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Synthesis and in vitro anticancer and anti-HIV evaluation of new 2-mercaptobenzenesulfonamides

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Abstract

The reactions of 6-chloro-3-methylthio-1,4,2-benzodithiazine 1,1-dioxide derivatives with appropriate diamines were investigated. Depending on the reaction conditions 2-mercaptobenzenesulfonamide derivatives or their oxidation product disulfides were obtained. All the compounds were tested at the US National Cancer Institute (Bethesda) for their in vitro anticancer and anti-HIV activities. The highest sensibility against leukemia cell lines was found for bis[2-(6-chloro-4-phenyl-3,4-dihydroquinazolin-2-yl)aminosulfonyl-5-chloro-4-(4-R^2-phenylcarbamoyl)phenyl]disulfides ($R^2 = H$ or Cl). The results of anti-HIV tests displayed moderate activity of *N*-(pirydo[3,2-*d*]imidazol-2-yl)-2-mercaptobenzenesulfonamide. © 2001 Elsevier Science S.A. All rights reserved.

Keywords: 2-Mercaptobenzenesulfonamides; Synthesis; Anticancer and anti-HIV activities

1. Introduction

During the past 20 years, a variety of approaches have been taken for cancer chemotherapy, and many antitumor drugs have been developed for clinical use. In the treatment of solid tumors, however, the conventional approaches have met with only limited success, and cancer still remains as one of the leading causes of human mortality.

It is well known that benzenesulfonamide derivatives constitute an important class of therapeutical agents in medicinal chemistry. Recently, a variety of aromatic sulfides and sulfonic acid derivatives have been shown to possess anticancer or anti-HIV activity [1–7]. Human immunodeficiency virus type-1 integrase (HIV-1 IN), one of the three *pol* gene products, is required for the efficient insertion of the retroviral genome into host cell DNA. Several classes of IN inhibitors have been reported to date [8]; however, none has proven yet to be highly selective for IN. Among these, sulfonamides, diaryl sulfones, and aromatic disulfides were found to inhibit IN function, but only the 2-mercaptobenzenesulfonamide derivatives, previously obtained in our department, exhibited considerable antiviral activity [9,10]. Furthermore, our extensive studies on syntheses of 1,4,2-benzodithiazine 1,1-dioxide derivatives and their subsequent transformations into *N*-(azolyl or azinyl)-2-mercaptobenzenesulfonamide derivatives resulted in promising anticancer or/and anti-HIV agents [11–14]. It was confirmed that the biological potency of the tested compounds depends to a large extent on the size and electronic character of all substituents [11,12]. Therefore, the aim of this study was to synthesize new *N*-substituted 2-mercaptobenzenesulfonamides bearing various heterocyclic rings and to investigate their in vitro anticancer or anti-HIV activity.

2. Chemistry

The starting materials for the synthesis of compounds **2**–**11** were the 1,1-dioxides of 6-chloro-7-(methyl or phenylcarbamoyl)-3-methylthio-1,4,2-benzodithiazine (**1a**–**d**) previously synthesized in our laboratory [15,16] (Scheme 1).

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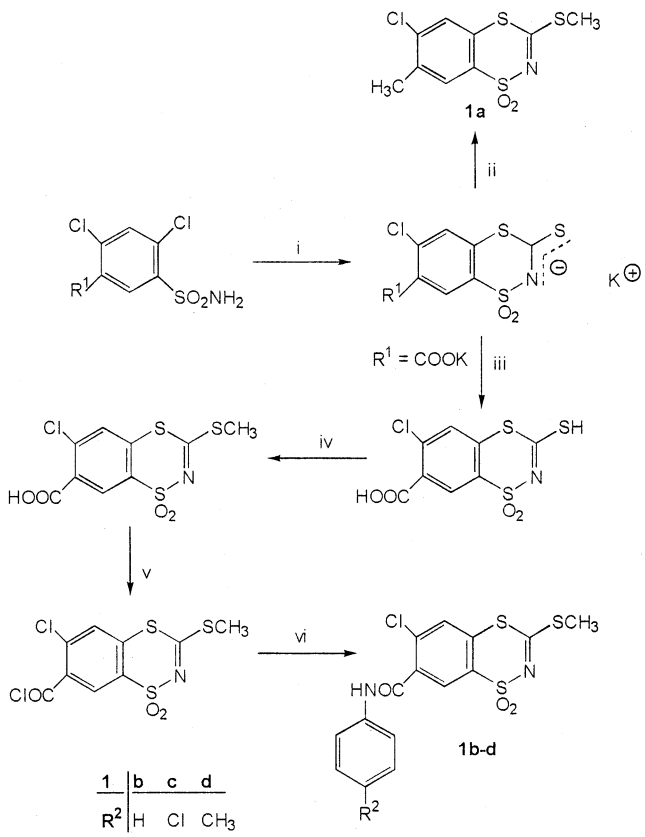
The reactions of **1a–d** with either the appropriate benzhydrylamine or 2,3-diaminopyridine were performed in boiling toluene in the presence of 4-(dimethylamino)pyridine (DMAP) to give 2-mercaptobenzenesulfonamides **2**, **3**, and **6** or disulfides **4a**, **5a**, **7a–9a** (Scheme 2). In turn, reactions of **1a** with ethylenediamines carried out under similar conditions (DMAP, toluene) led to the formation of the disulfides **10a** and **11a**, while in boiling methanol the expected 2-mercapto derivatives **10** and **11** were obtained (Scheme 2).

