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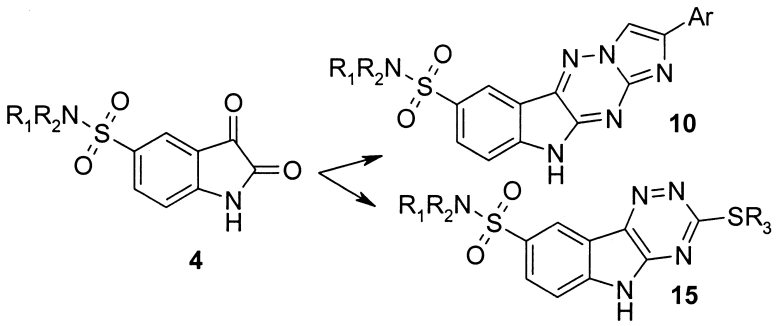

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New Scaffolds for Combinatorial Synthesis. 1. 5-Sulfamoylisatins and Their Reactions with 1,2-Diamines

Alexandre V. Ivachtchenko,* Alexey P. Il'yin, Vladimir V. Kobak, Denis A. Zolotarev, Larisa V. Boksha, Andrey S. Trifilenkov, and Dina M. Ugoleva

Chemical Diversity Labs, Inc., 11575 Sorrento Valley Road, Suite 211, San Diego, California 92121

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3,3-Dichloro-5-(4-methylpiperidinosulfonyl)-2-indolinone (**3**) and 5-sulfamoylisatins **4** have been synthesized from 5-chlorosulfonyl-3,3-dichloro-2-indolinone (**1**). Compounds **4** are promising scaffolds for the solid- and liquid-phase syntheses of new combinatorial libraries of various heterocycles. Thus, the reactions of **4** with 1,2-diamines, such as *o*-phenylenediamine (**5**) and aminoguanidine hydrochloride (**6**), 1,2-diaminoimidazoles (**9**), and thiosemicarbazide led, respectively, to new heterocycles **7** and **8** and new combinatorial libraries of triazinoindoles **10** and **15**. Chemsets **4**, **10**, and **15** were isolated as crystalline solids that were purified by recrystallization from a suitable solvent and characterized by spectroscopic methods.

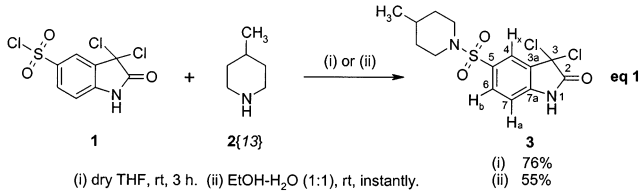
Introduction

Small-molecule combinatorial synthesis for the generation and optimization of leads for a variety of applications is steadily growing in importance. Thus, the search for novel scaffolds for the generation of new combinatorial libraries is a relevant and timely pursuit. In connection with this search, the chemistry of isatin (which opens the way to quinolines,[1,2] 1,2-dihydroquinoxalin-2(1*H*)-ones,[3−6] 4-hydroxy-2-oxo-1,2,3,4-tetrahydroquinazoline-4-carboxylic acids,[7,8] spiro-(*2H*-benzimidazolo)-2,3′-indolin-2-ones,[3−6] spiro-[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3*H*′)-triones,[9] triazinoindoles,[10] indolo[2,3-*b*]quinoxalines,[3−6] 10*H*-imidazo-[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indoles,[11,12] and other substituted heterocycles[13,14]) has attracted our attention. While substituted isatins and their derivatives exhibit a broad range of biological activities,[15−20] the chemistry of 5-sulfamoylisatins has not been widely explored.

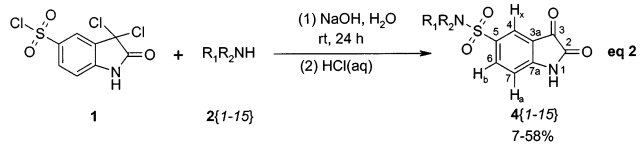
In our ongoing studies of isatin[3−6,11,12] and our continuing search for new scaffolds that possess several points of randomization,[21−29] we have chosen to explore the suitability of 5-chlorosulfonyl-3,3-dichloro-2-indolinone (**1**), which has at least three reaction sites. While **1** has great potential as a building block for combinatorial synthesis, its chemistry, similar to that of 5-sulfamoylisatins, is not well-known.[25,30]

Results and Discussion

First, we established that 3,3-dichloro-5-sulfamoylindolinones are intermediates in the preparation of 5-sulfamoylisatins from **1** and primary or secondary amines. Thus, the reaction of **1** with 2 equiv of 4-methylpiperidine, **2**{*13*} in either anhydrous THF (method A) or in 1:1 ethanol−water (method B) led to 3,3-dichloro-5-(4-methylpiperidinosulfonyl)-2-indolinone (**3**) in 76% and 55% yields, respectively (eq 1). As expected, treatment of **3** with aqueous sodium



hydroxide led to 5-(4-methylpiperidinosulfonyl)isatin, **4**{*13*}. In preparing the library of new 5-sulfamoylisatins, **4**{*1*−*15*}, we simplified this two step-process by carrying out both reactions in one pot and using equimolar amounts of **1** and amines **2**{*1*−*15*} (Figure 1) in aqueous sodium hydroxide (eq 2). After crystallization from dichloromethane, 5-sulfa-



moylisatins **4**{*1*−*15*} were isolated in 7−58% yields as yellowish, crystalline solids that decomposed at or above 165 °C. Chemset **4** was characterized spectroscopically, and its purity was determined to be >90% by HPLC.

The reactivity of chemset **4** toward 1,2-diamines was investigated for the purpose of generating a combinatorial library of fused, polycyclic heterocycles. For instance, **4**{*13*} readily reacted with *o*-phenylenediamine (**5**) and aminoguanidine hydrochloride (**6**) to generate the spiroannulated

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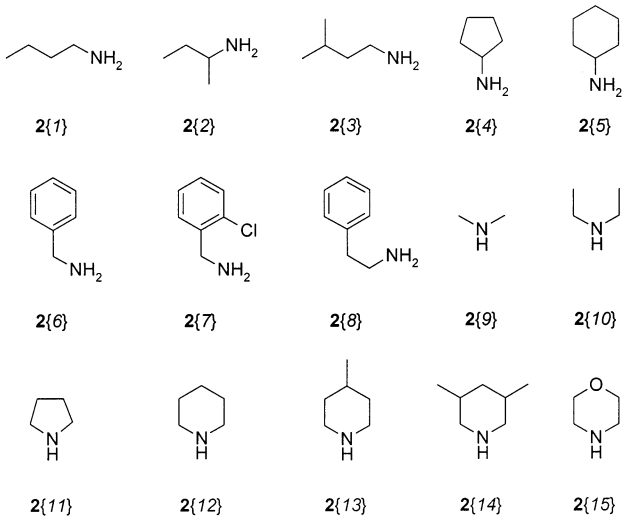
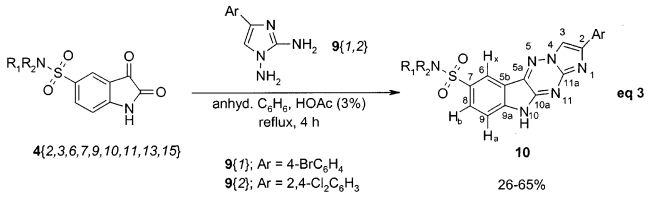


Figure 1. Diversity reagents **2**.

indolinone **7** and 3-aminotriazinoindole **8**, respectively (Scheme 1). On the other hand, a 12-member combinatorial library of previously unknown 2-arylimidazotriazinoindoles **10** (Table 1) was generated by reaction, in benzene and in the presence of a catalytic amount of acetic acid, of nine members of chemset **4** with diaminoimidazole **9**{*1*} and three members with diaminoimidazole **9**{*2*}, respectively (eq 3). Compounds **10** were obtained in 25−65% yield after crystallization from acetone. They consisted of dark-red fine crystalline solids that decomposed at or above 227 °C. Their



identity was established spectroscopically, and their purity was found to be >90% by HPLC.

The related 11-member library of the hitherto unknown 3-(alkylthio)triazinoindoles, **15**, was prepared by combining six members of chemset **4** with diversity reagents **14** (Figure 2) as described in Scheme 2. The intermediate thiosemicarbazones, **11**, were cyclized in situ by treatment with refluxing aqueous sodium hydroxide. The resulting thiolates were heated, without isolation, with diversity reagents **14** to generate chemset **15** in 16−72% yield (Table 2). To confirm the intermediacy of thiolates **12**, two members of chemset **12** were neutralized with dilute hydrochloric acid, and the resulting mercaptans, **13a**,**b**, were isolated and characterized. The crude final products, **15**, were obtained as yellowish crystalline solids, which were recrystallized from ethanol and identified mainly by ^{1}H NMR. Their purity was >90% by HPLC.

