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| --- | --- | --- | --- |
| Molecule | Species | MC2R Agonist | MC2R Antagonist |
| ACTH (7-38) (CIP, cortricotropin inhibiting peptide)1 | Rat | ø | Competitive antagoniste of ACTH(1-39) |
| ACTH (11-24) 2,3 | Frog | Dose related stimulation of cortico and aldosterone ( from 3.16x10-8M lower dose to 3.16x10-10M half maximum effect) | Competitive antagoniste of ACTH(1-39) and of ACTH(1-10)3,4 |
| ACTH(1-24 )2 Lys - dimer 2 | Frog | Weak induction of corticosterone and aldosterone (70 times less potent that ACTH 1-24 or ACTH1-39) | ø |
| ACTH(1-24)2 | Frog | Agonist | ø |
| ACTH(1-39)2  (10-9M) | Frog | Dose related stimulation of cortico and aldosterone ( from 3.16x10-11M lower dose to 3.16x10-10M half maximum effect) | ø |
| ACTH(11-24)2 Lys- dimer 2 3 | Frog | ø | Reduced ACTH (1-39) evoked stimulation of corticosterone and aldosterone release(63 and 62 %respectively) |
| ACTH Glu(11-24)2 - dimer  3,4 | Frog | ø | Antagonist |
| ACTH(5-24)  5 | Rat | Full agonist | ø |
| ACTH(6-24)  6 | Rat | ø | Competitive inhibitor of ACTH (1-39) |
| ACTH(6-39)  7 | Rat | ø | Competitive inhibitor of ACTH (1-39) |
| ACTH(1-24)  8 | Rat | Full agonist and as potent as ACTH(1-39) | ø |
| ACTH(5-24) 9,10 | Bovine9  Rat10 | Partial agonist  Full lipolytic agonist | ø |
| ACTH (6-24)9 | Bovine | Partial agonist | ø |
| ACTH(7-24)9,10 | Bovine9  Rat10 | Partial agonist  Do not stimuated lipolysis | ø |
| AGRP and agouti protein11 | Human | ø | MC4R natural antagonist |
| ACTH(8-39)12 | Human | ø | Partial antagonist (CIP) |
| ACTH(15-18)13 | Human | ø | Competitive antagonist of ACTH receptor |
| ACTH W9Y14 | Bovine | ø | Antagonist |
| ACTH(15-24)15,16  Dores RM. *ACTH Antagonist Peptides*. US Patent application US 2012/0309696 A1 (2012). | RAT  Mammalian  OS3 adrenal cell line transfected with a hmc2R cDNA | ø | Antagonist |
| GPS1573, a variant of ACTH (7-18) with an N terminal nor leucine-proline sequence and D-Phe and DD-Trp (in place of L-Phe, L-Trp) in the HFRW sequence17,18 | HEK293 cells (ATCC, CRL-1573) were stably transfected with human MC2R and MRAP cDNAs17  Rat18 | ø | Antagonist |
| GPS1574, a cyclized variant of GPS157317,18 | HEK293 cells (ATCC, CRL-1573) were stably transfected with human MC2R and MRAP cDNAs17  Rat18 | ø | Has alos antagonist effect on MC3R,MC4R and MC5R |
| IRC-27419 | HEK293 cells (ATCC, CRL-1573) were stably transfected with human MC2R and MRAP cDNAs | ø | Selective MC2R antagonist |
| -melanotan II (MTII)  -tetrapeptides  -MK-0489  -MK-0493  -urea-based piperazine  -Ro27-3225  -Cyclophanes  -ACTH(1-13) (α MSH)  -compound 1  -pyrrolidine diastereoisomer  -BIMs (BIM-22493 and BIM-22511)  -β-MSH analogues  20 | -Rat  -Rat  -Mice  -Human  -Rat  -Rat  -Rat  -Rat  -Mice  -HEK293 cells expressing  MC4R  - CHO-K1 cells transfected with MCR  -Rat | MC4R agonist | ø |
| Corticostation or defensin α 421 | Rat (isoleted from rabbit lung but tested on rat) | ø | Non specific MC2R antagonsit |
| ACTH (4-10)22 | HEK cells that expressed either the rat melanocortin MC3 receptor, the human melanocortin MC4 receptor or the ovine melanocortin MC5 receptor | ø | MC3R and MC4R antagonist |
| SEMAX23 |  | ø | MC4R antgonist |
| 153N624 | Frog | ø | MC1R antagonist but bind to MC3R,MC4R and MC5R with low affinity |
| [D-Trp7,D-Phe10]a-MSH (6 –11)amide25 | Mouse melanoma cells (which express the native receptor MC1) and MSH unresponsive human kidney 293 cells transfected with the expression vector pcDNA 1Neo | ø | MC3R antagonist |
| ACTH(1-17)26,27 | OS3 adrenal cell line 26  Hela cell line transfected with the cloned mouse adrenocorticotropin receptor expressed | Agonist (?)  But limited activity due to the lack of KKRRP sequence 27. | ø |