The structures of the newly obtained compounds **2**, **3**, **4a**, **5a**, **6**, **7a–9a**, **10**, **11**, **10a**, and **11a** were confirmed by IR, ^{1}H, and ^{13}C NMR spectra as well as elemental analyses.

The ^{1}H NMR spectra of **2**, **3**, **4a**, and **5a** showed dublets in the range of δ 5.86–5.52 ppm originating from 4-H of the quinazoline ring. The presence of the pyridine ring was indicated by characteristic signals of α, β and γ protons in the spectra of **6** and **7a–9a**. Two singlets observed in the spectrum of **6** (half proton each) of NH of the imidazole ring at δ 7.59 and δ 8.08 ppm are due to the known prototropic annular tautomerism of pyrido[3,2-*d*]imidazole system [17].

The formation of the imidazolidine ring was confirmed by signals of four protons which appeared as two multiplets or singlets in spectra of **10** and **11**, respectively. Spectra of all compounds revealed characteristic singlets of 3-H and 6-H of the benzenesulfonamide protons. Moreover, the IR spectra of the 2-mercaptobenzenesulfonamides **2**, **3**, **6**, **10**, and **11** showed the typical absorption of the SH group in the range 2560–2484 cm^{-1}.



Scheme 1. (i) KOH, CS_2,C_2H_5OH, reflux; (ii) $(CH_3)_2SO_4$, H_2O; (iii) HCl, H_2O; (iv) $(CH_3)_2SO_4$, NaOH, H_2O; (v) $SOCl_2$, benzene, reflux; (vi) 4-R^2PhNH_2, benzene.

3. Experimental

3.1. Chemistry

The melting points are uncorrected and were determined on a Büchi 535 apparatus. IR (KBr pellets) spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 200 or 80 MHz with a Varian Gemini or Tesla BS-857 spectrometer, respectively, using TMS as internal standard. The analytical results for C, H, and N were within $\pm$ 0.4% of the theoretical values. The intermediate 6-chloro-7-R^1-3-methylthio-1,4,2-benzodithiazine 1,1-dioxides **1a–d** were obtained by the method described previously [15,16]. The appropriate 2-amino-5-R^3-benzhydrylamine was prepared according to indications in the literature [18].

3.1.1. General procedure for the preparation of 4-chloro-2-mercapto-5-methyl-N-(6-R^3-4-phenyl-3,4-dihydroquinazolin-2-yl)benzenesulfonamides (**2**, **3**)

To a stirred solution of the appropriate 2-amino-5-R^3-benzhydrylamine (7.8 mmol) in anhydrous toluene (90 ml), **1a** (7.5 mmol) and DMAP (7.5 mmol) were added. The reaction mixture was refluxed under stirring until the evolution of CH_3SH had ceased (22 h). After cooling, the precipitate was collected by filtration, washed successively with toluene and methanol and without drying it was suspended in a solution of 0.1% HCl (150 ml), methanol (150 ml) and water (100 ml). The mixture was stirred at room temperature (r.t.) for 3 h, and then the product thus obtained was separated by suction, and washed successively with water and methanol. Yields, melting points, analytical and spectroscopic data of the sulfonamides **2** and **3** are reported in Table 1.

Compound ***3***. ^{13}C NMR (DMSO-d_6, δ ppm): 19.03 (5-CH_3); 55.36 (C-4 quinazol.); 117.24, 123.86, 125.95, 126.76, 127.38, 127.90, 128.76, 130.44, 131.18, 132.05, 132.27, 133.09, 136.64, 138.24, 142.99 (18C arom.); 151.26 (C=N).

