Synthesis of 2-Aryl-4-hydroxy-5-thio Substituted 1,3-Thiazin-6-ones *via* Sulfenylation of 2-Aryl-4-hydroxy-[1,3]thiazin-6-ones with Sulfenyl Chlorides

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A series of 2-aryl-4-hydroxy-5-thio substituted 1,3-thiazin-6-ones were synthesized for human immunodeficiency virus-1 protease inhibition. These compounds were synthesized by the treatment of 4-hydroxy-5-thio substituted-1,3-thiazin-6-ones with the corresponding sulfenyl chlorides. The products were obtained in good isolated yields, inspite of the presence of bulkyl substitutents at the ortho position of phenyl sulfenyl chloride portion.

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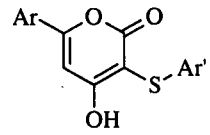
1,3-Thiazines are synthetically as well as biologically interesting compounds [1] and have found applications in medicine [2], in agriculture [3,4] and in other areas [5]. Recently, we have reported 4-hydroxy-3-thio substituted 2*H*-pyran-2-ones, **1** to be structurally novel and potent HIV-1 protease inhibitors [6,7]. Since the 1,3-thiazine ring system, **2**, is structurally similar to the pyran-2-one ring system, **1**, we thought one might derive potent HIV-1 protease inhibitors, based on such a template. Though electrophilic attack occurs at the 5-position of 4-hydroxy-1,3-thiazin-6-ones, 5-sulfenylated 1,3-thiazines are not yet reported in the literature. Due to our interest in 4-hydroxy-5-thio substituted 1,3-thiazin-6-ones, we have investigated the introduction of an *S*-aryl moiety at the 5-position of 2-aryl-4-hydroxy-1,3-thiazin-6-ones.



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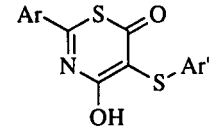
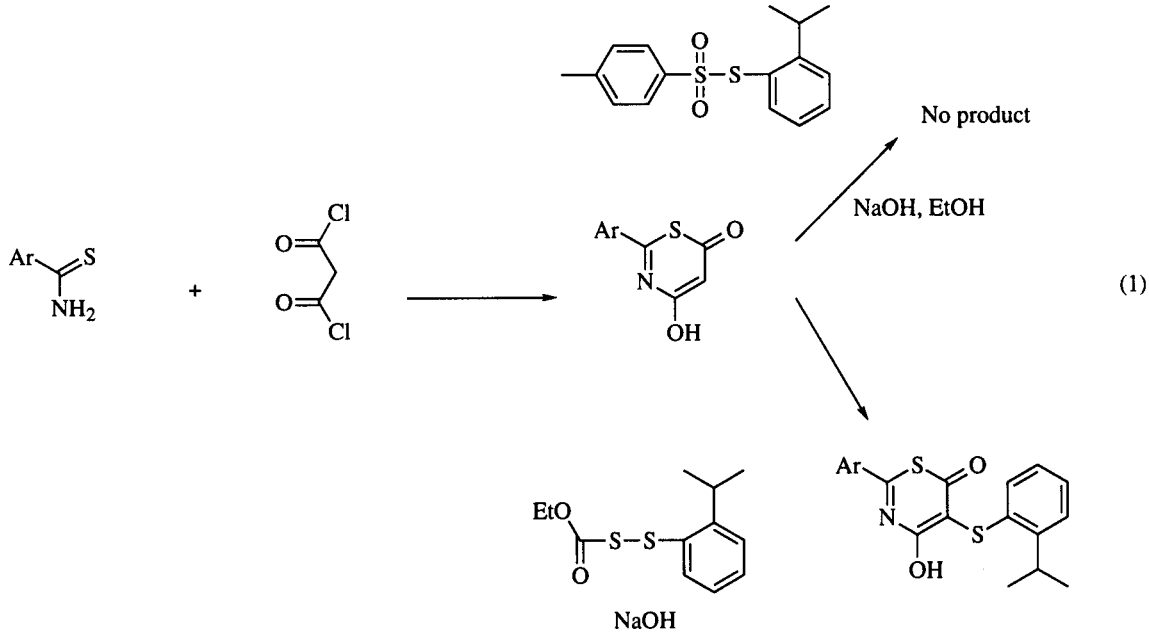


