Electronic Supplementary Material (ESI) for Metallomics.

Supplemental Methods

Title: "Pyrazolopyrimidinones, a novel class of copper-dependent bactericidal antibiotics against multi-drug resistant *S. aureus"*

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Synthesis of PZP 915. The strategy to synthesize PZP 915 is outlined in figure S10. The synthesis of (Z)-2-(4-chlorophenyl)-3-hydroxybut-2-enenitrile (tautomers **2A, 2B**) was performed in analogy to reaction conditions reported in Wei et al [1]. To a solution of 1.0 g (6.60 mmol, 1 equiv.) (4-chlorophenyl) acetonitrile (compound 1) in 20 ml anhydrous THF at 0 °C under argon, a suspension of 237 mg (9.89 mmol, 1.5 equiv.) NaH in 20 ml anhydrous THF at 0 °C was slowly added. The resulting reaction mixture was allowed to slowly warm to RT and then kept stirring under argon for 2 hrs. During that time the reaction color turned to dark brown. A solution of 1.0 mL (9.89 mmol, 1.5 equiv.) anhydrous ethyl acetate was added at RT and kept stirring under argon at RT overnight. The reaction mixture was concentrated to remove most of the THF. Then, 10 mL of icy water were added slowly, and the pH of the resulting aqueous solution was adjusted to 2.0 using 2N HCl aqueous solution. This aqueous phase was extracted with 20 mL ethyl acetate three times. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to dryness. Descending column chromatography using silica gel as stationary phase and a gradient mixture of EtOAc and hexanes as eluent gave 575 mg (yield 45%) of compounds 2A and 2B as yellow solid.

NMR peaks for compounds **2A** and **2B**: ^{1}H NMR (400 MHz, DMSO-d6) δ 7.62 (d, J = 8.7 Hz, 2H), 7.39 (d, J = 8.7 Hz, 2H), 2.32 (s, 3H).
^{13}C NMR (101 MHz, DMSO-d6) δ 169.24, 131.72, 130.37, 128.49 (2C), 128.33 (2C), 120.65, 85.67, 21.78. (spectra not shown)

The reaction to generate 4-(4-chlorophenyl)-3-methyl-1H-pyrazol-5-amine (**3**) from the tautomeric mixture of **2A** and **2B** was previously reported[2]. The reaction conditions were adjusted to maximize the purity of compound **3**. A solution of 867 mg (4.49 mmol, 1.0 equiv.) mixture of the tautomers 2A and 2B and 400 mg (5.39 mmol, 1.2 equiv.) acetyl

hydrazine in 20 mL n-BuOH were stirred under argon at 95 °C overnight. To this mixture, 0.65 mL (5.84 mmol, 1.3 equiv.) N-methylpiperazine was added. The reaction mixture was kept refluxing at 120 °C under argon overnight again. The reaction residue was concentrated to remove most n-BuOH. The residue was then diluted with 20 mL distilled water and extracted three times with 20 mL ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to dryness. Descending column chromatography using silica gel as stationary phase and a gradient mixture of CH_2Cl_2 and MeOH as eluent gave 282 mg (yield 49%) of compound 3 as a light yellow solid.

NMR peaks for compound **3:** ^{1}H NMR (400 MHz, Chloroform-d) δ 7.36 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 5.88 (bs, 3H, NH), 2.23 (s, 3H).
^{13}C NMR (101 MHz, Chloroform-d) δ 151.51, 138.66, 131.96, 131.66, 129.89 (2C), 129.11 (2C), 105.28, 11.04. (Spectra not shown)

The last reaction to obtain 5-benzyl-3-(4-chlorophenyl)-2-methylpyrazolo[1,5-a]pyrimidin-7(4H)-one (**4**; PZP 915)) carried out as reported in [3]. The reaction conditions were adjusted to maximize the purity of compound 4. A solution of 207 mg (0.99 mmol, 1 equiv.) compound 3 and 206 mg (0.99 mmol, 1 equiv.) ethyl 3-oxo-4-phenylbutanoate in 5.0 mL glacial acetic acid (AcOH) was kept refluxing overnight under argon. The reaction mixture was concentrated to dryness, then crystallized with MeOH, and re-crystallized from MeOH to give 140 mg (yield 41%) compound 4 as a light yellow solid.

NMR peaks for compound **4** (PZP 915)**:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1H, NH), 7.53 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.5 Hz, 2H), 7.38 – 7.22 (m, 5H), 5.46 (s, 1H), 3.94 (s, 2H), 2.25 (s, 3H). (Fig. S11)
^{13}C NMR (101 MHz, DMSO-d_6) δ 155.80, 153.18, 149.96, 138.75, 137.04, 131.66, 131.35 (2C), 129.58, 128.83 (2C), 128.65 (4C), 126.88, 102.01, 95.93, 37.49, 12.96. (Fig. S12)

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