**Supplementary Table 1.** **Chimeric ACTH/MC4 receptors and their functional properties**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Receptor | | -MRAP | | | +MRAP | | | Reference |
| Surface | ACTH | MSH | Surface | ACTH | MSH |
| MC4R |  | **++** | 1 | 1 | **+** | 1 | 1 |  |
| ACTHR |  | **-** | 0 | 0 | **++** | 1 | 0 |  |
| Ch1 |  | **+** | EC50×38.1MC4R | EC50×7.0MC4R  Ki×1.2MC4R |  |  |  | [1; 2] |
| Ch2 |  | **-** | EC50ND | EC50ND | **+** | EC50×129.1ACTHR  EC50×8.0MC4R | ND | [1] |
| 2C2a |  | **-** |  |  | **+** | RlucMax×5.4ACTHR  RlucMax×5.0MC4R | RlucMax×130.0MC4R | [3] |
| 2C1c |  | **+** |  |  | **++** | RlucMax×0.9ACTHR |  | [3] |
| Ch3 |  | **+** | EC50ND | EC50ND |  |  |  | [1] |
| 2C1 |  | **+** | RlucMax×ND | | **++** | RlucMax×18.2ACTHR  RlucMax×23.6MC4R | | [3] |
| 2C1a |  | **+** |  |  | **++** | RlucMax×1.0ACTHR |  | [3] |
| 2C1b |  | **+** |  |  | **++** | RlucMax×0.8ACTHR |  | [3] |
| Ch4 |  | **-** | EC50ND | EC50ND |  |  |  | [1] |
| Ch5 |  | **++** | EC50ND | EC50ND |  |  |  | [1] |
| 2C6 |  | **-** | RlucMax×18.2MC4R | | **-** | RlucMax×1.8ACTHR  RlucMax×2.4MC4R | | [3] |
| Ch6 |  | **++** | EC50ND  Ki×11.1MC4R | EC50ND  Ki×0.2MC4R |  |  |  | [1] |
| 4C4 |  | **-** | RlucMax×12.6MC4R | | **-** | RlucMax×2.2ACTHR  RlucMax×2.8MC4R | | [3] |
| Ch7 |  | **+** | EC50×62.3MC4R  Ki×1.8MC4R | EC50×37.9MC4R  Ki×0.7MC4R |  |  |  | [1] |
| Ch8 |  | **+** | EC50ND | EC50ND |  |  |  | [1] |
| hMC4R/TM2 hMC2R |  |  | EC50×0.04ACTHR+MRAP  Ki×0.3ACTHR+MRAP  EC50×1.9MC4R  Ki×2.2MC4R |  | **+** |  | EC50×1.4MC4R  Ki×2.0MC4R | [4; 5] |
| Ch9 |  | **+** | EC50ND | EC50ND |  |  |  | [1] |
| hMC4R/TM3 hMC2R |  |  | EC50×0.84ACTHR+MRAP  Ki×1.2ACTHR+MRAP  EC50×35.6MC4R  Ki×9.6MC4R |  | **+** |  | EC50×40.0MC4R  Ki×12.7MC4R | [4; 5] |
| hMC4R/TM4 hMC2R |  |  | EC50×0.04ACTHR+MRAP  Ki×0.2ACTHR+MRAP  EC50×1.7MC4R  Ki×1.6MC4R |  | **+** |  | EC50×2.1MC4R  Ki×1.9MC4R | [4; 5] |
| hMC4R/TM5 hMC2R |  |  | EC50×0.05ACTHR+MRAP  Ki×0.2ACTHR+MRAP  EC50×2.0MC4R  Ki×1.3MC4R |  | **+** |  | EC50×1.8MC4R  Ki×1.4MC4R | [4; 5] |
| Ch10 |  | **++** | EC50×124.3MC4R  Ki×12.7MC4R | EC50×137.0MC4R  Ki×3.1MC4R |  |  |  | [1] |
| hMC4R/TM6 hMC2R |  |  | EC50×0.04ACTHR+MRAP  Ki×0.2ACTHR+MRAP  EC50×1.7MC4R  Ki×1.4MC4R |  | **+** |  | EC50×1.6MC4R  Ki×1.7MC4R | [4; 5] |
| 4C2 |  | **++** | RlucMax×ND | | **+** | RlucMax×ND | | [3] |
| Ch11 |  | **++** | EC50ND  Ki×2.5MC4R | EC50ND  Ki×0.5MC4R |  |  |  | [1] |
| 4C3 |  | **++** | RlucMax×1.4MC4R | | **+** | RlucMax×0.9ACTHR  RlucMax×1.2MC4R | | [3] |
