

## Supporting material

### Understanding the Energetic Factors of type I Inhibitors Bound to c-Met Kinase: Experimental Studies and Quantum Mechanical Calculations

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**Table S1. Energy of various models in gas phase with M06-2X/6-31G+(d) methods (energy unit is AU except for salvation free energy, 1AU=627.51 kcal/mol )**

	Model 1	Model 2	Model 3	Model 4
<b>Solvation (Kcal/mol)</b>	<b>-18.31</b>	<b>-18.40</b>	<b>-20.23</b>	<b>-16.36</b>
<b>Lig optimized</b>	<b>-988.164526874</b>	<b>-988.182883510</b>	<b>-988.215660169</b>	<b>-972.184354788</b>
<b>complex</b>	<b>-2636.59270514</b>	<b>-2636.60071265</b>	<b>-2636.64094772</b>	<b>-2620.60285469</b>
<b>no Arg-1208</b>	<b>-2388.16974691</b>	<b>-2388.18795297</b>	<b>-2388.21734587</b>	<b>-2372.18300502</b>
<b>no Tyr-1230</b>	<b>-2250.64875057</b>	<b>-2250.65502458</b>	<b>-2250.69772422</b>	<b>-2234.65945852</b>
<b>no Asp-1222</b>	<b>-2388.16451492</b>	<b>-2388.17393269</b>	<b>-2388.21465334</b>	<b>-2372.17565145</b>
<b>No Met-1211</b>	<b>-2119.36377669</b>	<b>-2119.37035669</b>	<b>-2119.41151859</b>	<b>-2103.37435548</b>

Coordinates of complexes:

Ligand 1 + residues

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%nprocshared=4

%mem=2gb

# m062x/6-31+g(d) geom=connectivity

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58.45100000		
C(PDBName=C,ResName=LIG,ResNum=1)	27.68600000	9.32200000
59.84200000		
O(PDBName=O,ResName=LIG,ResNum=1)		28.61200000
9.74100000 60.54500000		
H(PDBName=H,ResName=LIG,ResNum=1)		27.08200000
8.71300000 57.80400000		
H(PDBName=H,ResName=LIG,ResNum=1)		28.38000000
7.74800000 58.54000000		
H(PDBName=H,ResName=LIG,ResNum=1)		28.72400000
9.37700000 57.95400000		
N(PDBName=N,ResName=LIG,ResNum=1)		26.40900000
9.34500000 60.21000000		
C(PDBName=C,ResName=LIG,ResNum=1)	25.97100000	9.81600000
61.52200000		
H(PDBName=H,ResName=LIG,ResNum=1)		25.65800000
9.14100000 59.56200000		
H(PDBName=H,ResName=LIG,ResNum=1)		26.82300000
10.23800000 62.09400000		
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10.61000000 61.41900000		
H(PDBName=H,ResName=LIG,ResNum=1)		25.55100000
8.98300000 62.11100000		
C(PDBName=C,ResName=LIG,ResNum=2)	14.72600000	16.46000000
62.75600000		
C(PDBName=C,ResName=LIG,ResNum=2)	15.83800000	16.66500000
61.72300000		
O(PDBName=O,ResName=LIG,ResNum=2)		16.21200000
15.72200000 61.01800000		
H(PDBName=H,ResName=LIG,ResNum=2)		14.48200000
17.33900000 63.35300000		
H(PDBName=H,ResName=LIG,ResNum=2)		13.81600000

16.12800000	62.23800000		
H(PDBName=H,ResName=LIG,ResNum=2)			15.02200000
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C(PDBName=C,ResName=LIG,ResNum=2)		17.33100000	18.29000000
60.62100000			
H(PDBName=H,ResName=LIG,ResNum=2)			16.03000000
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H(PDBName=H,ResName=LIG,ResNum=2)			18.32900000
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C(PDBName=C,ResName=LIG,ResNum=3)		22.75300000	14.25600000
62.03300000			
C(PDBName=C,ResName=LIG,ResNum=3)		21.83600000	14.59200000
60.86400000			
S(PDBName=S,ResName=LIG,ResNum=3)		22.08300000	13.52700000
59.45400000			
C(PDBName=C,ResName=LIG,ResNum=3)		21.21900000	12.05900000
60.01100000			
H(PDBName=H,ResName=LIG,ResNum=3)			22.61300000
14.96800000	62.85700000		
H(PDBName=H,ResName=LIG,ResNum=3)			22.56300000
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H(PDBName=H,ResName=LIG,ResNum=3)			23.81500000
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H(PDBName=H,ResName=LIG,ResNum=3)			20.15600000
12.24700000	60.20600000		
C(PDBName=C,ResName=LIG,ResNum=4)		22.50200000	19.31200000
58.57500000			
C(PDBName=C,ResName=LIG,ResNum=4)		21.39800000	19.83500000
57.66800000			
O(PDBName=O,ResName=LIG,ResNum=4)			21.00400000

20.99800000	57.78900000		
H(PDBName=H,ResName=LIG,ResNum=4)			23.48000000
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H(PDBName=H,ResName=LIG,ResNum=4)			22.48700000
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N(PDBName=N,ResName=LIG,ResNum=4)			20.90900000
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C(PDBName=C,ResName=LIG,ResNum=4)		19.80400000	19.32900000
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H(PDBName=H,ResName=LIG,ResNum=4)			19.66700000
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C(PDBName=C,ResName=LIG,ResNum=5)		14.45200000	13.95800000
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C(PDBName=C,ResName=LIG,ResNum=5)		15.66100000	14.10100000
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C(PDBName=C,ResName=LIG,ResNum=5)		16.09300000	13.03400000
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C(PDBName=C,ResName=LIG,ResNum=5)		17.19700000	13.15900000
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C(PDBName=C,ResName=LIG,ResNum=6)		16.10600000	12.87200000
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H(PDBName=H,ResName=LIG,ResNum=6)		18.53200000
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H(PDBName=H,ResName=LIG,ResNum=6)		19.10600000
16.82200000	58.60400000	
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Ligand 2 + residues

%chk=2.chk

%nprocshared=4

%mem=2gb

# m062x/6-31+g(d) geom=connectivity

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C(PDBName=C,ResName=LIG,ResNum=1)	27.96100000	8.75900000
58.45100000		
C(PDBName=C,ResName=LIG,ResNum=1)	27.68600000	9.32200000
59.84200000		
O(PDBName=O,ResName=LIG,ResNum=1)		28.61200000
9.74100000 60.54500000		
H(PDBName=H,ResName=LIG,ResNum=1)		27.08000000
8.71300000 57.80600000		
H(PDBName=H,ResName=LIG,ResNum=1)		28.37800000
7.74700000 58.54000000		
H(PDBName=H,ResName=LIG,ResNum=1)		28.72100000
9.37800000 57.95200000		
N(PDBName=N,ResName=LIG,ResNum=1)		26.40900000
9.34500000 60.21000000		
C(PDBName=C,ResName=LIG,ResNum=1)	25.97100000	9.81600000
61.52200000		
H(PDBName=H,ResName=LIG,ResNum=1)		25.65600000
9.13500000 59.56600000		

H(PDBName=H,ResName=LIG,ResNum=1)		26.82500000
10.22500000	62.10000000	
H(PDBName=H,ResName=LIG,ResNum=1)		25.22000000
10.61800000	61.41900000	
H(PDBName=H,ResName=LIG,ResNum=1)		25.53900000
8.98600000	62.10500000	
C(PDBName=C,ResName=LIG,ResNum=2)	14.72600000	16.46000000
62.75600000		
C(PDBName=C,ResName=LIG,ResNum=2)	15.83800000	16.66500000
61.72300000		
O(PDBName=O,ResName=LIG,ResNum=2)		16.21200000
15.72200000	61.01800000	
H(PDBName=H,ResName=LIG,ResNum=2)		14.48300000
17.34600000	63.34300000	
H(PDBName=H,ResName=LIG,ResNum=2)		13.81600000
16.12300000	62.24100000	
H(PDBName=H,ResName=LIG,ResNum=2)		15.01900000
15.65600000	63.44700000	
N(PDBName=N,ResName=LIG,ResNum=2)		16.35800000
17.89300000	61.64600000	
C(PDBName=C,ResName=LIG,ResNum=2)	17.33100000	18.29000000
60.62100000		
H(PDBName=H,ResName=LIG,ResNum=2)		16.06500000
18.63400000	62.26500000	
H(PDBName=H,ResName=LIG,ResNum=2)		17.45800000
17.47200000	59.88100000	
H(PDBName=H,ResName=LIG,ResNum=2)		16.98800000
19.19000000	60.08700000	
H(PDBName=H,ResName=LIG,ResNum=2)		18.31500000
18.49400000	61.07700000	
C(PDBName=C,ResName=LIG,ResNum=3)	22.75300000	14.25600000
62.03300000		
C(PDBName=C,ResName=LIG,ResNum=3)	21.83600000	14.59200000
60.86400000		
S(PDBName=S,ResName=LIG,ResNum=3)	22.08300000	13.52700000
59.45400000		
C(PDBName=C,ResName=LIG,ResNum=3)	21.21900000	12.05900000
60.01100000		
H(PDBName=H,ResName=LIG,ResNum=3)		22.61500000
14.97000000	62.85500000	
H(PDBName=H,ResName=LIG,ResNum=3)		22.55900000
13.25700000	62.44200000	
H(PDBName=H,ResName=LIG,ResNum=3)		23.81400000
14.29400000	61.75100000	

H(PDBName=H,ResName=LIG,ResNum=3)		20.77500000
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H(PDBName=H,ResName=LIG,ResNum=3)		21.30000000
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H(PDBName=H,ResName=LIG,ResNum=3)		21.64700000
11.65000000	60.93400000	
H(PDBName=H,ResName=LIG,ResNum=3)		20.15100000
12.24400000	60.18800000	
C(PDBName=C,ResName=LIG,ResNum=4)	22.50200000	19.31200000
58.57500000		
C(PDBName=C,ResName=LIG,ResNum=4)	21.39800000	19.83500000
57.66800000		
O(PDBName=O,ResName=LIG,ResNum=4)		21.00400000
20.99800000	57.78900000	
H(PDBName=H,ResName=LIG,ResNum=4)		23.48200000
19.49300000	58.11300000	
H(PDBName=H,ResName=LIG,ResNum=4)		22.48500000
19.85900000	59.52700000	
H(PDBName=H,ResName=LIG,ResNum=4)		22.42100000
18.24100000	58.78700000	
N(PDBName=N,ResName=LIG,ResNum=4)		20.90900000
18.98200000	56.76700000	
C(PDBName=C,ResName=LIG,ResNum=4)	19.80400000	19.32900000
55.86800000		
H(PDBName=H,ResName=LIG,ResNum=4)		21.21600000
18.01000000	56.70700000	
H(PDBName=H,ResName=LIG,ResNum=4)		19.68700000
18.55300000	55.09700000	
H(PDBName=H,ResName=LIG,ResNum=4)		18.85800000
19.43500000	56.42800000	
H(PDBName=H,ResName=LIG,ResNum=4)		19.99800000
20.29700000	55.37000000	
C(PDBName=C,ResName=LIG,ResNum=5)	13.12200000	13.97000000
55.66600000		
C(PDBName=C,ResName=LIG,ResNum=5)	14.45200000	13.95800000
56.42700000		
C(PDBName=C,ResName=LIG,ResNum=5)	15.66100000	14.10100000
55.52400000		
C(PDBName=C,ResName=LIG,ResNum=5)	16.09300000	13.03400000
54.73000000		
C(PDBName=C,ResName=LIG,ResNum=5)	16.36200000	15.30100000
55.45100000		

