## Antibacterial susceptibility of new copper(II) N-pyruvoyl anthranilate complexes against marine bacterial strains - in search of new antibiofouling candidate

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5. **Synthesis and characterization of the key starting materials**
   1. ***Instrumentation***

Melting points were measured using a MEL-TEMP II Laboratory apparatus, USA; all melting points were measured in open glass capillaries and are uncorrected. Elemental analyses were performed with a Vario EL instrument from Elementaranalysensysteme GmbH, Germany. FTIR spectra were recorded on a BRUKER Tensor-37 FTIR spectrophotometer in the range 400–4000 cm–1 with an ATR (attenuated total reflection) unit (Platinum ATR-QL, diamond). For signal intensities the following abbreviations were used: br (broad), sh (sharp), w (weak), m (medium), s (strong), vs (very strong). The NMR-spectra were obtained with a Bruker Avance DRX200 (200 MHz for 1H) or Bruker Avance DRX500 (125 MHz for 13C) spectrometer with calibration to the residual proton solvent signal in DMSO-*d*6 (1H NMR: 2.52 ppm, 13C NMR: 39.5 ppm), against TMS (δ = 0.00 ppm) for 1H and 13C (δ = 0.00 ppm). Multiplicities of the signals were specified s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). UV/Vis spectra were measured at 25 °C in DMSO (10–3 mol/L) on a Shimadzu UV-2450 spectrophotometer in the range 200–800 nm using quartz cuvettes (1 cm). Mass spectra (MS) were taken as Electron impact (EI) and chemical ionization (CI) using Thermo-Finnigan TSQ 700 mass spectrometer at 70 eV, with NH3 as ionization gas for CI.

* 1. ***Materials and Syntheses***

All reagents were commercially available and used with further purification. Methyl/ Ethyl (2-thenoyl)-pyruvatewas prepared according to a literature procedure [[[1]](#endnote-1)S1].

* + 1. **General procedure for the preparation of thenoylpyruvanthranilic acid ligands (TPXAH2, 2a-d)**

The thenoyl-pyruvoyl-anthranilide based ligands were synthesized according to the following method: A mixture of ethyl (2-thenoyl)-pyruvate (2.26 g, 10 mmol) and anthranilic acid derivative (10 mmol) was wetted with a few drops of glacial acetic acid (5-7 drops). The mixture was then heated gently, with swirling, until all the solids had melted and then this melt re-solidified completely by further heating for ~10 min. After that 30 mL of ethanol was added and the reaction mixture was refluxed with stirring for 1 h**,** then cooled down and the yellow powder of N-(2-Thenoyl-pyruvoyl)anthranilic acid derivatives (**2**a-d) was removed by filtration, washed with hot ethanol (3 x 5 mL) and then dried under vacuum. The crude products were purified by recrystallization from CH3COOH to give the final products for analysis.

***N-(2-Thenoyl)-pyruvoylanthranilic acid*** (TPAH2, **2a**):Light yellow crystals; 87 % Yield; m.p. 218-220 °C. FT-IR (ATR, cm-1): 3281 (m, br, *ν*(N-H), NHCO),2645 (m, br, *ν*(O-H), COOH), 1700 (s, sh, *ν*(C=O), COOH), 1670 (s, sh, *ν*(C=O), amide I), 1630 (w, sh, *ν*a(C=C-C=O) + δ(O-H)), 1575 (m, sh, *ν*s(C=C-C=O) + δ(O-H)), 1518 (s, sh, *ν*(CN) + δ(N-H), amide II), 1260 (m, sh,amide III), 1351 (m, sh, *ν*(CSC), thiophene), 1080 (m, sh, *ν*(C-O), COOH). 1H NMR (200 MHz, DMS0-*d6*) δ (ppm): 13.29 (s, 1 H), 12.07 (s, 1 H), 8.74 (d, 1 H), 7.92 (dd, *J*1 = 2.61 Hz, *J*2 = 5.28 Hz, 2H), 7.50 (m,2 H), 7.25 (t, *J*1 = *J*2 = 4.19 Hz,1 H), 7.15 (d, *J* = 2.81 Hz,2 H), 6.70 (s, 1 H). 13C NMR (125 MHz, DMSO-*d6*) δ (ppm): 198.41, 192.64, 189.84, 188.05, 169.72, 139.99, 137.79, 134.79, 131.95, 129.51, 127.25, 117.66, 113.22, 112.02, 99.27. EI-MS *m/z* calcd for C15H11NO5S: 317.32; found: 317.00; CI(NH3)-MS : found 335 [M + NH4]+, 318 ([M + H]+,98.2 %) and 317 ([M]+,100 %). Anal. Calcd. for C15H11NO5S (M = 317.32): C, 56.78; H, 3.49; N, 4.41; S, 10.11; Found: C, 56.38; H, 3.57; N, 4.16; S, 9.83.

