Discovery of kinase inhibitors by high-throughput docking and scoring based on a transferable linear interaction energy model

Supporting Information

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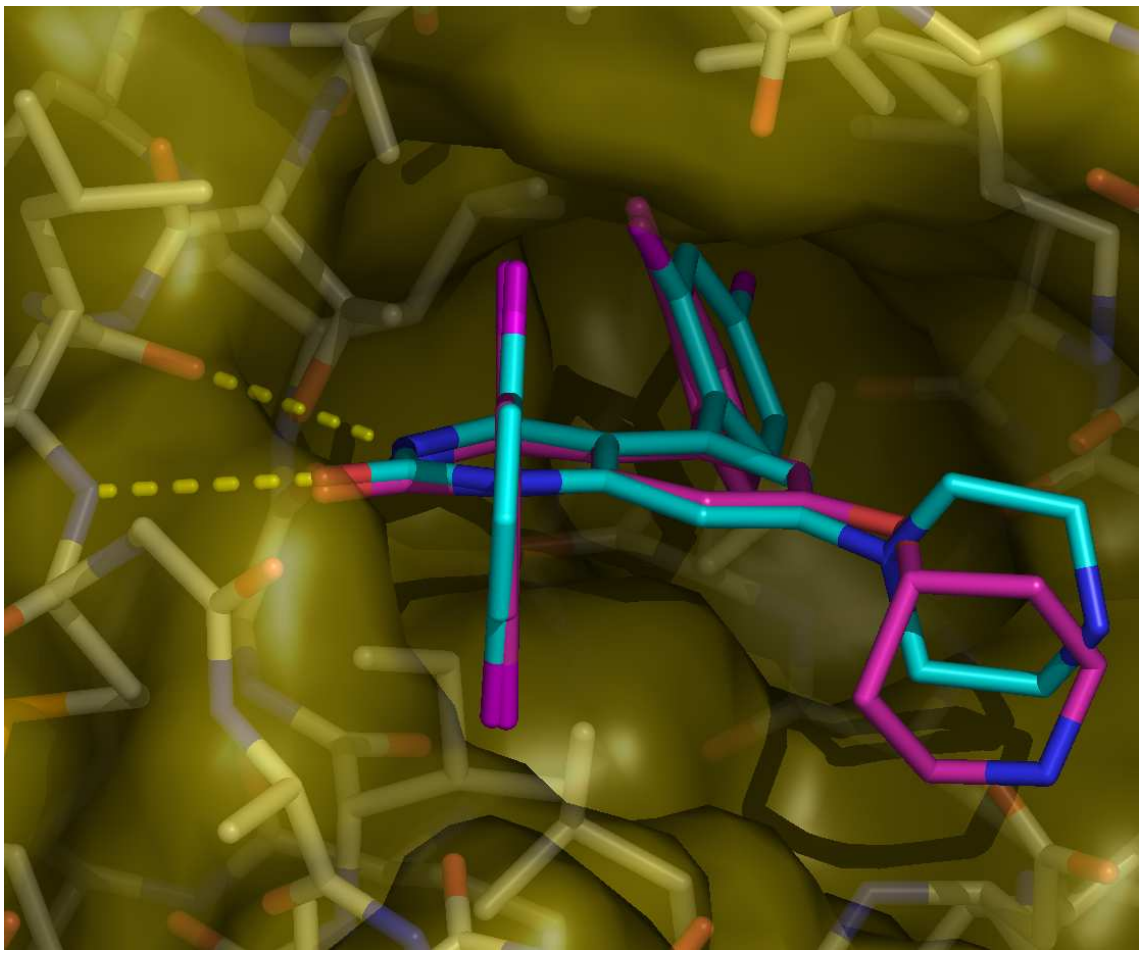


Figure S1: Comparison of the pose of the manually placed compound 14f (magenta) with the X-ray structure of compound 14e (cyan) in p38 (PDB code 1M7Q, compound names according to Stelmach et al., Bioorg. Med. Chem. Lett. 13, 277, 2003; see Figures S25 and S26). Figure prepared with PyMOL (DeLano Scientific, San Carlos, CA, USA).

