

Full Paper

Regioselective Synthesis of Novel N_2 - and N_4 -Substituted 7-Methylpyrazolo[4,5-*e*][1,2,4]thiadiazines

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Abstract: The new compound 7-methylpyrazolo[4,5-*e*][1,2,4]thiadiazin-3(2*H*,4*H*)-one 1,1-dioxide (**5**) was synthesized and its novel mono N_2 - or N_4 -substituted derivatives **6** and **7** were prepared by regioselective *N*-alkylation of **5** with different molar ratios of NaH and alkyl halides. Based on the regioselective alkylation conditions found a facile one-pot synthesis of N_2,N_4 -disubstituted pyrazolo[4,5-*e*][1,2,4] thiadiazines **8** was developed. The structures of the newly synthesized compounds were confirmed by IR, ¹H-NMR, ¹³C-NMR and MS spectral analysis.

Keywords: Pyrazolothiadiazines, regioselectivity, synthesis, alkylation, one-pot reaction

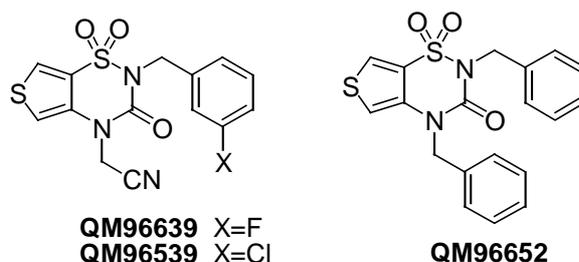
Introduction

Benzo/heterothiadiazine derivatives have become of particular interest to chemists and biologists because of their broad spectrum of biological activities and potential pharmacological applications. For example, 1,2,4-benzothiadiazines, such as chlorothiazide and diazoxide, are widely used as diuretic and antihypertensive drugs, respectively [1, 2]. Heterocycle-fused thiadiazine derivatives, such as

pyrido-, pyrazino-, imidazo- and triazolothiadiazines, show unique potential for the treatment of cerebro- and cardiovascular diseases, cognitive disorders, cancers, viral and bacterial infections [3-6].

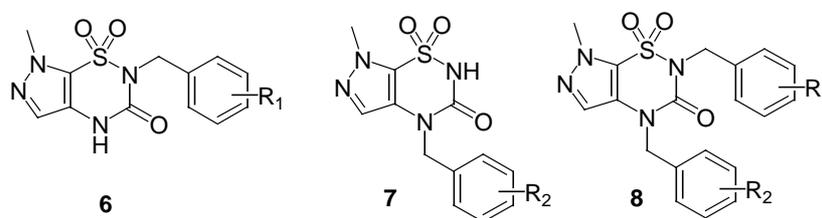
We recently reported the design and synthesis of 2,4-disubstituted thieno[3,4-*e*][1,2,4] thiadiazine derivatives (TTDs) [7], which selectively block HIV-1 replication at the reverse transcriptase step. The lead compounds QM96639, QM96539 and QM96652 (Figure 1) showed highly potent activity and selectivity against HIV-1 replication in cell culture at low concentration ranges (IC_{50} 0.05-0.10 μ M) [8,9].

Figure 1.



In continuation of our research, we decided to undertake a study of the pyrazole series, specifically regarding the 7-methylpyrazolo[4,5-*e*][1,2,4]thiadiazines, because of the known thiophene-pyrazole bioisosterism [10]. In this paper, we report the preparation of the new regioisomer 7-methylpyrazolo [4,5-*e*][1,2,4]thiadiazine (**5**) and its novel mono N_2 - or N_4 - substituted derivatives **6** and **7** by regioselective alkylation, as well as the one-pot synthesis of N_2 , N_4 -disubstituted 7-methylpyrazolo [4,5-*e*][1,2,4] thiadiazines **8** (Figure 2).

Figure 2



Results and Discussion

7-Methylpyrazolo[4,5-*e*][1,2,4]thiadiazin-3(2*H*, 4*H*)-one 1,1-dioxide (**5**) was synthesized in a similar manner to the thiophene and regioisomeric pyrazole series [7], by a route which started with hydrazinolysis of ethyl 1-methyl-5-sulfamoylpyrazole-4-carboxylate (**1**), a commercially available product, with hydrazine hydrate in refluxing ethanol, thus forming the hydrazide **2** in excellent yield. Carboxy azide **3**, which was obtained by the reaction of compound **2** with sodium nitrite in diluted hydrochloric acid at ca. 10°C, was pure enough for use in the next ring closure step without further purification. Thus, by refluxing compound **3** in anhydrous toluene, a classical Curtius rearrangement took place through the intermediacy of isocyanate **4** to afford compound **5**, a new regioisomer of 6-methylpyrazolo[4,5-*e*][1,2,4]thiadiazin-3(2*H*, 4*H*)-one 1,1-dioxide prepared by our previous work [7]. (Scheme 1). Structural assignments for the ring system in **5** were based on its 1 H- and 13 C-NMR, IR and MS spectral analysis.

