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Synthesis and anti-HIV-1 activity of a novel series of 1,4,2-benzodithiazine-dioxides

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Abstract—Previously, we discovered a series of novel benzodithiazines-dioxides with both antiviral and anticancer activities. In order to design compounds with distinct antiviral properties, we prepared new compounds with modifications on the imidazole and pyrimidine rings. Herein, we present the synthesis and antiviral activity of 8-chloro-2,3-dihydroimidazo[1,2-*b*][1,4,2]benzodithiazine 5,5-dioxides (**22**, **23**, **30**, and **31**) and 9-chloro-2,3,4-trihydropyrimido[1,2-*b*][1,4,2]benzodithiazine 6,6-dioxides (**14**, **24**, **25**, and **27**). We successfully identified a lead compound with remarkable anti-HIV-1 activity ($EC_{50} = 0.09\ \mu M$). These compounds showed minimal cytotoxicity and are therefore suitable for antiviral development.

Because of the recent increase of HIV-1 infection worldwide and the lack of cost-effective treatment for many of the economically disadvantaged patients, there is an urgent need to prepare novel antiviral drugs that are effective and inexpensive. Currently used antiretroviral drugs show serious side effects and the transmission of drug-resistance viruses is on the rise. It is now very clear that effective treatment against HIV infection requires a combination of highly active antiretroviral drugs. Therefore, developing drugs with novel mechanism of action is of paramount importance.

During the past several years we have discovered novel small-molecule sulfonamides with remarkable anticancer and antiviral activities. Selected examples showed significant cytotoxicity in cell-based assays even though they were very effective in HIV-1 integrase-based assays. Therefore, these compounds were subsequently modified for their antiviral properties. To separate these two properties it required the development of a coherent structure–activity relationship among several classes of closely related sulfonamides. Our interest in sulfonamides stems from several recent observations in our laboratories with these compounds and a growing body of literature detailing their different biological properties.[1,2] In general, these molecules are drug-like and numerous clinically used drugs broadly speaking belong to the sulfonamide class of drugs. In many cases they are readily synthesizable from very inexpensive starting materials. Moreover, their biological safety and efficacy are well documented.

Previously, we described the syntheses and anti-HIV activities of various 4-chloro-2-mercapto-5-methylbenzenesufonamide derivatives (I, Fig. 1) with a variety of heteroaromatic ring system substituted on the nitrogen atom of the sulfonamide moiety.[3–8] Some of these com-

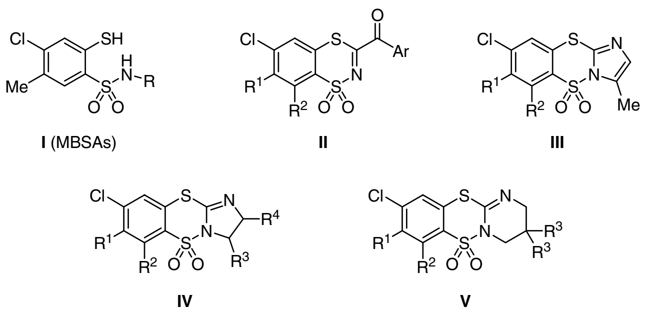

Figure 1.

Keywords: Imidazo[1,2-*b*][1,4,2]benzodithiazines; Pyrimido[1,2-*b*][1,4,2]benzodithiazines; Synthesis; Anti-HIV activity.

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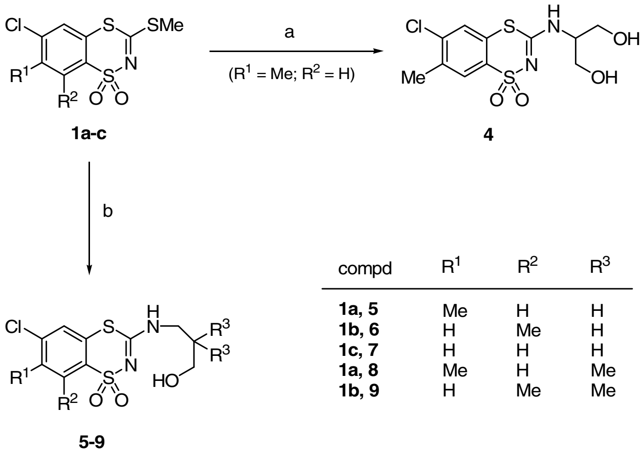
pounds inhibited purified HIV-1 integrase in the low micormolar range.[9,10] For example, the cyclic analogues of 2-mercaptobenzenesulfonamides (II and III, Fig. 1) inhibited integrase in vitro and a clear structure–activity relationship was then established among these congeners.[11,12] Interestingly, some of the compounds with antiviral activity in cell-based assays were inactive against purified integrase. These findings, therefore, prompted us to prepare new analogues and to develop new methodologies for the syntheses of the benzodithiazines of general formulas IV and V as potential anti-HIV agents. Herein, we show that several of these compounds are endowed with remarkable anti-HIV activity with minimal cytotoxicity.