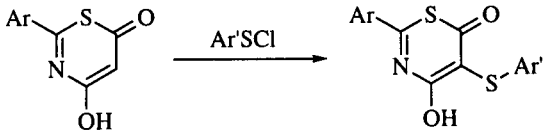
2

Synthesis of 4-hydroxy-5-thio substituted 6*H*-1,3-thiazin-6-ones by the reaction of 4-hydroxy-2-phenyl-1,3-thiazin-6-one with *p*-toluenethiosulfonates [8], which was successful for preparing **1**, in the presence of a base under ethanol refluxing conditions did not yield the expected product and only starting material was recovered. Another procedure, *i.e.*; treatment of 4-hydroxy-6-phenyl-1,3-thiazin-6-one with reagent derived from chlorocarbonylsulfenyl chloride, ethanol and 2-isopropylthiophenol [10] in the presence of a base yielded the expected product only in 10% isolated yield (equation 1).



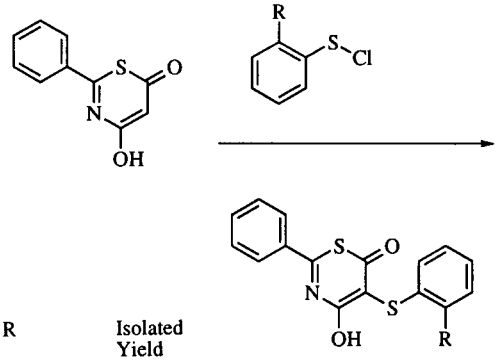
(1)

Finally, a superior sulfenylation of 1,3-thiazin-6-ones was achieved by the reaction of 2-aryl-4-hydroxy-1,3-thiazin-6-one with the corresponding sulfenyl chloride [11] in benzene and carbon tetrachloride (1:1 mixture) solvent system under refluxing conditions for 4-6 hours. The product was isolated either by filtration from the reaction mixture or by the silica gel column chromatography in 30-85% yields (equation 2). The starting material, 2-aryl-4-hydroxy-1,3-thiazin-6-one was prepared from the corresponding aryl thioamide and malonyl chloride [9].



(2)

The reaction tolerates various groups, possessing various steric requirements, present on the ortho position of the phenyl ring of the sulfenyl chloride. Thus, the reaction of 2-substituted phenyl sulfenyl chloride with 2-phenyl-4-hydroxy-1,3-thiazin-6-one afforded the corresponding products, **3**-**5** in 78-82% isolated yields (equation 3).

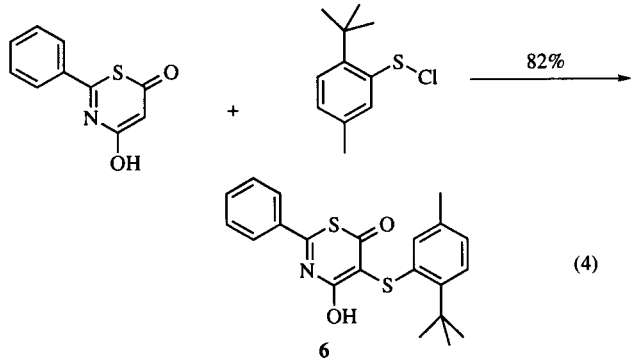


(3)

	R	Isolated Yield
3	ethyl	78%
4	*iso*-propyl	80%
5	*tert*-butyl	82%

Similarly, the reaction between 2-*tert*-butyl-5-methylphenylsulfenyl chloride and 2-phenyl-4-hydroxy-1,3-thiazin-6-one also occured smoothly to afford the corresponding product, **6**, in 82% isolated yield (equation 4).

