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Synthesis of some new phenothiazine and pyridine derivatives as antipsychotic and anticonvulsant agents

Ashok Kumar*, Hemlata Kaur, Sunil Kumar, K.K.Saxena

Medicinal Chemistry Division, Department of Pharmacology, L.L.R.M. Medical College, Meerut 250004, U.P., (INDIA)

E-mail : ashokraj.kumar744@gmail.com

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ABSTRACT

A series of 3-[{5-(heterocyclic methyl)-1,3,4-oxadiazol-2-yl}-2-(substitutedphenyl)]thiazolidin-4-ones **(5a-5i)** and 1-[{5-(heterocyclic methyl)1,3,4-oxadiazol-2-yl}-3-chloro-4-(substituted phenyl)]azetidin-2-one **(6a-6i)** have been synthesized by the reaction of 5-(heterocyclic methyl)-2-(substitutedbenzylidene)-1,3,4-oxadiazol-2-amines **(4a-4i)** with thioglycolic acid and chloroacetyl chloride respectively. All the newly synthesized compounds **(4a-4i)**, **(5a-5i)** and **(6a-6i)** were screened for their antipsychotic and anticonvulsant activities. Structures of all the compounds were established by elemental and spectral (IR, and ^{1}H NMR) analysis.

KEYWORDS

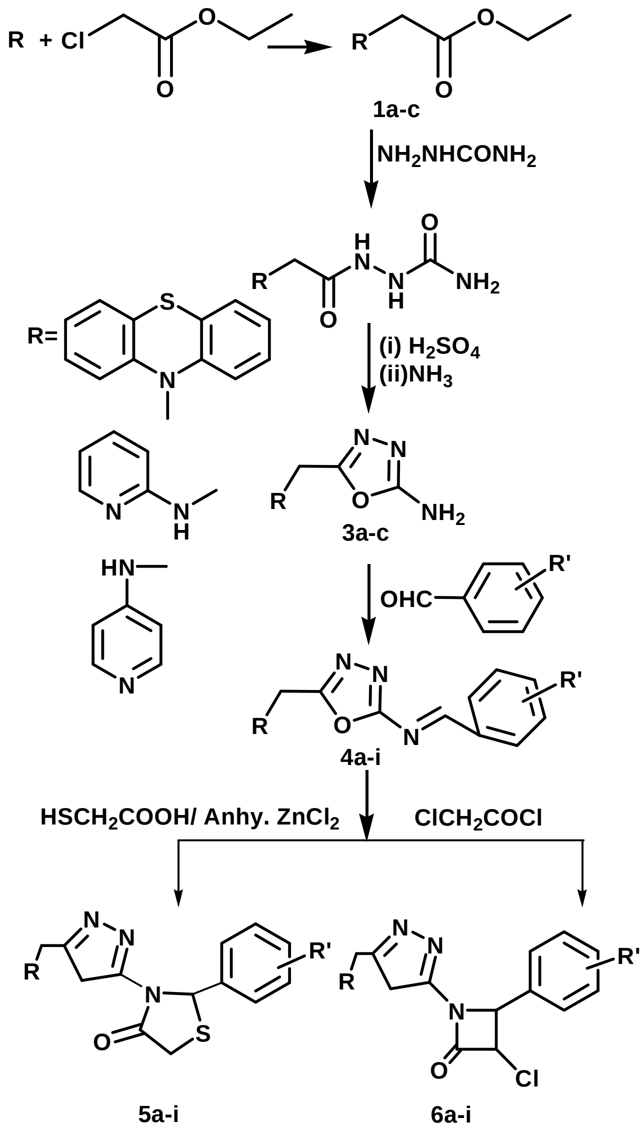
Phenothiazines;
Pyridines;
Oxadiazoles;
Thiazolidinones;
Azetidinones;
Antipsychotic activity;
Anticonvulsant activity.

INTRODUCTION

Chlorpromazine[1] a phenothiazine derivative, is currently drug used for the treatment of various psychotropic disorders and gave the impetus to explore to the activity of the phenothiazine derivatives. Various phenothiazine derivatives are known to possess different biological properties such as antipsychotic[2,3], antidepressant[4] and anticonvulsant[5] etc. Furthermore several pyridine derivatives were also found to have good antipsychotic[6] and anticonvulsant activities[7]. Moreover different derivatives of oxadiazole, thiazolidinone and azetidinone have been shown to possessed wide range of biological properties viz. antipsychotic[8-10], and anticonvulsant[11-14]. In the light of above discussion we have synthesized various derivatives of phenothiazine and pyridine by incorporating oxadiazole, thiazolidinones and azetidinone moieties with the hope to get better antipsychotic and anticonvulsant agents.

CHEMISTRY

The synthetic routes of the compounds are outlined in SCHEME 1. Compounds **(1a)**, **(1b)** and **(1c)** were synthesized by the reaction of phenothiazine, 2-amino pyridine and 4-amino pyridine respectively with ethyl chloro acetate in dry acetone. Compounds **(1a)**, **(1b)** and **(1c)** on reaction with semicarbazide, yielded (2-(2-(N^{10}-phenothiazinyl-10-yl)hydrazinecarboxamide, 2-(2-(pyridin-2-yl)acetyl)hydrazinecarboxamide and 2-(2-(pyridin-4-yl)acetyl)hydrazinecarboxamide i.e. compounds **(2a)**, **(2b)** and **(2c)**, which on cyclisation in presence of conc. H_2SO_4 and ammonia yielded their corresponding 2-Amino-5-(heterocyclicmethyl)-1,2,4-oxadiazoles i.e. compounds **(3a-3c)**. Compounds **(3a)**, **(3b)** and **(3c)** were reacted with various substituted aromatic aldehydes to give 5-(heterocyclicmethyl)-2-(4-substituted benzylidene)-1,3,4-oxadiazol-2-amines i.e. compounds **(4a-c)**, **(4d-**



Scheme 1

4f) and **(4g-4i)** respectively, which on further reaction with thioglycolic acid in presence of anhydrous zinc chloride yielded 3-(5-(heterocyclicmethyl)-1,3,4-oxadiazol-2-yl)-2-(substitute dphenyl) thiazolidin-4-ones i.e. compounds **(5a-5c)**, **(5d-5f)** and **(5g-5i)** respectively. Compounds **(4a-c)**, **(4d-f)** and **(4g-i)** on further reaction with chloroacetyl chloride in presence of triethyl amine gave their corresponding 1-(5-(heterocyclic methyl) 1,3,4-oxadiazol-2-yl)-3-chloro-4-(substituted phenyl) azetidin-2-one i.e. compounds **(6a-6c)**, **(6d-6f)** and **(6g-6i)** respectively.