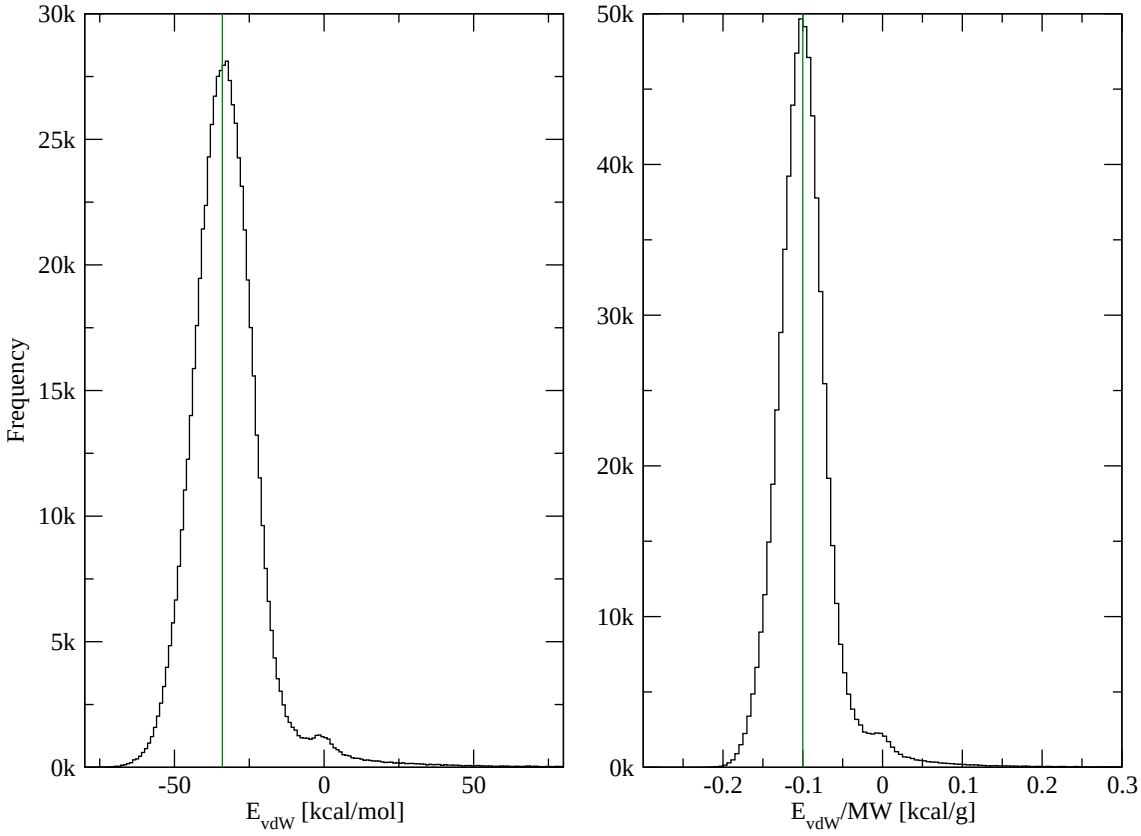


Figure S2: Histograms of the van der Waals interaction energy (left) and the van der Waals efficiency (right) of the 690530 poses of the 40735 diverse compounds from the ZINC library. The green lines are at the values which were used for the first filter (-35 kcal/mol for van der Waals energy and -0.1 kcal/g for van der Waals efficiency).

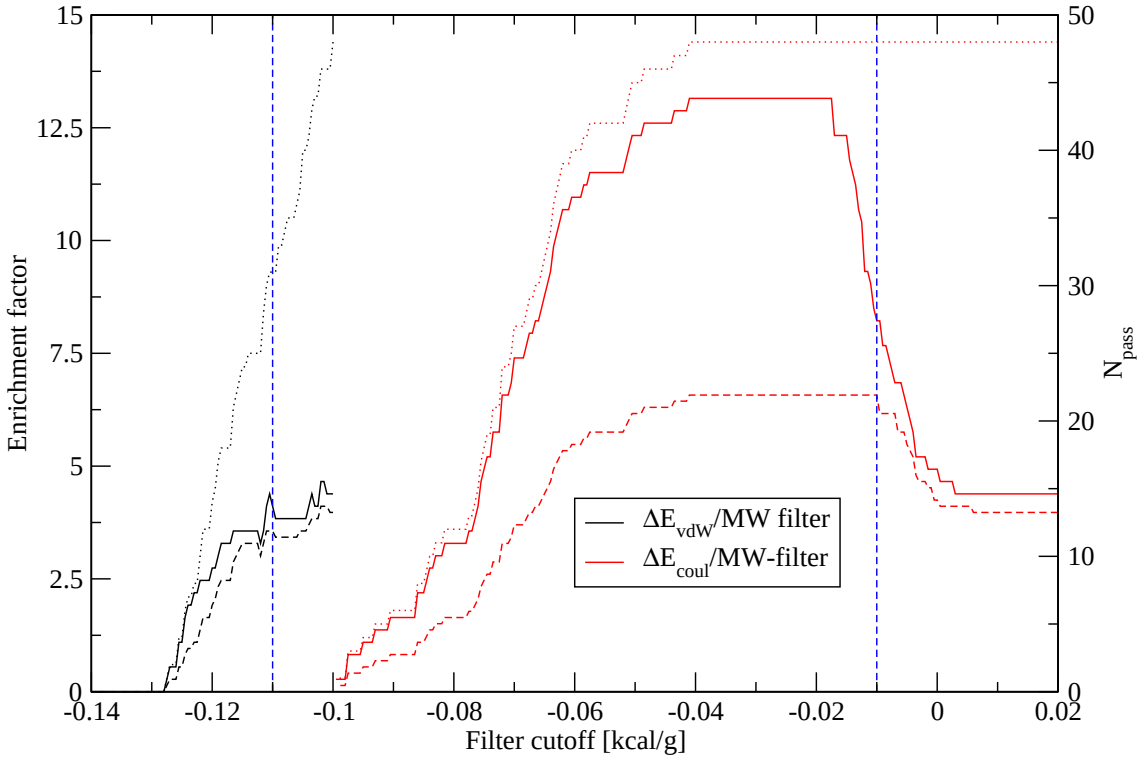


Figure S3: Dependency of the enrichment factors (EFs) on the values of the filter cutoffs and the window sizes chosen. The black curves were obtained by applying the $\Delta E_{vdW}/MW$-filter and the red curves by applying the $\Delta E_{coul}/MW$-filter, respectively. The blue dashed lines correspond to the cutoffs used in the manuscript. Enrichment factors were calculated in 0.0005 kcal/g steps, using the formula $\left(\frac{N_{inh,s\%}}{N_{cpds,s\%}}\right)\left(\frac{73}{40448}\right)^{-1}$. Two window sizes s were used to calculate the enrichment factors at each cutoff value: $s = 5\%$ (solid lines) and $s = 10\%$ (dashed lines). The amount of molecules in each window were always computed from the entire set of 40448 molecules, i.e., there are 2022 and 4044 molecules in the 5% and 10% windows, respectively. The dotted lines are the numbers of known inhibitors that pass the filters, $\mathrm{N_{pass}}$, which is shwon by the y-axis on the right of the plot.

	Enrichment factors[a]		
Filter	one-param.	two-param.	three-param.
$E_{coul}/MW \leq -0.01\,\mathrm{kcal/g}$	4.7	7.1	8.2
H-bond to hinge region	5.5	11.2	12.3
$E_{vdw}/MW \leq -0.11\,\mathrm{kcal/g}$	2.2	4.4	5.2
all filters	8.8[b]	8.8[b]	8.8[b]

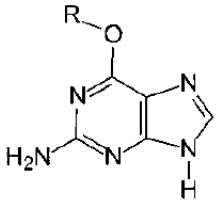
Table S1: Enrichment factors of CDK2 inhibitors calculated as $\left(\frac{N_{inh,5\%}}{N_{cpds,5\%}}\right)\left(\frac{73}{40448}\right)^{-1}$, where $N_{cpds,5\%} = 2022$ (5% of 40448). [a]Rankings were obtained using the CDK2 LIECE model with the number of parameters specified. [b]Note that using "all filters", all of the remaining 32 known inhibitors are ranked in the first 5% by all of the three LIECE models.