C(PDBName=C,ResName=LIG,ResNum=5) 53.89300000	17.19700000	13.15900000
C(PDBName=C,ResName=LIG,ResNum=5) 54.61700000	17.47300000	15.43700000
C(PDBName=C,ResName=LIG,ResNum=5) 53.84600000	17.88400000	14.35900000
O(PDBName=O,ResName=LIG,ResNum=5) 14.48300000 53.02400000		18.97800000
H(PDBName=H,ResName=LIG,ResNum=5) 13.86800000 56.35200000		12.27600000
H(PDBName=H,ResName=LIG,ResNum=5) 14.90500000 55.10800000		12.99400000
H(PDBName=H,ResName=LIG,ResNum=5) 13.14900000 54.94200000		13.07000000
H(PDBName=H,ResName=LIG,ResNum=5) 14.76600000 57.18800000		14.45100000
H(PDBName=H,ResName=LIG,ResNum=5) 13.01600000 57.00900000		14.54300000
H(PDBName=H,ResName=LIG,ResNum=5) 12.08700000 54.76600000		15.55400000
H(PDBName=H,ResName=LIG,ResNum=5) 16.15300000 56.05400000		16.04300000
H(PDBName=H,ResName=LIG,ResNum=5) 12.32500000 53.27000000		17.51700000
H(PDBName=H,ResName=LIG,ResNum=5) 16.38500000 54.57600000		18.00200000
H(PDBName=H,ResName=LIG,ResNum=5) 15.37200000 53.11500000		19.40000000
C(PDBName=C,ResName=LIG,ResNum=6) 60.01800000	15.39200000	10.70900000
N(PDBName=N,ResName=LIG,ResNum=6) 13.94900000 56.80700000		19.95200000
O(PDBName=O,ResName=LIG,ResNum=6) 9.04200000 58.46700000		24.00000000
C(PDBName=C,ResName=LIG,ResNum=6) 60.02200000	15.13900000	12.07900000
C(PDBName=C,ResName=LIG,ResNum=6) 57.28600000	19.05400000	13.01800000
C(PDBName=C,ResName=LIG,ResNum=6) 59.47300000	16.06500000	12.96200000
N(PDBName=N,ResName=LIG,ResNum=6) 15.95100000 56.64800000		20.94200000
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N(PDBName=N,ResName=LIG,ResNum=6)		21.51100000
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C(PDBName=C,ResName=LIG,ResNum=6)		17.50200000
58.91000000		11.09600000
C(PDBName=C,ResName=LIG,ResNum=6)		16.57600000
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N(PDBName=N,ResName=LIG,ResNum=6)		18.22900000
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C(PDBName=C,ResName=LIG,ResNum=6)		19.98000000
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C(PDBName=C,ResName=LIG,ResNum=6)		22.05500000
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C(PDBName=C,ResName=LIG,ResNum=6)		23.39500000
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C(PDBName=C,ResName=LIG,ResNum=6)		22.02900000
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C(PDBName=C,ResName=LIG,ResNum=6)		21.37300000
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H(PDBName=H,ResName=LIG,ResNum=6)		14.67200000
10.02100000	60.45300000	
H(PDBName=H,ResName=LIG,ResNum=6)		23.39000000
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H(PDBName=H,ResName=LIG,ResNum=6)		14.22300000
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H(PDBName=H,ResName=LIG,ResNum=6)		16.77900000
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16.59100000	58.81000000	

H(PDBName=H,ResName=LIG,ResNum=6)	20.43000000
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H(PDBName=H,ResName=LIG,ResNum=6)	21.97500000
12.97100000 54.20700000	
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12.81800000 55.94000000	
H(PDBName=H,ResName=LIG,ResNum=6)	25.09100000
11.20300000 57.43900000	
H(PDBName=H,ResName=LIG,ResNum=6)	21.50000000
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H(PDBName=H,ResName=LIG,ResNum=6)	20.33700000
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H(PDBName=H,ResName=LIG,ResNum=6)	19.04800000
12.03000000 56.82500000	

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87 101 1.0 88 1.5  
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89 90 1.5 102 1.0  
90 103 1.0  
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Ligand 3 + residues

%chk=3.chk

%nprocshared=4

%mem=2gb

# m062x/6-31+g(d) geom=connectivity

Title Card Required

0 1

C(PDBName=C,ResName=LIG,ResNum=1)

27.96100000

8.75900000

58.45100000		
C(PDBName=C,ResName=LIG,ResNum=1)	27.68600000	9.32200000
59.84200000		
O(PDBName=O,ResName=LIG,ResNum=1)		28.61200000
9.74100000 60.54500000		
H(PDBName=H,ResName=LIG,ResNum=1)		27.08700000
8.74600000 57.79500000		
H(PDBName=H,ResName=LIG,ResNum=1)		28.34500000
7.73400000 58.53700000		
H(PDBName=H,ResName=LIG,ResNum=1)		28.74700000
9.35700000 57.96700000		
N(PDBName=N,ResName=LIG,ResNum=1)		26.40900000
9.34500000 60.21000000		
C(PDBName=C,ResName=LIG,ResNum=1)	25.97100000	9.81600000
61.52200000		
H(PDBName=H,ResName=LIG,ResNum=1)		25.65500000
9.14000000 59.56500000		
H(PDBName=H,ResName=LIG,ResNum=1)		26.84000000
10.10400000 62.14800000		
H(PDBName=H,ResName=LIG,ResNum=1)		25.32300000
10.70500000 61.42300000		
H(PDBName=H,ResName=LIG,ResNum=1)		25.42000000
9.02100000 62.05200000		
C(PDBName=C,ResName=LIG,ResNum=2)	14.72600000	16.46000000
62.75600000		
C(PDBName=C,ResName=LIG,ResNum=2)	15.83800000	16.66500000
61.72300000		
O(PDBName=O,ResName=LIG,ResNum=2)		16.21200000
15.72200000 61.01800000		
H(PDBName=H,ResName=LIG,ResNum=2)		14.55200000
17.31600000 63.41000000		
H(PDBName=H,ResName=LIG,ResNum=2)		13.78800000
16.22200000 62.23600000		
H(PDBName=H,ResName=LIG,ResNum=2)		14.97200000
15.59100000 63.38400000		
N(PDBName=N,ResName=LIG,ResNum=2)		16.35800000
17.89300000 61.64600000		
C(PDBName=C,ResName=LIG,ResNum=2)	17.33100000	18.29000000
60.62100000		
H(PDBName=H,ResName=LIG,ResNum=2)		16.03700000
18.64200000 62.24200000		
H(PDBName=H,ResName=LIG,ResNum=2)		17.75900000
17.39900000 60.11000000		
H(PDBName=H,ResName=LIG,ResNum=2)		16.85600000

18.92200000	59.85200000		
H(PDBName=H,ResName=LIG,ResNum=2)			18.16900000
18.84400000	61.07600000		
C(PDBName=C,ResName=LIG,ResNum=3)		22.75300000	14.25600000
62.03300000			
C(PDBName=C,ResName=LIG,ResNum=3)		21.83600000	14.59200000
60.86400000			
S(PDBName=S,ResName=LIG,ResNum=3)		22.08300000	13.52700000
59.45400000			
C(PDBName=C,ResName=LIG,ResNum=3)		21.21900000	12.05900000
60.01100000			
H(PDBName=H,ResName=LIG,ResNum=3)			22.61500000
14.97100000	62.85500000		
H(PDBName=H,ResName=LIG,ResNum=3)			22.55900000
13.25700000	62.44200000		
H(PDBName=H,ResName=LIG,ResNum=3)			23.81400000
14.29300000	61.75100000		
H(PDBName=H,ResName=LIG,ResNum=3)			20.77500000
14.58300000	61.18700000		
H(PDBName=H,ResName=LIG,ResNum=3)			22.02200000
15.63400000	60.51600000		
H(PDBName=H,ResName=LIG,ResNum=3)			21.24500000
11.30900000	59.20600000		
H(PDBName=H,ResName=LIG,ResNum=3)			21.67900000
11.61400000	60.90000000		
H(PDBName=H,ResName=LIG,ResNum=3)			20.16200000
12.25600000	60.23300000		
C(PDBName=C,ResName=LIG,ResNum=4)		22.50200000	19.31200000
58.57500000			
C(PDBName=C,ResName=LIG,ResNum=4)		21.39800000	19.83500000
57.66800000			
O(PDBName=O,ResName=LIG,ResNum=4)			21.00400000
20.99800000	57.78900000		
H(PDBName=H,ResName=LIG,ResNum=4)			23.46900000
19.34600000	58.06000000		
H(PDBName=H,ResName=LIG,ResNum=4)			22.57500000
19.94800000	59.46800000		
H(PDBName=H,ResName=LIG,ResNum=4)			22.32200000
18.28000000	58.90200000		
N(PDBName=N,ResName=LIG,ResNum=4)			20.90900000
18.98200000	56.76700000		
C(PDBName=C,ResName=LIG,ResNum=4)		19.80400000	19.32900000
55.86800000			
H(PDBName=H,ResName=LIG,ResNum=4)			21.13700000

