Supplementary Material

New insights into the bacterial RNA polymerase inhibitor CBR703 as a starting point for optimization as an anti-infective agent

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Experimental Section

Chemistry.

Commercial reagents were purchased and used without further purification. If the acyl chloride was not available it was obtained from the carboxylic acid by refluxing in $SOCl_2$ for 4 h and removal of the volatiles. Proton nuclear magnetic resonance (^{1}H NMR) and carbon NMR (^{13}C NMR) spectra were recorded on a Bruker Fourier spectrometer (500 or 300 MHz) at ambient temperature with the chemical shifts recorded as δ values in ppm units by reference to the hydrogenated residues of deuterated solvent as internal standard. Coupling constants (*J*) are given in Hz and signal patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet, br, broad signal. The melting points (m.p.) were determined on a Stuart Scientific SMP3 apparatus and are uncorrected. The SpectraSystems-LC-system consisted of a pump, an autosampler, and a UV detector. Mass spectrometry was performed on a MSQ electro spray mass spectrometer (Thermo Fisher, Dreieich, Germany). The system was operated by the standard software Xcalibur. A RP C18 NUCLEODUR 100-5 (125 x 3 mm) column (Macherey-Nagel GmbH, Duehren, Germany) was used as stationary phase. Solvent system: In a gradient run the percentage of acetonitrile (containing 0.1 % trifluoroacetic acid) in 0.1 % triflouroacetic acid was increased from an initial concentration of 0% at 0 min to 100 % at 15 min and kept at 100 % for 5 min. The injection volume was 10 µL and flow rate was set to 800 µL/min. MS analysis was carried out at a spray voltage of 3800 V, a capillary temperature of 350 °C and a source CID of 10 V. Spectra were acquired in positive mode from 100 to 1000 *m/z* and at 254 nm for the UV trace.

General Procedure for the Preparation of compound 1 – 27 (1, 2).

To a stirred solution of the aniline (2.20 mmol) and triethylamine (404mg, 4.00 mmol) in CH_2Cl_2 (4 mL) at 0 °C (ice bath) was added drop wise a solution of acyl chloride (2.00 mmol) in CH_2Cl_2 (4 mL). The ice bath was removed and the reaction mixture was stirred for 2 h at room temperature. The solution was washed with 1N HCl and the organic layer was concentrated to give the crude product, which was purified by column chromatography (SiO_2, *n*-hexane/EtOAc) to yield the amides **1a** – **26a**.

The amide (1.00 mmol) and phosphorous pentachloride (260mg, 1.25 mmol) in 1, 2-dichloroethane (6 mL) was heated at 70 °C for 5 h. After cooling to room temperature, the solvent was evaporated under reduced pressure, toluene (2 mL) was added and the mixture was concentrated. The residual material was dissolved in acetonitrile (4 mL) and added at 0 °C to a solution of hydroxylamine (**1** – **25**) or O-methylhydroxylamine (**26**) or hydrazine (**27**) prepared by stirring the appropriate hydrochloride salt (2.50 mmol) and triethylamine (5.00 mmol) in acetonitrile (4 mL) at 0 °C for 1 h. After stirring at room temperature for 16 h, the solvent was removed *in vacuo*. The residue was dissolved partitioned between EtOAc and 0.5 N HCl. The organic layer was concentrated and purified by column chromatography (SiO_2, *n*-hexane/EtOAc).

Procedure for the Preparation of compound 6, 13 (3)**.**

A mixture of the nitro compound **1** or **8** (1.00 mmol) and stannous chloride hydrate (1.13 g, 5.00 mmol) in absolute EtOH (4 mL) was stirred at 70 °C under a nitrogen atmosphere. After 30 min the solid material disappeared indicating a complete reaction. The solution was cooled and poured into ice water. The pH was carefully adjusted to pH=7 – 8 by addition of 5% aqueous Na_2CO_3 solution and the mixture was extracted with EtOAc (x mL). The organic layer was washed with saturated brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO_2, *n*-hexane/EtOAc).

N'-hydroxy-N-phenyl-3-(trifluoromethyl)benzimidamide (CBR703) white solid, m.p. 118 – 120 °C; 73 % yield; Calc. for $C_{14}H_{11}F_3N_2O$ (*M*W = 280.25): C, 60.00; H, 3.96; N, 10.00; found: C, 59.73; H,3.82; N, 10.39; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.78 (br s, 1H), 8.46 (br s, 1H), 7.71 (d, 1H, *J* = 7.6 Hz), 7.66 (s, 1H), 7.62 (d, 1H, *J* = 7.9 Hz), 7.55 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.08 (dd, 2H, *J* = 8.3, 7.5 Hz), 6.82 (t, 1H, *J* = 7.5 Hz), 6.66 (d, 2H, *J* = 8.3 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 147.9, 141.0, 133.9, 131.6, 129.4, 128.9 (q, $J_{C\text{-}F}$ = 31.2 Hz), 128.4,

125.4 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.9 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.8 (q, $J_{C\text{-}F}$ = 3.7 Hz), 121.0, 120.0 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 281.01 (100 %), t_R= 11.15 min, 99.2 % pure (UV).

N-(4-nitrophenyl)-3-(trifluoromethyl)benzamide (1a) slight yellow solid, m.p. 181 – 183 °C; 65 % yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 8.29 (d, 2H, *J* = 9.1 Hz), 8.13 (m, 2H), 8.09 (d, 1H, *J* = 7.9 Hz), 7.87 (m, 3H), 7.69 (dd, 1H, *J* = 7.9, 7.9 Hz) ppm; LC/MS: *m/z* (%): $[M+MeCN]^+$ 351.67 (100 %), t_R= 12.17 min, 98.6 % pure (UV).

N'-hydroxy-N-(4-nitrophenyl)-3-(trifluoromethyl)benzimidamide (1) slight yellow solid, m.p. 195 – 197 °C; 43 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 11.46 (br s, 1H), 9.42 (br s, 1H), 8.01 (d, 2H, *J* = 9.3 Hz), 7.80 (m, 2H), 7.74 (d, 1H, *J* = 7.6 Hz), 7.64 (dd, 1H, *J* = 7.9, 7.6 Hz), 6.75 (d, 2H, *J* = 9.3 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 148.3, 145.4, 139.4, 133.5, 131.1, 129.9, 129.3 (q, $J_{C\text{-}F}$ = 32.1 Hz), 126.1 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.9, 123.9 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 122.8, 117.0 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 325.80 (100 %), t_R= 10.96 min, 98.1 % pure (UV).

N-(p-tolyl)-3-(trifluoromethyl)benzamide (2a) white solid, m.p. 128 – 130 °C; 79 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.39 (br s, 1H), 8.28 (s, 1H), 8.25 (d, 1H, *J* = 7.9 Hz), 7.95 (d, 1H, *J* = 8.1 Hz), 7.78 (dd, 1H, *J* = 8.1, 7.9 Hz), 7.65 (d, 2H, *J* = 8.5 Hz), 7.18 (d, 2H, *J* = 8.5 Hz), 2.29 (s, 3H) ppm; LC/MS: *m/z* (%): $[M+MeCN]^+$ 351.67 (100 %), t_R= 12.17 min, 98.6 % pure (UV).

N'-hydroxy-N-(p-tolyl)-3-(trifluoromethyl)benzimidamide (2) white solid, m.p. 170 – 172 °C; 48 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.68 (br s, 1H), 8.31 (s, 1H), 7.69 (d, 1H, *J* = 7.6 Hz), 7.66 (s, 1H), 7.57 (d, 1H, *J* = 7.9 Hz), 7.53 (dd, 1H, *J* = 7.9, 7.6 Hz), 6.89 (d, 2H, *J* = 8.2 Hz), 6.56 (d, 2H, *J* = 8.2 Hz), 2.14 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 148.3, 138.4, 134.0, 131.6, 130.1, 129.3, 128.9, 128.8 (q, $J_{C\text{-}F}$ = 32.1 Hz), 125.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.9 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.8 (q, $J_{C\text{-}F}$ = 3.7 Hz), 120.5, 20.1 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 294.88 (100 %), t_R= 11.82 min, 100 % pure (UV).

3-(trifluoromethyl)-N-(4-(trifluoromethyl)phenyl)benzamide (3a) white solid, m.p. 145 – 147 °C; 81 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.78 (br s, 1H), 8.31 (s, 1H), 8.28 (d, 1H, *J* = 7.9 Hz), 8.00 (m, 3H), 7.81 (dd, 1H, *J* = 8.1, 7.9 Hz), 7.75 (d, 2H, *J* = 8.5 Hz) ppm; LC/MS: *m/z* (%): $[M+MeCN]^+$ 374.63 (100 %), t_R= 13.61 min, 99.3 % pure (UV).

N'-hydroxy-3-(trifluoromethyl)-N-(4-(trifluoromethyl)phenyl)benzimidamide (3) white solid, m.p. 173 –175 °C; 56 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 11.15 (br s, 1H), 8.97 (br s, 1H), 7.76 (d, 1H, *J* = 7.6 Hz), 7.74 (s, 1H), 7.68 (d, 1H, *J* = 7.9 Hz), 7.60 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.43 (d, 2H, *J* = 8.5 Hz), 6.77 (d, 2H, *J* = 8.5 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 146.5, 145.0, 133.6, 131.3, 129.7, 129.2 (q, $J_{C\text{-}F}$ = 32.1 Hz), 125.8 (q, $J_{C\text{-}F}$ = 2.8 Hz), 125.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.9 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 120.2 (q, $J_{C\text{-}F}$ = 32.1 Hz), 118.4 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 348.69 (100 %), t_R= 12.56 min, 94.9 % pure (UV).

