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New products

New 2-sulfonamidothiazoles substituted at C-4: synthesis of polyoxygenated aryl derivatives and in vitro evaluation of antifungal activity

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Abstract – Polymethoxylated and polyhydroxylated derivatives of 2-amino-4-arylthiazoles bearing a halogenobenzenesulfonamide moiety at position 2 were synthesized as azole antifungal analogues. X-ray crystallography studies revealed the predominance of the 2-imino-2,3-dihydrothiazole form in the amino/imino tautomerism. In vitro assays against various pathogenic fungal strains (*Candida* and *Trichophyton* species) showed no activity in comparison to econazole as reference. These results are discussed on the basis of the estimated global lipophilicity of the molecules (Rekker's method) and the π-electron distribution (Mulliken population analysis, AM1 method) within the five-membered heterocycle. © 1999 Éditions scientifiques et médicales Elsevier SAS

2,4-disubstituted thiazoles / sulfonamides / antifungal testing

1. Introduction

The most commonly used imidazole antifungal agents, such as miconazole **1**, econazole **2** and ketoconazole **3** (*figure 1*), exhibit side effects including interference with steroidogenesis or hepatic toxicity [1]. Over the past few years, the discovery of triazole compounds including itraconazole **4** and fluconazole **5** with better tolerance gave rise to the synthesis of numerous related analogues [2].

Since the sulfonamide moiety seems to be a possible pharmacophore in fungicidal agents [3], we decided to introduce this functionality in position 2 of a thiazole nucleus. On the other hand, the lack of hydrosolubility which limits systemic distribution of azoles led us to include hydrophilic fragments and thus to synthesize new thiazole derivatives with a polyoxygenated phenyl component (**6–9**), as represented in *figure 1*.

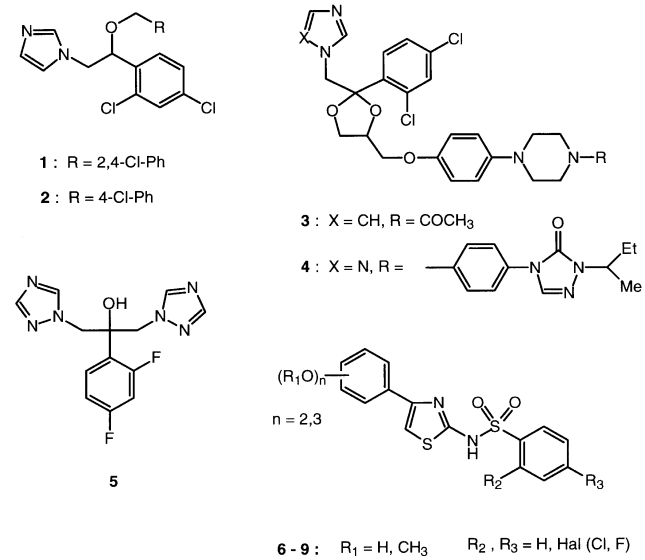

Figure 1. Structure of azole antifungals (**1**–**5**) and target compounds (**6**–**9**).

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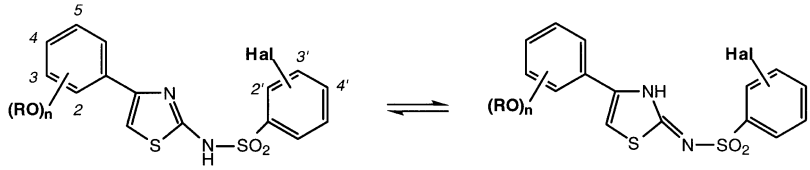
Table I. Chemical and physical properties of compounds **6–9.**



