The regioselective synthesis of 2-substituted [[(α-aryl-(α′-amino)]methyl]imidazoles through a catalyst-free, one-pot, three-component reaction: scope and limitations

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Abstract
An efficient, facile and catalyst-free method for the regioselective synthesis of 2-substituted [[(α-aryl-α′-amino)]methyl]imidazoles through a one-pot, three-component reaction of imidazole, aromatic aldehydes and cyclic secondary amines has been developed. Only C-2 substituted products were obtained, with no formation of either N-1 or C-4(5) substituted isomers. The position of substitution has been confirmed by X-ray crystal structures of two typical examples. A plausible mechanism for the formation of these products is depicted.

Keywords: 2-Substituted [[(α-aryl-α′-amino)]methyl]imidazoles, catalyst-free, one-pot, three-component reaction

Introduction

The imidazole nucleus is a common structural motif encountered in numerous biomolecules such as biotin, essential amino acid histidine and the pilocarpine alkaloids.[1] Among other naturally-occuring imidazoles, are purine nucleobases (adenine and guanine) and vitamin B_{12}. Several imidazole ring-containing drugs, such as ketoconazole, itraconazole and clotrimazole, are known to be potent cytochrome P450 (CYP) 3A inhibitors[2] and some imidazole alkaloids manifest antimicrobial, anticryptococcal and cytotoxic activities.[1a,3] Various imidazole derivatives have nitric oxide synthase,[4] 5-lipoxygenase inhibitors,[3,5] substrate with CB_1,[1b,6] VEGE receptors I and II,[1b,7] and neuropeptide Y antagonistic activities.[1b,8] Many functionalized imidazoles behave as antibiotics,[9] fungicides,[10] antiulceretics,[11] antidiabetics, antihypertensive and anti-inflammatory agents.[1b,12] Consequently, it is not surprising that developments of various strategies for their synthesis and selective functionalization has instigated a growing interest in both industry and academia and continues to be a significant subject in organic synthesis and medicinal chemistry.[13]

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The development of efficient methodologies in synthesizing biologically important heterocycles from readily available starting materials has emerged as an attractive topic in present day organic chemistry.[14] In this regard, multi-component reactions can be effective in constructing highly functionalized organic molecules from readily available starting materials in a single step with inherent flexibility for creating molecular complexity and diversity coupled with minimization of time, labour, cost and waste production.[15]

In continuation of our efforts towards the synthesis and functionalization of N-containing heterocycles,[16] we sought to develop new synthetic strategies that generate diverse 2-substituted imidazoles. Some orthogonally protected 2-(α-substitutedamidoalkyl)-imidazoles have been prepared by reaction of imidazolium ylides (generated from N-substituted imidazole and Boc_2O) with imines.[17] Another method is based on reaction of imines with lithiated imidazoles.[18] Several imidazoles can be obtained starting from amino acids.[19,20] The first example of a diastereoselective thio-Ugi reaction with chiral *R*-methylbenzylamine produced several chiral thioamides. The reaction of thioamides with ammonia resulted in substituted amidines, which after cyclization in aqueous HCl produced 2-aminoalkylimidazole derivatives.[21] A traceless solid phase base-catalyzed method[22] for the construction of 2-aminomethyl azole libraries by a two step procedure has been described. In the first step, a resin-bound carbamyl chloride, the azoles and aldehydes were loaded onto the solid phase to form the resin-bound 2-substituted azoles which after reaction with various nucleophiles under acid catalysis resulted in the formation of 2-aminomethyl azoles in the second step. Later, the formation of the same type of 2-aminomethyl azoles, again by a base-catalyzed two step procedure,[23] the products obtained from the reaction of an azolium ylide with reactive carbonyl compounds were transformed into 2-aminomethyl azoles after solvolysis in the presence of nucleophiles.