The method used for the regioselective preparation of the new N_2 -substituted 7-methylpyrazolo[4,5-*e*][1,2,4]thiadiazine derivatives **6** paralleled that described in ref. [8], including deprotonation of the **5** using one equivalent of sodium hydride in DMF solvent at a temperature below 5°C, and followed by alkylation with one equivalent of alkyl halide at 80°C for 2-8 h, thus giving the mono N_2 -substituted derivatives **6** (Scheme 2). The crude products were separated by flash column chromatography and purified by recrystallization from ethanol in good yields (81-85%, Table 1).

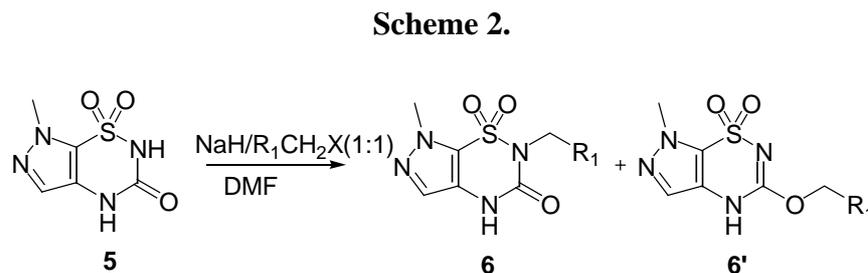
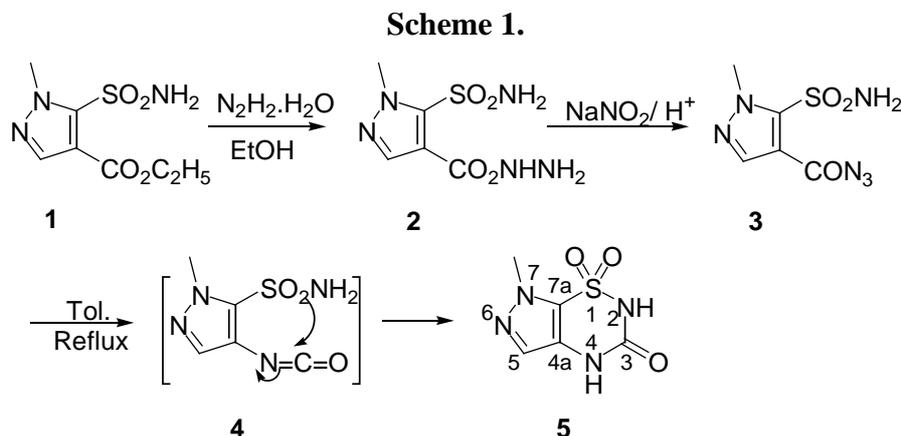


Table 1. N_2 -substituted derivatives **6a-d** and *O*-alkylated derivatives **6'a-d** of 7-methylpyrazolo[4,5-*e*][1,2,4]thiadiazin-3(2*H*,4*H*)-one 1,1-dioxide (**5**).

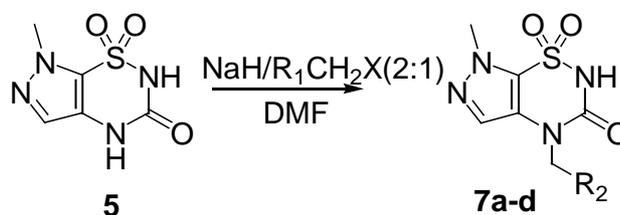
Entry	N_2 -/ <i>O</i> - CH_2R_1	Yield %	mp(°C)	δCH_2
5	H	75	216-218	—
6a	benzyl	81	175-177	5.06
6b	4-Cl-benzyl	80	192-194	4.95
6c	4-Br-benzyl	83	220-222	4.94
6d	3-Cl-benzyl	81	187-188	4.97
6'a	benzyl	12	215-216	5.40
6'b	4-Cl-benzy	14	238-240	5.34
6'c	4-Br-benzyl	13	246-248	5.34
6'd	3-Cl-benzyl	16	224-227	5.36

