*)-3-((2,5-Dimethyl-1-phenyl-1*H*-pyrrol-3-yl)methylene)indolin-2-one (**S68**).

The mother liquor from **S67** was purified by chromatography, eluting with a gradient (20–50%) of EtOAc/pet. ether, to give the *E*-isomer **S68** (74 mg, 12%) as an orange powder: ^{1}H NMR δ 8.00 (br s, 1H, CONH), 7.85 (s, 1H, H-1′), 7.81 (dd, *J* = 9.6, 2.5 Hz, 1H, H-4), 7.45–7.55 (m, 3H, H-2‴, H-4‴, H-6‴), 7.21 (ddd, *J* = 6.9, 2.5, 1.6 Hz, 2H, H-3‴, H-5‴), 6.81 (ddd, *J* = 8.9, 8.6, 2.5 Hz, 1H, H-6), 6.75 (dd, *J* = 8.5, 4.6 Hz, 1H, H-7), 6.58 (s, 1H, H-4″), 2.24 (s, 3H, CH_3), 2.07 (s, 3H, CH_3); MS *m/z* 333.2 (MH^+, 100%).

SN36230 *N*-(5-(3-Methylbenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S69**).

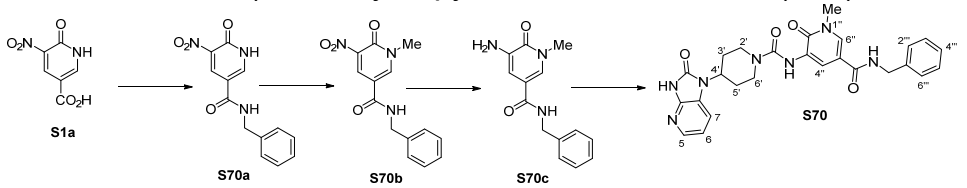


1-Methyl-5-(3-methylbenzyl)-3-nitropyridin-2(1*H*)-one (S69a). Prepared using Method A from **S1a** and 3-methylbenzylboronic acid. The crude mixture was purified by column chromatography, eluting with 5% EtOAc/DCM, and the residue was repurified by column chromatography eluting with EtOActo give pyridone **S69a** (250 mg, 38%) as a yellow powder: mp 147–150 °C; ^{1}H NMR δ 8.16 (d, *J* = 2.6 Hz, 1H, H-4), 7.44 (d, *J* = 2.6 Hz, 1H, H-6), 7.22–7.25 (m, 1H, H-5'), 7.10 (d, *J* = 7.5 Hz, 1H, H-4'), 6.95–6.97 (m, 2H, H-2', H-6'), 3.76 (s, 2H, CH_2), 3.64 (s, 3H, Me-1), 2.35 (s, 3H, Me-3'); MS *m/z* 259.6 (MH^+, 100%). Anal. calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.22; H, 5.39; N, 10.94%.

3-Amino-1-methyl-5-(3-methylbenzyl)-pyridin-2(1*H*)-one (S69b). Prepared using Method B from **S69a**. The resulting residue was purified by column chromatography, eluting with EtOAc, to give amine **S69b** (193 mg, quant.) as a brown oil: ^{1}H NMR δ 7.16–7.20 (m, 1H, H-5'), 7.02 (d, *J* = 7.36 Hz, 1H, H-4'), 6.95–6.97 (m, 2H, H-2', H-6'), 6.50 (m, 1H, H-6), 6.35 (d, *J* = 2.2 Hz, 1H, H-4), 4.20 (br s, 2H, NH_2-3), 3.57 (s, 2H, CH_2), 3.51 (s, 3H, Me-1), 2.31 (s, 3H, Me-3'); MS *m/z* 229.6 (MH^+, 100%).

***N*-(5-(3-Methylbenzyl)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S69).** Prepared using Method C from **S69b** and **S1d**. The crude mixture was purified by column chromatography, eluting with 5% MeOH/EtOAc, to give urea **S69** (78.9 mg, 60%) as a white solid: mp 207–210 °C; ^{1}H NMR δ 8.28 (br s, 1H, NH-3), 8.09 (d, *J* = 2.3 Hz, 1H, H-4''), 8.03 (br s, 1H, CONH), 8.01 (dd, *J* = 5.3, 1.3 Hz, 1H, H-5), 7.30 (dd, *J* = 7.9, 1.3 Hz, 1H, H-7), 7.20 (m, 1H, H-5'''), 7.05 (d, *J* = 7.7 Hz, 1H, H-6'''), 6.96–7.02 (m, 3H, H-6, H-2''', H-4'''), 6.67 (m, 1H, H-6''), 4.57 (tt, *J* = 13.1, 3.5 Hz, 1H, H-4'), 4.34 (d, *J* = 13.1 Hz, 2H, H_2-2' or H_2-6'), 3.70 (s, 2H, CH_2), 3.57 (s, 3H, Me-1''), 3.05 (td, *J* = 13.1, 3.5 Hz, 2H, H_2-2' or H_2-6'), 2.34 (s, 3H, Me-3'''), 2.26 (qd, *J* = 13.1, 3.5 Hz, 2H, H_2-3' or H_2-5'), 1.95 (dd, *J* = 13.1, 3.5 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR δ 157.3 (C-2''), 154.1 (CONH), 153.4 (C-2), 143.3 (C-3a), 140.5 (C-5), 139.6 (C-1'''), 138.5 (C-3'''), 130.1 (C-3''), 129.7 (C-2'''), 128.7 (C-5'''), 127.5 (C-6'''), 127.1 (C-6''), 125.9 (C-4'''), 123.3 (C-7a), 121.8 (C-4''), 120.5 (C-5''), 117.0 (C-6), 115.6 (C-7), 50.4 (C-4'), 44.0 (C-2', C-6'), 38.6 (CH_2), 37.9 (Me-1''), 29.5 (C-3', C-5'), 21.6 (Me-3'''); MS *m/z* 474.1 (MH^+, 100%). Anal. calcd for $C_{26}H_{28}N_6O_3 \cdot 0.25H_2O$: C, 65.46; H, 6.02; N, 17.62. Found: C, 65.61; H, 5.95; N, 17.46%.

SN36266 *N*-Benzyl-1-methyl-6-oxo-5-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamido)-1,6-dihydropyridine-3-carboxamide (**S70**).



5-(*N*-Benzylcarboxamide)-3-nitropyridin-2(1*H*)-one (S70a). 6-Hydroxy-5-nitronicotinic acid (500 mg, 0.27 mmol) and CDI (528 mg, 0.33 mmol) were stirred together in DMF (5 mL) at 60 °C for 1.5 h. The reaction mixture was cooled to 20 °C and benzyl amine (227 µL, 0.33 mmol) was added. The reaction mixture was allowed to stir at 20 °C for 17 h. The resulting mixture was diluted with EtOAc (50 mL), washed with water (50 mL) and brine (50 mL), dried and concentrated to a yellow gum. The crude material was triturated in EtOAc, filtered, and washed with EtOAc to obtain the amide **S70a** (301 mg, 41%) as a yellow powder: mp 288–291 °C, ^{1}H NMR δ 13.24 (NH-1), 9.06 (t, *J* = 5.8 Hz, CONH), 8.90 (d, *J* = 2.6 Hz, 1H, H-4), 8.44 (d, *J* = 2.6 Hz, 1H, H-6), 7.27–7.36 (m, 4H, H-2', H-3', H-5', H-6'), 7.23–7.27 (m, 1H, H-4'), 4.45 (d, *J* = 5.8 Hz, 1H, CH_2); ^{13}C NMR δ 161.9 (CONH), 154.3 (C-2), 144.0 (C-6), 139.1 (C-1'), 137.8 (C-4), 136.9 (C-3), 128.3 (C-3', C-5'), 127.4 (C-2', C-6'), 126.9 (C-4'), 110.9 (C-5), 42.7 (CH_2); MS *m/z* 272.5 ($[M-H]^-$, 100%). Anal. calcd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.16; H, 3.98; N, 15.24%.

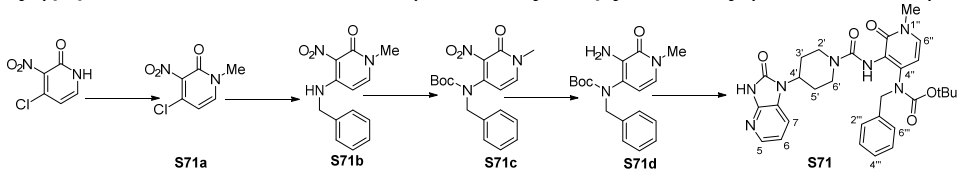
5-(*N*-Benzylcarboxamide)-1-methyl-3-nitropyridin-2(1*H*)-one (S70b). Prepared using Method E from methyl iodide and amide **S70a** at 20 °C. The crude material was triturated in EtOAc, filtered and washed with MeOH and EtOAc to obtain methyl pyridone **S70b** (182 mg, 98%) as a yellow powder: mp 204–206 °C; ^{1}H NMR δ 9.06 (t, *J* = 5.7 Hz, 1H, CONH), 8.93 (d, *J* = 2.6 Hz, 1H, H-4), 8.86 (d, *J* = 2.6 Hz, 1H, H-6), 7.31–7.36 (m, 4H, H-2', H-3', H-5', H-6'), 7.23–7.29 (m, 1H, H-4'), 4.47 (d, *J* = 5.7 Hz, 1H, CH_2), 3.62 (s, 3H, Me-1); ^{13}C NMR δ 161.9 (CONH), 154.0 (C-2), 148.4 (C-6), 139.1 (C-1'), 136.2 (C-4),

136.1 (C-3), 128.3 (C-3', C-5'), 127.5 (C-2', C-6'), 126.9 (C-4'), 109.9 (C-5), 42.8 (CH_2), 38.6 (Me-1); MS *m/z* 286.5 ([M-H]$^-$, 100%). Anal. calcd for $C_{14}H_{13}N_3O_4$: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.58; H, 4.61; N, 14.72%.

3-Amino-5-(*N*-Benzylcarboxamide)-1-methyl-pyridin-2(1*H*)-one (S70c). Prepared by Method B from **S70b** to give amine **S70c** (121 mg, 99%) as a light brown solid: mp 189–191 °C; ^{1}H NMR δ 7.49 (d, *J* = 2.3 Hz, 1H, H-6), 7.28–7.40 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 6.73 (d, *J* = 2.3 Hz, 1H, H-4), 6.10 (br s, 1H, CONH), 4.56 (t, *J* = 6.1 Hz, 2H, CH_2), 4.29 (s, 2H, NH_2-3), 3.60 (s, 3H, Me-1); ^{13}C NMR δ 165.0 (CONH), 158.4 (C-2), 138.1 (C-1'), 136.9 (C-3), 129.0 (C-3', C-5'), 128.6 (C-6), 128.1 (C-2', C-6'), 127.9 (C-4'), 114.1 (C-5), 108.3 (C-4), 44.2 (CH_2), 38.1 (Me-1); MS *m/z* 258.5 (MH$^+$, 100%). Anal. calcd for $C_{14}H_{15}N_3O_2 \cdot 0.25H_2O$: C, 64.23; H, 5.97; N, 16.05. Found: C, 64.04; H, 5.73; N, 15.87%.

***N*-Benzyl-1-methyl-6-oxo-5-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamido)-1,6-dihydropyridine-3-carboxamide (S70).** Prepared using Method C from **S70c** and **S1d**. The resulting solid was washed in 10% DCM/Et_2O and dried under vacuum to obtain urea **S70** (156 mg, 81%) as an off-white powder: mp 194–197 °C; ^{1}H NMR δ 9.89 (br s, 1H, NH-3), 8.46 (d, *J* = 2.3 Hz, 1H, H-4''), 8.02 (dd, *J* = 5.3, 1.2 Hz, 1H, H-5), 7.99 (s, 1H), 7.93 (d, *J* = 2.3 Hz, 1H, H-6''), 7.25–7.36 (m, 6H, H-2'', H-3'', H-4'', H-5'', H-6'', H-7), 6.96 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6), 6.81 (t, *J* = 5.8 Hz, 1H, CONH), 4.61 (d, *J* = 5.8 Hz, 2H, CH_2), 4.55 (tt, *J* = 13.5, 4.2 Hz, 1H, H-4'), 4.32 (br d, *J* = 13.5 Hz, 2H, H_2-2' or H_2-6'), 3.68 (s, 3H, Me-1''), 3.06 (br t, *J* = 13.5 Hz, 2H, H_2-2' or H_2-6'), 2.28 (qd, *J* = 13.5, 4.2 Hz, 2H, H_2-3' or H_2-5'), 1.96 (br d, *J* = 13.5 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR δ 164.3 (CONH-5''), 158.2 (C-2''), 154.1 (CONH), 153.4 (C-2), 143.2 (C-3a), 140.6 (C-5), 138.2 (C-1'''), 133.2 (C-6''), 129.3 (C-3''), 128.9 (C-2''', C-6'''), 128.1 (C-3''', C-5'''), 127.7 (C-4'''), 123.3 (C-7a), 117.1 (C-6), 115.6 (C-4''), 115.3 (C-7), 113.7 (C-5''), 50.4 (C-4'), 44.2 (CH_2), 44.0 (C-2', C-6'), 38.5 (Me-1''), 29.4 (C-3', C-5'); (+)-HRESIMS *m/z* [M+H]$^+$ 502.2185 (calcd for $C_{26}H_{28}N_7O_4$, 502.2197). Anal. calcd for $C_{26}H_{27}N_7O_4 \cdot 0.1$EtOAc: C, 59.52; H, 5.24; N, 18.54. Found: C, 60.01; H, 5.55; N, 18.15%.

SN36317 *tert*-Butyl Benzyl(1-methyl-2-oxo-3-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamido)-1,2-dihydropyridin-4-yl)carbamate (**S71**).



4-Chloro-1-methyl-3-nitropyridin-2(1*H*)-one (S71a). Prepared using Method E from methyl iodide and 4-chloro-3-nitro-2-pyridone at 20 °C. The resulting residue was dissolved in EtOAc (5 mL) and triturated with pet. ether (50 mL) to give pyridone **S71a** (440 mg, 81%) as a yellow solid: mp 101–103 °C; ^{1}H NMR δ 7.42 (d, *J* = 7.4 Hz, 1H, H-6), 6.33 (d, *J* = 7.4 Hz, 1H, H-5), 3.63 (s, 3H, Me-1); MS *m/z* 189.4 (MH$^+$, 100%). Anal. calcd for $C_6H_5ClN_2O_3$: C, 38.22; H, 2.67; N, 14.86. Found: C, 38.48; H, 2.71; N, 14.88%.

4-(Benzylamino)-1-methyl-3-nitropyridin-2(1*H*)-one (S71b). To a solution of chloride **S71a** (134 mg, 0.71 mmol) in DMSO (5 mL) was added Et_3N (981 µL, 7.08 mmol) and benzylamine (50 µL, 0.71 mmol). The reaction mixture was stirred at 90 °C for 18 h. The

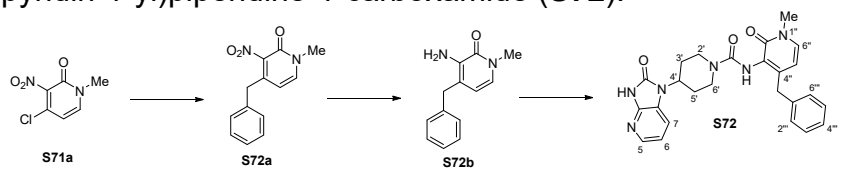
cooled reaction mixture was diluted with water (50 mL) and extracted with EtOAc (2 × 50 mL). The combined organic fractions were washed with water (100 mL) and brine (100 mL), dried and concentrated *in vacuo* to obtain a brown residue. The crude mixture was purified by column chromatography, eluting with 1–2% MeOH/EtOAc, to give amine **S71b** (128 mg, 73%) as a yellow solid: mp 160–163 °C; ^{1}H NMR δ 9.43 (br s, 1H, NH-4), 7.28–7.41 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 7.21 (d, *J* = 7.8 Hz, 1H, H-6), 5.79 (d, *J* = 7.8 Hz, 1H, H-5), 4.57 (d, *J* = 7.82 Hz, 2H, CH_2), 3.45 (s, 3H, Me-1); MS *m/z* 260.5 (MH^+, 100%). Anal. calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.49; H, 5.02; N, 16.04%.

4-(*tert*-Butyl-benzylcarbamate)-1-methyl-3-nitropyridin-2(1*H*)-one (S71c). Prepared using Method K from amine **S71b**. The crude mixture was purified by column chromatography, eluting with EtOAc, to give pyridone **S71c** (96 mg, 35%) as a yellow solid: mp 123–126 °C; ^{1}H NMR δ 7.28–7.35 (m, 6H, H-6, H-2', H-3', H-4', H-5', H-6'), 5.88 (d, *J* = 7.4 Hz, H-6), 4.79 (br s, 2H, CH_2), 3.57 (s, 3H, Me-1), 1.43 (s, 9H, *t*Bu); ^{13}C NMR δ 155.8 (C-2), 152.3 (CO), 146.5 (C-1'), 139.8 (C-6), 137.2 (C-3), 136.9 (C-4), 128.9 (C-3', C-5'), 128.0 (C-4'), 127.8 (C-2', C-6'), 104.5 (C-5'), 83.7 (Boc), 52.9 (CH_2), 38.3 (Me-1), 28.0 (Boc); (+)-HRESIMS *m/z* $[M+Na]^+$ 382.1374 (calcd for $C_{18}H_{21}N_3NaO_5$, 382.1373); Anal. calcd for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.44; H, 5.92; N, 11.60%.

3-Amino-4-(*tert*-butyl-benzylcarbamate)-1-methyl-pyridin-2(1*H*)-one (S71d). Prepared by Method B from **S71c**. The crude material was purified by column chromatography, eluting in EtOAc, to give amine **S71d** (158 mg, 52%) as an off-white solid: mp 201–204 °C; ^{1}H NMR δ 7.23–7.30 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 6.57 (br d, *J* = 7.0 Hz, 1H, H-6), 5.81 (br s, 1H, H-5), 4.68 (br s, 2H, CH_2), 4.20 (br s, 2H, NH-2), 3.52 (s, 3H, Me-1), 1.43 (s, 9H, *t*Bu); (+)-HRESIMS *m/z* $[M+H]^+$ 330.1819 (calcd for $C_{18}H_{24}N_3O_3$, 330.1812). Anal. calcd for $C_{18}H_{23}N_3O_3 \cdot 0.1H_2O$: C, 65.28; H, 7.06; N, 12.69. Found: C, 65.28; H, 7.22; N, 12.57%.

***tert*-Butyl Benzyl-(1-methyl-2-oxo-3-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamido)-1,2-dihydropyridin-4-yl)carbamate (S71).** Prepared using Method C from **S71d** and **S1d**. The crude material was purified by column chromatography, eluting with 10% MeOH/EtOAc, to give urea **S71** (137 mg, 78%) as an off-white solid: mp 168–171 °C; ^{1}H NMR δ 8.74 (s, 1H, NH-3), 8.02 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7), 7.24–7.34 (m, 5H, H-2''', H-3''', H-4''', H-5''', H-6'''), 6.96–7.02 (m, 2H, H-6, H-6''), 6.83 (s, 1H, CONH), 6.02 (d, *J* = 7.2 Hz, 1H, H-5''), 4.76 (br s, 2H, CH_2), 4.62 (tt, *J* = 12.7, 4.3 Hz, 1H, H-4'), 4.31 (d, *J* = 12.7 Hz, 2H, H_2-2' or H_2-6'), 3.55 (s, 3H, Me-1), 3.01 (t, *J* = 12.7 Hz, 2H, H_2-2' or H_2-6'), 2.35 (qd, *J* = 12.7, 4.3 Hz, 2H, H_2-3' or H_2-5'), 1.90 (dd, *J* = 12.7, 2.2 Hz, 2H, H_2-3' or H_2-5'), 1.42 (s, 9H, *t*Bu); ^{13}C NMR δ 160.7 (C-2''), 154.5 (CONH), 153.6 (C-2), 153.5 (CO-Boc), 143.2 (C-3a), 142.4 (C-4''), 140.3 (C-5), 138.7 (C-6'''), 132.6 (C-6''), 128.6 (C-2''', C-4'''), 127.4 (C-3''', C-5'''), 124.5 (C-3''),123.3 (C-7a), 117.2 (C-6), 116.4 (C-7), 106.6 (C-5''), 81.6 (*t*Bu), 51.9 (CH_2), 50.3 (C-4'), 44.6 (C-2', C-6'), 37.7 (Me-1''), 29.3 (C-3', C-5'), 28.3 (*t*Bu); MS *m/z* 575.5 (MH^+, 100%). Anal. calcd for $C_{30}H_{35}N_7O_5 \cdot 0.5H_2O$: C, 61.84; H, 6.23; N, 16.83. Found: C, 61.86; H, 6.22; N, 16.65%.

SN36318 *N*-(4-Benzyl-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S72**).

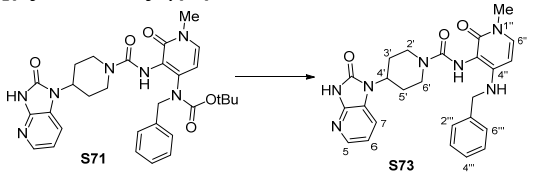


4-Benzyl-1-methyl-3-nitropyridin-2(1*H*)-one (S72a). Prepared using Method A from **S71a** and benzylboronic acid pinacol ester. The crude residue was purified by column chromatography, eluting with 5% EtOAc/CH_2Cl_2, to give pyridone **S72a** (153 mg, 59%) as a yellow oil: ^{1}H NMR δ 7.22–7.36 (m, 4H, H-6, H-3', H-4', H-5'), 7.16–7.20 (m, 2H, H-2', H-6'), 5.97 (d, *J* = 7.1 Hz, 1H, H-5), 3.82 (s, 2H, CH_2), 3.56 (s, 3H, Me-1); MS *m/z* 245.5 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 245.0922 (calcd for $C_{13}H_{13}N_2O_3$, 245.0921).

3-Amino-4-benzyl-1-methylpyridin-2(1*H*)-one (S72b). Prepared using Method B from **S72a**. The crude residue was purified by column chromatography, eluting in EtOAc, followed by trituration in diethyl ether of the residue to give amine **S72b** (109 mg, 91%) as an off-white solid: mp 109–111 °C; ^{1}H NMR δ 7.21–7.34 (m, 3H, H-3', H-4', H-5'), 7.16–7.20 (m, 2H, H-2', H-6'), 6.70 (d, *J* = 7.0 Hz, 1H, H-6), 5.95 (d, *J* = 7.0 Hz, 1H, H-5), 4.12 (s, 2H, NH_2-3), 3.76 (s, 2H, CH_2), 3.57 (s, 3H, Me-1); MS *m/z* 215.5 (MH^+, 100%). Anal. calcd for $C_{13}H_{14}N_2O\cdot0.1H_2O$: C, 72.27; H, 6.62; N, 12.97. Found: C, 72.29; H, 6.47; N, 13.00%.

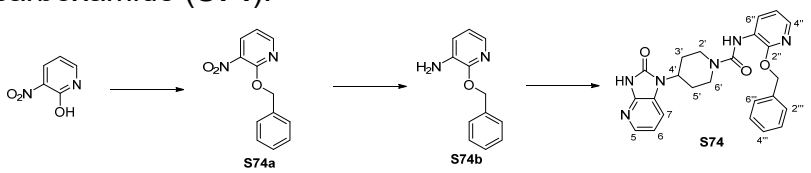
***N*-(4-Benzyl-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S72).** Prepared using Method C from **S72b** and **S1d**. The resulting white precipitate was filtered and washed with diethyl ether to give urea **S72** (94 mg, 63%) as an off-white solid: mp 271–274 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.54 (s, 1H, NH-3), 7.87 (dd, *J* = 5.2, 1.3 Hz, 1H, H-5), 7.79 (s, 1H, CONH), 7.58 (d, *J* = 7.9 Hz, 1H, H-7), 7.45 (d, *J* = 7.1 Hz, 1H, H-6''), 7.24–7.32 (m, 4H, H-2''', H-3''', H-5''', H-6'''), 7.18–7.23 (m, 1H, H-4'''), 6.84 (dd, *J* = 7.9, 5.2 Hz, 1H, H-6), 5.88 (d, *J* = 7.1 Hz, 1H, H-5''), 4.42–4.52 (m, 1H, H-4'), 4.24 (d, *J* = 12.7 Hz, 2H, H_2-2' or H_2-6'), 3.79 (s, 2H, CH_2), 3.44 (s, 3H, Me-1''), 2.95 (t, *J* = 12.7 Hz, 2H, H_2-2' or H_2-6'), 2.26 (qd, *J* = 12.7, 4.2 Hz, 2H, H_2-3' or H_2-5'), 1.71 (dd, *J* = 12.7, 3.0 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR [$(CD_3)_2SO$] δ 160.2 (C-2''), 156.6 (CONH), 153.0 (C-2), 146.9 (C-4''), 143.5 (C-3a), 139.6 (C-5), 139.0 (C-1'''), 135.4 (C-6''), 129.2 (C-2''', C-6'''), 128.4 (C-3''', C-5'''), 126.6 (C-3''), 126.3 (C-4'''), 123.0 (C-7a), 116.3 (C-6), 114.9 (C-7), 106.1 (C-4''), 49.6 (C-4'), 44.0 (C-2', C-6'), 36.8 (Me-1''), 36.6 (CH_2), 28.5 (C-3', C-5'); MS *m/z* 460.0 (MH^+, 100%). Anal. calcd for $C_{25}H_{26}N_6O_3\cdot0.9H_2O$: C, 63.25; H, 5.90; N, 17.70. Found: C, 63.20; H, 5.88; N, 17.56%.

SN36346 *N*-(4-(Benzylamino)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S73**).



***N*-(4-(Benzylamino)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S73).** Prepared using Method F from carbamate **S71** to give a cream coloured residue. The crude material was purified by column chromatography, eluting with 10–20% MeOH/CH_2Cl_2, to give urea **S71** (24.4 mg, 98%) as an off-white solid: mp 228 °C (decomp.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.54 (s, 1H, NH-3), 7.89 (dd, *J* = 5.2, 1.1 Hz, 1H, H-5), 7.80 (d, *J* = 7.7 Hz, 1H, H-6''), 7.26–7.35 (m, 5H, H-7, H-2''', H-3''', H-5''' and H-6'''), 7.19–7.23 (m, 1H, H-4'''), 6.96 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6), 6.38 (t, *J* = 6.5 Hz, 1H, NH-4''), 5.72 (d, *J* = 7.7 Hz, 1H, H-5''), 4.47 (tt, *J* = 12.4, 4.2 Hz, 1H, H-4'), 4.42 (d, *J* = 6.5 Hz, 1H, CH_2), 4.25 (d, *J* = 12.4 Hz, 2H, H_2-2' or H_2-6'), 3.29 (s, 3H, Me-1''), 2.92 (t, *J* = 12.4 Hz, 2H, H_2-2' or H_2-6'), 2.29–2.37 (m, 2H, H_2-3' or H_2-5'), 1.68 (d, *J* = 12.4 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR [$(CD_3)_2SO$] δ 157.2, 153.0, 151.6, 143.4, 140.1, 139.6, 136.6, 128.6, 128.2 (2), 127.2, 126.6 (2), 123.0, 116.4, 115.4, 106.1, 94.3, 49.6, 45.1, 44.0 (2), 35.9, 28.3 (2); MS *m/z* 473.2 (MH^+, 100%). Anal. calcd for $C_{25}H_{27}N_7O_3 \cdot 0.8$ EtOAc·$0.1H_2O$: C, 46.10; H, 4.54; N, 14.15. Found: C, 45.79; H, 4.99; N, 14.60%.

SN36371 *N*-(2-(Benzyloxy)pyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S74**).



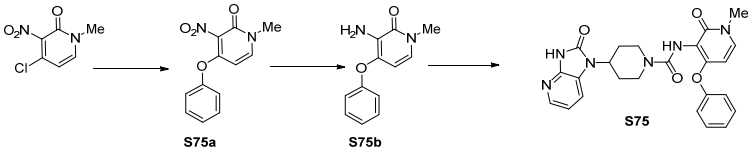
2-(Benzyloxy)-3-nitropyridine (S74a). 2-Hydroxy-3-nitropyridine (0.50 g, 3.57 mmol) and Ag_2CO_3 (1.08 g, 3.93 mmol) were stirred together in toluene (40 mL). Benzyl bromide (424 µL, 3.57 mmol) was added to the mixture, which was heated at 100 °C for 5 h. An additional portion of benzyl bromide (127 µL, 1.07 mmol) was added to the reaction mixture and was allowed to stir at 20 °C for another 66 h. The cooled reaction mixture was diluted with EtOAc (50 mL), washed with water (2 × 50 mL) and brine (50 mL), dried and concentrated *in vacuo*. The crude residue was purified by column chromatography, eluting with 10–30% EtOAc/pet. ether, to give ether **S74a** (0.53 g, 64%) as a yellow oil: ^{1}H NMR δ 8.40 (dd, *J* = 4.8, 1.8 Hz, 1H, H-6), 8.28 (dd, *J* = 7.9, 1.8 Hz, 1H, H-4), 7.47–7.53 (m, 2H, H-2', H-6'), 7.35–7.41 (m, 2H, H-3', H-5'), 7.29–7.35 (m, 1H, H-4'), 7.05 (dd, *J* = 7.9, 4.8 Hz, 1H, H-5), 5.60 (s, 2H, CH_2); (+)-HRESIMS *m/z* $[M+Na]^+$ 253.0587 (calcd for $C_{12}H_{10}N_2NaO_3$, 253.0584).

2-(Benzyloxy)pyridin-3-amine (S74b). Prepared using Method B from **S74a** using 5% Pt/C (sulfided) in *n*-butyl acetate. The residue was purified by column chromatography, eluting with 10–20% EtOAc/pet. ether, to give amine **S74b** (434 mg, 90%) as a yellow oil: ^{1}H NMR δ 7.59 (dd, *J* = 5.0, 1.6 Hz, 1H, H-6), 7.44–7.50 (m, 2H), 7.35–7.41 (m, 2H),

7.29–7.35 (m, 1H), 6.90 (dd, *J* = 7.5, 1.6 Hz, 1H, H-4), 6.74 (dd, *J* = 7.5, 5.0 Hz, 1H, H-5), 5.42 (s, 2H), 3.79 (s, 2H); MS *m/z* 201.5 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 201.1017 (calcd for $C_{12}H_{13}N_2O$, 201.1022).

***N*-(2-(Benzyloxy)pyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S74).** Prepared using Method C from **S74b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (25–100%) of EtOAc/pet. ether, to give urea **S74** (314 mg, 41%) as a white solid: mp (EtOAc/pet. ether) 193–196 °C; ^{1}H NMR δ 9.46 (br s, 1 H, CONH), 8.42 (dd, *J* = 7.9, 1.7 Hz, 1H, H-4″), 8.05 (dd, *J* = 5.3, 1.3 Hz, 1H, H-5′), 7.82 (dd, *J* = 5.0, 1.7 Hz, 1H, H-6″), 7.42–7.45 (m, 2H, H-2‴, H-6‴), 7.30–7.38 (m, 4H, H-7′, H-3‴, H-4‴, H-5‴), 7.17 (s, 1H, CONH), 7.98 (dd, *J* = 7.9, 5.3 Hz, 1H, H-5″), 6.94 (dd, *J* = 7.8, 5.0 Hz, 1H, H-6′), 5.47 (s, 2H, CH_2O), 4.58 (tt, *J* = 12.4, 4.1 Hz, 3H, H-4), 4.23 (br d, *J* = 13.8 Hz, 2H, H-2, H-6), 3.04 (dt, *J* = 13.7, 2.3 Hz, 2H, H-2, H-6), 2.27 (dq, *J* = 12.7, 4.3 Hz, 2H, H-3, H-5), 1.94 (dd, *J* = 12.1, 2.3 Hz, 2H, H-3, H-5); ^{13}C NMR δ 153.6, 153.0, 151.9, 142.8, 139.8, 138.3, 136.6, 128.1 (2), 127.7, 127.4 (2), 125.2, 123.4, 122.7, 117.3, 116.4, 114.9, 67.6, 49.8, 43.4 (2), 28.2 (2); MS *m/z* 445.2 (MH^+, 100%); HRMS calcd for $C_{24}H_{24}N_6O_3$ (MH^+) *m/z* 445.1983. Found 445.1985 (-0.5 ppm).

SN36527 *N*-(1-Methyl-2-oxo-4-phenoxy-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S75**).



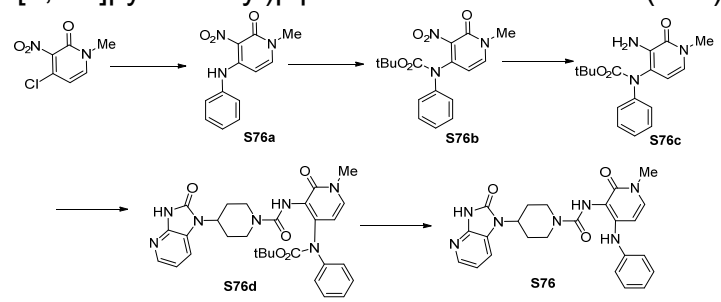
1-Methyl-3-nitro-4-phenoxypyridin-2(1*H*)-one (S75a). Prepared using Method E from **S71a** and phenol. The crude solid was purified by column chromatography, eluting with a gradient (5–90%) of EtOAc/pet. ether, to give nitropyridinone **S75a** (349 mg, 80%) as a yellow powder: mp (EtOAc/pet. ether) 174–176 °C; ^{1}H NMR δ 7.41–7.46 (m, 2H, H-3′, H-5′), 7.28–7.33 (m, 2H, H-6, H-4′), 7.10–7.14 (m, 2H, H-2′, H-6′), 5.75 (d, *J* = 7.8 Hz, 1H, H-5), 3.59 (s, 3H, NCH_3); MS *m/z* 247.2 ($M-H^-$, 100%).

3-Amino-1-methyl-4-phenoxypyridin-2(1*H*)-one (S75b). Prepared using Method B from **S75a**. The crude solid was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give aminopyridinone **S75b** (363 mg, 26%) as a gum: ^{1}H NMR $[(CD_3)_2SO]$ δ 7.31–7.37 (m, 2H, H-3′, H-5′), 7.12 (tt, *J* = 7.4, 1.0 Hz, 1H, H-4′), 6.99–7.03 (m, 2H, H-2′, H-6′), 6.70 (d, *J* = 7.5 Hz, 1H, H-5), 5.92 (d, *J* = 7.5 Hz, 1H, H-6), 4.13 (br s, 2H, NH_2), 3.58 (s, 3H, NCH_3); MS *m/z* 214.2 ($M-H^-$, 100%).

***N*-(1-Methyl-2-oxo-4-phenoxy-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S75).** Prepared using Method C from **S75b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give urea **S75** (139 mg, 68%) as a white powder: mp (MeOH/EtOAc) 270–273 °C; ^{1}H NMR $[(CD_3)_2SO]$ δ 11.52 (br s, 1H, CONH), 7.86 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.71 (br s, 1H, CONH), 7.57 (d, *J* = 7.6 Hz, 1H, H-6″), 7.40–7.47 (m, 3H, H-7′, H-3‴, H-5‴), 7.22 (dt, *J* = 7.4, 1.0 Hz, 1H, H-4‴), 7.10–7.15 (m, 2H, H-

4‴, H-6‴), 6.77 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 5.57 (d, *J* = 7.6 Hz, 1H, H-4″), 4.44 (tt, *J* = 12.4, 4.1 Hz, 1H, H-4), 4.17 (br d, *J* = 13.6 Hz, 2 H, H-2, H-6), 3.46 (s, 3H, NCH_3), 2.86 (br dd, *J* = 12.4, 11.1 Hz, 2H, H-2, H-6), 2.15 (dq, *J* = 12.5, 3.9 Hz, 2H, H-3, H-5), 1.65 (br d, *J* = 9.6 Hz, 2H, H-3, H-5); ^{13}C NMR [$(CD_3)_2SO$] δ 161.2, 158.6, 156.0, 154.8, 153.0, 143.5, 139.5, 136.7, 130.0 (2), 124.5, 122.9, 119.9 (2), 116.5, 116.2, 114.8, 98.1, 49.6, 44.0 (2), 36.6, 28.4 (2); MS *m/z* 464.2 (MH^+, 100%); HRMS calcd for $C_{24}H_{25}N_6O_4$ (MH^+) *m/z* 461.1932, found 461.1934. Anal. calcd for $C_{24}H_{24}N_6O_4 \cdot ½CH_3OH$: C, 58.51; H, 5.01; N, 16.71. Found: C, 58.52; H, 5.14; N, 16.86%.

SN36528 *N*-(1-Methyl-2-oxo-4-(phenylamino)-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S76**).



1-Methyl-3-nitro-4-(phenylamino)pyridin-2(1*H*)-one (S76a). A mixture of **S71a** (174 mg, 0.92 mmol), aniline (86 mg, 0.92 mmol) and Et_3N (1.28 mL, 9.20 mmol) in DMSO (10 mL) was stirred at 90 °C for 24 h. The mixture was cooled to 20 °C, diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (2 × 30 mL) and brine (30 mL), dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (10–100%) of EtOAc/pet. ether, to give nitropyridinone **S76a** (169 mg, 75%) as a yellow powder: mp (EtOAc/pet. ether) 219–221 °C; ^{1}H NMR δ 10.40 (br s, 1H, NH), 7.44–7.50 (m, 2H, H-3′, H-5′), 7.36 (tt, *J* = 7.4, 1.0 Hz, 1H, H-4′), 7.23–7.27 (m, 2H, H-2′, H-6′), 7.15 (d, *J* = 7.6 Hz, 1H, H-6), 5.88 (d, *J* = 7.8 Hz, 1H, H-5), 3.49 (s, 3H, NCH_3); MS *m/z* 246.2 ($M\text{-}H^-$, 100%). Anal. calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.73; H, 4.44; N, 17.19%.

***tert*-Butyl (1-Methyl-3-nitro-2-oxo-1,2-dihydropyridin-4-yl)(phenyl)carbamate (S76b).** Prepared using Method K from nitropyridinone **S76a**. The residue was purified by column chromatography, eluting with a gradient (25–80%) of EtOAc/pet. ether, to give nitropyridinone **S76b** (169 mg, 75%) as a yellow solid: mp (EtOAc/pet. ether) 161 °C (decomp.); ^{1}H NMR δ 7.39 (br dd, *J* = 7.4, 7.2 Hz, 2H, H-3′, H-5′), 7.28–7.33 (m, 4H, H-6, H-2′, H-4′, H-6′), 5.86 (d, *J* = 7.4 Hz, 1H, H-5), 3.59 (s, 3 H, NCH_3), 1.44 [s, 9H, $C(CH_3)_3$]; MS *m/z* 346.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{19}N_3O_5$: C, 59.12; H, 5.55; N, 12.17. Found: C, 59.15; H, 5.60; N, 12.01%.

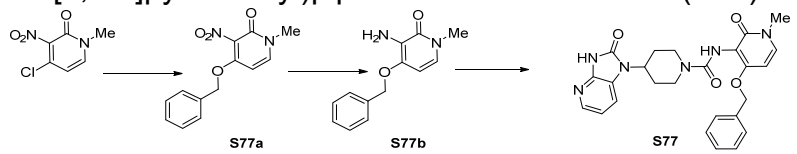
***tert*-Butyl (3-Amino-1-methyl-2-oxo-1,2-dihydropyridin-4-yl)(phenyl)carbamate (S76c).** Prepared by Method B from **S76b** (238 mg, 0.69 mmol) to give aminopyridinone **S76c** (363 mg, 26%) as a white solid: mp 170–171 °C; ^{1}H NMR δ 7.24–7.33 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.17 (tt, *J* = 7.1, 1.5 Hz, 1H, H-4′), 6.66 (d, *J* = 7.3 Hz, 1H, H-6), 6.00

(d, *J* = 7.3 Hz, 1H, H-5), 4.31 (br s, 2H, NH_2), 3.56 (s, 3H, NCH_3), 1.47 [s, 9H, $C(CH_3)_3$]; MS *m/z* 316.2 (MH^+, 100%).

***tert*-Butyl (1-Methyl-2-oxo-3-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamido)-1,2-dihydropyridin-4-yl)(phenyl)carbamate (S76d).** Prepared using Method C from **S76c** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/EtOAc, to give urea **S76d** (225 mg, 89%) as a white solid: mp (MeOH/EtOAc) 168 °C; ^{1}H NMR δ 9.15 (br s, 1H, CONH), 8.02 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.48 (d, *J* = 7.1 Hz, 1H, H-6″), 7.25–7.33 (m, 4H, H-2‴, H-3‴, H-5‴, H-6‴), 7.20 (tt, *J* = 7.1, 1.5 Hz, 1H, H-4‴), 7.00 (d, *J* = 7.5 Hz, 1H, H-7′), 6.93 (dd, *J* = 7.9, 5.2 Hz, 1H, H-6′), 6.70 (br s, 1H, CONH), 6.05 (br d, *J* = 7.2 Hz, 1H, H-5″), 4.57 (tt, *J* = 12.5, 4.1 Hz, 1H, H-4), 4.17 (br d, *J* = 13.5 Hz, 2H, H-2, H-6), 3.56 (s, 3H, NCH_3), 2.90 (br dd, *J* = 12.4, 12.0 Hz, 2H, H-2, H-6), 2.29 (dq, *J* = 12.6, 4.0 Hz, 2H, H-3, H-5), 1.86 (br d, *J* = 12.1 Hz, 2H, H-3, H-5) 1.49 [s, 9H, $C(CH_3)_3$]; MS *m/z* 560.3 (MH^+, 100%). Anal. calcd for $C_{29}H_{33}N_7O_5 \cdot ½CH_2Cl_2$: C, 60.48; H, 5.81; N, 16.88. Found: C, 60.33; H, 5.83; N, 16.97%.

***N*-(1-Methyl-2-oxo-4-phenoxy-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S76).** Prepared using Method F from carbamate **S76d** to give urea **S76** (97 mg, 67%) as a white solid: mp (MeOH/EtOAc) 168–161 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.54 (br s, 1H, CONH), 8.03 (br s, 1H, NH), 7.89 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.71(dd, *J* = 7.8, 1.1 Hz, 1H, H-7′), 7.49 (br s, 1H, CONH), 7.42 (d, *J* = 7.6 Hz, 1H, H-6″), 7.33 (dd, *J* = 8.3, 7.5 Hz, 2H, H-3‴, H-5‴), 7.10 (br d, *J* = 7.5 Hz, 2H, H-2‴, H-6‴), 7.04 (br t, *J* = 7.4 Hz, 1H, H-4‴), 6.92 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 6.10 (d, *J* = 7.6 Hz, 1H, H-5″), 4.46 (tt, *J* = 12.3, 4.2 Hz, 1H, H-4), 4.25 (br d, *J* = 13.6 Hz, 2H, H-2, H-6), 3.41 (s, 3H, NCH_3), 2.95 (br t, *J* = 12.3 Hz, 2H, H-2, H-6), 2.29 (dq, *J* = 12.4, 3.8 Hz, 2H, H-3, H-5), 1.70 (br d, *J* = 9.6 Hz, 2H, H-3, H-5); ^{13}C NMR [$(CD_3)_2SO$] δ 160.3, 156.8, 153.0, 146.6, 143.5, 140.5, 139.6, 135.9, 129.2 (2), 123.0, 122.6, 121.3 (2), 116.4, 115.2, 110.4, 96.2, 49.6, 44.0 (2), 36.2, 28.4 (2); MS *m/z* 460.2 (MH^+, 100%). HRMS calcd for $C_{24}H_{26}N_7O_3$ (MH^+) *m/z* 460.2092, found 460.2089. Anal. calcd for $C_{24}H_{25}N_7O_3 \cdot HCl$: C, 58.12; H, 5.28; N, 19.77. Found: C, 57.90; H, 5.69; N, 19.40%.

SN36551 *N*-(4-(Benzyloxy)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S77**).

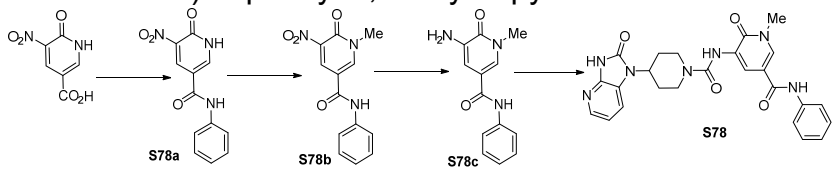


4-(Benzyloxy)-1-methyl-3-nitropyridin-2(1*H*)-one (S77a). Prepared using Method L from benzyl alcohol and chloride **S71a**. The crude solid was purified by column chromatography, eluting with a gradient (10–100%) of EtOAc/pet. ether, to give nitropyridinone **S77a** (145 mg, 53%) as an orange solid: mp (EtOAc/pet. ether) 166–167 °C; ^{1}H NMR δ 7.32–7.42 (m, 6H, H-6, H-2′, H-3′, H-4′, H-5′, H-6′), 6.08 (d, *J* = 7.8 Hz, 1H, H-5), 5.25 (s, 2H, CH_2O), 3.55 (s, 3H, NCH_3); MS *m/z* 261.2 (MH^+, 100%). Anal. calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 59.95; H, 4.61; N, 10.78%.

3-Amino-4-(benzyloxy)-1-methylpyridin-2(1*H*)-one (S77b). Prepared using Method G from nitropyridinone **S77a** to give aminopyridinone **S77b** (43 mg, 63%) as a gum: ^{1}H NMR δ 7.31–7.41 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.72 (d, *J* = 7.6 Hz, 1H, H-6), 6.11 (d, *J* = 7.6 Hz, 1H, H-5), 5.11 (s, 2H, CH_2O), 3.99 (br s, 2H, NH_2), 3.55 (s, 3H, NCH_3); MS *m/z* 231.2 (MH^+, 100%); HRMS calcd for $C_{13}H_{15}N_2O_2$ (MH^+) *m/z* 231.1128, found 231.1124.

***N*-(4-(Benzyloxy)-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S77).** Prepared using Method C from **S77b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/DCM, to give urea **S77** (100 mg, 66%) as a white solid: mp (MeOH/EtOAc) 187–190 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.53 (br s, 1H, CONH), 7.87 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.59 (d, *J* = 7.8 Hz, 1H, H-6″), 7.57 (dd, *J* = 7.8, 1.4 Hz, 1H, H-7′), 7.44–7.50 (m, 3H, CONH, H-3‴, H-5‴), 7.36 (dd, *J* =7.7, 7.2 Hz, 2H, H-2‴, H-6‴), 7.28 (tt, *J* = 7.3, 2.1 Hz, 1H, H-4‴), 6.88 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 6.26 (d, *J* = 7.8 Hz, 1H, H-5″), 5.22 (s, 2H, CH_2O), 4.43 (tt, *J* = 12.3, 4.0 Hz, 1H, H-4), 4.22 (br d, *J* = 13.2 Hz, 2H, H-2, H-6), 3.43 (s, 3H, NCH_3), 2.89 (br dd, *J* = 12.4, 12.0 Hz, 2H, H-2, H-6), 2.23 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3, H-5), 1.70 (br d, *J* = 9.5 Hz, 2H, H-3, H-5); ^{13}C NMR [$(CD_3)_2SO$] δ 161.0, 160.4, 156.2, 153.0, 143.5, 139.6, 136.9, 136.7, 128.4 (2), 127.7, 126.9 (2), 123.0, 116.3, 114.9, 113.3, 95.6, 69.5, 49.8, 44.0 (2), 36.5, 28.5 (2); MS *m/z* 475.2 (MH^+, 100%); HRMS calcd for $C_{25}H_{27}N_6O_4$ (MH^+) *m/z* 475.2088, found 475.2090.

SN36556 1-Methyl-6-oxo-5-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamido)-*N*-phenyl-1,6-dihydropyridine-3-carboxamide (**S78**).



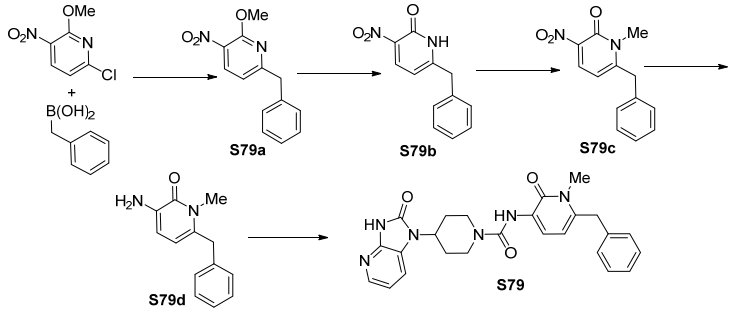
5-Nitro-6-oxo-*N*-phenyl-1,6-dihydropyridine-3-carboxamide (S78a). A mixture of 5-nitro-6-oxo-1,6-dihydropyridine-3-carboxylic acid (1.00 g, 5.43 mmol), and CDI (1.06 g, 6.52 mmol) in dry DMF was stirred at 60 °C for 2 h. Aniline (0.60 mL, 6.52 mmol) was added and the mixture was stirred at 60 °C for 16 h. The mixture was cooled to 20 °C, diluted with water (80 mL) and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (2 × 30 mL) and brine (30 mL), dried and the solvent evaporated to give nitropyridinone **S78a** (1.02 g, 72%) as a yellow powder: ^{1}H NMR [$(CD_3)_2SO$] δ 13.36 (br s, 1H, CONH), 10.23 (s, 1H, CONH), 8.95 (d, *J* = 2.6 Hz, 1H, H-2), 8.60 (d, *J* = 2.7 Hz, 1H, H-4), 7.70 (br dd, *J* = 8.5, 1.0 Hz, 2H, H-2′, H-6′), 7.34 (br t, *J* = 8.5 Hz, 2H, H-3′, H-5′), 7.11 (tt, *J* = 7.4, 1.0 Hz, 1H, H-4′); MS *m/z* 258.2 (MH^+, 100%).

1-Methyl-5-nitro-6-oxo-*N*-phenyl-1,6-dihydropyridine-3-carboxamide (S78b). Prepared using Method E from methyl iodide and carboxamide **S78a** at 20 °C. The crude solid was purified by column chromatography, eluting with a gradient (25–100%) of EtOAc/pet. ether, to give carboxamide **S78b** (927 mg, 92%) as a yellow powder: mp (EtOAc/pet. ether) 227–229 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.26 (s, 1H, CONH), 9.02 (d, *J* = 2.6 Hz, 1H, H-2), 8.98 (d, *J* = 2.6 Hz, 1H, H-4), 7.70 (ddd, *J* = 8.5, 1.9, 1.1 Hz, 2H, H-2′, H-6′), 7.37 (ddd, *J* = 8.5, 7.4, 1.9 Hz, 2H, H-3′, H-5′), 7.13 (tt, *J* = 7.4, 1.1 Hz, 1H, H-4′), 3.67 (s, 3H, NCH_3); MS *m/z* 274.2 (MH^+, 100%).

5-Amino-1-methyl-6-oxo-*N*-phenyl-1,6-dihydropyridine-3-carboxamide (S78c). Prepared using Method B from **S78b**. The crude solid was triturated with EtOAc to give aminopyridinone **S78c** (324 mg, quant.) as a yellow solid: mp (EtOAc) 172–174 °C; ^{1}H NMR δ 7.52–7.59 (m, 4H, H-4, CONH, H-2′, H-6′), 7.37 (ddd, *J* = 8.5, 7.5, 1.8 Hz, 2H, H-3′, H-5′), 7.15 (tt, *J* = 7.4, 1.1 Hz, 1H, H-4′), 6.85 (d, *J* = 2.3 Hz, 1H, H-2), 4.37 (br s, 2H, NH_2), 3.64 (s, 3H, NCH_3); MS *m/z* 244.2 (MH^+, 100%).

1-Methyl-6-oxo-5-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamido)-*N*-phenyl-1,6-dihydropyridine-3-carboxamide (S78). Prepared using Method C from **S78c** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/EtOAc, to give urea **S78** (232 mg, 49%) as a white solid: mp (EtOAc) 286–290 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (s, 1H, CONH), 10.05 (s, 1H, CONH), 8.44 (d, *J* = 2.4 Hz, 1H, H-2), 8.19 (d, *J* = 2.4 Hz, 1H, H-4), 8.05 (br s, 1H, CONH), 7.89 (dd, *J* = 5.2, 1.3 Hz, 1H, H-5‴), 7.69 (dd, *J* = 8.6, 1.1 Hz, 2H, H-2′, H-6′), 7.57 (dd, *J* = 7.9, 1.2 Hz, 1H, H-7‴), 7.34 (ddd, *J* = 8.4, 7.5, 1.2 Hz, 2H, H-3′, H-5′), 7.08 (tt, *J* = 7.4, 1.1 Hz, 1H, H-4′), 6.98 (d, *J* = 7.8 Hz, 1H, H-6‴), 4.43 (tt, *J* = 12.2, 4.0 Hz, 1H, H-4″), 4.18 (br d, *J* = 13.2 Hz, 2H, H-2″, H-6″), 3.62 (s, 3H, NCH_3), 3.04 (br dd, *J* = 12.5, 11.7 Hz, 2H, H-2″, H-6″), 2.25 (dq, *J* = 12.5, 4.0 Hz, 2H, H-3″, H-5″), 1.80 (br d, *J* = 10.1 Hz, 2H, H-3″, H-5″); ^{13}C NMR [$(CD_3)_2SO$] δ 163.1, 157.6, 153.7, 153.0, 143.4, 139.7, 139.1, 133.1, 128.7, 128.6 (2), 123.5, 123.2, 120.2 (2), 118.5, 116.4, 114.7, 113.4, 49.8, 43.4 (2), 37.8, 28.5 (2); MS *m/z* 488.2 (MH^+, 100%); HRMS calcd for $C_{25}H_{26}N_7O_4$ (MH^+) *m/z* 488.2043. Found 488.2042 (0.3 ppm).

SN36621 *N*-(6-Benzyl-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S79**).



6-Benzyl-2-methoxy-3-nitropyridine (S79a). Prepared using Method A from 6-chloro-2-methoxy-3-nitropyridine and benzylboronic acid. The crude solid was purified by column chromatography, eluting with a gradient (5–50%) of EtOAc/pet. ether, to give nitropyridine **S79a** (377 mg, 68%) as a yellow solid: mp (EtOAc/pet. ether) 73–76 °C; ^{1}H NMR δ 8.19 (d, *J* = 8.1 Hz, 1H), 7.24–7.35 (m obscured, 5H), 6.81 (d, *J* = 8.1 Hz, 1H), 4.1 (s, 5H); MS *m/z* 245.2 (MH^+, 100%). Anal. calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.10; H, 4.90; N, 11.49%.

