A New Type of Mixed Anhydride and Its Applications to the Synthesis of 7-Substituted 8-Chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazines with in Vitro Antitumor Activity

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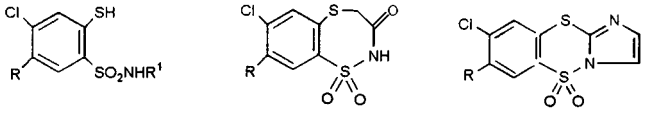
A new series of 8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine derivatives **8**−**25** with heteroaryloxycarbonyl or heteroarylcarbamoyl substituents at position 7 have been synthesized as potential antitumor agents. In this procedure a novel type of mixed anhydride **7** was prepared from 8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxylic acid **6** and methanesulfonyl chloride, which in turn was condensed either with heteroarylamines or heteroarylhydroxy compounds. All the compounds prepared were screened at the National Cancer Institute (NCI) for their activities against a panel of 60 tumor cell lines, and relationships between structure and antitumor activity in vitro are discussed. The amides **8**, **10**, **12**, **13**, **21**, and ester **25** were inactive, whereas the other compounds exhibited rather moderate activity against one or more human tumor cell lines. The prominent compound with remarkable activity (log GI_{50} < −8) and selectivity for the leukemia HL-60(TB) cell line was 2-methyl-8-quinolyl 8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxylate **24**.

Introduction

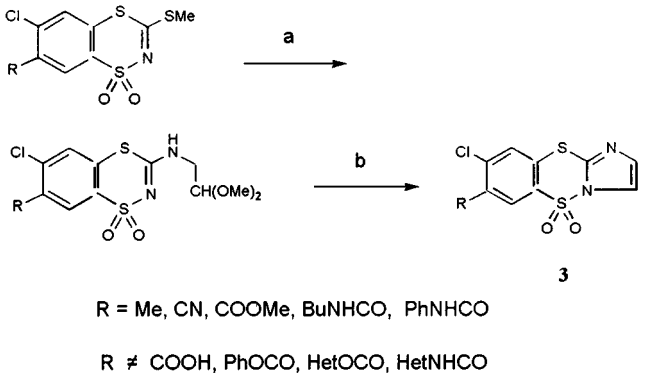
Recently, arylsulfonamides have attracted attention as anticancer[1−11] and anti-HIV[12−15] agents. We further found that cyclic analogues of 2-mercaptobenzenesulfonamides (**2** and **3**, Figure 1) also showed anti-HIV[31] and anticancer[32] properties. This led us to the assumption that expansion of a series of candidate antineoplastic agents of general formula **3** in which groups of varying sizes and electronic properties are placed at position 7 of 8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]-benzodithiazine ring may shed light on the structural features contributing to the antitumor activity. We reasoned that a relatively broad diversity of the structure **3** could be achieved by introducing either the heteroarylcarbamoyl or heteroaryloxycarbonyl at position 7. We also described the syntheses of various 4-chloro-2-mercaptobenzenesulfonamide derivatives **1** (MBSAs, Figure 1) with the nitrogen atom of sulfonamide moiety attached to a variety of heterocyclic ring systems. These compounds, depending on structure, exhibited either anticancer[18−27] or anti-HIV activities[18,21,25,26,28,29] and have been described by Neamati et al.[30] as a novel class of potent HIV-1 integrase inhibitors.



1 (MBSAs) **2** **3**

Figure 1.

Scheme 1. Previously Described Synthesis of the Compounds **3**[a]



R = Me, CN, COOMe, BuNHCO, PhNHCO

R ≠ COOH, PhOCO, HetOCO, HetNHCO

[a] Reagents and yields: (a) $H_2NCH_2CH(OMe)_2$ (1 molar equiv), dry toluene or benzene, reflux, 14−20 h, 51−79%; (b) 98% H_2SO_4, 20−37 °C, 8−10 h, 92−97%.

Results and Discussion

Our initial attempt was to obtain the desired compounds by the method described previously[31] and depicted in Scheme 1, but this strategy was not successful. Therefore, we have developed a method in which a new type of mixed anhydride **7** of the hypothetical methyleneorthosulfonic acid was a key intermediate. Starting from 6-chloro-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylic acid **4**[33] and aminoacetaldehyde dimethylacetal, we obtained compound **5**, which upon treatment with 98% sulfuric acid at room temperature for 18 h afforded the expected 8-chloro-5,5-dioxoimidazo-[1,2-*b*][1,4,2]benzodithiazine-7-carboxylic acid **6** in 96% yield (Scheme 2).

The reaction of a carboxylic acid with methanesulfonyl chloride in the presence of base usually gives rise to the corresponding mixed sulfonic−carboxylic anhydride.[34] However, when we treated **6** (1 equiv) with methanesulfonyl chloride (0.75 equiv) in methylene chloride at −15 °C in the presence of triethylamine (1.25

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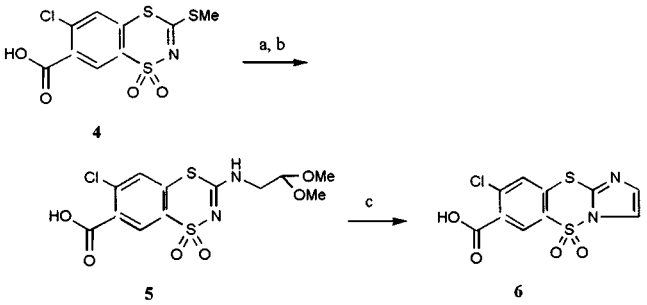
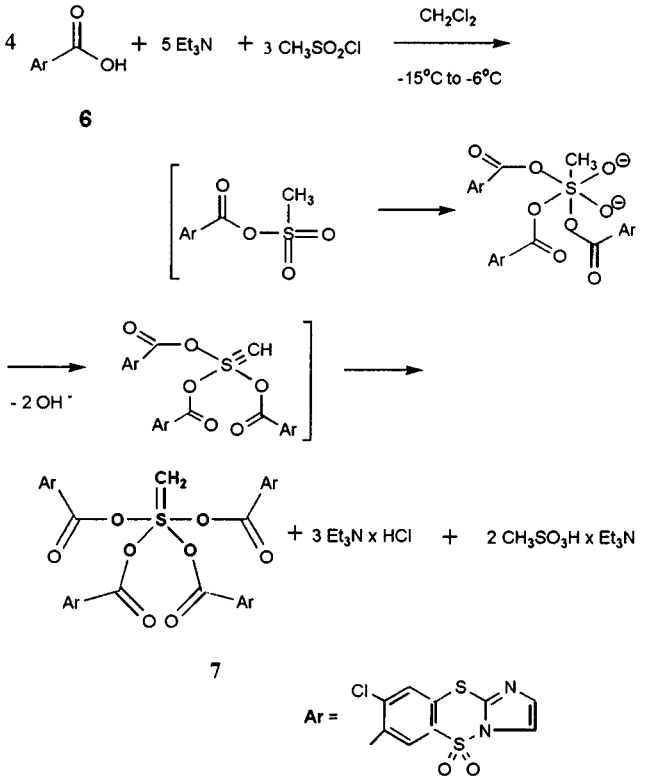
Scheme 2. Synthesis of the 8-Chloro-5,5-dioxoimidazo-[1,2-*b*][1,4,2]benzodithiazine-7-carboxylic Acid 6[a]



