4. EXPERIMENTAL

Experimental Part Index

4.1. Instrumental

Melting points (mp) and **decomposition temperatures** (decomp.) were measured on opened capillars on a Büchi-Tottoli 530 instrument and were not corrected.

Infrared spectra (IR) were recorded in a Nicolet Magna 560 FTIR spectrophotometer, at the Organic Chemistry Department at IQS, by Ms. M. Carmen Meca and Ms. Núria Ruiz, supervised by Dr. X. Batllori. Wave numbers are expressed in cm^{-1}. The used notation is: *st* (stretching), *b* (bending), KBr (potassium bromide pellet), film (evaporated film in $CHCl_3$), soln (solution in $CHCl_3$).

Nuclear Magnetic Ressonance spectra (^{1}H-NMR and ^{13}C-NMR) were recorded in a Varian Gemini 300HC instrument (operating at a field strength of 300 MHz and 75.5 MHz respectively) or a Varian Gemini 400-MR instrument (^{1}H-NMR 400 MHz and ^{13}C-NMR 100.6 MHz), at the Organic Chemistry Department at IQS, by Dr. X. Batllori, Ms. Núria Ruiz or myself, supervised by Dr. X. Batllori. Chemical shifts are reported in parts per million (δ-scale) and coupling constants (*J*) in Hz by using, in the case of ^{1}H-NMR spectroscopy, tetramethylsilane (TMS) or sodium 2,2,3,3-tetradeutero-3-(trimethylsilil)propionate (TSPNa) as an internal standard. In the case of ^{13}C-NMR spectra, solvent residual peak was taken as reference: $CDCl_3$ at 77.0 ppm, d6-DMSO at 39.5 ppm, d-TFA at 163.8 ppm, CD_3OD at 49.0 ppm. Standard and peak multiplicities are designated as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), qn (quintet), m (multiplet), br (broad signal), cs (complex signal). Interchangeable signals are marked with an asterisk (*).

Organic elemental analyses (OEA) were obtained on a Carlo Erba CHNS-O/EA 1108 analyzer, at the Organic Chemistry Department at IQS, by Ms. Núria Ruiz, supervised by Dr. X. Batllori.

Low resolution mass spectra (MS) were recorded at the Organic Chemistry Department at IQS by Ms. M. Carmen Meca and Ms. Núria Ruiz, supervised by Dr. X. Batllori, using an Agilent Technologies 5975 spectrometer, and at the Mass Spectrometry Service at the Universidad de Santiago de Compostela, supervised by Dr. E. Gutián, by using a Hewlett Packard HP5988A quadrupole mass spectrometer operating in electronic ionisation (EI) mode at 70 eV and at 4 kV accelerating potential, or a Bruker Biotoff II spectrometer operating in electrospray ionization (ESI) mode with a Time of Flight (TOF) detector.

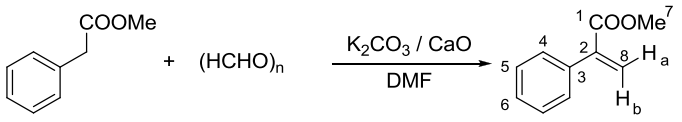
High resolution mass spectra (HRMS) were recorded at the Mass Spectrometry Service at the Universidad de Santiago de Compostela, supervised by Dr. E. Gutián, by using a VG AutoSpec (Micromass Instruments) Trisector EBE high resolution spectrometer (EI mode), a Bruker Biotof II mass spectrometer (ESI-TOF mode) or a Bruker Autoflex spectrometer (MALDI-TOF mode, HCCA matrix).

Specific optical rotations ($[\alpha]_D$) were measured with a Perkin Elmer 241 polarimeter at the Organic Chemistry Department at IQS, by Ms. Núria Ruiz. Sodium D line (589 nm) and a path length of 1 dm were used for measuring at room temperature.

Anti-HIV activities (EC_{50}) and **cytotoxicity** (CC_{50}) measurements in MT-4 cells were based on the viability of cells that had been infected or not infected with HIV-1, all of them having been exposed to various concentrations of the test compouds. After the MT-4 cells were allowed to proliferate for 5 days, the number of viable cells was quantified by a tetrazolium-based colorimetric method (MTT method). Biological evaluations were carried out by Dr. Imma Clotet-Codina and Ms. Maria Pau Mena, at the Retrovirology Laboratory IrsiCaixa, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, under the leadership of Dr. José A. Esté.

I thank them all for their excellent work.

4.2. Synthesis of methyl 2-phenylacrylate (15{*4*})



33 **34** **15**{*4*}

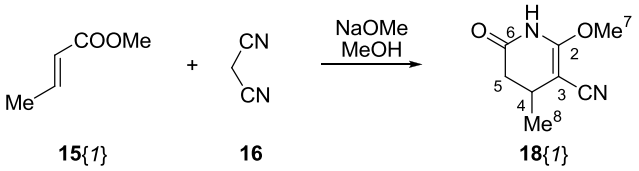
To a solution of 30.04 g (0.2 mol) of phenylacetate (**33**) in 100 ml of DMF were added, in this order, 11.22 g (0,2 mol) CaO, 27.64 g (0.2 mol) K_2CO_3 and 6.00 g (0,2 mol) paraformaldehyde. The mixture was heated to 40 ºC for 48 h, in which the starting material ran out (reaction can be followed by TLC). The mixture was cooled to room temperature and the milky suspension was dissolved in the minimum water volume and extracted with CH_2Cl_2 (3 · 100 ml). The organic extracts were combined, dried over $MgSO_4$, and the solvent was removed to give 17.77 g (0.11 mol, 55%) of **15**{*4*} as a colourless oil.

Spectroscopic data

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.31 (m, 5H, H-C4, H-C5, H-C6), 6.36 (s, 1H, Ha), 5.89 (s, 1H, Hb), 3.82 (s, 3H, H-C7)

4.3. Synthesis of 2-methoxy-6-oxo-1,4,5,6-tetrahydropyrido-3-carbonitriles 18

4.3.1. Synthesis of 2-methoxy-4-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (18{*1*})



15{*1*} **16** **18**{*1*}

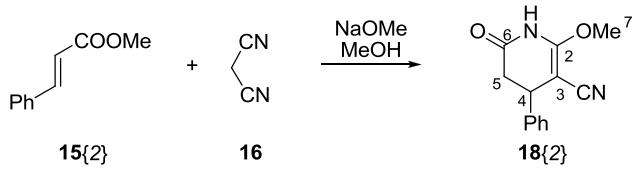
8.2 g (0.36 mmol) of sodium were dissolved in 250 ml of methanol. Once reacted, 25.0 g (0.30 mol) of methyl crotonate (**15**{*1*}) and 19.8 g (0.30 mol) of malononitrile (**16**) were added. The mixture was heated at reflux for 1.5 h, cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in the minimum water volume (150 ml), cooled to 0 ºC and slowly neutralized with HCl 6 M until pH = 8-9. The precipitate was filtered when appearing, rinsed with cold water and dried over P_2O_5. The desired product **18**{*1*} was obtained as a pale yellow solid (22.0 g, 0.13 mol, 53%), mp = 92-95 ºC.

Spectroscopic data

IR (KBr) ν (cm^{-1}): 3191, 3107 (*st* N-H), 2968, 2935 (*st* Csp^3-H), 2203 (*st* C≡N), 1693 (*st* C=O), 1645 (*st* C=C)

^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm): 3.88 (s, 3H, H-C7), 2.65 (dd, ^3J = 7 Hz, ^3J = 7 Hz, 1H, H-C4), 2.56 (dd, ^2J = 16 Hz, ^3J = 7 Hz, 1H, H-C5), 2.20 (dd, ^2J = 16 Hz, ^3J = 7 Hz, 1H, H-C5), 1.06 (d, ^3J = 7 Hz,3H, H-C8)

4.3.2. Synthesis of 2-methoxy-4-phenyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (18{*2*})



15{*2*} **16** **18**{*2*}

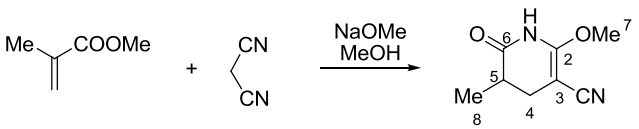
The procedure was the same as stated above for **18**{*1*} using 4.1 g (0.18 mol) of sodium, 150 ml of methanol, 24.3 g (0.15 mol) of methyl cynnamate (**15**{*2*}) and 19.8 g (0.30 mol) of malononitrile (**16**). The mixture was held at reflux for 2 h. Once the solvent was removed under reduced pressure, the residue was dissolved in the minimum water volume (150 ml). The desired product **18**{*2*} was obtained as a yellow solid (26.7 g, 0.12 mol, 78%), mp = 136 ºC.

Spectroscopic data

IR (KBr) ν (cm^{-1}): 3204, 3104 (*st* N-H), 3037, 3009 (*st* Csp^2-H), 2936 (*st* Csp^3-H), 2207 (*st* C≡N), 1697 (*st* C=O), 1641 (*st* C=C), 774, 708 (*b* C-H)

^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm): 10.78 (s, 1H, N-H), 7.40-7.24 (m, 5H, H-Ph), 3.97 (s, 3H, H-C7), 3.90 (dd, ^3J = 6 Hz, ^3J = 7 Hz, 1H, H-C4), 2.95 (dd, ^2J = 16 Hz, ^3J = 7 Hz, 1H, H-C5), 2.56 (dd, ^2J = 16 Hz, ^3J = 6 Hz, 1H, H-C5)

4.3.3. Synthesis of 2-methoxy-5-methyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (18{*3*})



15{*3*} **16** **18**{*3*}

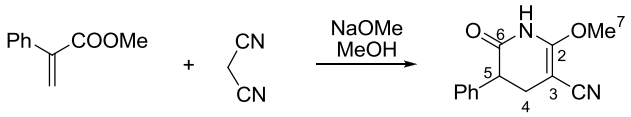
The procedure was the same as stated above for **18**{*1*} using 8.2 g (0.36 mol) of sodium, 250 ml of methanol, 25.0 g (0.30 mol) of methyl metacrylate (**15**{*3*}) and 19.8 g (0.30 mol) of malononitrile (**16**). The mixture was held at reflux for 1.5 h. Once the solvent was removed under reduced pressure, the residue was dissolved in the minimum water volume (150 ml) and the desired product **18**{*3*} was obtained as a yellow solid (17.6 g, 0.11 mol, 42%), mp = 138-140 ºC.

Spectroscopic data

IR (KBr) ν (cm^{-1}): 3207, 3108 (*st* N-H), 2995, 2968, 2955,2934 (*st* Csp^3-H), 2196 (*st* C≡N), 1694 (*st* C=O), 1638 (*st* C=C), 1261 (*st* C-O)

^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm): 10.53 (s, 1H, N-H), 3.89 (s, 3H, H-C7), 2.53 (dd, ^3J = 10 Hz, ^3J = 7 Hz, 1H, H-C5), 2.41 (dd, ^2J = 15 Hz, ^3J = 7 Hz, 1H, H-C4), 2.18 (dd, ^2J = 15 Hz, ^3J = 10 Hz, 1H, H-C5), 1.07 (d, ^3J = 7 Hz,3H, H-C8)

4.3.4. Synthesis of 2-methoxy-5-phenyl-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (18{*4*})



15{*4*} **16** **18**{*4*}

The procedure was the same as stated above for **18**{*1*} using 1.6 g (70 mmol) of sodium, 60 ml of methanol, 9.7 g (60 mmol) of phenyl acrylate **15**{*4*} and 4.0 g (61 mmol) of malononitrile (**16**). The mixture was held at reflux for 2 h. Once the solvent was removed under reduced pressure, the residue was dissolved in the minimum water volume (200 ml). The desired product **18**{*4*} was obtained as a yellow solid (5.5 g, 24 mmol, 40%), mp = 115-120 ºC.

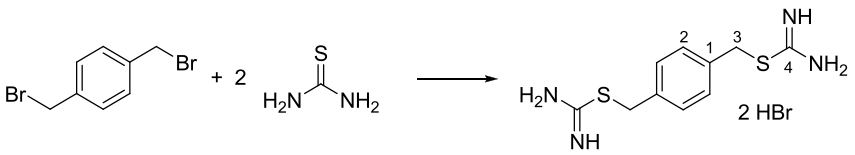
Spectroscopic data

IR (KBr) ν (cm^{-1}): 3210, 3117 (*st* N-H), 3032 (*st* Csp^2-H), 2955, 2923 (*st* Csp^3-H), 2201 (*st* C≡N), 1709 (*st* C=O), 1645 (*st* C=C), 1225 (*st* C-O), 762, 700 (*b* C-H)

^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm): 10.79 (s, 1H, N-H), 7.37-7.23 (m, 5H, H-Ph), 3.94 (s, 3H, H-C7), 3.85 (dd, ^3J = 8 Hz, ^3J = 10 Hz, 1H, H-C5), 2.73 (dd, ^2J = 15 Hz, ^3J = 10 Hz, 1H, H-C4), 2.57 (dd, ^2J = 15 Hz, ^3J = 8 Hz, 1H, H-C4)

4.4. Synthesis of *p*-xylylene spacers

4.4.1. Synthesis of *p*-xylylenbisisothiouronium dibromide (23·2HBr)



35a **20**{*3*} **23·2HBr**

A heterogeneous mixture of 5.28 g (20 mmol) of α,α'-dibromo-*p*-xylene (**35a**) and 3.04 g (40 mmol) of thiourea (**20**{*3*}) in 350 ml of isopropanol was held at reflux until total conversion of reagents (3 h, reaction can be followed by TLC). The resulting mixture was cooled to 4 ºC overnight and the white precipitate was collected by filtration and washed with cold isopropanol.

After drying, 8.04 g (19 mmol, 96%) of **23·2HBr** were obtained, mp = 252-253 ºC.

Spectroscopic data

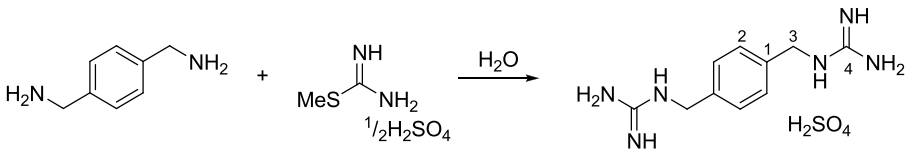
IR (KBr) ν (cm^{-1}): 3284, 3234, 3172 (*st* N-H), 3066 (*st* Csp^2-H), 2951, 2913 (*st* Csp^3-H), 1653, 1623 (*st* C=C, *st* C=N), 815 (*b* C-H)

^{1}H-NMR (300 MHz, D_2O) δ (ppm): 7.51 (s, 4H, H-C2), 4.44 (s, 4H, H-C3)

^{13}C-NMR (75.5 MHz, D_2O) δ (ppm): 170.7 (C4), 134.8 (C1), 130.0 (C2), 35.3 (C3)

OEA calculated for $C_{10}H_{16}Br_2N_4S_2$: C 28.86%, H 3.87%, N 13.46%, S 15.41%; found C 28.90%, H 3.86%, N 13.36%, S 15.71%

4.4.2. Synthesis of *p*-xylylendiguanidinium sulphate (24·H_2SO_4)



37 **20{*4*}·$^1/_2H_2SO_4$** **24·H_2SO_4**

A heterogeneous mixture of 1.36 g (10 mmol) of *p*-xylylenediamine (**37**) and 2.78 g (20 mmol) of *S*-methylthiourea sulphate (**20**{*4*}) in 10 ml of water was stirred at room temperature for 48 h. The reaction mixture was repeatedly concentrated, adding water until deplacing all methylmercaptane. The residue was stirred with 3 ml water for 10 minutes and crystalized at 4 ºC.

The white solid was recrystallized from water to obtain 2.25 g (7 mmol, 71%) of *p*-xylylendiguanidinium sulphate (**24·H_2SO_4**) as a white solid, mp > 250 ºC. A second, less pure fraction can be obtained by concentration of the filtrate, to reach a total yield of 81%.

Spectroscopic data

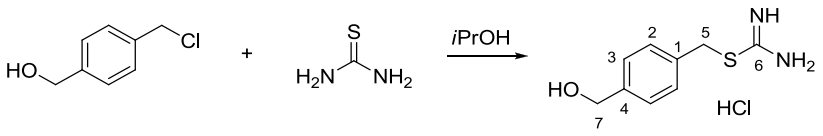
IR (KBr) ν (cm^{-1}): 3353, 3279, 3164 (*st* N-H), 3029 (*st* Csp^2-H), 2891 (*st* Csp^3-H), 1672, 1634 (*st* C=C, *st* C=N)

^{1}H-NMR (300 MHz, D_2O) δ (ppm): 7.37 (s, 4H, H-C2), 4.44 (s, 4H, H-C3)

^{13}C-NMR (75.5 MHz, D_2O) δ (ppm): 157.4 (C4), 136.3 (C1), 127.9 (C2), 44.8 (C3)

OEA calculated for $C_{10}H_{18}N_6O_4S$: C 37.73%, H 5.70%, N 26.40%, S 10.07%; found C 37.60%, H 5.86%, N 25.81%, S 10.29%

4.4.3. Synthesis of 2-(*p*-hydroxymethylbenzyl)isothiouronium chloride (27b·HCl)



36 **20**{*3*} **27b·HCl**

A heterogeneous mixture of 3.13 g (20 mmol) of α-chloro-α'-hydroxy-*p*-xylene (**36**) and 1.52 g (20 mmol) of thiourea (**20**{*3*}) in 300 ml of isopropanol was heated at reflux until complete conversion of reagents (3 h, reaction can be followed by TLC). The mixture was cooled to 4 ºC overnight and the white precipitate was collected by filtration and rinsed with cold isopropanol.

After drying over P_2O_5, 3.26 g (14 mmol, 85%) of 2-(*p*-hydroxymethylbenzyl)isothiouronium chloride (**27b·HCl**) were obtained, mp = 193-194 ºC.

Spectroscopic data

IR (KBr) ν (cm^{-1}): 3358, 3272, (*st* N-H, *st* O-H), 3012 (*st* Csp^2-H), 1647 (*st* C=C, *st* C=N, *b* N-H), 1008 (*st* C-O), 831 (*b* C-H)

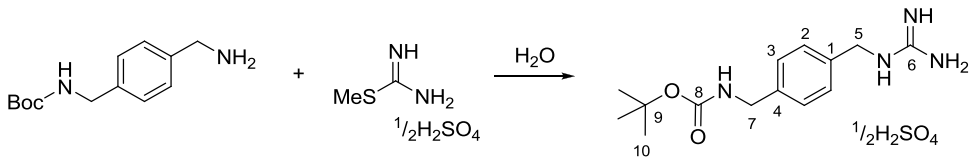
^{1}H-NMR (300 MHz, D_2O) δ (ppm): 7.46 (m, 2H, H-C3), 7.42 (m, 2H, H-C2), 4.63 (s, 2H, H-C7), 4.41 (s, 2H, H-C5)

^{13}C-NMR (75.5 MHz, D_2O) δ (ppm): 170.9 (C6), 140.9 (C4), 134.0 (C1), 129.6 (C2), 128.5 (C3), 64.0 (C7), 35.5 (C5)

MS (EI) *m/z* (%): 196 (100) $[M-1]^+$, 121 (78) $[C_8H_9O]^+$, 91 (37) $[C_7H_7]^+$, 77 (17) $[C_6H_5]^+$

OEA calculated for $C_9H_{13}ClN_2OS$: C 46.45%, H 5.63%, N 12.04%, S 13.78%; found C 46.55%, H 5.75%, N 11.94%, S 13.62%

4.4.4. Synthesis of 4-(guanidinomethyl)benzyl-*tert*-butylcarbamate sulphate (28·½H_2SO_4)



40 **20**{*4*}·$^1/_2H_2SO_4$ **28**·$^1/_2H_2SO_4$

A heterogeneous mixture of 0.974 g (4 mmol) of *p*-(aminomethyl)benzyl-*tert*-butylcarbamate (**40**) and 0.557 g (4 mmol) of *S*-methylthiourea sulphate (**20**{*4*}) in 10 ml of water was stirred at room temperature for 60 h. The reaction mixture was repeatedly concentrated, adding water until deplacing all methylmercaptane. The residue was stirred with 3 ml water for 10 minutes and crystalized at 4 ºC.

The white solid was recrystallized from water to obtain 0.332 g (1 mmol, 25%) of the desired product (**28·½H_2SO_4**) as a white solid. A second, less pure fraction can be obtained by concentration of the filtrate, to reach a total yield of 40%.

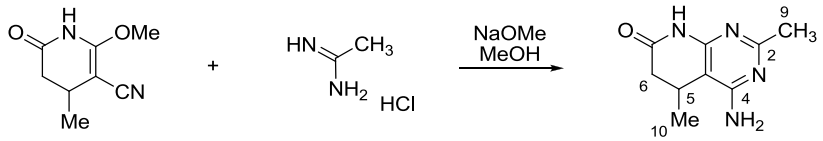
Spectroscopic data

IR (KBr) ν (cm^{-1}): 3358, 3335 (*st* N-H), 3051 (*st* Csp^2-H), 2977, 2931 (*st* Csp^3-H), 1685 (*st* C=O), 1645 (*st* C=C, *st* C=N), 1180 (*st* C-O)

^{1}H-NMR (300 MHz, D_2O) δ (ppm): 7.32-7.16 (m, 4H, H-C2, H-C3), 4.73 (t, ^3J = 6 Hz, 1H, NHCO), 4.09 (d, ^3J = 6 Hz, 2H, H-C7), 1.38 (s, 9H, H-C10)

4.5. Synthesis of pyrido[2,3-*d*]pyrimidine derivatives

4.5.1. Synthesis of 4-amino-2,5-dimethyl-7-oxo-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (21{*1*,*1*})



18{*1*} **20**{*1*}·**HCl** **21**{*1*,*1*}

0.41 g (18 mmo) of sodium were dissolved in 15 ml of methanol. 1.75 g (18 mmol) of acetamide hydrochloride (**20**{*1*}) were added and the mixture was heated at reflux for 15 minutes. After cooling to room temperature, the mixture was filtered to remove NaCl. 1.07 g (6 mmol) of carbonitrile **18**{*1*},were added to the so prepared amidine solution and heated at reflux for 24 hours.

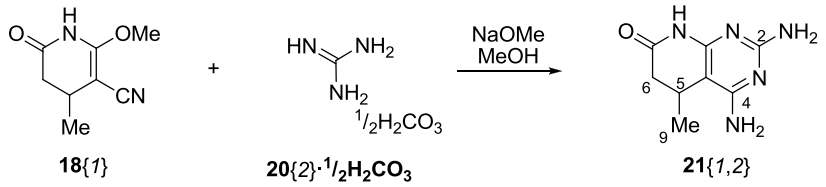
The formed precipitate was collected by filtration and washed thoroughly with cold methanol and dried over P_2O_5, providing 0.18 g (1 mmol, 15%) of **21**{*1*,*1*} as a white solid, whose spectral data were in agreement with authentic material.

Spectroscopic data

IR (KBr) ν (cm^{-1}): 3420, 3365, 3184, 3124 (*st* N-H), 2966, 2953, 2922 (*st* Csp^3-H), 1699 (*st* C=O), 1649, 1610, 1569 (*st* C=C, *st* C=N, *b* N-H)

^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm): 10.18 (s, 1H, NH), 6.58 (s, 2H, NH_2), 3.05 (m, ^3J = 7 Hz, ^3J = 7 Hz, ^3J = 1 Hz, 2H, H-C5), 2.70 (dd, ^2J = 16 Hz, ^3J = 7 Hz, 1H, H-C6), 2.27 (dd, ^2J = 16 Hz, ^3J = 1 Hz, 1H, H-C6), 2.22 (s, 3H, H-C9), 0.97 (d, ^3J = 7 Hz, 3H, H-C10)

4.5.2. Synthesis of 2,4-diamino-5-methyl-7-oxo-5,6,7,8-tetrahydropyrido[2,3-*d*]pyrimidine (21{*1*,*2*})



18{*1*} **20**{*2*}·$^1/_2$**H$_2$CO$_3$** **21**{*1*,*2*}

The procedure was the same as stated above for **21**{*1*,*1*} using 0.48 g (21 mmo) of sodium, 2.52 g (28 mmol) of guanidine carbonate (**20**{*2*}·**½H$_2$CO$_3$**) and 1.15 g (7 mmol) of 2-methoxycarbonitrile **18**{*1*}.

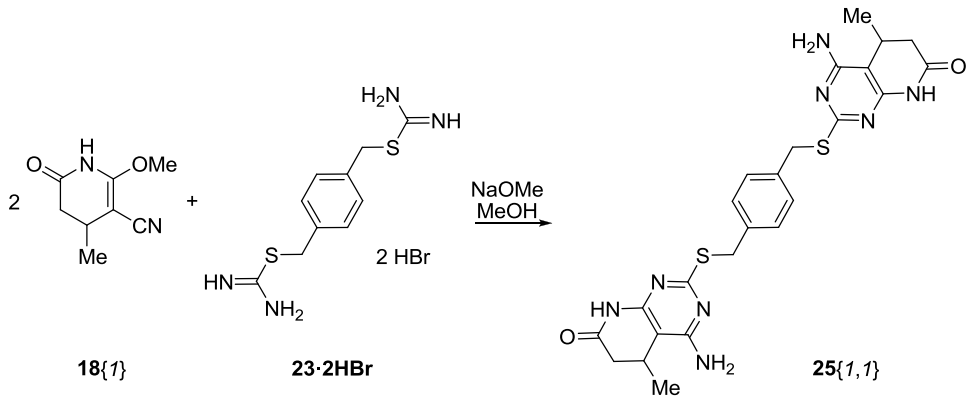
0.59 g (3 mmol, 44%) of the desired product **21**{*1*,*2*} were obtained, whose spectral data were in agreement with authentic material.

Spectroscopic data

IR (KBr) ν (cm^{-1}): 3454, 3339, 3225, 3104 (*st* N-H), 2987, 2938, 2883 (*st* Csp^3-H), 1666, 1642, 1570 (*st* C=C, *st* C=N, *b* N-H)

^{1}H-NMR (300 MHz, d$_6$-DMSO) δ (ppm): 9.95 (s, 1H, NH), 6.14 (s, 2H, NH$_2$-C4), 5.70 (s, 1H, NH$_2$-C2), 2.98 (m, ^3J = 7 Hz, ^3J = 7 Hz, ^3J = 1 Hz, 1H, H-C5), 2.64 (dd, ^2J = 16 Hz, ^3J = 7 Hz, 1H, H-C6), 2.18 (dd, ^2J = 16 Hz, ^3J = 1 Hz, 1H, H-C6), 0.93 (d, ^3J = 7 Hz, 3H, H-C9)

4.5.3. Synthesis of 2-((*p*-(4-amino-2-sulphanyl-5,6-dihydro-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one)-benzyl)sulphanyl)-4-amino-5,6-dihydro-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (25{*1,1*})



0.05 g (2.2 mmol) of sodium were dissolved in 40 ml of methanol and 0.42 g (1 mmol) of *p*-xylylenbisisothiouronium dibromide (**23·2HBr**) were added to the solution. The mixture was held at reflux for 15 minutes. Then a solution of 0.50 g (3 mmol) of the carbonitrile **18**{*1*} in 10 ml of methanol was added and the resulting mixture was heated at reflux for 5 days.

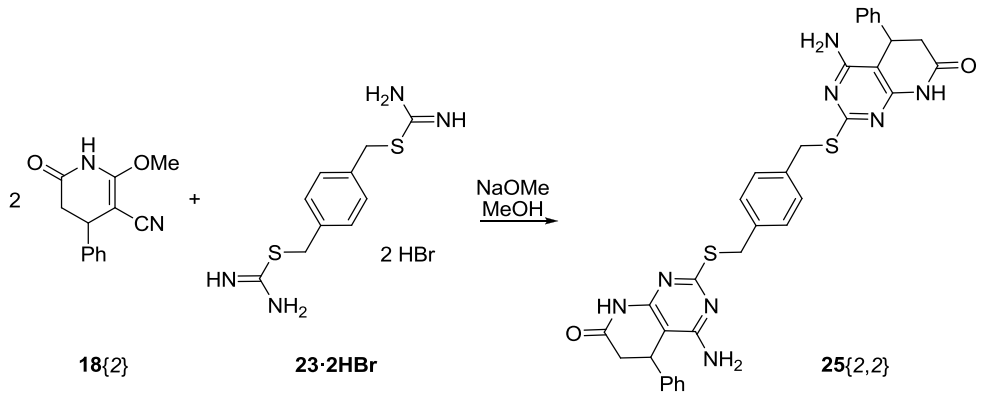
After collection by filtration, the precipitate was washed with methanol and cold water, and dried over P_2O_5 to yield 30 mg (0.06 mmol, 6%) of the desired product **25**{*1,1*}, as a light coloured solid, mp = 145-149 ºC.

Spectroscopic data

IR (KBr) ν (cm^{-1}): 3392 (*st* N-H), 3048, 3023, 3003 (*st* Csp^2-H), 2957, 2911, 2854 (*st* Csp^3-H), 1697 (*st* C=O), 1605, 1558, 1509 (*st* C=C, *st* C=N, *b* N-H), 836 (*b* C-H)

MS (MALDI-TOF, HCCA) *m/z* (%): 523.1 (100) $[M+1]^+$

4.5.4. Synthesis of 2-((*p*-(4-amino-2-sulphanyl-5,6-dihydro-5-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one)-benzyl)sulphanyl)-4-amino-5,6-dihydro-5-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (25{*2,2*})



The procedure was the same as stated above for **25**{*1,1*} using 0.05 g (2.2 mmol) of sodium, 40 ml of methanol, 0.42 g (1 mmol) of *p*-xylylenbisisothiouronium dibromide (**23·2HBr**) and 0.68 g (3 mmol) of the carbonitrile **18**{*2*} in 10 ml of methanol.

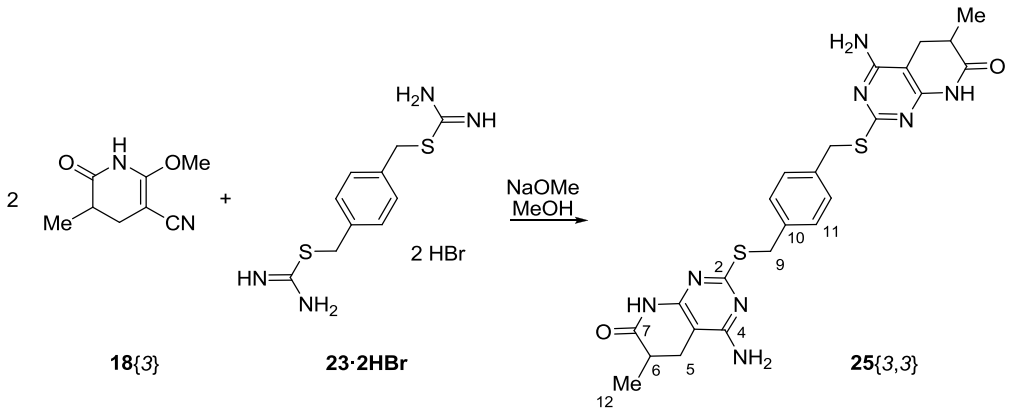
After 5 days at reflux, the precipitate was collected by filtration, rinsed with methanol and cold water and dried over P_2O_5 to yield 48 mg (0.07 mmol, 6%) of **25**{*2,2*} as a pale yellow solid, mp = 155-159 ºC.

Spectroscopic data

IR (KBr) ν (cm^{-1}): 3464, 3376, 3213 (*st* N-H), 3084, 3050, 3024 (*st* Csp^2-H), 2957, 2912 (*st* Csp^3-H), 1700 (*st* C=O), 1610, 1556, 1510 (*st* C=C, *st* C=N, *b* N-H), 837 (*b* C-H)

HRMS (MALDI-TOF, HCCA) *m/z* (%): calculated for $C_{34}H_{31}N_8S_2O_2$ $[M+1]^+$: 647.2011; found 647.1225 (100) $[M+1]^+$

4.5.5. Synthesis of 2-((*p*-(4-amino-2-sulphanyl-5,6-dihydro-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one)-benzyl)sulphanyl)-4-amino-5,6-dihydro-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (25{*3*,*3*})



The procedure was the same as stated above for **25**{*1*,*1*} using 0.05 g (2.2 mmol) of sodium, 40 ml of methanol, 0.42 g (1 mmol) of *p*-xylylenbisisothiouronium dibromide (**23·2HBr**) and 0.50 g (3 mmol) of the carbonitrile **18**{*3*} in 10 ml of methanol.

After 5 days at reflux, the precipitate was collected by filtration, rinsed with methanol and cold water and dried over P_2O_5 to yield 80 mg (0.15 mmol, 15%) of **25**{*3*,*3*} as a pale yellow solid, mp > 215 ºC.

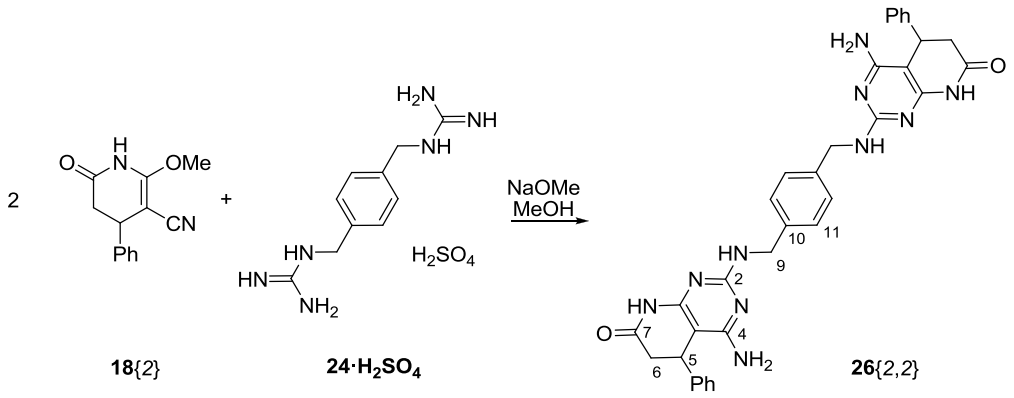
Spectroscopic data

IR (KBr) ν (cm^{-1}): 3472, 3308, 3178, 3124 (*st* N-H), 3048, 3024 (*st* Csp^2-H), 2967, 2930 (*st* Csp^3-H), 1692 (*st* C=O), 1638, 1599, 1557 (*st* C=C, *st* C=N, *b* N-H), 836 (*b* C-H)

^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm): 10.27 (s, 2H, NH), 7.36 (s, 4H, H-C11), 6.74 (s, 4H, NH_2) 4.24 (s, 4H, H-C9), 2.78 (m, ^2J = 16 Hz, ^3J = 7 Hz, 2H, H-C5), 2.28 (m, ^2J = 16 Hz, ^3J = 7 Hz, 2H, H-C5), 1.13 (d, ^3J = 7 Hz, 6H, H-C12)

MS (MALDI-TOF, HCCA) *m/z* (%): 545,4 (100) $[M+23]^+$, 523.6 (45) $[M+1]^+$

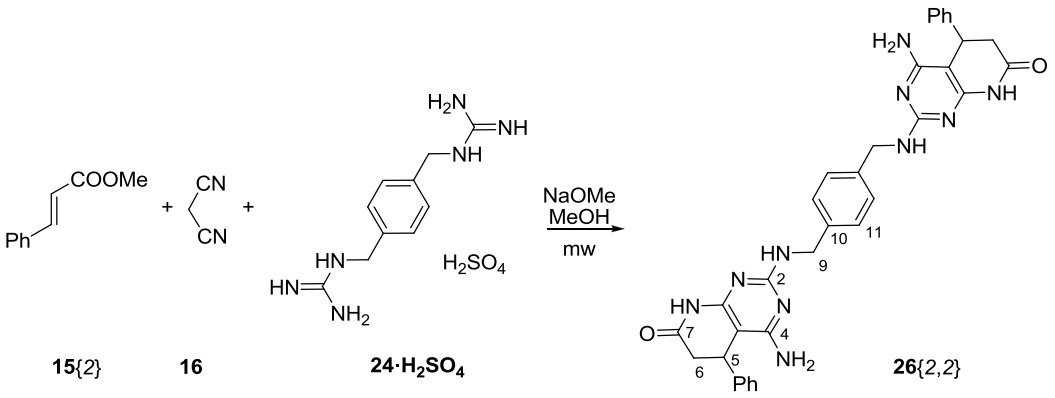
4.5.6. Synthesis of 2-((*p*-(4-amino-2-amino-5,6-dihydro-5-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one)benzyl)amino)-4-amino-5,6-dihydro-5-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (26{*2,2*})



0.32 g (3.0 mmol) of *p*-xylylendiguanidinium sulphate (**24·H_2SO_4**) were dissolved in a solution of 0.07 g (3.0 mmol) of sodium in 30 ml of methanol, and the resulting solution was heated at reflux for 15 minutes. Then 0.91 g (4 mmol) of **18**{*2*} were added and the mixture was held at reflux for 4 days

The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in 30 ml of water and neutralized with 6 M HCl. The desired product **26**{*2,2*} was collected by filtration, washed with cold water and methanol and dried over P_2O_5 to yield 97 mg (0.16 mmol, 16%) of a light coloured solid, mp = 210ºC.

4.5.7. One-pot synthesis of 2-((*p*-(4-amino-2-amino-5,6-dihydro-5-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one)benzyl)amino)-4-amino-5,6-dihydro-5-phenylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (26{*2*,*2*})



15{*2*} **16** **24·H_2SO_4** **26**{*2*,*2*}

To a solution of 0.06 g (2.5 mmol) of sodium in 10 ml of methanol were added 0.32 g (1 mmol) of *p*-xylylendiguanidinium sulphate (**24·H_2SO_4**) and the mixture was heated at reflux for 15 minutes. Then the solution was cooled to room temperature and the precipitated was filtered before addition of 0.41 g (2.5 mmol) of methyl cynnamate (**15**{*2*}) and 0.20 g (3 mmol) of malononitrile (**16**). The mixture was heated at reflux for 24 hours.

