Dynamic combinatorial chemistry with hydrazones: libraries incorporating heterocyclic and steroidal motifs‡

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Supporting material

Experimental section

General:

^{1}H NMR Spectra were recorded on Bruker DRX–400 MHz spectrometer unless otherwise stated. ^{13}C NMR were obtained on a DRX–400 operating at 100 MHz. All NMR spectra were recorded using $CDCl_3$ which was de–acidified prior to use by standing over anhydrous K_2CO_3. or filtering through a plug of basic alumina, unless stated otherwise. Chemical shifts (δ) are expressed relative to TMS (^{1}H, ^{13}C) and are quoted in ppm. Coupling constants are given in Hz and quoted to ± 0.05 Hz. The following abbreviations are used to indicate the multiplicity of the signals: s = singlet; d = doublet; dd = doublet of doublets; m = multiplet; t = triplet; dt = doublet of triplets; tt = triplet of triplets; q = quartet; brs = broad singlet. In the steroidal ^{1}H NMR spectra overlapping backbone resonances are not quoted. COSY, NOESY and VT spectra were obtained on a Bruker DRX–500 MHz spectrometer in $CDCl_3$. HPLC analysis was carried out using a Hewlett–Packard 1050 instrument, with UV analysis employing a HP 1050 DAD detector, and data was analysed using the HP ChemStation software. Reverse phase HPLC separations were carried out using a 15 cm x 4.6 mm i.d. 3Å particle size, Supelco ABZ$^+$ C_{16} alkylamide column using acetonitrile and *iso*–propanol gradients. Alternatively a Symmetry C_{18} reverse phase 18 cm x 4.6 mm i.d. 3Å particle size was used with H_2O and acetonitrile gradients were used. Positive–ion Electrospray mass spectra (ESI–MS) were obtained on a VG BioQ triple quadrupole apparatus with a mass–to–charge (m/z) range up to 4000 (VG Bio Tech Ltd, Altrincham, UK). The electrospray source was heated to 100˚C and the sampling cone voltage varied between 40–65 V. The samples were introduced into the mass spectrometer source with an LC pump (Shimadzu LC–9A LC pump) at a flow rate of 4μLmin^{-1} of acetonitrile/water (1:1). Calibration was performed using protonated horse myoglobin. The data system was operated as a multichannel analyser, and several scans were summed (>10) to obtain the final spectrum. A constant volume (5μL) of centrifuged solution was injected. Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer; the spectra of solids were run as solutions in deuterated chloroform. Fast atom bombardment (FAB) mass spectra were obtained using a *m*-nitrobenzyl alcohol matrix on a Kratos MS–50 instrument. Experimental peak (mode) masses are compared with calculated mean masses. Microanalyses were carried out by the University Chemical Laboratory Microanalysis Department in Cambridge. The synthesis of compounds **39-46** and **56-57** have been described elsewhere.[8]

General Procedures:

(A) *N*–alkylation of Heterocycles

The heterocycle (5 mmol) was dissolved in dry DMF (20 ml). To this were added the alkylating agent (1.2 equivalents) and finely powdered, dried K_2CO_3 (2.3 equivalents). The reaction mixture was then heated at 50˚C for 18 hours. After allowing the reaction mixture to cool to room temperature it was added to distilled water (200 ml) and extracted with EtOAc (4 x 50 ml). The combined organic layers were then washed thoroughly with saturated brine solution (4 x 100 ml), dried (anhydrous Na_2SO_4), filtered and the solvent removed under vacuum. Column chromatography was used to further purify if necessary.

(B) Hydrazinolysis of Heterocyclic Esters

The dimethyl acetal methyl or ethyl ester (5 mmol) was dissolved in distilled MeOH (10 ml). Hydrazine monohydrate (10 equivalents) was added and the reaction mixture heated at 80˚C for 24 hours. The solvent was removed under vacuum and the residue re–dissolved in EtOAc (100 ml). This was washed with distilled water (2 x 50 ml), saturated brine (50 ml), dried (anhydrous Na_2SO_4), filtered and the solvent removed under vacuum. The product was purified by column chromatography (5%MeOH/$CHCl_3$) to furnish the product.

(3)

α–Bromo–p–tolunitrile (6.00 g, 30.6 mmol) was dissolved in dry toluene (60 ml) and cooled in an ice–bath. DIBAL–H (1.0 M solution in hexanes, 40 ml, 40 mmol) was then added dropwise under argon and the solution stirred at 0˚C for an hour, after which chloroform (80 ml) and 10% HCl (200 ml) were added. Stirring was continued for a further hour at room temperature. The organic layer was separated, washed with distilled water (200 ml), dried (anhydrous $MgSO_4$) and filtered. The solvent was almost completely removed from the filtrate under vacuum, the residue cooled, filtered, then washed with cold hexane (2 x 50 ml) and the resulting white crystals dried under vacuum (4.4 g, 72%), ν_{max}/cm^{-1} ($CDCl_3$) 2831, 2741, 1706; ^{1}H NMR ($CDCl_3$) 4.50 (s, 2H), 7.52 (d, J = 8.3 Hz, 2H), 7.86 (d, J = 8.3 Hz, 2H), 10.0 (s, 1H); ^{13}C NMR ($CDCl_3$) 32.0, 129.7, 130.2, 136.2, 144.3, 191.5. Anal. Calcd. for C_8H_7BrO: C, 48.27; H, 3.54. Found: C, 48.32; H, 3.57.

(4)

α–Bromo–m–tolunitrile (5.00 g, 25.5 mmol) was dissolved in dry toluene (50 ml) under argon and cooled in an ice–bath. DIBAL–H (1.0 M solution in hexanes, 34 ml, 34 mmol) was then added dropwise. The reaction was completed and worked up as for (B). Trituration of the resulting clear oil with chlorobenzene and hexane produced a white solid (4.1 g, 80%), ^{1}H NMR ($CDCl_3$) 4.53 (s, 2H), 7.53 (t, J = 7.6 Hz, 1H), 7.67 (d, J= 7.6 Hz, 1H), 7.82 (d, J= 7.6 Hz, 1H), 7.92 (s, 1H), 10.02 (s, 1H); ^{13}C NMR ($CDCl_3$) 32.0, 129.6, 129.8, 129.9, 134.9, 136.9, 139.0, 191.7. Anal. Calcd. for C_8H_7BrO: C, 48.27; H, 3.54. Found: C, 48.65; H, 3.53.

(5)

Aldehyde (**3**) (1.0 g, 5.02 mmol) was dissolved in freshly distilled, dry MeOH (100 ml). TsOH monohydrate (0.502 mmol, 98.6 mg) was added and the reaction mixture stirred under argon for two hours, at room temperature, diluted with Et_2O (200 ml), washed with saturated $NaHCO_3$ solution (100 ml) and distilled water (2 x 100 ml). After drying (anhydrous Na_2SO_4), followed by filtration, the solvent was removed under vacuum to yield a colourless oil (1.23 g, 100%). R_f = 0.32 (3:1 hexane/EtOAc), ^{1}H NMR ($CDCl_3$) 3.31 (s, 6H), 4.49 (s, 2H), 5.37 (s, 1H), 7.39 (m, 4H); ^{13}C NMR ($CDCl_3$) 33.1, 52.7, 102.7, 127.2, 128.9, 138.0, 138.4.

(6)

Same procedure as for compound (**5**). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.32 (s, 6H), 4.49 (s, 2H), 5.38 (s, 1H), 7.31-7.39 (m, 3H), 7.48 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 35.2, 54.6, 104.5, 128.7, 129.2, 130.6, 131.0, 148.6, 149.9.

