Supporting Information

Analgesic properties of opioid/NK1 multitarget ligands with distinct *in vitro* profiles in naive and chronic constriction injury (CCI)-mice

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Compound characterization

H-Dmt-D-Arg-Aba-Gly-NMe-3',5'-$(CF_3)_2$-Bn (**3**, **SBCHM1**). Preparative HPLC yielded the desired compound (white powder, 34%). HPLC: t_R = 14.0 min. TLC R_f 0.72 (EBAW). HRMS (ESP^+) found m/z 821.3536 $[M + H]^+$, $[C_{39}H_{46}F_6N_8O_5 + H^+]$ requires 821.3568.

H-Dmt-D-Arg-Aba-β-*Ala-NMe-Bn* (**4**, **KGCHM2**). Preparative HPLC yielded the desired compound (white powder, 34%). HPLC: t_R = 11.7 min. TLC R_f 0.64 (EBAW). HRMS (ESP^+) found m/z 699.3955 $[M + H]^+$, $[C_{38}H_{50}N_8O_5 + H^+]$ requires 699.3977.

H-Dmt-D-Arg-Aba-Gly-NH_2 (**1 (AN81)**). Preparative HPLC yielded the desired compound (white powder). HPLC: t_R = 8.6 min. TLC R_f 0.55 (EBAW). HRMS (ESP^+) found m/z 581.3220 $[M + H]^+$, $[C_{29}H_{40}N_8O_5 + H^+]$ requires 581.3195.[56]

H-Dmt-D-Arg-Aba-β-*Ala-NH$_2$* (**2**, **KGOP01**). Preparative HPLC yielded the desired compound (white powder, 49.5%). HPLC: t_R = 10.1 min. TLC R_f 0.44 (EBAW). HRMS (ESP^+) found m/z 595.3394 $[M+H]^+$, [$C_{30}H_{43}N_8O_5 + H^+$] requires 595.3351.[22]

H-Dmt-D-Arg-Aba-β-*Ala-NcPr-3'-5'-(CF$_3$)$_2$-Bn* (**6**, **RCCHM1**). Preparative HPLC yielded the desired compound (white powder, 7%). HPLC: t_R = 14.7 min. TLC R_f 0.78 (EBAW). HRMS (ESP^+) found m/z 861.3876 $[M + H]^+$, [$C_{42}H_{50}F_6N_8O_5 + H^+$] requires 861.3881.

H-Dmt-D-Arg-Aba-β-*Ala-NcPr-Bn* (**7**, **RCCHM2**). Preparative HPLC yielded the desired compound (white powder, 20%). HPLC: t_R = 12.5 min. TLC R_f 0.76 (EBAW). HRMS (ESP^+) found m/z 725.4151 $[M + H]^+$, [$C_{40}H_{52}N_8O_5 + H^+$] requires 725.4133.

H-Dmt-D-Arg-Aba-Gly-NcPr-Bn (**8**, **RCCHM8**). Preparative HPLC yielded the desired compound (white powder, 9%). HPLC: t_R = 12.5 min. TLC R_f 0.81 (EBAW). HRMS (ESP^+) found m/z 711.3972 $[M + H]^+$, [$C_{39}H_{50}N_8O_5 + H^+$] requires 711.3977.

H-Dmt-D-Arg-Aba-β-*Ala-isoindoline* (**9**, **RCCHM4**). Preparative HPLC yielded the desired compound (white powder, 23%). HPLC: t_R = 11.2 min. TLC R_f 0.71 (EBAW). HRMS (ESP^+) found m/z 697.3843 $[M + H]^+$, [$C_{38}H_{48}N_8O_5 + H^+$] requires 697.3820.

H-Dmt-D-Arg-Aba-Gly-isoindoline (**10**, **RCCHM5**). Preparative HPLC yielded the desired compound (white powder, 16%). HPLC: t_R = 11.6 min. TLC R_f 0.76 (EBAW). HRMS (ESP^+) found m/z 683.3673 $[M + H]^+$, [$C_{37}H_{46}N_8O_5 + H^+$] requires 683.3664.

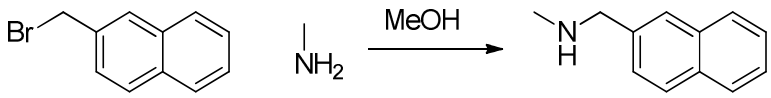
H-Dmt-D-Arg-Aba-Gly-NMe-2'-OMe-Bn (**11**, **RCCHM7**). Preparative HPLC yielded the desired compound (white powder, 29%). HPLC: t_R = 11.9 min. TLC R_f 0.73 (EBAW). HRMS (ESP^+) found m/z 729.4109 $[M + H]^+$, [$C_{41}H_{50}N_8O_5 + H^+$] requires 729.4083.

