Pharmacological Evaluation of Some New 6-Amino/Methyl Pyridine Derivatives

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In the present study, a series of 2-substituted-pyridines were synthesized and characterized by IR, ^{1}H-NMR and Elemental Analysis. The compounds were assayed against seizures induced by maximal electro shock (MES) and pentylenetetrazole (scMet). Neurologic deficit was evaluated by the rotarod test. The decrease in the elevated motor activity by introceptive chemical stimuli (amphetamine antagonistic activity) was studied at the dose level of 25 and 50 mg/kg, antihistaminic and cardiac activity were also studied. All the compounds exhibited significant anticonvulsant activity. Compounds 2-(2-hydroxy-3-piperazinopropylamino)-6-aminopyridine, 2-[2-hydroxy-3-(1-imidazolyl)propylamino]-6-aminopyridine, 2-[2-(1-imidazolyl)ethylamino]-6-methylpyridine and 2-[2-(methylamino)ethylamino]-6-methylpyridine were most active of the series against MES-induced seizures. Compounds 2-[2-(phenylamino)ethylamino]-6-aminopyridine, 2-[2-[bis(2-hydroxyethyl)amino]ethylamino]-6-aminopyridine, 2-[2-(diethylamino)ethylamino]-6-methylpyridine and 2-[2-hydroxy-3-(1-imidazolyl)propylamino]-6-methylpyridine exhibited significant decrease in the elevated motor activity at the dose of 50 mg/kg. Remarkable sympathetic blocking activity was observed with 2-(2-hydroxy-3-piperazinopropylamino)-6-aminopyridine, 2-(2-hydroxy-3-morpholinopropylamino)-6-methylpyridine and 2-(2-hydroxy-3-piperazinopropylamino)-6-methylpyridine only. Compounds 2-[2-(diethylamino)ethylamino]-6-aminopyridine, 2-[2-[bis(2-hydroxyethyl)amino]ethylamino]-6-aminopyridine, and 2-[2-(diethylamino)ethylamino]-6-methylpyridine exhibited significant blocking of histamine induced contraction on guinea pig ileum.

Key words antihistaminic; anticonvulsant; ethanediamine; arylaminopropanolamine; pyridine; sympatholytic

Pyridines were reported to possess anticonvulsant,[1,2] cardiotonic,[3] antihypertensive,[4] β-adrenergic blocking activity.[5] Aryloxypropanolamines were reported to be associated with β-adrenergic blocking,[6,7] CNS depressant[8] and hypotensive[9] activities. In view of this potential nature of these moieties, it was thought worthwhile to study the effects of two pharmacophoric moieties like pyridine and propanolamine/ethanediamine in a single molecule. We have reported the potential anticonvulsant activity of arylaminopropanolamine[10] of pyridine and arylaminopropanolamine/aryloxyaminopropane,[11—13] to continue our work with the same intention, it was envisaged that, chemical entities with both pyridine and arylaminopropanolamine/ethanediamine moieties would result in compounds of interesting biological activities.

In the present study, we report the synthesis, the pharmacological evaluation, and structure-activity relationship of 2-(3′-substituted-2′-hydroxypropylamino/2′-substituted-ethylamino)-pyridine. The compounds were characterized by IR, ^{1}H-NMR spectral and elemental analysis. The compounds were investigated for anticonvulsant activity, the decrease in the elevated motor activity by introceptive chemical stimuli (amphetamine antagonistic activity) at the dose level of 25 and 50 mg/kg, cardiac activity on isolated frog heart and antihistaminic on guinea pig ileum.

Chemistry

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded (in KBr) on Bomem FT-IR spectrophotometer M.B Serial II. ^{1}H-NMR spectra were recorded on 300 MHz Bruker DPX 200. The chemical shifts are reported as parts per million downfield from tetra methyl silane (Me_4Si). Microanalyses for C, H, N were performed in Heraeus CHN Rapid Analyzer. Analyses indicated by the symbols of the elements are within $\pm$0.4% of the theoretical values. ^{1}H-NMR and IR spectra were consistent with the assigned structures.

Synthesis of 2-(2-Chloroethylamino)-6-aminopyridine 2,6-Diaminopyridine was reacted with 1,2-dichloroethane, using the previously reported procedure.[10] A solution of sodium methoxide (0.113 mol of sodium and 75 ml of methanol) was added to 0.113 mol of 2,6-diaminopyridine and refluxed for 1 h. Then the methanol was completely removed from the medium and 10 ml of anhydrous dimethyl formamide (DMF) was added to the dry residue. A solution of 1,2-dichloroethane (0.113 mol) in 10 ml anhydrous dimethyl formamide was then added dropwise to the reaction mixture with continuous stirring. The mixture was stirred for 1 h at room temperature. The product was filtered, dried in vacuum and recrystallised by using chloroform–diethylether (1 : 1). Yield=56%, mp 175 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.22—7.56 (m, 3H, 3, 4, 5H), 5.82—5.91 (m, 1H, NH), 5.15—5.28 (s, 2H, 6-NH_2), 3.89—4.09 (s, 4H, CH_2–CH_2). IR (KBr) cm^{-1}: 1413 (C–H), 1134 (C–O), 745, 723 (Ar–H). *Anal.* Calcd for $C_7H_{10}N_3Cl$: C, 49.12; H, 5.84; N, 24.56. Found: C, 49.36; H, 5.58; N, 24.34.

General Method of Synthesis of 1a to m 2-(2-Chloroethylamino)-6-aminopyridine was reacted with various amines, using the previously reported procedure.[10] A solution of 2-(2-chloroethylamino)-6-aminopyridine (0.013 mol) and the appropriate amine (0.013 mol) in 40 ml of methanol was refluxed for 24 h. The product obtained was filtered, vacuum dried and recrystallized using 1 : 1 acetone–diethylether (**1c**, **1e**, **1f**, **1l**), 1 : 1 ethanol–diethylether (**1a**, **1h**, **1k**, **1m**), 1 : 1 chloroform–diethylether (**1b**, **1g**) and 1 : 1 methanol–diethylether (**1d**, **1i**, **1j**).

2-(2-Morpholinoethylamino)-6-aminopyridine **1a**: Yield=45%, mp 250 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.94—7.15 (m, 3H, 3, 4, 5H), 5.58—5.67 (m, 1H, NH), 5.15—5.28 (s, 2H, 6-NH_2), 4.14—4.25 (m, 4H, 2CH_2), 2.82—3.01 (m, 8H, 2″, 3″, 5″, 6″-CH_2). IR (KBr) cm^{-1}: 3125 (C–H), 1425 (C–N), 1325 (N–H), 1109 (C–O), 850, 790 (Ar–H). *Anal.* Calcd for $C_{11}H_{18}N_4O$: C, 59.45; H, 8.1; N, 25.22. Found: C, 59.13; H, 8.33; N, 25.51.

2-(2-Piperidinoethylamino)-6-aminopyridine **1b**: Yield=42%, mp 234 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.39—7.55 (m, 3H, 3, 4, 5H), 5.71—5.8 (m, 1H, NH), 5.49—5.62 (s, 2H, 7-NH_2), 4.23—4.46 (m, 4H, 2CH_2), 2.65—2.92(m, 10H, 2″, 3″, 4″, 5″, 6″-CH_2). IR (KBr) cm^{-1}: 1433 (C–H), 1384 (C–N), 1124, 1046 (C–O), 810, 762 (Ar–H). *Anal.* Calcd for $C_{12}H_{20}N_4$: C, 65.45; H, 9.09; N, 25.45. Found: C, 65.71; H, 8.81; N, 25.68.

2-(2-Piperazinoethylamino)-6-aminopyridine **1c**: Yield=49%, mp 190 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.02—7.25 (m, 3H, 3, 4, 5H), 5.8—5.91 (m, 1H, NH), 5.3—5.51 (s, 2H, 7-NH_2), 4.14—4.25 (m, 4H, 2CH_2), 2.82—3.01 (m, 8H,

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2″, 3″, 5″, 6″-CH_2). IR (KBr) cm^{-1}: 1421 (C–H), 1350 (C–N), 1132 (C–O), 806, 791 (Ar–H). *Anal.* Calcd for $C_{11}H_{19}N_5$: C, 59.72; H, 8.59; N, 31.67. Found: C, 59.99; H, 8.39; N, 31.25.

2-[2-(1-Imidazolyl)ethylamino]-6-aminopyridine **1d**: Yield=37%, mp 270 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.85—7.03 (m, 3H, 3, 4, 5H), 5.82—5.94 (m, 1H, NH), 5.52—5.61 (s, 2H, 7-NH_2), 5.1—5.24 (m, 1H, 2′CH), 5.17—5.33 (m, 1H, 4″, 5″(-CH)), 3.92—4.13 (m, 4H, 2CH_2). IR (KBr) cm^{-1}: 1435 (C–H), 1361 (C–N), 1118 (C–O), 812, 790 (Ar–H). *Anal.* Calcd for $C_{10}H_{13}N_5$: C, 59.11; H, 6.4; N, 34.48. Found: C, 59.35; H, 6.16; N, 34.21.