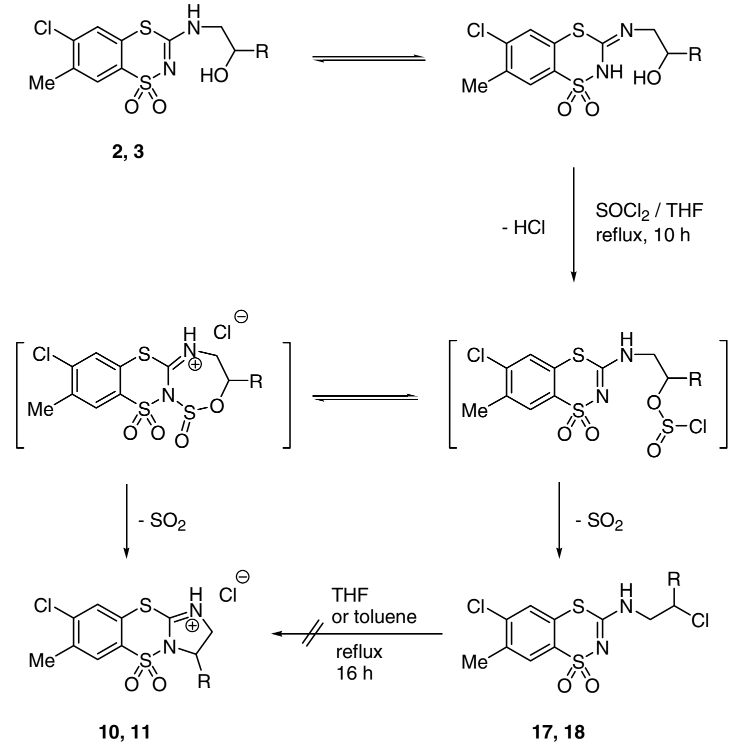


compd	R^1	R^2	R^3
1a, 5	Me	H	H
1b, 6	H	Me	H
1c, 7	H	H	H
1a, 8	Me	H	Me
1b, 9	H	Me	Me

Scheme 1. Synthesis of the *N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)aminopropanol derivatives **4**–**9**. Reagents and conditions: (a) 2-amino-1,3-propanediol (1.03 molar equiv), dry MeOH, rt, 54 h, 89%; (b) 3-aminopropanol or 3-amino-2,2-dimethylpropanol (1.1 molar equiv), dry MeOH, rt, 72 h, 89–93%.

The previously described methods were employed for the synthesis of 3-methylthio-1,4,2-benzodithiazines **1a-c**[13,14] and *N*-(1,2,4-benzodithiazin-3-yl)aminoalkanoles **2-3**[15]. In a similar fashion we prepared the novel *N*-(6-chloro-1,1-dioxo-1,4,2-benzodithiazin-3-yl)aminoalkanoles **4-9** (Scheme 1).

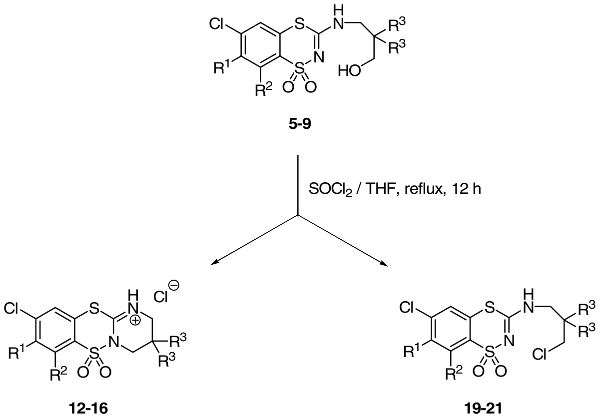
The syntheses of target compounds were achieved by a convenient two- or three-step procedure starting from *N*-(1,4,2-benzodithiazin-3-yl)aminoalkanoles **2**–**9** as shown in Schemes 2–5. First, the reaction of **2**–**9** with thionyl chloride carried out in tetrahydrofuran at elevated temperature led to the formation of 2,3-dihydroimidazo[1,2-*b*][1,4,2]benzodithiazine hydrochlorides (**10**–**11**, Scheme 2) and 2,3,4-trihydropyrimidine[1,2-*b*][1,4,2]benzodithiazine hydrochlorides (**12**–**16**, Scheme 3). We also isolated and characterized the 6-chloro-3-(chloroalkylamino)-1,4,2-benzodithiazine 1,1-dioxides that were formed as by products (**17**–**21**, Schemes 2 and 3) or the main product (**29**, Scheme 5). Second,