The precipitate was collected by filtration, rinsed with methanol and water and dried over P_2O_5, yielding 0.164 g (0.27 mmol, 27%) of **26**{*2*,*2*} as a pale yellow solid, mp > 250ºC.

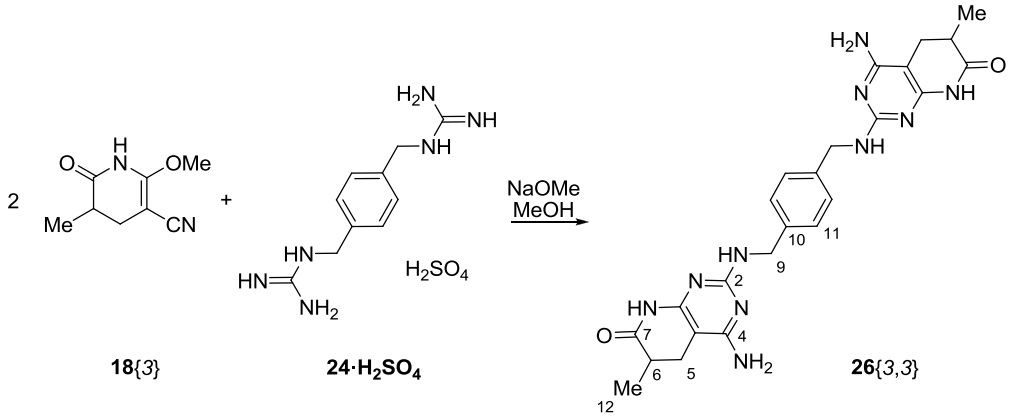
Spectroscopic data

IR (KBr) ν (cm^{-1}): 3448, 3341, 3192 (*st* N-H), 3064, 3028 (*st* Csp^2-H), 2970, 2922, 2852 (*st* Csp^3-H), 1679 (*st* C=O), 1627, 1587, 1545(*st* C=C, *st* C=N, *b* N-H)

^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm): 9.79 (s, 2H, NHCO), 7.28-7.10 (m, 14H, H-C11, H-Ar), 6.81 (s, 4H, NH_2), 5.98 (S, 2H, NH), 4.06 (s, 4H, H-C9), 3.02 (dd, ^3J = 7 Hz, ^2J = 14 Hz, 2H, H-C6), 2.38 (dd, ^2J = 14 Hz, ^3J = 7 Hz, 2H, H-C6)

HRMS (ESI-TOF) *m/z* (%): calculated for $C_{34}H_{33}N_{10}O_2$ $[M+1]^+$: 613.2782; found 613.2763 (53) $[M+1]^+$, 358.1357 (100)

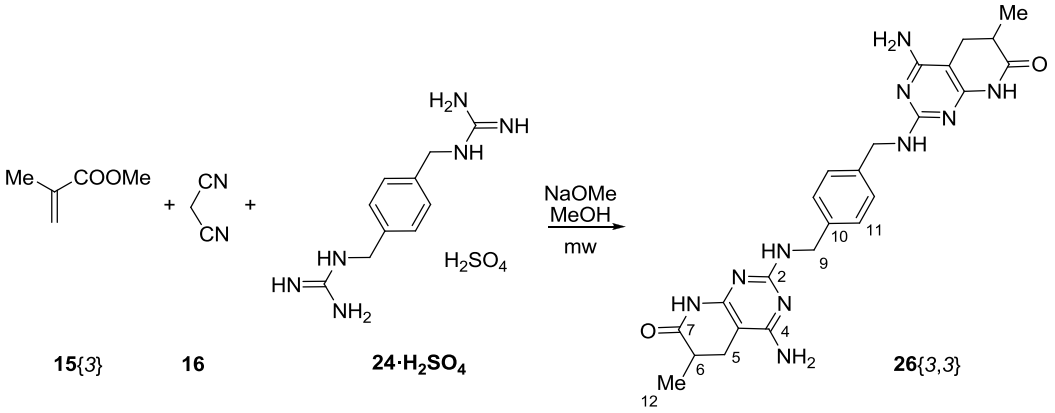
4.5.8. Synthesis of 2-((*p*-(4-amino-2-amino-5,6-dihydro-6-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one)benzyl)amino)-4-amino-5,6-dihydro-6-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one (26{*3*,*3*})



The procedure was the same as stated above for **26**{*2*,*2*} using 0.07 g (3.0 mmol) of sodium, 0.32 g (1 mmol) of *p*-xylylendiguanidinium sulphate (**24·H_2SO_4**) and 0.66 g (4 mmol) of the carbonitrile **18**{*3*}.

The solvent was removed under reduced pressure and the residue was neutralized with 6 M HCl. A pale coloured solid (**26**{*3*,*3*}) was collected (255 mg, 0.52 mmol, 52%), washed with water and cold methanol and dried over P_2O_5, mp = 215ºC.

4.5.9. One-pot synthesis of 2-((*p*-(4-amino-2-amino-5,6-dihydro-6-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one)benzyl)amino)-4-amino-5,6-dihydro-6-methylpyrido[2,3-d]pyrimidin-7(8*H*)-one (26{*3*,*3*})



15{*3*} **16** **24·H_2SO_4** **26**{*3*,*3*}

The procedure was the same as stated above for **26**{*2*,*2*} using 0.06 g (2.5 mmol) of sodium, 0.32 g (1 mmol) of *p*-xylylendiguanidinium sulphate (**24·H_2SO_4**), 0.25 g (2.5 mmol) of methyl metacrylate (**15**{*3*}) and 0.20 g (3 mmol) of malononitrile(**16**).

A yellow solid was obtained after 24 h, which was filtered, rinsed with cold water and methanol and dried over P_2O_5, yielding 0.150 g (0.30 mmol, 33%) of **26**{*2*,*2*} as a pale colourless solid, mp > 250ºC.

Spectroscopic data

IR (KBr) ν (cm^{-1}): 3466, 3333, 3197 (*st* N-H), 2962, 2927, 2869 (*st* Csp^3-H), 1636, 1588, 1555 (*st* C=C, *st* C=N, *b* N-H)

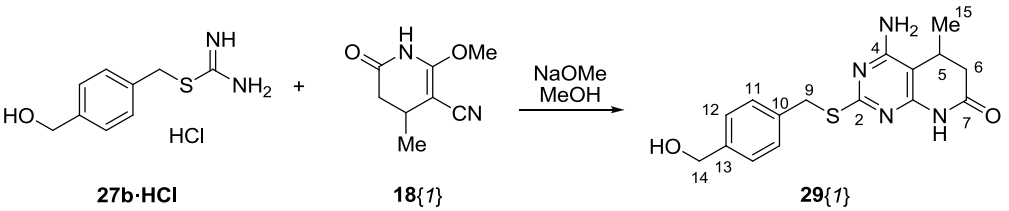
^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm): 9.76 (s, 2H, NHCO), 7.05 (s, 4H, H-C11), 6.79 (s, 4H, NH_2), 6.44 (s, 2H, NH), 4.33 (s, 4H, H-C9), 2.60 (dd, ^3J = 6 Hz, ^2J = 14 Hz, 2H, H-C5), 2.12 (dd, ^2J = 14 Hz, ^3J = 7 Hz, 2H, H-C5), 1.01 (d, ^3J = 7 Hz, 6H, H-C12)

HRMS (ESI-TOF) *m/z* (%): calculated for $C_{24}H_{29}N_{10}O_2$ $[M+1]^+$: 489.2469; found 489.2455 (36) $[M+1]^+$, 296.1497 (100)

Biological activity

EC_{50} > 25 μg/ml; **CC_{50}** > 25 μg/ml

4.5.10. Synthesis of 2-(*p*-(hydroxymethyl)benzyl)sulphanyl-4-amino-5,6-dihydro-5-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (29{*1*})



27b·HCl **18**{*1*} **29**{*1*}

0.55 g (2.4 mmol) of 2-(*p*-hydroxymethylbenzyl)isothiouronium chloride (27b·HCl) were added to a solution of 0.08 g (3.6 mmol) of sodium in 20 ml of methanol, and the mixture was heated at reflux for 15 minutes. Then 0.83 g (5 mmol) of the carbonitrile **18**{*1*} in 10 ml of methanolwere added to the mixture and held at reflux for 3 days.

The mixture was cold to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in 20 ml of water and neutralized with 6 M HCl. The precipitate was filtered, washed with cold methanol and dried over P_2O_5, to yield 78 mg (0.24 mmol, 10%) of **29**{*1*} as a white solid, mp > 250ºC

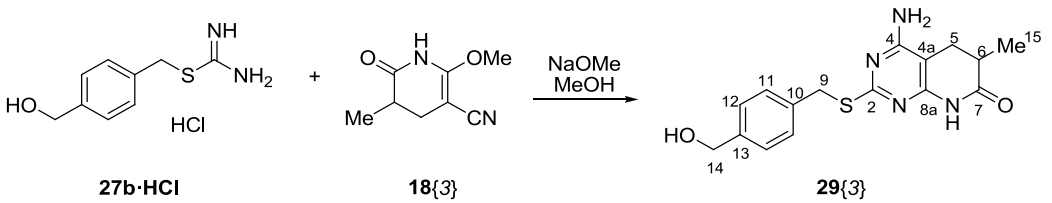
Spectroscopic data

IR (KBr) ν (cm^{-1}): 3343, 3256 (*st* N-H), 3050, 3024 (*st* Csp^2-H), 2962, 2927, 2918 (*st* Csp^3-H), 1697 (*st* C=O), 1655, 1617, 1577 (*st* C=C, *st* C=N, *b* N-H), 1011 (*st* C-O), 834 (*b* C-H)

^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm): 7.28 (m, 2H, H-C12), 7.22 (m, 2H, H-C11), 5.17 (t, ^3J = 6 Hz, 1H, OH), 4.47 (d, ^3J = 6 Hz, 2H, H-C14), 3.75 (s, 2H, H-C9), 1.01 (d, ^3J = 7 Hz, 3H, H-C15)

HRMS (ESI-TOF) *m/z* (%): calculated for $C_{16}H_{19}N_4O_2S$ $[M+1]^+$: 331.1223; found 331.1223 (89) $[M+1]^+$, 327.1451 (100)

4.5.11. Synthesis of 2-(*p*-(hydroxymethyl)benzyl)sulphanyl-4-amino-5,6-dihydro-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (29{*3*})



27b·HCl **18**{*3*} **29**{*3*}

The procedure was the same as stated above for **29**{*1*} using 0.82 g (3.6 mmol) of sodium, 0.54 g (2.4 mmol) of 2-(*p*-hydroxymethylbenzyl)isothiouronium chloride (**27b·HCl**) and 0.83 g (5 mmol) of the carbonitrile **18**{3}.

After concentration, the residue was dissolved in 20 ml water and neutralized with 6 M HCl. The precipitate was filtered, washed with cold methanol and dried over P_2O_5, to yield 64 mg (0.20 mmol, 9%) of **29**{*3*} as a white solid, mp > 250ºC

Spectroscopic data

IR (KBr) ν (cm^{-1}): 3474, 3364, 3280, 3233 (*st* N-H), 3055, 3026 (*st* Csp^2-H), 2965, 2930, 2876 (*st* Csp^3-H), 1699 (*st* C=O), 1625, 1575(*st* C=C, *st* C=N, *b* N-H), 1013 (*st* C-O), 836 (*b* C-H)

^{1}H-NMR (300 MHz, d_6-DMSO) δ (ppm): 10.27 (s, 1H, NH), 7.39 (d, ^3J = 8 Hz, 2H, H-C12), 7.22 (d, ^3J = 8 Hz, 2H, H-C11), 6.74 (s, 2H, NH_2), 5.12 (t, ^3J = 6 Hz, 1H, OH), 4.44 (d, ^3J = 6 Hz, 2H, H-C14), 4.25 (s, 2H, H-C9), 2.78 (dd, ^3J = 7 Hz, ^2J = 16 Hz, 1H, H-C5), 2.58 (m, ^3J = 7 Hz, ^3J = 7 Hz, ^3J = 11 Hz, 1H, H-C6), 2.24 (dd, ^2J = 16 Hz, ^3J = 11 Hz, 1H, H-C5), 1.12 (d, ^3J = 7 Hz, 3H, H-C15)

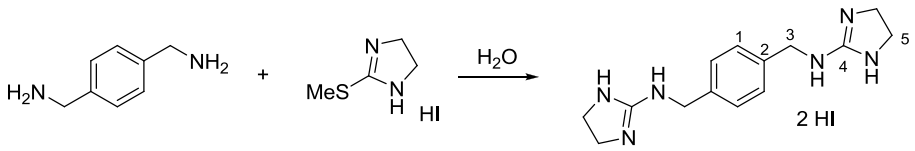
^{13}C-NMR (75.5 MHz, d_6-DMSO) δ (ppm): 173.4 (C7), 166.2 (C2), 160.7 (C4), 155.7 ($C8_a$), 140.9 (C13), 137.0 (C10), 128.7 (C11), 126.2 (C12), 89.7 ($C4_a$), 62.6 (C14), 34.1 (C6), 33.5 (C9), 25.2 (C5), 15.5 (C15)

HRMS (ESI-TOF) *m/z* (%): calculated for $C_{16}H_{19}N_4O_2S$ $[M+1]^+$: 331.1223; found 331.1211 (52) $[M+1]^+$, 233,1018 (100)

Biological activity

EC_{50} > 25 μg/ml; **CC_{50}** > 25 μg/ml

4.5.12. Synthesis of *N*,*N*'-bis(3,4-dihydro-1*H*-imidazole-2-yl)-1,4-bis(aminomethyl)benzene diiodine (39·2HI)



37 **38·HI** **39·2HI**

A heterogeneous mixture of 1.36 g (10 mmol) of *p*-xylylenediamine (**37**) and 4.88 g (20 mmol) of 2-methylmercapto-2-imidazoline iodine (**38·HI**) in 10 ml of water was stirred at room temperature for 48 h. The reaction mixture was repeatedly concentrated, adding water until deplacing all methylmercaptane.

The residue was stirred with 3 ml water for 10 minutes and crystalized at 4 ºC overnight. The precipitate was filtered to yield 3.39 g (6.4 mmol, 64%) of the desired product (**39·2HI**) as a white solid, mp > 250 ºC. A second, less pure fraction can be obtained by concentration of the filtrate.

Spectroscopic data

IR (KBr) ν (cm^{-1}): 3314, 3274, 3210, 3172, 3132 (*st* N-H), 3071, 3048 (*st* Csp^2-H), 2972, 2938, 2898 (*st* Csp^3-H), 1667, 1605 (*st* C=C, *st* C=N, *b* N-H)

^{1}H-NMR (300 MHz, D_2O) δ (ppm): 7.38 (s, 4H, H-C1), 4.46 (s, 4H, H-C3), 3.71 (s, 8H, H-C5)

^{13}C-NMR (75.5 MHz, D_2O) δ (ppm): 160.3 (C4), 136.5 (C2), 127.9 (C1), 46.0 (C5), 43.4 (C3)

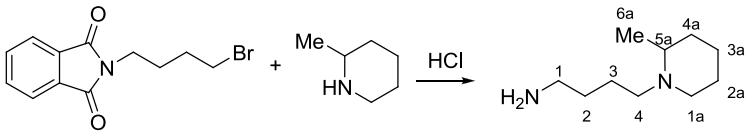
OEA calculated for $C_{14}H_{22}N_6I_2$: C 31.84%, H 4.20%, N 15.91%, found C 31.95%, H 4.47%, N 15.96%

Biological activity

EC_{50} > 25 μg/ml; **CC_{50}** > 25 μg/ml

4.6. Synthesis of new amines 5{*x*}

4.6.1. Synthesis of *N*-(4-aminobutyl)-2-pipecoline (5{*13*})



49 **50** **5**{*13*}

2.828 g (10 mmol) of *N*-(4-bromobutyl)phthalimide (**49**), 2.36 ml (20 mmol) of 2-pipecoline (**50**) and 40 ml of acetone were held at reflux for 12 hours. The piperidine bromide formed was then filtered and the solvent was removed under reduced pressure. The solid residue was redissolved in ethyl acetate and was washed with K_2CO_3 (2 M) and extracted with HCl (2 M). The aqueous phase was basified with NaOH and extracted with dichloromethane. The solvent was removed under reduced pressure, redissolved in 25 ml of HCl (6 M) and held at reflux for 12 hours. The result mixture was filtered, the aqueous phase was washed with dichloromethane and then basified and extracted again with dichloromethane. Finally, the solution was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 0.204 g (1.2 mmol, 12%) of a yellow oil **5**{*13*}.

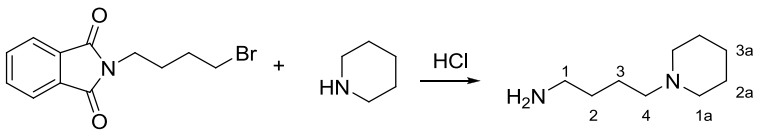
Spectroscopic data

IR (film) ν (cm^{-1}): 3303 (*st* N-H), 2930, 2856,2786 (*st* Csp^3-H), 1576, 1469 (*b* N-H), 1373 (*b* Csp^3-H)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm):2.84 (m, 2H, H-C1), 2.72 (m, 2H, H-C4), 2.33 (m, 2H, H-C1a) 2.16 (m, 1H, H-C5a), 1.46-1.60 (m, 10H, H-C2, H-C3, H-C2a, H-C3a, H-C4a), 1.1 (d, *J* = 6.5 Hz, 3H, H-C6a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 55.6 (C5a), 53.7 (C1a), 51.9 (C4), 41.9 (C1), 34.4 (C4a), 31.8 (C2a), 25.9 (C2), 23.8 (C3), 22.5 (C3a), 18.9 (C6a)

4.6.2. Synthesis of *N*-(4-aminobutyl)piperidine (5{*14*})



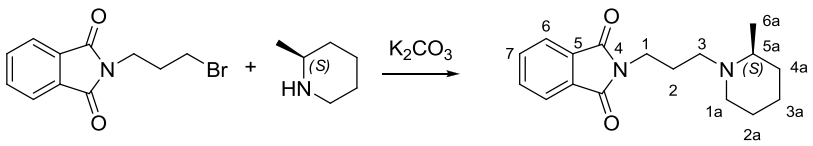
49 **51** **5**{*14*}

Procedure was the same as stated above for **5**{*13*} using 2.828 g (10 mmol) of *N*-(4-bromobutyl)phthalimide (**49**) and 2 ml (20 mmol) of piperidine (**51**) to obtain 0.941 g (6.03 mmol, 60%) of a yellow oil **5**{*14*}.

Spectroscopic data

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.22 (s, 2H, NH_2), 2.76 (t, J = 6.5 Hz, 2H, H-C1), 2.42 (m, 4H, H-C1a), 2.33 (m, 2H, H-C4), 1.58 (m, 8H, H-C2, H-C2a, H-C3a), 1.45 (m, 2H, H-C3)

4.6.3. Synthesis of (*S*)-*N*-(3-(2-pipecolin-1-yl)propyl)phthalimide (52*S*)



67 **50*S*** **52*S***

A solution of 0.41 ml (0.339 g, 3.3 mmol) of (*S*)-(+)-2-pipecoline (**50*S***) in 10 ml of acetonitrile was treated with 0.822 g (3.0 mmol) of *N*-(3-bromopropyl)phthalimide (**67**) and 0.698 g (5.0 mmol) anhydrous K_2CO_3 under reflux for 8 h. After concentration, the residue was diluted with 30 ml CH_2Cl_2 and washed with water. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give **52*S*** as a yellow oil (0.789 g; 92%).

Spectroscopic data

IR (film) ν (cm^{-1}): 2931, 2854, 2790 (*st* Csp^3-H), 1772, 1712 (*st* C=O), 1396, 1032 (*st* C-N), 720 (*b* C-H)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2H, H-C6), 7.71 (dd, ^3J = 5.5 Hz, ^4J = 3.0 Hz, 2H, H-C7), 3.70 (m, 2H, H-C1), 2.78 (m, 2H, H-C3, H-C1a), 2.38 (m, 1H, H-C3), 2.24 (m, 1H, H-C5a), 2.09 (m, 1H, H-C1a), 1.85 (qn, ^3J = 7.5, 2H, H-C2), 1.62-1.42 (m, 4H, H-C2a, H-C3a, H-C4a), 1.24 (m, 2H, H-C3a, H-C4a), 1.03 (d, J = 6.5 Hz, 3H, H-C6a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 168.3 (C4), 133.8 (C7), 132.2 (C5), 123.1 (C6), 55.8 (C5a), 51.8 (C3), 51.4 (C1a), 36.7 (C1), 34.5 (C4a), 26.1 (C2), 24.6 (C2a), 23.8 (C3a), 18.7 (C6a)

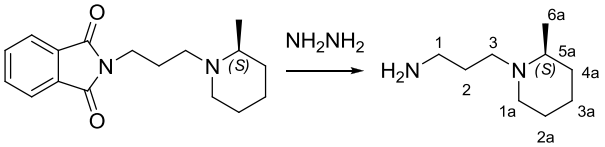
MS (ESI-TOF) *m/z* (%): 287.2 (100) [M^++H], 214.1 (2), 158.0 (5), 141.0 (4), 105.0 (6)

HRMS (ESI-TOF) calculated for $C_{17}H_{23}N_2O_2$ $[M+1]^+$: 287.1754; found: 287.1750

OEA calculated for $C_{17}H_{22}N_2O_2$: C 71.30%, H 7.74%, N 9.78%; found: C 70.95%, H 8.03%, N 9.78%

$[\alpha]_D$ = + 39.4 º (concentration 10 mg/ml, $CHCl_3$)

4.6.4. Synthesis of (*S*)-*N*-(3-aminopropyl)-2-pipecoline (5{8*S*})



52*S* **5**{*8S*}

A solution of 0.654 g (2.3 mmol) of (*S*)-*N*-(3-(2-pipecolin-1-yl)propyl)phthalimide (**52*S***) in 10 ml of ethanol was treated with 0.43 ml (8.8 mmol) of hydrazine hydrate under reflux for 1 h. The white precipitate of phthalhydrazide was filtered and the filtrate was concentrated. After diluting the residue with 5 ml of AcOEt, a new precipitate of phthalhydrazide appeared, which was filtered off. The filtrate was concentrated to dryness to give 0.283 g (1,81 mmol, 79%) of (*S*)-*N*-(3-aminopropyl)-2-pipecoline (**5**{*8S*}) as a pale yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3293 (*st* N-H), 2930, 2855, 2788 (*st* Csp^3-H), 1575, 1470 (*b* Csp^3-H), 1374, 1329 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.87 (m, 1H, H-C3), 2.72 (m, 3H, H-C1, H-C1a), 2.35 (m, 1H, H-C3), 2.26 (m, 1H, H-C5a), 2.12 (m, 1H, H-C1a), 1.80-1.50 (m, 8H, H-C2, H-C2a, H-C3a, H-C4a, NH_2), 1.28 (m, 2H, H-C3a, H-C4a), 1.06 (d, ^3J = 6.0 Hz, 3H, H-C6a)

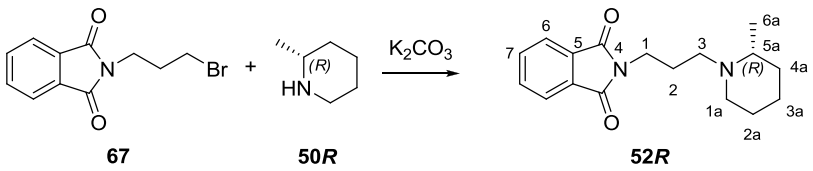
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 55.9 (C5a), 52.0 (C3), 51.7 (C1a), 41.0 (C1), 34.6 (C4a), 29.4 (C2), 26.1 (C2a), 23.9 (C3a), 19.0 (C6a)

MS (EI) *m/z* (%): 156.2 (7) $[M]^+$, 112.2 (100), 98.2 (100)

HRMS (EI) calculated for $C_9H_{20}N_2$ $[M]^+$: 156.1626; found: 156.1621

$[\alpha]_D$ = + 69.5 º (concentration 15 mg/ml, $CHCl_3$)

4.6.5. Synthesis of (*R*)-*N*-(3-(2-pipecolin-1-yl)propyl)phthalimide (52*R*)



67 **50*R*** **52*R***

A solution of (*R*)-(+)-2-pipecoline hydrochloride (**50*R*·HCl**) in 10% NaOH was extracted with CH_2Cl_2 to obtain the free amine **50*R***.

A solution of 0.826 g (8.3 mmol) of (*R*)-(+)-2-pipecoline (**50*R***) in 20 ml acetonitrile was treated with 1.653 g (6.0 mmol) *N*-(3-bromopropyl)phthalimide (**67**) and 1.50 g (11 mmol) of anhydrous K_2CO_3 under reflux for 8 h. After concentration, the residue was diluted with 30 ml CH_2Cl_2 and washed with water. The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give **52*R*** as a yellow oil (1.665 g; 97%).

Spectroscopic data

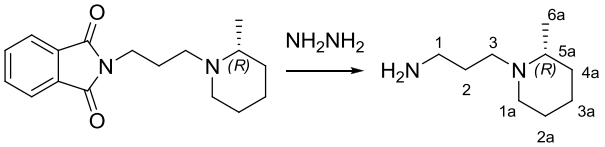
IR (film) ν (cm^{-1}): 2930, 2856, 2791 (*st* Csp^3-H), 1772, 1713 (*st* C=O), 1378, 1031 (*st* C-N), 720 (*b* C-H)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.84 (m, 2H, H-C6), 7.71 (m, 2H, H-C7), 3.70 (m, 2H, H-C1), 2.77 (m, 2H, H-C1a, H-C3), 2.38 (m, 1H, H-C3), 2.26 (m, 1H, H-C5a), 2.10 (dt, ^2J = 10.0 Hz, ^3J = 4.0 Hz, 1H, H-C1a), 1.85 (qn, ^3J = 7.5, 2H, HC2), 1.64-1.43 (m, 4H, H-C2a, H-C3a, HC4a), 1.24 (m, 2H, H-C3a, H-C4a), 1.03 (d, J = 6.5 Hz, 3H, H-C6a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 168.3 (C4), 133.8 (C7), 132.2 (C5), 123.1 (C6), 55.8 (C5a), 51.8 (C3), 51.4 (C1a), 36.7 (C1), 34.5 (C4a), 26.1 (C2), 24.6 (C2a), 23.8 (C3a), 18.7 (C6a)

$[\alpha]_D$ = - 11.7 º (concentration 11 mg/ml, $CHCl_3$), 30% ee

4.6.6. Synthesis of (*R*)-*N*-(3-aminopropyl)-2-pipecoline (5{*8R*})



52*R* **5**{*8R*}

A solution of 0.740 g (2.6 mmol) (*R*)-*N*-(3-(2-pipecolin-1-yl)propyl)phthalimide (**52*R***) in 10 ml of ethanol was treated with 0.50 ml (10 mmol) of hydrazine hydrate under reflux for 1 h. The white precipitate of phthalhydrazide was filtered and the filtrate was concentrated. After diluting the residue with 5 ml of AcOEt a new precipitate of phthalhydrazide appeared, which was filtered off. The filtrate was concentrated to dryness to give 0.299 g (1.9 mmol, 73%) of (*R*)-*N*-(3-aminopropyl)-2-pipecoline (**5**{*8R*}) as a yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3273 (*st* N-H), 2930, 2855, 2789 (*st* Csp^3-H), 1576, 1472 (*b* Csp^3-H), 1374, 1329 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.86 (dt, ^2J = 11.5 Hz, ^3J = 4.0 Hz, 1H, H-C3), 2.73 (m, 3H, H-C1, H-C1a), 2.35 (m, 1H, H-C3), 2.26 (m, 1H, H-C5a), 2.11 (dt, ^2J = 11.0 Hz, ^3J = 3.0 Hz, 1H, H-C1a), 1.67-1.51 (m, 8H, H-C2, H-C2a, H-C3a, H-C4a, NH_2), 1.27 (m, 2H, H-C3a, H-C4a), 1.06 (d, ^3J = 6.0 Hz, 3H, H-C6a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 55.9 (C5a), 52.1 (C3), 51.8 (C1a), 41.0 (C1), 34.7 (C4a), 29.5 (C2), 26.2 (C2a), 24.0 (C3a), 19.1 (C6a)

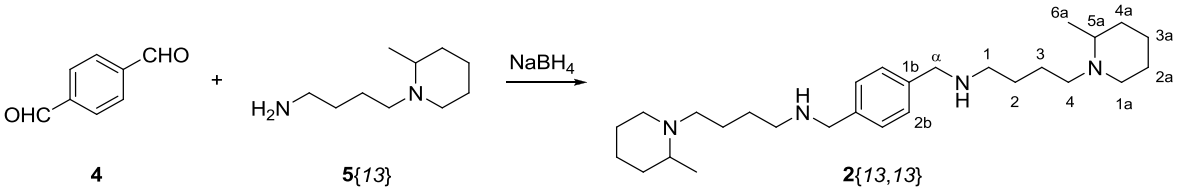
MS (EI) *m/z* (%): 156.1 (2) $[M]^+$, 112.2 (100), 98.1 (68)

HRMS (EI) calculated for $C_9H_{20}N_2$ $[M]^+$: 156.1626; found: 156.1624

$[\alpha]_D$ = - 17.5 º (concentration 10 mg/ml, $CHCl_3$)

4.7. Synthesis of symmetric substituted analogs

4.7.1. Synthesis of *N*-(4-((4-(2-methylpiperidin-1-yl)butanamino)methyl)benzyl)-4-(2-methylpiperidin-1-yl)butan-1-amine (2{*13*,*13*})



4 **5**{*13*} **2**{*13*,*13*}

0.177 g (1.3 mmol) of terephthalaldehyde (**4**), 0.442 g (2.6 mmol) of 4-piperidinobutylamine (**5**{*14*}) and Na_2SO_4 were mixed in 5 ml of anhydrous MeOH and placed in a microwave process vial containing a stir bar, sealed and subjected to microwave irradiation for 2 hours at 100 ºC. The solid was filtered and 0.1 g (3 mmol) of $NaBH_4$ were added to the intermediate imine in MeOH. After 12 hours, water was added and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give **2**{*13*,*13*} (0.230 g, 0.52 mmol; 40%).

Spectroscopic data

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.5 (s, 4H, H-C2b), 3.76 (s, 4H, H-Cα), 2.92 (m, 2H, H-C1), 2.71 (m, 6H, H-C1a, H-C5a), 2.40 (m, 4H, H-C4), 1.63 (m, 20H, H-C2, H-C3, H-C2a, H-C3a, H-C4a), 1.11 (m, 6H, H-C6a)

^{13}C-NMR (106.5 MHz, $CDCl_3$) δ (ppm): 139.8 (C1b), 128.4 (C2b), 56.0 (C5a), 54.5 (Cα), 51.7 (C1a), 49.0 (C1), 33.9 (C4a), 27.9 (C2), 25.6 (C3), 22.8 (C3a), 18.5 (C6a)

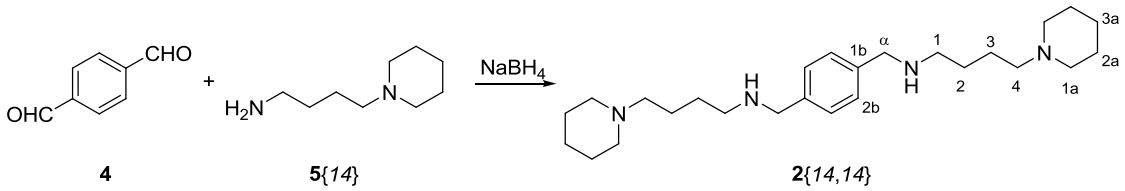
MS (FAB) *m/z* (%): 443.5 (82) $[M+1]^+$, 291.3 (66), 154.2 (60), 152.2 (31), 137.0 (32), 112.1 (100)

HRMS (CI) calculated for $C_{28}H_{50}N_4$ $[M+1]^+$: 443.4114; found: 443.4114

Biological activity

EC_{50} = 0.336 μg/ml; **CC_{50}** > 25 μg/ml

4.7.2. Synthesis of *N*-(4-((4-(piperidin-1-yl)butanamino)methyl)benzyl)-4-(piperidin-1-yl)butan-1-amine (2{*14*,*14*})



4 **5**{*14*} **2**{*14*,*14*}

Procedure was the same as stated above for **2**{*13*,*13*} using 0.4 g (3 mmol) of **5**{*14*}, 0.2 g (1.5 mmol) of **4** to give 0.35 g (0.85 mmol, 57%) of dark yellow oil **2**{*13*,*13*}.

Spectroscopic data

IR (film) ν (cm^{-1}): 3264 (*st* N-H, *st* O-H), 2932 (*st* C-H), 1444 (*b* Csp^3-H), 1123 (*st* C-O)

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.30 (s, 4H, H-C2b), 3.76 (s, 4H, H-Cα), 2.78 (s, 2H, NH), 2.63 (m, 4H, H-C1), 2.52 (m, 12H, H-C1a, H-C4), 1.50 (m, 20H, H-C2a, H-C3a, H-C2, H-C3)

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 138.9 (C1b), 128.2 (C2b), 59.2 (Cα), 54.5 (C1a), 53.5 (C4), 49.1 (C1), 28.0 (C2), 25.8 (C2a), 24.7 (C3a), 24.4 (C3)

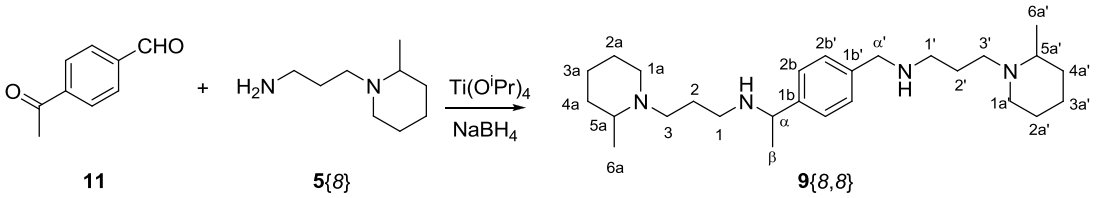
MS (FAB) *m/z* (%): 415.4 (74) $[M+1]^+$, 277.2 (50), 154.0 (30), 140.1 (100), 138.1 (32), 137.0 (42)

HRMS (CI) calculated for $C_{26}H_{46}N_4$ $[M+1]^+$: 415.3801; found: 415.3802

Biological activity

EC_{50} = 0.288 μg/ml; **CC_{50}** > 25 μg/ml

4.7.3. Synthesis of *N*-(1-(4-((3-(2-methylpiperidin-1-yl)propylamino)methyl)phenyl)ethyl)-3-(2-methylpiperidin-1-yl)propan-1-amine (9{*8*,*8*})



General procedure without catalysis

1.569 g (10 mmol) of **5**{*8*}, 0.745 g (5 mmol) of **11** and Na_2SO_4 were mixed in 5 ml of anhydrous MeOH and placed in a microwave process vial containing a stir bar, sealed and subjected to microwave irradiation for 2 hours at 100 ºC. The solid was filtered and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 1.424 g of crude product (83% purity), which represent 1.182 g (2.77 mmol, 55%) of **9**{*8*,*8*}.

The crude product can be partially purified by column chromatography (neutral alumina, CH_2Cl_2:MeOH 80:20).

General procedure with catalysis

2.274 g (8 mmol) of titanium isopropoxide (IV) were added to a mixture of 0.629 g (4 mmol) of **5**{*8*} and 0.246 g (2 mmol) of **11** and stirred in 20 ml of ethanol at room temperature under N_2 atmosphere overnight. 0.306 g (8 mmol) of $NaBH_4$ were added and the mixture was stirred for 6 hours at room temperature. Water was added until no more precipitate was formed. The solid was centrifuged, filtered and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 0.587 g (1.37 mmol, 69%) of **9**{*8*,*8*} as a yellow oil.

Spectroscopic data and biological activity

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.27 (m, 4H, H-C2b, H-C2b'), 3.75 (m, 3H, H-Cα, H-Cα'), 2.8 (m, 4H, H-C1, H-C1'), 2.6 (m, 4H, H-C3, H-C3'), 2.4 (m, 2H, H-C5a, H-C5a'), 2.1 (m, 4H, H-C1a, H-C1a'), 1.6 (m, 14H, H-C2a, H-C2a', H-C3a, H-C3a', H-C4a, H-C4a', H-C4, H-C4'), 1.34 (d, *J* = 5Hz, 3H, H-Cβ), 1.26 (m, 2H, H-C4a, H-C4a'), 1.03 (m, 6H, H-C6a, H-C6a')

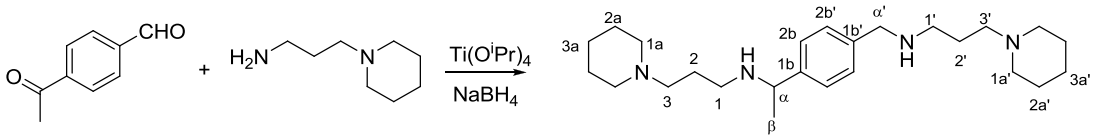
^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 144.2 (C1b), 138.1 (C1b'), 128.2 (C2b), 126.6 (C2b'), 58.1(Cα), 55.8 (C5a, C5a'), 54.0 (Cα'), 51.9 (C1a'), 48.4 (C3'), 46.8 (C1, C1'), 34.6 (C4a, C4a'), 36.1 (C2, C2'), 24.1 (C3a, C3a'), 23.8 (Cβ), 18.9 (C6a, C6a')

MS (FAB) *m/z* (%): 429.3 (45) $[M+1]^+$, 427.3 (14), 126.1 (25), 112 (100)

HRMS (CI) calculated for $C_{27}H_{48}N_4$ $[M+1]^+$: 429.3957; found: 429.3958

EC_{50} = 0.110 μg/ml; **CC_{50}** > 25 μg/ml

4.7.4. Synthesis of *N*-(1-(4-((3-(piperidin-1-yl)propylamino)methyl)phenyl)ethyl)-3-(piperidin-1-yl)propan-1-amine (9{*12*,*12*})



11 **5**{*12*} **9**{*12*,*12*}

Procedure was the same as stated above for **9**{*8*,*8*} without catalysis using 0.431 g (3 mmol) of **5**{*12*}, 0.225 g (1.5 mmol) of **11** and 0.114 g (3 mmol) of $NaBH_4$, to give 0.159 g of crude product (81% purity), which represent 0.129 g (0.32 mmol, 21%) of **9**{*12*,*12*}.

