Synthesis and Anti-HIV Activity of *N*-(3-Amino-3,4-dihydro-4-oxopyrimidin-2-yl)-4-chloro-2-mercapto-5-methylbenzenesulfonamide Derivatives

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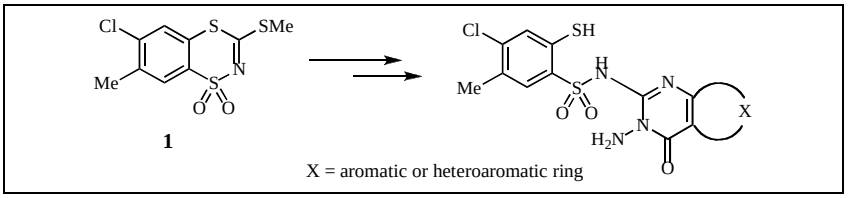

A series of *N*-(3-amino-3,4-dihydro-4-oxopyrimidin-2-yl)-4-chloro-2-mercapto-5-methylbenzenesulfonamide derivatives **10**-**17** have been synthesized as potential anti-HIV agents. The *in vitro* anti-HIV-1 activity of these compounds has been tested at the national Cancer Institute (Bethesda, MD), and the structure-activity relationships are discussed. The selected *N*-[3-amino-3,4-dihydro-6-(*tert*-butyl)-4-oxothieno[2,3-*e*]pyrimidin-2-yl]-4-chloro-2-metcapto-5-methylbenzenesulfonamide (**14**) showed good anti-HIV-1 activity with 50% effective concentration (EC_{50}) value of 15 μM and weak cytotoxic effect (IC_{50} = 106 μM).

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INTRODUCTION

Sulfonamides are among a growing list of compounds with desirable anticancer and anti-HIV activities [1-5]. Previously, we have described the syntheses of various 4-chloro-2-mercaptobenzenesulfonamide derivatives with the nitrogen atom of sulfonamide moiety attached to a variety of heterocyclic ring systems (**I**, Figure 1) [6-13]. Recently we have also reported on the syntheses of cyclic analogues of 4-chloro-2-mercaptobenzenesulfonamide (**II** and **III**, Figure 1) [22-26]. These compounds, depending on their structure, exhibited pronounced either anticancer [6-9,11,12,6-12,14-16,18] or anti-HIV [13,17,18] activities. Some of the compounds were described as novel class HIV-1 integrase inhibitors (MBS As) [13,17,19]. To better understand the nature of their anticancer versus their antiviral property we extended our studies to the synthesis of new series of 4-chloro-2-mercaptobenzenesulfonamides (**IV**, Figure 1) as potential anti-HIV agents.

