Supplementary Information

Molecular Scaffolds with High Propensity to Form Multi-Target Activity Cliffs

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Table S1. Scaffolds from CDB with high potency-based discontinuity scores.

Rank	ScaffoldID	PScS	#Cpds	#Targets	#TargetCliffs	MaxPot	ItvPot
1	6445	1	30	24	4	11.52	10.12
2	9793	1	5	28	1	10.05	4.67
3	2269	1	4	3	1	9.17	4.79
4	1901	1	4	6	1	7.80	2.94
5	3866	1	3	9	2	9.35	4.49
6	6302	1	3	5	3	7.52	3.80
7	3658	1	3	3	1	9.15	3.50
8	5372	1	3	4	1	8.86	3.30
9	8790	1	3	2	1	8.82	3.06
10	6683	1	3	4	2	8.89	3.06
11	6891	0.99	5	3	2	8.39	4.83
12	8575	0.99	5	3	2	8.96	4.21
13	8792	0.99	4	2	1	7.64	3.20
14	3123	0.99	4	2	2	10.40	3.09
15	6141	0.99	3	2	2	8.78	2.84
16	2623	0.98	24	9	1	9.96	7.92
17	5821	0.98	9	3	3	8.22	6.08
18	759	0.98	8	3	1	8.28	4.51
19	3199	0.98	6	2	1	10.00	3.51
20	5629	0.98	4	3	2	10.00	3.98
21	3395	0.98	4	2	2	7.89	2.59
22	679	0.98	3	2	1	8.70	3.92
23	12673	0.98	3	4	2	8.15	3.46
24	6024	0.98	3	6	4	9.25	3.43
25	189	0.98	3	2	1	8.00	2.45
26	8134	0.98	3	2	2	5.82	2.24
27	5749	0.97	15	2	1	8.96	5.39
28	8852	0.97	8	2	2	8.52	3.88
29	12478	0.97	3	3	2	9.70	3.70
30	5710	0.97	3	2	1	10.40	3.07
31	1572	0.97	3	2	2	7.89	2.48
32	2134	0.97	3	3	3	8.85	2.37
33	3659	0.96	27	3	2	10.70	5.13
34	11047	0.96	8	10	2	9.10	5.36
35	2534	0.96	7	4	3	9.52	4.53
36	5413	0.96	3	11	1	9.19	3.49

37	5607	0.96	3	2	1	7.59	2.22
38	1197	0.96	3	2	1	8.44	2.12
39	10707	0.95	46	22	7	10.00	6.92
40	8996	0.95	13	2	1	8.48	4.91
41	1927	0.95	10	8	3	9.35	5.85
42	3214	0.95	8	2	2	9.89	3.89
43	9536	0.95	6	2	1	8.78	2.56
44	3500	0.95	5	5	5	10.00	5.40
45	7637	0.95	3	2	3	10.64	4.15
46	1060	0.95	3	3	1	10.28	3.97
47	2457	0.95	3	2	2	9.15	3.52
48	5794	0.94	52	6	3	9.05	7.22
49	10683	0.94	6	12	4	8.52	4.85
50	3612	0.94	3	2	1	8.68	3.09
51	478	0.93	5	4	4	8.04	4.02
52	9230	0.93	5	3	1	9.70	3.90
53	3613	0.93	5	2	2	8.60	2.57
54	3895	0.93	4	3	1	10.40	4.19
55	12298	0.93	4	3	2	8.82	3.64
56	3352	0.93	3	2	1	7.42	2.25
57	5505	0.93	3	3	1	8.62	2.05
58	8417	0.93	3	2	2	8.70	2.04
59	347	0.92	28	3	2	10.40	5.26
60	10775	0.92	14	2	1	9.96	4.87
61	8115	0.92	9	3	3	9.30	4.64
62	572	0.92	7	3	3	8.47	4.42
63	9571	0.92	7	2	2	8.40	3.39
64	8430	0.92	4	2	1	9.52	4.51
65	3010	0.91	9	2	2	9.54	4.54
66	4991	0.91	3	3	1	9.70	4.26
67	10131	0.91	3	2	2	7.51	2.45
68	4196	0.90	16	15	1	8.60	5.81
69	7006	0.90	7	3	1	9.10	3.11
70	4315	0.90	5	4	1	10.70	3.77
71	4512	0.90	5	2	2	8.28	3.02
72	8451	0.90	5	3	1	7.47	3.01
73	2712	0.89	27	4	2	9.00	4.14
74	742	0.89	7	4	1	8.98	3.37
75	1500	0.89	4	3	2	9.52	4.38
76	5044	0.89	4	2	2	7.74	4.10

77	4696	0.89	4	6	2	8.28	3.24
78	4455	0.89	3	7	3	7.96	2.21
79	3219	0.88	5	2	1	9.00	3.43
80	12749	0.88	5	2	1	7.89	2.97
81	6508	0.88	4	3	2	9.72	3.92
82	12627	0.88	3	3	2	9.52	4.14
83	7394	0.88	3	3	3	8.00	1.56
84	11159	0.87	21	2	2	10.23	4.66
85	9992	0.87	19	4	2	9.40	5.48
86	10797	0.87	9	2	1	9.07	3.41
87	6967	0.87	4	6	1	11.00	5.78
88	4303	0.87	4	2	1	7.96	2.55
89	2644	0.87	3	2	1	8.00	2.98
90	10539	0.86	24	10	1	9.10	4.69
91	3062	0.86	11	9	1	9.24	3.65
92	1105	0.86	9	3	2	9.40	3.28
93	5834	0.86	6	4	1	9.40	3.75
94	2306	0.85	18	7	1	8.52	4.18
95	10235	0.85	12	2	1	9.33	5.25
96	12449	0.85	12	5	3	9.00	4.49
97	10483	0.85	12	3	2	9.48	4.21
98	2831	0.85	9	4	1	8.00	3.11
99	3970	0.85	7	2	1	6.92	2.89
100	5808	0.85	6	2	1	9.66	5.83
101	7970	0.85	5	3	2	8.37	3.67
102	8602	0.85	5	2	1	9.00	3.09
103	10941	0.85	5	3	2	7.68	2.98
104	8590	0.85	4	2	1	8.00	2.40
105	3211	0.85	3	3	1	9.30	3.72
106	5285	0.84	10	3	1	9.52	3.64
107	2423	0.84	4	3	2	8.40	3.67
108	8986	0.84	4	3	1	10.00	1.90
109	8944	0.84	3	3	1	9.92	2.68
110	4181	0.84	3	2	2	8.00	2.43
111	3355	0.83	27	2	2	9.32	5.22
112	9749	0.83	9	5	3	9.37	3.26
113	5527	0.83	8	4	1	9.01	3.10
114	4316	0.83	8	3	1	8.52	2.78
115	3936	0.83	4	5	2	7.70	2.81
116	5165	0.83	4	4	2	8.80	2.55

