Novel 1,1,3-Trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine Derivatives as Non-Nucleoside Reverse Transcriptase Inhibitors That Inhibit Human Immunodeficiency Virus Type 1 Replication

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The 1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazines (TTDs) represent a recently discovered chemical class of non-nucleoside reverse transcriptase inhibitors that selectively block human immunodeficiency virus type 1 replication. In a search for a better understanding of their mode of binding and with the aim of obtaining novel lead compounds, a second series of TTD derivatives was synthesized and evaluated for antiviral activity. The design of the new compounds was based on a variety of chemical modifications which were carried out in the original prototype **20a** (QM 96521). Substitution of a halogen at the meta position of the *N*-2 benzyl group resulted in an improvement of the antiviral activity by 1 order of magnitude. Compounds bearing at the *N*-4 position a cyanomethyl, propargyl, or benzyl substituent were found to be the most potent of the series. Modifying the thieno[3,4-*e*] ring fused to the 1,2,4-thiadiazine moiety to other heterocyclic ring systems decreased the potency. The results obtained in this investigation have provided new indications for the design of even more effective TTDs.

Introduction

We have recently described the synthesis and biological activity of a new family of inhibitors of the human immunodeficiency virus type 1 (HIV-1),[1] the 2,4-disubstituted 1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazines (TTDs). These compounds, the prototype being 2-benzyl-4-cyanomethyl-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine (**20a**, QM 96521), belong to the same group of

20a (QM 96521)

inhibitors as BHAP,[2] PETT,[3] α-APA,[4] nevirapine,[5] etc., which are known as non-nucleoside reverse transcriptase inhibitors (NNRTIs).[6,7] Like other NNRTIs, the TTDs selectively inhibit HIV-1 replication at the reverse transcription (RT) step. In our preceding publications we have described the discovery of the TTDs and the development of **20a** (QM 96521) as a lead for further studies.[1,8]

We discovered that compounds in this series with a benzyl moiety at *N*-2 showed RT inhibition, while unsubstituted compounds or compounds bearing other groups at this position (such as phenyl or alkyl substituents) were completely devoid of activity. We also found that alkylation of the *N*-4 position was essential for anti-

HIV-1 activity. Thus, while unsubstituted compounds at this position were inactive, the methyl, ethyl, and *n*-propyl containing derivatives showed inhibition of HIV-1 RT at sub-micromolar concentrations. The *N*-4 cyanomethyl derivative **20a**, an intermediate in the synthesis of amides (which were inactive), and the *N*-4 propargyl derivative **20d** showed, in this order, the highest activity. Why exactly the presence of the *N*-4 cyanomethyl moiety in **20a** ensures anti-HIV-1 activity relative to the ethyl or *n*-propyl substituents remains to be elucidated, but may be due to steric or electronic effects (i.e., the *n*-propyl group is not linear, the ethyl group is smaller, and the cyano group has π-electrons). The closely related benzo[1,2,4]thiadiazine derivative with the same nitrogen substitutions as **20a** was also synthesized and was found to be inactive, thus demonstrating the requirement of the thieno[3,4-*e*] fused heterocycle for activity.

Molecular modeling and X-ray diffraction studies carried out with these thieno[1,2,4]thiadiazines[8] demonstrated that the *N*-2 benzyl moiety allows the molecule to adopt the "butterfly" conformation which is commonly encountered in the NNRTIs. Interestingly, these investigations also demonstrated that the *N*-4 cyanomethyl substituent of **20a** is on the same side of the plane as the *N*-2 benzyl group, and consequently, the overall conformation of this compound is very similar to that of nevirapine.[9]

If HIV-1 was cultured in the presence of low concentrations of the TTD a resistant virus strain was generated with a unique amino acid change (V179D) in the reverse transcriptase.[8] In models of the binding of **20a** to HIV-1-RT, the *N*-4 substituent was found to be close

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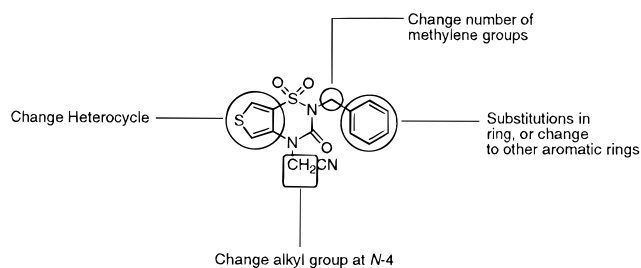‡ Rega Institute for Medical Research, Katholieke Universiteit Leuven.

Figure 1. Planned modifications to the lead compound.

to this amino acid, which may explain why the V179D mutation leads to resistance.[8]

In the present paper we disclose the results of our studies on a new series of TTDs. Our goal was to better understand the mode of binding and to obtain compounds with better activity and selectivity. The structural changes investigated are summarized in Figure 1. We have concentrated on four parts of the molecule: (i) the nature of the heterocycle fused to the 1,2,4-thiadiazine ring, (ii) the length of the methylene bridge between the bicyclic system and the phenyl ring at *N*-2, (iii) substitutions in the phenyl ring or changing the phenyl to pyridines, and (iv) other substitutions at *N*-4.

We thought that a heterocycle attached to the 1,2,4-thiadiazine ring would be important since the benzo fused bicycles are inactive; we therefore synthesized 1,2,4-thiadiazines with the thieno[2,3-*e*], thieno[3,2-*e*], and pyrazolo[4,3-*e*] modifications. With these new derivatives we could investigate the effect of changing the position and nature of the heteroatom on the HIV-1 inhibitory activity. We felt it necessary to study compounds with either one or two methylene groups in the bridge between the two π-electron containing systems because the PETT compounds have two methylene groups. Another obvious modification that we wished to study was the introduction of substitutions at the phenyl ring or its replacement for pyridine; halogenated phenyl rings and pyridines are often found in other NNRTIs such as α-APA, PETT, and TIBO. To gain insight in the role that the cyanomethyl group may play in the interaction of TTD derivatives with the HIV-1 RT, we also synthesized heterothiadiazines bearing other π-electron containing substituents at the *N*-4 position, such as benzyl, substituted benzyl, allyl, and propargyl groups; nevirapine, as is well known, bears in its structure a cyclopropyl group which has a certain π-character.[10]

Chemistry

For the synthesis of compounds **16**−**19** we designed a procedure based on the methods previously described for the preparation of the parent 1,1,3-trioxo-2*H*,4*H*-hetero[1,2,4]thiadiazines and their first 2,4-substituted derivatives.[1,11] The procedure, which is outlined in Schemes 1−4, consists of the cyclization of the sulfamoylheterocarboxylic derivatives **2a**−**c** and **7** through a typical Curtius reaction[12,13] followed by alkylation of the intermediate *N*-2 substituted thiadiazines thus obtained, to give the target *N*-2,*N*-4 dialkyl hetero[1,2,4]-thiadiazines.

Thus, reaction of methyl 4-chlorosulfonylthiophene-3-carboxylate (**1**) with phenethylamine, 2-picolylamine, and 3-picolylamine in dry tetrahydrofuran (THF) and
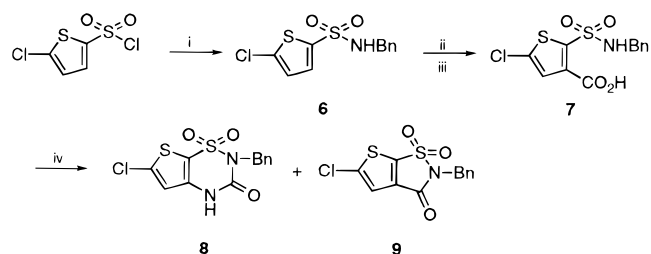
Scheme 1[a]
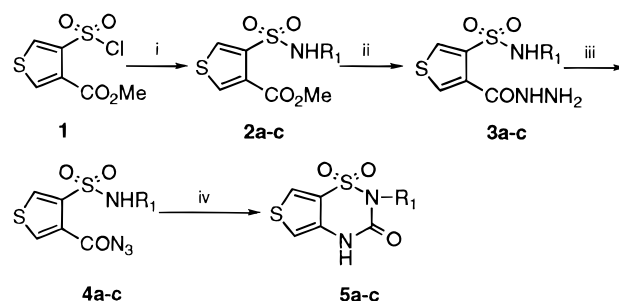
Compound	R_1
2a-5a	CH_2CH_2Ph
2b-5b	2-picolyl
2c-5c	3-picolyl

[a] Reagents: (i) R_1NH_2/THF; (ii) $N_2H_4 \cdot H_2O$/EtOH; (iii) 2 N HCl or HNO_3, $NaNO_2$, H_2O; (iv) Δ/toluene.

Scheme 2[a]

[a] Reagents: (i) benzylamine (2 equiv), THF; (ii) *n*-BuLi (1.2 equiv), THF, CO_2; (iii) H_3O^+; (iv) DPPA, TEA, toluene, Δ.
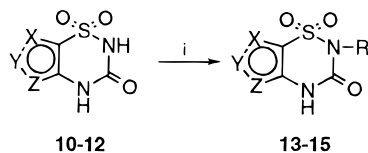
Scheme 3[a]

Compound	X	Y	Z
10 → 13a-g	CH	S	CH
11 → 14	CH	CH	S
12 → 15	N	NCH_3	CH

[a] Reagents: (i) NaH (1 equiv), DMF, benzyl halides.

in the in the presence of potassium carbonate (K_2CO_3) (Scheme 1) gave the corresponding sulfamoyl compounds **2a**−**c**. Treatment of **2a**−**c** with hydrazine hydrate in refluxing ethanol afforded the hydrazide derivatives **3a**−**c**, which were readily converted to the acyl azides **4a**−**c** by the action of nitrous acid. Heating **4a**−**c** in refluxing dry toluene led to the desired thieno-[3,4-*e*][1,2,4]thiadiazines **5a**−**c**, by spontaneous ring closure of the intermediate isocyanates formed in the rearrangement of these acyl azides. Benzylthienothiadiazine **8** (Scheme 2) was also synthesized from the carboxylic acid **7** by a modification of the Curtius reaction which involves the use of diphenylphosphoryl azide (DPPA).[14,15] Thus, reaction of 5-chloro-2-chlorosulfonylthiophene[16] with benzylamine in THF afforded the sulfamide **6**, which was converted to the carboxylic acid **7** by metalation at the 3-position with *n*-BuLi in dry THF, followed by carbonation of the formed organolithium compound with powdered dry ice and subse-

Scheme 4[a]

Compound	X	Y	Z
5a-c,13a-g → 16	CH	S	CH
14 → 17	CH	CH	S
15 → 18	N	NCH₃	CH
8 → 19	S	CCl	CH
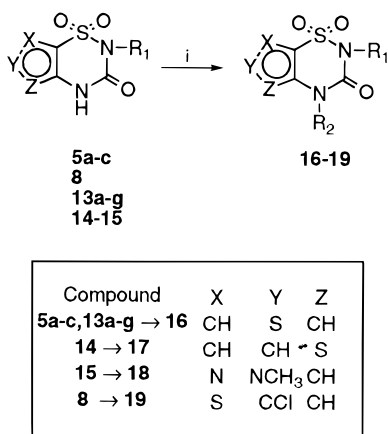
[a] Reagents: (i) NaH (1.2 equiv), DMF, R₂X.

quent acidification. Cyclization of compound **7** with DPPA in the presence of triethylamine in dry toluene afforded the required benzylthienothiadiazine **8** (38%), with the concomitant formation of 2-benzyl-5-chloro-1,1,3-trioxo-2,3-dihydrothieno[3,2-*d*]isothiazole (**9**) (26%).