Conclusions

The present study has clearly established that suitably functionalized isatins are versatile building blocks for poly-

Scheme 1. Reactions of 5-Sulfamoylisatin **4**{*13*} with 1,2-Diamines

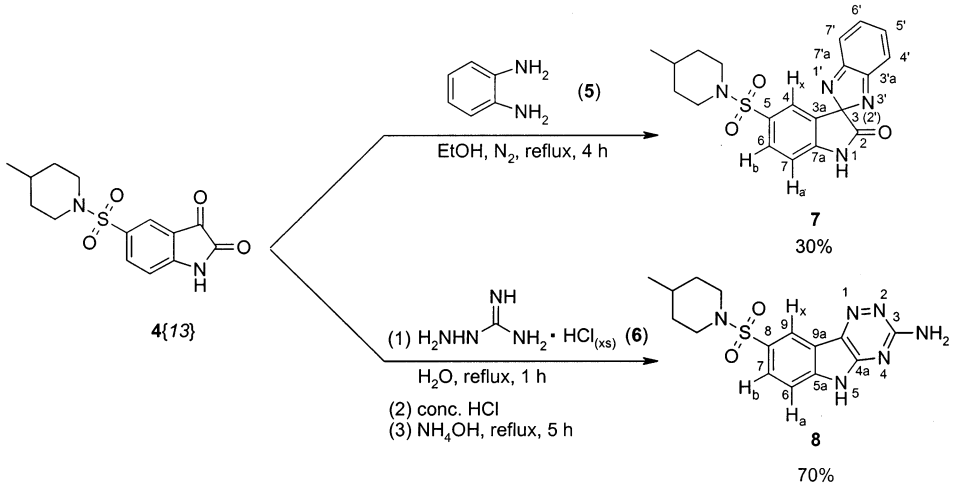


Table 1. Combinatorial Library of 2-Arylimidazotriazinoindoles **10**

		product				
entry	starting material	R_1, R_2	Ar	no.	yield,[a] %	purity,[b] %
1	**4**{*2*}	*sec*-butyl, H	4-BrC_6H_4	**10**{*2,1*}	29	95
2	**4**{*3*}	isopentyl, H	4-BrC_6H_4	**10**{*3,1*}	42	98
3	**4**{*6*}	benzyl, H	4-BrC_6H_4	**10**{*6,1*}	26	90
4	**4**{*7*}	*o*-chlorobenzyl, H	4-BrC_6H_4	**10**{*7,1*}	34	92
5	**4**{*9*}	methyl, methyl	4-BrC_6H_4	**10**{*9,1*}	65	99
6	**4**{*10*}	ethyl, ethyl	4-BrC_6H_4	**10**{*10,1*}	25	98
7	**4**{*10*}	ethyl, ethyl	2,4-$Cl_2C_6H_3$	**10**{*10,2*}	30	96
8	**4**{*11*}	pyrrolidino	4-BrC_6H_4	**10**{*11,1*}	51	95
9	**4**{*13*}	4-methylpiperidino	4-BrC_6H_4	**10**{*13,1*}	64	95
10	**4**{*13*}	4-methylpiperidino	2,4-$Cl_2C_6H_3$	**10**{*13,2*}	48	97
11	**4**{*15*}	morpholino	4-BrC_6H_4	**10**{*15,1*}	28	95
12	**4**{*15*}	morpholino	2,4-$Cl_2C_6H_3$	**10**{*15,2*}	34	98

[a] Isolated yields of products crystallized from acetone. [b] Determined by HPLC.

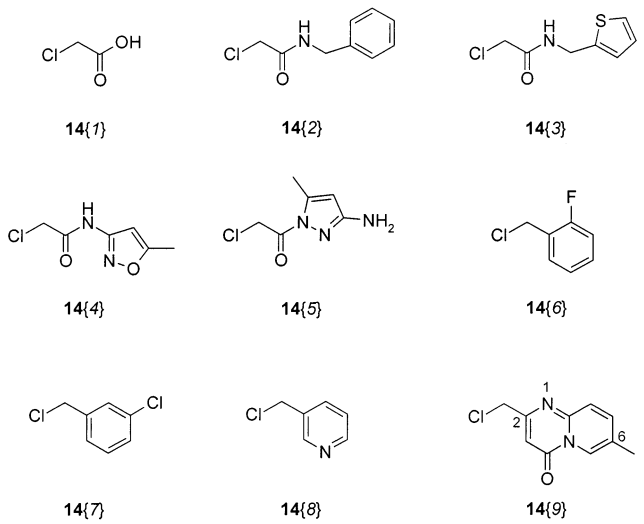


Figure 2. Diversity reagents **14**.

cyclic fused heteroaromatics. These heteroaromatics are of interest because of their potential biological activity in analogy to the antiviral drug VP32947 (**16**)[31] and the DNA-intercalating drug/DNA topoisomerase II inhibitor NCA0424 (**17**)[32] (Figure 3). Both compounds are obtained from an isatin. Since the synthetic approach employed is straightforward, it should be easily adaptable to the synthesis of a wide variety of small-molecule combinatorial libraries.

Experimental Section

General Information. All solvents and reagents were obtained from commercial sources and used without further purification. Anhydrous benzene and anhydrous THF were obtained by distillation over sodium metal. The syntheses, isolations, and purifications of the compounds reported were carried out using a proprietary technology platform, which includes all the equipment needed for parallel synthesis.[33]

Reagents **2** and **14**{*1,6*−*8*} were purchased from Acros Organics. Reagents **14**{*2*−*5,9*} were obtained from ChemDiv, Inc. The synthesized library compounds were purified by recrystallization from dichloromethane (chemset **4**), acetone (chemset **10**), or ethanol (chemset **15**). Melting points (mp) were determined on a Büchi model B-520 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on KBr pellets on a Perkin-Elmer model 457 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained at 400 and 125.76 MHz, respectively, in DMSO-d_6 on a Bruker model DRX-500 spectrometer; chemical shifts are reported in δ units (ppm) downfield from TMS as an internal standard. Low-resolution electron-impact mass spectra (MS) were measured at 70 eV and 250 °C (ionization chamber temperature) on a Kratos model MS-890 mass spectrometer.

Analytical TLC was carried out either on 5 cm × 15 cm aluminum plates precoated with Silufol UV_{254} (Kavalier, Czech Republic) or on 5 cm × 10 cm glass plates precoated with a 0.25 mm layer of silica gel 60 F_{254} (Merck, Germany). The plates were visualized with UV light at 254 nm. The purities of the final products were determined on a 4 mm × 100 mm, C_{18} reversible-phase column mounted in a Gilson model 714 gradient HPLC system, which was equipped with a UV detector (215 and 254 nm). The column was eluted with a linear gradient, starting with water and ending with a 95:5 v/v acetonitrile−water mixture, at a rate of 0.15 mL/min and with an analysis cycle time of 25 min.

3,3-Dichloro-5-(4-methylpiperidinosulfonyl)-2-indolinone (3). Method A. An amount of 2.36 g (23.8 mmol) of 4-methylpiperidine, **2**{*13*}, was added at room temperature with stirring to a solution of 3.58 g (11.9 mmol) of 3,3-

Scheme 2. Synthesis of Combinatorial Library of 3-(Alkylthio)triazinoindoles **15**

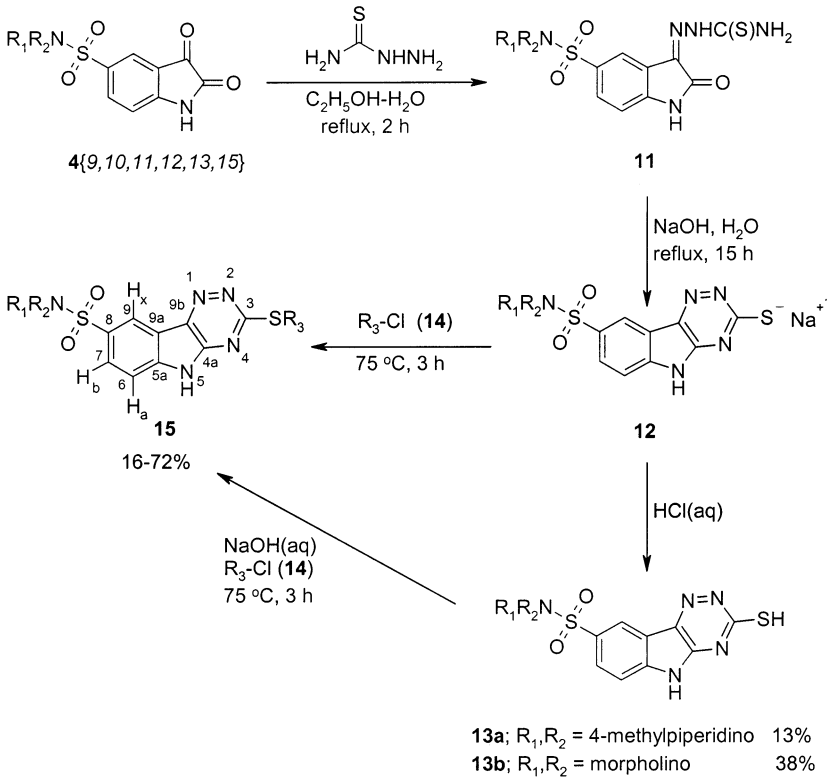


Table 2. Combinatorial Library of 3-(Alkylthio)triazinoindoles **15**

	starting material			product		
entry	no.	R_1, R_2	R_3−X	no.	yield,[a] %	purity,[b] %
1	**4**{*9*}	methyl, methyl	**14**{*4*}	**15**{*9,4*}	60	94
2	**4**{*9*}	methyl, methyl	**14**{*5*}	**15**{*9,5*}	32	92
3	**4**{*10*}	ethyl, ethyl	**14**{*1*}	**15**{*10,1*}	16	97
4	**4**{*10*}	ethyl, ethyl	**14**{*4*}	**15**{*10,4*}	72	95
5	**4**{*10*}	ethyl, ethyl	**14**{*8*}	**15**{*10,8*}	70	92
6	**4**{*11*}	pyrrolidino	**14**{*9*}	**15**{*11,9*}	38	96
7	**4**{*12*}	piperidino	**14**{*7*}	**15**{*12,7*}	60	91
8	**4**{*13*}	4-methylpiperidino	**14**{*2*}	**15**{*13,2*}	19	95
9	**4**{*15*}	morpholino	**14**{*3*}	**15**{*15,3*}	65	96
10	**4**{*15*}	morpholino	**14**{*6*}	**15**{*15,6*}	65	92
11	**4**{*15*}	morpholino	**14**{*8*}	**15**{*15,8*}	30	95

[a] Isolated yields of products crystallized from ethanol. [b] Determined by HPLC.

