

Supporting information

Selectfluor-promoted regioselective chlorination/bromination of aminopyridines and diazines using LiCl/LiBr

Jiao Hu,^{a,§} Gang Zhou,^{a,§} Yawei Tian^a and Xiaoming Zhao^{a*}

School of Chemical Science and Engineering, Tongji University, 1239 Siping Road, Shanghai
200092, P.R. China

E-mail: xmzhao08@mail.tongji.edu.cn

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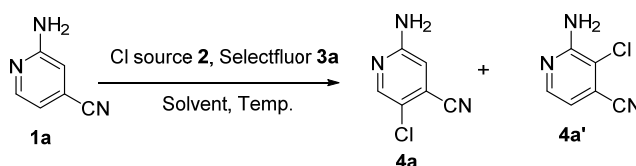
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I. General Remarks

All manipulations were carried out under the air atmosphere using standard Schlenk techniques. All glassware was oven or flame dried immediately prior to use. All solvents were purified and dried according to standard methods prior to use, unless stated otherwise. All reagents were obtained from commercial sources and used without further purification. ^1H NMR spectra were obtained at 400 MHz and recorded relative to tetramethylsilane signal (0 ppm) or residual protio-solvent. ^{13}C NMR spectra were obtained at 101 MHz, and chemical shifts were recorded relative to the solvent resonance (CDCl_3 , 77.0 ppm; DMSO, 39.5). ^{19}F NMR spectra were obtained at 376 MHz. Infrared (IR) spectra were recorded on an IR spectrometer with KBr wafers or a film on a KBr plate. High-resolution mass spectra (HRMS) were recorded on a microTOF II mass spectrometer using electrospray ionization (ESI). Data for ^1H NMR are recorded as follows: chemical shift (δ , ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ , ppm).

II.

SI-Table 1 Screening the chlorination reaction conditions ^a

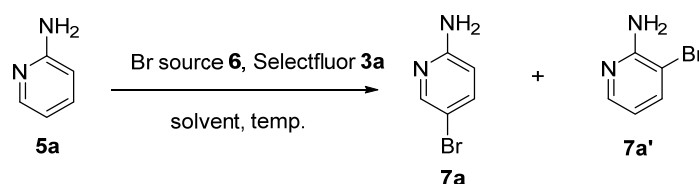


Entry	[Cl] 2	1a/2/3a	Solvent	T. °C	Yield (%) ^d	
					4a	4a'
1	LiCl	1/1/0	DMF	15	-	-
2	-	1/0/1	DMF	15	complex	complex
3 ^b	LiCl	1/1/0	DMF	15	-	-
4 ^c	LiCl	1/1/0	DMF	15	-	-
5	LiCl	1/1/1	DMF	15	70	8
6	LiCl	1/1/1	CH ₃ CN	15	50	20
7	LiCl	1/1/1	THF	15	35	<5
8	LiCl	1/1/1	DCM	15	<5	-
9	LiCl	1/1/1	Toluene	15	20	-
10	CuCl	1/1/1	CH ₃ CN	15	50	15

11	NaCl	1/1/1	CH ₃ CN	15	30	9
12	KCl	1/1/1	CH ₃ CN	15	35	12
13	LiCl	2/1/1	DMF	15	55	20
14	LiCl	2/2/1	DMF	15	45	10
15	LiCl	1/1/1	DMF	0	50	10
16	LiCl	1/1/1	DMF	40	52	15

[a] Reaction conditions: **1a** (0.10 mmol), Selectfluor **3a** (0.10 mmol), MCl **2a** (0.1 mmol) and solvent (2 mL) at 0-40 °C for 24h. [b] K₂CrO₄ (0.1 mmol) was used. [c] K₂S₂O₈ (0.1 mmol) was used. [d] ¹H NMR yield.

