Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Gemmacin B: Bringing Diversity back into Focus

Supporting Information

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General Experimental

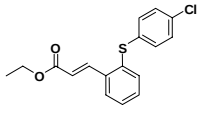
Except as otherwise indicated, reactions were carried out under argon with dry, freshly distilled solvents. Dichloromethane was distilled from calcium hydride. All other reagents were purified in accordance with the instructions in '*Purification of Laboratory Chemicals*'[1] or used as obtained from commercial sources.

Yields refer to chromatographically and spectroscopically pure compounds. All reactions were monitored by thin layer chromatography using glass plates precoated with Merck silica gel 60 F_{254} or aluminum oxide 60 F_{254}. Visualization was by the quenching of UV fluorescence (λ_{max} = 254 nm) or by staining with ceric ammonium molybdate or potassium permanganate or Dragendorff's reagent (0.08% w/v bismuth subnitrate and 2% w/v KI in 3 M aq. AcOH). Retention factors (R_f) are quoted to 0.01. Melting points were obtained using a Mel-Temp II melting point apparatus and are uncorrected. Infrared spectra were recorded neat on a diamond/ZeSe plate using a Perkin-Elmer Spectrum One FT-IR Universal ATR sampling accessory spectrometer with internal referencing. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and the following abbreviations are used: w, weak; m, medium; s, strong; br, broad. Proton magnetic resonance spectra were recorded on Bruker Ultrashield 400 or 500. Proton assignments are supported by ^1H–^1H spectra where necessary. Chemical shifts (δ_H) are quoted in ppm and are referenced to the residual non-deuterated solvent peak. Coupling constants (J) are reported in Hertz to the nearest 0.5 Hz. Data are reported as follows: chemical shift, integration, multiplicity [br, broad; s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; sept, septet; m, multiplet; or as a combination of these (*e.g.* dd, dt, *etc.*)], coupling constant(s) and assignment. Diastereotopic protons are assigned as X and X′, where the ′ indicates the lower field proton. Carbon magnetic resonance spectra were recorded on Bruker Ultrashield 500 spectrometers. Carbon spectra assignments are supported by DEPT editing and where necessary ^{13}C–^1H (HMQC) correlations. Chemical shifts (δ_C) are quoted in ppm to the nearest 0.01 ppm, and are referenced to the deuterated solvent. Fluorine magnetic resonance spectra (^{19}F) were recorded on a DPX 400 MHz spectrometer. Chemical shifts (δ_P) are quoted in ppm to the nearest 0.01 ppm and are referenced to CF_3CH_2OH (external).

Compounds **14**, **15**, and **5a-5c** are not shown in the article. They are included here for completeness. All compounds not included have been reported previously.

Synthesis of the scaffold 4

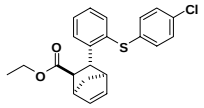
3-[2-(4-Chloro-phenylsulfanyl)-phenyl]acrylic acid ethyl ester (2)



To a solution of triethylphosphonacetate **1** (4 ml, 18.8 mol), lithium bromide (1.6 g, 18.8 mol) and DBU (3.7 ml, 18.8 ml) in THF (40 ml) under nitrogen was added *N,N*-2-(4-chlorophenylthio)benzaldehyde (4.68 g, 18.8 mmol). The solution was stirred for 3 hours until complete by LCMS, and then saturated ammonium chloride solution was added. The reaction was extracted with ethyl acetate and the organic layer washed with brine, dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to give the title compound as a yellow solid (4.68g, 78 %).

R_f 0.41 (SiO_2, 3:1 40:60 petrol : ether); ν_{max} (nujol mull) 2923, 2854, 1712 (C=O), 1632, 1463, 1316, 1183 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.20 (1H, d, *J* 16.0, C***H***CHC(O)OEt), 7.62 (1H, dd, *J* 8.0, 2.5, ArH), 7.39-7.28 (3H, m, ArH), 7.23 (2H, d, *J* 8.5, ArH), 7.15 (2H, d, *J* 8.5, ArH), 6.35 (1H, d, *J* 16.0, CHC***H***C(O)OEt), 4.24 (2H, q, *J* 7.0, OC***H***$_2$CH$_3$), 1.31 (3H, t, *J* 7.0, OCH$_2$C***H***$_3$), δ_C (100 MHz, $CDCl_3$) 166.54, 141.70, 136.40, 135.44, 134.49, 133.80, 132.97, 131.58, 130.57, 129.38, 128.45, 127.41, 120.70, 60.59, 14.29; HRMS $(M+H)^+$ found 319.0573, $C_{17}H_{16}O_2SCl$ requires 319.0560, Δ ppm +4.1; mp 79-82ºC (3:1 40:60 petrol : ether)