2-[2-(Diethylamino)ethylamino]-6-aminopyridine **1e**: Yield=47%, mp 65 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.73—6.96 (m, 3H, 3, 4, 5H), 5.67—5.84 (m, 1H, NH), 5.3—5.51 (s, 2H, 7-NH_2), 4.36—4.47 (m, 4H, 2CH_2), 1.45—1.79 (s, 10H, $(C_2H_5)_2$). IR (KBr) cm^{-1}: 3125 (C–H), 1445 (C–N), 1346 (N–H), 1186 (C–O), 856, 778 (Ar–H). *Anal.* Calcd for $C_{11}H_{20}N_4$: C, 63.46; H, 9.61; N, 26.92. Found: C, 63.17; H, 9.97; N, 26.58.

2-[2-(Diphenylamino)ethylamino]-6-aminopyridine **1f**: Yield=54%, mp 75 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.33—7.57 (m, 3H, 3, 4, 5H), 6.24—6.45 (m, 10H, $(C_6H_5)_2$), 5.8—5.91 (m, 1H, NH), 5.12—5.29 (s, 2H, 7-NH_2), 4.37—4.60 (m, 4H, 2CH_2). IR (KBr) cm^{-1}: 3067 (C–H), 1443 (C–N), 1355 (N–H), 1167 (C–O), 882, 767 (Ar–H). *Anal.* Calcd for $C_{19}H_{20}N_4$: C, 75.0; H, 6.57; N, 18.42. Found: C, 75.28; H, 6.37; N, 18.72.

2-[2-[Bis(2-hydroxyethyl)amino]ethylamino]-6-aminopyridine **1g**: Yield=56%, mp 85 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.28—6.59 (m, 3H, 3, 4, 5H), 5.69—5.78 (m, 1H, NH), 5.27—5.43 (s, 2H, 7-NH_2), 4.23—4.46 (m, 4H, 2CH_2), 3.22—3.43 (s, 2H, 2″(-$OH)_2$), 2.98—3.12 (m, 8H, $(C_2H_4)_2$). IR (KBr) cm^{-1}: 3455 (O–H), 3125 (C–H), 1425 (C–N), 1144 (C–O), 876, 783 (Ar–H). *Anal.* Calcd for $C_{11}H_{20}N_4O_2$: C, 55.0; H, 8.33; N, 23.33. Found: C, 55.28; H, 8.58; N, 23.61.

2-[2-(Phenylamino)ethylamino]-6-aminopyridine **1h**: Yield=44%, mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.44—6.67 (m, 3H, 3, 4, 5H), 5.81—5.9 (m, 1H, NH), 5.69—5.78 (m, 1H, NH), 5.4—5.53 (s, 2H, 7-NH_2), 5.03—5.18 (m, 1H, C_6H_5), 3.77—3.97 (m, 4H, 2CH_2). IR (KBr) cm^{-1}: 3125 (C–H), 1463 (C–N), 1325 (N–H), 1109 (C–O), 888, 745 (Ar–H). *Anal.* Calcd for $C_{13}H_{16}N_4$: C, 68.42; H, 7.01; N, 24.56. Found: C, 68.71; H, 6.87; N, 24.83.

2-[2-(4-Hydroxyphenylamino)ethylamino]-6-aminopyridine **1i**: Yield=49%, mp 70 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.94—7.15 (m, 3H, 3, 4, 5H), 6.43—6.65 (m, 1H, OH), 5.79—5.91(m, 1H, NH), 5.63—5.76 (m, 1H, NH), 5.36—5.51 (s, 2H, 7-NH_2), 5.03—5.14 (m, 1H, C_6H_5), 4.35—4.51 (m, 4H, 2CH_2). IR (KBr) cm^{-1}: 3455 (O–H), 3341 (Ar–NH_2), 3145 (C–H), 1473 (C–N), 1354 (N–H), 1166 (C–O), 867, 736 (Ar–H). *Anal.* Calcd for $C_{13}H_{16}N_4O$: C, 63.93; H, 6.55; N, 22.95. Found: C, 63.68; H, 6.83; N, 22.52.

2-[2-(Methylamino)ethylamino)-6-aminopyridine **1j**: Yield=52%, mp 210 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.79—6.91 (m, 3H, 3, 4, 5H), 5.83—5.98 (m, 1H, NH), 5.66—5.75 (m, 1H, NH), 5.3—5.51 (s, 2H, 7-NH_2), 5.03—5.14 (m, 3H, CH_3), 4.14—4.25 (m, 4H, 2CH_2). IR (KBr) cm^{-1}: 3162 (C–H), 1434 (C–N), 1377 (N–H), 1143 (C–O), 823, 754 (Ar–H). *Anal.* Calcd for $C_8H_{14}N_4$: C, 57.83; H, 8.43; N, 33.73. Found: C, 57.52; H, 8.71; N, 33.48.

2-[2-(2-Aminophenylamino)ethylamino]-6-aminopyridine **1k**: Yield=49%, mp 200 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.94—7.15 (m, 3H, 3, 4, 5H), 5.72—5.82 (m, 4H, C_6H_4), 5.57—5.67 (m, 1H, NH), 5.36—5.51 (m, 1H, NH), 5.13—5.24 (s, 2H, 7-NH_2), 4.35—4.51 (m, 4H, 2CH_2). IR (KBr) cm^{-1}: 3455 (O–H), 3341 (Ar–NH_2), 3145 (C–H), 1473 (C–N), 1354 (N–H), 1166 (C–O), 867, 736 (Ar–H). *Anal.* Calcd for $C_{11}H_{17}N_5$: C, 60.27; H, 7.76; N, 31.96. Found: C, 60.59; H, 7.99; N, 31.63.

2-[2-(4-Nitrophenylamino)ethylamino]-6-aminopyridine **1l**: Yield=52%, mp 125 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.94—7.15 (m, 3H, 3, 4, 5H), 5.82—5.94 (m, 4H, C_6H_4), 5.57—5.72 (m, 1H, NH), 5.3—5.51 (m, 1H, NH), 5.23—5.44 (s, 2H, 7-NH_2), 4.14—4.25 (m, 4H, 2CH_2). IR (KBr) cm^{-1}: 3162 (C–H), 1434 (C–N), 1377 (N–H), 1143 (C–O), 823, 754 (Ar–H). *Anal.* Calcd for $C_{11}H_{15}N_5O_2$: C, 53.01; H, 6.02; N, 28.11. Found: C, 53.37; H, 6.33; N, 27.88.

2-[2-(4-Bromophenylamino)ethylamino]-6-aminopyridine **1m**: Yield=52%, mp 85 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.94—7.15 (m, 3H, 3, 4, 5H), 5.85—5.98 (m, 4H, C_6H_4), 5.57—5.72 (m, 1H, NH), 5.3—5.51 (m, 1H, NH), 5.23—5.44 (s, 2H, 7-NH_2), 4.14—4.25 (m, 4H, 2CH_2). IR (KBr) cm^{-1}: 3162 (C–H), 1434 (C–N), 1377 (N–H), 1143 (C–O), 823, 754 (Ar–H). *Anal.* Calcd for $C_{11}H_{15}N_4Br$: C, 48.36; H, 5.49; N, 20.52. Found: C, 48.62; H, 5.61; N, 20.25.

Synthesis of 2-(2,3-Epoxypropylamino)-6-aminopyridine A solution of sodium methoxide (0.113 mol of sodium and 75 ml of methanol) was added to 0.113 mol of 2,6-diaminopyridine and refluxed for 1 h. Then the methanol was completely removed from the medium and 10 ml of anhydrous dimethyl formamide (DMF) was added to the dry residue. A solution of epichlorohydrin (0.113 mol) in 10 ml anhydrous dimethyl formamide was then added dropwise to the reaction mixture with continuous stirring. The mixture was stirred for 1 h at room temperature. The product was filtered, dried in vacuum and recrystallised by using ethanol–diethylether (1 : 1). Yield=41%, mp 205 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.32—7.55 (m, 3H, 3, 4, 5H), 5.72—5.85 (s, 2H, 7-NH_2), 3.66—3.83 (d, J=4.5 Hz, 2H, 3′-CH_2), 3.37—3.51 (d, J=5.7 Hz, 2H, 1′-CH_2), 2.54—2.67 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1410 (C–H), 1253 (epoxide C–O), 1144 (ether C–O) 833, 785 (Ar–H). *Anal.* Calcd for $C_8H_{11}N_3O$: C, 58.18; H, 6.66; N, 25.45. Found: C, 57.82; H, 6.35; N, 25.8.

General Method of Synthesis of 2a to j A solution of 2-(2,3-epoxypropylamino)-6-aminopyridine (0.013 mol) and the appropriate amine (0.013 mol) in 40 ml of methanol was refluxed for 24 h. The product obtained was filtered, vacuum dried and recrystallized using 1 : 1 acetone–diethylether (**2b**, **2d**, **2j**), 1 : 1 ethanol–diethylether (**2c**, **2f**, **2g**, **2i**), 1 : 1 chloroform–diethylether (**2a**) and 1 : 1 methanol–diethylether (**2e**, **2h**).