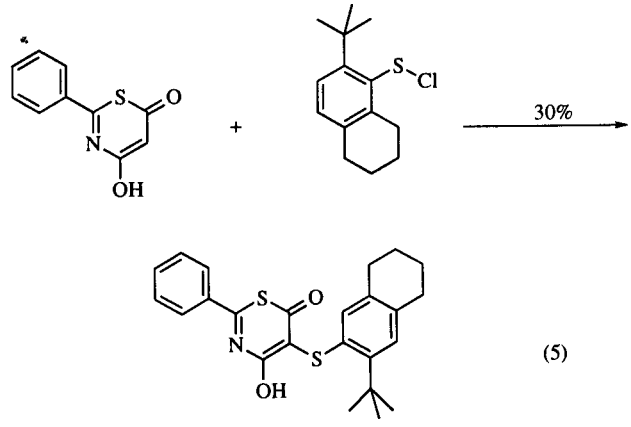
Equation 4



(4)

6

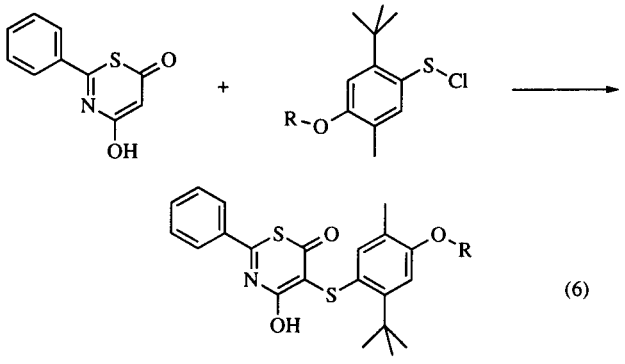
In addition, the 2-phenyl-4-hydroxy-1,3-thiazin-6-one also reacted with 2-*tert*-butyl(5,6,7,8-tetrahydronoaphthanlene)sulfenyl chloride to afford the corresponding thiazine, **7**, in 30% isolated yield (equation 5).



(5)

7

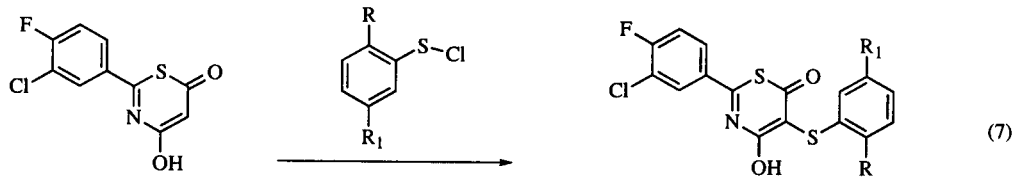
The reaction also tolerates polar functional groups, such as ester or phenol protected as TBS ether, on sulfenyl chloride to afford the corresponding products. Thus, the reaction of 2-phenyl-4-hydroxy-1,3-thiazin-6-one with (2-*tert*-butyl-5-methyl-4-(methoxycarbonylmethoxy)phenylsulfenyl chloride and [2-*tert*-butyl-5-methyl-4-(*tert*-butyldimethylsilanyloxy)phenyl]sulfenyl chloride afforded the corresponding thiazines, **8** and **9** in 60% and 63% yields, respectively (equation 6). These results also indicates that the reaction is not affected very much by the presence of electron-withdrawing group *para* to the sulfenyl chloride.



(6)

	R	Isolated Yield
8	$CH_2CO_2CH_3$	60%
9	TBS	63%

The reaction also tolerates the presence of various electron-withdrawing groups present on the phenyl group of the 4-hydroxy-1,3-thiazin-6-one. Thus, 2-(3-chloro-4-fluorophenyl)-4-hydroxy-1,3-thiazin-6-one with sulfenyl chloride afforded the corresponding products in 68-87% isolated yields (equation 7).



