Chapter V:

Experimental

"Learn from yesterday, live for today, hope for tomorrow. The important thing is to not stop questioning." — Albert Einstein,

5. Experimental

5.1 Chemistry

5.1.1. Materials and Methods

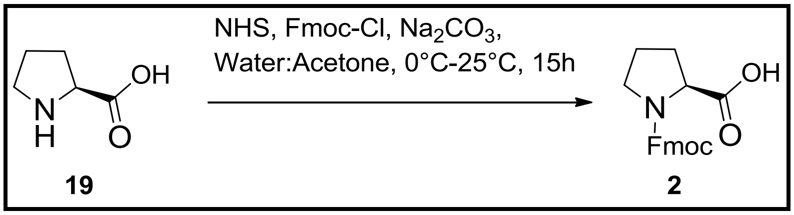
All the reagents used for the synthesis were purchased from Sigma Aldrich Company Limited, Dorset and were used without further purification. Solvents were procured from commercial source and used after distilling or drying according to the known methods. All the air and/or moisture sensitive reactions were carried out in dry solvents under nitrogen atmosphere. Melting points were recorded in open glass capillaries, using scientific melting point apparatus and are uncorrected.

The ^{1}H NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) relative to TMS either in CD_3OD, DMSO-d_6 or $CDCl_3$. Signal multiplicities are represented by s (singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), bs (broad singlet), and m (multiplet). ^{13}C NMR spectra were recorded on Bruker Avance-400 at 100 MHz either in $CDCl_3$ or Acetone-$d_{6.}$ Mass spectra (ESI-MS) were obtained on Shimadzu LCMS 2010-A spectrometer. Elemental analyses were carried out using a Perkin-Elmer 2400 CHN analyzer.

HPLC analyses were carried out at λ_{max} 220 nm using column. Progress of the reactions was monitored by TLC using precoated TLC plates (E. Merck Kieselgel 60 F254) and the spots were visualized in UV and/or in iodine vapours. The chromatographic purification was performed on silica gel (200-400 mesh). Few compounds were directly used for next step without purification and analysis. Detailed synthetic procedures and characterization data of all the final compounds and intermediates are described in this chapter.

5.1.2. Experimental Details : Cyanopyrrolidine containing peptidomimetic based DPP-IV inhibitors (First series)

5.1.2.1. (S)-1-(((9H-Fluoren-9-yl)methoxy)carbonyl)pyrrolidine-2-carboxylic acid (Fmoc-Pro-OH) (2)



N-Hydroxy succinamide (5.5 g) was charged in a 1L R B flask, to it was added Na_2CO_3 (3.7 g) dissolved in D.M. water (45 ml) and stirred for 15 minutes. Cool it to 0 ^oC to 5 ^oC using ice-salt bath and was added Fmoc-chloride (11.3 g) dissolved in acetone (45 ml) to the reaction mixture drop wise within 20 to 30 minutes maintaining temperature 0^oC-5^oC. The reaction mixture was stirred at 0 ^oC-5 ^oC for 30 minutes. Free amino acid L-Proline **19** (5 g) was dissolved in Na_2CO_3 (10.18 g in 45 ml D. M. water) solution followed by addition of acetone (45 ml). This solution was added to the reaction mixture using addition funnel within 5 to 10 minutes at temperature 0 ^oC-5 ^oC. The reaction mixture was stirred at this temperature for 30 minutes, after which the temperature was increased gradually to 25 ^oC and was stirred for 15hours.

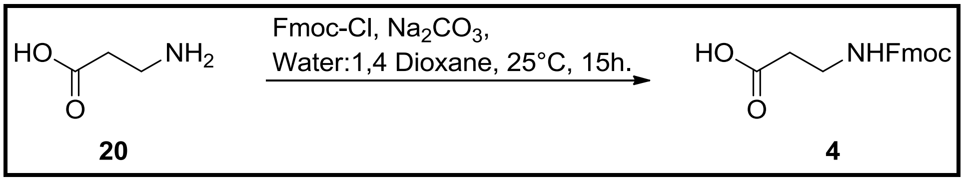
After completion of the reaction (TLC), it was poured into D.M.water (1L) and was basified with 1M Na_2CO_3 till pH increased to10. The resulting mixture was extracted with diisopropyl ether (2 X 150 ml) to remove the non-polar impurities. The aqueous layer was acidified with 1M HCl solution tol pH ~2 and was extracted with ethyl acetate (2 X 150 ml). The combined organic layers were washed with D.M.water (1 X 150 ml) and saturated NaCl solution (1 X 150 ml) and filtered through Hyflo supercel using filter flask and Buchner funnel) and dried over anhydrous Na_2SO_4 (~10 g) , and evaporated to dryness. Crude residue thus obtained was purified by column chromatography using 100-200 mesh size silica gel as a stationary phase and 0-40% Ethyl acetate in Dichloromethane as an eluting system to give 12.01 g (82% yield) of the title product **2** as a white amorphous solid. mp: 116-117 ^oC; Purity by HPLC: 96%.

ESI/MS (m/z) : 338.4 $(M+H)^+$. **Mol. Wt.** = 337.3 g

^{1}HNMR (400 MHz, DMSO-d_6) : δ 1.81-1.86 (m, 2H), 1.94-1.96 (m, 1H), 2.14-2.29 (m, 1H), 3.33-3.45 (m, 2H), 4.18-4.27 (m, 2H), 4.33 (dd, 1H, J_1 = 3.2Hz, J_2 = 8.8Hz), 7.31-

7.35 (m, 2H), 7.36-7.43 (m. 2H), 7.63-7.67 (m, 2H), 7.89 (t, 2H, J = 6.4Hz), 12.69 (bs, 1H, -COO**H**)

5.1.2.2.1. 3-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)propanoic acid (Fmoc-βAla-OH) (4)



4.0 g (45 mmol) of β-Alanine was suspended in 1,4-dioxane (40 ml) in a R B Flask, and 11.9 g (112 mmol) of Na_2CO_3 dissolved in D. M. water (80 ml) was added in a single portion to give clear solution. To this mixture was added 12.2 g (47 mmol) of Fmoc-Cl dissolved in 1,4-dioxane (20 ml) dropwise over a period of 30min.(During addition solid precipitated in reaction mixture). The mixture was stirred at room temperature for 15h.

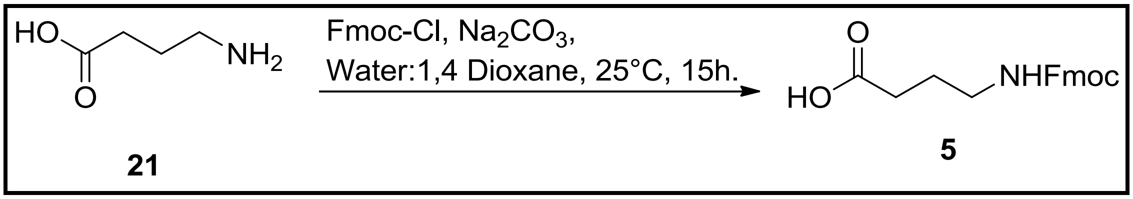
After completion (TLC), the reaction mixture was poured in water (200 ml), and was extracted with ether (3X100 ml) to remove unwanted impurities. Aqueous layer was then acidified with sat. citric acid to pH 3 and extracted with ethyl acetate (3X150 ml), combined organic layers were washed sequentially with water (1X150 ml) and brine (1x150 ml) solution. Organic layer was then dried over anhy. Na_2SO_4, filtered and evaporated to dryness to give thick gummy residue.

The residue thus obtained was purified by column chromatography using 100-200 mesh silica as stationary phase and 0-0.5 % MeOH in $CHCl_3$ as eluting system to give 8.85 g (63% yield) of desired product **4** as a white solid. Mp: 144-145 °C; Purity by HPLC: 97.4% AUC.

ESI/MS (m/z) : 312.4 $(M+H)^+$. **Mol. Wt.** = 311.3 g

^{1}HNMR (400 MHz, DMSO-*d₆*) : δ 2.37 (t, 2H, J = 6.9 Hz), 3.15-3.21 (m, 2H), 4.16-4.21 (t, 1H, J = 6.6 Hz), 4.28 (d, 2H, J = 6.6 Hz), 7.28-7.35 (m, 3H), 7.40 (t, 2H, J = 6.9 Hz), 7.68 (d, 2H, J = 7.3 Hz), 7.88 (d, 2H, J = 7.3 Hz), 12.21 (bs, 1H, -COO**H**).

5.1.2.2.2. 4-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)butanoic acid (Fmoc-GABA-OH) (5)

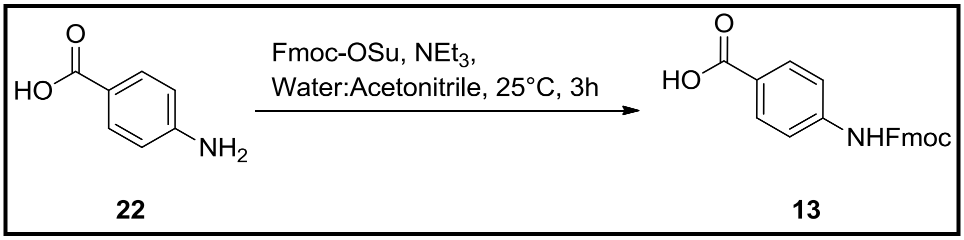


5 (1.2 g) was prepared by means of the general procedure described in **5.1.2.2.1.** with 78% yield as a white solid. 168-170 °C; Purity by HPLC: 98.3% AUC.

ESI/MS (m/z) : 326.4 $(M+H)^+$. **Mol. Wt.** = 325.4 g

^{1}HNMR (400 MHz, $CDCl_3$) : δ 1.98 (t, 2H, J=6.5 Hz), 2.71 (t, 2H, J=6.5 Hz), 3.32 (d, 2H, J=6.5 Hz), 4.21 (t, 2H, J=6.3 Hz), 4.45 (d, 2H, J=6.3 Hz), 4.85 (bs, 1H, -N**H**), 7.31 (t, 2H, J=7.5 Hz), 7.40 (t, 2H, J=7.5 Hz), 7.59 (d, 2H, J=7.5 Hz), 7.77 (d, 2H, J=7.5 Hz), 11.98 (bs, 1H, -COO**H**).

5.1.2.3. 4-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)benzoic acid (Fmoc-PABA-OH) (13)



5.0 g (36.5 mmol) of *p*-amino benzoic acid **22** was suspended in a 250 ml R.B. Flask containing 25 ml of D. M. water. To this suspension added triethylamine (5.07 ml, 36.5 mmol) in a single portion and stirred at room temperature for 30min. To this content added acetonitrile (25ml) followed by solid *N*-(9-Fluorenylmethoxycarbonyloxy) succinimide (Fmoc-Osu, 10.24 g, 30.4 mmol). Most of the solid dissolved within 30 min., reaction mixture became stirrable thick gel. Reaction mixture was stirred for 3h at room temperature to completion (TLC).

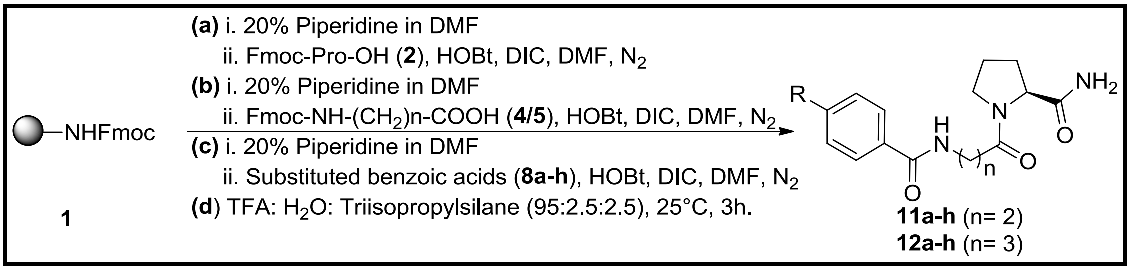
Acetonitrile of the reaction mixture was removed under reduced pressure and was extracted with ether to remove impurities if any. Aqueous layers were then acidified with 6N HCl to pH 2 and extracted with ethyl acetate (3X100 ml), combined organic layer was washed with water (1X100 ml) and brine (1X100 ml), dried over anhy. Na_2SO_4, filtered and solvent was removed under reduced pressure to give 11.66 g (89% yield) of the desired compound **13** as an off white solid. 268 °C dec.; Purity by HPLC: 96.8% AUC.

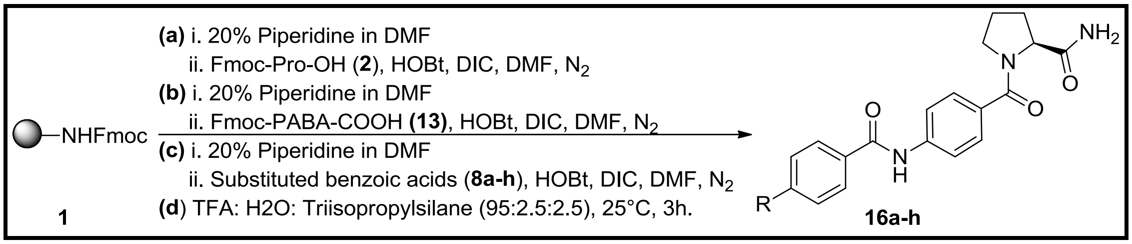
ESI/MS (m/z) : 360.3 $(M+H)^+$. **Mol. Wt.** = 359.2 g

^{1}HNMR (400 MHz, DMSO-*d*$_6$) : δ 4.29 (t, 1H, J = 6.5 Hz), 4.50 (d, 2H, J = 6.5 Hz), 7.36 (m, 4H), 7.42-7.51 (m, 3H), 7.72 (d, 2H, J = 7.2 Hz), 7.81 (d, 2H, J = 8.6 Hz), 7.88 (d, 2H, J = 7.4 Hz), 12.64 (s, 1H).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ 47.0, 66.2, 117.8, 120.6, 124.8, 125.5, 127.6, 128.2, 130.9, 142.3, 144.1, 153.7, 167.4.

5.1.3. General procedure for the synthesis of compounds (11a-h, 12a-h and 16a-h)





All the above compounds were synthesized using Fmoc based solid-phase peptide synthesis protocol (SPPS). Fmoc protected Rink amide MBHA resin **1** (750 mg, 0.58 mmol/g) was swollen in DMF for 20 min and washed with DMF (3 X 25 ml). Fmoc group of the resin was removed by agitating peptidyl resin in 20% piperidine solution (25 ml, 1 X 5 min and 1 X 30 min) for the next coupling reaction. Fmoc-Pro-OH **2** was coupled to the deprotected resin by agitating its pre-activated solution under N_2 atmosphere. [i.e. Fmoc-Pro-OH (4 eq), HOBt (4 eq), and 1,3-diisopropyl carbidiimide (DIC) (4 eq) in DMF (5ml) for 30 min)]. After completion of the coupling reaction confirmed by Kaiser ninhydrin and TNBS tests, peptidyl resin was washed with DMF, DCM and ether (3 X 25 ml each). However if coupling found incomplete by Kaiser ninhydrin test then coupling reaction was repeated by performing one more coupling cycle. Fmoc group of Fmoc-Pro-OH **2** coupled resin was then deprotected with 20% piperidine solution (25 ml, 1 X 5 min and 1 X 30 min). Fmoc-β-Ala-OH **4**/ Fmoc-GABA-

OH **5**/ Fmoc-PABA-OH **13** were coupled to the peptidyl resin by agitating their respective preactivated solutions under N_2 atmosphere. (i.e. Fmoc-XX-OH (4 equiv), HOBt (4 equiv), and DIC (4 equiv) in DMF (5 ml) for 30 min.). After completion of the coupling reaction confirmed by Kaiser ninhydrin and TNBS tests, peptidyl resin was washed with DMF, DCM and ether (3 X 25 ml each) and treated with 20% piperidine solution (25 ml, 1 X 5 min and 1 X 30 min) to remove Fmoc group. Peptidyl resin was then washed with DMF, DCM and ether (3 X 25 ml each) and swollen in DMF for 30 min for the coupling of substituted benzoic acids **8a-h**. Substituted benzoic acids **8a-h** were incorporated to the respective peptidyl resin by agitating peptidyl rasine in the preactivated coupling solution of respective benzoic acid under N_2 atm. over a period of 2-4hrs. Completion of coupling was confirmed by Kaiser ninhydrin and TNBS tests, whenever coupling was found incomplete one more coupling cycle was performed. Then, the resin was washed with DMF, DCM and ether (5 X 25ml each) and dried under vacuum for the global cleavage to get the desired peptidomimetics.

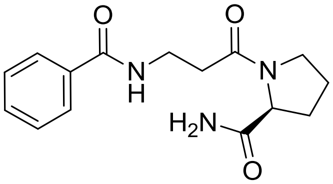
Cleavage;

The desired peptidomimetics were cleaved and deprotected from their respective peptidyl-resins by treatment with TFA cleavage mixture as follows. A solution of TFA / Water / Triisopropylsilane (95: 2.5: 2.5) (10 ml / 100 mg of peptidyl-resin) was added to peptidyl-resins and the mixture was kept at room temperature with occasional stirring. The resin was filtered, washed with a cleavage mixture and the combined filtrate was evaporated to dryness. Residue obtained was titrated with ether (20 ml each) to yield crude compounds, typically in >100% yield (Ca 200-230 mg). Crude compounds thus obtained were purified by preparative HPLC as follows:

Purification;

Preparative HPLC was carried out on a Shimadzu LC-8A liquid chromatograph. A solution of crude compounds dissolved in water: acetonotile (ACN) (1:1, 5ml) or Methanol (5ml) was injected into a semi-prep column (Luna 10 μ; C_{18}; 210-220 nm), dimension 250 X 21.20 mm and eluted with a linear gradient of ACN in water, both buffered with 0.1 % TFA, using a flow rate of 15 ml / min, with effluent monitoring by PDA detector at 220 nm. A typical gradient of 20 % to 70 % of water-ACN mixture, buffered with 0.1 % TFA was used, over a period of 100 minutes, with 1% gradient change per minute. The desired product eluted were collected in a single 50-80 ml fraction and pure peptidomimetics **11a-h, 12a-h** and **16a-h** were obtained as white solids either by lyophilisation of respective HPLC fractions or by normal work up procedure after evaporation of ACN from the fractions and extraction with DCM.

5.1.3.1. (S)-1-(3-Benzamidopropanoyl)pyrrolidine-2-carboxamide (11a)



11a (200 mg, 82%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 153-155 °C; Purity by HPLC: 99.05% AUC.

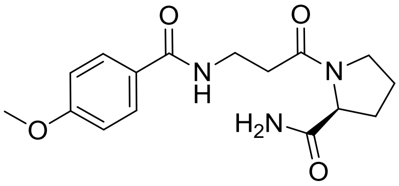
ESI/MS (m/z) : 290.1 $(M+H)^+$. **Mol. Wt.** = 289.3 g

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.96-2.13 (m, 3H), 2.19- 2.24 (m, 1H), 2.63-2.71 (m, 2H), 3.32-3.67(m, 4H), 4.38-4.41 (dd, 1H, J_1 = 3.6Hz, J_2 = 8.2Hz), 7.56-8.05 (m, 5H);

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.8, 23.8, 33.4, 38.7, 42.6, 61.5, 126.7, 128.6, 131.6, 138.4, 167.8, 176.4, 178.1.

Analysis : Mol. Formula: $C_{15}H_{19}N_3O_3$:
Calcd.: C 62.27, H 6.62, N 14.52.
Found: C 62.25, H 6.59, N 14.48.

5.1.3.2. (S)-1-(3-(4-Methoxybenzamido)propanoyl)pyrrolidine-2-carboxamide (11b)



11b (190 mg, 79%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 156-158 °C; Purity by HPLC: 99.21% AUC.

ESI/MS (m/z) : 320.3 $(M+H)^+$. **Mol. Wt.** = 319.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.84-2.03 (m, 3H), 2.17- 2.21 (m, 1H), 2.68-2.72 (m, 2H), 3.31-3.68 (m, 4H), 3.67 (s, 3H), 4.39-4.42 (dd, 1H, J_1 = 3.6Hz, J_2 = 8.4Hz), 6.82 (d, 2H, J = 8.8Hz), 7.68 (d, 2H, J = 8.8Hz).

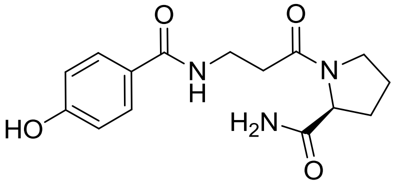
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 18.7, 23.4, 35.2, 38.7, 43.2, 55.8, 61.2, 115.4, 125.2, 127.6, 163.8, 167.3, 176.4, 178.3.

Analysis : Mol. Formula: $C_{16}H_{21}N_3O_4$

Calcd.: C 60.17, H 6.63, N 13.16.

Found: C 60.16, H 6.64, N 13.14.

5.1.3.3. (S)-1-(3-(4-Hydroxybenzamido)propanoyl)pyrrolidine-2-carboxamide (11c)



11c (188 mg, 78%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 143-145 °C; Purity by HPLC: 99.46% AUC.

ESI/MS (m/z) : 306.5 $(M+H)^+$. **Mol. Wt.** = 305.3 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.87-2.08 (m, 3H), 2.19- 2.23 (m, 1H), 2.65-2.71 (m, 2H), 3.31-3.65(m, 4H), 4.38-4.41 (dd, 1H, J_1 = 3.8Hz, J_2 = 8.2Hz), 6.93 (d, 2H, J = 9.2Hz), 7.75 (d, 2H, J = 9.2Hz).

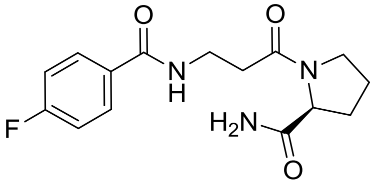
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.4, 23.6, 34.8, 39.4, 42.8, 61.3, 116.3, 126.5, 129.2, 161.4, 167.7, 176.3, 177.9.

Analysis : Mol. Formula: $C_{15}H_{19}N_3O_4$

Calcd.: C 59.01, H 6.27, N 13.76.

Found: C 58.98, H 6.24, N 13.73.

5.1.3.4. (S)-1-(3-(4-Fluorobenzamido)propanoyl)pyrrolidine-2-carboxamide (11d)



11d (184 mg, 75%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 165-167 °C; Purity by HPLC: 99.07% AUC.

ESI/MS (m/z) : 308.2 $(M+H)^+$. **Mol. Wt.** = 307.3 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.93-2.15 (m, 3H), 2.19- 2.26 (m, 1H), 2.67-2.71 (m, 2H), 3.32-3.64(m, 4H), 4.39-4.42 (m, 1H), 7.21 (m, 2H), 7.89 (m, 2H).

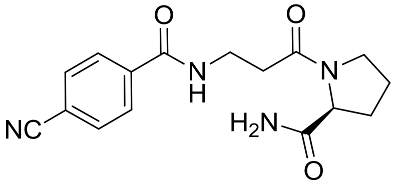
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.7, 23.4, 33.9, 39.2, 42.3, 61.5, 115.4 (d, J = 19.2Hz), 128.7 (d, J = 4.2Hz), 129.3, 166.2 (d, J = 246Hz), 167.8, 176.4, 178.1.

Analysis : Mol. Formula: $C_{15}H_{18}FN_3O_3$

Calcd.: C 58.62, H 5.90, N 13.67.

Found: C 58.64, H 5.87, N 13.66.

5.1.3.5. (S)-1-(3-(4-Cyanobenzamido)propanoyl)pyrrolidine-2-carboxamide (11e)



11e (192 mg, 83%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 147-149 °C; Purity by HPLC: 99.23% AUC.

ESI/MS (m/z) : 315.5 $(M+H)^+$. **Mol. Wt.** = 314.3 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 1.89-2.10 (m, 3H), 2.17- 2.23 (m, 1H), 2.64-2.70 (m, 2H), 3.31-3.65(m, 4H), 4.39-4.41 (m, 1H), 7.53 (d, 2H, J = 8.4Hz), 8.34 (d, 2H, J = 8.4Hz).

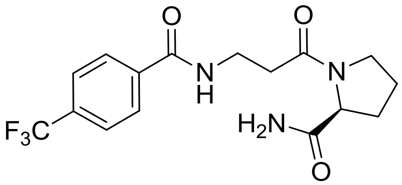
^{13}C NMR (100 MHz, Methanol-d_4): δ 19.5, 23.3, 33.7, 38.8, 42.4, 61.4, 115.8, 116.9, 128.4, 131.8, 137.6, 167.6, 176.4, 177.9.

Analysis : Mol. Formula: $C_{16}H_{18}N_4O_3$

Calcd.: C 61.13, H 5.77, N 17.82.

Found: C 61.16, H 5.79, N 17.85.

5.1.3.6. (S)-1-(3-(4-(Trifluoromethyl)benzamido)propanoyl)pyrrolidine-2-carboxamide (11f)



11f (195 mg, 80%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 169-171 °C; Purity by HPLC: 99.04% AUC.

ESI/MS (m/z) : 358.4 $(M+H)^+$. **Mol. Wt.** = 357.2 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 1.95-2.10 (m, 3H), 2.18- 2.23 (m, 1H), 2.64-2.71 (m, 2H), 3.31-3.65(m, 4H), 4.38-4.42 (dd, 1H, J_1 = 3.4Hz, J_2 = 8.0Hz), 7.74 (d, 2H, J = 8.8Hz), 7.89 (d, 2H, J = 8.8Hz).

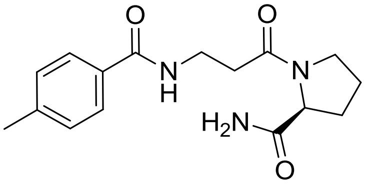
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.6, 23.3, 33.6, 39.4, 42.8, 61.3, 120.2, 125.7 (q, J = 271.3Hz), 128.5, 135.4 (q, J = 30.4Hz), 137.3, 167.2, 176.2, 178.3.

Analysis : Mol. Formula: $C_{16}H_{18}F_3N_3O_3$

Calcd.: C 53.78, H 5.08, N 11.76.

Found: C 53.74, H 5.06, N 11.73.

5.1.3.7. (S)-1-(3-(4-Methylbenzamido)propanoyl)pyrrolidine-2-carboxamide (11g)



11g (186 mg, 78%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 138-140 °C; Purity by HPLC: 99.13% AUC.

ESI/MS (m/z) : 304.5 $(M+H)^+$. **Mol. Wt.** = 303.4 g.

^1H NMR (400 MHz, Methanol-d$_4$): δ = 1.96-2.11 (m, 3H), 2.17- 2.21 (m, 1H), 2.39 (s, 3H), 2.65-2.72 (m, 2H), 3.31-3.67(m, 4H), 4.39-4.43 (dd, 1H, J_1 = 3.6Hz, J_2 = 8.2Hz), 7.31 (d, 2H, J = 8.6Hz), 7.84 (d, 2H, J = 8.6Hz).

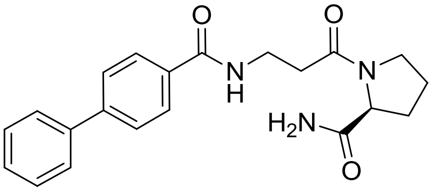
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.9, 21.3, 23.5, 33.4, 39.3, 42.5, 61.5, 128.3, 129.6, 131.2, 140.1, 167.6, 176.5, 177.8.

Analysis : Mol. Formula: $C_{16}H_{21}N_3O_3$

Calcd.: C 63.35, H 6.98, N 13.85.

Found: C 63.37, H 6.95, N 13.83.

5.1.3.8. (S)-1-(3-([1,1'-Biphenyl]-4-ylcarboxamido)propanoyl)pyrrolidine-2-carboxamide (11h)



11h (206 mg, 84%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 179-181 °C; Purity by HPLC: 99.17% AUC.

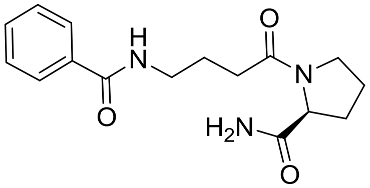
ESI/MS (m/z) : 366.2 $(M+H)^+$. **Mol. Wt.** = 365.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.97-2.12 (m, 3H), 2.19- 2.23 (m, 1H), 2.63-2.71 (m, 2H), 3.32-3.67(m, 4H), 4.38-4.41 (dd, 1H, J_1 = 3.6Hz, J_2 = 8.4Hz), 7.23-7.51 (m, 5H), 7.63 (d, 2H, J = 9.0Hz), 7.89 (d, 2H, J = 9.0Hz).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.6, 23.3, 33.2, 39.7, 42.3, 61.3, 127.3, 127.5, 127.6, 127.9, 128.1, 128.6, 129.3, 132.7, 137.2, 139.8, 167.8, 176.3, 178.2.

Analysis : Mol. Formula: $C_{21}H_{23}N_3O_3$
Calcd.: C 69.02, H 6.34, N 11.50.
Found: C 68.99, H 6.37, N 11.47.

5.1.3.9. (S)-1-(4-Benzamidobutanoyl)pyrrolidine-2-carboxamide (12a)



12a (178 mg, 73%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 172-175 °C; Purity by HPLC: 99.47% AUC.

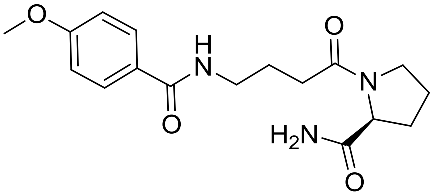
ESI/MS (m/z) : 304.2 $(M+H)^+$. **Mol. Wt.** = 303.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.83-1.87 (m, 3H), 1.93- 2.03 (m, 1H), 2.15-2.21 (m, 2H), 2.32-2.44 (m, 2H), 3.21-3.25 (m, 2H), 3.36-3.41 (m, 1H), 3.51-3.55 (m, 1H), 4.42-4.47 (dd, 1H, J_1 = 3.8Hz, J_2 = 8.2Hz), 7.67-8.04 (m, 5H).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.9, 23.3, 28.2, 29.4, 42.2, 42.9, 61.3, 126.5, 128.9, 131.9, 137.7, 167.9, 176.5, 176.7.

Analysis : Mol. Formula: $C_{16}H_{21}N_3O_3$
Calcd.: C 63.35, H 6.98, N 13.85.
Found: C 63.33, H 7.02, N 13.82.

5.1.3.10. (S)-1-(4-(4-Methoxybenzamido)butanoyl)pyrrolidine-2-carboxamide (12b)



12b (158 mg, 69%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 123-125 °C; Purity by HPLC: 99.64% AUC.

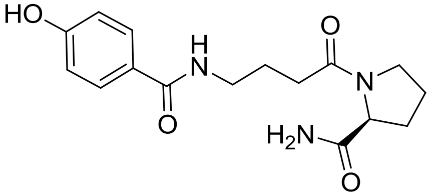
ESI/MS (m/z) : 334.2 $(M+H)^+$. **Mol. Wt.** = 333.4 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 1.82-1.89 (m, 3H), 1.92- 2.04 (m, 1H), 2.13-2.24 (m, 2H), 2.32-2.41 (m, 2H), 3.21-3.26 (m, 2H), 3.38-3.43 (m, 1H), 3.53-3.59 (m, 1H), 3.69 (s, 3H), 4.41-4.49 (dd, 1H, J_1 = 4.0Hz, J_2 = 7.8Hz), 6.93 (d, 2H, J = 8.4Hz), 7.65 (d, 2H, J = 8.4Hz).

^{13}C NMR (100 MHz, Methanol-d_4): δ 19.5, 23.3, 28.1, 29.4, 42.1, 43.9, 55.3, 61.3, 115.1, 125.6, 128.2, 164.8, 167.6, 176.4, 177.1.

Analysis : Mol. Formula: $C_{17}H_{23}N_3O_4$
Calcd.: C 61.25, H 6.95, N 12.60.
Found: C 61.28, H 6.98, N 12.61.

5.1.3.11. (S)-1-(4-(4-Hydroxybenzamido)butanoyl)pyrrolidine-2-carboxamide (12c)



12c (196 mg, 81%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 116-118 °C; Purity by HPLC: 99.28% AUC.

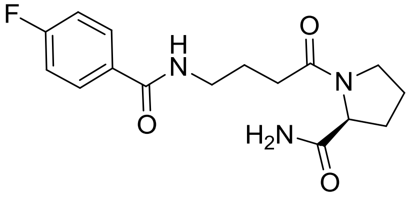
ESI/MS (m/z) : 320.2 $(M+H)^+$. **Mol. Wt.** = 319.4 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 1.84-1.89 (m, 3H), 1.91- 2.05 (m, 1H), 2.15-2.24 (m, 2H), 2.31-2.42 (m, 2H), 3.21-3.28 (m, 2H), 3.39-3.43 (m, 1H), 3.53-3.57 (m, 1H), 4.41-4.47 (dd, 1H, J_1 = 3.8Hz, J_2 = 7.6Hz), 6.98 (d, 2H, J = 8.6Hz), 7.71 (d, 2H, J = 8.6Hz).

^{13}C NMR (100 MHz, Methanol-d_6): δ 19.6, 23.5, 27.9, 29.2, 42.3, 43.6, 61.4, 115.9, 125.8, 128.9, 161.3, 167.8, 176.2, 177.0.

Analysis : Mol. Formula: $C_{16}H_{21}N_3O_4$
Calcd.: C 60.17, H 6.63, N 13.16.
Found: C 60.19, H 6.66, N 13.14.

5.1.3.12. (S)-1-(4-(4-Fluorobenzamido)butanoyl)pyrrolidine-2-carboxamide (12d)



12d (196 mg, 85%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 132-134 °C; Purity by HPLC: 99.79% AUC.

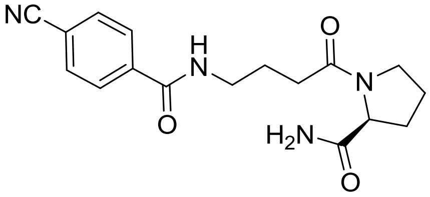
ESI/MS (m/z) : 322.1 $(M+H)^+$. **Mol. Wt.** = 321.4 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 1.86-1.89 (m, 3H), 1.93- 2.04 (m, 1H), 2.14-2.24 (m, 2H), 2.29-2.41 (m, 2H), 3.22-3.29 (m, 2H), 3.37-3.41 (m, 1H), 3.52-3.57 (m, 1H), 4.41-4.46 (dd, 1H, J_1 = 3.6Hz, J_2 = 7.8Hz), 6.98 (m, 2H), 7.71 (m, 2H).

^{13}C NMR (100 MHz, Methanol-d_4): δ 19.5, 22.8, 27.6, 28.9, 42.3, 43.1, 61.2, 115.8 (d, J = 21Hz), 129.2 (d, J = 3.8Hz), 129.5, 164.5 (d, J = 249Hz), 167.4, 176.2, 177.2.

Analysis : Mol. Formula: $C_{16}H_{20}FN_3O_3$
Calcd.: C 59.80, H 6.27, N 13.08.
Found: C 59.81, H 6.29, N 13.05.

5.1.3.13. (S)-1-(4-(4-Cyanobenzamido)butanoyl)pyrrolidine-2-carboxamide (12e)



12e (189 mg, 83%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 149-151 °C; Purity by HPLC: 99.04% AUC.

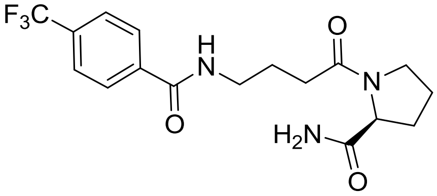
ESI/MS (m/z) : 329.6 $(M+H)^+$. **Mol. Wt.** = 328.4 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 1.83-1.88 (m, 3H), 1.91- 2.04 (m, 1H), 2.13-2.23 (m, 2H), 2.32-2.45 (m, 2H), 3.20-3.27 (m, 2H), 3.38-3.42 (m, 1H), 3.52-3.56 (m, 1H), 4.42-4.48 (dd, 1H, J_1 = 4.0Hz, J_2 = 8.2Hz), 7.72 (d, 2H, J = 8.4Hz), 8.21 (d, 2H, J = 8.4Hz).

^{13}C NMR (100 MHz, Methanol-d_4): δ 19.7, 23.4, 27.8, 29.1, 42.1, 42.9, 61.4, 115.8, 117.3, 128.1, 132.3, 136.8, 167.8, 176.3, 176.8.

Analysis : Mol. Formula: $C_{17}H_{20}N_4O_3$
Calcd.: C 62.18, H 6.14, N 17.06.
Found: C 62.14, H 6.12, N 17.04.

5.1.3.14. (S)-1-(4-(4-(Trifluoromethyl)benzamido)butanoyl)pyrrolidine-2-carboxamide (12f)



12f (183 mg, 78%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 193-195 °C; Purity by HPLC: 99.19% AUC.

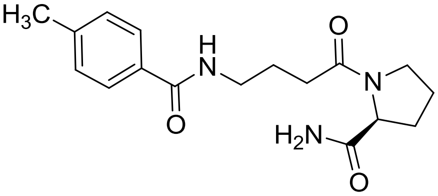
ESI/MS (m/z) : 372.2 $(M+H)^+$. **Mol. Wt.** = 371.3 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.82-1.87 (m, 3H), 1.91- 2.02 (m, 1H), 2.17-2.21 (m, 2H), 2.32-2.43 (m, 2H), 3.20-3.23 (m, 2H), 3.34-3.41 (m, 1H), 3.49-3.53 (m, 1H), 4.40-4.46 (dd, 1H, J_1 = 4.0Hz, J_2 = 7.8Hz), 7.69 (d, 2H, J = 8.6Hz), 7.93 (d, 2H, J = 8.6Hz).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.6, 22.9, 27.9, 29.2, 42.1, 42.3, 61.5, 119.7, 125.8 (q, J = 271.4Hz), 128.1, 133.8 (q, J = 29.8Hz), 137.2, 167.7, 176.4, 177.3.

Analysis : Mol. Formula: $C_{17}H_{20}F_3N_3O_3$
Calcd.: C 54.98, H 5.43, N 11.32.
Found: C 55.01, H 5.44, N 11.30.

5.1.3.15. (S)-1-(4-(4-Methylbenzamido)butanoyl)pyrrolidine-2-carboxamide (12g)



12g (181 mg, 72%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 145-147 °C; Purity by HPLC: 99.48% AUC.

ESI/MS (m/z) : 318.6 $(M+H)^+$. **Mol. Wt.** = 317.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.81-1.86 (m, 3H), 1.92- 2.03 (m, 1H), 2.16-2.23 (m, 2H), 2.31-2.44 (m, 3H), 3.21-3.26 (m, 2H), 3.36-3.42 (m, 1H), 3.51-3.54 (m, 1H), 4.41-4.45 (dd, 1H, J_1 = 3.6Hz, J_2 = 7.6Hz), 7.33 (d, 2H, J = 8.4Hz), 7.86 (d, 2H, J = 8.4Hz).

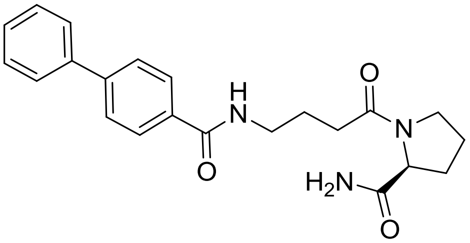
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.7, 21.3, 23.2, 28.4, 29.1, 42.2, 42.5, 61.5, 128.1, 130.2, 130.9, 141.7, 167.6, 176.3, 177.4.

Analysis : Mol. Formula: $C_{17}H_{23}N_3O_3$

Calcd.: C 64.33, H 7.30, N 13.24.

Found: C 64.29, H 7.32, N 13.20.

5.1.3.16. (S)-1-(4-([1,1'-Biphenyl]-4-ylcarboxamido)butanoyl)pyrrolidine-2-carboxamide (12h)



12h (206 mg, 84%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 204-206 °C; Purity by HPLC: 99.23% AUC.