(1*S, 2*R**, 3*R**, 4*R**)-3-[2-(4-Chloro-phenylsulfanyl)-phenyl]-bi-cyclo[2.2.1]hept-5-ene-2-carboxlic acid ethyl ester (3)**

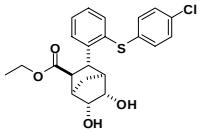


To a solution of **2** (4.62 g, 14.5 mmol) in CH_2Cl_2 (100 ml) at -78 ºC under nitrogen was added dimethylaluminium chloride (1M solution, 14.5 ml, 14.5 mmol) and cyclopentadiene (11.9 ml, 145 mmol). The reaction was stirred for 1 hour then allowed to warm to room temperature and stirred for 48 hours until complete by LCMS. The reaction was quenched with saturated ammonium chloride solution (150 ml), the organic layer removed and washed with brine. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield the title compound as a yellow oil (3.48 g, 62 %).

R_f 0.47 (SiO_2, 4:1 40:60 petrol: ether); ν_{max} (neat) 3057, 2977, 1730, 1474, 1174, 1091 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.41 (1H, d, *J* 8.0, ArH), 7.34-7.29 (2H, m, ArH), 7.25-7.23 (2H, m, ArH), 7.19-7.15 (3H, m, ArH), 6.38 (1H, dd, *J* 5.5, 3.0, ArCHCHC***H***CH), 6.11 (1H, dd, *J* 5.4, 3.0, ArCHCHCHC***H***), 4.15-3.98 (2H, m, OC***H***$_2$CH$_3$), 3.54 (1H, dd, *J* 5.0, 1.5, ArC***H***), 3.32 (1H, s, EtOC(O)CHC***H***), 3.15 (1H, dd, *J* 5.0, 3.5, EtOC(O)C***H***), 2.78 (1H, d, *J* 1.5, ArCHC***H***), 1.79 (1H, d, *J* 9.0, CHC***H***HCH) 1.52 (1H, ddd, *J* 9.0, 3.5, 1.5, CHCH***H***CH), 1.20 (3H, t, *J* 7.0, OCH$_2$C***H***$_3$); δ_C (120 MHz, $CDCl_3$) 173.97, 145.00, 138.66, 135.19, 134.94, 134.29, 133.74, 132.54, 131.47, 129.19,128.09, 127.05, 126.61, 60.32, 50.13, 49.94, 46.55, 46.48, 45.73, 14.23; HRMS $(M+H)^+$

found 385.1041, $C_{22}H_{22}O_2SCl$ requires 385.1029, Δ ppm +3.1.

(1*S, 2*R**, 3*R**, 4*R**, 5*S**, 6*R**)-3-[2-(4-Chloro-phenylsulfanyl)-phenyl]-5,6-dihydroxy-bi-cyclo[2.2.1]heptene-2-carboxlic acid ethyl ester (4)**



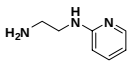
To a solution of **3** (3.2 g, 8.31 mmol) in acetone:water (10:1) was added NMO (1.95 g, 16.63 mmol) and osmium tetroxide (2.5 mol% in pentane). The reaction was stirred overnight until complete by TLC then quenched with saturated sodium sulfite solution. The aqueous layer was extracted with ethyl acetate and the organic layer dried ($MgSO_4$) and solvent removed *in vacuo*. The crude product was purified by flash column chromatography to yield the title compound as a pale yellow foam (2.65 g, 76 %).