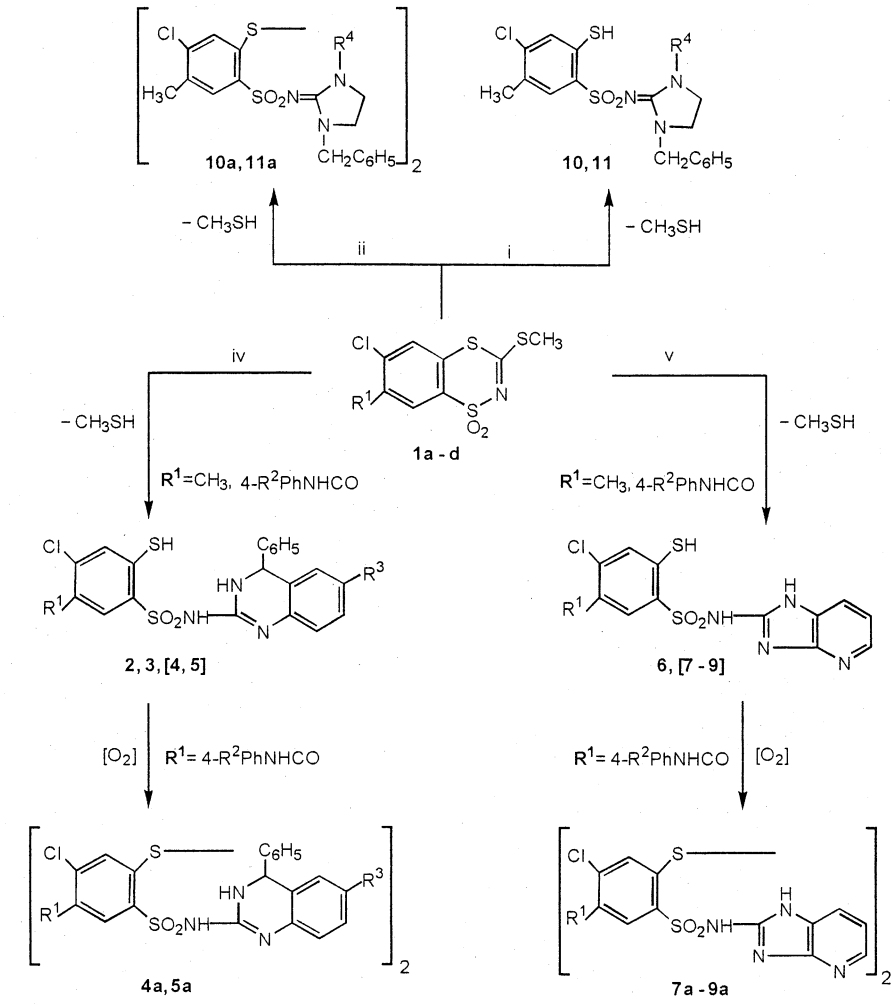
3.1.2. Bis[2-(6-chloro-4-phenyl-3,4-dihydroquinazolin-2-yl)aminosulfonyl-5-chloro-4-(4-R^2-phenylcarbamoyl)phenyl]disulfides (***4a***, ***5a***)

To a stirred solution of 2-amino-5-chlorobenzhydrylamine (7.8 mmol) in anhydrous toluene (90 ml) suit-

Table 1
Physico-chemical properties and spectroscopic (IR, ^{1}H NMR) data of 2-mercaptobenzenesulfonamides **2**, **3**, **6**, **10**, **11**, and disulfides **4a**, **5a**, **7a**–**11a** (^{1}H NMR spectra in $CDCl_3$, 200 MHz)