ESI/MS (m/z) : 380.3 $(M+H)^+$. **Mol. Wt.** = 379.5 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.79-1.84 (m, 3H), 1.90- 2.02 (m, 1H), 2.17-2.23 (m, 2H), 2.31-2.45 (m, 2H), 3.23-3.27 (m, 2H), 3.34-3.41 (m, 1H), 3.51-3.56 (m, 1H), 4.42-4.47 (dd, 1H, J_1 = 3.8Hz, J_2 = 7.8Hz), 7.24-7.49 (m, 5H), 7.65 (d, 2H, J = 8.7Hz), 7.98 (d, 2H, J = 8.7Hz).

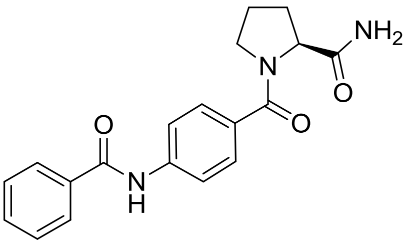
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.7, 23.3, 27.9, 28.7, 42.1, 42.8, 61.3, 127.5, 127.7, 127.8, 128.0, 128.1, 128.7, 129.2, 132.6, 137.4, 140.3, 167.7, 176.4, 177.1.

Analysis : Mol. Formula: $C_{22}H_{25}N_3O_3$

Calcd.: C 69.64, H 6.64, N 11.07.

Found: C 69.61, H 6.63, N 11.05.

5.1.3.17. (S)-1-(4-Benzamidobenzoyl)pyrrolidine-2-carboxamide (16a)



16a (184 mg, 83%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 184-186 °C; Purity by HPLC: 99.07% AUC.

ESI/MS (m/z) : 338.5 $(M+H)^+$. **Mol. Wt.** = 337.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.63-1.85 (m, 3H), 1.87- 1.98 (m, 1H), 3.31-3.42 (m, 1H), 3.45-3.51 (m, 1H), 4.64-4.70 (dd, 1H, J = 4.8Hz, J = 7.6Hz), 7.62-7.94 (m, 7H), 8.07 (d, 2H, J = 7.8Hz).

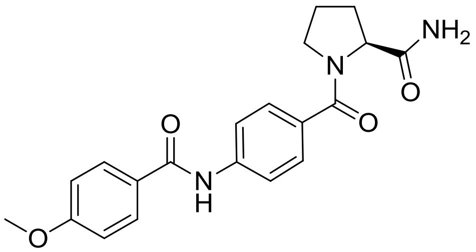
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.9, 23.3, 42.9, 61.8, 121.3, 124.1, 127.3, 128.4, 128.7, 129.5, 130.5, 131.6, 137.8, 140.3, 165.4, 169.9, 176.4.

Analysis : Mol. Formula: $C_{19}H_{19}N_3O_3$

Calcd.: C 67.64, H 5.68, N 12.46.

Found: C 67.61, H 5.65, N 12.42.

5.1.3.18. (S)-1-(4-(4-Methoxybenzamido)benzoyl)pyrrolidine-2-carboxamide (16b)



16b (173 mg, 79%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 158-160 °C; Purity by HPLC: 99.49% AUC.

ESI/MS (m/z) : 368.2 $(M+H)^+$. **Mol. Wt.** = 367.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.63-1.85 (m, 3H), 1.87- 1.98 (m, 1H), 3.34-3.43 (m, 1H), 3.47-3.52 (m, 1H), 3.68 (s, 3H), 4.63-4.72 (dd, 1H, J_1 = 5.2Hz, J_2 = 7.6Hz), 7.12 (d, 2H, J = 8.4Hz), 7.61 (d, 2H, J = 8.8Hz), 7.74 (d, 2H, J = 8.4Hz), 7.79 (d, 2H, J = 8.8Hz).

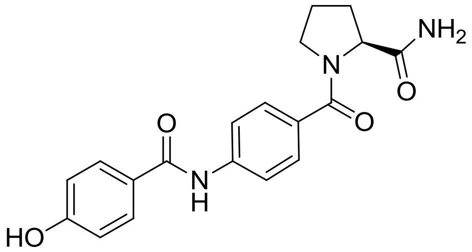
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.8, 23.4, 42.8, 54.8, 61.7, 114.7, 119.8, 126.3, 127.4, 128.4, 130.4, 140.1, 164.8, 165.3, 170.9, 176.6.

Analysis : Mol. Formula: $C_{20}H_{21}N_3O_4$

Calcd.: C 65.38, H 5.76, N 11.44.

Found: C 65.40, H 5.77, N 11.42.

5.1.3.19. (S)-1-(4-(4-Hydroxybenzamido)benzoyl)pyrrolidine-2-carboxamide (16c)



16c (176 mg, 77%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 146-148 °C; Purity by HPLC: 99.76% AUC.

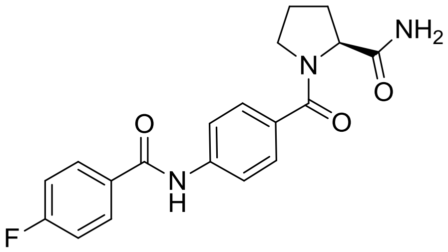
ESI/MS (m/z) : 354.6 $(M+H)^+$. **Mol. Wt.** = 353.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.65-1.87 (m, 3H), 1.89- 1.97 (m, 1H), 3.31-3.42 (m, 1H), 3.45-3.51 (m, 1H), 4.64-4.71 (dd, 1H, J_1 = 5.0Hz, J_2 = 7.8Hz), 7.08 (d, 2H, J = 8.7Hz), 7.63 (d, 2H, J = 8.6Hz), 7.76 (d, 2H, J = 8.7Hz), 7.81 (d, 2H, J = 8.6Hz).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.9, 23.3, 42.9, 61.9, 116.3, 120.3, 126.5, 127.6, 128.9, 130.7, 139.8, 161.2, 165.3, 170.4, 176.3.

Analysis : Mol. Formula: $C_{19}H_{19}N_3O_4$
Calcd.: C 64.58, H 5.42, N 11.89.
Found: C 64.54, H 5.40, N 11.86.

5.1.3.20. (S)-1-(4-(4-Fluorobenzamido)benzoyl)pyrrolidine-2-carboxamide (16d)



16d (211 mg, 85%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 168-170 °C; Purity by HPLC: 99.17% AUC.

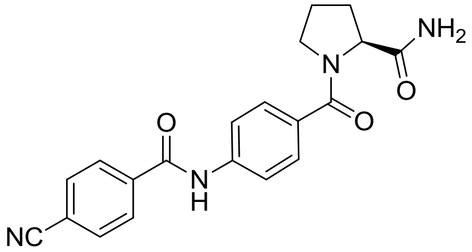
ESI/MS (m/z) : 355.3 $(M+H)^+$. **Mol. Wt.** = 355.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.66-1.89 (m, 3H), 1.90- 1.97 (m, 1H), 3.32-3.41 (m, 1H), 3.46-3.51 (m, 1H), 4.63-4.70 (dd, 1H, J_1 = 5.2Hz, J_2 = 7.4Hz), 7.19 (d, 2H, J = 8.4Hz), 7.68 (d, 2H, J = 8.6Hz), 7.73 (d, 2H, J = 8.4Hz), 7.81 (d, 2H, J = 8.6Hz).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.7, 23.1, 42.8, 61.5, 116.1(d, J = 21Hz), 120.4, 127.4, 129.2 (d, J = 4.2Hz), 129.9, 130.5, 139.6, 165.3, 165.8 (d, J = 249Hz), 169.9, 176.2.

Analysis : Mol. Formula: $C_{19}H_{18}FN_3O_3$
Calcd.: C 64.22, H 5.11, N 11.82.
Found: C 64.19, H 5.07, N 11.83.

5.1.3.21. (S)-1-(4-(4-Cyanobenzamido)benzoyl)pyrrolidine-2-carboxamide (16e)



16e (203 mg, 79%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 137-139 °C; Purity by HPLC: 99.06% AUC.

ESI/MS (m/z) : 363.3 $(M+H)^+$. **Mol. Wt.** = 362.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.64-1.86 (m, 3H), 1.89- 1.98 (m, 1H), 3.32-3.42 (m, 1H), 3.43-3.49 (m, 1H), 4.64-4.70 (m, 1H), 7.68 (d, 2H, J = 8.4Hz), 7.71 (d, 2H, J = 8.6Hz), 7.82 (d, 2H, J = 8.4Hz), 7.99 (d, 2H, J = 8.6Hz).

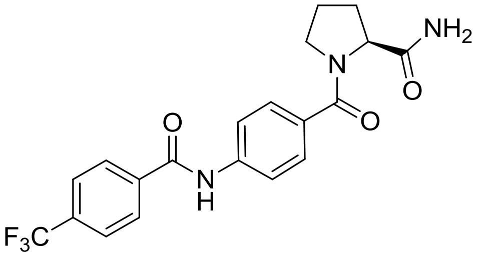
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.8, 23.4, 42.7, 61.6, 116.2, 116.7, 120.4, 127.5, 128.2, 130.7, 133.4, 138.4, 139.5, 165.1, 169.8, 176.1.

Analysis : Mol. Formula: $C_{20}H_{18}N_3O_4$

Calcd.: C 66.29, H 5.01, N 15.46.

Found: C 66.31, H 5.05, N 15.42.

5.1.3.22. (S)-1-(4-(4-(Trifluoromethyl)benzamido)benzoyl)pyrrolidine-2-carboxamide (16f)



16f (209 mg, 80%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 169-171 °C; Purity by HPLC: 99.18% AUC.

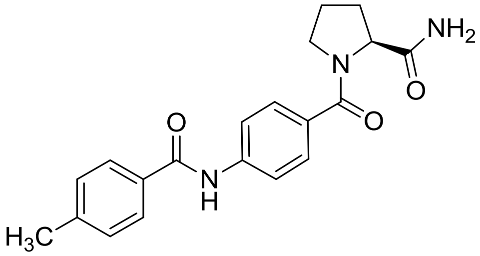
ESI/MS (m/z) : 406.2 $(M+H)^+$. **Mol. Wt.** = 405.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.65-1.86 (m, 3H), 1.88- 1.97 (m, 1H), 3.31-3.43 (m, 1H), 3.45-3.50 (m, 1H), 4.63-4.72 (dd, 1H, J = 5.0Hz, J = 7.4Hz), 7.62 (d, 2H, J = 8.6Hz), 7.68 (d, 2H, J = 8.9Hz), 7.83 (d, 2H, J = 8.6Hz), 7.87 (d, 2H, J = 8.9Hz).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.9, 23.4, 43.1, 61.9, 119.7, 120.4, 125.7(q, J = 271.6Hz), 127.9, 128.0, 130.3, 135.0 (q, J= 28.6Hz), 136.6, 139.4, 165.2, 169.7, 177.1.

Analysis : Mol. Formula: $C_{20}H_{18}F_3N_3O_3$
Calcd.: C 59.26, H 4.48, N 10.37.
Found: 59.23, H 4.44, N 10.34.

5.1.3.23. (S)-1-(4-(4-Methylbenzamido)benzoyl)pyrrolidine-2-carboxamide (16g)



16g (201 mg, 78%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 192-194 °C; Purity by HPLC: 99.26% AUC.

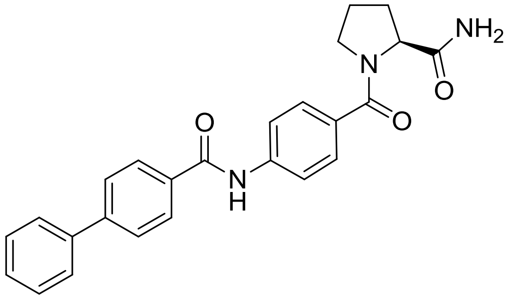
ESI/MS (m/z) : 352.3 $(M+H)^+$. **Mol. Wt.** = 351.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.63-1.86 (m, 3H), 1.87- 1.96 (m, 1H), 2.37 (s, 3H), 3.32-3.43 (m, 1H), 3.43-3.52 (m, 1H), 4.64-4.72 (dd, 1H, J = 5.1Hz, J = 7.6Hz), 7.31 (d, 2H, J = 8.8Hz), 7.63 (d, 2H, J = 8.6Hz), 7.69 (d, 2H, J = 8.8Hz), 7.89 (d, 2H, J = 8.6Hz).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.8, 21.2, 23.2, 43.3, 61.7, 120.2, 127.7, 127.9, 129.0, 130.2, 130.6, 139.0, 141.3, 165.4, 170.0, 176.9.

Analysis : Mol. Formula: $C_{20}H_{21}N_3O_3$
Calcd.: C 68.36, H 6.02, N 11.96.
Found: C 68.38, H 6.05, N 11.93.

5.1.3.24. (S)-1-(4-([1,1'-Biphenyl]-4-ylcarboxamido)benzoyl)pyrrolidine-2-carboxamide (16h)



16h (223 mg, 83%) was prepared by means of the general procedure described in **5.1.3.** as a white solid. 223-225 °C; Purity by HPLC: 99.73% AUC.

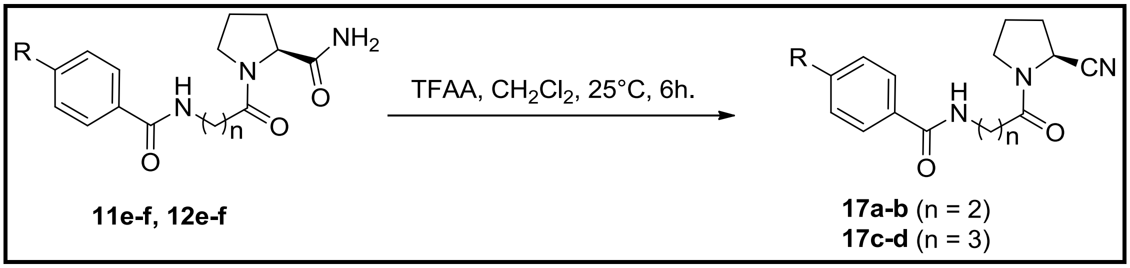
ESI/MS (m/z) : 414.7 $(M+H)^+$. **Mol. Wt.** = 413.5 g.

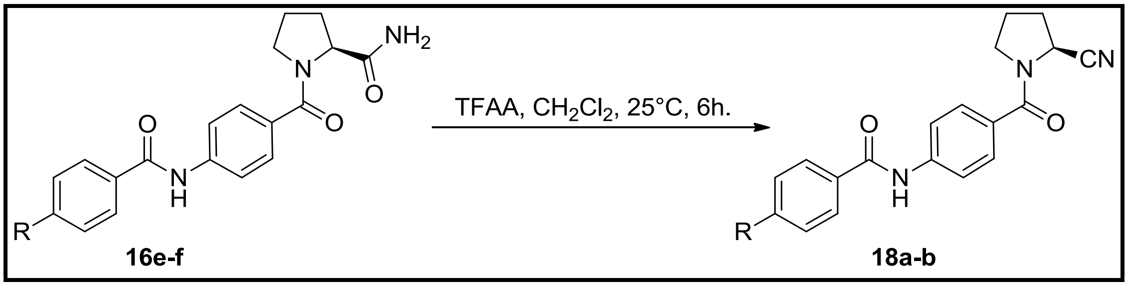
^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.64-1.84 (m, 3H), 1.86- 1.95 (m, 1H), 3.30-3.42 (m, 1H), 3.45-3.53 (m, 1H), 4.63-4.70 (dd, 1H, J = 4.8Hz, J = 7.8Hz), 7.23-7.49 (m, 5H), 7.63 (d, 2H, J = 8.6Hz), 7.65 (d, 2H, J = 8.7Hz), 7.91 (d, 2H, J = 8.6Hz), 7.98 (d, 2H, J = 8.7Hz).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.9, 23.3, 42.7, 61.9, 120.4, 127.3, 127.5, 127.7, 127.8, 127.9, 128.0, 129.2, 130.4, 133.1, 137.0, 139.1, 140.6, 165.4, 169.9, 176.7.

Analysis : Mol. Formula: $C_{25}H_{23}N_3O_3$
Calcd.: C 72.62, H 5.61, N 10.16.
Found: C 72.59, H 5.58, N 10.13.

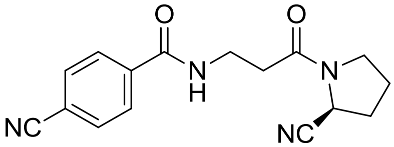
5.1.4. General procedure for the synthesis of compounds (17a-d and 18a-b)





To a solution of respective amide compounds **11e-f**, **12e-f** and **16e-f** (0.25 mmol) in dry CH_2Cl_2 (2.5 ml) at 0 °C was added dropwise trifluoroacetic anhydride (0.5 mmol) and the mixture was gradually warm to room temperature and stirred for 6hrs. After completion of reaction solvent was evaporated under reduced pressure and the residue thus obtained was subjected for purification by preparative HPLC method as described earlier in section **5.1.3.-purification**.

5.1.4.1. (S)-4-Cyano-N-(3-(2-cyanopyrrolidin-1-yl)-3-oxopropyl)benzamide (17a)



17a (260 mg, 85%) was prepared by means of the general procedure described in **5.1.4.** as a white solid. 84-86 °C; Purity by HPLC: 99.83% AUC.

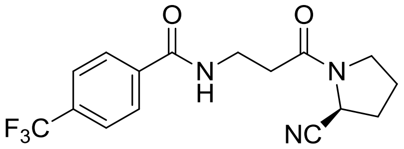
ESI/MS (m/z) : 297.1 $(M+H)^+$. **Mol. Wt.** = 296.3 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.17-2.19 (m, 2H), 2.24- 2.28 (m, 2H), 2.73-2.77 (m, 2H), 3.55-3.62 (m, 1H), 3.63-3.68 (m, 2H), 3.71-3.76 (m, 1H), 4.74-4.87 (dd, 1H, J_1 = 5.0Hz, J_2 = 7.6Hz), 7.71 (d, 2H, J = 8.4Hz), 8.02 (d, 2H, J = 8.4Hz).

^{13}C NMR (100 MHz, Methanol-d_4): δ 19.8, 23.1, 34.3, 39.2, 42.2, 43.6, 116.1, 116.4, 117.9, 127.9, 133.2, 137.7, 167.6, 177.4.

Analysis : Mol. Formula: $C_{16}H_{16}N_4O_2$
Calcd.: C 64.85, H 5.44, N 18.91.
Found: C 64.87, H 5.43, N 18.93.

5.1.4.2. (S)-N-(3-(2-Cyanopyrrolidin-1-yl)-3-oxopropyl)-4-(trifluoromethyl) benzamide (17b)



17b (280 mg, 81%) was prepared by means of the general procedure described in **5.1.4.** as a white solid. 77-79 °C; Purity by HPLC: 99.74% AUC.

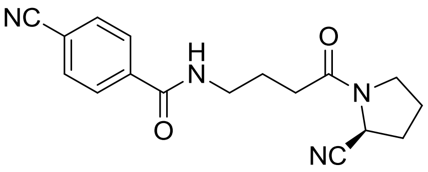
ESI/MS (m/z) : 340.2 $(M+H)^+$. **Mol. Wt.** = 339.3 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.14-2.16 (m, 2H), 2.23- 2.26 (m, 2H), 2.71-2.76 (m, 2H), 3.54-3.59 (m, 1H), 3.64-3.67 (m, 2H), 3.69-3.73 (m, 1H), 4.74-4.87 (dd, 1H, J_1 = 5.2Hz, J_2 = 7.8Hz), 7.68 (d, 2H, J = 8.9Hz), 7.89 (d, 2H, J = 8.9Hz).

^{13}C NMR (100 MHz, Methanol-d_4): δ 19.5, 23.2, 34.8, 38.9, 42.4, 43.7, 118.1, 119.4, 125.6 (q, J = 268.4Hz), 127.3, 134.5 (q, J = 26.7Hz), 137.0, 167.3, 177.8.

Analysis : Mol. Formula: $C_{16}H_{16}F_3N_3O_2$
Calcd.: C 56.64, H 4.75, N 12.38.
Found: C 56.60, H 4.73, N 12.35.

5.1.4.3. (S)-4-Cyano-N-(4-(2-cyanopyrrolidin-1-yl)-4-oxobutyl)benzamide (17c)



17c (284 mg, 81%) was prepared by means of the general procedure described in **5.1.4.** as a white solid. 97-99 °C; Purity by HPLC: 99.56% AUC.

ESI/MS (m/z) : 311.3 $(M+H)^+$. **Mol. Wt.** = 310.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.71-1.76 (m, 2H), 1.88- 2.01 (m, 2H), 2.11-2.15 (m, 2H), 2.35-2.39 (m, 2H), 3.23-3.31 (m, 2H), 3.42-3.45 (m, 1H), 3.57-3.64 (m, 1H), 4.71-4.73 (dd, 1H, J_1 = 4.2Hz, J_2 = 7.6Hz), 7.70 (d, 2H, J = 8.4Hz), 7.99 (d, 2H, J = 8.4Hz).

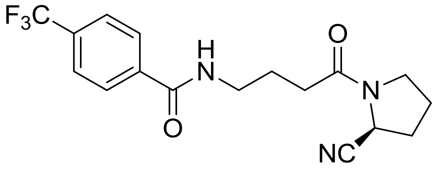
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.9, 23.1, 27.8, 29.2, 42.2, 42.7, 43.2, 116.2, 116.7, 117.8, 127.9, 133.3, 137.6, 167.9, 176.6.

Analysis : Mol. Formula: $C_{17}H_{18}N_4O_2$

Calcd.: C 65.79, H 5.85, N 18.05.

Found: C 65.76, H 5.85, N 18.04.

5.1.4.4. (S)-N-(4-(2-Cyanopyrrolidin-1-yl)-4-oxobutyl)-4-(trifluoromethyl)benzamide (17d)



17d (278 mg, 79%) was prepared by means of the general procedure described in **5.1.4.** as a white solid. 82-84 °C; Purity by HPLC: 99.27% AUC.

ESI/MS (m/z) : 354.2 $(M+H)^+$. **Mol. Wt.** = 353.3 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 1.73-1.77 (m, 2H), 1.89- 2.03 (m, 2H), 2.10-2.13 (m, 2H), 2.34-2.39 (m, 2H), 3.23-3.30 (m, 2H), 3.41-3.45 (m, 1H), 3.56-3.63 (m, 1H), 4.70-4.73 (dd, 1H, J_1 = 4.0Hz, J_2 = 7.6Hz), 7.67 (d, 2H, J = 8.6Hz), 7.96 (d, 2H, J = 8.6Hz).

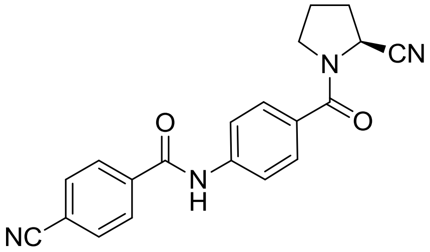
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.8, 22.9, 27.9, 29.0, 42.2, 42.9, 43.4, 118.0, 119.5, 125.8 (q, J = 269.2Hz), 127.8, 133.8 (q, J = 28.4Hz), 137.0, 167.8, 176.4.

Analysis : Mol. Formula: $C_{17}H_{18}F_3N_3O_2$

Calcd.: C 57.79, H 5.13, N 11.89.

Found: C 57.77, H 5.10, N 11.85.

5.1.4.5. (S)-4-Cyano-N-(4-(2-cyanopyrrolidine-1-carbonyl)phenyl)benzamide (18a)



18a (211 mg, 85%) was prepared by means of the general procedure described in **5.1.4.** as a white solid. 109-111 °C; Purity by HPLC: 99.68% AUC.

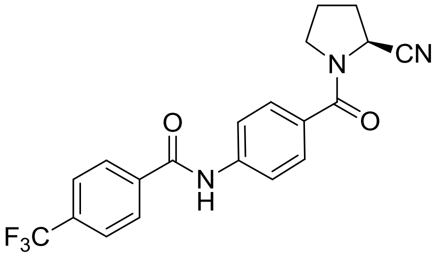
ESI/MS (m/z) : 345.6 $(M+H)^+$. **Mol. Wt.** = 344.4 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ 1.96-2.03 (m, 2H), 2.14-2.23 (m, 1H), 2.27-2.35 (m, 1H), 3.50-3.55 (m, 1H), 3.62-3.68 (m, 1H), 4.84-4.89 (dd, 1H, J = 5.0Hz, J = 7.8Hz), 7.69 (d, 2H, J = 8.4Hz), 7.73 (d, 2H, J = 8.6Hz), 7.82 (d, 2H, J = 8.4Hz), 7.98 (d, 2H, J = 8.6Hz).

^{13}C NMR (100 MHz, Methanol-d_4): δ 19.8, 22.9, 42.7, 43.9, 116.0, 116.4, 117.8, 120.3, 128.1, 128.3, 130.1, 131.9, 136.8, 139.3, 165.2, 169.6.

Analysis : Mol. Formula: $C_{20}H_{16}N_4O_2$
Calcd.: C 69.76, H 4.68, N 16.27.
Found: C 69.73, H 4.65, N 16.29.

5.1.4.6. (S)-N-(4-(2-Cyanopyrrolidine-1-carbonyl)phenyl)-4-(trifluoromethyl) benzamide (18b)



18a (224 mg, 83%) was prepared by means of the general procedure described in **5.1.4.** as a white solid. 132-134 °C; Purity by HPLC: 99.36% AUC.

ESI/MS (m/z) : 388.2 $(M+H)^+$. **Mol. Wt.** = 387.4 g.

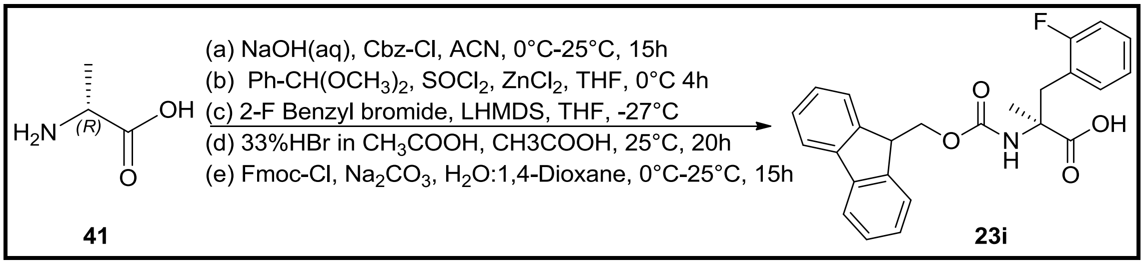
^{1}H NMR (400 MHz, Methanol-d_4): δ 1.95-2.01 (m, 2H), 2.13-2.21 (m, 1H), 2.27-2.36 (m, 1H), 3.49-3.55 (m, 1H), 3.61-3.67 (m, 1H), 4.85-4.89 (dd, 1H, J = 5.2Hz, J = 7.8Hz), 7.65 (d, 2H, J = 8.4Hz), 7.69 (d, 2H, J = 8.8Hz), 7.82 (d, 2H, J = 8.4Hz), 7.89 (d, 2H, J = 8.8Hz).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 19.9, 23.1, 42.8, 43.9, 117.9, 119.5, 120.3, 125.5 (q, J = 270.8Hz), 127.9, 128.0, 130.2, 134.8 (q, J = 29.3Hz), 136.7, 139.4, 165.4, 169.8.

Analysis : Mol. Formula: $C_{20}H_{16}F_3N_3O_2$
Calcd.: C 62.01, H 4.16, N 10.85.
Found: C 61.97, H 4.15, N 10.83.

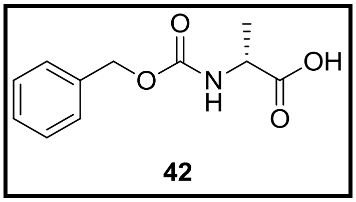
5.1.5. Experimental Details : Peptidomimetic based DPP-IV inhibitors, devoid of CYP liabilities (Second series)

5.1.5.1. (S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-fluorophenyl)-2-methyl propanoic acid (Fmoc-αMe-2F-Phe-OH)(23i)



41 **23i**

Step a: (R)-2-(((Benzyloxy)carbonyl)amino)propanoic acid (42)



42

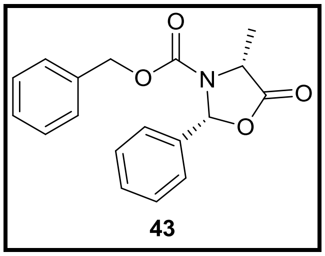
In a 500ml R.B. Flask was placed D-alanine **41** (10 g, 112 mmol), to it added 112.5 ml 2N NaOH (8.98 g, 224 mmol) solution at 0^{o}C-5^{o}C, (clear solution obtained.) followed by acetonitrile (100 ml) and stirred at 0^{o}C-5^{o}C for 10 min. Charged to this content 57.5 ml of 50% benzylchloroformate solution in toluene (28.7 g, 168 mmol) maintaining temperature 0^{o}C-5^{o}C over a period 30min. Reaction mixture was then slowly brought to room temperature and stirred for 15h.

After completion of reaction (TLC), solvent of the reaction mixture was evaporated under reduced pressure and diluted with D. M. water (150 ml). This aqueous layer was extracted with ether (2X100 ml) to remove impurities. Aqueous layer was then acidified to pH 2 with 2N HCl and extracted with ethyl acetate (3X100 ml). Combined organic layers were washed with water and brine solution, dried over anhy. Na_2SO_4, filtered and evaporated to dryness. Crude residue thus obtain was purified by column chromatography using 100-200 mesh silica as a stationary phase and 0-30% ethyl acetate in n-Hexane as mobile phase. Pure fractions were collected, combined and evaporated to dryness to give 18 g (72% yield) of the desired product Cbz-D-alanine **42** as a white powder. Mp: 83-84 ^{o}C, Purity by HPLC: 97.6% AUC.

ESI/MS (m/z) : 3 $(M+H)^+$. **Mol. Wt.** = 223.2 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (d, 3H, J = 7.35Hz), 4.45 (m, 1H), 5.12 (s, 2H), 5.32 (d, 1H, J = 7.26Hz, -N**H**), 7.32-7.35 (m, 5H), 7.98 (bs, 1H, -COO**H**).

Step b: (2R,4R)-Benzyl 4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylate (43)



43

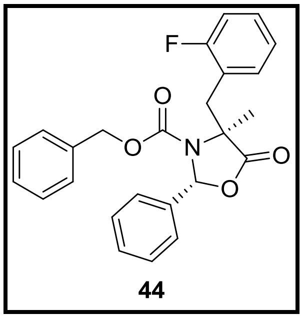
In a 250 ml 3-neck R. B. Flask was placed Cbz-D-Ala-OH **42** (18 g, 80.7 mmol) prepared in **step a**, and was dissolved in dry THF (135 ml) under nitrogen atmosphere. To the clear solution obtained was added 12.1 ml benzaldehyde dimethylacetal (12.26 g, 80.7 mmol) and cooled to 0^{o}C-5^{o}C using ice-bath. To this reaction mixture was charged dropwise $SOCl_2$ (5.85 ml, 80.7 mmol) maintaining temperature 0^{o}C-5^{o}C. After 5 min. charged anhy. $ZnCl_2$ (11.0 g, 80.7 mmol) portionwise.(Observation: colourless clear reaction mixture turned light yellow clear solution) Reaction mixture was stirred at this temperature for 3h then again charged sequentially $SOCl_2$ (1.2 ml, 16.2 mmol) and $ZnCl_2$ (2.2 g, 16.2 mmol) and stirred for additional 1h at 0^{o}C-5^{o}C.

After completion of reaction, reaction mixture was quenched with D. M. water (100 ml) in such a way that temperature should not rise above 10^{o}C. Compound was extracted with ether (3X100 ml), washed with water (100 ml) till became neutral to pH, washed with sat. $NaHCO_3$ (1X100 ml) and brine (1X100 ml). Organic layer was dried over anhy. Na_2SO_4, and evaporated to dryness, residue obtained was titurated with n-hexane (2X50 ml), solid precipitated, solvent was decanted and dried the solid under reduced pressure to give 17.07 g (68% yield) of (2R,4R)-benzyl 4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylate **43** as a white solid. The product was used as such in the next reaction step without any further purification. Purity by HPLC: 89.4% AUC.

ESI/MS (m/z) : 312.2 $(M+H)^+$. **Mol. Wt.** = 311.3 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (d, 3H, J = 6.9Hz), 4.49 (q, 1H, J = 6.9Hz), 5.15 (s, 2H), 6.64 (s, 1H), 7.25-7.40 (m, 10H).

Step c: (2R,4S)-Benzyl 4-(2-fluorobenzyl)-4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylate (44)



44

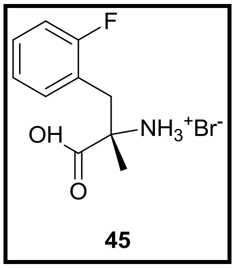
In a 250 ml R. B. Flask equipped with nitrogen inlet charged dry THF (170 ml) through septum and was cooled to -27 °C. To this added 115 ml solution of 0.5 M KHMDS in toluene (11.45 g, 57.4 mmol) at -27 °C. To this reaction mixture was charged dropwise premixed solution of oxazolidinone **43** (17 g, 54.6 mmol) and 2-fluoro benzyl bromide (6.6 ml, 54.6 mmol) dissolved in 35 ml of dry THF over a period of 30 min. maintaining temperature -30 °C to -28 °C. Stirred the reaction mixture at this temperature for 1h and then at room temperature for 1h. Reaction was monitored by TLC.

After completion of the reaction, the reaction mixture was poured in to an ice cold sat. $NaHCO_3$ solution (250 ml), extracted with ether (3X150 ml), washed the organic layer with water (1X150 ml) and brine (1X150 ml). Solvent was evaporated to dryness after drying over anhy. Na_2SO_4 to give 21.3 g (92% yield) of (2R,4S)-benzyl 4-(2-fluorobenzyl)-4-methyl-5-oxo-2-phenyloxazolidine-3-carboxylate **44** as a light yellow coloured thick oil. Purity by HPLC: 83.2% AUC.

ESI/MS (m/z) : 420.1 $(M+H)^+$, 443.8 $(M+Na)^+$ **Mol. Wt.** = 419.4 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (s, 1.5H), 2.02 (s, 1.5H), 2.98 (d, 0.5H, J = 13.95Hz), 3.09 (d, 0.5H, J = 13.86Hz), 3.66 (d, 0.5H, J = 13.98Hz), 3.91 (d, 0.5H, J = 13.89Hz), 5.15 (s, 1H), 5.26 (s, 1H), 5.53 (s, 0.5H), 5.60 (s, 0.5H), 6.80 (d, 1H, J = 7.02Hz), 7.09-7.78 (m, 13H).

Step d: (S)-2-Amino-3-(2-fluorophenyl)-2-methylpropanoic acid hydrobromide (45)



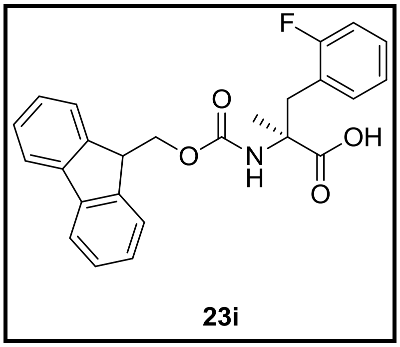
45

21 g, (50.1 mmol) of (2R,4S)-benzyl 4-(2-fluorobenzyl)-4-methyl-5-oxo-2-phenyl oxazolidine-3-carboxylate **44** prepared in above step was placed in single neck 100 ml R. B. Flask, to it added glacial acetic acid (42 ml) and stirred at room temperature for 15 min. To this reaction mixture was added 26 ml 33% HBr in acetic acid (9.22 g, 115.2 mmol) and stirred at room temperature for 20h. Acetic acid from the reaction mixture was distilled off and to the residue left was added D. M. water (168 ml) followed by addition of 2M $HBr_{(aq)}$ (32 ml, 62.6 mmol). This reaction content was extracted with ether (3X100 ml) to remove impurities. Aqueous layer was then evaporated to dryness and residue obtained was triturated with dry ether (3X100 ml) to give 10 g (72% yield) of (S)-2-amino-3-(2-fluorophenyl)-2-methylpropanoic acid hydrobromide **45** as a cream coloured crystalline solid. Mp: 248 °C dec., Purity by HPLC: 96.2% AUC.

ESI/MS (m/z) : 198.3 $(M+H)^+$. **Mol. Wt.** = 197.2 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.44 (s, 3H), 3.15 (m, 2H), 7.04-728 (m, 4H), 8.33 (bs, 3H, $-NH_3^+$), 13.62 (bs, 1H, -COO**H**).

Step d: (S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3-(2-fluorophenyl)-2-methyl propanoic acid (23i)



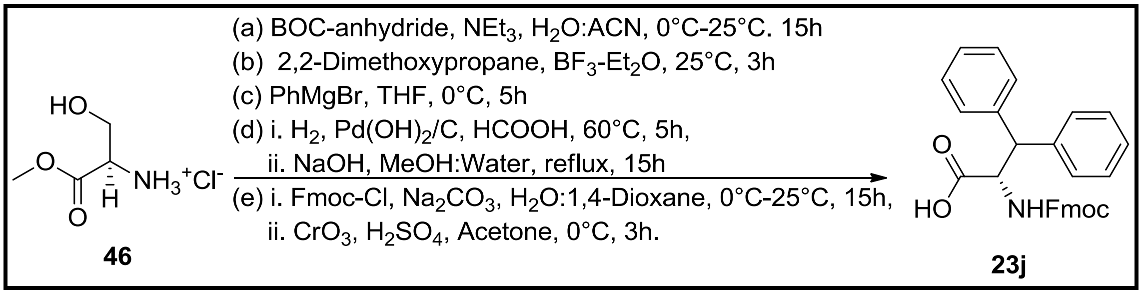
23i

(S)-2-Amino-3-(2-fluorophenyl)-2-methylpropanoic acid hydrobromide **45** was converted to its Fmoc derivative **23i** with 87% yield by using method reported for the synthesis of compound **4** as described in **section 5.1.2.2.1.** as a white fluffy solid. Mp: 187-189 °C, Purity by HPLC: 99.3% AUC, 98.45% ee., Specific optical rotation (SOR): -14.48° (C=1% in $CHCl_3$ at 25 °C)

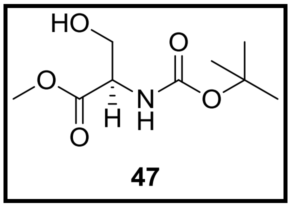
ESI/MS (m/z) : 420.3 $(M+H)^+$. **Mol. Wt.** = 419.4 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.60 (bs, 3H), 3.35-3.43 (m, 2H), 4.24 (t, 1H, J = 4.95Hz), 4.42 (bs, 2H), 5.38 (s, 1H, -N**H**), 6.97-7.00 (m, 3H), 7.05-7.18 (m, 1H), 7.19-7.31 (m, 2H), 7.39 (t, 2H, J = 5.4Hz), 7.57 (t, 2H, J = 6.3Hz), 7.76 (d, 2H, J = 5.4Hz), 8.70 (bs, 1H, -COO**H**).

5.1.6. (S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3,3-diphenylpropanoic acid (Fmoc-βPPA-OH)(23j)



Step a: (R)-Methyl 2-((tert-butoxycarbonyl)amino)-3-hydroxypropanoate (47)



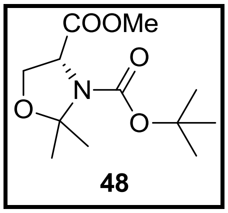
In a single neck R. B. Flash was placed 10 g (64.3 mmol) of D-serine methyl ester hydrochloride **46**, acetonitrile (100 ml) and D. M. water (100 ml). To the suspension formed was added triethylamine (22.4 ml, 160.75 mmol) at room temperature. The reaction mixture was stirred for 30 min. and then cool to $0^{o}C$-$5^{o}C$ and charged to it BOC-anhydride (17.8 ml, 77.4 mmol) dropwise over a period of 45 min. Reaction mixture was then brought to room temperature and stirred for 15h.

