Supporting Information

Discovery of novel bacterial RNA polymerase inhibitors: Pharmacophore based virtual screening and hit optimization

Stefan Hinsberger,[a] Kristina Hüsecken,[a] Matthias Groh,[a] Matthias Negri,[a] Jörg Haupenthal,[a] and Rolf W. Hartmann*[,a,b]

[a] *Helmholtz-Institute for Pharmaceutical Research Saarland, Campus C2.3, 66123 Saarbrücken, Germany*

[b] *Pharmaceutical and Medicinal Chemistry, Saarland University, Campus C2.3, 66123 Saarbrücken, Germany*

* Author to whom correspondence should be addressed.
Tel: +49 681 302 70300
Fax: +49 681 302 70308
e-mail: rwh@mx.uni-saarland.de or rolf.hartmann@helmholtz-hzi.de
http://www.pharmmedchem.de or www.helmholtz-hzi.de/hips

Contents:

a) General directions

Chemical names follow IUPAC nomenclature. Starting materials were purchased from Sigma-Aldrich, Acros, Maybridge, Combi Blocks, Fluka, ABCR, Alfa Aesar, Apollo and were used without purification.

Column chromatography (CC) was performed on silica gel (70–200 µm), preparative thin layer chromatography (TLC) on 1 mm SIL G-100 UV_{254} glass plates (Macherey-Nagel), and reaction progress was monitored by TLC on Alugram SIL G UV_{254} (Macherey-Nagel).

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM500 spectrometer (500 MHz and 125 MHz) at 300 K in $CDCl_3$ or CD_3SOCD_3. Chemicals shifts are reported in δ values (ppm), the hydrogenated residues of deuterated solvent were used as internal standard ($CDCl_3$: δ = 7.27 ppm in ^{1}H NMR and δ = 77.0 ppm in ^{13}C NMR, DMSO-d_6: δ = 2.50 ppm in ^{1}H NMR and δ = 39.5 ppm in ^{13}C NMR). Signals are described as s, d, t, dd, ddd, dt and m for singlet, doublet, triplet, doublet of doublet, doublet of doublet of doublet, doublet of triplet and multiplet, respectively. Coupling constants (*J*) are given in Hertz (Hz).

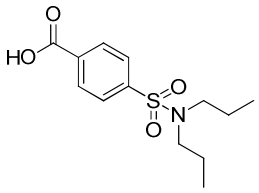
The reported yields are the isolated yields of purified material and are not optimized.

Purity of compounds **1** to **34** was determined using LC/MS as follows:
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. All solvents were HPLC grade.
Solvent system:
In a gradient run the percentage of acetonitrile (containing 0,1 % triflouro-acetic acid) in 0,1 % triflouro-acetic 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.

Melting points were determined on a Stuart Scientific melting point apparatus SMP3 and are uncorrected.

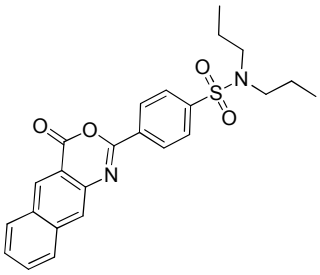
b) experimental and spectroscopic data of all compounds



4-(N,N-dipropylsulfamoyl)benzoic acid (Vb). To a solution of 4-(chlorosulfonyl)benzoic acid (1 equiv) in anhydrous CH_2Cl_2 at 0° C dipropylamine (3 equiv) was added slowly by means of a syringe. The reaction mixture was stirred at room temperature for 18 h followed by extraction with 1N HCl. The organic layer was washed with H_2O and dried over $MgSO_4$. Evaporation of the solvent provided the title compound; yield: 99 %. ^{1}H NMR (500 MHz, CD_3COCD_3) δ = 8.24–8.19 (m, 2 H), 7.99–7.94 (m, 2 H), 3.17–3.12 (m, 4 H), 1.61–1.51 (m, 4 H), 0.86 (t, *J* = 7.4 Hz, 6 H) ppm.

^{13}C NMR (125 MHz, CD_3COCD_3) δ = 166.6, 145.3, 134.9, 131.3, 128.1, 50.9, 22.8, 11.4 ppm.

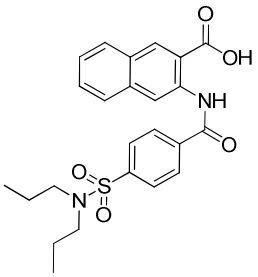
LC/MS: m/z = 286 [M + H^+]; t_R = 11.58 min; 94.8 % pure (UV).



4-(4-oxo-4H-naphtho[2,3-d][1,3]oxazin-2-yl)-N,N-dipropylbenzenesulfonamide (Va). 4-(N,N-dipropylsulfamoyl)benzoic acid (**Vb**, 1.5 equiv) was converted to the corresponding benzoyl chloride via reaction with thionyl chloride (3.75 equiv) in CH_2Cl_2 in the presence of catalytic amounts of dimethylformamide (4 h reflux). After evaporation of the solvent the resulting benzoyl chloride and 3-amino-2-naphthoic acid (1 equiv) were suspended in toluene and the mixture was refluxed for 18 h. The product was purified by CC (*n*-hexane/EtOAc 8:2); yield: 28 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.89 (s, 1 H), 8.49–8.44 (m, 2 H), 8.19 (s, 1 H), 8.09–8.00 (m, 2 H), 7.99–7.94 (m, 2 H), 7.74–7.69 (m, 1 H), 7.66–7.60 (m, 1 H), 3.19–3.12 (m, 4 H), 1.61–1.55 (m, 4 H), 0.90 (t, *J* = 7.4 Hz, 6 H, CH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 159.4, 153.8, 143.6, 140.8, 137.6, 133.9, 132.4, 131.4, 129.9, 129.7, 128.7, 128.3, 127.5, 127.3, 125.8, 115.4, 49.9, 21.9, 11.2 ppm.

LC/MS: m/z = 437 [M + H$^+$], 478 [M$^+$ + CH_3CN]; t_R = 17.57 min; 98.0 % pure (UV).

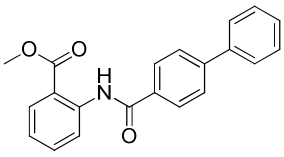


3-(4-(N,N-dipropylsulfamoyl)benzamido)-2-naphthoic acid[1] (V). 4-(4-oxo-4H-naphtho[2,3-d][1,3]oxazin-2-yl)-N,N-dipropylbenzenesulfonamide (**Va**) was dissolved in a mixture of THF/MeOH (2:1) and hydrolyzed by an aqueous solution containing 1 mol/L LiOH at room temperature (18 h). The mixture was acidified by the addition of 1 M HCl, filtered and the precipitate was successively washed with 1 M HCl. The

product was purified by preparative TLC (CH_2Cl_2/MeOH 9:1); yield: 24 %. ^{1}H NMR (500 MHz, CD_3SOCD_3) δ = 12.63 (br. s., 1 H, NH), 9.09 (s, 1 H), 8.76 (s, 1 H), 8.21–8.14 (m, 2 H), 8.06 (d, *J* = 8.2 Hz, 1 H), 8.04–7.99 (m, 2 H), 7.94 (d, *J* = 8.2 Hz, 1 H), 7.68–7.59 (m, 1 H), 7.56–7.47 (m, 1 H), 3.07 (t, *J* = 7.6 Hz, 4 H), 1.55–1.43 (m, 4 H), 0.82 (t, *J* = 7.4 Hz, 6 H, CH_3) ppm.

^{13}C NMR (125 MHz, CD_3SOCD_3) δ = 169.9, 163.5, 142.4, 138.2, 136.1, 135.4, 133.2, 129.2, 129.1, 128.6, 128.1, 127.5, 127.3, 125.8, 118.7, 117.0, 49.7, 21.7, 11.0 ppm.

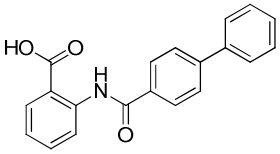
LC/MS: m/z = 455 [M + H$^+$]; t_R = 15.80 min; 99.0 % pure (UV).



methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)benzoate (1a) was prepared according to method BIII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 58 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.11 (br. s, 1 H, NH), 8.98 (dd, *J* = 8.5, 0.9 Hz, 1 H), 8.16–8.13 (m, 2 H), 8.11 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.78–7.75 (m, 2 H), 7.68–7.61 (m, 3 H), 7.51–7.47 (m, 2 H), 7.45–7.39 (m, 1 H), 7.18–7.12 (m, 1 H), 3.99 (s, 3 H, OCH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.1, 165.4, 144.7, 141.9, 140.0, 134.9, 133.6, 131.0, 128.9, 128.0, 127.9, 127.5, 127.2, 122.6, 120.5, 115.1, 52.5 (OCH_3) ppm.

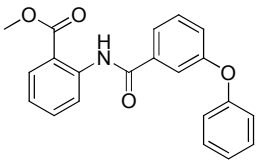
LC/MS: m/z = 332 [M + H$^+$], 373 [M + H$^+$ CH_3CN], 663 [2M + H$^+$]; t_R = 14.92 min; 100.0 % pure (UV).



2-([1,1'-biphenyl]-4-ylcarboxamido)benzoic acid[2] (1) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 74 %. Mp: 190 °C (decomposition). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.26 (br. s, 1 H, NH), 8.74 (dd, *J* = 8.5, 0.9 Hz, 1 H), 8.07 (dd, *J* = 7.9, 1.5 Hz, 1 H), 8.06–8.02 (m, 2 H), 7.90–7.86 (m, 2 H), 7.77–7.74 (m, 2 H), 7.70–7.63 (m, 1 H), 7.53–7.49 (m, 2 H), 7.46–7.40 (m, 1 H), 7.27–7.17 (m, 1 H) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ = 163.8, 163.7, 143.0, 143.0, 140.9, 140.7, 138.9, 133.9, 133.8, 131.5, 131.4, 130.9, 128.9, 128.0, 127.8, 126.8, 121.8, 121.7, 118.5, 118.4 ppm.

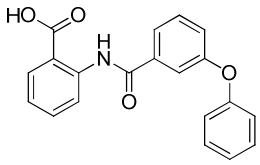
LC/MS: m/z = 318 [M + H$^+$], 635 [2M + H$^+$]; t_R = 12.38 min; 99.4 % pure (UV).



methyl 2-(3-phenoxybenzamido)benzoate (2a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 45 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.02 (br. s, 1 H, NH), 8.91 (dd, *J* = 8.5, 1.3 Hz, 1 H), 8.09 (dd, *J* = 8.0, 1.7 Hz, 1 H), 7.77–7.74 (m, 1 H), 7.71–7.69 (m, 1 H), 7.61 (ddd, *J* = 8.6, 7.2, 1.9 Hz, 1 H), 7.49 (dd, *J* = 7.9, 7.9 Hz, 1 H), 7.42–7.36 (m, 2 H), 7.21 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1 H), 7.18–7.11 (m, 2 H), 7.11–7.07 (m, 2 H), 3.96 (s, 3 H, OCH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.0, 165.1, 158.1, 156.5, 141.7, 136.9, 134.8, 130.9, 130.2, 129.9, 123.8, 122.7, 122.0, 121.5, 120.5, 119.5, 117.6, 115.2, 52.5 (OCH_3) ppm.

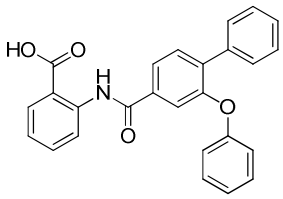
LC/MS: m/z = 348 [M + H$^+$], 389 [M + H$^+$ CH_3CN], 695 [2M + H$^+$]; t_R = 15.88 min; 96.9 % pure (UV).



2-(3-phenoxybenzamido)benzoic acid[3] (2) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 85 %. Mp: 204–206 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 14.64 (br. s, 1H, NH), 8.70 (dd, *J* = 8.2 Hz, 0.9 Hz, 1H), 8.18 (dd, *J* = 7.9 Hz, 1.6 Hz, 1H), 7.84–7.82 (m, 1H), 7.63 (t, *J* = 1.9 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 1H), 7.43–7.39 (m, 3H), 7.19–7.15 (m, 2H), 7.07–7.03 (m, 3H) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ = 171.7, 163.4, 157.2, 156.2, 140.8, 137.2, 131.6, 131.2, 130.4, 130.2, 123.9, 123.1, 122.0, 121.7, 121.5, 118.6, 119.0, 117.2 ppm.

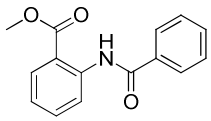
LC/MS: m/z = 334 [M + H$^+$]; t_R = 13.73 min; 96.9 % pure (UV).



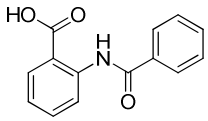
2-(2-phenoxy-[1,1'-biphenyl]-4-ylcarboxamido)benzoic acid[3] (3) was prepared using the procedure described by *Nie et al.*[3] ^{1}H NMR (500 MHz, Acetone-d_6) δ = 12.32 (br. s, 1 H, NH), 7.89 (dd, *J* = 8.5, 1.9 Hz, 1 H), 8.18 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.89 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.71 (d, *J* = 7.9 Hz, 1 H), 7.65–7.63 (m, 4 H), 7.44–7.41 (m, 2 H), 7.37–7.34 (m, 3 H), 7.23–7.20 (m, 1 H), 7.11–7.08 (m, 1 H), 7.03–7.00 (m, 2 H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.0, 164.9, 158.3, 155.0, 143.2, 138.1, 127.9, 136.7, 135.6, 132.8, 132.5, 131.0, 130.1, 129.2, 128.8, 124.3, 123.7, 123.3, 120.9, 120.8, 120.1, 119.2 ppm.

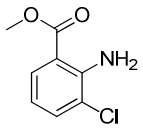
LC/MS: m/z = 410 [M + H$^+$]; t_R = 14.40 min; 95.2 % pure (UV).



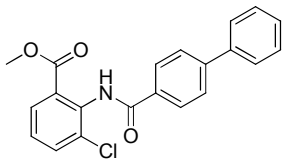
methyl 2-benzamidobenzoate (4a) was prepared according to method BIII. For purification the solvent was evaporated and the remaining solid was resolved in a small amount of CH_2Cl_2. After addition of MeOH the CH_2Cl_2 was evaporated. Crystals formed overnight in the remaining MeOH provided the pure compound; yield: 69 %.
^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.05 (br. s, 1 H, NH), 8.95 (dd, *J* = 8.5, 1.3 Hz, 1 H), 8.10 (dd, *J* = 7.9, 1.6 Hz, 1 H), 8.08–8.04 (m, 2 H), 7.64–7.60 (m, 1 H), 7.60–7.50 (m, 3 H), 7.17–7.09 (m, 1 H), 3.98 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.1, 165.7, 141.9, 134.9, 134.8, 131.9, 130.9, 128.8, 127.4, 122.6, 120.5, 115.2, 52.5 (OCH_3) ppm.
LC/MS: m/z = 256 [M + H$^+$], 511 [2M + H$^+$]; t_R = 12.32 min; 100.0 % pure (UV).



