Synthesis and Pharmacological Activities of 1,8-Naphthyridine Derivatives

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In the present study, a series of 2-substituted-4-methyl-7-amino/4,7-dimethyl-1,8-naphthyridines were synthesized and characterized by IR, ^{1}H-NMR and elemental analysis. The compounds were investigated for anticonvulsant (125, 250 mg/kg), cardiac and antimicrobial activities. The compounds were screened for antibacterial activity against gram (+) bacteria (*Staphylococcus epidermidis*, *Bacillus subtilis*, *Enterococcus faecalis* and *Micrococcus luteus*) and gram (−) bacteria (*Proteus vulgaris*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Salmonella typhi*). All the compounds except 2-(3′-phenylaminopropyloxy)-4-methyl-7-amino-1,8-naphthyridine exhibited significant anticonvulsant activity. The anticonvulsant activity of 2-(3-morpholino-2′-hydroxypropyloxy)-4-methyl-7-amino-1,8-naphthyridine, 2-(3′-diphenylamino-2′-hydroxypropyloxy)-4-methyl-7-amino-1,8-naphthyridine and 2-(3′-diethanolamino-propyloxy)-4,7-dimethy-1,8-naphthyridine at the dose of 250 mg/kg were found to be equivalent to diazepam (5 mg/kg). Sympathetic blocking activity was observed with 2-(3′-phenylamino-2′-hydroxypropyloxy)-4-methyl-7-amino-1,8-naphthyridine, 2-(3′-diethanolamino-2′-hydroxypropyloxy)-4-methyl-7-amino-1,8-naphthyridine and 2-(3′-diphenylamino-2′-hydroxypropyloxy)-4-methyl-7-amino-1,8-naphthyridine only. All the compounds were devoid of antibacterial activity against the tested bacteria.

Key words 1,8-naphthyridine; aryloxyaminopropane; anticonvulsant; sympatholytic

1,8-Naphthyridines were reported to possess antibacterial,[1,2] antimycobacterial,[3] antitumor,[4] antiinflammatory,[5] antiplatele,[6] gastric antisecretary,[7] antiallergic,[8] local anaesthetic[9] and benzodiazepine receptor activity.[10] 1,8-Naphthyridines were also reported to be associated with positive ionotropic,[11] β-adrenergic blocking[12] and antihypertensive[13] activities. Aryloxyaminopropanes were reported to posses CNS depressant,[14] neuroleptic,[15] antiarrhythmic,[16] hypotensive[17] and β-adrenergic activity.[18,19] Therefore, it was envisaged that chemical entities with both 1,8-naphthyridine and aryloxyaminopropane moieties would result in compounds of interesting biological activities.

In the present study, a series of 1,8-naphthyridine derivatives were synthesized. The compounds were characterized by IR, ^{1}H-NMR spectral and elemental analysis. The compounds were evaluated for anticonvulsant activity at the dose level of 125 and 250 mg/kg by maximal electroshock method, cardiac activity on isolated frog heart and antimicrobial activity against several kinds of gram (+) and gram (−) bacteria.

CHEMISTRY

Melting points were determined in open capillary tubes and are uncorrected. IR spectra was 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 ^{1}H-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 ±0.4% of the theoretical values. ^{1}H-NMR and IR spectra were consistent with the assigned structures.

Synthesis of 2-Hydroxy-4-methyl-7-amino-1,8-naphthyridine[20] Ethyl acetoacetate (0.1 mol) was added to 2-amino-6-methyl-pyridine (0.1 mol) and heated to 130 °C for 1 h. Then, 5 ml of concentrated sulphuric acid was added and heating was continued at 100 °C for 30 min. On cooling the reaction mixture, the product was separated out, filtered, dried under vacuum and recrystallized by using methanol–ether (1 : 1). Yield=37.1%, mp 301—302 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.22—7.56 (m, 3H, 3, 5, 6H), 5.72—6.05 (s, 2H, 7-NH_2), 3.89—4.09 (s, 1H, 2-OH), 3.07—3.26 (s, 3H, 4-CH_3). IR (KBr) cm^{-1}: 3435 (O–H), 3154 (N–H), 1413 (C–H), 783, 720 (Ar-H). *Anal.* Calcd for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.88; H, 5.04; N, 24.14.

Synthesis of 2-Hydroxy-4,7-dimethyl-1,8-naphthyridine[20] 2-Hydroxy-4,7-dimethyl-1,8-naphthyridine was synthesized in a similar manner as 2-hydroxy-4-methyl-7-amino-1,8-naphthyridine, using 2,6-diamino-pyridine instead of 2-amino-6-methyl-pyridine. Yield=40.2%, mp 232—233 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.58 (s, 1H, 3-H), 6.31—6.84 (d, J=8.2 Hz, 2H, 5, 6H), 3.87—4.11 (s, 1H, 2-OH), 3.26—3.74 (s, 3H, 7-CH_3), 2.09—2.49 (s, 3H, 4-CH_3). IR (KBr) cm^{-1}: 3289 (O–H), 1409 (C–H), 792, 729 (Ar-H). *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.18; H, 6.08; N, 15.95.