2-(2-Hydroxy-3-morpholinopropylamino)-6-aminopyridine **2a**: Yield=29%, mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.18—7.34 (m, 3H, 3, 4, 5H), 5.78—5.94 (m, 1H, NH), 5.3—5.51 (s, 2H, 7-NH_2), 3.84—4.06 (m, 4H, 1′, 3′-CH_2), 3.37—3.51 (s, 1H, 2′-OH), 2.41—2.68 (m, 4H, 2″, 3″, 5″, 6″H), 1.24—1.43 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1425 (C–H), 1389 (C–N), 1144, 1042 (C–O) 833, 785 (Ar–H). *Anal.* Calcd for $C_{12}H_{20}N_4O_2$: C, 57.14; H, 7.93; N, 22.22. Found: C, 57.48; H, 7.61; N, 22.01.

2-(2-Hydroxy-3-piperidinopropylamino)-6-aminopyridine **2b**: Yield=35%, mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.11—7.21 (m, 3H, 3, 4, 5H), 5.82—5.9 (m, 1H, NH), 5.23—5.46 (s, 2H, 7-NH_2), 3.82—3.98 (m, 4H, 1′, 3′-CH_2), 3.31—3.43 (s, 1H, 2′-OH), 2.11—2.2 (m, 10H, 2″, 3″, 4″, 5″, 6″H), 1.28—1.39 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1477 (C–H), 1383 (C–N), 1141 (C–O), 854, 757 (Ar–H). *Anal.* Calcd for $C_{13}H_{22}N_4O$: C, 62.4; H, 8.8; N, 22.4. Found: C, 62.12; H, 8.51; N, 22.69.

2-(2-Hydroxy-3-piperazinopropylamino)-6-aminopyridine **2c**: Yield=48%, mp 290 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.02—7.14 (m, 3H, 3, 4, 5H), 6.27—6.41 (s, 1H, –NH), 5.71—5.87 (s, 1H, –NH), 5.34—5.52 (s, 2H, 7-NH_2), 3.81—3.96 (m, 4H, 1′, 3′-CH_2), 3.67—3.82 (s, 1H, 2′-OH), 2.3—2.39 (m, 8H, 2″, 3″, 5″, 6″CH_2), 1.89—1.99 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1453 (C–H), 1347 (C–N), 1124 (C–O), 836, 745 (Ar–H). *Anal.* Calcd for $C_{12}H_{21}N_5O$: C, 57.37; H, 8.36; N, 27.88. Found: C, 57.6; H, 8.65; N, 27.54.

2-(2-Hydroxy-3-(1-imidazolyl)propylamino)-6-aminopyridine **2d**]: Yield=34%, mp 85 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.11—7.25 (m, 3H, 3, 4, 5H), 6.67—6.81 (m, 2H, 2″-CH), 6.49—6.58 (s, 1H, –NH), 6.29—6.41 (m, 2H, 4″, 5″-CH), 5.79—5.91 (s, 2H, 7-NH_2), 3.89—4.01 (m, 4H, 1′, 3′-CH_2), 3.31—3.46 (s, 1H, 2′-OH), 1.12—1.27 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1436 (C–H), 1338 (C–N), 1165 (C–O), 846, 757 (Ar–H). *Anal.* Calcd for $C_{11}H_{15}N_5O$: C, 56.65; H, 6.43; N, 30.04. Found: C, 56.83; H, 6.64; N, 30.35.

2-[3-(Diethylamino)-2-hydroxypropylamino]-6-aminopyridine **2e**: Yield=47%, mp 128 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.02—7.15 (m, 3H, 3, 4, 5H), 6.13—6.24 (s, 1H, –NH), 5.81—5.92 (s, 2H, 7-NH_2), 3.89—3.98 (m, 4H, 1′, 3′-CH_2), 3.31—3.43 (s, 1H, 2′-OH), 1.02—1.11 (s, 10H, $(C_2H_5)_2$). IR (KBr) cm^{-1}: 1434 (C–H), 1343 (C–N), 1154 (C–O), 845, 745 (Ar–H). *Anal.* Calcd for $C_{12}H_{22}N_4O$: C, 60.5; H, 9.24; N, 23.52. Found: C, 60.24; H, 9.58; N, 23.21.

2-[3-(Diphenylamino)-2-hydroxypropylamino]-6-aminopyridine **2f**: Yield=34%, mp 42 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.56—7.69 (m, 3H, 3, 4, 5H), 6.29—6.37(s, 1H, –NH), 6.03—6.14 (m, 10H, $(C_6H_5)_2$, 5.57—5.89 (s, 2H, 7-NH_2), 3.69—3.83 (m, 4H, 1′, 3′-CH_2), 3.32—3.43 (s, 1H, 2′-OH), 1.44—1.53 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1456 (C–H), 1334 (C–N), 1147 (C–O), 846, 789 (Ar–H). *Anal.* Calcd for $C_{20}H_{22}N_4O$: C, 71.85; H, 6.58; N, 16.76. Found: C, 71.62; H, 6.41; N, 16.46.

2-[3-[Bis(2-hydroxyethyl)amino]-2-hydroxypropylamino)-6-aminopyridine **2g**: Yield=43%, mp 240 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.02—7.17 (m, 3H, 3, 4, 5H), 6.11—6.2 (s, 1H, –NH), 5.68—5.81 (s, 2H, 7-NH_2), 3.81—3.94 (m, 4H, 1′, 3′-CH_2), 3.43—3.52 (s, 1H, 2′-OH), 2.49—2.63 (m, 4H, 2″, 3″, 5″, 6″H), 1.47—1.54 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1434 (C–H), 1357 (C–N), 1176 (C–O) 858, 755 (Ar–H). *Anal.* Calcd for $C_{12}H_{22}N_4O_3$: C, 53.33; H, 8.14; N, 20.74. Found: C, 53.63; H, 7.93; N, 20.44.

2-[2-Hydroxy-3-(phenylamino)propylamino]-6-aminopyridine **2h**: Yield=49%, mp 153 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.03—7.14 (m, 3H, 3, 4, 5H), 6.45—6.68 (s, 1H, –NH), 6.04—6.21 (m, 4H, C_6H_4), 5.45—5.61 (s, 2H, 7-NH_2), 3.74—3.86 (m, 4H, 1′, 3′-CH_2), 3.47—3.58 (s, 1H, 2′-OH), 1.65—1.82 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1445 (C–H), 1368 (C–N), 1187 (C–O), 863, 765 (Ar–H). *Anal.* Calcd for $C_{14}H_{18}N_4O$: C, 65.11; H, 6.97; N, 21.7. Found: C, 65.43; H, 6.67; N, 21.43.

2-[2-Hydroxy-3-(4-hydroxyphenylamino)propylamino]-6-aminopyridine **2i**: Yield=41%, mp 55 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.15—7.28 (m, 3H, 3, 4, 5H), 6.51—6.74 (s, 1H, –OH), 6.15—6.29 (s, 1H, –NH), 5.93—6.08 (m,

4H, C_6H_4), 5.78—5.94 (s, 2H, 7-NH_2), 3.88—3.98 (m, 4H, 1′,3′-CH_2), 3.37—3.51 (s, 1H, 2′-OH), 1.34—1.41 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1445 (C–H), 1356 (C–N), 1185 (C–O), 863, 768 (Ar–H). *Anal.* Calcd for $C_{14}H_{18}N_4O_2$: C, 61.31; H, 6.56; N, 20.43. Found: C, 61.12; H, 6.28; N, 20.71.

2-(2-Hydroxy-3-methylamino)propylamino)-6-amino pyridine **2j**: Yield=47%, mp 220—221 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.09—7.24 (m, 3H, 3, 4, 5H), 6.23—6.35 (s, 1H, –NH), 6.05—6.16 (s, 1H, –NH), 5.67—5.79 (s, 2H, 7-NH_2), 3.81—3.97 (m, 4H, 1′, 3′-CH_2), 3.47—3.58 (s, 1H, 2′-OH), 1.98—2.12 (m, 1H, 2′-CH), 1.29—1.42 (s, 3H, CH_3). IR (KBr) cm^{-1}: 1442 (C–H), 1378 (C–N), 1158 (C–O), 853, 754 (Ar–H). *Anal.* Calcd for $C_9H_{16}N_4O$: C, 55.1; H, 8.16; N, 28.57. Found: C, 55.36; H, 8.46; N, 28.2.

