Aqueous phase synthesis of bridgehead azaheterocycles in the presence of *β*-cyclodextrin

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Abstract
A simple and expeditious aqueous phase reaction of various *α*-bromoketones with 2-aminopyridine, 2-aminopyrimidine, 2-aminopyrazine, and their derivatives, and 2-aminobezothiazole in the presence of *β*-cyclodextrin has been demonstrated to furnish bridgehead azaheterocycles **5a-j**, **7a-e**, **9a-d**, **12a**, **12b** and benzo[*d*]imidazo[2,1-*b*]thiazoles **11a-c** respectively, in good to excellent yields.

Keywords: Heterocycles, *β*-cyclodextrin, and azaindolizines, green chemistry

Introduction

Imidazo[1,2-*a*]pyridine **1**, imidazo[1,2-*a*]pyrimidine **2** and imidazo[1,2-*a*]pyrazine **3** (Figure 1), are important structural motifs found in numerous natural and synthetic bioactive molecules, and have received significant attention from the pharmaceutical industry owing to their interesting biological activities displayed over a broad range of therapeutic classes. The members of these ring systems have several valuable biological properties and are used as hypotensive,[1] antiulcer[2] or anxyolitic agents[3] in addition to bradycardic,[4] antiasthmatic,[5] antimicrobial,[6] cytoprotective,[7] calcium channel blocking agents[8] and as HIF-1*α* prolyl hydroxylase inhibitors.[9] Imidazo[1,2-*a*]pyridines are also an important pharmocophore in a number of drug formulations currently available in the market.[10] Apart from the above, imidazo[1,2-*a*]pyridinium salts are also used to prepare styryl dyes.[11]

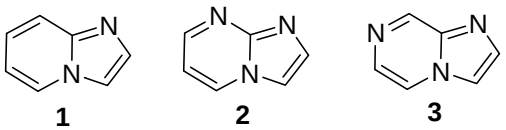


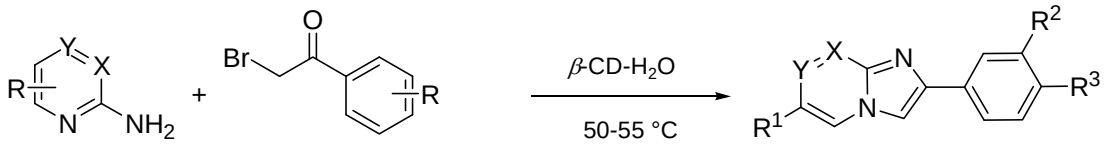
Figure 1. Some bioactive azaindolizine ring systems.

An increasing amount of published literature describes new synthetic routes for the preparation of azaindolizines. These methods include either solution phase[12] or solid phase,[13] coupling reaction of α-haloketones or equivalents with corresponding heteroaromatic amidines, or through multicomponent reaction by microwave-assisted reactions[14] and zinc chloride catalyzed reactions.[15] In spite of the existence of numerous methods[12,16] for the synthesis of fused imidazoles, these methods are associated with one or more of the following drawbacks: (i) long reaction times, (ii) unsatisfactory yields, and (iii) the use of expensive and hazardous reagents. Therefore, it seems highly desirable to find a one step and inexpensive protocol for the synthesis of azaindolizines systems for their experimental simplicity and effectiveness.

Water plays an essential role in life processes, and in the development of environmentally benign and clean synthetic procedure, however its use as a solvent has been limited in organic synthesis. Despite the fact that it is the cheapest, safest and most non-toxic solvent in the world, its presence is generally avoided through the dehydrative drying of substrates and solvents. The use of water as a medium for organic reactions is therefore one of the latest challenge for modern organic chemists. A number of reactions in water have been previously reported, and the supramolecular catalysis appeared to the best method for some of the reactions.[17]

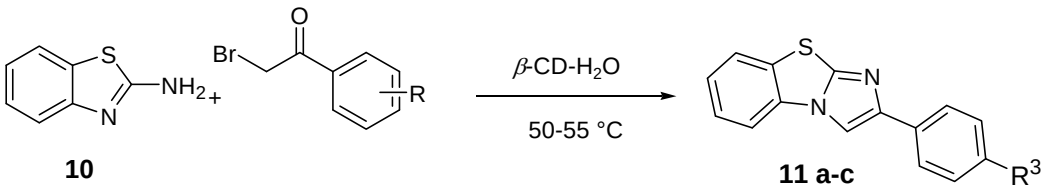
Cyclodextrins are cavity based cyclic oligosaccharides that catalyze chemical reactions on the basis of supramolecular catalysis. These molecules mimic the enzyme models in the formation of reversible host-guest complex by non-covalent interaction. Cyclodextrins consist of hydrophobic cavities, which selectively bind the hydrophobic portion of one of the reacting substrate and thereby catalyzing the reaction. Complexation depends on the size, shape and hydrophobicity of the guest molecule.

