Synthetic Approaches Towards the Sulfonamide Substituted-4,5-diaryl-4*H*-1,2,4-triazole-3-thiones

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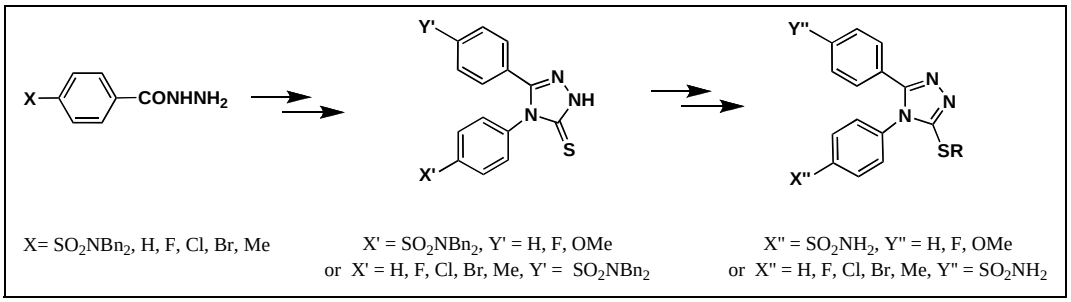
Received Nov 12, 2006

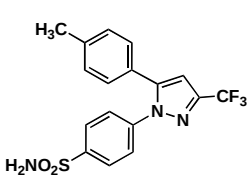


A new series of 3-alkylthio-4,5-diaryl-4*H*-1,2,4-triazoles having a SO_2NH_2 substituent in the *para*-position on one of the aryl rings (**19**/**25**) were prepared starting from the appropriate benzoic acid hydrazides (**15**/**21**). Reaction of the corresponding hydrazides with the appropriate isothiocyanates yielded **16**/**22**, which were cyclized in basic media to give 4,5-diaryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **17**/**23**. Alkylation of **17**/**23** afforded the alkylthio compounds **18**/**24**. Final debenzylation was achieved with concentrated sulfuric acid to give the target sulfonamides **19**/**25.**

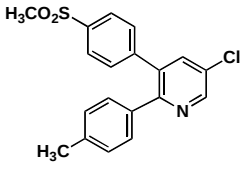
J. Heterocyclic Chem., **44**, 1323 (2007).

The selective COX-2 inhibitors celecoxib [1] and etoricoxib [2,3] have been clinically validated as anti-inflammatory therapeutics for indications such as rheumatoid arthritis with less gastrointestinal and renal toxicity (Figure 1) [4-7]. In addition to its role in rheumatoid arthritis and osteoarthritis, COX-2 is also implicated in colon cancer and Alzheimer disease [8-10].

Tricyclic compounds possessing a 1,2-diaryl substitution on a central heterocyclic or carbocyclic system constitute a major class of selective COX-2 inhibitors. Structure-activity relationship (SAR) studies have shown that a SO_2Me or SO_2NH_2 substituent in the *para*-position on one of the aryl rings often provides optimum COX-2 selectivity and inhibitory potency [11]. Whereas a small lipophilic substituent (Me, CF_3) on the central ring frequently enhances, or is often a requirement for COX-2 selectivity [12], modification of the substituents to identify new ligands with improved properties is desirable.



1 (Celecoxib)



2 (Etoricoxib)

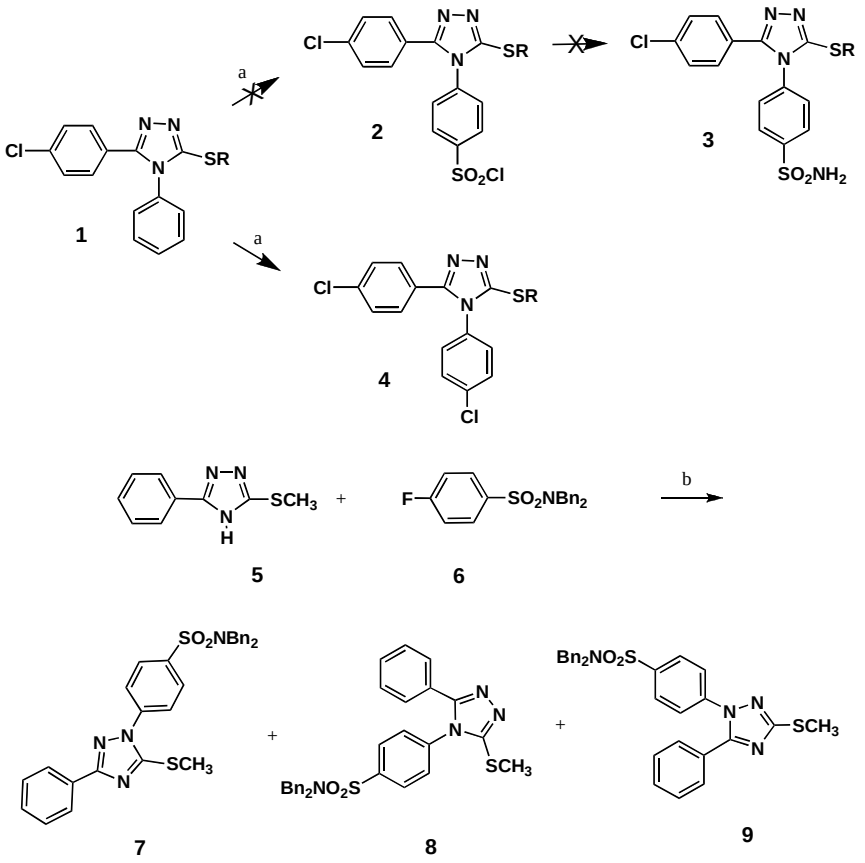
Figure 1. Representative Examples of Selective Tricyclic COX-2 Inhibitors.

As part of our ongoing program to design novel selective COX-2 inhibitors [13-18], we describe here the synthesis of a novel class of 4,5-diaryl-1,2,4-triazoles possessing a 3-alkylthio substituent on the central five-membered 1,2,4-triazole ring.

Syntheses of 1,2,4-triazole-3-thiones have been reported *via* several pathways [20-22]. In an attempt to prepare the target 4-(3-alkylthio-5-aryl-4*H*-1,2,4-triazol-4-yl)benzenesulfonamides **(19)**, chlorosulfonation of **1** was first investigated (see Scheme 1). This reaction was unsatisfactory at room temperature and the unchanged starting material was isolated. On refluxing of **1** with $ClSO_3H$, the expected chlorosulfonation reaction preceded by a competitive chlorination reaction that gave **4** (instead of **2**) [23]. The arylation reaction was next investigated using 3-methylthio-5-phenyl-4*H*-1,2,4-triazole (**5**) and fluorobenzene activated by an electron-withdrawing 4-*N,N*-dibenzylaminosulfonyl group **6** (see Scheme 1). In good agreement with our previous study [24], arylation occurred predominantly at the N-2 position of the triazole ring, affording *N,N*-dibenzyl-4-(3-methylthio-5-phenyl-2*H*-1,2,4-triazol-2-yl)benzenesulfonamide (**7**). However, N-4 and N-1 arylated compounds (**8** and **9**) were also formed in low yield. The differentiation between these two products **8** and **9** was possible on the basis of comparison with **18a** (see later). **8** was identical to **18a**.

Obviously, the most nucleophilic position at the 1,2,4-triazole should attack most rapidly. Since N-2 is receiving electron density by the adjacent alkylthio substituent -SR at the C-3 which acts as a donor substituent, arylation occurred predominantly at the N-2 position to produce **7**.

Scheme 1



Reagents and conditions: (a) $ClSO_3H$, reflux, overnight; (b) NaH, DMSO, 120°C, 20 h.

In an another attempt to prepare compound **19**, the reaction of **10** [25] and 4-amino-*N,N*-dibenzylbenzenesulfonamide **11** was investigated. However, because of the weak nucleophilicity of the amino group in **11**, this reaction was also unsatisfactory (Scheme 2).