Synthesis of 2-(2-Chloroethylamino)-6-methylpyridine A solution of sodium methoxide (0.113 mol of sodium and 75 ml of methanol) was added to 0.113 mol of 2-amino-6-methylpyridine and refluxed for 1 h. Then the methanol was completely removed from the medium and 10 ml of anhydrous dimethyl formamide (DMF) was added to the dry residue. A solution of 1,2-dichloroethane (0.113 mol) in 10 ml anhydrous dimethyl formamide was then added dropwise to the reaction mixture with continuous stirring. The mixture was stirred for 1 h at room temperature. The product was filtered, dried in vacuum and recrystallised by using chloroform–diethylether (1 : 1). Yield=56%, mp 78—79 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.22—7.56 (m, 3H, 3, 4, 5H), 3.89—4.09 (s, 4H, CH_2–CH_2), 3.32—3.68 (s, 3H, 4-CH_3). IR (KBr) cm^{-1}: 1413 (C–H), 1134 (C–O), 745, 723 (Ar–H). *Anal.* Calcd for $C_8H_{11}N_2Cl$: C, 56.47; H, 6.47; N, 10.47. Found: C, 56.15; H, 6.72; N, 10.66.

General Method of Synthesis of 3a to j A solution of 2-(2-chloroethylamino)-6-methylpyridine (0.013 mol) and the appropriate amine (0.013 mol) in 40 ml of methanol was refluxed for 24 h. The product obtained was filtered, vacuum dried and recrystallized using 1 : 1 acetone–diethylether (**3a**, **3d**, **3g**), 1 : 1 ethanol–diethylether (**3c**, **3e**, **3i**), 1 : 1 chloroform–diethylether (**3b**, **3j**) and 1 : 1 methanol–diethylether (**3f**, **3h**).

2-(2-Morpholinoethylamino)-6-methylpyridine **3a**: Yield=45%, mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.94—7.15 (m, 3H, 3, 4, 5H), 4.14—4.25 (m, 4H, $2CH_2$), 3.22—3.41 (s, 3H, 4-CH_3), 2.91—3.03 (m, 8H; 2″, 3″, 5″, 6″-CH_2). IR (KBr) cm^{-1}: 3122 (C–H), 1443 (C–N), 1345 (N–H), 1109 (C–O), 850, 790 (Ar–H). *Anal.* Calcd for $C_{12}H_{19}N_3O$: C, 65.15; H, 8.59; N, 19.0. Found: C, 65.47; H, 8.23; N, 19.31.

2-(2-Piperidinoethylamino)-6-methylpyridine **3b**: Yield=42%, mp 268—269 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.39—7.55 (m, 3H, 3, 4, 5H), 4.23—4.46 (m, 4H, $2CH_2$), 3.22—3.39 (s, 3H, 4-CH_3), 2.65—2.92 (m, 10H, 2″, 3″, 4″, 5″, 6″-CH_2). IR (KBr) cm^{-1}: 1433 (C–H), 1384 (C–N), 1124, 1046 (C–O), 810, 762 (Ar–H). *Anal.* Calcd for $C_{13}H_{21}N_3$: C, 71.23; H, 9.58; N, 19.17. Found: C, 71.55; H, 9.82; N, 19.45.

2-(2-Piperazinoethylamino)-6-methylpyridine **3c**: Yield=49%, mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.94—7.15 (m, 3H, 3, 4, 5H), 5.57—5.72 (m, 1H, NH), 4.14—4.25 (m, 4H, $2CH_2$), 3.49—3.53 (s, 3H, 4-CH_3), 2.82—3.01 (m, 8H, 2″, 3″, 5″, 6″-CH_2). IR (KBr) cm^{-1}: 1421 (C–H), 1350 (C–N), 1132 (C–O), 806, 791 (Ar–H). *Anal.* Calcd for $C_{12}H_{20}N_4$: C, 65.45; H, 9.09; N, 25.45. Found: C, 65.71; H, 9.33; N, 25.08.

2-[2-(1-Imidazolyl)ethylamino]-6-methylpyridine **3d**: Yield=37%, mp 265—266 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.85—7.03 (m, 3H, 3, 4, 5H), 5.6—5.84 (m, 1H, 2′CH), 5.27—5.43 (m, 1H, 4″, 5″(-CH)), 3.92—4.13 (m, 4H, $2CH_2$), 3.5—3.69 (s, 3H, 4-CH_3). IR (KBr) cm^{-1}: 1435 (C–H), 1361 (C–N), 1118 (C–O), 812, 790 (Ar–H). *Anal.* Calcd for $C_{11}H_{14}N_4$: C, 65.34; H, 6.93; N, 27.72. Found: C, 65.63; H, 6.77; N, 27.49.

2-[2-(Diethylamino)ethylamino]-6-methylpyridine **3e**: Yield=47%, mp 278—279 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.73—6.96 (m, 3H, 3, 4, 5H), 4.36—4.47 (m, 4H, $2CH_2$), 3.2—3.33 (s, 3H, 4-CH_3), 1.45—1.79 (s, 10H, $(C_2H_5)_2$). IR (KBr) cm^{-1}: 3125 (C–H), 1445 (C–N), 1346 (N–H), 1186 (C–O), 856, 778 (Ar–H). *Anal.* Calcd for $C_{12}H_{21}N_3$: C, 69.56; H, 10.14; N, 27.72. Found: C, 69.36; H, 10.37; N, 27.56.

2-[2(Diphenylamino)ethylamino]-6-methylpyridine **3f**: Yield=54%, mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.33—7.57 (m, 3H, 3, 4, 5H), 6.24—6.45 (m, 10H, $(C_6H_5)_2$), 4.37—4.60 (m, 4H, $2CH_2$), 3.39—3.53 (s, 3H, 4-CH_3). IR (KBr) cm^{-1}: 3067 (C–H), 1443 (C–N), 1355 (N–H), 1167 (C–O), 882, 767 (Ar–H). *Anal.* Calcd for $C_{20}H_{21}N_3$: C, 79.2; H, 6.93; N, 13.86. Found: C, 79.49; H, 6.68; N, 13.61.

2-[2-[Bis(2-hydroxyethyl)amino]ethylamino)-6-methylpyridine **3g**: Yield=56%, mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.28—6.59 (m, 3H, 3, 4, 5H), 4.23—4.46 (m, 4H, $2CH_2$), 3.45—3.52 (s, 3H, 4-CH_3), 3.22—3.43 (s, 2H, 2″(–$OH)_2$), 2.98—3.12 (m, 8H, $(C_2H_4)_2$). IR (KBr) cm^{-1}: 3455 (O–H), 3125 (C–H), 1425 (C–N), 1144 (C–O), 876, 783 (Ar–H). *Anal.* Calcd for $C_{12}H_{21}N_3O_2$: C, 64.57; H, 9.41; N, 18.83. Found: C, 64.22; H, 9.53; N, 18.56.

2-[2-(Phenylamino)ethylamino]-6-methylpyridine **3h**: Yield=44%, mp 223—224 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.44—6.67 (m, 3H, 3, 4, 5H), 5.57—5.72 (m, 1H, NH), 5.23—5.44 (m, 1H, C_6H_5), 3.77—3.97 (m, 4H, $2CH_2$), 3.42—3.54 (s, 3H, 4-CH_3). IR (KBr) cm^{-1}: 3125 (C–H), 1463 (C–N), 1325 (N–H), 1109 (C–O), 888, 745 (Ar–H). *Anal.* Calcd for $C_{14}H_{17}N_3$: C, 74.0; H, 7.48; N, 18.5. Found: C, 74.34; H, 7.18; N, 18.78.

2-[2-(4-Hydroxyphenylamino)ethylamino]-6-methylpyridine **3i**: Yield=49%, mp 79—80 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.94—7.15 (m, 3H, 3, 4, 5H), 6.43—6.65 (m, 1H, OH), 5.57—5.72 (m, 1H, NH), 5.23—5.44 (m, 1H, C_6H_5), 4.35—4.51 (m, 4H, $2CH_2$), 3.13—3.25 (s, 3H, 4-CH_3). IR (KBr) cm^{-1}: 3455 (O–H), 3341 (Ar–NH_2), 3145 (C–H), 1473 (C–N), 1354 (N–H), 1166 (C–O), 867, 736 (Ar–H). *Anal.* Calcd for $C_{14}H_{17}N_3O$: C, 69.13; H, 6.99; N, 17.28. Found: C, 69.26; H, 6.63; N, 17.49.

2-[2-(Methylamino)ethylamino]-6-methylpyridine **3j**: Yield=52%, mp 281—282 °C. ^{1}H-NMR ($CDCl_3$) δ: 6.99—7.11 (m, 3H, 3, 4, 5H), 5.67—5.79 (m, 1H, NH), 5.23—5.44 (m, 4H, C_6H_4), 4.24—4.35 (m, 4H, $2CH_2$), 3.32—3.68 (s, 3H, 4-CH_3). IR (KBr) cm^{-1}: 3162 (C–H), 1434 (C–N), 1377 (N–H), 1143 (C–O), 823, 754 (Ar–H). *Anal.* Calcd for $C_9H_{15}N_3$: C, 65.45; H, 9.09; N, 25.45. Found: C, 65.69; H, 9.29; N, 25.29.

