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Synthesis and biological evaluation of newer 1,3,4-oxadiazoles incorporated with benzothiazepine and benzodiazepine moieties

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Abstract: A series of thiazepines and diazepines having 1,3,4-oxadiazole moiety were synthesized, and they were analyzed for their in vitro antimicrobial activity against several bacteria (*Staphylococcus aureus*, *Staphylococcus pyogenes*, *Escherichia coli*, and *Pseudomonas aeruginosa*) and fungi (*Candida albicans*, *Aspergillus niger*, and *Aspergillus Clavatus*) and protozoa (*Entamoeba histolytica*, *Giardia lamblia*, *Trypanosoma cruzi* and *Leishmania mexicana*). Few of the selected compounds were tested for their antitubercular activity. However, it was noticed that the potency of final analogs against each strain placed reliance on the type of substituent present on aryl ring of oxadiazole as well as presence of thiophene, pyridine, and furan at benzothiazepines and benzodiazepines. The biological screening identified that some of the compounds were found to possess good antimicrobial and antitubercular (62.5–100 μg/mL of MIC) activity.

Keywords: antimicrobial activity; antituberculosis activity; benzodiazepines; benzothiazepines; 1,3,4-Oxadiazole.

1 Introduction

The worldwide prevalence of multi-drug-resistant bacteria strains in care stations, hospitals, and general community demands new compounds with novel mechanisms to combat these pathogens. In recent years, much attention has been focused on the multi-drug-resistant bacteria and fungi resulting from the widespread use and misuse of classical antimicrobial drugs. Developing novel antimicrobial agents with different mode of action than that of existing drugs is one of the main challenges to overcome antimicrobial resistance. In view of these facts, it is important to develop more effective antimicrobial agents. Thus, the synthesis and discovery of more efficient antimicrobial agents have been intensively considered during the last decade. Different heterocyclic compounds containing nitrogen, sulphur, and oxygen as hetero atoms have been explored for the development of new antimicrobial agents as well as for other bioactivities [1–4].

Among several heterocyclic compounds, 1,3,4-oxadiazole has become an important construction motif for the development of new drugs. Compounds containing 1,3,4-oxadiazole cores have a broad biological activity spectrum including antibacterial, antifungal [5], anti-HIV [6], antitumor [7], anti-inflammatory [8], antitubercular [9], anticancer [10], anticonvulsant, and anti-diabetic [11] properties. On the other hand, benzothiazepine derivatives have attracted considerable interest owing to their wide spectrum of biological activity [12, 13], including anticonvulsant [14, 15], antipsychotic [16], antitumor [17], anti-HIV [18], and antimicrobial [19] properties, while benzodiazepine analogs were found to show anti-inflammatory, anti-pyretic [20], anticancer [21], antidepressant [22], and anti-anxiety activity [23]. The 1,3,4-oxadiazole, benzothiazepine, and benzodiazepine nucleus has emerged as one of the potential pharmacophores responsible for diverse pharmacological properties. In a view of above bioactivity results found in literature survey aspired us to derive a system in which 1,3,4-oxadiazole incorporated with thiazepine and diazepines (Figure 1).

2 Results and discussion

2.1 Chemistry

The reaction arrangements adapted to furnish intermediates **3a–o** (thiazepines), **4a–o** (diazepines), and

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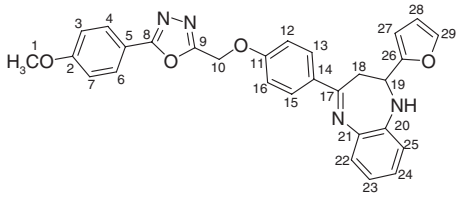
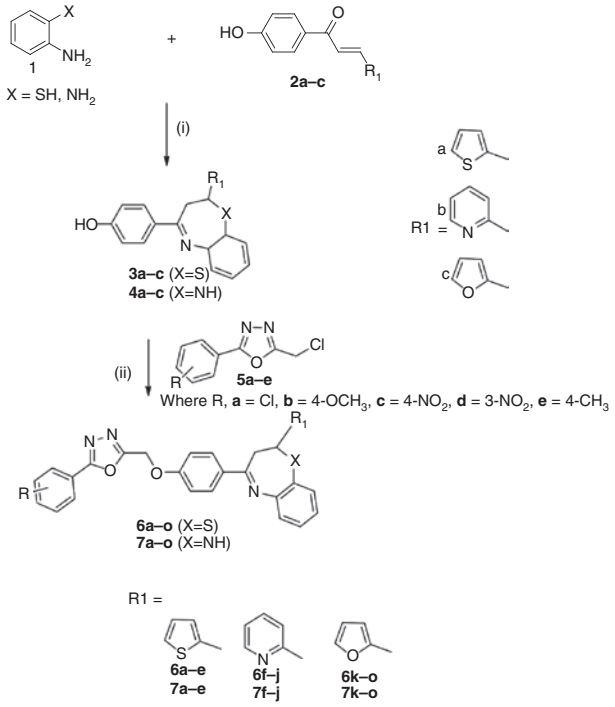


Figure 1: General structure and numeration for **6a–o, 7a–o**.



Scheme 1: Synthesis of thiazepine and diazepine derivatives. (i) Ethanol, TFA, refluxed 15–17 h; (ii) methanol, KOH, refluxed 12–15 h.

final derivatives **6a–o** and **7a–o** (1,3,4-oxadiazoles) are outlined in Scheme 1. Solvents and reagents were used as received or were dried prior to use as needed. In this work, as shown in Scheme 1, 2-amino thiophenol/o-phenylenediamine **1** on reaction with 1-(4-hydroxy-phenyl)-3-thiophene/pyridine/furan-2-yl-propenone **2** yielded the intermediate compounds **3a–c** and **4a–c** having thiazepine and diazepine moiety, respectively, clubbed with thiophene, pyridine, and furan ring.

In our previous work, we have already reported the synthesis of 2-chloromethyl-5-(substituted phenyl)-1,3,4-oxadiazoles [24]. Further on, the reaction of compounds **3a–c** and **4a–c** with 2-chloromethyl-5-(substituted phenyl)-1,3,4-oxadiazoles **5a–e** yielded the corresponding 1,3,4-oxadiazoles with thiazepine **6a–o** and diazepine **7a–o** final analogs.

The structures of the synthesized compounds were confirmed by spectral data and elemental analysis, and they were in full agreement with the proposed structures. As we have provided, the spectral data from that IR spectrum (see supplementary material data) of compound **3b** having thiazepine moiety showed band at 3290 cm^{-1} for O-H group, 2963 cm^{-1} and 2840 cm^{-1} for C-H asym and sym band, and 1616 cm^{-1} for >C=N-, while compound **4a** having diazepine moiety displayed band at 3341 cm^{-1} (N-H), 3258 cm^{-1} (O-H), and 1592 cm^{-1} (>C=N-). From ^{1}H NMR data, the structure of thiophene ring containing compound **3a** was confirmed by the presence of one proton of -O<u>H</u> as singlet at δ 8.35 ppm. Protons corresponding to the -C<u>H</u>$_2$ resonated at δ 3.06–3.74 ppm, and their peaks appeared as doublet of doublet (dd) and one dd peak was observed at δ 5.52–5.56 ppm, while aromatic protons appeared as multiplate at δ 6.91–8.03 ppm. In ^{1}H NMR of compound **4c** having furan ring, the presence of -NH was confirmed by singlet peak at δ 8.35 ppm. The appearance of two dd peaks for C<u>H</u>$_2$ at δ 3.07–3.75 ppm, one dd at δ 5.50–5.55 ppm, and aromatic hydrogen as multiplate at 7.15–8.10 ppm also gave confirmation for formation of compound **4c**. Therefore, in a similar way, structures of other compounds of **3a–o** and **4a–o** were confirmed.

In the case of final thiazepine analogs **6a–o**, the IR spectrum of final analog **6f** containing -Cl group on aryl ring of oxadiazole showed characteristic band at 743 cm^{-1} and 1618 cm^{-1} for >C=N. Compound **6m** having -NO_2 group on aryl ring showed asym and sym band at 1529 and 1349 cm^{-1}, respectively. In ^{1}H NMR of compound **6b**, the proton corresponding to -OCH_3 was observed at δ 3.85 ppm as singlet and other singlet peak at δ 5.28 ppm for protons of -CH_2O was observed. The mass spectrum of compound **6o** (mw = 493.58) showed the *m*/*z* value as 493.1 (M^+), 494.1 ($M^+ + 1$), and 495.1 ($M^+ + 2$).

In the case of diazepine analogs **7a–o**, compound **7a** having -Cl and **7I** having 3-NO_2 at aryl ring showed band at 747 cm^{-1} and 1545, 1360 cm^{-1} (asym, sym), respectively. The presence of -NH was confirmed by band at 3355 cm^{-1} (for **7a**) and 3360 cm^{-1} (for **7I**). In ^{1}H NMR data of compound **7l**, the singlet peak for one proton of N<u>H</u> appeared at δ 8.38 ppm. The presence of -OCH_3 was supported by singlet peak for three protons at δ 3.85 ppm. The singlet signal at δ 5.26 ppm for -CH_2O also gave correction to the formation of **7l**. The mass spectrum of compound **7k** (mw = 496.94) showed the *m*/*z* value as 497.3 (M^+), 498.3 ($M^+ + 1$), 499.1 ($M^+ + 2$), and 500.1 ($M^+ + 3$). Therefore, in a similar way, the structure confirmations of other final analogs were also confirmed by their spectral and elemental analysis, which is shown in the characterization data.

2.2 Biological activities

The synthesized compounds **3a–c**, **4a–c**, **6a–o**, and **7a–o** were evaluated for in vitro antibacterial, antifungal, and antiprotozoal activities against various Gram-positive and Gram-negative bacteria, fungal, and protozoal species. The results are shown in Tables 1–6.

From the antibacterial and antifungal activity of compounds **3a–c** and **4a–c** (Table 1), it was found that benzothiazepine compound **3c** having furan ring showed excellent activity (MIC = 100 μg/mL) against both Gram-negative bacteria and it is comparable to the standard drug ampicillin, while compound **3b** having pyridine ring showed a minimum value of MIC = 125 μg/mL against *Staphylococcus aureus* compared to other compounds. Compounds **3b**, **3c**, and **4b** inhibited *Streptococcus pyogenes* at similar MIC = 200 μg/mL.

The antibacterial and antifungal activity of compound **6a–o** (Table 2) showed that pyridin ring containing compound **6j** having 4-CH_3 group at aryl ring showed the best MIC = 62.5 μg/mL against *Pseudomonas aeruginosa* compared to other compounds. Compounds **6c** (4-NO_2), **6h** (4-NO_2), and **6l** (4-OCH_3) having thiophene, pyridine, and furan rings, respectively, showed significant MIC = 62.5 μg/mL against *S. aureus*, which is better than the MIC of ampicillin against the same bacteria. For antifungal activity, the

Table 1: In vitro antimicrobial activity of newly synthesized compounds **3a–c** and **4a–c**.

Compd. no.	R	Minimum inhibitory concentration (MIC) in (μg/mL)						
		Gram negative bacteria		Gram positive bacteria		Fungal species		
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*	*A. niger*	*A. Clavatus*
3a	Thiophen-2-yl	125	200	250	250	1000	1000	1000
3b	Pyridine-2-yl	200	250	125	200	500	>1000	>1000
3c	Furan-2-yl	100	100	200	200	1000	>1000	>1000
4a	Thiophen-2-yl	125	100	250	250	500	>1000	>1000
4b	Pyridine-2-yl	200	250	250	200	500	>1000	>1000
4c	Furan-2-yl	250	250	500	1000	>1000	500	500
Ampicillin		100	100	250	100	–	–	–
Chloramphenicol		50	50	50	50	–	–	–
Griseofulvin		–	–	–	–	500	100	100

Table 2: In vitro antimicrobial activity of thiazepine compounds **6a–o**.

