Syntheses of *N*-[3-(1-Methyl-1*H*-2-imidazolyl)propyl]benzamides and *N*-[3-(1-Methyl-1*H*-2-imidazolyl)propyl]benzenesulfonamides

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A series of substituted *N*-(4-substituted-benzoyl)-*N*-[3-(1-methyl-1*H*-imidazol-2-yl)propyl]amines (**13**) and *N*-arylsulfonyl-*N*-[3-(1-methyl-1*H*-imidazol-2-yl)propyl]amines (**14**) were prepared from the reaction of 3-(1-methyl-1*H*-imidazol-2-yl)propan-1-amine (**7**) with substituted benzoyl chloride or substituted-benzene sulfonyl chloride respectively. Compound **7** was prepared by two independent methods.

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Study of arachidonic acid cascade has led to the discovery of thromboxane A_2 (TXA_2) [1] and prostacyclin (PGI_2) [2], which play important roles in the cardiovascular system and the regulation of platelet function [3].

Agents that might selectively interfere with enzymes might be potential drugs useful in the treatment of cardiovascular disease. In particular, selective inhibition without inhibiting PGI_2 synthesis of TXA_2 appears to be an interesting target since TXA_2 causes seemingly adverse cardiovascular effects such as vasoconstriction [4], platelet aggregation [3], atherosclerosis [5], ischemia [6], and sudden death [7]. In addition, TXA_2 has been shown to be the most potent endogenous vasoconstrictor known, it was hoped that some TX inhibitors might have antihypertensive activity in certain forms of hypertension where in TX maintains blood pressure [8]. Several laboratories have investigated the selective inhibitors of thromboxane synthetase (TXS) such as dazoxiben [9] (**I**), 4'-(1H-imidazol-1-yl)acetophenone [10] and 4-[(2-pyridylmethyl)-amino]benzoic acid [11]. Also, the syntheses of *N*-[3-(1*H*-imidazol-1-yl)propyl]benzamides (**II**) as TXS inhibitor have been reported [8].

These agents were developed from an early observation that imidazole was a selective (if not potent) inhibitor of human platelet TXS [12]. Our approach to this problem involved the attachment of highly polar but neutral moieties such as aryl amides or aryl sulfonamides to 1-methylimidazole nucleus to give compounds **III** and **IV** (Figure 1) respectively.