After completion of reaction (TLC), solvent was removed under reduced pressure, followed by addition of ethyl acetate (150 ml), D. M. Water (150 ml), layers were separated and organic layer was washed with water (1X100 ml) and brine (1X100 ml). Organic layer was dried over anhy. Na_2SO_4 and evaporated to dryness. Crude residue thus obtained was purified by column chromatography using 100-200 mesh silica as stationary phase and 0-20% ethyl acetate in n-hexane as an eluting system. Pure fractions were collected and evaporated to dryness to give 11.86 g (84% yield) of (R)-methyl 2-((tert-butoxycarbonyl)amino)-3-hydroxypropanoate **47** as a colourless viscous liquid.

ESI/MS (m/z) : 220.3 $(M+H)^+$. **Mol. Wt.** = 219.2 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.49 (s, 9H), 3.63 (s, 3H), 3.84 (dd, 1H, J1 = 3.2Hz, J2 = 11.2Hz), 4.05 (m, 1H), 4.32-4.39 (m, 1H), 5.91 (bs, 1H, -N**H**), 6.65 (bs, 1H, -O**H**).

Step b: (R)-3-tert-Butyl 4-methyl-2,2-dimethyloxazolidine-3,4-dicarboxylate (48)



48

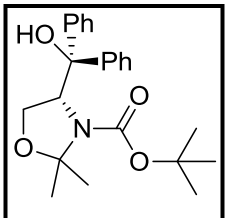
11 g (50.2 mmol) of product prepared in above step (R)-methyl 2-((tert-butoxycarbonyl)amino)-3-hydroxypropanoate **47** was placed in a two neck R. B. Flask and was dissolved in acetone (160 ml 2,2-dimethoxy propane (50 ml) and catalytic amount of $BF_3 \cdot Et_2O$ (0.4 ml) were added at room temperature. Reaction mixture changed from colourless to dark yellow clear solution. Reaction was stirred at room temperature for 3h. Reaction was monitored by TLC spotting.

After completion of reaction (TLC), triethylamine (1.0 ml) was added to quench the reaction, solvent was then evaporated to dryness. Crude residue thus obtained was purified by column chromatography (100-200 mesh silica gel, 0-30% Ethyl acetate in n-Hexane) to give 10.2 g (78% yield) of the title compound **48** as a colourless thick oil.

ESI/MS (m/z) : 260.5 $(M+H)^+$. **Mol. Wt.** = 259.3 g.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 1.35 (s, 9H), 1.51 (s, 6H), 3.67 (s, 3H), 4.03-4.07 (m, 2H), 4.35-4.39 (m, 1H).

Step c: (R)-tert-Butyl 4-(hydroxydiphenylmethyl)-2,2-dimethyloxazolidine-3-carboxylate (49)



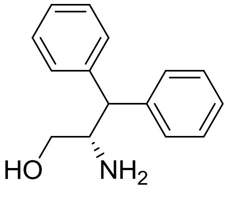
49

In a 500 ml 3-neck R. B. Flask were placed Magnesium metal (5.09 g, 212.3 mmol), dry THF (250 ml) and a small crystal of iodine. To this content bromobenzene (33.3 g, 193 mmol) was added dropwise with gentle heating of the R. B. flask. The reaction got initiated, remaining amount of bromobenzene was added cautiously so as to control the rate. After the Mg metal gets consumed, reaction content was stirred for additional 1h at room temperature. To the freshly prepared Grignard reagent was added 10 g (38.61 mmol) of the (R)-3-tert-butyl-4-methyl-2,2-dimethyloxazolidine-3,4-dicarboxylate **48** dissolved in dry THF (50 ml) dropwise through pressure equalizing dropping funnel in an inert atmosphere at room temperature over a period of 30min. After completion of the addition, reaction mixture was stirred at room temperature for further 5h.

After completion of reaction, reaction mixture was quenched with sat. NH_4Cl solution (300 ml) and extracted with ethyl acetate (3X250 ml). Combined organic extracts were washed with sat. $Na_2S_2O_3$ solution (1X250 ml) and brine (1X250 ml). Organic layer was dried over anhy. Na_2SO_4 and evaporated to dryness to give 11.98 g (81% yield) of (R)-tert-butyl-4-(hydroxydiphenylmethyl)-2,2-dimethyloxazolidine-3-carboxylate **49** as a light yellow thick oil. Crude product thus obtained was used as such for the next reaction step. Purity by HPLC: 78.6% AUC.

ESI/MS (m/z) : 384.4 $(M+H)^+$. **Mol. Wt.** = 383.5 g.

Step d: (S)-2-amino-3,3-diphenylpropan-1-ol (50)



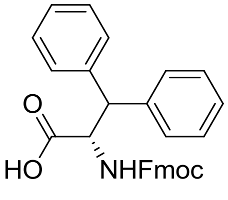
50

Deoxygenation of the tertiary hydroxyl group in the compound **49** was accomplished as described here. 11 g (28.7 mmol) of (R)-tert-butyl-4-(hydroxydiphenylmethyl)-2,2-dimethyloxazolidine-3-carboxylate **49** was placed in a Parr hydrogenation apparatus (preferably Autoclave) dissolved in formic acid (55 ml), to it added 20% $Pd(OH)_2$ on carbon (2.2 g, 20% by wt. of starting material) and hydrogenated at 60 ^oC under 10 bar pressure for 5h. Reaction mixture was then filtered through Hyflo supercel and evaporated to dryness. To the residue thus obtained was added NaOH (11.5 g, 287.2 mmol) dissolved in D. M. Water (125 ml), followed by addition of Methanol (125 ml), and then refluxed for 15h.

After completion of the reaction, solvent was evaporated to dryness under reduced pressure and residue was partition between ethyl acetate (200 ml) and sat. brine solution (100 ml). Layers were separated and aqueous layer was extracted repeatedly with ethyl acetate (3X100 ml). Combined organic layers were dried over anhy. Na_2SO_4 and evaporated to dryness to give 5.3 g (81% yield) of (S)-2-amino-

3,3-diphenylpropan-1-ol **50** as an off white solid. Product thus obtained was used as such for the next reaction step. Mp: 198-202 °C, Purity by HPLC: 83.6% AUC.
ESI/MS (m/z) : 228.4 $(M+H)^+$. **Mol. Wt.** = 227.3 g.

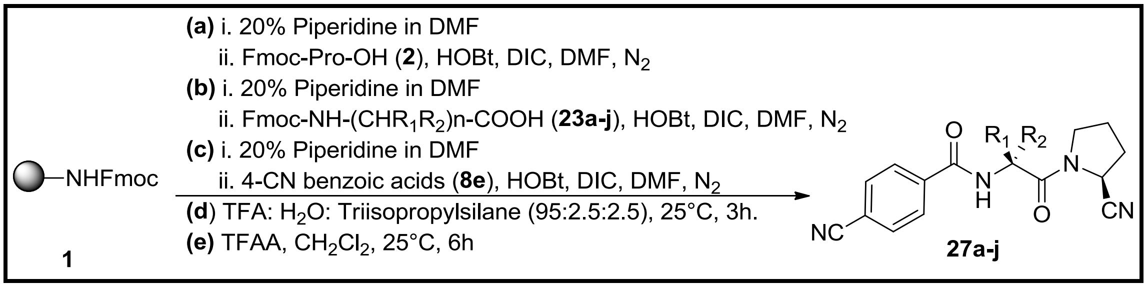
Step e: (S)-2-((((9H-Fluoren-9-yl)methoxy)carbonyl)amino)-3,3-diphenylpropanoic acid (23j)



23j

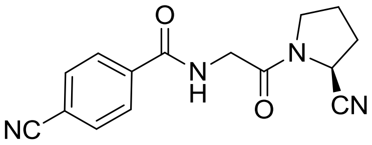
23j (7.26 g) was prepared by using the method described for the synthesis of compound **4** as illustrated in **section 5.1.2.2.1** with 81% yield as a white solid. Mp: 127-128 °C, Purity by HPLC: 99.07% AUC, Specific optical rotation SOR $[\alpha]_D$= -12° (C=1% in Chloroform).
ESI/MS (m/z) : 464.3 $(M+H)^+$. **Mol. Wt.** = 463.5 g.
^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 4.24 (t, 1H, J = 6.6 Hz), 4.38 (d, 2H, J = 6.6 Hz), 4.44 (d, 1H, J = 7.3 Hz), 4.76 (d, 1H, J = 8.8 Hz), 6.93 (d, 1H, J = 7.3 Hz, -N**H**), 7.14-7.29 (m, 12H), 7.41 (t, 2H, J = 6.8 Hz), 7.64 (d, 2H, J = 7.3 Hz), 7.82 (d, 2H, J = 7.2 Hz), 12.43 (bs, 1H, -COO**H**).

5.1.7. General procedure for the synthesis of compounds (27a-j)



The compounds **27a-j** were prepared using Fmoc based Solid Phase Peptide Synthesis (SPPS) approach using the practical methodology described for the synthesis of compounds **11a-h**, **12a-h** and **16a-h** as illustrated in experimental **section 5.1.3.** The crude carboxamides were obtained after global cleavage from the peptidyl resin were then transformed to respective nitrile derivative by dehydration using the method describe for the synthesis of compounds **17a-d** and **18a-b** as illustrated in experimental **section 5.1.4.** and purified by the method described in **section 5.1.3.-Purification** to give desired compounds **27a-j**.

5.1.7.1 (S)-4-Cyano-N-(2-(2-cyanopyrrolidin-1-yl)-2-oxoethyl)benzamide (27a)



27a (230 mg, 81%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 159-161 °C; Purity by HPLC: 97.65% AUC.

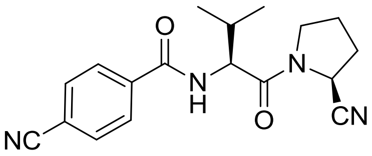
ESI/MS (m/z) : 283.1 $(M+H)^+$. **Mol. Wt.** = 282.3 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.76-1.94 (m, 3H), 2.09- 2.14 (m, 1H), 3.28-3.39 (m, 1H), 3.41-3.53 (m, 1H), 4.42 (d, 2H, J = 8.8Hz), 4.86 (dd, 1H, J_1 = 4.2Hz, J_2 = 7.6Hz), 8.12 (d, 2H, J = 8.4Hz), 8.28 (d, 2H, J = 8.4Hz), 8.72 (t, 1H, J = 8.8Hz, -NH).

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 22.8, 30.2, 41.6, 48.2, 50.1, 116.9, 117.2, 119.3, 126.7, 128.6, 138.4, 166.8, 167.2.

Analysis : Mol. Formula: $C_{15}H_{14}N_4O_2$
Calcd.: C 63.82, H 5.00, N 19.85.
Found: C 63.85, H 5.01, N 19.81.

5.1.7.2 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-3-methyl-1-oxobutan-2-yl)benzamide (27b)



27b (223 mg, 79%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 146-148 °C; Purity by HPLC: 98.21% AUC.

ESI/MS (m/z) : 325.3 $(M+H)^+$. **Mol. Wt.** = 324.2 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 0.943 (d, 3H, J = 6.4Hz), 0.991 (d, 3H, J = 6.4Hz), 1.77-1.85 (m, 2H), 1.92-2.03 (m, 2H), 2.12-2.18 (m, 1H), 3.62-3.66 (m, 1H), 3.84-3.89

(m, 1H), 4.43 (t, 1H, J = 8.6Hz), 4.89 (dd, 1H, J_1 = 4.4Hz, J_2 = 8.4Hz), 7.98 (d, 2H, J = 8.6Hz), 8.18 (d, 2H, J = 8.6Hz), 8.53 (d, 1H, J = 8.4Hz, -NH).

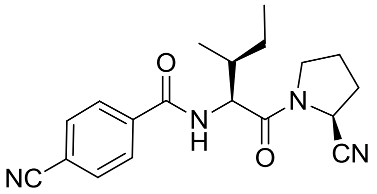
^{13}C NMR (100 MHz, DMSO-d_6): δ 18.5, 18.7, 22.4, 30.4, 32.1, 48.1, 50.3, 60.8, 116.7, 116.9, 117.8, 127.2, 127.9, 137.8, 167.3, 173.1.

Analysis : Mol. Formula: $C_{18}H_{20}N_4O_2$

Calcd.: C 66.65, H 6.21, N 17.27.

Found: C 66.62, H 6.19, N 17.23.

5.1.7.3. 4-Cyano-N-((2S,3S)-1-((S)-2-cyanopyrrolidin-1-yl)-3-methyl-1-oxopentan-2-yl) benzamide (27c)



27c (231 mg, 84%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 183-185 °C; Purity by HPLC: 99.41% AUC.

ESI/MS (m/z) : 339.1 $(M+H)^+$. **Mol. Wt.** = 338.2 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.825 (t, 3H, J = 7.4Hz), 0.955 (d, 3H, J = 6.8Hz), 1.09-1.21 (m, 1H), 1.52-1.63 (m, 1H), 1.77-1.85 (m, 2H), 1.93-2.05 (m, 3H), 3.61-3.65 (m, 1H), 3.87-3.93 (m, 1H), 4.49 (dd, 1H, J_1 = 8.0Hz, J_2 = 9.6Hz), 4.91 (dd, 1H, J_1 = 4.4Hz, J_2 = 8.0Hz), 8.02 (d, 2H, J = 8.4Hz), 8.17 (d, 2H, J = 8.4Hz), 8.58 (d, 1H, J = 8.0Hz, -NH).

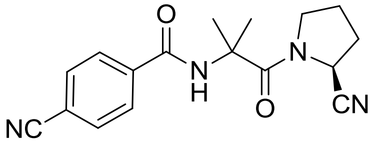
^{13}C NMR (100 MHz, DMSO-d_6): δ 10.7, 15.4, 22.6, 24.5, 31.1, 38.2, 48.3, 50.7, 58.3, 116.9, 117.2, 117.8, 127.2, 131.9, 138.3, 167.4, 172.9.

Analysis : Mol. Formula: $C_{19}H_{22}N_4O_2$

Calcd.: C 67.44, H 6.55, N 16.56.

Found: C 67.45, H 6.52, N 16.54.

5.1.7.4. (S)-4-Cyano-N-(1-(2-cyanopyrrolidin-1-yl)-2-methyl-1-oxopropan-2-yl) benzamide (27d)



27d (198 mg, 78%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 165-167 °C; Purity by HPLC: 97.87% AUC.

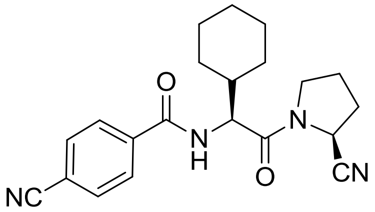
ESI/MS (m/z) : 311.2 $(M+H)^+$. **Mol. Wt.** = 310.1 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.41 (s, 3H), 1.45 (s, 3H), 1.67-1.91 (m, 3H), 2.01-2.09 (m, 1H), 3.49-3.53 (m, 1H), 3.55-3.72 (m, 1H), 4.86 (dd, 1H, J_1 = 5.6Hz, J_2 = 8.4Hz), 8.07 (d, 2H, J = 8.6Hz), 8.19 (d, 2H, J = 8.6Hz), 9.21 (s, 1H, -NH).

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 22.6, 26.7, 30.9, 48.5, 50.6, 67.3, 116.8, 117.1, 117.6, 127.6, 132.1, 138.7, 167.2, 172.9.

Analysis : Mol. Formula: $C_{17}H_{18}N_4O_2$
Calcd.: C 65.79, H 5.85, N 18.05.
Found: C 65.76, H 5.87, N 18.04.

5.1.7.5. 4-Cyano-N-((S)-2-((S)-2-cyanopyrrolidin-1-yl)-1-cyclohexyl-2-oxoethyl) benzamide (27e)



27e (174 mg, 83%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 143-145 °C; Purity by HPLC: 97.25% AUC.

ESI/MS (m/z) : 365.1 $(M+H)^+$. **Mol. Wt.** = 364.4 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.17-1.24 (m, 10H), 1.53-1.65 (m, 1H), 1.74-1.91 (m, 2H), 2.28-2.42 (m, 2H), 3.43-3.55 (m, 1H), 3.62-3.67 (m, 1H), 4.46 (dd, 1H, J_1 = 8.2Hz, J_2 = 9.2Hz), 4.92 (dd, 1H, J_1 = 4.8Hz, J_2 = 8.2Hz), 7.97 (d, 2H, J = 8.4Hz), 8.13 (d, 2H, J = 8.4Hz), 9.18 (d, 1H, J = 8.2Hz, -NH).

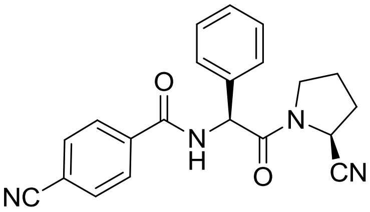
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 21.8, 25.3, 25.4, 26.7, 27.9, 30.7, 32.8, 48.3, 50.7, 56.4, 116.9, 117.7, 118.3, 127.4, 132.3, 138.5, 167.4, 172.5.

Analysis : Mol. Formula: $C_{21}H_{24}N_4O_2$

Calcd.: C 69.21, H 6.64, N 15.24.

Found: C 69.23, H 6.60, N 15.21.

5.1.7.6. 4-Cyano-N-((S)-2-((S)-2-cyanopyrrolidin-1-yl)-2-oxo-1-phenylethyl) benzamide (27f)



27f (178 mg, 80%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 182-184 °C; Purity by HPLC: 99.08% AUC.

ESI/MS (m/z) : 359.2 $(M+H)^+$. **Mol. Wt.** = 358.4 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.68-1.93 (m, 3H), 2.01-2.11 (m, 1H), 3.41-3.53 (m, 1H), 3.62-3.65 (m, 1H), 4.92 (dd, 1H, J_1 = 5.2Hz, J_2 = 8.0Hz), 5.21 (d, 1H, J = 8.2Hz), 7.21-7.30 (m, 5H), 8.04 (d, 2H, J = 8.4Hz), 8.19 (d, 2H, J = 8.4Hz), 8.96 (d, 1H, J = 8.2Hz, -NH).

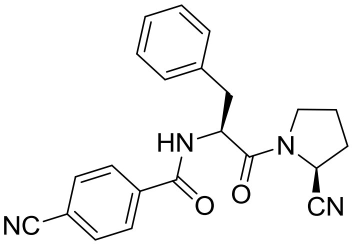
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 22.5, 31.2, 48.7, 50.4, 59,2, 116.8, 117.4, 118.6, 126.2, 127.3, 127.4, 128.8, 129.3, 132.3, 136.3, 138.5, 167.4, 172.7.

Analysis : Mol. Formula: $C_{21}H_{18}N_4O_2$

Calcd.: C 70.38, H 5.06, N 15.63.

Found: C 70.35, H 5.04, N 15.59.

5.1.7.7. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3-phenylpropan-2-yl) benzamide (27g)



27g (164 mg, 77%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 184-186 °C; Purity by HPLC: 98.53% AUC.

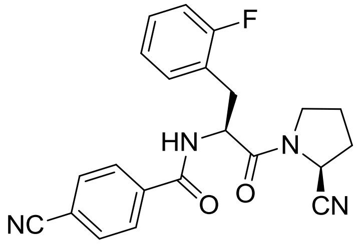
ESI/MS (m/z) : 373.5 $(M+H)^+$. **Mol. Wt.** = 372.4 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.67-1.93 (m, 3H), 2.01-2.08 (m, 1H), 2.98 (dd, 1H, J_1 = 8.0Hz, J_2 = 13.2Hz), 3.06 (dd, 1H, J_1 = 7.2Hz, J_2 = 13.2Hz), 3.37-3.46 (m, 1H), 3.58-3.63 (m, 1H), 4.74-4.78 (m, 1H), 4.87 (dd, 1H, J_1 = 4.8Hz, J_2 = 8.0Hz), 7.23-7.34 (m, 5H), 8.02 (d, 2H, J = 8.6Hz), 8.17 (d, 2H, J = 8.6Hz), 8.96 (d, 1H, J = 8.2Hz, -NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 22.3, 31.4, 37.9, 48.7, 50.4, 56,2, 117.0, 117.6, 118.5, 126.2, 127.4, 127.6, 128.8, 129.1, 132.1, 136.3, 138.6, 167.4, 173.9.

Analysis : Mol. Formula: $C_{22}H_{20}N_4O_2$
Calcd.: C 70.95, H 5.41, N 15.04.
Found: C 70.92, H 5.39, N 15.01.

5.1.7.8. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-3-(2-fluorophenyl)-1-oxopropan-2-yl)benzamide (27h)



27h (221 mg, 85%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 208-209 °C; Purity by HPLC: 99.27% AUC.

ESI/MS (m/z) : 391.2 $(M+H)^+$. **Mol. Wt.** = 390.4 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.78-1.81 (m, 1H), 1.83-1.97 (m, 1H), 2.02-2.15 (m, 2H), 2.96 (dd, 1H, J_1 = 7.8Hz, J_2 = 13.2Hz), 3.08 (dd, 1H, J_1 = 7.2Hz, J_2 = 13.2Hz), 3.39-3.46 (m, 1H), 3.53-3.64 (m, 1H), 4.75-4.78 (m, 1H), 4.92 (dd, 1H, J_1 = 5.2Hz, J_2 = 8.2Hz), 6.98-7.13 (m, 3H), 7.19-7.26 (m, 1H), 7.92 (d, 2H, J = 8.2Hz), 8.11 (d, 2H, J = 8.2Hz), 9.01 (d, 1H, J = 8.0Hz, -NH).

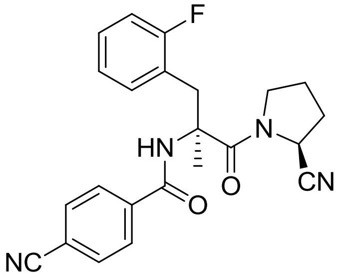
^{13}C NMR (100 MHz, DMSO-d_6): δ 21.9, 30.6, 31.2, 48.6, 50.3, 56,2, 115.4 (d, J = 31Hz), 117.0, 117.6, 118.5, 125.3, 126.1, 127.7(d, J = 14Hz), 128.2, 128.7, 129.1, 132.1, 132.7, 138.7, 162.4 (d, J= 243Hz), 167.3, 173.2.

Analysis : Mol. Formula: $C_{22}H_{19}FN_4O_2$

Calcd.: C 67.68, H 4.91, N 14.35.

Found: C 67.63, H 4.93, N 14.32.

5.1.7.9. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-3-(2-fluorophenyl)-2-methyl-1-oxopropan-2-yl)benzamide (27i)



27i (179 mg, 77%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 173-175 °C; Purity by HPLC: 98.42% AUC.

ESI/MS (m/z) : 405.2 $(M+H)^+$. **Mol. Wt.** = 404.4 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.27 (s, 3H), 1.69-1.78 (m, 1H), 1.81-1.95 (m, 1H), 2.01-2.15 (m, 2H), 3.02 (d, 1H, J = 13.6Hz), 3.13 (d, 1H, J = 13.6Hz), 3.41-3.48 (m, 1H), 3.52-3.63 (m, 1H), 4.91 (dd, 1H, J_1 = 4.8Hz, J_2 = 8.0Hz), 6.96-7.10 (m, 3H), 7.22-7.27 (m, 1H), 7.98 (d, 2H, J = 8.4Hz), 8.19 (d, 2H, J = 8.4Hz), 8.76 (bs, 1H, -NH).

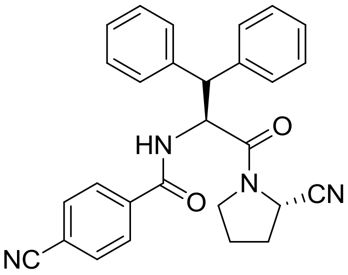
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 21.9, 23.7, 30.4, 34.2, 48.6, 50.5, 69,2, 115.6 (d, J = 30Hz), 117.2, 117.7, 118.5, 125.3, 126.2, 127.5(d, J = 14.2Hz), 128.3, 128.7, 129.3, 132.4, 132.7, 138.7, 162.8 (d, J = 247Hz), 167.8, 172.9.

Analysis : Mol. Formula: $C_{23}H_{21}FN_4O_2$

Calcd.: C 68.30, H 5.23, N 13.85.

Found: C 68.33, H 5.19, N 13.82.

5.1.7.10. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)benzamide (27j)



27j (233 mg, 84%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 129-131 °C; Purity by HPLC: 98.65% AUC.

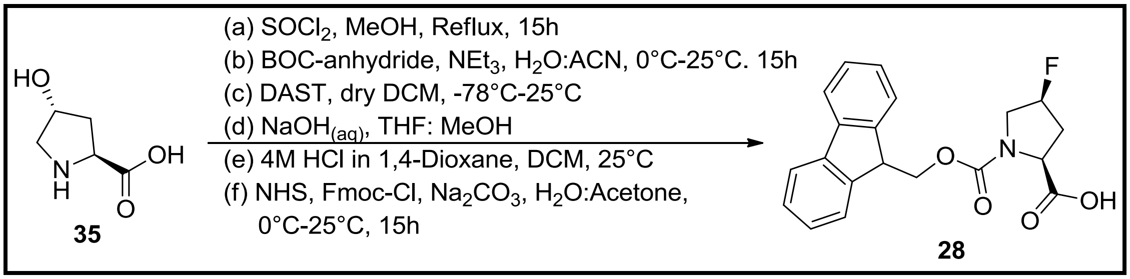
ESI/MS (m/z) : 449.3 $(M+H)^+$. **Mol. Wt.** = 448.5 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.68-1.83 (m, 3H), 1.85-1.91 (m, 1H), 3.61-3.65 (m, 1H), 3.98-4.01 (m, 1H), 4.63 (d, 1H, J = 11.6Hz), 4.87-4.92 (m, 1H), 5.74 (dd, 1H, J_1 = 8.8Hz, J_2 = 11.6Hz), 7.02-7.28 (m, 6H), 7.37-7.41 (m, 4H), 7.76 (d, 2H, J = 7.6Hz), 7.84 (d, 2H, J = 7.6Hz), 9.14 (d, 1H, J = 8.8Hz, -NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 22.1, 30.4, 42.4, 48.9, 51.3, 61.8, 116.4, 117.1, 117.6, 126.4, 126.6, 127.7, 127.8, 128.2, 128.7, 129.2, 129.3, 132.3, 137.9, 139.2, 167.6, 173.4.

Analysis : Mol. Formula: $C_{28}H_{24}N_4O_2$
Calcd.: C 74.98, H 5.39, N 12.49.
Found: C 75.01, H 5.41, N 12.47.

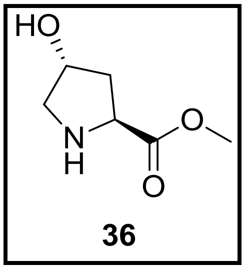
5.1.8. (2S,4S)-1-(((9H-Fluoren-9-yl)methoxy)carbonyl)-4-fluoropyrrolidine-2-carboxylic acid (Fmoc-*Cis* 4F-Pro-OH) (28)



35

28

Step a: (2S,4R)-methyl 4-hydroxypyrrolidine-2-carboxylate (36)



36

10 g (76.33 mmol) of commercially available *trans*-4-Hydroxy proline **35** was suspended in 250 ml R. B. Flask containing dry Methanol (150 ml) and cooled to 0^{o}C-5^{o}C using ice-bath. $SOCl_2$ (16.6 ml, 229 mmol) was added dropwise over a period of 30min. Reaction

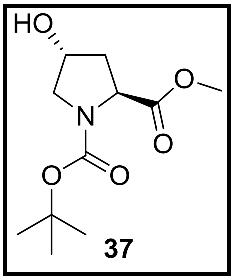
mixture was then brought to room temperature gradually and refluxed for 15h. Reaction was monitored by TLC.

After completion of the reaction, solvent was evaporated to dryness and residue obtained was triturated with n-hexane (3X150 ml) and di-isopropyl ether (3X150 ml) respectively. Crystalline solid obtained after decanting the solvent used for titration was dried well under reduced pressure using high vacuum pump to provide 9.85 g (89% Yield) hydrochloride salt of (2S,4R)-methyl 4-hydroxypyrrolidine-2-carboxylate **36** as a free flowing shiny crystalline solid. Mp: 268 °C dec.

ESI/MS (m/z) : 146.3 $(M+H)^+$. **Mol. Wt.** = 145.2 g.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 1.84 (bs, 1H, -O**H**), 1.98-2.19 (m, 2H), 2.73-2.78 (m, 1H), 3.02-3.23 (m, 2H), 3.47-3.51 (m, 1H), 3.66 (s, 3H), 6.93 (bs, 2H, >N**H$_2$**$^+$).

Step b: (2S,4R)-1-tert-Butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate (37)



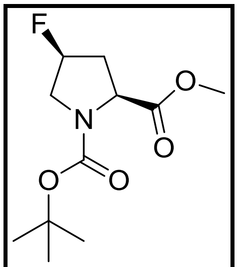
37

Titled compound **37** (11.06 g) was prepared by using the method describe for the synthesis of compound **47** as illustrated in experimental section **5.1.6. step b.** with 83% yield as a white solid. Mp: 96-97 °C, SOR $[\alpha]_D$= -65° (C=1% in Chloroform).

ESI/MS (m/z) : 246.1 $(M+H)^+$. **Mol. Wt.** = 245.3 g.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 1.49 (s, 9H), 1.94-2.15 (m, 2H), 2.34 (bs, 1H, -O**H**), 2.68-2.72 (m, 1H), 3.03-3.21 (m, 2H), 3.34-3.39 (m, 1H), 3.67 (s, 3H).

Step c: (2S,4S)-1-tert-Butyl 2-methyl 4-fluoropyrrolidine-1,2-dicarboxylate (38)



38

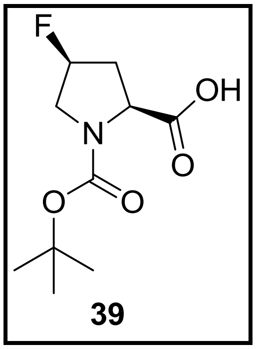
In a 2-neck R. B. Flask equipped with nitrogen inlet was charged 11 g (44.89 mmol) of product prepared in above step (2S,4R)-1-tert-butyl 2-methyl 4-hydroxypyrrolidine-1,2-dicarboxylate **37**, dissolved in dry DCM (165 ml) and cooled to -78 ^{o}C using dry ice-acetone bath. To this reaction mixture was added diethylaminosulfur trifluoride (DAST) (14.8 ml, 112.24 mmol) dropwise over a period of 45 min. Reaction mixture was then stirred at same temperature for 1h. Reaction mixture was then brought gradually to room temperature and stirred for 5h.

After completion of reaction, the mixture was poured in ice cold water (150 ml), followed by DCM (100 ml) and stirred, layers were separated and organic layer was washed with D. M. water (2X200 ml) and brine (1X100 ml). Organic layer was dried over anhy. Na_2SO_4 and evaporated to dryness. Thr residue thus obtained was purified by column chromatography to give 7.5 g (68% Yield) of (2S,4S)-1-tert-butyl 2-methyl 4-fluoropyrrolidine-1,2-dicarboxylate **38** as a light yellow oil.

ESI/MS (m/z) : 248.4 $(M+H)^+$. **Mol. Wt.** = 247.3 g.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 1.42 (s, 9H), 1.98-2.15 (m, 2H), 3.24 (m, 1H), 3.42-3.59 (m, 2H), 3.71 (s, 3H), 4.68-4.73 (m, 1H).

Step d: (2S,4S)-1-(tert-Butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (39)



39

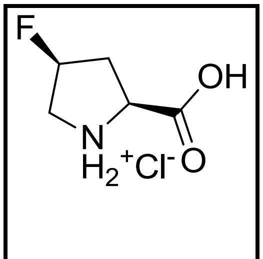
7.0 g (28.34 mmol) of (2S,4S)-1-tert-butyl 2-methyl-4-fluoropyrrolidine-1,2-dicarboxylate **38** was placed in a 150 ml 2-neck R. B. Flask, to it added methanol (35 ml), THF (35 ml) and stirred at room temperature for 5min. To the clear solution obtained was charged NaOH (1.7 g, 42.51 mmol) dissolved in D. M. Water (35 ml) at room temperature and stirred the reaction mixture for 3h.

After completion of the reaction (TLC), solvent was evaporated under reduced pressure and residue thus obtained was diluted with D. M. water (125 ml). This aqueous content was extracted with ether (3X100 ml) to remove impurities if any. Aqueous layer was then acidified to pH 4 with citric acid and extracted with ethyl acetate (3X100 ml). Combined extracts were washed successively with water (2X100 ml) and brine (1X100 ml), dried over anhy. Na_2SO_4 and concentrated under reduced pressure to give 6.47 g (98% Yield) of (2S,4S)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid **39** as a white wax.

ESI/MS (m/z) : 234.3 $(M+H)^+$. **Mol. Wt.** = 233.2 g.

^{1}H NMR (400 MHz, DMSO-*d_6*): δ 1.44 (s, 9H), 1.89-2.12 (m, 2H), 3.31-3.38 (m, 1H), 3.43-3.57 (m, 2H), 4.79-4.82 (m, 1H), 12.31 (bs, 1H, -COO**H**).

Step d: (2S,4S)-2-Carboxy-4-fluoropyrrolidin-1-ium chloride (40)



40

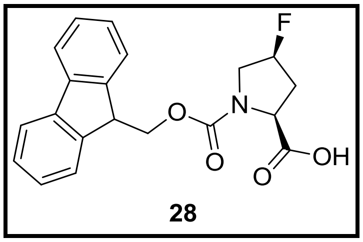
6.0 g (25.75 mmol) of (2S,4S)-1-(tert-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid **39** was dissolved in DCM (72 ml) and cooled to 10 °C. To this reaction mixture charged in-house prepared solution of 3.2M HCl in 1,4-dioxane (ml, mmol) dropwise within 15min. Reaction mixture was then brought to room temperature and stirred for 3h.

After completion of the reaction, solvent was evaporated to dryness under reduced pressure. Residue obtained was triturated with dry ether (3X75 ml), solvent was decanted and the solid precipitated was dried well under high vacuum to give 4.3 g (99% Yield) hydrochloride salt of (2S,4S)-4-fluoropyrrolidine-2-carboxylic acid **40** as a white solid.

ESI/MS (m/z) : 134.1 $(M+H)^+$. **Mol. Wt.** = 133.2 g.

^{1}H NMR (400 MHz, DMSO-*d_6*): δ 2.18 (m, 1H), 2.21-2.27 (m, 1H), 3.32-3.37 (m, 1H), 3.48-3.57 (m, 2H), 4.49-4.58 (m, 1H), 7.21 (bs, 2H, $-NH_2^+$), 12.07 (bs, 1H, -COO**H**).

Step e: (2S,4S)-1-(((9H-Fluoren-9-yl)methoxy)carbonyl)-4-fluoropyrrolidine-2-carboxylic acid (28)



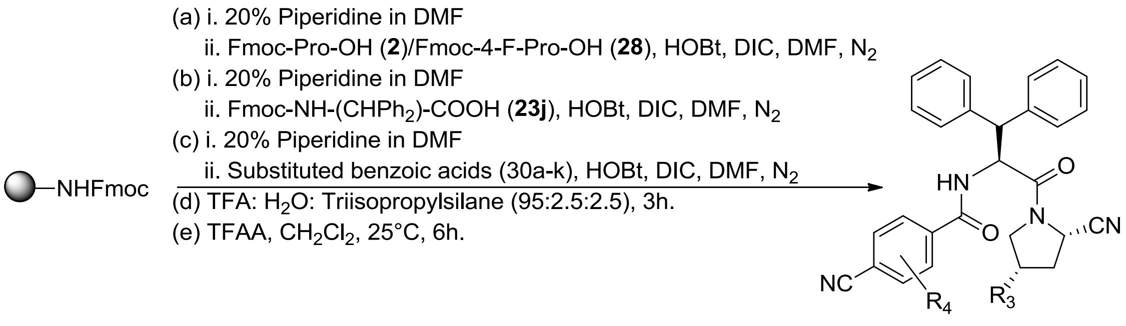
28

Compound **28** (7.22 g) was prepared according to the procedure described for the synthesis of compound **2** as illustrated in experimental **section 5.1.2.1.** with 85% yield as a white solid. Purity by HPLC: 98.37% AUC.

ESI/MS (m/z) : 356.2 $(M+H)^+$. **Mol. Wt.** = 355.4 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.89-1.94 (m, 1H), 2.21-2.26 (m, 1H), 3.31-3.36 (m, 1H), 3.48-3.57 (m, 2H), 4.43-4.56 (m, 2H), 4.92-5.01 (m, 2H), 7.34 (t, 2H, J=7.8 Hz), 7.42 (t, 2H, J=7.6 Hz), 7.59 (d, 2H, J=7.5 Hz), 7.72 (d, 2H, J=7.5 Hz), 11.94 (bs, 1H, -COO**H**).

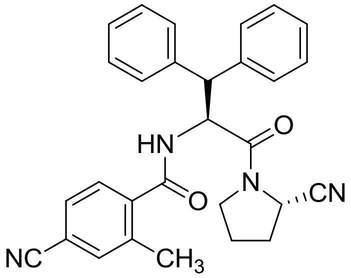
5.1.9. General procedure for the synthesis of compounds (34a-m)



1 **34a-m**

Compounds **34a-m** were prepared by Fmoc based Solid Phase Peptide Synthesis (SPPS) approach using the practical methodology described for the synthesis of compounds **11a-h**, **12a-h** and **16a-h** as illustrated in experimental **section 5.1.3.** The crude carboxamides **33a-m** obtained after global cleavage from the peptidyl resin were then transformed to respective nitrile derivative by dehydration using the method describe for the synthesis of compounds **17a-d** and **18a-b** as illustrated in experimental **section 5.1.4.** and purified by the method described in **section 5.1.3.-Purification** to give desired compounds **34a-m**.

5.1.9.1. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)-2-methylbenzamide (34a)



34a (202 mg, 81%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 126-128 °C; Purity by HPLC: 97.88% AUC.

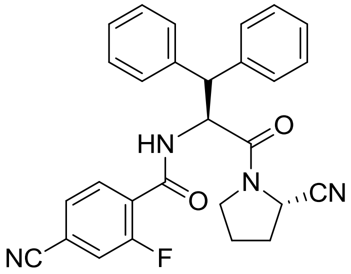
ESI/MS (m/z) : 462.7 $(M+H)^+$. **Mol. Wt.** = 462.5 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.78-1.82 (m, 3H), 1.85-1.93 (m, 1H), 2.46 (s, 3H), 3.61-3.65 (m, 1H), 3.98-4.01 (m, 1H), 4.51 (d, 1H, J = 11.6Hz), 4.84 (dd, 1H, J_1 = 2.8Hz, J_2 = 8.0Hz), 5.72 (dd, 1H, J_1 = 9.2Hz, J_2 = 11.6Hz), 7.01-7.19 (m, 7H), 7.22-7.39 (m, 5H), 7.56 (s, 1H), 9.01 (d, 1H, J = 8.8Hz, -NH).

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 18.2, 22.3, 30.2, 42.1, 48.6, 51.0, 60.4, 116.1, 116.9, 117.8, 126.2, 126.5, 127.8, 128.1, 128.2, 128.7, 129.2, 129.3, 133.3, 137.9, 140.2, 143.3, 167.4, 173.3.

Analysis : Mol. Formula: $C_{29}H_{26}N_4O_2$
Calcd.: C 75.30, H 5.67, N 12.11.
Found: C 75.28, H 5.64, N 12.10.