N-(4-cyanophenyl)-3-(trifluoromethyl)benzamide (4a) white solid, m.p. 182 – 184 °C; 70 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.83 (br s, 1H), 8.29 (s, 1H), 8.26 (d, 1H, *J* = 7.9 Hz), 7.95 (m, 3H), 7.84 (d, 2H, *J* = 8.8 Hz), 7.80 (dd, 1H, *J* = 8.1, 7.9 Hz) ppm; LC/MS: *m/z* (%): $[M+MeCN]^+$ 331.74 (100 %), t_R= 12.11 min, 95.4 % pure (UV).

N-(4-cyanophenyl)-N'-hydroxy-3-(trifluoromethyl)benzimidamide (4) white solid, m.p. 165 – 167 °C; 40 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 11.29 (br s, 1H), 9.14 (br s, 1H), 7.78 (d, 1H, *J* = 7.6 Hz), 7.76 (s, 1H), 7.69 (d, 1H, *J* = 7.9 Hz), 7.62 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.53 (d, 2H, *J* = 9.0 Hz), 6.73 (d, 2H, *J* = 9.0 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 145.9, 145.8, 133.5, 132.8, 131.2, 129.8, 129.6, 129.3 (q, $J_{C\text{-}F}$ = 32.1 Hz), 126.0 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.9 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.5 (q, $J_{C\text{-}F}$ = 4.6 Hz), 119.5, 118.2, 101.2 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 305.88 (100 %), t_R= 10.48 min, 96.8 % pure (UV).

N-(4-methoxyphenyl)-3-(trifluoromethyl)benzamide (5a) white solid, m.p. 129 – 131 °C; 79 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.34 (br s, 1H), 8.26 (m, 2H), 7.95 (d, 1H, *J* = 7.8 Hz), 7.77 (dd, 1H, *J* = 7.8, 7.6 Hz), 7.67 (d, 2H, *J* = 9.0 Hz), 6.94 (d, 2H, *J* = 9.0 Hz), 3.75 (s, 3H) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 295.87 (100 %), t_R= 11.83 min, 100 % pure (UV).

N'-hydroxy-N-(4-methoxyphenyl)-3-(trifluoromethyl)benzimidamide (5) white solid, m.p. 140 – 142 °C; 53 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.56 (br s, 1H), 8.20 (br s, 1H), 7.67 (d, 1H, *J* = 7.6 Hz), 7.64 (s, 1H), 7.56 (d, 1H, *J* = 7.9 Hz), 7.52 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.69 (d, 2H, *J* = 8.8 Hz), 6.63 (d, 2H, *J* = 8.8 Hz), 3.63 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 154.4, 148.8, 133.9, 131.8, 129.2, 128.8 (q, $J_{C\text{-}F}$ = 32.1 Hz), 125.2 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.1 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.9 (q, $J_{C\text{-}F}$ = 272.2 Hz), 122.7, 113.8, 55.1 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 310.88 (100 %), t_R= 10.93 min, 95.5 % pure (UV).

N-(4-aminophenyl)-N'-hydroxy-3-(trifluoromethyl)benzimidamide (6) white solid, m.p. 131 – 133 °C; 33 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.83 (br s, 1H), 9.12 (br s, 1H), 7.71 (d, 1H, *J* = 7.6 Hz), 7.68 (s, 1H), 7.60 (d, 1H, *J* = 7.9 Hz), 7.57 (dd, 1H, *J* = 7.9, 7.6 Hz), 6.93 (d, 2H, *J* = 8.2 Hz), 6.61 (d, 2H, *J* = 8.2 Hz), 4.87 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 148.3, 138.7, 134.0, 131.5, 130.0, 129.2, 128.9 (q, $J_{C\text{-}F}$ = 32.1 Hz), 128.8, 125.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.0 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.9 (q, $J_{C\text{-}F}$ = 272.2 Hz), 121.0 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 295.89 (100 %), t_R= 8.98 min, 96.8 % pure (UV).

N-(4-chlorophenyl)-3-(trifluoromethyl)benzamide (7a) white solid, m.p. 136 – 138°C; 85 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.58 (br s, 1H), 8.28 (s, 1H), 8.26 (d, 1H, *J* = 7.6 Hz), 7.97 (d, 1H, *J* = 7.9 Hz), 7.77 (m, 3H), 7.44 (d, 2H, *J* = 9.1 Hz) ppm; LC/MS: *m/z* (%): $[M+MeCN]^+$ 340.55 (100 %), t_R= 12.74 min, 99.5 % pure (UV).

N-(4-chlorophenyl)-N'-hydroxy-3-(trifluoromethyl)benzimidamide (7) white solid, m.p. 173 – 175 °C; 50 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.90 (br s, 1H), 8.64 (br s, 1H), 7.73 (d, 1H, *J* = 7.6 Hz), 7.69 (s, 1H), 7.62 (d, 1H, *J* = 7.9 Hz), 7.57 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.13 (d, 2H, *J* = 9.0 Hz), 6.65 (d, 2H, *J* = 9.0 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 147.4, 140.1, 133.6, 131.5, 129.5, 129.1 (q, $J_{C\text{-}F}$ = 32.1 Hz), 128.2, 125.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.6, 123.9 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.8 (q, $J_{C\text{-}F}$ = 3.7 Hz), 121.2 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 314.80 (100 %), t_R= 11.81 min, 99.2 % pure (UV).

N-(3-nitrophenyl)-3-(trifluoromethyl)benzamide (8a) slight yellow solid, m.p. 160 – 162 °C; 69 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.39 (br s, 1H), 8.78 (dd, 1H, *J* = 2.2, 2.2 Hz), 8.34 (s, 1H), 8.30 (d, 1H, *J* = 7.9 Hz), 8.21 (m, 1H), 8.00 (m, 2H), 7.82 (dd, 1H, *J* = 8.2, 8.2 Hz), 7.69 (dd, 1H, *J* = 7.9, 7.6 Hz) ppm; LC/MS: *m/z* (%): $[M+MeCN]^+$ 351.55 (100 %), t_R= 12.64 min, 99.2 % pure (UV).

N'-hydroxy-N-(3-nitrophenyl)-3-(trifluoromethyl)benzimidamide (8) slight yellow solid, m.p. 163.0 –164.4 °C; 40 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 11.17 (br s, 1H), 9.08 (br s, 1H), 7.77 (m, 2H), 7.72 (d, 1H, *J* = 7.6 Hz), 7.61 (m, 2H), 7.52 (dd, 1H, *J* = 2.5, 2.2 Hz), 7.36 (dd, 1H, *J* = 8.2, 8.2 Hz), 6.98 (m, 1H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 147.9, 146.2, 142.6, 133.5, 131.4, 129.8, 129.5, 129.3 (q, $J_{C\text{-}F}$ = 32.1 Hz) , 125.9 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.7, 123.9 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 114.6, 112.7 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 325.81 (100 %), t_R= 11.30 min, 100 % pure (UV).

N-(m-tolyl)-3-(trifluoromethyl)benzamide (9a) white solid, m.p. 116 – 118 °C; 77 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.38 (br s, 1H), 8.29 (s, 1H), 8.25 (d, 1H, *J* = 7.9 Hz), 7.96 (d, 1H, *J* = 7.8 Hz), 7.78 (dd, 1H, *J* = 7.9, 7.8 Hz), 7.61 (s, 1H), 7.57 (d, 1H, *J* = 8.0 Hz), 7.25 (dd, 1H, *J* = 8.0, 7.5 Hz), 6.95 (d, 1H, *J* = 7.5 Hz), 2.32 (s, 3H) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 279.90 (100 %), t_R= 12.74 min, 100 % pure (UV).

N'-hydroxy-N-(m-tolyl)-3-(trifluoromethyl)benzimidamide (9) white solid, m.p. 95 – 97 °C; 44 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.77 (br s, 1H), 8.36 (br s, 1H), 7.71 (d, 1H, *J* = 8.0 Hz), 7.66 (s, 1H), 7.61 (d, 1H, *J* = 7.6 Hz), 7.55 (dd, 1H, *J* = 8.0, 7.6 Hz), 6.93 (dd, 1H, *J* = 7.9, 7.6 Hz), 6.83 (d, 1H, *J* = 7.6 Hz), 6.57 (s, 1H), 6.35 (m, 1H), 2.11 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 148.0, 140.9, 137.6, 134.0, 131.5, 129.4, 128.9 (q, $J_{C\text{-}F}$ = 32.1 Hz), 128.2, 125.4 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.9 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.8 (q, $J_{C\text{-}F}$ = 4.6 Hz), 121.8, 120.6, 117.2, 21.0 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 294.89 (100 %), t_R= 11.93 min, 96.7 % pure (UV).