Under these conditions compounds **6** were the predominant products, mainly due to the more acidic nature of the hydrogen at the N_2 position and the resulting easier deprotonation than the hydrogen at the N_4 position, which is caused by the strong electric withdraw effect by the sulfonyl group. Meanwhile, the isomeric 3-*O*-alkylated pyrazolo[4,5-*e*][1,2,4]thiadiazine **6'** was observed as a

side product in approximately 15% yields, which is attributed to the tautomerism between the nitrogen anion and the carbonyl-oxygen anion. The O-alkylated isomers **6'a-d** have not been reported so far. In the $^1\text{H-NMR}$ spectra, the chemical shifts of the O-CH₂ groups are distinguished from that of mono *N*₂- or *N*₄-alkylated derivatives, while linking with the same substituent (Table 1 and Table 2, *e.g.* benzyl group, *N*₂-CH₂, δ 5.06; *N*₄-CH₂, δ 4.90; 3-*O*-CH₂, δ 5.40).

During our ongoing research on the alkylation reaction of the compound **5**, we used 2 equivalents of base rather than only one, in order to perform double deprotonation of **5**. Quenching of the disodium salt with one equivalent of the electrophile, we observed complete regioselectivity of the reaction, since only the *N*₄-alkylated regioisomers **7** were produced, and none of *N*₂-substituted compounds **6** was found. We speculate that the stronger nucleophilicity of *N*₄ anion allowed a preferential *N*₄ alkylation. We also deduced that the relatively high steric hindrance afforded by the 1-sulfonyl and 3-carbonyl groups further disfavored the alkylation at *N*₂ site.

Scheme 3.



The *N*₄-alkylated product was confirmed by the chemical shift of the CH₂ signal, and by means of NOE experiments and HMBC sequences to establish long-distance proton/carbon correlations. It was shown that the *N*₄-CH₂ correlated exclusively with the both quaternary carbon C-3 and C-4a, which is different from the *N*₂-CH₂, that only correlated with quaternary carbon C-3. A series of *N*₄-alkylated derivatives **7a-d** were prepared in high yield (80-86%) and the results were shown in Table 2.

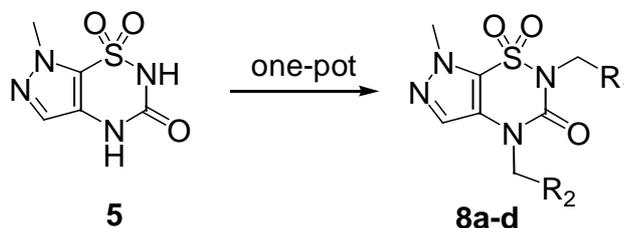
Table 2. *N*₄-substituted-7-methylpyrazolo[4,5-][1,2,4]thiadiazin-3(2*H*,4*H*)-one 1,1-dioxides.

Entry	<i>N</i> ₄ -CH ₂ R ₂	Yield %	Mp (°C)	δCH_2
7a	benzyl	85	187-189	4.90
7b	4-Cl-benzyl	84	218-230	4.86
7c	4-Br-benzyl	86	240-242	4.85
7d	3-Cl-benzyl	81	194-196	4.88

*N*₂,*N*₄-Disubstituted hetero[1,2,4]thiadiazines with different substituents are usually prepared by stepwise alkylation, first at *N*₂ and then at *N*₄ [7,9]. Using to the aforementioned regioselective alkylation method, *N*₂,*N*₄-disubstituted derivatives **8** were synthesized in a one-pot reaction, by addition of two equivalents of NaH and one equivalent of R₂CH₂X first, followed by addition of one equivalent of R₁CH₂X when the synthesis of intermediate **7** (monitored by TLC) was shown to be finished. The crude products **8** were obtained and purified by recrystallization to give white solids in ca. 80% yield (Scheme 4). A series of *N*₂,*N*₄-dialkylated derivatives **8a-d** was prepared by this method

and are listed in Table 3. The structures of all synthesized compounds were confirmed by ^1H - and ^{13}C -NMR, IR and MS spectroscopic analysis.

Scheme 4.



Reagents: (1)NaH/R₂CH₂X (2:1); (2)R₁CH₂X(1eq)

Table 3. *N*₂,*N*₄-substituted-7-methylpyrazolo[4,5-*e*][1,2,4]thiadiazine-3(2*H*,4*H*)-one 1,1-dioxides **8a-d**.

