Synthesis and Crystal Structure of Novel [1,2,4]Oxadiazolo[5,4-*d*] [1,5]benzothiozepine Derivatives Containing Pyrazole Moiety

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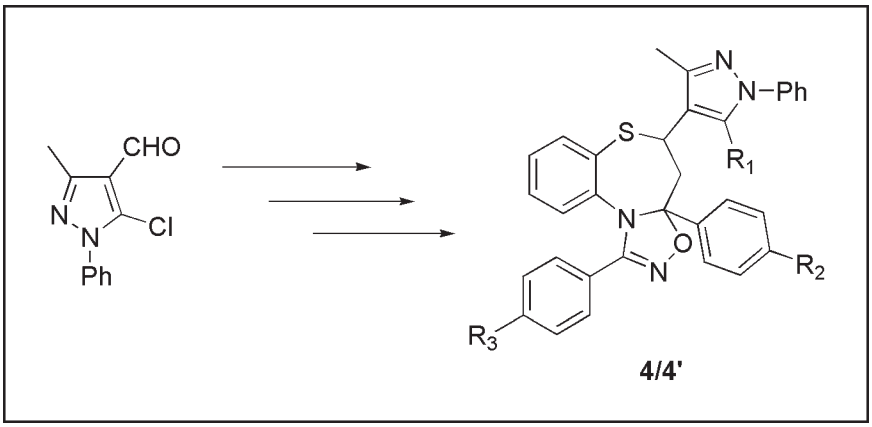

A series of new substituted-[1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepine derivatives containing pyrazole ring **4/4′** was synthesized by substituted-pyrazolo[1,5]benzothiazepines **2/2′** and substituted-benzohydroximinoyl chlorides **3** through the 1,3-dipolar cycloaddition reaction in the presence of Et_3N at room temperature, and characterized by MS, IR, ^1H NMR and elemental analyses. In addition, the structure of **4′l** was determined by X-ray crystallography.

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INTRODUCTION

The synthesis of benzothiazepine derivatives has attracted considerable attention of organic and medicinal chemists because of their broad spectrum of biological activity. The [1,5]benzothiazepine derivatives have been used as antihypertensive [1], antidepressant [2], anticoagulant [3], antiarteriosclerotic [4], anti-HIV [5], and antibacterial [6]. For example, Diltiazem is well known drug having the [1,5]benzothiazepine skeleton, which elicits antihypertensive effect [7]. Moreover, further potential therapeutic applications can be inferred from experimental data on different representative [1,5]benzothiazepine.

Pyrazole and its derivatives have attracted the attention of chemists mainly because of broad spectrum pharmacological activities such as hypotensive [8], antibacterial [9], antidepressant [10], antiinflammatory [11], and antitumor [12] exhibited by this class of compounds. Furthermore, pyrazole derivatives also have varied other activities to be used in pesticides, herbicides, and light emitting materials [13].

In addition, [1,2,4]oxadiazole is an important five-membered heterocycle, which displays antiinflammatory and antimicrobial activities [14]. In recent years, an enormous number of articles have been published highlighting the synthesis of [1,2,4]oxadiazole derivatives *via* 1,3-dipolar cycloaddition reaction [15,16].

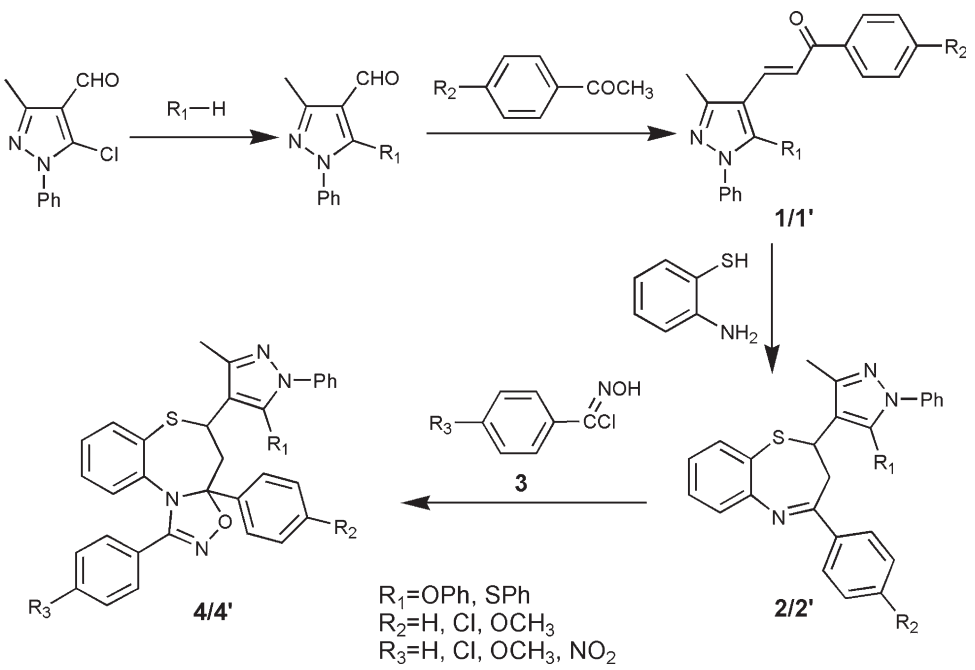
Recently, research result has shown that substitution with heterocyclic ring at position -2 or -4 of [1,5]benzothiazepine or fix an additional heterocycle to the heptaatomic nucleus provides more activities than parent molecule [17–19]. Keeping these observations in mind and in continuation of our interest to prepare fused hetercyclic compounds [20,21], we report herein the reaction of substituted [1,5]benzothiazepines containing pyrazole ring with substituted-benzohydroximinoyl chlorides through 1,3-dipolar cycloaddition to afford a new series of tricyclic systems, [1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepine derivatives with pyrazole moiety, which might have useful biological and therapeutic activities.

RESULTS AND DISCUSSION

We described in this research report the synthesis of eighteen new compounds. The synthesis of these compounds were carried out as shown in Scheme 1.