[a] Reagents and yields: (a) $H_2NCH_2CH(OMe)_2$ (2 molar equiv), MeOH, reflux, 12 h; (b) H_2O, HCl, pH 1.5, 89%; (c) 98% H_2SO_4, 20−38 °C, 18 h, 96%.

Scheme 3. Proposed Mechanism of the Formation of the Mixed Anhydride **7**



equiv), a crystalline product was formed in 87% yield, which was analyzed for the methyleneorthosulfonic tetrakis(8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]-benzodithiazine-7-carboxylic) anhydride (**7**) (Scheme 3). The ^{1}H NMR spectrum of the product **7**, containing a nonstandard functional group, showed a lack of methyl protons, but the presence of a two-proton singlet at δ 5.76 and the correlation between this methylene proton and the carbon atom at δ 54.20 ($^1J(^{13}C,^1H) = 181$ Hz) was found in the $^1H-^{13}C$ heterocorrelated spectrum (HSQC, heteronuclear single quantum coherence spectrum). Moreover, the 1D distortionless enhancement by polarization transfer−heteronuclear multiple-quantum coherence (DEPT−HMQC) experiment[35] confirmed the presence of the methylene group of the mixed anhydride **7**. Hence, results from spectral as well as elemental analyses are fully consistent with the proposed structure. Quantum chemical calculations performed at the ab initio level[36] revealed a square pyramidal configuration of the central sulfur atom of **7**. It should also be emphasized that anhydride **7** proved to be stable for ca. 1 month, but upon prolonged storage for 1 year, it slowly decomposed to a complex mixture of products.

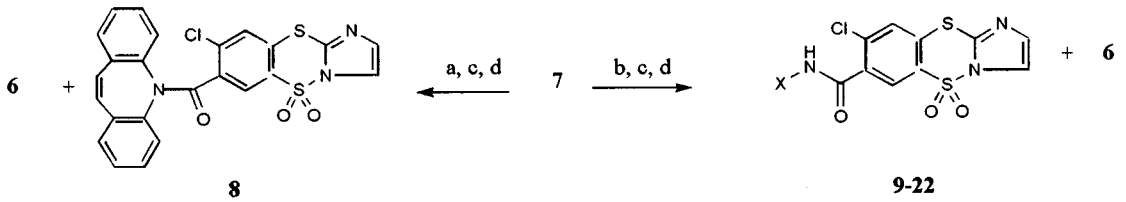
The desired imidazobenzodithiazinecarboxamides **8**−**22** and heteroaroyl imidazobenzodithiazinecarboxylates **23**−**25** were obtained by reacting the anhydride **7** with corresponding heteroarylamines (Scheme 4) and heteroarylols (Scheme 5), respectively. It is worthy noting that only two of four acyl groups of **7** are available for the formation of the desired products. Therefore, for the best results, the molar ratio of mixed anhydride **7**/primary or secondary amine/triethylamine was generally 1:2:2. In this way, the two remaining acyl groups could be recovered in the form of the corresponding carboxylic acid **6** by quenching the reaction mixture with water (pH 8−9) and filtering off the resulting amide. Acid **6** precipitated from the filtrate upon treatment with diluted hydrochloric acid (see Experimental Section).

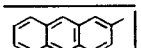
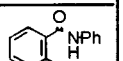
We have also developed methods for the syntheses of the 8-(3,4-dihydro-4-oxo)quinazoline derivative **26** and the previously not described 2-substituted 4,4,6-trioxo-5,6-dihydro-3,4,1,5-benzaoxathiadiazocine **27** (Scheme 6).

Compounds **8**−**13**, **16**, **18**, **19**, **21**, **22**, and **24**−**27** were submitted to the National Cancer Institute (Bethesda, MD) for testing against a panel of approximately 60 tumor cell lines. Details of this test system and the information, which is encoded by the activity pattern over all cell lines, have been published.[37−39] The antitumor activity of a test compound is given by three parameters for each cell line: log GI_{50} value (GI_{50} = molar concentration of the compound that inhibits 50% net cell growth), log TGI value (TGI = molar concentration of the compound leading to total inhibition of net cell growth), and log LC_{50} value (LC_{50} = molar concentration of the compound leading to 50% net cell death). Furthermore, a mean graph midpoint (MG_MID) is calculated for each of the mentioned parameters, giving an averaged activity parameter over all cell lines. For the calculation of the MG_MID, insensitive cell lines are included with the highest concentration tested. The discovery of compounds with new selectivity patterns is one of the intentions of the screening program. Selectivity of a compound with respect to one or more cell lines of the screen is characterized by a high deviation of the particular cell line parameter compared to the MG_MID value.