With in this context we have developed a biomimetic and green chemistry approach to synthesize fused imidazoles under aqueous condition through the supramolecular catalysis mediated by β-cyclodextrins. Herein, we described a simple and convenient supramolecular synthesis of some azaindolizines **5a-j**, **7a-e**, **9a-d**, **12a**, **12b** and benzo[*d*]imidazo[2,1-*b*]thiazoles **11a-c**, and the present method seems to overcome all of the above mentioned drawbacks. To best of our knowledge, there has been no report on cyclodextrin-mediated synthesis of bridgehead azaheterocycles.



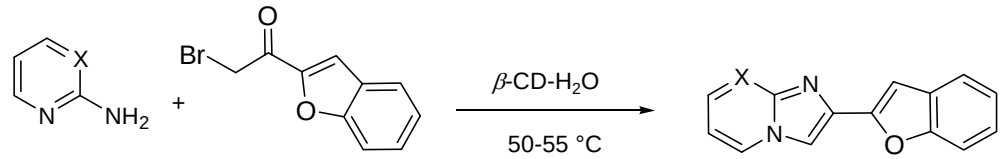
4, 6, 8 **5a-j, 7a-e, 9a-d**

Scheme 1



10 **11 a-c**

Scheme 2



X = CH, N

X = CH (12 a)
X = N (12 b)

Scheme 3

Results and Discussion

To establish the generality and scope of the method given in this report, a number of azaindolizines (with two nitrogen atoms) and benzo[*d*]imidazo[2,1-*b*]thiazole derivatives have been synthesized, and the results are shown in Table 1. All the reactions were carried out with one equivalent of each reactant in the aqueous solution of one equivalent of *β*-cyclodextrin. The reactions were carried out by dissolving *β*-cyclodextrin in water warmed to 50-55 °C. To resulting clear solution, phenacyl bromides were added. A milky suspension of *β*-CD-phenacyl bromide complex was formed, to which the amino compounds were added and stirred. The progress of reactions was monitored by TLC, and an appearance of blue fluorescent at Rf. of 0.1-0.4 in 10% methanol/chloroform indicated the formation of product. The reaction of various phenacyl bromides with 2-aminopyridines **4** (entry 1, Table 1), furnished the azaindolizines **5a-j**. Similarly, the reaction of 2-aminopyrimidines **6** (entry 2) and 2-aminopyrazines **8** (entry 3) furnished the compounds **7a-e** and **9a-d** respectively. By adopting similar synthetic protocols (Scheme 2 and 3), benzo[*d*]imidazo[2,1-*b*]thiazoles **11a-c** (entry 4) and azaindolizines **12a-b** (entry 5) were also synthesized in good to excellent yield. The method describes an easy and convenient route to furnish a number of azaheterocycles. The superiority of this procedure over existing protocol could be established while comparing the results obtained with few methods employed previously for the synthesis of 2-arylimidazo[1,2-*a*] pyridines, 2-arylimidazo[1,2-*a*]pyrimidines, as these methods[12,18] needed refluxing in organic solvents for 6 hours. The formation of 2-substituted benzo[*d*]imidazo[2,1-*b*]thiazole[20] needed 8 hours refluxing in dry ethanol, but the method given in this report is quite simple and the products were formed within a few minutes in very good yields. Under the similar reaction

Table 1. Synthesis of bridgehead azaheterocycles in the presence of *β*-cyclodextrin

