SnapShot: Kinase Inhibitors II

Jinhua Wang[1,2] and Nathanael S. Gray[1,2]
[1]Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
[2]Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School, Boston, MA 02115, USA

Molecular Cell

	Kinase name	Tool compound	IC_{50}	Known off targets	Other compounds	CAS number	PubMed ID
STE	MAP2K	Trametinib	MAP2K1: 0.92 nM; MAP2K2: 1.8 nM		PD0325901, PD184352	871700-17-3	21523318
	MAP2K1	Selumetinib	14 nM			606143-52-6	17332304
	MAP2K5	BIX 02188	4.3 nM	ERK5	BIX 02189	1094614-84-2	18834865
	MAP3K5	MSC2032964A	93 nM	CK1δ	TC ASK 10	1124381-43-6	21064192
	PAK4	PF-3758309	1.3 nM	PAK1/5/6		898044-15-0	20439741
TK	ABL	Bafetinib	5.8 nM	Lyn	Imatinib, nilotinib	859212-16-1	16105974
	ABL	GNF-5	220 nM		GNF-2	778277-15-9	20072125
	ALK	CH5424802	1.9 nM	GAK, LTK	LDK378, AP26113, ASP3026, crizotinib, TAE684	1256580-46-7	21575866
	BMX	BMX-IN-1	8 nM	BTK		1431525-23-3	23594111
	BTK	AVL-292	<0.5 nM	BMX, ITK, TEC, TXK	Ibrutinib	1202757-89-8	23709115
	BTK	CGI1746	1.9 nM			910232-84-7	21113169
	DDR	DDR1-IN-1	105 nM			1449685-96-4	23899692
	EGFR	Afatinib	0.4 nM	ErbB2	Gefitinib, lapatinib	439081-18-2	18408761
	ErbB2	CP-724714	10 nM		Lapatinib, AZD8931	537705-08-1	17942920
	ErbB3	TX-85-1	23 nM			1603845-32-4	25326665
	FAK	PND-1186	1.5 nM		PF-562271, defactinib, TAE226	1061353-68-1	20234191
	FGFR	BGJ-398	FGFR1: 0.9 nM; FGFR2: 1.4 nM; FGFR3: 1.0 nM; FGFR4: 60 nM	VEGFR2	AZD4547	872511-34-7	21936542
	FLT3	AC220	4.2 nM	KIT, PDGFRA, PDGFRB, RET, and CSF1R	MLN518	950769-58-1	19654408
	FMS	GW2580	60 nM		OSI-930, linifanib	870483-87-7	16249345
	IGF1R	NVP-AEW541	150 nM	INSR, FLT3, FLT3, TEK	OSI-906 (non-ATP competitive), BMS-536924	475489-16-8	15050915
	JAK2	Ruxolitinib	0.036 nM	JAK1	CEP33779	941678-49-5	22037378
	JAK3	Tofacitinib	1 nM	JAK1, JAK2		477600-75-2	14593182
	KIT	Imatinib	100 nM	PDGFR, v-Abl	Masitinib	152459-95-5	10910906
	LCK	WH-4-023	2 nM	Src	PP1, PP2	837422-57-8	16884310
	MET	SGX-523	4 nM		INCB28060, ARQ197 (non-ATP competitive)	1022150-57-7	19934279
	PDGFR	CP-673451	PDGFRα: 10 nM; PDGFRβ: 1 nM	c-Kit		343787-29-1	15705896
	SRC	AZD0530	2.7 nM	LCK, c-YES, Lyn, Fyn, FGR, BLK, v-Abl		379231-04-6	19393585
	SYK	P505-15	1 nM	FGR, MLK1	GSK143	1370261-96-3, 1370261-97-4 (HCl salt)	22040680
	TIE2	Compound 5	250 nM			948557-43-5	17618114
	TRK	GNF-5837	TrkA: 11 nM; TrkB: 9 nM; TrkC: 7 nM			1033769-28-6	24900443
	VEGFR	Axitinib	VEGFR1: 0.1 nM; VEGFR2: 0.2 nM; VEGFR3: 0.1-0.3 nM	PDGFRβ, c-Kit		319460-85-0	19010843
	VEGFR2	Cabozantinib	VEGFR1: 12 nM; VEGFR2: 0.035 nM; VEGFR3: 6 nM	c-MET, RET, FLT1/3/4, Tie2, AXL		849217-68-1, 1140909-48-3 (malate)	21613405
TKL	BRAF	GDC-0879	0.13 nM	RAF1	SB590885	905281-76-7	18676143
	DLK	GNE-3511	0.5 nM (K_i)	JNK		1496581-76-0	25341110
	LRRK2	GNE7915	9 nM	TTK, ALK	HG-10-102-01, GNE0877, GNE9605, LRRK2-IN-1	1351761-44-8	22985112
	MLK	URMC-099	MLK1: 19 nM; MLK2: 42 nM; MLK3: 14 nM	LRRK2, FLT3		1229582-33-5	24044867
	RAF1	GW5074	9 nM		ZM 336372	220904-83-6	15255937
	TAK1	(5Z)-7-Oxozeaenol	8.1 nM	MEKK1, MEKK4, NF-κB, JNK/p38	NG-25	66018-38-0	12624112
	TGFβR1/2	LY2109761	TGFβR1: 38 nM(K_i); TGFβR2: 300 nM(K_i)			700874-71-1	18413796
Other	Aur	AMG-900	AurA: 5 nM; AurB: 4 nM; AurC: 1 nM	p38α, DDR1, DDR2, LTK	VX-680, AT9283, SNS-314	945595-80-2	20935223
	AurA	MK-5108	AurA: 0.064 nM; AurB: 14.1 nM; AurC: 12.1 nM;	TrkA	MLN8054	1010085-13-8	20053775
	AurB	AZD1152	AurA: 1368 nM; AurB: 0.37 nM			722544-51-6	17495131
	CaMKK1/2	STO609	CaMKK1: 140 nM; CaMKK2: 40 nM			52029-86-4	11867640
	IKKβ	BI605906	380 nM	IGF1R	MLN120B, PHA408	960293-88-3	21138416
	Mps1	MPS1-IN-1	367 nM	ALK, LTK	MPI-0479605, AZ3146, NMS-P715	1125593-20-5	20383151
	PLK1	GSK461364	0.5 nM (K_i)		MLN0905, Ro3280	929095-18-1	19690138
	PLK1/2/3	BI2536	PLK1: 0.83 nM; PLK2: 3.5 nM; PLK3: 9.0 nM	BRD4	BI6727	755038-02-9	17291758
	PLK4	CFI-400945	2.8 nM	ABL T315I, TRKA, TRKB, BMX		1338800-06-8	25043604
	TBK1	MRT67307	19 nM	MARK1/2/3/4, SIK1/2/3, IKKε and NUAK1		1190378-57-4	21138416
	Wee1	MK-1775	5.2 nM			955365-80-7	19887545