Synthesis of 2-(2,3-Epoxypropylamino)-6-methylpyridine A solution of sodium methoxide (0.113 mol of sodium and 75 ml of methanol) was added to 0.113 mol of 2-amino-6-methylpyridine and refluxed for 1 h. Then the methanol was completely removed from the medium and 10 ml of anhydrous dimethyl formamide (DMF) was added to the dry residue. A solution of epichlorohydrin (0.113 mol) in 10 ml anhydrous dimethyl formamide was then added dropwise to the reaction mixture with continuous stirring. The mixture was stirred for 1 h at room temperature. The product was filtered, dried in vacuum and recrystallised by using ethanol–diethylether (1 : 1). Yield=41%, mp 213—214 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.32—7.55 (m, 3H, 3, 4, 5H), 3.66—3.83 (d, J=4.5 Hz, 2H, 3′-CH_2), 3.73—3.88 (s, 3H, 4-CH_3), 3.37—3.51 (d, J=5.7 Hz, 2H, 1′-CH_2), 2.54—2.67 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1410 (C–H), 1253 (epoxide C–O), 1144 (ether C–O) 833, 785 (Ar–H). *Anal.* Calcd for $C_9H_{12}N_2O$: C, 65.85; H, 7.31; N, 17.07. Found: C, 65.57; H, 7.58; N, 17.38.

General Method of Synthesis of 4a to j A solution of 2-(2,3-epoxypropylamino)-6-methylpyridine (0.013 mol) and the appropriate amine (0.013 mol) in 40 ml of methanol was refluxed for 24 h. The product obtained was filtered, vacuum dried and recrystallized using 1 : 1 acetone–diethylether (**4a**, **4f**, **4h**), 1 : 1 ethanol–diethylether (**4d**, **4e**, **4g**, **4j**), 1 : 1 chloroform–diethylether (**4b**) and 1 : 1 methanol–diethylether (**4c**, **4i**).

2-(2-Hydroxy-3-morpholinopropylamino)-6-methylpyridine **4a**: Yield=29%, mp 248—249 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.11—7.24 (m, 3H, 3, 4, 5H), 3.84—4.06 (m, 4H, 1′, 3′-CH_2), 3.42—3.52 (s, 3H, 4-CH_3), 3.37—3.51 (s, 1H, 2′-OH), 2.41—2.68 (m, 4H, 2″, 3″, 5″, 6″H), 1.29—1.39 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1425 (C–H), 1345 (C–N), 1134 (C–O), 864, 756 (Ar–H). *Anal.* Calcd for $C_{13}H_{21}N_3O_2$: C, 62.15; H, 8.36; N, 16.73. Found: C, 62.42; H, 8.65; N, 16.51.

2-(2-Hydroxy-3-piperidinopropylamino)-6-methylpyridine **4b**: Yield=35%, mp 224—225 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.57—7.82 (m, 3H, 3, 4, 5H), 3.73—3.89 (m, 4H, 1′, 3′-CH_2), 3.32—3.46 (s, 3H, 4-CH_3), 3.17—3.29 (s, 1H, 2′-OH), 2.49—2.58 (m, 10H, 2″, 3″, 4″, 5″, 6″H), 1.67—1.84 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1445 (C–H), 1343 (C–N), 1135 (C–O), 856, 745 (Ar–H). *Anal.* Calcd for $C_{14}H_{23}N_3O$: C, 67.46; H, 9.23; N, 16.86. Found: C, 67.19; H, 9.69; N, 16.51.

2-(2-Hydroxy-3-piperazinopropylamino)-6-methylpyridine **4c**: Yield=48%, mp 198—199 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.34—7.44 (m, 3H, 3, 4, 5H), 6.28—6.4 (s, 1H, –NH), 3.81—3.92 (m, 4H, 1′, 3′-CH_2), 3.39—3.53 (s, 3H, 4-CH_3), 3.39—3.49 (s, 1H, 2′-OH), 2.49—2.68 (m, 8H, 2″, 3″, 5″, 6″CH_2), 1.68—1.92 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1434 (C–H), 1374 (C–N), 1179 (C–O), 857, 758 (Ar–H). *Anal.* Calcd for $C_{13}H_{22}N_4O$: C, 62.4; H, 8.8; N, 22.4. Found: C, 62.2; H, 8.58; N, 22.07.

2-(2-Hydroxy-3-(1-imidazolyl)propylamino)-6-methylpyridine **4d**: Yield=34%, mp 185—186 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.23—7.32 (m, 3H, 3, 4, 5H), 6.66—6.82 (m, 2H, 2″-CH), 6.36—6.51 (m, 2H, 4″, 5″-CH), 3.78—3.93 (m, 4H, 1′, 3′-CH_2), 3.39—3.56 (s, 3H, 4-CH_3), 3.17—3.26 (s, 1H, 2′-OH), 1.44—1.58 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1435 (C–H), 1356 (C–N), 1164 (C–O), 858, 748 (Ar–H). *Anal.* Calcd for $C_{12}H_{16}N_4O$: C, 62.06; H, 6.89; N, 24.13. Found: C, 62.35; H, 6.64; N, 24.42.

2-[3-(Diethylamino)-2-hydroxypropylamino]-6-methylpyridine **4e**: Yield=47%, mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.28—7.39 (m, 3H, 3, 4, 5H), 3.82—3.95 (m, 4H, 1′, 3′-CH_2), 3.49—3.62 (s, 3H, 4-CH_3), 3.17—3.3 (s, 1H, 2′-OH), 1.44—1.56 (m, 1H, 2′-CH), 1.28—1.43 (s, 10H, $(C_2H_5)_2$). IR (KBr) cm^{-1}: 1435 (C–H), 1339 (C–N), 1136 (C–O), 845, 745 (Ar–H). *Anal.* Calcd for $C_{13}H_{23}N_3O$: C, 65.82; H, 9.7; N, 17.72. Found: C, 65.57; H, 9.48;

N, 17.46.

2-[3-(Diphenylamino)-2-hydroxypropylamino]-6-methylpyridine **4f**: Yield=34%, mp 285—286 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.37—7.52 (m, 3H, 3, 4, 5H), 6.45—6.58 (s, 1H, –NH), 6.12—6.28 (m, 10H, $(C_6H_5)_2$), 3.81—3.93 (m, 4H, 1′, 3′-CH_2), 3.31—3.44 (s, 3H, 4-CH_3), 3.06—3.21 (s, 1H, 2′-OH), 1.43—1.57 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1443 (C–H), 1394 (C–N), 1154 (C–O), 873, 737 (Ar–H). *Anal.* Calcd for $C_{21}H_{23}N_3O$: C, 75.67; H, 6.9; N, 12.61. Found: C, 75.37; H, 6.56; N, 12.75.

2-[3-[Bis(2-hydroxyethyl)amino]-2-hydroxypropylamino]-6-methylpyridine **4g**: Yield=43%, mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.28—7.4 (m, 3H, 3, 4, 5H), 3.81—3.93 (m, 4H, 1′, 3′-CH_2), 3.53—3.67 (s, 3H, 4-CH_3), 3.36—3.47 (s, 1H, 2′-OH), 2.43—2.56 (m, 4H, 2″, 3″, 5″, 6″H), 1.35—1.47 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1442 (C–H), 1353 (C–N), 1158 (C–O), 876, 756 (Ar–H). *Anal.* Calcd for $C_{13}H_{23}N_3O_3$: C, 57.99; H, 8.55; N, 15.61. Found: C, 57.63; H, 8.79; N, 15.88.

2-[2-Hydroxy-3-(phenylamino)propylamino)-6-methylpyridine **4h**: Yield=49%, mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.45—7.62 (m, 3H, 3, 4, 5H), 6.12—6.24 (s, 1H, –NH), 5.93—6.08 (m, 4H, C_6H_4), 3.69—3.82 (m, 4H, 1′, 3′-CH_2), 3.48—3.67 (s, 3H, 4-CH_3), 3.39—3.48 (s, 1H, 2′-OH), 1.45—1.67 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1475 (C–H), 1337 (C–N), 1187 (C–O), 843, 745 (Ar–H). *Anal.* Calcd for $C_{15}H_{19}N_3O$: C, 70.03; H, 7.39; N, 16.34. Found: C, 69.79; H, 7.51; N, 16.66.

2-[2-Hydroxy-3-(4-hydroxyphenylamino)propylamino]-6-methylpyridine **4i**: Yield=41%, mp 202—203 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.31—7.48 (m, 3H, 3, 4, 5H), 6.53—6.67 (s, 1H, –OH), 6.35—6.47 (s, 1H, –NH), 5.91—6.04 (m, 4H, C_6H_4), 3.83—3.97 (m, 4H, 1′, 3′-CH_2), 3.46—3.62 (s, 3H, 4-CH_3), 3.13—3.25 (s, 1H, 2′-OH), 1.4—1.61 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 1452 (C–H), 1323 (C–N), 1136 (C–O), 853, 745 (Ar–H). *Anal.* Calcd for $C_{15}H_{19}N_3O_2$: C, 65.93; H, 6.95; N, 15.38. Found: C, 65.59; H, 6.69; N, 15.61.

