Supporting Information
for
Triapine analogues and their copper(II) complexes: synthesis, characterization, solution speciation, redox activity, cytotoxicity and mR2 RNR inhibition

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1. Experimental details

1.1. Synthesis of oxidized thiosemicarbazones

N-(4-hydroxy-3,5-dimethylphenyl)-5-(pyridin-2-yl)-1,3,4-thiadiazol-2-amine

($\mathbf{H}\boldsymbol{L}^{\mathbf{1a'}}\cdot\mathbf{0.25H_2O}$). To a suspension of $\mathbf{HL^{1}\cdot 0.5H_2O}$ (217 mg, 0.70 mmol) in methanol (10 mL) was added dropwise a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 164 mg, 0.72 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature overnight. The yellow-greenish solid was filtered off, washed with methanol and dried in vacuo to give a first portion of material (108 mg). A second portion of the product (21 mg) was obtained from the filtrate by removal of the solvent and purification of the crude product by column chromatography on silica by using ethyl acetate as eluent. Second collected fraction with $R_f = 0.8$ is $\mathbf{H}\boldsymbol{L}^{\mathbf{1a'}}$, while the first minor fraction with $R_f = 0.93$ is $\mathbf{H}\boldsymbol{L}^{\mathbf{1a''}}$. Overall yield of $\mathbf{H}\boldsymbol{L}^{\mathbf{1a'}}\cdot\mathbf{0.25H_2O}$: 129 mg, 60.9%. Anal. Calcd for $C_{15}H_{14}N_4OS\cdot 0.25H_2O$ (M_r = 302.87), %: C, 59.48; H, 4.83; N, 18.50; S, 10.5. Found, %: C, 59.41; H, 4.67; N, 18.35; S, 11.01. Positive ion ESI-MS for $C_{15}H_{14}N_4OS$ (MeCN/MeOH +1% H_2O): *m/z* 299.17 $[\mathrm{H}L^{1a'}+\mathrm{H}]^+$, 321.16 $[\mathrm{H}L^{1a'}+\mathrm{Na}]^+$, negative ion ESI-MS: *m/z* 296.94 $[\mathrm{H}L^{1a'}-\mathrm{H}]^-$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.20 (s, 1H, H_{11}), 8.61 (d, *J* = 4.4 Hz, 1H, H_6), 8.11 (d, *J* = 7.9 Hz, 1H, H_3), 8.08 (s, 1H, H_{18}), 7.95 (td, *J* = 7.7, 1.7 Hz, 1H, H_4), 7.46 (ddd, *J* = 7.5, 4.9, 1.1 Hz, 1H, H_5), 7.16 (s, 2H, H_{13}+H_{17}), 2.17 (s, 6H, H_{19}+H_{20}). ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.77 (C_{10}), 158.40 (C_7), 149.73 (C_6), 149.28 (C_2), 148.97 (C_{15}), 137.52 (C_4), 132.53 (C_{12}), 125.11 (C_{14}+C_{16}), 124.61 (C_5), 119.25 (C_3), 118.67 (C_{13}+C_{17}), 16.87 (C_{19}+C_{20}). IR (ATR, selected bands, $\tilde{\upsilon}_{max}$): 2904.09, 1586.36, 1493.98, 1427.72, 1217.70, 1114.60, 1029.35, 668.90 cm^{-1}. UV–vis (MeOH), λ_{max}, nm (ε, $M^{-1}cm^{-1}$): 261 (17281), 348 (20800). Crystals of $\mathbf{H}\boldsymbol{L}^{\mathbf{1a'}}$·suitable for X-ray diffraction study were obtained upon re-crystallization from methanol.

N-(4-Oxocyclohexa-2,5-dien-1-ylidene)-5-(pyridin-2-yl)-1,3,4-thiadiazol-2-amine

($\mathbf{H}\boldsymbol{L}^{\mathbf{1a''}}\cdot\mathbf{0.5H_2O}$). To a suspension of $\mathbf{HL^{1}\cdot 0.5H_2O}$ (50 mg, 0.16 mmol) in methanol (2.5 mL) was added dropwise a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 75.6 mg, 0.33 mmol) in methanol (2.5 mL). The reaction mixture was stirred at room temperature for 1 h. Then the solvent was removed under reduced pressure and the bright orange product was purified by column chromatography on silica by using a mixture of ethyl acetate and chloroform (1:20) as eluent. The second fraction with $R_f = 0.44$ was collected. Yield: 71.63% (35 mg) as $\mathbf{H}\boldsymbol{L}^{\mathbf{1a''}}\cdot\mathbf{0.5H_2O}$. Anal. Calcd for $C_{15}H_{12}N_4OS\cdot 0.5H_2O$ (M_r = 305.36): C, 59.00; H, 4.29; N, 18.35; S, 10.50 %. Found, %: C, 58.64; H, 3.90; N, 18.02; S, 10.40. Positive ion ESI-MS for $C_{15}H_{12}N_4OS$ (MeCN/MeOH +1% H_2O): *m/z* 297.18 $[\mathrm{H}L^{1a''}+\mathrm{H}]^+$, 319.20 $[\mathrm{H}L^{1a''}+\mathrm{Na}]^+$. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.71 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H, H_6), 8.26 (dt, *J* = 7.9, 1.0 Hz, 1H, H_3), 8.06 (td, *J*

= 7.7, 1.7 Hz, 1H, H_4), 7.60 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H, H_5), 7.46 (dq, *J* = 2.8, 1.3 Hz, 1H, H_{13}), 7.20 (dq, *J* = 2.7, 1.5 Hz, 1H, H_{17}), 2.05 (d, *J* = 1.5 Hz, 3H, H_{20}), 2.00 (d, *J* = 1.5 Hz, 3H, H_{19}). ^{13}C NMR (126 MHz, DMSO-d_6) δ 187.14 (C_{15}), 171.58 (C_{10}), 169.98 (C_7), 162.21 (C_{12}), 150.25 (C_6), 148.19 (C_2), 143.89 (C_{14}), 143.11 (C_{16}), 138.06 (C_4), 136.08 (C_{17}), 126.14 (C_5), 125.96 (C_{13}), 120.04 (C_3), 16.10 (C_{19}), 15.66 (C_{20}). IR (ATR, selected bands, $\tilde{\upsilon}_{max}$): 2961.43, 1641.11, 1541.66, 1323.64, 1211.98, 1008.08, 942.99, 899.83, 778.65 cm^{-1}. UV–vis (MeOH), λ_{max}, nm (ε, M^{-1}cm^{-1}): 302 (36457), 410 sh. Crystals of **H*L*$^{1a''}$** suitable for X-ray diffraction study were obtained from DMSO-d_6.

2-Acetylpyridine (6-hydroxy-5,7-dimethyl-1,3-benzothiazol-2-yl)hydrazone (H*L*$^{2c'}$). A solution of phenyliodine(III) diacetate (PIDA, 205.2 mg, 0.64 mmol) in glacial acetic acid (3 mL) was added dropwise to a cold suspension of **HL^2·0.2H$_2$O** (200 mg, 0.63 mmol) in glacial acetic acid (7 mL). The solution was stirred at room temperature for 1 h. Then the solvent was partially removed under reduced pressure and the concentrated solution was left for crystallization at 4 °C. The light rosa precipitate of **H*L*$^{2c'}$·CH$_3$COOH** was filtered off, washed with cold methanol and dried *in vacuo*. Yield: 142.5 mg, 60.73%. Anal. Calcd for $C_{16}H_{16}N_4OS\cdot CH_3COOH$ (M_r = 372.44): C, 58.05; H, 5.41; N, 15.04; S, 8.61%. Found, %: C, 58.51; H, 5.38; N, 15.41; S, 8.58. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.76 (s, 2H, H_9+N*H*), 8.58 (d, *J* = 5.5 Hz, 1H, H_6), 8.18 (s, 1H, H_{18}), 8.08 (d, *J* = 8.0 Hz, 1H, H_3), 7.85 (td, *J* = 7.7, 1.4 Hz, 1H, H_4), 7.36 (dd, *J* = 6.7, 5.4 Hz, 1H, H_5), 7.02 (s, 1H, H_{13}), 2.40 (s, 3H, $H_{7'}$), 2.28 (s, 3H, H_{20}), 2.22 (s, 3H, H_{19}), 1.91 (s, 3H, C*H*$_3$COOH). ^{13}C NMR (151 MHz, DMSO-d_6) δ 172.00 (*C*=O, CH$_3$*C*OOH), 166.47 (C_{10}), 155.22 (C_2), 153.88 (C_{12}), 149.29 (C_7), 148.57 (C_6), 148.14 (C_{15}), 136.43 (C_4), 126.88 (C_{17}), 124.07 (C_{14} or C_{16}), 123.35 (C_5), 119.65 (C_3), 117.44 (C_{14} or C_{16}), 115.78 (C_{13}), 21.04 (*C*H$_3$, *C*H$_3$COOH), 17.08 (C_{19}), 15.47 (C_{20}), 12.55 ($C_{7'}$). ^{15}N NMR (61 MHz, DMSO-d_6) δ 337.75 (N_8), 309.86 (N_1). IR of (ATR, selected bands, $\tilde{\upsilon}_{max}$): 2322.13, 1571.13, 1426.14, 1201.77, 1038.02, 1013.17, 781.99, 643.45 cm^{-1}. UV–vis (MeOH), λ_{max}, nm (ε, M^{-1}cm^{-1}): 255 sh, 345 (18303), 465 sh. Then **H*L*$^{2c'}$·CH$_3$COOH** (120 mg, 0.32 mmol) was dissolved in water (10 mL) and pH was adjusted to 7-8 with a saturated solution of NaHCO$_3$. The crude **H*L*$^{2c'}$** was extracted with ethyl acetate (4 × 30 mL). Evaporation of ethyl acetate to ¼ of original volume afforded the first portion of *E*-isomer, which was isolated by filtration and drying in air (53 mg of beige powder). The filtrate was concentrated and purified chromatographically on silica by using EtOAc as eluent. A second portion of the *E*-isomer of **H*L*$^{2c'}$** (10 mg) was obtained by collecting the third fraction (fr$_3$, Rf = 0.63). Overall yield of *E*- **H*L*$^{2c'}$**: (63 mg, 63%) as **H*L*$^{2c'}$**. Second fraction (fr$_2$, R_f = 0.77) was collected as an orange powder and identified as the *Z*-isomer of **H*L*$^{2c'}$**. Yield: 10 mg, 10.0%. The first red fraction (fr$_1$, R_f = 0.92) was identified as **H$L^{2c''}$**. Anal. Calcd for $C_{16}H_{16}N_4OS$ (*E*-isomer, M_r = 312.39): C, 61.52; H, 5.16; N, 17.93; S, 10.26%. Found, %: C, 61.49; H, 5.21; N, 17.55; S, 10.01. Positive ion ESI-MS for $C_{16}H_{16}N_4OS$, *E*/*Z*-isomers of **H$L^{2c'}$** (MeCN/MeOH +1% H_2O): *m*/*z* 313.21 $[HL^{2c'}+H]^+$, negative ion ESI-MS: *m*/*z* 310.98 $[HL^{2c'}–H]^–$. ^1H NMR (500 MHz, DMSO-d_6, *E*-isomer) δ 11.58 (s, 1H, H_9), 8.58 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H, H_6), 8.20 (s, 1H, H_{18}), 8.07 (d, *J* = 8.1 Hz, 1H, H_3), 7.85 (td, *J* = 7.8, 1.7 Hz, 1H, H_4), 7.36 (ddd, *J* = 7.4, 4.9, 1.0 Hz, 1H, H_5), 7.02 (brs, 1H, H_{13}), 2.40 (s, 3H, $H_{7'}$), 2.28 (s, 3H, H_{20}), 2.22 (s, 3H, H_{19}). ^{13}C NMR (151 MHz, DMSO-d_6, *E*-izomer) δ 155.15 (C_2), 148.57 (C_6), 148.15 (C_{15}), 136.44 (C_4), 124.07 (C_{14} or C_{16}), 123.35 (C_5), 119.65 (C_3), 117.80 (C_{14} or C_{16}), 17.09 (C_{19}), 15.54 (C_{20}), 12.56 ($C_{7'}$). ^1H NMR (500 MHz, DMSO-d_6, *Z*-isomer) δ 15.00 (s, 1H, H_9), 8.85 (d, *J* = 3.5 Hz, 1H, H_6), 8.22 (s, 1H, H_{18}), 8.08 (t, *J* = 7.3 Hz, 1H, H_4), 7.79 (d, *J* = 7.7 Hz, 1H, H_3), 7.58 (m, 1H, H_5), 7.15 (s, 1H, H_{13}), 2.40 (s, 3H, $H_{7'}$), 2.31 (s, 3H, H_{20}), 2.22 (s, 3H, H_{19}). ^{13}C NMR (151 MHz, DMSO-d_6, *Z*-izomer) δ 152.61 (C_2), 148.39 (C_{15}), 147.63 (C_6), 138.29 (C_4), 124.26 (C_5), 124.08 (C_3), 118.98 (C_{13}), 117.67 (C_{14} or C_{16}), 21.72 ($C_{7'}$), 17.20 (C_{19}), 15.87 (C_{20}). IR (*E*-isomer, ATR, selected bands, $\tilde{\upsilon}_{max}$): 3309.21, 1565.44, 1462.63, 1428.84, 1213.07, 1149.94, 1103.32, 1016.42 cm^{-1}. IR (*Z*-isomer, ATR, selected bands, $\tilde{\upsilon}_{max}$): 2921.95, 2854.29, 2322.04, 1727.80, 1541.22, 1463.34, 1063.33, 832.32, 648.31 cm^{-1}. UV–vis (*E*-isomer, MeOH, λ_{max}, nm (ε, $M^{-1}cm^{-1}$)): 256 (16778), 346 (23875), 464 sh. UV–vis (*Z*-isomer, MeOH, λ_{max}, nm (ε, $M^{-1}cm^{-1}$)): 266 (3638), 367 (4387), 474 sh.

5,7-Dimethyl-2-{[1-(pyridin-2-yl)ethylidene]hydrazineylidene}benzo[*d*]thiazol-6(2*H*)-one (H$L^{2c''}$). A solution of phenyliodine(III) diacetate (PIDA, 103 mg, 0.32 mmol) in glacial acetic acid (4 mL) was added to a suspension of **HL^2·$0.2H_2O$** (50 mg, 0.16 mmol) in glacial acetic acid (1 mL). The solution was stirred at room temperature for 1.5 h. Then the solvent was partially removed under reduced pressure and the concentrated solution was left for crystallization at 4 °C. The red precipitate of **H$L^{2c''}$** was filtered off and washed with cold methanol. The collected precipitate was recrystallized from chloroform and afterwards dried *in vacuo*. Yield: 31 mg, 48.4%. Anal. Calcd for $C_{16}H_{14}N_4OS·0.75CHCl_3$ (M_r = 399.91): C, 50.31; H, 3.72; N, 14.01; S, 8.02%. Found, %: C, 50.32; H, 3.67; N, 14.24; S, 8.43. Positive ion ESI-MS for $C_{16}H_{14}N_4OS$ (MeCN/MeOH +1% H_2O): *m*/*z* 311.12 $[HL^{2c''}+H]^+$, 333.11 $[HL^{2c''}+Na]^+$, 643.14 $[2HL^{2c''}+Na]^+$, negative ion ESI-MS: *m*/*z* 309.01 $[HL^{2c''}–H]^–$. ^1H NMR (500 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.25 (d, *J* = 5.7 Hz, 1H), 8.06 – 7.91 (m, 1H), 7.65 (s, 1H), 7.57 (s, 1H), 2.61 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H). ^1H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.3 Hz, 1H, H_6), 8.34 (d, *J* = 8.0 Hz, 1H, H_3), 7.80 (td, *J* = 7.8, 1.3 Hz, 1H, H_4), 7.44 (brs, 1H, H_{13}), 7.38 (dd, *J* = 6.7, 5.2 Hz, 1H, H_5), 2.72 (s, 3H, $H_{7'}$), 2.18 (s, 3H, H_{19}), 2.14 (s, 3H, H_{20}). ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.43 (C_{15}), 173.74

(C$_{10}$), 169.74 (C$_{12}$), 169.42 (C$_7$), 154.97 (C$_2$), 149.29 (C$_6$), 145.86 (C$_{14}$ or C$_{16}$), 145.41 (C$_{14}$ or C$_{16}$), 136.46 (C$_4$), 129.52 (C$_{13}$), 129.25 (C$_{17}$), 125.34 (C$_5$), 122.31 (C$_3$), 17.38 (C$_{19}$), 15.54 (C$_{20}$), 14.88 (C$_{7'}$). IR (ATR, selected bands, $\tilde{\upsilon}_{max}$): 2918.15, 1616.23, 1584.52, 1464.22, 1362.22, 1245.16, 1157.17, 907.55, 780.68, 744.00, 687.98 cm^{-1}. UV–vis (MeOH), λ_{max}, nm (ε, M^{-1}cm^{-1}): 290 (8232), 391 (12367), 480 (8985). Crystals of **H$L^{2c''}$·0.5CHCl$_3$** suitable for X-ray diffraction study were obtained from chloroform solution.

4-(4-Hydroxy-3,5-dimethylphenyl)-5-methyl-5-(pyridin-2-yl)-4,5-dihydro-3H-1,2,4-triazole-3-thione (**HL^{2b}**) and **2-acetylpyridine {5-hydroxy-3-[(4-hydroxy-3,5-dimethylphenyl)amino]-4,6-dimethyl-1*H*-indol-2-yl}hydrazone** (**HL^{2e}**). A solution of *p*-benzoquinone (PBQ, 27 mg, 0.25 mmol) in methanol (1 mL) was added to suspension of **HL^2·0.2H$_2$O** (80 mg, 0.25 mmol) in methanol (8 mL). The reaction mixture was heated at 60 °C overnight. The methanol was removed by evaporation, the residue was chromatographed, using as eluent, mixture of ethyl acetate, hexane and methanol (2:6:1) to obtain the oxidation products **HL^{2b}** (R_f = 0.69) and **HL^{2e}** (R_f = 0.57) in small amounts. Positive ion ESI-MS for $C_{16}H_{16}N_4OS$ (**HL^{2b}**) (MeCN/MeOH +1% H_2O): *m/z* 313.25 [HL^{2b}+H]$^+$, 335.14 [HL^{2b}+Na]$^+$, negative ion ESI-MS: *m/z* 310.99 [HL^{2b}–H]$^-$. ^{1}H NMR (**HL^{2b}**, 500 MHz, DMSO-*d$_6$*) δ 8.67 (s, 1H, O*H*), 8.65 (ddd, *J* = 4.7, 1.7, 0.8 Hz, 1H, *H*py), 7.94 (td, *J* = 7.8, 1.8 Hz, 1H, *H*py), 7.59 (d, *J* = 8.0 Hz, 1H, *H*py), 7.51 (ddd, *J* = 7.6, 4.7, 0.9 Hz, 1H, *H*py), 6.39 (s, 2H, *H*ph), 2.06 (s, 3H, C*H*$_3$), 2.01 (s, 6H, 2C*H*$_3$). UV–vis (**HL^{2b},** MeOH), λ_{max}, nm (ε, M^{-1}cm^{-1}): 261 sh, 296 (5339), 346 (4985). Crystals suitable for X-ray diffraction study were obtained from ethanol (**HL^{2b}**) or methanol (**HL^{2e}**) solutions.

1.2. Synthesis of copper(II) complexes with oxidized ligands

[Cu(HL^{1d})$_2$Cl$_2$] (5). CuCl$_2$·2H$_2$O (23 mg, 0.13 mmol) was added to **H$L^{1a''}$·0.5H$_2$O** (40 mg, 0.13 mmol) in methanol (25 mL) and stirred at 80 °C for 72 h. The reaction mixture was allowed to stand at 4 °C overnight. The bright green precipitate was filtered off, washed with methanol and dried *in vacuo*. Yield: 19.5 mg. Positive ion ESI-MS for $C_{14}H_{12}N_8S_2CuCl_2$ (MeCN/MeOH+1% H$_2$O): *m/z* 209.50 [Cu(HL^{1d})$_2$]$^{2+}$, 419.03 [Cu^I(HL^{1d})$_2$]$^+$, 453.93 [Cu(HL^{1d})$_2$Cl]$^+$, 459.05 [Cu(HL^{1d})$_2$$^{2+}$+MeCN–H]$^+$. IR (ATR, selected bands, $\tilde{\upsilon}_{max}$): 3226.02, 3087.67, 2322.41, 1608.77, 1513.30, 1420.89, 1351.58, 1317.22, 1150.55, 782.01, 720.75 cm^{-1}. UV–vis (MeOH), λ_{max}, nm (ε, M^{-1}cm^{-1}): 249 (15476), 281 sh, 343 (13271). Crystals of **[Cu(HL^{1d})$_2$Cl$_2$]** suitable for X-ray diffraction study were grown from methanolic solution of **5**.

[Cu(H$L^{2c'}$)Cl$_2$] (6). CuCl$_2$·2H$_2$O (11 mg, 0.06 mmol) was added in one portion under argon to solution of **H$L^{2c'}$** (20 mg, 0.06 mmol) in anoxic methanol (5 mL) and stirred at room temperature for 1 h. The reaction mixture was allowed to stand at +4 °C overnight. The brown-reddish precipitate was filtered off, washed with anoxic methanol and dried *in vacuo*. Yield: 19 mg. Positive ion ESI-MS for $C_{16}H_{16}N_4OSCuCl_2$ (MeCN/MeOH+1% H_2O): *m/z* 374.08 $[Cu(HL^{2c\prime})^{2+}{-}H]^+$, 410.05 $[Cu(HL^{2c\prime})Cl]^+$, 820.95 $[2Cu(L^{2c\prime})Cl+H]^+$, negative ion ESI-MS: *m/z* 407.93 $[Cu(HL^{2c\prime})Cl^+{-}2H]^-$, 854.75 $[2Cu(L^{2c\prime})+3Cl]^-$. IR (ATR, selected bands, $\tilde{\upsilon}_{max}$): 2322.16, 1637.16, 1595.67, 1528.72, 1464.37, 1418.27, 1227.93, 1178.21, 1097.33, 1010.12, 896.16 cm^{-1}. UV–vis (MeOH), λ_{max}, nm (ε, $M^{-1}cm^{-1}$): 288 sh, 335 sh, 402 sh, 473 (5181). Crystals of **$[Cu(HL^{2c\prime})Cl_2]$** suitable for X-ray diffraction study were grown by slow diffusion of diethyl ether in methanol solution of **6**.

2. Characterization of the compounds

2.1. Physical measurements

Elemental analyses were carried out in a Carlo-Erba microanalyzer at the Microanalytical Laboratory of the University of Vienna. Electrospray ionization mass spectrometry (ESI-MS) was carried out with amaZon speed ETD Bruker instrument. Expected and experimental isotope distributions were compared. UV–vis spectra were measured on Perkin Elmer UV–vis spectrophotometer Lambda 35 in the 240 to 700 nm window using samples dissolved in methanol. IR spectra were recorded on a Bucker Vertex 70 Fourier transform IR spectrometer (4000–600 cm^{-1}) using the ATR technique. 1D (^{1}H, ^{13}C) and 2D (^{1}H-^{1}H COSY, ^{1}H-^{1}H TOCSY, ^{1}H-^{1}H NOESY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, ^{1}H-^{15}N HSQC, ^{1}H-^{15}N HMBC) NMR spectra were acquired on a Bruker AV NEO 500 or AV III 600 spectrometers in DMSO-d_6, MeOH-d_4, $CDCl_3$ at 25 °C.

2.2. Crystallographic Structure Determination

X-ray diffraction measurements were performed on either Bruker X8 APEX-II CCD or Bruker D8 Venture diffractometer. Single crystals were positioned at 30, 40, 27, 27, 26, 27, 26, 26, 26, 30, 30, 27, 30 and 26 mm from the detector, and 897, 158, 2225, 500, 1499, 2477, 884, 1279, 2395, 360, 360, 1081, 1959 and 1000 frames were measured, each for 2, 10, 10, 40, 20, 1, 15, 5, 4, 3, 10, 50, 10 and 2 s over 0.6, 1, 0.5, –0.360, 0.360, 0.360, –0.360, 0.360, 0.360, 0.5, 0.5, 0.5, 0.360 and –0.360° scan width for **$HL^1\cdot C_2H_5OH$**, **HL^2**, **HL^3**, **$HL^{1a\prime}$**, **$HL^{1a\prime\prime}$**, **ATSC´**, **HL^{2b}**, **$HL^{2c\prime\prime}\cdot 0.5CHCl_3$**, **$HL^{2e}$**, **$1^\prime\cdot CH_3OH$**, **$3^\prime\cdot CH_3OH$**, **4–6**, respectively. Compound **2´** was measured at the XRD2 structural biology beamline, Elettra synchrotron. The beamline is equipped with an Arinax MD2S diffractometer and a Pilatus 6M area detector and monochromated X-rays are provided by a superconducting wiggler followed by a dual crystal monochromator. Frame integration was performed using the XDS package.[1] Crystal data, data collection parameters, and structure refinement details are given in Tables S1–S3 in Supporting Information. The structures were solved by direct methods and refined by full-matrix least-squares techniques. Non-H atoms were refined with anisotropic displacement parameters. H atoms were inserted in calculated positions and refined with a riding model. The following computer programs and hardware were used: structure solution, *SHELXS-2014* and refinement, *SHELXL-2014*;[2] molecular diagrams, *ORTEP*; computer, Intel CoreDuo. CCDC 2074027 ($\mathbf{HL^{1}\cdot C_2H_5OH}$), 2074029 ($\mathbf{HL^{2}}$), 2074028 ($\mathbf{HL^{3}}$), 2074023 ($\mathbf{H}\boldsymbol{L}^{\mathbf{1a'}}$), 2074017 ($\mathbf{H}\boldsymbol{L}^{\mathbf{1a''}}$), 2074018 (**ATSC´**), 2074019 ($\mathbf{H}\boldsymbol{L}^{\mathbf{2b}}$), 2074341 ($\mathbf{HL^{2c''}\cdot 0.5CHCl_3}$) 2074025 ($\mathbf{H}\boldsymbol{L}^{\mathbf{2e}}$), 2074020 ($\mathbf{1'\cdot CH_3OH}$), 2074022 (**2´**), 2074021 ($\mathbf{3'\cdot CH_3OH}$), 2074030 **(4**), 2074026 (**5**) and 2074024 (**6**).

2.3. Spectroscopic studies: UV–vis titrations, kinetic measurements and lipophilicity determination

An Agilent Carry 8454 diode array spectrophotometer was used to record the UV–vis spectra in the interval 200–800 nm. The path length was 1 cm. Proton dissociation constants (pK_a) of the proligands were calculated by the computer program PSEQUAD.[3] Spectrophotometric titrations were performed on samples containing the proligands at 50-100 µM concentration by a KOH solution in the presence of 0.1 M KCl at 25.0 ± 0.1 ^oC in the pH range from 1 to 12.5 in 30% (v/v) DMSO/H_2O solvent mixture. An Orion 710A pH-meter equipped with a Metrohm combined electrode (type 6.0234.100) and a Metrohm 665 Dosimat burette were used for the titrations. The electrode system was calibrated to the $pH = -\log[H^+]$ scale by means of blank titrations (HCl vs KOH) according to the method suggested by Irving *et al.*[4] The average water ionization constant (pK_w) is 14.54 ± 0.05 in 30% (v/v) DMSO/H_2O, which corresponds well to literature data.[5] Argon was also passed over the solutions during the titrations. Measurements were carried out in the range *ca*. 1.0–2.0 by preparing individual samples in which KCl was partially or completely replaced by HCl and pH values were calculated from the strong acid content. The conditional stability constants (K') of the copper(II) complexes were calculated at pH 5.90 based on the spectral changes via the displacement reaction with EDTA in the presence 50 mM MES and 0.1 M KCl in 30% (v/v) DMSO/H_2O. In the competition experiments the samples contained 25 µM copper(II), 25 µM proligand and the concentration of EDTA was varied in the range from 0 to 150 µM. The conditional stability constants of the metal complexes (K') and the individual spectra of the species were calculated by the computer program PSEQUAD.[3]

The time-dependence of UV–vis absorption spectra was monitored for proligands **HL^2** at pH 7.4, 1.5 and 10.0 in 30% (v/v) DMSO/H_2O, and for **HL^1** and **HL^3** at pH 7.4.