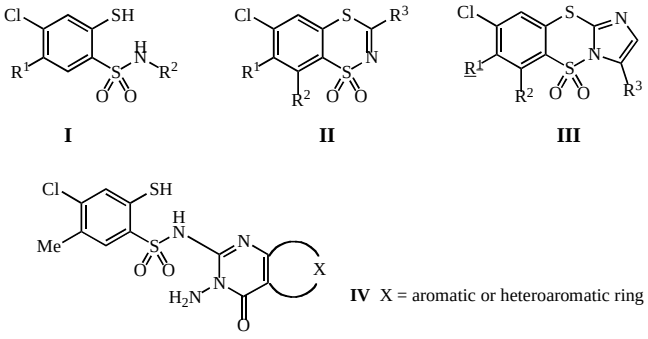


Figure 1

RESULTS AND DISCUSSION

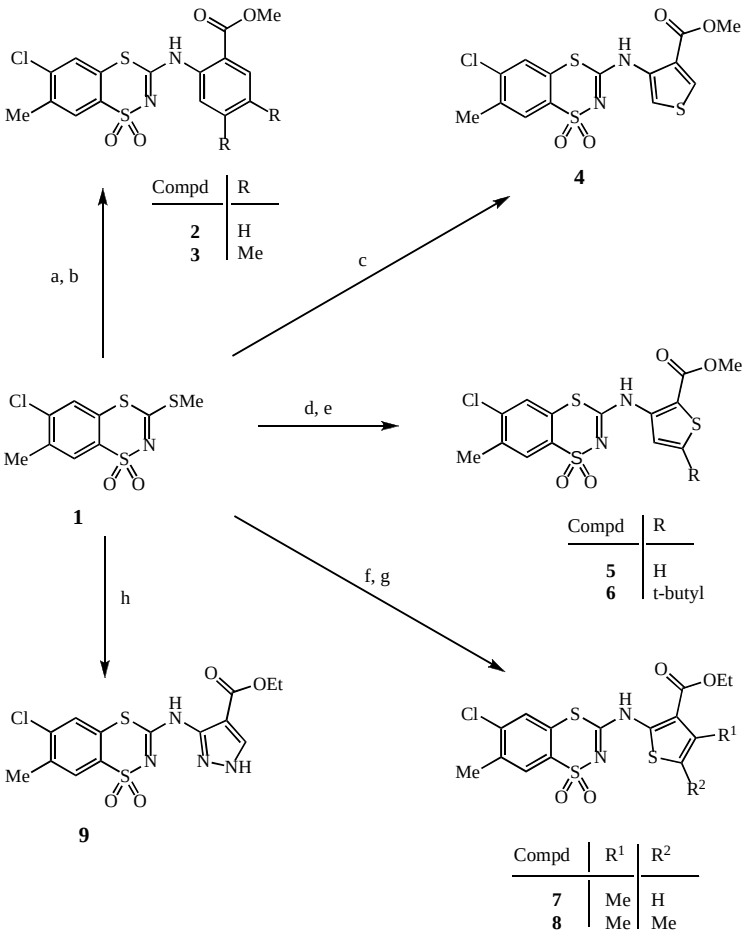
Synthesis. The syntheses of the target compounds **10**-**17** were achieved by a convenient two step procedure starting from 4-chloro-5-methyl-3-methylthio-1,4,2-benzodithiazine 1,1-dioxide **1** as shown in Schemes 1 and 2. First, the reaction of **1** with the appropriate alkyl *o*-amino-arylcarboxylates carried out in boiling toluene in the presence of pyridine led to the formation of alkyl *o*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)-arylcarboxylates **2**-**9** which were obtained in good yields (55-91%, Scheme 1). Then, upon treatment of **2**-**9** with hydrazine hydrate in methanol at room temperature (**2**-**6**, Method A) or in boiling toluene (**7**-**9**, Method B), the desired 2-mercaptobenzenesulfonamides **10**-**17** were obtained in 41-96% yield.

We propose a reaction sequence for the transformations as shown in Scheme 2. Nucleophilic attack of hydrazine at the carbon C-3 of benzodithiazine ring results in aminoguanidine intermediate **A**, which undergoes a spontaneous cyclocondensation reaction leading to the formation of final oxopyrimidine product **10**-**17**.

The structures of the compound **2**-**17** were confirmed by elemental analysis (C, H, N) and spectroscopic data presented in the experimental section. For example, in the ir spectra of esters **2**-**9** the C=O vibrations appear at 1675-1690 cm^{-1}, while characteristic feature of the ir spectra of *o*-mercaptobenzenesulfonamides **10**-**17** is the presence of S-H vibrations at 2550-2570 cm^{-1}.

It should be pointed out that 3-amino-2-arylsulfonamidoquinazolin-4(3*H*)-ones have not been described previously. However, it was found [20] that the amino-

Scheme 1

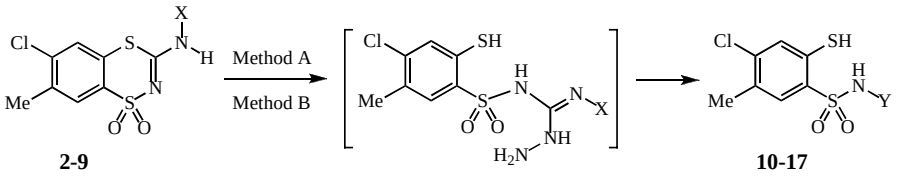


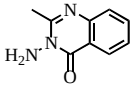
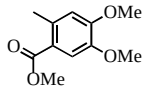
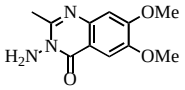
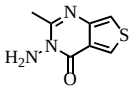
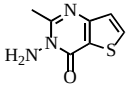
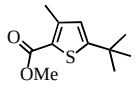
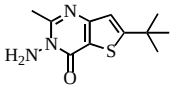
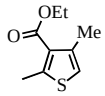
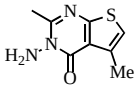
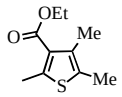
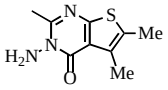
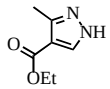
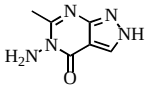
Synthesis of alkyl *o*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)arylcarboxylates **2-9**. Reagents and yields: (a) methyl 2-aminobenzoate (1 molar equiv), pyridine (1.33 molar equiv), toluene, reflux, 60%; (b) methyl 2-amino-4,5-dimethoxybenzoate (1 molar equiv), pyridine (1.33 molar equiv), toluene, reflux, 55%; (c) methyl 4-aminothiophene-3-carboxylate (1 molar equiv), pyridine (1.33 molar equiv), toluene, reflux, 91%; (d) 3-aminothiophene-2-carboxylate (1 molar equiv), pyridine (1.33 molar equiv), toluene, reflux, 79%; (e) 3-amino-5-(*tert*-butyl)thiophene-2-carboxylate (1 molar equiv), toluene, reflux, 61%; (f) ethyl 2-amino-4-methylthiophene-3-carboxylate (1 molar equiv), pyridine (1.33 molar equiv), toluene, reflux, 74%; (g) ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate (1 molar equiv), pyridine (1.33 molar equiv), toluene, reflux, 76%; (h) ethyl 3-aminopyrazole-4-carboxylate (1 molar equiv), pyridine (1.33 molar equiv), toluene, reflux, 89%.