117	6783	0.82	14	5	1	11.00	4.75
118	9066	0.82	14	3	2	8.70	3.56
119	10495	0.82	9	2	1	8.00	3.37
120	1995	0.82	8	3	1	9.55	4.16
121	1104	0.82	6	4	1	8.55	4.70
122	469	0.82	6	3	2	9.30	3.90
123	8045	0.82	5	2	1	8.68	2.60
124	12747	0.82	4	3	2	9.89	4.39
125	1779	0.82	3	4	2	8.07	4.66
126	5314	0.81	20	3	2	9.30	6.34
127	2849	0.81	19	3	1	9.40	4.88
128	6955	0.81	8	7	2	9.22	4.88
129	941	0.81	6	10	5	8.60	5.08
130	1821	0.81	5	5	2	7.74	2.89
131	8483	0.81	4	2	2	8.85	2.52
132	5717	0.81	3	3	1	7.33	2.76
133	2809	0.80	5	4	1	8.89	4.77
134	1389	0.80	5	3	2	7.38	2.95
135	2151	0.80	4	3	1	8.70	2.48
136	12471	0.80	4	2	0	8.82	2.18
137	12383	0.80	3	2	1	8.90	2.52

The complete set of 137 CDB scaffolds with PScS greater than 0.8 that represent more than two compounds active against more than one target is provided. For each scaffold, the score-based rank position (Rank), discontinuity score (PScS), the number of unique compounds it represents (#Cpds), the total number of targets (#Targets), the number of targets for which it forms activity cliffs (#TargetCliffs), the average maximal potency (MaxPot), and potency interval (ItvPot) are reported.

Table S2. Scaffolds from BDB with high potency-based discontinuity scores.

Rank	ScaffoldID	PScS	#Cpds	#Targets	#TargetCliffs	MaxPot	ItvPot
1	1990	1	6	2	1	9.30	3.70
2	413	1	4	2	2	7.82	3.54
3	455	1	4	2	2	7.89	3.45
4	1161	1	3	2	2	9.20	2.81
5	851	0.99	32	6	2	8.30	5.00
6	1921	0.99	3	3	1	8.70	3.31
7	363	0.98	17	4	2	10.89	5.66
8	299	0.98	4	2	1	7.10	3.54
9	546	0.98	3	2	2	7.89	2.59
10	1466	0.98	3	8	2	7.61	3.52
11	312	0.97	9	3	3	9.66	4.47
12	216	0.97	4	2	1	8.19	3.19
13	1601	0.97	4	2	2	8.69	2.96
14	1348	0.96	8	8	3	8.09	4.08
15	274	0.95	13	5	5	11.00	4.70
16	1304	0.95	13	4	1	9.59	3.51
17	453	0.95	7	2	2	7.68	3.62
18	424	0.95	5	3	2	9.70	4.26
19	2173	0.95	5	2	1	8.85	4.15
20	1144	0.94	9	3	1	7.68	2.95
21	1133	0.94	3	5	2	7.21	2.41
22	406	0.93	8	2	1	8.70	3.40
23	1538	0.93	4	2	1	9.30	5.78
24	2168	0.93	4	2	2	8.22	1.63
25	131	0.93	3	5	2	7.17	2.92
26	2115	0.93	3	3	1	9.30	4.20
27	1506	0.92	13	4	2	7.72	4.67
28	1922	0.92	8	4	1	7.41	2.73
29	2270	0.92	4	2	1	9.70	4.40
30	2395	0.92	4	5	1	9.77	5.26
31	1120	0.91	13	2	1	9.52	3.12
32	631	0.91	6	5	2	8.96	4.36
33	243	0.91	4	3	1	7.96	2.04
34	407	0.91	4	2	1	8.00	2.15
35	204	0.90	31	2	1	8.00	3.50
36	606	0.90	24	5	1	9.10	4.69

37	1495	0.90	8	2	1	8.70	3.63
38	2425	0.90	5	2	1	9.00	3.43
39	1255	0.90	3	10	4	8.68	3.65
40	1973	0.90	3	2	1	8.00	2.98
41	819	0.89	9	3	1	8.89	4.35
42	2389	0.88	60	22	4	10.72	7.28
43	1807	0.88	8	2	1	8.89	3.13
44	1845	0.88	8	2	1	9.80	3.77
45	1591	0.88	5	2	2	9.00	3.09
46	857	0.87	8	5	3	8.82	3.65
47	1373	0.87	4	3	2	8.40	3.67
48	1106	0.86	8	5	3	7.52	3.50
49	1063	0.86	4	3	1	8.00	2.08
50	1346	0.86	3	4	1	9.22	3.64
51	1457	0.85	14	2	1	6.63	3.59
52	39	0.85	12	4	1	7.52	4.52
53	1357	0.85	6	4	2	7.15	2.41
54	1169	0.84	10	6	4	9.00	4.20
55	1131	0.84	3	2	1	8.90	2.52
56	1257	0.83	148	7	2	11.22	7.22
57	1109	0.83	40	9	3	8.05	3.21
58	193	0.83	35	2	1	8.24	4.24
59	972	0.83	27	2	1	8.30	4.62
60	833	0.83	14	2	2	8.72	3.46
61	1385	0.83	14	3	1	9.36	5.60
62	2363	0.83	11	2	2	7.70	2.29
63	1152	0.82	63	12	4	9.05	6.12
64	810	0.82	13	2	1	8.40	3.17
65	1425	0.82	9	3	1	9.35	4.56
66	362	0.82	8	3	1	8.10	3.29
67	1577	0.82	3	3	2	9.00	3.20
68	1851	0.81	29	2	1	10.15	4.60
69	720	0.81	20	2	1	8.70	4.10
70	787	0.81	15	2	1	9.10	3.30
71	2401	0.81	13	2	1	9.48	3.42
72	2195	0.81	7	2	1	8.60	3.03
73	239	0.81	6	2	1	7.96	2.91
74	928	0.81	6	5	1	7.70	2.22
75	2152	0.81	4	2	1	8.55	2.77

The complete set of 75 BDB scaffolds with PScS greater than 0.8 that represent more than two compounds active against more than one target is provided. For each scaffold, the score-based rank position (Rank), discontinuity score (PScS), the number of unique compounds it represents (#Cpds), the total number of targets (#Targets), the number of targets for which it forms activity cliffs (#TargetCliffs), the average maximal potency (MaxPot), and potency interval (ItvPot) are reported.

Table S3. Scaffolds from CDB with high selectivity-based discontinuity scores.