The redox reaction of the copper(II) complexes (25 µM) with GSH (1250 µM) was studied at 7.40 (50 mM HEPES buffer with 0.1 M KCl) and at 25.0 ± 0.1 °C on Hewlett Packard 8452A diode array spectrophotometer using a special, tightly closed tandem cuvette (Hellma Tandem Cell, 238-QS) as described previously.[6,7] Calculation of the observed rate constants (k_{obs}) of the redox reaction was performed by using a reported approach.[6,7]

Distribution coefficients ($D_{7.4}$) values were determined by the traditional shake-flask method in *n*-octanol/buffered aqueous solution at pH 7.40 (50 mM HEPES buffer at 25.0 ± 0.2 °C as described previously in our previous work.[8]

2.4. Spectroelectrochemical studies

Cyclic voltammetry experiments with 0.5 mM solutions of Cu(II) complexes and corresponding ligands in 0.1 M *n*-Bu_4NPF_6 in both DMSO and methanol were performed under argon atmosphere using a three-electrode arrangement with glassy carbon 1 mm disc working electrode (from Ionode, Australia), platinum wire as counter electrode, and silver wire as pseudo-reference electrode. As a supporting electrolyte, 0.1 M *n*-Bu_4NPF_6 was used in DMSO (SeccoSolv max. 0.025% H_2O, Merck) and 0.1 M $LiClO_4$ (≥95.0%, Merck) in methanol. Ferrocene (Fc, from Sigma-Aldrich) served as the internal potential standard. The potentials vs Fc^+/Fc in DMSO solutions were recalculated to the corresponding values vs NHE using known value of $E_{1/2}(Fc^+/Fc) = +0.435$ V vs SCE in DMSO[9] (the potential of Saturated Calomel Electrode (SCE) is +0.241 V vs NHE). A Heka PG310USB (Lambrecht, Germany) potentiostat with a PotMaster 2.73 software package served for the potential control in voltammetry studies. In situ UV-visible-near infrared (UV–vis–NIR) spectroelectrochemical measurements were performed on a spectrometer Avantes (Model AvaSpec-2048x14-USB2) in the spectroelectrochemical cell kit (AKSTCKIT3) with the Pt-microstructured honeycomb working electrode (Pine Research Instrumentation). The cell was positioned in the CUV–UV Cuvette Holder (Ocean Optics) connected to the diode-array UV–vis–NIR spectrometer by optical fibres. UV–vis–NIR spectra were processed using the AvaSoft 7.7 software package. Halogen and deuterium lamps were used as light sources (Avantes, Model AvaLight-DH-S-BAL). The *in situ* EPR spectroelectrochemical experiments were carried out under argon atmosphere in the EPR flat cell equipped with a large platinum mesh working electrode. The freshly prepared solutions were carefully purged with argon and the electrolytic cell was polarised in the galvanostatic mode directly in the cylindrical EPR cavity TM-110 (ER 4103

TM) and the EPR spectra were measured *in situ*. The EPR spectra were recorded at room temperature with the EMX Bruker spectrometer (Germany).

2.5. *In vitro* cell studies

2.5.1. Cell lines and culture conditions

All cell culture reagents were obtained from Sigma-Aldrich and plastic ware from Sarstedt (Germany). Doxorubicin-sensitive human colonic Colo 205 and multidrug resistant Colo 320/MDR-LRP adenocarcinoma cell lines were purchased from LGC Promochem, Teddington, UK. The cells were cultured in Roswell Park Memorial Institute (RPMI) 1640 medium supplemented with 10% heat-inactivated fetal bovine serum, 2 mM L-glutamine, 1 mM Na-pyruvate and 100 mM Hepes. The cell lines were incubated at 37°C, in a 5% CO_2, 95% air atmosphere.

MRC-5 human embryonal lung fibroblast cell line (ATCC CCL-171) was purchased from LGC Promochem, Teddington, UK. The cell line was cultured in Eagle's Minimal Essential Medium (EMEM, containing 4.5 g/L glucose) supplemented with a non-essential amino acid mixture, a selection of vitamins and 10% heat-inactivated fetal bovine serum. The cells were incubated at 37°C, in a 5% CO_2, 95% air atmosphere. All cell lines were detached with Trypsin-Versene (EDTA) solution for 5 min at 37 °C.

2.5.2. MTT assays

The tested compounds were dissolved in DMSO using 10 mM concentration. Then stock solutions were diluted in complete culture medium in 96-well microtiter plates, and two-fold serial dilutions of compounds were prepared in 100 µL of RPMI 1640, horizontally. The semi-adherent colonic adenocarcinoma cells were treated with Trypsin-Versene (EDTA) solution. They were adjusted to a density of 1×10^4 cells in 100 µL of RPMI 1640 medium, and were added to each well, with the exception of the medium control wells. The final volume of the wells containing compounds and cells was 200 µL. The culture were incubated at 37 °C for 72 h; at the end of the incubation period, 20 µL of MTT solution (from a stock solution of 5 mg/mL) were added to each well. After incubation at 37 °C for 4 h, 100 µL of SDS solution (10% in 0.01 M HCI) were added to each well and the plates were further incubated at 37 °C overnight. The cell growth was determined using both methods by measuring the optical density (OD) at 450 nm (ref. 620 nm) with a Multiscan EX ELISA reader. Inhibition of the cell growth (expressed as IC_{50}: inhibitory concentration that reduces by 50% the growth of the cells exposed to the tested compounds) was determined from the sigmoid curve where 100 – $((OD_{sample} - OD_{medium\ control})/(OD_{cell\ control} - OD_{medium\ control})) \times 100$ values were plotted against the logarithm of compound concentrations. Curves were fitted by GraphPad Prism software[10] using the sigmoidal dose-response model (comparing variable and fixed slopes).

2.5.3. Mechanisms of cell death: assay for apoptosis induction

The assay was carried out for selected compounds using an Annexin V-FITC Apoptosis Detection Kit (Cat. No. APOAF-50TST) from Sigma according to the manufacturer's instructions. The concentration of the Colo320 cell suspension was adjusted to approximately 0.5×10^6 cells per mL in RPMI medium and the cell suspension was distributed in 1 mL aliquots into a 24-well plate, and then incubated overnight at 37 °C and 5% CO_2. On the following day, the medium was removed and replaced by 1 mL RPMI medium containing the compounds except the control samples. Colo320 cells were incubated in the presence of the compounds at 4 and 8 µM (**HL^1**), or 0.25 and 0.50 µM (**$Cu(HL^2)Cl_2$**) in the 24-well plate at 37 °C for 3 h, and 12*H*-benzo[α]phenothiazine (M627, 20 µM)[11] and cisplatin (Teva, 15 and 30 µM) were used as positive controls. After the incubation period the samples were washed with PBS and fresh RPMI medium was added to the samples. The cells were incubated overnight at 37 °C and 5% CO_2. The next day, 200 µL 0.25% Trypsin (Trypsin-Versen) was added to the samples until cells appeared detached followed by the addition of 400 µL of RPMI medium supplemented with 10% bovine serum. The cells were collected in Eppendorf tubes and centrifuged at 2000 *g* for 2 min. The harvested cells were resuspended in fresh serum free RPMI medium culture medium. After this step, the apoptosis assay was carried out according to the instructions of the manufacturer. The fluorescence was analyzed immediately using a ParTec CyFlow flow cytometer (Partec GmbH, Münster, Germany).

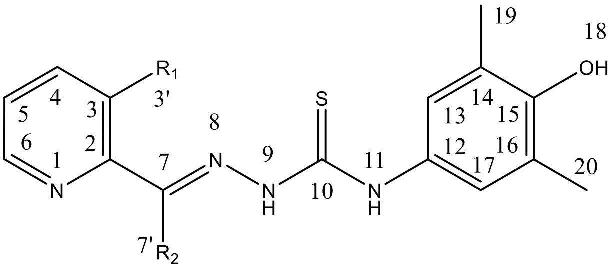
2.6. Tyrosyl radical reduction in mouse R2 RNR protein

The tyrosyl radical reduction in mR2 protein by **HL^1**, **HL^2**, **HL^3**, **$Cu(HL^1)Cl_2$**, **$[Cu(L^2)Cl]$**, **$Cu(HL^3)Cl_2$**, **$HL^{1a'}$**, **$HL^{1a''}$**, and **$HL^{2c'}\cdot CH_3COOH$** was measured by EPR spectroscopy at 30 K, on a Bruker Elexsys II E540 EPR spectrometer with an Oxford Instruments ER 4112HV helium cryostat, as described previously.[12,13] mR2 protein was expressed, purified, and iron-reconstituted as described previously,[14] and passed through a 5 mL HiTrap desalting column (GE Healthcare) to remove excess iron. The purified, iron-reconstituted mR2 protein resulted in the formation of 0.76 tyrosyl radical/polypeptide. Samples containing 20 µM mR2 in 50 mM HEPES buffer, pH 7.50/100 mM NaCl, and 20 µM respective compound in 1% (v/v) DMSO/H_2O, and 2 mM dithiothreitol (DTT) were incubated for indicated times and quickly frozen in cold isopentane. The same samples were used for repeated incubations at room temperature. The experiments were performed in duplicates.

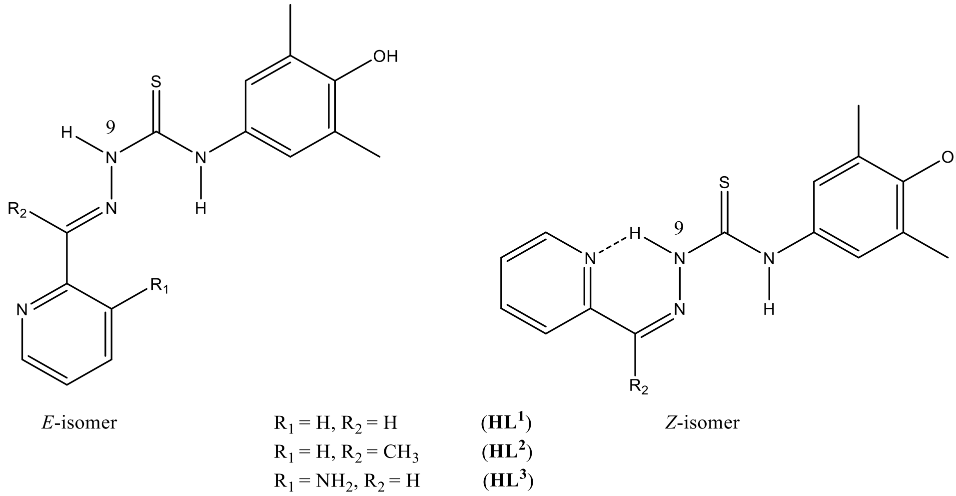
2.7. Computational details

The geometry optimizations of all key stationary points were carried out at the B3LYP level of theory[15] using Gaussian 16 suite[16] of quantum chemical programs. Pople's basis sets, 6-311++G(d,p) from Gaussian library[16] for all atoms were employed for geometry optimization. The effect of continuum solvation was incorporated by using the polarizable continuum model (PCM). Stability of the optimized structures was tested by vibrational analysis (no imaginary vibrations). Enthalpies and Gibbs free energies were obtained by adding unscaled zero-point vibrational energy corrections (ZPVE) and thermal contributions to the energies (temperature 298.150 Kelvin, pressure 1.000 atm). All transition states were fully optimized and characterized as a first-order saddle point by harmonic vibrational frequency analysis. One and only one imaginary frequency of the first-order saddle point was subjected to visual inspection to examine whether it represented the desired reaction coordinate. Furthermore, the intrinsic reaction coordinate (IRC) analysis was performed to authenticate that the transition state pertains to the desired reaction coordinate. The IRC calculations were done at the B3LYP/6-311++G(d,p) level of theory. Molecular orbitals were drawn using Molekel software.[17]

3. Schemes for assignment of resonances in HL^1 – HL^3 and their isomers

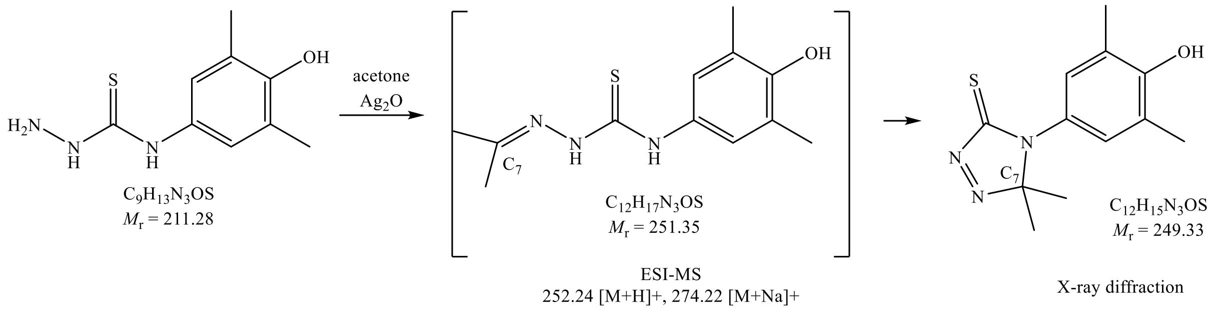


Scheme S1. The atom numbering for the assignment of resonances in **HL^1** – **HL^3**.



Scheme S2. The most stable conformers of **HL**$^{\mathbf{1}}$ – **HL**$^{\mathbf{3}}$ in solution.

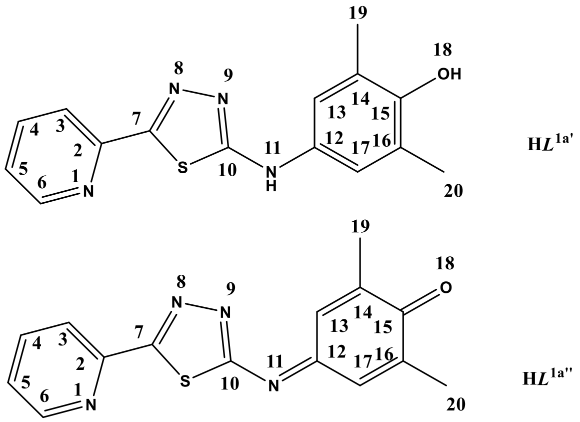
4. Oxidative cyclization in the presence of Ag_2O



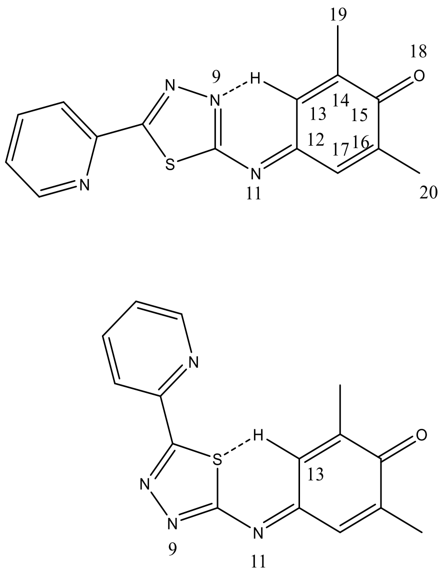
Scheme S3. The formation of acetone thiosemicarbazone in solution and its oxidative cyclization in the presence of Ag_2O.

Oxidation of **HL**$^{\mathbf{1}}$ with Ag_2O (at the molar ratio **HL**$^{\mathbf{1}}$/Ag_2O 1:1 at room temperature in acetone for 1–2 h) afforded minor amounts of 1,3,4-thiadiazoles **H*L***$^{\mathbf{1a'}}$ and **H*L***$^{\mathbf{1a''}}$. The reaction mainly led to complex formation of **HL**$^{\mathbf{1}}$ with Ag(I) (70–90%). This was confirmed by ESI mass spectra, in which peaks at *m*/*z* 407.15, 709.20 attributed to $[Ag(HL^1)]^+$ and $[Ag(HL^1)_2]^+$, respectively, as well as at *m*/*z* 402.73, 706.98 assigned to $[Ag(HL^{1a'})–2H]^–$, $[Ag(HL^1)_2–2H]^–$ were found. By applying the same reaction conditions (Ag_2O in acetone) to the starting thiosemicarbazide, *N*-(4-hydroxy-3,5-dimethylphenyl)hydrazinecarbothioamide (Scheme S3 in Supporting Information), the 1,2,4-triazole-3-thione ring formation as reported previously for **H*L***$^{\mathbf{2b}}$ was confirmed by SC-XRD (Figure S2), along with coordination of the oxidized product to Ag(I) by ESI-MS.

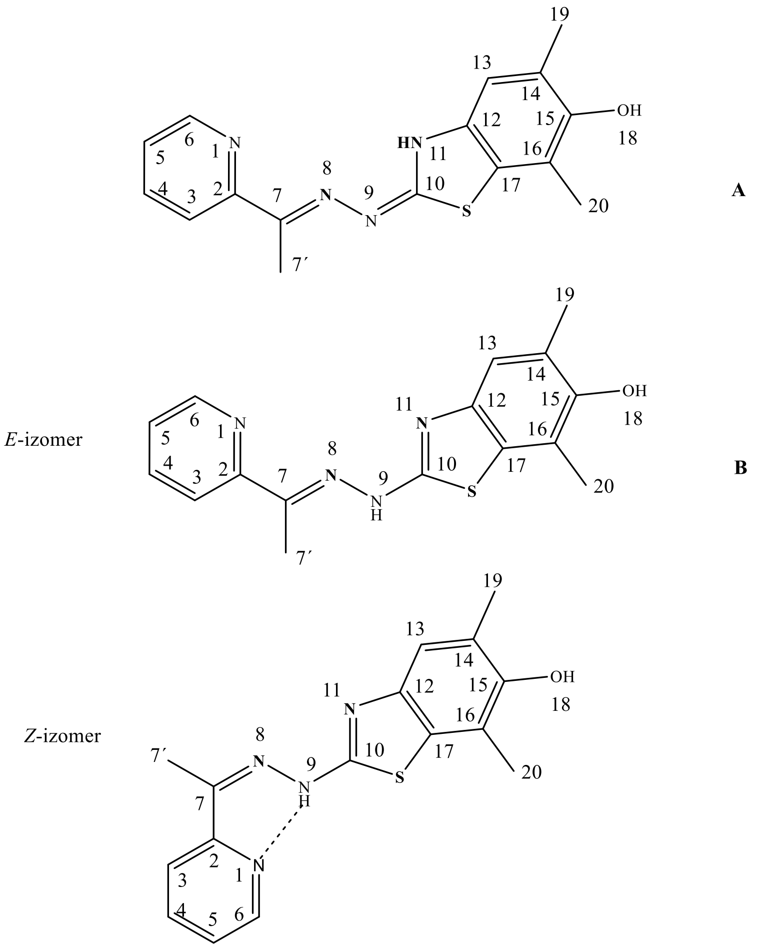
5. Schemes for assignment of resonances in H$L^{1a'}$, H$L^{1a''}$, H$L^{2c'}$, H$L^{2c''}$ and their isomers



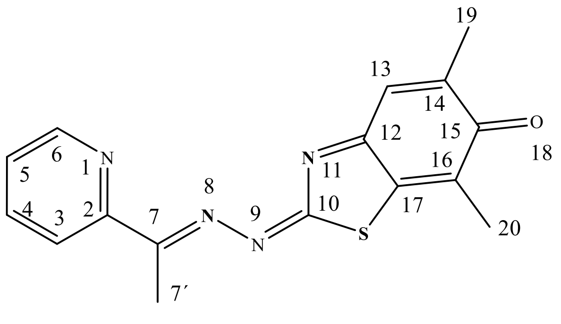
Scheme S4. The atom numbering for the assignment of resonances in **H$L^{1a'}$** and **H$L^{1a''}$**.



Scheme S5. The possible hydrogen bond formations of H_{13} to *N*- or *S*- of 1,3,4-thiadiazole ring in **H$L^{1a''}$**.

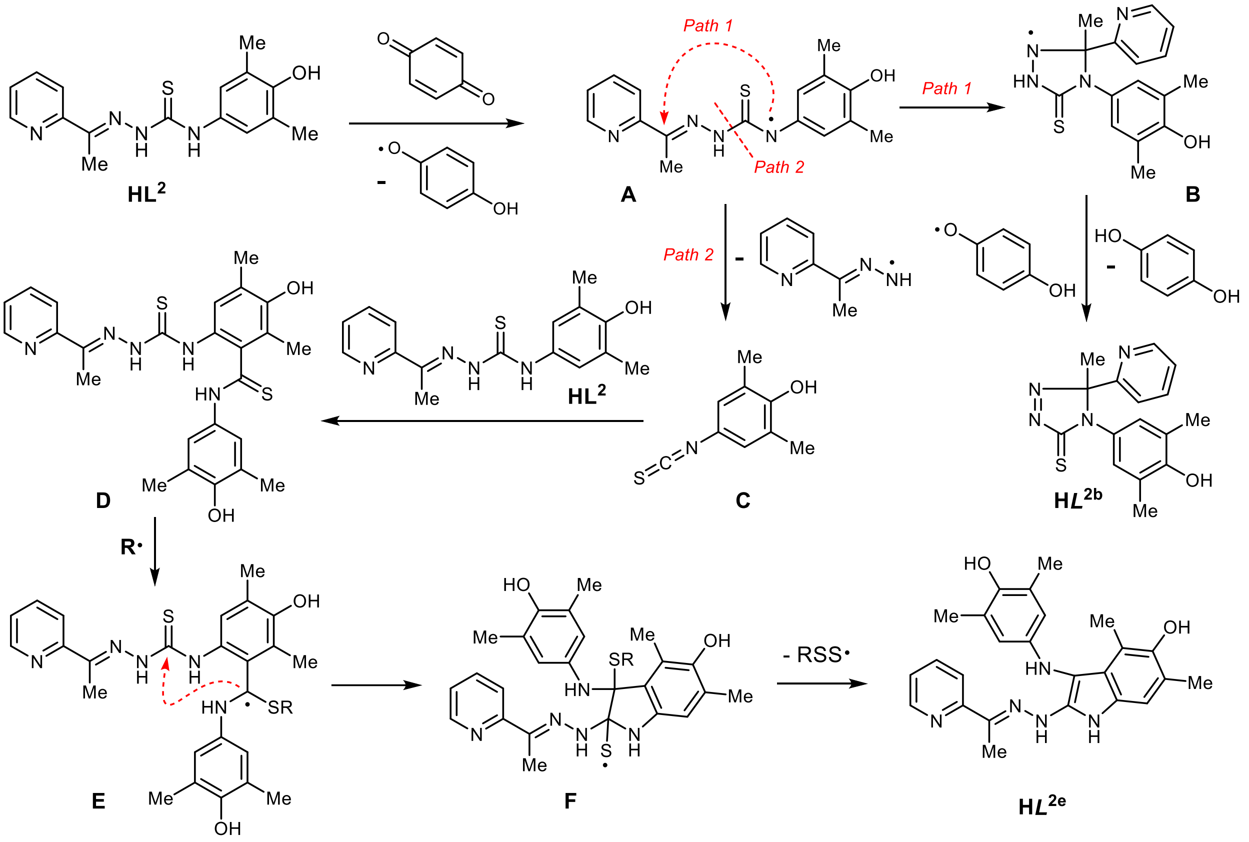


Scheme S6. The atom numbering for the assignment of resonances in **H*L*$^{\mathbf{2c'}}$** and tautomeric forms of **H*L*$^{\mathbf{2c'}}$** in solution.



Scheme S7. The atom numbering for the assignment of resonances in **H*L*$^{\mathbf{2c''}}$**.

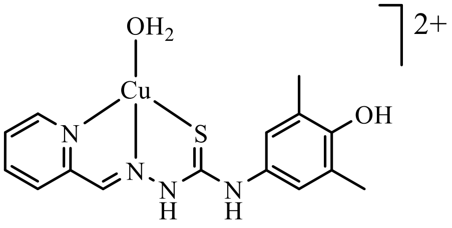
6. Oxidation of HL^2 with PBQ



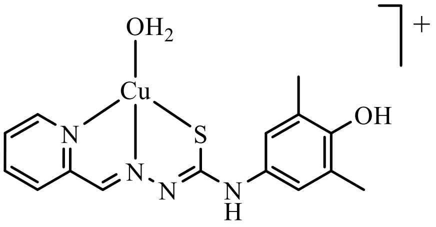
Scheme S8. Plausible pathway for the formation of compounds **H*L*^{2b}** and **H*L*^{2e}** by the oxidation of **HL^2** with PBQ.

Discussion of Scheme S8. We suppose that the initial step of the reaction of **HL^2** with PBQ involves one-electron oxidation of **HL^2** together with NH deprotonation to give a highly conjugated N/S-centered free radical species **A**. Intramolecular addition of the N4 atom in radical species **A** to the C=N double bond results in the triazole-based radical **B** which is then oxidized and deprotonated to form **H*L*^{2b}** (*Path 1*). Another transformation of radical **A** involves its fragmentation affording isothiocyanate **C** (*Path 2*). This path is supported by the literature data describing isothiocyanate syntheses by oxidation of thiosemicarbazides.[18,19] It should be also noted that formation of intermediate species **C** was observed upon oxidation of N-(4-hydroxy-3,5-dimethylphenyl)hydrazinecarbothioamide or **ATSC´** (Ag_2O, acetone), of HL^1 (Ag_2O, acetone; PBQ in ethanol), DDQ in methanol) and confirmed by the negative ion ESI mass spectra showing a peak with *m*/*z* value 177.95 attributed to $[M–H]^–$. Moreover this species was separated by column chromatography on silica when using ethyl acetate/hexane (v/v 1/1, R_f = 0.85). Electrophilic substitution in highly activated benzene ring of **HL^2** under the action of isothiocyanate **C** gives the corresponding thioamide **D**. Analogous S_E2 reactions have been described in the literature.[20] The final steps of indole **H*L*^{2e}** formation proceed presumably according to radical promoted Fukuyama-like indole synthesis.[21,22] Thus, the attack of a radical on the thioamide sulfur atom affords radical **E** followed by its cyclization into **F** and then aromatization to afford **H*L*^{2e}**.

7. Suggested structures for $[Cu(L^1)(H_2O)]^+$ and $[Cu(HL^1)(H_2O)]^{2+}$



$[Cu((HL^1)(H_2O)]^{2+}$



$[Cu((L^1)(H_2O)]^+$

Chart S1. Suggested structures for **$[Cu(L^1)(H_2O)]^+$** and **$[Cu(HL^1)(H_2O)]^{2+}$** complexes. (Notably, the chloride ions originally coordinated in solid phase are most likely replaced by water molecules due to the weak binding of the chlorido ligands in aqueous solution).

8. Frontier orbitals in HL^2

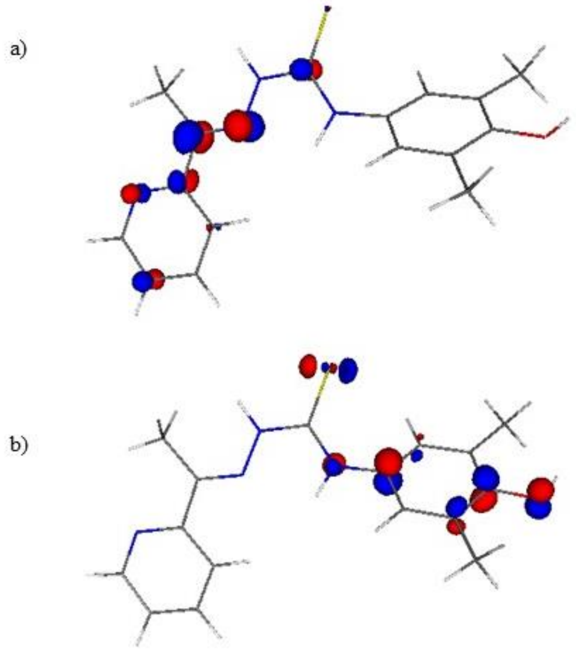


Figure S1. Frontier orbitals in **HL^2**: a) LUMO and b) HOMO.

9. ORTEP view of the ATSC

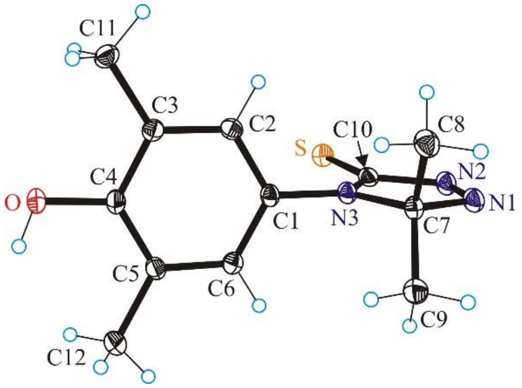


Figure S2. ORTEP view of the oxidation product of acetone *N*-(4-hydroxy-3,5-dimethylphenylthiosemicarbazone (ATSC) by Ag_2O.

10. *E*/*Z*-isomerization of H*L*$^{2c'}$

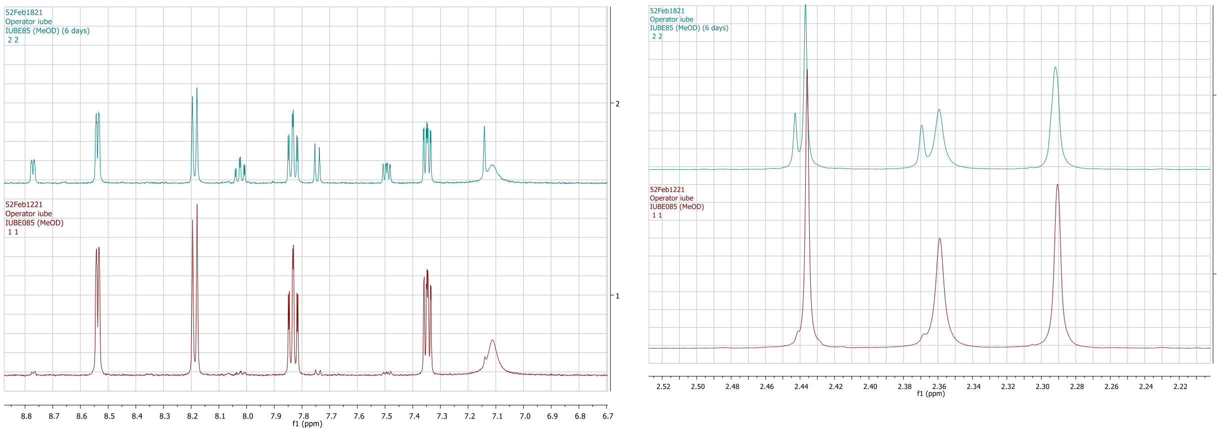
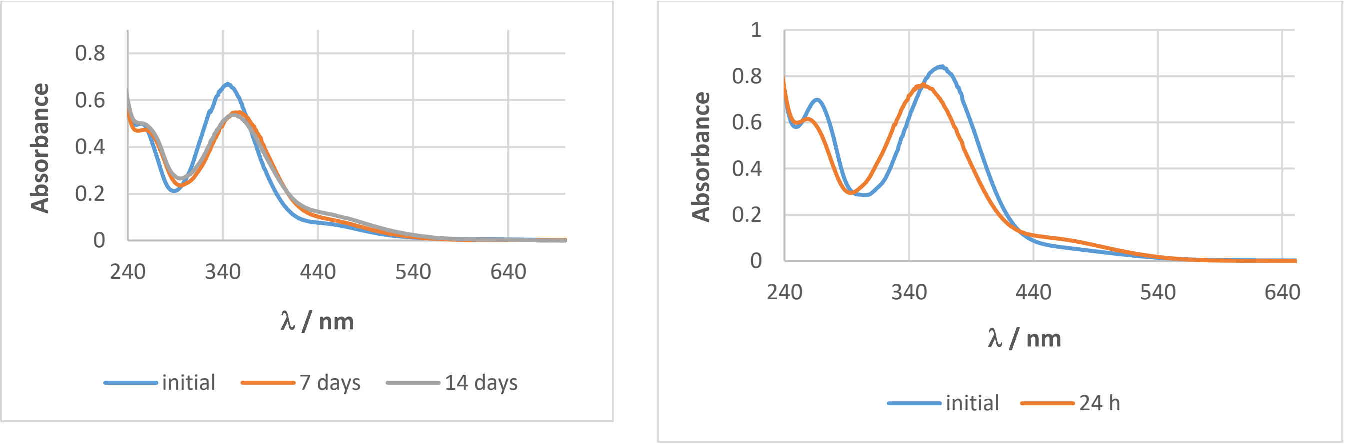


Figure S3. *E*/*Z*-isomerization of **H*L*$^{2c'}$** in MeOH-d_4 in 6 days (red spectra – fresh (*E*-), blue spectra – in 6 days (*E*-/*Z*- as 3/1)).