EXPERIMENTAL

All reagents and solvents were generally used as received from the commercial supplier. Reactions were routinely performed in oven-dried glassware. The melting points of compounds were determined in open capillaries with the help of thermonic melting point apparatus and were uncorrected. Homogeneity of all the newly synthesized compounds was routinely checked by thin layer chromatography (TLC) on silica gel G coated plate of 0.5mm thickness. The eluent was a mixture of different polar and nonpolar solvents in different proportions, and spots were visualized under iodine chamber. Elemental analysis (C, H, N) of all the compounds were performed on CHN analyzer, Carlo Erba 1108 analyzer at the Central Drug Research Institute (Lucknow, India). The IR spectra were recorded on Perkin Elmer 881 FTIR spectrophotometer (ν_{max} in cm^{-1}). The ^1H-NMR spectra were recorded in $CDCl_3$ and DMSOd6 on Brucker DRX-300 FTNMR instrument.

General procedure for synthesis of Ethyl-(heterocyclic) acetate (1a-1c)

To a solution of phenothiazine/ 2-aminopyridine/4-aminopyridine (1.0 mol) in dry acetone (100ml), ethyl chloro acetate (1.0 mol) were added dropwise in presence of anhydrous K_2CO_3 (8gm) in the mixture with stirring. The resulted mixture was refluxed on a water-bath for about 13 h. The semisolid thus obtained was filtered, dried and recrystallized from suitable solvents to give compounds **(1a)/(1b)/(1c)**.

Ethyl N^{10}-phenothiazinyl acetate (1a)

Yield 80% (Methanol); m.p. 114°C. IR (KBr) νcm^{-1}: 1304 (CN), 1670 (C = O), 1610 (C⎓C of aromatic ring), 698 (C-S-C); ^1H-NMR ($CDCl_3$+$DMSOd_6$) δ in ppm: δ 1.31(t, 3H, CH_2 CH_3), 3.60 (s, 2H, N-CH_2), 4.20 (q, 2H, CH_2 CH_3), 6.79-7.88 (m, 8H, Ar-H); Anal. Calcd. for $C_{16}H_{15}NO_2S$: C, 67.34 ; H,5.30; N,4.91. Found: C, 67.32; H, 5.34; N, 4.90 %.

Ethyl-2-aminopyridinyl acetate (1b)

Yield 78% (Ethanol); m.p. 110°C. IR (KBr) νcm^{-1}: 3434 (NH), 1672 (C = O), 1612 (C⎓C of aromatic ring), 1301 (CN); ^1H-NMR ($CDCl_3$). δ in ppm: 1.29 (t, 3H, CH_2 CH_3), 3.61 (s, 2H, N-CH_2), 4.21 (q, 2H, CH_2CH_3), 6.78-7.68 (m, 4H, Ar-H), 8.29 (t,1H, NH); Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71 ; N, 15.55. Found: C, 60.00; H, 6.70; N, 15.57 %.

Ethyl-4-aminopyridinyl acetate (1c)

Yield 79% (Peteroleum ether); m.p. 110°C. IR (KBr) νcm^{-1}: 3432 (NH), 1667 (C = O), 1613 (C⎓C of aromatic ring), 1303 (CN); ^{1}H-NMR ($CDCl_3$+DMSOd_6). δ in ppm: δ1.30 (t, 3H, CH_2CH_3), 3.59 (s, 2H, N-CH_2) 4.23 (q, 2H, CH_2 CH_3), 6.79-7.78 (m, 4H, Ar-H), 8.32 (t, 1H, NH). Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71 ; N, 15.55. Found: C, 60.00; H, 6.71; N, 15.57 %.

General procedure for synthesis of 2-(2-(heterocyclic)acetyl)hydrazinecarboxamides (2a-2c)

A mixture of Ethyl N'-phenothizinyl acetate **(1a-1c)** (0.5 mol) and semicarbazide (0.4 mol) in 1, 4 dioxan (100ml) was refluxed on a water-bath for about 8 h. The excess solvent was removed under reduced pressure and the product recrystallized from appropriate solvents to give compounds **(2a-2c)**.

(2-(2-(N^{10}-phenothiazinyl-10'-yl) hydrazine carboxamide (2a)

Yield 77% (Acetone); m.p. 122°C. IR (KBr) νcm^{-1}: 3340 (NH), 1673 (C = O), 1617 (C⎓C of aromatic ring), 1305 (CN), 699 (C-S-C); ^{1}H-NMR ($CDCl_3$+DMSOd_6). δ in ppm: 3.63 (s, 2H, N-CH_2), 6.88-7.89 (m, 8H, Ar-H), 8.35 (m, 4H, NHNHCONH_2); Anal. Calcd. for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82. Found: C, 57.30; H, 4.51; N, 17.80%.

2-(2-(pyridin-2-yl)acetyl)hydrazinecarboxamide (2b)

Yield 76% (Ethanol); m.p. 117°C. IR (KBr) νcm^{-1}: 3344 (NH), 1671 (C = O), 1615 (C⎓C of aromatic ring), 1303 (CN); ^{1}H-NMR ($CDCl_3$+DMSOd_6). δ in ppm: 3.64 (s, 2H, N-CH_2), 6.99-7.98 (m, 4H, Ar,-H), 8.34 (t, 1H, NH), 8.38 (m, 4H, NHNHCONH_2); Anal. Calcd. for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.96; H, 5.29; N, 33.44%.

2-(2-(pyridin-4-yl)acetyl)hydrazinecarboxamide (2c)

Yield 74% (Methanol); m.p. 113°C. IR (KBr) νcm^{-1}: 3341 (NH), 1306 (CN), 1675 (C = O), 1616 (C⎓C of aromatic ring); ^{1}H-NMR ($CDCl_3$). δ in ppm: 3.66 (s, 2H, N-CH_2), 6.98-7.95 (m, 4H, Ar-H), 8.28 (t, 1H, NH), 8.40 (m, 4H, NHNHCONH_2); Anal. Calcd. for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.96; H, 5.29; N, 33.44%.

General procedure for synthesis of 2-amino-5-(heterocyclicmethyl)-1, 3, 4-oxadiazoles (3a-3c)

A solution of 2-(2-(heterocyclic) acetyl) hydrazinecarboxamides **(2a-2c)** (0.2 mol) with conc. H_2SO_4 (30ml) was kept overnight at room temperature, then poured into ice cold water, neutralized with ammonia and extracted with ether. The ethereal solution was distilled off and the product obtained was recrystallized from appropriate solvents to give compounds **(3a-3c)**.

2-Amino-5-(N^{10}-phenothiazinomethyl)-1, 3, 4-oxadiazole (3a)

Yield 76% (Acetone); m.p. 141°C. IR (KBr) νcm^{-1}: 3335 (NH), 1614 (C⎓C of aromatic ring), 1581 (C = N), 1295 (N-N), 1015 (C-O-C), 702 (C-S-C); ^{1}H-NMR ($CDCl_3$+DMSOd_6). δ in ppm: 3.67 (s, 2H, N-CH_2), 6.97-7.90 (m, 8H, Ar,-H), 8.85 (s, 2H, NH_2) Anal. Calcd. for $C_{15}H_{12}N_4OS$: C, 60.79; H, 4.08; N, 18.91. Found: C, 60.77; H, 4.08; N, 18.90%.