Rank	ScaffoldID	#Cpds	SScS	#TPs	#TPCliffs	Max |SR|	Itv |SR|
1	9230	5	1	3	1	2.98	2.97
2	10683	4	1	34	5	3.97	3.97
3	4991	3	1	3	3	3.56	2.98
4	10707	16	0.99	27	9	5.69	5.68
5	2840	7	0.99	3	2	3.84	3.70
6	6582	3	0.99	10	7	3.45	3.40
7	12673	3	0.98	6	3	3.40	3.37
8	3211	3	0.97	3	2	3.72	3.65
9	3754	7	0.96	3	1	3.31	3.07
10	5304	5	0.96	6	2	2.32	1.90
11	572	5	0.95	3	2	3.64	3.58
12	7198	4	0.95	3	2	3.33	3.15
13	4266	3	0.95	3	1	3.89	3.70
14	8848	3	0.95	6	2	2.05	2.01
15	143	7	0.94	3	2	4.41	4.40
16	5834	6	0.93	6	3	2.36	1.86
17	7991	21	0.92	10	3	3.66	3.65
18	3153	3	0.92	3	1	1.31	1.22
19	10439	5	0.91	6	3	3.07	2.84
20	973	3	0.91	21	1	3.62	3.62
21	12298	4	0.90	3	2	2.33	2.33
22	1779	3	0.90	6	3	2.94	2.93
23	12627	3	0.90	3	2	3.56	3.46
24	2634	6	0.89	6	3	3.61	3.58
25	2712	8	0.88	6	2	3.73	3.54
26	1087	3	0.86	6	1	2.23	2.19
27	6611	13	0.84	3	1	2.02	2.01
28	9649	4	0.84	3	2	3.28	2.83
29	6332	17	0.83	35	3	4.22	4.22
30	12747	4	0.83	3	1	3.46	3.35
31	2008	3	0.82	3	2	3.09	3.09
32	6576	3	0.82	6	2	3.20	3.15
33	9011	66	0.81	3	1	2.77	2.77
34	347	23	0.81	3	2	2.71	2.70

All 34 CDB scaffolds with SScS greater than 0.8 that represent more than two compounds active against more than one target are listed. For each scaffold, the score-

based rank position (Rank), discontinuity score (SScS), the number of unique compounds it represents (#Cpds), the total number of target pairs (#TPs), the number of selectivity cliffs it forms (#TPCliffs), the average absolute maximal selectivity ratio (Max |SR|), and the selectivity interval (Itv |SR|) are reported.

Table S4. Scaffolds from BDB with high selectivity-based discontinuity scores.

Rank	ScaffoldID	SScS	#Cpds	#TPs	#TPCliffs	Max |SR|	Itv |SR|
1	2115	1	3	3	3	3.84	3.70
2	312	0.99	9	3	3	4.41	4.41
3	381	0.99	6	3	3	3.39	3.35
4	424	0.99	5	3	3	3.56	3.49
5	196	0.97	4	2	1	3.16	2.12
6	857	0.97	4	7	1	2.87	2.75
7	1425	0.96	6	3	1	2.90	1.85
8	733	0.96	3	3	1	2.07	2.07
9	1615	0.94	6	4	1	1.48	1.45
10	1008	0.94	3	4	2	3.07	2.94
11	1169	0.93	8	13	4	3.42	3.42
12	1001	0.92	4	4	2	2.01	1.54
13	1100	0.90	6	3	2	2.79	2.79
14	2005	0.88	8	3	2	3.26	3.18
15	511	0.87	10	3	1	3.40	3.00
16	466	0.87	9	3	3	2.88	2.53
17	1238	0.87	5	3	1	2.32	2.08
18	1152	0.86	21	9	2	3.66	3.65
19	362	0.85	6	3	1	2.54	2.28
20	1319	0.85	3	3	3	2.17	2.03
21	1106	0.84	5	10	4	2.26	2.24
22	2208	0.81	45	6	2	4.08	4.08
23	446	0.81	19	26	4	3.67	3.64

All 23 BDB scaffolds with SScS greater than 0.8 that represent more than two compounds active against more than one target are listed. For each scaffold, the score-based rank position (Rank), discontinuity score (SScS), the number of unique compounds it represents (#Cpds), the total number of target pairs (#TPs), the number of selectivity cliffs it forms (#TPCliffs), the average absolute maximal selectivity ratio (Max |SR|), and the selectivity interval (Itv |SR|) are reported.

Table S5. SMILES representations of multi-target activity cliff scaffolds.

ScaffoldID	SMILES
	BDB
131	C1C(=COc2ccccc12)c3ccccc3
274	C(CNC1CCCN(CC1)Sc2ccccn2)NCc3oc4ccccc4c3
312	C(CNCCNCCNC(CNCCNCCNCCc1ccccc1)Cc2c[nH]c3ccccc23)Cc4ccccc4
363	C(Nc1ccc(cc1)c2ccccc2)c3ccnn3c4ccccc4
413	C(Nc1ccccc1)Oc2ccc3OC4CC(CO4)c3c2
424	C(CNC(CNCCNC(CNCCNCCNCCc1ccccc1)Cc2c[nH]c3ccccc23)Cc4ccccc4)Cc5ccccc5
453	C(Sc1ccccc1)C2CCc3c(C2)[nH]c4ccccc34
455	C(Nc1ccccc1)Oc2ccc3OC4OCCC4c3c2
546	C(Nc1ccccc1)Oc2ccc3NC4OCCC4c3c2
631	C(NCc1ccccc1)c2ccccc2
833	C1Nc2ccccc2C1=CNc3ccccc3
851	C1COC(C1)n2cnc3cncnc23
857	C(COc1ccc2c(Nc3ccccc3)ncnc2c1)C[NH+]4CCOCC4
1106	C1CCc2[nH]c(C=C3CNc4cc(ccc34)c5ccccc5)cc2C1
1109	N(Sc1ccccc1)c2ccccc2
1133	c1ccc(cc1)c2ccncc2
1152	C1Cc2ccccc2C1
1161	C1CCC2C(C1)C(Oc3ccccc23)c4ccccc4
1169	o1ncc(n1)c2nc3cnccc3[nH]2
1255	C1NN=CS1
1257	N(c1ccccc1)c2ncnc3ccccc23
1348	C(NC1C[NH2+]CCCC1OCc2ccc(Cc3ccccc3)cc2)c4ccccc4
1357	C1CCN(C1)Sc2ccc3NCCc3c2
1373	C(CNc1ccccc1)NCC(CC2CCCCC2)NCN3CCOCC3
1466	C(Nc1ccccc1)C2CCCN2Sc3ccc4NCCc4c3
1506	c1ccc(cc1)n2cccn2
1577	C1COc2cc(Nc3nccc(n3)c4cnn5ncccc45)ccc2O1
1591	C(Nc1ccccc1)c2cccc(Nc3ncccc3c4ccncn4)c2
1601	C(Oc1cccc(c1)c2c(Cc3ccccc3)cnc4ccccc24)c5ccccc5
2168	C(CCCNc1c2CCCCc2[nH+]c3ccccc13)CCCNc4c5CCCCc5[nH+]c6ccccc46
2363	C(NN1CCCCC1)c2cc(n3cccc3)n(n2)c4ccccc4
2389	O(c1ccccc1)c2ccccc2
	CDB
347	C1C[C@@H]2CC(C[C@@H]1[NH2+]2)c3ccccc3
478	C(CN[C@@H]1CCc2ccccc12)Cc3ccccc3
572	C1CCn2nccc2C1
679	C([C@H]1CO[C@H]2CCC[C@H]12)c3ccccc3
941	c1nncs1
1060	C(C1CC1)[NH+]2CC[C@]34CCCCC3[C@H]2Cc5ccccc45