The following is to be noted regarding the tumor cell growth inhibition data with the tested compounds: (i) Compounds **8**, **10**, **12**, **13**, **21**, and **25** were inactive (log $GI_{50} > -4$), whereas the other compounds **9**, **11**, **16**, **18**, **19**, **22**, **24**, **26**, and **27** exhibited moderate activity against one or more human tumor cell lines (Table 1). (ii) Generally, the most active compounds were **22**, **24**, and **19** (Table 1). (iii) Different cancer cell lines of the same tumor type possessed a variable response to inhibition of growth in the presence of the new derivatives (Table 2). For example, the NCI-522 lung cancer cells were susceptible to inhibition by **19** (log $GI_{50} = -5.91$, log TGI = −5.55, log $LC_{50} = -5.18$), whereas other lung cancer cell lines (such as A549/ATCC, EKVX, etc.) showed a much lower level of inhibition (log GI_{50} ranged from −4.83 to −4.62). The same situation has

Scheme 4. Synthesis of the 8-Chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxamides **8** and **9**−**22**[a]



compd	X
9	
10	
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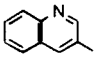
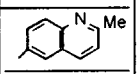
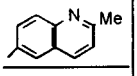
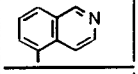
15	

compd	X
16	
17	
18	
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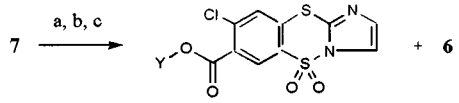
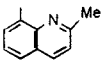
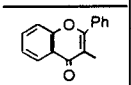
20	
21	
22	

[a] Reagents: (a) 5*H*-dibenzo[*b*,*f*]azepine or (b) primary amine X−NH_2, Et_3N, *p*-dioxane, reflux; (c) K_2CO_3, H_2O, 20 °C; (d) HCl, 71−90%.

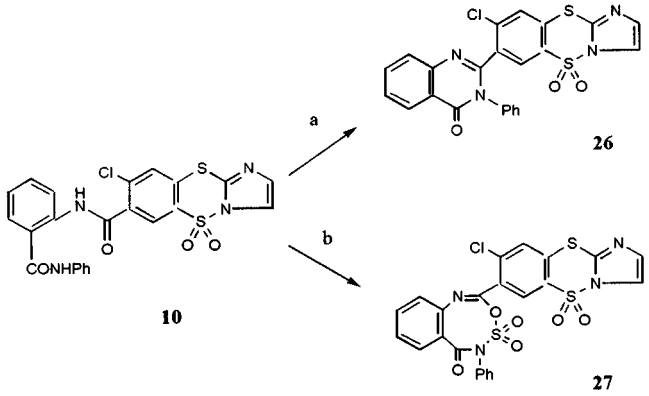
Scheme 5. Synthesis of the Heteroaryl 8-Chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxylates **23**−**25**[a]



compd	Y
23	
24	
25	

[a] Reagents: (a) hydroxy compounds Y−OH, *p*-dioxane, reflux; (b) $KHCO_3$, H_2O, 20 °C; (c) HCl, 87−90%.

Scheme 6. Synthesis of 8-Chloro-5,5-dioxoimidazo-[1,2-*b*][1,4,2]benzodithiazine Derivatives **26** and **27** by Cyclocondensation Reactions of Imidazobenzodithiazinecarboxamide **10**[a]



[a] Reagents: (a) thionyl chloride, reflux, 10 h, 71%; (b) sulfuric acid, room temperature, 12 h, 74%.

been evidenced in the case of diverse leukemia cell lines, with compound **24** acting selectively as a potent inhibitor (log GI_{50} < −8.00, log TGI < −8.00, log LC_{50} = −5.42) against the HL-60(TB) line, whereas other leukemia cell lines such as CCRF-CEM, K-62, and MOLT-4 did not reach the LC_{50} level. Other cell lines of this tumor, such as RMPI-8226 and SR, had an activity between the two extremes (log LC_{50} = −5.07 and −4.56) reported above . Also some of the tumors responded moderately to inhibition with compound **22**. This included HL-60(TB) and RMPI-8226 leukemia, UACC-257 melanoma, EKVX, HOP-62, NCIH322M, and NCI-460 non-small-cell lung cancer, OVCAR-3 ovarian cancer, HO-31 renal cancer, and MCF7 and T-470 breast cancer (Table 2).

Summary

We have developed a method for the synthesis of a new series of 7-substituted 8-chloro-5,5-dioxoimidazo-[1,2-*b*][1,4,2]benzodithiazine derivatives with antitumor activity, using a nonstandard mixed anhydride of a hypothetical methyleneorthosulfonic acid **7**. Compounds **22** and **24** were the most potent of all derivatives tested, and the latter displayed a high degree of selectivity against leukemia HL-60(TB) cells. The mechanism of the antitumor activity and further variations of the

Table 1. Overview of the Results of the in Vitro Antitumor Screening for Compounds **8**−**13**, **16**, **18**, **19**, **21**, **22,** and **24**−**27**[a,e]

compound	no. of the cell lines investigated	no. of the cell lines giving positive log GI_{50} [b] [M], log GTI [c] [M], and log LC_{50} [d] [M]					
		log GI_{50} [b] [M]		log GTI [c] [M]		log LC_{50} [d] [M]	
		no.	range	no.	range	no.	range
9	57	50	−5.19 to −4.06	10	−4.52 to −4.02	0	
11	58	58	−4.90 to −4.15	11	−4.51 to −4.02	1	−4.23
16	57	57	−5.40 to −4.47	55	−4.77 to −4.06	35	−4.35 to −4.00
18	57	56	−5.48 to −4.40	52	−4.70 to −4.04	18	−4.27 to −4.00
19	60	60	−5.91 to −4.55	60	−5.55 to −4.04	50	−5.18 to −4.01
22	60	60	−5.77 to −4.34	57	−5.49 to −4.31	46	−5.24 to −4.02
24	60	60	<−8.00 to −4.01	57	<−8.00 to −4.01	39	−5.42 to −4.04
26	57	46	−5.38 to −4.05	35	−4.81 to −4.07	19	−4.63 to −4.07
27	54	52	−5.33 to −4.09	27	−4.59 to −4.04	4	−4.20 to −4.04

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cells screen (see Table 2 and refs 37−39 for details). Compounds **8**, **10**, **12**, **13**, **21**, and **25** were inactive. [b] The log of the molar concentration that inhibitis 50% net cell growth. [c] The log of the molar concentration giving total growth inhibition. [d] The log of the molar concentration leading to 50% net cell death.

parent structure are currently being investigated to improve both potency and selectivity and to get more detailed information on the SAR.

Experimental Section

The following instruments and parameters were used: (melting points) Buchi 535 apparatus; (IR spectra) KBr pellets, 400−4000 cm^{-1} Perkin-Elmer 1600 FTIR spectrometer; (^{1}H NMR spectra) Varian Gemini 200 apparatus (chemical shifts are expressed as δ values relative to Me_4Si as standard). HSQC and DEPT−HMQC spectra were taken on a Varian Unity 500 spectrometer. Hydrogen and carbon spectral widths were 3749 and 18 518 Hz, respectively. Analyses of C, H, N were within ±O.4% of the theoretical values.