6-Benzyl-3-nitropyridin-2(1*H*)-one (S79b). TMSCl (189 µL, 1.49 mmol) was added to a mixture of nitropyridine **S79a** (331 mg, 1.36 mmol) and NaI (224 mg, 1.49 mmol) in MeCN (15 mL) at 20 °C and the mixture stirred at 20 °C for 16 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (50 mL). The organic fraction was dried and the

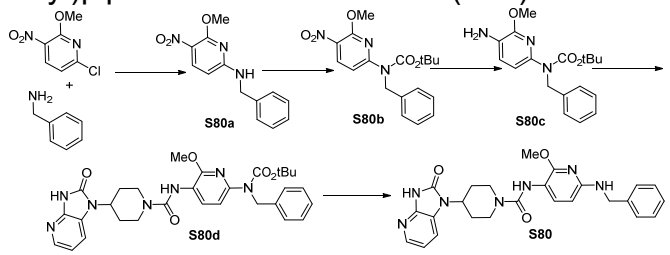
solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (0–75%) of EtOAc/pet. ether, to give pyridone **S79b** (179 mg, 57%) as a yellow powder: mp (EtOAc) 169–170 °C; ^{1}H NMR δ 8.40 (d, *J* = 8.0 Hz, 1H, H-4), 7.32–7.41 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.23 (d, *J* = 8.0 Hz, 1H, H-5), 4.05 (s, 2H, CH_2), CONH not observed; MS *m/z* 231.2 (MH^+, 100%).

6-Benzyl-1-methyl-3-nitropyridin-2(1*H*)-one (S79c). Prepared using Method E from methyl iodide and pyridone **S79b** (159 mg, 0.69 mmol) at 20 °C. The crude solid was purified by column chromatography, eluting with a gradient (0–60%) of EtOAc/pet. ether, to give nitropyridinone **S79c** (39 mg, 23%) as a yellow solid: mp (EtOAc/pet. ether) 128–130 °C; ^{1}H NMR δ 8.26 (d, *J* = 8.0 Hz, 1 H, H-4), 7.32–7.41 (m, 3H, H-3′, H-4′, H-5′), 7.14 (dd, *J* = 6.7, 1.5 Hz, 1H, H-2′, H-6′), 6.10 (d, *J* = 8.0 Hz, 1H, H-5), 4.08 (s, 2H, CH_2), 3.57 (s, 3H, NCH_3); MS *m/z* 245.2 (MH^+, 100%). Anal. calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 64.21; H, 5.07; N, 11.53%.

3-Amino-6-benzyl-1-methylpyridin-2(1*H*)-one (S79d). Prepared using Method B from **S79c**. The crude solid was purified by column chromatography, eluting with EtOAc, to give aminopyridinone **S79d** (30 mg, 88%) as a gum: ^{1}H NMR δ 7.31 (ddd, *J* = 7.5, 7.0, 1.5 Hz, 2H, H-3′, H-5′), 7.25 (tt, *J* = 7.3, 2.3 Hz, 1H, H-4′), 7.11 (br d, *J* = 7.0 Hz, 2H, H-2′, H-4′, H-6′), 7.52 (d, *J* = 7.3 Hz, 1H, H-4), 5.93 (d, *J* = 7.4 Hz, 1H, H-5), 4.13 (br s, 2H, NH_2), 3.92 (s, 2H, CH_2), 3.44 (s, 3H, NCH_3); MS *m/z* 215.2 (MH^+, 100%).

***N*-(6-Benzyl-1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S79).** Prepared using Method C from **S79d** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/EtOAc, to give urea **S79** (26 mg, 31%) as a white powder: mp (EtOAc) 239–241 °C; ^{1}H NMR δ 9.19 (s, 1H, CONH), 8.12 (d, *J* = 7.6 Hz, 1H, H-4″), 8.03 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.97 (s, 1H, CONH), 7.27–7.36 (m, 4H, H-7′, H-3‴, H-4″, H-5‴), 7.14 (br d, *J* = 7.2 Hz, 2H, H-2‴, H-6‴), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 6.17 (d, *J* = 7.7 Hz, 1H, H-5″), 4.58 (tt, *J* = 12.5, 4.1 Hz, 1H, H-4), 4.36 (br d, *J* = 13.9 Hz, 2H, H-2, H-6), 3.99 (s, 2H, CH_2), 3.47 (s, 3H, NCH_3), 3.06 (br dd, *J* = 12.4, 11.6 Hz, 2H, H-2, H-6), 2.27 (dq, *J* = 12.6, 4.2 Hz, 2H, H-3, H-5), 1.96 (br d, *J* = 9.9 Hz, 2H, H-3, H-5); ^{13}C NMR δ 159.1, 154.3, 153.1, 143.0, 140.6, 138.3, 136.7, 129.1 (2), 128.5, 128.4 (2), 127.3, 123.3, 123.3, 119.6, 117.2, 115.6, 108.7, 50.5, 44.0 (2), 39.7, 29.5 (2); MS *m/z* 459.2 (MH^+, 100%); HRMS calcd for $C_{25}H_{27}N_6O_3$ (MH^+) *m/z* 459.2139. Found 459.2143 (0.9 ppm).

SN36622 *N*-(6-(Benzylamino)-2-methoxypyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S80**).



***N*-Benzyl-6-methoxy-5-nitropyridin-2-amine (S80a).** A mixture of 6-chloro-2-methoxy-3-nitropyridine (500 mg, 2.65 mmol), benzylamine (185 µL, 2.65 mmol) and Et_3N (3.68 mL, 26.5 mmol) in DMSO (20 mL) was stirred at 90 °C for 24 h. The mixture was cooled to 20 °C, diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic fraction was washed with water (2 × 30 mL) and brine (30 mL), dried and the solvent evaporated. The crude solid was purified by column chromatography, eluting with a gradient (5–40%) of EtOAc/pet. ether, to give benzylamine **S80a** (531 mg, 77%) as a yellow powder: mp (EtOAc/pet. ether) 133–135 °C; ^{1}H NMR δ 8.24 (d, *J* = 8.9 Hz, 1H, H-4), 7.29–7.40 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 6.01 (d, *J* = 8.9 Hz, 1H, H-3), 5.48 (br s, 1H, NH,) 5.12 (br d, *J* = 4.9 Hz, 2H, CH_2N), 4.02 (s, 3H, OCH_3); MS *m/z* 260.2 (MH^+, 100%).

***tert*-Butyl Benzyl-(6-methoxy-5-nitropyridin-2-yl)carbamate (S80b).** Prepared using Method K from amine **S80a** to give carbamate **S80b** (652 mg, quant.) as a yellow solid: mp (EtOAc) 82–83 °C; ^{1}H NMR δ 8.36 (d, *J* = 9.0 Hz, 1H, H-4), 7.73 (d, *J* = 9.0 Hz, 1H, H-3), 7.20–7.32 (m, 5H, H-2′, H-3′, H-4′, H-5′, H-6′), 5.27 (s, 2H, CH_2N), 3.88 (s, 3H, OCH_3), 1.44 [s, 9H, $C(CH_3)_3$]; MS *m/z* 360.2 (MH^+, 100%).

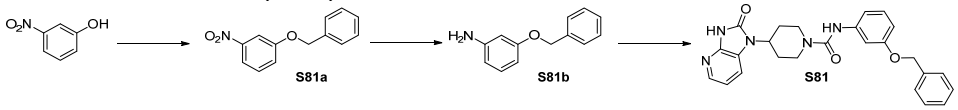
***tert*-Butyl (5-Amino-6-methoxypyridin-2-yl)(benzyl)carbamate (S80c).** Prepared using Method B from **S80b** to give aminopyridine **S80c** (152 mg, 99%) as a yellow oil: ^{1}H NMR δ 7.23–7.30 (m, 4H, H-3′, H-4′, H-5′, H-6′), 7.18 (tt, *J* = 6.9, 1.8 Hz, 1H, H-4′), 6.89 (br d, *J* = 8.2 Hz, 2H, H-4), 6.86 (d, *J* = 7.9 Hz, 1H, H-3), 5.02 (s, 2H, CH_2N), 3.86 (s, 3H, OCH_3), 3.62 (br s, 2H, NH_2), 1.41 [s, 9H, $C(CH_3)_3$]; MS *m/z* 330.2 (MH^+, 100%).

***tert*-Butyl Benzyl-(6-methoxy-5-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamido)pyridin-2-yl)carbamate (S80d).** Prepared using Method C from **S80b** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/EtOAc, to give urea **S80d** (174 mg, 72%) as a gum: ^{1}H NMR δ 8.56 (s, 1H, CONH), 8.34 (d, *J* = 8.5 Hz, 1H, H-4′), 8.03 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5″), 7.33 (dd, *J* = 7.9, 1.3 Hz, 1H, H-7″), 7.17–7.30 (m, 6H, H-3′, H-2‴, H-3‴, H-4‴, H-5‴, H-6‴), 6.99 (dd, *J* = 7.9, 5.2 Hz, 1H, H-6″), 6.90 (s, 1H, CONH), 5.09 (s, 2H, CH_2), 4.59 (tt, *J* = 12.4, 4.1 Hz, 1H, H-4), 4.28 (br d, *J* = 13.9 Hz, 2H, H-2, H-6), 3.87 (s, 3H, OCH_3), 3.06 (br dd, *J* = 12.8, 11.3 Hz, 2H, H-2, H-6), 2.30 (dq, *J* = 12.7, 4.1 Hz, 2H, H-3, H-5), 1.97 (br d, *J* = 12.2 Hz, 2H, H-3, H-5), 1.43 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR δ 159.1, 154.3, 153.1, 143.0, 140.6, 138.3, 136.7, 129.1 (2), 128.5, 128.4 (2), 127.3, 123.3, 123.3, 119.6, 117.2, 115.6, 108.7, 50.5, 44.0 (2), 39.7, 29.5 (2); MS *m/z* 574.2 (MH^+, 100%).

***N*-(6-(Benzylamino)-2-methoxypyridin-3-yl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S80).** Prepared using Method F from carbamate **S80d** to give urea **S80** (86 mg, 64%) as a grey solid: mp (EtOAc) 210–214 °C (decomp.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.55 (s, 1H, CONH), 7.90 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5′), 7.60 (s, 1H, CONH), 7.48 (dd, *J* = 7.8, 1.1 Hz, 1H, H-7′), 7.35 (br d, *J* = 6.8 Hz, 2H, H-2‴, H-6‴), 7.30 (br dd, *J* = 7.8, 7.3 Hz, 2H, H-3‴, H-5‴), 7.24 (d, *J* = 8.2 Hz, 1H, H-4″), 7.20 (br t, *J* = 7.2 Hz, 1H, H-4‴), 6.99 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6′), 6.93 (br s, 1H, NH), 6.01 (d, *J* = 8.2 Hz, 1H, H-5″), 4.34–4.46 (m, 3H, CH_2N, H-4), 4.17 (br d, *J* = 13.8 Hz, 2H, H-2, H-6), 3.73 (s, 3H, OCH_3), 2.87 (br dd, *J* = 12.5, 11.9 Hz, 2H, H-2, H-6), 2.17 (dq, *J* = 12.0, 4.0 Hz, 2H, H-3, H-5), 1.81 (br d, *J* = 9.9 Hz, 2H, H-3, H-5); ^{13}C NMR [$(CD_3)_2SO$] δ

156.7, 156.1, 154.6, 153.0, 143.4, 141.0, 139.6, 137.7, 128.1 (2), 127.2 (2), 126.4, 123.2, 116.4, 114.5, 110.0, 98.3, 52.6, 50.0, 44.7, 43.5 (2), 28.6 (2); MS *m/z* 474.2 (MH^+, 100%); HRMS calcd for $C_{25}H_{28}N_7O_3$ (MH^+) *m/z* 474.2251. Found 474.2260 (-1.9 ppm).

SN36707 *N*-(3-(Benzyloxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S81**).

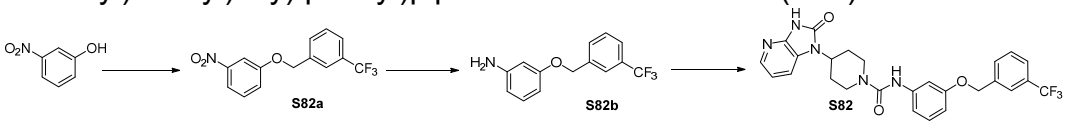


1-(Benzyloxy)-3-nitrobenzene (S81a). Prepared using Method E from benzyl bromide and 3-nitrophenol. The crude residue was purified by column chromatography, eluting with 10% EtOAc/pet. ether, to give ether **S81a** (746 mg, 91%) as a clear colourless oil: ^{1}H NMR δ 7.80–7.86 (m, 2H, H-2, H-6), 7.33–7.47 (m, 6H, H-5, H-2', H-3' H-4', H-5', H-6'), 7.29 (ddd, *J* = 8.3, 2.4, 1.1 Hz, 1H, H-4), 5.15 (s, 2H, CH_2); (+)-HRESIMS *m/z* $[M+Na]^+$ 252.0632 (calcd for $C_{13}H_{11}NNaO_3$, 252.0631).

3-(Benzyloxy)aniline (S81b). Prepared using Method G from nitrobenzene **S81a** to give amine **S81b** (564 mg, 94%) as a pale orange oil: ^{1}H NMR δ 7.35–7.44 (m, 4H, H-2', H-3', H-5', H-6'), 7.28–7.34 (m, 1H, H-4'), 7.06 (td, *J* = 8.1, 0.7 Hz, 1H, H-5), 6.40 (ddd, *J* = 8.1, 2.3, 0.7 Hz, 1H, H-4), 6.28–6.33 (m, 2H, H-2, H-6), 5.02 (s, 2H, CH_2), 3.70 (br s, 2H, NH_2); MS *m/z* 200.6 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 200.1071 (calcd for $C_{13}H_{14}NO$, 200.1070).

***N*-(3-(Benzyloxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S81).** Prepared using Method C from **S81b** and **S1d**. The resulting crude residue was purified by column chromatography, eluting with EtOAc, to give urea **S81** (400 mg, 74%) as a white solid: mp 238–240 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (s, 1H, NH-1), 8.57 (s, 1H, CONH), 7.90 (dd, *J* = 5.2, 1.3 Hz, 1H, H-5), 7.54 (dd, *J* = 7.9, 1.3 Hz, 1H, H-7), 7.42–7.47 (m, 2H, H-2''', H-6'''), 7.36–7.42 (m, 2H, H-3''', H-5'''), 7.30–7.35 (m, 1H, H-4'''), 7.29 (t, *J* = 2.3 Hz, 1H, H-2''), 7.14 (t, *J* = 8.2 Hz, 1H, H-5''), 7.08 (dt, *J* = 8.2, 1.1 Hz, 1H, H-6''), 6.99 (dd, *J* = 7.9, 5.2 Hz, 1H, H-6), 6.60 (ddd, *J* = 8.2, 2.3, 1.1 Hz, 1H, H-4''), 5.06 (s, 2H, CH_2), 4.41 (tt, *J* = 12.4, 3.9 Hz, 1H, H-4'), 4.30 (d, *J* = 12.4 Hz, 2H, H_2-2' or H_2-6'), 2.92 (t, *J* = 12.4 Hz, 2H, H_2-2' or H_2-6'), 2.21 (qd, *J* = 12.4, 3.9 Hz, 2H, H_2-3' or H_2-5'), 1.77 (dd, *J* = 12.4, 2.1 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR [$(CD_3)_2SO$] δ 158.5 (C-3''), 154.6 (CONH), 153.1 (C-2), 143.4 (C-3a), 142.0 (C-1''), 139.7 (C-5), 137.2 (C-1'''), 129.0 (C-5''), 128.4 (C-3'''), 127.8 (C-4'''), 127.6 (C-2'''), 123.3 (C-7a), 116.4 (C-6), 114.6 (C-7), 112.1 (C-6''), 107.9 (C-4''), 106.2 (C-2''), 69.0 (CH_2), 50.2 (C-4'), 43.4 (C-2', C-6'), 28.8 (C-3', C-5'); MS *m/z* 445.1 (MH^+, 100%). Anal. calcd for $C_{25}H_{25}N_5O_3 \cdot 0.35H_2O$: C, 66.76; H, 5.76; N, 15.57. Found: C, 66.95; H, 5.70; N, 15.28%.

SN36708 4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)-*N*-(3-((3-(trifluoromethyl)benzyl)oxy) phenyl)piperidine-1-carboxamide (**S82**).

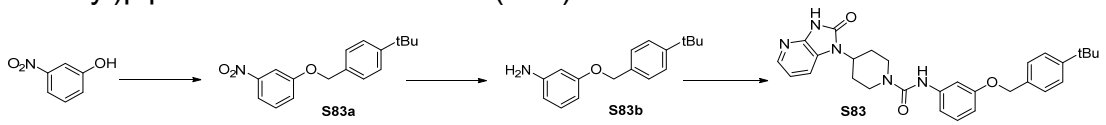


1-Nitro-3-((3-(trifluoromethyl)benzyl)oxy)benzene (S82a). Prepared using Method E from 3-trifluoromethylbenzyl bromide and 3-nitrophenol. The crude residue was purified by column chromatography, eluting in 10% EtOAc/pet. ether, to give ether **S82a** (1.14 g, quant.) as an off-white solid: mp 60–61 °C; ^{1}H NMR δ 7.88 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1H, H-6), 7.83 (t, *J* = 2.3 Hz, 1H, H-2), 7.73 (br s, 1H, H-2'), 7.64 (br d, *J* = 8.1 Hz, 2H, H-4', H-6'), 7.55 (t, *J* = 7.5 Hz, 1H, H-5'), 7.47 (t, *J* = 8.2 Hz, 1H, H-5), 7.31 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1H, H-4), 5.19 (s, 2H, CH_2); (+)-HRESIMS *m/z* $[M+Na]^+$ 320.0503 (calcd for $C_{14}H_{10}F_3NNaO_3$, 320.0505).

3-((3-(Trifluoromethyl)benzyl)oxy)aniline (S82b). Prepared using Method G from nitrobenzene **S82a**. The crude residue was purified by column chromatography, eluting with 10–20% EtOAc/pet. ether, to give amine **S82b** (776 mg, 80%) as an orange oil: ^{1}H NMR δ 7.69 (s, 1H, H-2'), 7.55–7.63 (m, 2H, H-4', H-6'), 7.49 (t, *J* = 7.7 Hz, 1H, H-5'), 7.04–7.10 (m, 1H, H-5), 6.39 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H, H-4), 6.30–6.35 (m, 2H, H-2, H-6), 5.07 (s, 2H, CH_2), 3.67 (br s, 2H, NH_2); MS *m/z* 268.6 (MH^+, 100%).

4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)-*N*-(3-((3-(trifluoromethyl)benzyl)oxy) phenyl)piperidine-1-carboxamide (S82). Prepared using Method C from **S82b** and **S1d**. The resulting crude residue was purified by column chromatography, eluting with EtOAc, to give urea **S82** (350 mg, 53%) as a white solid: mp 170–172 °C; ^{1}H NMR δ 9.15 (br s, 1H, NH-3), 8.04 (dd, *J* = 5.3, 1.3 Hz, 1H, H-5), 7.72 (s, 1H, H-2'''), 7.63 (d, *J* = 7.7 Hz, 1H, H-6'''), 7.59 (d, *J* = 7.7 Hz, 1H, H-4'''), 7.51 (t, *J* = 7.7 Hz, 1H, H-5'''), 7.31–7.35 (m, 2H, H-7, H-2''), 7.22 (t, *J* = 8.2 Hz, 1H, H-5''), 7.00 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6), 6.86 (ddd, *J* = 8.2, 2.2, 0.7 Hz, 1H, H-6''), 6.69 (ddd, *J* = 8.2, 2.2, 0.7 Hz, 1H, H-4''), 6.47 (s, 1H, CONH), 5.13 (s, 2H, CH_2), 4.59 (tt, *J* = 12.5, 4.2 Hz, 1H, H-4'), 4.30 (dt, *J* = 12.5, 2.2 Hz, 2H, H_2-2' or H_2-6'), 3.07 (dt, *J* = 12.5, 2.2 Hz, 2H, H_2-2' or H_2-6'), 2.32 (qd, *J* = 12.5, 4.2 Hz, 2H, H_2-3' or H_2-5'), 1.97 (dd, *J* = 12.5, 2.2 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR δ 159.2 (C-3''), 154.9 (CONH), 153.7 (C-2), 143.4 (C-3a), 140.6 (C-1''), 140.4 (C-5), 138.2 (C-1'''), 131.0 (C-3'''), 130.7 (C-6'''), 129.8 (C-5''), 129.1 (C-5'''), 124.8 (q, *J* = 3.8 Hz, C-4'''), 124.2 (d, *J* = 272.4 Hz, CF_3-3'''), 124.2 (q, *J* = 3.8 Hz, C-2'''), 123.4 (C-7a), 117.0 (C-6), 115.5 (C-7), 112.7 (C-6''), 109.9 (C-4''), 106.7 (C-2''), 69.3 (CH_2), 50.6 (C-4'), 44.2 (C-3', C-5'), 29.5 (C-2', C-6'); (+)-HRESIMS *m/z* $[M+H]^+$ 512.1894 (calcd for $C_{26}H_{25}F_3N_5O_3$, 512.1904). Anal. calcd for $C_{26}H_{24}F_3N_5O_3$: C, 61.05; H, 4.73; N, 13.69. Found: C, 61.26; H, 4.72; N, 13.82%.

SN36709 *N*-(3-((4-(*tert*-Butyl)benzyl)oxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S83**).

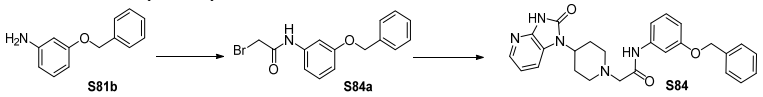


1-((4-(*tert*-Butyl)benzyl)oxy)-3-nitrobenzene (S83a). Prepared using Method E from 4-*tert*-butylbenzyl bromide and 3-nitrophenol. The crude residue was purified by column chromatography, eluting with 10% EtOAc/pet. ether, to give ether **S83a** (874 mg, 85%) as an off-white solid: mp 94–96 °C; ^{1}H NMR δ 7.80–7.87 (m, 2H, H-2, H-6), 7.35–7.46 (m, 5H, H-5, H-2', H-3', H-5', H-6'), 7.27–7.34 (m, 1H, H-4), 5.10 (s, 2H, CH_2), 1.34 (s, 9H, *tert*-butyl-4'); (+)-HRESIMS *m/z* $[M+Na]^+$ 308.1256 (calcd for $C_{14}H_{10}F_3NNaO_3$, 308.1257).

3-((4-(*tert*-Butyl)benzyl)oxy)aniline (S83b). Prepared using Method G from nitrobenzene **S83a**. The crude residue was purified by column chromatography, eluting with 10% EtOAc/pet. ether, to give amine **S83b** (414 mg, 57%) as a pale orange oil: ^{1}H NMR δ 7.41 (ddd, *J* = 8.5, 2.8, 2.2 Hz, 2H, H-3', H-5'), 7.34–7.37 (m, 2H, H-2', H-6'), 7.06 (t, *J* = 8.0 Hz, 1H, H-5), 6.41 (ddd, *J* = 8.0, 2.2, 0.8 Hz, 1H, H-4), 6.33 (t, *J* = 2.2 Hz, 1H, H-2), 6.30 (ddd, *J* = 8.0, 2.2, 0.8 Hz, 1H, H-6), 4.98 (s, 2H, CH_2), 3.65 (br s, 2H, NH_2-1); MS *m/z* 256.6 (MH^+, 100%).

***N*-(3-((4-(*tert*-Butyl)benzyl)oxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S83).** Prepared using Method C from **S83b** and **S1d**. The resulting crude residue was purified by column chromatography, eluting with EtOAc, to give urea **S83** (153 mg, 36%) as a white solid: mp 191–193 °C; ^{1}H NMR δ 9.11 (br s, 1H, NH-3), 8.04 (dd, *J* = 5.3, 1.3 Hz, 1H, H-5), 7.32–7.46 (m, 5H, H-7, H-2''', H-3''', H-5''', H-6'''), 7.18–7.24 (m, 2H, H-2'', H-5''), 6.99 (dd, *J* = 7.9, 5.3 Hz, 1H, H-6), 6.88 (ddd, *J* = 8.0, 2.2, 0.7 Hz, 1H, H-6''), 6.70 (ddd, *J* = 8.3, 2.2, 0.7 Hz, 1H, H-4''), 6.45 (s, 1H, CONH), 5.04 (s, 2H, CH_2), 4.59 (tt, *J* = 12.6, 4.2 Hz, 1H, H-4), 4.29 (d, *J* = 12.6 Hz, 2H, H_2-2 or H_2-6), 3.06 (td, *J* = 12.6, 2.1 Hz, 2H, H_2-2 or H_2-6), 2.31 (qd, *J* = 12.6, 4.2 Hz, 2H, H_2-3 or H_2-5), 1.96 (dd, *J* = 12.6, 2.1 Hz, 2H, H_2-3 or H_2-5), 1.33 (s, 9H, *t*-butyl); ^{13}C NMR δ 159.8 (C-3''), 154.8 (CONH), 153.2 (C-2), 151.2 (C-4'''), 143.1 (C-3a), 140.6 (C-5), 140.3 (C-1''), 134.0 (C-1'''), 129.8 (C-5''), 127.6 (C-2''', C-6'''), 125.7 (C-3''', C-5'''), 123.3 (C-7a), 117.2 (C-6), 115.6 (C-7), 112.3 (C-6''), 110.2 (C-4''), 106.6 (C-2''), 70.0 (CH_2), 50.6 (C-4'), 44.3 (C-2', C-6'), 34.7 (*t*-butyl-4'''), 31.5 (*t*-butyl-4'''), 29.5 (C-3', C-5'); MS *m/z* 501.3 (MH^+, 100%). Anal. calcd for $C_{29}H_{33}N_5O_3$: C, 69.72; H, 6.66; N, 14.02. Found: C, 69.83; H, 6.72; N, 14.14%.

SN36765 *N*-(3-(Benzyloxy)phenyl)-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidin-1-yl)acetamide (**S84**).

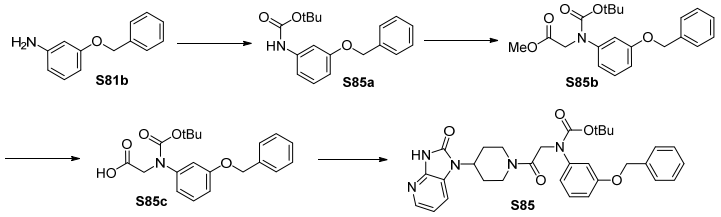


***N*-(3-(Benzyloxy)phenyl)-2-bromoacetamide (S84a).** Prepared using Method I from bromoacetyl bromide and amine **S81b**. The crude residue was purified by column chromatography, eluting with 10% EtOAc/pet. ether, to give bromide **S84a** (720 mg, quant.) as a pale orange powder: mp 123–125 °C; ^{1}H NMR δ 8.08 (s, 1H, CONH), 7.42–7.46 (m, 2H, H-2', H-6'), 7.36–7.41 (m, 3H, H-2, H-3', H-5'), 7.30–7.35 (m, 1H, H-4'), 7.22–7.28 (m, 1H, H-5), 7.02 (dd, *J* = 8.0, 1.8 Hz, 1H, H-6), 6.79 (ddd, *J* = 8.3, 1.8, 0.7 Hz, 1H, H-4), 5.08 (s, 2H, OCH_2), 4.02 (s, 2H, $BrCH_2$); MS *m/z* 320.6 (MH^+, 100%).

***N*-(3-(Benzyloxy)phenyl)-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidin-1-yl)acetamide (S84).** Prepared by Method E from bromide **S84a** and piperidine **S1d** with $CsCO_3$ at 20 °C. The crude residue was purified by column chromatography eluting in EtOAc. Solvent was removed and the residue was loaded onto alumina, and the product eluted in 10% MeOH/CH_2Cl_2 to give the product **S84** (118 mg, 39%) as a white solid: mp 236–238 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.55 (s, 1H, NH-1), 9.73 (s, 1H, CONH), 7.90 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 7.70 (dd, *J* = 7.8, 1.2 Hz, 1H, H-7), 7.43–7.48 (m, 3H, H-2'', H-2''', H-6'''), 7.36–7.41 (m, 2H, H-3''', H-5'''), 7.30–7.35 (m, 1H, H-4'''), 7.19–7.25 (m, 2H, H-5'', H-6''), 7.02 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6), 6.71–6.77 (m,

1H, H-4''), 5.09 (s, 2H, OCH_2), 4.15–4.25 (m, 1H, H-4'), 3.18 (s, 2H, NCH_2), 3.00 (d, *J* = 10.0 Hz, 2H, H_2-2' or H_2-6'), 2.31–2.44 (m, 4H, H_2-2', H_2-3', H_2-5' or H_2-6'), 1.69 (d, *J* = 10.0 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR [$(CD_3)_2SO$] δ 168.6 (CONH), 158.6 (C-3''), 153.1 (C-2), 143.5 (C-3a), 139.8 (C-1''), 139.6 (C-5), 137.1 (C-1'''), 129.5 (C-5''), 128.4 (C-3''', C-5'''), 127.8 (C-4'''), 127.7 (C-2''', C-6'''), 123.1 (C-7a), 116.4 (C-6), 115.0 (C-7), 112.2 (C-6''), 109.6 (C-4''), 106.5 (C-2''), 69.1 (OCH_2), 61.6 (NCH_2), 52.7 (C-2', C-6'), 49.7 (C-4'), 28.6 (C-3', C-5'); (+)-HRESIMS *m/z* $[M+H]^+$ 458.2200 (calcd for $C_{13}H_{14}NO$, 458.2187).

SN36874 *tert*-Butyl (3-(Benzyloxy)phenyl)(2-oxo-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)ethyl)carbamate (**S85**).



***tert*-Butyl (3-(Benzyloxy)phenyl)carbamate (S85a).** Prepared using Method K from aniline **S81b** to give carbamate **S85a** (248 mg, quant.) as a white solid: mp (EtOAc) 100–102 °C; ^{1}H NMR δ 7.43 (br d, *J* = 7.3 Hz, 2H, H-2′, H-6′), 7.38 (br ddd, *J* = 7.4, 7.1, 1.1 Hz, 2H, H-3′, H-5′), 7.32 (br tt, *J* = 7.1, 1.3 Hz, 1H, H-4′), 7.15–7.21 (m, 2H, H-2, H-5), 6.85 (dd, *J* = 8.1, 1.3 Hz, 1H, H-6), 6.65 (ddd, *J* = 8.3, 2.5, 0.8 Hz, 1H, H-4), 6.44 (br s, 1H, NH), 5.06 (s, 2H, CH_2O), 1.52 [s, 9H, $C(CH_3)_3$]; MS *m/z* 360.2 ($M\text{-}CO_2tBu^+$, 100%).

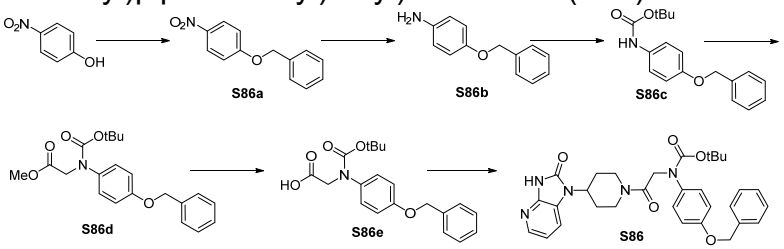
Methyl *N*-(3-(Benzyloxy)phenyl)-*N*-(*tert*-butoxycarbonyl)glycinate (S85b). Prepared using Method L from **S85a** and methyl bromoacetate. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of EtOAc/pet. ether, to give ester **S85b** (77 mg, 39%) as a clear oil: ^{1}H NMR δ 7.42 (br d, *J* = 7.2 Hz, 2H, H-2″, H-6″), 7.37 (br ddd, *J* = 7.5, 7.0, 1.1 Hz, 2H, H-3″, H-5″), 7.31 (br tt, *J* = 7.1, 1.5 Hz, 1H, H-4″), 7.22 (br t, *J* = 8.1 Hz, 1H, H-5′), 6.95 (br s, 1H, H-2′), 6.89 (br d, *J* = 7.2 Hz, 1H, H-6′), 6.82 (ddd, *J* = 8.3, 2.5, 0.8 Hz, 1H, H-4′), 5.04 (s, 2H, CH_2O), 4.26 (s, 2H, H-2), 3.74 (s, 3H, OCH_3), 1.43 [s, 9H, $C(CH_3)_3$]; MS *m/z* 372.2 (MH^+, 100%).

***N*-(3-(Benzyloxy)phenyl)-*N*-(*tert*-butoxycarbonyl)glycine (S85c).** Prepared using Method J from ester **S85b** to give acid **S85c** (73 mg, quant) as a clear oil: ^{1}H NMR δ 7.45 (br d, *J* = 6.9 Hz, 2H, H-2″, H-6″), 7.39 (br dd, *J* = 7.4, 7.0 Hz, 2H, H-3″, H-5″), 7.33 (br t, *J* = 7.1 Hz, 1H, H-4″), 7.22 (br t, *J* = 8.1 Hz, 1H, H-5′), 6.90 (br s, 1H, H-2′), 6.82–6.87 (m, 2H, H-4′, H-6′), 5.07 (s, 2H, CH_2O), 4.13 (s, 2H, H-2), 1.37 [s, 9H, $C(CH_3)_3$]; MS *m/z* 356.2 ($M\text{-}H^-$, 100%).

***tert*-Butyl (3-(Benzyloxy)phenyl)(2-oxo-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)ethyl)carbamate (S85).** Prepared using Method H from acid **S85c** and piperidine **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/EtOAc, to give carboxamide **S85** (73 mg, 64%) as a white solid: mp (EtOAc) 136 °C (dec.); ^{1}H NMR δ 9.80 (br s, 1H, CONH), 8.00 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5″), 7.42–7.47 (m, 3H, H-2‴, H-6‴), 7.38 (br dd, *J* = 7.4, 7.0 Hz, 2H, H-3‴, H-5⁗), 7.32 (d, *J* = 7.1 Hz, 1H, H-4‴), 7.22 (br t, *J* = 8.1 Hz, 1H, H-5‴), 7.04 (br t,

J = 2.2 Hz, 1H, H-2‴), 6.93–7.00 (m, 2H, H-6″, H-6‴), 6.84 (ddd, *J* = 8.2, 1.8, 0.7 Hz, 1H, H-4‴), 5.06 (s, 2H, CH_2O), 4.84 (m, 1H, H-4′), 4.55–4.66 (m, 2H, H-2), 4.25 (br d, *J* = 13.9 Hz, 1H, H-2′, H-6′), 3.95 (br d, *J* = 13.8 Hz, 1H, H-2′, H-6′), 3.20 (br dd, *J* = 13.3, 12.4 Hz, 1H, H-2′, H-6′), 2.70 (br dd, *J* = 12.9, 11.9 Hz, 1H, H-2′, H-6′), 2.08–2.18 (m, 2H, H-3′, H-5′), 1.96–2.06 (m, 2H, H-3′, H-5′), 1.47 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR δ 167.4, 159.2, 154.9, 153.4, 144.4, 143.2, 140.6, 137.0, 129.4, 128.8 (2), 128.2, 127.8 (2), 123.3, 119.7, 117.2, 113.9, 112.9, 81.1, 70.3, 51.3, 50.3, 44.7 (2), 42.4, 29.2 (2), 28.5 (3); MS *m/z* 558.2 (MH^+, 30%), 458.1 ($MH\text{-}CO_2tBu^+$, 100%); HRMS calcd for $C_{31}H_{35}N_5O_5$ (MH^+) *m/z* 558.2711. Found 558.2717 (-1.0 ppm).

SN36875 *tert*-Butyl (4-(Benzyloxy)phenyl)(2-oxo-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)ethyl)carbamate (**S86**).



1-(Benzyloxy)-4-nitrobenzene (S86a). Prepared using Method E from benzyl bromide and 4-nitrophenol. Ether **S86a** (990 mg, 94%) was obtained as a pale yellow solid and was used without further purification: mp 103–105 °C; ^{1}H NMR δ 8.19–8.23 (m, 2H), 7.34–7.44 (m, 5H), 7.01–7.05 (m, 2H), 5.17 (s, 2H).

4-(Benzyloxy)aniline (S86b). Prepared using Method G from **S86a**. The amine **S86b** (658 mg, 81%) was obtained as a brown solid: mp 40–41 °C; ^{1}H NMR δ 7.41–7.43 (m, 2H), 7.34–7.39 (m, 2H), 7.28–7.33 (m, 1H), 4.99 (s, 2H), 3.54 (br s, 2H); MS *m/z* 200.6 (MH^+, 100%).

***tert*-Butyl (4-(Benzyloxy)phenyl)carbamate (S86c).** Prepared using Method K from aniline **S86b** to give carbamate **S86c** (634 mg, 96%) as a brown solid: mp (EtOAc) 120–122 °C; ^{1}H NMR δ 7.42 (br d, *J* = 6.7 Hz, 2H, H-2′, H-6′), 7.36 (br dd, *J* = 7.6, 7.0 Hz, 2H, H-3′, H-5′), 7.31 (br ddd, *J* = 7.4, 6.7, 1.5 Hz, 1H, H-4′), 7.24–7.28 (m, 2H, H-2, H-6), 6.90 (ddd, *J* = 9.0, 3.5, 2.2 Hz, 2H, H-3, H-5), 6.32 (br s, 1H, $NHCO_2$), 5.03 (s, 2H, CH_2O), 1.51 [s, 9H, $C(CH_3)_3$]; MS *m/z* 398.3 ($M\text{-}H^-$, 100%).

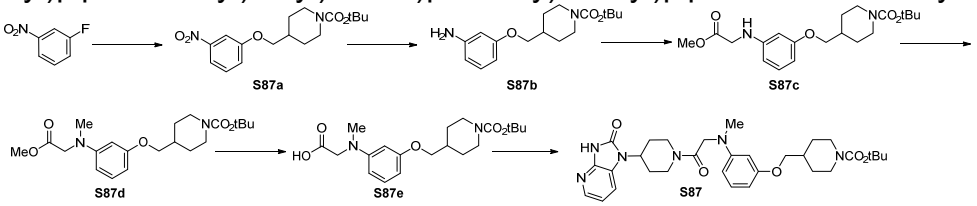
Methyl *N*-(4-(Benzyloxy)phenyl)-*N*-(*tert*-butoxycarbonyl)glycinate (S86d). Prepared using Method L from carbamate **S86c** and methyl bromoacetate. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of EtOAc/pet. ether, to give ester **S86d** (247 mg, 72%) as an orange oil: ^{1}H NMR δ 7.36–7.45 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.30–7.34 (m, 1H, H-4″), 7.15–7.22 (m, 2H, H-2′, H-6′), 6.89–6.95 (m, 2H, H-3′, H-5′), 5.05 (s, 2H, CH_2O), 4.21–4.28 (m, 2H, H-2), 3.71 and 3.73 (2 × s, 3H, OCH_3), 1.38 and 1.44 [2 × br s, 9H, $C(CH_3)_3$]; MS *m/z* 272.2 ($MH\text{-}CO_2tBu^+$, 100%).

***N*-(4-(Benzyloxy)phenyl)-*N*-(*tert*-butoxycarbonyl)glycine (S86e).** Prepared using Method J from ester **S86d** to give acid **S86e** (195 mg, 94%) as a white solid: mp (EtOAc)

118–121 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.45 (br d, *J* = 7.2 Hz, 2H, H-2″, H-6″), 7.39 (br dd, *J* = 7.5, 7.1 Hz, 2H, H-3″, H-5″), 7.32 (br t, *J* = 7.1 Hz, 1H, H-4″), 7.18 (br d, *J* = 8.9 Hz, 2H, H-2′, H-6′), 6.95 (ddd, *J* = 9.0, 3.3, 2.0 Hz, 1H, H-3′, H-5′), 5.08 (s, 2H, CH_2O), 4.07 (br s, 2H, H-2), 1.35 [s, 9H, $C(CH_3)_3$]; MS *m/z* 356.2 ($M-H^-$, 100%). Anal. calcd for $C_{20}H_{23}NO_5$: C, 67.21, H, 6.49; N, 3.92. Found: C, 67.04; H, 6.49; N, 3.83%.

***tert*-Butyl (4-(Benzyloxy)phenyl)(2-oxo-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)ethyl)carbamate (S86).** Prepared using Method H from **S86e** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–5%) of MeOH/EtOAc, to give urea **S86** (173 mg, 75%) as a yellow solid: mp (EtOAc) 138 °C (dec.); ^{1}H NMR δ 10.79 (br s, 1H, CONH), 8.07 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5″), 7.42–7.46 (m, 3H, H-6″, H-2‴, H-6‴), 7.39 (br dd, *J* = 7.6, 7.0 Hz, 2H, H-3‴, H-5‴), 7.33 (br t, *J* = 7.0 Hz, 1H, H-4‴), 7.29 (br d, *J* = 8.9 Hz, 2H, H-2‴, H-6‴), 6.97 (dd, *J* = 7.9, 5.2 Hz, 1H, H-7″), 6.93 (ddd, *J* = 9.0, 3.4, 2.1 Hz, 2H, H-3‴, H-5‴), 5.05 (s, 2H, CH_2O), 4.83 (br d, *J* = 12.2 Hz, 1H, H-2′, H-6′), 4.55–4.68 (m, 2H, H-2, H-4′), 4.20–4.28 (m, 1H, H-2), 3.95 (br d, *J* = 12.7 Hz, 1H, H-2′, H-6′), 3.21 (br dd, *J* = 12.8, 12.7 Hz, 1H, H-2′, H-6′), 2.72 (br dd, *J* = 12.7, 12.4 Hz, 1H, H-2′, H-6′), 2.18–2.30 (m, 2H, H-3′, H-5′), 1.87–1.96 (m, 2H, H-3′, H-5′), 1.44 [s, 9H, $C(CH_3)_3$]; ^{13}C NMR δ 167.4, 157.2, 155.4, 153.7, 143.5, 140.4, 137.0, 136.4, 128.8 (2), 128.5 (2), 128.2 (2), 127.7 (2), 123.3, 117.1, 116.1, 115.0, 80.8, 70.4, 52.0, 50.3, 44.7, 42.3, 29.8, 29.2, 28.5 (3); MS *m/z* 558.3 (MH^+, 100%); HRMS calcd for $C_{31}H_{35}N_5O_5$ (MH^+) *m/z* 558.2711. Found 558.2742 (-5.5 ppm).

SN36876 *tert*-Butyl 4-((3-(Methyl(2-oxo-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)ethyl)amino)phenoxy)methyl)piperidine-1-carboxylate (**S87**).



***tert*-Butyl 4-((3-Nitrophenoxy)methyl)piperidine-1-carboxylate (S87a).** Prepared using Method L from *tert*-butyl 4-(hydroxymethyl)piperidine-1-carboxylate and 3-fluoronitrobenzene at 90 °C. The crude solid was purified by column chromatography, eluting with a gradient (0–25%) of EtOAc/pet. ether, to give ether **S87a** (111 mg, 46%) as a white solid: mp (EtOAc/pet. ether) 92–93 °C; ^{1}H NMR δ 7.80 (ddd, *J* = 8.2, 2.1, 0.9 Hz, 1H, H-6′), 7.71 (t, *J* = 2.3 Hz, 1H, H-2′), 7.42 (t, *J* = 8.2 Hz, 1H, H-5′), 7.21 (ddd, *J* = 8.3, 2.5, 0.9 Hz, 1H, H-4′), 4.10–4.20 (m, 2H, H-2, H-6), 3.89 (d, *J* = 6.4 Hz, 2H, CH_2O), 2.76 (br t, *J* = 12.2 Hz, 2H, H-2, H-6), 1.95–2.05 (m, 1H, H-4), 1.82 (br d, *J* = 12.8 Hz, 2H, H-3, H-5), 1.48 [s, 9H, $C(CH_3)_3$], 1.30 (dq, *J* = 12.4, 4.0 Hz, 2H, H-3, H-5); MS *m/z* 237.2 (MH^+-CO_2tBu, 100%). Anal. calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.13. Found: C, 60.98; H, 7.03; N, 8.28%.

***tert*-Butyl 4-((3-Aminophenoxy)methyl)piperidine-1-carboxylate (S87b).** Prepared using Method B from **S87a**. The amine **S87b** (74 mg, 77%) was obtained as a tan solid: mp (MeOH) 98–100 °C; ^{1}H NMR δ 7.05 (t, *J* = 8.0 Hz, 1H, H-5′), 6.26–6.31(m, 2H, H-4′, H-6′), 6.23 (t, *J* = 2.2 Hz, 1H, H-2′), 4.10–4.18 (m, 2H, H-2, H-6), 3.76 (d, *J* = 6.4 Hz, 2H, CH_2O), 3.64 (br s, 2H, 3′-NH_2), 2.73 (br t, *J* = 12.3 Hz, 2H, H-2, H-6), 1.87–1.98 (m, 1H,

H-4), 1.80 (br d, *J* = 12.9 Hz, 2H, H-3, H-5), 1.46 [s, 9H, C(CH_3)$_3$], 1.24 (dq, *J* = 12.4, 4.2 Hz, 2H, H-3, H-5); MS *m/z* 307.2 (MH^+, 5%), 207.2 (MH^+-CO_2tBu, 100%). Anal. cald for $C_{17}H_{26}N_2O_3$·¼CH_3OH: C, 65.90; H, 8.66; N, 8.91. Found: C, 66.03; H, 8.57; N, 9.04%.

***tert*-Butyl 4-((3-((2-Methoxy-2-oxoethyl)amino)phenoxy)methyl)piperidine-1-carboxylate (S87c).** Prepared using Method E from methyl bromoacetate and aniline **S87b** at 20 °C. The crude solid was purified by column chromatography, eluting with a gradient (15–20%) of EtOAc/pet. ether, to give ester **S87c** (451 mg, 87%) as a white solid: mp (EtOAc/pet. ether) 79–80 °C; ^{1}H NMR δ 7.08 (t, *J* = 8.1 Hz, 1H, H-5′), 6.29 (ddd, *J* = 8.2, 2.3, 0.6 Hz, 1H, H-6′), 6.22 (ddd, *J* = 8.0, 2.2, 0.6 Hz, 1H, H-4′), 6.14 (t, *J* = 2.2 Hz, 1H, H-2′), 4.25 (br t, *J* = 5.4 Hz, 1H, NH), 4.08–4.16 (m, 2H, H-2, H-6), 3.90 (d, *J* = 5.4 Hz, 2H, H-1″), 3.79 (s, 3H, OCH_3), 3.76 (d, *J* = 6.4 Hz, 2H, CH_2O), 2.73 (br t, *J* = 12.1 Hz, 2H, H-2, H-6), 1.87–1.98 (m, 1H, H-4), 1.80 (br d, *J* = 12.9 Hz, 2H, H-3, H-5), 1.46 [s, 9H, C(CH_3)$_3$], 1.24 (dq, *J* = 12.4, 4.0 Hz, 2H, H-3, H-5); MS *m/z* 379.3 (MH^+, 20%), 279.3 (MH^+-CO_2tBu, 100%).

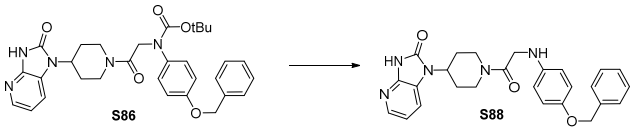
***tert*-Butyl 4-((3-((2-Methoxy-2-oxoethyl)(methyl)amino)phenoxy)methyl)piperidine-1-carboxylate (S87d).** Prepared using Method E from methyl iodide and carbamate **S87c** at 20 °C. The crude solid was purified by column chromatography, eluting with a gradient (0–20%) of EtOAc/pet. ether, to give ester **S87d** (175 mg, 43%) as a clear oil: ^{1}H NMR δ 7.11 (t, *J* = 8.2 Hz, 1H, H-5′), 6.26–6.31 (m, 2H, H-4′, H-6′), 6.22 (br s, 1H, H-2′), 4.10–4.16 (m, 2H, H-2, H-6), 4.06 (s, 2H, H-1″), 3.78 (d, *J* = 6.3 Hz, 2H, CH_2O), 3.71 (s, 3H, OCH_3), 3.04 (s, 3H, NCH_3), 2.73 (br dd, *J* = 12.3, 12.0 Hz, 2H, H-2, H-6), 1.87–1.97 (m, 1H, H-4), 1.82 (br d, *J* = 13.5 Hz, 2H, H-3, H-5), 1.46 [s, 9H, C(CH_3)$_3$], 1.20–1.30 (m, 2H, H-3, H-5); MS *m/z* 393.3 (MH^+, 30%), 337.3 (MH^+-tBu, 100%); HRMS calcd for $C_{21}H_{33}N_2O_5$ (MH^+) *m/z* 393.2384. Found 393.2394 (-2.6 ppm). Starting material (210 mg, 54%) was also isolated.

***N*-(3-((1-(*tert*-Butoxycarbonyl)piperidin-4-yl)methoxy)phenyl)-*N*-methylglycine (S87e).** Prepared using Method J from ester **S87d** to give acid **S87e** (225 mg, 96%) as a white solid: ^{1}H NMR [(CD_3)$_2$SO] δ 6.93 (t, *J* = 8.1 Hz, 1H, H-5′), 6.14 (dd, *J* = 8.2, 2.0 Hz, 1H, H-6′), 6.06 (dd, *J* = 8.0, 1.9 Hz, 1H, H-4′), 6.03 (t, *J* = 2.1 Hz, 1H, H-2′), 3.96 (br d, *J* = 11.5 Hz, 2H, H-2″, H-6″), 3.73 (d, *J* = 6.4 Hz, 2H, H-2), 3.47 (s, 2H, CH_2O), 2.88 (s, 3H, NCH_3), 2.65–2.78 (m, 2H, H-2″, H-6″), 1.81–1.92 (m, 2H, H-4″), 1.73 (br d, *J* = 11.1 Hz, 2H, H-3″, H-5″), 1.39 [s, 9H, C(CH_3)$_3$], 1.12 (dq, *J* = 12.4, 4.0 Hz, 2H, H-3″, H-5″), CO_2H not observed; MS *m/z* 377.3 ($M-H^-$, 100%).

***tert*-Butyl 4-((3-(Methyl(2-oxo-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)ethyl)amino)phenoxy)methyl)piperidine-1-carboxylate (S87).** Prepared using Method H from **S87d** and **S1d**. The crude solid was purified by column chromatography, eluting with a gradient (0–10%) of MeOH/DCM, to give urea **S87** (184 mg, 67%) as a grey solid: mp (EtOAc) 199–203 °C; ^{1}H NMR [(CD_3)$_2$SO] δ 11.56 (br s, 1H, CONH), 7.90 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5‴), 7.41 (dd, *J* = 7.8, 1.2 Hz, 1H, H-7‴), 7.03 (t, *J* = 8.2 Hz, 1H, H-5′), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6‴), 6.28 (dd, *J* = 8.4, 2.2 Hz, 1H, H-6′), 6.22 (dd, *J* = 8.0, 2.0 Hz, 1H, H-4′), 6.17 (t, *J* = 2.2 Hz, 1H, H-2′), 4.40–4.52 (m, 2H, H-2‴, H-6‴, H-4‴), 4.34 (br d, *J* = 17.1 Hz, 1H, H-2″), 4.23 (br d, *J* = 17.0 Hz, 1H, H-

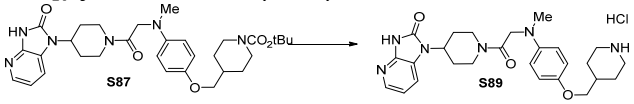
2″), 4.04 (br d, *J* = 11.4 Hz, 1H, H-2‴, H-6‴), 3.96 (br d, *J* = 11.7 Hz, 2H, H-2, H-6), 3.79 (d, *J* = 6.4 Hz, 2H, CH_2O), 3.18 (br dd, *J* = 13.0, 11.8 Hz, 1H, H-2‴, H-6‴), 2.95 (s, 3H, NCH_3), 2.65–2.75 (m, 3H, H-2, H-6, H-2‴, H-6‴), 2.20–2.30 (m, 1H, H-3‴, H-5‴), 1.96–2.07 (m, 1H, H-3‴, H-5‴), 1.84–1.92 (m, 1H, H-4), 1.68–1.82 (m, 4H, H-3, H-5, H-3‴, H-5‴), 1.39 [s, 9H, $C(CH_3)_3$], 1.12 (dq, *J* = 12.2, 4.0 Hz, 2H, H-3″, H-5″); ^{13}C NMR [$(CD_3)_2SO$] δ 167.5, 159.7, 153.9, 153.0, 150.9, 143.4, 139.8, 129.4, 123.1, 116.3, 114.6, 105.1, 101.6, 98.9, 78.5, 71.5, 53.2, 49.7, 43.7 (2), 41.0, 40.9 (2), 39.2, 35.4, 29.2, 28.7, 28.4, 28.1 (3); MS *m/z* 579.3 (MH^+, 100%); HRMS calcd for $C_{31}H_{43}N_6O_5$ (MH^+) *m/z* 579.3293. Found 579.3297 (-0.8 ppm).

SN36877 1-(1-((4-(Benzyloxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S88**).



1-(1-((4-(Benzyloxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S88). Prepared using Method F from carbamate **S86** to give pyridinone **S88** (70 mg, 88%) as a white solid: mp (EtOAc/pet. ether) 106–109 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.55 (br s, 1H, CONH), 7.88 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 7.40–7.47 (m, 3H, H-7, H-2‴, H-6‴), 7.37 (br dd, *J* = 7.6, 7.1 Hz, 2H, H-3‴, H-5‴), 7.30 (br t, *J* = 7.1 Hz, 1H, H-4‴), 6.93 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6), 6.81 (ddd, *J* = 8.9, 3.4, 2.1 Hz, 2H, H-3‴, H-5‴), 6.63 (ddd, *J* = 9.0, 3.4, 2.1 Hz, 2H, H-2‴, H-6‴), 5.27 (br t, *J* = 5.0 Hz, 1H, NH), 4.98 (s, 2H, CH_2O), 4.57 (br d, *J* = 11.3 Hz, 1H, H-2′, H-6′), 4.47 (tt, *J* = 12.4, 4.0 Hz, 1H, H-4′), 4.10 (br d, *J* = 13.9 Hz, 1H, H-2′, H-6′), 3.97 (dd, *J* = 16.2, 5.0 Hz, 1H, H-2″), 3.85 (dd, *J* = 16.2, 4.8 Hz, 1H, H-2″), 3.16 (br t, *J* = 12.2 Hz, 1H, H-2′, H-6′), 2.72 (br dd, *J* = 12.5, 11.7 Hz, 1H, H-2′, H-6′), 2.24 (dq, *J* = 12.3, 3.9 Hz, 1H, H-3′, H-5′), 2.00 (dq, *J* = 12.3, 3.9 Hz, 1H, H-3′, H-5′), 1.70–1.80 (m, 2H, H-3′, H-5′); ^{13}C NMR [$(CD_3)_2SO$] δ 167.9, 153.0, 149.9, 143.4, 142.7, 139.6, 137.7, 128.3 (2), 127.6, 127.5 (2), 123.0, 116.3, 115.7 (2), 114.8, 113.4 (2), 69.8, 49.7, 45.7, 43.5, 41.0, 29.0, 28.6; MS *m/z* 458.3 (MH^+, 100%); HRMS calcd for $C_{26}H_{28}N_5O_3$ (MH^+) *m/z* 458.2187. Found 458.2198 (-2.4 ppm).

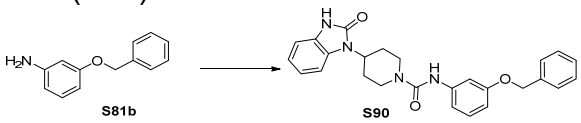
SN36920 1-(1-(*N*-Methyl-*N*-(4-(piperidin-4-ylmethoxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S89**).



