December 2009 Volume 5 Issue 4

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 5(4), 2009 [367-379]

# Synthesis and evaluation of some various 2-(Heterocyclic)-1, 5-benzothia/oxazepine-4 (5H) ones as antipsychotic and anticonvulsant agents

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*Received: 25th September, 2009 ; Accepted: 6th October, 2009*

## ABSTRACT

A series of 2-(Heterocyclic-amino/hydrazino-methylene)-1, 5-benzothia/oxazepine-4 (5H) ones (1-26) have been synthesized by the reaction of 2-bromomethyl-1, 5-benzo-thia/oxazepine 4(5H) ones with various substituted heterocyclic amines or hydrazines. All the newly synthesized compounds were screened for their antipsychotic and anticonvulsant activities at the dose of 40mg/kg i.p. and were compared with standard drugs. Compound 19 was the most potent compound of this series. Structure of all the synthesized compidated by elemental (C, H, N) and spectral (IR, and $^1$H-NMR) analysis.



## KEYWORDS

Indolylbenzothia/oxazepines;
Quinazolinonyl benzothia/oxazepines phenothiazinyl benzothia/oxazepines;
Barbituryl/benzothia/oxazepines;
Antipsychotic activity;
Anticonvulsant activity.

## INTRODUCTION

Psychopharamacological agents or psychotropic drugs are those having primary effect on psyche (mental process) and are used for treatment of psychiatric disorders. Psychoses are the mental disorder which results either due to some organic disease or due to alternations in the neurotransmitter of the brain. The personality of the patient gets deranged and he loses contact with reality. Moreover, epilepsy is very often associated with neurological psychiatric disorders, so a drug with both antipsychotic as well as antiepileptic activity will be more beneficial. Therefore, the need for more effective and less toxic antipsychotic drugs still exists. One of the most frequently encountered heterocyclic in medicinal chemistry is 1, 5-Benzothiazepine with wide applications including psychotropic[1], antidepressant[2] and anticonvulsant[3] activity. Furthermore, 1, 5-Benzoxazepines were also found to possess psychotropic[4] anticonvulsant[4] and CNS depressant[5] properties. Moreover several heterocyclic aromatic systems such as barbituric acid[6,7], quinazolinone[8,9], indole[10,11], and phenothiazine[12,13] having different substituents at symmetrical positions have been evaluated for their antipsychotic and anticonvulsant activities. In view of above observations, we have synthesized new derivatives of 1, 5 benzothia/oxazepine by incorporating barbituric acid, quinazolinone, indole and phenothiazine moieties in single molecular framework with the hope to get better antipsychotic & anticonvulsant agents.

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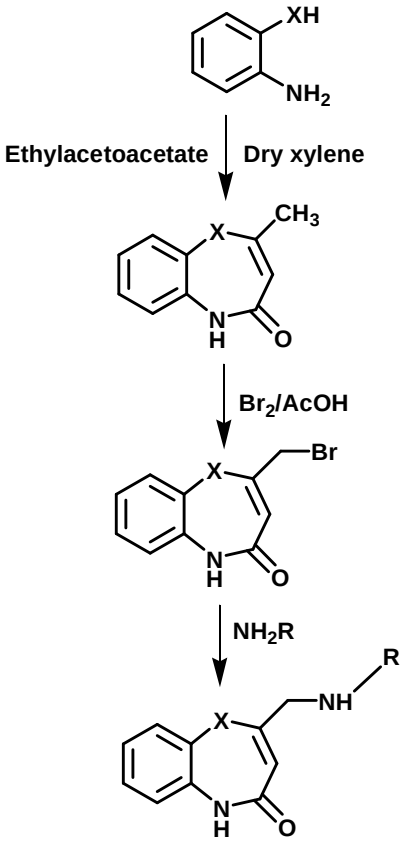
7,11-Diphenyl-9 aminoimino-2,4-diazaspiro [5,5] undecane-1, 3, 5-trione were reacted with different substituted heterocyclic amines or hydrazines to give com-

pounds 1-26. The purity of all synthesized compounds was determined by thin layer chromatography using several solvent systems of different polarity.

## 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 ($\nu_{max}$ in $cm^{-1}$). The $^1H$-NMR spectra were recorded in $CDCl_3$ and $DMSOd_6$ on Brucker DRX-300 FTNMR instrument.




(1-26)

X=O/S

Scheme-1

### General procedure for preparation of 2-Methyl-1, 5-benzothia/oxazepin-4-(5H)-one

To the solution of 2-amino benzene thiol/phenol (1.0 mol) in xylene (dry, 100ml) was added ethylacetoacetate (1.0 mol) in 20ml of dry xylene dropwise during 30 minutes. The reaction mixture was refluxed for 5-6 h and the solvent was distilled off and the residue thus obtained was washed with peteroleum ether and recrystallized from appropriate solvent to give 2-methyl-1,5-benzothia/oxazepine-4 (5H) ones.

### 2-methyl-1,5-benzothiazepin-4-(5H)-one

Yield 72% m.p.: 160: IR (KBr) $\nu cm^{-1}$: 3280 (NH), 1675 (C=O), 1620 (C=C), 700 (C-S-C). $^1H$ NMR ($CDCl_3$)δ in ppm: 8.00-7.20 (m, 5H, 4H Ar-H+1H$C_3$H), 8.70 (s, 1H, NH of thiazepine ring), 2.35 (s, 3H, $CH_3$); Anal. Calcd. for $C_{10}H_9NOS$. Calcd: C, 62.82; H, 4.71; N, 7.32; Found: C, 62.80; H, 4.72; N, 7.29;

### 2-methyl-1,5-benzoxazepin-4-(5H)-one

Yield 70% m.p.: 188°C. IR (KBr) $\nu cm^{-1}$: 3300 (NH), 1680 (C=O), 1621 (C=C), 1055 (C-O-C); $^1H$ NMR ($CDCl_3$)δ in ppm: 7.80-6.90 (m, 5H, 4H Ar-H+1H$C_3$H), 8.65 (s, 1H, NH of oxazepine ring), 2.30 (s, 3H, $CH_3$); Anal. Calcd. for $C_{10}H_9NO_2$.Calcd: C, 68.57; H, 5.14; N, 8.00; Found: C, 68.62; H, 5.10; N, 8.05.

### General procedure for preparation of 2-Bromomethyl-1,5-benzothiazepine-4-(5H)-one

To a solution of 2-methyl-1,5-benzothia/oxazepin, 4 (5H)-ones (0.5 mol) in glacial acetic acid (50ml) was added a solution of bromine (0.5 mol) in glacial acetic acid dropwise during 2-3 h with continuous stirring on mechanical stirrer. The reaction mixture was poured into crushed ice. The solid thus obtained was filtered, dried and recrystallised from appropriate solvent to furnish compounds 1-26.