guanidine compounds of type **A** generated by the treatment of 2-phenyliminomethyleneamino-benzoic acid esters with hydrazine underwent a facile cyclocondensation at room temperature giving rise to the formation of corresponding 3-amino-2-phenylamino-3*H*-quinoxalin-4-ones.

Biology. The final compounds **10**-**17** were tested for anti-HIV-1 activities at the National Cancer Institute (Bethesda, USA). The anti-HIV drug testing performed at NCI is based on a protocol described by Wieslow *et al* [21]. In brief, all compounds were dissolved in DMSO and diluted in 1:100 in cell culture medium. Exponentially growing T4 lymphocytes (CEM cell line) were added at 5000 cells per well. Frozen virus stock solution were thawed immediately before use, suspended in complete medium to yield the desired multiplicity of infection (≈ 0.1) and added to the microtiter wells, resulting in a 1:200 final dilution of the compound. Uninfected cells with the compound serve as a toxicity control, and infected and uninfected cells without the compound serve as basic controls. Cultures are incubated at 37°C in a 5% CO_2 atmosphere for 6 days. The tetrazolium salt, XTT [2,3-bis(2-methoxy-4-nitro-5-sulfenyl)-2*H*-tetrazolium-5-carboxamide] was added to all wells, and cultures are incubated to allow formazan colour development by viable cells. Individual wells were analyzed spectrophotometrically to quantitate formazan production and in addition are viewed microscopically for detection of viable cells and confirmation of protective activity.

Scheme 2



Compd	X	Method	Y
2, 10		**A**	
3, 11		**A**	
4, 12		**A**	
5, 13		**A**	
6, 14		**A**	
7, 15		**B**	
8, 16		**B**	
9, 17		**B**	

Synthesis of 2-mercaptobenzenesulfonamides **10**-**17**. Reagents, conditions, and yields: (Method A) hydrazine hydrate (3.4 molar equiv), methanol, room temperature 60-64 h, 90-96%; (Method B) hydrazine hydrate (2.2 molar equiv), toluene, room temperature 12 h, reflux 8 h, 41-81%.

The compound **15** proved to be inactive in the anti-HIV tests. However, other compounds exhibited good (**14**), moderate (**11**, **12** and **16**) or weak (**10**, **13** and **17**) activity (Table 1). It is noteworthy that the anti-HIV activity showed the compounds with substuituents varying in size and electronic properties such as quinazoline (**10**-**11**) thieno[3,4-*e*]pyrimidine (**12**), thieno[2,3-*e*]pyrimidine (**13**,**14**), thieno[3,2-*e*]pyrimidine (**16**) and pyrazolo[4,3-*e*]pyrimidine (**17**). The most potent compound **14** inhibited the replication of HIV-1 at EC_{50} of 15.0 μM, which is 7-fold below the cytotoxicity threshold.

The geometry of the most active compound **14** was optimized (Figure 2) by quantum-chemical calculations at *ab initio* level using HF/6.31** method [22]. Although the mechanism of anti-HIV action of this compound has not been investigated, it seems possible that it acts as a non-nucleoside reverse transcriptase inhibitor due to the butterfly-like conformation, similar to those found for Cl-α-APA and other flexible reverse transcriptase inhibitors [23].

Table 1

In vitro anti-HIV-1 drug screening results for N-(3-amino-3,4-dihydro-4-oxopyri-midin-2-yl)-6-chloro-2-mercapto-5-methylbenzenesulfonamide derivatives **10**-17.[a]

Compound	EC_{50} (μM)[b]	IC_{50}[c] (μM)	TI_{50}[d]	Comments[e]
10	41.1	87.7	2.13	M
11	29.8	>200.0	>6.90	A
12	29.7	129.0	4.36	A
13	41.1	>200.0	> 4.87	M
14	15.0	106.0	7.06	A
15	>200.0	113.0	-	I
16	29.6	135.0	4.56	A
17	97.6	>200.0	>2.05	M

[a] Data obtained from the NCI's *in vitro* anti-HIV primary screen; [b] Effective concentration 50% (protection of HIV-1 infected CEM cells); [c] Cytotoxic concentration 50% (toxicity to uninfected CEM cells); [d] Therapeutic index = IC_{50}/EC_{50}; [e] NCI designated activity: A (confirmed active); M (confirmed moderate); I (confirmed inactive).