CDK2 inhibitors, Gibson et al.

Gibson, A. E.; Arris, C. E.; Bentley, J.; Boyle, F. T.; Curtin, N. J.;

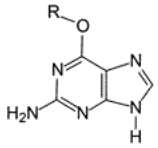
Probing the ATP ribose-binding domain of cyclin-dependent kinases 1 and 2 with O6-substituted guanine derivatives.

J. Med. Chem. **2002**. *45*, 3381–3393.



		CDK inhibition (IC_{50} (μM) or % inhibition at the concentration indicated)	
compd	R	CDK1/cyclin B	CDK2/cyclin A
1	Me	36 ± 1% (100 μM)	35 ± 1% (100 μM)
2	Et	48 ± 1% (100 μM)	51 ± 5% (100 μM)
3	*n*-Pr	75 ± 7	67 ± 5
4	*n*-Bu	32 ± 3	48 ± 7
5	$Me(CH_2)_3CH_2$	37 ± 6	49 ± 7
6	$Me(CH_2)_5CH_2$	62 ± 6	>100 μM
7	*i*-Pr	75 ± 14	75 ± 10
8	EtCH(Me)	27 ± 3	25 ± 1
9	$(Me)_2CHCH_2$	45 ± 8	42 ± 5
10	$EtCH(Me)CH_2$	17 ± 1	15 ± 2
11	$(Me)_2CHCH_2CH_2$	21 ± 4	26 ± 9

Figure S4: Gibson et al., table 1



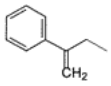
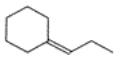
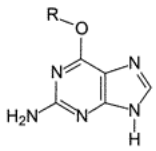
Compd.	R	CDK inhibition (IC_{50} (μM) or % inhibition at the concentration indicated)	
		CDK1/Cyclin B	CDK2/Cyclin A
12	$CH{\equiv}CCH_2$	91 ± 6	90 ± 7
13	$CH_2{=}CH(CH_2)_3CH_2$	41 ± 4	47 ± 4
14	*E*-$EtCH{=}CHCH_2CH_2$	76 ± 6	69 ± 8
15	$CH_2{=}CHCH_2$	68 ± 10	78 ± 13
16	$CH_2{=}C(Me)CH_2$	32 ± 9	35 ± 6
17	$CH_2{=}C(Et)CH_2$	19 ± 2	21 ± 2
18	$CH_2{=}C(i\text{-}Pr)CH_2$	11 ± 1	16 ± 1
19		25 ± 1	34 ± 3
20		21 ± 4% (10 μM)	12 ± 4% (10 μM)
21	$MeC(O)CH_2$	15 ± 3% (100 μM)	16 ± 3% (100 μM)
22	$i\text{-}PrC(O)CH_2$	41 ± 8% (100 μM)	31 ± 3% (100 μM)

Figure S5: Gibson et al., table 2



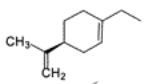
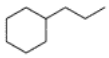
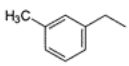
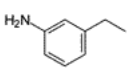
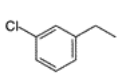
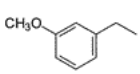
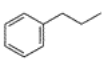
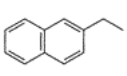
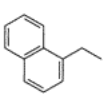
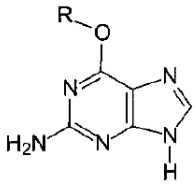
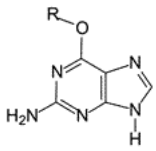
Compd.	R	CDK inhibition (IC_{50} (μM) or % inhibition at the concentration indicated)	
		CDK1/Cyclin B	CDK2/Cyclin A
23		15 ± 1	21 ± 4
24		19 ± 8	31 ± 7
25		7 ± 1	17 ± 2
26		11 ± 3	22 ± 4
27		6 ± 1	13, 19
28		17 ± 7% (10 μM)	18 ± 15% (10 μM)
29		55 ± 1% (10 μM)	29 ± 10% (10 μM)
30		37 ± 6	44 ± 3
31		24 ± 3	35 ± 6
32		70 ± 1% (100 μM)	52 ± 7% (100 μM)
33		65 ± 1% (100 μM)	52 ± 3% (100 μM)
34		28 ± 4% (10 μM)	19 ± 1% (10 μM)
35		65 ± 1% (100 μM)	49 ± 14% (10 μM)
36		59 ± 7	65 ± 6
37		12 ± 4% (10 μM)	9 ± 8% (10 μM)
38		10 ± 4% (10 μM)	3 ± 4% (10 μM)

Figure S6: Gibson et al., table 3



		CDK inhibition (IC_{50} (μM) or % inhibition at the concentration indicated)	
compd	R	CDK1/cyclin B	CDK2/cyclin A
39	$HOCH_2CH(OH)CH_2$	$35 \pm 8\%$ ($100\ \mu$M)	$33 \pm 12\%$ ($100\ \mu$M)
40	$MeOCH_2{-}CH(OMe)CH_2$	$49 \pm 9\%$ ($100\ \mu$M)	$41 \pm 5\%$ ($100\ \mu$M)
41	$MeC(OEt)_2CH_2$	36 ± 8	33 ± 6
42	$EtC(OMe)_2CH_2$	19 ± 2	20 ± 5

