

Expert Opinion

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Ligands of the melanocortin receptors, 2002 – 2003 update

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α -Melanocyte-stimulating hormone (α -MSH), an endogenous ligand for the melanocortin receptors, has been long recognised as a mediator of numerous physiological processes including, among others, energy homeostasis, immunity, inflammation, sexual function, pigmentation and neurite outgrowth. Compounds mimicking or suppressing actions of α -MSH could therefore be useful in the treatment of many clinically important conditions. Since the cloning of the five melanocortin receptors, medicinal chemistry efforts have centred on the development of melanocortin-4 receptor-specific agonists for the treatment of obesity and erectile dysfunction. Yet, the growing research interest in the other α -MSH functions, reflected in part by the constantly increasing repertoire of ligands specific for the other melanocortin receptors, suggests that some medicinal chemistry efforts might soon be directed towards identification of compounds suitable for treating other diseases. In previous reviews in this journal, the pharmacology of the melanocortin receptors and melanocortin receptor ligands has been discussed in detail. This article will only report the newest ligands, those disclosed in patents published at the end of 2002 and in 2003.

Keywords: α -melanocyte-stimulating hormone (MSH), cachexia, depression, inflammation, melanocortin receptor, melanocortin receptor (MCR) ligand, obesity, sexual dysfunction

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1. Introduction

Melanocortins are peptides derived from the pro-opiomelanocortin (POMC) gene, including α -melanocyte-stimulating hormone (α -MSH) and adrenocorticotrophic hormone (ACTH). Five melanocortin receptors have been identified so far, MC1 – 5R. The melanocortin system is involved in diverse physiological functions, including, most notably, energy balance, pigmentation, sexual function and inflammation. Extensive reviews on the melanocortin ligands and receptors have been published and readers are referred to those recent publications for the pharmacology and physiology of the melanocortin system [1-12]. This review will summarise advances made in 2002 – 2003.

Recent clinical studies on obese patients carrying melanocortin-4 receptor (MC4R) variants further strengthen the role of MC4R in energy balance. Farooqi *et al.* found that complete loss of function variants are associated with a more severe phenotype of obesity than those variants leading to only partial loss of function [13]. Branson *et al.* further showed that binge eating is characteristic of patients with MC4R variants [14]. Additional studies indicated that many of the MC4R variants found in obese patients tend to have defects in plasma membrane targeting, which is consistent with the notion that reduced MC4R surface expression can be a cause of obesity [15-17]. These results further predict additional mutations in the MC4R promoter region may also cause obesity by reducing surface expression.

The role of MC3R and MC4R in cachexia has been evaluated in mice. The MC4R knockout (KO) mice resist the loss of lean body mass caused by tumour

growth, while the MC3R KO mice showed enhanced wasting [18]. These data suggested a differential role of MC3R and MC4R in the development of cachexia and weight gain [18-20].

In the area of analgesia, MC1R gene mediates female-specific κ -opioid analgesia in both mice and humans. Women with two variant *MC1R* alleles exhibit greater analgesia from κ -opioid than all other groups [21]. This finding demonstrates the involvement of MC1R in pain modulation in addition to its well known role in pigmentation. Recent epidemiological studies confirmed that MC1R polymorphism clearly contributes to pigmentation along with two other genes [22-24].

The MC1R has been known to play a role in inflammatory response [10,11]. In addition, MC5R and MC1R immunoreactivity were found in human duodenal mucosa [25]. Further studies are needed to elucidate how other MC receptor subtypes modulate inflammatory response.

2. Patents

2.1 Piperidine- and piperazine-based ligands

Bristol-Myers Squibb has reported [101-104] a new series of piperidine and spiropiperidine derivatives as modulators of MC1R and MC4R. The compounds are related to a dipeptide-heterocycle template exemplified by compounds 1 and 2. *In vitro* and *in vivo* data were provided for compound 2 [26]. This melanocortin ligand was shown to be a highly potent and selective MC1R agonist (median inhibitory concentration [IC₅₀] value = 120 nM, effective concentration for half-maximum response [EC₅₀] value = 28 nM) which, even at micromolar concentration, did not activate MC3R and was a weak partial agonist at MC4R and MC5R. When tested in a murine lipopolysaccharide-induced cytokine accumulation model, compound 2 was able to elicit an anti-inflammatory effect; it decreased TNF- α production in a dose-dependent manner [26].