Synthesis of 2-(2′,3′-Epoxypropyloxy)-4-methyl-7-amino-1,8-naphthyridine 2-Hydroxy-4-methyl-7-amino-1,8-naphthyridine (0.1 mol, 17.5 g) was added to epichlorhydrine (0.1 mol, 9.3 g, 7.8 ml) in the presence of 15 ml of 10% alcoholic potassium hydroxide. The reaction mixture was refluxed for 4 h. On cooling the product was separated, filtered, dried under vacuum and recrystallized using chloroform–ether (1 : 1). Yield=48.4%, mp 215—216 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.04 (s, 1H, 3-H), 7.54—7.83 (d, J=7.9 Hz, 2H, 5, 6H), 6.72—6.94 (s, 2H, 7-NH_2), 3.42—3.67 (d, J=5.2 Hz, 2H, 3′-CH_2), 3.21—3.40 (d, J=6.3 Hz, 2H, 1′-CH_2), 2.98—3.21 (s, 3H, 4-CH_3), 2.67—2.91 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 3240 (N–H), 1406 (C–H), 1240 (epoxide C–O), 1120 (ether C–O) 812, 790 (Ar-H). *Anal.* Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.63; N, 18.17. Found: C, 62.54; H, 5.85; N, 17.98.

General Method of Synthesis of 1a to 1d One hun-

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dredth moles of the corresponding 1,8-naphthyridine was added to 0.01 mol of the appropriate amine in the presence of 20 ml of 10% alcoholic potassium hydroxide and refluxed for 4 h. On cooling, the products were separated, filtered, dried under vacuum and recrystallized using 1 : 1 acetone–diethyl ether (**1a**, **1b**, **1d**) and 1 : 1 methanol–diethyl ether (**1c**).

2-(3′-Phenylamino-2′-hydroxypropyloxy)-4-methyl-7-amino-1,8-naphthyridine (**1a**): Yield=40.2%, mp 248—249 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.98 (s, 1H, 3-H), 7.32—7.81 (d, J=8.1 Hz, 2H, 5, 6H), 7.14—7.25 (s, 1H, NH), (m, 5H, 2″, 3″, 4″, 5″, 6″H), 5.78—5.94 (s, 2H, 7-NH_2) 3.68—3.94 (m, 4H, 1′, 3′-CH_2), 3.32—3.68 (s, 3H, 4-CH_3), 3.15—3.29 (s, 1H, 2′-OH), 0.92—1.35 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 3455 (O–H), 3341 (Ar-NH_2), 3125 (C–H), 1425 (C–N), 1325 (N–H), 1109 (C–O), 850, 790 (Ar-H). *Anal.* Calcd for $C_{18}H_{20}N_{4>}O_2$: C, 66.65; H, 6.28; N, 17.27. Found: C, 66.80; H, 6.41; N, 16.91.

2-(3-Morpholino-2′-hydroxypropyloxy)-4-methyl-7-amino-1,8-naphthyridine (**1b**): Yield=36.2%, mp 261—262 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.85 (s, 1H, 3-H), 7.11—7.62 (d, J=7.7 Hz, 2H, 5, 6H), 6.84—7.05 (s, 2H, 7-NH_2), 3.71—4.11 (m, 4H, 1′,3′-CH_2), 3.34—3.61 (s, 3H, 4-CH_3), 3.12—3.33 (s, 1H, 2′-OH), 2.82—3.01 (m, 8H, 2″, 3″, 5″, 6″-CH_2–), 0.94–1.34 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 3405 (O–H), 3105 (Ar-NH_2), 1421 (C–H), 1384 (C–N), 1124, 1046 (C–O), 810, 762 (Ar-H). *Anal.* Calcd for $C_{16}H_{22}N_4O_3$: C, 60.36; H, 6.96; N, 17.60. Found: C, 60.29; H, 6.82; N, 17.82.