Compd. no.	R	Minimum inhibitory concentration (MIC) in (μg/mL)						
		Gram negative bacteria		Gram positive bacteria		Fungal species		
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*	*A. niger*	*A. Clavatus*
6a	4-Cl	125	100	200	200	1000	250	500
6b	4-OCH_3	100	125	250	250	500	500	500
6c	4-NO_2	125	200	62.5	100	250	1000	1000
6d	3-NO_2	250	250	100	125	500	1000	1000
6e	4-CH_3	200	200	250	125	500	>1000	>1000
6f	4-Cl	250	250	200	250	1000	500	500
6g	4-OCH_3	250	250	125	250	>1000	250	1000
6h	4-NO_2	500	1000	62.5	100	>1000	500	1000
6i	3-NO_2	250	125	125	200	>1000	500	500
6j	4-CH_3	125	62.5	250	250	>1000	>1000	>1000
6k	4-Cl	125	250	125	100	250	500	500
6l	4- OCH_3	200	250	62.5	125	250	500	500
6m	4-NO_2	100	200	100	200	1000	1000	1000
6n	3-NO_2	250	250	250	250	500	1000	>1000
6o	4-CH_3	200	100	200	250	1000	500	500
Ampicillin		100	100	250	100	–	–	–
Chloramphenicol		50	50	50	50	–	–	–
Griseofulvin		–	–	–	–	500	100	100

Table 3: In vitro antimicrobial activity of newly diazepine compounds **7a–o**.

Compd. no.	R	Minimum inhibitory concentration (MIC) in (μg/mL)						
		Gram negative bacteria		Gram positive bacteria		Fungal species		
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*	*A. niger*	*A. Clavatus*
7a	4-Cl	200	250	100	100	500	>1000	>1000
7b	4-OCH_3	200	250	62.5	200	500	>1000	>1000
7c	4-NO_2	200	125	200	250	250	>1000	>1000
7d	3-NO_2	125	100	200	250	500	500	1000
7e	4-CH_3	200	250	250	200	1000	500	500
7f	4-Cl	250	200	250	250	1000	1000	1000
7g	4-OCH_3	125	125	500	500	1000	1000	1000
7h	4-NO_2	200	62.5	250	500	>1000	>1000	>1000
7i	3-NO_2	250	125	200	250	>1000	>1000	>1000
7j	4-CH_3	200	200	100	1000	1000	500	500
7k	4-Cl	125	100	100	200	1000	1000	1000
7l	4-OCH_3	250	200	100	250	500	>1000	>1000
7m	4-NO_2	250	250	200	250	>1000	>1000	>1000
7n	3-NO_2	100	100	125	250	>1000	>1000	>1000
7o	4-CH_3	200	250	200	250	250	>1000	>1000
Ampicillin		100	100	250	100	–	–	–
Chloramphenicol		50	50	50	50	–	–	–
Griseofulvin		–	–	–	–	500	100	100

Table 4: Antitubercular activity of some selected compounds (MICs, μg/mL).

Compound	MIC (μg/mL)	Compound	MIC (μg/mL)	R
6a	21.0	**7a**	21.5	4-Cl
6b	>100	**7b**	21.5	4-OCH_3
6c	>100	**7c**	10.3	4-NO_2
6d	11.0	**7d**	47.5	3-NO_2
6e	11.9	**7e**	>100	4-CH_3
6f	>100	**7f**	40.5	4-Cl
6g	28.5	**7g**	45.7	4-OCH_3
6h	>100	**7h**	95.3	4-NO_2
6i	11.6	**7i**	>100	3-NO_2
6j	29.6	**7j**	23.0	4-CH_3
6k	44.8	**7k**	14.9	4-Cl
6l	44.6	**7l**	8.8	4-OCH_3
6m	43.7	**7m**	6.2	4-NO_2
6n	>100	**7n**	24.3	3-NO_2
6o	>100	**7o**	49.4	4-CH_3
Rifampicin	0.05			
Isoniazid	0.23			
Streptomycin	0.46			
PA-824	0.14			
TMC	0.12			

Table 5: Antiprotozoal activity of compounds **6a–o**.

Compound	R	IC_{50} (μg/mL)			
		T. vaginalis	*G. lamblia*	*T. cruzi*	*L. mexicana*
6a	4-Cl	>20	3.89	>50	>50
6b	4-OCH_3	>20	19.86	>50	>50
6c	4-NO_2	>20	2.01	>50	0.65
6d	3-NO_2	>20	5.95	>50	4.06
6e	4-CH_3	>20	8.64	>50	2.69
6f	4-Cl	>20	>20	>50	>50
6g	4-OCH_3	>20	4.86	>50	>50
6h	4-NO_2	>20	>10	>50	>50
6i	3-NO_2	>20	2.74	>50	3.02
6j	4-CH_3	>20	>20	>50	>50
6k	4-Cl	5.94	>20	>50	>50
6l	4-OCH_3	>20	16.21	>50	>50
6m	4-NO_2	>20	>20	>50	4.06
6n	3-NO_2	>20	>20	>50	4.73
6o	4-CH_3	>20	>20	>50	>50
Albendazole		0.016	1.083	–	–
Metronidazole		0.22	0.119	–	–
Nitazoxanide		0.007	0.308	–	–
Benznidazole		–	–	2.90	–
Miltefosine		–	–	–	0.55

activity of compounds **6c**, **6k**, and **6l** against *Candida albicans* is better than that of the standard drug griseofulvin.

In case of antibacterial and antifungal activity of compound **7a–o** (Table 3), bacterium *S. aureus* was inhibited at the lowest MIC = 62.5 μg/mL by **7b** (4-OCH_3) having thiophene ring. Compound **7a** having -Cl group at aryl ring and thiophene moiety showed equipotent activity with standard drug ampicillin (MIC = 100 μg/mL) against

Table 6: Antiprotozoal activity of compounds **7a–o**.

Compound	R	IC_{50} (μg/mL)			
		T. vaginalis	*G. lamblia*	*T. cruzi*	*L. mexicana*
7a	4-Cl	> 20	> 20	> 50	> 50
7b	4-OCH_3	> 20	13.44	> 50	> 50
7c	4-NO_2	> 20	> 20	0.91	0.19
7d	3-NO_2	> 20	> 20	> 50	2.78
7e	4-CH_3	> 20	10.80	> 50	> 50
7f	4-Cl	> 20	> 20	> 50	> 50
7g	4-OCH_3	> 20	8.63	> 50	0.33
7h	4-NO_2	> 20	12.79	5.14	0.92
7i	3-NO_2	> 20	> 20	> 50	2.20
7j	4-CH_3	> 20	5.29	> 50	> 50
7k	4-Cl	> 20	3.16	4.02	2.51
7l	4-OCH_3	> 20	1.85	1.03	0.82
7m	4-NO_2	> 20	15.38	> 50	5.90
7n	3-NO_2	16.12	> 20	> 50	> 50
7o	4-CH_3	> 20	> 20	> 50	> 50
Albendazole		0.016	1.083	–	–
Metronidazole		0.22	0.119	–	–
Nitazoxanide		0.007	0.308	–	–
Benznidazole		–	–	2.90	–
Miltefosine		–	–	–	0.55

S. pyogenes. Benzodiazepines **7c** and **7o** inhibited to *C. albicans* at MIC = 250 μg/mL, while others in the range of MICs = 500 to > 1000 μg/mL, against all fungi.

The antitubercular activity (Table 4) revealed that compounds **6a** (Cl), **6d** (3-NO_2), and **6e** (4-CH_3) showed MICs in the range of 11.0–21.0 μg/mL. In pyridine derivatives, **6g** and **6i** showed MIC values of 28.5 and 11.6 μg/mL, respectively. From the screening, it was found that compound **7m** with NO_2 group at 4-position on benzene and furan groups on benzodiazepine ring showed better MIC = 6.2 μg/mL.

In the case of antiprotozoal activity of **6a–o** (Table 5), biological activity on *G. lamblia* showed interesting results. Compound **6i** with a 4-NO_2 group showed the best IC_{50} with a value of 2.74 μg/mL, and compounds **6a**, **6c**, and **6g** showed values of $IC_{50} < 5.0$ μg/mL. These compounds have a thiophene and pyridine ring on benzothiazepine moiety. Compounds **6d**, **6e**, **6i**, **6m**, and **6n** demonstrated a good leishmanicidal activity with values of IC_{50} between 2.69 and 4.73 μg/mL against *L. mexicana* but with IC_{50} values above the control positive. Only compound **6c** with a NO_2 group at *para* position on benzene and thiophene ring on benzothiazepine moiety showed a significant IC_{50} of 0.65 μg/mL, a similar value with that of the standard drug miltefosine.

The antiprotozoal activity of **7a–o** (Table 6) displays that compounds **7k** (4-Cl) and **7l** (4-OCH_3) with a furan ring on benzodiazepine moiety showed the better biological activity on *Giardia lamblia* with MIC values of 3.16 and 1.85 μg/mL, respectively. In case of trypanocidal activity, compounds **7c** and **7l**, with NO_2 and OCH_3 groups at *para* position on benzene ring, respectively, showed better values of IC_{50} than the reference drug benznidazole. Also, **7c** and **7g** showed better values of IC_{50} on *Leishmania mexicana* than miltefosine. Interestingly, compound **7c** with an electron-withdrawing (NO_2) group at *para* position on benzene ring and thiophene on benzodiazepine moiety had a better biological activity against both parasites than that of the reference drugs.

3 Experimental

The solvents and reagents were used as received or were dried prior to use as needed. Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D and are uncorrected. IR spectra (4000–400 cm^{-1}) of synthesized compounds were recorded on a Shimadzu 8400-S FT-IR spectrophotometer using KBr pellets. Thin layer chromatography was performed on object glass slides (2 cm × 7.5 cm) coated with silica gel-G, and spots were visualized under UV irradiation. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 MHz model spectrometer using $CDCl_3$ as a solvent and TMS as internal standard with ^1H resonant frequency of 400 MHz and ^{13}C resonant frequency of 100 MHz. The ^1H NMR and ^{13}C NMR chemical shifts were reported as parts per million (ppm) downfield from TMS (Me_4Si). Splitting patterns are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; q, quartet; and m, multiplet. The mass spectra were recorded on an JEOL SX-102 (EI) model. Elemental analyses (C, H, and N) $CDCl_3$ were performed using a Heraeus Carlo Erba 1180 CHN analyzer. All chemicals and reagents were purchased from Sigma Aldrich, India.