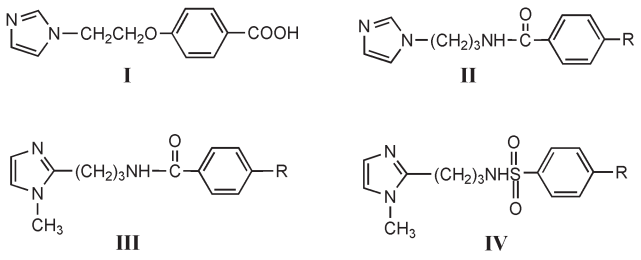


Figure 1

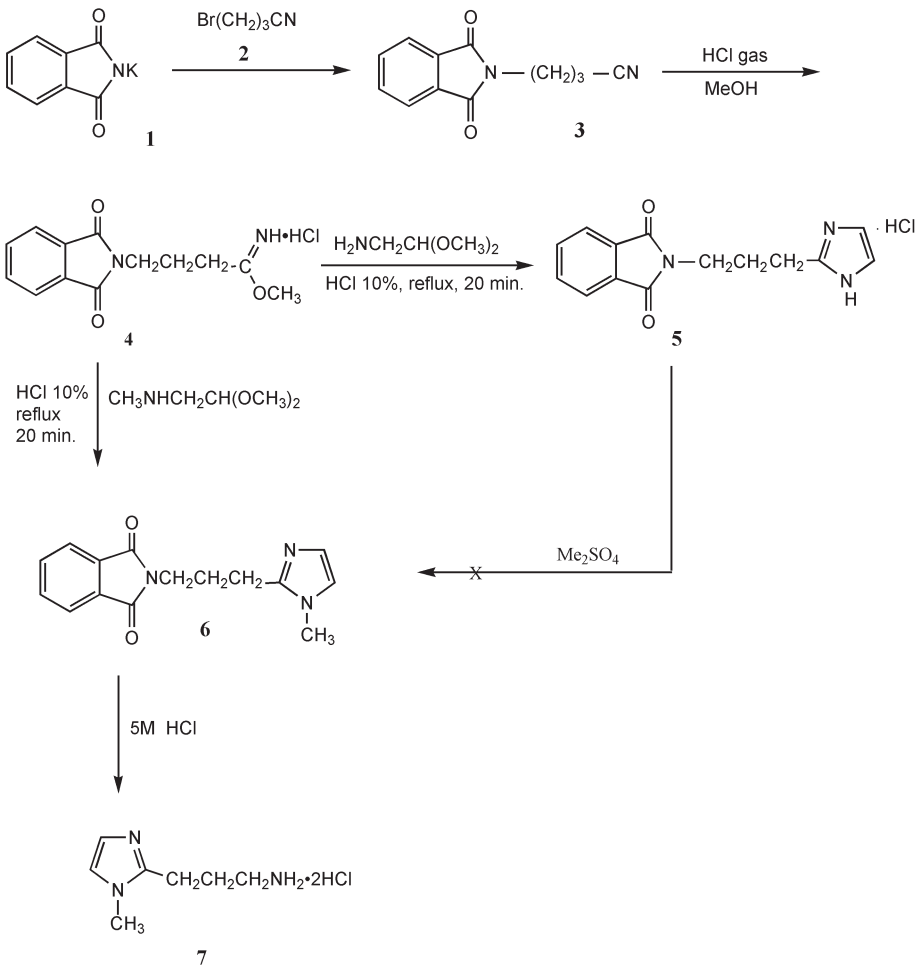
In the other hand, hypolipidemic and antibacterial activities of polyamides containing 1-methylimidazole-2-propylamine have been reported [13-15]. Finally, it has been shown that TXS is present in all stages of spermatogenesis cells; spermatogonia, spermatocytes, spermatides, and spermatozoa [16]. Thus, we would like to report the synthesis of the title compounds as possible drugs effective in fertility regulation [17,18].

Reaction of potassium phthalimide (**1**) with 4-bromobutyronitrile in dimethyl formamide gave 4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)butyronitrile (**3**) in 78% yield [19]. Compound **3** was converted to [3-(1*H*-imidazol-2-yl)propyl]-1*H*-isoindole-1,3(2H)-dione (**5**) by a known procedure [20].

Methylation of compound **5** with dimethyl sulfate or dimethyl carbonate failed and did not give the desired product **6**. However, compound **6** was directly prepared from the reaction of compound **4** with methylaminoacetaldehyde dimethylacetyal in methanol in 69% yield [21]. Hydrolysis of compound **6** with 5 *M* hydrochloric acid [22] gave the desired compound, namely, 3-(1-methyl-1*H*-imidazol-2-yl)propan-1-amine dihydrochloride [21] (**7**) in 62% yield (Scheme 1).

The second route for the preparation of compound **7** starts from the readily available 1-methyl-1*H*-imidazol-2-carbadehyde (**8**) [23]. Condensation of ethyl cyanoacetate with compound **8** gave ethyl 2-cyano-3-(1-methyl-1*H*-imidazol-2-yl)acrylate (**9**) [24]. Hydrolysis and decarboxylation of compound **9** for the preparation of compound **10** failed. The alternative method for the preparation of compound **10** could be through the intermediate **11**. The latter was prepared from the condensation of cyanoacetic acid with aldehyde **8**. Compound **11** was decarboxylated during the work up to give compound **10**. However, the yield of this procedure (32%) was not satisfactory. Finally, compound **10** could be prepared in good yield (75%) from the Wittig reaction of diethyl cyanomethylphosphonate [25] with aldehyde **8** [26,27].

