**Supporting Information for:**

# Low-affinity/high selectivity dopamine transport inhibition sufficient to rescue cognitive functions in the aging rat

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**Functional GPCRs agonist and antagonist screening**

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**Table S1** Agonist effect of S-CE-123 at 2.8E-06 M (IC50 for DAT re-uptake inhibition) in functional cellular assay. The results are expressed as a percent of control agonist response: (measured response / control response) x 100 obtained in the presence of S-CE-123.

| Compound I.D. | Client Compound I.D. | Test Concentration | % of Control Agonist Response 1st | 2nd | Mean |
|---|---|---|---|---|---|
| **A1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 5.3 | 0.8 | 3.0 |
| **$A_{2A}$ (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.9 | 1.2 | 0.2 |
| **$A_{2B}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.5 | 3.4 | 1.9 |
| **$A_3$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -7.5 | -41.0 | -24.3 |
| **$\alpha_{1A}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.5 | -2.4 | -2.5 |
| **$\alpha_{1B}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 7.2 | -8.5 | -0.6 |
| **alpha $_{1D}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.6 | 0.6 | 0.6 |
| **α2A *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 2.3 | 1.7 | 2.0 |
| **$\alpha_{2B}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.6 | -4.9 | -4.2 |
| **$\alpha_{2C}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 4.0 | 6.2 | 5.1 |
| **$\beta_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.1 | -3.9 | -2.0 |
| **$\beta_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.1 | 1.0 | -0.6 |
| **$\beta_3$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.2 | 3.8 | 0.3 |
| **$AT_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.6 | -1.2 | -2.4 |
| **APJ (apelin) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.0 | -13.1 | -6.5 |
| **TGR5 (h) (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.3 | 1.4 | 2.3 |
| **$BB_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.1 | -3.7 | -2.4 |
| **$BB_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.3 | 0.8 | 0.3 |
| **$BB_3$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -6.8 | -5.9 | -6.3 |
| **$B_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -12.4 | -11.5 | -11.9 |
| **$B_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -5.6 | -1.0 | -3.3 |
| **CGRP *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 7.4 | 7.2 | 7.3 |
| **CT (Calcitonin) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.4 | 0.9 | 2.2 |
| **CaS *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 2.2 | 1.9 | 2.0 |
| **$CB_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.3 | 5.2 | 2.0 |
| **$CB_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -16.9 | 25.9 | 4.5 |
| **CCR1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 8.1 | 6.8 | 7.4 |
| **CCR2 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 5.5 | 2.7 | 4.1 |

| Compound I.D. | Client Compound I.D. | Test Concentration | % of Control Agonist Response 1st | 2nd | Mean |
|---|---|---|---|---|---|
| **CCR3 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.4 | 1.2 | 1.3 |
| **CCR4 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.5 | -0.3 | -0.4 |
| **CCR5 (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.8 | -0.2 | -0.5 |
| **CCR6 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.8 | -2.1 | -1.9 |
| **CCR7 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.2 | 0.2 | 0.7 |
| **CCR8 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.1 | 3.8 | 3.4 |
| **CCR10 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.0 | 0.3 | 0.2 |
| **CX3CR1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.2 | 1.7 | 2.4 |
| **CXCR1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.0 | 0.3 | 0.1 |
| **CXCR2 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.9 | -2.9 | -0.5 |
| **CXCR3 (h) (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.1 | -0.4 | 0.4 |
| **CXCR4 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.3 | -0.2 | -0.2 |
| **CXCR5 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.0 | 0.9 | 0.9 |
| **CXCR6 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.4 | -1.2 | -0.8 |
| **$CCK_1$ ($CCK_A$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.4 | 0.6 | 0.5 |
| **$CCK_2$ ($CCK_B$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.2 | 0.2 | -1.0 |
| **C3aR *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.5 | -0.1 | -0.3 |
| **ChemR23 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.0 | 1.4 | 0.7 |
| **$CRF_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.2 | -3.7 | -2.5 |
| **$CRF_{2\ a}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.4 | -2.2 | -1.8 |
| **XCR1 / GPR5 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 2.3 | 0.4 | 1.3 |
| **$D_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.2 | -0.5 | -0.1 |
| **$D_{2S}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 9.2 | 11.7 | 10.5 |
| **$D_3$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -20.1 | 5.7 | -7.2 |
| **$D_{4.4}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -10.2 | -1.6 | -5.9 |
| **$D_5$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.0 | 0.6 | -0.7 |
| **$ET_A$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.0 | 1.4 | 1.2 |
| **$ET_B$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.5 | 2.7 | 1.1 |

| Compound I.D. | Client Compound I.D. | Test Concentration | % of Control Agonist Response 1st | 2nd | Mean |
|---|---|---|---|---|---|
| **FFA1 *(h)* (GPR40) (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.6 | -2.7 | -2.7 |
| **FFA2 *(h)* (GPR43) (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 6.4 | 6.7 | 6.6 |
| **FFA3 *(h)* (GPR41) (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -19.5 | 11.7 | -3.9 |
| **FFA4 (GPR120) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.3 | -0.5 | -0.1 |
| **GnRH *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.6 | -0.7 | -0.6 |
| **GPR39 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.8 | 1.9 | 0.6 |
| **OXGR1 GPR99 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.1 | 0.6 | 0.9 |
| **GPR103/QRFP *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.5 | -0.3 | 0.1 |
| **GPR109A *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.5 | 0.4 | 0.4 |
| **GPR119 (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 11.5 | -9.6 | 0.9 |
| **FPR1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -46.5 | -6.4 | -26.5 |
| **GABAB1b beta *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.3 | 0.2 | 0.0 |
| **GAL1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.8 | -1.7 | -1.3 |
| **$GAL_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 5.2 | 3.4 | 4.3 |
| **GIP *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.1 | 0.3 | 0.1 |
| **GLP-1 (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 10.7 | 13.4 | 12.0 |
| **secretin *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.1 | 2.7 | 0.8 |
| **TSH *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -4.3 | -3.6 | -3.9 |
| **GHRH *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.2 | 2.4 | 1.3 |
| **Ghrelin / GHSR-1a *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.7 | 2.6 | 2.2 |
| **$H_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.7 | -0.7 | -1.2 |
| **$H_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -4.4 | -0.6 | -2.5 |
| **$H_3$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.6 | 1.0 | -0.8 |
| **$H_4$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.2 | 1.7 | 0.7 |
| **KiSS1 / GPR54 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.3 | -0.7 | -0.5 |
| **$BLT_1$ ($LTB_4$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.6 | -1.4 | -1.0 |
| **$CysLT_1$ ($LTD_4$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.7 | -6.8 | -8.2 |
| **$CysLT_2$ ($LTC_4$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.5 | -1.9 | -1.2 |

| Compound I.D. | Client Compound I.D. | Test Concentration | % of Control Agonist Response 1st | 2nd | Mean |
|---|---|---|---|---|---|
| **LPA1(h) (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.1 | -0.2 | -0.2 |
| **$LPA_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.7 | 4.6 | 3.2 |
| **$LPA_3$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -11.6 | 2.6 | -4.5 |
| **$S_1P_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 8.3 | 11.5 | 9.9 |
| **$S_1P_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.7 | -8.9 | -4.1 |
| **$S_1P_3$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.3 | -1.1 | -1.2 |
| **S1P4 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -4.2 | -8.3 | -6.2 |
| **S1P5 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.1 | -0.4 | -0.2 |
| **$MCH_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.8 | 1.0 | 0.1 |
| **$MCH_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.6 | 5.7 | 4.6 |
| **$MC_1$ (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.0 | -2.1 | -2.1 |
| **$MC_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.8 | -1.6 | -2.7 |
| **$MC_3$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.5 | 0.3 | -1.1 |
| **$MC_4$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.2 | -0.4 | -1.8 |
| **$MC_5$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.0 | 3.0 | 3.0 |
| **$MT_1$ ($ML_{1A}$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 15.2 | 18.4 | 16.8 |
| **$MT_2$ ($ML_{1B}$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.8 | -59.1 | -29.9 |
| **motilin *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.7 | -2.7 | -1.7 |
| **$M_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.1 | -0.7 | -0.9 |
| **$M_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 16.8 | 17.3 | 17.1 |
| **$M_3$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.0 | 0.3 | 0.1 |
| **$M_4$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.7 | 1.9 | 1.8 |
| **$M_5$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.0 | -0.2 | -0.1 |
| **MrgD *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.0 | 3.5 | 0.7 |
| **MRGX1 / MRGPRX1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -10.7 | 0.2 | -5.2 |
| **MRGX2 / MGRPLX2 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.7 | 2.6 | 2.2 |
| **NPS *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.3 | 1.3 | -1.0 |
| **NPBW1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.1 | 15.5 | 6.2 |

| Compound I.D. | Client Compound I.D. | Test Concentration | % of Control Agonist Response 1st | 2nd | Mean |
|---|---|---|---|---|---|
| **$NK_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.1 | -0.1 | -0.1 |
| **$NK_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.3 | -1.4 | -0.9 |
| **$NK_3$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.5 | -0.8 | -0.2 |
| **NMU1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.7 | -1.2 | -0.9 |
| **NMU2 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.1 | 0.0 | 0.0 |
| **$NTS_1$ ($NT_1$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.6 | -2.8 | -0.6 |
| **$NTS_2$ (NT2) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.8 | 2.9 | 1.9 |
| **δ (DOP) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.3 | 0.9 | 1.1 |
| **κ (KOP) (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 33.6 | 9.3 | 21.4 |
| **μ (MOP) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.6 | -4.4 | -1.4 |
| **NOP *(h)* (ORL1) (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 20.7 | -3.6 | 8.6 |
| **$OX_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.5 | -8.8 | -9.2 |
| **$OX_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.5 | 0.3 | 0.9 |
| **PAF *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.8 | 2.0 | 1.9 |
| **PTH1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.8 | -2.9 | -3.4 |
| **$PK_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -5.1 | 0.6 | -2.3 |
| **$PK_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.8 | -2.4 | -1.6 |
| **$DP_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.0 | -4.3 | -2.7 |
| **$EP_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 4.6 | 0.8 | 2.7 |
| **$EP_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.8 | 2.2 | 2.0 |
| **EP3 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 2.3 | 2.2 | 2.3 |
| **$EP_4$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 4.6 | -0.3 | 2.2 |
| **FP *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.9 | -1.9 | -1.9 |
| **IP ($PGI_2$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.6 | -1.6 | -0.5 |
| **TP ($TXA_2$/$PGH_2$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.4 | -1.0 | -0.7 |
| **PAR1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.6 | 0.0 | 0.3 |
| **PAR2 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.9 | 15.0 | 7.1 |
| **P2Y1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.9 | 3.1 | 2.0 |

| Compound I.D. | Client Compound I.D. | Test Concentration | % of Control Agonist Response 1st | 2nd | Mean |
|---|---|---|---|---|---|
| **$P2Y_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 2.4 | -1.1 | 0.6 |
| **$P2Y_4$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.8 | -1.2 | -1.0 |
| **$P2Y_6$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -4.0 | 0.3 | -1.8 |
| **P2Y11 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.3 | 3.0 | 1.7 |
| **PTH2 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -4.1 | -4.5 | -4.3 |
| **RXFP1 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.5 | -0.5 | -2.0 |
| **5-HT1A *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.6 | -0.6 | 0.0 |
| **5HT1B (h) (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -30.4 | -31.0 | -30.7 |
| **$5\text{-}HT_{1D}$ (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.4 | 2.1 | 2.8 |
| **$5\text{-}HT_{2A}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 2.0 | -2.5 | -0.3 |
| **$5\text{-}HT_{2B}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.9 | 4.4 | 2.7 |
| **$5\text{-}HT_{2C}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.4 | -0.8 | 0.3 |
| **$5\text{-}HT_{4e}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.9 | 0.0 | -1.4 |
| **$5\text{-}HT_6$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.9 | -5.5 | -1.8 |
| **$5\text{-}HT_7$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.5 | 3.2 | -0.2 |
| **$sst_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -20.0 | -1.7 | -10.9 |
| **sst2 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.6 | -0.5 | 0.1 |
| **sst3 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.9 | 0.4 | 0.6 |
| **$sst_4$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 24.2 | 19.9 | 22.0 |
| **$sst_5$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 6.4 | 45.7 | 26.0 |
| **SUCNR1/GPR91 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.2 | -0.2 | -0.2 |
| **$TRH_1$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.0 | -0.6 | -0.8 |
| **UT *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.5 | 1.3 | 0.9 |
| **$PAC_1$ (PACAP) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.1 | 0.1 | 0.0 |
| **$VPAC_1$ ($VIP_1$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.5 | -1.2 | -1.8 |
| **$VPAC_2$ ($VIP_2$) *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -5.7 | 0.8 | -2.5 |
| **Y4 *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.2 | 0.1 | 0.1 |
| **$V_{1a}$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.8 | -1.5 | -2.1 |
| **V1B *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.9 | -0.3 | 0.3 |
| **$V_2$ *(h)* (agonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.4 | -6.1 | -3.3 |

