Arabian Journal of Chemistry (2012) 5, 271–283

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

REVIEW ARTICLE

Synthesis and biological evaluation of some new substituted benzoxazepine and benzothiazepine as antipsychotic as well as anticonvulsant agents

Hemlata Kaur [1], Sunil Kumar, Archana Chaudhary, Ashok Kumar *

Medicinal Chemistry Division, Department of Pharmacology, L.L.R.M. Medical College, Meerut 250004, Uttar Pradesh, India

Received 8 August 2010; accepted 14 September 2010
Available online 23 September 2010

KEYWORDS

Oxa/thiadiazolylbenzoxa/thiazepines;
Azetidinonyl/thiazolidinonylbenzoxa/thiazepines;
Antipsychotic activity;
Anticonvulsant activity;
Acute toxicity

Abstract Various 2-((2-((5-benzylideneamino)-1,3,4-oxa/thiadiazol-2-yl)methyl)hydrazinyl) methyl)-benzo[b][1,4]oxa/thiazepin-4(5H)-ones **(4a–4l)**, 2-((2-((5-(4-oxo-2-substitutedphenyl thiazolidin-3-yl)-1,3,4-oxa/thiadiazol-2-yl)methyl)hydrazinyl)methyl)benzo [b] [1,4]oxa/thiazepin-4(5H)-ones **(5a–5l)** and 2-((2-((5-(3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl)-1,3,4-oxa/thia diazol-2-yl)methyl)hydrazinyl)methyl)benzo[b][1,4]oxa/thiazepin-4(5H)-ones **(6a–6l)** have been synthesized. The structures of these compounds have been established by elemental (C, H, N) and spectral (IR, ^{1}H-NMR and Mass) analysis. The synthesized compounds were screened for their antipsychotic and anticonvulsant activities. Compound **5l** was found to be the most active compound of this series.

Contents

---

* Corresponding author. Tel.: +910121 2764084; Mobile: +91 9917053074; fax: +91 121 2760888.
E-mail address: kashokraj@gmail.com (A. Kumar).

[1] Part of the Ph.D. thesis work.

Peer review under responsibility of King Saud University.
doi:10.1016/j.arabjc.2010.09.011

Production and hosting by Elsevier

---

1. Introduction

Several organic compounds containing a fused seven membered heterocyclic ring, i.e., benzoxazepines and benzothiazepines make up a broad class that attracted attention in the past few years owing to its wide range of biological activities, especially antipsychotic (Bajaj et al., 2004; Kaur et al., 2009), anticonvulsant (Bajaj et al., 2003a; Nagarajan et al., 1985) and neuroleptic (Bajaj et al., 2003b). It is interesting to note from chemical literature that various new pharmacophores like oxadiazole, thiadiazole, azetidinone, and thiazolidinone derivatives were also found to possess wide spectrum of antipsychotic (Kaur et al., 2010; Sabb et al., 2001 Sadashiva et al., 2009) and anticonvulsant (Almasirad et al., 2004; Gupta et al., 2008; Agarwal et al., 2006) activities. In the light of above discussion we report herein the synthesis of new derivatives of benzoxazepine and benzothiazepine by incorporating above mentioned pharmacophores, with the hope to possess better antipsychotic and anticonvulsant activities with lower toxicity.

2. Experimental

2.1. Instrumentation

All reagents and solvents used in study are of analytical grade and procured locally. The progress of the reaction is monitored by TLC and product are purified through recrystallization and purity of the compounds was checked by thin layer chromatography (TLC) performed on silica gel G coated plate of 0.5 mm thickness. The elemental analysis, spectral studies, IR, and ^{1}H NMR were determined by standard methods. Infra red (IR) spectra were recorded in KBr on Perkin–Elmer-spectrum RX-I instrument and ν_{max} was recorded in cm^{-1}. The ^{1}H-NMR spectra were recorded in CDCl$_3$ and DMSO-d$_6$ on Brucker DRX-300 FTNMR instrument.

*2.1.1. General procedure for synthesis of Ethyl-2-((4-oxo-4, 5-dihydrobenzo[b] [1,4] oxa/thiazepin-2-yl)methyl) hydrazinocarboxylate **(1a–1b)***

To a solution of 2-Hydrazinomethyl-1,5-benzoxa/thiazepin-4(5H)-ones (2.0 mole) in dry acetone (100 mL), ethylchloro acetate (2.0 mole) was added dropwise in the presence of anhydrous K$_2$CO$_3$ (8 g) in the mixture with stirring. The resulting mixture was refluxed on a water-bath for about 13 h. The solid thus obtained was filtered, dried and recrystallized from appropriate solvents to obtain compounds **1a–1b.**

*2.1.1.1. Ethyl-2-((4-oxo-4,5-dihydrobenzo[b][1,4]oxazepin-2-yl)methyl)hydrazine carboxylate **(1a)***

Yield 82% (Methanol); m.p. 226 °C. IR ν_{max} (KBr, cm^{-1}): 3340 (NH), 1672 (C=O), 1611 (C$\overset{\cdots}{-}$C of aromatic ring), 1304 (C–N), 1040 (C–O–C). ^{1}H-NMR (300 MHz, δH, CDCl$_3$) in ppm**:** 2.30 (t, 3H, CH$_2$*CH$_3$*), 3.40 (d, 2H, *CH$_2$*), 3.60 (d, 2H, *CH$_2$CO*), 4.28 (q, 2H, *CH$_2$*CH$_3$), 8.30 (s, 2H, 2× *NH* exchangeable with D$_2$O), 6.80–7.61 (m, 5H, 4H*, Ar–H* + *1H, CH* of oxazepine ring), 9.71 (ss, 1H, *NH* of oxazepine ring) ppm; MS: [M]$^+$ at *m/z* 291.12. Anal. Calcd. for C$_{14}$H$_{17}$N$_3$O$_4$: C, 57.72; H, 5.88; N, 14.42; Found: C, 57.77; H, 4.95; N, 14.40%.

*2.1.1.2. Ethyl-2-((4-oxo-4,5-dihydrobenzo[b][1,4]thiazepin-2-yl)methyl)hydrazine carboxylate **(1b)***

Yield 75% (Ethanol); m.p. 222 °C. IR ν_{max} (KBr, cm^{-1}): 3342 (NH), 1670 (C=O), 1614 (C$\overset{\cdots}{-}$C of aromatic ring), 1304 (C–

N), 690 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$)**:** 2.32 (t, 3H, $\mathrm{CH_2}CH_3$), 3.39 (d, 2H, CH_2), 3.62 (d, 2H, CH_2CO), 4.22 (q, 2H, $CH_2\mathrm{CH_3}$), 8.31 (s, 2H, 2× *NH* exchangeable with D_2O), 6.82–7.71 (m, 5H, 4H, *Ar–H + 1H, CH* of thiazepine ring), 9.70 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 307.37. Anal. Calcd. for $C_{14}H_{17}N_3O_3S$: C, 54.71; H, 5.57; N, 13.66; Found: C, 54.70; H, 4.96; N, 13.70%.

*2.1.2. General procedure for synthesis of 2-(2-(2-(4-oxo-4,5-dihydro benzo[b][1,4]oxa/thiazepin-2-yl)methyl)hydrazinyl) acetyl)hydrazinyl carboxamide **(2a–2d)***

A mixture of compounds **1a–1b** (1.0 mole) and semi/thiosemicarbazide (1.0 mole) in 1, 4 dioxan (100 mL) were refluxed on a water-bath for about 8 h. The excess solvent was removed under reduced pressure and the product recrystallized from suitable solvents to give compound **2a/2d**.

*2.1.2.1. 2-(2-(2-(4-oxo-4,5-dihydrobenzo[b][1,4]oxazepin-2-yl)methyl)hydrazinyl) acetyl) hydrazinyl carboxamide **(2a)***

Yield 72% (Ethanol); m.p. 238 °C. IR ν_{max} (KBr, cm^{-1}): 3341 (NH), 1673 (C=O), 1615 (C$\overset{\cdots}{-}$C of aromatic ring), 1302 (C–N), 1038 (C–O–C). ^{1}H-NMR (300 MHz, δH, DMSO-d$_6$): 3.28 (d, 2H, CH_2), 3.40 (d, 2H, CH_2CO), 8.35 (s, 2H, 2× *NH* exchangeable with D_2O), 8.40 (m, 4H, *NHNH*CO*NH*$_2$), 6.82–7.80 (m, 5H, 4H, *Ar–H* + 1H, *CH* of oxazepine ring), 9.72 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 320.30. Anal. Calcd. for $C_{13}H_{16}N_6O_4$: C, 48.75; H, 5.03; N, 26.24; Found: C, 48.78; H, 5.02; N, 26.20%.

*2.1.2.2. 2-(2-(2-(4-oxo-4,5-dihydrobenzo[b][1,4]oxazepin-2-yl)methyl)hydrazinyl) acetyl) hydrazinyl carbothioamide **(2b)***

Yield 77% (Ethanol); m.p. 230 °C. IR ν_{max} (KBr, cm^{-1}): 3344 (NH), 1130 (C=S), 1671 (C=O), 1613 (C$\overset{\cdots}{-}$C of aromatic ring), 1305 (C–N), 1292 (N–N), 1041 (C–O–C). ^{1}H-NMR (300 MHz, δH, DMSO-d$_6$): 3.24 (d, 2H, CH_2CO), 3.38 (d, 2H, CH_2), 8.35 (s, 2H, 2× *NH* exchangeable with D_2O), 8.42 (m, 4H, *NHNH*CS*NH*$_2$), 6.77–7.79 (m, 5H, 4H, *Ar–H* + 1H, *CH* of oxazepine ring), 9.72 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 336.37. Anal. Calcd. for $C_{13}H_{16}N_6O_3S$: C, 46.42; H, 4.79; N, 24.98; Found: C, 46.40; H, 4.80; N, 24.90%.