17.98500000	56.78900000		
H(PDBName=H,ResName=LIG,ResNum=4)			20.09000000
19.11800000	54.82500000		
H(PDBName=H,ResName=LIG,ResNum=4)			18.89800000
18.75300000	56.12300000		
H(PDBName=H,ResName=LIG,ResNum=4)			19.55600000
20.40500000	55.94500000		
C(PDBName=C,ResName=LIG,ResNum=5)		13.12200000	13.97000000
55.66600000			
C(PDBName=C,ResName=LIG,ResNum=5)		14.45200000	13.95800000
56.42700000			
C(PDBName=C,ResName=LIG,ResNum=5)		15.66100000	14.10100000
55.52400000			
C(PDBName=C,ResName=LIG,ResNum=5)		16.09300000	13.03400000
54.73000000			
C(PDBName=C,ResName=LIG,ResNum=5)		16.36200000	15.30100000
55.45100000			
C(PDBName=C,ResName=LIG,ResNum=5)		17.19700000	13.15900000
53.89300000			
C(PDBName=C,ResName=LIG,ResNum=5)		17.47300000	15.43700000
54.61700000			
C(PDBName=C,ResName=LIG,ResNum=5)		17.88400000	14.35900000
53.84600000			
O(PDBName=O,ResName=LIG,ResNum=5)			18.97800000
14.48300000	53.02400000		
H(PDBName=H,ResName=LIG,ResNum=5)			12.27500000
13.86800000	56.35200000		
H(PDBName=H,ResName=LIG,ResNum=5)			12.99400000
14.90500000	55.10800000		
H(PDBName=H,ResName=LIG,ResNum=5)			13.07000000
13.14900000	54.94300000		
H(PDBName=H,ResName=LIG,ResNum=5)			14.45000000
14.76600000	57.18700000		
H(PDBName=H,ResName=LIG,ResNum=5)			14.54400000
13.01500000	57.00700000		
H(PDBName=H,ResName=LIG,ResNum=5)			15.56000000
12.08400000	54.77300000		
H(PDBName=H,ResName=LIG,ResNum=5)			16.04700000
16.15200000	56.05600000		
H(PDBName=H,ResName=LIG,ResNum=5)			17.52500000
12.32000000	53.28100000		
H(PDBName=H,ResName=LIG,ResNum=5)			18.00600000
16.38300000	54.58400000		
H(PDBName=H,ResName=LIG,ResNum=5)			19.27900000

15.42000000	52.97300000		
C(PDBName=C,ResName=LIG,ResNum=6)		15.32900000	10.70800000
59.51500000			
C(PDBName=C,ResName=LIG,ResNum=6)		19.98200000	13.98700000
56.79700000			
O(PDBName=O,ResName=LIG,ResNum=6)			23.99700000
9.05100000	58.47200000		
C(PDBName=C,ResName=LIG,ResNum=6)		15.13400000	12.07000000
59.73200000			
N(PDBName=N,ResName=LIG,ResNum=6)			19.06400000
13.08500000	57.19000000		
C(PDBName=C,ResName=LIG,ResNum=6)		16.08500000	12.99200000
59.30000000			
N(PDBName=N,ResName=LIG,ResNum=6)			21.15400000
15.97800000	56.74300000		
C(PDBName=C,ResName=LIG,ResNum=6)		17.24000000	12.55000000
58.64800000			
C(PDBName=C,ResName=LIG,ResNum=6)		21.67400000	15.11600000
55.85900000			
C(PDBName=C,ResName=LIG,ResNum=6)		17.43100000	11.17900000
58.43000000			
C(PDBName=C,ResName=LIG,ResNum=6)		16.47700000	10.26300000
58.86200000			
C(PDBName=C,ResName=LIG,ResNum=6)		18.25000000	13.50500000
58.17600000			
C(PDBName=C,ResName=LIG,ResNum=6)		18.36600000	14.82000000
58.74600000			
N(PDBName=N,ResName=LIG,ResNum=6)			19.26200000
15.72400000	58.35100000		
C(PDBName=C,ResName=LIG,ResNum=6)		20.09600000	15.32000000
57.36900000			
N(PDBName=N,ResName=LIG,ResNum=6)			20.97600000
13.90400000	55.82600000		
C(PDBName=C,ResName=LIG,ResNum=6)		21.31700000	12.70700000
55.07500000			
C(PDBName=C,ResName=LIG,ResNum=6)		22.05200000	11.73200000
55.99800000			
C(PDBName=C,ResName=LIG,ResNum=6)		23.39200000	11.95000000
56.32300000			
C(PDBName=C,ResName=LIG,ResNum=6)		24.04800000	11.04600000
57.16400000			
C(PDBName=C,ResName=LIG,ResNum=6)		23.36300000	9.93800000
57.66000000			
C(PDBName=C,ResName=LIG,ResNum=6)		22.02600000	9.71800000

57.32400000		
C(PDBName=C,ResName=LIG,ResNum=6)	21.37000000	10.62100000
56.48900000		
H(PDBName=H,ResName=LIG,ResNum=6)		14.58600000
9.99100000	59.85700000	
H(PDBName=H,ResName=LIG,ResNum=6)		23.38100000
8.36700000	58.83000000	
H(PDBName=H,ResName=LIG,ResNum=6)		14.24200000
12.41900000	60.24700000	
H(PDBName=H,ResName=LIG,ResNum=6)		15.91900000
14.05800000	59.48400000	
H(PDBName=H,ResName=LIG,ResNum=6)		18.32800000
10.83500000	57.91200000	
H(PDBName=H,ResName=LIG,ResNum=6)		16.62900000
9.20000000	58.69100000	
H(PDBName=H,ResName=LIG,ResNum=6)		20.37400000
12.25000000	54.67800000	
H(PDBName=H,ResName=LIG,ResNum=6)		21.94100000
12.97300000	54.19400000	
H(PDBName=H,ResName=LIG,ResNum=6)		23.92500000
12.82000000	55.94600000	
H(PDBName=H,ResName=LIG,ResNum=6)		25.08700000
11.21200000	57.44600000	
H(PDBName=H,ResName=LIG,ResNum=6)		21.49300000
8.85300000	57.70600000	
H(PDBName=H,ResName=LIG,ResNum=6)		20.31700000
10.46700000	56.24000000	
H(PDBName=H,ResName=LIG,ResNum=6)		22.52400000
15.32000000	55.22200000	
H(PDBName=H,ResName=LIG,ResNum=6)		17.69600000
15.13000000	59.56900000	

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Ligand 4 + residues

%chk=4.chk

%nprocshared=4

%mem=2gb

# m062x/6-31+g(d) geom=connectivity

Title Card Required

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C(PDBName=C,ResName=LIG,ResNum=1)	27.96100000	8.75900000
58.45100000		
C(PDBName=C,ResName=LIG,ResNum=1)	27.68600000	9.32200000
59.84200000		
O(PDBName=O,ResName=LIG,ResNum=1)		28.61200000
9.74100000 60.54500000		
H(PDBName=H,ResName=LIG,ResNum=1)		27.09100000
8.76000000 57.78900000		
H(PDBName=H,ResName=LIG,ResNum=1)		28.33000000
7.72800000 58.53600000		
H(PDBName=H,ResName=LIG,ResNum=1)		28.75700000
9.34800000 57.97200000		
N(PDBName=N,ResName=LIG,ResNum=1)		26.40900000
9.34500000 60.21000000		
C(PDBName=C,ResName=LIG,ResNum=1)	25.97100000	9.81600000
61.52200000		
H(PDBName=H,ResName=LIG,ResNum=1)		25.65500000
9.14700000 59.56300000		
H(PDBName=H,ResName=LIG,ResNum=1)		26.84200000
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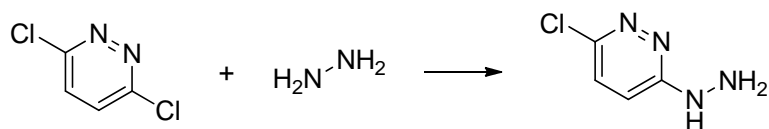
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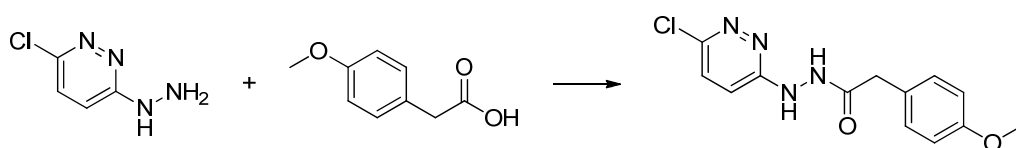
## Experiment Section

### Details of synthesis route for four ligands

#### Model ligand 1

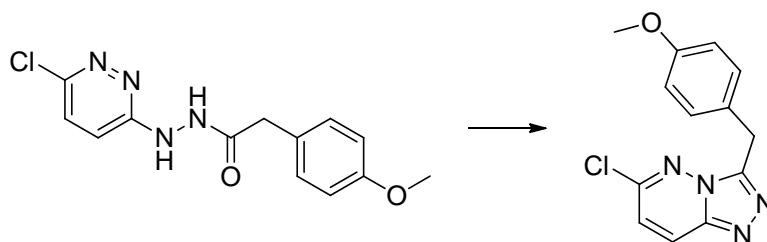


A solution of 3,6-dichloropyridazine (1 g, 6.76 mmol) and 85% hydrazine hydrate (846 mg, 13.52 mmol) in ethanol (30 ml) was heated to reflux for 1 h. The solvent was concentrated in vacuum and purified by flash chromatography (35:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide the 3-chloro-6-hydrazinylpyridazine (963 mg, 98.9%) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.26 (s, 1H), 7.43 (d, J = 9.4 Hz, 1H), 7.09 (d, J = 9.4 Hz, 1H), 4.64 (s, 2H) ; MS (ESI) m/z 145 (M + H)<sup>+</sup>.

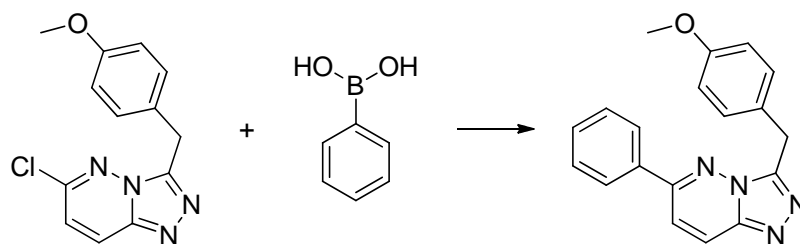


A solution of 3-chloro-6-hydrazinylpyridazine (500 mg, 3.47 mmol), 2-(4-methoxyphenyl)acetic acid (692 mg, 4.17 mmol), HATU (1.98 g, 5.21 mmol) and DIPEA (1.35 g, 10.42 mmol) in N,N-dimethylformamide (5 ml) was under microwave at 60 °C for 30 min. Then diluting with water (40 ml), the reaction mixture was extracted with dichloromethane (40 ml × 3). The organic phase was evaporated to dryness. The residue was purified by flash chromatography (10:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide

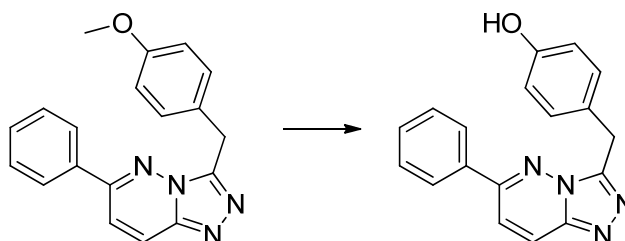
N'-(6-chloropyridazin-3-yl)-2-(4-methoxyphenyl)acetohydrazide (564 mg, 55.6 %) as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  10.18 (s, 1H), 9.15 (s, 1H), 7.53 (d,  $J = 9.3$  Hz, 1H), 7.23 (d,  $J = 8.5$  Hz, 2H), 6.93 (d,  $J = 9.4$  Hz, 1H), 6.88 (d,  $J = 8.6$  Hz, 2H), 3.73 (s, 3H), 3.46 (s, 2H) ; MS (ESI)  $m/z$  293 ( $M + H$ ) $^+$ .