In the synthesis of **2/2′**, because of —SH in *o*-aminothiophenol have nucleophilicity, 1,4-Michael addition reaction occurs firstly when it reacts with the conjugated

Scheme 1



double bond in chalcone, this was a key step in the reaction. Then, —NH_2 and —C=O dehydration condensation to yield **2/2′**. At room temperature, the pyrazolo[1,5]benzodiazepines **2/2′** were treated with benzonitrile oxide, generated *in situ* by the action of triethylamine on benzohydroximinoyl chlorides **3**, stirring 2 days at room temperature in dichloromethane furnished cycloadducts **4/4′** with complete regioselectivity.

At the same time, we found that the different substituents of R_2 affected the speed of the cycloaddition reaction. When R_2 is electron-donating(—OCH_3), the cycloaddition speed is faster than that is electron-withdrawing(—Cl). This maybe due to the formation of a conjugated system of electron-donating substituted benzene and enamine, so that the electron density of enamine(C=N) is increased, which benefits the 1,3-dipolar addition. To improve the yield of the reaction, the reaction was taken under refluxing, but, unfortunately, the yield was also not as high as expected. So, we presumed that the stereo-hindrance effect and dipole dimerization result in the low yield.

The cycloadducts **4/4′** have shown analytical and physicochemical data consistent with the assigned structure.

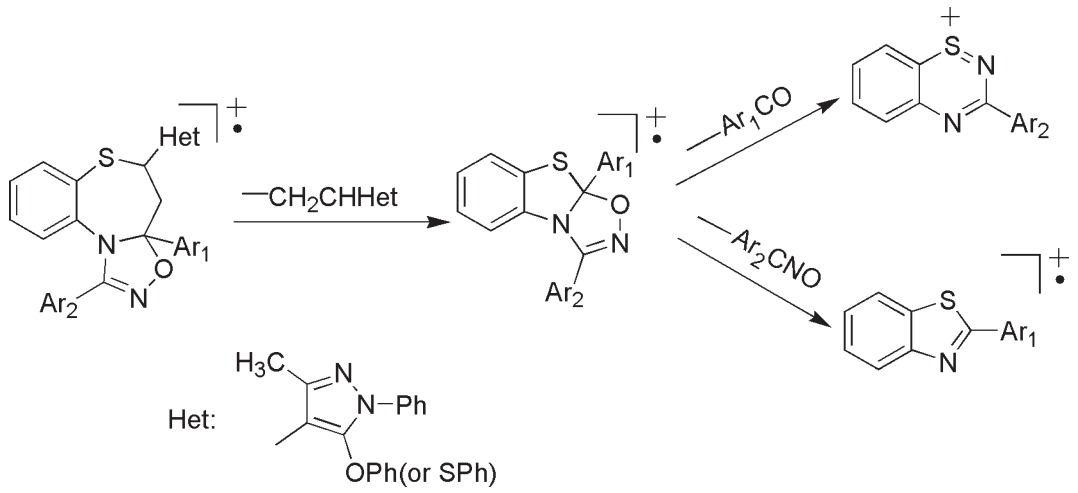
In the IR spectra of compounds **4/4′**, a less broad band in the range 3063–3055 cm^{-1} was obtained due to the Ar-H group. The C=N stretching vibrations was observed at 1567–1557 cm^{-1} as usual position. The C—S—C linkage of the seven membered ring caused a weak and sharp absorption band at 762–748 cm^{-1} in all the compounds.

The mass spectra of the final compounds **4/4′** showed correct molecular ions and the formation of diagnostic fragmentations. In particular, an intramolecular rearrangement from molecular ions, by loss of —CH_2CHHet, led to the formation of oxadiazolobenzothiazole ion radical. Then, it affords a benzothiadiazine ion by loss —Ar_1CO and affords a benzothiazole ion by loss —Ar_2CNO (Scheme 2).

The ^1H NMR chemical shifts and coupling constants observed for compounds **4/4′** in $CDCl_3$ solution were presented, and the ^1H NMR spectra of this series was quite similar. All compounds showed a complex multiplet of aromatic protons in the range δ: 8.45–6.53 ppm. Especially, the ^1H NMR spectra showed three distinct double doublets in the ABX pattern at δ: 3.82–2.57 ppm, which were the characteristic peaks of dihydrobenzothiazepine moiety. Other signals were observed at δ: 3.82–3.75 (s,3H,—OCH_3), 2.70–2.02 (s, 3H, —CH_3) ppm as usual positions. Combining the ^1H NMR data with MS fragment analysis, it was reasonable to conclude that the target products.

To confirm the assigned stereochemistry, single crystal X-ray analysis was carried out for compound **4′l**, as depicted in Figure 1. The higher occupancy in the three dimensional packing arrangement was shown in Figure 2. The crystal data and structure refinement of **4′l** were listed in Table 1. Selected bond distances and angles of **4′l** were tabulated in Table 2. Compound **4′l** was a compound with seven-heterocyclic as the center, and the ring was characterized by the endocyclic torsion

Scheme 2



angles(enumerated clockwise and starting with S(1)—C(11)— C(16)—N(5)): 0.50(18)°, 62.25(17)°, 9.86(18)°, 77.79(16)°, 52.66(15)°, 31.73(12)°, 66.35(13)°. N(5),S(1), C(10) and C(25) were nealy coplanar, while C(11), C(16) and C(33) were all below the plane, with their deviations being 1.2034(0.0017), 1.1981(0.0017), and 0.6439(0.0019) Å. Therefore, the seven-membered ring adopted a boat-like conformation. There was a five-membered ring in the molecule, resulting from the cycloaddition reaction. N(4), C(17), N(5), C(25) in the ring were nearly coplanar with similar bond angles (N(4)—C(17)—N(5) 114.85(13)°, C(17)— N(4)—O (4) 106.64(12)°, O(4)—C(25)—N(5) 101.75(10)°, N(4)—O(4)—C(25) 105.74(10)°, C(17)—N(5)—C(25) 101.26 (11)°). The five-membered ring of [1,2,4]oxadiazole adopted envelope conformation with the atom O(4) deviating from the plane defined by N(4), C(17), N(5), C(25) which indicated the ring is stable. The fact that there is no other region or stereoisomer was formed during the addition.

