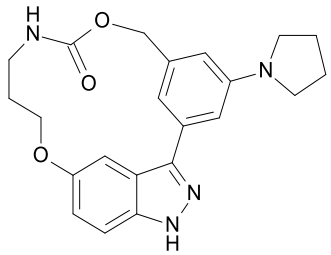
mmol) at RT. The reaction mixture was stirred under microwave irradiation for 45 min at 60°C. More pyrrolidine (2 µl; 0.021 mmol) was added and the reaction was stirred under microwave irradiation during 20 min at 60°C. After being cooled to RT, the reaction mixture was diluted with water and extracted with ethyl acetate twice. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash-column (5g SiO_2) chromatography (cyclohexane/Ethyl acetate, 1:0 to 50/50) affording 19-(oxan-2-yl)-4-(pyrrolidin-1-yl)-8,14-dioxa-10,19,20-triazatetracyclo[13.5.2.1^{2,6}.0^{18,21}]tricosa-1(20),2,4,6(23),15,17,21-heptaen-9-one **42** as a white powder.

LCMS method F: $[M+H]^+$ = 477.2, t_R = 3.00 min

Preparation of Example 12: 4-(pyrrolidin-1-yl)-8,14-dioxa-10,19,20-triazatetracyclo [13.5.2.1^{2,6}.0^{18,21}] tricosa-1(20),2,4,6(23),15,17,21-heptaen-9-one



To a mixture of 19-(oxan-2-yl)-4-(pyrrolidin-1-yl)-8,14-dioxa-10,19,20-triazatetracyclo [13.5.2.1^{2,6}.0^{18,21}]tricosa-1(20),2,4,6(23),15,17,21-heptaen-9-one **42** (60mg; 0.126mmol) in DCM (2.5mL) was added TFA (48µl; 0.630mmol). The reaction mixture was stirred under microwaves irradiation at 80°C during 30 min. The solvent was removed under reduced pressure, the mixture was dissolved in EtOAc and washed with 1N NaOH (pH=7), then with water. The organic layer was concentrated under reduced pressure and the product was purified by chromatography using a 4 g SiO2 column eluted with DCM/MeOH 100/0 to 90/10. The desired fractions were combined to give 4-(pyrrolidin-1-yl)-8,14-dioxa-10,19,20-triazatetracyclo[13.5.2.1^{2,6}.0^{18,21}]tricosa-1(20),2,4,6(23),15,17,21-heptaen-9-one **example 12** as a yellow powder.

LCMS method F: $[M+H]^+$ = 393.1, t_R = 2.39 min (current 20V)

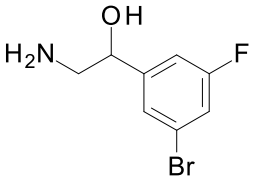
LCMS method G: $[M+H]^+$ = 393.1, t_R = 2.47 min (pH10 current 20V)

^{1}H NMR (400 MHz, *d*6-DMSO) δ 7.61 (1H, m), 7.47 - 7.44 (1H, m), 7.36 (1H, d, J = 2.7 Hz), 7.20 (1H, s), 7.04 (1H, t, J = 1.9 Hz), 6.95 (1H, dd, J = 2.4, 9.0 Hz), 6.50 (1H, s), 5.22 - 5.20

brown/orange oil. This residue was purified by flash chromatography on silica gel (Macherey Nagel, 120 g) with gradient elution : cyclohexane/EtOAc 0-30 % to give 1-(3-bromo-5-fluorophenyl)-2-nitroethan-1-ol **65** as a white solid.

LCMS method F: $[M-H]^-$ = 262.2, t_R = 2.28 min

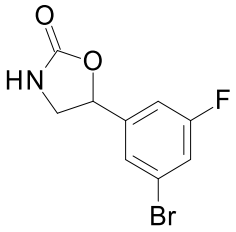
<u>Preparation of intermediate 66</u>: 2-amino-1-(3-bromo-5-fluorophenyl)ethan-1-ol



To a solution of 1-(3-bromo-5-fluorophenyl)-2-nitroethan-1-ol **65** (6.2 g, 15.2 mmol) in EtOH (100 mL) was added Raney®-Nickel (2 g) and 0.5 mL of acetic acid. Dihydrogen was bubbled in the mixture for 5 min. The reaction mixture was stirred for 16 h under dihydrogen atmosphere. The reaction mixture was filtered over celite and the solvent of the filtrate was removed under reduced pressure to give ~~a yellow solid as~~ 2-amino-1-(3-bromo-5-fluorophenyl)ethan-1-ol **66** ~~as a transparent oil used~~ which is directly used in the next step without purification.

LCMS method F: $[M+H]^+$ = 236, t_R = 1.12 min

<u>Preparation of intermediate 67</u>: 5-(3-bromo-5-fluorophenyl)-1,3-oxazolidin-2-one



To a solution of 2-amino-1-(3-bromo-5-fluorophenyl)ethan-1-ol **66** (1.75 g , 1.75 mmol) in THF (100 mL) were added 1,1′-carbonyldiimidazole (1.34 g, 8.25 mmol) and imidazole (0.561 g, 8.25 mmol). The reaction mixture was stirred at RT for 16h. To the reaction mixture was added a saturated aqueous solution of NH_4Cl (100 mL). The mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water and brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. **The crude product was purified by column chromatography on a Biotage eluting with cyclohexane / ethyl acetate (3-1) : 100/0 to 70/30 to give a white solid as 5-(3-bromo-5-fluorophenyl)-1,3-oxazolidin-2-one 67**.