Synthesis of New Hetero[1,2,4]thiadiazin-3-one S,S-Dioxides and Oxazolo[3,2-*b*]hetero[1,2,4]thiadiazine S,S-Dioxides as Potential Psychotropic Drugs

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Dedicated to Doctor Vicente Gómez Parra on the occasion of his 65th birthday

A series of 2-substituted 2*H*-thieno[3,4-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-dioxides (**2**), 2-substituted 2*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-dioxides (**3**), 2-substituted 4,6-dihydropyrazolo[4,3-*e*]-[1,2,4]thiadiazin-3(2*H*)-one 1,1-dioxides (**4**), 2-substituted 2,3-dihydrooxazolo[3,2-*b*]thieno[3,4-*e*]-[1,2,4]thiadiazine 5,5-dioxides, (**5**), 6-substituted 6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-dioxides (**6**) and 7-substituted 6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-dioxides (**7**) were synthesized as potential psychotropic agents.

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As part of an ongoing program on the synthesis and biological evaluation of novel heterocyclic sulfonamides with possible clinical utility, we have reported the synthesis of the hetero[1,2,4]thiadiazin-3-one S,S-dioxides **1** [2,3] (Figure 1). These compounds have partial structural analogy with the cardiovascular drugs diazoxide (3-methyl-4*H*-[1,2,4]benzothiadiazine 1,1-dioxide) [4,5] and chlorothiazide (6-chloro-7-sulfamoyl-4*H*-[1,2,4]benzothiadiazine 1,1-dioxide) [6,7]. They are also closely related to the non-nucleoside human immunodeficiency virus reverse transcriptase inhibitor NSC 287474 [8]. Several synthetic derivatives of the thiadiazines **1** prepared in our laboratory in the past have shown a wide range of important biological activities. In particular, some substituted thieno[3,4-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-dioxides (named by the acronym TTD), have demonstrated high activity as non-nucleoside reverse transcriptase inhibitors that inhibit human immunodeficiency virus type 1 replication [9-11] and were also found to be good antihypertensive agents in anaesthetized normotensive rats [12].

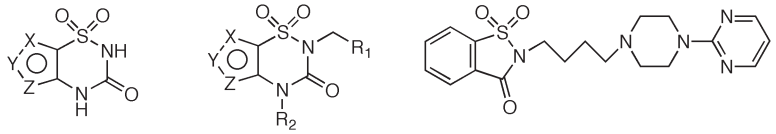


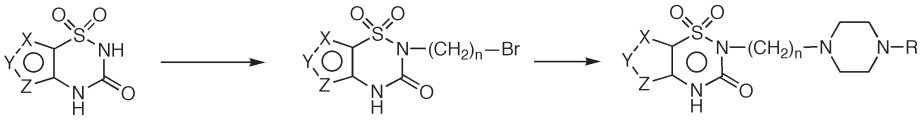
Figure 1

In this paper we describe the synthesis of a series of novel 2*H*-thieno[3,4-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-dioxides (**2**), 2*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-dioxides (**3**), and 4,6-dihydropyrazolo[4,3-*e*]-[1,2,4]thiadiazin-3(2*H*)-one 1,1-dioxides (**4**). These new compounds bear aryl- or heteroaryl-piperazinic substituents on the 2-N position of their structures. Such a substitution could confer them anxiolytic or antipsychotic activities comparable to those of the known drugs buspirone, trazodone, tiospirone and, especially, ipsapirone [13]. Two series of compounds were prepared. In the first one, the typical four-member polymethylenic chain of these drugs was included in the molecules. In the other one, the number of chain methylenic groups was reduced in order to decrease the affinity of these compounds for the dopaminergic receptors and obtain, therefore, a greater selectivity for the serotonergic ones [14,15].

In the paper we also describe the synthesis of a number of compounds which belong to the new 2,3-dihydrooxazolo[3,2-*b*]thieno[3,4-*e*][1,2,4]thiadiazine 5,5-dioxides (**5**) and 6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*]-[1,2,4]thiadiazine 9,9-dioxides(**6**-**7**) heterocyclic ring systems. Our initial rationale for their preparation was that the more rigid nature of these tricyclic derivatives might afford a better binding to the receptors so that they would show a higher pharmacological activity.

In general, the synthesis of the bicyclic compounds **2**-**4** was carried out by nucleophilic attack to the 2-(ω–bromoalkyl)thiadiazinones **11**-**13** by 1-heteroarylpiperazines (Scheme 1). Some of the thus formed compounds were isolated as their mono-hydrobromide salts from which the free bases could be obtained by treatment with 40% aqueous

Scheme 1



8-10 **11a-b** **2a-e**
12a-b **3a-j**
13a-b **4a-j**

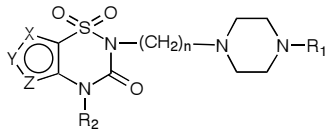
8, 11a X = CH, Y = S, Z = CH, n = 3
8, 11b, 2a-e X = CH, Y = S, Z = CH, n = 4
9, 12a, 3a-e X = CH, Y = CH, Z = S, n = 3
9, 12b, 3f-j X = CH, Y = CH, Z = S, n = 4
10, 13a, 4a-e X = N, Y = NCH_3, Z = CH, n = 3
10, 13b, 4f-j X = N, Y = NCH_3, Z = CH, n = 4

sodium hydroxide. The formation of compounds such as **2e** and **3j** was realized in the presence of potassium carbonate to neutralize the hydrogen bromide generated in the reaction. *o*-Chlorobenzene was initially used as the solvent in these reactions but, due to the poor solubility of the starting products, it was replaced by tetrahydrofuran. The 1-heteroarylpiperazines were chosen taking into account their easy commercial availability and their presence in other molecules with potent affinity for the 5-HT receptors [16,17]. Table 1 shows the bicyclic thiadiazines **2-4** prepared.

The easy alkylation of the thiadiazines **2-4** on the free NH of their 4-position allowed the synthesis of the corresponding 2,4-disubstituted compounds and provided a suitable way to gather a great number of these compounds

Table 1

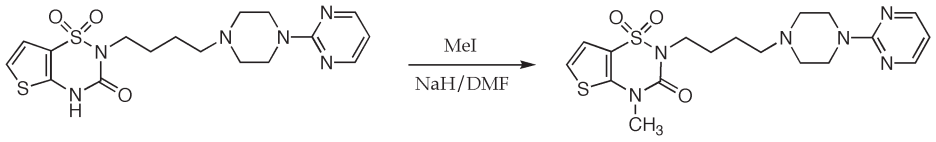
Compounds **2-4** Synthesized



Nº	X	Y	Z	R_1	R_2	n	Mp (°C)	Yield(%)
2a	CH	S	CH	Ph**	H	4	120-122[a]	72
2b	CH	S	CH	4-F-Ph**	H	4	136-138[b]	62
2c	CH	S	CH	2-MeO-Ph	H	4	97-99[a]	70
2d	CH	S	CH	2-Pyridyl	H	4	88-90[a]	80
2e	CH	S	CH	2-Pyrimidinyl**	H	4	132-134[a]	70
3a	CH	CH	S	Ph	H	3	146-148[c]	50*
3b	CH	CH	S	4-F-Ph	H	3	109-111[c]	56*
3c	CH	CH	S	2-MeO-Ph	H	3	124-126[c]	48*
3d	CH	CH	S	2-Pyridyl	H	3	131-133[c]	59*
3e	CH	CH	S	2-Pyrimidinyl	H	3	112-114[c]	91*
3f	CH	CH	S	Ph	H	4	126-128[b]	80
3g	CH	CH	S	4-F-Ph	H	4	133-135[b]	85
3h	CH	CH	S	2-MeO-Ph	H	4	119-120[a]	77
3i	CH	CH	S	2-Pyridyl	H	4	119-121[a]	81
3j	CH	CH	S	2-Pyrimidinyl	H	4	123-125[a]	68
3k	CH	CH	S	2-Pyrimidinyl	CH_3	4	143-145[a]	74
4a	N	NCH_3	CH	Ph	H	3	193-195[c]	49*
4b	N	NCH_3	CH	4-F-Ph	H	3	149-151[a]	76*
4c	N	NCH_3	CH	2-MeO-Ph	H	3	159-160[a]	88*
4d	N	NCH_3	CH	2-Pyridyl	H	3	147-149[a]	54*
4e	N	NCH_3	CH	2-Pyrimidinyl	H	3	154-156[c]	76*
4f	N	NCH_3	CH	Ph	H	4	182-184[a]	82
4g	N	NCH_3	CH	4-F-Ph	H	4	146-148[a]	65
4h	N	NCH_3	CH	2-MeO-Ph	H	4	123-125[a]	70
4i	N	NCH_3	CH	2-Pyridyl	H	4	164-166[a]	79
4j	N	NCH_3	CH	2-Pyrimidinyl	H	4	124-126[b]	63*

*Mono-hydrobromide salts. ** Compounds described in reference [12]. Recrystallization solvent: [a] ethanol; [b] methanol; [c] ethanol-water.

Scheme 2



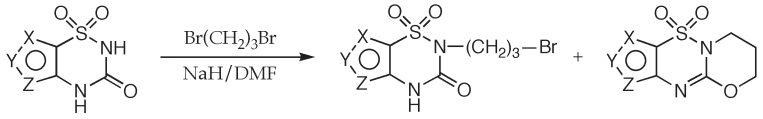
3j **3k**

for the study of their structure-activity relationships. For example, reaction of compound **3j** with methyl iodide and sodium hydride in *N*,*N*-dimethylformamide afforded the 4-methyl-2-[4-[1-[4-(2-pyrimidinyl)piperazinyl]]butyl]-2*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-dioxide (**3k**) in 74% yield (Scheme 2).

The intermediate 2-(ω-bromoalky)lhetero[1,2,4]thiadiazinones **11**-**13** were prepared according to a classical alkylation procedure, starting from the previously described parent compounds **8**-**10** [2] and using sodium hydride and 1,3-dibromopropane (or 1,4-dibromobutane) in the presence of *N*,*N*-dimethylformamide.

The reaction of compounds **8**-**10** with 1,3-dibromopropane afforded, in addition to the expected 2-(3-bromopropyl) derivatives **11a**-**13a**, other by-products (in the proportions of 11, 15 and 10%, respectively) (Scheme 3), to which the tricyclic structures **14**-**16** were assigned. Indeed, each of these side products shows scarce solubility in the common organic solvents, their melting points are above 200 °C and their microanalyses show an absence of halogen. On the other hand, the ^{1}H nmr spectra of the three products revealed the presence of a chain constituted by three methylene groups. It is worth mentioning that one of the triplets assigned to one of these groups shifted to low field (4.47, 4.50 and 4.45 ppm, respectively). This, and the presence in their ir spectra of a strong band at 1560-1600 cm^{-1}, typical of a C=N double bond, confirmed the tricyclic structure assigned to these products. They were surely formed by intramolecular ring closure of the bromopropyl derivatives **11a**-**13a** with a loss of hydrogen bromide.