(12)

Acid (**11**) (5.10 g, 28.8 mmol) suspended in dry MeOH (50 ml) was placed in an ice–bath and $SOCl_2$ (43.2 mmol, 3.15 ml) added dropwise under argon. After leaving the mixture stirring at 0˚C for an hour, the ice–bath was removed and stirring continued at room temperature for 48 hours. The solvent was removed from the pale yellow solution to leave a beige solid, which was triturated with distilled acetone, filtered and dried under vacuum to furnish the product as a white powder (5.35 g, 82%); ^{1}H NMR (DMSO) 3.18 (dd, J = 10.9, 16.8 Hz, 1H), 3.30 (dd, J = 5.5, 16.8 Hz, 1H), 3.79 (s, 3H), 4.32 (m, 2H), 4.55 (dd, J = 5.5, 10.9 Hz, 1H), 7.26 (s, 4H), 10.36, (brs, 1H); ^{13}C NMR (DMSO) 27.9, 43.6, 52.8, 52.9, 126.4, 126.8, 127.4, 128.3, 128.6, 130.4, 168.7; Anal. Calcd. for $C_{11}H_{14}NO_2Cl$: C, 58.02; H, 6.15; N, 6.15. Found: C, 57.89; H, 6.20; N, 6.12.

(13)

Amine (**12**) (1.0 g, 4.4 mmol) was alkylated with (**5**) (5.28 mmol, 1.29 g) according to general procedure (A). Following column chromatography (3:1 hexane/EtOAc) (9) was obtained as a pure, pale yellow oil (1.4 g, 90%). R_f = 0.34 (3:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) 3.12 (dd, J = 4.0, 16.3 Hz, 1H), 3.21 (dd, J = 6.0, 16.3 Hz, 1H), 3.34 (s, 6H), 3.66 (s, 3H), 3.78 (dd, J = 4.0, 6.0 Hz, 1H), 3.81 (d, J = 14.7 Hz, 1H), 3.93 (m, 2H), 4.04 (d, J = 15.6 Hz, 1H), 5.37 (s, 1H), 6.96 (m, 1H), 7.11 (m, 3H), 7.39 (m, 4H); ^{13}C NMR ($CDCl_3$) 31.4, 51.0, 51.4, 52.9, 52.9, 58.8, 59.0, 103.3, 126.0, 126.1, 126.5, 126.8, 128.6, 128.7, 132.2, 134.2, 137.1, 138.9, 173.0; ESI–MS: m/z 356 $[M+H]^+$, found 356.1841, $C_{21}H_{26}NO_4$ requires 356.1862.

(15)

Ester (**13**) (1.4 g, 3.94 mmol) was treated with hydrazine monohydrate (39.4 mmol, 1.97 g) according to general procedure (B). (10) was purified by column chromatography (5%MeOH/$CHCl_3$) to furnish a clear oil which crystallised on standing to yield a beige solid (1.3 g, 92.8%), R_f = 0.21 (5%MeOH/$CHCl_3$); ν_{max}/cm^{-1} ($CDCl_3$) 3402, 1670, 1623; ^{1}H NMR (DMSO) 2.92 (dd, J = 5.6, 16.5 Hz, 1H), 3.00 (dd, J = 6.3, 16.5 Hz, 1H), 3.22 (s, 6H), 3.42 (t, J = 6.4 Hz, 1H), 3.45 (d, J = 16.5 Hz, 1H), 3.55 (d, J = 13.4 Hz, 1H), 3.75 (d, J = 13.4 Hz, 1H), 3.81 (d, J = 16.0 Hz, 1H), 4.23 (brs, 2H), 5.37 (s, 1H), 6.92 (d, J = 7.1 Hz, 1H), 7.00–7.11 (m, 3H), 7.31 (d, J = 8.3 Hz), 7.36 (d, J = 8.3 Hz, 2H), 9.13 (brs, 1H); ^{13}C NMR (DMSO) 30.6, 52.0, 53.0, 58.2, 60.3, 103.2, 126.0, 126.4, 126.6, 126.9, 128.6, 128.8, 133.6, 134.6, 137.4, 139.4, 171.4 ; ESI–MS: m/z 356 $[M+H]^+$, 378 $[M+Na]^+$, found 378.1829, $C_{20}H_{25}N_3O_3Na$ requires 378.1794. Anal. Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.51; H, 7.07; N, 11.75.

(16)

Amine (**12**) (1.0 g, 4.4 mmol) was alkylated with (**6**), (5.26 mmol, 1.29 g) according to general procedure (A). The dimethyl acetal methyl ester (1.4 g, 90%) was treated with hydrazine monohydrate according to general procedure (B). The resulting clear oil was triturated with diethyl ether and dried under vacuum to furnish the product as a white powder (950 mg, 68%) , R_f = 0.34 (5%MeOH/$CHCl_3$), ν_{max}/cm^{-1} ($CDCl_3$) 3402, 1670, 1623; ^{1}H NMR (DMSO) 2.92 (dd, J = 5.6, 16.6 Hz, 1H), 3.02 (dd, J = 6.6, 16.6 Hz, 1H), 3.23 (s, 6H), 3.41 (t, J = 6.6 Hz, 1H), 3.44 (d, J = 15.7 Hz, 1H), 3.55 (d, J = 13.2 Hz, 1H), 3.79 (d, J = 13.2 Hz, 1H), 3.81 (d, J = 15.7 Hz, 1H), 4.27 (brs, 2H), 5.37 (s, 1H), 6.93 (d, J = 7.2 Hz, 1H), 7.04–7.11 (m, 3H), 7.25–7.35 (m, 3H), 7.38 (s, 1H), 9.19 (s, 1H); ^{13}C NMR (DMSO) 35.7, 56.9, 57.8, 58.2, 63.3, 65.2, 107.9, 130.5, 130.8, 131.2, 131.4, 131.9, 133.3, 133.4, 133.9, 139.3, 143.4, 143.9, 176.2; ESI–MS: m/z 356 $[M+H]^+$, found 356.1982, $C_{20}H_{26}N_3O_3$ requires 356.1974. Anal. Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.04; H, 7.20; N, 11.41,

(21)

The hydrazide (**21**) was synthesised from (**17**) (1.03 g, 4.82 mmol) by the same sequence of reactions as (**15**) from (**11**) *vide supra*. Finally (**21**) was triturated with Et_2O to furnish a white powder (650 mg, 43%), R_f = 0.23 (5%MeOH/DCM), ν_{max}/cm^{-1} ($CDCl_3$) 3402, 1670, 1623; ^{1}H NMR (DMSO) 2.92 (dd, J = 5.6, 16.5 Hz, 1H), 3.00 (dd, J = 6.3, 16.5 Hz, 1H), 3.22 (s, 6H), 3.41 (t, J = 6.1 Hz, 1H), 3.46 (d, J = 16.2 Hz, 1H), 3.56 (d, J = 13.4 Hz, 1H), 3.76 (d, J = 13.4 Hz, 1H), 3.82 (d, J = 15.6 Hz, 1H), 4.24 (brs, 2H), 5.35 (s, 1H), 6.93 (d, J = 7.2 Hz, 1H), 7.08 (m, 3H), 7.32 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 9.13 (brs, 1H); ^{13}C NMR (DMSO) 30.7, 52.0, 53.0, 58.2, 60.3, 103.1, 126.0, 126.4, 126.6, 126.9, 128.6, 128.8, 133.6, 134.6, 137.4, 139.4, 171.4; +FAB MS: m/z 356 $[M+H]^+$, found 356.1976, $C_{20}H_{26}N_3O_3$ requires 356.1974. Anal. Calcd. for $C_{20}H_{25}N_3O_3$: C, 67.58; H, 7.09; N, 11.82. Found: C, 67.42; H, 7.10; N, 11.66.