$^{-1}$H NMR (**H*L*$^{2c'}$**, 500 MHz, MeOH-d_4) δ 8.77 (ddd, *J* = 4.9, 1.7, 0.8 Hz, 1H, *Z*-isomer), 8.54 (ddd, *J* = 4.9, 1.6, 0.9 Hz, 3H, *E*-isomer), 8.19 (d, *J* = 8.1 Hz, 3H, *E*-isomer), 8.02 (td, *J* = 7.9, 1.8 Hz, 1H, *Z*-isomer), 7.83 (td, *J* = 7.8, 1.8 Hz, 3H, *E*-isomer), 7.75 (d, *J* = 8.1 Hz, 1H, *Z*-isomer), 7.49 (ddd, *J* = 7.6, 4.9, 0.9 Hz, 1H, *Z*-isomer), 7.35 (ddd, *J* = 7.4, 4.9, 1.1 Hz, 3H, *E*-isomer), 7.14 (s, 1H, *Z*-isomer), 7.11 (s, 3H, *E*-isomer), 2.44 (s, 3H, *Z*-isomer), 2.43 (s, 9H, *E*-isomer), 2.37 (s, 3H, *Z*-isomer), 2.36 (s, 9H, *E*-isomer), 2.29 (s, 3H+9H, *Z*-isomer and *E*-isomer).



E-isomer

Z-isomer

Figure S4. *E*/*Z*-isomerization of **H*L*$^{2c'}$** in MeOH investigated by UV–vis spectroscopy.

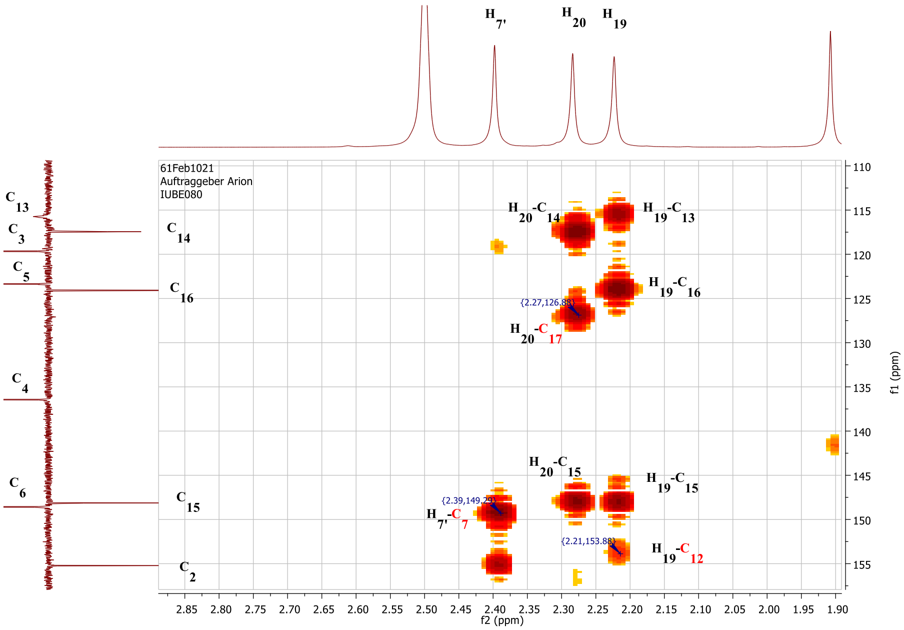


Figure S5. The fragment of ^{1}H,^{13}C HMBC of **H*L*$^{2c'}$·CH$_3$COOH** (to assign carbons C$_{12}$, C$_7$ and C$_{17}$).

11. ORTEP view of H*L*^{2e} and [Cu(*L*$^{1c´}$)Cl] (4)

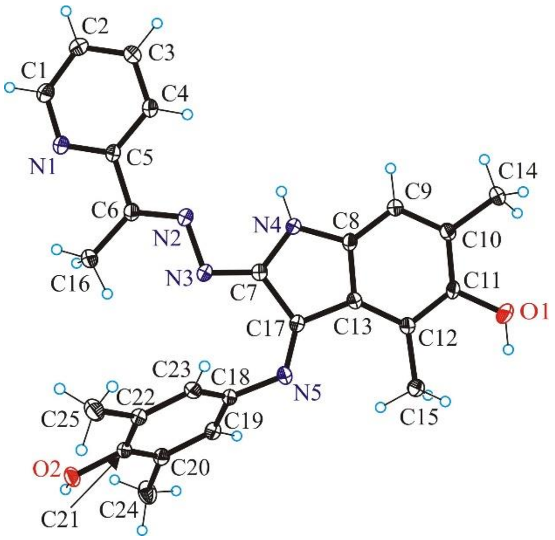


Figure S6. ORTEP view of **H*L*^{2e}** with thermal displacement parameters at 50% probability level. Selected bond distances (Å) and bond angles (°): C6–N2 1.2908(13), N2–N3 1.3999(12), N3–C7 1.2987(13), C7–N4 1.3656(12), N4–C8 1.3969(12), C8–C13 1.4006(14), C13–C17 1.4763(13), C17–C7 1.5149(14), C11–O1 1.3812(12), C17–N5 1.2861(13), N5–C18 1.4150(12), C21–O2 1.3729(11).

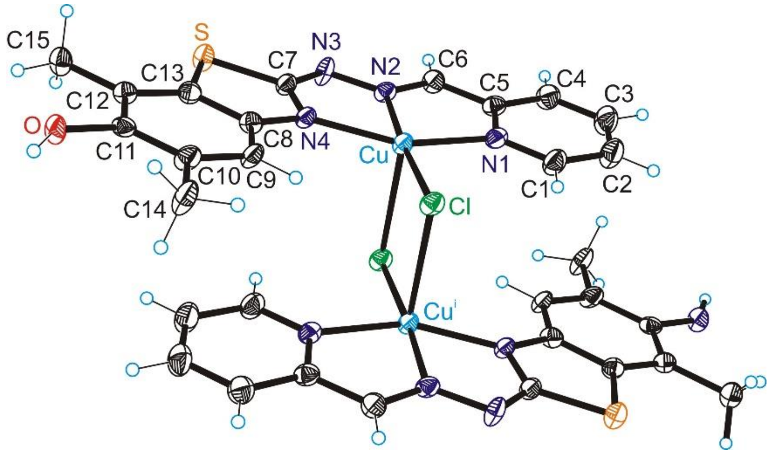


Figure S7. ORTEP view of centrosymmetric dimer in **[Cu(*L*$^{1c´}$)Cl]** (**4**) with thermal ellipsoids at 50% probability level. Bond lengths to bridging µ-chlorido ligands: Cu–Cl = 2.2575(12) Å, Cu–Cl^{i} = 2.7633(13) Å; (i denotes equivalent atom generated by symmetry transformation $–x + 1$, $–y + 1$, $–z + 1$.

12. Spectroscopic data

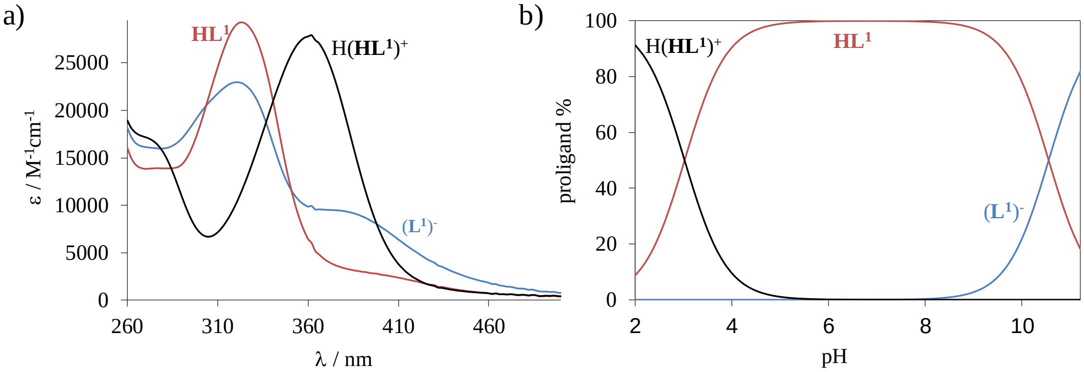


Figure S8. a) Molar absorbance spectra of the metal-free ligand **HL^{1}** in different protonation states. b) Concentration distribution curves for H(**HL^{1}**)$^{+}$, **HL^{1}** and (**L^{1}**)$^{–}$. {c_{HL} = 50 µM; 30% (v/v) DMSO/H$_2$O; I = 0.1 M (KCl); T = 25 °C}

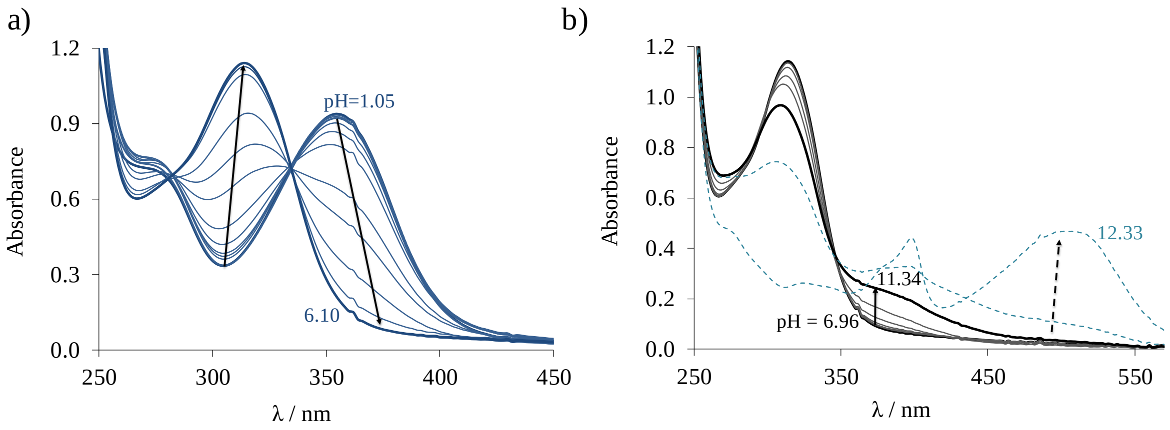


Figure S9. UV–vis absorption spectra recorded for proligand **HL^2** in the pH range a) 1.05 – 6.10 and b) 6.96 – 12.33. {$c_{\mathbf{HL}}$ = 50 μM; 30% (v/v) DMSO/H$_2$O; I = 0.1 M (KCl); T = 25 °C}.

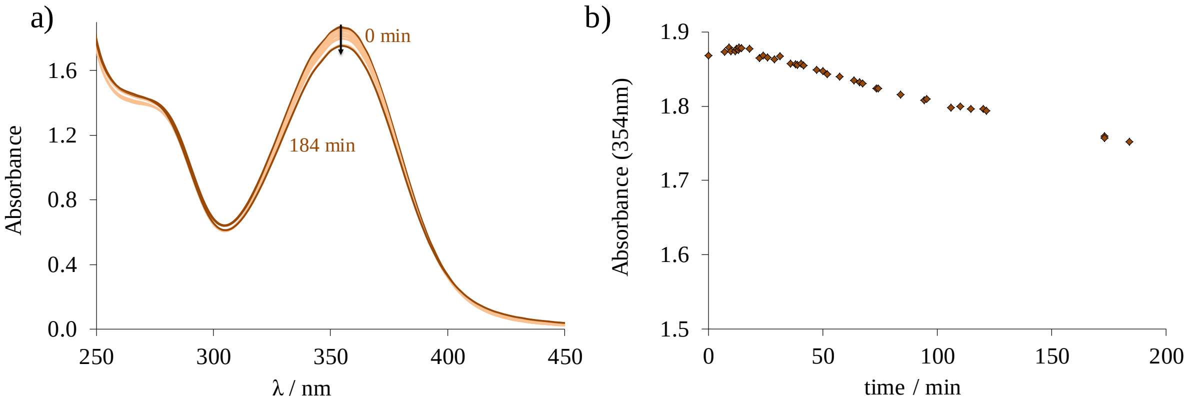


Figure S10. a) UV–vis absorption spectra recorded for proligand **HL^2** at pH 1.5 over 3 h. b) Absorbance values at 354 nm plotted against the time. {$c_{\mathbf{HL}}$ = 100 μM; 30% (v/v) DMSO/H$_2$O; I = 0.1 M (KCl); T = 25 °C}.

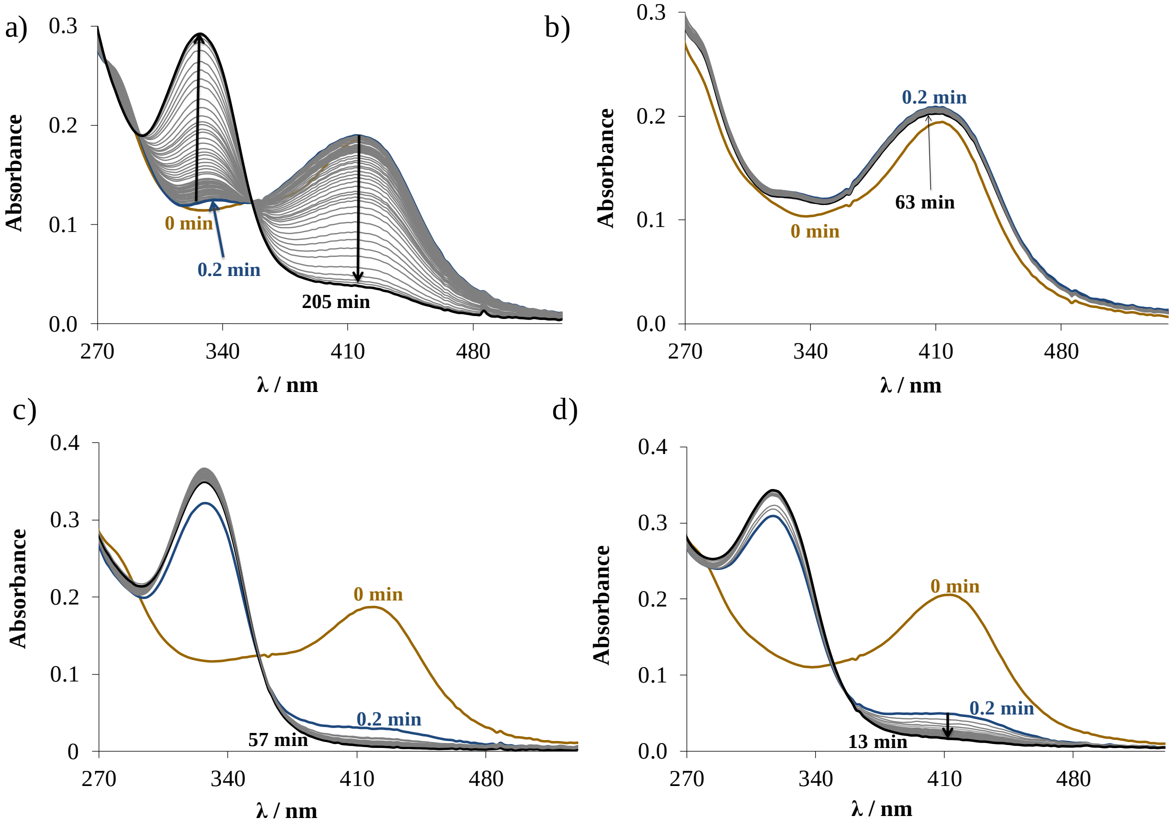


Figure S11. Time dependent changes of the UV–vis spectra of a) **Cu(HL^1)Cl$_2$** and b) **Cu(L^2)Cl** in the presence of 50 equiv GSH, c) **Cu(HL^1)Cl$_2$** and d) **Cu(L^2)Cl** in the presence of 50 equiv DTT, at pH 7.4 in 60% (v/v) DMSO/H$_2$O under anaerobic conditions {c_{complex} = 12.5 µM; $c_{\text{GSH or DTT}}$ = 600 µM; pH = 7.40; I = 0.1 M (KCl); T = 25 °C}.

13. Spectroelectrochemical data

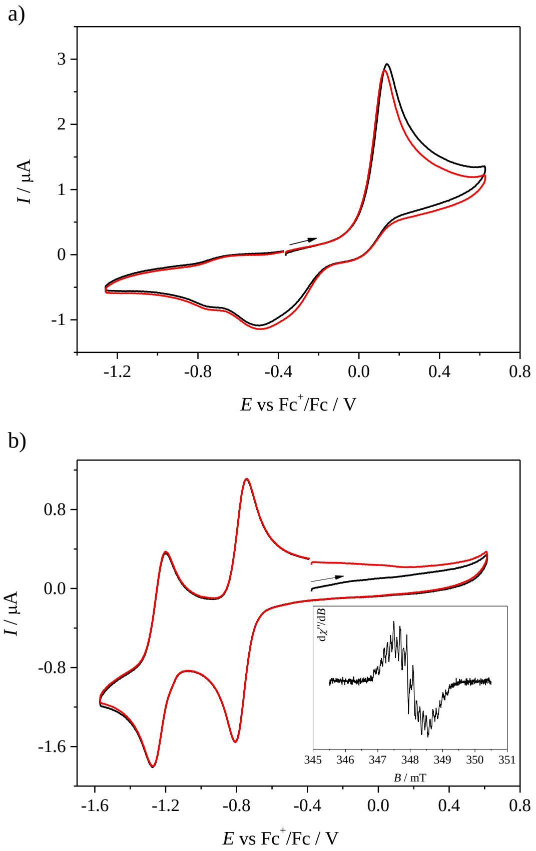


Figure S12. Cyclic voltammograms of a) 0.5 mM **H*L***$^{\mathbf{1a'}}$ and b) **H*L***$^{\mathbf{1a''}}$ in DMSO/*n*-Bu$_4$NPF$_6$ at glassy-carbon working electrode at scan rate of 100 mV s^{-1}. Inset in b): EPR spectrum measured upon cathodic reduction of **H*L***$^{\mathbf{1a''}}$ at the first reduction peak.

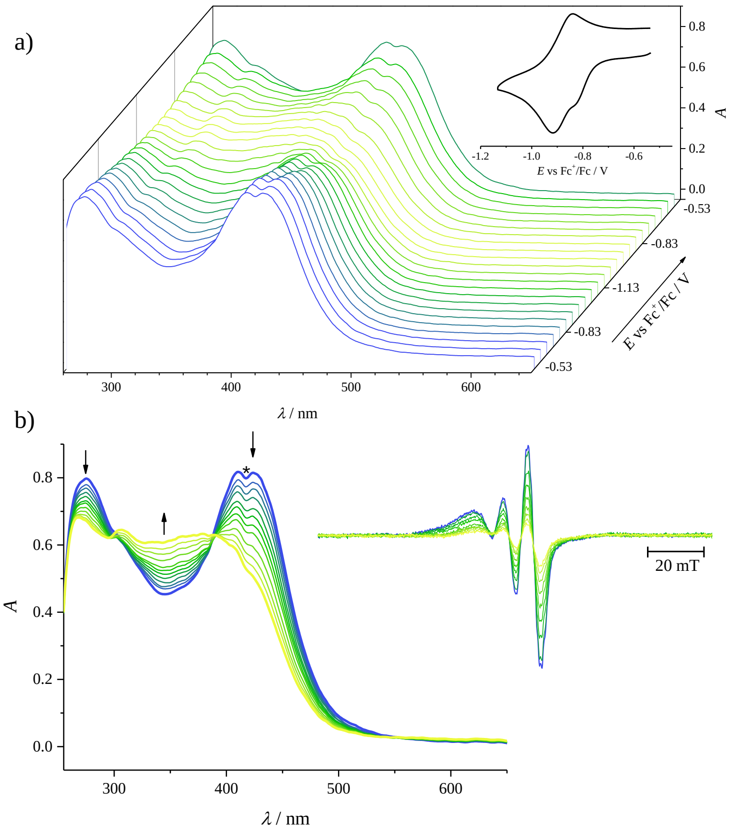


Figure S13. Spectroelectrochemistry of **2´** in n-Bu$_4$NPF$_6$/DMSO in the region of the first cathodic peak. a) Potential dependence of UV–vis spectra with the corresponding in situ cyclic voltammogram (Pt-microstructured honeycomb working electrode, scan rate of 5 mV s^{-1}); b) evolution of UV–vis spectra in 2D projection upon forward scan (* the peak marked by an asterisk is due to an artefact caused by the instrument; inset: evolution of EPR spectra measured at the first reduction peak using Pt mesh working electrode).

14. EPR measurement

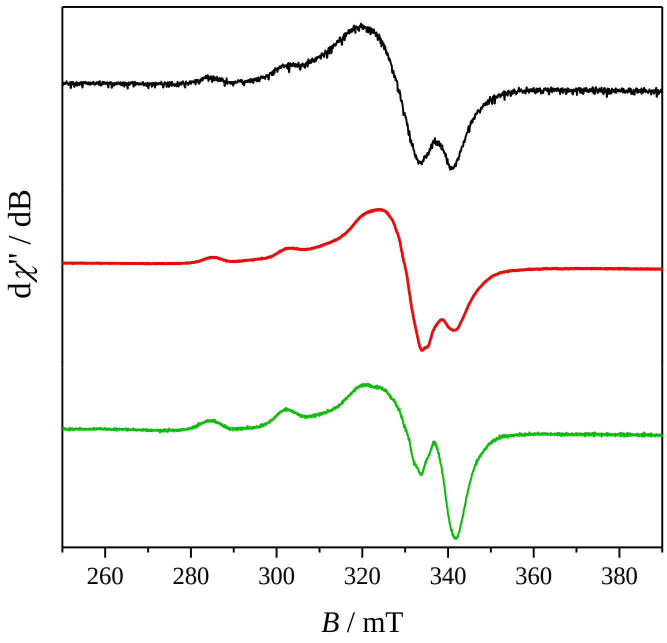


Figure S14. EPR spectra of **1** (black trace), **2´** (red trace) and **3** (green trace) measured in frozen *n*-Bu_4NPF_6/DMSO at 77 K.

15. Tyrosyl radical reduction kinetics in mouse R2 RNR protein

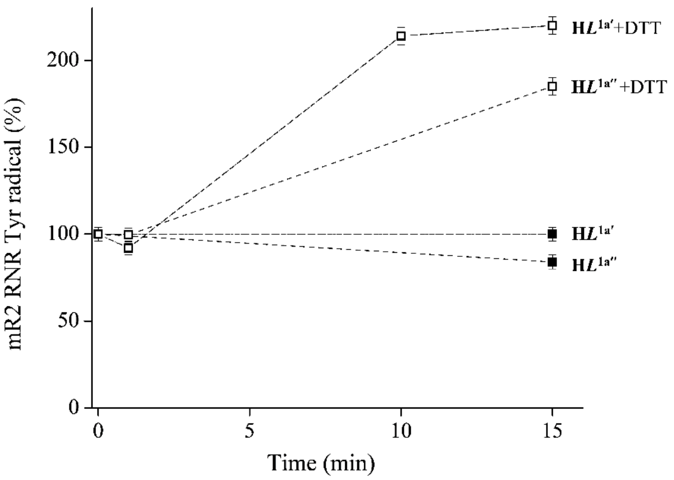


Figure S15. Tyrosyl radical reduction kinetics in mouse R2 RNR protein by **H*L*$^{1a'}$** and **H*L*$^{1a''}$**, in absence and presence of an external reductant, measured by 30 K EPR spectroscopy. The samples contained 20 µM mR2 in 50 mM Hepes buffer, pH 7.60 / 100 mM KCl, 20 µM compound in 1% (v/v) DMSO/H_2O, and 2 mM dithiothreiotol (DTT).

16. Cell cycle arrest

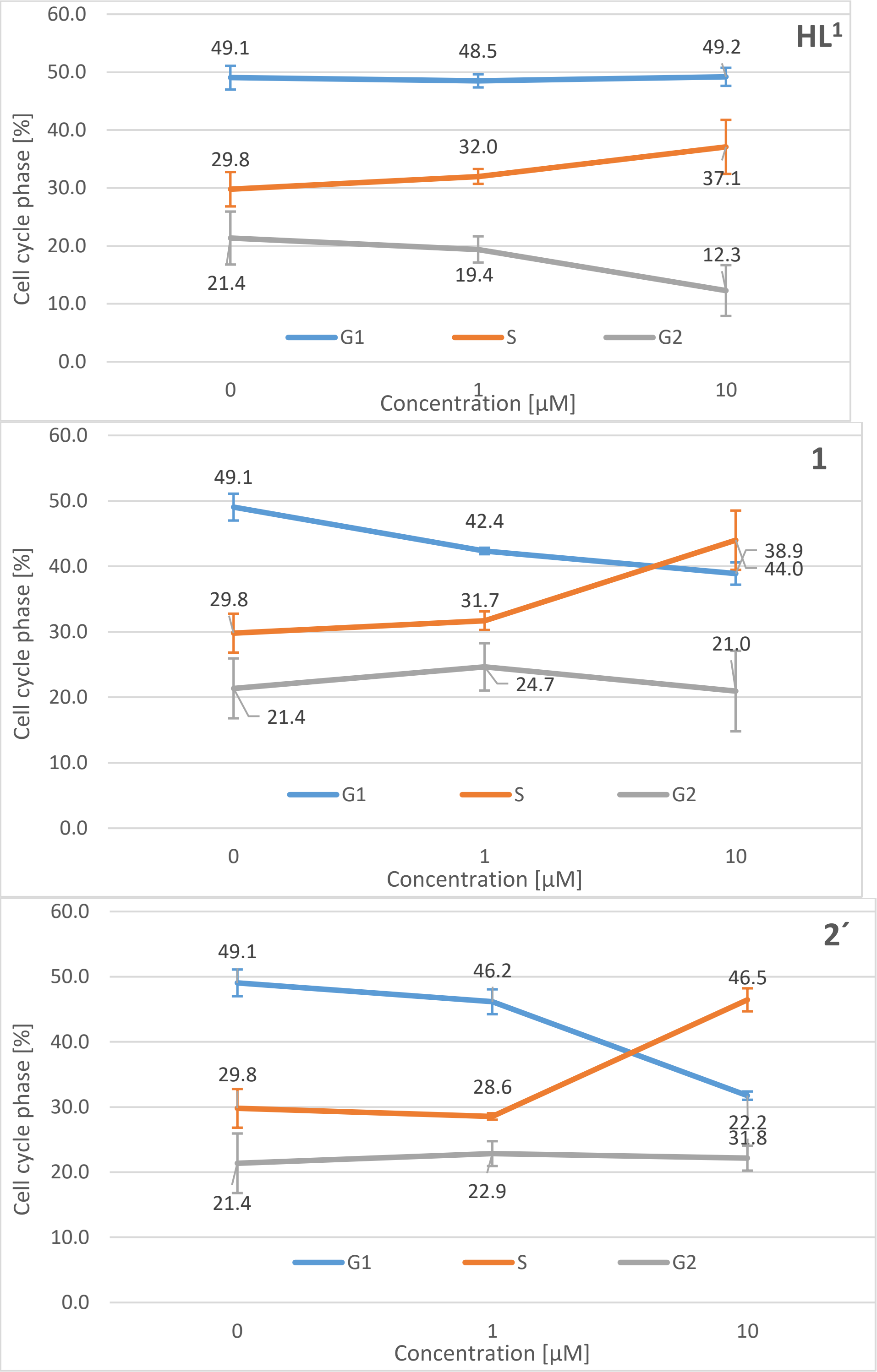


Figure S16. Cell cycle distribution of SW480 cells induced by increased concentrations of **HL^{1}** (top) and complexes **1** (middle) and **2´**(bottom) for 24 h compared to negative control (DMSO).