1-(1-(*N*-Methyl-*N*-(4-(piperidin-4-ylmethoxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S89). Prepared using Method F from carbamate **S87** to give amine **S89** (124 mg, 100%) as a tan gum: ^{1}H NMR [$(CD_3)_2SO$] δ 11.64 (br s, 1H, CONH), 8.95–9.05 (br s, 1H, NH), 8.60–8.70 (br s, 1H, NH), 7.90 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 7.45 (d, *J* = 7.8 Hz, 1H, H-7), 7.07 (t, *J* = 8.2 Hz, 1H, H-5‴), 6.99 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6), 6.33 (d, *J* = 8.4 Hz, 1H, H-4‴), 6.28 (d, *J* = 8.0 Hz, 1H, H-6‴), 6.25 (br s, 1H, H-2‴), 4.42–4.50 (m, 2H, H-2′, H-6′, H-4′), 4.38 (br d, *J* = 17.1 Hz, 1H, H-2″), 4.28 (br d, *J* = 17.1 Hz, 1H, H-2″), 3.98–4.06 (m, 1H, H-2′, H-6′), 3.81 (d, *J* = 6.2 Hz, 2H, CH_2O), 3.27 (br d, *J* = 12.3 Hz, 2H, H-2‴, H-6‴), 3.18 (br dd, *J* = 12.6, 10.8 Hz, 1H, H-2′, H-6′), 2.97 (s, 3H, NCH_3), 2.87 (br q, *J* = 12.3 Hz, 2H, H-2‴, H-6‴), 2.64–2.74

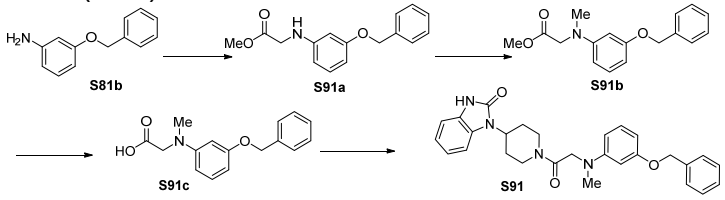
(m, 1H, H-2′, H-6′), 2.23–2.33 (m, 1H, H-3′, H-5′), 1.97–2.07 (m, 2H, H-3′, H-5′, H-4‴), 1.90 (br d, *J* = 13.0 Hz, 2H, H-3‴, H-5‴), 1.76 (br t, *J* = 13.9 Hz, 2H, H-3′, H-5′), 1.43–1.55 (m, 2H, H-3‴, H-5‴); ^{13}C NMR [$(CD_3)_2SO$] δ 167.1, 159.5, 153.0, 150.6, 143.3, 139.3, 129.6, 123.4, 116.4, 114.8, 105.7, 102.4, 99.3, 70.9, 53.4, 49.8, 43.7, 42.7 (2), 41.0, 39.4, 33.3, 29.2, 28.7, 25.3 (2); MS *m/z* 479.3 (MH^+, 100%); HRMS calcd for $C_{26}H_{35}N_6O_3$ (MH^+) *m/z* 479.2765. Found 479.2773 (-1.6 ppm).

SN36944 *N*-(3-(Benzyloxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-benzo[d]imidazol-1-yl)piperidine-1-carboxamide (**S90**).



***N*-(3-(Benzyloxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-benzo[d]imidazol-1-yl)piperidine-1-carboxamide (S90).** Prepared using Method C from **S81b** and 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one. The resulting crude residue was purified by column chromatography, eluting with EtOAc, to give urea **S90** (652 mg, 49%) as a white solid: mp 195–197 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.85 (s, 1H, NH-3), 8.58 (s, 1H, CONH), 7.43–7.47 (m, 2H, H-2‴, H-6‴), 7.37–7.42 (m, 2H, H-3‴, H-5‴), 7.30–7.36 (m, 1H, H-4‴), 7.29 (t, *J* = 2.3 Hz, 1H, H-2″), 7.18–7.23 (m, 1H, H-4), 7.14 (t, *J* = 8.0 Hz, 1H, H-5″), 7.06–7.10 (m, 1H, H-6″), 6.94–7.01 (m, 3H, H-5, H-6, H-7), 6.60 (ddd, *J* = 8.0 , 2.3, 1.1 Hz, 1H, H-4″), 5.06 (s, 2H, CH_2), 4.39 (tt, *J* = 12.4, 3.9 Hz, 1H, H-4′), 4.29 (d, *J* = 12.4 Hz, 2H, H_2-2′ or H_2-6′), 2.93 (t, *J* = 12.4 Hz, 2H, H_2-2′ or H_2-6′), 2.28 (qd, *J* = 12.4, 3.9 Hz, 2H, H_2-3′ or H_2-5′), 1.73 (dd, *J* = 12.4, 1.6 Hz, 2H, H_2-3′ or H_2-5′); ^{13}C NMR [$(CD_3)_2SO$] δ 158.5 (C-3″), 154.7 (CONH), 153.7 (C-2), 142.0 (C-1″), 137.2 (C-1‴), 129.3 (C-7a), 129.0 (C-5″), 128.4 (C-3‴, C-5‴), 128.3 (C-3a), 127.8 (C-4‴), 127.6 (C-2‴, C-6‴), 120.6 (C-6), 120.4 (C-5), 112.1 (C-6″), 108.8 (C-7), 108.5 (C-4), 107.9 (C-4″), 106.1 (C-2″), 69.0 (CH_2), 50.1 (C-4′), 43.6 (C-2′, C-6′), 28.7 (C-3′, C-5′); MS *m/z* 444.1 (MH^+, 100%). Anal. calcd for $C_{26}H_{26}N_4O_3$: C, 70.57; H, 5.92; N, 12.66. Found: C, 70.48; H, 5.78; N, 12.71%.

SN36962 1-(1-(*N*-(3-(Benzyloxy)phenyl)-*N*-methylglycyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one (**S91**).



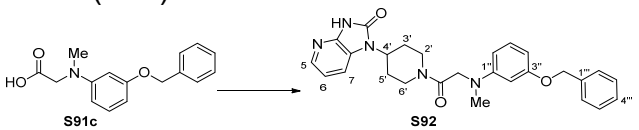
Methyl (3-(benzyloxy)phenyl)glycinate (S91a). Prepared using Method E from methyl bromoacetate and aniline **S81b** at 20 °C. The crude residue was purified by column chromatography, eluting with 20% EtOAc/pet. ether, to give methyl ester **S91a** (316 mg, 80%) as a white solid: mp 97–99 °C; ^{1}H NMR δ 7.41–7.45 (m, 2H, H-2′, H-6′), 7.35–7.40 (m, 2H, H-3′, H-5′), 7.29–7.34 (m, 1H, H-4′), 7.07–7.12 (m, 1H, H-5), 6.38–6.41 (m, 1H, H-6), 6.22–6.27 (m, 2H, H-2, H-4), 5.03 (s, 2H, OCH_2), 4.28 (t, *J* = 5.4 Hz, 1H, NH), 3.90 (d, *J* = 5.4 Hz, 2H, CH_2NH), 3.78 (s, 3H, OMe); MS *m/z* 272.6 (MH^+, 100%). Anal. calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.01; H, 6.26; N, 5.22%.

Methyl *N*-(3-(Benzyloxy)phenyl)-*N*-methylglycinate (S91b). Prepared using Method E from methyl iodide and methyl ester **S91a** at 20 °C. The crude residue was purified by column chromatography, eluting with 10–20% EtOAc/pet. ether, to give methylated amine **S91b** (134 mg, 62%) as a yellow oil: ^{1}H NMR δ 7.41–7.45 (m, 2H, H-2', H-6'), 7.35–7.41 (m, 2H, H-3', H-5'), 7.29–7.34 (m, 1H, H-4'), 7.11–7.16 (m, 1H, H-5), 6.37–6.41 (m, 1H, H-6), 6.29–6.33 (m, 2H, H-2, H-4), 5.04 (s, 2H, OCH_2), 4.05 (s, 2H, CH_2), 3.71 (s, 3H, OMe), 3.04 (s, 3H, Me); MS *m/z* 286.6 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 286.1438 (calcd for $C_{17}H_{20}NO_3$, 286.1438).

***N*-(3-(Benzyloxy)phenyl)-*N*-methylglycine (S91c).** Prepared using Method J from ester **S91b**. The product was recrystallised from pet. ether (10 mL) to give the acid **S91c** (79 mg, 71%) as a pale green solid: mp 112–114 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 12.54 (s, 1H, CO_2H), 7.42–7.46 (m, 2H, H-2', H-6'), 7.36–7.41 (m, 2H, H-3', H-5'), 7.29–7.34 (m, 1H, H-4'), 7.01–7.08 (m, 1H, H-5), 6.29–6.34 (m, 1H, H-6), 6.22–6.26 (m, 2H, H-2, H-4), 5.04 (s, 2H, OCH_2), 4.04 (s, 2H, CH_2), 2.94 (s, 3H, Me); MS *m/z* 272.6 (MH^+, 100%). Anal. calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.85; H, 6.41; N, 5.13%.

1-(1-(*N*-(3-(Benzyloxy)phenyl)-*N*-methylglycyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one (S91). Prepared using Method H from **S91c** and 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one. The resulting crude residue was purified by column chromatography, eluting with 1–3% MeOH/EtOAc, to give amide **S91** (269 mg, 56%) as a white solid: mp 152–154 °C; ^{1}H NMR δ 8.35 (s, 1H, NH-3), 7.42–7.46 (m, 2H, H-2''', H-6'''), 7.35–7.40 (m, 2H, H-3''', H-5'''), 7.29–7.34 (m, 1H, H-4'''), 7.16–7.22 (m, 1H, H-5''), 6.99–7.10 (m, 3H, H-5, H-6, H-7), 6.91 (d, *J* = 7.9 Hz, 1H, H-4), 6.44–6.47 (m, 1H, H-6''), 6.39–6.43 (m, 2H, H-2'', H-4''), 5.07 (s, 2H, OCH_2), 4.84 (br d, *J* = 12.8 Hz, 1H, H_2-2' or H_2-6'), 4.56 (tt, *J* = 12.8, 4.3 Hz, 1H, H-4'), 4.17 (br d, *J* = 1.9 Hz, 1H, $COCH_2$), 4.05 (br d, *J* = 12.8 Hz, 1H, H_2-2' or H_2-6'), 3.22 (br t, *J* = 12.8 Hz, 1H, H_2-2' or H_2-6'), 3.09 (s, 3H, N-Me), 2.73 (br t, *J* = 12.8 Hz, 1H, H_2-2' or H_2-6'), 2.30 (br p, *J* = 12.8 Hz, 2H, H_2-3' or H_2-5'), 1.90 (br d, *J* = 12.8 Hz, 1H, H_2-3' or H_2-5'); ^{13}C NMR δ 168.3 ($COCH_2$), 160.3 (C-3''), 155.1 (C-2), 150.9 (C-1''), 137.5 (C-1'''), 130.2 (C-5''), 129.0 (C-3a), 128.7 (C-3''', C-5'''), 128.2 (C-7a), 128.1 (C-4'''), 127.8 (C-2''', C-6'''), 121.6 (C-6), 121.5 (C-5), 110.0 (C-7), 109.4 (C-4), 106.2 (C-6''), 103.4 (C-4''), 100.6 (C-2''), 70.1 (OCH_2), 55.3 ($COCH_2$), 50.6 (C-4'), 44.9 (C-2' or C-6'), 42.3 (C-2' or C-6'), 40.0 (N-Me), 29.9 (C-3' or C-5'), 29.3 (C-3' or C-5'); MS *m/z* 472.2 (MH^+, 100%). Anal. calcd for $C_{28}H_{30}N_4O_3 \cdot 0.5H_2O$: C, 70.13; H, 6.52; N, 11.68. Found: C, 70.44; H, 6.38; N, 11.37%.

SN36963 1-(1-(*N*-(3-(Benzyloxy)phenyl)-*N*-methylglycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (**S92**).

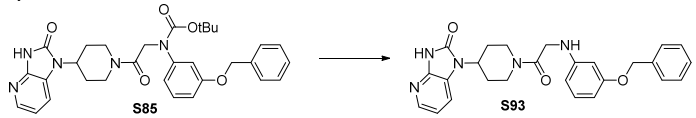


S91c S92

1-(1-(*N*-(3-(Benzyloxy)phenyl)-*N*-methylglycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (S92). Prepared using Method H from **S91c** and **S1d**. The resulting crude residue was purified by column chromatography, eluting with 1% MeOH/EtOAc, to give the amide **S92** (370 mg, 51%) as a white solid: mp 152–154 °C; ^{1}H NMR δ 10.66 (s, 1H, NH-3), 8.03 (dd, *J* = 5.2, 1.3 Hz, 1H, H-5), 7.39–7.45 (m, 2H, H-2''',

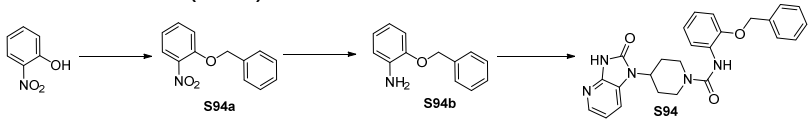
H-6‴), 7.32–7.38 (m, 2H, H-3‴, H-5‴), 7.27–7.32 (m, 1H, H-4‴), 7.14–7.21 (m, 1H, H-5″), 6.96 (dd, *J* = 7.9, 1.3 Hz, 1H, H-7), 6.88 (dd, *J* = 7.9, 5.2 Hz, 1H, H-6), 6.46 (dd, *J* = 7.8, 2.0 Hz, 1H, H-4″), 6.39–6.43 (m, 2H, H_2-2″, H_2-6″), 5.05 (s, 2H, OCH_2), 4.81 (d, *J* = 12.6 Hz, 1H, H_2-2′ or H_2-6′), 4.59 (tt, *J* = 12.6, 4.2 Hz, 1H, H-4′), 4.15 (s, 2H, $COCH_2$), 4.03 (d, *J* = 12.6 Hz, 1H, H_2-2′ or H_2-6′), 3.20 (t, *J* = 12.6 Hz, 1H, H_2-2′ or H_2-6′), 3.07 (s, 3H, N-Me), 2.71 (t, *J* = 12.6 Hz, 1H, H_2-2′ or H_2-6′), 2.01–2.21 (m, 2H, H_2-3′ or H_2-5′), 1.88 (d, *J* = 12.6 Hz, 2H, H_2-3′ or H_2-5′); ^{13}C NMR δ 168.4 ($COCH_2$), 160.3 (C-3″), 153.6 (C-2), 150.9 (C-1″), 143.4 (C-3a), 140.4 (C-5), 137.4 (C-1‴), 130.3 (C-5″), 128.8 (C-3‴, C-5‴), 128.1 (C-4‴), 127.8 (C-2‴, C-6‴), 123.3 (C-7a), 117.1 (C-6), 115.6 (C-7), 106.2 (C-6″), 103.6 (C-4″), 100.6 (C-2″), 70.1 (OCH_2), 55.7 ($COCH_2$), 50.3 (C-4′), 44.9 (C-2′, C-6′), 42.2 (C-2′, C-6′), 40.3 (N-Me), 30.0 (C-3′, C-5′), 29.5 (C-3′, C-5′); MS *m/z* 473.2 (MH^+, 100%). Anal. calcd for $C_{28}H_{29}N_5O_3$: C, 68.77; H, 6.20; N, 14.85. Found: C, 68.79; H, 6.21; N, 14.91%.

SN36972 1-(1-((3-(Benzyloxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S93**).



1-(1-((3-(Benzyloxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S93). Prepared using Method F from carbamate **S85** to give pyridinone **S93** (28 mg, 100%) as a white solid: mp (EtOAc/pet. ether) 163 °C (dec.); ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (s, 1, CONH), 7.89 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 7.41–7.48 (m, 3H, H-7, H-2⁗, H-6⁗), 7.35–7.40 (m, 2H, H-3⁗, H-5⁗), 7.28–7.35 (m, 1H, H-4⁗), 7.00 (t, *J* = 8.1 Hz, 1H, H-5⁗), 6.94 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6), 6.37 (t, *J* = 2.2 Hz, 1H, H-2⁗), 6.32 (dd, *J* = 8.1, 1.5 Hz, 1H, H-4⁗), 6.27 (dd, *J* = 8.1, 1.8 Hz, 1H, H-6⁗), 5.64 (t, *J* = 4.9 Hz, 1H, NH), 5.04 (s, 2H, CH_2O), 4.57 (d, *J* = 12.4 Hz, 1H, H-2′, H-6′), 4.48 (tt, *J* = 12.3, 4.0 Hz, 1H, H-4′), 4.11 (br d, *J* = 14.0 Hz, 1H, H-2′, H-6′), 4.01 (dd, *J* = 16.3, 4.6 Hz, 1H, H-2″), 3.88 (dd, *J* = 16.3, 4.6 Hz, 1H, H-2″), 3.18 (br dd, *J* = 13.0, 12.0 Hz, 1H, H-2′, H-6′), 2.75 (br d, *J* = 12.0 Hz, 1H, H-2′, H-6′), 2.20–2.30 (m, 1H, H-3′, H-5′), 1.96–2.07 (m, 1H, H-3′, H-5′), 1.72–1.81 (m, 2H, H-3′, H-5′); ^{13}C NMR [$(CD_3)_2SO$] δ 167.6, 159.5, 153.0, 149.5, 143.4, 139.6, 137.4, 129.5, 128.3 (2), 127.7 (2), 123.0, 116.4, 114.8, 105.9, 102.4, 99.1, 68.9, 49.6, 45.0, 43.5, 41.0 (2), 29.0, 28.7. MS *m/z* 458.4 (MH^+, 100%); HRMS calcd for $C_{26}H_{28}N_5O_3$ (MH^+) *m/z* 458.2187. Found 458.2191 (-1.0 ppm).

SN36973 *N*-(2-(Benzyloxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S94**).

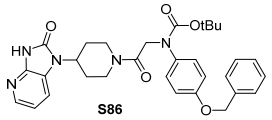


1-(Benzyloxy)-2-nitrobenzene (S94a). Prepared using Method E from benzyl bromide and 2-nitrophenol. The ether **S94a** (817 mg, 99%) was obtained as yellow oil and used without further purification: ^{1}H NMR δ 7.86 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.45–7.52 (m, 3H), 7.38–7.42 (m, 2H), 7.33–7.35 (m, 1H), 7.12 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.02–7.06 (m, 1H), 5.24 (s, 2H).

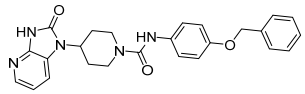
2-(Benzyloxy)aniline (S94b). Prepared using Method G from **S94a**. Amine **S94b** (428 mg, 67%) was obtained as a clear yellow oil: ^{1}H NMR δ 7.43–7.46 (m, 2H), 7.37–7.41 (m, 2H), 7.31–7.35 (m, 1H), 6.86 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.79–6.83 (m, 1H), 6.69–6.76 (m, 2H), 5.08 (s, 2H), 3.83 (br s, 2H); MS *m/z* 200.6 (MH^+, 100%).

***N*-(2-(Benzyloxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S94).** Prepared using Method C from **S94b** and **S1d**. The resulting crude residue was purified by column chromatography, eluting with EtOAc to give urea **S94** (566 mg, 62%) as a white solid: mp 137–140 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (s, 1H), 7.89 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.82 (s, 1H), 7.65 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 2H), 7.47 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.36 (tt, *J* = 7.3, 1.4 Hz, 2H), 7.28 (tt, *J* = 7.3, 1.4 Hz, 1H), 7.08 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.01 (dt, *J* = 8.0, 1.6 Hz, 1H), 6.88–6.96 (m, 2H), 5.17 (s, 2H), 4.40 (m, 1H), 4.20 (d, *J* = 13.2 Hz, 2H), 2.96 (dd, *J* = 12.1, 12.1 Hz, 2H), 2.21 (m, 2H), 1.74 (dd, *J* = 11.9, 2.0 Hz, 2H); ^{13}C NMR [$(CD_3)_2SO$] δ 154.7, 153.1, 149.6, 143.5, 139.7, 137.3, 129.1, 128.4 (2), 127.7, 127.2 (2), 123.6, 123.3, 123.0, 120.6, 116.4, 114.5, 112.8, 69.8, 50.0, 43.5 (2), 28.7 (2); MS *m/z* 445.0 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 444.2042 (calcd for $C_{25}H_{26}N_5O_3$, 444.2030).

SN36987 *N*-(4-(Benzyloxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (**S95**).



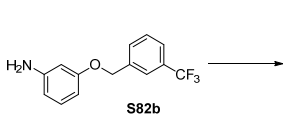
S86



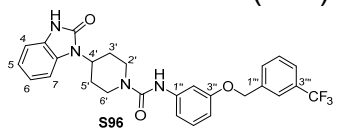
S95

***N*-(4-(Benzyloxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (S95).** Prepared using Method C from **S86** and **S1d**. The crude residue was purified by column chromatography, eluting with 2–4% MeOH/DCM, to give urea **S95** (134 mg, 26%) as an orange solid: mp (MeOH/DCM) 265–268 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.55 (s, 1H), 8.43 (s, 1H), 7.89 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.54 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.41–7.47 (m, 1H), 7.29–7.41 (m, 1H), 6.99 (dd, *J* = 7.8, 5.2 Hz, 1H), 6.90–6.92 (m, 1H), 5.05 (s, 1H), 4.36–4.42 (m, 1H), 4.28 (d, *J* = 3.9 Hz, 1H), 2.90 (dd, *J* = 12.4, 12.4 Hz, 1H), 2.18–2.20 (m, 1H), 1.76 (dd, *J* = 12.4, 2.1 Hz, 1H); ^{13}C NMR [$(CD_3)_2SO$] δ 155.0, 153.5, 153.4, 143.9, 139.6, 137.4, 133.9, 128.4 (2), 127.7, 127.6 (2), 123.4, 121.5 (2), 116.2, 114.5 (2), 114.4, 69.4, 50.1, 43.4 (2), 28.8 (2); MS *m/z* 445.3 (MH^+, 100%). Anal. calcd for $C_{25}H_{25}N_5O_3$: C, 67.70; H, 5.68; N, 15.79. Found: C, 67.51; H, 5.57; N, 15.87%.

SN36988 4-(2-Oxo-2,3-dihydro-1*H*-benzo[d]imidazol-1-yl)-*N*-(3-((3-(trifluoromethyl)benzyl)oxy)phenyl)piperidine-1-carboxamide (**S96**).



S82b

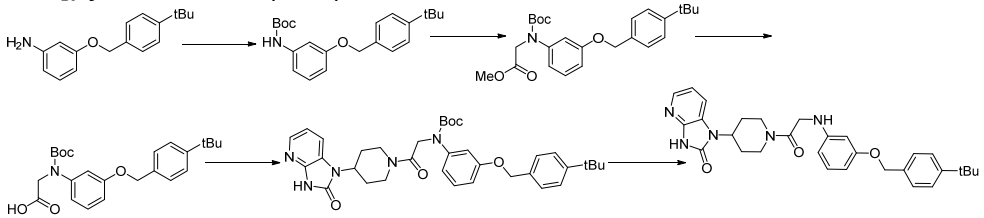


S96

4-(2-Oxo-2,3-dihydro-1*H*-benzo[d]imidazol-1-yl)-N-(3-((3-(trifluoromethyl)benzyl)oxy)phenyl)piperidine-1-carboxamide (S96). Prepared using Method C from **S82b** and 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one. The resulting crude residue was purified by column chromatography, eluting with EtOAc to give urea **S96** (254 mg, 48%) as a white solid: mp 181–183 °C; ^{1}H NMR [$(CD_3)_2SO$] δ

10.84 (s, 1H, NH-3), 8.59 (s, 1H, CONH), 7.81 (s, 1H, H-2'''), 7.77 (d, *J* = 2.1 Hz, 1H, H-6'''), 7.70 (d, *J* = 2.1 Hz, 1H, H-4'''), 7.65 (t, *J* = 7.7 Hz, 1H, H-5'''), 7.32 (t, *J* = 2.3 Hz, 1H, H-2''), 7.18–7.23 (m, 1H, H-4), 7.15 (t, *J* = 8.0 Hz, 1H, H-5''), 7.06–7.12 (m, 1H, H-6''), 6.93–7.01 (m, 3H, H-5, H-6, H-7), 6.62 (ddd, *J* = 8.0, 2.3, 1.0 Hz, 1H, H-4''), 5.17 (s, 2H, CH_2), 4.39 (tt, *J* = 12.4, 3.9 Hz, 1H, H-4'), 4.29 (d, *J* = 12.4 Hz, 2H, H_2-2' or H_2-6'), 2.94 (t, *J* = 12.4 Hz, 2H, H_2-2' or H_2-6'), 2.28 (qd, *J* = 12.4, 3.9 Hz, 2H, H_2-3' or H_2-5'), 1.73 (dd, *J* = 12.4, 1.9 Hz, 2H, H_2-3' or H_2-5'); ^{13}C NMR [$(CD_3)_2SO$] δ 158.2 (C-3''), 154.6 (CONH), 153.7 (C-2), 142.0 (C-1''), 138.8 (C-1'''), 131.5 (C-6'''), 129.5 (C-7a), 129.3 (C-5'''), 129.2 (q, *J* = 31.6 Hz, C-3'''), 129.1 (C-5''), 128.3 (C-3a), 124.5 (q, *J* = 3.7 Hz, C-4'''), 124.2 (CF_3-3'''), 123.9 (q, *J* = 3.8 Hz, C-2'''), 120.6 (C-6), 120.4 (C-5), 112.3 (C-6''), 108.8 (C-7), 108.4 (C-4), 107.8 (C-4''), 106.2 (C-2''), 68.1 (CH_2), 50.1 (C-4'), 43.5 (C-2', C-6'), 28.7 (C-3', C-5'); MS *m/z* 512.6 (MH^+, 100%). Anal. calcd for $C_{27}H_{25}F_3N_4O_3$: C, 63.52; H, 4.95; N, 10.97. Found: C, 63.48; H, 4.87; N, 10.93%.

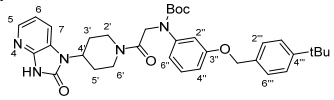
SN37102 1-(1-((3-((4-(*tert*-Butyl)benzyl)oxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (**S97**).



***tert*-Butyl (3-((4-(*tert*-Butyl)benzyl)oxy)phenyl)carbamate (S97a).** Prepared using Method K from aniline **S83b**. The crude residue was purified by column chromatography, eluting with 10% EtOAc/pet. ether, to give carbamate **S97a** (227 mg, 94%) as an off-white solid: mp 130–133 °C; ^{1}H NMR δ 7.35–7.42 (m, 4H), 7.15–7.19 (m, 2H), 6.86 (dd, *J* = 8.0, 1.3 Hz, 1H), 6.65 (m, 1H), 6.45 (br s, 1H), 5.02 (s, 2H), 1.52 (s, 9H), 1.33 (s, 9H); MS *m/z* 354.9 ($M-H^-$, 100%).

Methyl *N*-(*tert*-Butoxycarbonyl)-*N*-(3-((4-(*tert*-butyl)benzyl)oxy)phenyl)glycinate (S97b). Prepared using Method I from amine **S97a** and methyl bromoacetate. The crude residue was purified by column chromatography, eluting with 10% EtOAc/pet. ether, to give ester **S97b** (100 mg, 43%) as a clear colourless gum: ^{1}H NMR δ 7.40–7.42 (m, 2H), 7.35–7.37 (m, 2H), 7.21–7.23 (m, 1H), 6.89–6.95 (m, 1H), 6.82–6.85 (m, 1H), 5.01 (s, 2H), 4.27 (s, 2H), 3.76 (s, 3H), 1.43 (br s, 9H), 1.33 (s, 9H).

***N*-(*tert*-Butoxycarbonyl)-*N*-(3-((4-(*tert*-butyl)benzyl)oxy)phenyl)glycine (S97c).** Prepared using Method J from ester **S97b** to give acid **S97c** (110 mg, 85%) as a clear colourless gum: ^{1}H NMR [$(CD_3)_2SO$] δ 7.35–7.42 (m, 4H), 7.23 (dd, *J* = 8.1, 8.1 Hz, 1H), 6.90–6.91 (m, 1H), 6.83–6.86 (m, 2H), 5.03 (s, 2H), 4.17 (s, 2H), 1.36 (br s, 9H), 1.28 (s, 9H); MS *m/z* 413.0 ($M-H^-$, 100%).

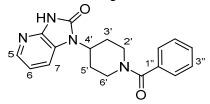


***tert*-Butyl (3-((4-(tert-Butyl)benzyl)oxy)phenyl)(2-oxo-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)ethyl)carbamate (S105).** Prepared using Method H using **S97c** and **S1d**. The crude residue was purified by column

chromatography, eluting in EtOAc, to give amide **S105** (35 mg, 45%) as white residue: mp 209–211 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.53 (br s, 1H), 7.89 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.35–7.44 (m, 4H), 7.23 (dd, *J* = 8.1, 8.1 Hz, 1H), 6.92–6.97 (m, 2H), 6.86–6.91 (m, 1H), 6.84 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.04 (s, 2H), 4.32–4.61 (m, 4H), 3.97 (m, 1H), 3.16 (dd, *J* = 12.7, 12.7 Hz, 1H), 2.70–2.75 (m, 1H), 2.24–2.27 (m, 1H), 2.03–2.08 (m, 1H), 1.77 (br d, *J* = 11.3 Hz, 2H), 1.38 (s, 9H), 1.28 (s, 9H); ^{13}C NMR [$(CD_3)_2SO$] δ 166.6, 158.2, 153.7, 153.1, 150.3, 144.2, 143.6, 139.7, 134.0, 128.9, 127.6 (2), 125.2 (2), 123.2, 118.7, 116.2, 114.4, 113.1, 111.5, 79.7, 69.1, 51.5, 49.7, 43.5, 41.2, 34.3, 31.1 (3), 29.0, 28.6, 27.9 (3); (+)-HRESIMS *m/z* [M+H]$^+$ 614.3323 (calcd for $C_{35}H_{44}N_5O_5$, 614.3337).

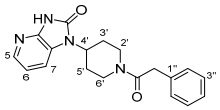
1-(1-((3-((4-(*tert*-Butyl)benzyl)oxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S97). Prepared using Method F from carbamate **S105** to give the amine **S97** (25 mg, 88%) as an off-white solid: mp 137–140 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.55 (br s, 1H), 7.88 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.31–7.43 (m, 5H), 6.98 (dd, *J* = 8.1, 8.1 Hz, 1H), 6.92 (dd, *J* = 7.8, 5.2 Hz, 1H), 6.35 (t, *J* = 2.2, 2.2 Hz, 1H), 6.29 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.25 (dd, *J* = 8.1, 1.6 Hz, 1H), 5.65 (t, *J* = 5.0, 5.0 Hz, 1H), 4.98 (s, 2H), 4.57 (d, *J* = 13.1 Hz, 1H), 4.44–4.50 (m, 1H), 4.11 (d, *J* = 13.1 Hz, 1H), 3.99–4.04 (m, 1H), 3.88 (dd, *J* = 16.5, 4.5 Hz, 1H), 3.17 (t, *J* = 13.2, 13.2 Hz, 1H), 2.73 (dd, *J* = 12.3, 12.3 Hz, 1H), 2.20–2.29 (m, 1H), 1.96–2.05 (m, 1H), 1.75 (m, 2H), 1.26 (s, 9H); ^{13}C NMR [$(CD_3)_2SO$] δ 167.7, 159.5, 153.0, 150.1, 149.5, 143.4, 139.6, 134.4, 129.6, 127.5 (2), 125.1 (2), 123.0, 116.4, 114.8, 105.8, 102.5, 99.0, 68.6, 49.6, 45.1, 43.6, 41.0, 34.2, 31.1 (3), 29.0, 28.7; MS *m/z* 515.6 (MH$^+$, 100%); (+)-HRESIMS *m/z* [M+H]$^+$ 514.2824 (calcd for $C_{30}H_{36}N_5O_3$, 514.2813).

SN37103 1-(1-Benzoylpiperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S98**).



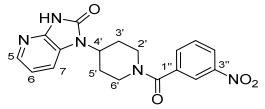
1-(1-Benzoylpiperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S98). Piperidine **S1d** (46 mg, 0.18 mmol) was stirred in water (2 mL) as a suspension. Et_3N (50 µL, 0.36 mmol) was added followed by dropwise addition of benzoyl chloride (21 µL, 0.18 mmol). The mixture was allowed to stir at 20 °C for 20 min before diluted with water (50 mL) and extracted with EtOAc (50 mL). The organic layer was washed with water (50 mL), brine (50 mL), dried and concentrated. The crude residue was purified by column chromatography, eluting with EtOAc, to give amide **S98** (29 mg, 49%) as a white solid: mp 272–274 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.57 (br s, 1H), 7.90 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.69 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.45–7.49 (m obsc., 5H), 7.00 (dd, *J* = 7.8, 5.2 Hz, 1H), 4.66 (br s, 1H), 4.44–4.52 (m, 1H), 3.70 (br s, 1H), 3.21 (br s, 1H), 2.91 (br s, 1H), 2.24 (m, 2H), 1.73–1.81 (m, 2H); ^{13}C NMR [$(CD_3)_2SO$] δ 169.1, 153.1, 143.5, 139.7, 136.2, 129.4, 128.4, 126.7, 123.1, 116.4, 115.0, 59.7, 49.8, 46.6, 28.8, 28.6, 20.7, 14.1; MS *m/z* 323.8 (MH$^+$, 100%); (+)-HRESIMS *m/z* [M+H]$^+$ 323.1507 (calcd for $C_{18}H_{19}N_4O_2$, 323.1503).

SN37104 1-(1-(2-Phenylacetyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (**S99**).



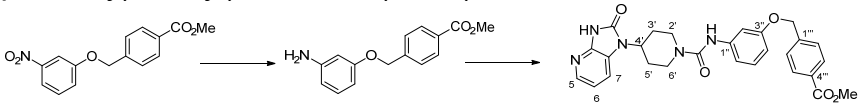
1-(1-(2-Phenylacetyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S99). Piperidine **S1d** (87 mg, 0.34 mmol) was stirred in MeOH (1 mL) as a suspension. Ammonia was added until dissolution. Solvent was removed and the residue was dried under vacuum. The residue was suspended in DMF (2 mL). Et_3N (94 µL, 0.68 mmol) and phenylacetyl chloride (45 µL, 0.34 mmol) was added in a dropwise manner. The mixture was allowed to stir at 20 °C for 16 h before diluted with water (50 mL) and extracted with EtOAc (50 mL). The organic layer was washed with water (50 mL), brine (50 mL), dried and concentrated. The crude residue was purified by column chromatography, eluting with EtOAc, to give amide **S99** (71 mg, 62%) as an off-white solid: mp 232–233 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.53 (br s, 1H), 7.88 (dd, *J* = 5.2, 1.3 Hz, 1H), 7.22–7.37 (m, 6H), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H), 4.56–4.59 (m, 1H), 4.38–4.56 (m, 1H), 4.07–4.11 (m, 1H), 3.71–3.83 (m, 2H), 3.10–3.16 (m, 1H), 2.64–2.70 (m, 1H), 1.82–2.04 (m, 2H), 1.71–1.73 (m, 1H), 1.62–1.65 (m, 1H); ^{13}C NMR [$(CD_3)_2SO$] δ 168.6, 152.9, 143.4, 139.6, 135.9, 128.8 (2), 128.3 (2), 126.3, 122.8, 116.2, 114.5, 49.4, 44.8, 40.7, 39.7, 28.8, 28.4; MS *m/z* 337.8 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 337.1661 (calcd for $C_{19}H_{21}N_4O_2$, 337.1659).

SN37105 1-(1-(3-Nitrobenzoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (**S100**).



1-(1-(3-Nitrobenzoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (S100). Prepared using Method H from **S1d** and 3-nitrobenzoic acid. The crude residue was purified by column chromatography, eluting in 2–5% MeOH/EtOAc, to give amide **S100** (137 mg, 62%) as an off-white solid: mp 213–215 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.58 (s, 1H, NH-1), 8.29–8.33 (m, 2H, H-2'', H-4''), 7.95 (dt, *J* = 7.6, 1.2 Hz, 1H, H-6''), 7.91 (dd, *J* = 5.2, 1.3 Hz, 1H, H-5), 7.74–7.80 (m, 2H, H-7, H-5''), 7.01 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6), 4.68 (d, *J* = 10.3 Hz, 1H, H_2-2' or H_2-6'), 4.51 (tt, *J* = 10.3, 3.9 Hz, 1H, H_2-4'), 3.64 (d, *J* = 10.3 Hz, 1H, H_2-2' or H_2-6'), 3.32 (obscured, 1H, H_2-2' or H_2-6'), 2.96 (t, *J* = 10.3 Hz, 1H, H_2-2' or H_2-6'), 2.16–2.37 (m, 2H, H_2-3' or H_2-5'), 1.85 (d, *J* = 10.3 Hz, 1H, H_2-3' or H_2-5'), 1.69 (d, *J* = 10.3 Hz, 1H, H_2-3' or H_2-5'); ^{13}C NMR [$(CD_3)_2SO$] δ 166.8 (NCO), 153.1 (C-2), 147.7 (C-3''), 143.5 (C-3a), 139.7 (C-5), 137.7 (C-1''), 133.3 (C-6''), 130.2 (C-5''), 124.2 (C-4''), 123.1 (C-7a), 121.8 (C-2''), 116.4 (C-6), 115.1 (C-7), 49.6 (C-4'), 46.6 (C-2' or C-6'), 41.1 (C-2' or C-6'), 29.0 (C-3' or C-5'), 28.4 (C-3' or C-5'); MS *m/z* 368.9 (MH^+, 100%). Anal. calcd for $C_{18}H_{17}N_5O_4 \cdot 0.2H_2O$: C, 58.28; H, 4.73; N, 18.88. Found: C, 58.48; H, 4.77; N, 18.69%.

SN37106 Methyl 4-((3-(4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamido)phenoxy)methyl)benzoate (**S101**).

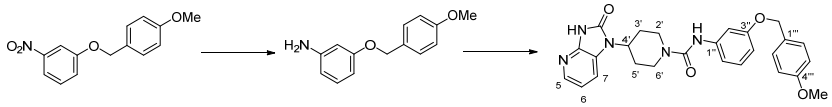


Methyl 4-((3-Nitrophenoxy)methyl)benzoate (S101a). Prepared using Method E from methyl 4-(bromomethyl)benzoate and 3-nitrophenol. A white precipitate formed and was removed by filtration to give ether **S101a** (1.52 mg, 74%) as an off-white solid which was used without futher purification: mp 141–143 °C; ^{1}H NMR δ 8.07–8.10 (m, 2H), 7.85–7.87 (m, 1H), 7.81 (dd, *J* = 2.3, 2.3 Hz, 1H), 7.51–7.53 (m, 2H), 7.45 (dd, *J* = 8.2, 8.2 Hz, 1H), 7.30 (ddd, *J* = 8.3, 2.6, 0.9 Hz, 1H), 5.21 (s, 2H), 3.93 (s, 3H).

Methyl 4-((3-Aminophenoxy)methyl)benzoate (S101b). Prepared using Method G from **S101a**. The crude residue was purified by column chromatography, eluting with 25–50% EtOAc/pet. ether, to give amine **S101b** (427 mg, 53%) as an off-white solid: mp 96–98 °C; ^{1}H NMR δ 8.03–8.06 (m, 2H), 7.48–7.50 (m, 2H), 7.04–7.08 (m, 1H), 6.36–6.69 (m, 1H), 6.31–6.33 (m, 2H), 5.09 (s, 2H), 3.92 (s, 3H), 3.66 (br s, 2H); MS *m/z* 258.6 (MH^+, 100%).

Methyl 4-((3-(4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamido)phenoxy)methyl)benzoate (S101). Prepared using Method C from **S101b** and **S1d**. The crude residue was purified by column chromatography, eluting with 1% MeOH/EtOAc, to give urea **S101** (92 mg, 32%) as a white solid: mp 209–211 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (br s, 1H), 8.58 (s, 1H), 7.98–8.00 (m, 2H), 7.89 (dd, *J* = 5.2, 1.3 Hz, 1H), 7.58–7.60 (d, *J* = 8.4 Hz, 2H), 7.54 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.31 (dd, *J* = 2.1, 2.1 Hz, 1H), 7.14 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.08–7.10 (m, 1H), 6.98 (dd, *J* = 7.8, 5.2 Hz, 1H), 6.59–6.62 (m, 1H), 5.16 (s, 2H), 4.36–4.44 (m, 1H), 4.30 (d, *J* = 13.4, 2H), 2.92 (dd, *J* = 12.1, 12.1 Hz, 2H), 2.16–2.26 (m, 2H), 1.76–1.78 (m, 2H); ^{13}C NMR [$(CD_3)_2SO$] δ 166.0, 158.2, 154.6, 153.1, 143.5, 142.9, 142.0, 139.6, 129.3 (2), 129.1, 128.9, 127.4 (2), 123.3, 116.4, 114.5, 112.2, 107.8, 106.2, 68.4, 52.1, 50.1, 43.4 (2), 28.8 (2); (+)-HRESIMS *m/z* $[M+H]^+$ 502.2071 (calcd for $C_{27}H_{28}N_5O_5$, 502.2085).

SN37107 *N*-(3-((4-Methoxybenzyl)oxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S102**).

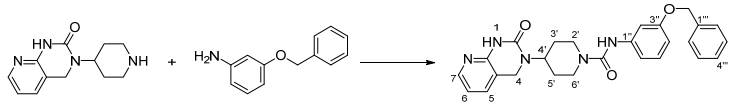


1-((4-Methoxybenzyl)oxy)-3-nitrobenzene (S102a). Prepared using Method E from 3-nitrophenol and 4-methoxybenzyl chloride. The crude residue was purified by column chromatography, eluting with 20% EtOAc/pet. ether, to give the ether **S102a** (1.96 g, quant.) as pale yellow solid: mp 83–85 °C; ^{1}H NMR δ 7.81–7.84 (m, 2H), 7.40–7.44 (m, 1H), 7.35–7.39 (m, 2H), 7.27–7.29 (m, 1H), 6.92–6.96 (m, 2H), 5.07 (s, 2H), 3.83 (s, 3H).

3-((4-Methoxybenzyl)oxy)aniline (S102b). Prepared using Method G from **S102a** and was used directly.

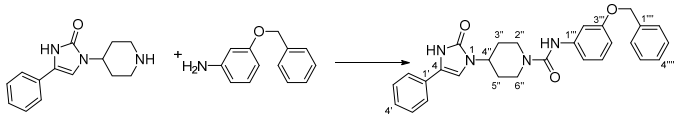
***N*-(3-((4-Methoxybenzyl)oxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S102).** Prepared using Method C from **S102b** and **S1d**. The crude residue was purified by column chromatography, eluting with 1% MeOH/EtOAc, to give urea **S102** (21 mg, 13%) as an off-white solid: mp 136–139 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (s, 1H), 8.55 (s, 1H), 7.90 (dd, *J* = 5.2, 1.3 Hz, 1H), 7.54 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.34–7.40 (m, 2H), 7.27 (dd, *J* = 2.1, 2.1 Hz, 1H), 7.12 (t, *J* = 8.0, 8.0 Hz, 1H), 7.04–7.09 (m, 1H), 6.99 (dd, *J* = 7.9, 5.2 Hz, 1H), 6.92–6.97 (m, 2H), 6.58 (m, 1H), 4.96 (s, 2H), 4.40 (m, 1H), 4.30 (d, *J* = 13.5 Hz, 2H), 3.76 (s, 3H), 2.92 (dd, *J* = 12.2, 12.2 Hz, 2H), 2.21 (m, 2H), 1.77 (d, *J* = 12.0 Hz, 2H); ^{13}C NMR [$(CD_3)_2SO$] δ 158.9, 158.5, 154.6, 153.1, 143.4, 141.9, 139.6, 129.4 (2), 129.1, 129.0, 123.3, 116.4, 114.5, 113.8 (2), 111.9, 108.0, 106.1, 68.8, 55.1, 50.1, 43.4 (2), 28.8 (2); MS *m/z* 473.3 (MH^+, 100%).

SN37130 *N*-(3-(Benzyloxy)phenyl)-4-(2-oxo-1,4-dihydropyrido[2,3-*d*]pyrimidin-3(2*H*)-yl)piperidine-1-carboxamide (**S103**).



***N*-(3-(Benzyloxy)phenyl)-4-(2-oxo-1,4-dihydropyrido[2,3-*d*]pyrimidin-3(2*H*)-yl)piperidine-1-carboxamide (S103).** Prepared using Method C from 3-(piperidin-4-yl)-3,4-dihydroquinazolin-2(1*H*)-one and **S81b**. The resulting crude residue was purified by column chromatography, eluting with 2% MeOH/DCM, to give urea **S103** (175 mg, 38%) as a white solid: mp 237–240 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.22 (s, 1H), 8.53 (s, 1H), 7.42–7.47 (m, 2H), 7.36–7.42 (m, 2H), 7.30–7.35 (m, 1H), 7.28 (dd, *J* = 2.2, 2.2 Hz, 1H), 7.05–7.16 (m, 4H), 6.85 (dt, *J* = 7.5, 7.5, 1.1 Hz, 1H), 6.76 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.59 (ddd, *J* = 8.0, 2.5, 1.2 Hz, 1H), 5.05 (s, 2H), 4.36 (m, 1H), 4.31 (s, 2H), 4.24–4.27 (m, 2H), 2.85 (dd, *J* = 11.9, 11.9 Hz, 2H), 1.68–1.78 (m, 2H), 1.57–1.60 (m, 2H); ^{13}C NMR [$(CD_3)_2SO$] δ 158.5, 154.5, 153.7, 142.0, 137.5, 137.2, 129.0, 128.4 (2), 127.7 (2), 127.6 (2), 125.6, 120.9, 118.3, 112.9, 112.0, 107.9, 106.1, 69.0, 51.0, 43.5, 42.3 (2), 28.2 (2); MS *m/z* 456.3 ($M\text{-}H^-$, 100%); (+)-HRESIMS *m/z* $[M+Na]^+$ 479.2051 (calcd for $C_{27}H_{28}N_4NaO_3$, 479.2054). Anal. calcd for $C_{27}H_{28}N_4O_3$: C, 71.03; H, 6.18; N, 12.27. Found: C, 71.09; H, 6.14; N, 12.33%.

SN37131 *N*-(3-(Benzyloxy)phenyl)-4-(2-oxo-4-phenyl-2,3-dihydro-1*H*-imidazol-1-yl)piperidine-1-carboxamide (**S104**).

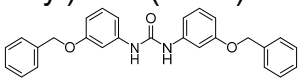


***N*-(3-(Benzyloxy)phenyl)-4-(2-oxo-4-phenyl-2,3-dihydro-1*H*-imidazol-1-yl)piperidine-1-carboxamide (S104).** Prepared using Method C from 4-phenyl-1-(piperidin-4-yl)-1,3-dihydro-2*H*-imidazol-2-one and **S81b**. The resulting crude residue was purified by column chromatography, eluting with 4% MeOH/EtOAc, to give urea **S104** (226 mg, 48%) as a white solid: mp 211–214 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.70 (d, *J* = 1.6 Hz, 1H), 8.55 (s, 1H), 7.49–7.53 (m, 2H), 7.42–7.47 (m, 2H), 7.37–7.42 (m, 2H), 7.27–7.35 (m, 4H), 7.22 (d, *J* = 2.2 Hz, 1H), 7.14–7.19 (m, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 7.08–7.10 (m, 1H), 6.60 (ddd, *J* = 7.9, 2.5, 1.2 Hz, 1H), 5.05 (s, 2H), 4.28 (d, *J* = 13.6 Hz, 2H),

4.02–4.13 (m, 1H), 2.91 (dd, *J* = 11.8, 11.8 Hz, 2H), 1.67–1.82 (m, 4H); ^{13}C NMR [$(CD_3)_2SO$] δ 158.5, 154.5, 153.0, 141.9, 137.2, 129.7, 129.0, 128.6 (2), 128.4 (2), 127.7, 127.6 (2), 126.2, 122.7 (2), 120.8, 112.1, 107.9, 106.2, 105.9, 69.0, 49.4, 43.2 (2), 31.2 (2); (+)-HRESIMS *m/z* $[M+H]^+$ 469.2219 (calcd for $C_{28}H_{29}N_4O_3$, 469.2234). Anal. calcd for $C_{28}H_{28}N_4O_3$: C, 71.78; H, 6.02; N, 11.96. Found: C, 71.77; H, 6.05; N, 11.91%.

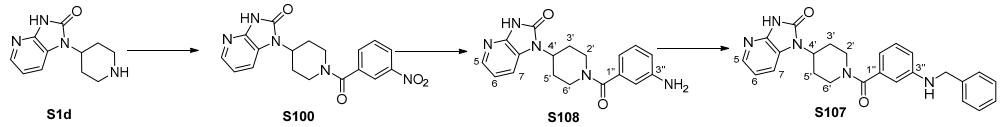
SN37134 *tert*-Butyl (3-((4-(*tert*-Butyl)benzyl)oxy)phenyl)(2-oxo-2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidin-1-yl)ethyl)carbamate (**S105**).
Preparation reported in the synthesis of SN37102 1-(1-((3-((4-(*tert*-butyl)benzyl)oxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S97**).

SN37135 1,3-bis(3-(Benzyloxy)phenyl)urea (**S106**).



1,3-bis(3-(Benzyloxy)phenyl)urea (S106). Prepared using Method K from amine **S81b**. The crude residue was purified by column chromatography, eluting with 30–50% EtOAc/pet. ether, to give the urea **S106** (40 mg, 7%) as a white solid: mp 196–198 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.65 (br s, 1H), 7.45–7.47 (m, 2H), 7.38–7.42 (m, 2H), 7.31–7.35 (m, 1H), 7.25 (dd, *J* = 2.2, 2.2 Hz, 1H), 7.17 (dd, *J* = 8.2, 8.2 Hz, 1H), 6.93–6.95 (m, 1H), 6.62–6.65 (m, 1H), 5.08 (s, 2H); ^{13}C NMR [$(CD_3)_2SO$] δ 158.8, 152.3, 140.8, 137.1, 129.5, 128.4 (2), 127.8, 127.6 (2), 110.8, 108.0, 104.9, 69.1; MS *m/z* 426.0 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 425.1862 (calcd for $C_{27}H_{25}N_2O_3$, 425.1860).

SN37163 1-(1-(3-(Benzylamino)benzoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S107**).

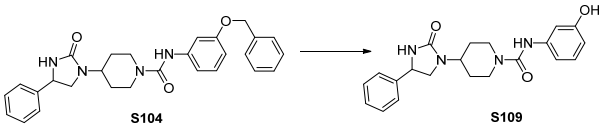


1-(1-(3-(Benzylamino)benzoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S107). Amine **S108** (183 mg, 0.54 mmol) and benzaldehyde (55 µL, 0.54 mmol) were stirred in DCM (5 mL) for 4 h. $NaBH(OAc)_3$ (172 mg, 0.81 mmol) was added and the mixture was allowed to stir at 20 °C for 20 h. Solvent was removed and the crude residue was purified by column chromatography, eluting in 2–6% MeOH/EtOAc. Solvent was removed and the residue was triturated in EtOAc to give the benzylamine **S107** (165 mg, 71%) as a white solid: mp 200–203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.57 (br s, 1H), 7.91 (dd, *J* = 5.2, 1.3 Hz, 1H), 7.61 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.34–7.36 (m, 2H), 7.24–7.28 (m, 2H), 7.15–7.19 (m, 1H), 7.11 (dd, *J* = 7.8 Hz, 1H), 7.01 (dd, *J* = 7.8, 5.2 Hz, 1H), 6.63–6.66 (m, 1H), 6.56 –6.59 (m, 2H), 6.56 (dd, *J* = 1.0 Hz, 1H), 4.60 (br s, 1H), 4.39–4.46 (m, 1H), 4.29 (d, *J* = 6.0 Hz, 2H), 3.67 (br s, 1H), 2.83–3.06 (m, 2H), 2.04–2.18 (m, 2H), 1.79 (br s, 1H), 1.59 (br s, 1H); ^{13}C NMR [$(CD_3)_2SO$] δ 169.6, 153.1, 148.5, 143.5, 139.9, 139.7, 136.8, 128.9, 128.3 (2), 127.1 (2), 126.6, 123.1, 116.4, 114.9, 113.9, 113.2, 110.0, 49.8, 46.2, 40.8, 40.3, 29.0, 28.6; MS *m/z* 429.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 428.2093 (calcd for $C_{25}H_{26}N_5O_2$, 428.2081).

SN37164 1-(1-(3-Aminobenzoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (**S108**).

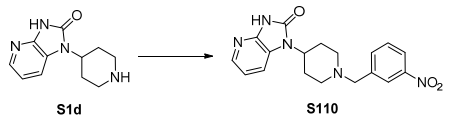
1-(1-(3-Aminobenzoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (S108). Prepared using Method B from **S100**. The crude residue was purified by column chromatography, eluting with 4–10% MeOH/EtOAc to give amine **S108** (110 mg, 32%) as an off-white solid: mp 268–271 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.57 (br s, 1H), 7.90 (dd, *J* = 5.2, 1.3 Hz, 1H), 7.62 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.05–7.09 (m, 1H), 7.00 (dd, *J* = 7.8, 5.2 Hz, 1H), 6.60–6.62 (m, 2H), 6.53–6.56 (m, 1H), 5.26 (s, 2H), 4.62 (br s, 1H), 4.42–4.50 (m, 1H), 3.80 (br s, 1H), 3.14 (br s, 1H), 2.86 (br s, 1H), 2.20 (br s, 2H), 1.77 (br s, 2H); ^{13}C NMR [$(CD_3)_2SO$] δ 169.7, 153.1, 148.7, 143.4, 139.7, 136.8, 128.8, 123.2, 116.4, 114.8, 114.6, 113.7, 111.8, 49.9, 46.4, 40.8, 29.2, 28.7; MS *m/z* 337.38 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 338.1615 (calcd for $C_{18}H_{20}N_5O_2$, 338.1612).

SN37176 *N*-(3-Hydroxyphenyl)-4-(2-oxo-4-phenylimidazolidin-1-yl)piperidine-1-carboxamide (**S109**).



***N*-(3-Hydroxyphenyl)-4-(2-oxo-4-phenylimidazolidin-1-yl)piperidine-1-carboxamide (S109).** Prepared using Method B from **S104** (67 mg, 0.14 mmol) and 10% Pd/C. The crude residue was purified by column chromatography, eluting in 10% EtOAc/pet. ether, to give phenol **S109** (44 mg, 81%) as a white solid: mp 155–158 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.16 (s, 1H), 8.35 (s, 1H), 7.31–7.40 (m, 1H), 7.26–7.31 (m, 1H), 7.00 (t, *J* = 2.2, 2.2 Hz, 1H), 6.92–6.98 (m, 1H), 6.82 (ddd, *J* = 8.1, 1.9, 0.9 Hz, 1H), 6.31 (ddd, *J* = 8.0, 2.4, 0.9 Hz, 1H), 4.66 (t, *J* = 8.4 Hz, 1H), 4.17 (dd, *J* = 13.9, 13.9 Hz, 2H), 3.69–3.81 (m, 2H), 3.02 (m, 1H), 2.73–2.88 (m, 2H), 1.44–1.64 (m, 4H); ^{13}C NMR [$(CD_3)_2SO$] δ 160.7, 157.3, 154.7, 142.7, 141.7, 128.8, 128.5 (2), 127.5, 126.0 (2), 110.3, 108.7, 106.7, 52.9, 49.2, 48.7, 43.3, 43.2, 29.2, 28.5; (+)-HRESIMS *m/z* $[M+H]^+$ 381.1922 (calcd for $C_{21}H_{25}N_4O_3$, 381.1921).