2-Amino-5-(2-aminopyridinomethyl)-1, 3, 4-oxadiazole (3b)

Yield 81% (Petroleum ether); m.p. 134°C. IR (KBr) νcm^{-1}: 3330 (-NH), 1614 (C⎓C of aromatic ring), 1589 (C = N), 1291 (N-N), 1013 (C-O-C); ^{1}H-NMR ($CDCl_3$). δ in ppm: 3.59 (d, 2H, NHCH_2), 6.87-7.89 (m, 4H, Ar,-H), 8.32 (t, 1H, NH CH_2), 8.80 (s, 2H, NH_2); Anal. Calcd. for $C_8H_9N_5O$: C, 50.26; H, 4.74; N, 36.63. Found: C, 50.25; H, 4.72; N, 36.60%.

2-Amino-5-(4-aminopyridenylmethyl)-1, 3, 4-oxadiazole (3c)

Yield 85% (Methanol); m.p. 135°C. IR (KBr) νcm^{-1}: 3331 (NH), 1616 (C⎓C of aromatic ring), 1587 (C = N), 1294 (N-N), 1016 (C-O-C); ^{1}H-NMR ($CDCl_3$+DMSOd_6). δ in ppm: 3.51 (d, 2H, NHCH_2), 6.79-7.88 (m, 4H, Ar-H), 8.35 (t, 1H, NH CH_2), 8.82 (s, 2H, NH_2); Anal. Calcd. for $C_8H_9N_5O$: C, 50.26; H, 4.74; N, 36.63. Found: C, 50.24; H, 4.71; N, 36.60%.

General procedure for synthesis of 5-(heterocyclicmethyl)-2-(substitutedbenzylidene)-1, 3, 4-oxadiazol-2-amine 4a-4i

2-Amino-5-(heterocyclicmethyl)-1, 3, 4-oxadiazoles **(3a-3c)** (0.1 mole), various substituted aromatic aldehydes (0.17 mol) and glacial acetic acid (5ml) were refluxed in methanol (100ml) for about 6 h. The solid mass thus obtained was re-crystallized from suitable solvents to obtained compounds **(4a-i)**.

5-((10H-phenothiazin-10-yl)methyl)-2-(4-hydroxybenzylidene)-1,3,4-oxadiazol-2-amine (4a)

Yield 77% (Acetone); m.p. 189°C. IR (KBr) νcm^{-1}: 3440 (OH), 1618 (C=C of aromatic ring), 1586 (C = N), 1580 (N = CH), 1293 (N-N), 1020 (C-O-C) 697 (C-S-C); ^{1}H-NMR ($CDCl_3$ + $DMSOd_6$). δ in ppm: 6.28 (s, 2H, N-CH_2), 6.80-7.82 (m, 12H, Ar,-H), 8.62 (s, 1H, N = CH), 11.20 (s, 1H, OH); Anal. Calcd. for $C_{22}H_{16}N_4O_2S$: C, 65.98; H, 4.03; N, 13.99. Found: C, 65.97; H, 4.02; N, 14.00%.

5-((10H-phenothiazin-10-yl) methyl)-2-(4-hydroxy-3-methoxybenzylidene)-1,3,4-oxadiazol-2-amine (4b)

Yield 74% (Ethanol); m.p. 198°C. IR (KBr) νcm^{-1}: 3439 (OH), 1622 (C=C of aromatic ring), 1582 (N = CH), 1520 (C = N), 1293 (N-N), 1226 (OCH_3), 1038 (C-O-C), 697 (C-S-C); ^{1}H-NMR ($CDCl_3$+$DMSOd_6$). δ in ppm: 3.36 (s, 3H, OCH_3), 6.25 (s, 2H, N-CH_2), 6.82-7.84 (m, 11H, Ar-H), 8.65 (s, 1H, N = CH), 11.19 (s, 1H, OH). Anal. Calcd. for $C_{23}H_{18}N_4O_3S$: C, 64.17; H, 4.21; N, 13.01. Found: C, 64.16; H, 4.22; N, 13.02%.

5-((10H-phenothiazin-10-yl)methyl)-2-(4-NN'-dimethylaminobenzylidene)-1,3,4-oxadiazol-2-amine (4c)

Yield 78% (Methanol); m.p. 192°C. IR (KBr) νcm^{-1}: 1621 (C=C of aromatic ring), 1584 (C = N), 1575 (N = CH), 1291 (N-N), 1021 (C-O-C), 699 (C-S-C); ^{1}H-NMR ($CDCl_3$+$DMSOd_6$). δ in ppm: 1.50 (s, 6H, $N(CH_3)_2$), 6.24 (s, 2H, CH_2), 6.78-7.83 (m, 12H, Ar-H), 8.64 (s, 1H, N = CH). Anal. Calcd. for $C_{24}H_{21}N_5OS$: C, 67.43; H, 4.95; N, 16.38. Found: C, 67.44; H, 4.96; N, 16.34%.

5-((1,4-dihydropyridin-2-ylamino)methyl)-2-(4-hydroxybenzylidene)-1,3,4-oxadiazol-2-amine (4d)

Yield 75% (Acetone); m.p. 159°C. IR (KBr) νcm^{-1}: 3441 (OH), 3430 (NH), 1619 (C=C of aromatic ring), 1584 (N = CH), 1521 (C = N), 1290 (N-N), 1022 (C-O-C). ^{1}H-NMR ($CDCl_3$ + $DMSOd_6$). δ in ppm: 6.30 (d, 2H, $NHCH_2$), 6.69-7.78 (m, 8H, Ar-H), 8.30 (t, 1H, NH), 8.60 (s, 1H, N = CH), 11.21 (s, 1H, OH); Anal. Calcd. for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 59.09; H, 4.45; N, 23.74%.

5-((1,4-dihydropyridin-2-ylamino)methyl)-2-(4-hydroxy-3-methoxybenzylidene)-1,3,4-oxadiazol-2-amine (4e)

Yield 72% (Methanol); m.p. 163°C. IR (KBr) νcm^{-1}: 3441 (OH), 3432 (NH), 1616 (C=C of aromatic ring), 1582 (N = CH), 1295 (N-N), 1590 (C = N), 1225 (OCH_3), 1027 (C-O-C); ^{1}H-NMR ($CDCl_3$ + $DMSOd_6$). δ in ppm: 3.38 (s, 3H, OCH_3) 6.29 (d, 2H, $NHCH_2$), 6.72-7.79 (m, 7H, Ar-H), 8.35 (t, 1H, NH), 8.61 (s, 1H, N = CH), 11.21 (s, 1H, OH); Anal. Calcd. for $C_{16}H_{15}N_5O_3$: C, 59.08; H, 4.67; N, 21.54. Found: C, 60.00; H, 4.64; N, 21.55%.

5-((1,4-dihydropyridin-2-ylamino)methyl)-2-(4-(dimethylaminobenzylidene)-1,3,4-oxadiazol-2-amine (4f)

Yield 80% (Ethanol); m.p. 160°C. IR (KBr) νcm^{-1}: 3443 (NH), 1620 (C=C of aromatic ring), 1593 (C = N), 1585 (N = CH), 1282 (N-N), 1029 (C-O-C); ^{1}H-NMR ($CDCl_3$+$DMSOd_6$). δ in ppm: 1.51 (s, 6H, $N(CH_3)_2$), 6.31 (d, 2H, $NHCH_2$), 6.70-7.80 (m, 8H, Ar,-H), 8.39 (t 1H,NH), 8.63 (s, 1H, N = CH). Anal. Calcd. for $C_{17}H_{18}N_6O$: C, 63.34; H, 5.63; N, 26.07. Found: C, 63.35; H, 5.63; N, 26.05%.