CONCLUSIONS

The present study describes the stereoselective synthesis of a series of new 3a,4,5,11-tetrahydro-1,3a-diaryl-5-

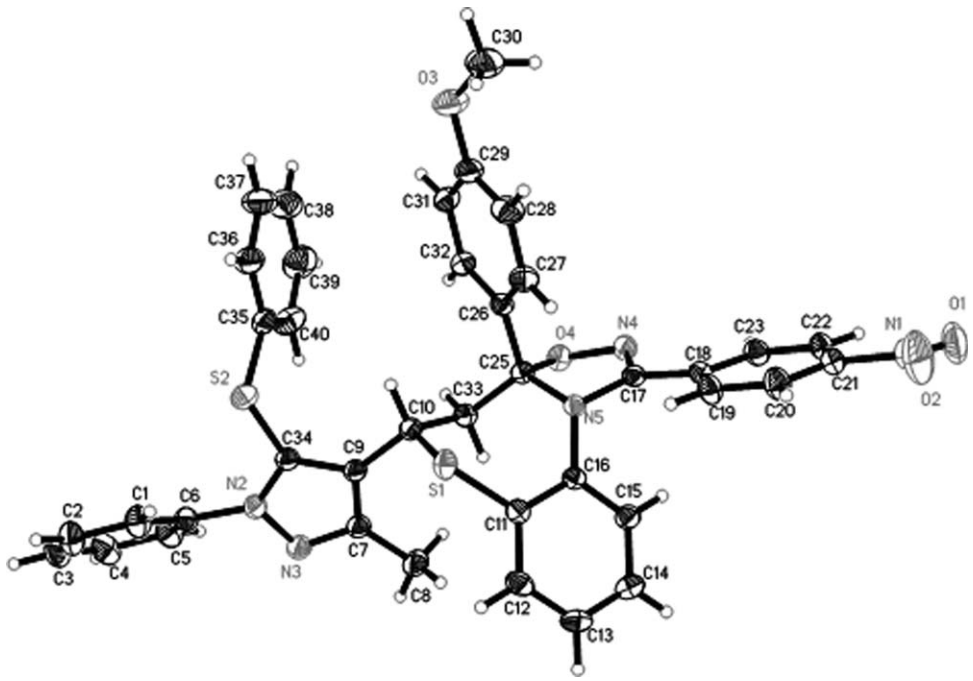


Figure 1. The molecular structure for **4′l** with the atomic numbering scheme.

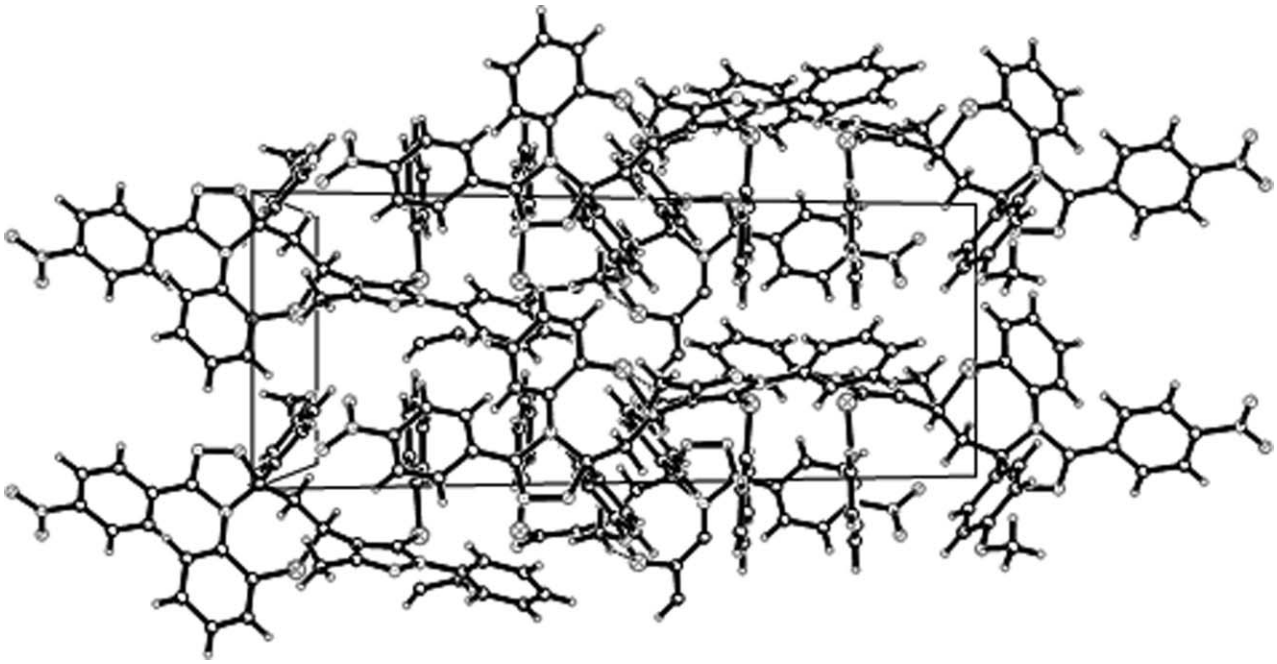


Figure 2. The crystal packing of **4′l** viewed down.

(3-methyl-1-phenyl-5-substituted-1*H*-pyrazol-4-yl)-[1,2,4] oxadiazolo[5,4-*d*][1,5]benzothiazepine derivatives **4**/**4′** through 1,3-dipolar cycloaddition reaction, and the crystal structure of **4′l** was reported first. The result showed that the seven-membered ring adopted a twist-boat-like conformation. Further investigations on the synthetic utility of **2**/**2′** in the construction of novel fused heterocycles are under progress in our research group.

EXPERIMENTAL

All chemical reagents were obtained from a commercial source and used without further purification. Melting points were recorded on a X-5 micro melting point apparatus and tempreture were uncorrected. ^{1}H NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer using TMS as an internal standard and $CDCl_3$ as solvent at room temperature. The IR spectra were recorded from KBr on a Bruker Tensor 27 spectrophotometer. MS were recorded on an Agilent 5975 mass selective detector. X-ray diffraction data were obtained on a Hitachi F-4500 R-AXIS SPDER diffractometer. Element analyses were performed on a Perkin-Elmer 240 CHN analyzer.