(22)

Synthesised from the ester (**20**) (0.775 g, 2.18 mmol). This was dissolved in absolute EtOH (10 mL) and hydrazine hydrate (2.5 mL) was added. The reaction mixture was heated to reflux over night. The reaction mixture was cooled to room temperature and the volatiles were evaporated off *in vacuo*. The residue was dissolved in CH_2Cl_2 (200 mL) and washed with water (150 mL). The organic phase was dried (Na_2SO_4), filtered through paper and concentrated. The residue was purified by dry column vacuum chromatography (hexane to MeCN with 10 % gradient and then 10% MeOH in MeCN with 1% gradient) to yield the target compound as a white solid. Yield: 0.658 g, 85 %. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.11 (d, 2H), 3.32 (s, 6H), 3.58 (t, 1H), 3.64 (d, 1H), 3.68 (s, 2H), 3.74-3.77 (m, 2H), 3.82 (d, 1H), 5.38 (s, 1H), 6.99 (d, 1H), 7.13-7.22 (m, 3H), 7.27-7.38 (m, 4H), 8.18 (br s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.1, 51.6, 53.2, 53.3, 59.2, 61.4, 103.5, 126.4, 126.8, 126.9, 127.4, 127.5, 128.6, 128.9, 129.3, 134.2, 134.9, 138.3, 139.0, 173.6. MS (ESI^+): m/z 356 $[M+H]^+$. HRMS (ESI^+) found 356.1982, $C_{20}H_{26}N_3O_3$ requires 356.1974.

(25)

Imidazole (**23**), (900 mg, 5.84 mmol) was dissolved in dry DMF (20 ml). Bromide (**5**), (5.84 mmol, 1.43 g) was added, followed by finely ground, dry K_2CO_3 (10 mmol, 1.38 g). Following general procedure (A) and column chromatography (1:2 hexane/EtOAc) (**24**) was obtained as a regiochemically pure white solid (800 mg, 43%), R_f = 0.23 (1:2 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) 1.27 (t, J = 7.1 Hz, 3H), 2.48 (s, 3H), 3.29 (s, 6H), 4.22 (q, J = 7.1 Hz, 2H), 5.34 (s, 1H), 5.44 (s, 2H), 7.10 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.48 (s, 1H); ^{13}C NMR ($CDCl_3$) 14.3, 16.0, 50.3, 52.7, 60.3, 102.8, 118.7, 126.9, 127.2, 137.0, 137.9, 140.5, 148.7, 161.0; ESI–MS: m/z 319 $[M+H]^+$, found 319.1640, $C_{17}H_{23}N_2O_4$ requires 319.1658. Ester (**24**) (700 mg, 2.2 mmol) was dissolved in distilled EtOH (10 ml). Hydrazine monohydrate (22.2 mmol, 1.10 g) was added and the reaction mixture heated to reflux overnight. LC–MS indicated that no product had formed after 18 hours so a further portion of hydrazine (22.2 mmol, 1.10 g) was added. After refluxing was continued for a further four days the reaction had reached completion by LC–MS. The solvent was removed under vacuum and the product purified by column chromatography (10%MeOH/$CHCl_3$). The hydrazide (**25**) was obtained as a pure white solid after trituration with Et_2O (440 mg, 63%), R_f = 0.42 (10%MeOH/$CHCl_3$), ν_{max}/cm^{-1} ($CDCl_3$) 3440, 1662, 1625; ^{1}H NMR (DMSO) 2.19 (s, 3H), 3.19 (s, 6H), 4.38 (brs, 2H), 5.31 (s, 1H), 5.33 (s, 2H), 7.14 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 7.76 (s, 1H), 9.13 (brs, 1H); ^{13}C NMR (DMSO) 14.9, 48.5, 53.1, 102.9, 121.9, 127.2, 127.5, 138.0, 138.5, 139.4, 139.8, 161.4; ESI–MS: m/z 305 $[M+H]^+$, found 305.1635, $C_{15}H_{21}N_4O_3$ requires 305.1613. Anal. Calcd. for $C_{15}H_{20}N_4O_3 \cdot 0.5\ H_2O$: C, 57.50; H, 6.70; N, 17.89. Found: C, 57.25; H, 6.44; N, 17.60.

(28)

Piperidine (**26**) (800 mg, 5.1 mmol) was added to a solution of (**5**), (5.1 mmol, 1.25 g) in dry DMF (20 ml) containing K_2CO_3 (10 mmol, 1.38 g). Following general procedure (A) column chromatography (1:1 hexane/EtOAc) furnished (18) as a clear oil (1.2 g, 73%), R_f = 0.34 (1:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) 1.23 (t, J = 7.1 Hz, 3H), 1.7–2.9 (m, 9H), 3.32 (s, 6H), 3.47 (s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 5.36 (s, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) 14.2, 28.3, 41.2, 52.8, 52.9, 60.3, 63.0, 103.3, 126.6, 128.9, 136.8, 138.8, 175.3; FAB^+ MS: m/z 322 $[M+H]^+$, found 322.2023, $C_{18}H_{28}NO_4$ requires 322.2018. Ester (**27**) (1.2 g, 3.74 mmol) was dissolved in MeOH (10 ml) and hydrazine monohydrate (37.3 mmol, 1.87 g) added. Following general procedure (B) (**28**) was obtained as a white solid (800 mg, 69%), R_f = 0.23 (5%MeOH/DCM), ν_{max}/cm^{-1} ($CDCl_3$) 3440, 3340, 1670, 1625; ^{1}H NMR ($CDCl_3$) 1.7–3.0 (m, 9H), 3.32 (s, 6H), 3.48 (s, 2H), 3.88 (brs, 2H), 5.36 (s, 1H), 6.84 (br s, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) 28.7, 41.7, 52.9, 53.0, 62.9, 103.3, 126.6, 128.9, 136.9, 138.7, 175.8; FAB^+ MS: m/z 308 $[M+H]^+$, found 308.1971, $C_{16}H_{26}N_3O_3$ requires 308.1974. Anal. Calcd for $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.21; N, 13.63. Found: C, 62.19; H, 8.13; N, 13.40.