*2.1.2.3. 2-(2-(2-(4-oxo-4,5-dihydrobenzo[b][1,4]thiazepin-2-yl)methyl)hydrazinyl) acetyl) hydrazinyl carboxamide **(2c)***

Yield 69% (DMF-Water); m.p. 236 °C. IR ν_{max} (KBr, cm^{-1}): 3344 (NH), 1671 (C=O), 1613 (C$\overset{\cdots}{-}$C of aromatic ring), 1305 (C–N), 1292 (N–N), 695 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.26 (d, 2H, CH_2), 3.42 (d, 2H, CH_2CO), 8.33 (s, 2H, 2× *NH* exchangeable with D_2O), 8.45 (m, 4H, *NHNH*CO*NH*$_2$), 6.77–7.79 (m, 5H, 4H, *Ar–H* + 1H, *CH* of thiazepine ring), 9.72 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 336.37. Anal. Calcd. for $C_{13}H_{16}N_6O_3S$: C, 46.42; H, 4.79; N, 24.98; Found: C, 46.41; H, 4.81; N, 24.94%.

*2.1.2.4. 2-(2-(2-(4-oxo-4,5-dihydrobenzo[b][1,4]thiazepin-2-yl)methyl)hydrazinyl) acetyl) hydrazinyl carbothioamide **(2d)***

Yield 68% (Acetone); m.p. 240 °C. IR ν_{max} (KBr, cm^{-1}): 3346 (NH), 1031 (C=S), 1680 (C=O), 1613 (C$\overset{\cdots}{-}$C of aromatic ring), 1305 (C–N), 1292 (N–N), 694 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.26 (d, 2H, CH_2), 3.39 (d, 2H, CH_2CO), 8.37 (s, 2H, 2× *NH* exchangeable with D_2O), 8.44 (m, 4H, *NHNH*CS*NH*$_2$), 6.79–7.85 (m, 5H, 4H, *Ar–H* + 1H, *CH* of thiazepine ring), 9.70 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 352.44. Anal. Calcd. for $C_{13}H_{16}N_6O_2S_2$: C, 44.30; H, 4.58; N, 23.85; Found: C, 44.28; H, 4.55; N, 23.86%.

*2.1.3. General procedure for synthesis of 2-((2-((5-Amino-1,3,4-oxa/thiadiazolyl) methyl)hydrazinyl)methyl] benzo[b][1,4]oxa/thiazepin-4(5H)-ones **(3a–3d)***

A solution of compounds **2a–2d** (0.6 mole) with conc. H_2SO_4 (30 mL) 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 furnish compounds **3a–3d**.

*2.1.3.1. 2-((2-((5-Amino-1,3,4-oxadiazolyl)methyl)hydrazinyl)methyl]benzo[b][1,4] oxazepin-4(5H)-one **(3a)***

Yield 70% (Petroleum ether); m.p. 250 °C. IR ν_{max} (KBr, cm^{-1}): 3346 (NH), 1672 (C=O), 1614 (C$\overset{\cdots}{-}$C of aromatic ring), 1580 (C=N), 1294 (N–N), 1040 (C–O–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.22 (d, 4H, 2× CH_2), 4.45 (s, 2H, C–NH_2), 8.37 (s, 2H, 2× *NH* exchangeable with D_2O), 6.97–7.88 (m, 5H, 4H, *Ar–H* + 1H, *CH* of oxazepine ring), 9.70 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 304.29. Anal. Calcd. for $C_{13}H_{14}N_6O_3$: C, 51.65; H, 4.67; N, 27.88; Found: C, 51.55; H, 4.69; N, 27.87%.

*2.1.3.2. 2-((2-((5-Amino-1,3,4-thiadiazolyl)methyl)hydrazinyl)methyl]benzo[b][1,4] oxazepin-4(5H)-one **(3b)***

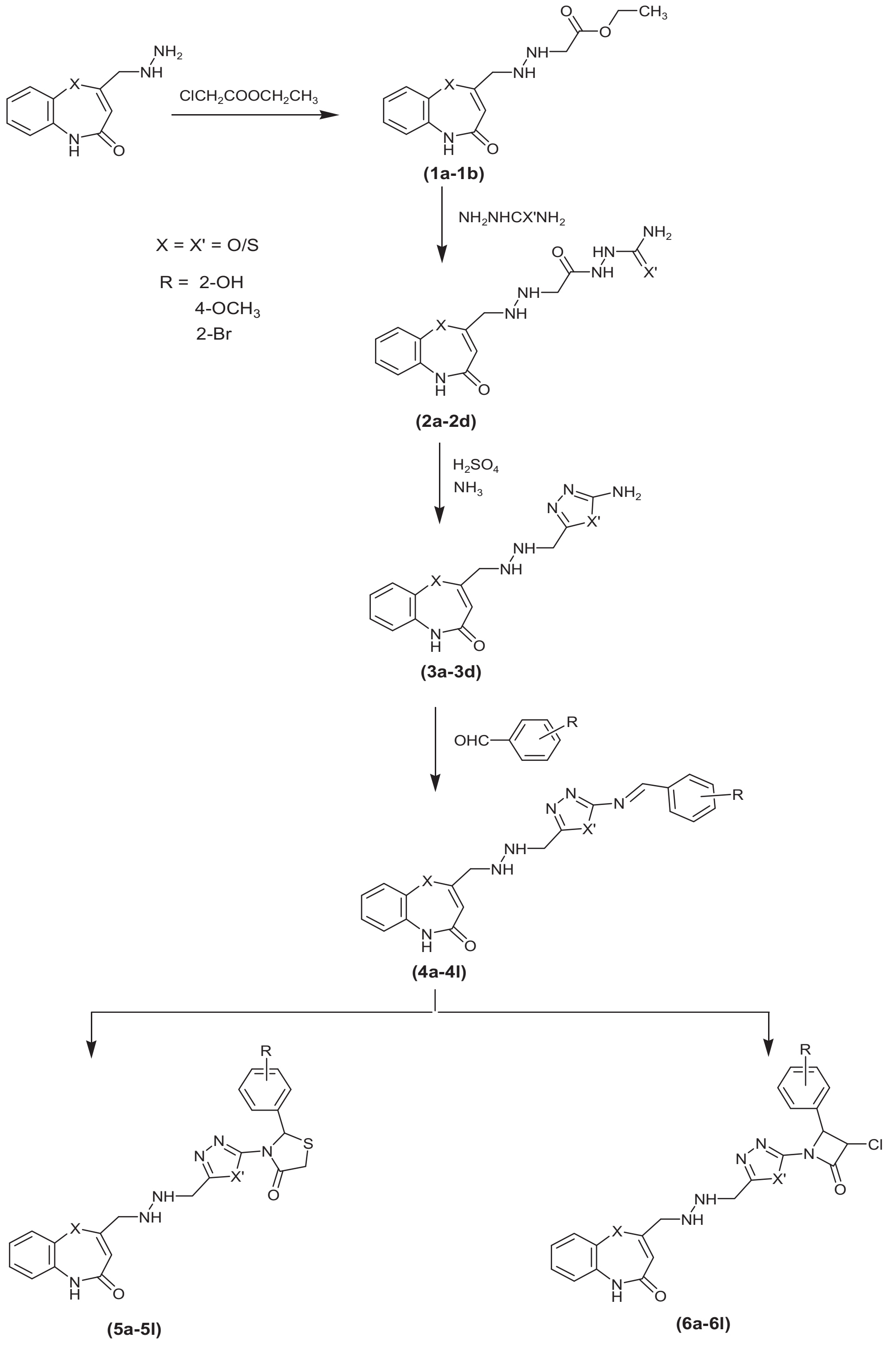
Yield 69% (Methanol); m.p. 255 °C. IR ν_{max} (KBr, cm^{-1}): 3344 (NH), 1680 (C=O), 1616 (C$\overset{\cdots}{-}$C of aromatic ring), 1584 (C=N), 1293 (N–N), 1038 (C–O–C), 692 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.25 (d, 4H, 2× CH_2), 4.43 (s, 2H, C–NH_2), 8.33 (s, 2H, 2× *NH* exchangeable with D_2O), 6.98–7.83 (m, 5H, 4H, *Ar–H* + 1H, *CH* of oxazepine ring), 9.72 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 318.35. Anal. Calcd. for $C_{13}H_{14}N_6O_2S$: C, 49.05; H, 4.43; N, 26.40; Found: C, 49.01; H, 4.40; N, 26.39%.

*2.1.3.3. 2-((2-((5-Amino-1,3,4-oxadiazolyl)methyl)hydrazinyl)methyl]benzo[b][1,4] thiazepin-4(5H)-one **(3c)***

Yield 75% (Ethanol); m.p. 257 °C. IR ν_{max} (KBr, cm^{-1}): 3341 (NH), 1679 (C=O), 1612 (C$\overset{\cdots}{-}$C of aromatic ring), 1582 (C=N), 1295 (N–N), 1037 (C–O–C), 696 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.22 (d, 4H, 2× CH_2), 4.45 (s, 2H, C–NH_2), 8.34 (s, 2H, 2× *NH* exchangeable with D_2O), 6.97–7.88 (m, 5H, 4H, *Ar–H* + 1H, *CH* of thiazepine ring), 9.70 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 318.35. Anal. Calcd. for $C_{13}H_{14}N_6O_2S$: C, 49.05; H, 4.43; N, 26.40; Found: C, 49.06; H, 4.43; N, 26.43%.

