Supporting Information

Discovery of a Potent and Orally Bioavailable Benzolactam-Derived Inhibitor of Polo-Like Kinase 1 (MLN0905)

Matthew O. Duffey, Tricia J. Vos, Ruth Adams, Jennifer Alley, Justin Anthony, Cynthia Barrett, Indu Bharathan, Douglas Bowman, Nancy J. Bump, Ryan Chau, Courtney Cullis, Denise L. Driscoll, Amy Elder, Nancy Forsyth, Jonathan Frazer, Jianping Guo, Luyi Guo, Marc L. Hyer, David Janowick, Bheemashankar Kulkarni, Su-Jen Lai, Kerri Lasky, Gang Li, Jing Li, Debra Liao, Jeremy Little, Bo Peng, Mark G. Qian, Dominic J. Reynolds, Mansoureh Rezaei, Margaret Porter Scott, Todd B. Sells, Vaishali Shinde, Qiuju Judy Shi, Michael D. Sintchak, Francois Soucy, Kevin T. Sprott, Stephen G. Stroud, Michelle Nestor, Irache Visiers, Gabriel Weatherhead, Yingchun Ye, and Natalie D'Amore.*

Millennium Pharmaceuticals, Inc, 40 Landsdowne St, Cambridge, MA 02139.

Supporting Information Contents:

Supporting Information Table 1. Summary of kinase binding data for **12b**.

Ambit Binding Data: Compound 12b [a]

Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM	Target KinasE	% INH @ 1 μM
AAK1	13	CAMK2B	16	DCAMKL1	91	FES	88
ABL1	26	CAMK2D	4	DCAMKL2	23	FGFR1	75
ABL2	26	CAMK2G	13	DCAMKL3	53	FGFR2	48
ACVR1	0	CAMK4	4	DDR1	77	FGFR3	60
ACVR1B	4	CAMKK1	19	DDR2	88	FGFR4	80
ACVR2A	0	CAMKK2	23	DLK	11	FGR	0
ACVR2B	6	CDC2L1	0	DMPK	7	FLT1	79
ACVRL1	7	CDC2L2	0	DMPK2	0	FLT3	76
ADCK3	0	CDK11	10	DRAK1	3	FLT4	100
ADCK4	0	CDK2	19	DRAK2	30	FRK	44
AKT1	5	CDK3	0	DYRK1A	15	FYN	17
AKT2	3	CDK5	8	DYRK1B	12	GAK	18
AKT3	15	CDK7	68	DYRK2	65	GRK1	41
ALK	92	CDK8	21	EGFR	0	GRK4	0
AMPK-α1	38	CDK9	28	EPHA1	5	GRK7	16
AMPK-α2	25	CDKL2	2	EPHA2	18	GSK3A	27
ANKK1	0	CDKL3	9	EPHA3	0	GSK3B	40
ARK5	25	CDKL5	3	EPHA4	6	HCK	13
ASK1	0	CHEK1	27	EPHA5	12	HIPK1	0
ASK2	0	CHEK2	38	EPHA6	0	HIPK2	0
AURKA	6	CIT	17	EPHA7	9	HIPK3	0
AURKB	12	CLK1	57	EPHA8	0	HIPK4	39
AURKC	10	CLK2	47	EPHB1	25	HPK1	0
AXL	5	CLK3	38	EPHB2	0	HUNK	4
BIKE	5	CLK4	51	EPHB3	0	ICK	8
BLK	43	CSF1R	81	EPHB4	7	IGF1R	69
BMPR1A	3	CSK	2	EPHB6	1	IKKα	10
BMPR1B	0	CSNK1A1L	42	ERBB2	4	IKKβ	4
BMPR2	0	CSNK1D	18	ERBB3	5	IKKε	16
BMX	0	CSNK1E	15	ERBB4	4	INSR	60
BRAF	2	CSNK1G1	16	ERK1	7	INSRR	60
BRK	8	CSNK1G2	16	ERK2	8	IRAK1	55
BRSK1	9	CSNK1G3	9	ERK3	29	IRAK3	0
BRSK2	2	CSNK2A1	20	ERK4	29	ITK	4
BTK	0	CSNK2A2	15	ERK5	58	JAK1(JH1)	33
CAMK1	10	CTK	55	ERK8	16	JAK1(JH2)	10
CAMK1D	67	DAPK1	46	ERN1	21	JAK2(JH1)	2
CAMK1G	14	DAPK2	30	FAK	89	JAK3(JH1)	13
CAMK2A	17	DAPK3	45	FER	91	JNK1	2

Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM
JNK2	2	MKNK1	1	PCTK1	36	PRKG2	0
JNK3	16	MKNK2	35	PCTK2	2	PRKR	17
KIT	81	MLCK	10	PCTK3	0	PRKX	0
LATS1	5	MLK1	15	PDGFRA	11	PRP4	0
LATS2	0	MLK2	43	PDGFRB	99	PYK2	73
LCK	33	MLK3	37	PDPK1	8	QSK	15
LIMK1	0	MRCKA	0	PFTAIRE2	14	RAF1	21
LIMK2	0	MRCKB	9	PFTK1	4	RET	5
LKB1	0	MST1	0	PHKG1	23	RIOK1	1
LOK	27	MST1R	2	PHKG2	30	RIOK2	28
LTK	99	MST2	0	PIK3C2B	0	RIOK3	2
LYN	16	MST3	27	PIK3C2G	0	RIPK1	0
LZK	0	MST4	29	PIK3CA	0	RIPK2	21
MAK	0	MUSK	39	PIK3CB	31	RIPK4	18
MAP3K1	12	MYLK	0	PIK3CD	24	ROCK1	66
MAP3K15	26	MYLK2	0	PIK3CG	32	ROCK2	18
MAP3K2	65	MYO3A	15	PIK4CB	17	ROS1	60
MAP3K3	0	MYO3B	9	PIM1	18		
MAP3K4	21	NDR1	32	PIM2	8		
MAP4K2	0	NDR2	1	PIM3	11		
MAP4K3	21	NEK1	13	PIP5K1A	0		
MAP4K4	42	NEK2	55	PIP5K2B	19		
MAP4K5	5	NEK5	12	PKAC-α	20		
MAPKAPK2	0	NEK6	83	PKAC-β	27		
MAPKAPK5	0	NEK7	38	PKMYT1	10		
MARK1	1	NEK9	8	PKN1	12		
MARK2	0	NIM1	87	PKN2	27		
MARK3	18	NLK	10	PLK1	96		
MARK4	0	OSR1	64	PLK2	49		
MAST1	0	p38-α	2	PLK3	94		
MEK1	26	p38-β	0	PLK4	34		
MEK2	38	p38-δ	4	PRKCD	0		
MEK3	0	p38-γ	8	PRKCE	46		
MEK4	0	PAK1	17	PRKCH	0		
MEK6	15	PAK2	16	PRKCQ	0		
MELK	0	PAK3	11	PRKD1	78		
MERTK	99	PAK4	20	PRKD2	94		
MET	15	PAK6	10	PRKD3	93		
MINK	0	PAK7	14	PRKG1	21		

Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM
RPS6KA1(Kin.Dom.1-N-terminal)	5	TIE1	9
RPS6KA1(Kin.Dom.2-C-terminal)	22	TIE2	17
RPS6KA2(Kin.Dom.1-N-terminal)	6	TLK1	15
RPS6KA2(Kin.Dom.2-C-terminal)	25	TLK2	13
RPS6KA3(Kin.Dom.1-N-terminal)	9	TNIK	11
RPS6KA4(Kin.Dom.1-N-terminal)	15	TNK1	49
RPS6KA4(Kin.Dom.2-C-terminal)	98	TNK2	94
RPS6KA5(Kin.Dom.1-N-terminal)	12	TNNI3K	29
RPS6KA5(Kin.Dom.2-C-terminal)	62	TRKA	15
RPS6KA6(Kin.Dom.1-N-terminal)	10	TRKB	12
RPS6KA6(Kin.Dom.2-C-terminal)	31	TRKC	5
SBK1	18	TSSK1B	27
SgK085	0	TTK	23
SgK110	11	TXK	0
SIK	27	TYK2(JH1)	9
SIK2	54	TYK2(JH2)	66
SLK	41	TYRO3	15
SNARK	81	ULK1	96
SRC	33	ULK2	85
SRMS	14	ULK3	21
SRPK1	0	VEGFR2	11
SRPK2	8	WEE1	10
SRPK3	0	WEE2	37
STK16	9	YANK2	4
STK33	88	YANK3	15
STK35	18	YES	6
STK36	0	YSK1	5
STK39	75	YSK4	28
SYK	18	ZAK	0
TAK1	0	ZAP70	24
TAO1	0		
TAOK1	0		
TAOK3	0		
TBK1	14		
TEC	8		
TESK1	0		
TGFBR1	19		
TGFBR2	9		

[a]Compound **12b** was evaluated in a multi-kinase binding screen, KINOMEscan™. Developed and marketed by Ambit Biosciences, KINOMEscan™ is a competition binding assay that quantitatively measures the ability of a compound to compete with an immobilized, active-site directed ligand (see: http://www.kinomescan.com). **12b** was screened against 359 kinases at 1 μM.

Supporting Information Table 1. Summary of kinase binding data for **12c**.

Ambit Binding Data: Compound 12c [a]

Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM	Target KinasE	% INH @ 1 μM
AAK1	8	CAMK2B	21	DCAMKL1	90	FES	84
ABL1	7	CAMK2D	0	DCAMKL2	11	FGFR1	53
ABL2	20	CAMK2G	6	DCAMKL3	56	FGFR2	42
ACVR1	0	CAMK4	25	DDR1	61	FGFR3	47
ACVR1B	4	CAMKK1	12	DDR2	76	FGFR4	71
ACVR2A	0	CAMKK2	16	DLK	12	FGR	0
ACVR2B	0	CDC2L1	0	DMPK	0	FLT1	68
ACVRL1	27	CDC2L2	0	DMPK2	0	FLT3	58
ADCK3	18	CDK11	0	DRAK1	0	FLT4	98
ADCK4	0	CDK2	12	DRAK2	23	FRK	30
AKT1	5	CDK3	0	DYRK1A	15	FYN	8
AKT2	0	CDK5	2	DYRK1B	10	GAK	17
AKT3	9	CDK7	66	DYRK2	59	GRK1	37
ALK	89	CDK8	24	EGFR	0	GRK4	16
AMPK-α1	22	CDK9	14	EPHA1	0	GRK7	28
AMPK-α2	3	CDKL2	0	EPHA2	8	GSK3A	3
ANKK1	0	CDKL3	3	EPHA3	14	GSK3B	36
ARK5	0	CDKL5	3	EPHA4	0	HCK	3
ASK1	0	CHEK1	20	EPHA5	8	HIPK1	0
ASK2	0	CHEK2	21	EPHA6	1	HIPK2	0
AURKA	9	CIT	10	EPHA7	10	HIPK3	1
AURKB	9	CLK1	67	EPHA8	3	HIPK4	22
AURKC	10	CLK2	41	EPHB1	22	HPK1	0
AXL	0	CLK3	60	EPHB2	0	HUNK	7
BIKE	4	CLK4	53	EPHB3	0	ICK	9
BLK	16	CSF1R	77	EPHB4	7	IGF1R	42
BMPR1A	0	CSK	0	EPHB6	0	IKKα	22
BMPR1B	0	CSNK1A1L	17	ERBB2	6	IKKβ	0
BMPR2	0	CSNK1D	8	ERBB3	0	IKKε	13
BMX	7	CSNK1E	22	ERBB4	12	INSR	34
BRAF	0	CSNK1G1	14	ERK1	7	INSRR	26
BRK	8	CSNK1G2	15	ERK2	8	IRAK1	60
BRSK1	8	CSNK1G3	21	ERK3	30	IRAK3	0
BRSK2	0	CSNK2A1	15	ERK4	2	ITK	1
BTK	0	CSNK2A2	0	ERK5	48	JAK1(JH1)	5
CAMK1	0	CTK	39	ERK8	17	JAK1(JH2)	0
CAMK1D	43	DAPK1	34	ERN1	4	JAK2(JH1)	9
CAMK1G	8	DAPK2	20	FAK	65	JAK3(JH1)	20
CAMK2A	12	DAPK3	28	FER	81	JNK1	0

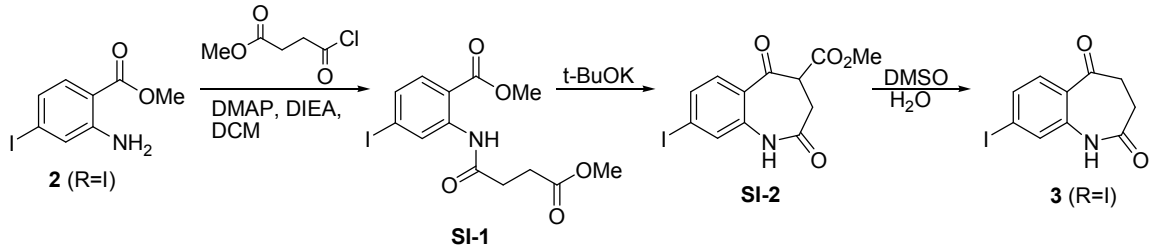
Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM
JNK2	3	MKNK1	16	PCTK1	27	PRKG2	6
JNK3	14	MKNK2	0	PCTK2	3	PRKR	6
KIT	40	MLCK	0	PCTK3	0	PRKX	0
LATS1	14	MLK1	9	PDGFRA	0	PRP4	0
LATS2	0	MLK2	18	PDGFRB	99	PYK2	53
LCK	28	MLK3	28	PDPK1	5	QSK	0
LIMK1	5	MRCKA	0	PFTAIRE2	21	RAF1	10
LIMK2	0	MRCKB	4	PFTK1	0	RET	6
LKB1	0	MST1	0	PHKG1	18	RIOK1	0
LOK	8	MST1R	14	PHKG2	25	RIOK2	22
LTK	98	MST2	0	PIK3C2B	0	RIOK3	0
LYN	12	MST3	18	PIK3C2G	0	RIPK1	0
LZK	2	MST4	8	PIK3CA	0	RIPK2	10
MAK	6	MUSK	25	PIK3CB	23	RIPK4	17
MAP3K1	27	MYLK	0	PIK3CD	31	ROCK1	36
MAP3K15	22	MYLK2	0	PIK3CG	36	ROCK2	24
MAP3K2	44	MYO3A	2	PIK4CB	9	ROS1	50
MAP3K3	0	MYO3B	14	PIM1	18		
MAP3K4	10	NDR1	35	PIM2	0		
MAP4K2	0	NDR2	4	PIM3	11		
MAP4K3	15	NEK1	16	PIP5K1A	0		
MAP4K4	26	NEK2	66	PIP5K2B	19		
MAP4K5	6	NEK5	2	PKAC-a	7		
MAPKAPK2	21	NEK6	77	PKAC-b	13		
MAPKAPK5	6	NEK7	22	PKMYT1	9		
MARK1	0	NEK9	2	PKN1	0		
MARK2	7	NIM1	80	PKN2	3		
MARK3	18	NLK	3	PLK1	95		
MARK4	0	OSR1	16	PLK2	54		
MAST1	0	p38-α	11	PLK3	94		
MEK1	17	p38-β	0	PLK4	33		
MEK2	30	p38-δ	22	PRKCD	0		
MEK3	0	p38-γ	2	PRKCE	48		
MEK4	0	PAK1	19	PRKCH	0		
MEK6	11	PAK2	13	PRKCQ	0		
MELK	0	PAK3	6	PRKD1	79		
MERTK	95	PAK4	9	PRKD2	70		
MET	10	PAK6	9	PRKD3	90		
MINK	0	PAK7	13	PRKG1	8		

Target Kinase	% INH @ 1 μM	Target Kinase	% INH @ 1 μM
RPS6KA1(Kin.Dom.1-N-terminal)	0	TIE1	30
RPS6KA1(Kin.Dom.2-C-terminal)	31	TIE2	7
RPS6KA2(Kin.Dom.1-N-terminal)	0	TLK1	17
RPS6KA2(Kin.Dom.2-C-terminal)	21	TLK2	9
RPS6KA3(Kin.Dom.1-N-terminal)	8	TNIK	11
RPS6KA4(Kin.Dom.1-N-terminal)	4	TNK1	50
RPS6KA4(Kin.Dom.2-C-terminal)	95	TNK2	88
RPS6KA5(Kin.Dom.1-N-terminal)	9	TNNI3K	21
RPS6KA5(Kin.Dom.2-C-terminal)	36	TRKA	1
RPS6KA6(Kin.Dom.1-N-terminal)	14	TRKB	4
RPS6KA6(Kin.Dom.2-C-terminal)	41	TRKC	7
SBK1	11	TSSK1B	19
SgK085	0	TTK	1
SgK110	5	TXK	0
SIK	8	TYK2(JH1)	1
SIK2	40	TYK2(JH2)	60
SLK	19	TYRO3	17
SNARK	71	ULK1	97
SRC	18	ULK2	94
SRMS	5	ULK3	15
SRPK1	0	VEGFR2	44
SRPK2	31	WEE1	3
SRPK3	14	WEE2	30
STK16	12	YANK2	0
STK33	79	YANK3	4
STK35	10	YES	7
STK36	0	YSK1	13
STK39	47	YSK4	16
SYK	14	ZAK	0
TAK1	7	ZAP70	12
TAO1	0		
TAOK1	0		
TAOK3	0		
TBK1	17		
TEC	6		
TESK1	0		
TGFBR1	17		
TGFBR2	8		

[a]Compound **12c** was evaluated in a multi-kinase binding screen, KINOMEscan™. Developed and marketed by Ambit Biosciences, KINOMEscan™ is a competition binding assay that quantitatively measures the ability of a compound to compete with an immobilized, active-site directed ligand (see: http://www.kinomescan.com). **12c** was screened against 359 kinases at 1 μM.

Procedures for the syntheses of compounds in Table 1

Method 1: Synthesis of benzolactam intermediates (general structure **3** from Scheme 1)

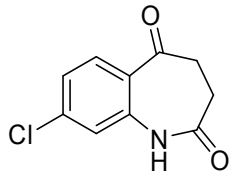


Methyl 4-iodo-2-[(4-methoxy-4-oxobutanoyl)amino]benzoate (SI-1)
To a solution of methyl 2-amino-4-iodobenzoate (17 g, 61.3 mmol) in DCM (200 mL), was added DIEA (10.6 mL, 64.4 mmol) and DMAP (37.5 mg, 0.31 mmol). To this solution was added 3-(carbomethoxy)propionyl chloride (8.3 mL, 67.4 mmol) dropwise, and the reaction mixture was allowed to stir at rt for 2 h. To the reaction mixture was then added H_2O (80 mL) and the mixture was allowed to stir for 30 min. The organic solution was separated and the aqueous solution was extracted with DCM (2 x 100 mL). The organic solutions were combined, washed with H_2O (2 x 100 mL) and brine (1 x 100 mL), dried over Na_2SO_4, filtered and concentrated to give **SI-1** (24.6 g, 99%). ^{1}H NMR (400 MHz, DMSO) δ 10.61 (s, 1H), 8.67 (d, *J* = 1.7 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.55 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.84 (s, 3H), 3.59 (s, 3H), 2.73 – 2.54 (m, 4H). LCMS (FA) *m/z* = 392.1 (M+H).

Methyl 8-iodo-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine- 4-carboxylate (SI-2)
To a solution of methyl 4-iodo-2-[(4-methoxy-4-oxobutanoyl)amino] benzoate (24.6 g, 63 mmol) in THF (240 mL) at 10 °C was added a 1 M solution of *t*-BuOK in THF (185 mL, 185 mmol) dropwise over 30 min while maintaining the temperature at 10 °C. After 2.5 h, 50 mL of H_2O followed by 190 mL of 1N HCl were added to bring the solution to pH = 4. The resulting mixture was allowed to stir at rt for 40 min. The organic solution was separated and the aqueous solution was extracted with EtOAc (2 x 200 mL). The organic solutions were combined, dried over Na_2SO_4, filtered and concentrated to give **SI-2** (22 g, 97%). ^{1}H NMR (400 MHz, DMSO) δ 10.35 (s, 1H), 7.60 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.54 (dd, *J* = 11.0, 5.0 Hz, 2H), 3.82 (s, 3H), 3.32 (s, 1H), 2.93 (s, 2H). LCMS (FA) *m/z* = 360.0 (M+H).

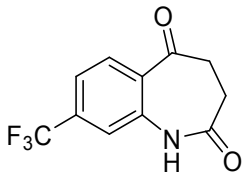
8-Iodo-3,4-dihydro-1*H*-1-benzazepine-2,5-dione (**3**; R=I)
A mixture of methyl 8-iodo-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine- 4-carboxylate (74 g, 0.2 mol) in DMSO (560 mL) and H_2O (16 mL) was heated at 150 °C for 4 h. The reaction mixture was allowed to cool to rt, ice (1.0 L) was added, and the mixture was allowed to stir 12 h. To the flask was added 1N HCl (1.0 L) at 0 ^{o}C and the mixture allowed to stir for 3 h. The resulting precipitate was filtered and dried under

reduced pressure to afford **3** (R=I) (60 g**,** 97%). ^{1}H NMR (300 MHz, DMSO) δ 10.08 (s, 1H), 7.60 – 7.45 (m, 3H), 2.95 – 2.83 (m, 2H), 2.66 (dd, *J* = 7.7, 4.5 Hz, 2H). LCMS (FA) *m/z* = 302.1 (M+H).



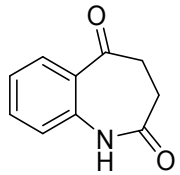
3 (R=Cl)

8-Chloro-3,4-dihydro-1*H*-1-benzazepine-2,5-dione (**3**; R=Cl)
Prepared by method 1 using methyl 2-amino-4-chlorobenzoate in step 1.
^{1}H NMR (400 MHz, DMSO) δ 10.19 (s, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.30 – 7.13 (m, 2H), 2.96 – 2.84 (m, 2H), 2.75 – 2.61 (m, 2H). LCMS (FA) *m/z* = 210.1 (M+H).



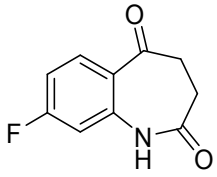
3 (R=CF_3)

8-Trifluoromethyl-3,4-dihydro-1*H*-1-benzazepine-2,5-dione (**3**; R=CF_3)
Prepared by method 1 using methyl 2-amino-4-trifluoromethylbenzoate in step 1.
^{1}H NMR (400 MHz, DMSO) δ 10.26 (d, *J* = 27.1 Hz, 1H), 7.97 (t, *J* = 12.7 Hz, 1H), 7.49 (dd, *J* = 23.1, 14.8 Hz, 2H), 2.95 (dt, *J* = 27.8, 12.6 Hz, 2H), 2.75 – 2.63 (m, 2H). LCMS (FA) *m/z* = 244.2 (M+H).



3 (R=H)

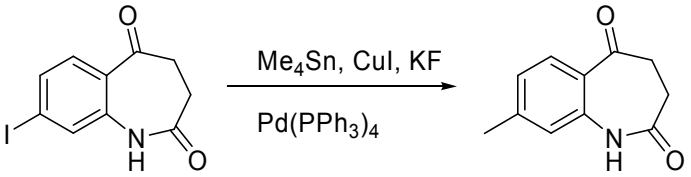
3,4-dihydro-1*H*-1-benzazepine-2,5-dione (**3**; R=H)
Prepared by method 1 using methyl 2-aminobenzoate in step 1.
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.91 (s, 1H), 7.54 – 7.44 (m, 1H), 7.22 – 7.16 (m, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 3.06 – 2.94 (m, 2H), 2.80 (dd, *J* = 7.9, 4.4 Hz, 2H).



3 (R=F)

8-Fluoro-3,4-dihydro-1*H*-1-benzazepine-2,5-dione (**3**; R=F)

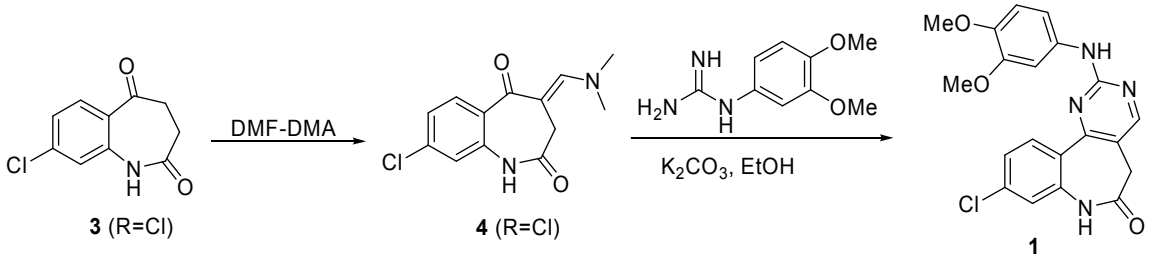
Prepared by method 1 using methyl 2-amino-4-fluorobenzoate in step 1.
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.08 (dd, *J* = 9.0, 6.3 Hz, 1H), 6.92 (ddd, *J* = 9.0, 7.5, 2.4 Hz, 1H), 6.83 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.05 – 2.98 (m, 2H), 2.87 – 2.78 (m, 2H).



3 (R=I) **3** (R=Me)

8-Methyl-3,4-dihydro-1*H*-1-benzazepine-2,5-dione (**3**; R=Me)
To a degassed solution of 8-iodo-3,4-dihydro-1*H*-1-benzazepine-2,5-dione (**3**; R=I) (0.3 g, 1.0 mmol) in DMF (5 mL) was added CuI (19 mg, 0.1 mmol), KF (116 mg, 2.0 mmol), Me_4Sn (0.28 mL, 2.0 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.1 mmol). The reaction mixture was allowed to stir at 120 °C for 4 h. After being allowed to cool to rt, EtOAc (50 mL) and a 1M aqueous KF solution (25 mL) were added and the solution was allowed to stir for an additional 40 min. The mixture was filtered over Celite®. The organic solution was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography to provide **3** (R=Me) (60 mg, 32%). ^{1}H NMR (400 MHz, DMSO) δ 10.07 (d, *J* = 38.6 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.96 (s, 1H), 3.00 – 2.75 (m, 2H), 2.73 – 2.57 (m, 2H), 2.30 (s, 3H). LCMS (FA) *m/z* = 190.1 (M+H).

