# Syntheses of Potentially Bioactive [1,2,4]Oxadiazolo [5,4-*d*]benzothiazepines by 1,3-Dipolar Cycloaddition

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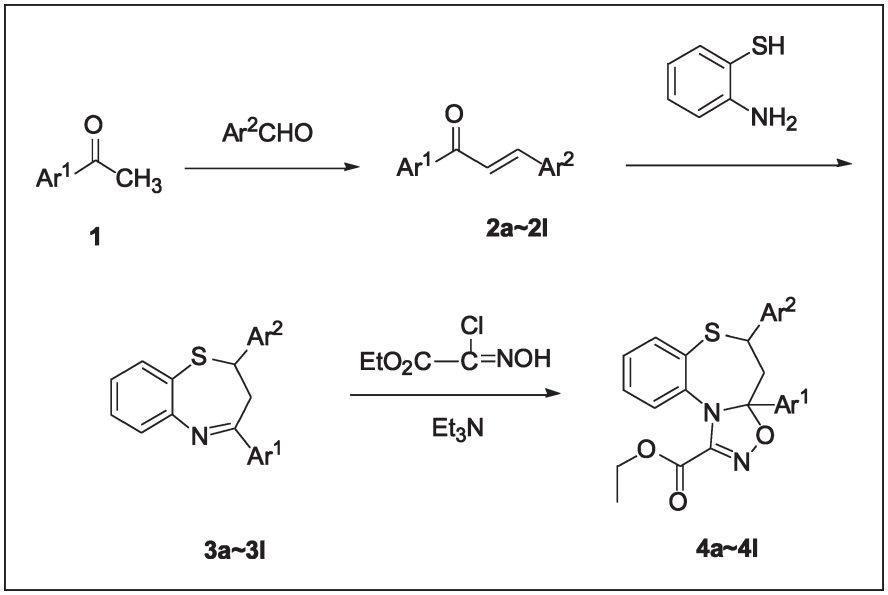


The chalcones, **2a-2l** reacted with *o*-aminobenzenthiol to give a series of 1,5-benzothiazepines, **3a-3l**. The [3+2] 1, 3-dipolar cycloaddition reactions of **3a-3l** with ethyl chlorooximidoacetate in the presence of $Et_3N$ afforded the target compounds, **4a-4l** possessing an additional 1,2,4-oxadiazole ring fused to the heptaatomic nucleus. The structures have been elucidated by spectral methods and X-ray crystallographic analysis.

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## INTRODUCTION

The Synthesis of benzothiazepine derivatives has attracted considerable attention of organic and medicinal chemists due to their broad spectrum of biological activity. The 1,5-benzothiazepine derivatives have been used as cardiovascular modulators [1], coronary vasodilators [2], elastase [3]/ACE inhibitors [4], anti-HIV [5], antihypertensives [6], anti-depressants [7], and anti-bacterial activity [8]. In recent years, a large number of 1,5-benzothiazepine derivatives containing anticancer activity [9,10], hemodynamic effects [11], antiulcer activity [12,13], and spasmolytic activities [14–18] have also been reported. Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which include quetiapine fumarate and thiazesim [19–21].

Oxadiazoles are naturally occurring five-membered heterocycles with utility in synthetic and medicinal chemistry. They serve as the core components of a large number of substances that possess a wide range of interesting biological activities. The 1,2,4-oxadiazole scaffolds are associated with significant biological activities, such as anti-hypertensive [22], antikinetoplastid [23], antimicrobial and anti-inflammatory [24].

Recent work has demonstrated the interest to fix an additional heterocycle on 1,5-benzothiazepines. Pharmaceutical properties of such compounds are magnified when the heterocycle is bound to the heptatomic nucleus [25,26]. Keeping these observations in mind and in continuation of our interest to prepare a seven-membered ring [27,28], we report herein the reaction of 1,5-benzothiazepines **3a-3l** with ethyl chlorooximidoacetate through 1,3-dipolar cycloaddition to afford a new series of tricyclic system, [1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepine derivatives, which might have useful biological and therapeutic activities (Table 1).

**Table 1**

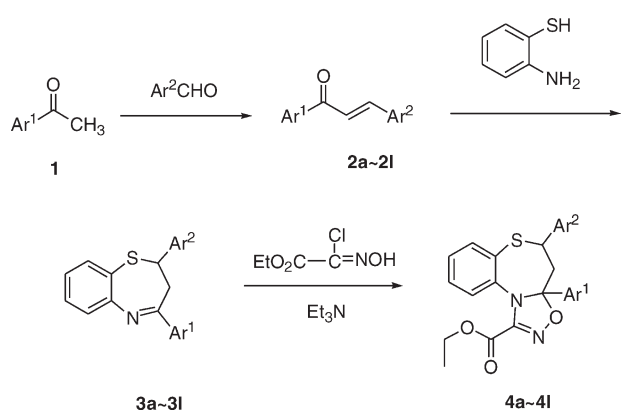
Physical and analytical data of compounds **4**.