compds	R	Yield %
2, 10	H	45
3, 11	Me	41

compds	R	Yield %
2, 17	H	47
3, 18	Me	47

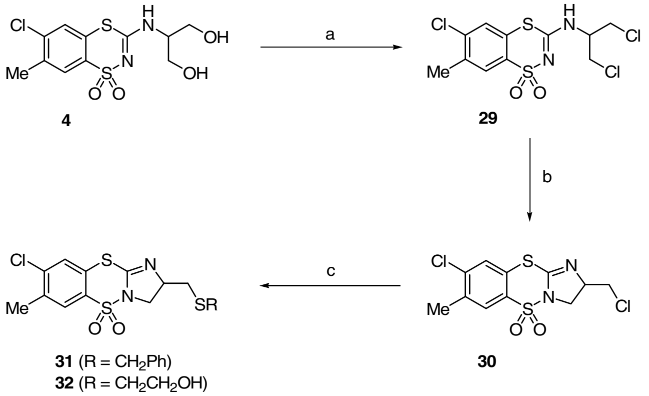
Scheme 2. Synthesis and proposed mechanism of the formation of the 2,3-dihydro-imidazo[1,2-*b*][1,4,2]benzodithiazine hydrochlorides **10**, **11** and 3-(chloroalkylamino)-1,4,2-benzodithiazines **17**, **18**.



compds	R^1	R^2	R^3	Yield %
5, 12	Me	H	H	57
6, 13	H	Me	H	49
7, 14	H	H	H	43
8, 15	Me	H	Me	89
9, 16	H	Me	Me	91

compds	R^1	R^2	R^3	Yield %
5, 19	Me	H	H	35
6, 20	H	Me	H	47
7, 21	H	H	H	49

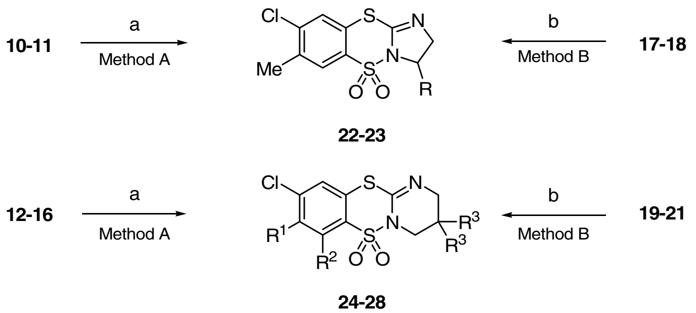
Scheme 3. Synthesis of the 2,3,4-trihydropyrimidino[1,2-*b*][1,4,2]benzodithiazine hydrochlorides **12**–**16** and 3-(3-chloropropylamino)-1,4,2-benzodithiazines **19**–**21**.



Scheme 5. Synthesis of the 2-substituted 8-chloro-2,3-dihydro-7-methyl-5,5-dioxoimidazo [1,2-*b*][1,4,2]benzodithiazines **30**–**32**. Reagents and conditions: (a) $SOCl_2$ (large excess), THF, rt 1 h and reflux 15 h, 90%; (b) K_2CO_3 (1.13 molar equiv), anhydrous acetone, rt 2 h and reflux 6 h, 90%; (c) phenylmethanethiol or 2-mercaptoethanol (1.08 molar equiv), K_2CO_3 (1.25 molar equiv), anhydrous acetone, rt 2 h, reflux 12 h, 70–72%.

upon treatment of the hydrochlorides **10**–**16** with NaOH in water at pH 8 the desired free benzodithiazines **22**–**28** were obtained in 90–98% yields (Scheme 4, Method A). The benzodithiazines **22**–**26** and **30** were also obtained in 70–90% yields by the reaction of corresponding 3-(chloroalkylamino)-1,4,2-benzodithiazines **17**–**21** (Scheme 4, Method B) **29** (Scheme 5) with K_2CO_3 in acetone. Third, the subsequent reactions of 2-(chloromethyl)-2,3-dihydroimidazo[1,2-*b*][1,4,2]benzodithiazine **30** with K_2CO_3 and phenylmethanethiol or 2-mercaptoethanol in anhydrous acetone afforded the expected thioesters **31** and **32**, respectively (Scheme 5). Structures of the compounds described in this paper were confirmed by elemental analyses, IR and NMR spectroscopic data[16] (Supporting Information).