General Procedure for the Preparation of Alkyl *o*-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)aryl-carboxylates 2-9.

To a solution of 6-chloro-7-methyl-3-methylthio-1,4,2-benzodithiazine 1,1-dioxide **1** (4.4 g, 0.015 mol) and the appropriate alkyl *o*-aminoarylcarboxylate (0.015 mol) in dry toluene (15 ml) was added anhydrous pyridine (1.6 g, 0.02 mol). The reaction mixture was refluxed with stirring until the evolution of MeSH had ceased (42-65 h) (CAUTION: due to a high toxicity, MeSH should be trapped into aqueous NaOH salution). After cooling to room temperature the suspension was left overnight. The precipitate was collected by filtration, washed with toluene (4 x 2.5 ml) and methanol (4 x 2.5 ml), dried and recrystallized from DMF (12-25 ml). In this manner, the following products were obtained:

Methyl 2-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)benzoate (2).

Starting from methyl 2-aminobenzoate (2.27 g), the title compound **2** was obtained (3.6 g, 60%): mp 225-226°; ir (KBr) 3215 (NH), 1685 (C=O), 1325, 1160 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.27 (s, 3H, CH_3), 3.37 (s, 3H, CH_3O), 6.96-7.04 (m, 1H, arom.), 7.06 (s, 1H, H-5, benzodithiazine), 7.39-7.48 (m, 1H, arom.), 7.84 (s, 1H, H-8, benzodithiazine), 7.89 (d, J = 1.6 Hz, 1H, arom.), 8.62 (d, J = 8.4 Hz, 1H, arom.), 11.72 ppm (s, 1H, NH); ^{13}C nmr ($CDCl_3$) δ 19.97, 52.86, 115.80, 121.68, 124.48, 127.20, 127.61, 130.06, 130.96, 135.03,138.20, 138.60, 139.95, 147.20, 160.02, 168.92 ppm. *Anal.* Calcd. for $C_{16}H_{13}ClN_2O_4S_2$ (396.85): C, 48.42, H, 3.30, N, 7.06. Found: C, 48.48, H, 3.34, N, 7.11.

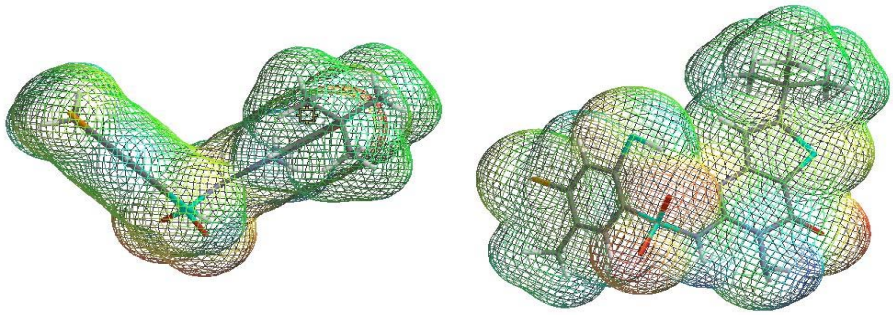


Figure 2. Shape of compound **14**.

CONCLUSION

We have demonstrated that the anti-HIV activity is characteristic for a variety of N-(3-amino-3,4-dihydro-4-oxopyrimidin-2-yl)-4-chloro-2-mercapto-5-methyl-benzenesulfonamide derivatives containing the pyrimidine moiety fused with an aromatic or hetero-aromatic ring. Further structural modifications aimed at optimization of their potency are in progress.

EXPERIMENTAL

The following instruments and parameters were used: (melting points) Büchi 535 apparatus; (IR Spectra) KBr pellets, 400-4000 cm^{-1} Perkin-Elmer 1600 FTIR spectrometer; (^1H- and ^{13}C NMR spectra) Varian Gemini 200 spectrometer at 200 and 50 MHz, respectively (chemical shifts are expressed as δ values relative to Me_4Si as standard). The starting 6-chloro-7-methyl-3-methylthio-1,4,2-benzodithiazine-1,1-dioxide (**1**) was prepared according to a know method [24].