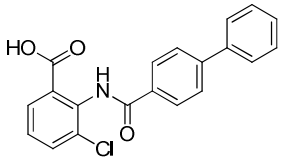
2-benzamidobenzoic acid[4] (4) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 94 %. Mp: 179–181 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.18 (br. s, 1 H, NH), 8.72 (dd, *J* = 8.2, 0.9 Hz, 1 H), 8.06 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.98–7.94 (m, 2 H), 7.69–7.63 (m, 2 H), 7.62–7.57 (m, 2 H), 7.23–7.19 (m, 1 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 170.0, 164.7, 141.1, 134.5, 134.3, 132.2, 131.3, 129.0, 127.0, 122.9, 119.9, 116.5 ppm.
LC/MS: m/z = 242 [M + H$^+$], 483 [2M + H$^+$]; t_R = 9.88 min; 100.0 % pure (UV).



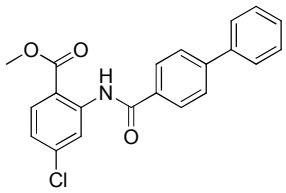
methyl 2-amino-3-chlorobenzoate (5b) was prepared according to method A. The product was purified by CC (*n*-hexane/EtOAc 1:1); yield: 60 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.82 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.41 (dd, *J* = 7.9, 1.6 Hz, 1 H), 6.59 (dd, *J* = 7.9, 7.9 Hz, 1 H), 6.28 (br. s, 2 H, NH_2), 3.89 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.1, 146.6, 133.78, 129.9, 120.2, 115.7, 111.8, 51.8 (OCH_3) ppm.
LC/MS: m/z = 186 [M + H^+], 227 [M + H^+ CH_3CN]; t_R = 11.68 min; 98.4 % pure (UV).



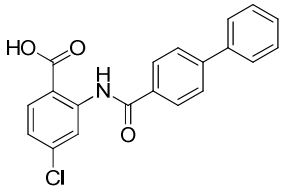
methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-3-chlorobenzoate (5a) was prepared according to method BIII. For purification the solvent was evaporated and the remaining solid was resolved in a small amount of CH_2Cl_2. After addition of MeOH the CH_2Cl_2 was evaporated. Crystals formed overnight in the remaining MeOH provided the pure compound; yield: 40 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 9.51 (br. s, 1 H, NH), 8.12–8.06 (m, 2 H), 7.90 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.77–7.72 (m, 2 H), 7.68 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.67–7.63 (m, 2 H), 7.52–7.46 (m, 2 H), 7.44–7.39 (m, 1 H), 7.27 (dd, *J* = 7.9, 7.9 Hz, 1 H), 3.90 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.1, 165.0, 145.1, 140.0, 135.7, 134.3, 132.5, 131.2, 129.1, 128.9, 128.2, 128.1, 127.5, 127.3, 126.0, 126.0, 52.7 (OCH_3) ppm.
LC/MS: m/z = 365 and 367 [M + H^+], 731 and 733 [2M + H^+]; t_R = 13.00 min; 93.8 % pure (UV).



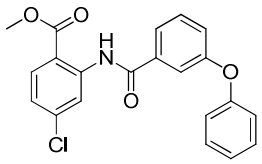
2-([1,1'-biphenyl]-4-ylcarboxamido)-3-chlorobenzoic acid (5) was prepared according to method C. The product was purified by preparative TLC (*n*-hexane/EtOAc 1:1); yield: 93 %. Mp: 203–205 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.33 (br. s, 1 H, NH), 8.11–8.07 (m, 2 H), 7.86–7.75 (m, 6 H), 7.54–7.49 (m, 2 H), 7.47–7.40 (m, 2 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 166.8, 165.1, 143.3, 139.2, 134.7, 132.8, 132.7, 131.9, 129.9, 129.0, 128.5, 128.2, 127.6, 127.0, 126.7 ppm.
LC/MS: m/z = 352 [2 + H^+], 703 [2M + H^+]; t_R = 11.55 min; 99.2 % pure (UV).



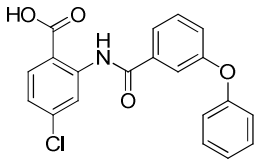
methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-4-chlorobenzoate (6a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 59 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.13 (br. s, 1 H, NH), 9.08 (d, *J* = 2.1 Hz, 1 H), 8.14–8.09 (m, 2 H), 8.01 (d, *J* = 8.8 Hz, 1 H), 7.78–7.74 (m, 2 H), 7.69–7.61 (m, 2 H), 7.53–7.45 (m, 2 H), 7.44–7.38 (m, 1 H), 7.10 (dd, *J* = 8.8, 2.1 Hz, 1 H), 3.98 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.5, 165.4, 144.9, 142.7, 141.2, 139.9, 133.0, 132.0, 128.9, 128.1, 127.9, 127.5, 127.2, 122.8, 120.3, 113.3, 52.6 (OCH_3) ppm.
LC/MS: m/z = 367 [M + H^+], 733 [2M + H^+]; t_R = 16.36 min; 98.2 % pure (UV).



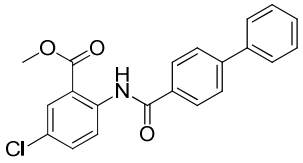
2-([1,1'-biphenyl]-4-ylcarboxamido)-4-chlorobenzoic acid (6) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 55 %. Mp: 323–324 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 15.29 (br. s, 1 H, NH), 8.81 (d, J = 2.2 Hz, 1 H), 8.15–8.08 (m, 3 H), 7.84–7.78 (m, 2 H), 7.74–7.68 (m, 2 H), 7.52–7.45 (m, 2 H), 7.44–7.38 (m, 1 H), 7.09 (dd, J = 8.2, 2.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.6, 164.2, 143.3, 142.0, 139.0, 134.8, 133.6, 133.1, 129.0, 128.2, 127.9, 126.9, 126.9, 122.8, 121.5, 117.9 ppm.
LC/MS: m/z = 351 and 353 [M + H$^+$]; t_R = 14.11 min; 99.1 % pure (UV).



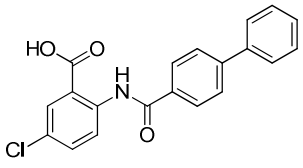
methyl 4-chloro-2-(3-phenoxybenzamido)benzoate (7a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 71 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.07 (br. s, 1 H, NH), 9.02 (d, J = 2.2 Hz, 1 H), 8.00 (d, J = 8.8 Hz, 1 H), 7.75–7.71 (m, 1 H), 7.70–7.65 (m, 1 H), 7.49 (dd, J = 8.2, 8.2 Hz, 1 H), 7.41–7.37 (m, 2 H), 7.22 (ddd, J = 8.2, 2.2, 0.9 Hz, 1 H), 7.19–7.15 (m, 1 H), 7.14–7.07 (m, 3 H), 3.96 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.4, 165.1, 158.2, 156.4, 142.5, 141.2, 136.3, 133.0, 130.2, 130.0, 124.0, 123.0, 122.2, 121.4, 120.4, 119.5, 117.5, 113.4, 52.6 (OCH_3) ppm.
LC/MS: m/z = 382 [M + H$^+$]; t_R = 15.99 min; 95.5 % pure (UV).



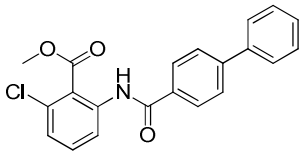
4-chloro-2-(3-phenoxybenzamido)benzoic acid (7) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 61 %. Mp: 205–206 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.26 (br. s, 1 H, NH), 8.75 (d, J = 1.9 Hz, 1 H), 8.03 (d, J = 8.5 Hz, 1 H), 7.72–7.66 (m, 1 H), 7.61 (dd, J = 7.9, 7.9 Hz, 1 H), 7.52 (s, 1 H), 7.47–7.41 (m, 2 H), 7.33–7.25 (m, 2 H), 7.23–7.17 (m, 1 H), 7.16–7.02 (m, 2 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.3, 164.2, 157.4, 155.9, 141.9, 138.7, 136.0, 132.9, 130.9, 130.3, 124.1, 123.0, 122.3, 121.6, 119.2, 119.1, 116.9, 115.4 ppm.
LC/MS: m/z = 368 [M + H$^+$], 409 [M + H$^+$ CH_3CN]; t_R = 13.98 min; 100.0 % pure (UV).



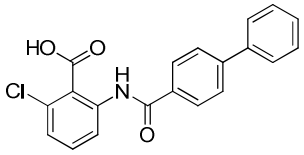
methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-5-chlorobenzoate (8a) was prepared according to method BII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 86 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.02 (br. s, 1 H, NH), 8.97 (d, J = 9.1 Hz, 1 H), 8.13–8.10 (m, 2 H), 8.07 (d, J = 2.5 Hz, 1 H), 7.78–7.75 (m, 2 H), 7.67–7.64 (m, 2 H), 7.57 (dd, J = 9.1, 2.5 Hz, 1 H), 7.52–7.47 (m, 2 H), 7.45–7.37 (m, 1 H), 4.00 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.1, 165.3, 144.9, 140.5, 139.9, 134.7, 133.2, 130.5, 128.9, 128.1, 127.9, 127.6, 127.5, 127.2, 121.9, 116.3, 52.8 (OCH_3) ppm.
LC/MS: m/z = 366 [M + H$^+$], 731 [2M + H$^+$]; t_R = 16.76 min; 97.0 % pure (UV).



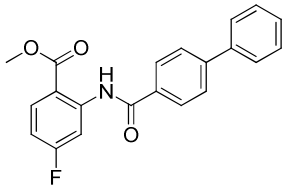
2-([1,1'-biphenyl]-4-ylcarboxamido)-5-chlorobenzoic acid (8) was prepared according to method C. For purification the remaining solid was washed with MeOH and CH_2Cl_2 to provide the pure compound; yield: 96 %. Mp: 274–276 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.14 (br. s, 1 H, NH), 8.74 (d, J = 9.1 Hz, 1 H), 8.05–8.02 (m, 2 H), 8.00 (d, J = 2.5 Hz, 1 H), 7.91–7.86 (m, 2 H), 7.79–7.75 (m, 2 H), 7.73 (dd, J = 9.1, 2.5 Hz, 1 H), 7.54–7.48 (m, 2 H), 7.47–7.41 (m, 1 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 168.8, 164.4, 143.8, 139.9, 138.8, 133.9, 132.9, 130.4, 129.1, 128.3, 127.8, 127.2, 127.0, 126.5, 121.8, 118.6 ppm.
LC/MS: m/z = 352 and 354 [M + H$^+$]; t_R = 14.32 min; 99.3 % pure (UV).



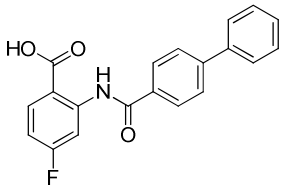
methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-6-chlorobenzoate (9a) was prepared according to method BII. The product was purified by CC (*n*-hexane/EtOAc 8:2); yield: 76 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.27 (br. s, 1 H, NH), 8.56 (dd, J = 8.2, 0.9 Hz, 1 H), 8.04–8.01 (m, 2 H), 7.77–7.74 (m, 2 H), 7.67–7.64 (m, 2 H), 7.52–7.41 (m, 4 H), 7.24 (dd, J = 8.2, 0.9 Hz, 1 H), 4.03 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.9, 165.0, 145.1, 139.8, 139.7, 133.6, 132.9, 132.6, 129.0, 128.2, 127.8, 127.6, 127.2, 125.9, 120.2, 119.9, 52.8 (OCH_3) ppm.
LC/MS: m/z = 366 [M + H$^+$], 731 [2M + H$^+$]; t_R = 13.90 min; 98.2 % pure (UV).



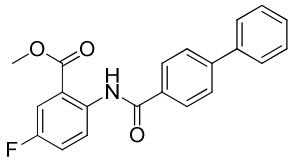
2-([1,1'-biphenyl]-4-ylcarboxamido)-6-chlorobenzoic acid (9) was prepared according to method C. For purification the remaining solid was washed with CH_2Cl_2 to provide the pure compound; yield: 79 %. Mp: 218–219 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.36 (br. s, 1 H, NH), 8.04–8.01 (m, 2 H), 7.86–7.83 (m, 2 H), 7.78–7.75 (m, 2 H), 7.61–7.58 (m, 1 H), 7.53–7.49 (m, 3 H), 7.46–7.40 (m, 2 H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 166.2, 165.2, 143.4, 139.0, 136.9, 132.7, 130.8, 130.5, 129.6, 129.1, 128.3, 128.2, 126.9, 126.8, 126.7, 125.1 ppm.
LC/MS: m/z = 352 [M + H$^+$], 705, 707 [2M + H$^+$]; t_R = 12.25 min; 100.0 % pure (UV).



methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-4-fluorobenzoate (10a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 42 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.25 (br. s, 1 H, NH), 8.80 (dd, J = 11.8, 2.4 Hz, 1 H), 8.21–8.03 (m, 3 H), 7.82–7.72 (m, 2 H), 7.72–7.61 (m, 2 H), 7.57–7.48 (m, 2 H), 7.48–7.39 (m, 1 H), 6.96–6.79 (m, 1 H), 3.99 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.5, 166.1 (d, J = 253.9 Hz), 165.6, 145.0, 144.1 (d, J_{CF} = 12.8 Hz), 139.9, 133.3 (d, J_{CF} = 11.0 Hz), 133.1, 128.9, 128.1, 127.9, 127.5, 127.2, 111.3 (d, J_{CF} = 2.7 Hz), 109.9 (d, J_{CF} = 22.9 Hz), 107.6 (d, J_{CF} = 28.4 Hz), 52.5 ppm (OCH_3).
LC/MS: m/z = 350 [M + H$^+$], 391 [M + H$^+$ CH_3CN], 699 [2M + H$^+$]; t_R = 15.69 min; 96.4 % pure (UV).