3.1 Synthesis

3.1.1 Synthesis of 4-(2-thiophen-2-yl-2,3,5a,9a-tetrahydro-benzo[b][1,4]thiazepin-4-yl)-phenol (3a) and 4-[2-(1H-pyrrol-2-yl)-2,3,5a,9a-tetrahydro-benzo[b][1,4]thiazepin-4-yl]-phenol (4a)

A solution of 1-(4-hydroxy-phenyl)-3-thiophen-2-yl-propenone **2a** (0.01 mol) and 2-amino thiophenol (for **3a**)/*o*-phenylenediamine (for **4a**) (0.015 mol) in 60 mL ethanol was refluxed for 30 min; afterwards, 3 mL trifluoroacetic

acid was added and refluxed for another 15–17 h. Progress of the reaction was checked by TLC using toluene : methanol (80 : 20) as mobile phase. Reaction mixture was diluted with 50 mL 10% NaOH solution and extracted with 20 × 3 mL methylene dichloride. The aqueous solution was acidified with dilute HCl. The solid obtained was filtered and washed with water. Purification by column chromatography : mobile phase toluene : ethylacetate (7.5 : 2.5) has been selected after putting TLC in different solvent systems. In particular, system impurity and product were well separated with R_f value of 0.84 (impurity) and 0.59 (product). Pecked silica column was saturated with mobile phase, and solution of compound was added; 10–15 fractions were collected separately. Pure compound was obtained by putting the TLC of every fraction.

By similar process, pyridine (**3b, 4b**) and furan (**3c, 4c**) compounds were synthesized.

3.1.1.1 Characterization of 3a–c and 4a–c 4-(2-thiophen-2-yl-2,3,5a,9a-tetrahydro-benzo[b][1,4]thiazepin-4-yl)-phenol (3a)

Yield: 68%; m.p. 103–106°C; IR (KBr, cm^{-1}): 3287 (O-H), 2955, 2838 (C-H asym, sym), 1610 (> C=N-); ^{1}H NMR ($CDCl_3$): 3.06–3.12 (dd, 1H, J_{BA} = 17.56, J_{BX} = 4.52), 3.66–3.74 (dd, 1H, J_{AB} = 17.56, J_{AX} = 11.76), 5.52–5.56 (d, 1H, J_{XB} = 4.52, J_{XA} = 11.76), 6.91–8.03 (m, 14H, Ar-H), 8.35 (s, 1H, OH). MS (EI) *m*/*z*: 340.1 (M + 1); Anal. Calcd for $C_{19}H_{17}NOS_2$: C, 67.22; H, 5.05; N, 4.13%. Found: C, 67.16; H, 3.97; N, 7.82%.

3.1.1.2 4-(2-Pyridin-2-yl-2,3,5a,9a-tetrahydro-benzo[b][1,4]thiazepin-4-yl)-phenol (3b)

Yield: 71%; m.p. 121–125°C; IR (KBr, cm^{-1}): 3290 (O-H), 2963, 2840 (C-H asym, sym), 1616 (> C=N-); ^{1}H NMR ($CDCl_3$): 3.11–3.15 (dd, 1H, J_{BA} = 17.34, J_{BX} = 4.43), 3.62–3.71 (dd, 1H, J_{AB} = 17.51, J_{AX} = 11.65), 5.61–5.68 (d, 1H, J_{XB} = 4.47, J_{XA} = 11.68), 6.82–8.01 (m, 14H, Ar-H), 8.31(s, 1H, OH). MS (EI) *m*/*z*: 335.3 (M + 1); Anal. Calcd for $C_{20}H_{18}N_2OS$: C, 71.83; H, 5.42; N, 8.38%. Found: C, 71.75; H, 5.33; N, 8.43%.

3.1.1.3 4-(2-Furan-2-yl-2,3,5a,9a-tetrahydro-benzo[b][1,4]thiazepin-4-yl)-phenol (3c)

Yield: 69%; m.p. 133–135°C; IR (KBr, cm^{-1}): 3282 (O-H), 2968, 2847 (C-H asym, sym), 1627 (> C=N-); ^{1}H NMR ($CDCl_3$): 3.14–3.18 (dd, 1H, J_{BA} = 17.45, J_{BX} = 4.41), 3.55–3.61 (dd, 1H, J_{AB} = 17.49, J_{AX} = 11.61), 5.58–5.63 (d, 1H, J_{XB} = 4.36, J_{XA} = 11.58), 6.69–8.11 (m, 14H, Ar-H), 8.42 (s, 1H, OH); MS (EI) *m*/*z*: 324.5 (M + 1); Anal. Calcd for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.30; N, 4.33%. Found: C, 70.51; H, 5.37; N, 4.33%.

3.1.1.4 4-(4-Thiophen-2-yl-4,5,5a,9a-tetrahydro-3*H*-benzo[b][1,4]diazepin-2-yl)-phenol (4a)

Yield: 77%; m.p. 119–122°C; IR (KBr, cm^{-1}): 3341 (N-H), 3258 (O-H), 2916, 2830 (C-H asym, sym), 1592 (> C=N-); ^{1}H NMR ($CDCl_3$): δ 3.21–3.30 (dd, 1H, J_{BA} = 17.42, J_{BX} = 3.81), 3.60–3.73 (dd, 1H, J_{AB} = 17.45, J_{AX} = 11.32), 5.81–5.88 (dd, 1H, J_{XA} = 3.77, J_{XB} = 11.27), 6.83–7.66 (m, 13H, Ar-H), 8.25(s, 1H, > NH), 8.47 (s, 1H, OH); MS (EI) *m*/*z*: 323.4 (M + 1); Anal. Calcd for $C_{19}H_{18}N_2OS$: C, 70.78; H, 5.63; N, 8.69%. Found: C, 70.86; H, 5.58; N, 8.62%.

3.1.1.5 4-(4-Pyridin-2-yl-4,5,5a,9a-tetrahydro-3*H*-benzo[b][1,4]diazepin-2-yl)-phenol (4b)

Yield: 75%; m.p. 144–146°C; IR (KBr, cm^{-1}): 3337 (N-H), 3265 (O-H), 2931, 2843 (C-H asym, sym), 1583 (> C=N-); ^{1}H NMR ($CDCl_3$): δ 3.28–3.34 (dd, 1H, J_{BA} = 17.34, J_{BX} = 3.87), 3.67–3.75 (dd, 1H, J_{AB} = 17.27, J_{AX} = 11.43), 5.77–5.83 (dd, 1H, J_{XA} = 3.60, J_{XB} = 11.45), 6.92–7.89 (m, 14H, Ar-H), 8.20 (s, 1H, > NH), 8.53 (s, 1H, OH); MS (EI) *m*/*z*: 318.1 (M + 1); Anal. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24%. Found: C, 75.61; H, 6.15; N, 13.17%.

3.1.1.6 4-(4-Furan-2-yl-4,5,5a,9a-tetrahydro-3*H*-benzo[b][1,4]diazepin-2-yl)-phenol (4c)

Yield: 80%; m.p. 134–136°C; IR (KBr, cm^{-1}): 3345 (N-H), 3271 (O-H), 2953, 2840 (C-H asym, sym), 1612 (> C=N-); ^{1}H NMR ($CDCl_3$): δ 3.07–3.12 (dd, 1H, J_{BA} = 17.41, J_{BX} = 4.11), 3.68–3.75 (dd, 1H, J_{AB} = 17.67, J_{AX} = 11.71), 5.50–5.55 (dd, 1H, J_{XA} = 4.32, J_{XB} = 11.50), 7.15–8.10 (m, 13H, Ar-H), 8.35 (s, 1H, > NH), 8.68 (s, 1H, OH); MS (EI) *m*/*z*: 307.8 (M + 1); Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14%. Found: C, 74.42; H, 5.88; N, 9.22%.

3.1.2 Synthesis of 4-{4-[5-(4-chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-thiophen-2-yl-2,3-dihydro-benzo[b][1,4]thiazepine (6a) and 4-{4-[5-(4-chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-thiophen-2-yl-2,3-dihydro-1*H*-benzo[b][1,4]diazepine (7a)

Solution of 2-chloromethyl-5-(4-chlorophenyl)-1,3,4-oxadiazole **5a** (0.01 mol) in 15 mL methanol was added part wise in 15 mL methanolic solution of **3a**/**4a** (0.01 mol) and potassium hydroxide (0.15 mol). After addition, reaction mixture was refluxed on water bath for 12–15 h. Progress of the reaction was checked by TLC using toluene : methanol (75 : 25) as mobile phase. The reaction mixture was cooled and poured into crushed ice with continuous stirring. The resulting solid thus obtained was collected by filtration,

washed well with cold water, dried, and recrystallized from absolute ethanol and yielded the compound **6a**/**7a**. Other 1,3,4-oxadiazolyl-benzothiazepines and 1,3,4-oxadiazolyl-benzodiazepines have been prepared by the same method with thiophene-2-aldehyde (for synthesis of **6b–e** and **7b–e**), pyridine-2-aldehyde (for synthesis of **6f–j** and **7f–j**), and furan-2-aldehyde (for synthesis of **6k–o** and **7k–o**).

3.2 Characterization data of compound 6a–o

3.2.1 4-{4-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-thiophen-2-yl-2,3-dihydro-benzo[b][1,4]thiazepine (6a)

Yield: 57%; m.p. 141–143°C; IR (KBr, cm^{-1}): 2958, 2862 (C-H asym, sym), 1612 (> C=N-), 758 (C-Cl); ^{1}H NMR ($CDCl_3$): δ 3.26–3.32 (dd, 1H, J_{BA} = 17.45, J_{BX} = 3.89), 3.67–3.75 (dd, 1H, J_{AB} = 17.45, J_{AX} = 11.32), 5.31 (s, 2H, -CH_2O-), 5.89–5.94 (dd, 1H, J_{XA} = 3.86, J_{XB} = 11.37), 6.86–8.25 (m, 15H, Ar-H); ^{13}C NMR ($CDCl_3$): 42.46 (C-18), 44.21 (C-19), 72.76 (C-10), 116.97 (C-22), 119.11 (C-14), 121.19 (C-29), 121.56 (C-27), 122.76 (C-23), 124.23 (C-28), 125.15 (C-24), 126.52 (C-12, C-16), 127.46 (C-3, C-7), 128.33 (C-25), 129.14 (C-4, C-6), 129.67 (C-13, C-15), 133.66 (C-5), 135.33 (C-2), 140.22 (C-20), 140.65 (C-26), 142.56 (C-21), 144.47 (C-17), 144.78 (C-11), 162.33 (C-8), 164.13 (C-9); MS (EI) *m*/*z*: 531.1 (M + 1); Anal. Calcd for $C_{28}H_{20}N_3O_2ClS_2$: C, 63.45; H, 3.80; N, 7.93%. Found: C, 63.41; H, 3.87; N, 7.87%.

3.2.2 4-{4-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-thiophen-2-yl-2,3-dihydro-benzo[b][1,4]thiazepine (6b)

Yield: 62%; m.p. 161–163°C; IR (KBr, cm^{-1}): 2953, 2860 (C-H asym, sym), 1616 (> C=N-), 1289 (-OCH_3); ^{1}H NMR ($CDCl_3$): δ 3.29–3.34 (dd, 1H, J_{BA} = 17.48, J_{BX} = 3.84), 3.65–3.72 (dd, 1H, J_{AB} = 17.48, J_{AX} = 11.36), 3.85 (s, 3H, -OCH_3), 5.28 (s, 2H, -CH_2O-), 5.87–5.91 (dd, 1H, J_{XA} = 3.80, J_{XB} = 11.32), 6.90–8.30 (m, 15H, Ar-H); ^{13}C NMR ($CDCl_3$): 42.28 (C-18), 44.52 (C-19), 59.29 (C-1), 72.68 (C-10), 117.15 (C-22), 119.18 (C-14), 121.14 (C-29), 121.21 (C-27), 123.45 (C-23), 124.51 (C-28), 125.48 (C-24), 126.59 (C-12, C-16), 127.15 (C-3, C-7), 128.45 (C-25), 129.05 (C-4, C-6), 129.53 (C-13, C-15), 133.37 (C-5), 140.50 (C-20), 140.86 (C-26), 142.22 (C-21), 144.16 (C-17), 145.58 (C-11), 153.88 (C-2), 162.78 (C-8), 164.82 (C-9); MS (EI) *m*/*z*: 526.0 (M + 1); Anal. Calcd for $C_{29}H_{23}N_3O_3S_2$: C, 66.26; H, 4.41; N, 7.99%. Found: C, 66.23; H, 4.48; N, 7.91%.