1104	C1CCC(C1)Nc2ncnc3c2ncn3[C@H]4CCC5C[C@H]45
1105	C1CCC(=CC1)c2c[nH]c3ccccc23
1500	C(CN[C@@H](CN1CC[C@H](C1)OCc2ccc3ccccc3c2)Cc4ccccc4)Cc5c[nH]cn5
1572	C(CCCCCCOc1ccccc1)CCCCCNC2CC2
1779	C1NSc2ccccc2N1
1821	C1NCC(CN1)c2ccc(Oc3ccccc3)cc2
1927	N(Sc1ccccc1)c2nncs2
2423	C(CNc1ccccc1)NC[C@H](CC2CCCCC2)NCN3CCOCC3
2534	C1C[NH+]=C(Nc2ccccc2)N1
2712	C(Nc1ncnc2c1ncn2[C@H]3CCCO3)c4ccccc4
2809	C(N1CCC(CC1)c2ccccc2)c3cccc(c3)c4onc(n4)c5cccs5
3010	C(COCc1ccccc1)COc2ccc(cc2)N3CC[NH2+]C[C@@H]3COc4ccc5CCCNc5c4
3214	C1C[NH+]2CCC1C(C2)C#CC(c3ccccc3)c4ccccc4
3355	C(CCc1ccccc1)CN2CCC[C@H]2CNCc3ccccc3
3395	C(Nc1ccccc1)Oc2ccc3N[C@@H]4OCCC4c3c2
3500	C1CCCn2cc(CCCNCC1)c3ccccc23
3658	C(C1=[NH+]CCN1)c2ccccc2
3659	C(CNCCNCCNCCc1ccccc1)Cc2ccccc2
3866	C1CCCOc2ccc(CCNCC1)cc2
3936	c1ccc(cc1)c2cc3ccccc3[nH]2
4455	C(CN1CC[NH2+]CC1)NC[C@@H]2CCCCNCOCCCC[C@@H](Cc3ccc(cc3)c4ccccc4)CN2
4512	C(CCCCCNC1CC1)CCCCCOc2ccccc2
4696	C(NPc1ccccc1)c2ccccc2
5044	C(Cc1ccccc1)NCNc2nncs2
5165	C1CCCNCCc2ccc(OCCC1)cc2
5314	N(c1ccccc1)c2ncnc3cnccc23
5629	o1nc(nc1c2cccnc2)c3ccccc3
5710	C(Cc1ccccn1)Nc2nccc3oc(Cc4ccccc4n5cncn5)nc23
5794	C1CCOC1
5821	C(Oc1cccc2ccccc12)c3cccs3
6024	C(CCSc1cccs1)CNCCc2ccccc2
6141	C(C[NH+]1CC[C@@H](C1)N2CNC(C2)(c3ccccc3)c4ccccc4)Oc5ccccc5
6445	C1CCCCC1
6508	C(Cc1ccccc1)[NH+]2CC[C@]3(CCC[C@@H]2C3)c4ccccc4
6891	C(CN1CCCC1)[NH2+]C2CCCCC2
6955	C(N[C@@H]1CCC[C@H]1OCc2ccc(Cc3ccccc3)cc2)c4ccccc4
7394	C1Cc2ccccc2CN1Sc3ccccc3
7637	C(CN[C@H]1CNc2ccccc2SC1)NC[C@H](NCCNC[C@@H]3CCCN3C[C@@H]4CCCN4)C5Cc6ccccc6C5
7970	C(CN1CC[C@H](C1)OCc2ccc3ccccc3c2)Cc4ccccc4
8115	C(CN1CCN(CCc2ccc3ccccc3c2)CC1)Cc4ccccc4
8417	C(Nc1ccccc1)Nc2ccc(cc2)c3c(oc4ncncc34)c5ccccc5
8483	o1nc(c2ccc3ccccc3c2)c4ccccc14
8575	C(CN1CCCC1)C2CCCC2
8790	o1nc(c2cccc3ccccc23)c4ccccc14

8792	C(Nc1ccccc1)Oc2ccc3O[C@@H]4OCCC4c3c2
8852	C1CC2[C@@H](Nc3ccccc23)[NH2+]1
8944	C(CC1CCOCC1)[NH2+]CC2COc3ccccc3OC2
9066	C1CN2N(C1)c3nc(Nc4ccccc4)ncc3C=C2c5ccccc5
9230	C(Nc1ccccc1)[C@H]2CC[C@H]3C2CC[C@@H]4[C@@H]3CNC5=CCCCC45
9571	C1CC2[C@H](Nc3ccccc23)[NH2+]1
9749	C1CCN(CC1)Sc2ccccc2
9992	C([NH+]1CCC(CC1)c2ccccc2)c3ccccc3
10131	N(c1ccc2nccnc2c1)c3ncc[nH]3
10483	C(Nc1ncnc2c1ncn2[C@@H]3CCCO3)c4ccccc4
10683	C(NSc1ccccc1)c2ccccc2
10707	C1CCNC1
10941	C(CN[C@@H](CN1CC[C@H](C1)OCc2ccc3ccccc3c2)Cc4ccccc4)Cc5ccccc5
11047	C1CCC=CC1
11159	C1C(=Cc2ccccc12)c3ccccc3
12298	C(CNCCNCCN[C@@H](CNCCNCCNCCc1ccccc1)Cc2c[nH]c3ccccc23)Cc4ccccc4
12449	C(c1nc2ccccc2[nH]1)c3nc4ccccc4[nH]3
12478	C(C1CC1)[NH+]2CC[C@]34[C@@H]5CCCC3[C@H]2Cc6cccc(O5)c46
12627	C1CC(CCC1N2Cc3ccccc3C2)[NH+]4CCN(CC4)c5ccccc5
12673	C1CN(CC[NH2+]1)c2ccc(cc2)c3ccccc3
12747	C(CC[NH+]1CCN(CC1)c2ccccc2)CNCc3oc4ccccc4c3

SMILES strings are provided for BDB and CBD scaffolds that are represented by at least three active compounds and that form multi-target activity cliffs.

Table S6. SMILES representations of multi-target selectivity cliff scaffolds.