Eli Lilly has expanded its repertoire of MC4R agonists with yet another group of substituted piperazines and 1,4-diazepanes [105]. The structures of the new compounds include the dipeptide D-Tic-D-Phe(4Cl) segment and the piperazine ring modified with various piperidine derivatives. Compounds published are related to compound 3 (EC₅₀ = 4.3 nM at MC4R) and have been claimed for the treatment of obesity, diabetes and male and female sexual dysfunction.

Merck's collection of patents on MC4R agonists [1-3] has been supplemented by 4 new applications [106-109]. Previously published compounds [1-3] derived mostly from dipeptide-piperidine, dipeptide-spiropiperidine and dipeptide-piperazine templates and were claimed for the treatment of obesity, diabetes mellitus and sexual dysfunction. Recent compounds are also piperidine derivatives, 4-substituted *N*-acylpiperidines. Although, in the structures of compounds claimed in WO0307949 [109], the dipeptide-piperidine template is retained, as in compound 4, compounds of the other patents [106-108] have the piperidine moiety substituted with isonipicotic acid or cyclopentanecarboxylic acid or 3-carboxy-pyrrolidine derivatives, exemplified by compound 5. The new

agonists have been claimed for the treatment of obesity, diabetes mellitus and sexual dysfunction but no specific biological data has been given.

Recently, Merck has also detailed [27] its efforts directed towards the design and syntheses of new MC4R agonists based on structural motifs other than the piperidine and piperazine templates. A series of pyridazinone derivatives, such as compound 6 (IC₅₀ = 33 nM and EC₅₀ = 177 nM at hMC4R), has been reported. These compounds could provide new leads for the development of MC4R agonists suitable for the treatment of obesity.