***N-(2-Thenoyl)-pyruvoyl-5-chloroanthranilic acid*** (TPCAH2, **2b**):Light yellow crystals; 81 % Yield; m.p. 231-232 °C. FT-IR (ATR, cm-1): 3203 (m, br, *ν*(N-H), NHCO),2517 (m, br, *ν*(O-H), COOH), 1693 (s, sh, *ν*(C=O), COOH), 1652 (s, sh, *ν*(C=O), amide I), 1576 (m, sh, *ν*(C=C-C=O) + δ(O-H)), 1509 (s, sh, *ν*(CN) + δ(N-H), amide II), 1354 (m, sh, *ν*(CSC), thiophene), 1224 (m, sh,amide III), 1063 (m, sh, *ν*(C-O), COOH). 1H NMR (200 MHz, DMSO-*d6*) δ (ppm): 12.64 (s, 1 H), 12.43 (s, 1 H), 8.75 (d, *J* = 7.76 Hz, 1 H), 8.30 (dd, *J*1 = 0.75 Hz, *J*2 = 3.82 Hz, 1H), 8.20 (dd, *J*1 = 0.70 Hz, *J*2 = 4.82 Hz,1H), 8.10 (m,1 H), 7.71 (m, 1 H), 7.34 (m, 2 H), 7.21 (s, 1 H), 4.62 (s, 1 H). 13C NMR (125 MHz, DMS0-*d6*) δ (ppm): 196.85, 191.13, 189.66, 179.02, 167.56, 164.10, 158.22, 140.79, 139.57, 138.30, 134.63, 132.77, 131.81, 128.23, 118.94, 117.38, 116.01, 108.13, 60.73. EI-MS *m/z* calcd for C15H10ClNO5S: 351.76; found: 351.63; CI(NH3)-MS : found 352.73 ([M + H]+,95.3 %) and 351.71 ([M]+,100 %). Anal. Calcd. for C15H10ClNO5S (M = 351.76): C, 51.22; H, 2.87; N, 3.98; S, 9.12; Found: C, 51.99; H, 2.95; N, 4.03; S, 9.01.

***N-(2-Thenoyl)-pyruvoyl-5-bromoanthranilic acid*** (TPBAH2, **2**c):Yellow crystals; 77 % Yield; m.p. 248-249 °C. FT-IR (ATR, cm-1): 3230 (m, br, *ν*(N-H), NHCO),2525 (m, br, *ν*(O-H), COOH), 1691 (s, sh, *ν*(C=O), COOH), 1655 (s, sh, *ν*(C=O), amide I), 1574 (m, sh, *ν*(C=C-C=O) + δ(O-H)), 1508 (s, sh, *ν*(CN) + δ(N-H), amide II), 1353 (m, sh, *ν*(CSC), thiophene), 1221 (m, sh,amide III), 1069 (m, sh, *ν*(C-O), COOH). 1H NMR (200 MHz, DMS0-*d6*) δ (ppm): 12.57 (s, 1 H), 12.36 (s, 0.27 H), 8.68 (dd, *J*1 = 1.93 Hz, *J*2 = 9.12 Hz,1H), 8.29 (s, br, 1 H), 8.15 (m, 3 H), 7.90 (d, *J* = 9.07 Hz, 1 H), 7.35 (dd, *J*1 = 2.76 Hz, *J*2 = 3.85 Hz,1H), 7.19 (s, 1H), 4.63 (s, 0.51 H). ). 13C NMR (125 MHz, DMS0-*d6*) δ (ppm): 196.97, 190.96, 189.64, 180.75, 168.56, 163.71, 158.07, 140.72, 139.41, 138.30, 134.64, 133.33, 131.90, 128.22, 118.94, 117.52, 115.73, 107.06, 60.65. EI-MS *m/z* calcd for C15H10BrNO5S: 396.21; found: 396.10; CI(NH3)-MS : found 397.19 ([M + H]+,95.3 %) and 396.18 ([M]+,100 %). Anal. Calcd. for C15H10BrNO5S (M = 396.21): C, 45.47; H, 2.54; N, 3.54; S, 8.09; Found: C, 45.17; H, 2.14; N, 3.58; S, 8.03.

***N-(2-Thenoyl)-pyruvoyl-5-nitroanthranilic acid*** (TPNAH2, **2**d):Light yellow crystals; 82 % Yield; m.p. 225-227 °C. FT-IR (ATR, cm-1): 3324 (m, br, *ν*(N-H), NHCO),2630 (m, br, *ν*(O-H), COOH), 1693 (s, sh, *ν*(C=O), COOH), 1670 (s, sh, *ν*(C=O), amide I), 1619 (w, sh, *ν*a(C=C-C=O) + δ(O-H)), 1572 (m, sh, *ν*s(C=C-C=O) + δ(O-H)), 1510 (s, sh, *ν*(CN) + δ(N-H), amide II), 1349 (m, sh, *ν*(CSC), thiophene), 1262 (m, sh,amide III), 1061 (m, sh, *ν*(C-O), COOH). 1H NMR (200 MHz, DMS0-*d6*) δ (ppm): 13.09 (s, 1 H), 12.57 (s, 0.51 H), 8.72 (d, *J* = 7.89 Hz, 1 H), 8.16 (m, 1H), 8.10 (d, *J* = 1.72 Hz,1H), 8.05 (dd, *J*1 = 1.49 Hz, *J*2 = 5.09 Hz,1 H), 7.62 (m,1 H), 7.31 (m, 2 H), 7.09 (s, 1 H), 4.61 (s, 0.48 H). 13C NMR (125 MHz, DMS0-*d6*) δ (ppm): 197.45, 191.42, 190.04, 184.55, 167.83, 163.76, 158.65, 156.60, 140.84, 137.05, 134.69, 132.67, 129.80, 127.97, 119.28, 117.25, 115.16, 112.26, 101.58, 59.91. EI-MS *m/z* calcd for C15H10FNO5S: 335.31; found: 335.11; CI(NH3)-MS : found 336.26 ([M + H]+,95.3 %) and 335.08 ([M]+,100 %). Anal. Calcd. for C15H10FNO5S (M = 335.31): C, 53.73; H, 3.01; N, 4.18; S, 9.56; Found: C, 53.49; H, 3.19; N, 4.07; S, 9.21.