3.2.3 4-{4-[5-(4-Nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-thiophen-2-yl-2,3-dihydro-benzo[b][1,4]thiazepine (6c)

Yield: 58%; m.p. 193–195°C; IR (KBr, cm^{-1}): 2962, 2859 (C-H asym, sym), 1615 (> C=N-), 1531, 1347 (-NO_2 asym, sym); ^{1}H NMR ($CDCl_3$): δ 3.34–3.39 (dd, 1H, J_{BA} = 17.45, J_{BX} = 3.91), 3.60–3.66 (dd, 1H, J_{AB} = 17.40, J_{AX} = 11.28), 5.32 (s, 2H, -CH_2O-), 5.83–5.90 (dd, 1H, J_{XA} = 3.82, J_{XB} = 11.30), 6.92–8.32 (m, 15H, Ar-H); ^{13}C NMR ($CDCl_3$): 42.33 (C-18), 43.68 (C-19), 71.96 (C-10), 116.91 (C-22), 119.56 (C-14), 121.22 (C-29), 121.32 (C-27), 122.71 (C-23), 124.39 (C-28), 125.19 (C-24), 126.47 (C-12, C-16), 127.97 (C-3, C-7), 128.56 (C-25), 128.95 (C-4, C-6), 129.55 (C-13, C-15), 134.12 (C-5), 140.35 (C-20), 140.77 (C-26), 142.13 (C-21), 144.54 (C-17), 144.89 (C-11), 148.31 (C-2), 161.90 (C-8), 164.27 (C-9); MS (EI) *m*/*z*: 541.2 (M + 1); Anal. Calcd for $C_{28}H_{20}N_4O_4S_2$: C, 62.21; H, 3.73; N, 10.36%. Found: C, 62.28; H, 3.76; N, 10.30%.

3.2.4 4-{4-[5-(3-Nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-thiophen-2-yl-2,3-dihydro-benzo[b][1,4]thiazepine (6d)

Yield: 60%; m.p. 174–175°C; IR (KBr, cm^{-1}): 2959, 2863 (C-H asym, sym), 1621 (> C=N-), 1535, 1351 (-NO_2 asym, sym); ^{1}H NMR ($CDCl_3$): δ 3.32–3.38 (dd, 1H, J_{BA} = 17.43, J_{BX} = 3.93), 3.65–3.71 (dd, 1H, J_{AB} = 17.36, J_{AX} = 11.35), 5.37 (s, 2H, -CH_2O-), 5.81–5.88 (dd, 1H, J_{XA} = 3.76, J_{XB} = 11.37), 6.87–8.25 (m, 15H, Ar-H); ^{13}C NMR ($CDCl_3$): 42.69 (C-18), 44.15 (C-19), 72.37 (C-10), 117.54 (C-22), 119.32 (C-14), 121.33 (C-29), 121.52 (C-27), 122.64 (C-23), 124.20 (C-28), 125.36 (C-24), 126.55 (C-12, C-16), 128.25 (C-3, C-7), 128.59 (C-25), 129.21(C-4, C-6), 129.44 (C-13, C-15), 134.10 (C-5), 140.39 (C-20), 140.89 (C-26), 142.25 (C-21), 144.77 (C-17), 145.11 (C-11), 147.52 (C-2), 162.23 (C-8), 164.49 (C-9); MS (EI) *m*/*z*: 541.1 (M + 1); Anal. Calcd for $C_{28}H_{20}N_4O_4S_2$: C, 62.21; H, 3.73; N, 10.36%. Found: C, 62.24; H, 3.71; N, 10.40%.

3.2.5 2-Thiophen-2-yl-4-[4-(5-p-tolyl-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]-2,3-dihydro-benzo[b][1,4]thiazepine (6e)

Yield: 68%; m.p. 152–154°C; IR (KBr, cm^{-1}): 2958, 2864 (C-H asym, sym), 1611 (> C=N-), 1446 (-CH_3); ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H, -CH_3), 3.31–3.36 (dd, 1H, J_{BA} = 17.41, J_{BX} = 3.87), 3.61–3.68 (dd, 1H, J_{AB} = 17.43, J_{AX} = 11.32), 5.32 (s, 2H, -CH_2O-), 5.85–5.89 (dd, 1H, J_{XA} = 3.77, J_{XB} = 11.26), 6.92–8.32 (m, 15H, Ar-H); ^{13}C NMR ($CDCl_3$): 42.21 (C-18), 44.63 (C-19), 21.27 (C-1),

72.76 (C-10), 117.11 (C-22), 119.12 (C-14), 120.94 (C-29), 121.52 (C-27), 123.63 (C-23), 124.11 (C-28), 125.40 (C-24), 126.35 (C-12, C-16), 127.10 (C-3, C-7), 128.32 (C-25), 129.18 (C-4, C-6), 129.67 (C-13, C-15), 133.29 (C-5), 138.17 (C-2), 140.66 (C-20), 140.81 (C-26), 142.10 (C-21), 144.23 (C-17), 145.63 (C-11), 162.64 (C-8), 164.22 (C-9); MS (EI) *m/z*: 510.1 (M+1); Anal. Calcd for $C_{29}H_{23}N_3O_2S_2$: C, 68.34; H, 4.55; N, 8.25%. Found: C, 68.39; H, 4.50; N, 8.17%.

3.2.6 4-{4-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-pyridin-2-yl-2,3-dihydro-benzo[b][1,4]thiazepine (6f)

Yield: 61%; m.p. 169–171°C; IR (KBr, cm^{-1}): 2969, 2865 (C-H asym, sym), 1618 (>C=N-), 743 (C-Cl); ^{1}H NMR ($CDCl_3$): δ 3.35–3.41 (dd, 1H, J_{BA}=17.34, J_{BX}=3.87), 3.61–3.72 (dd, 1H, J_{AB}=17.32, J_{AX}=11.37), 5.22 (s, 2H, -CH_2O-), 5.88–5.93 (dd, 1H, J_{XA}=3.87, J_{XB}=11.33), 6.90–8.30 (m, 16H, Ar-H); ^{13}C NMR ($CDCl_3$): 42.17 (C-18), 44.75 (C-19), 72.68 (C-10), 117.11 (C-22), 119.56 (C-14), 121.32 (C-29), 122.56 (C-27), 122.62 (C-23), 125.11 (C-24), 126.82 (C-12, C-16), 127.30 (C-3, C-7), 128.12 (C-25), 129.25 (C-4, C-6), 129.79 (C-13, C-15), 133.52 (C-5), 134.91 (C-28), 135.10 (C-2), 140.49 (C-20), 142.22 (C-21), 144.69 (C-17), 144.86 (C-11), 151.53 (C-30), 161.31 (C-26), 162.88 (C-8), 164.45 (C-9); MS (EI) *m/z*: 526.0 (M+1); Anal. Calcd for $C_{29}H_{21}N_4O_2ClS$: C, 66.34; H, 4.03; N, 10.67%. Found: C, 66.24; H, 4.10; N, 10.71%.

3.2.7 4-{4-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-pyridin-2-yl-2,3-dihydro-benzo[b][1,4]thiazepine (6g)

Yield: 72%; m.p. 178–180°C; IR (KBr, cm^{-1}): 2959, 2855 (C-H asym, sym), 1610 (>C=N-), 1285 (-OCH_3); ^{1}H NMR ($CDCl_3$): δ 3.33–3.38 (dd, 1H, J_{BA}=17.32, J_{BX}=3.81), 3.63–3.70 (dd, 1H, J_{AB}=17.38, J_{AX}=11.32), 3.79 (s, 3H, -OCH_3), 5.27 (s, 2H, -CH_2O-), 5.91–5.96 (dd, 1H, J_{XA}=3.83, J_{XB}=11.36), 6.95–8.35 (m, 16H, Ar-H); ^{13}C NMR ($CDCl_3$): 42.54 (C-18), 43.95 (C-19), 59.56 (C-1), 72.12 (C-10), 117.95 (C-22), 119.23 (C-14), 121.45 (C-29), 122.76 (C-27), 122.88 (C-23), 125.24 (C-24), 126.37 (C-12, C-16), 127.29 (C-3, C-7), 128.05 (C-25), 129.34 (C-4, C-6), 130.11 (C-13, C-15), 133.43 (C-5), 135.12 (C-28), 135.10 (C-2), 140.49 (C-20), 142.22 (C-21), 144.69 (C-17), 144.86 (C-11), 151.53 (C-30), 161.46 (C-26), 162.92 (C-8), 164.66 (C-9); MS (EI) *m/z*: 521.3 (M+1); Anal. Calcd for $C_{30}H_{24}N_4O_3S$: C, 69.21; H, 4.65; N, 10.76%. Found: C, 69.26; H, 4.61; N, 10.85%.

3.2.8 4-{4-[5-(4-Nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-pyridin-2-yl-2,3-dihydro-benzo[b][1,4]thiazepine (6h)

Yield: 78%; m.p. 187–189°C; IR (KBr, cm^{-1}): 2961, 2868 (C-H asym, sym), 1623 (>C=N-), 1532, 1347 (-NO_2 asym, sym); ^{1}H NMR ($CDCl_3$): δ 3.25–3.31 (dd, 1H, J_{BA}=17.26, J_{BX}=3.85), 3.70–3.77 (dd, 1H, J_{AB}=17.35, J_{AX}=11.32), 5.30 (s, 2H, -CH_2O-), 5.91–5.96 (dd, 1H, J_{XA}=3.84, J_{XB}=11.42), 6.83–8.22 (m, 16H, Ar-H); ^{13}C NMR ($CDCl_3$): 42.35 (C-18), 44.65 (C-19), 72.21 (C-10), 117.49 (C-22), 119.44 (C-14), 121.67 (C-29), 122.23 (C-27), 122.53 (C-23), 125.74 (C-24), 126.41 (C-12, C-16), 127.22 (C-3, C-7), 128.29 (C-25), 129.38 (C-4, C-6), 129.90 (C-13, C-15), 133.41 (C-5), 134.88 (C-28), 140.41 (C-20), 142.06 (C-21), 144.32 (C-17), 145.17 (C-11), 148.29 (C-2), 151.66 (C-30), 161.39 (C-26), 163.12 (C-8), 164.65 (C-9); MS (EI) *m/z*: 536.1 (M+1); Anal. Calcd for $C_{29}H_{21}N_5O_4S$: C, 65.04; H, 3.95; N, 13.08%. Found: C, 65.09; H, 3.91; N, 13.02%.