Table S2 Reference compounds for agonist effect.

| Compound I.D. | $EC_{50}$ (M) | nH |
|---|---|---|
| **A1 *(h)* (agonist effect)** | | |
| CPA | 1.6E-09 M | n/a |
| **$A_{2A}$ (agonist effect)** | | |
| NECA | 1.3E-08 M | n/a |
| **$A_{2B}$ *(h)* (agonist effect)** | | |
| NECA | 8.5E-08 M | n/a |
| **$A_3$ *(h)* (agonist effect)** | | |
| IB-MECA | 5.6E-10 M | n/a |
| **$\alpha_{1A}$ *(h)* (agonist effect)** | | |
| epinephrine | 5.8E-10 M | n/a |
| **$\alpha_{1B}$ *(h)* (agonist effect)** | | |
| epinephrine | 1.9E-07 M | n/a |
| **alpha $_{1D}$ *(h)* (agonist effect)** | | |
| Epinephrine | 1.6E-09 M | n/a |
| **α2A *(h)* (agonist effect)** | | |
| Epinephrine | 3.3E-10 M | n/a |
| **$\alpha_{2B}$ *(h)* (agonist effect)** | | |
| dexmedetomidine | 1.9E-08 M | n/a |
| **$\alpha_{2C}$ *(h)* (agonist effect)** | | |
| epinephrine | 1.4E-09 M | n/a |
| **$\beta_1$ *(h)* (agonist effect)** | | |
| isoproterenol | 6.0E-10 M | n/a |
| **$\beta_2$ *(h)* (agonist effect)** | | |
| isoproterenol | 3.9E-09 M | n/a |
| **$\beta_3$ *(h)* (agonist effect)** | | |
| isoproterenol | 4.7E-07 M | n/a |
| **$AT_1$ *(h)* (agonist effect)** | | |
| angiotensin-II | 1.2E-10 M | n/a |
| **APJ (apelin) *(h)* (agonist effect)** | | |
| apelin-13 | 7.3E-11 M | n/a |
| **TGR5 (h) (agonist effect)** | | |
| Lithocholic Acid | 8.2E-07 M | n/a |
| **$BB_1$ *(h)* (agonist effect)** | | |
| neuromedin B | 5.0E-13 M | n/a |
| **$BB_2$ *(h)* (agonist effect)** | | |
| GRP | 2.7E-11 M | n/a |
| **$BB_3$ *(h)* (agonist effect)** | | |
| Bn(6-14) | 2.1E-09 M | n/a |
| **$B_1$ *(h)* (agonist effect)** | | |
| LysdesArg$^9$-BK | 2.1E-10 M | n/a |
| **$B_2$ *(h)* (agonist effect)** | | |
| bradykinin | 5.1E-12 M | n/a |
| **CGRP *(h)* (agonist effect)** | | |
| hCGRPα | 4.5E-11 M | n/a |
| **CT (Calcitonin) *(h)* (agonist effect)** | | |
| human calcitonin | 8.6E-10 M | n/a |
| **CaS *(h)* (agonist effect)** | | |
| neomycin | 1.7E-05 M | n/a |

| Compound I.D. | $EC_{50}$ (M) | nH |
|---|---|---|
| **$CB_1$ *(h)* (agonist effect)** | | |
| CP 55940 | 5.1E-11 M | n/a |
| **$CB_2$ *(h)* (agonist effect)** | | |
| WIN 55212-2 | 1.4E-10 M | n/a |
| **CCR1 *(h)* (agonist effect)** | | |
| MIP-1alpha | 1.2E-10 M | n/a |
| **CCR2 *(h)* (agonist effect)** | | |
| MCP-1 | 1.5E-09 M | n/a |
| **CCR3 *(h)* (agonist effect)** | | |
| Human Eotaxin(CCL11) | 1.7E-09 M | n/a |
| **CCR4 *(h)* (agonist effect)** | | |
| TARC | 2.4E-10 M | n/a |
| **CCR5 (agonist effect)** | | |
| MIP-1a | 5.0E-09 M | n/a |
| **CCR6 *(h)* (agonist effect)** | | |
| MIP-3a | 1.8E-10 M | n/a |
| **CCR7 *(h)* (agonist effect)** | | |
| MIP-3b | 3.4E-10 M | n/a |
| **CCR8 *(h)* (agonist effect)** | | |
| I-309 | 2.5E-10 M | n/a |
| **CCR10 *(h)* (agonist effect)** | | |
| CTACK/CCL27 | 6.5E-09 M | n/a |
| **CX3CR1 *(h)* (agonist effect)** | | |
| Human Fractalkine(CX3CL1) | 9.0E-10 M | n/a |
| **CXCR1 *(h)* (agonist effect)** | | |
| rhIL-8 | 2.9E-10 M | n/a |
| **CXCR2 *(h)* (agonist effect)** | | |
| rhGROa | 4.9E-10 M | n/a |
| **CXCR3 (h) (agonist effect)** | | |
| I-TAC | 3.2E-09 M | n/a |
| **CXCR4 *(h)* (agonist effect)** | | |
| SDF-1a | 2.4E-10 M | n/a |
| **CXCR5 *(h)* (agonist effect)** | | |
| CXCL13/BLC/BCA-1 | 2.5E-09 M | n/a |
| **CXCR6 *(h)* (agonist effect)** | | |
| CXCL16 | 1.7E-09 M | n/a |
| **$CCK_1$ ($CCK_A$) *(h)* (agonist effect)** | | |
| CCK-8s | 6.3E-08 M | n/a |
| **$CCK_2$ ($CCK_B$) *(h)* (agonist effect)** | | |
| CCK-8s | 2.4E-09 M | n/a |
| **C3aR *(h)* (agonist effect)** | | |
| Complement C3a human | 7.0E-10 M | n/a |
| **ChemR23 *(h)* (agonist effect)** | | |
| Chemerin | 9.6E-10 M | n/a |
| **$CRF_1$ *(h)* (agonist effect)** | | |
| ovine CRF | 9.6E-09 M | n/a |
| **$CRF_{2\ a}$ *(h)* (agonist effect)** | | |
| human CRF | 4.7E-08 M | n/a |
| **XCR1 / GPR5 *(h)* (agonist effect)** | | |
| Lymphotactin | 1.3E-09 M | n/a |
| **$D_1$ *(h)* (agonist effect)** | | |
| dopamine | 2.1E-08 M | n/a |
| **$D_{2S}$ *(h)* (agonist effect)** | | |
| dopamine | 3.3E-09 M | n/a |
| **$D_3$ *(h)* (agonist effect)** | | |
| dopamine | 3.5E-09 M | n/a |
| **$D_{4.4}$ *(h)* (agonist effect)** | | |
| dopamine | 1.2E-08 M | n/a |

| Compound I.D. | $EC_{50}$ (M) | nH |
|---|---|---|
| **$D_5$ *(h)* (agonist effect)** | | |
| dopamine | 1.1E-08 M | n/a |
| **$ET_A$ *(h)* (agonist effect)** | | |
| endothelin-1 | 4.5E-10 M | n/a |
| **$ET_B$ *(h)* (agonist effect)** | | |
| endothelin-1 | 1.7E-10 M | n/a |
| **FFA1 *(h)* (GPR40) (agonist effect)** | | |
| linoleic acid | 6.2E-06 M | n/a |
| **FFA2 *(h)* (GPR43) (agonist effect)** | | |
| sodium acetate | 1.9E-04 M | n/a |
| **FFA3 *(h)* (GPR41) (agonist effect)** | | |
| sodium propionate | 2.0E-06 M | n/a |
| **FFA4 (GPR120) *(h)* (agonist effect)** | | |
| GW9508 | 7.4E-06 M | n/a |
| **GnRH *(h)* (agonist effect)** | | |
| LHRH | 4.1E-10 M | n/a |
| **GPR39 *(h)* (agonist effect)** | | |
| ZnCl2 | 1.7E-05 M | n/a |
| **OXGR1 GPR99 *(h)* (agonist effect)** | | |
| alpha Ketoglutaric acid | 1.8E-04 M | n/a |
| **GPR103/QRFP *(h)* (agonist effect)** | | |
| 26Rfa Hypothalamic Peptide(Peptide 518) | 4.9E-10 M | n/a |
| **GPR109A *(h)* (agonist effect)** | | |
| Nicotinic Acid Free Acid | 4.7E-08 M | n/a |
| **GPR119 (agonist effect)** | | |
| AR231453 | 3.4E-08 M | n/a |
| **FPR1 *(h)* (agonist effect)** | | |
| fMLP | 1.6E-10 M | n/a |
| **GABAB1b beta *(h)* (agonist effect)** | | |
| 3-APMPA | 1.2E-07 M | n/a |
| **GAL1 *(h)* (agonist effect)** | | |
| Galanin (1-30) | 1.4E-10 M | n/a |
| **$GAL_2$ *(h)* (agonist effect)** | | |
| human galanin | 3.4E-10 M | n/a |
| **GIP *(h)* (agonist effect)** | | |
| GIP | 6.1E-10 M | n/a |
| **GLP-1 (agonist effect)** | | |
| GLP-1(7-37) | 7.6E-11 M | n/a |
| **secretin *(h)* (agonist effect)** | | |
| human secretin | 1.2E-10 M | n/a |
| **TSH *(h)* (agonist effect)** | | |
| TSH | 2.2E-08 M | n/a |
| **GHRH *(h)* (agonist effect)** | | |
| human GHRF(1-29) | 2.3E-09 M | n/a |
| **Ghrelin / GHSR-1a *(h)* (agonist effect)** | | |
| Ghrelin(human) | 4.0E-10 M | n/a |
| **$H_1$ *(h)* (agonist effect)** | | |
| histamine | 4.7E-08 M | n/a |
| **$H_2$ *(h)* (agonist effect)** | | |
| histamine | 4.8E-07 M | n/a |
| **$H_3$ *(h)* (agonist effect)** | | |
| histamine | 3.2E-08 M | n/a |
| **$H_4$ *(h)* (agonist effect)** | | |
| histamine | 4.8E-09 M | n/a |
| **KiSS1 / GPR54 *(h)* (agonist effect)** | | |
| Metastin 45-54 | 2.4E-09 M | n/a |
| **$BLT_1$ ($LTB_4$) *(h)* (agonist effect)** | | |
| $LTB_4$ | 4.6E-10 M | n/a |