Compounds **14**, **22**–**25**, **27**, **30**, and **31** were tested for their anti-HIV activities in cell-based assays. The antiviral assay performed at the National Cancer Institute is based on a protocol described by Wieslow et al.[17] The following is to be noted regarding the anti-HIV activity data with the tested compounds: (i) compound **31** was inactive ($EC_{50} > 200.0\ \mu M$), whereas the other compounds exhibited weak (**27**), moderate (**22**) or high (**14**, **23**–**25**, and **30**) activity (Table 1); (ii) the most active compounds were 4-chloro-2,3,4-trihydropyrimido[1,2-*b*][1,4,2]benzodithiazines **14**, **24**, and **25** (EC_{50} = 0.09–4.75 μM) (Table 1); (iii) pyrimido[1,2-*b*][1,4,2]benzodi-

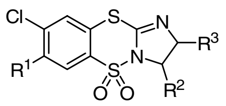


compds	R	Yield %
10, 22	H	98
17, 22	H	86
11, 23	Me	93
18, 23	Me	72

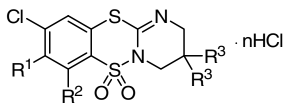
compds	R^1	R^2	R^3	Yields %
12, 24	Me	H	H	94
19, 24	Me	H	H	77
13, 25	H	Me	H	94
20, 25	H	Me	H	70
14, 26	H	H	H	98
21, 26	H	H	H	80
15, 27	Me	H	Me	90
16, 28	H	Me	Me	95

Scheme 4. Preparation of the imidazobenzodithiazines **22**–**23** and pyrimidobenzodithiazines **24**–**28** from their hydrochlorides **10**–**16** (Method A) and/or from 3-(chloroalkylamino)-1,4,2-benzodithiazines **17**–**21** (Method B). Reagents and conditions: (a) water, 1% aq solution of NaOH to pH 8, rt, 1 h; (b) K_2CO_3 (1.25 molar equiv), acetone, rt, 2 h and reflux 5 h.

Table 1. In vitro anti-HIV-1 drug screening results for 2,3-dihydroimidazo[1,2-*b*][1,4,2]benzodithiazines (**22**, **23**, **30**, **31**) and 2,3,4-trihydropyrimido[1,2-*b*][1,4,2]benzodithiazines (**14**, **24**, **25**, **27**)[a]



22, 23, 30, 31



14, 24, 25, 27

Compound	R^1	R^2	R^3	*n*	EC_{50}[b] (μM)	IC_{50}[c] (μM)	TI_{50}[d]
22	Me	H	H		16.50	134.7	8.2
23	Me	Me	H		8.52	107.0	12.6
30	Me	H	CH_2Cl		4.04	28.0	6.4
31	Me	H	CH_2SCH_2Ph		>200.0	>200.0	—
14	H	H	H	1	4.75	>200.0	>42.1
24	Me	H	H	0	0.98	>200.0	>204.1
25	H	Me	H	0	0.09	106.0	1177.7
27	Me	H	Me	0	162.50	>200.0	>1.23

[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}.

thiazine **25** bearing an electron-donating methyl group at position 7 showed the highest anti-HIV activity ($EC_{50} = 0.09\ \mu M$) and a very high therapeutic index (TI = 1177.7); (iv) the 8-methyl analogue **24** was less active ($EC_{50} = 0.98\ \mu M$) and further loss of activity was observed for the unsubstituted analogue **14** ($EC_{50} = 4.75\ \mu M$) and for compound **27** bearing three methyl groups at positions 3, 3 and 7 ($EC_{50} = 162.50\ \mu M$).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.07.089.

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16. General procedure for the preparation of benzodithiazinylaminopropanoles **5**–**9**: a mixture of the corresponding methylthiobenzodithiazine **1a**, **1b** or **1c** (0.02 mol) and 3-aminopropanol (1.65 g, 0.022 mol) or 3-amino-2,2-dimethylpropanol (2.27 g, 0.022 mol) in anhydrous methanol (45 mL) was stirred at room temperature for 72 h. To this reaction mixture, water (45 mL) was added drop wise with stirring at room temperature. After 4 h, product that precipitated was collected by filtration, washed with 50% aq solution of methanol (4× 5 mL), and dried at temperatures gradually increasing to 100 °C. In this manner 3-(6-chloro-8-methyl-1,1-dioxo-1,4,2-benzodithiazin-3-yl)aminopropanol (**6**) was obtained starting from methylthiobenzodithiazine **1b** (5.9 g) and 3-aminopropanol: yield 5.8 g (90%); mp 171–172 °C; IR (KBr) 3440 (OH), 3200 (NH), 1570 (C=N), 1290, 1155 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.68 (quin., 2H, CH_2), 2.62 (s, 3H, CH_3), 3.38 (t, $J = 7.1$ Hz, 2H, NCH_2), 3.44 (t, $J = 6.2$ Hz, 2H, CH_2O), 4.55 (br s, 1H, OH), 7.50 (d, $J = 1.4$ Hz, 1H, H-5), 7.68 (d, $J = 1.4$ Hz, 1H, H-7), 9.57 (br s, 1H, NH) ppm. General procedure for the preparation of 2,3,4-trihydropyrimido[1,2-*b*][1,4,2]benzodithiazine hydrochlorides **12**–**16** and 3-(3-chloropropylamino)benzodithiazines **19**–**21**: a

