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Novel luminescence dyes and ligands based on 4-hydroxythiazole

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The condensation reaction of N-heteroaromatic nitriles with D,L-mercaptolactic acid results in the formation of 4-hydroxythiazoles. The products are sparingly soluble in most solvents in which they display only a weak fluorescence. However, upon derivatization of the OH-group by etherification, blue emitting luminescence dyes with high quantum yields and large stokes shifts were obtained. The luminescence of these thiazoles is affected by the 2-substituents and lies in the region of 410 nm, with quantum yields between 30% and 90%.

Employing this method, not only new fluorophores were obtained, but also derivatives that offer good requirements for the construction of metal complexes due to their diazadiene substructure.

Keywords: 4-hydroxythiazole; fluorescence; ligands; diazadiene; oligopyridines

1. Introduction

Since their discovery in 1883 (*1*), a broad variety of different thiazoles have been synthesized and the chemistry of this type of heterocycles is well established (*2*). Being part of some natural products (*3*), several 1,3-thiazoles are biologically active and are seldom used in medical applications (*4*). In the last decade, 2,4-substituted thiazoles bearing a diazadiene substructure were tested as potential ligands in the complexation of various metals. It was shown for these types of complexes that 1,3-thiazoles are able to act as N-donor ligands (*5*). The authors described several pyridyl substituted thiazoles, their properties and applications as ligands (*6*). Astonishingly, no luminescence properties for the complexes obtained have been reported. Contrary to this fact, 2,5-diaryl-substituted thiazoles were described as luminescent dyes, which were implemented as scintillating compounds (*7*).

Our aim was therefore to combine these two features in order to obtain thiazole-based ligands for metals which are also potent fluorophores. The intensity and range of absorptions/emissions of obtained metal complexes make them interesting for applications such as in sensor systems and for the harvesting of photons. Usually, the syntheses of substituted thiazoles were realized by a condensation reaction of thioamides with α-halogenocarbonyl compounds ('thiazole synthesis of Hantzsch'). Employing this synthetic entry, a broad variety of 2,4,5-trisubstituted thiazoles can be obtained in good yields. Another, less common approach was used in the synthesis of luciferine

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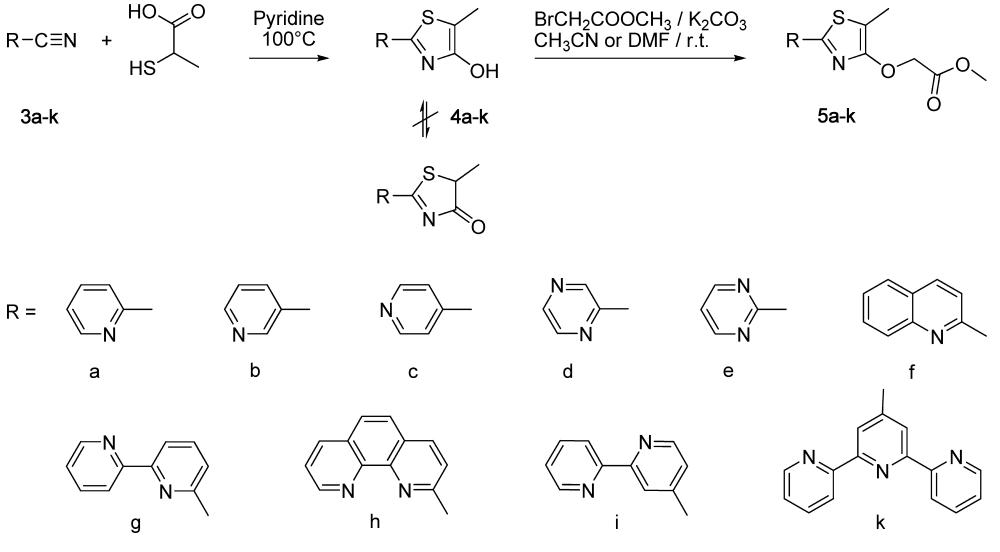
and its derivatives (*8*). Following this synthetic route, a ring closure reaction between an aromatic nitrile and α-mercaptoacids takes place under smooth conditions. However, this reaction is limited by the availability of α-mercaptoacids.

2. Results and discussion

Our synthetic entry to 4-hydroxythiazoles followed a synthesis developed for the preparation of lipoxygenase inhibitors (*9*). The heteroaromatic nitriles **3a-k** and D,L-mercaptolactic acid were melted together at 100 °C in the presence of small amounts of pyridine in an argon atmosphere (Scheme 1). After a certain period, the reaction mixture became solid and the 4-hydroxythiazoles **4a-k** were isolated after recrystallization from alcohols in moderate yields of ~ 70%. The yellow colored compounds are only sparingly soluble in common organic solvents. However, they show a good solubility in DMF, DMSO and DMA. In solutions of derivatives of type **4**, only a weak fluorescence was detected. The spectra showed an absorption maximum at about 340 nm and a very broad emission band with a maximum of 470 nm. The quantum yields are generally lower than 10%. Although many authors describe an equilibrium between a supposedly keto-form and its enol equivalent (Scheme 1), all compounds in this protocol prevail in the enol-form, as indicated by ^{1}H-NMR-,^{13}C-NMR- and IR-spectroscopy.



Scheme 1.

