Synthesis and Anticonvulsant Activity of Novel 1-Substituted-1,2-dihydro-pyridazine-3,6-diones

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The synthesis and pharmacological evaluation of novel 1-substituted-1,2-dihydro-pyridazine-3,6-diones (4a—l, 5a—j) as potential anticonvulsant agents are described. The compounds were tested *in vivo* for the anticonvulsant activity. The compound which have maximum protection against MES induced seizures is 1-[3-(2-aminophenylamino)-2-hydroxypropyl)-1,2-dihydro-pyridazine-3,6-dione 4h (ED_{50}=44.7 mg·kg^{-1} i.p.) 1-[2-hydroxy-3-piperazin1-yl-propyl)-1,2-dihydro-pyridazine-3,6-dione 4c (ED_{50}=72 mg·kg^{-1} i.p.) and 1-[2-hydroxy-3-imidazol-1-yl-propyl)-1,2-dihydro-pyridazine-3,6-dione 4d (ED_{50}=79 mg·kg^{-1} i.p.) were also found to have maximum protection against MES induced seizures. Whereas all these compounds failed to protect the animals from subcutaneous pentylenetetrazole (Metrozol) seizure threshold test (sc-Met).

Key words aminopropane; anticonvulsant; propanolamine; pyridazine-3,6-dione

Pyridazine derivatives were reported to possess anti-inflammatory,[1] antioxidant,[2] vasorelaxant,[3] anticonvulsant[4,5,6] and antihypertensive[7,8] activities. Propanolamines were reported to be associated with β-adrenergic blocking,[9,10] CNS depressant,[11] hypotensive,[12] diurtetic[13] and antiarrhythmic[14] activities. Aminopropane were reported to possess CNS depressant[11] and neuroleptic[15] properties. In view of these new biodynamic agents from heterocyclic compounds, it was thought worthwhile to study the effects of two pharmacophoric moieties like pyridazine and propanolamine/aminopropane in a single molecule, on the biological activity. We have reported the potential anticonvulsant activity of substituted aminopropanes and propanol amines from our lab[16—21] to continue our work in the same direction, it was envisaged that the chemical entities with pyridazine, and propanolamine/aminopropane 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 1-substituted-1,2-dihydro-pyridazine-3,6-dione derivatives. The compounds were characterized by IR, ^{1}H-NMR spectral and Elemental analysis. The compounds were also investigated for anticonvulsant activity.

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Solvents for reaction under anhydrous conditions were dried according to standard procedures. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded (in KBr) on Perkin-Elmer IR spectrophotometer 298. ^{1}H-NMR spectra were recorded on 300 MHz Bruker DPX 200. The chemical shifts are reported as parts per million downfield from tetramethylsilane (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 Pyridazine-3,6-dione (1) Pyridazine-3,6-dione was prepared with procedure of Hedaya[22] by refluxing maleic anhydride (0.1 mol) with hydrazine monohydrate (0.1 mol) in ethanol 25 (ml) and 30% acetic acid (15 ml) for 30 min. The reaction mixture was cooled and washed with pet. ether 40—60 °C (3×40 ml) and recrystallized with methanol–ether (1 : 1) mp 299—300 °C. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.3—9.5 (s, 2H, $(NH)_2$), 6.48—6.66 (s, 2H, 4, 5-CH). IR (KBr) cm^{-1}: 3240, 1406, 1240, 1120. *Anal.* Calcd for $C_4H_4N_2O_2$. Found (calculated): C, 42.97 (42.85); H, 3.69 (3.57); N, 24.72 (25.0).