2-(3′-Diethanolamino-2′-hydroxypropyloxy)-4-methyl-7-amino-1,8-naphthyridine (**1c**): Yield=42.8%, mp 254—255 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.49 (s, 1H, 3-H), 6.71—7.25 (d, J=8.0 Hz, 2H, 5, 6H), 6.14—6.35 (s, 2H, 7-NH_2), 3.47—3.78 (m, 4H, 1′, 3′-CH_2), 3.05—3.34 (s, 2H, 2″-$(OH)_2$), 2.88—2.99 (m, 8H, 1″, 2″-$(CH_2)_2$), 2.62—2.71 (s, 3H, 4-CH_3), 2.23—2.62 (s, 1H, 2′-OH), 0.94—1.32 (m, H, 2′-CH). IR (KBr) cm^{-1}: 3410 (O–H), 3142 (Ar-NH_2), 1421 (C–H), 1350 (C–N), 1132 (C–O), 806,791 (Ar-H). *Anal.* Calcd for $C_{16}H_{24}N_4O_4$: C, 57.13; H, 7.19; N, 16.66. Found: C, 56.91; H, 7.44; N, 17.01.

2-(3′-Diphenylamino-2′-hydroxypropyloxy)-4-methyl-7-amino-1,8-naphthyridine (**Id**): Yield=33.4%, mp 270—271 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.14—7.66 (m, 3H, 3, 5, 6H), 6.22—7.14 (m, 10H, N$(C_6H_5)_2$), 5.85—6.16 (s, 2H, 7-NH_2), 3.66—4.00 (m, 4H, 1′, 3′-CH_2), 3.24—3.66 (s, 3H, 4-CH_3), 2.95—3.24 (s, 1H, 2′-OH), 1.35—1.56 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 3450 (O–H), 3291 (Ar-NH_2), 1435 (C–H), 1361 (C–N), 1118 (C–O), 812, 790 (Ar-H). *Anal.* Calcd for $C_{24}H_{24}N_4O_2$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.29; H, 5.72; N, 14.31.

Synthesis of 2-(3′-Chloropropyloxy)-4-methyl-7-amino-1,8-naphthyridine One tenth moles of 2-hydroxy-4-methyl-7-amino-1,8-naphthyridine was added to 0.1 mol (15.7 g, 10.5 ml) of 1-bromo-3-chloropropane in the presence of 15 ml of 10% potassium hydroxide and refluxed for 10 h. On cooling, the product was separated, filtered, dried under vacuum and recrystallized using chloroform–ether (1 : 1). Yield=31%, mp 210—211 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.26 (s, 1H, 3-H), 7.99—8.10 (d, J=8.1 Hz, 2H, 5, 6H), 6.37—6.62 (s, 2H, 7-NH_2), 2.46—2.81 (m, 4H, 1′, 3′-CH_2), 2.38—2.44 (s, 3H, 4-CH_3), 1.12—1.31 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 3242 (N–H), 1396 (C–H), 1124 (C–O), 811, 797 (Ar-H), 754 (C–Cl). *Anal.* Calcd for $C_{12}H_{14}ClN_3O$: C, 57.26; H, 5.61; N, 16.69. Found: C, 57.36; H, 5.36; N, 16.96.

Synthesis of 2-(3′-Chloropropyloxy)-4,7-dimethyl-1,8-naphthyridine 2-(3′-Chloro-propyloxy)-4,7-dimethyl-1,8-naphthyridine was synthesized in a similar manner as 2-(3′-chloro-propyloxy)-4-methyl-7-amino-1,8-naphthyridine using 2-hydroxy-4,7-dimethyl-1,8-naphthyridine instead of 2-hydroxy-4-methyl-7-amino-1,8-naphthyridine. Yield=54.4%, mp 200—201 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.85 (s, 1H, 3-H), 7.63—7.75 (d, J=7.8 Hz, 2H, 5, 6H), 3.42—3.90 (m, 4H, 1′, 3′-CH_2), 3.12—3.35 (s, 3H, 7-CH_3), 2.85—3.05 (s, 3H, 4-CH_3), 1.15—1.23 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 1409 (C–H), 1142 (C–O), 811, 792 (Ar-H), 742 (C–Cl). *Anal.* Calcd for $C_{13}H_{15}ClN_2O$: C, 62.27; H, 6.05; N, 11.17. Found: C, 61.99; H, 5.76; N, 11.44.

General Method of Synthesis of 2a to 2j One hundredth moles of the corresponding 1,8-naphthyridine was added to 0.01 mol of the appropriate amine in the presence of 20 ml of 10% alcoholic potassium hydroxide and refluxed for 5 h. On cooling, the products were separated, filtered, dried under vacuum and recrystalized using 1 : 1 acetone–diethyl ether (**2a**, **2b**, **2c**, **2f**) and 1 : 1 methanol–diethyl ether (**2d**, **2e**, **2g**, **2i**, **2j**) and diethyl ether (**2h**).