ID	Murcko
BDB	
312	C(CNCCNCCNC(CNCCNCCNCCc1ccccc1)Cc2c[nH]c3ccccc23)Cc4ccccc4
381	N(c1ccccc1)c2ncnc3[nH]nc(c4ccccc4)c23
424	C(CNC(CNCCNC(CNCCNCCNCCc1ccccc1)Cc2c[nH]c3ccccc23)Cc4ccccc4)Cc5ccccc5
446	C1Nc2ccccc2C1=Cc3ccc[nH]3
466	C(N(c1ccccc1)n2cnnc2)c3ccccc3
1001	C(Cc1ccccc1)NCc2ccccc2
1008	c1cn[nH]c1
1100	C(OC1CCCCO1)c2cn(nn2)c3ccccc3
1106	C1CCc2[nH]c(C=C3CNc4cc(ccc34)c5ccccc5)cc2C1
1152	C1Cc2ccccc2C1
1169	o1ncc(n1)c2nc3cnccc3[nH]2
1319	C1CC(CC[NH2+]1)c2cccc3CC=C(Oc23)Sc4ccccc4
2005	C(CNc1cc2ncc(cc2cn1)c3ccccc3)C[NH+]4CC[NH2+]CC4
2115	c1ccc2nc(cnc2c1)c3nc4ccccc4[nH]3
2208	C(CN1CCCC1)Cc2ccc(cc2)c3ccccc3
CDB	
143	C(CNCCNCCN[C@H](CNCCNCCNCCc1ccccc1)Cc2c[nH]c3ccccc23)Cc4ccccc4
347	C1C[C@@H]2CC(C[C@@H]1[NH2+]2)c3ccccc3
572	C1CCn2nccc2C1
1779	C1NSc2ccccc2N1
2008	C(NC1=Nc2ccccc2N3CN(N=C13)c4ccccc4)c5ccccc5
2634	C1NCC=CN1
2712	C(Nc1ncnc2c1ncn2[C@H]3CCCO3)c4ccccc4
2840	c1ccc2nc(cnc2c1)c3nc4ccccc4[nH]3
3211	C(CC[NH+]1CCN(CC1)c2ccccc2)CNCc3cc4ccccc4s3
4991	C(CN[C@@H](CNCCN[C@H](CNCCNCCNCCc1ccccc1)Cc2c[nH]c3ccccc23)Cc4ccccc4)Cc5ccccc5
5304	C1C[NH+](CCC1c2c[nH]c3ccccc23)[C@@H]4Cc5cccc6cccc4c56
5834	c1cnn(n1)c2nc3cncnc3[nH]2
6332	C(c1ccccc1)n2c3CCCc3c4ccccc24
6576	C(CNCNc1ccccc1)C[C@H]2C[C@H](Cc3ccccc3)CCN2
6582	C(NCC1CCCCC1)[C@H](Cc2c[nH]c3ccccc23)NCN4CCC5(CC4)C=Cc6ccccc56
7198	C1C[NH+](CCC1c2c[nH]c3ncccc23)[C@@H]4Cc5cccc6cccc4c56
7991	C1Cc2ccccc2C1
8848	C([NH+]1CCC2(CC1)CNCN2c3ccccc3)c4ccc5OCOc5c4
9649	C(Nc1ccc2ncccc2c1)\C=C\c3ccccc3
10439	C([C@@H]1CNCCN[C@@H](Cc2c[nH]c3ccccc23)CNCCCCNCCNCCN1)c4ccccc4
10683	C(NSc1ccccc1)c2ccccc2
10707	C1CCNC1
12298	C(CNCCNCCN[C@@H](CNCCNCCNCCc1ccccc1)Cc2c[nH]c3ccccc23)Cc4ccccc4

12627	C1CC(CCC1N2Cc3ccccc3C2)[NH+]4CCN(CC4)c5ccccc5
12673	C1CN(CC[NH2+]1)c2ccc(cc2)c3ccccc3

SMILES strings are provided for BDB and CBD scaffolds that are represented by at least three active compounds and form multi-target selectivtiy cliffs.

Supplementary Figure Legends

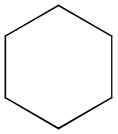
Figure S1. Scaffolds from CDB with high propensity to form activity cliffs. Scaffolds from CDB are shown that represent more than two compounds and produce activity cliffs for at least three targets. Scaffold IDs and target annotations are provided.

Figure S2. Scaffolds from BDB with high propensity to form activity cliffs. Scaffolds from BDB are shown that represent more than two compounds and produce activity cliffs for at least three targets. Scaffold IDs and target annotations are provided.

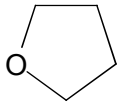
Figure S3. Scaffolds from CDB with high propensity to form selectivity cliffs. Scaffolds from CDB are shown that represent more than two compounds and produce selectivity cliffs for at least three target pairs. Scaffolds IDs and target pair annotations are provided. For example, "A / B; C; D" means that a scaffold forms selectivity cliffs for three target pairs, i.e. A / B (i.e. A over B), A / C, and A / D.

Figure S4. Scaffolds from BDB with high propensity to form selectivity cliffs. Scaffolds from BDB are shown that represent more than two compounds and produce selectivity cliffs for at least three target pairs. Scaffolds IDs and target pair annotations are provided.

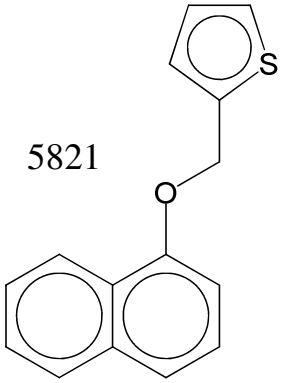
Figure S1

6445 

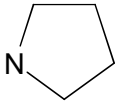
Cathepsin B, K, L
Sphingosine 1-phosphate receptor Edg-1

5794 

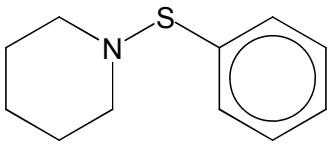
Protein kinase C alpha, delta
Cytochrome P450 1A2

5821 

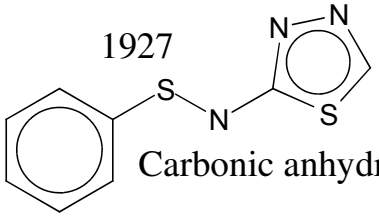
Norepinephrine transporter
Serotonin transporter
Dopamine transporter

10707 

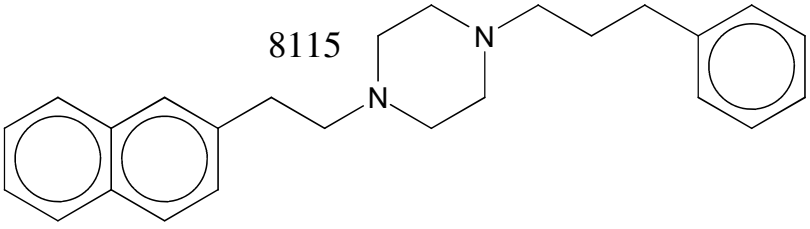
Prostanoid EP4 receptor
Oligopeptide transporter small intestine isoform
Dipeptidyl peptidase 4, 8, 9
Renin
Prolyl endopeptidase