3-Methyl-1-phenyl-5-substituted-4-pyrazolocarbaldehyde were prepared by literature reported methods [22,23].

4-Substituted-benzohydroximinoyl chlorides were prepared by literature reported methods [24].

3-(3-Methyl-1-phenyl-5-substituted-1*H*-pyrazol-4-yl)-1-(4-substituted-phenyl)-2-propen-1-one 1/1′ were prepared by literature reported methods [22]. The physical and analytical data of compounds 1′ are presented in Table 3.

3-(3-Methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-1-phenyl-2-propen-1-one(1′a). This compound was obtained as pale yellow crystals. IR(KBr)υ/cm^{-1}: 3056 (Ar-H), 1649 (C=O),

Table 1

Crystal parameters data collections and structure refinements for **4′l**.

Empirical formula	$C_{39}H_{31}N_5O_4S_2$
Formula weight	697.81
Temperature/K	293(2)
Crystal system	Monoclinic
Space group	*P*2(1)/*c*
a/Å	18.3633(7)
b/Å	8.5437(4)
c/Å	23.3101(10)
V/Å^3	3395.1(3)
Z	4
D_c/(Mg·m^{-3})	1.365
F(000)	1456
μ/mm^{-1}	0.207
α/(°)	90
β/(°)	111.8210(10)
γ/(°)	90
Crystal size/mm^3	0.64 × 0.55 × 0.48
θrange of data collection/(°)	3.00 < θ < 27.48
Index ranges	−22<=*h*<=23, −11<=*k*<=11, −29<=*l*<=30
Total reflections collected	31947
Independent reflection	7754
Max.and min.transmission	0.9070 and 0.8787
Data/restraints/parameters	6470/0/371
Final *R* indices[$I > 2\sigma(I)$]	$R_1 = 0.0544$, $wR_2 = 0.1506$
Goodness-of-fit on F^2	1.052
Refine method	Full-matrix least-squares on F^2
R indices (all data)	$R_1 = 0.0482$, $wR_2 = 0.1162$

Table 2

Selected bond lengths (Å) and angles (°) of compound **4′l**.

S(1)—C(11)	1.7658 (15)
S(1)—C(10)	1.8453 (15)
S(2)—C(34)	1.7485 (15)
S(2)—C(35)	1.777 (2)
O(1)—N(1)	1.213 (2)
O(2)—N(1)	1.213 (3)
O(3)—C(29)	1.378 (2)
O(3)—C(30)	1.405 (3)
N(1)—C(21)	1.474 (2)
N(2)—N(3)	1.3605 (19)
N(2)—C(34)	1.3699 (19)
N(2)—C(6)	1.4301 (19)
N(3)—C(7)	1.333 (2)
O(4)—N(4)	1.4129 (17)
O(4)—C(25)	1.4718 (17)
N(5)—C(17)	1.4222 (18)
N(5)—C(16)	1.4329 (18)
N(5)—C(25)	1.4742 (18)
C(7)—C(9)	1.412 (2)
C(7)—C(8)	1.495 (2)
C(9)—C(34)	1.381 (2)
C(10)—C(33)	1.527 (2)
C(17)—N(4)	1.2818 (19)
C(17)—C(18)	1.472 (2)
C(25)—C(33)	1.517 (2)
C(11)—S(1)—C(10)	103.09 (7)
C(34)—S(2)—C(35)	104.20 (8)
N(3)—N(2)—C(34)	111.00 (12)
C(7)—N(3)—N(2)	105.80 (12)
N(4)—O(4)—C(25)	105.74 (10)
C(17)—N(5)—C(25)	101.26 (11)
C(16)—N(5)—C(25)	120.45 (11)
N(3)—C(7)—C(9)	111.17 (14)
N(3)—C(7)—C(8)	118.04 (14)
C(34)—C(9)—C(7)	104.88 (13)
C(34)—C(9)—C(10)	125.00 (13)
C(7)—C(9)—C(10)	130.12 (14)
C(9)—C(10)—C(33)	113.04 (12)
C(9)—C(10)—S(1)	112.41 (11)
C(33)—C(10)—S(1)	112.02 (10)
C(16)—C(11)—S(1)	121.69 (11)
C(15)—C(16)—N(5)	121.16 (13)
C(11)—C(16)—N(5)	119.76 (12)
N(4)—C(17)—N(5)	114.85 (13)
N(4)—C(17)—C(18)	120.97 (13)
N(5)—C(17)—C(18)	124.06 (13)
C(17)—N(4)—O(4)	106.64 (12)
O(4)—C(25)—N(5)	101.75 (10)
O(4)—C(25)—C(33)	105.46 (11)
N(5)—C(25)—C(33)	115.91 (12)
O(4)—C(25)—C(26)	106.57 (11)
N(2)—C(34)—C(9)	107.14 (13)
N(2)—C(34)—S(2)	123.24 (12)
C(9)—C(34)—S(2)	129.58 (12)

1557 (C=N); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68–6.99 (m, 17H, Ar-H, CH=CH), 2.53 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 396(M^+), 287(100), 105, 77.

3-(3-Methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-1-(4-chlorophenyl)-2-propen-1-one(1′b). This compound was obtained as yellow crystals. IR(KBr)υ/cm^{-1}: 3051(Ar-H), 1653 (C=O), 1555 (C=N); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.64–6.93 (m, 16H, Ar-H, CH=CH), 2.52 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 430(M^+), 321(100), 139, 77.

3-(3-Methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-1-(4-methoxyphenyl)-2-propen-1-one(1′c). This compound was obtained as pale yellow crystals. IR(KBr)υ/cm^{-1}: 3052(Ar-H), 1651 (C=O), 1554 (C=N); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.66–7.01 (m, 16H, Ar-H, CH=CH), 3.72 (s, 3H, —OCH_3), 2.52 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 426(M^+), 317(100), 135, 77.

2,3-Dihydro-2-(3-methyl-1-phenyl-5-substituted-1*H*-pyrazol-4-yl)-4-substituted-1,5-benzothiazepine 2/2′ were prepared by literature reported methods [25]. The physical and analytical data of compounds 2′ are presented in Table 3.