| Comp. | $Ar^1$ | $Ar^2$ | mp(°C) | Yield % | Molecular formula | Analysis %(Calcd./found) C | H | *N* |
|---|---|---|---|---|---|---|---|---|
| **4a** | Ph | Ph | 177–178 | 34 | $C_{25}H_{22}N_2O_3S$ | 69.75 | 5.15 | 6.51 |
| | | | | | | 69.73 | 5.12 | 6.54 |
| **4b** | Ph | *p*-$ClC_6H_4$ | 174–175 | 35 | $C_{25}H_{21}ClN_2O_3S$ | 64.58 | 4.55 | 6.02 |
| | | | | | | 64.57 | 4.58 | 5.99 |
| **4c** | Ph | *p*-$CH_3OC_6H_4$ | 132–133 | 35 | $C_{26}H_{24}N_2O_4S$ | 67.81 | 5.25 | 6.08 |
| | | | | | | 67.83 | 5.24 | 6.07 |
| **4d** | Ph | *p*-$NO_2C_6H_4$ | 195–196 | 33 | $C_{25}H_{21}N_3O_5S$ | 63.15 | 4.45 | 8.84 |
| | | | | | | 63.12 | 4.46 | 8.83 |
| **4e** | *p*-$ClC_6H_4$ | Ph | 193–194 | 31 | $C_{25}H_{21}ClN_2O_3S$ | 64.58 | 4.55 | 6.02 |
| | | | | | | 64.59 | 4.53 | 6.01 |
| **4f** | *p*-$ClC_6H_4$ | *p*-$ClC_6H_4$ | 165–166 | 30 | $C_{25}H_{20}Cl_2N_2O_3S$ | 60.12 | 4.04 | 5.61 |
| | | | | | | 60.14 | 4.02 | 5.63 |
| **4g** | *p*-$ClC_6H_4$ | *p*-$CH_3OC_6H_4$ | 143–144 | 23 | $C_{26}H_{23}ClN_2O_4S$ | 63.09 | 4.68 | 5.66 |
| | | | | | | 63.12 | 4.67 | 4.63 |
| **4h** | *p*-$ClC_6H_4$ | *p*-$NO_2C_6H_4$ | 232–233 | 25 | $C_{25}H_{20}ClN_3O_5S$ | 58.88 | 3.95 | 8.24 |
| | | | | | | 58.85 | 3.96 | 8.25 |
| **4i** | *p*-$CH_3OC_6H_4$ | Ph | 130–131 | 26 | $C_{26}H_{24}N_2O_4S$ | 67.81 | 5.25 | 6.08 |
| | | | | | | 67.80 | 5.28 | 6.04 |
| **4j** | *p*-$CH_3OC_6H_4$ | *p*-$ClC_6H_4$ | 213–214 | 32 | $C_{26}H_{23}ClN_2O_4S$ | 63.09 | 4.68 | 5.66 |
| | | | | | | 63.13 | 4.66 | 5.65 |
| **4k** | *p*-$CH_3OC_6H_4$ | *p*-$CH_3OC_6H_4$ | 173–174 | 36 | $C_{27}H_{26}N_2O_5S$ | 66.10 | 5.34 | 5.71 |
| | | | | | | 66.08 | 5.35 | 5.74 |
| **4l** | *p*-$CH_3OC_6H_4$ | *p*-$NO_2C_6H_4$ | 213–214 | 20 | $C_{26}H_{23}N_3O_6S$ | 61.77 | 4.59 | 8.31 |
| | | | | | | 61.74 | 4.60 | 8.34 |

## RESULTS AND DISCUSSION

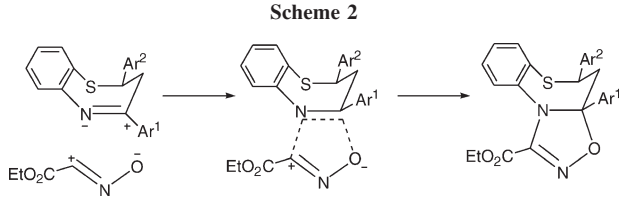
The title compounds were prepared according to the Scheme 1. The chalcones, **2a-2l** were readily prepared by condensation of aryl aldehydes with substituted acetophenones [29]. **2a-2l** were subsequently reacted with *o*-aminobenzenthiol in MeOH/AcOH to give the desired 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines, **3a-3l**. The formation of **3** may proceeded via two steps [30,31]. In the first step, nucleophilic attack by the sulfhydryl electrons of 2-aminobenzenethiol takes place on the activated β-carbon atom of the α, β-unsaturated carbonyl compounds to give Michael-adduct type intermediates, which simultaneously undergo dehydrative cyclization to give final products in the second step. Finally, the 1, 3-dipolar cycloaddition reaction between 1,5-benzothiazepine derivatives, **3a-3l** and nitrile oxide, generated *in situ* from ethyl chlorooximidoacetate and triethylamine, leads to the target compounds; 1,2,4-oxadiazolo[5,4-*d*]-1,5-benzothiazepine derivatives, **4a-4l** (Scheme 1) in which an oxadiazole ring is fused at the ''d'' edge of the heptatomic nucleus.