### 2-Bromomethyl-1,5-benzothiazepin-4-(5H)-one

Yield 75% (Xylene) m.p.: 199°C. IR (KBr) $\nu cm^{-1}$:

3280 (NH), 1685 (C=O), 1630 (C=C), 690 (C-S-C). $^1$H NMR ($CDCl_3$)δ in ppm: 8.30-7.60 (m, 5H, 4H Ar-H+1H$C_3$H), 8.40 (s, 1H, NH of thiazepine ring), 3.80 (s, 2H, $CH_2$). Anal. Calcd. for $C_{10}H_8NOSBr$. Calcd: C, 44.44; H, 2.96; N, 5.18; Found: C, 44.49; H, 3.01; N, 5.12;

**2-Bromo methyl-1,5-benzoxazepin-4-(5H) one**

Yield 72% (Methanol) m.p.: 182°C. IR (KBr) νcm$^{-1}$: 3260 (NH), 1681 (C=O), 1620 (C=O), 1050 (C-O-C); $^1$H NMR ($CDCl_3$+$DMSOd_6$)]δ in ppm: 8.20-7.60 (m, 5H, 4H Ar-H+1H$C_3$H), 8.00 (s, 1H, NH), 3.75 (s, 2H, $CH_2$). Anal. Calcd. for $C_{10}H_8NO_2Br$. Calcd: C, 47.24; H, 3.14; N, 5.51; Found: C, 47.26; H, 3.10; N, 5.55.

**General procedure for preparation of 2-(Heterocyclic-amino/hydrazino-methylene)-1, 5-benzothia/oxazepine-4-(5H)-one (1-26)**

A solution of 7,11-Diphenyl -9 aminoimino-2,4-diazaspiro [5,5] undecane-1, 3, 5- trione (0.04 mol) was added to the solution of 2-bromomethyl-1,5-benzothiazepine, 4 (5H)-one (0.04 mol) in absolute ethanol (dry 50ml) reaction mixture was stirred for 15 minutes at room temperature and then refluxed for 8-10 h. On cooling the solvent was distilled off and the residue upon cooling recrystallised from appropriate solvents to furnish compounds 1-26.

**2-[(7, 11-diphenyl-9-aminoimino-2, 4-diazaspiro [5, 5] undecane-1, 3, 5-trione) methylene]-1,5-benzothiazepin-4-(5H)-one (1)**

Yield 50% m.p.: 228°C. IR (KBr) νcm$^{-1}$: 3600 (NH), 1700, 1680, 1669, 1660 (C=O), 1620 (C-C of aromatic ring), 1590 (C=N), 700 (C-S-C). $^1$H NMR ($DMSOd_6$)δ in ppm: 8.10 (m, 2H, 2×N<u>H</u>CO), 7.85-6.50 (m, 15H, 14HAr-H+1H$C_3$H), 9.70 (bs, 1H, NH of thiazepine ring), 4.91 (t, 1H, NH), 4.75 (dd, 7H & 11H, 3.82 (d, 2H, C<u>H</u>$_2$NH), 3.40 (dd, 2H, 8$H_{Ax}$& 10$H_{AX}$,), 2.25 (dd, 2H, 8$H_{eq}$ & 10$H_{eq}$). Anal. Calcd. for $C_{31}H_{27}N_5O_4S$. Calcd: C, 65.84; H, 4.60; N, 12.38; Found: C, 65.76; H, 4.70; N, 12.30.

**2-[(7, 11-(4-methoxy)-diphenyl-9-aminoimino-2, 4-diazaspiro [5,5] undecane-1, 3, 5-trione) methylene]-1,5-benzothiazepin-4-(5H)-one (2)**

Yield 75% (Acetic acid) m.p.: 252°C, IR (KBr) νcm$^{-1}$: 3590 (NH), 1701, 1682, 1675, 1662 (C=O), 1623 (C-C of aromatic ring), 1595 (C=N), 702 (C-S-C), 1225 ($OCH_3$). $^1$H NMR ($DMSOd_6$)δ in ppm: 8.16 (m, 2H, 2×N<u>H</u>CO), 7.80-6.49 (m, 15H, 12H Ar-H+1H$C_3$H), 4.80-5.3 (bs, 1H, NH of thiazepine ring), 4.90 (t, 1H, NH), 4.78 (dd, 2H, 7H & 11H), 3.85 (d, 2H, C<u>H</u>$_2$-NH), 3.42 (dd, 2H, 8$H_{AX}$ & 10$H_{AX}$,), 2.27 (dd, 2H, 8$H_{eq}$ & 10$H_{eq}$), 3.35 (s, 6H, 2×OC<u>H</u>$_3$). Anal. Calcd. for $C_{33}H_{31}N_5O_6S$. Calcd: C, 63.36; H, 4.96; N, 11.20; Found: C, 63.20;H, 5.18; N, 10.88.

**2-[{7,11-(4-NN′-dimethylamino)-diphenyl-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,3,5-trione} methylene]-1,5-benzothiazepin- 4-(5H)-one (3)**

Yield 80% (DMF/water) m.p.: 298°C, IR (KBr) νcm$^{-1}$: 3599 (NH), 1699, 1684, 1670, 1665 (C=O), 1625 (C-C of aromatic ring), 1598 (C=N), 699 (C-S-C). $^1$H NMR ($DMSOd_6$)δ in ppm:8.32 (m, 2H, 2xN<u>H</u>CO), 7.82-6.49 (m, 13H, 12H Ar-H+1H$C_3$H), 9.73 (bs, 1H, NH of thiazepine ring), 4.91 (t, 1H, NH), 4.79 (dd, 2H, 7H & 11H), 3.83 (d, 2H, C<u>H</u>$_2$-NH), 3.45 (dd, 2H, 8$H_{AX}$ & 10$H_{AX}$), 2.24 (dd, 2H, 8$H_{eq}$ & 10$H_{eq}$), 1.9 (s, 12H, 2×N($CH_3$)$_2$). Anal. Calcd. for $C_{35}H_{37}N_7O_4S$. Calcd: C, 64.51; H, 5.68; N, 15.05; Found: C, 64.65; H, 5.42; N,15.19.