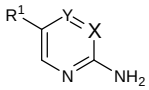
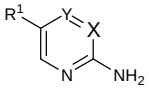
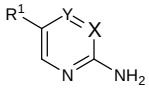
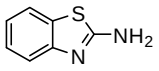
Entry	Substrates	Products				Time (min)	Yield %	mp (°C)	Lit. mp (°C)
		Comp. no.	R^1	R^2	R^3				
1	 **4** X=Y=CH, R^1=H, Cl, CH_3	**5a**	H	H	Cl	10 min	82 8[m]	205-207	208[12b]
		5b	H	H	Br	5 min	85	215-217	215-216[12b]
		5c	H	Cl	Cl	10 min	79	168-170	172[19a]
		5d	H	H	OCH_3	10 min	81	132-134	134[12b]
		5e	H	H	CH_3	10 min	80	135-136	137[19b]
		5f	H	H	H	15 min	80 5[m]	131-133	134[12b]
		5g	Cl	Cl	Cl	15 min	75	172-174	174[13]
		5h	Cl	H	H	15 min	65	205-207	204-207[12b]
		5i	CH_3	H	CH_3	15 min	63	227-229	N
		5j	Cl	H	OCH_3	20 min	74	227-228	N
2	 **6** X=N, Y=CH R^1=H	**7a**	H	H	Br	15 min	80	225-227	228[6]
		7b	H	H	H	15 min	76	190-192	193[6]
		7c	H	OCH_3	OCH_3	15 min	68	145-147	N
		7d	H	Cl	Cl	15 min	72	226-228	228[6]
		7e	H	H	Cl	15 min	75	265-267	270[6]
3	 **8** X=CH, Y=N R^1=H,	**9a**	H	H	Cl	25-30 min.	65	180-182	N
		9b	H	H	H	25-30 min	67	132-134	N
		9c	H	Cl	Cl	25-30 min	69	143-145	N
		9d	H	H	Br	25-30 min	70	156-158	N

Table 1. Continued

Entry	Substrates	Products				Time (min)	Yield %	mp (°C)	Lit. mp (°C)
		Comp. no.	R^1	R^2	R^3				
4	 **10**	**11a**	-	H	H	20 min	70 5[m]	102-104	106[20]
		11b	-	H	Cl	20 min	70 10[m]	157-159	160[20]
		11c		H	OCH_3	20 min	69	175-177	181[20]
5		**12a**	-	-	-	5 min	75	197-199	N
		12b	-	-	-	15 min	74	174-176	N

[m] : in absence of *β*-cyclodextrin.
N: Lit. is not available.Conditions, in the absence of *β*-cyclodextrin only 5-10% products could be isolated.

Cyclodextrin by supramolecular interaction effects solubilization and activation of phenacyl bromides through formation of host-guest complex during the course of reaction and thus facilitates the condensation (Figure 2).

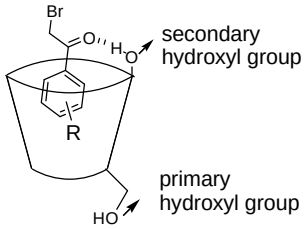


Figure 2. Host-guest complex of *β*-cyclodextrin and phenacyl bromide.

The evidence for the proposed mechanism could be deduced from ^{1}H NMR spectroscopy of *β*-CD and freeze-dried reaction mixture of *β*-CD-2-bromo-1-phenylethanone complex with 2-aminopyrdine. Binding of phenacyl bromide into the cyclodextrin cavity was confirmed by the significant changes in the chemical shift of H3, H6 and H5 protons (located inside the cavity), whereas only little changes in the chemical shifts of H2 and H4 protons (located outside the cavity) of *β*-cyclodextrin were observed (Figure 3). This observation was consistent with inclusion complex formation between *β*-CD and phenacyl bromide. The structures of all the synthesized fused imidazoles were confirmed by spectroscopic data. The physical and spectroscopic data of the reported compounds were comparable with literature.

Thus, we have developed an operationally simple and novel route for the preparation of bridgehead nitrogen heterocycles in water. The low cost, ease of handling and non-toxicity of *β*-cyclodextrin, makes the method employed in the present report an environment friendly.