A solution of N'-(6-chloropyridazin-3-yl)-2-(4-methoxyphenyl)acetohydrazide (262 mg, 0.90 mmol) and p-toluenesulfonic acid monohydrate (205 mg, 1.08 mmol) in methanol (5 ml) was heated to reflux for 4 h. Diluting with water (30 ml), the reaction mixture was extracted with dichloromethane (30 ml  $\times$  3). The organic phase was evaporated to dryness. The residue was purified by flash chromatography (15:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) to provide 6-chloro-3-(4-methoxybenzyl)-[1,2,4]triazolo[4,3-b]pyridazine (196 mg, 79.7%) as a white solid.  $^1\text{H}$  NMR (400 MHz, DMSO)  $\delta$  10.18 (s, 1H), 9.15 (s, 1H), 7.53 (d,  $J = 9.3$  Hz, 1H), 7.23 (d,  $J = 8.5$  Hz, 2H), 6.93 (d,  $J = 9.4$  Hz, 1H), 6.88 (d,  $J = 8.6$  Hz, 2H), 3.73 (s, 3H), 3.46 (s, 2H) ; MS (ESI)  $m/z$  275 ( $M + H$ ) $^+$ .



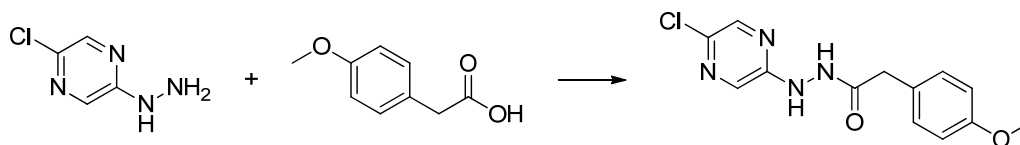
A solution of 6-chloro-3-(4-methoxybenzyl)-[1,2,4]triazolo[4,3-b]pyridazine (100 mg, 0.36 mmol), phenylboronic acid (67 mg, 0.55 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (21 mg, 0.018 mmol) and potassium carbonate (151 mg, 1.09 mmol) in 1,4-dioxane:ethanol:water(2.5ml, 2:2:1, v/v/v) in a microwave tube was flushed with N<sub>2</sub> for 5 mins then sealed. The tube was placed in the microwave cavity and heated at 160 °C for 30 min. Then the reaction mixture was evaporated to dryness. The residue was purified by flash chromatography (15:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide 3-(4-methoxybenzyl)-6-phenyl-[1,2,4]triazolo[4,3-b]pyridazine (96 mg, 83.2 %) as a colorless solid. <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.43 (d, J = 9.8 Hz, 1H), 8.12 (m, 2H), 7.95 (d, J = 9.8 Hz, 1H), 7.68 – 7.54 (m, 3H), 7.33 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.52 (s, 2H), 3.70 (s, 3H) ; MS (ESI) m/z 317 (M + H)<sup>+</sup>.



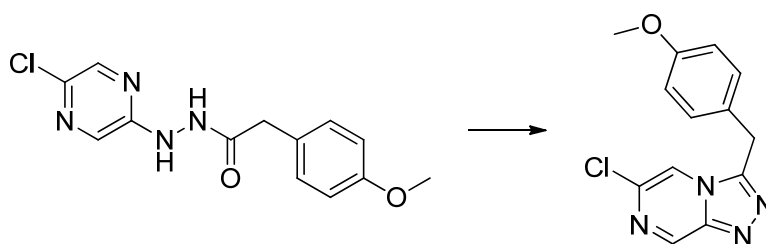
A solution of

3-(4-methoxybenzyl)-6-phenyl-[1,2,4]triazolo[4,3-b]pyridazine (63 mg, 0.20 mmol) in anhydrous dichloromethane (5 ml) was cooled to -78 °C and stirred for 30 min. BBr<sub>3</sub> in dichloromethane (1 mol/L, 0.40 ml, 0.40 mmol) was added by drops over 10 min. When the dropping was finished, the reaction mixture was stirred at -78 °C for 30 min then heated to room temperature for 1 h. The reaction mixture was cooled to -78 °C then methanol (5 ml) was added by drops over 20 min. The reaction mixture was heated to room temperature and evaporated to dryness. The residue was purified by flash chromatography (10:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide 4-((6-phenyl-[1,2,4]triazolo[4,3-b]pyridazin-3-yl)methyl)phenol (43 mg, 71.4 %) as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.48 (d, J = 9.8 Hz, 1H), 8.19 – 8.09(m, 2H), 8.05 (d, J = 9.9 Hz, 1H), 7.68 – 7.57 (m, 3H), 7.21 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 8.4 Hz, 2H), 4.49 (s, 2H); MS (ESI) m/z 303 (M + H)<sup>+</sup>; HRMS Calcd for C<sub>18</sub>H<sub>15</sub>N<sub>4</sub>O: 303.1246. Found: 303.1223.

## Model ligand 2

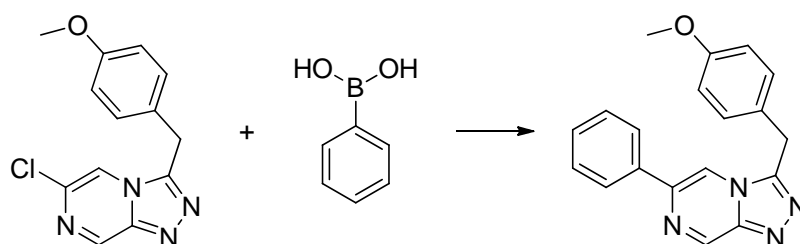


A solution of 2-chloro-5-hydrazinylpyrazine (500 mg, 3.47 mmol), 2-(4-methoxyphenyl)acetic acid (692 mg, 4.17 mmol), HATU (1.98 g, 5.21 mmol) and DIPEA (1.35 g, 10.41 mmol) in N,N-dimethylformamide (6 ml) in a microwave tube was sealed. The tube was placed in the microwave cavity and heated at 160 °C for 30 min. Then diluting with water (40 ml), the reaction mixture was extracted with dichloromethane (40 ml  $\times$  3). The organic phase was evaporated to dryness. The residue was purified by flash chromatography (10:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide N'-(5-chloropyrazin-2-yl)-2-(4-methoxyphenyl)acetohydrazide (892 mg, 88.3 %) as a light yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.08 (s, 1H), 7.77 (s, 1H), 7.49 (s, 1H), 7.24 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 3.2 Hz, 1H), 3.82 (s, 3H), 3.63 (s, 2H); MS (ESI) m/z 293 (M + H)<sup>+</sup>.



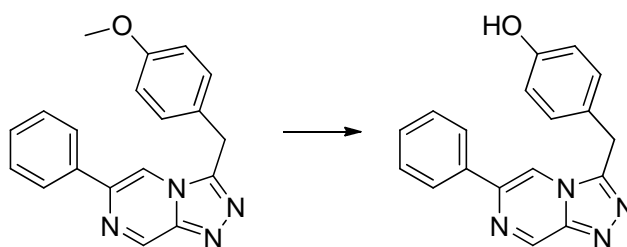
A solution of N'-(5-chloropyrazin-2-yl)-2-(4-methoxyphenyl)acetohydrazide (400 mg,

1.37 mmol) in acetic acid (5 ml) in a microwave tube was sealed. The tube was placed in the microwave cavity and heated at 180 °C for 2 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography (15:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide 6-chloro-3-(4-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyrazine (200 mg, 53.2%) as a pale yellow liquid. <sup>1</sup>H NMR (400 MHz, DMSO) δ 9.30 (d, J = 1.5 Hz, 1H), 8.90 (d, J = 1.5 Hz, 1H), 7.26 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.50 (s, 2H), 3.71 (s, 3H); MS (ESI) m/z 275 (M + H)<sup>+</sup>.



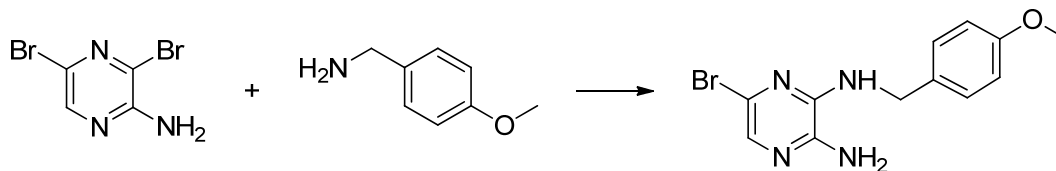
A solution of 6-chloro-3-(4-methoxybenzyl)-[1,2,4]triazolo[4,3-a]pyrazine (150 mg, 0.55 mmol), phenylboronic acid (100 mg, 0.82 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (32 mg, 0.027 mmol) and potassium carbonate (227 mg, 1.64 mmol) in 1,4-dioxane:ethanol:water(5ml, 2:2:1, v/v/v) in a microwave tube was flushed with N<sub>2</sub> for 5 mins then sealed. The tube was placed in the microwave cavity and heated at 160 °C for 30 min. Then the reaction mixture was evaporated to dryness. The residue was purified by flash chromatography (15:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide

3-(4-methoxybenzyl)-6-phenyl-[1,2,4]triazolo[4,3-a]pyrazine (65 mg, 37.6 %) as a colorless solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.42 (d,  $J = 1.5$  Hz, 1H), 7.91 (d,  $J = 1.6$  Hz, 1H), 7.78 (dd,  $J = 8.1, 1.5$  Hz, 2H), 7.50 – 7.42 (m, 3H), 7.21 (d,  $J = 8.7$  Hz, 2H), 6.89 (d,  $J = 8.7$  Hz, 2H), 4.58 (s, 2H), 3.79 (s, 3H); MS (ESI)  $m/z$  317 ( $\text{M} + \text{H}$ ) $^+$ .