R_f 0.27 (SiO_2, 4:1 ether: 40:60 petrol); ν_{max} (neat) 3359 (OH), 2976, 1725 (C=O), 1474, 1176, 1091, 1031 cm^{-1}; δ_H (400 Mhz; $CDCl_3$) 7.29-7.22 (5H, m, ArH), 7.18-7.12 (3H, m, ArH), 4.07 (2H, q, *J* 7.0, OC***H***$_2$CH$_3$), 4.03 (1H, d, *J* 6.0, EtOC(O)CHCHC***H***OH), 3.96 (1H, d, *J* 6.0, ArCHCHC***H***OH), 3.54 (1H, d, *J* 5.5, ArC***H***), 2.97 (1H, dd, *J* 6.5, 4.5, EtOC(O)C***H***), 2.75 (2H, br s, OH) 2.59 (1H, d, *J* 2.5, EtOC(O)CHC***H***) 2.13 (1H, s, ArCHC***H***), 1.93 (1H, dd, *J* 11.0, 2.5, CHC***H***HCH), 1.63 (1H, dt, *J* 11.0, 1.5, CHCH***H***'CH), 1.20 (3H, t, *J* 7.0, OCH$_2$C***H***$_3$) δ_C (100 MHz; $CDCl_3$) 172.88, 144.73, 135.02, 134.42, 133.84, 132.67, 131.38, 129.28, 128.17, 127.31, 126.29, 73.82, 70.36, 60.81, 51.40, 49.90, 47.24, 42.67, 31.61, 14.16; HRMS $(M+Na)^+$ found 441.0885, $C_{22}H_{23}O_4SClNa$ requires 441.0903, Δ ppm -4.1.

General procedure for formation of amine:

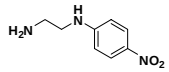
The chloro derivative (1.0 equiv.) was added to ethylenediamine (21.0 equiv) and refluxed overnight. Excess ethylenediamine was removed under reduced pressure, the residue diluted with sodium hydroxide and extracted with chloroform. The solvent was removed *in vacuo* and the residue given charcoal treatment. If necessary the crude product was purified by flash column chromatography.

2-(2-aminoethylamine)pyridine (14)



Title compound isolated as a yellow oil (1.006g, 83 %); R_f 0.18 (SiO_2, 90:8:2 CH_2Cl_2:MeOH:NH_3 (aq)) ν_{max} (neat) 3266, 2933, 2860, 1597, 1508, 1487, 1442, 1417, 1327, 1288, 1149 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.07 (1H, d, *J* 6.0, ArH) 7.39 (1H, ddd, *J* 8.0, 6.0, 2.0, ArH), 6.54 (1H, t, *J* 6.0, ArH) 6.40 (1H, d, *J* 8.0, ArH), 4.76 (1H, br s, NH), 3.36 (2H, q, *J* 6.0, $NH_2CH_2C\boldsymbol{H}_2NH$), 2.93 (2H, t, *J* 6.0, $NH_2C\boldsymbol{H}_2$), 1.35 (2H, br s, NH_2); δ_C (100 MHz; $CDCl_3$) 158.90, 148.06, 137.29, 112.77, 107.10, 44.76, 41.40. Data agrees with literature values.[2]

***N*-(4-nitrophenyl)ethane-1,2-diamine (15)**

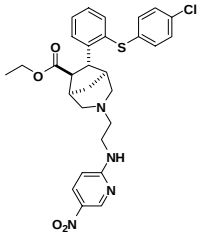


Title compound isolated as a yellow solid (308.4 mg, 38 %); mp 127-130 ºC (CH_2Cl_2:MeOH:NH_3 (aq)); R_f 0.14 (SiO_2, 90:8:2 CH_2Cl_2:MeOH:NH_3 (aq)) ν_{max} (neat) 3298, 2954, 1597 (NO2), 1466, 1284 (NO_2), 1110 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.05 (2H, d, *J* 9.0, ArH), 6.53 (2H, d, *J* 9.0, ArH), 5.09 (1H, br s, NH), 3.24 (2H, q, *J* 5.5, $NH_2CH_2C\boldsymbol{H}_2NH$), 2.99 (1H, t, *J* 6.0, $NH_2C\boldsymbol{H}_2CH_2NH$); δ_C (100 MHz; $CDCl_3$) 153.50, 137.92, 126.42, 111.12, 45.27, 40.53.