Entry	<i>N</i> ₂ -CH ₂ R ₁	<i>N</i> ₄ -CH ₂ R ₂	Yield %	mp(°C)	δ _{<i>N</i>₂-CH₂}	δ _{<i>N</i>₄-CH₂}
8a	benzyl	2-Br-benzyl	82	107-108	5.17	5.14
8b	benzyl	2-Cl-benzyl	80	105-107	5.19	5.13
8c	4-Cl-benzyl	2-Br-benzyl	81	129-131	5.15	5.08
8d	4-Cl-benzyl	2-Cl-benzyl	79	117-119	5.15	5.02

Conclusions

In summary, we have synthesized the new regioisomer 7-methylpyrazolo[4,5-*e*][1,2,4]thiadiazin-3(2*H*,4*H*)-one 1,1-dioxide **5** and studied its regioselective *N*-alkylation reactions. In the preparation of *N*₂-substituted pyrazolo[4,5-*e*][1,2,4]thiadiazines **6**, we observed that formation of their *O*₃-alkylated isomers **6'** accompanied the reaction, which often went undetected and thus probably unreported previously. We have also developed an efficient, regioselective alkylation at the *N*₄ site of **5** by use of a 2:1 molar ratio of NaH and alkyl halide. The achieved conditions for the regioselective *N*-alkylation were used to efficiently prepare the *N*₂,*N*₄-dialkylated derivatives **8** by a facile one-pot reaction. This method can be used for the synthesis of other mono *N*₂- and *N*₄- or *N*₂, *N*₄-disubstituted heterocycle-fused 1,2,4-thiadiazine derivatives.

Experimental Section

General

All melting points were determined on a micromelting point apparatus and are uncorrected. ^1H -NMR (600 MHz) and ^{13}C -NMR (150 MHz) spectra were obtained on a Bruker Avance-600 instrument in the indicated solvent. Chemical shifts are expressed in δ units and TMS as internal reference. Infrared spectra (IR) were recorded with a Nexus 470FT-IR Spectrometer. Mass spectra were taken on a LC Autosampler Device: Standard G1313A instrument. Flash column chromatography was performed on column packed with silica gel 60 (230-400 mesh). Solvents were reagent grade and

when necessary, were purified and dried by standard methods. Concentration of the reaction solutions involved the use of a rotary evaporator under reduced pressure.

Synthesis of 7-Methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-e][1,2,4]thiadiazine (**5**)

The synthesis was carried out in analogy to the preparation of the corresponding thieno[3,4-e][1,2,4]thiadiazine and the regioisomeric 6-methylpyrazo[3,4-e][1,2,4]thiadiazine derivatives [7,8]. Recrystallization from ethanol gave a white solid. IR (KBr, cm^{-1}): 3244, 3152 (NH); 3014 (Py-CH); 1692 (C=O); 1342, 1141 (SO_2); $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 11.49 (s, 1H, exchanged with deuterium by D_2O addition, NH); 7.40 (s, 1H, Py-CH); 3.94 (s, 3H, CH_3); $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$) δ : 152.4 (C=O), 125.3 (C-5), 124.3 (C-4a), 123.4 (C-7a), 38.3 (CH_3); MS (EI) m/z : 202.2 (M^+); Anal. calcd for $\text{C}_5\text{H}_6\text{N}_4\text{O}_3\text{S}$: C, 29.70; H, 2.99; N, 27.71; Found: C 29.76; H 3.03; N 27.66.

General Procedure for the Preparation of 2-Substituted-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-e][1,2,4]thiadiazines **6a-d** and 3-Substituted-7-methyl-1,1-dioxo-4H-pyrazolo[4,5-e][1,2,4]thiadiazines **6'a-d**

To a solution of compound **5** (1 equiv.) in dry DMF (4 mL) was added sodium hydride (60% dispersion in mineral oil, 1 equiv.) in portions, under an inert atmosphere (N_2), while the temperature was kept below 10°C . After stirring for 15 min, the alkyl halide (1 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 20 min and at $30\text{--}50^\circ\text{C}$ for 12–20 h (checked by TLC). After the solvent was evaporated under reduced pressure, the products were separated by flash column chromatography (1:3 ethyl acetate/cyclohexane) to give the compounds **6** and **6'** respectively, which were purified by recrystallization from ethanol.