| 4C1 |  | **-** | RlucMax×7.8MC4R | | **-** | RlucMax×4.8ACTHR  RlucMax×6.2MC4R | | [3] |
| Ch12 |  | **+** | EC50ND | EC50ND |  |  |  | [1] |
| Ch14 |  | **++** | EC50ND  Ki×0.5MC4R | EC50ND  Ki×1.0MC4R |  |  |  | [1] |
| 4C6 |  | **+** | RlucMax×ND | | **-** | RlucMax×18.4ACTHR  RlucMax×23.9MC4R | | [3] |
| Ch13 |  | **-** | EC50ND | EC50ND |  |  |  | [1] |
| Ch15 |  | **+** | EC50×4.0MC4R  K×i0.3MC4R | EC50×1.7MC4R  Ki×0.3MC4R |  |  |  | [1] |
| 2C4 |  | **+** | RlucMax×ND | | **+** | RlucMax×ND | | [3] |
| 4C5 |  | **-** | RlucMax×25.1MC4R | | **+** | RlucMax×ND | | [3] |
| 2C2 |  | **-** | RlucMax×4.0MC4R | | **+** | RlucMax×2.1ACTHR  RlucMax×1.9MC4R | RlucMax×1.9MC4R | [3] |
| RlucMax×1.7ACTHR  RlucMax×2.3MC4R | |
| Ch16 |  | **+** | EC50ND | EC50ND | **-** | EC50×4.5ACTHR  EC50×0.3MC4R | EC50ND | [2] |
| Ch19 |  | **++** | EC50ND | EC50ND | **++** | EC50×239.3ACTHR  EC50×14.9MC4R | EC50ND | [2] |
| 2C3 |  | **+** | RlucMaxND | | **++** | RlucMax×1.0ACTHR  RlucMax×1.3MC4R | | [3] |
| hMC2R/TM4 hMC4R |  | **-** | EC50ND | EC50ND | **-** | EC50ND | EC50ND | [5] |
| Ch20 |  | **++** | EC50ND | EC50ND | **++** | EC50×16.2ACTHR  EC50×1.0MC4R | EC50ND | [2] |
| Ch21 |  | **++** | EC50ND | EC50ND | **-** | EC50ND | EC50ND | [2] |
| Ch17 |  | **++** | EC50ND | EC50ND | **+** | EC50×5.3ACTHR  EC50×0.3MC4R | EC50ND | [2] |
| Ch18 |  | **-** | EC50ND | EC50ND | **-** | EC50ND | EC50ND | [2] |
| hMC2R/TM5 hMC4R |  | **-** | EC50ND | EC50ND | **-** | EC50ND | EC50ND | [5] |
| hMC2R/TM6 hMC4R |  | **-** | EC50ND | EC50ND | **-** | EC50ND | EC50ND | [5] |
| Ch22 |  | **-** | EC50ND | EC50ND | **++** | EC50ND | EC50ND | [2] |
| hMC2R/TM3 hMC4R |  | **-** | EC50ND | EC50ND | **-** | EC50ND | EC50ND | [5] |
| 2C2c |  | **-** |  |  | **++** | RlucMax×4.7ACTHR  RlucMax×4.4MC4R | RlucMax×43.3MC4R | [3] |
| hMC2R/TM2 hMC4R |  | **-** | EC50ND | EC50ND | **-** | EC50ND | EC50ND | [5] |
| 2C2b |  | **-** |  |  | **-** | RlucMax×7.3ACTHR  RlucMax×6.7MC4R | RlucMax×130.0MC4R | [3] |
| 2C5 |  | **-** | RlucMax×6.6MC4R | | **-** | RlucMax×3.6ACTHR  RlucMax×4.7MC4R | | [3] |

× , fold difference; Superscript, compared values; Subscript, wild type receptor to which measurement was compared;  
ND, not determined; Regions from the MC4R are shaded grey; Regions from the ACTHR are shaded black; empty field, no data available.  
++, high membrane transportation; +, low membrane transportation; , no membrane transportation;  
Approximate RlucMax values from Hinkle et al. [3] were acquired through digitalization of the included bar graphs.

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