The conversion of the OH-group of derivatives **4a-k** into ester or ether substructures drastically changes the spectroscopic properties. The substances become colorless, whereas the solubility increases strongly. When irradiated with UV light, their solutions display a bright blue emission and, in addition, a solid state fluorescence can be observed. As depicted in Scheme 1, bromoacetic acid methyl ester was chosen as an electrophile for the derivatization. The thus prepared carboxymethyl moiety leads to high luminescence quantum yields and may additionally work as an anchor group for further functionalization/immobilization. Derivative **5g** in which a 2,2′-bipyridyl substructure is connected with the thiazole ring offers good prerequisites for the synthesis of metal complexes. Figure 1 shows the motif of a ruthenium complex of **5g** with bipyridines as additional ligands. The syntheses and spectroscopic properties of such novel complexes will be

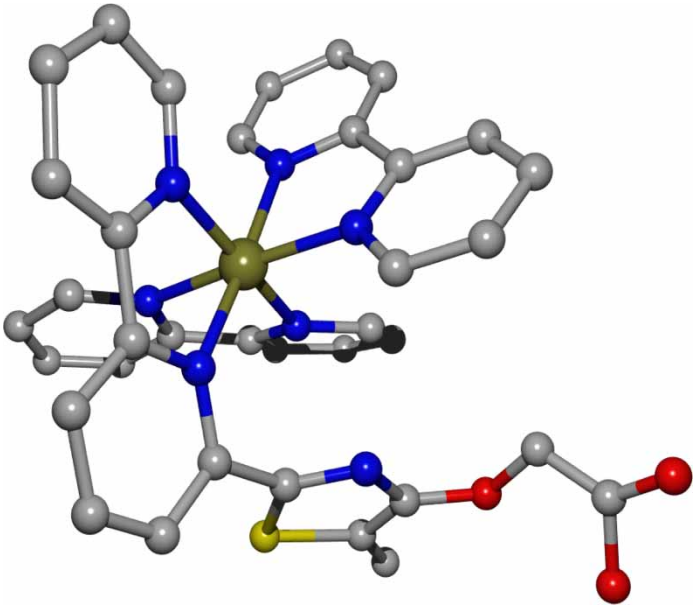


Figure 1. Motif of the Ru-complex with thiazole derivative **5g** as ligand.

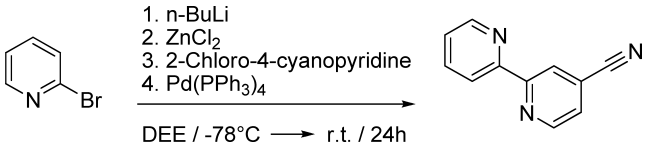
Table 1. Spectroscopic data of compounds **5a-k** in dioxane.

Compound **5**	$\lambda_{Abs,max}$ (nm)	$\lambda_{Em,max}$ (nm)	Stokes shift (cm^{-1})	Quantum yield† (Φ)
a	342	410	4850	0.96
b	357	439	5230	0.77
c	333	389	4900	0.30
d	338	389	4460	0.54
e	344	413	4860	0.61
f	366	438	4490	0.20
g	345	414	4860	0.43
h	383	446	3690	0.33
i	348	413	4520	0.66
k	346	415	4510	0.45

Note: †Quantum yields were determined using quinine sulfate as standard.

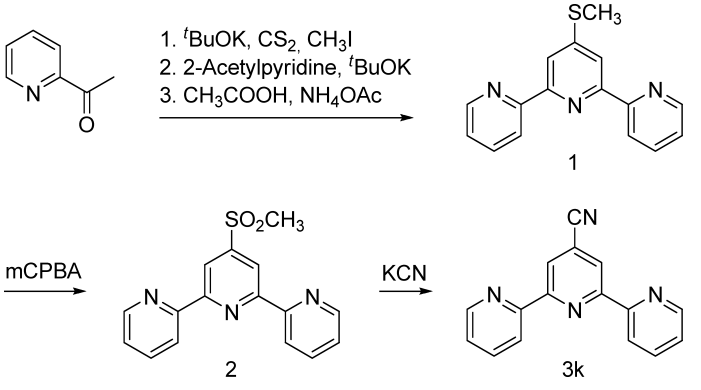
the subject of a forthcoming publication. All derivatives **5a-k** were synthesized under mild conditions; their structures were determined by elemental analyses and by spectroscopic methods. A Stokes shift of $> 4500\ cm^{-1}$ is comparatively large for molecules of the given size. Spectroscopic investigations and quantum chemical calculations were carried out on **5a** to allocate a significant geometry change in the excited state (*10*). The spectroscopic data of **5a-k** are listed in Table 1.

The different substituted cyanopyridines **3a-c**, cyanopyrazine **3d**, cyanopyrimidine **3e** and cyanochinoline **3f** were commercially available, whereas the cyano-substituted bipyridines **3g,i**, cyanophenanthroline **3h** and cyanoterpyridine **3k** were synthesized according to the modified literature procedure. Nitriles **3f-h** were obtained by a nucleophilic ortho-substitution of the corresponding N-oxides (*11*). This applied two-step reaction represents a general synthetic method for the synthesis of 2-substituted pyridine derivatives working with moderate yields of 60–70% for every step. 4-Cyano-2,2′-bipyridine **3i** was synthesized via Negishi coupling as described by Fang and Hanan (*12*) in a modified method (Scheme 2). We used a one-pot synthesis starting from 2-bromopyridine to generate the 2-pyridylzinc chloride (*13*).



Scheme 2.