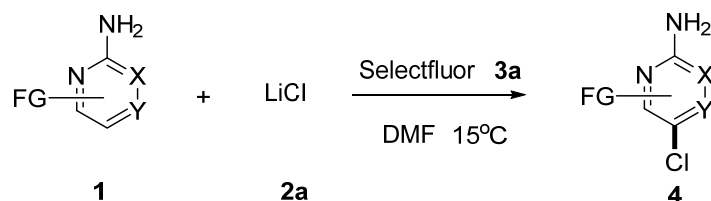
SI-Table 2 Screening the bromination reaction conditions. ^a



Entry	Catalyst	[Br] 6	5a/6/3a	Solvent	T. °C	Yield (%) ^b	
						7a	7a'
1 ^a	SelectF	-	1/0/1	DMF	30	trace	trace
2	FeBr ₃	Br ₂	1/1/0	DMF	30	46	17
3	-	DBDMH	1/1/0	DMF	30	50	25
4	SelectF	LiBr	1/1/1	DMF	30	75	-
5	SelectF	LiBr	1/1/1	CH ₃ CN	30	65	-
6	SelectF	LiBr	1/1/1	THF	30	35	-
7	SelectF	LiBr	1/1/1	DCM	30	<5	-
8	SelectF	LiBr	1/1/1	Toluene	30	20	-
9	SelectF	CuBr	1/1/1	CH ₃ CN	30	65	-
10	SelectF	NaBr	1/1/1	CH ₃ CN	30	46	-
11	SelectF	KBr	1/1/1	CH ₃ CN	30	52	-
12	SelectF	LiBr	2/1/1	DMF	30	70	-
13	SelectF	LiBr	2/2/1	DMF	30	55	-
14	SelectF	LiBr	1/1/1	DMF	15	60	-
15	SelectF	LiBr	1/1/1	DMF	40	70	-

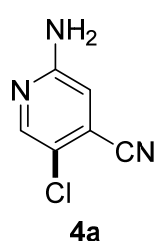
[a] Reaction conditions: **5a** (0.10 mmol), Selectfluor **3a** (0.10 mmol), MBr **6a** (0.1 mmol) and solvent (2 mL) at 15-40 °C for 24h. [b] ¹H NMR yield.

III. General Procedure for the Synthesis of 4a-4n



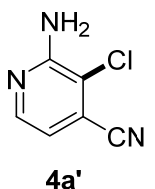
2-Aminoheterocycle **1** (0.10 mmol) and LiCl **2a** (0.10 mmol) and selectfluor **3a** (0.10 mmol) were dissolved in DMF (2 mL) in a sealed tube, then the reaction mixture was stirred at 15 °C for 12 h. The mixture was diluted with NaCl solution and EA (3 × 10 mL), dried with Na₂SO₄. After concentration of the filtrate to dryness, purification of the residue by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1–5/1) gave the desired products **4a-4k**.

5-Chloro-4-cyano-2-pyridinamine (**4a**)^[1,2]



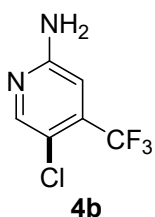
Pale yellow solid; 70% yield (10.7 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.17 (s, 1H), 6.85 (s, 1H), 6.75 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 158.5, 147.9, 120.0, 115.8, 114.7, 111.8; HRMS (ESI): [M +H⁺] Calc. 154.0172, Found: 154.0167.

3-Chloro-4-cyano-2-pyridinamine (**4a'**)^[1,2]



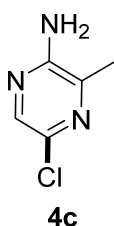
Pale yellow solid; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.92 (d, *J* = 2.3 Hz, 1H), 7.54 (d, *J* = 2.3 Hz, 1H), 6.78 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆): δ 159.9, 149.6, 119.7, 117.5, 112.0, 109.8; HRMS (ESI): [M +H⁺] Calc. 154.0172, Found: 154.0165.

5-Chloro-4-trifluoromethyl-2-pyridinamine (**4b**)^[1,2]



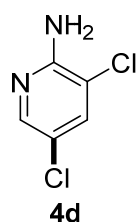
Pale yellow solid; 70% yield (13.7 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.14 (s, 1H), 6.74 (s, 1H), 4.81 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 157.1, 149.6, 137.0 (d, *J* = 32.6 Hz), 121.6 (d, *J* = 274.2 Hz), 116.8, 106.1 (t, *J* = 5.3 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -65.06; HRMS (ESI): [M +H⁺] Calc. 197.0093; Found: 197.0099.