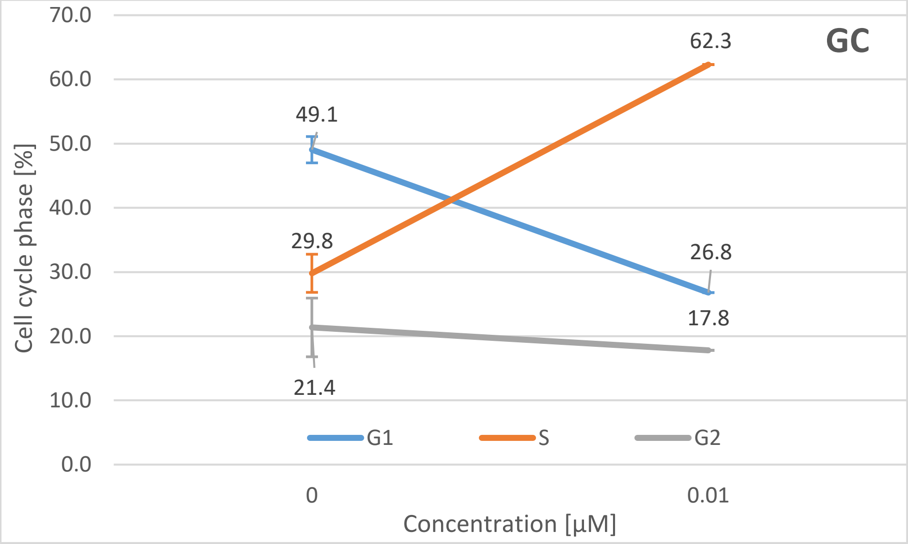


Figure S17. Cell cycle distribution of SW480 cells induced by increased concentrations of Gemcitabine (GC) for 24 h compared to negative control (DMSO).

17. Crystal Data and Details of Data Collection

Table S1. Crystal Data and Details of Data Collection for **HL^1**$\cdot C_2H_5OH$, **HL^2** and **HL^3**

Compound	**HL^1**$\cdot C_2H_5OH$	**HL^2**	**HL^3**
empirical formula	$C_{17}H_{22}N_4O_2S$	$C_{16}H_{18}N_4OS$	$C_{15}H_{17}N_5OS$
fw	346.45	314.40	315.40
space group	triclinic, $P\bar{1}$	monoclinic, $P2_1/c$	monoclinic, $P2_1/c$
a, Å	8.0232 (4)	7.4870 (11)	14.7916 (7)
b, Å	10.4578 (6)	8.6775 (15)	13.1867 (7)
c, Å	11.2363 (5)	24.709 (5)	15.9256 (8)
α,°	76.4523 (19)	90	90
β, °	74.485 (3)	90.387 (6)	105.1976 (19)
γ, °	82.121 (2)	90	90
V [Å^3]	880.36 (8)	1605.3 (5)	2997.7 (3)
Z	2	4	8
λ [Å]	0.71073	0.71073	0.71073
ρ_{calcd}, g cm^{-3}	1.307	1.301	1.398
cryst size, mm^3	0.10 × 0.09 × 0.04	0.10 × 0.08 × 0.01	0.20 × 0.10 × 0.08
T [K]	110(2)	120(2)	120(2)
μ, mm^{-1}	0.201	0.209	0.226
$R_1{}^a$	0.0347	0.0570	0.0562
$wR_2{}^b$	0.0827	0.1871	0.1526
GOF^c	1.047	1.072	1.008

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$. [c] GOF $= \{\Sigma[w(F_o^2 - F_c^2)^2]/(n - p)\}^{1/2}$, where n is the number of reflections and p is the total number of parameters refined .

Table S2. Crystal Data and Details of Data Collection for **H*L*$^{1a'}$**, **H*L*$^{1a''}$**, **H*L*^{2b}**, **H*L*^{2e}** and **ATSC′**

Compound	**H*L*$^{1a'}$**	**H*L*$^{1a''}$**	**H*L*^{2b}**	**HL$^{2c''}$·0.5CHCl$_3$**	**H*L*^{2e}**	**ATSC′**
empirical formula	$C_{15}H_{14}N_4OS$	$C_{15}H_{12}N_4OS$	$C_{16}H_{18}N_4OS$	$C_{16.5}H_{14.5}Cl_{1.5}N_4OS$	$C_{25}H_{25}N_5O_2$	$C_{12}H_{15}N_3OS$
fw	298.36	296.35	314.40	370.06	427.50	249.33
space group	monoclinic, $P2_1/n$	monoclinic, *Cc*	monoclinic, $P2_1/c$	triclinic, *P*-1	triclinic, $P\bar{1}$	monoclinic, $P2_1/n$
a, Å	13.7285(3)	22.449(2)	7.5533(4)	8.5138(3)	9.8871(7)	12.3755(3)
b, Å	4.8713(1)	3.8288(4)	20.6597(10)	11.0999(5)	10.8202(5)	7.2202(2)
c, Å	20.8797(4)	16.289(3)	9.5891(7)	17.9548(6)	11.9861(5)	13.9172(4)
α,°				85.5846(15)	116.4987(18)	
β, °	106.100(1)	100.513(6)	91.511(3)	87.0782(14)	92.850(2)	91.824(1)
γ, °				89.039(3)	106.217(3)	
V [Å^3]	1341.58(5)	1376.5(3)	1495.85(15)	1689.39(11)	1078.99(10)	1242.92(6)
Z	4	4	4	4	2	4
λ [Å]	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
ρ_{calcd}, g cm^{-3}	1.477	1.430	1.387	1.455	1.316	1.332
cryst size, mm^3	0.35 × 0.23 × 0.01	0.09 × 0.06 × 0.03	0.14 × 0.13 × 0.08	0.20 × 0.15 × 0.01	0.23 × 0.20 × 0.09	0.62 × 0.55 ×0.13
T [K]	100(2)	100(2)	100(2)	125(2)	100(2)	100(2)
μ, mm^{-1}	0.246	0.239	0.224	0.440	0.086	0.248
R_1[a]	0.0355	0.0314	0.0466	0.0581	0.0456	0.0323
wR_2[b]	0.0932	0.0724	0.1174	0.1653	0.1360	0.0843
GOF[c]	1.090	1.026	1.055	1.069	1.046	1.064

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$. [c] GOF = $\{\Sigma[w(F_o^2 - F_c^2)^2]/(n - p)\}^{1/2}$, where n is the number of reflections and p is the total number of parameters refined .

Table S3. Crystal Data and Details of Data Collection for **1′**·CH_3OH, **2′**, **3′**·CH_3OH, **4–6**

Compound	**1′**·CH_3OH	**2′**	**3′**·CH_3OH	**4**	**5**	**6**
empirical formula	$C_{16}H_{19}N_4O_2SCuCl$	$C_{16}H_{17}N_4OSCuCl$	$C_{16}H_{20}N_5O_2SCuCl$	$C_{15}H_{13}N_4OSCuCl$	$C_{14}H_{16}Cl_2CuN_8O_2S$	$C_{17}H_{20}Cl_2CuN_4O_2S$
fw	430.40	412.39	445.42	396.34	526.91	478.87
space group	monoclinic, $P2_1/c$	triclinic, $P\bar{1}$	monoclinic, $P2_1/c$	monoclinic, $P2_1/c$	monoclinic, $P2_1/n$	triclinic, $P\bar{1}$
a, Å	14.0310(5)	7.3880(15)	13.9941 (10)	8.8847(16)	9.8513(2)	8.4395(5)
b, Å	6.7988(2)	8.6970(17)	9.6773 (4)	18.122(2)	8.12370(10)	10.9171(13)
c, Å	18.4126(6)	13.884(3)	14.0005 (9)	9.2690(17)	12.6408(2)	11.1165(7)
α, °		84.84(3)				79.343(4)
β, °	91.286(3)	87.45(3)	103.980 (3)	92.814(6)	101.7347(8)	86.602(2)
γ, °		68.64(3)				71.706(4)
V [Å^3]	1756.01(10)	827.4(3)	1839.86 (19)	1490.5(4)	990.49(3)	955.68(14)
Z	4	2	4	4	2	2
λ [Å]	0.71073	0.70000	0.71073	0.71073	0.71073	0.71073
ρ_{calcd}, g cm^{-3}	1.628	1.655	1.608	1.766	1.767	1.664
cryst size, mm^3	0.12 × 0.12 × 0.03	0.05 × 0.02 × 0.01	0.09 × 0.09 × 0.02	0.15 × 0.03 × 0.02	0.19 × 0.13 × 0.08	0.06 × 0.05 × 0.04
T [K]	120(2)	100(2)	120(2)	100(2)	100(2)	100(2)
μ, mm^{-1}	1.533	1.556	1.467	1.793	1.614	1.553
R_1[a]	0.0369	0.0659	0.0348	0.0477	0.0238	0.0283
wR_2[b]	0.0951	0.1999	0.0802	0.1116	0.0599	0.0668
GOF[c]	1.089	1.060	1.054	1.054	1.078	1.058

[a] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$. [c] GOF = $\{\Sigma[w(F_o^2 - F_c^2)^2]/(n - p)\}^{1/2}$, where n is the number of reflections and p is the total number of parameters refined.

18. ^{1}H and ^{13}C NMR Data

Table S4. ^{1}H NMR (DMSO-d_6)

		HL^1 (*E*-)	**HL**^{2} (*E*-)	**HL**^{3} (*E*-)	**H*L***$^{1a'}$	**H*L***$^{1a''}$	**H*L***$^{2c'}$·CH$_3$COOH (*E*-)	**H*L***$^{2c'}$ (*E*-)	**H*L***$^{2c''}$ (CDCl$_3$)
H$_3$	C*H*$_{py}$	8.43 (d, 1H)	8.54 (d, 1H)	-	8.11 (d, 1H)	8.26 (dt, 1H)	8.08 (d, 1H)	8.07 (d, 1H)	8.34 (d, 1H)
H$_{3'}$	N*H*$_2$	-	-	6.49 (s, 2H)	-	-	-	-	-
H$_4$	C*H*$_{py}$	7.82 (td, 1H)	7.79 (td, 1H)	7.15 (dd, 1H)	7.95 (td, 1H)	8.06 (td, 1H)	7.85 (td, 1H)	7.85 (td, 1H)	7.80 (td, 1H)
H$_5$	C*H*$_{py}$	7.37 (m, 1H)	7.39 (dd, 1H)	7.08 (dd, 1H)	7.46 (ddd, 1H)	7.60 (ddd, 1H)	7.36 (dd, 1H)	7.36 (ddd, 1H)	7.38 (dd, 1H)
H$_6$	C*H*$_{py}$	8.57 (d, 1H)	8.59 (d, 1H)	7.85 (dd, 1H)	8.61 (d, 1H)	8.71 (ddd, 1H)	8.58 (d, 1H)	8.58 (ddd, 1H)	8.70 (d, 1H)
H$_7$	C*H*=N	8.16 (s, 1H)	-	8.39 (s, 1H)	-	-	-	.	
H$_{7'}$	C*H*$_3$(C=N)	-	2.44 (s, 3H)	-	-	-	2.40 (s, 3H)	2.40 (s, 3H)	2.72 (s, 3H)
H$_9$	N*H* (closer to py)	11.86 (s, 1H)	10.46 (s, 1H)	11.47 (s, 1H)	-	-	11.76 (s, 1H)	11.58 (s, 1H)	
H$_{11}$	N*H* (closer to ph)	10.00 (s, 1H)	9.94 (s, 1H)	9.70 (s, 1H)	10.20 (s, 1H)	-	-	-	
H$_{13}$+H$_{17}$	C*H*$_{ph}$	7.02 (s, 2H)	7.02 (s, 2H)	6.92 (s, 2H)	7.16 (s, 2H)	7.46 (dq, 1H, H$_{13}$)	7.02 (s, 1H, H$_{13}$)	7.02 (brs, 1H)	7.44 (brs, 1H)
						7.20 (dq, 1H, H$_{17}$)			
H$_{18}$	O*H*$_{ph}$	8.22 (s, 1H)	8.22 (s, 1H)	8.21 (s, 1H)	8.08 (s, 1H)	-	8.18 (s, 1H)	8.20 (s, 1H)	
H$_{19}$+H$_{20}$	C*H*$_{3ph}$	2.17 (s, 6H)	2.17 (s, 6H)	2.16 (s, 6H)	2.17 (s, 6H)	2.05 (d, 3H, H$_{20}$)	2.28 (s, 3H, H$_{20}$)	2.28 (s, 3H, H$_{20}$)	2.18 (s, 3H, H$_{19}$)
						2.00 (d, 3H, H$_{19)}$	2.22 (s, 3H, H$_{19}$)	2.22 (s, 3H, H$_{19}$)	2.14 (s, 3H, H$_{20}$)

		HL^1 (*Z*-)	**HL**^{2} (*Z*-)	**HL**^{3} (*Z*-)	**H*L***$^{2c'}$ (*Z*-)
H$_3$	C*H*$_{py}$	n.a.	n.a.	n.a.	7.79 (d, 1H)
H$_{3'}$	N*H*$_2$	-	-	6.21 (s, 2H)	-
H$_4$	C*H*$_{py}$	n.a.	n.a.	n.a.	8.08 (t, 1H)
H$_5$	C*H*$_{py}$	n.a.	n.a.	n.a.	7.58 (m, 1H)
H$_6$	C*H*$_{py}$	n.a.	n.a.	n.a.	8.85 (d, 1H)
H$_{7'}$	C*H*$_3$(C=N)	-	2.43 (s, 3H)	-	2.40 (s, 3H)
H$_9$	N*H* (closer to py)	14.26 (s, 1H)	14.40 (s, 1H)	14.57 (s, 1H)	15.00 (s, 1H)
H$_{11}$	N*H* (closer to ph)	10.17 (s, 1H)	9.99 (s, 1H)	9.95 (s, 1H)	-
H$_{13}$	C*H*$_{ph}$	n.a.	n.a.	n.a.	7.15 (s, 1H)
H$_{18}$	O*H*$_{ph}$	n.a.	n.a.	n.a.	8.22 (s,1H)
H$_{19}$+H$_{20}$	C*H*$_{3ph}$	2.16 (s, 6H)	2.16 (s, 6H)	2.15 (s, 6H)	2.31 (s, 3H, H$_{20}$)
					2.22 (s, 3H, H$_{19}$)

Table S5. ^{13}C NMR (DMSO-*d*$_6$)

		HL^{1} (*E*-)	**HL^{2}** (*E*-)	**HL^{3}** (*E*-)	**H*L*$^{1a'}$**	**H*L*$^{1a''}$**	**H*L*$^{2c'}$**·CH$_3$COOH (*E*-)	**H*L*$^{2c'}$** (*E*-)	**H*L*$^{2c''}$** (CDCl$_3$)
C$_2$	*C*$_{py}$	153.31	154.59	132.97	149.28	148.19	155.22	155.15	154.97
C$_3$	*C*H$_{py}$/*C*$_{py}$	120.54	121.18	143.99	119.25	120.04	119.65	119.65	122.31
C$_4$	*C*H$_{py}$	136.43	136.34	122.34	137.52	138.06	136.43	136.44	136.46
C$_5$	*C*H$_{py}$	124.10	124.00	124.52	124.61	126.14	123.35	123.35	125.34
C$_6$	*C*H$_{py}$	149.27	148.43	137.25	149.73	150.25	148.57	148.57	149.29
C$_7$	*C*=N	142.51	148.54	149.23	-	-	149.29*	n.a.	169.42
C$_7$	thiadiazole	-	-	-	158.40	169.98	-	-	-
C$_{7'}$	*C*H$_3$(C=N)	-	12.31	-	-	-	12.55	12.56	14.88
C$_{10}$	*C*=S	176.55	177.36	176.13	-	-	-	-	-
C$_{10}$	S-*C*-N	-	-	-	166.77	171.58	166.47	n.a.	173.74
C$_{12}$	*C*$_{ph}$	130.18	130.36	130.59	132.53	162.21	153.88*	n.a.	169.74
C$_{13}$+C$_{17}$	*C*H$_{ph}$	126.26	126.33	126.88	118.67	136.08 (C$_{17}$)	126.88* (C$_{17}$)	n.a.	129.52 (C$_{13}$)
						125.96 (C$_{13}$)	115.78 (C$_{13}$)	n.a.	129.25 (C$_{17}$)
C$_{14}$+C$_{16}$	*C*(CH$_3$)$_{ph}$	123.84	123.83	123.83	125.11	143.89 (C$_{14}$)	124.07	124.07	145.86
						143.11 (C$_{16}$)	117.44	117.80*	145.41
C$_{15}$	*C*(OH)$_{ph}$	151.10	151.12	151.17	148.97	187.14	148.14	148.15	184.43
C$_{19}$+C$_{20}$	C(*C*H$_3$)$_{ph}$	16.62	16.63	16.63	16.87	16.10 (C$_{19}$)	17.08 (C$_{19}$)	17.09 (C$_{19}$)	17.38 (C$_{19}$)
						15.66 (C$_{20}$)	15.47 (C$_{20}$)	15.54C$_{20}$)	15.54 (C$_{20}$)

		HL^{1} (*Z*-)	**HL^{2}** (*Z*-)	**HL^{3}** (*Z*-)	**H*L*$^{2c'}$** (*Z*-)
C$_2$	*C*$_{py}$				152.61
C$_3$	*C*H$_{py}$				124.08*
C$_4$	*C*H$_{py}$				138.29
C$_5$	*C*H$_{py}$				124.26*
C$_6$	*C*H$_{py}$				147.63
C$_{7'}$	*C*H$_3$(C=N)	-	21.73	-	21.72
C$_{13}$	*C*H$_{ph}$				118.98 (C$_{13}$)
C$_{14}$+C$_{16}$	*C*(CH$_3$)$_{ph}$				117.67* (C$_{14}$ or C$_{16}$)
C$_{15}$	*C*(OH)$_{ph}$				148.39
C$_{19}$+C$_{20}$	C(*C*H$_3$)$_{ph}$				17.20 (C$_{19}$)
					15.87 (C$_{20}$)

* detected from ^{1}H,^{13}C HMBC, ^{1}H,^{13}C HSQC

Table S6. ^{15}N NMR (DMSO-*d*$_6$)

		HL^{1} (*E*-)	**HL^{2}** (*E*-)	**HL^{3}** (*E*-)	**H*L*$^{2c'}$**·CH$_3$COOH (*E*-)
N$_1$	*N*$_{py}$	315.07	310.61	321.53	309.86
N$_{3'}$	*N*H$_2$	-	-	71.10	-
N$_8$	C=*N*	325.04	312.94	312.8	337.75
N$_9$	*N*H (closer to py)	174.22	168.53	174.57	n.a.
N$_{11}$	*N*H (closer to ph)	128.93	129.34	126.69	-

Assignment of *E*- and *Z*-isomers in HL$^{\mathbf{1}}$–HL$^{\mathbf{3}}$. The assignment of *E*- and *Z*-isomers was based on ^{1}H, ^{1}H NOESY cross-peaks between N*H*(9) and protons of R$_1$ in *E*-isomer, whereas the 'diagnostic' signature of *Z*-isomer is the downfield shifted proton N*H*(9) due to the hydrogen bond to pyridine nitrogen atom. The N*H* signals of the *Z*-isomer of **HL**$^{\mathbf{1}}$–**HL**$^{\mathbf{3}}$ are seen at 14.26, 14.40, 14.57 (H$_9$) and 10.17, 9.99, 9.95 (H$_{11}$) ppm, while those for the *E*-isomer at 11.86, 10.46, 11.47 (H$_9$), and 10.00, 9.94, 9.70 (H$_{11}$) ppm. The *E*/*Z* ratio is 23:1, 17:1 and 31:1 for **HL**$^{\mathbf{1}}$–**HL**$^{\mathbf{3}}$, respectively. The predominance of *E*-isomer in DMSO makes the assignment of other protons of minor *Z*-isomer difficult, since they are often overlapped with the proton resonances of the *E*-isomer. Two N*H* signals for *E*-isomers were assigned based on ^{1}H, ^{1}H NOESY spectra, where the correlations between the H$_{11}$ signal and the C*H* protons (H$_{13}$ and H$_{17}$) of phenolic moiety, as well as between the H$_9$ signal and the aldimine C*H* proton (H$_7$) in **HL**$^{\mathbf{1}}$, **HL**$^{\mathbf{3}}$ or the methyl protons at the ketimine group (H$_{7'}$) in **HL**$^{\mathbf{2}}$ were found.

Even more remarkable differences due to the presence of two different isomeric forms in DMSO were observed in the ^{13}C NMR spectrum of **HL**$^{\mathbf{2}}$. The carbon atom of the methyl group (C$_{7'}$) in *E*-isomer resonates at 12.31 ppm, whereas in *Z*-isomer at 21.73 ppm, as also reported for 2-acetylpyridine *N*,*N*-dimethyl(chalcogen)semicarbazones.[23] Of note is also that the signals of methyl protons in both isomers in the ^{1}H NMR spectrum show almost the same chemical shifts at 2.44 (*E*) and 2.43 (*Z*) ppm. The protons of the amine group (H$_{3'}$) in **HL**$^{\mathbf{3}}$ due to the hydrogen bond formation to nitrogen N8 in *E*-isomer resonate at 6.49 ppm, whereas in the case of *Z*-isomer the signal of H$_{3'}$ protons is slightly upfield shifted to 6.21 ppm.

Assignment of resonances in H*L*$^{\mathbf{1a'}}$ and H*L*$^{\mathbf{1a''}}$. The protons H$_{13}$/H$_{17}$, H$_{19}$/H$_{20}$, and carbon atoms C$_{13}$/C$_{17}$, C$_{14}$/C$_{16}$ and C$_{19}$/C$_{20}$ in **H*L***$^{\mathbf{1a''}}$ are magnetically non-equivalent in contrast to these atoms in **HL**$^{\mathbf{1}}$–**HL**$^{\mathbf{3}}$ and **H*L***$^{\mathbf{1a'}}$. This can be explained by the involvement of atom H$_{13}$ and nitrogen atom N$_9$ in hydrogen bond formation, the latter being more electronegative than the S atom of 1,3,4-thiadiazole ring (see Scheme S5). It is also worth mentioning the different multiplicity of protons H$_{13}$/H$_{17}$, H$_{19}$/H$_{20}$ of 1,4-benzoquinone imine moiety in **H*L***$^{\mathbf{1a''}}$. The protons of C*H* (H$_{13}$+H$_{17}$) or C*H*$_3$ (H$_{19}$+H$_{20}$) groups in **HL**$^{\mathbf{1}}$–**HL**$^{\mathbf{3}}$ and **H*L***$^{\mathbf{1a'}}$ appear as singlets with intensity ratio 2:6, correspondingly, whereas in **H*L***$^{\mathbf{1a''}}$ as two doublets of quartet for H$_{13}$ and H$_{17}$ (dq, ^4J = 2.8 (or 2.7), 1.3 (or 1.5) Hz, coupled with C*H* and C*H$_3$* protons, respectively) and as two doublets for methyl protons H$_{20}$ and H$_{19}$ (d, ^4J = 1.5 Hz, coupled with the C*H* proton) with the intensity ratio 1(dq):1(dq):3(d):3(d). The resonance signal of hydrogen bond proton H$_{13}$ is downfield shifted to 7.46 ppm vs 7.20 ppm for atom H$_{17}$. The assignment of methyl groups in **H*L***$^{\mathbf{1a''}}$ was done accounting for the correlation between the C*H* and the CH_3 protons (H_{13} – H_{19}, H_{17} – H_{20}) in the ^{1}H, ^{1}H NOESY spectrum.

19. Complexation of $\mathbf{H}\mathbf{\mathit{L}}^{\mathbf{1a'}}$ and $\mathbf{H}\mathbf{\mathit{L}}^{\mathbf{1a''}}$

Table S7. Summarized ESI-MS experiment of the complexation of 1,3,4-thiadiazoles $\mathbf{H}\mathbf{\mathit{L}}^{\mathbf{1a'}}$ and $\mathbf{H}\mathbf{\mathit{L}}^{\mathbf{1a''}}$

H*L*	**Reaction conditions**	**Positive ESI-MS peaks detected**			
$\mathbf{H}\mathbf{\mathit{L}}^{\mathbf{1a'}}$	MeOH, r.t. under argon MeOH, r.t. under air MeOH, 50°C under air, 3 h DMF, r.t., under air, 10 min DMF, ice bad, under air, 1 h	659.16 $[Cu(\mathbf{H}\mathbf{\mathit{L}}^{1a'})_2]^+$ 657.13 $[Cu(\mathbf{H}\mathbf{\mathit{L}}^{1a'})(\mathbf{H}\mathbf{\mathit{L}}^{1a''})]^+$ 655.18 $[Cu(\mathbf{H}\mathbf{\mathit{L}}^{1a''})_2]^+$	402.10 $[Cu(\mathbf{H}\mathbf{\mathit{L}}^{1a'})+CH_3CN]^+$ 400.10 $[Cu(\mathbf{H}\mathbf{\mathit{L}}^{1a''})+CH_3CN]^+$		
	chromatography (SiO_2, MeOH)	655.18 $[Cu(\mathbf{H}\mathbf{\mathit{L}}^{1a''})_2]^+$	400.10 $[Cu(\mathbf{H}\mathbf{\mathit{L}}^{1a''})+CH_3CN]^+$	537.15 $[Cu(\mathbf{H}\mathbf{\mathit{L}}^{1a''})(\mathbf{H}\mathbf{\mathit{L}}^{1d})]^+$	
$\mathbf{H}\mathbf{\mathit{L}}^{\mathbf{1a''}}$	MeOH, 50°C under air, 1 h			537.15 $[Cu(\mathbf{H}\mathbf{\mathit{L}}^{1a''})(\mathbf{H}\mathbf{\mathit{L}}^{1d})]^+$	419.08 $[Cu(\mathbf{H}\mathbf{\mathit{L}}^{1d})_2]^+$
	MeOH, 50°C under air, 36 h				419.08 $[Cu(\mathbf{H}\mathbf{\mathit{L}}^{1d})_2]^+$

20. Cell apoptosis assay

Table S8. Gated events (%) in Colo320 cells measured by flow cytometry with 3 h induction time

Colo320 colon adenocarcinoma cells		Gated events %		
A+: annexin positive I+: propidium iodide positive	Concentration	**Early apoptosis % Q3**	**Late apoptosis** and **necrosis % Q2**	**Cell death % Q1**
Control A-I+	-	0	0	0.074
Control A+I-	-	0.032	0.010	5.24
Control A+I+	-	3.70	5.34	3.44
Control A+I+	-	3.25	9.99	6.93
DMSO	0.8%	3.26	3.05	1.35
M627 (12*H*-benzophenothiazine) *positive control*	10 µM	12.4	31.5	4.59
M627 (12*H*-benzophenothiazine) *positive control*	20 µM	11.1	26.1	7.85
cisplatin (Teva) *positive control*	15 µM	1.68	2.24	1.64
cisplatin (Teva) *positive control*	30 µM	4.90	4.07	0.79
HL^1	4 µM	6.19	12.4	2.79
HL^1	8 µM	7.65	7.0	1.57
Cu(L^2)Cl	0.25 µM	6.28	5.12	1.13
Cu(L^2)Cl	0.5 µM	6.33	17.2	3.76
Control A+I+	-	4.73	7.18	2.89

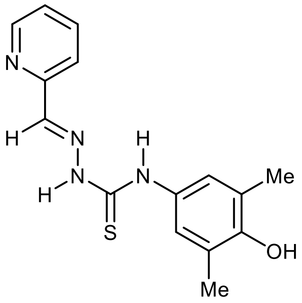
Table S9. Percentage of cell cycle distributions of SW480 cells induced by the TSC **HL^1** and complexes **1** and **2´** at the concentration of 10 µM for 24 h compared to the negative control

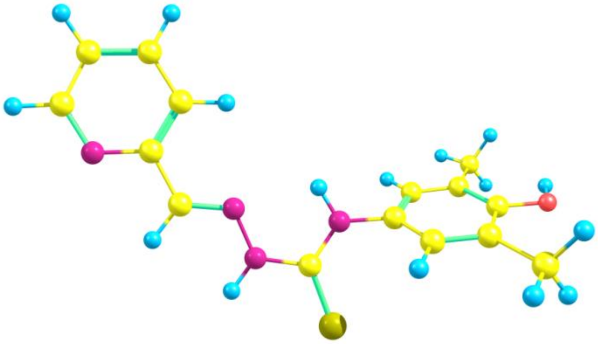
Cell cycle phase	Negativ control	**HL^1**	**1**	**2´**
G0/G1	49.1 ± 2.1	49.2 ± 1.6	38.9 ± 1.7	31.8 ± 0.6
S	29.8 ± 3.0	37.1 ± 4.7	44.0 ± 4.5	46.5 ± 1.8
G2/M	21.4 ± 4.6	12.3 ± 4.4	21.0 ± 6.2	22.2 ± 1.9

21. Computational data

Geometry optimization of *s-trans*- and *s-cis*-conformers around the N2-C3 thioamide bond for *E*- and *Z*-isomers of HL^1–HL^3

Data 1: Cartesian coordinates and energies of the optimized geometry for the *s-trans*-conformer of (*E*)-**HL^1** (DMSO solution).