| Compound I.D. | $EC_{50}$ (M) | nH |
|---|---|---|
| **NPBW1 *(h)* (agonist effect)** | | |
| NPB29 | 1.8E-10 M | n/a |
| **$NK_1$ *(h)* (agonist effect)** | | |
| [$Sar^9$,$Met(O_2)^{11}$]-SP | 6.3E-11 M | n/a |
| **$NK_2$ *(h)* (agonist effect)** | | |
| [$Nleu^{10}$]-NKA (4-10) | 1.3E-09 M | n/a |
| **$NK_3$ *(h)* (agonist effect)** | | |
| [$MePhe^7$]-NKB | 4.9E-11 M | n/a |
| **NMU1 *(h)* (agonist effect)** | | |
| NMU-25 (human) | 1.0E-10 M | n/a |
| **NMU2 *(h)* (agonist effect)** | | |
| Neuromedian U-25 | 6.3E-10 M | n/a |
| **$NTS_1$ ($NT_1$) *(h)* (agonist effect)** | | |
| neurotensin | 1.5E-11 M | n/a |
| **$NTS_2$ (NT2) *(h)* (agonist effect)** | | |
| SR 142948 | 3.3E-09 M | n/a |
| **δ (DOP) *(h)* (agonist effect)** | | |
| DPDPE | 3.6E-09 M | n/a |
| **κ (KOP) (agonist effect)** | | |
| U 50488 | 2.8E-10 M | n/a |
| **μ (MOP) *(h)* (agonist effect)** | | |
| DAMGO | 1.8E-09 M | n/a |
| **NOP *(h)* (ORL1) (agonist effect)** | | |
| nociceptin | 3.1E-11 M | n/a |
| **$OX_1$ *(h)* (agonist effect)** | | |
| orexin-A | 3.4E-10 M | n/a |
| **$OX_2$ *(h)* (agonist effect)** | | |
| orexin-B | 9.5E-10 M | n/a |
| **PAF *(h)* (agonist effect)** | | |
| PAF(C16) | 4.9E-10 M | n/a |
| **PTH1 *(h)* (agonist effect)** | | |
| PTHrP (1-34) | 1.0E-10 M | n/a |
| **$PK_1$ *(h)* (agonist effect)** | | |
| PK1 | 1.7E-09 M | n/a |
| **$PK_2$ *(h)* (agonist effect)** | | |
| PK2 | 5.3E-10 M | n/a |
| **$DP_1$ *(h)* (agonist effect)** | | |
| BW 245C | 2.2E-09 M | n/a |
| **$EP_1$ *(h)* (agonist effect)** | | |
| $PGE_2$ | 1.6E-10 M | n/a |
| **$EP_2$ *(h)* (agonist effect)** | | |
| $PGE_2$ | 1.2E-08 M | n/a |
| **EP3 *(h)* (agonist effect)** | | |
| Prostaglandin E2 | 1.2E-09 M | n/a |
| **$EP_4$ *(h)* (agonist effect)** | | |
| $PGE_2$ | 3.2E-09 M | n/a |
| **FP *(h)* (agonist effect)** | | |
| PGF2alpha | 5.2E-10 M | n/a |
| **IP ($PGI_2$) *(h)* (agonist effect)** | | |
| iloprost | 3.7E-10 M | n/a |
| **TP ($TXA_2$/$PGH_2$) *(h)* (agonist effect)** | | |
| U 44069 | 1.3E-09 M | n/a |
| **PAR1 *(h)* (agonist effect)** | | |
| TFLLR-$NH_2$ | 1.4E-06 M | n/a |
| **PAR2 *(h)* (agonist effect)** | | |
| trypsin | 1.2E-08 M | n/a |
| **P2Y1 *(h)* (agonist effect)** | | |
| 2MeSATP | 6.0E-10 M | n/a |

| Compound I.D. | $EC_{50}$ (M) | nH |
|---|---|---|
| **$CysLT_1$ ($LTD_4$) *(h)* (agonist effect)** | | |
| $LTD_4$ | 2.6E-11 M | n/a |
| **$CysLT_2$ ($LTC_4$) *(h)* (agonist effect)** | | |
| $LTC_4$ | 1.7E-09 M | n/a |
| **LPA1(h) (agonist effect)** | | |
| Oleoyl-LPA | 1.0E-07 M | n/a |
| **$LPA_2$ *(h)* (agonist effect)** | | |
| LPA | 3.8E-09 M | n/a |
| **$LPA_3$ *(h)* (agonist effect)** | | |
| LPA | 9.2E-09 M | n/a |
| **$S_1P_1$ *(h)* (agonist effect)** | | |
| S1P | 8.1E-10 M | n/a |
| **$S_1P_2$ *(h)* (agonist effect)** | | |
| $S_1P$ | 1.1E-08 M | n/a |
| **$S_1P_3$ *(h)* (agonist effect)** | | |
| $S_1P$ | 1.1E-09 M | n/a |
| **S1P4 *(h)* (agonist effect)** | | |
| Sphingosine 1-phosphate (S1P) | 5.2E-09 M | n/a |
| **S1P5 *(h)* (agonist effect)** | | |
| Sphingosine 1-phosphate (S1P) | 1.3E-08 M | n/a |
| **$MCH_1$ *(h)* (agonist effect)** | | |
| human MCH | 1.4E-09 M | n/a |
| **$MCH_2$ *(h)* (agonist effect)** | | |
| human MCH | 8.4E-10 M | n/a |
| **$MC_1$ (agonist effect)** | | |
| NDP-α-MSH | 2.5E-10 M | n/a |
| **$MC_2$ *(h)* (agonist effect)** | | |
| ACTH (1-39) | 4.2E-09 M | n/a |
| **$MC_3$ *(h)* (agonist effect)** | | |
| NDP-α-MSH | 8.2E-10 M | n/a |
| **$MC_4$ *(h)* (agonist effect)** | | |
| NDP-α-MSH | 1.0E-10 M | n/a |
| **$MC_5$ *(h)* (agonist effect)** | | |
| α-MSH | 3.9E-07 M | n/a |
| **$MT_1$ ($ML_{1A}$) *(h)* (agonist effect)** | | |
| melatonin | 3.3E-11 M | n/a |
| **$MT_2$ ($ML_{1B}$) *(h)* (agonist effect)** | | |
| melatonin | 6.5E-11 M | n/a |
| **motilin *(h)* (agonist effect)** | | |
| motilin | 8.0E-12 M | n/a |
| **$M_1$ *(h)* (agonist effect)** | | |
| acetylcholine | 9.6E-10 M | n/a |
| **$M_2$ *(h)* (agonist effect)** | | |
| acetylcholine | 6.2E-08 M | n/a |
| **$M_3$ *(h)* (agonist effect)** | | |
| acetylcholine | 1.1E-08 M | n/a |
| **$M_4$ *(h)* (agonist effect)** | | |
| acetylcholine | 1.4E-08 M | n/a |
| **$M_5$ *(h)* (agonist effect)** | | |
| Acetylcholine | 1.1E-09 M | n/a |
| **MrgD *(h)* (agonist effect)** | | |
| Beta-alanine | 1.4E-06 M | n/a |
| **MRGX1 / MRGPRX1 *(h)* (agonist effect)** | | |
| BAM(8-22) | 2.1E-09 M | n/a |
| **MRGX2 / MGRPLX2 *(h)* (agonist effect)** | | |
| Proadrenomedullin fragment, 1-20 (PAMP) | 8.5E-08 M | n/a |
| **NPS *(h)* (agonist effect)** | | |
| NPS | 6.0E-10 M | n/a |

| Compound I.D. | $EC_{50}$ (M) | nH |
|---|---|---|
| **$P2Y_2$ *(h)* (agonist effect)** | | |
| UTP | 4.4E-08 M | n/a |
| **$P2Y_4$ *(h)* (agonist effect)** | | |
| UTP | 5.6E-09 M | n/a |
| **$P2Y_6$ *(h)* (agonist effect)** | | |
| UDP | 1.1E-09 M | n/a |
| **P2Y11 *(h)* (agonist effect)** | | |
| ATP | 6.6E-06 M | n/a |
| **PTH2 *(h)* (agonist effect)** | | |
| TIP-39 | 7.0E-09 M | n/a |
| **RXFP1 *(h)* (agonist effect)** | | |
| H2 relaxin | 5.5E-10 M | n/a |
| **5-HT1A *(h)* (agonist effect)** | | |
| Serotonine | 1.5E-09 M | n/a |
| **5HT1B (h) (agonist effect)** | | |
| 5-HT | 2.1E-08 M | n/a |
| **$5\text{-}HT_{1D}$ (agonist effect)** | | |
| serotonin | 5.6E-10 M | n/a |
| **$5\text{-}HT_{2A}$ *(h)* (agonist effect)** | | |
| serotonin | 2.7E-08 M | n/a |
| **$5\text{-}HT_{2B}$ *(h)* (agonist effect)** | | |
| serotonin | 5.0E-09 M | n/a |
| **$5\text{-}HT_{2C}$ *(h)* (agonist effect)** | | |
| serotonin | 3.3E-09 M | n/a |
| **$5\text{-}HT_{4e}$ *(h)* (agonist effect)** | | |
| serotonin | 1.5E-09 M | n/a |
| **$5\text{-}HT_6$ *(h)* (agonist effect)** | | |
| serotonin | 6.0E-08 M | n/a |
| **$5\text{-}HT_7$ *(h)* (agonist effect)** | | |
| serotonin | 5.2E-08 M | n/a |
| **$sst_1$ *(h)* (agonist effect)** | | |
| somatostatin-28 | 1.3E-10 M | n/a |
| **sst2 *(h)* (agonist effect)** | | |
| Somatostatin | 7.6E-10 M | n/a |
| **sst3 *(h)* (agonist effect)** | | |
| Somatostatin | 7.7E-10 M | n/a |
| **$sst_4$ *(h)* (agonist effect)** | | |
| somatostatin-14 | 8.2E-11 M | n/a |
| **$sst_5$ *(h)* (agonist effect)** | | |
| somatostatin-14 | 6.6E-09 M | n/a |
| **SUCNR1/GPR91 *(h)* (agonist effect)** | | |
| Sodium Succinate | 6.8E-05 M | n/a |
| **$TRH_1$ *(h)* (agonist effect)** | | |
| TRH | 7.2E-11 M | n/a |
| **UT *(h)* (agonist effect)** | | |
| human urotensin-II | 7.0E-10 M | n/a |
| **$PAC_1$ (PACAP) *(h)* (agonist effect)** | | |
| $PACAP_{1-38}$ | 1.7E-10 M | n/a |
| **$VPAC_1$ ($VIP_1$) *(h)* (agonist effect)** | | |
| VIP | 1.6E-10 M | n/a |
| **$VPAC_2$ ($VIP_2$) *(h)* (agonist effect)** | | |
| VIP | 3.7E-09 M | n/a |
| **Y4 *(h)* (agonist effect)** | | |
| Pancreatic polypeptide human | 1.3E-10 M | n/a |
| **$V_{1a}$ *(h)* (agonist effect)** | | |
| AVP | 2.3E-10 M | n/a |
| **V1B *(h)* (agonist effect)** | | |
| Vasopressin | 1.2E-10 M | n/a |

**Table S3** Antagonist effect of S-CE-123 at 2.8E-06 M (IC50 for DAT re-uptake inhibition) in functional cellular assay. The results are expressed as a percent inhibition of control agonist response: 100 –((measured response /control response) x 100).