5-Chloro-3-methyl-2-pyrazinamine (**4c**)^[1,2]



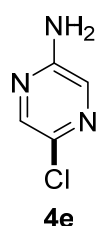
Pale yellow solid; 60% yield (9 mg); ¹H NMR (400 MHz, CDCl₃) δ 7.87 (s, 1H), 4.58 (s, 2H), 2.38 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 151.6, 139.1, 138.7, 136.5, 20.0; HRMS (ESI): [M +H⁺] Calc. 144.0328, Found: 144.0319.

3,5-Dichloro-2-pyridinamine (4d)^[1,2]



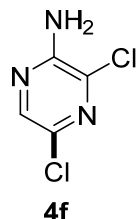
Pale yellow solid; 70% yield (11 mg); ¹H NMR (400 MHz, CDCl₃) δ 7.94 (s, 1H), 7.50 (s, 1H), 4.95 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 153.3, 144.7, 136.3, 120.3, 115.0. HRMS (ESI): [M +H⁺] Calc. 162.9830, Found: 162.9838.

5-Chloro-2-pyrazinamine (4e)^[1,2]



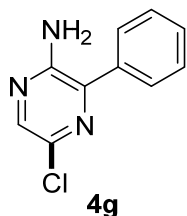
Yellow solid; 60% yield (7.8 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.97 (s, 1H), 7.67 (s, 1H), 6.63 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 155.1, 140.7, 133.7, 130.9; HRMS (ESI): [M +H⁺] Calc. 130.0172, Found: 130.0178.

3,5-Dichloro-2-pyrazinamine (4f)^[1,2]



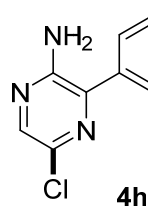
Pale yellow solid; 80% yield (13 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.08 (s, 1H), 7.05 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 151.7, 140.1, 130.4, 129.9; HRMS (ESI): [M +H⁺] Calc. 163.9782, Found: 163.9788.

5-Chloro-3-phenyl-2-pyrazinamine (4g)^[1,2]



Yellow solid; 55% yield (11.3 mg); ¹H NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H), 7.71 (d, *J* = 6.9 Hz, 2H), 7.52-7.44 (m, 3H), 4.84 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 150.9, 139.9, 139.6, 137.3, 135.8, 129.5, 129.1, 128.1; HRMS (ESI): [M +H⁺] Calc. 206.0485, Found: 206.0480.

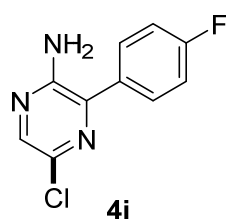
5-Chloro-3-(4-nitrophenyl)-2-pyrazinamine (4h)



Yellow solid; mp: 191.2-191.8 °C; 75% yield (18.8 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.33 (d, *J* = 8.8 Hz, 2H), 8.14 (s, 1H), 7.98 (d, *J* = 8.8 Hz, 2H), 6.70 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 152.4, 147.2, 142.4, 141.3, 135.3, 134.0, 129.5, 123.8; IR (KBr): 3495, 3296, 1641, 1597, 1510, 1351, 1106, 854 cm⁻¹; HRMS (ESI): [M +H⁺] Calc. 251.0036, Found:

251.0041.

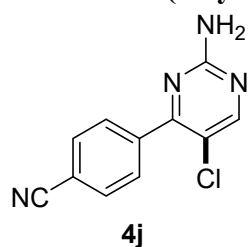
5-Chloro-3-(4-fluorophenyl)-2-pyrazinamine (4i)



Yellow solid; mp: 128.1-129.3 °C; 70% yield (15 mg); ¹H NMR (400 MHz, CDCl₃) δ 7.98 (s, 1H), 7.72 (dd, *J* = 8.7, 5.3 Hz, 2H), 7.18 (t, *J* = 8.6 Hz, 2H), 4.81 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 163.3 (d, *J* = 250.2 Hz), 150.8, 140.0, 138.6, 137.4, 131.9 (d, *J* = 3.3 Hz), 130.2 (d, *J* = 8.4 Hz), 116.2 (d, *J* = 21.8 Hz); ¹⁹F NMR

(376 MHz, CDCl₃) δ -110.67; IR (KBr): 3393, 3305, 2920, 2848, 1603, 1508, 1441, 1149, 842 cm⁻¹; HRMS (ESI): [M +H⁺] Calc. 224.0391, Found: 224.0398.