Monosubstituted heterothiadiazines **13a**−**g**, **14**, and **15** (Scheme 3) were achieved by alkylation of 1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*]-, 1,1,3-trioxo-2*H*,4*H*-thieno-[2,3-*e*]-, and 6-methyl-1,1,3-trioxo-2*H*,4*H*-pyrazolo[4,3-*e*][1,2,4]thiadiazines[11] (**10**−**12**) with a variety of benzyl halides in the presence of sodium hydride (NaH) and *N,N*-dimethylformamide (DMF), following a recently reported method.[1] Finally the target heterothiadiazines **16**−**19** (Scheme 4) were synthesized by alkylation at *N*-4 of 2-substituted compounds **5**, **8**, and **13**−**15** with alkyl halides also using the NaH/DMF system. The structures of all newly synthesized compounds were established on the basis of analytical and NMR data.

Biological Results and Discussion

In our previous publications dealing with the first generation of TTD derivatives we have shown that active compounds require the presence of both an *N*-2 benzyl group and alkyl substituent at the *N*-4 position.[1,8] The earliest compounds in this family that exhibited inhibition of HIV possessed the methyl, ethyl, or propyl groups at *N*-4. Marked improvements in the activity of these compounds were observed with the *N*-4 cyanomethyl, propargyl, and benzyl derivatives, whereas the allyl and cyanoethyl bearing analogues were less potent. In the present work we have synthesized a second series of compounds **16**−**19** in order to better understand how the TTDs interact with the NNRTI binding site and to begin to optimize the structure of these inhibitors. The results are presented in Table 1. The synthesis and antiviral activity of the TTD derivatives **20** have been reported previously;[1] their EC₅₀ and CC₅₀ values were included for comparative purposes.
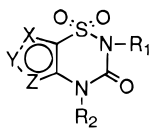
We first studied the effect of the introduction of halogens in the phenyl ring of the *N*-2 benzyl substituent of the lead compound **20a**. Such a modification had been demonstrated in other NNRTIs to lead to an improvement in their potencies.[3,4,17] Thus, we synthesized the TTD analogues **16e**−**q** which all bear halogenated benzyl moieties and differ in their *N*-4 substitutions (initially limited to Me, Et, CH₂C≡N, and CH₂C≡

CH). When the EC₅₀ and CC₅₀ values of the chlorinated derivatives **16e**−**h** and **16k**−**n** were compared with those of their corresponding nonhalogenated analogues **20b** and **20c**, the presence of the *o*-, *p*-, and 2,6-dichlorobenzyl substituents appeared to be deleterious. This was particularly pronounced for the *para*-chlorinated analogues **16k** and **16l** which were completely inactive. The *N*-2-(3-chlorobenzyl)-*N*-4-methyl analogue **16g** was less active than **20b**; however, the observed improvement in the EC₅₀ value of the *N*-4-ethyl derivative **16h** with respect to **20c** encouraged us to prepare more *N*-2-(3-chlorobenzyl) bearing derivatives.

Compounds **16i** and **16j** were 10-fold more active than their unsubstituted counterparts **20a** and **20d**, with selectivity indices ranging from >3800 to 376, respectively, thus demonstrating that the presence of a chlorine atom at this position results in a marked improvement in the anti-HIV-1 activity of these compounds. Replacement of the chlorine atom by other halogens led to the *meta*-brominated compound **16o**, which was as active as **16i**, and the fluorine substituted **16p**, which was the most active compound (EC₅₀ = 0.05 μM) of the series. Although the 3,5-difluorobenzyl containing compound **16q** is 3 times more active than **20a**, it is not as potent as **16p**. This seems to suggest that one substituent in the phenyl ring of the *N*-2 benzyl group is optimal for maximal anti-HIV-1 activity, but more studies are required to prove this hypothesis.

The effect of the halogen atom in the meta position is as yet not clear and may be due to steric, lipophilic, or perhaps electrostatic interactions within the NNRTI binding site. To clarify this point, we produced the picoline substituted analogues **16u**−**x**, since the nitrogen atom in the pyridine ring of these compounds would impart electrostatic interactions rather than steric or lipophilic ones. The 2-picolyl derivatives **16u** and **16v** were less active than their respective benzyl analogues **20c** and **20a**. Surprisingly, **16w** was 6 times more active than the related compound **20e**. We are as yet uncertain as to why this should be so, but it may be due to subtle differences in the binding of **20e** and **16w** relative to **20a** brought about by the presence of the larger *N*-4 benzyl group in the former compounds. The 3-picolyl derivative **16x** was found to be 4 times as potent as its prototype **20a**, which supports the argument for a favorable electrostatic interaction between the *N*-2 substituent of the TTDs and RT. The *N*-2 phenylethyl substitution in **16r**−**t** gave rise to compounds with much less activity than their benzylated counterparts.

We were also interested in understanding the role played by the thiophene ring of the thieno[3,4-*e*][1,2,4]-thiadiazine bicyclic system. We have observed that the benzo fused bicycle containing TTD-like compounds were inactive, and thus we wished to investigate the effect of other heterocycles attached to the 1,2,4-thiadiazine. In Table 1, we include the results obtained for the thieno[2,3-*e*] (**17**), 6-methylpyrazolo[3,4-*e*] (**18**), and 6-chlorothieno[3,2-*e*] (**19**) fused TTD analogues. In general, such modifications in the TTD bicyclic nucleus resulted in less active molecules; this is easier to see in the compounds of series **17** which are all less active than the thieno[3,4-*e*] analogues. The analysis of the inhibitory effects brought about by the other ring systems

Table 1. Anti-HIV-1 Activity and Cytotoxicity of 2,4-Disubstituted 1,1,3-Trioxo-2H,4H-hetero[1,2,4]thiadiazines **16−19**

compd no.	X	Y	Z	R₁	R₂	EC₅₀ (μM)[a]	CC₅₀ (μM)[b]	SI
						HIV-1 (III^B)		
16a	CH	S	CH	Bn	2-Cl-benzyl	0.10	>119.0	>1190
16b	CH	S	CH	Bn	3-Cl-benzyl	0.8	>119.0	>149
16c	CH	S	CH	Bn	4-Cl-benzyl	1.4	18.6	13
16d	CH	S	CH	Bn	CH₂CO₂Et	7.4	129.6	18
16e	CH	S	CH	2-Cl-benzyl	Me	>446.3	446.3	<1
16f	CH	S	CH	2-Cl-benzyl	Et	7.3	605.3	83
16g	CH	S	CH	3-Cl-benzyl	Me	7.6	>729	>96
16h	CH	S	CH	3-Cl-benzyl	Et	2.1	>700.6	>334
16i	CH	S	CH	3-Cl-benzyl	CH₂CN	0.09	>340	>3778
16j	CH	S	CH	3-Cl-benzyl	CH₂C≡CH	0.1	65.7	657
16k	CH	S	CH	4-Cl-benzyl	Me	>417	417	<1
16l	CH	S	CH	4-Cl-benzyl	Et	>273	273	<1
16m	CH	S	CH	2,6-di-Cl-benzyl	Me	>527.5	527.5	<1
16n	CH	S	CH	2,6-di-Cl-benzyl	Et	>74.1	74.1	<1
16o	CH	S	CH	3-Br-benzyl	CH₂CN	0.09	68.6	762
16p	CH	S	CH	3-F-benzyl	CH₂CN	0.05	93.6	1872
16q	CH	S	CH	3,5-di-F-benzyl	CH₂CN	0.3	102.0	340
16r	CH	S	CH	phenethyl	Et	8.6	330.0	38
16s	CH	S	CH	phenethyl	CH₂CN	3.6	40.3	11
16t	CH	S	CH	phenethyl	Bn	10.9	226.0	21
16u	CH	S	CH	2-picolyl	Et	41.4	>387.0	>9
16v	CH	S	CH	2-picolyl	CH₂CN	1.1	>374	>340
16w	CH	S	CH	2-picolyl	Bn	0.4	166.0	415
16x	CH	S	CH	3-picolyl	CH₂CN	0.2	>150.0	>750
17a	CH	CH	S	Bn	Me	>811	>811.0	1
17b	CH	CH	S	Bn	Et	20.5	374	18
17c	CH	CH	S	Bn	n-Pr	>403	403.0	>1
17d	CH	CH	S	Bn	CH₂CN	3.0	219.0	73
17e	CH	CH	S	Bn	Bn	8.3	>650	>78
18a	N	NCH₃	CH	Bn	Me	>498.5	498.5	<1
18b	N	NCH₃	CH	Bn	Et	>320.6	320.6	<1
19a	S	CCl	CH	Bn	CH₂CN	24.5	152.0	6
19b	S	CCl	CH	Bn	Bn	4.5	>119.0	>26
20a[c]	CH	S	CH	Bn	CH₂CN	0.9	502.7	559
20b[c]	CH	S	CH	Bn	Me	2.7	527.9	196
20c[c]	CH	S	CH	Bn	Et	2.5	>775.0	>310
20d[c]	CH	S	CH	Bn	CH₂C≡CH	1.0	>376	>376
20e[c]	CH	S	CH	Bn	Bn	2.2	>650	>296
Nevirapine						0.03	683	22,767
AZT						0.0007	35.6	50,587

[a] EC₅₀: dose of compound required to achieve 50% protection of MT-4 cells from HIV-1 induced cytopathogenicity, as determined by the MIT method. [b] CC₅₀: dosage required to reduce the viability of mock-infected cells by 50%, as determined by the MTT method. [c] The synthesis and antiviral properties of these compounds were previously described.[1] All data represent mean values for at least two separate experiments.

