Bis(4-hydroxythiazoles): Novel Functional and Switchable Fluorophores

Eric Täuscher,[a] Lorena Calderón-Ortiz,[a] Dieter Weiß,*[a] Rainer Beckert,*[a] Helmar Görls[b]

[a] Institute of Organic and Macromolecular Chemistry, Friedrich-Schiller-University Jena, Humboldtstr. 10, 07743 Jena, Germany
Fax +49(3641)948212; E-mail: C6bera@uni-jena.de

[b] Institute of Inorganic and Analytical Chemistry, Friedrich-Schiller-University Jena, Lessingstr. 8, 07743 Jena, Germany

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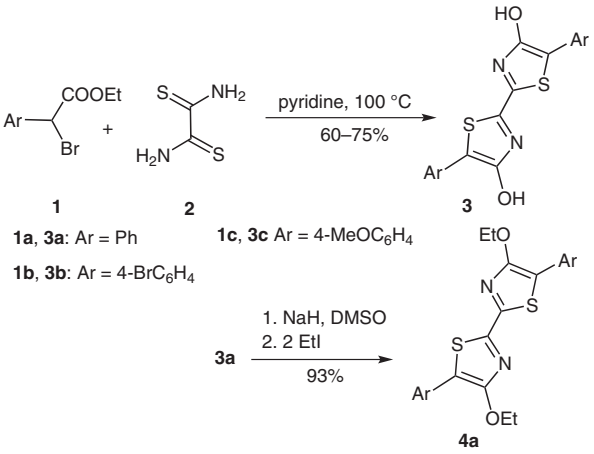
Abstract: A series of 2,2′- and 5,5′-bis(4-hydroxythiazoles) was synthesized according to Hantzsch synthesis. Both phenols and their corresponding anions display a strong fluorescence in the visible spectrum, whereas the emission is shifted bathochromically upon deprotonation. This easy switch makes them suitable for widespread applications, mainly in analysis and supramolecular chemistry. Due to their 1,4-diazadiene substructure, the 2,2′-bithiazoles possess prerequisites for the complexation of metals, however, instead of a copper complex, a dimer which constitutes the 5,5′-C–C coupled product was isolated. In addition, tris(thiazoles) could be constructed.

Key words: heterocycles, chromophores, bifunctional compounds, condensation, thiazole

4-Hydroxythiazoles are well-known compounds[1] and there are known biologically active derivatives.[2,3] In contrast to their biological data, there is hardly any information on their physicochemical properties such as color and fluorescence. Therefore, we have been working on the syntheses and applications of 2,5-disubstituted 4-hydroxythiazoles.[4] In this context, we found these compounds to be fluorescent, and recently, highly fluorescent 2-pyridyl-substituted 4-hydroxythiazoles and related systems have been reported.[5] In order to obtain a better understanding of structure–property relationships, quantum chemical calculations were carried out.[6]

Therefore, we were interested in the synthesis of systems with more than one hydroxythiazole unit as represented in **3** (2,2′-bithiazole-4,4′-diols) and **15** [5,5′-(1,4-phenylene)bis(thiazol-4-ols)]. Molecules containing two or more thiazole rings play an important role in both biochemistry[7] and material science.[8] Although hydroxy groups show interesting electronic effects combined with a variety of chemical variations, only very little data exists until now for bis(hydroxythiazoles). Thus, starting from cyanogen and α-mercapto acids, some 2,2′-bis(thiazoles) possessing hydroxy groups in the 4,4′-positions were synthesized.[9] Recently, a new bithiazole chemosensor with phenolic substituents at the 2,2′-positions of the thiazole rings was reported.[10]

Since cyanogen is difficult to obtain and handle, we chose a different approach based on dithiooxamide (rubeanic acid). This binucleophilic building block has already been successfully employed for the synthesis of a series of 2,2′-bis(thiazoles), however, without hydroxy groups.[11] According to the conditions of the classical Hantzsch synthesis, dithiooxamide (**2**) was cyclized with α-aryl-α-bromoacetic acids **1a–c** at 80–100 °C in the presence of a base, such as pyridine. As depicted in Scheme 1, three different 4,4′-dihydroxy-substituted 2,2′-bithiazoles were prepared 60–75% yields. It should be noted that at higher temperatures (>130 °C), considerable amounts of O-alkylation products (monoethyl ether/diethyl ether of **3**) were formed as byproducts.



Scheme 1 Synthetic route for the formation of 2,2′-bithiazole-4,4′-diols **3a–c** and alkylation of **3a**

Being typical aromatic hydroxy derivatives (heterocyclic phenols), the bithiazoles **3** can easily be alkylated; for example, **4a** was synthesized by deprotonation of **3a** with sodium hydride in dimethyl sulfoxide and subsequent alkylation with ethyl iodide. The molecular structure of the bis(ethyl ether) **4a** obtained by single crystal X-ray analysis is shown in Figure 1. The structure reveals that both thiazole subunits are present and almost perfectly planar.

