Anti-obesity Agents: A Focused Review on the Structural Classification of Therapeutic Entities

Sangmi Oh1, Koon Soon Kim3, Young Sun Chung4, Minho Shong5 and Seung Bum Park*1,2

1Department of Chemistry and 2Department of Biophysics and Chemical Biology, College of Natural Science, Seoul National University, Seoul 151-747, Korea; 3Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea; 4Department of Counseling, Korea Cyber University, Seoul 110-340, Korea; 5Division of Endocrinology, Department of Internal Medicine, Chungnam National University School of Medicine, Daejeon, Korea.

Abstract: In addition to its enormous impacts on an individual’s quality of life, obesity is a daunting health problem in the world today and the increasing rate of obesity is now causing a severe burden on health care systems. Fortunately, the normalization or reduction of increased body fat reverses the obesity-associated morbidities, such as hypertension, glucose intolerance, dyslipidemia, and fatty liver diseases. However, the modification of lifestyle in a case of established clinical obesity is very difficult to achieve. Recent breakthroughs in relation to the molecular mechanism regulating body weight and energy metabolism give us hopes for the development of anti-obesity drugs. Even with the high social demand for an effective treatment for obesity and extensive researches, both in academia and the pharmaceutical industry, only two weight-loss drugs, sibutramine and orlistat, have been approved by the FDA for long-term treatment. In addition, the current bottleneck in drug discovery shows that a more detailed understanding of the pathogenesis of obesity is an essential element for the development of efficacious treatment. In this review article, we focus on the structural origin of chemical entities for anti-obesity treatment along with the rationale for drug discovery, rather than categorizing the clinical efficacy or pharmacological target of obesity. For the clarification of the structural origin, we formed a collection with 4 major groups, including natural products, natural product mimetics, synthetic small molecules, and peptides/hormones. This analysis might provide strategic plans for medicinal chemists, biologists, and physicians to begin an optimistic era with a new class of pharmaceutical adjuncts for obesity therapy.

Keywords: Obesity, satiety, energy expenditure, structural origins, anti-obesity drugs.

INTRODUCTION

Obesity is defined as the state of possessing a high amount of body fat or adipose tissue in relation to lean body mass. The term overweight refers to an increased body weight in relation to height that may or may not be due to increases in body fat. Excess fat accumulation and adipose tissues expansion is a daunting health problem in today’s world and the increasing rates of obesity are now causing severe burdens on health care systems. Obesity and overweight negatively impact an individual’s psychological well-being and may contribute to the development of depression. In addition to the enormous impact on the quality of life [1], obesity is a strong risk factor for the development of type 2 diabetes, coronary artery diseases or cerebrovascular strokes, non-alcoholic fatty liver diseases, sleep apnea, osteoarthritis, and certain forms of cancers [2]. Although genes are important in the determination of obesity development, the rising epidemic is mostly the result of profound changes in socioeconomic status and behavioral patterns over recent decades.

The most effective way to reduce obesity-related health problems is the prevention of obesity. When such prevention fails or is ineffective, medicinal treatment may become a necessity. Fortunately, the normalization or reduction of increased body fat mass reverses the obesity-associated morbidities, such as hypertension, glucose intolerance, dyslipidemia, and fatty liver diseases [3]. Currently, the modification of lifestyle, including a low calorie diet and regular exercise, is the most effective modality for the prevention or treatment of obesity and its related metabolic syndrome phenotypes. However, the modification of lifestyle in patients with established clinical obesity is very difficult to achieve. Recent breakthroughs related to the molecular mechanisms that regulate body weight and energy metabolism give us hopes for the development of new anti-obesity drugs. The primary actions of the drugs currently being used or developed are related to one of the following mechanisms: reducing food intake, blocking nutrient absorption, modulating fat storage, increasing thermogenesis, and modulating hypothalamic food intake regulation [4].