5.1.9.2. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)-2-fluorobenzamide (34b)



34b (202 mg, 85%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 142-144 °C; Purity by HPLC: 98.79% AUC.

ESI/MS (m/z) : 467.3 $(M+H)^+$. **Mol. Wt.** = 466.5 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.81-1.92 (m, 3H), 1.93-1.98 (m, 1H), 3.62-3.65 (m, 1H), 4.00-4.04 (m, 1H), 4.53 (d, 1H, J = 11.6Hz), 4.87 (dd, 1H, J_1 = 2.8Hz, J_2 = 8.0Hz), 5.69 (dd, 1H, J_1 = 9.0Hz, J_2 = 11.6Hz), 7.07-7.18 (m, 3H), 7.22-7.31 (m, 5H), 7.39-7.75 (m, 4H), 7.92-7.96 (m, 1H), 9.01 (d, 1H, J = 8.8Hz, -NH).

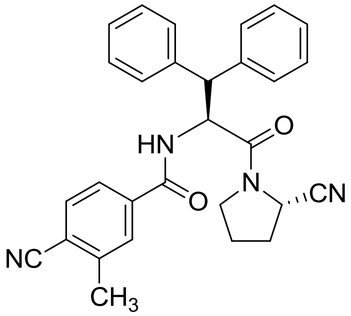
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 22.4, 30.4, 42.2, 48.7, 50.8, 60.1, 116.1(d, J = 28Hz), 116.9, 117.8, 119,5, 126.2, 126.5, 127.6, 128.2, 128.4, 128.7, 129.2, 129.3, 129.8, 140.3, 158.7(d, J = 248Hz), 167.4, 173.3.

Analysis : Mol. Formula: $C_{28}H_{23}FN_4O_2$

Calcd.: C 72.09, H 4.97, N 12.01.

Found: C 72.05, H 4.95, N 11.98.

5.1.9.3. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)-3-methylbenzamide (34c)



34c (211 mg, 83%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 169-171 °C; Purity by HPLC: 97.14% AUC.

ESI/MS (m/z) : 463.6 $(M+H)^+$. **Mol. Wt.** = 462.5 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.76-1.81 (m, 3H), 1.84-1.92 (m, 1H), 2.49 (s, 3H), 3.62-3.65 (m, 1H), 3.89-3.95 (m, 1H), 4.54 (d, 1H, J = 11.6Hz), 4.84-4.93 (dd, 1H, J_1 = 3.2Hz, J_2 = 8.0Hz), 5.72 (dd, 1H, J_1 = 9.2Hz, J_2 = 11.6Hz), 7.03-7.22 (m, 7H), 7.25-7.39 (m, 5H), 7.96 (s, 1H), 9.03 (d, 1H, J = 8.4Hz, -NH).

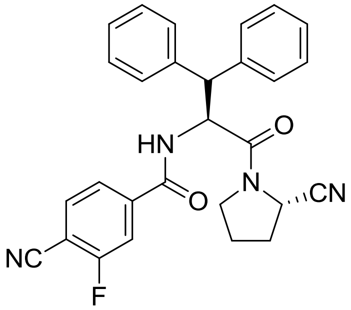
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 18.1, 22.4, 30.5, 42.1, 48.5, 51.1, 59.7, 116.2, 116.7, 117.8, 126.1, 126.4, 127.7, 128.1, 128.2, 128.6, 129.1, 129.3, 133.2, 137.8, 140.2, 143.2, 167.4, 172.9.

Analysis : Mol. Formula: $C_{29}H_{26}N_4O_2$

Calcd.: C 75.30, H 5.67, N 12.11.

Found: C 75.27, H 5.66, N 12.14.

5.1.9.4. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)-3-fluorobenzamide (34d)



34d (184 mg, 79%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 197-198 °C; Purity by HPLC: 98.39% AUC.

ESI/MS (m/z) : 466.2 $(M+H)^+$. **Mol. Wt.** = 466.5 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.82-1.93 (m, 3H), 1.95-2.04 (m, 1H), 3.59-3.63 (m, 1H), 3.97-4.02 (m, 1H), 4.53 (d, 1H, J = 11.6Hz), 4.87-4.91 (dd, 1H, J_1 = 3.8Hz, J_2 = 8.0Hz), 5.64 (dd, 1H, J_1 = 8.8Hz, J_2 = 11.6Hz), 7.09-7.18 (m, 3H), 7.21-7.33 (m, 4H), 7.38-7.76 (m, 4H), 7.82-7.91 (m, 2H), 7.93-7.96 (m, 1H), 9.04 (d, 1H, J = 8.6Hz, -NH).

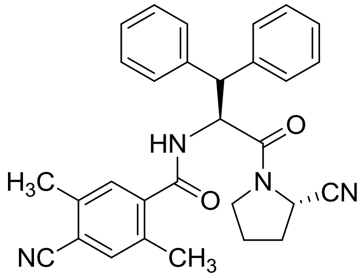
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 22.4, 30.4, 42.2, 48.6, 50.5, 59.7, 113.8 (d, J = 30Hz), 116.9, 117.8, 121,5, 126.2, 126.5, 127.8, 128.1, 128.2, 128.4, 128.7, 129.2, 129.3, 129.8, 140.1, 140.3, 161.2 (d, J = 253Hz), 167.5, 173.1.

Analysis : Mol. Formula: $C_{28}H_{23}FN_4O_2$

Calcd.: C 72.09, H 4.97, N 12.01.

Found: C 72.07, H 4.98, N 12.03.

5.1.9.5. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)-2,5-dimethylbenzamide (34e)



34e (172 mg, 75%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 144-147 °C; Purity by HPLC: 98.48% AUC.

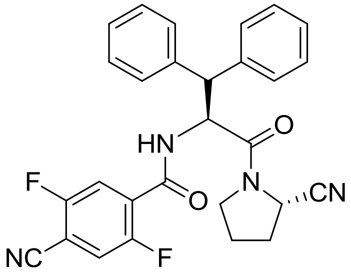
ESI/MS (m/z) : 477.8 $(M+H)^+$. **Mol. Wt.** = 476.6 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.78-1.82 (m, 3H), 1.84-1.92 (m, 1H), 2.44 (s, 3H), 2.49 (s, 3H), 3.61-3.65 (m, 1H), 3.97-4.01 (m, 1H), 4.52 (d, 1H, J = 11.4Hz), 4.85 (dd, 1H, J_1 = 3.2Hz, J_2 = 8.0Hz), 5.71 (dd, 1H, J_1 = 9.0Hz, J_2 = 11.4Hz), 7.09-7.24 (m, 6H), 7.29-7.42 (m, 4H), 7.76 (s, 1H), 7.98 (s, 1H), 9.03 (d, 1H, J = 8.2Hz, -NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 17.6, 19.1, 22.3, 30.3, 42.1, 48.6, 50.3, 60.1, 115.9, 116.9, 117.8, 126.2, 126.5, 128.2, 128.3, 128.5, 128.7, 129.2, 129.3, 133.3, 139.3, 139.7, 140.2, 140.3, 167.4, 173.3.

Analysis : Mol. Formula: $C_{30}H_{28}N_4O_2$
Calcd.: C 75.61, H 5.92, N 11.76.
Found: C 75.58, H 5.89, N 11.73.

5.1.9.6. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)-2,5-difluorobenzamide (34f)



34e (237 mg, 85%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 214-216 °C; Purity by HPLC: 98.73% AUC.

ESI/MS (m/z) : 485.4 $(M+H)^+$. **Mol. Wt.** = 484.5 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.79-1.89 (m, 3H), 1.92-2.01 (m, 1H), 3.60-3.63 (m, 1H), 3.98-4.03 (m, 1H), 4.53 (d, 1H, J = 11.6Hz), 4.87 (dd, 1H, J_1 = 2.8Hz, J_2 = 8.0Hz), 5.64 (dd, 1H, J_1 = 8.4Hz, J_2 = 11.6Hz), 7.07-7.16 (m, 3H), 7.21-7.33 (m, 5H), 7.38-7.76 (m, 3H), 7.81-7.89 (m, 1H), 9.03 (d, 1H, J = 8.2Hz, -NH).

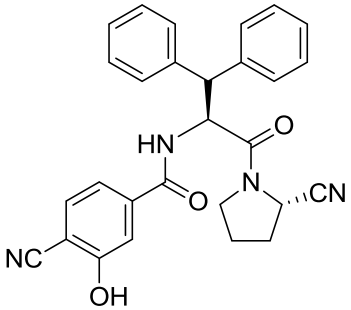
^{13}C NMR (100 MHz, DMSO-d_6): δ 22.1, 30.4, 42.1, 48.7, 50.7, 59.9, 114.8 (d, J = 30Hz), 116.3, 117.6, 120.6 (d, J = 23Hz), 121,5, 126.2, 126.5, 128.2, 128.4, 128.6, 129.2, 129.3, 131.3, 140.2, 155.3 (d, J = 248Hz), 156.9 (d, J = 253Hz), 167.5, 173.1.

Analysis : Mol. Formula: $C_{28}H_{22}F_2N_4O_2$

Calcd.: C 69.41, H 4.58, N 11.56.

Found: C 69.43, H 4.57, N 11.53.

5.1.9.7. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)-3-hydroxybenzamide (34g)



34g (184 mg, 81%) was prepared by using general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 234-236 °C; Purity by HPLC: 99.17% AUC.

ESI/MS (m/z) : 465.6 $(M+H)^+$. **Mol. Wt.** = 464.5 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.79-1.84 (m, 3H), 1.88-1.94 (m, 1H), 3.60-3.65 (m, 1H), 3.97-4.02 (m, 1H), 4.53 (d, 1H, J = 11.6Hz), 4.86 (dd, 1H, J_1 = 3.2Hz, J_2 = 8.0Hz), 5.71 (dd, 1H, J_1 = 8.8Hz, J_2 = 11.6Hz), 7.01-7.15 (m, 4H), 7.18-7.23 (m, 2H), 7.27-7.39 (m, 4H), 7.64 (d, 1H, J = 7.8Hz), 7.74-7.79 (m, 2H), 9.01 (d, 1H, J = 8.6Hz, -NH), 9.51 (s, 1H, -OH).

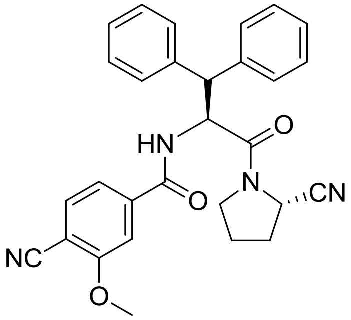
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 22.1, 30.4, 42.3, 48.3, 51.1, 59.8, 106.5, 113.4, 115.9, 116.5, 120.7, 126.2, 126.5, 127.8, 128.1, 128.3, 128.7, 129.2, 129.3, 133.8, 140.2, 141.3, 159.4, 167.5, 173.2.

Analysis : Mol. Formula: $C_{28}H_{24}N_4O_3$

Calcd.: C 72.40, H 5.21, N 12.06.

Found: C 72.38, H 5.23, N 12.03.

5.1.9.8. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)-3-methoxybenzamide (34h)



34h (178 mg, 79%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 158-160 °C; Purity by HPLC: 97.74% AUC.

ESI/MS (m/z) : 479.6 $(M+H)^+$. **Mol. Wt.** = 478.5 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.81-1.86 (m, 3H), 1.89-1.94 (m, 1H), 3.61-3.66 (m, 1H), 3.84 (s, 3H), 3.99-4.03 (m, 1H), 4.56 (d, 1H, J = 11.6Hz), 4.89 (dd, 1H, J_1 = 3.4Hz, J_2 = 8.2Hz), 5.73 (dd, 1H, J_1 = 8.6Hz, J_2 = 11.6Hz), 7.04-7.25 (m, 6H), 7.27-7.38 (m, 4H), 7.73 (d, 1H, J = 8.4Hz), 7.76-7.79 (m, 2H), 9.03 (d, 1H, J = 8.0Hz, -NH).

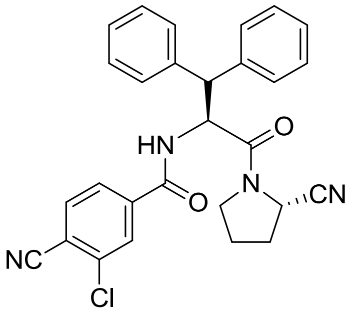
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 22.3, 30.3, 42.5, 48.2, 51.0, 55.7, 59.9, 104.8, 112.5, 115.7, 116.3, 120.6, 126.2, 126.5, 127.8, 128.1, 128.3, 128.7, 129.2, 129.3, 133.3, 140.2, 141.3, 163.4, 167.3, 173.5.

Analysis : Mol. Formula: $C_{29}H_{26}N_4O_3$

Calcd.: C 72.79, H 5.48, N 11.71.

Found: C 72.76, H 5.46, N 11.68.

5.1.9.9. 3-Chloro-4-cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)benzamide (34i)



34i (154 mg, 85%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 166-168 °C; Purity by HPLC: 99.06% AUC.

ESI/MS (m/z) : 483.6 $(M+H)^+$. **Mol. Wt.** = 483.0 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.83-1.87 (m, 3H), 1.89-1.95 (m, 1H), 3.60-3.64 (m, 1H), 4.01-4.03 (m, 1H), 4.56 (d, 1H, J = 11.4Hz), 4.92 (dd, 1H, J_1 = 3.4Hz, J_2 = 8.2Hz), 5.72 (dd, 1H, J_1 = 8.8Hz, J_2 = 11.4Hz), 7.07-7.25 (m, 6H), 7.28-7.36 (m, 4H), 7.76 (d, 1H, J = 7.8Hz), 8.09-8.12 (m, 2H), 8.98 (d, 1H, J = 8.2Hz, -NH).

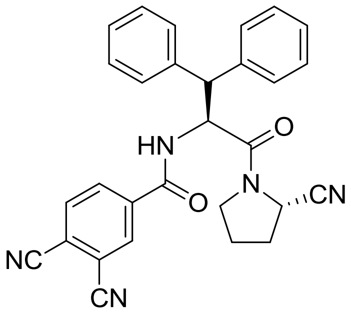
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 22.1, 30.2, 42.1, 48.2, 50.4, 59.7, 115.7, 116.3, 116.8, 126.3, 126.4, 127.9, 128.2, 128.3, 128.5, 128.6, 129.2, 129.4, 133.8, 134.5, 139.8, 141.3, 167.4, 173.2.

Analysis : Mol. Formula: $C_{28}H_{23}ClN_4O_2$

Calcd.: C 69.63, H 4.80, N 11.60.

Found: C 69.59, H 4.78, N 11.61.

5.1.9.10. 3,4-Dicyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenyl propan-2-yl)benzamide (34j)



34j (169 mg, 82%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 198-201 °C; Purity by HPLC: 98.37% AUC.

ESI/MS (m/z) : 474.7 $(M+H)^+$. **Mol. Wt.** = 473.5 g.

^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 1.78-1.84 (m, 3H), 1.87-1.95 (m, 1H), 3.58-3.63 (m, 1H), 3.98-4.03 (m, 1H), 4.56 (d, 1H, J = 11.6Hz), 4.89 (dd, 1H, J_1 = 3.2Hz, J_2 = 8.4Hz), 5.75 (dd, 1H, J_1 = 8.6Hz, J_2 = 11.6Hz), 7.09-7.25 (m, 6H), 7.27-7.36 (m, 4H), 7.96 (d, 1H, J = 7.4Hz), 8.24 (d, 1H, J = 7.4Hz), 8.63 (s, 1H), 9.03 (d, 1H, J = 8.0Hz, -NH).

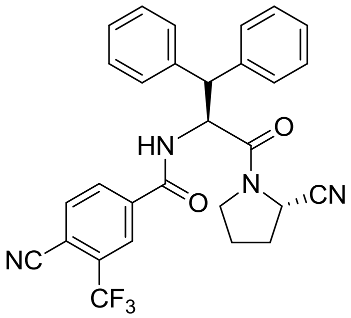
^{13}C NMR (100 MHz, DMSO-d$_6$): δ 22.1, 30.3, 42.4, 48.3, 50.1, 60.1, 115.7, 115.8, 116.4, 119.8, 126.2, 126.3, 127.9, 128.0, 128.3, 128.4, 128.6, 129.2, 129.4, 131.3, 131.8, 132.5, 139.3, 141.3, 167.5, 173.3.

Analysis : Mol. Formula: $C_{29}H_{23}N_5O_2$

Calcd.: C 73.56, H 4.90, N 14.79.

Found: C 73.53, H 4.87, N 14.82.

5.1.9.11. 4-Cyano-N-((S)-1-((S)-2-cyanopyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)-3-(trifluoromethyl)benzamide (34k)



34k (178 mg, 79%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 137-139 °C; Purity by HPLC: 97.46% AUC.

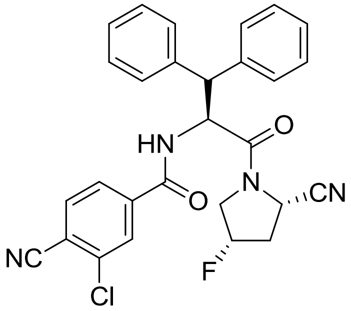
ESI/MS (m/z) : 517.4 $(M+H)^+$. **Mol. Wt.** = 516.5 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.81-1.86 (m, 3H), 1.87-1.94 (m, 1H), 3.60-3.63 (m, 1H), 3.99-4.03 (m, 1H), 4.58 (d, 1H, J = 11.6Hz), 4.89 (dd, 1H, J_1 = 2.8Hz, J_2 = 8.8Hz), 5.73 (dd, 1H, J_1 = 8.4Hz, J_2 = 11.6Hz), 7.09-7.18 (m, 4H), 7.21-7.28 (m, 2H), 7.29-7.35 (m, 4H), 7.76 (d, 1H, J = 7.8Hz), 8.24-8.31 (m, 2H), 9.07 (d, 1H, J = 8.4Hz, -NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 22.2, 30.1, 42.5, 48.5, 50.2, 60.0, 112.7, 115.6, 116.4, 119.4 (d, J = 28.4Hz), 124.3, 126.2, 126.3, 127.9, 128.0, 128.3, 128.4, 129.0, 129.2, 129.4, 131.3, 132.5, 134.5 (d, J = 248Hz), 138.9, 140.7, 167.3, 173.2.

Analysis : Mol. Formula: $C_{29}H_{23}F_3N_4O_2$
Calcd.: C 67.43, H 4.49, N 10.85.
Found: C 67.39, H 4.51, N 10.82.

5.1.9.12. 3-Chloro-4-cyano-N-((S)-1-((2S,4S)-2-cyano-4-fluoropyrrolidin-1-yl)-1-oxo-3,3-diphenylpropan-2-yl)benzamide (34l)



34l (198 mg, 72%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 129-131 °C; Purity by HPLC: 99.38% AUC.

ESI/MS (m/z) : 501.7 $(M+H)^+$. **Mol. Wt.** = 501.0 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.29-2.41 (m, 2H), 3.64-3.68 (m, 1H), 4.01-4.04 (m, 1H), 4.57 (d, 1H, J = 11.6Hz), 4.91 (dd, 1H, J_1 = 3.2Hz, J_2 = 8.8Hz), 5.21 (m, 1H), 5.74 (dd, 1H, J_1 = 8.2Hz, J_2 = 11.6Hz), 7.13-7.22 (m, 3H), 7.25-7.31 (m, 3H), 7.34-7.41 (m, 4H), 7.74 (d, 1H, J = 8.4Hz), 8.11-8.24 (m, 2H), 9.04 (d, 1H, J = 8.2Hz, -NH).

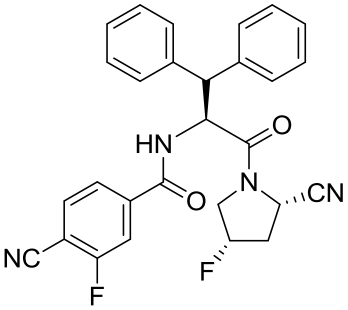
^{13}C NMR (100 MHz, DMSO-d_6): δ 28.1 (d, J = 23Hz), 42.6, 43.2, 49.8, 60.1, 91.2 (d, J = 177Hz), 115.7, 116.3, 116.8, 126.2, 126.3, 126.7, 127.9, 128.1, 128.3, 128.4, 129.0, 129.2, 129.4, 133.5, 134.7, 139.8, 140.5, 140.6, 167.4, 173.3.

Analysis : Mol. Formula: $C_{28}H_{22}ClFN_4O_2$

Calcd.: C 67.13, H 4.43, N 11.18.

Found: 67.14, H 4.44, N 11.15.

5.1.9.13. 4-Cyano-N-((S)-1-((2S,4S)-2-cyano-4-fluoropyrrolidin-1-yl)-1-oxo-3,3-diphenyl propan-2-yl)-3-fluorobenzamide (34m)



34m (186 mg, 78%) was prepared by means of the general procedure described in section **5.1.3.** and section **5.1.4.** as a white solid. 179-182 °C; Purity by HPLC: 98.76% AUC.

ESI/MS (m/z) : 485.4 $(M+H)^+$. **Mol. Wt.** = 484.5 g.

^1H NMR (400 MHz, DMSO-d_6): δ = 2.27-2.43 (m, 2H), 3.62-3.67 (m, 1H), 3.99-4.02 (m, 1H), 4.56 (d, 1H, J = 11.6Hz), 4.97 (dd, 1H, J_1 = 3.2Hz, J_2 = 8.8Hz), 5.21 (m, 1H), 5.73 (dd, 1H, J_1= 8.4Hz, J_2 = 11.6Hz), 7.10-7.28 (m, 4H), 7.31-7.36 (m, 2H), 7.37-7.41 (m, 4H), 7.76-7.79 (m, 2H), 7.87 (d, 1H, J = 8.6Hz), 9.01 (d, 1H, J = 8.4Hz, -NH).

^{13}C NMR (100 MHz, DMSO-d_6): δ 28.2 (d, J = 20Hz), 42.4, 43.6, 49.9, 59.8, 91.6 (d, J = 178Hz), 113.7 (d, J = 31Hz), 115.6 (d, J = 3.8Hz), 116.4, 121.4, 123.9, 126.3, 126.7, 127.9, 128.1, 128.3, 128.4, 129.2, 129.4, 133.7, 139.9, 140.5, 140.7, 161.3 (d, J = 252Hz), 167.4, 173.3.

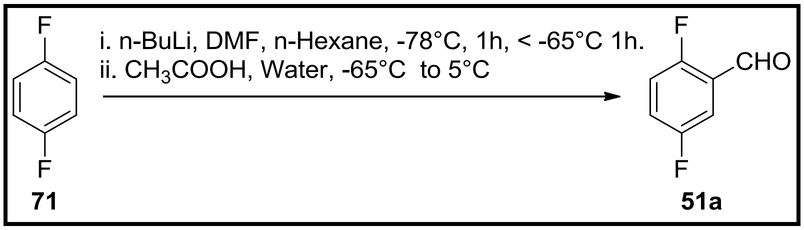
Analysis : Mol. Formula: $C_{28}H_{22}F_2N_4O_2$

Calcd.: C 69.41, H 4.58, N 11.56.

Found: 69.39, H 4.56, N 11.52.

5.1.10. Experimental Details : Aminomethylpiperidone based DPP-IV inhibitors (Third series)

5.1.10.1. 2,5-Difluorobenzaldehyde (51a)

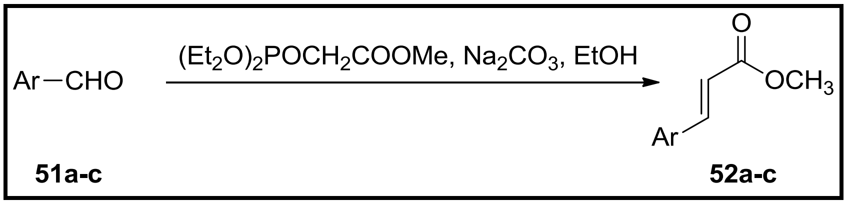


A solution of 1,4-difluorobenzene **71** (10 g, 87.6 mmol) in THF (175 ml, 17.5 vol) was stirred under nitrogen and cooled to -78°C. n-Butyllithium (82 ml of 1.6 M solution in hexanes, 131.4 mmol, 1.5 eq) was added to the reaction mixture over a period of 30 minutes maintaining the temperature below -65°C. After an hour DMF (10.16 ml, 131.4 mmol, 1.5 eq) was added within 10 min. maintaining the temperature below -65° C. The reaction mixture was quenched after 10 minutes by the addition of acetic acid (17.5 ml, 1.75 eq) directly followed by D. M. water (440 ml, 36.4 vol). This caused the reaction to exotherm to 5°C. The cold bath was then removed, *tert*-Butyl methyl ether (TBME) (220 ml, 22 vol) added and the reaction was stirred for 5 minutes. The layers were separated and the aqueous layer was extracted with TBME (2×220 ml). Combined organic layers were washed with 0.2 M HCl (1X220 ml), sat. Na_2CO_3 (1X220 ml) and brine (1X220 ml, 22 vol), dried over Na_2SO_4 and concentrated on a rotary evaporator to afford the crude product (11.8 g). Column chromatographic purification gave 7.8 g (62% Yield) of 2,5-difluorobenzaldehyde **51a** as a pale yellow oil. Purity by HPLC: 98.3% AUC.

ESI/MS (m/z) : 143.2 $(M+H)^+$. **Mol. Wt.** = 142.1 g

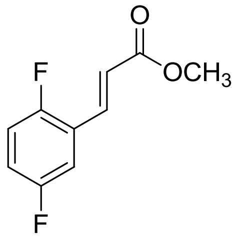
^{1}HNMR (400 MHz, DMSO-d_6) : δ 7.15-7.20 (m, 1H), 7.26-7.33 (m, 1H), 7.51-7.55 (m, 1H), 10.32 (s, 1H, -C**H**O)

5.1.11. General procedure for the synthesis of compounds (52a-c)



Synthesis of **52a-c** was commenced with Horner-Wadsworth-Emmons reaction of aldehydes **51a-c** by using protocol reported by J. Villieras et.al. **[282]**. 50.0 mmol of aldehyde **51a-c** was placed in a 50 ml single neck R. B. Flask, to it was added rectified spirit (1 vol by weight of starting material) and stirred at room temperature. To this clear solution was charged triethyl phosphonoacetate (1.05 eq) in a single portion followed by addition of 3M K_2CO_3 solution (2.0 eq). Reaction mixture was stirred at room temperature for 2h. After completion of reaction(TLC), reaction mixture was diluted with D. M. water (140 ml) and extracted with ethyl acetate (3X100 ml). Combined organic extracts were washed with brine (1X100 ml), dried over anhy. Na_2SO_4 and evaporated to dryness under reduced pressure. Crude residue thus obtained was purified by column chromatography (100-200 mesh silica gel, 0-20% ethyl acetate in n-hexane) to give desired (E)-methyl acrylates **52a-c**.

5.1.11.1. (E)-Methyl 3-(2,5-difluorophenyl)acrylate (52a)

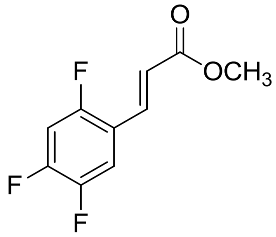


52a (7 g, 81%) was prepared from **51a** by means of the general procedure described in **5.1.11.** as a colourless oil; Purity by HPLC: 99.55% AUC.

ESI/MS (m/z) : 198.7 $(M+H)^+$. **Mol. Wt.** = 198.2 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.72 (s, 3H), 6.26 (d, 1H, J =13.6Hz), 7.05-7.11 (m, 2H), 7.26-7.39 (m, 1H), 7.93 (d, 1H, J = 13.6Hz).

5.1.11.2. (E)-Methyl 3-(2,4,5-trifluorophenyl)acrylate (52b)

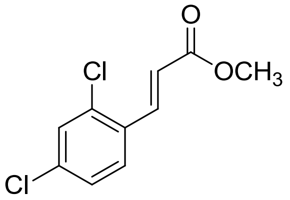


52b (8.3 g, 86%) was prepared from **51b** by means of the general procedure described in **5.1.11.** as a colourless oil; Purity by HPLC: 96.71% AUC.

ESI/MS (m/z) : 217.3 $(M+H)^+$. **Mol. Wt.** = 216.2 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.71 (s, 3H), 6.27 (d, 1H, J =14.0Hz), 7.26-7.30 (m, 1H), 7.43-7.50 (m, 1H), 7.89 (d, 1H, J = 14.0Hz).

5.1.11.3. (E)-Methyl 3-(2,4-dichlorophenyl)acrylate (52c)

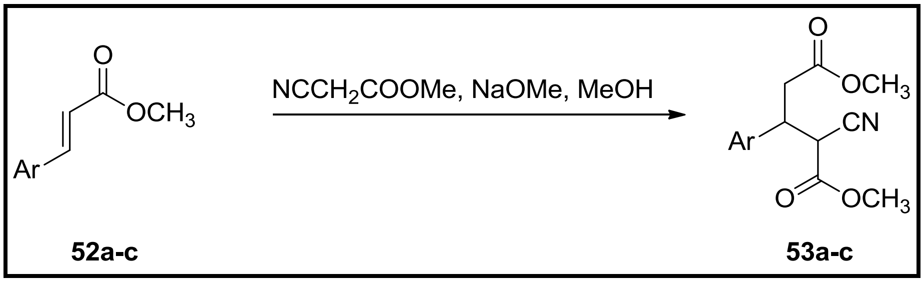


52c (8.3 g, 86%) was prepared from **51c** by means of the general procedure described in **5.1.11.** as a colourless oil; Purity by HPLC: 97.43% AUC.

ESI/MS (m/z) : 231.7 $(M+H)^+$. **Mol. Wt.** = 231.1 g.

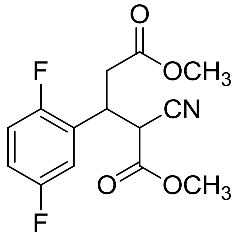
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.77 (s, 3H), 6.24 (d, 1H, J =13.6Hz), 7.4 (dd, 1H, J_1 = 8.4Hz, J_2 = 2.0Hz), 7.46 (d, 1H, J = 8.4Hz), 7.53 (d, 1H, J = 1.6Hz), 7.97 (d, 1H, J = 13.6Hz).

5.1.12. General procedure for the synthesis of compounds (53a-c)



To a solution of sodium methoxide (1.03 eq by wt. of starting material) in 200 ml of methanol was added (1.0 eq) of methyl cyanoacetate and the mixture was stirred at ambient temperature for 30 min. To this solution was added (E)-methyl acrylates **52a-c** (62 mmol) 50 ml of methanol and the resulting yellow mixture was heated to reflux for 6 h. The mixture was then quenched at ambient temperature with 1N $HCl_{(aq)}$ (100 ml) and concentrated to remove methanol. The resulting mixture was extracted with ethyl acetate (3X300 ml) portions, and the organic phases combined and washed sequentially with 1N HCl, saturated aqueous $NaHCO_3$ solution, and brine (1X100 ml each), dried over magnesium sulfate, filtered, and evaporated in vacuo to yield a viscous oil. The crude material was purified by flash chromatography (230-400 silica gel, 0 to 25% ethyl acetate/hexanes gradient) to give the title compounds 3-aryl-2-cyanopentane diesters **53a-c** as a mixture of stereoisomers.

5.1.12.1. Dimethyl 2-cyano-3-(2,5-difluorophenyl)pentanedioate (53a)



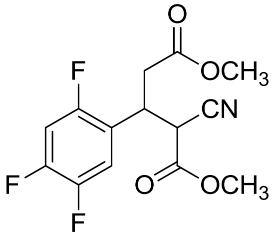
53a (14.9 g, 83%) was prepared from **52a** by means of the general procedure described in **5.1.12.** as light yellow coloured oil; Purity by HPLC: 99.22% AUC.

ESI/MS (m/z) : 298.2 $(M+H)^+$. **Mol. Wt.** = 297.3 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.48-2.52 (m, 2H), 3.63 (s, 3H), 3.72 (s, 3H), 3.94 (d, 1H, J = 8.6 Hz), 4.35-4.41 (m, 1H), 6.92-6.98 (m, 2H), 7.08-7.14 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 29.4, 37.6, 40.2, 51.3, 52.7, 108.9 (d, J = 178Hz), 113.7 (d, J = 31Hz), 115.6 (d, J = 3.8Hz), 116.4, 136.7, 158.2 (d, J = 246Hz), 161.3 (d, J = 252Hz), 167.4, 170.3.

5.1.12.2. Dimethyl 2-cyano-3-(2,4,5-trifluorophenyl)pentanedioate (53b)

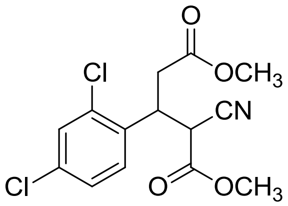


53b (13.6 g, 73%) was prepared from **52b** by means of the general procedure described in **5.1.12.** as light yellow coloured oil; Purity by HPLC: 97.34% AUC.

ESI/MS (m/z) : 316.1 $(M+H)^+$. **Mol. Wt.** = 315.2 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.82-3.05 (m, 2H), 3.64 (s, 3H), 3.69 (s, 3H), 3.91 (d, 1H, J = 9.2 Hz), 4.33-4.40 (m, 1H), 7.26-7.31 (m, 1H), 7.43-7.52 (m, 1H).

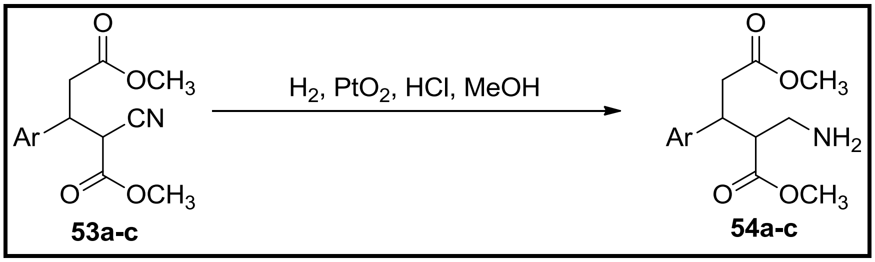
5.1.12.3. Dimethyl 2-cyano-3-(2,4-dichlorophenyl)pentanedioate (53c)



53c (14.2 g, 78%) was prepared from **52c** by means of the general procedure described in **5.1.12.** as light yellow coloured oil; Purity by HPLC: 96.84% AUC.
ESI/MS (m/z) : 331.1 $(M+H)^+$. **Mol. Wt.** = 330.2 g.

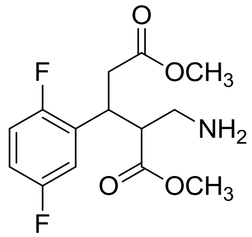
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.68-2.91 (m, 2H), 3.62 (s, 3H), 3.71 (s, 3H), 3.87 (d, 1H, J = 9.4 Hz), 4.23-4.37 (m, 1H), 7.21 (d, 1H, J = 8.2 Hz), 7.34 (dd, 1H, J_1 = 2.2 Hz, J_2 = 8.2 Hz), 7.65 (d, 1H, J = 2.2 Hz).

5.1.13. General procedure for the synthesis of compounds (54a-c)



To 450 ml of methanol at 0 ^{0}C was carefully added acetyl chloride (30 ml) and the resulting solution was allowed to stir at ambient temperature for 30 min. The resulting solution was added to 3-aryl-2-cyanopentane diesters **53a-c** (43 mmol) and the reaction mixture was then shaken with 5.0 g of platinum oxide under 50 psi of hydrogen for 20 h. The mixture was filtered through a pad of Celite and the filter cake washed with methanol and dichloromethane. The combined filtrate and washings were concentrated under reduced pressure. Residue obtained was triturated with ether (3X100 ml), solid obtained was dried well to give the compounds **54a-c** as a hydrochloride salt, which were neutralized with sat. $NaHCO_3$ solution and extracted with DCM to give free amines **54a-c**.

5.1.13.1. Dimethyl 2-(aminomethyl)-3-(2,5-difluorophenyl)pentanedioate (54a)



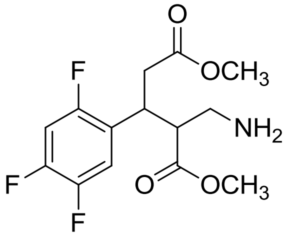
54a (11.4 g, 69%) was prepared from **53a** by means of the general procedure described in **5.1.13.** as a white solid; mp: 139-141^{0}C Purity by HPLC: 98.97% AUC.

ESI/MS (m/z) : 302.1 $(M+H)^+$. **Mol. Wt.** = 301.3 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45-2.49 (m, 2H), 2.79 (d, 1H, J = 7.6 Hz), 2.97-3.04 (m, 1H), 3.14 (d, 1H, J = 7.8 Hz), 3.63 (s, 3H), 3.78 (s, 3H), 3.87 (d, 1H, J = 9.4 Hz), 4.35-4.41 (m, 1H), 6.92-6.98 (m, 2H), 7.08-7.14 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 35.4, 38.7, 40.3, 51.3, 52.3, 53.1, 114.2 (d, J = 29Hz), 116.6 (d, J = 3.8Hz), 117.4(d, J = 178Hz), 154.2 (d, J = 242Hz), 157.3 (d, J = 247Hz), 166.8, 167.3.

5.1.13.2. Dimethyl 2-(aminomethyl)-3-(2,4,5-trifluorophenyl)pentanedioate (54b)

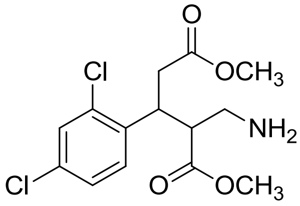


54b (12.4 g, 72%) was prepared from **53b** by means of the general procedure described in **5.1.13.** as a white solid; mp: 157-159^{0}C Purity by HPLC: 95.29% AUC.

ESI/MS (m/z) : 320.1 $(M+H)^+$. **Mol. Wt.** = 319.3 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45-2.47 (m, 2H), 2.77 (d, 1H, J = 7.8 Hz), 2.97-3.02 (m, 1H), 3.14 (d, 1H, J = 7.8 Hz), 3.64 (s, 3H), 3.77 (s, 3H), 3.86 (d, 1H, J = 8.8 Hz), 4.35-4.41 (m, 1H), 6.92-7.01 (m, 1H), 7.11-7.24 (m, 1H).

5.1.13.3. Dimethyl 2-(aminomethyl)-3-(2,4-dichlorophenyl)pentanedioate (54c)

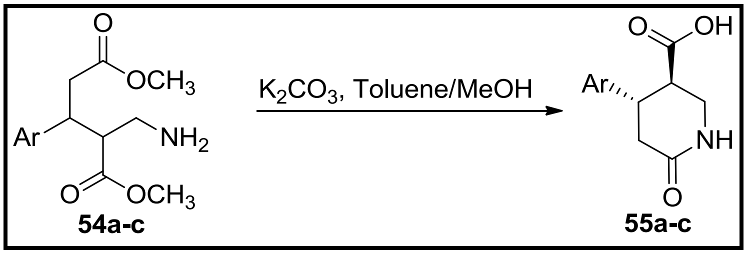


54c (11.9 g, 64%) was prepared from **53c** by means of the general procedure described in **5.1.13.** as a thick wax; Purity by HPLC: 95.29% AUC.

ESI/MS (m/z) : 320.1 $(M+H)^+$. **Mol. Wt.** = 319.3 g.

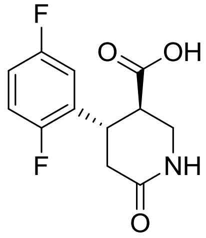
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43-2.45 (m, 2H), 2.67-2.72 (m, 1H), 2.96-3.02 (m, 1H), 3.15 (d, 1H, J = 7.6 Hz), 3.65 (s, 3H), 3.74 (s, 3H), 3.92 (d, 1H, J = 8.9 Hz), 4.36-4.42 (m, 1H), 7.23 (d, 1H, J = 8.4 Hz), 7.37 (dd, 1H, J_1 = 1.8 Hz, J_2 = 8.2 Hz), 7.63 (d, 1H, J = 2.0 Hz).