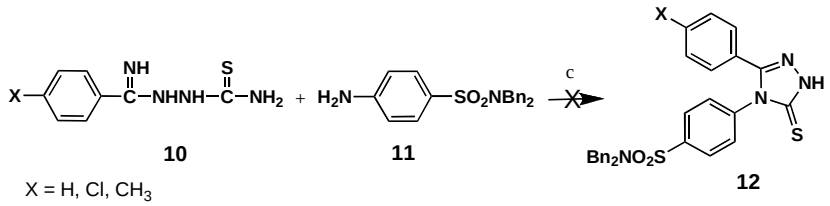
Finally, the previously reported reaction of benzoic acid hydrazide **15** and the appropriate isothiocyanate [26] was extended for the preparation of compound **19**. The synthetic reactions used for the synthesis of compound **19** are outlined in Scheme 3.

Treatment of the corresponding hydrazides **15** with *N,N*-dibenzyl-4-isothiocyanatobenzenesulfonamide **14** and subsequent cyclization of the intermediate **16** in saturated sodium carbonate gave **17**. Alkylation of **17** using alkyl iodide in basic media, followed by debenzylation in concentrated H_2SO_4 afforded the title sulfonamides **19** [26, 27].

We were also interested in preparing 4,5-diaryl-1,2,4-triazole-3-thiones in which the 4-sulfonylphenyl moiety is attached in a 1,3-relationship relative to thio substituent of the triazole, namely 4-(3-alkylthio-4-aryl-4*H*-1,2,4-triazol-5-yl)benzenesulfonamides **25**.

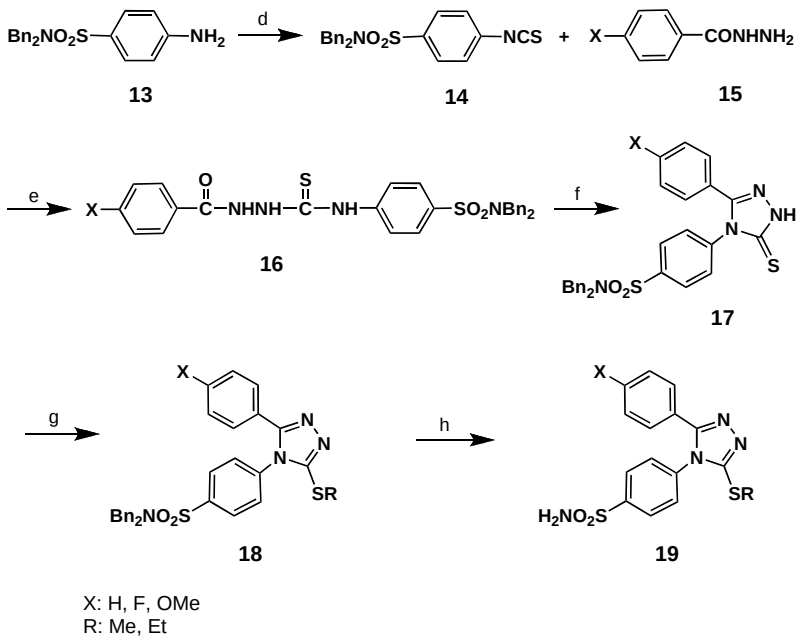
The reaction of 4-(*N,N*-dibenzylaminosulfonyl)benzoic acid hydrazide **21** and the corresponding isothiocyanates was then investigated, which in four steps gave the desired compounds **25** (Scheme 4) [26,27].

Scheme 2



Reagents and conditions: (c) dry DMF, reflux, 24 h.

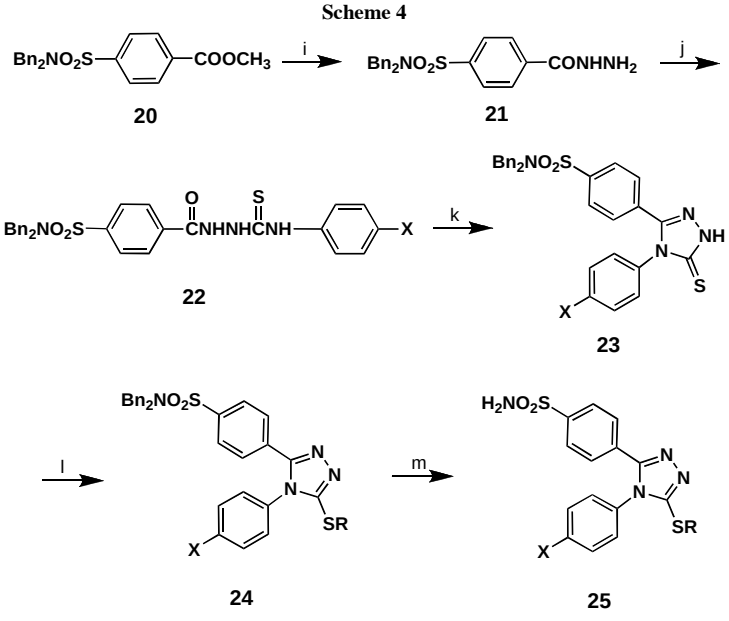
Scheme 3



Reagents and conditions: (d) $CSCl_2$, H_2O/HCl, r.t., overnight; (e) EtOH, r.t., overnight; (f) Na_2CO_3, reflux, overnight; (g) RI, KOH, EtOH, r.t., overnight; (h) H_2SO_4 concentrated, r.t., 20 min.

4-(*N,N*-Dibenzylaminosulfonyl)benzoic acid hydrazide **21** was prepared by the reaction of methyl 4-(*N,N*-dibenzylaminosulfonyl)benzoate **20** with hydrazine hydrate (5 equiv.). Reaction of the corresponding hydrazide **21** with the respective 4-substituted phenyl isothiocyanates yielded **22**, which were cyclized in saturated sodium carbonate solution to triazole-3-thiones **23** in good yields. Subsequent alkylation of **23** using alkyl iodide in basic media afforded the alkylthiotriazoles **24**. Final debenzylation was achieved using concentrated sulfuric

Scheme 4



Reagents and conditions: (i) $NH_2NH_2.H_2O$, MeOH, 4 h; (j) Ar-N=C=S, EtOH, r.t., overnight; (k) Na_2CO_3 aq., reflux, overnight; (l) RI, KOH, r.t., overnight; (m) H_2SO_4 concentrated, r.t., 20 min.

acid to give the title sulfonamides **25** (Scheme 4).

EXPERIMENTAL

Melting points were determined with a Reichert-Jung hot-stage microscope and are uncorrected. ^{1}H nmr (400 or 80 MHz) spectra were recorded on a Varian Utility plus 400 spectrometer or a Brucker 80 MHz spectrometer using deuteriochloroform or dimethylsulfoxide-d_6 as solvent. Chemical shifts (δ) are reported in ppm relative to TMS as internal standard. Infrared spectra were acquired on a Nicolet Magna 550-FT spectrometer. Mass spectra were obtained with a Finnigan Mat TSQ-70 spectrometer. Elemental microanalyses were within ± 0.4% of the theoretical values for C, H and N.

3-Methylthio-4,5-bis(4-chlorophenyl)-4*H*-1,2,4-triazole (4). A suspension of **1** (150 mg, 0.45 mmole) in $ClSO_3H$ (3 m1) was refluxed overnight. The mixture was poured into ice. The resulting mixture was extracted with chloroform, dried (Na_2SO_4) and evaporated to give **4** (70 mg, 42%) as a white solid; mp 189-190°C; ^{1}H nmr (deuteriochloroform): δ 7.72-7.41 (m, 4H), 7.35-7.05 (m, 4H), 2.73 (s, 3H); ms: m/z 335 (M^+, 5), 248 (5), 197 (10), 163 (12), 150 (100), 145 (48), 123 (32), 108 (18), 90 (48), 76 (33). The physical data was similar to those reported [24]. *Anal.* Calcd. for $C_{15}H_{11}Cl_2N_3S$: C, 53.58; H, 3.30; N, 12.50. Found: C, 53.47; H, 3.39; N, 12.42.