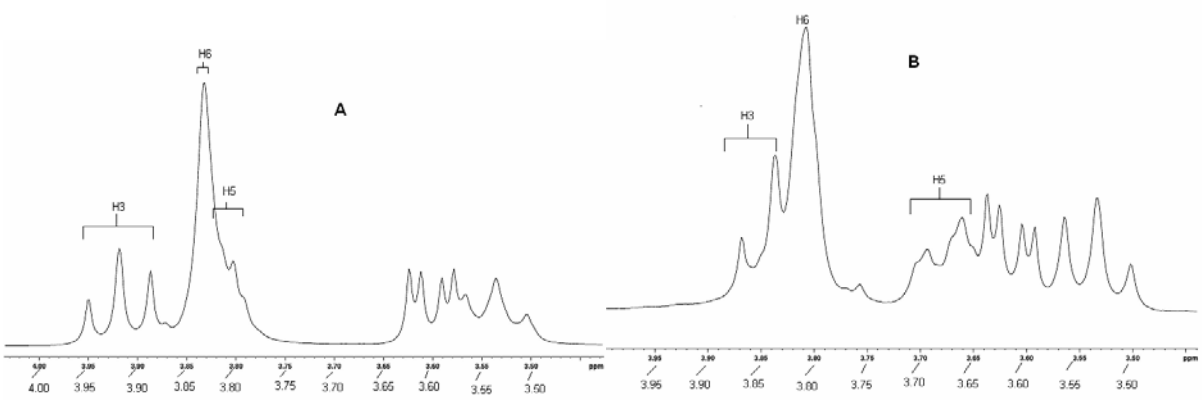


Figure 3. ^{1}H NMR spectra (D_2O, 300 MHz) of: (A): *β*-CD; (B): a freeze-dried reaction mixture of *β*-CD-phenacyl bromide complex with 2-aminopyridine after 15min.

Experimental Section

General Procedures. Reaction progress was monitored by TLC aluminium sheets silica gel 60 F_{254}. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Supercon Magnet DPX-200 or DRX-300 spectrometers (operating at 200 and 300 MHz respectively for 1H; 50 and 75 MHz respectively for 13C) using $CDCl_3$, DMSO-d_6, CD_3OD or their mixture as solvent. Infrared spectra were recorded on a Perkin-Elmer FT-IR RXI spectrophotometer. Electrospray mass spectra (ES-MS) were recorded on a Micromass Quattro II triple quadruple mass spectrometer. High-resolution electron impact mass spectra (HREIMS) were obtained on JEOL MS route 600H instrument. Elemental analysis were performed on Vario EL-III C H N S analyzer. Column chromatography was performed over Merck silica gel (particle size: 60-120 Mesh) procured from Qualigens (India), and flash silica gel (particle size: 230-400 Mesh). Commercially available grades of organic solvents of adequate purity are used in many reactions.

General reaction conditions

β-Cyclodextrin (1mmol) was dissolved in 10mL distilled water by heating at 50-55 °C, to it was added dropwise, phenacyl bromide (1mmol) dissolved in acetone (1mL). After five minutes of continuous stirring at same temperature, amine (1mmol) in acetone (1mL) was added and the mixture was stirred at same temperature. After completion of the reaction, the crude products were isolated by extracting with ethyl acetate (5mL×3). The organic phase were separated and

washed with brine, dried over sodium sulphate and evaporated under vacuum. The product was further purified by column chromatography using 2% methanol/chloroform.

2-(4-Chlorophenyl)-imidazo[1,2-*a*]pyridine (5a). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.77-6.81 (m, 1H), 7.16-7.21 (m, 1H), 7.40 (d, 2H, *J* 8.5 Hz), 7.62 (d, 1H, *J* 9.0 Hz), 7.84 (s, 1H), 7.89 (d, 2H, *J* 8.5 Hz), 8.1 (d, 1H, *J* 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 108.63 (CH), 113.16 (CH), 117.85 (CH), 125.55 (CH), 126.05 (CH), 127.71 (CH), 129.33 (CH), 132.46 (C), 134.21 (C), 144.86 (C), 145.99 (C); IR (KBr) cm^{-1}: 1634, 760, 670; ES-MS (*m/z*): 229 $[M+H]^+$; HRMS-EI: found: 228.0450, calculated: 228.0455.

2-(4-Bromophenyl)-imidazo[1,2-*a*]pyridine (5b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.48-6.52 (m, 1H), 6.65-6.69 (m, 2H), 7.35 (d, 1H, *J* 9.0 Hz), 7.51 (d, 2H, *J* 8.3 Hz), 7.60 (d, 2H, 7.5 Hz), 7.86 (s, 1H), 8.13 (d, 1H, *J* 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 109.33, 113.26, 117.94, 125.57, 127.23, 130.32, 132.01, 134.32, 134.45, 144.69, 146.82; IR (KBr) cm^{-1}: 1632, 765, 506; ES-MS (*m/z*): 273(Br^{78}), 275(Br^{80}) $[M+H]^+$; HRMS-EI: found: 271.9937, calculated: 271.9950.