5-((1,4-dihydropyridin-4-ylamino)methyl)-2-(4-hydroxybenzylidene)-1,3,4-oxadiazol-2-amine (4g)

Yield 76% (Acetone); m.p. 162°C. IR (KBr) νcm^{-1}: 3444 (OH), 3334 (NH), 1615 (C=C of aromatic ring), 1586 (C = N), 1588 (N = CH), 1032 (C-O-C) 1295 (N-N); ^{1}H-NMR ($CDCl_3$+$DMSOd_6$). δ in ppm: 6.34 (d, 2H, $NHCH_2$), 6.71-7.77 (m, 8H, Ar,-H), 8.35 (t, 1H, NH), 8.62 (s, 1H, N = CH), 11.23 (s, 1H, OH). Anal. Calcd. for $C_{15}H_{13}N_5O_2$: C, 61.01; H, 4.44; N, 23.72. Found: C, 59.09; H, 4.45; N, 23.74%.

5-((1,4-dihydropyridin-4-ylamino)methyl)-2-(4-hydroxy-3-methoxybenzylidene)-1,3,4-oxadiazol-2-amine (4h)

Yield 87% (Methanol); m.p. 166°C. IR (KBr) νcm^{-1}:

3443 (OH), 3437 (NH), 1618 (C⎓C of aromatic ring), 1594 (C = N), 1575 (N = CH), 1296 (N-N), 1223 (OCH_3) 1032 (C-O-C); ^{1}H-NMR ($CDCl_3$ + $DMSOd_6$). δ in ppm: 3.39 (s, 3H, OCH_3), 6.30 (d, 2H, $NHCH_2$), 6.75 -7.81 (m, 7H, Ar-H), 8.37 (t, 1H, NH), 8.66 (s, 1H, N = CH), 11.20 (s, 1H, OH); Anal. Calcd. for $C_{16}H_{15}N_5O_3$: C, 59.08; H, 4.67; N, 21.54. Found: C, 60.00; H, 4.64; N, 21.55%.

5-((4-aminopyridine) -2-(4-(dimethylamino ben-zylidene) -1,3,4-oxadiazol-2-amine (4i)

Yield 78% (Acetone); m.p. 164°C. IR (KBr) νcm^{-1}: 3436 (NH), 1622 (C⎓C of aromatic ring), 1596 (C = N), 1578 (N = CH), 1287 (N-N), 1030 (C-O-C) ; ^{1}H-NMR ($CDCl_3$+$DMSOd_6$). δ in ppm: 1.53 (s, 6H, $N(CH_3)_2$), 6.32 (d, 2H, $NHCH_2$), 6.80 -7.82 (m, 8H, Ar,-H), 8.33 (t, 1H, NH), 8.65 (s, 1H, N = CH); Anal. Calcd. for $C_{17}H_{18}N_6O$: C, 63.34; H, 5.63; N, 26.07. Found: C, 63.35; H, 5.63; N, 26.05%.

General procedure for synthesis of 3-(5-(heteocylicmethyl)-1,3,4-oxadiazol-2-yl)-2-(substitutedphenyl)thiazolidin-4-ones (5a-5i)

To a solution of 5-(heterocyclicmethyl)-2-(4-substitutedbenzylidene)-1, 3, 4-oxadiazol-2-amine **(4a-4i)** (0.05 mol) and thioglycolic acid (0.05 mol) in methanol (100 ml) in presence of anhydrous $ZnCl_2$ (a pinch) was kept four days at room temperature and the mixture was refluxed for 10 h on water bath, distilled off, poured into ice-cold water, filtered and finally recrystallized from suitable solvents to furnish compounds **(5a-5i)**.

3-(5-(N^{10}-phenothiazinomethyl)-1,3,4-oxadiazol-2-yl)-2-(4-hydroxyphenyl)thiazolidin-4-one (5a)

Yield 70% (Acetone); m.p. 210°C. IR (KBr) νcm^{-1}: 3445 (OH), 1685 (C = O), 1623 (C⎓C of aromatic ring), 1595 (C = N), 1295 (N-N), 1041 (C-Cl), 1034 (C-O-C), 701 (C-S-C); ^{1}H-NMR ($CDCl_3$ + $DMSOd_6$). δ in ppm: 6.90-7.90 (m, 12H, Ar-H), 2.33 (s, 2H, N -CH_2), 3.95 (s, 2H, CH_2 of thiazolidinone ring), 4.15 (s, 1H, CH-Ar), 11.24 (s, 1H, OH). Anal. Calcd. for $C_{24}H_{18}N_4O_3S_2$: C, 60.74; H, 3.82; N, 11.81. Found: C, 60.75; H, 3.80; N, 11.80%.

3-(5-(N^{10}-phenothiazinomethyl)-1,3,4-oxadiazol-2-yl)-2-(4-hydroxy, 3-methoxyphenyl)- thiazolidin-4-one (5b)

Yield 74% (Ethanol); m.p. 222°C. IR (KBr) νcm^{-1}: 3440 (OH), 1624 (C⎓C of aromatic ring), 1689 (C = O), 1593 (C = N), 1297 (N-N), 1224 (OCH_3), 1035 (C-O-C), 703 (C-S-C); ^{1}H-NMR ($CDCl_3$ + $DMSOd_6$). δ in ppm: 2.38 (s, 2H, N-CH_2), 3.40 (s, 3H, OCH_3), 3.97 (s, 2H, CH_2 of thiazolidinone ring), 4.17 (s, 1H, CH-Ar), 6.89-7.90 (m, 11H, Ar-H), 11.18 (s, 1H, OH); Anal. Calcd. for $C_{25}H_{20}N_4O_4S_2$: C, 59.09; H, 4.00; N, 11.10. Found: C, 59.10; H, 4.02; N, 11.09%.

3-(5-(N^{10}-phenothiazinomethyl)-1,3,4-oxadiazol-2-yl)-2-(4-NN'-dimethylaminophenyl) thiazolidin-4-one (5c)

Yield 72% (Methanol); m.p. 216°C. IR (KBr) νcm^{-1}: 1681 (C = O), 1625 (C⎓C of aromatic ring), 1596 (C = N), 1298 (N-N), 1040 (C-Cl), 1034 (C-O-C), 702 (C-S-C); ^{1}H-NMR ($CDCl_3$+$DMSOd_6$). δ in ppm: 1.54 (s, 6H, $N(CH_3)_2$), 2.35 (s, 2H, N-CH_2) 3.90 (s, 2H, CH_2 of thiazolidinone ring), 4.16 (s, 1H, CH-Ar), 6.80-7.94 (m, 12H, Ar,-H); Anal. Calcd. for $C_{26}H_{23}N_5O_2S_2$: C, 62.25; H, 4.62; N, 13.96. Found: C, 62.24; H, 4.61; N, 13.96%.