Results and Discussion

We, herein for the first time, report a three-component reaction of imidazole, secondary amines and aromatic aldehydes to form diverse 2-substituted [[(α-aryl-α′-amino)]methyl]imidazoles under catalyst–free conditions. In order to develop standard conditions, the reaction of 4-chlorobenzaldehyde (2 mmol), imidazole (1 mmol) and piperidine (3 mmol) was studied. At room temperature for 24 h no appreciable conversion of imidazole into the desired product was observed. Heating at 110 ºC for 24 h led only to very poor conversion (Table 1, entry 2). The reaction was tried in different solvents and after some screening with several polar and non-polar solvents, toluene was fond to be the best choice. Complete conversion of imidazole occurred after only 6 h of reflux in toluene. Bases such as K_2CO_3, Cs_2CO_3, Et_3N, $(^iPr)_3N$, DABCO had no additional influence in this reaction suggesting excess amine (3 equivalents) itself providing the basic condition required. With lesser equivalents of the starting secondary amine, the reaction did not go to completion. The complete optimization is summarised in Table 1.

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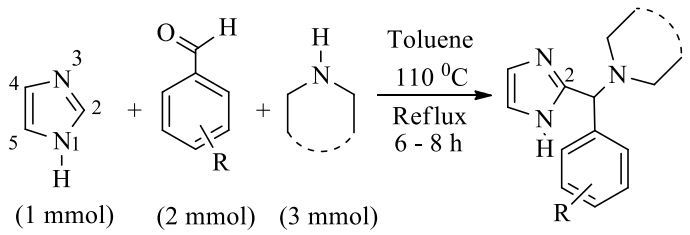
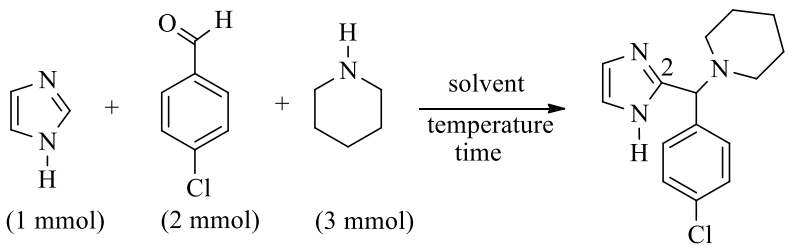


Scheme 1. Synthesis of 2-substituted imidazoles by a three-component reaction.

Table 1. Three component reaction of imidazole, 4-chlorobenzaldehyde and piperidine



Entry	Solvent	Temperature (°C)	Time (h)	Yield (%) (isolated)
1	-	Room temperature	24	nil
2	-	110	24	25
3	CH_2Cl_2	45	24	10
4	MeOH	65	24	20
5	EtOH	80	24	20
6	THF	65	24	15
7	MeCN	85	24	50
8	1,4-dioxane	100	24	55
9	xylene	110	24	50
10	toluene	110	6	88

After standardizing the reaction conditions, the reaction was carried out with various aromatic aldehydes possessing both electron-donating and electron-withdrawing groups along with cyclic secondary amines. The yields were excellent in almost all cases. Unfortunately, we were not able to isolate a product from treatment of N-methylimidazole with secondary amines and aromatic aldehydes. Other substituted imidazoles e.g., 2-methylimidazole, 4,5-diphenylimidazoles and various substituted benzimidazoles did not react at all under the present conditions. We, therefore propose that the basicity [$pK_{BH^+}(MeNO_2)$ = 14.64][24] and hence corresponding nucleophilicity of the starting imidazole is a very important factor in this reaction.

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Thus, imidazole is quite a strong base in nitromethane, whereas, the pK_{BH}^{+} of benzimidazole is 1.7 units lower due to the annulated benzene ring. One of the most interesting facts about this reaction is that only 2-substituted imidazoles were formed and no 1-, 4- or 5-substituted products were obtained. Thus, the position of attack was highly selective. Another point that needs to be mentioned is that this methodology works well only with cyclic secondary amines. A possible explanation is that since the reaction goes via the formation of an iminium ion (as suggested in the mechanism, Scheme 2), the interaction of the NCH_2 protons with those of the aromatic aldehyde nucleus is probably lower for cyclic amines compared to acyclic ones.