4′-Cyanoterpyridine was synthesized as described by Potts and Usifier (*14*), starting from 2-acetylpyridine, as shown in Scheme 3. The first step was carried out in a one-pot synthesis, starting from 2-acetylpyridine which leads to methylsulfanylterpyridine **1**. The following oxidation reaction with *m*-chloroperbenzoic acid (*m*CPBA) in dichloromethane and the subsequent nucleophilic substitution of the resulting sulfonyl group finally gave the corresponding nitrile **3k**.



Scheme 3.

3. Conclusion

A series of new 1,3-thiazoles that contain additional N-heterocyclic substructures was synthesized. In a subsequent reaction, carboxymethyl ethers are successfully synthesized and may serve as anchor groups for further derivatization/immobilization processes. The latter substructures not only improve the solubility of thiazoles, but also drastically increase their fluorescence. These thiazoles combine high luminescence quantum yields with the structural opportunity to work as N-donor ligands. First attempts to create metal complexes of ruthenium(II), europium(III) and iridium(III) were successful and will be published in the near future.

4. Experimental

4.1. *General*

All reagents were commercially obtained and used as received. TLC: Merck Polygram SIL G/UV$_{254}$ or Merck aluminum oxide 60 F$_{254}$. Column chromatography: Merck silica gel 60 or Merck aluminum oxide 90 active neutral (activity stage I, 15m% water). Melting points: Kruess KSPS 1000, uncorrected. NMR spectra: Bruker AC-250 (250 MHz) and Bruker AC-400

(400 MHz) with $CDCl_3$ or DMSO-d_6 as internal standard. Mass spectroscopy (EI): Finnigan MAT SSQ 710. UV–VIS spectra: Unicam UV 500. Fluorescence spectra: Jasco FP 6500. Elemental analysis: Leco CHNS-932.

4′-Methylsulfanyl-(2,2′;6′,2″)-terpyridine (1): In an argon atmosphere, potassium-*tert*-butoxide (7.4 g, 66 mmol) was suspended in THF (250 mL). 2-Acetylpyridine (3.7 mL, 33 mmol) was added by syringe over a period of 15 min, followed by carbon disulfide (2 mL, 33 mmol) within 20 min and methyliodide (4.2 mL, 66 mmol) over a period of 30 min. The dark red mixture was stirred for 5 h, and additional THF (70 mL), potassium-*tert*-butoxide (7.4 g, 66 mmol) and 2-acetylpyridine (3.7 mL, 33 mmol) were then added. After the suspension was stirred for 14 h at room temperature, glacial acetic acid (40 mL) and dry ammonium acetate (25.4 g) were added and heated to reflux. After 2 h, the reflux condenser was replaced by a distillation head, and THF was removed over a 7 h period. The brown mixture was cooled on an ice bath and poured over ice (100 g). After addition of water (100 mL), the solution was stored at room temperature overnight. The grey precipitate was collected by filtration, washed with water and dried *in vacuo*. The solid was purified by soxhlet extraction with hexane from which it crystallized at −10 °C. Yield: 4.4 g (16 mmol, 48%) grey needles, m.p. 106.5 °C; ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 8.70$ (ddd, $^3J = 4.8$ Hz, $^4J = 1.8$ Hz, $^5J = 0.9$ Hz, 2H), 8.61 (ddd, $^3J = 8.0$ Hz, $^4J = 1.1$ Hz, $^5J = 1.0$ Hz, 2H), 8.32 (s, 2H, 3′-H/5′-H), 7.86 (ddd, $^3J = 7.9$ Hz, $^3J = 7.8$ Hz, $^4J = 1.8$ Hz, 2H), 7.34 (ddd, $^3J = 7.5$ Hz, $^3J = 4.8$ Hz, $^4J = 1.2$ Hz, 2H), 2.67 (s, 3H, SCH_3) ppm; ^{13}C NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 155.9$, 154.9, 152.4, 149.0, 136.8, 123.8, 121.4, 116.9, 14.0 ppm; MS (EI): m/z (%) = 279 (100), 232 (96), 155 (36), 129 (60), 78 (75); $C_{16}H_{13}N_3S$ (279.1): calcd: C 68.79, H 4.69, N 15.04, S 11.48; found: C 68.73, H 4.61, N 15.00, S 11.49.

4′-Methanesulfonyl-(2,2′;6′,2″)-terpyridine (2): Terpyridine **1** (1.0 g, 4.0 mmol) was added to dichloromethane (10 mL) and cooled to 0 °C. MCPBA (1,95 g, 85%, 8.0 mmol) was added in small portions over a period of 1 h. After complete addition the mixture was stirred for 4 h at room temperature, and diluted with chloroform (20 mL). The solution was washed with aq. $NaHCO_3$ solution (2×) and with water. After separation, the organic layer was dried over Na_2SO_4 and evaporated. The crude product was then recrystallized from ethanol. Yield: 750 mg (2.4 mmol, 60%) colorless solid, m.p. 201.1 °C; ^{1}H NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 8.83$ (s, 2H, 3′-H/5′-H), 8.78 (m, 2H), 8.66 (d, $^3J = 7.9$ Hz, 2H), 8.06 (ddd, $^3J = 7.8$ Hz, $^3J = 7.9$ Hz, $^4J = 1.8$ Hz, 2H), 7.57 (ddd, $^3J = 7.4$ Hz, $^4J = 4.8$ Hz, $^5J = 1.0$ Hz, 2H), 3.44 (s, 3H, SO_2CH_3) ppm. - ^{13}C NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 157.2$, 154.0, 151.7, 150.1, 138.3, 125.8, 121.7, 117.5, 43.2 ppm; MS (EI): m/z (%) = 311 (34), 232 (34), 128 (100), 78 (100); $C_{16}H_{13}N_3O_2S$ (311.1): calcd: C 61.72, H 4.21, N 13.50, S 10.30; found: C 61.20, H 4.32, N 13.34, S 10.03.