Furthermore, we were able to construct new bis- and tris(4-hydroxythiazoles) with pyridine and benzene as the center core (Schemes 2 and 3). Thus, **6a** can be prepared by the same method using the corresponding dithioamide **5a** and two equivalents of ethyl bromoacetate **1a**. Even the tris(thiazole) **6b** was prepared in the same manner, starting from pyridine-2,4,6-tricarbothioamide (**5b**) in good yields.

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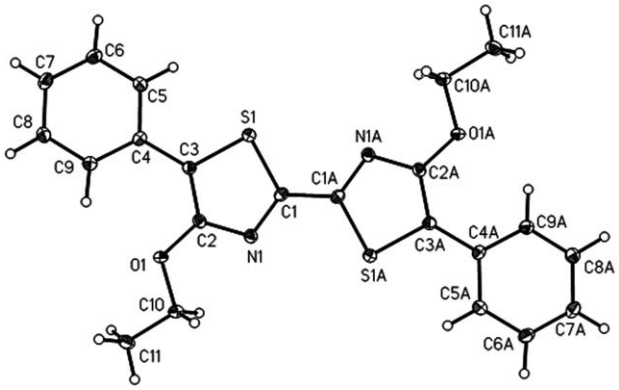
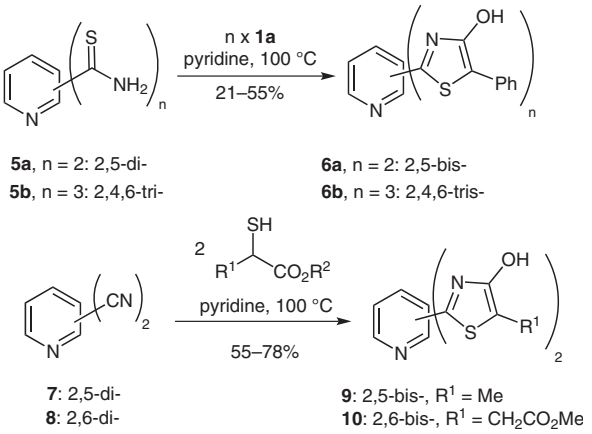
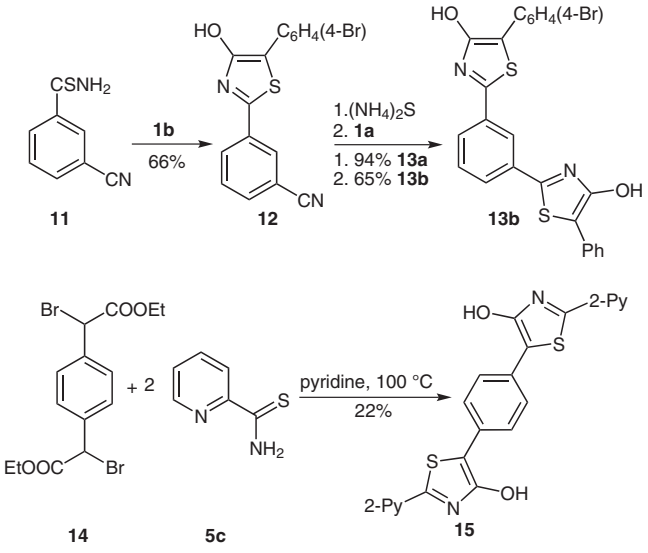


Figure 1 X ray crystal structure of **4a**. C1–C1A: 1.442(5) Å; C2–O1: 1.352(3) Å; N1–C1–C1: 124(3)°, torsion angle between thiazole units: 0.2°; torsion angle between thiazole/phenyl ring: 6.08°; C1–N1: 1.317(3) Å; N1–C2: 1.358(4) Å; C2–C3: 1.382(4) Å; C3–S1: 1.732(3) Å.



Scheme 2 Synthetic approach for the formation of pyridine based bis- and tris(thiazoles)



Scheme 3 Step-by-step approach to the formation of **13b** and synthesis of 5,5′-bis(thiazole) **15**

Alternatively, **9** and **10** can be prepared from 2,5-dicyanopyridine (**7**) or 2,6-dicyanopyridine (**8**) and thiolactic acid esters or thiomalic acid esters, as described earlier.[2] However, attempts to prepare a system with three different thiazole subunits failed, giving only mixtures of all possible isomers. Nevertheless, we finally succeeded in synthesizing mixed thiazoles, such as compound **13b**, using a stepwise protocol. Accordingly, the first thiazole subunit **12** was synthesized starting from **11**; thereafter, the cyano group was transformed using ammonium sulfide into the thioamide **13a** in very good yields and, finally, the second thiazole was formed. The overall yield of **13b** (three steps) is moderate. Employing such a step-by-step approach for the construction of unsymmetrical substituted tris(thiazoles) is part of our ongoing research.