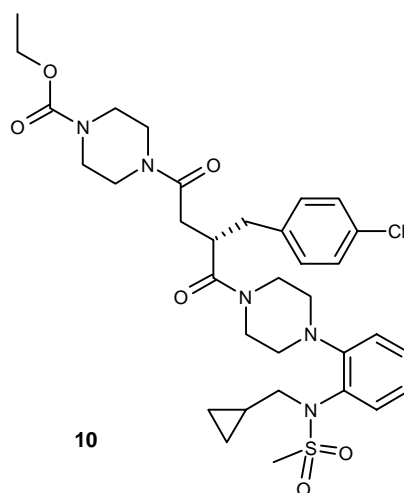
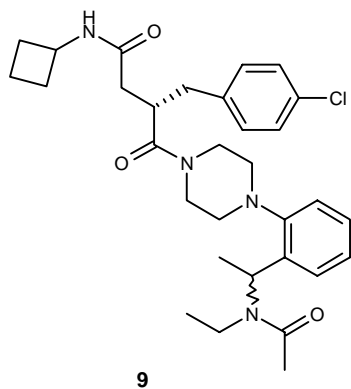
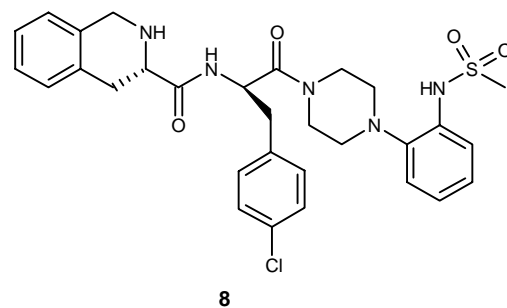
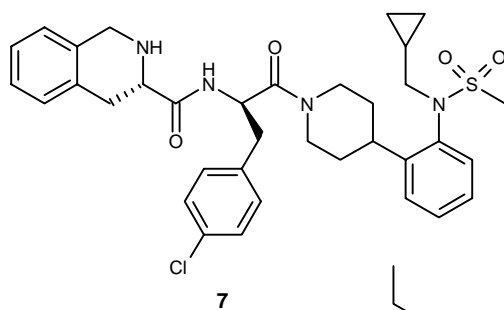
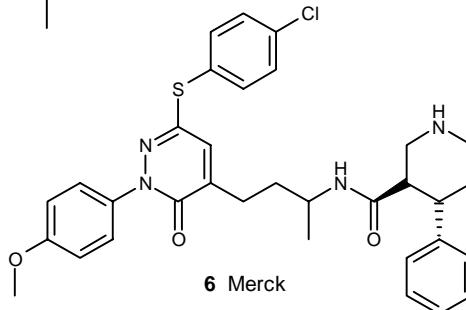
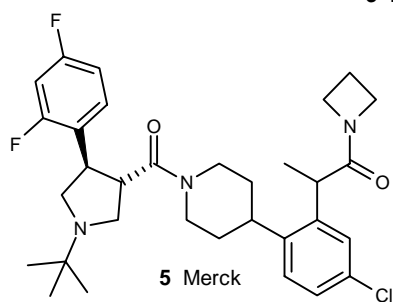
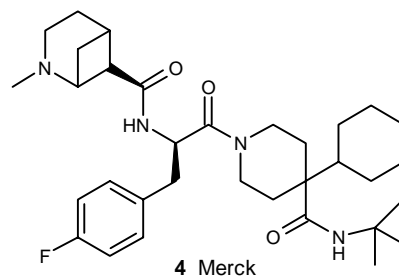
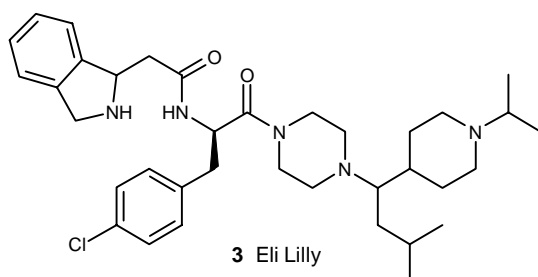
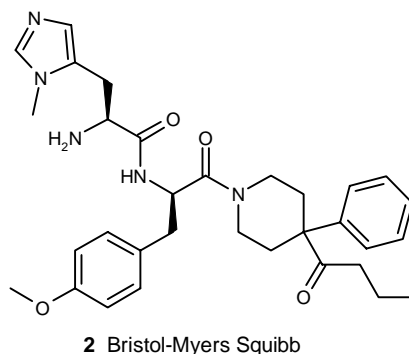
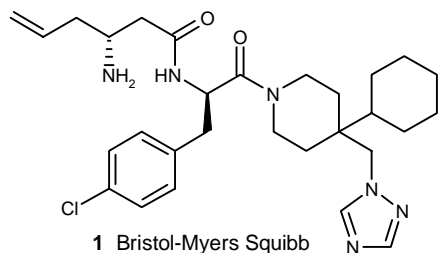
Amgen has recently joined other pharmaceutical companies in pursuit of low molecular weight hMC4R agonists based on the Tic-D-Phe(4Cl) dipeptide-piperazine/piperidine template. Two patents published [110,111] cover a huge number of substituted *N*-acylpiperidines and 1-acylpiperazines related to compounds 7 and 8, respectively. Claims have been made for the treatment of obesity, diabetes, cancer, inflammation and Alzheimer's diseases. Separately, two other groups of piperazine derivatives related to compounds 9 and 10, with a succinamide core in place of Phe(4Cl), have been reported [28] to be potent and selective MC4R agonists and antagonists.

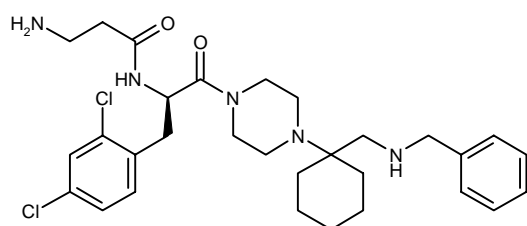
Similarly, Neurocrine has disclosed [112,113] ligands for MC3R and MC4R having structures related to compounds 11 and 12 in which the dipeptide-piperazine template has been retained. Compound 12 was reported to be a selective MC4R agonist with an EC₅₀ value of 24 nM at MC4R and an EC₅₀ value of > 3000 nM at hMC1R, hMC3R and hMC5R [29]. Claims have been made for a broad range of therapeutic applications, including eating disorders and sexual dysfunctions. These Neurocrine substituted phenyl piperazines and cyclohexyl piperazines [112,113], together with Amgen's sulfonamide-substituted phenyl piperazines [111] and Eli Lilly's substituted piperidyl piperazines [105], substantially expand the family of melanocortin ligands based on the dipeptide-piperazine template [3].

Another application from Neurocrine [114] has claimed substituted-pyrroles of structures similar to compound 13 for the treatment of eating and skin disorders; no biological data have been reported. The novel pyrrole template of compounds disclosed might offer further opportunities for the new ligand design.