***N,N*-Dibenzyl-4-fluorobenzenesulfonamide (6).** To a solution of dibenzylamine (5.06 g, 25.6 mmoles) in THF (100 ml) was added dropwise 4-fluorobenzenesulfonyl chloride (5 g, 25.6 mmoles) dissolved in THF (50 ml) under N_2 at 0°C followed by addition of triethylamine (3.55 ml, 25.6 mmoles). The reaction mixture was stirred overnight at room temperature, filtered and the precipitate was washed with THF. The filtrate was concentrated and partitioned between water and ethyl acetate. The organic phase was dried, evaporated and the residue crystallized from diethyl ether to give **6** (6.47g, 71%) as a white solid; mp 85-87°C; ir (potassium bromide): 1325, 1148 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform): δ 7.82 (dd, J = 5.1, 8.9 Hz, 2H), 7.3-6.90 (m, 12H), 4.33 (s, 4H). *Anal.* Calcd. for $C_{20}H_{18}FNO_2S$: C, 67.58; H, 5.10; N, 3.94. Found: C, 67.45; H, 4.92; N, 3.87.

Arylation of 3-methylthio-5-phenyl-1*H*-1,2,4-triazole. To a solution of 3-methylthio-5-phenyl-1*H*-1,2,4-triazole **5** (0.8 g, 4.2 mmoles) in DMSO (10 ml) was added sodium hydride (100 mg, 4.2 mmoles). After 20 minutes of stirring at room temperature, *N,N*-dibenzyl-4-fluorobenzenesulfonamide **6** (1.49 mg, 0.42 mmoles) was added. The reaction mixture was heated at 120-130 °C for 20 hours, cooled to room temperature, and poured out into ice and extracted with ethyl acetate. The solvent was evaporated and the residue was chromatographed (ethyl acetate/hexane, 1:3). The fast moving fraction gave **7** (0.46 g, 21%). The slow moving fractions gave **8** (0.04 g, 1.8%) and **9** (0.06 g, 3%), respectively.

***N,N*-Dibenzyl-4-(3-methylthio-5-phenyl-4*H*-1,2,4-triazol-1-yl)benzenesulfonamide (7).** Following the arylation procedure, **7** was obtained (0.46 g, 21%); mp 113-115°C; ir (potassium bromide): 1356, 1163 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform): δ 8.22 (m, 2H), 7.99 (d, J = 8.7 Hz, 2H), 7.91 (d, J = 8.7 Hz, 2H), 7.55-7.45 (m, 3H), 7.36-7.23 (m, 6H), 7.18-7.10 (m, 4H), 4.24 (s, 4H), 2.91 (s, 3H); ^{13}C nmr (deuteriochloroform): δ 162.87, 155.15, 140.96, 140.43, 135.73, 130.65, 130.56, 129.08, 129.02, 129.01, 128.86, 128.30, 126.98, 123.71, 51.06, 16.48; ms: m/z 526 (M^+, 19), 435 (12), 331 (44), 266 (28), 251 (24), 196 (38), 103 (13), 90 (100). *Anal.* Calcd. for $C_{29}H_{26}N_4O_2S_2$: C, 66.13; H, 4.98; N, 10.64. Found: C, 66.25; H, 5.12; N, 10.46.

***N,N*-Dibenzyl-4-(3-methylthio-5-phenyl-4*H*-1,2,4-triazol-4-yl)benzenesulfonamide (8).** Following the arylation procedure, **8** was obtained (0.04 g, 1.8%); mp 190-192°C; ir (potassium bromide): 1342, 1158 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform): δ 7.87 (d, J = 8.6 Hz, 2H), 7.55-7.48 (m, 4H), 7.53-7.39 (m, 3H), 7.33-7.27 (m, 6H), 7.16-7.10 (m, 4H), 4.39 (s, 4H), 2.75 (s, 3H); ms: m/z 526 (M^+, 25), 435 (8), 331 (28), 266 (17), 251 (12), 196 (19), 104 (8), 91 (100). *Anal.* Calcd. for $C_{29}H_{26}N_4O_2S_2$: C, 66.13; H, 4.98; N, 10.64. Found: C, 66.02; H, 5.12; N, 10.81.

***N,N*-Dibenzyl-4-(3-methylthio-5-phenyl-4*H*-1,2,4-triazol-1-yl)benzenesulfonamide (9).** Following the arylation procedure, **9** was obtained (0.06 g, 3%); mp 153-155°C; ir (potassium bromide): 1347, 1163 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform): δ 8.14 (d, J = 8.7 Hz, 2H), 7.48-7.58 (m, 4H), 7.35-7.20 (m, 9H), 7.05-7.14 (m, 4H), 4.41 (s, 4H), 2.89 (s, 3H); ms: m/z 526 (M^+, 18), 435 (7), 350 (5), 331 (18), 251 (10), 196 (20), 130 (15), 91 (100). *Anal.* Calcd. for $C_{29}H_{26}N_4O_2S_2$: C, 66.13; H, 4.98; N, 10.64. Found: C, 66.22; H, 4.80; N, 10.75.

***N,N*-Dibenzyl-4-isothiocyanatobenzenesulfonamide (14).** 4-Amino-*N,N*-dibenzylbenzenesulfonamide **13** (5.0 g, 14.2 mmoles) was dissolved in water (50 ml) containing concentrated HCl (12.5 ml). To this, thiophosgene (1.63 g, 14.2 mmoles) was added. Stirring was begun immediately and continued overnight. The product was filtered, washed with water, and recrystallized from hexane to give **14** (2.5 g, 45%) as a white solid; mp 119-121°C; ir (potassium bromide): 2080 (NCS), 1337, 1158 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 7.78 (d, J = 8.7 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 7.25-6.85 (m, 10H), 4.33 (s, 4H). *Anal.* Calcd. for $C_{21}H_{18}N_2O_2S_2$: C, 63.93; H, 4.60; N, 7.10. Found: C, 63.77; H, 4.44; N, 7.26.

General Procedure for the Preparation of 1-(4-Substituted benzoyl)-4-(4-*N,N*-dibenzylaminosulfonylphenyl)thiosemicarbazides (16a-c). To a solution of 4-substituted benzoic acid hydrazide **15** (1.5 mmoles) in ethanol (10 ml) was added *N,N*-dibenzyl-4-isocyanatobenzenesulfonamide **14** (0.6 g, 1.5 mmoles) and the mixture was stirred at room temperature for 24 hours. Then, the product was filtered and crystallized from ethanol to give the title compounds **16a-c** as white solids.

1-Benzoyl-4-(4-*N,N*-dibenzylaminosulfonylphenyl)thiosemicarbazide (16a). Following the general procedure, **16a** was obtained (0.53 g, 66%); mp 174-176°C; ir (potassium bromide): 3309, 3255, 3198 (NH), 1655 (CO), 1337, 1158 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 10.32 (s, 1H, NH), 9.81 (s, 1H, NH), 8.1-7.65 (m, 4H, aromatic), 7.68-7.4 (m, 3H, aromatic), 7.38-6.85 (m, 12H,aromatic), 4.30 (s, 4H, CH_2) ; ^{13}C nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 171.82, 162.53, 143.55, 135.90, 135.88, 132.52, 132.23, 128.91, 128.77, 128.73, 128.71, 128.57, 128.09, 128.04, 127.95, 127.92, 123.13, 51.01. *Anal.* Calcd. for $C_{28}H_{26}N_4O_3S_2$: C, 63.37; H, 4.94; N, 10.56. Found: C, 63.20; H, 4.82; N, 10.72.

1-(4-Fluorobenzoyl)-4-(4-*N,N*-dibenzylaminosulfonylphenyl)-thiosemicarbazide (16b). Following the general procedure, **16b** was obtained (0.66 g, 79%); mp 171-173°C; ir (potassium bromide): 3257, 3191 (NH), 1680 (CO), 1327, 1153 cm^{-1} (SO_2); ^{1}H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 10.18 (s, 1H, NH), 9.72 (s, 1H, NH), 8.1-7.65 (m, 6H, aromatic), 7.38-6.85 (m, 12H, aromatic), 4.30 (s, 4H, CH_2). *Anal.* Calcd. for $C_{28}H_{25}FN_4O_3S_2$: C, 61.30; H, 4.59; N, 10.21. Found: C, 61.16; H, 4.68; N, 10.08.

1-(4-Methoxybenzoyl)-4-(4-*N,N*-dibenzylaminosulfonylphenyl)thiosemicarbazide (16c). Following the general

procedure, **16c** was obtained (0.67 g, 79%); mp 164-165°C; ir (potassium bromide): 3263, 3135 (NH), 1670 (CO), 1332, 1158 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 10.20 (s, 1H, NH), 9.71 (s, 1H, NH), 7.95-7.65 (m, 6H, aromatic), 7.45-6.9 (m, 12H, aromatic), 4.30 (s, 4H, CH_2), 3.87 (s, 3H, CH_3). *Anal.* Calcd. for $C_{29}H_{28}N_4O_4S_2$: C, 62.12; H, 5.03; N, 9.99. Found: C, 61.98; H, 4.94; N, 10.14.