Method 2: Used for the syntheses of **1** and **5a-g** (Table 1)
Representative procedure:

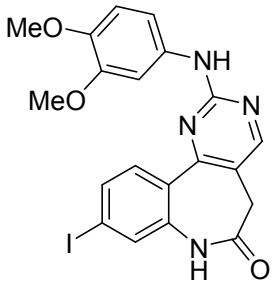


3 (R=Cl) **4** (R=Cl) **1**

9-chloro-2-(3,4-dimethoxyphenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (1)
Step 1: To a 250 mL round bottom flask with magnetic stirrer were added 8-chloro-3,4-dihydro-1H-1-benzazepine-2,5-dione (**3**; R=Cl) (52.0 g, 0.248 mol) and THF (364 mL). 1,1-Dimethoxy-N,N-dimethylmethanamine (175 mL, 1.24 mol) was added, then the flask was fitted with a reflux condenser. The resulting reaction mixture was heated at 60 °C under an atmosphere of argon for 2 hrs. The light orange solution with a suspended solid was allowed to cool to room temperature. Ether (250 mL) was added and the precipitated material was collected via suction filtration, washed with ether and dried in vaccuum oven (40 ^{o}C) for 2 days to give 62g (94%) of **4** (R=Cl) as a gray solid. ^{1}H NMR (400

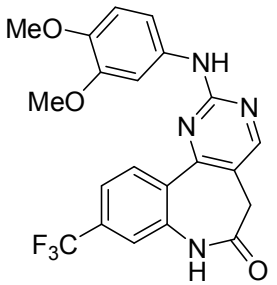
MHz, DMSO) δ 10.05 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.62 (s, 1H), 7.23 – 7.16 (m, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 3.33 (s, 2H), 3.23 (s, 6H). LCMS (FA) *m/z* = 265.2 (M+H).

Step 2: A mixture of **4** (R=Cl) (101 mg, 0.382 mmol), N-(3,4-dimethoxyphenyl)guanidine·HNO_3 (118 mg, 0.458 mmol) and potassium carbonate (132 mg, 0.954 mol) in ethanol (2.7 mL) was heated to reflux overnight. The mixture was cooled to room temperature and added to water (20 mL). The resulting suspension was stirred for 2 hours and the solid was collected by filtration and dried to give 136 mg (90%) of **1**. ^{1}H NMR (400 MHz, DMSO) δ 10.35 (s, 1H), 9.60 (s, 1H), 8.49 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.69 (s, 1H), 7.41 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.28 (d, *J* = 2.1 Hz, 1H), 7.22 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.39 (s, 2H). LCMS (FA) *m/z* = 397.1 (M+H).



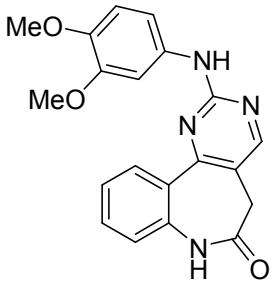
9-iodo-2-(3,4-dimethoxyphenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (5a)

Prepared by Method 2 using **3** (R=I) in step 1. Yield of **5a**: 1.7 g (67%)
^{1}H NMR (300 MHz, DMSO) δ 10.24 (s, 1H), 9.57 (s, 1H), 8.46 (s, 1H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.59 (s, 1H), 7.22 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.36 (s, 2H). LCMS (FA) *m/z* = 489.1 (M+H).

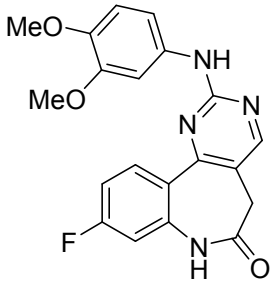


9-trifluoromethyl-2-(3,4-dimethoxyphenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (5b)

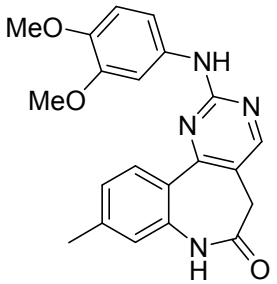
Prepared by Method 2 using **3** (R=CF_3) in step 1. Yield of **5b**: 0.38 g (79%).
^{1}H NMR (300 MHz, DMSO) δ 10.44 (s, 1H), 9.63 (s, 1H), 8.51 (s, 1H), 8.27 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.54 (s, 1H), 7.22 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 3.73 (s, 3H), 3.69 (s, 3H), 3.41 (s, 2H). LCMS (FA) *m/z* = 431.4 (M+H).



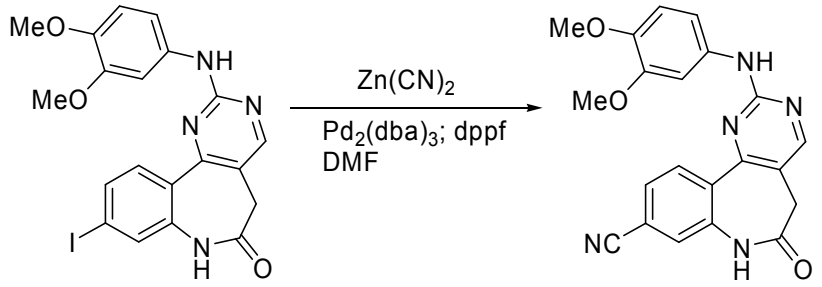
2-(3,4-dimethoxyphenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (5c)
Prepared by Method 2 using **3** (R=H) in step 1. Yield of **5c**: 0.17 g (55%).
^{1}H NMR (400 MHz, DMSO) δ 10.22 (s, 1H), 9.53 (s, 1H), 8.47 (s, 1H), 8.10 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.72 (s, 1H), 7.63 – 7.50 (m, 1H), 7.38 – 7.28 (m, 1H), 7.28 – 7.18 (m, 2H), 6.89 (d, *J* = 8.8 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.35 (s, 2H). LCMS (FA) *m/z* = 363.2 (M+H).



9-fluoro-2-(3,4-dimethoxyphenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (5d)
Prepared by Method 2 using **3** (R=F) in step 1. Yield of **5d**: 65 mg (57%).
^{1}H NMR (300 MHz, DMSO) δ 10.34 (s, 1H), 9.56 (s, 1H), 8.46 (s, 1H), 8.14 (dd, *J* = 8.8, 6.7 Hz, 1H), 7.68 (s, 1H), 7.21 (ddd, *J* = 10.8, 5.3, 2.5 Hz, 2H), 7.02 (dd, *J* = 10.4, 2.5 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.38 (s, 2H). LCMS (FA) *m/z* = 381.1 (M+H).



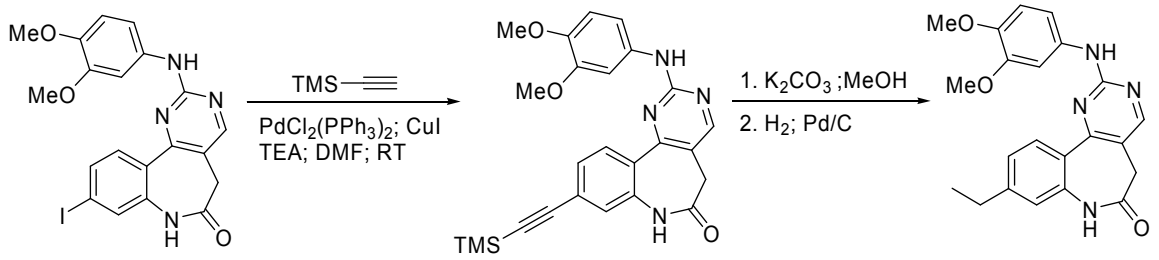
9-methyl-2-(3,4-dimethoxyphenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (5e)
Prepared by Method 2 using **3** (R=Me) in step 1. Yield of **5e**: 62 mg (57%).
^{1}H NMR (300 MHz, DMSO) δ 10.16 (s, 1H), 9.52 (s, 1H), 8.44 (s, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.72 (s, 1H), 7.18 (dd, *J* = 23.7, 8.4 Hz, 2H), 7.01 (s, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.33 (s, 2H), 2.36 (s, 3H). LCMS (FA): *m/z* = 377.4 (M+H).



5a **5f**

9-cyano-2-(3,4-dimethoxyphenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (5f)

A mixture of **5a** (100 mg, 0.21 mmol), $Zn(CN)_2$ (14 mg, 0.12 mmol), $Pd_2(dba)_3$ (9.5 mg, 0.01 mmol), and dppf (14 mg, 0.02 mmol) was stirred in DMF (2 mL). A drop of water was added and the mixture heated at 120 ^oC overnight with stirring. The reaction was then allowed to cool to room temperature and diluted with EtOAc and a solution of saturated $NaHCO_3$ (aq.). The organic layer was separated and washed with brine and water, then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified on silica gel to give **5f** (75 mg, 92%). ^1H NMR (300 MHz, DMSO) δ 10.46 (s, 1H), 9.65 (s, 1H), 8.53 (s, 1H), 8.24 (d, J = 8.2 Hz, 1H), 7.76 (dd, J = 8.2, 1.6 Hz, 1H), 7.66 (s, 1H), 7.61 (d, J = 1.4 Hz, 1H), 7.20 (dd, J = 8.7, 2.4 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 3.74 (s, 3H), 3.70 (s, 3H), 3.41 (s, 2H). LCMS (FA) *m/z* = 388.2 (M+H).



5a **SI-3** **5g**

9-ethyl-2-(3,4-dimethoxyphenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (5g)

Step 1. To a solution of **5a** (300mg, 0.614mmol) in DMF (4 mL) at 22^0C was added dichlorobis(triphenylphosphine)palladium (15mg, 0.02mmol), copper iodide (9mg, 0.05mmol), and triethylamine (0.34mL, 2.45mmol). The solution was degassed with Ar, and stirred at 22^0C for 1 hr. (Trimethylsilyl)acetylene (120 mg, 1.22 mmol) was added and the solution was stirred at 22^0C for 2 hr. Water was added to the reaction and the resulting precipitate was filtered and purified by silica gel chromatography to give **SI-3** (180 mg, 64%). LCMS (FA) *m/z* 459 (M+H).

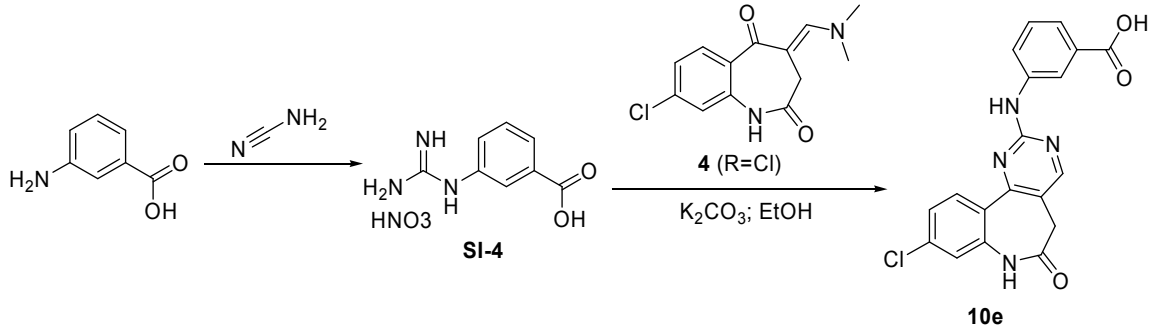
Step 2. **SI-3** (180 mg, 0.39 mmol) was then dissolved in methanol (4 mL) and potassium carbonate (217 mg, 1.57 mmol) was added. The reaction stirred at 22 ^0C overnight. The mixture was then concentrated in-vacuo, redissolved in water (100mL) and extracted with methylene chloride (3 x 100mL). The organic fractions were combined, washed with brine, dried over Na_2SO_4 and concentrated in-vacuo to give 2-(3,4-Dimethoxy-

phenylamino)-9-ethynyl-5H,7H-benzo[b]-pyrimido[4,5-d]azepin-6-one (130 mg, 85%). ^{1}H NMR (300 MHz, MeOH) δ 8.36 (s, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 2.4 Hz, 1H), 7.42 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.33 (d, *J* = 1.4 Hz, 1H), 7.16 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.73 (s, 1H), 3.41 (s, 2H). HRMS: Calcd. for $C_{22}H_{18}N_4O_3$: 387.1457, Found 387.1451

Step 3. 130 mg (0.33 mmol) of 2-(3,4-Dimethoxy-phenylamino)-9-ethynyl-5H,7H-benzo[b]-pyrimido[4,5-d]azepin-6-one was dissolved in methanol. The reaction vessel was evacuated and backfilled with an atmosphere of nitrogen. To the solution was added Pd/C and the resulting suspension was purged with a hydrogen balloon. The suspension was stirred 1 hour at room temperature. The suspension was then filtered through a pad of celite followed by washing with methanol. The filtrate was concentrated and purified via HPLC to give 30 mg (23%) of **5g**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 2H), 7.56 (s, 1H), 7.25 (d, *J* = 3.6 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.90 – 6.71 (m, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.46 (s, 2H), 2.70 (q, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.5 Hz, 3H). HRMS Calcd. For $C_{22}H_{22}N_4O_3$: 391.1770, Found 391.1796 (M+H).

Procedures for the syntheses of compounds in Table 2

Method 3. Formation of guanidine intermediates using cyanamide followed by coupling to form aminopyrimidine.Representative Procedure:

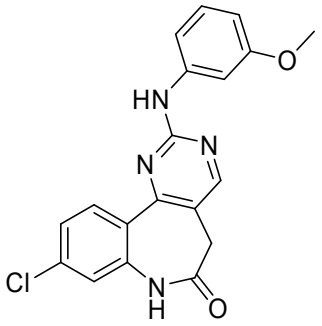


3-[(9-chloro-6-oxo-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepin-2-yl)amino]benzoic acid (10e)

Step 1. To a solution of 3-aminobenzoic acid (5.40 g, 0.0386 mol) in ethanol (60 mL, 1 mol) was added nitric acid (2.43 mL, 0.0405 mol) slowly at 0 °C. Then cyanamide (1.70 g, 0.0405) in water (2.7 mL) was added to the mixture with stirring. The reaction mixture was then allowed to heat at reflux overnight. After the mixture was cooling with ice-bath, solid was formed. The solid was filtered and washed with ethanol (2 x 5 mL) to give **SI-4** (4.17 g, 45%). ^{1}H NMR (300 MHz, dmso) δ 13.17 (s, 1H), 9.65 (s, 1H), 7.80 (dt, J = 7.6, 1.3 Hz, 1H), 7.73 (t, J = 1.7 Hz, 1H), 7.53 (t, J = 7.8 Hz, 1H), 7.48 – 7.38 (m, 4H). LCMS (FA): m/z = 180.0 (M+H).

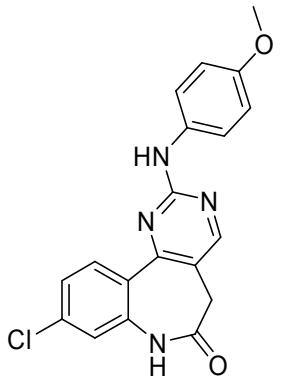
Step 2. To a solution of **4** (R=Cl) (522 mg, 1.97 mmol) in ethanol (35.0 mL, 0.599 mmol) was added **SI-4** (539 mg, 2.24 mol) and potassium carbonate (1.63 g, 11.8 mmol). The mixture was allowed to heat at 90 °C overnight. After cooling down to room temperature, the reaction mixture was diluted with water (30 mL) and the pH of the resulting solution was adjusted to 3 via 1N HCl. Resulting mixture was filtered and the

resulting solid material was washed with additional water and ether (2 x 30 mL) to give **10e** (636 mg, 85%). ^{1}H NMR (300 MHz, DMSO) δ 12.87 (s, 1H), 10.37 (s, 1H), 10.01 (s, 1H), 8.65 (s, 1H), 8.57 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.47 – 7.34 (m, 2H), 7.29 (d, J = 1.8 Hz, 1H), 3.43 (s, 2H). LCMS (AA): m/z = 381.1 (M+H).



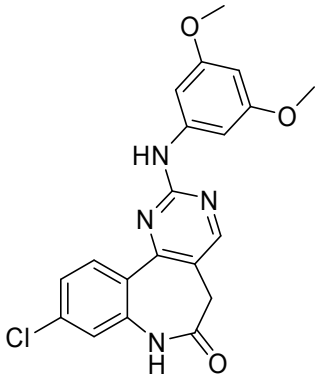
9-Chloro-2-(3-methoxy-phenylamino)-5H,7H-benzo[b]pyrimido[4,5-d]azepin-6-one (10a)

10a was prepared following method 3 using commercial 1-(3-methoxyphenyl)guanidine. Yield of **10a**: 68 mg (25%) of a white solid. ^{1}H NMR (300 MHz, DMSO) δ 10.36 (s, 1H), 9.79 (s, 1H), 8.53 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.65 (s, 1H), 7.42 (dd, J = 8.5, 2.0 Hz, 1H), 7.37 – 7.24 (m, 2H), 7.18 (t, J = 8.2 Hz, 1H), 6.53 (dd, J = 8.1, 1.9 Hz, 1H), 3.75 (s, 3H), 3.41 (s, 2H). HRMS Calcd. for $C_{19}H_{15}ClN_4O_2$: 367.0961, Found 367.0961 (M+H).



9-Chloro-2-(4-methoxy-phenylamino)-5H,7H-benzo[b]pyrimido[4,5-d]azepin-6-one (10b)

10b was prepared following method 3 using commercial 1-(4-methoxyphenyl)guanidine. Yield of **10b**: 84 mg (39%) of a white solid. ^{1}H NMR (300 MHz, DMSO) δ 10.33 (s, 1H), 9.58 (s, 1H), 8.46 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 9.0 Hz, 2H), 7.41 (dd, J = 8.5, 2.0 Hz, 1H), 7.27 (d, J = 2.0 Hz, 1H), 6.88 (d, J = 9.0 Hz, 2H), 3.72 (s, 3H), 3.38 (s, 2H). HRMS Calcd. for $C_{19}H_{15}ClN_4O_2$: 367.0960, Found 367.0975 (M+H).

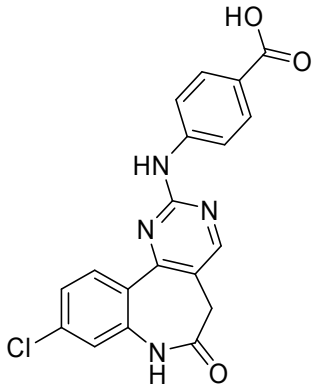


9-Chloro-2-(3,5-dimethoxy-phenylamino)-5H,7H-benzo[b]pyrimido[4,5-d]azepin-6-one (10c)

Method 3 used for the preparation of **10c**

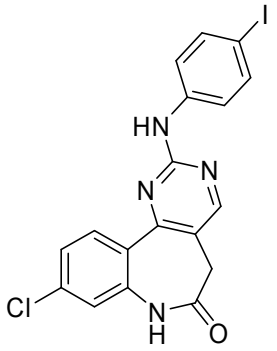
Step 1. 1-(3,5-dimethoxyphenyl)guanidine nitrate was prepared from commercial 3,5-dimethoxyaniline. Yield: 2.64 g (39%) of a solid. 1H NMR (300 MHz, MeOD) δ 6.52 – 6.45 (m, 1H), 6.43 (d, J = 2.2 Hz, 2H), 3.80 (s, 6H). LCMS: m/z = 196 (M-H).

Step 2. **10c** was prepared from 1-(3,5-dimethoxyphenyl) guanidine nitrate. Yield of **10c**: 57 mg (62%) of a white solid. ^{1}H NMR (400 MHz, DMSO) δ 10.34 (s, 1H), 9.73 (s, 1H), 8.54 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.41 (dd, J = 8.5, 2.1 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.16 (d, J = 2.2 Hz, 2H), 6.12 (t, J = 2.2 Hz, 1H), 3.72 (s, 6H), 3.42 (s, 2H). HRMS Calcd. for $C_{19}H_{15}ClN_4O_2$: 367.0960, Found 367.0975 (M+H).



4-(9-Chloro-6-oxo-6,7-dihydro-5H-benzo[b]pyrimido[4,5-d]azepin-2-ylamino)-benzoic acid (10f)

10f was prepared following method 3 using commercial 4-guanidinobenzoic acid. Yield of **10f**: 40 mg (68%) of a white solid. ^{1}H NMR (300 MHz, DMSO) δ 12.51 (s, 1H), 10.38 (s, 1H), 10.21 (s, 1H), 8.61 (s, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.91 (q, J = 9.0 Hz, 4H), 7.44 (dd, J = 8.5, 2.1 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 3.45 (s, 2H). HRMS Calcd. for $C_{19}H_{13}ClN_4O_3$: 381.0754, Found 381.0721 (M+H).

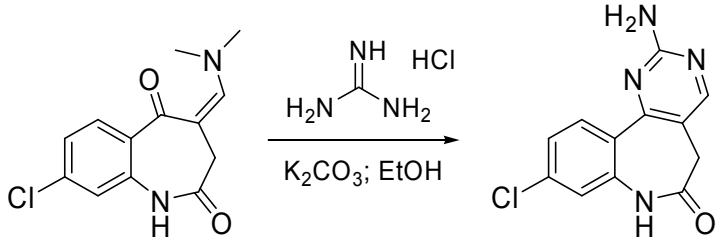


9-Chloro-2-(4-iodo-phenylamino)-5H,7H-benzo[b]pyrimido[4,5-d]azepin-6-one (10g)

Method 3 used for the preparation of **10g**

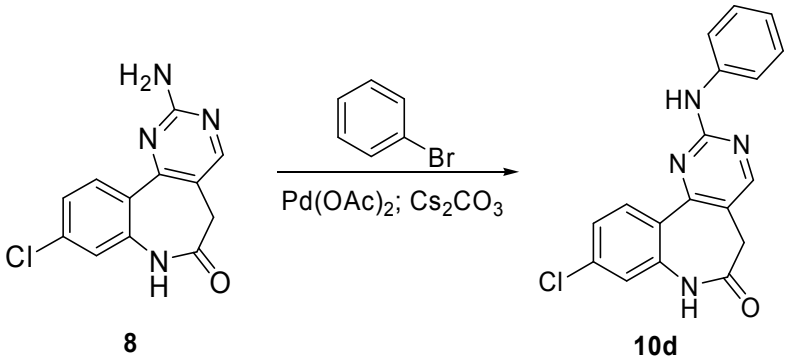
Step 1. 2-(4-iodophenyl)guanidine nitrate was prepared using commercial 2-iodo-aniline. Yield: 3.24 g (50%) of a solid. ^{1}H NMR (300 MHz, MeOD) δ 7.84 – 7.63 (m, 2H), 7.13 – 6.90 (m, 2H). LCMS: m/z = 262 (M-H).

Step 2. **10g** was prepared from 2-(4-iodophenyl)guanidine nitrate. Yield of **10g**: 30 mg (62%) of a white solid. ^{1}H NMR (300 MHz, DMSO) δ 10.36 (s, 1H), 9.93 (s, 1H), 8.55 (s, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.64 (m, 3H), 7.41 (dd, J = 8.5, 2.1 Hz, 1H), 7.28 (d, J = 2.0 Hz, 1H), 3.42 (s, 2H). HRMS Calcd. for $C_{18}H_{12}ClIN_4O$: 462.9822, Found 462.9818 (M+H).



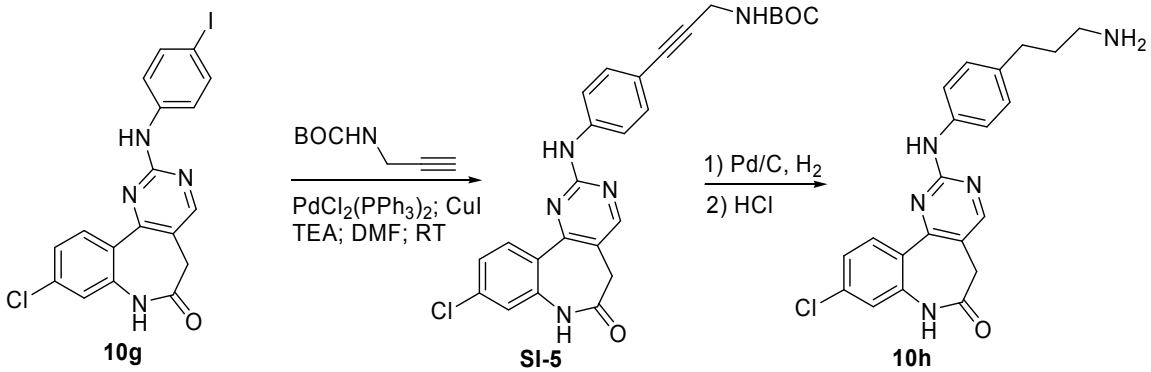
4 (R=Cl) **8**

2-amino-9-chloro-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (8)
To a solution of **4** (R=Cl) (11.8 g, 44.6 mmol) in EtOH (300 mL) was added guanidine hydrochloride (4.68 g, 49.0 mmol) and potassium carbonate (20.0 g, 145 mmol). The reaction mixture was allowed to stir, overnight, at 75 ^{o}C. Most of the solvent was removed in vacuo and the remaining mixture was diluted in water (500 mL). The resulting solution was stirred, at room temperature, for 30 min. The cloudy mixture was filtered and washed with water and MeOH to give **8** (10.5 g, 90%) as a white solid.
^{1}H NMR (400 MHz, DMSO) δ 10.24 (s, 1H), 8.25 (s, 1H), 7.99 – 7.89 (m, 1H), 7.33 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.22 (d, *J* = 2.1 Hz, 1H), 6.74 (s, 2H), 3.27 (s, 2H).
LCMS (FA): *m/z* = 261.1 (M+H)



8 10d

9-chloro-2-(phenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (10d)
To a solution of **8** (148 mg, 0.568 mmol), 1-bromobenzene (0.072 mL, 0.681 mmol), Cs_2CO_3 (333 mg, 1.02 mmol), and BINAP (53 mg, 0.085 mmol) in 4 mL toluene was added $Pd(OAc)_2$ (12.8 mg, 0.057 mmol), and the reaction was stirred at 100°C for 12 h. The reaction mixture was then treated with H_2O and extracted with CH_2Cl_2 (2 x 30 mL). The organic fractions were combined, filtered, dried over $MgSO_4$ and concentrated in vacuo to give an orange oil which was purified by HPLC to afford **10d** (1.8 mg, 0.9%). ^{1}H NMR (300 MHz, DMSO) δ 10.35 (s, 1H), 9.77 (s, 1H), 8.53 (s, 1H), 8.08 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 7.9 Hz, 2H), 7.43 (dd, J = 8.5, 2.0 Hz, 1H), 7.29 (m, 3H), 6.95 (t, J = 7.2 Hz, 1H), 3.41 (s, 2H). HRMS Calcd. for $C_{18}H_{13}ClN_4O$: 337.0856, Found 337.0853 (M+H).