Compound	m.p. (°C)	Yield (%)	Analysis	IR (KBr, λ cm^{-1})	^{1}H NMR (δ ppm)
2	142–144	68	$C_{21}H_{17}ClN_3O_2S_2$ (443.99)	3312, 2549, 1622, 1604, 1528, 1369, 1143	2.19 (s, 3H, 5-CH_3); 5.70 (d, $J = 2.2$ Hz, 1H, 4-H quinazol.); 6.84–6.99 (m, 1H, 5-H quinazol.); 7.04–7.30 (m, 9H, 6-, 7-, 8-H quinazol., 5H arom., 3-H); 7.74 (s, 1H, 6-H); 7.81 (brs, 1H, NH); 9.30 (brs, 1H, SO_2NH)
3	159–161	81	$C_{21}H_{17}Cl_2N_3O_2S_2$ (478.42)	3342, 3271, 3218, 2484, 1625, 1601, 1522, 1369, 1146	2.19 (s, 3H, 5-CH_3); 5.66 (d, $J = 1.47$ Hz, 1H, 4-H quinazol.); 6.85 (d, $J_{5,7} = 1.83$ Hz, 1H, 5-H quinazol.); 7.11–7.35 (m, 8H, 7-, 8-H quinazol., 5H arom., 3-H); 7.71 (s, 1H, 6-H); 7.84 (brs, 1H, NH); 9.54 (brs, 1H, SO_2NH)
4a	301–304 (dec.)	79	$C_{54}H_{38}Cl_4N_8O_6S_4$ (1165.04)	3312, 1660, 1622, 1600, 1311, 1149	5.87 (d, $J = 2.85$ Hz, 2H, 2 × 4-H quinazol.); 6.91–7.58 (m, 28H, 2 × 5-, 7-, 8-H quinazol., 20H arom., 2 × 6-H); 7.80 (s, 2H, 2 × 3-H); 8.26 (brs, 2H, 2 × NH); 9.64 (brs, 2H, 2 × SO_2NH); 9.93 (brs, 2H, 2 × CONH) [a]
5a	304–306 (dec.)	78	$C_{54}H_{36}Cl_6N_8O_6S_4$ (1233.92)	3312, 1654, 1622, 1598, 1316, 1146	5.52 (d, $J = 2.67$ Hz, 2H, 2 × 4-H quinazol.); 6.60–6.84 (m, 2H, 2 × 5-H quinazol.); 7.26–7.79 (m, 20H, 2 × 7-, 8-H quinazol., 8H arom., 2 × 6-H and 2 × 3-H); 8.19 (brs, 2H, 2 × NH); 9.25 (brs, 2H, 2 × SO_2NH); 9.51 (brs, 2H, 2 × CONH)
6	297–299	88	$C_{13}H_{11}ClN_4O_2S_2$ (354.84)	3436, 3201, 3166, 2549, 1340, 1146	2.31 (s, 3H, 5-CH_3); 7.14–7.20 (dd, 1H, $J_{\beta,\alpha} = 5.1$ Hz, $J_{\gamma,\beta} = 7.87$ Hz, β-H py); 7.59 (s, ∼0.5H, NH imidazol.); 7.63–7.68 (m, 2H, γ-H py and 3-H); 7.99 (s, 1H, 6-H); 8.08 (s, ∼0.5H, NH imidazol.); 8.10–8.15 (m, 1H, α-H py); 11.98 (brs, 1H, SO_2NH) [b]
7a	302–304	74	$C_{38}H_{26}Cl_2N_{10}O_6S_4$ (917.84)	3365, 3295, 1654, 1631, 1616, 1595, 1313, 1143	7.0–7.22 (m, 2H, 2 × β-H py); 7.26–7.77 (m, 16H, 10H arom., 2 × 6-H, 2 × NH imidazol., 2 × γ-H py); 7.96–8.15 (m, 2H, 2 × α-H py); 8.31 (s, 2H, 2 × 3-H); 10.71 (brs, 2H, 2 × CONH); 11.71 (brs, 2H, 2 × SO_2NH) [b]
8a	292–295	65	$C_{38}H_{24}Cl_4N_{10}O_6S_4$ (986.74)	3401, 3307, 3248, 1654, 1631, 1595, 1307, 1143	7.12–7.18 (m, 2H, 2 × β-H py); 7.35–7.78 (m, 14H, 8H arom., 2 × 6-H, 2 × NH imidazol., 2 × γ-H py); 8.05–8.15 (m, 2H, 2 × α-H py); 8.31 (s, 2H, 2 × 3-H); 10.57 (brs, 2H, 2 × CONH); 11.90 (brs, 2H, 2 × SO_2NH) [b]
9a	285–289	84	$C_{40}H_{30}Cl_2N_{10}O_6S_4$ (945.90)	3385, 3283, 3189, 1654, 1628, 1592, 1310, 1146	2.27 (s, 6H, 2 × 4-CH_3); 7.10–7.19 (m, 2H, 2 × β-H py); 7.32–7.67 (m, 14H, 8H arom., 2 × 6-H, 2 × NH imidazol., 2 × γ-H py); 8.0–8.20 (m, 2H, 2 × α-H py); 8.31 (s, 2H, 2 × 3-H); 10.73 (brs, 2H, 2 × CONH); 11.89 (brs, 2H, 2 × SO_2NH) [b,c]
10	168–169	66	$C_{17}H_{18}ClN_3O_2S_2$ (385.93)	3377, 2560, 1592, 1578, 1357, 1168	2.34 (s, 3H, 5-CH_3); 3.30–3.40 (m, 2H, NHCH_2 imidazol.); 3.55–3.63 (m, 2H, NCH_2 imidazol.); 4.49 (s, 2H, CH_2Ph); 6.92 (s, 1H, $NH$$CH_2$); 7.17–7.37 (m, 5H arom.); 7.80 (s, 1H, 3-H); 7.91 (s, 1H, 6-H)
10a	192–193	76	$C_{34}H_{34}Cl_2N_6O_4S_4$ (789.85)	3395, 2919, 2854, 1592, 1578, 1340, 1163	2.33 (s, 6H, 2 × 4-CH_3); 3.29–3.38 (m, 4H, 2 × NHCH_2 imidazol.); 3.54–3.62 (m, 4H, 2 × NCH_2 imidazol.); 4.49 (s, 4H, 2 × CH_2Ph); 6.92 (s, 2H, 2 × $NH$$CH_2$); 7.16–7.3 (m, 10H arom.); 7.79 (s, 2H, 2 × 6-H); 7.91 (s, 2H, 2 × 3-H)
11	135–137	78	$C_{24}H_{24}ClN_3O_2S_2$ (486.05)	2549, 1584, 1554, 1515, 1354, 1128	2.32 (s, 3H, 5-CH_3); 3.35 (s, 4H, CH_2CH_2 imidazol.); 4.68 (s, 4H, 2 × CH_2Ph); 7.22–7.36 (m, 10H arom.); 7.73 (s, 1H, 3-H); 7.97 (s, 1H, 6-H)
11a	170–171	62	$C_{48}H_{46}Cl_2N_6O_4S_4$ (970.18)	1557, 1516, 1337, 1131	2.28 (s, 6H, 2 × 4-CH_3); 3.34 (s, 8H, 2 × CH_2CH_2 imidazol.); 4.72 (s, 8H, 4 × CH_2Ph); 7.15–7.32 (m, 20H arom.); 7.74 (s, 2H, 2 × 6-H); 7.93 (s, 2H, 2 × 3-H)