(compounds **18** and **19**) is complicated by the presence of the *N*-methyl group in **18** (these compounds are not active and are noncytotoxic) and the 6-chloro group in **19**. These negative results suggest that there may be limited space around this part of the TTD molecule when bound to the RT.

Since earlier studies on the TTDs revealed that the *N*-4 benzyl derivative **20e** was fairly potent, it appeared of interest to verify if halogenation of this benzyl group would increase the activity of these analogues. Derivatives **16a**, **16b**, and **16c**, bearing *o*-, *m*- and *p*-chlorobenzyl substituents at *N*-4, respectively, were more effective than their prototype **20e**; compounds **16b** and **16c**, however, were less selective. The *o*-Cl substituted derivative **16a**, with an EC₅₀ value of 0.10 μM and a selectivity index of >1190, was one of the most active TTDs of this series, and this makes it another lead compound for the synthesis of further TTD analogues.

In conclusion, we have described the synthesis and structure−activity relationships of a second generation of TTD analogues, which showed improved potency as inhibitors of the human immunodeficiency virus type 1 [HIV-1(III_B)] replication in MT-4 cells. We have demonstrated that the introduction of a meta-halogenated benzyl substituent at the *N*-2 position resulted in compounds which exhibit a 10-fold increase in their ability to inhibit the HIV-1 reverse transcriptase with respect to the nonhalogenated lead compound (in the order F > Cl ≈ Br). The presence of the halogen probably improves the binding of the TTDs to RT via a favorable electrostatic interaction, since a similar although less marked effect is also observed with the *N*-2 substituted picolyl derivatives. The fact that the most active TTDs bear a cyanomethyl, propargyl, or benzyl group at their *N*-4 position points to the importance of the presence of π-electron containing substituents at

this nitrogen. Halogenated benzyl moieties at *N*-4 are responsible for the observed increase in the activity of these derivatives relative to their nonhalogenated parent compound. The work reported here generated the new lead compounds **16a** (QM 96625), **16i** (QM 96539), and **16p** (QM 96639) which are now subject of further optimization in our laboratory.

Experimental Section

Chemical Procedures. Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. Elemental analyses were performed with a Heraeus CHN-RAPID instrument at the Centro Nacional de Química Orgánica, CSIC, Madrid. Analytical results which are only indicated by symbols were found within ±0.4% of the theoretical values. ¹H NMR spectra (300 MHz) were recorded on a Varian XL-300 spectrometer in the indicated solvent. Chemical shifts are expressed in δ units from tetramethylsilane (TMS) as an internal standard. IR spectra were measured with a Shimadzu IR-435 spectrometer. Silica gel/TLC cards (Fluka, silica gel-precoated aluminum cards with fluorescent indicator 254 nm) were used for thin-layer chromatography (TLC). Developed plates were visualized by UV light. Flash column chromatography was performed on columns packed with silica gel 60 (230−400 mesh) (Merck).

General Procedure for the Preparation of Derivatives 2a−c. Example: 4-(*N*-Phenethylsulfamoyl)thiophene-3-methyl Carboxylate (2a). To a mixture of **1** (5.0 g, 20 mmol), K₂CO₃ (1.44 g, 10 mmol), and THF (25 mL) was added dropwise a solution of 2-phenylethylamine (2.42 g, 2.9 mL, 20 mmol) in the same solvent, maintaining the temperature below 10 °C. The reaction mixture was stirred at 5 °C for 1 h, and then it was refluxed for 6 h. The solvent was evaporated, and the residue was purified by column chromatography using hexane/AcOEt 3:1 as eluent to give **2a** (75%) as an oil. IR (film, cm⁻¹): 3300 (NH); 1722 (C=O); 1335, 1165 (SO₂); 1250 (C−O). ¹H NMR (DMSO-d_6, δ): 8.43 (d, 1H, *J* = 3.3 Hz, thiophene); 8.25 (d, 1H, *J* = 3.3 Hz, thiophene); 7.28−7.06 (m, 5H, benzene); 6.82 (t, 1H, *J* = 5.7 Hz, NH); 3.76 (s, 3H, CH₃); 3.12 (dt, 2H, *J* = 5.7 Hz, *J* = 7.2 Hz, CH₂N); 2.96 (t, 2H, *J* = 7.2 Hz, CH₂). Anal. (C₁₄H₁₅NO₄S₂) C, H, N, S.

4-[*N*-(2-Picolyl)sulfamoyl]thiophene-3-methyl Carboxylate (2b). Yield: 67%. mp 72−74 °C (EtOH). IR (KBr, cm⁻¹): 3242 (NH); 1720 (C=O); 1335, 1170 (SO₂); 1250 (C−O). ¹H NMR (DMSO-d_6, δ): 12.00−9.00 (bs, 1H, NH); 8.38 (d, 1H, *J* = 3.4 Hz, thiophene); 8.20 (d, 1H, *J* = 3.4 Hz, thiophene); 7.67 (dt, 1H, $J_{4'6'}$ = 1.8 Hz, $J_{4'3'}$ = 7.7 Hz, pyridine H-4′); 7.49 (dd, 1H, $J_{6'5'}$ = 4.8 Hz, $J_{6'4'}$ = 1.7 Hz, pyridine H-6′); 7.28 (d, 1H, $J_{3'4'}$ = 7.7 Hz, pyridine H-3′); 7.19 (dd, 1H, $J_{5'6'}$ = 4.8 Hz, $J_{5'4'}$ = 7.3 Hz, pyridine H-5′); 4.22 (s, 2H, CH₂); 3.83 (s, 3H, CH₃). Anal. (C₁₂H₁₂N₂O₄S₂) C, H, N, S.

4-[*N*-(3-Picolyl)sulfamoyl]thiophene-3-methyl Carboxylate (2c). Yield: 50%; mp 108−110 °C (EtOH−H₂O). IR (KBr, cm⁻¹): 3290 (NH); 1717 (C=O); 1255 (C−O); 1330, 1152 (SO₂). ¹H NMR (DMSO-d_6, δ): 8.39 (m, 2H, pyridine, H-2′, H-6′); 8.35 (d, 1H, *J* = 3.4 Hz, thiophene); 8.19 (d, 1H, thiophene); 7.60 (dt, 1H, *J* = 7.9 Hz, *J* = 2.0 Hz, pyridine, H-4′); 7.54 (bs, 1H, NH); 7.24 (dd, 1H, *J* = 7.9 Hz, *J* = 4.8 Hz, pyridine, H-5′); 4.18 (s, 2H, CH₂); 3.82 (s, 3H, CH₃). Anal. (C₁₂H₁₂N₂O₄S₂) C, H, N, S.

General Procedure for the Preparation of Derivatives 3a−c. Example: 4-(*N*-Phenethylsulfamoyl)thiophene-3-carbohydrazide (3a). A mixture of compound **2a** (5 g, 15 mmol) and hydrazine hydrate (98%) (2.06 g, 2 mL, 40 mmol) in ethanol (11 mL) was refluxed for 1 h. The precipitate formed was filtered off, washed with ice cold ethanol, and purified by recrystallization to yield **3a** (3.20 g, 64%); mp 152−154 °C (MeOH). IR (KBr, cm⁻¹): 3330, 3290 (NH); 1660 (C=O); 1332, 1175 (SO₂). ¹H NMR (DMSO-d_6, δ): 9.94 (bs, 1H, NH); 8.25 (d, 1H, *J* = 3.1 Hz, thiophene); 8.05 (d, 1H, *J* = 3.1 Hz, thiophene); 7.21−7.13 (m, 6H, benzene and NH); 4.60 (bs, 2H, NH₂); 3.05 (t, 2H, *J* = 7.3 Hz, CH₂); 2.70 (t, 2H, *J* = 7.3 Hz, CH₂). Anal. (C₁₃H₁₅N₃O₃S₂) C, H, N, S.

4-[*N*-(2-Picolyl)sulfamoyl]thiophene-3-carbohydrazide (3b). Yield: 90%; mp 173−174 °C (EtOH). IR (KBr, cm⁻¹): 3405, 3342, 3220 (NH); 1660 (C=O); 1327, 1160 (SO₂). ¹H NMR (DMSO-d_6, δ): 9.93 (bs, 1H, NH); 8.42 (dd, 1H, $J_{6'5'}$ = 4.5 Hz, *J* = 1.0 Hz, pyridine H-6′); 8.18 (d, 1H, *J* = 3.2 Hz, thiophene); 8.02 (d, 1H, *J* = 3.2 Hz, thiophene); 7.69 (dt, 1H, $J_{4'5'}$ = 7.8 Hz, *J* = 1.8 Hz, pyridine H-4′); 7.63 (bs, 1H, NH); 7.35 (d, 1H, $J_{3'4'}$ = 7.8 Hz, pyridine H-3′); 7.23 (ddd, 1H, $J_{5'4'}$ = 7.8 Hz, $J_{5'6'}$ = 4.5 Hz, $J_{5'3'}$ = 1.0 Hz, H-5′); 4.13 (s, 2H, CH₂). Anal. (C₁₁H₁₂N₄O₃S₂) C, H, N, S.