2-(3′-Phenylaminopropyloxy)-4-methyl-7-amino-1,8-naphthyridine (**2a**): Yield=15.6%, mp 284—285 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.87 (s, 1H, 3-H), 7.31—7.74 (d, J=8.0 Hz, 2H, 5, 6H), 7.14—7.31 (s, 1H, NH), 6.41—6.68 (m, 5H, 2″, 3″, 4″, 5″, 6″H), 5.76—5.93 (s, 2H, 7-NH_2), 3.84—4.06 (m, 4H, 1′, 3′-CH_2), 3.60—3.76 (s, 3H, 4-CH_3), 0.65—1.30 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 3241 (Ar N–H), 1391 (C–H), 1370 (C–N), 1322 (N–H), 1145 (C–O), 822,804 (Ar-H). *Anal.* Calcd for $C_{18}H_{20}N_4O$: C, 70.11; H, 6.54; N, 18.17. Found: C, 70.35; H, 6.71; N, 18.42.

2-[3′-(4″-Nitrophenylamino)-propyloxy]-4-methyl-7-amino-1,8-naphthyridine (**2b**): Yield=40%, mp 180—181 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.87 (s, 1H, 3-H), 7.31—7.66 (d, J=7.9 Hz, 2H, 5, 6H), 7.09—7.31 (s, 1H, NH), 6.46—6.67 (m, 4H, 2″, 3″, 5″, 6″H), 5.74—5.99 (s, 2H, 7-NH_2), 3.88—4.17 (m, 4H, 1′, 3′-CH_2), 3.65—3.88 (s, 3H, 4-CH_3), 0.86—1.28 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 3367 (Ar N–H), 1524 (N–O), 1426 (C–H), 1370 (C–N), 1303 (N–H), 1112 (C–O), 841, 783 (Ar-H). *Anal.* Calcd for $C_{18}H_{19}N_5O_3$: C, 61.18; H, 5.42; N, 19.82. Found: C, 60.94; H, 5.66; N, 20.06.

2-[3′-(4″-Hydroxyphenylamino)-propyloxy]-4-methyl-7-amino-1,8-naphthyridine (**2c**): Yield=40.1%, mp 170—171 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.81 (s, 1H, 3-H), 7.30—7.67 (d, J=7.8 Hz, 2H, 5, 6H), 7.15—7.29 (s, 1H, NH), 6.47—6.71 (m, 4H, 2″, 3″, 5″, 6″H), 5.74—6.00 (s, 2H, 7-NH_2), 4.31—4.77 (s, 1H, 4′-OH), 3.86—4.16 (m, 4H, 1′, 3′-CH_2), 3.63—3.84 (s, 3H, 4-CH_3), 0.92—1.28 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 3425 (O–H), 3340 (Ar N–H), 1414 (C–H), 1394 (C–N), 1320 (N–H), 1110 (C–O), 830, 792 (Ar-H). *Anal.* Calcd for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.35; H, 5.94; N, 17.14.

2-(3′-Diethanolaminopropyloxy)-4-methyl-7-amino-1,8-naphthyridine (**2d**): Yield=15.7%, mp 291—292 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.42 (s, 1H, 3-H), 6.31—6.81 (d, J=8.1 Hz, 2H, 5, 6H), 6.06—6.24 (s, 2H, 7-NH_2), 3.41—3.89 (m, 4H, 1′, 3′-CH_2), 3.06—3.41 (s, 2H, 2″-$(OH)_2$), 2.34—2.97 (m, 8H, 1″, 2″-$(CH_2)_2$), 2.07—2.35 (s, 3H, 4-CH_3), 1.16—1.64 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 3427 (O–H), 3196 (Ar N–H), 1385 (C–H), 1360 (C–N), 1096 (C–O), 834, 824 (Ar-

H). *Anal.* Calcd for $C_{16}H_{24}N_4O_3$: C, 59.98; H, 7.55; N, 17.49. Found: C, 60.21; H, 7.69; N, 17.66.

2-(3′-Diphenylaminopropyloxy)-4-methyl-7-amino-1,8-naphthyridine (**2e**): Yield=35.9%, mp 298—299 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.06—7.82 (m, 3H, 3, 5, 6H), 6.14—7.06 (m, 10H, $N(C_6H_5)_2$), 5.74—6.04 (s, 2H, 7-NH_2), 3.65—3.92 (m, 4H, 1′, 3′-CH_2), 3.04—3.48 (s, 3H, 4-CH_3), 1.02—1.26 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 3370 (Ar N–H), 1425 (C–H), 1370 (C–N), 1120 (C–O), 841, 783 (Ar-H). *Anal.* Calcd for $C_{24}H_{24}N_4O$: C, 74.97; H, 6.29; N, 14.57. Found: C, 75.11; H, 6.04; N, 14.49.