Spectroscopic data

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.32 (m, 4H, H-C2b, H-C2b'), 3.77 (m, 3H, H-Cα, H-Cα'), 2.67 (m, 4H, H-C1, H-C1'), 2.38 (m, 12H, H-C3, H-C3', H-C1a, H-C1a'), 2.0 (m, 2H, NH), 1.7 (m, 4H, H-C2, H-C2'), 1.56 (m, 15H, H-Cβ, H-C2a', H-C3a')

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 128.2 (C2b'), 126.6 (C2b), 58.0 (Cα'), 57.8 (Cα), 54.6 (C1a, C1a'), 53.5 (C3, C3'), 46.8 (C1, C1'), 30.9 (C2, C2'), 25.2 (C3a, C3a'), 24.4 (Cβ)

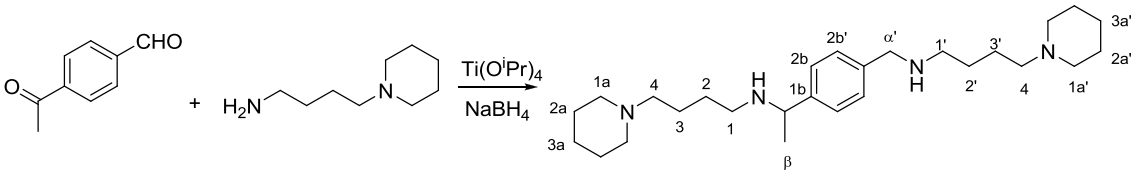
MS (FAB) *m/z* (%): 401.3 (54) $[M+1]^+$, 277.2 (36), 231.0 (45), 126.1 (51), 112.1 (52)

HRMS (CI) calculated for $C_{25}H_{44}N_4$ $[M+1]^+$: 401.3644; found: 401.3647

Biological activity

EC_{50} = 0.404 μg/ml; **CC_{50}** > 25 μg/ml

4.7.5. Synthesis of *N*-(1-(4-((4-(piperidin-1-yl)butylamino)methyl)phenyl)ethyl)-4-(piperidin-1-yl)butan-1-amine (9{*14*,*14*})



11 **5**{*14*} **9**{*14*,*14*}

Procedure was the same as stated above for **9**{*8*,*8*} with catalysis using 0.543 g (3.48 mmol) of **5**{*14*}, 0.26 g (1.74 mmol) of **11**, 1.978 g (6.96 mmol) of titanium isopropoxide (IV) and 0.132 g (3.48 mmol) of $NaBH_4$, to give 0.502 g of crude product (80%) which represent 0.402 g (0.94 mmol, 54%) of **9**{*14*,*14*}.

Spectroscopic data

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.29 (m, 4H, H-C2b, H-C2b'), 3.76 (m, 3H, H-Cα, H-Cα'), 2.6 (m, 4H, H-C1, H-C1'), 2.3 (m, 12H, H-C4, H-C4', H-C1a, H-C1a'), 1.5 (m, 23H, H-C2, H-C2', H-C3, H-C3', H-C2a, H-C2a', H-C3a, H-C3a', H-Cβ)

^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm): 145.0 (C1b'), 139.0 (C1b'), 128.3 (C2b), 125.5 (C2b'), 59.2 (Cα), 54.5 (C1a, C1a'), 53.6 (Cα'), 49.2 (C4, C4'), 49.1 (C1'), 47.5 (C1), 27.9 (C2, C2'), 25.8 (C3, C3'), 25.3 (C2a, C2a'), 24.5 (C3a, C3a'), 24.1 (Cβ)

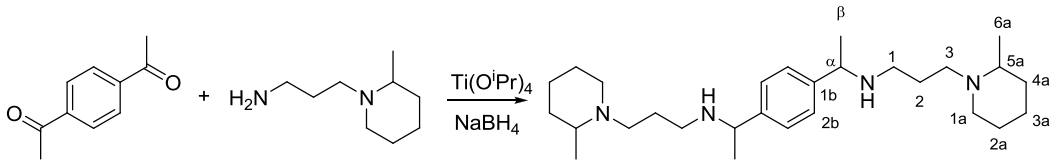
MS (FAB) *m/z* (%): 429.3 (12) $[M+1]^+$, 219.2 (100), 231.0 (54), 140.1 (28), 136.9 (97), 108.9 (26)

HRMS (CI) calculated for $C_{27}H_{48}N_4$ $[M+1]^+$: 429.3957; found: 429.3945

Biological activity

EC_{50} = 0.513 μg/ml; **CC_{50}** > 25 μg/ml

4.7.6. Synthesis of *N*-(1-(4-(1-(3-(2-methylpiperidin-1-yl)propylamino)ethyl)phenyl)ethyl)-3-(2-methylpiperidin-1-yl)propan-1-amine (12{*8*,*8*})



14 **5**{*8*} **12**{*8*,*8*}

Procedure was the same as stated above for **9**{*8*,*8*} with catalysis, using 0.625 g (4 mmol) of **5**{*8*}, 0.324 g (2 mmol) of **14**, 2.274 g (8 mmol) of titanium isopropoxide (IV) and 0.306 g (8 mmol) of $NaBH_4$, to give 0.190 g (0.43 mmol, 21%) of **12**{*8*,*8*}.

Spectroscopic data

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.27 (s, 4H, H-C2b), 3.75 (q, 2H, *J* = 6.5 Hz, H-Cα), 2.8 (m, 4H, H-C1), 2.6 (m, 4H, H-C3), 2.27 (m, 4H, H-C1a), 2.1 (m, 2H, H-C5a), 1.8 (m, 12H, H-C2a, H-C3a, H-C4a, H-C2), 1.34 (d, *J* = 6.5 Hz, 6H, H-Cβ), 1.26 (m, 2H, H-C4a), 1.03 (d, *J* = 6.3 Hz, 6H, H-C6a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 143.8 (C1b), 126.2 (C2b), 58.2 (Cα), 55.9 (C5a), 51.7 (C1a), 46.9 (C3), 46.7 (C1), 34.5 (C4a), 25.9 (C2), 23.9 (C2a), 23.6 (C3a), 18.9 (Cβ)

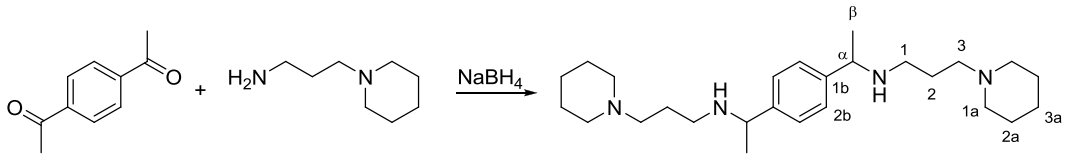
MS (FAB) *m/z* (%): 443.4 (84) $[M+1]^+$, 126.1 (28), 112.1 (100), 109.1 (18)

HRMS (CI) calculated for $C_{28}H_{50}N_4$ $[M+1]^+$: 443.4114; found: 443.4113

Biological activity

EC_{50} = 0.075 μg/ml; **CC_{50}** > 25 μg/ml

4.7.7. Synthesis of *N*-(1-(4-(1-(3-(piperidin-1-yl)propylamino)ethyl)phenyl)ethyl)-3-(piperidin-1-yl)propan-1-amine (12{*12*,*12*})



14 **5**{*12*} **12**{*12*,*12*}

Procedure was the same as stated above for **9**{*8*,*8*} without catalysis using 2.84 g (20 mmol) of **5**{*12*}, 1.62 g (10 mmol) of **14** and 0.76 g (20 mmol) of $NaBH_4$, to give 0.602 g of crude product (85% purity), which represent 0.511 g (1.23 mmol, 12%) of **12**{*12*,*12*}.

Spectroscopic data

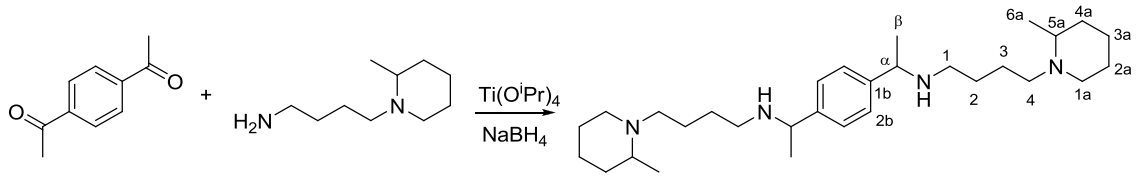
^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.3 (s, 4H, H-C2b), 3.72 (q, *J* = 6.5 Hz, 2H, H-Cα), 2.49 (m, 4H, H-C1), 2.32 (m, 12H, H-C3, H-C1a), 1.62 (m, 4H, H-C2), 1.55 (m, 12H, H-C2a, H-C3a), 1.33 (d, *J* = 6.5 Hz, 6H, H-Cβ)

13C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 144.3 (C1b), 126.5 (C2b), 58.0 (Cα), 57.9 (C1a), 54.6 (C3), 46.8 (C1), 27.1 (C2), 26.0 (C2a, C3a), 24.6 (Cβ)

Biological activity

EC_{50} = 0.162 μg/ml; **CC_{50}** > 25 μg/ml

4.7.8. Synthesis of *N*-(1-(4-(3-(2-(2-methylpiperidin-1-yl)butylamino)ethyl)phenyl)ethyl)-3-(2-methylpiperidin-1-yl)butan-1-amine (12{*13*,*13*})



14 **5**{*13*} **12**{*13*,*13*}

A solution of 0.061 g (0.36 mmol) of **5**{*13*} and 0.029 g (0.18 mmol) of **14** was prepared in 5 ml of ethanol. Then 0.10 g (0.37 mmol) of titanium isopropoxide (IV) were added and the reaction was stirred under N_2 atmosphere for 24 hours at room temperature. 0.020 g of $NaBH_4$ (0.5 mmol) was added and the mixture was stirred for 6 hours. Afterwards, 20 ml of water with some drops of NH_3 were added to stop the reaction. The solution was filtered and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give **12**{*13*,*13*} with a yield < 5%.

Spectroscopic data

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.3(s, 4H, H-C2b), 3.72 (m, 2H, H-Cα), 2.63 (m, 14H, H-C1, H-C4, H-C1a, H-C5a), 1.46 (m, 26H, H-Cβ, H-C2, H-C3, H-C2a, H-C3a, H-C4a), 1.04 (m, 6H, H-C6a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 145.2 (C1b), 126.5 (C2b), 55.7 (Cα), 53.7 (C5a), 52.1 (C4), 47.6 (C1), 34.5 (C4a), 28.3 (C2), 25.1 (C3, C2a), 23.0 (C3a), 22.6 (Cβ), 19.1 (C6a)

MS (FAB) *m/z* (%): 471.5 (6.2), 409.4 (14, 320.3 (25), 319 .3 (63), 172.2 (27), 169.2 (32), 137.0 (25), 112.1 (100)

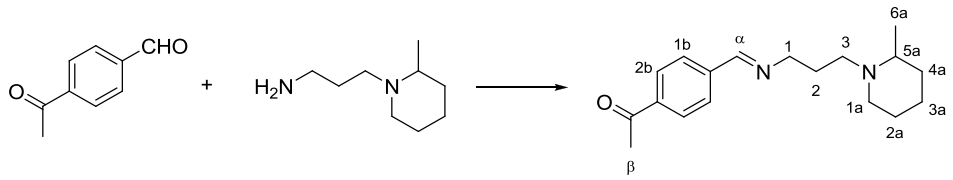
HRMS (CI) calculated for $C_{30}H_{54}N_4$ $[M+1]^+$: 471.4427; found: 471.4421

Biological activity

EC_{50} = 1.848 μg/ml; **CC_{50}** > 25 μg/ml

4.8. Synthesis of asymmetric substituted analogs

4.8.1. Synthesis of 1-4((3-(2-methylpiperidin-1-yl)propylimino)methyl)phenyl)ethanone (66{*8*})



11 **5**{*8*} **66**{*8*}

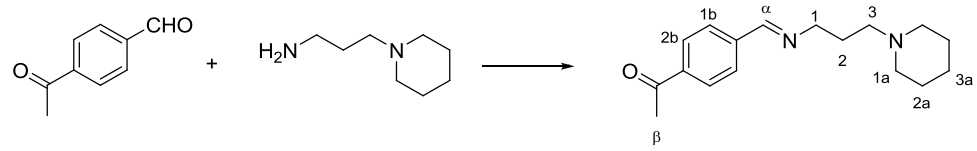
A solution of 0.375 g (2.53 mmol) of 4-acetylbenzaldehyde (**11**) and 0.395 g (2.53 mmol) of **5**{*8*} in 20 ml of methanol was prepared. Na_2SO_4 was added and the mixture was stirred for 6 hours at room temperature and under N_2 atmosphere.

Na_2SO_4 was filtered and 20mL of water were added. The product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 0.651 g (2.27 mmol, 90%) of **66**{*8*} as an orange oil.

Spectroscopic data

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 8.34 (s, 1H, H-Cα), 7.99 (d, *J* = 8.5 Hz, 2H, H-C2b), 7.81 (d, *J* = 8.5 Hz, 2H, H-C1b), 3.65 (m, 2H, H-C1), 2.85 (m, 2H, H-C3), 2.63 (s, 3H, H-Cβ), 2.46 (m, 1H, H-C5a), 2.20 (m, 2H, H-C1a), 1.90 (m, 2H, H-C2), 1.40 (m, 6H, H-C2a, H-C3a, H-C4a), 1.03 (d, *J* = 4.5 Hz, 3H, H-C6a)

4.8.2. Synthesis of 1-4((3-(piperidin-1-yl)propylimino)methyl)phenyl)ethanone (66{*12*})



11 **5**{*12*} **66**{*12*}

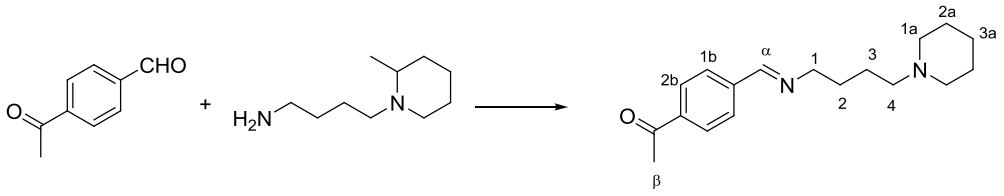
A solution of 0.597 g (4.03 mmol) of **11** and 0.574 g (4.03 mmol) of **5**{*12*} in 30 ml of methanol was prepared. Na_2SO_4 was added and the mixture was stirred for 2 hours at room temperature and under N_2 atmosphere.

Na_2SO_4 was filtered and 10 ml of water were added. The product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 1.018 g (3.74 mmol, 93%) of **66**{*12*} as a yellow oil.

Spectroscopic data

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 8.34 (s, 1H, H-Cα), 8.0 (d, *J* = 8 Hz, 2H, H-C2b), 7.81 (d, *J* = 8 Hz, 2H, H-C1b), 3.68 (t, *J* = 7 Hz, 2H, H-C1), 2.63 (s, 3H, H-Cβ), 2.40 (m, 1H, H-C1a, H-C3), 1.9 (m, 2H, H-C2), 1.6 (m, 6H, H-C2a, H-C3a)

4.8.3. Synthesis of 1-4((4-(piperidin-1-yl)propylimino)methyl)phenyl)ethanone (66{*13*})



11 **5**{*13*} **66**{*14*}

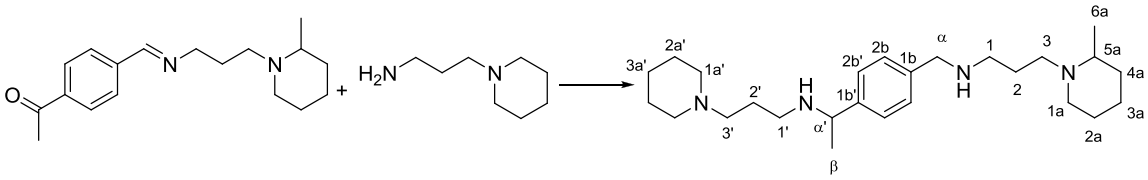
A solution of 0.627 g (4.02 mmol) of **5**{*13*} and 0.595 g (4.02 mmol) of **11** in 20 ml of methanol was prepared. Na_2SO_4 was added and the mixture was stirred for 48 hours at room temperature and under N_2 atmosphere.

Na_2SO_4 was filtered and 15 ml of water were added. The product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 0.792 g (2.77 mmol, 70%) of **66**{*13*}.

Spectroscopic data

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.32 (s, 1H, H-Cα), 8.0 (d, *J* = 8 Hz, 2H, H-C2b), 7.80 (d, *J* = 8 Hz, 2H, H-C1b), 3.68 (t, *J* = 7 Hz, 2H, H-C1), 2.63 (s, 3H, H-Cβ), 2.38 (m, 6H, H-C1a, H-C4), 1.92 (m, 2H, H-C2), 1.6 (m, 6H, H-C2a, H-C3a), 1.43 (m, 2H, H-C3)

4.8.4. Synthesis of *N*-(1-(4-((3-(2-methylpiperidin-1-yl)propylamino)methyl)phenyl)ethyl)-3-(piperidin-1-yl)propan-1-amine (9{*12*,*8*})



66{*8*} **5**{*12*} **9**{*12*,*8*}

1.137 g (4 mmol) of titanium isopropoxide (IV) were added to a mixture of 0.284 g (2 mmol) of **5**{*12*} and 0.572 g (2 mmol) of **66**{*8*} and stirred in 20 ml of ethanol at room temperature under N_2 atmosphere for 6 hours. Afterwards, 0.151 g (4 mmol) of $NaBH_4$ were added and the mixture was stirred for 6 hours. Water with some drops of NH_3, was added until no precipitate was formed. The solid was filtered and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 0.633 g of crude product (85% purity), which represent 0.538 g (1.292 mmol, 65%) of **9**{*12*,*8*} as a yellow oil.

Spectroscopic data

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 8.29 (m, 4H, H-C2b, H-C2b'), 3.77 (m, 3H, H-Cα, H-Cα'), 2.85 (m, 2H, H-C4), 2.63 (2, 3H, H-C6), 2.46 (m, 1H, H-C1a), 2.2 (m, 1H, H-C5a), 1.9 (m, 2H, H-C3), 1.4 (m, 6H, H-C2a, H-C3a, H-C4a), 1.03 (d, *J* = 4.5 Hz, 3H, H-C6a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 145.2 (C1b), 143.9 (C2b), 58.0 (Cα), 55.9 (C5a), 55.4 (C1a'), 53.5 (C1a) 52.3 (C3'), 51.9 (C3), 48.2 (C1), 46.7 (C1'), 35.4 (C4a), 26.6 (C2, C2'), 25.8 (C2a), 25.4 (C2a', C3a'), 24.3 (C3a), 23.8 (Cβ), 18.8 (C6a)

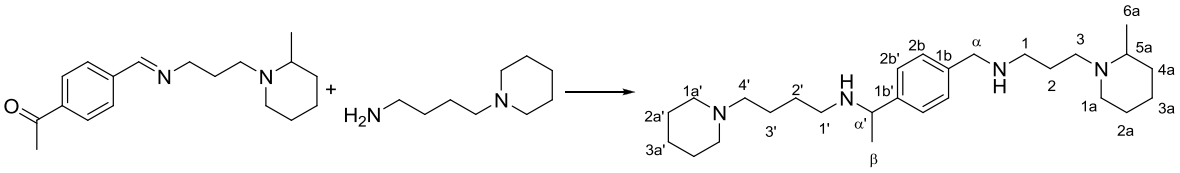
MS (FAB) *m/z* (%): 415.4 (58) $[M+1]^+$, 401.4 (25), 126.1 (27), 112.1 (100)

HRMS (FAB) calculated for $C_{26}H_{46}N_4$ $[M+1]^+$: 415.3801; found: 415.3801

Biological activity

EC_{50} = 0.123 μg/ml; **CC_{50}** > 25 μg/ml

4.8.5. Synthesis of *N*-(1-(4-((3-(2-methylpiperidin-1-yl)propylamino)methyl)phenyl)ethyl)-3-(piperidin-1-yl)butan-1-amine (9{*14,8*})



66{*8*} **5**{*14*} **9**{*14,8*}

Procedure was the same as stated above for **9**{*12,8*} using 0.858 g (3 mmol) of **66**{*8*}, 0.468 g (3 mmol) of **5**{*14*}, 1.705 g (6 mmol)of titanium isopropoxide (IV) and 0.113 g (3 mmol) of $NaBH_4$, to give 1.089 g of crude product (80% purity), which represent 0.871 g (2.04 mmol, 68%) of **9**{*14,8*}.

Spectroscopic data

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.33 (m, 4H, H-C2b, H-C2b'), 4.2 (s, 2H, NH), 3.81 (m, 3H, H-Cα, H-Cα'), 2.63 (m, 4H, H-C1, H-C1'), 2.3 (m, 8H, H-C4', H-C3, H-C1a, H-C1a'), 2.1 (m, 1H, H-C5a), 1.5 (m, 16H, H-C2a, H-C2a', H-C3a, H-C3a', H-C4a, H-C2, H-C2', H-C3'), 1.34 (d, *J* = 5.0 Hz, 3H, H-Cβ), 1.26 (m, 3H, H-C6a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 128.7 (C1b'), 126.9 (C1b), 125.6 (C2b, C2b'), 58.9 (Cα'), 58.0 (C5a), 56.1 (Cα), 54.4 (C1a'), 54.1 (C4'), 52.9 (C1a), 51.6 (C3), 48.1 (C1), 46.7 (C1'), 33.9 (C4a), 27.8 (C2'), 27.5 (C2), 25.5 (C2a), 25.4 (C3a', C4a'), 24.4 (C3'), 24.1 (C3a), 23.3 (Cβ), 18.5 (C6a)

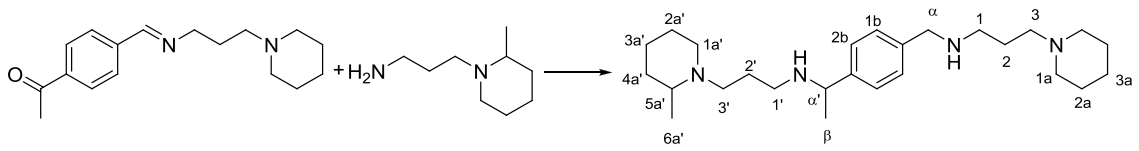
MS (FAB) *m/z* (%): 429.4 (56) $[M+1]^+$, 291.2 (41), 231.0 (35), 154.0 (84), 136.9 (100), 112.1 (48), 109.9 (28)

HRMS (CI) calculated for $C_{27}H_{48}N_4$ $[M+1]^+$: 429.3957; found: 429.3958

Biological activity

EC_{50} = 0.346 μg/ml; **CC_{50}** > 25 μg/ml

4.8.6. Synthesis of *N*-(4-(1-(3-(2-methylpiperidin-1-yl)propylamino)ethyl)benzyl)-3-(piperidin-1-yl)propan-1-amine (9{*8*,*12*})



66{*12*} **5**{*8*} **9**{*8*,*12*}

0.853 g (3 mmol) of titanium isopropoxide (IV) were added to a mixture of 0.408 g (1.5 mmol) of **66**{*12*} and 0.234 g (1.5 mmol) of **5**{*8*} in 20 ml of ethanol and stirred under N_2 atmosphere at 60º of temperature overnight. 0.113 g (3 mmol) of $NaBH_4$ was added and the mixture was stirred for 4 hours. Water with some drops of NH_3 was added to stop the reaction. The TiO_2 obtained was filtered and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 0.200 g (0.48 mmol, 32%) of **9**{*8*,*12*}.

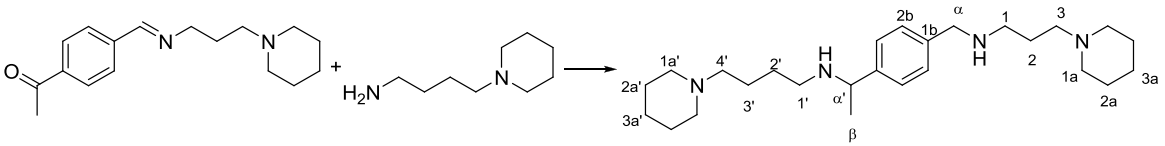
Spectroscopic data

HRMS (CI) calculated for $C_{26}H_{46}N_4$ $[M+1]^+$: 415.380; found: 415.3799

Biological activity

EC_{50} = 0.158 μg/ml; **CC_{50}** > 25 μg/ml

4.8.7. Synthesis of *N*-(4-(1-(3-(2-methylpiperidin-1-yl)propylamino)ethyl)benzyl)-4-(piperidin-1-yl)butan-1-amine (9{*14*,*12*})



66{*12*} **5**{*14*} **9**{*14*,*12*}

Procedure was the same as stated above for **9**{*8*,*12*} using 0.544 g (2 mmol) of **66**{*12*}, 0.312 g (2 mmol) of **5**{*14*}, 1.137 g (4 mmol)of titanium isopropoxide (IV) and 0.151 g (4 mmol) of $NaBH_4$, to give 0.278 of crude product (83% purity), which represent 0.231 g (0.56 mmol, 28%) of **9**{*14*,*12*} as red oil.

Spectroscopic data

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.27 (m, 4H, H-C2b, H-C2b'), 3.78 (m, 3H, H-Cα, H-Cα'), 2.68 (m, 4H, H-C1, H-C1'), 2.37 (m, 12H, H-C4', H-C3, H-C1a, H-C1a', H-N), 1.48 (m, 14H, H-C2a, H-C2a', H-C3a, H-C3a', H-C4a, H-C2), 1.42 (m, 4H, H-C2', H-C3'), 1.36 (q, *J* = 6.5 Hz, 3H, H-Cβ)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 128.2 (C1b), 126.6 (C1b'), 125.4 (C2b, C2b'), 59.2 (Cα), 58.0 (Cα'), 54.4 (C1a, C1a'), 53.6 (C4'), 49.3 (C3), 48.3 (C1), 47.6 (C1'), 28.2 (C2'), 28.0 (C2), 26.8 (C3'), 25.9 (C2a, C2a', C3a, C3a'), 24.2 (Cβ)

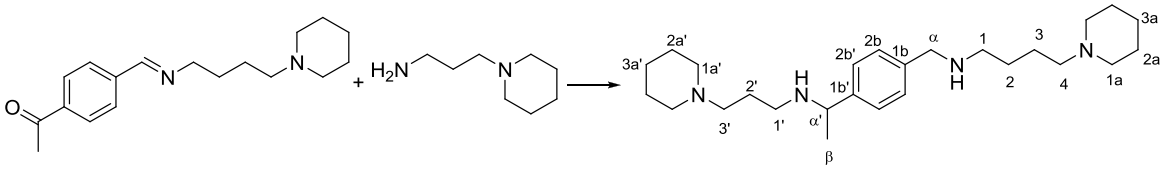
MS (FAB) *m/z* (%): 415.5 (100) $[M+1]^+$, 155.2 (34), 154.0 (72), 140.2 (89), 124.1 (34), 112.1 (37)

HRMS (CI): calculated for $C_{26}H_{46}N_4$ $[M+1]^+$: 415.3801; found: 415.3803

Biological activity

EC_{50} = 0.290 μg/ml; **CC_{50}** > 25 μg/ml

4.8.8. Synthesis of *N*-(4-(1-(3-(piperidin-1-yl)propylamino)ethyl)benzyl)-4-(piperidin-1-yl)butan-1-amine (9{*12*,*14*})



66{*14*} **5**{*12*} **9**{*12*,*14*}

Procedure was the same as stated above for **9**{*8*,*12*} using 0.264 g (0.92 mmol) of **66**{*14*}, 0.128 g (0.9 mmol) of **5**{*12*}, 0.508 g (1.8 mmol)of titanium isopropoxide (IV) and 0.07 g (1.8 mmol) of $NaBH_4$, to give 0.327 g (0.79 mmol, 86%) of **9**{*12*,*14*} as yellow oil.

Spectroscopic data

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.33 (m, 4H, H-C2b, H-C2b'), 3.79 (m, 3H, H-Cα, H-Cα'), 2.84 (m, 4H, H-C1, H-C1'), 2.70 (m, 4H, H-C4', H-C4), 2.39 (m, 10H, H-C1a, H-C1a', H-N), 1.74 (m, 14H, H-C2a, H-C2a', H-C3a, H-C3a', H-C2') 1.40 (m, 7H, H-C2, H-C3, H-Cβ)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 128.5 (C1b'), 128.4 (C1b), 125.5 (C2b, C2b'), 58.9 (Cα'), 57.7 (Cα), 54.5 (C1a, C1a', C4), 53.3 (C3'), 48.8 (C1), 48.1 (C1'), 26.1 (C2), 25.7 (C2'), 25.5 (C2a, C2a', C3a, C3a'), 25.2 (C3), 24.1 (Cβ)

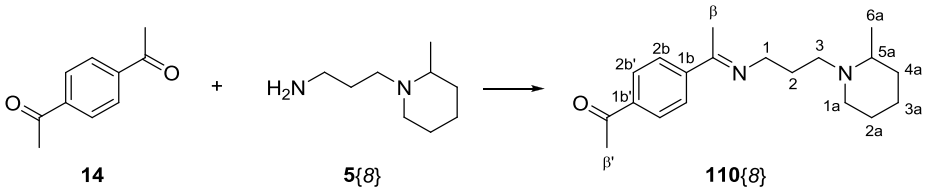
MS (FAB) *m/z* (%): 415.4 (33) $[M+1]^+$,401.4 (26), 291.3 (66), 278.2 (21), 277.2 (100), 157.2 (26), 155.2 (22), 140.2 (47), 124.1 (25), 112.1 (35)

HRMS (CI) calculated for $C_{26}H_{46}N_4$ $[M+1]^+$: 415.3801; found: 415.3799

Biological activity

EC_{50} = 0.695 μg/ml; **CC_{50}** > 25 μg/ml

4.8.9. Synthesis of 1-(4-(1-(3-(2-methylpiperidin-1-yl)propylamino)ethyl)phenyl)ethanone (110{*8*})



14 **5**{*8*} **110**{*8*}

0.780 g (5 mmol) of **5**{*8*} were slowly added into a solution of 1.62 g (10 mmol) of **14** and 2.84 g (10 mmol) of titanium isopropoxide (IV) in 20 ml of ethanol, under N_2 atmosphere. The mixture was stirred at room temperature for 24 hours.

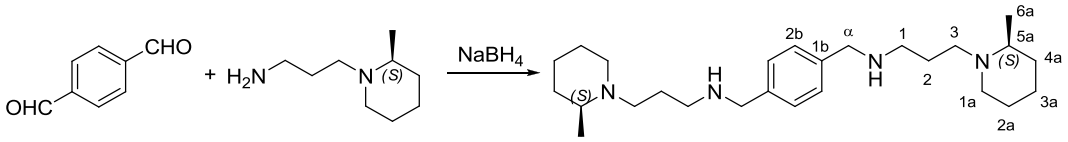
Water with some drops of NH_3, was added to stop the reaction. The solid was filtered and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure. A mixture of the desired product **110**{*8*} and **14** was obtained, which was partially purified by column chromatography (neutral alumina, ethyl acetate:hexane 1:2).

Spectroscopic data

^{1}H-NMR (300 MHz, $CDCl_3$): δ (ppm) 7.8 (m, 4H, H-C2b, H-C2b'), 3.48 (m, 2H, H-C3), 2.8 (m, 4H, H-C3, H-C8), 2.6 (m, 4H, H-C5, H-C10), 2.4 (m, 2H, H-C1a, H-C1c), 2.1 (m, 4H, H-C5a, H-C5c), 1.6 (m, 14H, H-C2a, H-C2c, H-C3a, H-C3c, H-C4a, H-C4c, H-C4, H-C9), 1.34 (d, J = 5.0 Hz, 3H, H-C2), 1.26 (m, 2H, H-C2a, H-Cc), 1.03 (m, 6H, H-C6, H-C11)

4.9. Synthesis of 2{*8,8*} stereoisomers

4.9.1. Synthesis of (*S*)-*N*,*N'*-(1,4-phenylenebis(methylene))bis(3-((*S*)-2-methylpiperidin-1-yl)propan-1-amine) (2{*8S,8S*})



4 **5**{*8S*} **2**{*8S*,*8S*}

0.0954 g (0.71 mmol) of terephthalaldehyde (**4**), 0.2259 g (1.45 mmol) of (*S*)-*N*-(3-aminopropyl)-2-pipecoline (**5**{*8S*}) and Na_2SO_4 were mixed in 6 ml of anhydrous MeOH and the mixture heated at reflux under N_2 atmosphere for 24 h. The solid was filtered and the intermediate imine in MeOH was cooled to 0 ºC and treated with 0.056 g (1.45 mmol) of solid $NaBH_4$. The reaction mixture was stirred at rt overnight. Then water was added and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 0.286 g (0.67 mmol, 97%) of **2**{*8S*,*8S*} as a yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3282 (*st* N-H), 2929, 2854, 2793 (*st* Csp^3-H), 1449, 1372 (*b* Csp^3-H)

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 (m, 4H, H-C2b), 3.79 (d, 4H, H-Cα), 2.92 (m, 2H, H-C1a), 2.79 (m, 2H, H-C3), 2.68 (m, 4H, H-C1), 2.44-2.33 (m, 8H, H-C3, H-C5a, H-C1a), 2.16 (m, 2H, NH), 1.80-1.48 (m, 12H, H-C2, H-C2a, H-C4a, H-C3a), 1.29 (m, 4H, H-C4a, H-C3a), 1.07 (d, 6H, , ^3J = 8.0 Hz, H-C6a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 138.7 (C1b), 127.8 (C2b), 55.8 (C5a), 53.6 (Cα), 52.2 (C3), 52.1 (C1a), 48.2 (C1), 34.7 (C4a), 26.2 (C2a), 25.7 (C2), 23.9 (C3a), 19.1 (C6a)

MS (CI) *m/z* (%): 415.3 (100), 258.2 (42), 112.0 (51)

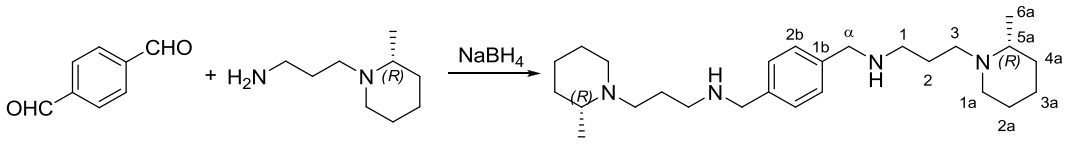
HRMS (CI) calculated for $C_{26}H_{47}N_4$ $[M+1]^+$: 415.3801; found: 415.3811

$[\alpha]_D$ = + 35.4 º (concentration 11 mg/ml, $CHCl_3$)

Biological activity

EC_{50} = 0.070 μg/ml; **CC_{50}** > 25 μg/ml

4.9.2. Synthesis of (*R*)-*N*,*N*′-(1,4-phenylenebis(methylene))bis(3-((*R*)-2-methylpiperidin-1-yl)propan-1-amine) (2{*8R*,*8R*})



4 **5**{*8R*} **2**{*8R*,*8R*}

0.0653 g (0.48 mmol) of terephthalaldehyde (**4**), 0.150 g (0.96 mmol) of (*R*)-*N*-(3-aminopropyl)-2-pipecoline (**5**{*8R*}) and Na_2SO_4 were mixed in 5 ml of anhydrous MeOH and the mixture heated at reflux under N_2 atmosphere for 24 h. The solid was filtered and the intermediate imine in MeOH was cooled to 0 ºC and treated with 0.037 g (0.96 mmol) of solid $NaBH_4$. The reaction mixture was stirred at rt overnight. Then water was added and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 0.167 g (0.4 mmol, 83%) of **2**{*8R*,*8R*} as a yellow oil.