(7)

	R	R_1	Isolated Yield
10	ethyl	H	68%
11	*iso*-propyl	H	72%
12	*tert*-butyl	H	72%
13	*tert*-butyl	CH_3	87%

In conclusion, we have developed a very simple procedure to synthesize 4-hydroxy-5-thiosubstituted-1,3-thiazin-6-ones in very good isolated yields, inspite of the presence of bulkyl substitutents at the ortho position of phenyl sulfenyl chloride portion. This procedure allows us to synthesize highly functionalized 1,3-thiazines in a simple fashion and also allows a rapid preparation of structurally diversified analogues to explore structure-activity relationship as human immunodeficiency virus protease inhibitors.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Hoover melting point apparatus and are uncorrected. Infra red spectra were determined on a Nicolet FT IR SX-20 spectrophotometer. Proton magnetic resonance were recorded on a Bruker AM 250 spectrometer and chemical shifts are reported in δ units relative to internal tetramethylsilane. All mass spectra were obtained on a Finnigan 4500 GCMS or a VG analytical 7070E/F spectrometer. Elemental analyses were performed on a Perkin-Elmer Model 240 elemental analyzer, and all compounds had analytical results of ± 0.4% of theoretical values. Flash column or medium pressure chromatography were performed using silica gel (230 to 400 mesh) and concentrations were performed *in vacuo* 10-30 mmHg.

General Procedures.

Preparation of 4-Hydroxy-2-aryl-1,3-thiazin-6-one.

The syntheses of 4-hydroxy-2-aryl-1,3-thiazin-6-ones were performed from the corresponding thioamides and malonyl chloride according to the procedure described in the literature [9].

Preparation of 5-(Arylsulfanyl)-4-hydroxy-2-aryl[1,3]thiazin-6-one.

To a solution of 4-hydroxy-2-aryl-1,3-thiazin-6-one (1 equivalent) in benzene and carbon tetrachloride (1:1) was added the corresponding sulfenyl chloride [11] (1-4 equivalents) under a nitrogen atmosphere. The solution was kept under reflux for 4 to 6 hours. The reaction mixture was cooled and the product which precipitated was either filtered and washed with cold diethyl ether or subjected to chromatography to provide the 1,3-thiazine.

Examples.

5-(2-Ethylphenylsulfanyl)-4-hydroxy-2-phenyl[1,3]thiazin-6-one (**3**).

The compound was prepared according to the general procedure using 2-phenyl-4-hydroxy-1,3-thiazin-6-one (0.5 g, 1.94 mmoles), (2-ethylphenyl)sulfenyl chloride (0.67 g, 3.88 mmoles) and carbon tetrachloride and benzene (1:1, 10 ml). Product **5** was separated by column chromatography in 78% yield, mp 172-173°; ir (potassium bromide): 3053, 2962, 1585, 1558, 1503, 1203, 1055, 741, 680 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 1.22 (t, 3H), 2.74 (q, 2H), 6.96 (d, 1H), 7.06 (m, 2H), 7.18 (m, 1H), 7.61 (t, 2H), 7.72 (t, 1H), 8.07 (d, 2H); ms: 342 (M+H), 236, 206, 177, 138, 121, 111, 91.

Anal. Calcd. for $C_{18}H_{15}O_2S_2N{\cdot}0.34H_2O$: C, 62.60; H, 4.55; N, 4.03. Found: C, 62.20; H, 4.42; N, 4.07.

5-(2-isopropylphenylsulfanyl)-4-hydroxy-2-phenyl[1,3]thiazin-6-one (**4**).

The compound was prepared according to the general procedure using 4-hydroxy-2-phenyl-1,3-thiazin-6-one (0.5 g, 2.43 mmoles), (2-isopropylylphenyl)sulfenyl chloride (0.91 g, 4.87 mmoles) and carbon tetrachloride and benzene (1:1, 10 ml). Product **3** was isolated in 82% yield by silica gel column chromatography, mp 149-150°; ir (potassium bromide): 3174, 2959, 1617, 1496, 1363, 1181, 1055, 761 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 1.25 (d, 6H), 3.44 (m, 1H), 6.99 (d, 1H), 7.04 (t, 1H), 7.11 (t, 1H), 7.26 (d, 1H), 7.63 (t, 2H), 7.72 (t, 1H), 8.06 (d, 2H); ms: 356 (M+H), 206, 177, 152, 137, 104, 91.