4′-Cyano-(2,2′;6′,2″)-terpyridine (3k): Terpyridine **2** (500 mg, 1.6 mmol) and potassium cyanide (350 mg, 5.5 mmol) were added to dry DMF (40 mL) and heated to 110 °C for 23 h. After that time the solution was allowed to cool to room temperature and diluted with water (40 mL). The mixture was extracted with chloroform (2 × 60 mL) and the combined organic layers were dried over Na_2SO_4 and evaporated. The crude product was recrystallized from ethanol. Yield: 240 mg (0.93 mmol, 58%) colorless solid, m.p. 154.0 °C; ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 8.72$ (ddd, $^3J = 4.8$ Hz, $^4J = 1.7$ Hz, $^5J = 0.9$ Hz, 2H), 8.69 (s, 2H, 3′-H/5′H), 8.58 (d, $^3J = 8.0$ Hz, 2H), 7.89 (ddd, $^3J = 7.9$ Hz, $^3J = 7.8$ Hz, $^4J = 1.8$ Hz, 2H), 7.40 (ddd, $^3J = 7.5$ Hz, $^4J = 4.8$ Hz, $^5J = 1.2$ Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 156.7$, 154.2, 149.4, 137.1, 124.7, 122.5, 121.2, 117.7, 116.9 ppm; MS (EI): m/z (%) = 258 (100), 230 (28), 180 (16), 78 (17); $C_{16}H_{10}N_4$ (258.1): calcd: C 74.40, H 3.90, N 21.69; found: C 74.31, H 3.81, N 21.68.

4-Cyano-2,2′-bipyridine (3i): In an inert atmosphere, a mixture of dry diethylether (16 mL) and 1.6 M *n*-butyllithium in hexane (14 mL) was cooled to −75 °C (dry ice/ethanol). 2-Bromopyridine (2 mL, 20 mmol) was added dropwise by syringe over a period of 25 min. After complete addition, the temperature was allowed to rise to 0 °C, kept there for 10 minutes and cooled back to −75 °C. A 1 M solution of zinc chloride in diethylether (21 mL) was then added in a dropwise fashion over a period of 1 h. After complete addition, dry THF (10 mL) was added and the dark green mixture was kept overnight at room temperature. 2-Chloro-4-cyanopyridine (2.0 g, 15.0 mmol) and $Pd(PPh_3)_4$ (380 mg, 0.33 mmol) in THF (14 mL) were added by syringe within 10 min. After stirring at room temperature for 24 h, the mixture was poured into aq. solution of EDTA/Na_2CO_3 (300 mL). After the precipitate had completely dissolved, the mixture was extracted with diethylether (3 × 200 mL) and dried over Na_2SO_4. The obtained brown oil crystallized on cooling at −10 °C overnight. The residue was purified by chromatography on silica gel with 3:1 hexane:ethylacetate. Yield: 1.20 g (6.6 mmol, 50%) colorless solid, m.p. 90.0 °C; ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 8.83$ (dd, $^3J = 4.9$ Hz, $^4J = 0.8$ Hz, 1H), 8.70 (m, 2H), 8.42 (ddd, $^3J = 8.0$ Hz, $^4J = 0.8$ Hz, $^4J = 0.8$ Hz, 1H), 7.85 (ddd, $^3J = 7.8$ Hz, $^3J = 7.8$ Hz, $^4J = 1.8$ Hz, 1H), 7.51 (dd, $^3J = 4.9$ Hz, $^4J = 1.5$ Hz, 1H), 7.38 (ddd, $^3J = 7.5$ Hz, $^3J = 4.9$ Hz, $^4J = 1.1$ Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 157.5$, 154.0, 150.0, 149.4, 137.2, 124.8, 124.7, 122.9, 121.4, 121.2, 116.7 ppm; MS (EI): m/z (%) = 181 (100), 155 (22), 103 (8), 77 (7); $C_{11}H_7N_3$ (181.1): calcd: C 72.92, H 3.89, N 23.19; found: C 73.28, H 4.27, N 22.97.

General procedure for the synthesis of hydroxythiazoles (4a-k): D,L-Mercaptolactic acid and the corresponding nitrile were loaded into a Schlenk tube, evacuated, flushed with argon and heated to 100 °C. Pyridine was added and the suspension was stirred for 2 h. After that, the mixture became solid, which was collected by filtration, washed with ethanol and recrystallized.

5-Methyl-2-pyridin-2-yl-1,3-thiazol-4-ol (4a): According to (*10*), from **3a** (5.2 g, 47 mmol), mercaptolactic acid (5.3 g, 50 mmol) and pyridine (1 mL). Yield: 6.7 g (69%) yellow solid, m.p. 229 °C (Lit.: 230 °C).