Table 2. Three-component reaction between imidazole, aromatic aldehydes and cyclic secondary amines

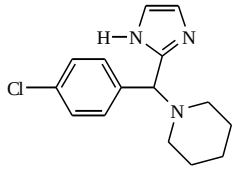
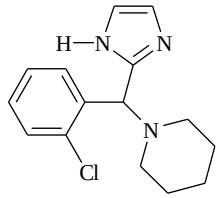
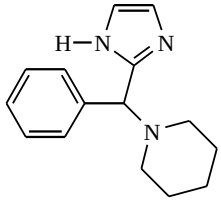
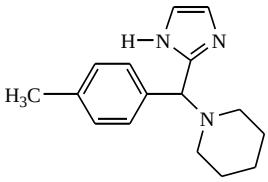
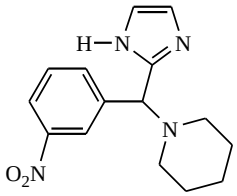
Entry	Product	Time (h)	Yield (%) (isolated)
1		6	88
2		6	86
3		6	85
4		7	85
5		7	80

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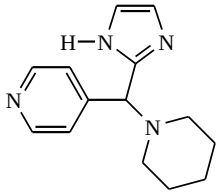
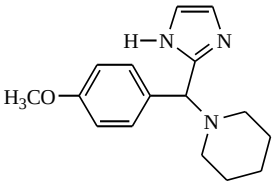
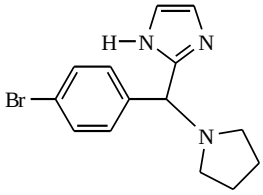
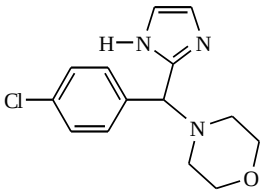
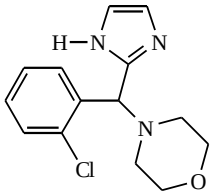
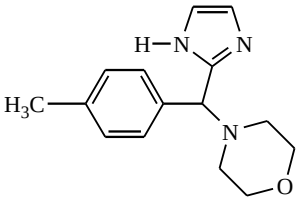
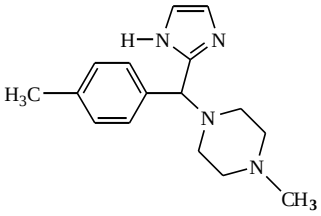
Table 2. Continued

Entry	Product	Time (h)	Yield (%) (isolated)
6		6.5	84
7		8	81
8		8	80
9		6	86
10		6	85
11		6	86
12		8	81

Imidazole and *N*-methylimidazole are well-known to acylate at the 2-position via reaction with an acid chloride in the presence of a base and the reaction is believed to involve conversion

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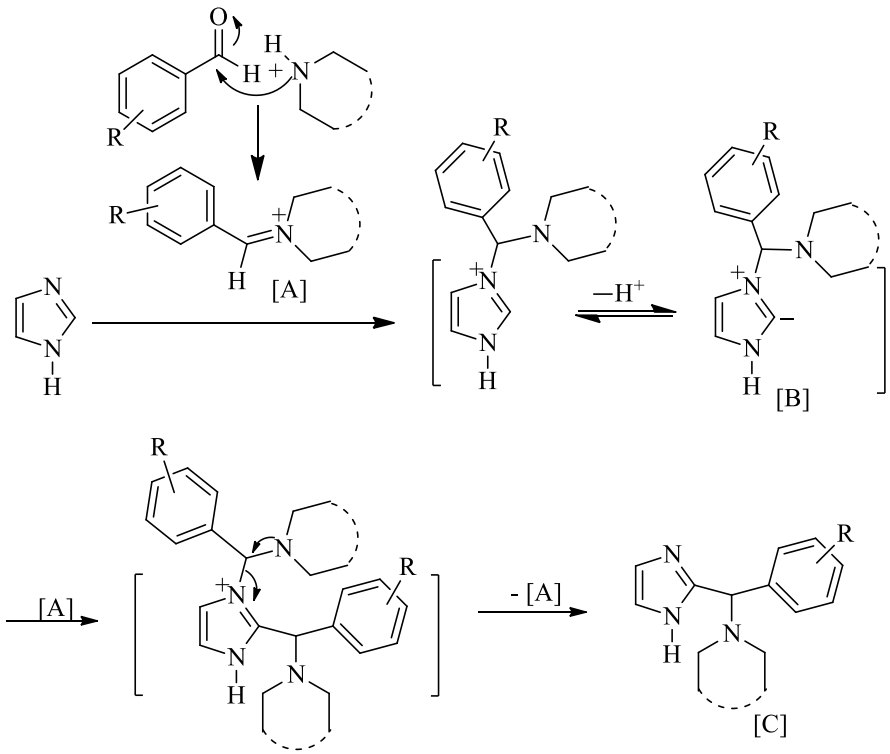
into an imidazolium ylide as an intermediate.[25] The ylide is proposed to react with a second equivalent of benzoyl chloride in a bimolecular fashion to form a 2-benzoylimidazole. The exclusive formation of 2-substituted imidazole in our case, is strong evidence in favor of the involvement of the imidazolium ylide as an intermediate in the mechanistic pathway because normal Mannich-type substitution would be expected to lead to 4- or 5-substituted imidazoles.[26] The suggested mechanism is shown in Scheme 2 in which imidazolium ylide [B] formed by the reaction of imidazole and iminium ion [A], reacts with another molecule of iminium ion at the 2-position to give the final product [C].