3-(trifluoromethyl)-N-(3-(trifluoromethyl)phenyl)benzamide (10a) white solid, m.p. 126 – 128 °C; 83 % yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 8.13 (s, 1H), 8.07 (d, 1H, *J* = 7.9 Hz), 8.00 (br s, 1H), 7.94 (s, 1H), 7.88 (d, 1H, *J* = 8.0 Hz), 7.83 (d, 1H, *J* = 7.9 Hz), 7.65 (dd, 1H, *J* = 7.9, 7.9 Hz), 7.51 (dd, 1H, *J* = 8.0, 7.8 Hz), 7.44 (d, 1H, *J* = 7.8 Hz) ppm; LC/MS: *m/z* (%): $[M+MeCN]^+$ 374.63 (100 %), t_R= 12.98 min, 99.1 % pure (UV).

N'-hydroxy-3-(trifluoromethyl)-N-(3-(trifluoromethyl)phenyl)benzimidamide (10) white solid, m.p. 104 –106 °C; 55 % yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 8.59 (br s, 1H), 7.75 (s, 1H), 7.66 (d, 1H, *J* = 7.8 Hz), 7.57 (d, 1H, *J* = 7.9 Hz), 7.45 (dd, 1H, *J* = 7.9, 7.8 Hz), 7.38 (br s, 1H), 7.21 (m, 2H), 6.91 (s, 1H), 6.77 (d, 1H, *J* = 7.6 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ= 150.2, 139.7, 131.5, 131.4 (q, $J_{C\text{-}F}$ = 33.0 Hz), 131.2 (q, $J_{C\text{-}F}$ = 33.0 Hz), 129.5, 129.2, 126.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 125.1 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.0, 123.6 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.5 (q, $J_{C\text{-}F}$ = 272.2 Hz), 119.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 117.6 (q, $J_{C\text{-}F}$ = 3.7 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 348.70 (100 %), t_R= 12.11 min, 100 % pure (UV).

N-(3-cyanophenyl)-3-(trifluoromethyl)benzamide (11a) white solid, m.p. 142 – 144 °C; 80 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.75 (br s, 1H), 8.30 (s, 1H), 8.27 (d, 1H, *J* = 7.9 Hz), 8.24 (s, 1H), 8.05 (m, 1H), 8.00 (d, 1H, *J* = 7.6 Hz), 7.81 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.60 (m, 2H) ppm; LC/MS: *m/z* (%): $[M+MeCN]^+$ 331.92 (100 %), t_R= 12.10 min, 98.2 % pure (UV).

N-(3-cyanophenyl)-N'-hydroxy-3-(trifluoromethyl)benzimidamide (11) white solid, m.p. 152 – 154 °C; 45 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 11.08 (br s, 1H), 8.90 (br s, 1H), 7.76 (d, 1H, *J* = 7.9 Hz), 7.73 (s, 1H), 7.67 (d, 1H, *J* = 7.6 Hz), 7.60 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.28 (dd, 1H, *J* = 8.2, 7.6 Hz), 7.23 (d, 1H, *J* = 7.6 Hz), 7.05 (s, 1H), 6.88 (d, 1H, *J* = 8.2 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 146.5, 142.1, 133.4, 131.5, 129.7, 129.6, 129.2 (q, J_{C-F} = 31.2 Hz), 125.8 (q, J_{C-F} = 3.7 Hz), 123.9 (q, J_{C-F} = 272.2 Hz), 123.8 (q, J_{C-F} = 3.7 Hz), 123.8, 123.7, 121.8, 118.8, 111.1 ppm; LC/MS: *m/z* (%): $[M+ MeCN]^+$ 346.77 (100 %), t_R= 10.27 min, 97.7 % pure (UV).

N-(3-methoxyphenyl)-3-(trifluoromethyl)benzamide (12a) white solid, m.p. 121 – 123 °C; 74 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.43 (br s, 1H), 8.28 (s, 1H), 8.25 (d, 1H, *J* = 8.2 Hz), 7.96 (d, 1H, *J* = 8.2 Hz), 7.79 (dd, 1H, *J* = 8.2, 8.2 Hz), 7.46 (dd, 1H, *J* = 2.4, 2.2 Hz), 7.37 (d, 1H, *J* = 7.9 Hz), 7.28 (dd, 1H, *J* = 8.2, 7.9 Hz), 6.72 (dd, 1H, *J* = 8.2, 2.4 Hz), 3.76 (s, 3H) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 295.84 (100 %), t_R= 12.32 min, 96.5 % pure (UV).

N'-hydroxy-N-(3-methoxyphenyl)-3-(trifluoromethyl)benzimidamide (12) white solid, m.p. 109 – 111 °C; 48 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.81 (br s, 1H), 8.44 (br s, 1H), 7.72 (d, 1H, *J* = 8.2, 7.8 Hz), 8.68 (s, 1H), 7.62 (d, 1H, *J* = 7.9 Hz), 7.56 (dd, 1H, *J* = 7.9, 7.9 Hz), 6.96 (dd, 1H, *J* =3.0 Hz), 6.38 (dd, 1H, *J* = 8.2, 2.3 Hz), 6.26 (dd, 1H, *J* = 2.3, 2.0 Hz), 6.18 (dd, 1H, *J* = 7.9, 2.0 Hz), 3.55 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 159.4, 147.9, 142.2, 134.0, 131.6, 129.4, 129.1, 129.0 (q, J_{C-F} = 32.1 Hz) 125.4 (q, J_{C-F} = 3.7 Hz), 123.9 (q, J_{C-F} = 272.2 Hz), 123.8 (q, J_{C-F} = 3.7 Hz), 112.2, 106.5, 105.7, 54.6 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 310.84 (100 %), t_R= 11.27 min, 97.4 % pure (UV).

N-(3-aminophenyl)-N'-hydroxy-3-(trifluoromethyl)benzimidamide (13) white solid, m.p. 130 – 132 °C; 40 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.66 (br s, 1H), 8.01 (br s, 1H), 7.69 (d, 1H, *J* = 7.9 Hz), 7.67 (s, 1H), 7.61 (d, 1H, *J* = 7.6 Hz), 7.54 (dd, 1H, *J* = 7.9, 7.6 Hz), 6.69 (dd, 1H, *J* = 8.2, 7.9 Hz), 6.06 (m, 1H), 6.00 (dd, 1H, *J* = 2.2, 1.9 Hz), 5.75 (dd, 1H, *J* = 7.9, 2.2 Hz), 4.88 (s, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 148.9, 148.5, 141.6, 134.2, 131.4, 129.2, 128.8 (q, J_{C-F} = 32.1 Hz), 128.7, 125.3 (q, J_{C-F} = 3.7 Hz), 123.9 (q, J_{C-F} = 272.2 Hz), 123.6 (q, J_{C-F} = 4.6 Hz), 108.8, 107.9, 106.1 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 295.88 (100 %), t_R= 9.46 min, 100 % pure (UV).

N-phenyl-2-(trifluoromethyl)benzamide (14a) white solid, m.p. 152 – 154 °C; 55 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.54 (br s, 1H), 7.85 (d, 1H, *J* = 7.9 Hz), 7.79 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.70 (m, 4H), 7.35 (dd, 2H, *J* = 8.5, 7.6 Hz), 7.11 (t, 1H, *J* = 7.6 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 265.98 (100 %), t_R= 10.95 min, 99.4 % pure (UV).

N'-hydroxy-N-phenyl-2-(trifluoromethyl)benzimidamide (14) white solid, m.p. 140 – 142 °C; 49 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.52 (br s, 1H), 8.49 (br s, 1H), 7.78 (m, 1H), 7.60 (m, 2H), 7.40 (m, 1H), 7.00 (dd, 2H, *J* = 7.6, 7.2 Hz), 6.76 (t, 1H, *J* = 7.2 Hz), 6.59 (d, 2H, *J* = 7.6 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 147.0, 140.2, 132.2, 131.8, 131.5, 129.6, 128.4, 128.3, 128.1 (q, $J_{C\text{-}F}$ = 30.2 Hz), 126.7 (q, $J_{C\text{-}F}$ = 4.6 Hz), 123.8 (q, $J_{C\text{-}F}$ = 274.0 Hz), 121.3, 119.7 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 280.98 (100 %), t_R= 10.30 min, 97.2 % pure (UV).

N-phenyl-4-(trifluoromethyl)benzamide (15a) white solid, m.p. 210.0 – 211.7 °C; 68 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.47 (br s, 1H), 8.15 (d, 2H, *J* = 8.4 Hz), 7.91 (d, 2H, *J* = 8.4 Hz), 7.78 (d, 2H, *J* = 8.0 Hz), 7.37 (dd, 2H, *J* = 8.0, 7.4 Hz), 7.13 (t, 1H, *J* = 7.4 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 265.89 (100 %), t_R= 12.07 min, 97.4 % pure (UV).

N'-hydroxy-N-phenyl-4-(trifluoromethyl)benzimidamide (15) white solid, m.p. 133 – 136 °C; 44 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.85 (br s, 1H), 8.45 (br s, 1H), 7.69 (d, 2H, *J* = 8.0 Hz), 7.57 (d, 2H, *J* = 8.0 Hz), 7.08 (dd, 2H, *J* = 7.6, 7.5 Hz), 6.80 (t, 1H, *J* = 7.5 Hz), 6.65 (d, 2H, *J* = 7.6 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 148.1, 141.0, 137.0, 129.0 (q, $J_{C\text{-}F}$ = 31.2 Hz), 128.5, 128.3, 125.2 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.0 (q, $J_{C\text{-}F}$ = 272.2 Hz), 120.9, 119.9 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 280.96 (100 %), t_R= 11.39 min, 93.6 % pure (UV).