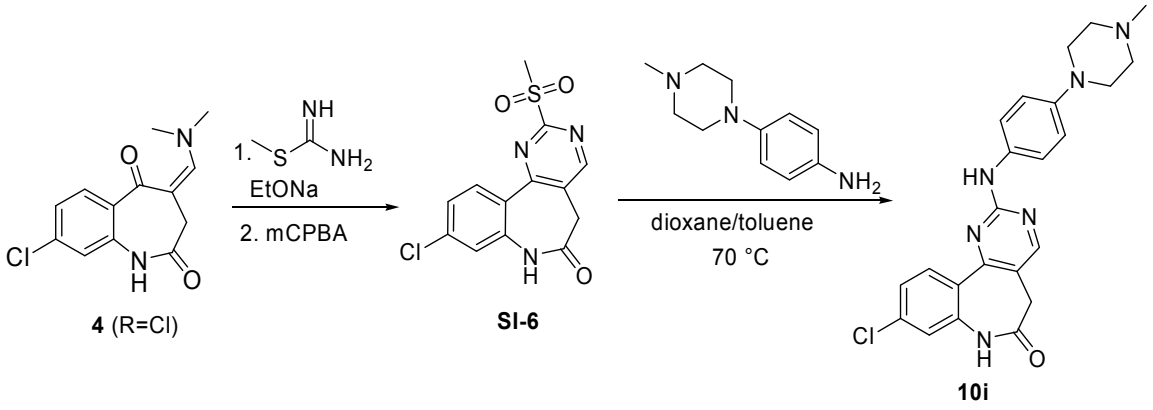


10g SI-5 10h

2-[4-(3-Amino-propyl)-phenylamino]-9-chloro-5*H*,7*H*-benzo[*b*]pyrimido[4,5-*d*]azepin-6-one (10h)
Step 1. To a solution of **10g** (204 mg, 0.442 mmol) in 4 mL DMF at 22°C was added dichlorobis (triphenylphosphine) palladium (10.8 mg, 0.0154 mmol), copper iodide (3.83 mg, 0.035 mmol), and triethylamine (0.25 mL, 1.96 mmol). The solution was degassed with argon, and stirred at 22°C for 1 h. tert-Butyl prop-2-ynylcarbamate (137 mg, 0.884 mmol) was added and the solution was stirred at 22°C for 2 h. Water was added to the reaction mixture, and the resulting precipitate was filtered and purified by silica gel chromatography to give **SI-5** (160mg, 72%) as yellow oil. LCMS (FA): m/z = 490.2 (M+H).

Step 2. To a solution of **SI-5** (0.052 g, 0.11 mmol) in EtOH (5 mL) was added Pd/C (10% wt, ~50% H_2O, 0.01 g). The mixture was placed under H_2 (1 atm) and stirred for 12 h at 22°C. The reaction mixture was filtered through celite and the filtrate concentrated in

vacuo. The resulting solid was dissolved in ethanol (10 mL) and 1M HCl in ether solution (8 mL) was added. The resulting mixture was then allowed to stir at room temperature for 24 h. The mixture as concentrated in vacuo and then dilute with methanol. Ethyl acetate was added to the solution, the resulting precipitate was filtered and washed with extra ethyl acetate (2 x 1 mL) to give **10h** (10 mg, 24%). 1H NMR (400 MHz, DMSO) δ 10.33 (s, 1H), 9.71 (s, 1H), 8.50 (s, 1H), 8.07 (t, J = 7.3 Hz, 1H), 7.88 – 7.76 (m, 2H), 7.72 (d, J = 8.5 Hz, 2H), 7.41 (dd, J = 8.5, 2.1 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 2.78 (d, J = 14.4 Hz, 2H), 2.60 (t, J = 7.7 Hz, 2H), 1.91 – 1.74 (m, 2H). HRMS Calcd. for $C_{21}H_{20}ClN_5O$: 394.1434, Found 394.1448 (M+H).

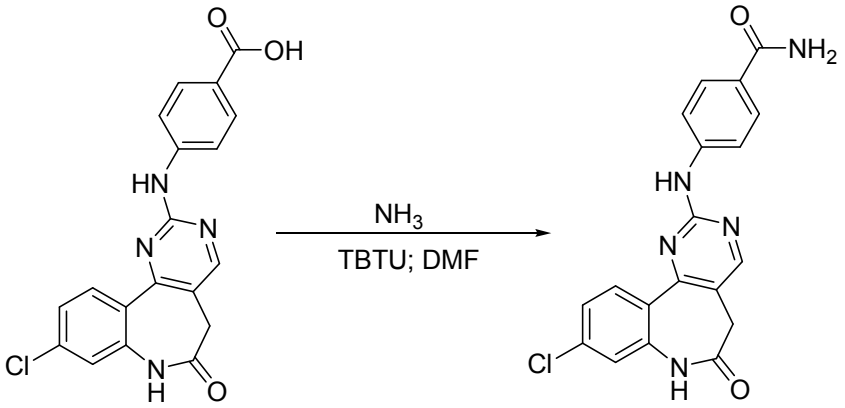


9-chloro-2-(4-(4-methylpiperazin-1-yl)phenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (10i)

Step 1/2. To a round bottomed flask was added 2-methyl-2-thiopseudourea sulfate (400 mg, 1.44 mmol) and ethanol (4 mL). To this was added 2.6 M of sodium ethoxide in ethanol (0.55 mL, 1.44 mmol). The resulting mixture was allowed to stir for an hour and the solid was removed by filtration. The filtrate was added to a microwave vial containing **4** (R=Cl) (380 mg, 1.44 mmol). The reaction mixture was stirred for 20 min at 160 °C in a microwave reactor. Water was then added and the resulting solid was removed via filtration. The solid was washed with cold water and ethyl ether and vacuum dried. This intermediate was dissolved in DCM (18 mL) and m-chloroperbenzoic acid (933 mg, 5.41 mmol) was added. The reaction was allowed to stir overnight at room temperature. The reaction was diluted with DCM and water. The reaction mixture was filtered to remove solid and the organic layer was washed with a 10% $Na_2S_2O_3$ (aq.) solution and a 10% K_2CO_3 (aq.) solution. The organic layer was separated and washed with water and brine, dried over $MgSO_4$, filtered and concentrated to give 9-chloro-2-(methylsulfonyl)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (**SI-6**) as a yellow solid (166 mg, 36%) ^{1}H NMR (300 MHz, dmso) δ 10.65 (s, 1H), 9.16 (t, *J* = 10.0 Hz, 1H), 8.15 – 8.09 (m, 1H), 7.49 – 7.43 (m, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 3.73 (d, *J* = 9.2 Hz, 2H), 3.51 – 3.43 (m, 3H). LCMS (FA): *m/z* 324.0 (M+H).

Step 3. **10i** was synthesized in a library format. To a reaction block was added **SI-6** (0.048g, 0.148 mmol), 1.5 ml solvent (dioxane/toluene=1/1), DIEA (0.18 ml, 1.04 mmol), and 4-(4-methylpiperazin-1-yl)aniline (7 eq). The mixture was heated to 70 °C and stirred overnight. The mixture was concentrated down. The residue was purified by HPLC to yield **10i** (31 mg, 48%).^{1}H NMR (400 MHz, DMSO) δ 10.31 (s, 1H), 9.50 (s,

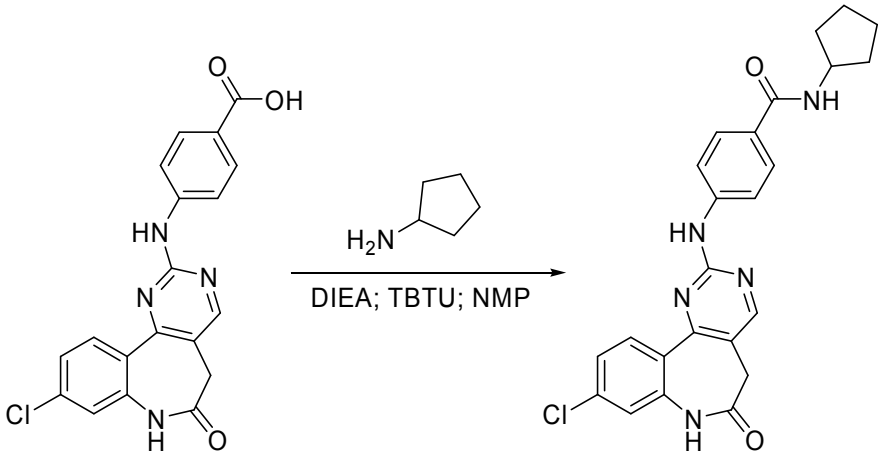
1H), 8.44 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 9.1 Hz, 2H), 7.39 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.26 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 9.1 Hz, 2H), 3.36 (s, 2H), 3.14 – 2.95 (m, 4H), 2.46 – 2.41 (m, 4H), 2.21 (s, 3H). LCMS (FA): *m/z* 435.6 (M+H).



10f **10j**

4-(9-chloro-6-oxo-6,7-dihydro-5H-benzo[b]pyrimido[4,5-d]azepin-2-ylamino)benzamide (10j)

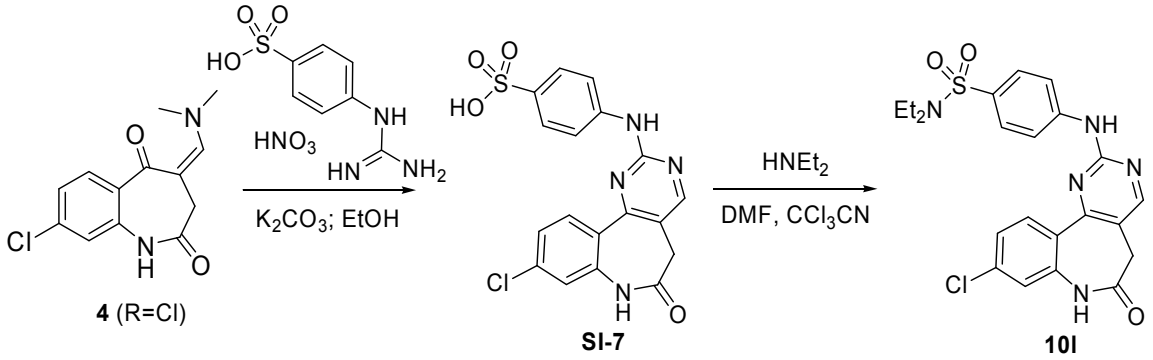
10f (150 mg, 0.37 mmol), Ammonium chloride (20 mg, 0.37 mmol), Benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (260 mg, 0.56 mmol) and N-Methylmorpholine (290 μL, 2.6 mmol) in DMF (5.45 mL) was stirred at room temperature overnight. The reaction was diluted with 10 mL of water and filtered. The solids were washed with 20 mL of water and the crude product was dried on the filter. The crude product was then purified by HPLC. The product was then slurried in 3 mL of MeOH and then added 4.0 M of HCl in 1,4-Dioxane (0.37 mL). The solution quickly became clear. This solution was then added to 20 mL of ether and the product crashed out of solution. The solids were then filtered and dried to yield **10j** as the HCl salt (9.5 mg, 6%). ^{1}H NMR (300 MHz, DMSO) δ 10.37 (s, 1H), 10.06 (s, 1H), 8.58 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.84 (m, 5H), 7.43 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.29 (d, *J* = 1.9 Hz, 1H), 7.15 (s, 1H), 3.43 (s, 2H). LCMS (FA): *m/z* 380.0 (M+H).



10f **10k**

3-[(9-chloro-6-oxo-6,7-dihydro-5H-pyrimido[5,4-d][1]benzazepin-2-yl)amino]-N-(2-morpholin-4-ylethyl)benzamide (10k)

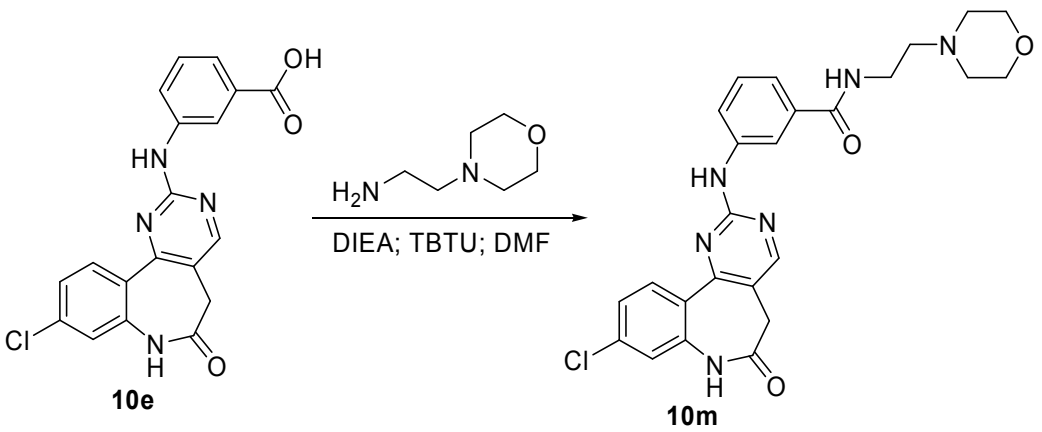
10k was synthesized as part of a 96 well array library synthesis. To a reaction vessel was added **10f** (35 mg, 0.092 mmol) and TBTU (35 mg, 0.11 mmol) in NMP (1.5 mL). DIEA (0.070 mL, 0.37 mmol) was added and the vessel shaken for 2 hrs. Cyclopentanamine (0.015 mL, 0.15 mmol) in NMP (0.5 mL) was then added and the vessel agitated for 3 days. The reaction was then quenched with water (6 mL) and a solid crashed out of solution. The mixture was centrifuged and the water was decanted. The remaining solid was dried under vacuum and purified by HPLC to yield **10k** (5 mg, 11%). ^{1}H NMR (300 MHz, dmso) δ 10.32 (s, 1H), 10.00 (s, 1H), 8.53 (d, *J* = 7.5 Hz, 1H), 8.13 – 7.97 (m, 2H), 7.77 (dd, *J* = 22.1, 8.9 Hz, 3H), 7.37 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.23 (d, *J* = 1.9 Hz, 1H), 4.15 (m, 1H), 3.37 (s, 2H), 1.92 – 1.36 (m, 8H). LCMS (FA): *m/z* 448.0 (M+H).



4-(9-chloro-6-oxo-6,7-dihydro-5H-benzo[b]pyrimido[4,5-d]azepin-2-ylamino)-N,N-diethylbenzenesulfonamide (10l)

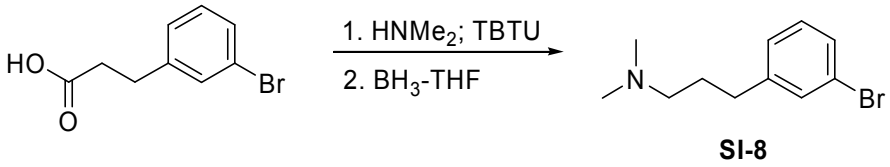
Step 1. Method 2 was used for the synthesis of **SI-7**. Yield of **SI-7**: 740 mg (90%) ^{1}H NMR (400 MHz, DMSO) δ 10.33 (s, 1H), 9.83 (s, 1H), 8.54 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.44 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 1H), 3.42 (s, 2H). LCMS (FA): *m/z* 417.0 (M+H).

Step 2. **10l** was synthesized as part of a 96 well array synthesis. To each individual reaction block was added 200 mg PL-TPP resin and **SI-7** (29 mg, 0.07 mmol) dissolved in DMA (2.44 mL). This was followed by the addition of CCl_3CN (0.060 mL). The mixture was shaken 60 min at RT. Triethylamine (0.080 mL, 0.57 mmol) and diethylamine (35 uL, 0.34 mmol) was added. The resulting mixture was shaken 60 min at RT. The mixture was filtered and the filtrate was concentrated. The residue was purified by HPLC to yield **10l** (5 mg, 20%). ^{1}H NMR (400 MHz, DMSO) δ 10.38 (s, 1H), 10.30 (s, 1H), 8.61 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.43 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.29 (d, *J* = 1.9 Hz, 1H), 3.45 (s, 2H), 3.12 (q, *J* = 7.1 Hz, 4H), 1.02 (t, *J* = 7.1 Hz, 6H). LCMS (FA): *m/z* 472.5 (M+H).



3-(9-chloro-6-oxo-6,7-dihydro-5H-benzo[b]pyrimido[4,5-d]azepin-2-ylamino)-N-(2-morpholinoethyl)benzamide (10m)

A 25 mL round bottom flask with magnetic stirrer was purged with nitrogen and into the flask was added **10e** (150.3 mg, 0.395 mmol) in DMF (7.60 mL). Next, N,N-Diisopropylethylamine (0.350 mL, 2.0 mmol), TBTU (334.4 mg, 1.04 mmol) and Morpholinoethylamine (0.0700 mL, 0.533 mmol) were added into the reaction. The reaction was stirred at room temperature 15 hr under an atmosphere of Nitrogen. The reaction mixture was added slowly to 50-60 mL of water with vigorous stirring (fine precipitate forms almost immediately). The mixture was filtered (frit) via suction filtration and the resulting solid was washed with water and air-dried to afford **10m** as a brown solid (170.7 mg, 83%). ^{1}H NMR (300 MHz, DMSO) δ 10.37 (s, 1H), 9.95 (s, 1H), 8.67 (d, *J* = 5.5 Hz, 1H), 8.55 (s, 1H), 8.41 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.29 (d, *J* = 1.3 Hz, 1H), 3.61 (dd, *J* = 13.9, 8.1 Hz, 4H), 3.56 (d, *J* = 0.9 Hz, 2H), 3.42 (s, 2H), 3.05 (s, 2H), 2.01 (s, 2H), 1.94 – 1.77 (m, 2H). LCMS (FA): *m/z* 477.0 (M+H)

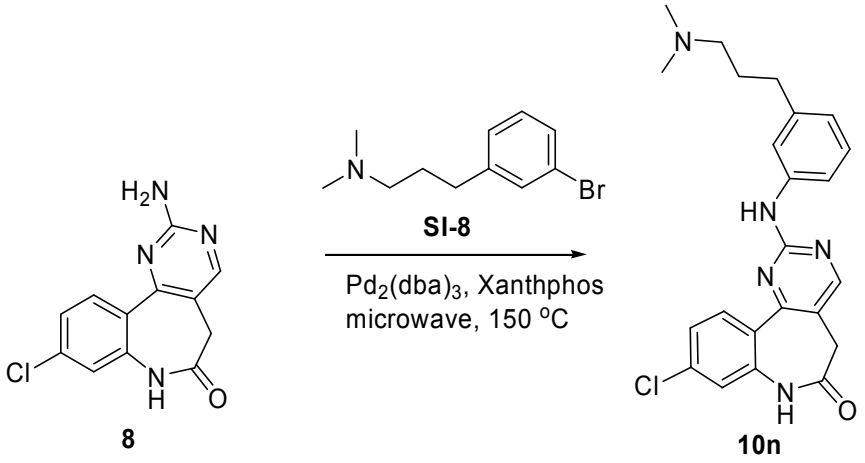


3-(3-bromophenyl)-N,N-dimethylpropan-1-amine (SI-8)

Step 1. To a reaction flask was added 3-(3-bromophenyl)propionic acid (3.67 g, 16.0 mmol), TBTU (5.66 g, 17.6 mmol), 30 ml DCM, and N,N-Diisopropylethylamine (6.97 mL, 40.0 mmol). The resulting mixture was stirred at RT 10 minutes then Dimethylamine hydrochloride (5.22 g, 64.0 mmol) was added. The resulting mixture was stirred at RT 15 hrs. Dichloromethane and 1M NaOH were added. The organic layer was separated and dried with magnesium sulfate. After filtration and concentration of the filtrate the residue was purified on silica gel (AcOEt/hexane=1/1) to give 3.64 g (88%) of 3-(3-bromophenyl)-N,N-dimethylpropanamide. LCMS (FA): *m/z* 256.0 (M+H).

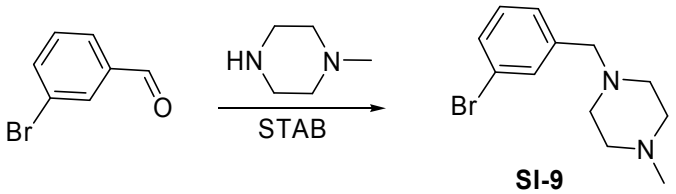
Step 2. To a RBF was added the 3-(3-bromophenyl)-N,N-dimethylpropanamide (3.6 g), and 10 mL THF at 0 °C. Then 35 mL borane-THF complex (1M in THF) was added slowly. The mixture was stirred 10 min at 0 °C then heated to 50 °C for 3 hr. It was then concentrated and 25 ml 3M HCl was added. The resulting mixture was stirred at 80 °C

for 3 hr. The reaction was cooled to room temp an solid NaOH was added until the mixture turned basic. The mixture was extracted with AcOEt (3x). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 3.4 g (87%) **SI-8**, which was used in the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.33 (m, 1H), 7.32 – 7.29 (m, 1H), 7.15 – 7.11 (m, 2H), 2.65 – 2.57 (m, 2H), 2.33 – 2.25 (m, 2H), 2.24 (s, 6H), 1.77 (ddd, *J* = 17.7, 8.3, 6.8 Hz, 2H). LCMS (FA): *m/z* 242.0 (M+H).



2-(3-(3-aminopropyl)phenylamino)-9-chloro-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (10n)

To a microwave tube was added **SI-8** (1.53 g, 6.31 mmol), **8** (1.64 g, 6.31 mmol), cesium carbonate (2.88 g, 8.83 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.22 g, 0.38 mmol), and tris(dibenzylideneacetone)dipalladium (0) (0.23 g, 0.25 mmol) and dioxane (30 mL). The resulting mixture was heated at 150 °C for 70 min in a microwave reactor. The reaction mixture was cooled to room temp, then 80 mL THF was added to the mixture. It was then filtered and the filtrate was concentrated. The crude residue was purified on silica gel to give **10n** (1.92 g; 72%). ^{1}H NMR (400 MHz, DMSO) δ 10.35 (s, 1H), 9.69 (s, 1H), 8.51 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.73 (s, 1H), 7.60 – 7.50 (m, 1H), 7.40 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.27 (d, *J* = 2.1 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 7.6 Hz, 1H), 3.39 (s, 2H), 2.60 – 2.51 (m, 2H), 2.20 (t, *J* = 7.2 Hz, 2H), 2.10 (s, 6H), 1.69 (dt, *J* = 14.7, 7.5 Hz, 2H). LCMS (FA): *m/z* 422.0 (M+H).

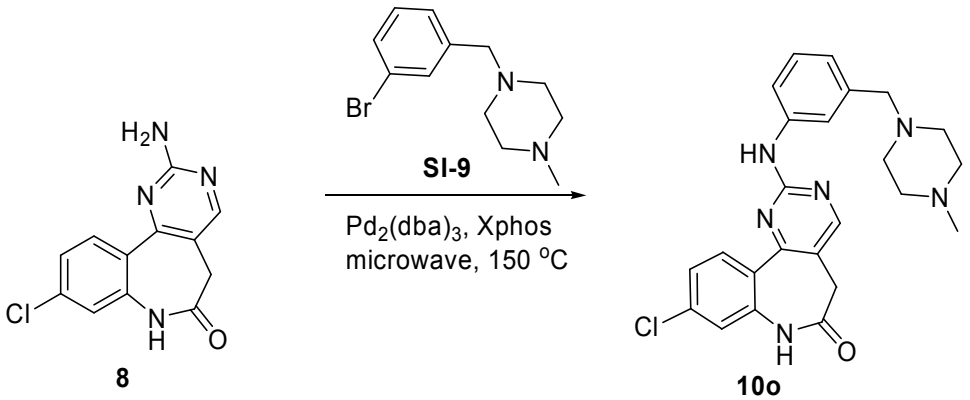


1-(3-bromobenzyl)-4-methylpiperazine (SI-9)

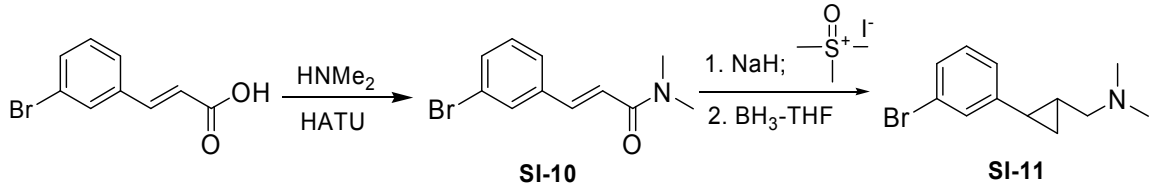
To a round bottom flask was added 3-bromobenzaldehyde (0.240 g, 1.30 mmol), sodium triacetoxyborohydride (0.82 g, 3.9 mmol), 1-methyl-piperazine (0.195 g, 1.94 mol), and methylene chloride (12.9 mL). The resulting mixture was stirred at RT overnight. The rxn was concentrated down and the residue was chromatographed on silica gel (DCM/MeOH=9/1) to give 0.23g (66%) of **SI-9**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J*

= 1.5 Hz, 1H), 6.97 – 6.90 (m, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 6.76 – 6.69 (m, 1H), 3.02 (s, 2H), 2.20 – 1.88 (m, 8H), 1.85 (s, 3H). LCMS (FA): *m/z* 271.1 (M+2H).