Synthesis of 6-Chloro-3-(2,2-dimethoxyethylamino)-1,1-dioxo-1,4,2-benzo-dithiazine-7-carboxylic Acid (5). To an ice-cold suspension of 6-chloro-3-methylthio-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylic acid **4**[33] (32.4 g, 0.1 mol) in anhydrous methanol (140 mL) was added with stirring aminoacetaldehyde dimethylacetal (21.03 g, 02 mol). After 0.5 h, the ice bath was removed and the reaction mixture was refluxed until the evolution of MeSH had ceased (10−12 h) (CAUTION: because of high toxicity, MeSH should be trapped in an aqueous NaOH solution). The solvent was evaporated under reduced pressure. The residue was dissolved in water (400 mL) and acidified to pH 3.5 with 1% hydrochloric acid. After 0.5 h of stirring, a small amount of insoluble side product was filtered out together with charcoal added, and the filtrate was slowly acidified to pH 1.5 with 0.5% hydrochloric acid. The title product, which precipitated, was immediately collected by filtration, washed thoroughly with water, and dried at temperatures gradually increasing to 105 °C: yield 34.0 g, 89%; mp 166−168 °C dec; IR (KBr) 3385, 3285 (OH, NH), 1710 (C═O), 1570 (C═N), 1310, 1160 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.29 (s, 6H, $2OCH_3$), 3.50 (t, J = 5.3 Hz, 2H, CH_2), 4.52 (t, J = 5.3 Hz, CH−O), 8.09 (s, 1H, 5-H), 8.29 (s, 1H, 8-H), 10.00 (t, 1H, NH) ppm. Anal. ($C_{12}H_{13}ClN_2O_6S_2$) C, H, N.

Synthesis of 8-Chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]-benzodithiazine-7-carboxylic acid (6). The benzodithiazine **5** (32.4 g 0.085 mol) was added portionwise at room temperature to 98% sulfuric acid (100 mL). After the exothermic reaction was complete (1 h, 36−38 °C), the reaction mixture was kept at room temperature for 18 h. The solution obtained was poured onto a water−crushed ice mixture (800−900 g, 0−3 °C) and stirred at room temperature for 3 h. The precipitated solid was collected by filtration, washed with water, and dried at 100 °C to afford the acid **6** (26.1 g, 96%): mp 305−310 °C dec; IR (KBr) 3155, 3130, 3080 (C−H, arom), 2920, 2860, 2805, 2730, 2625, 2550, 2490, 1722 (COOH), 1580 (C═N), 1375, 1195, 1180 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.37 (d, J = 1.7 Hz, 1H, 2-H), 8.17 (d, J = 1.7 Hz, 3-H), 8.38 (s, 1H, 9-H), 8.55 (s, 1H, 6-H) ppm. Anal. ($C_{10}H_5ClN_2O_4S_2$) C, H, N.

Synthesis of Methyleneorthosulfonictetrakis(8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxylic) Anhydride (7). To a suspension of carboxylic acid **6** (31.7 g, 0.1 mol) in anhydrous CH_2Cl_2 (75 mL) was added with stirring triethylamine (12.65 g, 0.125 mol). The solution obtained was cooled to −15 °C in an ice−NaCl bath, and to this was added dropwise over 45 min a solution of methanesulfonyl chloride (8.6 g, 0.075 mol) in anhydrous CH_2Cl_2 (50 mL). The reaction mixture was stirred for an additional 3 h at −12 to −6 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to 18 °C. The solid that precipitated was collected by filtration and washed successively with CH_2Cl_2 (5 × 10 mL), cold water (6 × 20 mL), and acetone (4 × 10 mL), CH_2Cl_2 (2 × 10 mL). Drying under vacuum gave anhydride **7** (28.5 g, 87%): mp 257−259 °C dec; IR (KBr) 1800, 1740 (C═O, anhydride), 1370, 1195, 1175 (SO_2), and other characteristics at 1580, 1530, 1505, 1430, 1325, 1290, 1095, 1030, 1005, 905, 875, 765, 685, 670, 610 cm^{-1}; ^{1}H NMR (DMSO-d_6,) δ 5.76 (s, 2H, S═CH_2), 7.37 (d, J = 1.6 Hz, 4H, 2-H), 8.16 (d, J = 1.6 Hz, 4H, H-3), 8.37 (s, 4H, 9-H), 8.54 (s, 4H, 6-H) ppm; ^{13}C NMR (DMSO-d_6) δ 54.20 (S═C), 164.18 (C═O), 117.53, 127.61, 130.58, 130.79, 131.93, 134.52, 137.77, 138.25 ppm. Anal. ($C_{41}H_{18}Cl_4N_8O_{16}S_9$) C, H, N.

General Procedure for the Preparation of Imidazobenzodithiazinecarboxamides 8 and 9−**22.** To a suspension of anhydride **7** (3.27 g, 0.0025 mol) and the appropriate amine (0.005 mol) in anhydrous *p*-dioxane (70 mL) was added triethylamine (0.5 g, 0.005 mol). The reaction mixture was stirred at room temperature for 1 h, followed by reflux for 12 h. The solvent was evaporated under reduced pressure. To the residue a solution of K_2CO_3 (2.2 g) in water (150 mL) was added, and this was stirred at room temperature for 1 h. The precipitate of the adequate carboxamide obtained was filtered out, washed successively with water (6 × 5 mL) and ethanol (5 × 4 mL), and dried. The water−filtrates (pH 9−10) mixture was acidified with 1% hydrochloric acid to pH 1. Carboxylic acid **6** thus obtained as a side product (yield: 0.9−1.2 g, 57−76%) was filtered out, washed with water, and dried at temperatures gradually increasing to 105 °C.

In this manner the following carboxamides were obtained.

5-(8-Chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazin-7-yl-carbonyl)-5*H*-dibenzo[*b,f*]azepine (8). Starting from 5*H*-dibenzo[*b,f*]azepine (0.97, 0.005 mol), the title compound **8** was obtained (2.2 g, 89%): mp 241−242 °C; IR (KBr) 1675 (C═O), 1375, 1355, 1190 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.14 (d, J = 12 Hz, 2H), 7.19−7.26 (m, 2H), 7.36 (d, J = 1.7 Hz, 1H), 7.40−7.48 (m, 4H), 7.55 (s, 1H), 7.59−7.83 (m, 2H), 8.12 (s, 1H), 8.17 (d, J = 1.7 HZ, 1H) ppm. Anal. ($C_{24}H_{14}ClN_3O_3S_2$) C, H, N.