Scheme 3



8-10 **11a-13a** **14-16**

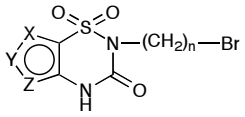
8, 11a, 14 X = CH, Y = S, Z = CH
9, 12a, 15 X = CH, Y = CH, Z = S
10, 13a, 16 X = N, Y = NCH$_3$, Z = CH

However, in the reaction of the heterothiadiazines **8**-**10** with 1,4-dibromobutane, the above side process was not observed giving the bromobutyl derivatives **11b**-**13b** as a sole product although in lower yields than those obtained for compounds **11a**-**13a** (Table 2).

With respect to the synthesis of the tricyclic compounds **5**, **6** and **7**, it was carried out following the method used for the preparation of their bicyclic congeners **2-4**. As described above, a direct condensation of the 2- and 6-(bromomethyl)oxazolo[3,2-*b*]hetero[1,2,4]thiadiazines S,S-dioxides **17b** and **18a-b** with two equivalents of 1-(2-pyridyl)piperazine or 1-(2-pyrimidinyl)piperazine in *N*,*N*-dimethylformamide led to the final compounds **5a-b**-**6a-d** in moderate to good yields (Scheme 4).

Table 2

Compounds **11-13** Synthesized

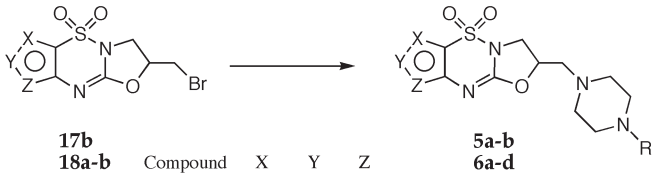


ir SO_2 (cm^{-1})

N°	X	Y	Z	n	sym	asym	Mp (°C)	Yield (%)
11a	CH	S	CH	3	1175	1330	136-138[a]	37
11b	CH	S	CH	4	1160	1340	111-113	34*
12a	CH	CH	S	3	1150	1320	152-154[b]	38
12b	CH	CH	S	4	1155	1320	122-124[b]	34
13a	N	NCH$_3$	CH	3	1160	1330	173-175[a]	23
13b	N	NCH$_3$	CH	4	1120	1320	112-114[b]	27

* **11b** was described in reference [12]; Recrystallization solvent: [a] ethanol; [b] ethanol-water

Scheme 4



17b
18a-b

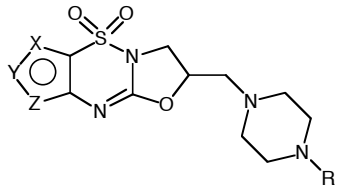
5a-b
6a-d

Compound	X	Y	Z
17b, 5a-b	CH	S	CBr
18a, 6a-b	N	NCH_3	CH
18b, 6c-d	N	NCH_3	CBr
19	CH	CH	S

Surprisingly, the reaction of the 2-(bromomethyl)oxazolo[3,2-*b*]thieno[2,3-*e*]thiadiazine **19** (X = CH, Y = CH, Z = S) (Scheme 4) with these amines under the same conditions did not afford the expected piperazinic derivatives but very complex mixtures from which no pure compound could be isolated. We thought that the lack of stability of compound **19** in the reaction medium could be responsible for its abnormal behavior in this process (Table 3).

Table 3

Compounds **5** and **6** Synthesized



Nº	X	Y	Z	R	Mp (°C)*	Yield (%)
5a	CH	S	CBr	2-Pyridyl	208-209[a]	45
5b	CH	S	CBr	2-Pyrimidinyl	199-201[a]	68
6a	N	NCH_3	CH	2-Pyridyl	176-178[b]	40
6b	N	NCH_3	CH	2-Pyrimidinyl	204-206[c]	59
6c	N	NCH_3	CBr	2-Pyridyl	211-213[d]	64
6d	N	NCH_3	CBr	2-Pyrimidinyl	198-200[c]	61

* Recrystallization solvent: [a] acetonitrile; [b] methanol-water; [c] methanol; [d] acetone.

Operating under similar conditions, the 7-(bromomethyl) derivative **20** reacted with 1-(2-pyrimidinyl)piperazine to give the 3-bromo-2-methyl-7-[1-[4-(2-pyrimidinyl)piperazinyl]]methyl-6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-dioxide (**7**) in 29% yield (Scheme 5).

As is known, serotonin receptor dysfunction has been implicated in a wide array of neuropsychiatric disorders including anxiety, depression and schizophrenia [18,19]. Since the compounds here described were designed as potential psychotropic agents, they were tested *in vitro* as new 5-HT1A and 5-HT2A receptor ligands. The pharmacological results of this study will be published elsewhere.

EXPERIMENTAL

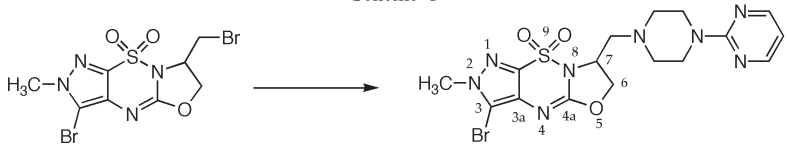
Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. Ir spectra were recorded using a Shimadzu IR-435 instrument. ^{1}H nmr spectra (300 or 400 MHz) and ^{13}C nmr spectra (75 or 100 MHz) were measured with Varian XL-300 or Varian Inova 400 spectrometers in the indicated solvent. Chemical shift values are expressed in δ units relative to tetramethylsilane (TMS) as an internal standard. The assignments were made by means of different standard homo- and heteronuclear correlation experiments, mainly NOE, HMQC and HMBC. Mass spectra were recorded on a Hewlett-Packard 5973 MSD instrument. Silica gel/tlc cards (Fluka, silica gel-precoated aluminium cards with fluorescent indicator 254 nm) were used for thin-layer chromatography (tlc), which were run with cyclohexane-ethyl acetate mixtures (2:1 and 1:1 v/v) as eluents. Medium-pressure chromatography was performed on columns packed with silica gel 60 with (230-400 mesh) purchased from E. Merck, Inc. Elemental analysis were performed on a Heraeus CHN-RAPID instrument. Analytical results were found to be within ± 0.4% of the theoretical values.

Synthesis of the 2-(ω-Bromoalkyl)thiadiazinones **11**-**13**.

General Method.

To a solution of thiadiazines **8-10** (1 equivalent) in dry *N*,*N*-dimethylformamide, under an inert atmosphere, was added slowly sodium hydride (60% dispersion in mineral oil, 1 equivalent) maintaining the temperature below 10°. After 15 min, the corresponding dibromoalkane (1 equivalent) was added and the reaction mixture was heated at 50-80° for the time indicated in each case. The solvent was evaporated to dryness and the crude solid was treated with water. The insoluble solid was collected by filtration, dried and recrystallized from the appropriate solvent to give compounds **14-16**. The filtrate was extracted with ethyl acetate. The organic layer was separated, washed with water, dried (magnesium sulfate) and evaporated *in vacuo*. The residue, containing the compounds **11-13**, was purified by silica gel flash chromatography using the appropriate solvent.

Scheme 5



20 **7**

2-(3-Bromopropyl)-2*H*-thieno[3,4-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**11a**) and 3,4-Dihydro-2*H*-[1,3]oxazino[3,2-*b*]-thieno[3,4-*e*][1,2,4]thiadiazine 6,6-Dioxide (**14**).

These compounds were synthesized by heating the thiadiazine **8** (1.0 g, 4.9 mmol), 60% sodium hydride (0.21 g, 5.2 mmol), 1,3-dibromopropane (0.5 ml, 4.9 mmol) and *N*,*N*-dimethylformamide (20 ml) at 50° for 48 hours. Treatment of the residue with water gave compound **14** (11%) as a white solid of mp >270° (d) (ethanol-*N*,*N*-dimethylformamide); ir (potassium bromide): C=N 1560, SO_2 1300, 1140 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.25 (m, 2H, CH_2), 3.91 (t, J = 6.2 Hz, 2H, CH_2N), 4.47 (t, J = 5.3 Hz, 2H, CH_2O), 7.47 (d, J = 3.2 Hz, 1H, thiophene) 8.41 (d, J = 3.2 Hz, 1H, thiophene); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.2 (3-C), 44.9 (4-C), 67.1 (2-C), 108.5 (9-C), 125.5 (7-C), 127.5 (6a-C), 136.4 (9a-C), 151.2 (10a-C).

Anal. Calcd. For $C_8H_8N_2O_3S_2$: C, 39.33; H, 3.30; N, 11.47; S, 26.25. Found: C, 39.21; H, 3.35; N, 11.41; S, 26.15.

The residue from the organic extracts was purified by silica gel flash chromatography using hexane/ethyl acetate 3:1 and 1:1 (v/v) as eluents. Compound **11a** was isolated as a white solid; ir (potassium bromide): NH 3180, C=O 1685 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.14 (m, 2H, CH_2), 3.53 (t, J = 6.4 Hz, 2H, CH_2Br), 3.85 (t, J = 7.0 Hz, 2H, CH_2N), 7.00 (d, J = 3,3 Hz, 1H, thiophene), 8.59 (d, J = 3,3 Hz, 1H, thiophene), 11.30 (broad s, 1H, NH, exchangeable with D_2O); ms: m/z 325.9 (M^++2), 323.9 (M^+), 245.1 (M^+-Br), 96.9 ($C_4H_3NS^+$).

Anal. Calcd. For $C_8H_9BrN_2O_3S_2$: C, 29.54; H, 2.79; N, 8.61. Found: C, 29.81; H, 2.83; N, 8.64.

2-(3-Bromopropyl)-2*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**12a**) and 7,8-Dihydro-6*H*-[1,3]oxazino[3,2-*b*]thieno[2,3-*e*][1,2,4]thiadiazine 4,4-Dioxide (**15**).

These compounds were synthesized by heating the thiadiazine **9** (1.0 g, 4.9 mmol), 60% sodium hydride (0.2 g, 5.0 mmol), 1,3-dibromopropane (0.5 ml, 4.9 mmol) and *N*,*N*-dimethylformamide (20 ml) at 60° for 41 hours. Treatment of the residue with water gave compound **15** (15%) as a greyish solid of mp >260° (d) (ethanol-*N*,*N*-dimethylformamide); ir (potassium bromide): C=N 1590, SO_2 1290, 1130 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.28 (m, 2H, CH_2), 3.94 (t, J = 6.1 Hz, 2H, CH_2N), 4.50 (t, J = 5.2 Hz, 2H, CH_2O), 7.32 (d, J = 5.7 Hz, 1H, thiophene) 7.47 (d, J = 5.7 Hz, 1H, thiophene); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 20.3 (7-C), 46.7 (6-C), 67.0 (8-C), 119.7 (3a-C), 120.5, 120.0 (2-C, 3-C), 145.6 (10a-C), 149.3 (9a-C).