Synthesis of 1-(2′,3′-Epoxypropyl)1,2-dihydro-pyridazine-3,6-dione (2) 1-(2′,3′-Epoxypropyl)-1,2-dihydro-pyridazine-3,6-dione was prepared by refluxing 1,2-dihydro-pyridazine-3,6-dione (0.1 mol) with epichlorohydrine (0.1 mol) in the presence of silver chloride (0.0007 mol), sodium iodide (0.0006 mol) and methanol (50 ml) for about 20 h.The resultant product was purified by recrystallization with chloroform–ether (1 : 1) Yield=57%, mp >325 °C. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.7—9.9 (s, 1H, NH), 6.92—7.09 (s, 2H, 4, 5-CH), 3.42—3.67 (d, J=5.2 Hz, 2H, 3′-CH_2), 3.21.4 (d, J=6.3 Hz, 2H, 1′-CH_2), 2.67—2.91 (m, 1H, 2′-CH). IR (KBr) cm^{-1}: 3214, 1429, 1254, 1153. *Anal.* Calcd for $C_{14}H_8N_4O_2$. Found (calculated): C, 49.71 (50.0); H, 4.63 (4.76); N, 16.84 (16.66).

General Procedure for the Synthesis of 1-Substituted-1,2-dihydro-pyridazine-3,6-dione (4a—l) A mixture of 1-(2′,3′-epoxypropyl)-1,2-dihydro-pyridazine-3,6-dione (0.005 mol) and amine (0.005 mol) were refluxed with 10% methanolic potassium hydroxide (25 ml). The reaction mixture was filtered and the filterate on concentration yielded the product. The products were dried under vacuum and recrystallized using 1 : 1 acetone–ether (**4a**, **f**, **g**, **h**, **l**), 1 : 1 ethanol–ether (**4b**, **e**, **i**), 1 : 1 methanol–ether (**4c**, **d**, **j**) and 1 : 1 chloroform–ether (**4k**).

1-[2′-Hydroxy-3′-(1″-morpholino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**4a**): Yield=72%, mp >325 °C. IR (KBr) cm^{-1}: 1455, 1375, 1071. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.3—9.5 (s, 1H, NH), 6.67—6.9 (s, 2H, 4, 5-CH), 3.68—3.8 (m, 1H, 2′-CH), 3.27—3.3 (m, 4H, 1′, 3′-CH_2), 2.4—2.62 (m, 8H, 2″, 3″, 5″, 6″-CH_2), 0.84—1.06 (s, 1H, 2′-OH). *Anal.* Calcd for $C_{11}H_{17}N_3O_4$. Found (calculated): C, 51.54 (51.76);

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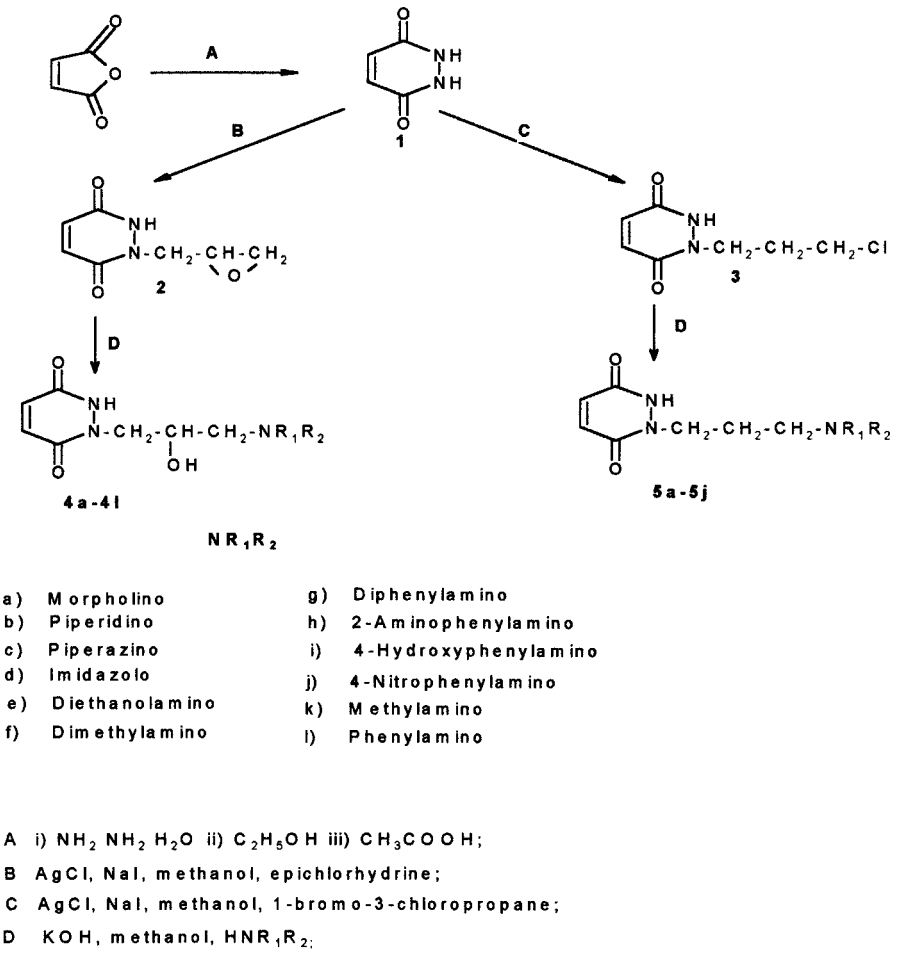