5-Methyl-2-pyridin-4-yl-1,3-thiazol-4-ol (4b): From **3b** (5.2 g, 47 mmol), mercaptolactic acid (5.3 g, 50 mmol) and pyridine (1 mL). Yield: 5.9 g (64%), yellow plates, m.p. 221 °C (ethanol), ^{1}H NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 10.58$ (s, 1H), 8.62 (m, 2H), 7.69 (m, 2H), 2.23 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 250 MHz): $\delta = 160.1$, 155.4, 151.0, 140.2, 119.11, 106.3, 9.7 ppm; MS (EI): m/z (%) = 192 (30), 105 (100), 88 (70), 60 (90), 59 (80), 51 (50); UV/VIS (acetonitrile): $\lambda_{max}(\log \varepsilon) = 248$ (3.8), 290 (3.5), 335 (3.8) nm; $C_9H_8N_2OS$ (269.1): calcd: C 56.23, H 4.19, N 14.57, S 16.68; found: C 56.04, H 4.11, N 14.71, S 16.66.

5-Methyl-2-pyridin-3-yl-1,3-thiazol-4-ol (4c): From **3c** (5.2 g, 47 mmol), mercaptolactic acid (5.3 g, 50 mmol) and pyridine (1 mL). Yield: 4.5 g (47%), yellow needles, m.p. decomp. (dioxane). - ^{1}H NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 10.18$ (m, 1H), 8.98 (s, 1H), 8.58 (m, 1H), 8.10 (m, 1H), 7.47 (m, 1H), 2.25 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 159.7$, 155.6, 150.5, 146.3, 132.6, 129.8, 124.5, 104.6, 9.5 ppm; UV/VIS (acetonitrile): $\lambda_{max}(\log \varepsilon) = 242$ (3.5), 282 (3.3), 330 (3.6) nm; $C_9H_8N_2OS$ (269.1): calcd: C 56.23, H 4.19, N 14.57, S 16.68; found: C 56.20, H 4.23, N 14.72, S 16.66.

5-Methyl-2-pyrazin-2-yl-1,3-thiazol-5-ol (4d): From **3d** (1.5 g, 14 mmol), mercaptolactic acid (1.5 g, 14 mmol) and pyridine (1 mL). Yield: 0.470 g (17%), fine yellow needles, m.p. 267 °C (ethanol) - ^{1}H NMR (DMF-d_7, 400 MHz, 30 °C): $\delta = 9.17$ (s, 1H), 8.61 (m, 2H), 8.03, 2.35 (s, 1H) ppm; ^{13}C NMR (DMF-d_7, 400 MHz, 30 °C) $\delta = 160.3$, 156.5, 146.8, 144.8, 144.2, 140.0,

107.9, 8.8 pm; MS (EI): m/z (%) = 106 (10), 59 (100); UV/VIS (methanol): $\lambda_{max}(\log \varepsilon) = 253$ (4.0), 363 (4.1) nm; $C_8H_7N_3OS$ (193.2): calcd: C 49.73, H 3.65, N 21.75, S 16.59; found: C 50.00, H 3.78, N 22.01, S 16.81.

5-Methyl-2-pyrimidin-2-yl-1,3-thiazol-5-ol (4e): From **3e** (1.0 g, 9 mmol), mercaptolactic acid (1.0 g, 9 mmol) and pyridine (1 mL). Yield: 1.35 g (73%), yellow needles, m.p. 247 °C (methanol); ^{1}H NMR (DMSO- d_6, 250 MHz, 25 °C): $\delta = 10.69$ (s, 1H), 8.82 (m, 2H), 7.43 (m, 1H), 2.23 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 160.5$, 159.1, 158.3, 156.9, 9.7 ppm; MS (EI): m/z (%) = 106 (60), 59 (100); UV/VIS (methanol): λ_{max} ($\log \varepsilon$) = 212 (3.8), 239 (3.7), 353 (4.0) nm; MS (EI): m/z (%) = 265 (10), 192 (30), 59 (100); $C_8H_7N_3OS$ (193.2): calcd: C 49.73, H 3.65, N 21.75, S 16.59; found: C 49.66, H 3.72, N 22.66, S 16.61.

5-Methyl-2-quinolin-2-yl-1,3-thiazol-4-ol (4f): From **3f** (1.5 g, 10 mmol), mercaptolactic acid (1.3 g, 13 mmol) and pyridine (1 mL). Yield: 1.8 g (74%), yellow crystals, m.p. 205 °C (methanol) - ^{1}H NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 10.44$ (s, 1H), 10.44 (m, 1H), 8.46 (m, 1H), 8.07-7.56 (m, 5H), 2.27, (s, 2H) ppm; ^{13}C NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 159.2$, 158.8, 150.5, 147,0, 137.4, 130.3, 128.4, 128.4, 128.0, 127.9, 126.8, 116.5, 107.1, 9.4 ppm; MS (EI): m/z (%) = 242 (20), 155 (100) 128 (30); $C_{13}H_{10}N_2OS$ (242.3): calcd: C 64.44. H 4.16, N 11.56, O 6.6, S 13.23; found: C 64.40, H 4.04, N 11.68, S 13.22. UV/VIS (methanol): $\lambda_{max}(\log \varepsilon) = 228$ (2.0), 389 (2.5) nm.