Anal. Calcd. For $C_8H_8N_2O_3S_2$: C, 39.33; H, 3.30; N, 11.47; S, 26.25. Found: C, 39.28; H, 3.41; N, 11.44; S, 26.05.

The residue from the organic extracts was purified by silica gel flash chromatography using hexane/ethyl acetate 2:1 (v/v) as eluent. Compound **12a** was isolated as a white solid; ir (potassium bromide): NH 3200, C=O 1675 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.18 (m, 2H, CH_2), 3.55 (t, J = 6.5 Hz, 2H, CH_2), 3.86 (t, J = 7.1 Hz, 2H, CH_2), 7.26 (d, 2H, thiophene), 12.25 (broad s, 1H, NH, exchangeable with D_2O); ms: m/z 325.9 (M^++2), 323.9 (M^+), 245.1 (M^+-Br), 97.0 ($C_4H_3NS^+$).

Anal. Calcd. For $C_8H_9BrN_2O_3S_2$: C, 29.54; H, 2.79; N, 8.61. Found: C, 29.83; H, 2.77; N, 8.84.

2-(3-Bromopropyl)-6-methyl-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide (**13a**) and 2-Methyl-7,8-dihydro-6*H*-[1,3]oxazino[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 10,10-Dioxide (**16**).

These compounds were synthesized by heating the thiadiazine **10** (1.0 g, 4.9 mmol), 60% sodium hydride (0.2 g, 5.0 mmol), 1,3-dibromopropane (0.5 ml, 4.9 mmol) and *N*,*N*-dimethylformamide (30 ml) at 50° for 48 hours. Treatment of the residue with water gave compound **16** (10%) as a white solid of mp 244-246° (water); ir (potassium bromide): C=N 1600, SO_2 1300, 1155 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.22 (m, 2H, CH_2), 3.81 (t, J = 6.2 Hz, 2H, CH_2N), 3.98 (s, 3H, CH_3), 4.45 (t, J = 5.3 Hz, 2H, CH_2O), 8.09 (s, 1H, pyrazole); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 19.8 (7-C), 40.1 (CH_3), 44.8 (8-C), 67.0 (6-C), 118.9 (3-C), 125.0 (3a-C), 135.3 (10a-C), 148.9 (4a-C).

Anal. Calcd. For $C_8H_{10}N_4O_3S$: C, 39.66; H, 4.16; N, 23.13; S, 13.24. Found: C, 39.88; H, 3.91; N, 23.25; S, 13.55.

The residue from the organic extracts was purified by silica gel flash chromatography using chloroform/ethanol 50:1 and 30:1 (v/v) as eluents. Compound **13a** was isolated as a white solid; ir (potassium bromide): NH 3200, C=O 1680 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.15 (m, 2H, CH_2), 3.54 (t, J = 6.5 Hz, 2H, CH_2), 3.85 (t, J = 6.5 Hz, 2H, CH_2), 3.92 (s, 3H, CH_3), 7.72 (s, 1H, pyrazole), 11.02 (broad s, 1H, NH, exchangeable with D_2O); ms: m/z 324.0 (M^++2), 322.1 (M^+), 243.2 (M^+-Br), 42.4 ($C_3H_6^+$).

Anal. Calcd. For $C_8H_{11}BrN_4O_3S$: C, 29.73; H, 3.43; N, 17.33. S, 9.92. Found: C, 30.02; H, 3.64; N, 17.51, S, 10.15.

2-(4-Bromobutyl)-2*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**12b**).

This compound was synthesized by heating the thiadiazine **9** (1.73 g, 8.5 mmol), 60% sodium hydride (0.34 g, 8,5 mmol), 1,4-dibromobutane (1.0 ml, 8.5 mmol) and *N*,*N*-dimethylformamide (25 ml) at 75° for 70 hours. The residue from the organic extracts was purified by silica gel flash chromatography using hexane/ethyl acetate 1:1 (v/v) as eluent. Compound **12b** was isolated as a white solid; ir (potassium bromide): NH 3200, C=O 1675 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.85 (m, 4H, CH_2-CH_2), 3.60 (t, 2H, CH_2), 3.83 (t, 2H, CH_2), 7.30 (d, 2H, thiophene), 12.10 (s, 1H, NH, exchangeable with D_2O); ms: m/z 340.0 (M^++2), 338.0 (M^+), 259.1 (M^+-Br), 160.9 ($C_4H_3NO_2S_2^+$), 97.2 ($C_4H_3NS^+$).

Anal. Calcd. For $C_9H_{11}BrN_2O_3S_2$: C, 31.87; H, 3.27; N, 8.26. Br, 23.55. Found: C, 31.90; H, 3.45; N, 8.06, Br, 23.41.

2-(4-Bromobutyl)-6-methyl-4,6-dihydropyrazolo[4,3-*e*]-[1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide (**13b**).

This compound was synthesized by heating the thiadiazine **10** (1.72 g, 8.5 mmol), 60% sodium hydride (0.34 g, 8.5 mmol), 1,4-dibromobutane (1.0 ml, 8.5 mmol) and *N*,*N*-dimethylformamide (20 ml) at 80° for 142 hours. The residue from the organic extracts was purified by silica gel flash chromatography using ethyl acetate as eluent. Compound **12b** was isolated as a white solid; ir (potassium bromide): NH 3360, C=O 1700 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.80 (m, 4H, CH_2-CH_2), 3.54 (t, 2H, CH_2), 3.76 (t, 2H, CH_2), 3.95 (s, 3H, CH_3), 7.75 (s, 1H, pyrazole), 11.02 (s, 1H, NH, exchangeable with D_2O); ms: m/z 337.9 (M^++2), 336.0 (M^+), 257.0 (M^+-Br), 42.2 ($C_3H_6^+$).

Anal. Calcd. For $C_9H_{13}BrN_4O_3S$: C, 32.05; H, 3.88; N, 16.61. S, 9.51. Found: C, 31.97; H, 4.05; N, 16.56, S, 9.60.

Synthesis of Thiadiazines **2c-d, 3a-j and 4a-j**.

General Method.

To a solution of the bromoalkylthiadiazines **11**-**13** (1 equivalent) in dry tetrahydrofuran was added dropwise the aryl or

heteroarylpiperazine (1 equivalent). The reaction mixture was heated under reflux for the time indicated in each case. The tetrahydrofuran was evaporated *in vacuo* and the oily residue was treated with 40% NaOH and extracted with ethyl acetate. The organic layer was separated, washed with water and brine, dried (magnesium sulfate) and concentrated to dryness under reduced pressure. The residue was recrystallized or purified by silica gel flash chromatography using appropriate solvents.

2-[4-[1-[4-(2-Methoxyphenyl)piperazinyl]]butyl]-2*H*-thieno-[3,4-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**2c**).

This compound was prepared by refluxing the 2-(4-bromobutyl) thiadiazine **11b** and 1-(2-methoxyphenyl)piperazine for 3 hours. The white solid was purified by silica gel flash chromatography using hexane/ethyl acetate 1:1 (v/v) as eluent; ir (potassium bromide): NH 3375, C=O 1670, SO_2 1340, 1145 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.82 (m, 4H, $2CH_2$) 3.11 (m, 4H, CH_2N), 3.22-3.29 (m, 4H, CH_2N), 3.69 (t, 4H, CH_2N), 3.89 (s, 3H, CH_3), 6.87-7.02 (m, 4H, benzene), 8.79 (broad s, 1H, NH, exchangeable with D_2O), 8.87 (d, 2H, thiophene); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 24.7, 43.6, 47.8, 49.9 (CH_2), 55.3 (CH_3), 110.0 (5-C), 111.8 (3'-C), 118.3 (6'-C), 120.8 (4'-C), 122.9 (5'-C), 125.8 (7a-C), 131.7 (7-C), 134.0 (4a-C), 140.7 (1'-C), 152.0 (2'-C), 153.3 (3-C); ms: m/z 450.2 (M^+), 162.2 ($C_{10}H_{12}NO^+$), 70.1 ($C_4H_8N^+$).

Anal. Calcd. For $C_{20}H_{26}N_4O_4S_2$: C, 53.31; H, 5.82; N, 12.43; S, 14.23. Found: C, 53.19; H, 5.63; N, 12.48; S, 14.40.

2-[4-[1-[4-(2-Pyridyl)piperazinyl]]butyl]-2*H*-thieno[3,4-*e*][1,2,4]-thiadiazin-3(4*H*)-one 1,1-Dioxide (**2d**).

This compound was prepared by refluxing the 2-(4-bromobutyl) thiadiazine **11b** and 1-(2-pyridyl)piperazine for 7 hours. The white solid was purified by silica gel flash chromatography using hexane/ethyl acetate 2:1 and 1:1 (v/v) as eluents; ir (potassium bromide): NH 3370, C=O 1660, SO_2 1345, 1145 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.82 (m, 4H, $2CH_2$) 3.28 (m, 4H, CH_2N), 3.66 (m, 8H, CH_2N), 6.66 (d, J = 8.6 Hz, 1H, 3'-H pyridine), 6.67 (dd, J = 7.3 Hz, J = 4.9 Hz, 1H, 5'-H pyridine), 7.52 (ddd, J = 8.6 Hz, J = 7.3 Hz, J = 1.5 Hz, 1H, 4'-H pyridine), 7.87 (d, 2H, thiophene), 8.21 (dd, J = 4.9 Hz, J = 1.5 Hz, 1H, 6'-H pyridine), 8.79 (bs, 1H, NH, exchangeable with D_2O); ^{13}C nmr (deuteriochloroform): δ 25.1, 43.3, 44.7, 47.9 (CH_2), 107.1 (3'-C), 109.4 (5-C), 113.8 (5'-C), 126.1 (7a-C), 129.7 (7-C), 134.3 (4a-C), 137.7 (4'-C), 148.0 (6'-C), 154.0 (3-C), 158.9 (2'-C); ms: m/z 421.2 (M^+), 163.2 ($C_9H_{13}N_3^+$).

Anal. Calcd. For $C_{18}H_{23}N_5O_3S_2$: C, 51.28; H, 5.50; N, 16.61; S, 15.21. Found: C, 51.00; H, 5.38; N, 16.66; S, 15.46.

2-[3-[1-(4-Phenylpiperazinyl)]propyl]-2*H*-thieno[2,3-*e*][1,2,4]-thiadiazin-3(4*H*)-one 1,1-Dioxide Mono-hydrobromide (**3a**).