Fig. 1. Synthesis of **4a**—**l** and **5a**—**j**

H, 6.41 (6.66); N, 16.22 (16.47).

1-[2′-Hydroxy-3′-(1″-piperidino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**4b**): Yield=79%, mp 291 °C. IR (KBr) cm^{-1}: 1454, 1372, 1156. ^{1}H-HMR ($CDCl_3$, δ): 9.72—9.91 (s, 1H, NH), 6.98—7.13 (s, 2H, 4, 5-CH), 3.8—3.92 (m, 1H, 2′-CH), 3.52—3.62 (m, 4H, 1′, 3′-CH_2), 2.9—3.35 (m, 10H, 2″, 3″, 4″, 5″, 6″-CH_2), 0.92—1.12 (s, 1H, 2′-OH). *Anal.* Calcd for $C_{12}H_{19}N_3O_3$. Found (calculated): C, 56.77 (56.91); H, 7.38 (7.5); N, 16.91 (16.6).

1-[2′-Hydroxy-3′-(1″-piperazino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**4c**): Yield=80%, mp >325 °C. IR (KBr) cm^{-1}: 1379, 1305, 1161. ^{1}H-HMR ($CDCl_3$, δ): 9.69—9.83 (s, 1H, NH), 8.7—8.9 (m, 1H, NH), 6.46—6.7 (s, 2H, 4, 5-CH), 3.72—3.86 (m, 1H, 2′-CH), 3.35—3.56 (m, 4H, 1′, 3′-CH_2), 3.0—3.37 (m, 8H, 2″, 3″, 5″, 6″-CH_2), 0.96—1.24 (s, 1H, 2′-OH). *Anal.* Calcd for $C_{11}H_{17}N_3O_4$. Found (calculated): C, 52.11 (51.96); H, 7.17 (7.08); N, 21.88 (22.04).

1-[2′-Hydroxy-3′-(1″-imidazolo)propyl]-1,2-dihydro-pyridazine-3,6-dione (**4d**): Yield=82%, mp 268 °C. IR (KBr) cm^{-1}: 1459, 1372, 1156. ^{1}H-HMR ($CDCl_3$, δ): 9.34—9.47 (s, 1H, NH), 7.2—7.31 (s, 2H, 4, 5-CH), 6.7—6.9(m, 1H, 2″-CH) 6.23—6.47 (m, 2H, 4″, 5″-CH), 3.8—3.92 (m, 1H, 2′-CH), 3.5—3.6 (m, 4H, 1′, 3′-CH_2), 0.92—1.12 (s, 1H, 2′-OH). *Anal.* Calcd for $C_{10}H_{12}N_4O_3$. Found (calculated): C, 50.56 (50.84); H, 4.92 (5.08); N, 23.97 (23.72).

1-{3′-[Bis-(2″-hydroxyethyl)amino]-2′-hydroxypropyl}-1,2-dihydro-pyridazine-3,6-dione (**4e**): Yield=87%, mp 319 °C. IR (KBr) cm^{-1}: 1455, 1368, 1324, 1161. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.39—9.52 (s, 1H, NH), 6.46—6.67 (s, 2H, 4, 5-CH), 3.56—3.78 (m, 4H, 1′, 3′-CH_2), 3.4—3.62 (m, 1H, 2′-CH), 2.84—3.05 (m, 8H, 1″, 2″-$(C_2H_4)_2$), 2.26—2.84 (s, 1H, 2′-OH), 0.98—1.26 (s, 2H, 2″-OH). *Anal.* Calcd for $C_{11}H_{19}N_3O_5$. Found (calculated): C, 48.13 (48.35); H, 6.79 (6.95); N, 15.16 (15.38).