Method 4. Buchwald coupling with Pd_2dba_3 and Xphos
General procedure:



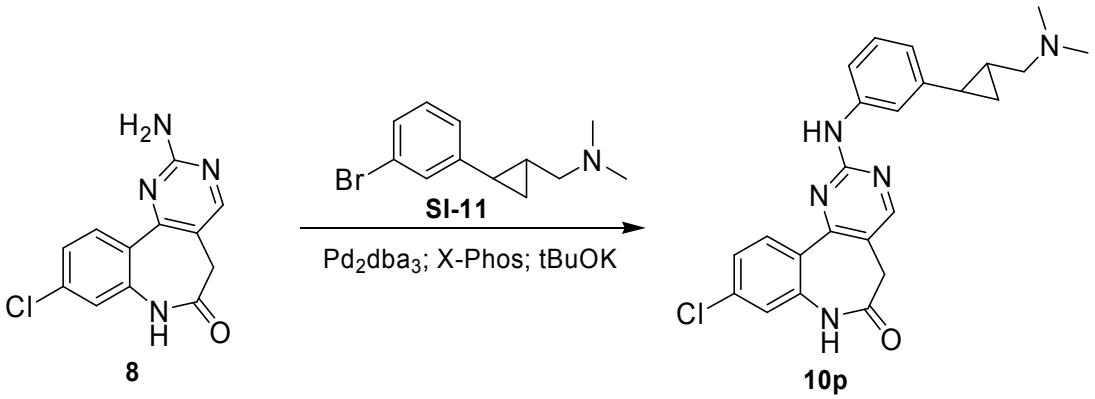
9-chloro-2-(3-((4-methylpiperazin-1-yl)methyl)phenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (10o)
A mixture of **SI-9** (0.14 g, 0.52 mmol), **8** (0.14 g, 0.52 mmol), 2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (Xphos) (20 mg, 0.042 mmol), and tris(dibenzylideneacetone)dipalladium(0) (19 mg, 0.021 mmol) in a sealed microwave tube was evacuated and purged with nitrogen three times. To the solids were added *tert*-butyl alcohol (3.6 mL) and *t*-BuOK (1M in *t*-BuOH, 0.78 mL). The mixture was stirred well and then subjected to microwave irradiation (150 watts) while heating at 120 °C for 15 min. The reaction mixture was then poured into water (5 mL) with vigorous stirring. The precipitate that formed was filtered, washed with water, and air dried. The residue was purified on silica gel to give **10o** (0.13 g, 57%). ^{1}H NMR (400 MHz, DMSO) δ 9.96 (s, 1H), 9.34 (s, 1H), 8.12 (s, 1H), 7.68 (t, *J* = 9.3 Hz, 1H), 7.40 (s, 1H), 7.32 – 7.19 (m, 1H), 7.00 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.89 (d, *J* = 2.1 Hz, 1H), 6.82 (t, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 3.02 (s, 2H), 3.01 (s, 2H), 2.08 – 1.79 (m, 8H), 1.72 (s, 3H). LCMS (FA): *m/z* 449.2 (M+H).



1-[2-(3-bromophenyl)cyclopropyl]-N,N-dimethylmethanamine (SI-11)
Step 1. To a solution of 3-bromocinnamic acid (3.7 g, 16 mmol) and N,N-diisopropylethylamine (3.4 mL, 20 mmol) in DMF (75 mL) was added N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uranium hexafluorophosphate (7.4 g, 20 mmol). The reaction mixture was allowed to stir at room temperature for 1h. A 2.0M solution of dimethylamine in THF (8.6 mL, 17 mmol) was added and the resulting mixture was stirred for 5h. The reaction was quenched with water and then extracted with EtOAc. The combined organic layers were washed in brine, dried over magnesium sulfate,

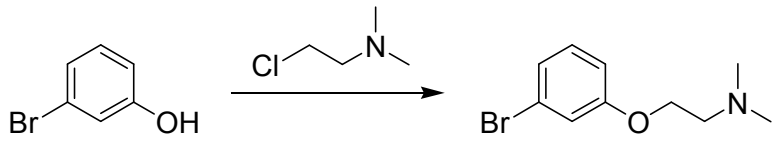
filtered, and then concentrated. To the crude product was added water and the resulting precipitate was filtered to give **SI-10** (3.51 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (t, *J* = 1.6 Hz, 1H), 7.58 (d, *J* = 15.4 Hz, 1H), 7.51 – 7.36 (m, 2H), 7.25 (d, *J* = 7.0 Hz, 1H), 6.87 (d, *J* = 15.4 Hz, 1H), 3.12 (s, 6H). LCMS (FA): *m/z* 256.1 (M+H)

Step 2/3. To a mixture of trimethylsufoxonium iodide (0.583 g, 2.65 mmol) and sodium hydride (0.106 g, 2.65 mmol), under argon gas, was added DMSO (10 mL), dropwise, over 5 min. The reaction mixture was allowed to stir, at room temperature, for 30 min. A solution of (2E)-3-(3-bromophenyl)-N,N-dimethylacrylamide (0.500 g, 1.97 mmol) in DMSO (12 mL) was added dropwise over 5 minutes. The resulting mixture was allowed to stir, at 50^{o}C, overnight. The reaction was quenched with water and then extracted with EtOAc. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and then concentrated to give 0.530 grams of 2-(3-bromophenyl)-N,N-dimethylcyclopropanecarboxamide. To a solution of the crude intermediate (0.530 grams, 2.0 mmol) in THF (3.7 mL) was added a 2.0M solution of borane-THF complex in THF (4.9 mL, 4.9 mmol). The reaction mixture was allowed to stir, at reflux, for 3h. The solvent was removed en vacuo, and then re-dissolved in THF (2 mL). To the mixture was added 1N aqueous HCl (5 mL) and then the reaction mixture was stirred at 75 ^{o}C overnight. The resulting mixture was quenched with water, and then extracted with EtOAc. The combined organic layers were dried over magnesium sulfate, filtered, and then concentrated to give **SI-11** (0.39 grams, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 – 6.86 (m, 1H), 6.81 (t, *J* = 1.8 Hz, 1H), 6.72 (t, *J* = 7.8 Hz, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 1.91 (d, *J* = 10.6 Hz, 6H), 1.78 (t, *J* = 9.8 Hz, 2H), 1.33 – 1.23 (m, 1H), 0.89 – 0.78 (m, 1H), 0.62 – 0.54 (m, 1H), 0.49 (dt, *J* = 8.6, 5.4 Hz, 1H). LCMS (FA): *m/z* 256.2 (M+H)



9-chloro-2-[(3-{2-[(dimethylamino)methyl]cyclopropyl}phenyl)amino]-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (10p)

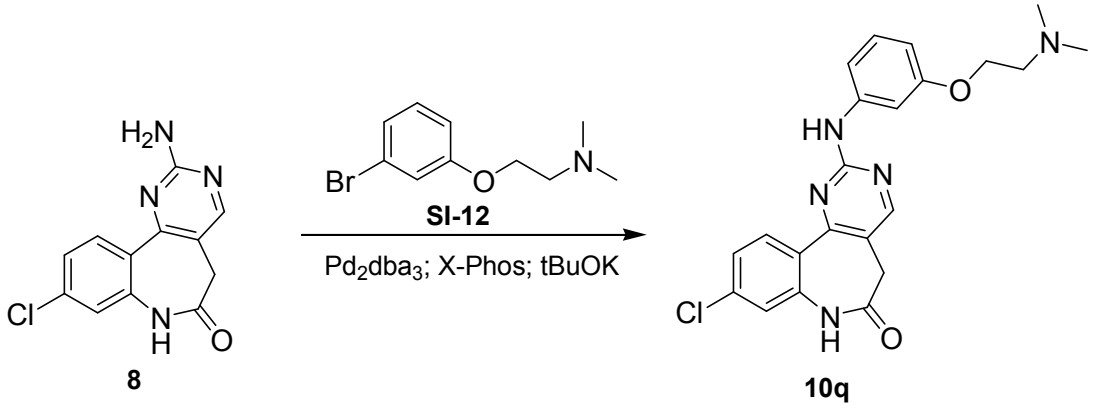
8 was coupled with **S1-11** using method 4 to provide **10p** (0.23 g, 42%).
^{1}H NMR (400 MHz, MeOD) δ 7.97 (s, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.20 (t, *J* = 1.8 Hz, 1H), 7.05 (ddd, *J* = 8.1, 2.1, 0.9 Hz, 1H), 6.98 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.86 (t, *J* = 3.9 Hz, 1H), 6.77 (t, *J* = 7.9 Hz, 1H), 6.38 (d, *J* = 7.7 Hz, 1H), 3.02 (s, 2H), 2.17 (dd, *J* = 12.6, 5.9 Hz, 1H), 1.91 (d, *J* = 8.1 Hz, 6H), 1.88 (dd, *J* = 15.6, 8.2 Hz, 1H), 1.40 – 1.28 (m, 1H), 0.87 – 0.73 (m, 1H), 0.63 (dt, *J* = 8.6, 5.0 Hz, 1H), 0.48 (dt, *J* = 8.7, 5.2 Hz, 1H). LCMS (FA): *m/z* 434.3 (M+H)



SI-12

[2-(3-Bromo-phenoxy)-ethyl]-dimethyl-amine (SI-12)

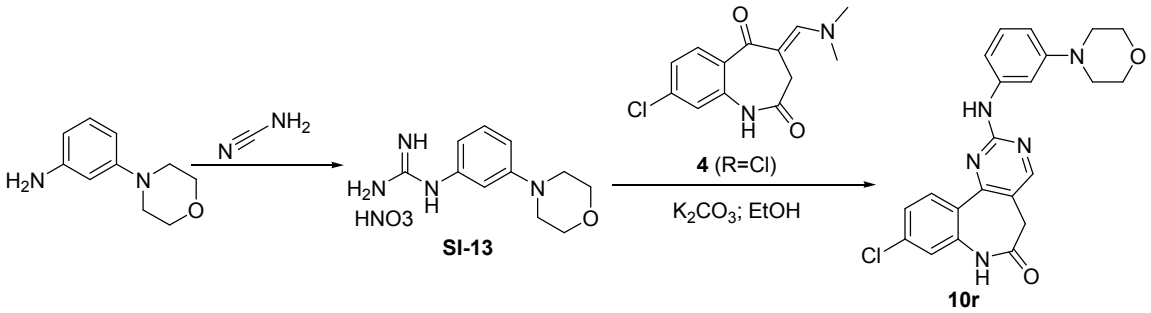
To a solution of 3-bromophenol (225 mg, 1.30 mmol) in acetonitrile (5 mL) was added potassium carbonate (899 mg, 6.50 mmol), potassium iodide (45 mg, 0.27 mmol), and dimethylaminoethyl chloride-HCl (375 mg, 2.60 mmol). The reaction mixture was stirred at 90 ^{o}C overnight. To the mixture was added potassium carbonate (360 mg, 2.60 mmol) and dimethylaminoethyl chloride-HCl (188 mg, 1.30 mmol) and then stirred at 115 ^{o}C overnight. The solvent was removed en vacuo and then purified by column chromatography to give **SI-12** (253 mg, 72%). ^{1}H NMR (300 MHz, DMSO) δ 7.21 (t, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 2.1 Hz, 1H), 7.11 – 7.06 (m, 1H), 6.95 – 6.90 (m, 1H), 4.03 (t, *J* = 5.8 Hz, 2H), 2.58 (t, *J* = 5.8 Hz, 2H), 2.17 (d, *J* = 2.9 Hz, 6H). LCMS (FA): *m/z* 246.0 (M+H).



8 **10q**

9-chloro-2-({3-[2-(dimethylamino)ethoxy]phenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (10q)

8 was coupled with **SI-12** using method 4 to provide **10q** (39 mg, 10%).
^{1}H NMR (300 MHz, DMSO) δ 10.38 (s, 1H), 10.11 (s, 1H), 9.87 (s, 1H), 8.55 (d, *J* = 5.3 Hz, 1H), 8.10 (dd, *J* = 8.5, 5.4 Hz, 1H), 7.70 (s, 1H), 7.44 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.26 (ddd, *J* = 16.3, 14.3, 10.6 Hz, 3H), 6.61 (d, *J* = 5.6 Hz, 1H), 3.53 (s, 2H), 3.42 (s, 2H), 2.85 (s, 2H), 2.57 – 2.33 (m, 6H). LCMS (FA): *m/z* 424.0 (M+H).



10r

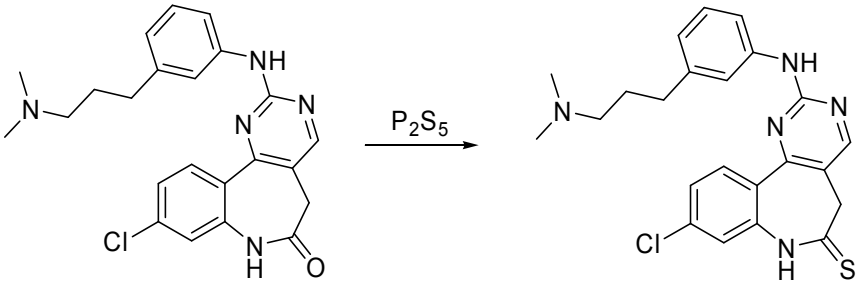
9-chloro-2-(3-morpholinophenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (10r)

Step 1. 1-(3-morpholinophenyl)guanidine nitrate (**SI-13**) was prepared following method 3 using commercial 3-morpholinoaniline. Yield: 322 mg (50%). LCMS (FA): *m/z* = 221.0 (M+H).

Step 2. Following method 3, **10g** was prepared from **SI-13** (170 mg, 0.49 mmol). Product was converted to the HCl salt by dissolving in MeOH and adding 2 eq. of HCl/Et_2O. The mixture was concentrated to give 23 mg (10%) of the HCl salt. ^{1}H NMR (400 MHz, DMSO) δ 10.35 (s, 1H), 9.64 (s, 1H), 8.50 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.67 (s, 1H), 7.39 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.28 (dd, *J* = 5.4, 2.1 Hz, 1H), 7.20 – 7.06 (m, 2H), 6.55 (dd, *J* = 8.1, 1.5 Hz, 1H), 3.78 – 3.67 (m, 4H), 3.39 (s, 2H), 3.12 – 3.03 (m, 4H). LCMS (FA): *m/z* = 421.9 (M+H).

Procedures for the syntheses of compounds in Table 3

Method 5. Conversion of lactam to thiolactam using phosphorous pentasulfide



10s **11a**

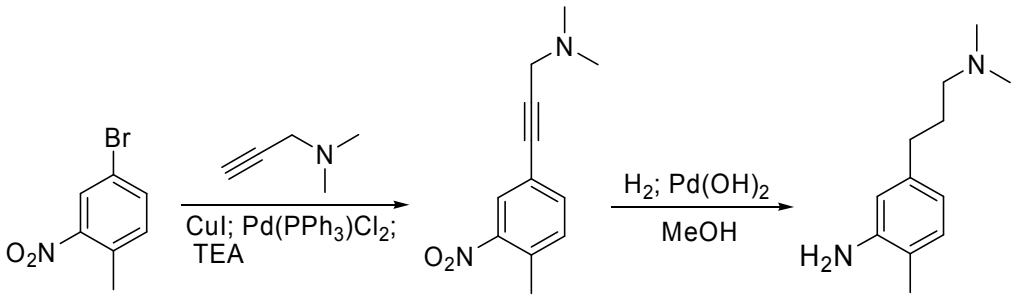
9-chloro-2-({3-[3-(dimethylamino)propyl]phenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (11a)

A mixture of **10s** (940 mg, 2.2 mmol) and phosporous pentasulfide (1.14 g, 5.12 mmol) in pyridine (17 mL) was allowed to stir overnight at 60^{0}C. At this point additional phosporous pentasulfide (66 mg, 0.30 mmol) was added and the reaction mixture was allowed to stir for another one hour. The reaction mixture was then added dropwise into a stirred soln of 1:1 water/1M aq. $NaHCO_3$ solution (160 mL) and allowed to stir for an hour. The resulting solid was obtained after filtration and a wash with water and ether. The yellowish tan solid obtained was vacuum dried to give **11a** (980 mg; 100%). LCMS (FA): m/z 438.2 (M+H).

11a (920 mg, 2.1 mmol) was then dissolved in tetrahydrofuran (37 mL) and to this 2.00 M of HCl in ether (2.10 mL, 4.20 mmol) was added and allowed to stir for 10 min. Ether (170 mL) was added and then allowed to stir for 30 min. The resulting solid was filtered and washed with ether and dried under vacuum to give **11a** as the bis-HCl salt (944 mg; 88%) ^{1}H NMR (400 MHz, DMSO) δ 12.27 (s, 1H), 10.22 (s, 1H), 9.82 (s, 1H), 8.49 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.56 (dd, *J* = 8.5, 1.9

Hz, 1H), 7.42 (d, *J* = 1.8 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.4 Hz, 1H), 3.85 (s, 2H), 3.03 (m, 2H), 2.72 (s,3H), 2.71(s, 3H), 2.60 (m, 2H), 1.95 (m, 2H). LCMS (FA): m/z 438.2 (M+H).

Method 6. Sonagashira coupling and reduction of alkyne to dimethylaminopropylaniline



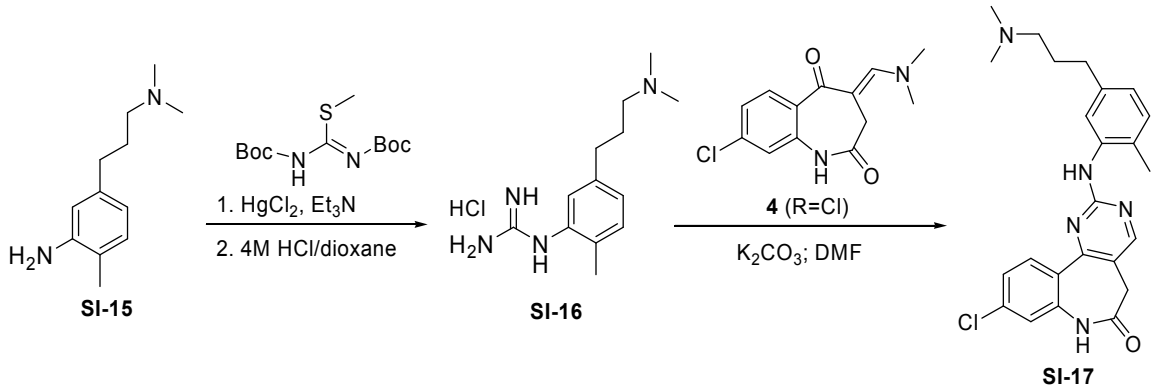
SI-14 **SI-15**

5-[3-(dimethylamino)propyl]-2-methylaniline (SI-14)

Step 1. To 4-bromo-2-nitrotoluene (3.4 g, 15.6 mmol) was added triethylamine (109 mL) and argon gas was bubbled through the reaction mixture for 15 min. To this copper(I) iodide (0.6 g, 3.1 mmol) and bis(triphenylphosphine)palladium(II) chloride (1.1 g, 1.56 mmol) were added and the resulting mixture was allowed to stir at room temp for 45 min. Propargyl(dimethylamine) (5.1 mL, 47 mmol) was then added and then stirred at 80 ^{0}C overnight. The reaction was allowed to cool to room temperature and then filtered through a bed of celite. The filtrate was concentrated to an oily residue which was purified on silica gel to give (**SI-14**) (3.1 g; 91%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 1.5 Hz, 1H), 7.52 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.27 (d, J=7.9Hz, 1H), 3.47 (s, 2H), 2.58 (s, 3H), 2.36 (s, 6H). LC-MS (FA): m/z 219.2 (M+H)

Step 2. To **SI-14** (3.1 g, 14.2 mmol) in a Parr shaker bottle was added ethanol (180 mL). This reaction vessel was flushed with nitrogen gas followed by the addition of palladium hydroxide (10% on carbon; 968 mg, 0.7 mmol). This suspension was allowed to shake 3 day at 35-40 psi of hydrogen. The reaction mixture was then filtered through a bed of celite and the filter bed was washed with fresh methanol. The filtrate was concentrated to give **SI-15** (2.6 g; 97%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 8.7 Hz, 1H), 6.53(s, 1H), 3.55 (s, 2H), 2.52 (m, 2H), 2.3 7 – 2.26 (m, 2H), 2.23 (s, 6H), 2.13 (s, 3H), 1.77 (m, 2H). LCMS (FA): m/z 193.3 (M+H).

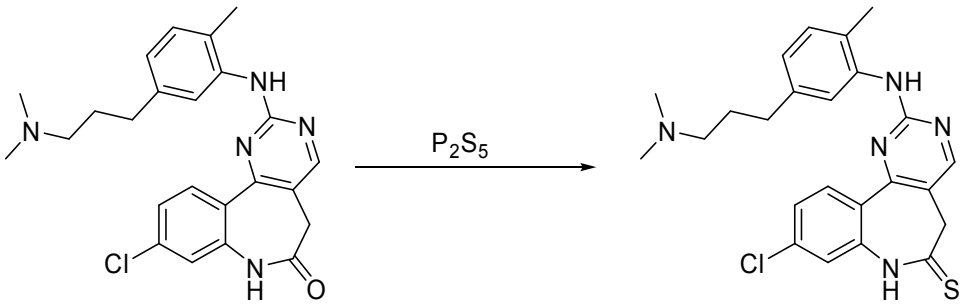
Method 7. Formation of guanidines with 1,3-bis(tert-butoxycarbonyl)-2-methyl-2-thiopseudourea and subsequent formation of aminopyrimidine.



9-chloro-2-({5-[3-(dimethylamino)propyl]-2-methylphenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-17)

Step 1. To **SI-15** (2.6 g, 13.6 mmol), 1,3-bis(tert-butoxycarbonyl)-2-methyl-2-thiopseudourea (4.3 g, 14.9 mmol) and mercury(II) chloride (4.1 g, 14.9 mmol) in DCM (200 mL) was added triethylamine (6.2 mL, 45 mmol) under an atmosphere of nitrogen. The mixture was stirred at room temperature 15 hours. The mixture was filtered through Celite and the pad washed with DCM (100 mL). The filtrate was washed with water (150 mL), sat $NaHCO_3$ (150 mL) and brine (150 mL) then dried over $MgSO_4$, filtered and concentrated. The residue was purified on silica gel to give di-tert-butyl [(Z)-({5-[3-(dimethylamino)propyl]-2-methylphenyl}amino)methylylidene]biscarbamate (3.14g; 53%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.65 (s, 1H), 10.08 (s, 1H), 7.70 (s, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.89 (dd, *J* = 7.7, 1.6 Hz, 1H), 3.47 (s, 2H), 2.63 (m, 2H), 2.47 – 2.34 (m, 2H), 2.29 (s, 6H), 2.25 (s, 3H), 1.92 – 1.75 (m, 2H), 1.53 (s, 9H), 1.45 (s, 9H). LCMS (FA): m/z 435.3 (M+H).

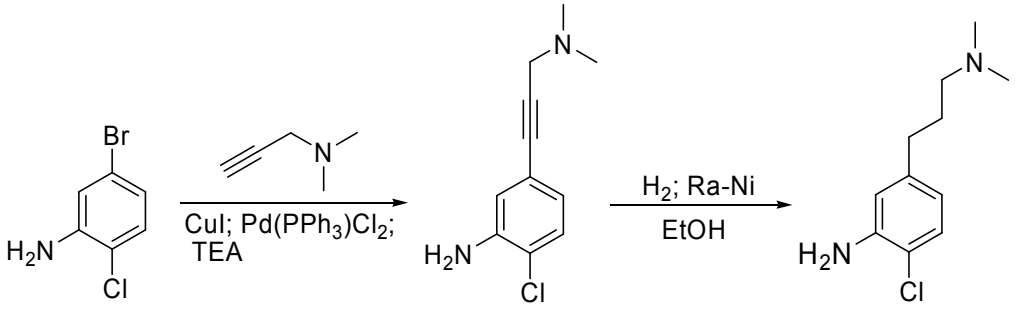
Steps 2/3. di-tert-butyl [(Z)-({5-[3-(dimethylamino)propyl]-2-methylphenyl}amino)methylylidene]biscarbamate (0.9 g, 2.1 mmol) was dissolved in 1,4-dioxane (7.5 mL) then 4.0 M of hydrochloric acid in dioxane (8.2 mL, 33 mmol) was added and the solution stirred overnight at room temperature. All volatiles were removed in vacuo and the resulting white powder (**SI-16**) was then suspended in DMF (11 mL) and potassium carbonate (1.5 g, 10.8 mmol) and **4** (R=Cl) (0.46 g, 1.7 mmol) were added in succession under an atmosphere of nitrogen. A condenser was fitted and the suspension was heated at 125 °C for 15 hr. After cooling to room temperature, water was added to the solution and the precipitated solids were collected by filtration by a fritted funnel. The solids were washed with water and ether. The crude product was purified on silica gel to give **SI-17** (349 mg, 46%). ^{1}H NMR (300 MHz, DMSO) δ 10.37 (s, 1H), 10.32 (s, 1H), 8.90 (s, 1H), 8.40 (s, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.43 – 7.34 (m, 2H), 7.26 (d, *J* = 1.9 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 3.37 (s, 2H), 3.01 (m, 2H), 2.70 (s, 3H), 2.69 (s, 3H), 2.58 (m, 2H), 2.19 (s, 3H), 1.92 (m, 2H). LC-MS (FA): m/z 436.2 (M+H).