5.1.14. General procedure for the synthesis of compounds (55a-c)



2-Aminomethyl-3-aryl pentane diesters **54a-c** (50 mmol) prepared in **section 5.1.13.** were taken up in 400 ml of 1:1 methanol/toluene with K_2CO_3 (28 g, 200 mmol). The resulting mixture was heated to reflux for 4 h, then cooled to 0 ^{0}C and quenched with 1N $HCl_{(aq)}$ until the solution was acidic to pH paper. The resulting mixture was then extracted with mixture of 3: 1 chloroform/isopropyl alcohol (5X300 ml) and the organic phases combined and washed with brine (1X300 ml), dried over anhy. Na_2SO_4, filtered, and evaporated in vacuo to yield the compounds **55a-c**. Compounds prepared were used as such without any purification in the next reaction step.

5.1.14.1. *trans*-4-(2,5-Difluorophenyl)-6-oxopiperidine-3-carboxylic acid (55a)



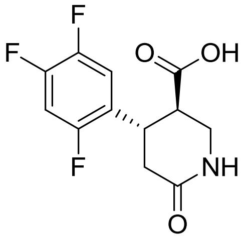
55a (9.3 g, 61%) was prepared from **54a** by means of the general procedure described in **5.1.14.** as a white solid; Mp: 206-208^{0}C Purity by HPLC: 95.98% AUC.

ESI/MS (m/z) : 256.1 $(M+H)^+$. **Mol. Wt.** = 255.2 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.59 (dd, 1H, J_1 = 10.8Hz, J_2 = 18.0Hz), 2.75 (dd, 1H, J_1 = 9.6Hz, J_2 = 18.2Hz), 3.21 (dd, 1H, J_1 = 10.8Hz, J_2 = 9.6Hz), 3.37-3.49 (m, 2H), 3.59-3.62 (m, 1H), 6.08 (bs, 1H), 6.92-6.99 (m, 2H), 7.09-7.11 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 36.5, 38.4, 46.3, 48.9, 105.4 (d, J = 23Hz), 116.4 (d, J = 3.8Hz), 117.2 (d, J = 178Hz), 127.3 (d, J = 21Hz), 148.2 (d, J = 246Hz), 154.3 (d, J = 253Hz), 170.8, 178.6.

5.1.14.2. *trans*-6-Oxo-4-(2,4,5-trifluorophenyl)piperidine-3-carboxylic acid (55b)

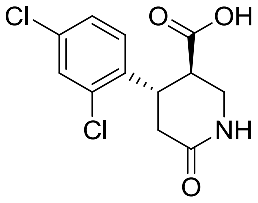


55b (10.1 g, 64%) was prepared from **54b** by means of the general procedure described in **5.1.14.** as a white solid; Mp: 197-199^{0}C Purity by HPLC: 97.31% AUC.

ESI/MS (m/z) : 273.9 $(M+H)^+$. **Mol. Wt.** = 273.2 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.54 (dd, 1H, J_1 = 10.6Hz, J_2 = 16.4Hz), 2.73 (dd, 1H, J_1 = 9.8Hz, J_2 = 16.2Hz), 3.18 (dd, 1H, J_1 = 10.8Hz, J_2 = 9.6Hz), 3.35-3.46 (m, 2H), 3.56-3.59 (m, 1H), 6.02 (bs, 1H), 6.92-7.03 (m, 1H), 7.09-7.21 (m, 1H).

5.1.14.3. *trans*-6-Oxo-4-(2,4-dichlorophenyl)piperidine-3-carboxylic acid (55c)

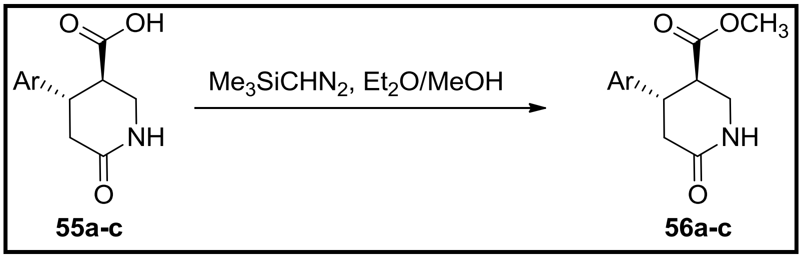


55c (8.3 g, 54%) was prepared from **54c** by means of the general procedure described in **5.1.14.** as an off white solid; Mp: 171-174^{0}C Purity by HPLC: 95.46% AUC.

ESI/MS (m/z) : 288.6 $(M+H)^+$. **Mol. Wt.** = 288.1 g.

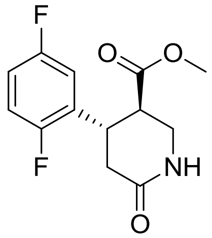
^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.56 (dd, 1H, J_1 = 9.8Hz, J_2 = 15.2Hz), 2.76 (dd, 1H, J_1 = 10.2Hz, J_2 = 15.2Hz), 3.19 (dd, 1H, J_1 = 10.4Hz, J_2 = 9.6Hz), 3.37-3.48 (m, 2H), 3.56-3.61 (m, 1H), 6.08 (bs, 1H), 7.25 (d, 1H, J = 8.4 Hz), 7.37 (m, 1H), 7.67 (d, 1H, J = 2.0 Hz).

5.1.15. General procedure for the synthesis of compounds (56a-c)



Compounds **56a-c** were prepared by using literature reported method **[283]**. The Compounds **55a-c** (75 mmol) prepared in section **5.1.14.** were dissolved in a mixture of 1 : 1 diethyl ether/methanol (500 ml) and cooled to 0 ^{0}C. To this solution was added 75 ml solution of 2M trimethylsilyldiazomethane in hexane (150 mmol) dropwise until a yellow colour persisted. After warming to room temperature, the solution was stirred for an additional 2 h, and then concentrated in vacuo. The compounds **56a-c** were collected as a colorless crystalline solid (obtained as *cis*: *trans* mixture having >85% *trans* stereo configuration) which were purified by column chromatography to remove the *cis* isomer.

5.1.15.1. Methyl-*trans*-4-(2,5-difluorophenyl)-6-oxopiperidine-3-carboxylate (56a)



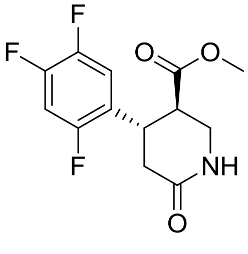
56a (9.8 g, 89%) was prepared from **55a** by means of the general procedure described in **5.1.15.** as a white solid; Mp: 174-177^{0}C Purity by HPLC: 98.40% AUC.

ESI/MS (m/z) : 270.3 $(M+H)^+$. **Mol. Wt.** = 269.2 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.42 (dd, 1H, J_1 = 9.6Hz, J_2 = 14.8Hz), 2.58 (dd, 1H, J_1 = 9.2Hz, J_2 = 14.8Hz), 3.28 (dd, 1H, J_1 = 9.2Hz, J_2 = 9.6Hz), 3.36-3.49 (m, 2H), 3.59-3.63 (m, 1H), 3.77 (s, 3H), 6.90-6.99 (m, 3H), 7.07-7.12 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 37.5, 40.6, 47.5, 49.2, 52.2, 106.7 (d, J = 28Hz), 116.9 (d, J = 3.8Hz), 117.2 (d, J = 38Hz), 121.3 (d, J = 21Hz), 148.2 (d, J = 249Hz), 157.3 (d, J = 250Hz), 166.6, 170.6.

5.1.15.2. Methyl-*trans*-6-oxo-4-(2,4,5-trifluorophenyl)piperidine-3-carboxylate (56b)

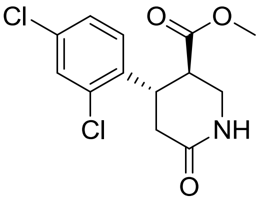


56a (9.3 g, 87%) was prepared from **55b** by means of the general procedure described in **5.1.15.** as a white solid; Mp: 162-164^{0}C Purity by HPLC: 97.87% AUC.

ESI/MS (m/z) : 288.3 $(M+H)^+$. **Mol. Wt.** = 287.2 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.44 (m, 1H), 2.54 (dd, 1H, J_1 = 9.6Hz, J_2 = 15.2Hz), 3.27 (dd, 1H, J_1 = 9.4Hz, J_2 = 9.6Hz), 3.36-3.47 (m, 2H), 3.56-3.62 (m, 1H), 3.78 (s, 3H), 6.37 (bs, 1H), 6.96-7.13 (m, 2H).

5.1.15.c. Methyl-*trans*-4-(2,4-dichlorophenyl)-6-oxopiperidine-3-carboxylate (56c)

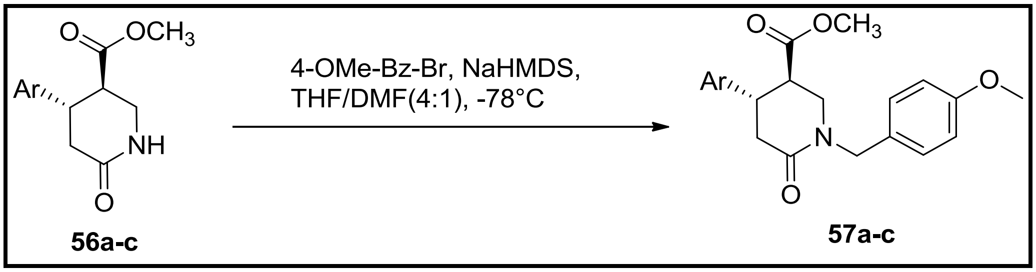


56c (10.6 g, 93%) was prepared from **55c** by means of the general procedure described in **5.1.15.** as a white solid; Mp: 137-139^{0}C Purity by HPLC: 96.82% AUC.

ESI/MS (m/z) : 303.3 (M+H)$^+$. **Mol. Wt.** = 302.2 g.

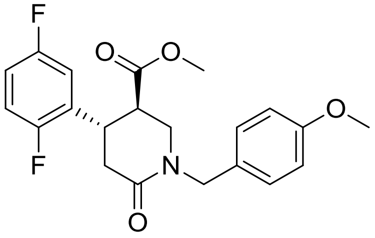
^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.47 (dd, 1H, J_1 = 9.4Hz, J_2 = 13.8Hz), 2.54 (dd, 1H, J_1 = 10.4Hz, J_2 = 13.8Hz), 3.25 (dd, 1H, J_1 = 9.4Hz, J_2 = 10.6Hz), 3.34-3.51 (m, 2H), 3.56-3.61 (m, 1H), 3.77 (s, 3H), 6.83 (bs, 1H), 7.45 (d, 1H, J = 8.4Hz), 7.51 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.6Hz), 7.92 (d, 1H, J = 1.6Hz).

5.1.16. General procedure for the synthesis of compounds (57a-c)



To a stirred solution of compounds **56a-c** (28 mmol) in a mixture of 4:1 THF/DMF (150 ml) at -78 ^{0}C was added 32 ml solution of 1M sodium bis(trimethylsilyl)amide in THF (32 mmol) and the resulting solution was stirred at -78 ^{0}C for 30 min. *p*-methoxy benzyl bromide (35 mmol) was then added and the resulting solution was stirred at 0^{0}C for 60 min, then allowed to warm to ambient temperature over 12 h. The mixture was quenched with 1N HCl$_{(aq)}$ (100 ml) and concentrated to remove the THF. The resulting mixture was extracted with ethyl acetate (3X300 ml), and the organic phases combined and washed sequentially with 1N HCl, saturated NaHCO$_3$ solution, and brine (1X100 ml each). The organic phase was dried over anhy. Na$_2$SO$_4$ and evaporated in vacuo to yield viscous oil. The crude material was purified by flash chromatography (230-400 mesh silica gel, 0 to 50% ethyl acetate/hexanes gradient) to give the compounds **57a-c**.

5.1.16.1. Methyl-*trans*-4-(2,5-difluorophenyl)-1-(4-methoxybenzyl)-6-oxopiperidine-3-carboxylate (57a)



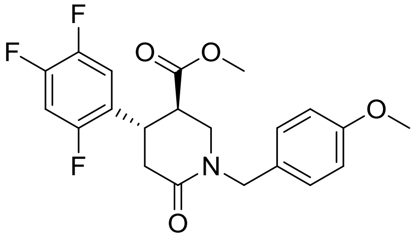
57a (8.3 g, 73%) was prepared from **56a** by means of the general procedure described in **5.1.16.** as a colourless thick oil; Purity by HPLC: 99.60% AUC.

ESI/MS (m/z) : 390.1 $(M+H)^+$. **Mol. Wt.** = 389.4 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.56 (dd, 1H, J_1 = 9.8Hz, J_2 = 14.2Hz), 2.69 (dd, 1H, J_1 = 8.1Hz, J_2 = 14.2Hz), 3.21 (dd, 1H, J_1 = 8.4Hz, J_2 = 9.8Hz), 3.40-3.47 (m, 1H), 3.57-3.59 (m, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 4.36 (d, 1H, J = 9.6Hz), 4.44 (d, 1H, J = 9.6Hz), 6.90-7.01 (m, 4H), 7.11-7.15 (m, 1H), 7.23 (d, 2H, J = 7.4Hz).

^{13}C NMR (100 MHz, CDCl$_3$): δ 37.9, 40.3, 47.5, 49.2, 49.8, 52.2, 56.7, 106.7 (d, J = 28Hz), 114.3, 116.4, 116.9 (d, J = 3.2Hz), 117.2 (d, J = 39Hz), 126.3 (d, J = 23Hz), 128.3, 131.3, 148.2 (d, J = 247Hz), 157.5 (d, J = 252Hz), 166.6, 170.6.

5.1.16.2. Methyl-*trans*-1-(4-methoxybenzyl)-6-oxo-4-(2,4,5-trifluorophenyl) piperidine-3-carboxylate (57b)



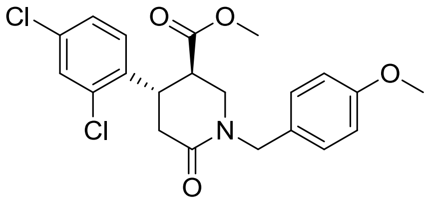
57b (8.9 g, 81%) was prepared from **56b** by means of the general procedure described in **5.1.16.** as a colourless thick oil; Purity by HPLC: 97.21% AUC.

ESI/MS (m/z) : 408.1 $(M+H)^+$. **Mol. Wt.** = 407.4 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.58 (dd, 1H, J_1 = 9.4Hz, J_2 = 14.2Hz), 2.67 (dd, 1H, J_1 = 8.4Hz, J_2 = 14.2Hz), 3.22 (dd, 1H, J_1 = 8.4Hz, J_2 = 9.4Hz), 3.42-3.49 (m, 1H), 3.57-3.61

(m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 4.37 (d, 1H, J = 9.4Hz), 4.43 (d, 1H, J = 9.4Hz), 6.92-7.03 (m, 3H), 7.09-7.10 (m, 1H), 7.11-7.15 (m, 1H), 7.23 (d, 2H, J = 7.8Hz).

5.1.16.3. Methyl-*trans*-4-(2,4-dichlorophenyl)-1-(4-methoxybenzyl)-6-oxopiperidine-3-carboxylate (57c)

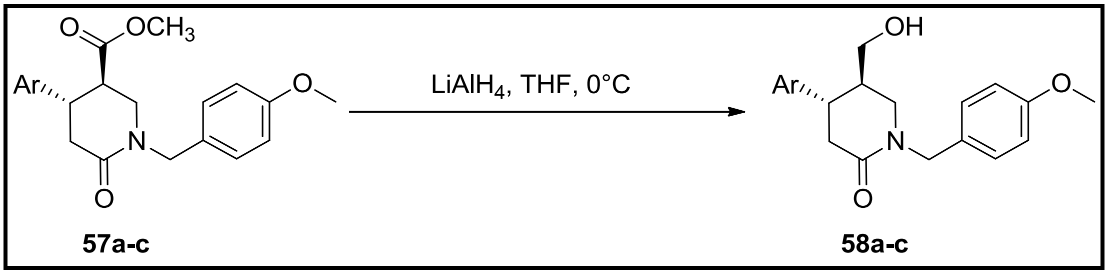


57c (7.3 g, 68%) was prepared from **56c** by means of the general procedure described in **5.1.16.** as a colourless thick oil; Purity by HPLC: 98.24% AUC.

ESI/MS (m/z) : 423.4 $(M+H)^+$. **Mol. Wt.** = 422.3 g.

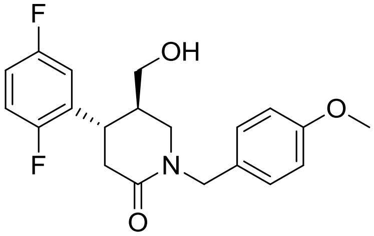
^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (m, 1H), 2.63 (dd, 1H, J_1 = 8.6Hz, J_2 = 14.2Hz), 3.19 (dd, 1H, J_1 = 8.6Hz, J_2 = 9.6Hz), 3.42-3.49 (m, 1H), 3.56-3.63 (m, 2H), 3.76 (s, 3H), 3.78 (s, 3H), 4.36 (d, 1H, J = 9.4Hz), 4.43 (d, 1H, J = 9.4Hz), 6.92-7.03 (m, 3H), 7.18 (d, 2H, J = 7.8Hz), 7.23 (d, 2H, J = 7.8Hz) 7.45 (d, 1H, J = 8.4Hz), 7.52 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.6Hz), 7.92 (d, 1H, J = 1.6Hz).

5.1.17. General procedure for the synthesis of compounds (58a-c)



A solution of compounds **57a-c** (20 mmol) in dry THF (105 ml) was cooled to 0 ^{0}C. To the clear solution obtained was charged $LiAlH_4$ (24 mmol) in portions. Each portion was added after hydrogen gas evolution ceased. Reaction mixture was stirred at 0 ^{0}C for 2h. After completion of reaction, reaction mixture was quenched with sat. Na_2SO_4 solution (5 ml). Stirred the content at room temperature for 30 min., diluted it with DCM (100 ml). Reaction content was then filtered through celite and filtrate was dried over anhy. Na_2SO_4 and evaporated to dryness under reduced pressure to give title compounds **58a-c**.

5.1.17.1. *trans*-4-(2,5-Difluorophenyl)-5-(hydroxymethyl)-1-(4-methoxybenzyl) piperidin-2-one (58a)



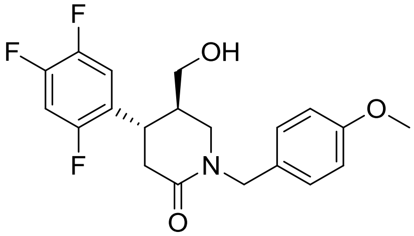
58a (6.9 g, 98%) was prepared by means of the general procedure described in **5.1.17.** as a colourless thick oil; Purity by HPLC: 98.37% AUC.

ESI/MS (m/z) : 362.2 $(M+H)^+$. **Mol. Wt.** = 361.4 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.36-2.40 (m, 2H), 2.50-2.59 (m, 2H), 2.94-2.95 (m, 1H), 3.09-3.12 (m, 1H), 3.30-3.32 (m,2H), 3.51-3.59 (m, 2H), 3.80 (s, 3H), 4.29 (d, 1H, J = 9.6Hz), 4.32 (d, 1H, J = 9.6Hz), 7.21-7.25 (m, 4H), 7.39-7.44 (m, 1H), 7.91 (d, 2H, J = 7.2Hz).

^{13}C NMR (100 MHz, CDCl$_3$): δ 37.7, 40.3, 47.5, 49.2, 49.8, 56.7, 62.3, 104.7 (d, J = 28Hz), 114.3, 116.4, 117.9 (d, J = 3.2Hz), 118.2 (d, J = 38Hz), 126.5 (d, J = 27Hz), 128.3, 131.3, 148.2 (d, J = 252Hz), 155.5 (d, J = 258Hz), 158.4, 166.6.

5.1.17.2. *trans*-5-(Hydroxymethyl)-1-(4-methoxybenzyl)-4-(2,4,5-trifluorophenyl) piperidin-2-one (58b)

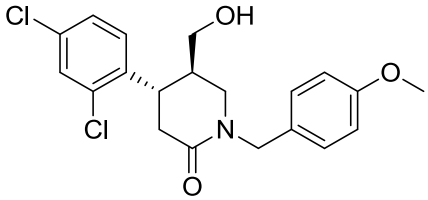


58b (7.1 g, 96%) was prepared by means of the general procedure described in **5.1.17.** as a colourless thick oil; Purity by HPLC: 97.45% AUC.

ESI/MS (m/z) : 380.2 $(M+H)^+$. **Mol. Wt.** = 379.4 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.35-2.40 (m, 2H), 2.51-2.59 (m, 2H), 2.91-2.96 (m, 1H), 3.09-3.12 (m, 1H), 3.30-3.32 (m,2H), 3.51-3.57 (m, 2H), 3.79 (s, 3H), 4.28 (d, 1H, J = 9.6Hz), 4.32 (d, 1H, J = 9.6Hz), 7.26-7.33 (m, 3H), 7.43-7.52 (m, 1H), 7.91 (d, 2H, J = 7.8Hz).

5.1.17.2. *trans*-4-(2,4-Dichlorophenyl)-5-(hydroxymethyl)-1-(4-methoxybenzyl) piperidin-2-one (58c)

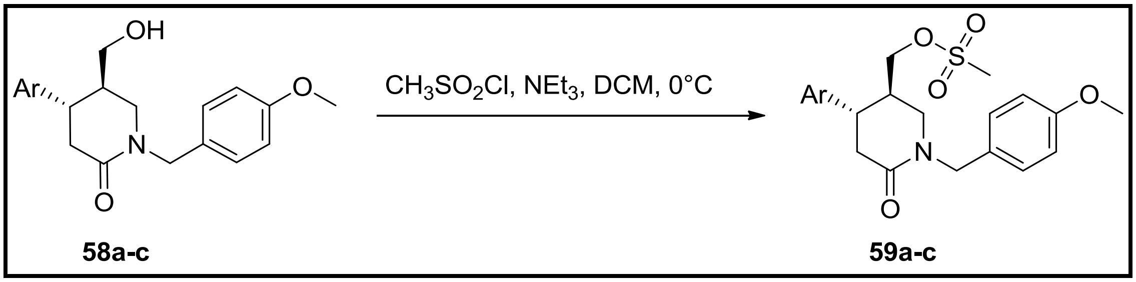


58c (7.3 g, 97%) was prepared by means of the general procedure described in **5.1.17.** as a colourless thick oil; Purity by HPLC: 97.67% AUC.

ESI/MS (m/z) : 394.7 $(M+H)^+$. **Mol. Wt.** = 394.3 g.

^{1}**H NMR (400 MHz, CDCl$_3$):** δ = 2.37-2.42 (m, 2H), 2.51-2.58 (m, 2H), 2.92-2.96 (m, 1H), 3.09-3.12 (m, 1H), 3.30-3.34 (m,2H), 3.51-3.57 (m, 2H), 3.79 (s, 3H), 4.29 (d, 1H, J = 9.6Hz), 4.31 (d, 1H, J = 9.6Hz), 7.21 (d, 1H, J = 8.2 Hz), 7.26 (d, 2H, J = 7.8Hz), 7.34 (dd, 1H, J_1 = 2.2 Hz, J_2 = 8.2 Hz), 7.65 (d, 1H, J = 2.2 Hz), 7.91 (d, 2H, J = 7.8Hz).

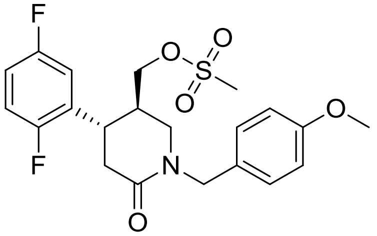
5.1.18. General procedure for the synthesis of compounds (59a-c)



To a solution of compounds **58a-c** (18 mmol) in dry DCM (85 ml) was added triethyl amine (27 mmol) in a single portion. Reaction mixture was cooled to 0 ^{0}C and charged to it methane sulfonyl chloride (21.6 mmol) dropwise over a period of 15 min. After completion of addition, reaction mixture was stirred at the same temperature for 2h.

After completion of reaction, reaction mixture was poured in to D. M. water (100 ml), layers were separated and aqueous layer was extracted with DCM (1X100 ml). Combined organic extracts were washed with D. M. water (3X150 ml), sat. $NaHCO_3$ solution (1X150 ml) and brine (1X100 ml). Organic layer was dried over anhy. Na_2SO_4 and solvent was removed under reduced pressure to give mesylate compounds **59a-c** as colourless oil.

5.1.18.1. *trans*-4-(2,5-Difluorophenyl)-1-(4-methoxybenzyl)-6-oxopiperidin-3-yl)methyl methanesulfonate (59a)



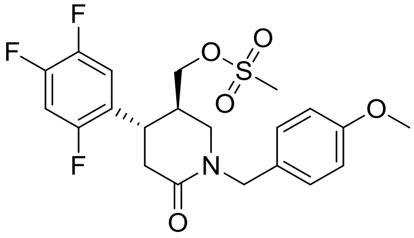
59a (8.7 g, 94%) was prepared from **58a** by means of the general procedure described in **5.1.18.** as a colourless thick oil; Purity by HPLC: 97.04% AUC.

ESI/MS (m/z) : 440.3 $(M+H)^+$. **Mol. Wt.** = 439.5 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.36-2.40 (m, 2H), 2.52 (t, 1H, J = 16.3Hz), 2.55-2.58 (m, 4H), 2.94-2.95 (m, 1H), 3.09-3.12 (m, 1H), 3.30-3.32 (m,2H), 3.51-3.59 (m, 2H), 3.81 (s, 3H), 4.29 (d, 1H, J = 9.6Hz), 4.31 (d, 1H, J = 9.6Hz), 7.21-7.25 (m, 4H), 7.40-7.44 (m, 1H), 7.93 (d, 2H, J = 7.4Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 37.7, 40.3, 41.5, 43.2, 49.8, 56.7, 67.3, 106.6 (d, J = 23Hz), 114.4, 116.7, 117.7 (d, J = 2.8Hz), 118.2 (d, J = 34Hz), 127.1 (d, J = 28Hz), 128.5, 131.3, 148.7 (d, J = 248Hz), 157.0 (d, J = 258Hz), 158.4, 166.7.

5.1.18.2. *trans*-1-(4-Methoxybenzyl)-6-oxo-4-(2,4,5-trifluorophenyl)piperidin-3-yl)methyl methanesulfonate (59b)

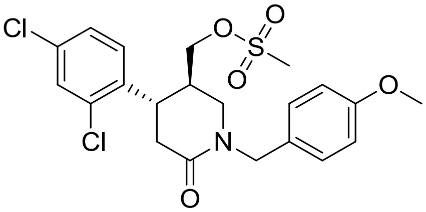


59b (7.6 g, 96%) was prepared from **58b** by means of the general procedure described in **5.1.18.** as a colourless thick oil; Purity by HPLC: 98.21% AUC.

ESI/MS (m/z) : 458.6 $(M+H)^+$. **Mol. Wt.** = 457.5 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.35-2.40 (m, 2H), 2.52-2.54 (m, 1H), 2.55-2.57 (m, 1H), 2.59 (s, 3H), 2.94-2.97 (m, 1H), 3.09-3.12 (m, 1H), 3.30-3.32 (m,2H), 3.51-3.59 (m, 2H), 3.81 (s, 3H), 4.28 (d, 1H, J = 9.4Hz), 4.30 (d, 1H, J = 9.4Hz), 6.92-7.03 (m, 1H), 7.09-7.21 (m, 1H),7.22 (d, 2H, J = 7.8Hz), 7.93 (d, 2H, J = 7.8Hz).

5.1.18.3. *trans*-4-(2,4-dichlorophenyl)-1-(4-methoxybenzyl)-6-oxopiperidin-3-yl)methyl methanesulfonate (59c)

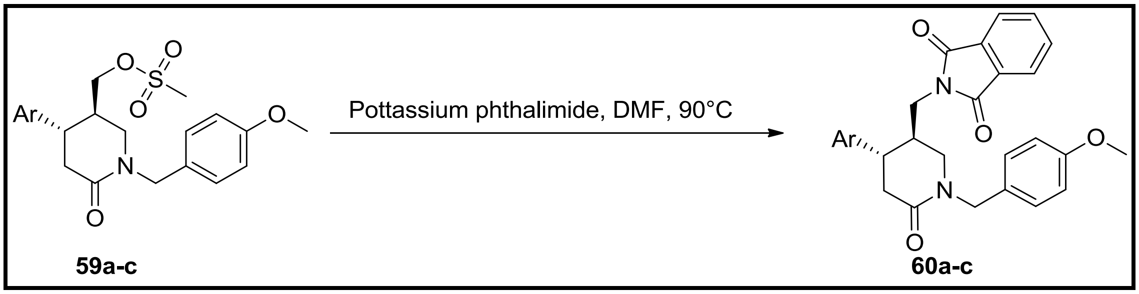


59c (8.1 g, 96%) was prepared from **58c** by means of the general procedure described in **5.1.18.** as a colourless thick oil; Purity by HPLC: 97.84% AUC.

ESI/MS (m/z) : 473.1 $(M+H)^+$. **Mol. Wt.** = 472.4 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33-2.40 (m, 2H), 2.48-2.52 (m, 1H), 2.55-2.57 (m, 1H), 2.61 (s, 3H), 2.94-2.97 (m, 1H), 3.09-3.12 (m, 1H), 3.29-3.32 (m,2H), 3.51-3.59 (m, 2H), 3.80 (s, 3H), 4.29 (d, 1H, J = 9.4Hz), 4.30 (d, 1H, J = 9.4Hz), 7.22 (d, 2H, J = 7.8Hz), 7.45 (d, 1H, J = 8.4Hz), 7.51 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.6Hz), 7.92 (d, 1H, J = 1.6Hz), 7.93 (d, 2H, J = 7.8Hz).

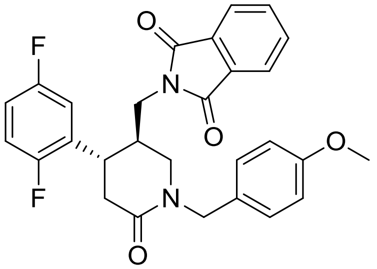
5.1.19. General procedure for the synthesis of compounds (60a-c)



To a solution of the compounds **59a-c** (16 mmol) in dry DMF (85 ml) was charged pottassium phthalimide (20.8 mmol) in a single portion under nitrogen atmosphere at room temperature. Reaction mixture was then heated to 90 °C for 8h.

After completion of reaction (TLC), reaction mixture was cool to room temperature and poured in ice cold D. M. water (425 ml). solid precipitates was filtered through Wattman filter paper and washed with plenty of D. M. water. Solid was then dried under suction to give desired title compounds **60a-c [284]**.

5.1.19.1. *trans*-2-((4-(2,5-Difluorophenyl)-1-(4-methoxybenzyl)-6-oxopiperidin-3-yl)methyl) isoindoline-1,3-dione (60a)



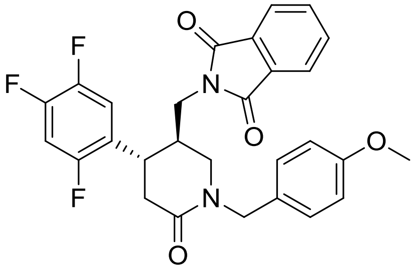
60a (5.3 g, 68%) was prepared from **59a** by means of the general procedure described in **5.1.19.** as a White solid; Mp: 214-217^{0}C, Purity by HPLC: 98.57% AUC.

ESI/MS (m/z) : 490.6 $(M+H)^+$. **Mol. Wt.** = 490.5 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.36-2.39 (m, 1H), 2.41-2.56 (m, 1H), 2.89-2.92 (m, 1H), 3.09-3.12 (m, 1H), 3.30-3.32 (m,2H), 3.53-3.59 (m, 2H), 3.79 (s, 3H), 4.36 (d, 1H, J = 9.6Hz), 4.44 (d, 1H, J = 9.6Hz), 6.90-7.01 (m, 4H), 7.09-7.12 (m, 1H), 7. 23 (d, 2H, J = 7.4Hz), 7.81-7.87 (m, 4H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 38.1, 41.3, 42.2, 42.5, 49.8, 51.7, 56.7, 109.6 (d, J = 23Hz), 114.4, 116.7, 117.7 (d, J = 2.8Hz), 118.2 (d, J = 34Hz), 122.8, 127.1 (d, J = 29Hz), 128.5, 131.3, 131.7, 132.1, 148.3 (d, J = 248Hz), 157.3 (d, J = 258Hz), 158.9, 166.7, 168.2.

5.1.19.2. *trans*-2-((1-(4-Methoxybenzyl)-6-oxo-4-(2,4,5-trifluorophenyl)piperidin-3-yl) methyl)isoindoline-1,3-dione (60b)

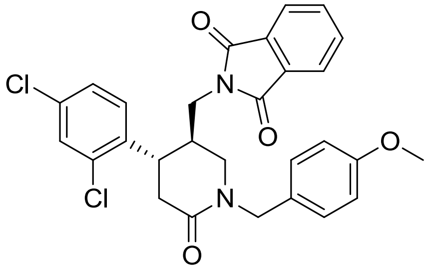


60b (6.0 g, 75%) was prepared from **59b** by means of the general procedure described in **5.1.19.** as a White solid; Mp: 221-224^{0}C, Purity by HPLC: 96.52% AUC.

ESI/MS (m/z) : 509.3 $(M+H)^+$. **Mol. Wt.** = 508.5 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.36-2.39 (m, 1H), 2.41-2.56 (m, 1H), 2.89-2.92 (m, 1H), 3.09-3.12 (m, 1H), 3.30-3.32 (m,2H), 3.53-3.59 (m, 2H), 3.79 (s, 3H), 4.34 (d, 1H, J = 9.4Hz), 4.43 (d, 1H, J = 9.4Hz), 7.23 (d, 2H, J = 7.4Hz), 7.26-7.33 (m, 3H), 7.43-7.52 (m, 1H), 7.83-7.89 (m, 4H).

5.1.19.3. *trans*-2-((4-(2,4-Dichlorophenyl)-1-(4-methoxybenzyl)-6-oxopiperidin-3-yl)methyl) isoindoline-1,3-dione (60c)

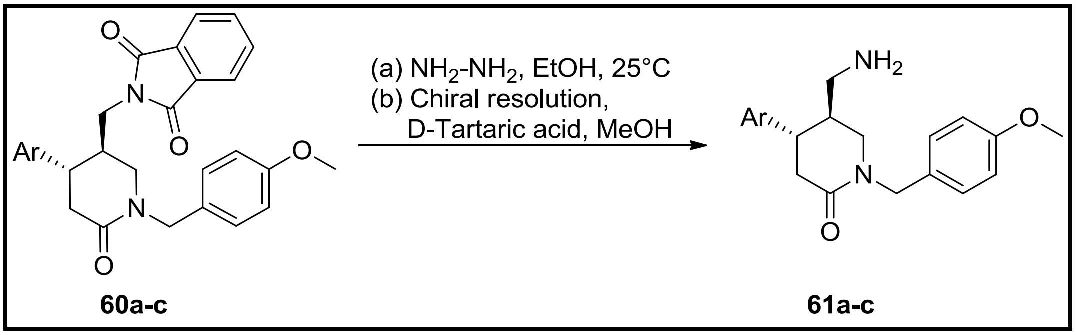


60c (6.2 g, 72%) was prepared from **59c** by means of the general procedure described in **5.1.19.** as a White solid; Mp: 178-186^{0}C (No clear melting point), Purity by HPLC: 97.21% AUC.

ESI/MS (m/z) : 523.9 $(M+H)^+$. **Mol. Wt.** = 523.4 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32-2.37 (m, 1H), 2.39-2.52 (m, 1H), 2.87-2.91 (m, 1H), 3.07-3.10 (m, 1H), 3.28-3.31 (m,2H), 3.49-3.52 (m, 2H), 3.77 (s, 3H), 4.31 (d, 1H, J = 9.6Hz), 4.39 (d, 1H, J = 9.6Hz), 7.21 (d, 1H, J = 8.2 Hz), 7.23 (d, 2H, J = 7.4Hz), 7.29-7.37 (m, 3H), 7.65 (d, 1H, J = 2.2 Hz), 7.83-7.91 (m, 4H).

5.1.20. General procedure for the synthesis of compounds (61a-c)



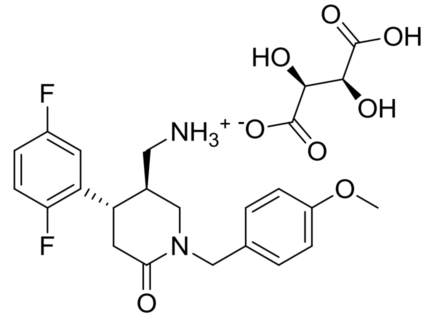
Deprotection of phthalimido group was accomplished by treatment with hydrazine-hydrate **[285]**. Phthalimido compounds **60a-c** (15 mmol) prepared above were dissolved in ethanol (75 ml). To the clear solution obtained was added hydrazine-hydrate (75 mmol) and reaction mixture was stirred at room temperature for 5h.

After completion of reaction (TLC), D. M. water (150 ml) was added to the reaction mixture and ethanol was removed under reduced pressure. Aqueous layer was then extracted with ethyl acetate (4X100 ml). Combined organic layers were washed with brine (1X100 ml). Organic layer was then dried over anhy. Na_2SO_4 and concentrated under reduced pressure to give fairly pure (>95% purity) *trans*- racemic compounds **61a-c**. However this deprotection of phthlimide group to get primary amine can also be accomplish by the mild condition reported by John Osby et al **[286]**.

Chiral resolution:

Amino-methyl pipyridones **61a-c** prepared above were dissolved in methanol (100 ml)- and D-Tartaric acid (16.5 mmol) was added at room temperature and the reaction mixture was stirred for 15h at the same temperature. White solid precipitated in the reaction mixture was filtered through hot filter paper and washed it with methanol (2X100 ml) and dried under suction. Solid was then transferred in drying tray and dried in an air drier at 50^{0}C till constant weight obtained (approximately 5h). Thus tartrate salt of compounds **61a-c** was obtained as a white free flowing powder with absolute stereo configuration (4S, 5S).

5.1.20.1. ((3S,4S)-4-(2,5-Difluorophenyl)-1-(4-methoxybenzyl)-6-oxopiperidin-3-yl) methanaminium (2S,3S)-3-carboxy-2,3-dihydroxypropanoate (61a)



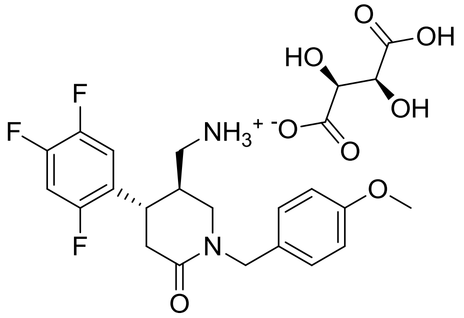
61a (2.48 g, 41%) was prepared from **60a** by means of the general procedure described in **5.1.20.** as a white solid; Mp: 198-201^{0}C, Purity by HPLC: 98.94% AUC, Chiral purity:98.18%ee AUC.

ESI/MS (m/z) : 361.4 $(M+H)^+$. **Mol. Wt.** = 360.4 g.