*2.1.3.4. 2-((2-((5-Amino-1,3,4-thiadiazolyl)methyl)hydrazinyl)methyl]benzo[b][1,4] thiazepin-4(5H)-one **(3d)***

Yield 76% (Methanol); m.p. 251 °C. IR ν_{max} (KBr, cm^{-1}): 3343 (NH), 1681 (C=O), 1617 (C$\overset{\cdots}{-}$C of aromatic ring), 1580 (C=N), 1290 (N–N), 692 (C–S–C). ^{1}H-NMR (300 MHz, δH, DMSOd$_6$): 3.25 (d, 4H, 2× CH_2), 4.41 (s, 2H, C–NH_2), 8.39 (s, 2H, 2× *NH* exchangeable with D_2O), 6.89–7.81 (m, 5H, 4H, *Ar–H* + 1H, *CH* of thiazepine ring), 9.71 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z*



Scheme 1

334.42. Anal Calcd. for $C_{13}H_{14}N_6OS_2$: C, 46.69; H, 4.22; N, 25.13; Found: C, 46.70; H, 4.20; N, 25.15%.

*2.1.4. General procedure for synthesis of 2-((2-((5-benzylideneamino)-1,3,4-oxa/thiadiazol-2-yl)methyl) hydrazinyl)methyl)benzo[b][1,4]oxa/thiazepin-4(5H)-ones **(4a–4l)***

2-((2-((5-Amino-1,3,4-oxa/thiadiazolyl)methyl)hydrazinyl) methyl)benzo[b][1,4]oxa/thiazepin-4(5H)-one **3a–3d** (0.2 mole), various substituted aromatic aldehydes (0.2 mole) and glacial acetic acid (5 mL) were refluxed in methanol (100 mL) for about 6 h. The solid mass thus obtained was recrystallized from appropriate solvents to obtain compounds **4a–4l**.

*2.1.4.1. 2-(2-(5-(2-hydroxybenzylideneamino)-1,3,4-oxadiazol-2-yl)methyl)hydrazinyl) methyl) benzo[b] [1,4]oxazepin-4(5H)-one **(4a)***

Yield 75% (Acetone); m.p. 275 °C. IR ν_{max} (KBr, cm^{-1}): 3435 (OH), 3350 (NH), 1690 (C=O), 1619 (C⋯C of aromatic ring), 1589 (C=N), 1570 (N=CH), 1295 (N–N), 1039 (C–O–C). ^{1}H-

NMR (300 MHz, δH, $CDCl_3$): 3.42 (d, 4H, 2× *CH_2*), 5.90 (s, 1H, N=*CH–Ar*), 6.64–7.70 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.80 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, *NH* of oxazepine ring), 11.20 (s, 1H, *OH*) ppm; MS: $[M]^+$ at *m/z* 406.39. Anal. Calcd. for $C_{20}H_{18}N_6O_4$: C, 59.11; H, 4.46; N, 20.68; Found: C, 59.13; H, 4.43; N, 20.65%.

2.1.4.2. 2-(2-(5-(4-methoxybenzylideneamino)-1,3,4-oxadiazol-2-yl)methyl)hydra zinyl) methyl)benzo[b] [1,4]oxazepin-4(5H)-one ***(4b)***

Yield 77% (DMF-Water); m.p. 270 °C. IR ν_{max} (KBr, cm^{-1}): 3348 (NH), 1688 (C=O), 1618 (C⋯C of aromatic ring), 1590 (C=N), 1572 (N=CH), 1291 (N–N), 1041 (C–O–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.36 (d, 4H, 2× *CH_2*), 3.52 (s, 3H, *OCH_3*), 5.92 (s, 1H, N=*CH–Ar*), 6.61–7.76 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.81 (s, 2H, 2× *NH* exchangeable with D_2O), 9.71 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 420.42. Anal. Calcd. for $C_{21}H_{20}N_6O_4$: C, 59.99; H, 4.79; N, 19.99; Found: C, 60.00; H, 4.80; N, 20.00%.

2.1.4.3. 2-(2-(5-(2-bromobenzylideneamino)-1,3,4-oxadiazol-2-yl)methyl)hydrazinyl) methyl) benzo[b] [1,4]oxazepin-4(5H)-one ***(4c)***

Yield 72% (Methanol); m.p. 272 °C. IR ν_{max} (KBr, cm^{-1}): 3351 (NH), 1690 (C=O), 1615 (C⋯C of aromatic ring), 1591 C=N), 1573 (N=CH), 1293 (N–N), 1040 (C–O–C), 614 (C–Br). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.38 (d, 4H, 2× *CH_2*), 5.90 (s, 1H, N=*CH–Ar*), 6.69–7.78 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.85 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 469.29. Anal. Calcd. for $C_{20}H_{17}BrN_6O_4$: C, 51.19; H, 3.65; N, 17.91; Found: C, 51.17; H, 3.63; N, 17.90%.

2.1.4.4. 2-(2-(5-(2-hydroxybenzylideneamino)-1,3,4-thiadiazol-2-yl)methyl)hydra-zinyl) methyl) benzo[b] [1,4]oxazepin-4(5H)-one ***(4d)***

Yield 78% (Ethanol); m.p. 278 °C. IR ν_{max} (KBr, cm^{-1}): 3438 (OH), 3350 (NH), 1693 (C=O), 1617 (C⋯C of aromatic ring), 1595 (C=N), 1572 (N=CH), 1294 (N–N), 1042 (C–O–C), 689 (C–S–C). ^{1}H-NMR (300, δH, $CDCl_3$): 3.36 (d, 4H, 2× *CH_2*), 5.88 (s, 1H, N=*CH–Ar*), 6.70–7.79 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.82 (s, 2H, 2× *NH* exchangeable with D_2O), 9.72 (ss, 1H, *NH* of oxazepine ring), 11.18 (s, 1H, *OH*) ppm; MS: $[M]^+$ at *m/z* 422.46. Anal. Calcd. for $C_{20}H_{18}N_6O_3S$: C, 56.80; H, 4.29; N, 19.89; Found: C, 56.87; H, 4.30; N, 19.90%.

2.1.4.5. 2-(2-(5-(4-methoxybenzylideneamino)-1,3,4-thiadiazol-2-yl)methyl)hydra zinyl) methyl) benzo[b] [1,4]oxazepin-4(5H)-one ***(4e)***

Yield 79% (DMF-Water); m.p. 271 °C. IR ν_{max} (KBr, cm^{-1}): 3345 (NH), 1693 (C=O), 1620 (C⋯C of aromatic ring), 1594 (C=N), 1574 (N=CH), 1296 (N–N), 1040 (C–O–C), 698 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.39 (d, 4H, 2× *CH_2*), 3.45 (s, 3H, *OCH_3*), 5.91 (s, 1H, N=*CH–Ar*), 6.74-7.70 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.85 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 436.49. Anal. Calcd. for $C_{21}H_{20}N_6O_3S$: C, 57.79; H, 4.62; N, 19.25; Found: C, 57.80; H, 4.61; N, 19.24%.

2.1.4.6. 2-((2-((5-(2-bromobenzylideneamino)-1,3,4-thidiazol-2-yl)methyl)hydrazinyl) methyl) benzo[b] [1,4]oxazepin-4(5H)-one ***(4f)***

Yield 74% (Methanol); m.p. 274 °C. IR ν_{max} (KBr, cm^{-1}): 3345 (NH), 1695 (C=O), 1623 (C⋯C of aromatic ring), 1592 (C=N), 1576 (N=CH), 1293 (N–N), 1041 (C–O–C), 698 (C–S–C), 611 (C–Br). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.43 (d, 4H, 2× *CH_2*), 5.87 (s, 1H, N=*CH–Ar*), 6.79–7.88 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.86 (s, 2H, 2× *NH* exchangeable with D_2O), 9.72 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 485.36. Anal. Calcd. for $C_{20}H_{17}BrN_6O_2S$: C, 49.49; H, 3.53; N, 17.32; Found: C, 49.50; H, 3.57; N,17.30%.

2.1.4.7. 2-((2-((5-(2-hydroxybenzylideneamino)-1,3,4-oxadiazol-2-yl)methyl)hydra zinyl) methyl) benzo[b][1,4]thiazepin-4(5H)-one ***(4g)***

Yield 76% (Acetone); m.p. 272 °C. IR ν_{max} (KBr, cm^{-1}): 3450 (OH), 3351 (NH), 1689 (C=O), 1620 (C⋯C of aromatic ring), 1594 (C=N), 1578 (N=CH), 1290 (N–N), 1040 (C–O–C), 698 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.42 (d, 4H, 2× *CH_2*), 5.82 (s, 1H, N=*CH–Ar*), 6.75–7.74 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.80 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, *NH* of thiazepine ring), 11.22 (s, 1H, *OH*) ppm; MS: $[M]^+$ at *m/z* 422.46. Anal. Calcd. for $C_{20}H_{18}N_6O_3S$: C, 56.86; H, 4.29; N, 18.89; Found: C, 56.84; H, 4.30; N, 18.88%.

2.1.4.8. 2-((2-((5-(4-methoxybenzylideneamino)-1,3,4-oxadiazol-2-yl)methyl)hydrazi- nyl) methyl)benzo [b][1,4]thiazepin-4(5H)-one ***(4h)***

Yield 72% (Petroleum ether); m.p. 270 °C. IR ν_{max} (KBr, cm^{-1}): 3351 (NH), 1692 (C=O), 1621 (C⋯C of aromatic ring), 1588 (C=N), 1579 (N=CH), 1292 (N–N), 1043 (C–O–C), 697 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.38 (d, 4H, 2× *CH_2*), 3.43 (s, 3H, *OCH_3*), 5.91 (s, 1H, N=*CH–Ar*), 6.75–7.72 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.83 (s, 2H, 2× *NH* exchangeable with D_2O), 9.72 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 436.49. Anal. Calcd. for $C_{21}H_{20}N_6O_3S$: C, 57.79; H, 4.62; N, 19.25; Found: C, 57.80; H, 4.64; N, 19.26%.