[a] ^{1}H NMR spectra in $(CD_3)_2CO$.
[b] ^{1}H NMR spectra in DMSO-d_6.
[c] 80 MHz spectrometer.



Comp.	R^1	R^2	R^3	R^4
1a, 2, 6, 10, 10a	CH_3	–	–	H
1a, 3, 11, 11a	CH_3	–	Cl	$C_6H_5CH_2$
1b, [4], 4a, [7], 7a	4-R^2PhNHCO	H	Cl	–
1c, [5], 5a, [8], 8a	4-R^2PhNHCO	Cl	Cl	–
1d, [9], 9a	4-R^2PhNHCO	CH_3	–	–

Scheme 2. (i) $R^1NH(CH_2)_2NHCH_2Ph$, CH_3OH (under reflux); (ii) $R^1NH(CH_2)_2NHCH_2Ph$, toluene (under reflux), DMAP; (iv) 2-amino-5-R^3-benzhydrylamine, toluene (under reflux), DMAP; (v) 2,3-diaminopyridine, toluene (under reflux), DMAP.

able **1b–c** (7.5 mmol) and DMAP (7.5 mmol) were added. The reaction mixture was refluxed under stirring until the evolution of CH_3SH had ceased (70–75 h). Then, the corresponding disulfide was obtained under the method described in Section 3.1.1. Yields, melting points, analytical and spectroscopic data of the disulfides **4a** and **5a** are reported in Table 1.

*3.1.3. General procedure for the preparation of 4-chloro-2-mercapto-5-methyl-N-(pyrido[3,2-d]-imidazol-2-yl)benzenesulfonamide (**6**) and bis[2-(pyrido[3,2-d]imidazol-2-yl)aminosulfonyl-5-chloro-4-(4-R^2-phenylcarbamoyl)phenyl]disulfides (**7a–9a**)*

Equimolar amounts (7.5 mmol) of suitable dioxide **1a–d** and DMAP were added to a solution of 2,3-di-

aminopyridine (7.8 mmol) in anhydrous toluene (90 ml). The mixture was refluxed under stirring until the evolution of CH_3SH had ceased (45–50 h). Then, corresponding **6** and **7a**–**9a** were obtained under the method described in Section 3.1.1. Yields, melting points, analytical and spectroscopic data of the sulfonamides **6** and **7a**–**9a** are reported in Table 1.

