Discovery of Mebendazole as a novel TRAF2- and NCK-interacting kinase inhibitor

Zhi Tan[1,2,*], Lu Chen[1,2,*], Shuxing Zhang [1,2,]

[1]Integrated Molecular Discovery Laboratory, Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030
[2]The University of Texas Graduate School of Biomedical Sciences, Houston, TX 77030, USA.

[*]These authors contributed equally to this work.
Correspondence and requests for materials should be addressed to Shuxing Zhang, Ph.D.
Tel: +1-(713)745-2958
Fax: +1-(713)794-5577
Email: shuzhang@mdanderson.org

Supplementary Table 1. 72 kinase inhibitors and their type of binding mode. We used K_d = 100 μM to indicate the inactive compounds. The actives are shaded in yellow, and the inactives are shaded in blue.

Compound	Binding Mode	Alternative Name	K_d to TNIK (μM)	pK_d to TNIK	PDB ID of reference structure
A-674563	Type I		0.1400	6.854	2UZT, 2UZW
AB-1010	Type II	Masitinib	100.0000	4.000	
ABT-869	Type II	Linifanib	2.8000	5.553	
AC220	Type II	Quizartinib	2.8000	5.553	
AG-013736	Type I	Axitinib	0.1800	6.745	4AG8
AMG-706	Type II	Motesanib	100.0000	4.000	3EFL
AST-487	Type II		0.0690	7.161	3UGC (similar)
AT-7519	Type I		100.0000	4.000	2VU3
AZD-1152HQPA	Type II		8.5000	5.071	
AZD-2171	Type I	Cediranib	0.8100	6.092	
AZD-6244/ARRY-886	Allosteric	Selumetinib	100.0000	4.000	
BI-2536	Type I		100.0000	4.000	2RKU
BIBF-1120 (derivative)	Type I		0.0530	7.276	3C7Q
BIBW-2992	Type I	Afatinib	100.0000	4.000	4G5J
BIRB-796	Type II	Doramapimod	0.1400	6.854	1KV2
BMS-345541	Type I		100.0000	4.000	
BMS-387032/SNS-032	Type I		100.0000	4.000	
BMS-540215	Type I	Brivanib	0.1600	6.796	
CEP-701	Type I	Lestaurtinib	0.0054	8.268	1R0P (similar)
CHIR-258/TKI-258	Type I	Dovitinib	0.0240	7.620	
CHIR-265/RAF-265	Type II		1.5000	5.824	
CI-1033	Type I	Canertinib	8.2000	5.086	2VRX (similar)
CI-1040	Allosteric		100.0000	4.000	3EQC
CP-690550	Type I	Tofacitinib	100.0000	4.000	3LXK
Crizotinib	Type I		100.0000	4.000	2YFX
Dasatinib	Type I		2.0000	5.699	2Y6O, 3G5D
Erlotinib	Type I		4.5000	5.347	1M17
EXEL-2880/GSK1363089	Type II	Foretinib	0.2100	6.678	3LQ8
Flavopiridol	Type I	Alvocidib	100.0000	4.000	3BLR
GDC-0879	Type I		2.3000	5.638	3D4Q (similar)
GDC-0941	Type I		100.0000	4.000	2WXP
Gefitinib	Type I		6.9000	5.161	3UG2
GSK-1838705A	Type I		100.0000	4.000	3EKK (similar)
GSK-461364A	Type I		100.0000	4.000	2XNM (similar)
GSK-690693	Type I		100.0000	4.000	3D0E
GW-2580	Type II		100.0000	4.000	4AT5

HKI-272	Type I	Neratinib	0.1400	6.854	3W2Q
Imatinib	Type II		100.0000	4.000	2HYY, 2PL0
INCB18424	Type I	Ruxolitinib	100.0000	4.000	
JNJ-28312141	Type I		0.1500	6.824	3KRJ
Ki-20227	Type II		2.3000	5.638	2RL2 (similar)
KW-2449	Type I		0.0280	7.553	
Lapatinib	Type I		100.0000	4.000	3BBT, 1XKK
LY-317615	Type I	Enzastaurin	100.0000	4.000	1UU7 (similar)
LY-333531	Type I	Ruboxistaurin	100.0000	4.000	1UU3
MLN-120B	Type I		100.0000	4.000	
MLN-518	Type II	Tandutinib	100.0000	4.000	
MLN-8054	Type I		100.0000	4.000	2X81
Nilotinib	Type II		100.0000	4.000	3GP0
Pazopanib	Type I		0.3100	6.509	3CJG (similar)
PD-173955	Type I		0.4300	6.367	1M52
PHA-665752	Type I		0.3100	6.509	2WKM
PI-103	Type I		100.0000	4.000	2X6K
PKC-412	Type I	Midostaurin	1.6000	5.796	1AQ1 (similar)
PLX-4720	Type I		2.5000	5.602	3C4C
PP-242	Type I		0.2700	6.569	3T3V (similar)
PTK-787	undetermined	Vatalanib	100.0000	4.000	
R406	Type I	Tamatinib	1.3000	5.886	3FQS
R547	Type I		100.0000	4.000	2FVD
SB-203580	Type I		0.8200	6.086	3ZS5
SGX-523	Type I		100.0000	4.000	3DKG
SKI-606	Type I	Bosutinib	0.0310	7.509	3UE4
Sorafenib	Type II		7.9000	5.102	3HEG
Staurosporine	Type I		0.0047	8.328	4ERW
SU-14813	Type I		0.0900	7.046	3G0E (similar)
Sunitinib	Type I		0.0250	7.602	3G0E
TAE-684	Type I		1.2000	5.921	2XB7
TG-100-115	Type I		100.0000	4.000	
TG-101348	Type I		100.0000	4.000	
Vandetanib	Type I		2.3000	5.638	
VX-680/MK-0457	Type I	Tozasertib	1.8000	5.745	3E5A, 2XYN
VX-745	Type I		100.0000	4.000	3ZSI