1-[2′-Hydroxy-3′-(dimethylamino)-propyl]-1,2-dihydro-pyridazine-3,6-dione (**4f**): Yield=83%, mp 256 °C. IR (KBr) cm^{-1}: 1475, 1373, 1327. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.67—9.81 (s, 1H, NH), 6.41—6.52 (s, 2H, 4, 5-CH), 3.63—3.88 (m, 1H, 2′-CH), 3.45—3.68 (m, 4H, 1′, 3′-CH_2), 2.16—2.66 (s, 1H, 2′-OH), 1.24—1.45 (s, 6H, $(CH_3)_2$). *Anal.* Calcd for $C_9H_5N_3O_3$. Found (calculated): C, 50.52 (50.7); H, 7.13 (7.04); N, 19.83 (19.71).

1-[2′-Hydroxy-3′-(diphenylamino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**4g**): Yield=62%, mp >325 °C. IR (KBr) cm^{-1}: 1459, 1345, 1134. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.42—9.56 (s, 1H, NH), 6.58—6.7 (s, 2H, 4, 5-CH), 6.23—6.48 (m, 10H, $(C_6H_5)_2$), 3.64—3.77 (m, 1H, 2′-CH), 3.24—3.46 (m, 4H, 1′, 3′-CH_2), 0.98—1.24 (s, 1H, 2′-OH). *Anal.* Calcd for $C_{19}H_{19}N_3O_3$. Found (calculated): C, 67.43 (67.65); H, 5.35 (5.63); N, 12.27 (12.46).

1-[2′-Hydroxy-3′-(2″-aminophenylamino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**4h**): Yield=77%, mp >325 °C. IR (KBr) cm^{-1}: 1445, 1356, 1149. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.22—9.39 (s, 1H, NH), 6.84—6.95 (s, 2H, 4, 5-CH),

6.48—6.66 (m, 4H, C_6H_4), 5.54—5.66 (s, 2H, NH_2), 4.41—4.56 (m, 1H, NH), 3.73—3.89 (m, 1H, 2′-CH), 3.33—3.48 (m, 4H, 1′, 3′-CH_2), 0.86—1.04 (s, 1H, 2′-OH). *Anal.* Calcd for $C_{13}H_{16}N_4O_3$. Found (calculated): C, 56.33 (56.52); H, 5.86 (5.79); N, 20.04 (20.28).

1-[2′-Hydroxy-3′-(4″-hydroxyphenylamino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**4i**): Yield=68%, mp 274 °C. IR (KBr) cm^{-1}: 3310, 1478, 1394, 1176. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.14—9.3 (s, 1H, NH), 8.64—8.83 (s, 1H, NH), 6.93—7.08 (s, 2H, 4, 5-CH), 6.23—6.57 (m, 4H, C_6H_4), 3.72—3.88 (m, 1H, 2′-CH), 3.45—3.56 (m, 4H, 1′, 3′-CH_2), 0.85—1.04 (s, 1H, 2′-OH). *Anal.* Calcd for $C_{13}H_{15}N_3O_4$. Found (calculated): C, 55.29 (55.12); H, 5.18 (5.3); N, 17.12 (16.96).

1-[2′-Hydroxy-3′-(4″-nitrophenylamino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**4j**): Yield=80%, mp 297 °C. IR (KBr) cm^{-1}: 1493, 1375, 1112. ^{1}H-HMR ($CDCl_3$, δ): 9.49—9.62 (s, 1H, NH), 6.87—6.98 (s, 2H, 4, 5-CH), 6.34—6.66 (m, 4H, C_6H_4), 4.26—4.43 (m, 1H, NH), 3.74—3.87 (m, 1H, 2′-CH), 3.45—3.62 (m, 4H, 1′, 3′-CH_2), 0.76—0.94 (s, 1H, 2′-OH). *Anal.* Calcd for $C_{13}H_{14}N_4O_5$. Found (calculated): C, 51.07 (50.98); H, 4.51 (4.57); N, 18.17 (18.3).