General Procedure for the Preparation of *N,N*-Dibenzyl-4-(5-aryl-3-thio-2,4-dihydro-3*H*-1,2,4-triazol-4-yl)benzene sulfonamides (17a-c). A stirring mixture of compounds **16a-c** (1.1 mmole) and saturated aqueous sodium carbonate solution (15 ml) was refluxed overnight. After cooling, the solution was acidified with hydrochloric acid and the precipitate was filtered and washed with water. The precipitate was crystallized from ethanol to give the title compounds **17a-c**.

***N,N*-Dibenzyl-4-(5-phenyl-3-thio-2,4-dihydro-3*H*-1,2,4-triazol-4-yl)benzene sulfonamide (17a).** Following the general procedure, **17a** was obtained (0.51 g, 90%); mp 214-216°C; ir (potassium bromide): 3354 (NH), 1326, 1153 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 13.80 (s, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.75-6.85 (m, 17H), 4.33 (s, 4H); ^{13}C nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 164.85, 135.40, 130.92, 129.65, 129.12, 128.95, 128.81, 128.75, 128.60, 128.50, 128.44, 128.17, 50.67. *Anal.* Calcd. for $C_{28}H_{24}N_4O_2S_2$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.47; H, 4.55; N, 11.09.

***N,N*-Dibenzyl-4-[5-(4-fluorophenyl)-3-thio-2,4-dihydro-3*H*-1,2,4-triazol-4-yl]benzenesulfonamide (17b).** Following the general procedure, **17b** was obtained (0.5 g, 86%); mp 226-228°C; ir (potassium bromide): 3257 (NH), 1327, 1153 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 13.95 (s, 1H), 7.92 (d, J = 8.5 Hz, 2H), 7.70-6.7 (m, 16H), 4.32 (s, 4H). *Anal.* Calcd. for $C_{28}H_{23}FN_4O_2S_2$: C, 63.38; H, 4.37; N, 10.56. Found: C, 63.53; H, 4.22; N, 10.44.

***N,N*-Dibenzyl-4-[5-(4-methoxyphenyl)-3-thio-2,4-dihydro-3*H*-1,2,4-triazol-4-yl]benzenesulfonamide (17c).** Following the general procedure, **17c** was obtained (0.52 g, 88%); mp 210-212°C; ir (potassium bromide): 3375 (NH), 1332, 1153 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 14.05 (s, 1H), 7.94 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.38-7.85 (m, 12H), 6.78 (d, J = 9 Hz, 2H), 4.35 (s, 4H), 3.75 (s, 3H). *Anal.* Calcd. for $C_{29}H_{26}N_4O_3S_2$: C, 64.18; H, 4.83; N, 10.32. Found: C, 64.33; H, 5.91; N, 10.22.

General Procedure for the Preparation of *N,N*-Dibenzyl-4-(3-alkylthio-5-aryl-4*H*-1,2,4-triazol-4-yl)benzene sulfonamides (18a-f). To a stirring solution of compounds **17a-c** (0.5 mmole) and sodium hydroxide (1 mmole) in ethanol (5 ml) was added alkyl iodide (0.2 ml) and the mixture was stirred overnight. The volatiles were evaporated. The residue was poured into water and extracted with ethyl acetate and dried (Na_2SO_4). Purification by flash chromatography (silica gel), eluting with EtOAc, gave the title compounds **18a-f.**

***N,N*-Dibenzyl-4-(3-methylthio-5-phenyl-4*H*-1,2,4-triazol-4-yl)benzenesulfonamide (18a).** Following the general procedure, **18a** was obtained (0.22 g, 84%); mp 190-192°C; ir (potassium bromide): 1347, 1167 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.87 (d, J = 8.6 Hz, 2H), 7.55-7.48 (m, 4H), 7.53-7.39 (m, 3H), 7.33-7.27 (m, 6H), 7.16-7.10 (m, 4H), 4.39 (s, 4H), 2.75 (s, 3H); ^{13}C nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 154.83, 153.21, 142.26, 137.57, 135.20, 130.17, 128.86, 128.78, 128.67, 128.47, 128.33, 128.30, 128.01, 126.29, 50.53, 14.99. *Anal.* Calcd. for $C_{29}H_{26}N_4O_2S_2$: C, 66.13; H, 4.98; N, 10.64. Found: C, 66.24; H, 4.82; N, 10.50.

***N,N*-Dibenzyl-4-(3-ethylthio-5-phenyl-4*H*-1,2,4-triazol-4-yl)benzenesulfonamide (18b).** Following the general procedure, **18b** was obtained (0.22 g, 81%); mp 148-150°C; ir (potassium bromide): 1322, 1153 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.87 (d, J = 8.6 Hz, 2H), 7.58-7.44 (m, 4H), 7.53-7.42 (m, 3H), 7.33-7.25 (m, 6H), 7.18-7.07 (m, 4H), 4.38 (s, 4H), 3.35 (q, J = 7.4 Hz, 2H), 1.48 (t, J = 7.4 Hz, 3H). *Anal.* Calcd. for $C_{30}H_{28}N_4O_2S_2$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.49; H, 5.36; N, 10.53.

***N,N*-Dibenzyl-4-[5-(4-fluorophenyl)-3-methylthio-4*H*-1,2,4-triazol-4-yl]benzene sulfonamide (18c).** Following the general procedure, **18c** was obtained (0.24 g, 88%); mp 182-184°C; ir (potassium bromide): 1337, 1158 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.92 (d, J = 8.4 Hz, 2H), 7.45-6.80 (m, 16H), 4.39 (s, 4H), 2.79 (s, 3H). *Anal.* Calcd. for $C_{29}H_{25}FN_4O_2S_2$: C, 63.95; H, 4.63; N, 10.29. Found: C, 63.81; H, 4.56; N, 10.40.

***N,N*-Dibenzyl-4-[3-ethylthio-5-(4-fluorophenyl)-4*H*-1,2,4-triazol-4-yl]benzene sulfonamide (18d).** Following the general procedure, **18d** was obtained (0.21 g, 78%); mp 149-151°C; ir (potassium bromide): 1337, 1153 cm^{-1} (SO_2); ^1H nmr (deutériochloroform): δ 7.91 (d, J = 8.4 Hz, 2H), 7.48-6.75 (m, 16H), 6.39 (s, 4H), 3.34 (q, J = 7.3 Hz, 2H), 1.47 (t, J = 7.3 Hz, 3H). *Anal.* Calcd. for $C_{30}H_{27}FN_4O_2S_2$: C, 64.49; H, 4.87; N, 10.03. Found: C, 64.33; H, 4.66; N, 10.21.

***N,N*-Dibenzyl-4-[3-methylthio-5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-4-yl]benzene sulfonamide (18e).** Following the general procedure, **18e** was obtained (0.21 g, 75%); mp 172-174°C; ir (potassium bromide): 1337, 1158 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.90 (d, J = 8.4 Hz, 2H), 7.41-7.88 (m, 14H), 6.79 (d, J = 8.8 Hz, 2H), 4.39 (s, 4H), 3.79 (s, 3H), 2.77 (s, 3H). *Anal.* Calcd. for $C_{30}H_{28}N_4O_3S_2$: C, 64.72; H, 5.07; N, 10.06. Found: C, 64.59; H, 5.23; N, 9.98.

***N,N*-Dibenzyl-4-(3-ethylthio-5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-4-yl)benzene sulfonamide (18f).** Following the general procedure, **18f** was obtained (0.23 g, 80%); mp 135-137°C; ir (potassium bromide): 1337, 1158 cm^{-1} (SO_2); ^1H nmr (deutériochloroform): δ 7.89 (d, J = 8.5 Hz, 2H), 7.45-6.95 (m, 14H), 6.79 (d, J = 8.8 Hz, 2H), 4.39 (s, 4H), 3.79 (s, 3H), 3.34 (q, J = 7.3 Hz, 2H), 1.74 (t, J = 7.3 Hz, 3H). *Anal.* Calcd. for $C_{31}H_{30}N_4O_3S_2$: C, 65.24; H, 5.30; N, 9.82. Found: C, 65.12; H, 5.22; N, 9.99.