This compound was prepared by refluxing the 2-(3-bromopropyl) thiadiazine **12a** and 1-phenylpiperazine for 1 hour. It was isolated as the mono-hydrobromide salt. The white solid was purified by silica gel flash chromatography using hexane/ethyl acetate 2:1 (v/v) as eluent; ir (potassium bromide): NH 3320, C=O 1642, SO_2 1312, 1145 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.03 (m, 2H, CH_2) 3.27-3.44 (m, 8H, CH_2N), 3.69 (t, J = 5.1 Hz, 4H, CH_2N), 5.00 (bs, 1H, NH, exchangeable with D_2O), 6.77 (d, J = 5.9 Hz, 1H, thiophene), 6.87-7.00 (m, 4H, benzene), 7.25-7.33 (m, 2H, thiophene and benzene), 9.76 (s, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 30.2 (CH_2), 32.1, 41.3, 43.8, 49.1 (CH_2N), 115.1 (7a-C), 116.6 (2'-C), 116.9 (7-C), 120.6 (4'-C), 121.9 (6-C), 129.3 (3'-C), 147.2 (4a-C), 150.6 (1'-C), 152.5 (3-C); ms: m/z 406.1 (M^+-HBr), 175.1 ($C_{11}H_{15}N_2^+$), 119.9 ($C_8H_{10}N^+$).

Anal. Calcd. For $C_{18}H_{22}N_4O_3S_2$·HBr C, 44.35; H, 4.75; N, 11.49; S, 13.16. Found: C, 44.08; H, 5.00; N, 11.65; S, 12.98.

2-[3-[1-[4-(4-Fluorophenyl)piperazinyl]]propyl]-2*H*-thieno[2,3-*e*]-[1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide Mono-hydrobromide (**3b**).

This compound was prepared by refluxing the 2-(3-bromopropyl) thiadiazine **12a** and 1-(4-fluorophenyl)piperazine for 2 hours. It was isolated as the mono-hydrobromide salt. The white solid was purified by silica gel flash chromatography using chloroform/ethanol 50:1 (v/v) as eluent; ir (potassium bromide): NH 3340, 3270, C=O 1645, SO_2 1305, 1130 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.95-2.07 (m, 2H, CH_2) 3.04-3.46 (m, 8H, CH_2N), 3.69 (t, J = 4.9 Hz, 4H, CH_2N), 4.84 (q, 1H, NH, exchangeable with D_2O), 6.78-7.04 (m, 6H, benzene and thiophene), 9.77 (bs, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 30.1 (CH_2), 32.2, 41.2, 43.9, 50.3 (CH_2N), 115.2 (7a-C), 115.6, 116.0 (3'-C), 116.9 (7-C), 118.6, 118.7 (2'-C), 122.0 (6-C), 147.2 (4a-C), 147.3 (1'-C), 152.5 (3-C), 155.3, 160.1 (4'-C); ms: m/z 424.2 (M^+-HBr), 138.0 ($C_8H_9NF^+$), 96.9 ($C_4H_3NS^+$).

Anal. Calcd. For $C_{18}H_{21}FN_4O_3S_2$·HBr C, 42.77; H, 4.39; N, 11.09; S, 12.69. Found: C, 42.54; H, 4.38; N, 11.31; S, 12.54.

2-[3-[1-[4-(2-Methoxyphenyl)piperazinyl]]propyl]-2*H*-thieno-[2,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide Monohydrobromide (**3c**).

This compound was prepared by refluxing the 2-(3-bromopropyl)thiadiazine **12a** and 1-(2-methoxyphenyl)piperazine for 2 hours. It was isolated as the mono-hydrobromide salt. The white solid was purified by silica gel flash chromatography using hexane/ethyl acetate 2:1and 1,1 (v/v) as eluents; ir (potassium bromide): NH 3350, 3270, C=O 1645, SO_2 1312, 1130 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.04 (m, 2H, CH_2) 3.12-3.20 (m, 6H, CH_2N), 3.45 (t, J = 6.1 Hz, 2H, CH_2N), 3.72 (t, J = 4.7 Hz, 4H, CH_2N), 3.89 (s, 3H, CH_3), 4.86 (t, 1H, NH, exchangeable with D_2O), 6.77-7.08 (m, 6H, benzene and thiophene), 9.76 (bs, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 30.0 (CH_2), 32.2, 41.2, 44.2, 50.4 (CH_2N), 55.5 (CH_3), 111.5 (3'-C), 115.2, (7a-C), 116.8 (7-C), 118.5 (6'-C), 121.1 (4'-C), 122.0 (6-C), 123.7 (5'-C), 140.5 (1'-C), 147.3 (4a-C), 152.3, (2'-C) 152.7 (3-C); ms: m/z 518.2 (M^++2), 516.1 (M^+), 436.0 (M^+-HBr), 150.0 ($C_9H_{12}NO^+$), 96.9 ($C_4H_3NS^+$).

Anal. Calcd. For $C_{19}H_{24}N_4O_4S_2$·HBr C, 44.10; H, 4.87; N, 10.83; S, 12.39. Found: C, 43.89; H, 5.07; N, 11.05; S, 12.09.

2-[3-[1-[4-(2-Pyridyl)piperazinyl]]propyl]-2*H*-thieno[2,3-*e*][1,2,4]-thiadiazin-3(4*H*)-one 1,1-Dioxide Mono-hydrobromide (**3d**).

This compound was prepared by refluxing the 2-(3-bromopropyl) thiadiazine 1,1 dioxide (**12a**) and 1-(2-pyridyl)piperazine for 2 hours. It was isolated as the mono-hydrobromide salt. The white solid was purified by silica gel flash chromatography using hexane/ethyl acetate 2:1and 1,1 (v/v) as eluents; ir (potassium bromide): NH 3345, C=O 1665, SO_2 1295 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.03 (m, 2H, CH_2) 3.13 (q, J = 6.4 Hz, 2H, CH_2N), 3.44 (t, J = 6.2 Hz, CH_2N), 3.65 (s, 8H, CH_2N), 5.16 (bs, 1H, NH, exchangeable with D_2O), 6.61-6.74 (m, 2H, 3'-H and 5'-H), 6.77 (d, J = 5.9 Hz, 1H, thiophene), 6.98 (d, J = 5.9 Hz, 1H,

thiophene), 7.46-7.55 (dt, J = 7.2 Hz, J = 1.5 Hz, 1H, 4'-H pyridine), 8.18-8.21 (dd, J = 4.9 Hz, J = 1.5 Hz, 1H, 6'-H pyridine), 9.73 (bs, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 30.2 (CH_2), 32.1, 41.1, 43.3, 44.5 (CH_2N), 107.1 (3'-C), 113.9, (5'-C), 115.3 (7a-C), 116.8 (7-C), 122,0 (6-C), 137.7 (4'-C), 146.9 (4a-C), 147.9 (6'-C), 152.6, (3-C) 158.7 (2'-C); ms: m/z 489.0 (M^++2), 487.0 (M^+), 244.0 (M^+-$C_9H_{13}N_3$), 121.1 ($C_7H_9N_2^+$), 97.0 ($C_4H_3NS^+$).

Anal. Calcd. For $C_{17}H_{21}N_5O_3S_2$·HBr C, 41.80; H, 4.54; N, 14.34; S, 13.13. Found: C, 42.02; H, 4.81; N, 14.60; S, 12.98.

2-[3-[1-[4-(2-Pyrimidinyl)piperazinyl]]propyl]-2*H*-thieno[2,3-*e*]-[1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide Mono-hydrobromide (**3e**).

This compound was prepared by refluxing 2-(3-bromoproyl) thiadiazine **12a** and 4-(2-pyrimidinyl)piperazine for 2 hours. It was isolated as the mono-hydrobromide salt. The white solid was purified by silica gel flash chromatography using chloroform/ethanol 9:1 (v/v) as eluent; ir (potassium bromide): NH 3360, C=O 1665, SO_2 1315 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.03 (m, 2H, CH_2) 3.14 (q, J = 6.5 Hz, 2H, CH_2N), 3.44 (t, J = 6.2 Hz, CH_2N), 3.62 (t, J = 5.2 Hz, 4H, CH_2N), 3.92 (t, J = 5.2 Hz, 4H, CH_2N), 5.08 (t, 1H, NH, exchangeable with D_2O), 6.55 (t, J = 4.8 Hz, 2H, 5'-H pyrimidine), 6.78 (d, J = 5.9 Hz, 1H, thiophene), 6.99 (d, J = 5.9 Hz, 1H, thiophene), 8.33 (d, J = 4.8 Hz, 2H, 4'-H and 6'-H pyrimidine), 9.74 (bs, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 30.1 (CH_2), 32.1, 41.1, 43.1, 43.5 (CH_2N), 110.6 (5'-C), 115.3 (7a-C), 116.9 (7-C), 122,0 (6-C), 147.0 (4a-C), 152.7, (3-C) 157.8 (4'-C and 6'-C) 161.3 (2'-C); ms: m/z 490.0 (M^++2), 488.0 (M^+), 224.0 (M^+-SO_2), 122.2 ($C_6H_8N_3^+$), 97.0 ($C_4H_3NS^+$).

Anal. Calcd. For $C_{16}H_{20}N_6O_3S_2$·HBr C, 39.26; H, 4.33; N, 17.17; S, 13.10. Found: C, 39.56; H, 4.44; N, 17.10; S, 13.40.

2-[4-[1-(4-Phenylpiperazinyl)]butyl]-2*H*-thieno[2,3-*e*]-[1,2,4]thiadiazin-3(4*H*)-one 1,1-dioxide (**3f**).

This compound was prepared by refluxing the 2-(4-bromobutyl) thiadiazine **12b** and 1-phenylpiperazine for 3 hours. The white solid was recrystallized from methanol; ir (potassium bromide): NH 3320, C=O 1665, SO_2 1305, 1130 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.70 (m, 4H, $2CH_2$) 3.13-3.25 (m, 8H, CH_2N), 3.55 (m, 4H, CH_2N), 6.80 (t, J = 7.7 Hz, 1H, benzene), 6.96 (d, J = 8.6 Hz, 2H, benzene), 7.06 (d, 2H, thiophene), 7.23 (t, J = 7.7 Hz, 2H, benzene), 9.55 (bs, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 24.7 (CH_2-CH_2), 47.7, 47.6, 49.1 (CH_2N), 113.4 (7a-C), 115.7 (2'-C), 117.0 (7-C), 119.2 (4'-C), 122.3 (6-C), 128.9 (3'-C), 146.4 (4a-C), 150.5 (1'-C), 152.1 (3-C); ms: m/z 420.1 (M^+), 258.0 (M^+-$C_{10}H_{14}N_2$), 189.0 (M^+-$C_{14}H_{21}N_3$), 119.9 ($C_8H_{10}N^+$).

Anal. Calcd. For $C_{19}H_{24}N_4O_3S_2$ C, 54.26; H, 5.75; N, 13.32; S, 15.25. Found: C, 54.49; H, 5.93; N, 13.14; S, 14.99.