***N*-(2-Anthryl)-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]-benzodithiazine-7-carboxamide (9).** Starting from 2-aminoanthracene (0.97 g), the title compound **9** was obtained (2.0 g, 81%): mp 298−300 °C dec; IR (KBr) 3280 (NH), 1665 (C═O), 1370, 1360, 1190, 1175 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.39−7.67 (m, 4H), 8.05−8.20 (m, 4H), 8.44−8.63 (m, 5H), 10.98 (s, 1H, NH) ppm. Anal. ($C_{24}H_{14}ClN_3O_3S_2$) C, H, N.

***N*-[2-(Phenylcarboamoyl)phenyl]-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxamide (10).** Starting from 2-aminobenzanilide (1.06 g), the title compound

Table 2. Inhibition of in Vitro Cancer Cell Lines by Selected Imidazo [1,2-*b*][1,4,2]benzodithiazine derivatives **19**, **22**, and **24**[a]

	response parameters: (A) log GI_{50} [b] [M], (B) log TGI [c] [M], (C) log LC_{50} [d] [M], and MG_MID[e]								
	compd **19**			compd **22**			compd **24**		
panel cell line	A	B	C	A	B	C	A	B	C
leukemia									
CCRF-CEM	−5.30	−4.61	−4.02	−5.49	−4.87	*e*	−5.60	−4.77	*e*
HL-60 (TB)	−4.87	−4.51	−4.15	−5.73	−5.43	5.13	<−8.00	<−8.00	−5.42
K-562	−4.80	−4.33	−4.06	−5.39	−4.70	*e*	−5.39	−4.42	*e*
MOLT-4	−4.72	−4.38	−4.03	−5.56	−5.03	−4.08	−5.34	−4.70	*e*
RMPI-8226	−5.03	−4.63	−4.24	−5.68	−5.39	−5.10	−5.77	−5.42	−5.07
SR	−5.52	−4.92	−4.33	−5.70	−5.32	*e*	−5.65	−5.23	−4.56
non-small-cell lung cancer									
A 549/ATCC	−4.62	−4.20	*e*	−4.90	−4.41	*e*	−4.91	−4.59	−4.20
EKVX	−4.69	−4.35	−4.01	−5.64	−5.33	−5.01	−4.77	−4.59	−4.11
HOP-62	−4.83	−4.52	−4.21	−5.78	−5.42	−5.06	−7.31	−4.79	−4.40
HOP-92	−4.82	−4.40	*e*	−5.23	−4.59	−4.02	−4.84	−4.17	*e*
NCI-H226	−4.71	−4.45	−4.19	−4.72	−4.48	−4.23	−4.82	−4.24	*e*
NCI-H23	−4.77	−4.47	−4.17	−4.93	−4.60	−4.26	−4.86	−4.25	*e*
NCI-H322M	−4.76	−4.47	−4.19	−5.75	−5.49	−5.24	−4.92	−4.61	−4.30
NCI-46-	−4.8-	−4.53	−4.26	−5.69	−5.37	−5.05	−5.58	−5.11	−4.57
NCI-522	−5.91-	−5.55	−5.18	−5.27	−4.65	−4.05	−4.98	4.58	−4.18
colon cancer									
COLO 205	−4.77	−4.51	−4.25	−4.76	−4.51	−4.25	−4.77	−4.51	−4.26
HCC-2998	−4.80	−4.53	−4.27	−5.47	−4.93	−4.26	−5.74	−5.33	−4.84
HCT-116	−4.79	−4.53	−4.26	−5.59	−5.27	−4.89	−5.34	−4.77	−4.39
HCT-15	−4.91	−4.47	−4.03	−5.28	−4.67	−4.14	−5.32	−4.56	*e*
HT29	−4.70	−4.33	*e*	−5.65	−5.28	−4.54	−5.02	−4.25	*e*
KM12	−4.91	−4.58	−4.24	−5.69	−5.41	−5.13	−5.18	−4.72	−4.36
SW-620	−4.77	−4.38	*e*	−4.92	−4.33	*e*	−5.11	−4.63	−4.23
melanoma									
LOX IMVI	−4.96	−4.59	−4.22	−5.28	−4.39	*e*	−5.30	−4.74	−4.34
MALME 3M	−4.70	−4.43	−4.16	−4.18	*e*	*e*	−4.77	−4.48	−4.19
M14	−4.75	−4.46	−4.17	−4.76	−4.33	−4.16	−5.14	4.64	−4.24
SK-MEL-2	−4.76	−4.48	−4.20	−5.00	−4.59	−4.19	−4.88	−4.49	−4.11
SK-MEL-28	−4.70	−4.42	−4.15	−5.61	−5.17	−4.33	−5.02	−4.57	−4.12
SK-MEL-5	-−4.78	−4.52	−4.26	−4.80	−4.47	−4.14	−4.97	−4.63	−4.30
UACC-257	−4.86	−4.57	−4.28	−5.74	−5.47	−5.20	−4.86	−4.57	−4.29
UACC-62	−4.84-	−4.56	−4.28	−5.27	−4.75	−4.38	−4.84	4.51	−4.17
prostate cancer									
PC-3	−4.77	−4.48	−4.18	−5.72	−5.45	−5.19	−5.57	−4.98	−4.49
PU-145	−4.79	−4.52	−4.56	−5.76	−5.49	−5.22	−5.26	−4.75	−4.37
CNS cancer									
SF-268	−4.72	−4.33	*e*	−5.47	−4.79	*e*	−5.02	*e*	*e*
SF-295	−4.74	−4.46	−4.19	−4.95	−4.60	−4.26	−4.94	−4.61	−4.27
SF-539	−4.71	−4.43	−4.14	−5.65	−5.31	−4.81	−5.74	−5.31	−4.59
SNB-19	−4.72	−4.43	−4.14	−4.92	−4.61	−4.30	−4.99	−4.47	*e*
SNB-75	−4.73	−4.45	−4.18	−5.41	−4.57	*e*	−5.16	−4.51	*e*
U251	−4.76	−4.51	−4.25	−5.34	−4.80	−4.35	−5.46	4.84	−4.42
ovarian cancer									
IGROV1	−4.93	−4.53	−4.12	−5.26	−4.63	4.10	−5.49	−5.16	−4.63
OVCAR-3	−4.82	−4.55	−4.27	−5.75	−5.46	−5.18	−5.53	−4.94	−4.46
OVCAR-4	−4.79	−4.41	−4.04	−5.56	−4.99	−4.06	−4.96	−4.61	−4.21
OVCAR-5	−4.66	−4.34	−4.01	−4.53	−4.08	*e*	−4.79	−4.43	−4.04
OVCAR-8	−4.76	4.43	−4.10	−5.63	−5.15	4.42	−5.42	−4.84	−4.27
SK-OV-3	−4.61	−4.19	*e*	−4.34	*e*	*e*	−4.57	−4.01	*e*
renal cancer									
768-0	−4.80	−4.53	−4.27	−4.78	−4.52	−4.26	−4.79	−4.42	−4.04
A498	−4.72	−4.46	−4.20	−4.87	−4.58	−4.20	−4.79	−4.39	*e*
ACHN	−4.75	−4.49	−4.23	−4.90	−4.44	*e*	−5.07	−4.47	*e*
CAKI-1	−5.07	−4.43	*e*	−5.32	−4.72	−4.29	−4.63	−4.20	*e*
RXF 393	−4.72	−4.40	−4.08	−5.33	−4.54	−4.25	−5.02	−4.60	−4.19
SN12C	−4.77	−4.49	−4.20	−4.82	−4.54	−4.25	−4.91	*e*	*e*
TK-10	−4.72	−4.46	−4.20	−4.98	−4.64	−4.30	−5.07	−4.68	−4.34
UO-31	−5.36	−4.83	−4.33	−5.68	−5.36	−4.30	−5.99	−4.37	*e*
breast cancer									
MCF 7	−5.17	−4.70	−4.35	−5.76	−5.47	5.18	−5.49	−4.83	−4.41
NCI/ADR-RES	−4.72	−4.35	*e*	−4.75	−4.41	−4.08	−4.84	−4.38	*e*
MDA-MB-231/ATCC	−4.71	−4.44	−4.17	−5.22	−4.61	−4.27	−4.94	−4.62	−4.31
HS 578T	−4.55	−4.04	*e*	−5.38	*e*	*e*	−4.87	*e*	
MDA-MB-435	−4.76	−4.50	−4.24	−5.09	−4.31	*e*	−5.10	−4.64	−4.26
MDA-N	−4.75	−4.48	−4.21	−4.87	−4.56	−4.25	−4.86	−4.04	*e*
BT 549	−4.74	−4.45	−4.16	−4.91	−4.49	−4.07	−4.94	−4.22	*e*
T-470	−4.63	−4.19	*e*	−5.77	−5.24	−5.11	−5.62	−5.20	−4.42
MG_MID	−4.83	−4.48	−4.17	−5.23	−4.75	−4.34	−5.10	−4.54	−4.16