2,3-Dihydro-2-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-4-phenyl-1,5-benzothiazepine(2′a). This compound was obtained as pale yellow crystals. IR(KBr)υ/cm^{-1}: 3052(Ar-H), 1596 (C=N), 701 (C—S—C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.74–6.65 (m, 19H, Ar-H), 4.99–4.96 (dd, 1H, H_{2x}, J_{ax} = 5.2 Hz, J_{bx} = 12.4 Hz), 3.19–3.15 (dd, 1H, H_{3a}, J_{ax} = 5.2 Hz, J_{ab} = 13.6 Hz), 3.11–3.08 (dd, 1H, H_{3b}, J_{bx} = 12.4 Hz, J_{ab} = 13.6 Hz), 2.31(s, 3H, —CH_3); MS(EI)*m*/*z*(%): 503(M^+), 394, 292(100), 211, 183, 77.

2,3-Dihydro-2-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-4-(4-chlorophenyl)-1,5-benzothiazepine(2′b). This compound was obtained as pale yellow crystals. IR(KBr)υ/cm^{-1}: 3059 (Ar-H), 1597 (C=N), 699 (C—S—C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.71–6.71 (m, 18H, Ar-H), 4.96–4.92 (dd, 1H, H_{2x}, J_{ax} = 4.8 Hz, J_{bx} = 12.4 Hz), 3.20–3.15 (dd, 1H, H_{3a}, J_{ax} = 4.8 Hz, J_{ab} = 14.0 Hz), 3.09–3.06 (dd, 1H, H_{3b}, J_{bx} = 12.4 Hz, J_{ab} = 14.0 Hz), 2.31(s, 3H, —CH_3); MS(EI)*m*/*z*(%): 537(M^+), 428, 292(100), 245, 183, 77.

2,3-Dihydro-2-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-4-(4-methoxyphenyl)-1,5-benzothiazepine(2′c). This compound was obtained as yellow crystals. IR(KBr)υ/cm^{-1}: 3061 (Ar-H), 1599 (C=N), 701 (C—S—C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68–6.69 (m, 18H, Ar-H), 4.98–4.95(dd, 1H, H_{2x}, J_{ax} = 5.2 Hz, J_{bx} = 12.8 Hz), 3.81(s, 3H, —OCH_3), 3.41–3.36 (dd, 1H, H_{3a}, J_{ax} = 5.2 Hz, J_{ab} = 14.0 Hz), 3.29–3.26 (dd, 1H, H_{3b}, J_{bx} = 12.8 Hz, J_{ab} = 14.0 Hz), 2.33 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 533(M^+), 424, 292(100), 241, 183, 77.

General procedure for synthesis of 3a,4,5,11-tetrahydro-1,3a-diaryl-5-(3-methyl-1-phenyl-5-substituted-1*H*-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-*d*][1,5]benzothiazepine 4/4′. The physical and analytical data of compounds **4**/**4′** are presented in Table 4. A mixture of compounds **2**/**2′**(1.0 mmol) and benzohydroximinoyl chlorides(1.5 mmol) were stirred in 20 mL CH_2Cl_2 at room temperature, then the triethylamine(0.8 mmol) was dropwise added. Stirring was continued for 24 h, detected by TLC. The triethylamine hydrochloric acid salt was removed by filtration after completing the reaction. The solution was concentrated and the residue was separated through silica gel column with ethylacetate:petroleum ether(1:8;v/v). Single crystals suitable for X-ray measurements of compound **4′l** was obtained by recrystallization from ethanol and petroleum ether at room temperature.

3a,4,5,11-Tetrahydro-1,3a-diphenyl-5-(3-methyl-1-phenyl-5-phenyloxyl-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4a). This compound was obtained as pale yellow crystals. IR(KBr)υ/cm^{-1}: 3058(Ar-H), 1635, 1561 (C=N), 748 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.53–6.58 (m, 24H, Ar-H), 3.82–3.76 (dd, 1H, H_{5x}, J_{ax} = 4.8 Hz,

Table 3

Physical and analytical data of compounds **1′** and **2′**.

					Analysis (%) Calcd/Found		
Compd. No.	R_1	Yield (%)	M.P. (°C)	Molecular formula	C	H	N
1′a	H	81	112–115	$C_{25}H_{20}N_2OS$	75.73	5.08	7.07
					75.70	5.14	7.04
1′b	Cl	83	159–162	$C_{25}H_{19}ClN_2OS$	69.68	4.44	6.50
					69.60	4.48	6.44
1′c	OCH_3	89	133–135	$C_{26}H_{22}N_2O_2S$	73.21	5.20	6.57
					73.11	5.25	6.55
2′a	H	73	168–170	$C_{31}H_{25}N_3OS_2$	73.92	5.00	8.34
					73.83	5.11	8.30
2′b	Cl	74	188–191	$C_{31}H_{24}ClN_3OS_2$	69.19	4.50	7.81
					69.01	4.59	7.71
2′c	OCH_3	77	167–168	$C_{32}H_{27}N_3O_2S_2$	72.01	5.10	7.87
					71.84	5.23	7.82