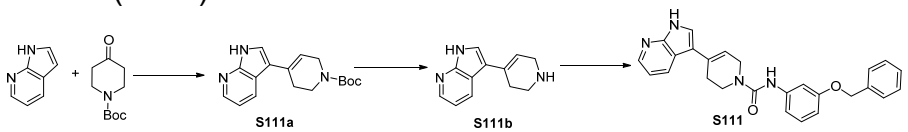
SN37177 1-(1-(3-Nitrobenzyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S110**).



1-(1-(3-Nitrobenzyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S110). To a solution of piperidine **S1d** (1.15 g, 4.51 mmol) and Et_3N (1.25 mL, 9.02 mmol) in DMF (20 mL) was added 3-nitrobenzyl bromide (974 mg, 4.51 mmol). The resulting mixture was allowed to stir at 20 °C for 20 h. The resulting mixture was diluted with EtOAc (100 mL) and was washed with water (2 × 100 mL), brine (100 mL), dried and concentrated *in vacuo*. The crude residue was purified by column chromatography, eluting with EtOAc, to give amine **S110** (1.02 g, 64%) as an off-white solid: mp 177–180 °C; ^{1}H NMR δ 9.56 (br s, 1H), 8.28 (dd, *J* = 1.7, 1.7 Hz, 1H), 8.12–8.15 (m, 1H), 8.05 (dd, *J* = 5.3, 1.3 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 1H), 7.47–7.54 (m, 2H), 7.02 (dd, *J* = 7.9, 5.3 Hz, 1H), 4.38–4.47 (m, 1H), 3.65 (s, 2H), 3.00–3.03 (m, 2H), 2.32–2.43 (m, 2H), 2.21–2.27 (m, 2H), 1.84–1.87 (m, 2H); ^{13}C NMR δ 153.8, 148.7, 143.4, 141.1, 140.3, 135.1,

129.4, 123.9, 123.6, 122.5, 117.0, 115.9, 62.2, 53.3 (2), 50.6, 29.6 (2); MS *m/z* 354.9 (MH^+, 100%). Anal. calcd for $C_{18}H_{19}N_5O_3$: C, 61.18; H, 5.42; N, 19.82. Found: C, 61.14; H, 5.46; N, 19.85%.

SM37178 *N*-(3-(Benzyloxy)phenyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxamide (**S111**).

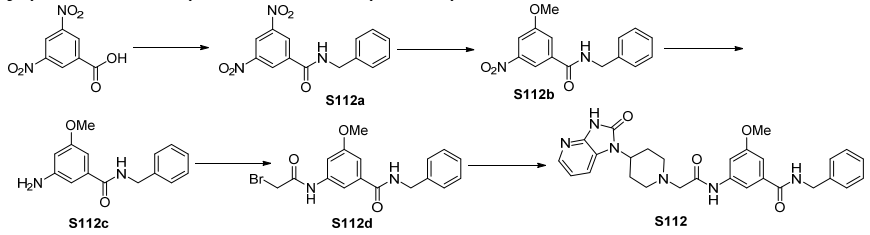


***tert*-Butyl 4-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (S111a).** 7-Azaindole (500 mg, 4.23 mmol), *tert*-butyl 4-oxopiperidine-1-carboxylate (1.68 g, 8.47 mmol) and KOH (950 mg, 16.92 mmol) were stirred together in MeOH at 65 °C for 24 h. The resulting mixture was cooled to 20 °C and diluted with EtOAc (100 mL). The organic layer was washed with water (100 mL) and brine (100 mL), dried and concentrated *in vacuo* to obtain a crude orange gum. The crude product was triturated in EtOAc/pet. ether to give the carbamate **S111a** (898 mg, 71%) as a yellow solid: mp 171–173 °C; ^{1}H NMR δ 9.39 (s, 1H), 8.33 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.19 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.13 (dd, *J* = 8.0, 4.7 Hz, 1H), 6.15 (s, 1H), 4.11–4.15 (m, 2H), 3.69 (t, *J* = 5.7, 5.7 Hz, 2H), 2.57 (br s, 2H), 1.50 (s, 9H); MS *m/z* 300.7 (MH^+, 100%).

3-(1,2,3,6-Tetrahydropyridin-4-yl)-1*H*-pyrrolo[2,3-b]pyridine Hydrochloride (S111b). Prepared using Method F from carbamate **S111a** to give amine **S111b** (77 mg, 61%) as a cream coloured solid: mp 275–278 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.99 (br s, 1H), 9.10 (br s, 2H), 8.28–8.34 (m, 2H), 7.69 (d, *J* = 2.5 Hz, 1H), 7.17–7.20 (m, 1H), 6.22 (s, 1H), 3.76 (br s, 2H), 3.32–3.34 (m, 2H), 2.73 (m, 2H); MS *m/z* 200.5 (MH^+, 100%).

***N*-(3-(Benzyloxy)phenyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-3,6-dihydropyridine-1(2*H*)-carboxamide (S111).** Prepared using Method C from **S111b** and **S81b**. The resulting residue was triturated in 10% EtOAc/pet. ether to give urea **S111** (73 mg, 25%) as a cream coloured solid: mp 158–161 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.70 (s, 1H), 8.54 (s, 1H), 8.26 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.23 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.42–7.46 (m, 2H), 7.36–7.42 (m, 2H), 7.27–7.36 (m, 2H), 7.06–7.16 (m, 3H), 6.58–6.61 (m, 1H), 6.22 (m, 1H), 5.05 (s, 2H), 4.18 (d, *J* = 2.7 Hz, 2H), 3.69 (t, *J* = 5.7, 5.7 Hz, 2H), 2.58 (s, 2H); ^{13}C NMR [$(CD_3)_2SO$] δ 158.5, 154.9, 149.1, 142.8, 141.9, 137.2, 129.8, 129.0, 128.4 (2), 128.3, 127.7, 127.6 (2), 123.4, 117.1, 116.8, 115.8, 114.4, 112.2, 107.9, 106.2, 69.0, 43.8, 40.4, 27.3; (+)-HRESIMS *m/z* $[M+H]^+$ 425.1986 (calcd for $C_{26}H_{25}N_4O_2$, 425.1972).

SN37179 *N*-Benzyl-3-methoxy-5-(2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidin-1-yl)acetamido)benzamide (**S112**).



***N*-Benzyl-3,5-dinitrobenzamide (S112a).** A mixture of 3,5-dinitrobenzoic acid (5.00 g, 23.57 mmol) and CDI (4.59 g, 28.28 mmol) in DMF (25 mL) was heated to 60 °C for 1 h. Benzylamine (2.53 g, 23.57 mmol) was added and the reaction mixture was heated at 60 °C for 24 h. Once cooled, the resulting mixture was diluted with EtOAc (100 mL), then washed with water (2 × 100 mL), brine (100 mL), dried and concentrated. The resulting solids were removed by filtration, washed with EtOAc and dried. The amide **S112a** (4.22 g, 59%) was obtained as an off-white solid: mp 200–202 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.75 (t, *J* = 5.8 Hz, 1H), 9.11 (d, *J* = 2.1 Hz, 2H), 8.97 (dd, *J* = 2.1, 2.1 Hz, 1H), 7.33–7.39 (m, 4H), 7.25–7.29 (m, 1H), 4.56 (d, *J* = 5.8 Hz, 2H); MS *m/z* 300.6 ([M-H]$^-$, 100%).

***N*-Benzyl-3-methoxy-5-nitrobenzamide (S112b).** Sodium methoxide (0.97 g, 17.92) was added to a solution of amide **S112a** (3.60 g, 11.95 mmol) in DMF (50 mL). The resulting mixture was heated at 60 °C over 65 h. Once cooled, the mixture was diluted with EtOAc (200 mL), washed with water (2 × 200 mL), brine (200 mL), dried and concentrated. The crude residue was purified by column chromatography, eluting with DCM, to give the amide **S112b** (1.13 g, 33%) as a yellow solid: ^{1}H NMR [$(CD_3)_2SO$] δ 9.40 (t, *J* = 5.9, 5.9 Hz, 1H), 8.33–8.34 (m, 1H), 7.87–7.90 (m, 2H), 7.31–7.37 (m, 4H), 7.23–7.29 (m, 1H), 4.51 (d, *J* = 5.9 Hz, 2H), 3.93 (s, 3H); MS *m/z* 285.6 ([M-H]$^-$, 100%).

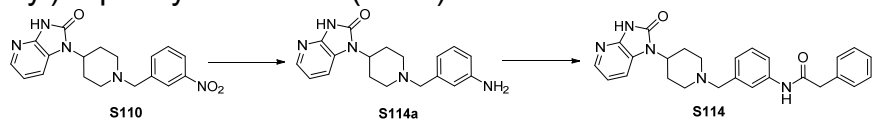
3-Amino-*N*-benzyl-5-methoxybenzamide (S112c). Prepared using Method B from **S112b** and 10% Pd/C. The crude residue was purified by column chromatography, eluting with 60% EtOAc/pet. ether, to give amine **S112c** (177 mg, 63%) as a pale orange solid: mp 115–117 °C; ^{1}H NMR δ 7.33–7.38 (m, 4H), 7.28–7.32 (m, 1H), 7.68–6.70 (m, 2H), 6.34 (dd, *J* = 2.2 Hz, 1H), 6.28 (br s, 1H), 4.63 (d, *J* = 5.7 Hz, 2H), 3.79 (s, 3H), 3.77 (br s, 2H); MS *m/z* 257.6 (MH$^+$, 100%).

***N*-Benzyl-3-(2-bromoacetamido)-5-methoxybenzamide (S112d).** Prepared using Method I from bromoacetyl bromide and amine **S112c**. The bromide **S112d** (298 mg, 68%) was obtained as an off-white solid: mp 191–194 °C; ^{1}H NMR δ 10.51 (s, 1H), 9.03 (t, *J* = 6.0 Hz, 1H), 7.61 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.44 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.30–7.35 (m, 4H), 7.23–7.26 (m, 1H), 7.19–7.20 (m, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.04 (s, 2H), 3.79 (s, 3H); MS *m/z* 379.9 (MH$^+$, 100%).

***N*-Benzyl-3-methoxy-5-(2-(4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidin-1-yl)acetamido)benzamide (S112).** Prepared using Method I from bromide **S112d** and piperidine **S1d** with Et_3N in DMF. The crude residue was purified by column chromatography, eluting with EtOAc, to give amide **S112** (87 mg, 60%) as an off-white solid: mp 162–165 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.55 (s, 1H), 9.88 (s, 1H), 9.01 (t, *J* = 6.0, 6.0 Hz, 1H), 7.90 (dd, *J* = 5.2, 1.3 Hz, 1H), 7.71 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.67 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.55 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.30–7.36 (m, 4H), 7.21–7.28 (m, 1H), 7.18 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.00 (dd, *J* = 7.8, 5.2 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 2H), 4.13–4.25 (m, 1H), 3.80 (s, 3H), 3.20 (s, 2H), 3.01 (d, *J* = 8.7 Hz, 2H), 2.31–2.47 (m, 4H), 1.69 (d, *J* = 10.1 Hz, 2H); ^{13}C NMR [$(CD_3)_2SO$] δ 168.8, 166.0, 159.3, 153.1, 143.5, 139.7, 139.6, 136.0, 128.3 (2), 127.2 (2), 126.7, 123.2, 116.4, 114.9, 111.7, 108.5, 107.3, 61.6, 55.4, 52.7 (2), 49.7, 42.6, 28.6 (2), 1 carbon signal not observed; (+)-HRESIMS *m/z* [M+H]$^+$ 515.2384 (calcd for $C_{28}H_{31}N_6O_4$, 515.2401).

SN37180 1-(1-(4,4-bis(4-Fluorophenyl)butyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one (**S113**) was obtained from AK Scientific.

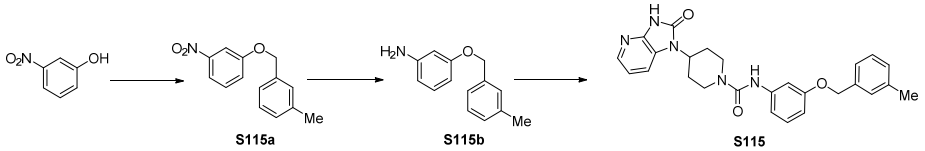
SN37241 *N*-(3-((4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)methyl)phenyl)-2-phenylacetamide (**S114**).



1-(1-(3-Aminobenzyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (S114a). Prepared using Method B from **S110** and 10% Pd/C. The crude residue was purified by column chromatography, eluting with 5% MeOH/EtOAc, to give amine **S114a** (344 mg, 99%) as a yellow solid: ^{1}H NMR [$(CD_3)_2SO$] δ 11.52 (s, 1H, NH-3), 7.89 (dd, *J* = 5.2, 1.3 Hz, 1H), 7.53 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.92–7.03 (m, 2H), 6.57 (t, *J* = 1.7 Hz, 1H), 6.42–6.48 (m, 2H), 4.99 (s, 2H, NH_2-3''), 4.14 (tt, *J* = 11.9, 3.3 Hz, 1H, H-4'), 3.35 (s, 2H, CH_2), 2.94 (d, *J* = 11.9 Hz, 2H, H-2' or H-6'), 2.28 (m, 2H, H-3' or H-5'), 2.04 (t, *J* = 11.9 Hz, 2H, H-2' or H-6'), 1.67 (dd, *J* = 12.0, 3.3 Hz, 2H, H-3' or H-5); ^{13}C NMR [$(CD_3)_2SO$] δ 153.1 (C-2), 148.5 (C-3''), 143.4 (C-3a), 139.6 (C-5), 139.0 (C-1''), 128.6 (C-5''), 123.3 (C-7a), 116.4 (C-6, C-6''), 114.6 (C-7), 114.3 (C-2''), 112.6 (C-4''), 62.4 (CH_2), 52.6 (C-2', C-6'), 50.3 (C-4'), 28.7 (C-3', C-5'); MS *m/z* 324.9 (MH^+, 100%).

***N*-(3-((4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)methyl)phenyl)-2-phenylacetamide (S114).** Prepared using Method I with phenylacetyl chloride and amine **S114a** with Et_3N. The crude residue was purified by column chromatography, eluting with 3% MeOH/DCM, to give amide **S114** (53 mg, 34%) as a white solid: mp 131–134 °C; ^{1}H NMR δ 8.02 (dd, *J* = 5.3, 1.1 Hz, 1H), 7.55–7.60 (m, 3H), 7.29–7.43 (m, 7H), 7.25 (dd obscured, *J* = 7.8, 7.8 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.98 (dd, *J* = 7.9, 5.3 Hz, 1H), 4.39–4.45 (m, 1H), 3.75 (s, 2H), 3.63 (s, 2H), 3.11 (br d, *J* = 10.8 Hz, 2H), 2.47–2.49 (m, 2H), 2.24–2.30 (m, 2H), 1.79–1.81 (m, 2H); ^{13}C NMR δ 169.5, 153.8, 143.3, 140.2, 138.3, 134.7, 129.7 (2), 129.6, 129.4 (2), 129.3, 127.8, 125.7, 123.5, 121.0, 119.5, 117.2, 116.4, 62.3, 52.8 (2), 50.0, 45.0, 28.7 (2); MS *m/z* 443.3 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 442.2237 (calcd for $C_{26}H_{28}N_5O_2$, 442.2238).

SN37242 *N*-(3-((3-Methylbenzyl)oxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (**S115**).

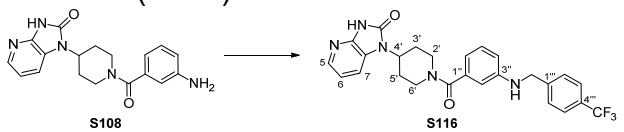


1-Methyl-3-((3-nitrophenoxy)methyl)benzene (S115a). Prepared using Method E from 3-methylbenzyl bromide and 3-nitrophenol. The crude residue was purified by column chromatography, eluting with 5% EtOAc/pet. ether, to give **S115a** (1.55 g, 88%) as a clear yellow oil: ^{1}H NMR δ 7.82–7.85 (m, 2H), 7.41–7.45 (m, 1H), 7.17–7.32 (m, 5H), 5.10 (s, 2H), 2.39 (s, 3H).

3-((3-Methylbenzyl)oxy)aniline (S115b). Prepared using Method G from **S115a**. The crude residue was purified by column chromatography, eluting with 5–10% EtOAc/pet. ether, to give amine **S115b** (1.22 g, 93%) as a dark red oil: ^{1}H NMR δ 7.20–7.29 (m, 3H), 7.13 (d, *J* = 7.36 Hz, 1H), 7.04–7.08 (m, 1H), 6.39–6.42 (m, 1H), 6.29–6.33 (m, 2H), 4.98 (s, 2H), 3.66 (br s, 2H), 2.37 (s, 3H); MS *m/z* 214.6 (MH^+, 100%).

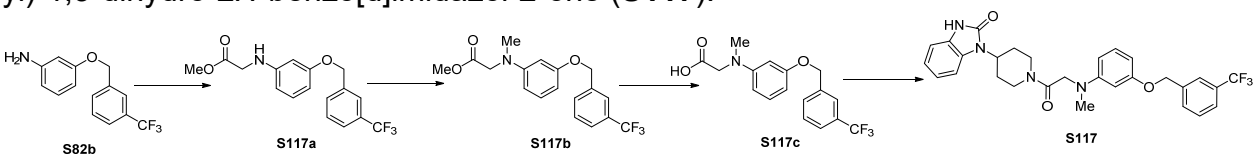
***N*-(3-((3-Methylbenzyl)oxy)phenyl)-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxamide (S115).** Prepared using Method C from **S115b** and **S1d**. The resulting crude residue was purified by column chromatography, eluting with EtOAc, to give urea **S115** (231 mg, 47%) as a white solid: mp 197–200 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (s, 1H), 8.57 (s, 1H), 7.90 (dd, *J* = 5.2, 1.3 Hz, 1H), 7.54 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.20–7.31 (m, 4H), 7.05–7.18 (m, 3H), 6.99 (dd, *J* = 7.8, 5.2 Hz, 1H), 6.59 (ddd, *J* = 8.0, 2.5, 1.1 Hz, 1H), 5.01 (s, 2H), 4.37–4.44 (m, 1H), 4.30 (d, *J* = 13.5 Hz, 2H), 2.92 (dd, *J* = 12.1, 12.1 Hz, 2H), 2.32 (s, 3H), 2.16–2.26 (m, 2H), 1.77 (dd, *J* = 11.9, 2.2 Hz, 2H); ^{13}C NMR [$(CD_3)_2SO$] δ 158.5, 154.6, 153.1, 143.5, 141.9, 139.6, 137.5, 137.1, 129.0, 128.4, 128.3, 128.1, 124.7, 123.3, 116.4, 114.5, 112.0, 107.9, 106.1, 69.0, 50.1, 43.4 (2), 28.8 (2), 21.0; MS *m/z* 458.3 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 458.2201 (calcd for $C_{26}H_{28}N_5O_3$, 458.2187).

SN37243 1-(1-(3-((4-(Trifluoromethyl)benzyl)amino)benzoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (**S116**).



1-(1-(3-((4-(Trifluoromethyl)benzyl)amino)benzoyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (S116). Amine **S108** (246 mg, 0.73 mmol) and 4-trifluoromethyl benzaldehyde (99 µL, 0.73 mmol) were stirred together in CH_2Cl_2 (10 mL) at 20 °C for 3 h. $NaBH(OAc)_3$ (231 mg, 1.09 mmol) was added to the mixture, and was stirred at 20 °C for 23 h. A white precipitate formed in the resulting mixture, which was diluted with CH_2Cl_2 (100 mL), washed with water (2 × 100 mL) and brine (100 mL), and concentrated *in vacuo*. The crude residue was purified by column chromatography, eluting with 1–10% EtOAc/MeOH, H to give amide **S116** (89 mg, 25%) as an off-white solid: mp 248–251 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.56 (s, 1H, NH-3), 7.92 (dd, *J* = 5.2, 1.2 Hz, 1H, H-5), 7.59 (dd, *J* = 7.8, 1.2 Hz, 1H, H-7), 7.49–7.55 (m, 4H, H-2''', H-3''', H-5''', H-6'''), 7.09–7.15 (m, 1H, H-5''), 7.01 (dd, *J* = 7.8, 5.2 Hz, 1H, H-6), 6.63–6.69 (m, 2H, H-4'', NH-3''), 6.57 (dt, *J* = 6.4, 1.5 Hz, 1H, H-6''), 6.51 (br t, *J* = 1.5 Hz, 1H, H-2''), 4.58 (s, 1H, H_2-2' or H_2-6'), 4.35–4.45 (m, 3H, H-4', CH_2), 3.56 (s, 1H, H_2-2' or H_2-6'), 3.00 (s, 1H, H_2-2' or H_2-6'), 2.80 (s, 1H, H_2-2' or H_2-6'), 2.19 (s, 1H, H_2-3' or H_2-5'), 1.78 (s, 2H, H_2-3' or H_2-5'), 1.41 (s, 1H, H_2-3' or H_2-5'); ^{13}C NMR [$(CD_3)_2SO$] δ 169.6 (COPh), 153.0 (C-2), 148.0 (C-3''), 145.1 (C-1'''), 143.5 (C-3a), 139.7 (C-5), 136.9 (C-1''), 129.1 (C-5''), 127.5 (C-2''', C-6'''), 127.2 (*J* = 31.5 Hz, C-4'''), 125.2 (*J* = 3.7 Hz, C-3''', C-5'''), 124.3 (*J* = 272.0 Hz, CF_3-4'''), 123.0 (C-7a), 116.4 (C-6), 115.0 (C-7), 114.2 (C-6''), 113.6 (C-4''), 109.6 (C-2''), 49.6 (C-4'), 46.3 (C-2' or C-6'), 45.6 ($NHCH_2$), 40.9 (C-2' or C-6'), 28.8 (C-3' or C-5'), 28.5 (C-3' or C-5'); (+)-HRESIMS *m/z* $[M+H]^+$ 496.1943 (calcd for $C_{26}H_{25}F_3N_5O_2$, 496.1955). Anal. calcd for $C_{26}H_{24}F_3N_5O_2 \cdot 0.75H_2O$: C, 61.35; H, 5.05; N, 13.76. Found: C, 61.26; H, 4.89; N, 13.67%.

SN37244 1-(1-(*N*-Methyl-*N*-(3-((3-(trifluoromethyl)benzyl)oxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one (**S117**).



Methyl (3-((3-(Trifluoromethyl)benzyl)oxy)phenyl)glycinate (S117a). Prepared using Method E from methyl bromoacetate and aniline **S82b**. The resulting crude residue was purified by column chromatography, eluting with 10% EtOAc/pet. ether, to give the methyl ester **S117a** (459 mg, 88%) as an off-white solid: mp 51–52 °C; ^{1}H NMR δ 7.70 (s, 1H, H-2'), 7.62 (d, *J* = 7.6 Hz, 1H, H-6'), 7.58 (d, *J* = 7.6 Hz, 1H, H-4'), 7.50 (t, *J* = 7.6 Hz, 1H, H-5'), 7.11 (t, *J* = 8.1 Hz, 1H, H-5), 6.38 (ddd, *J* = 8.1, 2.3, 0.7 Hz, 1H, H-6), 6.27 (ddd, *J* = 8.1, 2.3, 0.7 Hz, 1H, H-4), 6.24 (t, *J* = 2.3 Hz, 1H, H-2), 5.08 (s, 2H, OCH_2), 4.31 (t, *J* = 5.0 Hz, 1H, NH), 3.91 (d, *J* = 5.0 Hz, 2H, $COCH_2$), 3.79 (s, 3H, OMe); MS *m/z* 340.7 (MH^+, 100%). Anal. calcd for $C_{17}H_{16}F_3NO_3$: C, 60.18; H, 4.75; N, 4.13. Found: C, 60.22; H, 4.74; N, 4.08%.

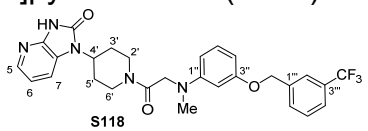
Methyl *N*-Methyl-*N*-(3-((3-(trifluoromethyl)benzyl)oxy)phenyl)glycinate (S117b). Prepared using Method E from methyl iodide and aniline **S117a**. The crude residue was purified by column chromatography, eluting with 5% EtOAc/pet. ether, to give methyl ester **S117b** (577 mg, 85%) as a yellow oil: ^{1}H NMR δ 7.71 (s, 1H, H-2'), 7.63 (d, *J* = 7.7 Hz, 1H, H-6'), 7.58 (d, *J* = 7.7 Hz, 1H, H-4'), 7.50 (t, *J* = 7.7 Hz, 1H, H-5'), 7.12–7.18 (m, 1H, H-5), 6.36–6.40 (m, 1H, H-6), 6.30–6.35 (m, 2H, H-2, H-4), 5.09 (s, 2H, OCH_2), 4.06 (s, 2H, $COCH_2$), 3.71 (s, 3H, OMe), 3.05 (s, 3H, N-Me); MS *m/z* 354.9 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 354.1304 (calcd for $C_{18}H_{19}F_3NO_3$, 354.1312).

***N*-Methyl-*N*-(3-((3-(trifluoromethyl)benzyl)oxy)phenyl)glycine (S117c).** Prepared using Method J from methyl ester **S117b** to give the acid **S117c** (514 mg, 95%) as a yellow oil: ^{1}H NMR [$(CD_3)_2SO$] δ 7.79 (s, 1H, H-2'), 7.75 (d, *J* = 7.7 Hz, 1H, H-6'), 7.68 (d, *J* = 7.7 Hz, 1H, H-4'), 7.62 (t, *J* = 7.7 Hz, 1H, H-5'), 6.97–7.03 (m, 1H, H-5), 6.19–6.28 (m, 3H, H-2, H-4, H-6), 5.13 (s, 2H, OCH_2), 3.79 (s, 2H, $COCH_2$), 2.92 (s, 3H, N-Me); (+)-HRESIMS *m/z* $[M+H]^+$ 340.1144 (calcd for $C_{17}H_{17}F_3NO_3$, 340.1155).

1-(1-(*N*-Methyl-*N*-(3-((3-(trifluoromethyl)benzyl)oxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one (S117). Prepared using Method H from **S117b** and 1-(4-piperidinyl)-1,3-dihydro-2*H*-benzimidazol-2-one. The resulting crude residue was purified by column chromatography, eluting with EtOAc, to give amide **S117** (288 mg, 73%) as a white solid: mp 210–212 °C; ^{1}H NMR δ 9.66 (s, 1H, NH-3), 7.70 (s, 1H, H-2'''), 7.62 (d, *J* = 7.7 Hz, 1H, H-6'''), 7.57 (d, *J* = 7.7 Hz, 1H, H-4'''), 7.47 (t, *J* = 7.7 Hz, 1H, H-5'''), 7.16–7.22 (m, 1H, H-5''), 7.09 (dd, *J* = 7.7, 1.4 Hz, 1H, H-7), 7.04 (dt, *J* = 7.7, 7.5, 1.4 Hz, 1H, H-6), 6.99 (dt, *J* = 7.6, 7.5, 1.4 Hz, 1H, H-5), 6.90 (d, *J* = 7.6 Hz, 1H, H-4), 6.39–6.44 (m, 3H, H-2'', H-4'', H-6''), 5.09 (s, 2H, OCH_2), 4.83 (d, *J* = 12.6 Hz, 1H, H_2-2' or H_2-6'), 4.55 (tt, *J* = 12.6, 4.2 Hz, 1H, H-4'), 4.12–4.24 (m, 2H, $COCH_2$), 4.04 (d, *J* = 12.6 Hz, 1H, H_2-2' or H_2-6'), 3.23 (t, *J* = 12.6 Hz, 1H, H-2' or H-6'), 3.09 (s, 3H, N-Me), 2.73 (t, *J* = 12.6 Hz, 1H, H_2-2' or H_2-6'), 2.22–2.40 (m, 2H, H_2-3' or H_2-5'), 1.90 (br s, 2H, H_2-3' or

H_2-5'); ^{13}C NMR δ 168.3 ($COCH_2$), 160.0 (C-3''), 155.0 (C-2), 151.0 (C-1''), 138.5 (C-1'''), 131.1 (*J* = 32.5 Hz, C-3'''), 131.0 (C-6'''), 130.4 (C-5''), 129.2 (C-5'''), 129.0 (C-3a), 128.1 (C-7a), 124.9 (*J* = 3.8 Hz, C-4'''), 124.4 (*J* = 3.8 Hz, C-2'''), 124.3 (*J* = 272.4 Hz, CF_3-3'''), 121.7 (C-6), 121.5 (C-5), 110.0 (C-7), 109.4 (C-4), 106.5 (C-6''), 103.3 (C-4''), 100.5 (C-2''), 69.3 (OCH_2), 55.2 ($COCH_2$), 50.7 (C-4'), 44.9 (C-2' or C-6'), 42.3 (C-2' or C-6'), 40.1 (N-Me), 29.9 (C-3' or C-5'), 29.3 (C-3' or C-5'); MS *m/z* 540.7 (MH^+, 100%). Anal. calcd for $C_{29}H_{29}F_3N_4O_3$: C, 64.67; H, 5.43; N, 10.40. Found: C, 64.61; H, 5.35; N, 10.33%.

SN37245 1-(1-(*N*-Methyl-*N*-(3-((3-(trifluoromethyl)benzyl)oxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (**S118**).

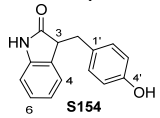


S118

1-(1-(*N*-Methyl-*N*-(3-((3-(trifluoromethyl)benzyl)oxy)phenyl)glycyl)piperidin-4-yl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (S118). Prepared using Method H from **S117c** and **S1d**. The resulting crude residue was purified by column chromatography, eluting with EtOAc, to give amide **S118** (237 mg, 60%) as a white solid: mp 166–168 °C; ^{1}H NMR δ 9.01 (s, 1H, NH-3), 8.00 (dd, *J* = 5.2, 1.3 Hz, 1H, H-5), 7.71 (s, 1H, H-2'''), 7.62 (d, *J* = 7.7 Hz, 1H, H-6'''), 7.57 (d, *J* = 7.7 Hz, 1H, H-4'''), 7.48 (t, *J* = 7.7 Hz, 1H, H-5'''), 7.16–7.22 (m, 1H, H-5''), 6.96 (dd, *J* = 7.9, 1.3 Hz, 1H, H-7), 6.89 (dd, *J* = 7.9, 5.2 Hz, 1H, H-6), 6.40–6.46 (m, 3H, H-2'', H-4'', H-6''), 5.10 (s, 2H, OCH_2), 4.82 (d, *J* = 12.9 Hz, 1H, H-2' or H-6'), 4.57 (tt, *J* = 12.9, 4.2 Hz, 1H), 4.17 (s, 2H), 4.04 (d, *J* = 12.9 Hz, 1H, H-2' or H-6'), 3.21 (t, *J* = 12.9 Hz, 1H, H-2' or H-6'), 3.08 (s, 3H), 2.71 (t, *J* = 12.9 Hz, 1H, H-2' or H-6'), 2.03–2.23 (m, 2H, H-3' or H-5'), 1.90 (br s, 2H, H-3' or H-5'); ^{13}C NMR δ 168.3 ($COCH_2$), 160.0 (C-3''), 153.6 (C-2), 151.0 (C-1''), 143.4 (C-3a), 140.4 (C-5), 138.5 (C-1'''), 131.1 (*J* = 32.4 Hz, C-3'''), 130.9 (C-6'''), 130.4 (C-5''), 129.2 (C-5'''), 124.9 (*J* = 3.8 Hz, C-4'''), 124.4 (*J* = 3.8 Hz, C-2'''), 124.3 (*J* = 272.4 Hz, CF_3-3'''), 123.3 (C-7a), 117.1 (C-6), 115.5 (C-7), 106.5 (C-6''), 103.4 (C-4''), 100.5 (C-2''), 69.3 (OCH_2), 55.6 ($COCH_2$), 50.3 (C-4'), 44.9 (C-2' or C-6'), 42.2 (C-2' or C-6'), 40.3 (Me), 30.0 (C-3' or C-5'), 29.5 (C-3' or C-5'); (+)-HRESIMS *m/z* $[M+H]^+$ 540.2217 (calcd for $C_{28}H_{29}F_3N_5O_3$, 540.2226).

Chemical synthesis of compounds S154-S240 (Table S3)

SN37308 3-(4-Hydroxybenzyl)indolin-2-one (S154).

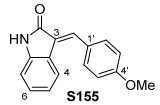


S154

3-(4-Hydroxybenzyl)indolin-2-one (S154). Prepared using Method M from alkene **2**. The crude material was purified by column chromatography, eluting with 40–50% EtOAc/pet. ether, to give indolinone **S154** (115 mg, 52%) as a white solid: mp 198–201 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.25 (s, 1H, NH-1), 9.15 (s, 1H, OH-4'), 7.06–7.11 (m, 1H, H-6), 6.91 (dt, *J* = 8.5, 2.0 Hz, 2H, H-2, H-6), 6.80–6.86 (m, 2H, H-4, H-5), 6.71 (d, *J* = 7.7 Hz, 1H, H-7), 6.57 (dt, *J* = 8.5, 2.0 Hz, 2H, H-3', H-5'), 3.68 (dd, *J* = 7.8, 4.9 Hz, 1H, H-3), 3.20 (dd, *J* = 13.8, 4.9 Hz, 1H, CH_2), 2.81 (dd, *J* = 13.8, 7.8 Hz, 1H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 178.2 (CO-2), 155.7 (C-4'), 142.6 (C-7a), 130.2 (C-2', C-6'), 129.1 (C-3a), 128.0 (C-1'), 127.5 (C-6), 124.3 (C-4), 120.8 (C-5), 114.8 (C-3', C-5'), 109.0 (C-7), 46.7

(C-3), 34.5 (CH_2); MS *m/z* 240.6 (MH^+, 100%). Anal. calcd for $C_{15}H_{13}NO_2 \cdot 0.05\ H_2O$: C, 75.01; H, 5.50; N, 5.83. Found: C, 74.90; H, 5.59; N, 5.77%.

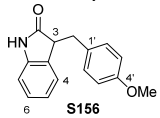
SN37309 (*E*)-3-(4-Methoxybenzylidene)indolin-2-one (**S155**).



S155

(*E*)-3-(4-Methoxybenzylidene)indolin-2-one (S155). Prepared using Method N from oxindole and *p*-anisaldehyde. The crude residue was purified by column chromatography, eluting with 20–50% EtOAc/pet. ether, to give alkene **S155** (626 mg, 83%) as a yellow solid: mp 159–161 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.55 (s, 1H, NH-1), 7.71 (ddd, *J* = 8.7, 2.9, 2.0 Hz, 2H, H-2', H-6'), 7.65 (d, *J* = 7.5 Hz, 1H, H-4), 7.58 (s, 1H, =CH), 7.22 (td, *J* = 7.5, 1.1 Hz, 1H, H-6), 7.09 (ddd, *J* = 8.7, 2.9, 2.0 Hz, 2H, H-3', H-5'), 6.84–6.90 (m, 2H, H-5, H-7), 3.84 (s, 3H, OMe-4'); ^{13}C NMR [$(CD_3)_2SO$] δ 168.9 (C-2), 160.5 (C-4'), 142.7 (C-7a), 136.0 (=C), 131.5 (C-2', C-6'), 129.7 (C-6), 126.6 (C-1'), 125.6 (C-3), 122.1 (C-4), 121.2 (C-3a), 121.1 (C-5), 114.3 (C-3', C-5'), 110.0 (C-7), 55.4 (OMe-4'); MS *m/z* 252.2 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.30; H, 5.27; N, 5.54%.

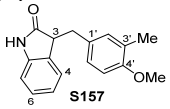
SN37310 3-(4-Methoxybenzyl)indolin-2-one (**S156**).



S156

3-(4-Methoxybenzyl)indolin-2-one (S156). Prepared using Method M from alkene **S155**. The crude material was purified by column chromatography, eluting with 30% EtOAc/pet. ether, to give indolinone **S156** (123 mg, 56%) as an off-white solid: mp 117–118 °C; ^{1}H NMR [$(CD_3)_2SO$]δ 10.27 (s, 1H, NH-1), 7.06–7.11 (m, 1H, H-6), 7.03 (ddd, *J* = 8.7, 3.0, 2.1 Hz, 2H, H-2', H-6'), 6.90 (d, *J* = 7.5 Hz, 1H, H-4), 6.84 (td, *J* = 7.5, 1.0 Hz, 1H, H-5), 6.75 (ddd, *J* = 8.7, 3.0, 2.1 Hz, 2H, H-3', H-5'), 6.71 (d, *J* = 7.5 Hz, 1H, H-7), 3.73 (dd, *J* = 7.6, 5.0 Hz, 1H, H-3), 3.68 (s, 3H, OMe-4'), 3.24 (dd, *J* = 13.8, 5.0 Hz, 1H, CH_2), 2.89 (dd, *J* = 13.8, 7.6 Hz, 1H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 178.1 (C-2), 157.7 (C-4'), 142.6 (C-7a), 130.3 (C-2', C-6'), 129.8 (C-1'), 129.0 (C-3a), 127.5 (C-6), 124.3 (C-4), 120.9 (C-5), 113.4 (C-3', C-5'), 109.1 (C-7), 54.9 (OMe-4'), 46.6 (C-3), 34.3 (CH_2); MS *m/z* 254.2 (MH^+, 100%). Anal. calcd for $C_{16}H_5NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.96; H, 5.97; N, 5.58%.

SN37312 3-(4-Methoxy-3-methylbenzyl)indolin-2-one (**S157**).



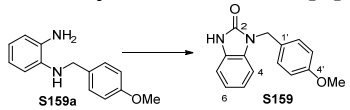
S157

3-(4-Methoxy-3-methylbenzyl)indolin-2-one (S157). Prepared using Method M from alkene **3**. The crude material was purified by column chromatography, eluting with 20% EtOAc/pet. ether, to give indolinone **S157** (440 mg, 87%) as an off-white solid: mp (EtOAc) 142–144 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.27 (s, 1H, NH-1), 7.06–7.12 (m, 1H, H-6), 6.86–6.93 (m, 3H, H-4, H-2', H-6'), 6.83 (td, *J* = 7.3, 1.0 Hz, 1H, H-5), 6.70–6.76 (m, 2H, H-7, H-5'), 3.69–3.74 (m, 4H, OMe-4', H-3), 3.21 (dd, *J* = 13.8, 4.9 Hz, 1H, CH_2), 2.83

(dd, *J* = 13.8, 7.9 Hz, 1H, CH_2), 2.04 (s, 3H, Me-3'); ^{13}C NMR [$(CD_3)_2SO$] δ 178.2 (C-2), 155.8 (C-4'), 142.6 (C-7a), 131.4 (C-2'), 129.4 (C-1'), 129.1 (C-3a), 127.6 (C-6'), 127.5 (C-6), 124.8 (C-3'), 124.3 (C-4), 120.9 (C-5), 109.7 (C-7), 109.1 (C-5'), 55.0 (OMe-4'), 46.6 (C-3), 34.4 (CH_2), 16.1 (Me-3'); MS *m/z* 268.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.57; H, 6.41; N, 5.27%.

SN37321 Ethyl Acetyltyrosinate (**S158**) was obtained from BDH Chemicals.

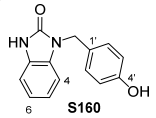
SN37322 1-(4-Methoxybenzyl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one (**S159**).



***N*^{1}-(4-Methoxybenzyl)benzene-1,2-diamine (S159a).** Prepared using Method E from 4-methoxybenzyl chloride and *o*-phenylene diamine. The crude residue was purified by column chromatography, eluting in 20% EtOAc/pet. ether, to give diamine (**S159a**) (772 mg, 37%) as a pale brown solid: mp (EtOAc) 97–99 °C; ^1H NMR δ 7.32 (dt, *J* = 8.8, 2.1 Hz, 2H, H-2', H-6'), 6.89 (dt, *J* = 8.7, 2.1 Hz, 2H, H-3', H-5'), 6.79–6.84 (m, 1H, H-4), 6.67–6.76 (m, 3H, H-3, H-5, H-6), 4.24 (s, 2H, CH_2), 3.81 (s, 3H, OMe), 3.60 (br s, 1H, NH), 3.34 (br s, 2H, NH_2); (+)-HRESIMS *m/z* $[M+H]^+$ 229.1334 (calcd for $C_{14}H_{17}N_2O$, 229.1335). Anal. calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.87; H, 7.00; N, 12.29%.

1-(4-Methoxybenzyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (S159). Prepared using Method O from **S159a**. The product **S159** (500 mg, 84%) was recrystallised from EtOAc as a pale brown solid: mp 181–184 °C; ^1H NMR [$(CD_3)_2SO$] δ 10.91 (s, 1H, NH-1), 7.27 (ddd, *J* = 8.8, 2.9, 2.1 Hz, 2H, H-2', H-6'), 7.00–7.05 (m, 1H, H-4), 6.90–6.99 (m, 3H, H-5, H-6, H-7), 6.88 (ddd, *J* = 8.8, 2.9, 2.1 Hz, 2H, H-3', H-5'), 4.91 (s, 2H, CH_2), 3.70 (s, 3H, OMe-4'); ^{13}C NMR [$(CD_3)_2SO$] δ 158.6 (C-4'), 154.3 (C-2), 129.9 (C-3a), 129.2 (C-1'), 128.8 (C-2', C-6'), 128.3 (C-7a), 120.9 (C-6), 120.5 (C-5), 114.0 (C-3', C-5'), 108.8 (C-7), 108.1 (C-4), 55.0 (OMe-4'), 42.6 (CH_2); MS *m/z* 255.2 (MH^+, 100%). Anal. calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.81; H, 5.47; N, 10.98%. ^1H and ^{13}C NMR spectra were consistent with literature values [5].

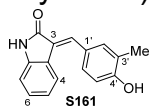
SN37340 1-(4-Hydroxybenzyl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one (**S160**).



1-(4-Hydroxybenzyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (S160). A solution of BBr_3 (149 µL, 1.57 mmol) in CH_2Cl_2 (5 mL) was slowly added to a solution of methyl ether **S159** (200 mg, 0.79 mmol) in CH_2Cl_2 (10 mL) at -78 °C. The reaction mixture was stirred at -78 °C, and allowed to warm to 20 °C overnight. The reaction was quenched with MeOH, neutralised with sat. aq. $NaHCO_3$ and a pale brown precipitate formed. The solid was removed by filtration, washed with EtOAc and dried under vacuum to give product **S160** (163 mg, 86%) as a pale brown solid: mp 250–251 °C; ^1H NMR [$(CD_3)_2SO$] δ 10.89 (s, 1H, NH-1), 9.39 (s, 1H, OH-4'), 7.15 (ddd, *J* = 8.5, 2.8, 1.9 Hz, 2H, H-2', H-6'), 6.99–7.04 (m, 1H, H-4), 6.90–6.99 (m, 3H, H-5, H-6, H-7), 6.69 (ddd, *J* = 8.5, 2.8, 1.9 Hz, 2H, H-3', H-5'), 4.85 (s, 2H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 156.7 (C-4'), 154.3 (C-2), 130.0 (C-

3a), 128.8 (C-2', C-6'), 128.2 (C-7a), 127.4 (C-1'), 120.9 (C-6), 120.4 (C-5), 115.3 (C-3', C-5'), 108.7 (C-7), 108.2 (C-4), 42.8 (CH_2); MS *m/z* 241.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 241.0977 (calcd for $C_{14}H_{13}N_2O_2$, 241.0972).

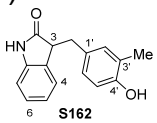
SN37341 (*E*)-3-(4-Hydroxy-3-methylbenzylidene)indolin-2-one (**S161**).



S161

(*E*)-3-(4-Hydroxy-3-methylbenzylidene)indolin-2-one (S161). BBr_3 (143 µL, 1.51 mmol) was added to a solution of alkene **3** (200 mg, 0.75 mmol) in DCM (10 mL) at -78 °C. The reaction mixture was stirred at -78 °C, and allowed to warm to 20 °C overnight. The mixture was neutralised with sat. aq. $NaHCO_3$ and extracted with EtOAc (3 × 50 mL). The organic layer was washed with brine (50 mL), dried and concentrated to ~10 mL. Pet. ether was added and the resulting solid was filtered to give alkene **S161** (170 mg, 90%) as a yellow solid: mp 234–237 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.50 (s, 1H, NH-1), 7.71 (d, *J* = 7.6 Hz, 1H, H-4), 7.51 (s, 1H, =CH), 7.44–7.50 (m, 2H, H-2', H-6'), 7.20 (td, *J* = 7.7, 1.0 Hz, 1H, H-6), 6.92 (d, *J* = 8.1 Hz, 1H, H-5'), 6.84–6.90 (m, 2H, H-5, H-7), 2.18 (s, 1H, Me-3'); ^{13}C NMR [$(CD_3)_2SO$] δ 169.1 (C-2), 157.6 (C-4'), 142.2 (C-7a), 136.9 (=CH), 132.7 (C-2'), 129.3 (C-6), 129.1 (C-6'), 124.9 (C-3'), 124.4 (C-3, C-1'), 122.0 (C-4), 121.4 (C-3a), 121.0 (C-5), 114.8 (C-5'), 109.9 (C-7), 15.9 (Me-3'); MS *m/z* 252.2 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.65; H, 5.32; N, 5.59%.

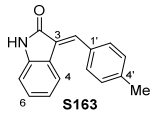
SN37342 3-(4-Hydroxy-3-methylbenzyl)indolin-2-one (**S162**).



S162

3-(4-Hydroxy-3-methylbenzyl)indolin-2-one (S162). Prepared using Method M from **S161**. The crude residue was purified by column chromatography, eluting with 40–50% EtOAc/pet. ether, to give indolinone **S162** (119 mg, 72%) as a white solid: mp 198–200 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.26 (s, 1H, NH-1), 9.03 (s, 1H, OH-4'), 7.05–7.12 (m, 1H, H-6), 6.80–6.86 (m, 3H, H-4, H-5, H-2'), 6.72 (d, *J* = 7.9 Hz, 2H, H-6, H-7), 6.57 (d, *J* = 7.9 Hz, 1H, H-5'), 3.67 (dd, *J* = 8.0 , 4.9 Hz, 1H, H-3), 3.17 (dd, *J* = 13.8, 4.9 Hz, 1H, CH_2), 2.75 (dd, *J* = 13.8, 8.0 Hz, 1H, CH_2), 2.01 (s, 3H, Me-3'); ^{13}C NMR [$(CD_3)_2SO$] δ 178.2 (C-2), 153.7 (C-4'), 142.6 (C-7a), 131.5 (C-2'), 129.2 (C-3a), 128.0 (C-1'), 127.5 (C-6), 127.3 (C-6'), 124.4 (C-4), 123.2 (C-3'), 120.8 (C-5), 114.1 (C-5'), 109.0 (C-7), 46.7 (C-3), 34.6 (CH_2), 16.0 (Me-3'); MS *m/z* 254.2 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.6; H, 5.92; N, 5.52%.

SN37343 (*E*)-3-(4-Methylbenzylidene)indolin-2-one (**S163**).

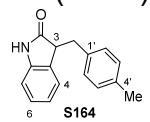


S163

(*E*)-3-(4-Methylbenzylidene)indolin-2-one (S163). Prepared using Method N from oxindole and p-tolualdehyde. The crude material was purified by column chromatography, eluting with 10–50% EtOAc/pet. ether, to give **S163** (525 mg, 85%) as a yellow solid: mp 192–194 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.58 (s, 1H, NH-1), 7.55–7.64 (m, 4H, H-4, =CH, H-

2', H-6'), 7.34 (d, *J* = 8.0 Hz, 2H, H-3', H-5'), 7.22 (td, *J* = 7.7, 1.1 Hz, 1H, H-6), 6.83–6.89 (m, 2H, H-5, H-7), 2.39 (s, 3H, Me-4'); ^{13}C NMR [$(CD_3)_2SO$] δ 168.7 (C-2), 142.8 (C-7a), 139.7 (C-4'), 136.0 (=C), 131.5 (C-1'), 130.0 (C-6), 129.4 (C-3', C-5'), 129.3 (C-2', C-6'), 126.9 (C-3), 122.2 (C-4), 121.1 (C-5), 121.0 (C-3a), 110.1 (C-7), 21.1 (Me-4'); MS *m/z* 236.2 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.92; H, 5.53; N, 6.02%.

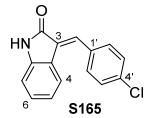
SN37344 3-(4-Methylbenzyl)indolin-2-one (**S164**).



S164

3-(4-Methylbenzyl)indolin-2-one (S164). Prepared using Method M from **S163**. The crude material was purified by column chromatography, eluting with 20–30% EtOAc/pet. ether, to give **S164** (231 mg, 75%) as a white solid: mp 150–151 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.27 (s, 1H, NH-1), 7.06–7.11 (m, 1H), 6.97–7.03 (m, 4H), 6.89 (d, *J* = 7.2 Hz, 1H), 6.83 (td, *J* = 7.4, 1.0 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 3.75 (dd, *J* = 7.7, 5.0 Hz, 1H), 3.26 (dd, *J* = 13.8, 5.0 Hz, 1H), 2.91 (dd, *J* = 13.8, 7.7 Hz, 1H), 2.21 (s, 1H); ^{13}C NMR [$(CD_3)_2SO$] δ 178.1 (C-2), 142.6 (C-7a), 135.2 (C-4'), 134.9 (C-1'), 129.1 (C-2', C-6'), 129.0 (C-3a), 128.6 (C-3', C-5'), 127.6 (C-6), 124.3 (C-4), 120.9 (C-5), 109.1 (C-7), 46.5 (C-3), 34.8 (CH_2), 20.6 (Me-4'); MS *m/z* 238.2 (MH^+, 100%). Anal. calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.06; H, 6.35; N, 5.98%.

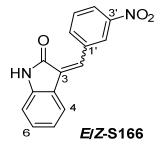
SN37345 (*E*)-3-(4-Chlorobenzylidene)indolin-2-one (**S165**).



S165

(*E*)-3-(4-Chlorobenzylidene)indolin-2-one (S165). Prepared using Method N from oxindole and 4-chlorobenzaldehyde. The crude material was purified by column chromatography, eluting with 10–50% EtOAc/pet. ether, to give **S165** (398 mg, 58%) as a yellow solid: mp 190–191°C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.63 (s, 1H, NH-1), 7.70–7.75 (m, 2H, H-2', H-6'), 7.56–7.60 (m, 3H, =CH, H-3', H-5'), 7.48 (d, *J* = 7.7 Hz, 1H, H-4), 7.24 (td, *J* = 7.7, 1.1 Hz, 1H, H-6), 6.82–6.89 (m, 2H, H-5, H-7); ^{13}C NMR [$(CD_3)_2SO$] δ 168.5 (C-2), 143.1(C-7a), 134.3 (=CH), 133.6 (C-4'), 133.3 (C-1'), 131.1 (C-2', C-6'), 130.4 (C-6), 128.9 (C-3', C-5'), 128.2 (C-3), 122.5 (C-4), 121.2 (C-5), 120.6 (C-3a), 110.2 (C-6); MS *m/z* 254.1 ($M-H^-$, 100%). Anal. calcd for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.26; H, 4.06; N, 5.49%.

SN37365 (*E/Z*)-3-(3-Nitrobenzylidene)indolin-2-one (**S166**).

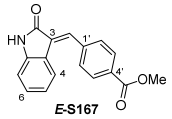


***E/Z*-S166**

(*E*/*Z*)-3-(3-Nitrobenzylidene)indolin-2-one (S166). Prepared using Method N from oxindole and 3-nitrobenzaldehyde. The crude residue was triturated with 50% EtOAc/pet. ether to obtain (*E*/*Z*)-**S166** (860 mg, 86%) as a mixture of *E*/*Z* isomers as an orange solid: mp 228–230 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *Z*-isomer (major) 10.73 (s, 1H, NH), 9.39 (t, *J* =

2.1 Hz, 1H, H-2'), 8.64 (d, *J* = 7.8 Hz, 1H, H-4'), 8.28 (ddd, *J* = 8.3, 2.1, 0.9 Hz, 1H, H-6'), 7.97 (s, 1H, =CH), 7.72–7.79 (m, 2H, H-4, H-5'), 7.26 (td, *J* = 7.6, 1.0 Hz, 1H, H-6), 7.03 (td, *J* = 7.6, 1.0 Hz, 1H, H-5), 6.85 (d, *J* = 7.6 Hz, 1H, H-7); *E*-isomer (minor) 8.52 (s, 1H), 8.28–8.32 (m, 1H), 8.13–8.14 (d, *J* = 7.7 Hz, 1H), 7.82 (t, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.24–7.28 (obscured, 1H), 6.90 (d, *J* = 7.76 Hz, 1H), 6.82–6.84 (m, 1H); ^{13}C NMR [$(CD_3)_2SO$] δ *Z*-isomer (major) 167.0 (C=O), 147.7 (C-3'), 141.3 (C-7a), 137.8 (C-4'), 135.4 (C-1'), 133.8 (=CH), 129.8 (C-6), 129.6 (C-5'), 129.1 (C-3), 125.8 (C-2'), 124.4 (C-6'), 124.3 (C-3a), 121.3 (C-5), 120.3 (C-4), 109.6 (C-7); *E*-isomer (minor) 168.2, 148.0, 143.4, 136.2, 135.6, 132.9, 130.9, 130.4, 129.6, 124.0, 123.6, 122.5, 121.4, 120.4, 110.4; MS *m/z* 267.1 (MH^+, 100%). Anal. calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52. Found: C, 67.66; H, 3.63; N, 10.56%.

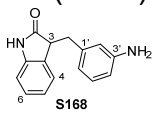
SN37366 Methyl (*E*)-4-((2-Oxoindolin-3-ylidene)methyl)benzoate (**S167**).



E-**S167**

Methyl (*E*)-4-((2-Oxoindolin-3-ylidene)methyl)benzoate (S167). Prepared using Method N from oxindole and methyl 4-formylbenzoate. The crude material was triturated in EtOAc/pet.ether to give **S167** (776 mg, 85%) as a yellow solid: mp 240–242 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.66 (s, 1H, NH-1), 8.08 (d, *J* = 8.3 Hz, 2H, H-3', H-5'), 7.83 (d, *J* = 8.3 Hz, 2H, H-2', H-6'), 7.65 (s, 1H, =CH), 7.43 (d, *J* = 7.7 Hz, 1H, H-4), 7.25 (td, *J* = 7.7, 1.0 Hz, 1H, H-6), 6.88 (d, *J* = 7.7 Hz, 1H, H-7), 6.84 (td, *J* = 7.7, 1.0 Hz, 1H, H-5), 3.89 (s, 3H, COOMe-4'); ^{13}C NMR [$(CD_3)_2SO$] δ 168.3 (C-2), 165.8 (COOMe-4'), 143.3 (C-7a), 139.4 (C-1'), 134.1 (=CH), 130.7 (C-6), 129.5 (C-2', C-3', C-5', C-6'), 129.2 (C-3), 128.8 (C-4'), 122.7 (C-4), 121.3 (C-5), 120.5 (C-3a), 110.3 (C-7), 52.3 (COOMe); MS *m/z* 280.1 ($M+H^+$, 100%). Anal. calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.92; H, 4.73; N, 4.99%.

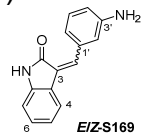
SN37367 3-(3-Aminobenzyl)indolin-2-one (**S168**).