Figure S7: Gibson et al., table 4



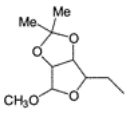
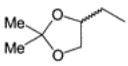
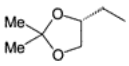
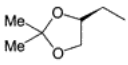
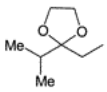
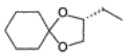
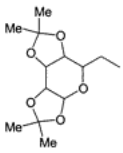
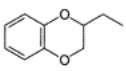
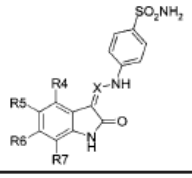
Compd.	R	CDK inhibition (IC_{50} (μM) or % inhibition at the concentration indicated)	
		CDK1/Cyclin B	CDK2/Cyclin A3
43		49 ± 7% (100 μM)	40 ± 3% (100 μM)
44		10 ± 3% (100 μM)	16 ± 5% (100 μM)
45		43 ± 8% (100 μM)	36 ± 5% (100 μM)
46		46 ± 4% (100 μM)	39 ± 2% (100 μM)
47		31 ± 3% (100 μM)	27 ± 3% (100 μM)
48		39 ± 12	65 ± 2
49		26 ± 7% (100 μM)	29 ± 3% (100 μM)
50		50 ± 4% (100 μM)	43 ± 2% (100 μM)
51		10 ± 6% (100 μM)	4 ± 5% (100 μM)
52		52 ± 2% (100 μM)	52 ± 2% (100 μM)
53		70 ± 1% (100 μM)	64 ± 6% (100 μM)
54		52 ± 2% (100 μM)	43 ± 7% (100 μM)
55		22 ± 6% (100 μM)	15 ± 5% (100 μM)
56		50 ± 5% (100 μM)	35 ± 4% (100 μM)
57		58 ± 8% (100 μM)	43 ± 5% (100 μM)
58		55 ± 3% (100 μM)	43 ± 3% (100 μM)

Figure S8: Gibson et al., table 5

CDK2 inhibitors, Bramson et al.

Bramson, H. N.; Corona, J.; Davis, S. T.; Dickerson, S. H.; Edelstein, M.; Oxindole-based inhibitors of cyclin-dependent kinase 2 (CDK2): Design, synthesis, enzymatic activities, and X-ray crystallographic analysis.

J. Med. Chem. **2001**. *44*, 4339–4358.



cmpd no.	R4	R5	R6	R7	X	kinase IC_{50} (nM) CDK1	CDK2
		Lead					
16	H	Br	H	H	N	780	60
		Linker					
17	H	H	H	H	N	1300	120
18	H	H	H	H	CH	3000	690
19	H	H	H	H	CCH_3	2300	360
20	H	Cl	H	H	N	300	43
21	H	Cl	H	H	CCH_3	220	22
22	H	5-oxazolyl	H	H	N	10	2.3
23	H	5-oxazolyl	H	H	CH	17.	2.5
24	H	5-oxazolyl	H	H	CCH_3	7.1	2.0
		4-Substituents					
25	I	H	H	H	N	110	4.6
26	$-CH_2CH_3$	H	H	H	N	46	7.9
27	$-CH(CH_3)_2$	H	H	H	N	37	2.5
28	$-CH_2CH(CH_3)_2$	H	H	H	N	19	1.2
29	$-CH{=}C(CH_3)_2$	H	H	H	N	15	1.5
30	$-OCH_2CH_3$	H	H	H	N	550	93
31	$-OCH(CH_3)_2$	H	H	H	N	41	3.4
32	-OPh	H	H	H	N	290	13
33	$-(CH_2)_2$-(4-pyridyl)	H	H	H	N	290	21
34	-CH=CH-(4-phenol)	H	H	H	N	170	9.3
35	$-(CH_2)_2$-(4-phenol)	H	H	H	N	150	12
36	3-pyrazolyl	H	H	H	N	250	19
37	$-CO_2CH_2CH_3$	H	H	H	CH	130	8.9
38	$-CH_2OH$	H	H	H	CH	1700	54
39	$-NO_2$	H	H	H	N	>1000	2400
40	$-CONH_2$	H	H	H	N	>1000	>1000
		5-Substituents					
41	H	F	H	H	N	290	34
42	H	I	H	H	N	95	11
43	H	$-CH_3$	H	H	N	330	46
44	H	-OH	H	H	N	77	10
45	H	$-OCH_3$	H	H	N	210	12
46	H	$-NO_2$	H	H	N	710	15
47	H	$-NH_2$	H	H	N	1400	74
48	H	$-N(CH_3)_2$	H	H	CH	2800	310
49	H	$-SO_2CH_3$	H	H	N	350	16
50	H	$-SO_2NH_2$	H	H	N	170	43
51	H	$-SO_3H$	H	H	N	130	15
52	H	$-CO_2H$	H	H	CH	150	28
53	H	$-CO_2CH_3$	H	H	CH	12	2.1
54	H	$-CO_2CH_2CH(CH_3)_2$	H	H	CH	19	3.0
55	H	$-COCH_2CH(CH_3)_2$	H	H	CH	16	1.9
56	H	$-CONH_2$	H	H	N	2.8	4.5
57	H	$-CON(CH_3)_2$	H	H	N	130	17
58	H	$-CONH(CH_2)_2$-(1*H*-Imidazol-4-yl)	H	H	N	69	12
59	H	$-CONH(CH_2)_3$-(1*H*-Imidazol-1-yl)	H	H	N	230	25
60	H	$-CONHCH_2$-(4-pyridyl)	H	H	N	74	8.9
61	H	$-CONHCH_2$-(3-pyridyl)	H	H	N	51	2.1
62	H	$-CONHCH_2C(CH_3)_2CH_2OH$	H	H	N	60	6.8
63	H	$-CONHCH_2$-(2,6-dimethoxyphenyl)	H	H	N	9.3	1.7
		6-Substituents					
64	H	H	Br	H	N	520	43
65	H	H	$-CH_2CH_3$	H	N	660	21
66	H	H	$-CH(CH_3)_2$	H	N	790	75
67	H	H	$-C(CH_3)_3$	H	N	>10 000	>10 000
68	H	H	$-CH_2OH$	H	CH	740	61
69	H	H	-OPh	H	N	>10 000	>10 000

Figure S9: Bramson et al., table 1

cmpd no.	R4	R5	R6	R7	X	kinase IC_{50} (nM) CDK1	CDK2
			7-Substituents				
70	H	H	H	$-CH_3$	CH	>10 000	>10 000
71	H	$-CH_3$	H	$-CH_3$	CH	>10 000	>10 000
72	H	Cl	H	$-CH_3$	CH	>10 000	>10 000
			4,5-Substituents				
73	Cl	$-CH_3$	H	H	N	250	13
74	Cl	$-OCH_3$	H	H	N	1700	54
75	$-CH_3$	$-NO_2$	H	H	N	87	4.6
76	-CH=N-NH-		H	H	N	120	13
77	-C(Cl)=N-NH-		H	H	N	83	2.2
78	-N=N-NH-		H	H	N	150	9.5
79	-S-CH=N-		H	H	N	43	7.1
80	-S-CH=N-		H	H	CH	29	2.8
81	-CH=CH-CH=N-		H	H	N	12	1.6
82	-CH=CH-CH=N-		H	H	CH	15	1.5

Figure S10: Bramson et al., table 1 continued

Lck inhibitors, part 1

Chen, P.; Norris, D.; Iwanowicz, E. J.; Spergel, S. H.; Lin, J.;
Discovery and initial SAR of imidazoquinoxalines as inhibitors of the src-family kinase p56(Lck).
Bioorg. Med. Chem. Lett. **2002**. *12*, 1361–1364.