9749 

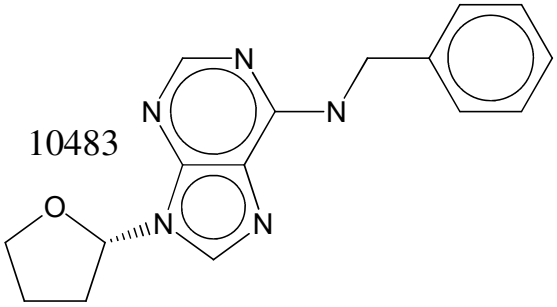
ADAM17
Matrix metalloproteinase 3, 9

1927 

Carbonic anhydrase I, II, IX

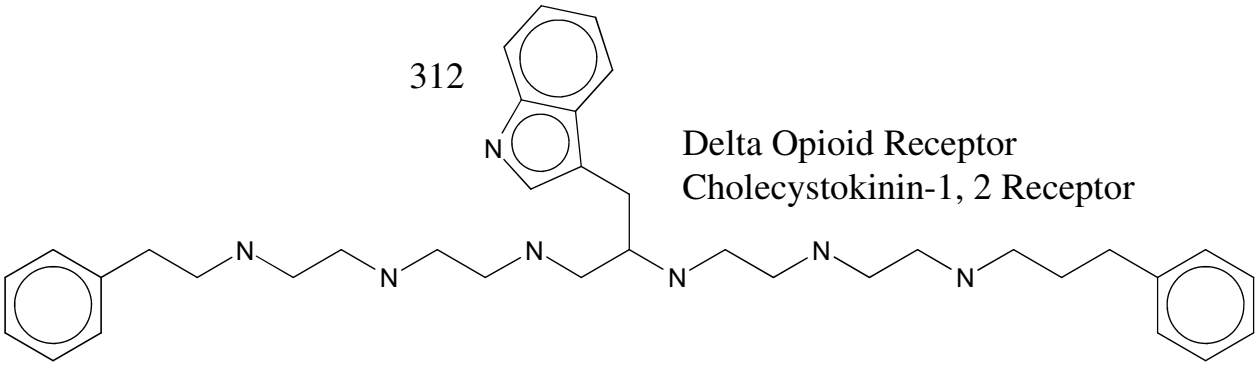
8115 

Melanocortin receptor 1, 3, 4

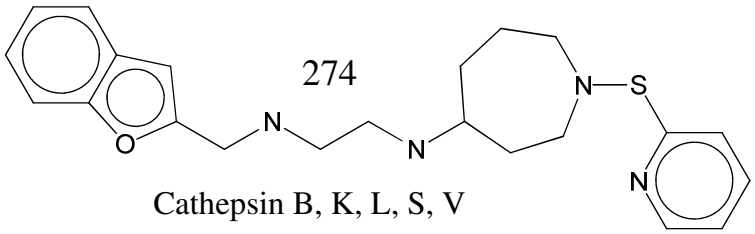
10483 

Adenosine A1, A2a, A3 receptor

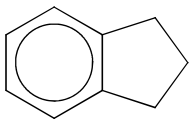
Figure S2



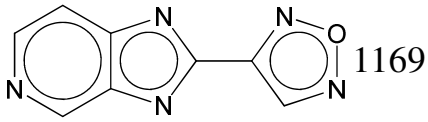
Delta Opioid Receptor
Cholecystokinin-1, 2 Receptor



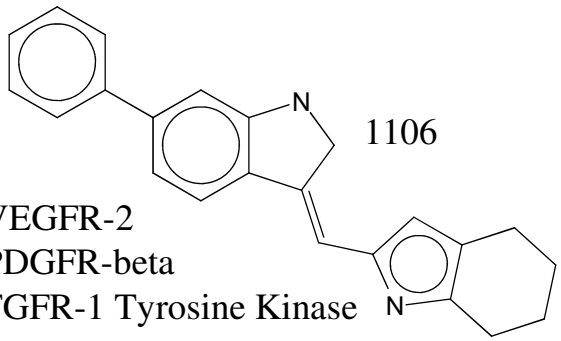
Cathepsin B, K, L, S, V



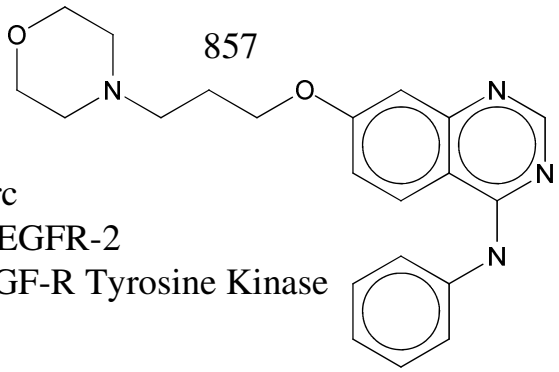
EGF-R Tyrosine Kinase
Carbonic Anhydrase II, IX
Acetylcholinesterase



Protein kinase B Akt 1, Akt2
Mitogen- and Stress-Activated Protein Kinase 1
Ribosomal S6 Kinase 1

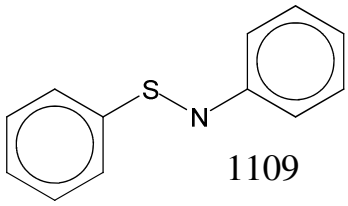


VEGFR-2
PDGFR-beta
FGFR-1 Tyrosine Kinase



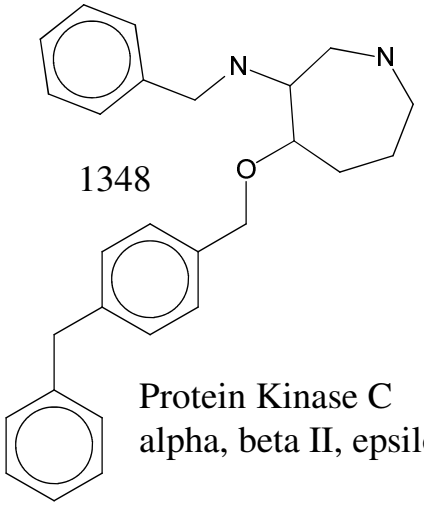
857

Src
VEGFR-2
EGF-R Tyrosine Kinase



1109

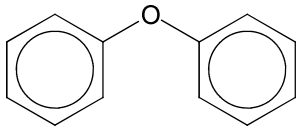
Carbonic Anhydrase I
Pregnane X Receptor
Methionine Aminopeptidase Type 2