General Procedure for the Preparation of 4-(3-Alkylthio-5-aryl-4*H*-1,2,4-triazol-4-yl)benzene sulfonamides (19a-f). A suspension of **18a-e** (0.25 mmole) in concentrated H_2SO_4 (2 ml) was stirred at room temperature for 20 minutes. The mixture was poured into ice. The resulting solid was collected by filtration, washed with water, and dried. Purification by flash chromatography (silica gel), eluting with CH_3Cl/MeOH (9:1), gave the title compounds **19a-f.**

4-(3-Methylthio-5-phenyl-4*H*-1,2,4-triazol-4-yl)benzene sulfonamide (19a). Following the general procedure, **19a** was obtained (73 mg, 85%); mp 235-237°C; ir (potassium bromide): 3447, 3309 (NH_2), 1347, 1168 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.93 (d, J = 8.4 Hz, 2H), 7.75-7.52 (m, 4H), 7.36 (s, 5H), 2.63 (s, 3H); ^{13}C nmr (dimethylsulfoxide-d_6): δ 155.09, 153.53, 145.52, 136.98, 130.21, 128.97, 128.48, 128.18, 127.85, 126.46, 15.07; ms: m/z 346 (M^{+}, 67), 314 (10), 266 (17), 234 (8), 180 (13), 171 (20), 159 (24), 104 (27), 77 (37), 46 (100). *Anal.* Calcd. for $C_{15}H_{14}N_4O_2S_2$: C, 52.01; H, 4.07; N, 16.17. Found: C, 52.18; H, 4.23; N, 16.02.

4-(3-Ethylthio-5-phenyl-4*H*-1,2,4-triazol-4-yl)benzene sulfonamide (19b). Following the general procedure, **19b** was obtained (75 mg, 83%); mp 251-253°C; ir (potassium bromide):

3422, 3304 (NH_2), 1350, 1163 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 8.05 (d, J = 8.4 Hz, 2H), 7.60 (s, 5H), 7.44-7.30 (m, 4H), 3.18 (q, J = 7.2 Hz, 2H), 1.43 (t, J = 7.2 Hz, 3H); ms: m/z 360 (M^+, 24), 332 (25), 252 (18), 185 (18), 171 (42), 149 (25), 122 (32), 104 (35), 77 (38), 61 (100). *Anal.* Calcd. for $C_{16}H_{16}N_4O_2S_2$: C, 53.31; H, 4.47; N, 15.54. Found: C, 53.20; H, 4.31; N, 15.68.

4-[5-(4-Fluorophenyl)-3-methylthio-4*H*-1,2,4-triazol-4-yl]-benzenesulfonamide (19c). Following the general procedure, **19c** was obtained (70 mg, 76%); mp 245-247°C; ir (potassium bromide): 3432, 3309 (NH_2), 1347, 1163 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.96 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H), 7.45-7.25 (m, 4H), 7.17 (d, J = 8.8 Hz, 2H), 3.17 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ms: m/z 364 (M^+, 65), 346 (26), 330 (10), 282 (14), 278 (15), 252 (8), 208 (10), 198 (14), 177 (28), 164 (34), 122 (52), 120 (65), 107 (50), 76 (44), 76 (58), 46 (100). *Anal.* Calcd. for $C_{15}H_{13}FN_4O_2S_2$: C, 49.44; H, 3.60; N, 15.37. Found: C, 49.61; H, 3.52; N, 15.49.

4-[3-Ethylthio-5-(4-fluorophenyl)-4*H*-1,2,4-triazol-4-yl]-benzenesulfonamide (19d). Following the general procedure, **19d** was obtained (75 mg, 80%); mp 264-266°C; ir (potassium bromide): 3442, 3298 (NH_2), 1344, 1163 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.93 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.3 Hz, 2H), 7.45-7.25 (m, 4H), 7.15 (d, J = 8.8 Hz, 2H), 3.17 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ms: m/z 378 (M^+, 10), 349 (58), 283 (8), 278 (10), 196 (19), 191 (27), 150 (8), 122 (22), 120 (47), 77 (35), 61 (49), 46 (100). *Anal.* Calcd. for $C_{16}H_{15}FN_4O_2S_2$: C, 50.78; H, 4.00; N, 14.80. Found: C, 50.59; H, 3.82; N, 14.96.

4-[3-Methylthio-5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-4-yl]benzenesulfonamide (19e). Following the general procedure, **19e** was obtained (40 mg, 43%); mp 271-273°C; ir (potassium bromide): 3442, 3304 (NH_2), 1345, 1158 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.97 (d, J = 8.7 Hz, 2H), 7.60-7.48 (m, 4H), 7.27 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 2.61 (s, 3H); ms: m/z 376 (M^+, 5), 298 (17), 286 (18), 268 (20), 253 (7), 210 (12), 164 (25), 149 (27), 133 (75), 91 (57), 76 (63), 46 (100). *Anal.* Calcd. for $C_{16}H_{16}N_4O_3S_2$: C, 51.05; H, 4.28; N, 14.88. Found: C, 51.23; H, 4.12; N, 14.72.

4-[3-Ethylthio-5-(4-methoxyphenyl)-4*H*-1,2,4-triazol-4-yl]-benzenesulfonamide (19f). Following the general procedure, **19f** was obtained (45 mg, 47%); mp 261-263°C; ir (potassium bromide): 3324, 3302 (NH_2), 1342, 1168 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.95 (d, J = 8.7 Hz, 2H), 7.65-7.50 (m, 4H), 7.29 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 3.15 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); ms: m/z 390 (M^+, 95), 361 (95), 357 (43), 290 (26), 282 (10), 208 (82), 203 (74), 185 (22), 148 (57), 132 (77), 91 (71), 75 (98), 46 (100). *Anal.* Calcd. for $C_{17}H_{18}N_4O_3S_2$: C, 52.29; H, 4.65; N, 14.35. Found: C, 52.42; H, 4.88; N, 14.20.

4-*N*,*N*-Dibenzylaminosulfonylbenzoic acid hydrazide (21). To a solution of methyl 4-*N*,*N*-dibenzylaminosulfonyl benzoate **20** (5.5 g, 13.9 mmoles) in methanol (20 ml) was added hydrazine hydrate (3.48 g, 69.6 mmoles) and the mixture was stirred at room temperature for 10 hours. To the reaction mixture water was added water (20 ml). The precipitate was collected by filtration and crystallized from methanol to give **21** (4.2 g, 75%) as a white solid; mp 124-125°C; ir (potassium bromide): 3474, 3344, 3258 (NH), 1625 (CO), 1334, 1158 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.40-6.85 (m, 14H), 4.35 (s, 4H), 4.08 (bs, 1H); ms: m/z 395 (M^+, 14), 364 (100), 304 (29), 272 (4), 196 (8), 91 (9). *Anal.* Calcd. for $C_{21}H_{21}N_3O_3S$: C, 63.78; H, 5.35; N, 10.63. Found: C, 63.60; H, 5.49; N, 10.55.

General Procedure for the Preparation of 1-(4-*N*,*N*-Dibenzylaminosulfonylbenzoyl)-4-arylthiosemicarbazides (22a-e).To a solution of 4-(*N*,*N*-dibenzylaminosulfonyl)benzoic acid hydrazide **21** (1.5 g, 3.8 mmoles) in ethanol (10 ml) was added respective isothiocyanate (3.8 mmoles) and the mixture was stirred at room temperature for 24 hours. The product was filtered and crystallized from ethanol to give the title compounds **22a-e** as white solids.

1-(4-*N*,*N*-Dibenzylaminosulfonylbenzoyl)-4-phenylthiosemicarbazide (22a). Following the general procedure, **22a** was obtained (1.79 g, 89%); mp 192-194°C; ir (potassium bromide): 3365, 3288 (NH), 1675 (CO), 1311, 1148 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 10.45 (s, 1H), 9.44 (s, 1H), 8.10 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.75-6.90 (m, 15H), 4.34 (s, 4H); ms: m/z 531 (M^+, 3), 477 (5), 453 (22), 387 (11), 356 (100), 337 (22), 296 (14), 281 (8), 190 (11), 89 (10).*Anal.* Calcd. for $C_{28}H_{26}N_4O_3S_2$: C, 63.37; H, 4.94; N, 10.56. Found: C, 63.25; H, 4.80; N, 10.38.