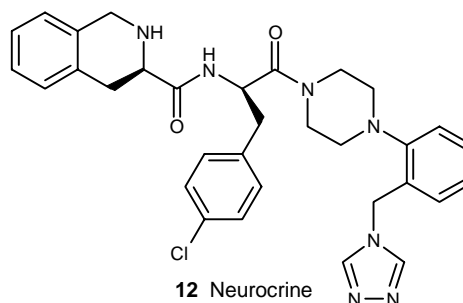
Two recent patents from Proctor and Gamble [115,116] have centred on yet another series of 4,4-disubstituted *N*-acylpiperidines as agents suitable for treating eating disorders. These compounds, represented by compound 14, are the structure-activity relationship (SAR) extensions of Merck's previously discussed compound 15 and feature various replacements for the Tic and [1,2,4]triazole-1-ylmethyl moieties. The 4,4-disubstituted *N*-acylpiperidine derivatives with different substitutions in the same positions have been the subject of the above-cited recent patent disclosures from Bristol-Myers Squibb [101,102] and Merck [109].

Taisho has claimed [117-119] peptide and low molecular weight MC4R antagonists (dipiperazine derivatives) for the

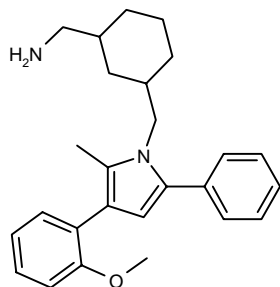




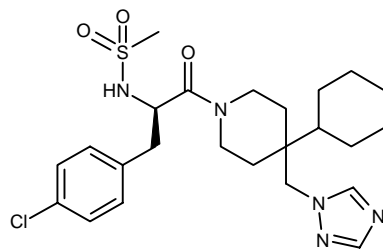
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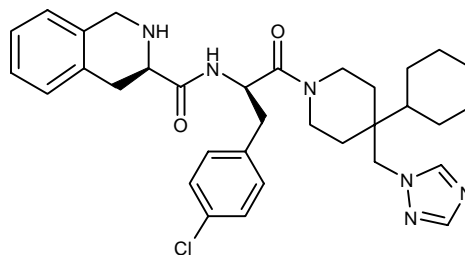
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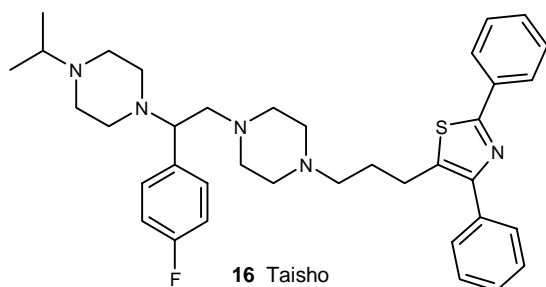
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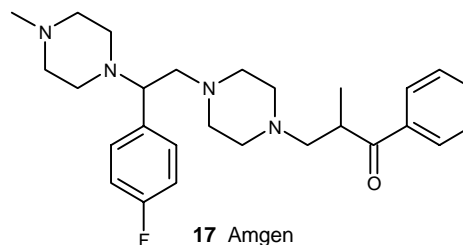
14 Procter and Gamble



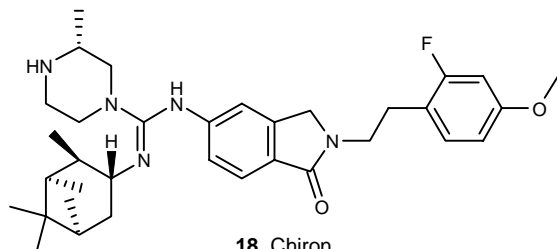
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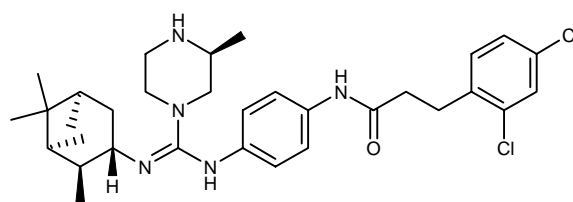
16 Taisho