**Scheme 1**




The structures of title compounds have been characterized by IR, $^1$H-NMR, mass, and elemental analysis. The infrared spectra of these compounds show C=O absorption bands around 1740 $cm^{-1}$. In the nuclear magnetic resonance spectra, title compounds exhibited multiplet between δ 8.15–6.55ppm due to the aromatic protons, the signal for ethoxycarbonyl $CH_2$ and $CH_3$ appeared at δ 4.30–4.38 ppm and δ 1.29–1.31 ppm respectively, 3 distinct double doublets in the ABX pattern (a CH proton and 2 anisochronous protons of a $CH_2$) appeared at δ 3.60–2.50 ppm, as has been

**Scheme 2**



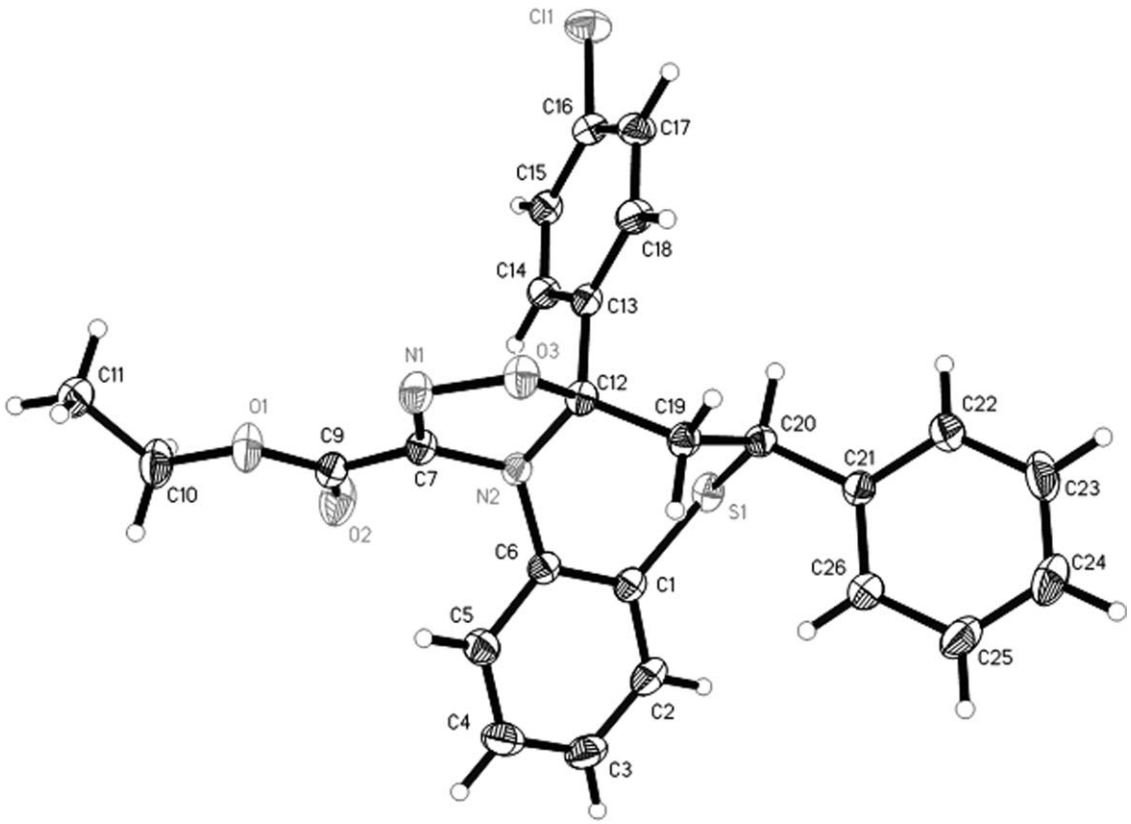



**Figure 1.** Molecular structure of **4e**.

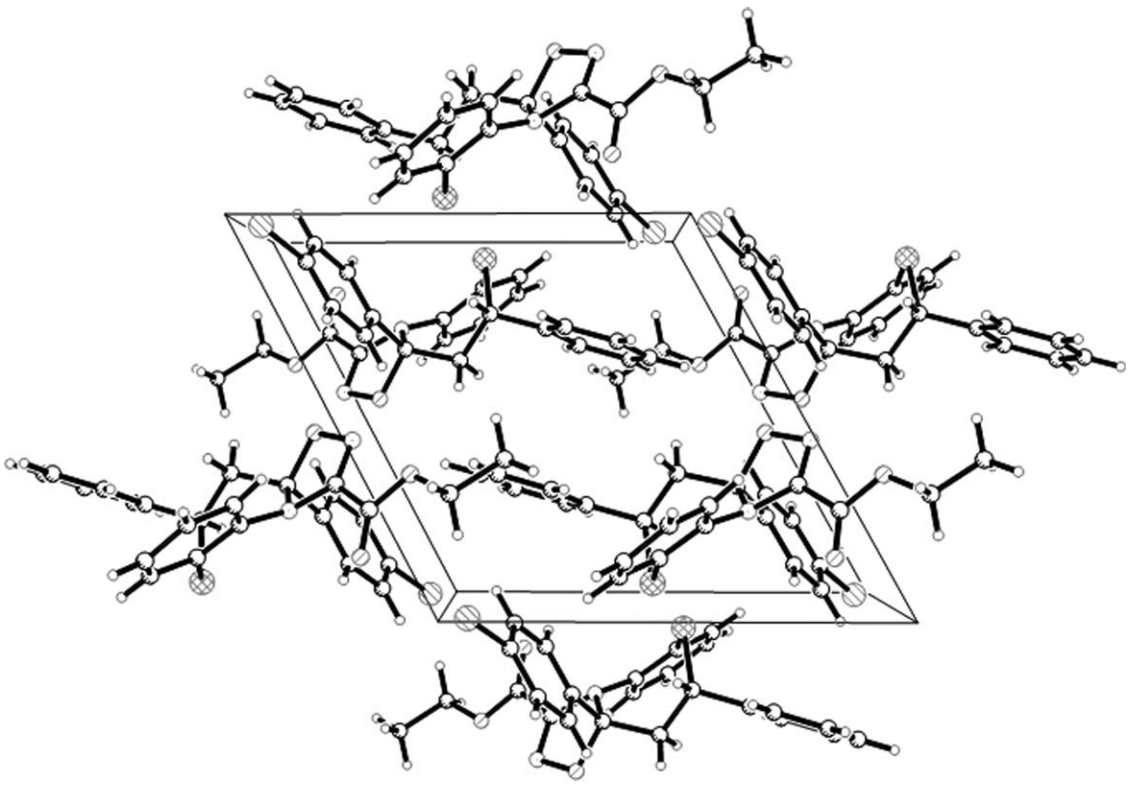


**Figure 2.** Packing of molecules in a unit cell of **4e**.

**Table 2**

Crystal data and structure refinement for compound **4e**.

| | | | |
|---|---|---|---|
| Empirical formula | $C_{25}H_{21}ClN_2O_3S$ | V, Å$^3$ | 1092.7(3) |
| Formula weight | 464.95 | Z | 2 |
| Temperature | 293(2) K | *D*c, mg/m$^3$ | 1.413 |
| Wavelength | 0.71073 A | Crystal size, mm | 0.55 × 0.45 × 0.35 |
| Crystal system | Triclinic | θ range, deg | 3.10–27.48 |
| Space group | P-1 | μ, mm$^{-1}$ | 0.302 |
| *a*, Å | 10.4744(13) | Reflections collected | 10,141 |
| *b*, Å | 10.9320(16) | Independent reflection | 4792 [*R*(int) = 0.0258] |
| *c*, Å | 10.971(2) | Data/restraints/parameters | 4792 / 0 / 290 |