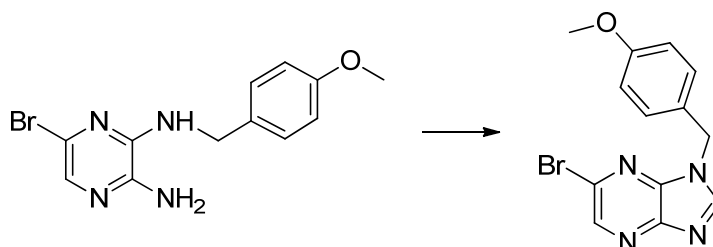


A solution of 3-(4-methoxybenzyl)-6-phenyl-[1,2,4]triazolo[4,3-a]pyrazine (50 mg, 0.16 mmol) in anhydrous dichloromethane (5 ml) was cooled to  $-78$  °C and stirred for 30 min.  $\text{BBr}_3$  in dichloromethane (1 mol/L, 0.32 ml, 0.32 mmol) was added by drops. When the dropping was finished, the reaction mixture was stirred at  $-78$  °C for 30 min then heated to room temperature for 1 h. The reaction mixture was cooled to  $-78$  °C then methanol (5 ml) was added by drops. When finished, the reaction mixture was heated to room temperature then evaporated to dryness. The residue was purified by flash chromatography (10:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) to provide 4-((6-phenyl-[1,2,4]triazolo[4,3-a]pyrazin-3-yl)methyl)phenol (32 mg, 67.0 %) as a light yellow solid.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.39 (s, 1H), 7.91 (s, 1H), 7.83 – 7.72 (m, 2H), 7.56 – 7.38 (m, 3H), 7.13 (d,  $J = 7.8$  Hz, 2H), 6.82 (d,  $J = 7.9$  Hz, 2H), 4.55 (s, 2H); MS (ESI)  $m/z$  303 ( $\text{M} + \text{H}$ ) $^+$ ; HRMS Calcd for  $\text{C}_{18}\text{H}_{14}\text{N}_4\text{ONa}$ : 325.1065. Found: 325.1078.

### Model ligand 3

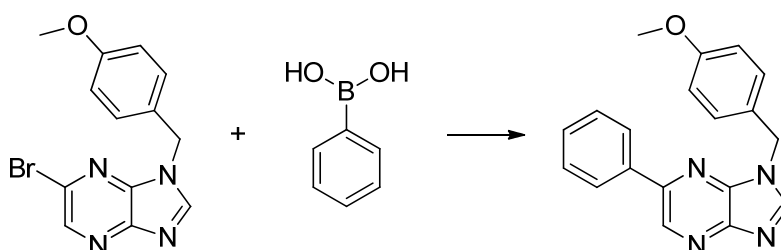


A solution of 3,5-dibromopyrazin-2-amine (1.00 g, 3.99 mmol) and (4-methoxyphenyl)methanamine (1.09 g, 7.97 mmol) in Butan-1-ol (8 ml) in a microwave tube was sealed. The tube was placed in the microwave cavity and heated at 220 °C for 1 h. The reaction mixture was condensed under reduced pressure, dissolved in ethyl acetate (60 ml), washed with brine, extracted with ethyl acetate (60 ml  $\times$  3), organics were pooled, dried over sodium sulfate, filtered, after condensation under vacuum, the residue was purified by flash chromatography (15:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide 6-bromo-N<sup>2</sup>-(4-methoxybenzyl)pyrazine-2,3-diamine (844 mg, 68.7%) as a light yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.36 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 8.6 Hz, 1H), 4.74 (d, J = 5.5 Hz, 2H), 3.81 (s, 3H); MS (ESI) m/z 309 (M + H)<sup>+</sup>.



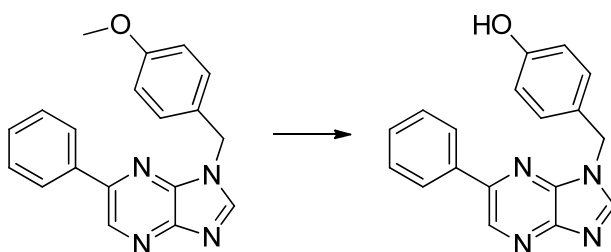


A solution of 6-bromo- $N^2$ -(4-methoxybenzyl)pyrazine-2,3-diamine (700 mg, 2.27 mmol) in trimethoxymethane (10 ml, 0.712 mmol) was refluxed for 4 h. The starting material was disappeared completely, monitoring by TLC. Then toluene (20 ml) was added after evaporation of trimethoxymethane, and the solution was refluxed for 18 h, then evaporated to dryness. The residue was purified by flash chromatography (20:1  $\text{CH}_2\text{Cl}_2/\text{MeOH}$ ) to provide 6-bromo-1-(4-methoxybenzyl)-1*H*-imidazo[4,5-*b*]pyrazine (420 mg, 58.1 %) as a white solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.63 (s, 1H), 8.21 (s, 1H), 7.29 (d,  $J = 8.7$  Hz, 2H), 6.91 (d,  $J = 8.7$  Hz, 2H), 5.37 (s, 2H), 3.81 (s, 3H) ; MS (ESI)  $m/z$  319 ( $\text{M} + \text{H}$ ) $^+$ .



A solution of 6-bromo-1-(4-methoxybenzyl)-1*H*-imidazo[4,5-*b*]pyrazine (219 mg, 0.69 mmol), phenylboronic acid (126 mg, 1.03 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (40 mg, 0.034 mmol) and potassium carbonate (286 mg, 2.07 mmol) in 1,4-dioxane:ethanol:water (5ml, 2:2:1, v/v/v) in a microwave tube was flushed with  $\text{N}_2$  for 5 mins then sealed. The tube was placed in the microwave cavity and heated at 160  $^\circ\text{C}$  for 30 min. Then the reaction mixture was evaporated to dryness. The residue was purified by flash

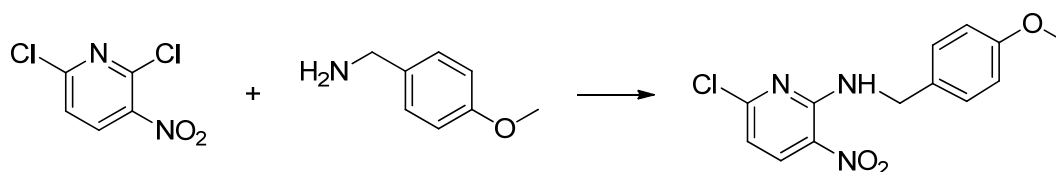
chromatography (20:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide 1-(4-methoxybenzyl)-6-phenyl-1*H*-imidazo[4,5-*b*]pyrazine (172 mg, 79.0 %) as a colorless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.03 (s, 1H), 8.26 (s, 1H), 8.13 - 8.08 (m, 2H), 7.57 - 7.51 (m, 2H), 7.48 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.38 - 7.32 (m, 2H), 6.93 - 6.87 (m, 2H), 5.45 (s, 2H), 3.80 (s, 3H); MS (ESI) *m/z* 317 (M + H)<sup>+</sup>.



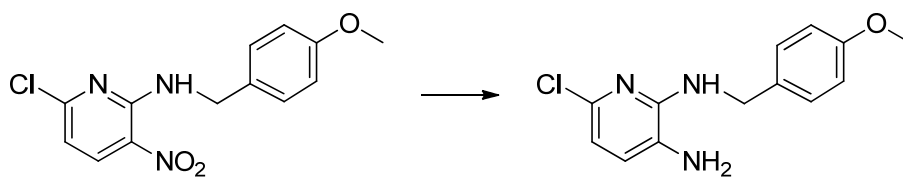
A solution of 1-(4-methoxybenzyl)-6-phenyl-1*H*-imidazo[4,5-*b*]pyrazine (100 mg, 0.32 mmol) in anhydrous dichloromethane (5 ml) was cooled to -78°C and stirred for 30 min. BBr<sub>3</sub> in dichloromethane (1 mol/L, 0.64 ml, 0.64 mmol) was added by drops. When the dropping was finished, the reaction mixture was stirred at -78°C for 30 min then heated to room temperature for 1 h. The reaction mixture was cooled to -78°C then methanol (5 ml) was added by drops. When finished, the reaction mixture was heated to room temperature then evaporated to dryness. The residue was purified by flash chromatography (15:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide 4-((6-phenyl-1*H*-imidazo[4,5-*b*]pyrazin-1-yl)methyl)phenol (82 mg, 85.8 %) as a colorless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.49 (s, 1H), 9.14 (s, 1H), 8.90 (s, 1H), 8.20(d, *J* = 7.5 Hz, 2H), 7.53 (dt, *J* = 28.7, *J* =

7.4 Hz, 3H), 7.32 (d, J = 8.4 Hz, 2H), 6.73 (J = 8.5 Hz, 2H), 5.45 (s, 2H) ;  
MS (ESI) m/z 303 (M + H)<sup>+</sup>; HRMS Calcd for C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>ONa: 325.1065.  
Found: 325.1059.

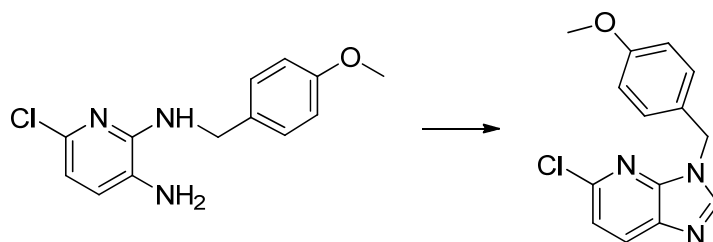
#### Model ligand 4



To a stirred solution of 2,6, dichloro-3-nitropyridine (1.00 g, 5.21 mmol) and potassium carbonate (864 mg, 6.25 mmol) in ethanol (20 ml) was added (4-methoxyphenyl)methanamine (1.07 g, 7.81 mmol) by drops and the reaction stirred for 12 h at 40°C, then evaporated to dryness. The resulting mixture was diluted with water (60 ml) and extracted with dichloromethane (60 ml × 3). The organic layer was dried over sodium sulfate, filtered and evaporated to dryness. The residue was purified by flash chromatography (50:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide 6-chloro-N<sup>2</sup>-(4-methoxybenzyl)-3-nitropyridin-2-amine (550 mg, 36.0%) as a yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.54 (s, 1H), 8.36 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.65 (d, J = 8.6 Hz, 1H), 4.74 (d, J = 5.5 Hz, 2H), 3.81 (s, 3H) ; MS (ESI) m/z 294 (M + H)<sup>+</sup>.

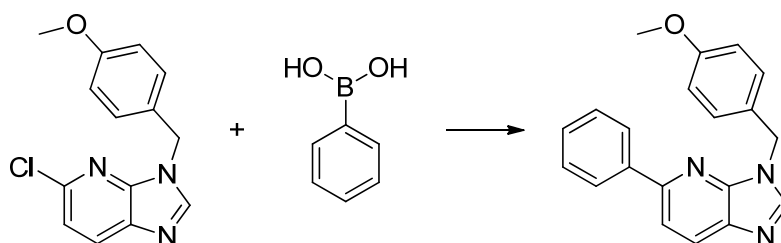


To a stirred solution of 6-chloro-N<sup>2</sup>-(4-methoxybenzyl)-3-nitropyridin-2-amine (450 mg, 1.54 mmol) and potassium carbonate (864 mg, 6.25 mmol) in toluene (5 ml) and water (5 ml) was added Ammonium formate (968 mg, 15.36 mmol) and iron powder (686 mg, 12.28 mmol). The reaction mixture was heated to reflux for 16 h. Then the iron powder was filtered off and the solution was diluted with water (30 ml), then the reaction mixture was extracted with ethyl acetate (30 ml × 3). The organic phase was evaporated to dryness. The residue was purified by flash chromatography (20:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide 6-chloro-N<sup>2</sup>-(4-methoxybenzyl)pyridine-2,3-diamine (330 mg, 81.7%) as a colorless liquid. <sup>1</sup>H NMR (400 MHz, DMSO) δ 7.26 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.69 (d, J = 7.7 Hz, 1H), 6.36 (d, J = 7.7 Hz, 1H), 6.31 (s, 0H), 6.31 (t, J = 5.6 Hz, 1H), 4.87 (s, 2H), 4.42 (d, J = 5.6 Hz, 1H), 3.72 (s, 2H) ; MS (ESI) m/z 229 (M + H)<sup>+</sup>.