1-(4-*N*,*N*-Dibenzylaminosulfonylbenzoyl)-4-(4-fluorophenyl)thiosemicarbazide (22b). Following the general procedure, **22b** was obtained (1.88 g, 90%); mp 197-199°C; ir (potassium bromide): 3365, 3288 (NH), 1675 (CO), 1311, 1148 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 10.45 (s, 1H), 9.44 (s, 1H), 8.10 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H), 7.75-6.90 (m, 14H), 4.34 (s, 4H); ms: m/z 547 (M^+, 5), 477 (8), 404 (10), 367 (22), 338 (100), 282 (28), 245 (5), 183 (10), 172 (9), 87 (10), 49 (13). *Anal.* Calcd. for $C_{28}H_{25}FN_4O_3S_2$: C, 61.30; H, 4.59; N, 10.21. Found: C, 61.17; H, 4.75; N, 10.10.

4-(4-Chlorophenyl)-1-(4-*N*,*N*-dibenzylaminosulfonylbenzoyl)thiosemicarbazide (22c). Following the general procedure, **22c** was obtained (1.95 g, 91%); mp 198-200°C; ir (potassium bromide): 3373, 3288 (NH), 1671 (CO), 1319, 1151 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 9.54 (s, 1H), 8.10 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 7.75-6.85 (m, 14H), 4.33 (s, 4H); ms: m/z 566 (M^+, 15), 564 (5), 543 (6), 519 (4), 494 (5), 447 (4), 420 (11), 382 (43), 352 (100), 293 (37), 279 (6), 189 (23), 163 (38), 108 (5), 90 (13). *Anal.* Calcd. for $C_{28}H_{25}ClN_4O_3S_2$: C, 59.51; H, 4.46; N, 9.91. Found: C, 59.36; H, 4.64; N, 10.08.

4-(4-Bromophenyl)-1-(4-*N*,*N*-dibenzylaminosulfonylbenzoyl)thiosemicarbazide 22d). Following the general procedure, **22d** was obtained (2.1 g, 91%); mp 200-202°C; ir (potassium bromide): 3371, 3287 (NH), 1670 (CO), 1319, 1151 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 10.55 (s, 1H), 9.58 (s, 1H), 8.12 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.4 Hz, 2H), 7.75-6.90 (m, 14H), 4.34 (s, 4H); ms: m/z 610 (M^+, 2), 608 (2), 578 (2), 576 (2), 560 (4), 477 (5), 435 (13), 395 (15), 364 (100), 345 (12), 304 (10), 196 (11), 91 (3). *Anal.* Cacld. for $C_{28}H_{25}BrN_4O_3S_2$: C, 55.17; H, 4.13; N, 9.19. Found: C, 55.29; H, 4.28; N, 9.36.

1-(4-*N*,*N*-Dibenzylaminosulfonylbenzoyl)-4-(4-methylphenyl)thiosemicarbazide (22e). Following the general procedure, **22e** was obtained (1.87 g, 91%); mp 180-182°C; ir (potassium bromide): 3365, 3287 (NH), 1671 (CO), 1321, 1152 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 10.49 (s, 1H), 9.32 (s, 1H), 8.08 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H), 7.50-6.95 (m, 14H), 4.35 (s, 4H), 2.34 (s, 3H); ms: m/z 545 (M^+, 9), 497 (12), 462 (38), 433 (17), 395

(15), 364 (100), 345 (31), 303 (27), 288 (6), 196 (30), 193 (10), 91 (14). *Anal.* Calcd. for $C_{29}H_{28}N_4O_3S_2$: C, 63.95; H, 5.18; N, 10.29. Found: C, 63.83; H, 5.09; N, 10.45.

General Procedure for the Preparation of *N,N*-Dibenzyl-4-(4-aryl-3-thio-2,4-dihydro-3*H*-1,2,4-triazol-5-yl)benzene sulfonamides (23a-e). A stirring mixture of compounds **22a-e** (3 mmoles) and saturated aqueous sodium carbonate solution (25 ml) was refluxed overnight. After cooling, the solution was acidified with hydrochloric acid and the precipitate was collected by filtration and washed with water. The precipitate was crystallized from ethanol to give the title compounds **23a-e**.

***N,N*-Dibenzyl-4-(4-phenyl-3-thio-2,4-dihydro-3*H*-1,2,4-triazol-5-yl)benzene sulfonamide (23a).** Following the general procedure, **23a** was obtained (1.35 g, 88%); mp 245-247 °C; ir (potassium bromide): 3365, 3287 (NH), 1671 (CO), 1321, 1152 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 8.89 (s, 1H), 7.72 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.52-6.95 (m, 15H), 4.29 (s, 4H); ms: m/z 513 (M^+, 5), 462 (8), 395 (17), 362 (100), 303 (16), 135 (5); ^{13}C nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 165.53, 143.29, 139.90, 137.12, 136.31, 129.69, 128.99, 128.96, 128.77, 128.23, 127.54, 125.78, 51.70. *Anal.* Calcd. for $C_{28}H_{24}N_4O_2S_2$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.74; H, 4.63; N, 10.81.

***N,N*-Dibenzyl-4-[4-(4-fluorophenyl)-3-thio-2,4-dihydro-3*H*-1,2,4-triazol-5-yl]benzenesulfonamide (23b).** Following the general procedure, **23b** was obtained (1.36 g, 86%); mp 250-252 °C; ir (potassium bromide): 3440, 3327 (NH), 1337, 1161 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 8.44 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.68-6.88 (m, 14H), 4.33 (s, 4H). *Anal.* Calcd. for $C_{28}H_{23}FN_4O_2S_2$: C, 63.38; H, 4.37; N, 10.56. Found: C, 63.25; H, 4.21; N, 10.43.

***N,N*-Dibenzyl-4-[4-(4-chlorophenyl)-3-thio-2,4-dihydro-3*H*-1,2,4-triazol-5-yl]benzenesulfonamide (23c).** Following the general procedure, **23c** was obtained (1.46 g, 90%); mp 231-233 °C; ir (potassium bromide): 3416, 3310 (NH), 1330, 1160 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 8.75 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.75-6.90 (m, 14H), 4.32 (s, 4H). *Anal.* Calcd. for $C_{28}H_{23}ClN_4O_2S_2$: C, 61.47; H, 4.24; N, 10.24. Found: C, 61.29; H, 4.40; N, 10.34.

***N,N*-Dibenzyl-4-[4-(4-bromophenyl)-3-thio-2,4-dihydro-3*H*-1,2,4-triazol-5-yl]benzenesulfonamide (23d).** Following the general procedure, **23d** was obtained (1.63 g, 92%); mp 190-192 °C; ir (potassium bromide): 3426, 3328 (NH), 1329, 1158 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 8.55 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 7.55-6.95 (m, 14H), 4.34 (s, 4H). *Anal.* Calcd. for $C_{28}H_{23}BrN_4O_2S_2$: C, 56.85; H, 3.92; N, 9.47. Found: C, 56.76; H, 4.06; N, 9.22.

***N,N*-Dibenzyl-4-[4-(4-methylphenyl)-3-thio-2,4-dihydro-3*H*-1,2,4-triazol-5-yl]benzenesulfonamide (23e).** Following the general procedure, **23e** was obtained (1.41 g, 90%); mp 237-239 °C; ir (potassium bromide): 3430, 3315 (NH), 1333, 1159 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 8.35 (s, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 7.42-6.85 (m, 14H), 4.29 (s, 4H), 2.45 (s, 3H); ms: m/z 527 (M^+, 9), 514 (100), 498 (12), 463 (9), 432 (10), 404 (8), 364 (14), 332 (13). *Anal.* Calcd. for $C_{29}H_{26}N_4O_2S_2$: C, 66.13; H, 4.98; N, 10.64. Found: C, 66.01; H, 4.85; N, 10.77.