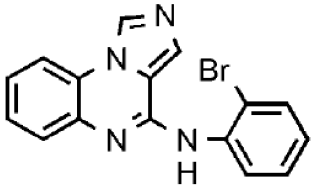


Figure S11: Chen et al., 2002a, scaffold 1

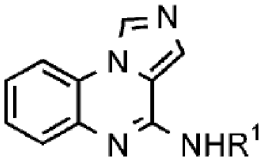


Figure S12: Chen et al., 2002a, scaffold 6

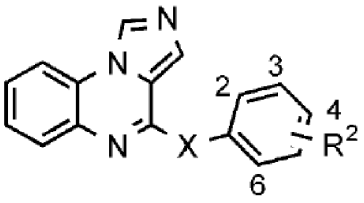


Figure S13: Chen et al., 2002a, scaffold 7

Compd	R^1 or R^2	X	Lck IC_{50} (nM)[13a]
1	2-Br	NH	170
6a	Cyclohexyl	na[a]	3170
6b	Cyclopropyl	na	3170
6c	*n*-Propyl	na	2680
6d	*n*-Hexyl	na	> 12,500
6e	Benzyl	na	> 12,500
6f	3-Cl-phenethyl	na	4390
6g	3-Pyridyl	na	820
6h	4-Pyridyl	na	> 12,500
7a	2-Br	O	3700
7b	2-Br	S	> 12,500
7c	2,6-di-Me	—	> 12,500
7d	2-Cl	N-Me	> 12,500
7e	2-Br	–NHCO—	60
7f	2-Me	–NHCO—	> 12,500
7g	2,6-di-Cl	–NHCO—	810

Figure S14: Chen et al., 2002a, table 1

Compd	R^2	X	Lck IC_{50} (nM)[13a]
1	2-Br	NH	170
7h	H	NH	890
7i	2-F	NH	390
7j	3-F	NH	1330
7k	2-Cl	NH	60
7l	2-OMe	NH	5520
7m	2-NO_2	NH	> 12,500
7n	4-Br	NH	> 12,500
7o	2-Cl, 4-Me	NH	240
7p	2-Cl, 4,6-di-Me	NH	30
7q	2,4,6-tri-Me	NH	40
7r	2,6-di-Me	NH	16
7s	2,6-di-Br	NH	50
7t	2,6-di-Cl	NH	9
7u	2,6-di-F	NH	360
7v	2-Cl, 6-Me	NH	9
7w	2,6-di-Et	NH	1690

Figure S15: Chen et al., 2002a, table 2

12

Figure S16: Chen et al., 2002a, scaffold 12

No.	R1	R2	R3	R4	IC_{50} (nM)[13a]
1	H	H	H	2-Br	170
7k	H	H	H	2-Cl	60
7r	H	H	H	2,6-di-Me	16
7s	H	H	H	2-Cl, 6-Me	9
12a	H	H	Ph	2-Br	> 12,500
12b	H	H	Me	2-Cl	30
12c	H	Me	H	2-Br	180
12d	7,8-di-MeO	Me	H	2-Cl, 6-Me	7.4
12e	7,8-di-MeO	CH_2OH	H	2-Cl, 6-Me	6.2
12f	7,8-di-MeO	CHO	H	2-Cl, 6-Me	10
12g	7,8-di-MeO	CHN=OH	H	2-Cl, 6-Me	4.3
12h	7,8-di-MeO	CHOHMe	H	2-Cl, 6-Me	53
12i	7,8-di-MeO	CHOH*i*-Pr	H	2-Cl, 6-Me	238
12j	7,8-di-MeO	$(CH_2)_3OH$	H	2-Cl, 6-Me	69
12k	7,8-di-MeO	C(=O)NHEt	H	2-Cl, 6-Me	665
12l	7,8-di-MeO	H	H	2, 6-di-Me	2.4
12m	7,8-di-MeO	H	H	2-Cl, 6-Me	2

Figure S17: Chen et al., 2002a, table 3

Lck inhibitors, part 2

Chen, P.; Iwanowicz, E. J.; Norris, D.; Gu, H. H.; Lin, J.;

Synthesis and SAR of novel imidazoquinoxaline-based Lck inhibitors: Improvement of cell potency.

Bioorg. Med. Chem. Lett. **2002**. *12*, 3153–3156.

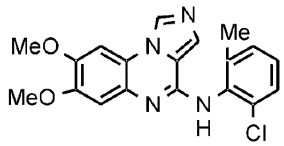


Figure S18: Chen et al., 2002b, scaffold 2

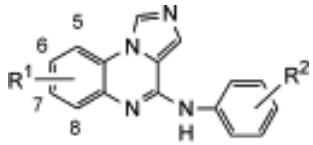
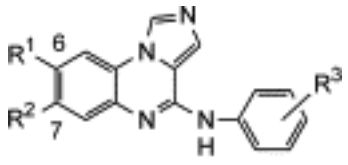