2-[2-Hydroxy-3-(methylamino)propylamino]-6-methylpyridine **4j**: Yield=47%, mp 290—291 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.34—7.45 (m, 3H, 3, 4, 5H), 3.82—3.94 (m, 4H, 1′, 3′-CH_2), 3.42—3.55 (s, 3H, 4-CH_3), 3.22—3.41 (s, 1H, 2′-OH), 2.37—2.51 (m, 1H, 2′-CH), 1.63—1.74 (s, 3H, CH_3). IR (KBr) cm^{-1}: 1453 (C–H), 1334 (C–N), 1134 (C–O), 858, 775 (Ar–H). *Anal.* Calcd for $C_{10}H_{17}N_3O$: C, 61.53; H, 8.71; N, 21.53. Found: C, 61.31; H, 8.95; N, 21.79.

Pharmacology

All the synthesized compounds were screened for anticonvulsant activity. The amphetamine antagonism was done at the dose of 25 mg and 50 mg/kg. The experimental dose for the amphetamine antagonism was selected between the minimal effective and maximal non-lethal dose. The compounds were also screened for the cardiac activity on isolated frog heart. All the compounds were soluble in water and administered to the animals as a solution in water for injection and triple glass distilled water. Wistar albino mice (18—25 g) and hartely guinea pig of either sex were procured from King Institute, Guindy, Chennai. They were kept in colony cages at 25±2 °C, relative humidity 45—55% under 12 h light and dark cycle (0600 to 1800 h-light; 1800 to 0600 h-dark). All the animals were acclimatized for a week before use. Small frogs (Rana trigana, 80—120 g) were procured locally and used on the same day. Unpaired Student *t*-test[14] was performed to ascertain the significance of the exhibited activity.

Anticonvulsant activity The compounds were tested for anticonvulsant activity by using the procedures described previously.[15,16] All compounds were tested for anticonvulsant activity with wistar albino mice (n=5). Each compound was administered intraperitoneally at three dose levels (30, 100, 300 mg/kg). Three tests were performed for each compound; maximal electroshock (MES) induced convulsions, subcutaneous Metrozol (sc-Met) induced convulsions and rotarod neurotoxicity test (Tox). The compounds were made solution with water for injection.

Maximal electroshock seizures (MES) were induced 30 min after drug treatment by application of 50 mA current for 0.2 s *via* corneal electrodes into the eyes. The protection was defined as the abolition of hind leg and tonic maximal extension component of the seizure. The subcutaneous pentylenetetrazole (Metrozol) seizure threshold test (sc-Met) was carried out by the subcutaneous administration of pentylenetetrazole (85 mg/kg). Animals were observed for over 30 min. Failure to observe the generalised clonic seizure is defined as protection.

Minimal neurotoxicity (TD_{50}) was measured by the rotarod test (Tox). Wistar albino mice (n=4) were placed in 1-in. diameter knurled plastic rod rotating 6 rpm after administration of the drug, and their ability to maintain their balance was tested. Neurological deficit was indicated by the inability of the animal to maintain the equilibrium for 1 min on the rotating rod in each of three trials. The results are tabulated in Ta-

Table 1. Anticonvulsant and Toxicity Screening Data in Mice (i.p.)

Compd.	MES[a,b]		scMet[a,c]		Rotarod toxicity[a,d]	
	30 min	4 h	30 min	4 h	30 min	4 h
1a	+	−	−	−	+	−
1b	+	−	−	−	+	−
1c	++	−	−	−	+	−
1d	++	−	−	−	+	−
1e	−	−	−	−	−	−
1f	+	−	+	−	−	−
1g	++	+	+	−	+	−
1h	+	−	+	−	−	−
1I	+	−	−	−	+	+
1j	+	+	+	−	+	−
1k	+	−	+	−	+	−
1l	+	+	+	−	+	−
1m	+	+	+	+	+	+
2a	++	−	−	−	−	−
2b	+	−	+	−	+	+
2c	++	−	+	−	+	−
2d	++	+	+	−	+	−
2e	+	+	+	+	+	+
2f	+	−	+	−	+	−
2g	+	+	+	−	+	−
2h	+	+	+	+	+	+
2I	++	−	−	−	++	−
2j	+	−	−	−	+	−
3a	+	−	−	−	+	−
3b	+	−	−	−	−	−
3c	++	−	+	−	−	+
3d	++	+	+	−	+	−
3e	+	−	+	−	−	+
3f	++	−	−	−	+	+
3g	+	+	+	−	+	−
3h	+	−	+	−	+	−
3I	+++	+	+	−	+	−
3j	+	+	+	+	+	+
4a	++	−	−	−	−	−
4b	++	−	+	−	+	+
4c	++	−	+	−	+	−
4d	++	+	+	−	+	−
4e	+	+	+	+	+	+
4f	+	−	−	−	+	−
4g	+	−	+	−	+	+
4h	+	+	+	−	+	−
4I	++	+	+	+	+	+
4j	+	−	−	−	+	−

a) Key: +++=activity at 30 mg/kg, ++=activity at 100 mg/kg, +=activity at 300 mg/kg, −=no activity at 300 mg/kg. *b*) Maximal electroshock seizure test. *c*) Subcutaneous pentylenetetrazole seizure test. *d*) Neurologic toxicity (rotarod) test.

Table 2. Quantitative Anticonvulsant Data in Mice (Test Drug Administered i.p.)

Compound	ED_{50} [a]		TD_{50} [b]
	MES	ScMet	
1c	115.9 (95—135)[c]	>200	250 (231—272)
1d	102.6 (92—124)	150 (135—165)	175 (152—203)
1g	135 (110—163)	>100	227 (209—244)
2a	111 (93—129)	159 (137—180)	245 (225—266)
2c	89 (74—104)	>190	206 (178—234)
2d	95 (78—114)	172 (153—190)	288 (258—314)
2I	126 (104—145)	155 (134—173)	188 (168—208)
3c	145 (122—163)	>170	177 (153—198)
3d	98 (81—114)	182 (165—203)	256 (225—279)
3f	123 (105—145)	159 (141—179)	220 (194—258)
3I	41.9 (31—53)	>200	188 (156—219)
4a	142 (120—165)	179 (157—197)	225 (193—255)
4b	130 (112—153)	156 (138—174)	184 (156—207)
4c	105 (86—124)	>175	227 (192—258)
4d	125 (102—148)	156 (135—174)	175 (155—197)
4I	129 (101—153)	>250	195 (177—224)
Phenytoin	9.9 (6.3—13.1)	>300	69.8 (57.2—80.7)
Carbamazepine	9.2 (6.9—11.7)	>125	74.4 (59.1—87.5)
Valproate	264 (236—297)	157 (133—185)	408 (364—437)

a) Doses measured in mg/kg at the peak effect. *b*) Doses (mg/kg) determined by rotarod test at the time of peak neuro toxic effect. *c*) 95% confidence limits.

bles 1 and 2.

Amphetamine Antagonistic Activity The decrease in the motor activity[17] induced by introceptine stimuli of the compounds was studied by amphetamine antagonism. Wistar albino mice ($n=6$) of either sex were selected by random sampling technique. The compounds were administered at a dose level 25 mg and 50 mg/kg, i.p. 30 min prior to the administration of amphetamine (5 mg/kg, i.p.). Phenobarbital (10 mg/kg, i.p.) was used as the standard drug. The motor activity of the animals (groupwise) was observed for 15 min in an octophotometer after 10 min of amphetamine administration. 70% decrease in motor activity is defined as significant decrease in motor activity. The percentage reduction of motor activity by the compounds are presented in Table 3.

Cardiac Activity[18] Isolated frog heart was mounted using normal amphibian ringer solution. The effect of the compounds on the rate and force of contraction was observed from 1 to 400 μg/animal. The effect of the compounds at various concentration with simultaneous administration of adrenaline (100, 200, 400 μg/dose) was also studied (Table 4).

Evaluation of Antihistaminic Activity[19] The terminal portion of the guinea pig ileum was dissected out from overnight fasted (water given *ad libitum*) healthy hartely strain of guinea pigs. Antihistaminic activity based on the antagonism to the contraction of smooth muscle and the capillary dilation produced by histamine. The ileum was mounted by using tyrode solution bubbled with O_2 (95%) and CO_2 (5%) mixture at 37±0.5 °C. The effect of the compounds (250, 500, 1000 μg/dose) on histamine-induced contractions was reported in Table 5.