**2-[{7,11-difuronyl-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,3,5-trione} methylene]-1,5-benzothiazepin-4-(5H)-one (4)**

Yield 52% (Methanol) m.p.: 278°C. IR (KBr) νcm$^{-1}$: 3595 (NH), 1698, 1691, 1682, 1659 (C=O), 1626 (C-C of aromatic ring), 1592 (C=N), 697 (C-S-C). $^1$H NMR ($DMSOd_6$)δ in ppm: 8.21 (m, 2H, 2×N<u>H</u>CO), 7.83-6.51 (m, 11H, 10HAr-H+1H$C_3$H), 9.70 (bs, 1H, NH of thiazepine ring), 4.91 (t, 1H, NH), 4.80 (dd, 2H, 7H & 11H), 3.83 (d, 2H, C<u>H</u>$_2$-NH), 3.46 (dd, 2H, 8$H_{AX}$ & 10$H_{AX}$), 2.24 (dd, 2H, 8$H_{eq}$ & 10$H_{eq}$). Anal. Calcd. for $C_{27}H_{23}N_5O_6S$. Calcd: C, 59.44; H, 4.22; N, 12.84; Found: C, 59.52; H, 4.25; N, 12.80.

**2-[{7, 11-diphenyl-3-thio-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,5-dione} methylene]-1,5-benzothiazepin-4-(5H)-one (5)**

Yield 50% (DMF/water) m.p.: 244°C. IR (KBr) νcm$^{-1}$: 3596 (NH), 1699, 1689, 1671 (C=O), 1624

(C-C of aromatic ring), 1593 (C=N), 703 (C-S-C), 1131 (C=S). $^1$H NMR ($DMSOd_6$)δ in ppm: 8.22 (m, 2H, 2×NHCO), 7.84-6.51 (m, 15H, 14H Ar-H+1$HC_3$H), 9.71 (bs, 1H, NH of thiazepine ring), 4.91 (t, 1H, NH), 4.77 (dd, 2H, 7H & 11H), 3.85 (d, 2H, $CH_2$-NH), 3.39 (dd, 2H, $8H_{AX}$ & $10H_{AX}$), 2.27 (dd, 2H, $8H_{eq}$ & $10H_{eq}$). Anal. Calcd. for $C_{31}H_{27}N_5O_3S_2$. Calcd: C, 64.02; H, 4.64; N, 12.04; Found: C, 64.14; H, 4.72; N,12.14.

**2-[{7,11-(4-methoxy)-diphenyl-3-thio-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,5-dione} methylene]-1,5-benzothiazepin-4-(5H)-one (6)**

Yield 75% (Ethanol) m.p.: 267°C, IR (KBr) νcm$^{-1}$: 3598 (NH), 1702, 1699, 1670 (C=O), 1630 (C-C of aromatic ring), 1585 (C=N), 705 (C-S-C), 1129 (C=S), 1224 ($OCH_3$). $^1$H NMR ($DMSOd_6$)δ in ppm: 8.43 (m, 2H, 2×NHCO), 7.86-6.49 (m, 13H, 12HAr-H+1$HC_3$H), 9.70 (bs, 1H, NH of thiazepine ring), 4.91 (t, 1H, NH), 4.72 (dd, 2H, 7H & 11H), 3.79 (d, 2H, $CH_2$-NH), 3.49 (dd, 2H, $8H_{AX}$ & $10H_{AX,}$), 2.19 (dd, 2H, $8H_{eq}$ & $10H_{eq}$), 3.39 (s, 6H, 2×$OCH_3$). Anal. Calcd. for $C_{33}H_{31}N_5O_5S_2$. Calcd: C, 61.77; H, 4.83; N, 10.92; Found: C, 61.82; H, 4.80; N,10.85.

**2-[{7,11-(4-NN'-dimethylamino)-3-thio-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,5-dione} methylene]-1,5-benzothiazepin-4-(5H)-one (7)**

Yield 75% (Acetone) m.p.: 320°C. IR (KBr) νcm$^{-1}$: 3594 (NH), 1704, 1685, 1665 (C=O), 1622 (C-C of aromatic ring), 1595 (C=N), 701 (C-S-C), 1130 (C=S). $^1$H NMR ($DMSOd_6$)δ in ppm: 8.29 (m, 2H, 2×NHCO), 7.82-6.49 (m, 13H, 12H Ar-H+1$HC_3$H), 9.70 (bs, 1H, NH of thiazepine ring), 4.91 (t, 1H, NH), 4.69 (dd, 2H, 7H & 11H), 3.80 (d, 2H, $CH_2$-NH), 3.39 (dd, 2H, $8H_{AX}$ & $10H_{AX,}$), 2.20 (dd, 2H, $8H_{eq}$ & $10H_{eq}$), 1.8 (s, 12H, 2×$N(CH_3)_2$). Anal. Calcd. for $C_{35}H_{37}N_7O_3S_2$. Calcd: C, 62.96; H, 5.54; N, 14.70; Found: C, 63.19; H, 5.25; N,14.14.

**2-[{7,11-difuronyl-3-thio-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,5-dione} methylene]-1,5-benzothiazepin-4-(5H)-one (8)**

Yield 70% (Chloroform) m.p.: 282°C. IR (KBr) νcm$^{-1}$: 3589 (NH), 1703, 1679, 1658 (C=O), 1622 (C-C of aromatic ring), 1592 (C=N), 698 (C-S-C), 1135 (C=S). $^1$H NMR ($DMSOd_6$)δ in ppm: 8.41 (m, 2H, 2×NHCO), 7.85-6.49 (m, 11H, 10H Ar-H+1$HC_3$H), 9.73 (bs, 1H, NH of thiazepine ring), 4.91 (t, 1H, NH), 4.67 (dd, 2H, 7H & 11H), 3.81 (d, 2H, $CH_2$-NH), 3.43 (dd, 2H, $8H_{AX}$ & $10H_{AX,}$), 2. (dd, 2H, $8H_{eq}$ & $10H_{eq}$). Anal. Calcd. for $C_{27}H_{23}N_5O_5S_2$. Calcd: C, 57.75; H, 4.09; N, 12.47; Found: C, 57.70; H, 4.12; N, 12.44.

***2*-[{7, 11-diphenyl-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,3,5-trione} methylene]-1,5-benzoxazepin-4-(5H)-one (9)**

Yield 78% (Acetone) m.p.: 210°C. IR (KBr) νcm$^{-1}$: 3600 (NH), 1700, 1689, 1669, 1657 (C=O), 1619 (C-C of aromatic ring), 1585 (C=N), 710 (C-S-C). $^1$H NMR ($DMSOd_6$)δ in ppm: 8.30 (m, 2H, 2×NHCO), 7.84-6.50 (m, 15H, 14 Ar-H+$C_3$H), 9.69 (bs, 1H, NH of oxazepine ring), 4.91 (t, 1H, NH), 4.74 (dd, 2H, 7H & 11H), 3.79 (d, 2H, $CH_2$-NH), 3.45 (dd, 2H, 8H & 10H), 2.18 (dd, 2H, $8H_{eq}$ & $10H_{eq}$). Anal. Calcd. for $C_{31}H_{27}N_5O_5$. Calcd: C, 67.75; H, 4.91; N, 12.75; Found: C, 67.78; H, 4.88; N, 12.73.

