Supporting Information

The Design, Synthesis, and Biological Evaluation of Potent c-Met Inhibitors

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Table 1: Elemental Analysis Results

		Calculated			Found		
Compound	Formula	%C	%H	%N	%C	%H	%N
7	$C_{29}H_{24}FN_3O_4 \bullet 0.1CH_2Cl_2$	69.07	4.82	8.30	69.30	4.77	8.29
22	$C_{35}H_{35}FN_4O_5 \bullet 0.2CH_2Cl_2$	67.36	5.68	8.93	67.60	5.72	8.98
37	$C_{29}H_{25}FN_4O_4 \bullet 0.5CH_2Cl_2$	63.84	4.72	10.09	63.60	4.78	9.78
39	$C_{32}H_{29}FN_4O_5 \bullet 0.2CH_2Cl_2$	66.05	5.06	9.57	66.23	5.13	9.48
41	$C_{32}H_{30}FN_5O_5 \bullet 0.3CH_2Cl_2$	63.69	5.06	11.50	63.55	5.20	11.31
42	$C_{36}H_{37}FN_4O_5 \bullet 0.6CH_2Cl_2$	65.06	5.70	8.29	64.66	5.72	8.06
43	$C_{35}H_{34}F_2N_4O_5 \bullet 0.2CH_2Cl_2$	65.48	5.37	8.68	65.90	5.70	8.30
51	$C_{34}H_{33}F_2N_5O_5 \bullet 0.4CH_2Cl_2$	62.26	5.13	10.55	62.37	5.30	10.33
62	$C_{33}H_{33}FN_6O_5 \bullet 0.4CH_2Cl_2$	62.04	5.27	13.00	61.76	5.61	12.99

Table 2: HPLC Methods

Compound	Method	Compound	Method
23	A	**38**	E
24	B	**40**	C
25	A	**48**	C
26	A	**49**	F
27	A	**50**	F
34	C	**55**	A
35	D	**56**	A

Method A: Column: LUNA C8(2) 5µ 100 x 4.6 mm; Flow rate 1.0 ml/min. Solvent A: water (with 0.1% TFA). Solvent B: MeCN (with 0.1% TFA). Gradient: 0.5 min (5% B) -> 7.3 min (95% B) -> 9.5 min (95% B) -> 9.8 min (5% B) -> 10 min (5% B).

Method B: Column: Synergi 4µ MAX-RP 50 x 2.0 mm @ 40 C; Flow rate 0.8 ml/min. Solvent A: water (with 0.1% TFA). Solvent B: MeCN (with 0.1% TFA). Gradient: 0.1 min (10% B) -> 7.0 min (100% B) -> 9.0 min (100% B) -> 10 min (10% B).

Method C: Column: Agilent Zorbaz SB-C18 3.5µ, 50 x 3.0 mm @ 40 C; Flow rate 1.5 ml/min. Solvent A: water (with 0.1% TFA). Solvent B: MeCN (with 0.1% TFA). Gradient: 0 min (10% B) -> 3.0 min (95% B) -> 3.5 min (95% B) -> 3.51 min (10% B).

Method D: Column: LUNA C8(2) 5µ 100 x 4.6 mm; Flow rate 1.0 ml/min. Solvent A: water (with 0.1% TFA). Solvent B: MeCN (with 0.1% TFA). Gradient: 0.1 min (10% B) -> 2.0 min (100% B) -> 3.8 min (100% B) -> 4 min (10% B).

Method E: Column: Phemonenex Synergi MAX-RP, 4µ 50 x 2.0 mm @ 40 C; Flow rate 0.8 ml/min. Solvent A: water (with 0.1% HCOOH). Solvent B: MeCN (with 0.1% HCOOH). Gradient: 0.2 min (10% B) -> 3.0 min (100% B) -> 4.5 min (100% B) -> 5.0 min (10% B).

Method F: Column: Synergy MAX-RP, 5µ 50 x 2.0 mm; Flow rate 0.8 ml/min. Solvent A: water (with 0.1% TFA). Solvent B: MeCN (with 0.1% TFA). Gradient: 0.0 min (10% B) -> 2.0 min (100% B) -> 3.8 min (100% B) -> 4.0 min (10% B).

Table 3. X-ray data collection and refinement statistics

Compound	**7**	**50**
Data Collection		
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions (Å)	a=74.74, b=78.65, c=129.26	a=76.21, b=78.25, c=129.68
Resolution (Å)	20.0 – 2.60 (2.69 – 2.60)	20.0 – 2.20 (2.28 – 2.20)
Total reflections	75,108	143,055
Unique reflections	23,678	39,332
Completeness (%)	99.1 (96.7)	97.8 (93.9)
R_{merge}	0.068 (0.311)	0.057 (0.422)
$I/\sigma(I)$	17.4 (2.6)	21.7 (2.5)
Refinement		
Reflections used	22,426	37,276
R_{cryst}	0.244 (0.42)	0.256 (0.37)
R_{free}	0.288 (0.47)	0.292 (0.40)
Average B-value ($Å^2$)	43.0	38.4
Number of protein atoms	4,320	4,298
Number of ligand atoms	74	76
Number of solvent atoms	82	114
r.m.s.d. bonds (Å)	0.007	0.007
r.m.s.d. angles (º)	1.08	1.10

Table 4. Enzyme Selectivity of Compounds 22, 51, and 62

Tyrosine Kinases			
Enzyme	Compd **22** IC_{50} (nM)	Compd **51** IC_{50} (nM)	Compd **62** IC_{50} (nM)
LCK	8	< 4	33
BTK	19	27	126
cFMS	37	26	Not determined
Tie2	285	127	221
JAK2	>25,000	3,400	Not determined
JAK3	>8,300	>1,000	>25,000
ZAP70	>5,400	>8,300	Not determined
EGFR	1,700	1,700	Not determined
Flt1	>1,000	45	Not determined
Flt4	120	5	Not determined
FgfRK	>1,000	>25,000	1,300
FgfRK2	>1,000	140	Not determined
Serine / Threonine Kinases			
P70S6	10,000	5,700	65,000
PKAα	>100,000	>100,000	>25,000
MSK1	>100,000	>100,000	52,000
CDK5	>100,000	>100,000	>100,000
ERK1	>100,000	>100,000	>100,000
JNK2	>100,000	>100,000	4,700

P38	>25,000	3,600	>100,000
Aurora2	116	>200	426
PIM1	>30,000	Not determined	7,800
PIM2	>25,000	Not determined	>25,000
PKBα	>100,000	>100,000	>100,000