Compound ***6***. ^{13}C NMR (DMSO-d_6, δ ppm): 19.21 (5-CH_3); 118.66, 119.0, 123.68, 126.03, 131.38, 132.75, 134.81, 137.83, 139.61, 142.81 (10C arom.); 144.10 (C=N imidazol.); 150.19 (C=N py).

*3.1.4. Preparation of 1-benzyl- and 1,3-dibenzyl-2-(4-chloro-2-mercapto-5-methylbenzenesulfonylimino)imidazolidines (**10**, **11**)*

A solution of dioxide **1a** (5 mmol) and *N*-benzyl- or *N*,*N*′-dibenzyl-1,2-diaminoethane (5.3 mmol) in anhydrous methanol (35 ml) was stirred at r.t. for 2 h, and then heated under reflux until the evolution of CH_3SH had ceased (30–35 h). The precipitate thus obtained was collected by filtration, washed with methanol and dried. Yields, melting points, analytical and spectroscopic data of the sulfonamides **10** and **11** are shown in Table 1.

Compound ***10***. ^{13}C NMR ($CDCl_3$, δ ppm): 19.42 (5-CH_3); 40.72 ($NHCH_2$ imidazol.); 44.54 (NCH_2 imidazol.); 48.24 (CH_2Ph); 127.43, 127.84, 128.14, 128.20, 128.68, 130.60 (6C, CH_2Ph); 130.80, 133.76, 134.58, 135.24, 138.66, 139.10 (6C arom.); 158.67 (C=N).

Compound ***11***. ^{13}C NMR ($CDCl_3$, δ ppm): 18.71 (5-CH_3); 43.60 (CH_2CH_2 imidazol.); 50.39, 50.47 ($2 \times CH_2$Ph); 126.36, 127.23, 127.29, 127.63, 128.06, 129.29, 129.44, 129.55 (12C, $2 \times CH_2Ph$); 130.0, 132.14, 133.61, 134.60, 137.31, 139.68 (6C arom.); 156.35 (C=N).

*3.1.5. Bis[2-(1-benzyl- and 1,3-dibenzylimidazolin-2-yl)iminosulfonyl-5-chloro-4-methylphenyl]disulfides (**10a**, **11a**)*

To a solution of *N*-benzyl- or *N*,*N*′-dibenzyl-1,2-diaminoethane (5.3 mmol) in anhydrous toluene (30 ml), **1a** (5 mmol) and DMAP (5 mmol) were added. The stirred mixture was heated under reflux until the evolution of CH_3SH had ceased (60 h). The resulting solid was collected by filtration, washed successively with toluene and methanol and, without drying, suspended in a solution of 0.1% HCl (100 ml), methanol (100 ml) and water (50 ml). After stirring for 3 h, the mixture was filtered off and the product thus obtained was washed successively with water and methanol. Yields, melting points, analytical and spectroscopic data of the disulfides **10a** and **11a** are reported in Table 1.

3.2. Pharmacology

The compounds **2**, **3**, **4a**, **5a**, **6**, **7a**, **8a**, **9a**, **10**, and **11** were tested at the US National Cancer Institute (Bethesda) for their in vitro anticancer and anti-HIV activities. The tests of anti-HIV activity were performed on T-4 lymphocytes (CEM-SS cell line) uninfected or infected with HIV-1. The viability of the cells was determined spectrophotometrically using the tetrazolium assay procedure [19]. The antitumor activities of the investigated compounds were evaluated using a total of 60 human cell lines derived from nine different cancer types (lung, colon, melanoma, prostate, breast, renal, ovarian, CNS, and leukemia). The compounds were tested in a broad concentration range (10^{-4} to 10^{-8} M). The response parameters GI_{50}, TGI, and LC_{50} are interpolated values representing the concentration at which the percentage growth is $+50$, 0, and -50, respectively, and were calculated from dose–response curves [20]. The results of these screenings are presented in Table 2.