* + 1. **General method for preparation of thenoyl-pyruvate compounds (3a-d)**

Ethyl (2-thenoyl)-pyruvate (2.26 g, 10 mmol) was added to the anthranilic acid derivative (10 mmol) in 10 mL glacial acetic acid. The reaction mixture was then heated under reflux for ~30 min, cooled, and kept for one day at room temperature. The yellow precipitate of (**3**a-d) was collected by filtration, washed with hot ethanol (3 x 5 mL) and then dried under vacuum. The crude products were purified by recrystallization from glacial acetic acid to yield;

***Ethyl(4-(2-thienyl)-4-oxo-2-(o-carboxyphenylamino))but-2-enoate*** (**3**a):Light yellow microcrystals; 67 % Yield; m.p. 140-142 °C. FT-IR (ATR, cm-1): 3450, 3313 (m, br, *ν*(N-H), NH2), 3267 (m, br, *ν*(N-H)),1732 (s, sh, *ν*(C=O), COOMe), 1678 (s, sh, *ν*(C=O), COOH), 1608 (w, sh, *ν*a(C=C-C=O)), 1566 (m, sh, *ν*s(C=C-C=O)), 1496 (s, sh, *ν*(CN) + δ(N-H)), 1351 (m, sh, *ν*(CSC), thiophene), 1055 (m, sh, *ν*(C-O), COOH). 1H NMR (200 MHz, DMS0-*d6*) δ (ppm): 13.48 (s, 1 H), 12.34 (s, 1 H), 8.04 (d, *J* = 3.77 Hz, 1 H), 7.98 (t, *J*1 = *J*2 = 6.25 Hz,1 H), 7.72 (d, *J* = 8.26 Hz, 1 H), 7.55 (t, *J*1 = *J*2 = 7.74 Hz, 1 H), 7.24 (td, *J*1 = 4.10 Hz, *J*2 = 4.10 Hz,*J*3 = 15.42 Hz,2 H), 6.88 (d, *J* = 8.10 Hz,1 H), 6.76 (d, *J* = 8.34 Hz,1 H), 6.55 (s, 1 H), 4.22 (q, *J*1 = 7.13 Hz, *J*2 = 7.13 Hz,*J*3 = 7.19 Hz,2 H), 1.12 (t, *J*1 = *J*2 = 7.09 Hz, 3 H). 13C NMR (125 MHz, DMS0-*d6*) δ (ppm): 183.00, 171.99, 165.32, 150.71, 145.69, 141.30, 135.92, 133.69, 131.89, 129.43, 128.47, 119.42, 115.38, 110.17, 107.15, 62.45, 13.19. EI-MS *m/z* calcd for C17H15NO5S.~0.5(C7H7NO2): 413.94; Found: 412.99; CI(NH3)-MS : Found 431.23 [M + (C7H7NO2)0.5 + NH4]+, 414.01 ([M + (C7H7NO2) 0.5 + H]+,98.2 %) and 345.26 ([M]+,100 %). Anal. Calcd. for C17H15NO5S(C7H7NO2)0.5 (M = 413.94): C, 59.48; H, 4.50; N, 5.08; S, 7.75; Found: C, 59.53; H, 4.56; N, 5.14; S, 8.10.

***Ethyl(4-(2-thienyl)-4-oxo-2-(2-carboxy-5-chlorophenylamino))but-2-enoate*** (**3**b):pale yellow crystals; 71 % Yield; m.p. 163-165 °C. FT-IR (ATR, cm-1): 3198 (m, br, *ν*(N-H), NHCO),2555 (m, br, *ν*(O-H), COOH), 1732 (s, sh, *ν*(C=O), COOMe), 1687 (s, sh, *ν*(C=O), COOH), 1609 (w, sh, *ν*a(C=C-C=O)), 1578 (m, sh, *ν*s(C=C-C=O)), 1511 (s, sh, *ν*(CN) + δ(N-H)), 1352 (m, sh, *ν*(CSC), thiophene), 1063 (m, sh, *ν*(C-O), COOH). 1H NMR (200 MHz, DMS0-*d6*) δ (ppm): 12.35 (s, 1 H), 8.04 (dd, *J*1 = 4.56 Hz, *J*2 = 7.06 Hz, 2 H), 7.78 (d, *J* = 2.19 Hz, 1 H), 7.72 (dd, *J*1 = 1.84 Hz, *J*2 = 8.69 Hz, 1 H), 7.40 (dd, *J*1 = 2.18 Hz, *J*2 = 8.89 Hz, 1 H), 7.24 (t, *J*1 = *J*2 = 3.81 Hz, 1 H), 6.82 (d, *J* = 8.68 Hz, 1 H), 6.75 (d, *J* = 8.90 Hz, 1 H), 6.64 (s, 1 H), 4.24 (q, *J*1 = 6.77 Hz, *J*2 = 6.77 Hz, *J*3 = 6.61 Hz, 2 H), 1.16 (t, *J*1 = *J*2 = 7.08 Hz, 3 H). 13C NMR (125 MHz, DMS0-*d6*) δ (ppm): 183.71, 170.39, 166.78, 152.45, 147.10, 145.71, 140.51, 133.31, 132.63, 130.54, 129.72, 119.43, 112.12, 109.81, 106.99, 61.55, 14.36. EI-MS *m/z* calcd for C17H14ClNO5S: 379.03; found: 379.00; CI(NH3)-MS : found 379.98 ([M + H]+,95.3 %) and 379.01 ([M]+,100 %). Anal. Calcd. for C17H14ClNO5S (M = 379.03): C, 53.76; H, 3.72; N, 3.69; S, 8.44; Found: C, 53.83; H, 3.79; N, 3.51; S, 8.30.