Even with the high social demand for an effective treatment for obesity and the extensive studies that have been done, both in academia and the pharmaceutical industry, only two weight-loss drugs, sibutramine and orlistat, have been approved by the FDA for long-term treatment. Moreover, these two anti-obesity medications have failed to gain a large market share, due to their prominent side effects [4]. Therefore, the market for a safe and efficacious drug is potentially huge, and development strategies for new therapeutic agents that can overcome the limitations of existing drugs or those currently being
developed attract ample attention from the scientific community. In addition, the current bottleneck in drug discovery shows that a more detailed understanding of the pathogenesis of obesity is an essential element for the development of efficacious treatment. However, any potential long-term therapeutic that targets the complex central energy homeostasis mechanism, which interacts and overlaps with many other physiological processes, will lead to unacceptable side-effect profiles. The complexity of protein networks in neurobiology and pharmacological physiology will not allow an effective treatment for obesity to be provided by tackling a single molecular target or molecular pathway. In order to achieve meaningful and sustainable weight-loss without a long-term safety issue, various new chemical entities might be needed to tackle multiple biological targets in the natural regulatory circuits.

Owing to both an increasing patient population and the availability of new therapeutic approaches, many review papers have presented anti-obesity agents that are currently used in clinical practice as well as potential candidates, categorized by their efficacy or pharmacological target, from ongoing research. In this article, we turned our attention to the structural origin of chemical entities for anti-obesity treatment along with the rationale for drug discovery. As shown in Fig. (1), FDA-approved therapeutic agents in all disease areas from 01/1981 to 06/2006 can be categorized into 8 subgroups based on their structural origins [5]. To clarify these structural origins, we collected these subgroups into four major structural origin categories as follows: (1) Natural products have long been a significant source of drugs, from the natural product itself or its structural derivatives. (2) Natural product mimetics are designed and synthesized based on the structural motifs from natural products. (3) Synthetic small molecules discovered from high throughput screening also make up a significant percentage of new chemical entities. (4) Peptides/hormones and biologics have become significant structural entities in drug discovery. Based on these four major structural classifications, we will discuss the current effort for the development of anti-obesity agents, along with the discovery rationale in medicinal chemistry.

1. ANTI-OBESEITY AGENTS DERIVED FROM NATURAL PRODUCTS

1.1. Lipase Inhibitor: Orlistat

Orlistat (Xenical® of Roche), known as tetrahydrolipstatin, has been one of the few drugs for the long-term treatment of obesity since it was launched in 1998. The mode of action of orlistat is the reduction of energy intake by preventing fat absorption through the irreversible inhibition of lipase activity in the gastrointestinal tract. As shown in Fig. (2), orlistat is a synthetic derivative of lipstatin, a potent natural inhibitor of pancreatic lipases, isolated from Streptomyces toxytricini [6,7]. Orlistat was synthesized as one of the lipstatin analogues and recognized as an anti-obesity agent by its selective inhibition of pancreatic lipase activity. It has the additional advantages of physical stability and being easy to be synthesized, compared to its parent lipstatin [8,9]. Hadváry and coworkers at Hoffmann-La Roche beautifully illustrated the lipase-inhibition mechanism of orlistat: the β-lactone moiety of orlistat is covalently modified with the hydroxyl group of Ser152 at the active site of porcine pancreatic lipase, which inhibits the hydrolysis and concomitant absorption of dietary triacylglycerol [10]. In that study, the exact serine residue was identified through a quantitative amino acid analysis, N-terminal sequencing, and mass spectrometry after the proteolytic degradation of pancreatic lipase inhibited with radioactively labeled orlistat.

![Fig. (1). All new chemical entities, 01/1981-06/2006, by Source (N = 1,184) [5].
B – biological, usually a large peptide or protein; N – natural product; ND – derived from a natural product and is usually a semi-synthetic modification; S – totally synthetic drug found by random screening or modification of an existing agent; S* – made by total synthesis, but the pharmacophore is from a natural product; NM – natural product mimetics; V - vaccine.](image-url)
1.2. Appetite Suppressor

Contrave® is a combination therapy of naltrexone and bupropion, and is currently undergoing Phase III clinical trials by Orexigen Therapeutics. Bupropion has been used for the treatment of depression and smoking addiction, while naltrexone has been independently used to treat opium addiction withdrawal. It was claimed that the combination of these two drugs, naltrexone and bupropion, synergistically increases the firing of neurons and reduces food intake through the stimulation of satiety. One of these two components, naltrexone, is known as an antagonist of opioid receptors and competitively binds to the same binding site as morphine, which is a highly potent opioid analgesic natural compound isolated from the plant poppy. Naltrexone can be synthetically described as a substituted oxymorphone and oxymorphine is a semi-synthetic morphine derivative with a more potent analgesic effect than morphine itself. Based on the concept of structure-activity relationship in medicinal chemistry, molecules with structural similarities tend to have similar biological activities, especially in the case of enzymatic activities. However, due to the complexity of biological systems, a small perturbation of structural elements can result in exactly opposite biological activities. As shown in Fig. (3), oxymorphine and morphine are agonists of the opioid receptor, while naltrexone serves as an antagonist, despite their structural similarities.