2-(3,4-Dichlorophenyl)-imidazo[1,2-*a*]pyridine (5c). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 6.96-7.00 (m, 1H), 7.34-7.41 (m, 1H), 7.53 (d, 1H, *J* 8.4 Hz), 7.81-7.89 (m, 2H), 8.09 (m, 2H), 8.34 (d, 1H, *J* 6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$+CD_3OD): δ 110.02, 113.99, 114.68, 124.88, 126.95, 127.30, 129.09, 129.84, 130.58, 132.69, 133.70, 143.91; IR (KBr) cm^{-1}: 1654, 1463, 760, 673; ES-MS (*m/z*): 263 $[M+H]^+$; HRMS-EI: found: 262.0065, calculated:. 262.0064.

2-(4-Methoxyphenyl)-imidazo[1,2-*a*]pyridine (5d). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.82 (s, 3H), 6.83-6.86 (m, 1H), 7.02 (d, 2H, *J* 8.2 Hz), 7.22-7.33 (m, 1H), 7.56 (m, 1H), 7.86 (d, 2H, *J* 8.2 Hz), 8.30 (s, 1H), 8.49-8.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 55.80, 108.32, 113.32, 115.54, 116.81, 119.01, 126.20, 128.58, 132.81, 133.01, 145.86, 161.82; IR (KBr) cm^{-1}: 1635, 1247, 760; ES-MS (*m/z*): 225 $[M+H]^+$; HRMS-EI: found: 224.0952, calculated:. 224.0950.

2-p-Tolylimidazo[1,2-*a*]pyridine (5e). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 3H), 6.59-6.68 (m, 1H), 7.10-7.14 (m, 1H), 7.23 (d, 2H, *J* 7.9 Hz), 7.60-7.62 (m, 1H), 7.80 (s, 1H), 7.85 (d, 2H, *J* 8.0 Hz), 8.06 (d, 1H, *J* 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6): δ 21.41, 108.35, 113.41, 117.82, 125.92, 126.31, 129.32, 130.21, 132.32, 134.29, 144.21; IR (KBr) cm^{-1}: 1634, 765; ES-MS (*m/z*): 209 $[M+H]^+$; HRMS-EI: found: 208.1005, calculated: 208.1001.

2-Phenylimidazo[1,2-*a*]pyridine (5f). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.85-6.91 (m, 1H), 7.23-7.25 (m, 1H), 7.30-7.34 (m, 1H), 7.43-7.46 (m, 2H), 7.59 (d, 1H, *J* 6.9 Hz), 7.97-7.80 (m, 2H), 8.42 (s, 1H), 8.52-8.54 (m, 1H); ^{13}C NMR (50 MHz, DMSO-d_6): δ 108.31, 113.40, 116.79, 125.69, 126.73, 127.21, 127.92, 130.01, 133.10, 143.92; IR (KBr) cm^{-1}: 1634, 762; ES-MS (*m/z*): 195 $[M+H]^+$; HRMS-EI: found: 194.0839, calculated: 194.0843.

6-Chloro-2-(3,4-dichlorophenyl)-imidazo[1,2-*a*]pyridine (5g). ^{1}H NMR (300 MHz, CD_3OD): δ 7.76-7.84 (m, 2H), 7.91 (d, 1H, *J* 9.6 Hz), 8.00 (dd, 1H, *J* 9.6, 1.6 Hz), 8.12 (d, 1H, *J* 1.2 Hz), 8.60 (s, 1H), 9.01 (m, 1H); ^{13}C NMR (50 MHz, CD_3OD) δ 111.24, 111.53, 124.28, 124.82, 125.50, 126.02, 127.08, 130.46, 132.40, 133.52, 136.88, 138.51; IR (KBr) cm^{-1}: 1650, 1215, 766, 671; ES-MS (*m/z*): 297 $[M+H]^+$; HRMS-EI: found: 295.9670, calculated: 295.9674.

6-Chloro-2-phenylimidazo[1,2-*a*]pyridine (5h). ^{1}H NMR (300 MHz, $CDCl_3$+ DMSO-d_6): δ 7.29-7.37 (m, 2H), 7.50-7.53 (m, 2H), 7.65 (d, 1H, *J* 7.0 Hz), 7.96-7.99 (m, 2H), 8.41 (s, 1H), 8.82-8.83 (m, 1H); IR (KBr) cm^{-1}: 1632, 750; ES-MS (*m/z*): 229 $[M+H]^+$; HRMS-EI: found: 228.0459, calculated: 228.0454.