| Compound I.D. | Client Compound I.D. | Test Concentration | % Inhibition of Control Agonist Response | | |
|---|---|---|---|---|---|
| | | | 1st | 2nd | Mean |
| **A1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 6.3 | 14.9 | 10.6 |
| **$A_{2A}$ (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 20.0 | -0.7 | 9.7 |
| **$A_{2B}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -20.5 | -3.0 | -11.8 |
| **$A_3$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -6.0 | 2.3 | -1.8 |
| **$\alpha_{1A}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 4.3 | 1.9 | 3.1 |
| **$\alpha_{1B}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -25.8 | -4.5 | -15.1 |
| **alpha $_{1D}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.4 | -2.5 | -2.4 |
| **α2A *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -7.6 | -9.2 | -8.4 |
| **$\alpha_{2B}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 10.4 | -27.0 | -8.3 |
| **$\alpha_{2C}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.6 | 1.2 | 0.3 |
| **$\beta_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 28.0 | 8.9 | 18.4 |
| **$\beta_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -10.2 | 7.9 | -1.2 |
| **$\beta_3$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 22.9 | 8.1 | 15.5 |
| **$AT_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 6.5 | -0.6 | 3.0 |
| **APJ (apelin) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.9 | 13.2 | 6.2 |
| **TGR5 (h) (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.7 | 1.0 | -0.3 |
| **$BB_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -14.8 | -6.2 | -10.5 |
| **$BB_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -29.2 | -17.3 | -23.2 |
| **$BB_3$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.2 | 9.2 | 6.2 |
| **$B_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.8 | -18.1 | -10.4 |
| **$B_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -23.2 | -41.0 | -32.1 |
| **CGRP *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -37.7 | 0.2 | -18.8 |
| **CT (Calcitonin) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -36.5 | -6.9 | -21.7 |
| **CaS *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -7.9 | -4.9 | -6.4 |
| **$CB_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.3 | -3.9 | -2.1 |
| **$CB_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 8.6 | 8.6 | 8.6 |
| **CCR1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.7 | 0.7 | -1.5 |
| **CCR2 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.1 | 1.0 | 2.0 |

| Compound I.D. | Client Compound I.D. | Test Concentration | % Inhibition of Control Agonist Response | | |
|---|---|---|---|---|---|
| | | | 1st | 2nd | Mean |
| **CCR3 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -11.7 | -9.6 | -10.7 |
| **CCR4 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -5.5 | -6.1 | -5.8 |
| **CCR5 (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 18.7 | 34.7 | 26.7 |
| **CCR6 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -33.1 | -20.3 | -26.7 |
| **CCR7 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -4.0 | 9.6 | 2.8 |
| **CCR8 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -20.5 | -19.2 | -19.9 |
| **CCR10 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -14.8 | 0.9 | -6.9 |
| **CX3CR1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -17.2 | -14.5 | -15.8 |
| **CXCR1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -6.6 | -19.5 | -13.0 |
| **CXCR2 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.2 | 7.9 | 3.8 |
| **CXCR3 (h) (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.4 | -6.1 | -7.8 |
| **CXCR4 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -62.8 | -18.6 | -40.7 |
| **CXCR5 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.8 | -3.0 | -1.9 |
| **CXCR6 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -10.8 | -4.4 | -7.6 |
| **$CCK_1$ ($CCK_A$) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 28.8 | 7.7 | 18.2 |
| **$CCK_2$ ($CCK_B$) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -19.7 | 5.9 | -6.9 |
| **C3aR *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 2.3 | 20.5 | 11.4 |
| **ChemR23 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -5.3 | 2.0 | -1.6 |
| **$CRF_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -13.8 | -19.9 | -16.9 |
| **$CRF_{2\alpha}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 5.7 | 36.6 | 21.1 |
| **XCR1 / GPR5 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -15.3 | -3.1 | -9.2 |
| **$D_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -15.8 | 4.6 | -5.6 |
| **$D_{2S}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 23.8 | 12.5 | 18.1 |
| **$D_3$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 7.1 | -10.9 | -1.9 |
| **$D_{4.4}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.6 | -6.1 | -7.9 |
| **$D_5$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 11.0 | -32.6 | -10.8 |
| **$ET_A$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.3 | 2.4 | -0.5 |
| **$ET_B$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -4.6 | 7.6 | 1.5 |

| Compound I.D. | Client Compound I.D. | Test Concentration | % Inhibition of Control Agonist Response | | |
|---|---|---|---|---|---|
| | | | 1st | 2nd | Mean |
| **FFA1 *(h)* (GPR40) (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.5 | -4.1 | -2.8 |
| **FFA2 *(h)* (GPR43) (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.2 | 4.6 | 2.9 |
| **FFA3 *(h)* (GPR41) (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.9 | -1.8 | -1.4 |
| **FFA4 (GPR120) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -12.9 | -15.9 | -14.4 |
| **GnRH *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 4.4 | 3.4 | 3.9 |
| **GPR39 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 8.6 | -5.3 | 1.6 |
| **OXGR1 GPR99 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -7.4 | -12.9 | -10.2 |
| **GPR103/QRFP *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -10.3 | -7.4 | -8.8 |
| **GPR109A *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -13.5 | -9.8 | -11.6 |
| **GPR119 (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.8 | -1.8 | -5.8 |
| **FPR1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.3 | -0.1 | 1.6 |
| **GABAB1b beta *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.1 | -22.3 | -10.6 |
| **GAL1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.8 | 3.9 | 2.3 |
| **$GAL_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.0 | -0.5 | -4.8 |
| **GIP *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -6.2 | -7.0 | -6.6 |
| **GLP-1 (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -27.8 | -37.0 | -32.4 |
| **secretin *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 5.7 | 29.6 | 17.6 |
| **TSH *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 8.9 | -21.2 | -6.1 |
| **GHRH *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 28.8 | -5.4 | 11.7 |
| **Ghrelin / GHSR-1a *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -14.6 | -8.7 | -11.7 |
| **$H_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.0 | -2.8 | -1.9 |
| **$H_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.7 | -2.0 | -2.4 |
| **$H_3$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.4 | 0.8 | -0.3 |
| **$H_4$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 4.4 | 2.4 | 3.4 |
| **KiSS1 / GPR54 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.5 | -2.0 | -2.8 |
| **$BLT_1$ ($LTB_4$) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -4.9 | -4.6 | -4.7 |
| **$CysLT_1$ ($LTD_4$) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.2 | -16.7 | -12.9 |
| **$CysLT_2$ ($LTC_4$) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 4.2 | 4.8 | 4.5 |

| Compound I.D. | Client Compound I.D. | Test Concentration | % Inhibition of Control Agonist Response | | |
|---|---|---|---|---|---|
| | | | 1st | 2nd | Mean |
| **LPA1(h) (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.4 | 9.2 | 4.4 |
| **$LPA_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -12.7 | -9.1 | -10.9 |
| **$LPA_3$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -22.3 | -46.4 | -34.4 |
| **$S_1P_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 5.0 | 6.7 | 5.9 |
| **$S_1P_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -10.4 | -0.1 | -5.2 |
| **$S_1P_3$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 13.9 | 10.5 | 12.2 |
| **S1P4 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -14.2 | -14.9 | -14.6 |
| **S1P5 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 10.1 | -2.8 | 3.7 |
| **$MCH_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.7 | -0.2 | -0.9 |
| **$MCH_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.8 | 4.4 | 3.1 |
| **$MC_1$ (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -27.7 | -24.3 | -26.0 |
| **$MC_3$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -0.1 | 6.2 | 3.1 |
| **$MC_3$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -25.9 | 10.3 | -7.8 |
| **$MC_4$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -11.0 | 15.7 | 2.3 |
| **$MC_5$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 5.8 | -23.6 | -8.9 |
| **$MT_1$ ($ML_{1A}$) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 7.6 | 7.6 | 7.6 |
| **$MT_2$ ($ML_{1B}$) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 2.3 | 10.2 | 6.2 |
| **motilin *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.5 | -0.9 | -5.2 |
| **$M_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 2.0 | 3.2 | 2.6 |
| **$M_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.4 | -15.0 | -9.2 |
| **$M_3$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 4.1 | -2.5 | 0.8 |
| **$M_4$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -8.8 | -8.2 | -8.5 |
| **$M_5$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -5.2 | -6.6 | -5.9 |
| **MrgD *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 26.9 | 33.0 | 30.0 |
| **MRGX1 / MRGPRX1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 6.4 | 3.4 | 4.9 |
| **MRGX2 / MGRPLX2 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 9.6 | 4.5 | 7.1 |
| **NPS *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -13.9 | -14.7 | -14.3 |
| **NPBW1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.1 | -4.0 | -1.9 |

| Compound I.D. | Client Compound I.D. | Test Concentration | % Inhibition of Control Agonist Response | | |
|---|---|---|---|---|---|
| | | | 1st | 2nd | Mean |
| **$NK_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -11.5 | 1.0 | -5.3 |
| **$NK_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -1.4 | -0.2 | -0.8 |
| **$NK_3$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -10.2 | -0.1 | -5.1 |
| **NMU1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -25.8 | -16.8 | -21.3 |
| **NMU2 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -17.1 | -18.4 | -17.7 |
| **$NTS_1$ ($NT_1$) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -19.0 | -1.0 | -10.0 |
| **$NTS_2$ (NT2) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 26.2 | 19.6 | 22.9 |
| **δ (DOP) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.2 | -3.3 | -2.8 |
| **κ (KOP) (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 12.8 | 2.8 | 7.8 |
| **μ (MOP) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.2 | 12.2 | 5.0 |
| **NOP *(h)* (ORL1) (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 19.3 | 17.6 | 18.4 |
| **$OX_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -16.5 | -12.5 | -14.5 |
| **$OX_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.7 | 4.7 | 4.2 |
| **PAF *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -38.5 | -39.8 | -39.1 |
| **PTH1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -11.0 | -10.2 | -10.6 |
| **$PK_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 12.9 | -7.9 | 2.5 |
| **$PK_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.5 | 11.1 | 7.3 |
| **$DP_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.7 | 4.7 | -2.5 |
| **$EP_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -13.9 | -9.8 | -11.9 |
| **$EP_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -11.0 | 12.3 | 0.7 |
| **EP3 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -33.0 | -28.7 | -30.8 |
| **$EP_4$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.8 | -0.3 | -1.5 |
| **FP *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 7.8 | 5.6 | 6.7 |
| **IP ($PGI_2$) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 23.9 | 8.7 | 16.3 |
| **TP ($TXA_2$/$PGH_2$) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 0.7 | 4.3 | 2.5 |
| **PAR1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.3 | 3.0 | 2.1 |
| **PAR2 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -17.9 | -20.9 | -19.4 |
| **P2Y1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -6.6 | -6.8 | -6.7 |

| Compound I.D. | Client Compound I.D. | Test Concentration | % Inhibition of Control Agonist Response 1st | 2nd | Mean |
|---|---|---|---|---|---|
| **$P2Y_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -29.4 | -12.2 | -20.8 |
| **$P2Y_4$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.2 | -3.8 | -3.5 |
| **$P2Y_6$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 5.6 | 1.8 | 3.7 |
| **P2Y11 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 2.9 | -4.1 | -0.6 |
| **PTH2 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -2.4 | -1.3 | -1.9 |
| **RXFP1 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 21.4 | -19.4 | 1.0 |
| **5-HT1A *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.6 | -6.7 | -8.2 |
| **5HT1B (h) (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -12.7 | -9.8 | -11.3 |
| **$5\text{-}HT_{1D}$ (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -3.8 | 1.9 | -0.9 |
| **$5\text{-}HT_{2A}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.3 | -1.2 | -5.2 |
| **$5\text{-}HT_{2B}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 8.7 | -0.6 | 4.1 |
| **$5\text{-}HT_{2C}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 6.4 | -5.5 | 0.4 |
| **$5\text{-}HT_{4e}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 34.4 | 18.8 | 26.6 |
| **$5\text{-}HT_6$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -12.0 | 14.9 | 1.4 |
| **$5\text{-}HT_7$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 2.0 | 0.5 | 1.3 |
| **$sst_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.9 | -3.3 | -6.6 |
| **sst2 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 1.5 | -13.1 | -5.8 |
| **sst3 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -4.5 | -6.3 | -5.4 |
| **$sst_4$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 16.0 | 2.4 | 9.2 |
| **$sst_5$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -5.6 | 2.7 | -1.4 |
| **SUCNR1/GPR91 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -9.9 | -6.0 | -7.9 |
| **$TRH_1$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 3.0 | 7.2 | 5.1 |
| **UT *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 14.5 | 10.7 | 12.6 |
| **$PAC_1$ (PACAP) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 20.9 | 38.9 | 29.9 |
| **$VPAC_1$ ($VIP_1$) *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 19.4 | 8.5 | 13.9 |
| **Y4 *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -10.2 | -4.2 | -7.2 |
| **$V_{1a}$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -19.2 | -16.1 | -17.6 |
| **V1B *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | -4.6 | -7.1 | -5.9 |
| **$V_2$ *(h)* (antagonist effect)** | | | | | |
| 100043705-1 | S-CE-123 | 2.8E-06 M | 25.0 | 15.1 | 20.1 |