**2-[{7,11-(4-methoxy)-diphenyl-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,3,5-trione} methylene]-1,5-benzoxazepin-4-(5H)-one (10)**

Yield 50% (DMF/water) m.p.: 235°C. IR (KBr) νcm$^{-1}$: 3590 (NH), 1699, 1688, 1677, 1660 (C=O), 1620 (C-C of aromatic ring), 1590 (C=N), 1029 (C-O-C). $^1$H NMR ($DMSOd_6$)δ in ppm: 8.31 (m, 3H, 3xNHCO), 7.89-6.40 (m, 13H, 14HAr-H+1$HC_3$H), 9.73 (bs, 1H, NH of oxazepine ring), 4.90 (t, 1H, NH), 4.77 (dd, 2H, 7H & 11H), 4.84 (d, 2H, $CH_2$-NH), 3.50 (dd, 2H, $8H_{AX}$ & $10H_{AX,}$), 2.17 (dd, 2H, $8H_{eq}$ & $10H_{eq}$), 3.35 (s, 6H, 2×$OCH_3$). Anal. Calcd. for $C_{33}H_{31}N_5O_7$. Calcd: C, 65.02; H, 5.09; N, 11.49; Found: C, 65.22; H, 5.15; N, 11.61.

**2-[{7,11-(4-NN'-dimethylamino)-diphenyl-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,3,5-trione} methylene]-1,5-benzoxazepin-4-(5H)-one (11)**

(Methanol/water) m.p.: 261°C, Yield 75%, IR (KBr) νcm$^{-1}$: 3594 (NH), 1698, 1674, 1663, 1637 (C=O), 1618 (C-C of aromatic ring), 1688 (C=N), 1042 (C-O-C). $^1$H NMR ($DMSOd_6$)δ in ppm: 8.20 (m, 2H, 2×NHCO), 7.81-6.41 (m, 13H, 12H Ar-

H+1HC$_3$H), 9.69 (bs, 1H, NH of oxazepine ring), 4.91 (t, 1H, NH), 4.79 (dd, 2H, 7H & 11H), 4.85 (d, 2H, C$\underline{H}_2$-NH), 3.55 (dd, 2H, 8H$_{AX}$ & 10H$_{AX}$), 2.18 (dd, 2H, 8H$_{eq}$ & 10H$_{eq}$), 1.8 (s, 12H, 2×N(C$\underline{H}_3$)$_2$. Anal. Calcd. for $C_{35}H_{37}N_7O_5$. Calcd: C, 66.14; H, 5.82; N, 15.43; Found: C, 66.30;H, 5.45; N,15.54.

**2-[{7,11-difuronyl-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,3,5-trione} methylene]-1,5-benzoxazepin-4-(5H)-one (12)**

Yield 50% (Petroleum ether) m.p.: 252°C, IR (KBr) νcm$^{-1}$: 3596 (NH), 1710, 1696, 1620, 1600, (C=O), 1621 (C-C of aromatic ring), 1690 (C=N), 1040 (C-O-C). $^1$H NMR (DMSOd$_6$)δ in ppm: 8.35 (m, 2H, 2×N$\underline{H}$CO), 7.82-6.40 (m, 11H, 10H Ar-H+1HC$_3$H), 9.72 (bs, 1H, NH of oxazepine ring), 4.91 (t, 1H, NH), 4.80 (dd, 2H, 7H & 11H, ), 4.89 (d, 2H, C$\underline{H}_2$-NH), 3.60 (dd, 2H, 8H$_{AX}$ & 10H$_{AX,}$), 12.20 (dd, 2H, 8H$_{eq}$ & 10H$_{eq}$). Anal. Calcd. for $C_{27}H_{23}N_5O_7$. Calcd: C, 61.24; H, 4.34; N, 13.23; Found: C, 61.60;H, 4.12; N,13.02.

**2-[{7,11-diphenyl-3-thio-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,5-dione} methylene]-1,5-benzoxazepin-4-(5H)-one (13)**

Yield 48% (Chloroform) m.p.: 220°C. IR (KBr) νcm$^{-1}$: 3600 (NH), 1700, 1765, 1690 (C=O), 1626 (C-C of aromatic ring), 1689 (C=N), 1775 (C-O-C), 1130 (C=S). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.68 (bs, 1H, NH of oxazepine ring), 8.09 (m, 2H, 2×N$\underline{H}$CO), 7.80-6.28 (m, 15H, Ar-H+1HC$_3$H), 4.91 (t, 1H, NH), 4.79 (dd, 2H, 7H & 11H), 4.71 (d, 2H, C$\underline{H}_2$-NH), 3.62 (dd, 2H, 8H$_{AX}$ & 10H$_{AX,}$), 2.19 (dd, 2H, 8H$_{eq}$ & 10H$_{eq}$). Anal. Calcd. for $C_{31}H_{27}N_5O_4S$. Calcd: C, 65.84; H, 4.77; N, 12.38; Found: C, 65.88; H, 4.72; N,12.28.

**2-[{7,11-(4-methoxy)-diphenyl-3-thio-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,5-dione} methylene]-1,5-benzoxazepin-4-(5H)-one (14)**

Yield 80% (Ethanol/water) m.p.: 258°C, IR (KBr) νcm$^{-1}$: 3599 (NH), 1710, 1680, 1610 (C=O), 1620 (C-C of aromatic ring), 1690 (C=N), 1772 (C-O-C), 1133 (C=S). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.71 (bs, 1H, NH of oxazepine ring), 8.80 (m, 2H, 2×N$\underline{H}$CO), 7.81-6.39 (m, 13H, 12H Ar-H+1HC$_3$H), 4.91 (t, 1H, NH), 4.77 (dd, 7H & 11H), 4.84 (d, 2H, C$\underline{H}_2$-NH), 3.56 (dd, 2H, 8H$_{AX}$ & 10H$_{AX,}$), 2.18 (dd, 2H, 8H$_{eq}$ & 10H$_{eq}$), 3.38 (s, 6H, 2×OC$\underline{H}_3$). Anal. Calcd. for $C_{33}H_{31}N_5O_6S$. Calcd: C, 63.36; H, 4.96; N, 11.20; Found: C, 63.84; H, 5.18; N, 11.59.