4. Results and discussion

Regarding chemistry, it is interesting to note that the reactions of the dioxides **1a**–**d** with either 2-aminobenzhydrylamines or 2,3-diaminopyridine required higher temperature and proceeded advantageously in boiling toluene, in the presence of DMAP. When **1a** ($R^1 = CH_3$) was used as a substrate, the reaction gave rise to the formation of the target 2-mercaptobenzenesulfonamides **2**, **3**, and **6**. However, in analogous reactions of **1b**–**d** ($R^1 = 4\text{-}R^2PhNHCO$), the primarily formed 2-mercaptobenzenesulfonamides [**4,5,7**–**9**] could not be separated due to their oxidation to disulfides **4a**, **5a**, **7a**–**9a.** The reactions of **1a** with more basic ethylenediamines carried out under similar conditions (DMAP, toluene) led to the formation of the disulfides **10a** and **11a**, while in boiling methanol in the absence of DMAP, the expected 2-mercapto derivatives **10** and **11** were obtained (Scheme 2).

The compounds **2**, **3**, **4a**, **5a**, **6**, **7a**, **8a**, **9a**, **10**, and **11** were evaluated for their in vitro anti-HIV activity. Most of the tested compounds were essentially inactive, while two pyrido[3,2-*d*]imidazole derivatives displayed moderate activity. The disulfide **7a** ($EC_{50} = 113.0$ μM, $TI_{50} > 1.77$, percent of protection = 96) showed a lower range of percent protection than 2-mercaptobenzenesulfonamide **6** ($EC_{50} = 32.1$ μM, $TI_{50} = 6.2$, percent of protection = 116).

The data in Table 2 show that the compounds **2**, **3**, **4a**, **5a**, **6**, **8a**, **10**, **11** exhibited a moderate anticancer activity against some human cell lines. From the data in Table 2 we can observe that quinazoline derivatives (**2**, **3**, **4a**, and **5a**) exhibited interesting selectivity at low molar concentrations (10^{-7} to 10^{-5}) and being placed in decreasing order of activity **4a** > **5a** > **2** > **3**. These sulfonamides show significant selectivities in subpanel cell lines with values of percent growth inhibition at

Table 2
In vitro anticancer data for compounds **2**, **3**, **4a**, **5a**, **6**, **8a**, **10**, **11** [a]

No.	Panel cell line	GI_{50} (μM)	TGI (μM)	LC_{50} (μM)
2	*Leukemia*			
	CCRF-CEM	32.6	[b]	[b]
	SR	23.3	58.3	[b]
	Non-small cell lung cancer			
	A549/ATCC	18.1	[b]	[b]
	NCI-H322M	15.2	[b]	[b]
	NCI-H460	12.9	[b]	[b]
	Colon cancer			
	HCT-116	7.12	[b]	[b]
	HCT-15	59.3	[b]	[b]
	KM12	58.6	[b]	[b]
	CNS cancer			
	SF-268	39.0	[b]	[b]
	SF-295	31.5	[b]	[b]
	SNB-19	34.0	[b]	[b]
	U251	37.6	[b]	[b]
	Melanoma			
	LOX IMVI	39.3	[b]	[b]
	Ovarian cancer			
	OVCAR-4	13.6	[b]	[b]
	Renal cancer			
	768-0	8.19	[b]	[b]
	CAKI-1	45.8	[b]	[b]
	RXF 393	48.2	[b]	[b]
	SN12C	50.7	[b]	[b]
	UO-31	24.9	46.5	86.7
	Prostate cancer			
	PC-3	16.4	80.9	[b]
	Breast cancer			
	MDA-MB-435	31.7	[b]	[b]
	T-47D	6.56	[b]	[b]
3	*Leukemia*			
	CCRF-CEM	57.8	[b]	[b]
	SR	14.3	[b]	[b]
	Non-small cell lung cancer			
	A549/ATCC	17.8	[b]	[b]
	NCI-H226	15.4	[b]	[b]
	NCI-H322M	20.3	[b]	[b]
	NCI-H460	8.80	[b]	[b]
	Colon cancer			
	HCT-116	36.8	[b]	[b]
	CNS cancer			
	SF-268	9.13	[b]	[b]
	SF-295	20.9	[b]	[b]
	SNB	28.5	[b]	[b]
	U251	33.8	[b]	[b]
	Melanoma			
	LOX IMVI	47.5	[b]	[b]
	Ovarian cancer			
	OVCAR-4	43.6	[b]	[b]
	Renal cancer			
	UO-31	46.1	83.7	[b]
	Prostate cancer			
	PC-3	1.84	[b]	[b]
	Breast cancer			
	T-47D	9.01	[b]	[b]
4a	*Leukemia*			
	CCRF-CEM	0.25	0.79	13.0
	HL-60 (TB)	13.0	29.1	64.9
	K-562	18.5	[b]	[b]
	MOLT-4	14.9	34.0	77.4
	RPMI-8226	55.3	[b]	[b]
	SR	4.44	7.15	26.8
	Non-small cell lung cancer			
	HOP-62	64.8	[b]	[b]
	Melanoma			
	M14	33.0	[b]	[b]
	Ovarian cancer			
	OVCAR-5	37.8	[b]	[b]
	Breast cancer			
	MDA-MB-231/ATCC	20.5	69.9	[b]
5a	*Leukemia*			
	CCRF-CEM	4.94	16.1	44.2
	HL-60 (TB)	0.41	18.2	47.3
	K-562	23.4	[b]	[b]
	MOLT-4	17.5	38.0	82.2
	SR	15.9	37.5	88.6
	Melanoma			
	M14	50.9	[b]	[b]
	SK-MEL-5	53.6	[b]	[b]
	Breast cancer			
	MDA-MB-231/ATCC	14.0	[b]	[b]
6	*Non-small cell lung cancer*			
	NCI-H226	52.3	[b]	[b]
	CNS cancer			
	SF-295	58.0	[b]	[b]
	Breast cancer			
	MDA-MB-231/ATCC	45.3	[b]	[b]
	T-47D	46.8	[b]	[b]
8a	*Leukemia*			
	K-562	3.86	[b]	[b]
	Renal cancer			
	RXF-393	28.6	[b]	[b]
10	*Leukemia*			
	CCRF-CEM	7.34	[b]	[b]
	RPMI-8226	10.5	[b]	[b]
	MOLT-4	47.2	[b]	[b]
	Non-small cell lung cancer			
	NCI-H522	40.7	[b]	[b]
	Melanoma			
	MALME-3M	43.7	[b]	[b]
11	*Non-small cell lung cancer*			
	NCI-H460	56.0	[b]	[b]
	NCI-H522	40.5	[b]	[b]
	CNS cancer			
	SF-268	36.0	[b]	[b]
	SF-295	48.9	[b]	[b]
	U251	54.9	[b]	[b]
	Renal cancer			
	UO-31	17.7	47.4	[b]
	PC-3	27.8	[b]	[b]
	Breast cancer			
	T47D	10.8	[b]	[b]