Spectroscopic data

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31 (s, 4H, H-C2b), 3.79 (d, 4H, H-Cα), 2.91 (m, 2H, H-C1a), 2.78 (m, 2H, H-C3), 2.68 (m, 4H, H-C1), 2.43-2.32 (m, 8H, H-C3, H-C5a, H-C1a), 2.16 (m, 2H, NH), 1.79-1.49 (m, 12H, H-C2, H-C2a, H-C3a, H-C4a), 1.28 (m, 4H, H-C4a, H-C3a), 1.07 (d, 6H, , ^3J = 8.0 Hz, H-C6a)

MS (CI) *m/z* (%): 415.3 (100), 258.1 (31), 112.0 (53)

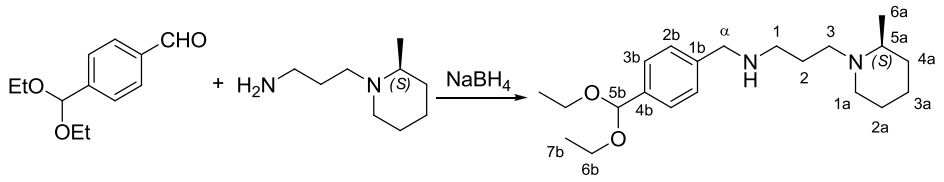
HRMS (CI): calculated for $C_{26}H_{47}N_4$ $[M+1]^+$: 415.3801; found: 415.3800

$[\alpha]_D$ = - 12.9 º (concentration 12 mg/ml, $CHCl_3$), 36% ee

Biological activity

EC_{50} = 0.077 μg/ml; **CC_{50}** > 25 μg/ml

4.9.3. Synthesis of (*S*)-*N*-(4-(diethoxymethyl)benzyl)-3-(2-methylpiperidin-1-yl)propan-1-amine (64{*8S*})



6 **5**{*8S*} **64**{*8S*}

0.345 g (1.6 mmol) of 4-(diethoxymethyl)benzaldehyde (**6**), 0.2505 g (1.6 mmol) of (*S*)-*N*-(3-aminopropyl)-2-pipecoline (**5**{*8S*}) and Na_2SO_4 were mixed in 5 ml of anhydrous MeOH and the mixture was held at reflux under N_2 atmosphere for 24 h. The solid was filtered and the intermediate imine in MeOH was cooled to 0 ºC and treated with 0.056 g (1.45 mmol) of solid $NaBH_4$. The reaction mixture was stirred at rt overnight. Then water was added and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 0,466 g (1.3 mmol, 84%) of the corresponding 4-(diethyoxymethyl)benzylamine **64**{8*S*} as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3283 (*st* N-H), 2973, 2930, 2798 (*st* Csp^3-H), 1663 (*st* C=C), 1444, 1371 (*b* Csp^3-H), 1114, 1055 (*st* C-O)

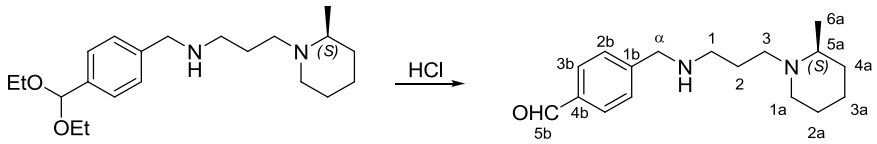
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.44 (m, 2H, H-C3b), 7.34 (m, 2H, H-C2b), 5.49 (s, 1H, H-C5b), 3.82 (d, ^3J = 9.0 Hz, 2H, H-Cα), 3.72-3.44 (m, 4H, H-C6b), 2.94 (m, 1H, H-C1a), 2.83 (m, 1H, H-C3), 2.71 (m, 2H, H-C1), 2.48-2.36 (m, 3H, H-C3, H-C5a, C1a), 2.21 (m, 1H, NH), 1.84-1.55 (m, 8H, H-C2, H-C2a, H-C3a, H-C4a), 1.24 (m, 6H, H-C7b), 1.09 (d, ^3J = 6.5 Hz, 3H, H-C6a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 140.1 (C1b), 137.8 (C4b), 127.9 (C2b), 126.7 (C3b), 101.4 (C5b), 64.7 (C5a), 61.0 (C6b), 56.0 (C1a), 53.6 (C3), 52.2 (C1), 48.2 (Cα), 34.4 (C4a), 25.9 (C2), 25.5 (C2a), 23.8 (C3a), 18.9 (C6a), 15.1 (C7b)

MS (EI) *m/z* (%): 348 (3), 303 (6), 165 (14), 155 (11), 126 (15), 112 (100), 98 (34), 91 (12)

HRMS (CI) calculated for $C_{21}H_{36}N_2O_2$ $[M]^+$: 348.2777; found: 348.2778

4.9.4. Synthesis of (*S*)-4-((3-(2-methylpiperidin-1-yl)propylamino)methyl)benzaldehyde (65{*8S*})



64{*8S*} **65**{*8S*}

0.495 g (1.42 mmol) of the intermediate aminoacetal **64**{*8S*} were treated with 5ml of 2 M HCl at room temperature for 2h. The resulting mixture was basified with NaOH and extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 0.314 g (1.14 mmol, 80%) of the desired product **65**{*8S*} as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3281 (*st* N-H), 2929, 2852, 2797, 2729 (*st* Csp^3-H), 1701 (*st* C=O), 1606 (*st* C=C), 1444, 1371 (*b* Csp^3-H), 1209 (*st* C-N)

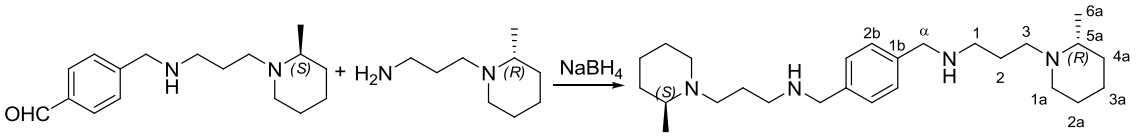
^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 10.00 (s, 1H, H-C5b), 7.84 (d, ^3J = 8.0 Hz, 2H, H-C3b), 7.50 (d, ^3J = 8.0 Hz, 2H, H-C2b), 3.87 (s, 2H, H-Cα), 2.90 (m, 1H, H-C1a), 2.79 (m, 1H, H-C3), 2.66 (t, ^3J = 7.0 Hz, 2H, H-C1), 2.42-2.36 (m, 2H, H-C3, H-C5a), 2.20-1.96 (m, 2H, H-C1a, NH), 1.75-1.55 (m, 6H, H-C2, H-C2a, H-C4a, H-C3a), 1.34-1.24 (m, 2H, H-C4a, H-C3a), 1.09 (d, ^3J = 6.5 Hz, 3H, H-C6a)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 192.0 (C5b), 147.8 (C1b), 135.3 (C4b), 129.9 (C3b), 128.5 (C2b), 56.1 (C5a), 53.7 (Cα), 52.3 (C3), 52.0 (C1a), 48.5 (C1), 34.5 (C4a), 26.0 (C2a), 25.8 (C2), 23.8 (C3a), 18.9 (C6a)

MS (EI) *m/z* (%): 274 (6), 183 (3), 155 (7), 126 (9), 119 (10), 112 (100), 98 (39), 91 (14)

HRMS (EI) calculated for $C_{17}H_{26}N_2O$ $[M]^+$: 274.2045; found: 274.2037

4.9.5. Synthesis of 3-((*R*)-2-methylpiperidin-1-yl)-*N*-(4-((3-((*S*)-2-methylpiperidin-1-yl)propylamino)methyl)benzyl)propan-1-amine (2{*8S*,*8R*})



65{*8S*} **5**{*8R*} **2**{*8S*,*8R*}

0.314 g (1.14 mmol) of (*S*)-4-((3-(2-methylpiperidin-1-yl)propylamino)methyl)benzaldehyde (**65**{*8S*}), 0.178 g (1.44 mmol) of (*R*)-*N*-(3-aminopropyl)-2-pipecoline (**5**{*8R*}) and Na_2SO_4 were mixed in 8 ml of anhydrous MeOH and the mixture was heated at reflux under N_2 atmosphere for 24 h. The solid was filtered and the intermediate imine in MeOH was cooled to 0 ºC and treated with 0.044 g (1.14 mmol) of solid $NaBH_4$. The reaction mixture was stirred at room temperature overnight. Then water was added and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 0.394 g (0.95 mmol, 83%) of **2**{*8S*,*8R*} as a yellow oil.

Spectroscopic data

^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 7.30 (s, 4H, H-C2b), 3.79 (d, 4H, H-Cα), 2.89 (m, 2H, H-C1a), 2.77 (m, 2H, H-C3), 2.67 (m, 4H, H-C1), 2.41-2.27 (m, 8H, H-C3, H-C5a, H-C1a), 2.16 (m, 2H, NH), 1.75-1.48 (m, 12H, H-C2, H-C2a, H-C4a, H-C3a), 1.29 (m, 4H, H-C4a, H-C3a), 1.06 (d, 6H, , ^3J = 8.0 Hz, H-C6a)

MS (CI) *m/z* (%): 415.4 (56), 199.1 (100), 157.1 (71), 112.0 (95)

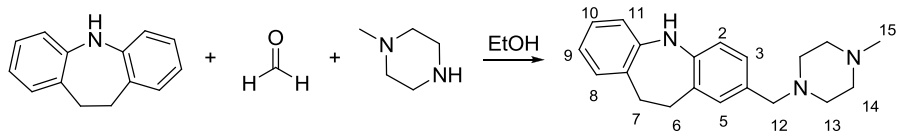
HRMS (CI) calculated for $C_{26}H_{47}N_4$ $[M+1]^+$: 415.3801; found: 415.3803

Biological activity

EC_{50} = 0.078 μg/ml; **CC_{50}** = 18 μg/ml

4.10. Synthesis of privileged structures derivatives

4.10.1. Synthesis of 3-((4-methylpiperazin-1-yl)methyl)-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (71{*3*})



68 **69** **70**{*3*} **71**{*3*}

To 2.8 ml (25 mmol) of *N*-methylpiperazine (**70**{*3*}) cooled in an ice bath were added slowly 1.5 ml (20 mmol) of formaldehyde (**69**) 37% in water. 2.01 g (10 mmol) of 10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine (**68**), 1.7 ml (30 mmol) of acetic acid and 40 ml of ethanol were added and the reaction mixture was heated under reflux for 30 h. After concentration, the residue was neutralized with NaClO 1% and extracted with $CHCl_3$. The organic layers were combined, washed with water, dried over $MgSO_4$, filtered and concentrated. The brown residue was digested from hexane to give 1.44 g (4.7 mmol, 47%) of **71**{*3*} as a light brown solid.

Spectroscopic data

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.03 (m, 4H, H-C10, H-C8, H-C5, H-C3), 6.73 (m, 3H, H-C2, H-C11, H-C9), 5.96 (s, 1H, NH), 3.40 (s, 2H, H-C12), 3.07 (s, 4H, H-C6, H-C7), 2.70-2.30 (br, 8H, H-C13, H-C14), 2.28 (s, 3H, H-C16)

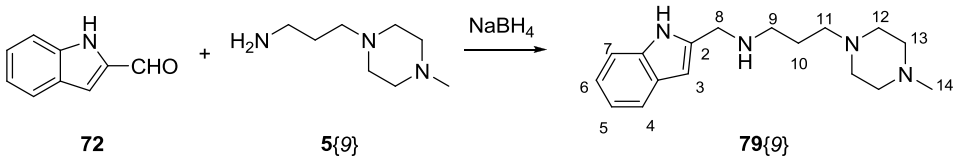
MS (EI) *m/z* (%): 307.3 (55) $[M]^+$, 208.2 (100), 195.2 (72), 99.2 (71)

HRMS (EI) calculated for $C_{20}H_{25}N_3$ $[M]^+$: 307.2048; found: 307.2045

Biological activity

EC_{50} > 9.9 μg/ml; **CC_{50}** = 9.9 μg/ml

4.10.2. Synthesis of *N*-((1*H*-indol-2-yl)methyl)-3-(4-methylpiperazin-1-yl)propanamine (79{*9*})



72 **5**{*9*} **79**{*9*}

0.314 g (2.1 mmol) of 1*H*-indole-2-carbaldehyde (**72**), 0.36 ml (2.1 mmol) of 3-(4-methylpiperazin-1-yl)propanamine (**5**{*9*}) and Na_2SO_4 were mixed in 30 ml of anhydrous MeOH and the mixture was heated at reflux under N_2 atmosphere for 24 h. The solid was filtered and the intermediate imine in MeOH was cooled to 0 ºC and treated with 0.081 g (2.1 mmol) of solid $NaBH_4$. The reaction mixture was stirred at room temperature overnight. Then water was added and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 0.572 g (2.0 mmol, 95%) of **79**{*9*} as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3185 (*st* N-H), 3080 (*st* Csp^2-H), 2937, 2798, 2680 (*st* Csp^3-H), 1457, 1287 (*b* Csp^3-H), 1164 (*st* C-N), 745 (*b* N-H)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 9.21 (s, 1H, NH), 7.54 (d, ^3J = 8.0 Hz, 1H, H-C7), 7.37 (d, ^3J = 8.0 Hz, 1H, H-C4), 7.15 (t, ^3J = 7.0 Hz, 1H, H-C5), 7.07 (t, ^3J = 7.0 Hz, 1H, H-C6), 6.36 (s, 1H, H-C3), 4.2 (br, 1H, NH), 4.03 (s, 2H, H-C8), 2.80 (t, ^3J = 6.5 Hz, 2H, H-C9), 2.6-2.2 (br, 10H, H-C12, H-C13, H-C11), 2.16 (s, 3H, H-C14), 1.76 (qn, ^3J = 6.5 Hz, 2H, H-C10)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 136.5 (C7a), 133.2 (C2), 127.8 (C3a), 122.0 (C6), 120.2 (C4), 119.8 (C5), 111.3 (C7), 102.0 (C3), 57.0 (C11), 54.6 (C13), 52.9 (C12), 47.9 (C8), 45.7 (C14), 24.2 (C9), 22.8 (C10)

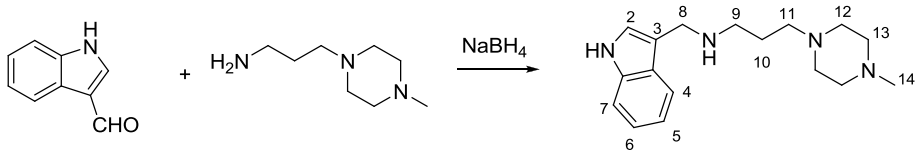
MS (EI) *m/z* (%): 286.3 (20) $[M]^+$, 214.2 (13), 130.1 (100)

HRMS (EI) calculated for $C_{17}H_{26}N_4$ $[M]^+$: 286.2157; found: 286.2156

Biological activity

EC_{50} > 3.8 μg/ml; **CC_{50}** = 3.8 μg/ml

4.10.3. Synthesis of *N*-((1*H*-indol-3-yl)methyl)-3-(4-methylpiperazin-1-yl)propanamine (80{*9*})



73 **5**{*9*} **80**{*9*}

0.311 g (2.1 mmol) of 1*H*-indole-3-carbaldehyde (**73**), 0.36 ml (2.1 mmol) of 3-(4-methylpiperazin-1-yl)propanamine (**5**{*9*}) and Na_2SO_4 were mixed in 30 ml of anhydrous MeOH and the suspension was held at reflux under N_2 atmosphere for 24 h. The solid was filtered and the intermediate imine in MeOH was cooled to 0 ºC and treated with 0.081 g (2.1 mmol) of solid $NaBH_4$. The reaction mixture was stirred at room temperature overnight. Then water was added and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 0.5560 g (1.9 mmol, 92%) of **80**{*9*} as a yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3176 (*st* N-H), 3055 (*st* Csp^2-H), 2938, 2800, 2684 (*st* Csp^3-H), 1456, 1356, 1285 (*b* Csp^3-H), 1163 (*st* C-N), 745 (*b* N-H)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.67 (s, 1H, NH), 7.63 (d, ^3J = 8.0 Hz, 1H, H-C4), 7.40 (d, ^3J = 8.0 Hz, 1H, H-C7), 7.27 (s, 1H, H-C2), 7.20 (m, 1H, H-C5), 7.14 (m, 1H, H-C6), 4.05 (s, 2H, H-C8), 2.89 (t, ^3J = 6.5 Hz, 2H, H-C9), 2.6-2.2 (br, 10H, H-C11, H-C12, H-C13), 2.15 (s, 3H, H-C14), 1.81 (qn, ^3J = 6.5 Hz, 2H, H-C10)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 136.2 (C7a), 126.5 (C3a), 125.7 (C2), 122.3 (C6), 120.0 (C5), 117.8 (C4), 112.0 (C7), 111.4 (C3), 57.4 (C11), 54.5 (C13), 52.8 (C12), 48.4 (C8), 45.6 (C14), 42.8 (C9), 22.9 (C10)

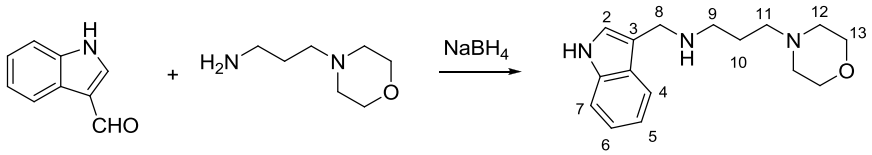
MS (EI) *m/z* (%): 286.1 (1) $[M]^+$, 245.1 (9), 158.0 (16), 130.0 (100), 113.1 (52), 70.1 (66)

HRMS (EI) calculated for $C_{17}H_{26}N_4$ $[M]^+$: 286.2157; found: 286.2152

Biological activity

EC_{50} = 15.9 μg/ml; **CC_{50}** = 50.8 μg/ml

4.10.4. Synthesis of *N*-((1*H*-indol-3-yl)methyl)-3-morpholinopropanamine (80{*11*})



73 **5**{*11*} **80**{*11*}

0.311 g (2.1 mmol) of 1*H*-indole-3-carbaldehyde (**73**), 0.31 ml (2.1 mmol) of 3-morpholinopropanamine (**5**{*11*}) and Na_2SO_4 were mixed in 30 ml of anhydrous MeOH and the mixture heated at reflux under N_2 atmosphere for 24 h. The solid was filtered and the intermediate imine in MeOH was cooled to 0 ºC and treated with 0.081 g (2.1 mmol) of solid $NaBH_4$. The reaction mixture was stirred at room temperature overnight. Then water was added and the product was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent was removed to give 0.5624 g (2.06 mmol, 98%) of **80**{*11*} as a yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3183 (*st* N-H), 3055 (*st* Csp^2-H), 2928, 2854, 2813 (*st* Csp^3-H), 1458, 1356 (*b* Csp^3-H), 1116 (*st* C-N), 747 (*b* N-H)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.78 (s, 1H, NH), 7.62 (d, ^3J = 8.0 Hz, H-C4), 7.38 (d, ^3J = 8.0 Hz, H-C7), 7.20-7.12 (m, 3H, H-C5, H-C6, H-C2), 4.03 (s, 2H, H-C8), 3.70 (br, 1H, NH), 3.55 (t, ^3J = 4.5 Hz, 4H, H-C13), 2.86 (t, ^3J = 6.5 Hz, 2H, H-C9) 2.41 (m, 6H, H-C11, H-C12), 1.79 (qn, ^3J = 6.5 Hz, 2H, H-C10)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 136.3 (C7a), 126.8 (C3a), 123.6 (C2), 122.2 (C5), 119.6 (C6), 118.3 (C4), 112.1 (C3), 111.5 (C7), 66.7 (C13), 57.6 (C11), 53.6 (C12), 48.3 (C9), 44.1 (C8), 25.1 (C10)

MS (EI) *m/z* (%): 273.1 (6) $[M]^+$, 245.1 (11), 130.0 (100), 100.1 (80)

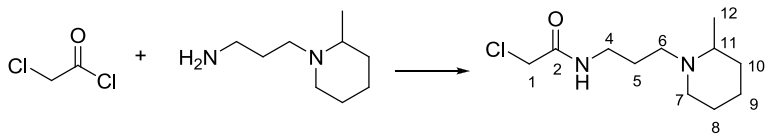
HRMS (EI) calculated for $C_{16}H_{23}N_3O$ $[M]^+$: 273.1841; found: 273.1847

Biological activity

EC_{50} > 51.4 μg/ml; **CC_{50}** = 51.4 μg/ml

4.11. Synthesis of *de novo* designed amides with ethylene spacer

4.11.1. Synthesis of 2-chloro-*N*(3-(2-methylcyclohexyl)propyl)acetamide (93c{*8*})



94c **5**{*8*} **93c**{*8*}

0.92 ml (5.0 mmol) of **5**{*8*} and 2.00 g (14.5 mmol) of K_2CO_3 were mixed in 10 ml of anhydrous ACN and cooled to 0 ºC under N_2 atmosphere. A solution of 0.44 ml (5.5 mmol) of chloroacetyl chloride (**94c**) in 8 ml of anhydrous ACN was added dropwise for 1 hour. The suspension was stirred overnight, filtered and the solvent was removed under reduced pressure. 1.16 g (5.0 mmol, quantitative) of the desired product **93c**{*8*} were obtained as a brown oil without further purification.

Spectroscopic data

IR (film) ν (cm^{-1}): 3293 (*st* N-H), 2931, 2856, 2793 (*st* Csp^3-H), 1666 (*st* C=O), 1532 (*st* C-N)

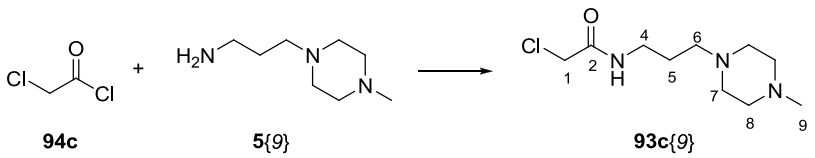
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.39 (br, 1H, NH), 4.03 (s, 2H, H-C1), 3.58-3.48 (m, 1H, H-C4), 3.31-3.21 (m, 1H, H-C4), 2.98-2.82 (m, 2H, H-C7, H-C6), 2.30-2.19 (m, 2H, H-C6, H-C11) 2.06-1.97 (m, 1H, H-C7), 1.83-1.51 (m, 6H, H-C10, H-C9, H-C5*, H-C8*), 1.41-1.22 (m, 2H, H-C10, H-C9), 1.08 (d, ^3J = 6.5 Hz, 3H, H-C12)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 166.2 (C2), 57.1 (C11), 53.9 (C6), 52.6 (C7), 42.9 (C1), 41.0 (C4), 34.6 (C10), 26.0 (C5*), 25.0 (C8*), 24.0 (C9), 19.2 (C12)

MS (EI) *m/z* (%): 232.2 (3) $[M]^+$, 217.2 (34), 112.2 (100)

HRMS (EI) calculated for $C_{11}H_{21}ClN_2O$ $[M]^+$: 232.1342; found: 232.1346

4.11.2. Synthesis of 2-chloro-*N*(3-(4-methylpiperazin-1-yl)propyl)acetamide (93c{*9*})



94c **5**{*9*} **93c**{*9*}

Procedure was the same as stated above for **93c**{*8*} but using 0.87 ml (5.0 mmol) of 1-(3-aminopropyl)-4-methylpiperazine (**5**{*9*}), 1.42 g (10.3 mmol) of K_2CO_3 and 0.44 ml (5.5 mmol) of chloroacetyl chloride (**94c**). After stirring overnight, the suspension was filtered, and the solvent removed under reduced pressure. 1.16 g (5.0 mmol, quantitative) of the desired product **93c**{*9*} were obtained as a brown oil without further purification.

Spectroscopic data

IR (film) ν (cm^{-1}): 3212 (*st* N-H), 2938, 2877, 2795, 2679 (*st* Csp^3-H), 1674 (*st* C=O), 1557 (*b* N-H), 1459 (*st* Csp^2-H), 1372 (*st* Csp^3-H)

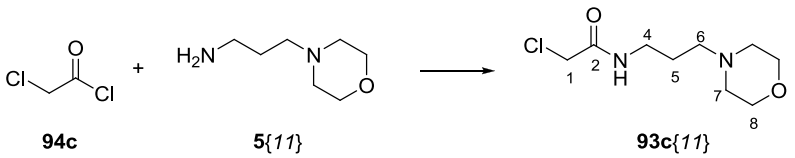
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (br, 1H, NH), 4.04 (s, 2H, H-C1), 3.41 (q, ^3J=6.2 Hz, 2H, H-C4), 2.67-2.40 (m, 10H, H-C6, H-C7, H-C8), 2.30 (s, 3H, H-C9), 1.72 (qn, ^3J=6.2 Hz, 2H, H-C5)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 166.2 (C2), 58.1 (C6), 54.9* (C8), 53.5* (C7), 46.1 (C9), 42.8 (C1), 40.6 (C4), 24.6 (C5)

MS (ESI-TOF) *m/z* (%): 268.1 (100) $[M+Cl]^-$, 160.8 (36)

HRMS (ESI-TOF) calculated for $C_{10}H_{20}Cl_2N_3O$ $[M+Cl]^-$: 268.0978; found: 268.0977

4.11.3. Synthesis of 2-chloro-*N*(3-morpholinopropyl)acetamide (93c{*11*})



94c **5**{*11*} **93c**{*11*}

Procedure was the same as stated above for **93c**{*8*} but using 0.29 ml (2.0 mmol) of 3-morpholinopropylamine (**5**{*11*}), 0.80 g (5.8 mmol) of K_2CO_3 and 0.23 ml (2.0 mmol) of chloroacetyl chloride (**94c**). 0.40 g (1.8 mmol, 90%) of the desired amide **93c**{*11*} were obtained as a brown oil without further purification.

Spectroscopic data

IR (film) ν (cm^{-1}): 3301 (*st* N-H), 2953, 2857, 2813 (*st* Csp^3-H), 1666 (*st* C=O), 1535 (*b* N-H), 1117 (*st* C-O-C), 862 (*st* C-O-C)

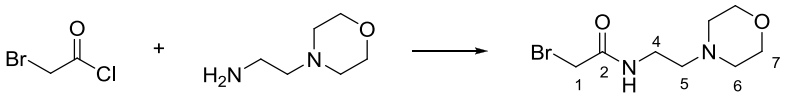
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.02 (br s, 1H, NH), 4.05 (s, 2H, H-C1), 3.80-3.67 (m, 4H, H-C8), 3.46-3.38 (m, 2H, H-C4), 2.55-2.40 (m, 6H, H-C7, H-C6), 1.80-1.67 (m, 2H, H-C5)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 166.2 (C2), 66.9 (C8), 58.6 (C6), 54.1 (C7), 42.9 (C1), 40.5 (C4), 24.4 (C5)

MS (ESI-TOF) *m/z* (%): 255.1 (100) $[M+Cl]^-$

HRMS (ESI-TOF) calculated for $C_9H_{17}Cl_2N_2O_2$ $[M+Cl]^-$: 255.0667; found: 255.0662

4.11.4. Synthesis of 2-bromo-*N*(2-morpholinoethyl)acetamide (93b{*10*})



94b **5**{*10*} **93b**{*10*}

0.46 ml (5.8 mmol) of bromoacetyl chloride at 0 ºC were added dropwise to a solution of 0.66 ml (5.0 mmol) of 4-(2-aminoethyl)morpholine (**5**{*10*}) and 0.85 ml of NEt_3 (6.2 mmol) in 25 ml of anhydrous CH_2Cl_2 at 0 ºC and under N_2. The mixture was stirred overnight at room temperature. Then, 75 ml of K_2CO_3 solution (40%) were added and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with 50 ml of water, dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash chromatography (silica, CH_2Cl_2:MeOH:NH_3 100:0.0 to 80:20:1 in 18 minutes) afforded 0.280 g (1.1 mmol, 22%), of the desired product **93b**{*10*} as a brown oil.

Spectroscopic data

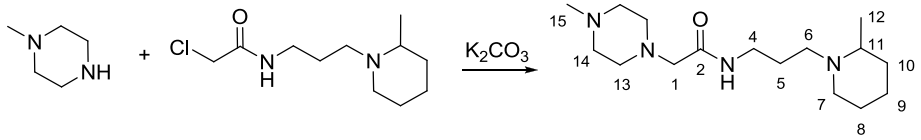
IR (film) ν (cm^{-1}): 3305 (*st* N-H), 2955, 2855, 2813 (*st* Csp^3-H), 1668 (*st* C=O), 1534 (*b* N-H), 1117 (*st* C-O-C), 867 (*st* C-O-C)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.18 (br, 1H, NH), 4.06 (s, 2H, H-C1), 3.78-3.68 (m, 4H, H-C7), 3.44-3.36 (m, 2H, H-C4), 2.54 (t, ^3J=6.1 Hz, 2H, H-C5), 2.51-2.45 (m, 4H, H-C6)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 165.9 (C2), 67.0 (C7), 56.4 (C5), 53.2 (C6), 42.7 (C1), 35.9 (C4)

MS (EI) *m/z* (%):171.1 (2), 157.1 (4), 100.2 (100), 70.1 (20), 56.1 (44), 42.1 (27)

4.11.5. Synthesis of *N*-(3-(2-methylcyclohexyl)propyl)-2-(4-methylpiperazin-1-yl)acetamide (92{*3*,*8*})



70{*3*} **93c**{*8*} **92**{*3*,*8*}

1.16 g (5.0 mmol) of **93c**{*8*} , 0.55 ml (4.9 mmol) of 1-methylpiperazine (**70**{*3*}) and 3.65 g (26.4 mmol) of K_2CO_3 were mixed in 20 ml ACN and heated under microwave irradiation at 100 ºC for 1 hour. The mixture was filtered and the solvent was removed under reduced pressure. 0.72 g of crude product were purified using flash chromatography (basic alumina, CH_2Cl_2:MeOH 100:0 to 95:5 in 14 minutes) to afford 0.260 g (0.9 mmol, 18%) of the desired **92**{*3*,*8*} as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3332 (*st* N-H), 2933, 2794 (*st* Csp^3-H), 1674 (*st* C=O), 1519 (*b* N-H), 1456, 1374 (*b* Csp^3-H)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.49 (br, 1H, NH), 3.41-3.22 (m, 2H, H-C4), 3.00, 2.99 (s, 2H, H-C1), 2.90-2.80 (m, 1H, H-C7), 2.80-2.70 (m, 1H, H-C6), 2.65-2.20 (m, 13H, H-C15, H-C14, H-C13, H-C11, H-C6), 2.13-2.03 (m, 1H, H-C7), 1.72-1.48 (m, 6H, H-C10, H-C9, H-C8, H-C5), 1.38-1.23 (2H, H-C10, H-C9), 1.06 (d, 3H, ^3J=6.2 Hz, H-C12).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 170.1 (C2), 61.8 (C1), 56.3 (C11), 55.2 (C14*), 53.6 (C13*), 52.2 (C7), 52.0 (C6), 43.1 (C15), 38.0 (C4), 34.7 (C10), 26.2 (C8), 25.9 (C5), 24.0 (C9), 19.2 (C12)

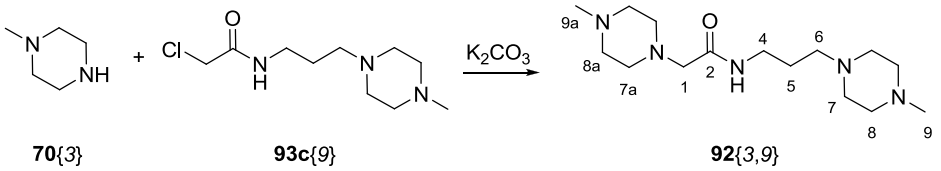
MS (EI) *m/z* (%): 296.3 $[M]^+$ (10), 183.2 (95), 113.1 (100), 70.1 (87)

HRMS (EI) calculated for $C_{16}H_{32}N_4O$ $[M]^+$: 296.2576; found: 296.2574

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 70 μg/ml

4.11.6. Synthesis of 2-(4-methylpiperazin-1-yl)-*N*-(3-(4-methylpiperazin-1-yl)propyl)acetamide (92{*3*,*9*})



70{*3*} **93c**{*9*} **92**{*3*,*9*}

Procedure was the same as stated above for **92**{*3*,*8*}, using 1.16 g (5.0 mmol) of **93c**{*9*} , 0.56 ml (5.0 mmol) of 1-methylpiperazine (**70**{*3*}) and 4.03 g (28.9 mmol) of K_2CO_3.

The crude product was purified using flash chromatography (basic alumina, CH_2Cl_2:MeOH 100:0 to 95:5 in 20 minutes) to afford 0.327 g (1.1 mmol, 22%) of the desired **92**{*3*,*9*} as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3343 (*st* N-H), 2937, 2877, 2796, 2693 (*st* Csp^3-H), 1667 (*st* C=O), 1522 (b N-H), 1457, 1373 (*b* Csp^3-H)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36 (br, 1H, NH), 3.34 (q, ^3J=6.6 Hz, 2H, H-C4), 3.00 (s, 2H, H-C1), 2.78-2.33 (m, 18H, H-C7, H-C8, H-C6, H-C7a, H-C8a), 2.30 (s, 6H, H-C9, H-C9a), 1.70 (qn, ^3J=6.8 Hz, 2H, H-5).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 170.2 (C2), 61.7 (C1), 56.4 (C6), 55.2 (C7), 55.2 (C7a), 53.6 (C8*), 53.4 (C8a*), 46.1 (C9), 46.1 (C9a), 37.7 (C4), 26.7 (C5)

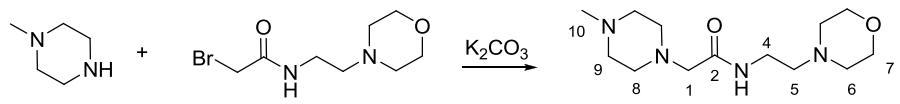
MS (EI) *m/z* (%): 297.3 $[M]^+$ (14), 184.2 (53), 113.1 (100), 70.1 (85)

HRMS (EI) calculated for $C_{15}H_{31}N_5O$ $[M]^+$: 297.2529; found: 297.2528

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 95 μg/ml

4.11.7. Synthesis 2-(4-methylpiperazin-1-yl)-*N*-(2-morpholinoethyl)acetamide (92{*3,10*})



70{*3*} **93b**{*10*} **92**{*3,10*}

Procedure was the same as stated above for **92**{*3,8*}, using 0.253 g (5.0 mmol) of **93c**{*10*} , 0.11 ml (0.8 mmol) of 1-methylpiperazine (**70**{*3*}) and 0.22 g (1.6 mmol) of K_2CO_3.

The crude product was purified using flash chromatography (basic alumina, CH_2Cl_2:MeOH:NH_3 100:0:0 to 74:25:1 in 32 minutes) to afford 0.159 g (0.6 mmol, 60%) of the desired product **92**{*3,10*} as a brown oil.

Spectroscopic data

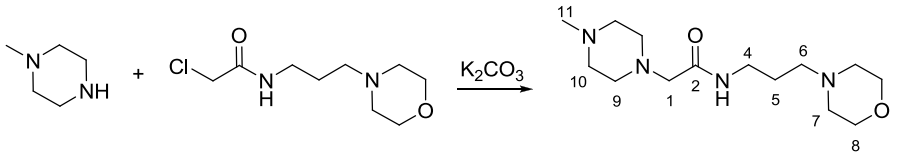
IR (film) ν (cm^{-1}): 3351 (*st* N-H), 2937, 2795, 2694 (*st* Csp^3-H), 1679 (*st* C=O), 1516 (*b* N-H), 1456, 1374 (*b* Csp^3-H), 1118 (*st* C-O), 866

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.56 (br s, 1H, NH), 3.80-3.65 (m, 4H, H-C7), 3.42-3.34 (m, 2H, H-C4), 3.01 (s, 2H, H-C1), 2.70-2.35 (m, 14H, H-C5, H-C6, H-C8, H-C9), 2.30 (s, 3H, H-C10).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 170.2 (C2), 67.2 (C7), 61.5 (C1), 57.2 (C5), 55.5 (C6), 53.5 (C8*), 55.5 (C9*), 46.2 (C10), 35.2 (C4).

MS (EI) *m/z* (%):270.3 $[M]^+$ (28), 157.2 (8), 113.2 (93), 100.1 (100), 70.1 (84), 56.1 (28), 42.1 (38)

4.11.8. Synthesis of 2-(4-methylpiperazin-1-yl)-*N*-(3-morpholinopropyl)acetamide (92{*3*,*11*})



70{*3*} **93c**{*11*} **92**{*3*,*11*}

Procedure was the same as stated above for **92**{*3*,*8*}, using 1.00 g (4.4 mmol) of **93c**{*11*} , 0.50 ml (4.5 mmol) of 1-methylpiperazine (**70**{*3*}) and 0.92 g (6.7 mmol) of K_2CO_3.

The crude product was purified using flash chromatography (basic alumina, CH_2Cl_2:MeOH 100:0 to 95: 5 in 30 minutes) to afford 0.646 g (2.3 mmol, 52%) of the desired product **92**{*3*,*11*} as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3338 (*st* N-H), 2937, 2849, 2796, 2693 (*st* Csp^3-H), 1674 (*st* C=O), 1519 (*b* N-H), 1456, 1374 (*st* Csp^3-H), 1118 (*st* C-O), 867

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.38 (br, 1H, H-C3), 3.78-3.68 (m, 4H, H-C8), 3.35 (q, ^3J=7.0 Hz, 2H, H-C4), 3.00 (s, 2H, H-C1), 2.65-2.35 (m, 14H, H-C7, H-C6, H-C9, H-C10), 2.30 (s, 2H, H-C11), 1.71 (qn, ^3J=7.0 Hz, 2H, H-C5)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 170.2 (C2), 67.1 (C8), 61.8 (C1), 57.0 (C6), 55.3 (C7), 53.9 (C9), 53.6 (C10), 46.2 (C11), 37.6 (C4), 26.5 (C5)

MS (EI) *m/z* (%): 284.2 $[M]^+$ (30), 171.1 (35), 113.2 (100), 100.1 (28), 70.1 (70)

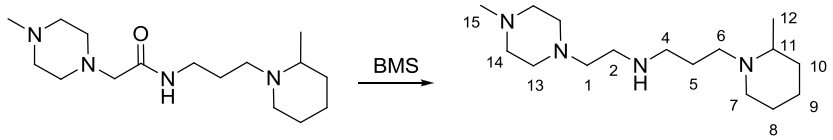
HRMS (EI) calculated for $C_{14}H_{28}N_4O_2$ $[M]^+$: 284.2212; found: 284.2215

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 91 μg/ml

4.12. Synthesis of *de novo* designed amines with ethylene spacer

4.12.1. Synthesis of 3-(2-methylcyclohexyl)-*N*-(2-(4-methylpiperazin-1-yl)ethyl)propan-1-amine (83{*3,8*})



92{*3,8*} **83**{*3,8*}

0.584 g (2 mmol) of **92**{*3,8*} were dissolved in 9 ml of anhydrous THF and 0.65 ml (6.9 mmol) of borane dimethylsulfide complex were added dropwise. The solution was held at reflux for 5 days, cooled to room temperature and diluted with 10.1 ml of 1.25 M HCl/MeOH.