1348

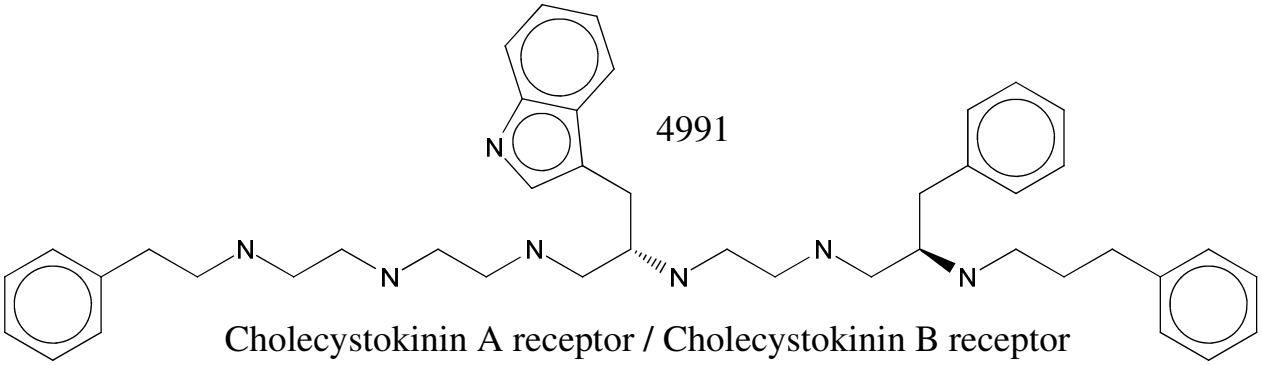
Protein Kinase C
alpha, beta II, epsilon

2389

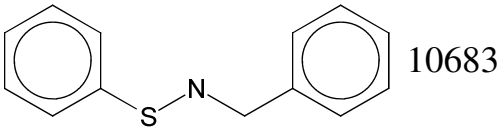


Matrix Metalloproteinase-1,13
Thyroid Hormone Receptor alpha, beta

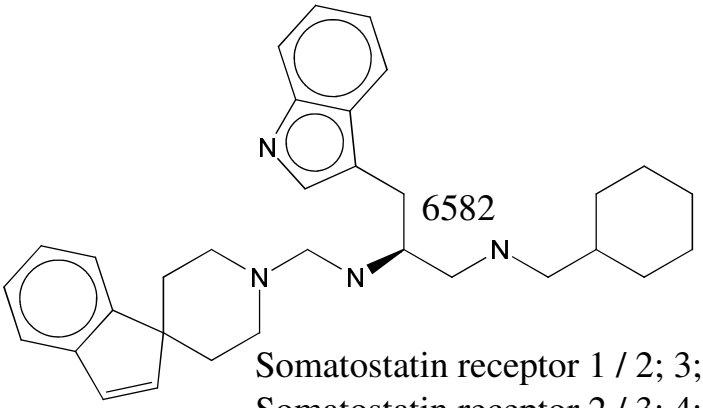
Figure S3



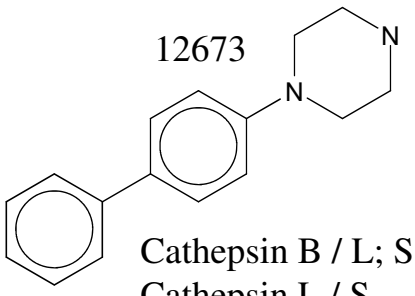
Cholecystokinin A receptor / Cholecystokinin B receptor / Delta opioid receptor
Cholecystokinin B receptor / Delta opioid receptor



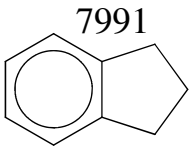
Carbonic anhydrase XII / II; I; IX
Carbonic anhydrase I / IX; II



Somatostatin receptor 1 / 2; 3; 4; 5
Somatostatin receptor 2 / 3; 4; 5

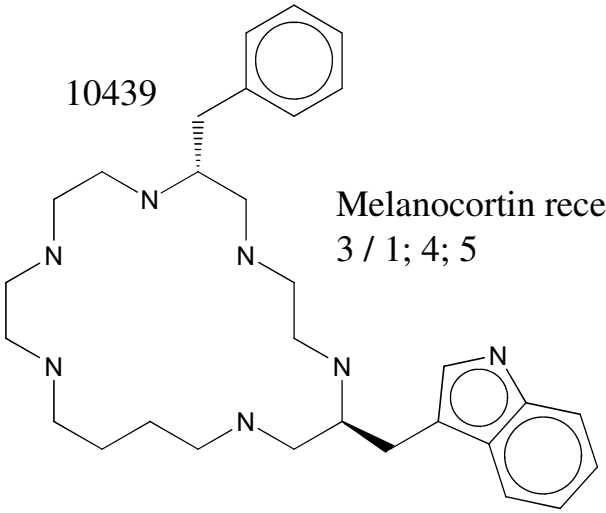


Cathepsin B / L; S
Cathepsin L / S

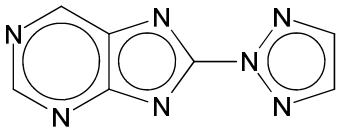


Carbonic anhydrase IX / I; II
Carbonic anhydrase I / II

10439

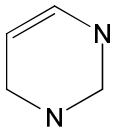


Melanocortin receptor
3 / 1; 4; 5



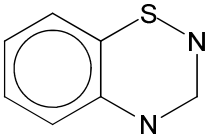
5834

Adenosine A1 receptor / A2a; A2b
Adenosine A2a receptor / A2b



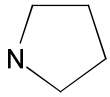
2634

Glutamate receptor ionotropic kainate 5 /
AMPA1; 2; 4

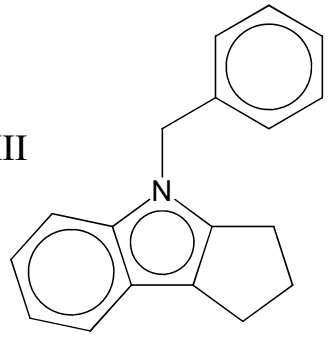


1779

Carbonic anhydrase II / I; IX; XII

10707 

Dipeptidyl peptidase 4 / 2; 9;
/ Prolyl endopeptidase;
/ Fibroblast activation protein alpha
Dipeptidyl peptidase 2 / 8; 9;
/ Fibroblast activation protein alpha
Fibroblast activation protein alpha / Dipeptidyl peptidase 8; 9