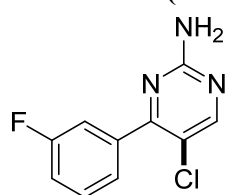
5-Chloro-4-(4-cyanophenyl)-2-pyrimidinamine (4j)



4j

Pale yellow solid; mp: 183.5-184.1 °C; 70 % yield (16.2 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.41 (s, 1H), 7.98 (d, *J* = 8.2 Hz, 2H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.09 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 162.1, 160.7, 158.6, 140.6, 132.1, 129.7, 118.4, 114.8, 112.2; IR (KBr): 3434, 3323, 3172, 2918, 2848, 2232, 1644, 1576, 789 cm⁻¹; HRMS (ESI): [M +H⁺] Calc. 231.0437, Found: 231.0430.

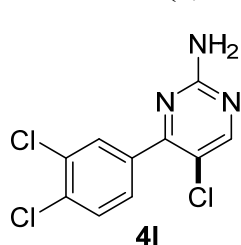
5-Chloro-4-(3-fluorophenyl)-2-pyrimidinamine (4k)



4k

Pale yellow solid; mp: 180.1-180.9 °C; 80 % yield (18 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.38 (s, 1H), 7.64 – 7.42 (m, 3H), 7.35 (s, 1H), 7.03 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 162.8, 162.0, 160.8 (d, *J* = 2.4 Hz), 158.5, 138.4 (d, *J* = 7.9 Hz), 130.2 (d, *J* = 8.2 Hz), 125.0 (d, *J* = 2.7 Hz), 116.6 (d, *J* = 20.8 Hz), 115.6 (d, *J* = 23.0 Hz), 114.8; ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -113.05; IR (KBr): 3431, 3326, 2988, 1644, 1530, 1192, 517 cm⁻¹; HRMS (ESI): [M +H⁺] Calc. 224.0391, Found: 224.0399.

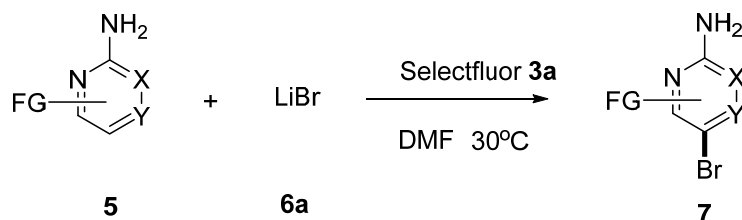
5-Chloro-4-(3,4-dichlorophenyl)-2-pyrimidinamine (4l)



4l

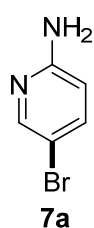
Pale yellow solid; mp: 187.8-188.5 °C; 80% yield (22 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.39 (s, 1H), 7.95 (s, 1H), 7.75 (d, *J* = 11.8 Hz, 2H), 7.08 (s, 2H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 162.0, 159.5, 158.6, 136.6, 132.5, 130.9, 130.7, 130.4, 129.1, 114.7; IR (KBr): 3436, 3325, 2981, 1652, 1536, 1468, 788 cm⁻¹; HRMS (ESI): [M +H⁺] Calc. 273.9706, Found: 273.9701.

IV. General Procedure for the Synthesis of 7a-7l



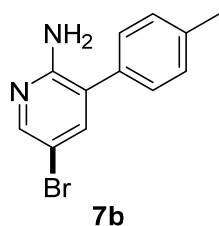
2-Aminoheterocycle **5** (0.10 mmol) and LiBr **6a** (0.10 mmol) and Selectfluor (0.10 mmol) were dissolved in DMF (2 mL) in a sealed tube, then the reaction mixture was stirred at 30 °C for 24 h. The mixture was diluted with NaCl solution and EA (3 × 10 mL), dried with Na₂SO₄. After concentration of the filtrate to dryness, purification of the residue by column chromatography on silica gel (petroleum ether/ethyl acetate = 10/1–5/1) gave the desired products **7a-7l**.