General procedure for oxidative cleavage and reductive amination:

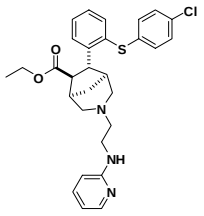
To a solution of **4** (1.0 equiv) in THF:water (1:1) was added sodium periodate (1.8 equiv) at 0 ºC. The reaction was stirred for 3 hours then extracted with chloroform. The organic layer was dried and solvent removed *in vacuo*. The crude product was dissolved in dry DCE and the amine (1.0 equiv) was added. The reaction was stirred at room temperature for 1 hour then sodium triacetoxyborohydride (2.0 equiv) was added and the reaction stirred overnight. The reaction was poured into water and extracted with chloroform.

(1*S, 5*R**, 6*S**, 7*R**)-7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-[2-(5-nitropyridin-2-ylamino-ethyl]-3-aza-bi-cyclo[3.2.1]octane-6-carboxlic acid ethyl ester (5a)**



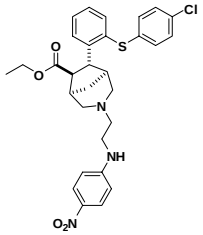
Title compound isolated as a yellow solid (411 mg, 61 %); mp 117-120 °C (ether : 40:60 petrol); R_f 0.43 (SiO_2, 4:1 ether : 40:60 petrol); ν_{max} (neat) 3343, 2939, 1712 (C=O), 1603, 1537, 1462, 1320, 1290, 1187 cm^{-1}; δ_H (500 MHz; $CDCl_3$) 9.01 (1H, d, *J* 2.5, ArH), 7.99 (1H, dd, *J* 9.5, 2.5, ArH), 7.38 (1H, d, *J* 7.5, ArH), 7.33 (2H, d, *J* 4.0, ArH), 7.19-7.15 (1H, m, ArH), 7.10 (2H, d, *J* 6.5, ArH), 6.92 (1H, br s, NH), 6.81 (2H, d, *J* 8.5, ArH), 6.75 (1H, d, *J* 7.0, ArH), 4.54 (1H, d, *J* 6.0, ArC***H***), 4.16-4.05 (2H, m, OC***H***$_2$CH$_3$), 3.49 (1H, m, NCH$_2$C***H***H'NH), 3.32 (1H, m, NCH$_2$CH***H***'NH), 3.27 (1H, t, *J* 6.0, EtOC(O)C***H***), 2.77-2.69 (2H, m, EtOC(O)CHC***H***, ArCHC***H***), 2.57 (1H, d, *J* 10.5, EtOC(O)CHCHC***H***H'N), 2.55-2.45 (2H, m, NC***H***$_2$CH$_2$NH), 2.36 (1H, d, *J* 10.5, EtOC(O)CHCHCH***H***'N), 2.11-2.06 (1H, m, ArCHCHC***H***H'N), 1.92 (1H, d, *J* 10.5, ArCHCHCH***H***'N), 1.87 (1H, s, CHC***H***H'CH), 1.50 (1H, d, *J* 11.5, CHCH***H***'CH), 1.21 (3H, t, *J* 7.0, OCH$_2$C***H***$_3$); δ_C (100 MHz; $CDCl_3$) 174.39, 161.44, 148.70, 146.96, 136.21, 135.24, 135.03, 132.88, 131.79, 131.47, 129.45, 129.18, 129.12, 128.90, 127.11, 126.50, 60.75, 57.16, 56.69, 54.45, 54.03, 45.34, 44.01, 40.46, 37.73, 37.21, 14.35; HRMS $(M+H)^+$ found 567.1829, $C_{29}H_{32}N_4O_4SCl$ requires 567.1833, Δ ppm -0.6.

(1*S, 5*R**, 6*S**, 7*R**)-7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-[2-(pyridin- 2-ylamino-ethyl]-3-aza-bi-cyclo[3.2.1]octane-6-carboxlic acid ethyl ester (5b)**