Scheme 2. Plausible mechanism of the three-component reaction of imidazole, secondary amines and aromatic aldehydes

The structures of two of the products (Table 2, entries 1 and 2) were confirmed by X-ray diffraction analyses of single crystals and are shown below in Figures 1 and 2. Spectra of some representative products are given in the supplementary information.

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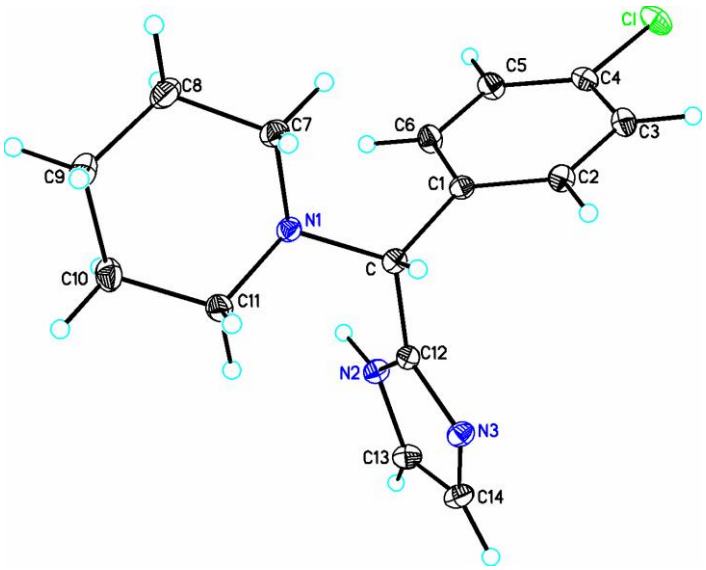

Figure 1. ORTEP diagram of a single crystal of 1-[(4-chlorophenyl)-(1*H*-imidazol-2-yl)methyl]-piperidine (Table 2, entry 1) showing the crystallographic numbering (CCDC 777835).