Anal. Calcd. for $C_{19}H_{17}O_2S_2N{\cdot}0.13H_2O$: C, 63.79; H, 4.86; N, 3.92. Found: C, 63.79; H, 4.83; N, 4.0.

5-(2-*tert*-Butylphenylsulfanyl)-4-hydroxy-2-phenyl[1,3]thiazin-6-one (**5**).

The compound was prepared according to Method A using 2-phenyl-4-hydroxy-1,3-thiazin-6-one (0.5 g, 2.43 mmoles), (2-*tert*-butylphenyl)sulfenyl chloride (1.47 g, 7.32 mmoles) and carbon tetrachloride and benzene (1:1, 10 ml). Product **7** was isolated in 82% yield by column chromatography, mp 189-190°; ir (potassium bromide): 3187, 2963, 1617, 1499, 1364, 1251, 1179, 1054, 754 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 1.53 (s, 9H), 7.03 (m, 3H), 7.32 (dd, 1H), 7.61 (t, 2H), 7.71 (t, 1H), 8.07 (d, 2H); ms: 370 (M+H), 314, 222, 207, 177, 152, 166, 151, 138, 104, 91.

Anal. Calcd. for $C_{20}H_{19}O_2S_2N{\cdot}0.2H_2O$: C, 64.38; H, 5.24; N, 3.76. Found: C, 64.41; H, 5.37; N, 3.85.

5-(2-*tert*-Butyl-5-methylphenylsulfanyl)-4-hydroxy-2-phenyl-[1,3]thiazin-6-one (**6**).

The compound was prepared as described in the general procedure using 2-phenyl-4-hydroxy-1,3-thiazin-6-one (0.5 g, 2.43 mmoles), (2-*tert*-butyl-5-methylphenyl)sulfenyl chloride (1.57 g, 7.31 mmoles) and carbon tetrachloride and benzene (1:1, 10 ml). Product **9** was separated by column chromatography in 82% yield, mp 203-204°; ir (potassium bromide): 3064, 2965, 1613, 1495, 1369, 1056, 770, 686 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 1.5 (s, 9H), 2.11 (s, 3H), 6.8 (s, 1H), 6.86 (d, 1H), 7.19 (d, 1H), 7.61 (t, 2H), 7.71 (t, 1H), 8.08 (d, 2H); ms: 384 (M+H), 383, 328, 236, 206, 180, 165, 138, 121, 104, 91.

Anal. Calcd. for $C_{21}H_{21}O_2S_2N{\cdot}0.54H_2O$: C, 64.13; H, 5.66; N, 3.56. Found: C, 64.13; H, 5.51; N, 3.43.

5-(3-*tert*-Butyl-5,6,7,8-tetrahydronaphthalen-2-ylsulfanyl)-4-hydroxy-2-phenyl[1,3]thiazin-6-one (**7**).

The compound was prepared as described in the general procedure using 2-phenyl-4-hydroxy-1,3-thiazin-6-one (0.3 g, 1.46 mmoles), (2-*tert*-butyl-5,6,7,8-tetrahydronaphthalene)sulfenyl chloride (l.0 g, 4.39 mmoles) and carbon tetrachloride and benzene (1:1, 10 ml). Product **11** was separated by column chromatography in 30% yield, mp 195-197° ir (potassium bromide): 2931, 1658, 1533, 1503, 1363, 1212, 685 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 1.5 (s, 9H), 1.65 (m, 5H), 3.63 (t, 3H), 6.67(s, 1H), 6.99 (s, 1H), 7.61 (t, 2H), 7.72 (t, 1H), 8.07 (d, 2H); ms: 438 (M+CH_3), 379, 283, 220, 205, 163, 104, 91.