***Ethyl(4-(2-thienyl)-4-oxo-2-(2-carboxy-5-bromophenylamino))but-2-enoate*** (**3**c):Yellow needle crystals; 75 % Yield; m.p. 174-176 °C. FT-IR (ATR, cm-1): 3250 (m, br, *ν*(N-H), NHCO),2517 (m, br, *ν*(O-H), COOH), 1729 (s, sh, *ν*(C=O), COOMe), 1678 (s, sh, *ν*(C=O), COOH), 1610 (w, sh, *ν*a(C=C-C=O)), 1576 (m, sh, *ν*s(C=C-C=O)), 1495 (s, sh, *ν*(CN) + δ(N-H)), 1350 (m, sh, *ν*(CSC), thiophene), 1058 (m, sh, *ν*(C-O), COOH). 1H NMR (200 MHz, DMS0-*d6*) δ (ppm): 12.26 (s, 1 H), 8.04 (dd, *J*1 = 4.63 Hz, *J*2 = 7.13 Hz, 2 H), 7.77 (d, *J* = 2.35 Hz, 1 H), 7.73 (m, 1 H), 7.37 (dd, *J*1 = 2.27 Hz, *J*2 = 8.92 Hz, 1 H), 7.27 (m, 1 H), 6.82 (d, *J* = 8.61 Hz, 1 H), 6.75 (d, *J* = 8.97 Hz, 1 H), 6.63 (s, 1 H), 4.25 (q, *J*1 = 7.05 Hz, *J*2 = 7.05 Hz, *J*3 = 6.95 Hz, 2 H), 1.17 (t, *J*1 = *J*2 = 7.08 Hz, 3 H). 13C NMR (125 MHz, DMS0-*d6*) δ (ppm): 183.68, 170.40, 166.78, 152.43, 147.00, 140.51, 133.27, 132.63, 131.54, 130.42, 129.70, 120.01, 112.13, 109.80, 107.03, 61.48, 14.35. EI-MS *m/z* calcd for C17H14BrNO5S: 424.27; found: 424.26; CI(NH3)-MS : found 425.27 ([M + H]+,95.3 %) and 424.25 ([M]+,100 %). Anal. Calcd. for C17H14BrNO5S (M = 424.27): C, 48.13; H, 3.33; N, 3.30; S, 7.56; Found: C, 48.00; H, 3.47; N, 3.21; S, 7.54.

***Ethyl(4-(2-thienyl)-4-oxo-2-(2-carboxy-5-nitrophenylamino))but-2-enoate*** (**3**d):white powder; 65 % Yield; m.p. 133-135 °C. FT-IR (ATR, cm-1): 3279 (m, br, *ν*(N-H)),1729 (s, sh, *ν*(C=O), COOMe), 1669 (s, sh, *ν*(C=O), COOH), 1611 (w, sh, *ν*a(C=C-C=O)), 1576 (m, sh, *ν*s(C=C-C=O)), 1507 (s, sh, *ν*(CN) + δ(N-H)), 1353 (m, sh, *ν*(CSC), thiophene), 1063 (m, sh, *ν*(C-O), COOH). 1H NMR (200 MHz, DMS0-*d6*) δ (ppm): 12.35 (s, 1 H), 8.04 (d, *J* = 3.88 Hz, 1 H), 8.01 (d, *J* = 0.97 Hz, 1 H), 7.96 (dd, *J*1 = 1.25 Hz, *J*2 = 8.13 Hz, 1 H), 7.54 (m, 1 H), 7.24 (m, 2 H), 6.88 (d, *J*1 = 8.13 Hz, 1 H), 6.56 (s, 1 H), 4.21 (q, *J*1 = 7.08 Hz, *J*2 = 7.08 Hz, *J*3 = 7.09 Hz, 2 H), 1.11 (t, *J*1 = *J*2 = 7.08 Hz, 3 H). 13C NMR (125 MHz, DMS0-*d6*) δ (ppm): 185.11, 171.49, 169.55, 165.32, 154.10, 147.39, 141.32, 133.21, 132.75, 130.77, 129.34, 114.28, 109.92, 107.06, 105.95, 60.84, 14.99. EI-MS *m/z* calcd for C17H14N2O7S: 390.37; found: 389.93; CI(NH3)-MS : found 391.26 ([M + H]+,95.3 %) and 390.07 ([M]+,100 %). Anal. Calcd. for C17H14N2O7S (M = 390.37): C, 52.31; H, 3.61; N, 7.18; S, 8.21; Found: C, 52.07; H, 3.81; N, 8.88; S, 8.09.