Compound	**(RO)$_n$**	**Hal**	M.p.(°C)	Yield (%)	Formula (MW) [a]	log *P*calc [c]
6a	*2,5*-OMe	*4′*-Cl	130	75	$C_{17}H_{15}ClN_2O_4S_2$ (410.90)	2.44
6b		*4′*-F	136	36	$C_{17}H_{15}FN_2O_4S_2$ (394.43)	1.92
6c		*2′,4′*-Cl	148–150	51	$C_{17}H_{14}Cl_2N_2O_4S_2$ (445.35)	3.18
6d		*2′,4′*-F	140	31	$C_{17}H_{14}F_2N_2O_4S_2$ (412.44)	2.13
7a	*2,5*-OH	*4′*-Cl	260	45	$C_{15}H_{11}ClN_2O_4S_2$ (382.84)	1.25
7b		*4′*-F	218	47	$C_{15}H_{11}FN_2O_4S_2$ (366.39)	0.73
7c		*2′,4′*-Cl	240	56	$C_{15}H_{10}Cl_2N_2O_4S_2$ (417.29)	1.99
7d		*2′,4′*-F	232	78	$C_{15}H_{10}F_2N_2O_4S_2$ (384.38)	0.94
8a	*3,4,5*-OMe	*4′*-Cl	b	58	$C_{18}H_{17}ClN_2O_5S_2$ (440.92)	2.51
8b		*4′*-F	b	67	$C_{18}H_{17}FN_2O_5S_2$ (424.47)	1.99
8c		*2′,4′*-Cl	165–166	56	$C_{18}H_{16}Cl_2N_2O_5S_2$ (475.37)	3.25
8d		*2′,4′*-F	178–180	20	$C_{18}H_{16}F_2N_2O_5S_2$ (442.46)	2.20
9a	*3,4,5*-OH	*4′*-Cl	220	67	$C_{15}H_{11}ClN_2O_5S_2$ (398.85)	0.73
9b		*4′*-F	218–220	53	$C_{15}H_{11}FN_2O_5S_2$ (382.39)	0.20
9c		*2′,4′*-Cl	b	65	$C_{15}H_{10}Cl_2N_2O_5S_2$ (433.29)	1.47
9d		*2′,4′*-F	219	84	$C_{15}H_{10}F_2N_2O_5S_2$ (400.38)	0.42

[a]All compounds were analysed for C, H, N, S and when present Cl or F; analytical results are within ± 0.4% of the theoretical values. [b]Decomposition over 80 °C. [c]According to Rekker fragmental system [10].

2. Chemistry

The target compounds (*table I*) were synthesized following *figure 2*. The key step in the preparation of derivatives **6** and **8** resulted in the reaction of bromomethylketones **13** with the appropriate arylsulfonylthioureas **12** in refluxing THF, according to a modified Hantzsch condensation [4]. The thioureas **12** were obtained by reaction of *N*-cyanoarylsulfonamide sodium salts **11** with thiosulfuric acid (generated in situ upon treatment of sodium thiosulfate with aqueous-H_2SO_4 [5]).

3. Structural data

As an example, ^{1}H and ^{13}C NMR data for **6a** are shown in *table II*. The chemical shifts for the carbon atoms at positions *7, 8* and *9* are consistent with data of substituted thiazoles [6] and therefore confirm the heterocyclisation reaction. The main information is provided by the long-range ^{1}H -^{13}C correlations (HMBC spectrum). The quaternary carbon *7* exhibits correlation with proton H*6*, belonging to the oxygenated ring The *7,9*-functionalization on the heterocyclic ring was therefore established.

X-ray diffraction analysis of **6b** *(figure 3)* confirmed a structure close to that of a thiazoline derivative [7]. Noteworthy, the exocyclic C(9)-N(12) bond shows significant shortening from the value of the endocyclic N(8)-C(9) *(table III)*. Consequently, this phenomenon is indicative of an exocyclic C=N double bond and confirms that the imino form is the predominant tautomer, at least in the crystalline state. This conclusion agrees with previous reports on 2-substituted thiazoles [8, 9].

4. Antifungal evaluation and discussion

The antifungal activity of compounds **6–9** was evaluated in vitro, against yeasts (*Candida albicans* ATCC 10231 and *Candida krusei* CBS 573) and filamentous fungi (*Trichophyton mentagrophytes* IP 1468-83 and *T. rubrum* IP 2073-92), according to described methods [11, 12]. By comparison with econazole, used as reference substance, all the tested thiazoles were found inactive (data not shown). These results confirm that lipophilicity plays a fundamental role for antifungal