Electronic Energy =	-1273.92279515 a.u.
Zero-point correction =	0.290366 (Hartree/Particle)
Thermal correction to Energy =	0.310592
Thermal correction to Enthalpy =	0.311537
Thermal correction to Gibbs Free Energy =	0.238748
Sum of electronic and zero-point Energies =	-1273.632429
Sum of electronic and thermal Energies =	-1273.612203
Sum of electronic and thermal Enthalpies =	-1273.611259
Sum of electronic and thermal Free Energies =	-1273.684047

Standard orientation:

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 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
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      1          6           0        6.354331   -1.876923    0.484469
      2          6           0        5.022374   -2.281758    0.567958
      3          6           0        4.020322   -1.345744    0.353563
      4          6           0        4.385427   -0.024199    0.059896
      5          7           0        5.669748    0.371471   -0.021612
      6          6           0        6.622125   -0.542318    0.187761
      7          7           0        2.139385    0.809972   -0.142103
      8          7           0        1.305047    1.850332   -0.384060
      9          6           0       -0.057903    1.695421   -0.379636
     10         16           0       -1.026132    3.039151   -0.733290
     11          7           0       -0.485091    0.453246   -0.096686
     12          6           0       -1.840524    0.004615   -0.014167
     13          6           0       -2.274403   -0.993306   -0.882296
     14          6           0       -3.572125   -1.504034   -0.798827
     15          6           0       -4.428186   -0.974129    0.177792
     16          6           0       -4.010072    0.028557    1.067887
     17          6           0       -2.703752    0.501626    0.961281
     18          6           0       -4.957861    0.560914    2.111552
     19          6           0       -4.044863   -2.589625   -1.734778
     20          8           0       -5.720569   -1.413485    0.320114
     21          6           0        3.401237    1.035836   -0.184541
     22          1           0        1.663572    2.771749   -0.617638
     23          1           0        0.247970   -0.240446    0.013234
     24          1           0       -5.921282   -2.089256   -0.337672
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     25          1           0        7.166983   -2.574533    0.644307
     26          1           0        4.771091   -3.310909    0.796334
     27          1           0        2.974526   -1.618220    0.408562
     28          1           0        7.647030   -0.191227    0.114744
     29          1           0       -1.596654   -1.378703   -1.635988
     30          1           0       -2.355303    1.265447    1.645510
     31          1           0       -4.469784    1.318908    2.725736
     32          1           0       -5.842853    1.009888    1.650723
     33          1           0       -5.314964   -0.237684    2.768402
     34          1           0       -4.905379   -2.268196   -2.332659
     35          1           0       -4.338423   -3.496052   -1.192911
     36          1           0       -3.253560   -2.869010   -2.430803
     37          1           0        3.809319    2.024966   -0.404396
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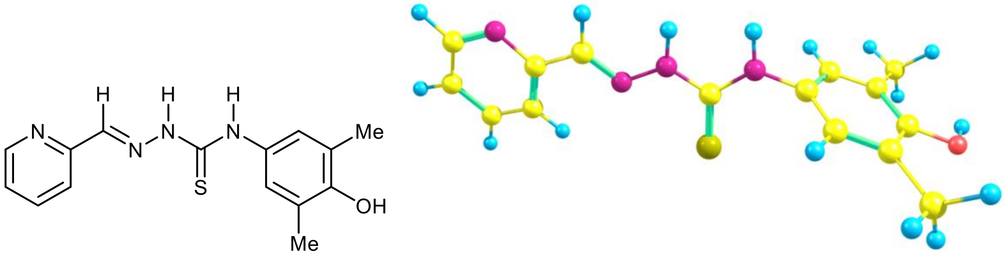
Data 2: Cartesian coordinates and energies of the optimized geometry for the *s*-*cis*-conformer of (*E*)-**HL^1** (DMSO solution).



Electronic Energy = -1273.91322461 a.u.

Zero-point correction = 0.289784 (Hartree/Particle)

Thermal correction to Energy = 0.310316

Thermal correction to Enthalpy = 0.311261

Thermal correction to Gibbs Free Energy = 0.236149

Sum of electronic and zero-point Energies = -1273.623441

Sum of electronic and thermal Energies = -1273.602908

Sum of electronic and thermal Enthalpies = -1273.601964

Sum of electronic and thermal Free Energies = -1273.677075

Standard orientation:

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 Number     Number       Type             X           Y           Z
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      2          6           0       -6.366146    0.604539    1.351675
      3          6           0       -5.054316    0.417087    0.939585
      4          6           0       -4.819235   -0.161892   -0.315835
      5          7           0       -5.816661   -0.543016   -1.135531
      6          6           0       -7.074369   -0.355341   -0.723146
      7          7           0       -2.423788   -0.082110   -0.166164
      8          7           0       -1.226563   -0.343876   -0.737898
      9          6           0       -0.029096   -0.062044   -0.124829
     10         16           0        0.096594    0.692569    1.377698
     11          7           0        1.035870   -0.460041   -0.862417
     12          6           0        2.415456   -0.269656   -0.516982
     13          6           0        3.152631   -1.337414   -0.015552
     14          6           0        4.510979   -1.195072    0.278200
     15          6           0        5.105736    0.056576    0.057211
     16          6           0        4.381876    1.146917   -0.452805
     17          6           0        3.031385    0.960094   -0.741094
     18          6           0        5.063191    2.471549   -0.680698
     19          6           0        5.319125   -2.349132    0.819770
     20          8           0        6.432264    0.280551    0.324345
     21          6           0       -3.467881   -0.399985   -0.838100
```

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     22          1           0       -1.218199   -0.777935   -1.659166
     23          1           0        0.861386   -0.975774   -1.717040
     24          1           0        6.845794   -0.518165    0.671661
     25          1           0       -8.440959    0.339622    0.788033
     26          1           0       -6.578985    1.049495    2.316690
     27          1           0       -4.219398    0.706657    1.564075
     28          1           0       -7.855202   -0.673270   -1.407522
     29          1           0        2.665447   -2.291447    0.151956
     30          1           0        2.449649    1.782520   -1.141175
     31          1           0        4.363003    3.200611   -1.090858
     32          1           0        5.470058    2.873227    0.252162
     33          1           0        5.903220    2.372198   -1.374407
     34          1           0        6.148272   -2.615144    0.154072
     35          1           0        4.695520   -3.236345    0.931959
     36          1           0        5.744724   -2.123661    1.804259
     37          1           0       -3.415910   -0.862209   -1.827589
 ---------------------------------------------------------------------
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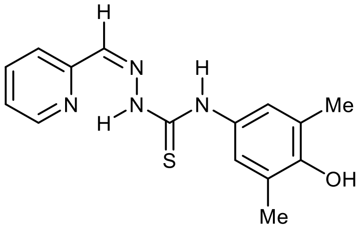
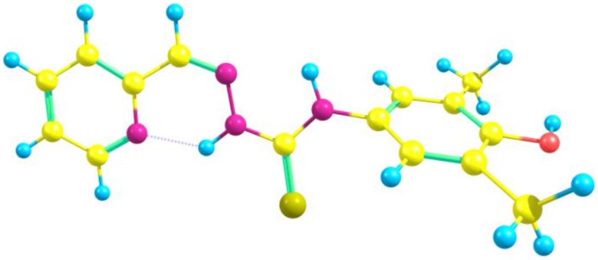
Data 3: Cartesian coordinates and energies of the optimized geometry for the *s*-*trans*-conformer of (*Z*)-**HL**^{1} (DMSO solution).





Electronic Energy =	-1273.92510682 a.u.
Zero-point correction =	0.290951 (Hartree/Particle)
Thermal correction to Energy =	0.310883
Thermal correction to Enthalpy =	0.311827
Thermal correction to Gibbs Free Energy =	0.239855
Sum of electronic and zero-point Energies =	-1273.634156
Sum of electronic and thermal Energies =	-1273.614224
Sum of electronic and thermal Enthalpies=	-1273.613280
Sum of electronic and thermal Free Energies=	-1273.685251

Standard orientation:

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 Number     Number       Type             X           Y           Z
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      3          6           0        5.598466   -1.190785    0.776857
      4          6           0        4.358412   -0.641034    0.418763
      5          7           0        4.263846    0.482332   -0.325951
      6          6           0        5.390323    1.076347   -0.726770
      7          7           0        1.895795   -0.993456    0.668379
      8          7           0        1.591263    0.111097   -0.054136
      9          6           0        0.283260    0.449436   -0.286942
     10         16           0       -0.049410    1.826932   -1.217498
     11          7           0       -0.625387   -0.379623    0.253884
     12          6           0       -2.049138   -0.266572    0.179211
     13          6           0       -2.773426   -1.248662   -0.490358
     14          6           0       -4.169411   -1.208044   -0.534297
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     17          6           0       -2.718495    0.772960    0.823501
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     19          6           0       -4.958609   -2.269706   -1.261023
     20          8           0       -6.186678   -0.028940    0.111421
     21          6           0        3.131638   -1.309698    0.867175
     22          1           0        2.352039    0.677647   -0.440824
     23          1           0       -0.235349   -1.191362    0.724017
     24          1           0       -6.587865   -0.762777   -0.368273
     25          1           0        7.541137    1.118272   -0.766791
     26          1           0        7.731913   -0.967629    0.616871
     27          1           0        5.638217   -2.092786    1.375082
     28          1           0        5.271631    1.975407   -1.322833
     29          1           0       -2.246628   -2.055771   -0.987357
     30          1           0       -2.149701    1.526348    1.354954
     31          1           0       -4.148085    2.655793    1.969982
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     33          1           0       -5.539757    1.591973    2.235550
     34          1           0       -5.651163   -2.793675   -0.592450
     35          1           0       -4.292457   -3.019000   -1.689368
     36          1           0       -5.547850   -1.848685   -2.083688
     37          1           0        3.268490   -2.210010    1.458089
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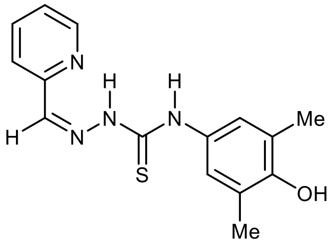
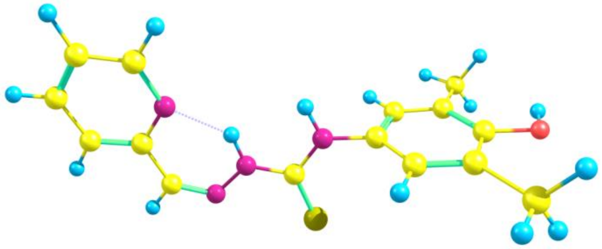
Data 4: Cartesian coordinates and energies of the optimized geometry for the *s*-*cis*-conformer of (*Z*)-**HL^1** (DMSO solution).





Electronic Energy = -1273.91615582 a.u.
Zero-point correction = 0.290434 (Hartree/Particle)
Thermal correction to Energy = 0.309645
Thermal correction to Enthalpy = 0.310589
Thermal correction to Gibbs Free Energy = 0.240966
Sum of electronic and zero-point Energies = -1273.625722
Sum of electronic and thermal Energies = -1273.606511
Sum of electronic and thermal Enthalpies = -1273.605567
Sum of electronic and thermal Free Energies = -1273.675190

Standard orientation:

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      4          6           0       -4.457984   -0.218277   -0.042171
      5          7           0       -3.717798    0.890248    0.180967
      6          6           0       -4.348654    2.043480    0.418124
      7          7           0       -2.518563   -1.771466   -0.365938
      8          7           0       -1.623851   -0.778751   -0.166512
      9          6           0       -0.270013   -1.001679   -0.215046
     10         16           0        0.437287   -2.510801   -0.484485
     11          7           0        0.439575    0.137540   -0.023579
     12          6           0        1.869189    0.245245    0.020726
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     13          6           0        2.560063    0.712396   -1.092687
     14          6           0        3.946795    0.877700   -1.058823
     15          6           0        4.620597    0.555938    0.129326
     16          6           0        3.943393    0.087795    1.267214
     17          6           0        2.559119   -0.056017    1.193500
     18          6           0        4.706310   -0.240088    2.524641
     19          6           0        4.703646    1.385312   -2.261919
     20          8           0        5.981265    0.687761    0.243828
     21          6           0       -3.778112   -1.493414   -0.304819
     22          1           0       -2.012291    0.156827    0.024074
     23          1           0       -0.076410    1.004250    0.072251
     24          1           0        6.360703    1.001191   -0.585337
     25          1           0       -6.196481    3.121078    0.644281
     26          1           0       -7.586358    1.071923    0.232238
     27          1           0       -6.424776   -1.090593   -0.212228
     28          1           0       -3.716774    2.908359    0.592031
     29          1           0        2.014421    0.947834   -1.999556
     30          1           0        2.010357   -0.410859    2.058333
     31          1           0        4.029165   -0.580855    3.309130
     32          1           0        5.447184   -1.024898    2.345176
     33          1           0        5.253520    0.631338    2.896182
     34          1           0        5.218768    2.329520   -2.051632
     35          1           0        4.025140    1.563969   -3.096381
     36          1           0        5.457182    0.666488   -2.603460
     37          1           0       -4.426398   -2.347143   -0.477374
 ---------------------------------------------------------------------
```
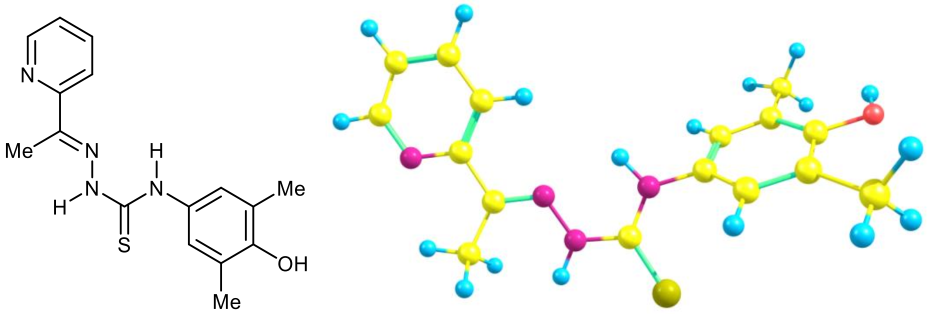

Data 5: Cartesian coordinates and energies of the optimized geometry for the *s*-*trans*-conformer of (*E*)-**HL**^{2} (DMSO solution).



Electronic Energy =	-1313.25113329 a.u.
Zero-point correction =	0.317993 (Hartree/Particle)
Thermal correction to Energy =	0.339858
Thermal correction to Enthalpy =	0.340802
Thermal correction to Gibbs Free Energy =	0.263747
Sum of electronic and zero-point Energies =	-1312.933140
Sum of electronic and thermal Energies =	-1312.911275
Sum of electronic and thermal Enthalpies =	-1312.910331
Sum of electronic and thermal Free Energies =	-1312.987386

Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0        5.773179   -2.460848    0.491110
      2          6           0        4.391878   -2.641751    0.560430
      3          6           0        3.558347   -1.550015    0.367322
      4          6           0        4.129701   -0.293556    0.107115
      5          7           0        5.460191   -0.120262    0.042662
      6          6           0        6.252444   -1.181127    0.230335
      7          7           0        2.009304    0.736192   -0.093054
```

```
      8          7           0        1.200705    1.809045   -0.290196
      9          6           0       -0.165367    1.677993   -0.300354
     10         16           0       -1.110003    3.053271   -0.597170
     11          7           0       -0.614336    0.431387   -0.078133
     12          6           0       -1.973497   -0.005751   -0.018106
     13          6           0       -2.402367   -0.991196   -0.903259
     14          6           0       -3.704011   -1.494997   -0.842878
     15          6           0       -4.569996   -0.970978    0.128025
     16          6           0       -4.157444    0.018681    1.035032
     17          6           0       -2.846981    0.485084    0.951578
     18          6           0       -5.115529    0.544299    2.072770
     19          6           0       -4.170340   -2.567066   -1.797452
     20          8           0       -5.867002   -1.404012    0.248118
     21          6           0        3.287957    0.915536   -0.112905
     22          1           0        1.565190    2.735294   -0.481601
     23          1           0        0.111663   -0.274324   -0.002152
     24          1           0       -6.062744   -2.071400   -0.419638
     25          1           0        6.460288   -3.285264    0.635556
     26          1           0        3.972045   -3.620260    0.762848
     27          1           0        2.483792   -1.655390    0.415984
     28          1           0        7.320814   -0.996088    0.169030
     29          1           0       -1.717115   -1.372520   -1.652282
     30          1           0       -2.503542    1.238259    1.649752
     31          1           0       -4.630660    1.291118    2.702993
     32          1           0       -5.991335    1.005122    1.606092
     33          1           0       -5.486680   -0.260073    2.714627
     34          1           0       -5.019240   -2.232930   -2.404900
     35          1           0       -4.478792   -3.476902   -1.269757
     36          1           0       -3.370556   -2.845116   -2.484274
     37          6           0        3.937446    2.252107   -0.341811
     38          1           0        3.660372    2.657495   -1.321025
     39          1           0        3.620693    2.972374    0.420192
     40          1           0        5.018304    2.157341   -0.302328
 ---------------------------------------------------------------------
```

Data 6: Cartesian coordinates and energies of the optimized geometry for the *s-cis*-conformer of (*E*)-**HL**^{2} (DMSO solution).

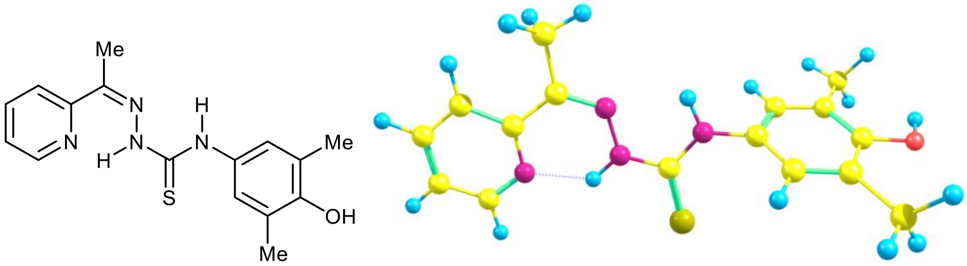
Electronic Energy = -1313.24090817 a.u.
Zero-point correction = 0.317413 (Hartree/Particle)
Thermal correction to Energy = 0.339522
Thermal correction to Enthalpy = 0.340466
Thermal correction to Gibbs Free Energy = 0.262335
Sum of electronic and zero-point Energies = -1312.923495
Sum of electronic and thermal Energies = -1312.901386
Sum of electronic and thermal Enthalpies = -1312.900442
Sum of electronic and thermal Free Energies = -1312.978573

Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0       -7.083824   -0.889030   -0.618321
      2          6           0       -5.925049   -1.503056   -1.094885
      3          6           0       -4.690433   -0.976928   -0.745542
```

4	6	0	-4.642717	0.159747	0.079019
5	7	0	-5.758522	0.751021	0.536071
6	6	0	-6.942941	0.232723	0.191662
7	7	0	-2.283891	0.156881	0.074584
8	7	0	-1.080333	0.671516	0.419861
9	6	0	0.107000	0.089141	0.042965
10	16	0	0.210044	-1.364093	-0.806180
11	7	0	1.183941	0.817227	0.430766
12	6	0	2.559899	0.459044	0.248795
13	6	0	3.330991	1.154239	-0.677241
14	6	0	4.689758	0.870334	-0.837653
15	6	0	5.249789	-0.141465	-0.043456
16	6	0	4.491057	-0.853991	0.900078
17	6	0	3.142711	-0.531474	1.037470
18	6	0	5.135525	-1.928428	1.737327
19	6	0	5.531974	1.625048	-1.837466
20	8	0	6.573928	-0.486528	-0.141857
21	6	0	-3.343661	0.765752	0.488528
22	1	0	-1.045356	1.524053	0.970881
23	1	0	1.019013	1.730437	0.837265
24	1	0	7.013183	0.047905	-0.813364
25	1	0	-8.068037	-1.266414	-0.866724
26	1	0	-5.985567	-2.379038	-1.730412
27	1	0	-3.770477	-1.424047	-1.095636
28	1	0	-7.818894	0.741329	0.583586
29	1	0	2.870790	1.925454	-1.284869
30	1	0	2.537144	-1.059762	1.764522
31	1	0	4.411970	-2.367906	2.425317
32	1	0	5.542944	-2.727455	1.110654
33	1	0	5.969657	-1.529854	2.322195
34	1	0	6.353588	2.165697	-1.353793
35	1	0	4.928836	2.360463	-2.370471
36	1	0	5.971195	0.958582	-2.588546
37	6	0	-3.331787	2.010449	1.335028
38	1	0	-4.347887	2.323729	1.555928
39	1	0	-2.810436	1.834478	2.282329
40	1	0	-2.821903	2.830933	0.818043

Data 7: Cartesian coordinates and energies of the optimized geometry for the *s*-*trans*-conformer of (*Z*)-**HL**^{2} (DMSO solution).

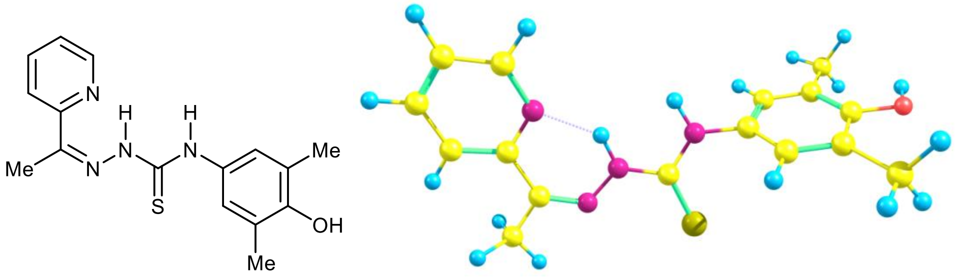


Electronic Energy = -1313.25257029 a.u.
Zero-point correction = 0.318281 (Hartree/Particle)
Thermal correction to Energy = 0.339815
Thermal correction to Enthalpy = 0.340760
Thermal correction to Gibbs Free Energy = 0.265192
Sum of electronic and zero-point Energies = -1312.934290
Sum of electronic and thermal Energies = -1312.912755
Sum of electronic and thermal Enthalpies = -1312.911811
Sum of electronic and thermal Free Energies = -1312.987378

Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0       -6.410224   -1.080010   -0.432918
      2          6           0       -6.607361    0.202899    0.068490
      3          6           0       -5.502355    0.987009    0.379325
      4          6           0       -4.212560    0.468127    0.181190
      5          7           0       -4.033946   -0.779569   -0.306846
      6          6           0       -5.101108   -1.523623   -0.602092
      7          7           0       -1.773092    0.924599    0.373502
      8          7           0       -1.434183   -0.301527   -0.098492
      9          6           0       -0.117439   -0.641758   -0.240484
     10         16           0        0.271161   -2.173785   -0.862446
     11          7           0        0.762942    0.305994    0.126926
     12          6           0        2.189618    0.220319    0.091296
     13          6           0        2.898819    1.053776   -0.768989
     14          6           0        4.295905    1.043256   -0.791982
     15          6           0        4.963262    0.161991    0.071443
     16          6           0        4.269392   -0.684953    0.951040
     17          6           0        2.876708   -0.635367    0.951429
     18          6           0        5.025555   -1.609660    1.869881
     19          6           0        5.067496    1.947790   -1.721892
     20          8           0        6.333425    0.084516    0.106672
     21          6           0       -3.011831    1.282255    0.503719
     22          1           0       -2.180752   -0.951322   -0.364786
     23          1           0        0.342082    1.185009    0.414356
     24          1           0        6.722323    0.695671   -0.529560
     25          1           0       -7.242775   -1.723393   -0.687660
     26          1           0       -7.608059    0.591067    0.216726
     27          1           0       -5.643799    1.984709    0.769254
     28          1           0       -4.898844   -2.516690   -0.990431
     29          1           0        2.358921    1.719658   -1.433122
     30          1           0        2.319688   -1.271175    1.629049
     31          1           0        4.337318   -2.183091    2.492449
     32          1           0        5.643532   -2.312914    1.303556
     33          1           0        5.701515   -1.053112    2.525748
     34          1           0        5.723684    2.633349   -1.173533
     35          1           0        4.387590    2.556748   -2.318225
     36          1           0        5.692435    1.379300   -2.420095
     37          6           0       -3.212490    2.677700    1.041797
     38          1           0       -2.241742    3.135810    1.223259
     39          1           0       -3.765886    3.302648    0.334752
     40          1           0       -3.773563    2.667179    1.980875
 ---------------------------------------------------------------------
```

Data 8: Cartesian coordinates and energies of the optimized geometry for the *s*-*cis*-conformer of (*Z*)-**HL**^{2} (DMSO solution).



Electronic Energy = -1313.24330419 a.u.
Zero-point correction = 0.317896 (Hartree/Particle)
Thermal correction to Energy = 0.339566
Thermal correction to Enthalpy = 0.340511
Thermal correction to Gibbs Free Energy = 0.264186

Sum of electronic and zero-point Energies = -1312.925408

Sum of electronic and thermal Energies = -1312.903738

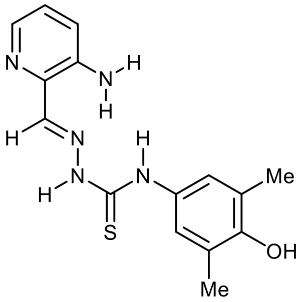
Sum of electronic and thermal Enthalpies = -1312.902794

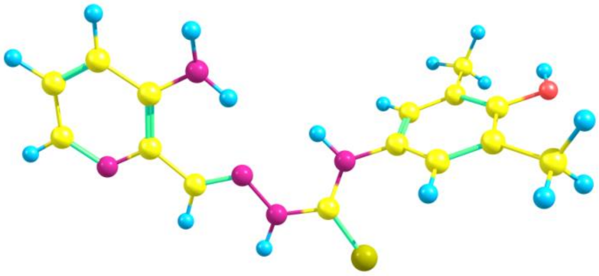
Sum of electronic and thermal Free Energies = -1312.979118

Standard orientation:

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0       -5.265614    2.595963    0.614420
      2          6           0       -6.139591    1.540176    0.372104
      3          6           0       -5.622708    0.285023    0.073205
      4          6           0       -4.230506    0.107217    0.022150
      5          7           0       -3.393045    1.141949    0.259285
      6          6           0       -3.898641    2.343475    0.545251
      7          7           0       -2.385738   -1.527886   -0.366184
      8          7           0       -1.438056   -0.586607   -0.149963
      9          6           0       -0.102499   -0.883642   -0.208685
     10         16           0        0.522143   -2.431693   -0.473768
     11          7           0        0.670416    0.220031   -0.031880
     12          6           0        2.100730    0.266945    0.011173
     13          6           0        2.793783    0.896297   -1.018529
     14          6           0        4.185503    1.017620   -0.980101
     15          6           0        4.863978    0.478230    0.122577
     16          6           0        4.185697   -0.158380    1.175215
     17          6           0        2.797124   -0.246595    1.104454
     18          6           0        4.953205   -0.716403    2.345965
     19          6           0        4.940637    1.701698   -2.093734
     20          8           0        6.230098    0.548924    0.234549
     21          6           0       -3.643379   -1.222519   -0.292327
     22          1           0       -1.781355    0.363106    0.064912
     23          1           0        0.200160    1.116575   -0.000612
     24          1           0        6.607912    0.999767   -0.529362
     25          1           0       -5.627116    3.588640    0.850718
     26          1           0       -7.211920    1.689744    0.414739
     27          1           0       -6.292609   -0.541149   -0.116540
     28          1           0       -3.178423    3.134827    0.726201
     29          1           0        2.246167    1.296569   -1.864667
     30          1           0        2.250080   -0.723377    1.909063
     31          1           0        4.274769   -1.159496    3.076376
     32          1           0        5.661903   -1.485689    2.024738
     33          1           0        5.537487    0.061813    2.845721
     34          1           0        5.508823    2.566226   -1.731720
     35          1           0        4.253452    2.062833   -2.859289
     36          1           0        5.647741    1.023466   -2.584788
     37          6           0       -4.584579   -2.372256   -0.561185
     38          1           0       -5.232481   -2.168287   -1.418959
     39          1           0       -4.002787   -3.267895   -0.772074
     40          1           0       -5.230749   -2.571493    0.298905
 ---------------------------------------------------------------------
```

Data 9: Cartesian coordinates and energies of the optimized geometry for the *s*-*trans*-conformer of (*E*)-**HL**^{3} (DMSO solution).





Electronic Energy = -1329.3054550 a.u.