| α, deg | 61.811(3) | Final *R* indices [$I > 2\sigma(I)$] | *R*1 = 0.0469, *wR*2 = 0.1397 |
| β, deg | 88.031(5) | *R* indices (all data) | *R*1 = 0.0568, *wR*2 = 0.1585 |
| γ, deg | 81.064(3) | | |

observed in 2,3-dihydro-1,5-benzothiazepines. In MS spectra, molecular ion peaks of all title compounds were obtained from EI-MS, but the intensities of molecular ion peaks were very weak.

A plausible intramolecular 1,3-diploar cycloaddition mechanism is proposed as shown in Scheme 2. According to the literatures [32], the conformations of the central heteroazepine ring in 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines adopt boat-like conformations and the 1,3-diploar cycloaddition reactions occurred in a concerted mechanism. In the presence of $Et_3N$, the nitrile oxide generated *in situ* and C═N double bond in benzothiazepine formed a cyclic transition state, then the σ-bonds of C─N and C─O were formed simultaneously to afford the 1,2,4-oxadiazole ring, the central thiazepine ring of the cycloadduct also adopts a boat-like conformation.

The X-ray crystallography of **4e** identified the structure of the desired products (Fig. 1). The higher occupancy in the 3-dimensional packing arrangement is shown in Figure 2. The crystal data and structure refinement of **4e** are listed in Table 2. Selected bond distances and angles of **4e** are tabulated in Table 3.