(31)

Piperidine (**29**), (800 mg, 5.1 mmol) was added to a solution of DMF (20 ml) containing (**5**) (5.1 mmol, 1.25 g) and dry, finely powdered K_2CO_3 (10 mmol, 1.38 g). Following general procedure (A) (**30**) was obtained as a clear oil (1.6 g, 98%), R_f = 0.27 (2:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) 1.27 (t, J = 7.1 Hz, 3H), 1.4–3.2 (m, 9H), 3.31 (s, 6H), 3.37 (d, J = 13.3 Hz, 1H), 3.78 (d, J = 13.3 Hz, 1H), 4.19 (dq, J = 1.0, 7.1 Hz, 2H), 5.35 (s, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$) 14.3, 22.6, 25.3, 29.6, 50.2, 52.8, 60.3, 60.3, 64.6, 103.3, 126.5, 129.1, 136.9, 138.6, 173.9; ESI–MS: m/z 322 $[M+H]^+$, found 322.2031, $C_{18}H_{28}NO_4$ requires 322.2018. Ester (**30**) (1.6 g, 4.98 mmol) was dissolved in MeOH (10 ml). Hydrazine monohydrate (99.6 mmol, 4.99 g) was added and the mixture heated to reflux. After 24 hours LC–MS indicated that no product had been formed so a further portion of hydrazine was added (49.8 mmol, 2.5 g). Refluxing was continued for a further 7 days after which time the reaction had proceeded to 50% completion. The reaction mixture was diluted with EtOAc (200 ml), washed with distilled water (4 x 100 ml) then dried (anhydrous Na_2SO_4). After removal of the solvent under reduced pressure pure title compound (500 mg, 54% based on recovered starting material) was obtained following column chromatography (gradient; 5%MeOH/$CHCl_3$ to

8%MeOH/$CHCl_3$), R_f = 0.25 (10% MeOH/$CHCl_3$), ν_{max}/cm^{-1} ($CDCl_3$) 3409, 1672, 1625; ^1H NMR ($CDCl_3$) 1.2–3.0 (m, 9H), 3.20 (d, J = 13.7 Hz, 1H), 3.2 (s, 6H), 3.79–3.85 (m, 3H), 5.36 (s. 1H), 7.26 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.84 (br, 1H); ^{13}C NMR ($CDCl_3$) 23.3, 24.4, 29.9, 51.6, 52.8, 60.4, 66.5, 103.1, 126.8, 128.4, 137.2, 138.2, 175.0; ESI–MS: m/z 308 $[M+H]^+$, 330 $[M+Na]^+$, found 330.1798, $C_{16}H_{25}N_3O_3Na$ requires 330.1794.

(33)

Aldehyde (**32**) (5.0 g, 38.1 mmol) was dissolved in dry MeOH. NH_4Cl (57.1 mmol, 3.0 g) was added and the mixture refluxed for 4 hours. TLC (3:1 hexane/EtOAc) indicated that the reaction had gone to completion after which the solvent was removed under vacuum and the residue partitioned between $CHCl_3$ (100 ml) and distilled water (100 ml). The organic layer was washed with saturated $NaHCO_3$ solution, dried (anhydrous $MgSO_4$), filtered and the solvent removed under vacuum. Following column chromatography (3:1 hexane/EtOAc) the acetal was obtained as a pale yellow oil (6.6 g, 98%), R_f = 0.43 (3:1 hexane/EtOAc). 4–Cyanobenzaldehyde dimethyl acetal (3.0 g, 16.9 mmol) was dissolved in dry THF (20 ml) which was added dropwise to a stirred suspension of $LiAlH_4$ (16.9 mmol, 641 mg) in dry THF (20 ml) at 0°C. The solution gradually turned from light blue to form a green suspension after two hours. The ice–bath was then removed and the solution left to stand at room temperature overnight. The excess $LiAlH_4$ was quenched by slowly adding 10% NaOH solution (~ 10 ml) at 0°C. The reaction mixture was then extracted with EtOAc (4 x 100 ml), washed with brine (2 x 100 ml), dried (anhydrous Na_2SO_4) and the solvent removed to afford the title compound as a pale brown oil (2.85 g, 93%); ^1H NMR ($CDCl_3$) 1.57 (brs, 2H), 3.31 (s, 6H), 3.86 (s, 2H), 5.37 (s, 1H), 7.29 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) 46.2, 52.6, 103.0, 126.9, 136.7, 143.5; ESI–MS: m/z 356 $[M+H]^+$, 378 $[M+Na]^+$, found 378.1829, $C_{20}H_{25}N_3O_3Na$ requires 378.1794.

(36)

Trifluoroacetic anhydride (32 mmol, 4.53 ml) was added dropwise to a stirred suspension of (**34**) (5.0 g, 31 mmol) in dry DCM (150 ml). After one hour benzyl alcohol (31 mmol, 3.2 ml) was added to the pink suspension and the solution stirred under N_2 for a further hour. A 2 M solution of Na_2CO_3 (150 ml) was added and the organic layer separated. The aqueous layer was extracted with DCM (150 ml) and the combined organic layers dried (anhydrous $MgSO_4$) and filtered. The solution was left to stand over finely ground charcoal for 30 minutes then filtered and evaporated to furnish a beige solid which was triturated with ether/cyclohexane to give the benzyl ester as a white solid (5.28 g, 67.7%), R_f = 0.32 (2:1 hexane/EtOAc), ν_{max}/cm^{-1} ($CDCl_3$) 3466, 1698; ^1H NMR ($CDCl_3$) 5.4 (s, 2H), 7.2–7.5 (m, 8H), 7.93 (d, J = 3.0 Hz, 1H), 8.20 (m, 1H), 8.75 (br, 1H); ^{13}C NMR ($CDCl_3$) 65.7, 108.7, 111.6, 121.6, 122.2, 123.3, 125.9, 128.1, 128.6, 131.4, 136.2, 136.7, 165.1; ESI–MS: m/z 252 $[M+H]^+$, 274 $[M+Na]^+$, found 274.0867, $C16H13NO2Na$ requires 274.0844. The benzyl ester (**35**) (2.0 g, 7.97 mmol) was dissolved in dry DMF (20 ml). Methyl bromoacetate (9.56 mmol, 1.46 g) and finely powdered, dry K_2CO_3 (15.9 mmol, 2.19 g) were added and the reaction mixture heated at 50°C for 18 hours. After column chromatography (2:1 light petroleum/EtOAc) (**36**) was obtained as a white solid (1.97 g, 76.5%), R_f = 0.3 (2:1 light petroleum/EtOAc); ^1H NMR ($CDCl_3$) 3.74 (s, 3H), 4.86 (s, 2H), 5.38 (s, 2H), 7.23–7.49 (m, 8H), 7.84 (s, 1H), 8.21 (m, 1H); ^{13}C NMR ($CDCl_3$) 48.0, 52.8, 65.6, 108.4, 109.5, 122.0, 122.4, 123.4, 126.6, 128.1, 128.2, 128.6, 135.2, 136.7, 136.9, 164.6, 168.0; ESI–MS: m/z 346 $[M+Na]^+$, found 346.1043, $C_{19}H_{17}NO_4Na$ requires 346.1055.

(37)

Benzyl ester (**36**) (1.97 g, 6.1 mmol) was dissolved in THF (50 ml). Palladium on charcoal (10%) (500 mg) was added and the flask evacuated and charged with argon twice. The flask was evacuated once more, then filled with H_2 under which atmosphere the reaction was stirred until TLC (2:1 hexane/EtOAc) indicated that no (**36**) remained. After 4 hours, the palladium was removed by filtration using a plug of pre–packed celite and the solvent removed to furnish the carboxylic acid as a white solid (1.0 g, 70.4%), ^1H NMR (DMSO) 3.68 (s, 3H), 5.23 (s, 2H), 7.21 (m, 2H), 7.48 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 8.0 Hz 1H), 8.03 (s, 1H), 12.02 (br, 1H). Indole–1–(methyl acetoxy)–3–carboxylic acid (300 mg, 1.28 mmol) was suspended in dry DCM (15 ml) and (**33**) (1.92 mmol, 347 mg) and DMAP (0.13 mmol, 16 mg) added. After cooling in an ice–bath EDC (1.92 mmol, 368 mg) was added and stirring continued at 0°C for 30 minutes before allowing to warm up to room temperature at which it was stirred overnight. The solvent was removed under reduced pressure and following column chromatography (1:2 hexane/EtOAc), (**37**) was obtained as a waxy beige solid (428 mg, 84%), R_f = 0.28 (1:2 hexane/EtOAc); ^1H NMR ($CDCl_3$) 3.31 (s, 6H), 3.72 (s, 3H), 4.67 (d, J = 5.7 Hz, 2H), 4.81 (s, 2H), 5.36 (s, 1H), 6.30 (t, J = 5.7 Hz, 1H), 7.21–7.30 (m, 3H), 7.40 (m, 4H), 7.65 (s, 1H), 7.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 43.3, 47.9, 52.7, 52.8, 103.0, 109.7, 112.2, 120.6, 121.9, 123.1, 125.5, 127.1, 127.7, 131.7, 136.9, 137.4, 139.0, 164.7, 168.1; +FAB MS: m/z 365 $[M–OMe]^+$, 397 $[M+H]^+$, found 397.1762, $C_{22}H_{25}N_2O_2$ requires 397.1764.