Species of the African plant Hoodia, in particular Hoodia pilifera and Hoodia gordonii, have long been used as an herbal medicine for treating indigestion or satisfying hunger. The active ingredient isolated from Hoodia species is an oxypregnane steroidal glycoside (P57) [11,12]. P57 was licensed by the pharmaceutical company Phytopharm as an appetite suppressant and they proceeded with Phase I and II clinical trials for the treatment of obesity. The mechanism of action of P57 has not yet been clearly understood despite a statistically significant reduction in body fat content with a satisfactory overall safety profile. However, Phytopharm decided not to continue with further clinical trials, but announced its intention to develop hoodia extract as a satiety stimulator.

2. ANTI-OBESITY AGENTS FROM NATURAL PRODUCT-MIMETICS

2.1. Anorectic Agents: Derivatives of Monoamine Neurotransmitters

The monoaminergic neuronal systems have been shown to be involved in feeding behavior, energy balance, and the maintenance of body weight [13]. Most of their functions are regulated by the active interplay of monoamine neurotransmitters, such as serotonin (5-HT), dopamine (DA), and noradrenalin (NE). An anorectic effect can be expected through the modulation of the monoaminergic system, either by controlling the release level of neurotransmitters, by inhibiting the re-uptake of neurotransmitters, or both [14]. As shown in Fig. (5), monoamine neurotransmitters share a common structural element, and the systematic modification of this key moiety has been provided by a series of potential anorectic agents through their structural similarity with monoamine neurotransmitters.

The first example of these approaches is noradrenergic agents derived from monoamine neurotransmitters for the treatment of obesity as appetite suppressants. Amphetamine...
has long been known as a sympathomimetic derivative of a
monoamine neurotransmitter that increases the level of
noradrenalin, serotonin, and dopamine in the brain. Amphet-
amine-like agents, including diethylpropion, phendime-
trazine, and phentermine, are currently used as anti-obesity
drugs only in short term therapy because of the high risks of
addiction and serious cardiovascular complications, most
likely related to their dopaminergic effects [15]. Phentermine
is a synthetic analogue of amphetamine with only an
additional methyl group on the carbon adjacent to the amine
moiety. However, this small structural change results in a
significant difference in potency and selectivity on the
release and reuptake of monoamine neurotransmitters [13].

![Diagram of P57](image)

**Fig. (4).** The structure of P57, a natural anti-obesity agent.

![Diagram of Monoamine Neurotransmitters](image)

**Fig. (5).** Monoamine neurotransmitters related to the discovery of anti-obesity agents.

related to adrenergic drugs. However, the trifluoromethyl
group on the phenyl ring dramatically stimulates seroto-
nergic activity [16]. Dexfenfluramine is the therapeutically
active dextrorotatory stereoisomer of fenfluramine, which
ensures its enhanced selectivity on the release and re-uptake
of serotonin compared to fenfluramine. Bupropion, a
derivative of a monoamine neurotransmitter, is currently
being evaluated in Phase III clinical trials as an anti-obesity
drug in combination with naltrexone. It has been reported
that the combination therapy of bupropion and naltrexone
(Contrave®) synergistically stimulates the pro-opiomela-
nocortin (POMC) system by enhancing the release of α-
melanocyte-stimulating hormone (α-MSH) and cocaine and
amphetamine regulated transcript (CART), which is
associated with a reduction in food intake [17]. However,
bupropion was originally developed as an antidepressant
drug (Wellbutrin®). Through clinical observations, bupro-
pion was seen to help patients stop smoking and thus became
the first drug marketed as a smoking cessation aid (Zyban®).
In fact, various pharmacological activities of a single
therapeutic agent can be identified during clinical trials or
practice, which can be immediately associated with a new
chemical entity with different therapeutic efficacy, namely
drug repositioning. Bupropion is an excellent example for
the approach of drug repositioning.