2-Benzyl-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-e][1,2,4]thiadiazine (6a) and 3-Benzyloxy-7-methyl-1,1-dioxo-4H-pyrazolo[4,5-e][1,2,4]thiadiazine (6'a). Compound **5** was alkylated with benzyl bromide at 30°C for 12 h to give **6a** and **6'a**, which after purification gave white solids: **6a**: IR (KBr, cm^{-1}): 3266 (NH); 1693 (C=O); 1328, 1197 (SO_2); $^1\text{H-NMR}$ (CDCl_3) δ : 9.09 (s, 1H, NH), 7.20 (s, 1H, PyH), 7.49 (d, 2H, $J=7.31$, PhH), 7.29–7.36 (m, 3H, PhH), 5.06 (s, 2H, NCH_2), 4.13 (s, 3H, CH_3); $^{13}\text{C-NMR}$ (CDCl_3) δ : 150.3 (C=O), 135.4 (C-1'), 128.7, 128.5, 128.1, 125.0 (C-4a), 123.0 (C-5), 122.1 (C-7a), 44.0 ($\text{N}_2\text{-CH}_2$), 39.0 (CH_3); MS (EI): m/z 293.3 ($\text{M}+1$); **6'a**: IR (KBr, cm^{-1}): 3276 (NH); 1614 (C=N); 1300, 1176 (SO_2); $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 12.33 (s, 1H, NH), 7.49 (s, 1H, PyH), 7.64 (dd, 1H, $J=7.34\text{Hz}$, $J=1.85\text{Hz}$, PhH), 7.55 (dd, 1H, $J=7.73$, $J=1.16$, PhH), 7.42–7.46 (m, 3H, PhH), 5.40 (s, 2H, NCH_2), 3.98 (s, 3H, CH_3); $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$) 151.7 (C=N), 133.4 (C-1'), 132.4, 131.4, 131.0, 129.7, 127.7, 125.5 (C-4a), 123.9 (C-5), 123.4 (C-7a), 68.0 (O- CH_2), 38.4 (CH_3); MS (EI): m/z 292.3 (M^+).

2-(p-Chlorobenzyl)-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-e][1,2,4]thiadiazine (6b) and 3-(p-chlorobenzyloxy)-7-methyl-1,1-dioxo-4H-pyrazolo[4,5-e][1,2,4]thiadiazine (6'b). Reaction of compound **5** and 4-chlorobenzyl chloride at 50°C for 20 h gave compounds **6b** and **6'b** as white solids after purification. **6b**: IR (KBr, cm^{-1}): 3225 (NH), 1682 (C=O), 1334, 1185 (SO_2); $^1\text{H-NMR}$ (DMSO-

*d*₆) δ : 11.37 (s, 1H, NH), 7.45 (s, 1H, PyH), 7.36-7.41 (m, 4H, PhH), 4.95 (s, 2H, NCH₂), 4.03 (s, 3H, CH₃); ¹³C-NMR (DMSO-*d*₆) δ : 148.8 (C=O), 135.6 (C-1'), 132.4, 129.9, 128.6, 125.7 (C-4a), 123.8 (C-5), 121.4 (C-7a), 42.3 (N₂-CH₂), 38.9 (CH₃); MS(EI): m/z 327.3 (M+1); **6'b**: IR (KBr, cm⁻¹): 3242 (NH); 1610 (C=N); 1290, 1176(SO₂); ¹H-NMR (DMSO-*d*₆) δ : 12.32 (s, 1H, NH), 7.53 (s, 1H, PyH), 7.48-7.51 (m, 4H, PhH), 5.34 (s, 2H, NCH₂), 3.96 (s, 3H, CH₃); ¹³C-NMR (DMSO-*d*₆): 151.9 (C=N), 134.1 (C-1'), 133.5, 130.7, 128.8, 125.6 (C-4a), 124.0 (C-5), 123.6 (C-7a), 69.7 (O-CH₂), 38.4 (CH₃); MS (EI): m/z 327.3 (M+1).

2-(*p*-Bromobenzyl)-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-*e*][1,2,4]thiadiazine (**6c**) and 3-(*p*-Bromobenzyloxy)-7-methyl-1,1-dioxo-4H-pyrazolo[4,5-*e*][1,2,4]thiadiazine (**6'c**). Compound **5** and 4-bromobenzyl bromide at 30°C for 12 h gave after purification compounds **6c** and **6'c** as white solids. **6c**: IR (KBr, cm⁻¹): 3302 (NH); 1686 (C=O); 1364, 1197(SO₂); ¹H-NMR (DMSO-*d*₆) δ : 11.28 (s, 1H, NH), 7.43 (s, 1H, PyH), 7.53 (d, 2H, *J*=7.91, PhH), 7.31 (d, 2H, *J*=7.70, PhH), 4.94 (s, 2H, NCH₂), 4.03 (s, 3H, CH₃); ¹³C-NMR (DMSO-*d*₆) δ : 148.7 (C=O), 136.0 (C-1'), 131.4, 130.0, 125.6, 123.8 (C-4a), 121.3 (C-5), 120.1 (C-7a), 42.3 (N₂-CH₂), 38.8 (CH₃); MS (EI): m/z 373.1 (M+2), 371.2 (M⁺); **6'c**: IR (KBr, cm⁻¹): 3292(NH); 1605(C=N); 1274, 1173 (SO₂); ¹H-NMR (DMSO-*d*₆) δ : 12.24 (s, 1H, NH), 7.47 (s, 1H, PyH), 7.62 (d, 2H, *J*=7.33, PhH), 7.45 (d, 2H, *J*=7.44, PhH), 5.34 (s, 2H, NCH₂), 3.96 (s, 3H, CH₃); ¹³C-NMR (DMSO-*d*₆) δ : 151.8 (C=N), 134.4 (C-1'), 131.6, 130.8, 125.5, 123.9 (C-4a), 123.5 (C-5), 122.0 (C-7a), 69.7 (O-CH₂), 38.3 (CH₃); MS: m/z 373.1 (M+2), 371.2 (M⁺).