(38)

Ester (**37**) (428 mg, 1.08 mmol) was dissolved in MeOH (10 ml). Hydrazine monohydrate (10.8 mmol, 541 mg) was added and the mixture left to stir at room temperature. After 2 hours, a white precipitate began to form and the reaction mixture was left standing in the fridge overnight. The white solid was filtered, washed with cold MeOH (100 ml) and dried under vacuum to afford the title compound as a white solid (300 mg, 70%), ^1H NMR (DMSO) 3.22 (s, 6H), 4.36 (s, 2H), 4.49 (d, J = 5.3 Hz, 2H), 4.81 (s, 2H), 5.36 (s, 1H), 7.14 (t, J = 6.9 Hz, 1H), 7.20 (t, J = 6.9 Hz, 1H), 7.34 (s, 4H), 7.45 (d, J = 8.0 Hz, 1H), 8.07 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 8.56 (brs, 1H), 9.55 (s, 1H); ^{13}C NMR ($CDCl_3$) 41.6, 47.6, 52.3, 102.5, 109.9, 110.1, 120.6, 121.2, 121.9, 126.4, 126.5, 126.9, 132.0, 136.4, 140.5, 164.0, 166.0; FAB$^+$ MS: m/z 397 $[M+H]^+$, found 397.1880, $C_{21}H_{25}N_4O_4$ requires 397.1876. Anal. Calcd. for $C_{21}H_{24}N_4O_4$: C, 63.60; H, 6.10; N, 14.13. Found: C, 63.44; H, 6.02; N, 14.03.

General procedure for Heterodimer formation

The heterocycle (0.029 mmol) and steroid (0.029 mmol) were dissolved in dry, freshly distilled DCM (11.6 ml) to form a 2.5 mM solution of each monomer. TFA (2.5% v/v, 290 μL) was added and the reaction mixture stirred at room temperature under Argon for 7 days to equilibrate. After this time the reaction mixture was neutralised with excess Et_3N. The heterodimer was then isolated by preparative TLC, using 5%MeOH/DCM as eluant.

(47)

Heterocyclic buuilding block (**15**) (10.3 mg, 0.029 mmol) and steroid dimer (**39**) (20.0 mg, 0.029 mmol) were employed in the general procedure. (**47**) was obtained as a glassy solid (62 %), ν_{max}/cm^{-1} ($CDCl_3$) 3632, 3481, 1710, 1677; ^1H NMR ($CDCl_3$) 0.88 (s, 3H, 18–Me), 0.96 (s, 3H, 19–Me), 0.98 (d, *J* = 6.6 Hz, 21–Me), 2.55 (m, 2H, 23–H), 3.16 (dd, *J* = 6.6, 17.7 Hz, 1H, H_{IQ}–4), 3.49 (dd, *J* = 7.8, 17.7 Hz, 1H, H_{IQ}–4), 3.78 (m, 4H, H_{IQ}–1, H_ι), 4.19 (t, *J* = 6.6 Hz, 1H, H_{IQ}–3), 4.96 (tt, *J* = 5.5, 10.4 Hz, 1H, 3βH), 5.49 (m, 1H, 12βH), 6.83 (d, *J* = 7.5 Hz, 1H, H_{IQ}–8), 7.13 (t, *J* = 7.5 Hz, 1H, H_{IQ}–7), 7.18-7.30 (m, 6H, H_{IQ}–5,6, $H_{\kappa,\lambda}$), 7.46 (t, *J* = 7.7 Hz, 1H, H_ε), 7.58 (s, 1H, H_μ), 7.67 (s, 1H, H_γ), 8.05 (dt, *J* = 1.4, 7.7 Hz, 1H, H_δ), 8.13 (dt, *J* = 1.4, 7.7 Hz, 1H, H_η), 8.15, (dd, *J* = 1.7, 4.3 Hz, 2H, β–pyridyl), 8.59 (s, 1H, H_{cis}), 9.00 (s, 1H, H_θ), 9.10 (dd, *J* = 1.7, 4.3 Hz, 2H, α–pyridyl), 11.60 (s, 1H, NH_{trans}); ^{13}C NMR ($CDCl_3$) 12.6, 18.1, 22.8, 23.2, 25.4, 25.8, 25.9, 26.2, 26.3, 26.9, 28.5, 31.9, 32.3, 33.6, 34.6, 34.6, 35.5, 41.3, 45.1, 45.7, 49.7, 51.1, 54.4, 62.0, 73.9, 77.6, 123.3, 126.4, 126.7, 127.0, 128.2, 129.0, 129.2, 129.6, 130.9, 131.0, 131.6, 132.2, 132.5, 133.3, 134.7, 138.6, 140.6, 142.7, 148.5, 150.9, 163.6, 165.0, 169.1, 175.2. Two resonances missing or degenerate; ESI–MS; m/z 917 $[M+H]^+$, 939 $[M+Na]^+$, found 917.5055, $C_{56}H_{65}N_6O_6$ requires 917.4965.

(48)

Heterocyclic building block (**15**) (10.3 mg, 0.029 mmol) and steroid dimer (**40**) (20.0 mg, 0.029 mmol) were employed in the general procedure. (**48**) was obtained as a glassy solid (2.12 mg). ^1H NMR ($CDCl_3$) 0.74 (s, 3H, 18–Me), 1.02-1.03 (m, 6H, 19, 21–Me), 2.43 (m, 1H, 23–H), 2.77 (m, 1H, H–23), 3.35 (m, 2H, H_{IQ}–4), 3.46 (d, *J* = 16.0