6-Methyl-2-*p*-tolylimidazo[1,2-*a*]pyridine (5i). ^{1}H NMR (300 MHz, CD_3OD): δ 2.44 (s, 3H), 2.50 (s, 3H), 7.42 (d, 2H, *J* 8.2 Hz), 7.76 (d, 2H, *J* 8.3 Hz), 7.77-7.87 (m, 2H), 8.42 (s, 1H), 8.59 (s, 1H); ^{13}C NMR (50 MHz, CD_3OD) δ 16.97, 20.44, 110.54, 111.09, 123.65, 126.28, 126.89, 128.64, 130.30, 136.58, 136.68, 139.46, 141.55; IR (KBr) cm^{-1}: 1216, 761, 671; ES-MS (*m/z*): 223 $[M+H]^+$; HRMS-EI: found: 222.1159, calculated: 222.1156; *Anal*. Calcd for $C_{15}H_{14}N_2$: C, 81.06; H, 6.35; N, 12.61. Found: C, 81.13; H, 6.31; N, 12.53.

6-Chloro-2-(4-methoxyphenyl)-imidazo[1,2-*a*]pyridine (5j). ^{1}H NMR (300 MHz, CD_3OD + DMSO-d_6): δ 3.04 (s, 3H), 6.33 (d, 2H, *J* 8.8 Hz), 7.07 (d, 2H, *J* 8.8 Hz), 7.14 (m, 2H), 7.81 (s, 1H), 8.35 (s, 1H); ^{13}C NMR (50 MHz, CD_3OD + DMSO-d_6) δ 56.04, 110.92, 113.52, 114.77, 115.54, 119.03, 124.53, 127.48, 128.57, 129.50, 133.92, 137.47, 139.43, 161.88; IR (KBr) cm^{-1}: 1649, 1216, 760, 671; ES-MS (*m/z*): 259 $[M+H]^+$; HRMS-EI: found: 258.0560, calculated: 258.0557; *Anal*. Calcd for $C_{14}H_{11}ClN_2O$: C, 65.00; H, 4.29; N, 10.83. Found: C, 65.09; H, 4.26; N, 10.81.

2-(4-Bromophenyl)-imidazo[1,2-*a*]pyrimidine (7a). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94-6.97 (m, 1H), 7.57 (d, 2H, *J* 8.4 Hz), 7.84 (s, 1H), 7.93 (d, 2H, *J* 8.5 Hz), 8.51-8.53 (m, 1H), 8.79 (dd, 1H, *J* 6.9, 2.1 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 108.19, 109.51, 124.89, 129.79, 132.30, 133.01, 133.95, 138.23, 149.68, 152.72; IR (KBr) cm^{-1}: 1630, 760, 504; ES-MS (*m/z*): 274 (Br^{78}), 276 (Br^{80}), $[M+H]^+$; HRMS-EI: found: 272.9909, calculated: 272.9901.

2-Phenylimidazo[1,2-*a*]pyrimidine (7b). ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 6.81-6.83 (m, 1H), 7.43-8.16 (m, 5H), 7.80 (s, 1H), 8.42-8.43 (m, 1H), 8.52-8.53 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 108.21, 108.93, 127.40, 127.83, 128.62, 130.40, 133.86, 138.13, 149.53, 152.16; IR (KBr) cm^{-1}: 1687, 1597, 1076, 765; ES-MS (*m/z*): 196 $[M+H]^+$; HRMS-EI: found: 195.0796, calculated: 195.0794.

2-(3,4-Dimethoxyphenyl)-imidazo[1,2-*a*]pyrimidine (7c). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H), 3.87 (s, 3H), 7.10-7.13 (m, 1H), 7.65-7.70 (m, 3H), 8.54 (s, 1H), 8.55-8.56 (m, 1H), 9.05-9.07 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 56.03, 56.10, 109.01, 110.21, 110.32, 112.04, 121.81, 127.11, 133.86, 138.61, 149.73, 151.81; IR (KBr) cm^{-1}: 1642, 1082, 730, 665; ES-MS (*m/z*): 256 $[M+H]^+$; HRMS-EI: found: 255.1009, calculated: 255.1006; *Anal*. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.12; N, 16.46. Found: C, 65.94; H, 5.10; N, 16.51.

2-(3,4-Dichlorophenyl)-imidazo[1,2-*a*]pyrimidine (7d). ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.89-6.91 (m, 1H), 7.63-7.65 (m, 3H), 8.06 (s, 1H), 8.56-8.57 (m, 1H), 8.66-8.68 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 107.89, 109.31, 127.71, 128.31, 130.32, 133.01, 133.35, 133.83, 134.51, 138.14, 148.32, 151.83; IR (KBr) cm^{-1}: 1658, 1082, 731, 670; ES-MS (*m/z*): 264 $[M+H]^+$; HRMS-EI: found: 263.0018, calculated: 263.0016.