Results and Discussion

The initial evaluation (phase I) of anticonvulsant activity of synthesized compounds were presented in the Table 1. The compounds were administered intraperitoneally at three

Table 3. Amphetamine Antagonism of the Compounds

Compound	Dose (mg/kg)	% Reduction of motor activity
1a	25	34.26*
	50	68.48*
1b	25	30.34*
	50	60.22*
1c	25	42.24*
	50	84.56*
1d	25	33.44*
	50	66.82*
1e	25	32.34*
	50	64.24*
1f	25	26.28*
	50	52.66*
1g	25	25.46*
	50	50.84*
1h	25	46.52**
	50	92.48*
1I	25	36.46*
	50	72.84*
1j	25	22.6**
	50	44.42*
1k	25	16.46*
	50	32.62**
1l	25	33.44**
	50	66.48*
1m	25	39.42*
	50	68.68*
2a	25	41.24**
	50	82.48*
2b	25	28.44**
	50	56.28*
2c	25	21.68**
	50	42.46*
2d	25	43.56*
	50	86.84*
2e	25	25.34**
	50	50.36*
2f	25	32.54*
	50	64.46*
2g	25	52.48*
	50	98.88*
2h	25	36.2**
	50	72.66*
2I	25	19.58*
	50	38.46*
2j	25	32.24**
	50	64.48*
3a	25	22.36**
	50	44.48*
3b	25	41.48*
	50	82.82*
3c	25	29.54**
	50	58.42*
3d	25	33.36*
	50	66.48**
3e	25	48.2*
	50	96.28*
3f	25	22.48*
	50	44.66*
3g	25	11.36*
	50	22.28*
3h	25	31.54*
	50	62.64*
3I	25	43.56*
	50	86.42*
3j	25	41.46*
	50	82.24*
4a	25	21.48*
	50	42.24*

Table 3. Continued

Compound	Dose (mg/kg)	% Reduction of motor activity
4b	25	39.54*
	50	78.58*
4c	25	34.34*
	50	68.46*
4d	25	46.44*
	50	92.84*
4e	25	39.44*
	50	78.56*
4f	25	42.32*
	50	84.64*
4g	25	42.48*
	50	84.82*
4h	25	22.48*
	50	44.36*
4I	25	23.52*
	50	46.34*
4j	25	45.44*
	50	90.14*
Phenobarbitone	10	98.44*

* $p<0.05$, ** $p<0.01$, compared to control.

doses (30, 100, 300 mg/kg).

As result of preliminary screening, compounds **1c**, **1d**, **1g**, **2a**, **2c**, **2d**, **2I**, **3c**, **3d**, **3f**, **3I**, **4a**, **4b**, **4c**, **4d** and **4I** were considered for the phase II trails. The estimation of ED_{50} and TD_{50} values for the protection and their confidence limits are calculated by probit analysis of the data using the number of dosed *vs.* the number of surviving animals. This provides an evaluation of the median ED_{50} and median neurotoxic dose (TD_{50}). These datas are shown in the Table 2. Most of the compounds were active at 30 min but not at 4 h. Some of these derivatives showed high degree of protection against MES-induced seizures. But they were found to be less effective against scMet-induced seizures. Compound **3i** was the best in the MES test having ED_{50} of 41.9 mg/kg. In the MES test, the ED_{50} of compounds was found to be **2c** (89 mg/kg), **2d** (95 mg/kg) and **3d** (98 mg/kg).

The following structure–activity relationships were observed. In the entire series of propanol, 6-amino substituted compounds are more active than the corresponding 6-methyl substituted compounds. In the propanol series of 6-amino (**2a**—**j**), only compounds **2a**, **2c**, **2d** and **2i** were found to have a high degree of protection against MES-induced convulsions. Imidazolo substituted compound at the 3rd position showed higher protection than the other heterocyclic substitution like morpholino, piperidino and piperazino compounds. Among the secondary amines, 4-hydroxyphenylamino substituted at 3rd position offered more protection than other secondary amino compounds (phenylamino, methylamino). In the propanol series of 6-methyl (**4a**—**j**), only compounds **4a**, **4b**, **4c**, **4d** and **4i** were found to have a high degree of protection against MES-induced convulsions. Piperazino substituted compound at the 3rd position showed higher protection than the other heterocyclic substitution like morpholino, piperidino and imidazolo compounds. Among the secondary amines, 4-hydroxyphenylamino substituted at 3rd position offered more protection than other secondary amino compounds (phenylamino, methylamino).

In the ethane series of 6-amino (**1a**—**m**), compounds **1c**,

Table 4. Cardiac Activity of the Compounds

Compound	Concentration	Effect on systole
2a	1—100 μg of **2a**	Normal
	200 μg of **2a**	Negative ionotropic
	200 μg of **2a** + 100 μg of adrenaline	Positive ionotropic
	400 μg of **2a** + 100 μg of adrenaline	Normal
2b	1—50 μg of **2b**	Normal
	100 μg of **2b**	Negative ionotropic
	200 μg of **2b** + 100 μg of adrenaline	Positive ionotropic
	400 μg of **2b** + 100 μg of adrenaline	Normal
2c	1—50 μg of **2c**	Normal
	50—80 μg of **2c**	Negative ionotropic
	80 μg of **2c** + 100 μg of adrenaline	Positive ionotropic
	100 μg of **2c** + 100 μg of adrenaline	Normal
2d	1—80 μg of **2d**	Negative ionotropic
	100 μg of **2d** + 100 μg of adrenaline	Positive ionotropic
	200 μg of **2d** + 100 μg of adrenaline	Normal
2e	1—50 μg of **2e**	Normal
	60—100 μg of **2e**	Negative ionotropic
	200 μg of **2e** + 100 μg of adrenaline	Positive ionotropic
	400 μg of **2e** + 100 μg of adrenaline	Normal
2f	1—100 μg of **2f**	Normal
	200 μg of **2f**	Negative ionotropic
	400 μg of **2f** + 100 μg of adrenaline	Positive ionotropic
	800 μg of **2f** + 100 μg of adrenaline	Normal
2g	1—50 μg of **2g**	Normal
	60—100 μg of **2g**	Negative ionotropic
	200 μg of **2g** + 100 μg of adrenaline	Positive ionotropic
	400 μg of **2g** + 100 μg of adrenaline	Normal
2h	1—50 μg of **2h**	Normal
	100 μg of **2h**	Negative ionotropic
	200 μg of **2h** + 100 μg of adrenaline	Positive ionotropic
	400 μg of **2h** + 100 μg of adrenaline	Normal
2I	1—100 μg of **2I**	Negative ionotropic
	100 μg of **2I** + 100 μg of adrenaline	Positive ionotropic
	200 μg of **2I** + 100 μg of adrenaline	Normal
2j	1—100 μg of **2j**	Normal
	200 μg of **2j**	Negative ionotropic
	200 μg of **2j** + 100 μg of adrenaline	Positive ionotropic
	400 μg of **2j** + 100 μg of adrenaline	Normal
4a	1—50 μg of **4a**	Negative ionotropic
	50 μg of **4a** + 100 μg of adrenaline	Positive ionotropic
	100 μg of **4a** + 100 μg of adrenaline	Normal
4b	1—50 μg of **4b**	Normal
	50—100 μg of **4b**	Negative ionotropic
	100 μg of **4b** + 100 μg of adrenaline	Positive ionotropic
	200 μg of **4b** + 100 μg of adrenaline	Normal
4c	1—20 μg of **4c**	Normal
	20—40 μg of **4c**	Negative ionotropic
	50 μg of **4c** + 100 μg of adrenaline	Positive ionotropic
	100 μg of **4c** + 100 μg of adrenaline	Normal
4d	1—60 μg of **4d**	Normal
	70—200 μg of **4d**	Negative ionotropic
	200 μg of **4d** + 100 μg of adrenaline	Positive ionotropic
	400 μg of **4d** + 100 μg of adrenaline	Normal
4e	1—100 μg of **14**	Normal
	200 μg of **14** + 100 μg of adrenaline	Negative ionotropic
	400 μg of **14** + 100 μg of adrenaline	Positive ionotropic
	800 μg of **14** + 100 μg of adrenaline	Normal
4f	1—40 μg of **4f**	Normal
	50—100 μg of **4f**	Negative ionotropic
	200 μg of **4f** + 100 μg of adrenaline	Positive ionotropic
	400 μg of **4f** + 100 μg of adrenaline	Normal
4g	1—40 μg of **4g**	Normal
	50—100 μg of **4g**	Negative ionotropic
	100 μg of **4g** + 100 μg of adrenaline	Positive ionotropic
	200 μg of **4g** + 100 μg of adrenaline	Normal
4h	1—50 μg of **4h**	Normal
	60—200 μg of **4h**	Negative ionotropic
	200 μg of **4h** + 100 μg of adrenaline	Positive ionotropic
	400 μg of **4h** + 100 μg of adrenaline	Normal

Table 5. Antihistaminic Activity

Compound	Contractile response of guinea pig ileum (in mm)				% inhibition of contraction
	Treatment				
	Histamine (500 ng)	Histamine (500 ng)+test compound (250 μg)	Histamine (500 ng)+test compound (500 μg)	Histamine (500 ng)+test compound (1000 μg)	
1a	39	36	33	32	17.94
1b	46	43	40	39	15.21
1c	41	38	36	34	17.07
1d	39	38	35	34	12.82
1e	40	37	34	31	22.5
1f	42	40	37	34	19.04
1g	37	34	31	28	24.32
1h	39	37	35	33	15.38
1I	39	36	34	32	17.94
1j	41	39	37	35	14.63
1k	44	41	39	38	13.63
1l	38	36	35	34	10.52
1m	39	37	35	33	15.38
3a	40	38	36	34	15
3b	42	39	38	36	14.28
3c	38	36	33	31	18.42
3d	41	39	37	35	14.63
3e	38	35	32	29	23.68
3f	39	36	33	31	17.94
3g	39	35	32	30	23.07
3h	41	39	37	35	14.63
3I	39	37	35	33	15.38
3j	39	36	34	32	17.94
CPM	38	35	32	28	26.31

CPM, chlopheniramine maleate.