Methyl 2-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)-4,5-dimethoxy-benzoate (3). Starting from methyl 2-amino-4,5-dimethoxybenzoate (3.17 g), the title compound **3** was obtained (3.8 g, 55%): mp 223-225°; ir (KBr) 3200, 3115 (NH), 1685 (C=O), 1615 (C=N), 1360, 1165 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.48 (s, 3H, CH_3), 3.88 (s, 3H, 5-CH_3OPh), 3.91 (s, 3H, 4-CH_3OPh), 4.03 (s, 3H, CH_3O-CO), 7.47 (s, 1H, H-3, Ph), 7.48 (s, 1H, H-6, Ph), 8.04 (s, 1H, H-5, benzodithiazine), 8.51 (s, 1H, H-8, benzodithiazine), 12.04 ppm (s, 1H, NH); ^{13}C nmr ($CDCl_3$) δ 20.28, 52.91, 56.41, 56.70, 105.00, 107.96, 112.15, 127.64, 127.89, 127.96, 130.60, 136.24, 138.47, 138.90, 145.51, 154.25, 159.94, 168.98 ppm. *Anal.* Calcd. For $C_{18}H_{17}ClN_2O_6S_2$ (456.91); C, 47.31, H, 3.75, N, 6.13. Found: C, 47.30; H, 3.79; N, 6.18.

Methyl 4-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)thiophene-3-carboxylate (4). Starting from methyl 4-aminothiophene-3-carboxylate (2.36 g), the title compound **4** was obtained (5.5 g, 91%): mp 261-262°; ir (KBr) 3180 (NH), 1680 (C=O), 1570 (C=N), 1340, 1315, 1160 (SO_2) cm^{-1}; ^1H Nnmr ($CDCl_3$) δ 2.48 (s, 3H, CH_3-7), 3.95 (s, 3H, CH_3O), 7.47 (s, 1H, H-5, benzodithiazine), 8.05 (s, 1H, H-8, benzodithiazine), 8.11 (d, *J* = 3.5 Hz, 1H, H-5, thiophene), 8.30 (d, *J* = 3.5 Hz, 1H, H-2, thiophene), 10.73 ppm (s, 1H, NH); ^{13}C nmr ($CDCl_3$) δ 19.68, 52.13, 114.24, 120.71, 126.72, 127.35, 129.99, 132.85, 134.49, 137.89, 138.29, 158.47, 164.44 ppm. *Anal.* Calcd. For $C_{14}H_{11}ClN_2O_4S_3$ (402.89): C, 41.73; H, 2.75; N, 6.95. Found: C, 47.80; H, 2.91; N, 6.99.

Methyl 3-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)thiophene-2-carboxylate (5). Starting from methyl 3-aminothiophene-2-carboxylate (2.36 g), the title compound **5** was obtained (4.8 g, 79%): mp 278-279°; ir (KBr) 3190 (NH), 1675 (C=O), 1575 (C=N), 1340, 1320, 1155 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.49 (s, 3H, CH_3-7), 2.95 (s, 3H, CH_3O), 7.48 (s, 1H, H-5, benzodithiazine), 7.56 (d, *J* = 5.5 Hz, 1H, H-4, thiophene), 8.06 (s, 1H, H-8, benzodithiazine), 8.29 (d, *J* = 5.5 Hz, 1H, H-5, thiophene), 10.79 ppm (s, 1H, NH); ^{13}C nmr ($CDCl_3$) δ 20.05, 52.49, 112.71, 123.17, 126.82, 127.68, 127.74, 130.00, 132.03, 138.79, 142.93, 159.31, 164.93 ppm. *Anal.* Calcd. for $C_{14}H_{11}ClN_2O_4S_3$ (402.89): C, 41.73; H, 2.75; N, 6.95. Found: C, 41.70; H, 2.82; N, 6.92.

Methyl 5-(*tert*-butyl)-3-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)thiophene-2-carboxylate (6). Starting from 3-amino-5-(*tert*-butyl)thiophene-2-carboxylate (3.2 g), the title compound **6** was obtained (4.2 g, 61%): mp 261-262°; ir (KBr) 3185 (NH), 1680 (C=O), 1585 (C=N), 1350, 1325, 1170 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.42 (s, 9H, *tert*-butyl), 2.49 (s, 3H, CH_3-7), 3.91 (s, 3H, CH_3O), 7.48 (s, 1H, H-4, thiophene), 8.01 (s, 1H, H-5, benzodithiazine), 8.06 (s, 1H, H-8, benzodithiazine), 10.84 ppm (s, 1H, NH). *Anal.* Calcd. for $C_{18}H_{19}ClN_2O_4S_3$ (458.99): C, 47.09; H, 4.17; N, 6.10. Found: C, 47.15; H, 4.21; N, 6.21.