Table 4

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

							Analysis (%) Calcd/Found		
Compd. No.	R_1	R_2	R_3	Yield (%)	M.P. (°C)	Molecular formula	C	H	N
4a	OPh	H	H	25	258–260	$C_{38}H_{30}N_4O_2S$	75.22	4.98	9.23
							75.21	5.11	9.17
4b	OPh	H	OCH_3	20	201–203	$C_{39}H_{32}N_4O_3S$	73.56	5.07	8.80
							73.48	5.15	8.77
4c	OPh	CL	H	19	244–246	$C_{38}H_{29}ClN_4O_2S$	71.18	4.56	8.74
							71.07	4.63	8.70
4d	OPh	CL	OCH_3	23	221–223	$C_{39}H_{31}ClN_4O_3S$	69.79	4.66	8.35
							69.73	4.71	8.32
4e	OPh	OCH_3	H	31	164–166	$C_{39}H_{32}N_4O_3S$	73.56	5.07	8.80
							73.51	5.17	8.72
4f	OPh	OCH_3	OCH_3	36	195–197	$C_{40}H_{34}N_4O_4S$	72.05	5.14	8.40
							72.01	5.20	8.38
4′a	SPh	H	H	26	202–205	$C_{38}H_{30}N_4OS_2$	73.28	4.86	9.00
							73.27	4.83	9.00
4′b	SPh	H	CL	21	198–200	$C_{38}H_{29}ClN_4OS_2$	69.44	4.45	8.52
							69.39	4.52	8.51
4′c	SPh	H	OCH_3	28	226–228	$C_{39}H_{32}N_4O_2S_2$	71.75	4.94	8.58
							71.81	4.93	8.57
4′d	SPh	H	NO_2	27	230–232	$C_{38}H_{29}N_5O_3S_2$	68.34	4.38	10.49
							68.30	4.39	10.44
4′e	SPh	CL	H	19	259–261	$C_{38}H_{29}ClN_4OS_2$	69.44	4.45	8.52
							69.37	4.54	8.50
4′f	SPh	CL	CL	21	224–226	$C_{38}H_{28}Cl2N_4OS_2$	65.98	4.08	8.10
							65.92	4.11	8.12
4′g	SPh	CL	OCH_3	21	195–196	$C_{39}H_{31}ClN_4O_2S_2$	68.16	4.55	8.15
							68.08	4.60	8.14
4′h	SPh	CL	NO_2	24	212–214	$C_{38}H_{28}ClN_5O_2S_2$	64.99	4.02	9.97
							64.94	4.03	9.98
4′i	SPh	OCH_3	H	27	229–231	$C_{39}H_{32}N_4O_2S_2$	71.75	4.94	8.58
							71.77	4.95	8.58
4′j	SPh	OCH_3	CL	26	207–209	$C_{39}H_{31}ClN_4O_2S_2$	68.16	4.55	8.15
							68.15	4.57	8.12
4′k	SPh	OCH_3	OCH_3	30	197–199	$C_{40}H_{34}N_4O_3S_2$	70.36	5.02	8.20
							70.31	5.08	8.21
4′l	SPh	OCH_3	NO_2	38	205–207	$C_{39}H_{31}N_5O_4S_2$	67.13	4.48	10.04
							67.13	4.48	10.04

J_{bx} = 12.8 Hz), 2.93–2.86 (dd, 1H, H_{4a}, J_{ax} = 4.8 Hz, J_{ab} = 13.6 Hz), 2.69–2.60 (dd, 1H, H_{4b}, J_{bx} = 12.8 Hz, J_{ab} = 13.6 Hz), 2.05(s, 3H, —CH_3); MS(EI)*m*/*z*(%): 606(M^+), 513, 394, 330, 287, 226, 211, 105(100), 77.

3a,4,5,11-Tetrahydro-1-(4-methoxyphenyl)-3a-phenyl-5-(3-methyl-1-phenyl-5-phenyloxyl-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4b). This compound was obtained as white crystals. IR(KBr)υ/cm^{-1}: 3055 (Ar-H), 1633, 1560 (C=N), 752 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.78–6.54 (m, 23H, Ar-H), 3.79 (s, 3H, —OCH_3), 3.44–3.39 (dd, 1H, H_{5x}, J_{ax} = 4.4 Hz, J_{bx} = 12.4 Hz), 2.89–2.85 (dd, 1H, H_{4a}, J_{ax} = 4.4 Hz, J_{ab} = 14.8 Hz), 2.65–2.60 (dd, 1H, H_{4b}, J_{bx} = 12.4Hz, J_{ab} = 14.8 Hz), 2.06 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 636(M^+), 543, 394, 360, 287, 256, 211, 105(100), 77.

3a,4,5,11-Tetrahydro-1-phenyl-3a-(4-chlorophenyl)-5-(3-methyl-1-phenyl-5-phenyloxyl-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4c). This compound was obtained as pale yellow crystals. IR(KBr)υ/cm^{-1}: 3058(Ar-H), 1635, 1561 (C=N), 749 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.41–6.61 (m, 23H, Ar-H), 3.81–3.75 (dd, 1H, H_{5x}, J_{ax} = 5.2 Hz, J_{bx} = 12.8 Hz), 3.10–3.05(dd, 1H, H_{4a}, J_{ax} = 5.2 Hz, J_{ab} = 13.6 Hz), 3.02–2.96 (dd, 1H, H_{4b}, J_{bx} = 12.8 Hz, J_{ab} = 13.6 Hz), 2.08 (s, 3H, —CH_3); MS(EI)*m*/*z*(%):640(M^+), 547, 431, 364, 321, 245, 226, 139(100), 77.

3a,4,5,11-Tetrahydro-1-(4-methoxyphenyl)-3a-(4-chlorophenyl)-5-(3-methyl-1-phenyl-5-phenyloxyl-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4d). This compound was obtained as white crystals. IR(KBr)υ/cm^{-1}: 3061 (Ar-H), 1631, 1557 (C=N), 751 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.80–6.58 (m, 22H, Ar-H), 3.82 (s, 3H, —OCH_3), 3.35–3.32 (dd, 1H, H_{5x}, J_{ax} = 4.4 Hz, J_{bx} = 13.2 Hz), 2.83–2.76 (dd, 1H, H_{4a}, J_{ax} = 4.4 Hz, J_{ab} = 14.0 Hz), 2.63–2.57 (dd, 1H, H_{4b}, J_{bx} = 13.2 Hz, J_{ab} = 14.0 Hz), 2.10 (s, 3H, —CH_3); MS(EI)*m*/*z*(%):670(M^+), 577, 431, 394, 321, 256, 245, 139(100), 77.

3a,4,5,11-Tetrahydro-1-phenyl-3a-(4-methxoyphenyl)-5-(3-methyl-1-phenyl-5-phenyloxyl-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4e). This compound was obtained as white crystals. IR(KBr)υ/cm^{-1}: 3059 (Ar-H), 1634, 1560 (C=N), 750 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.58–6.61 (m, 23H, Ar-H), 3.76 (s, 3H, —OCH_3), 3.74–3.68 (dd, 1H, H_{5x}, J_{ax} = 5.2 Hz, J_{bx} = 12.8 Hz), 3.06–3.02 (dd, 1H, H_{4a}, J_{ax} = 5.2 Hz, J_{ab} = 13.6 Hz), 3.01–2.94 (dd, 1H, H_{4b}, J_{bx} = 12.8 Hz, J_{ab} = 13.6 Hz), 2.06(s, 3H, —CH_3); MS(EI)*m*/*z*(%):636(M^+), 543, 427, 360, 317, 241, 226, 135(100), 77.