mixture of the corresponding 1,4,2-benzodithiazyn-3-ylaminopropanol **5**, **6**, **7**, **8** or **9** (0.015 mol), THF (20 mL), and $SOCl_2$ (8 mL) was refluxed with stirring for 12 h, then cooled to room temperature and left overnight. The precipitate of the appropriate pyrimidobenzodithiazine hydrochloride **12**–**16** was filtered, washed with THF (3× 1.5 mL) and toluene (4× 1.5 mL), and dried. From the filtrates mixture, the excess $SOCl_2$, THF, and toluene were evaporated under reduced pressure. The dry residue thus obtained was recrystallized from toluene, giving the adequate 3-(3-chloropropylamino-1,4,2-benzodithiazines **19**–**21**. In this manner 9-chloro-2,3,4-trihydro-7-methyl-6,6-dioxopyrimido[1,2-*b*][1,4,2]benzodithiazine hydrochloride (**13**) and 6-chloro-3-(3-chloropropylamino)-8-methyl-1,4,2-benzodithiazine 1,1-dioxide (**20**) were obtained starting from 3-(8-methyl-1,4,2-benzodithiazin-3-yl)aminopropanol **6** (4.81 g). Compound **13**, yield 2,5 g (49%): mp 191–192 °C; IR (KBr) 2735, 2630, 2470, 2375, 2260, 2070 (NH^+), 1620 (C=N), 1365, 1350, 1175 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.03 (quin., $J = 5.6$ Hz, 2H, H-3,3), 2.63 (s, 3H, CH_3-7), 3.52 (t, $J = 5.6$ Hz, 2H, H-2,2), 3.94 (t, $J = 5.6$ Hz, 2H, H-4,4), 5.45 (br s, 1H, NH^+), 7.71 (s, 1H, H-8), 7.92 (s, 1H, H-10) ppm. Compound **20**, yield 2.4 g (47%): mp 141–143 °C; IR (KBr) 32.70 (NH), 1575 (C=N), 1360, 1145 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.98 (quin., $J = 6.3$ Hz, 2H, CH_2–*CH_2*–CH_2), 2.61 (s, 3H, CH_3), 3.43 (t, $J = 6.3$ Hz, 2H, N–CH_2), 3.68 (t, $J = 6.3$ Hz, 2H, CH_2-Cl), 7.51 (s, 1H, H-7), 7.69 (s, 1H, H-5), 9.69 (s, 1H, NH) ppm. General procedure for the preparation of imidazobenzodithiazines **22**–**23** and pyrimidobenzodithiazines **24**–**28** from hydrochlorides **10**–**16** (Method A): to a stirred suspension of the corresponding imidazobenzodithiazine hydrochloride **10**–**11** or pyrimidobenzodithiazine hydrochloride **12**–**16** (0.006 mol) in water (50 mL), 1% aq solution of NaOH was dropped to pH 8. After 1 h of stirring, the precipitate was filtered off, washed thoroughly with water and 50% aq solution of methanol (2× 2 mL), and dried at 80 °C. In this manner 9-chloro-2,3,4-trihydro-8-methyl-6,6-dioxopyrimido[1,2-*b*][1,4,2]benzodithiazine (**25**) was obtained starting from pyrimidobenzodithiazine hydrochloride **13** (2.04 g); yield 1.7 g (94%): mp 126–127 °C; IR (KBr) 1625 (C=N), 1335, 1165 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (quin., $J = 5.1$ Hz, 2H, H-3,3), 2.60 (s, 3H, CH_3), 3.47 (t, $J = 5.1$ Hz, 2H, H-2,2), 3.80 (t, $J = 5.1$ Hz, 2H, H-4,4), 7.50 (s, 1H, H-7), 7.69 (s, 1H, H-10) ppm.

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