2-(*m*-Chlorobenzyl)-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-*e*][1,2,4]thiadiazine (**6d**) and 3-(*m*-Chlorobenzyloxy)-7-methyl-1,1-dioxo-4H-pyrazolo[4,5-*e*][1,2,4]thiadiazine (**6'd**). Compound **5** and 3-chlorobenzyl chloride at 50°C for 20h gave compounds **6d** and **6'd** as white solids after purification. **6d**: IR (KBr, cm⁻¹): 3223 (NH); 1678 (C=O); 1334, 1181 (SO₂); ¹H-NMR (DMSO-*d*₆) δ : 11.39 (s, 1H, NH), 7.45 (s, 1H, PyH), 7.31-7.40 (m, 4H, PhH), 4.97 (s, 2H, NCH₂), 4.03 (s, 3H, CH₃); ¹³C-NMR (DMSO-*d*₆) δ : 148.8 (C=O), 139.1 (C-1'), 133.1, 130.5, 127.7, 126.6, 125.7, 123.8 (C-4a), 121.3 (C-5), 120.1 (C-7a), 42.4 (N₂-CH₂), 38.9 (CH₃); MS: m/z 327.3 (M+1); **6'd**: IR (KBr, cm⁻¹): 3211 (NH), 1610 (C=N); 1312, 1174 (SO₂); ¹H-NMR (DMSO-*d*₆) δ : 12.34 (s, 1H, NH), 7.50 (s, 1H, PyH), 7.59 (s, 1H, PhH), 7.45 (s, 3H, PhH), 5.36 (s, 2H, NCH₂), 3.97 (s, 3H, CH₃); ¹³C-NMR (DMSO-*d*₆) δ : 151.9 (C=N), 137.6 (C-1'), 133.4, 130.7, 128.7, 128.4, 127.2, 125.6 (C-4a), 124.0 (C-5), 123.6 (C-7a), 69.6 (O-CH₂), 38.4 (CH₃); MS (EI): m/z 327.3 (M+1).

General Procedure for the Preparation of 4-Substituted-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-*e*][1,2,4]thiadiazines (**7a-d**)

To a solution of compound **5** (1 equiv.) in dry DMF (4 mL) was added sodium hydride (60% dispersion in mineral oil, 2 equiv.) in portions, under an inert atmosphere (N₂) while the temperature was kept below 10°C. After 60 min stirring, the alkyl halide (1 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 20 min and at 40-60°C for 8-12h (checked by TLC), and acidified with dilute hydrochloric acid (pH 4-6). The crude products obtained after the solvent was evaporated under reduced pressure were then separated by flash column chromatography using the indicated solvent system and purified by recrystallization from ethanol.

*4-Benzyl-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-*e*][1,2,4]thiadiazine (7a)*. Compound **5** was reacted with benzyl bromide at 30°C for 10 h to give **7a** as a white solid after by flash column chromatography separation (CH₂Cl₂/CH₃OH 4:1) of the crude product and recrystallization. IR (KBr, cm⁻¹): 1694 (C=O); 1342, 1141 (SO₂); ¹H-NMR (DMSO-*d*₆) δ: 7.18-7.29 (*m*, 5H, PhH), 7.09 (*s*, 1H, PyH), 4.90 (*s*, 2H, NCH₂), 3.83 (*s*, 3H, CH₃); ¹³C-NMR (DMSO-*d*₆) δ: 152.3 (C=O), 138 (C-1'), 128.4, 128.2, 127, 126.1 (C-4a), 125.0 (C-5), 123.2 (C-7a), 46.2 (CH₂), 37.3 (CH₃); MS (EI): *m/z* 292.3 (M⁺).