2-(2,2′-Bipyridin-6-yl)-5-methyl-1,3-thiazol-4-ol (4g): From **3g** (1.8 g, 10 mmol), mercaptolactic acid (1.3 g, 13 mmol) and pyridine (1 mL). Yield: 1.86 g (67%), yellow crystals, m.p. 197 °C (methanol); ^{1}H NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 10.40$ (s, 1H), 8.71 (m, 1H), 8.39 (m, 2H), 8.03 (m, 3H), 7.48 (m, 1H), 2.26 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 159.7$, 159.3, 155.4, 154.8, 150.6, 149.8, 139.2, 137.9, 125.0, 121.1, 120.9, 118.5, 106.7, 9.8 ppm; MS (EI): m/z (%) = 269 (50), 182 (100), 155 (30) – UV/Vis (methanol): $\lambda_{max}(\log \varepsilon) = 236$ (2.0), 266 (1.0), 349 (1.3) nm; $C_{14}H_{11}N_3OS$ (269.3): calcd: C 62.44, H 4.12, N 15.60, S 11.91; found: C 62.04, H 4.05, N 15.50, S 11.97.

5-Methyl-2-(1,10-phenanthrolin-2-yl)-1,3-thiazol-4-ol (4h): From **3h** (2.0 g, 10 mmol), mercaptolactic acid (1.3 g, 13 mmol) and pyridine (1 mL), reaction time 4 h. Yield: 2.0 g (70%), yellow crystals, m.p. 214 °C (methanol) - ^{1}H NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 10.45$ (s, 1H), 9.16 (m, 1H), 8.64 (m, 2H), 8.29 (m, 1H), 7.97 (s, 2H), 7.75 (m, 1H), 2.30 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 159.3$, 159.2, 150.2, 150.0, 145.1, 144.8, 137,5, 136.2, 128.9, 128.5, 126.9, 126.3, 124.3, 123.4, 117.9, 107.3, 9.4 ppm; MS (EI): m/z (%) = 293 (60), 206 (100), 179 (40); UV/VIS (methanol): $\lambda_{max}(\log \varepsilon) = 234.5$ (3.8), 273.0 (3.6), 379.5 (3.5) nm; $C_{16}H_{11}N_3OS$ (293.3): calcd: C 65.51, H 3.78, N 14.32, S 10.93; found: C 65.4, H 3.72, N 14.32, S 10.92.

2-(2,2′-Bipyridin-4-yl)-5-methylthiazol-4-ol (4i): From **3g** (520 mg, 2.8 mmol), mercaptolactic acid (320 mg, 3.1 mmol) and pyridine (0.5 mL). Yield: 450 mg (1.7 mmol, 60%), bright yellow crystals, m.p. 189 °C (ethanol); ^{1}H NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 10.67$ (s, 1H, OH), 8.76 (d, $^4J = 1.1$ Hz, 1H), 8.71 (d, $^3J = 5.2$ Hz, 1H), 8.96 (ddd, $^3J = 7.8$ Hz, $^3J = 7.9$ Hz, $^4J = 1.8$ Hz, 1H), 8.39 (d, $^3J = 7.9$ Hz, 1H), 7.73 (dd, $^3J = 5.2$ Hz, $^4J = 1.8$ Hz, 1H), 7.47 (ddd, $^3J = 7.5$ Hz, $^3J = 4.8$ Hz, $^4J = 1.1$ Hz, 1H), 2.26 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 160.2$, 156.7, 155.6, 155.0, 150.9, 149.9, 141.3, 137.9, 125.0, 121.0, 119.3, 115.6, 106.5, 9.8 ppm; MS (EI): m/z (%) = 341 (69), 268 (88), 182 (100), 156 (38); UV/VIS (DMSO): $\lambda_{max}(\log \varepsilon) = 250$ (4.0), 359 (4.1) nm; $C_{14}H_{11}N_3OS$ (269.3): calcd: C 62.44, H 4.12, N 15.60, S 11.91; found: C 62.05, H 4.58, N 15.27, S 11.51.

5-Methyl-2-[(2,2′;6′,2″)-terpyridin-4′-yl]-thiazol-4-ol (4k): From **3k** (320 mg, 1.2mmol), mercaptolactic acid (140 mg, 1.3 mmol) and pyridine (0.5 mL). Reaction time 1 h. Yield: 250 mg (0.72 mmol, 58%) slightly yellow crystals, m.p. 248 °C (ethanol); ^{1}H NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 10.71$ (s, 1H, OH), 8.73 (s, 2H, 3′-H/5′-H), 8.71 (m, 2H), 8.59 (d, $^3J = 7.9$ Hz, 2H), 7.99 (ddd, $^3J = 7.8$ Hz, $^3J = 7.7$ Hz, $^4J = 1.6$ Hz, 2H), 7.49 (dd, $^3J = 7.2$ Hz, $^4J = 4.8$ Hz, 2H), 2.29 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6, 250 MHz, 25 °C): $\delta = 160.2$, 156.4, 155.7, 154.8, 149.8, 142.4, 137.9, 125.1, 121.2, 115.6, 106.5, 9.8 ppm. MS (EI): m/z (%) = 346 (32), 259 (100), 230 (6), 78 (20); UV/VIS (DMSO): λ_{max} (log ε) = 248 (3.8), 356 (3.9) nm; $C_{19}H_{14}N_4OS$ (346.1): calcd: C 65.88, H 4.07, N 16.17, S 9.26; found: C 65.77, H 4.00, N 16.01, S 9.05.

General procedure for the synthesis of compounds (5a-k): One mol of the corresponding hydroxythiazole and 1.1 mol of K_2CO_3 were suspended in acetonitrile or DMF at room temperature and stirred. Then 1 mol of bromomethylacetate was added dropwise. After the starting material had been consumed (indicated by TLC), the solvent was evaporated and the crude product purified by column chromatography or recrystallization.