**2-[{7,11-(4-NN'-dimethylamino)-diphenyl-3-thio-9-aminoimino-2,4-diazaspiro[5,5] undecane-1,5-dione} methylene]-1,5-benzoxazepin-4-(5H)-one (15)**

Yield 78% (Methanol) m.p.: 280°C. IR (KBr) νcm$^{-1}$: 3589 (NH), 1700, 1750, 1690 (C=O), 1628 (C-C of aromatic ring), 1580 (C=N), 1042 (C-O-C), 1133 (C=S). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.74 (bs, 1H, NH of oxazepine ring), 8.41 (m, 2H, 2×N$\underline{H}$CO), 7.82-6.38 (m, 13H, 12H Ar-H+1HC$_3$H), 4.91 (t, 1H, NH), 4.78 (dd, 7H & 11H), 4.81 (d, 2H, C$\underline{H}_2$-NH), 3.57 (dd, 2H, 8H$_{AX}$ & 10H$_{AX,}$), 2.17 (dd, 2H, 8H$_{eq}$ & 10H$_{eq}$), 1.7 (s, 12H, 2×N(CH$_3$)$_2$. Anal. Calcd. for $C_{35}H_{37}N_7O_4S$. Calcd: C, 64.51; H, 5.68; N, 15.05; Found: C, 64.77; H, 5.43; N, 15.03.

**2-[{7,11-difuronyl-3-thio-9-aminoimino-2,4-diazaspiro [5,5] undecane-1,5-dione} methylene]-1,5-benzoxazepin-4-(5H)-one (16)**

Yield 65% (Peteroleum ether) m.p.: 277°C, IR (KBr) νcm$^{-1}$: 3598 (NH), 1708, 1695, 1655 (C=O), 1621 (C-C of aromatic ring), 1589 (C=N), 1039 (C-O-C), 1132 (C=S). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.28-8.10 (s, 2H, 2×N$\underline{H}$CO), 7.83-6.40 (m, 11H, 10H, Ar-H+1HC$_3$H), 9.73 (bs, 1H, NH of oxazepine ring), 4.91 (t, 1H, NH), 4.77 (dd, 2H, 7H & 11H), 4.82 (d, 2H, C$\underline{H}_2$-NH), 3.60 (dd, 2H, 8H$_{AX}$ & 10H$_{AX}$), 2.19 (dd, 2H, 8H$_{eq}$ & 10H$_{eq}$). Anal. Calcd. for $C_{27}H_{23}N_5O_6S$. Calcd: C, 59.44; H, 4.22; N, 12.84; Found: C, 59.40; H, 4.29; N, 12.88.

**2-[{3-amino-2-methyl-quinazolin-4-onyl} methylene]-1,5-benzothiazepin-4-(5H)-one (17)**

Yield 75% (Methanol) m.p.: 175°C. IR (KBr) νcm$^{-1}$: 3588 (NH), 1700, 1795 (C=O), 1624 (C-C of aromatic ring), 1620 (C=N), 1470 (C-N), 750 (C-S-C). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.70 (brs, 1H, NH of thiazepine ring), 8.84 (brs, 1H, NHCH$_2$), 7.70 (m, 9H, 8H, Ar-H+1HC$_3$H), 4.75 (d, 2H, C$\underline{H}_2$-NH), 2.40 (s, 3H, CH$_3$). Anal. Calcd. for $C_{19}H_{16}N_4O_2S$. Calcd: C, 62.63; H, 4.39; N, 15.38. Found: C, 62.45; H, 4.62; N, 15.15.

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**2-[{3-amino-6-bromo-2-methyl-quinazolin-4-onyl} methylene]-1,5-benzothiazepin-4-(5H)-one (18)**

Yield 70% (Acetone) m.p.: 168°C. IR (KBr) νcm$^{-1}$: 3590 (NH), 1710, 1696 (C=O), 1620 (C-C of aromatic ring), 1622 (C=N), 1469 (C-N), 745 (C-S-C). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.73 (bs, 1H, NH of thiazepine ring), 8.72 (brs, 1H, NHCH$_2$), 7.72 (m, 8H, 7H Ar-H+1HC$_3$H), 4.79 (d, 2H, CH$_2$NH), 2.42 (s, 3H, CH$_3$). Anal. Calcd. for $C_{19}H_{15}N_4O_2SBr$. Calcd: C, 51.46; H, 3.38; N, 12.64; Found: C, 51.42;H, 3.56; N, 13.03.

**2-[{3-amino-5,7 dibromo-2-methyl-quinazolin-4-onyl} methylene]-1,5-benzothiazepin-4-(5H)-one (19)**

Yield 68% (Acetic acid) m.p.: 189°C. IR (KBr) νcm$^{-1}$: 3592 (NH), 1711, 1698 (C=O), 1625 (C-C of aromatic ring), 1587 (C=N), 1472 (C=N), 743 (C-S-C). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.70 (bs, 1H, NH of thiazepine ring), 8.80 (brs, 1H, NHCH$_2$), 7.75-6.87 (m, 7H, 6H Ar-H+1HC$_3$H), 4.80 (d, 2H, CH$_2$NH), 2.47 (s, 3H, CH$_3$). Anal. Calcd. for $C_{19}H_{14}N_4O_2SBr_2$. Calcd: C, 43.67; H, 2.68; N, 10.72; Found: C, 45.20; H, 2.82; N, 10.44.

**2-[{3-amino-2-methyl-quinazolin-4-onyl} methylene]-1,5-benzoxazepin-4-(5H)-one (20)**

Yield 55% (Methanol/water) m.p.: 230°C. IR (KBr) νcm$^{-1}$:3580 (NH), 1700, 1690 (C=O), 1624 (C-C of aromatic ring), 1587 (C=N), 1469 (C-N), 1044 (C-O-C). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.72 (brs, 1H, NH of oxazepine ring), 8.70 (brs, 1H, NHCH$_2$), 7.74-6.80 (m, 9H, 8H, Ar-H+1HC$_3$H), 4.77 (d, 2H, CH$_2$NH), 2.41 (s, 3H, CH$_3$). Anal. Calcd. for $C_{19}H_{16}N_4O_3$. Calcd: C, 65.51; H, 4.59; N, 16.09; Found: C, 65.55; H, 4.55; N, 16.21.