2-[4-[1-[4-(4-Fluorophenyl)piperazinyl]]butyl]-2*H*-thieno[2,3-e]-[1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**3g**).

This compound was prepared by refluxing the 2-(4-bromobutyl) thiadiazine **12b** and 1-(4-fluorophenyl)piperazine for 7 hours. The white solid was recrystallized from methanol; ir (potassium bromide): NH 3300, C=O 1662, SO_2 1300, 1120 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): 1.71 (m, 4H, $2CH_2$) 3.14-3.21 (m, 8H, CH_2N), 3.56 (m, 4H, CH_2N), 6.94-7.11 (m, 6H, benzene and thiophene), 9.65 (s, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 24.8 (CH_2-CH_2), 43.3, 47.8, 48.7 (CH_2N), 113.3 (7a-C), 115.2, 115.6 (3'-C), 117.1 (7-C), 117.6, 117.8 (2'-C), 122.1 (6-C), 146.5 (4a-C), 147.5 (1'-C), 152.1 (3-C), 153.9, 158.7 (4'-C); ms: m/z 438.0 (M^+), 259.1 (M^+-$C_{10}H_{12}FN_2$) 258.1 (M^+-$C_{10}H_{13}FN_2$), 180.1 ($C_{10}H_{13}FN_2^+$), 138.0 ($C_8H_9FN^+$).

Anal. Calcd. For $C_{19}H_{23}FN_4O_3S_2$ C, 52.04; H, 5.29; N, 12.78; S, 14.62. Found: C, 52.30; H, 5.09; N, 12.69; S, 14.90.

2-[4-[1-[4-(2-Methoxyphenyl)piperazinyl]]butyl]-2*H*-thieno-[2,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**3h**).

This compound was prepared by refluxing the 2-(4-bromobutyl) thiadiazine **12b** and 1-(2-methoxyphenyl)piperazine for 7 hours. The white solid was recrystallized from ethanol; ir (potassium bromide): NH 3350, C=O 1667, SO_2 1315, 1135 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.80 (m, 4H, $2CH_2$) 3.09 (t, J = 4.9 Hz, 4H, CH_2N), 3.24 (t, J = 6.6 Hz, 4H, CH_2N), 3.69 (t, J = 4.9 Hz, 4H, CH_2N), 3.87 (s, 3H, CH_3), 6.74-7.01 (m, 6H, benzene and thiophene), 9.83 (bs, 1H, NH, exchangeable with D_2O); ^{13}C nmr (deuteriochloroform): δ 25.2 (CH_2-CH_2), 44.1, 47.8, 50.3 (CH_2N), 55.4 (CH_3), 111.3 (6'-C), 113.5 (7a-C), 116.3 (7-C), 118.4 (3'-C), 121.0 (4'-C), 122.2 (6-C), 123.6 (5'-C), 140.4 (1'-C), 147.1 (4a-C), 152.1 (2'-C), 152.6, (3-C); ms: m/z 450.2 (M^+), 219.3 ($C_{13}H_{19}N_2O^+$), 192.1 ($C_{11}H_{16}N_2O^+$), 162.1 ($C_{10}H_{12}NO^+$), 150.0 ($C_9H_{12}NO^+$), 70.0 ($C_4H_8N^+$).

Anal. Calcd. For $C_{20}H_{26}N_4O_4S_2$ C, 53.31; H, 5.82; N, 12.43; S, 14.23. Found: C, 52.60; H, 6.01; N, 12.21; S, 13.98.

2-[4-[1-[4-(2-Pyridyl)piperazinyl]]butyl]-2*H*-thieno[2,3-*e*]-[1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**3i**).

This compound was prepared by refluxing the 2-(4-bromobutyl) thiadiazine **12b** and 1-(2-pyridyl)piperazine for 4 hours. The white solid was purified by silica gel flash chromatography using hexane/ethyl acetate 2:1 and 1:1 (v/v) as eluents; ir (potassium bromide): NH 3330, C=O 1660, SO_2 1317, 1135 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.83 (m, 4H, $2CH_2$) 3.26 (m, 4H, CH_2N), 3.67 (s, 8H, CH_2N), 6.65 (d, J = 8.7 Hz, 1H, 3'-H, pyridine), 6.68 (dd, J = 4.9 Hz, J = 7.1 Hz, 1H, 5'-H, pyridine), 6.77 (d, J = 5.9 Hz, 1H, thiophene), 6.99 (d, J = 5.9 Hz, 1H, thiophene), 7.52 (ddd, J = 8.7 Hz, J = 7.1 Hz, J = 1.9 Hz, 1H, 4'-H, pyridine), 8.20 (ddd, J = 4.9 Hz, J = 1.9 Hz, J = 0.7 Hz, 1H, 6'-H, pyridine), 9.85 (bs, 1H, NH, exchangeable with D_2O); ^{13}C nmr (deuteriochloroform): δ 25.3 (CH_2-CH_2), 43.3, 44.7, 47.9 (CH_2N), 107.2 (3'-C), 113.7 (5'-C), 113.9 (7a-C), 116.4 (7-C), 122.2 (6-C), 137.8 (4'-C), 147.0 (4a-C), 147.8 (6'-C), 152.7 (3-C), 158.7, (2'-C); ms: m/z 421.3 (M^+), 258.1 ($C_9H_{10}N_2O_3S_2^+$), 163.3 ($C_9H_{13}N_3^+$), 121.1 ($C_7H_9N_2^+$), 106.9 ($C_6H_7N_2^+$), 70.0 ($C_4H_8N^+$).

Anal. Calcd. For $C_{18}H_{23}N_5O_3S_2$ C, 51.28; H, 5.50; N, 16.61; S, 15.21. Found: C, 50.99; H, 5.35; N, 16.41; S, 15.02.

2-[4-[1-[4-(2-Pyrimidinyl)piperazinyl]]butyl]-2*H*-thieno[2,3-*e*]-[1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**3j**).

This compound was prepared by refluxing the 2-(4-bromobutyl)thiadiazine **12b** and 4-(2-pyrimidinyl)piperazine for 7 hours. The white solid was purified by silica gel flash chromatography using hexane/ethyl acetate 1:1 (v/v) as eluent; ir (potassium bromide): NH 3300, C=O 1660, SO_2 1310, 1122 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.71 (m, 4H, $2CH_2$) 3.15 (m, 4H, CH_2N), 3.53 (m, 4H, CH_2N), 3.84 (m, 4H, CH_2N), 6.67 (t, J = 4.7 Hz, 1H, 5'-H, pyrimidine), 7.06 (d, 2H, thiophene), 8.39 (d,

J = 4.7 Hz, 2H, 4'-H and 6'-H pyrimidine), 9.61 (s, 1H, NH, exchangeable with D_2O); ^{13}C nmr (deuteriochloroform): δ 24.7 (CH_2-CH_2), 42.6, 42.8, 47.7 (CH_2N), 110.5 (5'-C), 113.4 (7a-C), 117.0 (7-C), 122.3 (6-C), 146.4 (4a-C), 152.2 (3-C), 157.9 (4'-C and 6'-C), 160.9, (2'-C); ms: m/z 422.1 (M^+), 70.1 ($C_4H_8N^+$).

Anal. Calcd. For $C_{17}H_{22}N_6O_3S_2$ C, 48.34; H, 5.21; N, 19.90. Found: C, 48.15; H, 4.98; N, 20.21.

6-Methyl-2-[3-[1-(4-phenylpiperazinyl)]propyl]-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide Monohydrobromide (**4a**).

This compound was prepared from the 2-(3-bromopropyl)thiadiazine **13a** and 1-phenylpiperazine maintaining the reaction at room temperature for 24 hours. It was isolated as the monohydrobromide salt. The white solid was purified by silica gel flash chromatography using dichloromethane/ethanol 40:1 (v/v) as eluent; ir (potassium bromide): NH 3430, C=O 1677, SO_2 1320, 1145 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.00-2.14 (m, 2H, CH_2) 3.15-3.28 (m, 6H, CH_2N), 3.47 (t, J = 6.3 Hz, 2H, CH_2N), 3.64 (t, J = 5.2 Hz, 4H, $2CH_2N$), 3.92 (s, 3H, CH_3), 5.13 (bs, 1H, NH, exchangeable with D_2O), 6.87-6.95 (m, 3H, benzene), 7.25-7.29 (m, 2H, benzene), 7.99 (bs, 1H, NH, exchangeable with D_2O), 8.05 (s, 1H, pyrazole); ^{13}C nmr (deuteriochloroform): δ 30.2 (CH_2), 40.2 (CH_3), 32.3, 41.4, 43.8 49,1 (CH_2N), 116.5 (2'-C), 120.4 (4'-C), 122.0 (5-C), 123.9 (4a-C), 129.2 (3'-C), 135.2 (7a-C), 150.7 (1'-C), 153.5 (3-C); ms: m/z 486.0 (M^++2), 484.0 (M^+), 404.0 (M^+-HBr), 119.8 ($C_8H_{10}N^+$), 42.1 ($C_3H_6^+$).

Anal. Calcd. For $C_{18}H_{24}N_6O_3S$·HBr C, 44.53; H, 5.19; N, 17.31; S, 6.61. Found: C, 44.34; H, 4.98; N, 17.10; S, 6.50.

2-[3-[1-[4-(4-Fluorophenyl)piperazinyl]]propyl]-6-methyl-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide Mono-hydrobromide (**4b**).

This compound was prepared from the 2-(3-bromopropyl)thiadiazine **13a** and 1-(4-fluorophenyl)piperazine maintaining the reaction at room temperature for 24 hours. It was isolated as the mono-hydrobromide salt. The white solid was purified by silica gel flash chromatography using dichloromethane/ethanol 100:1 (v/v) as eluent; ir (potassium bromide): NH 3430, 3300 C=O 1663, SO_2 1320, 1150 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.94-2.14 (m, 2H, CH_2) 3.08-3.40 (m, 8H, CH_2N), 3.60 (m, 4H, CH_2N), 3.89 (s, 3H, CH_3), 5.23 (t, 1H, NH, exchangeable with D_2O), 6.82-7.00 (m, 4H, benzene), 7.96 (bs, 1H, NH, exchangeable with D_2O), 8.02 (s, 1H, pyrazole); ^{13}C nmr (deuteriochloroform): δ 30.2 (CH_2), 40.2 (CH_3), 32.3, 41.7, 43.8 50.2 (CH_2N), 115.5 115.9 (3'-C), 118.4, 118.6 (2'-C), 122.0 (5-C), 123.9 (4a-C), 129.2 (3'-C), 135.2 (7a-C), 147.4, 147.5 (1'-C), 153.5 (3-C) 155.2, 159.9 (4'-C); ms: m/z 504.3 (M^++2), 138.1 ($C_8H_9FN^+$), 42.2 ($C_3H_6^+$).