The new solution was heated at reflux for 1 hour. The solvent was removed under reduced pressure and the crude was diluted with NaOH 1 M until pH = 14. The aqueous solution was extracted twice with CH_2Cl_2 and dried over $MgSO_4$. After concentration, the crude product was purified using flash chromatography (basic alumina, CH_2Cl_2:MeOH 100:0 to 95:5 in 11 minutes) to afford 0.237 g (1.0 mmol, 50%) of the desired amine **83**{*3,8*} as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3300 (*st* N-H), 2931, 2793 (*st* Csp^3-H), 1456, 1373 (*b* Csp^3-H)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.96-2.87 (m, 1H, H-C7), 2.84-2.22 (m, 21H, H-C1, H-C2, NH, H-C4, H-C6, H-C11, H-C13, H-C14, H-C15), 2.19-2.07 (m, 1H, H-C7), 1.83-1.46 (m, 6H, H-C5, H-C8, H-C9, H-C10), 1.42-1.19 (m, 2H, H-C9, H-C10), 1.08 (d, 3H, ^3J=6.3 Hz, H-C12)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 57.6 (C1), 56.2 (C11), 55.2 (C14*), 53.4 (C13*), 52.4 (C6), 52.1 (C7), 49.1 (C4), 46.5 (C2), 46.2 (C15), 34.6 (C10), 26.1 (C8), 25.4 (C5), 23.9 (C9), 19.1 (C12)

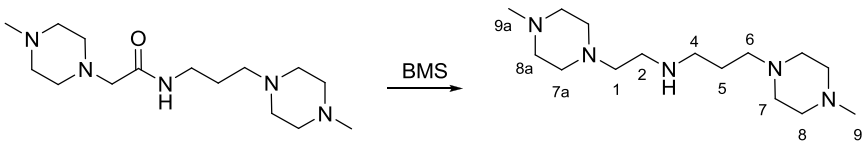
MS (EI) *m/z* (%): 183.2 (7), 169.2 (80), 126.2 (15), 112.2 (100), 98.2 (21), 70.1 (46)

HRMS (EI) calculated for $C_{16}H_{35}N_4$ $[M+1]^+$: 283.2862; found: 283.2869

Biological activity

EC_{50} = 0.71 μg/ml; **CC_{50}** > 25 μg/ml

4.12.2. Synthesis of 3-(4-methylpiperazin-1-yl)-*N*-(2-(4-methylpiperazin-1-yl)ethyl)propan-1-amine (83{*3*,*9*})



92{*3*,*9*} **83**{*3*,*9*}

0.350 g (1.2 mmol) of **92**{*3*,*9*} were dissolved in 9 ml of anhydrous THF and 0.4 ml (4.2 mmol) of borane dimethylsulfide complex were added dropwise. The solution was held at reflux for 5 days, cooled to room temperature and diluted with 7 ml of 1.25 M HCl/MeOH.

The new solution was heated at reflux for 1 hour. The solvent was removed under reduced pressure and the crude was diluted with NaOH 1 M until pH = 14. The aqueous solution was extracted with CH_2Cl_2, dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford 0.103 g (0.4 mmol, 33%) of **83**{*3*,*9*} as a yellow oil without further purification.

Spectroscopic data

IR (film) ν (cm^{-1}): 3299 (s*t* N-H), 2936, 2876, 2794 (s*t* Csp^3-H), 1457, 1372 (*b* Csp^3-H)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 2.90-1.90 (cs, 19H, H-C7, H-C7a, H-C8, H-C8a, H-C6, NH), 2.69 (t, ^3J=6.0 Hz, 2H, H-C2), 2.65 (t, ^3J=7.0 Hz, 2H, H-C4), 2.49 (t, ^3J=6.0 Hz, 2H, H-C1), 2.28 (s, 3H, H-C9*), 2.28 (s, 3H, H-C9a*), 1.75-1.63 (m, 2H, H-C5)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 57.9 (C1), 56.9 (C6), 55.3 (C7*), 55.2 (C7a*), 53.3 (C8, C8a), 48,7 (C4), 46,6 (C2), 46.1 (C9, C9a)

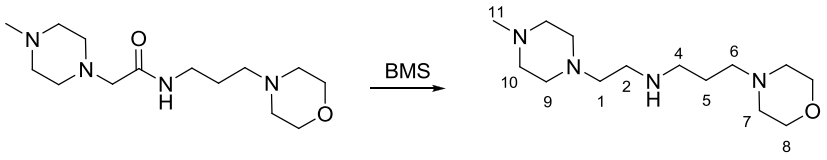
MS (EI) *m/z* (%):283.3 (1) $[M]^+$, 170.1 (39), 113.1 (100), 70.1 (51)

HRMS (EI) calculated for $C_{15}H_{33}N_5$ $[M]^+$: 283.2736; found: 283.2730

Biological activity

EC_{50} > 25 μg/ml; **CC_{50}** > 25 μg/ml

4.12.3. Synthesis of *N*-(2-(4-methylpiperazin-1-yl)ethyl)-3-morpholinopropan-1-amine (83{*3,11*})



92{*3,11*} **83**{*3,11*}

0.367 g (1.2 mmol) of **92**{*3,11*} were dissolved in 9 ml of anhydrous THF and 0.5 ml (5.3 mmol) of borane dimethylsulfide complex were added dropwise. The solution was held at reflux for 3 days, cooled to room temperature and diluted with 8 ml of 1.25 M HCl/MeOH.

The new solution was heated at reflux for 1 hour. The solvent was removed under reduced pressure and the crude was diluted with NaOH 2 M until pH = 14. The aqueous solution was extracted with CH_2Cl_2 and dried over $MgSO_4$.

After concentration, the crude product was purified by preparative TLC chromatography (basic alumina, CH_2Cl_2:MeOH 93:7) to afford 26 mg (0.1 mmol, 7%) of **83**{*3,11*} as a yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 2924, 2853, 2809 (*st* Csp^3-H), 1457, 1376 (*b* Csp^3-H), 1121 (*st* C-O)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.77-3.71 (cs, 4H, H-C8), 2.90-2.81 (m, 4H, H-C6, H-C2), 2.67-2.60 (m, 2H, H-C1), 2.58-2.37 (m, 15H, H-C10, H-C9, H-C7, H-C4, H-N3), 2.29 (s, 3H, H-C11), 1.88 (qn, ^3J=6.5 Hz, 2H, H-C5)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 67.1 (C8), 58.0 (C6), 56.2 (C1), 55.1 (C10*), 53.9 (C7), 53.4 (C9*), 49.3 (C4), 46.2 (C11), 45.9 (C2), 24.5 (C5)

MS (EI) *m/z* (%): 270.2 $[M]^+$ (1), 157.2 (48), 113.2 (73), 100.1 (100), 70.1 (64)

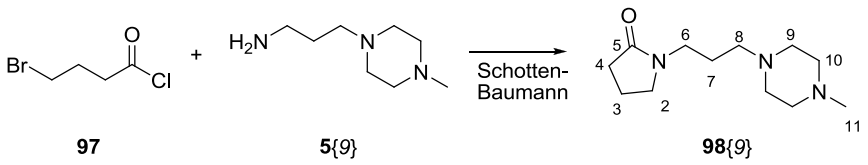
HRMS (ESI-TOF) calculated for $C_{14}H_{31}N_4O$ $[M+1]^+$: 271.2498; found: 271.2492

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 76 μg/ml

4.13. Synthesis of *de novo* designed amides with tetramethylene spacer

4.13.1. Synthesis of 1-(3-(4-methylpiperazin-1-yl)propyl)pyrrolidin-2-one (98{*9*})



97 **5**{*9*} **98**{*9*}

0.61 ml (5 mmol) of 4-bromobutyryl chloride (**97**) was added dropwise to an ice-bath cooled solution of 0.87 ml (5 mmol) 3-(4-methylpiperazin-1-yl)propanamine (**5**{*9*}) in anhydrous dichloromethane (15 ml). The mixture was stirred for an additional half hour at room temperature and 15 ml of a solution of 50% K_2CO_3 was added. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give 0.953 g (4.2 mmol, 85%) of **98**{*9*} as a yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 2936, 2795 (*st* Csp^3-H), 1705 (*st* C=O), 1459, 1284 (*b* Csp^3-H), 1166, 1146, 1032, 1014 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.24 (t, ^3J = 7.0 Hz, 2H, H-C2), 3.25 (t, ^3J = 7.0 Hz, 2H, H-C6), 2.51-2.39 (m, 12H, H-C8, H-C9, H-C4, H-C10), 2.28 (s, 3H, H-C11), 2.09 (qn, ^3J = 7.0 Hz, 2H, H-C3), 1.74 (qn, ^3J = 7.5 Hz, 2H, H-C7)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 163.2 (C5), 70.1 (C2), 56.8 (C8), 55.2 (C10), 53.2 (C9), 46.0 (C6), 45.5 (C11), 28.8 (C4), 28.3 (C7), 23.5 (C2)

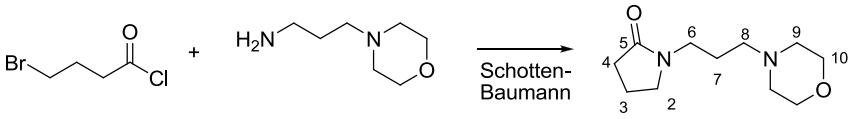
MS (EI) *m/z* (%): 225.2 (1) $[M]^+$, 155.1 (18), 113.1 (63), 70.0 (100)

HRMS (EI) calculated for $C_{12}H_{23}N_3O$ $[M]^+$: 225.1841; found: 225.1844

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** > 125 μg/ml

4.13.2. Synthesis of 1-(3-morpholinopropyl)pyrrolidin-2-one (98{*11*})



97 **5**{*11*} **98**{*11*}

0.61 ml (5 mmol) of 4-bromobutyryl chloride (**97**) was added dropwise to an ice-bath cooled solution of 0.75 ml (5 mmol) of 3-morpholinopropanamine (**5**{*11*}) in 15 ml of anhydrous dichloromethane. The mixture was stirred for an additional half hour at room temperature and a solution of 50% K_2CO_3 (15 ml) was added. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give 0.730 g (2.5 mmol, 50%) of **98**{*11*} as a yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 2949, 2893, 2853, 2808 (*st* Csp^3-H), 1707 (*st* C=O), 1181, 1118, 1033 (*st* C-N), 991, 862

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.24 (t, ^3J = 7.0 Hz, 2H, H-C2), 3.71 (t, ^3J = 4.5 Hz, 4H, H-C10), 3.26 (d, ^3J = 7.0 Hz, 2H, H-C6), 2.54-2.38 (m, 8H, H-C4, H-C8, H-C9), 2.10 (qn, ^3J = 7.0 Hz, 2H, H-C3), 1.74 (qn, ^3J = 7.0 Hz, 2H, H-C7)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 163.2 (C5), 70.1 (C2), 67.0 (C10), 57.2 (C8), 53.7 (C9), 45.4 (C6), 28.8 (C4), 27.9 (C7), 23.4 (C3)

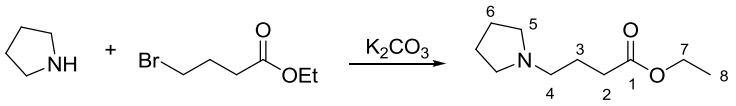
MS (EI) *m/z* (%): 213.0 (1) $[M+1]^+$, 127.0 (12), 114.0 (9), 100.0 (100)

HRMS (EI) calculated for $C_{11}H_{20}N_2O_2$ $[M+1]^+$: 213.1603; found: 213.1602

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** > 125 μg/ml

4.13.3. Synthesis of ethyl 4-(pyrrolidin-1-yl)butanoate (106{*1*})



70{*1*} **107** **106**{*1*}

A suspension of 0.73 ml (8.7 mmol) of pyrrolidine (**70**{*1*}), 1.437 g (7 mmol) of ethyl 4-bromobutyrate (**107**) and 0.977 g (7 mmol) of anhydrous K_2CO_3 in 25 ml of ACN was heated at reflux for 2 h. After concentration, 25 ml of water were added and the reaction mixture was extracted with dichloromethane (2·30 ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 1.130 g (87%) of ethyl 4-(pyrrolidin-1-yl)butanoate (**106**{*1*}) as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 2964, 2788 (*st* Csp^3-H), 1737 (*st* C=O), 1373 (*b* Csp^3-H), 1177 (*st* C-O)

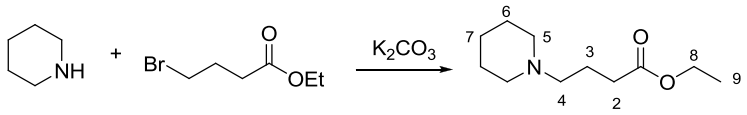
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.12 (q, ^3J = 7.0 Hz, 2H, H-C7), 2,51 (m, 6H, H-C5, H-C2), 2.35 (t, ^3J = 7.5 Hz, H-C4), 1.84 (qn, ^3J = 7.5 Hz, 2H, H-C3), 1.77 (m, 4H, H-C6), 1.25 (t, ^3J = 7.0 Hz, 3H, H-C8)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 173.5 (C1), 60.1 (C7), 55.6 (C4), 54.0 (C5), 32.4 (C2), 24.3 (C3), 23.4 (C6), 14.2 (C8)

MS (EI) *m/z* (%): 184.1 (32) $[M-1]^-$, 84.1 (100)

HRMS (EI) calculated for $C_{10}H_{19}NO_2$ $[M-1]^-$: 184.1338; found: 184.1338

4.13.4. Synthesis of ethyl 4-(piperidin-1-yl)butanoate (106{*2*})



70{*2*} **107** **106**{*2*}

A suspension of 0.88 ml (8.7 mmol) of piperidine (**70**{*2*}), 1.437 g (7 mmol) of ethyl 4-bromobutyrate (**107**) and 0.977 g (7 mmol) of anhydrous K_2CO_3 in 25 ml ACN was heated at reflux for 2 h. After concentration, 25 ml of water were added and the reaction mixture was extracted with dichloromethane (2·30 ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give ethyl 4-(piperidin-1-yl)butanoate (**106**{*2*}) as a yellow oil (1.199 g; 86%).

Spectroscopic data

IR (film) ν (cm^{-1}): 2935, 2854, 2802, 2763 (*st* Csp^3-H), 1737 (*st* C=O), 1445, 1372 (*b* Csp^3-H), 1161 (*st* C-O)

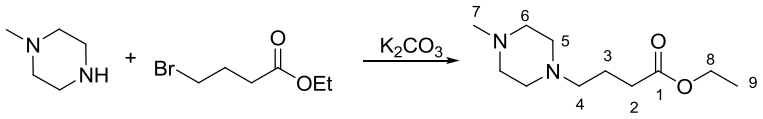
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.12 (q, ^3J = 7.0 Hz, 2H, H-C8), 2.36-2.29 (m, 8H, H-C5, H-C2, H-C4), 1.81 (qn, ^3J = 7.0 Hz, 2H, H-C3), 1.56 (qn, ^3J = 5.5 Hz, 4H, H-C6), 1.42 (m, 2H, H-C7), 1.25 (t, ^3J = 7.0 Hz, 3H, H-C9)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 173.6 (C1), 60.2 (C8), 58.5 (C4), 54.4 (C5), 32.4 (C2), 26.0 (C6), 24.4 (C7), 22.3 (C3), 14.2 (C9)

MS (EI) *m/z* (%): 199.2 (3) $[M]^+$, 167.1 (13), 149.1 (36), 112.1 (17), 98.2 (100)

HRMS (EI) calculated for $C_{11}H_{21}NO_2$ $[M]^+$: 199.1572; found: 199.1571

4.13.5. Synthesis of ethyl 4-(4-methylpiperazin-1-yl)butanoate (106{*3*})



70{*3*} **107** **106**{*3*}

A suspension of 0.98 ml (8.7 mmol) of *N*-methylpiperazine (**70**{*3*}), 1.437 g (7 mmol) ethyl 4-bromobutyrate (**107**) and anhydrous K_2CO_3 (0.977 g, 7 mmol) in ACN (25 ml) was heated at reflux for 2 h. After concentration, water (25 ml) was added and the reaction mixture was extracted with dichloromethane (2·30 ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give 1.139 g (76%) of ethyl 4-(4-methylpiperazin-1-yl)butanoate (106{*3*}) as a yellow oil

Spectroscopic data

IR (film) ν (cm^{-1}): 2937, 2794 (*st* Csp^3-H), 1736 (*st* C=O), 1459, 1372 (*b* Csp^3-H), 1165 (*st* C-O)

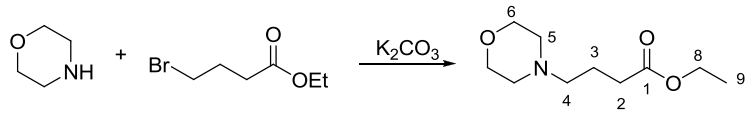
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.13 (q, ^3J = 7.0 Hz, 2H, H-C8), 2.5-2.3 (m, 12H, H-C2, H-C4, H-C5, H-C6), 2.28 (s, 3H, H-C7), 1.81 (qn, ^3J = 7.0 Hz, 2H, H-C3), 1.26 (t, ^3J = 7.0 Hz, 3H, H-C9)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 173.4 (C1), 60.1 (C8), 57.5 (C4), 55.1 (C6), 53.0 (C5), 46.0 (C7), 32.2 (C2), 22.1 (C3), 14.1 (C9)

MS (EI) *m/z* (%): 214.2 (28) $[M]^+$, 169.1 (29), 113.1 (100), 70.1 (70)

HRMS (EI) calculated for $C_{11}H_{22}N_2O_2$ $[M]^+$: 214.1681; found: 214.1679

4.13.6. Synthesis of ethyl 4-morpholinobutanoate (106{*4*})



70{*4*} **107** **106**{*4*}

A suspension of 0.77 ml (8.7 mmol) of morpholine (**70**{*4*}), 1.437 g (7 mmol) ethyl 4-bromobutyrate (**107**) and anhydrous K_2CO_3 (0.977 g, 7 mmol) in 25 ml ACN was heated at reflux for 2 h. After concentration, water (25 ml) was added and the reaction mixture was extracted with dichloromethane (2·30 ml). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated to give ethyl 4-morpholinobutanoate (**106**{*4*}) as a yellow oil (1.338 g; 95%).

Spectroscopic data

IR (film) ν (cm^{-1}): 2958, 2855, 2809 (*st* Csp^3-H), 1735 (*st* C=O), 1447, 1372 (*b* Csp^3-H), 1185 (*st* C-O)

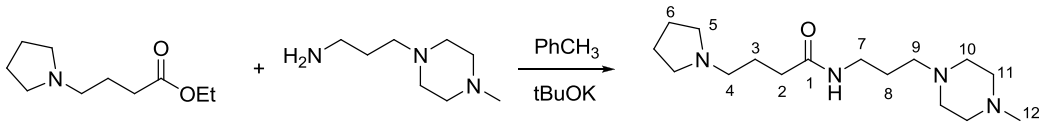
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.13 (t, ^3J = 7.0 Hz, 2H, H-C7), 3.70 (t, ^3J = 4.5 Hz, H-C6), 2.43 (t, ^3J = 4.5 Hz, H-C5), 2.35 (m, 4H, H-C2, H-C4), 1.81 (qn, ^3J = 7.0 Hz, 2H, H-C3), 1.26 (t, ^3J = 7.0 Hz, 3H, H-C8)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 173.5 (C1), 67.0 (C6), 60.2 (C7), 58.0 (C4), 53.6 (C5), 32.2 (C2), 21.8 (C3), 14.2 (C8)

MS (EI) *m/z* (%): 201.1 (2) $[M]^+$, 156.1 (16), 114.1 (18), 110.1 (100)

HRMS (EI) calculated for $C_{10}H_{19}NO_3$ $[M]^+$: 201.1365; found: 201.1360

4.13.7. Synthesis of *N*-(3-(4-methylpiperazin-1-yl)propyl)-4-(pyrrolidin-1-yl)butanamide (95{*1*,*9*})



106{*1*} **5**{*9*} **95**{*1*,*9*}

A mixture of 0.278 g (1.5 mmol) of ethyl 4-(pyrrolidin-1-yl)butanoate (**106**{*1*}), 0.241 g (1.5 mmol) of 1-(3-aminopropyl)-4-methylpiperazine (**5**{*9*}) and 0.241 g (1.5 mmol) of *t*BuOK in toluene (4 ml) was placed in a microwave process vial containing a stir bar, sealed and subjected to microwave irradiation for 20 min at 180 ºC. After gas jet cooling to room temperature, the formed gel was neutralized with 2.3 ml methanolic HCl (1.25 M) and salts were filtered thereoff. Solvents were removed under reduced pressure to give 0.401 g (1.35 mmol, 90%) of **95**{*1*,*9*} as white solid.

Spectroscopic data

IR (film) ν (cm^{-1}): 3359 (*st* N-H), 2939, 2800 (*st* Csp^3-H), 1570 (*st* C=O), 1460, 1400 (*b* Csp^3-H), 1165 (*st* C-O)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.19 (br, 1H, NH), 2.76 (t, ^3J = 7.0 Hz, 2H, H-C7), 2.71 (m, 4H, H-C5), 2.62 (t, ^3J = 7.0 Hz, 2H, H-C4*), 2.58-2.38 (br, 8H, H-C10, H-C11), 2.41 (t, ^3J = 7.0 Hz, 2H, H-C9*)2.29 (s, 3H, H-C12), 2.27 (t, ^3J = 7.0 Hz, 2H, H-C2*), 1.83 (m, 4H, H-C6), 1.77 (m, 2H, H-C4**), 1.64 (qn, ^3J = 7.0 Hz, 2H, H-C8**)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 178.8 (C1), 56.5 (C5), 56.3 (C4), 55.2 (C11), 53.6 (C9), 53.3 (C10), 46.0 (C12), 40.8 (C7), 36.2 (C3), 30.4 (C8), 24.3 (C3), 23.3 (C6)

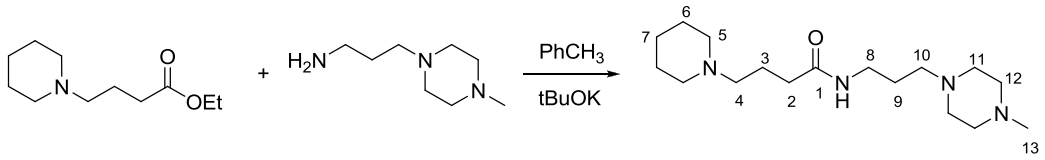
MS (EI) *m/z* (%): 296 (0.2) $[M]^+$, 157 (19), 127 (13), 113 (30), 101 (14), 84 (100), 70 (56), 56 (19)

HRMS (EI) calculated for $C_{16}H_{32}N_4O$ $[M]^+$: 296.2576; found: 296.2582

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 86 μg/ml

4.13.8. Synthesis of *N*-(3-(4-methylpiperazin-1-yl)propyl)-4-(piperidin-1-yl)butanamide (95{*2*,*9*})



106{*2*} **5**{*9*} **95**{*2*,*9*}

Procedure was the same as stated above for **95**{*1*,*9*} using ethyl 4-(piperidin-1-yl)butanoate (**106**{*2*}) (0.302 g, 1.5 mmol), 1-(3-aminopropyl)-4-methylpiperazine (**5**{*9*}) (0.241 g, 1.5 mmol), *t*BuOK (0.310 g, 2.6 mmol) and 1.25 M HCl/MeOH (2.1 ml). Concentration yielded **95**{*2*,*9*} as a white solid (0.456 g, 1.47 mmol; 98%).

Spectroscopic data

IR (film) ν (cm^{-1}): 3359 (*st* N-H), 2935, 2801 (*st* Csp^3-H), 1569 (*st* C=O), 1459, 1401 (*b* Csp^3-H), 1165(*st* C-O)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.38 (br, 1H, NH), 2.77 (t, ^3J = 7.0 Hz, 2H, H-C8), 2.47-2.39 (cs, 16H, H-C4, H-C5, H-C10, H-C11, H-C12), 2.29 (m, 5H, H-C13, H-C2), 1.76 (qn, ^3J = 7.0 Hz, 2H, H-C3), 1.66 (m, 6H, H-C6, H-C7), 1.48 (m, 2H, H-C9)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 178.7 (C1), 59.1 (C4), 56.5 (C5), 55.1 (C12), 54.0 (C10), 53.2 (C11), 45.9 (C13), 40.7 (C8), 36.4 (C2), 29.9 (C9), 24.8 (C6), 23.7 (C7), 22.3 (C3)

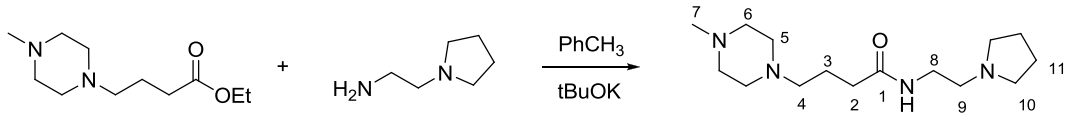
MS (EI) *m/z* (%): 310 (0.1) $[M]^+$, 171 (13), 127 (14), 113 (31), 101 (16), 98 (100), 84 (15), 70 (55)

HRMS (EI) calculated for $C_{17}H_{34}N_4O$ $[M]^+$: 310.2733; found: 310.2743

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 63 μg/ml

4.13.9. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(2-(pyrrolidin-1-yl)ethyl)butanamide (95{*3*,*4*})



106{*3*} **5**{*4*} **95**{*3*,*4*}

Procedure was the same as stated above for **95**{*1*,*9*} using 0.259 g (1.2 mmol) of ethyl 4-(4-methylpiperazin-1-yl)butanoate (**106**{*3*}), 0.142 g (1.2 mmol) of 1-(2-aminoethyl)pyrrolidine (**5**{*4*}), 0.282 g (2.4 mmol) of *t*BuOK and 1.9 ml methanolic HCl (1.25 M). Concentration yielded **95**{*3*,*4*} as white solid (0.332 g, 1.18 mmol; 98%).

Spectroscopic data

IR (film) ν (cm^{-1}): 2936, 2793 (*st* Csp^3-H),1704, 1564 (*st* C=O), 1459, 1399 (*b* Csp^3-H), 1164 (*st* C-O), 1013 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 5.59 (br, 1H, NH), 2.86 (t, ^3J = 6.5 Hz, 2H, H-C8), 2.65-2.45 (cs, 16H, H-C10, H-C9, H-C6, H-C5, H-C4), 2.30 (m, 5H, H-C7, H-C2), 1.80 (m, 6H, H-C11, H-C3)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 177.9 (C1), 58.8 (C9), 58.5 (C4), 54.3 (C6), 54.0 (C10), 52.7 (C5), 45.7 (C7), 40.4 (C8), 35.7 (C2), 23.4 (C11), 22.4 (C3)

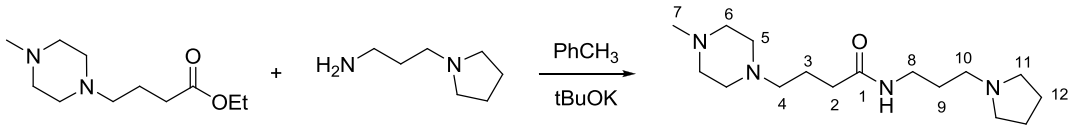
MS (CI) *m/z* (%): 283.2 (24) $[M+1]^+$, 215 (26), 187 (100), 115 (72), 113 (50), 98 (49)

HRMS (CI) calculated for $C_{15}H_{31}N_4O$ $[M+1]^+$: 283.2498; found: 283.2504

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 69 μg/ml

4.13.10. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(3-(pyrrolidin-1-yl)propyl)butanamide (95{*3*,*5*})



106{*3*} **5**{*5*} **95**{*3*,*5*}

Procedure was the same as stated above for **95**{*1*,*9*} using ethyl 4-(4-methylpiperazin-1-yl)butanoate (**106**{*3*}) (0.260 g, 1.2 mmol), 1-(3-aminopropyl)pyrrolidine (**5**{*5*}) (0.160 g, 1.2 mmol), *t*BuOK (0.284 g, 2.4 mmol) and 1.25 M HCl/MeOH (1.9 ml). Concentration yielded **95**{*3*,*5*} as a white solid (0.338 g, 1.14 mmol; 95%).

Spectroscopic data

IR (film) ν (cm^{-1}): 2936, 2792 (*st* Csp^3-H), 1568 (*st* C=O), 1459, 1398 (*b* Csp^3-H), 1164 (*st* C-O), 1013 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 5.87 (br, 1H, NH), 2.83 (t, ^3J = 6.5 Hz, 2H, H-C8), 2.61-2.40 (cs, 16H, H-C10, H-C11, H-C5, H-C6, H-C4), 2.28 (m, 5H, H-C7, H-C2), 1.82-1.71 (cs, 8H, H-C12, H-C3, H-C9)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 178.3 (C1), 58.5 (C4), 54.5 (C6), 54.4 (C10), 53.9 (C11), 52.8 (5), 45.8 (C7), 40.5 (C8), 35.7 (C2), 30.5 (C9), 23.4 (C12), 22.7 (C3)

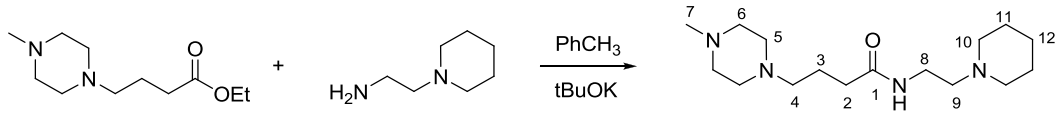
MS (CI) *m/z* (%): 297 (30) $[M+1]^+$, 215 (36), 186 (49), 129 (100), 112 (59), 84 (45)

HRMS (CI) calculated for $C_{16}H_{33}N_4O$ $[M+1]^+$: 297.2654; found: 297.2653

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 71 μg/ml

4.13.11. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(2-(piperidin-1-yl)ethyl)butanamide (95{*3*,*7*})



106{*3*} **5**{*7*} **95**{*3*,*7*}

Procedure was the same as stated above for **95**{*1*,*9*} using ethyl 4-(4-methylpiperazin-1-yl)butanoate (**106**{*3*}) (0.325 g, 1.5 mmol), 1-(2-aminoethyl)piperidine (**5**{*7*}) (0.197 g, 1.5 mmol), *t*BuOK (0.354 g, 3.0 mmol) and 2.4 ml methanolic HCl (1.25 M). Concentration yielded **95**{*3*,*7*} as a white solid (0.428 g, 1.44 mmol; 96%).

Spectroscopic data

IR (soln) ν (cm^{-1}): 3356 (*st* N-H), 2939, 2802 (*st* Csp^3-H), 1637, 1563 (*st* C=O), 1460, 1398 (*b* Csp^3-H), 1162 (*st* C-O), 1010 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 5.82 (br, 1H, NH), 2.85 (t, ^3J = 6.5 Hz, 2H, H-C8) 2.70-2.35 (cs, 16H, H-C5, H-C6, H-C9, H-C10, H-C4), 2.29 (s, 3H, H-C7), 2.19 (t, ^3J = 7.0 Hz, 2H, H-C2), 1.74 (qn, ^3J = 7.0 Hz, 2H, H-C3), 1.58 (m, 2H, H-C11), 1.44 (m, 2H, H-C12)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 178.8 (C1), 60.9 (C9), 58.4 (C4), 54.5 (C6*), 54.4 (C10), 52.8 (C5*), 45.7 (C7), 38.3 (C8), 35.6 (C2), 25.8 (C11), 24.3 (C12), 22.8 (C3)

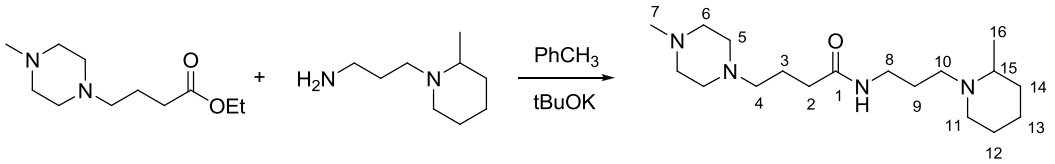
MS (EI) *m/z* (%): 296 (1) $[M]^+$, 186 (49), 113 (81), 98 (100), 70 (77)

HRMS (EI) calculated for $C_{16}H_{32}N_4O$ $[M]^+$: 296.2576; found: 296.2580

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 96 μg/ml

4.13.12. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(3-(2-methylpiperidin-1-yl)propyl)butanamide (95{*3*,*8*})



106{*3*} **5**{*8*} **95**{*3*,*8*}

Procedure was the same as stated above for **95**{*1*,*9*} using ethyl 4-(4-methylpiperazin-1-yl)butanoate (**106**{*3*}) (0.326 g, 1.5 mmol), *N*-(3-aminopropyl)-2-pipecoline (**5**{*8*}) (0.245 g, 1.5 mmol), *t*BuOK (0.345 g, 2.9 mmol) and 2.3 ml methanolic HCl (1.25 M). Concentration yielded **95**{*3*,*8*} as a white solid (0.438 g, 1.35 mmol; 90%).

Spectroscopic data

IR (soln) ν (cm^{-1}): 3343 (*st* N-H), 2933, 2795 (*st* Csp^3-H), 1639, 1564 (*st* C=O), 1449, 1397 (*b* Csp^3-H), 1162 (*st* C-O), 1011 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.78 (br, 1H, NH), 2.88 (m, 1H, H-C11), 2.77 (m, 3H, H-C8, H-C10), 2.7-2.3 (cs, 12H, H-C4, H-C5, H-C6, H-C10, H-C 15), 2.28 (s, 3H, H-C7), 2.15 (m, 3H, H-C2, H-C11), 1.8-1.3 (cs, 8H, H-C3, H-C9, H-C12, H-C13, H-C14), 1.32 (m, 2H, H-C13, H-C14), 1.08 (d, ^3J = 6.5 Hz,3H, H-C16)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 179.2 (C1), 58.5 (C15), 56.0 (C4), 54.8 (C6), 53.0 (C5), 51.9 (C11), 51.7 (C10), 45.9 (C7), 40.8 (C8), 35.7 (C14), 34.3 (C2), 27.9 (C9), 25.9 (C12), 23.6 (C3), 23.3 (C13), 18.6 (C16)

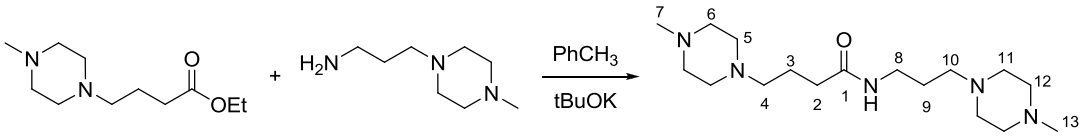
MS (EI) *m/z* (%): 324 (2) $[M]^+$, 186 (58), 113 (100), 98 (99), 70 (94)

HRMS (EI) calculated for $C_{18}H_{36}N_4O$ $[M+1]^+$: 324.2889; found: 324.2896

Biological activity

EC_{50} = 9.20 μg/ml; **CC_{50}** = 99 μg/ml

4.13.13. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(3-(4-methylpiperazin-1-yl)propyl)butanamide (95{*3*,*9*})



106{*3*} **5**{*9*} **95**{*3*,*9*}

Procedure was the same as stated above for **95**{*1*,*9*} using ethyl 4-(4-methylpiperazin-1-yl)butanoate (**106**{*3*}) (0.325 g, 1.5 mmol), 1-(3-aminopropyl)-4-methylpiperazine (**5**{*9*}) (0.241 g, 1.5 mmol), *t*BuOK (0.359 g, 3.0 mmol) and 1.25 M HCl/MeOH (2.4 ml). Concentration yielded **95**{*3*,*9*} as a pale yellow solid (0.474 g, 1.46 mmol; 97%).

Spectroscopic data

IR (soln) ν (cm^{-1}): 3347 (*st* N-H), 2941, 2803 (*st* Csp^3-H), 1635, 1564 (*st* C=O), 1461, 1400 (*b* Csp^3-H), 1162 (*st* C-O), 1010 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.44 (br, 1H, NH), 2.79 (t, ^3J = 7.0 Hz, 2H, H-C8), 2.70-2.30 (m, 20H, H-C5, H-C6, H-C12, H-C12, H-C10, H-C4), 2.29 (s, 3H, H-C7), 2.29 (s, 3H, H-C13), 2.18 (t, ^3J = 7.0 Hz, 2H, H-C2), 1.65-1.75 (m, 4H, H-C3, H-C9)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 179.1 (C1), 58.4 (C4), 56.6 (C10), 55.0 (C11*), 54.6 (C6*), 53.2 (C5*), 52.9 (C12*), 45.9 (C7), 45.9 (C13), 40.7 (C8), 35.7 (C2), 29.4 (C9), 23.0 (C3)

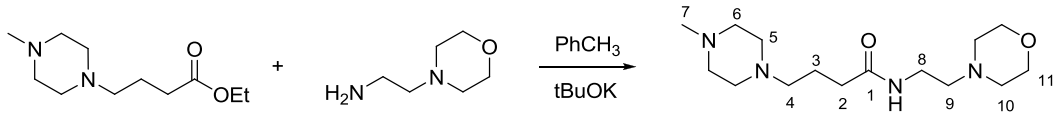
MS (EI) *m/z* (%): 325 (1) $[M]^+$, 186 (37), 127 (31), 113 (83), 70 (100)

HRMS (EI) calculated for $C_{17}H_{35}N_5O$ $[M]^+$: 325.2842; found: 325.2853

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 90 μg/ml

4.13.14. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(2-morpholinoethyl)butanamide (95{*3*,*10*})



106{*3*} **5**{*10*} **95**{*3*,*10*}

Procedure was the same as stated above for **95**{*1*,*9*} using ethyl 4-(4-methylpiperazin-1-yl)butanoate (**106**{*3*}) (0.258 g, 1.2 mmol), 4-(2-aminoethyl)morpholine (**5**{*10*}) (0.160 g, 1.2 mmol), *t*BuOK (0.283 g, 2.4 mmol) and 1.25 M HCl/MeOH (1.9 ml). Concentration yielded **95**{*3*,*10*} as a white solid (0.347 g, 1.16 mmol; 97%).