SI-17 **11b**

9-chloro-2-(5-(3-(dimethylamino)propyl)-2-methylphenylamino)-5H-benzo[b]pyrimido[4,5-d]azepine-6(7H)-thione (11b)

Method 5 for the conversion of lactams to thiolactams using P_2S_5 was used to give **11b** as the formate salt after HPLC purification (115 mg, 29%). ^{1}H NMR (300 MHz, DMSO) δ 8.94 (s, 1H), 8.37 (s, 1H), 7.94 (m, 1H), 7.46 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 3.80 (s, 2H), 3.74 (d, *J* = 5.3 Hz, 1H), 2.59 – 2.51 (m, 2H), 2.45 – 2.34 (m, 2H), 2.23 (s, 6H), 2.18 (s, 3H), 1.81 – 1.64 (m, 2H). LC-MS (FA): m/z 452.2 (M+H).



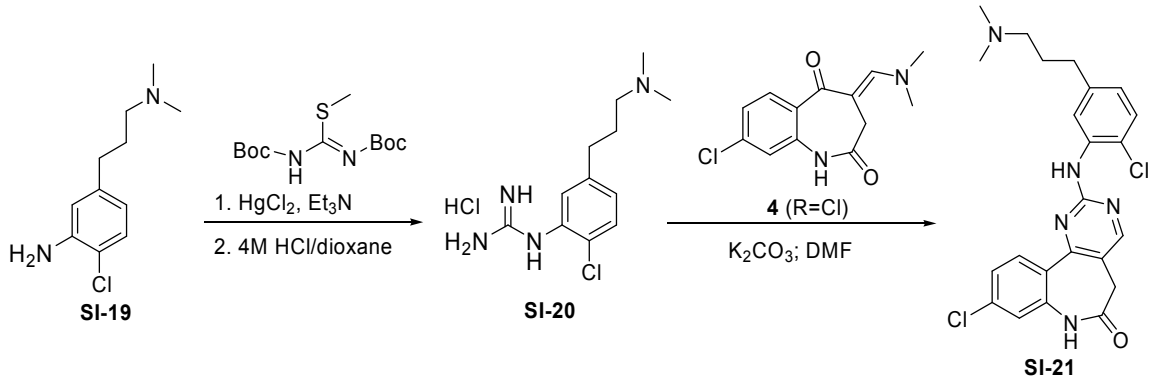
SI-18 **SI-19**

2-chloro-5-[3-(dimethylamino)propyl]aniline (SI-19)

Step 1 of method 6 was used for the conversion of 5-bromo-2-chloroaniline to 2-chloro-5-[3-(dimethylamino)prop-1-yn-1-yl]aniline (**SI-18**).

Step 1. 5-bromo-2-chloroaniline (14.1 g, 68.3 mmol) gave 12.8 g (85%) of **SI-18**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 1.8 Hz, 1H), 6.76 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.43 (s, 2H), 2.33 (s, 6H). LC-MS (FA): m/z 209.2 (M+H).

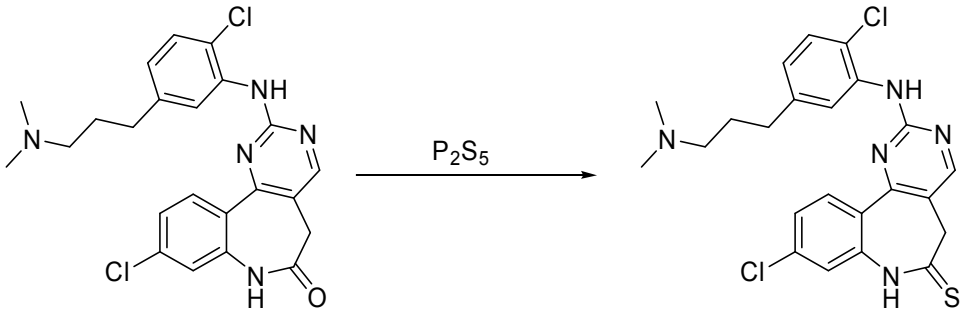
Step 2. **SI-18** (12.1 g, 58.0 mmol) was dissolved in Ethanol (250 mL) and placed under an atmosphere of nitrogen. Then Raney nickel [slurry in water (50%, v/v; 140 mmol)] was added. The reaction mixture was stirred under an atmosphere of hydrogen for 3 hrs. Celite was added and the reaction mixture was filtered through a pad of celite and washed with dichloromethane. The filtrate was concentrated in vacuo and the residue was purified on silica gel to give **SI-19** (6.95 g, 56%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.1 Hz, 1H), 6.61 (d, *J* = 1.9 Hz, 1H), 6.50 (dd, *J* = 8.1, 2.0 Hz, 1H), 4.27 – 3.86 (b, 2H), 2.53 (m, 2H), 2.42 (m, 2H), 2.35 (s, 6H), 1.92 – 1.76 (m, 2H). LCMS (FA): m/z 213.2 (M+H).



9-chloro-2-({2-chloro-5-[3-(dimethylamino)propyl]phenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-21)
Method 7 was used to synthesize **SI-21**

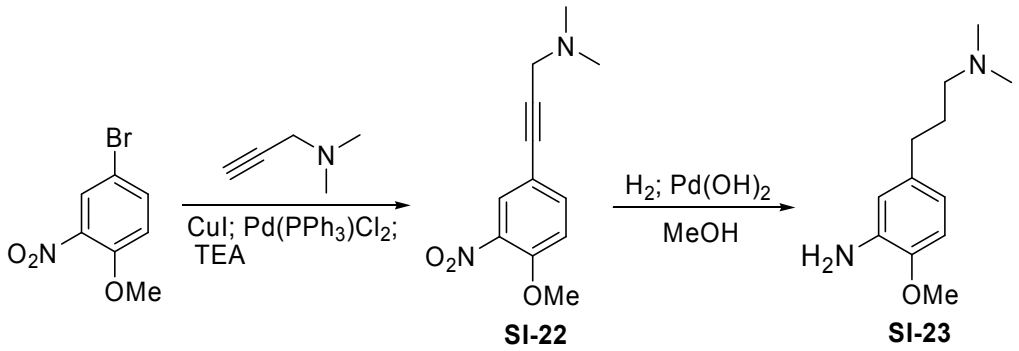
Step 1. 6.89 g (32.4 mmol) of **SI-19** gave (Z)-tert-butyl (tert-butoxycarbonylamino)(2-chloro-5-(3-(dimethylamino)propyl)phenylamino)methylenecarbamate (8.6 g; 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.61 (s, 1H), 10.61 (s, 1H), 8.20 (s, 1H), 7.25 (d, 8.2Hz, 1H), 6.88 (dd, *J* = 8.2, 2.0 Hz, 1H), 2.71 – 2.59 (m, 2H), 2.44 – 2.33 (m, 2H), 2.29 (s, 6H), 1.85 (m, 2H), 1.53 (s, 9H), 1.50 (s, 9H). LCMS (FA): m/z 455.3 (M+H).

Steps 2/3. Deprotection of (Z)-tert-butyl (tert-butoxycarbonylamino)(2-chloro-5-(3-(dimethylamino)propyl)phenylamino)methylenecarbamate (1.30 g, 2.9 mmol) and subsequent condensation of **SI-20** with **4** (R=Cl) (0.61 g, 2.3 mmol) gave **SI-21** (520 mg; 50%). ^{1}H NMR (400 MHz, DMSO) δ 10.36 (s, 1H), 8.90 (s, 1H), 8.49 (s, 1H), 8.09 (d, J=8.5Hz, 1H), 7.75 (d, *J* = 2.0 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.27 (d, *J* = 2.1 Hz, 1H), 7.00 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.41 (s, 2H), 2.63 – 2.54 (m, 2H), 2.26 – 2.16 (m, 2H), 2.10 (s, 6H), 1.76 – 1.65 (m, 2H). LCMS (FA): m/z 456.2 (M+H).



9-chloro-2-({2-chloro-5-[3-(dimethylamino)propyl]phenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (11c)
Method 5 for the conversion of lactams to thiolactams using P_2S_5 was used to give **11c**. After purification by HPLC **11c** was isolated as the formate salt (1.9 g, 46%).^{1}H NMR (400 MHz, DMSO) δ 9.03 (s, 1H), 8.46 (s, 1H), 8.23 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.68 (d, *J* = 1.6 Hz, 1H), 7.49 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.41 (s, 1H), 7.40 (d, *J* = 5.1 Hz, 1H), 7.02 (dd, *J* = 8.2, 1.8 Hz, 1H), 3.86 (s, 2H), 2.59 (m, 2H), 2.36 (m, 2H), 2.22 (s,

6H), 1.81 – 1.68 (m, 2H). LCMS (FA): m/z 472.1 (M+H).

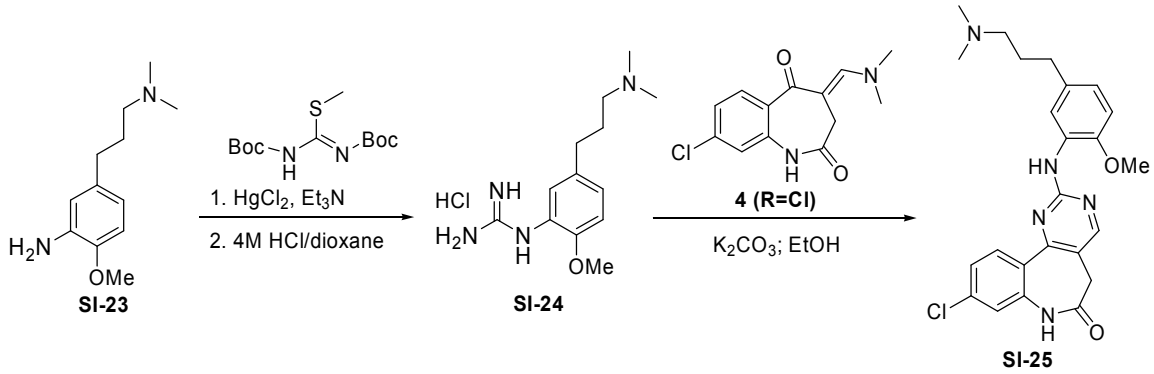


SI-22 **SI-23**

5-(3-(dimethylamino)propyl)-2-methoxyaniline (SI-23)
Method 6 was used for the conversion of 4-bromo-1-methoxy-2-nitrobenzene to **SI-23**.

Step 1. 4-bromo-1-methoxy-2-nitrobenzene (4.9 g, 21.2 mmol) gave 4.4 g (89%) of 3-(4-methoxy-3-nitrophenyl)-N,N-dimethylprop-2-yn-1-amine (**SI-22**). (M+H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, *J* = 2.1 Hz, 1H), 7.62 – 7.54 (m, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 3.97 (s, 3H), 3.44 (s, 2H), 2.36 (s, 6H). LCMS (FA): m/z 235.2

Step 2. **SI-22** (4.4 g, 18.9 mmol) gave 3.9 g (99%) of **SI-23**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.75 – 6.61 (m, 1H), 6.61 – 6.44 (m, 2H), 5.30 (s, 1H), 4.29 (s, 2H), 3.84 (s, 3H), 2.56 – 2.46 (m, 2H), 2.44 – 2.35 (m, 2H), 2.31 (s, 6H), 1.79 (m, 2H).
LCMS (FA): m/z 209.2 (M+H).



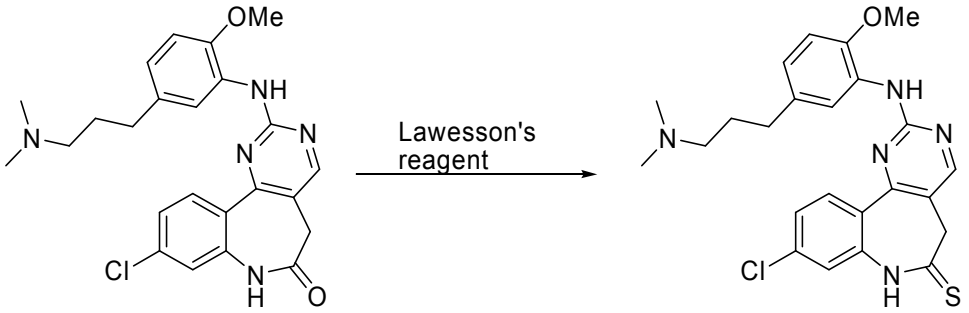
SI-23 **SI-24** **SI-25**

9-chloro-2-(5-(3-(dimethylamino)propyl)-2-methoxyphenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (SI-25)
Method 7 was used to synthesize **SI-25**

Step 1. 4.2 g (20.2 mmol) of **SI-23** gave di-tert-butyl [(Z)-({5-[3-(dimethylamino)propyl]-2-methylphenyl}amino)methylylidene]biscarbamate (3.6 g; 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.59 (s, 1H), 10.61 (s, 1H), 8.27 (d, *J* = 2.0 Hz, 1H), 8.01 (s, 1H), 6.86 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 3.89 (d, *J* = 10.7 Hz, 3H), 2.95 (s, 3H), 2.88 (s, 3H), 2.66 – 2.57 (m, 2H), 2.37 – 2.31 (m, 2H), 1.81 (m, 2H), 1.53 (s, 9H), 1.50 (s, 9H). LCMS (FA): m/z 451.4 (M+H).

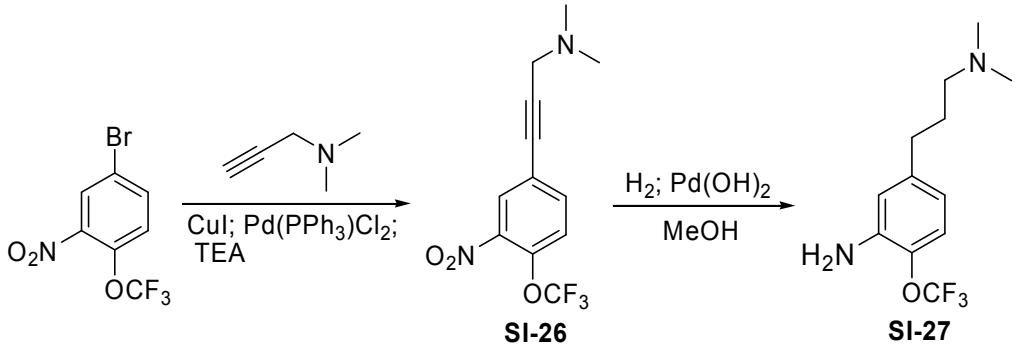
Steps 2/3. Deprotection of di-tert-butyl [(Z)-({5-[3-(dimethylamino)propyl]-2-methylphenyl}amino)methylylidene]biscarbamate and subsequent condensation of **SI-24** with **4** (R=Cl) (2.5 g, 7.7 mmol) using EtOH as solvent gave **SI-25** (2.1 g; 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.38 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.87 (s, 1H), 7.59 (s, 1H), 7.37 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 6.87 – 6.75 (m, 2H), 3.91 (s, 3H), 3.45 (s, 2H), 2.62 (t, *J* = 8.0 Hz, 2H), 2.38 (m, 2H), 2.27 (s, 6H), 1.86 (m, 2H). LCMS (FA): m/z 452.1 (M+H).

Method 8. Conversion to thioamide with Lawesson's reagent



SI-25 **11d**

9-chloro-2-({5-[3-(dimethylamino)propyl]-2-methoxyphenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (11d)
Into a round-bottomed flask was added **SI-25** (0.18 g, 0.40 mmol), 2,4-Bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (0.33 g, 0.81 mmol) and THF (6 mL). The mixture was stirred at 60 °C for 1 hour. The mixture was then partitioned between DCM (50 mL) and sat. $NaHCO_3$ (aq.) (20 mL). The organic phase was washed with water and brine. The solution was then dried over Na_2SO_4, filtered and concentrated. The residue was triturated with ether to give a yellow solid, which was redissolved in THF. 2N HCl in ether was added to give a yellow solid which was collected by filtration. Obtained **11d** as the HCl salt (160 mg, 85%). ^{1}H NMR (400 MHz, MeOD) δ 8.04 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.48 (s, 1H), 7.15 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.04 (d, *J* = 2.0 Hz, 1H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 3.68 (s, 2H), 3.60 (s, 3H), 2.79 (m, 2H), 2.53 (s, 6H), 2.43 (m, 2H), 1.80 (m, 2H). LCMS (FA): m/z 468.9 (M+H).

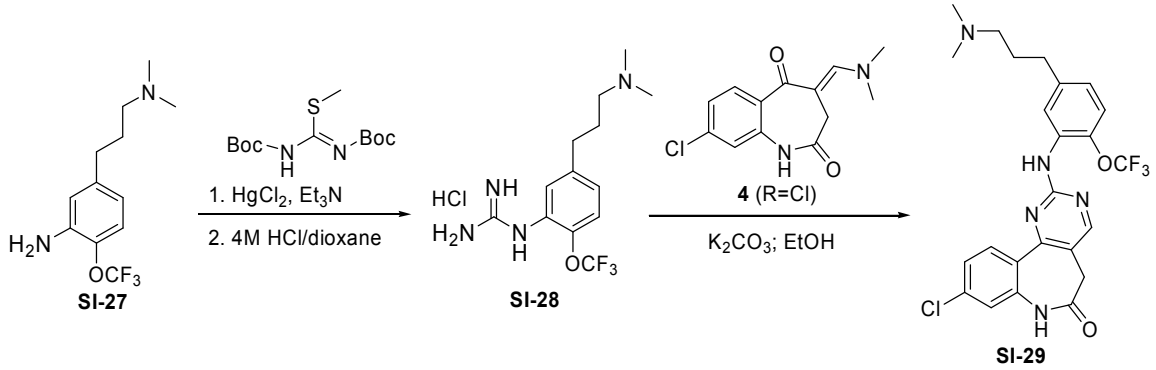


SI-26 **SI-27**

5-[3-(dimethylamino)propyl]-2-(trifluoromethoxy)aniline (SI-27)
Method 6 was used for the synthesis of **SI-27**.

Step 1. 4-bromo-1-trifluoromethoxy-2-nitrobenzene (2.7 g, 9.5 mmol) gave 2.3 g (84%) of 3-(4-trifluoromethoxy-3-nitrophenyl)-N,N-dimethylprop-2-yn-1-amine (**SI-6**). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, *J* = 2.0 Hz, 1H), 7.67 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.38 (dd, *J* = 8.6, 1.3 Hz, 1H), 3.48 (s, 2H), 2.37 (s, 6H). LCMS (FA): m/z 289.1 (M+H).

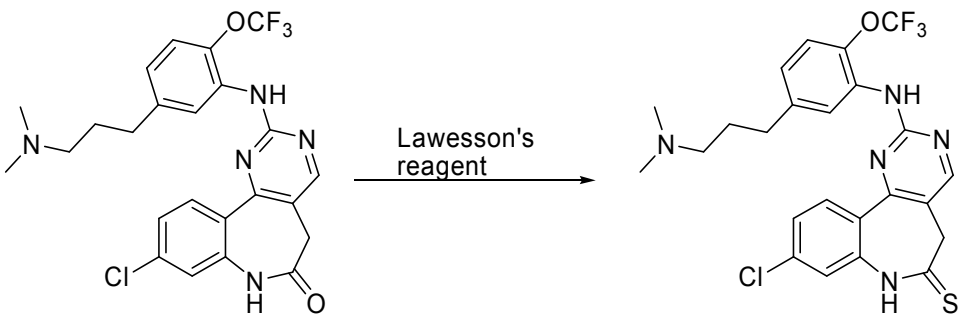
Step 2. **SI-26** (2.3 g, 7.8 mmol) gave 2.0 g (97%) of **SI-27**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (dd, *J* = 8.3, 1.5 Hz, 1H), 6.62 (d, *J* = 2.0 Hz, 1H), 6.54 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.81 (s, 2H), 2.58 – 2.46 (m, 2H), 2.35 – 2.25 (m, 2H), 2.23 (s, 6H), 1.75 (m, 2H). LCMS (FA): m/z 263.2 (M+H).



9-chloro-2-{[5-[3-(dimethylamino)propyl]-2-(trifluoromethoxy)phenyl]amino}-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-29)
Method 7 was used to synthesize **SI-29**

Step 1. 1.97 g (7.5 mmol) of **SI-27** gave di-tert-butyl ((Z)-{[5-[3-(dimethylamino)propyl]-2-(trifluoromethoxy)phenyl]amino}methylylidene)biscarbamate (2.4 g; 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.56 (s, 1H), 10.77 (s, 1H), 8.30 (d, *J* = 1.8 Hz, 1H), 7.14 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.93 (dd, *J* = 8.4, 2.1 Hz, 1H), 2.75 – 2.61 (m, 2H), 2.49 – 2.39 (m, 2H), 2.33 (s, 6H), 1.95 – 1.81 (m, 2H), 1.51 (s, 18H). LCMS (FA): m/z 505.2 (M+H).

Steps 2/3. Deprotection of di-tert-butyl ((Z)-{[5-[3-(dimethylamino)propyl]-2-(trifluoromethoxy)phenyl]amino}methylylidene)biscarbamate (1.54 g, 3.05 mmol) and subsequent condensation of **SI-28** with **4** (R=Cl) (0.67 g, 2.5 mmol) in EtOH gave **SI-29** (228 mg). The product was dissolved in THF. 1N HCl in ether (0.28 mL) was added followed by additional ether. The resulting solid was collected to give **SI-29** as the HCl salt (270 mg; 20%). ^{1}H NMR (300 MHz, DMSO) δ 10.36 (s, 1H), 10.27 (s, 1H), 9.23 (s, 1H), 8.48 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 1.9 Hz, 1H), 7.41 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.32 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.08 (dd, *J* = 8.4, 2.1 Hz, 1H), 3.56 (s, 4H), 3.40 (s, 2H), 3.04 (m, 2H), 2.72 (s, 3H), 2.70 (s, 3H), 2.65 (m, 2H), 1.96 (m, 2H). LCMS (FA): m/z 506.1 (M+H).

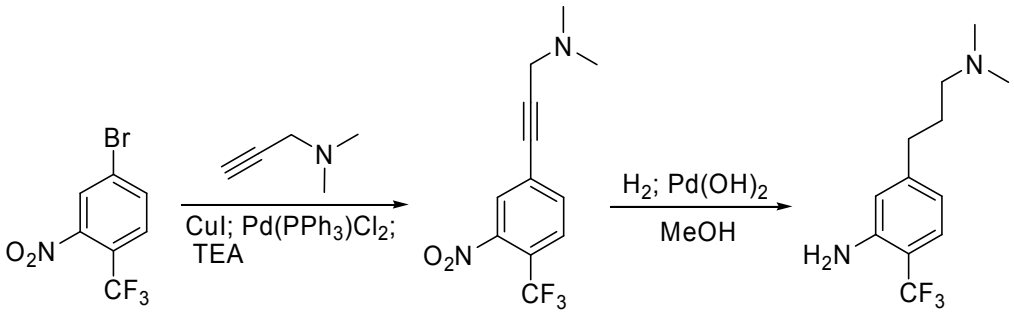


SI-29 **11e**

9-chloro-2-{[5-[3-(dimethylamino)propyl]-2-(trifluoromethoxy)phenyl]amino}-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (11e)

Method 8 was used for conversion to the thioamide.

Obtained **11e** (60 mg, 32%) as the formate salt after HPLC purification. ^{1}H NMR (300 MHz, DMSO) δ 9.27 (s, 1H), 8.46 (s, 1H), 8.16 (s, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.78 (s,1H), 7.49 (d, *J* = 8.5, 1H), 7.40 (S, 1H), 7.28 (d, *J* = 8.4, 1H), 7.05 (d, *J* = 8.41H), 3.85 (s, 2H), 3.76 – 3.67 (m, 1H), 2.65 – 2.54 (m, 2H), 2.27 (s, 6H), 1.75 (m, 2H). LCMS (FA): m/z 522.1 (M+H).



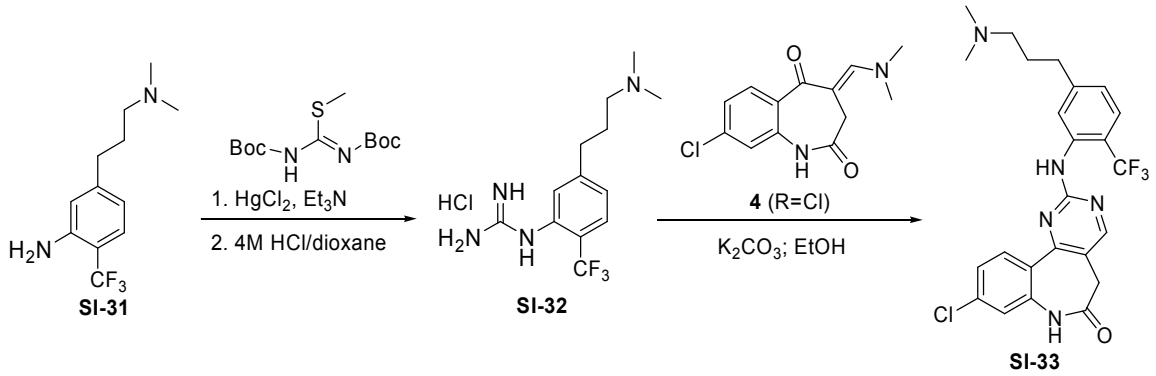
SI-30 **SI-31**

5-[3-(dimethylamino)propyl]-2-(trifluoromethyl)aniline (SI-31)

Method 6 was used for the synthesis of **SI-31**.