See online version for legend and references.

SnapShot: Kinase Inhibitors II

Jinhua Wang[1,2] and Nathanael S. Gray[1,2]
[1]Department of Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
[2]Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School, Boston, MA 02115, USA

Molecular Cell

Selective small-molecule inhibitors of kinases can serve as powerful tools to elucidate biological function. Efforts to develop potential drug candidates have yielded a wealth of kinase inhibitors. However, selecting the optimal kinase inhibitor for a particular application can be challenging. While the optimal inhibitor will be application specific, we have attempted to summarize some of the best reported inhibitors for various kinases.

Typical considerations for selecting kinase inhibitors include requirements for selectivity, potency, cellular and in vivo bioavailability, and commercial accessibility (Knapp et al., 2013; Cohen, 2010). Because most kinase inhibitors target the highly conserved ATP-binding pocket, selectivity data have been emphasized (Davies et al., 2000; Bain et al., 2003, 2007; Davis et al., 2011; Uitdehaag et al., 2012). Users are encouraged to always validate their results with more than one kinase inhibitor at concentrations as low as possible and, ideally, to "rescue" the inhibitor-induced phenomena through expression of an inhibitor-resistant allele of the kinase (Cohen, 2010; Clark et al., 2012).

Kinase inhibitors are grouped by family (Manning et al., 2002). The first column of the table indicates the kinase family names.

Inhibition constant (Ki) or dissociation constant (Kd) is listed for compounds without reported IC_{50}.

ACKNOWLEDGMENTS

We thank Dr. Philip Cohen (University of Dundee) and Dr. Taebo Sim (Korea Institute of Science and Technology) for their advice.

REFERENCES

Bain, J., McLauchlan, H., Elliott, M., and Cohen, P. (2003). Biochem. J. *371*, 199–204.

Bain, J., Plater, L., Elliott, M., Shpiro, N., Hastie, C.J., McLauchlan, H., Klevernic, I., Arthur, J.S., Alessi, D.R., and Cohen, P. (2007). Biochem. J. *408*, 297–315.

Clark, K., MacKenzie, K.F., Petkevicius, K., Kristariyanto, Y., Zhang, J., Choi, H.G., Peggie, M., Plater, L., Pedrioli, P.G., McIver, E., et al. (2012). Proc. Natl. Acad. Sci. USA *109*, 16986–16991.

Cohen, P. (2010). Biochem. J. *425*, 53–54.

Davies, S.P., Reddy, H., Caivano, M., and Cohen, P. (2000). Biochem. J. *351*, 95–105.

Davis, M.I., Hunt, J.P., Herrgard, S., Ciceri, P., Wodicka, L.M., Pallares, G., Hocker, M., Treiber, D.K., and Zarrinkar, P.P. (2011). Nat. Biotechnol. *29*, 1046–1051.

Knapp, S., Arruda, P., Blagg, J., Burley, S., Drewry, D.H., Edwards, A., Fabbro, D., Gillespie, P., Gray, N.S., Kuster, B., et al. (2013). Nat. Chem. Biol. *9*, 3–6.

Manning, G., Whyte, D.B., Martinez, R., Hunter, T., Sudarsanam, S. (2002). Science. 298, 1912-34.

Uitdehaag, J.C., Verkaar, F., Alwan, H., de Man, J., Buijsman, R.C., and Zaman, G.J. (2012). Br. J. Pharmacol. *166*, 858–876.

  DOI http://dx.doi.org/10.1016/j.molcel.2015.05.002