Figure 1 is the stereo structure of compound **4e**. There is a five-membered ring in the molecule, resulting from the cycloaddition reaction. All atoms [N(1), C(7), N(2), C(12), O(3)] in the ring are nearly coplanar with similar bond angles (N(1)─O(3) ─C(12) 106.32(14)°, O(3) ─C(12) ─N(2) 101.36(14)°, C(12) ─N(2) ─C(7) 102.60(14)°, N(2) ─C(7) ─N(1) 115.39(18)°, C(7) ─N(1) ─O(3) 105.94(16)°), indicating the ring is stable. The five-membered ring is characterized by the endocyclic torsion angles (enumerated clockwise and starting with O(3)─N(1)─C(7)─N(2)): −2.1(2)°, 19.7(2)°, −28.29(17)°, 25.87(17)°, −16.1(2)°. The five-membered ring plane adopts an envelope conformation with atom C(12) deviating from the plane defined by N(2), O(3), N(1), C(7) of 0.1684Å. The bond length of N(1)─C(7), 1.286(3)Å, indicates it is a double bond.

There is also a seven-membered ring in the molecule. 1,5-Benzothiazepine ring is characterized by the endocyclic torsion angles (enumerated clockwise and starting with S(1)─C(1)─C(6)─N(2)): 0.7(3)°, −53.6(3)°, −1.8(3)°, 82.5(2)°, −48.60(19)°, −35.20(15)°, 64.81(17)°. N(2), S(1), C(12) and C(20) are coplanar, while C(1), C(6) and C(19) are all above the plane. Therefore, the seven-membered ring adopts a boat-like conformation.

CCDC-768069 (for **4e**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/const/retrieving.html.

In conclusion, we have achieved an efficient one step synthesis of new [1,2,4]oxadiazolo[5,4-d][1,5]benzodiazepinones, **4a-4l** by way of highly regioselective 1,3-dipolar cycloaddition of ethyl chlorooximidoacetate to 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines, **3a-3l**.

## EXPERIMENTAL

All reagents were of commercial availability. Reactions were monitored by thin-layer chromatography (TLC). Melting points were measured on a mettler FP-5 capillary melting point apparatus and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer. The IR spectra were determined as potassium bromide pellet on a Bruker Equinox 55 FTIR spectrophotometer. The $^1$H-NMR spectra were recorded on a Varian Inova-400 spectrophotometer using TMS as an internal standard. EI-ms spectra were recorded with an Agilent 5975 apparatus. X-ray crystal

**Table 3**

Selected bond lengths (Å) and angles (°) of compounds **4e**.

| | | | |
|---|---|---|---|
| S(1)─C(20) | 1.843(2) | N(1)─O(3)─C(12) | 106.32(14) |
| C(19)─C(20) | 1.522(3) | C(6)─N(2)─C(12) | 124.19(15) |
| O(3)─N(1) | 1.417(2) | N(1)─C(7)─N(2) | 115.39(18) |
| O(3)─C(12) | 1.469(2) | N(1)─C(7)─C(9) | 121.43(17) |
| N(2)─C(7) | 1.393(2) | O(2)─C(9)─O(1) | 126.2(2) |
| N(2)─C(6) | 1.428(2) | O(1)─C(9)─C(7) | 110.78(18) |
| N(2)─C(12) | 1.472(2) | O(3)─C(12)─C(13) | 106.65(14) |
| O(1)─C(10) | 1.448(3) | C(12)─C(19)─C(20) | 115.18(15) |
| O(1)─C(9) | 1.322(3) | N(2)─C(12)─C(19) | 114.91(15) |

**Table 4**

Yield (%) and mp (°C) of Compounds **3**.

| Comp | $Ar^1$ | $Ar^2$ | Yield | mp |
|---|---|---|---|---|
| **3a** | Ph | Ph | 86 | 113–115 |
| **3b** | Ph | p-$ClC_6H_4$ | 72 | 137–139 |
| **3c** | Ph | p-$CH_3OC_6H_4$ | 81 | 128–130 |
| **3d** | Ph | p-$NO_2C_6H_4$ | 43.2 | 201–202 |
| **3e** | *p*-$ClC_6H_4$ | Ph | 65.7 | 134–136 |
| **3f** | *p*-$ClC_6H_4$ | *p*-$ClC_6H_4$ | 70.5 | 138–140 |
| **3g** | *p*-$ClC_6H_4$ | *p*-$CH_3OC_6H_4$ | 75.2 | 130–133 |
| **3h** | *p*-$ClC_6H_4$ | *p*-$NO_2C_6H_4$ | 47.3 | 195–196 |
| **3i** | *p*-$CH_3OC_6H_4$ | Ph | 44.6 | 124–125 |
| **3j** | *p*-$CH_3OC_6H_4$ | *p*-$ClC_6H_4$ | 65.3 | 128–130 |
| **3k** | *p*-$CH_3OC_6H_4$ | *p*-$CH_3OC_6H_4$ | 43.1 | 130–132 |
| **3l** | *p*-$CH_3OC_6H_4$ | *p*-$NO_2C_6H_4$ | 41.7 | 185–187 |

structure was obtained using R-AXIS SPIDER X-ray diffraction. The ethyl chlorooximidoacetate was obtained according to the known procedure [33–34].