Zero-point correction = 0.306858 (Hartree/Particle)

Thermal correction to Energy = 0.328532

Thermal correction to Enthalpy = 0.329476

Thermal correction to Gibbs Free Energy = 0.253551

Sum of electronic and zero-point Energies = -1328.998597

Sum of electronic and thermal Energies = -1328.976923

Sum of electronic and thermal Enthalpies = -1328.975979

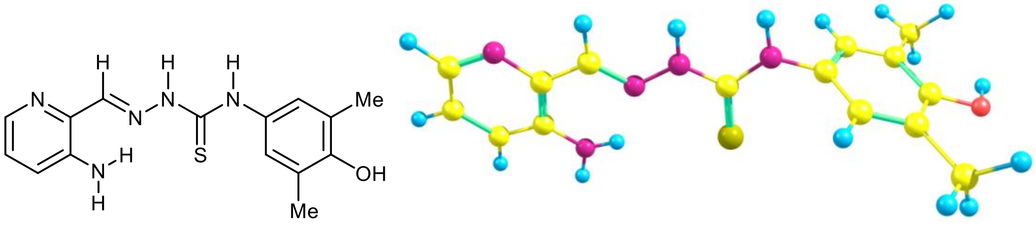
Sum of electronic and thermal Free Energies = -1329.051904

Standard orientation:

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0        6.502298   -1.495965    0.291889
      2          6           0        5.263337   -2.009369    0.618894
      3          6           0        4.108585   -1.219080    0.454614
      4          6           0        4.295128    0.101109   -0.044809
      5          7           0        5.519877    0.584917   -0.352840
      6          6           0        6.587870   -0.184806   -0.196071
      7          7           0        1.969237    0.815349   -0.088513
      8          7           0        1.116415    1.860853   -0.299114
      9          6           0       -0.241329    1.713164   -0.305812
     10         16           0       -1.206783    3.085740   -0.558735
     11          7           0       -0.684852    0.456051   -0.120611
     12          6           0       -2.046045    0.023295   -0.051515
     13          6           0       -2.514720   -0.885563   -0.996000
     14          6           0       -3.819528   -1.380891   -0.931153
     15          6           0       -4.646298   -0.928175    0.107532
     16          6           0       -4.193153   -0.015211    1.073925
     17          6           0       -2.881048    0.444669    0.982313
     18          6           0       -5.110807    0.437394    2.180299
     19          6           0       -4.330263   -2.367070   -1.953188
     20          8           0       -5.943184   -1.358144    0.238364
     21          6           0        3.224963    1.063408   -0.253867
     22          1           0        1.476323    2.785633   -0.514897
     23          1           0        0.029670   -0.262045   -0.112447
     24          1           0       -6.164364   -1.982536   -0.462217
     25          1           0        7.397980   -2.093235    0.412733
     26          1           0        5.163994   -3.019334    1.001713
     27          1           0        7.547654    0.248053   -0.459221
     28          1           0       -1.859425   -1.212276   -1.795912
     29          1           0       -2.505532    1.138561    1.724363
     30          1           0       -4.595012    1.123877    2.853131
     31          1           0       -5.992413    0.947024    1.779932
     32          1           0       -5.475829   -0.411161    2.766252
     33          1           0       -5.179800   -1.966870   -2.518132
```

```
      34            1             0        -4.654219    -3.305684    -1.489276
      35            1             0        -3.549666    -2.613922    -2.673213
      36            1             0         3.567218     2.051754    -0.570221
      37            7             0         2.869659    -1.728843     0.733710
      38            1             0         2.102874    -1.076942     0.812224
      39            1             0         2.818262    -2.557320     1.307301
 ---------------------------------------------------------------------
```

Data 10: Cartesian coordinates and energies of the optimized geometry for the *s*-*cis*-conformer of (*E*)-**HL**^{3} (DMSO solution).



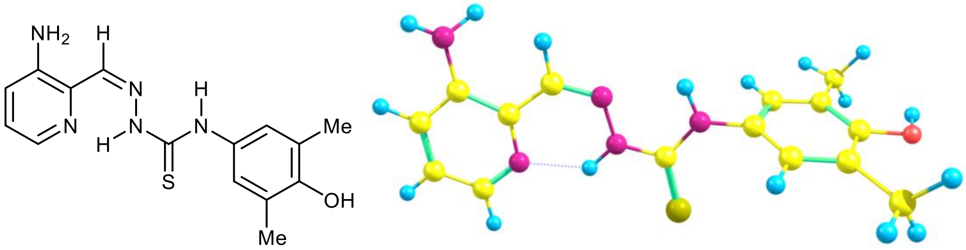
Electronic Energy = -1329.29878937 a.u.
Zero-point correction = 0.306062 (Hartree/Particle)
Thermal correction to Energy = 0.328048
Thermal correction to Enthalpy = 0.328992
Thermal correction to Gibbs Free Energy = 0.251925
Sum of electronic and zero-point Energies = -1328.992727
Sum of electronic and thermal Energies = -1328.970742
Sum of electronic and thermal Enthalpies = -1328.969798
Sum of electronic and thermal Free Energies = -1329.046864

Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
       1            6             0        -7.234294     0.201152     0.193219
       2            6             0        -6.252195     0.843318     0.920859
       3            6             0        -4.891992     0.573235     0.662872
       4            6             0        -4.610760    -0.369827    -0.371339
       5            7             0        -5.589070    -0.987337    -1.068069
       6            6             0        -6.859578    -0.715986    -0.797775
       7            7             0        -2.211726    -0.246000    -0.228100
       8            7             0        -1.008650    -0.660227    -0.697430
       9            6             0         0.171773    -0.193375    -0.183090
      10           16             0         0.247867     0.966183     1.043400
      11            7             0         1.260595    -0.760806    -0.758449
      12            6             0         2.628398    -0.447097    -0.460335
      13            6             0         3.375915    -1.313056     0.331219
      14            6             0         4.724431    -1.060297     0.594629
      15            6             0         5.299103     0.094289     0.041666
      16            6             0         4.564957     0.979957    -0.764296
      17            6             0         3.224984     0.686299    -1.009567
      18            6             0         5.224754     2.204290    -1.344337
      19            6             0         5.542503    -1.996428     1.450519
      20            8             0         6.614874     0.417577     0.255895
      21            6             0        -3.264749    -0.743629    -0.777023
      22            1             0        -0.992527    -1.338330    -1.456688
      23            1             0         1.113089    -1.507239    -1.427348
      24            1             0         7.036364    -0.240299     0.820859
      25            1             0        -8.282073     0.400972     0.383471
      26            1             0        -6.513498     1.556034     1.695713
      27            1             0        -7.608949    -1.237684    -1.384424
      28            1             0         2.904200    -2.194190     0.751608
      29            1             0         2.636316     1.349464    -1.632892
```

```
      30          1           0        4.517773    2.773777   -1.949239
      31          1           0        5.607932    2.858922   -0.555887
      32          1           0        6.078260    1.935286   -1.973651
      33          1           0        6.391260   -2.417226    0.899362
      34          1           0        4.933864   -2.832002    1.796905
      35          1           0        5.941710   -1.494191    2.339122
      36          1           0       -3.209372   -1.475525   -1.587593
      37          7           0       -3.909670    1.173717    1.391089
      38          1           0       -4.148178    1.926610    2.016520
      39          1           0       -2.940895    1.043583    1.125990
 ---------------------------------------------------------------------
```

Data 11: Cartesian coordinates and energies of the optimized geometry for the *s-trans*-conformer of (*Z*)-**HL^3** (DMSO solution).



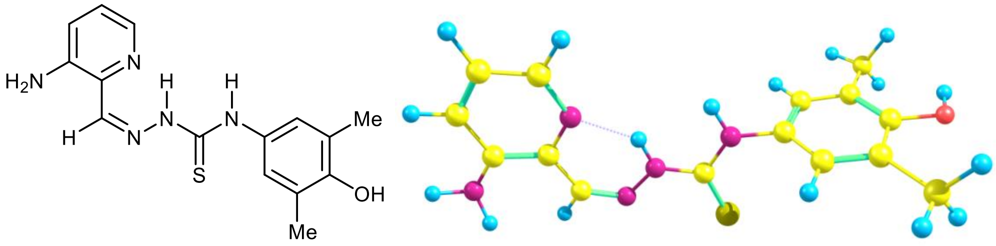
Electronic Energy = -1329.30412103 a.u.
Zero-point correction = 0.307308 (Hartree/Particle)
Thermal correction to Energy = 0.328812
Thermal correction to Enthalpy = 0.329757
Thermal correction to Gibbs Free Energy = 0.253594
Sum of electronic and zero-point Energies = -1328.996813
Sum of electronic and thermal Energies = -1328.975309
Sum of electronic and thermal Enthalpies = -1328.974364
Sum of electronic and thermal Free Energies = -1329.050527

Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0       -6.285087   -1.136183   -0.487999
      2          6           0       -6.502376    0.129006    0.026292
      3          6           0       -5.413996    0.944253    0.381614
      4          6           0       -4.110285    0.396555    0.212013
      5          7           0       -3.926239   -0.837274   -0.310041
      6          6           0       -4.971339   -1.583044   -0.651194
      7          7           0       -1.672415    0.875512    0.495502
      8          7           0       -1.299930   -0.283015   -0.103917
      9          6           0        0.024614   -0.583252   -0.267482
     10         16           0        0.448734   -2.042894   -1.022707
     11          7           0        0.884452    0.342895    0.189998
     12          6           0        2.313703    0.276954    0.146698
     13          6           0        3.010605    1.114605   -0.718878
     14          6           0        4.407535    1.115318   -0.749025
     15          6           0        5.086363    0.242733    0.114685
     16          6           0        4.404479   -0.608514    0.999556
     17          6           0        3.011312   -0.571776    1.004739
     18          6           0        5.173185   -1.524275    1.916860
     19          6           0        5.167335    2.023237   -1.685263
     20          8           0        6.456964    0.178023    0.144315
     21          6           0       -2.929835    1.157386    0.618964
     22          1           0       -2.030191   -0.932439   -0.413163
     23          1           0        0.451295    1.179485    0.569972
```

```
      24           1           0        6.837894     0.792223    -0.493832
      25           1           0       -7.117100    -1.769348    -0.770362
      26           1           0       -7.511388     0.506994     0.150456
      27           1           0       -4.758948    -2.563406    -1.063556
      28           1           0        2.461208     1.774170    -1.381397
      29           1           0        2.461737    -1.212571     1.684237
      30           1           0        4.492941    -2.104738     2.541680
      31           1           0        5.797461    -2.220935     1.349383
      32           1           0        5.844575    -0.959738     2.570622
      33           1           0        5.819545     2.716695    -1.142129
      34           1           0        4.479581     2.623843    -2.281050
      35           1           0        5.794437     1.457615    -2.383829
      36           1           0       -3.093860     2.101514     1.125705
      37           7           0       -5.638108     2.194880     0.923734
      38           1           0       -6.576638     2.554550     0.822747
      39           1           0       -4.939593     2.909205     0.786891
 ---------------------------------------------------------------------
```

Data 12: Cartesian coordinates and energies of the optimized geometry for the *s*-*cis*-conformer of (*Z*)-**HL**^{3} (DMSO solution).



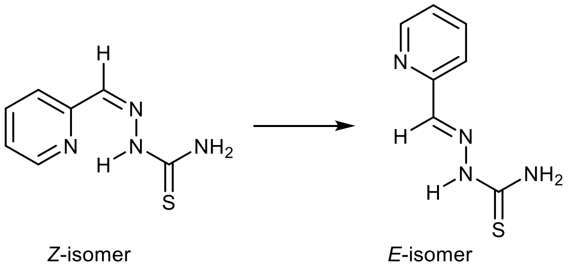
Electronic Energy = -1329.2951134 a.u.
Zero-point correction = 0.306872 (Hartree/Particle)
Thermal correction to Energy = 0.327593
Thermal correction to Enthalpy = 0.328537
Thermal correction to Gibbs Free Energy = 0.255784
Sum of electronic and zero-point Energies = -1328.988241
Sum of electronic and thermal Energies = -1328.967520
Sum of electronic and thermal Enthalpies = -1328.966576
Sum of electronic and thermal Free Energies = -1329.039330

Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
       1           6           0       -5.276443     2.400869     0.520168
       2           6           0       -6.107099     1.309660     0.337216
       3           6           0       -5.562172     0.042766     0.068227
       4           6           0       -4.144287    -0.047564    -0.028787
       5           7           0       -3.356347     1.033314     0.169871
       6           6           0       -3.894585     2.219395     0.436480
       7           7           0       -2.246844    -1.629921    -0.450307
       8           7           0       -1.323209    -0.675114    -0.194089
       9           6           0        0.021240    -0.935349    -0.247281
      10          16           0        0.685412    -2.460393    -0.543621
      11           7           0        0.765437     0.179038    -0.033545
      12           6           0        2.196546     0.245084     0.020273
      13           6           0        2.901875     0.763753    -1.060982
      14           6           0        4.292373     0.892204    -1.016227
      15           6           0        4.955599     0.477721     0.148634
      16           6           0        4.264294    -0.044662     1.254106
```

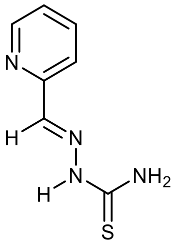
```
     17          6           0        2.876929   -0.146996    1.171799
     18          6           0        5.016334   -0.471567    2.488229
     19          6           0        5.063378    1.456339   -2.184742
     20          8           0        6.319302    0.566043    0.271492
     21          6           0       -3.500757   -1.319026   -0.364348
     22          1           0       -1.692286    0.265936    0.015381
     23          1           0        0.275280    1.061351    0.052928
     24          1           0        6.707331    0.929742   -0.532767
     25          1           0       -5.687542    3.379720    0.733848
     26          1           0       -7.183915    1.419901    0.407567
     27          1           0       -3.208460    3.045916    0.585144
     28          1           0        2.364437    1.069585   -1.951693
     29          1           0        2.318060   -0.540568    2.012982
     30          1           0        4.328924   -0.840809    3.250600
     31          1           0        5.734497   -1.264819    2.259943
     32          1           0        5.588043    0.359001    2.912660
     33          1           0        5.610454    2.366159   -1.912124
     34          1           0        4.389192    1.715525   -3.001414
     35          1           0        5.791167    0.737989   -2.579116
     36          1           0       -4.147854   -2.154760   -0.605519
     37          7           0       -6.398478   -1.035570   -0.147044
     38          1           0       -7.358110   -0.910775    0.142395
     39          1           0       -6.053494   -1.959148    0.064398
 ---------------------------------------------------------------------
```

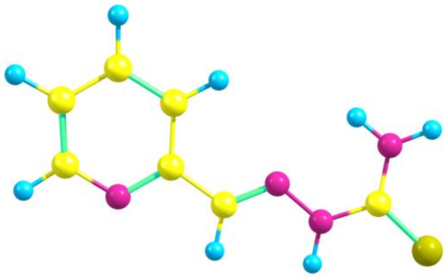
Pathways of Z/E-isomerization of 2-formylpyridine thiosemicarbazone



Pathway 1: *inversion at the imine nitrogen*

Data 13: Cartesian coordinates and energies of the optimized geometry for the *s-trans*-conformer of (*E*)-2-formylpyridine thiosemicarbazone (the gas phase).





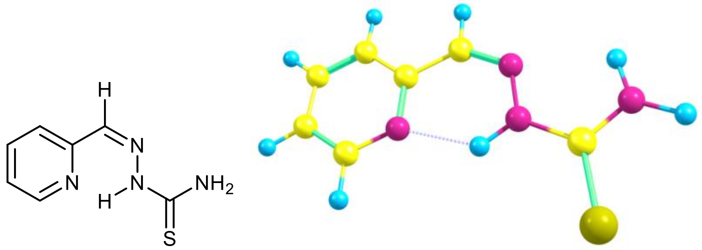
Electronic Energy = -888.903948096 a.u.
Zero-point correction = 0.150920 (Hartree/Particle)
Thermal correction to Energy = 0.162107
Thermal correction to Enthalpy = 0.163051
Thermal correction to Gibbs Free Energy = 0.112272
Sum of electronic and zero-point Energies = -888.753028

Sum of electronic and thermal Energies = -888.741842
Sum of electronic and thermal Enthalpies = -888.740897
Sum of electronic and thermal Free Energies = -888.791676

Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
---------------------------------------------------------------------
      1          7           0       -2.734797    1.582155    0.000009
      2          6           0       -2.957665    0.254332    0.000006
      3         16           0       -4.470016   -0.460424   -0.000024
      4          7           0       -1.826491   -0.527053    0.000034
      5          7           0       -0.584168    0.006379    0.000021
      6          6           0        0.412457   -0.802118    0.000014
      7          6           0        1.801146   -0.333263    0.000004
      8          7           0        2.720722   -1.313890   -0.000000
      9          6           0        4.008538   -0.966137   -0.000009
     10          6           0        4.448645    0.355673   -0.000013
     11          6           0        3.491256    1.369770   -0.000009
     12          6           0        2.147578    1.026098   -0.000001
     13          1           0       -1.792388    1.942562    0.000018
     14          1           0       -3.528899    2.198351   -0.000007
     15          1           0       -1.975561   -1.532220   -0.000000
     16          1           0        0.285972   -1.887965    0.000015
     17          1           0        4.722406   -1.784850   -0.000011
     18          1           0        5.508357    0.580208   -0.000021
     19          1           0        3.790770    2.411774   -0.000013
     20          1           0        1.371004    1.779666    0.000003
---------------------------------------------------------------------
```

Data 14: Cartesian coordinates and energies of the optimized geometry for the *s-trans*-conformer of (*Z*)-2-formylpyridine thiosemicarbazone (the gas phase).

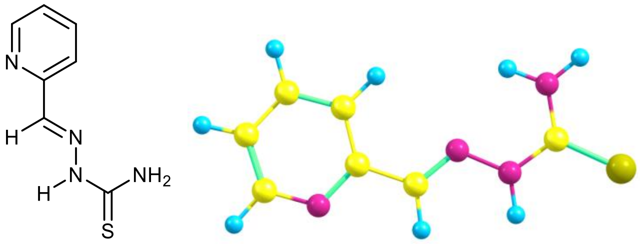


Electronic Energy = -888.907275770 a.u.
Zero-point correction = 0.151825 (Hartree/Particle)
Thermal correction to Energy = 0.162581
Thermal correction to Enthalpy = 0.163525
Thermal correction to Gibbs Free Energy = 0.114097
Sum of electronic and zero-point Energies = -888.755451
Sum of electronic and thermal Energies = -888.744695
Sum of electronic and thermal Enthalpies = -888.743751
Sum of electronic and thermal Free Energies = -888.793178

Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0        3.352750    1.232371   -0.000010
      2          6           0        2.641479    0.089384   -0.000002
      3         16           0        3.309919   -1.444462    0.000003
      4          7           0        1.273601    0.249257   -0.000003
      5          7           0        0.732573    1.479665    0.000002
      6          6           0       -0.551314    1.632909    0.000004
      7          6           0       -1.616111    0.627305    0.000002
      8          7           0       -1.286020   -0.681378    0.000001
      9          6           0       -2.265084   -1.587462   -0.000001
     10          6           0       -3.617214   -1.254278   -0.000002
     11          6           0       -3.964879    0.095783   -0.000001
     12          6           0       -2.956907    1.048777    0.000001
     13          1           0        2.877856    2.123552    0.000011
     14          1           0        4.355810    1.170652    0.000017
     15          1           0        0.666987   -0.574100   -0.000006
     16          1           0       -0.871957    2.670365    0.000007
     17          1           0       -1.950236   -2.626525   -0.000001
     18          1           0       -4.371161   -2.031622   -0.000004
     19          1           0       -5.005910    0.398165   -0.000002
     20          1           0       -3.190242    2.107003    0.000001
 ---------------------------------------------------------------------
```

Data 15: Cartesian coordinates and energies of the optimized geometry for the *s-trans*-conformer of (*E*)-2-formylpyridine thiosemicarbazone (DMSO solution).



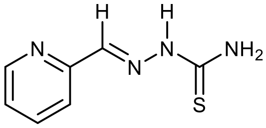
Electronic Energy = -888.919911607 a.u.
Zero-point correction = 0.151064 (Hartree/Particle)
Thermal correction to Energy = 0.162156
Thermal correction to Enthalpy = 0.163100
Thermal correction to Gibbs Free Energy = 0.112612
Sum of electronic and zero-point Energies = -888.768847
Sum of electronic and thermal Energies = -888.757755
Sum of electronic and thermal Enthalpies = -888.756811
Sum of electronic and thermal Free Energies = -888.807299

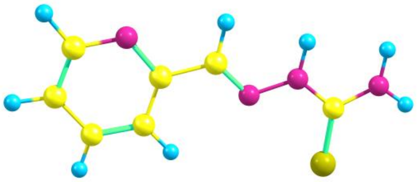
Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0       -2.717623    1.576292    0.000008
      2          6           0       -2.935974    0.257524   -0.000007
      3         16           0       -4.478509   -0.448616    0.000014
      4          7           0       -1.827995   -0.537936   -0.000004
      5          7           0       -0.579445   -0.004332   -0.000004
      6          6           0        0.411486   -0.817764    0.000001
```

```
      7          6           0        1.799823   -0.342262   -0.000003
      8          7           0        2.728326   -1.316911    0.000002
      9          6           0        4.015227   -0.956666   -0.000001
     10          6           0        4.441448    0.369791   -0.000008
     11          6           0        3.475508    1.375608   -0.000013
     12          6           0        2.134096    1.019233   -0.000010
     13          1           0       -1.774504    1.939818    0.000007
     14          1           0       -3.502624    2.206044    0.000022
     15          1           0       -1.972931   -1.543565    0.000000
     16          1           0        0.278039   -1.902014    0.000006
     17          1           0        4.739288   -1.765801    0.000003
     18          1           0        5.498838    0.603361   -0.000010
     19          1           0        3.765088    2.419894   -0.000018
     20          1           0        1.352426    1.767536   -0.000013
 ---------------------------------------------------------------------
```

Data 16: Cartesian coordinates and energies of the optimized geometry for the *s-cis*-conformer of (*E*)-2-formylpyridine thiosemicarbazone (DMSO solution).



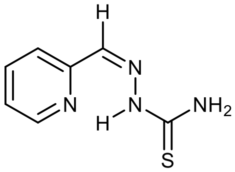


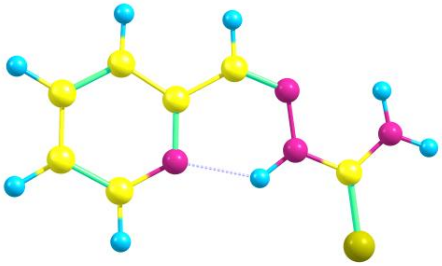
Electronic Energy = -888.911230345 a.u.
Zero-point correction= 0.150613 (Hartree/Particle)
Thermal correction to Energy= 0.161969
Thermal correction to Enthalpy= 0.162913
Thermal correction to Gibbs Free Energy= 0.111671
Sum of electronic and zero-point Energies= -888.760617
Sum of electronic and thermal Energies= -888.749261
Sum of electronic and thermal Enthalpies= -888.748317
Sum of electronic and thermal Free Energies= -888.799560

Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0       -4.130487   -1.047284    0.000023
      2          6           0       -3.059984   -0.229883   -0.000024
      3         16           0       -3.224327    1.452494    0.000002
      4          7           0       -1.862075   -0.889360   -0.000018
      5          7           0       -0.672317   -0.241639   -0.000012
      6          6           0        0.381118   -0.970714   -0.000006
      7          6           0        1.724856   -0.378338   -0.000002
      8          7           0        2.733813   -1.269112    0.000002
      9          6           0        3.985220   -0.799277    0.000006
     10          6           0        4.295762    0.558636    0.000007
     11          6           0        3.246423    1.477387    0.000003
     12          6           0        1.940673    1.007024   -0.000002
     13          1           0       -4.058490   -2.054941    0.000042
     14          1           0       -5.049722   -0.636865    0.000056
     15          1           0       -1.859996   -1.907882   -0.000013
     16          1           0        0.343549   -2.063364   -0.000005
     17          1           0        4.776163   -1.543222    0.000010
     18          1           0        5.329138    0.882396    0.000011
     19          1           0        3.445152    2.542735    0.000004
     20          1           0        1.096496    1.683990   -0.000005
 ---------------------------------------------------------------------
```

Data 17: Cartesian coordinates and energies of the optimized geometry for the *s*-*trans*-conformer of (*Z*)-2-formylpyridine thiosemicarbazone (DMSO solution).



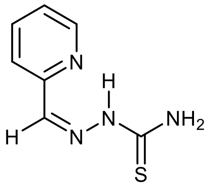


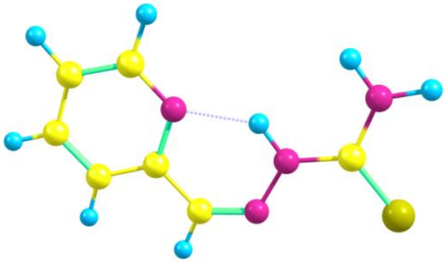
Electronic Energy = -888.922156341 a.u.
Zero-point correction = 0.151750 (Hartree/Particle)
Thermal correction to Energy = 0.162479
Thermal correction to Enthalpy = 0.163423
Thermal correction to Gibbs Free Energy = 0.114031
Sum of electronic and zero-point Energies = -888.770407
Sum of electronic and thermal Energies = -888.759678
Sum of electronic and thermal Enthalpies = -888.758734
Sum of electronic and thermal Free Energies = -888.808126

Standard orientation:

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0       -3.354941   -1.222205   -0.000002
      2          6           0       -2.623073   -0.103060    0.000000
      3         16           0       -3.291342    1.458426   -0.000000
      4          7           0       -1.269228   -0.260841    0.000001
      5          7           0       -0.730347   -1.506926    0.000003
      6          6           0        0.552739   -1.643983    0.000003
      7          6           0        1.611545   -0.627166    0.000001
      8          7           0        1.271881    0.680435   -0.000001
      9          6           0        2.248054    1.590967   -0.000003
     10          6           0        3.601974    1.259578   -0.000003
     11          6           0        3.956139   -0.087415   -0.000002
     12          6           0        2.950175   -1.045724    0.000000
     13          1           0       -2.900226   -2.125272    0.000006
     14          1           0       -4.359121   -1.157757    0.000007
     15          1           0       -0.644015    0.551238   -0.000001
     16          1           0        0.886856   -2.676953    0.000005
     17          1           0        1.934210    2.629779   -0.000004
     18          1           0        4.352316    2.039979   -0.000005
     19          1           0        4.997743   -0.385562   -0.000002
     20          1           0        3.186845   -2.102676    0.000002
 ---------------------------------------------------------------------
```

Data 18: Cartesian coordinates and energies of the optimized geometry for the *s*-*cis*-conformer of (*Z*)-2-formylpyridine thiosemicarbazone (DMSO solution).

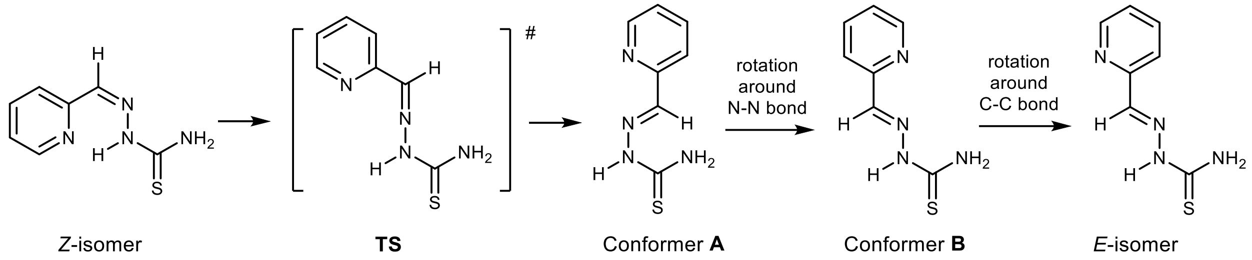




Electronic Energy = -888.914231651 a.u.
Zero-point correction = 0.151507 (Hartree/Particle)
Thermal correction to Energy = 0.162382
Thermal correction to Enthalpy = 0.163326
Thermal correction to Gibbs Free Energy = 0.113630
Sum of electronic and zero-point Energies = -888.762725
Sum of electronic and thermal Energies = -888.751849
Sum of electronic and thermal Enthalpies = -888.750905
Sum of electronic and thermal Free Energies = -888.800602

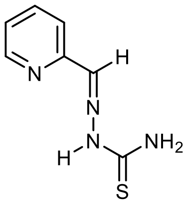
Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0        2.696044    1.820786   -0.000001
      2          6           0        2.525585    0.483940    0.000001
      3         16           0        3.847473   -0.574243   -0.000003
      4          7           0        1.214427    0.101239    0.000004
      5          7           0        0.856849   -1.204860    0.000002
      6          6           0       -0.398699   -1.502650    0.000001
      7          6           0       -1.582958   -0.633044    0.000000
      8          7           0       -1.415401    0.707772   -0.000001
      9          6           0       -2.499605    1.487431   -0.000002
     10          6           0       -3.799162    0.985251   -0.000002
     11          6           0       -3.977117   -0.396452   -0.000000
     12          6           0       -2.857292   -1.218606    0.000001
     13          1           0        1.924127    2.472242    0.000018
     14          1           0        3.632619    2.189648    0.000011
     15          1           0        0.446011    0.788985    0.000006
     16          1           0       -0.596799   -2.570236    0.000002
     17          1           0       -2.320305    2.557578   -0.000003
     18          1           0       -4.643697    1.662516   -0.000002
     19          1           0       -4.971942   -0.825567    0.000000
     20          1           0       -2.957525   -2.297054    0.000002
 ---------------------------------------------------------------------
```

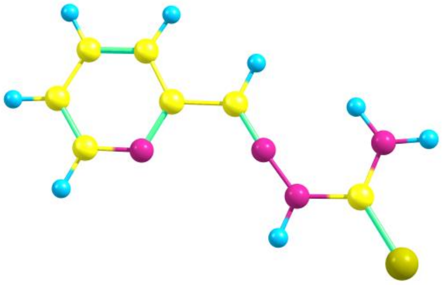


The gas phase

Data 19: Cartesian coordinates, energy, imaginary frequency of the transition state for the transformation of the most stable conformer of (*Z*)-2-formylpyridine thiosemicarbazone into conformer **A** of the (*E*)-isomer (the gas phase).