***Methyl(4-(2-thienyl)-4-oxo-2-(o-carboxyphenylamino))but-2-enoate*** (**3**e):Light yellow crystals; 68 % Yield; m.p. 128-130 °C. FT-IR (ATR, cm-1): 3268 (m, br, *ν*(N-H)),1736(s, sh, *ν*(C=O), COOMe), 1677 (s, sh, *ν*(C=O), COOH), 1607 (w, sh, *ν*a(C=C-C=O)), 1570 (m, sh, *ν*s(C=C-C=O)), 1511 (s, sh, *ν*(CN) + δ(N-H)), 1351 (m, sh, *ν*(CSC), thiophene), 1061 (m, sh, *ν*(C-O), COOH). 1H NMR (200 MHz, DMS0-*d6*) δ (ppm): 12.35 (s, 1 H), 8.04 (dd, *J*1 = 1.02 Hz, *J*2 = 3.84 Hz, 1 H), 7.97 (m, 2 H), 7.55 (t, *J*1 = *J*2 = 7.70 Hz, 1 H), 7.27 (dd, *J*1 = 3.04 Hz, *J*2 = 5.72 Hz,1 H), 7.19 (t, *J*1 = *J*2 = 7.70 Hz,1 H), 6.58 (d, *J* = 8.25 Hz,1 H), 6.45 (s, 1 H), 3.76 (s, 3 H). 13C NMR (125 MHz, DMS0-*d6*) δ (ppm): 183.11, 171.02, 165.33, 150.71, 145.73, 141.29, 134.01, 133.68, 131.87, 129.50, 128.47, 119.43, 115.36, 110.16, 107.20, 52.45. EI-MS *m/z* calcd for C16H13NO5S: 331.34; found: 331.23; CI(NH3)-MS: Found 332.33 ([M + H]+,98.2 %) and 331.28 ([M]+,100 %). Anal. Calcd. for C16H13NO5S (M = 331.34): C, 58.00; H, 3.95; N, 4.23; S, 9.68; Found: C, 57.88; H, 4.03; N, 4.15; S, 9.49.

1. **Tables**

**Table S1** Inhibition zone (mm/mg sample) for the enaminones, anthranilides salts and their Cu(II)-complexes.

**Table S2** Anisotropic displacement parameters for **3a**, in Å2

**Table S3** Selected geometricparameters for **3a**

**Table S1** Inhibition zone (mm/mg sample) for the enaminones, anthranilides salts and their Cu(II)-complexes.

|  |  |  |  |
| --- | --- | --- | --- |
| **Compound** | **Diameter of inhibition zone (mm)** | | |
| *S. aureus* | *E. coli* |  |
| TPAH2 (**2a**)  TPCAH2 (**2b**)  TPBAH2 (**2c**)  TPNAH2 (**2d**)  **3a**  **3b**  **3c**  **3d**  **3e**  [Cu(TPA)H2O].H2O (**4a**)  [Cu(TPCA)(H2O)] (**4b**)  [Cu(TPBA)(H2O)] (**4c**)  [Cu(TPNA)(H2O)2] (**4d**)  Ampiciline | 16.1±0.3  19.2±0.4  22.3±0.3  23.0±0.3  20..2±0.2  21..9±0.1  24.4±0.4  30.1±0.2  18.9±0.5  34.6±0.5  37.7±0.4  35.6±0.3  40.8±0.2  35.4±0.2 | 13.1±0.3  14.1±0.2  16.2±0.5  19.1±0.2  14.8±0.7  20.3±0.6  22.7±0.3  26.5±0.5  16.2±0.4  32.3±0.2  35.8±0.2  35.2±0.5  39.7±0.4  38.1±0.3 | |