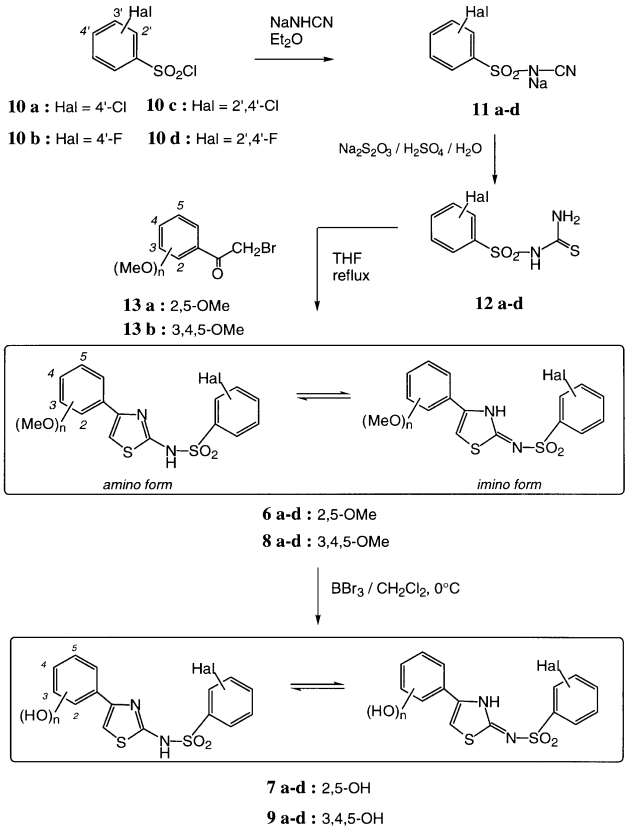


Figure 2. General synthetic pathway for 2,4-functionalized thiazoles **6**–**9.**

properties [13]: the estimated log *P* values for compounds **6–9**, ranging from 0.2–3.25 (*table I*) are significantly lower than that calculated for econazole (log *P* = 5.17).

We have also investigated the electron density distribution in econazole and compound **6b**, respectively. The AM1 method [14] with Mulliken population analysis was selected for its usefulness in predicting the aromaticity of 5-membered heterocycles [15]. From the data presented in *figure 4*, it is shown that the imidazole ring of econazole displays a high level of aromaticity (π overlap populations ranging from 23–40%), while in the thiazole moiety, the π-electrons are unequally spread over the intracyclic bonds (furthest values: 11–44%), thus indicative of a weak aromatic character for **6b**.

In conclusion, it appears that the association of a polyoxygenated phenyl ring and an arylsulfonamido moiety on a thiazolic framework does not lead to antifungal activity. The electronic properties of the five-membered ring, which differ strongly from those of the imidazole antifungals, might be a determining factor in the biological response.

5. Experimental protocols

Melting points were determined with a Köfler apparatus and are uncorrected. NMR spectra were obtained in $CDCl_3$, at 29 °C, using a Bruker AMX 500 spectrometer (^{1}H: 500 MHz, ^{13}C: 125 MHz). Chemical shifts are given in ppm from TMS as an internal standard (coupling constants *J*, in Hz). Multiplicities in ^{13}C NMR spectra were derived from JMOD experiments. When necessary, HMQC, HMBC and ^{1}H-^{1}H COSY experiments were used for structural assignments.

5.1. Chemistry

5.1.1. General procedure for N-aminothioxomethyl-arylsulfonamides **12a–d**

To a stirred suspension of sodium cyanamide [16] (0.08 mol) in anhydrous Et_2O (20 mL) was added appropriate arylsulfonyl chloride **10a–d** (0.04 mol). Stirring was continued for 6 h under reflux, and the insoluble Na salt of *N*-cyanoarylsulfonamide **11a–d** was washed (dry ether, then acetone) and dried (yields: 65–75%).

A cooled solution (0 °C) of the convenient sodium salt **11** (20 mmol) in H_2O (10 mL) was neutralized with 2 N H_2SO_4 (10 mL). Solid $Na_2S_2O_3$, $5H_2O$ (60 mmol) was added in one portion under stirring and the mixture was treated with more 2 N H_2SO_4 (15 mL). After further stirring overnight at 20 °C, the resulting precipitate was washed with cold H_2O (2 × 10 mL), and recrystallized from methanol/H_2O (50:50) to afford the expected product **12** as white needles (45–61%).

5.1.1.1. N-Aminothioxomethyl-4-chlorobenzenesulfonamide **12a**

M.p. = 149–151 °C. ^{1}H-NMR δ 7.61 (d, *J* = 8.8, 2H); 7.94 (d, *J* = 8.8, 2H); ^{13}C- NMR δ 130.0 (C2, C6); 130.6 (C3, C5); 139.3 (C4); 141.3 (C1); 182.3 (C7).