Spectroscopic data

IR (film) ν (cm^{-1}): 2936, 2794 (*st* Csp^3-H), 1562 (*st* C=O), 1458, 1397 (*b* Csp^3-H), 1164 (*st* C-O), 1012 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 5.14 (br, 1H, NH), 3.71 (t, ^3J = 5.0 Hz, 4H, H-C11), 2.81 (t, ^3J = 6.0 Hz, 2H, H-C8), 2.70-2.42 (cs, 16H, H-C5, H-C6, H-C4, H-C10, H-C9), 2.29 (m, 5H, H-C7, H-C2), 1.76 (qn, ^3J = 7.0 Hz, 2H, H-C3)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 177.9 (C1), 67.0 (C11), 61.1 (C9), 58.4 (C4), 54.2 (C6), 53.7 (C10), 52.7 (C5), 45.6 (C7), 38.2 (C8), 35.8 (C2), 22.3 (C3)

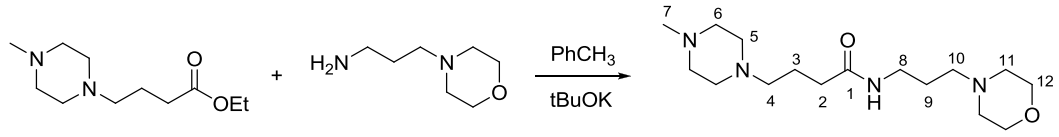
MS (CI) *m/z* (%): 299 (27) $[M+1]^+$, 187 (100), 143 (57), 131 (91), 114 (97), 100 (81)

HRMS (CI) calculated for $C_{15}H_{31}N_4O_2$ $[M+1]^+$: 299.2447; found: 299.2443

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 90 μg/ml

4.13.15. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(3-morpholinopropyl)butanamide (95{*3*,*11*})



106{*3*} **5**{*11*} **95**{*3*,*11*}

Procedure was the same as stated above for **95**{*1*,*9*} using ethyl 4-(4-methylpiperazin-1-yl)butanoate (**106**{*3*}) (0.323 g, 1.5 mmol), 3-morpholinopropylamine (**5**{*11*}) (0.219 g, 1.5 mmol), *t*BuOK (0.352 g, 3.0 mmol) and 2.4 ml of 1.25 M HCl/MeOH. Concentration yielded **95**{*3*,*11*} as a white solid (0.464 g, 1.49 mmol; 99%).

Spectroscopic data

IR (soln) ν (cm^{-1}): 2944, 2806 (*st* Csp^3-H), 1637, 1564 (*st* C=O), 1461, 1401 (*b* Csp^3-H), 1162, 1009 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.97 (br, 4H, H-C12), 3.36 (br, 4H, H-C11), 3.25-3.12 (cs, 10H, H-C10, H-C6, H-C5), 3.08 (m, 2H, H-C8), 2.95 (m, 2H, H-C4), 2.74 (s, 3H, H-C7), 2.32 (t, ^3J = 7.0 Hz, 2H, H-C2), 2.15 (m, 2H, H-C9), 1.92 (m, 2H, H-C3)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 176.8 (C1), 66.7 (C12), 57.9 (C4), 57.6 (C10), 53.4 (C11), 53.1 (C5*), 51.6 (C6*), 44.7 (C7), 39.9 (C8), 35.1 (C2), 22.9 (C9*), 22.7 (C3*)

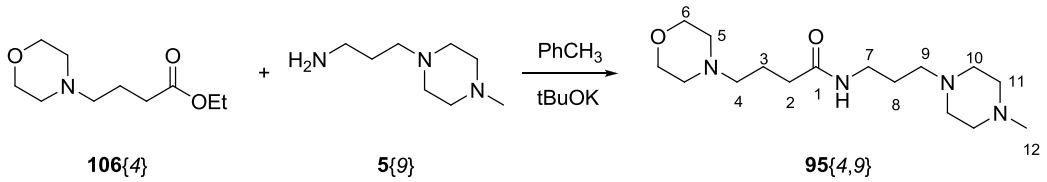
MS (EI) *m/z* (%): 312 (1) $[M]^+$, 186 (33), 127 (27), 113 (85), 100 (100), 70 (71)

HRMS (EI) calculated for $C_{16}H_{32}N_4O_2$ $[M]^+$: 312.2525; found: 312.2530

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 94 μg/ml

4.13.16. Synthesis of *N*-(3-(4-methylpiperazin-1-yl)propyl)-4-morpholinobutanamide (95{*4*,*9*})



106{*4*} **5**{*9*} **95**{*4*,*9*}

Procedure was the same as stated above for **95**{*1*,*9*} using ethyl 4-morpholinobutanoate (**106**{*4*}) (0.307 g, 1.5 mmol), 1-(3-aminopropyl)-4-methylpiperazine (**5**{*9*}) (0.243 g, 1.5 mmol), *t*BuOK (0.344 g, 2.9 mmol) and 2.3 ml of methanolic HCl (1.25 M). Concentration yielded **95**{*4*,*9*} as a white solid (0.436 g, 1.4 mmol; 92%).

Spectroscopic data

IR (film) ν (cm^{-1}): 3374 (*st* N-H), 2941, 2811 (*st* Csp^3-H), 1567 (*st* C=O), 1462, 1402 (*b* Csp^3-H), 1164 (*st* C-O), 1009 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.24 (br, 1H, NH), 3.70 (t, ^3J = 4.0 Hz, 4H, H-C6), 2.80 (t, ^3J = 6.5 Hz, 2H, H-C7), 2.70-2.40 (cs, 14H, H-C5, H-C9, H-C10, H-C11), 2.35 (t, ^3J = 7.0 Hz, 2H, H-C4), 2.29 (s, 3H, H-C12), 2.17 (t, ^3J = 7.5 Hz, 2H, H-C2), 1.65-1.72 (m, 4H, H-C3, H-C8)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 179.4 (C1), 66.6 (C6), 58.8 (C4), 56.6 (C5), 55.0 (C11), 53.6 (C9), 53.1 (C10), 45.9 (C12), 40.7 (C7), 35.4 (C2), 29.1 (C8), 22.8 (C3)

MS (EI) *m/z* (%): 312 (1) $[M]^+$, 173 (8), 127 (7), 113 (14), 100 (100), 84 (6), 70 (51), 56 (30), 42 (29)

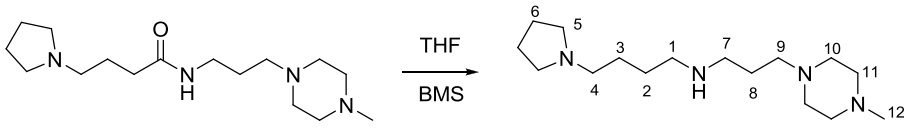
HRMS (EI) calculated for $C_{16}H_{32}N_4O_2$ $[M]^+$: 312.2525; found: 312.2513

Biological activity

EC_{50} > 125 μg/ml; **CC_{50}** = 90 μg/ml

4.14. Synthesis of *de novo* designed amides with tetramethylene spacer

4.14.1. Synthesis of *N*-(3-(4-methylpiperazin-1-yl)propyl)-4-(pyrrolidin-1-yl)butan-1-amine (84{*1*,*9*})



95{*1*,*9*} **84**{*1*,*9*}

0.296 g (1 mmol) of **95**{*1*,*9*} were dissolved in 10 ml of anhydrous THF and 0.57 ml (6 mmol) of borane dimethylsulfide complex were added dropwise. The solution was held at reflux for 48 hours, cooled to room temperature and diluted with 8 ml of methanolic HCl (1.25 M).

The new solution was heated at reflux for 1 hour. The solvent was removed under reduced pressure and the crude was diluted with NaOH 1 M until reaching pH = 14. The aqueous solution was extracted twice with CH_2Cl_2 and dried over $MgSO_4$. After concentration, the crude product was purified using flash chromatography (basic alumina, CH_2Cl_2:MeOH 100:0 to 95:5 in 15 minutes) to afford 0.148 g (0.5 mmol, 50%) of the desired amine **84**{*1*,*9*} as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3330 (*st* N-H), 2931, 2853 (*st* Csp^3-H), 1457, 1373 (*b* Csp^3-H)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.05 (t, ^3J = 7.0 Hz, 2H, H-C4), 2.62-2.27 (cs, 10H, H-C1, H-C5, H-C7, H-C9), 2.33 (m, 8H, H-C10, H-C11), 2.31 (s, 3H, H-C12), 1.80-1.63 (cs, 6H, H-C6, H-C3), 1.47 (m, 2H, H-C8), 1.34 (m, 2H, H-C2)

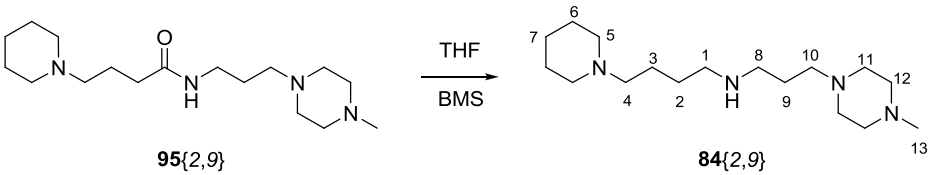
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 57.0 (C9), 56.7(C5), 56.3 (C4), 55.3 (C10), 53.4 (C11), 50.0 (C1), 48.7 (C7), 46.1 (C12), 38.3 (C8), 23.9 (C3), 23.3 (C6), 18.9 (C2)

HRMS (EI): calculated for $C_{16}H_{34}N_4$ $[M]^+$: 282.2783; found: 282.2782

Biological activity

EC_{50} > 25 μg/ml; **CC_{50}** > 25 μg/ml

4.14.2. Synthesis of *N*-(3-(4-methylpiperazin-1-yl)propyl)-4-(piperidin-1-yl)butan-1-amine (84{*2,9*})



95{*2,9*} **84**{*2,9*}

Procedure was the same as stated above for **84**{*1,9*} using 0.310 g (1 mmol) of **95**{*2,9*}, 0.57 ml (6 mmol) BMS and 8 ml HCl/MeOH (1.25 M). Column chromatography with basic alumina (CH_2Cl_2:MeOH 100:0 to 95:5 in 20 minutes) and concentration afforded 98 mg (0.33 mol, 33%) of the desired amine **84**{*2,9*} as a yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3361 (*st* N-H), 2932, 2856, 2783 (*st* Csp^3-H), 1462, 1368 (*b* Csp^3-H), 1130 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.02 (t, ^3J = 7.0 Hz, 2H, H-C4), 2.60-2.29 (cs, 10H, H-C1, H-C5, H-C8, H-C10), 2.32 (m, 8H, H-C11, H-C12), 2.29 (s, 3H, H-C13), 1.80-1.60 (cs, 8H, H-C6, H-C7, H-C3), 1.45 (m, 2H, H-C9), 1.30 (m, 2H, H-C2)

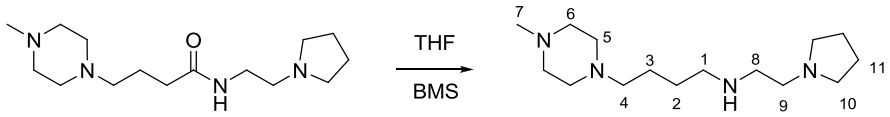
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 57.2 (C10), 56.5 (C5), 56.3 (C4), 55.0 (C11), 53.5 (C12), 49.7 (C1), 48.8 (C8), 46.3 (C13), 38.3 (C9), 24.5 (C3), 24.3 (C6), 23.7 (C7), 19.8 (C2)

HRMS (ESI-TOF): calculated for $C_{17}H_{37}N_4$ $[M+1]^+$: 297.3018; found: 297.3022

Biological activity

EC_{50} > 25 μg/ml; **CC_{50}** > 25 μg/ml

4.14.3. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(2-(pyrrolidin-1-yl)ethyl)butan-1-amine (84{*3,4*})



95{*3,4*} **84**{*3,4*}

Procedure was the same as stated above for **84**{*1,9*} using 0.283 g (1 mmol) of **95**{*3,4*}, 0.57 ml (6 mmol) BMS and 8 ml HCl/MeOH (1.25 M). The crude product was purified by column chromatography with basic alumina (CH_2Cl_2:MeOH 100:0 to 95:5 in 20 minutes). Concentration afforded 127 mg (0.47 mol, 47%) of the desired amine **84**{*3,4*} as a yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3362 (*st* N-H), 2930, 2856 (*st* Csp^3-H), 1455, 1370 (*b* Csp^3-H), 1150 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.69 (t, ^3J = 6.5 Hz, 2H, H-C4), 2.8-2.5 (cs, 10H, H-C1, H-C5, H-C6), 2.48-2.30 (cs, 8H, H-C8, H-C9, H-C10), 2.25 (s, 3H, H-C7), 1.83-1.57 (cs, 8H, H-C3, H-C2, H-C11)

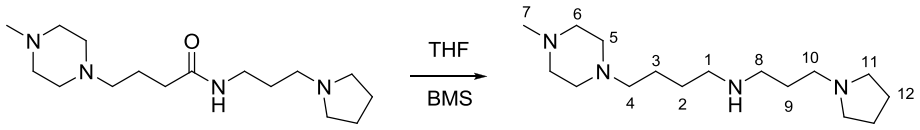
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 58.5 (C1), 55.0 (C9), 54.6 (C6), 54.0 (C10), 52.9 (C5), 46.8 (C7, C8), 45.8 (C4), 25.5 (C2, C3), 23.5 (C11)

HRMS (EI) calculated for $C_{15}H_{32}N_4$ $[M]^+$: 268.2627; found: 268.2620

Biological activity

EC_{50} > 25 μg/ml; **CC_{50}** > 25 μg/ml

4.14.4. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(3-(pyrrolidin-1-yl)propyl)butan-1-amine (84{*3,5*})



95{*3,5*} **84**{*3,5*}

Procedure was the same as stated above for **84**{*1,9*} using 0.296 g (1 mmol) of **95**{*3,5*}, 0.57 ml (6 mmol) BMS and 8 ml HCl/MeOH (1.25 M). The crude product was purified by column chromatography with basic alumina (CH_2Cl_2:MeOH 100:0 to 95:5 in 18 minutes) and concentration afforded 130 mg (0.46 mol, 46%) of the desired amine **84**{*3,5*} as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3358 (*st* N-H), 2929, 2850 (*st* Csp^3-H), 1452, 1373 (*b* Csp^3-H), 1152 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.65 (t, ^3J = 7.0 Hz, 2H, H-C4), 2.9-2.55 (cs, 10H, H-C1, H-C5, H-C6), 2.50-2.35 (cs, 8H, H-C8, H-C10, H-C11), 2.27 (s, 3H, H-C7), 1.9-1.6 (cs, 8H, H-C3, H-C2, H-C12), 1.52 (m, 2H, H-C9)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 58.6 (C1), 55.5 (C11), 54.7 (C6), 52.9 (C5), 52.0 (C10), 46.8 (C8), 46.2 (C7), 45.9 (C4), 28 (C9), 25.6 (C2, C3), 23.5 (C12)

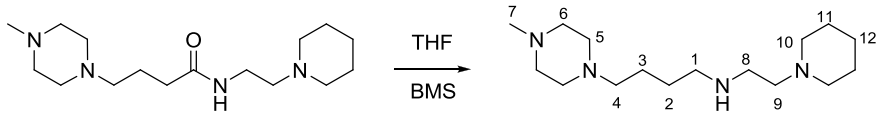
MS (ESI-TOF) *m/z* (%): 283.3 (1) $[M+1]^+$, 201.2 (2), 173.2 (100), 155.2 (5), 116.1 (13)

HRMS (ESI-TOF) calculated for $C_{16}H_{35}N_4$ $[M+1]^+$: 283.2862; found: 283.2856

Biological activity

EC_{50} > 25 μg/ml; **CC_{50}** > 25 μg/ml

4.14.5. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(2-(piperidin-1-yl)ethyl)butan-1-amine (84{*3,7*})



95{*3,7*} **84**{*3,7*}

Procedure was the same as stated above for **84**{*1,9*} using 0.296 g (1 mmol) of **95**{*3,7*}, 0.57 ml (6 mmol) BMS and 8 ml HCl/MeOH (1.25 M). Column chromatography with basic alumina (CH_2Cl_2:MeOH 100:0 to 95:5 in 20 minutes) and concentration afforded 103 mg (0.36 mol, 36%) of the desired amine **84**{*3,7*} as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3357 (*st* N-H), 2929, 2856, 2811 (*st* Csp^3-H), 1460, 1372 (*b* Csp^3-H), 1149, 1045 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.66 (t, ^3J = 6.5 Hz, 2H, H-C4), 3.2-2.8 (cs, 10H, H-C1, H-C8, H-C9, H-C10), 2.6-2.4 (br, 8H, H-C5, H-C6), 2.27 (s, 3H, H-C7), 1.90 (m, 2H, H-C3), 1.71 (m, 2H, H-C2), 1.60 (m, 2H, H-C11), 1.45 (m, 2H, H-C12)

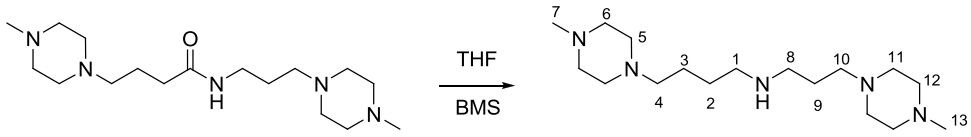
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 58.6 (C1), 55.5 (C9), 54.8 (C6), 54.5 (C10), 53.0 (C5), 49.2 (C8), 45.8 (C7, C4), 25.9 (C11), 25.5 (C2, C3), 24.5 (C12)

HRMS (EI) calculated for $C_{16}H_{34}N_4$ $[M]^+$: 282.2783; found: 282.2789

Biological activity

EC_{50} > 25 μg/ml; **CC_{50}** > 25 μg/ml

4.14.6. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(3-(4-methylpiperazin-1-yl)propyl)butan-1-amine (84{*3,9*})



95{*3,9*} **84**{*3,9*}

Procedure was the same as stated above for **84**{*1,9*} using 0.326 g (1 mmol) of **95**{*3,9*} and 0.57 ml (6 mmol) BMS. Treatment with 8 ml HCl/MeOH (1.25 M) afforded 0.128 mg (0.4 mol, 40%) of **84**{*3,9*} as a yellow oil without further purification.

Spectroscopic data

IR (film) ν (cm^{-1}): 3333 (*st* N-H), 2932, 2857, 2803 (*st* Csp^3-H), 1460, 1373 (*b* Csp^3-H), 1162, 1010 (*st* C-N)

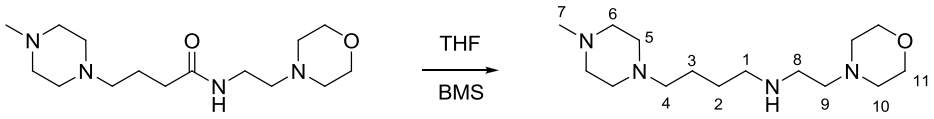
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.69 (t, ^3J = 6.5 Hz, 2H, H-C4), 3.58 (m, 6H, H-C1, H-C8, H-C10), 2.8-2.2 (br, 16H, H-C5, H-C6, H-C11, H-C12), 2.29 (s, 6H, H-C7, H-C13), 1.90 (m, 2H, H-C3), 1.69 (4H, H-C2, H-C9)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 58.5 (C1), 56.9 (C10), 54.6 (C6, C12), 52.9 (C11, C5), 48.7 (C8), 46.1 (C13), 45.9 (C7), 45.8 (C4), 32.7 (C9), 25.5 (C2, C3)

Biological activity

EC_{50} > 25 μg/ml; **CC_{50}** > 25 μg/ml

4.14.7. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(2-morpholinoethyl)butan-1-amine (84{*3,10*})



95{*3,10*} **84**{*3,10*}

Procedure was the same as stated above for **84**{*1,9*} using 0.300 g (1 mmol) of **95**{*3,10*}, 0.57 ml (6 mmol) BMS and 8 ml HCl/MeOH (1.25 M). The crude residue was purified by column chromatography with basic alumina (CH_2Cl_2:MeOH 100:0 to 90:10 in 17 minutes) and concentration afforded 148 mg (0.52 mol, 52%) of **84**{*3,10*} as a yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3345 (*st* N-H), 2924, 2853 (*st* Csp^3-H), 1458, 1377 (*b* Csp^3-H), 1115 (*st* C-O), 1080 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.75 (t, ^3J = 7.0 Hz, 4H, H-C11), 3.72 (t, ^3J = 6.5 Hz, 2H, H-C4), 2.8-2.5 (cs, 10H, H-C1, H-C5, H-C6), 2.48 (cs, 8H, H-C8, H-C9, H-C10), 2.28 (s, 3H, H-C7), 1.80 (m, 4H, H-C3, H-C2)

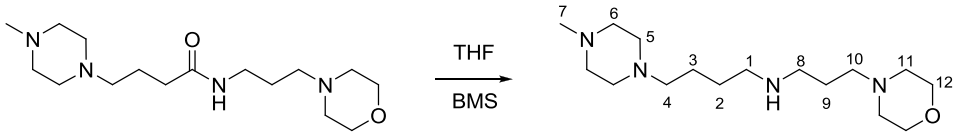
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 67.1 (C11), 60.2 (C9), 58.5 (C1), 54.6 (C6), 54.0 (C10), 53.0 (C5), 47.1 (C8), 45.8 (C7, C4), 25.5 (C2, C3)

HRMS (EI) calculated for $C_{15}H_{32}N_4O$ $[M]^+$: 284.2576; found: 284.2576

Biological activity

EC_{50} = 3.00 μg/ml; **CC_{50}** > 25 μg/ml

4.14.8. Synthesis of 4-(4-methylpiperazin-1-yl)-*N*-(3-morpholinopropyl)butan-1-amine (84{*3,11*})



95{*3,11*} **84**{*3,11*}

Procedure was the same as stated above for **84**{*1,9*} using 0.312 g (1 mmol) of **95**{*3,11*}, 0.57 ml (6 mmol) BMS and 8 ml HCl/MeOH (1.25 M). The crude product was purified using column chromatography with basic alumina (CH_2Cl_2:MeOH 100:0 to 95:5 in 28 minutes) and concentration afforded 153 mg (0.51 mol, 51%) of the desired amine **84**{*3,11*} as a yellow oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3298 (*st* N-H), 2940, 2883, 2853 (*st* Csp^3-H), 1447, 1372 (*b* Csp^3-H), 1115 (*st* C-O), 1101 (*st* C-N)

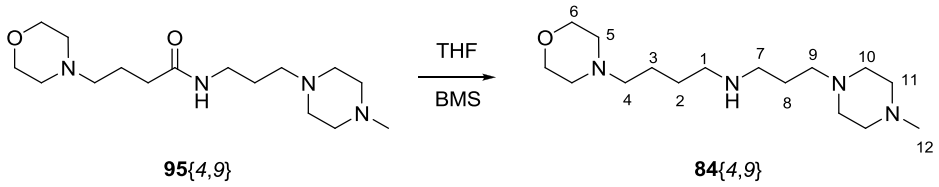
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.72 (t, ^3J = 7.0 Hz, 4H, H-C12), 3.68 (t, ^3J = 6.5 Hz, 2H, H-C4), 2.8-2.5 (cs, 10H, H-C1, H-C5, H-C6), 2.5-2.35 (cs, 8H, H-C8, H-C10, H-C11), 2.28 (s, 3H, H-C7), 2.15 (m, 2H, H-C9), 1.83 (m, 4H, H-C3, H-C2)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 67.0 (C12), 58.9 (C10), 58.3 (C1), 54.5 (C6), 54.0 (C11), 52.8 (C5), 47.8 (C8), 45.9 (C7), 45.7 (C4), 25.5 (C2, C3), 24.5 (C9)

Biological activity

EC_{50} = 18.25 μg/ml; **CC_{50}** > 25 μg/ml

4.14.9. Synthesis of *N*-(3-(4-methylpiperazin-1-yl)propyl)-4-morpholinobutan-1-amine (84{*4*,*9*})



95{*4*,*9*} **84**{*4*,*9*}

Procedure was the same as stated above for **84**{*1*,*9*} using 0.310 g (1 mmol) of **95**{*2*,*9*}, 0.57 ml (6 mmol) BMS and 8 ml HCl/MeOH (1.25 M). The crude product was purified by column chromatography with basic alumina (CH_2Cl_2:MeOH 100:0 to 90:10 in 20 minutes) and concentration afforded 98 mg (0.33 mol, 33%) of the desired amine **84**{*4*,*9*} as a brown oil.

Spectroscopic data

IR (film) ν (cm^{-1}): 3305 (*st* N-H), 2940, 2853 (*st* Csp^3-H), 1446, 1370 (*b* Csp^3-H), 1118 (*st* C-O), 1079 (*st* C-N)

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.81 (br, 4H, H-C6), 3.69 (t, ^3J = 6.5 Hz, 2H, H-C4), 2.68 (m, 8H, H-C1, H-C5, H-C7), 2.55-2.35 (cs, 10H, H-C10, H-C11, H-C9), 2.30 (s, 3H, H-C12), 1.85 (m, 4H, H-C3, H-C2), 1.68 (m, 2H, H-C8)

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ (ppm): 67.1 (C6), 55.3 (C10), 57.3 (C4), 56.9 (C7), 54.5 (C1), 54.0 (C9), 53.2 (C11), 52.8 (C5), 46.1 (C12), 25.5 (C2*), 25.4 (C3*), 24.5 (C8)

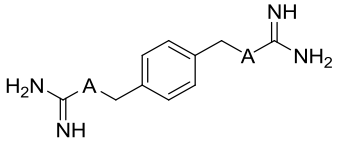
HRMS (EI): calculated for $C_{16}H_{34}N_4O$ $[M]^+$: 298.2733; found: 298.2731

Biological activity

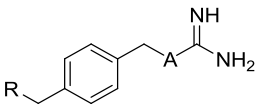
EC_{50} > 25 μg/ml; **CC_{50}** > 25 μg/ml

5. CONCLUSIONS

1. S'han sintetitzat els espaiadors bi i monodentats **23**, **24**, **27** i **28**. Els derivats sulfurats **23** i **27** s'han obtingut a partir de *p*-xilens halogenats i tiourea, amb rendiments satisfactoris, mentre que els derivats nitrogenats **24** i **28** s'han sintetitzat per reacció de *p*-xililendiamines amb *S*-metiltiourea amb rendiments més discrets. La inestabilitat a l'aire dels espaiadors ha forçat la seva obtenció com a sals. Els derivats sulfurats han resultat també inestables en medis bàsics, rendint el disulfur de *p*-hidroximetilbenzil.

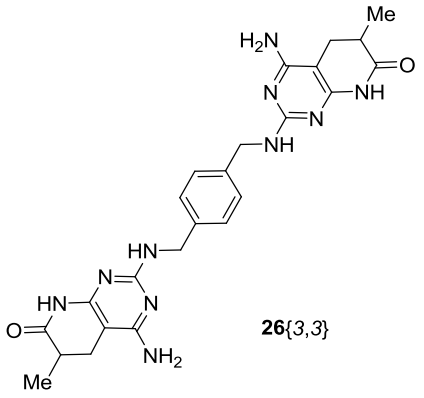


23 A = S
24 A = NH

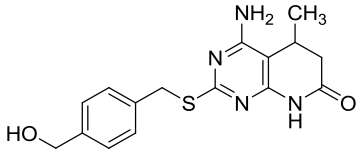


27 A = S R = OH
28 A = NH R = NHBoc

2. Els carbonitrils **18**{*x*}, obtinguts a partir d'un èster α,β-insaturat **15**{*x*} i malononitril (**16**) s'han fet reaccionar amb els espaiadors **23**, **24** i **27** per tal d'obtenir els corresponents adductes bis(pirido[2,3-*d*]pirimidínics) (**25**{*x*,*x*} i **26**{*x*,*x*}) i pirido[2,3-*d*]pirimidínics (**29**{*x*}) objectiu. S'han obtingut els bisadductes **26**{*2*,*2*} i **26**{*3*,*3*} i els monoadductes **29**{*1*} i **29**{*3*}. S'ha avaluat l'activitat biològica de **26**{*3*,*3*} i **29**{*3*}, que no han resultat ni actius ni tòxics a la màxima concentració assajada de 25 μg/ml. Els adductes **25**{*1*,*1*}, **25**{*2*,*2*} i **25**{*3*,*3*} només s'han pogut caracteritzar per espectroscòpia d'infraroig i espectroscòpia de masses d'alta resolució degut a la seva elevada insolubilitat en dissolvents comuns, la qual cosa no ha permès avaluar-ne l'activitat biològica.

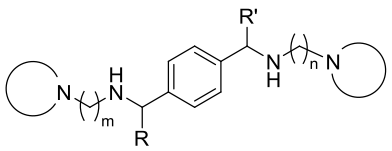


26{*3*,*3*}



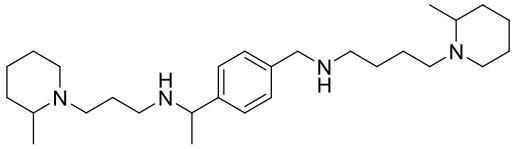
29{*3*}

3. La quimioteca d'anàlegs de l'AMD3100 anteriorment descrita al GEM s'ha ampliat amb 36 compostos a partir de dos nous substrats, *p*-acetilbenzaldehid (**11**) i *p*-acetilacetofenona (**14**), i les dues amines *N*-(4-aminobutil)-2-pipecolina (**5**{*13*}) i *N*-(4-aminobutil)piperidina (**5**{*14*}), obtingudes per síntesi de Gabriel. S'han seleccionat, per a ésser sintetitzats, deu compostos simètricament disubstituïts d'estructura **2**{*x*,*x*}, **9**{*x*,*x*} i **12**{*x*,*x*} i sis asimètricament disubstituïts d'estructura **9**{*x*,*y*}. Dels 16 nous compostos seleccionats se n'ha aconseguit obtenir 14 per aminació reductora, emprant isopropòxid de titani (IV) com a catalitzador en els derivats dels precursors **11** i **14**.



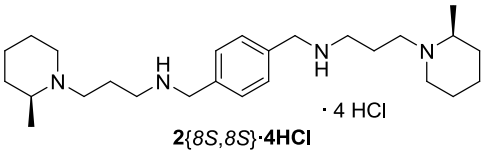
2{*x*,*y*} R = R' = H
9{*x*,*y*} R = Me, R' = H
12{*x*,*y*} R = R' = Me

4. S'ha avaluat l'activitat antiviral dels 14 compostos objectiu sintetitzats, arribant a valors d'EC_{50} de l'ordre del cap de sèrie **2**{*8,8*} anteriorment descrit al GEM, però sense aconseguir millorar-la en cap cas. El compost sintetitzat que ha presentat major activitat biològica ha estat **9**{*8,13*} (EC_{50} = 0,060 μg/ml), reafirmant l'amina **5**{*8*} com un precursor idoni de cara a inhibir el coreceptor CXCR4. S'ha demostrat que ni l'augment de la distància entre els dos àtoms de nitrogen que es troben al mateix costat de l'espaiador aromàtic ni la presència de substituents metil en posició benzílica no millora considerablement l'activitat anti-VIH.



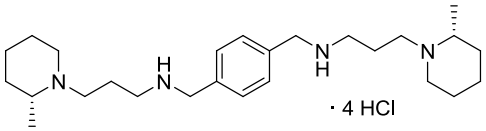
9{*8,13*}
EC_{50} = 0,060 μg/ml
CC_{50} > 25 μg/ml

5. S'han obtingut els tres estereoisòmers del compost més actiu identificat al grup: **2**{*8S,8S*}, **2**{*8R,8R*} i **2**{*8S,8R*} a partir de les amines homoquirals prèviament sintetitzades per síntesi de Gabriel. L'avaluació de l'activitat anti-VIH de les tres mostres enriquides en els tres estereoisòmers corresponents no ha presentat valors substancialment diferents de la mescla estereoisomèrica.



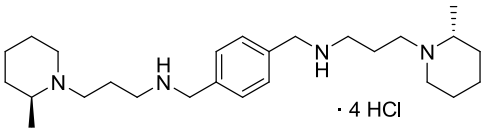
· 4 HCl

2{*8S,8S*}·**4HCl**
EC_{50} = 0,070 μg/ml
CC_{50} > 25 μg/ml



· 4 HCl

2{*8R,8R*}·**4HCl**
EC_{50} = 0,077 μg/ml
CC_{50} > 25 μg/ml

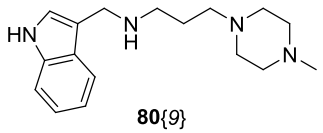


· 4 HCl

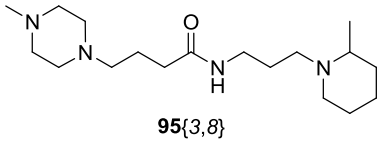
2{*8S,8R*}·**4HCl**
EC_{50} = 0,078 μg/ml
CC_{50} = 18 μg/ml

6. S'ha dissenyat *de novo* una quimioteca virtual de potencials inhibidors del coreceptor CXCR4 a partir de l'estructura del coreceptor modelada al GEM i mitjançant el programari Ludi. De la quimioteca virtual obtinguda s'han identificat els fragments més rellevants i se n'ha generat una segona de major accessibilitat sintètica. El cribratge de la nova quimioteca virtual ha permès seleccionar 16 compostos de tres famílies diferents: derivats d'heterocicles aromàtics privilegiats, derivats amb dues baules metilèniques i derivats amb quatre baules metilèniques.

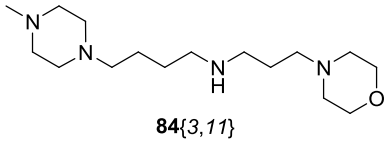
   S'ha avaluat l'activitat antiviral de tots els compostos finals obtinguts, així com de 14 amides precursores. De la primera família, tan sols l'indole **80**{*9*} ha resultat més actiu que tòxic, mentre que l'amida **95**{*3,8*} i l'amina **84**{*3,11*} han presentat activitats moderades.



80{*9*}
EC_{50} = 15,9 μg/ml
CC_{50} = 50,8 μg/ml

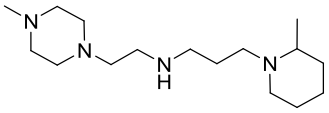


95{*3,8*}
EC_{50} = 9,20 μg/ml
CC_{50} = 99 μg/ml

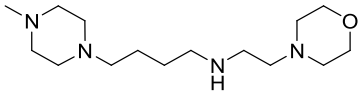


84{*3,11*}
EC_{50} = 18,25 μg/ml
CC_{50} > 25 μg/ml

El disseny *de novo* i la posterior síntesi i avaluació de l'activitat anti-VIH dels candidats seleccionats ha permès identificar les amines **83**{*3,8*} i **84**{*3,10*} com a compostos prototip de noves famílies d'inhibidors de l'agent etiològic de la sida, per a futurs processos d'optimització a precandidats.



83{*3,8*}
EC_{50} = 0,71 μg/ml
CC_{50} > 25 μg/ml



84{*3,10*}
EC_{50} = 3,00 μg/ml
CC_{50} > 25 μg/ml

6. BIBLIOGRAFIA

1. D. Voet, J.G. Voet; *Bioquímica,* 1 ed. Omega: Barcelona, 1992.
2. National Institute of Allergy and Infectious Diseases; *Understanding the Immune System,* 2007.
3. S.A. Hofmeyr; An interpretative introduction to the immune system, *Design principles for the immune system and other distributed autonomous systems,* 2001.
4. A. Does; HIV and AIDS, *Rediscovering Biology: Molecular to global perspectives,* Annenberg Media: 2003.
5. J. Trowsdale; "Both man & bird & beast": comparative organization of MHC genes. *Immunogenetics* **1995**, 41, 1-17.
6. R. Twyman; The major histocompatibility complex; The human genome: *http://genome.wellcome.ac.uk/doc_WTD020754.html.* Consulta: 31/08/2010.
7. C.K. Mathews; *Bioquímica,* 1 ed. Pearson: Madrid, 2004.
8. A. Bernard, L. Boumsell; Human leukocyte differentiation antigens. *Presse Med.* **1984**, 13, 2311-2316.
9. H. Fiebig, I. Behn, R.T. Gruhn H., H. Kupper, H. Ambrosius; Charachterization of a series of monoclonal antibodies against human T cells. *Allerg. Immunol.* **1984**, 30, 242-250.
10. M.A. Bracho; Virus, els monstres invisibles. *Mètode* **2005**, 45, 55-110.
11. R.Y. Stanier, J.L. Ingraham, M.L. Wheelis, P.R. Painter; Los virus, *Microbiología,* 2a ed. Editorial Reverté, S.A.: Barcelona, 1996.
12. T. McKee, J. McKee; *Bioquímica. La base molecular de la vida,* 3 ed. McGraw-Hill: Madrid, 2003.
13. R.C. Gallo; History of the discoveries of the first human retroviruses HTLV-1 and HTLV-2. *Oncogene* **2005**, 24, 5926-5930.
14. Center for Disease Control; Pneumocystis pneumonia - Los Angeles. *MMWR* **1981**, 30, 250-252.
15. M.S. Gottlieb, R. Schroff, H.M. Schanker, J.D. Weisman, P.T. Fan, R.A. Wolf, A. Saxon; *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men - evidence of a new acquired cellular immunodeficiency. *N.Engl.J.Med.* **1981**, 305, 1425-1431.
16. K.A. Sepkowitz; AIDS - The first 20 years. *N.Engl.J.Med.* **2001**, 344, 1764-1772.
17. R.C. Gallo, L. Montaigner; The discovery of HIV as the cause of AIDS. *N.Engl.J.Med.* **2003**, 349, 2283-2285.
18. V. Quagliarello; The Acquired Immunodeficiency Syndrome: current status. *Yale J.Biol.Med.* **1982**, 55, 443-452.
19. F. Barré-Sinoussi; HIV: a discovery opening the road to novel scientific knowledge and global health improvement (Nobel Lecture). *Angew.Chem.Int.Ed.* **2009**, 48, 5809-5814.
20. M. Tsuchiya, H. Yoshida, T. Ogata, S. Inokawa; The Schotten-Baumann reaction of dimethylaminobenzyl alcohols. *B.Chem.Soc.Jpn* **1969**, 42, 1756-1757.
21. L. Montaigner; 25 years after HIV discovery: prospects for cure and vaccine (Nobel Lecture). *Angew.Chem.Int.Ed.* **2009**, 48, 5815-5826.
22. Nobel Foundation; Nobelprize.org The official web site of the Nobel Prize: *http://nobelprize.org/*. Consulta: 11/10/2010.

23. M.T. Madigan, J.M. Martinko, J. Parker; *Brock Biología de los Microorganismos,* 8a ed. Prentice Hall: Madrid, 1999.

24. International Committee on Taxonomy of Viruses; Virus Taxonomy: *http://www.ictvonline.org*. Consulta: 23/09/2010.

25. E.O. Freed; Retroviruses, *Encyclopedia of Cancer,* 2a ed. Elsevier Science: San Diego, 2002.

26. D. Baltimore; Expression of animal virus genomes. *Bacteriol.Rev.* **1971**, 35, 235-241.

27. S.P. Goff; *Retroviridae*: The retroviruses and their replication, *Fields Virology,* 4a ed. Lippincott Williams & Wilkins: New York, 2001.