TS



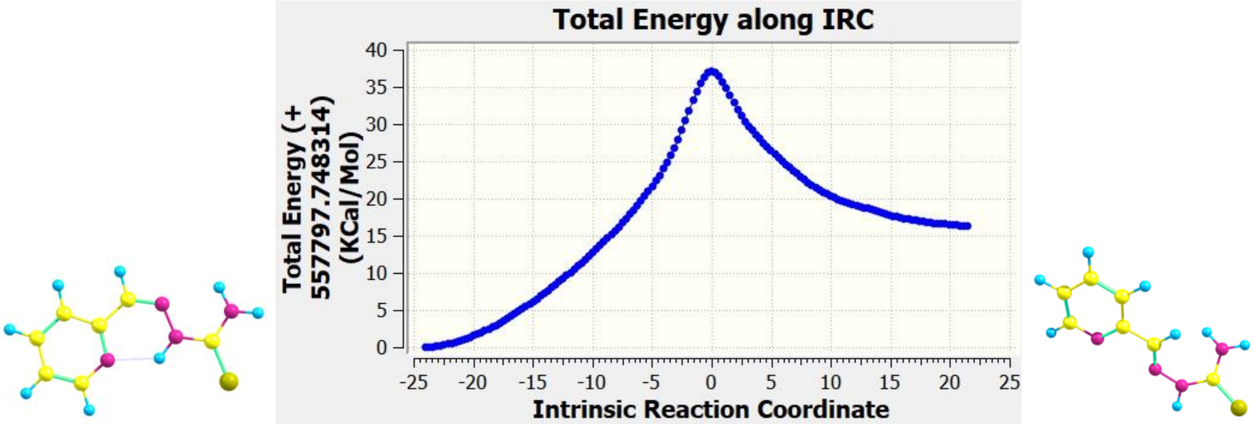
Imaginary Frequency = -389.4919 cm^{-1}
Electronic Energy = -888.848199567 a.u.
Zero-point correction = 0.149264 (Hartree/Particle)
Thermal correction to Energy = 0.160171
Thermal correction to Enthalpy = 0.161115
Thermal correction to Gibbs Free Energy = 0.111157
Sum of electronic and zero-point Energies = -888.698936
Sum of electronic and thermal Energies = -888.688029
Sum of electronic and thermal Enthalpies = -888.687085
Sum of electronic and thermal Free Energies = -888.737042

Standard orientation:

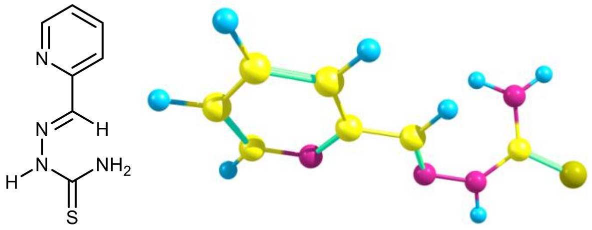
```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0        2.965830    1.497613    0.000000
      2          6           0        2.980319    0.153637    0.000000
      3         16           0        4.336690   -0.808205    0.000000
      4          7           0        1.705393   -0.432123    0.000000
      5          7           0        0.594941    0.208011   -0.000000
      6          6           0       -0.442777    0.917679   -0.000000
      7          6           0       -1.815759    0.349077   -0.000000
      8          7           0       -1.945175   -0.987080   -0.000000
      9          6           0       -3.176507   -1.493810   -0.000000
     10          6           0       -4.336982   -0.716764    0.000000
     11          6           0       -4.199865    0.667919    0.000000
     12          6           0       -2.919823    1.210787    0.000000
     13          1           0        2.094148    2.004995   -0.000001
     14          1           0        3.841828    1.990956   -0.000001
     15          1           0        1.704933   -1.451068    0.000000
```

```
      16           1             0        -0.406909     2.020878    -0.000001
      17           1             0        -3.245728    -2.578534    -0.000000
      18           1             0        -5.312012    -1.188869     0.000000
      19           1             0        -5.072307     1.311808     0.000001
      20           1             0        -2.769549     2.285015     0.000000
 ---------------------------------------------------------------------
```

Data 20: The intrinsic reaction coordinate analysis for the transformation of the most stable conformer of (*Z*)-2-formylpyridine thiosemicarbazone into conformer **A** of the (*E*)-isomer (the gas phase).



Data 21: Cartesian coordinates and energies of the optimized geometry for the conformer **A** of (*E*)-2-formylpyridine thiosemicarbazone (the gas phase).



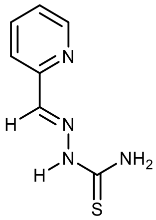
Electronic Energy = -888.881488140 a.u.
Zero-point correction = 0.151444 (Hartree/Particle)
Thermal correction to Energy = 0.162429
Thermal correction to Enthalpy = 0.163374
Thermal correction to Gibbs Free Energy = 0.112737
Sum of electronic and zero-point Energies = -888.730044
Sum of electronic and thermal Energies = -888.719059
Sum of electronic and thermal Enthalpies = -888.718115
Sum of electronic and thermal Free Energies = -888.768751

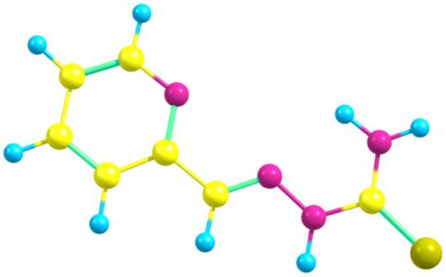
Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0        -2.356166     1.250978     0.756314
      2          6           0        -2.810104     0.126306     0.130661
      3         16           0        -4.418003    -0.105958    -0.260216
```

```
      4          7           0       -1.885383   -0.850278   -0.171453
      5          7           0       -0.524587   -0.919550   -0.061724
      6          6           0        0.203235    0.132558   -0.162203
      7          6           0        1.671161    0.054193   -0.078780
      8          7           0        2.250147   -1.110859    0.254459
      9          6           0        3.578004   -1.152979    0.306566
     10          6           0        4.404361   -0.057224    0.041213
     11          6           0        3.804036    1.150336   -0.296542
     12          6           0        2.415847    1.210158   -0.355933
     13          1           0       -1.512521    1.203954    1.311998
     14          1           0       -3.088278    1.846683    1.112339
     15          1           0       -2.298364   -1.743152   -0.397569
     16          1           0       -0.207978    1.120654   -0.368922
     17          1           0        4.012499   -2.111268    0.578849
     18          1           0        5.481401   -0.155776    0.103343
     19          1           0        4.402297    2.028816   -0.509940
     20          1           0        1.911681    2.133299   -0.619716
 ---------------------------------------------------------------------
```

Data 21: Cartesian coordinates and energies of the optimized geometry for the conformer **B** of (*E*)-2-formylpyridine thiosemicarbazone (the gas phase).





Electronic Energy =	-888.900127943 a.u.
Zero-point correction =	0.150988 (Hartree/Particle)
Thermal correction to Energy =	0.162051
Thermal correction to Enthalpy =	0.162995
Thermal correction to Gibbs Free Energy =	0.112568
Sum of electronic and zero-point Energies =	-888.749140
Sum of electronic and thermal Energies =	-888.738077
Sum of electronic and thermal Enthalpies =	-888.737133
Sum of electronic and thermal Free Energies =	-888.787560

Standard orientation:

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0       -2.681565    1.575982    0.000003
      2          6           0       -2.945576    0.258133   -0.000000
      3         16           0       -4.474355   -0.421858   -0.000003
      4          7           0       -1.831536   -0.553033    0.000003
      5          7           0       -0.590195   -0.031995    0.000002
      6          6           0        0.409701   -0.833773    0.000002
      7          6           0        1.796720   -0.354545    0.000001
      8          7           0        2.027911    0.969899   -0.000000
      9          6           0        3.292873    1.380158   -0.000001
     10          6           0        4.393060    0.518432   -0.000002
     11          6           0        4.152516   -0.851057   -0.000001
     12          6           0        2.835604   -1.296996    0.000000
     13          1           0       -1.724493    1.902172    0.000002
```

```
     14          1           0       -3.454868    2.218010   -0.000000
     15          1           0       -2.004097   -1.554967   -0.000001
     16          1           0        0.265567   -1.919364    0.000002
     17          1           0        3.443150    2.456576   -0.000002
     18          1           0        5.400523    0.916396   -0.000003
     19          1           0        4.972819   -1.559776   -0.000001
     20          1           0        2.609382   -2.357400    0.000001
 ---------------------------------------------------------------------
```

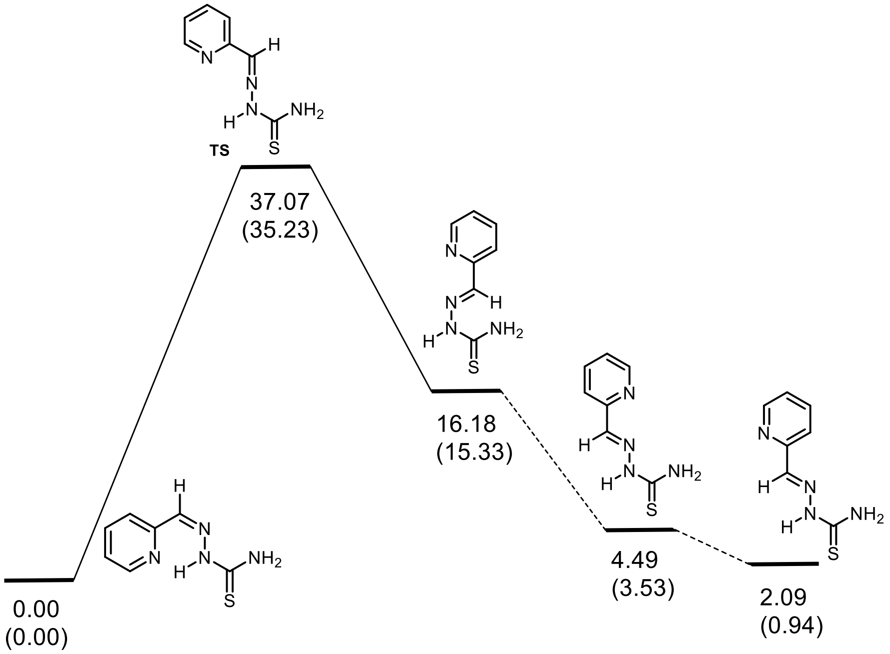
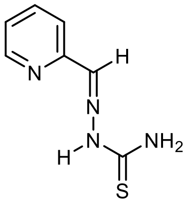


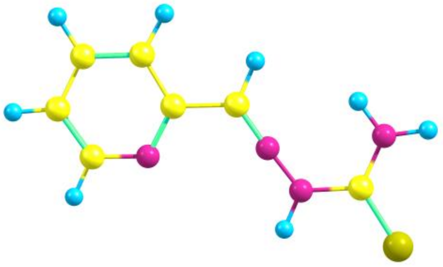
Figure S14. Electronic energy and Gibbs free energy profiles (in kcal/mol) for the transformation of the most stable conformer of (*Z*)-2-formylpyridine thiosemicarbazone into the most stable conformer of (*E*)-2-formylpyridine thiosemicarbazone in the gas phase. Free energies (in parentheses) at 298 K and 1 atm.

DMSO solution

Data 22: Cartesian coordinates, energy, imaginary frequency of the transition state for the transformation of the most stable conformer of (*Z*)-2-formylpyridine thiosemicarbazone into conformer **A** of the (*E*)-isomer (DMSO solution).



TS



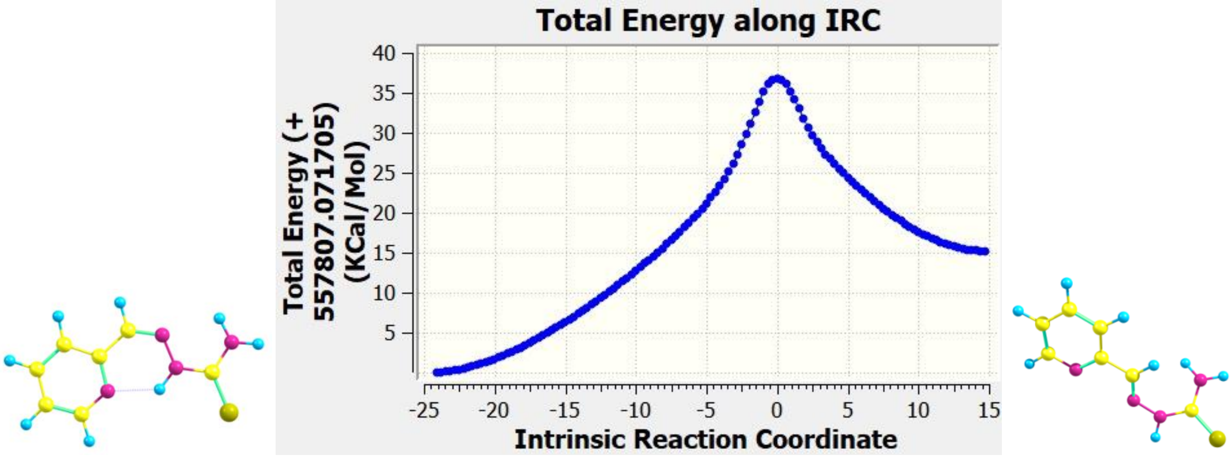
Imaginary Frequency = -414.4982 cm^{-1}
Electronic Energy = -888.86340949 a.u.
Zero-point correction = 0.149585 (Hartree/Particle)

Thermal correction to Energy = 0.160351
Thermal correction to Enthalpy = 0.161295
Thermal correction to Gibbs Free Energy = 0.111633
Sum of electronic and zero-point Energies = -888.713825
Sum of electronic and thermal Energies = -888.703059
Sum of electronic and thermal Enthalpies = -888.702115
Sum of electronic and thermal Free Energies = -888.751777

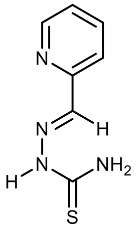
Standard orientation:

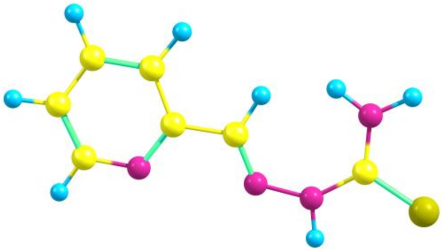
```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0       -2.985819    1.496245    0.000000
      2          6           0       -2.975101    0.165038    0.000000
      3         16           0       -4.337983   -0.825007    0.000000
      4          7           0       -1.708226   -0.419986    0.000000
      5          7           0       -0.601707    0.233207    0.000000
      6          6           0        0.449146    0.925383    0.000000
      7          6           0        1.818901    0.346209   -0.000000
      8          7           0        1.949694   -0.991850   -0.000000
      9          6           0        3.184168   -1.498589   -0.000000
     10          6           0        4.342405   -0.718836   -0.000000
     11          6           0        4.203748    0.666057   -0.000000
     12          6           0        2.922462    1.208000   -0.000000
     13          1           0       -2.122289    2.021070    0.000000
     14          1           0       -3.863291    1.990142    0.000000
     15          1           0       -1.702486   -1.438909    0.000000
     16          1           0        0.422023    2.025240    0.000000
     17          1           0        3.258066   -2.582561   -0.000000
     18          1           0        5.317490   -1.190032   -0.000000
     19          1           0        5.074986    1.310770   -0.000000
     20          1           0        2.771264    2.281520    0.000000
 ---------------------------------------------------------------------
```

Data 23: The intrinsic reaction coordinate analysis for the transformation of the most stable conformer of (*Z*)-2-formylpyridine thiosemicarbazone into conformer **A** of the (*E*)-isomer (DMSO solution).



Data 24: Cartesian coordinates and energies of the optimized geometry for the conformer **A** of (*E*)-2-formylpyridine thiosemicarbazone (DMSO solution).



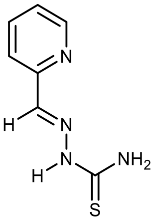


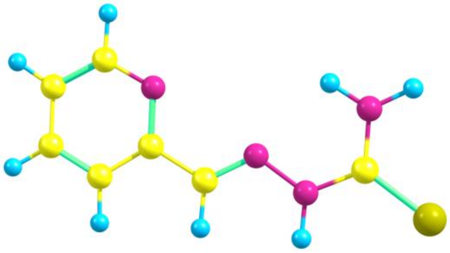
Electronic Energy = -888.897966374 a.u.
Zero-point correction = 0.150811 (Hartree/Particle)
Thermal correction to Energy = 0.161452
Thermal correction to Enthalpy = 0.162396
Thermal correction to Gibbs Free Energy = 0.112766
Sum of electronic and zero-point Energies = -888.747156
Sum of electronic and thermal Energies = -888.736515
Sum of electronic and thermal Enthalpies = -888.735570
Sum of electronic and thermal Free Energies = -888.785200

Standard orientation:

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0       -2.864719   -0.820168   -0.000000
      2          6           0       -2.123072   -1.933289   -0.000000
      3         16           0       -2.837293   -3.476619   -0.000000
      4          7           0       -0.748796   -1.871613   -0.000000
      5          7           0        0.205122   -0.900508   -0.000000
      6          6           0       -0.000000    0.363051    0.000000
      7          6           0        1.134085    1.308227    0.000000
      8          7           0        2.392453    0.833437    0.000000
      9          6           0        3.391405    1.715387    0.000000
     10          6           0        3.206029    3.100291    0.000000
     11          6           0        1.904518    3.588995    0.000000
     12          6           0        0.850487    2.680380    0.000000
     13          1           0       -2.499441    0.115232    0.000000
     14          1           0       -3.867145   -0.926229   -0.000000
     15          1           0       -0.326615   -2.788951   -0.000000
     16          1           0       -0.968809    0.853351    0.000000
     17          1           0        4.395536    1.300964    0.000000
     18          1           0        4.060745    3.765154    0.000000
     19          1           0        1.710274    4.654982    0.000000
     20          1           0       -0.177001    3.025125    0.000000
 ---------------------------------------------------------------------
```

Data 25: Cartesian coordinates and energies of the optimized geometry for the conformer **B** of (*E*)-2-formylpyridine thiosemicarbazone (DMSO solution).



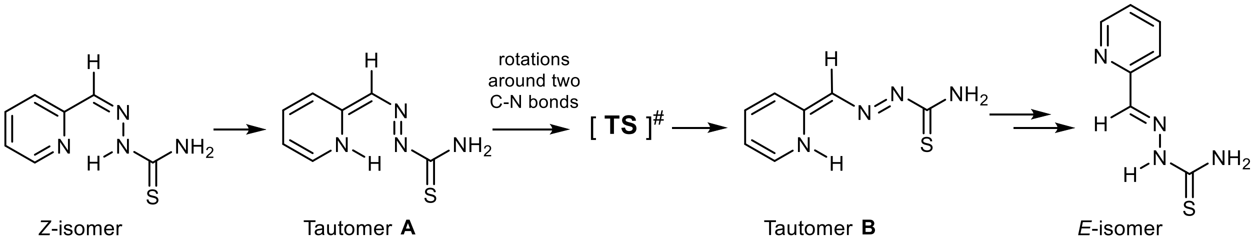


Electronic Energy =	-888.917947875 a.u.
Zero-point correction =	0.151125 (Hartree/Particle)
Thermal correction to Energy =	0.162198
Thermal correction to Enthalpy =	0.163142
Thermal correction to Gibbs Free Energy =	0.112708
Sum of electronic and zero-point Energies =	-888.766823
Sum of electronic and thermal Energies =	-888.755750
Sum of electronic and thermal Enthalpies =	-888.754806
Sum of electronic and thermal Free Energies =	-888.805240

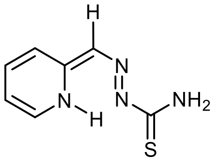
Standard orientation:

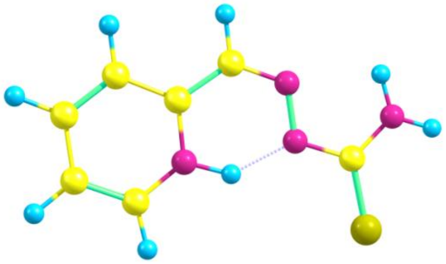
```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0       -2.727373    1.579333    0.000001
      2          6           0       -2.942013    0.260090   -0.000003
      3         16           0       -4.482412   -0.451424    0.000002
      4          7           0       -1.830685   -0.530703   -0.000002
      5          7           0       -0.585746    0.012272   -0.000002
      6          6           0        0.407138   -0.798590   -0.000000
      7          6           0        1.801646   -0.337079   -0.000000
      8          7           0        2.057565    0.984829   -0.000001
      9          6           0        3.332481    1.371438    0.000000
     10          6           0        4.413525    0.485584    0.000001
     11          6           0        4.146643   -0.878782    0.000001
     12          6           0        2.820079   -1.299289    0.000001
     13          1           0       -1.783987    1.942872    0.000001
     14          1           0       -3.513559    2.207549    0.000004
     15          1           0       -1.971865   -1.537094   -0.000001
     16          1           0        0.254588   -1.880815   -0.000001
     17          1           0        3.507749    2.443456   -0.000000
     18          1           0        5.428133    0.863888    0.000001
     19          1           0        4.952269   -1.603356    0.000002
     20          1           0        2.571949   -2.354056    0.000001
 ---------------------------------------------------------------------
```

Pathway 2: *via tautomeric shift*



Data 26: Cartesian coordinates and energies of the optimized geometry for the tautomer **A** formed via tautomeric shift in *s*-*trans*-conformer of (*Z*)-2-formylpyridine thiosemicarbazone (the gas phase).



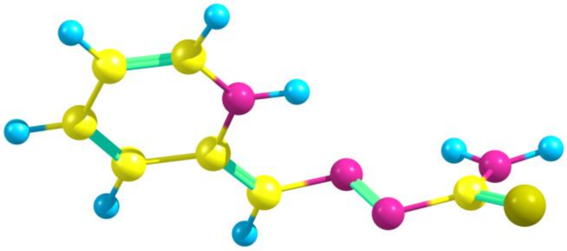


Electronic Energy = -888.8852658404 a.u.
Zero-point correction = 0.150269 (Hartree/Particle)
Thermal correction to Energy = 0.160867
Thermal correction to Enthalpy = 0.161811
Thermal correction to Gibbs Free Energy = 0.112901
Sum of electronic and zero-point Energies = -888.734997
Sum of electronic and thermal Energies = -888.724399
Sum of electronic and thermal Enthalpies = -888.723455
Sum of electronic and thermal Free Energies = -888.772365

Standard orientation:

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0       -3.328544   -1.188378   -0.000003
      2          6           0       -2.550630   -0.086955    0.000001
      3         16           0       -3.163957    1.475238   -0.000001
      4          7           0       -1.175554   -0.265794    0.000003
      5          7           0       -0.770731   -1.517454    0.000006
      6          6           0        0.539792   -1.732737    0.000005
      7          6           0        1.559622   -0.739482    0.000001
      8          7           0        1.200273    0.582147    0.000001
      9          6           0        2.092972    1.592671   -0.000002
     10          6           0        3.441755    1.336077   -0.000005
     11          6           0        3.866706   -0.011252   -0.000005
     12          6           0        2.945464   -1.032573   -0.000001
     13          1           0       -2.891987   -2.099465    0.000003
     14          1           0       -4.327880   -1.082147    0.000001
     15          1           0        0.848307   -2.770547    0.000007
     16          1           0        1.675192    2.591108   -0.000001
     17          1           0        4.151187    2.151905   -0.000008
     18          1           0        4.926153   -0.240043   -0.000007
     19          1           0        3.257462   -2.069178   -0.000001
     20          1           0        0.132675    0.686420    0.000004
 ---------------------------------------------------------------------
```

Data 27: Cartesian coordinates, energy, imaginary frequency of the transition state for the transformation of the tautomer **A** into the tautomer **B** (the gas phase).

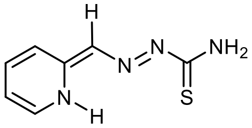


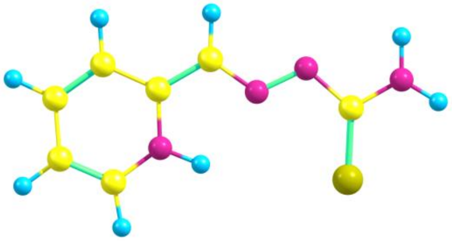
Imaginary Frequency = -519.9298 cm^{-1}
Electronic Energy = -888.829551222 a.u.
Zero-point correction = 0.148768 (Hartree/Particle)
Thermal correction to Energy = 0.159665
Thermal correction to Enthalpy = 0.160610
Thermal correction to Gibbs Free Energy = 0.109717
Sum of electronic and zero-point Energies = -888.680783
Sum of electronic and thermal Energies = -888.669886
Sum of electronic and thermal Enthalpies = -888.668942
Sum of electronic and thermal Free Energies = -888.719834

Standard orientation:

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0       -3.253799   -0.936688    1.023174
      2          6           0       -2.813325   -0.124869    0.052076
      3         16           0       -3.583918    1.198469   -0.562451
      4          7           0       -1.523356   -0.474764   -0.522372
      5          7           0       -0.774763   -1.058262    0.284785
      6          6           0        0.514532   -1.425210   -0.233039
      7          6           0        1.601274   -0.625903   -0.111951
      8          7           0        1.508920    0.683542    0.389800
      9          6           0        2.587452    1.516014    0.547240
     10          6           0        3.839015    1.119526    0.217436
     11          6           0        4.005819   -0.206581   -0.320572
     12          6           0        2.945073   -1.033211   -0.479104
     13          1           0       -2.599089   -1.587714    1.439544
     14          1           0       -4.118286   -0.718136    1.492070
     15          1           0        0.588179   -2.441093   -0.596501
     16          1           0        2.359419    2.496926    0.943722
     17          1           0        4.677726    1.787944    0.346960
     18          1           0        4.996642   -0.544668   -0.601992
     19          1           0        3.067873   -2.030413   -0.883081
     20          1           0        0.592176    1.046264    0.598270
 ---------------------------------------------------------------------
```

Data 28: Cartesian coordinates and energies of the optimized geometry for the tautomer **B** formed from the tautomer **A** (the gas phase).





Electronic Energy = -888.876986628 a.u.

Zero-point correction = 0.151034 (Hartree/Particle)

Thermal correction to Energy = 0.161938

Thermal correction to Enthalpy = 0.162883

Thermal correction to Gibbs Free Energy = 0.112987

Sum of electronic and zero-point Energies = -888.725952

Sum of electronic and thermal Energies = -888.715048

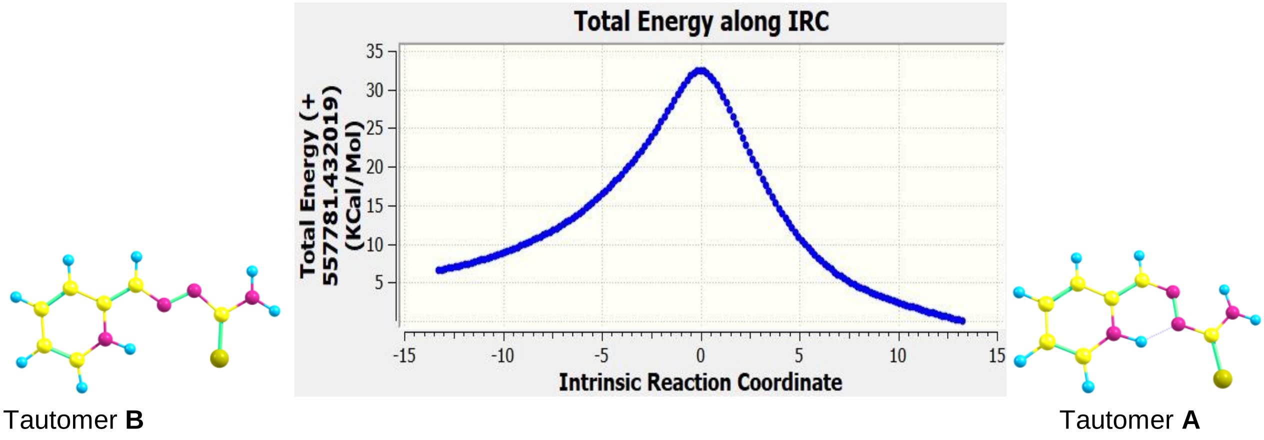
Sum of electronic and thermal Enthalpies = -888.714104

Sum of electronic and thermal Free Energies = -888.764000

Standard orientation:

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          7           0       -4.118575   -0.829948   -0.000008
      2          6           0       -2.932777   -0.179586   -0.000000
      3         16           0       -2.836387    1.497573    0.000007
      4          7           0       -1.886599   -1.114137    0.000002
      5          7           0       -0.723313   -0.576802    0.000002
      6          6           0        0.357087   -1.349003    0.000004
      7          6           0        1.584646   -0.659442   -0.000003
      8          7           0        1.551196    0.717070   -0.000011
      9          6           0        2.650689    1.503200   -0.000006
     10          6           0        3.901749    0.947431    0.000002
     11          6           0        4.000991   -0.467527    0.000004
     12          6           0        2.875936   -1.252434    0.000001
     13          1           0       -4.127215   -1.839041   -0.000019
     14          1           0       -4.975450   -0.303777   -0.000013
     15          1           0        0.319064   -2.435826    0.000008
     16          1           0        2.469430    2.569887   -0.000012
     17          1           0        4.779039    1.578110    0.000006
     18          1           0        4.979780   -0.933355    0.000010
     19          1           0        2.944765   -2.332616    0.000004
     20          1           0        0.603895    1.106346   -0.000006
 ---------------------------------------------------------------------
```

Data 29: The intrinsic reaction coordinate analysis for the transformation of the tautomer **A** into the tautomer **B** (the gas phase).



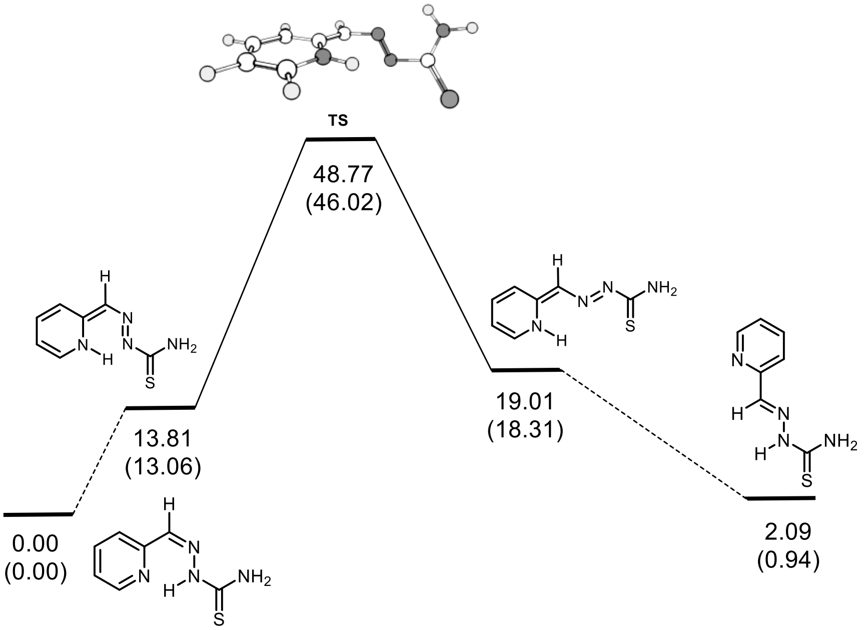
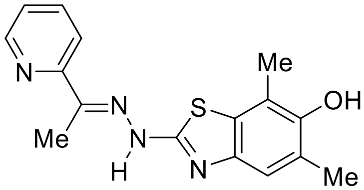
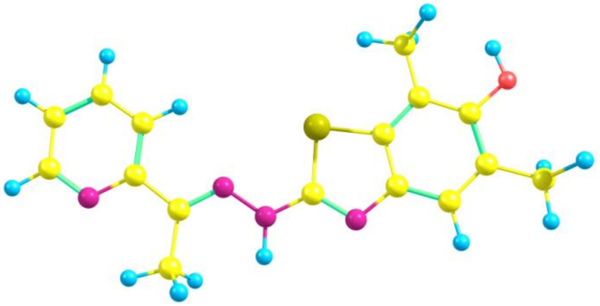


Figure S15. Electronic energy and Gibbs free energy profiles (in kcal/mol) for the transformation of the most stable conformer of (*Z*)-2-formylpyridine thiosemicarbazone into the most stable conformer of (*E*)-2-formylpyridine thiosemicarbazone in the gas phase. Free energies (in parentheses) at 298 K and 1 atm.