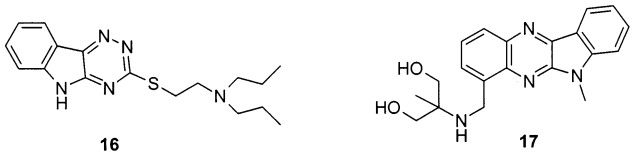


Figure 3. Polycyclic fused heteroaromatics with established biological activities.

dichloro-2-oxo-5-indolinesulfonyl chloride (**1**) in 50 mL of anhydrous tetrahydrofuran. 4-Methylpiperidine hydrochloride precipitated after a few minutes. The reaction mixture was then stirred for 3 h, and the progress of the reaction was monitored by TLC (silica gel 60 F_{254}; $CHCl_3$−CH_3OH, 49:1 v/v; three times after desiccation of the plate). 4-Methylpiperidine hydrochloride was filtered, and the filtrate was evaporated under reduced pressure on a rotary evaporator. The viscous oily residue was carefully dispersed in water (about 75 mL), and the resulting crystalline solid was filtered, washed with water, and dried first in air and then in a vacuum desiccator over anhydrous $CaCl_2$ to yield 3.30 g (76%) of **3**.

Method B. An amount of 1.84 g (18.5 mmol) of **2**{*13*} was added at room temperature with stirring to 2.78 g (9.26 mmol) of **1** in 50 mL of ethanol−water (1:1, v/v). The crude product precipitated out immediately and was filtered, rinsed with water, and dried first in air and then in a vacuum desiccator over anhydrous $CaCl_2$, affording 1.84 g (55%) of **3**.

Dichloroindolinone **3** is a light-yellow crystalline solid that is only moderately soluble in chloroform, dichloromethane, and ethyl acetate and is practically insoluble in hexane: mp 187−190 °C; IR 1725 cm^{-1} ($\nu_{C=O}$); ^1H NMR δ 0.87 (d, J = 5.40 Hz, 3H, CH_3 at piperidine ring), 1.29 (m, 3H, piperidine ring H), 1.69 (d, J = 11.10 Hz, 2H, piperidine ring H), 2.17 (m, 2H, piperidine ring H), 3.66 (d, J = 11.10 Hz, 2H, piperidine ring H), 7.13 (d, J_{AB} = 8.25 Hz, 1H, H_a), 7.71 (dd, J_{AB} = 8.25 Hz, J_{BX} = 1.20 Hz, 1H, H_b), 7.80 (d, J_{BX} = 1.20 Hz, 1H, H_x), 11.62 (s, 1H, NH); ^{13}C NMR δ 21.20 (CH_3 at piperidine ring), 29.17 (piperidine ring C4), 32.71 (piperidine ring C3 and C5), 45.91 (piperidine ring C2 and C6), 73.67 (C3), 112.06 (C7), 123.60 (C6), 129.42 (C3a), 130.86 (C5), 132.29 (C4), 143.14 (C7a), 168.93 (C2); MS *m*/*z* 362 (366) ($M^{\bullet+}$ − 1).

General Procedure for the Synthesis of 5-(Sulfamoyl)-isatins, Chemset 4{*1*−*15*}. An amount of 0.26 mol of amine **2**{*1*−*15*} was dispersed in a solution of 40 g (1.0 mol) of sodium hydroxide in 2 L of water. The resulting dispersion was stirred vigorously at room temperature and then cooled to 0−5 °C. While maintaining vigorous stirring, 75 g (0.25 mol) of preground **1** was added in portions at such a rate to ensure that no lumps were formed. Following completion of addition, the reaction mixture was stirred at room temperature for ca. 24 h and its pH was kept at about 10. For a given combination of **1** and **2**, the exact reaction time was determined by monitoring the disappearance of **1** by TLC (silica gel 60 F_{254}; $CHCl_3$−CH_3OH, 9:1 v/v). The 2,3-indolinedione products, **4**, are slightly more polar (R_f 0.45−0.70) than **1** (R_f 0.95).

The reaction mixture was then filtered, and the filtrate was acidified to pH 4.0−5.0 with dilute hydrochloric acid (1:3, v/v). The resulting precipitate was filtered, rinsed with water, and dried in air. An additional amount of crude **4** was recovered by concentrating the mother liquor on the rotary evaporator and allowing it to stand at 0 °C for 24 h. The combined dried product was then purified by extraction with dichloromethane in a Soxhlet apparatus; the progress of the extraction was monitored by TLC (silica gel 60 F_{254}; $CHCl_3$−CH_3OH, 19:1 v/v; R_f 0.1−0.5). The dichloromethane extract was then kept at 10 °C for 24 h. The precipitate was filtered, rinsed with hexane, and dried. A second crop of product **4** was recovered by concentrating the mother liquor to ca. $^2/_3$ of its volume, followed by cooling. The purity of the second crop was checked by TLC. The purified isatins, **4**, are yellowish crystalline solids that are moderately soluble in chloroform, dichloromethane, ethyl acetate, and ethanol and are practically insoluble in hexane.

5-[(1-Butylamino)sulfonyl]-1*H*-indole-2,3-dione, 4{*1*}: yield 25%; mp 253 °C (dec); ^1H NMR δ 0.87 (m, J = 7.30 Hz, 3H, CH_3), 1.30 (m, 2H, $NHCH_2CH_2CH_2CH_3$), 1.39 (m, 2H, $NHCH_2CH_2CH_2CH_3$), 2.68 (m, 2H, $NHCH_2CH_2CH_2CH_3$), 7.00 (d, J_{AB} = 8.30 Hz, 1H, H_a), 7.34 (t, J = 5.5 Hz, 1H, $NHSO_2$), 7.82 (d, J_{BX} = 1.40 Hz, 1H, H_x), 7.90 (dd, J_{BX} = 1.40, J_{AB} = 8.30 Hz, 1H, H_b), 11.39 (br s, 1H, NH); ^{13}C NMR δ 21.20 ($CH_3CH_2CH_2CH_2NH$), 19.16 ($CH_3CH_2CH_2CH_2NH$), 30.96 ($CH_3CH_2CH_2CH_2NH$), 42.13 ($CH_3CH_2CH_2CH_2NH$), 112.42 (C7), 117.96 (C3a), 122.38 (C4), 134.63 (C5), 135.99 (C6), 153.00 (C7a), 159.41 (C2), 183.11 (C3); MS *m*/*z* 282 ($M^{\bullet+}$).

5-[(2-Butylamino)sulfonyl]-1*H*-indole-2,3-dione, 4{*2*}: yield 58%; mp 206 °C (dec); ^1H NMR δ 0.79 (t, J = 7.12 Hz, 3H, $NHCH(CH_3)CH_2CH_3$), 0.92 (d, J = 7.15 Hz, 3H,

NHCH(C*H*$_3$)CH$_2$CH$_3$), 1.25−1.45 (m, 2H, NHCH(CH$_3$)C*H*$_2$-CH$_3$), 3.01 (m, 1H, NHC*H*(CH$_3$)CH$_2$CH$_3$), 7.01 (d, J_{AB} = 8.25 Hz, 1H, H$_a$), 7.34 (d, J = 7.90 Hz, 1H, NHSO$_2$), 7.85 (d, J_{BX} = 1.40 Hz, 1H, H$_x$), 7.94 (dd, J_{BX} = 1.40 Hz, J_{AB} = 8.25 Hz, 1H, H$_b$), 11.36 (br s, 1H, NH).

5-[(3-Methylbutyl)aminosulfonyl]-1*H*-indole-2,3-dione, 4{*3*}: yield 30%; mp 245 °C (dec); ^{1}H NMR δ 0.83 (d, J = 6.70 Hz, 6H, CH$_3$), 1.30 (m, 2H, NHCH$_2$C*H*$_2$CH-(CH$_3$)$_2$), 1.60 (m, 1H, NHCH$_2$CH$_2$C*H*(CH$_3$)$_2$), 2.70 (m, 2H, NHC*H*$_2$CH$_2$CH(CH$_3$)$_2$), 7.03 (d, J_{AB} = 8.30 Hz, 1H, H$_a$), 7.35 (t, J = 6.00 Hz, 1H, NHSO$_2$), 7.83 (d, J_{BX} = 1.40 Hz, 1H, H$_x$), 7.92 (dd, J_{BX} = 1.40 Hz, J_{AB} = 8.30 Hz, 1H, H$_b$), 11.40 (br s, 1H, NH); ^{13}C NMR δ 22.08 (NHCH$_2$CH$_2$CH-(*C*H$_3$)$_2$), 24.74 (NHCH$_2$CH$_2$*C*H(CH$_3$)$_2$), 37.76 (NHCH$_2$*C*H$_2$-CH(CH$_3$)$_2$), 40.73 (NH*C*H$_2$CH$_2$CH(CH$_3$)$_2$), 112.46 (C7), 117.95 (C3a), 122.38 (C4), 134.57 (C5), 136.00 (C6), 153.01 (C7a), 159.41 (C2), 183.12 (C3); MS *m*/*z* 296 (M$^{\bullet+}$).

5-(Cyclopentylaminosulfonyl)-1*H*-indole-2,3-dione, 4{*4*}: yield 41%; mp 180 °C (dec); ^{1}H NMR δ 1.25−1.50 (m, 4H, cyclopentane ring H-3 and H-4), 1.50−1.70 (m, 4H, cyclopentane ring H-2 and H-5), 3.35 (m, 1H, cyclopentane ring H-1), 7.02 (d, J_{AB} = 7.90 Hz, 1H, H$_a$), 7.44 (d, J = 7.45 Hz, 1H, NHSO$_2$), 7.85 (d, J_{BX} = 1.30 Hz, 1H, H$_x$), 7.94 (dd, J_{BX} = 1.30 Hz, J_{AB} = 7.90 Hz, 1H, H$_b$), 11.40 (br s, 1H, NH); ^{13}C NMR δ 22.76 (cyclopentane ring C3 and C4), 32.40 (cyclopentane ring C2 and C5), 54.40 (cyclopentane ring C1), 111.39 (C7), 116.88 (C3a), 121.43 (C4), 135.77 (C6), 135.63 (C5), 153.00 (C7a), 159.58, (C2), 184.16 (C3).