One of the leading pharmacological therapies in obesity
management is sibutramine (Meridia® of Abbott), a typical
serotonin and noradrenalin re-uptake inhibitor (SNRI),
which was approved by the FDA in 1997. Initially, sibutra-
mame was developed for the treatment of depression, but it
was later repositioned as an anti-obesity drug, because
weight loss was consistently observed after treating depres-
sed patients with sibutramine [18]. Sibutramine contains the
β-phenylethylamine moiety found in monoamine neuro-
transmitters, which is also shared by amphetamine-like

Unlike noradrenergic agents, fenfluramine and dexfen-
fluramine are classified as serotonergic anti-obesity agents.
From the structural point of view, fenfluramine is closely

![Diagram of Amphetamine-like Noradrenergic Agents](image)

**Fig. (6).** Amphetamine-like noradrenergic agents for the stimulation
of noradrenalin release: diethylpropion, phendimetrazine, and
phentermine.
anorectic agents. However, the introduction of bulky substituents at the α- and β-positions from the amine moiety resulted in a significant difference in the pharmacological mode of action compared to several other classes of anorectic agents [19]. Sibutramine also appears to have a low potential for abuse liability because of its selective re-uptake inhibition of serotonin and noradrenalin without the stimulation of neurotransmitters, especially dopamine, from nerve endings [19]. Interestingly, sibutramine itself has a marginal in vitro activity and is a racemic mixture of (R)- and (S)-enantiomers, as shown in Fig. (7). In comparison, its metabolites, desmethylishibutramine and didesmethylishibutramine, can predominantly mediate the re-uptake inhibition of noradrenalin and serotonin over dopamine with significantly enhanced efficacy and selectivity (see Table 1) [19]. Both (R)-enantiomers of its demethylated metabolites are considerably more potent than (S)-enantiomers as well as their parent (R/S)-sibutramine [13,20].

Fig. (7). Phenylethylamine derivatives marketed as anorectic agents. Serotonergic agents (stimulators on serotonin release): fenfluramine and dexfenfluramine; Noradrenalin and dopamine re-uptake inhibitor: Bupropion; Serotonin and noradrenalin re-uptake inhibitor (SNRI): Sibutramine (Meridia™ of Abbott).

2.2. 5-HT2C Receptor Agonist: Lorcaserin

Lorcaserin (APD-356) is a serotonergic anti-obesity drug that is currently under evaluation in the final phase of clinical trials by Arena Pharmaceuticals. It is a selective serotonin receptor 5-HT2C agonist. The identification of selective agonists toward 5-HT2C, among the 5-HT2 receptor family, which includes 5-HT2A, 5-HT2B, and 5-HT2C, is the key to discovering serotonergic anti-obesity drugs, because agonism on the 5-HT2B and 5-HT2A receptors can cause side effects, such as valvular heart defects and hallucinations, respectively [21,22]. Lorcaserin also contains the β-phenylethylamine substructure incorporated in a rigid molecular framework, 3-benzazepines. The introduction of conformational rigidity is one of the well-established approaches in medicinal chemistry to enhance the pharmacological activity of bioactive small molecules through the prepaid entropic penalty. Therefore, enhanced selectivity and potency toward proteins-of-interest can be achieved through the structural modification of conformationally rigid derivatives with the desired geometry and orientation. The azepinoindole compound PNU-22394A is a good example of structural modification via the introduction of conformational rigidity to an endogenous monoamine neurotransmitter, serotonin. But PNU-22394A is a nonselective agonist toward all human 5-HT2 receptor subtypes [23]. Through extensive structure-activity relationship studies for the identification of a selective agonist on the 5-HT2C receptor, researchers at Arena Pharmaceuticals recognized the importance of the chloro substituent at the C-8 position on the 3-benzazepine skeleton for selectivity and potency [21]. The further structural modification of 8-chlorobenzazepine 1 revealed that a methyl substituent in the C-1 position increases 5-HT2C selectivity over 5-HT2A and the resulting lorcaserin was developed as the first drug candidate with a benzazepine structure [21,24].