3-(5-(2-aminopyridinomethyl)-1,3,4-oxadiazol-2-yl)-2-(4-hydroxyphenyl)thiazolidin-4-one (5d)

Yield 70% (Acetone); m.p. 170°C. IR (KBr) νcm^{-1}: 3440 (OH), 3332 (NH), 1684 (C = O), 1619 (C⎓C of aromatic ring), 1597 (C = N), 1299 (N-N), 1041 (C-Cl), 1033 (C-O-C); ^{1}H-NMR ($CDCl_3$ + $DMSOd_6$). δ in ppm: 3.73 (d, 2H, NH CH_2), 3.96 (s, 2H, CH_2 of thiazolidinone ring), 4.16 (s, 1H, CH-Ar), 5.73 (t, 1H, $NHCH_2$), 6.82 -7.84 (m, 8H, Ar-H), 11.26 (s, 1H, OH); Anal. Calcd. for $C_{17}H_{15}N_5O_3S$: C, 55.27; H, 4.09; N, 18.96. Found: C, 55.28; H, 4.10; N, 1897%.

3-(5-(2-aminopyridinomethyl)-1,3,4-oxadiazol-2-yl)-2-(4-hydroxy,3-methoxyphenyl)- thiazolidin-4-one (5e)

Yield 69% (Methanol); m.p. 179°C. IR (KBr) νcm^{-1}: 3442 (OH), 3432 (NH), 1688 (C = O), 1622 (C⎓C of aromatic ring), 1593 (C = N), 1299 (N-N), 1046 (C-Cl), 1224 (OCH_3), 1037 (C-O-C); ^{1}H-NMR ($CDCl_3$). δ in ppm: 3.41 (s, 3H, OCH_3), 3.74 (t, 2H, NH CH_2), 3.99 (s, 2H, CH_2 of thiazolidinone ring), 4.20 (s, 1H, CH-Ar), 5.74 (t, 1H, NH), 6.84-7.80 (m, 7H, Ar-H), 11.24 (s, 1H, OH). Anal. Calcd. for $C_{18}H_{17}N_4O_4S$: C, 54.13; H, 4.29; N, 16.02. Found: C, 54.14; H, 4.30; N, 16.03%.

3-(5-(2-aminopyridinomethyl)-1,3,4-oxadiazol-2-yl)-2-(4-NN'-dimethylaminophenyl) thiazolidin-4-one (5f)

Yield 70% (Ethanol); m.p. 173°C. IR (KBr) νcm^{-1}: 3336 (NH), 1686 (C = O), 1622 (C⎓C of aromatic ring), 1592 (C = N), 1291 (N-N),1046 (C-Cl), 1036 (C-O-C); ^{1}H-NMR ($CDCl_3$+$DMSOd_6$). δ in ppm: 1.57 (s, 6H, N $(CH_3)_2$), Ar-H), 3.72 (s, 2H, NH CH_2), 3.95 (s, 2H, CH_2 of thiazolidinone ring), 4.14 (s, 1H, CH-Ar), 5.74 (t, 1H, NH CH_2), 6.83-7.82 (m, 8H). Anal. Calcd. for $C_{19}H_{20}N_6O_2S$: C, 57.56; H, 5.08; N, 21.20. Found: C, 57.53; H, 5.10; N, 21.22%.

3-(5-(4-aminopyridinomethyl)-1,3,4-oxadiazol-2-yl)-2-(4-hydroxyphenyl)thiazolidin-4-one (5g)

Yield 78% (Acetone); m.p. 175°C. IR (KBr) νcm^{-1}: 3440 (OH), 3332 (NH), 1680 (C = O), 1619 (C⎓C of aromatic ring), 1597 (C = N), 1299(N-N),1045 (C-Cl),1035(C-O-C);^{1}H-NMR ($CDCl_3$+$DMSOd_6$). δ in ppm: 3.76 (d, 2H, NH CH_2), 3.94 (s, 2H, CH_2 of thiazolidinone ring), 4.20 (s, 1H, CH-Ar), 5.75 (t, 1H, NH CH_2), 6.82 -7.84 (m, 8H, Ar-H), 11.26 (s, 1H, OH). Anal. Calcd. for $C_{17}H_{15}N_5O_3S$: C, 55.27; H, 4.09; N, 18.96. Found: C, 55.28; H, 4.10; N, 18.97%.

3-(5-(4-aminopyridinomethyl)-1,3,4-oxadiazol-2-yl)-2-(4-hydroxy,3-methoxyphenyl)- thiazolidin-4-one (5h)

Yield 76% (Methanol); m.p. 180°C. IR (KBr) νcm^{-1}: 3442 (OH), 3334 (NH), 1685 (C = O), 1624 (C⎓C of aromatic ring), 1525 (C = N), 1224 (OCH_3), 1294 (N-N), 1046 (C-Cl), 1037 (C-O-C); ^{1}H-NMR ($CDCl_3$+$DMSOd_6$). δ in ppm: 3.41 (s, 3H, OCH_3), 3.77 (t, 2H, NH CH_2), 3.91 (s, 2H, CH_2 of thiazolidinone ring), 4.18 (s, 1H, CH-Ar), 5.76 (t, 1H, NH CH_2), 6.84-7.80 (m, 7H, Ar-H), 11.24 (s, 1H, OH); Anal. Calcd. for $C_{18}H_{17}N_5O_4S$: C, 54.13; H, 4.29; N, 16.02. Found: C, 54.14; H, 4.30; N, 16.03%.

3-(5-(4-aminopyridinomethyl)-1,3,4-oxadiazol-2-yl)-2-(4-NN'-dimethylaminophenyl) thiazolidin-4-one (5i)

Yield 75% (Petroleum ether); m.p. 177°C. IR (KBr) νcm^{-1}: 3337 (NH), 1684 (C = O), 1625 (C⎓C of aromatic ring), 1528 (C = N), 1292 (N-N), 1044 (C-Cl), 1039 (C-O-C); ^{1}H-NMR ($CDCl_3$ + $DMSOd_6$). δ in ppm: 1.57 (s, 6H, N $(CH_3)_2$), 3.76 (s, 2H, NH CH_2), 3.92 (s, 2H, CH_2 of thiazolidinone ring), 4.19 (s, 1H, CH-Ar), 5.75 (t, 1H, NH CH_2), 6.83-7.82 (m, 8H, Ar-H); Anal. Calcd. for $C_{19}H_{20}N_6O_2S$: C, 57.56; H, 5.08; N, 21.20. Found: C, 57.53; H, 5.10; N, 21.22%.

General procedure for synthesis of 1-(5-(heterocyclic methyl)1,3,4-oxadiazol-2-yl)-3-chloro-4-(substituted phenyl)azetidin-2-ones (6a-i)

To a stirred solution of 5-[(heterocyclic methyl)-2-(substitutedbenzylidene)]-1,3,4-oxadiazol-2-amines **(4a-4i)** (0.01 mol) in dioxan (100ml), chloro acetyl chloride (0.01 mol) was added dropwise at 0-5°C temperature in presence of triethyl amine. The reaction mixture was stirred for about 6 h and the precipitated amine hydrochloride was filtered off. The filtrate was refluxed for 2 h and the separated solid was recrystallized from appropriate solvents to furnish compounds **(6a-6i)**.