Geometry optimization of some stereoisomers and tautomers of H$L^{1c'}$ (DMSO solution)

Data 30: Cartesian coordinates and energies of the optimized geometry for the *s-cis*-conformer (around the exocyclic C-N bond) of (*E*)-**H*L*$^{1c'}$** (DMSO solution).





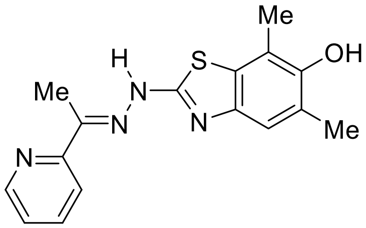
Electronic Energy =	-1312.03278232 a.u.
Zero-point correction =	0.294370 (Hartree/Particle)
Thermal correction to Energy =	0.315455
Thermal correction to Enthalpy =	0.316400
Thermal correction to Gibbs Free Energy =	0.242121
Sum of electronic and zero-point Energies =	-1311.738412
Sum of electronic and thermal Energies =	-1311.717327
Sum of electronic and thermal Enthalpies =	-1311.716383
Sum of electronic and thermal Free Energies =	-1311.790661

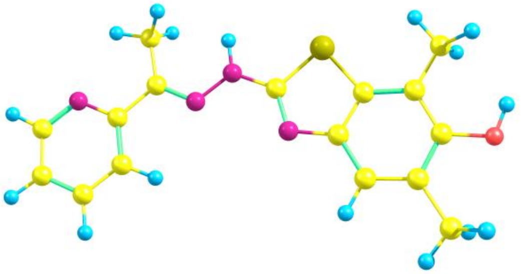
Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0       -4.682881    0.712121   -0.000273
      2          6           0       -4.914397   -0.678482   -0.001004
      3          6           0       -3.821036   -1.540094   -0.000631
      4          6           0       -2.519794   -1.030147    0.000239
      5          6           0       -2.331651    0.366295    0.001174
      6          6           0       -3.396275    1.270489    0.001767
      7          6           0       -6.327816   -1.203236   -0.002423
      8          6           0       -3.201235    2.766733    0.001988
      9          7           0       -1.357156   -1.793646    0.000520
     10          6           0       -0.313353   -1.028133    0.001255
     11         16           0       -0.598220    0.724366    0.001568
     12          8           0       -5.805079    1.508537   -0.002297
     13          7           0        0.968856   -1.505303    0.001432
     14          7           0        2.008329   -0.643601    0.000984
     15          1           0       -5.557939    2.440092   -0.000578
     16          1           0        1.092122   -2.512992    0.000244
     17          6           0        3.211064   -1.115437    0.000254
     18          6           0        3.526957   -2.585487   -0.000061
     19          6           0        4.309882   -0.112675   -0.000336
     20          6           0        4.043812    1.267834   -0.001395
     21          6           0        5.106137    2.158655   -0.001904
     22          6           0        6.410095    1.660986   -0.001397
     23          6           0        6.581181    0.280949   -0.000408
     24          7           0        5.565817   -0.590418    0.000106
     25          1           0       -3.973911   -2.613502   -0.001117
     26          1           0       -6.333046   -2.294252   -0.001819
     27          1           0       -6.882488   -0.856543    0.874649
     28          1           0       -6.880367   -0.857577   -0.881253
     29          1           0       -2.144704    3.032473    0.038606
```

```
     30          1           0       -3.678534    3.237182    0.868929
     31          1           0       -3.617373    3.229446   -0.899930
     32          1           0        4.601888   -2.740253   -0.000541
     33          1           0        3.104839   -3.074987   -0.884981
     34          1           0        3.105583   -3.075216    0.885080
     35          1           0        3.020899    1.617682   -0.001824
     36          1           0        4.922775    3.227012   -0.002729
     37          1           0        7.268736    2.320859   -0.001793
     38          1           0        7.578611   -0.149024   -0.000015
 ---------------------------------------------------------------------
```

Data 31: Cartesian coordinates and energies of the optimized geometry for the *s*-*trans*-conformer (around the exocyclic C-N bond) of (*E*)-**H***L*$^{\mathbf{1c'}}$ (DMSO solution).





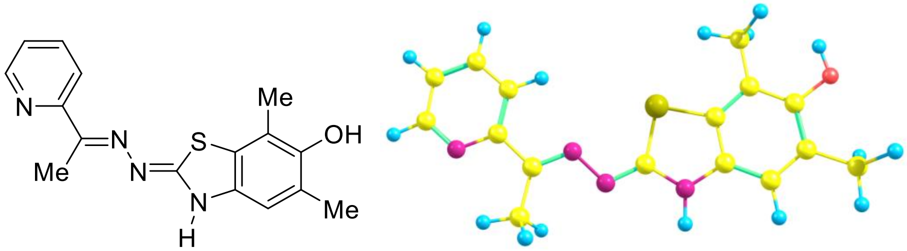
Electronic Energy =	-1312.02804160 a.u.
Zero-point correction =	0.294415 (Hartree/Particle)
Thermal correction to Energy =	0.315485
Thermal correction to Enthalpy =	0.316429
Thermal correction to Gibbs Free Energy =	0.242521
Sum of electronic and zero-point Energies =	-1311.733626
Sum of electronic and thermal Energies =	-1311.712557
Sum of electronic and thermal Enthalpies =	-1311.711612
Sum of electronic and thermal Free Energies =	-1311.785520

Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0       -4.773395    0.534649   -0.000016
      2          6           0       -4.093151    1.769325    0.000009
      3          6           0       -2.701030    1.768454    0.000027
      4          6           0       -1.993837    0.563171    0.000020
      5          6           0       -2.713812   -0.647993   -0.000005
      6          6           0       -4.109270   -0.700725   -0.000023
      7          6           0       -4.877312    3.056859    0.000016
      8          6           0       -4.880865   -1.997080   -0.000050
      9          7           0       -0.607583    0.447187    0.000039
     10          6           0       -0.252306   -0.794194    0.000027
     11         16           0       -1.574662   -1.997280   -0.000010
     12          8           0       -6.147255    0.605371   -0.000032
     13          7           0        1.033971   -1.272778    0.000047
     14          7           0        2.088894   -0.424904    0.000019
     15          1           0       -6.532004   -0.278308   -0.000049
     16          1           0        1.176014   -2.276127    0.000035
     17          6           0        3.277495   -0.931572    0.000023
     18          6           0        3.559744   -2.409354    0.000056
     19          6           0        4.403121    0.042661   -0.000000
     20          6           0        4.171891    1.429417    0.000025
     21          6           0        5.256198    2.293342    0.000001
     22          6           0        6.547263    1.763083   -0.000047
     23          6           0        6.683685    0.379209   -0.000067
```

```
     24          7           0        5.646660   -0.466380   -0.000044
     25          1           0       -2.156448    2.705933    0.000046
     26          1           0       -4.205476    3.916434    0.000040
     27          1           0       -5.526345    3.127794   -0.877925
     28          1           0       -5.526375    3.127767    0.877936
     29          1           0       -4.213808   -2.859246   -0.000062
     30          1           0       -5.520342   -2.087387   -0.885221
     31          1           0       -5.520351   -2.087418    0.885112
     32          1           0        4.630878   -2.588195    0.000031
     33          1           0        3.128482   -2.890267   -0.885240
     34          1           0        3.128529   -2.890215    0.885403
     35          1           0        3.157764    1.803705    0.000063
     36          1           0        5.099734    3.365980    0.000020
     37          1           0        7.422201    2.401225   -0.000066
     38          1           0        7.670066   -0.075562   -0.000104
 ---------------------------------------------------------------------
```

Data 32: Cartesian coordinates and energies of the optimized geometry for (*E*,*Z*)-**H*L***$^{\mathbf{1c'}}$ (DMSO solution).



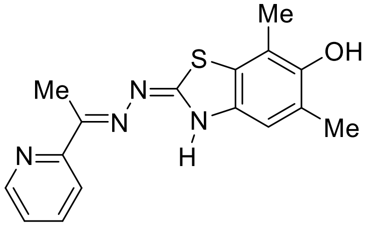
Electronic Energy = -1312.03026828 a.u.
Zero-point correction = 0.294120 (Hartree/Particle)
Thermal correction to Energy = 0.315330
Thermal correction to Enthalpy = 0.316275
Thermal correction to Gibbs Free Energy = 0.241220
Sum of electronic and zero-point Energies = -1311.736149
Sum of electronic and thermal Energies = -1311.714938
Sum of electronic and thermal Enthalpies = -1311.713994
Sum of electronic and thermal Free Energies = -1311.789049

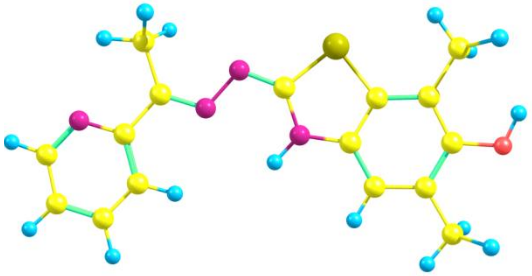
Standard orientation:

```
---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0        4.643360    0.745229   -0.001618
      2          6           0        4.905944   -0.636294    0.000197
      3          6           0        3.830575   -1.525793    0.000897
      4          6           0        2.531772   -1.028976    0.000114
      5          6           0        2.295064    0.348496   -0.002231
      6          6           0        3.341301    1.271991   -0.004409
      7          6           0        6.328818   -1.132585    0.001838
      8          6           0        3.109218    2.762076   -0.005206
      9          7           0        1.350249   -1.771151    0.000863
     10          6           0        0.192676   -1.058499    0.000271
     11         16           0        0.547148    0.693265   -0.001588
     12          8           0        5.745256    1.568370    0.000729
     13          7           0       -0.984243   -1.606206    0.001715
     14          7           0       -1.988757   -0.668028    0.001023
     15          1           0        5.476690    2.493937   -0.004168
     16          6           0       -3.197608   -1.129597    0.002832
     17          6           0       -3.525509   -2.597665    0.005425
     18          6           0       -4.291036   -0.119574    0.001660
     19          6           0       -4.014160    1.259916    0.014818
     20          6           0       -5.066559    2.162082    0.012630
```

```
     21          6           0       -6.375817    1.678203   -0.002625
     22          6           0       -6.559843    0.299834   -0.014745
     23          7           0       -5.554087   -0.582535   -0.012562
     24          1           0        4.010449   -2.594727    0.002240
     25          1           0        6.357656   -2.223084    0.000961
     26          1           0        6.875319   -0.773202   -0.875074
     27          1           0        6.872814   -0.774802    0.880987
     28          1           0        2.047929    3.002315   -0.070389
     29          1           0        3.597955    3.246520   -0.857684
     30          1           0        3.489607    3.230291    0.909333
     31          1           0       -4.600825   -2.751691    0.018812
     32          1           0       -3.074481   -3.082211    0.875697
     33          1           0       -3.098717   -3.080585   -0.878171
     34          1           0       -2.987006    1.596352    0.026655
     35          1           0       -4.872162    3.228589    0.022910
     36          1           0       -7.227966    2.346588   -0.004746
     37          1           0       -7.561975   -0.119503   -0.026697
     38          1           0        1.326992   -2.781612    0.002548
 ---------------------------------------------------------------------
```

Data 33: Cartesian coordinates and energies of the optimized geometry for (*E*,*E*)-**H*L***$^{\mathbf{1c'}}$ (DMSO solution).





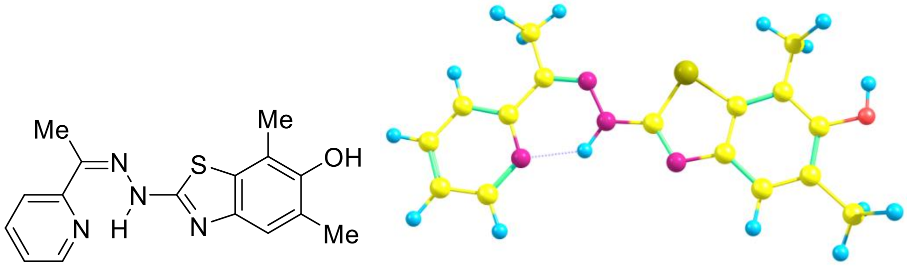
Electronic Energy = -1312.02751003 a.u.
Zero-point correction = 0.294159 (Hartree/Particle)
Thermal correction to Energy = 0.315299
Thermal correction to Enthalpy = 0.316243
Thermal correction to Gibbs Free Energy = 0.241616
Sum of electronic and zero-point Energies = -1311.733351
Sum of electronic and thermal Energies = -1311.712212
Sum of electronic and thermal Enthalpies = -1311.711267
Sum of electronic and thermal Free Energies = -1311.785894

Standard orientation:

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
      1          6           0        4.658551    0.611942    0.007697
      2          6           0        3.920983    1.809087    0.018823
      3          6           0        2.526579    1.742170    0.017983
      4          6           0        1.899657    0.501136    0.006269
      5          6           0        2.657144   -0.674749   -0.004332
      6          6           0        4.051553   -0.654700   -0.003924
      7          6           0        4.637478    3.134689    0.031350
      8          6           0        4.882362   -1.912756   -0.015757
      9          7           0        0.527604    0.249067    0.004128
     10          6           0        0.157803   -1.059971   -0.008165
     11         16           0        1.593569   -2.100899   -0.017085
     12          8           0        6.027148    0.745900    0.008730
     13          7           0       -1.039327   -1.573132   -0.013252
     14          7           0       -2.009061   -0.588618   -0.012030
     15          1           0        6.452937   -0.118787    0.000783
```

16	6	0	-3.232586	-1.010475	-0.001348
17	6	0	-3.609407	-2.466717	0.014265
18	6	0	-4.294394	0.033707	-0.003877
19	6	0	-3.978053	1.402496	-0.078658
20	6	0	-5.002389	2.336569	-0.075588
21	6	0	-6.323899	1.894446	0.001839
22	6	0	-6.548149	0.523641	0.071254
23	7	0	-5.569717	-0.388662	0.068252
24	1	0	1.940033	2.653638	0.026359
25	1	0	3.923723	3.959584	0.040392
26	1	0	5.282780	3.228428	0.909712
27	1	0	5.280936	3.246134	-0.846314
28	1	0	4.257833	-2.806298	-0.018968
29	1	0	5.528623	-1.977588	0.866388
30	1	0	5.521195	-1.965630	-0.904102
31	1	0	-4.689273	-2.585273	0.006881
32	1	0	-3.195250	-2.953949	0.901442
33	1	0	-3.176711	-2.975583	-0.851273
34	1	0	-2.943167	1.707932	-0.139239
35	1	0	-4.776732	3.395348	-0.133597
36	1	0	-7.155196	2.588576	0.006835
37	1	0	-7.561276	0.136152	0.131880
38	1	0	-0.190635	0.960826	0.009656

Data 34: Cartesian coordinates and energies of the optimized geometry for the *s*-*cis*-conformer (around the exocyclic C-N bond) of (*Z*)-**H*L***$^{1c'}$ (DMSO solution).

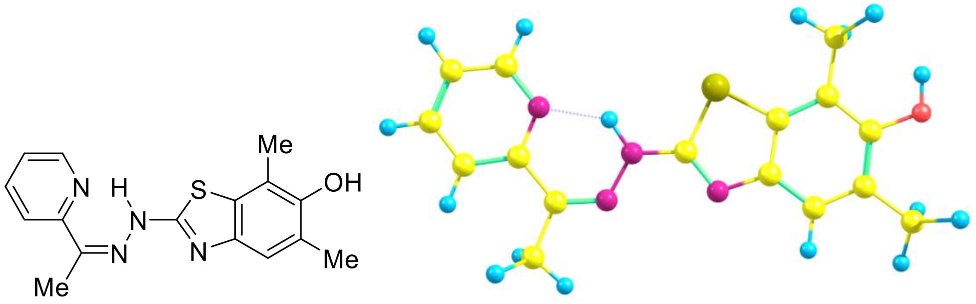


Electronic Energy = -1312.03479280 a.u.
Zero-point correction = 0.294827 (Hartree/Particle)
Thermal correction to Energy = 0.315436
Thermal correction to Enthalpy = 0.316380
Thermal correction to Gibbs Free Energy = 0.244300
Sum of electronic and zero-point Energies = -1311.739966
Sum of electronic and thermal Energies = -1311.719357
Sum of electronic and thermal Enthalpies = -1311.718413
Sum of electronic and thermal Free Energies = -1311.790493
Standard orientation:

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	4.742819	-0.063880	0.000896
2	6	0	4.437850	-1.440095	-0.000881
3	6	0	3.101570	-1.830961	-0.002471
4	6	0	2.083984	-0.872524	-0.002245
5	6	0	2.431485	0.493239	-0.000755
6	6	0	3.757030	0.933927	-0.000034
7	6	0	5.552425	-2.455591	-0.000477
8	6	0	4.131464	2.395632	0.004540
9	7	0	0.721307	-1.147749	-0.003756
10	6	0	0.034099	-0.048407	-0.003020
11	16	0	0.959008	1.473975	-0.000138

```
      12          8           0        6.082186    0.255059    0.004940
      13          7           0       -1.328421   -0.010517   -0.003369
      14          7           0       -1.953058    1.184649   -0.003110
      15          1           0        6.202848    1.211218    0.001762
      16          1           0       -1.899293   -0.866465   -0.002294
      17          6           0       -3.248322    1.270639   -0.001886
      18          6           0       -3.788691    2.680160   -0.002165
      19          6           0       -4.208616    0.141369   -0.000128
      20          6           0       -5.594577    0.376561    0.001432
      21          6           0       -6.469702   -0.702254    0.003506
      22          6           0       -5.954955   -1.996255    0.003981
      23          6           0       -4.571891   -2.149994    0.002253
      24          7           0       -3.721483   -1.120888    0.000241
      25          1           0        2.843377   -2.884106   -0.003848
      26          1           0        5.148713   -3.469223   -0.003521
      27          1           0        6.197500   -2.340087   -0.876680
      28          1           0        6.193467   -2.343880    0.879195
      29          1           0        3.249084    3.033593   -0.047545
      30          1           0        4.762983    2.655758   -0.852256
      31          1           0        4.674307    2.671855    0.915382
      32          1           0       -4.407104    2.873687   -0.883932
      33          1           0       -2.956754    3.382647   -0.003413
      34          1           0       -4.405382    2.874748    0.880570
      35          1           0       -5.982968    1.384918    0.001076
      36          1           0       -7.540107   -0.533509    0.004760
      37          1           0       -6.601959   -2.864185    0.005623
      38          1           0       -4.124572   -3.138910    0.002497
 ---------------------------------------------------------------------
```

Data 35: Cartesian coordinates and energies of the optimized geometry for the *s-trans*-conformer (around the exocyclic C-N bond) of (*Z*)-**H***L*$^{1c'}$ (DMSO solution).



Electronic Energy = -1312.03016376 a.u.
Zero-point correction = 0.294962 (Hartree/Particle)
Thermal correction to Energy = 0.315536
Thermal correction to Enthalpy = 0.316480
Thermal correction to Gibbs Free Energy = 0.244493
Sum of electronic and zero-point Energies = -1311.735201
Sum of electronic and thermal Energies = -1311.714628
Sum of electronic and thermal Enthalpies = -1311.713683
Sum of electronic and thermal Free Energies = -1311.785671

Standard orientation:

```
 ---------------------------------------------------------------------
 Center     Atomic      Atomic             Coordinates (Angstroms)
 Number     Number       Type             X           Y           Z
 ---------------------------------------------------------------------
       1          6           0       -4.733494   -0.290988   -0.000004
       2          6           0       -4.578378    1.109876    0.000015
       3          6           0       -3.291785    1.642004    0.000025
```

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      4          6           0       -2.176045    0.800313    0.000015
      5          6           0       -2.376888   -0.594843   -0.000005
      6          6           0       -3.646287   -1.177359   -0.000012
      7          6           0       -5.795151    2.000205    0.000025
      8          6           0       -3.862057   -2.670814   -0.000023
      9          7           0       -0.852632    1.226191    0.000026
     10          6           0       -0.043895    0.216794    0.000011
     11         16           0       -0.806999   -1.402796   -0.000016
     12          8           0       -6.029973   -0.753093   -0.000005
     13          7           0        1.322393    0.253152    0.000020
     14          7           0        1.970252    1.440459   -0.000015
     15          1           0       -6.045391   -1.716606   -0.000082
     16          1           0        1.897585   -0.599748    0.000014
     17          6           0        3.267976    1.486287   -0.000024
     18          6           0        3.847897    2.880747   -0.000058
     19          6           0        4.202768    0.334274   -0.000004
     20          6           0        5.593900    0.536475    0.000014
     21          6           0        6.443672   -0.562476    0.000030
     22          6           0        5.899095   -1.844164    0.000025
     23          6           0        4.512944   -1.965765    0.000007
     24          7           0        3.687156   -0.916761   -0.000006
     25          1           0       -3.147899    2.716633    0.000040
     26          1           0       -5.502355    3.051215    0.000012
     27          1           0       -6.422283    1.818604   -0.877974
     28          1           0       -6.422258    1.818620    0.878045
     29          1           0       -2.914844   -3.210280   -0.000022
     30          1           0       -4.417733   -3.000366   -0.885119
     31          1           0       -4.417743   -3.000374    0.885065
     32          1           0        4.470599    3.057969    0.882189
     33          1           0        3.035318    3.605398   -0.000097
     34          1           0        4.470635    3.057911   -0.882291
     35          1           0        6.006135    1.535246    0.000017
     36          1           0        7.517711   -0.418691    0.000045
     37          1           0        6.525857   -2.726814    0.000036
     38          1           0        4.042624   -2.943913    0.000004
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References

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[1] Kabsch, W. *XDS*. *Acta Crystallogr D Biol Crystallogr* **2010**, *66* (2), 125–132. https://doi.org/10.1107/S0907444909047337.

[2] Sheldrick, G. M. A Short History of *SHELX*. *Acta Crystallogr A Found Crystallogr* **2008**, *64* (1), 112–122. https://doi.org/10.1107/S0108767307043930.

3. Zékány L.; Nagypál I. In *Computational Methods for the Determination of Stability Constants*; Plenum Press: New York, NY, 1985; pp 291–353.

4. Irving, H. M.; Miles, M. G.; Pettit, L. D. A Study of Some Problems in Determining the Stoicheiometric Proton Dissociation Constants of Complexes by Potentiometric Titrations Using a Glass Electrode. *Analyt. Chim. Acta* **1967**, *38*, 475–488.

5. Enyedy, É. A.; Zsigó, É.; Nagy, N. V.; Kowol, C. R.; Roller, A.; Keppler, B. K.; Kiss, T. Complex-Formation Ability of Salicylaldehyde Thiosemicarbazone towards Zn(II), Cu (II), Fe(II), Fe(III) and Ga(III) Ions. *Eur. J. Inorg. Chem.* **2012**, 4036–4047.

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6. Hager, S.; Pape, V. F. S.; Pósa, V.; Montsch, B.; Uhlik, L.; Szakács, G.; Tóth, S.; Jabronka, N.; Keppler, B. K.; Kowol, C. R.; Enyedy, E. A.; Heffeter, P. High Copper Complex Stability and Slow Reduction Kinetics as Key Parameters for Improved Activity, Paraptosis Induction and Impact on Drug-Resistant Cells of Anticancer Thiosemicarbazones. *Antioxid.Redox Signal.* **2020**, 33, 395-414.

7. Petrasheuskaya, T. V.; Kiss, M. A.; Dömötör, O.; Holczbauer, T.; May, N. V.; Spengler, G.; Kincses, A.; Čipak Gašparović, A.; Frank, É.; Enyedy, É. A. Salicylaldehyde Thiosemicarbazone Copper Complexes: Impact of Hybridization with Estrone on Cytotoxicity, Solution Stability and Redox Activity. *New J. Chem.* **2020**, *44*, 12154–12168.

8. Kowol, C. R.; Nagy, N. V.; Jakusch, T.; Roller, A.; Heffeter, P.; Keppler, B. K.; Enyedy, É. A. Vanadium(IV/V) Complexes of Triapine and Related Thiosemicarbazones: Synthesis, Solution Equilibrium and Bioactivity. *J. Inorg. Biochem.* **2015**, *152*, 62–73.

9. Aranzaes, J. R.; Daniel, M. C.; Astruc, D. Metallocenes as References for the Determination of Redox Potentials by Cyclic Voltammetry. Permethylated Iron and Cobalt Sandwich Complexes, Inhibition by Polyamine Dendrimers, and the Role of Hydroxy-Containing Ferrocenes. *Can. J. Chem.* **2006**, *84*, 288–299.

10. *GraphPad Software I, GraphPad Prism*; GraphPad Software, Inc., 2007.

11. Mucsi, I.; Varga, A.; Kawase, M.; Motohashi, N.; Molnar, J. Interaction between various resistance modifiers and apoptosis inducer 12H-benzo[alpha]phenothiazine. *Anticancer Res*., 2002, 22, 2833–2836.

12. Ohui, K.; Afanasenko, E.; Bacher, F.; Ting, R. L. X.; Zafar, A.; Blanco-Cabra, N.; Torrents, E.; Dömötör, O.; May, N. V.; Darvasiova, D.; Enyedy, É. A.; Popović-Bijelić, A.; Reynisson, J.; Rapta, P.; Babak, M. V.; Pastorin, G.; Arion, V. B. New Water-Soluble Copper(II) Complexes with Morpholine–Thiosemicarbazone Hybrids: Insights into the Anticancer and Antibacterial Mode of Action. *J. Med. Chem.* **2019**, *62*, 512–530.

13. Popović-Bijelić, A.; Kowol, C. R.; Lind, M. E. S.; Luo, J.; Himo, F.; Enyedy, É. A.; Arion, V. B.; Gräslund, A. Ribonucleotide Reductase Inhibition by Metal Complexes of Triapine (3-Aminopyridine-2-Carboxaldehyde Thiosemicarbazone): A Combined Experimental and Theoretical Study. *J. Inorg. Biochem.* **2011**, *105*, 1422–1431.

14. Zaltariov, M. F.; Hammerstad, M.; Arabshahi, H. J.; Jovanović, K.; Richter, K. W.; Cazacu, M.; Shova, S.; Balan, M.; Andersen, N. H.; Radulović, S.; Reynisson, J.; Andersson, K. K.; Arion, V. B. New Iminodiacetate–Thiosemicarbazone Hybrids and Their Copper(II) Complexes Are Potential

Ribonucleotide Reductase R2 Inhibitors with High Antiproliferative Activity. *Inorg. Chem.* **2017**, *56*, 3532–3549.

15. Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

16. *Gaussian 16, Revision A.03*, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.

17. Varetto, U., Molekel 5.4.0.8, Swiss National Supercomputing Centre, Lugano, Switzerland, 2009.

18. Hoggarth, E.; Young, E. H. P. Compounds related to thiosemicarbazide, Part VII. Benzylthiosemicarbazides *J. Chem. Soc.* **1950**, 1582–1584.

19. Schantl, J. G; Hebeisen, P.; Minach, L. α-Arylazoalkyl Isocyanates and Isothiocyanates by Potassium Permanganate Oxidation of 2,5,5-Trisubstituted 1,2,4-Triazolidin-3-ones and 1,2,4-Triazolidin-3-thiones *Synthesis* **1984**, 1984, 315–317.

20. Abdou, W. M.; Salem, M. A. I.; Sediek, A. A. Cyclic oxyphosphoranes in synthesis. A novel synthesis of oxathiaphospholenes, fused pyrimidines and aminooxyphosphoranes *Arkivoc* **2005**, xiv, 102–117.

21. Gribble, G.W. Indole Ring Synthesis: From Natural Products to Drug Discovery, *John Wiley & Sons, Ltd. Published* **2016**.

22. Tokuyama, H.; Yamashita, T.; Reding, M. T.; Kaburagi, Y.; Fukuyama, T. Radical Cyclization of 2-Alkenylthioanilides: A Novel Synthesis of 2,3-Disubstituted Indoles *J. Am. Chem. Soc.* **1999**, *121*, 3791–3792.

23. Kowol, C. R.; Nagy, N. V.; Jakusch, T.; Roller, A.; Heffeter, P.; Keppler, B. K.; Enyedy, É. A. Vanadium(IV/V) Complexes of Triapine and Related Thiosemicarbazones: Synthesis, Solution Equilibrium and Bioactivity. *J. Inorg. Biochem.* **2015**, *152*, 62–73.