2.1.4.9. 2-((2-((5-(2-bromobenzylideneamino)-1,3,4-oxadiazol-2-yl)methyl)hydrazinyl)methyl) benzo [b] [1,4]thiazepin-4(5H)-one ***(4i)***

Yield 78% (Ethanol); m.p. 278 °C. IR ν_{max} (KBr, cm^{-1}): 3354 (NH), 1687 (C=O), 1624 (C⋯C of aromatic ring), 1594 (C=N), 1580 (N=CH), 1294 (N–N), 1042 (C–O–C), 685 (C–S–C), 611 (C–Br). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.46 (d, 4H, 2× *CH_2*), 5.80 (s, 1H, N=*CH–Ar*), 6.74–7.73 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.82 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 485.36. Anal. Calcd. for $C_{20}H_{17}N_6O_2S$: C, 49.40; H, 3.53; N, 17.32; Found: C, 49.38; H, 3.55; N, 17.33%.

2.1.4.10. 2-((2-((5-(2-hydroxybenzylideneamino)-1,3,4-thiadiazol-2-yl)methyl)hydrazi nyl) methyl)benzo [b][1,4]thiazepin-4(5H)-one ***(4j)***

Yield 75% (Methanol); m.p. 277 °C. IR ν_{max} (KBr, cm^{-1}): 3452 (OH), 3344 (NH), 1686 (C=O), 1620 (C⋯C of aromatic ring), 1590 (C=N), 1575 (N=CH), 1293 (N–N), 682 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.40 (d, 4H, 2× *CH_2*), 5.87

(s, 1H, N=*CH–Ar*), 6.70–7.69 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.81 (s, 2H, 2× *NH* exchangeable with D_2O), 9.72 (ss, 1H, *NH* of thiazepine ring), 11.20 (s, 1H, *OH*) ppm; MS: $[M]^+$ at *m/z* 438.53. Anal. Calcd. for $C_{20}H_{18}N_6O_2S_2$: C, 54.78; H, 4.14; N, 19.16; Found: C, 54.76; H, 4.12; N, 19.18%.

*2.1.4.11. 2-((2-((5-(4-methoxybenzylideneamino)-1,3,4-thiadiazol-2-yl)methyl)hydra-zinyl) methyl)benzo [b][1,4]thiazepin-4(5H)-one **(4k)***

Yield 76% (DMF-Water); m.p. 269 °C. IR ν_{max} (KBr, cm^{-1}): 3342 (NH), 1685 (C=O), 1624 (C⋯C of aromatic ring), 1593 (C=N), 1572 (N=CH), 1291 (N–N), 697 (C–S–C). ^{1}H-NMR (300 MHz, δH, DMSOd$_6$): 3.42 (d, 4H, 2× CH_2), 3.48 (s, 3H, OCH_3), 5.90 (s, 1H, N=*CH–Ar*), 6.64–7.70 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.80 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 452.55. Anal. Calcd. for $C_{21}H_{20}N_6O_2S_2$: C, 55.73; H, 4.45; N, 18.57; Found: C, 55.77; H, 4.44; N, 18.54%.

*2.1.4.12. 2-((2-((5-(2-bromobenzylideneamino)-1,3,4-thiadiazol-2-yl)methyl)hydrazinylmethyl)benzo [b][1,4]thiazepin-4(5H)-ones **(4l)***

Yield 73% (Petroleum ether); m.p. 270 °C. IR ν_{max} (KBr, cm^{-1}): 3340 (NH), 1684 (C=O), 1624 (C⋯C of aromatic ring), 1591 (C=N), 1571 (N=CH), 1292 (N–N), 684 (C–S–C), 614 (C–Br). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.43 (d, 4H, 2× CH_2), 5.87 (s, 1H, N=*CH–Ar*), 6.64–7.76 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.86 (s, 2H, 2× *NH* exchangeable with D_2O), 9.73 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 501.42. Anal. Calcd. for $C_{20}H_{17}BrN_6OS_2$: C, 47.91; H, 3.42; N, 16.76; Found: C, 47.87; H, 3.40; N, 16.80%

*2.1.5. General procedure for synthesis of 2-((2-((5-(4-oxo-2-substituted phenylthiazolidin-3-yl)-1,3,4-oxa/thiadiazol-2-yl) methyl)hydrazinyl)methyl)benzo[b][1,4]oxa/thiazepin-4(5H)-ones **(5a–5l)***

To a solution of compounds **4a–4l** (0.05 mole) and thioglycolic acid (0.05 mole) in methanol (100 mL) $ZnCl_2$ (a pinch) was added and the reaction mixture was kept for 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–5l**.

*2.1.5.1. 2-((2-((5-(4-oxo-2-(2-hydroxyphenyl)thiazolidin-3-yl)-1,3,4-oxadiazol-2-yl) methyl)hydrazinyl)methyl)benzo[b] [1,4]oxazepin-4(5H)-one **(5a)***

Yield 70% (Methanol); m.p. 297 °C. IR ν_{max} (KBr, cm^{-1}): 3448 (OH), 3342 (NH), 1710 (C=O), 1680 (C=O), 1623 (C⋯C of aromatic ring), 1606 (C=N), 1290 (N–N), 1035 (C–O–C). ^{1}H-NMR (300 MHz, δH, DMSO-d$_6$): 3.40 (d, 4H, 2× CH_2), 3.85 (s, 2H, CH_2 of thiazolidinone ring), 5.90 (s, 1H, *CH–Ar*), 6.90–8.01 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.40 (s, 2H, 2× *NH* exchangeable with D_2O), 9.71 (ss, 1H, *NH* of oxazepine ring), 11.19 (s, 1H, *OH*) ppm; MS: $[M]^+$ at *m/z* 480.40. Anal. Calcd. for $C_{22}H_{20}N_6O_5S$: C, 54.99; H, 4.20; N, 17.49; Found: C, 54.94; H, 4.25; N, 17.50%.

*2.1.5.2. 2-((2-((5-(4-oxo-2-(4-methoxyphenyl)thiazolidin-3-yl)-1,3,4-oxadiazol-2-yl)methyl) hydrazinyl) methyl)benzo[b] [1,4]oxazepin-4(5H)-one **(5b)***

Yield 73% (Ethanol); m.p. 298 °C. IR ν_{max} (KBr, cm^{-1}): 3340 (NH), 1724 (C=O), 1689 (C=O), 1625 (C⋯C of aromatic ring), 1604 (C=N), 1293 (N–N), 1226 (OCH_3), 1037 (C–O–C). ^{1}H-NMR (300 MHz, δH, DMSOd$_6$): 3.41 (d, 4H, 2× CH_2), 3.50 (s, 3H, OCH_3), 3.86 (s, 2H, CH_2 of thiazolidinone ring), 5.93 (s, 1H, *CH–Ar*), 6.98–8.00 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.43 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 494.52. Anal. Calcd. for $C_{23}H_{22}N_6O_5S$: C, 55.86; H, 4.48; N, 16.99; Found: C, 55.87; H, 4.50; N, 17.00%.

*2.1.5.3. 2-((2-((5-(4-oxo-2(2-bromophenyl)thiazolidin-3-yl)-1,3,4-oxadiazol-2-yl) methyl) hydrazinyl) methyl) benzo[b] [1,4]oxazepin-4(5H)-one **(5c)***

Yield 76% (Methanol); m.p. 295 °C. IR ν_{max} (KBr, cm^{-1}): 3342 (NH), 1700 (C=O), 1683 (C=O), 1624 (C⋯C of aromatic ring), 1603 (C=N), 1292 (N–N), 1040 (C–O–C), 615 (C–Br). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.42 (d, 4H, 2× CH_2), 3.87 (s, 2H, CH_2 of thiazolidinone ring), 5.92 (s, 1H, *CH–Ar*), 6.99–7.96 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.43 (s, 2H, 2× *NH* exchangeable with D_2O), 9.71 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 543.39. Anal. Calcd. for $C_{22}H_{19}BrN_6O_4S$: C, 48.63; H, 3.52; N, 15.47; Found: C, 48.60; H, 3.57; N, 15.49%.

*2.1.5.4. 2-((2-((5-(4-oxo-2-phenyl(2-hydroxyphenyl)thiazolidin-3-yl)-1,3,4-thiadia- zol-2-yl)methyl) hydrazinyl)methyl) benzo[b][1,4]oxazepin-4(5H)-one **(5d)***

Yield 78% (Acetone); m.p. 299 °C. IR ν_{max} (KBr, cm^{-1}): 3448 (OH), 3342 (NH), 1705 (C=O), 1686 (C=O), 1623 (C⋯C of aromatic ring), 1606 (C=N), 1290 (N–N), 1041 (C–O–C), 688 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.44 (d, 4H, 2× CH_2), 3.85 (s, 2H, CH_2 of thiazolidinone ring), 5.90 (s, 1H, *CH–Ar*), 6.90–8.01 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.41 (s, 2H, 2× *NH* exchangeable with D_2O), 9.72 (ss, 1H, *NH* of oxazepine ring), 11.17 (s, 1H, *OH*) ppm; MS: $[M]^+$ at *m/z* 496.56. Anal. Calcd. for $C_{22}H_{20}N_6O_4S_2$: C, 53.21; H, 4.06; N, 16.92; Found: C, 53.22; H, 4.00; N, 16.90%.