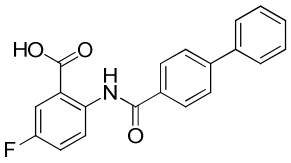


2-([1,1'-biphenyl]-4-ylcarboxamido)-4-fluorobenzoic acid (10) was prepared according to method C. For purification the compound was recrystallized from MeOH; yield: 24 %. Mp: 258–260 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.47 (br. s, 1 H, NH), 8.59 (dd, J = 12.3, 2.5 Hz, 1 H), 8.14 (dd, J = 9.0, 6.8 Hz, 1 H), 8.07–8.00 (m, 2 H), 7.93–7.87 (m, 2 H), 7.81–7.72 (m, 2 H), 7.57–7.49 (m, 2 H), 7.49–7.41 (m, 1 H), 7.10–7.01 (m, 1 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.4, 165.1 (d, J_{CF} = 248.0 Hz), 164.6, 143.9, 143.3 (d, J_{CF} = 12.8 Hz), 138.8, 134.0 (d, J_{CF} = 11.0 Hz), 132.7, 129.1, 128.3, 127.7, 127.2, 127.0, 112.8 (d, J_{CF} = 2.7 Hz), 109.9 (d, J_{CF} = 22.0 Hz), 106.3 (d, J_{CF} = 28.4 Hz) ppm.
LC/MS: m/z = 336 [M + H$^+$], 377 [M + H$^+$ CH_3CN], 671 [2M + H$^+$]; t_R = 13.94 min; 100.0 % pure (UV).

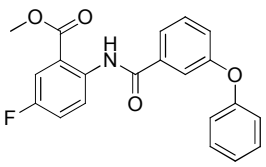


methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-5-fluorobenzoate (11a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 64 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.94 (br. s, 1 H, NH), 8.99 (dd, J = 9.1, 4.7 Hz, 1 H), 8.16–8.05 (m, 2 H), 7.81–7.71 (m, 3 H), 7.70–7.60 (m, 2 H), 7.54–7.45 (m, 2 H), 7.45–7.38 (m, 1 H), 7.38–7.30 (m, 1 H), 4.00 (s, 3 H, OCH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.1, 165.3, 157.4 (d, J_{CF} = 244.0 Hz), 144.8, 140.0, 138.3 (d, J_{CF} = 2.7 Hz), 133.3, 128.9, 128.1, 127.9, 127.5, 127.2, 122.3 (d, J_{CF} = 6.4 Hz), 121.9 (d, J_{CF} = 22.0 Hz), 117.0, (d, J_{CF} = 23.8 Hz), 116.4 (d, J_{CF} = 7.3 Hz), 52.8 ppm (OCH_3).
LC/MS: m/z = 350 [M + H^+], 391 [M + H^+ CH_3CN], 699 [2M + H^+]; t_R = 15.11 min; 96.7 % pure (UV).



2-([1,1'-biphenyl]-4-ylcarboxamido)-5-fluorobenzoic acid (11) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 61 %. Mp: 259–263 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 14.97 (br. s, 1 H, NH), 8.75 (dd, J = 9.1, 5.4 Hz, 1 H), 8.15–8.07 (m, 2 H), 7.85 (dd, J = 9.9, 3.3 Hz, 1 H), 7.83–7.79 (m, 2 H), 7.75–7.70 (m, 2 H), 7.53–7.45 (m, 2 H), 7.44–7.37 (m, 1 H), 7.28–7.19 (m, 1 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 168.9 (d, J_{CF} = 1.8 Hz), 163.7, 156.9 (d, J_{CF} = 239.2 Hz), 143.1, 139.1, 137.4 (d, J_{CF} = 1.8 Hz), 134.0, 129.1, 128.1, 127.8, 126.9, 126.6 (d, J_{CF} = 7.3 Hz), 120.1 (d, J_{CF} = 7.3 Hz), 117.3 (d, J_{CF} = 22.9 Hz), 117.2 (d, J_{CF} = 22.9 Hz), 117.0 ppm.
LC/MS: m/z = 334 [M - H^+]; t_R = 12.89 min; 96.8 % pure (UV).

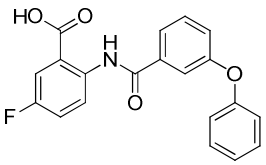


methyl 5-fluoro-2-(3-phenoxybenzamido)benzoate (12a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid

was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 20 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.86 (br. s, 1 H, NH), 8.92 (dd, *J* = 9.4, 5.0 Hz, 1 H), 7.77–7.71 (m, 2 H), 7.71–7.65 (m, 1 H), 7.49 (dd, *J* = 7.9, 7.9 Hz, 1 H), 7.42–7.35 (m, 2 H), 7.32 (ddd, *J* = 9.4, 7.5, 3.0 Hz, 1 H), 7.21 (ddd, *J* = 8.1, 2.4, 0.8 Hz, 1 H), 7.19–7.12 (m, 1 H), 7.12–7.07 (m, 2 H), 3.97 (s, 3 H, OCH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.9 (d, J_{CF} = 2.7 Hz), 164.9, 158.1, 157.6 (d, J_{CF} = 242.9 Hz), 138.1 (d, J_{CF} = 1.8 Hz), 136.5, 130.2, 129.9, 123.9, 122.2 (d, *J* = 7.3 Hz), 122.0, 121.8 (d, *J* = 22.0 Hz), 121.4, 120.8, 119.4, 117.5, 117.0 (d, J_{CF} = 23.8 Hz), 116.4 (d, J_{CF} = 7.3 Hz), 52.8 (OCH_3) ppm.

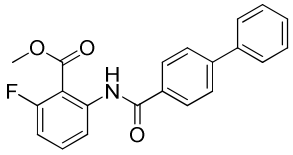
LC/MS: m/z = 366 [M + H$^+$]; t_R = 14.93 min; 93.7 % pure (UV).



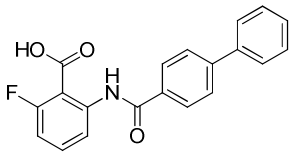
5-fluoro-2-(3-phenoxybenzamido)benzoic acid (12) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 87 %. Mp: 186–187 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.02 (br. s, 1 H, NH), 8.62 (dd, *J* = 9.4, 5.2 Hz, 1 H), 7.74 (dd, *J* = 9.4, 3.2 Hz, 1 H), 7.72–7.68 (m, 1 H), 7.59 (dd, *J* = 7.9, 7.9 Hz, 1 H), 7.56–7.50 (m, 2 H), 7.49–7.39 (m, 2 H), 7.27 (ddd, *J* = 7.9, 2.6, 0.9 Hz, 1 H), 7.23–7.16 (m, 1 H), 7.14–7.04 (m, 2 H) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ = 168.7 (d, J_{CF} = 1.8 Hz), 163.8, 157.3, 157.0 (d, J_{CF} = 242.0 Hz), 156.0, 137.2 (d, J_{CF} = 1.8 Hz), 136.3, 130.8, 130.2, 124.1, 122.3 (d, J_{CF} = 7.3 Hz), 122.0, 121.6, 120.9 (d, J_{CF} = 22.0 Hz), 119.4 (d, J_{CF} = 7.3 Hz),119.1, 117.0 (d, J_{CF} = 22.0 Hz), 116.9 ppm.

LC/MS: m/z = 351 [M + H$^+$], 392 [M + H$^+$ CH_3CN]; t_R = 12.87 min; 96.2 % pure (UV).

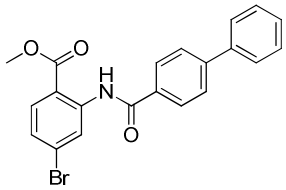


methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-6-fluorobenzoate (13a) was prepared according to method BII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 90 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.68 (br. s, 1 H, NH), 8.70 (d, *J* = 8.8 Hz, 1 H), 8.12–8.07 (m, 2 H), 7.78–7.73 (m, 2 H), 7.68–7.64 (m, 2 H), 7.57–7.52 (m, 1 H), 7.51–7.47 (m, 2 H), 7.45–7.39 (m, 1 H), 6.89 (ddd, *J* = 11.0, 8.8, 0.9 Hz, 1 H), 4.03 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.9 (d, J_{CF} = 3.7 Hz), 165.3, 162.4 (d, J_{CF} = 258.4 Hz), 144.9, 142.1 (d, J_{CF} = 2.7 Hz), 139.9, 134.8 (d, J_{CF} = 11.0 Hz), 133.2, 128.9, 128.1, 127.9, 127.5, 127.2, 116.5 (d, J_{CF} = 3.7 Hz), 111.1 (d, J_{CF} = 23.8 Hz), 106.2 (d, J_{CF} = 12.8 Hz), 52.9 (OCH_3) ppm.
LC/MS: m/z = 350 [M + H^+], 699 [2M + H^+]; t_R = 15.22 min; 97.5 % pure (UV).

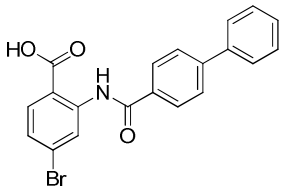


2-([1,1'-biphenyl]-4-ylcarboxamido)-6-fluorobenzoic acid (13) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 87 %. Mp: 232–233 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 11.23 (br. s, 1 H, NH), 8.05–8.00 (m, 3 H), 7.90–7.84 (m, 2 H), 7.79–7.73 (m, 2 H), 7.61 (td, *J* = 8.3, 6.1 Hz, 1 H), 7.53–7.49 (m, 2 H), 7.46–7.41 (m, 1 H), 7.11 (ddd, *J* = 10.6, 8.4, 0.9 Hz, 1 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 166.5 (d, J_{CF} = 1.8 Hz), 164.7, 160.8 (d, J_{CF} = 254.0 Hz), 143.6, 139.7 (d, J_{CF} = 4.6 Hz), 138.9, 133.2 (d, J_{CF} = 11.0 Hz), 132.9, 129.1, 128.3, 128.0, 126.9, 118.3 (d, J_{CF} = 3.7 Hz), 112.0 (d, J_{CF} = 14.7 Hz), 111.8 (d, J_{CF} = 22.9 Hz) ppm.

LC/MS: m/z = 336 [M + H^+], 671 [2M + H^+]; t_R = 12.85 min; 100.0 % pure (UV).

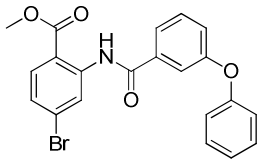


methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-4-bromobenzoate (14a) was prepared according to method BII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 69 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.12 (br. s, 1 H, NH), 9.25 (d, *J* = 1.9 Hz, 1 H), 8.14–8.09 (m, 2 H), 7.94 (d, *J* = 8.5 Hz, 1 H), 7.79–7.74 (m, 2 H), 7.68–7.63 (m, 2 H), 7.52–7.47 (m, 2 H), 7.45–7.39 (m, 1 H), 7.27 (dd, *J* = 8.5, 1.9 Hz, 1 H), 3.99 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.7, 165.4, 145.0, 142.7, 139.9, 133.0, 132.0, 129.9, 128.9, 128.1, 127.9, 127.5, 127.2, 125.8, 123.3, 113.7, 52.7 (OCH_3) ppm.
LC/MS: m/z = 409 and 411 [M + H^+]; t_R = 17.07 min; 100.0 % pure (UV).

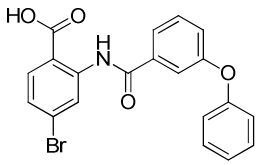


2-([1,1'-biphenyl]-4-ylcarboxamido)-4-bromobenzoic acid (14) was prepared according to method C. For purification the remaining solid was washed with MeOH and CH_2Cl_2 to provide the pure compound; yield: 81 %. Mp: 246–250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.30 (br. s, 1 H, NH), 8.99 (d, *J* = 1.9 Hz, 1 H), 8.05–8.00 (m, 2 H), 7.97 (d, *J* = 8.5 Hz, 1 H), 7.93–7.87 (m, 2 H), 7.80–7.73 (m, 2 H), 7.55–7.48 (m, 2 H), 7.47–7.41 (m, 1 H), 7.41 (dd, *J* = 8.5, 1.9 Hz, 1 H) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.5, 164.6, 143.9, 142.1, 138.8, 133.0, 132.7, 129.1, 128.3, 127.8, 127.8, 127.2, 127.0, 125.8, 122.1, 115.5 ppm.
LC/MS: m/z = 793 [2M + H^+]; t_R = 14.71 min; 96.4 % pure (UV).

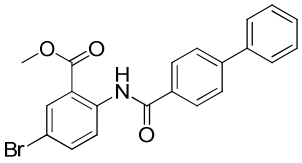


methyl 4-bromo-2-(3-phenoxybenzamido)benzoate (15a) was prepared according to method BII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 61 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.04 (br. s, 1 H, NH), 9.18 (d, *J* = 2.2 Hz, 1 H), 7.92 (d, *J* = 8.5 Hz, 1 H), 7.73 (dd, *J* = 1.6, 0.9 Hz, 1 H), 7.69–7.65 (m, 1 H), 7.49 (dd, *J* = 7.9, 7.9 Hz, 1 H), 7.42–7.35 (m, 2 H), 7.26 (dd, *J* = 8.5, 2.2 Hz, 1 H), 7.22 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1 H), 7.19–7.14 (m, 1 H), 7.12–7.07 (m, 2 H), 3.96 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.5, 165.0, 158.2, 156.3, 142.5, 136.3, 132.0, 130.2, 130.0, 129.9, 126.0, 124.0, 123.3, 122.2, 121.4, 119.5, 117.4, 113.8, 52.7 (OCH_3) ppm.
LC/MS: m/z = no ionization; t_R = 16.93 min; 99.8 % pure (UV).

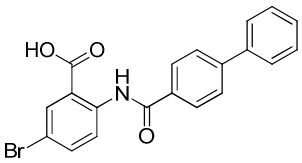


4-bromo-2-(3-phenoxybenzamido)benzoic acid (15) was prepared according to method C. For purification the remaining solid was washed with MeOH and CH_2Cl_2 to provide the pure compound; yield: 74 %. Mp: 194–195 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.22 (br. s, 1 H, NH), 8.90 (d, *J* = 2.2 Hz, 1 H), 7.95 (d, *J* = 8.5 Hz, 1

H), 7.70–7.68 (m, 1 H), 7.61 (dd, *J* = 7.9, 7.9 Hz, 1 H), 7.53–7.51 (m, 1 H), 7.46–7.40 (m, 3 H), 7.29 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1 H), 7.21 (tt, *J* = 7.4, 1.1 Hz, 1 H), 7.11–7.08 (m, 2 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.4, 164.1, 157.4, 155.9, 141.8, 136.0, 132.9, 130.9, 130.3, 127.7, 125.9, 124.1, 122.3, 122.2, 121.6, 119.1, 116.8, 115.8 ppm.
LC/MS: m/z = 823 and 825 and 827 [2M + H^+]; t_R = 14.65 min; 100.0 % pure (UV).