^{1}H NMR (400 MHz, D_2O): δ = 2.34-2.39 (m, 1H), 2.41-2.53 (m, 1H), 2.89-2.93 (m, 1H), 3.09-3.13 (m, 1H), 3.31-3.34 (m,2H), 3.51-3.57 (m, 2H), 3.79 (s, 3H), 4.36 (d, 1H, J = 9.6Hz), 4.44 (d, 1H, J = 9.6Hz), 4.49 (s, 2H), 6.93-7.04 (m, 4H), 7.09-7.12 (m, 1H), 7. 23 (d, 2H, J = 7.4Hz).

^{13}C NMR (100 MHz, D_2O): δ 37.2, 40.3, 40.9, 45.3, 49.4, 49.9, 55.7, 78.3, 109.6 (d, J = 27Hz), 114.4, 116.7, 117.7 (d, J = 2.8Hz), 118.2 (d, J = 32Hz), 127.1 (d, J = 26Hz), 128.3, 131.4, 148.6 (d, J = 248Hz), 156.3 (d, J = 252Hz), 158.9, 166.7, 176.3.2.

5.1.20.2. ((3S,4S)-1-(4-Methoxybenzyl)-6-oxo-4-(2,4,5-trifluorophenyl)piperidin-3-yl)methanaminium (2S,3S)-3-carboxy-2,3-dihydroxypropanoate (61b)

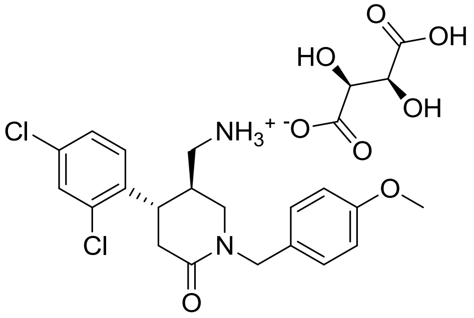


61b (2.17 g, 38%) was prepared from **60b** by means of the general procedure described in **5.1.20.** as a white solid; Mp: 217-219^{0}C, Purity by HPLC: 99.04% AUC, Chiral purity:98.47%ee AUC.

ESI/MS (m/z) : 379.2 $(M+H)^+$. **Mol. Wt.** = 378.4 g.

^{1}H NMR (400 MHz, D_2O): δ = 2.32-2.37 (m, 1H), 2.41-2.53 (m, 1H), 2.92-2.97 (m, 1H), 3.09-3.15 (m, 1H), 3.31-3.34 (m,2H), 3.49-3.56 (m, 2H), 3.77 (s, 3H), 4.33 (d, 1H, J = 9.6Hz), 4.41 (d, 1H, J = 9.6Hz), 4.49 (s, 2H), 6.96-7.07 (m, 1H), 7.09-7.19 (m, 3H), 7. 26 (d, 2H, J = 7.4Hz).

5.1.20.3. ((3S,4S)-4-(2,4-Dichlorophenyl)-1-(4-methoxybenzyl)-6-oxopiperidin-3-yl)methanaminium (2S,3S)-3-carboxy-2,3-dihydroxypropanoate (61c)

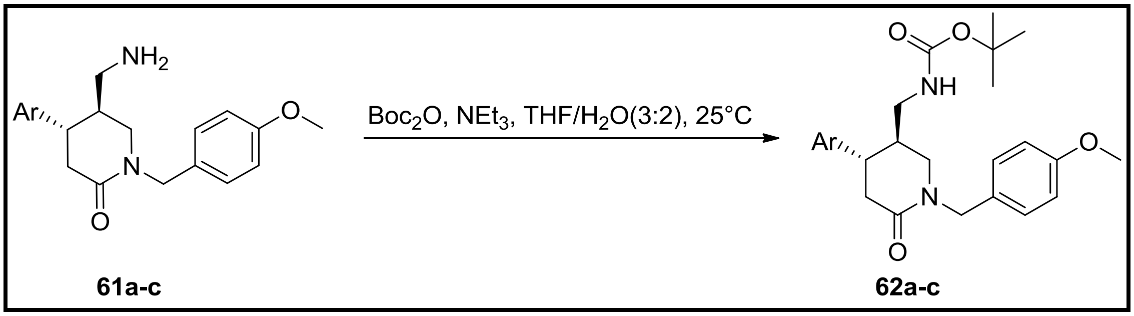


61c (3.2 g, 40%) was prepared **60c** by means of the general procedure described in **5.1.20.** as a white solid; Mp: 168-171^{0}C, Purity by HPLC: 98.24% AUC, Chiral purity:99.07%ee AUC.

ESI/MS (m/z) : 394.0 $(M+H)^+$. **Mol. Wt.** = 393.3 g.

^{1}H NMR (400 MHz, D_2O): δ = 2.33-2.37 (m, 1H), 2.41-2.53 (m, 1H), 2.92-2.96 (m, 1H), 3.09-3.15 (m, 1H), 3.31-3.34 (m,2H), 3.49-3.56 (m, 2H), 3.78 (s, 3H), 4.34 (d, 1H, J = 9.6Hz), 4.44 (d, 1H, J = 9.6Hz), 4.48 (s, 2H), 7.16-7.21 (m, 3H), 7. 26 (d, 2H, J = 7.4Hz), 7.34 (dd, 1H, J_1 = 2.2 Hz, J_2 = 8.2 Hz), 7.65 (d, 1H, J = 2.2 Hz).

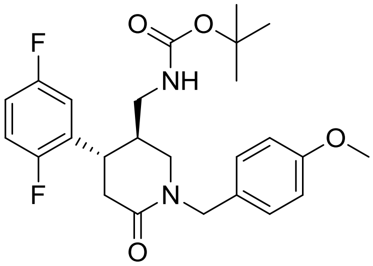
5.1.21. General procedure for the synthesis of compounds (62a-c)



Chiral pure compounds **61a-c** (10 mmol) were dissolved in a mixture of 3:2 THF/D. M. water (30 ml) and triethyl amine (30 mmol) was added in a single portion. Reaction mixture was stirred for 15 min. at room temperature then cool to 0 °C and charged to it Boc-anhydride (12 mmol) dropwise over a period of 15min. Reaction mixture was then gradually brought to room temperature and stirred at the same temperature for 15h.

After completion of reaction, solvent of the reaction mixture was evaporated under reduced pressure and diluted with D. M. water (100 ml). Aqueous layer was then extracted with ethyl acetate (3X75 ml). Combined organic layers were washed with water (2X75 ml), 1N Hall (1X75 ml), water (1X75 ml) and brine (1X75 ml). Organic layer was dried over any. Na_2SO_4 and solvent was removed under reduced pressure to give the compounds **62a-c**, which were used for next reaction step without any purification.

5.1.21.1. tert-Butyl (((3S, 4S)-4-(2, 5-difluorophenyl)-1-(4-methoxybenzyl)-6-oxopiperidin-3-yl) methyl) carbamate (62a)



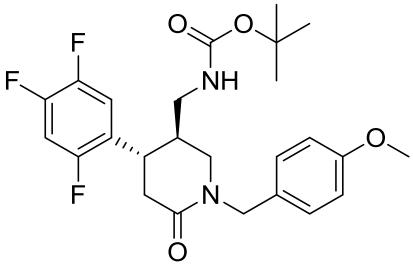
62a (3.2 g, 98%) was prepared from **61a** by means of the general procedure described in **5.1.21.** as a White solid; MP: 187-189^{0}C, Purity by HPLC: 97.31% AUC.

ESI/MS (m/z) : 461.5 $(M+H)^+$. **Mol. Wt.** = 460.5 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.39 (s, 9H), 2.34-2.49 (m, 2H), 2.89-2.93 (m, 1H), 3.09-3.13 (m, 1H), 3.31-3.34 (m,2H), 3.51-3.57 (m, 2H), 3.80 (s, 3H), 4.34 (d, 1H, J = 9.6Hz), 4.42 (d, 1H, J = 9.6Hz), 4.48 (bs, 1H), 6.85-6.94 (m, 4H), 7.09-7.12 (m, 1H), 7. 24 (d, 2H, J = 7.8Hz).

^{13}C NMR (100 MHz, CDCl$_3$): δ 28.2, 37.5, 40.6, 40.8, 42.3, 42.8, 49.9, 56.7, 80.3, 110.2 (d, J = 24Hz), 114.3, 116.5, 117.3 (d, J = 2.4Hz), 118.6 (d, J = 38Hz), 127.3 (d, J = 23Hz), 128.3, 132.0, 148.3 (d, J = 253Hz), 156.3 (d, J = 250Hz), 158.9, 166.7.

5.1.21.2. tert-Butyl (((3S,4S)-1-(4-methoxybenzyl)-6-oxo-4-(2,4,5-trifluorophenyl) piperidin-3-yl)methyl)carbamate (62b)

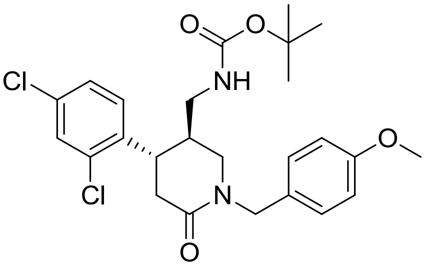


62b (2.9 g, 97%) was prepared from **61b** by means of the general procedure described in **5.1.21.** as a White solid; Mp: 199-203^{0}C, Purity by HPLC: 98.06% AUC.

ESI/MS (m/z) : 479.4 (M+H)$^+$. **Mol. Wt.** = 478.5 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.42 (s, 9H), 2.33-2.49 (m, 2H), 2.89-2.94 (m, 1H), 3.10-3.15 (m, 1H), 3.31-3.38 (m,2H), 3.49-3.57 (m, 2H), 3.80 (s, 3H), 4.32 (d, 1H, J = 9.4Hz), 4.42 (d, 1H, J = 9.4Hz), 4.48 (bs, 1H), 6.92-7.03 (m, 3H), 7.09-7.21 (m, 1H), 7. 24 (d, 2H, J = 7.8Hz).

5.1.21.3. tert-Butyl (((3S,4S)-4-(2,4-dichlorophenyl)-1-(4-methoxybenzyl)-6-oxopiperidin-3-yl)methyl)carbamate (62c)

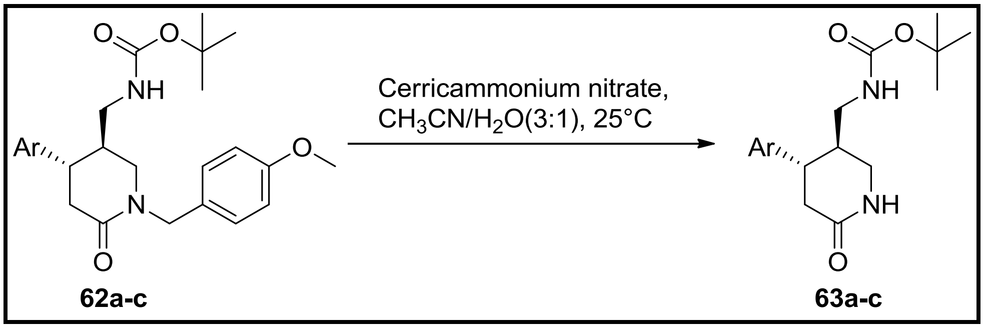


62c (3.1 g, 98%) was prepared from **61c** by means of the general procedure described in **5.1.21.** as a White solid; Mp: 211-213^{0}C, Purity by HPLC: 97.66% AUC.

ESI/MS (m/z) : 493.9 (M+H)$^+$. **Mol. Wt.** = 493.4 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.42 (s, 9H), 2.31-2.49 (m, 2H), 2.89-2.94 (m, 1H), 3.09-3.15 (m, 1H), 3.31-3.38 (m,2H), 3.49-3.56 (m, 2H), 3.79 (s, 3H), 4.32 (d, 1H, J = 9.4Hz), 4.42 (d, 1H, J = 9.4Hz), 4.46 (bs, 1H), 6.93 (d, 2H, J = 7.8 Hz), 7.23 (d, 1H, J = 8.4 Hz), 7. 24 (d, 2H, J = 7.8Hz), 7.37 (dd, 1H, J_1 = 1.8 Hz, J_2 = 8.2 Hz), 7.63 (d, 1H, J = 2.0 Hz).

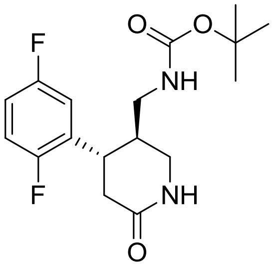
5.1.22. General procedure for the synthesis of compounds (63a-c)



Oxidative removal of *p*-methoxy benzyl group of compounds **62a-c** prepared in experimental section **5.1.21.** was accomplished using the method reported by Masanori Yamaura et al **[287]**. Compounds **62a-c** (8 mmol) were dissolved in a mixture of acetonitrile (100 ml) and D. M. water (33 ml) and aqueous 0.25M ceric ammonium nitrate solution (32 mmol) was added in a single portion and stirred at room temperature for 2h.

After completion of reaction (TLC), the reaction mixture was diluted with D. M. water (100 ml) and extracted with ethyl acetate (6X100 ml). Combined organic layers were washed with sat. $NaHCO_3$ solution (2X100 ml) and brine (1X100 ml). Organic layer was dried over anhy. Na_2SO_4 and solvent was removed under reduced pressure. Crude product thus obtained was purified by column chromatography (stationary phase: 100-200 mesh silica, Mobile phase: 0-3% Methanol in DCM gradient) to give title compounds **63a-c** as a white solid.

5.1.22.1. tert-Butyl (((3R,4S)-4-(2,5-difluorophenyl)-6-oxopiperidin-3-yl)methyl) carbamate (63a)



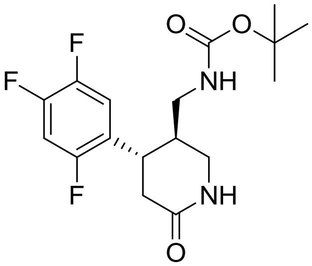
63a (1.98 g, 68%) was prepared from **62a** by means of the general procedure described in **5.1.22.** as a White solid; Mp: 243-246^{0}C, Purity by HPLC: 98.27% AUC.

ESI/MS (m/z) : 341.2 $(M+H)^+$. **Mol. Wt.** = 340.4 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9H), 2.34-2.49 (m, 2H), 2.89-2.93 (m, 1H), 3.09-3.13 (m, 1H), 3.31-3.34 (m,2H), 3.51-3.57 (m, 2H), 4.48 (bs, 1H), 6.08 (bs, 1H), 6.92-6.99 (m, 2H), 7.09-7.12 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 36.4, 38.5, 41.3, 41.8, 46.1, 80.3, 109.8 (d, J = 24Hz), 117.3 (d, J = 2.4Hz), 118.6 (d, J = 39Hz), 127.3 (d, J = 23Hz), 149.3 (d, J = 253Hz), 156.3 (d, J = 250Hz), 159.3, 170.6.

5.1.22.2. tert-Butyl (((3R,4S)-6-oxo-4-(2,4,5-trifluorophenyl)piperidin-3-yl)methyl) carbamate (63b)

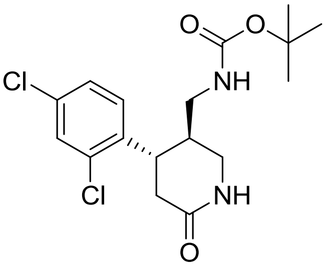


63b (2.1 g, 72%) was prepared from **62b** by means of the general procedure described in **5.1.22.** as a White solid; Mp: 278-281^{0}C, Purity by HPLC: 97.14% AUC.

ESI/MS (m/z) : 359.3 $(M+H)^+$. **Mol. Wt.** = 358.4 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9H), 2.34-2.49 (m, 2H), 2.89-2.93 (m, 1H), 3.10-3.16 (m, 1H), 3.31-3.34 (m,2H), 3.51-3.57 (m, 2H), 4.52 (bs, 1H), 6.09 (bs, 1H), 6.96-7.04 (m, 1H), 7.09-7.11 (m, 1H).

5.1.22.3. tert-Butyl (((3R,4S)-4-(2,4-dichlorophenyl)-6-oxopiperidin-3-yl)methyl) carbamate (63c)

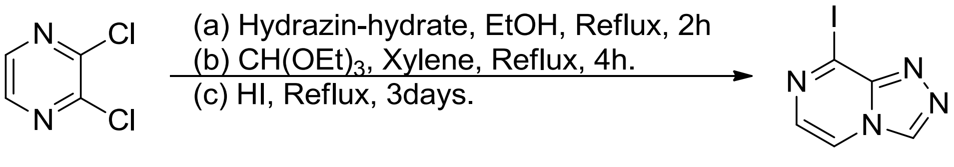


63c (1.8 g, 62%) was prepared from **62c** by means of the general procedure described in **5.1.22.** as a White solid; Mp: 185-189^{0}C, Purity by HPLC: 96.76% AUC.

ESI/MS (m/z) : 373.9 $(M+H)^+$. **Mol. Wt.** = 373.3 g.

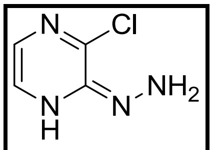
^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.41 (s, 9H), 2.34-2.49 (m, 2H), 2.89-2.93 (m, 1H), 3.09-3.15 (m, 1H), 3.31-3.34 (m,2H), 3.51-3.57 (m, 2H), 4.49 (bs, 1H), 6.08 (bs, 1H), 7.21 (d, 1H, J = 8.4 Hz), 7.34 (dd, 1H, J_1 = 2.0 Hz, J_2 = 8.4 Hz), 7.63 (d, 1H, J = 2.0 Hz).

5.1.23. Procedure for the synthesis of 8-Iodo-[1,2,4]triazolo[4,3-a]pyrazine (64n)



72 **64n**

Step a: (E)-3-Chloro-2-hydrazono-1,2-dihydropyrazine (73)



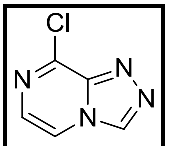
73

2,3-Dichloropyrazine **72** (4 ml, 26 mmol) was dissolved in 95% ethanol (8 ml) and to this was added, dropwise and with stirring, hydrazine anhydrous (4 ml, 134 mmol). During the addition of the Hydrazine the solution became warm and yellowish. Reaction mixture was refluxed for 2h. After completion and cooling of this mixture in an ice bath, the resulting solid material was isolated by filtration, washed with cold aqueous 95% ethanol and dried well under suction to give 3.02 g (73% yield) of (E)-3-chloro-2-hydrazono-1,2-dihydropyrazine **73** as white crystals. Purity by HPLC: 97.67% AUC.

ESI/MS (m/z) : 145.3 $(M+H)^+$. **Mol. Wt.** = 144.6 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.94 (d, 1H, J = 7.8 Hz), 7.21 (bs, 2H, -NH-N**H$_2$**), 8.12 (d, 1H, J = 7.8 Hz), 12.89 (s, 1H, -N**H**-NH$_2$)

Step b: 8-Chloro-[1,2,4]triazolo[4,3-a]pyrazine (74)



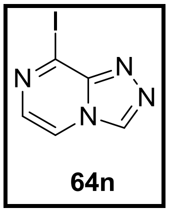
74

To (E)-3-chloro-2-hydrazono-1,2-dihydropyrazine **73** (2.0 g, 13.84 mmol), prepared in **step a** was added trimethyl orthoformate (30 ml). After refluxing for 10 h, the reaction was cooled to room temperature and the precipitated product was filtered. Washed the product with ether and dried well under suction to give 1.27 g (62% yield) of the title compound **74** as a white solid. Purity by HPLC: 95.27% AUC.

ESI/MS (m/z) : 155.0 $(M+H)^+$. **Mol. Wt.** = 154.6 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, 2H, J = 5.2 Hz), 8.50 (d, 2H, J = 5.2 Hz). 9.40 (s, 1H).

Step c: 8-Iodo-[1,2,4]triazolo[4,3-a]pyrazine (64n)



64n

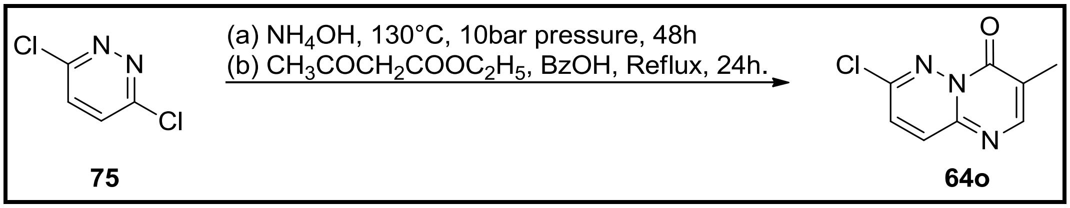
In a 25 ml 2-neck R. B. Flask placed 8-chloro-[1,2,4]triazolo[4,3-a]pyrazine **74** (7.75 mmol), to it charged sodium iodide (11.64 mmol) and Hydroiodic acid (57wt% in water, stabilized with <1.5%hypophosphorous acid) (77.5 mmol). Reaction mixture was heated to reflux and stirred at reflux temperature for 3 days.

After completion of reaction, reaction mixture was cooled to room temperature and basified with 25% aq. NaOH. Aqueous layer was then extracted with DCM (4X 50 ml). dried over anhy. Na_2SO_4 and concentrated under reduced pressure. Crude product thus obtained was crystallized from IPA to give 1.44 g (76% yield) of the title compound **64n** as a light yellow solid. Purity by HPLC: 97.43% AUC.

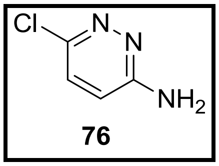
ESI/MS (m/z) : 247.1 $(M+H)^+$. **Mol. Wt.** = 246.0 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, 2H, J = 5.0 Hz), 8.63 (d, 2H, J = 5.0 Hz). 9.41 (s, 1H).

5.1.24. Procedure for the synthesis of 7-Chloro-3-methyl-4H-pyrimido[1,2-b]pyridazin-4-one (64o)



Step a: 6-Chloropyridazin-3-amine (76)

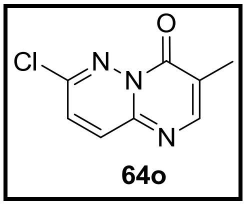


3,6-Dichloropyridazine **75** (33.5 mmol) was placed in an autoclave of 300 ml capacity. To it charged ethanol (50 ml) and liquor NH_3 (100 ml, 20 vol. by wt. of starting material) and the clear solution formed was heated to 130 $^{\circ}$C. Reaction mixture was stirred at same temperature for 48h under 10bar pressure. After completion, Crystals precipitated in the reaction mixture were filtered and washed with cold ethanol (2X20 ml). Filtrate was concentrated to a volume of 40 ml under reduced pressure, solid precipitated from filtrate was filtered and washed with ethanol (2X10 ml). Combined solid was dried well under reduced pressure till constant weight to give 3.37 g (78% Yield) of 6-chloropyridazin-3-amine **76** as an off white crystalline solid. Mp: 226-228^{0}C, Purity by HPLC: 96.43% AUC.

ESI/MS (m/z) : 130.4 $(M+H)^+$. **Mol. Wt.** = 129.5 g.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ 6.61 (bs, 2H), 6.83 (d, 1H, J = 9.2 Hz), 7.36 (d, 1H, J = 9.2 Hz). 7.81 (bs, 2H).

Step b: 7-Chloro-3-methyl-4H-pyrimido[1,2-b]pyridazin-4-one (64o)

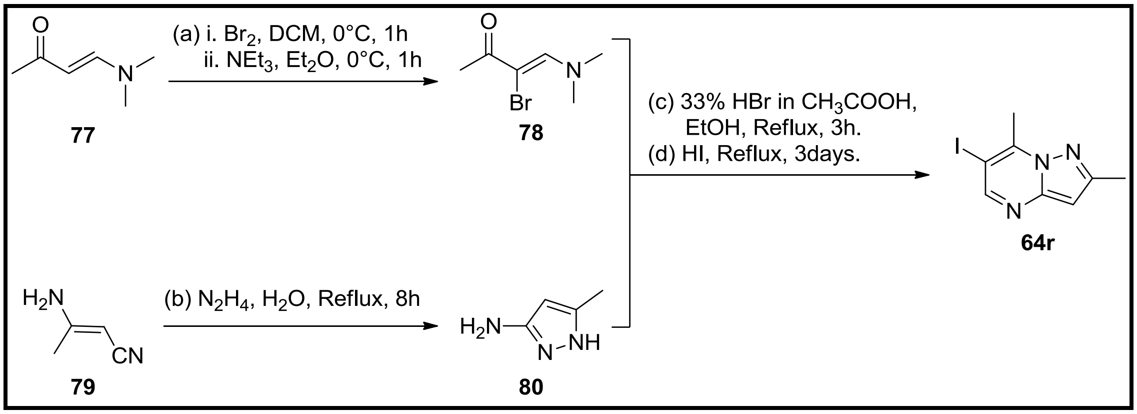


7-Chloro-3-methyl-4H-pyrimido[1,2-b]pyridazin-4-one **64o** was prepared by optimizing a route reported by Avellana et al **[272]**. To a stirred solution of 6-chloropyridazin-3-amine **76** (3.0 g, 23.1 mmol) in benzyl alcohol (15 ml) was added ethyl acetoacetate (4.41 ml, 34.65 mmol). The resulting solution was refluxed for 24 h then evaporated in vacuo to yield a crude solid which was purified by flash chromatography (230-400 mesh silica gel, 0 to 80% ethyl acetate/hexanes gradient) to give 7-chloro-3-methyl-4H-pyrimido[1,2-b]pyridazin-4-one **64o** as a light yellow crystalline solid. Mp: 193-196^{0}C dec., Purity by HPLC: 98.27% AUC.

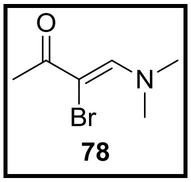
ESI/MS (m/z) : 196.3 $(M+H)^+$. **Mol. Wt.** = 195.6 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.38 (s, 3H), 6.84 (d, 1H, J = 8.2 Hz), 7.06 (d, 1H, J = 8.2 Hz). 7.68 (s, 1H).

5.1.25. procedure for the synthesis of 6-Iodo-2,7-dimethylpyrazolo[1,5-a]pyrimidine (64r)



Step a: 3-Bromo-4-(dimethylamino)but-3-en-2-one (78)

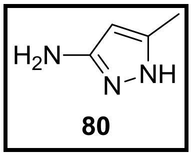

78

To an ice cold solution of (E)-4-(dimethylamino)but-3-en-2-one (5.0 g, 44.25 mmol) in DCM (50 ml) was added dropwise Bromine (2.71 ml, 48.67 mmol) via an addition funnel. The reaction mixture was stirred at 0 °C for 0.5 h and then Triethylamine (7.4 ml, 48.67 mmol) in 10 ml of ether was added dropwise. The mixture was stirred at 0 °C for 1 h and allowed to warm up to room temperature. A light yellow solid precipitated from the solution, and it was filtered. The filtrate was then concentrated to give 7.05 g (82% Yield) of 3-Bromo-4-(dimethylamino)but-3-en-2-one **78** as a yellow solid. The product was used in the next reaction without any further purification. Mp: 89-93^{0}C, Purity by HPLC: 93.47% AUC.

ESI/MS (m/z) : 193.0 (M+H)$^{+}$. **Mol. Wt.** = 192.1 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ 2.31 (s, 3H), 2.93 (s, 6H), 7.32 (s, 1H).

Step b: 5-Methyl-1H-pyrazol-3-amine (80)



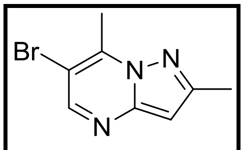
80

3-Aminocrotonnitrile **79** (5.0 g, 61 mmol) was dissolved in ethanol (25 ml) at room temperature and 85% hydrazine-hydrate (80 ml) was added there to, followed by stirring the mixture at room temperature. The mixture was heated to an internal temperature of 65 °C and stirring was conducted for 12 hours. After cooling the mixture to room temperature, the solvent was distilled off under reduced pressure to obtain 4.55 g (77% Yield) of 5-methyl-1H-pyrazol-3-amine **80** as a brown oily compound. The product was used in the next reaction without further purification. Purity by HPLC: 95.28% AUC.

ESI/MS (m/z) : 98.3 $(M+H)^+$. **Mol. Wt.** = 97.1 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (3H, s), 5.42 (1H, s).

Step c: 6-Bromo-2,7-dimethylpyrazolo[1,5-a]pyrimidine (81)



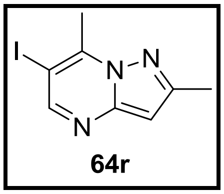
81

To a solution of 3-bromo-4-(dimethylamino)but-3-en-2-one **78** (4.0 g, 20.8 mmol) and 5-methyl-1H-pyrazol-3-amine **80** (2.02 g, 20.8 mmol) in ethanol (50 ml) was added 33% HBr in acetic acid solution (2.6 ml, mmol) and the resulting mixture was heated at reflux for 3 h. The reaction mixture was cooled to room temperature and concentrated to give brown residue which was titurated with 30% ethyl acetate in hexane (100 ml) to give a precipitates which were filtered, and then washed with ethyl acetate (2X50 ml). The combined organic extracts were evaporated to give orange solid which was chromatographed (100-200 mesh silica gel, 0% to 10% ethyl acetate in DCM gradient) to give 2.64 g (57% Yield) of 6-bromo-2,7-dimethylpyrazolo[1,5-a]pyrimidine **81** as a yellow solid. Mp: 232-234^{0}C, Purity by HPLC: 97.14% AUC.

ESI/MS (m/z) : 227.0 $(M+H)^+$. **Mol. Wt.** = 226.1 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (3H, s), 2.67 (s, 3H), 5.69 (1H, s), 8.52 (s, 1H).

Step d: 6-Iodo-2,7-dimethylpyrazolo[1,5-a]pyrimidine (64r)



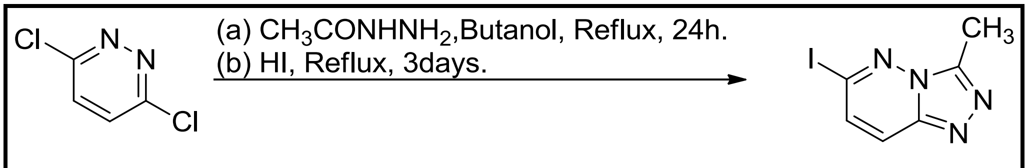
64r

64r (1.6 g, 68%) was prepared by means of the general procedure described in experimental **section 5.1.23. step-c** as a yellow solid; Mp: 187-189^{0}C, Purity by HPLC: 97.36% AUC.

ESI/MS (m/z) : 274.2 $(M+H)^+$. **Mol. Wt.** = 273.1 g.

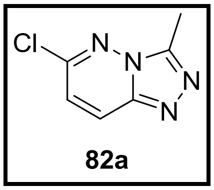
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (3H, s), 2.68 (s, 3H), 5.69 (1H, s), 8.63 (s, 1H).

5.1.26. Procedure for the synthesis of 6-Iodo-3-methyl-[1,2,4]triazolo[4,3-b]pyridazine (64s)



75 **64s**

Step a: 6-Chloro-3-methyl-[1,2,4]triazolo[4,3-b]pyridazine (82a)



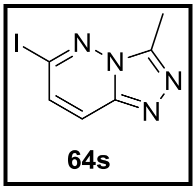
82a

To a stirred solution of 3,6-dichloropyridazine **75** (2.0 g, 13.4 mmol) in butanol (10 ml) was added 500 mg (6.7 mmol) of acetic hydrazide (1.0 g, 13.4 mmol) and the resulting solution was stirred under nitrogen at refluxed for 24 h. The reaction mixture was then cooled to ambient temperature, filtered, and the resulting precipitates were washed with ethyl acetate and methanol. The combined filtrate and washings were concentrated and dissolved in mixture of 10:1 chloroform/methanol (250 ml) then washed with brine solution (2X100 ml). The organic phase was then dried over anhy. Na_2SO_4, filtered, and evaporated in vacuo to yield a yellow solid. The crude material was purified by flash chromatography (230-400 mesh silica gel, 0 to 80% ethyl acetate/hexanes gradient) to give 1.56 g (69% Yield) of the title compound **82a** as light yellow crystalline solid.. Mp: 163-165^{0}C, Purity by HPLC: 98.79% AUC.

ESI/MS (m/z) : 168.9 $(M+H)^+$. **Mol. Wt.** = 168.6 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.67 (3H, s), 7.24 (d, 1H, J = 9.6 Hz), 8.43 (d, 1H, J = 9.6 Hz).

Step b: 6-Iodo-3-methyl-[1,2,4]triazolo[4,3-b]pyridazine (64s)



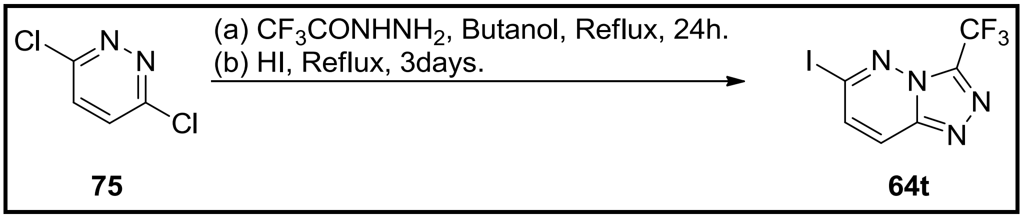
64s

64s (1.2 g, 64%) was prepared by means of the general procedure described in experimental **section 5.1.23. step-c** as a light yellow solid; Mp: 194-197^{0}C, Purity by HPLC: 96.62% AUC.

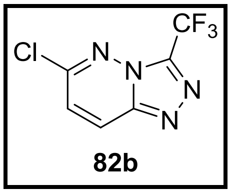
ESI/MS (m/z) : 260.8 $(M+H)^+$. **Mol. Wt.** = 260.0 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.67 (3H, s), 7.26 (d, 1H, J = 9.8 Hz), 8.44 (d, 1H, J = 9.8 Hz).

5.1.27. Procedure for the synthesis of 6-Iodo-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (64t)



Step a: 6-Chloro-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (82b)



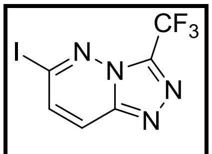
82b

82b (2.3 g, 64%) was prepared using 2,2,2-trifluoro acetic hydrazide by means of the general procedure described in experimental **section 5.1.23. step-c** as a white solid; Mp: 159-161^{0}C, Purity by HPLC: 95.78% AUC.

ESI/MS (m/z) : 223.2 $(M+H)^+$. **Mol. Wt.** = 222.6 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, 1H, J = 9.8 Hz), 8.46 (d, 1H, J = 9.8 Hz).

Step b: 6-Iodo-3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazine (64t)



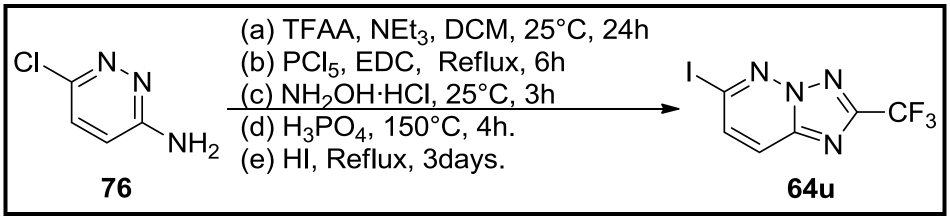
64t

64t (1.03 g, 67%) was prepared by means of the general procedure described in experimental **section 5.1.23. step-c** as a light yellow solid; Mp: 208-210^{0}C, Purity by HPLC: 95.32% AUC.

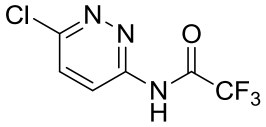
ESI/MS (m/z) : 314.9 $(M+H)^+$. **Mol. Wt.** = 314.0 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, 1H, J = 9.8 Hz), 8.46 (d, 1H, J = 9.8 Hz).

5.1.28. Procedure for the synthesis of 6-Iodo-2-(trifluoromethyl)-[1,2,4]triazolo[1,5-b]pyridazine (64u)



Step a: N-(6-Chloropyridazin-3-yl)-2,2,2-trifluoroacetamide (83)



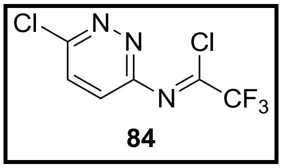
83

To a solution of 6-chloropyridazin-3-amine **76** (4 g, 30 mmol) and triethylamine (4.8 ml, 34 mmol) in DCM (150 ml) at 0 ^{0}C was carefully added trifluoroacetic acid anhydride (4.2 ml, 30 mmol). The resulting solution was allowed to warm to ambient temperature then concentrated in vacuo and dissolved in a mixture of 3: 1 chloroform/IPA (200 ml). The resulting solution was washed sequentially with saturated $NaHCO_3$ solution and brine solution (200 ml each). The organic phase was then dried over anhy. Na_2SO_4 and evaporated in vacuo to yield a crude oil which was purified by column chromatography to give 6.2 g (89% yield) of N-(6-chloropyridazin-3-yl)-2,2,2-trifluoroacetamide **83** as a colourless oil; Purity by HPLC: 99.03% AUC.

ESI/MS (m/z) : 242.9 $(M+NH_4)^+$. **Mol. Wt.** = 225.6 g.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.63 (d, 1H, J = 9.6 Hz), 8.46 (d, 1H, J = 9.6 Hz), 9.16 (bs, 1H).

Step b: (Z)-N-(6-Chloropyridazin-3-yl)-2,2,2-trifluoroacetimidoyl chloride (84)

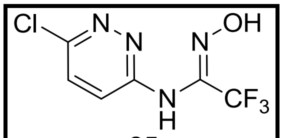


84

A solution of N-(6-chloropyridazin-3-yl)-2,2,2-trifluoroacetamide **83** (3.8 g, 17 mmol) and phosphorous pentachloride (4.2 g, 22 mmol) in dichloroethane (200 ml) was heated at reflux temperature under nitrogen. After 6 h the reaction was cooled to ambient temperature then concentrated in vacuo to give 3.87 g (95% yield) of (Z)-N-(6-chloropyridazin-3-yl)-2,2,2-trifluoroacetimidoyl chloride **84** as a yellow oil. The product was used in the next reaction without any further purification.

ESI/MS (m/z) : 244.7 $(M+H)^+$. **Mol. Wt.** = 244.0 g.

Step c: (E)-N-(6-Chloropyridazin-3-yl)-2,2,2-trifluoro-N'-hydroxyacetimidamide (85)



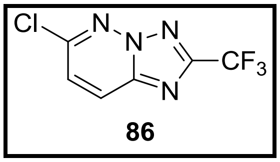
85

To a solution of the crude product (Z)-N-(6-chloropyridazin-3-yl)-2,2,2-trifluoroacetimidoyl chloride **84** (3.0 g, 12.3 mmol), in dry THF (150 ml) was carefully added hydroxylamine-hydrochloride (1.03 g, 14.7 mmol). The resulting solution was stirred under nitrogen at room temperature. After 1 h the solution was concentrated in vacuo then dissolved in 100 ml ethyl acetate and washed sequentially with saturated $NaHCO_3$ solution and brine (100 ml each). The organic phase was then dried over anhy. Na_2SO_4 and evaporated in vacuo to give 2.63 g (89% Yield) of (E)-N-(6-chloropyridazin-3-yl)-2,2,2-trifluoro-N'-hydroxyacetimidamide **85** as a white solid; Mp: 259-261^{0}C, Purity by HPLC: 97.83% AUC.

ESI/MS (m/z) : 241.0 $(M+H)^+$. **Mol. Wt.** = 240.6 g.

^{1}H NMR (400 MHz, DMSO-*d$_6$*): δ 7.11 (d, 1H, J = 9.2 Hz), 7.69 (d, 1H, J = 9.2 Hz), 9.78 (bs, 1H), 12.32 (bs, 1H).