5-(Cyclohexylaminosulfonyl)-1*H*-indole-2,3-dione, 4{*5*}: yield 58%; mp >300 °C (dec); ^{1}H NMR δ 1.16 (m, 5H, cyclohexane ring H), 1.62 (m, 5H, cyclohexane ring H), 2.88 (m, 1H, C*H*NHSO$_2$), 7.02 (d, J_{AB} = 8.70 Hz, 1H, H$_a$), 7.44 (d, J = 7.60 Hz, 1H, NHSO$_2$), 7.84 (d, J_{BX} = 1.20 Hz, 1H, H$_x$), 7.94 (d, J_{BX} = 1.20 Hz, J_{AB} = 8.70 Hz, 1H, H$_b$), 11.43 (br s, 1H, NH); ^{13}C NMR δ 24.24 (cyclohexane ring C3 and C5), 24.76 (cyclohexane ring C4), 33.12 (cyclohexane ring C2 and C6), 52.02 (cyclohexane ring C1), 111.40 (C7), 116.88 (C3a), 121.44 (C4), 135.42 (C6), 136.39 (C5), 150.57 (C7a), 159.59 (C2), 184.16 (C3); MS *m*/*z* 308 (M$^{\bullet+}$).

5-(Benzylaminosulfonyl)-1*H*-indole-2,3-dione, 4{*6*}: yield 13%; mp 237 °C (dec); ^{1}H NMR δ 3.96 (d, J = 6.45 Hz, 2H, NHC*H*$_2$C$_6$H$_5$), 7.02 (d, J_{AB} = 8.10 Hz, 1H, H$_a$), 7.10−7.30 (m, 5H, C$_6$H$_5$), 7.77 (d, J_{BX} = 1.00 Hz, 1H, H$_x$), 7.92 (dd, J_{BX} = 1.00 Hz, J_{AB} = 8.10 Hz, 1H, H$_b$), 8.06 (t, J = 6.45 Hz, 1H, NHSO$_2$), 11.44 (br s, 1H, NH); ^{13}C NMR δ 46.09 (CH$_2$), 112.43 (C7), 117.78 (C3a), 122.55 (phenyl C4), 127.04 (C4), 127.53 (phenyl C2 and C6), 127.59 (phenyl C3 and C5), 134.85 (phenyl C1), 136.08 (C6), 137.29 (C5), 153.06 (C7a), 159.36 (C2), 183.08 (C3); MS *m*/*z* 316 (M$^{\bullet+}$).

5-[(2-Chlorobenzyl)aminosulfonyl]-1*H*-indole-2,3-dione, 4{*7*}: yield 20%; mp 219 °C (dec); ^{1}H NMR δ 4.04 (d, J = 6.30 Hz, 2H, CH$_2$), 6.98 (d, J_{AB} = 7.90 Hz, 1H, H$_a$), 7.11−7.28 (m, 3H, benzene ring H-4, H-5, and H-6), 7.44 (d, J = 6.60 Hz, 1H, benzene ring H-3), 7.82 (d, J_{BX} = 1.00 Hz, 1H, H$_x$), 7.92 (dd, J_{BX} = 1.00 Hz, J_{AB} = 7.90 Hz, 1H, H$_b$), 8.58 (t, J = 6.30 Hz, 1H, NHSO$_2$), 11.37 (br s, 1H, NH); MS *m*/*z* 350 (352) (M$^{\bullet+}$).

5-[(2-Phenylethyl)aminosulfonyl]-1*H*-indole-2,3-dione, 4{*8*}: yield 7%; mp 235 °C (dec); ^{1}H NMR δ 2.65−2.75 (t, J = 6.60 Hz, 2H, NHCH$_2$C*H*$_2$C$_6$H$_5$), 2.90−3.00 (m, 2H, NHC*H*$_2$CH$_2$C$_6$H$_5$), 7.00 (d, J = 8.20 Hz, 1H, H$_a$), 7.08−7.25 (m, 5H, C$_6$H$_5$), 7.59 (t, J = 6.50 Hz, 1H, NHSO$_2$), 7.82 (br s, 1H, H$_x$), 7.91 (d, J = 8.20 Hz, 1H, H$_b$), 11.39 (br s, 1H, NH).

5-(Dimethylaminosulfonyl)-1*H*-indole-2,3-dione, 4{*9*}: yield 10%; mp 233 °C (dec); ^{1}H NMR δ 2.66 (s, 6H, CH$_3$), 7.12 (d, J_{AB} = 8.35 Hz, 1H, H$_a$), 7.72 (d, J_{BX} = 1.00 Hz, 1H, H$_x$), 7.87 (dd, J_{BX} = 1.00 Hz, J_{AB} = 8.35 Hz, 1H, H$_b$), 11.50 (br s, 1H, NH); ^{13}C NMR δ 37.49 (CH$_3$), 112.71 (C7), 118.04 (C3a), 123.26 (C4), 128.78 (C5), 136.98 (C6), 153.63 (C7a), 159.34 (C2), 182.90 (C3); MS *m*/*z* 254 (M$^{\bullet+}$).

5-(Diethylaminosulfonyl)-1*H*-indole-2,3-dione, 4{*10*}: yield 20%; mp 188 °C (dec); ^{1}H NMR δ 1.12 (m, J = 7.10 Hz, 6H, CH$_3$), 3.17 (m, J = 7.10 Hz, 4H, CH$_2$), 7.06 (d, J_{AB} = 8.50 Hz, 1H, H$_a$), 7.75 (d, J_{BX} = 1.90 Hz, 1H, H$_x$), 7.92 (dd, J_{BX} = 1.90 Hz, J_{AB} = 8.50 Hz, 1H, H$_b$), 11.40 (br s, 1H, NH); ^{13}C NMR δ 14.05 (CH$_3$), 41.79 (CH$_2$), 112.76 (C7), 117.98 (C3a), 122.45 (C4), 133.81 (C5), 136.22 (C6), 153.35 (C7a), 159.32 (C2), 183.00 (C3); MS *m*/*z* 282 (M$^{\bullet+}$).

5-(1-Pyrrolidinosulfonyl)-1*H*-indole-2,3-dione, 4{*11*}: yield 10%; mp 225 °C (dec); ^{1}H NMR δ 1.76 (m, 4H, pyrrolidine ring H-3 and H-4), 3.18 (m, 4H, pyrrolidine ring H-2 and H-5), 7.08 (d, J_{AB} = 8.25 Hz, 1H, H$_a$), 7.77 (d, J_{BX} = 1.00 Hz, 1H, H$_x$), 7.92 (dd, J_{BX} = 1.00 Hz, J_{AB} = 8.25 Hz, 1H, H$_b$), 11.45 (br s, 1H, NH).

5-(1-Piperidinosulfonyl)-1*H*-indole-2,3-dione, 4{*12*}: yield 28%; mp 225 °C (dec); ^{1}H NMR δ 1.43 (m, 2H, piperidine ring H-4), 1.64 (m, 4H, piperidine ring H-3 and H-5), 2.92 (t, J = 5.30 Hz, 4H, piperidine ring H-2 and H-6), 7.09 (d, J_{AB} = 8.20 Hz, 1H, H$_a$), 7.69 (d, J_{BX} = 1.50 Hz, 1H, H$_x$), 7.84 (dd, J_{BX} = 1.50 Hz, J_{AB} = 8.20 Hz, 1H, H$_b$), 11.51 (br s, 1H, NH); ^{13}C NMR δ 22.82 (piperidine ring C4), 24.58 (piperidine ring C3 and C5), 46.49 (piperidine ring C2 and C6), 112.71 (C7), 118.00 (C3a), 123.13 (C4), 129.53 (C5), 136.88 (C6), 153.64 (C7a), 159.32 (C2), 182.94 (C3); MS *m*/*z* 294 (M$^{\bullet+}$).

5-[(4-Methylpiperidino)sulfonyl]-1*H*-indole-2,3-dione, 4{*13*}: yield 46%; mp 234 °C (dec); IR 1730 and 1750 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR δ 0.93 (d, J = 5.50 Hz, 3H, CH$_3$ at piperidine ring), 1.27 (m, 3H, piperidine ring H), 1.69 (d, J = 10.85 Hz, 2H, piperidine ring H), 2.22 (m, 2H, piperidine ring H), 3.64 (d, J = 10.85 Hz, 2H, piperidine ring H), 7.08 (d, J_{AB} = 8.10 Hz, 1H, H$_a$), 7.69 (d, J_{BX} = 1.40 Hz, 1H, H$_x$), 7.85 (dd, J_{BX} = 1.40 Hz, J_{AB} = 8.10 Hz, 1H, H$_b$), 11.47 (br s, 1H, NH); ^{13}C NMR δ 21.18 (*C*H$_3$ at piperidine ring), 29.24 (piperidine ring C4), 32.73 (piperidine ring C3 and C5), 45.94 (piperidine ring C2 and C6), 112.68 (C7), 118.01 (C3a), 123.14 (C4), 129.62 (C5), 136.87 (C6), 153.58 (C7a), 159.33 (C2), 182.91 (C3); MS *m*/*z* 308 (M$^{\bullet+}$).

5-[(3,5-Dimethylpiperidino)sulfonyl]-1*H*-indole-2,3-dione, 4{*14*}: yield 40%; mp 165 °C (dec); ^{1}H NMR δ 0.50 (m, 1H, piperidine ring H), 0.88 (d, J = 6.00 Hz, 6H, CH$_3$), 1.60−1.80 (m, 5H, piperidine ring H), 3.61 (d, J = 8.60 Hz, 2H, piperidine ring H), 7.11 (d, J_{AB} = 8.60 Hz, 1H, H$_a$), 7.71 (d, J_{BX} = 1.75 Hz, 1H, H$_x$), 7.85 (dd, J_{BX} = 1.75 Hz, J_{AB} = 8.60 Hz, 1H, H$_b$), 11.59 (br s, 1H, NH); MS *m*/*z* 322 (M$^{\bullet+}$).