3-cyano-N-phenylbenzamide (16a) white solid, m.p. 175 – 177 °C; 82 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.41 (br s, 1H), 8.40 (dd, 1H, *J* = 1.6, 1.3 Hz), 8.25 (m, 1H), 8.06 (ddd, 1H, *J* = 7.9, 1.6, 1.3 Hz), 7.76 (m, 3H), 7.38 (dd, 2H, *J* = 8.5, 7.6 Hz), 7.13 (t, 1H, *J* = 7.6 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 223.17 (100 %), t_R= 10.14 min, 98.5 % pure (UV).

3-cyano-N'-hydroxy-N-phenylbenzimidamide (16) white solid, m.p. 145 – 147 °C; 43 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.82 (br s, 1H), 8.47 (br s, 1H), 7.81 (ddd, 1H, *J* = 7.6, 1.6, 1.3 Hz), 7.76 (dd, 1H, *J* = 1.6, 1.6 Hz), 7.63 (dt, 1H, *J* = 8.2, 1.6, 1.3 Hz), 7.52 (dd, 1H, *J* = 8.2, 7.6 Hz), 7.09 (dd, 2H, *J* = 8.5, 7.2 Hz), 6.82 (t, 1H, *J* = 7.2 Hz), 6.65 (d, 2H, *J* = 8.5 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 147.6, 140.9, 134.2, 132.5, 132.3, 131.0, 129.5, 128.4, 121.1,

120.1, 118.4, 111.4 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 238.12(100 %), t_R= 9.27 min, 95.2 % pure (UV).

3- chloro-N-phenylbenzamide (17a) white solid, m.p. 142 – 144 °C; 89 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.34 (br s, 1H), 8.00 (dd, 1H, *J* = 1.9, 1.6 Hz), 7.91 (m, 1H), 7.76 (d, 2H, *J* = 8.0 Hz), 7.66 (m, 1H), 7.57 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.36 (dd, 2H, *J* = 8.0, 7.6 Hz), 7.12 (t, 1H, *J* = 7.6 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 232.06 (100 %), t_R= 11.61 min, 99.4 % pure (UV).

3-chloro-N'-hydroxy-N-phenylbenzimidamide (17) white solid, m.p. 102 – 104 °C; 55 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.72 (br s, 1H), 8.37 (br s, 1H), 7.41 (m, 1H), 7.39 (dd, 1H, *J* = 1.6, 1.6 Hz), 7.34 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.28 (ddd, 1H, *J* = 7.9, 1.6, 1.3 Hz), 7.08 (dd, 2H, *J* = 8.0, 7.6 Hz), 6.80 (t, 1H, *J* = 7.6 Hz), 6.66 (d, 2H, *J* = 8.0 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 148.0, 141.1, 135.0, 132.8, 130.1, 128.8, 128.4, 127.2, 126.3, 120.9, 119.8 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 246.95 (100 %), t_R= 10.73 min, 98.7 % pure (UV).

4-nitro-N-phenyl-3-(trifluoromethyl)benzamide (18a) white solid, m.p. 185 – 187 °C; 51 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.68 (br s, 1H), 8.50 (s, 1H), 8.46 (d, 1H, *J* = 8.3 Hz), 8.34 (d, 1H, *J* = 8.3 Hz), 7.76 (d, 2H, *J* = 8.0 Hz), 7.40 (dd, 2H, *J* = 8.5, 7.6 Hz), 7.17 (t, 1H, *J* = 7.3 Hz) ppm; LC/MS: *m/z* (%): $[M+ MeCN]^+$ 351.41(100 %), t_R= 11.73 min, 100 % pure (UV).

N'-hydroxy-4-nitro-N-phenyl-3-(trifluoromethyl)benzimidamide (18) white solid, m.p. 167 – 169 °C; 47 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 11.19 (br s, 1H), 8.66 (br s, 1H), 8.10 (d, 1H, *J* = 8.5 Hz), 7.91 (d, 1H, *J* = 1.9 Hz), 7.81 (dd, 1H, *J* = 8.5, 1.9 Hz), 7.13 (dd, 2H, *J* = 8.0, 7.6 Hz), 6.86 (t, 1H, *J* = 7.6 Hz), 6.70 (d, 2H, *J* = 8.0 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 146.7, 140.6, 137.8, 132.8, 128.6, 126.5 (q, $J_{C\text{-}F}$ = 5.5 Hz), 125.8, 124.0 (q, $J_{C\text{-}F}$ = 273.1 Hz), 121.5, 121.4 (q, $J_{C\text{-}F}$ = 33.0 Hz), 120.3 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 325.76 (100 %), t_R= 11.09 min, 98.5 % pure (UV).

4- fluoro -N-phenyl-3-(trifluoromethyl)benzamide (19a) white solid, m.p. 167 – 169 °C; 58 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.46 (br s, 1H), 8.35 (m, 2H), 7.75 (d, 2H, *J* = 8.0 Hz), 7.71 (dd, 1H, *J* = 10.4, 8.8 Hz), 7.38 (dd, 2H, *J* = 8.0, 7.6 Hz), 7.14 (t, 1H, *J* = 7.6 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 283.78 (100 %), t_R= 11.84 min, 100 % pure (UV).

4-fluoro-N'-hydroxy-N-phenyl-3-(trifluoromethyl)benzimidamide (19) white solid, m.p. 136 – 138 °C; 49 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.81 (br s, 1H), 8.52 (br s, 1H), 7.69

(dd, 1H, J = 6.9, 1.9 Hz), 7.65 (m, 1H), 7.47 (dd, 1H, J = 10.4, 9.1 Hz), 7.10 (dd, 2H, J = 8.0, 7.6 Hz), 6.83 (t, 1H, J = 7.6 Hz), 6.67 (d, 2H, J = 8.0 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 158.8 (dq, $J_{C\text{-}F}$ = 255.7, 1.8 Hz), 147.2, 140.8, 134.3 (d, $J_{C\text{-}F}$ = 9.2 Hz), 129.8 (d, $J_{C\text{-}F}$ = 3.7 Hz), 128.5, 126.1 (q, $J_{C\text{-}F}$ = 4.6 Hz), 122.3 (q, $J_{C\text{-}F}$ = 272.2 Hz), 121.2, 120.2, 117.2 (dq, $J_{C\text{-}F}$ = 20.6, 12.8 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 298.83 (100 %), t_R= 11.13 min, 98.5 % pure (UV).

3-chloro-4-fluoro-N-phenylbenzamide (20a) white solid, m.p. 157 – 159 °C; 71 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.34 (br s, 1H), 8.20 (dd, 1H, J = 8.0, 2.2 Hz), 8.00 (m, 1H), 7.75 (d, 2H, J = 8.2 Hz), 7.59 (dd, 1H, J = 8.8, 8.0 Hz), 7.36 (dd, 2H, J = 8.2, 7.6 Hz), 7.12 (t, 1H, J = 7.6 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 249.86 (100 %), t_R= 11.33 min, 99.2 % pure (UV).

3-chloro-4-fluoro-N'-hydroxy-N-phenylbenzimidamide (20) white solid, m.p. 138 – 140 °C; 47 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.74 (br s, 1H), 8.43 (br s, 1H), 7.69 (dd, 1H, J = 7.1, 2.0 Hz), 7.65 (m, 1H), 7.47 (dd, 1H, J = 9.1, 8.8 Hz), 7.10 (dd, 2H, J = 8.0, 7.6 Hz), 6.83 (t, 1H, J = 7.6 Hz), 6.67 (d, 2H, J = 8.0 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 157.3 (d, $J_{C\text{-}F}$ = 248.4 Hz), 147.3, 141.0, 130.7 (d, $J_{C\text{-}F}$ = 3.7 Hz), 129.5, 128.5, 128.4, 121.0, 120.0, 119.4 (d, $J_{C\text{-}F}$ = 18.3 Hz), 116.8 (d, $J_{C\text{-}F}$ = 22.0 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 264.80 (100 %), t_R= 10.70 min, 97.2 % pure (UV).

4-(trifluoromethyl)-N-(3-(trifluoromethyl)phenyl)benzamide (21a) white solid, m.p. 117 – 119 °C; 77 % yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.99 (d, 2H, J = 8.0 Hz), 7.94 (s , 1H), 7.86 (d, 1H, J = 8.0 Hz), 7.77 (d, 2H, J = 8.0 Hz), 7.51 (dd, 1H, J = 8.2, 8.0 Hz), 7.44 (d, 1H, J = 8.2 Hz) ppm; LC/MS: *m/z* (%): $[M+ MeCN]^+$ 374.65 (100 %), t_R= 13.04 min, 99.4 % pure (UV).