Scheme 1



Compound **10** was a mixture of *cis* and *trans* which was separated by preparative tlc and characterized by NMR. Direct reduction of compound **10** to compound **7** using Raney nickel [28] or sodium borohydride-aluminium chloride in diglyme [29] failed and did not give compound **7**. However, compound **10** could be reduced to the desired compound **7** in two steps. The double bond was reduced with magnesium turning in methanol to give 3-(1-methyl-1*H*-imidazol-2-yl)propionitrile **12**. Usual method for reduction of nitrile with lithium aluminum hydride for the preparation of **7** failed [30-32]. However the nitrile could be reduced by catalytic hydrogenation using Raney nickel in methanol and ammonia [8].

Reaction of amine **7** with 4-substituted-benzoyl chloride gave 4-substituted-*N*-[3-(1-methyl-1*H*-imidazol-2-yl)propyl]benzamides (**13**). Similarly 4-substituted-*N*-[3-(1-methyl-1*H*-imidazol-2-yl)propyl]benzene sulfonamides (**14**) was prepared from the reaction of substituted-benzenesulfonyl chloride with the amine **7** (Scheme 2).

The physicochemical data of compounds **13** and **14** are summarized in Table 1.

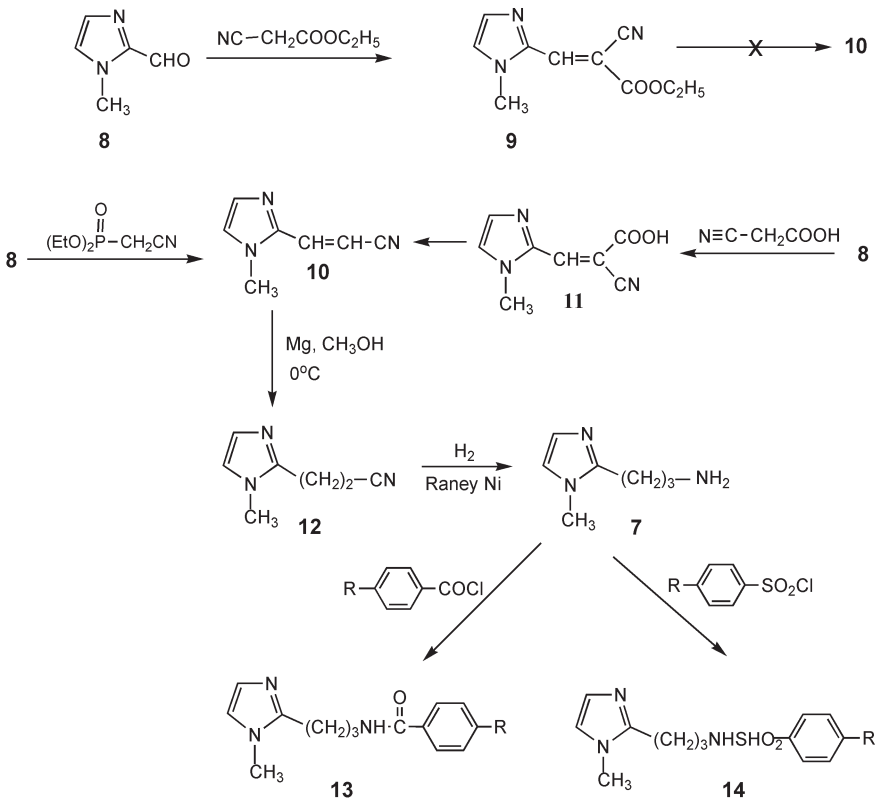
EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perking-Elmer Model 781 or Nicollet FT-IR Magna 550 spectrographs. The ^{1}H-nmr spectra were obtained on a Bruker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were obtained on a Finnigan MAT TSQ 70 spectrometer at 70 eV. Silica gel HT-25 (E. Merck) was used for thin-layer chromatography.