Ethyl 2-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)-4-methylthio-phene-3-carboxylate (7). Starting from ethyl 2-amino-4-methylthiophene-3-carboxylate (2.8 g), the title compound **7** was obtained (4,8 g, 74%): mp 244-245°; ir (KBr) 3120 (NH), 1670 (C=O), 1625 (C=N), 1320, 1160 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.43 (t, *J* = 7.1 Hz, 3H., CH_3 of EtO), 2.38 (s, 3H, CH_3-4 of thiophene), 2.48 (s, 3H, CH_3-7), 4.42 (q, J = 7.1 Hz, 2H, CH_2 of EtO), 6.57 (s, 1H, H-5, thiophene) 7.48 (s, 1H, H-5, benzodithiazine), 8.07 (s, 1H, H-8, benzodithiazine), 12,17 ppm (s, 1H, NH).; ^{13}C nmr ($CDCl_3$) δ 16.19, 19.87, 22.05, 63.45, 116.16, 117.39, 128.70, 129.72, 129.79, 132.32, 137.31, 140.49, 140.77, 150.92, 159.33, 168.90 ppm. *Anal.* Calcd. for $C_{16}H_{15}ClN_2O_4S_3$ (430.94): C, 44.59; H, 3.50; N, 6.50. Found: C, 44.64; H, 3.51; N, 6.55.

Ethyl 2-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)-4,5-dimethyl-thiophene-3-carboxylate (8). Starting from ethyl 2-amino-4,5,-dimethylthiophene-3-carbo-xylate (3.0 g), the title compound **8** was obtained (5.1 g, 76%): mp 229-231°; ir (KBr) 3200 (NH), 1675 (C=O), 1550 (C=N), 1330, 1165 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.42 (t, *J* = 7.1 Hz, 3H, CH_3 of EtO), 2.25 (s, 3H, CH_3-4 of thiophene), 2.30 (s, 3H, CH_3-5 of thiophene), 2.47 (s, 3H, CH_3-7), 4.39 (q, J = 7.1 Hz, 2H, CH_2 of EtO), 7.46 (s, 1H, H-5, benzodithiazine), 8.06 (s, 1H, H-8, benzodithiazine), 12.16 ppm (s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{17}ClN_2O_4S_3$ (444.97): C, 45.88; H, 3.85; N, 6.29. Found: C, 45.85; H, 3.92; N, 6.39.

Ethyl 3-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)-1*H*-pyrazole-4-carboxylate (9). Starting from ethyl 3-aminopyrazole-4-carboxylate (2.32 g), the title compound **9** was obtained (5.3 g, 88%): mp. 272-273 °C; ir (KBr) 3240, 3140 (NH), 1690 (C=O), 1580 (C=N), 1325, 1160 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6) δ 1.13 (t, J = 7.1 Hz, 3H, CH_3 of EtO), 2.47 (s, CH_3-7), 4.14 (q, *J* = 7.1 Hz, 2H of EtO), 7.93 (s, 1H, H-5, benzodithiazine), 8.00 (s, 1H, H-8, benzodithiazine), 8.44 (s, 1H, H-5, pyrazole), 11.46 (s, 1H, H-1, pyrazole), 13.60 ppm (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_{13}ClN_4O_4S_2$ (400.84): C, 41.94; H, 3.27; N, 13.97. Found: C, 41.91; H, 3.30; N, 13.95.

Procedures for the Preparation of 4-Chloro-2-mercapto-benzenesulfonamide derivatives 10-17. Method A (for 10-14). A mixture of the corresponding methyl carboxylate **2**-**6** (0.0075 mol) and 99-100% hydrazine hydrate (1.3 g, 0.026 mol) in methanol (30 ml) was stirred at room temperature for 60-64 h. The precipitate hydrazinium salt of the desired product obtained was collected by filtration, washed with methanol (3 x 1,5 ml) and then mixed with 1% hydrochloric acid (100 ml). The reaction mixture was kept at room temperature for 2 h. The product that precipitated was again collected by filtration, washed with plenty of water until neutral pH was achieved, and dried initially at room temperature and then at 90°C. In this manner the following 2-mercaptobenzenesulfonamides were obtained:

***N*-(3-Amino-3,4-dihydro-4-oxoquinazolin-2-yl)-4-chloro-2-mercapto-5-methylbenzene-sulfonamide (10).** Starting from methyl 2-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)benzoate **2** (2.98 g), the title compound **10** was obtained (2.7 g, 91%): mp 284-286° dec., ir (KBr) 3350, 3300, 3265 (NH_2 and NH), 2550 (SH), 1670 (C=O), 1345, 1130 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.34 (s, 3H, CH_3), 3.55 (s, 1H, SH), 5.30 (s, 2H, NH_2), 7.40 (t, *J* = 7.3 Hz, 1H, H-8, quinazoline), 7.73 (s, 1H, H-3, Ph SO_2), 7.77-7.84 (m, 2H, H-6 and H-7, quinazoline), 7.89-8.06 (m, 2H, H-6 of $PhSO_2$ and H-3 of quinazoline), 10.92 ppm (s, 1H, NH). *Anal.* Calcd. for $C_{15}H_{13}ClN_4O_3S_2$ (396.85): C, 45.39; H, 3.30; N, 14.12. Found: C, 35.31; H, 3.41; N, 14.10.