**Table S2** Anisotropic displacement parameters for **3a**, in Å2

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | | | | |
|  | |  |  |  |  |  |  |  |  |
| **Atom** | **U11** | **U22** | **U33** | **U12** | **U13** | **U23** |  |  |  |
| C1 | 0.0371(9) | 0.0481(11) | 0.045(1) | -0.0158(8) | -0.0124(8) | 0.0039(9) |  |  |  |
| C3 | 0.0675(15) | 0.106(2) | 0.0601(14) | -0.0202(15) | -0.0355(12) | 0.0209(14) |  |  |  |
| C4 | 0.0644(15) | 0.128(2) | 0.0784(17) | -0.0477(17) | -0.0258(13) | -0.0073(17) |  |  |  |
| SA | 0.0697(16) | 0.0603(12) | 0.0495(10) | -0.0199(10) | -0.0269(10) | 0.0165(9) |  |  |  |
| C5A | 0.097(10) | 0.133(10) | 0.063(6) | -0.036(7) | -0.037(6) | 0.020(7) |  |  |  |
| C5B | 0.069(7) | 0.080(9) | 0.108(10) | -0.025(6) | -0.058(6) | 0.015(6) |  |  |  |
| SB | 0.0535(9) | 0.0689(11) | 0.0578(12) | -0.0348(9) | -0.0214(8) | 0.0087(9) |  |  |  |
| O1 | 0.0488(7) | 0.0648(9) | 0.0475(7) | -0.0337(7) | -0.0158(6) | 0.0181(6) |  |  |  |
| O2 | 0.0721(10) | 0.0997(12) | 0.0686(10) | -0.0651(10) | -0.0255(8) | 0.0354(9) |  |  |  |
| O3 | 0.0600(8) | 0.0706(9) | 0.0381(7) | -0.0374(7) | -0.0087(6) | 0.0115(6) |  |  |  |
| O4 | 0.0492(7) | 0.0586(8) | 0.0633(8) | -0.0343(7) | -0.0264(7) | 0.0224(7) |  |  |  |
| O5 | 0.0557(8) | 0.0614(9) | 0.0659(9) | -0.0384(7) | -0.0267(7) | 0.0156(7) |  |  |  |
| N1 | 0.0361(7) | 0.0453(8) | 0.0416(8) | -0.0236(7) | -0.0124(6) | 0.0126(7) |  |  |  |
| C6 | 0.0355(9) | 0.0431(10) | 0.0425(9) | -0.0168(8) | -0.0084(7) | 0.0049(8) |  |  |  |
| C7 | 0.0368(9) | 0.0538(11) | 0.0466(10) | -0.0253(8) | -0.0109(8) | 0.0113(9) |  |  |  |
| C8 | 0.0376(9) | 0.0426(10) | 0.0415(9) | -0.0222(8) | -0.0092(7) | 0.0074(8) |  |  |  |
| C9 | 0.0386(9) | 0.0522(11) | 0.0462(10) | -0.0226(9) | -0.0095(8) | 0.0128(9) |  |  |  |
| C10 | 0.0917(18) | 0.129(2) | 0.0420(12) | -0.0651(18) | -0.0139(12) | 0.0276(13) |  |  |  |
| C11 | 0.109(2) | 0.163(3) | 0.0562(15) | -0.066(2) | -0.0306(15) | 0.0269(18) |  |  |  |
| C12 | 0.0358(9) | 0.0431(10) | 0.0323(8) | -0.0180(7) | -0.0072(7) | 0.0032(7) |  |  |  |
| C13 | 0.0469(10) | 0.0453(11) | 0.0468(10) | -0.0228(9) | -0.0106(8) | 0.0065(8) |  |  |  |
| C14 | 0.0608(12) | 0.0429(11) | 0.0566(12) | -0.0173(9) | -0.0155(10) | 0.0091(9) |  |  |  |
| C15 | 0.0534(12) | 0.0524(12) | 0.0615(13) | -0.0104(10) | -0.025(1) | 0.0077(10) |  |  |  |
| C16 | 0.0414(10) | 0.0554(12) | 0.0522(11) | -0.0193(9) | -0.0171(8) | 0.0011(9) |  |  |  |
| C17 | 0.0375(9) | 0.0442(10) | 0.0358(9) | -0.0188(8) | -0.0086(7) | 0.0022(7) |  |  |  |
| C18 | 0.0324(9) | 0.0507(11) | 0.0420(9) | -0.0218(8) | -0.0068(7) | 0.0001(8) |  |  |  |
| C20 | 0.0519(13) | 0.143(3) | 0.0413(11) | -0.0478(17) | -0.0199(9) | 0.0266(16) |  |  |  |
| O6 | 0.052(3) | 0.140(7) | 0.044(3) | -0.037(4) | -0.010(2) | 0.023(4) |  |  |  |
| N2 | 0.075(5) | 0.069(5) | 0.081(4) | -0.021(4) | -0.029(3) | -0.002(4) |  |  |  |
| C21 | 0.039(3) | 0.060(5) | 0.056(4) | -0.017(4) | -0.006(2) | 0.026(4) |  |  |  |
| C22 | 0.058(3) | 0.067(3) | 0.068(3) | -0.036(2) | -0.020(2) | 0.027(2) |  |  |  |
| C23 | 0.15(1) | 0.036(4) | 0.122(11) | -0.050(5) | -0.024(7) | -0.004(4) |  |  |  |
| C24 | 0.0478(14) | 0.159(3) | 0.0400(14) | -0.0436(19) | -0.0142(11) | 0.0178(18) |  |  |  |
| O7 | 0.0509(15) | 0.0690(19) | 0.0501(16) | -0.0323(14) | 0.0036(13) | 0.0018(14) |  |  |  |