2-(4-Chlorophenyl)-imidazo[1,2-*a*]pyrimidine (7e). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87-6.89 (m, 1H), 7.45-7.89 (m, 4H), 7.89 (s, 1H), 8.42-8.44 (m, 1H), 8.53-8.55 (m, 1H); ^{13}C NMR (75

MHz, DMSO-d_6) δ 108.31, 109.53, 127.36, 129.81, 131.17, 133.89, 134.20, 139.61, 148.31, 152.01; IR (KBr) cm^{-1}: 1611, 1076 735, 675; ES-MS (*m/z*): 207 $[M+H]^+$; HRMS-EI: found: 206.1096, calculated: 206.1094; *Anal*. Calcd for $C_{12}H_8ClN_3$: C, 62.75; H, 3.51; N, 18.30. Found: C, 62.82; H, 3.47; N, 18.27.

2-(4-Chlorophenyl)-imidazo[1,2-*a*]pyrazine (9a). ^1H NMR (300 MHz, $CDCl_3$): δ 7.44-7.49 (m, 2H), 7.91-7.93 (m, 2H), 7.95-7.97 (m, 2H), 8.08-8.10 (m, 1H), 9.13 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$ + DMSO-d_6) δ 109.80, 119.13, 126.04, 127.69, 130.01, 130.44, 131.62, 133.60, 142.79, 143.86; IR (KBr) cm^{-1}: 2350, 1610, 1215, 761, 672; ES-MS (*m/z*): 230 $[M+H]^+$; HRMS-EI: found: 229.0408, calculated: 229.0406. *Anal*. Calcd for $C_{12}H_8ClN_3$: C, 62.75; H, 3.51; N, 18.30. Found: C, 62.84; H, 3.49; N, 18.27.

2-Phenylimidazo[1,2-*a*]pyrazine (**9b).** ^1H NMR (200 MHz, $CDCl_3$): δ 7.39-7.53 (m, 4H), 7.89 (d, 1H, *J* 6.9 Hz), 7.96-8.01 (m, 2H), 8.10 (dd, 1H, *J* 6.9, 2.2 Hz), 9.12 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 109.70, 119.11, 126.88, 128.78, 129.35, 129.95, 130.45, 133.07, 133.59, 143.91; IR (KBr) cm^{-1}: 2358, 1595, 1216, 761, 670; ES-MS (*m/z*): 196 $[M+H]^+$; HRMS-EI: found: 195.0798, calculated: 195.0796; *Anal*. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.64; N, 21.52. Found: C,73.89; H, 4.61; N, 21.55.

2-(3,4-Dichlorophenyl)-imidazo[1,2-*a*]pyrazine (9c). ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6): δ 7.63-7.65 (m, 3H), 7.93-7.96 (m, 2H), 8.01-8.03 (m, 1H), 8.90 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 109.69, 119.01, 127.76, 128.29, 129.89, 130.10, 130.43, 130.53, 131.50, 133.58, 133.71, 143.90, IR (KBr) cm^{-1}: 2281, 1601, 1197, 758, 672; ES-MS (*m/z*): 264 $[M+H]^+$; HRMS-EI: found: 263.0017, calculated: 263.0016; *Anal*. Calcd for $C_{12}H_7Cl_2N_3$: C, 54.57; H, 2.67; N, 15.90. Found: C,54.65; H, 2.63; N, 15.84.

2-(4-Bromophenyl)-imidazo[1,2-*a*]pyrazine (9d). ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 7.57 (d, 2H, *J* 7.8 Hz), 7.80 (d, 2H, *J* 7.7 Hz), 7.94-8.00 (m, 2H), 8.03-8.04 (m, 1H), 9.0 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 108.90, 118.91, 122.11, 127.58, 128.79, 130.43, 130.62, 130.72 133.61, 142.80, IR (KBr) cm^{-1}: 2300, 1589, 1203, 750, 671; ES-MS (*m/z*): 274 (Br^{78}), 276 (Br^{80}), $[M+H]^+$; HRMS-EI: found: 272.9903, calculated: 272.9901; *Anal*. Calcd for $C_{12}H_8BrN_3$: C, 52.56; H, 2.94; N, 15.35. Found: C, 52.64; H, 2.91; N, 15.38.