Furthermore, a new bis(hydroxythiazole) derivative **15** was prepared by the condensation reaction of two molecules of thioamide **5c** with bis(bromoacetate) **14** under the reaction conditions mentioned above; the 5,5′-bithiazole **15** was isolated in 22% yield.

The new hydroxybithiazole derivatives **3** form orange to reddish powders, derivatives **6**, **9**, **10**, **13b** are yellow, and **15** is buff-colored. All 4-hydroxythiazoles are very poorly soluble in ethanol or acetone and only slightly soluble in *N*,*N*-dimethylformamide, dimethyl sulfoxide, or tetrahydrofuran. They can be purified by recrystallization from dimethyl sulfoxide or *N*,*N*-dimethylformamide and form crystals that bind solvent molecules tenaciously, which makes elementary analysis almost impossible. Elementary analysis of **3c** was performed on a high-vacuum-sublimed sample (~260 °C, 9×10^{-6} mbar).

According to NMR data, only the enol (hydroxyl) form exists in solution,[12] which is in agreement with our latest findings.[6] Their solutions show a bright green fluorescence [**3a** $\lambda_{max} = 449$ nm, $\lambda_{max}(em) = 528$ nm, $t_{1/2} = 2.8$ ns, $\Phi = 96\%$ (Rh 6G)]. For fluorescence intensity decay measurements, the Chameleon laser was tuned to 950 nm, pulse picked to a 4 MHz repetition rate (Coherent 9200Pulse Picker), and finally frequency doubled (APE-GmbH SHG Unit) to afford sample excitation, $\lambda_{ex} = 400$ nm.[13] Upon deprotonation in dimethyl sulfoxide, the bi(hydroxythiazole) derivatives of type **3** form deep violet

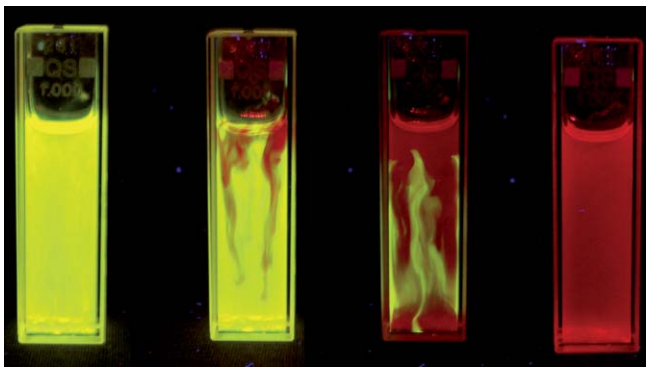


Figure 2 Varying fluorescence of **3a** (excitation: 366 nm diode array) from left to right: solution in DMSO, addition of KOH solution, deprotonated form)

Table 1 Absorption and Emission Wavelengths of Thiazoles Measured in DMSO[a]

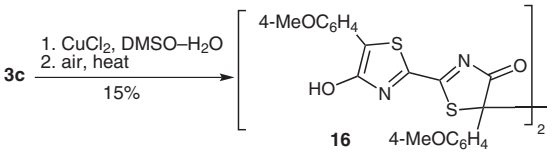
Compound	Absorption/emission OH/ether form λ_{max} (nm)	Absorption/emission deprotonated form λ_{max} (nm)
3a	445/528	580/656
3b	455/520	530/645
3c	466/535	620/649
4a	442/500[b]	–
6a	400/543	540/697
6b	416/533	553/630
9	365/440	490/594
10	365/568	no fluorescence
12	381/426	510/621
13b	380/427	489/627
15	432/532	620/703
16	500/564	–

[a] Unless otherwise indicated.
[b] In THF.

solutions of their dianions (**3a**/dianion: λ_{max} = 656 nm, Figure 2), which display a deep red fluorescence. Generally, 2-pyridyl-substituted 4-hydroxythiazoles absorb and emit more bathochromically than 2-phenyl-substituted derivatives,[6] whereas bithiazoles of type **3** display the longest wavelengths of all examined hydroxythiazoles.

Apparently, solutions of the anions react rapidly with carbon dioxide from the air with reformation of the OH derivative. ESR data of deprotonated **15** proved the existence of radicals. The first analysis showed one radical species interacting with four equivalent protons of the symmetrical phenyl unit (1:4:6:4:1; g = 2.0048, hfcc [G] = 2.4). These findings suggest the existence of a reversible two-electron redox system in which the radical represents the SEM-form (extended hydroquinone). Additional research is in progress at the moment and will be reported.