Anal. Calcd. For $C_{18}H_{23}FN_6O_3S$·HBr C, 42.94; H, 4.81; N, 16.70; S, 6.37. Found: C, 43.10; H, 4.90; N, 16.50; S, 6.25.

6-Methyl-2-[3-[1-[4-(2-methoxyphenyl)piperazinyl]]propyl]-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide Mono-hydrobromide (**4c**).

This compound was prepared from the 2-(3-bromopropylthiadiazine **13a** and 1-(2-methoxyphenyl)piperazine maintaining the reaction at room temperature for 24 hours. It was isolated as the mono-hydrobromide salt. The white solid was purified by silica gel flash chromatography using dichloromethane/ethanol 50:1 (v/v) as eluent; ir (potassium bromide): NH 3425, 3290 C=O 1660, SO_2 1325, 1150 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.05 (m, 2H, CH_2) 3.09 (t, J = 6.3 Hz, 4H, CH_2N), 3.14-3.25 (m, 2H, CH_2N), 3.46 (t, J = 6.3 Hz, CH_2CN), 3.65 (t, J = 5.0 Hz, CH_2CN), 3.88 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 5.35 (bs, 1H, NH, exchangeable with D_2O), 6.87-7.08 (m, 4H, benzene), 7.99 (bs, 1H, NH, exchangeable with D_2O), 8.07 (s, 1H, pyrazole); ^{13}C nmr (deuteriochloroform): δ 30.2 (CH_2), 40.1 (CH_3), 32.3, 41.7, 44.1 50.3 (CH_2N), 55.4 (CH_3), 111.2 (6'-C), 118.3 (3'-C), 121.0 (4'-C), 122.0 (5-C), 123.5 (5'-C), 123.9 (4a-C), 135.2 (7a-C), 140.5 (1'-C), 152.1 (2'-C) 153.6 (3-C); ms: m/z 516.3 (M^++2), 514.3 (M^+), 434.21(M^+-HBr), 150 ($C_9H_{12}NO^+$), 42.2 ($C_3H_6^+$).

Anal. Calcd. For $C_{19}H_{26}N_6O_4S$·HBr C, 44.27; H, 5.81; N, 16.31; S, 6.22. Found: C, 44.00; H, 5.61; N, 16.06; S, 6.09.

6-Methyl-2-[3-[1-[4-(2-pyridyl)piperazinyl]]propyl]-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide Mono-hydrobromide (**4d**).

This compound was prepared from the 2-(3-bromopropyl) thiadiazine **13a** and 1-(2-pyridyl)piperazine maintaining the reaction at room temperature for 24 hours. It was isolated as the mono-hydrobromide salt. The white solid was purified by silica gel flash chromatography using dichloromethane/ethanol 40:1 (v/v) as eluent; ir (potassium bromide): NH 3475, 3290 C=O 1677, SO_2 1315, 1145 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.99 (m, 2H, CH_2) 3.10-3.20 (m, 2H, CH_2N), 3.39 (t, J = 6.3 Hz, 2H, CH_2N), 3.54 (s, 8H, CH_2CN), 3.85 (s, 3H, CH_3), 5.48-5.51 (bs, 1H, NH, exchangeable with D_2O), 6.54-6.62 (m, 2H, 5'-H and 3'-H pyridine), 7.39-7.47 (dt, J = 7.1 Hz, J = 2.0 Hz, 1H, 4'-H pyridine), 7.90 (bs, 1H, NH, exchangeable with D_2O), 7.98 (s, 1H, pyrazole), 7.99-8.14 (ddd, J = 4.9 Hz, J = 2.0 Hz, J = 0.9 Hz, 1H, 6'-H pyridine),; ^{13}C nmr (deuteriochloroform): δ 30.2 (CH_2), 40.1 (CH_3), 32.3, 41.4, 43.3 44.6 (CH_2N), 107.1 (3'-C), 113.8 (5'-C), 122.1 (5-C), 123.7 (4a-C), 135.4 (7a-C), 137.7 (4'-C), 147.9 (6'-C), 153.6 (3-C) 158.8 (2'-C); ms: m/z 485.1 (M^+-1), 121.1 ($C_7H_9N_2^+$), 42.2 ($C_3H_6^+$).

Anal. Calcd. For $C_{17}H_{23}N_7O_3S$·HBr C, 41.97; H, 4.97; N, 20.16; S, 6.59. Found: C, 42.10; H, 5.01; N, 19.98; S, 6.45.

6-Methyl-2-[3-[1-[4-(2-pyrimidinyl)piperazinyl]]propyl]-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide Mono-hydrobromide (**4e**).

This compound was prepared from 2-(3-bromopropyl)thiadiazine **13a** and 1-(2-pyrimidinyl)piperazine maintaining the reaction at room temperature for 24 hours. It was isolated as the mono-hydrobromide salt. The white solid was purified by silica gel flash chromatography using dichloromethane/ethanol 40:1 (v/v) as eluent; ir (potassium bromide): NH 3420, 3270 C=O 1670, SO_2 1317, 1150 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.04 (m, 2H, CH_2) 3.23 (q, J = 6.3 Hz, 2H, CH_2N), 3.48 (t, J = 6.3 Hz, 2H, CH_2N), 3.58 (m, 4H, CH_2CN), 3.88 (m, 4H, CH_2CN), 3.99 (s, 3H, CH_3), 5.26 (t, 1H, NH, exchangeable with D_2O), 6.55 (t, J = 4.8 Hz, 1H, 5'-H pyrimidine), 7.98 (bs, 1H, NH, exchangeable with D_2O), 8.06 (s, 1H, pyrazole), 8.33 (d, J = 4.8 Hz, 2H, 4'-H and 6'-H pyrimidine); ^{13}C nmr (deuteriochloroform): δ 30.1 (CH_2), 40.1 (CH_3), 32.3, 41.5, 43.2 43.5 (CH_2N), 110.5 (5'-C), 122.1 (5-C), 123.6 (4a-C), 135.5 (7a-C), 153.7 (3-C), 157.8 (4'-C and 6'-C), 161.5 (2'-C); ms: m/z 488.0 (M^++2), 486.0 (M^+), 406.1 (M^+-HBr), 122.1 ($C_6H_8N_3^+$), 42.2 ($C_3H_6^+$).

Anal. Calcd. For $C_{16}H_{22}N_8O_3S$·HBr C, 39.43; H, 4.75; N, 22.99; S, 6.58. Found: C, 39.40; H, 4.69; N, 22.70; S, 6.37.

6-Methyl-2-[4-[1-(4-phenylpiperazinyl)]butyl]-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide (**4f**).

This compound was prepared by refluxing the 2-(4-bromobutyl)thiadiazine **13b** and 1-phenylpiperazine for 5 hours. The white solid was recrystallized from ethanol; ir (potassium bromide): NH 3400, C=O 1675, SO_2 1325, cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.70 (m, 4H, $2CH_2$) 3.12-3.25 (m, 6H, CH_2N), 3.50 (t, J = 5.0 Hz, 4H, CH_2N), 3.89 (s, 3H, CH_3), 6.79 (dd, J = 7.2 Hz, J = 1.0 Hz, 1H, benzene), 6.91-6.95 (dd, J = 8.7 Hz, J = 1.0 Hz, 2H, benzene), 7.17 (dd, J = 8.7 Hz, J = 7.2 Hz, 2H, benzene), 7.95 (s, 1H, NH, exchangeable with D_2O), 8.07 (s, 1H, pyrazole); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 24.8 (CH_2), 40.7 (CH_3), 43.3 48.0 (CH_2N), 115.7 (2'-C), 119.2 (4'-C), 123.0 (5-C), 123.4 (4a-C), 128.9 (3'-C), 134.2 (7a-C), 150.7 (1'-C), 153.3 (3-C); ms: m/z 418.1 (M^+), 257.0 (M^+-$C_{10}H_{13}N_2$), 237.9 ($C_8H_5N_4O_3S^+$).

Anal. Calcd. For $C_{19}H_{26}N_6O_3S$ C, 54.52; H, 6.26; N, 20.08; S, 7.66. Found: C, 54.41; H, 6.40; N, 19.89; S, 7.50.

2-[4-[1-[4-(4-Fluorophenyl)piperazinyl]]butyl]-6-methyl-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide (**4g**).

This compound was prepared by refluxing the 2-(4-bromobutyl)thiadiazine **13b** and 1-(4-fluorophenyl)piperazine for 3 hours. The white solid was purified by silica gel flash chromatography using dichloromethane/ethanol 50:1 (v/v) as eluent; ir (potassium bromide): NH 3400, C=O 1674, SO_2 1330, cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.81-1.85 (m, 4H, $2CH_2$) 3.14 (t, J = 5.0 Hz, 4H, CH_2N), 3.37-3.41 (m, 4H, CH_2N), 3.63 (t, J = 5.0 Hz, 4H, CH_2N), 3.92 (s, 3H, CH_3), 6.87-7.02 (m, 4H, benzene), 8.05 (s, 1H, pyrazole); 8.13 (bs, 1H, NH, exchangeable with D_2O); ^{13}C nmr (deuteriochloroform): δ 25.4 ($2CH_2$), 40.2 (CH_3), 43.9 48.3, 50.2 (CH_2N), 115.5, 115.9 (3'-C), 118.4, 118.6 (2'-C), 121.5 (5-C), 124.6 (4a-C), 134.1 (7a-C), 147.5 (1'-C), 153.6 (3-C), 155.2, 160.0 (4'-C); ms: m/z 436.1 (M^+), 257.1 (M^+-$C_{10}H_{12}FN_2$), 138.2 ($C_8H_9FN^+$), 70.0 ($C_3H_6N_2^+$).

Anal. Calcd. For $C_{19}H_{25}FN_6O_3S$ C, 52.28; H, 5.77; N, 19.25; S, 7.35. Found: C, 52.01; H, 5.90; N, 19.32; S, 7.41.

6-Methyl-2-[4-[1-[4-(2-methoxyphenyl)piperazinyl]]butyl]-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide (**4h**).

This compound was prepared by refluxing the 2-(4-bromobutyl) thiadiazine **13b** and 1-(2-methoxyphenyl)piperazine for 6 hours. The white solid was purified by silica gel flash chromatography using dichloromethane/ethanol 50:1 (v/v) as eluent; ir (potassium bromide): NH 3400, C=O 1665, SO_2 1340, 1145, cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.82 (m, 4H, $2CH_2$) 3.09 (t, J = 5.0 Hz, 4H, CH_2N), 3.36-3.41 (m, 4H, CH_2N), 3.58 (t, J = 5.0 Hz, 4H, CH_2N), 3.89 (s, 3H, CH_3), 6.88-6.94 (m, 3H, benzene), 7.02 (m, 1H, benzene), 8.07 (s, 1H, pyrazole); 8.13 (bs, 1H, NH, exchangeable with D_2O); ^{13}C nmr (deuteriochloroform): δ 25.3 ($2CH_2$), 40.1 (CH_3), 44.1 48.2, 50.3 (CH_2N), 55.4 (CH_3), 111.2 (6'-C), 118.3, (3'-C), 121.0 (4'-C), 121.5 (5-C), 123,5 (5'-C), 124.8 (4a-C), 133.9 (7a-C), 140.6 (1'-C), 152.2 (2'-C), 153.7 (3-C); ms: m/z 448.0 (M^+), 162.0 ($C_{11}H_6NO^+$), 134.1 ($C_9H_{12}NO^+$), 70.0 ($C_4H_8N^+$).