General Procedure for the Preparation of *N,N*-Dibenzyl-4-(3-alkylthio-4-aryl-4*H*-1,2,4-triazol-5-yl)benzenesulfonamides (24a-j). To a stirring solution of compounds **23a-e** (1 mmole) and sodium hydroxide (2 mmoles) in ethanol (5 ml) was added alkyl iodide (0.5 ml) and the mixture was stirred overnight. The volatiles were evaporated. Purification by flash chromatography (silica gel), eluting with CH_3Cl/MeOH (20:1), and crystallization from ethanol gave the title compounds **24a-j**.

***N,N*-Dibenzyl-4-(3-methylthio-4-phenyl-4*H*-1,2,4-triazol-5-yl)benzenesulfonamide (24a).** Following the general procedure, **24a** was obtained (0.4 g, 78%); mp 168-170 °C; ir (potassium bromide): 1325, 1158 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.72 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.42-6.85 (m, 15H), 4.30 (s, 4H), 2.75 (s, 3H) ^{13}C nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 154.82, 153.42, 141.40, 135.41, 133.77, 130.73, 130.55, 130.44, 128.55, 128.50, 127.87, 127.29, 50.79, 14.77. *Anal.* Calcd. for $C_{29}H_{26}N_4O_2S_2$: C, 66.13; H, 4.98; N, 10.64. Found: C, 66.23; H, 4.80; N, 10.56.

***N,N*-Dibenzyl-4-(3-ethylthio-4-phenyl-4*H*-1,2,4-triazol-5-yl)benzenesulfonamide (24b).** Following the general procedure, **24b** was obtained (0.44 g, 83%); mp 178-180 °C; ir (potassium bromide): 1322, 1155 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.75 (d, J = 8.3 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 7.40-6.80 (m, 15H), 4.31 (s, 4H), 3.31 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H). *Anal.* Calcd. for $C_{30}H_{28}N_4O_2S_2$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.46; H, 5.11; N, 10.49.

***N,N*-Dibenzyl-4-[4-(4-fluorophenyl)-3-methylthio-4*H*-1,2,4-triazol-5-yl]benzene sulfonamide (24c).** Following the general procedure, **24c** was obtained (0.48 g, 88%); mp 176-178 °C; ir (potassium bromide): 1328, 1157 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.73 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.42-6.85 (m, 14H), 4.32 (s, 4H), 2.76 (s, 3H). *Anal.* Calcd. for $C_{29}H_{25}FN_4O_2S_2$: C, 63.95; H, 4.63; N, 10.29. Found: C, 63.83; H, 4.49; N, 10.15.

***N,N*-Dibenzyl-4-[3-ethylthio-4-(4-fluorophenyl)-4*H*-1,2,4-triazol-5-yl]benzene sulfonamide (24d).** Following the general procedure, **24d** was obtained (0.41 g, 75%); mp 158-160 °C; ir (potassium bromide): 1327, 1156 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.74 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 7.31-6.75 (m, 14H), 4.32 (s, 4H), 3.33 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H). *Anal.* Calcd. for $C_{30}H_{27}FN_4O_2S_2$: C, 64.49; H, 4.87; N, 10.03. Found: C, 64.63; H, 4.99; N, 10.20.

***N,N*-Dibenzyl-4-[4-(4-chlorophenyl)-3-methylthio-4*H*-1,2,4-triazol-5-yl]benzene sulfonamide (24e).** Following the general procedure, **24e** was obtained (0.47 g, 85%); mp 137-139 °C; ir (potassium bromide): 1330, 1152 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.75 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.35-6.89 (m, 14H), 4.33 (s, 4H), 2.75 (s, 3H). *Anal.* Calcd. for $C_{29}H_{25}ClN_4O_2S_2$: C, 62.07; H, 4.49; N, 9.98. Found: C, 62.22; H, 4.66; N, 10.16.

***N,N*-Dibenzyl-4-[4-(4-chlorophenyl)-3-ethylthio-4*H*-1,2,4-triazol-5-yl]benzene sulfonamide (24f).** Following the general procedure, **24f** was obtained (0.45 g, 80%); mp 148-150 °C; ir (potassium bromide): 1325, 1149 cm^{-1} (SO_2); ^1H nmr (deutériochloroform): δ 7.74 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.33-6.78 (m, 14H), 4.31 (s, 4H), 3.32 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H). *Anal.* Calcd. for $C_{30}H_{27}ClN_4O_2S_2$: C, 62.65; H, 4.73; N, 9.74. Found: C, 62.79; H, 4.59; N, 9.59.

***N,N*-Dibenzyl-4-[4-(4-bromophenyl)-3-methylthio-4*H*-1,2,4-triazol-5-yl]benzene sulfonamide (24g).** Following the general procedure, **24g** was obtained (0.48 g, 80%); mp 168-170 °C; ir (potassium bromide): 1328, 1160 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.76 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.52-6.85 (m, 14H), 4.32 (s, 4H), 2.76 (s, 3H). *Anal.* Calcd. for $C_{29}H_{25}BrN_4O_2S_2$: C, 57.52; H, 4.16; N, 9.25. Found: C, 57.69; H, 4.25; N, 9.38.

***N,N*-Dibenzyl-4-[4-(4-bromophenyl)-3-ethylthio-4*H*-1,2,4-triazol-5-yl]benzene sulfonamide (24h).** Following the general procedure, **24h** was obtained (0.61 g, 85%); mp 152-154°C; ir (potassium bromide): 1327, 1159 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.73 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.55-6.90 (m, 14H), 4.32 (s, 4H), 3.33 (q, J = 7.2 Hz, 2H), 1.45 (t, J = 7.2 Hz, 3H). *Anal.* Calcd. for $C_{30}H_{27}BrN_4O_2S_2$: C, 58.15; H, 4.39; N, 9.04. Found: C, 58.29; H, 4.22; N, 8.88.

***N,N*-Dibenzyl-4-[4-(4-methylphenyl)-3-methylthio-4*H*-1,2,4-triazol-5-yl]benzene sulfonamide (24i).** Following the general procedure, **24i** was obtained (0.42 g, 78%); mp 175-177°C; ir (potassium bromide): 1325, 1156 cm^{-1} (SO_2); ^1H nmr (deuteriochloroform): δ 7.72 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.38-6.88 (m, 14H), 4.31 (s, 4H), 2.75 (s, 3H), 2.34 (s, 3H). *Anal.* Calcd. for $C_{30}H_{28}N_4O_2S_2$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.77; H, 5.10; N, 10.21.

***N,N*-Dibenzyl-4-[3-ethylthio-4-(4-methylphenyl)-4*H*-1,2,4-triazol-5-yl]benzene sulfonamide (24j).** Following the general procedure, **24j** was obtained (0.44 g, 80%); mp 163-165°C; ir (potassium bromide): 1328, 1160 cm^{-1} (SO_2); ^1H NMR (deuteriochloroform): δ 7.74 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.35-6.92 (m, 14H), 4.31 (s, 4H), 3.29 (q, J = 7.2 Hz, 2H), 2.35 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H). *Anal.* Calcd. for $C_{31}H_{30}N_4O_2S_2$: C, 67.12; H, 5.45; N, 10.10. Found: C, 67.01; H, 5.61; N, 10.28.

General Procedure for the Preparation of 4-(3-Alkylthio-4-aryl-4*H*-1,2,4-triazol-5-yl)benzenesulfonamides (25a-j). A suspension of **24a-j** (0.5 mmole) in concentrated H_2SO_4 (2 ml) was stirred at room temperature for 20 minutes. The mixture was poured into ice. The resulting solid was collected by filtration, washed with water, and dried. Purification by flash chromatography (silica gel), eluting with CH_3Cl/MeOH (9:1), gave the title compounds **25a-j.**

4-(3-Methylthio-4-phenyl-4*H*-1,2,4-triazol-5-yl)benzene sulfonamide (25a). Following the general procedure, **25a** was obtained (56 mg, 33%); mp 243-245°C; ir (potassium bromide): 3299 (NH), 1334, 1170 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.77 (d, J = 8.4 Hz, 2H), 7.62-7.56 (m, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.48-7.38 (m, 3H), 7.21-6.75 (bs, 2H), 2.64 (s, 3H); ^{13}C nmr (dimethylsulfoxide-d_6): δ 154.41, 154.26, 145.66, 134.43, 131.10, 130.97, 130.55, 129.49, 129.28, 128.46, 126.70, 15.28; ms: m/z 346 (M^+, 100), 331 (8), 313 (10), 266 (8), 237 (6), 118 (10), 91 (14), 78 (12), 43 (18). *Anal.* Calcd. for $C_{15}H_{14}N_4O_2S_2$: C, 52.01; H, 4.07; N, 16.17. Found: C, 51.88; H, 3.95; N, 16.32.