**Table S3** Selected geometricparameters for **3a**

|  |  |  |  |
| --- | --- | --- | --- |
| **Atoms 1,2** | **d 1,2 [Å]** | **Atoms 1,2** | **d 1,2 [Å]** |
| C1—C5A | 1.408(13) | C11—H11B | 0.9600 |
| C1—C5B | 1.442(17) | C11—H11C | 0.9600 |
| C1—C6 | 1.462(2) | C12—C13 | 1.393(2) |
| C1—SA | 1.641(5) | C12—C17 | 1.411(2) |
| C1—SB | 1.671(3) | C13—C14 | 1.377(3) |
| C3—C4 | 1.341(4) | C13—H13 | 0.9300 |
| C3—SA | 1.547(6) | C14—C15 | 1.385(3) |
| C3—C5B | 1.59(2) | C14—H14 | 0.9300 |
| C3—H3 | 0.9300 | C15—C16 | 1.375(3) |
| C4—SB | 1.531(6) | C15—H15 | 0.9300 |
| C4—C5A | 1.611(19) | C16—C17 | 1.403(2) |
| C4—H4 | 0.9300 | C16—H16 | 0.9300 |
| C5A—H5A | 0.9300 | C17—C18 | 1.474(2) |
| C5B—H5B | 0.9300 | C20—C21 | 1.133(9) |
| O1—C6 | 1.246(2) | C20—C20i | 1.393(5) |
| O2—C9 | 1.202(2) | C20—C24 | 1.455(4) |
| O3—C9 | 1.322(2) | C20—N2 | 1.643(7) |
| O3—C10 | 1.461(2) | O6—C24 | 1.226(7) |
| O4—C18 | 1.230(2) | N2—H2A | 0.8600 |
| O5—C18 | 1.321(2) | N2—H2B | 0.8600 |
| O5—H5 | 0.8200 | C21—C22 | 1.42(1) |
| N1—C8 | 1.370(2) | C21—H21 | 0.9300 |
| N1—C12 | 1.401(2) | C22—C23 | 1.443(14) |
| N1—H | 0.8600 | C22—H22 | 0.9300 |
| C6—C7 | 1.446(2) | C23—C24i | 1.406(10) |
| C7—C8 | 1.356(2) | C23—H23 | 0.9300 |
| C7—H7A | 0.9300 | C24—O7 | 1.221(4) |
| C8—C9 | 1.514(2) | C24—C23i | 1.406(10) |
| C10—C11 | 1.456(3) | O7—H7 | 0.8200 |
| C10—H10A | 0.9700 | O5—O7 | 3.1430(36) |
| C10—H10B | 0.9700 | O1—H | 2.1427(13) |
| C11—H11A | 0.9600 | O4—H | 2.0523(16) |
|  | | | |
| **Atoms 1,2,3** | **Angle 1,2,3 [°]** | **Atoms 1,2,3** | **Angle 1,2,3 [°]** |
| C5A—C1—C5B | 113.8(12) | C10—C11—H11B | 109.500 |
| C5A—C1—C6 | 124.7(8) | H11A—C11—H11B | 109.500 |
| C5B—C1—C6 | 121.4(8) | C10—C11—H11C | 109.500 |
| C5A—C1—SA | 113.5(8) | H11A—C11—H11C | 109.500 |
| C6—C1—SA | 121.8(2) | H11B—C11—H11C | 109.500 |
| C5B—C1—SB | 112.7(8) | C13—C12—N1 | 120.79(15) |
| C6—C1—SB | 125.9(2) | C13—C12—C17 | 118.75(15) |
| SA—C1—SB | 112.3(3) | N1—C12—C17 | 120.43(15) |
| C4—C3—SA | 117.5(3) | C14—C13—C12 | 121.01(17) |
| C4—C3—C5B | 110.4(7) | C14—C13—H13 | 119.500 |
| C4—C3—H3 | 121.200 | C12—C13—H13 | 119.500 |
| SA—C3—H3 | 121.200 | C13—C14—C15 | 120.75(18) |
| C5B—C3—H3 | 128.400 | C13—C14—H14 | 119.600 |
| C3—C4—SB | 117.0(2) | C15—C14—H14 | 119.600 |
| C3—C4—C5A | 107.8(5) | C16—C15—C14 | 119.04(18) |
| C3—C4—H4 | 126.100 | C16—C15—H15 | 120.500 |
| SB—C4—H4 | 116.900 | C14—C15—H15 | 120.500 |
| C5A—C4—H4 | 126.100 | C15—C16—C17 | 121.60(17) |
| C3—SA—C1 | 96.5(3) | C15—C16—H16 | 119.200 |
| C1—C5A—C4 | 104.7(11) | C17—C16—H16 | 119.200 |
| C1—C5A—H5A | 127.600 | C16—C17—C12 | 118.76(16) |
| C4—C5A—H5A | 127.600 | C16—C17—C18 | 119.22(15) |
| C1—C5B—C3 | 103.1(12) | C12—C17—C18 | 121.91(15) |
| C1—C5B—H5B | 128.400 | O4—C18—O5 | 122.48(16) |
| C3—C5B—H5B | 128.400 | O4—C18—C17 | 123.33(15) |
| C4—SB—C1 | 96.6(2) | O5—C18—C17 | 114.14(15) |
| C9—O3—C10 | 116.39(16) | C21—C20—C20i | 116.5(6) |
| C18—O5—H5 | 109.500 | C21—C20—C24 | 122.3(5) |
| C8—N1—C12 | 126.27(14) | C20i—C20—C24 | 121.1(5) |
| C8—N1—H | 116.900 | C20i—C20—N2 | 120.3(5) |
| C12—N1—H | 116.900 | C24—C20—N2 | 118.4(4) |
| O1—C6—C7 | 121.65(16) | C20—N2—H2A | 120.000 |
| O1—C6—C1 | 119.70(16) | C20—N2—H2B | 120.000 |
| C7—C6—C1 | 118.64(15) | H2A—N2—H2B | 120.000 |
| C8—C7—C6 | 124.14(15) | C20—C21—C22 | 123.5(8) |
| C8—C7—H7A | 117.900 | C20—C21—H21 | 118.300 |
| C6—C7—H7A | 117.900 | C22—C21—H21 | 118.300 |
| C7—C8—N1 | 123.80(15) | C21—C22—C23 | 132.0(7) |
| C7—C8—C9 | 116.42(15) | C21—C22—H22 | 114.000 |
| N1—C8—C9 | 119.46(15) | C23—C22—H22 | 114.000 |
| O2—C9—O3 | 125.10(16) | C24i—C23—C22 | 100.2(8) |
| O2—C9—C8 | 123.45(17) | C24i—C23—H23 | 129.900 |
| O3—C9—C8 | 111.39(14) | C22—C23—H23 | 129.900 |
| C11—C10—O3 | 108.8(2) | O7—C24—O6 | 118.1(4) |
| C11—C10—H10A | 109.900 | O7—C24—C23i | 112.9(7) |
| O3—C10—H10A | 109.900 | O7—C24—C20 | 120.3(4) |
| C11—C10—H10B | 109.900 | O6—C24—C20 | 121.6(4) |
| O3—C10—H10B | 109.900 | C23i—C24—C20 | 126.6(7) |
| H10A—C10—H10B | 108.300 | C24—O7—H7 | 109.500 |
| C10—C11—H11A | 109.500 |  |  |
| (i) 1-x, 1-y, -z. | | | |