N'-hydroxy-4-(trifluoromethyl)-N-(3-(trifluoromethyl)phenyl)benzimidamide (21) white solid, m.p. 147 –149 °C; 53 % yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 8.82 (br s, 1H), 7.60 (d, 2H, J = 8.2 Hz), 7.55 (d, 1H, J = 8.2 Hz), 7.37 (br s, 1H), 7.22 (m, 2H), 6.94 (s, 1H), 6.74 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ= 150.2, 139.8, 134.1, 132.0 (q, $J_{C\text{-}F}$ = 33.0 Hz), 131.6 (q, $J_{C\text{-}F}$ = 32.5 Hz), 129.5, 128.6, 125.6 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.0, 123.7 (q, $J_{C\text{-}F}$ = 272.2 Hz), 123.5 (q, $J_{C\text{-}F}$ = 272.2 Hz), 119.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 117.6 (q, $J_{C\text{-}F}$ = 3.7 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 348.70 (100 %), t_R= 12.11 min, 96.8 % pure (UV).

3-chloro-N-(3-methoxyphenyl)benzamide (22a) white solid, m.p. 104 – 106 °C; 74 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.31 (br s, 1H), 8.00 (dd, 1H, J = 1.9, 1.6 Hz), 7.90 (m, 1H), 7.66 (m, 1H), 7.57 (dd, 1H, J = 7.9, 7.9 Hz), 7.45 (dd, 1H, J = 2.5, 2.2 Hz), 7.36 (m, 1H), 7.26

(dd, 1H, *J* = 8.2, 7.9 Hz), 6.70 (m, 1H), 3.76 (s, 3H) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 262.80 (100 %), t_R= 11.29 min, 98.3 % pure (UV).

3-chloro-N'-hydroxy-N-(3-methoxyphenyl)benzimidamide (22) white solid, m.p. 135 – 137 °C; 55 % yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 8.11 (br s, 1H), 7.50 (dd, 1H, *J* = 2.2, 1.6 Hz), 7.34 (m, 1H), 7.29 (ddd, 1H, *J* = 7.9, 1.6, 1.3 Hz), 7.23 (dd, 1H, *J* = 7.9, 7.9 Hz), 7.21 (br s, 1H), 7.03 (dd, 1H, *J* = 8.2, 7.9 Hz), 6.50 (m, 1H), 6.26 (m, 1H), 6.23 (dd, 1H, *J* = 2.2, 2.2 Hz), 3.63 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ= 154.8, 145.6, 135.3, 129.2, 127.9, 124.6, 124.40, 124.39, 123.0, 121.3, 108.5, 103.5, 101.9, 49.9 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 277.80 (100 %), t_R= 10.39 min, 98.3 % pure (UV).

3-chloro-N-(3- chlorophenyl)benzamide (23a) white solid, m.p. 118 – 120 °C; 83 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.49 (br s, 1H), 8.00 (dd, 1H, *J* = 1.9, 1.6 Hz), 7.95 (dd, 1H, *J* = 1.9, 1.9 Hz), 7.91 (m, 1H), 7.69 (m, 1H), 7.58 (dd, 1H, *J* = 8.2, 7.6 Hz), 7.39 (dd, 1H, *J* = 8.2, 8.2 Hz), 7.18 (m, 1H), 6.70 (m, 1H) ppm; LC/MS: *m/z* (%): $[M+ MeCN]^+$ 306.57 (100 %), t_R= 13.49 min, 99.2 % pure (UV).

3-chloro-N-(3-chlorophenyl)-N'-hydroxybenzimidamide (23) white solid, m.p. 127 – 129 °C; 56 % yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 8.62 (br s, 1H), 7.49 (m, 1H), 7.37 (m, 1H), 7.27 (m, 3H), 7.03 (dd, 1H, *J* = 8.2, 8.2 Hz), 6.93 (m, 1H), 6.73 (dd, 1H, *J* = 2.2, 1.9 Hz), 6.48 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ= 150.3, 140.6, 134.6, 132.5, 130.1, 129.8, 128.2, 126.5, 123.1, 121.0, 119.2 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 281.80 (100 %), t_R= 12.38 min, 98.9 % pure (UV).

N-(4-chlorophenyl)-3-cyanobenzamide (24a) white solid, m.p. 206 – 208 °C; 68 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.53 (br s, 1H), 8.39 (dd, 1H, *J* = 1.9, 3 Hz), 8.24 (m, 1H), 8.07 (m, 1H), 7.80 (d, 2H, *J* = 9.1 Hz), 7.76 (dd, 1H, *J* = 8.5, 7.9 Hz), 7.43 (d, 2H, *J* = 9.1 Hz) ppm; LC/MS: *m/z* (%): $[M+ MeCN]^+$ 297.85 (100 %), t_R= 10.86 min, 100 % pure (UV).

N-(4-chlorophenyl)-3-cyano-N'-hydroxybenzimidamide (24) white solid, m.p. 164 – 166 °C; 39 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.92 (br s, 1H), 8.65 (br s, 1H), 7.84 (ddd, 1H, *J* = 7.9, 1.6, 1.3 Hz), 7.80 (dd, 1H, *J* = 1.6, 1.3 Hz), 7.62 (ddd, 1H, *J* = 8.3, 1.6, 1.6 Hz), 7.54 (dd, 1H, *J* =8.3, 7.9 Hz), 7.13 (d, 2H, *J* = 8.8 Hz), 6.65 (d, 2H, *J* = 8.8 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 147.1, 140.0, 133.9, 132.6, 132.3, 131.0, 129.6, 128.2, 124.7, 121.3, 118.4, 111.5 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 272.82 (100 %), t_R= 10.18 min, 97.5 % pure (UV).

4-methoxy-N-(4-(trifluoromethyl)phenyl)benzamide (25a) white solid, m.p. 226 – 228 °C; 71 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.41 (br s, 1H), 7.99 (m, 4H), 7.70 (d, 2H, *J* = 8.7 Hz), 7.08 (d, 2H, *J* = 8.7 Hz), 3.85 (s, 3H) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 295.83 (100 %), t_R= 11.89 min, 100 % pure (UV).

N'-hydroxy-4-methoxy-N-(4-(trifluoromethyl)phenyl)benzimidamide (25) white solid, m.p. 139 – 141 °C; 41 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.70 (br s, 1H), 8.74 (br s, 1H), 7.40 (d, 2H, *J* = 8.6 Hz), 7.35 (d, 2H, *J* = 9.1 Hz), 6.93 (d, 2H, *J* = 9.1 Hz), 6.76 (d, 2H, *J* = 8.6 Hz), 3.76 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 165.2, 162.1, 142.9, 129.7, 126.7, 125.7 (q, J_{C-F} = 3.6 Hz), 125.2, 124.3 (q, J_{C-F} =271.3 Hz), 123.2 (q, J_{C-F} =32.1 Hz), 119.9, 55.4 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 311.04 (100 %), t_R= 10.33 min, 99.0 % pure (UV).

N-phenyl-3-(trifluoromethyl)benzamide (26a) white solid, m.p. 145 – 147 °C; 87 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.46 (br s, 1H), 8.30 (s, 1H), 8.26 (d, 1H, *J* = 8.2 Hz), 7.97 (d, 1H, *J* = 7.6 Hz), 7.78 (m, 3H), 7.38 (dd, 2H, *J* = 8.5, 7.6 Hz), 6.75 (t, 1H, *J* = 7.6 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 164.0, 138.8, 135.8, 131.8, 129.7, 129.1 (q, J_{C-F} = 32.1 Hz), 128.6, 128.1 (q, J_{C-F} = 3.7 Hz), 124.2 (q, J_{C-F} = 3.7 Hz), 124.0, 123.9 (q, J_{C-F} = 273.1 Hz), 120.5 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 265.91 (100 %), t_R= 11.65 min, 100 % pure (UV).

N'-methoxy-N-phenyl-3-(trifluoromethyl)benzimidamide (26) colorless oil; 62 % yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.76 (s, 1H), 7.59 (d, 1H, *J* = 7.6 Hz), 7.56 (d, 1H, *J* = 7.9 Hz), 7.39 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.17 (br s, 1H), 7.12 (t, 2H, *J* = 7.9, 7.6 Hz), 6.95 (t, 1H, *J* = 7.6 Hz), 6.65 (d, 2H, *J* = 7.9 Hz), 4.00 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ= 149.8, 139.3, 132.1, 131.7, 131.0 (q, J_{C-F} = 32.1 Hz), 128.9, 128.8, 126.2 (q, J_{C-F} = 3.7 Hz), 125.2 (q, J_{C-F} = 3.7 Hz), 123.7 (q, J_{C-F} = 272.2 Hz), 123.2, 121.5, 61.9 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 294.86 (100 %), t_R= 10.39 min, 96.9 % pure (UV).

N-phenyl-3-(trifluoromethyl)benzohydrazonamide (27) white solid, m.p. 143 – 145 °C; 23 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 7.72 (m, 2H), 7.40 (m, 5H), 7.26 (dd, 2H, *J* = 7.6, 7.6 Hz), 7.14(t, 1H, *J* = 7.6 Hz), 6.98(d, 2H, *J* = 7.6 Hz) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 153.8, 147.6, 134.7, 132.8, 130.8, 130.6, 130.4, 129.7 (q, J_{C-F} = 31.2 H 6z), 128.8, 128.2, 126.9 (q, J_{C-F} = 3.2 Hz), 125.2 (q, J_{C-F} = 4.3 Hz), 124.1 (q, J_{C-F} = 272.4 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 279.93 (100 %), t_R= 6.74 min, 94.0 % pure (UV). This unsealed compound turns red and forms dimer (the mixture analyzed by LC/MS) after days under room temperature.