4-[*N*-(3-Picolyl)sulfamoyl]thiophene-3-carbohydrazide (3c). Yield: 72%; mp 142−144 °C (EtOH). IR (KBr, cm⁻¹): 3335, 3260 (NH); 1665 (C=O); 1327, 1150 (SO₂). ¹H NMR (DMSO-d_6, δ): 9.91 (bs, 1H, NH); 8.42−8.39 (m, 2H, pyridine, H-2′, H-6′); 8.15 (d, 1H, *J* = 3.2 Hz, thiophene); 8.00 (d, 1H, *J* = 3.2 Hz, thiophene); 7.70 (bs, 1H, NH); 7.64 (dt, 1H, *J* = 7.8 Hz, *J* = 2.0 Hz, pyridine, H-4′); 7.26 (dd, 1H, *J* = 7.8 Hz, *J* = 4.7 Hz, pyridine H-5′); 4.58 (bs, 2H, NH₂); 4.13 (s, 2H, CH₂). Anal. (C₁₁H₁₂N₄O₃S₂) C, H, N, S.

General Procedure for the Preparation of Derivatives 4a−b. Example: 4-(*N*-Phenethylsulfamoyl)thiophene-3-carboxy azide (4a). To a suspension of **3a** (0.5 g, 1.5 mmol) in 2 N hydrochloric acid (6 mL) and acetic acid (5 mL) was added dropwise a solution of sodium nitrite (0.2 g, 2.9 mmol) in water (0.5 mL), maintaining the temperature below 10 °C. The reaction mixture was stirred at this temperature for 2 h, and the precipitate was filtered off, washed with water, and dried to yield **4a** (0.43 g, 83%). The compound was pure enough to be used as such in the following step. IR (KBr, cm⁻¹): 3250 (NH); 2160, 1215 (N₃); 1677 (C=O); 1322, 1160 (SO₂).

4-[*N*-(2-Picolyl)sulfamoyl]thiophene-3-carboxy Azide (4b). Yield: 76%. IR (KBr, cm⁻¹): 3260 (NH); 2150, 1210 (N₃); 1673 (C=O); 1325, 1150 (SO₂).

General Procedure for the Preparation of Derivatives 5a−c. Example: 2-(2-Phenylethyl)-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine (5a). A solution of compound **4a** (0.5 g, 1.4 mmol) in dry toluene (25 mL) was refluxed for 5 h. The precipitate was filtered and recrystallized from Et₂O−Ligroin to give **5a** (70%) as white crystals; mp 136−138 °C. IR (KBr, cm⁻¹): 1695 (C=O); 1337, 1167 (SO₂). ¹H NMR (DMSO-d_6, δ): 11.26 (bs, 1H, NH); 8.56 (d, 1H, *J* = 3.1 Hz, thiophene); 7.26−7.17 (m, 5H, benzene); 7.01 (d, 1H, *J* = 3.1 Hz, thiophene); 3.92 (t, 2H, *J* = 7.6 Hz, CH₂N); 2.90 (t, 2H, *J* = 7.6 Hz, CH₂). EI-MS, *m/z*: 308 (M⁺). Anal. (C₁₃H₁₂N₂O₃S₂) C, H, N, S.

2-Picolyl-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]-thiadiazine (5b). Yield: 85%; mp 210−212 °C (EtOH). IR (KBr, cm⁻¹): 1705 (C=O); 1335, 1170 (SO₂). ¹H NMR (DMSO-d_6, δ): 8.59 (d, 1H, *J* = 3.2 Hz, thiophene); 8.46 (ddd, 1H, *J* = 4.8 Hz, *J* = 1.7 Hz, *J* = 1.0 Hz, pyridine H-3′); 7.75 (dt, 1H, *J* = 7.7 Hz, *J* = 1.7 Hz, pyridine H-5′); 7.29 (d, 1H, *J* = 7.9 Hz, pyridine H-6′); 7.25 (ddd, 1H, *J* = 7.4 Hz, *J* = 4.8 Hz, *J* = 1.0 Hz, pyridine H-4′); 7.06 (d, 1H, *J* = 3.2 Hz, thiophene); 5.02 (s, 2H, CH₂). EI-MS, *m/z*: 295 (M⁺). Anal. (C₁₁H₉N₃O₃S₂) C, H, N, S.

2-(3-Picolyl)-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]-thiadiazine (5c). To a solution of compound **3c** (0.64 g, 2.0 mmol) in 2 N nitric acid (7 mL) was added dropwise a solution of sodium nitrite (0.27 g) in water (0.5 mL), maintaining the temperature below 10 °C. The reaction mixture was stirred at this temperature for 2 h, and then it was extracted three times with toluene. The organic extracts were combined, washed with water, and dried. The solution was filtered and refluxed for 5 h. The solvent was evaporated at reduced pressure, and the residue was recrystallized to yield **5c** (51%); mp 192−194 °C (acetonitrile). IR (KBr, cm⁻¹): 1695 (C=O); 1340, 1180 (SO₂). ¹H NMR (DMSO-d_6, δ): 11.40 (bs, 1H, NH); 8.64 (d, 1H, *J* = 3.2 Hz, thiophene); 8.56 (d, 1H, $J_{2'4'}$ = 2.0 Hz, pyridine H-2′); 8.48 (dd, 1H, $J_{6'5'}$ = 4.9 Hz, $J_{6'4'}$ = 1.5 Hz, pyridine H-6′); 7.73 (dt, 1H, $J_{4'3'}$ = 7.8 Hz, $J_{4'2'}$ = $J_{4'6'}$ = 1.9 Hz, pyridine H-4′); 7.37 (dd, 1H, $J_{4'5'}$ = 7.8 Hz, $J_{5'6'}$ = 4.9 Hz,

pyridine H-5′); 7.05 (d, 1H, J = 3.2 Hz, thiophene); 4.96 (s, 2H, CH$_2$). EI-MS, m/z: 295 (M$^+$). Anal. (C$_{11}$H$_9$N$_3$O$_3$S$_2$) C, H, N, S.

2-(*N*-Benzylsulfamoyl)-5-chlorothiophene (6). To a solution of 5-chloro-2-chlorosulfonylthiophene (6.0 g, 30 mmol) in THF (10 mL) was added a solution of benzylamine (6.30 mL, 60 mmol) in THF (3 mL), maintaining the temperature below 10 °C. The reaction mixture was stirred at room temperature for 1 h, and then it was refluxed for 30 min. After cooling, the precipitate was filtered and washed with ethyl ether. The filtrate was washed with 2 N HCl and water, and the organic layer was dried (Na$_2$SO$_4$) and concentrated in vacuo. Recrystallization of the residue gave **6** (6.97 g, 88%) as a white solid; mp 81–83 °C (EtOH–H$_2$O). IR (KBr, cm^{-1}): 3290, 3270 (NH); 1330, 1155 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.51 (bs, 1H, exchange with D$_2$O, NH); 7.44 (d, 1H, J = 4.0 Hz, thiophene); 7,27 (m, 5H, benzene); 7.20 (d, 1H, J = 4.0 Hz, thiophene); 4.10 (s, 2H, CH$_2$). Anal. (C$_{11}$H$_{10}$ClNO$_2$S$_2$) C, H, N, S.

2-(*N*-Benzylsulfamoyl)-5-chlorothiophene-3-carboxylic Acid (7). To a solution of **6** (1.0 g, 3.5 mmol) in dry THF (10 mL), under N$_2$ and at −60 °C, was added dropwise *n*-BuLi (2.5 M solution in hexane) (3.47 mL, 8.7 mmol). The reaction mixture was stirred at −30 °C for 90 min and then was poured over solid CO$_2$. After the mixture was stirred for 2 h, the solvent was evaporated, and the residue was treated with water and acidified with 35% HCl. The mixture was extracted with ethyl ether, and the organic layer was separated, washed with water, and dried (Na$_2$SO$_4$). Removal of the solvent furnished **7** (1.0 g, 88%) which was recrystallized from toluene; mp 152–154 °C. IR (KBr, cm^{-1}): 3350 (NH); 1720, 1700 (C=O); 1335, 1157 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 16.00–10.00 (bs, 1H, exchange with D$_2$O, CO$_2$H); 8.05 (t, 1H, J = 5.5 Hz, exchange with D$_2$O, NH); 7.37 (s, 1H, thiophene); 7.21 (s, 5H, benzene; 4.21 (d, 2H, J = 5.5 Hz, CH$_2$). Anal. (C$_{12}$H$_{10}$ClNO$_4$S$_2$) C, H, N, S.

2-Benzyl-6-chloro-1,1,3-trioxo-2*H*,4*H*-thieno[3,2-*e*][1,2,4]-thiadiazine (8) and 2-Benzyl-5-chloro-1,1,3-trioxo-2,3-dihydro-thieno[3,2-*d*]isothiazole (9). To a suspension of **7** (0.50 g, 1.5 mmol) and diphenylphosphoryl azide (DPPA) (0.21 mL, 1.5 mmol) in dry toluene (15 mL) was added triethylamine (0.21 mL (1.5 mmol). The reaction mixture was stirred at 80 °C for 24 h. The solvent was evaporated in vacuo, and the oily residue was purified by column chromatography (hexane/AcOEt 6:1). The faster moving fractions gave the thienosaccharine **9** (0.12 g, 26%; mp 164–166 °C). IR (KBr, cm^{-1}): 1737 (C=O); 1340, 1180 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 7.76 (s, 1H, thiophene); 7.37–7.31 (m, 5H, benzene); 4.85 (s, 2H, CH$_2$). The slower moving fractions gave the thienothiadiazine **8** (38%) which was recrystallized from EtOH–H$_2$O; mp 187–189 °C. IR (KBr, cm^{-1}): 3230 (NH); 1680 (C=O); 1345, 1185 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 11.20 (bs, 1H, NH); 7.38–7.24 (m, 5H, benzene); 6.99 (s, 1H, thiophene); 4.96 (s, 2H, CH$_2$). EI-MS, m/z: 329 (M$^+$+1). Anal. (C$_{12}$H$_9$ClN$_2$O$_3$S$_2$) C, H, N, S.

General Method for the Synthesis of the 2-Substituted 1,1,3-Trioxo-2*H*,4*H*-hetero[1,2,4]thiadiazine (13–15). To a solution of the previously described 1,1,3-trioxo-2*H*,4*H*-hetero[1,2,4]thiadiazine[11] **10**–**12** (1 equiv) in dry DMF, under N$_2$, was added slowly sodium hydride (60% dispersion in mineral oil) (1 equiv), maintaining the temperature below 10 °C. After 15 min, the appropriate alkyl halide (1 equiv) was added, and the reaction mixture was stirred at 5–60 °C for 15–48 h. After cooling, the solvent was evaporated to dryness at reduced pressure, and the crude residue was purified by column chromatography or by recrystallization.