Due to their 1,4-diazadiene subunit, the bithiazoles **3** furfil the preconditions for the construction of metal complexes.[14] Therefore, the reactivity of **3c** towards selected metal ions with regard to the formation of complexes was tested. When a solution of bithiazole **3c** in dimethyl sulfoxide is added to an aqueous solution of copper(II) chloride, a deep purple precipitation is formed almost immediately. The MS data indicated the mass of starting material **3c** attached to copper(II) chloride, however, due to its low solubility, all attempts to obtain single crystals suitable for X-ray analysis have failed so far. Treatment of the complex with dimethyl sulfoxide in the presence of air generated a new compound, **16**, in low yields. The latter was purified by recrystallization from dimethyl sulfoxide as green-shining, glossy dark red crystals (Scheme 4).



Scheme 4 Dimerization of **3c** in the presence of copper(II) chloride

The complex NMR spectra of **16** and the few reliable MS data gave no further structural information, and only IR spectra revealed the presence of a carbonyl group, so that an X-ray structural analysis was the final and unambiguous proof of its structure (Figure 3).

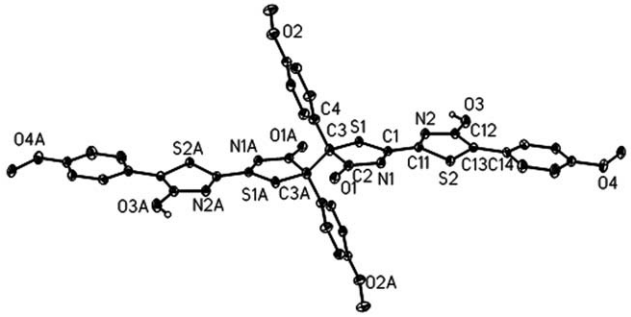


Figure 3 ORTEP plot (50% probability ellipsoids) of the solid-state molecular structure (X-ray crystal structure analysis) of derivative **16**. C3A–C3: 1.553(6) Å; C3–C2: 1.568(4) Å; C3–C4: 1.550(5) Å; C2–N1: 1.385(4) Å; C1–N1: 1.309(4) Å; C1–S1: 1.470(3) Å; C4–C3–C3A: 112.9(3)°; C3A–C3–C2: 109.5(3)°.

The unexpected structure of **16** consists of two molecules of the starting material which are linked at the5,5′-positions. Simultaneously, a transformation of both hydroxy groups to carbonyl groups to form thiazolones took place. Most likely, the formation of **16** is the result of a copper-mediated oxidative dimerization reaction. This dimerization reaction shows remarkable similarity to the oxidative coupling reaction of 2-naphthol.[15]

Reagents were purchased from commercial sources and were used directly unless otherwise stated in the text. Aq 48% $(NH_4)_2S$ solution was obtained from Aldrich. All solvents were of reagent grade and were dried according to common practice and distilled prior to use. Reactions were monitored by TLC, carried out on 0.2 mm Merck silica gel plates (60 F_{254}). ^1H and ^{13}C NMR spectra were recorded on Bruker AVANCE 250 and 400 spectrometers, shifts (δ) are given relative to signals arising from the solvent. Melting points were measured with a Galen III apparatus (Boëtius system) and are corrected.

Crystal structure determination: The intensity data were collected on a Nonius KappaCCD diffractometer, using graphite-monochromated MoKα radiation. Data were corrected for Lorentz and polarization effects, but not for absorption.[16,17]

The structure was solved by direct methods (SHELXS)[17] and refined by full-matrix least squares techniques against Fo^2 (SHELXL-97).[18] All hydrogen atoms for the compound **4a** and for the hydroxy group O3 for compound **16** were located by difference Fourier synthesis and refined isotropically. XP (Siemens Analytical X-ray Instruments, Inc.) was used for structure representations.[19]

Crystal Data for **4a**: $C_{22}H_{20}N_2O_2S_2$, M_r = 408.52 g mol^{-1}, red prism, size 0.05 × 0.05 × 0.03 mm^3, monoclinic, space group $P2_1/c$, a = 4.9317(3), b = 10.1208(9), c = 19.491(2) Å, β = 95.265(5)°, V = 968.7(1) Å^3, T = –140 °C, Z = 2, ρ_{calcd} = 1.401 g cm^{-3}, μ(MoKα) = 2.96 cm^{-1}, F(000) = 428, 9060 reflections in h(–5/6), k(–13/11), l(–25/25), measured in the range 2.10° ≤ Θ ≤ 27.47°, completeness Θ_{max} = 99.8%, 2220 independent reflections, R_{int} = 0.1459, 1346 reflections with $F_o > 4\sigma(F_o)$, 167 parameters, 0 restraints, $R1_{obs}$ = 0.0539, wR^2_{obs} = 0.1091, $R1_{all}$ = 0.1165, wR^2_{all} = 0.1317, GOOF = 0.969, largest difference peak and hole: 0.320/–0.488 e Å^{-3}.