4-(3-Ethylthio-4-phenyl-4*H*-1,2,4-triazol-5-yl)benzene sulfonamide (25b). Following the general procedure, **25b** was obtained (72 mg, 40%); mp 189-191°C; ir (potassium bromide): 3283 (NH), 1340, 1166 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.75 (d, J = 8.4 Hz, 2H), 7.58-7.52 (m, 3H), 7.51 (d, J = 8.4 Hz, 2H), 7.44-7.34 (m, 4H), 3.17 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H); ms: m/z 360 (M^+, 34), 344 (46), 324 (32), 277 (23), 209 (10), 195 (92), 147 (85), 82 (81), 53 (100). *Anal.* Calcd. for $C_{16}H_{16}N_4O_2S_2$: C, 53.31; H, 4.47; N, 15.54. Found: C, 53.19; H, 4.41; N, 15.39.

4-[4-(4-Fluorophenyl)-3-methylthio-4*H*-1,2,4-triazol-5-yl]-benzenesulfonamide (25c). Following the general procedure, **25c** was obtained (48 mg, 27%); mp 236-238°C; ir (potassium bromide): 3432 (NH), 1342, 1165 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.79 (d, J = 8.4 Hz, 2H), 7.64-7.45 (m, 6H), 7.42 (t, J = 8.8 Hz, 2H), 2.63 (s, 3H); ms: m/z 364 (M^+, 8), 350 (8), 341 (13), 303 (100), 278 (2), 277 (13), 251 (92), 231 (7), 186 (26), 175 (80), 173 (60), 162 (38), 128 (76), 106 (43), 79 (18), 51 (23), 40 (39). *Anal.* Calcd. for $C_{15}H_{13}FN_4O_2S_2$: C, 49.44; H, 3.60; N, 15.37. Found: C, 49.56; H, 3.78; N, 15.21.

4-[3-Ethylthio-4-(4-fluorophenyl)-4*H*-1,2,4-triazol-5-yl]-benzenesulfonamide (25d). Following the general procedure, **25d** was obtained (65 mg, 35%); mp 242-244°C; ir (potassium bromide): 3302 (NH), 1334, 1169 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.79 (d, J = 8.4 Hz, 2H), 7.58-7.51 (m, 4H), 7.46-7.37 (m, 4H), 3.16 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ms: m/z 378 (M^+, 41), 350 (81), 350 (100), 284 (4), 277 (14), 251 (46), 211 (10), 197 (20), 167 (12), 136 (24), 123 (87), 95 (25), 57 (25), 43 (40), 40(76). *Anal.* Calcd. for $C_{16}H_{15}FN_4O_2S_2$: C, 50.78; H, 4.00; N, 14.80. Found: C, 50.66; H, 4.09; N, 14.62.

4-[4-(4-Chlorophenyl)-3-methylthio-4*H*-1,2,4-triazol-5-yl]-benzenesulfonamide (25e). Following the general procedure, **25e** was obtained (83 mg, 43%); mp 196-198°C; ir (potassium bromide): 3436 (NH), 1339, 1162 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.80 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.52-7.42 (m, 4H), 2.64 (s, 3H); ms: m/z 382 (M^+, 33), 380 (100), 374 (20), 366 (38), 345 (24), 330 (10), 293 (7), 250 (16), 237 (12), 125 (9), 64 (25). *Anal.* Calcd. for $C_{15}H_{13}ClN_4O_2S_2$: C, 47.30; H, 3.44; N, 14.71. Found: C, 47.48; H, 3.59; N, 14.59.

4-[4-(4-Chlorophenyl)-3-ethylthio-4*H*-1,2,4-triazol-5-yl]-benzenesulfonamide (25f). Following the general procedure, **25f** was obtained (63 mg, 38%); mp 184-186°C; ir (potassium bromide): 3402 (NH), 1341, 1164 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.80 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.52-7.42 (m, 4H), 3.17 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ms: m/z 396 (M^+, 22), 394 (56), 369 (45), 366 (100), 331 (14), 313 (9), 251 (28), 213 (12). *Anal.* Calcd. for $C_{16}H_{15}ClN_4O_2S_2$: C, 48.66; H, 3.83; N, 14.19. Found: C, 48.85; H, 3.74; N, 14.10.

4-[4-(4-Bromophenyl)-3-methylthio-4*H*-1,2,4-triazol-5-yl]-benzenesulfonamide (25g). Following the general procedure, **25g** was obtained (80 mg, 38%); mp 204-206°C; ir (potassium bromide): 3268 (NH), 1341, 1164 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.80 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.46 (bs, 2H), 7.42 (d, J = 8.4 Hz, 2H), 2.64 (s, 3H); ms: m/z 425 (M^+, 100), 423 (100), 393 (11), 391 (11), ,345 (10), 340 (12), 338 (7), 313 (10), 237 (7), 197 (15), 195 (15), 171 (11), 169 (11). *Anal.* Calcd. for $C_{15}H_{13}BrN_4O_2S_2$: C, 42.36; H, 3.08; N, 13.17. Found: C, 42.48; H, 2.90; N, 13.01.

4-[4-(4-Bromophenyl)-3-ethylthio-4*H*-1,2,4-triazol-5-yl]-benzenesulfonamide (25h). Following the general procedure, **25h** was obtained (90 mg, 42%); mp 190-192°C; ir (potassium bromide): 3352 (NH),1336, 1163 cm^{-1} (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.78 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.42 (bs, 2H), 7.37 (d, J = 8.8 Hz, 2H), 3.17 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ms: m/z 439 (M^+, 25), 437 (25), 424 (15), 422 (15), 374 (10), 359 (34), 331 (19), 329 (19), 278 (35), 226 (25), 224 (25), 198 (28), 196 (28), 185 (69), 183 (69), 118 (25), 105 (32). *Anal.* Calcd. for $C_{16}H_{15}BrN_4O_2S_2$: C, 43.74; H, 3.44; N, 12.75. Found: C, 43.60; H, 3.26; N, 12.91.

4-[4-(4-Methylphenyl)-3-methylthio-4*H*-1,2,4-triazol-5-yl]-benzenesulfonamide (25i). Following the general procedure, **25i** was obtained (68 mg, 38%); mp 219-221°C; ir (potassium bromide): 3273 (NH), 1344, 1175 cm-1 (SO_2); ^1H nmr (dimethylsulfoxide-d_6): δ 7.78 (d, J = 8.4 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.43 (bs, 2H), 7.37 (d, J = 8 Hz, 2H), 7.29 (d, J = 8 Hz, 2H), 2.63 (s, 3H), 2.39 (s, 3H); ms: m/z 361 (M^+, 18), 360

(100), 358 (72), 344 (3), 327 (17), 279 (13), 272 (12), 131 (12), 105 (8). *Anal.* Calcd. for $C_{16}H_{16}N_4O_2S_2$: C, 53.31; H, 4.47; N, 15.54. Found: C, 53.48; H, 4.59; N, 15.68.

4-[3-Ethylthio-4-(4-methylphenyl)-4*H*-1,2,4-triazol-5-yl]-benzenesulfonamide (25j). Following the general procedure, **25j** was obtained (78 mg, 41%); mp 216-217°C; ir (potassium bromide): 3271 (NH), 1343, 1170 cm-1 (SO_2); ^{1}H nmr (dimethylsulfoxide-d_6): δ 7.79 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.43 (bs, 2H), 7.36 (d, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H), 3.16 (q, J = 7.2 Hz, 2H), 2.38 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ms: m/z 375 (M^+, 87), 373 (85), 358 (23), 345 (100), 328 (12), 326 (10), 296 (20), 267 (20), 266 (32), 251 (11), 159 (14). *Anal.* Calcd. for $C_{17}H_{18}N_4O_2S_2$: C, 54.52; H, 4.84; N, 14.96. Found: C, 54.39; H, 4.99; N, 14.82.

Acknowledgement. This research was supported by grants from the Research Council of Tehran University of Medical Sciences and INSF (Iran National Science Foundation).

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