Step 1. 4-bromo-2-nitro-1-(trifluoromethyl)benzene (2.12 g, 7.85 mmol) gave 1.3 g (61%) of 3-(4-trifluoromethyl-3-nitrophenyl)-N,N-dimethylprop-2-yn-1-amine **(SI-30)**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.78 – 7.68 (m, 2H), 3.50 (s, 2H), 2.37 (s, 6H). LCMS (FA): m/z 273.2 (M+H).

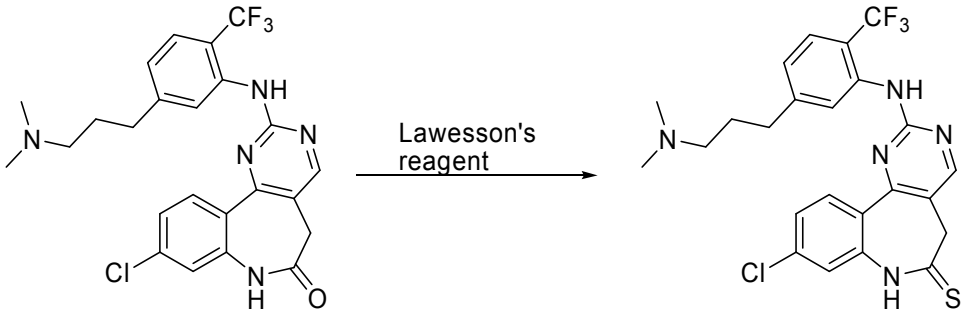
Step 2. **SI-30** (0.84 g, 3.1 mmol) gave 2.0 g (97%) of **SI-31**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.56 (s, 1H), 4.11 (s, 2H), 2.62 – 2.51 (m, 2H), 2.32 – 2.25 (m, 2H), 2.23 (s, 6H), 1.76 (m, 2H). LCMS (FA): m/z 247.3 (M+H).



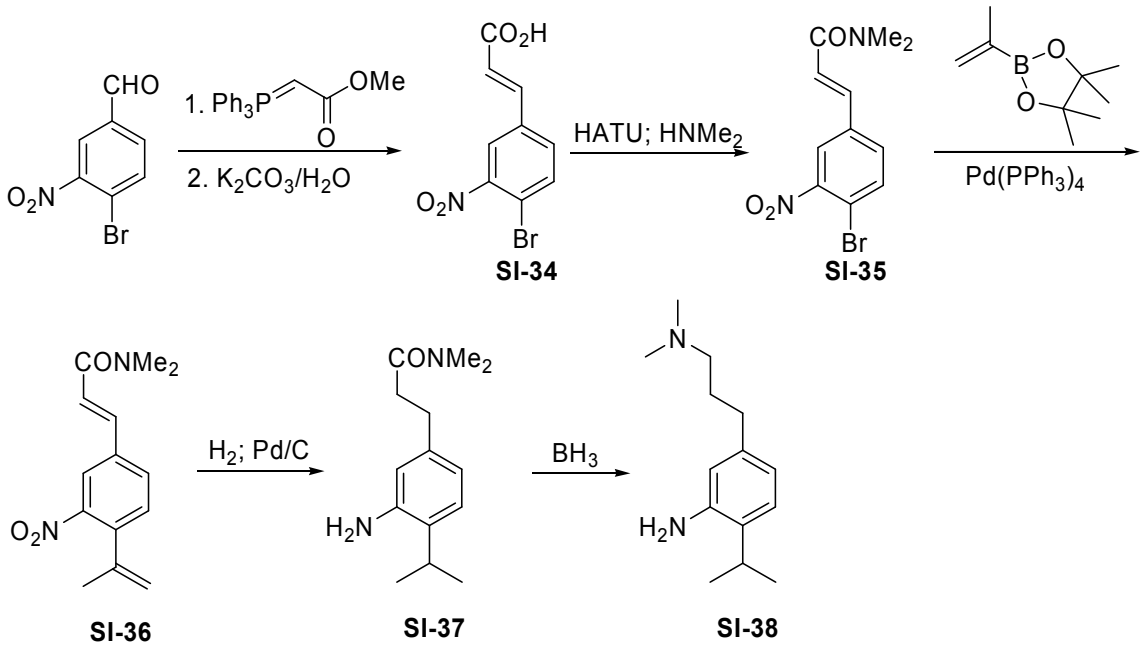
9-chloro-2-{[5-[3-(dimethylamino)propyl]-2-(trifluoromethyl)phenyl]amino}-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-33)
Method 7 was used to synthesize **SI-33**

Step 1. 765 mg (3.1 mmol) of **SI-31** gave di-tert-butyl ((Z)-{[5-[3-(dimethylamino)propyl]-2-(trifluoromethyl)phenyl]amino}methylylidene)biscarbamate (780 mg; 51%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.66 (s, 1H), 10.48 (s, 1H), 7.86 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 2.73 (m, 2H), 2.47 (m, 7.6 Hz, 2H), 2.37 (s, 6H), 1.99 – 1.85 (m, 2H), 1.47 (s, 18H). LCMS (FA): m/z 489.2 (M+H).

Steps 2/3. Deprotection of di-tert-butyl ((Z)-{[5-[3-(dimethylamino)propyl]-2-(trifluoromethyl)phenyl]amino}methylylidene)biscarbamate and subsequent condensation of **SI-32** with **4** (R=Cl) (350 mg, 1.3 mmol) gave **SI-33** (6 mg; 1%) as the formate salt after HPLC purification. ^{1}H NMR (300 MHz, DMSO) δ 10.33 (s, 1H), 8.88 (s,, 1H), 8.41 (s, 1H), 8.22 (s, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.69 – 7.54 (m, 2H), 7.39 – 7.29 (m, 1H), 7.29 – 7.16 (m, 2H), 3.39 (m, 2H), 2.71 – 2.60 (m, 2H), 2.41 – 2.30 (m, 2H), 2.22 (s, 6H), 1.84 – 1.64 (m, 2H). LCMS (FA): m/z 490.1 (M+H).



9-chloro-2-(5-(3-(dimethylamino)propyl)-2-(trifluoromethyl)phenylamino)-5H-benzo[b]pyrimido[4,5-d]azepine-6(7H)-thione (11f)
Method 8 was used for conversion to the thioamide.
Obtained **11f** as the formate salt after HPLC purification (8 mg, 20%). ^{1}H NMR (300 MHz, DMSO) δ 8.97 (s, 1H), 8.38 (s, 1H), 8.17 (s, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.56 (s, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.38 (s, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 3.82 (m, 2H), 2.65 (m, 2H), 2.31 (m, 2H), 2.18 (s, 6H), 1.74 (m, 2H). LCMS (FA): m/z 506.1 (M+H).



5,5-[3-(dimethylamino)propyl]-2-isopropylaniline (SI-38)

Step 1/2. To a round bottomed flask was added 4-Bromo-3-nitro-benzaldehyde (8.41 g, 36.6 mmol), Tetrahydrofuran (170 mL) and (carbomethoxymethylene)triphenylphosphorane (14.0 g, 42.0 mol) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and overnight at RT. The mixture was concentrated and then triturated with DCM. The light beige solid was filtered to give 6g methyl (2E)-3-(4-bromo-3-nitrophenyl)acrylate. The filtrate purified on silica gel to give 3.3g methyl (2E)-3-(4-bromo-3-nitrophenyl)acrylate. Both batches (9.3 g) were combined and dissolved in methanol (160 mL). A solution of potassium carbonate (12.0 g, 87 mmol) in water (80 mL) was then added and stirred at 60 ^{0}C for 5 hours. The mixture was then acidified with 3N HCl and extracted with EtOAc. The combined organic layers were dried over MgSO4, filtered and concentrated to give a white solid: (2E)-3-(4-bromo-3-nitrophenyl)acrylic acid (**SI-34**) (8.6 g, 86%). ^{1}H NMR (400 MHz, DMSO) δ 12.63 (s, 1H), 8.38 (s, 1H), 7.97 – 7.84 (m, 2H), 7.59 (d, *J* = 18.1Hz, 1H), 6.73 (d, *J* = 16.1 Hz, 1H), 3.33 (s, 1H).

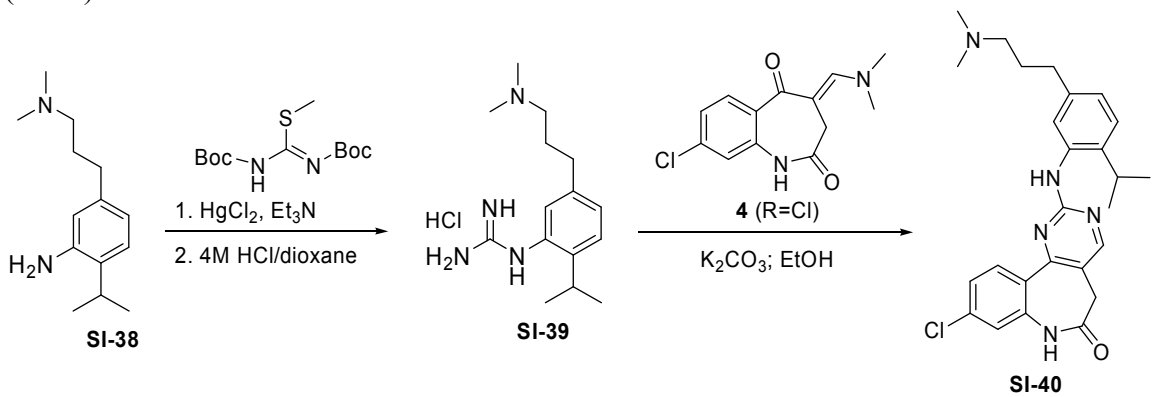
Step 3. A solution of **SI-34** (1.00 g, 3.68 mmol), HATU (1.68 g, 4.4 mmol), and N,N-diisopropylethylamine (0.77 mL, 4.4 mmol) in DMF (17 mL) was stirred at room temp for 2 hrs. 2.0 M of Dimethylamine in tetrahydrofuran (1.9 mL, 3.8 mmol) was then added and the resulting solution was stirred at room temperature for 2 hrs. The reaction was then quenched by the addition of water. A white solid crashed out, which was collected. The filtrate showed some desired product and the filtrate was allowed to sit overnight. More product crashed out of the solution and was collected to give a cream colored solid (2E)-3-(4-bromo-3-nitrophenyl)-N,N-dimethylacrylamide (**SI-35**) (0.80 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98(S, 1H), 7.74(d, J=8.09Hz,1H), 7.60 (d, *J* = 15.5 Hz, 1H), 7.52 (d, *J* = 8.04 Hz, 1H), 6.96 (d, *J* = 15.2 Hz, 1H), 3.19 (S, 1H), 3.08 (S, 1H). LCMS (FA): m/z 299.2 (M+H).

Step 4. Sodium carbonate (2.1 g, 20 mmol) was weighed into a flask. Water (17 mL) was

then added followed by addition of a suspension of **SI-35** (2.0 g, 6.7 mmol) in 1,2-dimethoxyethane (33 mL). Isopropenylbornic acid pinacol ester (2.8 mL, 13.4 mmol) was added next followed by addition of tetrakis(triphenylphosphine)palladium(0) (0.39 g, 0.33 mol). The reaction mixture was capped and heated at 80 °C with stirring for 15 hrs. The reaction was quenched with water then extracted with ethyl acetate (3x). Combined organic layers were dried, filtered and concentrated. The crude product was purified on silica gel to give 1.42 g (82%) (2E)-3-(4-isopropenyl-3-nitrophenyl)-N,N-dimethylacrylamide (**SI-36**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 1.7 Hz, 1H), 7.64 (d, *J* = 15.8 Hz, 1H), 7.63 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 15.5 Hz, 1H), 5.20 (m, 1H), 4.96 (m, 1H), 3.20 (s, 3H), 3.08 (s, 3H). 2.08 (s, 3H). LCMS (FA): m/z 261.3 (M+H).

Step 5. **SI-36** (1.40 g, 5.38 mmol), Ethyl acetate (45 mL), and Pd (10% on Carbon)(0.86g, 0.81 mmol) were added to a round bottomed flask. The reaction mixture was stirred under an atmosphere of Hydrogen overnight. The reaction mixture was then filtered through celite and washed with EtOAc. The solvent was evaporated to give 3-(3-amino-4-isopropylphenyl)-N,N-dimethylpropanamide (**SI-37**) (1.23 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 7.8 Hz, 1H), 6.63 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.55 (d, *J* = 1.6 Hz, 1H), 2.93 (d, *J* = 3.9 Hz, 6H), 2.90 – 2.78 (m, 3H), 2.62 – 2.53 (m, 2H), 1.23 (d, *J* = 6.8 Hz, 6H). LCMS (FA): m/z 235.3 (M+H).

Step 6. 1.0 M of Borane-THF complex in THF (15 mL, 15 mmol) was added to a solution of **SI-37** (1.40 g, 6.0 mmol) in THF (11 mL) at room temp under argon. The reaction was heated to reflux with stirring for 2.5 hours. Solvent was then evaporated to give a clear oil. 1N HCl was added (~2 mL) and a white solid formed. THF (3 mL) was added to solubilize followed by an additional 15 mL 1N HCl and the mixture stirred at 75 °C overnight. The rxn mixture was cooled to room temp and washed with EtOAc (2x). The aqueous layer was basified and extracted with EtOAc(3x). The combined organic layers were dried, filtered, and concentrated to give **SI-38** (1.07 g, 81%) without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J=7.8Hz, 1H), 6.61 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.52 (d, *J* = 1.7 Hz, 1H), 3.62 (m, 2H), 2.85 (dq, *J* =m, 1H), 2.51 (m, 2H), 2.30 (m, 2H), 2.22 (s, 6H), 1.76 (m, 2H), 1.24 (d, *J* = 6.8 Hz, 6H). LCMS (FA): m/z 221.3 (M+H).



SI-38 SI-39 SI-40

9-chloro-2-(5-(3-(dimethylamino)propyl)-2-isopropylphenylamino)-5H-benzo[b]pyrimido[4,5-d]azepin-6(7H)-one (SI-40)

Method 7 was used to synthesize **SI-40**

Step 1. 100 mg (0.45 mmol) of **SI-38** gave di-tert-butyl [(Z)-({5-[3-(dimethylamino)propyl]-2-isopropylphenyl}amino)methylylidene] biscarbamate (0.18 g; 86%). LCMS (FA): m/z 463.3 (M+H).

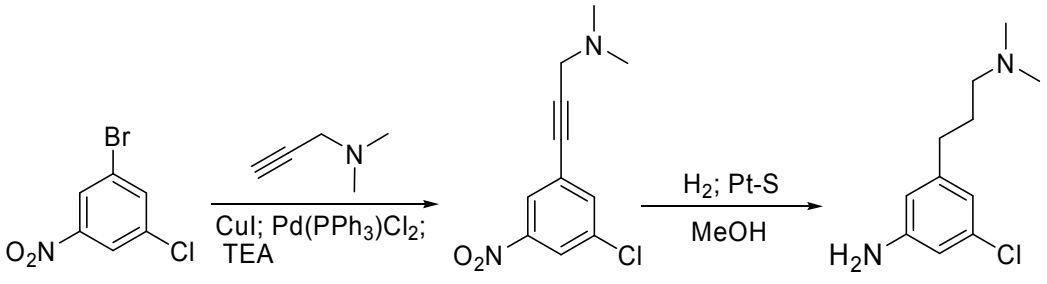
Steps 2/3. Deprotection of di-tert-butyl [(Z)-({5-[3-(dimethylamino)propyl]-2-isopropylphenyl}amino)methylylidene] biscarbamate (0.18g, 0.39 mmol) and subsequent condensation of **SI-39** with **4** (R=Cl) (79 mg, 0.3 mmol) gave **SI-40** (85 mg; 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.22 (s, 1H), 8.05 (t, *J* = 7.9 Hz, 1H), 7.68 (d, *J* = 1.5 Hz, 1H), 7.31 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.23 (s, 1H), 7.12 (d, *J* = 2.0 Hz, 1H), 7.03 – 6.96 (m, 2H), 3.42 (s, 2H), 3.14 (dq, *J* = 13.6, 6.8 Hz, 1H), 2.71 – 2.64 (m, 2H), 2.63 (s, 2H), 2.46 (s, 6H), 2.00 (dd, *J* = 18.5, 10.9 Hz, 2H), 1.25 (d, *J* = 6.8 Hz, 6H). LCMS (FA): m/z 464.4 (M+H).

SI-40 **11g**

9-chloro-2-({5-[3-(dimethylamino)propyl]-2-isopropylphenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (11g)

Method 8 was used for conversion to the thioamide.

Obtained **11g** as the formate salt after HPLC purification (22 mg, 44%).^{1}H NMR (400 MHz, DMSO) δ 9.00 (s, 1H), 8.34 (d, *J* = 9.3 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.47 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 3.78 (m, 2H), 3.76 – 3.69 (m, 1H), 3.28 (m, 1H), 3.19 (m, 1H), 2.54 (m, 2H), 2.33 (s, 6H), 1.82 – 1.69 (m, 2H), 1.11 (d, *J* = 6.8 Hz, 6H). LCMS (FA): m/z 480.4 (M+H).



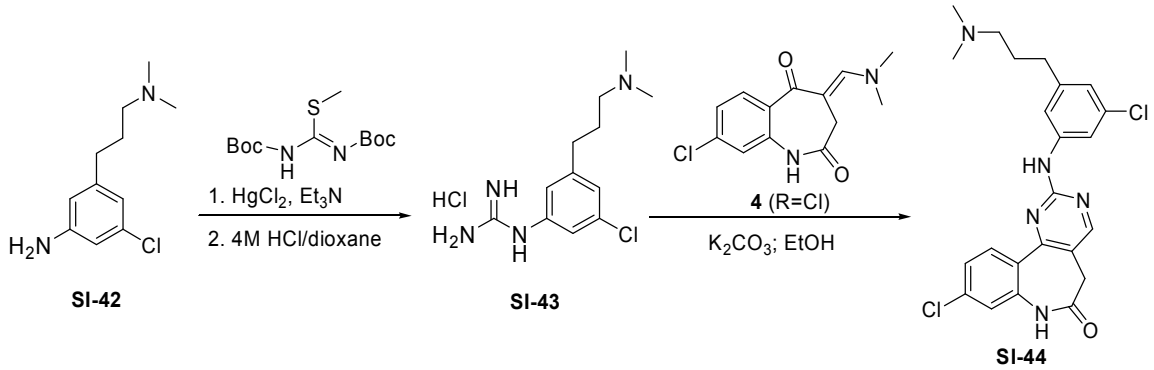
SI-41 **SI-42**

3-chloro-5-[3-(dimethylamino)propyl]aniline (SI-42)

Step 1. 1-Bromo-3-chloro-5-nitrobenzene (0.59 g, 2.5 mmol), propargyl(dimethylamine) (0.29 mL, 2.7 mmol) and cesium carbonate (1.6 g, 5.0 mmol) were suspended in DMF (12 mL). Argon was bubbled through the suspension for 15 minutes.

Bis(acetonitrile)palladium(II) chloride (32 mg, 0.12 mmol) and 2-dicyclohexylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl (150 mg, 0.32 mmol) were added, the suspension was purged three times with nitrogen then stirred at 50°C for 16 hrs. The mixture was then concentrated and 40 mL EtOAc was added and the mixture was filtered. The filtrate was concentrated and the residue was purified on silica gel to give 0.32 g (54%) of **SI-41**. LCMS (FA): m/z 239.1 (M+H).

Step 2. To a round bottom flask was added **SI-41** (0.32 g, 1.3 mmol), 5% sulfided platinum (5:0.1:95, Platinum:Sulfur hexamer:carbon; 80 mg), and methanol (20 mL). The resulting mixture was stirred at room temperature under a hydrogen balloon for 170 min. The mixture was then filtered through celite and concentrated to give **SI-42** (0.24g, 84%). LCMS (FA): m/z 213.2 (M+H).

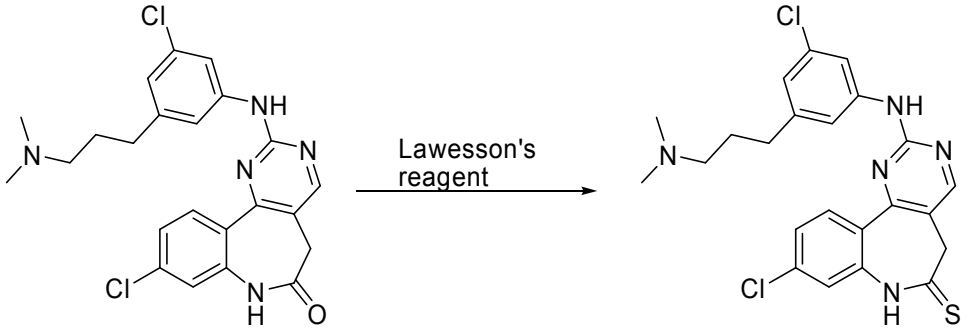


SI-42 **SI-43** **SI-44**

9-chloro-2-({3-chloro-5-[3-(dimethylamino)propyl]phenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-44)
Method 7 for was used to synthesize **SI-44**

Step 1. 0.24 g (1.1 mmol) of **SI-42** gave di-tert-butyl [(Z)-({3-chloro-5-[3-(dimethylamino)propyl]phenyl}amino)methylylidene]biscarbamate (0.34 g, 66%). LCMS (FA): m/z 455 (M+H).

Steps 2/3. Deprotection of di-tert-butyl [(Z)-({3-chloro-5-[3-(dimethylamino)propyl]phenyl}amino)methylylidene]biscarbamate (0.34 g, 0.75 mmol) and subsequent condensation of **SI-43** with **4** (R=Cl) (0.26 g, 0.97 mmol) gave **SI-44** (170 mg; 50%). LCMS (FA): m/z 456.2 (M+H).

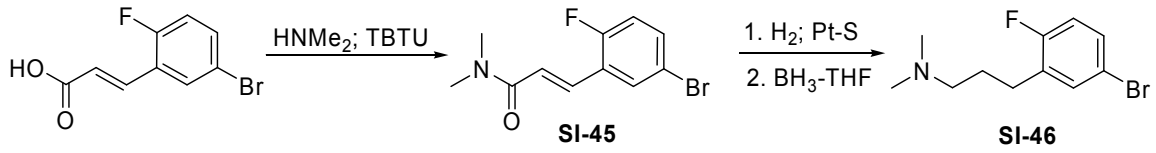


SI-44 **11h**

9-chloro-2-({3-chloro-5-[3-(dimethylamino)propyl]phenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (11h)

Method 8 was used for conversion to the thioamide.

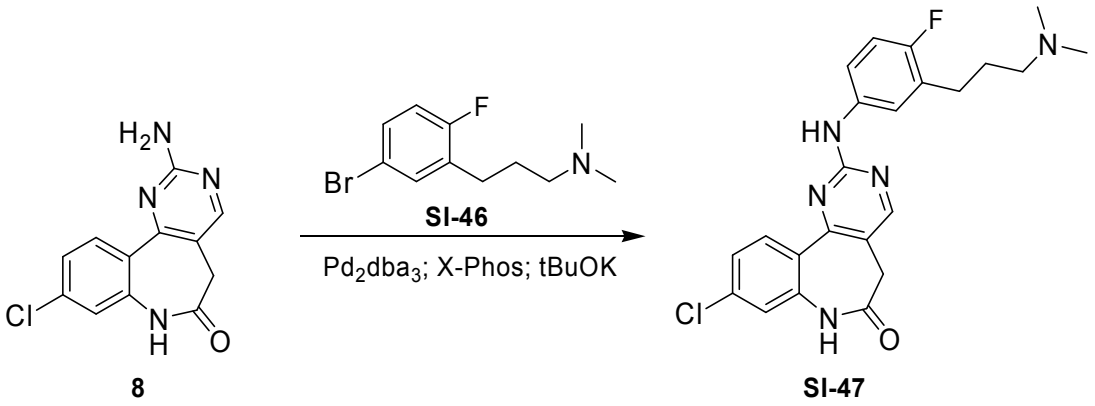
Obtained **11h** as the formate salt after HPLC purification (0.16 g, 41%) ^{1}H NMR (400 MHz, DMSO) δ 10.01 (s, 1H), 8.55 (s, 1H), 8.25 (s, 1H), 8.09 (t, *J* = 6.7 Hz, 1H), 7.79 (s, 1H), 7.63 (s, 1H), 7.54 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 6.87 (s, 1H), 3.88 (s, 2H), 2.60 – 2.54 (m, 2H), 2.45 (s, 2H), 2.29 (s, 6H), 1.76 (s, 2H). LCMS (FA): m/z 472.1 (M+H).