Crystal Data for **16**: $C_{40}H_{30}N_4O_8S_4$ 2 C_3H_7NO, M_r = 969.11 g mol^{-1}, red-brown prism, size 0.05 × 0.05 × 0.04 mm^3, monoclinic, space group $P2_1/n$, a = 10.4220(4), b = 21.1752(9), c = 10.6172(4) Å, β = 107.599(2)°, V = 2233.42(15) Å^3, T = –140 °C, Z = 2, ρ_{calcd} = 1.441 g cm^{-3}, μ (MoKα) = 2.8 cm^{-1}, F(000) = 1012, 13706 reflections in h(–13/13), k(–21/27), l(–13/13), measured in the range 2.26° ≤ Θ ≤ 27.49°, completeness Θ_{max} = 99.4%, 5101 independent reflections, R_{int} = 0.0577, 3746 reflections with $F_o > 4\sigma(F_o)$, 306 parameters, 0 restraints, $R1_{obs}$ = 0.0614, wR^2_{obs} = 0.1225, $R1_{all}$ = 0.0959, wR^2_{all} = 0.1395, GOOF = 1.075, largest difference peak and hole: 0.604/–0.328 e Å^{-3}.

4-Hydroxythiazoles 3a–c, 6a,b, 9, 10 and 12; Typical Procedure

A mixture of pyridine (0.87 g, 11 mmol), the corresponding thioamide **2** or **5** (10 mmol) and the corresponding ethyl bromophenylacetate **1** or sulfanylacetate (11 mmol) was stirred under argon at 100–110 °C until the mixture solidified. After 1 h, EtOH (30 mL) was added and the mixture was stirred at r.t. for 30 min. After filtration the crude product was recrystallized (EtOH–DMF) and dried in vacuo.

5,5′-Diphenyl-2,2′-bithiazole-4,4′-diol (3a)

Following the typical procedure using **1a** (1.1 equiv) and **2** (1 equiv); orange-red crystals or powder; yield: 40–60%; mp 335–338 °C.

IR (ATR): 2699, 2557, 1411, 1369 1211, 1001, 751 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 11.94 (s, 2 H), 7.78 (d, J = 7.5 Hz, 4 H), 7.44 (dd, J = 7.5 Hz, 4 H), 7.28 (dd, J = 7.3 Hz, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 159.1, 158.2, 152.7, 131.7, 129.4, 127.2, 126.6.

MS (EI): m/z (%) = 352 (12) [M$^+$], 203 (13), 121 (100), 77 (19).

UV/Vis (DMSO): λ_{max} = 445 nm; deprotonated (KOH) λ_{max} = 580 nm.

Fluorescence (DMSO): λ_{max} = 528 nm; Φ = 96% (Rh 6G), $t_{1/2}$ = 2.8 ns; deprotonated (KOH) λ_{max} = 656 nm. Φ = 22% (Rh 6G).

5,5′-Bis(4-bromophenyl)-2,2′-bithiazole-4,4′-diol (3b)

Following the typical procedure using **1b** (1.1 equiv) and **2** (1 equiv); deep red powder; yield: 75%; mp >360 °C.

IR (ATR): 2654, 2553, 1380, 1423, 1207, 1006, 808 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 11.77 (s, 2 H), 7.73 (d, J = 8.6 Hz, 2 H), 7.63 (d, J = 8.6 Hz, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 159.5, 153.2, 132.2, 131.1, 128.6, 119.6, 110.2.

MS (EI): m/z (%) = 512 (17), 510 (23), 508 (14), 283 (31), 201 (100), 199 (93), 121 (50), 120 (69).

UV/Vis (DMSO): λ_{max} = 455 nm; deprotonated (KOH) λ_{max} = 530 nm.

Fluorescence (DMSO): λ_{max} = 520 nm; deprotonated (KOH) λ_{max} = 645 nm.

5,5′-Bis(4-methoxyphenyl)-2,2′-bithiazole-4,4′-diol (3c)

Following the typical procedure using **1c** (1.1 equiv) and **2** (1 equiv); red powder; yield: 70%; mp 348–350 °C.

IR (ATR): 2954, 2553, 1504, 1404, 1246, 1053, 840 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 11.67 (s, 2 H), 7.69 (d, J = 8.8 Hz, 4 H), 6.99 (d, J = 8.8 Hz, 4 H), 3.77 (s, 6 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 158.6, 158.0, 151.6, 128.0, 124.1, 114.8, 110.7, 55.6.

MS (EI): m/z (%) = 412 (7) [M$^+$], 233 (11), 151 (100), 108 (41).

UV/Vis (DMSO): λ_{max} = 466 nm; deprotonated (KOH) λ_{max} = 620 nm.