28. V.M. Vogt; Retroviral virions and genomes, *Retroviruses,* 1a ed. Cold Spring Harbor Laboratory Press: New York, 1997.

29. J.M. Coffin; Retroviridae and their replication, *Fields Virology,* 2a ed. Raven Press Ltd.: New York, 1990.

30. R.A. Weiss; Retrovirus classification and cell interactions. *J.Antimicrob.Chemother.* **1996**, 37 (suppl B), 1-11.

31. S. Sierra, B. Kupfer, R. Kaiser; Basics of the virology of HIV-1 and its replication. *J.Clin.Virol.* **2005**, 34, 233-244.

32. Sierra García de Quevedo,José Julio; Taxonomía y virus de la inmunodeficiencia humana. *Rev.Mex.Patol.Clin.* **2004**, 51, 37-41.

33. E.O. Freed, M.A. Martin; HIVs and their replication, *Fields Virology,* 4a ed. Lippincott Williams & Wilkins: New York, 2001.

34. A.D. Frankel, J.A. Young; HIV-1: Fifteen proteins and an RNA. *Annu.Rev.Biochem.* **1998**, 67, 1-25.

35. E.O. Freed, S.R. Ross; Retroviruses 2004: Review of the 2004 Cold Spring Harbor Retroviruses conference. *Retrovirology* **2004**, 1.

36. E. Hunter; Viral entry and receptor, *Retroviruses,* Cold Spring Harbor Laboratory Press: New York, 1997.

37. S. Bour, R. Geleziunas, M.A. Wainberg; The human immunodeficiency virus type 1 (HIV-1) CD4 receptor and its central role in promotion of HIV-1 infection. *Microbiol.Rev.* **1995**, 59, 63-93.

38. E.O. Freed; HIV-1 replication. *Som.Cell Mol.Genet.* **2001**, 26, 13-33.

39. G. Alkhatib, E.A. Berger; HIV coreceptors: from discovery and designation to new paradigms and promise. *Eur.J.Med.Res.* **2007**, 12, 375-384.

40. S.E. Ryu, P.D. Kwong, A. Truneh, T.G. Porter, J. Arthos, M. Rosenberg, X.P. Dai, N.H. Xuong, R. Axel, R.W. Sweet, W.A. Hendrickson; Cristal structure of an HIV-binding recombinant fragment of human CD4. *Nature* **1990**, 348, 419-426.

41. J.H. Wang, Y.W. Yan, T.P. Garrett, J.H. Liu, D.W. Rodgers, R.L. Garlick, G.E. Tarr, Y. Husain, E.L. Reinherz, S.C. Harrison; Atomic structure of a fragment of human CD4 containing two immunoglobulinlike domains. *Nature* **1990**, 348, 411-418.

42. E.A. Berger, G. Alkhatib; HIV gp120 interactions with coreceptors: insights from studies with CCR5-based peptides. *Eur.J.Med.Res.* **2007**, 12, 403-407.

43. S.G. Ward, K. Bacon, J. Westwick; Chemokines and T lymphocytes: more than an attraction. *Immunity* **1998**, 9, 1-11.

44. K. Sackett, A. TerBush, D.P. Weliky; HIV gp41 six-helix bundle constructs induce rapid vesicle fusion at pH 3.5 and little fusion at pH 7.0: understanding pH dependence of protein aggregation, membrane binding, and electrostatics, and implications for HIV-host cell fusion. *Eur.Biophys.J.* **2011**, 11.

45. L.M. Mansky, H.M. Temin; Lower in vivo mutation rate of human immunodeficiency virus type 1 than that predicted from the didelity of purified reverse transcriptase. *J.Virol.* **1995**, 69, 5087-5094.

46. A. Moumen, R. Galetto, V. Giacomoni-Fernandes, L. Polomack, M. Veron, H. Buc, M. Negroni; Mechanism of genetic recombination in HIV: role of the structure of the genomic RNA. *Antivir.Ther.* **2003**, 8, S261.

47. L. Moutouh, J. Corbeil, D.D. Richman; Recombination leads to the rapid emergence of HIV-1 dually resistant mutants under selective drug pressure. *Proc.Natl.Acad.Sci.* **1996**, 93, 6106-6111.

48. M.T. Bretscher, C.L. Althaus, V. Müller, S. Bonhoeffer; Recombination in HIV and the evolution of drug resistance: for better or for worse? *BioEssays* **2004**, 26, 180-188.

49. D.S. Burke; Recombination in HIV: an important viral evolutionary strategy. *Emerg.Infect.Dis.* **1997**, 3, 253-259.

50. M.E. Quiñones-Mateu, E.J. Arts; Recombination in HIV-1: Update and implications. *AIDS Rev.* **1999**, 1, 89-100.

51. F. Clavel, M.D. Hoggan, R.L. Willey, K. Strebel, M.A. Martin, R. Repaske; Genetic recombination of human immunodeficiency virus. *J.Virol.* **1989**, 63, 1455-1459.

52. R. Nájera, E. Delgado, L. Pérez-Álvarez, M.M. Thomson; Genetic recombination and its role in the development of the HIV-1 pandemic. *AIDS* **2002**, 16, S3-S16.

53. D.F.J. Purcell, M.A. Martin; Alternative splicing of human immunodeficiency virus type 1 mRNA modulates viral protein expression, replication and infectivity. *J.Virol.* **1993**, 67, 6365-6378.

54. D.G. Demirov, E.O. Freed; Retrovirus budding. *Virus Res.* **2004**, 106, 87-102.

55. J.A.G. Briggs, J.D. Riches, B. Glass, V. Bartonova, G. Zanetti, H.G. Kräusslich; Structure and assembly of immature HIV. *Proc.Natl.Acad.Sci.* **2009**, 106, 11090-11095.

56. S.G. Ward, J. Westwick; Chemokines: understanding their role in T-lymphocyte biology. *Biochem.J.* **1998**, 333, 457-470.

57. K. Palczewski, T. Kumasaka, T. Hori, C.A. Behnke, H. Motoshima, B.A. Fox, I. Le Trong, D.C. Teller, T. Okada, R.E. Stenkamp, M. Yamamoto, M. Miyano; Crystal structure of rhodopsin: a G protein-coupled receptor. *Science* **2000**, 289, 739-745.

58. S.G.F. Rasmussen, H. Choi, D.M. Rosenbaum, T.S. Kobilka, F.S. Thian, P.C. Edwards, M. Burghammer, V.R.P. Ratnala, R. Sanishvili, R.F. Fischetti, G.F.X. Schertler, W.I. Weis, B.K. Kobilka; Crystal structure of the human β_2 adrenergic G-protein-coupled receptor. *Nature* **2007**, 450, 383-387.

59. V. Cherezov, D.M. Rosenbaum, M.A. Hanson, S.G.F. Rasmussen, F.S. Thian, T.S. Kobilka, H. Choi, P. Kuhn, W.I. Weis, B.K. Kobilka, R.C. Stevens; High-resolution crystal structure of an engineered human β_2-adrenergic G protein-coupled receptor. *Science* **2007**, 318, 1258-1265.

60. B. Wu, E.Y.T. Chien, C.D. Mol, G. Fenalti, W. Liu, V. Katritch, R. Abagyan, A. Brooun, P. Wells, F.C. Bi, D.J. Hamel, P. Kuhn, T.M. Handel, V. Cherezov, R.C. Stevens; Structures of the CXCR4 chemokine GPCR with small-molecule and cyclic peptide antagonists. *Science* **2010**.

61. Y. Feng, C.C. Broder, P.E. Kennedy, E.A. Berger; HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* **1996**, 272, 872-877.

62. E.A. Berger, P.M. Murphy, J.M. Farber; Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism and disease. *Annu.Rev.Immunol.* **1999**, 17, 657-700.

63. K.B. Napier, Z. Wang, S.C. Peiper, J.O. Trent; CCR5 interactions with the variable 3 loop of gp120. *J.Mol.Model.* **2007**, 13, 29-41.

64. N. Zhou, Z. Luo, J. Luo, D. Liu, J.W. Hall, R.J. Pomerantz, Z. Huang; Structural and functional characterization of human CXCR4 as a chemokine receptor and HIV-1 co-receptor by mutagenesis and molecular modeling studies. *J.Biol.Chem.* **2001**, 276, 42826-42833.

65. E.A. Berger, R.W. Doms, E.-. Fenyö, B.T.M. Korber, D.R. Littman, J.P. Moore, Q.J. Sattentau, H. Schuitemaker, J. Sodroski, R.A. Weiss; A new classification for HIV-1. *Nature* **1998**, 391, 240.

66. A. Valentin, H. Trivedi, W. Lu, L.G. Kostrikis, G.N. Pavlakis; CXCR4 mediates entry and productive infection of syncytia-inducing (X4) HIV-1 strains in primary macrophages. *Virology* **2000**, 269, 294-304.

67. J.P. McGowan, S. Shah; Understanding HIV tropism. *The PRN Notebook* **2010**, 15.

68. C.C. Bleul, M. Farzan, H. Choe, C. Parolin, I. Clark-Lewis, J. Sodroski, T.A. Springer; The lymphocyte chemoattractant SDF-1 is a ligand for LESTR/fusin and blocks HIV-1 entry. *Nature* **1996**, 382, 829-833.

69. E. Oberlin, A. Amara, F. Bachelerie, C. Bessia, J. Virelizier, F. Arenzana-Seisdedos, O. Schwartz, J. Heard, I. Clark-Lewis, D.F. Legier, M. Loetscher, M. Baggiolini, B. Moser; The CXC chemokine SDF-1 is the ligand for LESTR/fusin and prevents infection by T-cell-line-adapted HIV-1. *Nature* **1996**, 382, 833-835.

70. C.T. Veldkamp, J.J. Ziarek, F.C. Peterson, Y. Chen, B.F. Vokman; Targeting SDF-1/CXCL12 with a ligand that prevents activation of CXCR4 through structure-based drug design. *J.Am.CHem.Soc.Comm.* **2010**, 132, 7242-7243.

71. R.S.Y. Wong, V. Bodart, M. Metz, J. Labrecque, G. Bridger, S.P. Fricker; Comparison of the potential multiple binding modes of bicyclam, monocyclam, and noncyclam small-molecule CXC chemokine receptor 4 inhibitors. *Mol.Pharmacol.* **2008**, 74, 1485-1495.

72. C.H. Swan, B. Bühler, M.P. Tschan, C.F. Barbas, B.E. Torbett; T-cell protection and enrichment through lentiviral CCR5 intrabody gene delivery. *Gene Ther.* **2006**, 13, 1-13.

73. J.C. Stephens, D.E. Reich, D.B. Goldstein, H.D. Shin, M.W. Smith, M. Carrington, C. Winkler, G.A. Huttley, R. Allikmets, L. Schriml, B. Gerrard, M. Malasky, M.D. Ramos, S. Morlot, M. Tzetis, C. Oddoux, F.S. di Giovine, G. Nasioulas, D. Chandler, M. Aseev, M. Hanson, L. Kalaydjieva, D. Glavac, P. Gasparini, E. Kanavakis, M. Claustres, M. Kambouris, H. Ostrer, G. Duff, V. Baranov, H. Sibul, A. Metspalu, D. Goldman, N. Martin, D. Duffy, J. Schmidtke, X. Estivill, S.J. O'Brien, M. Dean; Dating the origin of the CCR5-D32 AIDS-resistance allele by the coalescence of haplotypes. *Am.J.Hum.Genet.* **1998**, 62, 1507-1515.

74. J.M. Farber, E.A. Berger; HIV's response to a CCR5 inhibitor: I'd rather tighten than switch! *Proc.Natl.Acad.Sci.* **2002**, 99, 1749-1751.

75. J.P. Moore, R.W. Doms; The entry of entry inhibitors: a fusion of science and medicine. *Proc.Natl.Acad.Sci.* **2003**, 100, 10598-10602.

76. E.G. Cormier, T. Dragic; An overview of HIV-1 co-receptor function and its inhibitors, *HIV Sequence Compendium,* 2000.

77. G. Pantaleo, C. Graziosi, A.S. Fauci; New concepts in the immunopathogenesis of human immunodeficiency virus infection. *N.Engl.J.Med.* **1993**, 328, 327-335.

78. M. Gougeon, R. Olivier, S. Garcia, D. Guetard, T. Dragic, C. Dauguet, L. Montaigner; Mise en évidence d'un processus d'engagement vers la mort cellulaire par apoptose dans les lymphocytes de patients infectés par le VIH. *C.R.Acad.Sci.Ser.III* **1991**, 312, 529-537.

79. L. Gil, G. Martínez, I. González, A. Tarinas, A. Álvarez, A. Giuliani, R. Molina, R. Tápanes, J. Pérez, O.S. León; Contribution to characterization of oxidative stress in HIV/AIDS patients. *Pharmacol.Res.* **2003**, 47, 217-224.

80. N. Israël, M.A. Gougerot-Pocidalo; Oxidative stress in human immunodeficiency virus infection. *Cell Mol.Life Sci.* **1997**, 53, 864-870.

81. B. Levine, D.L. Sodora; HIV and CXCR4 in a kiss of autophagic death. *J.Clin.Invest.* **2006**, 116, 2078-2080.

82. H.M. Díaz Torres, A.L. Lubián Caballero; Definición de caso y clasificación de la infección por VIH y SIDA. *Rev.Cubana Med.* **1998**, 37, 157-165.

83. Fundació "la Caixa"; Sida; saber ajuda: *http://www.sidasaberajuda.com*. Consulta: 27/09/2010.

84. UNAIDS, WHO; AIDS epidemic update. **2009**.

85. UNAIDS, WHO; AIDS epidemic update. **2007**.

86. University of California, San Francisco; HIV InSite; Gateway to HIV and AIDS knowledge: *http://hivinsite.ucsf.edu/InSite*. Consulta: 28/10/2010.

87. K.M. Johnston, A.R. Levy, V.D. Lima, R.S. Hogg, M.W. Tyndall, P. Gustafson, A. Briggs, J.S. Montaner; Expanding access to HAART: a cost-effective approach for treating and preventing HIV. *AIDS* **2010**, 24, 1929-1935.

88. S. Broder; The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. *Antiviral Res.* **2010**, 85, 1-18.

89. J.A. Esté, T. Cihlar; Current status and challenges of antiretroviral research and therapy. *Antiviral Res.* **2010**, 85, 25-33.

90. R.C. Rathbun, M.D. Liedtke, S.M. Lockhart, R.A. Greenfield; HIV infection, antiretroviral therapy. *eMedicine* **2009**, http://emedicine.medscape.com/article/1533218, .

91. J.P. Horwitz, J. Chua, M. Noel; Nucleosides V. The monomesylates of 1-(2-(deoxy-beta-D-lyxofuranosyl)thymine. *J.Org.Chem.* **1964**, 29, 2076-2078.

92. Y. Mehellou, E. De Clercq; Twenty-six years of anti-HIV drug discovery: where do we stand and where do we go? *J.Med.Chem.* **2010**, 53, 521-538.

93. L. Sannes; Emerging HIV therapies: *http://www.healthtech.com/*. Consulta: 9/11/2007.

94. S. Pettersson, I. Clotet-Codina, J.A. Esté, J.I. Borrell, J. Teixidó; Recent advances in combinatorial chemistry applied to development of anti-HIV drugs. *Mini Rev.Med.Chem.* **2006**, 6, 91-108.

95. S.K. Saxena, N. Mishra, R. Saxena; Advances in antiviral drug discovery and development: Part I: Advancements in antiviral drug discovery. *Future Virol.* **2009**, 4, 101-107.

96. D.E. Smith, B.D. Walker, D.A. Cooper, E.S. Rosenberg, J.M. Kaldor; Is anitretroviral treatment of primary HIV infection clinically justified on the basis of current evidence? *AIDS* **2004**, 18, 709-718.

97. M.M. Kitahata, S.J. Gange, A.G. Abraham, B. Merriman, M.S. Saag, A.C. Justice, R.S. Hogg, S.G. Deeks, J.J. Eron, J.T. Brooks, S.B. Rourke, M.J. Gill, R.J. Bosch, J.N. Martin, M.B. Klein, L.P. Jacobson,

B. Rodriguez, T.R. Sterling, G.D. Kirk, S. Napravnik, A.R. Rachlis, L.M. Calzavara, M.A. Horberg, M.J. Silverberg, K.A. Gebo, J.J. Goedert, C.A. Benson, A.C. Collier, S.E. van Rompaey, H.M. Crane, R.G. McKaig, B. Lau, A.M. Freeman, R.D. Moore; Effect of early versus deferred antiretroviral therapy for HIV on survival. *N.Engl.J.Med.* **2009**, 360, 1815-1826.

98. F. Dyda, A.B. Hickman, T.M. Jenkins, A. Engelman, R. Craigie, D.R. Davies; Crystal structure of the catalytic domain of HIV-1 integrase: similarity to other polynucleotidyl transferases. *Science* **1994**, 266, 1981-1986.

99. R. Arakaki, H. Tamamura, M. Premanathan, K. Kanbara, S. Ramanan, K. Mochizuki, M. Baba, N. Fujii, H. Nakashima; T134, a small-molecule CXCR4 inhibitor, has no cross-drug resistance with AMD3100, a CXCR4 antagonist with a different structure. *J.Virol.* **1999**, 73, 1719-1723.

100. V. Briz, E. Poveda, V. Soriano; HIV entry inhibitors: mechanisms of action and resistance pathways. *J.Antimicrob.Chemother.* **2006**, 57, 619-627.

101. T. Murakami, N. Yamamoto; Role of CXCR4 in HIV infection and its potential as a therapeutic target. *Future Microbiol.* **2010**, 5, 1025-1039.

102. P. Dorr, M. Perros; CCR5 inhibitors in HIV-1 therapy. *Expert Opin. Drug Dis.* **2008**, 3, 1345-1361.

103. Maraviroc, recomendado para su aprobación en EEUU.

104. C.S. Adamson, E.O. Freed; Novel approaches to inhibiting HIV-1 replication. *Antiviral Res.* **2010**, 85, 119-141.

105. S.K. Saxena, N. Mishra, R. Saxena; Advances in antiviral drug discovery and development: Part II: Advancements in antiviral drug development. *Future Virol.* **2009**, 4, 209-215.

106. AIDSInfoNet; Other antiretroviral drugs in development. *Fact Sheet* **2010**, 470.

107. J.C. Tilton, R.W. Doms; Entry inhibitors in the treatment of HIV-infection. *Antiviral Res.* **2010**, 85, 91-100.

108. S. Rusconi, A. Scozzafava, A. Mastrolorenzo, C.T. Supuran; An update in the development of HIV entry inhibitors. *Curr.Top.Med.Chem.* **2007**, 7, 1273-1289.

109. A. Mastrolorenzo, A. Maresca, S. Rusconi, C.T. Supuran; Update on the development of HIV entry inhibitors. *Future HIV Ther.* **2008**, 2, 479-507.

110. S. Nawale, S. Neve, V.J. Kadam, M.P. Toraskar; Emerging drug targets for HIV therapy: a review. *International Journal of ChemTech Research* **2010**, 2, 1180-1185.

111. E. De Clercq; Highlights in the development of new antiviral agents. *Mini Rev.Med.Chem.* **2002**, 2002, 163-175.

112. E. De Clercq; New anti-HIV agents in preclinical or clinical development. *Advances in antiviral drug design* **2004**, 2004, 1-62.

113. S. Rusconi, A. Scozzafava, A. Mastrolorenzo, C.T. Supuran; New advances in HIV entry inhibitors development. *Current drug targets: infectious disorders* **2004**, 4, 339-355.

114. S.L. Davies, N. Serradell, J. Bolós, M. Bayés; Plerixafor hydrochloride. *Drugs of the Future* **2007**, 32, 123-123.

115. A.J. Wagstaff; Plerixafor. *Drugs* **2009**, 69, 319-319.

116. A. Stanic, J.C. Grana; Review of antiretroviral agents for the treatment of HIV infection. *Formulary* **2009**, 44, 47-54.

117. C. Hoffmann; ART 2009/2010: The horizon and beyond, *HIV 2010,* Medizin Fokus Verlag: Hamburg, 2010.

118. O.M. Klibanov, S.H. Williams, C.A. Iler; Cenicriviroc, an orally active CCR5 antagonist for the potential treatment of HIV infection. *Curr.Opin.Investig.Drugs* **2010**, 11, 940-950.

119. Avexa Ltd.; Avexa closes apricitabine (ATC) program. *Avexa* **2010**.

120. L.E. Orgel; The maintenance of the accuracy of protein synthesis and its relevance to ageing. *Proc.Natl.Acad.Sci.* **1963**, 49, 517-521.

121. L.E. Orgel; The maintenance of the accuracy of protein synthesis and its relevance to ageing: a correction. *Proc.Natl.Acad.Sci.* **1970**, 67, 1476.

122. L.E. Orgel; Ageing of clones of mammalian cells. *Nature* **1973**, 243, 441-445.

123. GEM-IQS; Grup d'Enginyeria Molecular: *http://gem.iqs.url.edu/.* Consulta: 15/12/2010.

124. R. Pascual; Estudios sobre la metodología computacional para el diseño de bibliotecas combinatorias: desarrollo del programa Pralins y aplicaciones en el campo del HIV. Tesi Doctoral, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 2004.

125. R. Pascual, M. Mateu, J. Gasteiger, J.I. Borrell, J. Teixidó; Design and analysis of a combinatorial library of HEPT analogues: comparison of selection methodologies and inspections of the actually covered chemical space. *J.Chem.Inf.Comp.Sci.* **2003**, 43, 199-207.

126. R. Pascual, J.I. Borrell, J. Teixidó; Analysis of selection methodologies for combinatorial library design. *Mol.Divers.* **2003**, 6, 121-133.

127. M. Mateu; Disseny computacional de quimioteques combinatòries d'anàlegs d'HEPT amb potencial activitat anti-VIH. Treball Final de Carrera, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 2002.

128. O. Rabal; Herramientas de cribado virtual aplicadas a inhibidores de tirosina quinasas. Contribución al desarrollo del programa Pralins para el diseño de quimiotecas combinatorias. Tesi Doctoral, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 2006.

129. L. Giménez; Disseny d'una ruta sintètica per obtenir anàlegs d'HEPT. Part I. Treball Final de Carrera, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 2005.

130. R. Puig de la Bellacasa; Disseny, síntesi i avaluació biològica d'inhibidors potencials de les etapes inicials del cicle de replicació del VIH. Tesi Doctoral, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 2010.

131. Fundació La Marató; La Marató de TV3: *http://www.tv3.cat/marato.* Consulta: 22/11/2010.

132. V.I. Pérez-Nueno; SIDA: Estudio de los coreceptores CXCR4 y CCR5. Docking y cribado virtual de inhibidores de entrada del VIH. Treball Final de Carrera, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 2006.

133. V.I. Pérez-Nueno; Herramientas de cribado virtual aplicadas a inhibidores de entrada del VIH. Diseño de nuevos compuestos anti-VIH. Tesi Doctoral, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 2009.

134. E. De Clercq, N. Yamamoto, R. Pauwels, M. Baba, D. Schols, H. Nakashima, J. Balzarini, Z. Debyser, B.A. Murrer, D. Schwartz, D. Thornton, G. Bridger, S. Fricker, G. Henson, M.J. Abrams, D. Picker; Potent and selective inhibition of human immunodeficiency virus (HIV)-1 and HIV-2 replication by a class of bicyclams interacting with a viral uncoating event. *Proc.Natl.Acad.Sci.* **1992**, 89, 5286-5290.

135. W. Zhan, Z. Liang, A. Zhu, S. Kurtkaya, H. Shim, J.P. Snyder, D.C. Liotta; Discovery of small molecule CXCR4 antagonists. *J.Med.Chem.* **2007**, 50, 5655-5664.

136. G.A. Donzella, D. Schols, S.W. Lin, J.A. Esté, K.A. Nagashima, P.J. Maddon, G.P. Allaway, T.P. Sakmar, G. Henson, E. De Clercq, J.P. Moore; AMD3100, a small molecule inhibitor of HIV-1 entry via the CXCR4 co-receptor. *Nat.Med.* **1998**, 4, 72-77.

137. F. Grande, A. Garofalo, N. Neamati; Small molecules anti-HIV therapeutics targeting CXCR4. *Curr.Pharm.Des.* **2008**, 14, 385-404.

138. M. Rosenkilde, L. Gerlach, S. Hatse, R. Skerlj, D. Schols, G. Bridger, T.W. Schwartz; Molecular mechanism of action of monocyclam versus bicyclam non-peptide antagonists in the CXCR4 chemokine receptor. *J.Biol.Chem.* **2007**, 282, 27354-27365.

139. G.J. Bridger, R. Skerlj, S. Padmanabhan, S.A. Martellucci, G.W. Henson, S. Struyf, M. Witvrouw, D. Schols, E. De Clercq; Synthesis and structure-activity relationships of phenylenebis(methylene)-linked bis-azamacrocycles that inhibit HIV-1 and HIV-2 replication by antagonism of the chemokine receptor CXCR4. *J.Med.Chem.* **1999**, 42, 3971-3981.

140. K. Princen, S. Hatse, K. Vermeire, S. Aquaro, E. De Clercq, L. Gerlach, M. Rosenkilde, T.W. Schwartz, R. Skerlj, G. Bridger, D. Schols; Inhibition of Human Immunodeficiency Virus replication by a dual CCR5/CXCR4 antagonist. *J.Virol.* **2004**, 2004, 12996-13006.

141. J.A. Esté, C. Cabrera, E. De Clercq, S. Struyf, J. van Damme, G. Bridger, R. Skerlj, M.J. Abrams, G. Henson, A. Gutiérrez, B. Clotet, D. Schols; Activity of different bicyclam derivatives against human immunodeficiency virus depends on theris interaction with the CXCR4 chemokine receptor. *Mol.Pharmacol.* **1999**, 1999, 67-73.

142. E. De Clercq; Inhibition of HIV infection by bicyclams, highly potent and specific CXCR4 antagonists. *Mol.Pharmacol.* **2000**, 2000, 833-839.

143. G.J. Bridger, R.T. Skerlj, P.E. Hernandez-Abad, D.E. Bogucki, Z. Wang, Y. Zhou, S. Nan, E.M. Boehringer, T. Wilson, J. Crawford, M. Metz, S. Hatse, K. Princen, E. De Clercq, D. Schols; Synthesis and Structure-Activity Relationships of azamacrocyclic C-X-C chemokine receptor 4 antagonists: analogues containing a single azamacrocyclic ring are potent inhibitors of T-cell tropic (X4) HIV-1 replication. *J.Med.Chem.* **2010**, 53, 1250-1260.

144. S. Hatse, K. Princen, E. De Clercq, M. Rosenkilde, T.W. Schwartz, P.E. Hernandez-Abad, R. Skerlj, G. Bridger, D. Schols; AMD3465, a monomacrocyclic CXCR4 antagonist and potent HIV entry inhibitor. *Biochem.Pharmacol.* **2005**, 70, 752-761.

145. S. Pettersson, V.I. Pérez-Nueno, L. Ros-Blanco, R. Puig de la Bellacasa, M.O. Rabal, X. Batllori, B. Clotet, I. Clotet-Codina, M. Armand-Ugón, J.A. Esté, J.I. Borrell, J. Teixidó; Discovery of novel non-cyclam polynitrogenated CXCR4 coreceptor inhibitors. *ChemMedChem* **2008**, 3, 1549-1557.

146. S. Pettersson; Diseño, selección y síntesis de nuevos inhibidores de entrada del VIH. Tesi Doctoral, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 2009.

147. S. Pettersson, L. Ros-Blanco, J. Teixidó, X. Batllori, R. Puig de la Bellacasa, J.I. Borrell, S. Nonell, M.O. Rabal, V.I. Pérez-Nueno, J.A. Esté, I. Clotet-Codina, M. Armand-Ugón; Novel polynitrogenated systems as anti-HIV agents. Patent WO2008049950 (A1), **2008.**

148. P. Victory, R. Nomen, O. Colomina, M. Garriga, A. Crespo; New synthesis of pyrido[2,3-*d*]pyrimidines. 1. Reaction of 6-alkoxy-5-cyano-3,4-dihydro-2-pyridones with guanidine and cyanamide. *Heterocycles* **1985**, 23, 1135-1141.

149. N. Mont, J. Teixidó, J.I. Borrell, C.O. Kappe; A three-component synthesis of pyrido[2,3-*d*]pyrimidines. *Tetrahedron Lett.* **2003**, 44, 5385-5387.

150. N. Mont, J. Teixidó, C.O. Kappe, J.I. Borrell; A one-pot microwave-assisted synthesis of pyrido[2,3-*d*]pyrimidines. *Mol.Divers.* **2003**, 7, 153-159.

151. N. Mont, L. Fernández-Megido, J. Teixidó, C.O. Kappe, J.I. Borrell; A diversity-oriented, microwave-assisted synthesis of 4-oxo and 4-chloropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones. *QSAR Comb.Sci.* **2004**, 23, 836-849.

152. X. Berzosa, X. Bellatriu, J. Teixidó, J.I. Borrell; An unusual Michael addition of 3,3-dimethoxypropanenitrile to 2-aryl acrylates: a convenient route to 4-unsubstituted 5,6-dihydropyrido[2,3-*d*]pyrimidines. *J.Org.Chem.* **2010**, 75, 487-490.

153. P. Victory, J.I. Borrell; 6-alkoxy-5-cyano-3,4-dihydro-2-pyridones as starting materials for the synthesis of heterocycles. *Trends Heterocyclic Chem.* **1993**, 3, 235-247.

154. J.I. Borrell, J. Teixidó, B. Martínez-Teipel, B. Serra, J.L. Matallana, M. Costa, X. Batllori; An unequivocal synthesis of 4-amino-1,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-2,7-diones and 2-amino-3,5,6,8-tetrahydropyrido[2,3-*d*]pyrimidine-4,7-diones. *Collect.Czech.Chem.Commun.* **1996**, 61, 901-909.

155. N. Mont; Diseño y síntesis combinatoria de estructuras heterocíclicas como inhibidores potenciales de tirosina quinasas. Tesi Doctoral, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 2005.

156. P. Victory, J.M. Jover, J. Sempere; Contribución a la síntesis de glutarimidas III. *Afinidad* **1981**, 38, 491-495.

157. G. Holan, R. Waiser; Preparation of alkyl 2-aryl acrylates. Patent EP0003670A1, **1979.**

158. P. Victory, R. Nomen, M. Garriga, X. Tomàs, L.G. Sabaté; Utilización del método simplex de optimización en la obtención de la 5-ciano-3-metil-6-metoxi-1,2,3,4-tetrahidropiridin-2-ona. *Afinidad* **1984**, 41, 241-243.

159. A. Crespo; Nueva síntesis de pirido[2,3-*d*]pirimidinas. III. Deshidrogenación del anillo dihidropiridónico. Tesi Doctoral, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 1988.

160. J.I. Borrell, J. Teixidó, J.L. Matallana, B. Martínez-Teipel, E. Couceiro; Selective reduction of the 7-oxo group in pyrido[2,3-*d*]pyrimidine-4,7-diones: a new synthetic approach to 5,10-dideazatetrahydrofolic acid (DDATHF). *Heterocycles* **2000**, 52, 1207-1214.

161. P. Victory, J. Diago; Contribución a la síntesis de glutarimidas II. *Afinidad* **1978**, 35, 161-165.

162. P. Victory, J.M. Jover, R. Nomen; Las 3-ciano-2-metoxi-2,3-dehidropiperidin-6-onas como productos de partida en síntesis. Síntesis de heterociclos I. *Afinidad* **1981**, 38, 497-500.

163. P. Victory, J. Diago; Contribution to the synthesis of glutarimides. *Afinidad* **1978**, 35, 154-158.

164. Scifinder Scholar, versió 2004; Chemical Abstracts Service: Columbus, EUA, 2004.

165. D.M. Tal, S.J.D. Karlish; Synthesis of a novel series of arylmethylisothiouronium derivatives. *Tetrahedron* **1995**, 51, 3823-3830.

166. H. Schnell, G. Buchwald, W. Daum, G. Hermann; Improvements in and relating to chlorobenzylisothiuronium chlorides and compositions containing them. Patent GB936766, **1963.**

167. R. Fusco; Method for the purification of sewage waters which contain organic compounds of an anionic character. Patent US4178242 (A), **1979.**

168. B.S. Jensen, S.P. Olesen, L. Teuber, D. Peters, D. Strobaek; Bis(benzimidazole) derivatives serving as potassium blocking agents. Patent US6194447 (B1), **2001.**

169. B.R. Linton, M.S. Goodman, E. Fan, S.A. van Arman, A.D. Hamilton; Thermodynamic aspects of dicarboxylate recognition by simple artificial receptors. *J.Org.Chem.* **2001**, 66, 7313-7319.

170. C.S. Hunneche, H.J. Petersen; Cyanoguanidines as cell proliferation inhibitors. Patent US6300345 (B1), **1998.**

171. T.P. Wunz, R.T. Dorr, D.S. Alberts, C.L. Tunget, J. Einspahr, S. Milton, W.A. Remers; New antitumor agents containing the antracene nucleus. *J.Med.Chem.* **1987**, 30, 1313-1321.

172. K. Licha, W. Wrasidlo; Neue Benzylguanidinderivative für die Therapie, in-vivo und in-vitro-Diagnostik. Patent DE19817517 (A1), **1999.**

173. J.L. Matallana; Síntesi i activitat biològica d'anàlegs 7-oxo substituïts de l'àcid 5,10-dideaza-5,6,7,8-tetrahidrofòlic (DDATHF). Tesi Doctoral, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 1993.

174. J.I. Borrell, J. Teixidó, J.L. Matallana, B. Martínez-Teipel, C. Colominas, M. Costa, M. Balcells, E. Schuler, M.J. Castillo; Synthesis and biological activity of 7-oxo substituted analogues of 5-deaza-5,6,7,8-tetrahydrofolic acid (5-DATHF) and 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF). *J.Med.Chem.* **2001**, 44, 2366-2369.

175. C.J.C. Connolly, J.M. Hamby, M.C. Schroeder, M. Barvian, G.H. Lu, R.L. Panek, A. Amar, C. Shen, A.J. Kraker, D.W. Fry, W.D. Klohs, A.M. Doherty; Discovery and structure-activity studies of a novel series of pyrido[2,3-*d*]pyrimidine tyrosine kinase inhibitors. *Bioorg.Med.Chem.Lett.* **1997**, 7, 2415-2420.

176. J.M. Hamby, C.J.C. Connolly, M.C. Schroeder, R.T. Winters, H.D.H. Showalter, R.L. Panek, T.C. Major, B. Olsewski, M.J. Ryan, T. Dahring, G.H. Lu, J. Keiser, A. Amar, C. Shen, A.J. Kraker, V. Slintak, J.M. Nelson, D.W. Fry, L. Bradford, H. Hallak, A.M. Doherty; Structure-Activity relationships for a novel series of pyrido[2,3-*d*]pyrimidine tyrosine kinase inhibitors. *J.Med.Chem.* **1997**, 40, 2296-2303.

177. A. Agarwal, P.M.S. Chauhan; Solid supported synthesis of structurally diverse dihydropyrido[2,3-*d*]pyrimidines using microwave irradiation. *Tetrahedron Lett.* **2005**, 46, 1345-1348.

178. V.V. Mulwad, R.B. Pawar; Synthesis of some antibacterial compounds from 4-hydroxycoumarin. *Indian J.Chem.* **2003**, 42B, 2091-2096.

179. M.C. Parlato, C. Mugnaini, M.L. Renzulli, F. Corelli, M. Botta; Solid phase synthesis of 5,6-disubstituted pyrimidinone and pyrimidindione derivatives. *Arkivoc* **2004**, 5, 349-363.

180. C. Guérémy, F. Audiau, A. Uzan, G. Le Fur, J. Léger, A. Carpy; 2-amino-6-chloro-4-(*N*-methylpiperazino)pyrimidines, inhibitors of spiroperidol binding. *J.Med.Chem.* **1982**, 25, 1459-1465.

181. M. Feld; Process for the preparation of sodium thiobarbiturate. Patent US5274093 (A), **1993.**

182. P. Victory, M. Garriga; Cyclization of dinitriles by hydrogen halides. I: Hydrogen bromide. The temperature as a novel determining factor of the direction of cyclization. *Heterocycles* **1985**, 23, 1947-1950.

183. M. Garriga; Nueva síntesis de pirido[2,3-*d*]pirimidinas. II. Ciclación de dinitrilos con halogenuros de hidrógeno. Tesi Doctoral, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 1987.

184. P. Victory, A. Crespo, M. Garriga, R. Nomen; New synthesis of pyrido[2,3-*d*]pyrimidines. III. Nucleophilic substitution on 4-amino-2-halo and 2-amino-4-halo-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones. *J.Heterocyclic Chem.* **1988**, 25, 245-247.

185. P. Victory, M. Garriga; Cyclation of dinitriles by hydrogen halides. 2. Hydrogen chloride and hydrogen iodide. *Heterocycles* **1985**, 23, 2853-2858.

186. P. Victory, M. Garriga; Cyclation of dinitriles by hydrogen halides. 3. The influence of tautomerism. *Heterocycles* **1986**, 24, 3053-3058.

187. V.I. Pérez-Nueno, S. Pettersson, D.W. Ritchie; Discovery of novel HIV entry inhibitors for the CXCR4 receptor by prospective virtual screening. *J.Chem.Inf.Model.* **2009**, 49, 810-823.

188. P. Gund; Three-dimensional pharmacophore pattern searching, *Progress in molecular and subcellular biology,* Springer-Verlag: Berlin, 1977.

189. P. Ehrlich; Über den jetzigen Stand der Chemotherapie. *Ber.Dtsch.Chem.Ges.* **1909**, 42, 17-47.

190. L.B. Kier; *Molecular orbital theory in drug research,* 1a ed. Academic Press: New York, 1971.

191. J.H. van Drie; Monty Kier and the origin of the pharmacophore concept. *Internet Electron.J.Mol.Des.* **2007**, 6, 271-279.