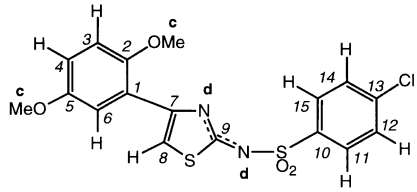
5.1.1.2. N-Aminothioxomethyl-4-fluorobenzenesulfonamide **12b**

M.p. = 120 °C. ^{1}H- NMR δ 7.33 (dd, *J* = 8.8, 8.6, 2H); 8.02 (dd, *J* = 9.0, 5.0, 2H); ^{13}C- NMR δ 117.5 (C3, C5); 131.4 (C2, C6); 136.8 (C1); 167.1 (C4); 182.4 (C7).

5.1.1.3. N-Aminothioxomethyl-2,4-dichlorobenzenesulfonamide **12c**

M.p. = 205 °C. ^{1}H- NMR δ 7.81 (dd, *J* = 2.0, 8.6, 1H); 7.94 (d, *J* = 2.0, 1H); 8.34 (d, *J* = 8.6, 1H); ^{13}C- NMR δ 128.5 (C2); 132.5 (C4); 133.8 (C6); 134.3 (C1); 136.6 (C5); 140.9 (C3); 181.1 (C7).

Table II. NMR data[a] and main HMQC, HMBC, and ^{1}H-^{1}H COSY correlations for **6a** ($CDCl_3$).



Positions	^{1}H	^{13}C	HMQC	HMBC
1	–	117.0	C*8*, H*8*	C*1*, H*8*
2	–	149.6	–	C*2*, H*6*; C*2*, H*4*
3	6.94 (d, 8.8)[b]	116.0	C*3*, H*3*	–
4	6.92 (dd, 9.1, 2.6)[b]	113.0	C*4*, H*4*	C*4*, H*6*
5	–	154.1	–	C*5*, H*6*; C*5*, H*4*
6	7.02 (d, 2.6)[b]	113.2	C*6*, H*6*	C*6*, H*4*
7	–	134.4	–	C*7*, H*6*; C*7*, H*8*
8	6.62 (s)	102.2	C*8*, H*8*	–
9	–	168.4	–	C*9*, H*8*
10	–	140.8	–	C*10*, H*12*; C*10*, H*14*
11	7.91 (d, 8.6)[b]	127.8	C*11*, H*11*	C*11*, H*15*
12	7.42 (d, 8.6)	128.9	C*12*, H*12*	C*12*, H*14*
13	–	138.4	–	C*13*, H*11*; C*13*, H*15*
14	7.42 (d, 8.6)	128.9	C*14*, H*14*	C*14*, H*12*
15	7.91 (d, 8.6)[b]	127.8	C*15*, H*15*	C*15*, H*11*

[a]Chemical shifts, ppm (multiplicity, *J* in Hz). [b]^{1}H-^{1}H COSY correlations. [c]The methoxy protons appeared at 3.79 and 3.91 ppm, as singlets. [d]The NH-proton was not obviously identifiable.

5.1.1.4. N-Aminothioxomethyl-2,4-difluorobenzenesulfonamide **12d**

M.p. = 102 °C. ^{1}H- NMR δ 7.03–7.15 (m, 2H); 7.95 (ddd, *J* = 8.0, 6.0, 6.0, 1H); ^{13}C- NMR δ 106.4 (C3); 112.4 (C5); 122.7 (C1); 131.8 (C6); 160.1 (C2); 166.9 (C4); 179.6 (C7).

Table III. Selected bond lengths (Å) for **6b**[a]

C(1)–C(7)	1.477 (4)	S(10)–C(11)	1.740 (3)
C(7)–C(11)	1.322 (4)	N(12)–S(13)	1.588 (2)
C(7)–N(8)	1.395 (4)	S(13)–O(15)	1.441 (2)
N(8)–C(9)	1.346 (3)	S(13)–O(14)	1.444 (2)
C(9)–N(12)	1.325 (4)	S(13)–C(16)	1.762 (3)
C(9)–S(10)	1.737 (3)		