Figure S19: Chen et al., 2002b, scaffold 11

No.	Syn. route	R^1	R^2	Lck IC_{50} (nM)[3]	T-cell prolif. IC_{50} (nM)[3]
2	**A**	6,7-di-OMe	2-Cl, 6-Me	2	670
2a	**A**	6,7-di-OMe	2,6-di-Me	2.4	1100
11a	**A**	6,7-di-OH	2-Cl, 6-Me	4	>9000
11b	**A**	6,7-OCH_2O	2-Cl, 6-Me	4	2000
11c	**A**	6,7-$O(CH_2)_2O$	2-Cl, 6-Me	10	2200
11d	**A**	6-OMe	2-Cl, 6-Me	3	1400
11f	**A**	7-OMe	2-Cl, 6-Me	8.7	2600
11g	**A**	8-OMe	2-Cl, 6-Me	280	—
11h	**A**	5-OMe	2-Cl, 6-Me	9.4	2300
11i	**A**	5-BnO	2-Cl, 6-Me	240	—
11j	**A**	5-NO_2	2,6-di-Me	100	—
11k	**A**	5-NH_2	2,6-di-Me	70	—
11l	**B**	6-F	2-Cl, 6-Me	26	—
11m	**B**	6-Br	2-Cl, 6-Me	15	—
11n	**A**	6-CO_2Me	2-Cl, 6-Me	26	—
11o	**A**	6-NO_2	2, 6-di-Cl	24	—
11p	**A**	6-CN	2-Cl, 6-Me	100	—
11q	**A**	6-NH_2	2-Cl, 6-Me	7	1600
11r	**A**	6-NHAc	2-Cl, 6-Me	3	1400
11s	**B**	7-Br	2-Cl, 6-Me	14	—
11t	**A**	7-NH_2	2-Cl, 6-Me	21	—
11u	**A**	7-NHAc	2-Cl, 6-Me	11	—
11v	**A**	7-$CONH_2$	2-Cl, 6-Me	30	—

Figure S20: Chen et al., 2002b, table 1



12a-z

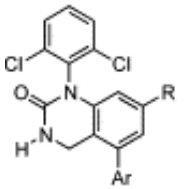
Figure S21: Chen et al., 2002b, scaffold 12

No.	Syn. Route	R^1	R^2	R^3	Lck enzyme[b] IC_{50} (nM)[3]	T-cell prolif.[c] IC_{50} (nM)[3]
12a	B[a]	NMe_2	H	2-Cl, 6-Me	5	2000
12b	B[a]	NEt_2	H	2-Cl, 6-Me	2	2600
12c	B[a]	NHEt	H	2-Cl, 6-Me	10	2200
12d	B[a]	$NHCH_2CH_2NMe_2$	H	2-Cl, 6-Me	6	880
12e	B[a]	$NHCH_2CH_2$–morpholine	H	2-Cl, 6-Me	7	1300
12f	B[a]	$NHCH_2CH_2CH_2$–morpholine	H	2-Cl, 6-Me	3	760
12g	B[a]	Morpholine	H	2-Cl, 6-Me	4	780
12h	B[a]	Piperazine	H	2-Cl, 6-Me	3	380
12i	B[a]	*N*-Me-piperazine	H	2-Cl, 6-Me	1	240
12j	B[a]	*N*-Et piperazine	H	2-Cl, 6-Me	2	270
12k	B[a]	*N*-Formyl piperazine	H	2-Cl, 6-Me	9	530
12l	B[a]	3,5-di-Me-piperazine	H	2-Cl, 6-Me	3	340
12m	B[a]	*N*-Me-homopiperazine	H	2-Cl, 6-Me	9	540
12n	B[a]	H	NEt_2	2-Cl, 6-Me	9	1700
12o	B[a]	H	$NHCH_2CH_2NMe_2$	2-Cl, 6-Me	10	520
12p	B[a]	H	$NHCH_2CH_2CH_2NMe_2$	2-Cl, 6-Me	9	480
12q	B[a]	H	Morpholine	2-Cl, 6-Me	6	1000
12r	B[a]	H	Piperazine	2-Cl, 6-Me	11	1000
12s	B[a]	H	*N*-Me-piperazine	2-Cl, 6-Me	8	720
12t	B[a]	H	3,5-di-Me-piperazine	2-Cl, 6-Me	13	570
12u	B[a]	OCH_2CH_2–morpholine	OMe	2-Cl, 6-Me	36	—
12v	B[a]	3,5-di-Me-piperazine	OMe	2-Cl, 6-Me	18	760
12w	B[a]	OMe	OCH_2CH_2–morpholine	2-Cl, 6-Me	2.4	470
12x	B[a]	OMe	$NHCH_2CH_2$–morpholine	2-Cl, 6-Me	5.4	280
12y	B[a]	OMe	$NHCH_2CH_2NMe_2$	2-Cl, 6-Me	1.7	190
12z	B[a]	OMe	$NHCH_2CH_2NMe_2$	2-Cl, 6-F	5	240

Figure S22: Chen et al., 2002b, table 2

p38 inhibitors

Stelmach, J. E.; Liu, L. P.; Patela, S. B.; Pivnichny, J. V.; Scapin, G.;
Design and synthesis of potent, orally bioavailable dihydroquinazolinone inhibitors of p38 MAP kinase.
Bioorg. Med. Chem. Lett. **2003**. *13*, 277–280.

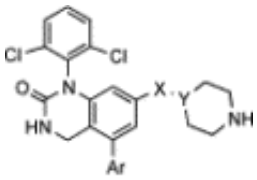


9 R= CO_2Me
10 R= OMe

Figure S23: Stelmach et al., scaffold 9 and 10

Compd	Ar	p38α IC_{50} (nM)
9a	Br	0% @ 1000 nM
9b	H	0% @ 1000 nM
9c	Phenyl	30
9d	2-Fl-Phenyl	7
9e	3-Fl-Phenyl	79
9f	4-Fl-Phenyl	22
9g	2-Cl-Phenyl	1
9h	3-Cl-Phenyl	67
9i	4-Cl-Phenyl	47
9j	2-CF_3-Phenyl	50% @ 890 nM
9k	3-CF_3-Phenyl	170
9l	4-CF_3-Phenyl	130
9m	2-CH_3-Phenyl	11
9n	3-CH_3-Phenyl	320
9o	4-CH_3-Phenyl	44
9p	2,4-di Fl-Phenyl	7
9q	2,6-di Fl-Phenyl	44
9r	2-CH_3-4-Fl-Phenyl	11
9s	-S-2,4-di Fl-Phenyl	48% @ 1000
10a	2-Cl-4-Fl-Phenyl	3
10b	2,4-di Fl-Phenyl	11
10c	2-Cl-Phenyl	6