1-[2′-Hydroxy-3′-(methylamino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**4k**): Yield=67%, mp 304 °C. IR (KBr) cm^{-1}: 1447, 1395, 1146. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.59—9.72 (s, 1H, NH), 6.86—6.91 (s, 2H, 4, 5-CH), 6.14—6.3 (s, 1H, NH), 3.68—3.84 (m, 1H, 2′-CH), 3.37—3.54 (m, 4H, 1′, 3′-CH_2), 2.42—2.65 (s, 1H, 2′-OH), 0.78—0.97 (s, 3H, CH_3). *Anal.* Calcd for $C_8H_{13}N_3O_3$. Found (calculated): C, 48.13 (48.24); H, 6.48 (6.53); N, 21.22 (21.1).

1-[2′-Hydroxy-3′-(phenylamino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**4l**): Yield=88%, mp 279 °C. IR (KBr) cm^{-1}: 1474, 1332, 1134. ^{1}H-HMR ($CDCl_3$, δ): 9.58—9.7 (s, 1H, NH), 6.96—7.24 (m, 5H, C_6H_5), 6.67—6.75 (s, 2H, 4, 5-CH), 6.34—6.52 (s, 1H, H), 3.69—3.86 (m, 1H, 2′-CH), 3.36—3.44 (m, 4H, 1′, 3′-CH_2), 0.83—1.04 (s, 1H, 2′-OH). *Anal.* Calcd for $C_{13}H_{15}N_3O_3$. Found (calculated): C, 59.65 (59.77); H, 5.63 (5.74); N, 16.36 (16.09).

Synthesis of 1-(3′-Chloropropyl)-1,2-dihydro-pyridazine-3,6-dione (3) 1-(3′-Chloropropyl)-1,2-dihydro-pyridazine-3,6-dione was prepared by refluxing 1,2-dihydropyridazine-3,6-dione (0.1 mol) with 1-bromo-3-chloro propane (0.1 mol) in the presence of silver chloride (0.0007 mol), sodium iodide (0.0006 mol) and methanol (50 ml) for about 20 h. The resultant product was purified by recrystallization with chloroform–ether (1 : 1) Yield=61%, mp 298 °C. ^{1}H-HMR ($CDCl_3$) δ: 9.35—9.52 (s, 1H, NH), 6.72—6.93 (s, 2H, 4, 5-CH), 3.29—3.43 (d, J=4.9 Hz, 4H, 1′, 3′-CH_2), 2.49—2.67 (m, 2H, 2′-CH_2). IR (KBr) cm^{-1}: 3210, 1432. *Anal.* Calcd for $C_7H_9N_2O_2Cl$. Found (calculated): C, 44.31 (44.68); H, 4.92 (4.78); N, 14.57 (14.89).

General Procedure for the Synthesis of 1-Substituted-1,2-dihydro-pyridazine-3,6-diones (5a—j) A mixture of 1-(3′-chloropropyl)-1,2-dihydro-pyridazine-3,6-dione (0.005 mol) and amine (0.005 mol) were refluxed with 10% methanolic potassium hydroxide (25 ml). The reaction mixture was filtered and the filterate on concentration yielded the product. The products were dried under vacuum and recrystallized using 1 : 1 acetone–ether (**5a**, **g**, **i**), 1 : 1 ethanol–ether (**5c**, **d**, **h**, **j**), 1 : 1 methanol–ether (**5b**, **e**, **f**).

1-[3′-(1″-Morpholino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**5a**): Yield=72%, mp 273 °C. IR (KBr) cm^{-1}: 1434, 1383, 1123. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.14—9.25 (s, 1H, NH), 6.34—6.5 (s, 2H, 4, 5-CH), 3.52—3.69 (m, 4H, 1′, 3′-CH_2), 2.57—2.69 (m, 8H; 2″, 3″, 5″, 6″-CH_2), 1.13—1.27 (m, 2H, 2′-CH_2). *Anal.* Calcd for $C_{11}H_{17}N_3O_3$. Found (calculated): C, 54.92 (55.23); H, 6.84 (7.11); N, 17.91 (17.57).