| ACTH (1-16)26 | OS3 adrenal cell line | Agonist (?)  But limited activity due to the lack of KKRRP sequence. | ø |
| NDP-MSH ([Nle4, DPhe7]-a-MSH)  28 | Human | non-selective  agonist for the human MC1, MC3, MC4 and MC5 receptors | ø |
| Melanotan II (MTII, the  lactam Ac-Nle4 cycle [Asp-His6-DPhe7-Arg8-Trp9-Lys10]-  amide)  28 | The coding regions of the genes for the hMCRs wild-type, and  mutants were subcloned into the pCDNA3.1. HEK-293 cell line  was purchased from ATCC | non-selective  agonist for the human MC1, MC3, MC4 and MC5 receptors | ø |
| SHU9119 : Substitution of a bulky hydrophobic amino acid at the  Phe position  28-30 | -The coding regions of the genes for the hMCRs wild-type, and  mutants were subcloned into the pCDNA3.1. HEK-293 cell line  was purchased from ATCC  - human and mouse  -prostate cancer cell | ø | converts the MTII peptide from an  agonist into an antagonist at the MC3 and MC4 receptors |
| SHU891429,31 | Human and mouse | ø | full agonists of the MC1-R and  MC5-R, weak partial agonists of hMC3-R and subsequently characterized  as potent antagonists of the hMC3-R  as well as the hMC4R |
| HS02432 | goldfish | ø | MC4R antagonist |
| Substitution of  tryptophan by phenylalanine or by Nα-methyltryptophan  as in [Gln5, Phe9]ACTH 1-20 amide or [Nα-Metrp9 ]ACTH l-2414 | Bovine cortical adrenal membrane |  | MC2R antagonist:  provides ACTH analogs that exhibit high  affinity for the ACTH receptor(s) but fail to activate the adenylate cyclase system |
| AC-Nle-Asp-Trp-D-Phe-Nle-Trp-Lys-NH233 | Mice  human | ø | MC1R antagonist with agonist effect on MC3R, MC4R and MC5R |
| c[Gly-Cpg-D-Nal(2’)-Arg-Trp-Glu]-Val-Val-Gly-NH234 | melanocortin-1 (MC1) receptor from Xenopus frog skin    recombinant human MC1, MC3, and MC4 receptors expressed in human embryonic kidney (HEK) cells | ø | MC1R antagonist but highly selective versus human MC4R and modestly selective versus MC3R |
| N-methyltryptophan instead of Trp at position 9 of ACTH 1-2414 | Bovine | ø | MC2R antagonist |
| Synthetic peptide GKVLKKRR (fragments 81-88 of pro IL 1α protein)35 | Rat | ø | MC2R antagonist |
| [D-Trp8]γ-MSH36 | WT C57BL/6J mice  MC3RKO mice and WT | ø | hMC3R selective agonist |
| ACTH(1-18)  Three  modifications (DSer was introduced instead of Ser on the  position 1, the sequence 15-18 was changed to Lys-Lys-Lys-  Lys and the C-terminus was amidated)8 | Rat | Full agonist, 5 fold more potent in vivo than ACTH(1-39) | ø |
| ACTH (1-23)8 | Rat | Full agonist | ø |
| ACTH (1-10)-(15-19)37 | Rat |  | ø |
| ACTH (7-39)27 | Hela cell line transfected with the cloned mouse adrenocorticotropin receptor expressed |  | Effective MC2R antagonist when used at 100 fold molar excess |
| ACTH(4-23)(NH2)38 | Rat | High activity but less potent than ACTH (1-24) |  |
| ACTH (5-23)38 | Rat | Less potent than ACTH (1-24) but induces corticosterone stimulation | ø |
| ACTH(6-24)38 | Rat | Low activity | ø |
| ACTH(1-10)38 | Rat | High activity in vivo and in vitro (stimulates corticosterone production) | ø |
| GPS157318 | Rat | In vivo : lead to a small corticosterone response to ACTH | In vitro MC2R antagonist17 |
| GPS157418 | Rat | Inhibition of corticosterone response to ACTH | In vitro MC2R antagonist17 |
| Substitution of Phe7 with D-Nal(2’) in ACTH(1–24)  39 | OS3 and HEK cell lines, lacking endogenous MC2R, were used for hMC4R, hMC2R, and chimeric receptor transfection | did not switch the ligand from agonist to antagonist at  MC2R, which was observed inMC3Rand MC4R |  |

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