**2-[{3-amino-6-bromo-2-methyl-quinazolin-4-onyl} methylene]-1,5-benzoxazepin-4-(5H)-one (21)**

Yield 50%, (Ethanol) m.p.: 260°C. IR (KBr) νcm$^{-1}$: 3582 (NH), 1700, 1695 (C=O), 1622 (C-C of aromatic ring), 1595 (C=N), 1470 (C-N), 1039 (C-O-C). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.71 (brs, 1H, NH of oxazepine ring), 8.75 (brs, 1H, NHCH$_2$), 7.76-6.92 (m, 8H, 7H Ar-H+1HC$_3$H), 4.78 (d, 2H, CH$_2$NH), 2.42 (s, 3H, CH$_3$). Anal. Calcd. for $C_{19}H_{15}N_4O_3Br$. Calcd: C, 53.39; H, 3.51; N, 13.11; Found C, 53.30; H, 3.45; N, 13.10.

**2-[{3-amino-5,7 dibromo-2-methyl-quinazolin-4-onyl} methylene]-1,5-benzoxazepin-4-(5H)-one (22)**

Yield 70% (Petroleum ether) m.p.: 228°C, IR (KBr) νcm$^{-1}$: 3584 (NH), 1702, 1698 (C=O), 1623 (C-C of aromatic ring), 1596 (C=N), 1472 (C-N), 1040 (C-O-C). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.70 (brs, 1H, NH of oxazepine ring), 8.80 (brs, 1H, NHCH$_2$), 7.80-6.90 (m, 7H, 6H Ar-H+1HC$_3$H), 4.79 (d, 2H, CH$_2$NH), 2.43 (s, 3H, CH$_3$). Anal. Calcd. for $C_{19}H_{14}N_4O_3SBr_2$. Calcd: C, 45.05; H, 2.76; N, 11.06; Found: C, 45.15; H, 2.83; N, 11.01.

**2-[(3-oxomethylene-indolyl)-hydrazino-methylene]-1,5-benzothiazepin-4-(5H)-one (23)**

Yield 68% (DMF/water) m.p.: 255°C. IR (KBr) νcm$^{-1}$: 3580, 3365 (NH), 1680, 1692 (C=O), 1620 (C-C of aromatic ring), 1472 (C-N), 1420 (N=N), 745 (C-S-C). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.74 (brs, 1H, NH of thiazepine ring), 8.92 (brs, 1H, NH of indole exchangeable with D$_2$O), 8.85 (brs, 1H, NH), 8.79 (brs, 1H, NH), 7.77-6.80 (m, 10H, 9H, Ar-H+1HC$_3$H), 4.89 (d, 2H, CH$_2$NH), 4.80 (d, 2H, CH$_2$NH). Anal. Calcd. for $C_{20}H_{18}N_4O_2S$. Calcd: C, 63.49; H, 4.76; N, 14.81; Found: C, 63.40; H, 4.64; N, 14.84.

**2-[(3-oxomethylene-indolyl)-hydrazino-methylene]-1,5-benzoxazepin-4-(5H)-one (24)**

Yield 70% (Acetone) m.p.: 248°C. IR (KBr) νcm$^{-1}$:3582 (NH), 1700, 1660 (C=O), 1625 (C-C of aromatic ring), 1473 (C-N), 1038 (C-O-C). $^1$H NMR (DMSOd$_6$)δ in ppm: 9.72 (brs, 1H, NH of oxazepine ring), 8.91 (brs, 1H, NH of indole exchangeable with D$_2$O), 8.78 (brs, 1H, NHCH$_2$), 7.80 6.98 (m, 10H, 9H, Ar-H+1HC$_3$H), 8.86 (brs, 1H, NH), 4.83 (d, 2H, CH$_2$NH), 4.78 (d, 2H, CH$_2$NH). Anal. Calcd. for $C_{20}H_{18}N_4O_3$. Calcd: C, 66.29; H, 4.97; N, 15.46; Found: C, 66.21; H, 4.81; N, 15.43.

**2-[(3-oxomethylene-phenothiazinyl)-hydrazino-methylene]-1,5-benzothiazepin-4-(5H)-one (25)**

Yield 52% (Ethanol) m.p.: 219°C, IR (KBr) νcm$^{-1}$:

3582 (NH), 1700, 1660 (C=O), 1621 (C-C of aromatic ring), 1473 (C-N), 750 (C-S-C). $^1$H NMR ($DMSOd_6$)δ in ppm: 9.73 (brs, 1H, NH of thiazepine ring), 8.80 (brs, 1H, $NHCH_2$), 8.77 (brs, 1H, N<u>H</u>), 7.80.6.84 (m, 13H, 12H, Ar-H+1$HC_3$H), 4.78 (d, 2H, C<u>H</u>$_2$NH), 4.82 (d, 2H, C<u>H</u>$_2$NH). Anal. Calcd. for $C_{24}H_{20}N_4O_2S_2$. Calcd: C, 62.60; H, 4.34; N, 12.61; Found: C, 66.52; H, 4.33; N, 12.12.

**2-[(3-oxomethylene-phenothiazinyl)-hydrazinomethylene]-1,5-benzoxazepin-4(5H)-one (26)**

Yield 50% (Toluene) m.p.: 206°C. IR (KBr) νcm$^{-1}$: 3580 (NH), 1690, 1685 (C=O), 1619 (C-C of aromatic ring), 1470 (C-N), 1040 (C-O-C). $^1$H NMRδ in ppm: 9.70 (bs, 1H, NH of oxazepine ring), 8.87 (brs, 1H, $NHCH_2$), 8.29 (brs, 1H, NH), 7.79 (m, 13H, 12H, Ar-H+1$HC_3$H), 4.77 (d, 2H, C<u>H</u>$_2$NH), 4.70 (d, 2H, C<u>H</u>$_2$NH,). Anal. Calcd. for $C_{24}H_{20}N_4O_3S$. Calcd: C, 64.86; H, 4.50; N, 12.61. Found: C, 64.32; H, 4.62; N, 12.13.

## RESULTS AND DISCUSSION

All the new synthesized compounds 1-26 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 substituted heterocyclic moieties at 2$^{nd}$ position of benzothiaepine and benzoxazepine ring.

### Antipsychotic activity

All the compounds have been evaluated for their antipsychotic activity according to following parameters.

### Amphetamine induced stereotyped behaviour

It was observed that compounds 1-16 (having different substituted oxo/thiobarbituric acid moieties at 2$^{nd}$ position of benzothia/oxazepine ring) showed results (i.e. 0-1.8 scores). The compounds 3, 5, 7, 8, 11 and 15 exhibited good activity (0.2-0.4 score) against amphetamine induced stereotyped behaviour. Furthermore, compounds 17-22 (various substituted quinazolinone ring) showed different results (0.0-1.0 score) against amphetamine induced stereotyped behaviour. Among compounds 17-22, compound 19 (having 5, 7-dibromoquinazolinone moiety) completely antagonized the stereotyped behaviour induced by amphetamine, which prove that it was the most potent antipsychotic agent of this series. Moreover, compounds 23, 24, 25 and 26 showed good response (0.4-0.8 score) against amphetamine induced stereotyped behaviour.