3. ANTI-OBESITY AGENTS FROM SYNTHETIC SMALL MOLECULES

3.1. CB1 Antagonist: Rimonabant

Marijuana (Indian hemp Cannabis sativa L.) has long been utilized as a folk remedy due to its beneficial effects, such as analgesia, antiemesis, anticonvulsive, appetite improvement, and so on. However, marijuana is regarded as a narcotic due to its psychoactive properties. In 1964, Gaoni
The paradigm to develop new artificial cannabinoids has focused on maximizing the beneficial effect (anorectic effect) and minimizing the detrimental effect (psychoactive effect). The first potent, orally active and selective CB1 receptor antagonist is rimonabant (SR141716, Acomplia® of Sanofi-Aventis), which has a novel diarylpyrazole core skeleton [28]. The structure-activity relationship (SAR) of rimonabant has been understood through various reports in the literature, including a computational approach, pharmacological assay-based approach with receptor binding affinities, activity-based approach on functional antagonistic effects, and so on. Makriyannis et al. reported the structural requirement for a potent and selective antagonist to the brain’s CB1 receptor through a systematic SAR study [29]. Through the construction of a series of pyrazole derivatives and associated competition binding studies with the CB1 receptor, they identified the following structural elements: (1) a para-substituted phenyl ring at the 5-position of the pyrazole ring, (2) a carboxamido group at the 3-position, and (3) a 2,4-dichlorophenyl substituent at the 1-position. Another structural requirement for a selective CB1 receptor antagonist was recognized to be an aminopiperidine moiety at the 3-position of the pyrazole ring, through a SAR study of amide and hydrazide analogues, as well as various halogenated derivatives of rimonabant, which was rationalized by a quantitative SAR study [30]. Due to the difficulties in obtaining crystals of the membrane-bound CB1 receptor, detailed structural information has not been sufficiently revealed. Therefore, the binding mode of rimonabant on the CB1 receptor was postulated as shown in Fig. (9) based on the pharmacophore model of the structural requirements and a SAR study for selective and potent CB1 receptor antagonists [31].

![Diagram of rimonabant and SAR study](image-url)
There are a series of rimonabant analogs with the diarylpyrazole skeleton as selective CB1 antagonists [31,33-35]. For example, surinabant (SR147778) is an analogue of rimonabant with a structural replacement of the 4-chlorophenyl group at the 5-position and the methyl group at the 4-position of the pyrazole ring with the 4-bromophenyl and ethyl groups, respectively. Even though surinabant was reported to have an enhanced oral bioactivity with an extended duration of action, compared to rimonabant, the development of surinabant for the treatment of smoking cessation was discontinued [36]. AM251 was originally reported to be a radioisotope 125I-labeled ligand for the radioimaging of the CB1 receptor [37]. The introduction of iodine instead of chlorine at the para position of the phenyl moiety at the 5-position of rimonabant exhibits slightly enhanced binding affinity and selectivity toward the CB1 receptor.

NESS 0327, which has a fused polycyclic pyrazole, was designed to introduce a conformational rigidity onto the pharmacologically active core skeleton of rimonabant [38], which is a well-established strategy in medicinal chemistry to enhance binding affinity and selectivity. It is more potent and selective to the CB1 receptor than the CB2, compared to rimonabant. However, NESS 0327 has been used only in academic research because of its poor bioavailability [31,34]. The indazole derivative O-1248, on the other hand, has poor affinity to the CB1 receptor due to its unfavorable conformational constraint [39]. The 3,4-diarylpyrazoline derivative ibipinabant (SLV319) was identified through a competitive CB1-receptor binding assay with endogenous arachidonic acid against small molecule collections containing the derivatives and isosteres of rimonabant with structural similarities. Based on an in vivo test, ibipinabant displayed in vivo activity similar to rimonabant. However, its opposite enantiomer has a significantly lower affinity to the CB1 receptor [40]. This experimental data were rationalized by their computational modeling studies, that is, the three-dimensional structure of ibipinabant nicely mimics that of rimonabant; however its enantiomer showed an unfavorable aromatic stacking pattern to the binding pocket of the CB1 receptor. X-ray diffraction also indicated the presence of intramolecular hydrogen bonding in ibipinabant, which is consistent with that of rimonabant. There are a series of rimonabant analogs with various core skeletons, such as bicyclic derivatives of diarylpyrazole (Otenabant, CP-945,598 of Pfizer) [35], arylbenzofuran (LY320135 of Eli-Lilly) [41], its acyclic analogue (Taranabant, MK-0364 of Merck) [42], and so on.