S168

3-(3-Aminobenzyl)indolin-2-one (S168). Prepared using Method M from alkene **S166**. The crude residue was purified by column chromatography, eluting with 75% EtOAc/pet. ether, to give indolinone **S168** (444 mg, 99%) as a pale yellow solid: mp 48–50 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.30 (s, 1H, NH), 7.07–7.12 (m, 1H, H-6), 6.86 (t, *J* = 7.7 Hz, 1H, H-5'), 6.77–6.83 (m, 2H, H-4, H-5), 6.75 (d, *J* = 7.7 Hz, 1H, H-7), 6.35–6.40 (m, 2H, H-2', H-4'), 6.30–6.32 (m, 1H, H-6'), 4.91 (s, 2H, NH_2), 3.67 (dd, *J* = 8.8, 4.8 Hz, 1H, CH), 3.18 (dd, *J* = 13.7, 4.8 Hz, 1H, CH_2), 2.65 (dd, *J* = 13.7, 8.8 Hz, 1H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 178.2 (C=O), 148.4 (C-3'), 142.6 (C-7a), 138.8 (C-1'), 129.2 (C-3a), 128.5 (C-5'), 127.5 (C-6), 124.3 (C-4), 120.8 (C-5), 116.7 (C-6'), 114.8 (C-2'), 112.1 (C-4'), 109.1 (C-7), 46.4 (CH_2), 35.7 (CH); (+)-HRESIMS *m/z* $[M+H]^+$ 239.1180 (calcd for $C_{15}H_{15}N_2O$, 239.1179).

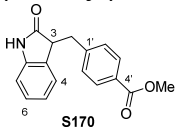
SN37368 (*E*/*Z*)-3-(3-Aminobenzylidene)indolin-2-one (**S169**).



E/*Z*-**S169**

(*E*/*Z*)-3-(3-Aminobenzylidene)indolin-2-one (S169). Prepared by Method G from indolinone **S166**. The residue was triturated in 10%EtOAc/pet. ether to give amine *E*/*Z*-**S169** (137 mg, 89%) as a mixture of isomers as a yellow solid: mp 126–129 °C; ^{1}H NMR [$(CD_3)_2SO$] δ (*Z*)-isomer (major) 10.54 (br s, 1H, NH), 7.68 (d, *J* = 7.5 Hz, 1H, H-4), 7.61 (s, 1H, =CH), 7.54–7.58 (m, 2H, H-2', H-6'), 7.17 (td obscured, *J* = 7.5, 1.0 Hz, 1H, H-6), 7.10 (t, *J* = 7.80 Hz, 1H, H-5'), 6.96 (td, *J* = 7.5, 1.0 Hz, 1H, H-5), 6.79–6.81 (m, 1H, H-7), 6.65–6.68 (m, 1H, H-4'), 5.15 (br s, 2H, NH_2); (*E*)-isomer (minor) 10.53 (br s, 1H, NH), 7.64 (d, *J* = 7.5 Hz, 1H, H-4), 7.49 (s, 1H, =CH), 7.20 (td obscured, *J* = 7.7, 1.1 Hz, 1H, H-6), 7.15 (t obscured, *J* = 7.7 Hz, 1H, H-5'), 6.84–6.88 (m, 3H, H-5, H-7, H-2'), 6.79–6.81 (m, 1H, H-6'), 6.65–6.68 (m, 1H, H-4'), 5.31 (br s, 2H, NH_2); ^{13}C NMR [$(CD_3)_2SO$] δ (*Z*)-isomer (major) 167.0 (C=O), 148.4 (C-3'), 140.5 (C-7a), 138.0 (=CH), 134.4 (C-1'), 128.6 (C-6, C-5'), 125.9 (C-3), 125.1 (C-3a), 120.9 (C-5), 120.2 (C-6'), 119.6 (C-4), 117.0 (C-2'), 116.5 (C-4'), 109.2 (C-7); (*E*)-isomer (minor) 168.8 (C=O), 149.0 (C-3'), 142.7 (C-7a), 137.0 (=CH), 134.9 (C-1'), 129.8 (C-6), 129.3 (C-5'), 126.8 (C-3), 122.8 (C-4), 121.1 (C-3a, C5), 116.8 (C-6'), 115.4 (C-4'), 113.9 (C-2'), 110.0 (C-7); MS *m/z* 237.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 237.1026 (calcd for $C_{15}H_{13}N_2O$, 237.1022).

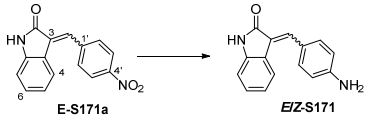
SN37369 Methyl 4-((2-Oxoindolin-3-yl)methyl)benzoate (**S170**).



S170

Methyl 4-((2-Oxoindolin-3-yl)methyl)benzoate (S170). Prepared using Method M from **S167**. The crude material was purified by column chromatography, eluting with 20–40% EtOAc/pet. ether, to give **S170** (317 mg, 79%) as a pale yellow solid: mp 158–160 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.32 (s, 1H), 7.79 (ddd, *J* = 8.4, 1.8, 1.8 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.12–7.06 (m, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 6.84 (dt, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 3.83–3.88 (m, 1H), 3.81 (s, 3H, COOMe), 3.35–3.40 (m, 1H), 3.06 (dd, *J* = 13.7, 7.5 Hz, 1H); ^{13}C NMR [$(CD_3)_2SO$] δ 177.9 (C-2), 166.1 (COOMe), 143.9 (C-1'), 142.6 (C-7a), 129.7 (C-2', C-6'), 128.9 (C-3', C-5'), 128.6 (C-3a), 127.8 (C-4'), 127.7 (C-6), 124.3 (C-4), 121.0 (C-5), 109.2 (C-7), 52.0 (COOMe-4'), 46.1 (C-3), 35.1 (CH_2); MS *m/z* 282.2 ($M+H^+$, 100%). Anal. calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.56; H, 5.25; N, 5.01%.

SN37443 (*E*/*Z*)-3-(4-Aminobenzylidene)indolin-2-one (**S171**).



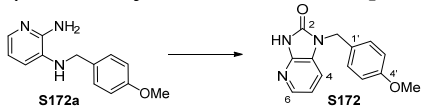
E-S171a *E*/*Z*-S171

(*E*)-3-(4-Nitrobenzylidene)indolin-2-one (S171a). Prepared using Method N from oxindole and 4-nitrobenzaldehyde. The crude material was triturated in 50% EtOAc/pet.ether to give **S171a** (1.52 g, 95%) as a yellow solid: mp 233–235 °C; 1H NMR [$(CD_3)_2SO$] δ (*E*)-isomer (major) 10.70 (s, 1H, NH-1), 8.35 (ddd, *J* = 8.7, 2.4, 1.8 Hz, 2H,

H-3', H-5'), 7.94–7.98 (m, 2H, H-2', H-6'), 7.67 (s, 1H, =CH), 7.41 (d, *J* = 7.7 Hz, 1H, H-4), 7.27 (td, *J* = 7.7, 1.0 Hz, 1H, H-6), 6.89 (d, *J* = 7.7 Hz, 1H, H-7), 6.85 (td, *J* = 7.7, 1.0 Hz, 1H, H-5); (*Z*)-isomer (minor) 10.70 (s, 1H, NH-1), 8.48–8.52 (m, 2H, H-3', H-5'), 8.27–8.31 (m, 2H, H-2', H-6'), 7.93 (s obscured, 1H, =CH), 7.75 (d, *J* = 7.4 Hz, 1H, H-4), 7.25–7.29 (m, 1H, H-6), 7.01 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H, H-5), 6.83–6.90 (m obscured, 1H, H-7); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 168.1, 166.8, 147.4, 147.4, 143.5, 141.5, 141.4, 140.2, 133.4, 132.9, 132.5 (2), 131.0, 130.4 (2), 130.2, 130.1, 130.1, 124.2, 123.9 (2), 123.1 (2), 122.9, 121.4, 120.7, 120.3, 110.4, 109.7, 1 carbon signal observed; MS *m/z* 267.1 ($M+H^+$, 100%); Anal. calcd for $C_{15}H_{10}N_2O_3$: C, 67.67; H, 3.79; N, 10.52. Found: C, 67.53; H, 3.72; N, 10.52%.

(*E*/*Z*)-3-(4-Aminobenzylidene)indolin-2-one (S171). Prepared by Method G from indolinone **S171a**. The crude residue was triturated in EtOAc to give amine *E*/*Z*-**S171** (107 mg, 55%) as a mixture of isomers as an orange solid: mp 223–225 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *Z*-isomer (major) 10.42 (br s, 1H, NH), 8.30–8.33 (m, 2H, H-2', H-6'), 7.58 (d, *J* = 7.6 Hz, 1H, H-4), 7.56 (s, 1H, =CH), 7.09 (td, *J* = 7.6, 1.0 Hz, 1H, H-6), 6.93 (td, *J* = 7.6, 1.0 Hz, 1H, H-5), 6.78 (d, *J* = 7.6 Hz, 1H, H-7), 6.58–6.61 (m, 2H, H-3', H-5'), 6.08 (br s, 2H, NH_2); *E*-isomer (minor) 10.42 (br s, 1H, NH), 7.77 (d, *J* = 7.7 Hz, 1H, H-4), 7.50–7.52 (m, 2H, H-2', H-5'), 7.46 (s, 1H, =CH), 7.15 (td, *J* = 7.7, 1.1 Hz, 1H, H-6), 6.89 (td obscured, *J* = 7.7, 1.1 Hz, 1H, H-5), 6.84 (d, *J* = 7.7 Hz, 1H, H-7), 6.65–6.68 (m, 2H, H-3', H-5'), 5.96 (br s, 2H, NH_2); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 169.5, 167.6, 152.1, 151.4, 141.9, 139.3, 138.4, 137.8, 135.2 (2), 132.3 (2), 128.5, 126.8, 126.2, 122.1, 121.9, 121.7, 121.5, 121.0, 120.8, 120.5, 119.5, 118.2, 113.3 (2), 112.9 (2), 109.7, 108.8; MS *m/z* 237.1 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 237.1026 (calcd for $C_{15}H_{13}N_2O$, 237.1022).

SN37444 1-(4-Methoxybenzyl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (**S172**).

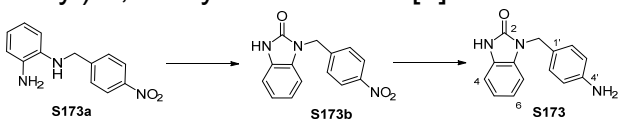


***N*^{3}-(4-Methoxybenzyl)pyridine-2,3-diamine (S172a).** Prepared using Method P from 2,3-diaminopyridine 4-methoxybenzaldehyde. The crude residue was purified by column chromatography, eluting with 70% EtOAc/pet. ether, Solvent to give diamine **S172a** (852 mg, 91%) as a brownish-yellow oil: ^{1}H NMR δ 7.62 (dd, *J* = 5.1, 1.4 Hz, 1H, H-6), 7.30 (ddd, *J* = 8.7, 2.9, 2.1 Hz, 2H, H-2', H-6'), 6.90 (d, *J* = 8.7, 2.9, 2.1 Hz, 2H, H-3', H-5'), 6.83 (dd, *J* = 7.7, 1.4 Hz, 1H, H-4), 6.69 (dd, *J* = 7.7, 5.1 Hz, 1H, H-5), 4.22 (d, *J* = 4.0 Hz, 2H, CH_2), 4.16 (s, 2H, NH_2-2), 3.82 (s, 3H, OMe-4'), 3.44 (s, 1H, NH-3); MS *m/z* 230.2 (MH^+, 100%).

1-(4-Methoxybenzyl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (S172). Prepared using Method O from **S172a**. The pale orange precipitate was filtered and washed with EtOAc to give the product **S172** (579 mg, 86%) as a pale brown solid: mp 196–198 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.61 (s, 1H, NH-1), 7.88 (dd, *J* = 5.2, 1.4 Hz, 1H, H-6), 7.35 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.28 (ddd, *J* = 8.8, 2.9, 2.1 Hz, 2H), 6.95 (dd, *J* = 7.8, 5.2 Hz, 1H, H-5), 6.88 (ddd, *J* = 8.8, 2.9, 2.1 Hz, 2H), 4.93 (s, 2H), 3.70 (s, 3H, OMe-4'); ^{13}C NMR [$(CD_3)_2SO$] δ 158.7 (C-4'), 153.7 (C-2), 143.5 (C-7a), 140.0 (C-6), 129.0 (C-2', C-6'), 128.6

(C-1'), 124.0 (C-3a), 116.6 (C-5), 114.1 (C-4), 114.0 (C-3', C-5'), 55.0 (OMe-4'), 42.6 (CH_2); MS *m/z* 256.2 (MH^+, 100%). Anal. calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.92; H, 5.06; N, 16.73%.

SN37446 1-(4-Aminobenzyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (**S173**).

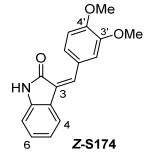


***N*^{1}-(4-Nitrobenzyl)benzene-1,2-diamine (S173a).** Prepared using Method E from 4-nitrobenzyl bromide and *o*-phenylene diamine. The crude residue was purified by column chromatography, eluting in 25–30% EtOAc/pet. ether, to give diamine **S173a** (278 mg, 19%) as an orange solid: mp 154–156 °C; ^{1}H NMR δ 8.20 (ddd, *J* = 8.8, 2.4, 2.0 Hz, 2H, H-3', H-5'), 7.53–7.58 (m, 2H, H-2', H-6'), 6.69–6.80 (m, 3H, H-3, H-4, H-5), 6.50 (dd, *J* = 7.8, 1.4 Hz, 1H, H-6), 4.47 (d, *J* = 4.7 Hz, 2H, CH_2), 3.95 (s, 1H, NH), 3.38 (s, 2H, NH_2); MS *m/z* 244.2 (MH^+, 100%). Anal. calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.38; H, 5.39; N, 17.04%.

1-(4-Nitrobenzyl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (S173b). Prepared using Method O from **S173a** . The crude residue was purified by column chromatography, eluting in 75–100% EtOAc/pet. ether, to give product **S173b** (243 mg, 88%) as an off-white solid: mp 189–191 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.04 (s, 1H, NH-1), 8.20 (d, *J* = 8.8, 2.5, 2.0 Hz, 2H, H-3', H-5'), 7.54 (d, *J* = 8.8, 2.5, 2.0 Hz, 2H, H-2', H-6'), 6.93–7.05 (m, 4H, H-4, H-5, H-6, H-7), 5.16 (s, 2H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 154.3 (C-2), 146.8 (C-4'), 145.0 (C-1'), 129.8 (C-3a), 128.4 (C-2', C-6'), 128.3 (C-7a), 123.8 (C-3', C-5'), 121.3 (C-5), 120.7 (C-6), 109.0 (C-4), 108.0 (C-7), 42.7 (CH_2); MS *m/z* 270.1 (MH^+, 100%). Anal. calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.54; H, 4.05; N, 15.70%.

1-(4-Aminobenzyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (S173). Prepared using Method B from **S173b** to give the amine **S173** (184 mg, 90%) as a white solid: mp 201–203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (br s, 1H, NH), 6.99–7.02 (m, 3H, H-7, H-2', H-6'), 6.91–6.96 (m, 3H, H-4, H-5, H-6), 6.46–6.49 (m, 2H, H-3', H-5'), 5.01 (br s, 2H, NH_2), 4.77 (s, 2H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 154.3, 148.0, 130.0, 128.5 (2), 128.2, 124.0, 120.7, 120.4, 113.7 (2), 108.7, 108.2, 43.0; MS *m/z* 240.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 240.1130 (calcd for $C_{14}H_{14}N_3O$, 240.1131).

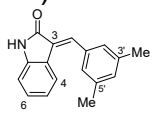
SN37510 (*Z*)-3-(3,4-Dimethoxybenzylidene)indolin-2-one (**S174**).



(*Z*)-3-(3,4-Dimethoxybenzylidene)indolin-2-one (S174). Prepared using Method N from oxindole and 3,4-dimethoxybenzaldehyde. The crude material was triturated in 75% EtOAc/pet.ether to give **S174** (423 mg, quant.) as a yellow solid: mp 150–152 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.55 (s, 1H, NH), 8.68 (d, *J* = 1.9 Hz, 1H, H-2'), 7.84 (dd, *J* = 8.6, 1.9 Hz, 1H, H-6'), 7.75 (s, 1H, =CH), 7.67 (d, *J* = 7.6 Hz, 1H, H-4), 7.18 (td, *J* = 7.6, 1.1 Hz, 1H,

H-6), 7.07 (d, *J* = 8.6 Hz, 1H, H-5'), 6.98 (td, *J* = 7.6, 0.9 Hz, 1H, H-5), 6.83 (d, *J* = 7.6 Hz, 1H, H-7), 3.84 (s, 3H, OMe-4'), 3.83 (s, 3H, OMe-3'); ^{13}C NMR [$(CD_3)_2SO$] δ 167.5, 151.1, 148.0, 140.2, 137.4, 128.1, 127.4, 127.2, 125.4, 123.9, 120.9, 119.2, 114.9, 111.1, 109.2, 55.6, 55.4; MS *m/z* 282.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.49; H, 5.40; N, 4.97%.

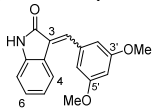
SN37511 (*E*)-3-(3,5-Dimethylbenzylidene)indolin-2-one (**S175**).



E-S175

(*E*)-3-(3,5-Dimethylbenzylidene)indolin-2-one (S175). Prepared using Method N from oxindole and 3,5-dimethylbenzaldehyde. The crude material was purified by column chromatography, eluting with 20–30% EtOAc/pet. ether, to give **S175** (284 mg, 76%) as a yellow solid: mp 160–162 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.58 (s, 1H, NH), 7.56 (s, 1H, =CH), 7.52 (d, *J* = 7.7 Hz, 1H, H-4), 7.30 (m, 2H, H-2', H-6'), 7.22 (td, *J* = 7.7, 1.0 Hz, 1H, H-6), 7.11 (s, 1H, H-4'), 6.83–6.88 (m, 2H, H-5, H-7), 2.33 (s, 6H, Me-3', Me-5'); ^{13}C NMR [$(CD_3)_2SO$] δ 168.7, 142.9, 137.9 (2), 136.1, 134.3, 131.1, 130.0, 127.4, 126.8 (2), 122.3, 121.1, 121.0, 110.1, 20.8 (2); MS *m/z* 250.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.67; H, 6.16; N, 5.62%.

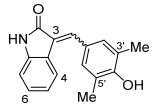
SN37513 (*E*/*Z*)-3-(3,5-Dimethoxybenzylidene)indolin-2-one (**S176**).



E/*Z*-S176

(*E*/*Z*)-3-(3,5-Dimethoxybenzylidene)indolin-2-one (S176). Prepared using Method N from oxindole and 3,5-dimethoxybenzaldehyde. The crude material was purified by column chromatography, eluting with 20–50% EtOAc/pet. ether, to give *E*/*Z*-S176 (383mg, 91%) as a mixture of isomers as a yellow solid: mp 152–155 °C; ^{1}H NMR (DMSO-d_6) δ *E*-isomer (major) 10.60 (s, 1H, NH), 7.59 (d, *J* = 7.4 Hz, 1H, H-4), 7.56 (s, 1H, =CH), 7.23 (td, *J* = 7.7, 1.1 Hz, 1H, H-6), 6.82–6.90 (m, 4H, H-5, H-7, H-2', H-6'), 6.60–6.61 (m, 1H, H-4'), 3.79 (s, 6H, OMe-3', OMe-5'); *Z*-isomer (minor) 10.60 (s, 1H, NH), 7.73–7.75 (m, 3H, =CH, H-2', H-6'), 7.70 (d, *J* = 7.3 Hz, 1H, H-4), 7.20–7.24 (m, 1H, H-6), 6.99 (td, *J* = 7.6, 0.9 Hz, 1H, H-5), 6.82–6.90 (m, 1H, H-7), 6.60–6.61 (m, 1H, H-4'), 3.80 (s, 6H, OMe-3', OMe-5'); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 168.6, 167.1, 160.5 (2), 160.0 (2), 143.1, 140.7, 136.9, 136.3, 135.7, 135.6, 130.2, 129.0, 127.9, 127.1, 124.9, 122.8, 121.1 (2), 120.8, 119.8, 110.2, 109.9 (2), 109.4, 107.0 (2), 103.0, 101.8, 55.4 (2), 55.3 (2); MS *m/z* 282.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.68; H, 5.34; N, 5.00%.

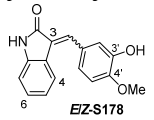
SN37514 (*E*/*Z*)-3-(4-Hydroxy-3,5-dimethylbenzylidene)indolin-2-one (**S177**).



E/*Z*-S177

(*E*/*Z*)-3-(4-Hydroxy-3,5-dimethylbenzylidene)indolin-2-one (S177). Prepared using Method N from oxindole and 3,5-dimethyl-4-hydroxybenzaldehyde. The crude material was purified by column chromatography, eluting with 30–60% EtOAc/pet. ether, to give *E*/*Z*-**S177** (373 mg, 94%) as a mixture of isomers as a yellow solid: mp 190–193 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.50 (s, 1H, NH), 8.96 (br s, 1H, OH), 7.70 (d, *J* = 7.6 Hz, 1H, H-4), 7.48 (s, 1H, =CH), 7.35 (s, 2H, H-2', H-6'), 7.19 (td, *J* = 7.6, 1.0 Hz, 1H, H-6), 6.85–6.90 (m, 2H, H-5, H-7), 2.22 (s, 6H, Me-3', Me-5); *Z*-isomer (minor) 10.47 (s, 1H, NH), 8.96 (br s, 1H, OH), 8.17 (s, 2H, H-2', H-6'), 7.61–7.63 (m, 2H, H-4, =CH), 7.15 (td, *J* = 7.6, 1.0 Hz, 1H, H-6), 6.95 (td, *J* = 7.6, 1.0 Hz, 1H, H-5), 6.80 (d, *J* = 7.6 Hz, 1H, H-7), 2.21 (s, 6H, Me-3', Me-5); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 169.1, 167.4, 156.4, 155.4, 142.5, 140.0, 137.7, 136.9, 133.5 (2), 130.3 (2), 129.3, 127.8, 125.7, 125.6, 125.1, 124.6, 124.5 (2), 123.7 (2), 122.8, 121.9, 121.4, 121.0, 120.8, 118.9, 109.9, 109.1, 16.7 (2), 16.5 (2); MS *m/z* 266.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.68; H, 5.71; N, 5.27%.

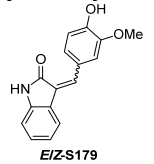
SN37515 (*E*/*Z*)-3-(3-Hydroxy-4-methoxybenzylidene)indolin-2-one (**S178**).



E/*Z*-S178

(*E*/*Z*)-3-(3-Hydroxy-4-methoxybenzylidene)indolin-2-one (S178). Prepared using Method N from oxindole and isovanillin. The crude material was purified by column chromatography, eluting with 30–50% EtOAc/pet. ether, to give (*E*/*Z*)-S178 (388 mg, 97%) as a yellow solid: mp 175–175 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.52 (s, 1H, NH), 9.39 (br s, 1H, OH), 7.73 (d, *J* = 7.6 Hz, 1H, H-4), 7.49 (s, 1H, =CH), 7.15–7.24 (m, 3H, H-6, H-2', H-6'), 7.05–7.08 (m, 1H, H-5'), 6.86–6.91 (m, 2H, H-5, H-7), 3.85 (s, 3H, OMe-4'); Z-isomer (minor) 10.52 (br s, 1H, NH), 9.13 (br s, 1H, OH), 8.17 (d, *J* = 2.1 Hz, 1H, H-2'), 7.83 (dd, *J* = 8.6, 2.1 Hz, 1H, H-6'), 7.65–7.67 (m, 2H, =CH, H-4), 7.15–7.24 (m, 1H, H-6), 7.02 (d, *J* = 8.6 Hz, 1H, H-5'), 6.96 (td, *J* = 7.6, 1.0 Hz, 1H, H-5), 6.80 (d, *J* = 7.6 Hz, 1H, H-7), 3.85 (s, 3H, OMe-4'); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 169.0, 167.3, 150.3, 149.4, 146.4, 145.7, 142.6, 140.2, 137.5, 136.5, 129.6, 128.1, 127.3, 126.9, 125.9, 125.4, 125.3, 123.8, 122.3, 122.2, 121.2, 121.0, 120.8, 119.2, 118.9, 116.2, 112.1, 111.3, 110.0, 109.1, 55.6, 55.6; MS *m/z* 268.2 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.61; H, 4.98; N, 5.18%.

SN37516 (*E*/*Z*)-3-(4-Hydroxy-3-methoxybenzylidene)indolin-2-one (**S179**).

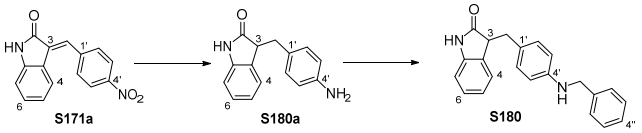


E/*Z*-S179

(*E*/*Z*)-3-(4-Hydroxy-3-methoxybenzylidene)indolin-2-one (S179). Prepared using Method N from oxindole and vanillin. The crude material was purified by column chromatography, eluting with 3–4% EtOAc/DCM, to give (*E*/*Z*)-**S179** (336 mg, 84%) as a yellow solid: mp 226–228 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *Z*-isomer (major) 10.51 (s, 1H, NH), 9.84 (br s, 1H, OH), 8.68 (d, *J* = 1.9 Hz, 1H, H-2'), 7.74 (d, *J* = 8.4, 1.9 Hz, 1H, H-6'), 7.69 (s, 1H, =CH), 7.6 (d, *J* = 7.6 Hz, 1H, H-4), 7.16 (td, *J* = 7.6, 1.1 Hz, 1H, H-6), 6.97 (td, *J* =

7.6, 1.0 Hz, 1H, H-5), 6.85 (d, *J* = 8.4 Hz, 1H, H-5'), 6.82 (d, *J* = 7.6 Hz, 1H, H-7), 3.85 (s, 3H, OMe); *E*-isomer (minor) 10.51 (s, 1H, NH), 9.84 (br s, 1H, OH), 7.75–7.77 (m, 1H, H-4), 7.54 (s, 1H, =CH), 7.32 (d, *J* = 1.9 Hz, 1H, H-2'), 7.19–7.26 (m, 2H, H-6, H-6'), 6.85–6.92 (m, 3H, H-5, H-7, H-5'), 3.81 (s, 3H, OMe); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 169.0, 167.3, 150.3, 149.4, 146.4, 145.7, 142.6, 140.2, 137.5, 136.5, 129.6, 128.1, 127.3, 126.9, 125.9, 125.4, 125.3, 123.8, 122.3, 122.2, 121.2, 121.0, 120.8, 119.2, 118.9, 116.2, 112.1, 111.3, 110.0, 109.1, 55.6, 55.6; MS *m/z* 268.1 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 72.15; H, 4.98; N, 5.28%.

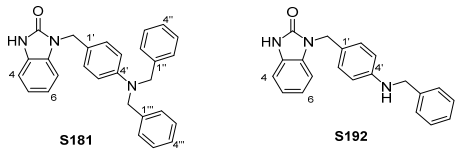
SN37517 3-(4-(Benzylamino)benzyl)indolin-2-one (**S180**).



3-(4-Aminobenzyl)indolin-2-one (S180a). Prepared using Method M from **S171a**. The crude residue was purified by column chromatography, eluting with 70–100% EtOAc/pet. ether, to give the amine **S180a** (135 mg, 25%) as a white solid: mp 125–126 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.23 (s, 1H, NH), 7.05–7.13 (m, 1H, H-6), 6.79–6.84 (m, 2H, H-4, H-5), 6.75–6.78 (m, 2H, H-2', H-6'), 6.71 (d, *J* = 7.7 Hz, 1H, H-7), 6.37–6.40 (m, 2H, H-3', H-5'), 4.82 (br s, 2H, NH_2), 3.63 (dd, *J* = 8.2, 5.0 Hz, 1H, CH), 3.14 (dd, *J* = 13.8, 5.0 Hz, 1H, CH_2), 2.71 (dd, *J* = 13.8, 8.2 Hz, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 178.3 (C=O), 146.8 (C-4'), 142.6 (C-7a), 129.7 (2', C-6'), 129.3 (C-3a), 127.4 (C-6), 124.8 (C-1'), 124.4 (C-4), 120.8 (C-5), 113.7 (C-3'), 109.0 (C-7), 46.9 (C-3), 34.7 (CH_2); MS *m/z* 239.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 239.1181 (calcd for $C_{15}H_{15}N_2O$, 239.1179).

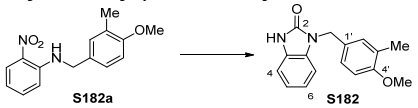
3-(4-(Benzylamino)benzyl)indolin-2-one (S180). Prepared using Method P from amine **S180a** and benzaldehyde. The crude residue was purified by column chromatography, eluting with 30% EtOAc/pet. ether, to give amine **S180** (25.8 mg, 7%) as a yellow solid: mp 152–155 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.23 (br s, 1H, NH), 7.28–7.35 (m, 4H, H-2'', H-3'', H-5'', H-6''), 7.19–7.23 (m, 1H, H-4''), 7.06–7.10 (m, 1H, H-6), 6.79–6.82 (m, 4H, H-4, H-5, H-2', H-6'), 6.71 (d, *J* = 7.7 Hz, 1H, H-7), 6.41–6.42 (m, 2H, H-3', H-5'), 6.01 (t, *J* = 6.0 Hz, 1H, $NHCH_2$), 4.19 (d, *J* = 6.0 Hz, 2H, CH_2), 3.63 (dd, *J* = 8.0, 4.8 Hz, 1H, CH), 3.14 (dd, *J* = 13.8, 4.8 Hz, 1H, CH_2), 2.71 (dd, *J* = 13.8, 8.0 Hz, 1H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 178.2 (C=O), 147.1 (C-4'), 142.6 (C-7a), 140.3 (C-1''), 129.7 (C-2', C-6'), 129.3 (C-3a), 128.2 (C-3'', C-5''), 127.4 (C-6), 127.3 (C-2'', C-6''), 126.6 (C-4''), 124.9 (C-1'), 124.3 (C-4), 120.8 (C-5), 112.0 (C-3', C-5'), 109.0 (C-7), 46.8 ($CHCH_2$), 46.7 ($NHCH_2$), 34.6 (CH); MS *m/z* 329.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 329.1637 (calcd for $C_{22}H_{21}N_2O$, 329.1648).

SN37518 1-(4-(Dibenzylamino)benzyl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one (**S181**) and SN37729 1-(4-(Benzylamino)benzyl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one (**S192**).



1-(4-(Dibenzylamino)benzyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (S181) and 1-(4-(Benzylamino)benzyl)-1,3-dihydro-2*H*-benzo[*d*]imidazol-2-one (S192). Prepared using Method P from amine **S173** and benzaldehyde. The crude mixture was purified by column chromatography, eluting with 20–30% EtOAc/DCM to give (a) the bis-alkylated product **S181** (58 mg, 33%) as a white solid: mp 173–175 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, NH), 7.28–7.31 (m, 4H, H-3'', H-5'', H-3''', H-5'''), 7.19–7.23 (m, 6H, H-2'', H-6'', H-2''', H-6'''), 7.03–7.09 (m, 3H, H-7, H-2', H-6'), 6.91–6.95 (m, 3H, H-4, H-5, H-6), 6.59–6.61 (m, 2H, H-3', H-5'), 4.79 (s, 2H, NCH_2), 4.64 (s, 4H, NCH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 154.3, 147.6, 138.9 (2), 130.0, 128.5 (6), 128.2, 126.7 (2), 126.6 (4), 124.5, 120.8, 120.4, 112.2 (2), 108.7, 108.1, 54.1 (2), 42.7; MS *m/z* 420.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 420.2074 (calcd for $C_{28}H_{26}N_3O$, 420.2070). Also isolated was (b) the mono-alkylated product **S192** (12 mg, 9%) as a white solid: mp 197–199 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.84 (s, 1H, NH), 7.26–7.33 (m, 4H, H-2'', H-3'', H-5'', H-6''), 7.17–7.21 (m, 1H, H-4''), 6.99–7.05 (m, 3H, H-7, H-2', H-6'), 6.89–6.97 (m, 3H, H-4, H-5, H-6), 6.50 (d, *J* = 8.6 Hz, 2H, H-3', H-5'), 6.23 (t, *J* = 6.0 Hz, 1H, $NHCH_2$), 4.77 (s, 2H, NCH_2), 4.21 (d, *J* = 6.0 Hz, 2H, $NHCH_2$); ^{13}C NMR [$(CD_3)_2SO$] δ 154.3, 148.0, 140.2, 130.0, 128.5 (2), 128.2 (3), 127.1 (2), 126.6, 124.1, 120.7, 120.4, 112.1 (2), 108.6, 108.1, 46.4, 42.9; MS *m/z* 330.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 330.1588 (calcd for $C_{22}H_{20}N_3O$, 330.1601).

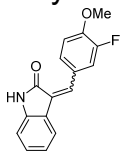
SN37519 1-(4-Methoxy-3-methylbenzyl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one (**S182**).



***N*-(4-Methoxy-3-methylbenzyl)-2-nitroaniline (S182a).** Prepared using Method P from 2-nitroaniline and 3-methyl-p-anisaldehyde. The crude mixture was purified by column chromatography, eluting with 1-3% EtOAc/pet. ether, to give nitroaniline **S182a** (277 mg, 70%) as a yellow solid: mp 89–91 °C; ^{1}H NMR δ 8.33 (br s, 1H, NH), 8.19 (dd, *J* = 8.6, 1.6 Hz, 1H, H-3), 7.37–7.41 (m, 1H, H-5), 7.12–7.15 (m, 1H, H-2', H-6'), 6.84 (dd, *J* = 8.6, 0.9 Hz, 1H, H-6), 6.80 (d, *J* = 8.1 Hz, 1H, H-3'), 6.64–6.68 (m, 1H, H-4), 4.44 (d, *J* = 5.4 Hz, 2H, CH_2), 3.83 (s, 3H, OMe), 2.22 (s, 3H, Me).

1-(4-Methoxy-3-methylbenzyl)-1,3-dihydro-2*H*-benzo[d]imidazol-2-one (S182). Prepared using Method B from nitroaniline **S182a**. The crude dianiline was used directly in Method O. The crude residue was purified by column chromatography, eluting in 75% EtOAc/pet. ether, to give **S182** (172 mg, 77% over 2 steps) as a white solid: mp 189–191 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.89 (br s, 1H, NH), 7.12–7.15 (m, 2H, H-2', H-6), 6.91–7.02 (m, 4H, H-4, H-5, H-6, H-7), 6.86 (d, *J* = 8.2 Hz, 1H, H-5'), 4.87 (s, 2H, CH_2), 3.73 (s, 3H, OMe), 2.09 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 156.6, 154.3, 129.9, 129.7, 128.7, 128.2, 126.3, 125.6, 120.9, 120.5, 110.2, 108.7, 108.1, 55.2, 42.7, 16.0; MS *m/z* 269.2 (MH^+, 100%). Anal. calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.66; H, 5.89; N, 10.46%.

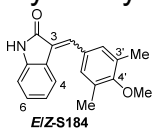
SN37520 (*E*/*Z*)-3-(3-Fluoro-4-methoxybenzylidene)indolin-2-one (**S183**).



***E*/*Z*-S183**

(*E*/*Z*)-3-(3-Fluoro-4-methoxybenzylidene)indolin-2-one (S183). Prepared using Method N from oxindole and 3-fluoro-4-methoxybenzaldehyde. The crude material was purified by column chromatography, eluting with 20–80% EtOAc/pet. ether, to give (*E*/*Z*)-**S183** (320 mg, 88%) as a yellow solid: mp 220–223 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *Z* isomer (major) 10.65 (s, 1H, NH), 8.82 (dd, *J* = 14.0, 2.1 Hz, 1H, H-2'), 8.01 (m, 1H, H-6'), 7.76 (s, 1H, =CH), 7.68 (d, *J* = 7.6 Hz, 1H, H-4), 7.28 (t, *J* = 8.9 Hz, 1H, H-5'), 7.20 (td, *J* = 7.6, 1.0 Hz, 1H, H-6), 6.99 (td, *J* = 7.6 Hz, 1H, H-5), 6.82 (d, *J* = 7.6 Hz, 1H, H-7), 3.92 (s, 3H, OMe); *E*-isomer (minor) 10.59 (s, 1H, NH), 7.57–7.61 (m, 3H, H-4, H-2', H-6'), 7.54 (s, 1H, =CH), 7.30–7.34 (m, 1H, H-5'), 7.23–7.24 (m, 1H, H-6), 6.86–6.90 (m, 2H, H-5, H-7), 3.92 (s, 3H, OMe); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 168.7, 167.4, 151.1 (d, *J* = 244.7 Hz), 150.5 (d, *J* = 242.6 Hz), 149.1 (d, *J* = 11.0 Hz), 148.4 (d, *J* = 10.7), 142.9, 140.5, 135.8 (d, *J* = 2.1 Hz), 134.7 (d, *J* = 1.4 Hz), 130.7 (d, *J* = 2.5 Hz), 130.1, 128.6, 127.3 (d, *J* = 7.9 Hz), 127.1 (d, *J* = 7.0 Hz), 126.8, 126.6 (d, *J* = 3.2 Hz), 125.3, 125.0, 122.2, 121.1, 121.0, 120.9, 119.5, 118.5 (d, *J* = 20.0 Hz), 117.0 (d, *J* = 18.2 Hz), 113.9 (d, *J* = 1.9 Hz), 113.2 (d, *J* = 1.3 Hz), 110.2, 109.3, 56.2, 56.1; MS *m/z* 270.1 (MH^+, 100%). Anal. calcd for $C_{16}H_{12}FNO_2$: C, 71.37; H, 4.49; N, 5.20. Found: C, 71.23; H, 4.38; N, 5.24%.

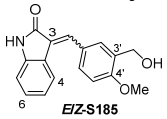
SN37562 (*E*/*Z*)-3-(4-Methoxy-3,5-dimethylbenzylidene)indolin-2-one (**S184**).



***E*/*Z*-S184**

(*E*/*Z*)-3-(4-Methoxy-3,5-dimethylbenzylidene)indolin-2-one (S184). Prepared using Method E from methyl iodide and phenol **S177**. The crude residue was purified by column chromatography, eluting in 10% EtOAc/pet. ether, to give (*E*/*Z*)-**S184** (43 mg, 40%) as a yellow solid: mp 200–203 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.56 (s, 1H, NH), 7.60–7.65 (m, 1H, H-4), 7.51 (s, 1H, =CH), 7.41 (m, 2H, H-2', H-6'), 7.22 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H, H-6), 6.86–6.89 (m, 2H, H-5, H-7), 3.73 (s, 3H, OMe), 2.28 (s, 2H, Me-3', Me-5'); *Z*-isomer (minor) 10.56 (s, 1H, NH), 8.15 (s, 2H, H-2', H-6'), 7.65–7.68 (m, 2H, H-4, =CH), 7.17–7.21 (m, 1H, H-6), 6.97 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.81 (d, *J* = 7.6 Hz, 1H, H-7), 3.71 (s, 3H, OMe), 2.27 (s, 2H, Me-3', Me-5'); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 168.8, 167.1, 158.7, 157.9, 142.8 (2), 140.5 (2), 136.6, 135.8, 133.1 (2), 130.9, 130.0 (3), 129.9, 129.7, 129.7, 128.5, 126.6, 125.3, 125.2, 122.2, 121.1, 121.0 (2), 119.4, 110.1, 109.2, 59.5, 59.4, 16.0 (2), 15.8 (2); MS *m/z* 280.2 (MH^+, 100%). Anal. calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.35; H, 6.06; N, 5.09%.

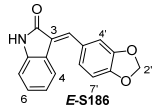
SN37563 (*E*/*Z*)-3-(3-(Hydroxymethyl)-4-methoxybenzylidene)indolin-2-one (**S185**).



***E*/*Z*-S185**

(*E*/*Z*)-3-(3-(Hydroxymethyl)-4-methoxybenzylidene)indolin-2-one (S185). Prepared using Method N from oxindole and 3-hydroxymethyl-4-methoxybenzaldehyde. The crude material was purified by column chromatography, eluting with 50–100% EtOAc/pet. ether, to give (*E*/*Z*)-**S185** (372 mg, 95%) as a yellow solid: mp 175–178 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.54 (s, 1H, NH), 7.83 (d, *J* = 1.8 Hz, 1H, H-2'), 7.74 (d obscured, *J* = 7.5 Hz, 1H, H-4), 7.64 (dd, *J* = 8.5, 1.8 Hz, 1H, H-6'), 7.58 (s, 1H, =CH), 7.20–7.24 (m, 1H, H-6), 7.11 (d, *J* = 8.5 Hz, 1H, H-5'), 6.84–6.88 (d, *J* = 7.6 Hz, 2H, H-5, H-7), 5.16 (t, *J* = 5.6 Hz, 1H, OH), 4.55 (d, *J* = 5.6 Hz, 2H, CH_2), 3.87 (s, 3H, OMe); *Z*-isomer (minor) 10.53 (s, 1H, NH), 8.67 (dd, *J* = 8.7, 2.1 Hz, 1H, H-6'), 8.31 (d, *J* = 2.1 Hz, 1H, H-2'), 7.77 (s obscured, 1H, =CH), 7.71 (d obscured, *J* = 7.7 Hz, 1H, H-4), 7.17 (ddd obscured, *J* = 7.7, 7.7, 0.9 Hz, 1H, H-6), 7.07 (d, *J* = 8.7 Hz, 1H, H-5'), 6.96 (ddd, *J* = 7.7, 7.7, 0.9 Hz, 1H, H-5), 6.81 (d, *J* = 7.7 Hz, 1H, H-7), 5.07 (t, *J* = 5.6 Hz, 1H, OH), 4.52 (d, *J* = 5.6 Hz, 2H, CH_2), 3.87 (s, 3H, OMe); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 169.0, 167.3, 158.2, 157.3, 142.6, 140.2, 137.3, 136.4, 132.6, 132.3, 130.8, 130.3, 130.0, 129.6, 128.1 (2), 126.6, 126.2, 125.5, 125.3, 123.9, 122.3, 121.2, 121.0, 120.9, 119.3, 110.4 (2), 110.0, 109.1, 59.7, 57.8, 57.6, 55.5; MS *m/z* 282.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 4.98; N, 5.01. Found: C, 72.31; H, 5.39; N, 4.84%.

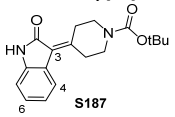
SN37657 (*E*)-3-(Benzo[*d*][1,3]dioxol-5-ylmethylene)indolin-2-one (**S186**).



E-S186

(*E*)-3-(Benzo[*d*][1,3]dioxol-5-ylmethylene)indolin-2-one (S186). Prepared using Method N from oxindole and piperonal. The crude material was purified by column chromatography, eluting with 50–100% EtOAc/pet. ether, to give **S186** (362 mg, 91%) as a yellow solid: mp 226–229 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.56 (s, 1H, NH), 7.63 (d, *J* = 7.6 Hz, 1H, H-4), 7.53 (s, 1H, =CH), 7.28–7.30 (m, 2H, H-4', H-6'), 7.22 (ddd, *J* = 7.6, 1.0 Hz, 1H, H-6), 7.07–7.09 (m, 1H, H-7'), 6.86–6.90 (m, 2H, H-5, H-7), 6.13 (s, 2H, CH_2-2'); ^{13}C NMR [$(CD_3)_2SO$] δ 168.8, 148.6, 147.6, 142.8, 136.0, 129.8, 128.2, 126.1, 124.6, 122.2, 121.1, 121.0, 110.1, 109.3, 108.6, 101.7; MS *m/z* 266.2 (MH^+, 100%). Anal. calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.56; H, 4.08; N, 5.30%.

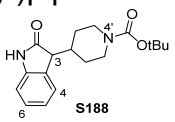
SN37658 *tert*-Butyl 4-(2-oxoindolin-3-ylidene)piperidine-1-carboxylate (**S187**).



S187

***tert*-Butyl 4-(2-oxoindolin-3-ylidene)piperidine-1-carboxylate (S187).** Prepared using Method N from oxindole and *N*-*tert*-butylcarbonate-4-piperidone. The crude material was purified by column chromatography, eluting with 25% EtOAc/pet. ether, to give **S187** (785 mg, 67%) as a yellow solid: mp 204–207 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.49 (s, 1H, NH), 7.57 (d, *J* = 7.7 Hz, 1H, H-4), 7.18 (ddd, *J* = 7.7, 7.7, 0.9 Hz, 1H, H-6), 6.94 (ddd, *J* = 7.7, 7.7, 0.9 Hz, 1H, H-5), 6.82 (dd, *J* = 7.7, 0.9 Hz, 1H, H-7), 3.58 (t, *J* = 6.0 Hz, 2H, CH_2N), 3.43 (br s, 4H, $=CCH_2$, CH_2N), 2.95 (t, *J* = 6.0 Hz, 2H, $=CCH_2$), 1.42 (s, 9H, tBu); ^{13}C NMR [$(CD_3)_2SO$] δ 168.5, 155.6, 154.0, 140.6, 128.1, 123.8, 122.9, 121.9, 121.0, 109.2, 78.8, 42.3, 41.4, 31.4, 28.1, 27.0; MS *m/z* 313.2 ($M-H^-$, 100%); (+)-HRESIMS *m/z* $[M+Na]^+$ 337.1527 (calcd for $C_{18}H_{22}N_2NaO_3$, 337.1523).

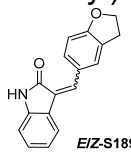
SN37659 *tert*-Butyl 4-(2-oxoindolin-3-yl)piperidine-1-carboxylate (**S188**).



S188

***tert*-Butyl 4-(2-oxoindolin-3-yl)piperidine-1-carboxylate (S188).** Prepared using Method M from alkene **S187**. The crude residue was triturated in EtOAc to obtain the oxindolyl **S188** (310 mg, quant.) as an off-white solid: mp 180–182 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.37 (s, 1H, NH), 7.24 (d, *J* = 7.5 Hz, 1H, H-4), 7.15–7.19 (m, 1H, H-6), 6.94 (ddd, *J* = 7.5, 1.0 Hz, 1H, H-5), 6.81 (d, *J* = 7.5 Hz, 1H, H-7), 3.91–4.02 (m, 2H, CH_2N), 3.41 (d, *J* = 3.5 Hz, CH-3), 3.64–2.67 (m, 2H, CH_2N), 2.12–2.19 (m, 1H, CH-1'), 1.17–1.54 (m, 4H, CH_2-2', CH_2-6'), 1.36 (s obscured, 9H, *t*Bu); ^{13}C NMR [$(CD_3)_2SO$] δ 177.8, 153.8, 143.0, 127.9, 127.7, 124.4, 121.2, 109.1, 78.5, 49.8, 43.8, 43.3, 38.0, 28.2, 28.0 (3), 27.3; MS *m/z* 315.2 ($M-H^-$, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 217.1337 (calcd for $C_{13}H_{17}N_2O$, 217.1335).

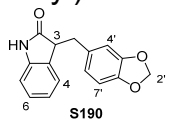
SN37660 (*E*/*Z*)-3-((2,3-Dihydrobenzofuran-5-yl)methylene)indolin-2-one (**S189**).



***E*/*Z*-S189**

(*E*/*Z*)-3-((2,3-Dihydrobenzofuran-5-yl)methylene)indolin-2-one (S189). Prepared using Method N from oxindole and 2,3-dihydrobenzofuran-5-carboxaldehyde. The crude material was purified by column chromatography, eluting with 30–80% EtOAc/pet. ether, to give (*E*/*Z*)-**S189** (182 mg, 46%) as a yellow solid: mp 207–210 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *Z*-isomer (major) 10.56 (s, 1H, NH), 8.60 (d, *J* = 1.2 Hz, 1H, H-4'), 8.20 (dd, *J* = 8.5, 1.2 Hz, 1H, H-6), 7.73 (s, 1H, =CH), 7.64–7.69 (m, 1H, H-4), 7.16 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H, H-6), 6.97 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H, H-5), 6.85–6.90 (m, 1H, H-7'), 6.81 (d, *J* = 7.6 Hz, 1H, H-7), 4.63 (t, *J* = 8.7 Hz, 2H, CH_2-2'), 3.20–3.29 (m, 2H, CH_2-3'); *E*-isomer (minor) 10.53 (s, 1H, NH), 7.64–7.69 (m, 2H, H-4, H-4'), 7.53–7.56 (m, 2H, =CH, H-6'), 7.20 (ddd, *J* = 7.8, 7.8, 1.1 Hz, 1H, H-6), 6.92 (d, *J* = 8.3 Hz, 1H, H-7'), 6.85–6.90 (m, 2H, H-5, H-7), 4.63 (t, *J* = 8.7 Hz, 2H, CH_2-2'), 3.20–3.29 (m, 2H, CH_2-3'); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 169.0, 167.4, 162.1, 161.3, 142.6, 140.1, 137.4, 136.6, 134.3, 130.6, 129.5, 129.2, 128.3, 128.0, 127.7, 127.2, 126.8, 126.6, 125.5, 125.0, 123.2, 122.0, 121.2, 121.0, 120.8, 119.0, 110.0, 109.2, 109.1, 108.9, 71.9, 71.7, 28.7, 28.6; MS *m/z* 264.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 264.1019 (calcd for $C_{17}H_{14}NO_2$, 264.1019).

SN37673 3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)indolin-2-one (**S190**).

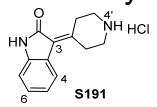


S190

3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)indolin-2-one (S190). Prepared using Method M from **S189**. The resulting residue was purified by column chromatography, eluting with 40% EtOAc/pet. ether, to give **S190** (98 mg, 59%) as a pale yellow solid: mp 136–138 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.29 (s, 1H, NH), 7.08–7.12 (m, 1H, H-6), 6.92 (d, *J* = 7.4 Hz, 1H, H-4), 6.84 (ddd, *J* = 7.4, 1.0 Hz, 1H, H-5), 6.71–6.74 (m, 3H, H-7, H-4', H-7'), 6.57

(dd, *J* = 7.9, 1.7 Hz, 1H, H-6'), 5.93 (s, 2H, CH_2-2), 3.75 (dd, *J* = 7.6, 5.1 Hz, 1H, CH), 3.22 (dd, *J* = 13.8, 5.1 Hz, 1H, $CHCH_2$), 2.88 (dd, *J* = 13.8, 7.6 Hz, 1H, $CHCH_2$); ^{13}C NMR [$(CD_3)_2SO$] δ 178.1, 146.9, 145.6, 142.6, 131.7, 128.9, 127.6, 124.3, 122.3, 120.9, 109.5, 109.1, 107.8, 100.6, 46.5, 34.8; MS *m/z* 268.1 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.77; H, 4.95; N, 5.24%.

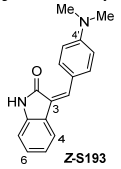
SN37674 3-(Piperidin-4-ylidene)indolin-2-one hydrochloride (**S191**).



S191

3-(Piperidin-4-ylidene)indolin-2-one hydrochloride (S191). Prepared using Method F from carbamate **S187** to give the amine **S191** (186 mg, quant.) as a yellow solid: mp 255–258 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.60 (s, 1H, NH), 9.24 (s, 2H, NH.HCl), 7.62 (d, *J* = 7.7 Hz, 1H, H-4), 7.21 (ddd, *J* = 7.7, 7.7, 0.8 Hz, 1H, H-6), 6.96 (ddd, *J* = 7.7, 7.7, 0.8 Hz, 1H, H-5), 6.84 (dd, *J* = 7.7, 0.8 Hz, 1H, H-7), 3.60 (t, *J* = 6.1 Hz, 2H, $=CCH_2$), 3.26–3.32 (m, 2H, CH_2), 3.19–3.24 (m, 2H, CH_2), 3.12 (t, *J* = 6.1 Hz, 2H, $=CCH_2$); ^{13}C NMR [$(CD_3)_2SO$] δ 168.5, 150.3, 140.9, 128.6, 124.0, 122.6, 122.5, 121.2, 109.5, 42.3, 41.9, 27.6, 24.0; *m/z* 215.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 215.1177 (calcd for $C_{13}H_{15}N_2O$, 215.1179).

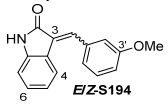
SN37730 (*Z*)-3-(4-(Dimethylamino)benzylidene)indolin-2-one (**S193**).



***Z*-S193**

(*Z*)-3-(4-(Dimethylamino)benzylidene)indolin-2-one (S193). Prepared using Method N from oxindole and *p*-dimethylaminobenzaldehyde. The crude material was triturated in 60% EtOAc/pet. ether to give **S193** (269 mg, 68%) as a red solid: mp 209–212 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.44 (s, 1H, NH), 8.43–8.46 (m, 2H, H-2', H-6'), 7.60–7.63 (m, 2H, =CH, H-4), 7.11 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-6), 6.94 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.76–6.80 (m, 3H, H-7, H-3', H-5'), 3.04 (s, 6H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 167.6, 151.7, 139.5, 138.0, 134.7 (2), 126.9, 126.1, 122.1, 120.5, 120.3, 118.4, 111.0 (2), 108.9, 39.6 (2); *m/z* 265.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.25; H, 6.08; N, 10.65%.

SN37731 (*E*/*Z*)-3-(3-Methoxybenzylidene)indolin-2-one (**S194**).

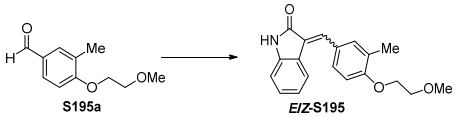


***E*/*Z*-S194**

(*E*/*Z*)-3-(3-Methoxybenzylidene)indolin-2-one (S194). Prepared using Method N from oxindole and *m*-anisaldehyde. The crude material was triturated in EtOAc/pet. ether to give (*E*/*Z*)-**S194** (231 mg, 61%) as a yellow solid: mp 134–137 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.60 (s, 1H, NH), 7.60 (s, 1H, =CH), 7.55 (d, *J* = 7.6 Hz, 1H, H-4), 7.44 (dd, *J* = 7.9, 7.9 Hz, 1H, H-5'), 7.20–7.29 (m, 3H, H-6, H-2', H-6'), 7.02–7.06 (m, 1H, H-4'), 6.86–6.88 (m, 2H, H-5, H-7), 3.80 (s, 3H, OMe); *Z*-isomer (minor) 10.60 (s, 1H, NH), 8.28–8.29 (m, 1H, H-2'), 7.82 (d, *J* = 7.9 Hz, 1H, H-4'), 7.79 (s, 1H, =CH), 7.71 (d, *J* = 7.6

Hz, 1H, H-4), 7.38 (dd, *J* = 7.9, 7.9 Hz, 1H, H-5'), 7.19–7.29 (m, 1H, H-6), 7.02–7.06 (m, 1H, H-6'), 6.99 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.82–6.88 (m, 1H, H-7), 3.82 (s, 3H, OMe); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 168.6, 167.1, 159.3, 158.9, 143.0, 140.7, 136.7, 135.8, 135.6, 135.2, 130.2, 129.9, 129.1, 129.0, 127.8, 126.9, 124.9 (2), 122.5, 121.4, 121.1 (2), 120.8, 119.8, 116.6, 116.4, 115.6, 114.3, 110.2, 109.3, 55.2, 55.1; MS *m/z* 252.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 252.1024 (calcd for $C_{16}H_{14}NO_2$, 252.1019).