[a]Estimated standard deviations are given in brackets

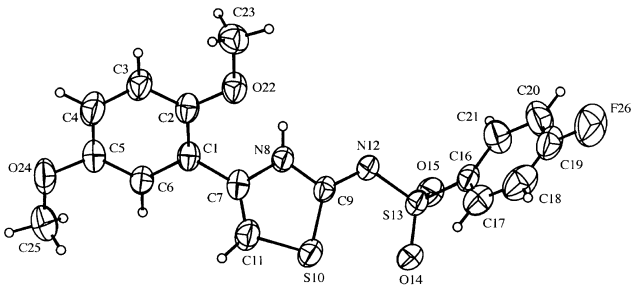


Figure 3. Molecular conformation of compound **6b** with special atom-numbering used in the crystallographic analysis. (displacement ellipsoids are shown for non-hydrogen atoms at 50% probability level).

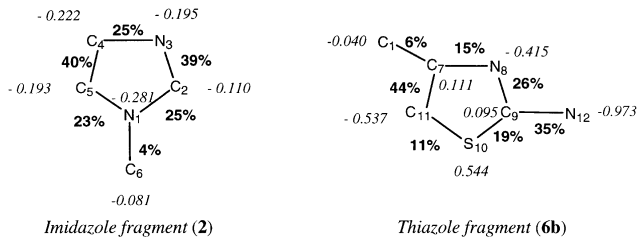


Figure 4. π-Interatomic overlap populations (%) calculated using the Mulliken population analysis for the heterocycles of econazole **2** and compound **6b** (AM1 results from X-ray structure data). Atomic charges are indicated in italic numbers.

5.1.2. General procedure for 1-aryl-2-bromoethanones **13**

These products were obtained by bromination of commercial acetophenones in CCl_4 [17], and chromatographed on silica gel column (eluent: hexane/CH_2Cl_2, 70:30) prior to use.

5.1.2.1. 1-(2,5-Dimethoxyphenyl)-2-bromoethanone **13a**

M.p. = 80 °C. ^{1}H- NMR δ 3.80 (s, 3H); 3.93 (s, 3H); 4.65 (s, 2H); 7.05 (m, 2H); 7.40 (d, *J* = 8.0, 1H).

5.1.2.2. 1-(3,4,5-Trimethoxyphenyl)-2-bromoethanone **13b**

M.p. = 71 °C. ^{1}H- NMR δ 4.00 (s, 9H); 4.46 (s, 2H); 7.30 (s, 2H).

5.1.3. General procedure for N-(4-aryl-2,3-dihydrothiazol-2-ylidene) arylsulfonamides **6a–d** *and* **8a–d**

A suspension of *N*-aminothioxomethylbenzenesulfonamide **12a–d** (4 mmol) and 1-aryl-2-bromoethanone **13a** or **13b** (4 mmol) in anhydrous THF (30 mL) was heated at reflux for 5 h under constant stirring. The mixture was then cooled to 20 °C and after removal of the volatile materials under vacuo, the crude residue was chromatographed on a silica-gel column (eluent: CH_2Cl_2/EtOAc, 80:20), then recrystallized from heptane (yields: 40–51%).

5.1.3.1. N-[2,3-Dihydro-4-(2,5-dimethoxyphenyl) thiazol-2-ylidene]-4-chlorobenzenesulfonamide **6a** *(see* table II *for spectral data)*

5.1.3.2. N-[2,3-Dihydro-4-(2,5-dimethoxyphenyl) thiazol-2-ylidene]-4-fluorobenzenesulfonamide **6b**

^{1}H- NMR δ 3.80 (s, 3H); 3.92 (s, 3H); 6.62 (s, 1H); 6.92 (dd, *J* = 9.0, 2.6, 1H); 6.95 (d, *J* = 9.0, 1H); 7.03 (d, *J* = 2.6, 1H); 7.13 (dd, *J* = 8.8, 8.6, 2H); 7.99 (dd, *J* = 8.8, 5.2, 2H). ^{13}C- NMR δ 55.8; 56.4; 102.2; 113.0; 113.3; 115.6; 115.8; 116.0; 117.0; 128.9; 129.0; 134.4; 138.5; 149.6; 154.1; 164.8 (d, $^1J_{C,\ F}$ = 250); 168.4.