Title compound isolated as a pale white oil (340mg, 55 %); R_f 0.21 (SiO_2, 2:1 ether : pet ether 40-60); ν_{max} (neat) 3370, 2942, 1722 (C=O), 1598, 1474, 1292 cm-1; δ_H (500 MHz; $CDCl_3$) 8.07 (1H, dd, *J* 5.0, 1.0, ArH), 7.39 (1H, d, *J* 7.5, ArH), 7.32-7.30 (2H, m, H11, ArH), 7.30-7.26 (1H, m, ArH), 7.16-7.12 (1H, m, ArH), 7.08 (2H, d, *J* 8.5, ArH), 6.79 (2H, d, *J* 8.5, ArH), 6.74 (1H, dd, *J* 8.5, 3.0, ArH), 6.46 (1H, t, *J* 6.0, ArH), 5.65 (1H, br s, NH), 4.58 (1H, d, *J* 6.0, ArC***H***), 4.16-4.02 (2H, m, OC***H***$_2$CH$_3$), 3.34-3.28 (1H, m, NCH$_2$C***H***H'NH), 3.23 (1H, t, *J* 3.0, OEtC(O)C***H***), 3.24-3.19 (1H, m, NCH$_2$CH***H***'NH), 2.81 (1H, d, *J* 10.0, EtOC(O)CHCHC***H***H'N), 2.70 (1H, s, EtOC(O)CHCHCH***H***'N), 2.49-2.47 (2H, m, EtOC(O)CHC***H***, ArCHC***H***), 2.22 (1H, d, *J* 10.5, ArCHCHC***H***H'N), 2.07-2.03 (1H, m, CHC***H***H'CH), 1.83 (1H, d, *J* 10.0, ArCHCHCH***H***'N), 1.76 (1H, s, CHC***H***H'CH), 1.44 (1H, d, *J* 11.5, CHCH***H***'CH), 1.17 (3H, t, *J* 7.0, OCH$_2$C***H***$_3$); δ_C (125 MHz; $CDCl_3$) 173.81, 159.19, 148.94, 147.35, 136.52, 136.36, 135.35, 133.03, 131.53, 129.67, 129.02, 128.88, 126.83, 126.61, 111.75, 110.32, 60.50, 57.80, 56.52, 55.36, 54.07, 45.97, 44.07, 39.94, 37.62, 37.19, 14.40.

(1*S, 5*R**, 6*S**, 7*R**)-7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-[2-(4-nitrophenylamino-ethyl]-3-aza-bi-cyclo[3.2.1]octane-6-carboxlic acid ethyl ester (5c)**

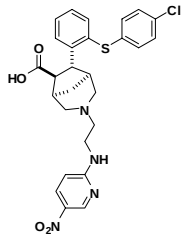


R_f 0.38 (SiO_2, 2:1 Ether : 40:60 petrol) ν_{max} (neat) 3334, 2926, 1718 (C=O), 1600, 1473, 1302, 1183, 1108 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 8.05 (2H, d, *J* 9.0, ArH), 7.38 (1H, d, *J* 8.0, ArH), 7.33 (1H, d, *J* 4.0, H11, ArH), 7.19-7.13 (1H, m, ArH), 7.08 (2H, d, *J* 8.5, ArH), 6.75-6.69 (3H, m, ArH), 6.22 (1H, br s, NH), 4.55 (1H, d, *J* 6.0, ArC***H***), 4.18-4.05 (2H, m, OC***H***$_2$CH$_3$), 3.25 (1H, t, *J* 6.0, EtOC(O)C***H***), 3.08-3.00 (2H, m, NCH$_2$C***H***$_2$NH), 2.78-2.71 (2H, m, EtOC(O)CHC***H***, ArCHC***H***), 2.55 (2H, m, NC***H***$_2$CH$_2$NH), 2.48 (1H, d, *J* 9.5, EtOC(O)CHCHC***H***H'N), 2.34 (1H, d, *J*, 9.5, ArCHCHC***H***H'N), 2.14-2.08 (1H, m, EtOC(O)CHCHCH***H***'N), 1.88 (1H, d, *J* 10.5, ArCHCHCH***H***'N), 1.83 (1H, s, CHC***H***H'CH), 1.49 (1H, d, *J* 11.5, CHCH***H***'CH), 1.20 (3H, t, *J* 7.0, OCH$_2$C***H***$_3$); δ_C (100 MHz; $CDCl_3$) 173.89, 245.23, 148.49, 137.17, 136.34, 135.14, 132.94, 131.67, 129.52, 129.07, 128.87, 127.05, 126.53, 126.29, 112.10, 60.65, 57.11, 56.72, 54.36, 54.28, 45.28, 43.93, 40.24, 39.03, 37.28, 14.37; m.p 50-52 ºC (ether : 40:60 petrol).