SN37732 (*E*/*Z*)-3-(4-(2-Methoxyethoxy)-3-methylbenzylidene)indolin-2-one (**S195**).

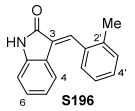


S195a *E*/*Z*-**S195**

4-(2-Methoxyethoxy)-3-methylbenzaldehyde (S195a). Prepared using Method E from 2-bromoethyl methyl ester and 4-hydroxy-3-methylbenzaldehyde. The crude residue was purified by column chromatography, eluting in 20% EtOAc/pet. ether, to give aldehyde **S195a** (260 mg, 91%) as a clear colourless oil: ^{1}H NMR δ 9.86 (s, 1H, CHO), 7.69–7.71 (m, 2H, H-2, H-6), 6.91–6.93 (m, 1H, H-5), 4.20–4.23 (m, 2H, OCH_2), 3.80–3.82 (m, 2H, CH_2O), 3.47 (s, 3H, OMe), 2.29 (s, 3H, Me); MS *m/z* 195.2 (MH^+, 100%).

(*E*/*Z*)-3-(4-(2-Methoxyethoxy)-3-methylbenzylidene)indolin-2-one (S195). Prepared using Method N from oxindole and aldehyde **S195a**. The crude material was purified by column chromatography, eluting with 40% EtOAc/pet. ether, to give (*E*/*Z*)-**S195** (82 mg, 75%) as a yellow solid: mp 141–144 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.54 (s, 1H, NH), 7.65–7.70 (m, 1H, H-4), 7.58 (dd, *J* = 8.5, 2.1 Hz, 1H, H-6'), 7.54 (m, 2H, =CH, H-2'), 7.21 (ddd, *J* = 7.7, 7.7, 1.0 Hz, 1H, H-6), 7.09 (d, *J* = 8.5 Hz, 1H, H-5'), 6.85–6.89 (m, 2H, H-5, H-7), 4.19–4.21 (m, 2H, OCH_2), 3.70–3.73 (m, 2H, CH_2O), 3.35 (s, 3H, OMe), 2.21 (s, 3H, Me); *Z*-isomer (minor) 10.54 (s, 1H, NH), 8.40 (dd, *J* = 8.7, 2.0 Hz, 1H, H-6'), 8.30 (d, *J* = 2.0 Hz, 1H, H-2'), 7.70 (s, 1H, =CH), 7.65–7.67 (m, 1H, H-4), 7.17 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-6), 7.05 (d, *J* =8.7 Hz, 1H, H-5'), 6.97 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.81 (d, *J* = 7.6 Hz, 1H, H-7), 4.19–4.21 (m, 2H, OCH_2), 3.70–3.73 (m, 2H, CH_2O), 3.34 (s, 3H, OMe), 2.20 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 168.9, 167.3, 158.7, 158.0, 142.6, 140.2, 137.0, 136.2, 134.9, 132.3, 132.0, 129.6, 129.1, 128.1, 126.7, 126.3 (2), 125.4 (3), 123.8, 122.0, 121.2, 121.0, 120.8, 119.1, 111.4, 111.0, 110.0, 109.1, 70.4 (2), 67.5 (2), 58.4 (2), 16.0, 15.9; MS *m/z* 310.2 (MH^+, 100%). Anal. calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.76; H, 6.27; N, 4.56%.

SN37769 (*E*)-3-(2-Methylbenzylidene)indolin-2-one (**S196**).

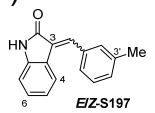


S196

(*E*)-3-(2-Methylbenzylidene)indolin-2-one (S196). Prepared using Method N from oxindole and *o*-tolualdehyde. The crude material was purified by column chromatography, eluting with 20–25% EtOAc/pet. ether, to give **S196** (330 mg, 93%) as a yellow solid: mp 129–132 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.61 (s, 1H, NH), 7.68 (s, 1H, =CH), 7.54 (d, *J* = 7.3 Hz, 1H, H-6'), 7.35–7.40 (m, 2H, H-3', H-4'), 7.30–7.34 (m, 1H, H-5'), 7.19 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H, H-6), 7.08 (d, *J* = 7.6 Hz, 1H, H-4), 6.86 (d, *J* = 7.6 Hz, 1H, H-7), 6.77

(ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H, H-5), 2.30 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 168.3, 142.8, 136.8, 134.7, 133.8, 130.4, 130.1, 129.4, 128.4, 128.2, 125.9, 122.3, 121.1 (2), 110.1, 19.5; MS *m/z* 236.1 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.45; H, 5.64; N, 6.02%.

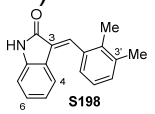
SN37770 (*E*/*Z*)-3-(3-Methylbenzylidene)indolin-2-one (**S197**).



E/*Z*-S197

(*E*/*Z*)-3-(3-Methylbenzylidene)indolin-2-one (S197). Prepared using Method N from oxindole and *m*-tolualdehyde. The crude material was purified by column chromatography, eluting with 20–25% EtOAc/pet. ether, to give (*E*/*Z*)-**S197** (326 mg, 92%) as a yellow solid: mp 130–133 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.59 (s, 1H, NH), 7.59 (s, 1H, =CH), 7.49–7.53 (m, 3H, H-2', H-4', H-6'), 7.42 (dd obscured, *J* = 7.8 Hz, 1H, H-5'), 7.30 (d, *J* = 7.8 Hz, 1H, H-4), 7.23 (ddd, *J* = 7.8, 7.8, 1.1 Hz, 1H, H-6), 6.81–6.88 (m, 2H, H-5, H-7), 2.38 (s, 3H, Me); *Z*-isomer (minor) 10.59 (s, 1H, NH), 8.23 (d, *J* = 7.8 Hz, 1H, H-6'), 8.16 (s, 1H, H-2'), 7.76 (s, 1H, =CH), 7.70 (d, *J* = 7.6 Hz, 1H, H-4), 7.36 (d, *J* = 7.8, 7.8 Hz, 1H, H-5'), 7.19–7.26 (m, 2H, H-4, H-6), 6.99 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.81–6.88 (m, 1H, H-7), 2.36 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 168.6, 167.0, 142.9, 140.7, 138.0, 137.2, 136.9, 135.9, 134.4, 133.9, 132.5, 131.0, 130.3, 130.1, 129.7, 129.0, 128.9, 128.6, 128.1, 127.5, 126.6, 126.3, 124.9, 122.3, 121.1, 121.0, 120.9, 119.7, 110.1, 109.3, 21.0, 20.9; MS *m/z* 236.2 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.84; H, 5.62; N, 6.00%.

SN37771 (*E*)-3-(2,3-Dimethylbenzylidene)indolin-2-one (**S198**).



S198

(*E*)-3-(2,3-Dimethylbenzylidene)indolin-2-one (S198). Prepared using Method N from oxindole and 2,3-dimethylbenzaldehyde. The crude material was triturated in EtOAc/pet. ether to give **S198** (332 mg, 89%) as a yellow solid: mp 181–184 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.59 (s, 1H, NH), 7.71 (s, 1H, =CH), 7.34 (d, *J* = 7.3 Hz, 1H, H-6'), 7.27 (d, *J* = 7.3 Hz, 1H, H-4'), 7.16–7.22 (m, 2H, H-6, H-5'), 7.01 (d, *J* = 7.6 Hz, 1H, H-4), 6.85 (d, *J* = 7.6 Hz, 1H, H-7), 6.75 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 2.31 (s, 3H, Me-3'), 2.19 (s, 3H, Me-2'); ^{13}C NMR [$(CD_3)_2SO$] δ 168.3, 142.8, 137.1, 135.6, 135.0, 133.9, 130.7, 129.9, 128.4, 126.0, 125.5 (2), 121.1 (2), 110.0, 19.9, 16.0; MS *m/z* 250.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.84; H, 6.19; N, 5.66%.

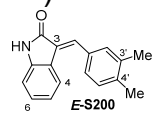
SN37797 (Z)-3-(1-(4-Methoxy-3-methylphenyl)ethylidene)indolin-2-one (**S199**).

1-(4-Methoxy-3-methylphenyl)ethan-1-one (S199a). Prepared using Method E from methyl iodide and 4-hydroxy-3-methylacetophenone. The crude residue was purified by column chromatography, eluting with 20% EtOAc/pet. ether, to give acetophenone **S199a**

(146 mg, 67%) as a colourless oil: ^{1}H NMR δ 7.81–7.84 (m, 1H, H-6), 7.77–7.78 (m, 1H, H-2), 6.85 (d, *J* = 8.5 Hz, 1H, H-5), 3.90 (s, 3H, OMe), 2.55 (s, 3H, MeCO), 2.25 (s, 3H, Me); MS *m/z* 165.2 (MH^+, 100%).

(*Z*)-3-(1-(4-Methoxy-3-methylphenyl)ethylidene)indolin-2-one (S199). Prepared using Method N from oxindole and acetophenone **S199a**. The crude material was purified by column chromatography, eluting with 20–25% EtOAc/pet. ether, to give alkene **S199** (67 mg, 27%) as orange crystals: mp 221–223 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.51 (s, 1H, NH), 7.13–7.18 (m, 2H, H-2', H-6'), 7.01–7.09 (m, 2H, H-6, H-5'), 6.76 (d, *J* = 7.6 Hz, 1H, H-7), 6.59 (dt, *J* = 7.6, 1.1 Hz, 1H, H-5), 6.22 (d, *J* = 7.6 Hz, 1H, H-4), 3.86 (s, 3H, OMe-3), 2.66 (s, 3H, =CMe), 2.18 (s, 3H, Me-3'); ^{13}C NMR [$(CD_3)_2SO$] δ 168.9 (C-2), 157.5 (C-4'), 154.1 (=C), 140.5 (C-7a), 134.2 (C-1'), 128.8 (C-2'), 128.0 (C-6), 126.3 (C-3'), 125.5 (C-6'), 123.2 (C-3), 123.0 (C-3a), 122.1 (C-4), 120.4 (C-5), 110.6 (C-5'), 109.2 (C-7), 55.4 (OMe-4'), 22.2 (=CMe), 16.0 (Me-3'); MS *m/z* 280.2 (MH^+, 100%). Anal. calcd for $C_{18}H_{17}NO_2 \cdot 0.15H_2O$: C, 76.65; H, 6.18; N, 4.97. Found: C, 76.65; H, 6.18; N, 4.94 %.

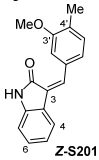
SN37798 (*E*)-3-(3,4-Dimethylbenzylidene)indolin-2-one (**S200**).



E-S200

(*E*)-3-(3,4-Dimethylbenzylidene)indolin-2-one (S200). Prepared using Method N from oxindole and 3,4-dimethylbenzaldehyde. The crude material was purified by column chromatography, eluting with 20–30% EtOAc/pet. ether to give **S200** (354 mg, 94%) as a yellow solid: mp 181–183 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.56 (s, 1H, NH), 7.59 (d, *J* = 7.6 Hz, 1H, H-4), 7.56 (s, 1H, =CH), 7.45–7.48 (m, 2H, H-2', H-6'), 7.29 (d, *J* = 7.7 Hz, 1H, H-5'), 7.22 (ddd, *J* =7.6, 7.6, 1.1 Hz, 1H, H-6), 6.83–6.88 (m, 2H, H-5, H-7), 2.30 (s, 3H, Me-4'), 2.29 (s, 3H, Me-3'); ^{13}C NMR [$(CD_3)_2SO$] δ 168.7, 142.8, 138.5, 136.7, 136.1, 131.9, 130.4, 129.9, 129.8, 126.8, 126.8, 122.2, 121.1, 110.1, 19.4, 19.3, (1 signal not observed); MS *m/z* 250.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.77; H, 6.16; N, 5.65%.

SN37799 (*Z*)-3-(3-Methoxy-4-methylbenzylidene)indolin-2-one (**S201**).

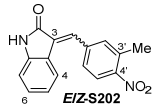


Z-S201

(*Z*)-3-(3-Methoxy-4-methylbenzylidene)indolin-2-one (S201). Prepared using Method N from oxindole and 3-methoxy-4-methylbenzaldehyde. The crude material was purified by column chromatography, eluting with 20–30% EtOAc/pet. ether, to give **S201** (288 mg, 72%) as a yellow solid: mp 225–227 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.58 (s, 1H, NH), 8.47 (d, *J* = 1.3 Hz, 1H, H-2'), 7.78 (s, 1H, =CH), 7.73 (dd, *J* = 7.7, 1.3 Hz, 1H, H-6'), 7.70 (d, *J* = 7.5 Hz, 1H, H-4), 7.24 (dd, *J* = 7.7, 0.6 Hz, 1H, H-5'), 7.20 (td, *J* = 7.5, 1.0 Hz, 1H, H-6), 6.99 (dt, *J* = 7.5, 1.0 Hz, 1H, H-5), 6.83 (d, *J* = 7.5 Hz, 1H, H-7), 3.87 (s, 3H, OMe-3'), 2.21 (s, 3H, Me-4'); ^{13}C NMR [$(CD_3)_2SO$] δ 167.3 (CONH), 156.9 (C-3'), 140.5 (C-7a), 137.3 (=CH), 133.2 (C-1'), 130.1 (C-5'), 129.1 (C-4'), 128.7 (C-6), 125.8 (C-3), 125.2 (C-6'), 125.2 (C-3a), 121.0 (C-5), 119.5 (C-4), 113.2 (C-2'), 109.3 (C-7), 55.2 (OMe-3'), 16.3

(Me-4'); MS *m/z* 266.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.91; H, 5.71; N, 5.36%.

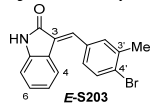
SN37800 (*E*/*Z*)-3-(3-Methyl-4-nitrobenzylidene)indolin-2-one (**S202**).



E/*Z*-**S202**

(*E*/*Z*)-3-(3-Methyl-4-nitrobenzylidene)indolin-2-one (S202). Prepared using Method N from oxindole and 3-methyl-4-nitrobenzaldehyde. The crude material was purified by column chromatography, eluting with 10% EtOAc/pet. ether, to give (*E*/*Z*)-**S202** (194 mg, 46%) as an orange solid: mp 202–205 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.68 (s, 1H, NH), 8.12 (d, *J* = 8.4 Hz, 1H, H-6'), 7.85 (s, 1H, H-2'), 7.76 (dd, *J* = 8.4, 1.8 Hz, 1H, H-5'), 7.60 (s, 1H, =CH), 7.40 (d, *J* = 7.7 Hz, 1H, H-4), 7.26 (d, *J* = 7.7, 7.7, 1.1 Hz, 1H, H-6), 6.86–6.90 (m, 2H, H-5, H-7), 2.58 (s, 3H, Me); *Z*-isomer (minor) 10.68 (s, 1H, NH), 8.37 (dd, *J* = 8.7, 2.3 Hz, 1H, H-6'), 8.30 (s, 1H, H-2'), 8.05 (d, *J* = 8.7 Hz, 1H, H-5'), 7.85 (s, 1H, =CH), 7.72–7.80 (m, 1H, H-4), 7.26 (d, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-6), 7.02 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.83–6.86 (m, 1H, H-7), 2.56 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 168.2, 166.8, 148.6 (2), 143.4, 141.4, 139.6, 138.5, 135.5, 133.5, 133.4, 133.3, 132.9, 132.3, 130.9, 130.0, 129.9, 129.8 (2), 127.7, 125.0, 124.2 (2), 122.8, 121.4, 121.3, 120.5, 120.4, 110.3, 109.6, 19.7, 19.6; MS *m/z* 281.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 296.1284 (calcd for $C_{18}H_{18}NO_3$, 296.1281). Anal. calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.50; H, 4.26; N, 10.07%.

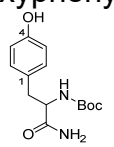
SN37801 (*E*)-3-(4-Bromo-3-methylbenzylidene)indolin-2-one (**S203**).



E-**S203**

(*E*)-3-(4-Bromo-3-methylbenzylidene)indolin-2-one (S203). Prepared using Method N from oxindole and 4-bromo-3-methylbenzaldehyde. The crude material was washed with pet. ether to give **S203** (391 mg, 83%) as a yellow solid: mp 194–197 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.62 (s, 1H, NH), 7.73 (d, *J* = 8.2 Hz, 1H, H-5'), 7.67 (d, *J* = 2.0 Hz, 1H, H-2'), 7.53 (s, 1H, =CH), 7.46–7.50 (m, 2H, H-4, H-6'), 7.24 (ddd, *J* = 7.7, 1.0 Hz, 1H, H-6), 6.84–6.88 (m, 2H, H-5, H-7), 2.41 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 168.5, 143.0, 137.9, 134.5, 134.0, 132.5, 131.8, 130.3, 128.4, 128.1, 125.4, 122.5, 121.3, 120.7, 110.2, 22.3; MS *m/z* 314.0, 316.0 (MH^+, 100%). Anal. calcd for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.46. Found: C, 61.34; H, 3.81; N, 4.46%.

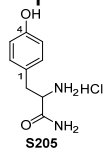
SN37836 *tert*-Butyl (1-Amino-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (**S204**).



***tert*-Butyl (1-Amino-3-(4-hydroxyphenyl)-1-oxopropan-2-yl)carbamate (S204).** Prepared using Method O from *(tert*-butoxycarbonyl)tyrosine. The crude mixture was purified by column chromatography, eluting with 70–80% EtOAc/pet. ether, to give carbamate **S204** (309 mg, 24%) as a white solid: mp 135–138 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.14 (s, 1H, OH), 7.29 (s, 1H, NH_2), 7.02 (d, *J* = 8.4 Hz, 2H, H-2, H-6), 6.96 (s, 1H, NH_2),

6.68 (d, *J* = 8.6 Hz, 1H, NH), 6.63 (d, *J* = 8.4 Hz, 2H, H-3, H-5), 3.99 (m, 1H, CH), 2.82 (dd, *J* = 13.8, 4.5 Hz, 1H, CH_2), 2.61 (dd, *J* = 13.8, 9.9 Hz, 1H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 173.8, 155.7, 155.2, 130.0 (2), 128.3, 114.8 (2), 77.8, 55.9, 36.7, 28.2 (3); MS *m/z* 279.2 ($M-H^-$, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 281.1494 (calcd for $C_{14}H_{21}N_2O_4$, 281.1496).

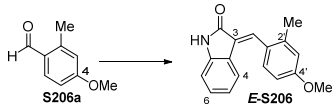
SN37837 2-Amino-3-(4-hydroxyphenyl)propanamide Hydrochloride (**S205**).



S205

2-Amino-3-(4-hydroxyphenyl)propanamide Hydrochloride (S205). Prepared using Method F from carbamate **S204** give phenol **S205** (161 mg, 93%) as a white solid: mp 243–246 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.38 (s, 1H, OH), 8.10 (br s, 3H, NH_3), 7.87 (s, 1H, NH_2), 7.50 (s, 1H, NH_2), 7.04–7.06 (m, 2H, H-2, H-6), 6.70–6.73 (m, 2H, H-3, H-5), 3.84 (m, 1H, CH), 2.98 (dd, *J* = 14.0, 6.1 Hz, 1H, CH_2), 2.87 (dd, *J* = 14.0, 7.4 Hz, 1H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 169.8, 156.5, 130.5 (2), 125.0, 115.3 (2), 53.7, 36.0; MS *m/z* 181.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 181.0971 (calcd for $C_9H_{13}N_2O_2$, 181.0972).

SN37838 (*E*)-3-(4-Methoxy-2-methylbenzylidene)indolin-2-one (**S206**).

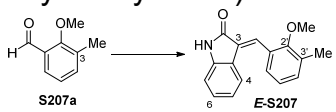


S206a ***E*-S206**

4-Methoxy-2-methylbenzaldehyde (S206a). Prepared using Method E from methyl iodide and 4-hydroxy-2-methylbenzaldehyde. The crude residue was purified by column chromatography, eluting with 10% EtOAc/pet. ether, to give aldehyde **S206a** (504 mg, 92%) as a colourless oil: ^{1}H NMR δ 10.12 (s, 1H, CHO), 7.76 (d, *J* = 8.6 Hz, 1H, H-6), 6.85 (d, *J* = 8.6, 2.4 Hz, 1H, H-5), 6.74 (d, *J* = 2.4 Hz, 1H, H-3), 3.87 (s, 3H, OMe), 2.65 (s, 3H, Me).

(*E*)-3-(4-Methoxy-2-methylbenzylidene)indolin-2-one (S206). Prepared using Method N from oxindole and aldehyde **S206a**. The alkene **S206** (396 mg, 90%) was obtained as a yellow solid: mp 173–176 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.56 (s, 1H, NH), 7.62 (s, 1H, =CH), 7.57 (d, *J* = 8.5 Hz, 1H, H-6'), 7.31 (d, *J* = 7.6 Hz, 1H, H-4), 7.19 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H, H-6), 6.95 (d, *J* = 2.6 Hz, 1H, H-3'), 6.90 (dd, *J* = 8.5, 2.6 Hz, 1H, H-5'), 6.86 (d, *J* = 7.4 Hz, 1H, H-7), 6.81 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H, H-5), 3.82 (s, 3H, OMe), 2.31 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 168.6, 160.3, 142.6, 139.4, 134.5, 130.1, 129.7, 126.8, 125.8, 122.1, 121.3, 121.0, 115.9, 111.3, 110.0, 55.2, 19.7; MS *m/z* 266.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 266.1175 (calcd for $C_{17}H_{16}NO_2$, 266.1176).

SN37839 (*E*)-3-(2-Methoxy-3-methylbenzylidene)indolin-2-one (**S207**).



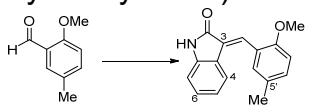
S207a ***E*-S207**

2-Methoxy-3-methylbenzaldehyde (S207a). Prepared using Method E from methyl iodide and 2-hydroxy-3- to give aldehyde **S207a** (396 mg, 90%) as a colourless oil: ^{1}H NMR δ 10.39 (d, *J* = 0.7 Hz, 1H, CHO), 7.68–7.71 (m, 1H, H-6), 7.44–7.46 (m, 1H, H-4),

7.45 (dd, *J* = 7.6, 7.6 Hz, 1H, H-5), 3.89 (s, 3H, OMe), 2.30 (s, 3H, Me); MS *m/z* 151.2 (MH^+, 100%).

(*E*)-3-(2-Methoxy-3-methylbenzylidene)indolin-2-one (S207). Prepared using Method N from oxindole and aldehyde **S207a**. The crude material was purified by column chromatography, eluting with 40–50% EtOAc/pet. ether, to give **S207** (393 mg, 94%) as a yellow solid: mp 160–162 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.62 (s, 1H, NH), 7.65 (s, 1H, =CH), 7.52 (d, *J* = 7.6 Hz, 1H, H-6'), 7.34–7.37 (m, 2H, H-4, H-4'), 7.22 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H, H-6), 7.17 (dd, *J* = 7.6, 7.6 Hz, 1H, H-5'), 6.87 (d, *J* = 7.7 Hz, 1H, H-7), 6.82 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H, H-5), 3.66 (s, 3H, OMe), 2.30 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 168.5, 157.1, 142.9, 132.9, 131.7, 131.3, 130.1, 128.2, 127.7, 127.6, 123.9, 122.5, 121.1, 121.0, 110.1, 61.0, 15.6; MS *m/z* 266.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 266.1174 (calcd for $C_{17}H_{16}NO_2$, 266.1176).

SN37840 (*E*)-3-(2-Methoxy-5-methylbenzylidene)indolin-2-one (**S208**).

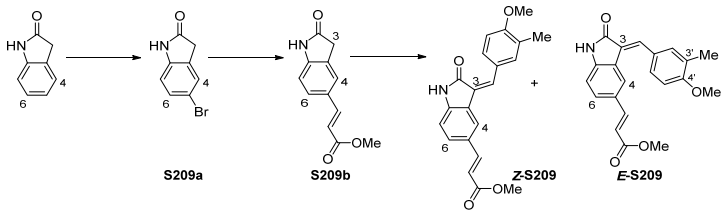


S208 ***E*-S208**

2-Methoxy-5-methylbenzaldehyde (S208a). Prepared using Method E from methyl iodide and 2-hydroxy-5-methylbenzaldehyde to give aldehyde **S208a** (417 mg, 95%) as a colourless oil: ^{1}H NMR δ 10.44 (s, 1H, CHO), 7.63 (d, *J* = 2.2 Hz, 1H, H-6), 7.34–7.37 (m, 1H, H-4), 6.89 (d, *J* = 8.5 Hz, 1H, H-3), 3.90 (s, 3H, OMe), 2.32 (s, 3H, Me); MS *m/z* 151.2 (MH^+, 100%).

(*E*)-3-(2-Methoxy-5-methylbenzylidene)indolin-2-one (S208). Prepared using Method N from oxindole and aldehyde **S208a**. The crude material was purified by column chromatography, eluting with 40–75% EtOAc/pet. ether, to give **S208** (341 mg, 93%) as a yellow solid: mp 244–247 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.56 (s, 1H, NH), 7.62 (s, 1H, =CH), 7.48 (d, *J* = 2.1 Hz, 1H, H-6'), 7.41 (d, *J* = 7.6 Hz, 1H, H-4), 7.29 (dd, *J* = 8.5, 2.1 Hz, 1H, H-4'), 7.21 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H, H-6), 7.05 (d, *J* = 8.5 Hz, 1H, H-3'), 6.82–6.87 (m, 2H, H-5, H-7), 3.82 (s, 3H, OMe), 2.29 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 168.6, 155.6, 142.7, 132.0, 131.8, 129.8, 129.7, 128.9, 127.2, 122.5, 122.2, 121.1 (2), 111.5, 110.0, 55.6, 19.9; MS *m/z* 266.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 266.1179 (calcd for $C_{17}H_{16}NO_2$, 266.1176).

SN37841 Methyl (*E*)-3-(3-((*E/Z*)-4-Methoxy-3-methylbenzylidene)-2-oxoindolin-5-yl)acrylate (**S209**).



S209a **S209b** ***Z*-S209** ***E*-S209**

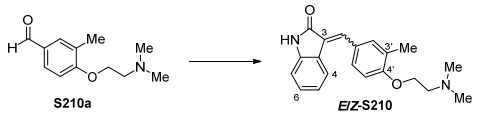
5-Bromooxindole (S209a). NBS (735 mg, 4.13 mmol) was added to a solution of oxindole (500 mg, 3.76) in MeCN (20 mL) at 0 °C. The reaction mixture was allowed to warm to 20 °C over 3 h. Solvent was removed and the residue triturated in EtOAc to

obtain the bromide **S209a** (634 mg, 80%) as a white solid: ^{1}H NMR [$(CD_3)_2SO$] δ 10.47 (s, 1H, NH), 7.38 (m, 1H, H-4), 7.32–7.35 (m, 1H, H-6), 6.76 (d, *J* = 8.2 Hz, 1H, H-7), 3.50 (s, 2H, CH_2); MS *m/z* 210.2, 212.0 ($M\text{-}H^-$, 100%).

Methyl (*E*)-3-(2-Oxoindolin-5-yl)acrylate (S209b). Bromooxindole **S209a** (225 mg, 1.06 mmol), $Pd(OAc)_2$ (36 mg, 0.16 mmol) and tri(*o*-tolyl)phosphine (65 mg, 0.21 mmol) were stirred in dioxane (5 mL) while purged with N_2 for 10 min. Methyl acrylate (144 µL, 1.59 mmol) and TEA (441 µL, 3.18 mmol) were added and purged with N_2 for another 15 min. The resulting mixture was heated to 120 °C for 5 h. Once cooled, the reaction mixture was diluted with EtOAc (50 mL), washed with water (50 mL), brine (50 mL), dried and concentrated. The crude residue was purified by column chromatography, eluting with 10–20% EtOAc/DCM, to give **S209b** (138 mg, 60%) as a white solid: mp 215–218 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.61 (s, 1H, NH), 7.61 (d obscured, *J* = 16.0 Hz, 1H, =CH), 7.61 (s obscured, 1H, H-4), 7.52 (d, *J* = 8.0 Hz, 1H, H-6), 6.84 (d, *J* = 8.0 Hz, 1H, H-7), 6.47 (d, *J* = 16.0 Hz, 1H, =CHCO), 3.70 (s, 3H, OMe), 3.51 (s, 2H, CH_2); MS *m/z* 218.2 (MH^+, 100%).

Methyl (*E*)-3-(3-((*E/Z*)-4-Methoxy-3-methylbenzylidene)-2-oxoindolin-5-yl)acrylate (S209). Prepared using Method N from oxindole **S209b** and 3-methyl-*p*-anisaldehyde. The resulting yellow solid was removed by filtration, washed with EtOH and dried to give **S209** (34 mg, 90%) as a yellow solid: mp 273–276 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.83 (s, 1H, NH), 7.95 (d, *J* = 1.2 Hz, 1H, H-4), 7.62–7.67 (m, 4H, =CH, H-6, H-2', H-6'), 7.56 (d, *J* = 16.0 Hz, 1H, =CH-3), 7.15 (d, *J* = 8.5 Hz, 1H, H-5'), 6.92 (d, *J* = 8.1 Hz, 1H, H-7), 6.27 (d, *J* = 16.0 Hz, 1H, =CHCO), 3.90 (s, 3H, OMe-4'), 3.70 (s, 3H, OMe), 2.23 (s, 3H, Me); *Z*-isomer (minor) 10.83 (s, 1H, NH), 8.41 (dd, *J* = 8.7, 1.8 Hz, 1H, H-6'), 8.33 (d, *J* = 1.8 Hz, 1H, H-2'), 8.19 (d, *J* = 1.4 Hz, 1H, H-4), 7.89 (s, 1H, =CH-3), 7.62–7.67 (m, 1H, =CH), 7.49 (dd, *J* = 8.0, 1.4 Hz, 1H, H-6), 7.09 (d, *J* = 8.7 Hz, 1H, H-5'), 6.84 (d, *J* = 8.0 Hz, 1H, H-7), 6.62 (d, *J* = 16.0 Hz, 1H, =CHCO), 3.89 (s, 3H, OMe-4'), 3.72 (s, 3H, OMe), 2.20 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 169.0, 167.5, 167.0, 166.7, 159.8, 159.1, 145.2, 144.9, 144.6, 142.2, 138.4, 137.7, 134.9, 132.7, 132.1, 130.5, 130.1, 129.7, 127.1, 126.9, 126.5, 126.3, 126.0, 125.9, 125.3, 124.4, 122.8, 121.9, 121.5, 118.2, 114.7, 114.6, 110.6, 110.3, 110.2, 109.2, 55.6 (2), 51.4, 51.3, 16.1, 15.8; MS *m/z* 350.2 (MH^+, 100%). Anal. calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 71.90; H, 5.37; N, 4.00%.

SN37847 (*E*/*Z*)-3-(4-(2-(Dimethylamino)ethoxy)-3-methylbenzylidene)indolin-2-one (**S210**).

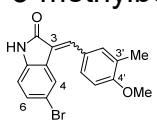


4-(2-(Dimethylamino)ethoxy)-3-methylbenzaldehyde (S210a). Prepared using Method E from 4-hydroxy-3-methylbenzaldehyde and 2-(dimethylamino)ethylchloride hydrochloride. The crude residue was purified by column chromatography, eluting with 3% MeOH/DCM, to give aldehyde **S210a** (92 mg, 30%) as a yellow oil: ^{1}H NMR δ 9.85 (s, 1H, CHO), 7.68–7.71 (m, 2H, H-2, H-6), 6.92 (d, *J* = 8.4 Hz, 1H, H-5), 4.17 (t, *J* = 5.8

Hz, 2H, OCH_2), 2.81 (t, *J* = 5.8 Hz, 2H, CH_2N), 2.37 (s, 6H, NMe_2), 2.27 (s, 3H, Me-3); MS *m/z* 208.2 (MH^+, 100%).

(*E*/*Z*)-3-(4-(2-(Dimethylamino)ethoxy)-3-methylbenzylidene)indolin-2-one (S210). Prepared using Method N from oxindole and aldehyde **S210a**. The crude material was purified by column chromatography, eluting with 8–20% MeOH/DCM, to give **S210** (102 mg, 73%) as a yellow-orange gum: ^1H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.53 (s, 1H, NH), 7.65–7.70 (m, 1H, H-4), 7.59 (dd, *J* = 8.5, 2.0 Hz, 1H, H-6'), 7.54 (m, 2H, =CH, H-2'), 7.20 (ddd, *J* = 7.7, 1.0 Hz, 1H, H-6), 7.11 (d, *J* = 8.5 Hz, 1H, H-5'), 6.85–6.89 (m, 2H, H-5, H-7), 4.14–4.17 (m, 2H, OCH_2), 2.70–2.72 (m, 2H, CH_2N), 2.26 (s, 6H, Me), 2.21 (s, 3H, Me); *Z*-isomer (minor) 10.53 (s, 1H, NH), 8.39 (dd, *J* = 8.7, 1.9 Hz, 1H, H-6'), 8.30 (d, *J* = 1.9 Hz, 1H, H-2'), 7.65–7.70 (m, 2H, H-4, =CH), 7.17 (ddd, *J* = 7.6, 1.0 Hz, 1H, H-6), 7.06 (d, *J* = 8.7 Hz, 1H, H-5'), 6.97 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.81 (d, *J* = 7.6 Hz, 1H, H-7), 4.14–4.17 (m, 2H, OCH_2), 2.70–2.72 (m, 2H, CH_2N), 2.26 (s, 6H, Me), 2.19 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 168.9, 167.3, 158.7, 158.0, 142.6, 140.2, 137.1, 136.3, 134.8, 132.4, 132.0, 129.6, 129.1, 128.1, 126.6, 126.2, 125.4 (3), 125.3, 123.8, 122.0, 121.2, 121.0, 120.8, 119.1, 111.3, 110.9, 110.0, 109.1, 66.3 (2), 57.6 (2), 45.6 (4), 16.1, 15.9; MS *m/z* 323.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 345.1565 (calcd for $C_{20}H_{22}N_2NaO_2$, 345.1573).

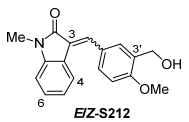
SN37883 (*E*/*Z*)-5-Bromo-3-(4-methoxy-3-methylbenzylidene)indolin-2-one (**S211**).



E/*Z*-S211

(*E*/*Z*)-5-Bromo-3-(4-methoxy-3-methylbenzylidene)indolin-2-one (S211). Prepared using Method N from oxindole **S209a** and 3-methyl-*p*-anisaldehyde. The crude residue was purified by column chromatography, eluting in 30–60% EtOAc/pet. ether, to give the product (*E*/*Z*)-**S211** (77 mg, 47%) as a yellow solid: mp 171–174 °C; ^1H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.70 (s, 1H, NH), 7.74 (d, *J* = 1.9 Hz, 1H, H-4), 7.59–7.62 (m, 2H, =CH, H-6'), 7.54 (m, 1H, H-2'), 7.40 (dd, *J* = 8.3, 1.9 Hz, 1H, H-6), 7.12 (d, *J* = 8.5 Hz, 1H, H-5'), 6.84 (d, *J* = 8.3 Hz, 1H, H-7), 3.89 (s, 3H, OMe), 2.21 (s, 3H, Me); *Z*-isomer (minor) 10.67 (s, 1H, NH), 8.41 (dd, *J* = 8.2, 1.8 Hz, 1H, H-6'), 8.35 (d, *J* = 1.8 Hz, 1H, H-2'), 7.91 (d, *J* = 1.9 Hz, 1H, H-4), 7.85 (s, 1H, =CH), 7.32 (8.2, 1.9 Hz, 1H, H-6), 7.07 (d, *J* = 8.2 Hz, 1H, H-5'), 6.77 (d, *J* = 8.2 Hz, 1H, H-7), 3.88 (s, 3H, OMe), 2.19 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 179.4, 168.5, 167.0, 159.9, 159.1, 141.7, 139.1, 138.2, 135.0, 133.0, 132.1, 131.8, 130.2, 129.3, 127.9, 126.4, 126.2, 125.7, 125.3, 124.4, 124.2, 123.4, 122.5, 121.9, 112.9, 112.5, 111.8, 111.0, 110.5, 110.1, 55.6 (2), 16.1, 15.8; MS *m/z* 344.1, 346.0 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 344.0287 (calcd for $C_{17}H_{15}BrNO_2$, 344.0281).

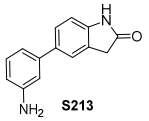
SN37884 (*E*/*Z*)-3-(3-(Hydroxymethyl)-4-methoxybenzylidene)-1-methylindolin-2-one (**S212**).



E/*Z*-S212

(*E*/*Z*)-3-(3-(Hydroxymethyl)-4-methoxybenzylidene)-1-methylindolin-2-one (S212). Prepared using Method E from methyl iodide and alcohol **S185**. The crude residue was purified by column chromatography, eluting in 40% EtOAc/pet. ether, to give the product (*E*/*Z*)-**S212** (66 mg, 59%) as a yellow solid: mp 173–176 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 7.84–7.85 (m, 1H, H-2'), 7.76–7.79 (m, 1H, H-4), 7.68 (s, 1H, =CH), 7.65 (dd, *J* = 8.5, 2.2 Hz, 1H, H-6'), 7.32 (ddd, *J* = 7.7, 7.7, 1.0 Hz, 1H, H-6), 7.12 (d, *J* = 8.5 Hz, 1H, H-5'), 7.03–7.07 (m, 1H, H-7), 6.95 (ddd, *J* = 7.7, 7.7, 1.0 Hz, 1H, H-5), 5.17 (t, *J* = 5.5 Hz, 1H, OH), 4.55 (d, *J* = 5.5 Hz, 2H, CH_2), 3.87 (s, 3H, OMe), 3.21 (s, 3H, NMe); *Z*-isomer (minor) 8.65 (dd, *J* = 8.7, 2.1 Hz, 1H, H-2'), 8.40 (d, *J* = 2.1 Hz, 1H, H-6'), 7.84 (s, 1H, =CH), 7.76–7.79 (m, 1H, H-4), 7.27 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H, H-6), 7.03–7.09 (m, 2H, H-5, H-5'), 6.99 (d, *J* = 7.7 Hz, 1H, H-7), 5.08 (t, *J* = 5.5 Hz, 1H, OH), 4.52 (d, *J* = 5.5 Hz, 1H, CH_2), 3.87 (s, 3H, OMe), 3.23 (s, 3H, NMe); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 167.6, 165.5, 158.3, 157.4, 143.8, 141.4, 137.7, 137.0, 132.8, 132.3, 130.8, 130.4, 130.1, 129.6, 128.2, 128.1, 126.5, 126.0, 124.4, 124.3, 122.7, 122.0, 121.6, 121.5, 120.5, 118.9, 110.5, 110.0, 108.7, 108.1, 57.8, 57.6, 55.6 (2), 26.0; MS *m/z* 350.2 (MH^+, 100%). Anal. calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 71.90; H, 5.37; N, 4.00%.

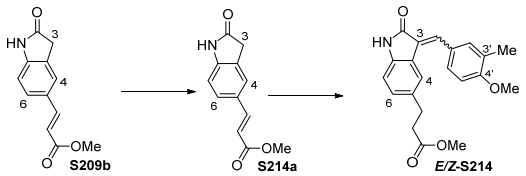
SN37943 5-(3-Aminophenyl)indolin-2-one (**S213**).



S213

5-(3-Aminophenyl)indolin-2-one (S213). Prepared using Method A from bromide **209a** and 3-aminophenylboronic acid. The crude residue was purified by column chromatography, eluting with 70–80% EtOAc/pet. ether, to give product **S213** (30 mg, 28%) as a yellow solid: mp 182–183 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.40 (s, 1H, NH), 7.38 (s, 1H, H-4), 7.35 (dd, *J* = 8.0, 1.8 Hz, 1H, H-6), 7.05 (dd, *J* = 7.8 Hz, 1H, H-5'), 6.85 (d, *J* = 8.0 Hz, 1H, H-7), 6.76 (dd, *J* = 1.9, 1.9 Hz, 1H, H-2'), 6.69–6.71 (m, 1H, H-6'), 6.48–6.51 (m, 1H, H-4'), 5.09 (s, 2H, NH_2), 3.52 (s, 2H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 176.4, 149.0, 142.9, 141.1, 134.4, 129.3, 126.4, 125.6, 122.6, 113.9, 112.5, 111.7, 109.2, 35.9; MS *m/z* 225.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 225.1023 (calcd for $C_{14}H_{13}N_2O$, 225.1022).

SN37944 Methyl (*E/Z*)-3-(3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-5-yl)propanoate (**S214**).

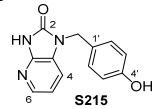


S209b **S214a** ***E/Z*-S214**

Methyl 3-(2-Oxoindolin-5-yl)propanoate (S214a). Prepared by Method M from alkene **S209b** to give oxindole **S214a** (79 mg, 92%) as a white solid: mp 145–147 °C; ^{1}H NMR δ 7.52 (s, 1H, NH), 7.08 (s, 1H, H-4), 7.03–7.06 (m, 1H, H-6), 6.77 (d, *J* = 7.9 Hz, 1H, H-7), 3.67 (s, 3H, OMe), 3.50 (s, 2H, CH_2), 2.91 (t, *J* = 7.7 Hz, 1H, CH_2), 2.61 (t, *J* = 7.7 Hz, 1H, CH_2CO); MS *m/z* 220.2 (MH^+, 100%).

Methyl (*E/Z*)-3-(3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-5-yl)propanoate (S214). Prepared using Method N from oxindole **S214a** and 3-methyl-p-anisaldehyde. The crude residue was purified by column chromatography, eluting with 40–50% EtOAc/pet. ether, to give the product (*E/Z*)-**S214** (69 mg, 87%) as a yellow solid: mp 152–154 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.45 (s, 1H, NH), 7.55–7.61 (m, 3H, H-4, H-2', H-6'), 7.52 (s, 1H, =CH), 7.06–7.11 (m, 2H, H-6, H-5'), 6.78 (d, *J* = 7.9 Hz, 1H, H-7), 3.88 (s, 3H, OMe-4'), 3.52 (s, 3H, OMe), 2.73 (t, *J* = 7.4 Hz, 2H, CH_2), 2.55 (t, *J* = 7.4 Hz, 2H, CH_2CO), 2.22 (s, 3H, Me); *Z*-isomer (minor) δ 10.45 (s, 1H, NH), 8.39 (dd, *J* = 8.6, 2.0 Hz, 1H, H-6'), 8.32 (d, *J* = 2.0 Hz, 1H, H-2'), 7.68 (s, 1H, =CH), 7.55–7.61 (m, 1H, H-4), 7.01–7.07 (m, 2H, H-6, H-5'), 6.72 (d, *J* = 7.9 Hz, 1H, H-7), 3.87 (s, 3H, OMe-4'), 3.59 (s, 3H, OMe), 2.83 (t, *J* = 7.7 Hz, 2H, CH_2), 2.65 (t, *J* = 7.7 Hz, 2H, CH_2CO), 2.19 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 172.7, 172.6, 169.0, 167.5, 159.4, 158.8, 140.9, 138.5, 136.9, 136.1, 134.7, 132.9, 132.9, 132.4, 131.9, 129.5, 129.4, 128.0, 126.6, 126.1, 126.0, 125.5, 125.3, 125.2, 123.9, 122.0, 121.3, 119.0, 110.5, 110.1, 109.8, 108.9, 55.5 (2), 51.3, 51.2, 35.3, 35.1, 30.2, 30.0, 16.1; MS *m/z* 352.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 352.1546 (calcd for $C_{21}H_{22}NO_4$, 352.1543).

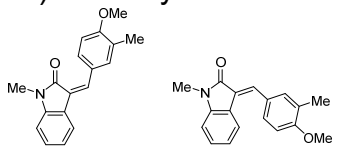
SN37988 1-(4-Hydroxybenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (**S215**).



S215

1-(4-Hydroxybenzyl)-1,3-dihydro-2*H*-imidazo[4,5-b]pyridin-2-one (S215). A solution of BBr_3 (330 µL, 3.51 mmol) in CH_2Cl_2 (5 mL) was slowly added to a stirred suspension of **S172** (448 mg, 1.76 mmol) in CH_2Cl_2 (15 mL) at -78 °C. The resulting mixture was allowed to warm to 20 °C over 17 h. The resulting mixture was cooled to 0 °C, quenched with MeOH, diluted with CH_2Cl_2 (30 mL) and washed with sat. $NaHCO_3$ (50 mL), followed by brine (50 mL). The organic layer was dried, concentrated under reduced pressure and triturated with EtOAc/pet. ether to obtain phenol **S215** (429 mg, quant.) as a pale brown solid: mp 203–206 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 11.64 (s, 1H, NH-1), 7.88 (dd, *J* = 5.3, 1.4 Hz, 1H, H-6), 7.35 (dd, *J* = 7.8, 1.4 Hz, 1H, H-4), 7.16 (ddd, *J* = 8.6, 2.8, 2.0 Hz, 2H, H-2', H-6'), 6.97 (dd, *J* = 7.8, 5.3 Hz, 1H, H-5), 6.70 (ddd, *J* = 8.6, 2.8, 2.0 Hz, 2H, H-3', H-5'), 4.88 (s, 2H, CH_2); ^{13}C NMR [$(CD_3)_2SO$] δ 156.9 (C-4'), 153.5 (C-2), 143.0 (C-7a), 138.6 (C-6), 129.0 (C-2', C-6'), 126.7 (C-1'), 124.5 (C-3a), 116.7 (C-5), 115.3 (C-3', C-5'), 114.8 (C-4), 42.8 (CH_2); MS *m/z* 242.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 242.0927 (calcd for $C_{13}H_{11}N_3O_2$, 242.0924).

SN37989 (*Z*)-3-(4-Methoxy-3-methylbenzylidene)-1-methylindolin-2-one (**S216**) and (*E*)-3-(4-Methoxy-3-methylbenzylidene)-1-methylindolin-2-one (**9**).

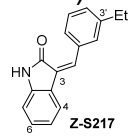


***Z*-S216** ***E*-9**

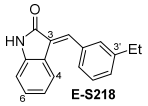
(*Z*)-3-(4-Methoxy-3-methylbenzylidene)-1-methylindolin-2-one (S216) and (*E*)-3-(4-Methoxy-3-methylbenzylidene)-1-methylindolin-2-one (9). Prepared using Method E from methyl iodide and indolin-2-one **3**. The crude residue was purified by column chromatography, eluting with DCM to give *Z*-**S216** (32 mg, 15%) as a yellow solid: mp

118–120 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 8.37–8.40 (m, 2H, H-2', H-6'), 7.77 (s, 1H, =CH), 7.72 (d, *J* = 7.5 Hz, 1H, H-4), 7.27 (ddd, *J* = 7.5, 7.5, 1.1 Hz, 1H, H-6), 7.03–7.07 (m, 2H, H-5, H-5'), 6.99 (d, *J* = 7.5 Hz, 1H, H-7), 3.88 (s, 3H, OMe), 3.22 (s, 3H, NMe), 2.20 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 165.5, 159.6, 141.3, 137.4, 134.7, 132.7, 128.1, 126.5, 125.2, 124.3, 122.6, 121.5, 118.8, 110.1, 108.1, 55.5, 25.8, 16.1; (+)-HRESIMS *m/z* $[M+H]^+$ 280.1341 (calcd for $C_{18}H_{18}NO_2$, 280.1332). Further elution with 5% EtOAc/DCM gave *E*-**9** (86 mg, 39%) as a yellow solid: mp 89–91 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 7.71 (d, *J* = 7.6 Hz, 1H, H-4), 7.62–7.64 (m, 2H, =CH, H-6'), 7.54–7.55 (m, 1H, H-2'), 7.32 (td, *J* = 7.6, 1.0 Hz, 1H, H-6), 7.11 (d, *J* = 8.5 Hz, 1H, H-5'), 7.04 (d, *J* = 7.6 Hz, 1H, H-7), 6.96 (td, *J* = 7.6, 1.0 Hz, 1H, H-5), 3.88 (s, 3H, OMe), 3.21 (s, 3H, NMe), 2.21 (s, 3H, Me); MS *m/z* 280.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 280.1338 (calcd for $C_{18}H_{18}NO_2$, 280.1332).

SN37991 (*Z*)-3-(3-Ethylbenzylidene)indolin-2-one (**S217**) and SN37992 (*E*)-3-(3-Ethylbenzylidene)indolin-2-one (**S218**).



Z-S217

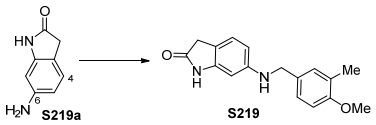


E-S218

(*Z*)-3-(3-Ethylbenzylidene)indolin-2-one (S217). Prepared using Method N from oxindole and 3-ethylbenzaldehyde. The crude material was purified by column chromatography, with the *Z* isomer eluting with 20% EtOAc/pet. ether to give *Z*-**S217** (41mg, 11%) as a yellow solid: mp 121–123 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.58 (s, 1H, NH), 8.24 (d, *J* = 7.8 Hz, 1H, H-6'), 8.21 (s, 1H, H-2'), 7.79 (s, 1H, =CH), 7.70 (d, *J* = 7.6 Hz, 1H, H-4), 7.38 (dd, *J* = 7.8, 7.8 Hz, 1H, H-5'), 7.30 (d, *J* = 7.8 Hz, 1H, H-4'), 7.21 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-6), 6.99 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.82 (d, *J* = 7.6 Hz, 1H, H-7), 2.66 (q, *J* = 7.6 Hz, 2H, CH_2), 1.23 (t, *J* = 7.6 Hz, 1H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 167.1, 143.5, 140.7, 137.0, 134.0, 131.4, 130.0, 129.3, 128.9, 128.1, 126.5, 125.0, 121.0, 119.7, 109.3, 28.1, 15.5; MS *m/z* 250.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.79; H, 5.81; N, 5.63%. Further elution with 20–30% EtOAc/pet. ether gave *E*-**S218** (284 mg, 76%) as a yellow-orange solid: mp 99–101 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.59 (s, 1H, NH), 7.61 (s, 1H, =CH), 7.50–7.54 (m, 3H, H-4, H-2', H-6'), 7.44 (dd, *J* = 7.6 Hz, 1H, H-5'), 7.32 (d, *J* = 7.6 Hz, 1H, H-4'), 7.22 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H, H-6), 6.82–6.88 (m, 2H, H-5, H-7), 2.68 (q, *J* = 7.6 Hz, 1H, CH_2), 1.22 (t, *J* = 7.6 Hz, 3H, CH_3); ^{13}C NMR [$(CD_3)_2SO$] δ 168.6, 144.2, 142.9, 136.0, 134.4, 130.1, 129.3, 128.7, 128.6, 127.5, 126.6, 122.3, 121.0, 120.9, 110.1, 28.0, 15.4; MS *m/z* 250.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.95; H, 5.95; N, 5.62%.

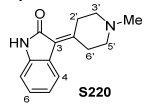
SN37993 6-((4-Methoxy-3-methylbenzyl)amino)indolin-2-one (**S219**).

6-Aminoindolin-2-one (S219a). 2,3-Dinitrophenyl acetic acid (5.09 g, 22.49 mmol) and 10% Pd/C (509 mg, 10% wt. of nitro) were stirred in AcOH (20 mL) at r.t. under H_2 (40 psi) overnight (26 h). The catalyst was removed by filtration over diatomaceous earth, washed with EtOAc and concentrated to a dark green-brownish gum. The residue was triturated in EtOAc to obtain amine **S219a** (2.69, 81%) as a dark grey solid: mp 197–200 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.07 (s, 1H, NH), 6.78–6.80 (m, 1H, H-7), 6.09–6.12 (m, 2H, H-4, H-5), 5.00 (s, 2H, NH_2), 3.23 (s, 2H, CH_2); MS *m/z* 149.2 (MH^+, 100%).



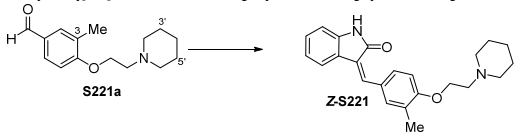
6-((4-Methoxy-3-methylbenzyl)amino)indolin-2-one (S219). Prepared using Method P from 6-aminooxindole **S219a** and 3-methyl-p-anisaldehyde. The crude residue was purified by column chromatography, eluting in 40–70% EtOAc/pet. ether, to give the amine **S219** (127 mg, 31%) as a yellow solid: mp 163–166 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.06 (s, 1H, NH), 7.09–7.11 (m, 2H, H-2', H-6'), 6.82–6.86 (m, 2H, H-4, H-5'), 6.09–6.13 (m, 3H, H-5, H-7, NH), 4.11 (d, *J* = 5.9 Hz, 1H, $NHCH_2$), 3.74 (s, 3H, OMe), 3.23 (s, 2H, CH_2), 2.12 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 177.2, 156.1, 148.7, 144.3, 131.5, 129.3, 125.6, 125.2, 124.5, 112.1, 110.0, 105.0, 94.5, 55.2, 46.1, 35.1, 16.1; MS *m/z* 283.2 (MH^+, 100%). Anal. calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.04; H, 6.71; N, 9.98%.

SN37994 3-(1-Methylpiperidin-4-ylidene)indolin-2-one (**S220**).



3-(1-Methylpiperidin-4-ylidene)indolin-2-one (S220). Prepared using Method N from oxindole and *N*-methyl-piperidine. The crude material was purified by column chromatography, eluting with 6–10% MeOH/DCM, to give **S220** (37 mg, 22%) as a yellow solid: mp 161–164 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.45 (s, 1H, NH), 7.61 (d, *J* = 7.7 Hz, 1H, H-7), 7.16 (ddd, *J* = 7.7, 7.7, 0.9 Hz, 1H, H-6), 6.92 (ddd, *J* = 7.7, 7.7, 0.9 Hz, 1H, H-5), 6.80 (dd, *J* = 7.7, 7.7, 0.9 Hz, 1H, H-4), 3.81 (t, *J* = 5.8 Hz, 2H, H_2-2'), 2.92 (t, *J* = 6.1 Hz, 2H, H_2-6'), 2.53 (t obscured, *J* = 6.1 Hz, 2H, H_2-5'), 2.45 (t, *J* = 5.8 Hz, 2H, H_2-3'), 2.21 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 168.8, 157.0, 140.6, 127.9, 123.7, 123.1, 120.9 (2), 109.2, 55.7, 55.4, 45.4, 31.3, 28.2; MS *m/z* 229.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 229.1334 (calcd for $C_{14}H_{17}N_2O$, 229.1335).

SN38047 (*Z*)-3-(3-Methyl-4-(2-(piperidin-1-yl)ethoxy)benzylidene)indolin-2-one (**S221**).

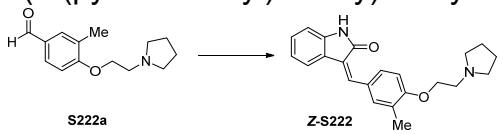


3-Methyl-4-(2-(piperidin-1-yl)ethoxy)benzaldehyde (S221a). Prepared using Method E from 4-hydroxy-3-methylbenzaldehyde and 1-(2-chloroethyl)piperidine hydrochloride to give aldehyde **S221a** (183 mg, quant.) as an orange oil: ^{1}H NMR δ 9.85 (s, 1H, CHO), 7.68–7.70 (m, 2H, H-2, H-6), 6.91 (d, *J* = 8.9 Hz, 1H, H-5), 4.20 (t, *J* = 6.0 Hz, 2H, OCH_2), 2.84 (t, *J* = 6.0 Hz, 2H, CH_2N), 2.53–2.55 (m, 4H, CH_2-2', CH_2-6'), 2.26 (s, 3H, Me), 1.58–1.64 (m, 4H, CH_2-3', CH_2-5'), 1.42–1.48 (m, 2H, CH_2-4'); MS *m/z* 248.2 (MH^+, 100%).