Ethyl 2-Cyano-3-(1-methyl-1*H*-imidazol-2-yl)acrylate (**9**).

To a stirred mixture of ethyl cyanoacetate (1.3 g, 0.01 mole) in aqueous solution of sodium carbonate (1.06 g, 0.01 mole in 10 mL H_2O) compound **8** (1.1 g, 0.01 mole) was added. After 2 hours the mixture was extracted with chloroform (3x50 mL). The solvent was evaporated and the residue was crystallized from petroleum ether to give 1.38 g (76%) of **9**; mp 142-145 °C; ir (KBr): ν 2220 (C≡N), 1715 cm^{-1} (C=O); ^{1}H-nmr (deuterio-

Scheme 2



chloroform): δ 7.98 (s, 1H, CH=), 7.48 (s, 1H, imidazole), 7.13 (s, 1H, imidazole), 4.39 (q, 2H, OCH_2), 3.84 (s, 3H, NCH_3), 1.39 (t, 3H, CH_3); ms: m/z (%) 206 (M^++1, 100), 205 (M^+,14), 161 (30), 132 (20), 107 (5).

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: C, 58.54; H, 5. 37; N, 20. 49. Found: C, 58.73; H, 5.19; N, 20.68.

3- (1-Methyl-1*H*-imidazol-2-yl)acrylonitrile (**10**).

To a stirred solution of compound **8** (1.1 g, 0.01 mole) in dry THF (5 mL) a solution of diethyl cyanomethyl phosphonate (1.78 g, 0.01 mole) in dry THF (5 mL), which was treated with sodium hydride (240 mg, 0.01 mole) at ice-bath temperature was added. After 30 minutes the solvent was evaporated. The residue was crystallized from chloroform-petroleum ether to give 1 g (75%) of compound **10** as a mixture of *cis* and *trans* isomers; mp 88-90 °C. ^{1}H-nmr (deuteriochloroform): δ 7.20 (d, *trans* CH=C-CN, J=15.9 Hz), 7.07 (d, *cis*, CH=C-CN, J=11.5 Hz), 6.95 (s, 1H, imidazole), 6.45 (s, 1H, imidazole), 6.84 (s, 1H, imidazole), 6.30 (d, *trans*, C=CHCN, J=15.9 Hz), 5.45 (d, *cis* C=CH-CN, J=11.5 Hz), 3.73 (s, 3H, N-CH_3); ms: m/z (%) 133 (M^+, 100), 107 (51), 79 (21), 64 (20). The mixture (0.5 g) was separated by thin layer chromatography (silica gel) using chloroform-ethanol (90:10) as eluent. The fast moving fraction gave the *trans* isomer which was crystallized from chloroform-petroleum ether mp 95-96 °C; ir (KBr): ν 2220 (C≡N), 1630 (C=C), 900 cm^{-1} (CH *trans*); ^{1}H-nmr (deuteriochloroform): δ 7.22 (d, 1H, J=15.9 Hz), 7.12 (s, 1H, imidazole), 7.03 (s, 1H, imidazole), 6.72 (d, 1H, J=15.9 Hz), 3.73 (s, 3H, N-CH_3).

The slow moving fraction was crystallized from chloroform-petroleum ether to give *cis* isomer mp 92-93 °C; ir (KBr): ν 2220 (C≡N), 1625 (C=C), 735 cm^{-1} (CH *cis*); ^{1}H-nmr (deuteriochloroform): δ 7.05 (s, 1H, imidazole), 6.99 (s, 1H, imidazole), 6.94 (d, 1H, J=11.8 Hz), 5.42 (d, 1H, J=11.8 Hz), 3.72 (s, 3H, N-CH_3).

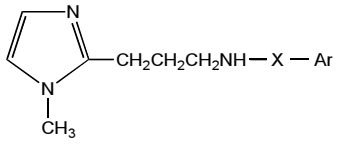
Method B.