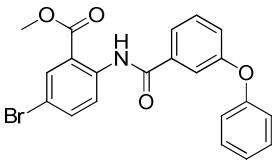


methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-5-bromobenzoate (16a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 26 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.01 (br. s, 1 H, NH), 8.91 (d, *J* = 9.1 Hz, 1 H), 8.22 (d, *J* = 2.5 Hz, 1 H), 8.15–8.08 (m, 2 H), 7.79–7.74 (m, 2 H), 7.71 (dd, *J* = 9.1, 2.5 Hz, 1 H), 7.68–7.62 (m, 2 H), 7.54–7.46 (m, 2 H), 7.45–7.38 (m, 1 H), 4.00 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.0, 165.4, 144.9, 141.0, 139.9, 137.5, 133.5, 133.1, 128.9, 128.1, 127.9, 127.5, 127.2, 122.1, 116.6, 115.0, 52.8 (OCH_3) ppm.
LC/MS: m/z = 409 and 411 [M + H^+], 820 and 822 [2M + H^+]; t_R = 16.41 min; 98.4 % pure (UV).

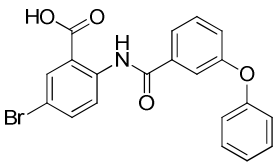


2-([1,1'-biphenyl]-4-ylcarboxamido)-5-bromobenzoic acid[5] (16) was prepared according to method C. Sufficient purity was achieved without further purification;

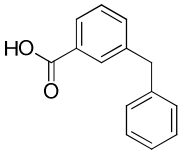
yield: 31 %. Mp: 289–293 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 15.22 (br. s, 1 H, NH), 8.68 (d, J = 8.8 Hz, 1 H), 8.23 (d, J = 2.5 Hz, 1 H), 8.15–8.06 (m, 2 H), 7.87–7.82 (m, 2 H), 7.79–7.70 (m, 2 H), 7.54 (dd, J = 8.8, 2.5 Hz, 1 H), 7.53–7.47 (m, 2 H), 7.45–7.39 (m, 1 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 168.3, 163.9, 143.2, 140.2, 139.0, 133.8, 133.8, 132.9, 129.0, 128.2, 127.9, 126.9, 120.6, 117.4, 115.8, 113.5 ppm.
LC/MS: m/z = 395 [2M - H^+]; t_R = 13.90 min; 98.3 % pure (UV).



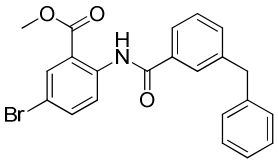
methyl 5-bromo-2-(3-phenoxybenzamido)benzoate (17a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 78 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.94 (br. s, 1 H, NH), 8.83 (d, J = 9.1 Hz, 1 H), 8.19 (d, J = 2.5 Hz, 1 H), 7.74–7.71 (m, 1 H), 7.70–7.66 (m, 2 H), 7.48 (dd, J = 7.9 7.9 Hz, 1 H), 7.42–7.36 (m, 2 H), 7.21 (ddd, J = 7.9, 2.5, 0.9 Hz, 1 H), 7.19–7.14 (m, 1 H), 7.11–7.07 (m, 2 H), 3.96 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.8, 165.0, 158.1, 156.4, 140.7, 137.5, 136.4, 133.4, 130.2, 129.9, 123.9, 122.1, 122.1, 121.4, 119.5, 117.5, 116.7, 115.1, 52.8 (OCH_3) ppm.
LC/MS: m/z = no ionization; t_R = 16.15 min; 95.1 % pure (UV).



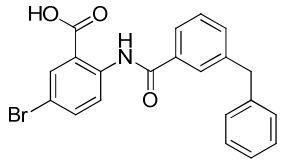
5-bromo-2-(3-phenoxybenzamido)benzoic acid[5] (17) was prepared according to method C. For purification the remaining solid was washed with hot MeOH to provide the pure compound; yield: 52 %. Mp: 240–242 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.05 (br. s, 1 H, NH), 8.59 (d, J = 9.1 Hz, 1 H), 8.10 (d, J = 2.5 Hz, 1 H), 7.83 (dd, J = 9.1, 2.5 Hz, 1 H), 7.72–7.67 (m, 1 H), 7.63–7.57 (m, 1 H), 7.53–7.50 (m, 1 H), 7.47–7.40 (m, 2 H), 7.30–7.26 (m, 1 H), 7.24–7.17 (m, 1 H), 7.14–7.06 (m, 2 H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 168.6, 163.9, 157.3, 156.0, 140.0, 136.7, 136.2, 133.2, 130.8, 130.2, 130.1, 124.1, 122.2, 122.1, 121.6, 119.0, 116.9, 114.5 ppm. LC/MS: m/z = 409 and 411 [M - H^+]; t_R = 13.90 min; 95.2 % pure (UV).



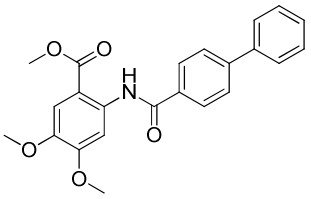
3-benzylbenzoic acid (18d). A mixture of methyl 3-(bromomethyl)benzoate (1 equiv), phenylboronic acid (1.5 equiv), $CsCO_3$ (3 equiv) and tetrakis(triphenylphosphine)-palladium (0.01 equiv) in a degased DME/water (1:1) solution was refluxed under a nitrogen atmosphere for 18 h. The reaction mixture was cooled to room temperature. The mixture was extracted with EtOAc. The combined organic layers were washed with 1 M HCl and dried over $MgSO_4$. The product was purified by CC (CH_2Cl_2); yield: 81 %. ^{1}H NMR (500 MHz, Acetone-d_6) δ = 7.93–7.92 (m, 1H), 7.89–7.87 (m, 1H), 7.52–7.50 (m, 1H), 7.44–7.41 (m, 1H), 7.31–7.26 (m, 4H), 7.22–7.17 (m, 1H), 4.07 (s, 2H, CH_2) ppm.
^{13}C NMR (125 MHz, Acetone-d_6) δ = 167.7, 143.0, 141.9, 134.3, 131.7, 130.9, 129.8, 129.5, 129.5, 128.3, 127.1, 42.1 (CH_2) ppm.
LC/MS: m/z = no ionization; t_R = 11.15 min; 98.4 % pure (UV).



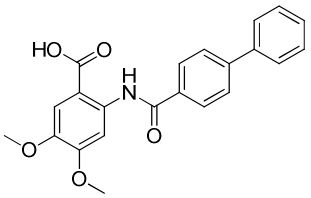
methyl 2-(3-benzylbenzamido)-5-bromobenzoate (18a) was prepared according to method BII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 23 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 11.94 (s, 1H), 8.87 (d, *J* = 9.0 Hz, 1H), 8.21 (d, *J* = 2.4 Hz, 1H), 7.93–7.89 (m, 1H), 7.89–7.82 (m, 1H), 7.69 (dd, *J* = 2.4, 9.0 Hz, 1H), 7.46–7.43 (m, 1H), 7.42–7.37 (m, 1H), 7.35–7.29 (m, 2H), 7.26–7.20 (m, 3H), 4.09 (s, 2H, CH_2), 3.98 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.8, 165.8, 142.1, 140.9, 140.4, 137.5, 134.7, 133.4, 132.7, 129.0, 129.0, 128.6, 128.2, 126.3, 124.9, 122.1, 116.7, 114.9, 52.8 (CH_3), 41.8 (CH_2) ppm.
LC/MS: m/z = 424 and 426 [M + H$^+$]; t_R = 16.82 min; 99.5 % pure (UV).



2-(3-benzylbenzamido)-5-bromobenzoic acid (18) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 98 %. Mp: 225–227 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.06 (s, 1H), 8.62 (d, *J* = 9.1 Hz, 1H), 8.10 (d, *J* = 2.2 Hz, 1H), 7.85–7.80 (m, 2H), 7.77–7.72 (m, 1H), 7.52–7.47 (m, 2H), 7.32–7.24 (m, 4H), 7.22–7.16 (m, 1H), 4.04 (s, 2H, CH_2) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 168.8, 164.9, 142.4, 140.8, 140.3, 136.8, 134.5, 133.3, 132.8, 129.2, 128.8, 128.7, 127.6, 126.3, 124.7, 122.1, 118.9, 114.4, 41.0 (CH_2) ppm.
LC/MS: m/z = 410 and 412 [M + H$^+$]; t_R = 14.62 min; 100.0 % pure (UV).

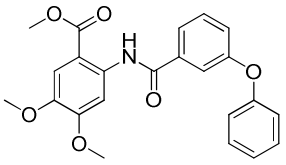


methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-4,5-dimethoxybenzoate (19a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 40 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.21 (br. s, 1 H, NH), 8.75 (s, 1 H), 8.15–8.12 (m, 2 H), 7.78–7.75 (m, 2 H), 7.68–7.65 (m, 2 H), 7.52 (s, 1 H), 7.51–7.47 (m, 2 H), 7.44–7.39 (m, 1 H), 4.05 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.8, 165.4, 154.1, 144.6, 144.0, 140.0, 138.1, 133.5, 128.9, 128.0, 127.8, 127.5, 127.2, 112.1, 106.8, 103.4, 56.2 (OCH_3), 56.1 (OCH_3), 52.3 (OCH_3) ppm.
LC/MS: m/z = 392 [M + H$^+$]; t_R = 14.81 min; 98.4 % pure (UV).

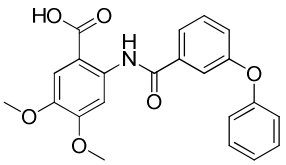


2-([1,1'-biphenyl]-4-ylcarboxamido)-4,5-dimethoxybenzoic acid (19) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 29 %. Mp: 185 °C (decomposition). ^{1}H NMR (500 MHz, DMSO-d_6) δ = 14.78 (br. s, 1 H, NH), 8.54 (s, 1 H), 8.14–8.08 (m, 2 H), 7.78–7.73 (m, 2 H), 7.72–7.61 (m, 3 H), 7.56–7.33 (m, 3 H), 3.81 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 163.4, 150.5, 143.2, 142.9, 139.0, 135.7, 134.1, 129.0, 128.1, 127.8, 126.8, 126.8, 117.6, 117.4, 114.3, 102.6, 55.5 (OCH_3), 55.4 (OCH_3) ppm.

LC/MS: m/z = 378 [M + H^+]; t_R = 12.37 min; 95.6 % pure (UV).

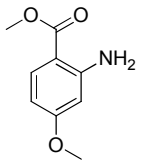


methyl 4,5-dimethoxy-2-(3-phenoxybenzamido)benzoate (20a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 57 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.12 (br. s, 1 H, NH), 8.67 (s, 1 H), 7.76–7.73 (m, 1 H), 7.69 (dd, *J* = 2.0, 2.0 Hz, 1 H), 7.51–7.47 (m, 2 H), 7.40–7.34 (m, 2 H), 7.21 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1 H), 7.17–7.12 (m, 1 H), 7.12–7.06 (m, 2 H), 4.01 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.6, 165.0, 158.1, 156.5, 154.0, 144.0, 137.9, 136.8, 130.1, 129.9, 123.8, 122.0, 121.3, 119.4, 117.4, 112.1, 106.8, 103.3, 56.1 (OCH_3), 56.1 (OCH_3), 52.2 (OCH_3) ppm.
LC/MS: m/z = 408 [M + H^+], 815 [2M + H^+]; t_R = 14.56 min; 95.5 % pure (UV).

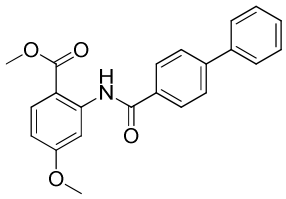


4,5-dimethoxy-2-(3-phenoxybenzamido)benzoic acid (20) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 98 %. Mp: 218–219 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.29 (br. s, 1 H, NH), 8.45 (s, 1 H), 7.70–7.66 (m, 1 H), 7.59 (dd, *J* = 7.9, 7.9 Hz, 1 H), 7.52–7.49 (m, 1 H), 7.49–7.41 (m, 3 H), 7.27 (ddd, *J* = 8.2, 2.5, 0.9 Hz, 1 H), 7.21 (tt, *J* = 7.5, 1.0 Hz, 1 H), 7.14–7.06 (m, 2 H), 3.84 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.8, 163.6, 157.4, 155.9, 153.3, 143.8, 136.7, 136.5, 130.8, 130.3, 124.1, 121.9, 121.3, 119.2, 116.7, 112.8, 107.8, 103.1, 55.6 (OCH_3), 55.6 (OCH_3) ppm.
LC/MS: m/z = 394 [M + H^+], 435 [M + H^+ CH_3CN]; t_R = 12.32 min; 96.9 % pure (UV).



methyl 2-amino-4-methoxybenzoate (21b) was prepared according to method A. The product was purified by CC (*n*-hexane/EtOAc 6:4); yield: 12 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.79 (d, *J* = 8.8 Hz, 1 H), 6.24 (dd, *J* = 8.8, 2.2 Hz, 1 H), 6.11 (d, *J* = 2.2 Hz, 1 H), 5.80 (br. s, 2 H, NH_2), 3.84 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.3, 164.2, 152.4, 133.0, 104.5, 104.4, 99.4, 55.1 (OCH_3), 51.2 (OCH_3) ppm.
LC/MS: m/z = 182 [M + H^+]; t_R = 8.73 min; 100.0 % pure (UV).

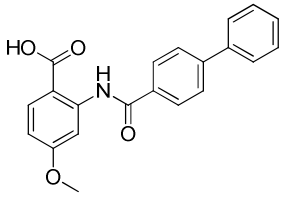


methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-4-methoxybenzoate (21a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 26 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.32 (br. s, 1 H, NH), 8.66 (d, *J* = 2.5 Hz, 1 H), 8.17–8.13 (m, 2 H), 8.02 (d, *J* = 8.8 Hz, 1 H), 7.78–7.75 (m, 2 H), 7.68–7.64 (m, 2 H), 7.51–7.47 (m, 2 H),

7.44–7.39 (m, 1 H), 6.67 (dd, *J* = 8.8, 2.5 Hz, 1 H), 3.96 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.0, 165.7, 164.7, 144.7, 144.1, 140.0, 133.5, 132.5, 128.9, 128.0, 127.9, 127.5, 127.2, 110.2, 107.7, 103.9, 55.6 (OCH_3), 52.2 (OCH_3) ppm.

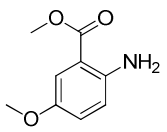
LC/MS: m/z = 362 [M + H^+], 403 [M + H^+ CH_3CN], 723 [2M + H^+]; t_R = 15.61 min; 99.6 % pure (UV).