2-(3′-Piperidinopropyloxy)-4-methyl-7-amino-1,8-naphthyridine (**2f**): Yield=25%, mp 304—305 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.15—7.40 (m, 3H, 3, 5, 6H), 5.81—6.15 (s, 2H, 7-NH_2), 3.80—3.92 (m, 4H, 1′, 3′-CH_2), 2.81—3.35 (m, 10H, 2″, 3″, 4″, 5″, 6″-CH_2–), 1.34—2.21 (s, 3H, 4-CH_3), 1.30—1.42 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 3292 (Ar N–H), 1434 (C–H), 1396 (C–N), 1135 (C–O), 781, 725 (Ar-H). *Anal.* Calcd for $C_{17}H_{24}N_4O$: C, 67.97; H, 8.05; N, 18.65. Found: C, 68.27; H, 7.88; N, 18.94.

2-(3′-Morpholinopropyloxy)-4-methyl-7-amino-1,8-naphthyridine (**2g**): Yield=30%, mp 131—132 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.14—7.38 (m, 3H, 3, 5, 6H), 5.73—6.09 (s, 2H, 7-NH_2), 3.66—4.03 (m, 4H, 1′, 3′-CH_2), 3.04—3.45 (s, 3H, 4-CH_3), 2.71—3.00 (m, 8H, 2″, 3″, 5″, 6″-CH_2–), 0.79—1.24 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 3292 (Ar N–H), 1436 (C–H), 1324 (C–N), 1135 (C–O), 827, 781 (Ar-H). *Anal.* Calcd for $C_{16}H_{22}N_4O_2$: C, 63.55; H, 7.33; N, 18.53. Found: C, 63.71; H, 7.04; N, 18.23.

2-(3′-Diethanolaminopropyloxy)-4,7-dimethy-1,8-naphthyridine (**2h**): Yield=40.2%, mp 274—275 °C. ^{1}H-NMR ($CDCl_3$) δ: 7.43 (s, 1H, 3-H), 6.31—6.80 (d, 2H, 5, 6H), 3.44—3.88 (m, 4H, 1′, 3′-CH_2), 3.12—3.44 (s, 3H, 7-CH_3), 2.53—2.97 (s, 2H, 2″-$(OH)_2$), 2.30—2.53 (m, 8H, 1″, 2″-$(CH_2)_2$), 2.17—2.30 (s, 3H, 4-CH_3), 0.94—1.28 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 3366 (O–H), 1405 (C–H), 1390 (C–N), 1122 (C–O), 819, 784 (Ar-H). *Anal.* Calcd for $C_{17}H_{25}N_3O_3$: C, 64.12; H, 7.89; N, 13.16. Found: C, 63.94; H, 8.12; N, 12.88.

2-(3′-Piperidinopropyloxy)-4,7-dimethyl-1,8-naphthyridine (**2i**): Yield=25.6%, mp 286—287 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.40 (s, 1H, 3-H), 7.24—7.54 (d, 2H, 5, 6H), 3.89—4.16 (m, 4H, 1′, 3′-CH_2), 3.15—3.75 (s, 3H, 7-CH_3), (m, 10H, 2″, 3″, 4″, 5″, 6″-CH_2–), 1.67—1.92 (s, 3H, 4-CH_3), 0.54–1.67 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 1382 (C–H), 1324 (C–N), 1118 (C–O), 882, 705, (Ar-H). *Anal.* Calcd for $C_{18}H_{25}N_3O$: C, 72.20; H, 8.41; N, 14.03. Found: C, 71.98; H, 8.69; N, 13.76.

2-(3′-Morpholinopropyloxy)-4,7-dimethyl-1,8-naphthyridine (**2j**): Yield=25.4%, mp 120—121 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.35 (s, 1H, 3-H), 7.26—7.65 (d, 2H, 5, 6H), 3.19—3.90 (m, 4H, 1′, 3′-CH_2), 2.77—3.03 (s, 3H, 7-CH_3), 2.13—2.67 (m, 8H, 2″, 3″, 5″, 6″-CH_2–), 1.66—1.89 (s, 3H, 4-CH_3), 0.53—1.55 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 1381 (C–H), 1335 (C–N), 1119 (C–O), 886, 705 (Ar-H). *Anal.* Calcd for $C_{17}H_{23}N_3O_2$: C, 67.95; H, 7.69; N, 13.94. Found: C, 68.24; H, 7.91; N, 14.21.

PHARMACOLOGY

All the synthesized compounds were screened for anticonvulsant activity at the dose of 125 and 250 mg/kg. The anticonvulsant dose was selected between the minimal effective dose and maximal non-lethal dose. All the compounds were soluble in water and administered to the animals as a solution in triple glass distilled water. The compounds were also screened for cardiac activity on isolated frog heart. Wistar albino rats (150—200 g) 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. All the animals were acclimatized for a week before use. Small frogs (Rana tigrina, 60—120 g) were procured locally and used on the same day. Unpaired Student-*t*-test[21] was performed to ascertain the significance of the exhibited anticonvulsant activity of the compounds.