*2.1.5.5. 2-((2-((5-(4-oxo-2(4-methoxyphenyl)thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl)methyl)hydrazinyl) methyl)benzo[b] [1,4]oxazepin-4(5H)-one **(5e)***

Yield 74% (Methanol); m.p. 287 °C. IR ν_{max} (KBr, cm^{-1}): 3345 (NH), 1714 (C=O), 1684 (C=O), 1627 (C⋯C of aromatic ring), 1602 (C=N), 1294 (N–N), 1227 (OCH_3), 1042 (C–O–C), 691 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.40 (d, 4H, 2× CH_2), 3.46 (s, 3H, OCH_3), 3.82 (s, 2H, CH_2 of thiazolidinone ring), 5.92 (s, 1H, *CH–Ar*), 6.90–8.01 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.45 (s, 2H, 2× *NH* exchangeable with D_2O), 9.71 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 510.59. MS: $[M]^+$ at *m/z*. Anal. Calcd. for $C_{23}H_{22}N_6O_4S_2$: C, 54.10; H, 4.34; N, 16.46; Found: C, 54.13; H, 4.34; N, 16.48%.

*2.1.5.6. 2-((2-((5-(4-oxo-2(2-bromophenyl)thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl) methyl) hydrazinyl) methyl) benzo[b] [1,4]oxazepin-4(5H)-one **(5f)***

Yield 75% (DMF–Water); m.p. 294 °C. IR ν_{max} (KBr, cm^{-1}): 3341 (NH), 1721 (C=O), 1676 (C=O), 1624 (C⋯C of aromatic ring), 1610 (C=N), 1291 (N–N), 1040 (C–O–C), 694 (C–S–C), 612 (C–Br). ^{1}H-NMR (300 MHz, δH, DMSO-d$_6$): 3.45 (d, 4H, 2× CH_2), 3.80 (s, 2H, CH_2 of thiazolidinone ring), 5.87 (s, 1H, *CH–Ar*), 6.87–7.85 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.40 (s, 2H, 2× *NH* exchangeable with

D_2O), 9.73 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 559.46. Anal. Calcd. for $C_{22}H_{19}BrN_6O_3S_2$: C, 47.23; H, 3.42; N, 14.28; Found: C, 47.30; H, 3.46; N, 14.25%.

2.1.5.7. 2-((2-((5-(4-oxo-2-(2-hydroxyphenyl)thiazolidin-3-yl)-1,3,4-oxadiazol-2-yl) methyl) hydrazinyl methyl) benzo[b][1,4]thiazepin-4(5H)-one **(5g)**

Yield 74% (Ethanol); m.p. 290 °C. IR ν_{max} (KBr, cm^{-1}): 3438 (OH), 3345 (NH), 1700 (C=O), 1679 (C=O), 1627 (C⎓C of aromatic ring), 1602 (C=N), 1294 (N–N), 1042 (C–O–C), 691 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.46 (d, 4H, 2× CH_2), 3.86 (s, 2H, CH_2 of thiazolidinone ring), 5.82 (s, 1H, *CH–Ar*), 6.88–7.78 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.43 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, *NH* of thiazepine ring), 11.17 (s, 1H, OH) ppm; MS: $[M]^+$ at *m/z* 496.56. Anal. Calcd. for $C_{22}H_{20}BrN_6O_4S_2$: C, 53.21; H, 4.06; N, 16.92; Found: C, 53.26; H, 4.03; N, 16.99%.

2.1.5.8. 2-((2-((5-(4-oxo-2(4-methoxyphenyl)thiazolidin-3-yl)-1,3,4-oxadiazol-2-yl) methyl) 2.1.5. hydrazinyl) methyl) benzo[b][1,4]thiazepin-4(5H)-one **(5h)**

Yield 74% (Petroleum ether); m.p. 297 °C. IR ν_{max} (KBr, cm^{-1}): 3341 (NH), 1712 (C=O), 1688 (C=O), 1624 (C⎓C of aromatic ring), 1610 (C=N), 1291 (N–N), 1038 (C–O–C), 694 (C–S–C). ^{1}H-NMR (300 MHz, δH, DMSO-d_6): 3.39 (d, 4H, 2× CH_2), 3.44 (s, 3H, OCH_3), 3.87 (s, 2H, CH_2 of thiazolidinone ring), 5.84 (s, 1H, *CH–Ar*), 6.84–7.85 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.42 (s, 2H, 2× *NH* exchangeable with D_2O), 9.71 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 510.59. Anal. Calcd. for $C_{23}H_{22}N_6O_4S_2$: C, 54.10; H, 4.34; N, 16.46; Found: C, 54.11; H, 4.36; N, 16.45%.

2.1.5.9. 2-((2-((5-(4-oxo-2(2-bromophenyl)thiazolidin-3-yl)-1,3,4-oxadiazol-2-yl) methyl) hydrazinyl) methyl)benzo[b][1,4]thiazepin-4(5H)-one **(5i)**

Yield 76% (Acetone); m.p. 295 °C. IR ν_{max} (KBr, cm^{-1}): 3438 (OH), 3345 (NH), 1720 (C=O), 1680 (C=O), 1627 (C⎓C of aromatic ring), 1602 (C=N), 1294 (N–N), 1041 (C–O–C), 691 (C–S–C), 614 (C–Br). ^{1}H-NMR (300 MHz, δH, DMSO-d_6): 3.34 (d, 4H, 2× CH_2), 3.89 (s, 2H, CH_2 of thiazolidinone ring), 5.83 (s, 1H, *CH–Ar*), 6.88–7.87 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.43 (s, 2H, 2× *NH* exchangeable with D_2O), 9.71 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 559.46. Anal. Calcd. for $C_{22}H_{19}BrN_6O_3S_2$: C, 47.23; H, 3.42; N, 15.02; Found: C, 47.20; H, 3.40; N, 15.06%.

2.1.5.10. 2-((2-((5-(4-oxo-2-(2-hydroxyphenyl)thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl)methyl) hydra zinyl methyl)benzo[b][1,4]thiazepin-4(5H)-one **(5j)**

Yield 79% (Methanol); m.p. 297 °C. IR ν_{max} (KBr, cm^{-1}): 3432 (OH), 3345 (NH), 1700 (C=O), 1686 (C=O), 1627 (C⎓C of aromatic ring), 16110 (C=N), 1294 (N–N), 690 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.44 (d, 4H, 2× CH_2), 3.85 (s, 2H, CH_2 of thiazolidinone ring), 5.92 (s, 1H, *CH–Ar*), 6.90–7.79 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.41 (s, 2H, 2× *NH* exchangeable with D_2O), 9.73 (ss, 1H, *NH* of thiazepine ring), 11.16 (s, 1H, *OH*) ppm; MS: $[M]^+$ at *m/z* 512.63. Anal. Calcd. for $C_{22}H_{20}N_6O_3S_3$: C, 51.55; H, 3.93; N, 16.39; Found: C, 51.57; H, 3.92; N, 16.40%.

2.1.5.11. 2-((2-((5-(4-oxo-2(4-methoxyphenyl)thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl)methyl) hydrazinyl) methyl)benzo[b][1,4]thiazepin-4(5H)-one **(5k)**.

Yield 73% (Acetone); m.p. 292 °C. IR ν_{max} (KBr, cm^{-1}): 3346 (NH), 1716 (C=O), 1679 (C=O), 1630 (C⎓C of aromatic ring), 1610 (C=N), 1293 (N–N), 692 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.37 (d, 4H, 2× CH_2), 3.41 (s, 3H, OCH_3), 3.86 (s, 2H, CH_2 of thiazolidinone ring), 5.89 (s, 1H, *CH–Ar*), 6.93–8.00 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.44 (s, 2H, 2× *NH* exchangeable with D_2O), 9.72 (ss, 1H, *NH* of thiazepine ring ppm;. MS: $[M]^+$ at *m/z* 526.65. Anal. Calcd. for $C_{23}H_{22}N_6O_3S_3$: C, 54.45; H, 4.21; N, 15.96; Found: C, 54.45; H, 4.20; N, 15.95%.

2.1.5.12. 2-((2-((5-(4-oxo-2-(2-bromophenyl)thiazolidin-3-yl)-1,3,4-thiadiazol-2-yl)methyl) hydra zinyl)methyl)benzo[b][1,4]thiazepin-4(5H)-one **(5l)**

Yield 72% (Ethanol); m.p. 298 °C. IR ν_{max} (KBr, cm^{-1}): 3438 (OH), 3345 (NH), 1725 (C=O), 1672 (C=O), 1629 (C⎓C of aromatic ring), 1605 (C=N), 1294 (N–N), 691 (C–S–C), 613 (C–Br) cm^{-1}; ^{1}H-NMR (300 MHz, δH, $CDCl_3$) δ in ppm: 3.40 (d, 4H, 2× CH_2), 3.85 (s, 2H, CH_2 of thiazolidinone ring), 5.90 (s, 1H, *CH–Ar*), 6.90–8.01 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.40 (s, 2H, 2× *NH* exchangeable with D_2O), 9.71 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 575.52. Anal. Calcd. for $C_{22}H_{19}BrN_6O_2S_3$: C, 45.91; H, 3.33; N, 14.60; Found: C, 45.90; H, 3.38; N, 14.62%.

2.1.6. General procedure for synthesis of 2-((2-((5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-1,3,4-oxa/thiadiazol-2-yl)methyl) hydrazinyl)methyl)benzo[b][1,4]oxa/ thiazepin-4(5H)-ones ***(6a–6l)***

To a stirred solution of compounds **4a–4l** (0.05 mole) and triethyl amine in dioxan (100 mL), chloro acetyl chloride (0.05 mole) was added dropwise at 0–5 °C temperature. 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 obtain compounds **6a–6l**.