*4-(*p*-Chlorobenzyl)-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-*e*][1,2,4]thiadiazine (7b)*. Compound **5** was reacted with 4-chlorobenzyl chloride at 50-60°C for 24 h to give **7b** as a white solid after flash column chromatography (CH₂Cl₂/CH₃OH 4:1) of the crude product and recrystallization. IR (KBr, cm⁻¹): 1692 (C=O); 1327, 1135 (SO₂); ¹H-NMR (DMSO-*d*₆) δ: 7.32-7.35 (*m*, 4H, PhH), 7.14 (*s*, 1H, PyH), 4.86 (*s*, 2H, NCH₂), 3.82 (*s*, 3H, CH₃); ¹³C-NMR (DMSO-*d*₆) δ: 152.0 (C=O), 137.1 (C-1'), 131, 128.9, 128.3, 128.1 (C-4a), 125.0 (C-5), 123.0 (C-7a), 46.0 (CH₂), 37.1 (CH₃); MS (EI): *m/z* 327.3 (M+1).

*4-(*p*-Bromobenzyl)-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-*e*][1,2,4]thiadiazine (7c)*. Compound **5** and 4-bromobenzyl bromide at 30°C for 10 h gave **7c** as a white solid after purification of the crude reaction product by flash column chromatography (CH₂Cl₂/CH₃OH 3:1) and recrystallization. IR (KBr, cm⁻¹): 1693 (C=O); 1323, 1136 (SO₂); ¹H-NMR (DMSO-*d*₆) δ: 7.20-7.47 (*m*, 4H, PhH), 7.14 (*s*, 1H, PyH), 4.85 (*s*, 2H, NCH₂), 3.82 (*s*, 3H, CH₃); ¹³C-NMR (DMSO-*d*₆) δ: 152.2 (C=O), 138.3 (C-1'), 131.2, 129.1, 128.3, 125.4 (C-4a), 123.2 (C-5), 119.0 (C-7a), 47.2 (CH₂), 37.3 (CH₃); MS (EI): *m/z* 371.2 (M+1).

*4-(*m*-Chlorobenzyl)-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-*e*][1,2,4]thiadiazine (7d)*. Compound **5** and 3-chlorobenzyl chloride at 50-60°C for 24 h gave **7d** as a white solid after separation of the crude product by flash column chromatography (CH₂Cl₂/CH₃OH 4:1) and recrystallization. IR (KBr, cm⁻¹): 1695 (C=O); 1335, 1141 (SO₂); ¹H-NMR (DMSO-*d*₆) δ: 7.22-7.33 (*m*, 4H, PhH), 7.18 (*s*, 1H, PyH), 4.88 (*s*, 2H, NCH₂), 3.83 (*s*, 3H, CH₃); ¹³C-NMR (DMSO-*d*₆) δ: 152 (C=O), 141.2 (C-1'), 132.8, 130.4, 128.0, 126.9, 126.8, 125.8 (C-4a), 125.7 (C-5), 123.2 (C-7a), 46.4 (CH₂), 37.3 (CH₃); MS (EI): *m/z* 327.3 (M+1).

*General Procedure for the Preparation of 2,4-Disubstituted 7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-*e*][1,2,4]thiadiazine Derivatives 8a-d*

To a solution of compound **5** (1 equiv.) in dry DMF (4 mL/mmol) was added sodium hydride (60% dispersion in mineral oil, 2 equiv.) in portions, under an inert atmosphere (N₂) and keeping the temperature below 10°C. After stirring for 60 min, the appropriate alkyl halide (R₂CH₂X, 1 equiv.) was added dropwise. The reaction mixture was stirred at room temperature for 20 min and at 30-60°C for 8-12h (checked by TLC), then the second alkyl halide (R₁CH₂X, 1 equiv.) was added dropwise. Stirring of the mixture was continued for 12-20 h at 40-60°C, and then it was acidified (pH 4-6) with dilute hydrochloric acid. After the solvent was evaporated under reduced pressure, the crude products obtained were purified by recrystallization from ethanol to give **8a-d** as white solids.

2-Benzyl-4-(o-bromobenzyl)-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-e][1,2,4]thiadiazine (**8a**). Compound **5** was alkylated with 2-bromobenzyl bromide (30–40°C for 12h), then with benzyl bromide (40–50°C for 12h) to give **8a**. IR (KBr, cm^{-1}): 1692 (C=O); 1324, 1192 (SO_2); $^1\text{H-NMR}$ (CDCl_3) δ : 7.11 (*s*, 1H, PyH), 7.60 (*d*, 1H, $J=7.87$, PhH), 7.51 (*d*, 2H, $J=7.46$, PhH), 6.91 (*d*, 1H, $J=7.57$, PhH), 6.90–7.52 (*m*, 5H, PhH), 5.17 (*s*, 2H, NCH_2), 5.14 (*s*, 2H, NCH_2), 4.15 (*s*, 3H, CH_3); $^{13}\text{C-NMR}$ (CDCl_3) δ : 148.3 (C=O), 133.3 (C-1'), 135.3 (C-1''), 129.2, 128.3, 132.9, 129.2, 127.9, 127.8, 126.9, 125.1, 125.3 (C-4a), 122.9 (C-5), 122.2 (C-7a), 49.1 ($\text{N}_4\text{-CH}_2$), 44.6 ($\text{N}_2\text{-CH}_2$), 38.9 (CH_3); MS (EI): m/z 463.3 (M+2), 461.3 (M^+).