2-([1,1'-biphenyl]-4-ylcarboxamido)-4-methoxybenzoic acid (21) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 98 %. Mp: 248–249 °C. ^1H NMR (500 MHz, DMSO-d_6) δ = 12.51 (br. s, 1 H, NH), 8.44 (d, *J* = 2.5 Hz, 1 H), 8.06–7.99 (m, 3 H), 7.92–7.85 (m, 2 H), 7.78–7.73 (m, 2 H), 7.55–7.48 (m, 2 H), 7.47–7.39 (m, 1 H), 6.77 (dd, *J* = 8.8, 2.5 Hz, 1 H), 3.86 (s, 3 H, OCH_3) ppm.

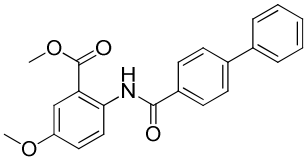
^{13}C NMR (125 MHz, DMSO-d_6) δ = 170.1, 164.5, 163.8, 143.8, 143.3, 138.9, 133.2, 133.2, 129.1, 128.3, 127.7, 127.2, 127.0, 108.8, 108.5, 104.5, 55.6 (OCH_3) ppm.

LC/MS: m/z = 348 [M + H^+], 389 [M + H^+ CH_3CN], 695 [2M + H^+]; t_R = 13.50 min; 100.0 % pure (UV).

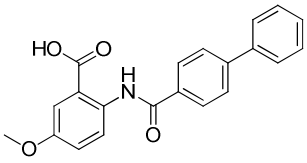


methyl 2-amino-5-methoxybenzoate (22b) was prepared according to method A. Sufficient purity was achieved without further purification; yield: 62 %. ^1H NMR (500

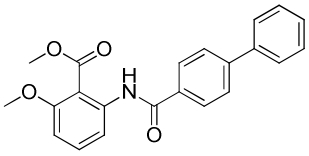
MHz, $CDCl_3$) δ = 7.36 (d, *J* = 3.2 Hz, 1 H), 6.96 (dd, *J* = 8.8, 3.2 Hz, 1 H), 6.64 (d, *J* = 8.8 Hz, 1 H), 5.43 (br. s, 2 H, NH_2), 3.88 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.3, 150.5, 145.1, 123.3, 118.2, 113.1, 110.7, 55.8 (OCH_3), 51.6 (OCH_3) ppm.
LC/MS: m/z = 182 [M + H^+], 223 [M + H^+ CH_3CN]; t_R = 5.88 min; 95.2 % pure (UV).



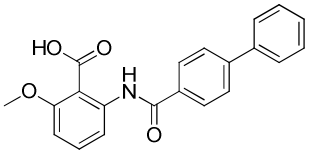
methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-5-methoxybenzoate (22a) was prepared according to method BII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 82 %. ^1H NMR (500 MHz, $CDCl_3$) δ = 11.85 (br. s, 1 H, NH), 8.91 (d, *J* = 9.1 Hz, 1 H), 8.13–8.11 (m, 2 H), 7.77–7.74 (m, 2 H), 7.67–7.64 (m, 2 H), 7.59 (d, *J* = 3.2 Hz, 1 H), 7.50–7.47 (m, 2 H), 7.44–7.38 (m, 1 H), 7.21 (dd, *J* = 9.1, 3.2 Hz, 1 H), 3.99 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.8, 165.0, 154.5, 144.5, 140.1, 135.6, 133.7, 128.9, 128.0, 127.8, 127.4, 127.2, 122.0, 121.2, 116.1, 114.7, 55.6 (OCH_3), 52.6 (OCH_3) ppm.
LC/MS: m/z = 362 [M + H^+], 403 [M + H^+ CH_3CN], 723 [2M + H^+]; t_R = 15.45 min; 98.1 % pure (UV).



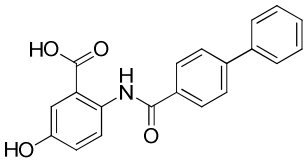
2-([1,1'-biphenyl]-4-ylcarboxamido)-5-methoxybenzoic acid (22) was prepared according to method C. For purification the remaining solid was washed with MeOH and CH_2Cl_2 to provide the pure compound; yield: 92 %. Mp: 236–239 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 11.90 (br. s, 1 H, NH), 8.61 (d, *J* = 9.1 Hz, 1 H), 8.04–8.00 (m, 2 H), 7.89–7.86 (m, 2 H), 7.77–7.73 (m, 2 H), 7.54 (d, *J* = 2.8 Hz, 1 H), 7.53–7.48 (m, 2 H), 7.45–7.39 (m, 1 H), 7.28 (dd, *J* = 9.1, 2.8 Hz, 1 H), 3.80 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.6, 163.9, 154.4, 143.5, 138.9, 134.5, 133.4, 129.1, 128.2, 127.6, 127.1, 126.9, 121.9, 120.3, 118.2, 115.0, 55.4 (OCH_3) ppm.
LC/MS: m/z = 348 [M + H$^+$], 695 [2M + H$^+$]; t_R = 13.07 min; 96.8 % pure (UV).



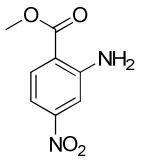
methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-6-methoxybenzoate (23a) was prepared according to method BIII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 46 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 10.78 (br. s, 1 H, NH), 8.31 (dd, *J* = 8.5, 0.9 Hz, 1 H), 8.07–8.04 (m, 2 H), 7.76–7.73 (m, 2 H), 7.67–7.64 (m, 2 H), 7.51–7.47 (m, 3 H), 7.44–7.39 (m, 1 H), 6.76 (dd, *J* = 8.5, 0.9 Hz, 1 H), 3.99 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.2, 165.1, 159.4, 144.7, 140.2, 140.0, 133.4, 133.4, 128.9, 128.0, 127.8, 127.4, 127.2, 113.8, 109.4, 107.2, 56.3 (OCH_3), 52.6 (OCH_3) ppm.
LC/MS: m/z = 362 [M + H$^+$], 723 [2M + H$^+$]; t_R = 13.57 min; 96.5 % pure (UV).



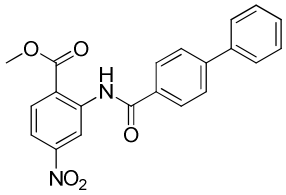
2-([1,1'-biphenyl]-4-ylcarboxamido)-6-methoxybenzoic acid (23) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 90 %. Mp: 158–162 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.44 (br. s, 1 H, NH), 8.02–7.99 (m, 2 H), 7.86–7.83 (m, 2 H), 7.77–7.75 (m, 2 H), 7.53–7.46 (m, 4 H), 7.45–7.41 (m, 1 H), 6.98 (dd, J = 7.9, 1.6 Hz, 1 H), 3.83 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 167.7, 164.7, 157.5, 143.4, 139.0, 137.2, 133.1, 131.3, 129.1, 128.2, 128.1, 126.9, 126.8, 116.8, 116.6, 108.6, 56.1 (OCH_3) ppm.
LC/MS: m/z = 348 [M + H$^+$], 695 [2M + H$^+$]; t_R = 13.30 min; 99.2 % pure (UV).



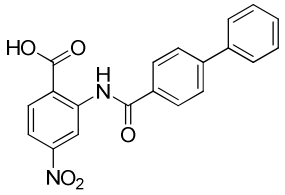
2-([1,1'-biphenyl]-4-ylcarboxamido)-5-hydroxybenzoic acid (24) was prepared according to method E. The product was purified by CC (starting with *n*-hexane/EtOAc 1:1 to EtOAc + 3 ‰ formic acid) followed by preparative TLC (CH_2Cl_2 + 7 drops formic acid per 10 mL solvent); yield: 34 %. Mp: 193–196 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 11.88 (br. s, 1 H, NH), 9.64 (br. s, 1 H, ArOH), 8.51 (d, J = 8.8 Hz, 1 H), 8.03–8.00 (m, 2 H), 7.89–7.85 (m, 2 H), 7.78–7.74 (m, 2 H), 7.53–7.49 (m, 2 H), 7.46 (d, J = 2.8 Hz, 1 H), 7.45–7.38 (m, 1 H), 7.08 (dd, J = 8.8, 2.8 Hz, 1 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.8, 163.7, 152.7, 143.3, 139.0, 133.6, 133.1, 129.1, 128.2, 127.6, 127.1, 126.9, 121.9, 121.1, 118.4, 116.8 ppm.
LC/MS: m/z = 334 [M + H$^+$], 667 [2M + H$^+$]; t_R = 11.31 min; 96.6 % pure (UV).



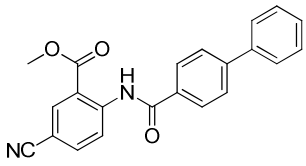
methyl 2-amino-4-nitrobenzoate (25b) was prepared according to method A. The product was purified by CC (*n*-hexane/EtOAc 6:4); yield: 37 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.01 (d, *J* = 8.8 Hz, 1 H), 7.51 (d, *J* = 2.2 Hz, 1 H), 7.41 (dd, *J* = 8.8, 2.2 Hz, 1 H), 6.06 (br. s, 2 H, NH_2), 3.93 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.3, 151.3, 150.7, 132.8, 114.9, 111.1, 110.1, 52.2 (OCH_3) ppm.
LC/MS: m/z = no ionization; t_R = 10.08 min; 100.0 % pure (UV).



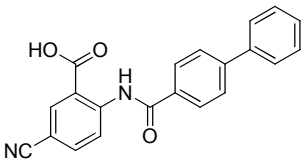
methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-4-nitrobenzoate (25a) was prepared according to method BI. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was exhaustively washed with MeOH and CH_2Cl_2 to provide the pure compound; yield: 15 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.17 (br. s, 1 H, NH), 9.89 (d, *J* = 2.2 Hz, 1 H), 8.28 (d, *J* = 8.8 Hz, 1 H), 8.21–8.10 (m, 2 H), 7.94 (dd, *J* = 8.8, 2.2 Hz, 1 H), 7.84–7.73 (m, 2 H), 7.72–7.61 (m, 2 H), 7.54–7.47 (m, 2 H), 7.47–7.39 (m, 1 H), 4.07 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.8, 165.6, 151.4, 145.3, 142.9, 139.8, 132.5, 132.1, 129.0, 128.2, 128.0, 127.6, 127.3, 119.3, 116.6, 115.5, 53.3 (OCH_3) ppm.
LC/MS: m/z = 377 [M + H^+], 418 [M + H^+ CH_3CN]; t_R = 15.03 min; 97.6 % pure (UV).



2-([1,1'-biphenyl]-4-ylcarboxamido)-4-nitrobenzoic acid (25) was prepared according to method C. For purification the remaining solid was washed with MeOH and CH_2Cl_2 to provide the pure compound; yield: 94 %. Mp: 280–283 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.48 (br. s, 1 H, NH), 9.55 (d, J = 2.2 Hz, 1 H), 8.28 (d, J = 8.8 Hz, 1 H), 8.09–8.04 (m, 2 H), 8.01 (dd, J = 8.8, 2.2 Hz, 1 H), 7.95–7.90 (m, 2 H), 7.81–7.74 (m, 2 H), 7.56–7.49 (m, 2 H), 7.47–7.41 (m, 1 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 168.6, 164.9, 150.2, 144.1, 141.5, 138.8, 132.8, 132.6, 129.1, 128.4, 127.9, 127.3, 127.0, 122.6, 117.2, 114.3 ppm.
LC/MS: m/z = 363 [M + H$^+$], 404 [M + H$^+$ CH_3CN], 725 [2M + H$^+$]; t_R = 13.25 min; 100.0 % pure (UV).



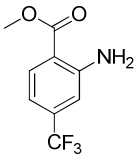
methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-5-cyanobenzoate (26a) was prepared according to method BII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 43 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.29 (br. s, 1 H, NH), 9.13 (d, J = 8.8 Hz, 1 H), 8.42 (d, J = 2.0 Hz, 1 H), 8.13–8.11 (m, 2 H), 7.84 (dd, J = 8.8, 2.0 Hz, 1 H), 7.79–7.76 (m, 2 H), 7.67–7.64 (m, 2 H), 7.51–7.48 (m, 2 H), 7.45–7.40 (m, 1 H), 4.04 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.6, 165.6, 145.4, 145.3, 139.7, 137.6, 135.4, 132.5, 129.0, 128.2, 128.0, 127.6, 127.2, 120.9, 118.0, 115.3, 105.9, 53.1 (OCH_3) ppm.
LC/MS: m/z = 357 [M + H$^+$], 713 [2M + H$^+$]; t_R = 15.32 min; 97.2 % pure (UV).



2-([1,1'-biphenyl]-4-ylcarboxamido)-5-cyanobenzoic acid[5] (26) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 80 %. Mp: 246–247 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.46 (br. s, 1 H, NH), 8.87 (d, J = 8.8 Hz, 1 H), 8.38 (d, J = 2.0 Hz, 1 H), 8.07 (dd, J = 8.8, 2.0 Hz, 1 H), 8.04–8.01 (m, 2 H), 7.90–7.87 (m, 2 H), 7.77–7.73 (m, 2 H), 7.53–7.48 (m, 2 H), 7.46–7.41 (m, 1 H) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ = 168.6, 164.7, 144.6, 144.1, 138.7, 137.5, 135.4, 132.5, 129.1, 128.4, 127.9, 127.2, 127.0, 120.2, 118.1, 117.2, 105.0 ppm.

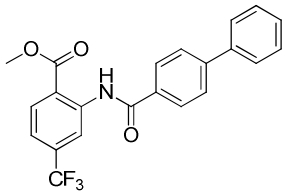
LC/MS: m/z = 343 [M + H$^+$], 685 [2M + H$^+$]; t_R = 13.30 min; 97.5 % pure (UV).



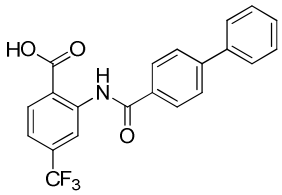
methyl 2-amino-4-(trifluoromethyl)benzoate (27b) was prepared according to method A. The product was purified by CC (*n*-hexane/EtOAc 1:1); yield: 61 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.96 (d, J = 8.2 Hz, 1 H), 6.93–6.89 (m, 1 H), 6.88–6.82 (m, 1 H), 5.92 (br. s, 2 H, NH_2), 3.91 (s, 3 H, OCH_3) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.7, 150.2, 135.7 (q, J_{CF} = 32.1 Hz), 132.2, 120.3 (q, J_{CF} = 272.0 Hz), 113.4 (q, J_{CF} = 3.7 Hz), 113.0 (q, J_{CF} = 1.8 Hz), 112.3 (q, J_{CF} = 3.7 Hz), 51.9 (OCH_3) ppm.