Methyl [(5-methyl-2-pyridin-2-yl-1,3-thiazol-4-yl)oxy]acetate (5a): According to (*10*), from **4b** (5.0 g, 26 mmol) in acetonitrile, chromatography on silica gel with 5:1 toluene:ethyl acetate, yield 5.6 g (81%), yellow crystals, m.p. 79 °C.

Methyl-[(5-methyl-2-pyridin-4-yl-1,3-thiazol-4-yl)oxy]acetate (5b): From **4b** (1.0 g, 5.2 mmol) in acetonitrile, chromatography on silica gel with 1:1 toluene:ethyl acetate. Yield: 0.86 g (62%), yellow crystals, m.p. 93 °C (cyclohexane); ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 8.61$ (d, $J = 4.6$ Hz, 2H), 7.62 (d, $J = 4.6$ Hz, 2H), 4.93 (s, 2H), 3.78 (s, 3H), 2.37 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 169.8$, 159.0, 156.0, 150.4, 140.3, 122.9, 118.9, 109.9, 66.4, 61.4, 9.3 ppm; MS (EI): m/z (%) = 191.1 (10), 59.1 (100), 45 (30); $C_{12}H_{12}N_2O_3S$ (193.2): calcd: C 54.53, H 4.58, N 10.60, S 12.13; found: C 54.48, H 4.69, N 10.57, S 11.97.

Methyl-[(5-methyl-2-pyridin-3-yl-1,3-thiazol-4-yl)oxy]acetate (5c): From **4c** (1.0 g, 5.2 mmol) in acetonitrile, chromatography on silica gel with 1:1 toluene:ethyl acetate. Yield: 0.45 g (33%), yellow crystals, m.p. 76 °C - ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 9.02$ (s, 1H), 8.56 (m, 1H), 8.06 (m, 1H), 7.30 (m, 1H), 4.93 (s, 2H), 3.78, (s, 1H), 2.36 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 169.9$, 158.7, 155.9, 150.0, 146.6, 132.2, 129.6, 123.5, 108.2, 66.4, 52.0, 9.2 ppm; MS (EI): m/z (%) = 264 (70), 191 (100), 105 (60), 73 (80) - $C_{12}H_{12}N_2O_3S$ (193.2): calcd: C 54.53, H 4.58, N 10.60, S 12.13; found: C 54.47, H 4.70, N 10.55, S 12.01.

Methyl-[(5-methyl-2-pyrazin-2-yl-1,3-thiazol-4-yl)oxy]acetate (5d): From **4d** (0.5 g, 2.6 mmol) in acetonitrile, chromatography on silica gel with 1:1 toluene:ethyl acetate. Yield: 0.48 g (71%), yellow crystals, m.p. 122 °C; ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 9.1$ (s, 1H), 8.4 (m, 2H), 4.9 (s, 1H), 3.7 (s, 3H), 2.3 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 169.8$, 159.2, 156.7, 146.7, 144.2, 143.6, 140.7, 111.9, 66.4, 52.0, 9.5 ppm; MS (EI): m/z (%) = 264 (10), 191 (19), 59 (100); $C_{11}H_{11}N_3O_3S$ (265.3): calcd: C 49.80, H 4.18, N 15.84, S 12.09; found: C 49.68, H 4.25, N 15.65, S 11.98.

Methyl-[(5-methyl-2-pyrimidin-2-yl-1,3-thiazol-4-yloxy]acetate (5e): From **4e** (1.0 g, 5.1 mmol), in acetonitrile (20 mL), chromatography on silica gel with 1:2 toluene:ethyl acetate. Yield: 1.0 g (4 mmol, 78%), yellow crystals, m.p. 148 °C; ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 8.77$ (m, 2H), 7.21 (m, 1H), 5.08 (s, 2H), 3.75 (s, 1H), 2.3 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 250 MHz, 25 °C): $\delta = 169.7$, 159.7, 159.3, 157.5, 157.2, 120.0, 114.3, 66.6, 51.9, 9.6 ppm; MS

(EI): m/z (%) = 265 (10), 192 (30), 59 (100); $C_{11}H_{11}N_3O_3S$ (265.3): calcd: C 49.80, H 4.18, N 15.84, S 12.09; found: C 49.72, H 4.12, N 15.75, S 11.95.

Methyl-[5-methyl-2-quinolin-2-yl-1,3-thiazol-4-yl)oxy]-acetate (5f): From **4f** (0.5 g, 2 mmol). Yield: 560 mg (1.8 mmol, 89%), yellow crystals, m.p. 174 °C (chloroform); ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 8.02 (m, 3H), 7.64 (m, 2H), 7.44 (m, 1H), 4.91 (s, 2H), 3.70 (s, 3H), 2.34 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 170.1, 160.1, 158.6, 151.0, 147.7, 136.6, 129.8, 129.2, 128.3, 127.3, 126.7, 117.1, 111,4, 66.5, 52.0, 9.5 ppm; MS (EI): m/z (%) = 314 (5), 155 (50); $C_{16}H_{14}N_2O_3S$ (314.3): calcd: C 61.13, H 4.49, N 8.91, S 10.20; found: C 60.89, H 4.35, N 8.84, S 10.20.