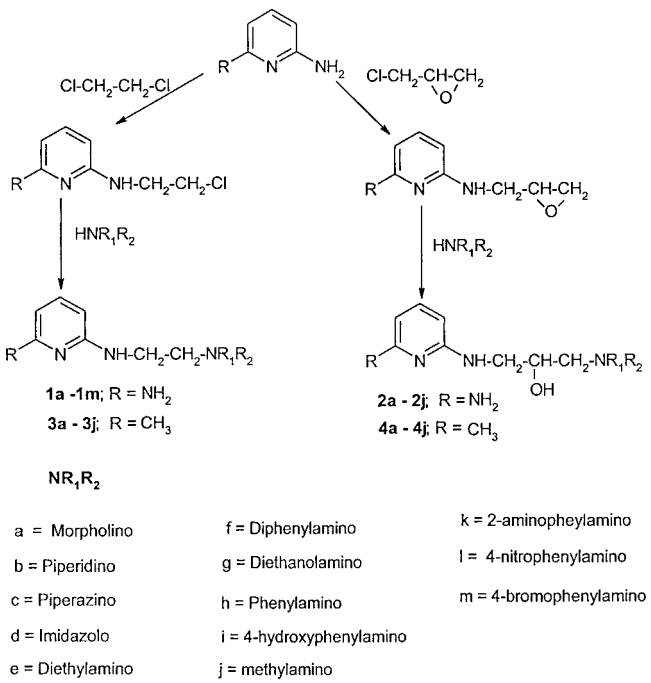

Fig. 1. Synthetic Scheme

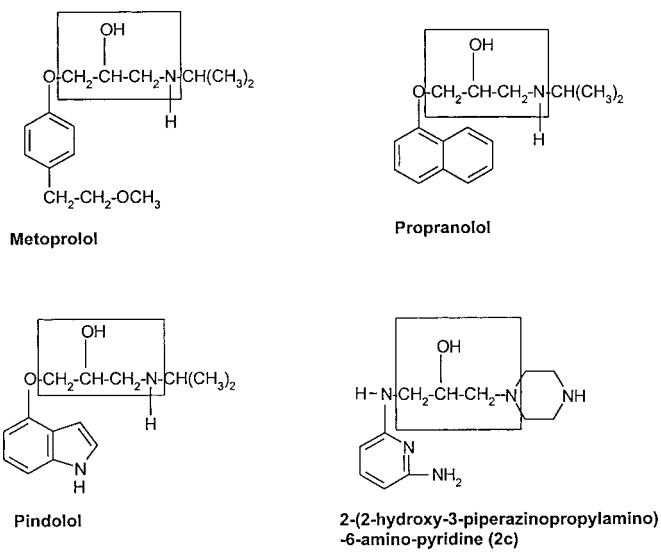

Fig. 2. Depiction of the Presence of the Pharmacophore in **2c** Similar to Sympatholytic Drugs

1d and **1g** were found to have high degree of protection against MES-induced seizures. Only heterocyclic (piperazino and imidazolo) groups substituted at the 2nd position showed more protection than the other substitution. In the ethane series of 6-methyl (**3a**—**j**), compounds **3c**, **3d**, **3f** and **3i** were found to have high degree of protection against MES-induced seizures. Piperazino and imidazolo groups substituted at the 2nd position showed more protection than the other substitutions. 4-Hydroxyphenylamino substituted compound is more active among all the substitutions.

β-Blockers and aryloxypropanolamines[20] inhibit adenylyl cyclase, which reduces the production of c-AMP (adenosine mono phosphate). c-AMP activates the phosphorylation of hydroxyl group containing aminoacids such as tyrosine, ser-

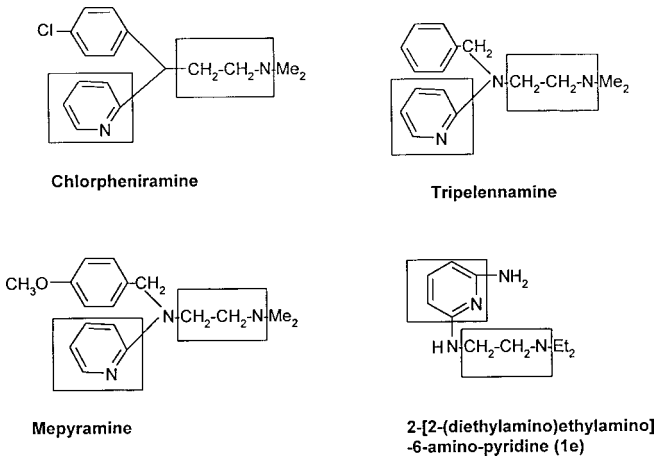

Fig. 3. Depiction of the Presence of the Pharmacophore in **1e** Similar to Antihistaminic Drugs

ine and threonine which causes the enzyme to change the shape, which causes the release of Ca^{2+}. Since β-blockers reduce c-AMP, less Ca ions are released. The propanol series of compounds may be correlated to the presence of the pharmacophore similarity to the chemical functionality present in β-adrenergic blocking agents. It may be hypothesized that the anticonvulsant activity exerted by some of the compounds by blocking Ca^{2+} channels. Calcium influx *via* voltage-activated Ca^{2+} channels also plays a role in epileptogenesis and neurodegenerative events, raising the possibility that the blockade of Ca^{2+} channels may represent the mechanism of action of these compounds.

1c, **1h**, **1I**, **2a**, **2d**, **2g**, **2h**, **3b**, **3e**, **3I**, **3j**, **4b**, **4d**, **4e**, **4f**, **4g** and **4j** compounds exhibited significant decrease (70%) motor activity.

With respect to the 6-amino derivatives, the decrease in motor activity by the compounds in ethane series (**1a**—**m**) was found to be in the order of **1h**>**1c**>**1i**. Among the heterocyclic groups substituted at the 2nd position piperazino substituted compound is more active than piperidino and imidazolo substituted compounds. None of the tertiary amines showed promising activity, whereas secondary amine substituted at the 2nd position, (phenylamino) showed better activity. The decrease in motor activity by the compounds with respect to propanol series (**2a**—**j**) was found to be in the order of **2g**>**2d**>**2a**>**2h**. Among the heterocyclic groups substituted at the 3rd position imidazolo substituted compound is more active than piperidino and piperazino substituted compounds. Among the tertiary amines diethanolamino compound showed promising activity, whereas secondary amine substituted at the 3rd position, phenylamino, showed better activity.

With respect to the 6-methyl derivatives, the decrease in motor activity by the compounds in ethane series (**3a**—**j**) was found to be in the order of **3e**>**3i**>**3b**>**3j**. Among the heterocyclic groups substituted at the 2nd position piperidino substituted compound is more active than imidazolo and piperazino substituted compounds. Among the tertiary amines diethylamino compound showed promising activity, methylamino substituted at the 2nd position showed better activity than 4-hydroxyphenylamino among the secondary amines. The decrease in motor activity by the compounds with respect to propanol series (**4a**—**j**) was found to be in the order of **4d**>**4j**>**4f**. Among the heterocyclic groups substituted at the 3rd position imidazolo substituted compound is more active than piperidino and piperazino substituted compounds. Among the tertiary amines diphenylamino compound showed promising activity, whereas secondary amine substituted at the 3rd position methylamino showed better activity.

2a, **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **2I**, **2j**, **4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **4g** and **4h** exhibited potential cardiac activity. None of ethane series compounds found to be active. Among the propanol series piperazino substituted compound showed better blocking activity than the other heterocyclic compounds where as all other compounds are less active than piperazino substituted compound. Among the tertiary amines substituted amino compounds is more active than the other compounds. 4-hydroxyphenylamino is more active among secondary amines. Electron pumping groups have prominent role in this effect. Proton pumping groups significantly downplayed the effect of blocking adrenaline in the entire series. The cardiac activity exhibited by these compounds may be correlated to the presence of the pharmacophore similarity to the chemical functionality present in β-adrenergic blocking agents. When administered concurrently with adrenaline, the compounds exhibited significant sympatholytic action. The compounds were able to block the effects of adrenaline (100, 200, 400 μg).

In the antihistaminic activity, almost all the ethane derivatives showed promising activity, whereas propanol series of compounds found to be inactive. The active compounds were **1c**, **1e**, **1f**, **1g**, **3c**, **3e**, **3f**, **3g** and **3j**. Diethanolamino and diethylamino substituted compounds found to be more active in the entire series. This promising activity may be because of similarity of the functionality with other antihistaminic agents.

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