LC/MS: m/z = 261 [M + H$^+$ CH_3CN]; t_R = 12.01 min; 85.2 % pure (UV).

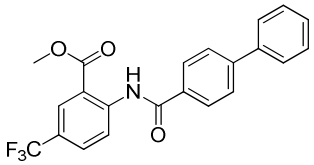


methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-4-(trifluoromethyl)benzoate (27a) was prepared according to method BII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 22 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.16 (br. s, 1 H, NH), 9.36 (dd, *J* = 1.3, 0.6 Hz, 1 H), 8.22 (d, *J* = 8.2 Hz, 1 H), 8.15–8.12 (m, 2 H), 7.79–7.76 (m, 2 H), 7.68–7.64 (m, 2 H), 7.51–7.47 (m, 2 H), 7.46–7.40 (m, 1 H), 7.38 (ddd, *J* = 8.2, 1.3, 0.6 Hz, 1 H), 4.04 (s, 3 H, OCH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.2, 165.6, 145.1, 142.3, 139.9, 136.1 (q, J_{CF} = 32.0 Hz), 132.9, 131.6, 129.0, 128.2, 127.9, 127.6, 127.2, 123.4 (q, J_{CF} = 273.1 Hz), 118.9 (q, J_{CF} = 3.7 Hz), 117.5 (q, J_{CF} = 4.2 Hz), 53.0 (OCH_3) ppm.
LC/MS: m/z = 400 [M + H^+], 441 [M + H^+ CH_3CN], 799 [2M + H^+]; t_R = 16.51 min; 100.0 % pure (UV).

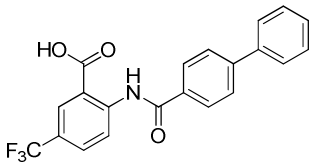


2-([1,1'-biphenyl]-4-ylcarboxamido)-4-(trifluoromethyl)benzoic acid (27) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 84 %. Mp: 245–246 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.35 (br. s, 1 H, NH), 9.10 (d, *J* = 1.6 Hz, 1 H), 8.26 (d, *J* = 8.2 Hz, 1 H), 8.08–8.04 (m, 2 H), 7.95–7.89 (m, 2 H), 7.81–7.75 (m, 2 H), 7.57 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.55–7.49 (m, 2 H), 7.47–7.41 (m, 1 H) ppm.

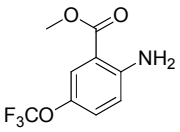
^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.0, 164.8, 144.0, 141.4, 138.8, 133.4 (q, J_{CF} = 32.0 Hz), 132.7, 132.5, 129.1, 128.4, 127.8, 127.2, 127.0, 122.9 (q, J_{CF} = 273.1 Hz), 119.2 (q, J_{CF} = 3.7 Hz), 116.3 (q, J_{CF} = 3.7 Hz) ppm.
LC/MS: m/z = 386 [M + H$^+$], 427 [M + H$^+$ CH_3CN], 771 [2M + H$^+$]; t_R = 14.11 min; 100.0 % pure (UV).



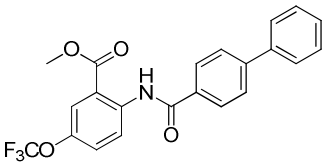
methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-5-(trifluoromethyl)benzoate (28a) was prepared according to method BII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH followed by CC (*n*-hexane/EtOAc 9:1) to provide the pure compound; yield: 42 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.24 (br. s, 1 H, NH), 9.13 (d, J = 8.8 Hz, 1 H), 8.38 (d, J = 2.0 Hz, 1 H), 8.15–8.12 (m, 2 H), 7.85 (dd, J = 8.8, 2.0 Hz, 1 H), 7.79–7.76 (m, 2 H), 7.68–7.65 (m, 2 H), 7.52–7.48 (m, 2 H), 7.45–7.40 (m, 1 H), 4.04 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.2, 165.6, 145.2, 144.6, 139.8, 132.9, 131.4 (q, J_{CF} = 3.6 Hz), 129.0, 128.3 (q, J_{CF} = 3.6 Hz), 128.2, 128.0, 127.6, 127.2, 124.5 (q, J_{CF} = 33.9 Hz), 120.6, 122.6 (q, J_{CF} = 271.3 Hz), 114.9, 52.9 (OCH_3) ppm.
LC/MS: m/z = 400 [M + H$^+$], 441 [M + H$^+$ CH_3CN], 799 [2M + H$^+$]; t_R = 16.70 min; 95.1 % pure (UV).



2-([1,1'-biphenyl]-4-ylcarboxamido)-5-(trifluoromethyl)benzoic acid (28) was prepared according to method C. For purification the remaining solid was washed with MeOH and CH_2Cl_2 to provide the pure compound; yield: 49 %. Mp: 265–266 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.41 (br. s, 1 H, NH), 8.93 (d, J = 8.8 Hz, 1 H), 8.28 (d, J = 2.0 Hz, 1 H), 8.06–8.03 (m, 2 H), 8.01 (dd, J = 8.8, 2.0 Hz, 1 H), 7.92–7.87 (m, 2 H), 7.78–7.73 (m, 2 H), 7.54–7.47 (m, 2 H), 7.46–7.40 (m, 1 H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6) δ = 168.9, 164.7, 144.3, 144.0, 138.8, 132.7, 130.9 (q, J_{CF} = 3.7 Hz) 129.1, 128.4, 127.9 (q, J_{CF} = 3.7 Hz), 127.8, 127.2, 127.0, 123.8 (q, J_{CF} = 271.3 Hz), 122.8 (q, J_{CF} = 33.0 Hz) 120.4, 116.8 ppm.
LC/MS: m/z = 386 [M + H$^+$], 771 [2M + H$^+$]; t_R = 14.60 min; 99.8 % pure (UV).

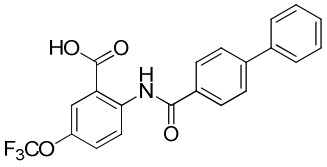


methyl 2-amino-5-(trifluoromethoxy)benzoate (29b) was prepared according to method A. The product was purified by CC (*n*-hexane/EtOAc 1:1); yield: 26 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.77–7.68 (m, 1 H), 7.20–7.11 (m, 1 H), 6.65 (d, J = 9.5 Hz, 1 H), 5.80 (br. s, 2 H, NH_2), 3.89 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 167.6, 149.2, 138.8 (q, J_{CF} = 1.8 Hz), 127.9, 123.8, 120.7 (q, J_{CF} = 256.0 Hz), 117.5, 110.5, 51.8 (OCH_3) ppm.
LC/MS: m/z = 236 [M + H$^+$], 277 [M + H$^+$ CH_3CN]; t_R = 12.13 min; 96.0 % pure (UV).

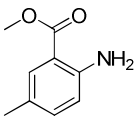


methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-5-(trifluoromethoxy)benzoate (29a) was prepared according to method BIII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was

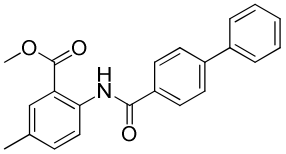
washed with MeOH to provide the pure compound; yield: 86 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.06 (br. s, 1 H, NH), 9.05 (d, *J* = 9.1 Hz, 1 H), 8.16–8.09 (m, 2 H), 7.96 (d, *J* = 2.5 Hz, 1 H), 7.81–7.74 (m, 2 H), 7.68–7.64 (m, 2 H), 7.51–7.48 (m, 3 H), 7.44–7.40 (m, 1 H), 4.02 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.0, 165.5, 145.0, 143.4 (q, J_{CF} = 1.8 Hz), 140.7, 139.9, 133.1, 130.7, 129.0, 128.1, 127.9, 127.5, 127.2, 123.4, 122.0, 120.5 (q, J_{CF} = 257.5 Hz), 116.1, 52.9 (OCH_3) ppm.
LC/MS: m/z = 416 [M + H^+], 457 [M + H^+ CH_3CN], 831 [2M + H^+]; t_R = 16.64 min; 100.0 % pure (UV).



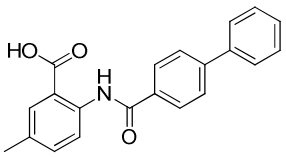
2-([1,1'-biphenyl]-4-ylcarboxamido)-5-(trifluoromethoxy)benzoic acid (29) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 98 %. Mp: 245–246 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.17 (br. s, 1 H, NH), 8.81 (d, *J* = 9.1 Hz, 1 H), 8.06–8.03 (m, 2 H), 7.92 (dd, *J* = 3.0, 0.8 Hz, 1 H), 7.91–7.88 (m, 2 H), 7.78–7.74 (m, 2 H), 7.74–7.68 (m, 1 H), 7.53–7.49 (m, 2 H), 7.46–7.41 (m, 1 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 168.6, 164.5, 143.9, 142.7 (q, J_{CF} = 1.8 Hz), 140.1, 138.8, 132.9, 129.1, 128.3, 127.8, 127.2, 127.0, 127.0, 123.3, 121.9, 118.6, 120.0 (q, J_{CF} = 256.0 Hz) ppm.
LC/MS: m/z = 402 [M + H^+], 803 [2M + H^+]; t_R = 14.58 min; 100.0 % pure (UV).



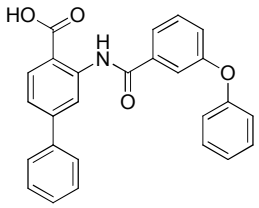
methyl 2-amino-5-methylbenzoate (30b) was prepared according to method A. Sufficient purity was achieved without further purification; yield: 82 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.67 (d, *J* = 2.2 Hz, 1 H), 7.10 (dd, *J* = 8.2, 2.2 Hz, 1 H), 6.60 (d, *J* = 8.2 Hz, 1 H), 5.55 (br. s, 2 H, NH_2), 3.88 (s, 3 H, OCH_3), 2.24 (s, 3 H, CH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.6, 148.3, 135.2, 130.8, 125.4, 116.8, 110.7, 51.4 (OCH_3), 20.2 (CH_3) ppm.
LC/MS: m/z = no ionization; t_R = 8.48 min; 98.0 % pure (UV).



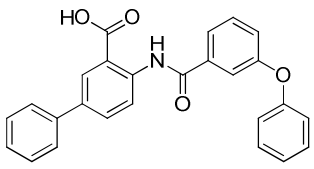
methyl 2-([1,1'-biphenyl]-4-ylcarboxamido)-5-methylbenzoate (30a) was prepared according to method BII. For purification the solvent was evaporated and the remaining solid was suspended in MeOH. After filtration the precipitate was washed with MeOH to provide the pure compound; yield: 85 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.00 (br. s, 1 H, NH), 8.86 (d, *J* = 8.8 Hz, 1 H), 8.15–8.12 (m, 2 H), 7.91 (d, *J* = 2.2 Hz, 1 H), 7.77–7.75 (m, 2 H), 7.68–7.65 (m, 2 H), 7.51–7.47 (m, 2 H), 7.44 (dd, *J* = 8.8, 2.2 Hz, 1 H), 7.43–7.39 (m, 1 H), 3.98 (s, 3 H, OCH_3), 2.38 (s, 3 H, CH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.1, 165.2, 144.5, 140.1, 139.5, 135.6, 133.7, 132.1, 131.0, 128.9, 128.0, 127.9, 127.4, 127.2, 120.4, 115.0, 52.4 (OCH_3), 20.7 (CH_3) ppm.
LC/MS: m/z = 346 [M + H^+], 691 [2M + H^+]; t_R = 16.44 min; 99.1 % pure (UV).



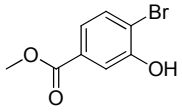
2-([1,1'-biphenyl]-4-ylcarboxamido)-5-methylbenzoic acid (30) was prepared according to method C. Sufficient purity was achieved without further purification; yield: 95 %. Mp: 246–248 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.13 (br. s, 1 H, NH), 8.63 (d, J = 8.8 Hz, 1 H), 8.05–8.01 (m, 2 H), 7.90–7.86 (m, 3 H), 7.79–7.74 (m, 2 H), 7.53–7.47 (m, 3 H), 7.46–7.40 (m, 1 H), 2.33 (s, 3 H, CH_3) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 170.1, 164.1, 143.6, 138.9, 138.8, 134.8, 133.3, 132.1, 131.3, 129.1, 128.3, 127.6, 127.1, 126.9, 119.9, 116.4, 20.2 (CH_3) ppm.
LC/MS: m/z = 332 [M + H$^+$], 663 [2M + H$^+$]; t_R = 13.78 min; 100.0 % pure (UV).



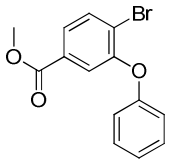
3-(3-phenoxybenzamido)-[1,1'-biphenyl]-4-carboxylic acid (31) was prepared according to method D. The product was purified by CC (*n*-hexane/EtOAc 8:2); yield: 91 %. Mp: 189–190 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.26 (br. s, 1 H, NH), 9.02 (d, J = 1.9 Hz, 1 H), 8.12 (d, J = 8.2 Hz, 1 H), 7.74–7.71 (m, 3 H), 7.62 (d, J = 7.9, 7.9 Hz, 1 H), 7.55–7.50 (m, 4 H), 7.47–7.42 (m, 3 H), 7.29 (ddd, J = 8.2, 2.5, 0.9 Hz, 1 H), 7.21 (tt, J = 7.4, 1.1 Hz, 1 H), 7.14–7.08 (m, 2 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.9, 164.1, 157.4, 155.9, 145.7, 141.4, 138.9, 136.4, 131.9, 130.8, 130.3, 129.2, 128.6, 126.9, 124.1, 122.1, 121.5, 121.3, 119.2, 117.9, 116.8, 115.4 ppm.
LC/MS: m/z = 410 [M + H$^+$], 819 [2M + H$^+$]; t_R = 15.23 min; 99.1 % pure (UV).