3.2.9 4-{4-[5-(3-Nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-pyridin-2-yl-2,3-dihydro-benzo[b][1,4]thiazepine (6i)

Yield: 65%; m.p. 156–158°C; IR (KBr, cm^{-1}): 2965, 2865 (C-H asym, sym), 1619 (>C=N-), 1539, 1341 (-NO_2 asym, sym); ^{1}H NMR ($CDCl_3$): δ 3.28–3.34 (dd, 1H, J_{BA}=17.22, J_{BX}=3.89), 3.73–3.81 (dd, 1H, J_{AB}=17.32, J_{AX}=11.37), 5.33 (s, 2H, -CH_2O-), 5.88–5.93 (dd, 1H, J_{XA}=3.88, J_{XB}=11.49), 6.80–8.18 (m, 16H, Ar-H); ^{13}C NMR ($CDCl_3$): 21.24 (C-1), 42.11 (C-18), 43.22 (C-19), 72.19 (C-10), 118.22 (C-22), 119.21 (C-14), 121.65 (C-29), 122.69 (C-27), 122.90 (C-23), 125.20 (C-24), 126.21 (C-12, C-16), 127.49 (C-3, C-7), 128.23 (C-25), 129.31 (C-4, C-6), 130.27 (C-13, C-15), 133.58 (C-5), 135.27 (C-28), 138.62 (C-2), 140.53 (C-20), 142.34 (C-21), 144.30 (C-17), 144.39 (C-11), 151.77 (C-30), 161.11 (C-26), 163.42 (C-8), 164.79 (C-9); MS (EI) *m/z*: 536.2 (M+1); Anal. Calcd for $C_{29}H_{21}N_5O_4S$: C, 65.04; H, 3.95; N, 13.08%. Found: C, 65.08; H, 3.88; N, 13.13%.

3.2.10 2-Pyridin-2-yl-4-[4-(5-p-tolyl-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]-2,3-dihydro-benzo[b][1,4]thiazepine (6j)

Yield: 68%; m.p. 146–148°C; IR (KBr, cm^{-1}): 2952, 2858 (C-H asym, sym), 1621 (>C=N-), 1449 (-CH_3); ^{1}H NMR ($CDCl_3$): δ 2.27 (s, 3H, -CH_3), 3.28–3.33 (dd, 1H, J_{BA}=17.29, J_{BX}=3.83), 3.67–3.74 (dd, 1H, J_{AB}=17.32, J_{AX}=11.35), 5.30 (s, 2H, -CH_2O-), 5.90–5.94 (dd, 1H, J_{XA}=3.81, J_{XB}=11.36), 6.85–8.25 (m, 16H, Ar-H); ^{13}C NMR ($CDCl_3$): 21.53 (C-1), 42.33 (C-18), 43.21(C-19), 72.11 (C-10), 117.64 (C-22), 119.20 (C-14), 121.22 (C-29), 122.34 (C-27), 122.92 (C-23), 125.21 (C-24), 126.76 (C-12, C-16), 127.47

(C-3, C-7), 128.11 (C-25), 129.27 (C-4, C-6), 130.56 (C-13, C-15), 133.21 (C-5), 135.39 (C-28), 138.90 (C-2), 141.41 (C-20), 142.36 (C-21), 144.32 (C-17), 144.70 (C-11), 151.31 (C-30), 161.77 (C-26), 162.88 (C-8), 164.89 (C-9); MS (EI) *m/z*: 505.0 (M + 1); Anal. Calcd for $C_{30}H_{24}N_4O_2S$: C, 71.41; H, 4.79; N, 11.10%. Found: C, 71.47; H, 4.82; N, 11.03%.

3.2.11 4-{4-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-furan-2-yl-2,3-dihydro-benzo[b][1,4]thiazepine (6k)

Yield: 59%; m.p. 196–197°C; IR (KBr, cm^{-1}): 2955, 2861 (C-H asym, sym), 1608 (> C=N-), 769 (C-Cl); ^{1}H NMR ($CDCl_3$): δ 3.24–3.31 (dd, 1H, J_{BA} = 17.19, J_{BX} = 4.27), 3.56–3.62 (dd, 1H, J_{AB} = 17.66, J_{AX} = 11.41), 5.25 (s, 2H, -CH_2O-), 5.92–5.97 (dd, 1H, J_{XA} = 4.51, J_{XB} = 11.77), 6.83–8.22 (m, 15H, Ar-H); ^{13}C NMR ($CDCl_3$): 42.38 (C-18), 55.15 (C-19), 71.91 (C-10), 117.49 (C-22), 119.58 (C-14), 102.33 (C-27), 104.20 (C-28), 122.47 (C-20), 124.32 (C-23), 125.58 (C-24), 126.29 (C-12, C-16), 127.46 (C-3, C-7), 128.49 (C-25), 129.77 (C-4, C-6), 129.64 (C-13, C-15), 133.47 (C-5), 135.78 (C-2), 137.16 (C-26), 137.28 (C-29), 142.40 (C-21), 143.92 (C-17), 145.25 (C-11), 163.15 (C-8), 165.10 (C-9); MS (EI) *m/z*: 514.4 (M + 1); Anal. Calcd for $C_{28}H_{20}N_3O_3ClS$: C, 65.43; H, 3.92; N, 8.18%. Found: C, 65.49; H, 3.96; N, 8.1%.

3.2.12 2-Furan-2-yl-4-{4-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2,3-dihydro-benzo[b][1,4]thiazepine (6l)

Yield: 63%; m.p. 182–184°C; IR (KBr, cm^{-1}): 2965, 2851 (C-H asym, sym), 1614 (> C=N-), 1281 (-OCH_3); ^{1}H NMR ($CDCl_3$): δ 3.26–3.31 (dd, 1H, J_{BA} = 17.11, J_{BX} = 4.22), 3.59–3.66 (dd, 1H, J_{AB} = 17.61, J_{AX} = 11.43), 3.85 (s, 3H, -OCH_3), 5.29 (s, 2H, -CH_2O-), 5.92–5.96 (dd, 1H, J_{XA} = 4.51, J_{XB} = 11.77), 6.87–8.27 (m, 15H, Ar-H); ^{13}C NMR ($CDCl_3$): 42.28 (C-18), 55.23 (C-19), 59.67 (C-1), 72.61 (C-10), 117.43 (C-22), 119.27 (C-14), 102.28 (C-27), 104.41 (C-28), 122.13 (C-20), 123.41 (C-23), 125.40 (C-24), 126.32 (C-12, C-16), 127.11 (C-3, C-7), 128.35 (C-25), 129.11 (C-4, C-6), 129.59 (C-13, C-15), 133.31 (C-5), 137.10 (C-26), 137.13 (C-29), 142.65 (C-21), 144.11 (C-17), 145.42 (C-11), 153.43 (C-2), 162.89 (C-8), 164.92 (C-9); MS (EI) *m/z*: 510.1 (M + 1); Anal. Calcd for $C_{29}H_{23}N_3O_4S$: C, 68.35; H, 4.55; N, 8.25%. Found: C, 68.30; H, 4.51; N, 8.28%.

3.2.13 2-Furan-2-yl-4-{4-[5-(4-nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2,3-dihydro-benzo[b][1,4]thiazepine (6m)

Yield: 60%; m.p. 136–137°C; IR (KBr, cm^{-1}): 2959, 2865 (C-H asym, sym), 1608 (> C=N-), 1529, 1349 (-NO_2 asym, sym); ^{1}H NMR ($CDCl_3$): δ 3.33–3.39 (dd, 1H, J_{BA} = 17.26, J_{BX} = 4.22), 3.63–3.69 (dd, 1H, J_{AB} = 17.49, J_{AX} = 11.55), 5.37 (s, 2H, -CH_2O-), 5.87–5.92 (dd, 1H, J_{XA} = 4.48, J_{XB} = 11.65), 6.79–8.36 (m, 15H, Ar-H); ^{13}C NMR ($CDCl_3$): 42.12 (C-18), 55.11 (C-19), 72.11 (C-10), 117.42 (C-22), 119.67 (C-14), 102.39 (C-27), 104.35 (C-28), 122.31 (C-20), 124.28 (C-23), 125.33 (C-24), 126.40 (C-12, C-16), 127.56 (C-3, C-7), 128.67 (C-25), 129.23 (C-4, C-6), 129.78 (C-13, C-15), 133.62 (C-5), 137.46 (C-26), 137.87 (C-29), 142.33 (C-21), 143.85 (C-17), 145.11 (C-11), 148.67 (C-2), 163.10 (C-8), 165.19 (C-9); MS (EI) *m/z*: 525.2 (M + 1); Anal. Calcd for $C_{28}H_{20}N_4O_5S$: C, 64.11; H, 3.84; N, 10.68%. Found: C, 64.14; H, 3.81; N, 10.73%.

3.2.14 2-Furan-2-yl-4-{4-[5-(3-nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2,3-dihydro-benzo[b][1,4]thiazepine (6n)

Yield: 59%; m.p. 165–166°C; IR (KBr, cm^{-1}): 2963, 2855 (C-H asym, sym), 1610 (> C=N-), 1535, 1345 (-NO_2 asym, sym); ^{1}H NMR ($CDCl_3$): δ 3.30–3.35 (dd, 1H, J_{BA} = 17.22, J_{BX} = 4.17), 3.60–3.66 (dd, 1H, J_{AB} = 17.42, J_{AX} = 11.46), 5.30 (s, 2H, -CH_2O-), 5.84–5.92 (dd, 1H, J_{XA} = 4.42, J_{XB} = 11.70), 6.82–8.32 (m, 15H, Ar-H); ^{13}C NMR ($CDCl_3$): 41.90 (C-18), 55.48 (C-19), 72.67 (C-10), 116.82 (C-22), 119.54 (C-14), 102.77 (C-27), 104.31 (C-28), 122.56 (C-20), 124.33 (C-23), 125.21 (C-24), 126.76 (C-12, C-16), 127.44 (C-3, C-7), 128.45 (C-25), 128.79 (C-4, C-6), 129.11 (C-13, C-15), 133.15 (C-5), 137.76 (C-26), 137.81 (C-29), 142.20 (C-21), 143.49 (C-17), 145.55 (C-11), 148.77 (C-2), 163.17 (C-8), 164.10 (C-9); MS (EI) *m/z*: 525.1 (M + 1); Anal. Calcd for $C_{28}H_{20}N_4O_5S$: C, 64.11; H, 3.84; N, 10.68%. Found: C, 64.19; H, 3.80; N, 10.72%.

3.2.15 2-Furan-2-yl-4-[4-(5-p-tolyl-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]-2,3-dihydro-benzo[b][1,4]thiazepine (6o)

Yield: 69%; m.p. 199–201°C; IR (KBr, cm^{-1}): 2953, 2859 (C-H asym, sym), 1613 (> C=N-), 1451 (-CH_3); ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H, -CH_3), 3.29–3.34 (dd, 1H, J_{BA} = 17.19, J_{BX} = 4.27), 3.64–3.71 (dd, 1H, J_{AB} = 17.58, J_{AX} = 11.48), 5.31 (s, 2H, -CH_2O-), 5.88–5.92 (dd, 1H, J_{XA} = 4.56, J_{XB} = 11.72), 6.91–8.31 (m, 15H, Ar-H); ^{13}C NMR ($CDCl_3$): 21.67 (C-1), 42.56 (C-18), 55.67 (C-19), 72.13 (C-10), 117.40 (C-22), 119.34 (C-14), 102.69 (C-27), 104.13 (C-28), 122.11 (C-20), 123.43 (C-23), 125.54 (C-24), 126.36 (C-12, C-16), 127.64 (C-3, C-7), 128.64 (C-25), 129.32 (C-4, C-6), 129.41 (C-13, C-15), 133.67 (C-5), 137.69 (C-26), 137.88 (C-29), 138.43 (C-2), 142.22 (C-21), 144.78 (C-17), 145.68 (C-11), 162.35 (C-8), 164.67 (C-9); MS (EI) *m/z*: 494.1 (M + 1); Anal. Calcd for $C_{29}H_{23}N_3O_3S$: C, 70.57; H, 4.70; N, 8.51%. Found: C, 70.62; H, 4.66; N, 8.43%.