[a] Data obtained from the NCI's in vitro disease-oriented human tumor cells screen (see refs 37−39 for details). [b] The log of the molar concentration that inhibits 50% net cell growth. [c] The log of the molar concentration giving total growth inhibition. [d] The log of the molar concentration leading to 50% net cell death. MG_MID = mean graph midpoint = arithmetical mean value for all tested cancer cell lines. If the indicated effect was not attainable within the used concentration interval, the highest tested concentration was used for the calculation. [e] The values of log TGI or log LC_{50} > −4.00.

10 was obtained (2.1 g, 82%): mp 265−265.5 °C dec; IR (KBr) 3280, 32235 (NH), 1665, 1660, 1640, (C=O, C=N), 1375, 1195, 1180 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.07−8.00 (m, 10H), 8.19 (s, 1H), 8.37 (s, 1H), 8.52 (s, 1H), 10.47 (s, 1H, NH), 10.98 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 117.60, 120.22, 120.49, 123.72, 125.00, 125.87, 128.03, 128.46, 128.55, 128.88, 130.57, 131.10, 131.16, 131.25, 133.21, 135.64, 135.94, 136.10, 139.00, 162.15, 166.14 ppm. Anal. ($C_{23}H_{15}ClN_4O_4S_2$) C, H, N.

***N*-(2-Pyridyl)-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]-benzodithiazine-7-carboxamide (11).** Starting from 2-aminopyridine 0.48 g), the title compound **11** was obtained (1.4 g, 71%): mp 358−360 °C dec; IR (KBr) 3140 (NH), 1650, 1625 (C=O, C=N), 1375, 1175 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.47 (s, 1H), 7.56−7.70 (m, 2H), 7.79 (s, 1H), 8.30 (t, J = 7.8 Hz, 1H), 8.96 (s, 1H), 9.10 (s, 1H), 9.19 (d, J = 6.8 Hz), 11.28 (s, 1H, NH) ppm. Anal. ($C_{15}H_9ClN_4O_3S_2$) C, H, N.

***N*-(4-Methyl-2-pyridyl)-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxamide (12).** Starting from 2-amino-4-methylpyridine (0.55 g), the title compound **12** was obtained (1.6 g, 77%): mp 355−357 °C dec; IR (KBr) 3135 (NH), 1655, 1625 (C=O, C=N), 1360, 1190, 1180 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.46 (s, 3H, CH_3), 7.41 (d, J = 6.7 Hz, 1H), 7.45 (s, 2H), 7.78 (s, 1H), 8.88 (s, 1H), 9.00 (d, J = 6.7 Hz, 1H), 9.07 (s, 1H), 11.29 (s, 1H, NH) ppm. Anal. ($C_{16}H_{11}ClN_4O_3S_2$) C, H, N.

***N*-(3-Methyl-2-pyridyl)-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxamide (13).** Starting from 2-amino-3-methylpyridine (0.55 g), the title compound **13** was obtained (1.8 g, 88%): mp 341−342 °C dec; IR (KBr) 3135 (NH), 1630, 1610 (C=O, C=N), 1375, 1185, 1175 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (s, 3H, CH_3), 7.20−7.54 (m, 4H), 7.89 (d, J = 7.5 Hz, 1H), 8.99 (d, J = 7.5 Hz, 1H), 9.22 (s, 1H, NH) ppm. Anal. ($C_{16}H_{11}ClN_4O_3S_2$) C, H, N.