3-(5-bromo-2-fluorophenyl)-N,N-dimethylpropan-1-amine (SI-46)

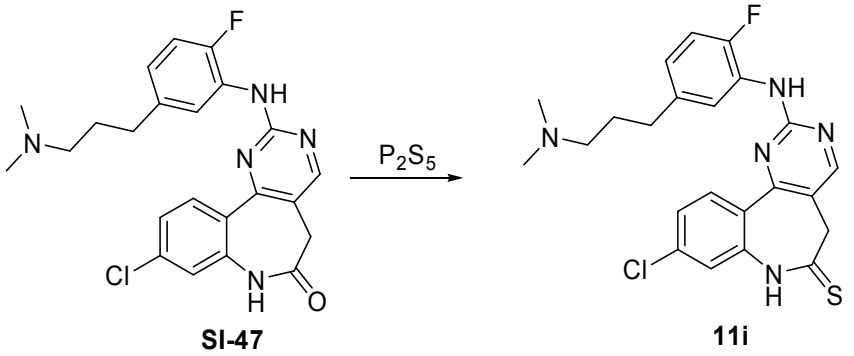
Step 1. To a reaction flask was added Dimethylamine (2M in THF; 8.2 mL, 16 mmol), 5-bromo-2-fluorocinnamic acid (2.0 g, 8.2 mmol), and TBTU (3.14 g, 9.8 mmol) in dichloromethane (20 mL). The mixture was cooled in an ice bath and a solution of N,N-diisopropylethylamine (4.3 mL, 24.5 mmol) in dichloromethane (150 mL) was added dropwise over 2 hours. The resulting mixture was stirred at room temperature for 16 hours. The reaction was quenched with water and the mixture extracted with DCM. The organic layer was separated and dried with magnesium sulfate. After filtration and concentration of the filtrate the residue was purified on silica gel to give 2.0 g (90%) of **SI-45**. LCMS (FA): *m/z* = 272.2 (M+H).

Step 2/3. To a round bottom flask was added **SI-45** (2.0 g, 7.2 mmol), 5% Sulfided platinum (5:0.1:95, Platinum:Sulfur hexamer:carbon; 2.0 g, 0.53 mmol) and methanol (300 mL). The resulting mixture was stirred at room temperature under a hydrogen balloon for 1 hr. The mixture was then filtered through celite and concentrated. The crude product was dissolved in THF (23 mL) and the mixture was cooled to 0 °C. Then borane-THF (15.2 mL, 1M in THF) was added and the mixture was heated at 50 °C for 2 hr with stirring. The mixture was then concentrated. 3M HCl (40 mL) was added and the solution was heated at 80 °C for 2 hr. The reaction was then cooled to room temperature and 1M KOH(aq.) was added until the solution became basic. The mixture was extracted with DCM (2x) and the combined extracts were washed with brine and dried over $MgSO_4$. After filtration the organic phase was concentrated and purified on silica gel to give **SI-46** (0.75g, 47%). LCMS (FA): m/z 260.2 (M+H).



9-chloro-2-({3-[3-(dimethylamino)propyl]-4-fluorophenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-47)

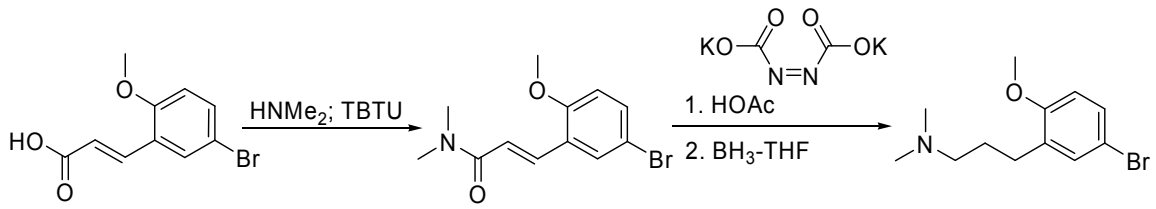
8 (420 mg, 1.6 mmol) was coupled with **SI-47** (420 mg, 1.6 mmol) using method 4 to provide **SI-47** (280 mg, 39%). ^{1}H NMR (400 MHz, DMSO) δ 10.44 – 10.25 (m, 2H), 9.79 (s, 1H), 8.51 (d, *J* = 5.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.75 (dd, *J* = 6.9, 2.6 Hz, 1H), 7.64 (ddd, *J* = 8.8, 4.5, 2.8 Hz, 1H), 7.45 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.11 (t, *J* = 9.3 Hz, 1H), 3.44 – 3.37 (m, 2H), 3.07 (qd, *J* = 10.9, 6.4 Hz, 2H), 2.74 (s, 3H), 2.72 (s, 3H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.90 - 2.00 (m, 2H). LCMS (FA): *m/z* = 440.3 (M+H).



9-chloro-2-({3-[3-(dimethylamino)propyl]-4-fluorophenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (11i)

Method 5 was used for conversion to the thioamide.

Obtained **11i** as the formate salt after purification by HPLC (80 mg, 40%). ^{1}H NMR (300 MHz, DMSO) δ 9.79 (s, 1H), 8.48 (s, 1H), 8.18 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 4.6 Hz, 1H), 7.55 (m, 1H), 7.53 – 7.48 (m, 1H), 7.41 (d, *J* = 1.9 Hz, 1H), 7.06 (t, *J* = 9.3 Hz, 1H), 3.85 (s, 2H), 2.63 – 2.54 (m, 2H), 2.34 (t, *J* = 7.1 Hz, 2H), 2.18 (s, 6H), 1.80 – 1.61 (m, 2H). LCMS (FA): m/z 456.3 (M+H).

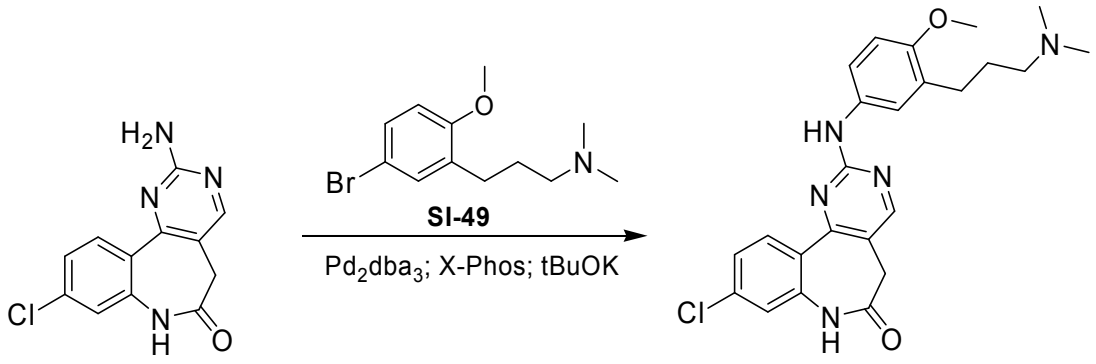


SI-48 **SI-49**

3-(5-bromo-2-methoxyphenyl)-N,N-dimethylpropan-1-amine (SI-49)

Step 1. To an ice cold mixture of 2.0 M of dimethylamine in tetrahydrofuran (5.8 mL, 12 mmol) , TBTU (3.0 g, 9.3 mmol) and 5-Bromo-2-methoxycinnamic acid (2.0 g, 7.8 mmol) in methylene chloride (20 mL) under stirring was added dropwise over ca. 2 hours a solution of N,N-diisopropylethylamine (4.06 mL, 23.3 mol) in 150 mL of methylene chloride. The reaction mixture was allowed to stir overnight. The reaction mixture was then quenched with water. The separated aqueous was extracted with methylene chloride. The combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. The crude material was purified on silica to give **SI-48** (1.95g, 88%). LCMS (FA): *m/z* 284.1 (M+H).

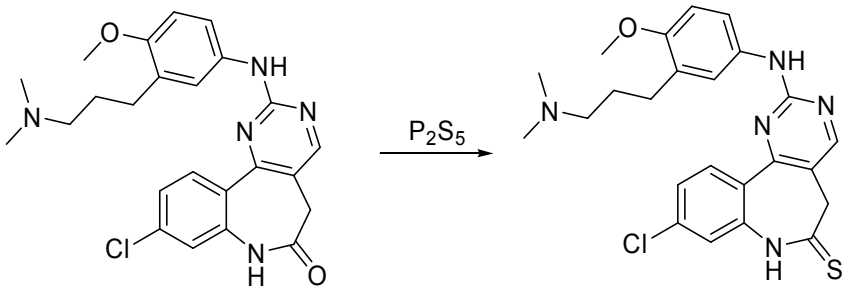
Step 2/3. Into a round bottom flask, **SI-48** (1.95 g, 6.86 mmol) in methanol (23 mL) was added into a well stirred suspension of dipotassium (E)-diazene-1,2-dicarboxylate (11 g, 57 mmol) in methanol (23 mL) . A mixture of acetic acid (3.90 mL, 68.6 mmol) and methanol (3 mL) was added dropwise to the mixture over 30 mins and this was stirred for 6h. A second mixture of acetic acid (1.18 mL, 20.8 mmol) and methanol (3.1 mL) was added over 20 mins and this was stirred for 2h. The reaction mixture was then concentrated and the residue was partitioned in water and methylene chloride. The separated organic layer was washed with saturated aqueous $NaHCO_3$, dried over sodium sulfate and concentrated. The crude product was dissolved in THF (25 mL).Then borane-THF (22 mL, 1M in THF) was added and the mixture was heated at 50 °C for 2 hr with stirring. The mixture was then concentrated. 3M HCl (40 mL) was added and the solution was heated at 80 °C for 2 hr. The reaction was then cooled to room temperature and 1M KOH(aq.) was added until the solution became basic. The mixture was extracted with DCM (2x) and the combined extracts were dried over $MgSO_4$. After filtration the organic phase was concentrated and purified on silica gel to give **SI-49** (1.45g, 78%). LCMS (FA): m/z 272.1 (M+H).



8 **SI-50**

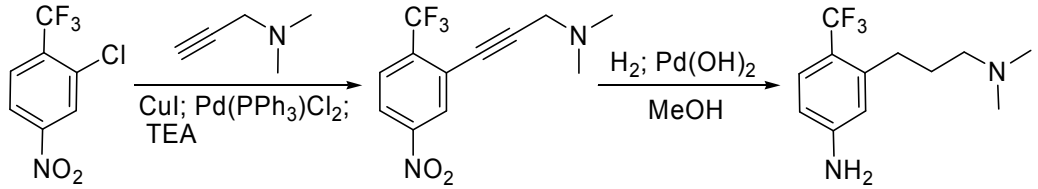
9-chloro-2-({3-[3-(dimethylamino)propyl]-4-methoxyphenyl}amino)-5,7-dihydro-

6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-50)
8 (890 mg, 3.4 mmol) was coupled with **SI-49** (930 mg, 3.4 mmol) using method 4 (heated for 45 min) to provide **SI-50** as the formate salt after purification by HPLC (100 mg, 30%). ^{1}H NMR (400 MHz, DMSO) δ 10.33 (s, 1H), 9.50 (s, 1H), 8.46 (s, 1H), 8.21 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.60 (d, *J* = 2.2 Hz, 1H), 7.53 (dd, *J* = 8.8, 2.7 Hz, 1H), 7.40 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.27 (d, *J* = 2.1 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 3.77 (s, 3H), 3.38 (s, 2H), 2.56 – 2.51 (m, 2H), 2.36 – 2.28 (m, 2H), 2.19 (s, 6H), 1.76 – 1.56 (m, 2H). LCMS (AA): *m/z* = 452.2 (M+H).



SI-50 **11j**

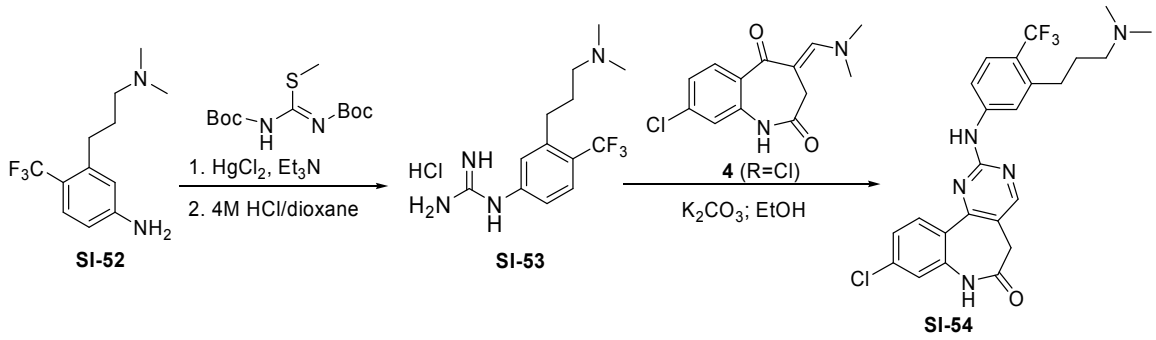
9-chloro-2-({3-[3-(dimethylamino)propyl]-4-methoxyphenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (11j)
Method 5 was used for conversion to the thioamide.
Obtained **11j** as its HCl salt (54 mg, 29%). ^{1}H NMR (400 MHz, DMSO) δ 9.57 (s, 1H), 8.43 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.56 (s, 1H), 7.55 – 7.47 (m, 2H), 7.41 (d, *J* = 2.1 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 3.82 (s, 2H), 3.74 (s, 3H), 2.56 – 2.51 (m, 4H), 2.39 – 2.28 (m, 2H), 2.20 (s, 6H), 1.67 (dt, *J* = 14.9, 7.6 Hz, 2H). LCMS (FA): m/z 468.4 (M+H).



SI-51 **SI-52**

3-[3-(dimethylamino)propyl]-4-(trifluoromethyl)aniline (SI-52)
Method 6 was used for the synthesis of **SI-52**.
Step 1. 2-Chloro-4-nitrobenzotrifluoride (1.00 g, 4.43 mmol) gave 1.1 g (91%) of N,N-dimethyl-3-[5-nitro-2-(trifluoromethyl)phenyl]prop-2-yn-1-amine (**SI-51**). LCMS (FA): m/z 273.2 (M+H)

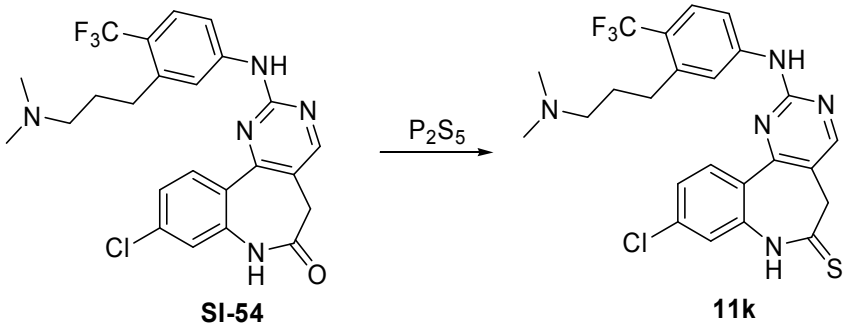
Step 2. (Hydrogenation conditions - 1 atmosphere of H_2 for 16 hrs): **SI-51** (1.1 g, 4.0 mmol) gave 640 mg (64%) of **SI-52**. LCMS (FA): m/z 247.2 (M+H).



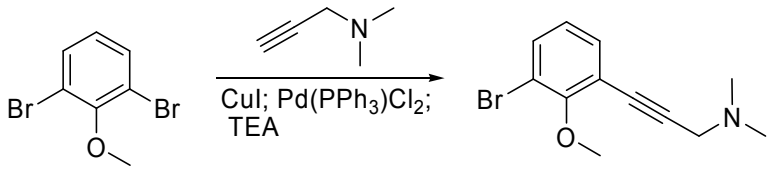
9-chloro-2-{[3-[3-(dimethylamino)propyl]-4-(trifluoromethyl)phenyl]amino}-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-54)
Method 7 was used to synthesize **SI-54**

Step 1. 0.64 g (2.6 mmol) of **SI-52** gave di-tert-butyl ((Z)-{[3-[3-(dimethylamino)propyl]-4-(trifluoromethyl)phenyl]amino}methylylidene)biscarbamate (650 mg; 51%). LCMS (FA): m/z 489.3 (M+H).

Steps 2/3. Deprotection of di-tert-butyl ((Z)-{[3-[3-(dimethylamino)propyl]-4-(trifluoromethyl)phenyl]amino}methylylidene)biscarbamate (0.36 g, 0.74 mmol) and subsequent condensation of **SI-53** with **4** (R=Cl) (0.25 g, 0.96 mmol) gave **SI-54** (140 mg; 35%) as the formate salt after HPLC purification. ^{1}H NMR (400 MHz, DMSO) δ 10.44 (s, 1H), 8.65 (s, 1H), 8.23 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.11 (s, 1H), 7.79 (d, *J* = 8.9 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.47 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.34 (d, *J* = 2.1 Hz, 1H), 3.50 (s, 2H), 2.83 – 2.67 (m, 2H), 2.36 (t, *J* = 7.1 Hz, 2H), 2.19 (s, 6H), 1.77 (dt, *J* = 14.7, 7.3 Hz, 2H). LCMS (FA): m/z 490.1 (M+H).



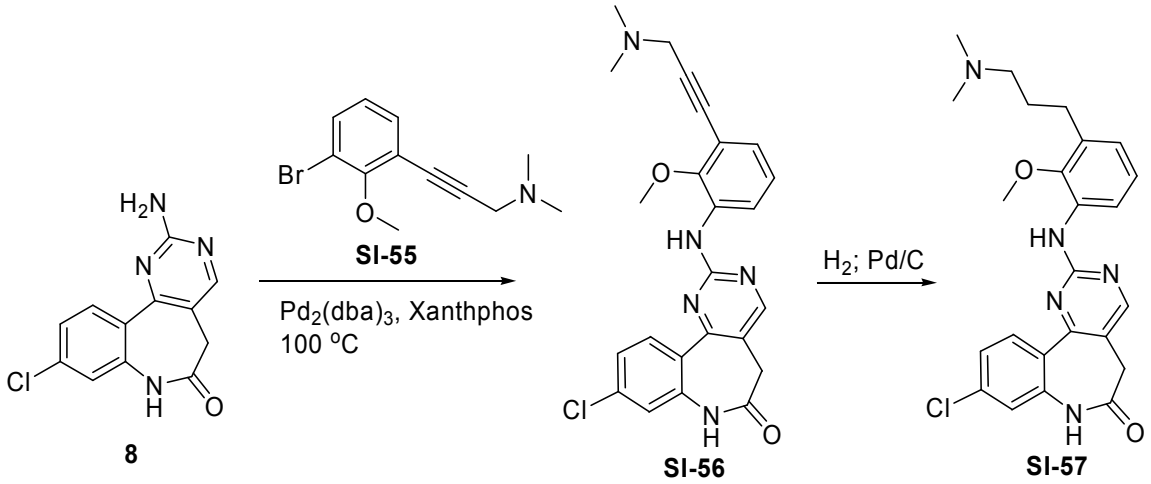
9-chloro-2-{[3-[3-(dimethylamino)propyl]-4-(trifluoromethyl)phenyl]amino}-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (11k)
Method 5 was used for conversion to the thioamide.
Obtained **11k** as the formate salt after HPLC purification (67 mg, 49%). ^{1}H NMR (400 MHz, DMSO) δ 10.22 (s, 1H), 8.59 (s, 1H), 8.18 (s, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 8.02 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.63 – 7.50 (m, 2H), 7.44 (d, *J* = 2.1 Hz, 1H), 3.91 (s, 2H), 2.80 – 2.63 (m, 2H), 2.48 – 2.41 (m, 2H), 2.26 (s, 6H), 1.77 (m, 2H). LCMS (FA): m/z 506.1 (M+H).



SI-55

3-(3-bromo-2-methoxyphenyl)-N,N-dimethylprop-2-yn-1-amine (SI-55)

Propargyl(dimethylamine) (0.20 mL, 1.88 mmol) and 2,6-Dibromoanisole (1.00 g, 3.76 mmol) were dissolved in Triethylamine (10.0 mL) and degassed with argon by evacuation followed by back filling. Bis(triphenylphosphine)palladium(II) chloride (0.132 g, 0.188 mmol) and copper (I) iodide (0.036 g, 0.188 mol) were added in one portion and the resulting solution degassed again. The tube was sealed and the reaction heated at 70 °C overnight with stirring. The reaction mixture was cooled to room temperature and filtered through celite eluting with diethyl ether (100mL). The solution was washed with saturated aqueous sodium bicarbonate, water(x2), and brine, then dried over sodium sulfate and concentrated in vacuo. The crude material was purified on silica gel to give **SI-55** (205 mg, 41%). LCMS (AA): m/z = 268.1 (M+H).

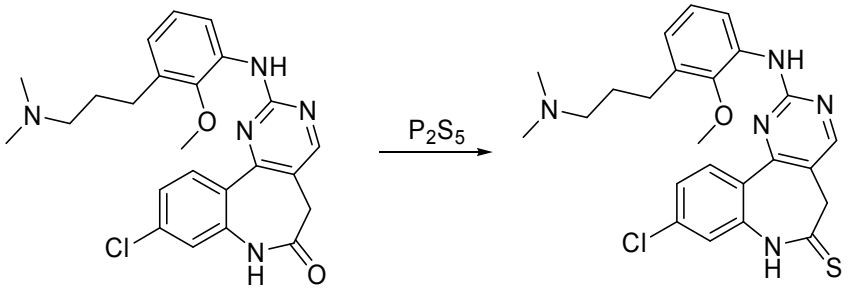


9-chloro-2-({3-[3-(dimethylamino)propyl]-2-methoxyphenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-57)

Step 1. A pressure vessel was charged with tris(dibenzylideneacetone)dipalladium (0) (3.64 mg, 3.98E-3 mmol), Xanthphos (5.50 mg, 9.51E-3 mmol), cesium carbonate (0.198 g, 0.608 mol)), **8** (82 mg, 0.32 mol) and 1,4-Dioxane (1.2 mL) (previously degassed with argon). **SI-55** (85 mg, 0.32 mmol) was added and the vessel subjected to three cycles of evacuation-backfilling with argon. The reaction mixture was heated at 100 °C overnight with stirring. The reaction mixture was cooled to room temperature, diluted with dioxane and filtered. The solids were washed with methanol and the filtrate was concentrated and the product was purified on silica gel to give **SI-56** (75mg, 53%). ^{1}H NMR (300 MHz, DMSO) δ 10.36 (s, 1H), 8.56 (s, 1H), 8.52 (s, 1H), 8.15 (dd, *J* = 5.8, 3.9 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.38 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.26 (d, *J* = 1.7 Hz, 1H), 7.10 (s, 1H), 7.07 (t, *J* = 4.9 Hz, 1H), 3.87 (s, 3H), 3.50 (s, 2H), 3.40 (s, 2H), 2.26 (s, 6H). LCMS (AA): m/z = 448.2 (M+H).

Step 2. **SI-56** (0.062 g, 0.14 mmol) was dissolved in a mixture of tetrahydrofuran (10

mL), 4.0 M HCl in dioxane (0.035 mL, 0.14 mmol) and water (0.05 mL). The solution was placed under an argon atmosphere then Pd (10% on Carbon, 0.0147 g, 0.014 mmol) was added in one portion. The reaction was purged with hydrogen gas then stirred at room temperature under a hydrogen atmosphere(1atm) for 90 mins. The reaction was filtered through Celite and the cake was washed with tetrahydrofuran and ethyl acetate. The filtrate was washed with 1N NaOH and brine then dried over sodium sulfate, filtered, and concentrated. Purification by HPLC gave **SI-57** (25 mg, 40%). ^{1}H NMR (300 MHz, dmso) δ 10.33 (s, 1H), 8.48 (s, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.37 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.94 – 6.87 (m, 1H), 3.67 (d, *J* = 6.1 Hz, 3H), 3.38 (s, 2H), 2.64 – 2.55 (m, 2H), 2.25 (t, *J* = 7.2 Hz, 2H), 2.13 (s, 6H), 1.69 (dd, *J* = 15.5, 7.4 Hz, 2H). LCMS (AA): m/z = 452.1 (M+H).

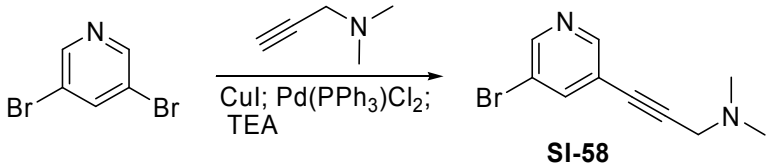


SI-57 **11l**

9-chloro-2-({3-[3-(dimethylamino)propyl]-2-methoxyphenyl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (11l)

Method 5 was used for conversion to the thioamide.

Obtained **11l** as the formate salt after HPLC purification (10mg, 49%). ^{1}H NMR (400 MHz, DMSO) δ 8.58 (s, 1H), 8.47 (d, *J* = 5.5 Hz, 1H), 8.22 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.50 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.40 (d, *J* = 2.1 Hz, 1H), 7.04 (t, *J* = 7.8 Hz, 1H), 6.95 (dd, *J* = 7.6, 1.5 Hz, 1H), 3.85 (s, 2H), 3.67 (s, 3H), 2.66 – 2.55 (m, 2H), 2.40 – 2.31 (m, 2H), 2.21 (s, 6H), 1.72 (m, 2H). LCMS (FA): m/z = 468.0 (M+H).