Step d: 6-Chloro-2-(trifluoromethyl)-[1,2,4]triazolo[1,5-b]pyridazine (86)



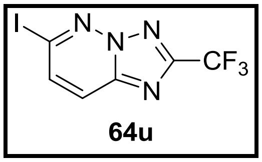
86

To (E)-N-(6-Chloropyridazin-3-yl)-2,2,2-trifluoro-N'-hydroxyacetimidamide **85** (2.2 g, 9.0 mmol) prepared in **Step C** was added concentrated polyphosphoric acid (2.0 ml) and the resulting mixture was stirred under nitrogen at 150 °C for 4 h. The reaction mixture was then cooled to 0 °C and quenched carefully with concentrated ammonium hydroxide solution until the solution was basic by pH paper. The resulting solution was then extracted with ethyl acetate (3X100 ml), and the organic phases combined and washed with brine solution (1X250 ml). The organic phase was then dried over anhy. Na_2SO_4, filtered, and evaporated in vacuum to yield a crude oil. The crude material was purified by flash chromatography (100-200 mesh silica gel, 0 to 80% ethyl acetate/Hexanes gradient) to give 1.59 g (78% Yield) of 6-chloro-2-(trifluoromethyl)-[1,2,4]triazolo[1,5-b]pyridazine **86** as a yellow crystalline solid. Mp: 274-276^{0}C, Purity by HPLC: 99.15% AUC.

ESI/MS (m/z) : 247.0 $(M+Na)^+$. **Mol. Wt.** = 222.6 g.

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, 1H, J = 9.2 Hz), 8.70 (d, 1H, J = 9.2 Hz).

Step e: 6-Iodo-2-(trifluoromethyl)-[1,2,4]triazolo[1,5-b]pyridazine (64u)



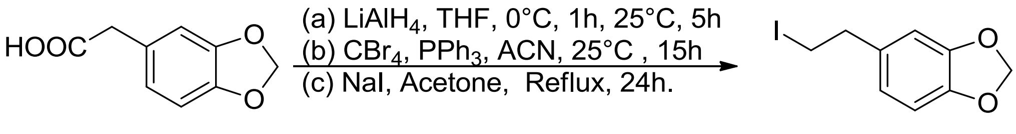
64u

64u (1.5 g, 67%) was prepared by means of the general procedure described in experimental **section 5.1.23. step-c** as a light yellow solid; Mp: 287-293^{0}C dec., Purity by HPLC: 97.63% AUC.

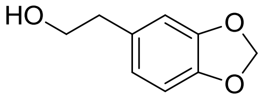
ESI/MS (m/z) : 314.5 $(M+H)^+$. **Mol. Wt.** = 314.0 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, 1H, J = 9.2 Hz), 8.73 (d, 1H, J = 9.6 Hz).

5.1.29. Procedure for the synthesis of 5-(2-Iodoethyl)benzo[d][1,3]dioxole (64v)



Step a: 2-(Benzo[d][1,3]dioxol-5-yl)ethanol (88)



88

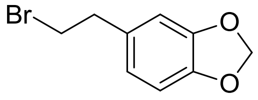
2-(Benzo[d][1,3]dioxol-5-yl)acetic acid **87** (5.0 g, 27.8 mmol) was dissolved in dry THF (60 ml), cooled to 0^0C and $LiAlH_4$ (2.3 g, 62.2 mmol) was added in portions under nitrogen atmosphere. Reaction mixture was stirred at same temperature for 1h then brought to room temperature and stirred for 4h.

After completion of reaction, reaction mixture was quenched with sat. Na_2SO_4 solution (10 ml), diluted with DCM and was filtered through celite. Filtrate was evaporated to dryness to give 3.69 g (80% Yield) of 2-(benzo[d][1,3]dioxol-5-yl)ethanol **88** as a colourless oil. Purity by HPLC; 94.89% AUC.

ESI/MS (m/z) : 167.1 $(M+H)^+$. **Mol. Wt.** = 166.2 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85 (t, 2H, J = 7.4Hz), 3.46 (t, 2H, J = 7.4Hz), 5.91 (s, 2H), 6.33 (dd, 1H, J_1 = 2.4Hz, J_2 = 8.4Hz), 6.55 (d, 1H, J= 2.4Hz), 6.70 (d, 1H, J= 8.4Hz).

Step b: 5-(2-Bromoethyl)benzo[d][1,3]dioxole (89)



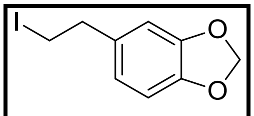
89

To a solution of 2-(benzo[d][1,3]dioxol-5-yl)ethanol **88** (3.5 g, 21.08 mmol) and Triphenylphosphene (4.97 g, 18.97 mmol) in acetonitrile (42 ml) was added carbon tetrabromide (7.13 g, 21.5 mmol) in portions. Resulting solution was stirred at room temperature for 15h. After completion of the reaction, solvent of the reaction mixture was evaporated under reduced pressure and the residue obtained was purified by column chromatography (100-200 mesh silica gel, 0 to 30% ethyl acetate/hexanes gradient) to yield 3.96 g (82% Yield) of 5-(2-bromoethyl)benzo[d][1,3]dioxole **89** as a colourless oil. Purity by HPLC: 96.31% AUC.

ESI/MS (m/z) : 228.4 $(M+H)^+$. **Mol. Wt.** = 229.1 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (t, 2H, J = 7.4Hz), 3.51 (t, 2H, J = 7.4Hz), 5.93 (s, 2H), 6.32 (dd, 1H, J_1 = 2.4Hz, J_2 = 8.4Hz), 6.57 (d, 1H, J= 2.4Hz), 6.71 (d, 1H, J= 8.4Hz).

Step c: 5-(2-Iodoethyl)benzo[d][1,3]dioxole (64v)



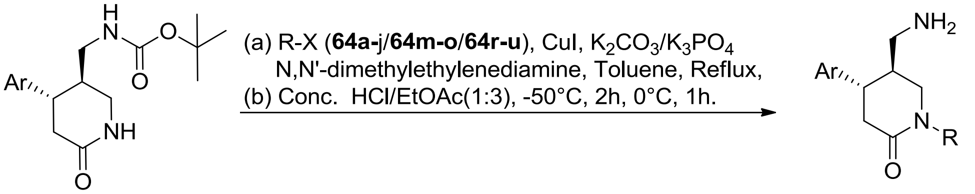
64v

To a solution of 5-(2-bromoethyl)benzo[d][1,3]dioxole **89** (3.5 g, 15.3 mmol) in acetone (52.5 ml) was added sodium iodide (11.5 g, 76.5 mmol). Reaction content was refluxed for 12h when additional sodium iodide (5.575 g, 38.25 mmol) was added and refluxed for 24h. After completion of reaction, solvent of the reaction mixture was evaporated under reduced pressure and the residue obtained was purified by column chromatography (100-200 mesh silica gel, 0 to 30% ethyl acetate/hexanes gradient) to give 3.92 g (92% Yield) of 5-(2-iodoethyl)benzo[d][1,3]dioxole **64v** as a colourless oil. Purity by HPLC: 97.86% AUC.

ESI/MS (m/z) : 277.3 $(M+H)^+$. **Mol. Wt.** = 276.1 g.

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.07 (t, 2H, J = 7.6Hz), 3.69 (t, 2H, J = 7.6Hz), 5.98 (s, 2H), 6.32 (dd, 1H, J_1 = 1.8Hz, J_2 = 8.4Hz), 6.57 (d, 1H, J= 1.8Hz), 6.72 (d, 1H, J= 8.4Hz).

5.1.30. General procedure for the synthesis of compounds (68a-j, 68m-o, 68r-u, 69b-d & 70b-d)



63a-c **68a-j, 68m-o, 68r-u, 69b-d &70b-d**

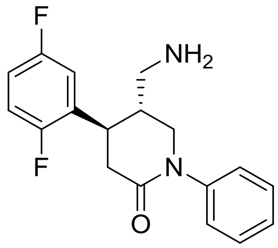
Synthesis of amino-methyl pipyridones **68a-j, 68m-o, 68r-u, 69b-d & 70b-d** was accomplished with Goldberg reaction reported by Klapars et al **[264]**. In a 50 ml 2-neck R. B. Flask placed compound **63a-c** (5 mmol), respective halo-aromatics **64a-j**, **64m-o** or **64r-u** (7.5 mmol), dry K_2CO_3 (10.5 mmol) and CuI (0.5 mmol) followed by addition of dry toluene (20 ml). Reaction mixture was purged with nitrogen and stirred for 30 min. at room temperature then N,N'-dimethyl ethylenediamine (1.0 mmol) was added and reaction mixture was purged again with nitrogen. Reaction mixture was then refluxed for 15h.

After completion of the reaction mixture was diluted with D. M. water (50 ml) and extracted with ethyl acetate (3X50 ml). Combined organic extracts were washed with 1N HCl (1X50 ml), sat. $NaHCO_3$ solution (1X50 ml) and brine (1X50 ml). Organic layer was dried over anhy. Na_2SO_4 and solvent was removed under reduced pressure to give amide -NH alkylated product with 65-80% yield.

Crude product thus obtained was dissolved in ethyl acetate (45 ml) and concentrated HCl (15 ml) was added at -50^0C and the reaction mixture was stirred at same temperature for 2h. Temperature of the reaction mixture was then gradually increased to 0 $^{\circ}$C and stirred for additional 1h at this temperature. After completion of reaction, reaction mixture was basified with sat. $NaHCO_3$ solution till pH 9 and extracted with ethyl acetate (3X50 ml). Combined organic extracts were washed with water (1X100 ml) and brine (1X100 ml). Organic layer was then dried over anhy. Na_2SO_4 and evaporated to dryness.

Crude residue thus obtain was purified by preparative HPLC method using the procedure as described in experimental **section 5.1.3.-Purification** to give desired amino-methyl pipyridones **68a-j, 68m-o, 68r-u, 69b-d & 70b-d**.

5.1.30.1. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-phenylpiperidin-2-one (68a)



68a (510 mg, 72%) was prepared by means of the general procedure as in section **5.1.30.** as a white solid. 179-182 °C; Purity by HPLC: 98.76% AUC, Chiral purity: 97.2%ee AUC.

ESI/MS (m/z) : 485.4 $(M+H)^+$. **Mol. Wt.** = 484.5 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ 2.33-2.38 (m, 1H), 2.41-2.49 (m, 3H), 2.73-2.78 (m, 1H), 3.25 (dd, J_1 = 10Hz, J_2 = 12Hz, 1H), 3.45-3.52 (m, 2H), 7.01-7.15 (m, 4H), 7.20 (dd, J_1 = 3.6Hz, J_2 = 8.2Hz, 1H), 7.22-7.25 (m, 2H), 7.28-7.31 (m, 1H).

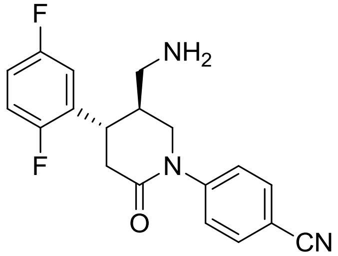
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 36.5, 40.3, 41.2, 47.3, 52.1, 115.4 (d, J = 25.1Hz), 117.7 (dd, J_1 = 24.9Hz, J_2 = 8.8Hz), 118.5 (dd, J_1 = 24.1Hz, J_2 = 9.0Hz), 119.3, 123.7, 127.6, 128.2, 155.2 (d, J = 241.3Hz), 157.6 (d, J = 240.1Hz), 168.7.

Analysis : Mol. Formula: $C_{18}H_{18}F_2N_2O$

Calcd.: C 68.34, H 5.74, N 8.86.

Found: C 68.30, H 5.77, N 8.83.

5.1.30.2. 4-((4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-2-oxopiperidin-1-yl) benzonitrile (68b)



68b (524 mg, 78%) was prepared by means of the general procedure described in section **5.1.30.** as a white solid. 166-168 °C; Purity by HPLC: 99.1% AUC, Chiral purity: 97.7%ee AUC.

ESI-MS: [M+H]$^+$ = 342.1 *m/z*. **Mol.Wt** = 341.3 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.33-2.37 (m, 1H), 2.41-2.48 (m, 3H), 2.74-2.79 (m, 1H), 3.25-3.30 (m, 1H), 3.47-3.54 (m, 2H), 7.22-7.27 (m, 2H), 7.29-7.33 (m, 1H), 7.53 (d, J = 8.1Hz, 2H), 7.81 (d, J = 8.1Hz, 2H).

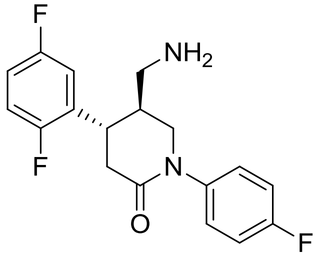
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 36.9, 40.4, 41.7, 47.9, 53.2, 111.3, 115.3 (d, J = 24.9Hz), 117.9 (dd, J_1 = 24.9Hz, J_2 = 8.8Hz), 118.4 (dd, J_1 = 24.3Hz, J_2 = 8.8Hz), 118.7, 122.7, 127.6, 128.2, 132.4, 155.6 (d, J = 240.8Hz), 157.9 (d, J = 240.3Hz), 169.8.

Analysis : Mol. Formula: $C_{19}H_{17}F_2N_3O$

Calcd.: C 66.85, H 5.02, N 12.31.

Found: C 66.86, H 5.07, N 12.34.

5.1.30.3. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(4-fluorophenyl) piperidin-2-one (68c)



68c (563 mg, 87%) was prepared using general procedure described in section **5.1.30.** as a white solid. 201-203 °C; Purity by HPLC: 98.6% AUC, Chiral purity: 98.7%ee AUC.

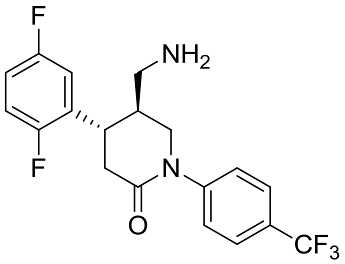
ESI-MS: $[M+H]^+$ = 335.5 *m/z*. **Mol.Wt** = 334.3 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.29-2.35 (m, 1H), 2.43-2.45 (m, 2H), 2.51-2.57 (m, 1H), 2.75-2.79 (m, 1H), 3.27 (dd, J_1 = 9.8Hz, J_2 = 12.1Hz, 1H), 3.46-3.52 (m, 2H), 7.22-7.25 (m, 2H), 7.28-7.31 (m, 3H), 7.39 (d, J = 7.8Hz, 2H).

^{13}C NMR (100 MHz, Methanol-d_4): δ 36.6, 40.1, 41.2, 47.5, 53.4, 115.4 (d, J = 25.2Hz), 115.7, 117.6 (dd, J_1 = 24.9Hz, J_2 = 9.0Hz), 118.6 (dd, J_1 = 24.4Hz, J_2 = 9.0Hz), 119.3, 123.7, 135.4, 155.2 (d, J = 241.3Hz), 157.6 (d, J = 240.1Hz), 161.2 (d, 237.2Hz), 170.4.

Analysis : Mol. Formula: $C_{18}H_{17}F_3N_2O$
Calcd.: C 64.66, H 5.13, N 8.38.
Found: C 64.61, H 5.17, N 8.34.

5.1.30.4. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(4-(trifluoromethyl)-phenyl) piperidin-2-one (68d)



68d (570 mg, 85%) was prepared by means of the general procedure described in section **5.1.30.** as a white solid. 193-195 °C; Purity by HPLC: 97.7% AUC, Chiral purity: 97.9%ee AUC.

ESI-MS: $[M+H]^+$ = 385.2 *m/z*. **Mol.Wt** = 384.3 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.34-2.39 (m, 1H), 2.41-2.47 (m, 3H), 2.72-2.78 (m, 1H), 3.27 (dd, J_1 = 10Hz, J_2 = 11.8Hz, 1H), 3.45-3.52 (m, 2H), 7.13 (d, J = 7.6Hz, 2H), 7.22-7.25 (m, 2H), 7.28-7.31 (m, 1H), 7.53 (2H, J = 7.6Hz, 2H).

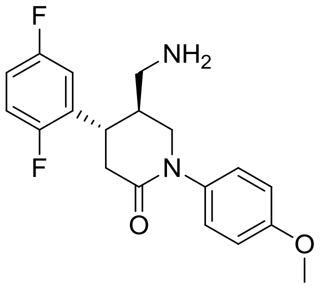
^{13}C NMR (100 MHz, Methanol-d_4): δ 36.9, 40.7, 41.3, 47.3, 53.2, 115.5 (d, J = 25.1Hz), 117.7 (dd, J_1 = 25.0Hz, J_2 = 8.8Hz), 118.5 (dd, J_1 = 24.3Hz, J_2 = 9.0Hz), 123.8, 124.5, 125.4, 127.6, 128.2, 132.6, 143.2, 155.2 (d, J = 241.3Hz), 157.6 (d, J = 240.1Hz), 170.7. Anal. Calcd. for $C_{19}H_{17}F_5N_2O$: C 59.37, H 4.46, N 7.29; Found: C 59.33, H 4.42, N 7.26.

Analysis : Mol. Formula: $C_{19}H_{17}F_5N_2O$

Calcd.: C 59.37, H 4.46, N 7.29.

Found: C 59.33, H 4.42, N 7.26.

5.1.30.5. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(4-methoxyphenyl) piperidin-2-one (68e)



68e (538 mg, 83%) was prepared by means of the general procedure described in section **5.1.30.** as a white solid. 175-178 °C; Purity by HPLC: 98.3% AUC, Chiral purity: 97.1%ee AUC.

ESI-MS: $[M+H]^+$ = 347.5 *m/z*. **Mol.Wt** = 346.4 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.33-2.37 (m, 1H), 2.43-2.48 (m, 3H), 2.72-2.79 (m, 1H), 3.25-3.29 (m, 1H), 3.47-3.54 (m, 2H), 3.81 (s, 3H), 7.11 (d, J = 8.2 Hz, 2H), 7.22-7.27 (m, 2H), 7.29-7.39 (m, 3H).

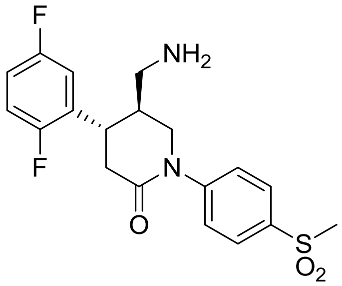
^{13}C NMR (100 MHz, Methanol-d_4): δ 36.7, 40.2, 41.6, 47.9, 53.3, 56.4, 114.8, 115.5 (d, J = 25.1Hz), 117.9 (dd, J_1 = 25.0Hz, J_2 = 9.0Hz), 118.7 (dd, J_1 = 24.3Hz, J_2 = 8.8Hz), 122.7, 123.4, 128.2, 132.1, 155.6 (d, J = 239.8Hz), 157.4 (d, J = 240.1Hz), 159.2, 168.5.

Analysis : Mol. Formula: $C_{19}H_{20}F_2N_2O_2$

Calcd.: C 65.88, H 5.82, N 8.09.

Found: C 65.85, H 5.79, N 8.07.

5.1.30.6. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(4-(methylsulfonyl) phenyl) piperidin-2-one (68f)



68f (567 mg, 80%) was prepared by means of the general procedure described in section **5.1.30.** as a white solid. 213-214 °C; Purity by HPLC: 99.2% AUC, Chiral purity: 97.6%ee AUC.

ESI-MS: $[M+H]^+$ = 395.3 *m/z*. **Mol.Wt** = 394.5 g,

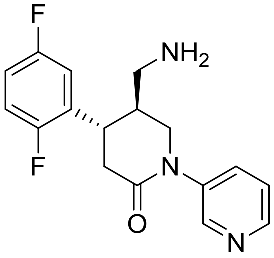
^1H NMR (400 MHz, Methanol-d_4): δ = 2.33-2.37 (m, 1H), 2.43-2.48 (m, 3H), 2.72-2.79 (m, 1H), 3.25-3.29 (m, 1H), 3.32 (s, 3H), 3.47-3.54 (m, 2H), 7.09 (d, J = 7.8 Hz, 2H), 7.22-7.27 (m, 2H), 7.29-7.39 (m, 1H), 7.47 (d, J = 7.8 Hz, 2H).

^{13}C NMR (100 MHz, Methanol-d_4): δ 36.8, 40.1, 41.6, 47.3, 47.9, 53.3, 115.5 (d, J = 25.3Hz), 117.9 (dd, J_1 = 25.2Hz, J_2 = 9.0Hz), 118.6 (dd, J_1 = 24.7Hz, J_2 = 8.8Hz), 122.5, 123.5, 128.4, 136.7, 146.3, 155.6 (d, J = 239.8Hz), 157.4 (d, J = 240.1Hz), 168.2.

Anal. Calcd. for $C_{19}H_{20}F_2N_2O_3S$: C 57.86, H 5.11, N 7.10, S 8.13; Found: C 57.85, H 5.09, N 7.14, S 8.12.

Analysis : Mol. Formula: $C_{19}H_{20}F_2N_2O_3S$
Calcd.: C 57.86, H 5.11, N 7.10, S 8.13.
Found: C 57.85, H 5.09, N 7.14, S 8.12.

5.1.30.7. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(pyridin-3-yl)piperidin-2-one (68g)



68g (610 mg, 73%) was prepared by means of the general procedure described in section **5.1.30.** as a white solid. 168-170 °C; Purity by HPLC: 98.5% AUC, Chiral purity: 98.4%ee AUC.

ESI-MS: $[M+H]^+$ = 318.5 *m/z*. **Mol.Wt** = 317.3 g.

^1H NMR (400 MHz, Methanol-d_4): δ = 2.34-2.38 (m, 1H), 2.42-2.49 (m, 3H), 2.73-2.78 (m, 1H), 3.27 (dd, J_1 = 10Hz, J_2 = 12Hz, 1H), 3.47-3.52 (m, 2H), 7.22-7.25 (m, 2H), 7.28-7.31 (m, 1H), 7.42 (d, J = 5.2Hz, 1H), 8.27-8.34 (m, 2H), 8.89 (s, 1H).

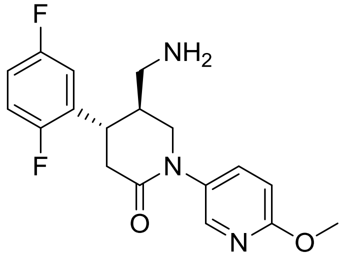
^{13}C NMR (100 MHz, Methanol-d_4): δ 36.8, 40.2, 41.2, 47.3, 52.1, 115.4 (d, J = 25.1Hz), 117.7 (dd, J_1 = 24.9Hz, J_2 = 8.8Hz), 118.5 (dd, J_1 = 24.1Hz, J_2 = 9.0Hz), 123.4, 123.7, 125.6, 141.6, 143.2, 150.8, 155.2 (d, J = 237.9Hz), 157.6 (d, J = 240.3Hz), 169.5.

Analysis : Mol. Formula: $C_{17}H_{17}F_2N_3O$

Calcd.: C 64.34, H 5.40, N 13.24.

Found: C 64.38, H 5.42, N 13.21.

5.1.30.8. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(6-methoxypyridin-3-yl) piperidin-2-one (68h)



68h (515 mg, 73%) was prepared by means of the general procedure described in section **5.1.30.** as a white solid. 174-176 °C; Purity by HPLC: 99.7% AUC, Chiral purity: 98.6%ee AUC.

ESI-MS: [M+H]$^+$ = 348.5 *m/z*. **Mol.Wt** = 347.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.32-2.37 (m, 1H), 2.42-2.49 (m, 3H), 2.73-2.78 (m, 1H), 3.25-3.29 (m, 1H), 3.47-3.52 (m, 2H), 3.81 (s, 3H), 7.11 (d, J = 6.4 Hz, 1H), 7.22-7.25 (m, 3H), 7.28-7.31 (m, 1H), 8.15 (d, J = 6.4Hz, 1H);

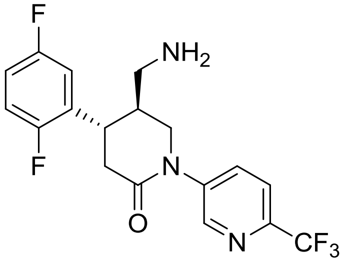
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 36.8, 40.2, 41.2, 47.3, 52.1, 54.8, 11.6, 115.4, 115.5, 115.9, 117.6 (dd, J_1 = 23.9Hz, J_2 = 8.8Hz), 118.5 (dd, J_1 = 24.4Hz, J_2 = 8.8Hz), 123.4, 128.3, 139.6, 143.2, 150.8, 155.2 (d, J = 239.7Hz), 157.6 (d, J = 241.0Hz), 159.6, 169.5;

Analysis : Mol. Formula: $C_{18}H_{19}F_2N_3O_2$

Calcd.: C 62.24, H 5.51, N 12.10.

Found: C 62.28, H 5.54, N 12.14.

5.1.30.9. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(6-(trifluoromethyl) pyridin-3-yl)piperidin-2-one (68i)



68i (640 mg, 79%) was prepared by means of the general procedure described in section **5.1.30.** as a white solid. 231-233 °C; Purity by HPLC: 99.4% AUC, Chiral purity: 99.2%ee AUC.

ESI-MS: [M+H]$^+$ = 386.2 *m/z*. **Mol.Wt** = 385.3 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.33-2.39 (m, 1H), 2.42-2.49 (m, 3H), 2.73-2.78 (m, 1H), 3.24-3.29 (m, 1H), 3.49-3.55 (m, 2H), 7.22-7.25 (m, 2H), 7.28-7.38 (m, 2H), 8.01 (d, J = 5.6 Hz, 1H), 8.12 (s, 1H);

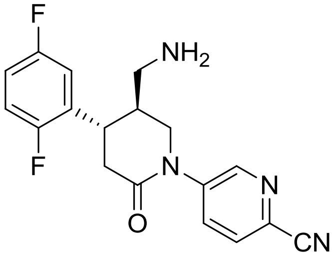
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 36.4, 40.3, 41.2, 47.4, 51.9, 115.4 (d, J = 25.0Hz), 117.7 (dd, J_1 = 25.1Hz, J_2 = 8.9Hz), 118.5 (dd, J_1 = 24.8Hz, J_2 = 9.0Hz), 119.8, 123.4, 124.7, 125.6, 126.9, 137.8, 139.4, 155.2 (d, J = 241.5Hz), 157.6 (d, J = 240.8Hz), 170.2;

Analysis : Mol. Formula: $C_{18}H_{16}F_5N_3O$

Calcd.: C 56.11, H 4.19, N 10.90.

Found: C 56.08, H 4.17, N 10.93.

5.1.30.10. 5-((4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-2-oxopiperidin-1-yl) picolinonitrile (68j)



68j (610 mg, 81%) was prepared by means of the general procedure described in section **5.1.30.** as a white solid. 123-125 °C; Purity by HPLC: 97.8% AUC, Chiral purity: 98.7%ee AUC.

ESI-MS: [M+H]$^+$ = 343.5 *m/z*. **Mol.Wt** = 342.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.34-2.39 (m, 1H), 2.41-2.49 (m, 3H), 2.73-2.78 (m, 1H), 3.27 (dd, J_1 = 9.8Hz, J_2 = 12Hz, 1H), 3.47-3.53 (m, 2H), 7.23-7.25 (m, 2H), 7.27-7.38 (m, 2H), 7.74 (d, J = 6.4Hz, 1H), 8.41 (d, J =6.4 Hz, 1H), 8.47 (s, 1H).

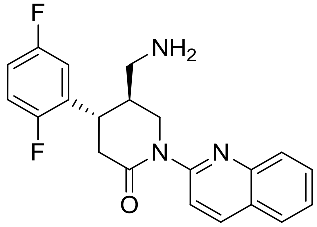
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 36.9, 40.4, 41.6, 47.3, 51.7, 115.6 (d, J = 24.8Hz), 117.4, 117.8 (dd, J_1 = 25.3Hz, J_2 = 9.0Hz), 118.5 (dd, J_1 = 24.8Hz, J_2 = 9.0Hz), 123.4, 127.9, 128.4, 129.4, 133.8, 141.5, 156.1 (d, J = 240.5Hz), 158.2 (d, J = 241.3Hz), 168.6.

Analysis : Mol. Formula: $C_{18}H_{16}F_2N_4O$

Calcd.: C 63.15, H 4.71, N 16.37.

Found: C 63.18, H 4.74, N 16.39.

5.1.30.11. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(quinolin-2-yl) piperidin-2-one (68m)



68m (570 mg, 81%) was prepared by means of the general procedure described in section **5.1.30.** as a thick oil. Purity by HPLC: 97.2% AUC, Chiral purity: 97.0%ee AUC.

ESI-MS: [M+H]$^+$ = 368.3 *m/z*. **Mol.Wt** = 367.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.34-2.39 (m, 1H), 2.43-2.47 (m, 3H), 2.71-2.76 (m, 1H), 3.25-3.29 (m, 1H), 3.47-3.53 (m, 2H), 7.23-7.27 (m, 2H), 7.29-7.34 (m, 1H), 7.43-7.79 (m, 4H), 7.98 (d, J = 6.8Hz, 1H), 8.09 (d, J= 7.6Hz, 1H).

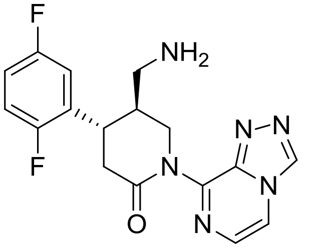
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 36.7, 40.1, 41.9, 47.2, 51.7, 112.1, 115.4 (d, J = 25.1Hz), 117.6 (dd, J_1 = 24.8Hz, J_2 = 8.8Hz), 118.7 (dd, J_1 = 25.2Hz, J_2 = 9.0Hz), 121.4, 122.3, 123.4, 125.8, 126.6, 129.6, 137.5, 146.8, 156.3 (d, J = 237.5Hz), 157.6 (d, J = 239.6Hz), 165.3, 169.4.

Analysis : Mol. Formula: $C_{21}H_{19}F_2N_3O$

Calcd.: C 68.65, H 5.21, N 11.44.

Found: C 68.61, H 5.23, N 11.40.

5.1.30.12. (4S,5S)-1-([1,2,4]Triazolo[4,3-a]pyrazin-8-yl)-5-(aminomethyl)-4-(2,5-difluorophenyl)piperidin-2-one (68n)



68n (680 mg, 94%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 196-197 °C. Purity by HPLC: 99.1% AUC, Chiral purity: 98.4%ee AUC.

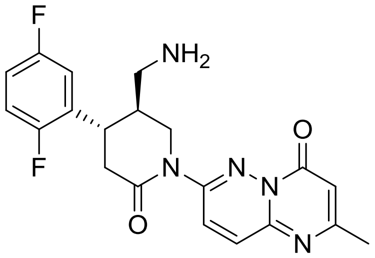
ESI-MS: [M+H]$^+$ = 359.4 *m/z*. **Mol.Wt** = 358.3 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.33-2.39 (m, 1H), 2.43-2.48 (m, 3H), 2.73-2.79 (m, 1H), 3.24-3.29 (m, 1H), 3.47-3.53 (m, 2H), 7.23-7.27 (m, 2H), 7.29-7.34 (m, 1H), 7.89 (d, J = 7.6Hz, 1H), 8.07 (d, J = 7.6Hz, 1H), 9.01 (s, 1H).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 36.8, 40.6, 41.9, 47.4, 52.3, 114.8, 115.6 (d, J = 25.0Hz), 117.6 (dd, J_1 = 24.9Hz, J_2 = 9.0Hz), 118.7 (dd, J_1 = 25.0Hz, J_2 = 8.6Hz), 123.4, 126.6, 137.2, 146.9, 147.3, 156.5 (d, J = 241.5Hz), 157.6 (d, J = 242.1Hz), 169.7.

Analysis : Mol. Formula: $C_{17}H_{16}F_2N_6O$
Calcd.: C 56.98, H 4.50, N 23.45.
Found: C 57.01, H 4.53, N 23.42.

5.1.30.13. 7-((4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-2-oxopiperidin-1-yl)-2-methyl-4H-pyrimido[1,2-b]pyridazin-4-one (68o)



68o (520 mg, 75%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 165-167 °C. Purity by HPLC: 97.0% AUC, Chiral purity: 97.6%ee AUC.

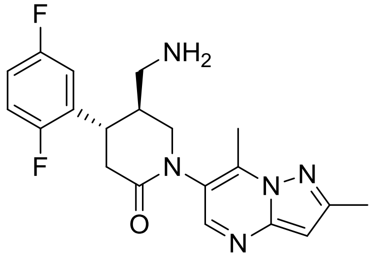
ESI-MS: [M+H]$^+$ = 400.2 *m/z*. **Mol.Wt** = 399.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.29 (s, 3H), 2.34-2.39 (m, 1H), 2.45-2.52 (m, 3H), 2.71-2.77 (m, 1H), 3.25-3.29 (m, 1H), 3.47-3.53 (m, 2H), 6.19 (s, 1H), 6.32 (s, 2H), 7.23-7.28 (m, 2H), 7.29-7.34 (m, 1H).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 28.3, 36.6, 40.3, 41.7, 46.9, 52.3, 110.8, 115.6 (d, J = 25.2Hz), 117.6 (dd, J_1 = 24.8Hz, J_2 = 9.1Hz), 118.6 (dd, J_1 = 24.9Hz, J_2 = 9.0Hz), 123.4, 130.2, 135.8, 148.9, 153.8, 156.5 (d, J = 241.5Hz), 158.2, 157.6 (d, J = 242.1Hz), 164.6, 168.8.

Analysis : Mol. Formula: $C_{20}H_{19}F_2N_5O_2$
Calcd.: C 60.14, H 4.79, N 17.53.
Found: C 60.10, H 4.82, N 17.50.

5.1.30.14. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(2,7-dimethylpyrazolo [1,5-a]pyrimidin-6-yl)piperidin-2-one (68r)



68r (575 mg, 73%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 187-188 °C. Purity by HPLC: 99.7% AUC, Chiral purity: 98.8%ee AUC.

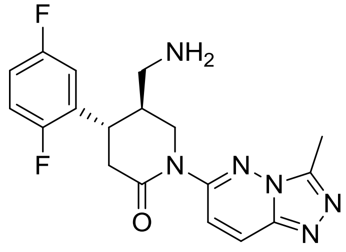
ESI-MS: [M+H]$^+$ = 386.5 *m/z*. **Mol.Wt** = 385.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.27 (s, 3H), 2.32 (s, 3H), 2.34-2.39 (m, 1H), 2.43-2.48 (m, 3H), 2.71-2.79 (m, 1H), 3.24-3.29 (m, 1H), 3.47-3.52 (m, 2H), 6.71 (s, 1H), 7.23-7.27 (m, 2H), 7.29-7.32 (m, 1H), 9.13 (s, 1H).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 16.7, 19.2, 37.9, 41.4, 41.7, 47.4, 52.3, 98.8, 115.4 (d, J = 24.3Hz), 117.6 (dd, J_1 = 25.3Hz, J_2 = 8.8Hz), 118.6 (dd, J_1 = 24.3Hz, J_2 = 8.8Hz), 123.4, 125.9, 148.9, 150.6, 155.3, 156.7 (d, J = 242.4Hz), 157.2, 157.8 (d, J = 242.7Hz), 169.9.

Analysis : Mol. Formula: for $C_{20}H_{21}F_2N_5O$
Calcd.: C 62.33, H 5.49, N 18.17.
Found: C 62.33, H 5.49, N 18.17.

5.1.30.15. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(3-methyl-[1,2,4] triazolo[4,3-b]pyridazin-6-yl)piperidin-2-one (68s)



68s (612 mg, 79%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 148-151 °C. Purity by HPLC: 98.9% AUC, Chiral purity: 97.6%ee AUC.

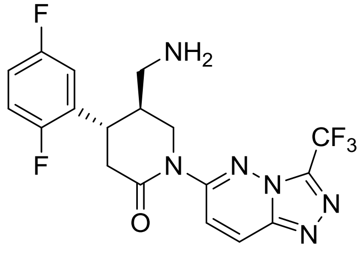
ESI-MS: $[M+H]^+$ = 373.5 *m/z*. **Mol.Wt** = 372.4 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.32-2.39 (m, 1H), 2.41 (s, 3H), 2.43-2.47 (m, 3H), 2.73-2.79 (m, 1H), 3.24-3.27 (m, 1H), 3.46-3.52 (m, 2H), 7.23-7.27 (m, 2H), 7.29-7.32 (m, 1H), 8.71 (s, 1H), 9.01 (s, 1H).

^{13}C NMR (100 MHz, Methanol-d_4): δ 14.3, 37.9, 41.2, 41.9, 47.4, 52.3, 115.6 (d, J = 25.2Hz), 117.6 (dd, J_1 = 25.3Hz, J_2 = 8.9Hz), 118.6 (dd, J_1 = 24.6Hz, J_2 = 8.8Hz), 123.4, 124.0, 124.6, 137.1, 143.9, 154.7, 156.7 (d, J = 241.0Hz), 157.6 (d, J = 241.3Hz), 169.5.

Analysis : Mol. Formula: for $C_{18}H_{18}F_2N_6O$
Calcd.: C 58.06, H 4.87, N 22.57.
Found: C 58.02, H 4.85, N 22.59.

5.1.30.16. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-2-one (68t)



68t (540 mg, 87%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 126-128 °C. Purity by HPLC: 97.6% AUC, Chiral purity: 97.5%ee AUC.

ESI-MS: $[M+H]^+$ = 427.4 *m/z*. **Mol.Wt** = 426.3 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.32-2.38 (m, 1H), 2.43-2.48 (m, 3H), 2.74-2.81 (m, 1H), 3.25-3.28 (m, 1H), 3.47-3.54 (m, 2H), 7.23-7.27 (m, 2H), 7.29-7.32 (m, 1H), 8.64 (d, J = 6.4Hz, 1H), 9.01 (d, J = 6.4Hz, 1H).

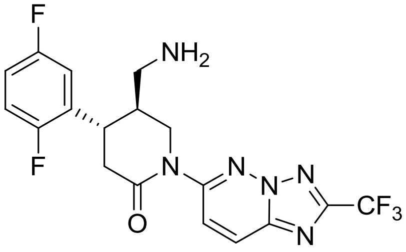
^{13}C NMR (100 MHz, Methanol-d_4): δ 37.8, 41.2, 41.6, 47.3, 52.7, 114.7, 115.6 (d, J = 25.8Hz), 117.6 (dd, J_1 = 24.6Hz, J_2 = 9.0Hz), 118.6 (dd, J_1 = 25.6Hz, J_2 = 8.7Hz), 123.4, 123.9, 124.7, 143.6, 154.6, 156.4 (d, J = 240.8Hz), 157.7 (d, J = 241.2Hz), 159.6, 169.8.

Analysis : Mol. Formula: for $C_{18}H_{15}F_5N_6O$

Calcd.: C 50.71, H 3.55, N 19.71.

Found: C 50.73, H 3.57, N 19.69.

5.1.30.17. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(2-(trifluoromethyl)-[1,2,4] triazolo[1,5-b]pyridazin-6-yl)piperidin-2-one (68u)



68u (630 mg, 95%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 186-187 °C. Purity by HPLC: 99.1% AUC, Chiral purity: 98.9%ee AUC.

ESI-MS: $[M+H]^+$ = 427.5 *m/z*. **Mol.Wt** = 426.3 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.33-2.39 (m, 1H), 2.41-2.47 (m, 3H), 2.72-2.78 (m, 1H), 3.24-3.27 (m, 1H), 3.45-3.50 (m, 2H), 7.22-7.27 (m, 2H), 7.29-7.31 (m, 1H), 8.57 (d, J = 6.8Hz, 1H), 8.78 (d, J = 6.8Hz, 1H).