3.2.16 4-{4-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-thiophen-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine (7a)

Yield: 57%; m.p. 131–133°C; IR (KBr, cm^{-1}): 3355 (N-H), 2960, 2867 (C-H asym, sym), 1616 (>C=N-), 747 (C-Cl); ^{1}H NMR ($CDCl_3$): δ 3.29–3.37 (dd, 1H, J_{BA} = 17.42, J_{BX} = 3.81), 3.62–3.71 (dd, 1H, J_{AB} = 17.44, J_{AX} = 11.41), 5.31 (s, 2H, -CH_2O-), 5.82–5.87 (dd, 1H, J_{XA} = 3.87, J_{XB} = 11.25), 6.77–7.53 (m, 15H, Ar-H), 8.39 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 42.21 (C-18), 44.56 (C-19), 72.12 (C-10), 110.64 (C-25), 112.43 (C-5), 115.12 (C-12, C-16), 115.66 (C-3, C-7), 119.23 (C-23), 121.21 (C-29), 121.40 (C-27), 122.15 (C-22), 124.64 (C-28), 127.18 (C-14), 128.11 (C-24), 129.11 (C-4, C-6), 129.65 (C-13, C-15), 129.68 (C-20, C-21), 134.97 (C-2), 140.62 (C-26), 140.76 (C-20), 154.32 (C-11), 160.45 (C-17), 163.31 (C-9), 166.63 (C-8); MS (EI) *m/z*: 514.0 (M+1); Anal. Calcd for $C_{28}H_{21}N_4O_2ClS$: C, 65.55; H, 4.13; N, 10.92%. Found: C, 65.59; H, 4.11; N, 10.97%.

3.2.17 4-{4-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-thiophen-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine (7b)

Yield: 62%; m.p. 165–167°C; IR (KBr, cm^{-1}): 3364 (N-H), 2951, 2853 (C-H asym, sym), 1610 (>C=N-), 1283 (-OCH_3); ^{1}H NMR ($CDCl_3$): δ 3.27–3.33 (dd, 1H, J_{BA} = 17.48, J_{BX} = 3.84), 3.66–3.71 (dd, 1H, J_{AB} = 17.48, J_{AX} = 11.36), 3.81 (s, 3H, -OCH_3), 5.36 (s, 2H, -CH_2O-), 5.85–5.89 (dd, 1H, J_{XA} = 3.80, J_{XB} = 11.32), 6.80–7.56 (m, 15H, Ar-H), 8.33 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 42.57 (C-18), 44.22 (C-19), 59.38 (C-1), 71.83 (C-10), 110.67 (C-25), 112.11 (C-5), 114.98 (C-12, C-16), 115.72 (C-3, C-7), 119.77 (C-23), 121.25 (C-29), 121.46 (C-27), 122.09 (C-22), 124.55 (C-28), 127.30 (C-14), 128.13 (C-24), 128.69 (C-4, C-6), 129.32 (C-13, C-15), 129.52 (C-20, C-21), 140.76 (C-26), 140.89 (C-20), 153.20 (C-2), 154.47 (C-11), 160.63 (C-17), 163.25 (C-9), 166.47 (C-8); MS (EI) *m/z*: 509.1 (M+1); Anal. Calcd for $C_{29}H_{24}N_4O_3S$: C, 68.49; H, 4.76; N, 11.02%. Found: C, 68.43; H, 4.72; N, 11.07%.

3.2.18 4-{4-[5-(4-Nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-thiophen-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine (7c)

Yield: 58%; m.p. 189–191°C; IR (KBr, cm^{-1}): 3353 (N-H), 2947, 2859 (C-H asym, sym), 1618 (>C=N-), 1535, 1348 (-NO_2 asym, sym); ^{1}H NMR ($CDCl_3$): δ 3.28–3.35 (dd, 1H, J_{BA} = 17.37, J_{BX} = 3.82), 3.66–33.72 (dd, 1H, J_{AB} = 17.36, J_{AX} = 11.40), 5.35 (s, 2H, -CH_2O-), 5.84–5.90 (dd, 1H, J_{XA} = 3.73, J_{XB} = 11.29), 6.85–7.61 (m, 15H, Ar-H), 8.42 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 42.49 (C-18), 43.96 (C-19), 72.89 (C-10), 110.50 (C-25), 112.21 (C-5), 115.47 (C-12, C-16), 116.11 (C-3, C-7), 119.44 (C-23), 121.26 (C-29), 121.56 (C-27), 121.98 (C-22), 124.60 (C-28), 126.89 (C-14), 128.15 (C-24), 129.21 (C-4, C-6), 129.77 (C-13, C-15), 129.85 (C-20, C-21), 140.43 (C-26), 140.82 (C-20), 148.06 (C-2), 154.67 (C-11), 160.31 (C-17), 164.55 (C-9), 166.22 (C-8); MS (EI) *m/z*: 524.2 (M+1); Anal. Calcd for $C_{28}H_{21}N_5O_4S$: C, 64.23; H, 4.04; N, 13.38%. Found: C, 64.21; H, 4.11; N, 13.33%.

3.2.19 4-{4-[5-(3-Nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-thiophen-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine (7d)

Yield: 60%; m.p. 152–154°C; IR (KBr, cm^{-1}):3363 (N-H), 2935, 2856 (C-H asym, sym), 1622 (>C=N-), 1541, 1364 (-NO_2 asym, sym);^{1}H NMR ($CDCl_3$): δ 3.34–3.41 (dd, 1H, J_{BA} = 17.39, J_{BX} = 3.87), 3.62–33.68 (dd, 1H, J_{AB} = 17.33, J_{AX} = 11.46), 5.32 (s, 2H, -CH_2O-), 5.88–5.94 (dd, 1H, J_{XA} = 3.79, J_{XB} = 11.26), 6.89–7.68 (m, 15H, Ar-H), 8.38 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 42.11 (C-18), 43.36 (C-19), 71.29 (C-10), 110.57 (C-25), 112.43 (C-5), 115.22 (C-12, C-16), 116.48 (C-3, C-7), 119.32 (C-23), 121.52 (C-29), 121.67 (C-27), 122.12 (C-22), 124.87 (C-28), 127.21 (C-14), 128.22 (C-24), 129.19 (C-4, C-6), 129.46 (C-13, C-15), 129.93 (C-20, C-21), 140.67 (C-26), 140.80 (C-20), 148.17 (C-2), 154.61 (C-11), 161.37 (C-17), 163.21 (C-9), 166.77 (C-8); MS (EI) *m/z*: 524.1 (M+1); Anal. Calcd for $C_{28}H_{21}N_5O_4S$: C, 64.23; H, 4.04; N, 13.38%. Found: C, 64.27; H, 4.01; N, 13.42%.

3.2.20 2-Thiophen-2-yl-4-[4-(5-p-tolyl-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]-2,3-dihydro-1H-benzo[b][1,4]diazepine (7e)

Yield: 68%; m.p. 161–163°C; IR (KBr, cm^{-1}): 3356 (N-H), 2951, 2859 (C-H asym, sym), 1623 (>C=N-), 1452 (-CH_3); ^{1}H NMR ($CDCl_3$): δ 2.41 (s, 3H, -CH_3), 3.25–3.31 (dd, 1H, J_{BA} = 17.42, J_{BX} = 3.88), 3.62–3.69 (dd, 1H, J_{AB} = 17.41, J_{AX} = 11.43), 5.39 (s, 2H, -CH_2O-), 5.89–5.93 (dd, 1H, J_{XA} = 3.76, J_{XB} = 11.27), 6.82–7.58 (m, 15H, Ar-H), 8.37 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 21.77 (C-1), 42.44 (C-18), 44.19 (C-19), 72.12 (C-10), 110.63 (C-25), 112.24 (C-5), 115.11 (C-12, C-16), 115.69 (C-3, C-7), 119.31 (C-23), 121.56 (C-29), 121.68 (C-27), 122.25 (C-22), 124.48 (C-28), 127.20 (C-14), 128.06 (C-24), 128.70 (C-4, C-6), 129.21 (C-13, C-15), 129.69 (C-20, C-21), 138.29 (C-2), 140.89 (C-26), 140.92 (C-20), 154.65 (C-11), 160.22 (C-17), 163.29 (C-9), 166.69 (C-8); MS (EI) *m/z*: 493.0 (M+1); Anal. Calcd for $C_{29}H_{24}N_4O_2S$: C, 70.71; H, 4.91; N, 11.37%. Found: C, 70.76; H, 4.86; N, 11.32%.

3.2.21 4-{4-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-pyridin-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine (7f)

Yield: 61%; m.p. 183–185°C; IR (KBr, cm^{-1}): 3358 (N-H), 2943, 2861 (C-H asym, sym), 1621 (>C=N-), 767 (C-Cl); ^{1}H NMR ($CDCl_3$): δ 3.34–3.39 (dd, 1H, J_{BA} = 17.37, J_{BX} = 3.91), 3.62–3.70 (dd, 1H, J_{AB} = 17.38, J_{AX} = 11.27), 5.33 (s, 2H, -CH_2O-), 5.82–5.88 (dd, 1H, J_{XA} = 3.84, J_{XB} = 11.31), 6.89–7.60 (m, 16H, Ar-H), 8.30 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 41.93 (C-18), 55.44 (C-19), 72.11 (C-10), 110.43 (C-25), 112.54 (C-5), 115.10 (C-12, C-16), 115.43 (C-3, C-7), 120.56 (C-23), 121.62 (C-29), 122.65 (C-22), 122.78 (C-27), 127.35 (C-14), 128.21 (C-24), 128.27 (C-4, C-6), 128.49 (C-13, C-15), 129.67 (C-20, C-21), 134.31 (C-28), 135.11 (C-2), 151.76 (C-30), 154.24 (C-11), 161.13 (C-17), 161.78 (C-26), 163.11 (C-9), 166.22 (C-8); MS (EI) *m/z*: 508.1 (M+1); Anal. Calcd for $C_{29}H_{22}N_5O_2Cl$: C, 68.57; H, 4.37; N, 13.79%. Found: C, 68.53; H, 4.41; N, 13.75%.

3.2.22 4-{4-[5-(4-Methoxy-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-pyridin-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine (7g)

Yield: 72%; m.p. 142–143°C; IR (KBr, cm^{-1}): 3368 (N-H), 2939, 2850 (C-H asym, sym), 1621 (>C=N-), 1287 (-OCH_3); ^{1}H NMR ($CDCl_3$): δ 3.31–3.37 (dd, 1H, J_{BA} = 17.31, J_{BX} = 3.85), 3.68–3.75 (dd, 1H, J_{AB} = 17.32, J_{AX} = 11.32), 3.78 (s, 3H, -OCH_3), 5.42 (s, 2H, -CH_2O-), 5.86–5.90 (dd, 1H, J_{XA} = 3.80, J_{XB} = 11.36), 6.92–7.68 (m, 16H, Ar-H), 8.34 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 42.31 (C-18), 55.16 (C-19), 59.20 (C-1), 71.89 (C-10), 110.79 (C-25), 112.11 (C-5), 114.90 (C-12, C-16), 115.80 (C-3, C-7), 120.13 (C-23), 121.33 (C-29), 122.15 (C-22), 122.46 (C-27), 127.41 (C-14), 128.33 (C-24), 128.51 (C-4, C-6), 128.33 (C-13, C-15), 129.42 (C-20, C-21), 134.11 (C-28), 140.22 (C-2), 151.22 (C-30), 154.19 (C-11), 160.98 (C-17), 161.67 (C-26), 163.24 (C-9), 166.66 (C-8); MS (EI) *m/z*: 504.0 (M+1); Anal. Calcd for $C_{30}H_{25}N_5O_3$: C, 71.56; H, 5.00; N, 13.91%. Found: C, 71.58; H, 5.06; N, 13.87%.