Anticonvulsant Activity[22] The anticonvulsant activity of the synthesized compounds were tested against maximal electroshock induced convulsions in rats. Wistar albino rats (n=6) of either sex were selected by random sampling technique. The compounds were administered at the dose level of 125 and 250 mg/kg orally by intragastric tube 30 min prior to an electric shock of 150 mA current for 0.2 s. Diazepam (5 mg/kg, oral) was used as the standard drug. The percentage protection of the compounds is presented in Table 1.

Cardiac Activity[23] 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 80 μg. The effect of the compounds at 40 μg concentration with simultaneous administration of adrenaline (10, 20, 30 μg) was also studied (Table 2).

Antibacterial Activity (Paper Disc Diffusion Method)[24] The antibacterial activity of the synthesized compounds was performed by paper disc diffusion method against gram (+) bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, *Entero-*

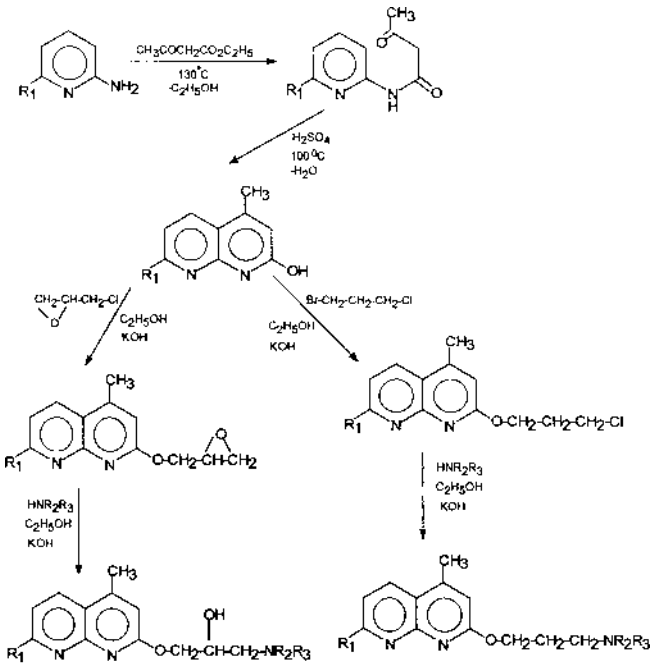
Table 1. Anticonvulsant Activity of the Compounds

Compound	Dose (mg/kg)	% Protection
1a	125	10.21*
	250	29.64***
1b	125	41.20***
	250	98.51***
1c	125	24.09***
	250	40.11***
1d	125	48.17***
	250	98.5***
2b	125	17.7**
	250	37.72***
2c	125	22.42**
	250	55.21***
2d	125	9.82*
	250	25.91***
2e	125	19.3**
	250	36.3***
2f	125	5.41
	250	11.12*
2g	125	20.84**
	250	41.18***
2h	125	44.6***
	250	98.5***
2i	125	18.44**
	250	39.26***
2j	125	29.46**
	250	48.15***
Diazepam	5	98.5***

* $p<0.05$, ** $p<0.01$, *** $p<0.001$ compared to control.

Table 2. Cardiac Activity of the Compounds

Compound	Concentration	Effect on systole
1a	1 μg to 80 μg of **1a**	Normal
	40 μg of **1a** + 10 μg of adrenaline	Normal
	40 μg of **1a** + 20 μg of adrenaline	Normal
	40 μg of **1a** + 30 μg of adrenaline	Normal
1c	1 μg to 80 μg of **1c**	Normal
	40 μg of **1c** + 10 μg of adrenaline	Normal
	40 μg of **1c** + 20 μg of adrenaline	Normal
	40 μg of **1c** + 30 μg of adrenaline	Normal
1d	1 μg to 80 μg of **1d**	Normal
	40 μg of **1d** + 10 μg of adrenaline	Normal
	40 μg of **1d** + 20 μg of adrenaline	Normal
	40 μg of **1d** + 30 μg of adrenaline	Normal
Adrenaline	10 μg	Positive ionotropic and chronotropic