General Procedure for cleavage of the ester group:

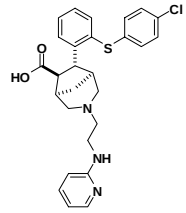
To a solution of the ethyl ester in THF was added 1M potassium hydroxide solution (6:1 methanol : water), in a ratio of 3:1 (THF : KOH solution). The reaction was heated at 50 ºC overnight then acidified with HCl and extracted with chloroform. The organic layer was reduced *in vacuo* and the crude product purified by flash column chromatography.

(1*S, 5*R**, 6*S**, 7*R**)- 7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-[2-(5-nitro-pyridin-2-ylamino)-ethyl]-2-aza-bi-cyclo[3.2.1]octane-6-carboxylic acid (gemmacin)**



Title compound isolated as a yellow solid (78.1 mg, 42 %); mp 97-99 ºC (ethanol); R_f 0.14 (SiO_2, ethanol); ν_{max} (neat) 2931, 2800, 1603 (C=O),1474, 1328, 1295, 1092 cm^{-1}; δ_H (500 MHz; MeOD) 8.89 (1H, d, *J* 2.5, ArH), 7.97 (1H, dd, *J* 9.5, 2.5, ArH), 7.44 (1H, d, *J* 7.0, ArH), 7.32 (1H, td, *J* 7.5, 1.5, ArH), 7.23 (1H, dd, *J* 8.0, 1.0, ArH), 7.18-7.12 (3H, m, H14, ArH), 6.91 (2H, d, *J* 8.5, ArH), 6.82 (1H, d, *J* 9.5, ArH), 4.38 (1H, d, *J* 5.5, ArC***H***), 3.72 (1H, br s, NCH$_2$C***H***H'NH), 3.46-3.40 (1H, m, NCH$_2$CH***H***'NH), 3.26 (1H, t, *J* 6.0, C***H***COOH), 3.13 (1H, d, *J* 10.5, ArCHCHC***H***H'N), 3.00 (1H, br s, NC***H***H'CHCHCOOH), 2.89-2.80 (2H, m, NC***H***$_2$CH$_2$NH), 2.74 (1H, br s, ArCHCHCH***H***'N), 2.69 (1H, d, *J* 10.5, ArCHC***H***), 2.37 (1H, br s, NCH***H'***CHCHCOOH), 2.11-2.06 (1H, m, CHC***H***H'CH), 1.94 (1H, br s, C***H***CHCOOH), 1.61 (1H, d, *J* 11.5, CHCH***H***'CH); δ_C (125 MHz; MeOD) 181.24, 161.50, 149.00, 145.91, 135.93, 135.12, 133.69, 133.51, 131.91, 131.18, 130.41, 128.79, 128.41, 126.66, 126.21, 57.04), 56.88, 55.97, 54.35, 47.85, 43.80, 39.68, 36.80, 35.60; HRMS $(M+H)^+$ found 539.1520, $C_{27}H_{28}N_4O_4SCl$ requires 539.1516, Δ ppm -0.4.

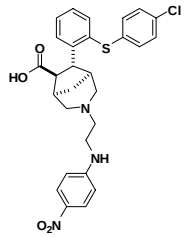
(1*S, 5*R**, 6*S**, 7*R**)-7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-[2-(pyridin-2-ylamino)-ethyl]-2-aza-bi-cyclo[3.2.1]octane-6-carboxylic acid (6)**



Isolated as a white solid (51.8 mg, 22%) . R_f 0.10 (SiO_2, ethanol); ν_{max} (neat) 3281, 2940, 1573 (C=O), 1515, 1418, 1331, 1292, 1091 cm^{-1}; δ_H (400 MHz; MeOD) 8.02 (1H, d, *J* 5.0, ArH), 7.48 (2H, d, *J* 8.5, ArH), 7.37 (1H, t, *J* 7.5, ArH), 7.33 (1H, d, *J* 7.5, ArH), 7.20 (1H, d, *J* 7.5, ArH), 7.17 (2H, d, *J* 8.5, ArH), 6.83 (2H, d, *J* 8.0, ArH), 6.78 (1H, d, *J* 8.5, ArH), 6.61 (1H, t, *J* 6.0, ArH), 4.44 (1H, d, *J* 5.0, ArC***H***), 3.49-3.40 (1H, m, NCH$_2$C***H***H'NH), 3.28 (1H, t, *J* 6.0, HOC(O)C***H***), 3.28-3.20 (1H, m, NCH$_2$CH***H***'NH, ArCHCHC***H***H'N), 2.97-2.80 (3H, m,