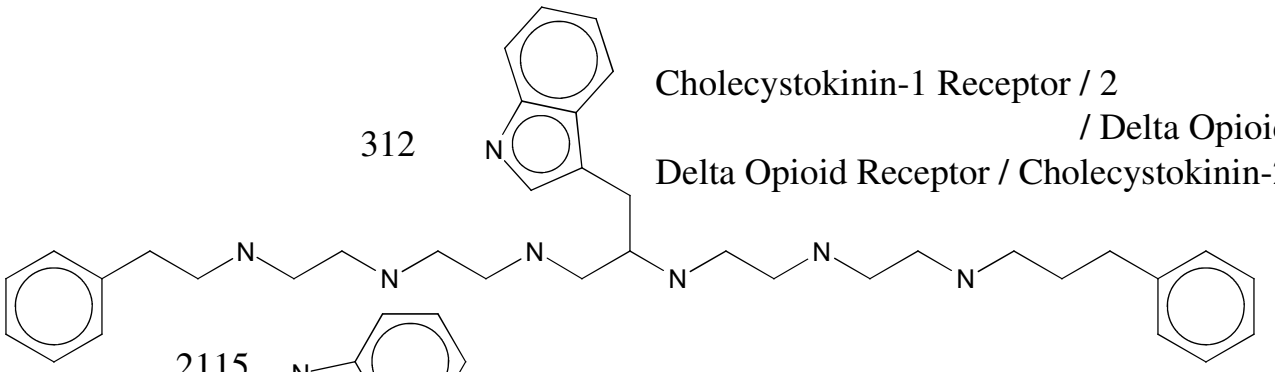


6332

Thromboxane A2 receptor /
Prostanoid EP2; DP receptor
Prostanoid IP receptor / EP1

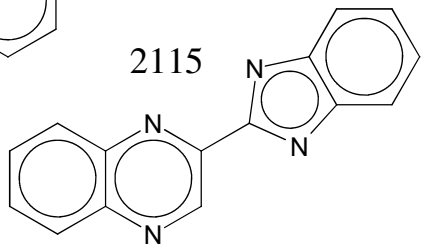
Figure S4

312

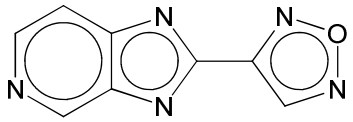


Cholecystokinin-1 Receptor / 2
/ Delta Opioid Receptor
Delta Opioid Receptor / Cholecystokinin-2 Receptor

2115

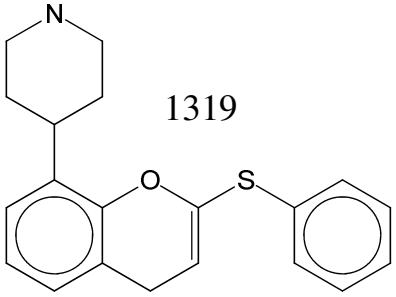


Adenosine Receptor A1 / A2A;A3
Adenosine Receptor A2A / A3



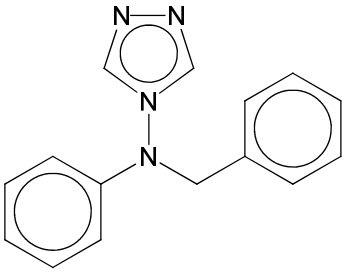
1169

Protein kinase B Akt 1 / Rho-kinase; Ribosomal S6 Kinase 1; Mitogen- and Stress-Activated Protein Kinase 1
Carbonic Anhydrase I / IX



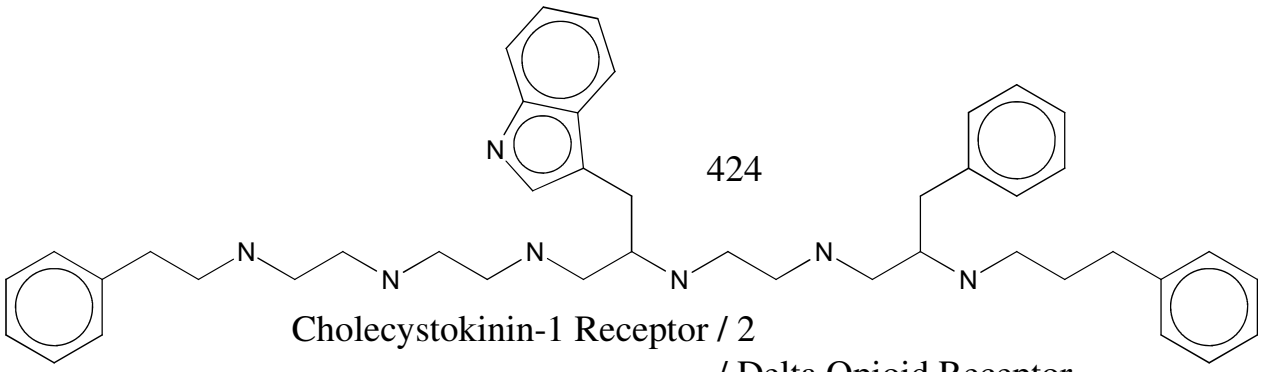
1319

Cyclin-Dependent Kinase 1 / 2; 4
Cyclin-Dependent Kinase 2 / 4



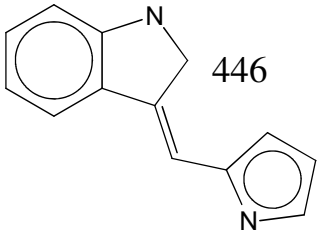
466

Carbonic Anhydrase II / Aromatase; Steroid Sulfatase
Aromatase / Steroid Sulfatase



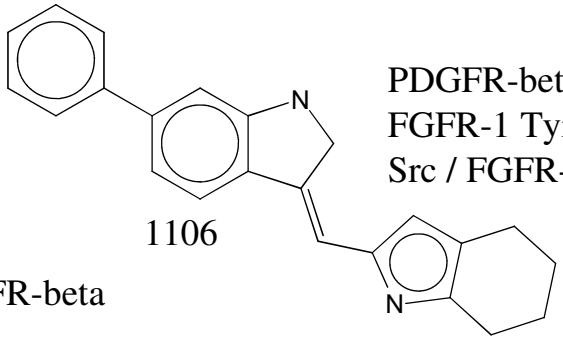
424

Cholecystokinin-1 Receptor / 2
/ Delta Opioid Receptor
Delta Opioid Receptor / Cholecystokinin-2 Receptor



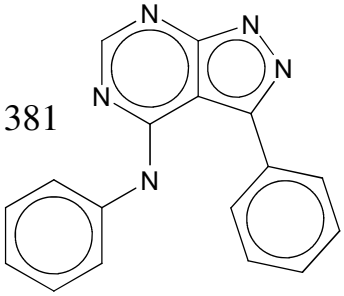
446

VEGFR-2 / Src; PDGFR-beta
FGFR-1 Tyrosine Kinase / Src; PDGFR-beta



1106

PDGFR-beta / Src; VEGFR-2;
FGFR-1 Tyrosine Kinase
Src / FGFR-1 Tyrosine Kinase



381

Cyclin-Dependent Kinase 1 / Src; EGF-R Tyrosine Kinase
Src / EGF-R Tyrosine Kinase