2-Benzyl-4-(o-chlorobenzyl)-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-e][1,2,4]thiadiazine (**8b**). Compound **5** was alkylated with 2-chlorobenzyl chloride (50–60°C for 12 h), then with benzyl bromide (40–50°C for 12 h) to give **8b**. IR (KBr, cm^{-1}): 1691 (C=O), 1326, 1193 (SO_2); $^1\text{H-NMR}$ (CDCl_3) δ : 6.95 (*s*, 1H, PyH), 7.13–7.51 (*m*, 9H, PhH), 5.19 (*s*, 2H, NCH_2), 5.14 (*s*, 2H, NCH_2), 4.15 (*s*, 3H, CH_3); $^{13}\text{C-NMR}$ (CDCl_3) δ : 149.3 (C=O), 132.5 (C-1'), 135.3 (C-1''), 128.6, 128.3, 131.8, 129.7, 129.0, 127.9, 127.2, 170.0, 125.3 (C-4a), 124.9 (C-5), 120.0 (C-7a), 46.6 ($\text{N}_4\text{-CH}_2$), 44.5 ($\text{N}_2\text{-CH}_2$), 38.9 (CH_3); MS (EI): m/z 417.4 (M+1).

2-(p-Chlorobenzyl)-4-(o-bromobenzyl)-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-e][1,2,4]thiadiazine (**8c**). Compound **5** was alkylated with 2-bromobenzyl bromide (30–40°C for 12 h), then with 4-chlorobenzyl chloride (50–60°C for 12 h) to give **8c**. IR (KBr, cm^{-1}): 1695 (C=O); 1331, 1192 (SO_2); $^1\text{H-NMR}$ (CDCl_3) δ : 7.12 (*s*, 1H, PyH), 7.60 (*dd*, 1H, $J=7.83$, $J=1.15$, PhH), 6.88–7.47 (*m*, 7H, PhH), 5.15 (*s*, 2H, NCH_2), 5.08 (*s*, 2H, NCH_2), 4.14 (*s*, 3H, CH_3); $^{13}\text{C-NMR}$ (CDCl_3) δ : 149.2 (C=O), 134.1 (C-1'), 137.3 (C-1''), 132.5, 131.6, 129.6, 129.5, 129.0, 128.4, 128.1, 127.2, 126.9, 126.7, 125.2 (C-4a), 125.0 (C-5), 122.6 (C-7a), 46.6 ($\text{N}_4\text{-CH}_2$), 43.7 ($\text{N}_2\text{-CH}_2$), 38.9 (CH_3); MS: m/z 497.3 (M+2), 495.2 (M^+).

2-(p-Chlorobenzyl)-4-(o-chlorobenzyl)-7-methyl-1,1,3-trioxo-2H,4H-pyrazolo[4,5-e][1,2,4]thiadiazine (**8d**). Compound **5** was alkylated with 2-chlorobenzyl chloride (40–50°C for 20 h), then with 4-chlorobenzyl chloride (50–60°C for 12 h) to give **8d**. IR (KBr, cm^{-1}): 1693 (C=O); 1331, 1193 (SO_2); $^1\text{H-NMR}$ ($\text{DMSO-}d_6$) δ : 7.75 (*s*, 1H, PyH), 7.50 (*dd*, 1H, $J=7.86$, $J=1.23$, PhH), 7.01 (*dd*, 1H, $J=7.63$, $J=1.25$, PhH), 7.26–7.41 (*m*, 6H, PhH), 5.15 (*s*, 2H, NCH_2), 5.02 (*s*, 2H, NCH_2), 4.08 (*s*, 3H, CH_3); $^{13}\text{C-NMR}$ ($\text{DMSO-}d_6$) δ : 148.8 (C=O), 133.0 (C-1'), 135.2 (C-1''), 132.1, 132.4, 129.9, 129.8, 129.5, 128.5, 127.7, 127.4, 126.3 (C-4a), 125.8 (C-5), 122.2 (C-7a), 47.2 ($\text{N}_4\text{-CH}_2$), 43.5 ($\text{N}_2\text{-CH}_2$), 39.1 (CH_3); MS (EI): m/z 453.4 (M+2), 451.4 (M^+).

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Sample Availability: Samples of the compounds are available from authors.