5-Bromo-2-pyridinamine (7a)^[1,2]



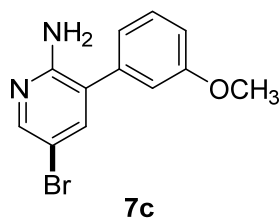
Yellow solid; 75% yield (13 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.08 (s, 1H), 7.48 (d, *J* = 8.7 Hz, 1H), 6.40 (d, *J* = 8.7 Hz, 1H), 4.58 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 157.0, 148.7, 140.1, 110.0, 108.3; HRMS (ESI): [M+H⁺] Calc. 172.9714, Found: 172.9718.

5-Bromo-3-(3-methylphenyl)-2-pyridinamine (7b)^[1,2]



Pale yellow solid; 70 % yield (18 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.08 (s, 1H), 7.45 (d, *J* = 2.0 Hz, 1H), 7.34-7.27 (m, 4H), 4.61 (s, 2H), 2.40 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 154.7, 147.4, 139.7, 138.2, 133.7, 129.9, 128.4, 126.3, 121.5, 21.2; HRMS (ESI): [M+H⁺] Calc. 263.0184, Found: 263.0188.

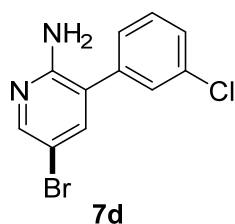
5-Bromo-3-(3-methoxyphenyl)-2-pyridinamine (7c)^[1,2]



White solid; 70 % yield (19 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.47 (d, *J* = 2.2 Hz, 1H), 7.38 (t, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 6.4 Hz, 2H), 4.65 (s, 2H), 3.84 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 160.2, 154.7, 147.7, 139.7, 138.0, 135.3, 130.3, 123.4, 120.7, 114.1, 113.9, 55.4; HRMS (ESI): [M+H⁺] Calc. 279.0133, Found:

279.0138.

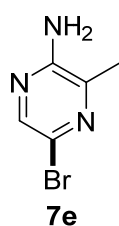
5-Bromo-3-(3-chlorophenyl)-2-pyridinamine (7d)



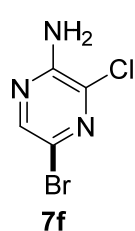
Pale yellow solid; mp: 131.6-141.5 °C; 65% yield (18.3 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.43 – 7.35 (m, 3H), 7.31 (d, *J* = 6.9 Hz, 1H), 4.69 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 154.4, 148.2, 139.8, 138.5, 135.1, 130.5, 128.7, 128.5, 126.7, 121.9, 108.4; IR (KBr): 3481, 3301, 3170, 2924, 1603, 1566, 1450, 1227, 701 cm⁻¹; HRMS (ESI):

[M+H⁺] Calc. 282.9638, Found: 282.9633.

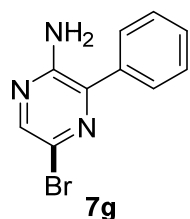
5-Bromo-3-methyl-2-pyrazinamine (7e)^[1,2]



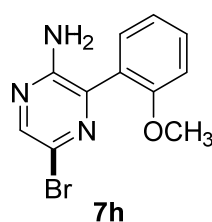
Pale yellow solid; 80 % yield (15 mg); ¹H NMR (400 MHz, CDCl₃) δ 7.96 (s, 1H), 4.55 (s, 2H), 2.38 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 151.9, 141.7, 140.1, 126.3, 20.0; HRMS (ESI): [M +H⁺] Calc. 187.9823, Found: 187.9818.

5-Bromo -3-chloro-2-pyrazinamine (7f) ^[1,2]

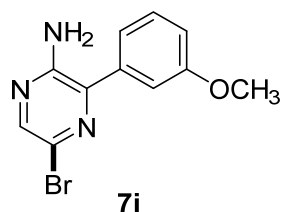
Pale yellow solid; 75 % yield (15.6 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.03 (s, 1H), 5.05 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 150.6, 142.9, 132.0, 123.5; HRMS (ESI): [M +H⁺] Calc. 207.9277, Found: 207.9272.