**General procedure for the preparation of the 2,4-diaryl-2,3-dihydro-1,5-benzothiazepines (3a-3l).** Chalcone **2** (6 mmol) and *o*-aminobenzenthiol (6 mmol) were dissolved in 25 ml containing glacial acetic acid methanol. After the mixture had cooled to room temperature, piperidine (5 drops) was added. Yellow floccule appeared in 0.5h, then a little methanol was added and the slurry was heated until all material dissolved. Glacial acetic acid (2 ml) was added and the mixture was allowed to stand overnight at a room temperature. The solid product was collected and recrystallized from anhydrous ethanol and benzene to give **3a-3l** as yellow crystals (Table 4).

**General procedure for the preparation of the 2,4-diaryl-2,3-dihydro-1,5-benzothiazepine derivatives containing 1,2,4-oxadiazole (4a-4l).** To a stirred solution of 1,5-benzothiazepine derivatives **3a-3l** (1 mmol) and ethyl chlorooximidoacetate (1.5 mmol) in $CH_2Cl_2$ (20 ml), a solution of triethylamine (0.5 ml) in the same solvent (5 ml) was added dropwise over a few minutes. The reaction mixture was kept under stirring at room temperature for 2 days. After the removal of the solvent at reduced pressure, ethyl acetate was added to the residue and the triethylamine hydrochloride was filtered. The solvent was then evaporated off and the residue subjected to silica gel column chromatography with ethyl acetate/light petroleum (V:V = 1:8). A series of compounds **4a-4l** were crystallized from ethyl acetate and light petroleum.

***Ethyl 3a,4-dihydro-3a,5-diphenyl-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4a).*** This compound was obtained as colorless crystals in 34% yield, mp 177–178°C. IR(KBr): 3072 (Ar—H), 1736 (C=O), 761 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.21–6.78 (m, 14H, Ar—H), 4.34 (q, 2H, $CH_2$), 3.49 (dd, 1H, H-5x, $J_{bx}$ = 5.53 Hz, $J_{ax}$ = 10.01 Hz), 3.06 (dd, 1H, H-4b, $J_{bx}$ = 5.53 Hz, $J_{ab}$ = 14.90 Hz), 2.66 (dd, 1H, H-4a, $J_{ax}$ = 10.01 Hz, $J_{ab}$ = 14.90 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 430 ($M^+$). Anal. Calcd. for $C_{25}H_{22}N_2O_3S$: C, 69.75; H, 5.15; N, 6.51; Found: C, 69.73; H, 5.12; N, 6.54.

***Ethyl 3a,4-dihydro-3a-phenyl-5-(4-chlorophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4b).*** This compound was obtained as colorless crystals in 35% yield, mp 174–175°C. IR(KBr): 3046 (Ar—H), 1735 (C—O), 763 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.18–6.65 (m, 13H, Ar—H), 4.35 (q, 2H, $CH_2$), 3.46 (dd, 1H, H-5x, $J_{bx}$ = 6.53 Hz, $J_{ax}$ = 11.62 Hz), 3.02 (dd, 1H, H-4b, $J_{bx}$ = 6.53 Hz, $J_{ab}$ = 15.88 Hz), 2.60 (dd, 1H, H-4a, $J_{ax}$ = 11.62 Hz, $J_{ab}$ = 15.88 Hz), 1.31 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 464 ($M^+$). Anal. Calcd. for $C_{25}H_{21}ClN_2O_3S$: C, 64.58; H, 4.55; N, 6.02; Found: C, 64.57; H, 4.58; N, 5.99.

***Ethyl 3a,4-dihydro-3a-phenyl-5-(4-methoxyphenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4c).*** This compound was obtained as colorless crystals in 35% yield, mp 132–133°C. IR(KBr): 3032 (Ar—H), 1740 (C=O), 764 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 7.58–6.61 (m, 13H, Ar—H), 4.33 (q, 2H, $CH_2$), 3.80 (s, 3H, $OCH_3$), 3.45 (dd, 1H, H-5x, $J_{bx}$ = 6.72 Hz, $J_{ax}$ = 11.56 Hz), 3.01 (dd, 1H, H-4b, $J_{bx}$ = 6.72 Hz, $J_{ab}$ = 15.70 Hz), 2.60 (dd, 1H, H-4a, $J_{ax}$ = 11.56 Hz, $J_{ab}$ = 15.70 Hz), 1.29 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 460 ($M^+$). Anal. Calcd. for $C_{26}H_{24}N_2O_4S$: C, 67.81; H, 5.25; N, 6.08; Found: C, 67.83; H, 5.24; N, 6.07.