Supplementary Table 2. Structural comparison indicated by CoMSIA fields.

Field(s)	Cmpd ID (pIC50)	Changes
S4 & E5	4 (**8.00**) → A46 (**7.80**)	4-H → 4-OMe
	A47 (**8.52**) → 4 (**8.00**)	4-pyridine → Phe
	A47 (**8.52**) → A69 (**8.15**)	4-pyridine → 5-pyrimidine
	1 (**8.05**) → 10 (**7.85**)	4-H → 4-Me
	1 (**8.05**) → A11 (**7.85**)	4-H → 4-OMe
	A11 (**7.85**) → A12 (**7.62**)	4-OMe → 4-NH_2
	A84 (**8.70**) → A55 (**8.00**)	3-pyridine → Phe-4-OMe
	A72 (**8.40**) → A23 (**8.00**)	3-pyridine → Phe-4-OMe
	A74 (**8.15**) → A22 (**7.82**)	3-pyridine → Phe-4-OMe
S3, E3, H2 & H3	9 (**7.17**) → 11 (**5.77**)	2-F → 2-Cl
	9 (**7.17**) → 13 (**6.74**)	2-F → 2,6-diF
	9 (**7.17**) → 12 (**5.77**)	2-F → 3-Br
	A103 (**8.00**) → 14 (**7.24**)	3,4-di-NH_2 → 3,4-di-OMe
	12 (**5.77**) → 5 (**5.11**)	3-Br → 3-OMe
S2 & H1	A23 (**8.10**) → A37 (**8.05**)	4-$NHCH_2CH_2OH$ → 4-$NHCOCH_2OH$
	A47 (**8.52**) → A76 (**8.15**)	4-OMe → 4-F
	A27 (**8.05**) → A42 (**7.74**)	4-$NH(CH_2)_2$-morpholine → 4-$NHCOCH_2$-N-methylpiperazine
E1	A37 (**8.05**) → A11 (**7.85**)	4-$NHCOCH_2OH$ → 4-$NHCOCH_3$
	A23 (**8.10**) → A24 (**7.96**)	4-$NH(CH_2)_2OH$ → 4-$NH(CH_2)_2N(CH_3)_2$
E4 & H4	15 (**7.51**) → 6 (**6.55**)	2-thiophene → CH_2-2-thiophene
	15 (**7.51**) → 16 (**5.39**)	2-thiophene → $CH(Et)_2$
S1	A49 (**8.30**) → A27 (**8.05**)	4-$NH(CH_2)_2$-piperidine → 4-$NH(CH_2)_2$-morpholine
	A49 (**8.30**) → A55 (**8.00**)	4-$NH(CH_2)_2$-piperidine → 4-$NH(CH_2)_2$-4-pyridine
	A49 (**8.30**) → A42 (**7.74**)	4-$NH(CH_2)_2$-piperidine → 4-$NHCOCH_2$-N-methylpiperazine

Supplementary Table 3. Details of the data splitting and predictions for the CoMSIA model. The predicted pIC_{50}s for the training set are the LOO cross-validated values.

Training set				**Test set**			
ID	Predicted pIC_{50}	Actual pIC_{50}	Predicted – Actual pIC_{50}	ID	Predicted pIC_{50}	Actual pIC_{50}	Predicted – Actual pIC_{50}
2	7.178	7.400	-0.222	1	8.010	8.050	-0.040
3	7.778	7.720	0.058	5	7.977	5.110	2.867
4	7.985	8.000	-0.015	6	6.837	6.550	0.287
7	6.824	6.740	0.084	9	7.374	7.170	0.204
8	6.564	6.890	-0.326	A2	7.608	7.770	-0.162
10	7.251	7.850	-0.599	A20	7.891	8.050	-0.159
11	6.628	5.770	0.858	A29	7.653	8.100	-0.447
12	6.733	5.770	0.963	A46	7.738	7.800	-0.062
13	6.500	6.740	-0.240	A72	8.732	8.400	0.332
14	7.522	7.240	0.282				
15	6.793	7.510	-0.717				
16	6.147	5.390	0.757				
17	6.545	5.510	1.035				
A1	7.703	8.220	-0.517				
A4	8.118	7.740	0.378				
A9	8.129	7.740	0.389				
A11	7.567	7.850	-0.283				
A19	8.405	7.620	0.785				
A22	8.013	7.820	0.193				
A23	7.996	8.100	-0.104				
A24	7.909	7.960	-0.051				
A27	8.281	8.050	0.231				
A31	8.057	8.000	0.057				
A37	7.646	8.050	-0.404				
A42	7.496	7.740	-0.244				
A43	8.224	7.890	0.334				
A44	7.838	7.960	-0.122				
A45	8.114	7.660	0.454				
A47	8.610	8.520	0.090				
A48	7.689	8.220	-0.531				
A49	7.953	8.300	-0.347				
A55	8.214	8.000	0.214				
A69	8.619	8.150	0.469				
A74	7.700	8.150	-0.450				
A76	7.877	8.150	-0.273				
A84	8.360	8.700	-0.340				
A92	8.382	8.520	-0.138				
A102	7.532	8.220	-0.688				
A103	8.162	8.000	0.162				