3a,4,5,11-Tetrahydro-1,3a-di(4-methxoyphenyl)-5-(3-methyl-1-phenyl-5-phenyloxyl-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4f). This compound was obtained as white crystals. IR(KBr)υ/cm^{-1}: 3060 (Ar-H), 1632, 1559 (C=N), 750 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.83–6.59 (m, 22H, Ar-H), 3.81 (s, 3H, —OCH_3), 3.75 (s, 3H, —OCH_3), 3.41–3.24 (dd, 1H, H_{5x}, J_{ax} = 5.2 Hz, J_{bx} = 12.0 Hz), 2.84–2.77 (dd, 1H, H_{4a}, J_{ax} = 5.2 Hz, J_{ab} = 14.8 Hz), 2.64–2.57 (dd, 1H, H_{4b}, J_{bx} = 12.0 Hz, J_{ab} = 14.8 Hz), 2.11 (s, 3H, —CH_3); MS(EI)*m*/*z*(%):666(M^+), 573, 427, 390, 317, 256, 241, 135(100), 77.

3a,4,5,11-Tetrahydro-1,3a-diphenyl-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′a). This compound was obtained as pale yellow crystals. IR(KBr)υ/cm^{-1}: 3061 (Ar-H), 1631, 1567 (C=N), 753 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.88–6.70 (m, 24H, Ar-H), 4.65–4.62 (dd, 1H, H_{5x}, J_{ax} = 4.8 Hz, J_{bx} = 12.4 Hz), 3.16–3.12 (dd, 1H, H_{4a}, J_{ax} = 4.8 Hz, J_{ab} = 13.6 Hz), 3.05–3.01 (dd, 1H, H_{4b}, J_{bx} = 12.4 Hz, J_{ab} = 13.6 Hz), 2.66 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 622(M^+), 513, 394, 330, 287, 226, 211, 105(100), 77.

3a,4,5,11-Tetrahydro-1-(4-chlorophenyl)-3a-phenyl-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′b). This compound was obtained as pale yellow crystals. IR(KBr)υ/cm^{-1}: 3058 (Ar-H), 1637, 1561 (C=N), 757 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.92–6.69 (m, 23H, Ar-H), 4.64–4.60 (dd, 1H, H_{5x}, J_{ax} = 5.2 Hz, J_{bx} = 12.4 Hz), 3.16–3.10 (dd, 1H, H_{4a}, J_{ax} = 5.2 Hz, J_{ab} = 14.0 Hz), 3.03–2.98 (dd, 1H, H_{4b}, J_{bx} = 12.4 Hz, J_{ab} = 14.0 Hz), 2.65 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 656(M^+), 547, 394, 364, 287, 260, 211, 105(100), 77.

3a,4,5,11-Tetrahydro-1-(4-methoxyphenyl)-3a-phenyl-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′c). This compound was obtained as white crystals. IR(KBr)υ/cm^{-1}: 3058 (Ar-H), 1641, 1562 (C=N), 759 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.83–6.65 (m, 23H, Ar-H), 4.64–4.59 (dd, 1H, H_{5x}, J_{ax} = 5.2 Hz, J_{bx} = 12.8 Hz), 3.89 (s, 3H, —OCH_3), 3.15–3.10 (dd, 1H, H_{4a}, J_{ax} = 5.2 Hz, J_{ab} = 13.6 Hz), 3.02–2.98 (dd, 1H, H_{4b}, J_{bx} = 12.8 Hz, J_{ab} = 13.6 Hz), 2.65 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 652(M^+), 543, 394, 360, 287, 256, 211, 105(100), 77.

3a,4,5,11-Tetrahydro-1-(4-nitrophenyl)-3a-phenyl-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′d). This compound was obtained as pale yellow crystals. IR(KBr)υ/cm^{-1}: 3058(Ar-H), 1634, 1559 (C=N), 759 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 8.30–6.64 (m, 23H, Ar-H), 4.71–4.67 (dd, 1H, H_{5x}, J_{ax} = 4.8 Hz, J_{bx} = 12.4 Hz), 3.24–3.19 (dd, 1H, H_{4a}, J_{ax} = 4.8 Hz, J_{ab} = 13.6 Hz), 3.12–3.08 (dd, 1H, H_{4b}, J_{bx} = 12.4 Hz, J_{ab} = 13.6 Hz), 2.70(s, 3H, —CH_3); MS(EI)*m*/*z*(%): 667(M^+), 558, 394, 375, 287, 271, 211, 105(100), 77.

3a,4,5,11-Tetrahydro-1-phenyl-3a-(4-chlorophenyl)-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′e). This compound was obtained as yellow crystals. IR(KBr)υ/cm^{-1}: 3063(Ar-H), 1635, 1561 (C=N), 760 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.84–6.71 (m, 23H, Ar-H), 4.58–4.55 (dd, 1H, H_{5x}, J_{ax} = 4.4 Hz, J_{bx} = 12.4 Hz), 3.08–3.04 (dd, 1H, H_{4a}, J_{ax} = 4.4 Hz, J_{ab} = 14.0 Hz), 3.00–2.95 (dd, 1H, H_{4b}, J_{bx} = 12.4 Hz, J_{ab} = 14.0 Hz), 2.64 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 656(M^+), 547, 431, 364, 321, 245, 226, 139(100), 77.

3a,4,5,11-Tetrahydro-1,3a-di(4-chlorophenyl)-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′f). This compound was obtained as pale yellow crystals. IR(KBr)υ/cm^{-1}: 3061 (Ar-H), 1635, 1560 (C=N), 760 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.89–6.65 (m, 22H, Ar-H), 4.59–4.55 (dd, 1H, H_{5x}, J_{ax} = 4.8 Hz, J_{bx} = 12.4 Hz), 3.08–3.04 (dd, 1H, H_{4a}, J_{ax} = 4.8 Hz, J_{ab} = 14.0 Hz), 3.00–2.95 (dd, 1H, H_{4b}, J_{bx} = 12.4 Hz, J_{ab} = 14.0 Hz), 2.65 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 690(M^+), 581, 431, 398, 321, 260, 245, 139(100), 77.