17 Amgen



18 Chiron

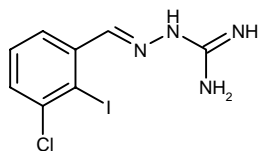


19 Chiron

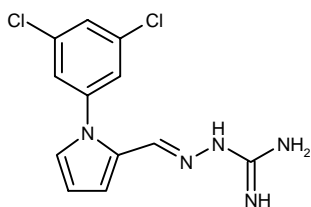
treatment of anxiety and depression. Anxiolytic and antidepressant activities have been reported [30] for MCL-0020, Ac-D-Nal(2')-Arg-Nal(2')-NH₂, upon intracerebroventricular injection in mice. This short peptide is a high affinity ligand for MC4R (IC₅₀ = 11.63 nM) and is 860-fold selective over MC1R and 89-fold selective over MC3R. A non-peptidic compound (16), MCL-0129, has been shown to elicit similar effects when administered subcutaneously or orally [31]. MCL-0129 binds to MC4R with an IC₅₀ value of 7.9 nM and displays no apparent affinity for MC1R and MC3R, even at 1 μM concentration. Recently reported by Amgen [32] are low molecular weight MC4R antagonists based on the same (piperazinyl-ethyl)piperazine template; compound 17 (IC₅₀ = 220 nM at MC4R) represents the Amgen series.

2.2 Guanidine-based ligands

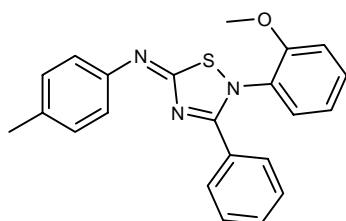
Chiron has claimed another series of guanidine-containing MC4R agonists for a number of therapeutic interventions [120-122]. In the previously reviewed patents [3], claims were made for guanidinobenzamide and guanidine compounds derived from 2-(S)-methylpiperazines and (+)-isocampherlamines. The latest applications centred on structures exemplified by compound 18, 5-guanidino-isoindole derivatives and compound 19, guanidinobenzamides derivatives. No specific biological data were given for compounds published but it was stated that a significant reduction in food intake and body weight was observed when these compounds were administered intraperitoneally to the ob/ob mice. Improvements in blood glucose, insulin and free



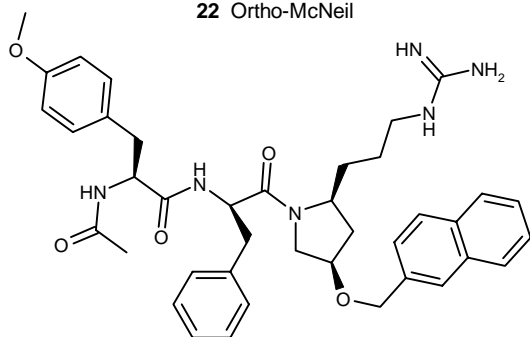
20 Melacure



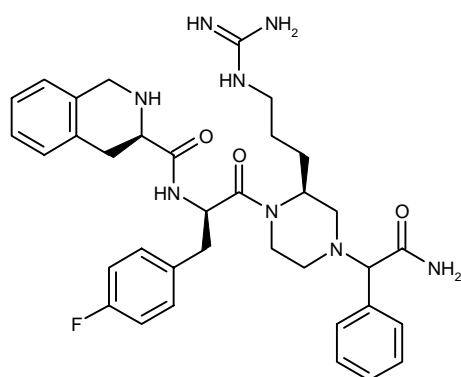
21 Melacure



22 Ortho-McNeil



23 Procter and Gamble



24 Procter and Gamble

fatty acid levels were also noted. Claims were for the treatment of obesity and Type 2 diabetes.

In a separate patent, Chiron claimed an intranasal route for delivering MC4-R agonists to mammalian subjects [123]; guanidine compounds described above were included.

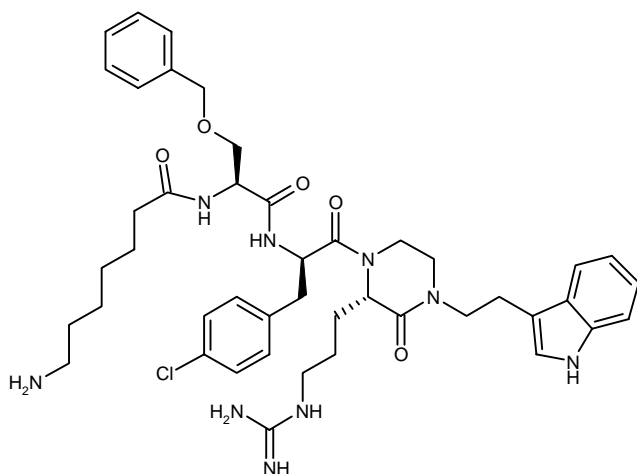
Melacure has previously published [1-3] hydroxyaminoguanidines and aminoguanidines as melanocortin receptor ligands. Recent patents [124-126] have claimed another set of aminoguanidines as agonists or antagonists for melanocortin receptors, thus containing substitutions with benzylidene or 1-phenylpyrrole moieties. The newer compounds, exemplified by compounds 20 and 21, have been tested for their effects on food intake, body weight and inflammation but no *in vivo* data have been provided. Only limited *in vitro* inhibition constant (K_i) binding affinities were reported. Compound 20 appeared to be the most selective MC1R and MC4R ligand: K_i values of 0.5 μM at MC1R, 5.8 μM at MC3R, 0.01 μM at MC4R and 4.9 μM at MC5R. The newer compounds have been claimed as useful in treating a broad range of clinical conditions, including inflammation and cardiac diseases.