Methyl-{[2-(2,2′-bipyridin-6-yl)-5-methyl-1,3-thiazol-4-yl]oxy}-acetate (5g): From **4g** (0.5 g, 1,8 mmol). Yield: 0.50 g (82%), yellow crystals, m.p. 102 °C (acetonitrile); ^{1}H NMR ($CDCl_3$, 400 MHz, 30 °C): δ = 8.67 (m, 1H), 8.52 (m, 1H), 8.40 (m, 1H), 7.96 (m, 1H), 7.85 (m, 2H), 7.32 (m, 1H), 4.96 (s, 2H), 3.79 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 171.4, 161.4, 159.8, 156.7, 151.8, 150.3, 139.0, 138.2, 125.2, 122.5, 122.2, 119.7, 111.7, 67.7, 53.3, 10.7 ppm; MS (EI): m/z (%) = 341 (20), 268 (30), 192 (100), 154 (20), 59 (60); $C_{17}H_{115}N_3O_3S$ (341.3): calcd: C 59.81, H 4.43, N 12.31, S 9.39; found: C 59.86, H 4.31, N 12.54, S 9.19.

Methyl-{[5-methyl-2-(1,10-phenanthrolin-2-yl)-1,3-thiazol-4-yl]oxy}acetate (5h): From **4g** (1.2 g, 4.4 mmol), reaction time 24 h in acetonitrile. Yield: 0.94 g (58%), yellow crystals, m.p. 174 °C (decomp); ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 9.22 (m, 1H), 8.37 (m, 3H), 7.88 (s, 2H), 7.63 (m, 1H), 5.00 (s, 2H), 3.81 (s, 3H), 2.43 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 169.2, 159.0, 158.0, 150.3, 149.5, 144.8, 136.0, 135.4, 128.2, 128.0, 125.8, 125.5, 122.2, 118.0, 111.1, 65.7, 51.2, 8.8 ppm; MS (EI): m/z (%) = 365 (50), 292 (30), 206 (100), 179 (30), 59 (30); $C_{19}H_{15}N_3O_3S$ (365.40); calcd: C 62.45, H 4.14, N 11.50, S 8.77; found: C 62.17, H 3.92, N 11.27, S 8.77.

Methyl-[2-(2,2′-bipyridin-4-yl)-5-methyl-thiazol-4-yloxy]-acetate (5i): From **4g** (290 mg, 1.1 mmol). Reaction time 24 h in DMF (20 mL), chromatography on silica gel with 9:1 ethyl acetate:methanol. Yield: 230 mg (0.7 mmol, 65%) colorless crystals, m.p. 106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, 30 °C): δ = 8.74 − 8.66 (m, 3H), 8.43 (d, ^3J = 8.0 Hz, 1H), 7.84 (ddd, ^3J = 7.9 Hz, ^3J = 7.8 Hz, ^4J = 1.7 Hz, 1H), 7.72 (dd, ^3J = 5.1 Hz, ^4J = 1.7 Hz, 1H), 7.35 (ddd, ^3J = 7.4 Hz, ^3J = 4.8 Hz, ^4J = 1.0 Hz, 1H), 5.00 (s, 2H CH_2), 3.83 (s, 3H, $COOCH_3$), 2.41 (s, 3H, thiazole-CH_3) ppm; ^{13}C NMR ($CDCl_3$, 400 MHz, 30 °C): δ = 169.9, 159.1, 157.1, 156.5, 155.7, 149.8, 149.2, 141.4, 136.9, 123.9, 121.2, 118.9. 116.6, 110.1, 66.6, 52.0, 9.4 ppm; MS (EI): m/z (%) = 341 (69), 268 (88), 182 (100), 156 (38); $C_{15}H_{17}N_3O_3S$ (341.1): calcd: C 59.81, H 4.43, N 12.31, S 9.39; found: C 59.71, H 4.50, N 12.35, S 9.32.

Methyl-[5-methyl-({2,2′;6′,2″}-terpyridin-4′-yl)-thiazol-4-yloxy]-acetate (5k): From **4k** (140 mg, 0.4 mmol). Reaction time 12 h in DMF (20 mL), chromatography on alumina with 3:2 heptane:ethyl acetate. Yield: 105 mg (0.25 mmol, 62%) colorless solid, m.p. 146 °C; ^{1}H NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 8.82 (s, 2H, 3′-H/5′-H), 8.74 (ddd, ^3J = 4.8 Hz, ^4J = 1.7 Hz, ^5J = 0.8 Hz, 2H), 8.62 (d, ^3J = 8.0 Hz, 2H), 7.87 (ddd, ^3J = 7.8 Hz, ^3J = 7.7 Hz, ^4J = 1.8 Hz, 2H), 7.36 (ddd, ^3J = 7.5 Hz, ^3J = 4.8 Hz, ^4J = 1.0 Hz, 2H), 5.05 (s, 2H, CH_2), 3.86 (s, 3H, $COOCH_3$), 2.42 (s, 3H, thiazole-CH_3) ppm; ^{13}C NMR ($CDCl_3$, 250 MHz, 25 °C): δ = 170.0, 159.0, 156.8, 156.3, 155.8, 149.2, 142.5, 136.8, 123.9, 121.3, 116.5, 110.0, 66.7, 52.0, 9.5 ppm; $C_{22}H_{18}N_4O_3S$ (418.1): calcd: C 63.14, H 4.34, N 13.39, S 7.66; found: C 62.80, H 4.36, N 13.28, S 7.47.

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