[a] The response parameters GI_{50}, TGI, and LC_{50} are interpolated values of the concentrations at which the percentage growth is +50, 0, and −50, respectively.

[b] TGI or LC_{50} values > 100 μM.

10^{-4} M for: **2** (leukemia SR, 129%; renal cancer UO-31, 161%; prostate cancer PC-3, 107%); **3** (renal cancer UO-31, 115%); **5a** (leukemia CCRF-CEM, 190%; HL-60 (TB), 189%; MOLT-4, 163%; SR, 157%); **4a** (leukemia CCRF-CEM, 191%; HL-60 (TB), 177%; MOLT-4, 166%; SR, 170%; breast cancer MDA-MB-231/ATCC, 115%). The selectivity of **4a** was maintained high at 145% at 10^{-5} M and 110% at 10^{-6} M (CCRF-CEM) and 135% at 10^{-5} M (SR) in the leukemia cell lines. The highest sensibility against leukemia cell lines for bis[2-(6-chloro-4-phenyl-3,4-dihydroquinazolin-2-yl)aminosulfonyl-5-chloro-4-(4-R^2-phenylcarbamoyl)-phenyl]disulfides (**4a**, $R^2 = H$; **5a**, $R^2 = Cl$) was confirmed by the mean graph midpoint values of $\log_{10}$ GI_{50}, $\log_{10}$ TGI, and $\log_{10}$ LC_{50} equal to -6.38 (-6.59), -4.74 (-6.10), -4.33 (-4.89), respectively.

An electron-withdrawing substituent R^1 (CONHPhR^2) seems to be advantageous for the anticancer activity of the quinazoline derivatives, while in the pyridoimidazole series the disulfides **7a** and **9a** (R^1 = CONHPhR^2) proved to be inactive towards all tumor cell lines. On the contrary, the substitution at the C-5 position of the benzene ring by the electron-donating methyl group still leads to an active compound **6**. At the present stage, we may infer that the antiproliferative activity of the tested compounds depends on the size and electronic character of all substituents. In view of these results together with the previous findings [11,13] we can conclude that further research among 2-mercaptobenzenesulfonamide derivatives could be useful for the discovery of new anticancer agents.

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