2.1.6.1. 2-((2-((5-(3-chloro-2-oxo-4-(2-hydroxyphenyl)azetidin-1-yl)-1,3,4-oxadiazol-2-yl)methyl) hydrazinyl) methyl) benzo[b][1,4]oxazepin-4(5H)-one **(6a)**

Yield 77% (Methanol); m.p. 289 °C. IR ν_{max} (KBr, cm^{-1}): 3448 (OH), 3350 (NH), 1710 (C=O), 1685 (C=O), 1624 (C⎓C of aromatic ring), 1604 (C=N), 1292 (N–N), 1038 (C–O–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.38 (d, 4H, 2× CH_2), 3.80 (d, 1H, *CH–Cl* of azetidinone ring), 5.82 (d, 1H, *CH–Ar*), 6.80-7.82 (m, 9H, *8H, Ar–H* + 1H, *CH* of oxazepine ring), 8.35 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, *NH* of oxazepine ring), 11.13 (s, 1H, *OH*) ppm; MS: $[M]^+$ at *m/z* 482.88. Anal. Calcd. for $C_{22}H_{19}ClN_6O_5$: C, 54.72; H, 3.93; N, 17.40; Found: C, 54.75; H, 3.97; N, 17.42%.

2.1.6.2. 2-((2-((5-(3-chloro-2-oxo-4-(4-methoxyphenyl)azetidin-1-yl)-1,3,4-oxadiazol-2-yl)methyl)hydrazinyl) methyl) benzo[b][1,4]oxazepin-4(5H)-one **(6b)**

Yield 75% (Acetone); m.p. 291 °C. IR ν_{max} (KBr, cm^{-1}): 3352 (NH), 1708 (C=O), 1682 (C=O), 1628 (C⎓C of aromatic ring), 1610 (C=N), 1294 (N–N), 1225 (OCH_3), 1036 (C–O–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.36 (d, 4H, 2× CH_2), 3.41 (s, 3H, OCH_3), 3.82 (d, 1H, *CH–Cl* of azetidinone ring), 5.85 (d, 1H, *CH–Ar*), 6.73–7.86 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.32 (s, 2H, 2× *NH* exchangeable with D_2O), 9.72 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 496.40. Anal. Calcd. for $C_{23}H_{21}ClN_6O_5$: C, 55.59; H, 4.26; N, 16.91; Found: C, 55.60; H, 4.27; N, 16.89%.

2.1.6.3. 2-((2-((5-(3-chloro-2-oxo-4-(2-bromophenyl)azetidin-1-yl)-1,3,4-oxadiazol-2-yl) methyl) hydrazinyl)methyl)benzo[b][1,4]oxazepin-4(5H)-one ***(6c)***

Yield 74% (DMF-Water); m.p. 288 °C. IR ν_{max} (KBr, cm^{-1}): 3349 (NH), 1711 (C=O), 1675 (C=O), 1625 (C⋯C of aromatic ring), 1605 (C=N), 1295 (N–N), 1035 (C–O–C), 615 (C–Br). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.37 (d, 4H, 2× *CH_2*), 3.83 (d, 1H, *CH–Cl* of azetidinone ring), 5.80 (d, 1H, *CH–Ar*), 6.82–7.80 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.38 (s, 2H, 2× *NH* exchangeable with D_2O), 9.71 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 545.77. Anal. Calcd. for $C_{22}H_{18}ClBrN_6O_4$: C, 48.41; H, 3.32; N, 15.40; Found: C, 48.46; H, 3.33; N, 15.43%.

2.1.6.4. 2-((2-((5-(3-chloro-2-oxo-4-(2-hydroxyphenyl)azetidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl) hydrazinyl) methyl) benzo[b][1,4]oxazepin-4(5H)-one ***(6d)***

Yield 73% (Ethanol); m.p. 295 °C. IR ν_{max} (KBr, cm^{-1}): 3446 (OH), 3350 (NH), 1712 (C=O), 1687 (C=O), 1629 (C⋯C of aromatic ring), 1608 (C=N), 1293 (N–N), 1040 (C–O–C), 684 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.32 (d, 4H, 2× *CH_2*), 3.82 (d, 1H, *CH–Cl* of azetidinone ring), 5.82 (d, 1H, *CH–Ar*), 6.82-7.82 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.38 (s, 2H, 2× *NH* exchangeable with D_2O), 9.73 (ss, 1H, *NH* of oxazepine ring), 11.20 (s, 1H, *OH*) ppm; MS: $[M]^+$ at *m/z* 498.94. Anal. Calcd. for $C_{22}H_{19}ClN_6O_4S$: C, 52.96; H, 3.84; N, 16.84; Found: C, 52.99; H, 3.80; N, 16.87%.

2.1.6.5. 2-((2-((5-(3-chloro-2-oxo-4-(4-methoxyphenyl)azetidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl) hydrazinyl) methyl) benzo[b][1,4]oxazepin-4(5H)-one ***(6e)***

Yield 73% (Acetone); m.p. 299 °C. IR ν_{max} (KBr, cm^{-1}): 3347 (NH), 1714 (C=O), 1685 (C=O), 1627 (C⋯C of aromatic ring), 1605 (C=N), 1220 (OCH_3), 1292 (N–N), 1041 (C–O–C) 690 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.36 (d, 4H, 2× *CH_2*), 3.43 (s, 3H, *OCH_3*), 3.84 (d, 1H, *CH–Cl* of azetidinone ring), 5.85 (d, 1H, *CH–Ar*), 6.79-7.80 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.35 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 512.10. Anal. Calcd. for $C_{23}H_{21}ClN_6O_4S$: C, 53.85; H, 4.13; N, 16.38; Found: C, 53.85; H, 4.15; N, 16.34%.

2.1.6.6. 2-((2-((5-(3-chloro-2-oxo-4-(2-bromophenyl)azetidin-1-yl)-1,3,4-thiadiazol-2-yl) methyl) hydrazinyl) methyl) benzo[b][1,4]oxazepin-4(5H)-one ***(6f)***.

Yield 72% (Petroleum ether); m.p. 298 °C. IR ν_{max} (KBr, cm^{-1}): 3348 (NH), 1710 (C=O), 1688 (C=O), 1628 (C⋯C of aromatic ring), 1607 (C=N), 1292 (N–N), 1041 (C–O–C), 676 (C–S–C), 612 (C–Br). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.40 (d, 4H, 2× *CH_2*), 3.80 (d, 1H, *CH–Cl* of azetidinone ring), 5.82 (d, 1H, *CH–Ar*), 6.87–7.77 (m, 9H, 8H, *Ar–H* + 1H, *CH* of oxazepine ring), 8.85 (s, 2H, 2× *NH* exchangeable with D_2O), 9.72 (ss, 1H, *NH* of oxazepine ring) ppm; MS: $[M]^+$ at *m/z* 561.84. Anal. Calcd. for $C_{22}H_{18}ClBrN_6O_3S$: C, 47.03; H, 3.23; N, 14.96; Found: C, 47.09; H, 3.22; N, 14.97%.

2.1.6.7. 2-((2-((5-(3-chloro-2-oxo-4-(2-hydroxyphenyl)azetidin-1-yl)-1,3,4-oxadiazol-2-yl) methyl) hydrazinyl)methyl) benzo[b][1,4]thiazepine-4(5H)-one ***(6g)***

Yield 78% (Ethanol); m.p. 294 °C. IR ν_{max} (KBr, cm^{-1}): 3445 (OH), 3349 (NH), 1726 (C=O), 1690 (C=O), 1630 (C⋯C of aromatic ring), 1606 (C=N), 1295 (N–N), 1038 (C–O–C) 686 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.38 (d, 4H, 2× *CH_2*), 3.78 (d, 1H, *CH–Cl* of azetidinone ring), 5.79 (d, 1H, *CH–Ar*), 6.92–7.83 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.31 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, *NH* of thiazepine ring), 11.17 (s, 1H, *OH*) ppm; MS: $[M]^{+\ \text{at}\ m/z.}$ Anal. Calcd. for $C_{22}H_{19}ClN_6O_4S$: C, 52.96; H, 3.84; N, 16.84; Found: C, 52.94; H, 3.83; N, 16.85%

2.1.6.8. 2-((2-((5-(3-chloro-2-oxo-4-(4-hydroxyphenyl)azetidin-1-yl)-1,3,4-oxadiazol-2-yl) methyl) hydrazinyl)methyl) benzo[b][1,4]thiazepine-4(5H)-one ***(6h)***

Yield 73% (DMF-Water); m.p. 295 °C. IR ν_{max} (KBr, cm^{-1}): 3350 (NH), 1719 (C=O), 1686 (C=O), 1629 (C⋯C of aromatic ring), 1605 (C=N), 1292 (N–N), 1226 (OCH_3), 1040 (C–O–C) 691 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.37 (d, 4H, 2× *CH_2*), 3.41 (s, 3H, *OCH_3*), 3.80 (d, 1H, *CH–Cl* of azetidinone ring), 5.84 (d, 1H, *CH–Ar*), 6.83–7.90 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.37 (s, 2H, 2× *NH* exchangeable with D_2O), 9.71 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 512.97. Anal. Calcd. for $C_{23}H_{21}ClN_6O_4S$: C, 53.85; H, 4.13; N, 16.38; Found: C, 53.84; H, 4.12; N, 16.40%.