1-(5-(N^{10}-phenothizinomethyl)1,3,4-oxadiazol-2-yl)-3-chloro-4-(2-hydroxy phenyl) azetidin-2-one (6a)

Yield 73% (Ethanol); m.p. 200°C. IR (KBr) νcm^{-1}: 3332 (NH), 1676 (C = O), 1623 (C⎓C of aromatic ring), 1528 (C = N), 1293 (N-N), 1043 (C-Cl), 1034 (C-O-C); ^{1}H-NMR ($CDCl_3$+$DMSOd_6$) δ in ppm: 1.57 (s, 6H, N $(CH_3)_2$), 3.76 (s, 2H, NH CH_2), 3.92 (d, 1H, CHCl of azetidinone ring), 5.20 (d, 1H, CH-Ar), 5.75 (t, 1H, NH CH_2), 6.84-7.80 (m, 8H, Ar-H); Anal. Calcd. for $C_{24}H_{19}N_4O_3SCl$: C, 60.44; H, 4.00; N, 11.70. Found: C, 60.43; H, 3.99; N, 11.72%.

1-(5-(N^{10}-phenothizinomethyl)1,3,4-oxadiazol-2-yl)-3-chloro-4-(4-hydroxy-3-methoxyphenyl) azetidin-2-one (6b)

Yield 74% (Methanol); m.p. 215°C. IR (KBr) νcm^{-1}: 3440 (OH), 1672 (C = O), 1624 (C$\cdots$C of aromatic ring), 1297 (N-N), 1592 (C = N), 1224 (OCH_3), 1040 (C-Cl), 1035 (C-O-C), 703 (C-S-C); ^{1}H-NMR ($CDCl_3$+DMSOd_6). δ in ppm: 2.44 (s, 2H, N-CH_2), 3.48 (s, 3H, OCH_3), 3.97 (d, 1H, CHCl of azetidinone ring), 5.23 (d, 1H, CH-Ar), 6.89-7.90 (m, 11H, Ar-H), 11.18 (s, 1H, OH); Anal. Calcd. for $C_{25}H_{19}N_4O_4SCl$: C, 59.23; H, 3.78; N, 11.05. Found: C, 59.26; H, 3.80; N, 11.10%.

1-(5-(N^{10}-phenothizinomethyl)1,3,4-oxadiazol-2-yl)-3-chloro-4-(4-NN'-dimethylaminophenyl)) azetidin-2-one (6c)

Yield 68% (Acetone); m.p. 185°C. IR (KBr) νcm^{-1}: 1671 (C = O), 1625 (C$\cdots$C of aromatic ring), 1596 (C = N), 1298 (N-N), 1040 (C-Cl), 1034 (C-O-C), 702 (C-S-C); ^{1}H-NMR ($CDCl_3$+DMSOd_6). δ in ppm: 1.54 (s, 6H, $N(CH_3)_2$), 2.43 (s, 2H, N-CH_2), 3.98 (d, 1H, CHCl of azetidinone ring), 5.18 (d, 1H, CH-Ar), 6.80-7.94 (m, 12H, Ar,-H); Anal. Calcd. For $C_{26}H_{22}N_5O_2SCl$: C, 61.96; H, 4.40; N, 13.90. Found: C, 61.90; H, 4.39; N, 13.98%.

1-(5-(2-aminopyridinomethyl)1,3,4-oxadiazol-2-yl)-3-chloro-4-(4-hydroxyphenyl) azetidin-2-one (6d)

Yield 68% (Ethanol); m.p. 185°C. IR (KBr) νcm^{-1}: 3440 (OH), 3332 (NH), 1674 (C = O), 1619 (C$\cdots$C of aromatic ring), 1597 (C = N), 1299 (N-N), 1041 (C-Cl), 1033 (C-O-C); ^{1}H-NMR ($CDCl_3$ + DMSOd_6). δ in ppm: 3.73 (d, 2H, $NHCH_2$), 3.96 (d, 1H, CHCl of azetidinone ring), 5.16 (d, 1H, CH-Ar), 5.73 (t, 1H, $NHCH_2$), 6.82 -7.84 (m, 8H, Ar-H), 11.26 (s, 1H, OH); Anal. Calcd. for $C_{17}H_{14}N_5O_3Cl$: C, 54.92; H, 3.80; N, 18.84 Found: C, 54.96; H, 3.79; N, 18.81%.

1-(5-(2-aminopyridinomethyl)1,3,4-oxadiazol-2-yl)-3-chloro-4-(4-hydroxy-3-methoxyphenyl) azetidin-2-one (6e)

Yield 72% (Methanol); m.p. 190°C. IR (KBr) νcm^{-1}: 3442 (OH), 3432 (NH), 1668 (C = O), 1622 (C$\cdots$C of aromatic ring), 1593 (C = N), 1299 (N-N), 1224 (OCH_3), 1046 (C-Cl), 1037 (C-O-C); ^{1}H-NMR ($CDCl_3$). δ in ppm: 3.41 (s, 3H, OCH_3), 3.74 (t, 2H, NH CH_2), 3.99 (d, 1H, CHCl of azetidinone ring), 5.24 (d, 1H, CH-Ar), 5.74 (t, 1H, NH), 6.84-7.80 (m, 7H, Ar-H), 11.24 (s, 1H, OH); Anal. Calcd. for $C_{18}H_{16}N_5O_4Cl$: C, 53.01; H, 5.44; N, 17.17. Found: C, 53.04; H, 5.45; N, 17.20%.

1-(5-(2-aminopyridinomethyl)1,3,4-oxadiazol-2-yl)-3-chloro-4-(4-NN'-dimethylaminophenyl) azetidin-2-one (6f)

Yield 70% (Acetone); m.p. 180°C. IR (KBr) νcm^{-1}: 3336 (NH), 1668 (C = O), 1622 (C$\cdots$C of aromatic ring), 1592 (C = N), 1291 (N-N), 1046 (C-Cl), 1036 (C-O-C); ^{1}H-NMR ($CDCl_3$+DMSOd_6). δ in ppm: 1.57 (s, 6H, $N(CH_3)_2$), 3.72 (s, 2H, NH CH_2), 3.95 (d, 1H, CHCl of azetidinone ring), 5.24 (d, 1H, CH-Ar), 5.74 (t, 1H, NH CH_2), 6.83-7.82 (m, 8H, Ar-H); Anal. Calcd. for $C_{19}H_{19}N_6O_2Cl$: C, 57.22; H, 4.80; N, 21.07; Found: C, 57.23; H, 4.79; N, 21.06%.