Fluorescence (DMSO): λ_{max} = 535 nm; deprotonated (KOH) λ_{max} = 649 nm.

Anal. Calcd for $C_{20}H_{16}N_2O_4N_2$: C, 58.24; H, 3.91; N, 6.79; S, 15.55. Found: C, 58.01; H, 4.05; N, 6.65; S, 15.84.

4,4′-Diethoxy-5,5′-diphenyl-2,2′-bithiazole (4a)

Compound **3a** (1 mmol) was dissolved in DMSO (20 mL). Under stirring, NaH (1.1 mmol, 60% suspension) was added. After 10 min, EtI (1.1 mmol) was added dropwise to the deep-violet soln. The mixture was stirred until the reaction was complete (TLC monitoring, $CHCl_3$). Then, H_2O (50 mL) was added and the formed suspension was filtered off and the crude product was dried in vacuo. The obtained solid was dissolved in CH_2Cl_2 and filtered through a short silica gel column and the solvent was removed; yield: 93%; light-red crystals; mp 201 °C.

IR (ATR): 1519, 1469, 1330, 1060, 760, 686 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.6 Hz, 4 H), 7.42–7.36 (m, 4 H), 7.28–7.25 (m, 2 H), 4.61 (q, J = 7.1 Hz, 4 H), 1.52 (t, J = 7.0 Hz, 6 H).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 159.1, 153.1, 131.5, 128.7, 126.9, 126.8, 113.9, 66.6, 15.2.

MS (EI): m/z (%) = 408 (89) [M$^+$], 380 (8), 231 (12), 203 (33), 121 (100), 77 (31).

UV/Vis (THF): λ_{max} = 442 nm.

Fluorescence (THF): λ_{max} = 500 nm.

Anal. Calcd for $C_{14}H_{10}N_2OS$: C, 64.68; H, 4.93; N, 6.86; S, 15.70. Found: C, 64.55; H, 5.11; N, 6.99; S, 15.41.

Pyridine-2,4,6-tricarbothioamide (5b)

Pyridine-2,4,6-tricarbonitrile (0.25 g, 1 mmol,) was dissolved in DMSO (40 mL). Aq $(NH_4)_2S$ soln (1.5 mL, 48%) was added in one portion. The mixture was stirred for 30 min and then H_2O (125 mL) was added. After 1 h, the crude product was filtered off, recrystallized (DMF) and dried in vacuo; yellow powder; yield: 56%; mp >300 °C (decomp.).

IR (ATR): 3371, 3263, 3159, 1581, 1420, 1265, 644 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 10.51–10.06 (m, 6 H), 8.95 (s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 197.6, 192.6, 149.4, 148.9, 123.9.

MS (EI): m/z (%) = 256 (100) [M$^+$], 239 (16), 222 (58), 206 (20), 180 (19), 60 (58).

HRMS (ESI): m/z calcd for $C_8H_8N_4S_3$: 255.9911; found: 255.9921.

UV/Vis (DMSO): λ_{max} = 350 nm.

2,2′-Pyridine-2,5-diylbis(5-phenylthiazol-4-ol) (6a)

Following the typical procedure using **1a** (2.1 equiv) and **5a** (1 equiv); yellow powder; yield: 21%; mp >300 °C (decomp).

IR (ATR): 3024, 2450, 1540, 1384, 1211, 751 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 11.41 (s, 1 H), 11.35 (s, 1 H), 9.10 (s, 1 H), 8.35 (m, 1 H), 8.11 (d, *J* = 8.3 Hz, 1 H), 7.81 (m, 4 H), 7.44 (m, 4 H), 7.28 (dd, *J* = 7.4 Hz, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 159.8, 159.5, 159.4, 156.4, 151.2, 146.7, 134.3, 132.2, 131.9, 129.9, 129.3, 129.2, 127.0, 126.9, 126.8, 126.8, 119.3, 112.4, 110.2.

MS (EI): *m*/*z* (%) = λ_{max} 429 (44) [M^+], 280 (55), 130 (23), 121 (100).

UV/Vis (DMSO): λ_{max} = 400 nm; deprotonated (KOH) λ_{max} = 540 nm.

Fluorescence (DMSO): λ_{max} = 543 nm; deprotonated (KOH) λ_{max} = 697 nm.

2,2′,2″-(Pyridine-2,4,6-triyl)tris(5-phenylthiazol-4-ol) (6b)
Following the typical procedure using **1a** (3.2 equiv) and **5b** (1 equiv); yellow powder; yield: 55%; mp 338 °C.

IR (ATR): 3090, 2557, 1593, 1381, 1207, 752 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 11.89 (s, 1 H), 11.67 (s, 2 H), 8.31 (s, 2 H), 7.82–7.76 (m, 6 H), 7.43–7.37 (m, 6 H), 7.28–7.24 (m, 3 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 162.7, 159.6, 159.3, 158.7, 155.6, 151.6, 142.1, 132.0, 131.5, 129.4, 129.2, 127.4, 127.0, 126.8, 126.7, 113.9, 112.4.