2.3 Other ligands

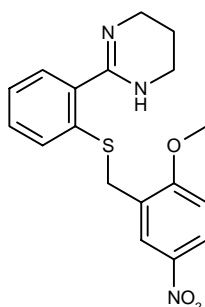
Ortho-McNeil has claimed [127,128] a series of 2,3-diaryl-5-anilino[1,2,4]thiadiazoles related to compound 22. This compound was reported [33] to be an MC4R agonist ($\text{IC}_{50} = 22 \text{ nM}$) but its agonist potency and selectivity profile were not disclosed. Although with intraperitoneal administration, compound 22 was able to significantly reduce food intake in fasted rats; it was not effective when orally dosed. Selected compounds were also evaluated for their ability to promote neurite outgrowth and/or for their stimulatory or inhibitory effect on human sebocyte differentiation and lipid production. Some of the compounds tested were superior to $\alpha\text{-MSH}$ in eliciting these effects. Compounds centred around compound 22 were claimed as melanocortin receptor modulators for a broad range of metabolic, CNS and dermatological diseases, including obesity, Type 2 diabetes, erectile dysfunction, acne and dry skin.

Procter & Gamble has reported [129] a series of conformationally restricted, peptide-like compounds as MC4R and/or MC3R modulators. These are dipeptide-heterocyclic derivatives such as compound 23. They are listed for a number of therapeutic applications: Type 2 diabetes mellitus, coronary artery disease, hypertension and dyslipidemia, among others, but no specific biological data are provided. The subsequent broad patent application [130] claims substituted cyclic agents (piperidines, piperazines and ketopiperazines) with structures similar to compound 24. Another application [131] features analogues of MT-II and SHU-9119, mainly with Tyr in place of His, that might be suitable for treating diseases mediated by the MC4R or MC3R.

Merck has claimed [34,132] high affinity, selective, peptide MC4R antagonists for the treatment of cachexia, anorexia and bulimia. The structures of these cyclic compounds, lactam macrocycles, are similar to the structures of peptide MC4R agonists discussed in an earlier review [3]. The most interesting MC4R antagonist is a compound called MBP-10, cyclo[CO-CH₂-CH₂-CO-D-Nal(2')-Arg-Trp-Lys]-NH₂, of ~125-fold higher antagonist selectivity for hMC4R than hMC3R ($K_i = 0.5 \text{ nM}$, binding constant [K_b] = 6.2 nM at



25 Palatin



26 Millenium

hMC4R and $K_i = 150$ nM, $K_b = 775$ nM at hMC3R.) This small cyclic peptide does not activate hMC1bR, hMC3R or hMC4R, even at micromolar concentrations, and is a weak agonist at hMC5R ($EC_{50} = 530$ nM.) An acute increase in food intake was observed when MBP-10 was injected centrally in satiated mice [35]. This peptide also reduced the inhibition of food intake induced by central injection of the cytokine IL-1 β in the mouse [35].

A recent patent [133] from Palatin on metallopeptides claims rhenium-complexed peptides as MC3R and/or MC4R agonists for the treatment of sexual dysfunction in mammals. A representative compound Ac-Nle-Ala-His-D-Phe-Arg-Trp-Cys-NH₂ was reported to be a potent initiator of penile erection (PE) in rats following intravenous or intranasal administration. The MC1R-specific agonist Ac-Nle-Ala-His-D-Phe-Arg-Cys-Trp-NH₂ was not able to initiate PE. Several complexes with analogues possessing D-Nal(2') in place of D-Phe (MC3R/MC4R antagonists) effectively inhibited the PE responses elicited by MT-II.