(*Z*)-3-(3-Methyl-4-(2-(piperidin-1-yl)ethoxy)benzylidene)indolin-2-one (S221). Prepared using Method N from oxindole and aldehyde **221a**. The crude material was purified by column chromatography, eluting with 0–10% MeOH/EtOAc, to give **S221** (152 mg, 69%) as a yellow solid: mp 170–172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.54 (s, 1H, NH), 8.39 (d, *J* = 8.7, 2.0 Hz, 1H, H-6'), 8.30 (d, *J* = 2.0 Hz, 1H, H-2'), 7.69 (s, 1H, =CH), 7.65 (d, *J* = 7.6 Hz, 1H, H-4), 7.17 (ddd, *J* = 7.6, 7.6, 0.9 Hz, 1H, H-6), 7.05 (d, *J* = 8.7 Hz, 1H, H-5'), 6.97 (ddd, *J* = 7.6, 7.6, 0.9 Hz, 1H, H-5), 6.81 (d, *J* = 7.6 Hz, 1H, H-7), 4.17 (t, *J* =

5.8 Hz, 2H, OCH_2), 2.71 (t, *J* = 5.8 Hz, 2H, CH_2N), 2.45–2.48 (m, 4H, CH_2-2", CH_2-6"), 2.18 (s, 3H, Me), 1.47–1.53 (m, 4H, CH_2-3", CH_2-5"), 1.36–1.40 (m, 2H, CH_2-4"); ^{13}C NMR [$(CD_3)_2SO$] δ 167.3, 158.8, 140.2, 137.1, 134.8, 132.4, 128.1, 126.5, 125.4, 125.3, 123.7, 120.8, 119.1, 110.9, 109.1, 66.3, 57.3, 54.4 (2), 25.7 (2), 23.9, 16.1; MS *m/z* 363.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 363.2071 (calcd for $C_{23}H_{27}N_2O_2$, 363.2067).

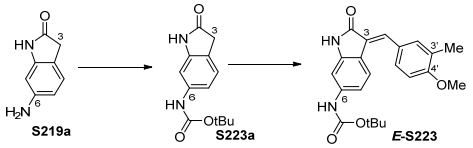
SN38048 (*Z*)-3-(3-Methyl-4-(2-(pyrrolidin-1-yl)ethoxy)benzylidene)indolin-2-one (**S222**).



3-Methyl-4-(2-(pyrrolidin-1-yl)ethoxy)benzaldehyde (S222a). Prepared using Method E from 4-hydroxy-3-methylbenzaldehyde and 1-(2-chloroethyl)pyrrolidine to give aldehyde **S222a** (178 mg, quant) as an orange oil: ^1H NMR δ 9.85 (s, 1H, CHO), 7.68–7.71 (m, 2H, H-2, H-6), 6.92 (m, 1H, H-5), 4.21 (t, *J* = 5.9 Hz, 2H, OCH_2), 2.97 (t, *J* = 5.9 Hz, 2H, CH_2N), 2.64–2.69 (m, 4H, CH_2-2', CH_2-5'), 2.27 (s, 3H, Me), 1.80–1.83 (m, 4H, CH_2-3', CH_2-4').

(*Z*)-3-(3-Methyl-4-(2-(pyrrolidin-1-yl)ethoxy)benzylidene)indolin-2-one (S222). Prepared using Method N from oxindole and aldehyde **S222a**. The crude material was purified by column chromatography, eluting with 5–10% MeOH/EtOAc, to give **S222** (28 mg, 13%) as a yellow solid: mp 168–171 °C; ^1H NMR [$(CD_3)_2SO$] δ 10.53 (s, 1H, NH), 8.39 (dd, *J* = 8.7, 2.1 Hz, 1H, H-6'), 8.30 (d, *J* = 2.1 Hz, 1H, H-2'), 7.70 (s, 1H, =CH), 7.66 (d, *J* = 7.6 Hz, 1H, H-4), 7.16 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-6), 7.05 (d, *J* = 8.7 Hz, 1H, H-5'), 6.97 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.81 (d, *J* = 7.6 Hz, 1H, H-7), 4.18 (t, *J* = 5.8 Hz, 2H, OCH_2), 2.84 (t, *J* = 5.8 Hz, 2H, CH_2N), 2.54–2.57 (m, 4H, CH_2-2", CH_2-5"), 2.19 (s, 3H, Me), 1.67–1.71 (m, 4H, CH_2-3", CH_2-4"); ^{13}C NMR [$(CD_3)_2SO$] δ 167.3, 158.7, 140.2, 137.1, 134.8, 132.4, 128.1, 126.5, 125.4, 125.3, 123.7, 120.8, 119.1, 110.8, 109.1, 67.4, 54.2 (3), 23.2 (2), 16.1; MS *m/z* 349.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 349.1919 (calcd for $C_{22}H_{25}N_2O_2$, 349.1911).

SN38049 *tert*-Butyl (*E*)-(3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)carbamate (**S223**).

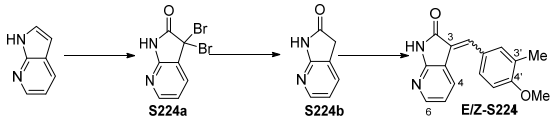


***tert*-Butyl (2-Oxoindolin-6-yl)carbamate (S223a).** Prepared using Method K from oxindole **S219a** to give carbamate **S223a** (287 mg, 43%) as a pale pink solid: mp 214 °C (decomp.); ^1H NMR [$(CD_3)_2SO$] δ 10.29 (s, 1H, NH), 9.30 (s, 1H, NH-Boc), 7.16 (s, 1H, H-7), 7.03 (d, *J* = 8.1 Hz, 1H, H-4), 6.91 (d, *J* = 8.1, 1.9 Hz, 1H, H-5), 3.36 (s, 2H, CH_2), 1.47 (s, 9H, *t*Bu); MS *m/z* 247.2 ($M-H^-$, 100%).

***tert*-Butyl (*E*)-(3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)carbamate (S223).** Prepared using Method N from oxindole **S223a** and 3-methyl-*p*-anisaldehyde. The resulting yellow solid was removed by filtration and washed with EtOH (10 mL), then with pet. ether (10 mL). The alkene **S223** (311 mg, 81%) was obtained as a yellow solid:

mp 232–235 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.47 (s, 1H, NH), 9.53 (s, 1H, NH-Boc), 7.57 (dd, *J* = 8.5, 2.0 Hz, 1H, H-6'), 7.54 (d, *J* = 8.5 Hz, 1H, H-4), 7.49 (d, *J* = 2.0 Hz, 1H, H-2'), 7.37 (s, 1H, =CH), 7.25 (d, *J* = 1.8 Hz, 1H, H-7), 7.07 (d, *J* = 8.5 Hz, 1H, H-5'), 6.85 (dd, *J* = 8.5, 1.8 Hz, 1H, H-5), 3.86 (s, 3H, OMe), 2.20 (s, 3H, Me), 1.47 (s, 9H, *t*Bu); ^{13}C NMR [$(CD_3)_2SO$] δ 169.5, 158.4, 152.5, 143.5, 140.9, 133.3, 131.8, 129.0, 126.5, 126.0, 125.2, 122.5, 115.1, 110.4, 110.3, 99.8, 79.3, 55.5, 28.1 (3), 15.9; MS *m/z* 381.2 (MH^+, 100%). Anal. calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.58; H, 6.53; N, 7.43%.

SN38050 (*E*/*Z*)-3-(4-Methoxy-3-methylbenzylidene)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (**S224**).

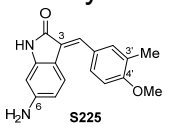


3,3-Dibromo-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (S224a). 7-Azaindole (500 mg, 4.23 mmol) was dissolved in *tert*-butanol (30 mL). Pyridinium bromide perbromide (5.41 g, 16.93 mmol) was added in small portions over 6 h. The resulting mixture was diluted with EtOAc (100 mL), washed with brine (100 mL), dried and concentrated. The residue was triturated in DCM (50 mL) to give the dibromide **S224a** (820 mg, 66%) as a light brown solid: ^{1}H NMR [$(CD_3)_2SO$] δ 11.99 (s, 1H, NH), 8.22 (dd, *J* = 5.2, 1.6 Hz, 1H, H-6), 8.01 (dd, *J* = 7.6, 1.6 Hz, 1H, H-4), 7.18 (dd, *J* = 7.6, 5.2 Hz, 1H, H-5); MS *m/z* 292.2 (MH^+, 100%).

1,3-Dihydro-2*H*-pyrrolo[2,3-b]pyridin-2-one (224b). Dibromide **S224a** (764 mg, 2.75 mmol) and 10% Pd/C (76 mg, 10% wt. of bromide) were stirred in EtOH (30 mL) under H_2 (50 psi) for 7 days. The catalyst was removed by filtration over Celite, washed with EtOAc (30 mL) and concentrated. The crude residue was used in the next step without further purification.

(*E*/*Z*)-3-(4-Methoxy-3-methylbenzylidene)-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one (S224). Prepared using Method N from crude residue containing azaoxindole **S224b** and 3-methyl-*p*-anisaldehyde. The crude residue was purified by column chromatography, eluting with 1% MeOH/DCM, to give a mixture of isomers (*E*/*Z*)-**S224** (50 mg, 7% over 2 steps) as a yellow solid: mp 169–172 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 11.16 (s, 1H, NH), 8.09 (dd, *J* = 5.2, 1.3 Hz, 1H, H-6), 7.94 (d, *J* = 7.6, 1.3 Hz, 1H, H-4), 7.68 (s, 1H, =CH), 7.64 (dd, *J* = 8.5, 1.8 Hz, 1H, H-6'), 7.56 (d, *J* = 1.8 Hz, 1H, H-2'), 7.12 (d, *J* = 8.5 Hz, 1H, H-5'), 6.93 (dd, *J* = 7.6, 5.2 Hz, 1H, H-5), 3.88 (s, 3H, OMe), 2.21 (s, 3H, Me); *Z*-isomer (minor) 11.16 (s, 1H, NH), 8.42 (dd, *J* = 8.7, 2.0 Hz, 1H, H-6'), 8.29 (d, *J* = 2.0 Hz, 1H, H-2'), 8.06 (dd, *J* = 5. 2, 1.4 Hz, 1H, H-6), 7.99 (dd, *J* = 7.5, 1.4 Hz, 1H, H-4), 7.79 (s, 1H, =CH), 7.09 (d obscured, *J* = 8.7 Hz, 1H, H-5'), 7.00 (d, *J* = 7.5, 5.2 Hz, 1H, H-5), 3.88 (s, 3H, OMe), 2.20 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 168.5, 166.9, 159.9, 159.2, 156.6, 154.4, 147.5, 146.4, 139.3, 138.3, 134.9, 132.8, 132.2, 129.6, 128.9, 126.3 (2), 126.1, 125.8, 125.4, 123.5, 121.8, 119.9, 117.3, 117.2, 115.6, 110.6, 110.2, 55.6 (2), 16.1, 15.9; MS *m/z* 267.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 267.1129 (calcd for $C_{16}H_{15}N_2O_2$, 267.1128).

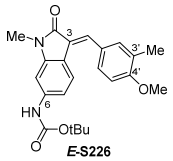
SN38051 (*E*)-6-Amino-3-(4-methoxy-3-methylbenzylidene)indolin-2-one (**S225**).



S225

(*E*)-6-Amino-3-(4-methoxy-3-methylbenzylidene)indolin-2-one (S225). Prepared using Method F from carbamate **S223** to give amine **S225** (122 mg, quant.) as an orange solid: mp 242–246 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.53(s, 1H, NH), 7.56–7.58 (m, 2H, H-4, H-6'), 7.49 (d, *J* = 2.0 Hz, 1H, H-2'), 7.38 (s, 1H, =CH), 7.08 (d, *J* = 8.5 Hz, 1H, H-5'), 6.55 (s, 1H, H-7), 6.49 (d, *J* = 7.6 Hz, 1H, H-5), 3.87 (s, 3H, OMe), 2.20 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 169.1, 158.8, 143.7, 136.0, 132.0, 129.3, 126.1 (2), 124.5, 122.9, 119.0, 114.1, 110.5, 103.5, 55.5, 15.9, (1 signal not observed); MS *m/z* 281.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 281.1283 (calcd for $C_{17}H_{17}N_2O_2$, 281.1285).

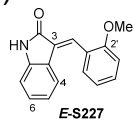
SN38052 *tert*-Butyl (*E*)-(3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)(methyl)carbamate (**S226**).



***E*-S226**

***tert*-Butyl (*E*)-(3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)(methyl)carbamate (S226).** Prepared using Method E from methyl iodide and carbamate **S223**. The crude residue was purified by column chromatography, eluting in DCM, to give **S226** (246 mg, 92%) as a yellow solid: mp 171–174 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 9.60 (s, 1H, NH), 7.58–7.61 (m, 2H), 7.51 (d, *J* = 2.1 Hz, 1H), 7.47 (s, 1H), 7.32 (d, *J* = 1.7 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 6.90 (dd, *J* = 8.4, 1.9 Hz, 1H), 3.87 (s, 3H, OMe), 3.16 (s, 3H, NMe), 2.20 (s, 3H, Me), 1.48 (s, 9H, *t*Bu); ^{13}C NMR [$(CD_3)_2SO$] δ 168.1, 158.5, 152.6, 144.6, 141.1, 134.0, 131.9, 129.1, 126.3, 126.0, 124.1, 122.3, 114.4, 110.7, 110.4, 98.5, 79.4, 55.5, 28.1 (3), 25.8, 15.9; MS *m/z* 395.2 (MH^+, 100%). Anal. calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 69.96; H, 6.69; N, 7.04%.

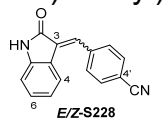
SN38053 (*E*)-3-(2-Methoxybenzylidene)indolin-2-one (**S227**).



***E*-S227**

(*E*)-3-(2-Methoxybenzylidene)indolin-2-one (S227). Prepared using Method N from oxindole and *o*-anisaldehyde. The crude material was purified by column chromatography, eluting with 30–60% EtOAc/pet. ether, to give **S227** (174 mg, 92%) as a yellow solid: mp 171–174 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.57 (s, 1H, NH), 7.68 (dd, *J* = 7.5, 1.3 Hz, 1H, H-6'), 7.65 (s, 1H, =CH), 7.47–7.51 (m, 1H, H-4'), 7.40 (d, *J* = 7.7 Hz, 1H, H-4), 7.21 (ddd, *J* = 7.7, 1.1 Hz, 1H, H-6), 7.17 (d, *J* = 7.9 Hz, 1H, H-3'), 7.08 (dd, *J* = 7.5, 7.5 Hz, 1H, H-5'), 6.81–6.87 (m, 2H, H-5, H-7), 3.86 (s, 3H, OMe); ^{13}C NMR [$(CD_3)_2SO$] δ 168.6, 157.6, 142.7, 131.7 (2), 129.9, 129.5, 127.3, 122.8, 122.2, 121.1, 121.0, 120.2, 111.6, 110.0, 55.6; MS *m/z* 252.2 (MH^+, 100%). Anal. calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.63; H, 5.11; N, 5.57%.

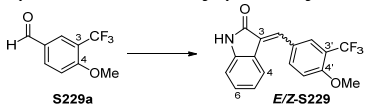
SN38054 (*E*/*Z*)-4-((2-Oxoindolin-3-ylidene)methyl)benzonitrile (**S228**).



***E*/*Z*-S228**

(*E*/*Z*)-4-((2-Oxoindolin-3-ylidene)methyl)benzonitrile (S228). Prepared using Method N from oxindole and 4-cyanobenzaldehyde. The crude material was purified by column chromatography, eluting with 30–60% EtOAc/pet. ether, to give (*E*/*Z*)-**S228** (126 mg, 68%) as an orange solid: mp 232–234 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.68 (s, 1H, NH), 7.98 (d, *J* = 8.2 Hz, 2H, H-3', H-5'), 7.87 (d, *J* = 8.2 Hz, 2H, H-2', H-6'), 7.63 (s, 1H, =CH), 7.38 (d, *J* = 7.7 Hz, 1H, H-4), 7.25 (ddd, *J* = 7.7, 7.7, 1.0 Hz, 1H, H-6), 6.88 (d, *J* = 7.7 Hz, 1H, H-7), 6.84 (ddd, *J* = 7.7, 7.7, 1.0 Hz, 1H, H-5); ^{13}C NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 168.2, 143.4, 139.5, 133.4, 132.6 (2), 130.9, 130.0 (2), 129.6, 122.7, 121.3, 120.3, 118.6, 111.6, 110.3; MS *m/z* 247.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 247.0867 (calcd for $C_{16}H_{10}N_2O$, 247.0866).

SN38055 (*E*/*Z*)-3-(4-Methoxy-3-(trifluoromethyl)benzylidene)indolin-2-one (**S229**).

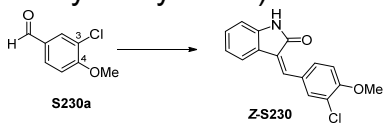


S229a ***E*/*Z*-S229**

4-Methoxy-3-(trifluoromethyl)benzaldehyde (S229a). Prepared using Method E from methyl iodide and 3-trifluoromethyl-4-hydroxybenzaldehyde to give aldehyde **S229a** (146 mg, 90%) as a yellow oil: ^{1}H NMR δ 9.93 (s, 1H, CHO), 8.12 (d, *J* = 1.9 Hz, 1H, H-2), 8.06 (dd, *J* = 8.6, 1.9 Hz, 1H, H-6), 7.14 (d, *J* = 8.6 Hz, 1H, H-5), 4.01 (s, 3H, OMe).

(*E*/*Z*)-3-(4-Methoxy-3-(trifluoromethyl)benzylidene)indolin-2-one (S229). Prepared using Method N from oxindole and aldehyde **S229a**. The crude material was purified by column chromatography, eluting with 20–50% EtOAc/pet. ether, to give (*E*/*Z*)-**S229** (178 mg, 89%) as a yellow solid: mp 212–214 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.61 (s, 1H, NH), 8.04 (d, *J* = 8.2, 1.9 Hz, 1H, H-6'), 7.97 (d, *J* = 1.9 Hz, 1H, H-2'), 7.62 (s, 1H, =CH), 7.50 (d, *J* = 7.7 Hz, 1H, H-4), 7.43 (d, *J* = 8.2 Hz, 1H, H-5'), 7.22–7.26 (m, 1H, H-6), 6.82–6.90 (m, 2H, H-5, H-7), 3.98 (s, 3H, OMe); *Z*-isomer (minor) 10.61 (s, 1H, NH), 9.01 (d, *J* = 2.0 Hz, 1H, H-2'), 8.63 (dd, *J* = 8.9, 2.0 Hz, 1H, H-6'), 7.85 (s, 1H, =CH), 7.69 (d, *J* = 7.5 Hz, 1H, H-4), 7.38 (d, *J* = 8.9 Hz, 1H, H-5'), 7.19–7.23 (m, 1H, H-6), 6.99 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H, H-5), 6.82–6.90 (m, 1H, H-7), 3.97 (s, 3H, OMe); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 168.6, 167.3, 158.3 (d, *J* = 1.1 Hz), 157.8 (d, *J* = 1.1 Hz), 143.0, 140.6, 138.4, 135.4, 135.2, 134.3, 130.7 (q, *J* = 5.4 Hz), 130.2, 128.8, 128.3 (q, *J* = 5.1 Hz), 127.2, 126.5, 126.4, 125.7, 124.9, 123.6 (q, *J* = 271.6 Hz), 123.4 (q, *J* = 278.8 Hz), 121.9, 121.1, 121.1, 120.8, 119.6, 117.1 (q, *J* = 30.5 Hz), 116.7 (q, *J* = 30.6 Hz), 113.3, 112.7, 110.2, 109.4, 56.5 (2); MS *m/z* 320.1 (MH^+, 100%). Anal. calcd for $C_{17}H_{12}F_3NO_2$: C, 63.95; H, 3.79; N, 4.39. Found: C, 63.96; H, 3.85; N, 4.41%.

SN38056 (*Z*)-3-(3-Chloro-4-methoxybenzylidene)indolin-2-one (**S230**).

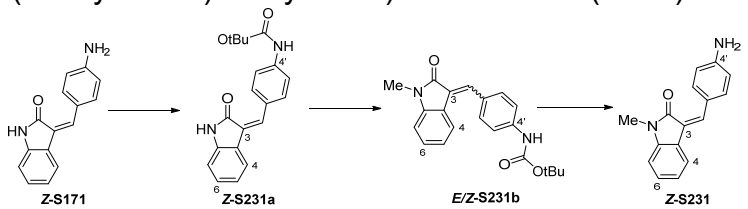


S230a ***Z*-S230**

3-Chloro-4-methoxybenzaldehyde (S230a). Prepared using Method E from methyl iodide and 3-chloro-4-hydroxybenzaldehyde to give aldehyde **S230a** (178 mg, quant.) as a yellow oil: ^{1}H NMR δ 9.86 (s, 1H, CHO), 7.92 (d, *J* = 2.0 Hz, 1H, H-2), 7.78 (dd, *J* = 8.5, 2.0 Hz, 1H, H-6), 7.05 (d, *J* = 8.5 Hz, 1H, H-5), 4.00 (s, 3H, OMe).

(*Z*)-3-(3-Chloro-4-methoxybenzylidene)indolin-2-one (S230). Prepared using Method N from oxindole and aldehyde **S230a**. The crude material was purified by column chromatography, eluting with 20–60% EtOAc/pet. ether, to give **S230** (207 mg, 78%) as an orange solid: mp 242–245 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.63 (s, 1H, NH), 8.88 (d, *J* = 2.1 Hz, 1H, H-2'), 8.29 (dd, *J* = 8.8, 2.1 Hz, 1H, H-6'), 7.75 (s, 1H, =CH), 7.67 (d, *J* = 7.6 Hz, 1H, H-4), 7.27 (d, *J* = 8.8 Hz, 1H, H-5'), 7.20 (ddd, *J* = 7.6, 1.0 Hz, 1H, H-6), 6.99 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.82 (d, *J* = 7.6 Hz, 1H, H-7), 3.94 (s, 3H, OMe); ^{13}C NMR [$(CD_3)_2SO$] δ 167.3, 156.1, 140.5, 135.3, 133.4, 133.1, 128.7, 127.8, 125.4, 125.0, 121.0, 120.7, 119.5, 112.3, 109.3, 56.4; MS *m/z* 286.2 (MH^+, 100%). Anal. calcd for $C_{16}H_{12}ClNO_2$: C, 67.26; H, 4.23; N, 4.90. Found: C, 67.10; H, 4.17; N, 4.92%.

SN38078 (*Z*)-3-(4-(Methylamino)benzylidene)indolin-2-one (**S231**).



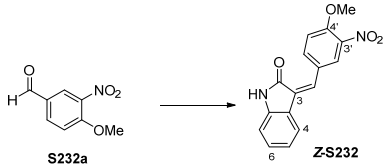
***tert*-Butyl (*Z*)-(4-((2-Oxoindolin-3-ylidene)methyl)phenyl)carbamate (S231a).** Prepared using Method K from amine **S171**. The crude residue was purified by column chromatography, eluting in 30–80% EtOAc/pet. ether, to give carbamate **S231a** (133 mg, 47%) as a yellow solid: ^{1}H NMR [$(CD_3)_2SO$] δ 10.56 (s, 1H, NH), 9.69 (s, 1H, NH-Boc), 8.39 (d, *J* = 8.8 Hz, 2H, H-2', H-6'), 7.70 (s, 1H, =CH), 7.66 (d, *J* = 7.6 Hz, 1H, H-4), 7.55 (d, *J* = 8.8 Hz, 2H, H-3', H-5'), 7.18 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-6), 6.97 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.81 (d, *J* = 7.6 Hz, 1H, H-7), 1.50 (s, 9H, *t*Bu).

***tert*-Butyl (*E/Z*)-(4-((1-Methyl-2-oxoindolin-3-ylidene)methyl)phenyl)carbamate (S231b).** Prepared using Method E from methyl iodide and carbamate **S231a**. The crude residue was purified by column chromatography, eluting in 20–30% EtOAc/pet. ether, to give methylamine (*E/Z*)-**S231b** (93 mg, 86%) as a yellow solid: ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 9.72 (s, 1H, $NHCO_2$), 7.60–7.73 (m, 6H, H-4, =CH, H-2', H-3', H-5', H-6'), 7.31 (ddd obscured, *J* = 7.7 Hz, 1H, H-6), 7.03–7.07 (m, 1H, H-7), 6.94–7.00 (m, 1H, H-5), 3.21 (s, 3H, NMe), 1.50 (s, 9H, *t*Bu); *Z*-isomer (minor) 9.72 (s, 1H, $NHCO_2$), 8.42 (d, *J* = 8.9 Hz, 2H, H-2', H-6'), 7.77 (s, 1H, =CH), 7.60–7.73 (m, 1H, H-4), 7.56 (d, *J* = 8.9 Hz, 2H, H-3', H-5'), 7.26–7.30 (m, 1H, H-6), 7.03–7.07 (m, 1H, H-5), 6.94–7.00 (m, 1H, H-7), 3.22 (s, 3H, NMe), 1.50 (s, 9H, *t*Bu); MS *m/z* 351.2 (MH^+, 100%).

(*Z*)-3-(4-Aminobenzylidene)-1-methylindolin-2-one (S231). Prepared using Method F from carbamate **S231b** to give amine **S231** (35 mg, 58%) was obtained as a brown solid: ^{1}H NMR [$(CD_3)_2SO$] δ 8.36 (d, *J* = 8.7 Hz, 2H, H-2', H-6'), 7.64–7.66 (m, 2H, H-4, =CH), 7.21 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-6), 7.01 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.96 (d, *J* = 7.6 Hz, 1H, H-7), 6.68 (d, *J* = 8.7 Hz, 2H, H-3', H-5'), 3.22 (s, 3H, NMe); MS *m/z*

251.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 251.1158 (calcd for $C_{16}H_{15}N_2O$, 251.1179).

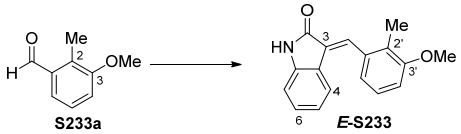
SN38079 (*Z*)-3-(4-Methoxy-3-nitrobenzylidene)indolin-2-one (**S232**).



4-Methoxy-3-nitrobenzaldehyde (S232a). Prepared using Method E from methyl iodide and 4-hydroxy-3-nitrobenzaldehyde to give aldehyde **S232a** (146 mg, 90%) was obtained as a pale yellow solid: ^{1}H NMR [$(CD_3)_2SO$] δ 9.95 (s, 1H), 8.36 (d, *J* = 2.1 Hz, 1H), 8.10 (d, *J* = 8.7, 2.1 Hz, 1H), 7.24 (d, *J* = 8.7 Hz, 1H), 4.07 (s, 3H).

(*Z*)-3-(4-Methoxy-3-nitrobenzylidene)indolin-2-one (S232). Prepared using Method N from oxindole and aldehyde **S232a**. The crude material was purified by column chromatography, eluting with 30–40% EtOAc/pet. ether, to give *Z*-**S232** (174 mg, 77%) as a yellow solid: mp 251–254 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.68 (s, 1H, NH), 9.24 (d, *J* = 2.2 Hz, 1H, H-2'), 8.60 (dd, *J* = 9.0, 2.2 Hz, 1H, H-6'), 7.85 (s, 1H, =CH), 7.69 (d, *J* = 7.5 Hz, 1H, H-4), 7.49 (d, *J* = 9.0 Hz, 1H, H-5'), 7.22 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H, H-6), 7.01 (ddd, *J* = 7.5, 1.0 Hz, 1H, H-5), 6.84 (d, *J* = 7.5 Hz, 1H, H-7), 4.01 (s, 3H, OMe); ^{13}C NMR [$(CD_3)_2SO$] δ 167.2, 153.2, 140.8, 138.7, 138.4, 134.1, 129.1, 128.1, 126.7, 126.6, 124.7, 121.2, 119.8, 114.1, 109.5, 57.0; MS *m/z* 297.1 (MH^+, 100%). Anal. calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.84; H, 3.95; N, 9.50%.

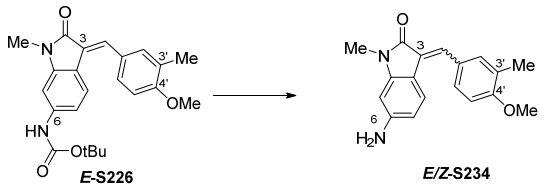
SN38082 (*E*)-3-(3-Methoxy-2-methylbenzylidene)indolin-2-one (**S233**).



3-Methoxy-2-methylbenzaldehyde (S233a). Prepared using Method E from methyl iodide and 3-hydroxy-3-methyl benzaldehyde to give aldehyde **S233a** (158 mg, 95%) as a colourless oil: ^{1}H NMR [$(CD_3)_2SO$] δ 10.33 (s, 1H, CHO), 7.43 (dd, *J* = 8.0, 0.9 Hz, 1H, H-6), 7.31 (dd, *J* = 8.0, 8.0 Hz, 1H, H-5), 7.08 (d, *J* = 8.0 Hz, 1H, H-4), 3.88 (s, 3H, OMe), 2.54 (s, 3H, Me); MS *m/z* 151.2 (MH^+, 100%).

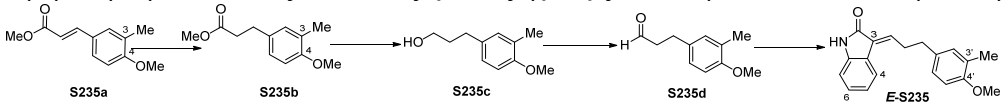
(*E*)-3-(3-Methoxy-2-methylbenzylidene)indolin-2-one (S233). Prepared using Method N from oxindole and aldehyde **S233a**. The crude material was purified by column chromatography, eluting with 20–30% EtOAc/pet. ether, to give **S234** (157 mg, 79%) as a yellow solid: mp 192–194 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.60 (s, 1H, NH), 7.66 (s, 1H, =CH), 7.29 (dd, *J* = 7.9, 7.4 Hz, 1H, H-5'), 7.19 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H, H-6), 7.01–7.10 (m, 3H, H-4, H-4', H-6'), 6.85 (d, *J* = 7.7 Hz, 1H, H-7), 6.77 (ddd, *J* = 7.7, 7.7, 1.1 Hz, 1H, H-5), 3.85 (s, 3H, OMe), 2.12 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 168.2, 157.5, 142.8, 135.0, 134.7, 130.0, 128.7, 126.7, 124.4, 122.6, 121.1 (2), 120.2, 111.2, 110.0, 55.5, 12.4; MS *m/z* 266.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 266.1176 (calcd for $C_{17}H_{16}NO_2$, 266.1176).

SN38146 (*E*/*Z*)-6-Amino-3-(4-methoxy-3-methylbenzylidene)-1-methylindolin-2-one (**S234**).



(*E*/*Z*)-6-Amino-3-(4-methoxy-3-methylbenzylidene)-1-methylindolin-2-one (S234). Prepared using Method F from carbamate **S226** to give amine (*E*/*Z*)-**S234** (28 mg, 37%) as an orange solid: mp 180–182 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 7.53 (dd, *J* = 8.5, 2.1 Hz, 1H, H-6'), 7.44 (d, *J* = 2.1 Hz, 1H, H-2'), 7.40 (d, *J* = 8.3 Hz, 1H, H-4), 7.20 (s, 1H, =CH), 7.05 (d, *J* = 8.5 Hz, 1H, H-5'), 6.19 (d, *J* = 2.0 Hz, 1H, H-7), 6.10 (dd, *J* = 8.3, 2.0 Hz, 1H, H-5), 5.67 (br s, 2H, NH_2), 3.85 (s, 3H, OMe), 3.11 (s, 3H, NMe), 2.19 (s, 3H, Me); *Z*-isomer (minor) 8.19–8.22 (m, 2H, H-2', H-6'), 7.32 (d, *J* = 8.1 Hz, 1H, H-4), 7.29 (s, 1H, =CH), 6.99 (d, *J* = 8.5 Hz, 1H, H-5'), 6.22 (dd, *J* = 8.1, 1.9 Hz, 1H, H-5), 6.16 (d, *J* = 1.9 Hz, 1H, H-7), 5.47 (br s, 2H, NH_2), 3.85 (s obscured, 3H, OMe), 3.12 (s obscured, 3H, NMe), 2.17 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 168.7, 157.9, 150.9, 145.5, 131.6, 129.1, 128.5, 127.1, 125.8, 124.9, 123.2, 110.3, 108.3, 106.3, 94.4, 55.4, 25.7, 16.0; MS *m/z* 295.2 (MH^+, 100%). Anal. calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.49; H, 6.40; N, 9.40%.

SN38147 (*E*)-3-(3-(4-Methoxy-3-methylphenyl)propylidene)indolin-2-one (**S235**).



Methyl (*E*)-3-(4-Methoxy-3-methylphenyl)acrylate (S235a). 3-Methyl-*p*-anisaldehyde (500 mg, 3.33 mmol) and carbomethoxymethylene triphenyl phosphorane (1.22 g, 3.66 mmol) were stirred in toluene (10 mL) at 120 °C for 4 h. A second equivalent of carbomethoxymethylene triphenyl phosphorane (1.22 g, 3.66 mmol) was added and the reaction mixture was heated at 120 °C for another 4 h. Once cooled, the reaction mixture was diluted with EtOAc (50 mL), washed with sat. $NaHCO_3$ (50 mL), then brine (50 mL), dried and concentrated *in vacuo*. The crude residue was purified by column chromatography, eluting with 5–10% EtOAc/pet. ether, to give acrylate **S235a** (703 mg, quant.) as a white solid: mp 75–77 °C; ^{1}H NMR δ 7.63 (d, *J* = 16.0 Hz, 1H, =CHAr), 7.33–7.35 (m, 2H, H-2, H-6), 6.81–6.83 (m, 1H, H-5), 6.30 (d, *J* = 16.0 Hz, 1H, COCH=), 3.86 (s, 3H, OMe-4), 3.79 (s, 3H, OMe), 2.22 (s, 3H, Me); MS *m/z* 207.2 (MH^+, 100%).

Methyl 3-(4-Methoxy-3-methylphenyl)propanoate (S235b). Prepared using Method M from alkene **S235a** to give ester **S235b** (384 mg, 68%) as a white solid: mp 40–41 °C; ^{1}H NMR δ 6.97–6.99 (m, 2H, H-2, H-6), 6.74 (d, *J* = 7.88 Hz, 1H, H-5), 3.80 (s, 3H, OMe-4), 3.67 (s, 3H, OMe), 2.86 (t, *J* = 7.84 Hz, 2H, CH_2), 2.57–2.61 (m, 2H, $COCH_2$), 2.19 (s, 3H, Me); MS *m/z* 209.2 (MH^+, 100%).

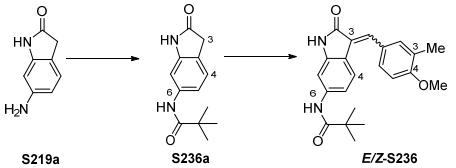
3-(4-Methoxy-3-methylphenyl)propan-1-ol (S235c). $NaBH_4$ (38 mg, 1.0 mmol) was added to asolution of ester **S235b** (209 mg, 1.0 mmol) in MeOH (5 mL) and the mixture was stirred at 20 °C for 7 h. Additional $NaBH_4$ (387 mg, 10.2 mmol) was added portionwise

over 2 days. The resulting mixture was diluted with EtOAc (50 mL), washed with water (50 mL) and brine (50 mL). The organic layer was dried and concentrated *in vacuo*. The crude residue was purified over column chromatography, eluting with 30% EtOAc/pet.ether, to give alcohol **S235c** (121 mg, 67%) as a white solid: mp 46–48 °C; ^{1}H NMR δ 6.97–7.00 (m, 2H, H-2, H-6), 6.74–6.76 (m, 1H, H-5), 3.80 (s, 3H, OMe), 3.67 (td, *J* = 6.3, 5.7 Hz, 2H, OCH_2), 2.60 (m, 2H, CH_2Ar), 2.20 (s, 3H, Me), 1.83–1.90 (m, 2H, CH_2), 1.22 (t, *J* = 5.7 Hz, 1H, OH).

3-(4-Methoxy-3-methylphenyl)propanal (S235d). IBX (466 mg, 1.66 mmol) was added to a solution of alcohol **S235c** (100 mg, 0.55 mmol) in DMSO (1.6 mL) and the mixture was stirred at 20 °C for 1.5 h. The resulting mixture was diluted with water (20 mL) and the precipitate removed by filtration. The solid was washed with DCM (20 mL) and the filtrate was partitioned. The organic layer was collected, dried and concentrated *in vacuo*. Solvent was removed to obtain aldehyde **S235d** (81 mg, 82%) as a pale yellow oil: ^{1}H NMR δ 9.81 (t, *J* = 1.50 Hz, 1H, CHO), 6.96–6.99 (m, 2H, H-2, H-6), 6.75 (d, *J* = 7.9 Hz, 1H, H-5), 3.80 (s, 3H, OMe), 2.88 (m, 2H, CH_2), 2.72–2.76 (m, 2H, CH_2CO), 2.19 (s, 3H, Me).

(*E*)-3-(3-(4-Methoxy-3-methylphenyl)propylidene)indolin-2-one (S235). Prepared using Method N from oxindole and aldehyde **S235d**. The crude material was purified by column chromatography, eluting with 5% EtOAc/DCM, to give **S235** (37 mg, 28%) as a yellow solid: mp 132–133 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.42 (s, 1H, NH), 7.55 (d, *J* = 7.6 Hz, 1H, H-4), 7.21 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-6), 7.06–7.07 (m, 2H, H-2', H-6'), 6.97 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H, H-5), 6.82–6.85 (m, 2H, H-7, H-5'), 6.76 (t, *J* = 7.3 Hz, 1H, =CH), 3.74 (s, 3H, OMe), 2.93 (m, 2H, $CHCH_2$), 2.80 (t, *J* = 7.3 Hz, 1H, CH_2), 2.12 (s, 3H, Me); ^{13}C NMR [$(CD_3)_2SO$] δ 167.9, 155.7, 142.1, 140.0, 132.2, 130.5, 129.0, 128.2, 126.6, 125.3, 123.6, 122.0, 121.4, 110.2, 109.7, 55.1, 32.9, 30.3, 16.0; MS *m/z* 294.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 294.1497 (calcd for $C_{19}H_{20}NO_2$, 294.1489).

SN38211 (*E/Z*)-*N*-(3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)pivalamide (**S236**).

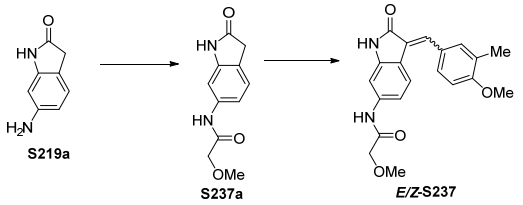


***N*-(2-Oxoindolin-6-yl)pivalamide (236a).** Aminooxindole **S219a** (200 mg, 1.35 mmol) and TEA (374 µL, 2.70 mmol) were stirred in DCM (5 mL). Trimethylacetyl chloride (166 µL, 1.35 mmol) was added and the reaction mixture was stirred at 20 °C. for 3 h. A pale purple solid appeared in the solution, which was removed by filtration and washed with DCM to give amide **S236a** (220 mg, 70%) as a pale purple solid: mp 261–264 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.37 (s, 1H, NH-1), 9.12 (s, 1H, NH-6), 7.32 (d, *J* = 1.8 Hz, 1H, H-7), 7.13 (dd, *J* = 8.1, 1.8 Hz, 1H, H-5), 7.08 (d, *J* = 8.1 Hz, 1H, H-4), 3.39 (s, 2H, CH_2), 1.20 (s, 9H, *t*Bu); MS *m/z* 233.2 (MH^+, 100%).

(*E/Z*)-*N*-(3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)pivalamide (S236). Prepared using Method N from oxindole **S236a** and 3-methyl-*p*-anisaldehyde. The crude

material was purified by column chromatography, eluting with 30–40% EtOAc/pet. ether, to give (*E/Z*)-**S236** (208 mg, 83%) as a yellow solid: mp 136–139 °C; ^{1}H NMR [$(CD_3)_2SO$] δ *E*-isomer (major) 10.56 (s, 1H, NH-1), 9.27 (s, 1H, NH-6), 7.56–7.61 (m, 2H, H-4, H-6'), 7.51 (m, 1H, H-2'), 7.44 (d, *J* = 1.9 Hz, 1H, H-7), 7.40 (s, 1H, =CH), 7.08–7.12 (m, 2H, H-5, H-5'), 3.87 (s, 3H, OMe), 2.20 (s, 3H, Me), 1.22 (s, 9H, *t*Bu); *Z*-isomer (minor) 10.56 (s, 1H, NH-1), 9.21 (s, 1H, NH-6), 8.35 (dd, *J* = 8.6, 2.1 Hz, 1H, H-6'), 8.25 (d, *J* = 2.1 Hz, 1H, H-2'), 7.56–7.61 (m, 1H, H-4), 7.54 (s, 1H, =CH), 7.36 (d, *J* = 1.8 Hz, 1H, H-7), 7.21 (dd, *J* = 8.3, 1.8 Hz, 1H, H-5), 7.04 (d, *J* = 8.6 Hz, 1H, H-5'), 3.87 (s, 3H, OMe), 2.18 (s, 3H, Me), 1.22 (s, 9H, *t*Bu); ^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 176.6, 176.4, 169.5, 167.8, 159.1, 158.5, 143.2, 140.7, 140.4, 139.6, 135.3, 134.4, 133.8, 132.1, 131.9, 129.0, 126.8, 126.4, 126.0, 125.2, 125.1, 123.8, 122.2, 120.4, 119.2, 116.1, 112.5, 112.2, 110.5, 110.0, 101.9, 101.4, 55.5, 27.2 (3), 27.1 (3), 16.1, 15.9, 2 signals obscured by DMSO peaks); MS *m/z* 365.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 365.1861 (calcd for $C_{22}H_{25}N_2O_3$, 365.1860).

SN38212 (*E*/*Z*)-2-Methoxy-*N*-(3-(4-methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)acetamide (**S237**).

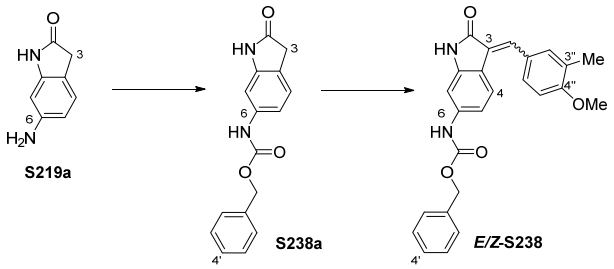


2-Methoxy-*N*-(2-oxoindolin-6-yl)acetamide (S237a). Oxalyl chloride (282 µL, 3.33 mmol) was added to a solution of methoxy acetic acid (170 µL, 2.22 mmol) and DMF (1 drop) in DCM (5 mL) at 0 °C and the reaction mixture was stirred at 20 ° for 19 h. The solvent was evaporated to give a yellow oil. The acid chloride was diluted in DCM (1 mL) and was added to a stirred suspension of aminooxindole **S219a** (100 mg, 0.67 mmol) and Et_3N (470 µL, 3.37 mmol) in DCM (5 mL). The reaction mixture was stirred at 20 °C for 4 h, then diluted with water (20 mL) and extracted with DCM (50 mL). The organic layer was washed with brine (20 mL), dried and concentrated *in vacuo*. The crude mixture was purified by column chromatography, eluting with EtOAc, to give amide **S237a** (65 mg, 44%) as an orange solid: mp 202–204 °C; ^{1}H NMR δ 8.28 (br s, 1H), 7.70 (br s, 1H), 7.58 (d, *J* = 1.9 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.9 Hz, 1H), 4.03 (s, 2H), 3.51 (s, 3H), 3.49 (s, 2H); MS *m/z* 221.2 (MH^+, 100%).

(*E/Z*)-2-Methoxy-*N*-(3-(4-methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)acetamide (S237). Prepared using Method N from amido-oxindole **S237a** and 3-methyl-p-anisaldehyde. The crude residue was purified by column chromatography, eluting with 75% EtOAc/pet. ether. Solvent was removed and the residue was triturated with EtOAc/pet. ether to give alkene (*E/Z*)-**S237** (66 mg, 83%) as a yellow solid: mp 132–135 °C, H-6'), 7.50–7.51 (m, 2H, H-7, H-2'), 7.42 (s obscured, 1H, =CH), 7.02–7.09 (m, 2H, H-5, H-5'), 4.00 (s, 2H, CH_2), 3.87 (s, 3H, OMe-4'), 3.36 (s, 3H, CH_2OMe), 2.20 (s, 3H, Me-3'); ^{1}H NMR [$(CD_3)_2SO$] δ *Z* isomer (minor) 10.55 (s, 1H, NH-1), 9.80 (s, 1H, NH-6), 8.35, (dd, *J* = 8.7, 2.0 Hz, 1H, H-6'), 8.25 (d, *J* = 2.0 Hz, 1H, H-2'), 7.55–7.60 (m, 2H, H-4, =CH), 7.42–7.44 (m, 1H, H-7), 7.17 (dd, *J* = 8.3, 1.9 Hz, 1H, H-5), 7.02–7.09 (m, 1H, H-5'), 4.00 (s, 2H, CH_2), 3.86 (s, 3H, OMe-4'), 3.37 (s, 3H, CH_2OMe), 2.18 (s, 3H, Me-3');

^{13}C NMR [$(CD_3)_2SO$] δ (both isomers) 169.4, 168.2, 168.0, 167.7, 159.2, 158.5, 143.3, 140.6, 139.7, 138.6, 135.5, 134.5, 134.2, 132.1, 131.9, 129.0, 126.7, 126.4, 126.0, 125.1 (2), 123.7, 122.4, 120.8, 119.4, 116.5, 112.1, 111.8, 110.4, 110.0, 101.4, 100.9, 71.7 (2), 58.6 (2), 55.5 (2), 16.1, 15.9; MS *m/z* 353.2 (MH^+, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 353.1500 (calcd for $C_{20}H_{21}N_2O_4$, 353.1496).

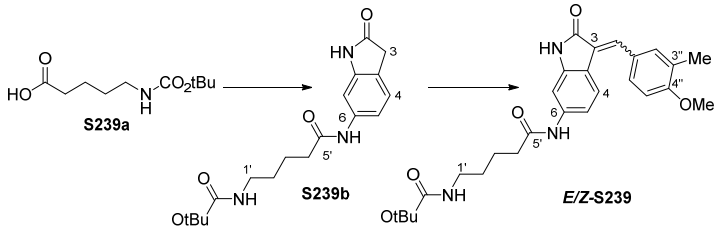
SN38303 Benzyl (*E*/*Z*)-(3-(4-methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)carbamate (**S238**).



Benzyl (2-oxoindolin-6-yl)carbamate (S238a). Benzyl chloroformate (90 µL, 0.63 mmol) was added dropwise to a solution of aminooxindole **S219a** (85 mg, 0.57 mmol) and Et_3N (160 µL, 1.15 mmol) in THF (5 mL) at 0 °C and the solution was stirred at 0 °C for 30 min. The solution was stirred at 20 °C for 24 h. The resulting mixture was diluted with EtOAc (20 mL), washed with water (20 mL), brine (20 mL), dried and concentrated *in vacuo*. The crude residue was purified by column chromatography, eluting with 50% EtOAc/pet. ether, to give oxindole **S238a** (58 mg, 36%) as a pale purple solid: mp 188–190 °C; ^{1}H NMR δ 7.35–7.42 (m, 6H, H-7, H-2', H-3', H-4', H-5', H-6'), 7.30 (br s, 1H, NH), 7.10 (d, *J* = 8.0 Hz, 1H, H-4), 6.73 (dd, *J* = 8.0, 2.0 Hz, 1H, H-5), 6.68 (br s, 1H, NH), 5.20 (s, 2H, OCH_2), 3.48 (s, 2H, CH_2); MS *m/z* 283.1 (MH^+, 100%).

Benzyl (*E/Z*)-(3-(4-methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)carbamate (S238). Prepared using Method N from oxindole **238a** and 3-methyl-*p*-anisaldehyde. The resulting residue was purified by column chromatography, eluting with 40% EtOAc/pet. ether to obtain (*E/Z*)-**S238** (75 mg, quant.) as a yellow solid: mp 200–203 °C; ^{1}H NMR δ *E*-isomer (major) 7.68 (d, *J* = 8.4 Hz, 1H, H-4), 7.66 (s, 1H, =CH), 7.48–7.54 (m, 3H, H-2'', H-6'', NH-1), 7.33–7.43 (m, 5H, H-2', H-3', H-4', H-5', H-6'), 7.31 (br s, 1H, H-7), 6.89 (d, *J* = 8.5 Hz, 1H, H-5'), 6.76 (m, 1H, NH-6), 6.62 (dd, *J* = 8.4, 2.1 Hz, 1H, H-5), 5.21 (s, 2H, OCH_2), 3.90 (s, 3H, OMe), 2.26 (s, 3H, Me); *Z*-isomer (minor) 8.32 (dd, *J* = 8.5, 2.0 Hz, 1H, H-6''), 8.06 (d, *J* = 2.0 Hz, 1H, H-2''), 7.48–7.54 (m, 1H, =CH), 7.33–7.43 (m, 6H, H-4, H-2', H-3', H-4', H-5', H-6'), 6.89 (d, *J* = 8.5 Hz, 1H, H-5''), 6.76–6.78 (m, 2H, H-5, H-7), 5.21 (s, 2H, OCH_2), 3.90 (s, 3H, OMe), 2.26 (s, 3H, Me), exchangeable protons were not observed; ^{13}C NMR δ (both isomers) 170.6, 168.3, 160.1, 159.3, 153.2 (2), 142.4, 140.0, 139.0, 138.1, 137.1, 136.7, 136.1, 136.0, 135.2, 132.4, 132.2, 129.2, 128.9 (2), 128.7 (3), 128.6 (4), 127.2, 127.1, 126.8, 126.7, 124.8, 123.5, 123.0, 121.5, 119.5, 117.7, 111.4, 110.0, 109.8, 100.7, 100.5, 67.5, 67.4, 55.7 (2), 16.4, 14.4, 2 signals not observed; MS *m/z* 413.2 (MH^+, 100%). Anal. calcd for $C_{25}H_{22}N_2O_4$: C, 72.45; H, 5.35; N, 6.76. Found: C, 72.17; H, 5.61; N, 6.63%.

SN38304 *tert*-Butyl (*E*/*Z*)-(5-((3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)amino)-5-oxopentyl)carbamate (**S239**).

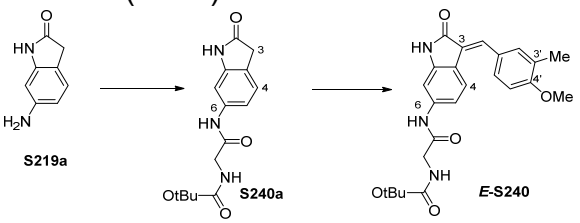


5-((*tert*-Butoxycarbonyl)amino)pentanoic acid (S239a). Prepared using Method K from 5-aminovaleric acid to give acid **S239a** (213 mg, 20%) as an off-white solid: mp 45–47 °C; ^{1}H NMR δ 4.59 (br s, 1H), 3.71 (s, 1H), 3.13–3.15 (m, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 1.63–1.68 (m, 2H), 1.52–1.57(m, 2H), 1.44 (br s, 9H); MS *m/z* 216.2 (M-H$^-$, 100%).

***tert*-Butyl (5-Oxo-5-((2-oxoindolin-6-yl)amino)pentyl)carbamate (S239b).** Prepared using Method H from acid **S239a** aminooxindole **S219a** to give oxindole **S239b** (253 mg, 74%) as a pale purple solid: mp 205–208 °C; ^{1}H NMR [(CD$_3$)$_2$SO] δ 10.34 (s, 1H, NH-1), 9.81 (s, 1H, NH-6), 7.35 (d, *J* = 1.7 Hz, 1H, H-7), 7.08 (d, *J* = 8.0 Hz, 1H, H-4), 6.99 (d, *J* = 8.0, 1.7 Hz, 1H, H-5), 6.80 (t, *J* = 5.9 Hz, 1H, NH-1'), 3.38 (s, 2H, CH$_2$-3), 2.92 (td, *J* = 6.8, 5.9 Hz, 2H, CH$_2$-1'), 2.27 (t, *J* = 7.40 Hz, 2H, CH$_2$-4'), 1.50–1.58 (m, 2H, CH$_2$-3'), 1.37–1.42 (m, 2H, CH$_2$-2'), 1.37 (s obscured, 9H, *t*Bu).

***tert*-Butyl (*E/Z*)-(5-((3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)amino)-5-oxopentyl)carbamate (S239).** Prepared using method N from oxindole **S239b** and 3-methyl-*p*-anisaldehyde. The resulting residue was purified by column chromatography, eluting with 60–70% EtOAc/pet. ether, to give (*E/Z*)-**S239** (210 mg, 76%) as a yellow solid: mp 197–200 °C; ***E*-isomer (major)** ^{1}H NMR [(CD$_3$)$_2$SO] δ *E*-isomer (major) 10.51 (s, 1H, NH-1), 9.98 (s, 1H, NH-6), 7.52–7.60 (m, 2H, H-4, H-6''), 7.50 (m, 1H, H-2'), 7.45 (d, *J* = 1.9 Hz, 1H, H-7), 7.40 (s, 1H, =CH), 7.09 (d, *J* = 8.5 Hz, 1H, H-5''), 6.94 (dd, *J* = 8.5, 1.9 Hz, 1H, H-5), 6.80 (t, *J* = 6.1 Hz, 1H, NH-1'), 3.87 (s, 3H, OMe), 2.92 (td, *J* = 6.4, 6.1 Hz, 1H, CH$_2$-1'), 2.29 (t, *J* = 7.3 Hz, 1H, H-4'), 2.20 (s, 3H, Me), 1.51–1.59 (m, 2H, CH$_2$-3'), 1.37–1.41 (m, 2H, CH$_2$-2'); *Z*-isomer (minor) 10.51 (s, 1H, NH-1), 9.91 (s, 1H, NH-6), 8.34 (dd, *J* = 8.63, 2.2 Hz, 1H, H-6''), 8.24–8.25 (m, 1H, H-2''), 7.52–7.60 (m, 2H, H-4, =CH), 7.37–7.40 (m, 1H, H-7), 7.02–7.05 (m, 2H, H-5, H-5'), 6.80 (t, *J* = 6.1 Hz, 1H, NH-1'), 3.86 (s, 3H, OMe), 2.92 (td, *J* = 6.4, 6.1 Hz, 1H, CH$_2$-1'), 2.29 (t, *J* = 7.3 Hz, 1H, CH$_2$-4'), 2.18 (s, 3H, Me), 1.51–1.59 (m, 2H, CH$_2$-3'), 1.37–1.41 (m, 2H, CH$_2$-2'); ^{13}C NMR [(CD$_3$)$_2$SO] δ (both isomers) 171.3, 169.4, 158.5, 155.6, 143.4, 140.6, 133.8, 131.9, 129.0, 126.4, 126.0, 125.1, 122.5, 115.9, 111.1, 110.4, 100.9, 77.3, 55.5, 36.2, 29.1, 28.3 (3), 22.4, 15.9, 1 signal not observed; MS *m/z* 478.2 (M-H$^-$, 100%) ; (+)-HRESIMS *m/z* [M+H]$^+$ 380.1972 (calcd for C$_{22}$H$_{26}$N$_3$O$_3$, 380.1969) – loss of *tert*-butyl-carbamate group.