Figure S24: Stelmach et al., table 1

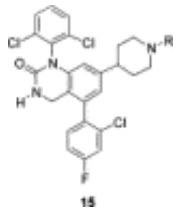


14

Figure S25: Stelmach et al., scaffold 14

Compd	Ar	X	Y	p38α IC_{50} (nM)	TNF-α Cell IC_{50} (nM)
14a	2-Cl-Phenyl	—	CH	0.9	2.0[a]
14b	2,4-di Fl-Phenyl	—	CH	0.2	1.3[a]
14c	2-Cl-4-Fl-Phenyl	—	CH	0.1	1.0[a]
14d	2-Cl-Phenyl	—	N	1.4	2.9[a]
14e	2,4-di Fl-Phenyl	—	N	2.6	7.8[a]
14f	2-Cl-Phenyl	O	CH	0.2	1.6[a]
14g	2-Cl-4-Fl-Phenyl	O	CH	0.1	0.7[b]
14h	2-Cl-Phenyl	NH	CH	0.5	4.4[b]
14i	2,4-di Fl-Phenyl	NH	CH	0.6	4.5[a]
14j	2-Cl-Phenyl	CH_2	N	0.1	1.4[a]
14k	2-Cl-4-Fl-Phenyl	CH_2	N	0.13	0.7[a]
14l	2-Cl-Phenyl	CO	N	1.5	11.4[a]
14m	2,4-di Fl-Phenyl	CO	N	2.4	26.8[a]
14n	2-Cl-4-Fl-Phenyl	CO	N	1.1	3.8[a]

Figure S26: Stelmach et al., table 2



15

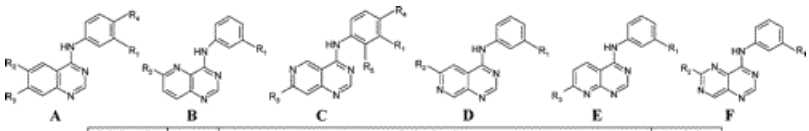
Figure S27: Stelmach et al., scaffold 15

Compd	R	p38α IC_{50} (nM)	TNF-α cellIC_{50} (nM)	TNF-α WBIC_{50} (nM)	IV $t_{1/2}$ (h)	Vd (L/kg)	Clp (mL/min/kg)	AUCn PO (μM h)	F (%)
15a	Methyl	0.5	1.3[a]	—	1.5	5.3	49.8	0.06	9.2
15b	Ethyl	1.2	0.7[b]	4.0	2.2	7.5	56.3	0.11	20.0
15c	*i*-Propyl	0.6	0.2[b]	5.6	1.9	12.2	84.8	0.06	16.0
15d	Cyclopropyl	1.1	16.6[a]	—	2.5	8.1	51.7	0.39	59.3
15e	Methyl Cyclopropyl	0.5	0.3[b]	7.6	1.9	6.3	50.9	0.15	22.6
15f	Ethyl 1-Cyclopropyl	0.3	—	7.0	2.0	4.7	31.1	0.36	38.0
15g	Cyclobutyl	0.4	0.5[b]	12.2	1.7	6.6	53.7	0.14	24.7
15h	Methyl Cyclobutyl	0.6	—	27.1	1.6	2.5	24.2	0.14	11.6
15i	*t*-butyl	0.2	0.6[b]	10.1	2.2	6.0	35.2	0.58	67.7

Figure S28: Stelmach et al., table 4

EGFR inhibitors, Aparna et al.

Aparna, V.; Rambabu, G.; Panigrahi, S. K.; Sarma, J. A. R. P.; Desiraju, G. R. Virtual screening of 4-anilinoquinazoline analogues as EGFR kinase inhibitors: Importance of hydrogen bonds in the evaluation of poses and scoring functions. *J. Chem. Inf. Model.* **2005**. *45*, 725–738.



Molecule No.	Class	Substitution					Activity
		R_1	R_2	R_3	R_4	R_5	pIC_{50}
1	A	-	-	-	-	-	6.46
2	A	Me	-	-	-	-	6.04
3	A	Cl	-	-	-	-	7.63
4	A	Br	-	-	-	-	7.56
5	A	I	-	-	-	-	7.09
6	A	CF_3	-	-	-	-	6.23
7	A	Br	NO_2	-	-	-	6.04
8	A	Br	OMe	-	-	-	6.45
9	A	Br	-	NO_2	-	-	6.0
10	A	Br	-	OMe	-	-	8.0
11	A	Br	OH	OH	-	-	9.76
12	A	Br	NH_2	NH_2	-	-	9.92
13	A	F	-	-	-	-	7.25
14	A	-	OMe	-	-	-	7.25
15	A	-	NH_2	-	-	-	6.11
16	A	CF_3	NH_2	-	-	-	6.24
17	A	-	OMe	-	-	-	6.92
18	A	-	-	NH_2	-	-	7.0
19	A	CF_3	-	NH_2	-	-	8.48
20	A	F	-	NO_2	-	-	5.21
21	A	Cl	-	NO_2	-	-	6.09
22	A	I	-	NO_2	-	-	6.26
23	A	-	OMe	OMe	-	-	7.53
24	A	F	OMe	OMe	-	-	8.42
25	A	Cl	OMe	OMe	-	-	9.5
26	A	I	OMe	OMe	-	-	9.05
27	A	CF_3	OMe	OMe	-	-	9.61
28	A	Br	NHMe	-	-	-	8.39
29	A	Br	NMe_2	-	-	-	7.07