2.1.6.9. 2-((2-((5-(3-chloro-2-oxo-4-(2-bromophenyl)azetidin-1-yl)-1,3,4-oxadiazol-2-yl) methyl) hydrazinyl)methyl)benzo[b][1,4]thiazepine-4(5H)-one ***(6i)***

Yield 72% (Petroleum ether); m.p. 289 °C. IR ν_{max} (KBr, cm^{-1}): 3348 (NH), 1710 (C=O), 1680 (C=O), 1628 (C⋯C of aromatic ring), 1610 (C=N), 1292 (N–N), 1039 (C–O–C), 672 (C–S–C), 612 (C–Br). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.38 (d, 4H, 2× *CH_2*), 3.80 (d, 1H, *CHCl* of azetidinone ring), 5.82 (d, 1H, *CH–Ar*), 6.80–7.82 (m, 9H, 8H*Ar–H* + 1H, *CH* of thiazepine ring), 8.35 (s, 2H, 2× *NH* exchangeable with D_2O), 9.72 (ss, 1H, *NH* of thiazepine ring)ppm; MS: $[M]^+$ at *m/z* 561.84. Anal. Calcd. for $C_{22}H_{18}ClBrN_6O_3S$: C, 47.03; H, 3.23; N, 14.96; Found: C, 47.00; H, 3.20; N, 14.95%.

2.1.6.10. 2-((2-((5-(3-chloro-2-oxo-4-(2-hydroxyphenyl)azetidin-1-yl)-1,3,4-thiadiazol-2-yl) methyl) hydrazinyl)methyl) benzo[b][1,4]thiazepine-4(5H)-one ***(6j)***

Yield 75% (Acetone); m.p. 287 °C. IR ν_{max} (KBr, cm^{-1}): 3448 (OH), 3350 (NH), 1710 (C=O), 1676 (C=O), 1626 (C⋯C of aromatic ring), 1604 (C=N), 1294 (N–N), 685 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.34 (d, 4H, 2× *CH_2*), 3.79 (d, 1H, *CH–Cl* of azetidinone ring), 5.83 (d, 1H, *CH–Ar*), 6.82–7.84 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.31 (s, 2H, 2× *NH* exchangeable with D_2O), 9.73 (ss, 1H, *NH* of thiazepine ring), 11.20 (s, 1H, *OH*) ppm; MS: $[M]^+$ at *m/z* 515.01. Anal. Calcd. for $C_{22}H_{19}ClN_6O_3S_2$: C, 51.31; H, 3.72; N, 16.32; Found: C, 51.30; H, 3.70; N, 16.30%.

2.1.6.11. 2-((2-((5-(3-chloro-2-oxo-4-(4-methoxyphenyl)azetidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl) hydrazinyl methyl) benzo[b][1,4]thiazepine-4(5H)-one ***(6k)***.

Yield 72% (Ethanol); m.p. 290 °C. IR ν_{max} (KBr, cm^{-1}): 3352 (NH), 1708 (C=O), 1678 (C=O), 1625 (C⋯C of aromatic ring), 1612 (C=N), 1294 (N–N), 1228 (OCH_3), 688 (C–S–C). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.35 (d, 4H, 2× *CH_2*), 3.44 (s, 3H, *OCH_3*), 3.89 (d, 1H, *CH–Cl* of azetidinone ring), 5.91 (d, 1H, *CH–Ar*), 6.78–7.80 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.40 (s, 2H, 2× *NH* exchangeable with D_2O), 9.72 (ss, 1H, *NH* of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 529.03. Anal. Calcd. for $C_{23}H_{21}ClN_6O_3S_2$: C, 52.22; H, 4.00; N, 15.89; Found: C, 52.24; H, 4.02; N, 15.90%.

2.1.6.12. *2-((2-((5-(3-chloro-2-oxo-4-(2-bromophenyl)azetidin-1-yl)-1,3,4-thiadiazol-2-yl)methyl) hydrazinyl)methyl) benzo b][1,4]thiazepine-4(5H)-one* ***(6l)***

Yield 73% (Methanol); m.p. 298 °C. IR v_{max} (KBr, cm^{-1}): 3349 (NH), 1711 (C=O), 1671 (C=O), 1628 (C⋯C of aromatic ring), 1611 (C=N), 1295 (N–N), 689 (C–S–C), 611 (C–Br). ^{1}H-NMR (300 MHz, δH, $CDCl_3$): 3.33 (d, 4H, 2× *CH_2*), 3.87 (d, 1H, *CH–Cl* of azetidinone ring), 5.93 (d, 1H, *CH–Ar*), 6.81–7.84 (m, 9H, 8H, *Ar–H* + 1H, *CH* of thiazepine ring), 8.41 (s, 2H, 2× *NH* exchangeable with D_2O), 9.70 (ss, 1H, NH of thiazepine ring) ppm; MS: $[M]^+$ at *m/z* 577.90. Anal. Calcd. for $C_{22}H_{18}ClBrN_6O_2S_2$; C, 45.72; H, 3.14; N, 14.54; Found: C, 45.70; H, 3.15; N, 14.58%.

3. Results and discussion

All the compounds were evaluated for antipsychotic activity by recording their responses towards amphetamine induced stereotyped behaviour, cataleptic behaviour and rotarod performance test and for anticonvulsant activity by the MES test, at a dose of 30 mg/kg each. Pharmacological data of the compounds have been given in Tables 1–3.

3.1. Antipsychotic activity

3.1.1. Amphetamine induced stereotyped behaviour

The compounds **4a–4l** showed mild to moderate response against amphetamine induced stereotyped behaviour. Furthermore, compounds **5c–5h, 5k, 6c, 6f, 6i, 6k** and **6l** showed interesting results. Furthermore, compounds **5i** and **5l** (2-bromophenyl moiety) have shown the most potent response because these compounds completely antagonized the stereotyped behaviour induced by amphetamine.

3.1.2. Cataleptic behaviour

Compounds **4l, 5c–5e, 5g–5j, 6f, 6h** and **6l** significantly antagonized the cataleptic behaviour. However, compound **5l** showed the most potent response because this compound did not exhibit any cataleptic behaviour.

3.2. Rotarod performance test

Compounds **4a–4l** exhibited moderate results in rotarod performance test, but compound **4l** showed better response in comparison to the compounds **4a–4k**. In the next step, compounds **5a–5l** (having substituted thiazolidinone ring) exhibited potent results (i.e. 94.0–102.6 s). Among the compounds **5a–5l**, compound **5l** showed the most potent result (i.e. 94.0 s) in rotarod performance test. On the other side, compounds **6a–6l** exhibited different results (i.e. 100.0–104.6 s), but compound **6l** showed good activity in rotarod test.

3.3. Anticonvulsant activity

Among the compounds **4a–4l**, compounds **4j, 4k** and **4l** showed good response (i.e. 50-60%) against MES test. The compounds **5a–5l** exhibited varying degrees (50-90%) of anticonvulsant activity; moreover, compound **5l** (having 2-bromophenyl ring at 2nd position of thiazolidinone ring) has shown 90% anticonvulsant activity which was more potent than the standard drug phenytoin sodium (30 mg/kg). On the other side, compounds **6a–6l**, substituted with different azetidinone moieties at the 2nd position of benzoxazepine and benzothiazepine ring have shown 30–70% protection. Moreover, the effect of 2-bromophenyl moiety was found to be similar in the case of **5l** and **6l**.

4. Conclusion

While considering the synthesized compounds of this series we may conclude that:

- Benzothiazepine derivatives showed more potent response than benzoxazepine derivatives.
- Compounds with thiadiazole moiety showed better antipsychotic and anticonvulsant activity in comparison to the compounds substituted with oxadiazole moiety.
- Compounds having 2-bromophenyl moiety at second position of benzothiazepine ring (i.e. compounds 5l and 6l) showed better biological activities than the other substituted compounds.

5. Biological methods

All the newly synthesized compounds **4a–4l**, **5a–5l** and **6a–6l** were tested for their antipsychotic and anticonvulsant activities. The effect of unknown compounds was compared with the standard drugs and the propylene glycol treated group served as a control.

5.1. Antipsychotic activity

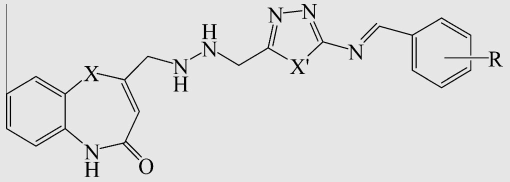
Effect on amphetamine induced stereotyped behaviour (SB):

It was done by the method of Castall and Naylor (1974). Before the administration of drugs, the animals were fasted for 12 h and were deprived of food during experiment. Amphetamine (4 mg/kg, i.p.) was used to induce the stereotyped behaviour (SB) in albino rats. The intensity of SB was assessed for 60 min after the 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 (4 mg/kg, i.p.) was used as standard and was injected 30 min. before the challenge, while propylene glycol (0.5 mL i.p.) or test compounds were given 20 min prior to the injection of amphetamine.

5.1.1. Induction of catalepsy

It was performed according to the method of Castall and Naylor (1974). According this method, the front limbs of the rat were placed over the wooden block of 8 cm high and the time

Table 1 Antipsychotic and anticonvulsant activity of compounds (**5a**–**5l**).