Hz, 1H, H_{IQ}–1), 3.59 (d, *J* = 12.7 Hz, 1H, H_ι), 3.74-3.78 (m, 2H, H_{IQ}–1,3), 4.13 (d, *J* = 12.7 Hz, 1H, H_ι), 4.93 (tt, *J* = 5.0, 11.4 Hz, 1H, 3βH_ι), 5.25 (m, 1H, 12βH), 6.89 (d, *J* = 7.5 Hz, 1H, H_{IQ}–1), 7.09 (m, 1H, H_{nic}–5), 7.17-7.29 (m, 3H, H_{IQ}–5,6,7), 7.44 (t, *J* = 7.7 Hz, 1H, H_ε), 7.47 (d, *J* = 8.0 Hz, 2H, H_λ), 7.64 (d, J = 8.0 Hz, 2H, H_κ), 7.68 (s, 1H, H_μ), 8.02 (d, J = 7.7 Hz, 1H, H_δ), 8.08 (s, 1H, H_γ), 8.22 (d, J = 7.7 Hz, 1H, H_η), 8.33 (dt, J = 1.8, 7.9 Hz, 1H, H_{nic}–4), 8.39 (dd, *J* = 1.8, 4.8 Hz, 1H, H_{nic}–6), 8.68 (s, 1H, NH_{cis}), 8.87 (s, 1H, H_θ), 9.43 (d, *J* = 1.8 Hz, 1H, H_{nic}-2), 10.48 (s, 1H, NH_{trans}); ^{13}C NMR ($CDCl_3$) 12.8, 18.1, 22.7, 23.3, 25.6, 25.8, 26.1, 26.4, 26.8, 27.3, 28.6, 30.9, 31.7, 32.3, 33.6, 34.4, 34.5, 35.5, 41.3, 45.3, 46.0, 49.3, 50.4, 50.6, 63.0, 73.5, 77.7, 124.2, 126.6, 126.6, 127.1, 127.4, 128.2, 128.9, 129.4, 129.8, 130.5, 131.0, 131.8, 133.0, 133.5, 133.7, 134.0, 137.9, 139.4, 142.6, 147.3, 149.9, 153.9, 164.2, 164.9, 175.2; Two resonances missing or degenerate; ESI–MS: m/z 917 $[M+H]^+$, found 917.5013, $C_{56}H_{65}N_6O_6$ requires 917.4960.

(49)

Building block (**15**) (10.3 mg, 0.029 mmol) and building block (**41**) (20.0 mg, 0.029 mmol) were employed in the general procedure. The macrocycle (**49**) was obtained as a glassy solid (55%), ν_{max}/cm^{-1} ($CDCl_3$) 3316, 1710, 1677; ^{1}H NMR ($CDCl_3$) 0.87 (s, 3H, 18–Me), 0.96 (m, 6H, 19, 21–Me), 2.39 (m, 1H, 23–H), 2.74 (m, 1H, H–23), 3.29 (m, 2H, H_{IQ}–4), 3.50 (d, *J* = 15.0 Hz, 1H, H_{IQ}–1), 3.60 (d, *J* = 13.0 Hz, 1H, H_ι), 3.70 (d, *J* = 15.0 Hz, 1H, H_{IQ}–1), 3.80 (t, *J* = 6.4 Hz, 1H, H_{IQ}–3), 3.94 (d, *J* = 13.0 Hz, 1H, H_ι), 4.99 (m, 1H, 3βH), 5.41 (m, 1H, 12βH), 6.92 (d, *J* = 8.5 Hz, 1H, H_{IQ}–8), 7.18 (m, 1H, H_{IQ}–7), 7.26 (m, 2H, H_{IQ}–5,6), 7.30 (d, *J* = 8.5 Hz, 2H, H_κ), 7.40–7.55 (m, 4H, Ph, H_λ, H_ε), 7.60 (m, 2H, Ph), 7.65 (s, 1H, H_μ), 7.96 (s, 1H, H_γ), 8.06 (m, 2H, $H_{\delta,\eta}$), 8.21 (m, 2H, Ph), 8.74 (brs, 1H, NH_{cis}), 8.86 (s, 1H, H_θ), 10.41 (s, 1H, NH_{trans}); ^{13}C NMR ($CDCl_3$) 12.8, 18.0, 22.8, 23.6, 25.3, 25.9, 25.9, 26.2, 26.6, 26.8, 27.2, 28.7, 32.0, 32.3, 33.7, 34.6, 35.7, 41.6, 45.2, 45.7, 49.3, 50.9, 63.1, 74.1, 77.2, 126.6, 127.4, 127.5, 128.3, 128.4, 128.9, 129.6, 129.6, 131.3, 131.3, 131.9, 132.0, 132.5, 133.2, 133.5, 133.7, 134.0, 139.3, 142.7, 148.9, 165.1, 165.7, 169.6, 175.5; Four resonances missing or degenerate; ESI–MS: m/z 916 $[M+H]^+$, 938 $[M+Na]^+$, found 916.4958, $C_{57}H_{66}N_5O_6$ requires 916.5008.

(50)

Building block (**15**) (10.3 mg, 0.029 mmol) and building block (**42**) (16.9 mg, 0.029 mmol) were combined in the general procedure. The macrocycle (**50**) was obtained as a frosted solid (40%); ^{19}F NMR (250 MHz) ($CDCl_3$) –75.2; ^{1}H NMR ($CDCl_3$) 0.84 (s, 3H, 18–Me), 0.98 (m, 6H, 19, 21–Me), 2.66 (m, 1H, 23–H), 3.22 (dd, *J* = 6.8, 17.0 Hz, 1H, H_{IQ}–4), 3.40 (dd, *J* = 6.8, 17.0 Hz, 1H, H_{IQ}–4), 3.64 (m, 3H, H_{IQ}–1, H_ι), 3.83 (d, *J* = 12.9 Hz, 1H, H_ι), 3.95 (t, *J* = 6.8 Hz, 1H, H_{IQ}–3), 5.07 (m, 1H, 3βH), 5.40 (m, 1H, 12βH), 6.85 (d, *J* = 7.3 Hz, 1H, H_{IQ}–8), 7.14 (m, 1H, H_{IQ}–7), 7.21 (m, 2H, H_{IQ}–5,6), 7.30 (d, *J* = 8.0 Hz, 2H, H_λ), 7.50 (t, *J* = 7.7 Hz, 1H, H_ε), 7.66 (d, *J* = 8.0 Hz, 2H, H_κ), 7.69 (s, 1H, H_μ), 8.06 (s, 1H, H_γ), 8.11 (d, *J* = 7.7 Hz, 1H, H_δ), 8.23 (d, *J* = 7.7 Hz, 1H, H_η), 8.40 (s, 1H, H_θ), 8.57 (s, 1H, NH_{cis}),10.27 (s, 1H, NH_{trans}); ESI–MS: m/z 908 $[M+H]^+$.

(51)

Heterocyclic building block (**15**) (10.3 mg, 0.029 mmol) and steroid dimer (**43**) (16.5 mg, 0.029 mmol) were employed in the general procedure. (**51**) was obtained as a white solid (88 %). ^{1}H NMR ($CDCl_3$) 0.71 (s, 3H, 18–Me), 0.95 (s, 3H, 19Me), 1.04 (d, *J* = 6.0 Hz, 3H, 21–Me), 2.56 (m, 1H, 23–H), 2.78 (m, 1H, H–23), 3.22 (dd, *J* = 7.0, 16.8 Hz, 1H, H_{IQ}–4), 3.36 (dd, *J* = 6.0, 16.8 Hz, 1H, H_{IQ}–4), 3.56 (d, *J* = 15.5 Hz, 1H, H_{IQ}–1), 3.65 (d, *J* = 12.8 Hz, 1H, H_ι), 3.70 (d, *J* = 15.7 Hz, 1H, H_{IQ}–1), 3.84 (t, *J* = 6.0, 1H, H_{IQ}–3), 3.87 (d, J = 12.8, 1H, H_ι), 5.09 (tt, *J* = 5.3, 11.0 Hz, 1H, 3βH), 6.89 (d, J = 7.8 Hz, 1H, H_{IQ}–1), 7.15 (m, 1H, H_{IQ}–7), 7.23 (m, 2H, H_{IQ}–5,6), 7.39 (d, *J* = 8.0 Hz, 2H, H_κ), 7.45 (t, J = 7.7 Hz, 1H, H_ε), 7.72 (d, J = 8.0 Hz, 2H, H_γ), 7.73 (s, 1H, H_μ), 8.11 (m, 2H, $H_{\delta,\eta}$), 8.22 (s, 1H, H_γ), 8.71 (s, 1H, H_θ), 8.92 (s, 1H, NH_{cis}), 10.26 (s, 1H, NH_{trans}); ^{13}C NMR ($CDCl_3$) 12.6, 18.1, 22.8, 23.2, 25.4, 25.8, 25.9, 26.3, 26.9, 28.5, 32.0, 32.3, 33.6, 34.6, 35.5, 41.3, 45.1, 45.7, 49.7, 51.2, 54.4, 62.0, 74.4, 126.5, 126.8, 127.2, 127.6, 128.3, 128.6, 128.8, 129.0, 129.6, 130.9, 131.4, 131.5, 131.9, 132.8, 133.2, 133.3, 134.1, 139.5, 142.7, 148.3, 165.2, 169.0, 175.8; ESI–MS: m/z 996.5 $[M+H]^+$.