2-(*o*-Chlorobenzyl)-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]-thiadiazine (13a). The thiadiazine **10** reacted with 2-chlorobenzyl chloride for 18 h. Yield: 51%; white solid mp 188–190 °C (EtOH). IR (KBr, cm^{-1}): 1695 (C=O); 1330, 1175 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 11.40 (bs, 1H, NH); 8.65 (d, 1H, J = 3.2 Hz, thiophene); 7.49–7.17 (m, 4H, benzene); 7.09 (d, 1H, J = 3.2 Hz, thiophene); 5.00 (s, 2H, CH$_2$). EI-MS, m/z: 328 (M$^+$). Anal. (C$_{12}$H$_9$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-(*m*-Chlorobenzyl)-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*]-[1,2,4]thiadiazine (13b). The thiadiazine **10** reacted with 3-chlorobenzyl bromide for 18 h. The residue was chromatographed (hexane/ethyl acetate 2:1). Yield: 55%; white solid mp 196–198 °C (acetonitrile). IR (KBr, cm^{-1}): 3190 (NH); 1695 (C=O); 1345, 1185 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 11.38 (bs, 1H, NH); 8.63 (d, 1H, J = 3.2 Hz, thiophene); 7.37–7.29 (m, 4H, benzene); 7.05 (d, 1H, J = 3.2 Hz, thiophene); 4.92 (s, 2H, CH$_2$). EI-MS, m/z: 328 (M$^+$). Anal. (C$_{12}$H$_9$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-(*p*-Chlorobenzyl)-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]-thiadiazine (13c). The thiadiazine **10** reacted with 4-chlorobenzyl chloride for 24 h. The residue was chromatographed (hexane/ethyl acetate 3:1). Yield: 61%; white solid mp 164–166 °C (EtOH). IR (KBr, cm^{-1}): 3190 (NH); 1695 (C=O); 1345, 1170 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 11.38 (bs, 1H, NH); 8.62 (d, 1H, J = 3.3 Hz, thiophene); 7.41–7.30 (d, 4H, benzene); 7.03 (d, 1H, J = 3.3 Hz, thiophene); 4.90 (s, 2H, CH$_2$). EI-MS, m/z: 328 (M$^+$). Anal. (C$_{12}$H$_9$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-(2,6-Dichlorobenzyl)-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*]-[1,2,4]thiadiazine (13d). The thiadiazine **10** reacted with 2,6-dichlorobenzyl bromide for 48 h. Yield: 53%; white solid mp 211–213 °C (EtOH). IR (KBr, cm^{-1}): 3200 (NH); 1695 (C=O); 1340, 1180 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 11.33 (bs, 1H, NH); 8.45 (d, 1H, J = 3.1 Hz, thiophene); 7.43–7.28 (m, 3H, benzene); 7.02 (d, 1H, J = 3.1 Hz, thiophene); 5.21 (s, 2H, CH$_2$). EI-MS, m/z: 362 (M$^+$). Anal. (C$_{12}$H$_8$Cl$_2$N$_2$O$_3$S$_2$) C, H, N, S.

2-(*m*-Bromobenzyl)-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*]-[1,2,4]thiadiazine (13e). The thiadiazine **10** reacted with 3-bromobenzyl bromide for 24 h. The residue was chromatographed (dichloromethane). Yield: 48%; white solid mp 182–184 °C (EtOH). IR (KBr, cm^{-1}): 1695 (C=O); 1345, 1182 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 11.50 (bs, 1H, NH); 8.73 (d, 1H, J = 3.2 Hz, thiophene); 7.51–7.28 (m, 4H, benzene); 7.05 (d, 1H, J = 3.2 Hz, thiophene); 4.91 (s, 2H, CH$_2$). EI-MS, m/z: 374 (M$^+$ + 2). Anal. (C$_{12}$H$_9$BrN$_2$O$_3$S$_2$) C, H, N, S.

2-(*m*-Fluorobenzyl)-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*]-[1,2,4]thiadiazine (13f). The thiadiazine **10** reacted with 3-fluorobenzyl bromide for 24 h. The residue was chromatographed (hexane/ethyl acetate 5:1). Yield: 44%; white solid mp 175–177 °C (EtOH). IR (KBr, cm^{-1}): 1700 (C=O); 1340, 1182 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 11.50 (bs, 1H, NH); 8.62 (d, 1H, J = 3.2 Hz, thiophene); 7.41–7.34 (m, 1H, benzene); 7.18–7-07 (m, 3H, benzene); 7.05 (d, 1H, J = 3.2 Hz, thiophene); 4.94 (s, 2H, CH$_2$). EI-MS, m/z: 312 (M$^+$). Anal. (C$_{12}$H$_9$FN$_2$O$_3$S$_2$) C, H, N, S.

2-(3,5-Difluorobenzyl)-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*]-[1,2,4]thiadiazine (13 g). The thiadiazine **10** reacted with 3,5-difluorobenzyl bromide for 24 h. The residue was chromatographed (hexane/ethyl acetate 5:1). Yield: 54%; white solid mp 182–184 °C. IR (KBr, cm^{-1}): 1695 (C=O); 1352, 1183 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 11.00 (bs, 1H, NH); 8.66 (d, 1H, J = 3.2 Hz, thiophene); 7.17–7.02 (m, 4H, thiophene and aromatic); 4.96 (s, 2H, CH$_2$). EI-MS, m/z: 330 (M$^+$). Anal. (C$_{12}$H$_8$F$_2$N$_2$O$_3$S$_2$) C, H, N, S.

2-Benzyl-1,1,3-trioxo-2*H*,4*H*-thieno[2,3-*e*][1,2,4]-thiadiazine (14) and 2,4-Dibenzyl-1,1,3-trioxo-2*H*,4*H*-thieno[2,3-*e*][1,2,4]thiadiazine (17e). The thiadiazine **11** reacted with benzyl bromide for 24 h. Purification of the residue by column chromatography (hexane/AcOEt 3:1) gave from the faster eluting fractions compound **17e** (7.5%); mp 125–127 °C. IR (KBr, cm^{-1}): 1695 (C=O); 1335, 1172 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 7.42–7.25 (m, 12H, thiophene and benzene); 5.18 (s, 2H, CH$_2$); 5.04 (s, 2H, CH$_2$). From the slower moving fractions the 2-benzyl derivative **14** (50%) was obtained; mp 167–169 °C (EtOH–H$_2$O). IR (KBr, cm^{-1}): 1675 (C=O); 1320, 1155 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 7.39–7.20 (m, 7H, thiophene and benzene); 4.93 (s, 2H, CH$_2$). EI-MS, m/z: 395 (M$^+$ + 1). Anal. (C$_{12}$H$_{10}$N$_2$O$_3$S$_2$) C, H, N, S.

2-Benzyl-6-methyl-1,1,3-trioxo-2*H*,4*H*-pyrazolo[4,3-*e*]-[1,2,4]thiadiazine (15). The thiadiazine **12** reacted with benzyl bromide for 24 h to give **15** (38%) as a white solid; mp 209–211 °C (AcOEt). IR (KBr, cm^{-1}): 3200 (NH); 1685 (C=

O); 1325, 1165 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 11.00 (bs, 1H, NH); 7.76 (s, 1H, pyrazole); 7.36−7.21 (m, 5H, benzene); 4.91 (s, 2H, CH$_2$); 3.96 (s, 3H, CH$_3$). EI-MS, *m/z*: 292 (M$^+$). Anal. (C$_{12}$H$_{12}$N$_4$O$_3$S) C, H, N, S.

General Procedure for the Synthesis of 2,4-Disubstituted 1,1,3-Trioxo-2*H*,4*H*-hetero[1,2,4]thiadiazines (16−19). To a solution of the corresponding 2-substituted heterothiadiazine (1 equiv) in dry DMF, under N$_2$, was added slowly sodium hydride (60% dispersion in mineral oil, 1.0−1.5 equiv) maintaining the temperature below 10 °C. After 15 min, the appropriate alkyl halide (1.0−1.2 equiv) was added, and the reaction mixture was stirred for 30−40 h at 50−60 °C. The solvent was evaporated to dryness, and the crude material was filtered, washed with water, dried, and chromatographed or recrystallized from a suitable solvent.

2-Benzyl-4-(2-chlorobenzyl)-1,1,3-trioxo-2*H*,4*H*-thieno-[3,4-*e*][1,2,4]thiadiazine (16a). This compound was obtained (80%) from reaction of 2-benzyl-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine^1 with 2-chlorobenzyl chloride. The crude material was chromatographed (hexane/dichloromethane 2:1); mp 156−158 °C. IR (KBr, cm^{-1}): 1697 (C=O); 1343, 1172 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.73 (d, 1H, J = 3.1 Hz, thiophene); 7.51 (dd, 1H, J = 7.7 Hz, benzene); 7.34−7.22 (m, 8H, thiophene and benzene); 6.98 (d, 1H, J = 7.6 Hz, benzene); 5.23 (s, 2H, CH$_2$); 5.00 (s, 2H, CH$_2$). Anal. (C$_{19}$H$_{15}$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-Benzyl-4-(3-chlorobenzyl)-1,1,3-trioxo-2*H*,4*H*-thieno-[3,4-*e*][1,2,4]thiadiazine (16b). This compound was obtained (75%) from reaction of 2-benzyl-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine^1 with 3-chlorobenzyl bromide. The crude material was chromatographed (hexane/dichloromethane 2:1); mp 148−150 °C. IR (KBr, cm^{-1}): 1693 (C=O); 1345, 1167 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.71 (d, 1H, J = 3.2 Hz, thiophene); 7.38−7.17 (m, 10H, thiophene and benzene); 5.21 (s, 2H, CH$_2$); 5.01 (s, 2H, CH$_2$). Anal. (C$_{19}$H$_{15}$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-Benzyl-4-(4-chlorobenzyl)-1,1,3-trioxo-2*H*,4*H*-thieno-[3,4-*e*][1,2,4]thiadiazine (16c). This compound was obtained (78%) from reaction of 2-benzyl-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine^1 with 4-chlorobenzyl chloride. The crude material was chromatographed (hexane/AcOEt 1:1); mp 135−137 °C. IR (KBr, cm^{-1}): 1692 (C=O); 1345, 1167 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.70 (d, 1H, J = 3.1 Hz, thiophene); 7.41−7.23 (m, 10H, thiophene CH and benzene); 5.19 (s, 2H, CH$_2$); 5.00 (s, 2H, CH$_2$). Anal. (C$_{19}$H$_{15}$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-Benzyl-4-(ethoxycarbonylmethyl)-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine (16d). This compound was obtained (78%) from reaction of 2-benzyl-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine^1 with ethyl bromoacetate. The crude material was chromatographed (dichloromethane); mp 129−131 °C. IR (KBr, cm^{-1}): 1762 (C=O); 1692 (C=O); 1345, 1175 (SO$_2$); 1200 (C−O). ^{1}H NMR (DMSO-d_6, δ): 8.72 (d, 1H, J = 3.2 Hz, thiophene); 7.45 (d, 1H, J = 3.2 Hz, thiophene); 7.30 (m, 5H, benzene); 4.97 (s, 2H, CH$_2$); 4.73 (s, 2H, CH$_2$); 4.12 (q, 2H, J = 7.1 Hz, CH$_2$O); 1.16 (t, 2H, J = 7.1 Hz, CH$_3$). Anal. (C$_{16}$H$_{16}$N$_2$O$_5$S$_2$) C, H, N, S.