5-(4-Morpholinosulfonyl)-1*H*-indole-2,3-dione, 4{*15*}: yield 57%; mp 233 °C (dec); ^{1}H NMR δ 2.91 (t, J = 4.50 Hz, 4H, CH_2NCH_2), 3.67 (t, J = 4.50 Hz, 4H, CH_2OCH_2), 7.12 (d, J_{AB} = 8.25 Hz, 1H, H_a), 7.72 (d, J_{BX} = 1.90 Hz, 1H, H_x), 7.88 (dd, J_{BX} = 1.90 Hz, J_{AB} = 8.25 Hz, 1H, H_b), 11.50 (br s, 1H, NH); ^{13}C NMR δ 45.80 (*C*H_2NCH_2), 65.18 (*C*H_2OCH_2), 112.80 (C7), 118.14 (C3a), 123.39 (C4), 128.28 (C5), 137.05 (C6), 153.94 (C7a), 159.34 (C2), 182.84 (C3); MS *m*/*z* 296 ($M^{\bullet+}$).

5-(4-Methylpiperidinosulfonyl)-spiro-(2*H*-benzimidazolo)-2′,3-indolin-2-one (7). An amount of 0.44 g (4.1 mmol) of *o*-phenylenediamine (**5**) was added to a suspension of 1.19 g (3.86 mmol) of **4**{*13*} in 25 mL of ethanol. The reaction mixture was then stirred and heated at reflux for 4 h under a nitrogen atmosphere (10 min after the start of the reaction, a red solution formed, and 20 min later, the reaction product separated out as a yellow precipitate). The reaction mixture was allowed to cool to room temperature, and the precipitate was filtered. The crude product was dispersed in 25 mL of boiling ethanol and filtered. This treatment with boiling ethanol was repeated once more, and the residual solid was dried first in air and then in a vacuum desiccator over P_2O_5, affording 0.46 g (30%) of spiro compound **7** as a yellowish crystalline solid that is slightly soluble in ethanol and practically insoluble in hexane: mp >305 °C (dec); TLC (silica gel 60 F_{254}, $CHCl_3$−CH_3OH, 19:1 v/v) R_f 0.1; IR 1715 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR δ 0.91 (d, J = 5.30 Hz, 3H, 4-CH_3), 1.16−1.40 (m, 3H, piperidine ring H), 1.69 (d, J = 10.50 Hz, 2H, piperidine ring H), 2.22 (m, 2H, piperidine ring H), 3.76 (d, J = 10.50 Hz, 2H, piperidine ring H), 7.70 (m, $J_{4'(7'),5'(6')}$ = 8.25 Hz, $J_{5',6'}$ = 6.40 Hz, 1H, H-5′ or H-6′), 7.71 (d, J_{AB} = 8.20 Hz, 1H, H_a), 7.77 (m, $J_{4'(7'),5'(6')}$ = 8.25 Hz, $J_{5',6'}$ = 6.40 Hz, 1H, H-5′ or H-6′), 7.94 (d, $J_{4'(7'),5'(6')}$ = 8.25 Hz, H-4′ or H-7′), 8.06 (d, $J_{4'(7'),5'(6')}$ = 8.25 Hz, 1H, H-4′ or H-7′), 8.24 (dd, J_{BX} = 1.80 Hz, J_{AB} = 8.20 Hz, 1H, H_b), 8.65 (d, J_{BX} = 1.80 Hz, 1H, H_x), 12.37 (br s, 1H, NH); ^{13}C NMR δ 21.17 (*C*H_3 at piperidine ring), 29.19 (piperidine ring C4), 32.82 (piperidine ring C3 and C5), 46.11 (piperidine ring C2 and C6), 112.53 (C7), 118.92 (C3/C2′), 121.64 (C5′ or C6′), 126.62 (C6), 127.40 (C3a), 127.62 (C5′ or C6′), 129.12 (C4′ or C7′), 129.39 (C4′ or C7′), 129.89 (C4), 138.85 (C5), 140.42 (C7a), 146.08 (C3′a, C7′a), 146.26 (C2); MS *m*/*z* 396 ($M^{\bullet+}$).

3-Amino-8-(4-methylpiperidinosulfonyl)-5*H*-1,2,4-triazino[6,5-*b*]indole (8). A mixture of 0.43 g (1.4 mmol) of **4**{*13*} and 1 g (10 mmol) of aminoguanidine hydrochloride (**6**) in 50 mL of water was heated at reflux for 1 h. An amount of 3 mL of concentrated hydrochloric acid was then added, and the reaction mixture was filtered while hot. While being stirred, the filtrate was allowed to cool to room temperature, and the resulting yellow precipitate was filtered and dried in air at 100 °C to yield 0.37 g (70%) of the hydrochloride salt. This salt was dissolved in 150 mL of water, enough ammonium hydroxide was added to raise the pH to ca. 8.0, and the resulting mixture was stirred and heated at reflux for 5 h. The precipitated free amine product was filtered while hot and washed with hot water and then with boiling acetone. Drying in air at 100 °C afforded 0.25 g (70%) of 3-aminotriazinoindole **8** as a yellow crystalline solid: mp >304 °C (dec); TLC (Silufol UV_{254}, chloroform−acetone 10:1 v/v) R_f 0.15; ^{1}H NMR δ 0.90 (d, J = 4.90 Hz, 3H, CH_3 at piperidine ring), 1.29 (m, 3H, piperidine ring H), 1.70 (d, J = 10.80 Hz, 2H, piperidine ring H), 2.19 (m, piperidine ring H), 3.64 (d, J = 10.80 Hz, 2H, piperidine ring H), 6.67 (br s, 2H, NH_2), 6.85 (d, J_{AB} = 8.30 Hz, 1H, H_a), 7.68 (dd, J_{BX} = 1.00 Hz, J_{AB} = 8.30 Hz, 1H, H_b), 8.55 (d, J_{BX} = 1.00 Hz, 1H, H_x), 10.50 (br s, 1H, NH).

General Procedure for the Synthesis of 2-Aryl-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole-7-sulfonamides, Chemset 10. A mixture of equimolar amounts (1.5 mmol) of 5-sulfamoylisatin **4**{*2*,*3*,*6*,*7*,*9*,*10*,*11*,*13*, or *15*} and 4-aryl-1,2-diaminoimidazole **9**{*1* or *2*} in 15 mL of anhydrous benzene was treated with 3% (v/v) of glacial acetic acid and heated at reflux for 4 h. The progress of the reaction was monitored by TLC (Silufol UV_{254}, chloroform−acetone 10:1 v/v; R_f 0.30−0.65 for chemset **10** and 0.15−0.25 for 5-sulfamoylisatins **4**) to determine the exact reaction time for each set of reagents. The reaction mixture was allowed to cool to room temperature, and the precipitated product was filtered. It was then purified by dispersing it in boiling acetone, allowing the acetone to cool back to room temperature, and filtering. The crystalline product was rinsed with acetone and dried in air at 70 °C. 2-Arylimidazotriazinoindoles **10** are dark-red, finely crystalline substances that are poorly soluble in all organic solvents.

2-(4-Bromophenyl)-7-[(2-butylamino)sulfonyl]-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*2*,*1*}: yield 29%; mp 266 °C (dec); ^{1}H NMR δ 0.77 (t, J = 7.20 Hz, 3H, CH_3), 0.90 (d, J = 7.20 Hz, 3H, CH_3), 1.35 (m, J = 7.20 Hz, 2H, CH_2), 3.00−3.10 (m, 1H, C*H*NH), 7.12−7.20 (m, 1H, $NHSO_2$), 7.46 (d, J_{AB} = 8.20 Hz, 1H, H_a), 7.55 (d, $J_{2(6),3(5)}$ = 8.60 Hz, 2H, H-2 and H-6 of *p*-C_6H_4Br), 7.86 (dd, J_{BX} = 1.70 Hz, J_{AB} = 8.20 Hz, 1H, H_b), 7.98 (d, $J_{2(6),3(5)}$ = 8.60 Hz, 2H, H-3 and H-5 of *p*-C_6H_4Br), 8.42 (d, J_{BX} = 1.70 Hz, 1H, H_x), 8.49 (s, 1H, imidazole ring H); MS *m*/*z* 498 (500) ($M^{\bullet+}$).

2-(4-Bromophenyl)-7-[(3-methylbutyl)aminosulfonyl]-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*3*,*1*}: yield 42%; mp >360 °C (dec); ^{1}H NMR δ 0.83 (d, J = 6.80 Hz, 6H, CH_3), 1.30 (m, 2H, CH_2), 1.60 (m, 1H, CH), 2.75 (m, 2H, CH_2NHSO$_2$), 7.49 (t, J = 5.85 Hz, 1H, $NHSO_2$), 7.60 (d, $J_{2(6),3(5)}$ = 8.60 Hz, 2H, H-2 and H-6 of *p*-C_6H_4Br), 7.61 (d, J_{AB} = 8.30 Hz, 1H, H_a), 8.03 (dd, J_{AB} = 8.30 Hz, $J_{2(6),3(5)}$ = 8.60 Hz, 3H, H-3 and H-5 of *p*-C_6H_4Br and H_b), 8.53 (br s, 1H, H_x) 8.80 (s, 1H, imidazole ring H-3), 12.63 (br s, 1H, indole NH); MS *m*/*z* 512 (514) ($M^{\bullet+}$).