1-[3′-(1″-Piperidino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**5b**): Yield=55%, mp 235 °C. IR (KBr) cm^{-1}: 1432, 1356, 1178. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.35—9.48 (s, 1H, NH), 6.73—6.87 (s, 2H, 4, 5-CH), 3.45—3.59 (m, 4H, 1′, 3′-CH_2), 2.78—2.97 (m, 10H, 2″, 3″, 4″, 5″, 6″-CH_2), 1.49—1.62 (m, 1H, 2′-CH_2). *Anal.* Calcd for $C_{12}H_{19}N_3O_2$. Found (calculated): C, 60.43 (60.75); H, 8.32 (8.01); N, 17.53 (17.72).

1-[3′-(1″-Piperazino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**5c**): Yield=67%, mp 279 °C. IR (KBr) cm^{-1}: 1389, 1334, 1176. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.75—9.87 (s, 1H, NH), 8.81—8.94 (m, 1H, NH), 6.56—6.71 (s, 2H, 4, 5-CH), 3.48—3.59 (m, 4H, 1′, 3′-CH_2), 3.21—3.39 (m, 8H, 2″, 3″, 5″, 6″-CH_2), 1.26—1.44 (s, 1H, 2′-CH_2). *Anal.* Calcd for $C_{11}H_{18}N_4O_2$. Found (calculated): C, 55.13 (55.46); H, 7.21 (7.56); N, 23.84 (23.52).

1-[3′-(1″-Imidazolo)propyl]-1,2-dihydro-pyridazine-3,6-dione (**5d**): Yield=49%, mp 239 °C. IR (KBr) cm^{-1}: 1478, 1345, 1189. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.38—9.49 (s, 1H, NH), 7.17—7.32 (s, 2H, 4, 5-CH), 6.81—6.95 (m, 1H, 2″-CH), 6.36—6.51 (m, 2H, 4″, 5″-CH_2), 3.32—3.46 (m, 4H, 1′, 3′-CH_2), 1.22—1.37 (m, 2H, 2′-CH_2). *Anal.* Calcd for $C_{10}H_{12}N_4O_2$. Found (calculated): C, 51.54 (51.76); H, 6.41 (6.66); N, 16.22 (16.47).

1-{3′-[Bis-(2″-hydroxyethyl)amino]-2(-hydroxypropyl}-1,2-dihydro-pyridazine-3,6-dione (**5e**): Yield=68%, mp 269 °C. IR (KBr) cm^{-1}: 1487, 1374, 1358, 1136. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.22—9.38 (s, 1H, NH), 6.25—6.42 (s, 2H, 4, 5-CH), 3.82—3.95 (m, 4H, 1′, 3′-CH_2), 3.53—3.69 (s, 2H, 2″ (–OH)$_2$), 2.76—2.95 (m, 8H, $(C_2H_4)_2$), 1.19—1.32 (m, 2H, 2′-CH_2). *Anal.* Calcd for $C_{11}H_{19}N_3O_4$. Found (calculated): C, 51.04 (51.36); H, 7.72 (7.39); N, 16.73 (16.34).

1-[3′-Dimethylaminopropyl]-1,2-dihydro-pyridazine-3,6-dione (**5f**): Yield=47%, mp 237 °C. IR (KBr) cm^{-1}: 1434, 1368, 1356. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.28—9.39 (s, 1H, NH), 6.17—6.31 (s, 2H, 4, 5-CH), 3.23—3.41 (m, 4H, 1′, 3′-CH_2), 2.63—2.83 (m, 2H, 2′-CH_2), 1.49—1.63 (s, 6H, 1′, 3′ $(CH_3)_2$). *Anal.* Calcd for $C_9H_{15}N_3O_2$. Found (calculated): C, 54.51 (54.82); H, 7.37 (7.61); N, 21.02 (21.31).