2-(2-Chlorobenzyl)-4-methyl-1,1,3-trioxo-2*H*,4*H*-thieno-[3,4-*e*][1,2,4]thiadiazine (16e). This compound was obtained (80%) from reaction of **13a** with methyl iodide; mp 198−200 °C (MeOH). IR (KBr, cm^{-1}):: 1685 (C=O); 1340, 1193 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.73 (d, 1H, J = 3.1 Hz, thiophene); 7.46−7.23 (m, 5H, thiophene and benzene); 5.03 (s, 2H, CH$_2$); 3.41 (s, 3H, CH$_3$). Anal. (C$_{13}$H$_{11}$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-(2-Chlorobenzyl)-4-ethyl-1,1,3-trioxo-2*H*,4*H*-thieno-[3,4-*e*][1,2,4]thiadiazine (16f). This compound was obtained (87%) from reaction of **13a** with ethyl iodide; mp 138−140 °C (MeOH). IR (KBr, cm^{-1}):: 1680 (C=O); 1340, 1190 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.70 (d, 1H, J = 3.2 Hz, thiophene); 7.54 (d, 1H, J = 3.2 Hz, thiophene); 7.48−7.17 (m, 4H, benzene); 5.04 (s, 2H, CH$_2$); 3.97 (q, 2H, J = 7.1 Hz, CH$_2$); 1.21 (t, 3H, J = 7.1 Hz, CH$_3$). Anal. (C$_{14}$H$_{13}$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-(3-Chlorobenzyl)-4-methyl-1,1,3-trioxo-2*H*,4*H*-thieno-[3,4-*e*][1,2,4]thiadiazine (16 g). This compound was obtained (90%) from reaction of **13b** with methyl iodide; mp 188−

190 °C (acetonitrile). IR (KBr, cm^{-1}): 1683 (C=O); 1337, 1192 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.72 (d, 1H, J = 3.2 Hz, thiophene); 7.41 (d, 1H, J = 3.2 Hz, thiophene); 7.38−7.31 (m, 4H, benzene); 4.95 (s, 2H, CH$_2$); 3.39 (s, 3H, CH$_3$). Anal. (C$_{13}$H$_{11}$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-(3-Chlorobenzyl)-4-ethyl-1,1,3-trioxo-2*H*,4*H*-thieno-[3,4-*e*][1,2,4]thiadiazine (16h). This compound was obtained (92%) from reaction of **13b** with ethyl iodide; mp 132−134 °C (acetonitrile). IR (KBr, cm^{-1}): 1670 (C=O); 1340, 1195 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.72 (d, 1H, J = 3.1 Hz, thiophene); 7.52 (d, 1H, J = 3.1 Hz, thiophene); 7.37−7.28 (m, 4H, benzene); 4.95 (s, 2H, CH$_2$); 3.95 (q, 2H, J = 7.0 Hz, CH$_2$); 1.19 (t, 3H, J = 7.0 Hz, CH$_3$). Anal. (C$_{14}$H$_{13}$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-(3-Chlorobenzyl)-4-cyanomethyl-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine (16i). This compound was obtained (80%) from reaction of **13b** with 2-chloroacetonitrile. The crude material was chromatographed (hexane/AcOEt 3:1); mp 188−190 °C. IR (KBr, cm^{-1}): 1695 (C=O); 1345, 1175 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.82 (d, 1H, J = 3.1 Hz, thiophene); 7.64 (d, 1H, J = 3.1 Hz, thiophene); 7.43−7.33 (m, 4H, benzene); 5.15 (s, 2H, CH$_2$); 5.00 (s, 2H, CH$_2$). Anal. (C$_{14}$H$_{10}$ClN$_3$O$_3$S$_2$) C, H, N, S.

2-(3-Chlorobenzyl)-4-propargyl-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine (16j). This compound was obtained (88%) from reaction of **13b** with propargyl bromide. The crude material was chromatographed (hexane/dichloromethane 2:1); mp 137−139 °C. IR (KBr, cm^{-1}): 3300; 1690 (C=O); 1330, 1145 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.74 (d, 1H, J = 3.1 Hz, thiophene); 7.48 (d, 1H, J = 3.1 Hz, thiophene); 7.38−7.29 (m, 4H, benzene); 4.97 (s, 2H, CH$_2$); 4.74 (d, 2H, J = 2.4 Hz, CH$_2$); 3.34 (t, 1H, J = 2.4 Hz, ≡CH). Anal. (C$_{15}$H$_{11}$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-(4-Chlorobenzyl)-4-methyl-1,1,3-trioxo-2*H*,4*H*-thieno-[3,4-*e*][1,2,4]thiadiazine (16k). This compound was obtained (90%) from reaction of **13c** with methyl iodide; mp 179−180 °C (acetonitrile). IR (KBr, cm^{-1}): 1685 (C=O); 1337, 1195 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.71 (d, 1H, J = 3.3 Hz, thiophene); 7.41−7.32 (m, 5H, benzene and thiophene); 4.93 (s, 2H, CH$_2$); 3.36 (s, 3H, CH$_3$). Anal. (C$_{13}$H$_{11}$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-(4-Chlorobenzyl)-4-ethyl-1,1,3-trioxo-2*H*,4*H*-thieno-[3,4-*e*][1,2,4]thiadiazine (16l). This compound was obtained (90%) from reaction of **13c** with ethyl iodide; mp 188−190 °C (acetonitrile). IR (KBr, cm^{-1}): 1692 (C=O); 1320, 1190 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.70 (d, 1H, J = 3.1 Hz, thiophene); 7.51 (d, 1H, J = 3.1 Hz, thiophene); 7.42−7.31 (d, 4H, benzene); 4.93 (s, 2H, CH$_2$); 3.94 (q, 2H, J = 6.9 Hz, CH$_2$); 1.18 (t, 3H, J = 6.9 Hz, CH$_3$). Anal. (C$_{14}$H$_{13}$ClN$_2$O$_3$S$_2$) C, H, N, S.

2-(2,6-Dichlorobenzyl)-4-methyl-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine (16m). This compound was obtained (90%) from reaction of **13d** with methyl iodide; mp 270−272 °C (acetonitrile). IR (KBr, cm^{-1}): 1695 (C=O); 1345, 1190 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.56 (d, 1H, J = 3.1 Hz, thiophene); 7.43−7.31 (m, 4H, benzene and thiophene); 5.22 (s, 2H, CH$_2$); 3.39 (s, 3H, CH$_3$). Anal. (C$_{13}$H$_{10}$Cl$_2$N$_2$O$_3$S$_2$) C, H, N, S.

2-(2,6-Dichlorobenzyl)-4-ethyl-1,1,3-trioxo-2*H*,4*H*-thieno-[3,4-*e*][1,2,4]thiadiazine (16n). This compound was obtained (93%) from reaction of **13d** with ethyl iodide; mp 184−186 °C (acetonitrile). IR (KBr, cm^{-1}): 1692 (C=O); 1345, 1175 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.52 (d, 1H, J = 3.1 Hz, thiophene); 7.49 (d, 1H, J = 3.1 Hz, thiophene); 7.43−7.27 (m, 3H, benzene); 5.25 (s, 2H, CH$_2$); 3.95 (q, 2H, J = 7.0 Hz, CH$_2$); 1.17 (s, 3H, J = 7.0 Hz, CH$_3$). Anal. (C$_{14}$H$_{12}$Cl$_2$N$_2$O$_3$S$_2$) C, H, N, S.

2-(3-Bromobenzyl)-4-cyanomethyl-1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]thiadiazine (16o). This compound was obtained (72%) from reaction of **13e** with 2-chloroacetonitrile. The crude material was chromatographed (dichloromethane); mp 182−184 °C. IR (KBr, cm^{-1}): 1692 (C=O); 1335, 1170 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 8.82 (d, 1H, J = 3.1 Hz, thiophene); 7.65 (d, 1H, J = 3.1 Hz, thiophene); 7.58−7.33 (m,

4H, benzene); 5.15 (s, 2H, CH₂); 5.00 (s, 2H, CH₂). Anal. (C₁₄H₁₀BrN₃O₃S₂) C, H, N, S.

4-Cyanomethyl-2-(3-fluorobenzyl)-1,1,3-trioxo-2H,4H-thieno[3,4-e][1,2,4]thiadiazine (16p). This compound was obtained (65%) from reaction of **13f** with 2-chloroacetonitrile. The crude material was chromatographed (hexane/dichloromethane 1:2); mp 152−153 °C. IR (KBr, cm⁻¹): 1692 (C=O); 1335, 1170 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 8.79 (d, 1H, *J* = 3.1 Hz, thiophene); 7.63 (d, 1H, *J* = 3.1 Hz, thiophene); 7.44−7.36 (m, 1H, benzene); 7.21−7.12 (m, 3H, benzene); 5.14 (s, 2H, CH₂); 5.01 (s, 2H, CH₂). Anal. (C₁₄H₁₀FN₃O₃S₂) C, H, N, S.