5.1.3.3. N-[2,3-Dihydro-4-(2,5-dimethoxyphenyl) thiazol-2-ylidene]-2,4-dichlorobenzenesulfonamide **6c**

^{1}H-NMR δ 3.80 (s, 3H); 3.92 (s, 3H); 6.64 (s, 1H); 6.92 (dd, *J* = 9.1, 2.6, 1H); 6.95 (d, *J* = 8.8, 1H); 7.04 (d, *J* = 2.4, 1H); 7.34 (dd, *J* = 8.0, 2.0, 1H); 7.47 (d, *J* = 2.0, 1 H); 8.16 (d, *J* = 8.5, 1H). ^{13}C-NMR δ 55.8; 56.3; 102.2; 113.0; 113.3; 116.0; 117.0; 126.8; 131.1; 131.2; 133.5; 134.5; 138.4; 149.7; 154.1; 169.0.

5.1.3.4. N-[2,3-Dihydro-4-(2,5-dimethoxyphenyl) thiazol-2-ylidene]-2,4-difluorobenzenesulfonamide **6d**

^{1}H-NMR δ 3.80 (s, 3H); 3.92 (s, 3H); 6.65 (s, 1H); 6.89 (m, 2H); 6.95 (m, 1H); 7.05 (d, *J* = 2.7, 1H); 8.03 (m, 1H); ^{13}C-NMR δ 55.8; 56.3; 102.3; 105.2 (dd, $^2J_{C,\ F}$ = 25, $^2J_{C,\ F}$ = 25); 111.1; 113.0; 113.3; 116.0; 117.0; 126.7; 131.1; 134.5; 149.7; 154.1; 160.1 (dd, $^1J_{C,\ F}$ = 250, $^3J_{C,\ F}$ = 10); 165.1 (dd, $^1J_{C,\ F}$ = 250, $^3J_{C,\ F}$ = 10); 169.0.

5.1.3.5. N-[2,3-Dihydro-4-(3,4,5-trimethoxyphenyl) thiazol-2-ylidene]-4-chlorobenzenesulfonamide **8a**

^{1}H-NMR δ 3.88 (s, 9H); 6.46 (s, 1H); 6.71 (s, 2H); 7.38 (d, *J* = 8.6, 2H); 7.89 (d, *J* = 8.6, 2H). ^{13}C-NMR δ 56.3; 60.8; 101.2; 103.2; 123.9; 127.9; 128.9; 137.5; 138.6; 139.5; 140.2; 153.7; 168.7.

5.1.3.6. N-[2,3-Dihydro-4-(3,4,5-trimethoxyphenyl) thiazol-2-ylidene]-4-fluorobenzenesulfonamide **8b**

^{1}H-NMR δ 3.85 (s, 9H); 6.46 (s, 1H); 6.73 (s, 2H); 7.07 (dd, *J* = 8.6, 8.6, 2H); 7.97 (dd, *J* = 8.8, 5.1, 2H). ^{13}C-NMR δ 56.3; 60.8; 101.3; 103.2; 115.7; 115.9; 124.5; 129.1; 137.6; 137.8; 139.2; 153.7; 164.8 (d, $^1J_{C,\ F}$ = 250); 168.7.

5.1.3.7. N-[2,3-Dihydro-4-(3,4,5-trimethoxyphenyl) thiazol-2-ylidene]-2,4-dichlorobenzenesulfonamide **8c**

^{1}H-NMR δ 3.88 (s, 9H); 6.49 (s, 1H); 6.71 (s, 2H); 7.32 (d, *J* = 4.2, 1H); 7.45 (s, 1H); 8.10 (d, *J* = 4.2, 1H). ^{13}C-NMR δ 56.3; 60.9; 101.4; 103.2; 123.9; 126.8; 131.1; 131.2; 133.4; 137.1; 137.8; 138.6; 139.5; 153.8; 169.3.

5.1.3.8. N-[2,3-Dihydro-4-(3,4,5-trimethoxyphenyl) thiazol-2-ylidene]-2,4-difluorobenzenesulfonamide **8d**

^{1}H-NMR δ 3.85 (s, 9H); 6.50 (s, 1H); 6.67 (s, 2H); 6.82 (m, 1H); 6.91 (m, 1H); 7.98 (m, 1H); ^{13}C-NMR δ 56.3; 60.8; 101.3; 103.2; 105.4 (dd, $^2J_{C,\ F}$ = 25, $^2J_{C,\ F}$ = 23); 111.2 (d, $^2J_{C,\ F}$ = 22); 123.9; 126.7 (d, $^2J_{C,\ F}$ = 23); 131.2 (d, $^3J_{C,\ F}$ = 10); 137.3; 139.3; 153.7; 159.9 (dd, $^1J_{C,\ F}$ = 250, $^3J_{C,\ F}$ = 10); 165.3 (dd, $^1J_{C,\ F}$ = 250, $^3J_{C,\ F}$ = 10); 169.4.