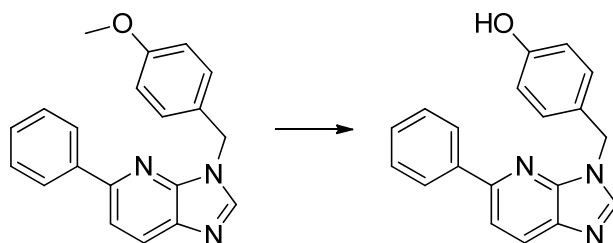
A solution of 6-chloro-N<sup>2</sup>-(4-methoxybenzyl)pyridine-2,3-diamine (200

mg, 0.76 mmol) in trimethoxymethane (5 ml) was refluxed for 4 h. The starting material was disappeared completely, monitoring by TLC. Then toluene (25 ml) was added after evaporation of trimethoxymethane, and the solution was refluxed for 18 h, then evaporated to dryness. The residue was purified by flash chromatography (25:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide 5-chloro-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-*b*]pyridine (160 mg, 77.1 %) as a white solid. <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.62 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.8 Hz, 2H), 6.91(d, J = 8.8 Hz, 3H), 5.39 (s, 2H), 3.71 (s, 3H) ; MS (ESI) m/z 229 (M + H)<sup>+</sup>.



A solution of 5-chloro-3-(4-methoxybenzyl)-3*H*-imidazo[4,5-*b*]pyridine (120mg, 0.44 mmol), phenylboronic acid (80 mg, 0.66 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (25 mg, 0.022 mmol) and potassium carbonate (182 mg, 1.32 mmol) in 1,4-dioxane:ethanol:water(10ml, 2:2:1, v/v/v) in a microwave tube was flushed with N<sub>2</sub> for 5 mins then sealed. The tube was placed in the microwave cavity and heated at 160°C for 30 min. Then the reaction mixture was evaporated to dryness. The residue was purified by flash

chromatography (20:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide 3-(4-methoxybenzyl)-5-phenyl-3*H*-imidazo[4,5-*b*]pyridine (110 mg, 79.7 %) as a colorless solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.15 (d, J = 8.4 Hz, 1H), 8.13 – 8.09 (m, 3H), 7.74 (d, J = 8.4 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.43 (dt, J = 9.4, 4.3 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.46 (s, 2H), 3.78 (s, 3H) ; MS (ESI) m/z 316 (M + H)<sup>+</sup>.



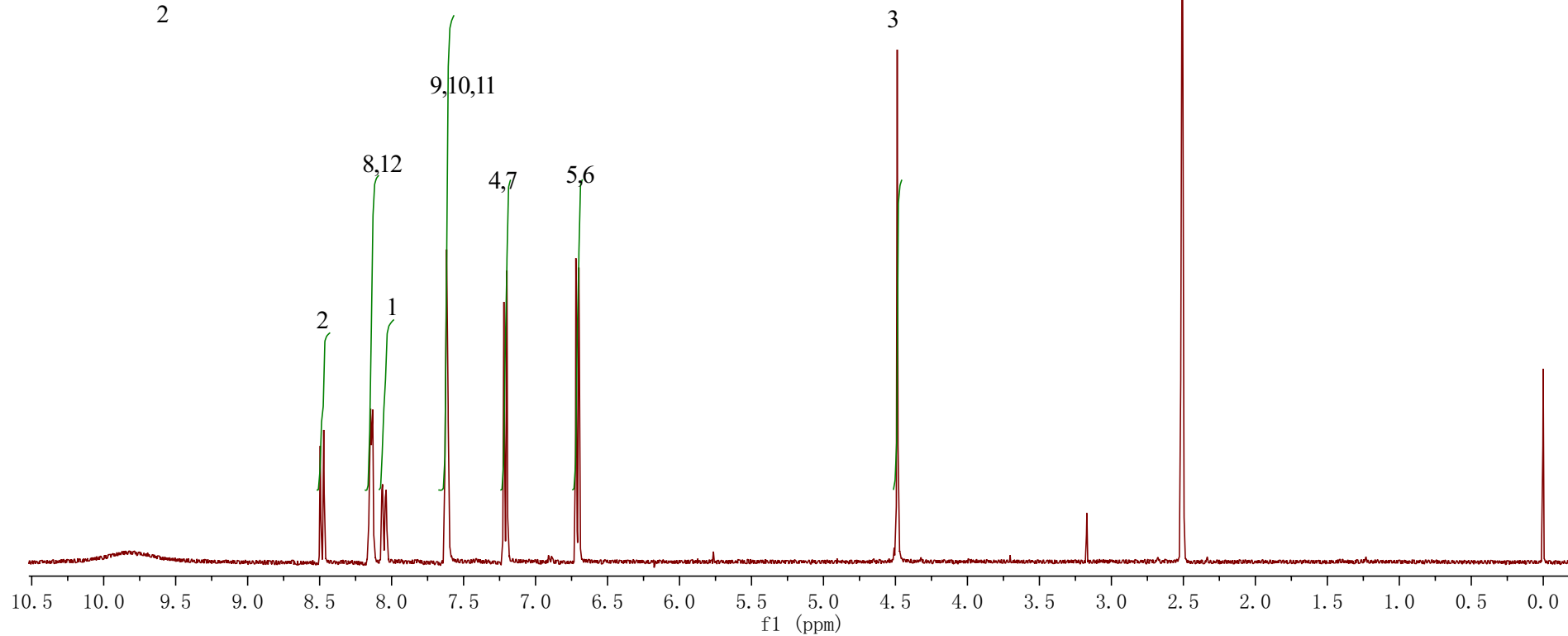
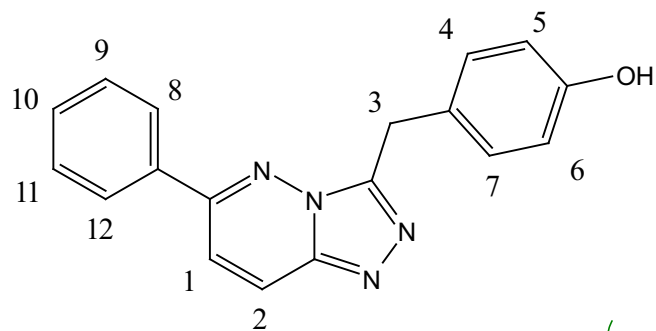
A solution of 3-(4-methoxybenzyl)-5-phenyl-3*H*-imidazo[4,5-*b*]pyridine (80 mg, 0.25 mmol) in anhydrous dichloromethane (5 ml) was cooled to -78°C and stirred for 30 min. BBr<sub>3</sub> in dichloromethane (1 mol/L, 0.51 ml, 0.51 mmol) was added by drops. When the dropping was finished, the reaction mixture was stirred at -78°C for 30 min then heated to room temperature for 1 h. The reaction mixture was cooled to -78°C then methanol (5 ml) was added by drops. When finished, the reaction mixture was heated to room temperature then evaporated to dryness. The residue was purified by flash chromatography (15:1 CH<sub>2</sub>Cl<sub>2</sub>/MeOH) to provide 4-((5-phenyl-3*H*-imidazo[4,5-*b*]pyridin-3-yl)methyl)phenol (47 mg, 61.5 %) as a light yellow solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.45 (s, 1H), 8.58 (s, 1H), 8.20 – 8.16(m, 2H), 8.14(d, J = 8.4 Hz, 1H), 7.88 (d, J

= 8.4 Hz, 1H), 7.48 (dt, J = 36.3 Hz, J = 7.4 Hz, 3H), 7.31 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 5.43 (s, 2H) ; MS (ESI) m/z 302 (M + H)<sup>+</sup>;  
HRMS Calcd for C<sub>19</sub>H<sub>16</sub>N<sub>3</sub>O: 302.1293. Found: 302.1306.

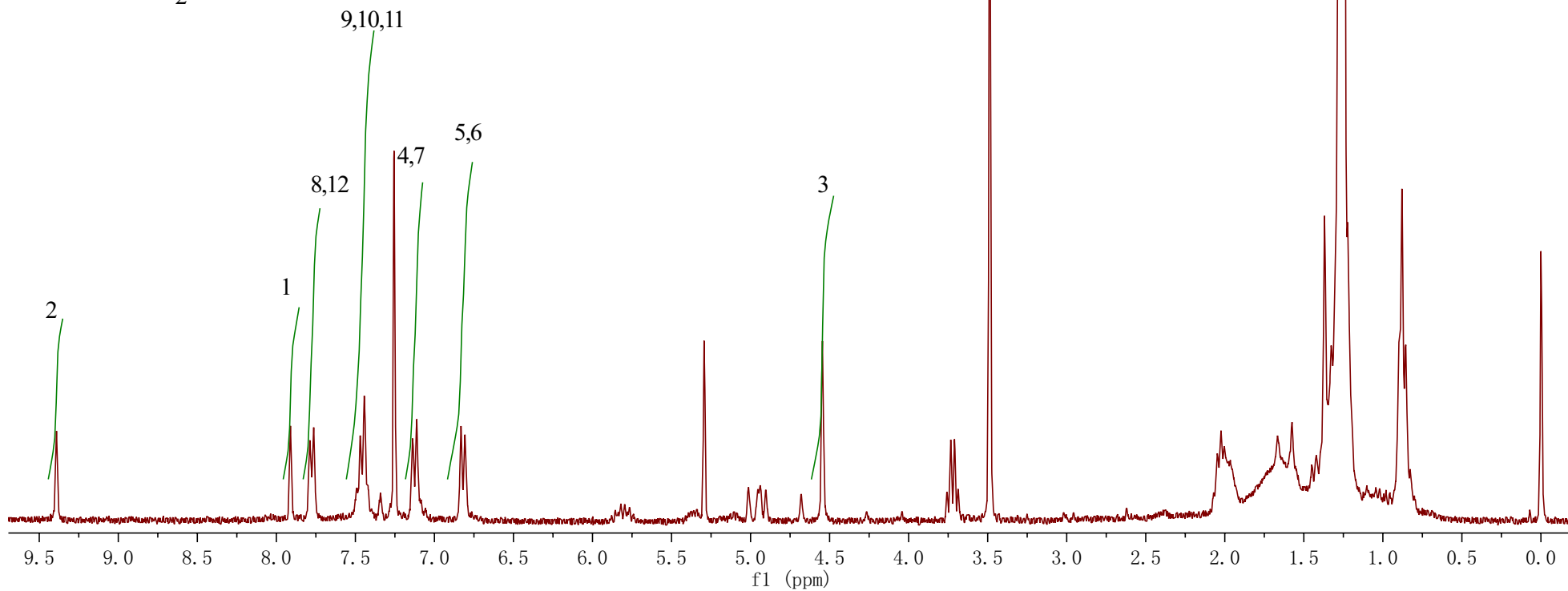
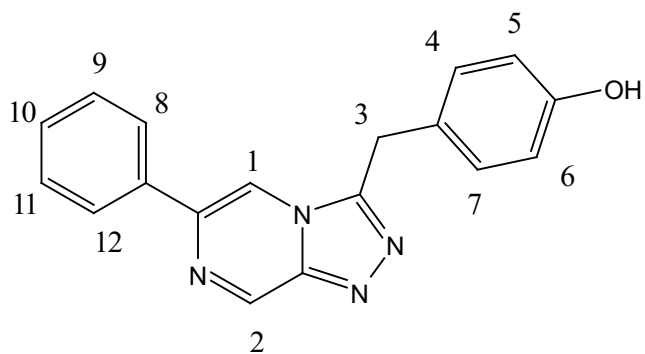
### **Enzymatic assay**