Anal. Calcd. For $C_{20}H_{28}N_6O_4S$ C, 53.55; H, 6.29; N, 18.74; S, 7.15. Found: C, 53.27; H, 6.21; N, 18.60; S, 6.98.

6-Methyl-2-[4-[1-[4-(2-pyridyl)piperazinyl]]butyl]-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide (**4i**).

This compound was prepared by refluxing the 2-(4-bromobutyl) thiadiazine **13b** and 1-(2-pyridyl)piperazine for 8 hours. The white solid was recrystallized from ethanol; ir (potassium bromide): NH 3400, C=O 1670, SO_2 1330, cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.69 (m, 4H, $2CH_2$) 3.22 (m, 4H, CH_2N), 3.46-3.56 (m, 8H, CH_2N), 3.89 (s, 3H, CH_3), 6.65 (dd, J = 7.0 Hz, J = 4.9 Hz, 1H, 5'-H pyridine), 6.83 (d, J = 8.8 Hz, 1H, 3'-H pyridine), 7.54 (ddd, J = 8.8 Hz, J = 7.0 Hz, J = 1.9 Hz, 1H, 4'-H pyridine), 8.01 (s, 1H, pyrazole), 8.06-8.13 (dd, J = 1.9 Hz, 1H, 6'-H pyridine), 8.13 (s, 1H, NH, exchangeable with D_2O); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 24.7 ($2CH_2$), 39.7 (CH_3), 42.9 44.0, 47.9 (CH_2N), 107.1 (3'-C), 113.2, (5'-C), 122.9 (5-C), 123,4 (4a-C), 134.2 (7a-C), 137.5 (4'-C), 147.5 (6'-C), 153.3 (3-C), 158.6 (2'-C); ms: m/z 420.5 (M^++1), 419.2 (M^+), 257.1 (M^+-$C_9H_{12}N_3$).

Anal. Calcd. For $C_{18}H_{25}N_7O_3S$ C, 51.53; H, 6.01; N, 23.37; S, 7.64. Found: C, 51.56; H, 6.30; N, 23.30; S, 7.38.

6-Methyl-2-[4-[1-[4-(2-pyrimidinyl)piperazinyl]]butyl]-4,6-dihydropyrazolo[4,3-*e*][1,2,4]thiadiazin-3(2*H*)-one 1,1-Dioxide Mono-hydrobromide (**4j**).

This compound was prepared from the 2-(4-bromobutyl)thiadiazine **13b** and 1-(2-pyrimidinyl)piperazine maintaining the reaction at room temperature for 2 hours. It was isolated as the mono-hydrobromide salt. The white solid was purified by silica gel flash chromatography using dichloromethane/ethanol 9:1 (v/v) as eluent; ir (potassium bromide): NH 3400, 3250, C=O 1660, SO_2 1310, 1145 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.61 (m, 4H, $2CH_2$) 2.87 (t, J = 6.8 Hz, 2H, CH_2N), 3.40-3.48 (m, 6H, CH_2N), 3.77-3.80 (m, 4H, CH_2N), 3.88 (s, 3H, CH_3), 6.67 (t, J = 4.7, 1H, 5'-H pyrimidine), 7.81 (bs, 1H, NH, exchangeable with D_2O), 7.94 (bs, 1H, NH, exchangeable with D_2O), 8.07 (s, 1H, pyrazole), 8.40 (d, J = 4.7 Hz, 2H, 4'-H and 6'-H pyrimidine); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 27.6, 29.3 (CH_2), 39.6 (CH_3), 34.5, 41.5 42.8, 43.0 (CH_2N), 110.4 (5'-C), 121.8, (4a-C), 123.0 (5-C), 137.1 (7a-C), 153.4 (3-C), 157.7 (4'-C and 6'-C), 160.9 (2'-C); ms: m/z 420.2 (M^+-HBr), 257.1 (M^+-$C_8H_{11}N_4$), 215.0 ($C_6H_7N_4O_3S^+$), 164,1 ($C_8H_{12}N_4^+$).

Anal. Calcd. For $C_{17}H_{25}BrN_8O_3S$ C, 40.72; H, 5.03; N, 22.35; S, 6.39. Found: C, 41.01; H, 4.93; N, 22.50; S, 6.18.

Synthesis of 4-Methyl-2-[4-[1-[4-(2-pyrimidinyl)piperazinyl]]-butyl]-2*H*-thieno[2,3-*e*][1,2,4]thiadiazin-3(4*H*)-one 1,1-Dioxide (**3k**).

To a solution of the 2-[4-[1-[4-(2-pyrimidinyl)-piperazinyl]]butyl]thiadiazine **3j** (0.3 g, 0.7 mmol) in dry *N*,*N*-dimethylformamide (10 ml), under an inert atmosphere, was added slowly sodium hydride (60% dispersion in mineral oil, 0.037 g, 0.9 mmol) maintaining the temperature below 10°. After 20 minutes, methyl iodide (57 ml, 0.9 mmol) was added and the reaction mixture was stirred at room temperature for 15 hours. The solvent was evaporated to dryness and the crude solid was treated with water. The brown solid precipitated was filtered, washed with water, dried and recrystallized from ethanol; ir (potassium bromide): C=O 1655, SO_2 1352, 1175 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.87 (m, 4H, $2CH_2$) 3.29-3.36 (m, 7H, CH_2N), 3.47 (m, 4H, CH_2N), 3.79 (m, 4H, CH_2N), 6.51 (t, J = 4.8 Hz, 1H, 5'-H, pyrimidine), 7.13 (d, 2H, thiophene), 8.30 (d, J = 4.8 Hz, 2H, 4'-H and 6'-H pyrimidine); ^{13}C nmr (deuteriochloroform): δ 25.5 (CH_2-CH_2), 42.7 (CH_3), 43.2, 45.7, 47.7 (CH_2N), 110.2 (5'-C), 122.1 (7-C), 125.3 (6-

C), 151.7 (3-C), 157.7 (4'-C and 6'-C), 161.0 (4a-C), 161.5, (2'-C); ms: m/z 436.3 (M^+), 191.1 ($C_{10}H_{15}N_4^+$), 122.2 ($C_6H_8N_3^+$).

Anal. Calcd. For $C_{18}H_{24}N_6O_3S_2$ C, 49.52; H, 5.54; N, 19.25; S, 14.69 Found: C, 49.71; H, 5.57; N, 18.98; S, 14.52.

Synthesis of the Oxazolohetero[1,2,4]thiadiazine S,S-Dioxides **5-7**.

General Method.

A mixture of the corresponding bromomethylthiadiazine **17b**, **18a-b, 20** (1 equivalent) and 1-(2-pyridyl)piperazine or 1-(2-pyrimidinyl)piperazine (2 equivalents) in *N*,*N*-dimethylformamide was heated at 50-60° for the time indicated in each case. The mixture was treated with water and the precipitate was collected by filtration, washed with water, dried and recrystallized from the appropriate solvent to give compounds **5-7**.

8-Bromo-2-[1-[4-(2-pyridyl)piperazinyl]]methyl-2,3-dihydrooxazolo[3,2-*b*]thieno[3,4-*e*][1,2,4]thiadiazine 5,5-Dioxide (**5a**).

This compound was synthesized by heating the 8-bromo-2-(bromomethyl)thiadiazine **17b** (0.5 g, 1.2 mmol), 1-(2-pyridyl)piperazine (0.38 ml, 2.5 mmol) and *N*,*N*-dimethylformamide (3 ml) at 50° for 5 hours; ir (potassium bromide): C=N 1650, SO_2 1327, 1170 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.71 (m, 4H, CH_2N), 2.83 (d, J = 5.4 Hz, 2H, CH_2-CH-O), 3.54 (t, J = 5.1 Hz, 4H, CH_2N), 4.09 (dd, J = 9.0 Hz, J = 7.2 Hz, 1H, 3-H), 4.24 (dd, J = 9.0 Hz, J = 7.9 Hz, 1H, 3-H), 5.02 (m, 1H, 2-H), 6.63-6.66 (m, 2H, 5'-H and 3'-H pyridine), 7.49 (ddd, J = 8.5 Hz, J = 7.2 Hz, J = 2.0 Hz, 1H, 4'-H pyridine), 8.07 (s, 1H, thiophene), 8.19 (m, 1H, 6'-H pyridine); ^{13}C nmr (deuteriochloroform): δ 43.7 45.2, 53.9, 59.7 (CH_2), 76.9 (CH), 103.9 (8-C), 107.1 (3'-C), 113.5, (5'-C), 124.1 (6-C), 125.1 (5a-C), 137.5 (4'-C), 140.8 (8a-C), 147.9 (6'-C), 154.9 (9a-C), 159.3 (2'-C); ms: m/z 484.9 (M^++2), 482.8 (M^+), 106.9 ($C_6H_7N_2^+$).

Anal. Calcd. For $C_{17}H_{18}BrN_5O_3S_2$ C, 42.15; H, 3.75; N, 14.46; S, 13.21. Found: C, 42.02; H, 3.65; N, 14.69; S, 13.08.

8-Bromo-2-[1-[4-(2-pyrimidinyl)piperazinyl]]methyl-2,3-dihydrooxazolo[3,2-*b*]thieno[3,4-*e*][1,2,4]thiadiazine 5,5-Dioxide (**5b**).

This compound was synthesized by heating the 8-bromo-2-(bromomethyl)thiadiazine **17b** (0.5 g, 1.2 mmol), 1-(2-pyrimidinyl)piperazine (0.41 g, 2.5 mmol) and *N*,*N*-dimethylformamide (3 ml) at 50° for 18 hours; ir (potassium bromide): C=N 1650, SO_2 1330, 1175 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.66 (m, 4H, CH_2N), 2.83 (d, J = 5.5 Hz, 2H, CH_2-CH-O), 3.83 (t, J = 5.0 Hz, 4H, CH_2N), 4.09 (dd, J = 8.9 Hz, J = 7.2 Hz, 1H, 3-H), 4.24 (t, J = 8.9 Hz, J = 8.9 Hz, 1H, 3-H), 5.02 (m, 1H, 2-H), 6.50 (t, J = 4.8 Hz, 1H, 5'-H pyrimidine), 8.07 (s, 1H, thiophene), 8.31 (d, J = 4.8 Hz, 2H, 4'-H and 6'-H pyrimidine); ^{13}C nmr (deuteriochloroform): δ 43.5 43.7, 53.9, 59.7 (CH_2), 76.8 (CH), 103.9 (8-C), 110.0 (5'-C), 124.2 (6-C), 125.0 (5a-C), 140.7 (8a-C), 154.8 (9a-C), 157.7 (4'-C and 6'-C), 161.5 (2'-C); ms: m/z 485.9 (M^++2), 483.9 (M^+), 177.1 ($C_9H_{13}N_4^+$).