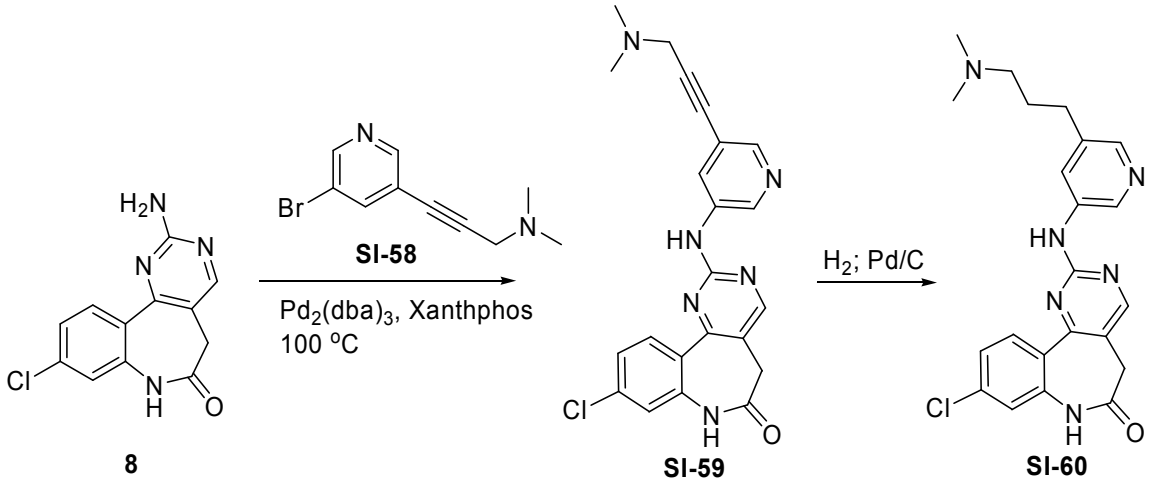


SI-58

3-(5-bromopyridin-3-yl)-N,N-dimethylprop-2-yn-1-amine (SI-58)

To a mixture of 3,5-dibromopyridine (1.50 g, 6.33 mmol), Copper(I) iodide (48 mg, 0.25 mmol), and Bis(triphenylphosphine)palladium(II) chloride (89 mg, 0.13 mol) in diethylamine (4.0 mL) was added propargyl(dimethylamine) (0.75 mL, 7.0 mmol). The mixture was stirred at room temperature for 2hrs (LCMS analysis showed ~35% starting material). Additional propargyl(dimethylamine) (0.18 mL, 1.7 mmol) was added. The mixture was stirred for another 1.5hr and was partitioned in ethyl acetate and water. Separated organic phase was washed with water and brine, dried over Na2SO4, filtered and concentrated. The residue was purified on silica gel to give **SI-58** (930 mg, 62%

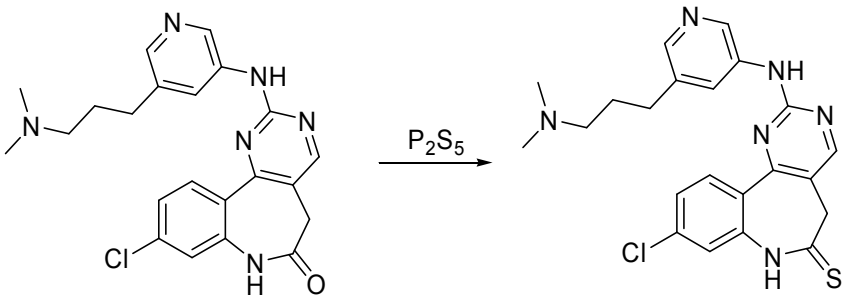
yield) as a light brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 5.9 Hz, 2H), 7.86 (s, 1H), 7.26 (s, 1H), 3.54 (s, 2H), 2.41 (s, 6H). LCMS (AA): m/z = 239.1 (M+H).



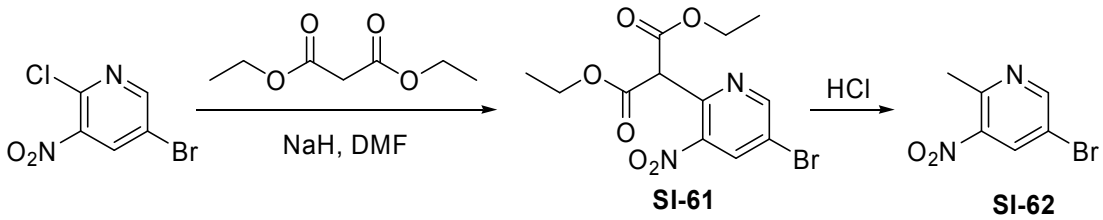
9-chloro-2-({5-[3-(dimethylamino)propyl]pyridin-3-yl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-60)

Step 1. A mixture of **8** (280 mg, 1.1 mmol), xanthphos (49 mg, 0.085 mmol), tris(dibenzylideneacetone)dipalladium(0) (28 mg, 0.031 mmol), **SI-58** (311 mg, 1.30 mmol) and cesium carbonate (705 mg, 2.16 mmol) in a microwave tube was evacuated and purged with nitrogen 3 times. 1,4-Dioxane (4.0 mL, 0.051 mol) was added and the reaction mixture was heated at 150°C in a microwave reactor for 30 minutes. The reaction mixture was then added to 25ml of water and stirred for 15 minutes. The resulting solid was collected by filtration, dried partially under suction and washed carefully with 20 mL of ethyl acetate. The solid was dried under high vacuum to give **SI-59** (376 mg, 83%). ^{1}H NMR (400 MHz, DMSO) δ 10.39 (s, 1H), 10.13 (s, 1H), 8.88 (d, *J* = 2.2 Hz, 1H), 8.60 (s, 1H), 8.40 (s, 1H), 8.20 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.48 – 7.20 (m, 2H), 3.49 (s, 2H), 3.43 (s, 2H), 2.24 (s, 6H). LCMS (FA): m/z = 419.2 (M+H).

Step 2. To a suspension of **SI-59** (141 mg, 0.303 mmol) in ethanol (21 mL) and tetrahydrofuran (21 mL) was added Pd (10% on Carbon)(110 mg, 0.10 mol). The mixture was purged with hydrogen and stirred under an atmosphere of hydrogen overnight. The reaction mixture was then filtered over celite and concentrated. The crude product was purified by HPLC to **SI-60** as the formate salt (48 mg, 33%). ^{1}H NMR (300 MHz, DMSO) δ 10.37 (s, 1H), 9.92 (s, 1H), 8.73 (d, *J* = 2.4 Hz, 1H), 8.56 (s, 1H), 8.20 (s, 1H), 8.16 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 1.8 Hz, 1H), 7.41 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.28 (d, *J* = 2.0 Hz, 1H), 3.41 (s, 2H), 2.65 – 2.52 (m, 2H), 2.34 – 2.25 (m, 2H), 2.17 (s, 6H), 1.73 (dt, *J* = 14.7, 7.4 Hz, 2H). LCMS (FA): m/z = 423.2 (M+H).



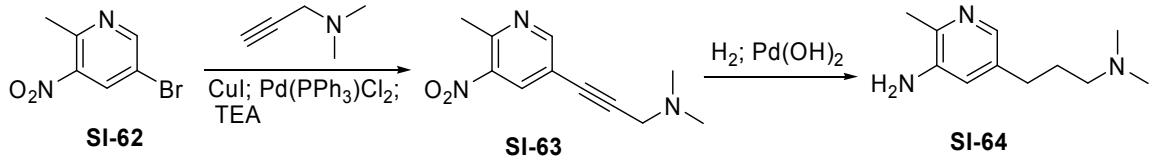
9-chloro-2-({5-[3-(dimethylamino)propyl]pyridin-3-yl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (12a)
Method 5 was used for conversion to the thioamide.
Obtained **12a** as the formate salt after HPLC purification (46mg, 20%). ^{1}H NMR (400 MHz, DMSO) δ 9.99 (s, 1H), 8.73 (d, *J* = 2.3 Hz, 1H), 8.54 (s, 1H), 8.18 (s, 1H), 8.14 (s, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 1.6 Hz, 1H), 7.53 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 3.88 (s, 2H), 2.57 (dd, *J* = 18.2, 10.7 Hz, 2H), 2.28 (t, *J* = 7.2 Hz, 2H), 2.15 (s, 6H), 1.78 – 1.64 (m, 2H). LCMS (FA): m/z 423.2 (M+H).



5-Bromo-2-methyl-3-nitropyridine (SI-62)
Step 1. To a suspension of NaH (60% in mineral oil, 27.9 g, 0.69 mol) in DMF (300 mL) at 5-10 °C was slowly added ethyl malonate (125 mL, 0.69 mol) over 30 min. The mixture was allowed to stir for 20 min at rt, during which time the suspension became a solution. A solution of 5-bromo-2-chloro-3-nitropyridine (75 g, 0.32 mol) in DMF (75 mL) was added slowly at 5-10 °C. The resulting dark red mixture was allowed to stir at 40 °C for 2 h. The reaction mixture was then poured into 1M AcOH (0.75 L) and extracted with DCM (3 x 250 mL). The organic solutions were combined, washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography to give diethyl (5-bromo-3-nitropyridin-2-yl)malonate (**SI-61**) (260 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 2.1 Hz, 1H), 8.63 (d, *J* = 2.1 Hz, 1H), 5.46 (d, *J* = 4.5 Hz, 1H), 4.39 – 4.22 (m, 4H), 1.30 (t, *J* = 7.1 Hz, 6H). LCMS (FA): m/z 361.1 (M+H).

Step 2. To **SI-61** (66 g, 0.18 mol) was added water (250 mL) and 12 M HCl (360 mL, 4.32 mol). The mixture was heated at 105 °C until TLC showed starting material was consumed. The reaction mixture was then allowed to cool to rt and brine (0.67 L) was added. The organic solution was separated and the aqueous solution was extracted with DCM (3 x 0.67 L). The organic solutions were combined, washed with brine, sat. aq. $NaHCO_3$, and brine again, dried over Na_2SO_4, filtered and concentrated to give **SI-62**

(34.7 g, 75%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 2.1 Hz, 1H), 8.43 (d, *J* = 2.1 Hz, 1H), 2.82 (s, 3H). LCMS (FA): m/z 217.0 (M+H).

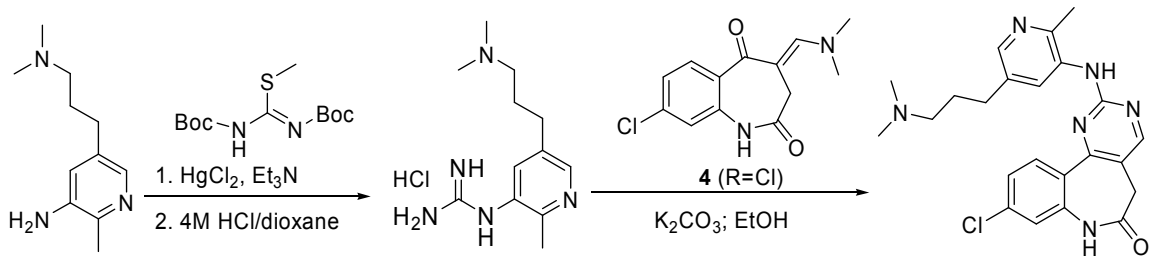


SI-62 **SI-63** **SI-64**

5-[3-(dimethylamino)propyl]-2-methylpyridin-3-amine (SI-64)

Step 1. To a mixture of **SI-62** (6.5 g, 30 mmol), copper(I) iodide (280 mg, 1.5 mmol), and bis(triphenylphosphine)palladium(II) chloride (520 mg, 0.75 mmol) in diethylamine (17 mL) was added propargyl(dimethylamine) (4.0 mL, 37.5 mmol). The reaction mixture was protected from light and stirred at room temperature. After 25min the mixture had reached boiling point. It was then cooled in a cold water bath for 10 minutes then left at room temperature overnight. The mixture was partitioned with EtOAc (200ml) and 1M Na_2CO_3 (150ml). Separated aqueous was extracted with EtOAc (2x100ml). Combined organic phases were washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified on silica gel to give N,N-dimethyl-3-(6-methyl-5-nitropyridin-3-yl)prop-2-yn-1-amine (**SI-63**) (5.98g, 91%) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (d, *J* = 1.3 Hz, 1H), 8.30 (d, *J* = 1.4 Hz, 1H), 3.69 (s, 2H), 2.88 (d, *J* = 20.1 Hz, 3H), 2.57 (d, *J* = 27.9 Hz, 6H). LCMS (FA): m/z 220.2 (M+H).

Step 2. To a solution of **SI-63** (810 mg, 3.7 mmol) in ethanol (35 mL) under an atmosphere of nitrogen was added 20% palladium hydroxide on charcoal (160 mg, 0.23 mmol). The mixture was purged with H_2 and shaken in Parr shaker under 50 psi of H_2 overnight. The mixture was filtered and the filtrate was concentrated to give 5-[3-(dimethylamino)propyl]-2-methylpyridin-3-amine (**SI-64**) (787 mg, 100%) as a brown oil. The material was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 34.0 Hz, 1H), 6.81 (s, 1H), 3.63 (s, 2H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.51 (dd, *J* = 12.5, 5.1 Hz, 2H), 2.40 (s, 6H), 1.98 – 1.81 (m, 2H). LCMS (AA): m/z 194.2 (M+H).



SI-64 **SI-65** **SI-66**

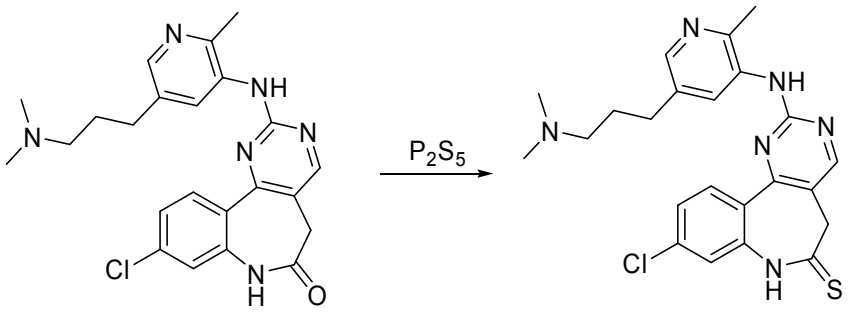
9-chloro-2-({5-[3-(dimethylamino)propyl]-2-methylpyridin-3-yl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-66)

Method 7 was used to synthesize **SI-66**

Step 1. 5.0 g (26.1 mmol) of **SI-64** gave di-tert-butyl [(Z)-({5-[3-(dimethylamino)propyl]-2-methylpyridin-3-yl}amino)methylylidene]biscarbamate (7.6 g;

67%).[1]H NMR (400 MHz, $CDCl_3$) δ 11.65 (s, 1H), 10.27 (s, 1H), 8.20 (s, 1H), 8.11 (s, 1H), 2.69 (t, *J* = 7.5 Hz, 2H), 2.54 (m, 2H), 2.53 (s, 3H), 2.43 (s, 6H), 2.03 – 1.89 (m, 2H), 1.56 – 1.44 (m, 18H). LCMS (FA): m/z 436.4 (M+H).

Steps 2/3. Deprotection of di-tert-butyl [(Z)-({5-[3-(dimethylamino)propyl]-2-methylpyridin-3-yl}amino)methylylidene]biscarbamate (7.6 g, 17.5 mmol) and subsequent condensation of **SI-65** with **4** (R=Cl) (4.2 g, 16 mmol) gave **SI-66** (2.2 g; 47%). %). [1]H NMR (400 MHz, DMSO) δ 10.33 (s, 1H), 9.07 (s, 1H), 8.45 (s, 1H), 8.05 (d, *J* = 1.9 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 1.7 Hz, 1H), 7.34 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.25 (d, *J* = 2.1 Hz, 1H), 3.38 (s, 2H), 2.54 (dd, *J* = 14.7, 6.8 Hz, 2H), 2.40 (s, 3H), 2.19 (t, *J* = 7.2 Hz, 2H), 2.09 (s, 6H), 1.76 – 1.63 (m, 2H). LCMS (FA): m/z 437.3 (M+H).



SI-66 **12b**

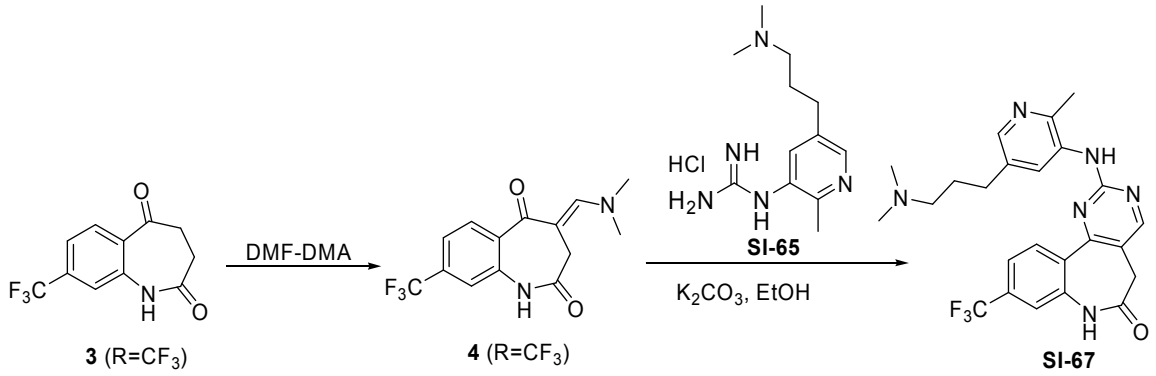
9-chloro-2-({5-[3-(dimethylamino)propyl]-2-methylpyridin-3-yl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (12b)

Method 5 was used for conversion to the thioamide.

Obtained **12b** as the formate salt after HPLC purification (240 mg, 53%)

[1]H NMR (400 MHz, DMSO) δ 9.16 (s, 1H), 8.42 (s, 1H), 8.21 (s, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 1.4 Hz, 1H), 7.47 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.39 (d, *J* = 2.1 Hz, 1H), 3.83 (s, 2H), 2.55 (dd, *J* = 13.1, 5.5 Hz, 2H), 2.40 (s, 3H), 2.35 (dd, *J* = 15.2, 7.7 Hz, 2H), 2.21 (s, 6H), 1.78 – 1.66 (m, 2H). LCMS (FA): m/z 453.2 (M+H).

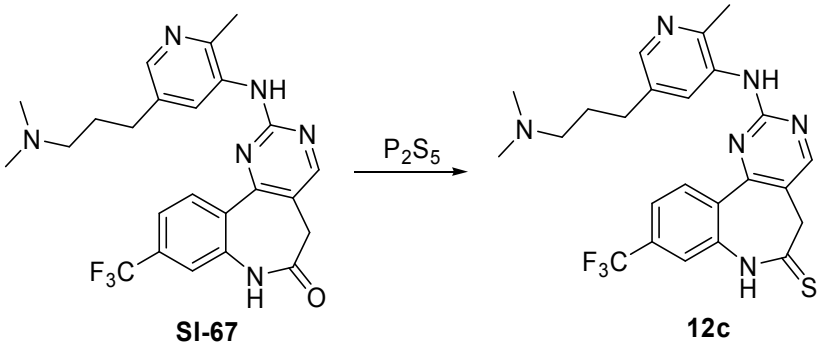
Procedures for the synthesis of 12c



9-trifluoromethyl-2-({5-[3-(dimethylamino)propyl]-2-methylpyridin-3-yl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepin-6-one (SI-67)
Method 2 was used for the synthesis of **SI-67**

Step 1. 50 g (206 mmol) of **3** (R=CF_3) gave (50.5 g, 82%) 8-trifluoromethyl-4-((dimethylamino)methylene)-3,4-dihydro-1H-benzo[b]azepine-2,5-dione (**4**; R=CF_3). ^{1}H NMR (400 MHz, DMSO) δ 10.16 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.67 (s, 1H), 7.47 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.37 (s, 1H), 3.32 (s, 2H), 3.24 (s, 6H). LCMS (FA): 299.3 m/z (M+H).

Step 2. **4** (R=CF_3) (5.2 g, 17.5 mmol) and **SI-65** (7.5 g, 19.7 mmol) gave **SI-67** (6.26g, 76%) ^{1}H NMR (400 MHz, DMSO) δ 10.44 (s, 1H), 9.13 (s, 1H), 8.50 (s, 1H), 8.12 (d, *J* = 8.2 Hz, 1H), 8.05 (d, *J* = 1.8 Hz, 1H), 7.85 (d, *J* = 1.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.53 (s, 1H), 3.41 (s, 2H), 2.54 (dd, *J* = 15.1, 7.3 Hz, 2H), 2.41 (s, 3H), 2.18 (t, *J* = 7.2 Hz, 2H), 2.07 (s, 6H), 1.72 – 1.62 (m, 2H). LCMS (FA): m/z 471.5 (M+H).



9-trifluoromethyl-2-({5-[3-(dimethylamino)propyl]-2-methylpyridin-3-yl}amino)-5,7-dihydro-6H-pyrimido[5,4-d][1]benzazepine-6-thione (12c)
Method 5 was used for conversion to the thioamide.
Obtained **12c** as the formate salt after HPLC purification (4.94 g, 72%)
^{1}H NMR (400 MHz, DMSO) δ 9.23 (s, 1H), 8.47 (s, 1H), 8.19 (s, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.08 (d, *J* = 1.8 Hz, 1H), 7.82 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.68 (s, 1H), 3.87 (s, 2H), 2.55 (dd, *J* = 14.2, 6.4 Hz, 2H), 2.41 (s, 3H), 2.38 (d, *J* = 7.7 Hz, 2H), 2.22 (s, 6H), 1.80 – 1.66 (m, 2H). LCMS (FA): m/z 487.2 (M+H).

Crystallography Methods

Crystallography Methods for Crystal Structure of 12b bound to PLK1.
Purified Plk1 kinase domain (residues 13-345, T210V mutant) at a concentration of 12 mg/mL in protein storage buffer (50 mM HEPES, pH 7.5, 5 mM TCEP) was incubated with 5 mM AMP-PNP and 5 mM MgCl2 prior to crystallization via the vapor diffusion method. Crystallization was done by mixing 1 μL of protein mixture with 1 μL of a reservoir solution consisting of 0.4 M Mg acetate, 0.24 M Zn acetate, and 8% PEG 4000. All crystal growth and manipulation took place at 4°C. Crystals were soaked for three hours in a solution containing 0.45 M Mg acetate, 0.27 M Zn acetate, 9% PEG 4000, 1 mM compound **12b**, and 10% DMSO. Crystals were briefly transferred into cryoprotectant consisting of 80% reservoir solution and 20% glycerol and flash cooled in liquid nitrogen. Data were collected using the SGXCAT beamline at the Advanced Photon Source (APS) synchrotron of the U.S. Department of Energy's Argonne National Laboratory (Chicago, USA) and processed using the HKL2000 software suite (Otwinowski, 1997). Starting coordinates were taken from Protein Data Bank entry 2OWB (Kothe et al, 2007). SigmaA-weighted Fo-Fc difference electron density for the active site was used to model inhibitor coordinates, starting with a conformation generated using the small-molecule topology generator PRODRG (Schuttelkopf, 2004). Manual rebuilding of the model was performed using the program Coot (Emsley and Cowtan, 2004) and refinement was carried out using the CCP4i graphical user interface (Potterton et al., 2003) to Refmac5 (Murshudov, 1997). The final model has R/Rfree = 0.250/0.291 for all data to 2.5 Å resolution. All structural figures were generated with PyMol (http://pymol.sourceforge.net/).

Kothe, M.; Kohls, D.; Low, S.; Coli, R.; Cheng, A.C.; Jacques, S.L.; Johnson, T.L.; Lewis, C.; Loh, C.; Nonomiya, J.; Sheils, A.L.; Verdries, K.A.; Wynn, T.A.; Kuhn, C.; Ding, Y-H. Structure of the Catalytic Domain of Human Polo-like Kinase 1, *Biochemistry*, **2007**, *46*, 5960–5971.

Otwinowski, Z.; Minor, W. Processing of X-ray Diffraction Data Collected in Oscillation Mode, *Methods in Enzymology*, Vol. *276*: Macromolecular Crystallography, part A, p.307-326, **1997**,C.W. Carter, Jr. & R. M. Sweet, Eds., Academic Press (New York).

Schüttelkopf, A.W.; van Aalten, D.M.F. PRODRG: a tool for high-throughput crystallography of protein-ligand complexes. *Acta Crystallogr. D Biol. Crystallogr.* **2004**, *60*, 1355-1363.

Emsley, P.; Cowtan, K. Coot: model-building tools for molecular graphics, *Acta Crystallogr. D Biol. Crystallogr.* **2004**, *60*, 2126-2132.

Potterton, E.; Briggs, P.; Turkenburg, M.; Dodson, E. A graphical user interface to the CCP4 program suite. *Acta Crystallogr. D Biol. Crystallogr.* **2003**, *59*, 1131-1137.

Murshudov, G.N.; Vagin, A.A.; Dodson, E.J. Refinement of macromolecular structures by the maximum-likelihood method, *Acta Crystallogr. D Biol. Crystallogr.* **1997**, *53*, 240-255.

Crystallographic data and refinement statistics

	Compound 12b
PDB ID	3THB
Space group	$P3_221$
Unit cell dimensions (Å)	a= 67.7 b= 67.7 c= 154.7
Wavelength (Å)	0.97989
Resolution (Å)	60 - 2.5
R_{sym}[a] (%)	8.4 (39.6)[b]
Total observations	87900
Unique reflections	13436
Average redundancy	6.5
$\langle I/\sigma \rangle$	10.6 (3.3)
Completeness (%)	90.6 (50.3)
Refinement resolution (Å)	60 – 2.5
Reflections (working/test)	11950/1317
R_{cryst}/R_{free} (%)[c]	25.0/29.1
Protein atoms	2243
ligand atoms	31
Zn^{2+} atoms	1
Water atoms	0
rmsd bond lengths (Å)	0.012
rmsd bond angles (°)	1.37
Ramachandran analysis	
most-favored (%/#)	87.0/220
additional allowable (%/#)	11.5/29
generously allowed (%/#)	1.6/4
disallowed (%/#)	0.0/0

[a] $R_{sym} = (\Sigma_{hkl} \Sigma_i |I_i(hkl) - \langle I(hkl) \rangle|) / \Sigma_{hkl} \Sigma_i I_i(hkl)$ for n independent reflections and i observations of a given reflection. $\langle I(hkl) \rangle$ is the average intensity of the i^{th} observation.

[b] numbers in parenthesis are for highest resolution shell

[c] $R_{cryst} = \Sigma_h ||F_o(h)| - |F_c(h)|| / \Sigma_h |F_o(h)|$, where F_o and F_c are the observed and calculated structure factors, respectively