(52)

Heterocyclic building block (**15**) (10.3 mg, 0.029 mmol) and steroid dimer (**44**) (20.0 mg, 0.029 mmol) were employed in the general procedure. (**52**) was obtained as a glassy solid (90 %). ^{1}H NMR ($CDCl_3$) 0.75 (s, 3H, 18–Me), 1.03 (m, 6H, 19, 21–Me), 2.40 (m, 1H, 23–H), 2.78 (m, 1H, H–23), 3.32 (m, 2H, H_{IQ}–4), 3.47 (d, *J* = 15.7 Hz, 1H, H_{IQ}–1), 3.58 (d, *J* = 13 Hz, 1H, H_ι), 3.68 (t, *J* = 6.4 Hz, 1H, H_{IQ}–3), 3.89 (d, *J* = 15.7 Hz, 1H, H_{IQ}–1), 4.06 (d, *J* = 13.0 Hz, 1H, H_ι), 4.90 (tt, *J* = 5.4, 11.3, 1H, 3βH), 5.18 (m, 1H, 7βH), 6.91 (d, *J* = 7.6 Hz, 1H, H_{IQ}–8), 7.18 (m, 1H, H_{IQ}–7), 7.26 (m, 1H, H_{IQ}–5,6), 7.44 (t, *J* = 7.7 Hz, 1H, H_ε), 7.52 (d, *J* = 8.2 Hz, 2H, H_κ), 7.58 (d, *J* = 8.2 Hz, 2H, H_λ), 7.70 (s, 1H, H_μ), 7.80 (s, 1H, H_γ), 7.93 (dd, *J* = 1.4, 4.5 Hz, 2H, β-$_{pyridyl}$), 8.01 (m, 2H, $H_{\delta,\eta}$), 8.71 (dd, *J* = 1.4, 4.5 Hz, 2H, α-$_{pyridyl}$), 8.80 (s, 1H, H_θ), 8.84 (brs, 1H, NH_{cis}); ^{13}C NMR ($CDCl_3$) 11.7, 18.7, 20.7, 22.5, 23.3, 25.0, 26.5, 27.4, 28.4, 29.3, 30.9, 33.0, 34.5, 34.6, 35.3, 38.2, 39.8, 40.5, 42.6, 50.3, 51.4, 53.9, 64.1, 73.2, 73.7, 123.1, 126.4, 126.6, 127.2, 127.3, 127.6, 128.0, 128.9, 129.5, 131.1, 131.6, 131.7, 132.8, 133.8, 134.5, 134.5, 138.6, 140.2, 143.2, 149.3, 150.7, 163.5, 165.0, 170.9, 175.4. Two resonances missing or degenerate; ESI–MS: m/z 917 $[M+H]^+$, 939 $[M+Na]^+$, found 917.5008, $C_{56}H_{65}N_6O_6$ requires 917.4965.

(53)

Heterocyclic building block (**15**) (10.3 mg, 0.029 mmol) and steroid dimer (**45**) (20.0 mg, 0.029 mmol) were employed in the general procedure. (**53**) was obtained as a glassy solid (45 %). ^{1}H NMR ($CDCl_3$) 0.73 (s, 3H, 18–Me), 1.03 (m, 6H, 19, 21–Me), 3.35 (m, 2H, H_{IQ}–4), 3.46 (d, *J* = 15.0 Hz, 1H, H_{IQ}–1), 3.59 (d, *J* = 12.7 Hz, 1H, H_ι), 3.76 (t, *J* = 15.0 Hz, 1H, H_{IQ}–1), 3.77 (d, 1H, H_{IQ}–3), 4.13 (d, *J* = 12.7 Hz, 1H, H_ι), 4.93 (tt, *J* = 5.0, 11.4, 1H, 3βH), 5.26 (m, 1H, 7βH), 6.88 (d, *J* = 7.1 Hz, 1H, H_{IQ}–8), 7.09 (dd, *J* = 7.8, 8.0 Hz, 1H, H_{nic}–5), 7.21 (m, 1H, H_{IQ}–7), 7.26 (m, 2H, H_{IQ}–5,6), 7.44 (t, *J* = 7.7 Hz, 1H, H_ε), 7.47 (d, *J* = 8.0 Hz, 2H, H_κ), 7.65 (d, *J* = 8.0 Hz, 2H, H_λ), 7.72 (s, 1H, H_μ), 8.02 (d, J = 7.7 Hz, 1H, H_η), 8.08 (s, 1H, H_γ), 8.22 (d, *J* = 7.7 Hz, 1H, H_δ), 8.33 (dt, *J* = 1.7, 7.8 Hz, 1H, H_{nic}-6), 8.39 (dd, *J* = 1.7, 4.7 Hz, 1H, H_{nic}-2), 8.86 (s, 1H, H_θ), 8.97 (brs, 1H, NH_{cis}), 9.43 (d, *J* = 1.7 Hz, 1H, H_{nic}-2), 10.49 (s, 1H, NH_{trans}); ^{13}C NMR ($CDCl_3$) 11.8, 18.8, 20.6, 22.4, 23.4, 25.1, 26.5, 27.4, 28.2, 28.6, 31.3, 32.9, 34.6, 38.1, 39.3, 40.4, 42.7, 45.9, 50.4, 50.9, 53.5, 63.2, 73.1, 73.3, 124.0, 126.4, 126.5, 127.1, 127.5, 127.7, 128.4, 128.8, 129.7, 129.9, 130.5, 131.0, 131.6, 133.1, 133.5, 133.8, 134.1, 138.0, 139.3, 142.9, 148.7, 149.8, 152.9, 164.2, 164.8, 169.7, 175.6; ESI–MS: m/z 917 $[M+H]^+$, found 917.4948, $C_{56}H_{65}N_6O_6$ requires 917.4965.