3.2.23 4-{4-[5-(4-Nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-pyridin-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine (7h)

Yield: 78%; m.p. 157–159°C; IR (KBr, cm^{-1}): 3357 (N-H), 2942, 2858 (C-H asym, sym), 1614 (>C=N-), 1549, 1355 (-NO_2asym, sym); ^{1}H NMR ($CDCl_3$): δ 3.25–3.31 (dd, 1H, J_{BA} = 17.36, J_{BX} = 3.77), 3.62–3.74(dd, 1H, J_{AB} = 17.33, J_{AX} = 11.31), 5.33 (s, 2H, -CH_2O-), 5.82–5.86 (dd, 1H, J_{XA} = 3.92, J_{XB} = 11.45), 6.82–7.60 (m, 16H, Ar-H), 8.27 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 42.14 (C-18), 55.32 (C-19), 72.56 (C-10), 110.37 (C-25), 112.64 (C-5), 115.22 (C-12, C-16), 115.68 (C-3, C-7), 120.63 (C-23), 121.22 (C-29), 122.34 (C-22), 122.65 (C-27), 127.21 (C-14), 128.22 (C-24), 128.55 (C-4, C-6), 128.48 (C-13, C-15), 129.61 (C-20, C-21), 134.39 (C-28), 148.23 (C-2), 151.33 (C-30), 154.74 (C-11), 161.26 (C-17), 161.71 (C-26), 163.39 (C-9), 166.54 (C-8); MS (EI) *m/z*: 519.1 (M+1); Anal. Calcd for $C_{29}H_{22}N_6O_4$: C, 67.17; H, 4.28; N, 16.21%. Found: C, 67.11; H, 4.22; N, 16.28%.

3.2.24 4-{4-[5-(3-Nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-pyridin-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine (7i)

Yield: 65%; m.p. 147–149°C; IR (KBr, cm^{-1}): 3360 (N-H), 2926, 2850 (C-H asym, sym), 1619 (>C=N-), 1545, 1360 (-NO_2 asym, sym); ^{1}H NMR ($CDCl_3$): δ 3.28–3.34 (dd, 1H, J_{BA} = 17.39, J_{BX} = 3.79), 3.60–3.68 (dd, 1H, J_{AB} = 17.37, J_{AX} = 11.36), 5.31 (s, 2H, -CH_2O-), 5.86–5.91 (dd, 1H, J_{XA} = 3.92, J_{XB} = 11.45), 6.87–7.69 (m, 16H, Ar-H), 8.23 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 42.27 (C-18), 55.45 (C-19), 72.69 (C-10), 111.15 (C-25), 112.35 (C-5), 115.46 (C-12, C-16), 115.87 (C-3, C-7), 120.67 (C-23), 121.34 (C-29), 122.67 (C-22), 122.77 (C-27), 127.35 (C-14), 128.10 (C-24), 128.67 (C-4, C-6), 128.85 (C-13, C-15), 129.12 (C-20, C-21), 134.62 (C-28), 148.10 (C-2), 151.46 (C-30), 154.33 (C-11), 161.20 (C-17), 161.89 (C-26), 163.47 (C-9), 165.11 (C-8); MS (EI) *m/z*: 519.1 (M+1); Anal. Calcd for $C_{29}H_{22}N_6O_4$: C, 67.17; H, 4.28; N, 16.21%. Found: C, 67.13; H, 4.20; N, 16.24%.

3.2.25 2-Pyridin-2-yl-4-[4-(5-p-tolyl-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]-2,3-dihydro-1H-benzo[b][1,4]diazepine (7j)

Yield: 68%; m.p. 136–138°C; IR (KBr, cm^{-1}): 3360 (N-H), 2955, 2862 (C-H asym, sym), 1624 (>C=N-), 1441 (-CH_3); ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H, -CH_3), 3.28–3.34 (dd, 1H, J_{BA} = 17.33, J_{BX} = 3.80), 3.64–3.71 (dd, 1H, J_{AB} = 17.31, J_{AX} = 11.37), 5.38 (s, 2H, -CH_2O-), 5.84–5.88 (dd, 1H, J_{XA} = 3.86, J_{XB} = 11.41), 6.87–7.63 (m, 16H, Ar-H), 8.36 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 21.37 (C-1), 42.52 (C-18), 55.11 (C-19), 72.14 (C-10), 110.55 (C-25), 112.65 (C-5), 114.32 (C-12, C-16), 115.11 (C-3, C-7), 120.28 (C-23), 121.54 (C-29), 122.68 (C-22), 122.76 (C-27), 127.64 (C-14), 128.21 (C-24), 128.59 (C-4, C-6), 128.66 (C-13, C-15), 129.41 (C-20, C-21), 134.43 (C-28), 138.69 (C-2), 151.56 (C-30), 154.25 (C-11), 160.91 (C-17), 161.33 (C-26), 163.16 (C-9), 166.31 (C-8); MS (EI) *m/z*: 488.2 (M+1); Anal. Calcd for $C_{30}H_{25}N_5O_2$: C, 73.90; H, 5.17; N, 14.36%. Found: C, 73.95; H, 5.14; N, 14.30%.

3.2.26 4-{4-[5-(4-Chloro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2-furan-2-yl-2,3-dihydro-1H-benzo[b][1,4]diazepine (7k)

Yield: 59%; m.p. 176–178°C; IR (KBr, cm^{-1}): 3361 (N-H), 2955, 2856 (C-H asym, sym), 1613 (>C=N-), 761 (C-Cl); ^{1}H NMR ($CDCl_3$): δ 3.11–3.15 (dd, 1H, J_{BA} = 17.52, J_{BX} = 4.36), 3.62–3.71 (dd, 1H, J_{AB} = 17.56, J_{AX} = 11.83), 5.32 (s, 2H, -CH_2O-), 5.47–5.53 (dd, 1H, J_{XA} = 4.50, J_{XB} = 11.82), 6.68–8.10 (m, 15H, Ar-H), 8.34 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 42.13 (C-18), 55.45 (C-19), 72.13 (C-10), 102.11 (C-27), 104.37 (C-28), 110.76 (C-25), 112.50 (C-5), 114.88 (C-12, C-16), 115.90 (C-3, C-7), 120.12 (C-23), 122.17 (C-22), 127.31 (C-14), 128.44 (C-24), 128.67 (C-4, C-6), 129.63 (C-13, C-15), 129.73 (C-20, C-21), 135.87 (C-2), 137.11 (C-29), 137.55 (C-26), 154.14 (C-11), 160.89 (C-17), 163.42 (C-9), 166.33 (C-8); MS (EI) *m*/*z*: 497.3 (M+1); Anal. Calcd for $C_{28}H_{21}N_4O_3Cl$: C, 67.67; H, 4.26; N, 11.27%. Found: C, 67.62; H, 4.29; N, 11.20%.

3.2.27 2-Furan-2-yl-4-{4-[5-(4-methoxy-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2,3-dihydro-1H-benzo[b][1,4]diazepine (7l)

Yield: 63%; m.p. 126–128°C; IR (KBr, cm^{-1}): 3360 (N-H), 2956, 2859 (C-H asym, sym), 1620 (>C=N-), 1280 (-OCH_3); ^{1}H NMR ($CDCl_3$): δ 3.06–3.11 (dd, 1H, J_{BA} = 17.56, J_{BX} = 4.56), 3.68–3.75 (dd, 1H, J_{AB} = 17.64, J_{AX} = 11.80), 3.85 (s, 3H, -OCH_3), 5.26 (s, 2H, -CH_2O-), 5.51–5.55 (dd, 1H, J_{XA} = 4.56, J_{XB} = 11.80), 6.71–8.12 (m, 15H, Ar-H), 8.38 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 42.36 (C-18), 55.26 (C-19), 59.23 (C-1), 71.94 (C-10), 102.05 (C-27), 104.45 (C-28), 110.92 (C-25), 112.18 (C-5), 114.94 (C-12, C-16), 115.84 (C-3, C-7), 119.93 (C-23), 122.02 (C-22), 126.60 (C-14), 127.39 (C-24), 128.27 (C-4, C-6), 128.52 (C-13, C-15), 129.52 (C-20, C-21), 136.96 (C-29), 137.86 (C-26), 140.83 (C-2), 154.08 (C-11), 160.91 (C-17), 163.35 (C-9), 166.52 (C-8); MS (EI) *m*/*z*: 493.2 (M+1); Anal. Calcd for $C_{29}H_{24}N_4O_4$: C, 70.72; H, 4.91; N, 11.38%. Found: C, 70.76; H, 4.87; N, 11.32%.

3.2.28 2-Furan-2-yl-4-{4-[5-(4-nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2,3-dihydro-1H-benzo[b][1,4]diazepine (7m)

Yield: 60%; m.p. 171–173°C; IR (KBr, cm^{-1}): 3356 (N-H), 2954, 2859 (C-H asym, sym), 1612 (>C=N-), 1539, 1345 (-NO_2 asym, sym); ^{1}H NMR ($CDCl_3$): δ 3.27–3.34 (dd, 1H, J_{BA} = 17.49, J_{BX} = 4.52), 3.56–3.62 (dd, 1H, J_{AB} = 17.61, J_{AX} = 11.75), 5.37 (s, 2H, -CH_2O-), 5.87–5.91 (dd, 1H, J_{XA} = 4.52, J_{XB} = 11.83), 6.95–7.74 (m, 15H, Ar-H), 8.39 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 42.44 (C-18), 55.32 (C-19), 72.27 (C-10), 102.29 (C-27), 104.31 (C-28), 110.34 (C-25), 112.47 (C-5), 114.91 (C-12, C-16), 115.69 (C-3, C-7), 120.19 (C-23), 122.26 (C-22), 127.55 (C-14), 128.38 (C-24), 128.51 (C-4, C-6), 129.47 (C-13, C-15), 129.66 (C-20, C-21), 137.43 (C-29), 137.65 (C-26), 148.22 (C-2), 154.33 (C-11), 160.44 (C-17), 163.77 (C-9), 166.48 (C-8); MS (EI) *m*/*z*: 508.2 (M+1); Anal. Calcd for $C_{28}H_{21}N_5O_5$: C, 66.27; H, 4.17; N, 13.80%. Found: C, 66.22; H, 4.13; N, 13.86%.