***N*-(3-Amino-3,4-dihydro-6,7-dimetoxy-4-oxoquinazolin-2-yl)-4-chloro-2-mercapto-5-methylbenzenesulfonamide (11).** Starting from methyl 2-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)-4,5-dimethoxybenzoate **3** (3.43 g), the title compound **11** was obtained (3.2 g, 93%); mp 194-195° dec.; ir (KBr) 3335, 3325, 3270, (NH_2 and NH), 2565 (SH), 1670 (C=O), 1360, 1130 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.37 (s, 3H, CH_3), 3.96 (s, 3H, CH_3O), 4.01 (s, 3H, CH_3O), 4.59 (s, 1H, SH), 6.71 (s, 2H, NH_2), 7.28 (s, 1H, H-7, quinazoline), 7.40 (s, 1H, H-5, quinazoline), 7.49 (s, 1H, H-3, $PhSO_2$), 7.97 (s, 1H, H-6, Ph SO_2), 10.86 ppm (s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{17}ClN_4O_5S_2$ (456.91): C, 44.68; H, 3.75; N, 12.26. Found: C, 44,70; H, 3.83; N, 12.30.

***N*-(3-Amino-3,4-dichydro-4-oxothieno[3,4-*e*]pyrimidin-2-yl)-4-chloro-2-mercapto-5-methylbenzenesulfoamide (12).** Starting from methyl 4-(chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yloamin)thiophene-3-carboxylate **4** (3.02 g), the title compound **12** was obtained (2.8 g, 92%): mp 197-198° dec.; ir (KBr) 3345, 3240 (NH_2 and NH), 2560 (SH), 1695 (C=O), 1360, 1140 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.34 (s, 3H, CH_3), 3.84 (s, 1H, SH), 5.75 (s, 2H, NH_2), 7.60 (d, *J* = 3.4 Hz, 1H, H-7, thienopyrimidine), 7.73 (s, 1H, H-3, Ph SO_2), 8.06 (s, 1H, H-6,

$PhSO_2$), 8.53 (d, J = 3.4 Hz, 1H, H-5, thienopyrimidine), 11.08 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6) δ 18.89, 108.88, 120.74, 126.75, 130.03, 130.64, 133.00, 133.72, 134.79, 138.00, 138.82, 145.90, 154.18 ppm. *Anal.* Calcd. for $C_{13}H_{11}ClN_4O_3S_3$ (402.89): C, 38.75; H, 2.75; N, 13.90. Found: C, 38.81; H, 2.84; N, 13.91.

***N*-(3-Amino-3,4-dihydro-4-oxothieno[2,3-*e*]pyrimidin-2-yl)-4-chloro-2-mercapto-5-methylbenzenesulfonamide (13).** Starting from methyl 3-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)thiophene-2-carboxylate **5** (3.02 g), the title compound **13** was obtained (2.9 g, 96%): mp 256-258° dec.; ir (KBr) 3345, 3260, 3215 (NH_2 and NH), 2565 (SH), 1675 (C=O), 1345, 1335, 1165 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.33 (s, 3H, CH_3), 3.68 (s, 1H, SH), 5.20 (s, 2H, NH_2), 7.45 (d, J = 5.3 Hz, 1H, H-7, thienopyrimidine), 7.71 (s, 1H, H-3, $PhSO_2$), 7.99 (s, 1H, H-6, $PhSO_2$), 8.15 (d, J = 5.3 Hz, 1H, H-6, thienopyrimidine), 10.94 ppm (s, 1H, NH); ^{13}C nmr (DMSO-d_6) δ 18.89, 113.47, 119.98, 130.45, 130.58, 132.08, 132.47, 136.24, 136.81, 137.59, 143.42, 146.02, 153.99 ppm. *Anal.* Calcd. for $C_{13}H_{11}ClN_4O_3S_3$ (402. 89): C, 38.75; H, 2.75; N, 13.90. Found: C, 38,69; H, 2.88; N, 13.89.

***N*-[3-Amino-3,4-dihydro-6-(*tert*-butyl)-4-oxothieno[2,3-*e*]-pyrimidin-2-yl]-4-chlor-2-mercapto-5-methylbenzenesulfonamide (14).** Starting from methyl 5-(tert-butyl)-3-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)thiophene-2-carboxylate **6** (3.44 g), the title compound **14** was obtained (3.0 g, 90%), mp 203-204° dec.; ir (KBr) 3320, 3270, 3225, (NH_2 and NH), 2560 (SH), 1700 (C=O), 1345, 1130 (SO_2) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.42 (s, 9H, tert-butyl), 2.37 (s, 3H, CH_3), 4.60 (s, 1H, SH) 5.47 (s, 2H, NH_2), 6.85 (s, 1H, H-7, thienopyrimidine), 7.41 (s, 1H, H-3, $PhSO_2$) 7 97 (s, 1H, H-6, $PhSO_2$) 11-20 ppm (s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{19}ClN_4O_3S_3$ (459.02): C, 44.48; H, 4.17; N, 12.20. Found: C, 44.53; H, 4.22; N, 12.28.