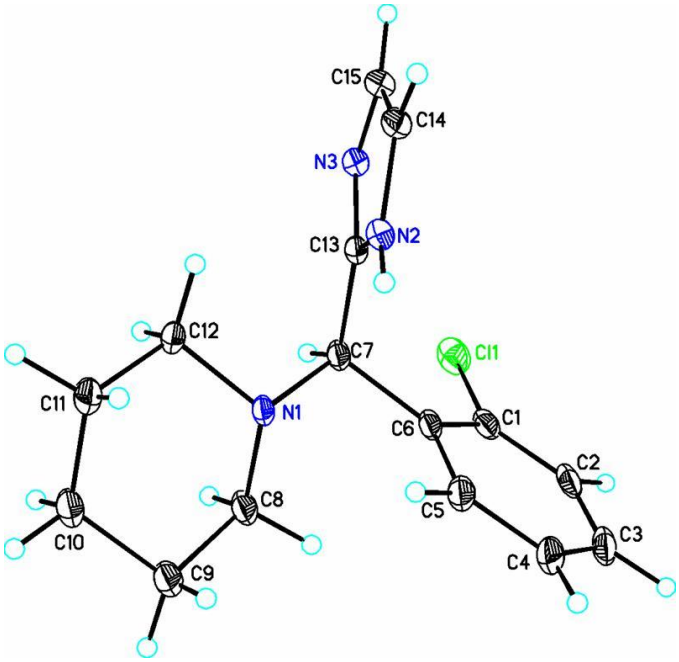

Figure 2. ORTEP diagram of a single crystal of 1-[(2-chlorophenyl)-(1*H*-imidazol-2-yl)methyl]-piperidine (Table 2, entry 2) showing the crystallographic numbering (CCDC 777834).

Conclusion

In summary, a new three-component reaction involving imidazole, aromatic aldehydes and secondary amines to form diverse 2-substituted [[(α-aryl-α′-amino)]methyl]imidazoles has been

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developed for the first time. Catalyst–free conditions, exclusive formation of the 2-substituted imidazoles, moderate reaction conditions and simple work-up are the major features of this methodology.

Experimental Section

General. Aromatic aldehyde (2 mmol), imidazole (1 mmol), secondary amine (3 mmol) and toluene (2 mL) were mixed together in a 25 mL Erlenmeyer flask and heated at reflux in an oil bath at 110 ºC for the stipulated time (monitored by TLC). After completion of the reaction, toluene was removed under reduced pressure in a rotary evaporator and the residue was dissolved in EtOAc (5 mL). The compound was then purified by column chromatography in basic alumina using petroleum ether (60-80 ºC) and EtOAc as eluant. The IR, ^{1}H NMR and ^{13}C NMR data of all the representative compounds are given below.

1-[(4-Chlorophenyl)-(1*H*-imidazol-2-yl)methyl]piperidine (Table 2, entry 1). White solid, mp 168-170 °C (EtOAc); IR (KBr): 2934, 2798, 2376, 1449, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.72 (s, 1H), 7.33–7.26 (m, 4H), 6.97 (s, 2H), 4.67 (s, 1H), 2.40–2.00 (m, 4H), 1.90 – 1.30 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.4, 136.7, 133.4, 129.9, 128.6, 69.4, 52.5, 26.2, 24.3; Anal. calcd. for $C_{15}H_{18}ClN_3$; C: 65.33, H: 6.58, N: 15.24%. Found: C: 65.22, H: 6.63, N: 15.30%.

1-[(2-Chlorophenyl)-(1*H*-imidazol-2-yl)methyl]piperidine (Table 2, entry 2): White crystalline solid, mp 188-190 °C (MeOH); IR (KBr): 2936, 2804, 2378, 1566, 1452, 1108 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.42 (s, 1H), 8.39 (d, J = 7.5 Hz, 1H), 7.86 – 7.75 (m, 2H), 7.73 – 7.65 (m, 1H), 7.45 (s, 1H), 7.25 (s, 1H), 5.43 (s, 1H), 2.90 – 2.50 (m, 4H), 1.91 (br. s, 4H), 1.83 (br. s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 146.2, 137.7, 133.1, 130.4, 129.2, 128.6, 127.5, 127.1, 116.3, 64.4, 52.1, 52.6, 24.2; Anal. calcd. for $C_{15}H_{18}ClN_3$; C: 65.33, H: 6.58, N: 15.24%. Found: C: 65.24, H: 6.62, N: 15.29%.

1-[(1*H*-Imidazol-2-yl)phenylmethyl]piperidine (Table 2, entry 3): White solid, mp 188-190 °C (EtOAc); IR (KBr): 2936, 2862, 2794, 1831, 1533, 1446, 1096, 735 cm^{-1}; ^{1}H NMR (300 MHz,$CDCl_3$ + three drops of DMSO-d_6) δ: 9.70 (s, 1H), 7.39 (d, J = 6.6 Hz, 2H), 7.34– 7.20 (m, 3H), 6.96 (s, 2H), 4.60 (s, 1H), 2.50 – 2.20 (m, 4H), 1.70 – 1.30 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$ + three drops of d_6 - DMSO) δ: 148.4, 139.0, 128.2, 127.1, 70.0, 52.5, 25.9, 24.1; Anal. calcd. for $C_{15}H_{19}N_3$; C: 74.65, H: 7.94, N: 17.41%. Found: C: 74.51, H: 8.02, N: 17.47%.