5.1.4. General procedure for phenolic compounds **7a–d** *and* **9a–d**

To a cooled (0 °C) solution of **6a–d** or **8a–d** (1 mmol) in anhydrous CH_2Cl_2, boron tribromide was added dropwise (2.2 mmol for dimethoxy compounds **6a–d**, or 3.3 mmol for trimethoxy compounds **8a–d**) under nitrogen. The mixture was stirred at 0 °C for 1 h, then quenched cautiously with H_2O (50 mL). Following 15 min hydrolysis, the resulting precipitate was collected, washed with cold H_2O and recrystallized from 50% ethanol, affording the expected polyhydroxylated compound in 53–78% yield.

5.1.4.1. N-[2,3-Dihydro-4-(2,5-dihydroxyphenyl) thiazol-2-ylidene]-4-chlorobenzenesulfonamide **7a**

^{1}H-NMR δ 4.77 (s, 2H); 6.69 (dd, *J* = 8.7, 2.8, 1H); 6.74 (d, *J* = 8.7, 1H); 6.88 (d, *J* = 2.8, 1H); 6.93 (s, 1H); 7.50 (d, *J* = 8.6, 2H); 7.88 (d, *J* = 8.6, 2H). ^{13}C-NMR δ 105.3; 114.7; 117.1; 118.3; 118.7; 129.1; 130.0; 137.1; 139.4; 142.2; 148.8; 151.6; 170.

5.1.4.2. N-[2,3-Dihydro-4-(2,5-dihydroxyphenyl) thiazol-2-ylidene]-4-fluorobenzenesulfonamide **7b**

^{1}H-NMR δ 4.76 (s, 2H); 6.69 (dd, *J* = 8.7, 2.8, 1H); 6.74 (d, *J* = 8.7, 1H); 6.89 (d, *J* = 2.8, 1H); 6.92 (s, 1H); 7.22 (dd, *J* = 8.9, 8.8, 2H); 7.99 (dd, *J* = 8.9, 5.1, 2H). ^{13}C-NMR δ 105.2; 114.7; 116.7; 116.9; 117.1; 118.3; 118.7; 130.2; 130.3; 139.7; 148.7; 151.6; 166.2 (d, $^1J_{C,\ F}$ = 250); 170.0.

5.1.4.3. N-[2,3-Dihydro-4-(2,5-dihydroxyphenyl) thiazol-2-ylidene]-2,4-dichlorobenzenesulfonamide **7c**

^{1}H-NMR δ 6.93 (dd, *J* = 8.7, 2.9, 1H); 7.03 (d, *J* = 8.7, 1H); 7.24 (s, 1H); 7.25 (d, *J* = 2.9, 1H); 7.69 (dd, *J* = 8.5, 2.0, 1H); 7.77 (d, *J* = 2, 1H); 8.3 (d, *J* = 8.5, 1H). ^{13}C-NMR δ 104.8; 114.4; 116.8; 118.5; 118.6; 127.9; 131.9; 132.2; 134.0; 138.7; 140.1; 147.9; 151.7; 171.4.

5.1.4.4. N-[2,3-Dihydro-4-(2,5-dihydroxyphenyl) thiazol-2-ylidene]-2,4-difluorobenzenesulfonamide **7d**

^{1}H-NMR δ 6.69 (dd, *J* = 8.8, 2.8, 1H); 6.75 (d, *J* = 8.8, 1H; 6.90 (d, *J* = 2.8, 1H); 6.95 (s, 1H); 7.05–7.13 (m, 2H); 6.69 (dd, *J* = 8.4, 6.3, 1H); ^{13}C-NMR δ 105.5; 106.5 (dd, $^2J_{C,\ F}$ = 25; $^2J_{C,\ F}$ = 23); 112.2; 114.7; 117.0; 118.3; 118.8; 127.7; 132.3; 137; 148.8; 151.7; 161.2 (dd, $^1J_{C,\ F}$ = 250, $^3J_{C,\ F}$ = 10); 166.9 (dd, $^1J_{C,\ F}$ = 250, $^3J_{C,\ F}$ = 10); 170.4.