1-[3′-Diphenylaminopropyl]-1,2-dihydro-pyridazine-3,6-dione (**5g**): Yield=59%, mp 293 °C. IR (KBr) cm^{-1}: 1465, 1387, 1186. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.11—9.29 (s, 1H, NH), 6.69—6.87 (s, 2H, 4, 5-CH), 6.13—6.38 (m, 10H, $(C_6H_5)_2$), 3.39—3.52 (m, 4H, 1′, 3′-CH_2), 1.48—1.61 (m, 2H, 2′-CH_2). *Anal.* Calcd for $C_{19}H_{19}N_3O_2$. Found (calculated): C, 71.34 (71.02); H, 5.63 (5.91); N, 13.38 (13.08).

1-[3′-(2″-Aminophenylamino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**5h**): Yield=58%, mp 258 °C. IR (KBr) cm^{-1}: 1456, 1387, 1176. ^{1}H-HMR ($CDCl_3$, δ, ppm): 9.08—9.29 (s, 1H, NH), 8.37—8.56 (m, 1H, NH), 6.82—6.91 (s, 2H, 4, 5-CH), 6.46—6.62 (m, 4H, C_6H_4), 5.68—5.82 (s, 2H, NH_2), 3.49—3.61 (m, 4H, 1′, 3′-CH_2), 1.17—1.3 (m, 2H, 2′-CH_2). *Anal.* Calcd for $C_{13}H_{16}N_4O_2$. Found (calculated): C, 60.34 (60.00); H, 6.42 (6.15); N, 21.29 (21.53).

1-[3′-(4″-Hydroxyphenylamino)propyl]-1,2-dihydro-pyri-

dazine-3,6-dione (**5i**): Yield=76%, mp 265 °C. IR (KBr) cm^{-1}: 3328, 1434, 1353, 1157. ^{1}H-HMR ($CDCl_3$, δ): 9.26—9.45 (s, 1H, NH), 8.35—8.48 (s, 1H, NH), 7.15—7.3 (s, 1H, –OH), 6.55—6.71 (s, 2H, 4, 5-CH), 6.13—6.37 (m, 4H, C_6H_4), 3.19—3.35 (m, 4H, 1′, 3′-CH_2), 1.15—1.28 (m, 2H, 2′-CH_2). *Anal.* Calcd for $C_{13}H_{15}N_3O_3$. Found (calculated): C, 59.43 (59.77); H, 5.48 (5.74); N, 16.37 (16.07).

1-[3′-(4″-Nitrophenylamino)propyl]-1,2-dihydro-pyridazine-3,6-dione (**5j**): Yield=39%, mp 245 °C. IR (KBr) cm^{-1}: 1476, 1345, 1176. ^{1}H-HMR ($CDCl_3$, δ): 9.23—9.42 (s, 1H, NH), 6.79—6.96 (s, 2H, 4, 5-CH), 6.17—6.29 (m, 4H, C_6H_4), 4.59—4.69 (m, 1H, NH), 3.67—3.78 (m, 4H, 1′, 3′-CH_2), 1.26—1.36 (m, 2H, 2′-CH_2). *Anal.* Calcd for $C_{13}H_{14}N_4O_4$. Found (calculated): C, 53.55 (53.79); H, 4.53 (4.82); N, 19.64 (19.31).

PHARMACOLOGY

All the synthesized compounds were screened for anticonvulsant activity. All the compounds were solubilized in water and administered to the animals as a solution in water for injection. Wistar albino mice (18—25 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.

Anticonvulsant Activity The compounds were tested for anticonvulsant activity by using the procedures described previously.[23,24] All the compounds were tested for anticonvulsant activity with wistar albino mice. Each compound was administered intraperitoneally at three dose levels (30, 100, 300 $mg \cdot kg^{-1}$). 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 electors in to 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 $mg \cdot kg^{-1}$). Animals were observed for 30 min. Failure to observe the generalized clonic seizure is defined as protection.

Minimal neurotoxicity (TD_{50}) was measured by the rotarod test (Tox). Mice 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 Tables 1 and 2.