The c-Met kinase activities were evaluated according to the known protocol. Briefly, in enzyme-linked-immunosorbent assay (ELISA), 20 µg/mL Poly (Glu, Tyr) 4:1 (Sigma) was pre-coated as a substrate in 96-well plates. 50 µL of 10 µM ATP solution diluted in kinase reaction buffer (50 mM HEPES pH 7.4, 50 mM MgCl<sub>2</sub>, 0.5 mM MnCl<sub>2</sub>, 0.2 mM Na<sub>3</sub>VO<sub>4</sub>, 1 mM DTT) was added to each well. Various concentrations of compounds diluted in 10 µL of 1% DMSO (v/v) were added to each reaction well, with 1% DMSO (v/v) used as the negative control. The kinase reaction was initiated by the addition of purified c-Met proteins diluted in 40 µL of kinase reaction buffer solution. After incubation for 60 min at 37 °C, the plate was washed three times with Phosphate Buffered Saline (PBS) containing 0.1% Tween 20 (T-PBS). Next, 100 µL of anti-phosphotyrosine (PY99) antibody (1:500 diluted in 5 mg/mL BSA T-PBS) was added. After 30 min incubation at 37 °C, the plate was washed three times. A solution of 100 µL horseradish peroxidase-conjugated goat anti-mouse IgG (1:2000 diluted in 5 mg/mL BSA T-PBS) was added. The plate was reincubated at 37 °C for 30 min, and washed as before. Finally, 100 µL of a solution containing 0.03% H<sub>2</sub>O<sub>2</sub> and 2 mg/mL *o*-phenylenediamine in 0.1 mM citrate buffer, pH 5.5, was added and samples were incubated at room temperature until color emerged. The reaction was terminated by the addition of 50 µL of 2 M H<sub>2</sub>SO<sub>4</sub>, and the plate was read using a multiwell spectrophotometer (VERSAmax™, Molecular Devices, Sunnyvale, CA, USA) at 490 nm. The inhibition rate (%) was calculated using the following equation:  $[1 - (A_{490}/A_{490 \text{ control}})] \times 100\%$ . IC<sub>50</sub> values were calculated from the inhibition curves.

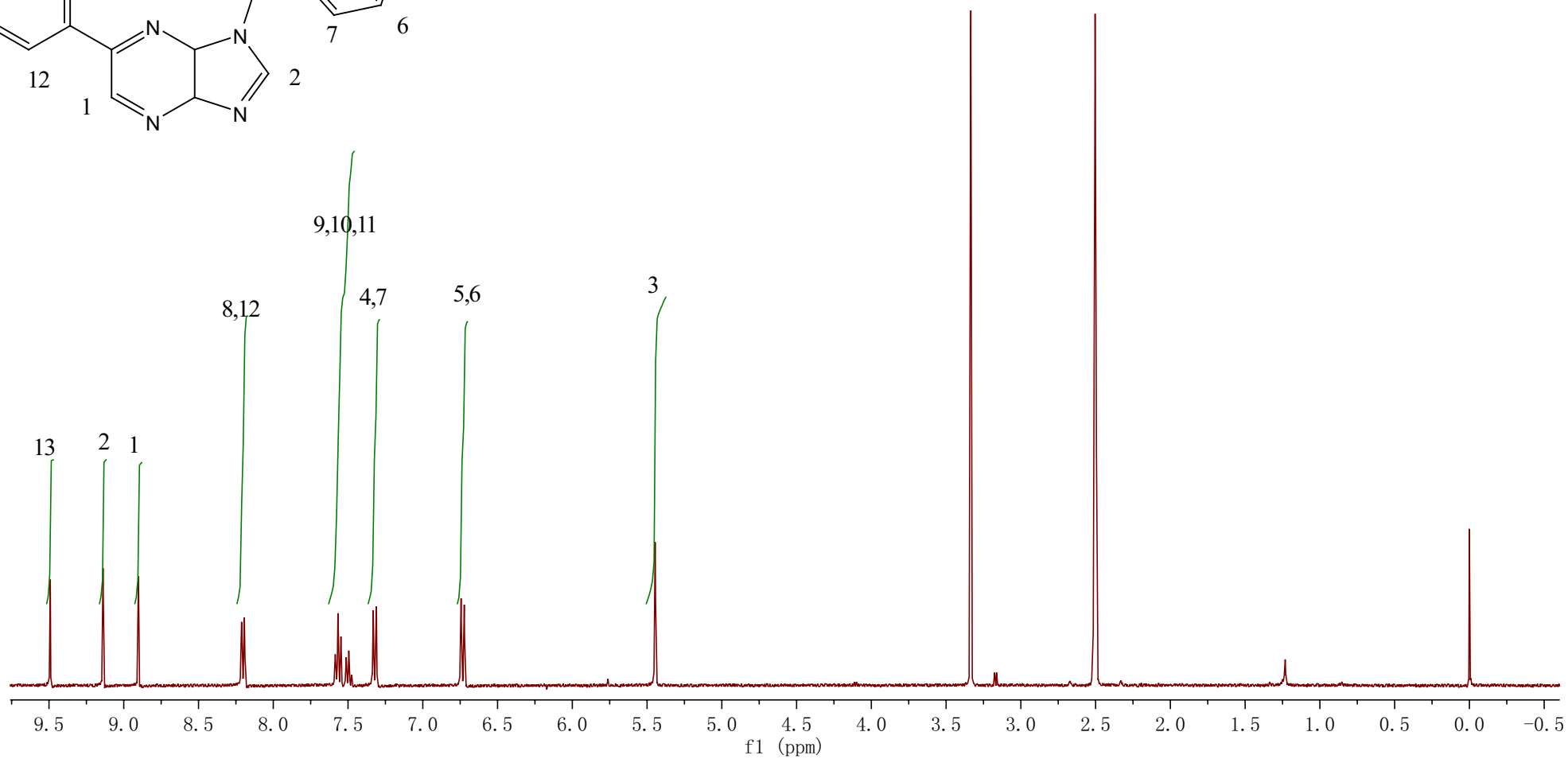
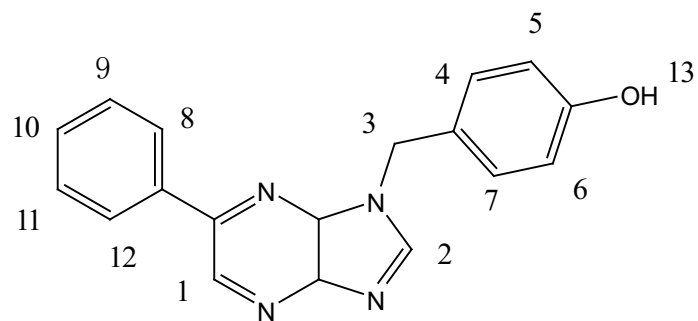




$^1\text{H NMR}$  (400 MHz, DMSO)  $\delta$  8.48 (d,  $J=9.8$  Hz, 1H), 8.19 – 8.09 (m, 2H), 8.05 (d,  $J=9.9$  Hz, 1H), 7.68 – 7.57 (m, 3H), 7.21 (d,  $J=8.4$  Hz, 2H), 6.71 (d,  $J=8.4$  Hz, 2H), 4.49 (s, 2H).

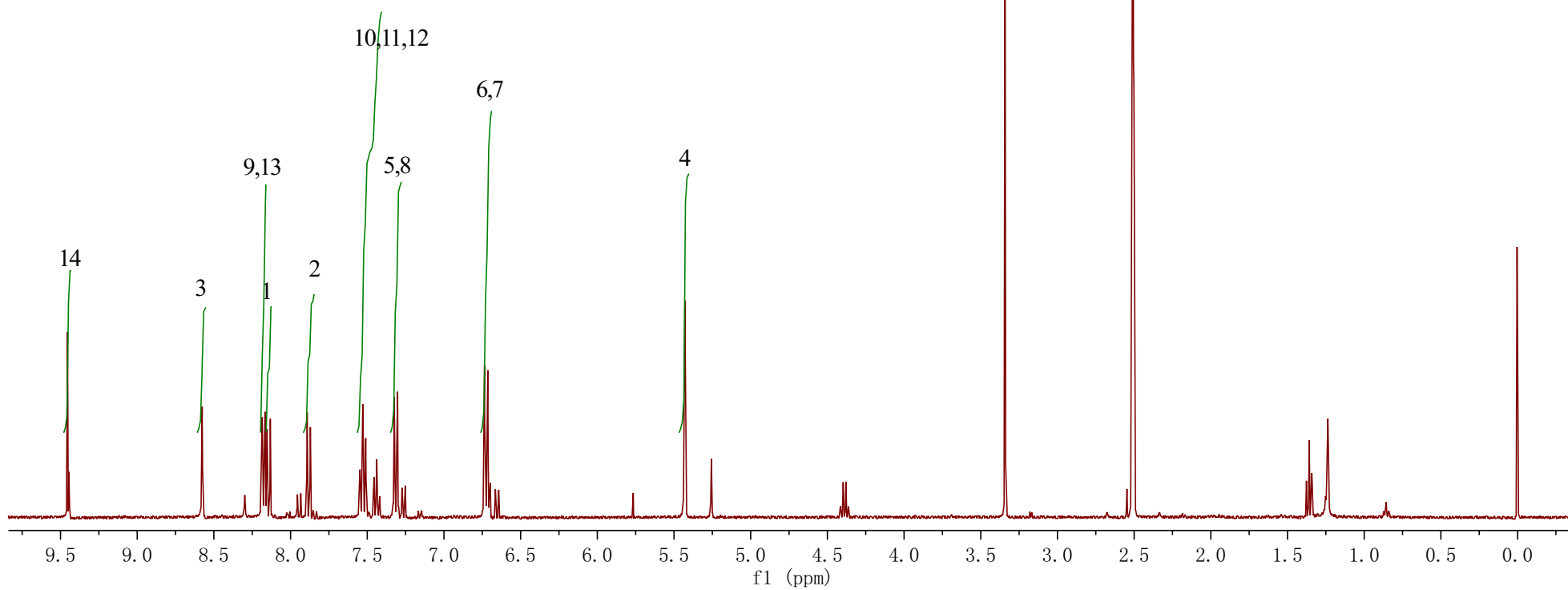
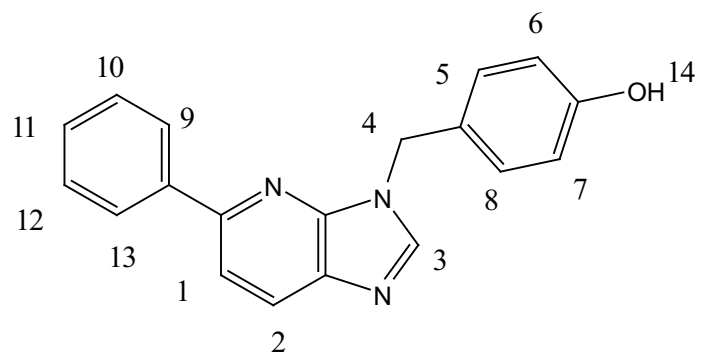