1-[(1*H*-Imidazol-2-yl)-(4-methylphenyl)methyl]piperidine (Table 2, entry 4): White solid, mp 174-176 °C (EtOAc); IR (KBr): 3051, 2929, 2801, 2371, 1560, 1441, 1288, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + three drops of DMSO-d_6) δ: 7.30 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 8.1 Hz, 2H), 6.93 (s, 2H), 4.55 (s, 1H), 2.41 – 2.25 (m, 7H), 1.59 – 1.41 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$ + three drops of d_6 - DMSO) δ: 148.7, 136.7, 135.9, 128.8, 128.1, 69.7, 52.5, 52.9,

24.2, 20.8; Anal. calcd. for $C_{16}H_{21}N_3$; C: 75.26, H: 8.29, N: 16.46%. Found: C: 75.20, H: 8.30, N: 16.51%.

1-[(1*H*-Imidazol-2-yl)-(3-nitrophenyl)methyl]piperidine (Table 2, entry 5): White solid, mp 184-186 °C (EtOAc); IR (KBr): 3033, 2988, 2880, 1891, 1572, 1408, 1206 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 12.01 (s, 1H), 8.30 (s, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 7.8 Hz,1H), 7.56 (d, *J* = 8.1 Hz, 1H), 6.92 (br. s, 2H), 4.70 (s, 1H), 2.27 – 2.13 (m, 4H), 1.43 (br. d, *J* = 5.1 Hz, 4H), 1.29 (br. d, *J* = 4.2 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 147.8, 146.1, 142.3, 135.2, 129.6, 122.9, 122.2, 117.8, 116.6, 67.7, 51.7, 25.7, 24.1; Anal. Calcd. for $C_{15}H_{18}N_4O_2$; C: 62.92, H: 6.34, N: 19.57%. Found: C: 62.80, H: 6.40, N: 19.63%.

1-[(1*H*-Imidazol-2-yl)-(4-pyridinyl)methyl]piperidine (Table 2, entry 6): Off - white solid, mp 170-172 °C (EtOAc); IR (KBr): 3035, 2964, 2808, 2325, 1898, 1564, 1441, 1088 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 11.89 (s, 1H), 8.46 (d, *J* = 4.5 Hz, 2H), 7.39 (d, *J* = 4.5 Hz, 2H), 7.00 (s, 1H), 6.77 (s, 1H), 4.53 (s, 1H), 2.25 – 2.12 (m, 4H), 1.45 (br. d, *J* = 5.1 Hz, 4H), 1.31 (br. d, *J* = 4.5 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 149.6, 148.8, 145.9, 123.5, 67.9, 51.9, 25.6, 24.1; Anal. calcd. for $C_{14}H_{18}N_4$; C: 69.39, H: 7.49, N: 23.12%. Found: C: 69.29, H: 7.55, N: 23.17%.

1-[(1*H*-Imidazol-2-yl)-(4-methoxyphenyl)methyl]piperidine (Table 2, entry 7): Pale yellow solid, mp 180-182 °C (EtOAc); IR (KBr): 2998, 2929, 2880, 2372, 1450, 1296, 1108 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.59 (s, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.96 (s, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.59 (s, 1H), 3.80 (s, 3H), 2.43 – 2.37(m, 2H), 2.27 – 2.24 (m, 2H), 1.60 – 1.53 (m, 4H), 1.46 – 1.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.0, 130.3, 129.6, 113.9, 69.4, 55.2, 52.6, 26.2, 24.3; Anal. calcd. for $C_{16}H_{21}N_3O$; C: 70.82, H: 7.80, N: 15.49%. Found: C: 70.69, H: 7.88, N: 15.54%.