4-Cyanomethyl-2-(3,5-difluorobenzyl)-1,1,3-trioxo-2H,4H-thieno[3,4-e][1,2,4]thiadiazine (16q). This compound was obtained (79%) from reaction of **13g** with 2-chloroacetonitrile The crude material was chromatographed (hexane/dichloromethane 1:2); mp 117−119 °C. IR (KBr, cm⁻¹): 1690 (C=O); 1335, 1175 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 8.80 (d, 1H, *J* = 3.1 Hz, thiophene); 7.64 (d, 1H, *J* = 3.1 Hz, thiophene); 7.22−7.04 (m, 3H, benzene); 5.14 (s, 2H, CH₂); 5.02 (s, 2H, CH₂). Anal. (C₁₄H₉F₂N₃O₃S₂) C, H, N, S.

4-Ethyl-2-(2-phenylethyl)-1,1,3-trioxo-2H,4H-thieno[3,4-e][1,2,4]thiadiazine (16r). This compound was obtained (80%) from reaction of **5a** with ethyl iodide. The crude material was chromatographed (dichloromethane); mp 97−98 °C. IR (KBr, cm⁻¹): 1665 (C=O); 1335, 1180 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 8.62 (d, 1H, *J* = 3.2 Hz, thiophene); 7.45 (d, 1H, *J* = 3.2 Hz, thiophene); 7.24−7.11 (m, 5H, benzene); 4.00−3.32 (m, 4H, 2CH₂); 2.89 (t, 2H, *J* = 7.7 Hz, CH₂); 1.16 (t, 3H, *J* = 6.8 Hz, CH₃). Anal. (C₁₅H₁₆N₂O₃S₂) C, H, N, S.

4-Cyanomethyl-2-(2-phenylethyl)-1,1,3-trioxo-2H,4H-thieno[3,4-e][1,2,4]thiadiazine (16s). This compound was obtained (89%) from reaction of **5a** with 2-chloroacetonitrile. The crude material was chromatographed (dichloromethane); mp 144−146 °C. IR (KBr, cm⁻¹): 1692 (C=O); 1335, 1165 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 8.68 (d, 1H, *J* = 3.0 Hz, thiophene); 7.58 (d, 1H, *J* = 3.0 Hz, thiophene); 7.24−7.13 (m, 5H, benzene); 5.11 (s, 2H, CH₂); 3.99 (t, 2H, *J* = 7.7 Hz, CH₂); 2.91 (t, 2H, *J* = 7.7 Hz, CH₂). Anal. (C₁₅H₁₃N₃O₃S₂) C, H, N, S.

4-Benzyl-2-(2-phenylethyl)-1,1,3-trioxo-2H,4H-thieno[3,4-e][1,2,4]thiadiazine (16t). This compound was obtained (85%) from reaction of **5a** with benzyl bromide. The crude material was chromatographed (hexane/AcOEt 6:1); mp 102−103 °C. IR (KBr, cm⁻¹): 1677 (C=O); 1325, 1165 (SO2). ¹H NMR (DMSO-*d*₆, δ): 8.61 (d, 1H, *J* = 3.3 Hz, thiophene); 7.33−7.15 (m, 11H, benzene and thiophene); 5.17 (s, 2H, CH₂); 4.03 (t, 2H, *J* = 7.8 Hz, CH₂); 2.95 (t, 2H, *J* = 7.8 Hz, CH₂). Anal. (C₂₀H₁₈N₂O₃S₂) C, H, N, S.

4-Ethyl-2-picolyl-1,1,3-trioxo-2H,4H-thieno[3,4-e][1,2,4]thiadiazine (16u). This compound was obtained (71%) from reaction of **5b** with ethyl iodide. The crude material was chromatographed (dichloromethane/ethanol 50:1); mp 132−134 °C. IR (KBr, cm⁻¹): 1675 (C=O); 1337, 1165 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 8.67 (d, 1H, *J* = 3.1 Hz, thiophene); 8.45 (ddd, 1H, *J* = 4.9 Hz, *J* = 1.7 Hz, *J* = 0.9 Hz, pyridine H-3′); 7.76 (dt, 1H, *J* = 7.7 Hz, *J* = 1.7 Hz, pyridine H-5′); 7.53 (d, 1H, *J* = 3.1 Hz, thiophene); 7.29 (d, 1H, *J* = 7.7 Hz, pyridine H-6′); 7.27−7.24 (ddd, 1H, *J* = 7.6 Hz, *J* = 4.9 Hz, *J* = 0.9 Hz, pyridine, H-4′); 5.05 (s, 2H, CH₂); 3.97 (q, 2H, *J* = 7.0 Hz, CH₂); 1.21 (t, 3H, *J* = 7.0 Hz, CH₃). Anal. (C₁₃H₁₃N₃O₃S₂) C, H, N, S.

4-Cyanomethyl-2-picolyl-1,1,3-trioxo-2H,4H-thieno[3,4-e][1,2,4]thiadiazine (16v). This compound was obtained (66%) from reaction of **5b** with 2-chloroacetonitrile. The crude material was chromatographed (dichloromethane/ethanol 50:1); mp 167−168 °C. IR (KBr, cm⁻¹): 2320 (CN); 1693 (C=O); 1347, 1167 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 8.74 (d, 1H, *J* = 3.1 Hz, thiophene); 8.44 (ddd, *J* = 4.8 Hz, *J* = 1.8 Hz, *J* = 1.0 Hz, pyridine H-3′); 7.77 (dt, 1H, *J* = 7.7 Hz, *J* = 1.8 Hz, pyridine H-5′); 7.63 (d, 1H, *J* = 3.1 Hz, thiophene); 7.35 (d, 1H, *J* = 7.9 Hz, pyridine H-6′); 7.27 (ddd, 1H, *J* = 7.5 Hz, *J* = 4.8 Hz, pyridine H-4′); 5.14 (s, 2H, CH₂); 5.10 (s, 2H, CH₂). Anal. (C₁₃H₁₀N₄O₃S₂) C, H, N, S.

4-Benzyl-2-picolyl-1,1,3-trioxo-2H,4H-thieno[3,4-e][1,2,4]thiadiazine (16w). This compound was obtained (63%) from reaction of **5b** with benzyl bromide; mp 125−127 °C (MeOH). IR (KBr, cm⁻¹): 1680 (C=O); 1330, 1165 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 8.67 (d, 1H, *J* = 3.2 Hz, thiophene); 8.49 (ddd, 1H, *J* = 4.8 Hz, *J* = 1.8 Hz, *J* = 0.9 Hz, pyridine H-3′); 7.78 (dt, 1H, *J* = 7.7 Hz, *J* = 1.8 Hz, pyridine H-5′); 7.34−7.24 (m, 8H, thiophene, benzene, and pyridine H-6′and H-4′); 5.21 (s, 2H, CH₂); 5.13 (s, 2H, CH₂). Anal. (C₁₈H₁₅N₃O₃S₂) C, H, N, S.

4-Cyanomethyl-2-(3-picolyl)-1,1,3-trioxo-2H,4H-thieno[3,4-e][1,2,4]thiadiazine (16x). This compound was obtained (66%) from reaction of **5c** with 2-chloroacetonitrile. The crude material was chromatographed (dichloromethane/EtOH 100:1); mp 151−153 °C. IR (KBr, cm⁻¹): 1698 (C=O); 1347, 1165 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 8.80 (d, 1H, *J* = 3.1 Hz, thiophene); 8.60 (d, 1H, *J*₂′₄′ = 1.9 Hz, pyridine H-2′); 8.50 (dd, 1H, *J*₆′₄′ = 1.6 Hz, *J*₆′₅′ = 4.7 Hz, pyridine H-6′); 7.77 (ddd, 1H, *J*₄′₅′ = 7.8 Hz, *J*₄′₂′ = 1.9 Hz, *J*₄′₆′ = 1.6 Hz, pyridine H-4′); 7.63 (d, 1H, *J* = 3.1 Hz, thiophene); 7.39 (dd, 1H, *J*₅′₄′ = 7.8 Hz, *J*₅′₆′ = 4.7 Hz, pyridine H-5′); 5.14 (s, 2H, CH₂); 5.03 (s, 2H, CH₂). Anal. (C₁₃H₁₀N₄O₃S₂) C, H, N, S.

2-Benzyl-4-methyl-1,1,3-trioxo-2H,4H-thieno[2,3-e][1,2,4]thiadiazine (17a). This compound was obtained (92%) from reaction of **14** with methyl iodide; mp 156−158 °C (EtOH). IR (KBr, cm⁻¹): 1682 (C=O); 1325, 1145 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 7.45 (d, 2H, thiophene); 7.34−7.20 (m, 5H, benzene); 4.95 (s, 2H, CH₂); 3.44 (s, 3H, CH₃). Anal. (C₁₃H₁₂N₂O₃S₂) C, H, N, S.

2-Benzyl-4-ethyl-1,1,3-trioxo-2H,4H-thieno[2,3-e][1,2,4]thiadiazine (17b). This compound was obtained (92%) from reaction of **14** with ethyl iodide; mp 116−117 °C (EtOH). IR (KBr, cm⁻¹): 1690 (C=O); 1322, 1140 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 7.45 (d, 2H, thiophene); 7.34−7.28 (m, 5H, benzene); 4.97 (s, 2H, CH₂); 3.93 (q, 2H, *J* = 7.1 Hz, CH₂); 1.23 (t, 3H, *J* = 7.1 Hz, CH₃). Anal. (C₁₄H₁₄N₂O₃S₂) C, H, N, S.

2-Benzyl-4-(n-propyl)-1,1,3-trioxo-2H,4H-thieno[2,3-e][1,2,4]thiadiazine (17c). This compound was obtained (90%) from reaction of **14** with n-propyl bromide; mp 139−140 °C (EtOH). IR (KBr, cm⁻¹): 1692 (C=O); 1325 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 7.45 (d, 2H, thiophene); 7.34−7.28 (m, 5H, benzene); 4.97 (s, 2H, CH₂); 3.88 (t, 2H, *J* = 7.2 Hz, CH₂); 1.67 (m, 2H, CH₂); 0.85 (t, 3H, *J* = 7.2 Hz, CH₃). Anal. (C₁₅H₁₆N₂O₃S₂) C, H, N, S.