Another patent [134] has disclosed compounds similar to compound 25, with non-peptidic ring structures in place of Arg-Trp segment of the previously reported [3] biologically active metallopeptides.

In addition, Palatin has also claimed cyclic and linear peptides as useful agents for decreasing food intake and for

stimulating sexual response [135]. The cyclic compounds are mainly derivatives of MT-II or SHU-9119 with Ser(Bzl) in place of His and Phe(4Cl) in place of Phe. The linear compounds are related to 7'-amino-heptanoyl-Ser(Bzl)-D-Phe(4Cl)-Arg-Trp-NH₂ ($K_i = 1$ nM at MC4R.)

University of Florida has reported [36,37,136] two tetrapeptides of unusual pharmacology at the brain melanocortin receptors MC3R and MC4R. The first compound, Ac-Anc-D-Phe-Arg-Trp-NH₂, Anc (amino-2-naphthyl carboxylic acid) is a potent mouse MC4R agonist ($EC_{50} = 21$ nM) and a weak mouse MC3R antagonist ($pA_2 = 5.6$, $K_i = 2.5$ nM; partial agonist.) The second compound, Ac-His-D-(pI)Phe-Arg-Trp-NH₂, is also a potent mouse MC4R agonist ($EC_{50} = 25$ nM) but a potent mouse MC3R antagonist ($pA_2 = 7.25$, $K_i = 56$ nM.) These small peptides have been claimed for the treatment of obesity and the control of appetite.

Millennium has claimed [137] a large number of MC4R-binding compounds, such as substituted 1,4,5,6-tetrahydropyrimidines related to compound 26. They are claimed as agonists, antagonists and modulators of MC4R, useful for the treatment of disorders associated with pigmentation, bone or weight loss.

Finally, Schering has claimed [138] usage of MC4R agonists (compounds not specified) in combination with phosphodiesterase 5 inhibitors for the treatment of erectile dysfunction and other disorders. Similarly, co-administration of melanocortin receptor agonists (MC1R or MC4R agonists) with phosphodiesterase inhibitors has been claimed by Bristol-Myers Squibb [139] for the treatment of inflammatory, immune and neurodegenerative diseases and/or stroke. Action Pharma APS has also claimed [140] a method for the treatment and prevention of inflammation, infection or cancer in which α -MSH and erythropoietin are co-administered.

3. Expert opinion

In the last 15 months, MC4R agonists have again dominated the patent literature of melanocortin receptor ligands. A number of laboratories previously involved in the pursuit of non-peptide MC4R agonists have claimed an additional series of compounds. Several other laboratories have also joined the field by publishing their MC4R agonists. Similar to the previously disclosed low molecular weight compounds [1-3], the majority of the new agonists are derivatives of piperidines, spiro-piperidines or piperazines (Amgen, Bristol-Myers Squibb, Eli Lilly, Merck, Neurocrine, Procter and Gamble) or substituted guanidines (Chiron and Melacure.). These compounds are claimed for the treatment of obesity and/or erectile dysfunction and appear to reflect an unwavering commitment of the pharmaceutical research community towards the development of drugs for these two therapeutic areas. Multiple nonspecific claims are almost routinely attached to the new melanocortin ligands. At the present time, it is impossible to discuss the usefulness of these compounds for potential clinical interventions because, with only a few exceptions, the results of their

biological evaluation have not been disclosed yet, neither in the patent nor in the general literature. This may be due to some unsatisfactory pharmacological properties or inadequate efficacy of compounds claimed or to confidentiality issues.

In the last 15 months, some efforts have also been made to apply novel templates to the design of low molecular weight melanocortin ligands. Of those, the new MC4R ligands from Neurocrine are based on the pyrrole template, from Merck on the pyridazone structure and from Ortho-McNeil on the thiaziazole motif. Similarly, the usefulness of these compounds for potential clinical application cannot be assessed at the present time because only limited biological data are available for the selected few. However, these agents may provide new directions to the drug discovery efforts.

A potential utility of MC4R agonists for the treatment of obesity is clearly substantiated by vast human genetic evidence. In addition, rodent pharmacological data suggest that MC4R agonists may be effective to treat erectile dysfunction. It remains to be determined whether selective MC4R agonists would be superior to non-selective MC agonists, which appear to be pro-erectile agents in humans.