1-(5-(4-aminopyridinomethyl)1,3,4-oxadiazol-2-yl)-3-chloro-4-(4-hydroxy-3-methoxyphenyl) azetidin-2-one (6g)

Yield 74% (Petroleum ether); m.p. 186°C. IR (KBr) νcm^{-1}: 3440 (OH), 3332 (NH), 1674 (C = O), 1619 (C$\cdots$C of aromatic ring), 1597 (C = N), 1299 (N-N), 1045 (C-Cl), 1035 (C-O-C); ^{1}H-NMR ($CDCl_3$+DMSOd_6). δ in ppm: 3.76 (d, 2H, $NHCH_2$), 3.94 (d, 1H, CHCl of azetidinone ring), 5.19 (d, 1H, CH-Ar), 5.75 (t, 1H, $NHCH_2$), 6.82 -7.84 (m, 8H, Ar-H), 11.26 (s, 1H, OH); Anal. Calcd. for $C_{17}H_{14}N_5O_3Cl$: C, 54.92; H, 3.80; N, 18.84 Found: C, 54.96; H, 3.79; N, 18.81%.

1-(5-(4-aminopyridinomethyl)1,3,4-oxadiazol-2-yl)-3-chloro-4-(4-hydroxy-3-methoxyphenyl) azetidin-2-one (6h)

Yield 72% (Methanol); m.p. 192°C. IR (KBr) νcm^{-1}: 3334 (NH), 3442 (OH), 1675 (C = O), 1624 (C$\cdots$C of aromatic ring), 1525 (C = N), 1294 (N-N), 1037 (C-O-C), 1046 (C-Cl), 1224 (OCH_3); ^{1}H-NMR ($CDCl_3$+DMSOd_6). δ in ppm: 3.41 (s, 3H, OCH_3), 3.77 (t, 2H, NH CH_2), 3.91 (d, 1H, CHCl of azetidinone ring), 5.18 (d, 1H, CH-Ar), 5.76 (t, 1H, NH CH_2), 6.84-7.80 (m, 7H, Ar-H), 11.24 (s, 1H, OH); Anal. Calcd. for $C_{18}H_{16}N_5O_4Cl$: C, 53.01; H, 5.44; N, 17.17. Found: C, 53.04; H, 5.45; N, 17.20%.

1-(5-(4-aminopyridinomethyl)1,3,4-oxadiazol-2-yl)-3-chloro-4-(4-NN'-dimethylaminophenyl) azetidin-2-one (6i)

Yield 70% (Ethanol); m.p. 188°C. IR (KBr) νcm^{-1}: 3337 (NH), 1673 (C = O), 1625 (C$\cdots$C of aromatic ring), 1528(C = N), 1292 (N-N), 1044 (C-Cl), 1039 (C-O-C); ^{1}H-NMR ($CDCl_3$+$DMSOd_6$). δ in ppm: 1.57 (s, 6H, N $(CH_3)_2$), δ 3.76 (s, 2H, NH CH_2), 3.92 (d, 1H, CH Cl of azetidinone ring), 5.21 (d, 1H, CH-Ar), 5.75 (t, 1H, $NHCH_2$), 6.83-7.82 (m, 8H, Ar-H); Anal. Calcd. for $C_{19}H_{19}N_6O_2Cl$: C, 57.22; H, 4.80; N, 21.07; Found: C, 57.23; H, 4.79; N, 21.06%.

RESULTS AND DISCUSSION

All the new synthesized compounds **(4a-4i)**, **(5a-5i)** and **(6a-6i)** were studied for their antipsychotic and anticonvulsant activities at a dose of 40mg/kg i.p. and pharmacological data of all the compounds of this series have been reported in TABLE 1. The characteristics feature of this series is the substitution by the different moieties at 10th position of phenothiazine ring and 2nd and 4th position of pyridine ring.

Antipsychotic activity

All the new synthesized compounds **(4a-4i)**, **(5a-5i)** and **(6a-6i)** were studied for their antipsychotic activity. According to following parameters.

Amphetamine induced stereotyped behaviour

While evaluating antipsychotic activity, compounds **(4a-4i)** elicited varying score against amphetamine induced stereotyped behaviour (1.2-1.8 score), while compounds **(4g)** and **(4i)** showed good results i.e. 1.0 score. Among the compounds **(5a-5i)**, compounds **(5a, 5c)** and **(5h)** showed interesting results towards amphetamine induced stereotyped behaviour (0.4 score). Compound **(5b)** namely 3-(5-(N^{10}-phenothiazinomethyl)-1,3,4-oxadiazol-2-yl)-2-(4-hydroxy, 3-methoxyphenyl) -thiazolidin-4-one was the most potent compound of this series, because this compound completely antagonized the amphetamine induced stereotyped behaviour and did not produce any cataleptic behaviour. On the other side, i.e. compounds **(6a-6i)** showed varying results towards amphetamine induced stereotyped behaviour (0.4-1.2 score). The compound **(6i)** showed interesting result against amphetamine induced stereotyped behaviour (0.4 score), whereas compounds **(6b)**, **(6c)**, **(6e)**, **(6g)** and **(6h)** showed equipotent results to each other towards amphetamine antagonism.

Cataleptic behaviour

Compounds **(4a-4i)** elicited different results towards cataleptic behaviour (i.e.1.0-1.6 score). In the next step compounds **(5a-5i)** compounds **(5c)** and **(5f)** showed promising results against cataleptic behaviour and compounds **(5a, 5e)** and **(5h)** elicited equipotent results in cataleptic behaviour. Compound **(5b)** showed most potent response against cataleptic behaviour, because this compound did not produce any cataleptic behaviour. Furthermore, the compounds **(6a-6i)** exhibited varying against cataleptic behaviour towards cataleptic behaviour. Moreover, compounds **(6b)**, **(6f)** and **(6h)** elicited equal scores (i.e. 1.0 score) against cataleptic behaviour.

Rotarod performance test

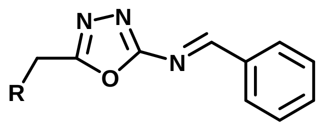
The compounds **(4a-4i)** exhibited significant activity in rotarod performance test (108.8-112.6 sec.).

In the next step, i.e. compounds **(5a-5i)**, compounds **(5a, 5c)** and **(5h)** showed interesting results in rotarod performance test. The latter compounds spent 100.4 seconds on rod in rotarod performance test. The compound **(5b)** exhibited promising result in rotarod performance test (i.e. 98.8 sec) which is more than reference drug chlorpromazine. On the other side, i.e. compounds **(6a-6i)** showed varying results in rotarod performance test (100.8-104.8 sec.). Among these compounds, compound **(6b)** showed better resulsts in rotarod performance test (i. e. 102.0 sec.) than other substituted azetidinones.

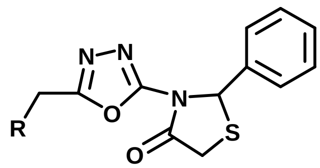
Anticonvulsant activity

The compounds **(4a-i)** elicited varying degree (30-60%) of anticonvulsant activity. The compounds **(4b)** and **(4h)** showed good anticonvulsant activity (i.e. 60%). In the next step compounds, the compound **(5b)** showed more potent (90%) anticonvulsant activity which was more potent than reference drug phenytoin sodium (30 mg/kg). Furthermore, the compounds **(6a-6i)** exhibited varying degree (50-80%) of anticonvulsant activ-

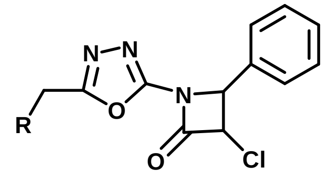
TABLE 1 : Antipsychotic and anticonvulsant activities of compounds synthesized (4a-4i), (5a-5i) and (6a-6i).