SN38305 *tert*-Butyl (*E*)-(2-((3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)amino)-2-oxoethyl)carbamate (**S240**).



***tert*-Butyl (2-Oxo-2-((2-oxoindolin-6-yl)amino)ethyl)carbamate (S240a).** Prepared using Method H using *N*-(*tert*-butoxycarbonyl)glycine and aminooxindole **S219a**. The crude residue was triturated in EtOAc to give the oxindole **S240a** (112 mg, 54%) as a pale purple solid: mp 215 °C (decomp.); ^{1}H NMR [$(CD_3)_2SO$] δ 10.35 (s, 1H, NH-1), 9.86 (s, 1H, NH-6), 7.33 (s, 1H, H-7), 7.09 (d, *J* = 8.0 Hz, 1H, H-4), 6.99–7.03 (m, 2H, H-5, NH-Boc), 3.69 (d, *J* = 6.12 Hz, 2H, CH_2NH), 3.39 (s, 2H, CH_2-3), 1.39 (s, 9H, *t*Bu); MS *m/z* 304.2 ($M-H^-$, 100%).

***tert*-Butyl (*E*)-(2-((3-(4-Methoxy-3-methylbenzylidene)-2-oxoindolin-6-yl)amino)-2-oxoethyl)carbamate (S240).** Prepared using Method N from oxindole **S240a** and 3-methyl-*p*-anisaldehyde. The crude residue was purified by column chromatography, eluting with 60–100% EtOAc/pet. ether, to give alkene *E*-**S240** (149 mg, quant.) as an orange solid: mp 205–208 °C; ^{1}H NMR [$(CD_3)_2SO$] δ 10.53 (s, 1H, NH-1), 10.05 (s, 1H, NH-6), 7.58–7.61 (m, 2H, H-4, H-6'), 7.50 (d, *J* = 2.0 Hz, 1H, H-2'), 7.41–7.43 (m, 2H, H-7, =CH), 7.09 (d, *J* = 8.5 Hz, 1H, H-5'), 7.02–7.06 (m, 1H, NH-Boc), 6.94 (dd, *J* = 8.4, 2.0 Hz, 1H, H-5), 3.87 (s, 3H, OMe), 3.71 (d, *J* = 6.04 Hz, 2H, CH_2), 2.20 (s, 3H, Me), 1.39 (s, 9H, *t*Bu); ^{13}C NMR [$(CD_3)_2SO$] δ 169.4, 168.4, 158.5, 155.9, 143.4, 140.2, 134.0, 131.9, 129.0, 126.4, 126.0, 125.1, 122.6, 116.1, 111.2, 110.5, 100.9, 78.0, 55.5, 43.9, 28.2 (3), 15.9; MS *m/z* 436.2 ($M-H^-$, 100%); (+)-HRESIMS *m/z* $[M+H]^+$ 438.2027 (calcd for $C_{24}H_{28}N_3O_5$, 438.2023).

Supplemental Biology Methods

CHO-K1 cAMP assays

CHO-K1 cells expressing AM_1 or CGRP receptors (CHO-AM_1 or CHO-CGRP cells respectively) were plated at 20,000 cells per well into 96-well SpectraPlates (PerkinElmer). Assays were completed the following day.

The experimental protocol is similar to cAMP assays for Cos7 and HMEC-1 cells, with the following modifications. On the day of assay, growth medium was replaced with assay medium (DMEM with 0.1% BSA and 1 mM 3-isobutyl-1-methylxanthine) containing compound or vehicle. Cells were serum starved for 30 minutes at room temperature, followed by addition of antagonists or compounds where relevant, and agonists. Cells were stimulated for 30 minutes at room temperature. Wells were then aspirated and 50 µL of ice-cold absolute ethanol added. Plates were stored at -30 °C before processing continued using the ALPHAScreen assay (PerkinElmer). Manufacturer's directions were followed with modifications for adherent cell lines as previously described.[6] The ethanol in plates was evaporated, and 50 µL/well of lysis buffer was added. Plates were gently shaken for 15 minutes, then 10 µL/well of cell lysate was transferred to a white 384-well OptiPlate (PerkinElmer). cAMP detection reagents were added, the plate was incubated for 18-24 h, then signal was read using an EnVision plate reader (PerkinElmer) and compared to a cAMP standard curve generated for each assay.

Application of an operational model of allostery

Concentration-response data using multiple concentrations of compound were fitted with an operational model of allostery to estimate a co-operativity factor (β) as a guide to quantify compound activity. The equation is described in Leach et al., 2007 and reproduced below.[7, 8] GraphPad Prism 8 was used. Parameters were either constrained (α, n, basal) or initial values for fitting were manually entered (τ_A, τ_B, K_A, K_B, β) as described below.

$$\text{Response} = (E_{max} - \text{Basal}) \frac{(\tau_A [A](K_B + \alpha\beta[B]) + \tau_B [B] K_A)^n}{([A]K_B + K_A K_B + K_A[B] + \alpha[A][B])^n + (\tau_A [A](K_B + \alpha\beta[B]) + \tau_B [B] K_A)^n} + \text{Basal}$$

Parameter	Initial value	Constraint	Note
Log τ_A	0.5		Shared value for all data sets.
Log τ_B	-0.5		Shared value for all data sets.
Log K_A	-9		Binding affinity for orthosteric ligand (AM), similar to that observed with radioligand binding.[9] Shared value for all data sets.
Log K_B	-6		Binding affinity for the allosteric ligand was assumed to be weak. Shared value for all data sets.
Log α		Set to 0 i.e. α = 1	The pattern of modulation indicated that the compounds had minimal effect on binding co-operativity[10], hence α was constrained to 1.
Log β	3		Shared value for all data sets.
n		Set to 1	
E_{max}	1*YMAX		Shared value for all data sets.
Basal		Set to 0%	Baseline without orthosteric or allosteric ligand. Initially this was not constrained and was set to 1*YMIN, which resulted in very small or negative numbers. Therefore for consistency this was constrained to zero, with minimal impact on other parameters.

Binding assays

RAMP1/2 ECD-CLR ECD fusion proteins

Plasmid construction, expression in HEK293T cells, and purification of MBP-RAMP1.24-111-$(GS)_5$-CLR.29-144-H_6 and MBP-RAMP2.55-140[L106R]-$(GS)_5$-CLR.29-144-H_6 fusion proteins are described elsewhere.[11]

Peptides/Compounds

All peptides were custom synthesized and HPLC purified by RS Synthesis (Louisville, KY). The sequences for the human peptides FITC-Ahx-AM$(_{37-52})NH_2$ S45W/Q50W, αCGRP$(_{8-37})NH_2$ and AM$(_{22-52})NH_2$ are available upon request. Compounds were reconstituted in 100% DMSO to a final concentration of 10 mM (compounds **4** and **6**) or 5 mM (telcagepant, **1**) and stored at -20 °C.

Fluorescence polarization/anisotropy (FP) peptide binding assay

Binding of peptides/compounds to receptor ECDs was performed as previously described.[11] Competition binding used 7 nM of FITC-Ahx-AM(37-52)NH_2 S45W/Q50W and either 40 nM of MBP-RAMP2 ECD-$(GS)_5$-CLR ECD or 60 nM MBP-RAMP1 ECD-$(GS)_5$-CLR ECD fusion proteins with a 2 h incubation at room temperature. Equilibrium dissociation constants for the unlabeled peptides/compounds were determined using exact analytical equations of Roehrl et al. (2004)[12] in GraphPad Prism v. 7.03 as previously described[13]. Equilibrium dissociation constants of the FITC-Ahx-AM(37-52)NH_2 S45W/Q50W probe were reported elsewhere.[11] Any background fluorescence of compounds was corrected using reactions containing the same compound serial dilution in reaction buffer and indicated fusion protein concentration. For peptide competition binding assays in the presence/absence of compound **6**, an equal volume of 100% DMSO was added to master mix containing no compound as a vehicle control.

Supplemental Results

CHO-K1 cell line validation

CHO-K1 cells were validated using both β-arrestin assays (protocol described in main text) and assays measuring cAMP accumulation (method described in Supplemental Biology Methods, page S161).

As shown in **Figure S1** and **Table S5**, AM was the most potent ligand when measuring β-arrestin recruitment in the CHO-AM_1 cells. CGRP was 278-fold less potent than AM at this receptor. Although we have fitted a curve to the data, the effect is partial compared to AM. We could not use higher concentrations to achieve a greater response. To confirm the pharmacology we also measured cAMP production at the AM_1 receptor in these cells. AM was again the most potent ligand. In this case CGRP was at least 1000-fold less potent than AM, although it was not possible to determine a potency value.

In the CHO-CGRP cells, both CGRP and AM stimulated β-arrestin recruitment to the CGRP receptor. AM was 17-fold less potent than CGRP (**Figure S1**). When measuring cAMP production in the CHO-CGRP cells, CGRP and AM were both potent ligands, with CGRP being 43-fold more potent than AM. We also observed a response to calcitonin in both cell types when measuring cAMP. Calcitonin did not have an effect on β-arrestin recruitment for either receptor. CHO cells are known to contain an endogenous calcitonin receptor[14]. Given the functional calcitonin response within the cells, care should be taken when measuring cAMP or signaling pathways other than β-arrestin recruitment using the PathHunter system.

Continuing our validation of the CHO-AM_1 and CHO-CGRP cell lines, we characterized AM and CGRP receptor antagonists using AM_{22-52}, telcagepant and olcegepant (**Figure S2**). In the CHO-AM_1 cells, 1 μM of AM_{22-52} was able to antagonize AM-mediated β-arrestin recruitment producing a parallel, rightward shift in the concentration-effect curve. The calculated pA_2 was 7.05 ± 0.05 (n=3), consistent with literature values for antagonism of cAMP production[15-18]. No change in AM activity was seen with 10 μM telcagepant or olcegepant.

The effects of telcagepant and olcegepant on CGRP-stimulated β-arrestin recruitment to the CGRP receptor are shown in **Figure S2**. Telcagepant was tested at a concentration of 50 nM, which resulted in a parallel, rightward shift of the concentration-effect curve, consistent with its expected competitive antagonism at the CGRP receptor[19]. The resulting pA_2 value was 8.30 ± 0.10 (n=3). In contrast, increasing concentrations of olcegepant resulted in successive reductions in E_{max}. This suggests olcegepant is behaving as a non-competitive antagonist in this assay, which prevents the calculation of a pA_2 for these data.

Overall the pharmacology of these cells is consistent with the known pharmacology of these receptors, which enabled their use in screening.

	β-arrestin recruitment		cAMP accumulation	
	CHO-AM_1	CHO-CGRP	CHO-AM_1	CHO-CGRP
AM	8.52 ± 0.12	7.08 ± 0.15[a]	9.08 ± 0.12	8.06 ± 0.10[b]
CGRP	6.08 ± 0.11[c]	8.32 ± 0.15	<6	9.70 ± 0.15
Calcitonin	<6	<6	[d]	8.41 ± 0.11
Amylin	ND	ND	<6	<6

Table S5. Cell line validation
Potency (pEC_{50}) values for AM, CGRP, calcitonin and amylin in CHO-AM_1 or CHO-CGRP cells, measuring either β-arrestin recruitment or cAMP accumulation. n=3-6. ND: experiments not done. [a]$p<0.05$ by unpaired *t*-test compared to CGRP in the CHO-CGRP cells, measuring β-arrestin. [b]$p<0.05$ by unpaired *t*-test compared to CGRP in the CHO-CGRP cells, measuring cAMP. [c]$p<0.05$ by unpaired *t*-test compared to AM. [d] A weak response to calcitonin was observed in two of the four experiments.

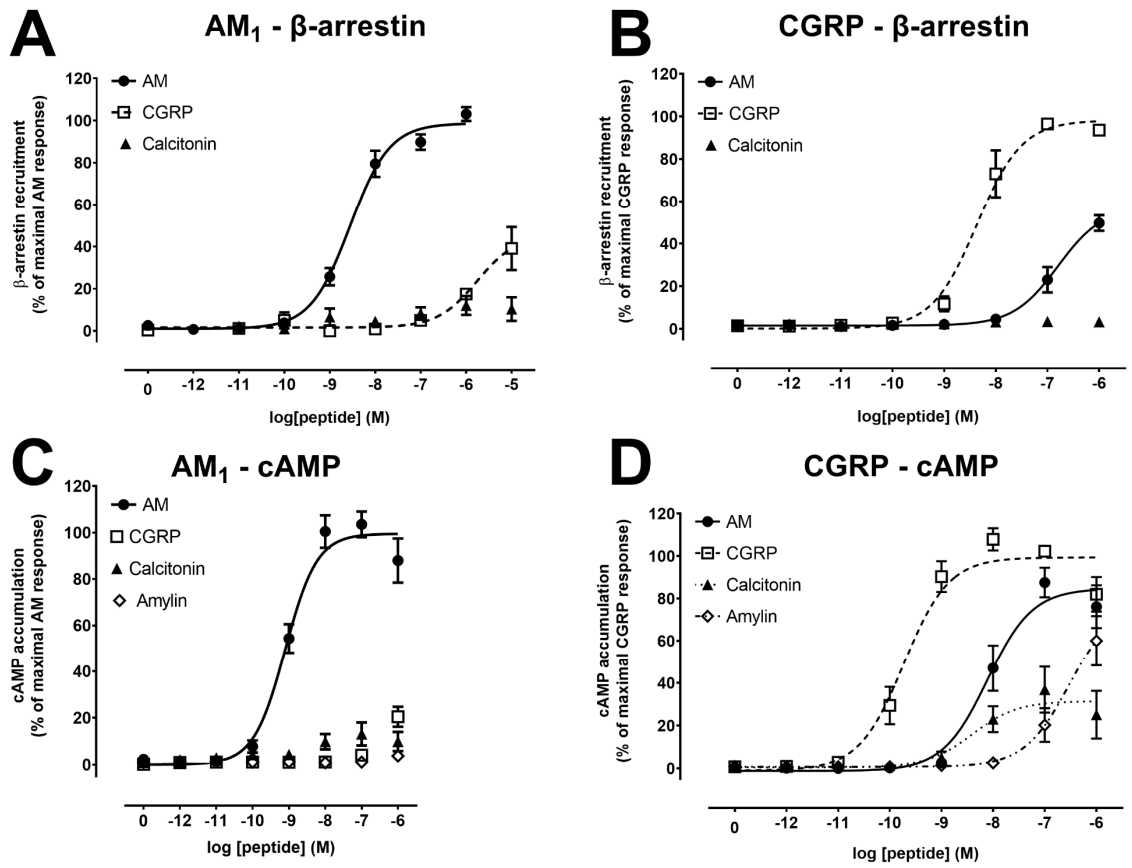


Figure S1
Validation of DiscoveRx CHO-AM_1 and CHO-CGRP cell lines measuring (A,B) β-arrestin recruitment or (C,D) cAMP production in response to peptide agonists (AM, CGRP, calcitonin or amylin). Data points are the mean ± s.e.m. of three to six independent experiments and are normalized to the maximal reponse with AM (A,C) or CGRP (B,D). Further experimental details are provided on page S161.

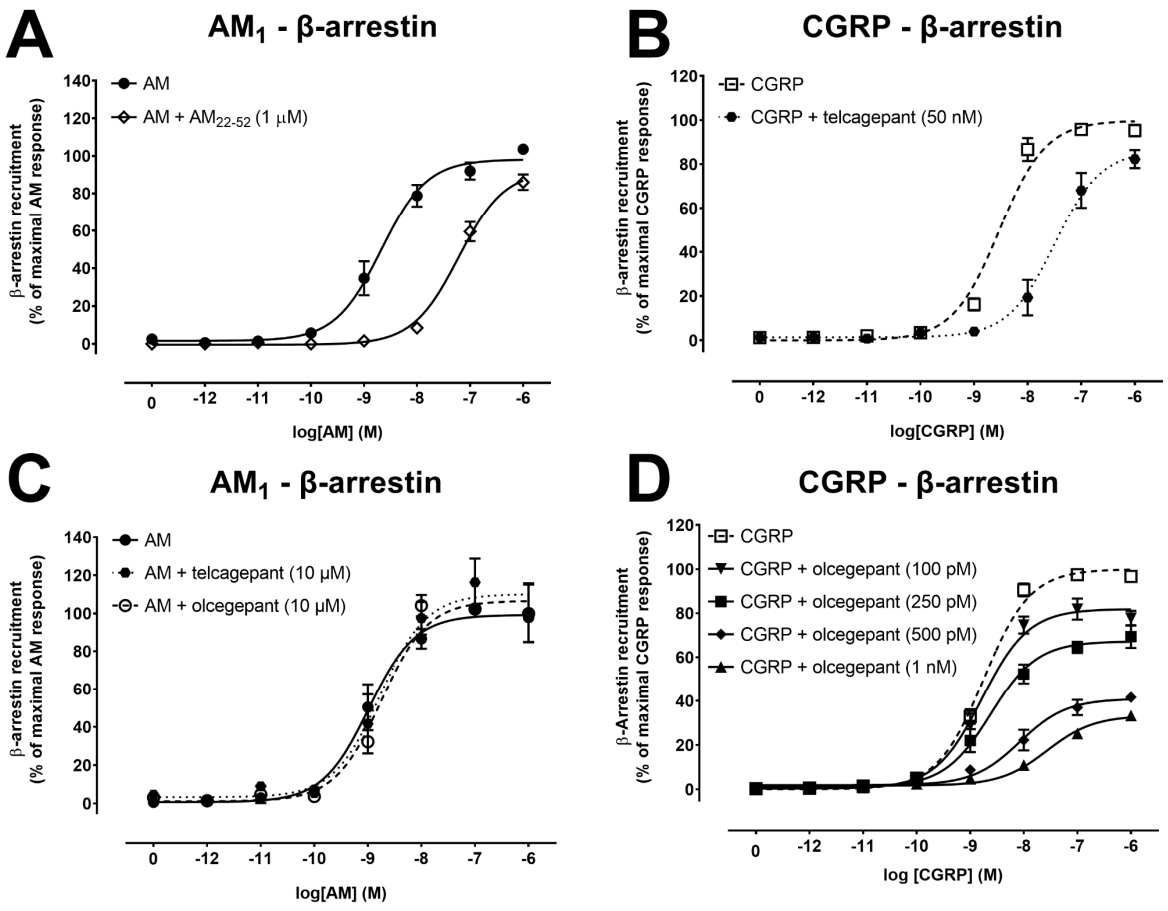


Figure S2
Validation of DiscoveRx CHO-AM_1 and CHO-CGRP cell lines using antagonists. Effects of antagonists on (A,B) β-arrestin recruitment or (C,D) cAMP production in response to AM or CGRP. Data points are the mean ± s.e.m. of three to six independent experiments and are normalized to the maximal response with AM or CGRP.

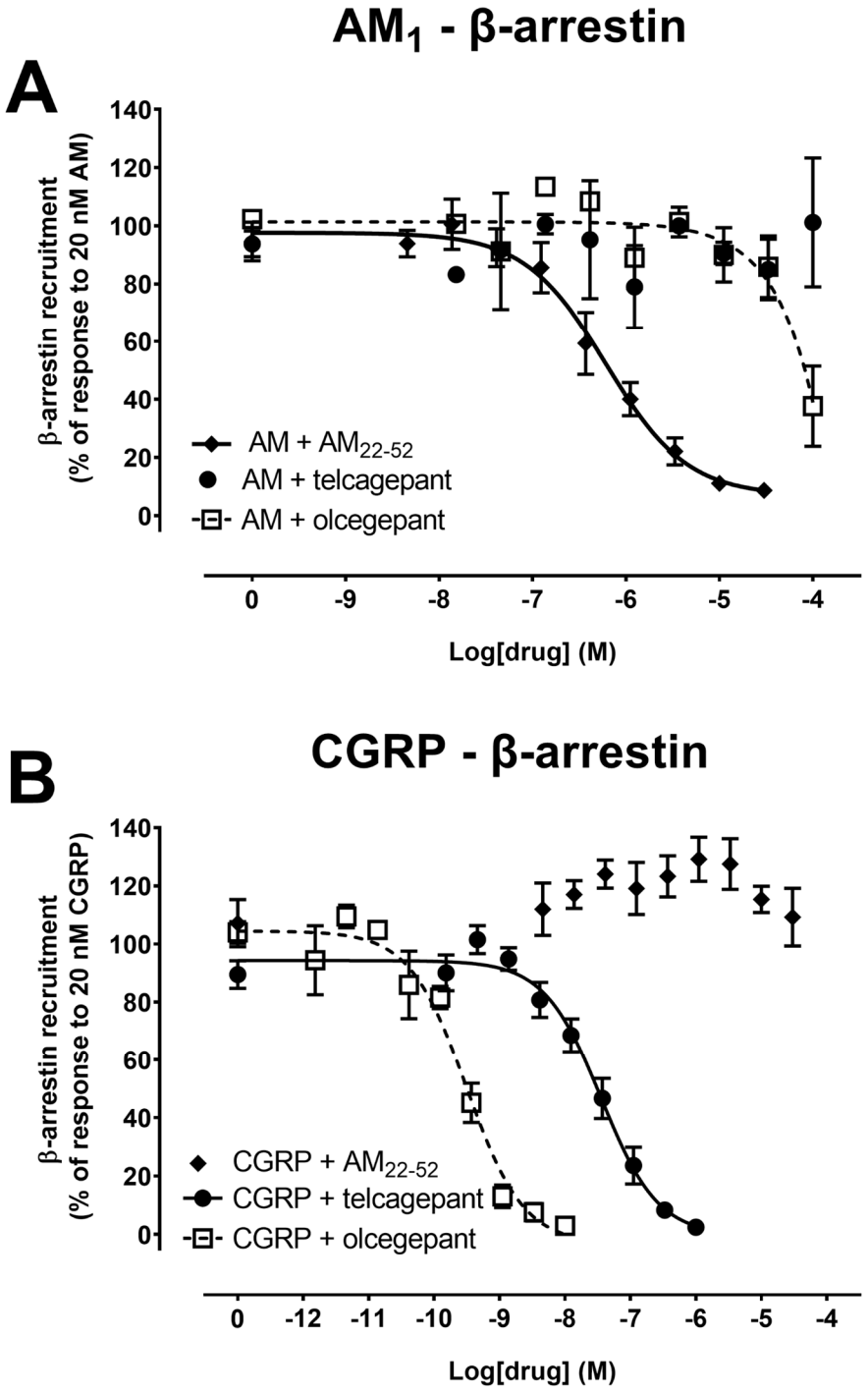


Figure S3
Validation of primary screening approach in (A) CHO-AM_1 cells or (B) CHO-CGRP cells. Effects of antagonists on β-arrestin recruitment in response to 20 nM AM or CGRP. Data points are the combined mean ± s.e.m. of two to eight independent experiments and are normalized to the maximal response with AM or CGRP.

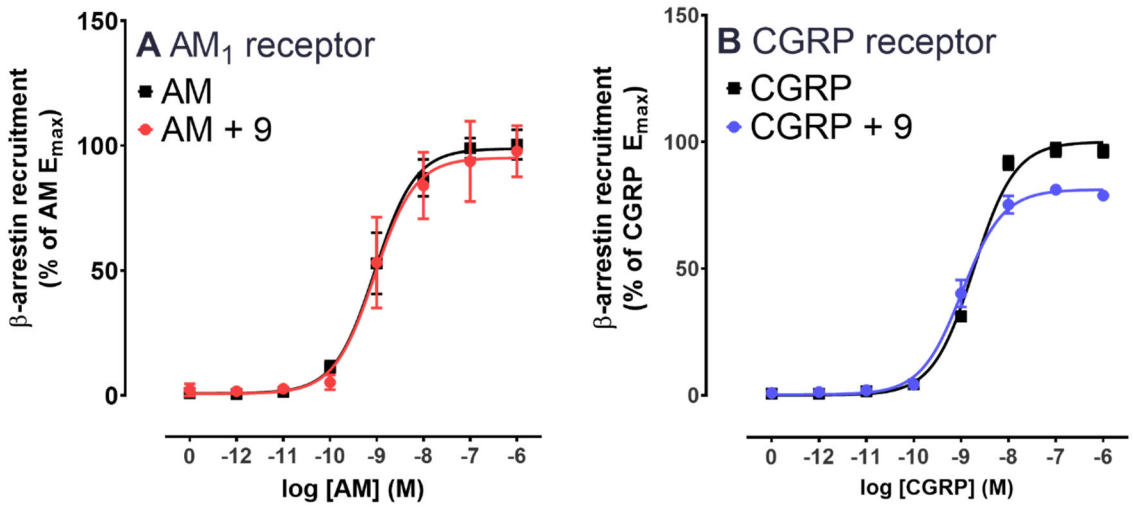


Figure S4
Compound **9** is a structurally-related inactive compound that does not positively modulate ligand-induced β-arrestin recruitment in CHO-AM_1 (A) or CHO-CGRP cells (B). Concentration-response curves are the combined mean ± s.e.m. from three independent experiments in triplicate wells comparing vehicle control with 50 μM of compound **9**.

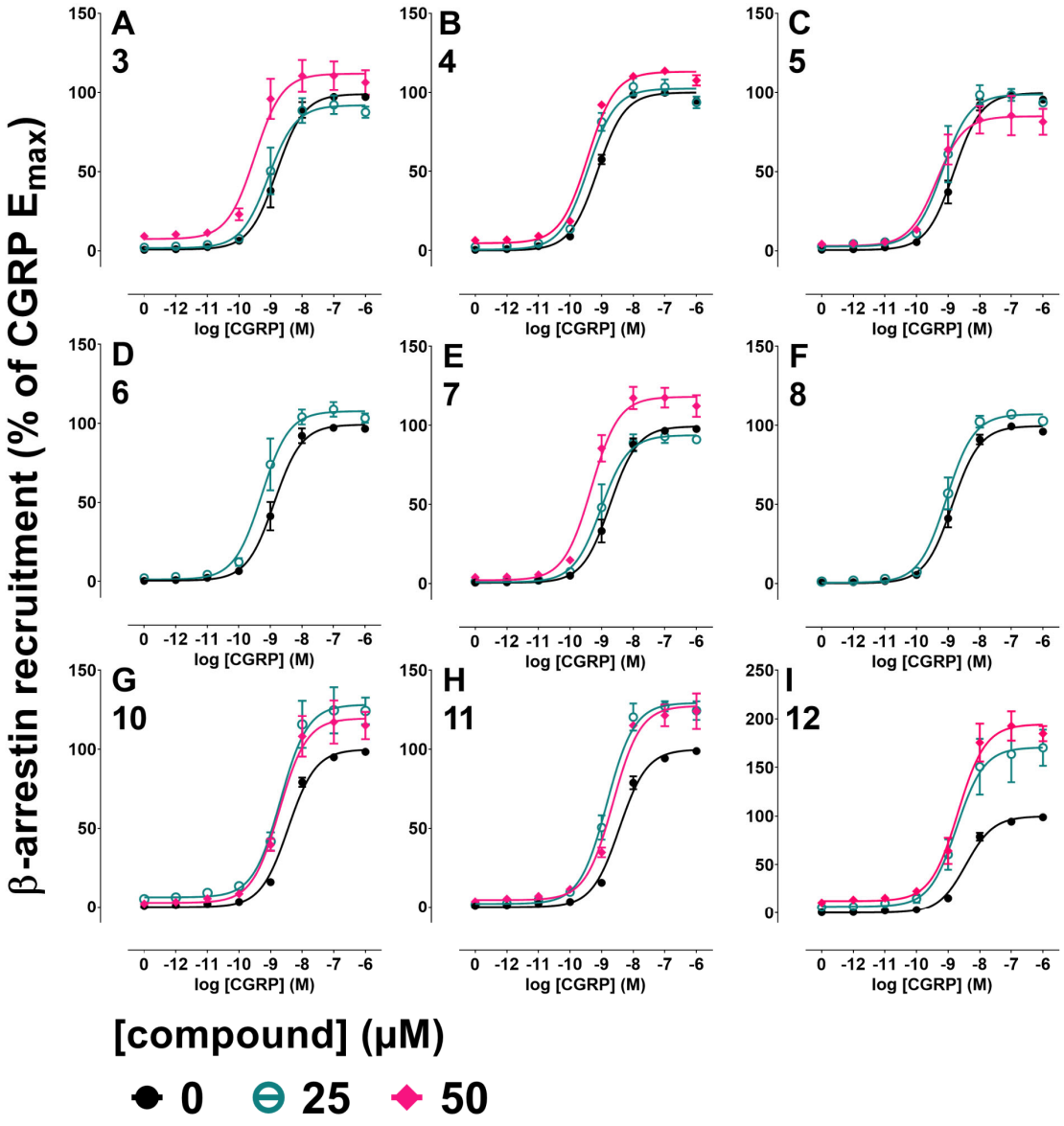


Figure S5
Weak modulation of CGRP-induced β-arrestin recruitment in CHO-CGRP cells by selected active compounds (**3-8, 10-12**). Concentration-response data shown are the mean ± s.e.m. from three to five independent experiments in triplicate wells, normalized to the response with CGRP + vehicle. Compounds **6** and **8** could not be tested at 50 μM due to solubility constraints.

		[Compound]							
		0	0.78125 μM	1.5625 μM	3.125 μM	6.25 μM	12.5 μM	25 μM	50 μM
3	pEC_{50}	9.06 ± 0.060		8.89 ± 0.24	8.96 ± 0.049*	8.91 ± 0.0075	9.19 ± 0.18	9.17 ± 0.061	9.63 ± 0.13
	E_{min}	0.00 ± 0.00		1.15 ± 2.13	0.66 ± 2.23	0.20 ± 1.80	2.33 ± 0.63	4.05 ± 0.81	34.1 ± 11.3
	E_{max}	100. ± 0.00		97.0 ± 4.55	102 ± 1.53	121 ± 5.30	138 ± 2.63*	155 ± 11.2	205 ± 44.5
4	pEC_{50}	8.96 ± 0.11		8.96 ± 0.027	9.11 ± 0.052	9.10 ± 0.057	9.42 ± 0.12	9.58 ± 0.047*	9.60 ± 0.12
	E_{min}	0.00 ± 0.00		-5.07 ± 1.36	-1.91 ± 3.45	-0.30 ± 1.91	4.01 ± 4.98	12.3 ± 7.05	43.0 ± 23.1
	E_{max}	100. ± 0.00		105 ± 5.63	110 ± 14.2	143 ± 17.0	184 ± 29.6	227 ± 44.4	240 ± 52.6
5	pEC_{50}	8.78 ± 0.11		8.98 ± 0.12*	9.01 ± 0.27	9.05 ± 0.25	9.29 ± 0.18	9.35 ± 0.091*	9.52 ± 0.13*
	E_{min}	0.00 ± 0.00		-0.56 ± 1.01	-0.24 ± 0.54	-0.36 ± 0.49	0.88 ± 3.05	9.16 ± 3.22	22.9 ± 4.75*
	E_{max}	100. ± 0.00		106 ± 4.57	120 ± 2.62	142 ± 5.21*	169 ± 9.27*	214 ± 20.3*	205 ± 9.84*
6	pEC_{50}	8.86 ± 0.020		8.90 ± 0.18	9.05 ± 0.16	9.00 ± 0.18	9.32 ± 0.15	9.39 ± 0.19	
	E_{min}	0.00 ± 0.00		0.142 ± 0.813	0.504 ± 1.50	-0.0212 ± 0.851	0.777 ± 0.704	4.61 ± 2.71*	
	E_{max}	100. ± 0.00		110 ± 7.87	129 ± 7.25	156 ± 5.97*	171 ± 1.49*	200. ± 6.04*	
7	pEC_{50}	8.96 ± 0.079		9.09 ± 0.089	9.13 ± 0.084	9.23 ± 0.12	9.34 ± 0.027*	9.47 ± 0.14	9.48 ± 0.070
	E_{min}	0.00 ± 0.00		0.455 ± 1.08	-0.301 ± 0.445	0.782 ± 2.93	-2.36 ± 1.07	5.44 ± 1.73	7.84 ± 5.86
	E_{max}	100. ± 0.00		109 ± 1.88	118 ± 3.55*	143 ± 4.41*	165 ± 11.4*	195 ± 8.70*	217 ± 14.0*
8	pEC_{50}	8.90 ± 0.18		8.98 ± 0.035	9.07 ± 0.10	8.96 ± 0.090	9.16 ± 0.039	9.20 ± 0.20	
	E_{min}	0.00 ± 0.00		-4.38 ± 2.30	0.257 ± 2.00	0.171 ± 1.09	2.47 ± 0.872	1.78 ± 2.17	
	E_{max}	100. ± 0.00		79.7 ± 6.92	99.4 ± 8.31	105 ± 3.27	112 ± 7.32	114 ± 12.0	
10	pEC_{50}	8.20 ± 0.12	8.37 ± 0.14	8.85 ± 0.21	8.32 ± 0.19	8.70 ± 0.32	8.77 ± 0.18	8.70 ± 0.13	8.37 ± 0.12
	E_{min}	0.00 ± 0.00	-2.27 ± 0.77	-3.64 ± 2.78	8.76 ± 3.42	3.66 ± 3.56	16.3 ± 11.7	41.0 ± 21.6	65.4 ± 24.5*
	E_{max}	100. ± 0.00	127 ± 22.8	132 ± 28.6	171 ± 38.2	209 ± 42.2	262 ± 90.2	334 ± 126	359 ± 102
11	pEC_{50}	8.12 ± 0.035	8.40 ± 0.16	8.71 ± 0.17	8.90 ± 0.15	8.73 ± 0.16	9.11 ± 0.10*	9.05 ± 0.038*	8.90 ± 0.070*
	E_{min}	0.00 ± 0.00	5.94 ± 3.62	21.9 ± 23.1	21.3 ± 22.3	31.9 ± 27.3	20.2 ± 17.6	43.6 ± 35.2	60.4 ± 43.1
	E_{max}	100. ± 0.00	129 ± 20.2	181 ± 53.7	236 ± 106	330 ± 159	317 ± 91.5	548 ± 250	409 ± 159
12	pEC_{50}	8.20 ± 0.10	8.01 ± 0.36	8.38 ± 0.085	8.81 ± 0.062	8.77 ± 0.030	8.72 ± 0.10	8.81 ± 0.10	8.58 ± 0.062
	E_{min}	0.00 ± 0.00	11.0 ± 9.50	14.8 ± 12.6	21.6 ± 24.6	32.0 ± 28.4	45.1 ± 32.5	91.2 ± 72.0	187 ± 119
	E_{max}	100. ± 0.00	155 ± 28.5	200 ± 64.0	203 ± 68.7	289 ± 95.2	391 ± 146	701 ± 301	1,010 ± 444

Table S6

Parameters for AM_1 receptor β-arrestin recruitment experiments conducted with multiple concentrations of compound and AM. Data are the same as Figure 5, but fitted with three parameter nonlinear regression and the pEC_{50}, E_{min} and E_{max} derived. Data are the mean ± s.e.m of three experiments as per Figure 5. pEC_{50} values were statistically tested using a repeated measures mixed-effects model with Dunnett's post hoc test compared to AM only. For testing differences in the E_{min} and E_{max}, the raw values were log-transformed, then the resultant values were analyzed using a repeated measures mixed-effects model with post hoc Dunnett's test compared to AM. Significance (*) was accepted at $p<0.05$.

		[Compound]		
		0	25 μM	50 μM
3	pEC_{50}	8.81 ± 0.17	8.98 ± 0.26	9.48 ± 0.076
	E_{min}	0.00 ± 0.00	-0.0511 ± 0.457	7.37 ± 1.98*
	E_{max}	100. ± 0.00	92.0 ± 4.35	112 ± 9.32
4	pEC_{50}	9.13 ± 0.047	9.43 ± 0.067*	9.44 ± 0.033*
	E_{min}	0.00 ± 0.00	0.517 ± 0.496	4.59 ± 1.54
	E_{max}	100. ± 0.00	103 ± 4.53	113 ± 1.98
5	pEC_{50}	8.87 ± 0.12	9.22 ± 0.29	9.47 ± 0.024*
	E_{min}	0.00 ± 0.00	1.40 ± 1.40	2.45 ± 0.231*
	E_{max}	100. ± 0.00	102 ± 3.17	90.2 ± 11.9
6	pEC_{50}	9.01 ± 0.090	9.46 ± 0.032$^{\#}$	
	E_{min}	0.00 ± 0.00	0.690 ± 0.893	
	E_{max}	100. ± 0.00	110 ± 3.12	
7	pEC_{50}	8.78 ± 0.13	9.07 ± 0.18*	9.45 ± 0.085*
	E_{min}	0.00 ± 0.00	0.0347 ± 0.261	1.37 ± 0.749
	E_{max}	100. ± 0.00	95.7 ± 2.22	114 ± 6.45
8	pEC_{50}	8.83 ± 0.084	8.98 ± 0.095	
	E_{min}	0.00 ± 0.00	0.439 ± 0.117$^{\#}$	
	E_{max}	100. ± 0.00	106 ± 0.0667$^{\#}$	
10	pEC_{50}	8.44 ± 0.025	8.74 ± 0.051*	8.69 ± 0.071*
	E_{min}	0.00 ± 0.00	2.61 ± 1.41	6.20 ± 1.70*
	E_{max}	100. ± 0.00	120 ± 12.1	129 ± 12.5
11	pEC_{50}	8.43 ± 0.033	8.83 ± 0.084*	8.65 ± 0.072
	E_{min}	0.00 ± 0.00	1.95 ± 0.521	4.52 ± 0.406*
	E_{max}	100. ± 0.00	130 ± 4.46*	128 ± 8.20
12	pEC_{50}	8.43 ± 0.033	8.74 ± 0.11	8.68 ± 0.096
	E_{min}	0.00 ± 0.00	6.27 ± 1.74	12.2 ± 1.49*
	E_{max}	100. ± 0.00	171 ± 25.7	195 ± 12.5*

Table S7

Parameters for CGRP receptor β-arrestin recruitment experiments conducted with multiple concentrations of compound and CGRP. Data are shown in Figure S5, fitted with a three parameter nonlinear regression and the pEC_{50}, E_{min} and E_{max} derived. Data are the mean ± s.e.m. of three to five experiments as per Figure S5. For compounds 3-5, 7 and 10-12, pEC_{50} values were statistically tested using a repeated measures mixed-effects model with Dunnett's post hoc test compared to AM only. For testing differences in the E_{min} and E_{max}, the raw values were log-transformed, then the resultant values were analyzed using a repeated measures mixed-effects model with post hoc Dunnett's test compared to AM. Significance (*) was accepted at $p<0.05$. Data from compounds 6 and 8 were similarly analyzed, using a paired *t*-test for pEC_{50} and ratio paired *t*-test for E_{min} and E_{max}. Significance ($^{\#}$) was accepted at $p<0.05$.

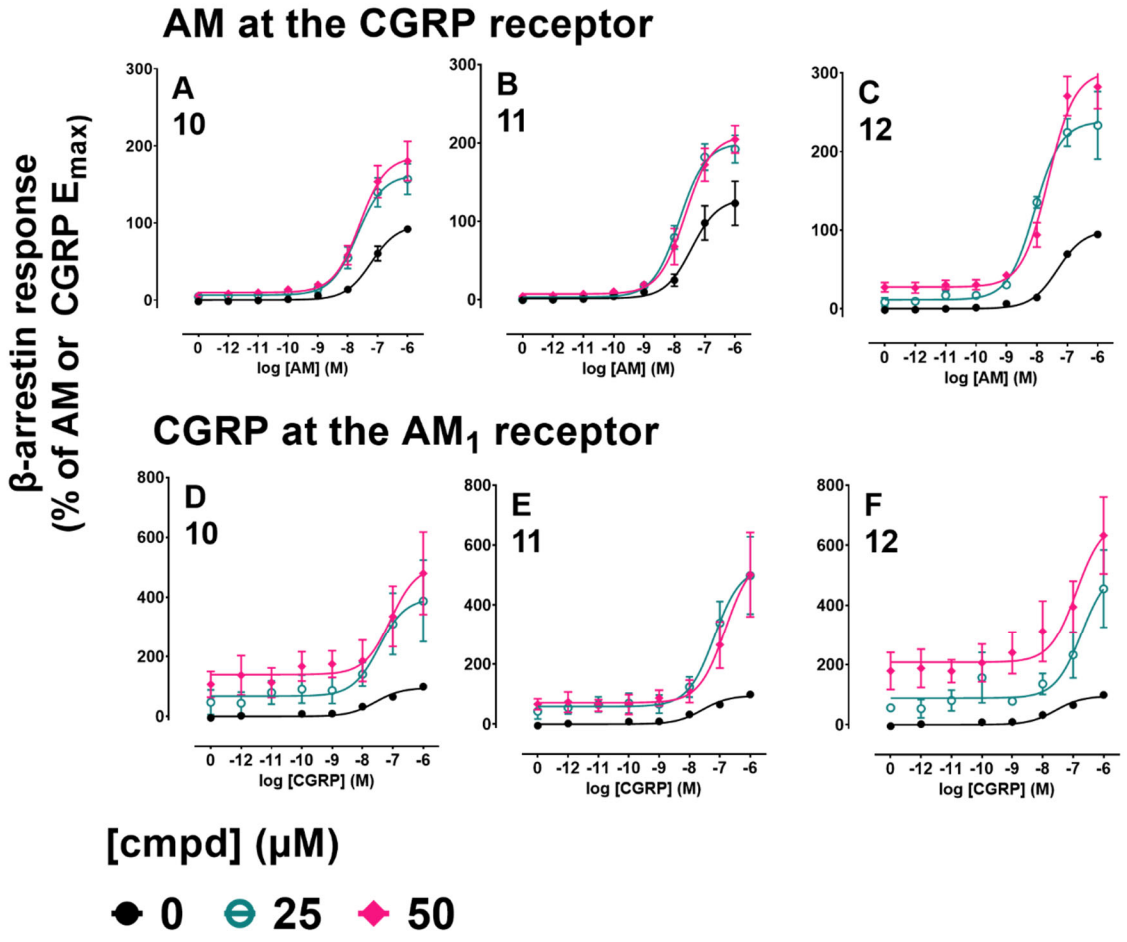


Figure S6
Ability of compounds **10-12** to modulate AM-induced β-arrestin recruitment in CHO-CGRP cells (A-C) or CGRP-induced β-arrestin recruitment in CHO-AM_1 cells (D-F). Concentration-response curves are the combined mean data from three to four independent experiments in triplicate wells, normalized to the response with CGRP or AM with vehicle. The mean ± s.e.m. has been plotted.

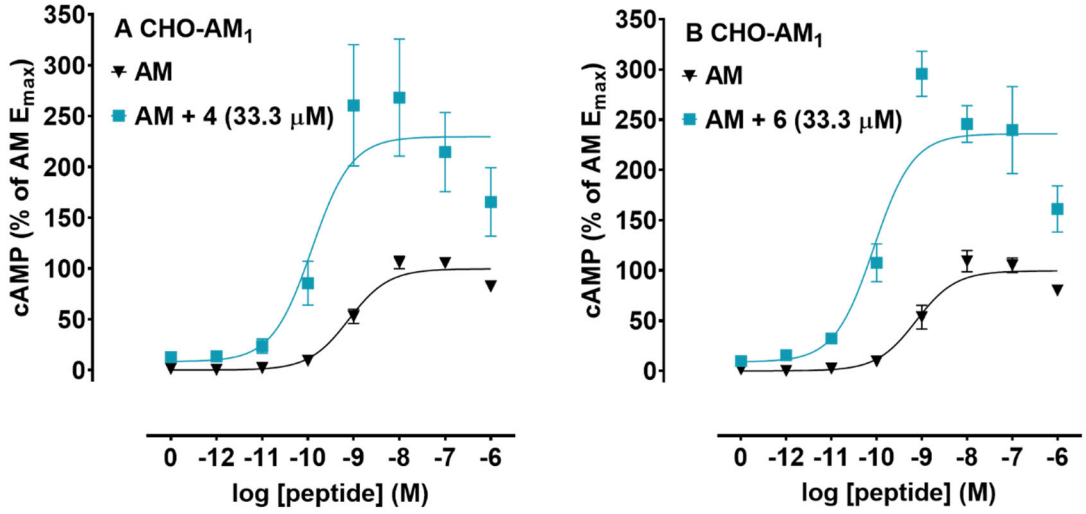


Figure S7
Modulation of AM-induced cAMP production in CHO-AM_1 cells by selected active compounds **4** (A) and **6** (B). Concentration-response curves are the combined mean data from three to five independent experiments in triplicate wells, normalized to the response with AM + vehicle. The mean ± s.e.m. has been plotted.

	+ vehicle		+ 25 μM compound 6				
	pEC_{50}	**s.e.m.**	**pEC_{50}**	**s.e.m.**	**E_{max}**	**s.e.m.**	**n**
Transfected Cos7 cells (Figure 6)							
AM at AM_1 receptor	9.11	0.09	9.84*	0.11	117%*[1]	4.90	14[2]
AM at CGRP receptor	8.09	0.13	9.20*	0.11	128%*[1]	9.74	6
AM at AM_2 receptor	9.43	0.17	9.95*	0.12	118%	17.1	6
CGRP at AM_1 receptor	6.87[2]	0.33	7.63*[3]	0.42	148%*[1]	17.1	4
CGRP at CGRP receptor	9.46	0.25	10.17*	0.17	112%	7.37	6
CGRP at AMY_1 receptor	9.37	0.10	9.52	0.15	113%	8.50	7
PACAP-38 at PAC_{1n} receptor	9.10	0.11	9.08	0.09	95.9%	4.01	5
CRF at CRF_1 receptor	9.82	0.20	9.90	0.21	98.3%	11.3	5
CT at CT receptor	9.89	0.25	9.88	0.21	117%	11.2	7
HMEC-1 cells (Figure 7)							
AM at endogenous AM-responsive receptors	8.99	0.12	10.4*	0.11	106%	10.0	6

Table S8
pEC_{50} and E_{max} values for modulation of cAMP production by compound **6** in transfected Cos7 cells or HMEC-1 cells. * indicates a significant difference compared to vehicle only control, $p<0.05$ by paired *t*-test. *[1]Significantly different from vehicle control by ratio paired *t*-test using E_{max} data before data was normalized to the E_{max} of the control curve. [2]AM at the AM_1 receptor has a higher n number because this was used as a control. Where two plates were processed on the same day, for statistical analysis the second AM curve was excluded. [3]In a further two experiments, no curve could be fitted to the data and these experiments were excluded from the analysis.

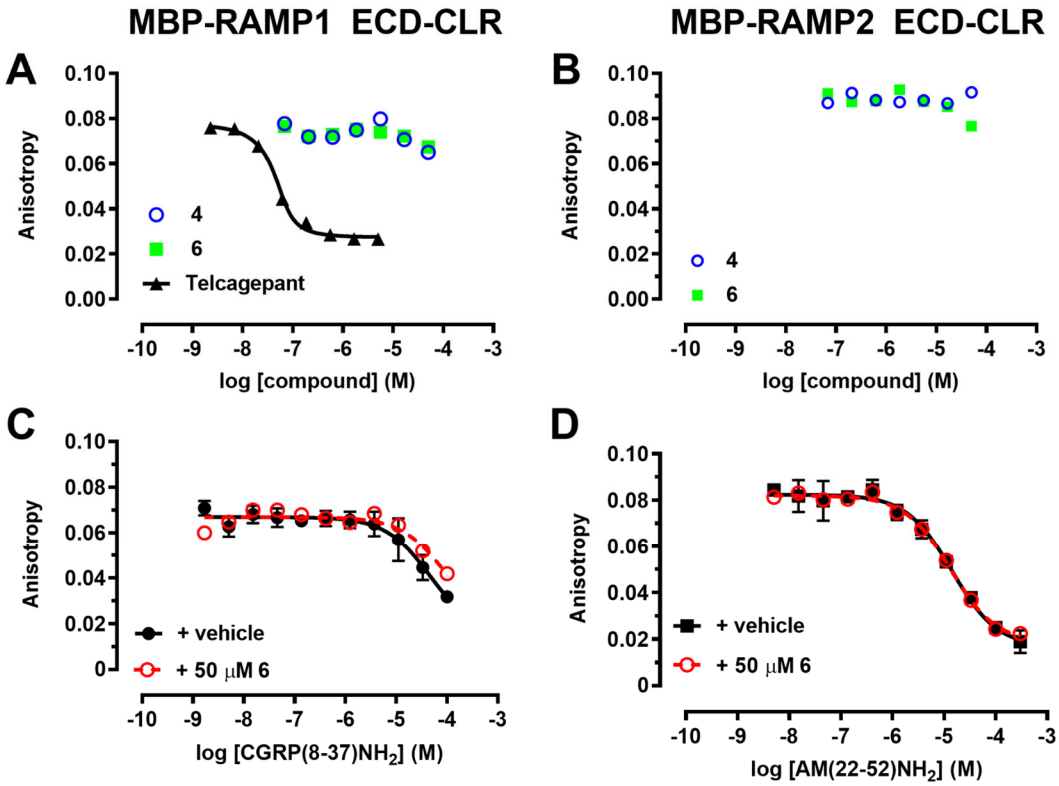


Figure S8

(A, B) Telcagepant displaces peptide probe binding to the CGRP receptor ECD preparation. Compounds **4** and **6** did not affect peptide probe binding to ECD protein preparations of the CGRP or AM_1 receptors. (**C, D**) Compound **6** does not affect binding of CGRP or AM probes to the CGRP or AM_1 receptor ECD protein preparations respectively. Two independent experiments were performed and a representative graph is shown. Under these assay conditions, **4** and **6** were assumed to be soluble.

References

[1] Burgey, C., Deng, Z., Nguyen, D., Paone, D., Shaw, A., and Williams, T. (2004) Cgrp Receptor Antagonists, MERCK & CO., INC., BURGEY, Christopher, S., DENG, Zhengwu, J., NGUYEN, Diem, N., PAONE, Daniel, V., SHAW, Anthony, W., WILLIAMS, Theresa, M.

[2] Obase, H., Takai, H., Teranishi, M., and Nakamizo, N. (1983) Synthesis of (1-substituted piperidin-4-yl)-1H-benzimidazoles and (1-substituted piperidin-4-yl)-3, 4-dihydroquinazolines as possible antihypertensive agents, *Journal of Heterocyclic Chemistry 20*, 565-573.

[3] Kislyi, V., and Semenov, V. (2001) Investigation of the regioselectivity of alkylation of 3-nitropyridin-2 (1H)-ones, *Russian Chemical Bulletin 50*, 460-463.

[4] Aciro, C., Bagal, S. K., Harvey, J. W., Jones, L. H., Mowbray, C. E., Owen, R. M., Sabnis, Y. A., Storer, R. I., and Yeap, S. K. (2010) Preparation of cyclobutenedione derivatives as modulators of CXCR-2 receptor for the treatment of asthma and COPD.

[5] McLaughlin, M., Palucki, M., and Davies, I. W. (2006) Efficient access to cyclic ureas via pd-catalyzed cyclization, *Organic letters 8*, 3311-3314.

[6] Gingell, J. J., Qi, T., Bailey, R. J., and Hay, D. L. (2010) A key role for tryptophan 84 in receptor activity-modifying protein 1 in the amylin 1 receptor, *Peptides 31*, 1400-1404.

[7] Leach, K., Sexton, P. M., and Christopoulos, A. (2007) Allosteric GPCR modulators: taking advantage of permissive receptor pharmacology, *Trends in pharmacological sciences 28*, 382-389.

[8] Huang, X.-P., Karpiak, J., Kroeze, W. K., Zhu, H., Chen, X., Moy, S. S., Saddoris, K. A., Nikolova, V. D., Farrell, M. S., and Wang, S. (2015) Allosteric ligands for the pharmacologically dark receptors GPR68 and GPR65, *Nature 527*, 477.

[9] Hay, D. L., Poyner, D. R., and Walker, C. S. (2019) Calcitonin receptors (version 2019.4) in the IUPHAR/BPS Guide to Pharmacology Database, *IUPHAR/BPS Guide to Pharmacology 2019*.

[10] Kenakin, T. P. (2014) Chapter 7 - Allosteric Modulation, In *A Pharmacology Primer (Fourth Edition)* (Kenakin, T. P., Ed.), pp 155-180, Academic Press, San Diego.

[11] Roehrkasse, A. M., Booe, J. M., Lee, S.-M., Warner, M. L., and Pioszak, A. A. (2018) Structure–function analyses reveal a triple β-turn receptor-bound conformation of adrenomedullin 2/intermedin and enable peptide antagonist design, *Journal of Biological Chemistry 293*, 15840-15854.

[12] Roehrl, M. H., Wang, J. Y., and Wagner, G. (2004) A general framework for development and data analysis of competitive high-throughput screens for small-molecule inhibitors of protein− protein interactions by fluorescence polarization, *Biochemistry 43*, 16056-16066.

[13] Lee, S.-M., Booe, J. M., Gingell, J. J., Sjoelund, V., Hay, D. L., and Pioszak, A. A. (2017) N-Glycosylation of asparagine 130 in the extracellular domain of the human calcitonin receptor significantly increases peptide hormone affinity, *Biochemistry 56*, 3380-3393.

[14] Horie, K., and Insel, P. A. (2000) Retrovirally Mediated Transfer of a G Protein-coupled Receptor Kinase (GRK) Dominant-negative Mutant Enhances Endogenous Calcitonin Receptor Signaling in Chinese Hamster Ovary Cells. GRK inhibition enhances expression of receptors and receptor mRNA, *Journal of Biological Chemistry 275*, 29433-29440.

[15] Robinson, S. D., Aitken, J. F., Bailey, R. J., Poyner, D. R., and Hay, D. L. (2009) Novel Peptide Antagonists of Adrenomedullin and Calcitonin Gene-Related Peptide Receptors: Identification, Pharmacological Characterization, and Interactions with Position 74 in Receptor Activity-Modifying Protein 1/3, *Journal of Pharmacology and Experimental Therapeutics 331*, 513-521.

[16] Watkins, H., Au, M., Bobby, R., Archbold, J., Abdul-Manan, N., Moore, J., Middleditch, M., Williams, G., Brimble, M., and Dingley, A. (2013) Identification of key residues involved in adrenomedullin binding to the AM1 receptor, *British journal of pharmacology 169*, 143-155.

[17] Hay, D. L., Howitt, S. G., Conner, A. C., Schindler, M., Smith, D. M., and Poyner, D. R. (2003) CL/RAMP2 and CL/RAMP3 produce pharmacologically distinct adrenomedullin receptors: a comparison of effects of adrenomedullin22–52, CGRP8–37 and BIBN4096BS, *British journal of pharmacology 140*, 477-486.
[18] Hay, D. L., Garelja, M. L., Poyner, D. R., and Walker, C. S. (2018) Update on the pharmacology of calcitonin/CGRP family of peptides: IUPHAR Review 25, *British journal of pharmacology 175*, 3-17.
[19] Walker, C. S., Raddant, A. C., Woolley, M. J., Russo, A. F., and Hay, D. L. (2017) CGRP receptor antagonist activity of olcegepant depends on the signalling pathway measured, *Cephalalgia*, 0333102417691762.