(54)

Heterocyclic building block (**15**) (10.3 mg, 0.029 mmol) and steroid dimer (**46**) (16.9 mg, 0.029 mmol) were employed in the general procedure. (**54**) was obtained as a glassy solid (19.9 mg, 75 %). ^{1}H NMR ($CDCl_3$) 0.72 (s, 3H, 18–Me), 0.96 (m, 3H, 19–Me), 1.05 (d, *J* = 6 Hz, 3H, 21–Me), 2.56 (m, 1H, 23–H), 2.77 (m, 1H, H–23), 3.24 (dd, *J* = 6.8, 16.6 Hz, 1H, H_{IQ}–4), 3.34 (dd, *J* = 6.0, 16.6 Hz, 1H, H_{IQ}–4), 3.55 (d, *J* = 15.5 Hz, 1H, H_{IQ}–1), 3.65 (d, *J* = 13 Hz, 1H, H_ι), 3.70 (d, *J* = 15.5 Hz, 1H, H_{IQ}–1), 3.83 (t, *J* = 6.0 Hz, 1H, H_{IQ}–3), 3.90 (d, *J* = 13.0, 1H, H_ι), 3.92 (m, 1H, 7βH), 4.97 (tt, *J* = 5.3, 11.5 Hz, 1H, 3βH), 6.88 (d, *J* = 7.2 Hz, 1H, H_{IQ}–8), 7.14 (m, 1H, H_{IQ}–7), 7.21 (m, 2H, H_{IQ}–5,6), 7.41 (d, *J* = 8.0 Hz, 2H, H_κ), 7.47 (t, *J* = 7.7 Hz, 2H, H_ε), 7.74 (s, 1H, H_μ), 7.75 (d, J = 8.0 Hz, 2H, H_λ), 8.10 (m, 2H, $H_{\delta,\eta}$), 8.22 (s, 1H, H_γ), 8.66 (s, 1H, H_θ), 8.91 (s, 1H, NH_{cis}), 10.29 (s, 1H, NH_{trans}); ^{13}C NMR ($CDCl_3$) 11.8, 18.8, 20.7, 22.6, 23.6, 25.4, 25.8, 26.6, 27.7, 28.7, 33.1, 33.6, 34.8, 34.9, 35.1, 39.0, 39.7, 41.0, 42.5, 45.9, 49.1, 50.9, 53.4, 62.6, 68.6, 74.1, 126.5, 126.8, 127.2, 127.7, 128.5, 128.7, 129.3, 129.6, 131.3, 131.4, 131.7, 133.0, 133.2, 133.5, 134.2, 139.5, 143.0, 148.2, 165.2, 169.0, 175.8; ESI–MS: m/z 812 $[M+H]^+$.

(55)

Heterocyclic building block (**22**) (10.3 mg, 0.029 mmol) and (**39**) (20.0 mg, 0.029 mmol) were employed in the general procedure. The heterocyclic dimer (**55**) was obtained as a glassy solid (16.4 mg, 62 %); ^{1}H NMR ($CDCl_3$) 0.87 (s, 3H, 18–Me), 0.95 (m, 6H, 19, 21–Me), 2.51 (m, 2H, 23–H), 3.32 (m, 2H, H_{IQ}–4), 3.42 (d, *J* = 14.7 Hz, 1H, H_{IQ}–1), 3.56 (d, *J* = 13.8 Hz, 1H, H_ι), 3.68 (t, *J* = 6.4 Hz, 1H, H_{IQ}–3), 3.84 (d, *J* = 14.7 Hz, 1H, H_{IQ}–1), 4.11 (d, *J* = 13.8 Hz, 1H, H_ι), 4.90 (m, 1H, 3βH), 5.46 (m, 1H, 12βH), 6.96 (d, *J* = 7.2 Hz, 1H, H_{IQ}–8), 7.18–7.27 (m, 5H,

H_{IQ}–5,6,7, $H\lambda$), 7.39 (d, *J* = 8.1 Hz, 2H, $H\kappa$), 7.45 (t, *J* = 7.8 Hz, 1H, $H\varepsilon$), 7.56 (s, 1H, $H\gamma$), 7.60 (s, 1H, $H\mu$), 8.03 (dt, *J* = 1.3, 7.7 Hz, 1H, $H\delta$), 8.08 (dd, *J* = 1.5, 4.5 Hz, 2H, β–pyridyl), 8.16 (d, *J* = 7.7 Hz, 1H, $H\eta$), 8.74 (brs, 1H, NH_{cis}), 8.80 (dd, *J* = 1.5, 4.5 Hz, 2H, α–pyridyl), 8.95 (s, 1H, $H\theta$), 11.52 (s, 1H, NH_{trans}); ^{13}C NMR ($CDCl_3$) 12.5, 18.1, 22.8, 23.2, 25.2, 25.8, 25.9, 26.1, 26.2, 26.9, 28.4, 30.2, 31.9, 32.3, 33.5, 34.6, 35.5, 41.3, 45.1, 45.5, 50.9, 51.4, 60.6, 64.1, 74.0, 77.5, 123.2, 126.2, 126.3, 126.8, 127.4, 128.0 128.4, 129.0, 129.0, 130.9, 131.7, 132.5, 133.9, 134.6, 135.1, 138.3, 140.3, 142.9, 149.4, 150.8, 163.4, 164.9, 171.2, 175.4; Two resonances missing or degenerate; ESI–MS: m/z 917 $[M+H]^+$, 939 $[M+Na]^+$, found 939.4758, $C_{56}H_{64}N_6O_6Na$ requires 939.4785.

(58)

Hydrazide (**15**) (57 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (30 mL) giving a 5 mM solution. TFA (0.15 mL) was added and the solution was stirred at ambient atmosphere and temperature for 7 days. Et_3N (0.5 mL) was added and the mixture was evaporated to dryness. The crude was purified by dry column vacuum chromatography (CH_2Cl_2 to 5% EtOH in CH_2Cl_2 with 1% Et_3N in all fractions) and then another dry column (hexane to MeCN with 10 % gradient) to yield the pure dimer. Yield: 35 mg, 75 % as a white solid material. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.13 (dd, 2H), 3.21-3.29 (m, 2H), 3.52 (d, 2H), 3.56-3.63 (m, 2H), 3.94 (d, 2H), 4.07 (d, 2H), 4.14-4.21 (m, 2H), 5.29 (s, 2H), 7.10-7.37 (m, 12H), 7.42-7.48 (m, 2H), 7.51-7.58 (m, 2H), 8.62 (br s, 2H). MS (ESI^+): m/z 583 $[M+H]^+$. HRMS: found 583.2840, $C_{36}H_{35}N_6O_2$ requires 583.2821.

(59)

Hydrazide (**22**) (57 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (30 mL) giving a 5 mM solution. TFA (0.15 mL) was added and the solution was stirred at ambient atmosphere and temperature for 7 days. Et_3N (0.5 mL) was added and the mixture was evaporated to dryness. The crude was purified by dry column vacuum chromatography (CH_2Cl_2 to 5% EtOH in CH_2Cl_2 with 1% Et_3N in all fractions) and then another dry column (hexane to MeCN with 10 % gradient) to yield the pure dimer. Yield: 39 mg, 83 % as a white solid material. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.09 (dd, 1H, IQ-4), 3,21 (dd, 1H, IQ-4), 3.53 (t, 1H, IQ-3, α-proton), 3.55 (d, 1H, IQ-1), 3.86 (d, 1H, IQ-1), 3.90 (d, 1H, benzyl), 4.03 (d, 1H, benzyl), 7.18-7.26 (m, 5H), 7.32 (t, 1H, H_ε), 7.39 (s, 1H, H_γ), 7.82 (d, 1H, H_η), 7.94 (s, 1H, H_μ), 10.14 (s, 1H, NH_{cis}). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 29.6, 53.4, 60.4, 62.6, 126.2, 126.5, 127.7, 128.0, 129.3, 130.5, 131.3, 134.0, 134.6, 135.4, 138.1, 148.1, 169.4. MS (ESI^+): m/z 583 $[M+H]^+$. HRMS: found 583.2837, $C_{36}H_{35}N_6O_2$ requires 583.2821.