(4a-4i)



(5a-5i)



(6a-6i)

Com. No	Dose mg/kg i.p.	Amphetamine induced SB (Mean score)[c]	Rotarod test[d] (Mean sec.)	Cataleps scored[e]	MES% seizures protection[f]	ALD$_{5g}$mg/kg
P.G.[a]	0.5 ml	3.8	120.0	0.0	0	
CPZ[a]	4.0	0.0	100.0	-	-	
HPL[b]	0.5 ml	-	-	1.8	0	
P.S.[b]	30	-	-	-	80***	
4a.	40	1.2	110.6	1.2	40	>1000
4b	40	1.4	110.0	1.0	60**	>1000
4c.	40	1.2	108.8	1.2	50*	>1000
4d.	40	1.6	112.6	1.4	40	>1000
4e.	40	1.6	110.8	1.2	40	>1000
4f.	40	1.8	110.4	1.6	50*	>1000
4g.	40	1.0	112.4	1.6	30	>1000
4h.	40	1.6	112.0	1.4	60**	>1000
4i.	40	1.0	112.2	1.4	40	>1000
5a.	40	0.4	100.4	0.6	70***	>1000
5b.	40	0.0	98.8	0.0	90***	>1600
5c.	40	0.4	100.4	0.4	80***	>1000
5d.	40	0.8	100.6	1.0	60**	>1000
5e.	40	0.6	100.8	0.6	80***	>1000
5f.	40	0.8	102.6	0.4	60**	>1000
5g.	40	0.6	102.8	1.0	70***	>1000
5h.	40	0.4	100.4	0.6	60**	>1000
5i.	40	0.8	102.4	0.8	60**	>1000
6a.	40	1.2	104.6	1.0	50*	>1000
6b.	40	1.0	102.0	0.8	80***	>1000
6c.	40	1.0	104.8	1.0	60**	>1000
6d.	40	1.2	104.6	1.2	60**	>1000
6e.	40	1.0	102.0	1.0	70***	>1000
6f.	40	1.2	102.8	0.8	70***	>1000
6g.	40	1.0	100.8	1.0	60**	>1000
6h.	40	1.0	102.2	0.8	70***	>1000
6i.	40	0.4	102.6	1.0	60**	>1000

$*P< .05$, $**P< .01$, $***P < .001$

[a]P.G. = Propylene glycol, CPZ = Chlorpromazine, [b]HPL = Haloperidol, P.S. = Phenytoin sodium.

[c]Protection against amphetamine (4mg/kg) induced stereotyped bahaviour (SB).

[d]Time spent on the rod (in sec.) in rotarod performance test.

[e]Score of cataleptic behaviour with reference to propylene glycol treated group of rats; Haloperidol (0.5 ml i.p.) induced group 1.8 with reference to control group.

[f]Percentage protection against convulsions in maximal electroshock seizure test.

[g]ALD_{50} of the compounds (4a-4i), (5a-4i) and (6a-6i).

ity. Among these compounds, compound **(6b)** showed better anticonvulsant activity (80%) than other substituted azetidinones.

The newly synthesized compounds were also tested for approximate lethal dose ALD_{50} and were found to exhibit a higher value of ALD_{50} i.e. more than 1000mg/kg i.p. except compound **(5b)** which exhibited ALD_{50} of more than 1600 mg/kg i.p. (maximum dose tested) thus indicating the safer nature of the compound.

Hence it can be concluded that:

1. Compounds having phenothiazine ring show the better antipsychotic and anticonvulsant activities than the compounds having 2/4 amino pyridine ring.
2. Compounds having 4-hydroxy, 3-methoxy phenyl ring at the 2nd position of thiazolidinone ring showed more potent activity than other substituted thiazolidinones.
3. Compounds with thiazolidinone ring showed better results than their corresponding azetidinones.

PHARMACOLOGICAL EVALUATION

Antipsychotic activity

Effect on amphetamine induced stereotyped behaviour (SB)

It was done by the method of Castall and Naylor [15]. Before the administration of drugs, the animals were fasted for 12 h and were deprived of food during experiment. Amphetamine (4mg/kg, i.p.) was used to induce the stereotyped behaviour (SB) in albino rats. The intensity of SB was assessed for 60 min after test compounds treatment, using the following scoring system. Periodic sniffing = 1 Score, continuous sniffing = 2 Score, periodic biting, gnawing or licking = 3 Score and continuous biting, gnawing or licking = 4 Score. The maximum intensity of SB scored by each rat in the group was taken to compute the mean value of the group. Chlorpromazine (4mg/kg, i.p.) was used as standard and was injected 30 min. before the challenge, while propylene glycol (0.5mL i.p.) or test compounds was given 20 min prior to the injection of amphetamine.

Induction of catalepsy

It was performed according to the method of Castall and Naylor[15]. According this method, the front limbs of the rat were placed over the wooden block of 8 cm high and measure the time the animal maintained the imposed posture. Animals maintaining the imposed posture for more than 10 sec were considered to be cataleptic. Animals were tested for catalepsy by using the scoring system to maintain the impose posture 0-10 sec = 0 score, 11-30 sec = 1 score, 31-60 sec = 2 score, 61-120 = 3 score, after injecting propylene glycol (0.5mL, i.p.) or test compounds or haloperidol (0.5mg/kg, i.p.) as standard.

Rotarod performance test

The rotarod performance test was essentially the same as described by Dunham and Miya[16]. It is a measure of strength and coordinated movement of animals. The animals were given a training session on the rotarod (rotating at 6 rpm) a day before the test session. As soon as the rat fell off the rotarod, it was immediately placed back. Training was terminated when the rat remained on the rod continuously for 2 min. On the second day, after administration of test compound, the rats were given the trials on the rotarod at 60 min and the cumulated time spent on the rotarod was recorded with a cut off of 2 min.

Anticonvulsant activity

Maximum electroshock seizure (MES) test: This activity was performed by method the of Toman et al.[17] on albino rats of the Charles foster strain of either sex, weighing, between 100-120g. Rats were divided into the groups of 10 animals each and pregnancy was excluded in female rats. The rats were treated with the test drugs 40mg/kg and phenytoin sodium 30mg/kg i.p. After 1 h they were subjected to the shock of 150mA by convulsiometer through ear electrodes for 0.2 sec. Abolition of the hind limb tonic extensor component of the seizure is defined as protection, and results are expressed as number of animals protected/ number of animals tested.

Acute toxicity study

The compounds were investigated for this acute toxicity (ALD_{50}) in albino mice by following the method of smith[22]. Test compounds were administered orally in one group and the same volume of normal saline in another group of animals consisting six mice each in graded doses. During the study, the animals were allowed to

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take water and food adlibidum. After 24 h of drug administration percent mortality in each group was observed. From the data obtained ALD_{50} was calculated.

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