Anal. Calcd. for $C_{24}H_{25}O_2S_2N{\cdot}0.5H_2O$: C, 66.57; H, 6.01; N, 3.24. Found: C, 66.65; H, 5.67; N, 3.23.

Methyl [5-*tert*-Butyl-4-(4-hydroxy-6-oxo-2-phenyl-6*H*-[1,3]thiazin-5-ylsulfanyl)-2-methylphenoxy]acetate (**8**).

The compound was prepared as described in the general procedure using 2-phenyl-4-hydroxy-1,3-thiazin-6-one (0.3 g, 1.46 mmoles), (2-*tert*-butyl-5-methyl-4-(methoxycarbonylmethoxy)-phenylsulfenyl chloride (0.443 g, 1.46 mmoles) and carbon tetrachloride and benzene (1:1, 10 ml). Product **12** was isolated in 60% yield by column chromatography, mp 192-193°; ir (potassium bromide): 3153, 2952, 1730, 1644, 1506, 1369, 1227, 1170, 1054, 765, 683 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 1.49 (s, 9H), 2.03 (s, 3H), 3.69 (s, 3H), 4.8 (s, 2H), 6.72 (s, 1H), 6.81 (s, 1H), 7.63 (t, 2H), 7.71 (t, 1H), 8.07 (d, 2H); ms: 471 (M+), 416, 354, 329, 299, 268, 253, 213, 181, 104, 91.

Anal Calcd. for $C_{24}H_{25}O_5S_2N{\cdot}0.9H_2O$: C, 59.10; H, 5.54; N, 2.87. Found: C, 59.10; H, 5.48; N, 2.74.

5-[2-*tert*-Butyl-4-(tertbutyldimethylsilanyloxy)-5-methylphenylsulfanyl]-4-hydroxy-2-phenyl[1,3]thiazin-6-one (**9**).

The compound was prepared as described in the general procedure using 2-phenyl-4-hydroxy-l,3-thiazin-6-one (0.5 g, 2.44 mmoles), [2-*tert*-butyl-5-methyl-4-(*tert*-butyldimethylsilanyloxy)phenyl]sulfenyl chloride (2.44 mmoles) and carbon tetrachloride and benzene (1:1, 10 ml). Product **13** was isolated in 63% yield by column chromatography, mp 189-190°; ir (potassium bromide): 3420, 2955, 1616, 1489, 1363, 1263, 1170, 875, 754 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 0.19 (s, 6H), 0.97 (s, 9H), 1.47 (s, 9H), 1.97 (s, 3H), 6.72 (s, 1H), 6.77 (s, 1H), 7.61 (t, 2H), 7.69 (t, 1H), 8.07 (m, 2H); ms: 513 (M+), 310, 255, 206, 197, 177, 138, 104, 91.

Anal. Calcd. for $C_{27}H_{35}O_3S_2NSi{\cdot}0.81H_2O$: C, 61.38; H, 6.99; N, 2.65. Found: C, 61.38; H, 6.67; N, 2.67.

2-(3-Chloro-4-fluorophenyl)-5-(2-ethylphenylsulfanyl)-4-hydroxy[1,3]thiazin-6-one (**10**).

The compound was prepared to according to Method A using 2-(3-chloro-4-fluorophenyl)-4-hydroxy-1,3-thiazin-6-one (0.3 g, 1.16 mmoles), (2-ethylphenylsulfenyl chloride (0.8 g, 4.64 mmoles) and carbon tetrachloride and benzene (1:1, 10 ml). Product **6** was separated by column chromatography in 68% yield, mp 168-170°; ir (potassium bromide): 3447, 2924, 1495, 1364, 1266, 1068, 746 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 1.22 (t, 3H), 2.72 (q, 2H), 6.94 (m, 1H), 7.04 (m, 2H), 7.17 (m, 1H), 7.67 (t, 1H), 8.06 (m, 1H), 8.25 (m, 1H); ms: 394 (M+H), 258, 229, 190, 156, 139, 123, 111, 105, 91.