A stirred solution of compound **8** (0.2 g, 1.8 mmoles), cyanoacetic acid (0.16 g, 1.8 mmoles), piperidine (0.16 g, 1.8 mmoles) and a few drops of acetic acid in toluene (20 mL) was refluxed under Dean-Stark trap for 18 hours. The solvent was evaporated under the reduced pressure. The residue was made alkaline with aqueous 0.5% sodium hydroxide solution and extracted with chloroform. The organic layer was evaporated and the residue was crystallized from chloroform-petroleum ether to give 80 mg (32%) of compound **10**, mp 88-90°C. Under the above condition compound **11** formed at first was decarboxylated under the work up condition and compound **10** was formed as *cis-trans* mixture.

3-(1-Methyl-1*H*-imidazol-2-yl)propanonitrile (**12**).

To a stirred solution of compound **10** (0.17 g, 1.31 mmoles) in dry methanol (13 mL) at ice-bath temperature magnesium turning (1.27 g, 53 mmoles) was added. Stirring was continued for 5 hours. The excess magnesium was destroyed with 6 *N* hydrochloric acid (24 mL). The pH of the solution was brought to 7-8 with sodium bicarbonate, and extracted with chloroform. The organic layer was dried (Na_2SO_4) filtered and evaporated to give 0.16 g (92%) of **12**