2-(4-Bromophenyl)-7-(benzylaminosulfonyl)-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*6*,*1*}: yield 26%; mp 240 °C (dec); ^{1}H NMR δ 3.85 (d, J = 6.30 Hz, 2H, CH_2NHSO$_2$), 7.17−7.24 (m, 5H, C_6H_5) 7.40 (d, J_{AB} = 8.40 Hz, 1H, H_a), 7.58 (d, $J_{2(6),3(5)}$ = 8.20 Hz, 2H, H-2 and H-6 of *p*-C_6H_4Br), 7.85 (dd, J_{BX} = 1.00 Hz, J_{AB} = 8.40 Hz, 1H, H_b), 7.85−7.92 (m, 1H, CH_2NHSO_2), 7.98 (d, $J_{2(6),3(5)}$ = 8.20 Hz, 2H, H-3 and H-5 of *p*-C_6H_4Br), 8.40 (d, J_{BX} = 1.00 Hz, 1H, H_x), 8.60 (br s, 1H, imidazole ring H-3), the indole NH is exchanged; MS *m*/*z* 532 (534) ($M^{\bullet+}$).

2-(4-Bromophenyl)-7-(2-chlorobenzylaminosulfonyl)-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*7*,*1*}:

yield 34%; mp 227 °C (dec); ^{1}H NMR δ 4.05 (d, J = 6.10 Hz, 2H, CH_2NHSO$_2$), 7.20−7.30 (m, 4H, *o*-ClC_6H_4), 7.48 (d, $J_{2(6),3(5)}$ = 8.20 Hz, 2H, H-2 and H-6 of *p*-C_6H_4Br), 7.50 (t, J = 6.10 Hz, 1H, CH$_2$N*H*SO$_2$), 7.57 (d, J = 8.30 Hz, 1H, H$_a$), 7.87 (d, J = 8.30 Hz, 1H, H$_b$), 7.95 (d, $J_{2(6),3(5)}$ = 8.20 Hz, 2H, H-3 and H-5 of *p*-C_6H_4Br), 8.42 (br s, 1H, H$_x$), 8.63 (br s, 1H, imidazole ring H-3), the indole NH is exchanged; MS *m*/*z* 566 (568) (M$^{\bullet+}$).

2-(4-Bromophenyl)-7-(dimethylaminosulfonyl)-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*9,1*}: yield 65%; mp >360 °C (dec); ^{1}H NMR δ 2.66 (s, 6H, CH$_3$), 7.38 (d, J = 8.40 Hz, 1H, H$_a$), 7.51 (d, $J_{2(6),3(5)}$ = 8.60 Hz, 2H, H-2 and H-6 of *p*-C_6H_4Br), 7.67 (d, J = 8.40 Hz, 1H, H$_b$), 7.94 (d, $J_{2(6),3(5)}$ = 8.60 Hz, 2H, H-3 and H-5 of *p*-C_6H_4Br), 8.26 (br s, 2H, H$_x$ and imidazole ring H-3), the indole NH is exchanged; ^{13}C NMR δ 37.77 (CH$_3$), 107.50 (C9), 115.92 (C8), 117.82 (C5b), 119.83 (C4 of *p*-C_6H_4Br), 120.05 (C2), 121.33 (C6), 127.16 (C2 and C6 of *p*-C_6H_4Br), 128.96 (C3), 131.37 (C3 and C5 of *p*-C_6H_4Br), 134.12 (C1 of *p*-C_6H_4Br), 140.15 (C5a), 140.57 (C7), 144.47 (C10a), 156.53 (C9a), 162.89 (C11a); MS *m*/*z* 470 (472) (M$^{\bullet+}$).

2-(4-Bromophenyl)-7-(diethylaminosulfonyl)-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*10,1*}: yield 25%; mp >301 °C (dec); ^{1}H NMR δ 1.11 (t, J = 6.90 Hz, 6H, CH$_3$), 3.15 (q, J = 6.90 Hz, 4H, CH$_2$), 7.31 (d, J = 8.50 Hz, 1H, H$_a$), 7.48 (d, $J_{2(6),3(5)}$ = 8.60 Hz, 2H, H-2 and H-6 of *p*-C_6H_4Br), 7.65 (d, J = 8.50 Hz, 1H, H$_b$), 7.74 (d, $J_{2(6),3(5)}$ = 8.60 Hz, 2H, H-3 and H-5 of *p*-C_6H_4Br), 8.25 (br s, 1H, H$_x$), 8.28 (br s, 1H, imidazole ring H-3), the indole NH is exchanged; MS *m*/*z* 498 (500) (M$^{\bullet+}$).

2-(2,4-Dichlorophenyl)-7-(diethylaminosulfonyl)-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*10,2*}: yield 30%, mp >360 °C (dec); ^{1}H NMR δ 1.11 (t, J = 7.00 Hz, 6H, CH$_3$), 3.18 (q, J = 7.00 Hz, 4H, CH$_2$), 7.31 (d, $J_{5,6}$ = 8.10 Hz, 1H, H-5 of 2,4-$Cl_2C_6H_3$), 7.40 (d, J_{AB} = 8.08 Hz, 1H, H$_a$), 7.48 (d, $J_{3,5}$ < 1.00 Hz, 1H, H-3 of 2,4-$Cl_2C_6H_3$), 7.67 (dd, J_{BX} = 1.00 Hz, J_{AB} = 8.08 Hz, 1H, H$_b$), 8.24 (d, J_{BX} = 1.00 Hz, 1H, H$_x$), 8.42 (d, $J_{5,6}$ = 8.10 Hz, 1H, H-6 of 2,4-$Cl_2C_6H_3$), 8.46 (s, 1H, imidazole ring H-3), the indole NH is exchanged; MS *m*/*z* 488 (492) (M$^{\bullet+}$).

2-(4-Bromophenyl)-7-(pyrrolidinosulfonyl)-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*11,1*}: yield 51%; mp 331 °C (dec); ^{1}H NMR δ 1.72 (t, J = 6.65 Hz, 4H, CH_2-CH_2N), 3.19 (t, J = 6.65 Hz, 4H, CH$_2$CH_2N), 7.36 (d, J_{AB} = 8.50 Hz, 1H, H$_a$), 7.50 (d, $J_{2(6),3(5)}$ = 8.20 Hz, 2H, H-2 and H-6 of *p*-C_6H_4Br), 7.70 (dd, J_{BX} = 1.90 Hz, J = 8.50 Hz, 1H, H$_b$), 7.94 (d, $J_{2(6),3(5)}$ = 8.20 Hz, 2H, H-3 and H-5 of *p*-C_6H_4Br), 8.25 (s, 1H, imidazole ring H-3), 8.31 (d, J_{BX} = 1.90 Hz, 1H, H$_x$), the indole NH is exchanged; ^{13}C NMR δ 24.50 (pyrrolidine ring C3 and C4), 47.73 (pyrrolidine ring C2 and C5), 107.46 (C9), 116.04 (C8), 117.78 (C5b), 120.02 (C2), 121.10 (C6), 121.38 (C4 of *p*-C_6H_4Br), 127.14 (C2 and C6 of *p*-C_6H_4Br), 128.76 (C3), 131.36 (C3 and C5 of *p*-C_6H_4Br), 134.14 (C1 of *p*-C_6H_4Br), 140.10 (C5a), 140.67 (C7), 144.51 (C10a), 156.63 (C9a), 163.05 (C11a).

2-(4-Bromophenyl)-7-(4-methylpiperidinosulfonyl)-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*13,1*}: yield 64%; mp 275 °C (dec); ^{1}H NMR δ 0.90 (d, J = 4.40 Hz, 3H, CH$_3$ at piperidine ring), 1.16−1.39 (m, 3H, piperidine ring H), 1.68 (d, J = 10.30 Hz, 2H, piperidine ring H), 2.19−2.35 (m, 2H, piperidine ring H), 3.69 (d, J = 10.30 Hz, 2H, piperidine ring H), 7.41 (d, J_{AB} = 8.20 Hz, 1H, H$_a$), 7.53 (d, $J_{2(6),3(5)}$ = 7.90 Hz, 2H, H-2 and H-6 of *p*-C_6H_4Br), 7.67 (dd, J_{BX} < 1.00 Hz, J_{AB} = 8.30 Hz, 1H, H$_b$), 7.96 (d, $J_{2(6),3(5)}$ = 7.90 Hz, 2H, H-3 and H-5 of *p*-C_6H_4Br), 8.26 (br s, 1H, H$_x$), 8.32 (br s, 1H, imidazole ring H-3), the indole NH is exchanged; ^{13}C NMR δ 21.21 (*C*H$_3$ at piperidine ring), 29.29 (piperidine ring C4), 32.88 (piperidine ring C3 and C5), 46.14 (piperidine ring C2 and C6), 107.60 (C9), 115.73 (C8), 117.72 (C5b), 120.10 (C2), 121.02 (C4 of *p*-C_6H_4Br), 121.17 (C6), 127.17 (C2 and C6 of *p*-C_6H_4Br), 128.91 (C3), 131.38 (C3 and C5 of *p*-C_6H_4Br), 134.05 (C1 of *p*-C_6H_4Br), 140.27 (C5a), 140.34 (C7), 144.32 (C10a), 156.02 (C9a), 162.06 (C11a).