Supplementary Table 4. Details of the data splitting and predictions for kNN model 1. The predicted pIC_{50}s for the training set are the LOO cross-validated values.

Training set				**Test set**			
ID	Predicted pIC_{50}	Actual pIC_{50}	Predicted – Actual pIC_{50}	ID	Predicted pIC_{50}	Actual pIC_{50}	Predicted – Actual pIC_{50}
2	7.398	7.669	-0.271	1	8.030	8.046	-0.016
4	8.000	8.285	-0.285	3	7.646	7.721	-0.075
7	6.745	7.453	-0.709	5	6.129	5.114	1.015
9	7.167	7.468	-0.301	6	6.297	6.553	-0.256
11	5.770	6.045	-0.275	8	6.252	6.886	-0.634
13	6.745	7.323	-0.578	10	7.889	7.854	0.035
15	7.509	7.258	0.250	12	5.429	5.770	-0.341
16	5.387	5.650	-0.262	14	7.953	7.244	0.709
17	5.509	5.545	-0.037	A1	7.522	8.222	-0.700
A2	7.770	7.438	0.332	A4	7.845	7.745	0.100
A11	7.854	7.981	-0.127	A9	8.028	7.745	0.283
A19	7.620	8.075	-0.455	A23	8.445	8.097	0.348
A20	8.046	8.072	-0.027	A24	8.007	7.959	0.048
A22	7.824	8.218	-0.394	A29	8.173	8.097	0.076
A27	8.046	8.116	-0.070	A37	8.435	8.046	0.389
A31	8.000	8.369	-0.369	A44	8.173	7.959	0.214
A42	7.745	8.173	-0.429	A45	8.173	7.658	0.515
A43	7.886	8.000	-0.114	A46	8.099	7.796	0.303
A47	8.523	8.077	0.445	A72	8.045	8.398	-0.353
A48	8.222	7.945	0.277	A92	8.315	8.523	-0.208
A49	8.301	7.945	0.356	A103	8.021	8.000	0.021
A55	8.000	7.925	0.075				
A69	8.155	8.185	-0.030				
A74	8.155	8.005	0.150				
A76	8.155	7.586	0.569				
A84	8.699	7.956	0.743				
A102	8.222	7.737	0.485				

Supplementary Table 5. Details of the data splitting and predictions for the CoMSIA-SIMCA model. The predicted classes of pK_ds for the training set are the five-group cross-validated values.

Training set			**Test set**		
ID	Predicted pK_d	Actual pK_d	ID	Predicted pK_d	Actual pK_d
A-674563	6	6	AT-7519	4	4
AG-013736	6	6	AZD-2171	5	6
BI-2536	4	4	Flavopiridol	4	4
BIBW-2992	5	4	Gefitinib	5	5
BMS-345541	4	4	Sunitinib	7	7
BMS-387032	4	4	Vandetanib	5	5
BMS-540215	6	6			
BIBF-1120	7	7			
CEP-701	7	7			
CHIR-258	7	7			
CI-1033	5	5			
CP-690550	4	4			
Crizotinib	4	4			
Dasatinib	5	5			
Erlotinib	5	5			
GDC-0879	5	5			
GDC-0941	4	4			
GSK-1838705A	4	4			
GSK-461364A	4	4			
GSK-690693	4	4			
HKI-272	6	6			
INCB18424	4	4			
JNJ-28312141	6	6			
KW-2449	7	7			
Lapatinib	4	4			
LY-317615	4	4			
LY-333531	4	4			
MLN-120B	4	4			
MLN-8054	4	4			
Pazopanib	6	6			
PHA-665752	6	6			
PD-173955	6	6			
PI-103	4	4			
PKC-412	5	5			
PLX-4720	5	5			
PP-242	6	6			
R406	5	5			
R547	4	4			
SB-203580	5	6			
SGX-523	4	4			

SKI-606	6	7
Staurosporine	7	7
SU-14813	7	7
TAE-684	6	5
TG-100-115	4	4
TG-101348	4	4
VX-680	5	5
VX-745	4	4

Supplementary Figure 1. Correlation between pIC50 and KierA2 or PEOE_VSA_HYD for the molecules with radius below 7.