Table 1



Comp.	X	Ar	mp°C [a]	yield (%)	ir (KBr), ^{1}H-nmr ($CDCl_3$), ms and CHN
13a	CO	phenyl	128-129	89	ir: 3205 (NH), 1653 cm^{-1}(C=O); ^{1}H-nmr: 8.34 (bs, 1H, NH), 7.81 (m, 2H, phenyl), 7.41 (m, 3H, phenyl), 6.94 (s, 1H, imidazole), 6.81 (s, 1H, imidazole), 3.57 (s, 3H, N-CH_3), 3.58 (t, 2H, CH_2), 2.83 (t, 2H, CH_2), 2.16 (m, 2H, CH_2); ms: m/z (%) 244 (M^++1, 100), 108 (14), 105 (13), 95 (12), 77 (13). *Anal.* Calcd for $C_{14}H_{17}N_3O$: C, 69.14; H, 7.00, N, 17.28. Found: C, 6.36; H, 7.30; N, 17.49.
13b	CO	4-bromophenyl	164-165	64	ir: 3201 (NH), 1644 cm^{-1}(C=O); ^{1}H-nmr: 8.84 (brs, 1H, NH), 7.75 (d, 2H, J=8.4 Hz, phenyl), 7.54 (d, 2H, J=8.4 Hz, phenyl), 6.93 (s, 1H, imidazole), 6.82 (s, 1H, imidazole), 3.58 (s, 3H, N-CH_3), 3.55 (t, 2H, CH_2), 2.84 (t, 2H, CH_2), 2.15 (m, 2H, CH_2); ms: m/z (%) 323 (M^++1, 100), 184 (5), 109 (39), 96 (18). *Anal.* Calcd for $C_{14}H_{16}BrN_3O$: C, 52.17; H, 4.97, N, 13.04. Found: C, 52.02; H, 5.08; N, 13.22.
13c	CO	4-tolyl	126-127	85	ir: 3270 (NH), 1631 cm^{-1}(C=O); ^{1}H-nmr: 8.11 (bs, 1H, NH), 7.71 (d, 2H, J=8.4 Hz, phenyl), 7.18 (d, 2H, J=8.4 Hz, phenyl), 6.93 (s, 1H, imidazole), 6.79 (s, 1H, imidazole), 3.55 (s, 3H, N-CH_3), 3.52 (t, 2H, CH_2), 2.80 (t, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.10 (m, 2H, CH_2); ms: m/z (%) 258 (M^++1, 99), 148 (5), 119 (40), 109 (100), 96 (60). *Anal.* Calcd for $C_{15}H_{19}N_3O$: C, 70.04; H, 7.39, N, 16.34. Found: C, 69.86; H, 7.17; N, 16.15.
13d	CO	4-ethylphenyl	109-111	75	ir: 3231 (NH), 1659 cm^{-1}(C=O); ^{1}H-nmr: 8.11 (brs, 1H, NH), 7.76 (d, 2H, J=8.0 Hz, phenyl), 7.32 (d, 2H, J=8.0 Hz, phenyl), 6.95 (s, 1H, imidazole), 6.81 (s, 1H, imidazole), 3.56 (s, 3H, N-CH_3), 3.55 (t, 2H, CH_2), 2.82 (t, 2H, CH_2), 2.69 (q, 2H, CH_2), 2.15 (m, 2H, CH_2), 1.24 (t, 3H, CH_3); ms: m/z (%) 272 (M^++1, 76), 133 (40), 109 (100), 96 (70). *Anal.* Calcd for $C_{16}H_{21}N_3O$: C, 70.85; H, 7.75, N, 15.50. Found: C, 70.67; H, 7.93; N, 15.72.
14a	SO_2	phenyl	112-114	80	ir: 3100 (NH), 1321, 1163 cm^{-1}(SO_2); ^{1}H-nmr: 7.81 (m, 2H, Phenyl), 7.50 (m, 3H, phenyl), 6.98 (bs, 1H, NH), 6.90 (s, 1H, imidazole), 6.74 (s, 1H, imidazole), 3.51 (s, 3H, NCH_3), 3.03 (t, 2H, CH_2), 2.68 (t, 2H, CH_2), 1.94 (m, 2H, CH_2); ms: m/z (%) 280 (M^++1, 100), 138 (14), 109 (57), 95 (37). *Anal.* Calcd for $C_{13}H_{17}N_3O_2S$: C, 55.91; H, 6.09, N, 15.05. Found: C, 56.15; H, 6.28; N, 15.31.
14b	SO_2	4-bromophenyl	92-94	69	ir: 3150 (NH), 1321, 1157 cm^{-1}(SO_2); ^{1}H-nmr: 7.62 (d, 2H, J=8.8 Hz, phenyl), 7.54 (d, 2H, J=8.8 Hz, phenyl), 6.86 (s, 1H, imidazole), 6.77 (s, 1H, imidazole), 3.50 (s, 3H, NCH_3), 2.98 (t, 2H, CH_2), 2.67 (t, 2H, CH_2), 1.90 (m, 2H, CH_2);ms: m/z (%) 359 (M^++1, 100), 357 (98), 138 (18), 109 (93), 95 (37). *Anal.* Calcd for $C_{13}H_{16}BrN_3O_2S$: C, 43.58; H, 4.47, N, 11.73. Found: C, 43.79; H, 4.62; N, 11.51.
14c	SO_2	4-tolyl	109-110	72	ir: 3155 (NH), 1311, 1163 cm^{-1}(SO_2); ^{1}H-nmr: 7.68 (d, 2H, J=8.0 Hz, phenyl), 7.25 (d, 2H, J=8.0 Hz, phenyl), 6.90 (s, 1H, imidazole), 6.83 (bs, 1H, NH), 6.79 (s, 1H, imidazole), 3.51 (s, 3H, NCH_3), 3.03 (t, 2H, CH_2), 2.68 (t, 2H, CH_2), 2.40 (s, 3H, CH_3), 1.96 (m, 2H, CH_2); ms: m/z (%): 294 (M^++1, 100), 138 (58), 109 (94), 95 (46). *Anal.* Calcd for $C_{14}H_{19}N_3O_2S$: C, 57.34; H, 6.48, N, 14.33. Found: C, 57.11; H, 6.29; N, 14.12.
14d	SO_2	4-chlorophenyl	100-101	69	ir: 3134 (NH), 1321, 1157 cm^{-1}(SO_2); ^{1}H-nmr: 7.73 (d, 2H, J=8.4 Hz, phenyl), 7.64 (bs, 1H, NH), 7.42 (d, 2H, J=8.4 Hz, phenyl), 6.92 (s, 1H, imidazole), 6.81 (s, 1H, imidazole), 3.52 (s, 3H, NCH_3), 3.06 (t, 2H, CH_2), 2.68 (t, 2H, CH_2), 1.96 (m, 2H, CH_2), ms: m/z (%): 315 (M^++1, 14), 313 (5), 279 (10), 109 (100), 95 (64). *Anal.* Calcd for $C_{13}H_{16}ClN_3O_2S$: C, 49.76; H, 5.10, N, 13.40. Found: C, 49.98; H, 5.26; N, 13.26.