Method B (for 15-17). A mixture of the corresponding ethyl carboxylate **7**, **8**, or **9** (0.005 mol) and 99-100% hydrazine hydrate (0.55 g, 0.011 mol) in dry toluene (30 ml) was stirred at room temperature for 12 h, followed by refluxing for 8 h. After cooling to room temperature the precipitate hydrazinium salt of the appropriate product obtained was collected by filtration, washed with toluene (3 x 1.5 ml) and immediately was acidified by refluxed in glacial acetic acid (20 ml) for 3 min. After cooling to room temperature, the precipitate was collected by filtration, washed successively with acetic acid (2 x 2 ml) and toluene (4 x 1.5 ml), and dried at temperatures gradually increasing to 90°C. In this manner the following 2-mercapto-benzenesulfonamides were obtained:

***N*-(3-Amino-3,4-dihydro-5-methyl-4-oxothieno[3,2-*e*]-pyrimidyn-2-yl)-4-chloro-2-mercapto-5-methylbenzene-sulfonamide (15).** Starting from ethyl 2-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)-4-methylthiophene-3-carboxylate **7** (2.16 g), the title compound **15** was obtained (1.7 g, 81%): mp 200-201° dec.; ir (KBr) 3295, 3225, 3125 (NH_2 and NH), 2565 (SH), 1665 (C=O), 1350, 1160 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.31 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.96 (s, 1H, SH), 4.95 (s, 2H, NH_2), 7.44 (s, 1H, H-6, thienopyrimidine), 7.51 (s, 1H, H-3, $PhSO_2$), 7.95 (s, 1H, H-6, $PhSO_2$), 10.86 ppm (s, 1H, NH).; ^{13}C nmr (DMSO-d_6) δ 16.05, 18.80, 112.83, 114.11, 125.04, 129.78, 132.56, 132.73, 132.85, 133.18, 136.68, 140.11, 147.53, 155.63 ppm. *Anal.* Calcd. for $C_{14}H_{13}ClN_4O_3S_3$ (416.91): C, 40.33; H, 3.14; N, 13.43. Found: C, 40.28; H, 3.19; N, 13.45.

***N*-(3-Amino-3,4-dihydro-5,6-dimethyl-4-oxothieno[3,2-*e*]-pyrimidin-2-yl)-4-chloro-2-mercapto-5-methylbenzene-sulfonamide (16).** Starting from ethyl 2-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino)-4,5-dimethylthiophene-3-carboxylate **8** (2.23 g), the title compound **16** was obtained (1.7 g, 79%): mp 220-221° dec.; ir (KBr) 3285, 3230, 3190 (NH_2 and NH), 2565 (SH), 1660 (C=O), 1350, 1160 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.21 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.65 (s, 1H, SH), 4.30 (s, 2H, NH_2), 7.50 (s, 1H, H-3, $PhSO_2$), 7.93 (s, 1H, H-6, $PhSO_2$), 10.72 ppm (s, 1H, NH). *Anal.* Calcd. for $C_{15}H_{15}ClN_4O_3S_3$ (430.94): C, 41.80; H, 3.51; N, 13.00. Found: C, 41.78; H, 3.62; N, 13.07.

***N*-(3-Amino-3,4-dihydro-4-oxo-6*H*-pyrazolo[4,3-*e*]pyrimidin-2-yl)-4-chloro-2-mer-capto-5-methylbenzenesulfonamide (17).** Starting from ethyl 2-(6-chloro-7-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-ylamino-1*H*-pyrazole-4-carboxylate **9** (2.0 g), the title compound **17** was obtained (0.8 g, 41.%): mp 236-239° dec.; ir (KBr) 3560, 3450, 3315, 3220 (NH_2 and NH) 2570 (SH), 1670 (C=O), 1350, 1140 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6) δ 2.40 (s, 3H, CH_3), 3.72 (s, 1H, SH), 4.96 (s, 2H, NH_2), 7.76 (s, 1H, H-3, $PhSO_2$), 7.81 (s, 1H, H-5, pyrazolopyrimidine), 8.17 (s, 1H, H-6, $PhSO_2$), 10.80 (s, 1H, H-6, pyrazolopyrimidine), 11.47 ppm (s, 1H, NH). *Anal.* Calcd. for $C_{12}H_{11}ClN_6O_3S_2$ (386.84): C, 37.25; H, 2.86; N, 21.72. Found: C, 37.22; H, 2.91; 21.70.

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