Table 2. The Representative Antagonists of CB1

<table>
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<tr>
<th>Compound*</th>
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<tr>
<td><img src="image" alt="Rimonabant" /></td>
<td>[28]</td>
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<tr>
<td>1. Rimonabant (SR141716, Acomplia®)</td>
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<tr>
<td>2. Sanofi-Aventis</td>
<td></td>
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<tr>
<td>3. The first-in-class selective cannabinoid receptor CB1 antagonist for anti-obesity drug</td>
<td>Approved in EU in 2006 but the rimonabant clinical development program was discontinued in 2008</td>
</tr>
<tr>
<td><img src="image" alt="Surinabant" /></td>
<td>[36]</td>
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<tr>
<td>1. Surinabant (SR147778)</td>
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<td>2. Sanofi-Aventis</td>
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<td>3. Longer duration of action than rimonabant</td>
<td>Discontinuation of clinical development for smoking cessation in 2008</td>
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<tr>
<td><img src="image" alt="Am251" /></td>
<td>[37]</td>
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<tr>
<td>1. AM251</td>
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<td>2. A. Makriyannis’ group in University of Connecticut</td>
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<td>3. Previously reported as a radioimaging ligand</td>
<td>More selective for the CB1 receptor compared to rimonabant</td>
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## Anti-obesity Agents: The Structural Classification of Therapeutic Entities

(Table 2) Contd….

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<td>3. Derivative of conformational rigidity onto pharmacologically active core skeleton of rimonabant</td>
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<td>2. B. R. Martin’s group in Virginia Commonwealth University</td>
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<td>3. Chiral 3,4-diarylpyrazoline derivative of rimonabant</td>
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<td>2. Pfizer</td>
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<td>3. Fused bicyclic purine derivative of rimonabant</td>
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<tr>
<td>2. Eli-Lilly</td>
<td></td>
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<tr>
<td>3. Arylbenzofuran derivative of rimonabant</td>
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* 1. Name of compound; 2. Research group; 3. Special features
Table 3. The Representative Agonists of the β3-Adrenergic Receptor

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<tr>
<th>Compound*</th>
<th>Ref.</th>
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| 1. Arylethanolamine derivatives | 1. BRL37344  
2. Beecham  
3. The representative compound of β3-adrenergic receptor ligands as thermogenic agents with an arylethanolamine substructure |
| ![Arylethanolamine derivative](image1) | [43] |
| 1. CL-316,243  
2. Wyeth  
3. Conformationally restricted compound with poor pharmacokinetic profile |
| ![Arylethanolamine derivative](image2) | [16] |
| 1. N-5984  
2. Nissin Kyorin Pharmaceuticals  
3. Conformationally restricted compound and the completion of Phase IIa clinical trials in 2007 |
| ![Arylethanolamine derivative](image3) | [44] |
| 1. L-757,793  
2. Merck  
3. Pyridylethanolamine derivative having sulfonamide moiety |
| ![Arylethanolamine derivative](image4) | [46] |
| 1. CP-331,684  
2. Pfizer  
3. Pyridylethanolamine derivative |
| ![Arylethanolamine derivative](image5) | [45] |
| 2. Aryloxypropanolamine derivatives | 1. Compound (2)  
2. ICI pharmaceuticals  
3. The representative aryloxypropanolamine derivative described as β3-adrenoceptor agonist |
| ![Aryloxypropanolamine derivative](image6) | [47] |
| 1. LY-377,604  
2. Eli Lilly  
3. An excellent agonistic activity toward β3-adrenoceptor along with antagonistic effects toward β1- or β2-adrenoceptors |
| ![Aryloxypropanolamine derivative](image7) | [45] |