<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 9.39 (s, 1H), 7.91 (s, 1H), 7.83 – 7.72 (m, 2H), 7.56 – 7.38 (m, 3H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.82 (d, *J* = 7.9 Hz, 2H), 4.55 (s, 2H).



$^1\text{H NMR}$  (400 MHz, DMSO)  $\delta$  9.49 (s, 1H), 9.14 (s, 1H), 8.90 (s, 1H), 8.20 (d,  $J = 7.5$  Hz, 2H), 7.53 (dt,  $J = 28.7, 7.4$  Hz, 3H), 7.32 (d,  $J = 8.4$  Hz, 2H), 6.73 (d,  $J = 8.5$  Hz, 2H), 5.45 (s, 2H).





$^1\text{H NMR}$  (400 MHz, DMSO)  $\delta$  9.45 (s, 1H), 8.58 (s, 1H), 8.20 – 8.16 (m, 2H), 8.14 (d,  $J = 8.4$  Hz, 1H), 7.88 (d,  $J = 8.4$  Hz, 1H), 7.48 (dt,  $J = 36.3, 7.4$  Hz, 3H), 7.31 (d,  $J = 8.5$  Hz, 2H), 6.72 (d,  $J = 8.5$  Hz, 2H), 5.43 (s, 2H).

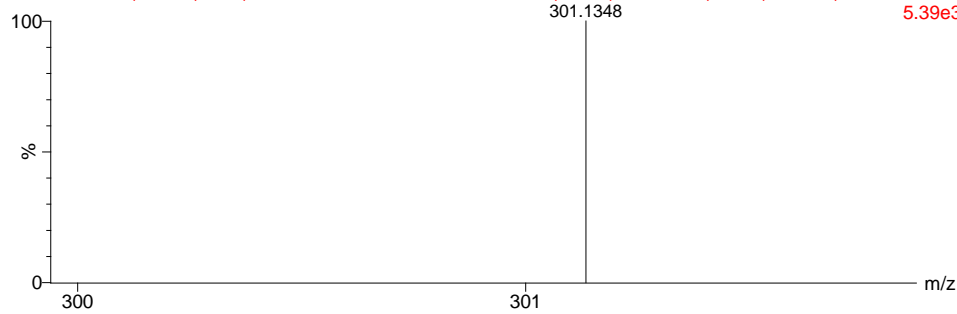
cc033-382

SIMM-Shuying Peng  
cc033-382

Q-ToF Ultima

15-Oct-2012 13:44:39

121015-1 574 (10.777) AM (Cen,5, 80.00, Ht,9000.0,325.11,0.70); Sm (Mn, 2x0.00); Cm (566:575) TOF MS ES+  
5.39e3



Elemental Composition Report

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0  
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions  
10 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)

Minimum:				-1.5	
Maximum:		200.0	10.0	50.0	
Mass	Calc. Mass	mDa	PPM	DBE	Score
	Formula				
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	C20 H17 N2 O				

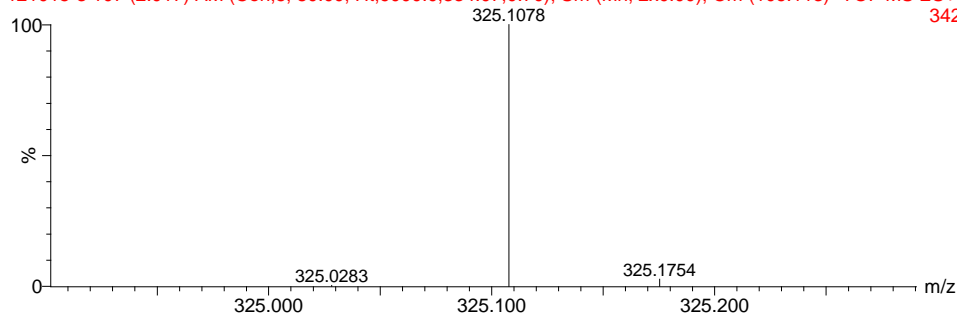
cc033-396

SIMM-Shuying Peng  
cc033-396

Q-ToF Ultima

15-Oct-2012 14:08:16

121015-3 107 (2.017) AM (Cen,5, 80.00, Ht,9000.0,334.07,0.70); Sm (Mn, 2x0.00); Cm (106:113) TOF MS ES+  
342



Elemental Composition Report

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0  
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions  
25 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)

Minimum:	50.00					-1.5
Maximum:	100.00			200.0	10.0	50.0
Mass	RA	Calc. Mass	mDa	PPM	DBE	
Score	Formula					
325.1078	100.00	325.1065	1.3	3.9	13.5	
1	C18 H14 N4 O Na					

cc033-myc-434

SIMM-Shuying Peng Q-ToF Ultima 15-Oct-201214:00:06  
cc033-myc-434

121015-2 182 (3.423) AM (Cen,5, 80.00, Ht,9000.0,301.13,0.70); Sm (Mn, 2x0.00); Cm (180:182) TOF MS ES+ 979



Elemental Composition Report

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0  
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

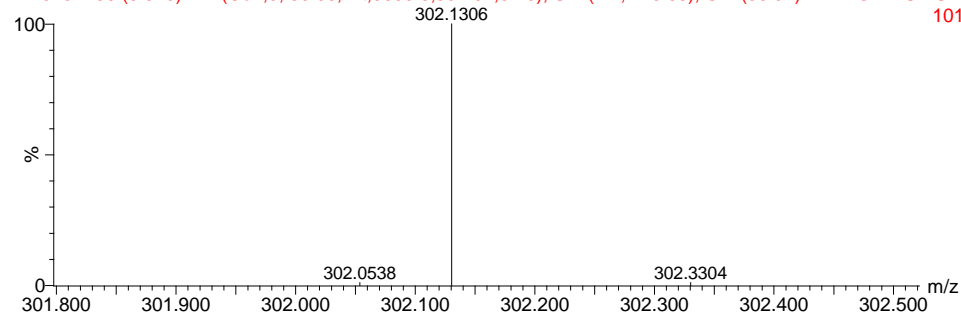
Monoisotopic Mass, Odd and Even Electron Ions  
14 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)

Minimum:	50.00					-1.5
Maximum:	100.00			200.0	10.0	50.0
Mass	RA	Calc. Mass	mDa	PPM	DBE	
Score	Formula					
303.1223	100.00	303.1246	-2.3	-7.5	13.5	
1	C18 H15 N4 O					

cc033-335

SIMM-Shuying Peng Q-ToF Ultima 15-Oct-201214:12:59  
cc033-335

121015-4 30 (0.570) AM (Cen,5, 80.00, Ht,9000.0,334.07,0.70); Sm (Mn, 2x0.00); Cm (30:31) TOF MS ES+ 101



Elemental Composition Report

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0  
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions  
12 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)

Minimum:	50.00					-1.5
Maximum:	100.00			200.0	10.0	50.0
Mass	RA	Calc. Mass	mDa	PPM	DBE	
	Score	Formula				
302.1306	100.00	302.1293	1.3	4.2	13.5	
	1	C19 H16 N3 O				

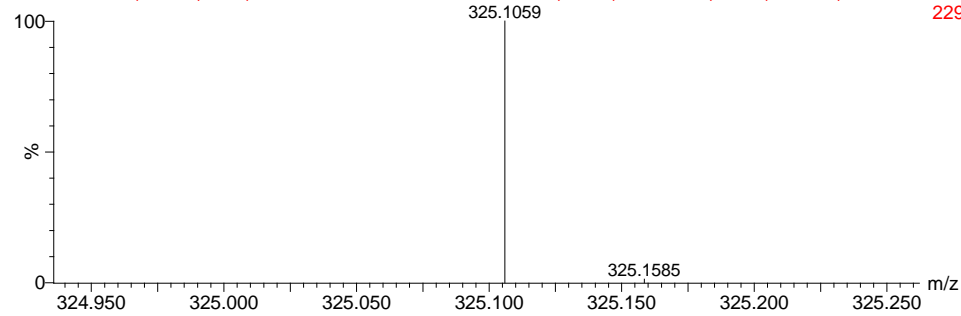
cc033-334

SIMM-Shuying Peng  
cc033-334

Q-ToF Ultima

15-Oct-2012 13:44:39

121015-1 574 (10.777) AM (Cen,5, 80.00, Ht,9000.0,301.13,0.70); Sm (Mn, 2x0.00); Cm (566:576) TOF MS ES+ 229



Elemental Composition Report

Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0  
Isotope cluster parameters: Separation = 1.0 Abundance = 1.0%

Monoisotopic Mass, Odd and Even Electron Ions  
25 formula(e) evaluated with 1 results within limits (up to 20 closest results for each mass)

Minimum:	50.00					-1.5
Maximum:	100.00			200.0	10.0	50.0
Mass	RA	Calc. Mass	mDa	PPM	DBE	
	Score	Formula				
325.1059	100.00	325.1065	-0.6	-1.9	13.5	
	1	C18 H14 N4 O Na				