2-(2,4-Dichlorophenyl)-7-(4-methylpiperidinosulfonyl)-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*13,2*}: yield 48%; mp 329 °C (dec); ^{1}H NMR δ 0.91 (d, J = 3.20 Hz, 3H, CH$_3$ at piperidine ring), 1.21−1.33 (m, 3H, piperidine ring H), 1.69 (d, J = 9.90 Hz, 2H, piperidine ring H), 2.23 (m, 2H, piperidine ring H), 3.68 (d, J = 9.90 Hz, 2H, piperidine ring H), 7.34−7.39 (m, 2H, H-5 of 2,4-$Cl_2C_6H_3$ and H$_a$), 7.45−7.48 (m, 1H, H-3 of 2,4-$Cl_2C_6H_3$), 7.61−7.66 (m, 1H, H$_b$), 8.20−8.22 (m, 1H, H$_x$), 8.37−8.42 (m, 1H, H-6 of 2,4-$Cl_2C_6H_3$), 8.44−8.46 (m, 1H, imidazole ring H-3), the indole NH is exchanged; ^{13}C NMR δ 21.26 (CH$_3$ at piperidine ring), 29.28 (piperidine ring C4), 32.88 (piperidine ring C3 and C5), 46.13 (piperidine ring C2 and C6), 111.00 (C9), 115.86 (C8), 117.76 (C5b), 121.19 (C2), 121.29 (C6), 127.38 (C5 of 2,4-$C_6H_3Cl_2$), 129.23 (C3), 129.54 (C6 of 2,4-$C_6H_3Cl_2$), 130.99 (C1 of 2,4-$C_6H_3Cl_2$), 131.38 (C3 of 2,4-$C_6H_3Cl_2$), 131.71 (C4 of 2,4-$C_6H_3Cl_2$), 131.77 (C2 of 2,4-$C_6H_3Cl_2$), 136.27 (C5a), 141.07 (C7), 143.47 (C10a), 156.54 (C9a), 162.70 (C11a).

2-(4-Bromophenyl)-7-(morpholinosulfonyl)-10*H*-imidazo-[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*15,1*}: yield 28%; mp 312 °C (dec); ^{1}H NMR δ 2.92 (m, 4H, NCH$_2$), 3.60 (m, 4H, OCH$_2$), 7.43 (d, J_{AB} = 8.50 Hz, 1H, H$_a$), 7.47 (d, $J_{2(6),3(5)}$ = 8.20 Hz, 2H, H-2 and H-6 of *p*-C_6H_4Br), 7.69 (dd, J_{BX} = 1.00 Hz, J_{AB} = 8.50 Hz, 1H, H$_b$), 7.90 (d, $J_{2(6),3(5)}$ = 8.20 Hz, 2H, H-3 and H-5 of *p*-C_6H_4Br), 8.15 (br s, 1H, H$_x$), 8.30 (s, 1H, imidazole ring H-3), the indole NH is exchanged.

2-(2,4-Dichlorophenyl)-7-(morpholinosulfonyl)-10*H*-imidazo[1′,2′:2,3][1,2,4]triazino[5,6-*b*]indole, 10{*15,2*}: yield 34%; mp 343 °C (dec); ^{1}H NMR δ 2.91−2.97 (m, 4H, NCH$_2$), 3.65−3.70 (m, 4H, OCH$_2$), 7.39 (dd, $J_{3,5}$ = 2.0 Hz, $J_{5,6}$ = 8.10 Hz, 1H, H-5 of 2,4-$Cl_2C_6H_3$), 7.45 (d, J_{AB} = 8.70 Hz, 1H, H$_a$), 7.47 (d, $J_{3,5}$ = 2.0 Hz, 1H, H-3 of 2,4-$Cl_2C_6H_3$), 7.69 (dd, J_{BX} = 1.80 Hz, J_{AB} = 8.70 Hz, 1H, H$_b$), 8.26 (d, J_{BX} = 1.80 Hz, 1H, H$_x$), 8.42 (d, $J_{5,6}$ = 8.10 Hz, 1H, H-6 of 2,4-$Cl_2C_6H_3$), 8.50 (s, 1H, imidazole ring H-3), the indole NH is exchanged; ^{13}C NMR δ 46.01 (NCH$_2$), 65.27 (OCH$_2$), 110.99 (C9), 116.02 (C8), 117.89 (C5b), 119.67 (C2), 121.60 (C6), 127.39 (C5 of 2,4-$C_6H_3Cl_2$), 129.34 (C3), 129.55 (C6 of 2,4-$C_6H_3Cl_2$), 131.00 (C1 of 2,4-$C_6H_3Cl_2$), 131.40 (C3 of 2,4-$C_6H_3Cl_2$), 131.71 (C4 of 2,4-$C_6H_3Cl_2$), 131.79 (C2 of 2,4-$C_6H_3Cl_2$), 136.30 (C5a), 141.10 (C7), 143.51 (C10a), 156.85 (C9a), 163.29 (C11a); MS *m*/*z* 502 (504) (M$^{\bullet+}$).

General Procedure for the Synthesis of Mercaptans 13a and 13b. A solution of 0.31 g (3.38 mmol) of thiosemicarbazide in 5 mL of boiling water was added with stirring to a solution of 3.38 mmol of **4**{*13*} or **4**{*15*} in 25 mL of boiling alcohol. The resulting mixture was stirred and heated at reflux for 2 h. The precipitated thiosemicarbazone was filtered and rinsed with ethanol. It was then dispersed in a solution of 0.14 g (3.38 mmol) of sodium hydroxide in 10 mL of water and heated at reflux for 15 h. When the mixture was cooled to room temperature, enough dilute hydrochloric acid (1:3, v/v) was added with stirring to take the pH down to ca. 3. The resulting yellow precipitate was filtered and rinsed with water and then with ethanol. It was recrystallized first from glacial acetic acid and then from ethanol. The recrystallized product was filtered and dried in air at 70 °C.

8-(4-Methylpiperidinosulfonyl)-5*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl-mercaptan (13a): yield 13%; mp >255 °C; ^{1}H NMR δ 0.89 (d, J = 2.30 Hz, 3H, CH_3 at piperidine ring), 1.22 (m, 3H, piperidine ring H), 1.68 (d, J = 10.90 Hz, 2H, piperidine ring H), 2.20 (m, 2H, piperidine ring H), 3.67 (d, J = 10.90 Hz, 2H, piperidine ring H), 7.61 (d, J_{AB} = 7.80 Hz, 1H, H_a), 7.88 (dd, J_{BX} = 1.00 Hz, J_{AB} = 7.80 Hz, 1H, H_b), 8.21 (d, J_{BX} = 1.00 Hz, 1H, H_x), 12.84 (br s, 1H, NH), 14.77 (s, 1H, SH).

8-(Morpholinosulfonyl)-5*H*-[1,2,4]triazino[5,6-*b*]indol-3-yl-mercaptan (13b): yield 38%; mp >305 °C; ^{1}H NMR δ 3.10 (br s, 4H, morpholine ring H), 3.70 (br s, 4H, morpholine ring H), 7.60 (d, J_{AB} = 7.85 Hz, 1H, H_a), 7.90 (dd, J_{BX} = 1.00 Hz, J_{AB} = 7.85 Hz, 1H, H_b), 8.10 (d, J_{BX} = 1.00 Hz, 1H, H_x), 12.80 (br s, 1H, NH), 14.80 (br s, 1H, SH).

General Procedure for the Synthesis of 3-Alkylmercapto-8-sulfamoyl-5*H*-[1,2,4]triazino[5,6-*b*]indoles, Chemset 15. An amount of 0.67 mmol of alkylating reagent **14** was added with stirring to a solution of 1.00 mmol of **13a** or **13b** in 15 mL of 0.1 M aqueous sodium hydroxide. The resulting mixture was stirred at 75 °C for ca. 3 h. The progress of the reaction was monitored by TLC (SiO_2; $CHCl_3$−CH_3OH, 29:1, v/v) to determine the exact reaction time for each pair of reactants. The precipitated yellowish product, **15**, was filtered, rinsed with water to neutral pH, and recrystallized from ethanol.

Compounds **12**{*1*−*4*} were prepared from **4**{*9*−*12*} as described for **13a**,**b** but were not isolated. Instead, the acidification step was omitted, and aqueous solutions of **12**{*1*−*4*} containing a 1.5-fold excess of sodium hydroxide were treated with diversity reagents **14** (as described in the preceding paragraph) to produce the corresponding members of chemset **15**.

***N*^{1}-(5-Methyl-3-isoxazolyl)-2-(8-dimethylsulfamoyl-5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylsulfanyl)acetamide, 15{*9,4*}:** yield 60%; mp 222−224 °C; ^{1}H NMR δ 2.45 (s, 3H, CH_3 at isoxazole ring), 2.73 (s, 6H, $(CH_3)_2NSO_2$), 4.20 (s, 2H, SCH_2CON), 6.58 (s, 1H, isoxazole ring H), 7.68 (d, J_{AB} = 7.90 Hz, 1H, H_a), 7.94 (dd, J_{BX} < 1.00 Hz, J_{AB} = 7.90 Hz, 1H, H_b), 8.59 (br s, 1H, H_x), 11.00 (br s, 1H, CONH), the indole NH is exchanged.

***N*^{8},*N*^{8}-Dimethyl-3-(2-(3-amino-5-methyl-1*H*-1-pyrazolyl)-2-oxoethylsulfanyl)-5*H*-[1,2,4]triazino[5,6-*b*]indole-8-sulfonamide, 15{*9,5*}:** yield 32%; mp 273 °C (dec); ^{1}H NMR δ 2.19 (s, 3H, CH_3 at pyrazole ring), 2.62 (s, 6H, $(CH_3)_2NSO_2$), 4.13 (s, 2H, SCH_2CON), 6.11 (s, 1H, pyrazole ring H), 7.70 (d, J_{AB} = 8.30 Hz, 1H, H_a), 7.90 (dd, J_{BX} < 1.00 Hz, J_{AB} = 8.30 Hz, 1H, H_b), 8.53 (br s, 1H, H_x), 10.50 (br s, 1H, indole NH), NH_2 is exchanged.

2-(8-Diethylsulfamoyl-5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylsulfanyl)acetic Acid, 15{*10,1*}: yield 16%; mp 215 °C (dec); ^{1}H NMR δ 1.12 (t, J = 5.75 Hz, 6H, CH_2CH_3), 3.20 (q, J = 5.75 Hz, 4H, CH_2CH_3), 4.02 (s, 2H, SCH_2CO_2), 7.70 (d, J_{AB} = 7.80 Hz, 1H, H_a), 8.00 (d, J_{AB} = 7.80 Hz, 1H, H_b), 8.70 (br s, 1H, H_x), the indole NH and the COOH are exchanged.