**Table S4** Reference compounds for **antagonist effect.**

| Compound I.D. | $IC_{50}$ (M) | $K_B$ (M) | nH |
|---|---|---|---|
| **A1 *(h)* (antagonist effect)** | | | |
| DPCPX | 5.1E-09 M | 1.2E-09 M | n/a |
| **$A_{2A}$ (antagonist effect)** | | | |
| ZM 241385 | 6.9E-10 M | 7.4E-11 M | n/a |
| **$A_{2B}$ *(h)* (antagonist effect)** | | | |
| XAC | 2.2E-07 M | 2.7E-08 M | n/a |
| **$A_3$ *(h)* (antagonist effect)** | | | |
| MRS 1220 | 6.4E-09 M | 3.0E-10 M | n/a |
| **$\alpha_{1A}$ *(h)* (antagonist effect)** | | | |
| WB 4101 | 1.7E-09 M | 2.3E-10 M | n/a |
| **$\alpha_{1B}$ *(h)* (antagonist effect)** | | | |
| L765314 | 8.5E-09 M | 9.1E-10 M | n/a |
| **alpha $_{1D}$ *(h)* (antagonist effect)** | | | |
| WB4101 | 2.9E-09 M | 8.3E-10 M | n/a |
| **α2A *(h)* (antagonist effect)** | | | |
| RX 821002 | 1.1E-08 M | 3.6E-09 M | n/a |
| **$\alpha_{2B}$ *(h)* (antagonist effect)** | | | |
| yohimbine | 4.0E-07 M | 5.2E-08 M | n/a |
| **$\alpha_{2C}$ *(h)* (antagonist effect)** | | | |
| rauwolscine | 3.6E-08 M | 1.7E-09 M | n/a |
| **$\beta_1$ *(h)* (antagonist effect)** | | | |
| atenolol | 2.3E-07 M | 2.8E-08 M | n/a |
| **$\beta_2$ *(h)* (antagonist effect)** | | | |
| ICI 118551 | 3.0E-09 M | 2.8E-10 M | n/a |
| **$\beta_3$ *(h)* (antagonist effect)** | | | |
| cyanopindolol | 4.0E-07 M | 1.4E-07 M | n/a |
| **$AT_1$ *(h)* (antagonist effect)** | | | |
| saralasin | 1.0E-09 M | 8.5E-11 M | n/a |
| **$BB_1$ *(h)* (antagonist effect)** | | | |
| PD 168368 | 2.2E-07 M | 5.3E-09 M | n/a |
| **$BB_2$ *(h)* (antagonist effect)** | | | |
| ICI 216,140 | 5.3E-07 M | 6.9E-08 M | n/a |
| **$B_1$ *(h)* (antagonist effect)** | | | |
| LysdesArg$^9$[Leu$^8$]-BK | 1.9E-10 M | 4.0E-11 M | n/a |
| **$B_2$ *(h)* (antagonist effect)** | | | |
| HOE 140 | 3.1E-08 M | 3.6E-09 M | n/a |
| **CGRP *(h)* (antagonist effect)** | | | |
| hCGRPα (8-37) | 4.5E-08 M | 7.7E-09 M | n/a |
| **CT (Calcitonin) *(h)* (antagonist effect)** | | | |
| salmon calcitonin 8-32 | 6.9E-08 M | 4.1E-09 M | n/a |
| **$CB_1$ *(h)* (antagonist effect)** | | | |
| AM 281 | 1.0E-08 M | 1.1E-09 M | n/a |
| **$CB_2$ *(h)* (antagonist effect)** | | | |
| AM 630 | 7.4E-07 M | 4.9E-08 M | n/a |
| **CCR1 *(h)* (antagonist effect)** | | | |
| J113863 | 6.2E-09 M | 1.0E-09 M | n/a |
| **CCR2 *(h)* (antagonist effect)** | | | |
| MIP-II | 2.6E-07 M | 2.1E-08 M | n/a |
| **CCR3 *(h)* (antagonist effect)** | | | |
| J113863 | 3.4E-09 M | 7.6E-10 M | n/a |

| Compound I.D. | $IC_{50}$ (M) | $K_B$ (M) | nH |
|---|---|---|---|
| **CXCR2 *(h)* (antagonist effect)** | | | |
| SB225002 | 1.7E-06 M | 1.6E-07 M | n/a |
| **CXCR4 *(h)* (antagonist effect)** | | | |
| MIP II | 6.5E-08 M | 1.6E-09 M | n/a |
| **$CCK_1$ ($CCK_A$) *(h)* (antagonist effect)** | | | |
| devazepide | 1.1E-10 M | 1.2E-11 M | n/a |
| **$CCK_2$ ($CCK_B$) *(h)* (antagonist effect)** | | | |
| YM022 | 6.0E-10 M | 7.3E-11 M | n/a |
| **C3aR *(h)* (antagonist effect)** | | | |
| SB290157 | 2.4E-06 M | 8.1E-08 M | n/a |
| **$CRF_1$ *(h)* (antagonist effect)** | | | |
| antalarmine | 9.6E-08 M | 3.4E-08 M | n/a |
| **$CRF_{2\ a}$ *(h)* (antagonist effect)** | | | |
| astressin | 4.9E-08 M | 4.8E-09 M | n/a |
| **$D_1$ *(h)* (antagonist effect)** | | | |
| SCH 23390 | 2.5E-09 M | 4.1E-10 M | n/a |
| **$D_{2S}$ *(h)* (antagonist effect)** | | | |
| butaclamol | 8.3E-09 M | 5.4E-10 M | n/a |
| **$D_3$ *(h)* (antagonist effect)** | | | |
| (+)butaclamol | 1.2E-08 M | 1.5E-09 M | n/a |
| **$D_{4.4}$ *(h)* (antagonist effect)** | | | |
| clozapine | 1.2E-07 M | 1.5E-08 M | n/a |
| **$D_5$ *(h)* (antagonist effect)** | | | |
| SCH 23390 | 1.3E-09 M | 3.9E-10 M | n/a |
| **$ET_A$ *(h)* (antagonist effect)** | | | |
| BQ-123 | 3.3E-10 M | 3.0E-11 M | n/a |
| **$ET_B$ *(h)* (antagonist effect)** | | | |
| BQ-788 | 3.6E-08 M | 9.6E-09 M | n/a |
| **GnRH *(h)* (antagonist effect)** | | | |
| Cetrorelix | 3.0E-09 M | 4.8E-10 M | n/a |
| **GABAB1b beta *(h)* (antagonist effect)** | | | |
| CGP55845A | 2.5E-09 M | 2.6E-10 M | n/a |
| **GLP-1 (antagonist effect)** | | | |
| exendin-3(9-39) | 3.1E-09 M | 5.9E-10 M | n/a |
| **GHRH *(h)* (antagonist effect)** | | | |
| [N-Acetyl-$Tyr^1$,D-$Arg^2$]-GHRF | 2.1E-08 M | 4.6E-09 M | n/a |
| **Ghrelin / GHSR-1a *(h)* (antagonist effect)** | | | |
| Substance P | 3.8E-08 M | 7.1E-09 M | n/a |
| **$H_1$ *(h)* (antagonist effect)** | | | |
| pyrilamine | 6.7E-09 M | 1.6E-09 M | n/a |
| **$H_2$ *(h)* (antagonist effect)** | | | |
| cimetidine | 5.9E-06 M | 9.1E-07 M | n/a |
| **$H_3$ *(h)* (antagonist effect)** | | | |
| thioperamide | 2.1E-06 M | 6.1E-08 M | n/a |
| **$H_4$ *(h)* (antagonist effect)** | | | |
| JNJ 7777120 | 3.9E-08 M | 2.3E-09 M | n/a |
| **$CysLT_1$ ($LTD_4$) *(h)* (antagonist effect)** | | | |
| MK 571 | 4.2E-10 M | 9.7E-11 M | n/a |
| **LPA1(h) (antagonist effect)** | | | |
| KI16425 | 7.6E-08 M | 6.9E-09 M | n/a |
| **$S_1P_1$ *(h)* (antagonist effect)** | | | |
| VPC23019 | 5.1E-08 M | 1.1E-08 M | n/a |
| **$S_1P_2$ *(h)* (antagonist effect)** | | | |
| JTE 013 | 4.8E-09 M | 1.0E-09 M | n/a |
| **$MC_1$ (antagonist effect)** | | | |
| AGRP (83-132) | 2.5E-07 M | 9.3E-09 M | n/a |
| **$MC_3$ *(h)* (antagonist effect)** | | | |
| SHU 9119 | 3.4E-08 M | 6.4E-10 M | n/a |

| Compound I.D. | $IC_{50}$ (M) | $K_e$ (M) | nH |
|---|---|---|---|
| **$MC_4$ *(h)* (antagonist effect)** | | | |
| SHU 9119 | 7.3E-10 M | 7.5E-11 M | n/a |
| **$MC_5$ *(h)* (antagonist effect)** | | | |
| AGRP (83-132) | 1.4E-07 M | 3.9E-08 M | n/a |
| **$MT_1$ ($ML_{1A}$) *(h)* (antagonist effect)** | | | |
| luzindole | 1.8E-06 M | 1.7E-07 M | n/a |
| **$M_1$ *(h)* (antagonist effect)** | | | |
| pirenzepine | 2.9E-08 M | 3.4E-09 M | n/a |
| **$M_2$ *(h)* (antagonist effect)** | | | |
| methoctramine | 1.4E-07 M | 1.6E-08 M | n/a |
| **$M_3$ *(h)* (antagonist effect)** | | | |
| 4-DAMP | 5.2E-09 M | 4.7E-10 M | n/a |
| **$M_4$ *(h)* (antagonist effect)** | | | |
| PD 102807 | 9.3E-08 M | 8.4E-09 M | n/a |
| **$M_5$ *(h)* (antagonist effect)** | | | |
| Atropine | 2.4E-09 M | 2.2E-10 M | n/a |
| **NPS *(h)* (antagonist effect)** | | | |
| SHA68 | 4.7E-08 M | 1.3E-09 M | n/a |
| **$NK_1$ *(h)* (antagonist effect)** | | | |
| L 733,060 | 1.2E-09 M | 1.8E-10 M | n/a |
| **$NK_2$ *(h)* (antagonist effect)** | | | |
| GR 159897 | 8.4E-10 M | 1.1E-10 M | n/a |
| **$NK_3$ *(h)* (antagonist effect)** | | | |
| SB 222200 | 4.2E-08 M | 3.8E-09 M | n/a |
| **$NTS_1$ ($NT_1$) *(h)* (antagonist effect)** | | | |
| SR142948 | 2.9E-08 M | 2.6E-09 M | n/a |
| **$NTS_2$ (NT2) *(h)* (antagonist effect)** | | | |
| neurotensin | 2.3E-07 M | 4.6E-08 M | n/a |
| **δ (DOP) *(h)* (antagonist effect)** | | | |
| Naltriben | 7.7E-09 M | 1.1E-09 M | n/a |
| **κ (KOP) (antagonist effect)** | | | |
| nor-BNI | 7.8E-10 M | 1.3E-10 M | n/a |
| **μ (MOP) *(h)* (antagonist effect)** | | | |
| CTOP | 7.9E-08 M | 7.2E-09 M | n/a |
| **NOP *(h)* (ORL1) (antagonist effect)** | | | |
| UFP-101 | 1.5E-07 M | 4.0E-08 M | n/a |
| **$OX_1$ *(h)* (antagonist effect)** | | | |
| SB 334867 | 5.8E-08 M | 1.2E-08 M | n/a |
| **$OX_2$ *(h)* (antagonist effect)** | | | |
| JNJ 10397049 | 9.5E-08 M | 1.3E-08 M | n/a |
| **PTH1 *(h)* (antagonist effect)** | | | |
| PTHrP (7-34) | 2.2E-07 M | 2.8E-08 M | n/a |
| **$DP_1$ *(h)* (antagonist effect)** | | | |
| MK0524 | 1.8E-09 M | 3.5E-10 M | n/a |
| **$EP_1$ *(h)* (antagonist effect)** | | | |
| SC 51322 | 2.6E-08 M | 4.1E-09 M | n/a |
| **$EP_2$ *(h)* (antagonist effect)** | | | |
| AH 6809 | 2.7E-06 M | 8.6E-07 M | n/a |
| **EP3 *(h)* (antagonist effect)** | | | |
| L798.106 | 4.4E-10 M | 7.3E-11 M | n/a |
| **$EP_4$ *(h)* (antagonist effect)** | | | |
| GW627368X | 7.7E-08 M | 7.3E-09 M | n/a |
| **IP ($PGI_2$) *(h)* (antagonist effect)** | | | |
| CAY10441 | 3.3E-08 M | 4.6E-09 M | n/a |
| **TP ($TXA_2$/$PGH_2$) *(h)* (antagonist effect)** | | | |
| L 670596 | 1.4E-09 M | 2.0E-10 M | n/a |
| **PAR1 *(h)* (antagonist effect)** | | | |
| SCH 79797 | 1.8E-06 M | 2.5E-07 M | n/a |