MS (EI): *m*/*z* (%) = 604 (16) [M^+], 305 (8), 196 (22), 163 (100), 121 (93), 91 (86), 79 (43).

UV/Vis (DMSO): λ_{max} = 416 nm; deprotonated (KOH) λ_{max} = 553 nm.

Fluorescence (DMSO): λ_{max} = 533 nm; deprotonated (KOH) λ_{max} = 630 nm.

2,2′-Pyridine-2,4-diylbis(5-methylthiazol-4-ol) (9)
Following the typical procedure[4] using ethyl thiolactate (2.1 equiv) and **7** (1 equiv); yellow powder; yield: 78%; mp 309 °C.

IR (ATR): 3001, 2665, 1591, 1420, 1126, 775 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 10.62 (s, 1 H), 10.4 (s, 1 H), 8.58 (d, *J* = 4.9 Hz, 1 H), 8.24 (s, 1 H), 7.67 (m, 1 H), 2.26 (s, 3 H), 2.23 (s, 3 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 160.2, 159.7, 158.6, 155.0, 151.9, 151.1, 122.5, 119.45, 119.2, 113.0, 106.9, 9.8, 9.8.

MS (EI): *m*/*z* (%) = 305 (69) [M^+], 218 (100), 130 (249), 59 (21).

UV/Vis (DMSO): λ_{max} = 365 nm; deprotonated (KOH) λ_{max} = 490 nm.

Fluorescence (DMSO): λ_{max} = 440 nm; deprotonated (KOH) λ_{max} = 594 nm.

Dimethyl 2,2′-[2,2′-(Pyridine-2,6-diyl)bis(4-hydroxythiazole-5,2-diyl)]diacetate (10)
The standard procedure was applied using dimethyl mercaptosuccinic acid (2.1 equiv) and **8** (1 equiv); yellow-orange powder; yield: 55%; mp 286 °C.

IR (ATR): 2954, 2619, 1731, 1558, 1404, 1203, 1064, 823 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 10.77 (s, 2 H), 8.05–8.00 (m, 1 H), 7.93 (d, *J* = 7.1 Hz, 2 H), 4.10 (s, 4 H), 3.65 (s, 6 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 171.1, 160.8, 160.6, 150.7, 139.8, 118.9, 103.9, 61.1, 30.2.

MS (EI): *m*/*z* (%) = 412.2 (94) [M^+], 362 (92), 276.3 (45), 216 (100), 87.3 (55).

UV/Vis (DMSO): λ_{max} = 365 nm.

Fluorescence (DMSO): λ_{max} = 568 nm.

3-[5-(4-Bromophenyl)-4-hydroxythiazol-2-yl]benzonitrile (12)
Following the typical procedure using **1b** (1.1 equiv) and **9** (1 equiv); yellow needles; yield: 66%; mp 207 °C.

IR (ATR): 2970, 2559, 2225, 1566, 1415, 1392, 1064, 803 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 11.92 (s, 1 H), 8.24 (s, 1 H), 8.19 (d, *J* = 8.1 Hz, 1 H), 7.95 (d, *J* = 7.8 Hz, 1 H), 7.74–7.57 (m, 5 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 159.1, 158.2, 152.7, 131.7, 129.4, 127.2, 126.6.

MS (EI): *m*/*z* (%) = 356 (100) [M^+], 230 (13), 199 (63), 129 (55).

UV/Vis (DMSO): λ_{max} = 381 nm; deprotonated (KOH) λ_{max} = 510 nm.

Fluorescence (DMSO): λ_{max} = 426 nm; deprotonated (KOH) λ_{max} = 621 nm.

3-[5-(4-Bromophenyl)-4-hydroxythiazol-2-yl]thiobenzamide (13a)
Compound **12** (1 mmol) was dissolved in DMSO (20 mL). Aq $(NH_4)_2S$ soln (0.5 mL, 48%) was added in one portion and the mixture was stirred for 30 min. Then H_2O (50 mL) was added under stirring. After 1 h the crude product was filtered off and recrystallized (EtOH–DMF) and dried in vacuo; deep-yellow powder; yield: 94%; mp 300 °C.

IR (ATR): 3282, 3087, 2881, 1651, 1485, 1353, 1300, 1234, 999, 690 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 11.94 (s, 1 H), 10.02 (s, 1 H), 9.68 (s, 1 H), 8.45 (s, 1 H), 7.98 (d, *J* = 7.9 Hz, 1 H), 7.91 (d, *J* = 7.9 Hz, 1 H), 7.70–7.51 (m, 5 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 199.7, 159.7, 159.6, 140.9, 132.9, 132.2, 131.5, 129.5, 128.9, 128.2, 128.0, 125.4, 119.3, 107.4.