***N*^{1}-(5-Methyl-3-isoxazolyl)-2-(8-diethylsulfamoyl-5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylsulfanyl)acetamide, 15{*10,4*}:** yield 72%; mp 207 °C (dec); ^{1}H NMR δ 1.10 (t, J = 7.05 Hz, 6H, CH_2CH_3), 2.40 (s, 3H, CH_3 at isoxazole ring), 3.20 (q, J = 7.05 Hz, 4H, CH_2CH_3), 4.10 (s, 2H, SCH_2CON), 6.60 (s, 1H, isoxazole ring H), 7.50 (d, J_{AB} = 8.45 Hz, 1H, H_a), 7.70 (dd, J_{BX} < 1.00 Hz, J_{AB} = 8.45 Hz, 1H, H_b), 8.40 (br s, 1H, H_x), 11.20 (br s, 1H, CONH), the indole NH is exchanged; MS m/z 378 (M − OH), 351 (M − CO_2).

***N*^{8},*N*^{8}-Diethyl-3-(3-pyridylmethylsulfanyl)-5*H*-[1,2,4]triazino[5,6-*b*]indole-8-sulfonamide, 15{*10,8*}:** yield 70%; mp 172−176 °C; ^{1}H NMR δ 1.12 (t, J = 6.20 Hz, 6H, $N(CH_2CH_3)_2$), 3.22 (q, J = 6.20 Hz, 4H, $N(CH_2CH_3)_2$), 4.55 (s, 2H, SCH_2), 7.18−7.28 (m, 1H, pyridine ring H), 7.72 (d, J_{AB} = 8.80 Hz, 1H, H_a), 7.84−7.95 (m, 2H, pyridine ring H), 8.38 (d, J_{AB} = 8.80 Hz, 1H, H_b), 8.61 (br s, 1H, H_x), 8.70 (s, 1H, pyridine ring H), the indole NH is exchanged; MS m/z 428 (429) ($M^{\bullet+}$).

6-Methyl-2-(8-tetrahydro-1*H*-1-pyrrolylsulfonyl-5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylsulfanylmethyl)-4*H*-pyrido-[1,2-*a*]pyrimidin-4-one, 15{*11,9*}: yield 38%; mp 210 °C (dec); ^{1}H NMR δ 1.63 (br s, 4H, pyrrolidine ring H), 2.50 (s, 3H, CH_3 at C-6 of pyridopyrimidine ring), 2.90 (br s, 4H, pyrrolidine ring H), 4.40 (s, 2H, SCH_2), 6.37 (s, 1H, aromatic H), 6.73 (m, 1H, aromatic H), 7.30 (m, 1H, aromatic H), 7.50 (m, 2H, aromatic H and H_a), 7.90 (d, J_{AB} = 8.45 Hz, 1H, H_b), 8.50 (br s, 1H, H_x), the indole NH is exchanged.

3-(3-Chlorobenzylsulfanyl)-5*H*-[1,2,4]triazino[5,6-*b*]indol-8-ylpiperidinosulfone, 15{*12,7*}: yield 60%; mp 251−254 °C; ^{1}H NMR δ 1.38 (br s, 2H, piperidine ring H), 1.62 (br s, 4H, piperidine ring H), 2.95 (br s, 4H, piperidine ring H), 4.66 (s, 2H, SCH_2), 7.19−7.31 (m, 2H, aromatic H), 7.39 (m, 1H, aromatic H), 7.68−7.78 (m, 2H, aromatic H and H_a), 7.90 (d, J_{AB} = 7.50 Hz, 1H, H_b), 8.55 (br s, 1H, H_x), the indole NH is exchanged; MS m/z 473 (475) ($M^{\bullet+}$).

***N*^{1}-Benzyl-2-(8-(4-methylpiperidinosulfonyl)-5*H*-[1,2,4]-triazino[5,6-*b*]indol-3-ylsulfanyl)acetamide, 15{*13,2*}:** yield 19%; mp >255 °C; ^{1}H NMR δ 0.82 (d, J = 3.20 Hz, 3H, CH_3 at piperidine ring), 1.23 (m, 3H, piperidine ring H), 1.67 (d, J = 11.20 Hz, 2H, piperidine ring H), 2.22 (m, 2H, piperidine ring H), 3.73 (d, J = 11.20 Hz, 2H, piperidine ring H), 4.11 (s, 2H, SCH_2CON), 4.34 (d, J = 4.80 Hz, 2H, $CONHCH_2$), 7.15−7.25 (m, 5H, C_6H_5), 7.86 (d, J_{AB} = 8.85 Hz, 1H, H_a), 7.95 (dd, J_{BX} < 1.00 Hz, J_{AB} = 8.85 Hz, 1H, H_b), 8.54 (br s, 1H, H_x), 8.78 (t, J = 4.80 Hz, 1H, $CONHCH_2$), the indole NH is exchanged.

***N*[1]-(2-Thienylmethyl)-2-(8-morpholinosulfonyl-5*H*-[1,2,4]-triazino[5,6-*b*]indol-3-ylsulfanyl)acetamide, 15{*15,3*}:** yield 65%; mp 242 °C (dec); ^{1}H NMR δ 2.96 (br s, 4H, morpholine ring H), 3.68 (br s, 4H, morpholine ring H), 4.03 (s, 2H, SCH_2CON), 4.47 (d, J = 6.10 Hz, 2H, NCH_2-2-thienyl), 6.84 (dd, $J_{3,4}$ = 3.50 Hz, $J_{4,5}$ = 5.00, 1H, thiophene ring H-4), 6.91 (d, $J_{3,4}$ = 3.50 Hz, 1H, thiophene ring H-3), 7.13 (d, $J_{3,4}$ = 1.20 Hz, $J_{4,5}$ = 5.00 Hz, 1H, thiophene ring H-5), 7.76 (d, J_{AB} = 8.60 Hz, 1H, H_a), 7.94 (dd, J_{BX} = 1.60 Hz, J_{AB} = 8.60 Hz, 1H, H_b), 8.60 (d, J_{BX} = 1.60 Hz, 1H, H_x), 8.65 (t, J = 6.12 Hz, 1H, CON*H*CH_2), the indole NH is exchanged; ^{13}C NMR δ 34.07 (S*C*H_2CO), 37.62 (NH*C*H_2-thienyl), 45.92 (NCH_2), 65.24 (OCH_2), 113.77 (C6), 118.06 (C9a), 121.13 (C7), 124.86 (thiophene ring C4), 125.35 (thiophene ring C3), 126.52 (C9), 127.96 (thiophene ring C2), 129.54 (thiophene ring C5), 140.78 (C9b), 141.92 (C8), 143.65 (C5a), 147.92 (C4a), 166.83 (C3), 167.53 (CO).

2-Fluorophenyl-(8-morpholinosulfonyl-5*H*-[1,2,4]triazino[5,6-*b*]indol-3-ylsulfanyl)methane, 15{*15,6*}: yield 65%; mp 261−263 °C; ^{1}H NMR δ 2.95 (br s, 4H, morpholine ring H), 3.67 (br s, 4H, morpholine ring H), 4.60 (s, 2H, SCH_2), 7.04−7.11 (m, 2H, aromatic H), 7.21−7.29 (m, 1H, aromatic H), 7.58−7.66 (m, 1H, aromatic H), 7.77 (d, J = 8.40 Hz, 1H, H_a), 7.90 (dd, J_{BX} < 1.00 Hz, J_{AB} = 8.40 Hz, 1H, H_b), 8.60 (br s, 1H, H_x), the indole NH is exchanged; ^{13}C NMR δ 27.48 (SCH_2), 45.94 (NCH_2), 65.23(OCH_2), 114.30 (C6), 115.28 (J_{CF} = 21.38 Hz, C3 of *o*-C_6H_4F), 118.40 (C9a), 121.10 (C7), 124.35 (C5 of *o*-C_6H_4F), 124.41 (J_{CF} = 13.83 Hz, C1 of *o*-C_6H_4F), 126.94 (C9b), 129.13 (C9), 129.40 (J_{CF} = 7.55 Hz, C4 of *o*-C_6H_4F), 131.25 (J_{CF} = 2.51 Hz, C6 of *o*-C_6H_4F), 141.41 (C8), 146.00 (C5a), 149.30 (C4a), 160.47 (J_{CF} = 245.23 Hz, C2 of *o*-C_6H_4F), 166.89 (C3); MS *m*/*z* 459 ($M^{\bullet+}$).

4-(3-(3-Pyridylmethylsulfanyl)-5*H*-[1,2,4]triazino[5,6-*b*]-indol-8-ylsulfonyl)morpholine, 15{*15,8*}: yield 30%; mp 264−265 °C; ^{1}H NMR δ 2.94 (br s, 4H, morpholine ring H), 3.66 (br s, 4H, morpholine ring H), 4.57 (s, 2H, SCH_2), 7.20−7.33 (m, 1H, pyridine ring H-5), 7.77 (d, J_{AB} = 8.40 Hz, 1H, H_a), 7.89 (d, J = 5.90 Hz, 1H, pyridine ring H-4), 7.96 (dd, J_{BX} < 1.00 Hz, J_{AB} = 8.40 Hz, 1H, H_b), 8.34−8.44 (m, 1H, pyridine ring H-6), 8.60 (d, J_{BX} < 1.00 Hz, 1H, H_x), 8.72 (br s, 1H, pyridine ring H-2), the indole NH is exchanged; MS *m*/*z* 442 ($M^{\bullet+}$).

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Supporting Information Available. ^{1}H NMR spectra of chemsets **4**, **10**, and **15** and compounds **3**, **7**, **8**, **13a**, and **13b** and IR and ^{13}C NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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