1. **Figures**

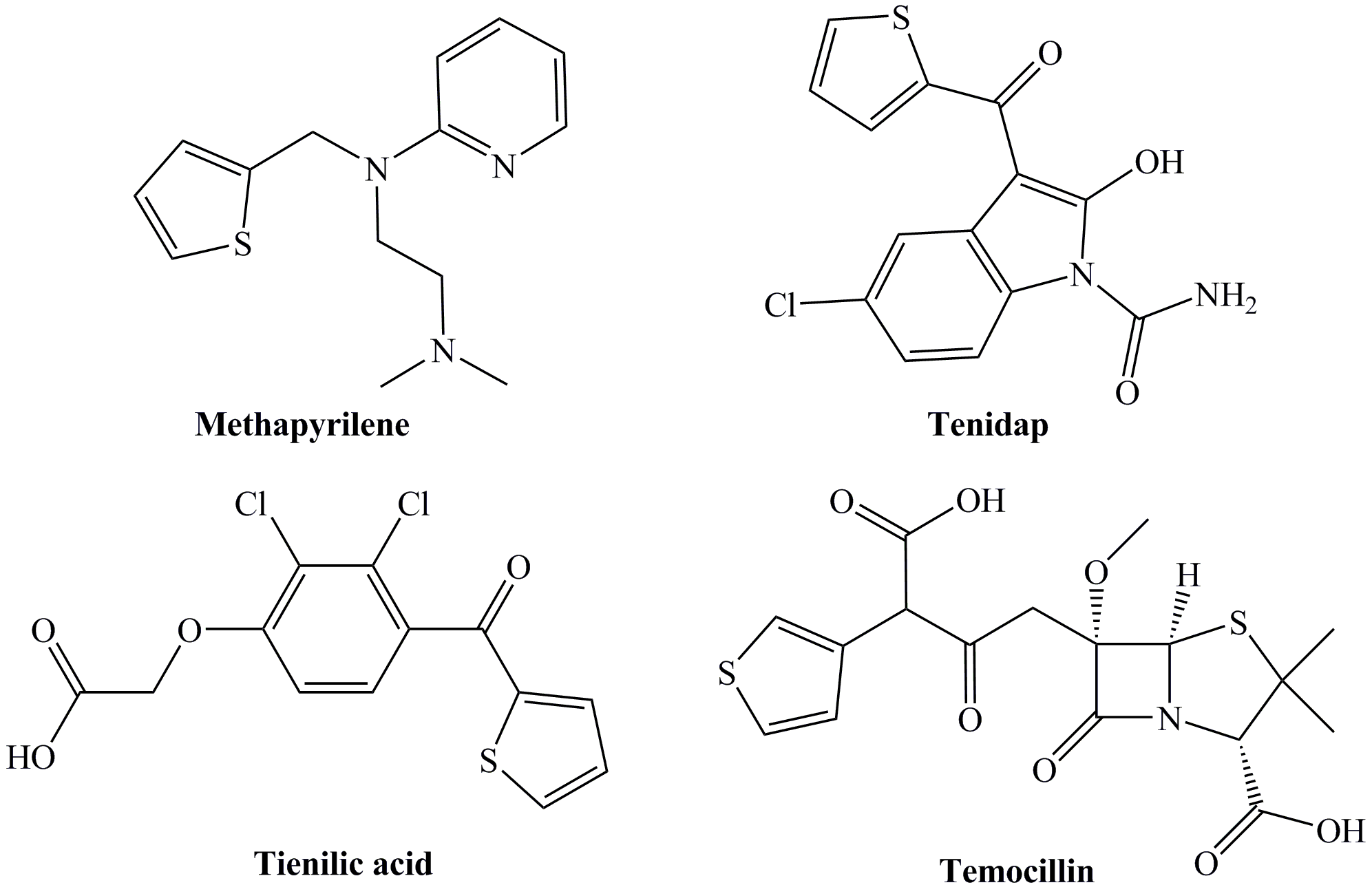
**Figure S1** Examples for important 2-thienyl-containing drugs.

**Figure S2** 1H NMR spectra of **2a** (200 MHz, DMSO-*d*6).

**Figure S3** 1H NMR spectra of **2c** (200 MHz, DMSO-*d*6).

**Figure S4** 1H-1H COSY NMR spectrum of **2a** (500 MHz, DMSO-*d*6).

**Figure S5** Co-crystal of ETCAOB and Anth.



**Figure S1** Examples for important 2-thienyl-containing drugs

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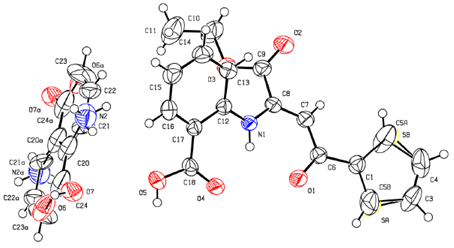
**Figure S2** 1H NMR spectra of **2a** (200 MHz, DMSO-*d*6).

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**Figure S3** 1H NMR spectra of **2c** (200 MHz, DMSO-*d*6).



**Figure S4** 1H-1H COSY NMR spectrum of **2a** (500 MHz, DMSO-*d*6).



**Figure S5** Co-crystal of ETCAOB and Anth

1. **Scheme**



**Scheme S1** Substitution of the sarcosine residue of sarmesin with oxanilic acid

**Refrences**

1. [S1] R.F.M Elshaarawy, H. K. Ibrahim, E. Eltamany, I. Mohy-Eldeen, Maced. J. Chem. Chem. Eng. 27(1) (2008) 65-79 [↑](#endnote-ref-1)