| Compound I.D. | $IC_{50}$ (M) | $K_B$ (M) | nH |
|---|---|---|---|
| **P2Y1 *(h)* (antagonist effect)** | | | |
| MRS 2500 | 1.9E-09 M | 4.3E-10 M | n/a |
| **$P2Y_2$ *(h)* (antagonist effect)** | | | |
| AR-C 118925XX | 3.9E-07 M | 6.6E-08 M | n/a |
| **5-HT1A *(h)* (antagonist effect)** | | | |
| (S)-WAY-100635 | 5.2E-09 M | 1.1E-09 M | n/a |
| **5HT1B (h) (antagonist effect)** | | | |
| GR55562 | 6.9E-08 M | 1.1E-08 M | n/a |
| **5-$HT_{1D}$ (antagonist effect)** | | | |
| methiothepin | 1.7E-07 M | 1.1E-08 M | n/a |
| **5-$HT_{2A}$ *(h)* (antagonist effect)** | | | |
| ketanserin | 6.5E-09 M | 1.3E-09 M | n/a |
| **5-$HT_{2B}$ *(h)* (antagonist effect)** | | | |
| SB 206553 | 1.9E-08 M | 2.9E-09 M | n/a |
| **5-$HT_{2C}$ *(h)* (antagonist effect)** | | | |
| SB 206553 | 1.3E-08 M | 2.9E-09 M | n/a |
| **5-$HT_{4e}$ *(h)* (antagonist effect)** | | | |
| GR 113808 | 3.8E-10 M | 5.6E-11 M | n/a |
| **5-$HT_6$ *(h)* (antagonist effect)** | | | |
| methiothepin | 6.3E-09 M | 9.8E-10 M | n/a |
| **5-$HT_7$ *(h)* (antagonist effect)** | | | |
| methiothepin | 1.1E-09 M | 1.3E-10 M | n/a |
| **$PAC_1$ (PACAP) *(h)* (antagonist effect)** | | | |
| $PACAP_{6-38}$ | 2.1E-08 M | 7.8E-09 M | n/a |
| **$VPAC_1$ ($VIP_1$) *(h)* (antagonist effect)** | | | |
| VIP $GRF_{8-27}$ | 9.0E-08 M | 1.8E-08 M | n/a |
| **$V_{1a}$ *(h)* (antagonist effect)** | | | |
| [d($CH_2$)$_5$ $^1$,Tyr(Me)$_2$]-AVP | 5.3E-09 M | 1.8E-10 M | n/a |
| **$V_2$ *(h)* (antagonist effect)** | | | |
| [adamantaneacetyl$^1$,O-Et-D-Tyr$^2$,Val$^4$,aminobutyryl$^6$]-AVP | 3.0E-08 M | 9.1E-09 M | n/a |

## Kinase binding assays

This study was outsourced to DiscoverX (KINOMEscan®, Freemont, CA, USA) and is compliant with the corresponding project BUY004-01-p-00001.

**Table S5** A list of the 450 protein and lipid kinases representative of all major human kinase families tested as potential targets of S-CE-123 at 2.8E-06 M ($IC_{50}$ for DAT re-uptake inhibition) *in vitro* binding assay. Results are reported as percent control (% Ctrl), where lower numbers indicate stronger hits in the matrix on the following page(s). %Ctrl calculation: ((test compound signal-positive control signal) / (negative control signal – positive control signal)) x 100.

| Target | S-CE-123 |
|---|---|
| Gene Symbol | %Ctrl @ 2800nM |
| AAK1 | 88 |
| ABL1(E255K)-phosphorylated | 73 |
| ABL1(F317I)-nonphosphorylated | 100 |
| ABL1(F317I)-phosphorylated | 92 |
| ABL1(F317L)-nonphosphorylated | 100 |
| ABL1(F317L)-phosphorylated | 100 |
| ABL1(H396P)-nonphosphorylated | 86 |
| ABL1(H396P)-phosphorylated | 90 |
| ABL1(M351T)-phosphorylated | 100 |
| ABL1(Q252H)-nonphosphorylated | 66 |
| ABL1(Q252H)-phosphorylated | 84 |
| ABL1(T315I)-nonphosphorylated | 100 |
| ABL1(T315I)-phosphorylated | 98 |
| ABL1(Y253F)-phosphorylated | 93 |
| ABL1-nonphosphorylated | 93 |
| ABL1-phosphorylated | 100 |
| ABL2 | 99 |
| ACVR1 | 99 |
| ACVR1B | 100 |
| ACVR2A | 100 |
| ACVR2B | 100 |
| ACVRL1 | 84 |
| ADCK3 | 87 |
| ADCK4 | 96 |
| AKT1 | 99 |
| AKT2 | 87 |
| AKT3 | 99 |
| ALK | 100 |
| ALK(C1156Y) | 100 |
| ALK(L1196M) | 100 |
| AMPK-alpha1 | 92 |
| AMPK-alpha2 | 97 |
| ANKK1 | 100 |
| ARK5 | 100 |
| ASK1 | 84 |
| ASK2 | 100 |
| AURKA | 91 |
| AURKB | 78 |
| AURKC | 100 |
| AXL | 96 |
| BIKE | 97 |
| BLK | 90 |
| BMPR1A | 100 |
| BMPR1B | 100 |
| BMPR2 | 100 |
| BMX | 57 |
| BRAF | 100 |
| BRAF(V600E) | 100 |

| Target | S-CE-123 |
|---|---|
| Gene Symbol | %Ctrl @ 2800nM |
| BRK | 96 |
| BRSK1 | 100 |
| BRSK2 | 100 |
| BTK | 100 |
| BUB1 | 100 |
| CAMK1 | 97 |
| CAMK1B | 100 |
| CAMK1D | 96 |
| CAMK1G | 82 |
| CAMK2A | 93 |
| CAMK2B | 87 |
| CAMK2D | 88 |
| CAMK2G | 95 |
| CAMK4 | 91 |
| CAMKK1 | 95 |
| CAMKK2 | 94 |
| CASK | 82 |
| CDC2L1 | 95 |
| CDC2L2 | 98 |
| CDC2L5 | 98 |
| CDK11 | 71 |
| CDK2 | 94 |
| CDK3 | 100 |
| CDK4 | 100 |
| CDK4-cyclinD1 | 100 |
| CDK4-cyclinD3 | 85 |
| CDK5 | 97 |
| CDK7 | 70 |
| CDK8 | 96 |
| CDK9 | 92 |
| CDKL1 | 100 |
| CDKL2 | 89 |
| CDKL3 | 81 |
| CDKL5 | 97 |
| CHEK1 | 89 |
| CHEK2 | 78 |
| CIT | 74 |
| CLK1 | 96 |
| CLK2 | 93 |
| CLK3 | 95 |
| CLK4 | 100 |
| CSF1R | 76 |
| CSF1R-autoinhibited | 100 |
| CSK | 98 |
| CSNK1A1 | 74 |
| CSNK1A1L | 100 |
| CSNK1D | 100 |
| CSNK1E | 96 |
| CSNK1G1 | 96 |

| Target | S-CE-123 |
|---|---|
| Gene Symbol | %Ctrl @ 2800nM |
| CSNK1G2 | 94 |
| CSNK1G3 | 98 |
| CSNK2A1 | 88 |
| CSNK2A2 | 100 |
| CTK | 51 |
| DAPK1 | 91 |
| DAPK2 | 96 |
| DAPK3 | 96 |
| DCAMKL1 | 100 |
| DCAMKL2 | 97 |
| DCAMKL3 | 96 |
| DDR1 | 100 |
| DDR2 | 100 |
| DLK | 100 |
| DMPK | 96 |
| DMPK2 | 88 |
| DRAK1 | 95 |
| DRAK2 | 95 |
| DYRK1A | 96 |
| DYRK1B | 40 |
| DYRK2 | 86 |
| EGFR | 92 |
| EGFR(E746-A750del) | 93 |
| EGFR(G719C) | 74 |
| EGFR(G719S) | 77 |
| EGFR(L747-E749del, A750P) | 93 |
| EGFR(L747-S752del, P753S) | 96 |
| EGFR(L747-T751del,Sins) | 57 |
| EGFR(L858R) | 92 |
| EGFR(L858R,T790M) | 99 |
| EGFR(L861Q) | 98 |
| EGFR(S752-I759del) | 66 |
| EGFR(T790M) | 98 |
| EIF2AK1 | 100 |
| EPHA1 | 96 |
| EPHA2 | 73 |
| EPHA3 | 97 |
| EPHA4 | 97 |
| EPHA5 | 86 |
| EPHA6 | 100 |
| EPHA7 | 96 |
| EPHA8 | 100 |
| EPHB1 | 100 |
| EPHB2 | 89 |
| EPHB3 | 100 |
| EPHB4 | 95 |
| EPHB6 | 89 |
| ERBB2 | 100 |
| ERBB3 | 89 |