### Cataleptic behaviour

Compounds 5, 8, 12, 15, 16, 21, 22 and 23 significantly antagonized the cataleptic behaviour. However, compound 19 showed the most potent response because this compound did not exhibit any cataleptic behaviour. Moreover, compounds 4, 6, 11, 14, 17, 18, 20 and 25 showed good activity against cataleptic behaviour (0.6-0.8).

### Anticonvulsant activity

It was observed that compounds 1-26 showed varying degree (40-90%) of anticonvulsant activity, but compound 7 (having NN'-dimethylaminophenyl oxobarbituric acid moiety) exhibited 80% anticonvulsant activity which was equipotent to the reference drug phenytoin sodium (30mg/kg i.p.). Furthermore, compound 19 (having 5, 7-dibromoquinazolinone ring) exhibited most potent anticonvulsant response i.e. 90% which was more potent than reference drug phenytoin sodium. Again compounds 1, 3-8, 12, 15, 16, 18, 22, 23 and 25 also showed good (60-70%) anticonvulsant activity. 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 19 which exhibited $ALD_{50}$ of more than 1600mg/kg i.p. (maximum dose tested). As these compounds have shown high value of $ALD_{50}$ thus indicating good safety margin.

### While considering all the newly synthesized compounds of this series we may concluded that

Compounds with benzothiazepine ring elicited more potent result than their benzoxazepine congeners.

The results show that compounds having elicit N-$(CH_3)_2$.$C_6H_4$-moiety (i.e. compound 7) exhibited better activity than the other substituted oxo/thiobarbituric acid derivatives.

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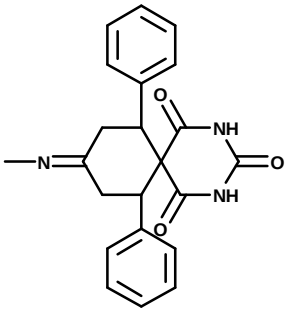
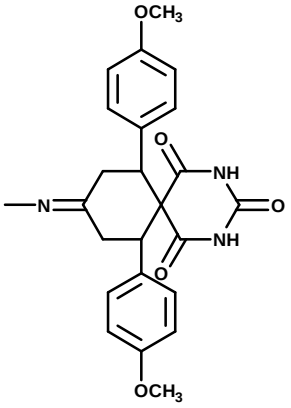
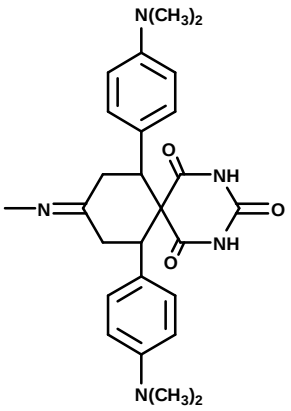
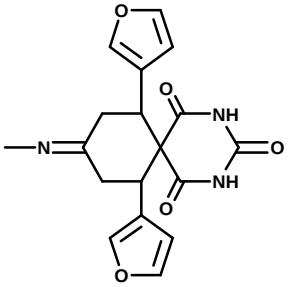
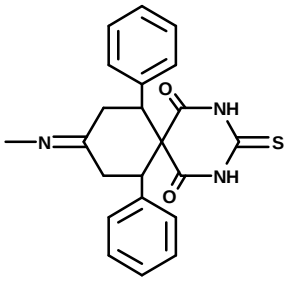
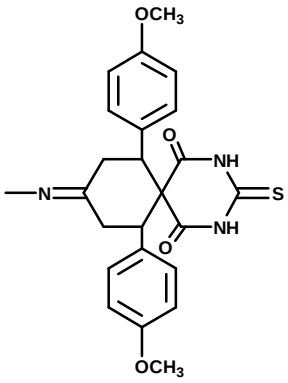
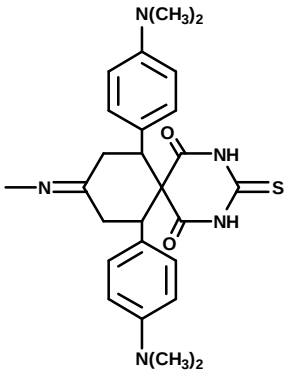
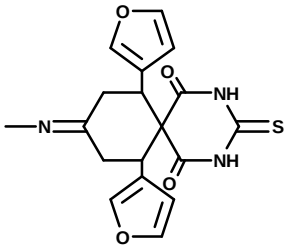
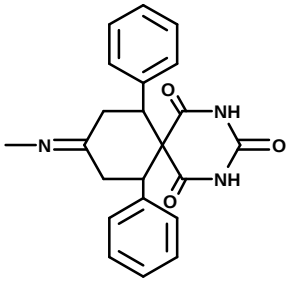
**TABLE 1 : Antipsychotic and anticonvulsant activities of compounds synthesized 1-26**

| Com. No | Dosemg/kg i.p. | R | Amphetamine induced SB (Mean score)[c] | Catalepsy scored[d] | MES % Seizures protection | $ALD_{50}$[f] |
|---|---|---|---|---|---|---|
| P.G.[a] | 0.5ml | - | 0.0 | 3.8 | 0 | |
| CPZ[a] | 4.0 | - | - | 0.0 | - | |
| HPL[b] | 0.5ml | - | 1.8 | - | 0 | |
| P.S.[b] | 30 | - | - | - | 80 | |
| 1. | 40 |  | 1.8 | 1.0 | 60** | >1000 |
| 2. | 40 |  | 1.0 | 1.0 | 50* | >1000 |
| 3. | 40 |  | 0.2 | 1.2 | 70*** | >1000 |
| 4. | 40 |  | 1.8 | 0.8 | 60** | >1000 |

| Com. No | Dosemg/kg i.p. | R | Amphetamine induced SB (Mean score)[c] | Catalepsy scored[d] | MES % Seizures protection | $ALD_{50}$[f] |
|---|---|---|---|---|---|---|
| 5. | 40 |  | 0.2 | 0.4 | 70*** | >1000 |
| 6. | 40 |  | 0.6 | 0.6 | 60** | >1000 |
| 7. | 40 |  | 0.2 | 0.2 | 80*** | >1000 |
| 8. | 40 |  | 0.2 | 0.2 | 70*** | >1000 |
| 9. | 40 |  | 0.8 | 2.0 | 50* | >1000 |