In the two recently disclosed human studies, peptidic MC4R agonists were evaluated. The analogue of MT-II (and previously, MT-II by itself [38]), Palatin's PT-141 compound [39], was shown to increase erectile activity in healthy men and in patients with erectile dysfunction when given intranasally. The α -MSH/ACTH(4-10) peptide was shown by Fehm *et al.* [40] to reduce body fat and plasma concentrations of leptin and insulin, when administered intranasally to normal weight humans. To the best of the authors knowledge, human studies have not been reported with any low molecular weight MC4R agonist.

Peptides, in general, are regarded to be unsuitable for drug development due to their low enzymatic stability, poor oral bioavailability and high cost of production. Yet, PT-141 and α -MSH/ACTH(4-10) were shown to be efficacious when an alternative route of delivery was applied. In the absence of safe and effective compounds suitable for oral delivery, the alternative routes of administration, for both peptides and low molecular weight compounds, may become methods of choice in treating erectile dysfunction and obesity as well. Probably, even an injectable antiobesity agent could become a welcome alternative to a gastric bypass surgery. Taking into account improvements in drug formulation and delivery and diminishing costs of peptide synthesis, a peptidic MC4R agonist with superior pharmacological, safety and efficacy properties should not be dismissed out of hand as unsuitable for drug development. Commercial success of numerous peptide drugs such as LH-RH agonists, somatostatin and vasopressin analogues, to name a few, supports this notion.

Invaluable role of peptides like NDP- α -MSH, MT-II and SHU-9119 (potent but non-selective melanocortin receptor ligands) in almost all aspects of melanocortin research, is broadly acknowledged across the field [1-12]. Yet, more

selective research tools are required to understand and validate the functions of the MC receptors in various clinical conditions, for example, MC1R and MC5R in skin disorders, MC1R and MC3R in inflammation and MC3R and MC4R in energy homeostasis. Given the complexity of the melanocortin system, ligands with 1000-fold or higher selectivity versus all other known melanocortin receptors would be desirable for such applications. Recent progress in peptide ligand design in the laboratories in academia (Hruby, Schiöth/Vikberg, Haskell-Luevano and Adan) and in industry (Merck, Hoffmann-La Roche, Melacure, Palatin and Procter and Gamble) suggests this to be an attainable goal, albeit not easy. Agonists and antagonists with improved selectivity for MC1R and MC5R have been reported [41-46]. Moreover, Melacure's MC1R agonists MS05 and MS09 have been claimed as anti-inflammatory agents [2,41].

Substituted piperidines and piperazines continue to serve as the structural templates for new non-peptidic MC4R agonists. It is interesting to note that recently disclosed (Amgen, Taisho) MC4R antagonists are piperazine-based compounds as well [31,32]. The Taisho compound has been claimed for the treatment of anxiety and depression [31], potential new opportunities for the utilisation of the MC4R ligands. Independently, growing pharmacological evidence in rodents suggests [18-20] that MC4R antagonists might be suitable for treating cachexia and anorexia, disorders of nutrient imbalance associated with many acute and chronic diseases such as cancer, heart failure, Alzheimer's disease and AIDS. Although human pharmacological validations are not yet available for these hypotheses, it is likely that some drug discovery efforts directed towards compounds which antagonise MC4R signalling might be initiated in the near future. Compounds from Amgen and Taisho might prompt medicinal chemists to revisit the piperazine (and piperidine) template for further designs and retesting of already existing compounds with similar structures. Available research tools [2,34] such as selective peptide MC4R antagonists (HS-014, HS-024, HS-131 and MBP-10) will undoubtedly aid in the research and drug discovery processes.

Similarly, better understanding of the role of α -MSH in inflammation and certain skin disorders [10,11] may intensify medicinal chemistry efforts directed towards MC1R ligands (and perhaps MC3R and MC5R ligands) suitable for treating these conditions; whereas, the recent reports [2,47] on antimicrobial effects of α -MSH and its analogues against *Staphylococcus aureus* and *Candida albicans* may encourage efforts focused on the development of α -MSH derivatives as a novel class of anti-infective agents (they may not necessarily be MCR ligands, since it is not yet known if the MCR exist in yeast).

In conclusion, advances have been made towards further understanding of the role of α -MSH in various clinical conditions, in particular eating disorders and erectile dysfunction. Yet, in spite of the intensive basic research and drug discovery efforts, the development of clinically useful agents for these two therapeutic areas remains a challenge.

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