%Ctrl Legend

| 0≤x<.1 | .1≤x<1 | 1≤x<10 | 10≤x<35 | x≥35 |
|---|---|---|---|---|

| Target | S-CE-123 |
|---|---|
| Gene Symbol | %Ctrl @ 2800nM |
| ERBB4 | 96 |
| ERK1 | 91 |
| ERK2 | 95 |
| ERK3 | 93 |
| ERK4 | 100 |
| ERK5 | 91 |
| ERK8 | 100 |
| ERN1 | 86 |
| FAK | 100 |
| FER | 100 |
| FES | 95 |
| FGFR1 | 100 |
| FGFR2 | 87 |
| FGFR3 | 91 |
| FGFR3(G697C) | 96 |
| FGFR4 | 100 |
| FGR | 100 |
| FLT1 | 100 |
| FLT3 | 96 |
| FLT3(D835H) | 58 |
| FLT3(D835V) | 100 |
| FLT3(D835Y) | 99 |
| FLT3(ITD) | 100 |
| FLT3(ITD,D835V) | 100 |
| FLT3(ITD,F691L) | 50 |
| FLT3(K663Q) | 96 |
| FLT3(N841I) | 91 |
| FLT3(R834Q) | 90 |
| FLT3-autoinhibited | 99 |
| FLT4 | 100 |
| FRK | 96 |
| FYN | 93 |
| GAK | 100 |
| GCN2(Kin.Dom.2,S808G) | 100 |
| GRK1 | 100 |
| GRK2 | 100 |
| GRK3 | 100 |
| GRK4 | 73 |
| GRK7 | 90 |
| GSK3A | 99 |
| GSK3B | 92 |
| HASPIN | 95 |
| HCK | 99 |
| HIPK1 | 90 |
| HIPK2 | 100 |
| HIPK3 | 91 |
| HIPK4 | 100 |
| HPK1 | 89 |
| HUNK | 100 |

| Target | S-CE-123 |
|---|---|
| Gene Symbol | %Ctrl @ 2800nM |
| ICK | 91 |
| IGF1R | 94 |
| IKK-alpha | 100 |
| IKK-beta | 96 |
| IKK-epsilon | 98 |
| INSR | 100 |
| INSRR | 94 |
| IRAK1 | 91 |
| IRAK3 | 96 |
| IRAK4 | 94 |
| ITK | 100 |
| JAK1(JH1domain-catalytic) | 93 |
| JAK1(JH2domain-pseudokinase) | 92 |
| JAK2(JH1domain-catalytic) | 100 |
| JAK3(JH1domain-catalytic) | 100 |
| JNK1 | 67 |
| JNK2 | 90 |
| JNK3 | 74 |
| KIT | 97 |
| KIT(A829P) | 98 |
| KIT(D816H) | 100 |
| KIT(D816V) | 97 |
| KIT(L576P) | 99 |
| KIT(V559D) | 97 |
| KIT(V559D,T670I) | 83 |
| KIT(V559D,V654A) | 100 |
| KIT-autoinhibited | 86 |
| LATS1 | 93 |
| LATS2 | 100 |
| LCK | 100 |
| LIMK1 | 98 |
| LIMK2 | 88 |
| LKB1 | 100 |
| LOK | 95 |
| LRRK2 | 100 |
| LRRK2(G2019S) | 96 |
| LTK | 93 |
| LYN | 83 |
| LZK | 94 |
| MAK | 94 |
| MAP3K1 | 85 |
| MAP3K15 | 84 |
| MAP3K2 | 100 |
| MAP3K3 | 86 |
| MAP3K4 | 84 |
| MAP4K2 | 100 |
| MAP4K3 | 100 |
| MAP4K4 | 100 |
| MAP4K5 | 95 |

| Target | S-CE-123 |
|---|---|
| Gene Symbol | %Ctrl @ 2800nM |
| MAPKAPK2 | 99 |
| MAPKAPK5 | 100 |
| MARK1 | 93 |
| MARK2 | 100 |
| MARK3 | 70 |
| MARK4 | 98 |
| MAST1 | 94 |
| MEK1 | 94 |
| MEK2 | 93 |
| MEK3 | 86 |
| MEK4 | 100 |
| MEK5 | 98 |
| MEK6 | 89 |
| MELK | 67 |
| MERTK | 63 |
| MET | 99 |
| MET(M1250T) | 99 |
| MET(Y1235D) | 99 |
| MINK | 87 |
| MKK7 | 100 |
| MKNK1 | 96 |
| MKNK2 | 69 |
| MLCK | 96 |
| MLK1 | 100 |
| MLK2 | 96 |
| MLK3 | 100 |
| MRCKA | 95 |
| MRCKB | 98 |
| MST1 | 97 |
| MST1R | 93 |
| MST2 | 80 |
| MST3 | 87 |
| MST4 | 100 |
| MTOR | 100 |
| MUSK | 100 |
| MYLK | 96 |
| MYLK2 | 99 |
| MYLK4 | 89 |
| MYO3A | 96 |
| MYO3B | 52 |
| NDR1 | 83 |
| NDR2 | 82 |
| NEK1 | 90 |
| NEK10 | 100 |
| NEK11 | 100 |
| NEK2 | 96 |
| NEK3 | 100 |
| NEK4 | 83 |
| NEK5 | 90 |

%Ctrl Legend

| 0≤x<.1 | .1≤x<1 | 1≤x<10 | 10≤x<35 | x≥35 |
|---|---|---|---|---|

| Target | S-CE-123 |
|---|---|
| Gene Symbol | %Ctrl @ 2800nM |
| NEK6 | 100 |
| NEK7 | 100 |
| NEK9 | 100 |
| NIK | 100 |
| NIM1 | 97 |
| NLK | 97 |
| OSR1 | 90 |
| p38-alpha | 100 |
| p38-beta | 94 |
| p38-delta | 95 |
| p38-gamma | 100 |
| PAK1 | 92 |
| PAK2 | 77 |
| PAK3 | 70 |
| PAK4 | 98 |
| PAK6 | 100 |
| PAK7 | 98 |
| PCTK1 | 97 |
| PCTK2 | 93 |
| PCTK3 | 99 |
| PDGFRA | 98 |
| PDGFRB | 99 |
| PDPK1 | 95 |
| PFCDPK1(P.falciparum) | 70 |
| PFPK5(P.falciparum) | 84 |
| PFTAIRE2 | 100 |
| PFTK1 | 92 |
| PHKG1 | 100 |
| PHKG2 | 96 |
| PIK3C2B | 98 |
| PIK3C2G | 66 |
| PIK3CA | 80 |
| PIK3CA(C420R) | 92 |
| PIK3CA(E542K) | 88 |
| PIK3CA(E545A) | 93 |
| PIK3CA(E545K) | 82 |
| PIK3CA(H1047L) | 100 |
| PIK3CA(H1047Y) | 100 |
| PIK3CA(I800L) | 84 |
| PIK3CA(M1043I) | 63 |
| PIK3CA(Q546K) | 97 |
| PIK3CB | 93 |
| PIK3CD | 86 |
| PIK3CG | 70 |
| PIK4CB | 94 |
| PIKFYVE | 100 |
| PIM1 | 100 |
| PIM2 | 100 |
| PIM3 | 100 |

| Target | S-CE-123 |
|---|---|
| Gene Symbol | %Ctrl @ 2800nM |
| PIP5K1A | 95 |
| PIP5K1C | 100 |
| PIP5K2B | 100 |
| PIP5K2C | 100 |
| PKAC-alpha | 95 |
| PKAC-beta | 100 |
| PKMYT1 | 88 |
| PKN1 | 100 |
| PKN2 | 86 |
| PKNB(M.tuberculosis) | 96 |
| PLK1 | 79 |
| PLK2 | 89 |
| PLK3 | 95 |
| PLK4 | 89 |
| PRKCD | 89 |
| PRKCE | 100 |
| PRKCH | 100 |
| PRKCI | 100 |
| PRKCQ | 100 |
| PRKD1 | 92 |
| PRKD2 | 98 |
| PRKD3 | 96 |
| PRKG1 | 100 |
| PRKG2 | 99 |
| PRKR | 93 |
| PRKX | 100 |
| PRP4 | 92 |
| PYK2 | 100 |
| QSK | 93 |
| RAF1 | 76 |
| RET | 96 |
| RET(M918T) | 89 |
| RET(V804L) | 91 |
| RET(V804M) | 95 |
| RIOK1 | 77 |
| RIOK2 | 99 |
| RIOK3 | 97 |
| RIPK1 | 80 |
| RIPK2 | 100 |
| RIPK4 | 97 |
| RIPK5 | 95 |
| ROCK1 | 100 |
| ROCK2 | 100 |
| ROS1 | 91 |
| RPS6KA4(Kin.Dom.1-N-terminal) | 100 |
| RPS6KA4(Kin.Dom.2-C-terminal) | 99 |
| RPS6KA5(Kin.Dom.1-N-terminal) | 100 |
| RPS6KA5(Kin.Dom.2-C-terminal) | 85 |
| RSK1(Kin.Dom.1-N-terminal) | 80 |

| Target | S-CE-123 |
|---|---|
| Gene Symbol | %Ctrl @ 2800nM |
| RSK1(Kin.Dom.2-C-terminal) | 92 |
| RSK2(Kin.Dom.1-N-terminal) | 100 |
| RSK2(Kin.Dom.2-C-terminal) | 96 |
| RSK3(Kin.Dom.1-N-terminal) | 100 |
| RSK3(Kin.Dom.2-C-terminal) | 87 |
| RSK4(Kin.Dom.1-N-terminal) | 100 |
| RSK4(Kin.Dom.2-C-terminal) | 94 |
| S6K1 | 90 |
| SBK1 | 100 |
| SGK | 94 |
| SgK110 | 72 |
| SGK2 | 100 |
| SGK3 | 100 |
| SIK | 100 |
| SIK2 | 100 |
| SLK | 100 |
| SNARK | 100 |
| SNRK | 98 |
| SRC | 100 |
| SRMS | 99 |
| SRPK1 | 92 |
| SRPK2 | 76 |
| SRPK3 | 76 |
| STK16 | 97 |
| STK33 | 80 |
| STK35 | 98 |
| STK36 | 88 |
| STK39 | 100 |
| SYK | 100 |
| TAK1 | 71 |
| TAOK1 | 100 |
| TAOK2 | 100 |
| TAOK3 | 91 |
| TBK1 | 100 |
| TEC | 100 |
| TESK1 | 96 |
| TGFBR1 | 86 |
| TGFBR2 | 88 |
| TIE1 | 100 |
| TIE2 | 100 |
| TLK1 | 91 |
| TLK2 | 95 |
| TNIK | 89 |
| TNK1 | 74 |
| TNK2 | 100 |
| TNNI3K | 100 |
| TRKA | 100 |
| TRKB | 100 |
| TRKC | 100 |

## %Ctrl Legend

| | | | | |
|---|---|---|---|---|
| 0≤x<.1 | .1≤x<1 | 1≤x<10 | 10≤x<35 | x≥35 |

| Target | S-CE-123 |
|---|---|
| Gene Symbol | %Ctrl @ 2800nM |
| TRPM6 | 100 |
| TSSK1B | 73 |
| TSSK3 | 100 |
| TTK | 86 |
| TXK | 89 |
| TYK2(JH1domain-catalytic) | 98 |
| TYK2(JH2domain-pseudokinase) | 100 |
| TYRO3 | 100 |
| ULK1 | 100 |
| ULK2 | 100 |
| ULK3 | 100 |
| VEGFR2 | 97 |
| VPS34 | 100 |
| VRK2 | 98 |
| WEE1 | 100 |
| WEE2 | 100 |
| WNK1 | 68 |
| WNK2 | 100 |
| WNK3 | 100 |
| WNK4 | 100 |
| YANK1 | 88 |
| YANK2 | 98 |
| YANK3 | 100 |
| YES | 100 |
| YSK1 | 88 |
| YSK4 | 96 |
| ZAK | 88 |
| ZAP70 | 96 |

%Ctrl Legend

| 0≤x<.1 | .1≤x<1 | 1≤x<10 | 10≤x<35 | x≥35 |
|---|---|---|---|---|

**Pharmacokinetics study in rats after single intra-peritoneal administration of *S*-CE-123 at 10 mg/kg/body weight**

**Animals**

Eighteen male Sprague Dawley (Rj Han:SD) rats

Age/weight: 200-225 grams at the day of the delivery day

Breeder: Janvier Labs , Le Genest-Saint-Isle, 53940 Saint Berthevin Cedex, France.

Pre-treatment period: after their arrival, the animals were acclimated for a period of at least 5 days before the beginning of the surgery or the dosing period.

From animal arrival at Evotec France, the animals were group-housed by 2 corresponding to the same compound treatment in dedicated home cages (1291H; size 820 cm2 , Tecniplast );

The animal room conditions were set as follow: temperature: 22 ± 2°C, relative humidity : 50 ± 10%, light/dark cycle : 12 h/12 h, air change rate : 12 to 15 cycles/hour of filtered, 100% fresh air. All animals

had free access to filtered tap water. All rats are fed with a maintenance chow (AO4C, Safe, 89290 Augy) during the acclimation and the study.