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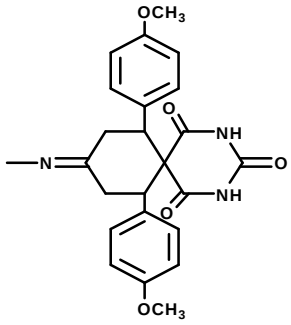
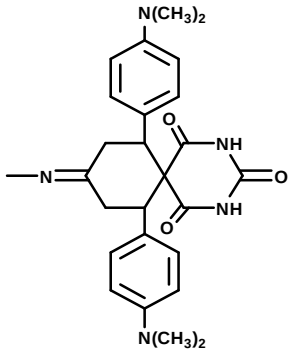
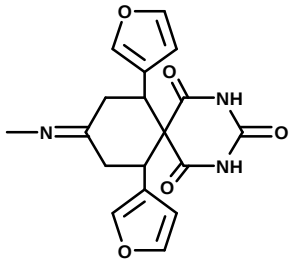
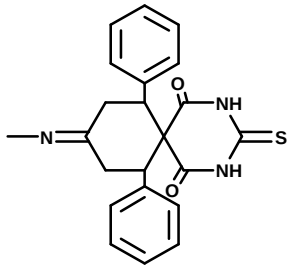
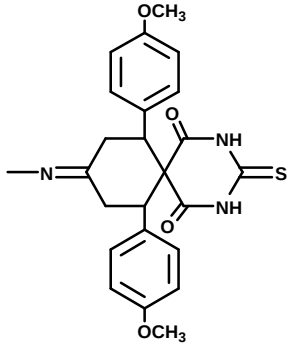
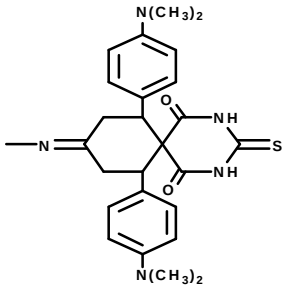
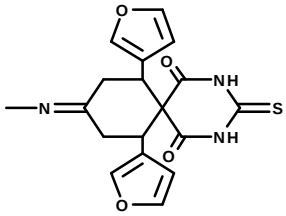
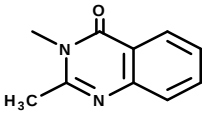
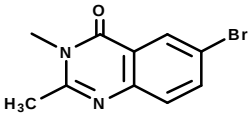
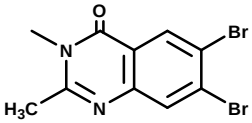
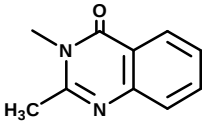
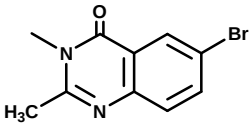
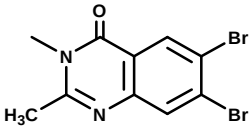
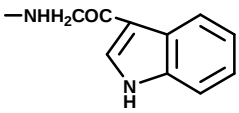
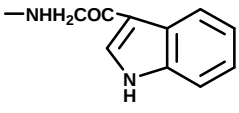
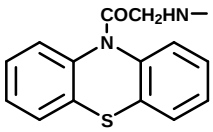
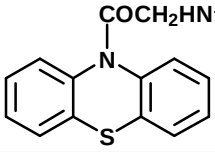
| Com. No | Dosemg/kg i.p. | R | Amphetamine induced SB (Mean score)[c] | Catalepsy scored[d] | MES % Seizures protection | $ALD_{50}$[f] |
|---|---|---|---|---|---|---|
| 10. | 40 |  | 1.8 | 1.8 | 40 | >1000 |
| 11. | 40 |  | 0.2 | 0.8 | 50* | >1000 |
| 12. | 40 |  | 1.0 | 0.4 | 70*** | >1000 |
| 13. | 40 |  | 1.2 | 1.2 | 40 | >1000 |
| 14. | 40 |  | 1.0 | 0.8 | 50* | >1000 |

| Com. No | Dosemg/kg i.p. | R | Amphetamine induced SB (Mean score)[c] | Catalepsy scored[d] | MES % Seizures protection | $ALD_{50}$[f] |
|---|---|---|---|---|---|---|
| 15. | 40 |  | 0.2 | 0.2 | 70*** | >1000 |
| 16. | 40 |  | 0.8 | 0.4 | 60** | >1000 |
| 17. | 40 |  | 0.8 | 0.8 | 50* | >1000 |
| 18. | 40 |  | 0.8 | 0.6 | 70*** | >1000 |
| 19. | 40 |  | 0.0 | 0.0 | 90*** | >1600 |
| 20. | 40 |  | 0.8 | 0.6 | 50* | >1000 |
| 21. | 40 |  | 0.4 | 0.2 | 40 | >1000 |
| 22. | 40 |  | 0.2 | 0.4 | 60** | >1000 |
| 23. | 40 |  | 0.4 | 0.2 | 70*** | >1000 |
| 24. | 40 |  | 0.6 | 1.0 | 50* | >1000 |
| 25. | 40 |  | 0.6 | 0.8 | 70*** | >1000 |

| Com. No | Dosemg/kg i.p. | R | Amphetamine induced SB (Mean score)[c] | Catalepsy scored[d] | MES % Seizures protection | $ALD_{50}$[f] |
|---|---|---|---|---|---|---|
| 26. | 40 |  | 0.8 | 1.0 | 50* | >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]Score of cataleptic behaviour with reference to propylene glycol treated group of rats; Haloperidol (0.5ml i.p.)induced group 1.8 with reference to control group.**

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

**[f]$ALD_{50}$ of the compounds 1-26.**

Substitution with bromine atom at 5 and 7 position of 4 (3H) amino quinazolinone nucleus (i.e. compound 19) exhibited maximum activity than the other compounds this series.

## PHARMACOLOGICAL EVALUATION

### Antipsychotic activity

All the compounds 1-26 have been evaluated for their antipsychotic activity according to following methods.

### (a) Effect on amphetamine induced stereotyped behaviour (SB)

It was done by the method of Castall and Naylor[14]. 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.

### (b) Induction of catalepsy

It was performed according to the method of Castall and Naylor[14]. 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.

### Anticonvulsant activity

Maximum electroshock seizure (MES) test: This activity was performed by method the of Toman et al.[15] 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 40 mg/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[16]. 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

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.

## ACKNOWLEDGEMENTS

Authors are thankful to Head, CDRI, Lucknow for providing analytical and spectral data for the compounds.

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