5-Bromo -3-phenyl-2-pyrazinamine (7g) ^[1,2]

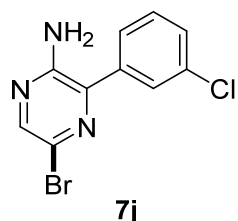
Pale yellow solid; 60 % yield (15 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 7.71 (d, *J* = 6.9 Hz, 2H), 7.53-7.45 (m, 3H), 4.80 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 151.2, 142.8, 140.8, 135.8, 129.6, 129.1, 128.1, 127.0; HRMS (ESI): [M +H⁺] Calc. 249.9974, Found: 249.9980.

5-Bromo-3-(2-methoxyphenyl)-2-pyrazinamine (7h) ^[1,2]

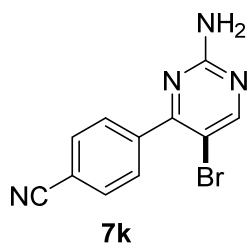
Pale yellow solid; 80% yield (24 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.10 (s, 1H), 7.49 – 7.37 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 4.70 (s, 2H), 3.85 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 156.4, 152.3, 142.9, 139.9, 131.8, 131.1, 126.4, 124.9, 121.6, 111.4, 55.8; HRMS (ESI): [M +Na⁺] Calc. 301.9899, Found: 301.9905.

5-Bromo-3-(3-methoxyphenyl)-2-pyrazinamine (7i) ^[1,2]

Pale yellow solid; 70 % yield (21.4 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.07 (s, 1H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.22 (s, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 4.83 (s, 2H), 3.86 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 160.2, 151.2, 142.9, 140.5, 137.1, 130.2, 126.9, 120.1, 115.5, 113.6, 55.4; HRMS (ESI): [M +Na⁺] Calc. 301.9899, Found: 301.9905.

5-Bromo-3-(3-chlorophenyl)-2-pyrazinamine (7j) ^[1,2]

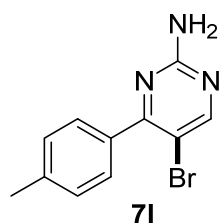
Yellow solid; 60 % yield (17 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.09 (s, 1H), 7.72 (s, 1H), 7.66 – 7.57 (m, 1H), 7.43 (d, *J* = 4.9 Hz, 2H), 4.82 (s, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 151.1, 143.5, 138.9, 137.5, 135.2, 130.4, 129.7, 128.4, 127.1, 126.1; HRMS (ESI): [M +Na⁺] Calc. 283.9585, Found: 283.9590.

5-Bromo-4-(4-cyanophenyl)-2-pyrimidinamine (7k)

Pale yellow solid; mp: 207.8-208.1 °C; 60 % yield (16.3 mg); ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.48 (s, 1H), 7.97 (d, *J* = 8.2 Hz, 2H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.10 (s, 2H); ¹³C NMR (101

MHz, DMSO-*d*₆) δ 162.5, 162.3, 160.8, 141.9, 132.0, 129.7, 118.4, 112.0, 103.4; IR (KBr): 3469, 3394, 2919, 1644, 1558, 1467, 575cm⁻¹; HRMS (ESI): [M+Na⁺] Calc. 296.9752, Found: 296.9746.

5-Bromo-4-(4-methylphenyl)-2-pyrimidinamine (71) ^[1,2]



White solid; 70 % yield (18.4 mg); ¹H NMR (400 MHz, CDCl₃) δ 8.41 (s, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 5.23 (s, 2H), 2.41 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 165.1, 161.7, 160.8, 140.1, 134.6, 128.9, 128.8, 106.4, 21.4; HRMS (ESI): [M+H]⁺ Calc. 264.0136, Found: 264.0131.

V. References:

- (1) Ko, Kwangseok; Kim, Hye-Jung; *J. Med. Chem.* **2018**, *61*, 2949.
- (2) Karthik, Murugan; Suresh, Palaniswamy; *ChemistrySelect.* **2017**, *23*, 6916.

VI. NMR spectra data