RESULTS AND DISCUSSION

The initial evaluation phase I of anticonvulsant activity of synthesized compounds presented in the Table 1. The compounds were administered intraperitoneally at three doses (30, 100, 300 $mg \cdot kg^{-1}$). Three tests were performed for each compound; maximal electroshock (MES)-induced convulsions, subcutaneous Metrozol (sc-Met)-induced convulsions and rotarod neurotoxicity test (Tox).

As a result of preliminary screening compounds **4a**, **c**, **d**, **e**, **g**, **h**, **k**, **5c**, **d**, **h** and **j** were considered for the phase II trials. This provides an evaluation of the median effective dose and median neurotoxic dose. The slope of the regression line and the SE of the slope were then calculated. These datas are shown in the Table 2. Some of these derivatives showed high degree of protection against MES-induced seizures. But they were found to be less effective against sc-Met induced seizures. Compound **4h** was the best in the MES test having ED_{50} of 44.7 $mg \cdot kg^{-1}$. In the MES test, the ED_{50} of compounds were found to be **4c** (72 $mg \cdot kg^{-1}$) and **4d** (79 $mg \cdot kg^{-1}$).

The following structure-activity relationships were observed. In the propanol series (**4a**—**l**), compounds **4a**, **c**, **d**, **e**,

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

Compd.	MES[a,b]		Sc-Met[c]		Rotarod toxicity[d]	
	30 min	4 h	30 min	4 h	30 min	4 h
4a	++	−	+	−	+	−
4b	+	−	−	−	++	−
4c	++	−	+	−	++	−
4d	++	−	+	−	++	−
4e	−	−	−	−	−	−
4f	+	−	−	−	+	−
4g	++	+	+	−	+	−
4h	+++	+	+	−	−	−
4i	+	−	−	−	+	−
4j	+	−	−	−	+	−
4k	++	−	−	−	+	−
4l	+	−	−	−	+	−
5a	+	−	−	−	+	−
5b	+	−	−	−	−	−
5c	++	−	−	−	+	−
5d	++	+	−	−	−	−
5e	+	−	−	−	−	−
5f	+	−	−	−	+	−
5g	+	−	−	−	−	−
5h	++	−	+	−	+	−
5i	+	−	−	−	−	−
5j	++	−	−	−	+	−

a) Key: +++=protection at 30 $mg \cdot kg^{-1}$, ++=protection at 100 $mg \cdot kg^{-1}$, +=protection at 300 $mg \cdot kg^{-1}$, −=no protection at 300 $mg \cdot kg^{-1}$. *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	Sc-Met	
4a	109 (90—132)	>200	221 (192—250)
4c	72 (55—89)	>200	177 (150—203)
4d	79 (64—95)	>250	226 (192—256)
4e	111 (94—128)	193 (176—213)	204 (172—235)
4g	84 (71—98)	142 (125—166)	232 (208—256)
4h	44.7 (32—57)	225 (206—242)	156 (132—179)
4k	92 (64—83)	250 (219—278)	203 (169—238)
5c	85 (67—99)	154 (132—179)	222 (189—246)
5d	106 (88—124)	206 (184—234)	255 (228—274)
5h	82 (65—96)	>200	200 (177—226)
5j	94 (78—110)	169 (152—188)	225 (201—253)
Phenytoin	9.9 (6.3—13.1)	>300	69.8 (57.2—80.7)
Carbama zepine	9.2 (6.9—11.7)	>200	74.4 (59.1—87.5)
Valproate	264 (236—297)	157 (133—185)	408 (364—437)

a) Doses measured in $mg \cdot kg^{-1}$ at the peak effect. *b*) Doses ($mg \cdot kg^{-1}$) determined by rotarod test at the time of peak effect.

g, **h** and **k** were found to have high degree of protection against MES-induced seizures. Among the heterocyclic substituted compounds, piperazino and imidazolo groups substituted at the 3 position showed more protection than the other substitution. Among the tertiary amine substituted compounds, diphenyl substituted compound is more potent than the other (dimethyl, diethanol) substitutions. Among the secondary amine substitutions, 2-aminophenylamine, methylamino substituted compounds are more active than the other (4-bromophenylamine, 4-nitrophenylamine and phenylamino) substitutions.

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