(4a-4l)

Comp. No.	R	X	X′	Dose (mg/kg)	Amphetamine induced SB (mean score)	Catalepsy scored	Rotarod performance test (Mean Sec.)	Anticonvulsant activity (% inhibition) in mice (for MES model)	ID_{50} mg/kg
P.G.*	–			0.5 ml	3.8	–	120.0	0	
P.S.	–	–	–	30	–	–	–	80***	
CPZ	–	–	–	4.0 ml	0.0	–	100.0	0	
HPL*	–	–	–	0.5 ml	–	1.8	–	0	
4a	2-OH	O	O	30	2.6	2.4	116.8	20	> 1000
4b	4-OCH_3	O	O	30	2.4	2.2	116.0	20	> 1000
4c	2-Br	O	O	30	2.6	2.0	110.2	30	> 1000
4d	2-OH	O	S	30	2.4	2.2	110.0	20	> 1000
4e	4-OCH_3	O	S	30	2.2	2.0	114.4	20	> 1000
4f	2-Br	O	S	30	2.2	2.0	108.8	40	> 1000
4g	2-OH	S	O	30	2.2	1.8	110.6	30	> 1000
4h	4-OCH_3	S	O	30	2.0	1.8	112.2	30	> 1000
4i	2-Br	S	O	30	1.0	2.0	108.8	40	> 1000
4j	2-OH	S	S	30	2.2	1.6	108.8	50*	> 1000
4k	4-OCH_3	S	S	30	1.8	1.8	108.4	50*	> 1000
4l	2-Br	S	S	30	1.0	0.6	104.2	60**	> 1000

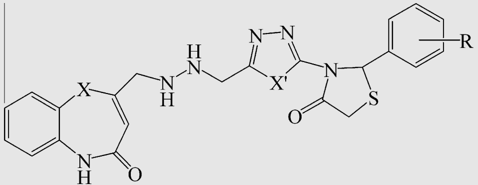
P.G., propylene glycol standard for control group; P.S., Phenytoin sodium standard drug for SMES pattern test; CPZ, chlorpromazine; HPL, haloperidol.

* $P < 0.05$.

** $P < 0.001$.

*** $P < 0.001$.

Table 2 Antipsychotic and anticonvulsant activity of compounds (**5a**–**5l**).



(5a-5l)

Comp. No.	R	X	X′	Dose (mg/kg)	Amphetamine induced SB (mean score)	Catalepsy scored	Rotarod performance test (Mean Sec.)	Anticonvulsant activity (% inhibition) in mice (for MES model)	ID_{50} (mg/kg)
P.G.*	–			0.5 ml	3.8	–	120.0	0	
P.S.	–	–	–	30	–	–	–	80***	
CPZ	–	–	–	4.0 ml	0.0	–	100.0	0	
HPL*	–	–	–	0.5 ml	–	1.8	–	0	
5a	2-OH	O	O	30	0.8	1.0	102.6	50*	> 1000
5b	4-OCH_3	O	O	30	1.0	1.2	102.2	50*	> 1000
5c	2-Br	O	O	30	0.6	0.4	100.4	60**	> 1000
5d	2-OH	O	S	30	0.4	0.6	102.2	50*	> 1000
5e	4-OCH_3	O	S	30	0.6	0.4	102.6	60**	> 1000
5f	2-Br	O	S	30	0.4	0.8	100.4	60**	> 1000
5g	2-OH	S	O	30	0.6	0.2	102.2	50*	> 1000
5h	4-OCH_3	S	O	30	0.2	0.2	100.4	50*	> 1000
5i	2-Br	S	O	30	0.0	0.4	100.2	70***	> 1000
5j	2-OH	S	S	30	0.8	0.2	100.2	60**	> 1000
5k	4-OCH_3	S	S	30	0.2	0.8	100.8	70***	> 1000
5l	2-Br	S	S	30	0.0	0.0	94.0	90***	> 1000

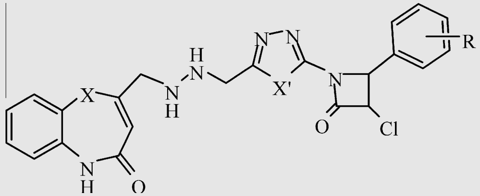
P.G., propylene glycol standard for control group; P.S., Phenytoin sodium standard drug for SMES pattern test; CPZ, chlorpromazine; HPL, haloperidol.

[*] $P < 0.05$.

[**] $P < 0.001$.

[***] $P < 0.001$.

Table 3 Antipsychotic and anticonvulsant activity of compounds (**6a**–**6l**).



Comp. No.	R	X	X′	Dose (mg/kg)	Amphetamine induced SB (mean score)	Catalepsy scored	Rotarod performance test (Mean Sec.)	Anticonvulsant activity (% inhibition) in mice (for MES model)	ID_{50} (mg/kg)
P.G.[*]	–			0.5 ml	3.8	–	120.0	0	
P.S.	–	–	–	30	–	–	–	80[***]	
CPZ	–	–	–	4.0 ml	0.0	–	100.0	0	
HPL[*]	–	–	–	0.5 ml	–	1.8	–	0	
6a	2-OH	O	O	30	1.2	2.0	104.6	30	> 1000
6b	4-OCH_3	O	O	30	1.0	1.6	103.0	40	> 1000
6c	2-Br	O	O	30	0.6	1.0	102.4	50[*]	> 1000
6d	2-OH	O	S	30	1.0	1.4	102.6	40	> 1000
6e	4-OCH_3	O	S	30	0.8	1.6	104.6	50[*]	> 1000
6f	2-Br	O	S	30	0.6	0.4	104.4	50[*]	> 1000
6g	2-OH	S	O	30	1.0	1.2	102.8	40	> 1000
6h	4-OCH_3	S	O	30	1.0	0.2	100.4	50[*]	> 1000
6i	2-Br	S	O	30	0.4	0.8	102.6	60[**]	> 1000
6j	2-OH	S	S	30	1.0	1.0	102.2	60[**]	> 1000
6k	4-OCH_3	S	S	30	0.6	0.8	102.8	60[***]	> 1000
6j	2-Br	S	S	30	0.2	0.2	100.0	70[**]	> 1000

P.G., propylene glycol standard for control group; P.S., Phenytoin sodium standard drug for SMES pattern test; CPZ, chlorpromazine; HPL, haloperidol.

[*] $P < 0.05$.

[**] $P < 0.001$.

[***] $P < 0.001$.

the animal maintained the imposed posture.was measured Animals maintaining the imposed posture for more than 10 s were considered to be cataleptic. Animals were tested for catalepsy by using the scoring system to maintain the imposed posture 0–10 s = 0 score, 11–30 s = 1 score, 31–60 s = 2 score, 61–120 s = 3 score, after injecting propylene glycol (0.5 mL, i.p.) or test compounds or haloperidol (0.5 mg/kg, i.p.) as standard.

5.1.2. Rotarod performance test

The rotarod performance was essentially the same as described by Dunham and Miya (1957). 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 the administration of test compound, the rats were given the trials on the rotarod for 60 min and the cumulated time spent on the rotarod was recorded with a cut off of 2 min.

5.2. Anticonvulsant activity

5.2.1. Supramaximal electroshock seizure (SMES) pattern test

This activity was performed by following the method of Toman et al., 1946; Qufeng et al., 2009. Male mice were divided into the groups of 10 animals each. The mice were treated with the test compounds and phenytoin sodium at a dose of 30 mg/kg p.o. After 1h they were subjected to the shock of 25 mA by convulsiometer through ear electrodes for 0.25 s Abolition of the hind limb tonic extensor component of the seizure is defined as protection, and the results are expressed as number of animals protected/number of animals tested.

Approximate lethal dose (*LD_{50}*)*:* The compounds were investigated for their acute toxicity (LD_{50}) which was estimated by following the method of smith 1960.

Acknowledgements

We are thankful to the SAIF Punjab University, Chandigarh, India for spectral and analytical analysis of newly synthesized compounds. One of the author, Hemlata Kaur is also thankful to the UGC New Delhi, India for the award of JRF - Rajiv Gandhi National Junior Research Fellowship and the financial support for this work.

References

Agarwal, A., Lata, S., Saxena, K.K., Srivastava, V.K., Kumar, A., 2006. Eur. J. Med. Chem. 41, 1223–1229.

Almasirad, A., Tabatabai, S.A., Faizi, M., Kebriacezadch, A., Mehrabi, N., Dalvandi, A., Shafiee, A., 2004. Bioorg. Med. Chem. Lett. 14, 6057–6059.

Bajaj, K., Srivastava, V.K., Lata, S., Chandra, R., Kumar, A., 2003a. Indian J. Chem. 42B, 1723–1728.

Bajaj, K., Srivastava, V.K., Kumar, A., 2003b. Indian J. Chem. 42B, 1149–1155.

Bajaj, K., Srivastava, V.K., Kumar, A., 2004. Indian J. Chem. 43B, 157–161.

Castall, B., Naylor, R.J., 1974. Eur. J. Pharmacol. 27, 46–58.

Dunham, S.M., Miya, T.S., 1957. J. Am. Pharm. Assoc. 426, 208–209.

Gupta, A., Mishra, P., Kashav, V., Stables, J.P., 2008. Eur. J. Med. Chem. 43, 749–754.

Kaur, H., Kumar, S., Saxena, K.K., Kumar, A., 2009. Org. Chem. An Indian J. 5 (4), 367–379.

Kaur, H., Kumar, S., Vishwakarma, P., Sharma, M., Saxena, K.K., Kumar, A., 2010. Eur. J. Med. Chem. 45, 2777–2783.

Nagarajan, K., David, J., Bhat, G.A., 1985. Indian J. Chem. 24B, 840–844.

Qufeng, Z., Yuan, P., Zaixu, X., Ruimin, L., Guofu, Q., Wenjin, X., Xianbing, K., Lamei, W., Xianming, H., 2009. Eur. J. Med. Chem. 44, 296–302.

Sabb, A.L., Vogel, L., Kelly, M.G., Palmer, Y., Smith, D.L., Andree, T.H., Schechter, L.E., 2001. Bioorg. Med. Chem. Lett. 11 (8), 1069–1071.

Sadashiva, C.T., Chandra, J.N.N.S., Kavitha, C.V., Thimmegoowda, A., Subhsh, M.N., Rangappa, K.S., 2009. Eur. J. Med. Chem. 44, 4848–4854.

Smith, Q.E., 1960. Pharmacological screening tests progress in medicinal chemistry, vol 2. Butterworth, London, pp. 1–33.

Toman, J.E.P., Swinyard, E.A., Goodman, L.S., 1946. J. Neurophysiol. 9, 231–240.