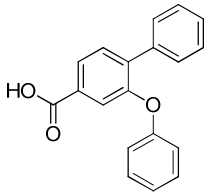
4-(3-phenoxybenzamido)-[1,1'-biphenyl]-3-carboxylic acid (32) was prepared according to method D. The product was purified by preparative TLC (*n*-hexane/EtOAc 1:1 + 7 drops formic acid per 10 mL solvent) and washed with CH_2Cl_2; yield: 42 %. Mp: 207–208 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.20 (br. s, 1 H, NH), 8.75 (d, *J* = 8.8 Hz, 1 H), 8.29 (d, *J* = 2.5 Hz, 1 H), 7.98 (dd, *J* = 8.8, 2.5 Hz, 1 H), 7.78–7.72 (m, 1 H), 7.71–7.66 (m, 2 H), 7.61 (dd, *J* = 7.9, 7.9 Hz, 1 H), 7.57–7.53 (m, 1 H), 7.53–7.42 (m, 4 H), 7.41–7.34 (m, 1 H), 7.32–7.25 (m, 1 H), 7.24–7.17 (m, 1 H), 7.16–7.04 (m, 2 H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 169.9, 163.9, 157.3, 156.0, 140.1, 138.7, 136.4, 134.7, 132.3, 130.8, 130.3, 129.1, 128.9, 127.6, 126.4, 124.1, 122.1, 121.6, 120.6, 119.1, 117.3, 116.9 ppm.
LC/MS: m/z = 410 [M + H$^+$], 451 [M + H$^+$ CH_3CN], 819 [2M + H$^+$]; t_R = 14.61 min; 100.0 % pure (UV).



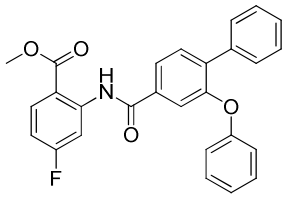
methyl 4-bromo-3-hydroxybenzoate (33f). To 3-hydroxybenzoate (1 equiv) in acetic acid was added bromine (1 equiv) dropwise. The reaction mixture was stirred at room temperature for 18 h, water was added and the mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The product was purified by CC (*n*-hexane/EtOAc 92.5:7.5) followed by crystallization from EtOAc/n-hexane (in fridge overnight); yield: 48 %. ^{1}H NMR (500 MHz, METHANOL-d_4) δ = 11.51 (br. s, 1 H, OH), 8.43 (d, *J* = 8.2 Hz, 1 H), 8.33 (d, *J* = 2.0 Hz, 1 H), 8.11 (dd, *J* = 8.2, 2.0 Hz, 1 H), 4.64 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, METHANOL-d_4) δ = 175.3, 163.9, 142.9, 139.7, 130.5, 126.0, 124.7, 61.9 (OCH_3) ppm.
LC/MS: m/z = no ionization; t_R = 9.28 min; 97.8 % pure (UV).



methyl 4-bromo-3-phenoxybenzoate (33e). A mixture of methyl 4-bromo-3-hydroxybenzoate (**33f**, 1 equiv), phenylboronic acid (2 equiv), copper acetate (1 equiv), triethylamine (5 equiv) and 3 Å molecular sieves in CH_2Cl_2 was stirred at room temperature for 72 h under a N_2 atmosphere. After filtration over celite the solvent was evaporated. Purification by CC (*n*-hexane/EtOAc 8:2) provided the pure compound; yield: 37 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.72 (d, *J* = 8.2 Hz, 1 H), 7.68 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.59 (d, *J* = 1.9 Hz, 1 H), 7.39–7.36 (m, 2 H), 7.16 (tt, *J* = 7.4, 1.1 Hz, 1 H), 7.02–6.97 (m, 2 H), 3.87 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, Acetone-d_6) δ = 148.0, 138.6, 136.5, 116.2, 113.2, 112.1, 107.5, 106.2, 102.2, 102.0, 100.5, 33.8 (OCH_3) ppm.
LC/MS: m/z = no ionization; t_R = 13.54 min; 97.5 % pure (UV).



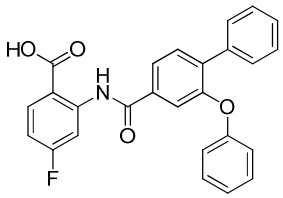
2-phenoxy-[1,1'-biphenyl]-4-carboxylic acid (33d) was prepared according to method D. The product was purified by CC (*n*-hexane/EtOAc 7:3); yield: 66 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.94 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.72 (d, *J* = 1.6 Hz, 1 H), 7.63–7.56 (m, 3 H), 7.43–7.39 (m, 2 H), 7.38–7.35 (m, 1 H), 7.34–7.29 (m, 2 H), 7.09 (tt, *J* = 7.4, 1.1 Hz, 1 H), 7.00–6.94 (m, 2 H) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 171.1, 157.1, 153.9, 139.0, 136.7, 131.4, 129.8, 129.6, 129.2, 128.3, 128.0, 125.5, 123.3, 121.2, 118.5 ppm.
LC/MS: m/z = no ionization; t_R = 12.33 min; 97.6 % pure (UV).



methyl 4-fluoro-2-(2-phenoxy-[1,1'-biphenyl]-4-ylcarboxamido)benzoate (33a) was prepared according to method BIII. The product was purified by CC (*n*-hexane/EtOAc 9:1); yield: 65 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.19 (br. s, 1 H, NH), 8.72 (dd, *J* = 12.1, 2.6 Hz, 1 H), 8.09 (dd, *J* = 9.0, 6.5 Hz, 1 H), 7.84 (dd, *J* = 8.0, 1.9 Hz, 1 H), 7.70 (d, *J* = 1.9 Hz, 1 H), 7.67–7.60 (m, 3 H), 7.44–7.32 (m, 5 H), 7.11–7.08 (m, 1 H), 7.06–7.01 (m, 2 H), 6.81 (ddd, *J* = 9.0, 7.5, 2.6 Hz, 1 H), 3.94 (s, 3 H, OCH_3) ppm.

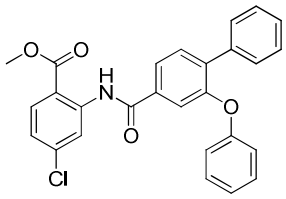
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.3, 166.4 (d, J_{CF} = 253.0 Hz), 164.9, 156.9, 154.5, 143.9 (d, J_{CF} = 13.7 Hz), 137.0, 136.8, 134.9, 133.2 (d, J_{CF} = 10.1 Hz), 131.7, 129.8, 129.2, 128.3, 127.9, 123.4, 122.0, 118.8, 118.8, 111.3 (d, J_{CF} = 2.7 Hz), 110.0 (d, J_{CF} = 22.0 Hz), 107.5 (d, J_{CF} = 28.4 Hz), 52.5 (OCH_3) ppm.

LC/MS: m/z = 442 [M + H^+], 483 [M + H^+ CH_3CN], 883 [2M + H^+]; t_R = 17.02 min; 89.0 % pure (UV).

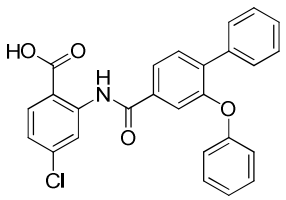


4-fluoro-2-(2-phenoxy-[1,1'-biphenyl]-4-ylcarboxamido)benzoic acid (33) was prepared according to method C. For purification the remaining solid was washed with MeOH to provide the pure compound; yield: 77 %. Mp: 223–227 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.45 (br. s, 1 H, NH), 8.50 (dd, *J* = 12.1, 2.6 Hz, 1 H), 8.14–8.09 (m, 1 H), 7.84–7.80 (m, 1 H), 7.73 (d, *J* = 8.2 Hz, 1 H), 7.62–7.59 (m, 2 H), 7.52 (d, *J* = 1.9 Hz, 1 H), 7.46–7.42 (m, 2 H), 7.41–7.34 (m, 3 H), 7.12 (tt, *J* = 7.3, 1.2 Hz, 1 H), 7.07–7.03 (m, 1 H), 7.03–6.99 (m, 2 H) ppm.

^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.4, 165.0 (d, J = 249.0 Hz), 163.9, 156.5, 153.5, 143.1 (d, J = 12.8 Hz), 136.7, 136.1, 134.7, 134.0 (d, J_{CF} = 11.0 Hz), 131.9, 130.2, 129.0, 128.4, 128.0, 123.5, 122.3, 118.5, 118.2, 113.0 (d, J_{CF} = 2.8 Hz), 110.1 (d, J_{CF} = 22.0 Hz), 106.4 (d, J_{CF} = 27.0 Hz) ppm.
LC/MS: m/z = 428 [M + H$^+$], 469 [M + H$^+$ CH_3CN], 855 [2M + H$^+$]; t_R = 15.13 min; 97.2 % pure (UV).



methyl 4-chloro-2-(2-phenoxy-[1,1'-biphenyl]-4-ylcarboxamido)benzoate (34a) was prepared according to method BIII. The product was purified by CC (*n*-hexane/EtOAc 9:1); yield: 22 %. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 12.08 (br. s, 1 H, NH), 9.01 (d, J = 2.2 Hz, 1 H), 8.00 (d, J = 8.5 Hz, 1 H), 7.83 (dd, J = 7.9, 1.9 Hz, 1 H), 7.68 (d, J = 1.9 Hz, 1 H), 7.64–7.60 (m, 3 H), 7.44–7.40 (m, 2 H), 7.38–7.31 (m, 3 H), 7.11–7.07 (m, 2 H), 7.05–7.01 (m, 2 H), 3.95 (s, 3 H, OCH_3) ppm.
^{13}C NMR (125 MHz, $CDCl_3$) δ = 168.4, 164.9, 156.9, 154.6, 142.6, 141.2, 137.0, 136.8, 134.9, 132.0, 131.7, 129.9, 129.2, 128.3, 127.9, 123.4, 123.0, 121.9, 120.3, 118.9, 118.7, 113.3, 52.6 (OCH_3) ppm.
LC/MS: m/z = 458 and 460 [M + H$^+$], 915 and 917 [2M + H$^+$]; t_R = 17.56 min; 97.5 % pure (UV).



4-chloro-2-(2-phenoxy-[1,1'-biphenyl]-4-ylcarboxamido)benzoic acid (34) was prepared according to method C. For purification the remaining solid was washed with MeOH to provide the pure compound; yield: 92 %. Mp: 230–234 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ = 12.31 (br. s, 1 H, OCH_3), 8.75 (d, J = 2.2 Hz, 1 H), 8.04 (d, J = 8.5 Hz, 1 H), 7.82 (dd, J = 7.9, 1.9 Hz, 1 H), 7.73 (d, J = 7.9 Hz, 1 H), 7.63–7.59 (m, 2 H), 7.52 (d, J = 1.9 Hz, 1 H), 7.46–7.42 (m, 2 H), 7.40–7.34 (m, 3 H), 7.27 (dd, J = 8.5, 2.2 Hz, 1 H), 7.16–7.09 (m, 1 H), 7.03–6.99 (m, 2 H) ppm.
^{13}C NMR (125 MHz, DMSO-d_6) δ = 169.3, 163.8, 156.5, 153.5, 141.9, 138.6, 136.7, 136.1, 134.7, 132.9, 131.9, 130.2, 129.0, 128.4, 128.0, 123.5, 123.0, 122.4, 119.3, 118.5, 118.2, 115.4 ppm.
LC/MS: m/z = 444 [M + H^+], 485 [M + H^+ CH_3CN], 887 [2M + H^+]; t_R = 15.37 min; 97.3 % pure (UV).

c) Computational Chemistry

Pharmacophore modelling and virtual screening. The following compounds **I–VII** were retrieved from literature[1,6–9]:

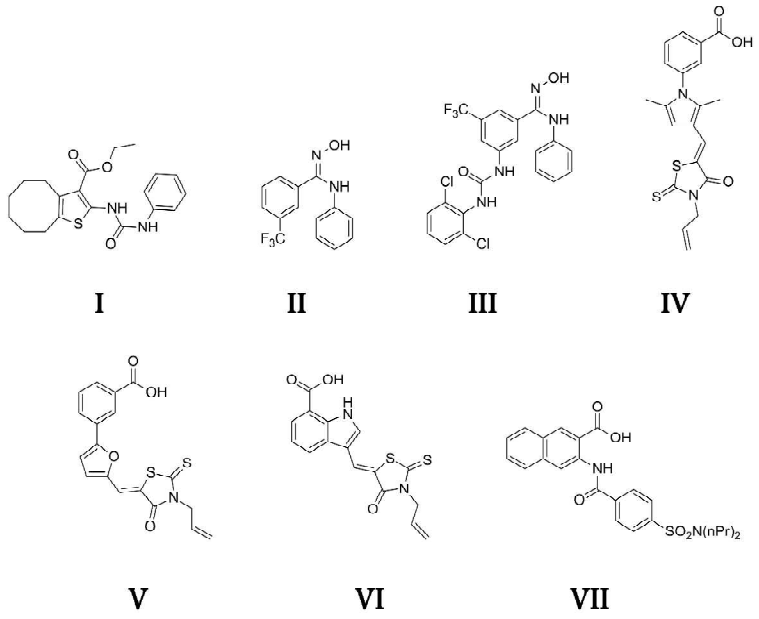


Figure S1. Compounds used for the flexible alignment

I: Published by Arhin et al.[6] ("compound 1") as inhibitor of *S. aureus* RNAP. It was shown that these compounds do not bind to the Rifamycin binding site, but the exact mode of action is not known.

II and **III**: Published by Artsimovitch et al.[7] ("CBR703 and CBR9379") as inhibitors of *E. coli* RNAP. They bind to a surface exposed groove at the junction of the β'-bridge helix and the β-subunit.

IV, **V** and **VI**: Published by André et al.[8] ("SB8 and SB2") and Villain-Guillot[9] ("compound 11b") as inhibitors of *E. coli* RNAP. The mode of action of these compounds is the prevention of the protein-protein interaction between σ^{70} and the RNAP core enzyme.

VII: Published by Larsen et al.[1] ("compound 1") as inhibitor of transcription/ translation in *S. aureus*. Resynthesis and testing in our *E. coli* RNAP *in vitro* inhibition assay revealed **VII** as a potent inhibitor of *E. coli* RNAP (IC_{50} 42 µM).

Compounds **I–VII** (Fig. S1) were aligned using the flexible alignment module of MOE (*Molecular Operating Environment*)[10] with the stochastic search option turned on. We modified the default flexible alignment settings; the Aromaticity and CO_2-type centroid weights were set at 2 – strikingly these two chemical moieties are present in most of the initial seven template compounds. Weights on volume and acceptor/donor projection features were switched on. Further, we set the configuration limit to 100 and conjugate gradient minimization steps to 1000. The alignment with the best similarity score was retained and refined within MOE.