1a - R_1=NH_2, -NR_2R_3 = phenylamino
1b - R_1=NH_2, -NR_2R_3 = morpholino
1c - R_1=NH_2, -NR_2R_3 = bis(2-hydroxyethyl)amino
1d - R_1=NH_2, -NR_2R_3 = diphenylamino
2a - R_1=NH_2, -NR_2R_3 = phenylamino
2b - R_1=NH_2, -NR_2R_3 = 4-nitrophenylamino
2c - R_1=NH_2, -NR_2R_3 = 4-hydroxyphenylamino
2d - R_1=NH_2, -NR_2R_3 = bis(2-hydroxyethyl)amino
2e - R_1=NH_2, -NR_2R_3 = diphenylamino
2f - R_1=NH_2, -NR_2R_3 = piperidino
2g - R_1=NH_2, -NR_2R_3 = morpholino
2h - R_1=CH_3, -NR_2R_3 = bis(2-hydroxyethyl)amino
2i - R_1=CH_3, -NR_2R_3 = piperidino
2j - R_1=CH_3, -NR_2R_3 = morpholino

Fig. 1. Synthetic Scheme

coccus faecalis and *Micrococcus luteus*) and gram (−) bacteria (*Proteus vulgaris*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Salmonella typhi*). The sterilized (autoclaved at 120 °C for 30 min), liquefied nutrient agar (40—50 °C) was inoculated (1 ml/100 ml of medium) with the suspension of

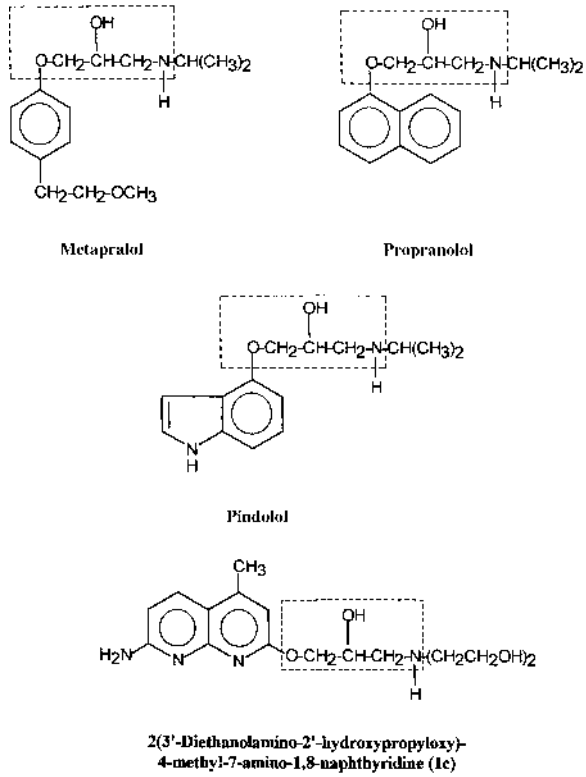


Fig. 2. Depiction of Presence of Pharmacophore in **1c** Similar to Sympatholytic Drugs

the microorganism (matched to McFarland barium sulphate standard) and poured into the petri dish to give a depth of 3—4 mm. The paper discs impregnated with the test compounds (1 g/ml in water) were placed on the solidified medium. The plates were refrigerated for two hours at 4 °C and then incubated at 37 °C for 24 h at the end of which the zone of inhibition was observed.

RESULTS AND DISCUSSION

The protection of the animals against maximal electroshock induced convulsions of the synthesized compounds were screened at the dose levels of 125 and 250 mg/kg. The compounds were screened for cardiac activity using isolated frog heart. The antibacterial activity of the synthesized compounds was tested against gram (+) bacteria (*Staphylococcus epidermidis*, *Bacillus subtilis*, *Enterococcus faecalis* and *Micrococcus luteus*) and gram (−) bacteria (*Proteus vulgaris*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Salmonella typhi*) by paper disc diffusion method.

All the synthesized compounds exhibited significant anticonvulsant activity except **2a**. The active compounds exhibited dose dependant anticonvulsant activity. The anticonvulsant activity of **1b**, **1d** and **2h** at the dose of 250 mg/kg were found to be equivalent to Diazepam (5 mg/kg). The anticonvulsant activity of the compounds with respect to 2′-hydroxy-7-amino-1,8-naphthridine series (**1a**—**d**) was found to be in the order of diphenylamino=morpholino>diethanolamino. The anticonvulsant activity of the compounds with respect to 7-amino-1,8-naphthridine series (**2a**—**g**) was found to be in the order of *p*-hydroxyanilino>morpholino> diphenylamino>diethanolamino. The anticonvulsant activity

of the compounds with respect to 7-methyl-1,8-naphthridine series (**2h**—**j**) was found to be in the order of diethanolamino> morpholino. It was also observed that 7-substitution in the 1,8-naphthyridine plays a significant role in the anticonvulsant activity (except **1b**) since methyl substituted compounds **2i**, **2j** and **2h** exhibited significantly higher protection than the corresponding amino substituted compounds **2f**, **2g** and **2d**, respectively.