Synthesis of 2-amino-1-(3-(trifluoromethyl)phenyl)ethanone hydrochloride (28a) (4). To a stirred solution of 3-(trifluoromethy1) acetophenone (5.20 g, 27.6 mmol) in CH_2C1_2 (80 mL) at 0 °C was carefully added a solution of bromine (4.40 g, 27.6 mmol) in CH_2C1_2 (75 mL). The reaction was warmed to room temperature and stirred for 1.5 h. The solvent was reduced under reduced pressure and the after the addition was completed and then crude α-bromoketone was used without further purification. The α-bromoketone was dissolved in CCl_4 (100 mL), hexamethylenetetramine (4.20 g, 30.7 mmol) was added. The mixture was stirred overnight, the precipitate was filtered and washed with CCl_4 (2 x 40 mL). The white solid (ca. 9.2 g) was treated with EtOH (150 mL) and concentrated HCl (21 mL) and stirred for 16 h. The mixture was filtered and the precipitate was washed with EtOH (2 x 50 mL). The filtrate was concentrated and the residue was crystallized from 4M HCl. The amino hydrochloride **28a** was obtained as colorless needles. Yield: 57 %. ^{1}H NMR (500 MHz, DMSO-d_6): δ= 8.65 (br s, 3H, NH_3), 8.32 (m, 1H), 8.29 (dd, 1H, J = 2.0, 2.0 Hz), 8.09 (m, 1H), 7.84 (dd, 1H, J = 7.9, 7.9 Hz), 4.69 (s, 2 H, CH_2) ppm. ^{13}C NMR (500 MHz, d_6-DMSO): δ= 192.3 (C=O), 134.5, 132.2, 130.7 (q, J_{C-F} = 3.7 Hz), 130.4, 129.7 (q, J_{C-F} = 32.1 Hz), 124.7 (q, J_{C-F} = 3.7 Hz), 123.7 (q, J_{C-F} = 272.2 Hz), 45.0 ppm.

Synthesis of 1-phenyl-5-(3-(trifluoromethyl)phenyl)-1H-imidazole-2(3H)-thione (28) (5). A mixture of the amino hydrochloridebromide **28a** (1.00 g, 3.38 mmol), phenylisothiocyanate (440 mg, 3.38 mmol) and triethylamine (342 mg, 3.38 mmol) in EtOH (10 mL) was refluxed in a sealed tube for 2 h. The clear solution was cooled to room temperature and the precipitate was filtered and washed with EtOH (2 x 5 mL). The 4-imidazoline-2-thione **28** was obtained as colorless crystals. Yield: 72%; m.p. 125.3 – 128.4 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 12.70 (br s, 1H), 7.56 (d, 1H, J = 7.3 Hz), 7.55 (s, 1H), 7.44 (m, 4H), 7.38 (d, 1H, J = 7.9 Hz), 7.26 (m, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 164.4, 136.4, 131.1, 129.5, 129.4, 129.3, 129.1 (q, J_{C-F} = 31.6 Hz), 129.0, 128.9, 128.6, 124.1 (q, J_{C-F} = 3.7 Hz), 123.7 (q, J_{C-F} = 272.2 Hz), 123.5 (q, J_{C-F} = 4.6 Hz), 115.0 ppm; LC/MS: *m/z* (%): $[M+H]^+$ 321.05 (100 %), t_R = 10.94 min, 98.4 % pure (UV).

Synthesis of 3-(trifluoromethyl)benzohydrazide (29a). A mixture of 3-(trifluoromethyl)benzoyl chloride (4.75 g, 22.8 mmol) and hydrazine hydrat (4.56 g, 91.2 mmol) in EtOH (15 mL) was refluxed overnight and cooled to room temperature. The clear solution was decanted from the oily residue and poured into ice water. The precipitate was filtered and washed with water (2 x 20 mL). The solid was dissolved in EtOAc (40 mL) washed with saturated NaCl

(2 x 30 mL), dried over MgSO4 and concentrated. The crude material (3.30 g) was crystallized from benzene/*n*-hexane (2:1, 120 mL) and washed with *n*-hexane (2 x 20 mL). The hydrazide **29a** was obtained as a colorless solid. Yield: 3.05 g, 66 %; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.04 (br s, 1H, CONH), 8.15 (dd, 1H, *J* = 2.0, 2.0 Hz), 8.11 (m, 1H), 7.88 (m, 1H), 7.71 (dd, 1H, *J* = 7.9, 7.9 Hz), 4.58 (br s, 2H, NH_2) ppm. ^{13}C NMR: δ= 164.2 (CONH), 134.2, 131.0, 129.6, 129.2 (q, J_{C-F} = 32.1 Hz), 127.6 (q, J_{C-F} = 3.7 Hz), 123.9 (q, J_{C-F} = 272.2 Hz), 123.6 (q, J_{C-F} = 3.7 Hz) ppm.

Synthesis of N-phenyl-2-(3-(trifluoromethyl)benzoyl)hydrazinecarbothioamide (29b). A mixture of 3-trifluoromethyl benzoic acid hydrazide (714 mg, 3.50 mmol) and phenylisothiocyanate (473 mg, 3.50 mmol) in EtOH (5 mL) was refluxed for 2 h. The solution was cooled to room temperature, the precipitate was filtered and washed with Et_2O (2 x 10 mL). The thiosemicarbazide **29b** was obtained as a white solid. Yield: 550 mg, 46 %; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 10.82 (br s, 1H, NH), 9.86 (br s, 1H, NH), 9.78 (br s, 1H, NH), 8.30 (dd, 1H, *J* = 2.0, 2.0 Hz), 8.24 (m, 1H), 7.97 (m, 1H), 7.77 (dd, 1H, *J* = 7.8, 7.8 Hz), 7.43 (m, 2H), 7.34 (m, 2H), 7.17 (m, 1 H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 181.1 (C=S), 164.7 (C=O), 139.1, 133.5, 131.9, 129.6, 129.0 (q, J_{C-F} = 32.1 Hz), 128.3 (q, J_{C-F} = 2.8 Hz), 128.0 (q, J_{C-F} = 2.8 Hz), 126.2, 125.2, 124.5, 123.9 (q, J_{C-F} = 272.2 Hz) ppm.

Synthesis of 4-phenyl-3-(3-(trifluoromethyl)phenyl)-1H-1,2,4-triazole-5(4H)-thione (29) (6). The semicarbazid **29b** (300 mg, 0.88 mmol) was suspended in an aqueous solution of NaOH (5 wt%, 15 mL) and heated under reflux. After the solid was completely dissolved the pale yellow solution was stirred for 2 h. The solution was cooled to 0 °C and acidified with 2M HCl. The precipitate was filtered, washed with water (3 x 30 mL) and air-dried. The crude material was crystallized from *n*-hexane/EtOH (2:1). **29** was obtained as colorless needles, m.p. 155.3 – 156.7 °C; 65 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 14.25 (br s, 1H), 7.78 (d, 1H, *J* = 7.6 Hz), 7.65 (d, 1H, *J* = 7.9 Hz), 7.60 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.51 (m, 4H), 7.40 (m, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 168.8, 149.2, 134.2, 132.2, 129.8, 129.6, 129.4, 129.1 (q, J_{C-F} = 32.1 Hz), 128.7, 126.9 (q, J_{C-F} = 3.7 Hz), 126.8, 124.7 (q, J_{C-F} = 3.7 Hz), 123.5 (q, J_{C-F} = 272.2 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 322.05 (100 %), t_R = 11.11 min, 98.3 % pure (UV).

Synthesis of N-(3-(trifluoromethyl)benzylidene)aniline (30a). A solution of 3-(trifluoromethyl)benzaldehyde (4.85 g, 27.9 mmol) and aniline (2.76 g, 27.9 mmol) in EtOH (30 mL) was refluxed for 2 h. The solution was cooled to room temperature and the solvent was

removed under reduced pressure. The imine **30a** was obtained as yellow oil and used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ= 8.42 (s, 1H, CHN), 8.12 (dd, *J* = 2.0, 2.0 Hz, 1H), 8.01 (m, 1H), 7.66 (m, 1H), 7.52 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.34 (m, 2H), 7.21−7.14 (m, 3 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ= 158.4 (CHN), 151.4, 136.9, 131.9, 131.4 (q, $J_{C\text{-}F}$ = 32.8 Hz), 129.3, 129.2, 127.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 126.5, 125.4 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.9 (q, $J_{C\text{-}F}$ = 272.0 Hz), 120.8 ppm.