**Jugular vein cannula implantation**

**Materials:**

• catheter C30PU-RJV1303 – polyurethane ; size : 3Fr (Ø 0.6X1.0 mm) L : 30cm ;

• pin-port and pin-port injector;

• heparinized saline solution: 5 mL d'Héparine ChoayND (25 000UI corresponding to 5000 UI/mL) in 45 mL of saline solution NaCl 0.9% corresponding to a final concentration of 500 UI/mL

• Isoflurane anesthesia (Isoflo 100%)

• Buprenorphine (Buprecare)

• Disinfectant soap (Polyvidone iode VetedineScrub) and disfectant (10% Vetedine solution)

• Alcohol 70°

• 5-0 non absorbable suture with curved needle

• Sterile gauze pads

• Heating pads

• Sterile saline

**Methods:**

The main step for the implantation of cannula in jugular vein are described as follows

• Remove the hair and disinfect the incision sites (dorsal and ventral) with appropriate disinfection protocol with Vetedine ScrubND, Alcohol 70° and Vetedine ND (repeated 3 times); apply lubricant ointment on the eye.

• Administer buprenorphine (BuprecareND, multidose 0.3 mg/ml, Axience) 0.05 mg/kg by SC route just before surgery and 8 H post-surgery

• Prepare the catheter and fill it in with heparinized saline solution

• Place the rat in dorsal recumbency on the heating pad

• Make a 1 cm ventral cervical skin incision right of the midline of the neck at the level of the clavicle

• Using a hemostat, bluntly dissect the right jugular vein, separate out the salivary and lymphatic tissues to visualize and isolate a 5 mm section of the vessel. Using 5-0 non absorbable suture, place a loose tie on both cranial and caudal ends of the vessel to maximize the exposure of the vessel. Using a micro surgical scissor make an incision large enough to pass the catheter, in line with the vessel between the two ligatures and tie the cranial ligature around the vessel.

• Insert the venous catheter into the vessel towards the heart with the assistance of the micro dissecting hook and forceps and advance the catheter until all of the PU 3F segment is in the vessel. Use the ligatures at the cranial and caudal ends to secure the catheter to the vessel.

• Place the rat in sternal recumbency; make a 1 cm dorsal skin incision at the center of the nape of the neck (between the scapulae).

• Through the ventral incision, a probe with the catheter is guided under the skin to the dorsal incision; the top of the catheter is now connecter to pin-port system.

• After blood flow observed in the PE, close the skin incision with 5-0 non absorbable suture and disinfect with vetedine ND.

Rats are recovered during two days before starting the study.

**Table S6** Study design

| Group | Number of animals/ Group | Test Article | Dose Level (mg/kg) | Route | Dose Volume (mL/kg) | Study design | Sampling time number | Blood sampling | Brain collection |
|---|---|---|---|---|---|---|---|---|---|
| IP group (serial design) – 10 mg/Kg | 3 | (S)-CE-123 | 10 | IP | 5 | Serial | 6 | Cannula | Yes @ 24 hrs as terminal sampling |
| IP group (destructive design) – 10 mg/Kg | 15 | (S)-CE-123 | 10 | IP | 5 | Destructive | 5 | Cava vena | Yes |

**Randomization**

Before surgery, the rats have been randomized depending on their weights to obtain groups

of rats with homogeneous weights for surgery.

On the day of dosing, the catheterized rats have also been randomized as well as the rats for

destructive design to obtain groups of three rats with homogeneous weights for the study.

**Dose Administration**

For intraperitoneal route, the dose formulation were administered by intraperitoneal injection in the rat's lower right quadrant using a stainless steel needle fitted on a plastic syringe. The volume of dose formulation administered to each animal was adjusted according to the body weight. A constant dosage volume of 5 mL/kg was used. The exact dose administered to each animal was measured by weighing the dosing system before and after administration. The dose formulations was maintained under delivery conditions (at room temperature, protected from light) throughout the dosing

procedure. The test item dose formulations was stirred for at least 5 minutes before and throughout the dosing procedure.

### Blood collection

### Serial design:

At each scheduled sampling time, 200µL of blood was collected from the cannula on conscious rats. Blood was collected in 1.5 ml Eppendorf vial. After withdrawing the blood, the withdrawn volume was replaced with sterile saline solution (approx. 200µL). At the last sampling time of the dosing day, the cannula was flushing with an anticoagulant solution (heparinized saline solution) and was closed tightly. Blood was centrifuged at 10000g for 3 min at +4°C. Plasma samples (approximately 40 µL) was collected in a 96 well plate in triplicate and then stored at -20°C until bioanalysis.

### Clinical observation

All animals were observed for mortality and general condition at least twice daily (once in the morning and once in the afternoon) during the week and once daily during the weekend. The adverse event, clinical signs or death were reported in the study book.

**Bioanalytical Methods**

- Pump : Thermo Accela
- Auto Sampler: Thermo Accela Open AS
- Column Oven : Agilent 1100 Heater
- Mass Spectrometer : Thermo TSQ Quantum Ultra
- Software : Excalibur version 2.1.0

**Chromatography**

- Column: Hypersil Gold C18 (50x2.1mm ; 1.9µm)
- Flow : 700µl/mn
- Oven temperature: 40°C
- Mobile phase :

    Phase A aqueous-acidic: formic acid (0.1%) / HPLC water

    Phase B organic-acidic: formic acid (0.1%) / Acetonitrile

**Table S7** Gradient mode

| **Time (min)** | 0 | 0.1 | 0.5 | 1.5 | 1.6 | 2.0 |
|---|---|---|---|---|---|---|
| **% Phase A** | 95 | 95 | 5 | 5 | 95 | 95 |
| **% Phase B** | 5 | 5 | 95 | 95 | 5 | 5 |

Injection Volume: 5 µL

**Mass spectrometry**

- Ionization mode: ESI positive mode

• Capillary Temperature: 350 °C

• Vaporizer Temperature: 350 °C

**Table S8** MS parameters.

| | |
|---|---|
| Skimmer offset | (S)-CE-123: unused<br>Tolbutamide (ISTD): unused |
| Collision Energy Voltage | (S)-CE-123: 11 V<br>Tolbutamide (ISTD): 30 V |
| Multiple Reaction Monitoring | (S)-CE-123: m/z 314.045 → 167.060<br>Tolbutamide m/z 271.4 → 91.2 |
| Retention Time | (S)-CE-123: 0.92mn<br>Tolbutamide: 0.93mn |

**Preparation of quality control and calibration samples**

Quality Control (QC) samples and Calibration Samples wereprepared daily by spiking rat plasma or brain homogenates with working solutions prepared from independent weighing. The calibration curve werecalculated from calibration levels at 2.5, 5, 10, 25, 50, 100, 200, 500, 1000, 2000 and 5000 ng/mL (at least 75% of all standards used to make up the curve will back-calculate to ± 20% of their nominal value and at least six non-zero concentrations that back-calculate to ± 20% of their nominal value wereused for the quantitation of the samples). The concentrations for Quality Controls were 12.5, 50, 150, 450, 1500 and 4000 ng/mL (At least 66% of all QC samples must be within ± 20% of their nominal value and at least 50% of QC samples at a given concentration must be within +/- 20% of their nominal value). Regressions used were linear or quadratic regressions (plasma and brain, respectively) not forced through the origin, and weighted by $1/x^2$ or $1/x$ (plasma and brain, respectively) (with R2 >0.98). The lower limit of quantification (LLOQ) was defined as being less or equal to 120% of the area of the first EB following the ULOQ.

**PK analysis**

The pharmacokinetic parameters were calculated from the individual plasma concentrations using the program WinNonLin 7.0 (Phoenix 64), non-compartmental model 200.

**Study Plan adherence and deviation**

No deviation was reported during the study

**Results**

**Table S9** Individual plasma concentrations of (S)-CE-123 (serial design)

| Animal | 1 | | 2 | | 3 | |
|---|---|---|---|---|---|---|
| Animal Weight (g) | 250 | | 258 | | 267 | |
| Dose Volume (mL) | 1.00 | | 1.03 | | 1.07 | |
| Actual Dose (mg/kg) | 10 | | 10 | | 10 | |
| Nominal Sampling Timepoint (h) | Actual Time (h) | Conc. (ng/mL) | Actual Time (h) | Conc. (ng/mL) | Actual Time (h) | Conc. (ng/mL) |
| 0.25 | 0.25 | 5295 | 0.25 | 9998 | 0.25 | 11591 |
| 0.50 | 0.50 | 3984 | 0.50 | 4836 | 0.50 | 8834 |
| 1.00 | 1.00 | 2238 | 1.00 | 2629 | 1.00 | 4878 |
| 3.00 | 3.00 | 260 | 3.00 | 464 | 3.00 | 1969 |
| 7.00 | 7.00 | 3.40 | 7.00 | 2.66 | 7.00 | 78.2 |
| 24.00 | 24.00 | BLQ | 24.00 | BLQ | 24.00 | BLQ |

**Table S10** Individual plasma and brain concentrations of (S)-CE-123 (destructive design and terminal sampling time of serial design@ 24hrs)

| Time h | Animal ID | Plasma ng/ml | Brain ng/g | Kp Br:Pl |
|---|---|---|---|---|
| 0.25 | 7 | 8738 | 5600 | 0.64 |
| | 8 | 3797 | 3787 | 1.00 |
| | 9 | 4413 | 4956 | 1.12 |
| | **MEAN** | **5649** | **4781** | **0.92** |
| | **SD** | **2692** | **919** | **0.25** |
| 0.5 | 10 | 2637 | 2586 | 0.98 |
| | 11 | 575 | 605 | 1.05 |
| | 12 | 4124 | 3795 | 0.92 |
| | **MEAN** | **2445** | **2329** | **0.98** |
| | **SD** | **1782** | **1611** | **0.07** |
| 1 | 13 | 1242 | 1335 | 1.08 |
| | 14 | 646 | 601 | 0.93 |
| | 15 | 1182 | 1268 | 1.07 |
| | **MEAN** | **1023** | **1068** | **1.03** |
| | **SD** | **328** | **406** | **0.08** |
| 3 | 16 | 182 | 183 | 1.0 |
| | 17 | 145 | 124 | 0.9 |
| | 18 | 31.5 | 26.6 | 0.8 |
| | **MEAN** | **120** | **111** | **0.90** |
| | **SD** | **78.5** | **79.1** | **0.09** |
| 7 | 19 | BLQ | BLQ | NC |
| | 20 | BLQ | BLQ | NC |
| | 21 | 10.7 | BLQ | NC |
| | **MEAN** | **BLQ** | **BLQ** | **NC** |
| | **SD** | - | - | - |
| 24 (brain serial) | 1 | BLQ | BLQ | NC |
| | 2 | BLQ | BLQ | NC |
| | 3 | BLQ | BLQ | NC |
| | **MEAN** | **BLQ** | **BLQ** | **NC** |
| | **SD** | - | - | - |
| | | | | **0.96** |
| | | | | **0.06** |

**Table S11** Individual plasma pharmacokinetics parameters of S-CE-123.

| PK Parameter | IP 10 mg/kg | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Dose (mg/kg) | 10 | 10 | 10 |
| Dose (µmol/kg) | 32 | 32 | 32 |
| $C_0$ / $C_{max}$ (ng/mL) | 5295 | 9998 | 11591 |
| $C_0$ / $C_{max}$ (nM) | 16838 | 31796 | 36862 |
| $T_{max}$ (h) | 0.25 | 0.25 | 0.25 |
| $t_{1/2}$ (h) | 0.64 | 0.59 | 0.98 |
| MRT (h) | - | - | - |
| Vdss (L/kg) | - | - | - |
| CL / CL_F (mL/min/kg) | 31 | 22 | 10 |
| $AUC_{inf}$ (ng.hr/mL) | 5406 | 7692 | 16187 |
| $AUC_{inf}$ (nM.hr) | 17191 | 24463 | 51475 |
| $AUC_{0-t}$ (ng.hr/mL) | 5403 | 7690 | 16076 |
| $AUC_{0-t}$ (nM.hr) | 17181 | 24456 | 51123 |
| Fraction Absorbed | - | - | - |
| $C_{last}$ (ng/mL) | 3.4 | 2.7 | 78.2 |
| Number of Points used for Lambda z | 3 | 3 | 3 |
| AUC % Extrapolation to infinity | 0.1 | 0.0 | 0.7 |
| $T_{last}$ (h) | 7 | 7 | 7 |