***N*-(2-Quinolyl)-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]-benzodithiazine-7-carboxamide (14).** Starting from 2-aminoquinoline (0.72 g), the title compound **14** was obtained (1.7 g, 77%): mp 219−221 °C dec; IR (KBr) 3200 (NH), 1690 (C=O), 1615 (C=N), 1385, 1190, 1175 (SO_2) cm $^{-1}$; ^1H NMR (DMSO-d_6) δ 7.39 (s, 1H), 7.51−7.81 (m, 3H), 7.98 (d, J = 8.2 Hz, 1H), 8.38−8.49 (m, 3H), 8.61 (s, 1H), 11.64 (s, 1H, NH) ppm. Anal. ($C_{19}H_{11}ClN_4O_3S_2$) C, H, N.

***N*-(3-Quinolyl)-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]-benzodithiazine-7-carboxamide (15)**. Starting from 3-aminoquinoline (0.72 g), the title compound **15** was obtained (1.8 g, 81%): mp 232−234 °C; IR (KBr) 3305 (NH), 1670 (C=O), 1610 (C=N), 1380, 1190, 1170 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.39 (d, J = 1.6 Hz, 1H), 7.58−7.74 (m, 2H), 7.99−8.04 (m, 2H), 8.20 (d, J = 1.6 Hz), 8.44 (s, 1H), 8.68 (s, 1H), 8.84 (s, 1H), 9.00 (s, 1H), 11.23 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 117.62, 123.18, 126.17, 127.26, 127.64, 127.90, 128.36, 128.60, 130.62, 131.03, 131.16, 132.19, 133.33, 135.63, 136.34, 138.55, 144.61, 149.02, 162.76 ppm. Anal. ($C_{19}H_{11}ClN_4O_3S_2$) C, H, N.

***N*-(6-Quinolyl)-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]-benzodithiazine-7-carboxamide (16).** Starting from 6-aminoquinoline (0.72 g), the title compound **16** was obtained (2.0 g, 90%): mp 255−257 °C dec; IR (KBr) 3240 (NH), 1675 (C=O), 1625 (C=N), 1365, 1190, 1175 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 739 (s, 1H), 7.50−7,56 (m, 1H), 7.86−8.07 (m, 2H), 8.20 (s, 1H), 8.37−8.63 (m, 4H), 8.84 (d, J = 3.4 Hz, 1H), 11.06 (s, 1H, NH). Anal. ($C_{19}H_{11}ClN_4O_3S_2$) C, H, N.

***N*-(2-Methyl-6-quinolyl)-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxamide (17).** Starting from 6-amino-3-methylquinoline (0.8 g), the title compound **17** was obtained (2.0 g, 88%): mp 286−288 °C dec; IR (KBr) 3300 (NH), 1665 (C=O), 1625 (C=N), 1375, 1190, 1175 (SO_2) cm^{-1}; H NMR (DMSO-d_6) δ 3.36 (s, 3H, CH_3), 7.37−7.40 (m, 2H), 7.42−7.95 (m, 2H), 8.17−8.26 (m, 2H), 8.42 (s, 2H), 8.60 (s, 1H), 10.98 (s, 1H, NH) ppm. Anal. ($C_{20}H_{13}ClN_4O_3S_2$) C, H, N.

***N*-(5-Isoquinolyl)-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]-bnezodithiazine-7-carboxamide (18).** Starting from 5-aminoisoquinoline (0.72 g), the title compound **18** was obtained (1.7 g, 77%): mp 256−257 °C dec; IR (KBr) 3220 (NH), 1685 (C=O), 1360, 1190, 1170 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.38 (d, J = 8 Hz, 1H), 7.75 (t, J = 7.9 Hz, 1H), 7.91−8.12 (m, 4H), 8.14 (d, J = 8 Hz, 1H), 8.57 (d, 7.75 (t, J = 7.9 Hz, 1H), 7.91−8.12 (m, 4H), 8.14 (d, J = 8 Hz, 1H), 8.57 (d, J = 5.9 Hz, 1H), 8.78 (s, 1H), 9.36 (s, 1H), 10.86 (s, 1H, NH) ppm. Anal. ($C_{19}H_{11}ClN_4O_3S_2$) C, H, N.

***N*-(2-Thiazolyl)-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]-benzodithiazine-7-carboxamide (19).** Starting from 2-aminothiazole (0.5 g), the title compound **19** was obtained (1.8 g, 90%): mp 367−370 °C dec; IR (KBr) 3240 (NH), 1660 (C=O), 1375, 1190, 1175 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.38 (s, 3H), 7.59 (s, 1H), 8.19 (s, 1H), 8.40 (s, 1H), 8.65 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 114.35, 117.59, 126.89, 130.61, 130,90, 130.95, 133.70, 133.85, 136.60, 137.41, 138.46, 157.99, 162.24 ppm. Anal. ($C_{13}H_7ClN_4O_3S_2$) C, H, N.

***N*-(4-Phenyl-2-thiazolyl)-8-chloro-5,5,-dioxoimidazo-[1,2-*b*][1,4,2]benzodithiazine-7-carboxamide (20).** Starting from 2-amino-4-phenylthiazole (0.9 g), the title compound **20** was obtained (2.1 g, 89%): mp 182−185 °C dec; IR (KBr) 3150 (NH), 1685 (C=O), 1375, 1185, 1175 (SO_2) cm^{-1}; ^1H NMR (DMSO-d) δ 7.30−7.48 (m, 4H), 7.77−7.94 (m, 3H), 8.19 (s, 1H), 8.40 (s, 1H), 8.68 (s, 1H), 13.12 (s, 1H, NH) ppm. Anal. ($C_{19}H_{11}ClN_4O_3S_3$) C, H, N.

***N*-(Benzothiazol-5-yl)-8-chloro-5,5,-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxamide (21).** Starting from 5-aminobenzothiazole (0.75 g), the title compound **21** was obtained (2.0 g, 89%): mp 308−309 °C dec; IR (KBr) 3285 (NH), 1665 (C=O), 1605 (C=N, arom ring), 1370, 1190, 1175 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.38 (t, J = 2 Hz, 1H), 7.67−7.73 (m, 1H), 8.09 (d, J = 8.8 Hz, 1H), 8.19 (d, J = 1.6 Hz, 1H), 8.43 (s, 1H), 8.60 (s, 1H), 8.65 (d, J = 1.6 Hz, 1H), 9.33 (s, 1H), 10.99 (s, 1H, NH) ppm. Anal. ($C_{17}H_9ClN_4O_3S_3$) C, H, N.