Synthesis of 1-phenyl-5-(3-(trifluoromethyl)phenyl)-1H-imidazole (30) (7). To a solution of the imine **30a** (1.54 g, 6.18 mmol) in MeOH (30 mL) and DME (15 mL) was added K_2CO_3 (4.15 g, 13.0 mmol) and *p*-toluenesulfonylmethylisocyanide (1.45 g, 7.42 mmol).The reaction mixture was refluxed for 6 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was partionated beetween EtOAc (50 mL) and saturated NaCl (50 mL). The organic layer was washed with saturated NaCl (2 x 30 mL), dried over $MgSO_4$ and concentrated. The crude material was purified by flash chromatography (SiO_2, *n*-hexane / EtOAc 2:1→1:1). The imidazole **30** was obtained as a pale yellow solid, m.p. 110.8 – 111.7 °C; 65 % yield; ^{1}H NMR (500 MHz, DMSO-d_6): δ= 8.07 (d, 1H, *J* = 1.0 Hz), 7.60 (d, 1H, *J* = 7.6 Hz), 7.53 (dd, 1H, *J* = 7.9, 7.6 Hz), 7.48 (m, 5H), 7.39 (s, 1H), 7.30 (m, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ= 140.2, 135.9, 131.3, 130.6, 130.2, 129.6, 129.5, 129.1(q, $J_{C\text{-}F}$ = 32.1 Hz), 128.4, 125.8, 123.8 (q, $J_{C\text{-}F}$ = 273.1 Hz), 123.7 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.6 (q, $J_{C\text{-}F}$ = 3.7 Hz) ppm; LC/MS: *m/z* (%): $[M+H]^+$ 288.90 (100 %), t_R = 12.59 min, 98.2 % pure (UV).

Validation of iron chelating property. **1) Color test with iron (III) chloride:** All compounds were dissolved as 0.01 M solution in ethanol and $FeCl_3$ was prepared as 0.01 M solution in water. The same volume of ethanolic solutions were mixed up with ferric chloride solution and taken same amount of ethanol as a blank control (8).

2) Determine the complex stability constants: The experiment was performed by potentiometric titration. Thereby, it was uncovered that already under acidic conditions (pH = 4) the formation of $Fe(OH)_3$ was observed indicating that the CBR compounds cannot form stable Fe(III) complexes under biological conditions (Data supplied by Professor Hegetschweiler's group).

Biology.

Transcription Inhibition Assay. The transcription inhibition experiments were performed as described earlier (9, 10). Purification and quantification of transcripts as well as the determination of IC_{50} values was performed as described by Haupenthal and colleagues (11).

Minimal inhibitory concentration (MIC) determinations. MIC values for *E. coli TolC* were determined for all compounds. Selected compounds were tested in *E.coli K12, Bacillus subtilis subsp. subtilis, Pseudomonas aeruginosa PAO1* and *Staphylococcus aureus subsp. aureus (Newman strain).* As a bacteria start OD_{600} we used 0.03 in a total volume of 200 µL in lysogeny broth (LB) containing the compounds predissolved in DMSO (maximal DMSO concentration in the experiment: 1 %). Final compound concentrations prepared from serial dilutions ranged from 0.02 to 100 µg/mL (double values for each concentration) and were adapted for each compound depending on their antibacterial activity and the observation of compound precipitation in the growth medium. The ODs were determined after addition of the compounds and again after incubation for 16 h at 37 °C and 50 rpm (200 rpm for *PAO1*) in 96 well plates (Sarstedt, Nümbrecht, Germany) using a PolarStar Omega (BMG labtech, Ortenberg, Germany). Given MIC values are means of two independent determinations (three if MIC < 10 µg/mL). They are defined as the lowest concentration of compounds that reduced OD_{600} by ≥ 95 % and were read off the inhibition curves. Standard deviation was less than 25 % (most cases: < 15 %).

Influence of iron (III) on the antibacterial activity of CBR703. The effect of DMSO, deferoxamine mesylate (DFO) (25 µg/mL) and CBR703 (3 µg/mL) on the growth of *E.coli TolC* was determined after 16 h (growth conditions as described in the MIC determinations section) by OD_{600} measurement in a PolarStar Omega. The experiment was performed in parallel either in presence or absence of 250 µM Fe (III) citrate. The DMSO concentration was kept at 1 % for all samples.

Cytotoxicity assay. HEK 293 cells ($2x10^5$ cells per well) were seeded in 24-well, flat-bottomed plates. Culturing of cells, incubations and OD measurements were performed as described previously (12) with small modifications. 24 h after seeding the cells the incubation was started by the addition of compounds in a final DMSO concentration of 1 %. The living cell mass was determined after 24 and 72 h followed by the calculation of LD_{50} values.

Precipitation experiment. CBR703 was diluted to different concentrations (0 – 400 µg/mL) in MHB in a total volume of 200 µL in a 96 well plate and a maximal DMSO concentration of 2 %. After 25 minutes the precipitation-derived turbidity was measured at 600 nm in a PolarStar Omega. The experiment was performed twice in quadruplicates.

Microtiter plate biofilm tests. 96-well biofilm assays were carried out in sterile clear flat bottom untreated microtiter plates (Nunc, Wiesbaden, Germany) in a volume of 100 µL. Aerobic overnight cultures were generated from a glycerol stock at 37 °C in 10 ml Medium T. Serial dilutions of the compounds with final concentrations from 7.3 to 400 µg/mL were added to a homogenized suspension of the clinical *S. aureus* isolate 11-02670 (MSSA ST30 strain) with an OD_{600} of 0.2 (final OD_{600} of 0.1). The plates were incubated for 17 h at 37 °C in a moist atmosphere. The optical density was determined at 600 nm. 20 µL of supernatant was removed with the pipetting robot Evolution P3 (PerkinElmer, Waltham, MA), transferred to a 396-well microtiter plate (Corning, Tewksbury, MA) and the optical density of planctonic bacteria was determined at 600 nm. Biofilm was quantified in the original 96-well plate by adding 10 µL of a solution of FITC in DMSO (1 mg/mL) to the wells followed by an incubation for 1 h. Planctonic bacteria were removed by three washes of 45, 30 and 15 min with 0.9 % NaCl. The washing was carried out by carefully submerging the plates in an upright orientation into the washing solution and slowly swirling the container at room temperature. The final wash contained 0.5 % peroxy acetic acid to decontaminate the plates before they were placed in the reader for fluorescence determination (excitation 485 nm, emission 535 nm).

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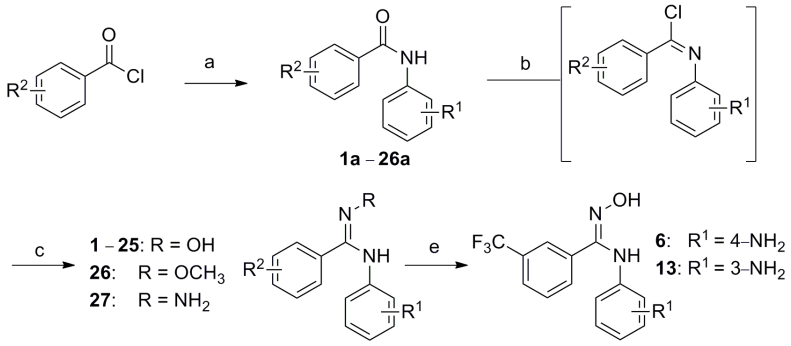
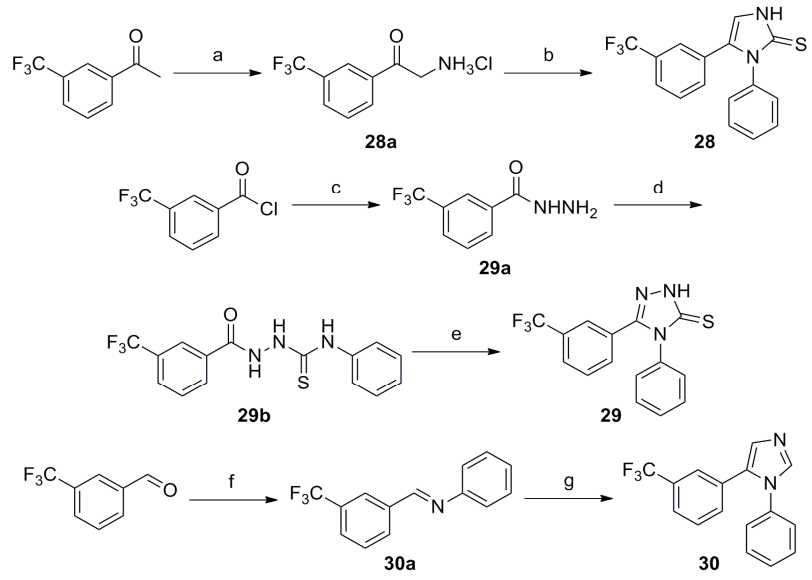
Supplementary Tables and Figures

SCHEME S1 Synthesis of compounds **1** – **27**.



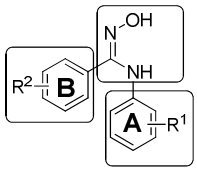
Reagents and conditions: (a) appropriate aniline, Et_3N, CH_2Cl_2, 0 °C to r. t. for 2 h; (b) PCl_5, 1,2-dichloroethane, 70 °C for 5 h; (c) $RNH_2 \cdot HCl$, Et_3N, acetonitrile, 0 °C to r. t., overnight; (d) $SnCl_2 \cdot 2H_2O$, EtOH, N_2, 70 °C for 30 min.

SCHEME S2 Synthesis of compound **28** – **30**.