2-Phenyl-benzo[d]imidazo[2,1-*b*]thiazole (11a). ^1H NMR (300 MHz, $CDCl_3$): δ 6.45-6.97 (m, 6H), 7.57-7.58 (m, 1H), 7.64-7.66 (m, 1H), 7.88-7.89 (m, 1H), 7.95 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 107.26, 113.07, 123.95, 124.85, 125.32, 125.67, 126.63, 127.99, 128.11, 129.15, 129.39, 140.12, 148.80; IR (KBr) cm^{-1}: 3400, 2360, 1592; ES-MS (*m/z*): 251 $[M+H]^+$; HRMS-EI: found: 250.0567, calculated: 250.0564.

2-(4-Chlorophenyl)-benzo[d]imidazo[2,1-*b*]thiazole (11b). ^1H NMR (300 MHz, $CDCl_3$): δ 7.33-7.38 (m, 3H), 7.44-7.45 (m, 1H), 7.56-7.57 (m, 1H), 7.65-7.67 (m, 1H), 7.76-7.80 (m, 2H), 7.91 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 107.13, 112.97, 123.80, 124.65, 125.73, 126.68, 126.70, 127.89, 128.90, 129.32, 132.10, 139.31, 148.62; IR (KBr) cm^{-1}: 3431, 2930, 1590; ES-MS (*m/z*): 285 $[M+H]^+$; HRMS-EI: found: 284.0178, calculated: 284.0176.

2-(4-Methoxyphenyl)-benzo[*d*]imidazo[2,1-*b*]thiazole (11c). ^1H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H), 6.93-6.97 (m, 2H), 7.25-7.45 (m, 2H), 7.46-7.47 (m, 1H), 7.53-7.54 (m, 1H), 7.66-

7.81 (m, 2H), 7.85 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.83, 107.36, 113.13, 113.91, 114.12, 122.98, 123.83, 125.32, 128.55, 129.31, 139.11, 152.41, 160.43; IR (KBr) cm^{-1}: 3401, 2930, 1598, 1487; ES-MS (*m/z*): 281 $[M+H]^+$; HRMS-EI: found: 280.0680, calculated: 280.0670; *Anal*. Calcd for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.31; N, 9.99. Found: C, 68.57; H, 4.35; N, 9.94.

2-Benzofuran-2-yl-imidazo[1,2-*a*]pyridine (12a). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.79-6.84 (m, 1H), 7.19-7.32 (m, 4H), 7.51-7.54 (m, 1H), 7.61-7.64 (m, 2H), 7.99 (s, 1H), 8.13-8.16 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 103.41, 109.99, 111.53, 113.28, 118.02, 121.61, 123.40, 124.82, 125.83, 126.20, 129.44, 137.87, 146.29, 151.78, 155.31; IR (KBr) cm^{-1}: 2358, 1654, 1030, 770, 665; ES-MS (*m/z*): 235 $[M+H]^+$; HRMS-EI: found: 234.0782, calculated: 234.0793; *Anal*. Calcd for $C_{15}H_{10}N_2O$: C,76.92; H, 4.31; N, 11.96. Found: C,76.96; H, 4.29; N, 11.91.

2-Benzofuran-2-yl-imidazo[1,2-*a*]pyrimidine (12b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90 (dd, 1H, *J* 6.8, 4.1 Hz), 7.23-7.28 (m, 1H), 7.29-7.34 (m, 1H), 7.43 (d, 1H, *J* 0.5 Hz, long range coupling), 7.52 (dd, 1H, *J* 7.9, 0.7 Hz), 7.65 (dd, 1H, *J* 7.1, 1.5 Hz), 7.95 (s, 1H), 8.46 (dd, 1H, *J* 6.75, 2.0 Hz), 8.59 (dd, 1H, *J* 4.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 104.16, 109.36, 109.83, 111.54, 121.90, 123.85, 125.43, 128.86, 135.89, 137.15, 148.65, 151.33, 152.10, 154.75; IR (KBr) cm^{-1}: 2362, 1653, 1028, 771, 668; ES-MS (*m/z*): 236 $[M+H]^+$; HRMS-EI: found: 235.0747, calculated: 235.0746; *Anal*. Calcd for $C_{14}H_9N_3O$: C, 71.47; H, 3.85; N, 17.86. Found: C, 71.50; H, 3.80; N, 17.79.

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