Anal. Calcd. for $C_{18}H_{13}0_2S_2NFCl{\cdot}0.75H_2O$: C, 53.07; H, 3.59; N, 3.44. Found: C, 52.73; H, 3.17; N, 3.35.

2-(3-Chloro-4-fluorophenyl)-4-hydroxy-5-(2-isopropylphenylsulfanyl)[1,3]thiazin-6-one (**11**).

The compound was prepared according to Method A using 2-(3-chloro-4-fluorophenyl)-4-hydroxy-1,3-thiazin-6-one (0.5 g, 1.94 mmoles), (2-isopropylphenyl)sulfenyl chloride (0.725 g, 3.88 mmoles) and carbon tetrachloride and benzene (1:1, 10 ml). Product **4** was isolated in 72% yield by column chromatography, mp 147-149°; ir (potassium bromide): 3235, 2957, 1615, 1493, 1366, 1258, 1064, 751 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 1.25 (d, 6H), 3.44 (m, 1H), 6.97 (d, 1H), 7.06 (t, 1H), 7.13 (t, 1H), 7.28 (d, 1H), 7.68 (t, 1H), 8.06 (m, 1H), 8.28 (dd, 1H); ms: 408 (M+H), 372, 218, 190, 173, 152, 137, 119, 111, 91.

Anal. Calcd. for $C_{19}H_{15}O_2S_2NFCl{\cdot}0.1H_2O$: C, 55.64; H, 3.66; N, 3.42. Found: C, 55.46; H, 3.85; N, 3.36.

5-(2-*tert*-Butylphenylsulfanyl)-2-(3-chloro-4-fluorophenyl)-4-hydroxy[1,3]thiazin- 6-one (**12**).

The compound was prepared according to Method A using 2-(3-chloro-4-fluorophenyl)-4-hydroxy-1,3-thiazin-6-one (0.2 g, 0.776 mmoles), (2-*tert*-butylphenyl)sulfenyl chloride (0.467 g, 2.33 mmoles) and carbon tetrachloride and benzene (1:1, 10 ml). Product **8** was isolated by column chromatography in 72% yield, mp 167-168°; ir (potassium bromide): 3058, 2955, 1492, 1371, 1260, 1066, 751 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 1.53 (s, 9H), 7.03 (m, 3H), 7.33 (d, 1H), 7.69 (t, 1H), 8.06 (m, 1H), 8.26 (dd, 1H); ms: 422 (M+H), 366, 258, 190, 173, 166, 151, 123, 91.

Anal. Calcd. for $C_{20}H_{17}O_2S_2NFCl$: C, 56.93; H, 4.06; N, 3.32. Found: C, 56.84; H, 4.32; N, 3.35.

5-(2-*tert*-Butyl-5-methylphenylsulfanyl)-2-(3-chloro-4-fluorophenyl)-4-hydroxy[1,3]thiazin-6-one (**13**).

The compound was prepared as described in general procedure using 2-(3-chloro-4-fluorophenyl)-4-hydroxy-1,3-thiazin-6-one (0.2 g, 0.78 mmoles), (2-*tert*-butyl-5-methyl)phenylsulfenyl chloride (0.5 g, 2.33 mmoles) and carbon tetrachloride and benzene (1:1, 5 ml). Product **10** was isolated in 87% yield by column chromatography, mp 117-119°; ir (potassium bromide): 2967, 1653, 1497, 1364, 1264, 818 cm^{-1}; ^1H nmr (400 MHz, dimethyl sulfoxide-d_6): δ 1.5 (s, 9H), 2.11 (s, 3H), 6.8 (s, 1H), 6.86 (d, 1H), 7.21 (d, 1H), 7.69 (t, 1H), 8.07 (m, 1H), 8.28 (dd, 1H); ms: 435 (M+), 380, 310, 190, 180, 165, 156, 91.

Anal. Calcd. for $C_{21}H_{19}O_2S_2NFCl{\cdot}1.0H_2O$: C, 55.51; H, 4.62; N, 3.09. Found: C, 55.33; H, 4.22; N, 2.90.

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* To whom correspondence should be addressed.

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