3.2.29 2-Furan-2-yl-4-{4-[5-(3-nitro-phenyl)-[1,3,4]oxadiazol-2-ylmethoxy]-phenyl}-2,3-dihydro-1H-benzo[b][1,4]diazepine (7n)

Yield: 59%; m.p. 191–193°C; IR (KBr, cm^{-1}): 3362 (N-H), 2920, 2843 (C-H asym, sym), 1622 (>C=N-), 1542, 1367 (-NO_2 asym, sym); ^{1}H NMR ($CDCl_3$): δ 3.30–3.37 (dd, 1H, J_{BA} = 17.42, J_{BX} = 4.58), 3.60–3.66 (dd, 1H, J_{AB} = 17.67, J_{AX} = 11.71), 5.30 (s, 2H, -CH_2O-), 5.85–5.90 (dd, 1H, J_{XA} = 4.44, J_{XB} = 11.81), 6.93–7.72 (m, 15H, Ar-H), 8.35 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 42.67 (C-18), 55.21 (C-19), 72.68 (C-10), 102.33 (C-27), 104.66 (C-28), 110.15 (C-25), 112.33 (C-5), 115.22 (C-12, C-16), 115.61 (C-3, C-7), 120.44 (C-23), 122.56 (C-22), 127.20 (C-14), 128.56 (C-24), 128.64 (C-4, C-6), 129.11(C-13, C-15), 129.29 (C-20, C-21), 137.56 (C-29), 137.59 (C-26), 148.67 (C-2), 154.39 (C-11), 160.20 (C-17), 164.11 (C-9), 166.69 (C-8); MS (EI) *m*/*z*: 508.1 (M+1); Anal. Calcd for $C_{28}H_{21}N_5O_5$: C, 66.27; H, 4.17; N, 13.80%. Found: C, 66.21; H, 4.19; N, 13.82%.

3.2.30 2-Furan-2-yl-4-[4-(5-p-tolyl-[1,3,4]oxadiazol-2-ylmethoxy)-phenyl]-2,3-dihydro-1H-benzo[b][1,4]diazepine (7o)

Yield: 69%; m.p. 179–181°C; IR (KBr, cm^{-1}): 3362 (N-H), 2952, 2852 (C-H asym, sym), 1611 (>C=N-), 1449 (-CH_3); ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H, -CH_3), 3.32–3.38 (dd, 1H, J_{BA} = 17.56, J_{BX} = 4.56), 3.61–3.68 (dd, 1H, J_{AB} = 17.64, J_{AX} = 11.80), 5.40 (s, 2H, -CH_2O-), 5.90–5.94 (dd, 1H, J_{XA} = 4.56, J_{XB} = 11.80), 6.90–7.66 (m, 15H, Ar-H), 8.41 (s, 1H, >NH); ^{13}C NMR ($CDCl_3$): 21.79 (C-1), 42.10 (C-18), 55.34 (C-19), 71.89 (C-10), 102.29 (C-27), 104.31 (C-28), 111.12 (C-25), 112.28 (C-5), 115.13 (C-12, C-16), 115.81 (C-3, C-7), 119.65 (C-23), 122.16 (C-22), 126.44 (C-14), 127.59 (C-24), 128.37 (C-4, C-6), 128.66 (C-13, C-15), 129.40 (C-20, C-21), 136.92 (C-29), 137.73 (C-26), 138.20 (C-2), 154.11 (C-11), 160.54 (C-17), 163.19 (C-9), 166.69 (C-8); MS (EI) *m*/*z*: 477.1 (M+1); Anal. Calcd for $C_{29}H_{24}N_4O_3$: C, 73.09; H, 5.08; N, 11.76%. Found: C, 73.12; H, 5.11; N, 11.72%.

3.3 Biological activities

The MICs of synthesized compounds were carried out by broth micro dilution method as described by Rattan [25]. The antitubercular activity (MICs values) was assessed in vitro against *Mycobacterium tuberculosis* $H_{37}Rv$ ATCC 27294 according to a modified Microplate Alamar Blue Assay [26]. For antiprotozoal activity, in vitro susceptibility assays and the growth inhibition test were performed on promastigotes of *L. mexicana* and epimastigotes of *Trypanosoma cruzi* were performed using a method previously described [27, 28].

4 Conclusion

Thirty newer 1,3,4-oxadiazolyl-benzodiazepines and benzothiazepines analogues were synthesized and examined for biological activity. From the study of structure activity relationship (SAR) and the results of biological screening, it is clearly indicated that the pharmacological properties of synthesized compounds depend on electron withdrawing/donating groups present on aryl ring at 1,3,4-oxadiazole moiety. The presence of thiophene, pyridine, and furan at benzothiazepine and benzodiazepine ring also plays a major role in bioactivity profile. In case of antibacterial and antifungal activity, few of the compounds showed equipotent activity when compared to standard drugs.

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References

1. Shyma PC, kalluraya B. Peethambar SK, Telkar S, Arulmoli T. Synthesis, characterization and molecular docking studies of some new 1,3,4-oxadiazolines bearing 6-methylpyridine moiety for antimicrobial property. Eur J Med Chem 2013;68:394–404.
2. Nasr T, Bondock S, Eid S. Design, synthesis, antimicrobial evaluation and molecular docking studies of some new thiophene, pyrazole and pyridone derivatives bearing sulfisoxazole moiety. Eur J Med Chem 2014;84:491–504.
3. Saeedi M, Goli F, Mahdavi M, Dehghan G, Faramarzi MA, Foroumadi A, et al. Synthesis and biological investigation of some novel sulfonamide and amide derivatives containing coumarin moieties. Iran J Pharm Res 2014;13:881–92.
4. Deng X, Song M, Wang S, Quan Z. Synthesis and anticonvulsant evaluation of some new 6-(substituted-phenyl)thiazolo[3,2-b][1,2,4]triazole derivatives in mice. Iran J Pharm Res 2014;13:459–69.
5. Kumar S. Synthesis and biological activity of 5-substituted-2-amino-1,3,4-oxadiazole derivatives. Turk J Chem 2011;35:99–108.
6. Syed T, Akhtar, Al-Masoudi NA, Jones PG, Hameed S. Synthesis, QSAR and anti-HIV activity of new 5-benzylthio-1,3,4-oxadiazoles derived from α-amino acids. J Enzyme Inhi Med Chem 2011;26:668–80.
7. Bondock S, Adel S, Etman HA, Badria FA. Synthesis and antitumor evaluation of some new 1,3,4-oxadiazole-based heterocycles. Eur J Med Chem 2012;48:192–9.
8. Omar FA, Mahfouz NM, Rahman MA. Design, synthesis and antiinflammatory activity of some 1,3,4-oxadiazole derivatives. Eur J Med Chem 1996;31:819–25.
9. Ahsan MJ, Samy JG, Jain CB, Dutt KR, Khalilullah H, Nomani MS. Discovery of novel antitubercular 1,5-dimethyl-2-phenyl-4-([5-(arylamino)- 1,3,4-oxadiazol-2-yl]methylamino)-1,2-dihydro-3*H*-pyrazol-3-one analogues. Bioorg Med Chem Lett 2012;22:969–72.
10. Gudipati R, Anreddy RN, Manda S. Synthesis, characterization and anticancer activity of certain 3-{4-(5-mercapto-1,3,4-oxadiazole-2-yl)phenylimino}indolin-2-one derivatives. Saudi Pharmaceutical J 2011;19:153–8.
11. Shingalapur RV, Hosamani KM, Keri RS, Hugar MH. Derivatives of benzimidazole pharmacophore: synthesis, anticonvulsant, antidiabetic and DNA cleavage studies. Eur J Med Chem 2010;46:1753–9.
12. Saleh TS, El-Rahman NM, Assaker RS. Microwave promoted a green protocol for solvent free synthesis of 1,5- benzothiazepine incorporating thiophene moiety. Green Chem Lett Rev 2012;5:315–20.
13. Bhat KI, Chauhan MK, Kumar A, Kumar P. Synthesis, pharmacological, and biological screening of novel derivatives of benzodiazepines. J Heterocyclic Chem 2014;51:1189–92.
14. Garg N, Chandra T, Jain AB, Kumar A. Synthesis and evaluation of some new substituted benzothiazepine and benzoxazepine derivatives as anticonvulsant agents. Eur J Med Chem 2010;45:1529–35.
15. Kaur H, Kumar S, Chaudhary A, Kumar A. Synthesis and biological evaluation of some new substituted benzoxazepine and benzothiazepine as antipsychotic as well as anticonvulsant agents. Arabian J Chem 2012;5:271–83.
16. Campiani G, Butini S, Fattorusso C, Catalanotti B, Gemma S, Nacci V, et al. Pyrrolo[1,3]benzothiazepine-based serotonin and dopamine receptor antagonists. Molecular modeling, further structure-activity relationship studies, and identification of novel atypical antipsychotic agents. J Med Chem 2004;47:143–57.
17. Ansari FL, Iftikhar F, Haq T, Mirza B, Baseer M, Rashid U. Solid-phase synthesis and biological evaluation of a parallel library of 2,3-dihydro-1,5-benzothiazepines. Bioorg Med Chem 2008;16:7691–7.
18. Struga M, Kossakowski J, Koziol AE, Kedzierska E, Fidecka S, Colla PL, et al. Synthesis, pharmacological and antiviral activity of 1,3-thiazepine derivatives. Eur J Med Chem 2009;44:4960–9.
19. Ghotekar DS, Joshi RS, Mandhane PG, Bhagat SS, Gill CH. Synthesis of some biologically important fluorinated

3-chlorochromones and 1,5-benzothiazepines as antimicrobial and antifungal agents. Ind J Chem 2010;49B:1267–70.
20. Ambrogil V, Furlani A, Grandolini G, Papaioannou A, Periolil L, Scarciaz V, et al. Synthesis, antimicrobial and cytostatic activities of some derivatives of indolo[2,3-b]-1,5-benzothiazepine, a novel heterocyclic ring system. Eur J Med Chem 1993;28:659–67.
21. Kamal A, Balakishan G, Ramakrishna G, Shaik TB, Sreekanth K, Balakrishna M, et al. Synthesis and biological evaluation of cinnamido linked pyrrolo [2, 1-c][1, 4] benzodiazepines as antimitotic agents. Eur J Med Chem 2010;45:3870–84.
22. Press JB, Hofmann CM, Eudy NH, Fansha WJ, Day IP, Greenblatt EN, et al. 10-(Alkylamino)-4H-thieno[3,4-b][1,5]benzodiazepines. A novel class of potential neuroleptic agents. J Med Chem 1979;22:725–31.
23. Kusanur RA, Ghate M, Kulkarni MV. Synthesis of spiro [indolo-1, 5-benzodiazepines] from 3- acetyl coumarins for use as antianxiety agents. J Chem Sci 2004;116:265–70.
24. Patel NB, Patel SD. Synthesis and in vitro antimicrobial studies of 4-thiazolidinone incorporated 1,3,4-oxadiazoles. Chem Biol Interface 2012;2:182–97.
25. Rattan A. Antimicrobials in laboratory medicine. New Delhi: Churchill BI Livingstone, 2000.
26. Franzblau SG, Witzig RS, Mclaughlin JC, Torres P, Madico G, Hernandez A, et al. Rapid, low-technology MIC determination with clinical mycobacterium tuberculosis isolates by using the microplate alamar blue assay. J Clin Microbiol 1998;36:362–6.
27. Hernández-Núñez E, Tlahuext H, Moo-Puc R, Torres-Gómez H, Reyes-Martínez R, Cedillo-Rivera R, et al. Synthesis and in vitro trichomonicidal, giardicidal and amebicidal activity of N-acetamide(sulfonamide)-2-methyl-4-nitro-1H-imidazoles. Eur J Med Chem 2009;44:2975–84.
28. Chan-Bacab MJ, Hernández-Núñez E, Navarrete-Vázquez G. Nitazoxanide, tizoxanide and a new analogue [4-nitro-N-(5-nitro-1,3-thiazol-2-yl)benzamide; NTB] inhibit the growth of kinetoplastid parasites (Trypanosoma cruzi and Leishmania mexicana) in vitro. J Antimicrob Chem 2009;63:1292–3.

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