H-Dmt-D-Arg-Aba-β-*Ala-NMe-2'-naphthyl* (**12, RCCHM3)**). Preparative HPLC yielded the desired compound (white powder, 20%). HPLC: t_R = 13.2 min. TLC R_f 0.77 (EBAW). HRMS (ESP^+) found m/z 749.4146 $[M + H]^+$, [$C_{42}H_{52}N_8O_5 + H^+$] requires 749.4133.

H-Dmt-D-Arg-Aba-Gly-NMe-2'-naphthyl (**13, RCCHM6)**). Preparative HPLC yielded the desired compound (white powder, 21%). HPLC: t_R = 13.0 min. TLC R_f 0.80 (EBAW). HRMS (ESP^+) found m/z 735.3989 $[M + H]^+$, [$C_{41}H_{50}N_8O_5 + H^+$] requires 735.3977.

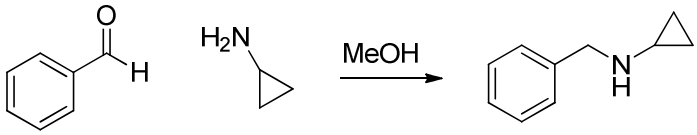
Synthesis of benzylamine derivates

Synthesis of *N*-methyl-1-(naphthalen-2-yl)methanamine



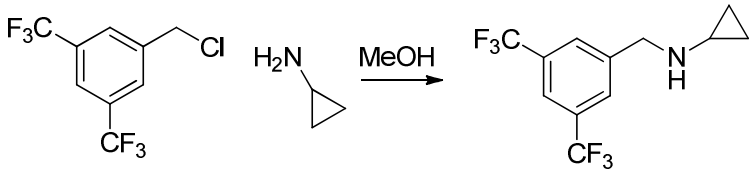
A 40 % solution of methylamine in water (1.78 g, 22.9 mmol, 10.14 equiv.) was dissolved in 10 ml of methanol in a two-headed round bottom flask which was equipped with a stirbar, a cooler and an oil bath. The mixture was heated to 50°C and a solution of 2-(bromomethyl)naphthalane (0.5 g, 2.26 mmol, 1 equiv.) in methanol (5 ml) was added dropwise during 1 hour. After 6 hours, the reaction was complete and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (300 ml) and washed with a 20% NaOH-solution (2 x 50 ml) and water (2 x 50 ml). The organic phase was dried, filtrated and evaporated to give a yellow liquid. Purification was done using flash chromatography with MeOH/CH_2Cl_2 (1:9) as eluent to give a brown oil in 70 % yield. **Yield:** 70% (271 mg); **Formula:** $C_{12}H_{13}N$; **MW**: 276.15 g/mol.

Synthesis of N-cyclopropylbenzylamine



Benzaldehyde (500 mg, 4.71 mmol, 1 equiv.) was dissolved in MeOH and cyclopropylamine (326 µL, 4.71 mmol, 1 equiv.) was added. After 15 min of stirring at room temperature, the solution was cooled to 0° C and $NaBH_4$ (1 eq.) was added portionwise. After 2 h the reaction was complete and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 and washed with water and brine, dried with $MgSO_4$ and the solvent was evaporated *in vacuo* to obtain a yellow oil. The oil was dissolved in 1 N HCl and lyophilized to obtain the product as a white powder in 82% yield. **Yield:** 82% (569 mg); **Formula:** $C_{10}H_{13}N$; **MW**: 147.22 g/mol.

Synthesis of N-cyclopropyl-3',5'-bis(trifluoromethyl)benzylamine



Cyclopropylamine (1.32 ml, 19.0 mmol, 10 equiv.) was dissolved in MeOH and the solution was heated to 50 °C. 3,5-Bis(trifluoromethyl)benzyl chloride (500 mg, 1.90 mmol, 1 equiv.) was dissolved in MeOH and added dropwise to reaction mixture. After 4 h the solvent was evaporated, the residue was dissolved in CH_2Cl_2 and washed twice with 20% NaOH, H_2O and brine. The organic layer was dried with $MgSO_4$ and evaporated to give a yellow oil, which was purified on flash chromatography using CH_2Cl_2/DIPEA (99:1) as eluent. The product was lyophilized in 1 N HCl to obtain the product as a yellow powder in 55% yield. **Yield:** 55% (243 mg); **Formula:** $C_{12}H_{11}F_6N$; **MW**: 283.21 g/mol.