***Ethyl 3a,4-dihydro-3a-phenyl-5-(4-nitrophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4d).*** This compound was obtained as yellow crystals in 33% yield, mp 195–196°C. IR(KBr): 3041 (Ar—H), 1744 (C=O) 760 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.11–6.56 (m, 13H, Ar—H), 4.36 (q, 2H, $CH_2$), 3.40 (dd, 1H, H-5x, $J_{bx}$ = 5.76 Hz, $J_{ax}$ = 11.33 Hz), 3.02 (dd, 1H, H-4b, $J_{bx}$ = 5.76 Hz, $J_{ab}$ = 15.76 Hz), 2.58 (dd, 1H, H-4a, $J_{ax}$ = 11.33 Hz, $J_{ab}$ = 15.76 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 475 ($M^+$). Anal. Calcd. for $C_{25}H_{21}N_3O_5S$: C, 63.15; H, 4.45; N, 8.84; Found: C, 63.12; H, 4.46; N, 8.83.

***Ethyl 3a,4-dihydro-3a-(4-chlorophenyl)-5-phenyl-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4e).*** This compound was obtained as colorless crystals in 31% yield, mp 193–194°C. IR(KBr): 3063 (Ar—H), 1744 (C=O), 760 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.10–6.68 (m, 13H, Ar—H), 4.35 (q, 2H, $CH_2$), 3.50 (dd, 1H, H-5x, $J_{bx}$ = 5.69 Hz, $J_{ax}$ = 10.11 Hz), 2.96 (dd, 1H, H-4b, $J_{bx}$ = 5.69 Hz, $J_{ab}$ = 13.01 Hz), 2.64 (dd, 1H, H-4a, $J_{ax}$ = 10.11 Hz, $J_{ab}$ = 13.01 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 464 ($M^+$). Anal. Calcd. for $C_{25}H_{21}ClN_2O_3S$: C, 64.58; H, 4.55; N, 6.02; Found: C, 64.59; H, 4.53; N, 6.01.

***Ethyl 3a,4-dihydro-3a-(4-chlorophenyl)-5-(4-chlorophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4f).*** This compound was obtained as colorless crystals in 30% yield, mp 165–166°C. IR(KBr): 3057 (Ar—H), 1733 (C=O), 765 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.05–6.70 (m, 12H, Ar—H), 4.37 (q, 2H, $CH_2$), 3.48 (dd, 1H, H-5x, $J_{bx}$ = 5.19 Hz, $J_{ax}$ = 10.56 Hz), 2.92 (dd, 1H, H-4b, $J_{bx}$ = 5.19 Hz, $J_{ab}$ = 13.21 Hz), 2.55 (dd, 1H, H-4a, $J_{ax}$ = 10.56 Hz, $J_{ab}$ = 13.21 Hz), 1.31 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 498 ($M^+$). Anal. Calcd. for $C_{25}H_{20}Cl_2N_2O_3S$: C, 60.12; H, 4.04; N, 5.61; Found: C, 60.14; H, 4.02; N, 5.63.

***Ethyl 3a,4-dihydro-3a-(4-chlorophenyl)-5-(4-methoxyphenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4g).*** This compound was obtained as colorless crystals in 23% yield, mp 143–144°C. IR(KBr): 3102 (Ar—H), 1736 (C=O), 763 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.09–6.68 (m, 12H, Ar—H), 4.34 (q, 2H, $CH_2$), 3.82 (s, 3H, $OCH_3$), 3.46 (dd, 1H, H-5x, $J_{bx}$ = 5.30 Hz, $J_{ax}$ = 10.77 Hz), 2.91 (dd, 1H, H-4b, $J_{bx}$ = 5.30 Hz, $J_{ab}$ = 13.72 Hz), 2.56 (dd, 1H, H-4a, $J_{ax}$ = 10.77 Hz, $J_{ab}$ = 13.72 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m/z* (%): 494 ($M^+$). Anal. Calcd. for $C_{26}H_{23}ClN_2O_4S$: C, 63.09; H, 4.68; N, 5.66; Found: C, 63.12; H, 4.67; N, 4.63.

***Ethyl 3a,4-dihydro-3a-(4-chlorophenyl)-5-(4-nitrophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4h).*** This compound was obtained as colorless crystals in 25% yield, mp 232–233°C. IR(KBr): 3116 (Ar—H), 1744 (C=O), 765 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.10–6.62 (m, 12H, Ar—H), 4.38 (q, 2H, $CH_2$), 3.50 (dd, 1H, H-5x, $J_{bx}$ = 5.32 Hz, $J_{ax}$ = 11.01 Hz), 2.92 (dd, 1H, H-4b, $J_{bx}$ = 5.32 Hz, $J_{ab}$ = 13.82 Hz), 2.58 (dd, 1H, H-4a, $J_{ax}$ = 11.01 Hz, $J_{ab}$ = 13.82 Hz), 1.31 (t, 3H, $CH_3$). MS (70 eV) *m*/*z* (%): 509 ($M^+$). Anal. Calcd. for $C_{25}H_{20}ClN_3O_5S$: C, 58.88; H, 3.95; N, 8.24; Found: C, 58.85; H, 3.96; N, 8.25.