5.1.4.5. N-[2,3-Dihydro-4-(3,4,5-trihydroxyphenyl) thiazol-2-ylidene]-4-chlorobenzenesulfonamide **9a**

^{1}H-NMR δ 6.55 (s, 1H); 6.57 (s, 2H); 7.49 (d, *J* = 8.8, 2H); 7.86 (d, *J* = 8.8, 2H). ^{13}C-NMR δ 101.7; 106.4; 121.4; 129.0; 130.0; 136.1; 139.4; 139.7; 142.3; 147.4; 171.1.

5.1.4.6. N-[2,3-Dihydro-4-(3,4,5-trihydroxyphenyl) thiazol-2-ylidene]-4-fluorobenzenesulfonamide **9b**

^{1}H-NMR δ 6.55 (s, 1H); 6.57 (s, 2H); 7.21 (dd, *J* = 8.8, 8.7, 2H); 7.93 (dd, *J* = 8.8, 5.2, 2H); ^{13}C-NMR δ 101.6; 106.4; 116.7; 116.8; 121.4; 130.1; 130.2; 136.0; 139.7; 139.8; 147.4; 166.2 (d, $^1J_{C,\ F}$ = 250); 171.0.

5.1.4.7. N-[2,3-Dihydro-4-(3,4,5-trihydroxyphenyl) thiazol-2-ylidene]-2,4-dichlorobenzenesulfonamide **9c**

^{1}H-NMR δ 6.58 (s, 2H); 6.59 (s, 1H); 7.45 (dd, *J* = 8.5; 2.0, 1H); 7.59 (d, *J* = 2.0, 1H); 8.10 (d, *J* = 8.5, 1H); ^{13}C-NMR δ 101.9; 106.4; 121.3; 129.0; 132.4; 134.5; 136.1; 139.5; 139.6; 139.7; 147.5; 171.4.

5.1.4.8. N-[2,3-Dihydro-4-(3,4,5-trihydroxyphenyl) thiazol-2-ylidene]-2,4-difluorobenzenesulfonamide **9d**

^{1}H-NMR δ 6.57 (s, 2H); 6.60 (s, 1H); 7.06–7.11 (m, 2H); 7.98 (ddd, *J* = 8.0, 6.0, 6.0, 1H); ^{13}C-NMR δ 102.0; 106.3 (dd, $^2J_{C,\ F}$ = 25, $^2J_{C,\ F}$ = 22); 106.4; 112.2 (d, $^2J_{C,\ F}$ = 22); 121.3; 126.9; 132.3; 136.0; 139.7; 147.5; 161.2 (dd, $^1J_{C,\ F}$ = 250, $^3J_{C,\ F}$ = 10); 166.8 (dd, $^1J_{C,\ F}$ = 250, $^3J_{C,\ F}$ = 10); 171.4.

5.2. X-ray structure determination

A suitable crystal of **6b** (size 0.30 × 0.15 × 0.01 mm) was obtained from a $CHCl_3$ solution. $C_{17}H_{15}FN_2O_4S_2$, *M* = 394.43, triclinic, space group P-1, *a* = 7.026(4), *b* = 9.068, *c* = 14.442(7) Å, α = 88.74(4), β = 77.70(5), γ = 80.63(4)°, *V* = 886.9(8) Å^3, *Z* = 2, *D* = 1.477 Mg m^{-3}. The data collection was performed on a Nonius CAD4 diffractometer using graphite monochromated Cu Kα radiation (λ = 1.54178 Å). 2 977 independent reflexions were measured, of which 2 461 were used in the refinements.

Refinement was carried out by the full-matrix least-squares method based on F^2 with the SHELXL-93 program [18]. (Final R indices: R1 = 0.0466, WR2 = 0.1546). Full experimental details are available as supplementary material.

5.3. Computational studies

Calculations were performed using the MOPAC [19] program implemented in Chem3D, V 3.5 [20]. The atomic coordinates of the heavy atoms considered in the calculations were those obtained by crystallographic data (compound **6b**: see above; econazole: see reference [21]). The atomic charges were analysed using the AM1 potential function with the "Mulliken charges" option and the "PI" keyword.

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