Compounds **1a**, **1c** and **1d** exhibited potential cardiac activity. The cardiac activity exhibited by these compounds may be correlated to the presence of the pharmacophore similar to the chemical functionality present in β-adrenergic blocking agents (Fig. 2). Compounds **1a**, **1c** and **1d** did not exhibit chronotropic or ionotropic activity when administered alone but when concurrently administered with adrenaline, the compounds exhibited significant sympatholytic action. The compounds were completely able to block the effects of adrenaline (10, 20, 30 μg). All the synthesized compounds were devoid of antibacterial activity against the tested bacteria.

REFERENCES

1) Bouzard D., DiCesare P., Essiz M., Jacquet J. P., Ledoussal B., Remuzon P., Kessler R. E., Fung Tomc J., *J. Med. Chem.*, **35**, 518—525 (1992).
2) Rao G. R., Mogilaiah K., Sreenivasulu B., *Indian J. Chem.*, **35B**, 339—334 (1996).
3) Ferrarini P. L., Manera C., Mori C., Badawneh M., Saccomanni G., *Farmaco.*, **53**, 741—746 (1998).
4) Zhang S. X., Bastow K. F., Tachibana Y., Kuo S. C., Hamel E., Mauger A., Narayanan V. L., Lee K. H., *J. Med. Chem.*, **42**, 4081—4087 (1999).
5) Kuroda T., Suzuki F., Tamura T., Ohmori K., Hosoe H., *J. Med. Chem.*, **35**, 1130—1136 (1992).
6) Ferrarini P. L., Badawneh M., Franconi F., Manera C., Miceli M., Mori C., Saccomanni G., *Farmaco.*, **56**, 311—318 (2001).
7) Santilli A., Scotese A. C., Bauer R. F., Bell S. C., *J. Med. Chem.*, **30**, 2270—2277 (1987).
8) Kuo S.-C., Tsai S.-Y., Li H.-T., Wu C.-H., Ishii K., Nakamura H., *Chem. Pharm. Bull.*, **36**, 4403—4407 (1988).
9) Ferrarini P. L., Mori C., Tellini N., *Farmaco.*, **45**, 385—389 (1990).
10) DaSettimo A., Primofiore G., DaSettimo F., Simorini F., Barili P. L., Senatore G., Martini C., Lucacchini A., *Drug Des. Discov.*, **11**, 307—328 (1994).
11) Herzig S., Heber D., Mescheder A., Reifenstein-Herzig U., Thormann T., Verborg M., Mohr K., *Arzneim-Forsch.*, **44**, 937—942 (1994).
12) Ferrarini P. L., Mori C., Badawneh M., Calderone V., Greco R., Manera C., Martinelli A., Nieri P., Saccomanni G., *Eur. J. Med. Chem.*, **35**, 815—826 (2000).
13) Ferrarini P. L., Mori C., Primofiore G., *J. Heterocyclic Chem.*, **23**, 601—604 (1986).
14) Agarwal S. K., Saxena A. K., Jain P. C., Anand N., Sur R. N., Srimal R. C., Dhawan B. N., *Indian J. Chem.*, **29B**, 80—84 (1990).
15) Sur R. N., Shanker G., Rathore R. K. S., Chak I. M., Agarwal S. K., Jain P. C., *Indian J. Exp. Biol.*, **18**, 1190—1191 (1980).
16) Starling S. K., Rastogi S. N., Anand N., Srimal R. C., Kar K., *Indian J. Chem.*, **15B**, 715—719 (1977).
17) Agarwal S. K., Kumar Y., Saxena A. K., Jain P. C., Anand N., *Indian J. Chem.*, **21B**, 435—439 (1982).
18) Nathanson J. A., Hunnicutt E. J., *J. Pharm. Pharmacol.*, **40**, 803—805 (1988).
19) Marwah A. K., Marwah P., Rao G. S., Trivedi B. S., Rao B. E., Thomas G. P., Kaushal R., Varma R. S., *Indian J. Chem.*, **34B**, 197—200 (1995).
20) Hauser C. R., Reynolds G. A., *J. Am. Chem. Soc.*, **70**, 2402—2404 (1948).
21) Spiegel M. R., Meddis R., "Probability and Statistics," McGraw-Hill Book Company, New York, 1980.
22) Bhattacharya S. K., Chakrabarti A., *Indian J. Exp. Biol.*, **36**, 118—121 (1998).
23) Laurence D. R., Bacharach A. L. (ed.), "Evaluation of Drug Activities: Pharmacometrics," Academic Press, New York, 1964.
24) Gillespie S. H., "Medical Microbiology-Illustrated," Butterworth Heinemann Ltd., United Kingdom, 1994, pp. 234—247.