[a] All compounds were crystallized from ethanol-ether.

as an oil; ir (KBr): ν 2260 cm^{-1} (C≡N); ^{1}H-nmr (deuteriochloroform): 6.88 (d, 1H, imidazole, J=0.8 Hz), 6.83 (d, 1H, imidazole, J=0.8 Hz), 3.57 (s, 3H, NCH_3), 2.93 (t, 2H, CH_2), 2.83 (t, 2H, CH_2); ms: m/z (%) 135 (M^+, 47), 109 (8), 95 (100), 81 (5)·

3-(1-Methyl-1*H*-imidazol-2-yl)propanamine (**7**).

A mixture of compound **12** (13.5 g, 0.1 mole), 25% aqueous ammonium hydroxid solution 25%, (75 mL) and Raney nickel alloy, was hydrogenated at 50 p.s.i. for 6 hours. The mixture was

filtered. The solvent was evaporated to give 12 g (86%) of **7** as an oil which was converted to dihydrochloride salt with 5 *M* hydrochloric acid mp 176-178 °C [ref. 21, mp 178°]; ^{1}H-nmr (D_2O): δ 7.40 (s, 2H, imidazole), 3.90 (s, 3H, N-CH_3), 3.15 (m, 4H, CH_2), 2.15 (m, 2H, CH_2).

Anal. Calcd. for $C_7H_{15}Cl_2N_3$: C, 39.62; H, 7.08; N, 19.81. Found: C, 39.84; H, 7.29; N, 19.60.

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N-(4-Substituted-benzolyl)-*N*-[3-(1-methyl-1*H*-imidazol-2-yl)-propyl]amine (**13**).

To a stirred of mixture compound **7** or its dihydrochloride salt (2.6 mmoles) in dichloromethane (40 mL) 1 *N* aqueous sodium hydroxide solution (30 mL) and 4-substituted-benzoyl chloride (2.6 mmoles) in dichloromethane (16 mL) was added. The mixture was stirred at room temperature for 2 hours. The organic layer was washed with water, dried (Na_2SO_4), filtered and evaporated. The residue was chromatographed (silica gel, 230-400 mesh) using CH_2Cl_2-MeOH (95:5) as eluent. The desired compound was crystallized from CH_2Cl_2-ether to give compound **13**. The physiochemical data of compounds **13a-13d** are summarized in Table 1.

N-Arylsulfonyl-*N*-[1-(1-methyl-1H-imidazol-2-yl)propyl]amine (**14**).

To a stirred mixture of compound **7** or its dihydrochloride salt (2 mmoles) in dichloromethane (30 mL) a saturated aqueous sodium bicarbonate solution (20 mL) and 4-substituted-benzenesulfonyl chloride (3 mmoles) in dichloromethane (10 mL) were added. The mixture was stirred at room temperature for 2 hours. The organic layer was washed with water, dried (Na_2SO_4), filtered and evaporated. The residue was crystallized from ethanol-ether to give compound **14**. The physicochemical data of compounds **14b-14d** are summarized in Table 1.

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