192. MOE (Molecular Operating Environment), versió 2006.08; Chemical Computing Group, Inc: Montreal, Canadà, 2004.

193. V.I. Pérez-Nueno, D.W. Ritchie, O. Rabal, R. Pascual, J.I. Borrell, J. Teixidó; Comparison of ligand-based and receptor-based virtual screening of HIV entry inhibitors for the CXCR4 and CCR5 receptors using 3D ligand shape matching and ligand-receptor docking. *J.Chem.Inf.Model.* **2008**, 48, 509-533.

194. M.S. Gibson, R.W. Bradshaw; The Gabriel synthesis of primary amines. *Angew.Chem.Int.Ed.* **1968**, 7, 919-939.

195. N. Ljungdahl, L. Martikainen, N. Kann; Rapid microwave-assisted preparation of amino-functionalized polymers. *Tetrahedron Lett.* **2008**, 49, 6108-6110.

196. Scifinder Scholar, versió 2007; Chemical Abstracts Service: Columbus, EUA, 2007.

197. J. Apelt, X. Ligneau, H.H. Pertz, J. Arrang, C.R. Ganellin, J. Schwartz, W. Schunack, H. Stark; Development of a new class of nonimidazole histamine H_3 receptor ligands with combined inhibitory histamine *N*-methyltransferase activity. *J.Med.Chem.* **2002**, 45, 1128-1141.

198. M.N. Jo, H.J. Seo, Y. Kim, S.H. Seo, H. Rhim, Y.S. Cho, J.H. Cha, H.Y. Koh, H. Choo, A.N. Pae; Novel T-type calcium channel blockers: dioxoquinazoline carboxamide derivatives. *Bioorg.Med.Chem.* **2007**, 15, 365-373.

199. A. Kamal, A.H. Babu, A.V. Ramana, R. Sinha, J.S. Yadav, S.K. Arora; Antitubercular agents. Part 1: Synthesis of phthalimido- and naphthalimido-linked phenazines as new prototype antitubercular agents. *Bioorg.Med.Chem.Lett.* **2005**, 15, 1923-1926.

200. A. Kamal, A.A. Shaik, R. Sinha, J.S. Yadav, S.K. Arora; Antitubercular agents. Part 2: New thiolactomycin analogues active against *Mycobacterium tuberculosis*. *Bioorg.Med.Chem.Lett.* **2005**, 15, 1927-1929.

201. P.T. Anastas, J.C. Warner; *Green Chemistry: Theory and Practice,* 1a ed. Oxford University Press: New York, 1998.

202. M. Amon, X. Ligneau, J. Schwartz, H. Stark; Fluorescent non-imidazole histamine H_3 receptor ligands with nanomolar affinities. *Bioorg.Med.Chem.Lett.* **2006**, 16, 1938-1940.

203. T.Q. Pham, I. Greguric, X. Liu, P. Berghofer, P. Ballantyne, J. Chapman, F. Mattner, B. Dikic, T. Jackson, C. Loc'h, A. Katsifis; Synthesis and evaluation of novel radioiodinated benzamides for malignant melanoma. *J.Med.Chem.* **2007**, 50, 3561-3572.

204. S.N. Haydar, C. Ghiron, M. Valacchi, U. Zanelli; Alpha7 nicotinic acetylcholine receptor inhibitors. Patent US0016360A1, **2010.**

205. R.H. Mach, Y. Huang, R.A. Freeman, L. Wu, S. Vangveravong, R.R. Luedtke; Conformationally-flexible benzamide analogues as dopamine D_3 and sigma$_2$ receptor ligands. *Bioorg.Med.Chem.Lett.* **2004**, 14, 195-202.

206. J. Contreras, Y.M. Rival, S. Chayer, J. Bourguignon, C.G. Wermuth; Aminopyridazines as acetylcholinesterase inhibitors. *J.Med.Chem.* **1999**, 42, 730-741.

207. C.F. Lane; Sodium cyanoborohydride, a highly selective reducing agent for organic functional groups. *Synthesis* **1975**, 1975, 135-146.

208. R.F. Borch; Nitrilium salts. New method for the synthesis of secondary amines. *J.Org.Chem.* **1969**, 34, 627-629.

209. J. March, M.B. Smith; *Advanced Organic Chemistry,* 5a ed. Wiley-Interscience: New York, 2001.

210. S. Sato, T. Sakamoto, E. Miyazawa, Y. Kikugawa; One-pot reductive amination of aldehydes and ketones with a-picoline borane in methanol, in water and in neat conditions. *Tetrahedron* **2004**, 60, 7899-7906.

211. H. Sajiki, T. Ikawa, K. Hirota; Reductive and catalytic monoalkylation of primary amines using nitriles as an alkylating reagent. *Org.Lett.* **2004**, 6, 4977-4980.

212. K.A. Neidigh, M.A. Avery, J.S. Williamson, S. Bhattacharyya; Facile preparation of *N*-methyl secondary amines by titanium(IV) isopropoxide-mediated reductive amination of carbonyl compounds. *J.Chem.Soc. Perkin Trans.1* **1998**, 1998, 2527-2531.

213. C.O. Kappe; Controlled microwave heating in modern organic synthesis. *Angew.Chem.Int.Ed.* **2004**, 43, 6250-6284.

214. S. Bhattacharyya; Reductive alkylation of dimethylamine using titanium(IV) isopropoxide and sodium borohydride: an efficient, safe, and convenient method for the syntesis of *N*,*N*-dimethylated tertiary amines. *J.Org.Chem.* **1995**, 60, 4928-4929.

215. Y. Chi, Y. Zhou, X. Zhang; Highly enantioselective reductive amination of simple aryl ketones catalyzed by Ir-f-binaphane in the presence of titanium(IV) isopropoxide and iodine. *J.Org.Chem.* **2003**, 68, 4120-4122.

216. S. Bhattacharyya; Titanium(IV) isopropoxide and sodium borohydride: a reagent of choice for reductive amination. *Tetrahedron Lett.* **1994**, 35, 2401-2404.

217. H. Takahashi, T. Tsubuki, K. Higashiyama; A new method for the synthesis of a-substituted phenethylamines via titanium amide complexes. *Synthesis* **1988**, 1988, 238-240.

218. E.J. Ariëns; Stereochemistry, a basis for sophisticated nonsense in pharmacokinetics and clinical pharmacology. *Eur.J.Clin.Pharmacol.* **1984**, 26, 663-668.

219. A.K. Peepliwal, S.B. Bagade, C.G. Bonde; Stereochemical consideration and eudismic ration in chiral drug development. *J.Biomed.Sci and Res.* **2010**, 2, 29-45.

220. H. Kubinyi; In search for new leads. *EFMC Yearbook* **2003**.

221. H. Kubinyi; In search of new leads. *Industrial Pharmacy* **2004**, 2004, 7-10.

222. I. Agranat, H. Caner, J. Caldwell; Putting chirality to work: the strategy of chiral switches. *Nature Reviews* **2002**, 1, 753-768.

223. H. Caner, E. Groner, L. Levy, I. Agranat; Trends in the development of chiral drugs. *Drug Discovery Today* **2004**, 9, 105-110.

224. R. Shimazawa, N. Nagai, S. Toyoshima, H. Okuda; Present state of new chiral drug development and review in Japan. *J.Health Sci.* **2008**, 54, 23-29.

225. M.C. Nunez, M.E. Garcia-Rubino, A. Conejo-Garcia, O. Cruz-Lopez, M. Kimatrai, M.A. Gallo, A. Espinosa, J.M. Campos; Homochiral drugs: a demanding tendency of the pharmaceutical industry. *Curr.Med.Chem.* **2009**, 16, 2064-2074.

226. EMEA; Investigation of chiral active substances. *Eur.J.Med.Res.* **1993**.

227. C. Chen, W. Shieh, P. Lu, S. Harriman, C. Chen; Metabolic stereoisomeric inversion of ibuprofen in mammals. *BBA - Protein Struct.M.* **1991**, 1078, 411-417.

228. D. Doller, R. Davies, S. Chackalamannil; A practical preparation of (*R*)- and (*S*)-*N*-Boc-2-methylpiperidines. *Tetrahedron-Asymmetr.* **1997**, 8, 1275-1278.

229. Scifinder web version, versió web; Chemical Abstracts Service: Columbus, EUA, 2008.

230. M. Kawaguchi, O. Hayashi, N. Sakai, M. Hamada, Y. Yamamoto; An asymmetric synthesis of 2-substituted piperidines through ozonolisis of cyclopentenes and reductive aminocyclization. *Agric.Biol.Chem.* **1986**, 50, 3107-3112.

231. T. Mosmann; Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J.Immunol.Methods* **1983**, 65, 55-63.

232. I. Clotet-Codina; Determinació de l'activitat antiviral de nous compostos inhibidors del VIH-1. Tesi Doctoral, Universitat Autònoma de Barcelona. Badalona, 2007.

233. Genzyme; Mozobil (plerixafor), medicamento de Genzyme, constituye la mayor novedad en este campo en los últimos diez años. *Genzyme* **2010**.

234. F. Balkwill; Cancer and the chemokine network. *Nature Rev. Cancer* **2004**, 4, 540-550.

235. T.E. Allsopp, M.E. Bunnage, P.V. Fish; Small molecule modulation of stem cells in regenerative medicine: recent applications and future direction. *Med.Chem.Commun.* **2010**, 1, 16-29.

236. Y.M. Li, Y. Pan, Y. Wei, X. Cheng, B.P. Zhou, M. Tan, X. Zhou, W. Xia, G.N. Hortobagyi, D. Yu, M. Hung; Upregulation of CXCR4 is essential for HER2-mediated tumor metastasis. *Cancer Cell* **2004**, 6, 459-469.

237. Z. Liang, Y. Yoon, J. Votaw, M.M. Goodman, L. Williams, H. Shim; Silencing of CXCR4 blocks breast cancer metastasis. *Cancer Res.* **2005**, 65, 967-971.

238. Z. Liang, T. Wu, H. Lou, X. Yu, R.S. Taichman, S.K. Lau, S. Nie, J. Umbreit, H. Shim; Inhibition of breast cancer metastasis by selective synthetic polypeptide against CXCR4. *Cancer Res.* **2004**, 64, 4302-4308.

239. M. Darash-Yahana, E. Pikarsky, R. Abramovitch, E. Zeira, B. Pal, R. Karplus, K. Beider, S. Avniel, S. Kasem, E. Galun, A. Peled; Role of high expression levels of CXCR4 in tumor growth, vascularization, and metastasis. *The FASEB Journal* **2004**, doi: 10.1096/fj.03-0935fje.

240. D.J. Newman, G.M. Cragg; Natural products as sources of new drugs over the last 25 years. *J.Nat.Prod.* **2007**, 70, 461-477.

241. A.C. Anderson; The process of structure-based drug design. *Chem.Biol.* **2003**, 10, 787-797.

242. Research Collaboratory for Structural Bioinformatics; RCSB Protein Data Bank: *http://www.rcsb.org/pdb/home/home.do*. Consulta: 29/1/2011.

243. E. Pebay-Peyroula, G. Rummel, J.P. Rosenbusch, E.M. Landau; X-ray structure of bacteriorhodopsin at 2.5 angstroms form microcrystals grown in lipidic cubic phases. *Science* **1997**, 277, 1676-1681.

244. M. Congreve, F. Marshall; The impact of GPCR structures on pharmacology and structure-based drug design. *British Journal of Pharmacology* **2010**, 159, 986-996.

245. A. Carrieri, V.I. Pérez-Nueno, A. Fano, C. Pistone, D.W. Ritchie, J. Teixidó; Biological profiling of anti-HIV agents and insight into CCR5 antagonist binding using in silico techniques. *ChemMedChem* **2009**, 4, 1153-1163.

246. V.I. Pérez-Nueno, D.W. Ritchie, J.I. Borrell, J. Teixidó; Clustering and classifying diverse HIV entry inhibitors using a novel consensus shape-based virtual sreening approach: further evidence for multiple binding sites within the CCR5 extracellular pocket. *J.Chem.Inf.Model.* **2008**, 48, 2146-2165.

247. C. Lipinski, A. Hopkins; Navigating chemical space for biology and medicine. *Nature* **2004**, 432, 855-861.

248. A. Schüller, M. Suhartono, U. Fechner, Y. Tanrikulu, S. Breitung, U. Scheffer, M.W. Göbel, G. Schneider; The concept of template-based de novo design from drug-derived molecular fragments and its application to TAR RNA. *J.Comput.Aided Mol.Des.* **2008**, 2008, 59-68.

249. Cerius2, Accelrys Inc.: 2001.

250. R.W. DeSimone, K.S. Currie, S.A. Mitchell, J.W. Darrow, D.A. Pippin; Privileged structures: applications in drug discovery. *Comb.Chem.Hig Throughput Screen.* **2004**, 7, 473-494.

251. M.E. Welsch, S.A. Snyder, B.R. Stockwell; Privileged scaffolds for library design and drug discovery. *Curr.Opin.Chem.Biol.* **2010**, 14, 347-361.

252. J. Lehuédé, J. Vierfond, M. Miocque; Aminométhylation de l'homoacridane, de l'iminodibenzyle et de l'iminostilbène. *B.Soc.Chim.Fr.* **1981**, 5-6, 185-191.

253. A. Hallberg, D. Deardorf, A. Martin; A modified Bischler synthesis of some tetracyclic indole derivatives. *Heterocycles* **1982**, 19, 75-82.

254. M. Salas, J.A. Joule; Cyclic allylamine-enamine systems. Part 9. Further isomerisations using tris(triphenylphosphine)rhodium(I) chloride and their synthetic utility. *J.Chem.Research Synopses* **1990,** 98.

255. A.R. Katritzky, K. Akutagawa; Activation of the 2-alkyl group of a 2-alkylindole toward proton loss and subsequent electrophilic substitution. *J.Am.Chem.Soc.* **1986**, 1986, 6808-6809.

256. B. Mohan, D. Nagarathnam, M. Vedachalam, P.C. Srinivasan; Synthesis of 2-(2-arylethyl)-indoles. *Synthesis* **1985**, 1985, 188-190.

257. M. Vedachalam, B. Mohan, P.C. Srinivasan; A facile preparation of 2-alkylindoles potential intermediates for alkaloids. *Tetrahedron Lett.* **1983**, 24, 3531-3532.

258. D. Nagarathnam, M. Vedachalam, P.C. Srinivasan; 1-Benzenesulfonyl-2-bromomethyl-3-phenylthioindole as a synthon for 2-substituted indoles: a new synthesis of 2-aminomethylindoles. *Synthesis* **1983**, 1983, 156-157.

259. D. Nagarathnam, P.C. Srinivasan; A convenient synthesis of 2-(2-arylethyl)-3-ethoxycarbonyl-5-methoxyindoles via the Wittig-Horner reaction. *Synthesis* **1982**, 1982, 926-927.

260. M.L. Verdonk, J.C. Cole, M.J. Hartshorn, C.W. Murray, R.D. Taylor; Improved protein-ligand docking using GOLD. *Proteins Struct.Funct.Genet.* **2003**, 52, 609-623.

261. D.W. Ritchie, G.J.L. Kemp; Protein docking using spherical polar Fourier correlations. *Proteins Struct.Funct.Genet.* **2000**, 39, 178-194.

262. QikProp, versió 2.3; Schrödinger, Inc: New York, EUA, 2005.

263. QikSim, versió 2.3; Schrödinger, Inc: New York, EUA, 2005.

264. T.T. Tanimoto; An elementary mathematical theory of classification and prediction. *IBM International Report* **1958**.

265. P.M. O'Neill, A. Mukhtar, P.A. Stocks, L.E. Randle, S. Hindley, S.A. Ward, R.C. Storr, J.F. Bickley, I.A. O'Neil, J.L. Maggs, R.H. Hughes, P.A. Winstanley, P.G. Bray, B.K. Park; Isoquine and related amodiaquine analogues: a new generation of improved 4-aminoquinoline antimalarials. *J.Med.Chem.* **2003**, 46, 4933-4945.

266. I.N. Nazarov, A.V. Semenovsky; Mechanism of halomethylation. *Russian Chemical Bulletin* **1957**, 6, 997-999.

267. R.N. Salvatore, C.H. Yoon, K.W. Jung; Synthesis of secondary amines. *Tetrahedron* **2001**, 57, 7785-7811.

268. C. Chen, C.H. Senanayake, T.J. Bill, R.D. Larsen, T.R. Verhoeven, P.J. Reider; Improved Fischer indole reaction for the preparation of *N*,*N*-dimethyltryptamines: synthesis of L-695,894, a Potent 5-HT_{1D} receptor antagonist. *J.Org.Chem.* **1994**, 59, 3738-3741.

269. R. Mahesh, R. Venkatesha Perumal, P.V. Pandi; Microwave-assisted solvent-free synthesis of 3-[(4-substituted piperazin-1-yl)alkyl] imidazo[2,1-*b*][1,3]benzothiazol-2(3*H*)-ones as serotonin$_3$ (5-HT_3) receptor antagonists. *Pharmazie* **2005**, 60, 411-414.

270. J.P. Gilday, M.J. Welham; A process of manufacturing gefitinib via rearrangement of iminoquinazoline derivative. Patent WO2005023783, **2005.**

271. J.P. Gilday, D. Moody; Preparation of 4-(3'-chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline. Patent WO2004024703, **2004.**

272. R.M. Pulla, C.N. Venkaiah; Process for the preparation of 4-(*N*,*N*-disubstituted-amino)butyraldehyde acetals via the Grignard reaction of 3-(*N*,*N*-disubstituted-amino)propylmagnesium halides with orthoformate triesters. Patent WO2003101931, **2003.**

273. H.L. Yale; 3-chloro-10-(dialkylaminoalkyl)phenothiazines. *J.Am.Chem.Soc.* **1955**, 77, 2270-2272.

274. L. Santana, E. Uriarte, Y. Fall, M. Teijeira, C. Terán, E. García-Martínez, B. Tolf; Synthesis and structure-activity relationships of new arylpiperazines: *para* substitution with electron-withdrawing groups decrease binding to 5-HT_{1A} and D_{2A} receptors. *Eur.J.Med.Chem.* **2002**, 37, 503-510.

275. B.S. Polanskyj, J.M. Solomon, D.R. Chisholm, B.R. Bluestein; Procédé continu de fabrication d'amines à longue chaîne. Patent FR2103968, **1972.**

276. R. Widder, F. Reicheneder; *N*-substituted *p*-xylylenediamines. Patent DE1808789, **1970.**

277. K.P. Boegesoe, J. Arnt, V. Boeck, A.V. Christensen, J. Hyttel, K.G. Jensen; Antihypertensive activity in a series of 1-piperazino-3-phenylindans with potent 5-HT2-antagonistic activity. *J.Med.Chem.* **1988**, 31, 2247-2256.

278. F. Cardullo, D. Donati, V. Fusillo, G. Merlo, A. Paio, M. Salaris, A. Solinas, M. Taddei; Parallel protocol for the selective methylation and alkylation of primary amines. *J.Comb.Chem.* **2006**, 8, 834-840.

279. C. Chiappe, D. Pieraccini; Direct mono-N-alkylation of amines in ionic liquids: chemoselectivity and reactivity. *Green Chem.* **2003**, 5, 193-197.

280. C.B. Singh, V. Kavala, A.K. Samal, B.K. Patel; Aqueous-mediated *N*-alkylation of amines. *Eur.J.Org.Chem.* **2007**, 2007, 1369-1377.

281. J.L. Romera, J.M. Cid, A.A. Trabanco; Potassium iodide catalysed monoalkylation of anilines under microwave irradiation. *Tetrahedron Lett.* **2004**, 45, 8797-8800.

282. B. Blank, S. Michlik, R. Kempe; Selective Iridium-catalyzed alkylation of (hetero)aromatic amines and diamines with alcohols under mild reaction conditions. *Chem.Eur.J.* **2009**, 15, 3790-3799.

283. R.N. Salvatore, A.S. Nagle, K.W. Jung; Cesium effect: high chemoselectitity in direct *N*-alkylation of amines. *J.Org.Chem.* **2002**, 67, 674-683.

284. R.N. Salvatore, A.S. Nagle, S.E. Schmidt, K.W. Jung; Cesium hydroxide promoted chemoselective *N*-alkylation for the generally efficient synthesis of secondary amines. *Org.Lett.* **1999**, 1, 1893-1896.

285. T. Gunnlaugsson, D.F. Brougham, A. Fanning, M. Nieuwenhuyzen, J.E. O'Brien, R. Viguier; Effect on pKa of metal-bound water molecules in lanthanide ion-induced cyclen "cavities". *Org.Lett.* **2004**, 6, 4805-4808.

286. H.E. Zimmerman, O.D. Mitkin; Conical intersection control of heterocyclic photochemical bond scission. *J.Am.Chem.Soc.* **2006**, 128, 12743-12749.

287. R.N. Misra, H. Xiao, K.S. Kim, S. Lu, W. Han, S.A. Barbosa, J.T. Hunt, D.B. Rawlins, W. Shan, S.Z. Ahmed, L. Qian, B. Chen, R. Zhao, M.S. Bednarz, K.A. Kellar, J.G. Mulheron, R. Batorsky, U. Roongta, A. Kamath, P. Marathe, S.A. Ranadive, J.S. Sack, J.S. Tokarski, N.P. Pavletich, F.Y.F. Lee, K.R. Webster, S.D. Kimball; *N*-(cycloalkylamino)acyl-2-aminothiazole inhibitors of cyclin-dependent kinase 2. *N*-[5-[[[5-(1,1-Dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (BMS-387032), a highly efficacious and selective antitumor agent. *J.Med.Chem.* **2004**, 47, 1719-1728.

288. V. Vecchietti, G.D. Clarke, R. Colle, G. Giardina, G. Petrone, M. Sbacchi; (1*S*)-1-(aminomethyl)-2-(arylacetyl)-1,2,3,4-tetrahydroisoquinoline and heterocycle-condensed tetrahydropyridine derivatives: members of a novel class of very potent k opioid analgesics. *J.Med.Chem.* **1991**, 34, 2624-2633.

289. K.M. Boy, J.M. Guernon, S. Sit, K. Xie, P. Hewawasam, C.G. Boissard, S.I. Dworetzky, J. Natale, V.K. Gribkoff, N. Lodge, J.E.J. Starrett; 3-thio-quinolinone maxi-K openers for the treatment of erectile dysfunction. *Bioorg.Med.Chem.Lett.* **2004**, 14, 5089-5093.

290. J.L. Romine, S.W. Martin, N.A. Meanwell, V.K. Gribkoff, C.G. Boissard, S.I. Dworetzky, J. Natale, S. Moon, A. Ortiz, S. Yeleswaram, L. Pajor, Q. Gao, J.E.J. Starrett; 3-[(5-Chloro-2-hydroxyphenyl)methyl]-5-[4-(trifluoromethyl)phenyl]-1,3,4-oxadiazol-2(3*H*)-one, BMS-191011: opener of large-conductance Ca^{2+}-activated potassium (Maxi-K) channels, identification, solubility, and SAR. *J.Med.Chem.* **2007**, 50, 528-542.

291. H. Jary, T. Temal, P. Deprez; Nouveaux derivés de l'ureée substituée par un thiazole ou benzothiazole, leur procédé de préparation, leur application a titre de medicaments, les compositions pharmaceutiques les renfermant et utilisation. Patent FR2885129, **2006.**

292. T. Mtro, D. Gomez Pardo, J. Cossy; Syntheses of (*S*,*S*)-reboxetine via a catalytic stereospecific rearrangement of ß-amino alcohols. *J.Org.Chem.* **2008**, 73, 707-710.

293. C. Zhi, Z. Long, A. Manikowski, N.C. Brown, P.M. Tarantino, K. Holm, E.J. Dix, G.E. Wright, K.A. Foster, M.M. Butler, W.A. LaMarr, D.J. Skow, I. Motorina, S. Lamothe, R. Storer; Synthesis and

antibacterial activity of 3-substituted-6-(3-ethyl-4-methylanilino)uracils. *J.Med.Chem.* **2005**, 48, 7063-7074.

294. E. Brenner, R.M. Baldwin, G. Tamagnan; Asymmetric synthesis of (+)-(*S*,*S*)-reboxetine via a new (*S*)-2-(hydroxymethyl)morpholine preparation. *Org.Lett.* **2005**, 7, 937-939.

295. K. Sénéchal-David, J.P. Leonard, S.E. Plush, T. Gunnlaugsson; Supramolecular self-assembly of mixed f-d metal ion conjugates. *Org.Lett.* **2006**, 8, 2727-2730.

296. M. Oklobdzija, G. Comisso, E. Decorte, T. Kovac, C. Angeli, F. Moimas, P. Zanon, F. Zonno, R. Toso, V. Sunjie; Attempts at new synthesis of 5,11-dihydro-6*H*-pyrido[2,3-*b*][1,4]dibenzodiazepin-6-one. *J.Heterocyclic Chem.* **1983**, 20, 1335-1338.

297. D.L. Ladd, J. Weinstock, M. Wise, G.W. Gessner, J.L. Sawyer, K.E. Flaim; Synthesis and dopaminergic binding of 2-aryldopamine analogs: phenethylamines, 3-benzazepines and 9-(aminomethyl)fluorenes. *J.Med.Chem.* **1986**, 29, 1904-1912.

298. R. Sívek, O. Pytela, F. Bures; Design and synthesis of optically active 2-phenylimidazolecarboxamides featuring aminoacid motive. *J.Heterocyclic Chem.* **2008**, 45, 1621-1627.

299. I. Grig-Alexa, A. Finaru, L. Ivan, P. Caubère, G. Guillaumet; Efficient synthesis of 3-bromo-2-[(N-substituted)amino]pyridines and their hetarynic cyclization. *Synthesis* **2006**, 2006, 619-628.

300. J.E. Nordlander, M.J. Payne, M.A. Balk, J.L. Gress, F.D. Harris, J.S. Lane, R.F. Lewe, S.E. Marshall, D. Nagy, D.J. Rachlin; General method for the synthesis of selectively *N*-alkylated polyamines. *J.Org.Chem.* **1984**, 49, 133-138.

301. B.S. Jursic, Z. Zdravkovski; A simple preparation of amides from acids and amines by heating of their mixture. *Synth.Commun.* **1993**, 23, 2761-2770.

302. L. Zhang, X. Wang, J. Wang, N. Grinberg, D. Krishnamurthy, C.H. Senanayake; An improved method of amide synthesis using acyl chlorides. *Tetrahedron Lett.* **2009**, 50, 2964-2966.

303. T. Asaba, T. Suzuki, R. Ueda, H. Tsumoto, H. Nakagawa, N. Miyata; Inhibition of human sirtuins by in situ generation of an acetylated lysine-ADP-ribose conjugate. *J.Am.Chem.Soc.* **2009**, 131, 6989-6996.

304. T.N. Lokhande, C.L. Viswanathan, A. Joshi, A. Juvekar; Design, synthesis and evaluation of naphthalene-2-carboxamides as reversal agents in MDR cancer. *Bioorg.Med.Chem.* **2006**, 14, 6022-6026.

305. C.A.G.N. Montalbetti, V. Falque; Amide bond formation and peptide coupling. *Tetrahedron* **2005**, 61, 10827-10852.

306. E. Valeur, M. Bradley; Amide bond formation: beyond the myth of coupling reagents. *Chem.Soc.Rev.* **2009**, 38, 606-631.

307. A.I. Vogel; *Textbook of practical organic chemistry,* 1989.

308. C. Schotten; Ueber die Oxydation des Piperidins. *Ber.Dtsch.Chem.Ges.* **1884**, 17, 2544-2547.

309. E. Baumann; Ueber eine einfache Methode der Darstellung von Benzoësäureäthern. *Ber.Dtsch.Chem.Ges.* **1886**, 19, 3218-3222.

310. S. Villa Gonzalez, P. Carlsen; Tartaric acid amides by the Gabriel route. *Eur.J.Org.Chem.* **2007**, 2007, 3495-3502.

311. J.R. Vaughan, R.L. Osato; The preparation of peptides using mixed carbonic-carboxylic acid anhydrides. *J.Am.Chem.Soc.* **1952**, 74, 676-678.

312. L. Routaboul, N. Vanthuyne, S. Gastaldi, G. Gil, M. Bertrand; Highly efficient photochemically induced thiyl radical-mediated racemization of aliphatic amines at 30 ºC. *J.Org.Chem.* **2008**, 73, 364-368.

313. A. Barge, L. Tei, D. Upadhyaya, F. Fedeli, L. Beltrami, R. Stefanìa, S. Aime, G. Cravotto; Bifunctional ligands based on the DOTA-monoamide cage. *Org.Biomol.Chem.* **2008**, 6, 1176-1184.

314. N.B. Cech, C.G. Enke; Practical implications of some recent studies in electrospray ionization fundamentals. *Mass Spectrom.Rev.* **2001**, 20, 363-387.

315. J.I. Luengo, A.T. Price, A. Shaw, K. Wiggall; CXCR4 Receptor antagonists - Thrombopoietin mimetics. Patent WO00/66112, **2000.**

316. X. Sheng, L. Meng, J. Zhu; Preparation of 99Tcm-labeled dopamine D2 receptor imaging agent m-Br-p-EBZM. *Hejishu* **2006**, 29, 358-361.

317. G. Cravotto, P. CIntas; The combined use of microwaves and ultrasound: improved tools in process chemistry and organic synthesis. *Chem.Eur.J.* **2007**, 13, 1902-1909.

318. J. Zabicky; *The chemistry of amides,* 1a ed. Interscience: New York, 1970.

319. H.C. Brown, P. Heim; Selective reductions. 18. Fast reaction of primary, secondary and tertiary amides with diborane. Simple, convenient procedure for the conversion of amides to the corresponding amines. *J.Org.Chem.* **1973**, 38, 912-916.

320. B. Martínez-Teipel; Síntesis y actividad biológica de análogos del ácido 5,10-dideaza-5,6,7,8-tetrahidrofólico (DDATHF). Tesi Doctoral, Escola Tècnica Superior IQS, Universitat Ramon Llull. Barcelona, 1997.

321. J.V. Paukstelis, M. Kim; *N*-acyl-*N*,*N*,*N*-trialkylammonium fluoroborates. Synthesis and reactions. *J.Org.Chem.* **1974**, 39, 1503-1507.

322. P.K. Patra, K. Nishide, K. Fuji, M. Node; Dod-S-Me and methyl 6-morpholinohexyl sulfide (MMS) as new odorless dorane carriers. *Synthesis* **2004**, 50, 1003-1006.

323. H.C. Brown, Y.M. Choi, S. Narasimhan; Selective Reductions. 29. A simple technique to achieve an enhanced rate of reduction of representative organic compounds by borane-dimethyl sulfide. *J.Org.Chem.* **1982**, 47, 3153-3163.

324. T. Pirali, G. Callipari, E. Ercolano, A.A. Genazzani, G.B. Giovenzana, G.C. Tron; A concise entry into nonsymmetrical alkyl polyamines. *Org.Lett.* **2008**, 10, 4199-4202.

325. D.E. Frantz, D.G. Weaver, J.P. Carey, M.H. Kress, U.H. Dolling; Practical synthesis of aryl triflates under aqueous conditions. *Org.Lett.* **2002**, 4, 4717-4718.

326. K.S. Bhandari, J.A. Eenkhoorn, A. Wu, V. Snieckus; Photocyclization of 2-indolylalkyl N-chloroacetamides. *Synth.Commun.* **1975**, 5, 79-86.

327. A.I.D. Alanine, C.W.G. Fishwick, C.J. Szantay; Facile preparation of 2-imino tetrahydrofurans, pyrans and oxepans. *Tetrahedron Lett.* **1989**, 30, 6571-6572.

328. C.J.M. Stirling; Intramolecular reactions of amides. Part II. Cyclisation of amides of w-bromocarboxylic acids. *J.Chem.Soc.* **1960,** 255-262.

329. A. Wilk, M.K. Chmielewski, A. Grajkowski, L.R. Phillips, S.L. Beaucage; The 3-(*N*-tert-butylcarboxamido)-1-propyl group as an attractive phosphate/thiophosphate protecting group for solid-phase oligodoxyribonucleotide synthesis. *J.Org.Chem.* **2002**, 67, 6430-6438.

330. A. Fukuzawa, H. Sato, T. Masamune; Synthesis of (±)-prepinnaterpene, a bromoditerpene from the red alga *laurencia pinnata* yamada. *Tetrahedron Lett.* **1987**, 28, 4303-4306.

331. J. Zakrzewski, J. Grodner, J.M. Bobbitt, M. Karpinska; Oxidation of unsaturated primary alcohols and w-haloalkanols with 4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate. *Synthesis* **2007**, 2007, 2491-2494.

332. C. Meyer, I. Marek, G. Courtemanche, J. Normant; Intramolecular carbometallation of organozinc reagents. *Tetrahedron* **1994**, 50, 11665-11692.

333. G. Glaros; The oxidation of primary alcohols to aldehydes with pyridinium chlorochromate. *J.Chem.Ed.* **1978**, 55, 410-410.

334. M. Vuagnoux-d'Augustin, A. Alexakis; Copper-catalyzed asymmetric conjugate addition of trialkylaluminium reagents to trisubstituted enones: construction of chiral quaternary centers. *Chem.Eur.J.* **2007**, 13, 9647-9662.

335. L. Crombie, D. Fisher; Synthons for general routes to natural insecticidal lipid isobutylamides. *Tetrahedron Lett.* **1985**, 26, 2477-2480.

336. S. Ohsugi, K. Nishide, K. Oono, K. Okuyama, M. Mudesaka, S. Kodama, M. Node; New odorless method for the Corey-Kim and Swern oxidations utilizing dodecyl methyl sulfide (Dod-S-Me). *Tetrahedron* **2003**, 59, 8393-8398.

337. J. Einhorn, C. Einhorn, F. Ratajczak, J. Pierre; Efficient and highly selective oxidation of primary alcohols to aldehydes by *N*-chlorosuccinimide mediated by oxoammonium salts. *J.Org.Chem.* **1996**, 61, 7452-7454.

338. S.D. Meyer, S.L. Schreiber; Acceleration of the Dess-Martin oxidation by water. *J.Org.Chem.* **1994**, 59, 7549-7552.

339. J.S. Yadav, B.V.S. Reddy, A.K. Basak, A.V. Narsaiah; Recyclable 2nd generation ionic liquids as green solvents for the oxidation of alcohols with hypervalent iodine reagents. *Tetrahedron* **2004**, 60, 2131-2135.

340. S. Velusamy, A. Srinivasan, T. Punniyamurthy; Copper(II) catalyzed selective oxidation of primary alcohols to aldehydes with atmospheric oxygen. *Tetrahedron Lett.* **2006**, 47, 923-926.

341. M. Leopoldo, F. Berardi, N.A. Colabufo, M. Contino, E. Lacivita, M. Niso, R. Perrone, V. Tortorella; Structure-affinity relationship study on *N*-(1,2,3,4-tetrahydronaphthalen-1-yl)-4-aryl-1-piperazinealkylamides, a new class of 5-hydroxytryptamine$_7$ receptor agents. *J.Med.Chem.* **2004**, 47, 6616-6624.

342. Y.H. Na, S.H. Hong, J.H. Lee, W. Park, D. Baek, H.Y. Koh, Y.S. Cho, H. Choo, A.N. Pae; Novel quinazolinone derivatives as 5-HT$_7$ receptor ligands. *Bioorg.Med.Chem.* **2008**, 16, 2570-2578.

343. S.T. Tong, D. Barker; A concise synthesis of (±) and a total synthesis of (+)-epiquinamide. *Tetrahedron Lett.* **2006**, 47, 5017-5020.

344. L. Cortizo, L. Santana, E. Ravina, F. Orallo, J.A. Fontenla, E. Castro, J.M. Calleja, M.L.d. Ceballos; Synthesis and antidopaminergic activity of some 3-(aminomethyl)tetralones as analogues of butyrophenone. *J.Med.Chem.* **1991**, 34, 2242-2247.

345. F.A. Carey, R.J. Sundberg; Reactions of carbonyl compounds, *Advanced organic chemistry: structure and mechanisms,* Kluwer Academic: 2000.

346. R.S. Varma, K.P. Naicker; Solvent-free synthesis of amides from non-enolizable esters and amines using microwaves irradiation. *Tetrahedron Lett.* **1999**, 40, 6177-6180.

347. T. Gustafsson, F. Pontén, P.H. Seeberger; Trimethylaluminium mediated amide bond formation in a continuous flow microreactor as key to the synthesis of rimonabant and efaproxiral. *Chem.Comm.* **2008,** 1100-1102.

348. J.F. Bower, T. Riis-Johannessen, P. Szeto, A.J. Whitehead, T. Gallagher; Stereospecific construction of substituted piperidines. Synthesis of (-)-paroxetine and (+)-laccarin. *Chem.Comm.* **2007**, 2007, 728-730.

349. E.T. Roe, J.T. Scanlan, D. Swern; Fatty acid amides. I. Preparation of amides of oleic and the 9,10-dihydroxystearic acids. *J.Am.Chem.Soc.* **1949**, 71, 2215-2218.

350. A. Loupy, L. Perreux, M. Liagre, K. Burle, M. Moneuse; Reactivity and selectivity under microwaves in organic chemistry. Relation with medium effects and reaction mechanisms. *Pure Appl.Chem.* **2001**, 73, 161-166.

351. L. Perreux, A. Loupy, M. Delmotte; Microwave effects in solvent-free esters aminolysis. *Tetrahedron* **2003**, 59, 2185-2189.

352. A. Loupy, A. Petit, J. Hamelin, F. Texier-Boullet, P. Jacquault, D. Mathé; New solvent-free organic synthesis using focused microwaves. *Synthesis* **1998**, 1998, 1213-1234.

353. A. Talvik, A. Tuulmets, E. Vaino; Kinetics and mechanism of aminolysis of aliphatic esters in aprotic solvents. *J.Phys.Org.Chem.* **1999**, 12, 747-750.

354. G. Bram, A. Loupy, M. Majdoub, E. Gutiérrez, E. Ruiz-Hitzky; Alkylation of potassium acetate in "dry media" thermal activation in commercial microwave ovens. *Tetrahedron* **1990**, 46, 5167-5176.

355. Y.I. Khurgin, M.G. Dmitrieva; Mechanism of catalysis in aminolysis of esters in an aprotic medium. *Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya* **1974**2140-2142.

Aquesta Tesi Doctoral s'ha dut a terme al Laboratori de Síntesi
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