ArCHC***H***, HOC(O)CHCHC***H***H'N, ArCHCHCH***H***'N), 2.79-2.70 (2H, m, NC***H***$_2$CH$_2$NH), 2.38 (1H, br s, HOC(O)CHCHCH***H***'N), 2.10 (1H,m, CHC***H***H'CH), 1.91 (1H, br s, HOC(O)CHC***H***), 1.64 (1H, d, *J* 11.5, CHCH***H***'CH); δ_C (100 MHz; MeOD) 183.55, 160.11, 147.70, 139.13, 137.73, 135.71, 134.27, 133.00, 131.29, 131.09, 130.24, 129.87, 128.14, 127.86, 113.81, 110.56, 58.65, 58.34, 57.62, 56.42, 49.29, 45.12, 40.82, 38.63, 36.96; HRMS $(M+Na)^+$ found 494.1660, $C_{27}H_{29}N_3O_2SCl$ requires 494.1669, Δ ppm -1.8; m.p 190-192 ºC.

(1*S, 5*R**, 6*S**, 7*R**)-7-[2-(4-Chloro-phenylsulfanyl)-phenyl]-3-[2-(4-nitrophenylamino)-ethyl]-2-aza-bi-cyclo[3.2.1]octane-6-carboxylic acid (gemmacin B, (13))**



Isolated as a yellow solid (65.7 mg, 58 %). R_f 0.14 (SiO_2, 10:1 CH_2Cl_2 : methanol) ν_{max} (neat) 3311, 2941, 1706, 1600 (C=O), 1473, 1303, 1184, 1109, 1091 cm^{-1}; δ_H (500 MHz; MeOD) 7.97 (2H, d, *J* 9.5, ArH), 7.43 (1H, d, *J* 7.5, ArH), 7.34 (1H, t, *J* 7.5, ArH), 7.30 (1H, dd,. *J* 7.5, 1.0, ArH), 7.16 (1H, td, *J* 7.5, 1.0, ArH), 7.10 (2H, d, *J* 8.5, ArH), 6.83 (2H, d, *J* 8.5, ArH), 6.73 (2H, d, *J* 9.0, ArH), 4.36 (1H, d, *J* 6.0, ArC***H***), 3.40-3.34 (1H, m, NCH$_2$C***H***H'NH), 3.31 (1H, t, *J* 5.0, HOC(O)C***H***), 3.26 (1H, m, NCH$_2$CH***H***'NH), 3.18 (1H, d, *J* 11.0, ArCHCHC***H***H'N), 2.96-2.85 (3H, m, HOC(O)CHCHC***H***H'N, NC***H***$_2$CHH'NH), 2.79-2.73 (2H, m, ArCHCHCH***H***'N, ArCHC***H***), 2.46 (1H, d, *J* 11.0, HOC(O)CHCHCH***H***'N), 2.12-2.08 (1H, m, CHC***H***H'CH), 1.97 (1H, br s, HOC(O)CHC***H***), 1.65 (1H, d, *J* 12.0, CHCH***H***'CH); δ_C (125 MHz; MeOD) 179.36, 155.41, 148.75, 138.67, 137.51, 135.88, 134.44, 133.19, 131.72, 130.35, 130.16, 128.46, 127.67, 127.19, 112.64, 58.84, 58.36, 56.84, 55.85, 48.53, 44.86, 40.62, 39.35, 36.83; HRMS $(M+Na)^+$ found 538.1538, $C_{28}H_{28}N_3O_4SCl$ requires 538.1567, Δ ppm 3.2; m.p 90-92 ºC.

References

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2. T. Mega, Y. Hamazume and T. Ikenaka, *Bull. Chem. Soc. Japan*, 1988, **61**, 4315-4321.