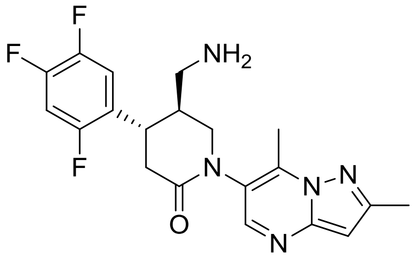
^{13}C NMR (100 MHz, Methanol-d_4): δ 37.9, 41.2, 41.7, 47.2, 52.7, 115.6 (d, J = 25.8Hz), 117.6 (dd, J_1 = 24.6Hz, J_2 = 9.0Hz), 118.6 (dd, J_1 = 25.6Hz, J_2 = 8.7Hz), 123.4, 123.7, 126.4, 144.6, 147.6, 154.3, 156.5 (d, J = 240.2Hz), 157.7 (d, J = 241.0Hz), 169.7.

Analysis : Mol. Formula: for $C_{18}H_{15}F_5N_6O$

Calcd.: C 50.71, H 3.55, N 19.71.

Found: C 50.74, H 3.56, N 19.67.

5.1.30.18. (4S,5S)-5-(Aminomethyl)-1-(2,7-dimethylpyrazolo[1,5-a]pyrimidin-6-yl)-4-(2,4,5-trifluorophenyl)piperidin-2-one (69b)



69b (560 mg, 76%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 197-199 °C. Purity by HPLC: 99.6% AUC, Chiral purity: 97.6%ee AUC.

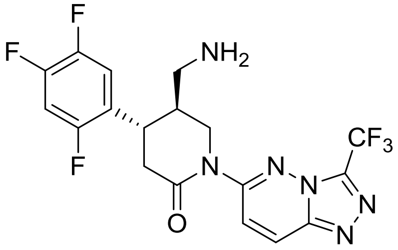
ESI-MS: $[M+H]^+$ = 404.5 *m/z*. **Mol.Wt** = 403.4 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.28 (s, 3H), 2.31 (s, 3H), 2.34-2.39 (m, 1H), 2.43-2.48 (m, 3H), 2.71-2.79 (m, 1H), 3.24-3.29 (m, 1H), 3.47-3.52 (m, 2H), 6.74 (s, 1H), 7.34-7.40 (m, 1H), 7.49-7.54 (m, 1H), 9.14 (s, 1H).

^{13}C NMR (100 MHz, Methanol-d_4): δ 16.8, 19.2, 37.8, 41.2, 41.7, 47.4, 52.3, 101.2, 105.6 (dd, J_1 = 21.3Hz, J_2 = 27.6Hz), 116.4 (dd, J_1 = 19.9Hz, J_2 = 5.8Hz), 123.2 (dt, J_1= 15.4Hz, J_2 = 5.0Hz), 125.6, 145.9 (ddd, J_1 = 246.4Hz, J_2 = 12.5Hz, J_3 = 3.8Hz), 149.6, 150.2 (dt, J_1 = 251.6Hz, J_2 = 13.4Hz), 150.8, 154.4, 156.3 (ddd, J_1 = 246.3Hz, J_2 = 10.3Hz, J_3 = 3.0Hz), 157.3, 167.6.

Analysis : Mol. Formula: for $C_{20}H_{20}F_3N_5O$
Calcd.: C 59.55, H 5.00, N 17.36.
Found: C 59.57, H 5.03, N 17.33.

5.1.30.19. (4S,5S)-5-(Aminomethyl)-1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)-4-(2,4,5-trifluorophenyl)piperidin-2-one (69c)



69c (586 mg, 87%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 212-215 °C. Purity by HPLC: 97.7% AUC, Chiral purity: 98.1%ee AUC.

ESI-MS: $[M+H]^+$ = 445.4 *m/z*. **Mol.Wt** = 444.3 g.

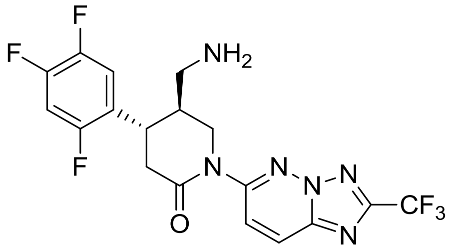
^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.32-2.37 (m, 1H), 2.43-2.47 (m, 3H), 2.73-2.79 (m, 1H), 3.25-3.28 (m, 1H), 3.47-3.54 (m, 2H), 7.32-7.40 (m, 1H), 7.46-7.54 (m, 1H), 8.62 (d, J = 6.2Hz, 1H), 8.95 (d, J = 6.2Hz, 1H).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 37.8, 41.2, 41.7, 47.4, 52.3, 105.6 (dd, J_1 = 21.3Hz, J_2 = 28.2Hz), 114.5, 116.4 (dd, J_1 = 19.8Hz, J_2 = 5.4Hz), 123.3 (dt, J_1= 15.4Hz, J_2 = 5.0Hz), 123.8, 124.6, 143.5, 146.2 (ddd, J_1 = 246.4Hz, J_2 = 12.5Hz, J_3 = 3.8Hz), 150.4 (dt, J_1 = 251.6Hz, J_2 = 13.4Hz), 154.3, 156.5 (ddd, J_1 = 246.3Hz, J_2 = 10.3Hz, J_3 = 3.0Hz), 159.8, 166.8.

Anal. Calcd. for $C_{18}H_{14}F_6N_6O$: C 48.66, H 3.18, N 18.91; Found: C 48.63, H 3.15, N 18.88.

Analysis : Mol. Formula: for $C_{18}H_{14}F_6N_6O$
Calcd.: C 48.66, H 3.18, N 18.91.
Found: C 48.63, H 3.15, N 18.88.

5.1.30.20. (4S,5S)-5-(Aminomethyl)-1-(2-(trifluoromethyl)-[1,2,4]triazolo[1,5-b]pyridazin-6-yl)-4-(2,4,5-trifluorophenyl)piperidin-2-one (69d)



69d (670 mg, 93%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 137-139 °C. Purity by HPLC: 98.1% AUC, Chiral purity: 97.2%ee AUC.

ESI-MS: $[M+H]^+$ = 445.5 *m/z*. **Mol.Wt** = 444.3 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.33-2.39 (m, 1H), 2.41-2.47 (m, 3H), 2.72-2.78 (m, 1H), 3.24-3.27 (m, 1H), 3.45-3.50 (m, 2H), 7.34-7.40 (m, 1H), 7.49-7.54 (m, 1H), 8.57 (d, J = 6.4Hz, 1H), 8.77 (d, J = 6.4Hz, 1H).

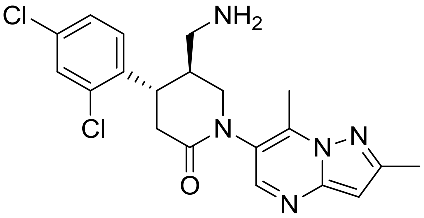
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 37.9, 41.2, 41.8, 47.4, 52.7, 105.6 (dd, J_1 = 20.8Hz, J_2 = 28.6Hz), 116.5 (dd, J_1 = 20.4Hz, J_2 = 5.4Hz), 119.7, 123.3 (dt, J_1= 15.4Hz, J_2 = 5.2Hz), 123.6, 126.4, 144.6, 146.3 (ddd, J_1 = 246.4Hz, J_2 = 12.7Hz, J_3 = 3.8Hz), 147.7, 150.6 (dt, J_1 = 251.4Hz, J_2 = 13.4Hz), 154.3, 156.4 (ddd, J_1 = 246.2Hz, J_2 = 10.3Hz, J_3 = 2.8Hz), 167.3.

Analysis : Mol. Formula: for $C_{18}H_{14}F_6N_6O$

Calcd.: C 48.66, H 3.18, N 18.91.

Found: C 48.67, H 3.16, N 18.89.

5.1.30.21. (4S,5S)-5-(Aminomethyl)-4-(2,4-dichlorophenyl)-1-(2,7-dimethylpyrazolo [1,5-a]pyrimidin-6-yl)piperidin-2-one (70b)



70b (550 mg, 86%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 132-134 °C. Purity by HPLC: 98.2% AUC, Chiral purity: 97.8%ee AUC.

ESI-MS: $[M+H]^+$ = 418.9 *m/z*. **Mol.Wt** = 418.3 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.26 (s, 3H), 2.31 (s, 3H), 2.34-2.37 (m, 1H), 2.43-2.48 (m, 3H), 2.71-2.79 (m, 1H), 3.25 (dd, J_1 = 10Hz, J_2 = 11.8Hz, 1H), 3.47-3.52 (m, 2H), 6.74 (s, 1H), 7.38 (dd, J_1 = 8.2Hz, J_2 = 2.2Hz, 1H), 7.44 (d, J = 8.2Hz, 1H), 7.53 (d, J = 2.2Hz, 1H), 9.14 (s, 1H).

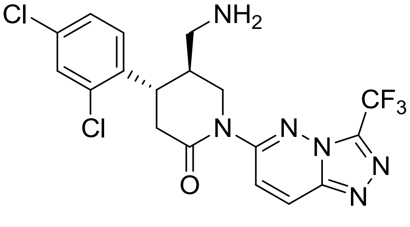
^{13}C NMR (100 MHz, Methanol-d_4): δ 16.8, 19.2, 37.8, 41.2, 41.7, 47.4, 52.3, 98.7, 125.6, 126.4, 127.4, 130.1, 132.2, 132.7, 133.8, 149.6, 150.8, 154.4, 157.3, 167.6.

Analysis : Mol. Formula: for $C_{20}H_{21}Cl_2N_5O$

Calcd.: C 57.42, H 5.06, N 16.74.

Found: C 57.39, H 5.02, N 16.72.

5.1.30.22. (4S,5S)-5-(Aminomethyl)-4-(2,4-dichlorophenyl)-1-(3-(trifluoromethyl)-[1,2,4]triazolo[4,3-b]pyridazin-6-yl)piperidin-2-one (70c)



70c (620 mg, 75%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 109-111 °C. Purity by HPLC: 99.1% AUC, Chiral purity: 99.3%ee AUC.

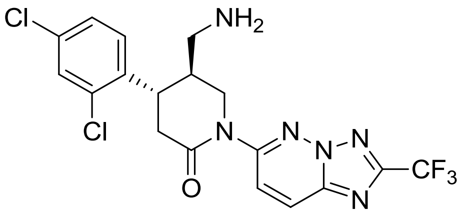
ESI-MS: [M+H]$^+$ = 459.9 *m/z*. **Mol.Wt** = 459.2 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.33-2.37 (m, 1H), 2.43-2.47 (m, 3H), 2.73-2.78 (m, 1H), 3.25-3.28 (m, 1H), 3.47-3.54 (m, 2H), 7.36 (dd, J_1 = 8.4Hz, J_2 = 1.8Hz, 1H), 7.43 (d, J = 8.4Hz, 1H), 7.53 (d, J = 2.0Hz, 1H), 8.58 (d, J = 5.8Hz, 1H), 8.89 (d, J = 5.8Hz, 1H).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 37.9, 41.3, 41.7, 47.4, 52.3, 114.6, 123.8, 124.6, 126.4, 127.2, 130.3, 132.3, 132.7, 133.6, 143.5, 154.4, 159.8, 167.5.

Analysis : Mol. Formula: for $C_{18}H_{15}Cl_2F_3N_6O$
Calcd.: C 47.07, H 3.29, N 18.30.
Found: C 47.04, H 3.26, N 18.28.

5.1.30.23. (4S,5S)-5-(Aminomethyl)-4-(2,4-dichlorophenyl)-1-(2-(trifluoromethyl)-[1,2,4]triazolo[1,5-b]pyridazin-6-yl)piperidin-2-one (70d)



70d (530 mg, 89%) was prepared by means of the general procedure described in section **5.1.30.** as a White solid; mp: 164-166 °C. Purity by HPLC: 98.7% AUC, Chiral purity: 98.9%ee AUC.

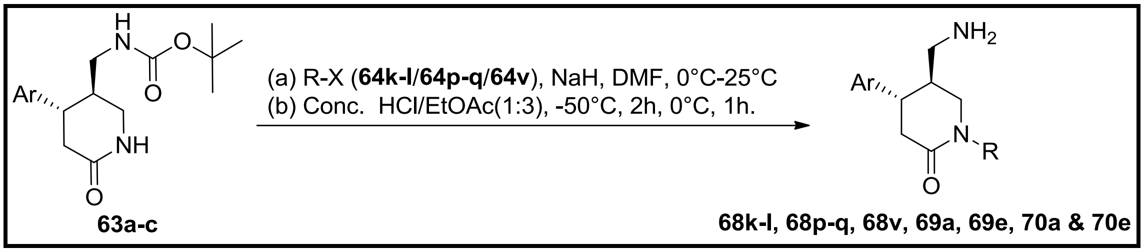
ESI-MS: [M+H]$^+$ = 460.1 *m/z*. **Mol.Wt** = 459.2 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.31-2.36 (m, 1H), 2.41-2.46 (m, 3H), 2.72-2.78 (m, 1H), 3.27 (dd, J_1 = 10.4Hz, J_2 = 12Hz, 1H), 3.45-3.50 (m, 2H), 7.34 (dd, J_1 = 8.6Hz, J_2 = 2.0Hz, 1H), 7.43 (d, J = 8.6Hz, 1H), 7.53 (d, J = 2.0Hz, 1H), 8.49 (d, J = 6.2Hz, 1H), 8.72 (d, J = 6.2Hz, 1H).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 37.9, 41.2, 41.8, 47.4, 52.7, 119.7, 123.6, 126.2, 126.4, 127.7, 130.6, 132.3, 132.8, 133.8, 144.6, 147.6, 154.3, 167.3.

Analysis : Mol. Formula: for $C_{18}H_{15}Cl_2F_3N_6O$
Calcd.: C 47.07, H 3.29, N 18.30.
Found: C 47.09, H 3.32, N 18.27.

5.1.31. General procedure for the synthesis of compounds (68k-l, 68p-q, 68v, 69a, 69e, 70a & 70e)



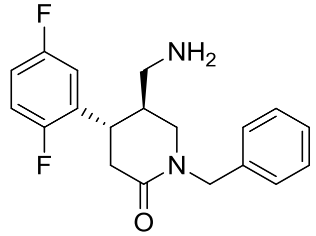
To a solution of compound **63a-c** (5 mmol) in dry DMF (25 ml) was added sodium hydride (6 mmol) in portions at 0^0C. After all the sodium hydride was added to the reaction mixture, the reaction was brought to room temperature gradually and stirred for 2h at same temperature. Reaction was cooled again to 0 °C and a solution of halo-aromatics of the interest **64k-l**, **64p-q** or **64v** dissolved in DMF (5 ml) was added dropwise over a period of 15min. Reaction was stirred at same temperature for 1h and then at room temperature for 2h.

After completion of the reaction, reaction mixture was poured in cold D. M. water (100 ml) and extracted with ethyl acetate (3X100 ml). Combined organic extracts were washed with water (2X100 ml) and brine (1X100 ml). Organic layer was then dried over anhy. Na_2SO_4 and evaporated under reduced pressure to give amide -NH alkylated product with 65-80% yield.

Crude product thus obtain was dissolved in ethyl acetate (45 ml), and concentrated HCl (15 ml) was added at -50^0C and the reaction mixture was stirred at the same temperature for 2h. Temperature of the reaction mixture was then gradually increased to 0^0C and stirred for additional 1h at this temperature. After completion of the reaction, reaction mixture was basified with sat. $NaHCO_3$ solution till pH 9 and extracted with Ethyl acetate (3X50 ml). Combined organic extracts were washed with water (1X100 ml) and brine (1X100 ml). Organic layer was then dried over anhy. Na_2SO_4 and evaporated to dryness.

Crude residue thus obtained was purified by preparative HPLC method using the procedure as illustrated in experimental **section 5.1.3.-Purification** to give desired amino-methyl pipyridones **68k-l, 68p-q, 68v, 69a, 69e, 70a & 70e**.

5.1.31.1. (4S,5S)-5-(Aminomethyl)-1-benzyl-4-(2,5-difluorophenyl)piperidin-2-one (68k)



68k (640 mg, 93%) was prepared by means of the general procedure described in section **5.1.31.** as a white solid. 119-121 °C; Purity by HPLC: 98.2% AUC, Chiral purity: 98.3%ee AUC.

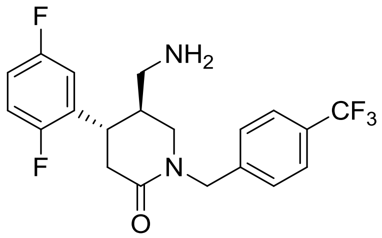
ESI/MS (m/z) : 331.2 $(M+H)^+$. **Mol. Wt.** = 330.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.34-2.39 (m, 1H), 2.43-2.47 (m, 3H), 2.71-2.76 (m, 1H), 3.23 (dd, J_1 = 10.2Hz, J_2 = 11.8Hz, 1H), 3.47-3.53 (m, 2H), 4.82 (s, 2H), 7.21-7.27 (m, 4H), 7.29-7.41 (m, 4H).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 36.9, 40.2, 41.6, 47.2, 51.7, 52.6, 115.6 (d, J = 24.9Hz), 117.8 (dd, J_1 = 25.3Hz, J_2 = 8.8Hz), 118.7 (dd, J_1 = 24.9Hz, J_2 = 9.0Hz), 123.4, 127.2, 127.9, 128.8, 136.5, 156.3 (d, J = 237.5Hz), 157.6 (d, J = 240.1Hz), 169.2.

Analysis : Mol. Formula: $C_{19}H_{20}F_2N_2O$
Calcd.: C 69.07, H 6.10, N 8.48.
Found: C 69.09, H 6.13, N 8.45.

5.1.31.2. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(4-(trifluoromethyl) benzyl) piperidin-2-one (68l)



68l (580 mg, 85%) was prepared by means of the general procedure described in section **5.1.31.** as a white solid. 147-149 °C; Purity by HPLC: 97.7% AUC, Chiral purity: 97.5%ee AUC.

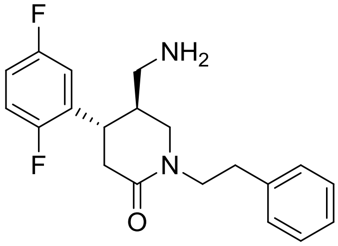
ESI/MS (m/z) : 399.2 $(M+H)^+$. **Mol. Wt.** = 398.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.32-2.37 (m, 1H), 2.42-2.47 (m, 3H), 2.73-2.78 (m, 1H), 3.23 (dd, J$_1$ = 10Hz, J$_2$ = 11.8Hz, 1H), 3.47-3.53 (m, 2H), 4.83 (s, 2H), 7.09 (d, J = 8.2Hz, 2H), 7.21-7.27 (m, 2H), 7.29-7.34 (m, 1H),7.47 (d, J = 8.2Hz, 2H).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 36.9, 40.2, 41.6, 47.2, 51.7, 52.7, 115.6 (d, J = 24.9Hz), 117.8 (dd, J$_1$ = 25.3Hz, J$_2$ = 8.8Hz), 118.7 (dd, J$_1$ = 24.9Hz, J$_2$ = 9.0Hz), 123.4, 124.3, 124.8, 129.3, 129.8, 139.5, 156.3 (d, J = 237.5Hz), 157.6 (d, J = 240.1Hz), 169.2.

Analysis : Mol. Formula: $C_{20}H_{19}F_5N_2O$
Calcd.: C 60.30, H 4.81, N 5.02.
Found: C 60.33, H 4.85, N 5.06.

5.1.31.3. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-phenethylpiperidin-2-one (68p)



68p (648 mg, 93%) was prepared by means of the general procedure described in section **5.1.31.** as a White solid; mp: 197-198 °C. Purity by HPLC: 99.5% AUC, Chiral purity: 98.7%ee AUC.

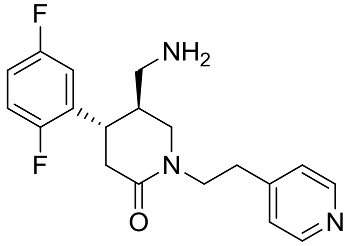
ESI-MS: [M+H]$^+$ = 345.3 *m/z*. **Mol.Wt** = 344.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.32-2.37 (m, 1H), 2.43-2.48 (m, 3H), 2.72-2.85 (m, 3H), 3.24-3.27 (m, 1H), 3.47-3.53 (m, 2H), 3.63 (t, J = 9.6Hz, 2H), 7.23-7.27 (m, 3H), 7.29-7.32 (m, 4H), 7.43 (m, 1H).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 34.3, 37.3, 41.2, 41.9, 46.9, 49.8, 52.3, 115.6 (d, J = 25.2Hz), 117.6 (dd, J$_1$ = 23.8Hz, J$_2$ = 7.8Hz), 118.6 (dd, J$_1$ = 24.3Hz, J$_2$ = 8.4Hz), 123.4, 125.6, 127.9, 128.4, 138.9, 156.5 (d, J = 240.3Hz), 157.6 (d, J = 240.1Hz), 170.1.

Analysis : Mol. Formula: $C_{20}H_{22}F_2N_2O$
Calcd.: C 69.75, H 6.44, N 8.13.
Found: C 69.77, H 6.47, N 8.10.

5.1.31.4. (4S,5S)-5-(Aminomethyl)-4-(2,5-difluorophenyl)-1-(2-(pyridin-4-yl)ethyl) piperidin-2-one (68q)



68q (544 mg, 88%) was prepared by means of the general procedure described in section **5.1.31.** as a White solid; mp: 167-169 °C. Purity by HPLC: 97.3% AUC, Chiral purity: 97.2%ee AUC.

ESI-MS: $[M+H]^+$ = 346.5 *m/z*. **Mol.Wt** = 345.4 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.29-2.35 (m, 1H), 2.41-2.46 (m, 3H), 2.71-2.79 (m, 3H), 3.25-3.29 (m, 1H), 3.47-3.52 (m, 2H), 3.59 (t, J = 8.8Hz, 2H), 7.18 (d, J = 5.6Hz, 2H), 7.23-7.27 (m, 2H), 7.29-7.32 (m, 1H), 8.49 (d, J = 5.6Hz, 2H).

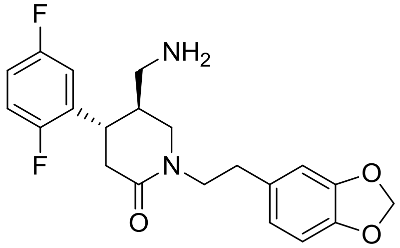
^{13}C NMR (100 MHz, Methanol-d_4): δ 34.2, 38.3, 41.2, 41.9, 47.4, 49.4, 52.3, 115.4 (d, J = 24.8Hz), 117.7 (dd, J_1 = 25.3Hz, J_2 = 8.8Hz), 118.6 (dd, J_1 = 24.3Hz, J_2 = 8.4Hz), 123.4, 124.1, 148.3, 149.6, 156.7 (d, J = 242.4Hz), 157.8 (d, J = 242.7Hz), 169.7.

Analysis : Mol. Formula: $C_{19}H_{21}F_2N_3O$

Calcd.: C 66.07, H 6.13, N 12.17.

Found: C 66.09, H 6.10, N 12.14.

5.1.31.5. (4S,5S)-5-(Aminomethyl)-1-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4-(2,5-difluorophenyl)piperidin-2-one (68v)



68v (524 mg, 85%) was prepared by means of the general procedure described in section **5.1.31.** as a White solid; mp: 177-179 °C. Purity by HPLC: 99.6% AUC, Chiral purity: 99.1%ee AUC.

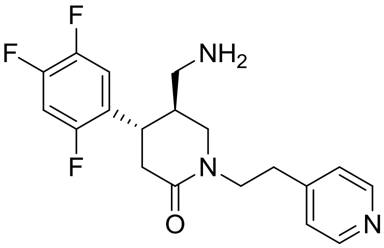
ESI-MS: [M+H]$^+$ = 389.5 *m/z*. **Mol.Wt** = 388.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.32-2.37 (m, 1H), 2.43-2.47 (m, 3H), 2.72-2.87 (m, 3H), 3.25-3.29 (m, 1H), 3.47-3.53 (m, 2H), 3.64 (t, J = 9.6Hz, 2H), 5.97 (s, 2H), 6.63-6.72 (m, 3H), 7.23-7.27 (m, 2H), 7.29-7.32 (m, 1H).

^{13}C NMR (100 MHz, Methanol-d$_4$): δ 34.5, 37.9, 41.3, 41.7, 46.9, 49.7, 52.2, 101.4, 107.6, 109.4, 115.6 (d, J = 25.2Hz), 117.6 (dd, J_1 = 23.8Hz, J_2 = 7.8Hz), 118.6 (dd, J_1 = 24.3Hz, J_2 = 8.4Hz), 122.8, 123.4, 130.9, 146.4, 148.8, 156.5 (d, J = 240.3Hz), 157.6 (d, J = 240.1Hz), 170.2.

Analysis : Mol. Formula: $C_{21}H_{22}F_2N_2O_3$
Calcd.: C 64.94, H 5.71, N 7.21.
Found: C 64.98, H 5.74, N 7.18.

5.1.31.6. (4S,5S)-5-(Aminomethyl)-1-(2-(pyridin-4-yl)ethyl)-4-(2,4,5-trifluorophenyl) piperidin-2-one (69a)



69a (510 mg, 80%) was prepared by means of the general procedure described in section **5.1.31.** as a White solid; mp: 169-171 °C. Purity by HPLC: 98.8% AUC, Chiral purity: 98.3%ee AUC.

ESI-MS: [M+H]$^+$ = 364.5 *m/z*. **Mol.Wt** = 363.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.32-2.37 (m, 1H), 2.41-2.46 (m, 3H), 2.71-2.83 (m, 3H), 3.25-3.29 (m, 1H), 3.47-3.52 (m, 2H), 3.59 (t, J = 8.8Hz, 2H), 7.21 (d, J = 6.8Hz, 2H), 7.34-7.40 (m, 1H), 7.49-7.54 (m, 1H), 8.47 (d, J = 6.8Hz, 2H).

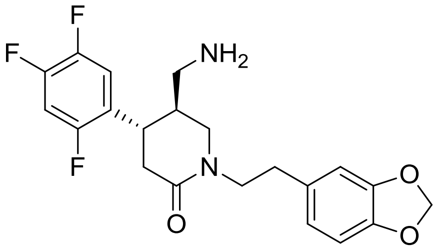
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 34.2, 39.3, 42.2, 43.5, 47.4, 49.4, 52.7, 105.6 (dd, J_1 = 21.1Hz, J_2 = 28.3Hz), 116.4 (dd, J_1 = 19.9Hz, J_2 = 5.8Hz), 123.2 (dt, J_1= 15.6Hz, J_2 = 5.2Hz), 123.8, 145.9 (ddd, J_1 = 246.2Hz, J_2 = 12.5Hz, J_3 = 3.8Hz), 148.4, 149.5, 150.2 (dt, J_1 = 251.3Hz, J_2 = 13.6Hz), 156.3 (ddd, J_1 = 245.1Hz, J_2 = 10.3Hz, J_3 = 2.7Hz), 167.8.

Analysis : Mol. Formula: $C_{19}H_{20}F_3N_3O$

Calcd.: C 62.80, H 5.55, N 11.56.

Found: C 62.83, H 5.57, N 11.53.

5.1.31.7. (4S,5S)-5-(Aminomethyl)-1-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4-(2,4,5-trifluorophenyl)piperidin-2-one (69e)



69e (524 mg, 74%) was prepared by means of the general procedure described in section **5.1.31.** as a White solid; mp: 121-123 °C. Purity by HPLC: 97.2% AUC, Chiral purity: 98.5%ee AUC.

ESI-MS: [M+H]$^+$ = 407.5 *m/z*. **Mol.Wt** = 406.4 g.

^{1}H NMR (400 MHz, Methanol-d$_4$): δ = 2.32-2.38 (m, 1H), 2.43-2.47 (m, 3H), 2.72-2.87 (m, 3H), 3.25-3.29 (m, 1H), 3.47-3.53 (m, 2H), 3.62 (t, J = 10.2Hz, 2H), 5.96 (s, 2H), 6.63-6.72 (m, 3H), 7.37-7.52 (m, 2H).

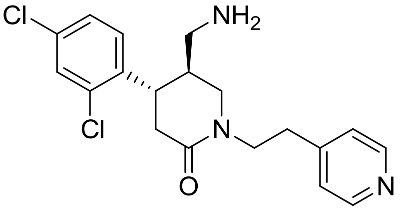
^{13}C NMR (100 MHz, Methanol-d$_4$): δ 34.4, 37.9, 41.3, 41.7, 46.9, 49.7, 52.2, 101.4, 107.6, 109.4, 105.4 (dd, J_1 = 21.2Hz, J_2 = 28.2Hz), 116.4 (dd, J_1 = 19.9Hz, J_2 = 5.8Hz), 122.6, 123.2 (dt, J_1= 18.6Hz, J_2 = 5.2Hz), 130.4, 145.9 (ddd, J_1 = 246.2Hz, J_2 = 12.5Hz, J_3 = 3.8Hz), 146.6, 148.3, 150.2 (dt, J_1 = 251.3Hz, J_2 = 13.6Hz), 156.4 (ddd, J_1 = 245.4Hz, J_2 = 10.4Hz, J_3 = 2.7Hz), 168.3.

Analysis : Mol. Formula: $C_{21}H_{21}F_3N_2O_3$

Calcd.: C 62.06, H 5.21, N 6.89.

Found: 62.02, H 5.18, N 6.92.

5.1.31.8. (4S,5S)-5-(Aminomethyl)-4-(2,4-dichlorophenyl)-1-(2-(pyridin-4-yl)ethyl) piperidin-2-one (70a)



70a (530mg, 79%) was prepared by means of the general procedure described in section **5.1.31.** as a White solid; mp: 94-96 °C. Purity by HPLC: 98.6% AUC, Chiral purity: 98.3%ee AUC.

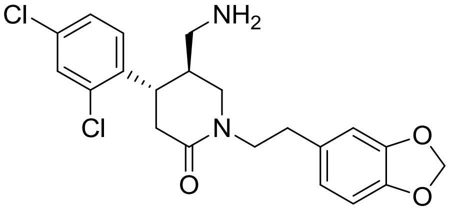
ESI-MS: $[M+H]^+$ = 378.5 *m/z*. **Mol.Wt** = 378.3 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.32-2.37 (m, 1H), 2.41-2.46 (m, 3H), 2.71-2.83 (m, 3H), 3.25-3.29 (m, 1H), 3.47-3.52 (m, 2H), 3.59 (t, J = 8.8Hz, 2H), 7.24 (d, J = 6.8Hz, 2H), 7.37 (dd, J_1 = 8.2Hz, J_2 = 2.0Hz, 1H), 7.44 (d, J = 8.2Hz, 1H), 7.53 (d, J = 2.0Hz, 1H), 8.44 (d, J = 6.8Hz, 2H);

^{13}C NMR (100 MHz, Methanol-d_4): δ 34.2, 38.4, 41.6, 42.3, 46.9, 49.8, 52.6, 123.4, 126.3, 127.8, 130.4, 132.2, 132.6, 133.9, 148.3, 149.2, 166.7;

Analysis : Mol. Formula: $C_{19}H_{21}Cl_2N_3O_2$
Calcd.: C 60.32, H 5.60, N 11.11.
Found: C 60.36, H 5.63, N 11.10.

5.1.31.9. (4S,5S)-5-(Aminomethyl)-1-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)-4-(2,4-dichlorophenyl)piperidin-2-one (70e)



70e (610mg, 83%) was prepared by means of the general procedure described in section **5.1.31.** as a White solid; mp: 132-134 °C. Purity by HPLC: 98.5% AUC, Chiral purity: 97.1%ee AUC.

ESI-MS: $[M+H]^+$ = 421.4 *m/z*. **Mol.Wt** = 421.3 g.

^{1}H NMR (400 MHz, Methanol-d_4): δ = 2.29-2.35 (m, 1H), 2.41-2.45 (m, 3H), 2.72-2.84 (m, 3H), 3.25-3.29 (m, 1H), 3.47-3.53 (m, 2H), 3.62 (t, J = 9.8Hz, 2H), 5.98 (s, 2H), 6.64-6.72 (m, 3H), 7.38 (dd, J_1 = 8.4Hz, J_2 = 2.0Hz, 1H), 7.44 (d, J = 8.4Hz, 1H), 7.53 (d, J = 2.0Hz, 1H).

^{13}C NMR (100 MHz, Methanol-d_4): δ 34.4, 38.4, 41.6, 42.3, 46.9, 49.8, 52.6, 101.3, 107.6, 109.4, 122.6, 126.3, 127.8, 130.4, 132.2, 132.6, 133.9, 146.6, 148.3, 168.9.

Analysis : Mol. Formula: $C_{21}H_{22}Cl_2N_2O_3$
Calcd.: C 59.87, H 5.26, N 6.65.
Found: C 59.89, H 5.24, N 6.68.

5.2. Biology

5.2.1. DPP-IV inhibitory activity and selectivity over other serine protease (*in vitro*)

Enzyme activity was determined by a fluorescence-based assay, adapted from the work of Blackmon et al **[242]**. H-Glycine-Proline-7-amino-4-methyl coumarin (Gly-Pro-AMC, 200 μM) (Bachem, PA) was used as substrate (which is cleaved by the enzyme to release the fluorescent aminomethylcoumarin (AMC)), and soluble human protein (DPP-IV enzyme) produced in a baculovirus expression system (Bac-To-Bac; Life Technologies), was used as the enzyme source. H-Gly-Pro-AMC (200 μM) was incubated with DPP-IV enzyme in the presence of various concentrations of test compounds. Reaction was carried out at pH 7.8 (HEPES buffer 25 mM containing 1.0% BSA, 140 mM NaCl, 16 mM $MgCl_2$, 2.8% DMSO) in a total volume of 100 μl at 25°C for 30 min., in the dark. Reaction was terminated with acetic acid (25 μl of 25% solution). Activity (fluorescence) was measured (expressed as fluorescent units (FU)) in a Spectra Max fluorometer (Molecular Devices, Sunnyvale CA) by exciting at 380 nm, and measuring emission at 460 nm. IC_{50} values were determined for test compounds using Graph Pad prism software.

DPP8.

Compounds were tested against human DPP8 (baculovirus) in a continuous fluorescent assay in 50 mmol/l sodium phosphate buffer, pH 8.0, and 0.1 mg/ml BSA, using Ala-Pro-7-amino-4-trifluormethylcoumarin as substrate at 100 μmol/l at 37°C for 15 min (excitation/emission: 400/505 nm).

DPP9.

Compounds were tested against human DPP9 (baculovirus) in a continuous fluorescent assay in 100 mmol/l Tris/HCl buffer, pH 7.4, and 0.1 mg/ml BSA, using Gly-Pro-AMC as substrate at 100 μmol/l at 37°C for 30 min (excitation/emission: 360/460 nm).

QPP/DPP2.

Compounds were tested against human QPP (baculovirus) in a continuous fluorescent assay in 100 mmol/l cacodylate buffer, pH 5.5, and 0.1 mg/ml BSA, using Nle-Pro-AMC as substrate at 5 μmol/l at 37°C for 15 min (excitation/emission: 360/460 nm).

Data analysis:

To measure the inhibition constants, serial dilutions of inhibitor were added to reactions containing enzyme and substrate. IC_{50} values were determined by a fit of the reaction rates to a three-parameter Hill equation by nonlinear regression. The data are reported as percentage inhibition calculated as follows: %Inhibition = 100 (1 – (V_t/V_c)), where V_t is the rate of reaction of treated sample and V_c is the rate of reaction of control sample.

5.2.2. CYP inhibition study (*in vitro*)

For CYP1A2, CYP2C8, CYP2C9, CYP2D6, CYP2C19 and CYP3A4 inhibition studies, Human liver microsomes (0.2 mg/ml), Testosterone (50 µM) / Dextromethorphan (5 µM) respectively, as probe substrates, potassium phosphate buffer (0.1 M; pH 7.4) and NADPH (1mM) were incubated with different concentrations of test compounds (@1, 10 and 100 µM concentrations) at 37°C for 10 min., enzyme activity (% of control) was determined and IC_{50} values were calculated **[262]**.

5.2.3. Pharmacodinemic study (Antidiabetic activity) (*in vivo*)

The *in- vivo* glucose lowering properties of some of the test compounds and standards were evaluated in db/db animal models as described below. Study was conducted in male C57BL/6J (using IPGTT protocol) or without glucose load, in db/db mice (age 8-12weeks). All animal experiments were conducted according to the internationally valid guidelines following approval by the ‘Zydus Research Center Animal Ethical Committee’. Two days prior to the study, the animals were randomized and divided into 2 groups (n = 6), based upon their fed glucose levels. Animals were left for 2 days under acclimatization and maintained on a standard diet. On the day of experiment, food was withdrawn from all the cages, water was given *ad-libitum* and were kept for overnight fasting. Briefly, in IPGTT protocol (C57 mice) overnight fasted mice were dosed orally (p.o.) with the test compounds (x mg/kg), 0.5 h prior to the intraperitoneal (i.p.) glucose load (1.5 g/kg), while in db/db mice, fed mice were dosed orally (p.o.) with the test compounds (x mg/kg) and the blood samples were collected at various time points. Blood samples were centrifuged and the separated serum was immediately subjected for the glucose estimation. The glucose estimation was carried out with DPEC-GOD/POD method (Ranbaxy Fine Chemicals Limited, Diagnostic division, India), using Spectramax-190, in 96-microwell plate reader (Molecular devices Corporation, Sunnyvale, California). Mean values of duplicate samples were calculated using Microsoft excel and the Graph Pad Prism software (Ver 4.0) was used to plot an area under the curve (0-240 min AUC). The AUC obtained from graphs were analyzed for two-way ANOVA, followed by Bonferroni post test, using Graph Pad prism software **[243-244]**.

5.3. Pharmacokinetic study (PK study)

Briefly, for single dose PK study, test compounds were administered orally / iv on a body weight basis (x mg/kg) to overnight fasted male C57BL/6J mice. Serial blood samples were collected in micro-centrifuge tubes containing EDTA at pre-dose, 0.15, 0.3, 0.5, 0.75, 1, 2, 4, 6, 8, 24, 36 and 48h post-dose after compounds administration. Approximately 0.2 ml of blood was collected at each time point and centrifuged at 4 °C. The obtained plasma was frozen, stored at -70 °C and the concentrations of compounds in plasma were determined by the LC-MS/MS (Shimadzu LC10AD, USA), using YMC hydrosphere C18 (2.0 x 50 mm, 3 μm) column (YMC Inc., USA). The pharmacokinetic parameters, such as Tmax, $t_{1/2}$, Cmax, AUC and %F were calculated using a non-compartmental model of WinNonlin software version 5.2.1.

5.4. Docking study

The molecular docking analysis of potent compounds from all the three series and standard compounds was carried out using extra precision (XP) Glide docking method, to understand its critical interactions with all the three binding sites (S1, S2 and S3) of DPP-IV enzyme. The crystal structure of the DPP-IV enzyme (PDB ID: 2I03/ 2AJL/2OQI) was obtained from the protein data bank and the protein structure was prepared using protein preparation wizard module of Schrödinger. After protein structure was prepared, the bound ligand of receptor was defined as grid binding box.

For docking experiments all the compounds were geometry optimized using the Optimized Potentials for Liquid Simulations-all atom (OPLS-AA) force field **[288]** with the steepest descent followed by a truncated Newton conjugate gradient protocol as implemented in Macromodel. DPP-IV was optimized for docking using the protein preparation wizard provided by Schrodinger LLC **[246]**. Partial atomic charges for compounds as well as protein were assigned according to the OPLS-AA force field. The extra precision (XP) Glide docking method was then used to dock all compounds into the catalytic site of DPP-IV **[245]**. Grids for Glide docking were calculated using the bound inhibitor as the reference of catalytic site in the DPP-IV. Upon completion of each docking calculation, 50 poses per ligand were allowed to generate. The top-scored pose was chosen using a Glidescore (Gscore) function **[289]**. The docking method was further validated by docking NVP-DPP728 and the binding mode was found similar as reported earlier.