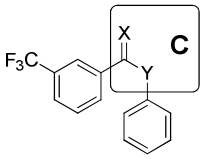
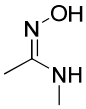
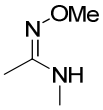
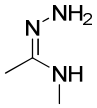
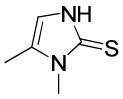
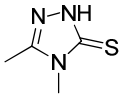
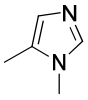
Reagents and conditions: (a) 1) Br_2, CH_2Cl_2, 0 °C to r. t. 2) Hexamethylenetetramine, CCl_4. 3) HCl, EtOH, r. t. (b) PhNCS, NEt_3, EtOH, reflux. (c) Hydrazine hydrate, EtOH, reflux. (d) PhNCS, EtOH, reflux. (e) NaOH, H_2O, reflux. (f) Aniline, EtOH, reflux. (g) TOSMIC, K_2CO_3, MeOH, DME.

TABLE S1 RNAP inhibition and antibacterial activities of derivatives of **CBR703**.

Compound			% Inhibition of *E. coli* RNAP (at 50 μM)	MIC *E. coli TolC* (μg/mL)[c]
	R^1	R^2		
CBR703	H	3-CF_3	18 μM[a]	14
1	4-NO_2	3-CF_3	16	>50
2	4-CH_3	3-CF_3	26	14
3	4-CF_3	3-CF_3	18[b]	8
4	4-CN	3-CF_3	n. i.	>25
5	4-OCH_3	3-CF_3	n. i.	>25
6	4-NH_2	3-CF_3	10	>100
7	4-Cl	3-CF_3	35	9
8	3-NO_2	3-CF_3	12	>50
9	3-CH_3	3-CF_3	24	12
10	3-CF_3	3-CF_3	15[b]	22
11	3-CN	3-CF_3	n. i.	42
12	3-OCH_3	3-CF_3	12	24
13	3-NH_2	3-CF_3	10	>100
14	H	2-CF_3	n. i.	>100
15	H	4-CF_3	n. i.	23
16	H	3-CN	n. i.	>100
17	H	3-Cl	32	41
18	H	3-CF_3-, 4-NO_2	23 μM[a]	20
19	H	3-CF_3-, 4-F	19 μM[a]	21
20	H	3-Cl-, 4-F	34	39
21	3-CF_3	4-CF_3	n. i.	8
22	3-OCH_3	3-Cl	20	45
23	3-Cl	3-Cl	25	9
24	4-Cl	3-CN	n. i.	68
25	4-CF_3	4-OCH_3	n. i.	15

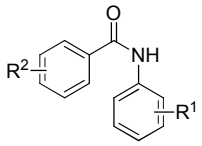
[a]: IC_{50} value; [b]: Compound was tested at 20 μM limited due to insufficient solubility of the compounds; [c] >: MIC-determination was limited due to insufficient solubility of the compound; n.i. = no inhibition (<10 % inhibition). The SD in these experiments was < 25 % (most cases: < 15 %).

TABLE S2 RNAP inhibition and antibacterial activities of derivatives of CBR703.

Compound		% Inhibition of *E. coli* RNAP (at 50 μM)	MIC *E. coli TolC* (μg/mL)[b]
CBR703		18 μM[a]	14
26		29	24
27		n.i.	23
28		n.i.	>50
29		n.i.	>50
30		n.i.	>25

[a]: IC_{50} value; [b] >: MIC-determination was limited due to insufficient solubility of the compound; n.i. = no inhibition (<10 % inhibition). The SD in these experiments was < 25 % (most cases: < 15 %).

TABLE S3 Biological activities of synthetic intermediates.

Compound			% Inhibition of *E. coli* RNAP (at 50 μM)	MIC *E. coli TolC* (μg/mL)[a]
	R^1	R^2		
1a	4-NO_2	3-CF_3	n. i.	>100
2a	4-CH_3	3-CF_3	n. i.	>25
3a	4-CF_3	3-CF_3	n. i.	2
4a	4-CN	3-CF_3	n. i.	>25
5a	4-OCH_3	3-CF_3	n. i.	>25
7a	4-Cl	3-CF_3	n. i.	7
8a	3-NO_2	3-CF_3	n. i.	>25
9a	3-CH_3	3-CF_3	n. i.	>25
10a	3-CF_3	3-CF_3	n. i.	4
11a	3-CN	3-CF_3	n. i.	24
12a	3-OCH_3	3-CF_3	n. i.	28
14a	H	2-CF_3	n. i.	>25
15a	H	4-CF_3	n. i.	23
16a	H	3-CN	n. i.	>25
17a	H	3-Cl	n. i.	>25
18a	H	3-CF_3-, 4-NO_2	n. i.	>25
19a	H	3-CF_3-, 4-F	n. i.	>50
20a	H	3-Cl-, 4-F	n. i.	>25
21a	3-CF_3	4-CF_3	n. i.	3
22a	3-OCH_3	3-Cl	n. i.	>25
23a	3-Cl	3-Cl	n. i.	7
24a	4-Cl	3-CN	n. i.	>25
25a	4-CF_3	4-OCH_3	n. i.	>25
26a	H	3-CF_3	n. i.	>25

[a] >: MIC-determination was limited due to insufficient solubility of the compound; n.i. = no inhibition (<10 % inhibition). The SD in these experiments was < 25 % (most cases: < 15 %).

TABLE S4 Inhibition of *E.coli TolC* growth in absence or presence of FCS.

Compound	*E. coli TolC* MIC (µg/mL)[a]	
	LB	LB + 10 % FCS
CBR703	14	>25
7	9	>25
19	21	50
26	24	>25
3a	2	14

The antibacterial activity of the tested compounds was abolished or drastically reduced by addition of FCS, which suggested the cytotoxicities of our compounds are even more pronounced in the absence of serum. FCS: Fetal calf serum; [a] >: MIC-determination was limited due to insufficient solubility of the compound. The SD in these experiments was < 25 % (most cases: < 15 %).

TABLE S5 Color test with iron (III) chloride.

compound	Color change reaction with Fe (III)
CBR703	positive
26	negative

For **CBR703** bearing an amidoxime moiety we observed a color variation (positive effect). In contrast the esterified **26** lacking a color change indicated that the free hydroxyl group was necessary to form complexes.

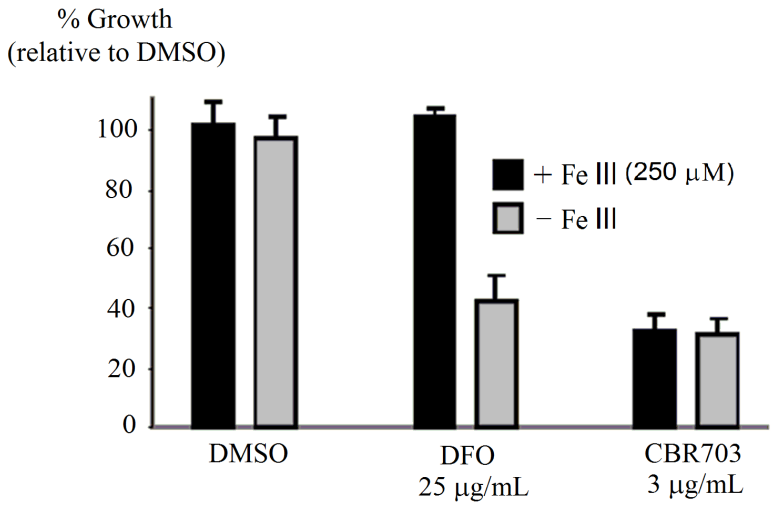


FIG. S1 Effect of **CBR703** and deferoxamine mesylate (DFO) on growth of *E. coli TolC* (OD_{600} determined after 16 h incubation) in presence or absence of Fe III. The antibacterial activity of DFO was eliminated by addition of Fe III, in contrast, no such effect was observed for **CBR703**.

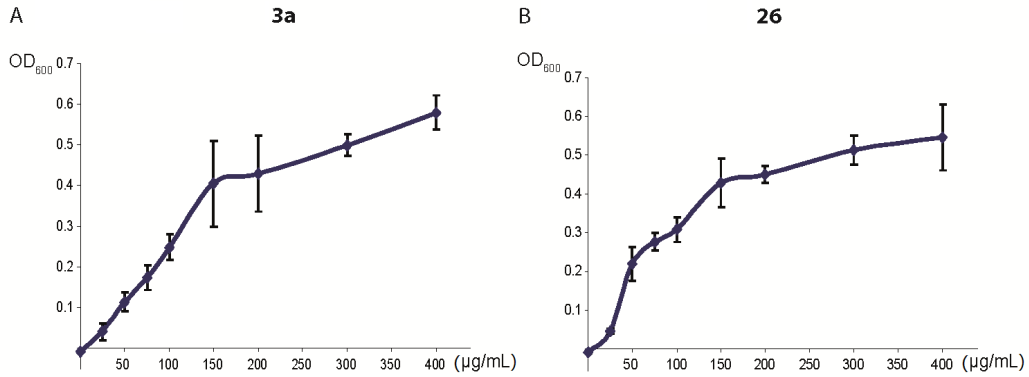


FIG. S2 Concentration dependent precipitation of **3a** and **26** in MHB.