2-Benzyl-4-cyanomethyl-1,1,3-trioxo-2H,4H-thieno[2,3-e][1,2,4]thiadiazine (17d). This compound was obtained (75%) from reaction of **14** with 2-chloroacetonitrile; mp 140−142 °C (EtOH). IR (KBr, cm⁻¹): 1705 (C=O); 1335, 1180 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 7.56 (d, 1H, *J* = 5.7 Hz, thiophene); 7.51 (d, 1H, *J* = 5.7 Hz, thiophene); 7.38−7.28 (m, 5H, benzene); 5.18 (s, 2H, CH₂); 5.01 (s, 2H, CH₂). Anal. (C₁₄H₁₁N₃O₃S₂) C, H, N, S.

2-Benzyl-4,6-dimethyl-1,1,3-trioxo-2H,4H-pyrazolo[4,3-e][1,2,4]thiadiazine (18a). This compound was obtained (86%) from reaction of **15** with methyl iodide; mp 147−149 °C (AcOEt−hexane). IR (KBr, cm⁻¹): 1695 (C=O); 1360, 1180 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 8.10 (s, 1H, pyrazole); 7.34−7.25 (m, 5H, benzene); 4.95 (s, 2H, CH₂); 4.00 (s, 3H, CH₃); 3.30 (s, 3H, CH₃). Anal. (C₁₃H₁₄N₄O₃S) C, H, N, S.

2-Benzyl-4-ethyl-6-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,3-e][1,2,4]thiadiazine (18b). This compound was obtained (80%) from reaction of **15** with ethyl iodide; mp 132−134 °C (AcOEt−hexane). IR (KBr, cm⁻¹): 1680 (C=O); 1322, 1180 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 8.19 (s, 1H, pyrazole); 7.30 (s, 5H, benzene); 4.95 (s, 2H, CH₂); 3.99 (s, 3H, CH₃); 3.79 (q, 2H, *J* = 7.0 Hz, CH₂); 1.14 (t, 3H, *J* = 7.0 Hz, CH₃). Anal. (C₁₄H₁₆N₄O₃S) C, H, N, S.

2-Benzyl-6-chloro-4-cyanomethyl-1,1,3-trioxo-2H,4H-thieno[3,2-e][1,2,4]thiadiazine (19a). This compound was obtained (66%) from reaction of **8** with 2-chloroacetonitrile; mp 143−145 °C (MeOH). IR (KBr, cm⁻¹): 1695 (C=O); 1355, 1175 (SO₂). ¹H NMR (DMSO-*d*₆, δ): 7.79 (s, 1H, thiophene); 7.37−7.35 (m, 5H, benzene); 5.14 (s, 2H, CH₂); 5.02 (s, 2H, CH₂). Anal. (C₁₄H₁₀ClN₃O₃S₂) C, H, N, S.

6-Chloro-2,4-dibenzyl-1,1,3-trioxo-2*H*,4*H*-thieno[3,2-*e*]-[1,2,4]thiadiazine (19b). This compound was obtained (78%) from reaction of **8** with benzyl bromide; mp 132−133 °C (MeOH). IR (KBr, cm^{-1}): 1677 (C=O); 1340, 1185 (SO$_2$). ^{1}H NMR (DMSO-d_6, δ): 7.56 (s, 1H, thiophene); 7.39−7.18 (m, 10H, benzene); 5.25 (s, 2H, CH$_2$); 5.05 (s, 2H, CH$_2$). Anal. (C$_{19}$H$_{15}$ClN$_2$O$_3$S$_2$) C, H, N, S.

References

(1) Arranz, M. E.; Díaz, J. A.; Ingate, S. T.; Witvrouw, M.; Pannecouque, C.; Balzarini, J.; De Clercq, Vega, S. Synthesis and anti-HIV activity of 1,1,3-trioxo-2*H*,4*H*-thieno[3,4-*e*][1,2,4]-thiadiazines (TTD): A new family of HIV-1 specific nonnucleoside reverse transcriptase inhibitors. *J. Med. Chem.* submitted for publication.

(2) Romero, D. L.; Busso, M.; Tan, C.-K.; Reusser, F.; Palmer, J. R.; Poppe, S. M.; Aristoff, P. A.; Downey, K. M.; So, A. G.; Resnick, L.; Tarpley, W. G. Nonnucleoside reverse transcriptase inhibitors that potently and specifically block human immunodeficiency virus type 1 replication. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 8806−8810.

(3) Ahgren, C.; Backro, K.; Bell, F. W.; Cantrell, A. S.; Clemens, M.; Colacino, J. M.; Deeter, J. B.; Engelhardt, J. A.; Hogberg, M.; Jaskunas, S. R.; Johansson, N. G.; Jordan, C. L.; Kasher, J. S.; Kinnick, M. D.; Lind, P.; Lopez, C.; Morin, J. M.; Muesing, M. A.; Noreen, R.; Oberg, B.; Paget, C. J.; Palkowitz, J. A.; Parrish, C. A.; Pranc, P.; Rippy, M. K.; Rydergard, C.; Sahlberg, C.; Swanson, S.; Ternansky, R. J.; Unge, T.; Vasileff, R. T.; Vrang, L.; West, S. J.; Zhang, H.; Zhou, X.-X. The PETT series, a new class of potent nonnucleoside inhibitors of human immunodeficiency virus type 1 reverse transcriptase. *Antimicrob. Agents Chemother.* **1995**, *39*, 1329−1335.

(4) Pauwels, R.; Andries, K.; Debyser, Z.; Van Daele, P.; Schols, D.; Stoffels, P.; De Vreese, K.; Woestenborghs, R.; Vandamme, A.-M.; Janssen, C. G. M.; Anné, J.; Cauwenberg, G.; Desmyter, J.; Heykants, J.; Janssen, M. A. C.; De Clercq, E. Janssen, P. A. J. Potent highly selective human immunodeficiency virus type 1 (HIV-1) inhibition by a series of α-anilinophenylacetamide derivatives targeted at HIV-1 reverse transcriptase. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 1711−1715.

(5) Merluzzi, V. J.; Hargrave, K. D.; Labadia, M.; Grozinger, K.; Skoog, M.; Wu, J. C.; Shih, C.-K.; Eckner, K.; Hattox, S.; Adams, J.; Rosenthal, A. S.; Faanes, R.; Eckner, R. J.; Koup, R. A.; Sullivan, J. L. Inhibition of HIV-1 replication by a nonnucleoside reverse transcriptase inhibitor. *Science* **1990**, *250*, 1411−1413.

(6) De Clercq, E. What can be expected from nonnucleoside reverse transcriptase inhibitors (NNRTIs) in the treatment of human immunodeficiency virus type 1 (HIV-1) infections? *Rev. Med. Virol.* **1996**, *6*, 97−117.

(7) De Clercq, E. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) for the treatment of human immunodeficiency virus type 1 (HIV-1) infections: strategies to overcome drug resistance development. *Med. Res. Rev.* **1996**, *16*, 125−157.

(8) Witvrouw, M.; Arranz, M. E.; Pannecouque, C.; Declercq, R.; Jonckheere, H.; Schmit, J.-C.; Vandamme, A.-M.; Díaz, J. A.; Ingate, S. T.; Desmyter, J.; Esnouf, R.; Van Meervelt, L.; Vega, S.; Balzarini, J.; De Clercq, E. 1,1,3-Trioxo-2*H*,4*H*-thieno[3,4-*e*]-[1,2,4]thiadiazines (TTD) derivatives: A new class of nonnucleoside HIV-1 reverse transcriptase inhibitors (NNRTIs) with anti-HIV-1 activity. *Antimicrob. Agents Chemother.* **1998**, *42*, 618−623.

(9) Ren, J.; Esnouf, R.; Garman, E.; Somers, D.; Ross, C.; Kirby, I.; Keeling, J.; Darby, G.; Jones, Y.; Stuart, D.; Stammers, D. High-resolution structures of HIV-1 RT from four RT-inhibitor complexes. *Nature Struct. Biol.* **1995**, *2*, 293−302.

(10) Weigert, F. J.; Roberts, J. D. Nuclear Magnetic resonance spectroscopy. Carbon−carbon coupling in cyclopropane derivatives. *J. Am. Chem. Soc.* **1967**, *89*, 5962−5963.

(11) Arranz, M. E.; Vega, S.; Díaz, J. A. Synthesis of hetero[1,2,4]thiadiazine 1,1-dioxides. *Heterocycles* **1997**, *45*, 1767−1774.

(12) Banthorpe, D. V. Rearrangements involving azido groups. In *The Chemistry of Azido Group;* Patai, S., Ed.; Interscience Publishers: London, 1971; pp 397−440.

(13) Shioiri, T. Degradation reactions. In *Comprehensive Organic Synthesis, Selectivity, Strategy and Efficiency in Modern Organic Chemistry,* 1st ed.; Trost, M. T., Fleming, I., Winterfeldt, E., Eds.; Pergamon Press Inc.: London, 1991; pp 795−827.

(14) Shoiri, T.; Ninomiya, K.; Yamada, S. Diphenylphosphoryl azide. A new convenient reagent for a modified Curtius raction and for the peptide synthesis. *J. Am. Chem. Soc.* **1972**, *94*, 6203−6205.

(15) Ninomiya, Shoiri, T.; K.; Yamada, S. Phosphorus in organic synthesis. Diphenylphosphorazidate (DPPA). A new convenient reagent for modified Curtius ractions. *Tetrahedron,* **1974**, *30*, 2151−2157.

(16) Unterhalt, B.; Moghaddam, S. 2,3-Dihydro-3-oxo-thienoisothiazol-1,1-dioxide und ihre 3-thioxo-verbindungen. *Pharmazie* **1994**, *49*, 115−117.

(17) Pauwels, R.; Andries, K.; Debyser, Z.; Kukla, M. J.; Schols, D.; Breslin, H. J.; Woestenborghs, R.; Desmyter, J.; Janssen, M. A. C.; De Clercq, E. Janssen, P. A. J. New tetraimidazo[4,5,1-*jk*]-[1,4]benzodiazepin-2(1H)-one and -thione derivatives are potent inhibitors of human immunodeficiency virus type 1 replication and are synergistic with 2′,3′-dideoxynucleoside analogues. *Antimicrob. Agents Chemother.* **1994**, *38*, 2863−2870.