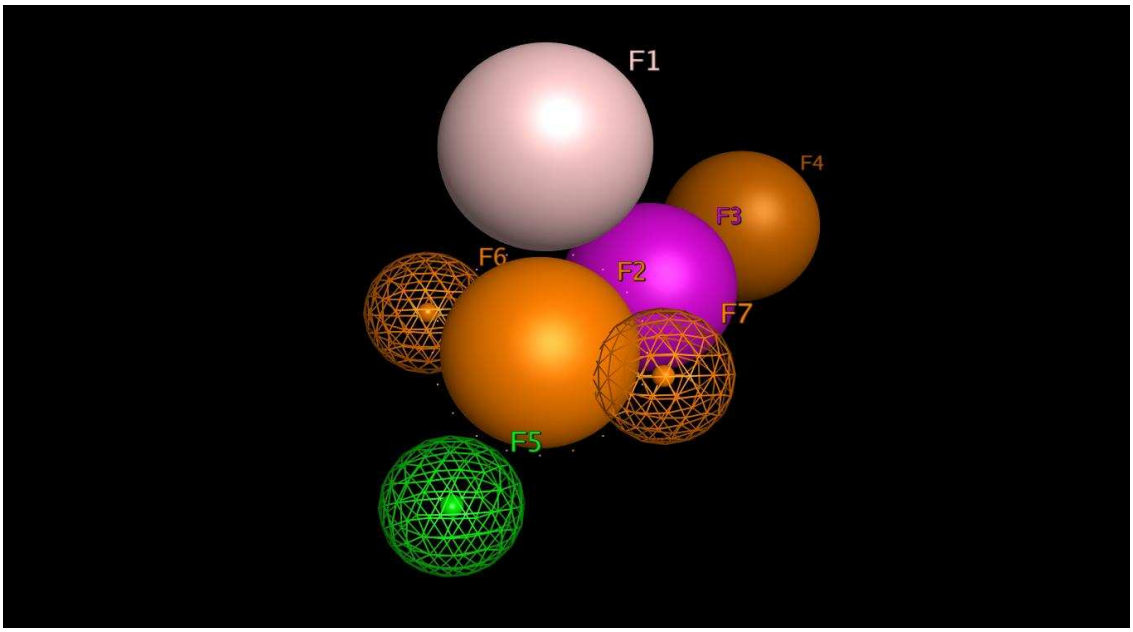


Figure S2. Final pharmacophore model used for virtual screening

This alignment was used to identify common features within the seven superimposed ligands via the Pharmacophore Consensus utility (tolerance of 1.2 and threshold value of 50% (ligands that match one feature)). The resulting pharmacophore model (consisting of 9 features) was manually refined and reduced to 7 features with 6 needed partial matches. The final pharmacophore model (Fig. S2) consisted of following features (F1-F4 - feature radius of 1.5 Å, F5-F7 - feature radius of 1 Å):

Feature F1 (rose): O2|Ani|N[O,o]|(O(C=O)C (this includes CO_2-like centroids (both acids and ester), anionic atoms as well as N.sp^2-O moieties (i.e. oximes, nitro)

Feature F2 (orange): Aro (all aromatic systems)

Feature F3 (violet): HBD/HBA/Aro (this feature can be matched by either a hydrogen-bond donor or acceptor or by an aromatic system)

Feature F4: Aro/Hyd/pi (in this position aromatic, hydrophobic or planar-conjugated pi systems are requested)

Feature F5 (green): Hydrophobic

Features F6+F7 (hatched orange): Aromatic ring projections

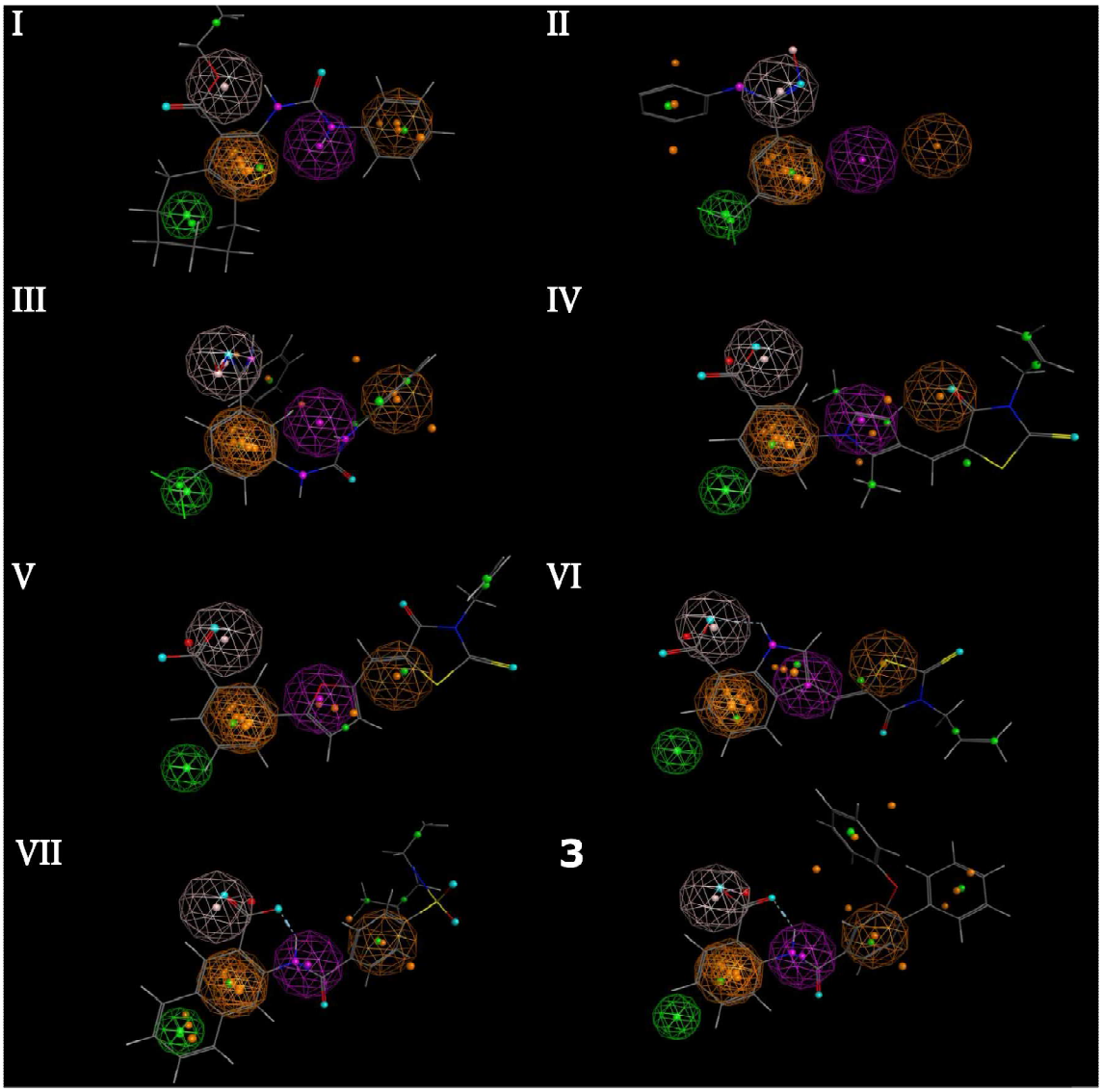


Figure S3. Overlay of the resulting pharmacophore model with inhibitors I–VII and 3

A virtual library was built including approximately 2000 synthetic *in-house* compounds that had been developed as aromatase, CYP17, CYP11B1, CYP11B2, thromboxane A2, 5α reductase, 17β HSD1, 17β HSD2, FabH and PqsD inhibitors. For each compound a conformational search was performed using the default parameters of the conformational search module of MOE2010. Conformers were energy minimized using MMFF94xs forcefield and the Generalized Born implicit solvent model. The obtained multiple-conformer database was now used in the pharmacophore search.

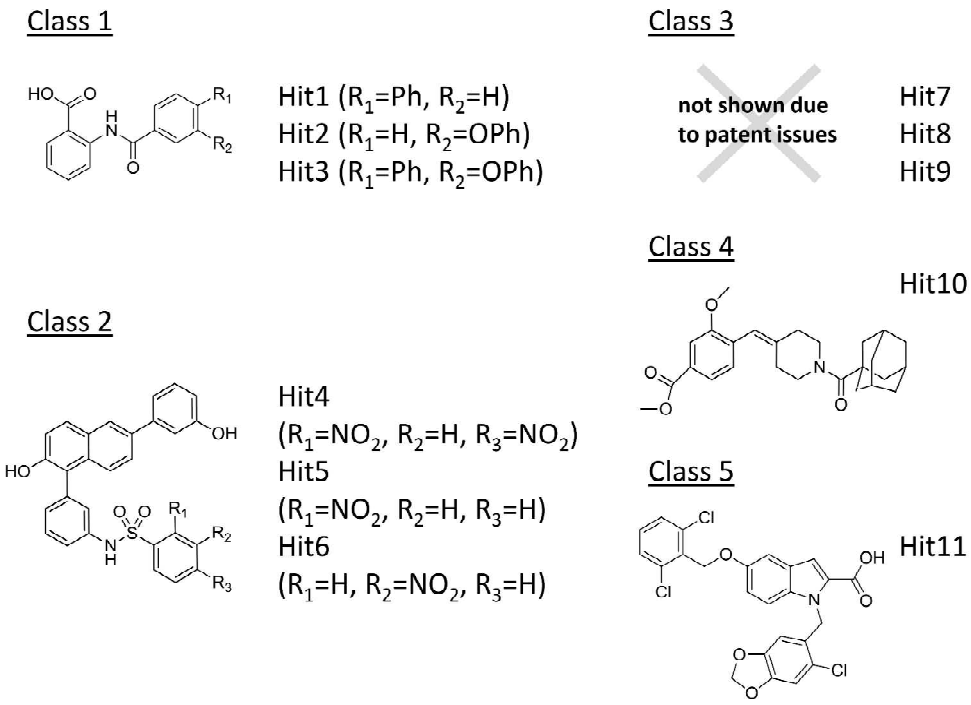


Figure S4. Experimentally validated virtual hit compounds

In total 64 hits were found matching at least the four core features and the two aromatic projections, while the presence of the accessory feature was not mandatory. All hit compounds were tested on inhibitory potency, for eleven of them (comprising five different structural classes) an inhibition >20% was measured at 200 µM (Fig. S4).

Based on the activities of **1**□**4**, the seven-feature pharmacophore model (Fig. S2) was extended by two additional features (F8 and F9):

Features F8+F9 (hatched yellow): Aro/Hyd (feature radius of 1.5 Å)

Using this model (Fig. S5) in further screenings, a compound will be defined as a hit if, beside the 4 core features, at least one of the new accessory features is present.

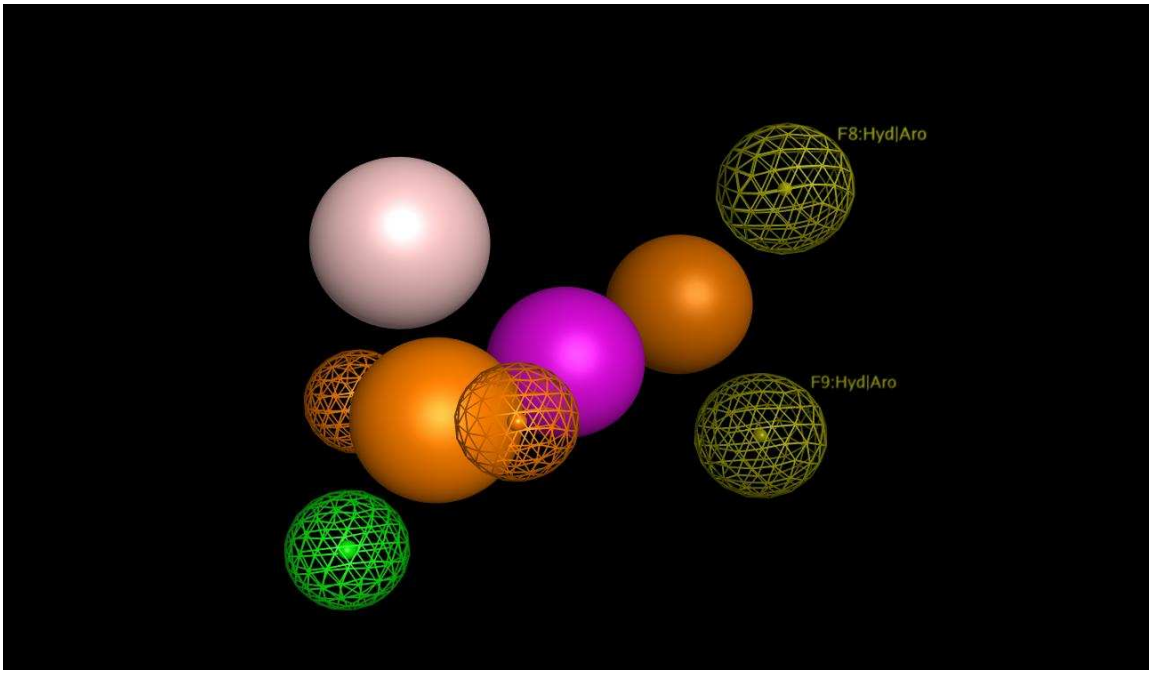


Figure S5. Extended pharmacophore model

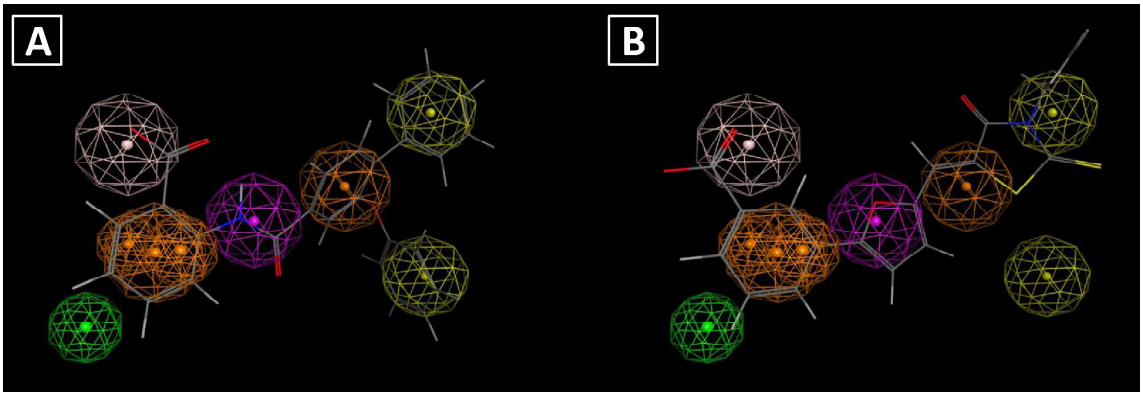


Figure S6. Overlay of the extended pharmacophore model with
A) most potent hit compound 3
B) described inhibitor V

e) References

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