* 1. Name of compound; 2. Research group; 3. Special features

3.2. β3-Adrenergic Receptor Agonists

The β3-adrenergic receptor (or β3-adrenoceptor) is primarily found in adipose tissue and mediates a variety of metabolic functions, including the increase of energy expenditure and the motility in the GI tract [16]. For example, the β3-adrenergic receptor can induce catecholamine-stimulated lipolysis in white and brown adipose tissue and thermogenesis in brown adipose tissue (BAT). Due to the fact that BAT thermogenesis is primarily responsible for the removal of excess fat in animal models, the identification of selective agonists to the β3-adrenergic receptor has been a key research topic for the development of thermogenic anti-obesity drugs [16]. Through extensive studies by various research groups, several compounds are currently under various stages of clinical evaluation and their structural features can be categorized into two classes: (1) arylethanolamine and (2) aryloxypropanolamine (see Table 3).
BRL37344 is one of the first β3-adrenergic receptor agonists with an aryloxypropanolamine substructure [43]. In its initial SAR study, the carboxylate moiety was essential to increase the functional selectivity for β3 over β1 or β2 adrenoceptors, and the (R,R)-diastereomer was the most active among four diastereomers [16]. CL-316,243 and N-5984 are derivatives of BRL37344 with a conformational restriction on the carboxylate moiety. They have been reported to increase metabolic rates and reduce body weight in clinic trials as full agonists of the human β3-adrenergic receptor. CL-316,243 was reported to have a poor pharmacokinetic profile because of the dicarboxylic acid moiety [16] and N-5984 was under evaluation in a Phase II clinical trials [7,44]. L-757,793 and CP-331,684 are also selective and potent β3-adrenergic receptor agonists with a pyridyl-ethanolamine core skeleton [45]. In the case of L-757,793, the sulfonamide group serves as a bioisostere of the carboxylate moiety in BRL37344-related compounds [46].

As a second class of human β3-adrenergic receptor agonist, compound (2) is a representative aryloxypropanolamine derivative described as a selective β3-adrenergic receptor agonist, discovered from a large number of related compounds [47]. A series of aryloxypropanolamine derivatives containing heteroatoms or its bioisosteres have been reported as selective β3-adrenoceptor agonists [16]. LY-377,604 demonstrated an excellent β3-adrenoceptor agonistic activity, along with antagonistic effects toward β1- or β2-adrenoceptors [45]. Even though an extensive effort has been put into the development of an anti-obesity drug from human β3-adrenergic receptor agonists, the clinical evaluation of β3-adrenergic receptor agonists for an anti-obesity drug was somewhat disappointing because of their poor efficacy and substantial β1- and β2-mediated side effects in human clinical trials, despite excellent profiles in preclinical results [16].

3.3. MCH-R1 Antagonists

Melanin-concentrating hormone receptor 1 (MCH-R1) has attracted significant attention as a promising therapeutic target for the treatment of obesity. Melanin-concentrating hormone (MCH) is a cyclic nonadecapeptide expressed in the lateral hypothalamus and the natural ligand for the seven-transmembrane G-protein-coupled receptors (GPCRs) known as MCH-R1 and MCH-R2 [48]. The role of MCH in feeding went unrecognized for many years, until it was discovered in 1996 that MCH is up-regulated during fasting in both normal and obese mice [49]. The MCH-knockout mice revealed a reduced calorie consumption, more resistance to diet-induced obesity, and enhanced metabolic rate [49]. MCH-R1 was originally identified in 1999 with the functional implication in feeding and energy homeostasis. In comparison, MCH-R2 was identified subsequently on the basis of the sequence homology to MCH-R1 without the elucidation of potential physiological functions because of its species-specific expression [49,50]. Many pharmaceutical research groups have reported the discovery of MCH-R1 antagonists as novel anti-obesity drug candidates through the extensive screening of a GPCR-biased small molecule library. Among those small-molecule-based MCH-R1 antagonists, GSK-856464 (GlaxoSmithKline), AMG-076 (Amen), and NGD-4715 (Neurogen) were reported to be evaluated in Phase I clinical trials without further information. This review focused on the recent progress on non-peptidic small-molecule MCH-R1 antagonists in the recent literature [48-50].

T-226296 was the first orally active MCH-R1 antagonist containing the biphenyl group as a key structural motif, which was identified from screening exercises on small molecule collections at Takeda. T-226296 showed the in vivo inhibition of MCH-induced food intake in rats [51]. SNAP-7941 was a novel, highly selective and potent MCH-R1 antagonist found by Synaptic from the screening of a GPCR-biased compound collection through a human MCH-R1 functional assay [52]. They also used this compound to study the behavioral effects of the pharmacological antagonism of MCH-R1. Since the development of these two candidates (T-226296 and SNAP-7941) as the first reports of chronic MCH-R1 antagonism in a disease model, many synthetic analogs or isostreres have been reported as MCH-R1 antagonists. For example, SB-568849 developed by GSK and compound (3) developed by Neurocrine were reported as MCH-R1 antagonists containing the biphenyl carboxamide substructure originally identified in T-226296 [53]. SB-568849 was developed through the structural modification of an initial hit compound using parallel high throughput synthetic techniques that allow the rapid exploration of the structure-activity relationship. Actually, GSK-856464 has a conformationally constrained amide isostere of SB-568849, and this structural change improved the drug-like properties of GSK-856464. Neurocrine also designed and synthesized an MCH-R1 antagonistic compound (3) containing biphenyl carboxamide-based bis-aminopyrroline urea with enriched chirality [54], along with its conformationally rigid analogs, a thienopyrindazinone-based compounds series [55].