Anal. Calcd. For $C_{16}H_{17}BrN_6O_3S_2$ C, 39.59; H, 3.53; N, 17.31; S, 13.21. Found: C, 39.82; H, 3.69; N, 17.66; S, 13.18.

2-Methyl-6-[1-[4-(2-pyridyl)piperazinyl]]methyl-6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-Dioxide (**6a**).

This compound was synthesized by heating the 6-(bromomethyl)thiadiazine **18a** (0.4 g, 1.25 mmol), 1-(2-pyridyl)-piperazine (0.38 ml, 2.5 mmol) and *N*,*N*-dimethylformamide (3 ml) at 60° for 7 hours; ir (potassium bromide): C=N 1665, SO_2 1360, 1125 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.72 (m, 4H, CH_2N), 2.82 (d, J = 5.4 Hz, 2H, CH_2-CH-O), 3.53 (t, J = 5.0 Hz, 4H, CH_2N), 4.01 (s, 3H, CH_3), 4.07 (dd, J = 7.0 Hz, J = 9.0 Hz, 1H, 7-H), 4.27 (dd, J = 8.0 Hz, J = 9.0 Hz, 1H, 7-H), 4.99 (m, 1H, 6-H), 6.62-6.64 (m, 2H, 5'-H and 3'-H pyridine), 7.40 (s, 1H, pyrazole), 7.47 (ddd, J = 8.5 Hz, J = 7.3 Hz, J = 2.0 Hz, 1H, 4'-H pyridine), 8.18 (dd, J = 2.0 Hz, J = 5.7 Hz, 1H, 6'-H pyridine); ^{13}C nmr (deuteriochloroform): δ 40.7 (CH_3), 43.6 45.2, 53.9, 59.9 (CH_2N), 76.6 (6-C), 103.9 (8-C), 107.1 (3'-C), 113.5, (5'-C), 123.5 (3-C), 131.6 (3a-C), 134.8 (9a-C), 137.5 (4'-C), 147.9 (6'-C), 154.1 (4a-C), 159.3 (2'-C); ms: m/z 403.0 (M^+), 309.1 (M^+-$C_4H_6N_2$), 121.0 ($C_7H_9N_2^+$), 106.9 ($C_6H_7N_2^+$).

Anal. Calcd. For $C_{17}H_{21}N_7O_3S$ C, 50.60; H, 5.25; N, 24,30; S, 7.95. Found: C, 50.35; H, 5.21; N, 24.15; S, 8.12.

2-Methyl-6-[1-[4-(2-pyrimidinyl)piperazinyl]]methyl-6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-Dioxide (**6b**).

This compound was synthesized by heating the 6-(bromomethyl)thiadiazine **18a** (0.4 g, 1.25 mmol), 1-(2-pyrimidinyl)piperazine (0.38 ml, 2.5 mmol) and *N*,*N*-dimethylformamide (3 ml) at 50° for 8 hours; ir (potassium bromide): C=N 1660, SO_2 1330, 1125 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.65 (m, 4H, CH_2N), 2.82 (d, J = 5.5 Hz, 2H, CH_2-CH-O), 3.81 (t, J = 5.0 Hz, 4H, CH_2N), 4.02 (s, 3H, CH_3), 4.08 (dd, J = 9.0 Hz, J = 7.0 Hz, 1H, 7-H), 4.29 (t, J = 9.0 Hz, J = 9.0 Hz, 1H, 7-H), 5.00 (m, 1H, 6-H), 6.49 (t, J = 4.7 Hz, 1H, 5'-H pyrimidine), 7.41 (s, 1H, pyrazole), 8.30 (d, J = 4.7 Hz, 2H, 4'-H and 6'-H pyrimidine); ^{13}C nmr (deuteriochloroform): δ 40.7 (CH_3), 43.6 53.9, 59.9 (CH_2N), 76.6 (6-C), 110.0 (5'-C), 123.5 (3-C), 131.5 (3a-C), 134.8 (9a-C), 154.1 (4a-C), 157.7 (4'-C and 6'-C), 161.5 (2'-C); ms: m/z 404.1 (M^+), 240.1 (M^+-$C_8H_{12}N_4$), 177.2 ($C_9H_{13}N_4^+$), 42.2 ($C_3H_6^+$).

Anal. Calcd. For $C_{16}H_{19}BrN_8O_3S$: C, 39.75; H, 3.96; N, 23.19; S, 6.63. Found: C, 40.00; H, 3.68; N, 22.99; S, 6.90.

3-Bromo-2-methyl-6-[1-[4-(2-pyridyl)piperazinyl]]methyl-6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-Dioxide (**6c**).

This compound was synthesized by heating the 3-bromo-6-(bromomethyl)thiadiazine **18b** (0.4 g, 1.25 mmol), 1-(2-pyridyl)piperazine (0.38 ml, 2.5 mmol) and *N*,*N*-dimethylformamide (3 ml) at 60° for 8 hours; ir (potassium bromide): C=N 1655, SO_2 1335, 1165 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.70 (m, 4H, CH_2N), 2.82 (d, J = 5.5 Hz, 2H, CH_2-CH-O), 3.53 (t, J = 5.0 Hz, 4H, CH_2N), 4.01 (s, 3H, CH_3), 4.09 (dd, J = 7.0 Hz, J = 9.0 Hz, 1H, 7-H), 4.28 (dd, J = 8.1 Hz, J = 9.0 Hz, 1H, 7-H), 4.99-5.04 (m, 1H, 6-H), 6.60-6.64 (m, 2H, 5'-H and 3'-H pyridine), 7.47 (ddd, J = 8.6 Hz, J = 7.1 Hz, J = 2.0 Hz, 1H, 4'-H pyridine), 8.18 (dd, J = 2.0 Hz, J = 5.6 Hz, 1H, 6'-H pyridine); ^{13}C nmr (deuteriochloroform): δ 39,3 (CH_3), 43.6 45.2, 53.9, 59.8 (CH_2N), 77.1 (6-C), 107.0 (3'-C), 107.5 (3-C), 113.4, (5'-C), 130.3 (3a-C), 135.3 (9a-C), 137.5 (4'-C), 147.9 (6'-C), 154.5 (4a-C), 159.3 (2'-C); ms: m/z 483.0 (M^++2), 481.0 (M^+), 106.9 ($C_6H_7N_2^+$).

Anal. Calcd. For $C_{17}H_{20}BrN_7O_3S$ C, 42.33; H, 4.18; N, 20,33; S, 6.65. Found: C, 42.26; H, 3.89; N, 20.08; S, 6.57.

3-Bromo-2-methyl-6-[1-[4-(2-pyrimidinyl)piperazinyl]]methyl-6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-Dioxide (**6d**).

This compound was synthesized by heating the 3-bromo-6-(bromomethyl)thiadiazine **18b** (0.4 g, 1.25 mmol), 1-(2-pyrimidinyl)piperazine (0.38 ml, 2.5 mmol) and *N*,*N*-dimethylformamide (3 ml) at 50° for 24 hours; ir (potassium bromide): C=N 1655, SO_2 1330, 1160 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.65 (m, 4H, CH_2N), 2.82 (d, J = 5.4 Hz, 2H, CH_2-CH-O), 3.81 (t, J = 5.0 Hz, 4H, CH_2N), 4.01 (s, 3H, CH_3), 4.09 (dd, J = 9.0 Hz, J = 7.0 Hz, 1H, 7-H), 4.28 (dd, J = 8.0 Hz, J = 9.0 Hz, 1H, 7-H), 4.98-5.05 (m, 1H, 6-H), 6.49 (t, J = 4.7 Hz, 1H, 5'-H pyrimidine), 8.30 (d, J = 4.7 Hz, 2H, 4'-H and 6'-H pyrimidine); ^{13}C nmr (deuteriochloroform): δ 39.3 (CH_3), 43.6 54.0, 59.8 (CH_2N), 76.2 (6-C), 107.6 (3-C), 110.0 (5'-C), 130.3 (3a-C), 135.4 (9a-C), 154.6 (4a-C), 157.7 (4'-C and 6'-C), 161.6 (2'-C); ms: m/z 484.0 (M^++2), 481.9 (M^+), 177.2 ($C_9H_{13}N_4^+$).

Anal. Calcd. For $C_{16}H_{19}BrN_8O_3S$ C, 39.75; H, 3.96; N, 23.19; S, 6.63. Found: C, 40.00; H, 3.68; N, 22.99; S, 6.90.

3-Bromo-2-methyl-7-[1-[4-(2-pyrimidinyl)piperazinyl]]methyl-6,7-dihydro-2*H*-oxazolo[3,2-*b*]pyrazolo[4,3-*e*][1,2,4]thiadiazine 9,9-Dioxide (**7**).

This compound was synthesized by heating the 3-bromo-7-(bromomethyl)thiadiazine **20** (0.4 g, 1.25 mmol), 1-(2-pyrimidinyl)piperazine (0.33 ml, 2.0 mmol) and *N*,*N*-dimethylformamide (3 ml) at 50° for 22 hours; ir (potassium bromide): C=N 1625, SO_2 1315, 1135 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 2.38-2.43 (m, 4H, CH_2N), 2.61-2.77 (m, 4H, CH_2N and CH_2-CH-O), 3.66 (m, 4H, CH_2N), 4.00 (s, 3H, CH_3), 4.76-4.83 (m, 2H, 7-H), 5.10 (m, 1H, 1-H), 6.61 (t, J = 4.7 Hz, 1H, 5'-H pyrimidine), 8.34 (d, J = 4.7 Hz, 2H, 4'-H and 6'-H pyrimidine); ^{13}C nmr (dimethylsulfoxide-d_6): δ 39.2 (CH_3), 43.3 53.5, (CH_2N), 54.4 (1-C), 71.5 (2-C), 100.1 (8-C), 110.1 (5'-C), 118.7 (8a-C), 134.4 (5a-C), 154.8 (3a-C), 157.9 (4'-C and 6'-C), 161.6 (2'-C); ms: m/z 484.0 (M^++2), 482.0 (M^+), 403.1 (M^+-Br), 177.1 ($C_9H_{13}N_4^+$), 122.1 ($C_6H_8N_3^+$).

Anal. Calcd. For $C_{16}H_{19}BrN_8O_3S$ C, 39.75; H, 3.96; N, 23.19; S, 6.63. Found: C, 39.81; H, 3.75; N, 22.97; S, 6.45.

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