2-[[(4-Bromophenyl)-(1-pyrrolidinyl)]methyl]imidazole (Table 2, entry 8): Pale yellow solid, mp 176-178 °C (EtOAc); IR (KBr): 3039, 2964, 2800, 1898, 1570, 1483, 1446, 1096, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 9.72 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.95 (s, 2H), 4.54 (s, 1H), 2.60 – 2.30(m, 4H), 1.26 (br. s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.9, 139.3, 131.8, 129.4, 121.5, 68.4, 53.0, 23.4; Anal. calcd. For $C_{14}H_{16}BrN_3$; C: 54.91, H: 5.27, N: 13.72%. Found: C: 54.79, H: 5.32, N: 13.79%.

4-[(4-Chlorophenyl)-(1*H*-imidazol-2-yl)methyl]morpholine (Table 2, entry 9): White solid, mp 172-174 °C (EtOAc); IR (KBr): 2959, 2857, 2807, 2651, 1842, 1565, 1485, 1452, 1289, 1107 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 12.25 (s, 1H), 7.78 (d, *J* = 8.7 Hz, 2H), 7.65 (d, *J* = 8.4 Hz, 2H), 7.19 (s, 2H), 4.78 (s, 1H), 3.85 – 8.81 (m, 4H), 2.70 – 2.30 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 146.4, 138.4, 131.9, 130.3, 128.3, 127.5, 116.9, 68.2, 66.2, 51.6; Anal. calcd. for $C_{14}H_{16}ClN_3O$; C: 60.54, H: 5.81, N: 15.13%. Found: C: 60.41, H: 5.88, N: 15.19%.

4-[(2-Chlorophenyl)-(1*H*-imidazol-2-yl)methyl]morpholine (Table 2, entry 10): Pale white solid, mp 170-172 °C (EtOAc); IR (KBr): 3027, 2957, 2860, 2813, 1935, 1820, 1561, 1451, 1278, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.71 (dd, *J* = 7.5 and 1.8 Hz, 1H), 7.35 (dd, *J* = 7.8 and 1.5 Hz, 1H), 7.30 – 7.15 (m, 2H), 7.00 (s, 2H), 5.22 (s, 1H), 3.90 – 3.70(m, 4H), 2.70 – 2.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 146.5, 135.6, 134.4, 130.0, 129.7, 128.9, 127.1,

67.0, 64.8, 51.9; Anal. calcd. for $C_{14}H_{16}ClN_3O$; C: 60.54, H: 5.81, N: 15.13%. Found: C: 60.44, H: 5.87, N: 15.17%.

4-[(1*H*-Imidazol-2-yl)-(4-methylphenyl)methyl]-morpholine (Table 2, entry 11): White solid, mp 172-174 °C (EtOAc); IR (KBr): 2963, 2856, 2804, 1852, 1566, 1372, 1290 and 1109 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ: 11.91 (s, 1H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.86 (s, 2H), 4.39 (s, 1H), 2.28 – 2.24 (m, 4H), 2.21 (s, 3H), 2.14 – 2.10 (m, 4H); ^{13}C NMR (75 MHz DMSO-d_6) δ: 147.7, 136.9, 136.9, 129.3, 128.8, 69.5, 66.7, 55.2, 21.1; Anal. calcd. for $C_{15}H_{19}N_3O$; C: 70.01, H: 7.44, N: 16.33%. Found: C: 69.88, H: 7.49, N: 16.41%.

1-[(1*H*-Imidazol-2-yl)-(4-methylphenyl)-methyl]-4-methyl-piperazine (Table 2, entry 12): White solid, mp 186-188 °C (EtOAc); IR (KBr): 2938, 2880, 2799, 1890, 1511, 1456, 1292, 1153, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.30 (d, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 6.95 (s, 2H), 4.56 (s, 1H), 2.41 (br. s, 8H), 2.28 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 148.4, 137.1, 135.7, 129.2, 128.1, 121.8, 69.2, 55.1, 51.4, 45.8, 20.9; Anal. calcd. for $C_{16}H_{22}N_4$; C: 71.08, H: 8.20, N: 20.72%. Found: C: 70.97, H: 8.27, N: 20.76%.

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