MS (EI): *m*/*z* (%) = 390 (50) [M^+], 358 (43), 201 (65), 163 (33), 129 (100), 120 (42).

UV/Vis (DMSO): λ_{max} = 378 nm; deprotonated (KOH) λ_{max} = 480 nm.

5-(4-Bromophenyl)-2-[3-(4-hydroxy-5-phenylthiazol-2-yl)phenyl]thiazol-4-ol (13b)
Following the typical procedure using **13a** (1.1 equiv) and **1a** (1 equiv); yellow microcrystals; yield: 65%; mp 301 °C.

IR (ATR): 2916, 2553, 1566, 1415, 1392, 1049, 750 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 11.52 (s, 1 H), 11.29 (s, 1 H), 8.43 (s, 1 H), 7.97 (m, 2 H), 7.77–7.56 (m, 7 H), 7.43 (m, 2 H), 7.26 (dd, *J* = 7.4 Hz, 1 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 159.5, 157.9, 134.2, 133.9, 132.2, 131.2, 131.1, 130.1, 129.0, 128.3, 119.6, 118.6, 112.9, 108.45.

MS (EI): *m*/*z* (%) = 508 (34) [M^+], 557 (12), 279 (53), 201 (24), 121 (100).

UV/Vis (DMSO): λ_{max} = 380 nm; deprotonated (KOH) λ_{max} = 489 nm.

Fluorescence (DMSO): λ_{max} = 427 nm; deprotonated (KOH) λ_{max} = 627 nm.

Anal. Calcd for $C_{24}H_{15}BrN_2O_2S_2$: C, 56.81; H, 2.98; N, 5.52; S, 12.64; Br, 15.74. Found: C, 56.52; H, 3.11; N, 5.43; S, 12.62; Br, 16.04.

5,5′-(1,4-Phenylene)bis[2-(pyridin-2-yl)thiazol-4-ol] (15)
A mixture of **14** (0.41 g, 1 mmol), **5c** (0.276 g, 2 mmol), and pyridine (1 mL) was stirred in DMF (5 mL) and heated to 100 °C for 2 h. After cooling, EtOH (25 mL) was added and the slurry was filtered off. The pure compound was obtained after recrystallization (hot DMSO); buff-colored powder; yield: 22%; mp >360 °C.

IR (ATR): 2978, 2549, 1562, 1458, 1408, 1101, 817, 771 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 11.32 (s, 2 H), 8.62 (s, 2 H), 8.01–7.96 (m, 6 H), 7.83 (s, 2 H), 7.46 (s, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 160.8, 159.3, 150.8, 150.2, 138.0, 130.4, 127.0, 125.2, 118.9, 111.3.

MS (EI): *m/z* (%) = 430 (100) [M^+], 309 (6), 204 (11), 121 (9), 105 (23).

UV/Vis (DMSO): λ_{max} = 432 nm; deprotonated (KOH) λ_{max} = 620 nm.

Fluorescence (DMSO): λ_{max} = 532 nm; deprotonated (KOH) λ_{max} = 703 nm.

2,2′-Bis[4-hydroxy-5-(4-methoxyphenyl)thiazol-2-yl]-5,5′-bis(4-methoxyphenyl)-5,5′-bithiazole-4,4′(5*H*,5′*H*)-dione (16)
Compound **3b** (0.41 g, 1 mmol) was dissolved in DMSO (50 mL), then a soln of $CuCl_2$ (1.7 g 10 mmol) in H_2O (5 mL) was added in one portion. The resulting deep blue-lilac mixture was stirred for 30 min and then filtered off. The compound obtained was dissolved in hot DMSO. Upon slow cooling to r.t. the pure compound was obtained; green-shining, glossy dark red crystals; yield: 15%; mp 300–305 °C.

IR (ATR): 1697, 1624, 1473, 1374, 1150, 1026, 7, 808 cm^{-1}.

^1H NMR (250 MHz, DMSO-d_6): δ = 12.32 (s, 2 H), 7.95–7.76 (m, 8 H), 7.03–6.91(m, 8 H), 3.79 (s, 6 H), 3.67 (s, 6 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = due to the low solubility of this compound no spectra could be recorded.

MS (EI): *m/z* (%) = 412 (52) [$M/2^+$], 397 (9), 232 (67), 151 (77), 73 (100).

UV/Vis (DMSO): λ_{max} = 500 nm.

Fluorescence (DMSO): λ_{max} = 564 nm.

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(19) Supporting Information Available: Crystallographic data deposited at the Cambridge Crystallographic Data Centre under CCDC-813194 for **4a**, and CCDC-813195 for **16** contain the supplementary crystallographic data excluding structure factors; this data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; or deposit@ccdc.cam.ac.uk.