***N*-(Benzo-2,1,3-thiodiazol-4-yl)-8-chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxamide (22)**. Starting from 4-aminobenzo-2,1,3-thiadiazole (0.76 g), the title compound **22** was obtained (1.8 g, 80%): mp 224−226 °C; IR (KBr) 3400 (NH), 1685 (C=O), 1610 (C=N), 1370, 1185, 1175 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.38 (s, 1H), 7.73−7.90 (m, 2H), 8.19 (s, 1H), 8.44 (t, J = 7.3 Hz, 2H), 8.57 (s, 1H), 11.34 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 116.94, 117.64, 118.10, 126.40, 128.31, 129.85, 130.61, 130.68, 130.76, 132.92, 135.97, 136.35, 138.65, 148.04, 154.70, 163.25 ppm. Anal. ($C_{16}H_8ClN_5O_3S_3$) C, H, N.

General Procedure for the Preparation of Aryl Imidazobenzodithiazinecarboxylates 23−25. A stirred mixture of anhydride **7** (2.62 g, 0.002 mol), the appropriate heteroaromatic hydroxy compound (0.005 mol), and anhydrous *p*-dioxane (25 mL) was refluxed for 8 h. The solvent was evaporated under reduced pressure. To the residue a solution of $KHCO_3$ (1 g) in water (100 mL) was added, and this was stirred at room temperature for 2 h. The precipitate of the adequate crude ester **20**, **21**, or **22** was filtered out, washed with water, dried, and recrystallized from acetone. The water−filtrates (pH 7.5−8.5) mixture was acidified with 1% hydrochloric acid to pH 1. The precipitate thus obtained was filtered out, washed with water, and dried at temperatures gradually increasing to 105 °C, giving 0.9−1.0 g (71−79%) of carboxylic acid **6** formed as a byproduct.

In this manner the following esters were obtained.

8-Quinolyl 8-Chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]-benzodithiazine-7-carboxylate (23). Starting from 8-hydroxyquinoline (0.73 g), the title compound **23** was obtained (1.6 g, 90%): mp 216−217 °C; IR (KBr) 1742 (C=O), 1620 (C=N), 1375, 1175 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.41 (d, J = 1.8 Hz, 1H), 7.62−7.86 (m, 3H), 8.0−8.05 (m, 1H), 8.22 (d, J = 1.8 Hz, 1H), 8.49−8.55 (m, 2H), 8.91−8.94 (m, 1H), 9.00 (s, 1H) ppm. Anal. ($C_{19}H_{10}ClN_3O_4S_2$) C, H, N.

2-Methyl-8-quinolyl 8-Chloro-5,5-dioxoimidazo[1,2-*b*]-[1,4,2]benzodithiazine-7-carboxylate (24). Starting from 8-hydroxy-2-methylquinoline (0.8 g), the title compound **24** was obtained (1.6 g, 87%): mp 185−186 °C; IR (KBr) 1745 (C=O), 1370, 1190, 1175 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.64 (s, 3H, CH_3), 7.40 (d, J = 1.7 Hz, 1H), 7.50−7.95 (m, 4 H), 8.23 (d, J = 1.7 Hz, 1H), 8.36 (d, J = 8.5 Hz, 1H), 8.52 (s, 1H), 9.13 (s, 1H). Anal. ($C_{20}H_{12}ClN_3O_4S_2$) C, H, N.

2-Phenyl-4-oxo-4*H*-chromen-3-yl 8-Chloro-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine-7-carboxylate (25). Starting from 3-hydroxyflavone (1.2 g), the title compound **25** was obtained (1.9 g, 88%): mp 249−251 °C; IR (KBr) 1765 (C═O, ester), 1640 (C═O, ketone), 1625, 1610 (C═N, C═C), 1360, 1190 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.36−7.41 (m, 2H), 7.58−7.65 (m, 4H), 7.86−7.99 (m, 3H), 8.14−8.21 (m, 2H), 8.53 (s, 1H), 8.69 (s, 1H) ppm. Anal. ($C_{25}H_{13}ClN_2O_6S_2$) C, H, N.

Synthesis of 8-Chloro-7-(3,4-dihydro-4-oxoquinoazolin-2-yl)-5,5-dioxoimidazo[1,2-*b*][1,4,2]benzodithiazine (26). A mixture of carboxamide **10** (2.04 g, 0.004 mol) and thionyl chloride (15 mL) was refluxed for 10 h. The thionyl chloride was evaporated in vacuo. The dry residue was dissolved in boiling toluene (40 mL), a small amount of insoluble side products was filtered out, and the filtrate was concentrated in vacuo. The resulting residue was recrystallized from ethanol (15 mL) to give **26** (1.4 g, 71%): mp 230−232 °C dec; IR (KBr) 1685 (C═O), 1625 (C═N), 1375, 1190, 1180 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.11−7.39 (m, 6H), 7.59−7.81 (m, 3H), 8.18−8.27 (m, 2H), 8.38 (s, 1H), 8.60 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6) δ 117.60, 119.17, 122.09, 124.13, 126.13, 126.98, 128.02, 128.74, 129.57, 129.66, 130.63, 131.11, 131.97, 134.30, 134.38, 137.58, 141.67, 144.93, 144.98, 151.70 ppm. Anal. ($C_{23}H_{13}ClN_4O_3S_2$) C, H, N.

Synthesis of 8-Chloro-7-(5-phenyl-4,4,6-trioxo-5,6-dihydro-3,4,1,5-benzoxathiadiazocyn-2-yl)-5,5-dioxoimidazo-[1,2-*b*][1,4,2]benzodithiazine (27). The carboxamide **10** (2.04 g, 0.004 mol) was added portionwise to 98% sulfuric acid (10 mL), and this was stirred at room temperature for 12 h. The solution obtained was poured into a water−crushed ice mixture (180−200 g, 0−3 °C). The resulting white precipitate was collected by filtration, washed thoroughly with water, dried, and recrystallized from toluene (130 mL) to give **27** (1.7 g, 74%): mp 261−262 °C; IR (KBr) 1765 (C═O), 1620 (C═N), 1380, 1190, 1180 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.40 (d, J = 1.4 Hz, 2H), 7.71−8.25 (m, 9H), 8.50 (s, 1H), 8.72 (s, 1H) ppm; ^{13}C NMR (DMSO-d_6) δ 117.05, 117.55, 127.30, 128.16, 129.78, 129.85, 130.67, 131.26, 132.01, 134.61, 137.16, 137.51, 145.48, 153.43, 158.36 ppm. Anal. ($C_{23}H_{13}ClN_4O_6S_3$) C, H, N.

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