3a,4,5,11-Tetrahydro-1-(4-methoxyphenyl)-3a-(4-chlorophenyl)-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′g). This compound was obtained as white crystals. IR(KBr)υ/cm^{-1}: 3061 (Ar-H), 1636, 1560 (C=N), 758 (C—S—C); ^{1}H NMR($CDCl_3$, 400

MHz) δ: 7.79–6.70 (m, 22H, Ar-H), 4.56–4.52 (dd, 1H, H_{5x}, J_{ax} = 5.2 Hz, J_{bx} = 12.8 Hz), 3.89(s, 3H, —OCH_3), 3.06–3.02 (dd, 1H, H_{4a}, J_{ax} = 5.2 Hz, J_{ab} = 14.0 Hz), 3.00–2.96 (dd, 1H, H_{4b}, J_{bx} = 12.8 Hz, J_{ab} = 14.0 Hz), 2.64 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 686(M^+), 577, 431, 394, 321, 256, 245, 139(100), 77.

3a,4,5,11-Tetrahydro-1-(4-nitrophenyl)-3a-(4-chlorophenyl)-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′h). This compound was obtained as yellow crystals. IR(KBr)υ/cm^{-1}: 3060 (Ar-H), 1635, 1558 (C=N), 759 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 8.45–6.68 (m, 22H, Ar-H), 4.68–4.65 (dd, 1H, H_{5x}, J_{ax} = 5.2 Hz, J_{bx} = 12.4 Hz), 3.26–3.22 (dd, 1H, H_{4a}, J_{ax} = 5.2 Hz, J_{ab} = 14.0 Hz), 3.16–3.11 (dd, 1H, H_{4b}, J_{bx} = 12.8 Hz, J_{ab} = 14.0 Hz), 2.67 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 701(M^+), 592, 431, 409, 321, 271, 245, 139(100), 77.

3a,4,5,11-Tetrahydro-1-phenyl-3a-(4-methoxyphenyl)-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′i). This compound was obtained as pale yellow crystals. IR(KBr)υ/cm^{-1}: 3063 (Ar-H), 1638, 1562 (C=N), 762 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.78–6.54 (m, 23H, Ar-H), 4.61–4.57 (dd, 1H, H_{5x}, J_{ax} = 4.8 Hz, J_{bx} = 12.8 Hz), 3.80 (s, 3H, —OCH_3), 3.13–3.09 (dd, 1H, H_{4a}, J_{ax} = 4.8 Hz, J_{ab} = 13.6 Hz), 3.01–2.96 (dd, 1H, H_{4b}, J_{bx} = 12.8 Hz, J_{ab} = 13.6 Hz), 2.64 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 652(M^+), 543, 427, 360, 317, 241, 226, 135(100), 77.

3a,4,5,11-Tetrahydro-1-(4-chlorophenyl)-3a-(4-methoxyphenyl)-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′j). This compound was obtained as white crystals. IR(KBr)υ/cm^{-1}: 3062 (Ar-H), 1635, 1561 (C=N), 761 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.71–6.53 (m, 22H, Ar-H), 4.63–4.59 (dd, 1H, H_{5x}, J_{ax} = 4.4 Hz, J_{bx} = 12.4 Hz), 3.79 (s, 3H, —OCH_3), 3.13–3.09 (dd, 1H, H_{4a}, J_{ax} = 4.4 Hz, J_{ab} = 13.6 Hz), 3.01–2.98 (dd, 1H, H_{4b}, J_{bx} = 12.4 Hz, J_{ab} = 13.6 Hz), 2.65 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 686(M^+), 577, 427, 394, 317, 260, 241, 135(100), 77.

3a,4,5,11-Tetrahydro-1,3a-di(4-methoxyphenyl)-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′k). This compound was obtained as white crystals. IR(KBr)υ/cm^{-1}: 3061 (Ar-H), 1635, 1562 (C=N), 760 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 7.81–6.63 (m, 22H, Ar-H), 4.61–4.57 (dd, 1H, H_{5x}, J_{ax} = 5.2 Hz, J_{bx} = 12.4 Hz), 3.81 (s, 3H, —OCH_3), 3.76 (s, 3H, —OCH_3), 3.15–3.11 (dd, 1H, H_{4a}, J_{ax} = 5.2 Hz, J_{ab} = 14.0 Hz), 3.05–3.01 (dd, 1H, H_{4b}, J_{bx} = 12.4 Hz, J_{ab} = 14.0 Hz), 2.64 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 682(M^+), 573, 427, 390, 317, 256, 241, 135(100), 77.

3a,4,5,11-Tetrahydro-1-(4-nitrophenyl)-3a-(4-methoxyphenyl)-5-(3-methyl-1-phenyl-5-phenylthio-1H-pyrazol-4-yl)-[1,2,4]oxadiazolo[5,4-d][1,5]benzothiazepine(4′l). This compound was obtained as yellow crystals. IR(KBr)υ/cm^{-1}: 3060 (Ar-H), 1636, 1562 (C=N), 761 (C—S—C); ^{1}H NMR($CDCl_3$, 400 MHz) δ: 8.21–6.56 (m, 22H, Ar-H), 4.64–4.60 (dd, 1H, H_{5x}, J_{ax} = 5.2 Hz, J_{bx} = 12.8 Hz), 3.79 (s, 3H, —OCH_3), 3.17–3.13 (dd, 1H, H_{4a}, J_{ax} = 5.2 Hz, J_{ab} = 13.6 Hz), 3.04–3.00 (dd, 1H, H_{4b}, J_{bx} = 12.8 Hz, J_{ab} = 13.6 Hz), 2.65 (s, 3H, —CH_3); MS(EI)*m*/*z*(%): 697(M^+), 588, 427, 405, 317, 271, 241, 135(100), 77.

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