***Ethyl 3a,4-dihydro-3a-(4-methoxyphenyl)-5-phenyl-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4i).*** This compound was obtained as colorless crystals in 26% yield, mp 130–131°C. IR(KBr): 3107 (Ar—H), 1734 (C=O), 762 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.12–6.66 (m, 13H, Ar—H), 4.34 (q, 2H, $CH_2$), 3.81 (s, 3H, $OCH_3$), 3.42 (dd, 1H, H-5x, $J_{bx}$ = 6.38 Hz, $J_{ax}$ = 11.43 Hz), 2.99 (dd, 1H, H-4b, $J_{bx}$ = 6.38 Hz, $J_{ab}$ = 15.56 Hz), 2.58 (dd, 1H, H-4a, $J_{ax}$ = 11.42 Hz, $J_{ab}$ = 15.56 Hz), 1.29 (t, 3H, $CH_3$). MS (70 eV) *m*/*z* (%): 460 ($M^+$). Anal. Calcd. for $C_{26}H_{24}N_2O_4S$: C, 67.81; H, 5.25; N, 6.08; Found: C, 67.80; H, 5.28; N, 6.04.

***Ethyl 3a,4-dihydro-3a-(4-methoxyphenyl)-5-(4-chlorophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4j).*** This compound was obtained as colorless crystals in 32% yield, mp 213–214°C. IR(KBr): 3075 (Ar—H), 1736 (C=O), 762 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.02–6.65 (m, 12H, Ar—H), 4.35 (q, 2H, $CH_2$), 3.83 (s, 3H, $OCH_3$), 3.49 (dd, 1H, H-5x, $J_{bx}$ = 5.21 Hz, $J_{ax}$ = 10.32 Hz), 2.95 (dd, 1H, H-4b, $J_{bx}$ = 5.21 Hz, $J_{ab}$ = 13.44 Hz), 2.58 (dd, 1H, H-4a, $J_{ax}$ = 10.32 Hz, $J_{ab}$ = 13.44 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m*/*z* (%): 494 ($M^+$). Anal. Calcd. for $C_{26}H_{23}ClN_2O_4S$: C, 63.09; H, 4.68; N, 5.66; Found: C, 63.13; H, 4.66; N, 5.65.

***Ethyl 3a,4-dihydro-3a-(4-methoxyphenyl)-5-(4-methoxyphenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4k).*** This compound was obtained as colorless crystals in 36% yield, mp 173–174°C. IR(KBr): 3121 (Ar—H), 1739 (C=O), 762 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.11–6.60 (m, 12H, Ar—H), 4.30 (q, 2H, $CH_2$), 3.80 (s, 6H, $OCH_3$), 3.38 (dd, 1H, H-5x, $J_{bx}$ = 6.52 Hz, $J_{ax}$ = 11.89 Hz), 2.95 (dd, 1H, H-4b, $J_{bx}$ = 2.95 Hz, $J_{ab}$ = 15.62 Hz), 2.60 (dd, 1H, H-4a, $J_{ax}$ = 11.89 Hz, $J_{ab}$ = 15.62 Hz), 1.29 (t, 3H, $CH_3$). MS (70 eV) *m*/*z* (%): 490 ($M^+$). Anal. Calcd. for $C_{27}H_{26}N_2O_5S$: C, 66.10; H, 5.34; N, 5.71; Found: C, 66.08; H, 5.35; N, 5.74.

***Ethyl 3a,4-dihydro-3a-(4-methoxyphenyl)-5-(4-nitrophenyl)-5H-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine-1-carboxylate (4l).*** This compound was obtained as yellow crystals in 20% yield, mp 213–214°C. IR(KBr): 3118 (Ar—H), 1738 (C=O), 761 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 400 MHz) δ: 8.04–6.69 (m, 12H, Ar—H), 4.37 (q, 2H, $CH_2$), 3.84 (s, 3H, $OCH_3$), 3.45 (dd, 1H, H-5x, $J_{bx}$ = 5.97 Hz, $J_{ax}$ = 11.65 Hz), 2.90 (dd, 1H, H-4b, $J_{bx}$ = 5.97 Hz, $J_{ab}$ = 15.71 Hz), 2.58 (dd, 1H, H-4a, $J_{ax}$ = 11.65 Hz, $J_{ab}$ = 15.71 Hz), 1.30 (t, 3H, $CH_3$). MS (70 eV) *m*/*z* (%): 505 ($M^+$). Anal. Calcd. for $C_{26}H_{23}N_3O_6S$: C, 61.77; H, 4.59; N, 8.31; Found: C, 61.74; H, 4.60; N, 8.34.

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