Figure S29: Aparna et al., table 1

Molecule No.	Class	Substitution					Activity
		R_1	R_2	R_3	R_4	R_5	pIC_{50}
30	A	Br	NHCOOMe	-	-	-	7.92
31	A	Br	-	OH	-	-	8.32
32	A	Br	-	NHAc	-	-	7.39
33	A	Br	-	NHMe	-	-	8.15
34	A	Br	-	NHEt	-	-	7.92
35	A	Br	-	NMe_2	-	-	7.95
36	A	Br	NH_2	NHMe	-	-	9.16
37	A	Br	NH_2	NMe_2	-	-	6.79
38	A	Br	NH_2	OMe	-	-	8.42
39	A	Br	NH_2	Cl	-	-	8.18
40	A	Br	NO_2	NHMe	-	-	7.16
41	A	Br	NO_2	OMe	-	-	7.82
42	A	Br	NO_2	Cl	-	-	7.6
43	A	Br	OEt	OEt	-	-	11.22
44	A	Br	O-n-Pr	O-n-Pr	-	-	9.76
45	A	H	OMe	OMe	Br	-	10.14
46	B	Br	-	-	-	-	7.46
47	B	Br	NH_2	-	-	-	8.11
48	B	Br	Cl	-	-	-	7.74
49	B	Br	F	-	-	-	7.35
50	B	Br	NHMe	-	-	-	8.5
51	B	Br	NMe_2	-	-	-	8.01
52	B	Br	OMe	-	-	-	8.36
53	C	Br	-	-	-	-	7.45
54	C	Br	-	NHAc	-	-	7.53
55	C	Br	-	F	-	-	7.88
56	C	Br	-	OMe	-	-	7.40
57	C	-	-	NH_2	-	-	6.60
58	C	NO_2	-	NH_2	-	-	7.39
59	C	-	-	NH_2	-	Br	6.61
60	C	Br	-	NH_2	-	-	8.00
61	C	-	-	NH_2	Br	-	7.59
62	C	-	-	NH_2	CF_3	-	5.32

Figure S30: Aparna et al., table 1, continued

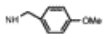
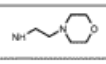
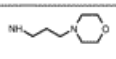
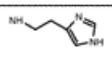
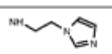
Molecule No.	Class	Substitution					Activity
		R_1	R_2	R_3	R_4	R_5	pIC_{50}
63	C	-	-	NH_2	-	OMe	5.43
64	C	OMe	-	NH_2	-	-	6.88
65	C	-	-	NH_2	OMe	-	6.17
66	C	-	-	NH_2	-	NH_2	5.27
67	C	NMe_2	-	NH_2	-	-	5.74
68	C	-	-	NH_2	NMe_2	-	5.31
69	C	F	-	NH_2	-	-	6.07
70	C	Cl	-	NH_2	-	-	6.92
71	C	OH	-	NH_2	-	-	7.15
72	C	Me	-	NH_2	-	-	7.39
73	D	Br	-	-	-	-	7.29
74	D	Br	Cl	-	-	-	7.39
75	D	Br	F	-	-	-	6.9
76	D	Br	OMe	-	-	-	8.58
77	D	Br		-	-	-	8.63
78	E	Br	-	-	-	-	6.16
79	E	Br	-	NH_2	-	-	6.02
80	E	Br	-	F	-	-	6.16
81	E	Br	-	NHMe	-	-	7.28
82	E	Br	-	NMe_2	-	-	6.48
83	E	Br	-	OMe	-	-	6.58
84	F	H	NHMe	-	-	-	7.88
85	F	Br	Cl	-	-	-	7.08
86	F	Br	NH_2	-	-	-	8.82
87	F	Br	NHMe	-	-	-	9.11
88	F	Br	NMe_2	-	-	-	9.02
89	F	Br	OMe	-	-	-	8.42
90	F	Br		-	-	-	9.09
91	F	Br		-	-	-	8.53
92	F	Br		-	-	-	9.6
93	F	Br		-	-	-	8.63

Figure S31: Aparna et al., table 1, continued

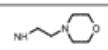
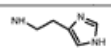
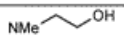
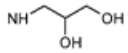
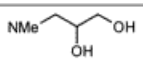
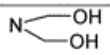
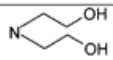
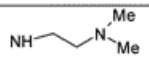
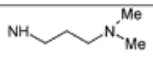
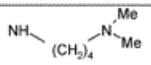
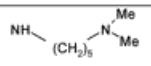
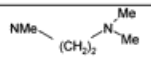
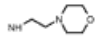
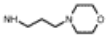
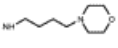
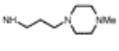
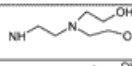
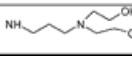
Molecule No.	Class	Substitution					Activity
		R_1	R_2	R_3	R_4	R_5	pIC_{50}
94	F	Me	Cl	-	-	-	6.42
95	F	Me	NH_2	-	-	-	7.76
96	F	Me	NHMe	-	-	-	8.36
97	F	Me	NMe_2	-	-	-	8.39
98	F	Me		-	-	-	8.63
99	F	Me		-	-	-	8.52
100	C	Br	-		-	-	9.61
101	C	Br	-		-	-	8.58
102	C	Br	-		-	-	9.03
103	C	Br	-		-	-	8.49
104	C	Br	-		-	-	7.85
105	C	Br	-		-	-	7.92
106	C	Br	-		-	-	7.34
107	C	Br	-		-	-	8.05
108	C	Br	-		-	-	8.13
109	C	Br	-		-	-	8.07
110	C	Br	-		-	-	7.39
111	C	Br	-		-	-	8.49
112	C	Br	-		-	-	8.72
113	C	Br	-		-	-	8.26
114	C	Br	-		-	-	8.30
115	C	Br	-		-	-	8.03
116	C	Br	-		-	-	8.92

Figure S32: Aparna et al., table 1, continued

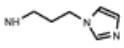
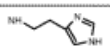
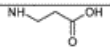
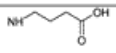
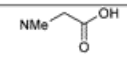
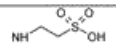
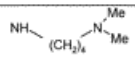
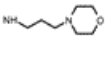
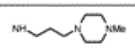
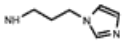
Molecule No.	Class	Substitution					Activity
		R_1	R_2	R_3	R_4	R_5	pIC_{50}
117	C	Br	-	$NHNH_2$	-	-	8.14
118	C	Br	-		-	-	9.29
119	C	Br	-		-	-	9.04
120	C	Br	-		-	-	8.82
121	C	Br	-		-	-	9.21
122	C	Br	-		-	-	9.55
123	C	Br	-		-	-	7.79
124	C	Br	-		-	-	8.85
125	C	Me	-		-	-	8.26
126	C	Me	-		-	-	8.03
127	C	Me	-		-	-	8.25
128	C	Me	-		-	-	8.45

Figure S33: Aparna et al., table 1, continued

EphB4 inhibitors, Berset et al.

Berset, C.; Audetat, S.; Tietz, J.; Gunde, T.; Barberis, A.; Schumacher, A.; Traxler, P.

Protein Kinase Inhibitors.

International Patent Application **2005**. Publication Number: WO/2005/120513