The small-molecule MCH-R1 antagonists discovered by Schering-Plough are exemplified by a biaryl urea-type compound (4), which was also identified through the structural modification of original hit compound for optimization in a SAR study [56]. Despite the promising pharmacokinetic profile of biaryl urea itself, the possible risk from exposure to a highly mutagenic biarylamine intermediate at any stage of the development of this series was considered unacceptable [56-58]. To overcome this problem, researchers at Schering-Plough identified and developed another series of MCH-R1 antagonists as orally efficacious anti-obesity therapeutics containing a bicycloalkyl urea-type substructure [57,58]. Procter & Gamble’s compound (5) was also developed through the introduction of a conformationally constrained amide isostere from an initial biphenyl amide-based hit compound, GSK-856464, and contains a quinoline moiety as a linker [59].

Compound (6) was identified by Argenta Discovery Ltd. using chemoinformatics with a computational screening approach based on the structures of 11 previously identified small-molecule MCH-R1 antagonists. All of the virtual searches were carried out within a database of approximately 615,000 commercially available compounds and the resulting compound (6), with the prediction of the highest potency, demonstrated antagonistic efficacy with IC50 = 55 nM. A follow-up SAR study was also pursued through the modification of the initial hit with the proposed binding mode of the antagonists toward MCH-R1 [60].
Table 4. The Representative Antagonists\textsuperscript{*} of MCH-R1

1. MCH-R1 antagonists that have progressed to Phase I clinical trials.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK-856464 (GW-803430)</td>
<td>GSK</td>
<td>3. No further information about development program since its initiation of Phase I clinical trials</td>
</tr>
<tr>
<td>NGD-4715</td>
<td>Neurogen</td>
<td>3. Discontinuation of Phase II clinical trials for anti-obesity in 2008</td>
</tr>
<tr>
<td>AMG 076</td>
<td>Amgen</td>
<td>3. Discontinuation of Phase I clinical trials for anti-obesity in 2007</td>
</tr>
</tbody>
</table>

2. MCH-R1 antagonists based on biphenyl scaffolds or isosteric replacements.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-226296</td>
<td>Takeda</td>
<td>3. The first orally active and selective MCH receptor antagonist [51]</td>
</tr>
<tr>
<td>SB568849</td>
<td>GSK</td>
<td>3. Effective MCH-R1 antagonist with low \textit{in vivo} clearance, good brain-blood ratio, and oral bioavailability [53]</td>
</tr>
<tr>
<td>Compound (3)</td>
<td>Neurocrine</td>
<td>3. Chiral small molecule derived from aminopyrrolidine urea with good MCH-R1 antagonistic activity and oral bioavailability [54]</td>
</tr>
</tbody>
</table>
4. ANTI-OBESITY PEPTIDES OR HORMONES

Important discoveries in relation to the neural networks of the hypothalamus and a number of hormones or peptides that are actively involved in hypothalamic regulation established a model for appetite regulation. The current model of appetite regulation is composed of central controllers and peripheral regulators that specifically modify feeding behaviors by acting on hypothalamic neurons [61]. The best characterized pathways are the orexigenic neuropeptide Y (NPY)/agouti-related protein (AgRP) and the anorexigenic pro-opiomelanocortin/cocaine- and amphetamine-related transcript neurons in the arcuate nucleus of the hypothalamus. These neuronal pathways are interconnected and projected to the brainstem, cortical areas, and reward pathways, all of which potentially influence food intake [62].

The hypothalamus-regulating peptides/hormones are present both in neuronal cells and in peripheral tissues, such as adipose and gut tissues. Interestingly, the neuronal activities of the hypothalamus are susceptible to the circulating levels of hormones. These findings provide therapeutic perspectives. Using the hormones or targeting their receptors offers the potential advantage of being able to manipulate appetite without significant side effects. Currently, the most promising hormones for the treatment of obesity are produced from gut tissues, and form the components of the gut-brain axis [63].

<table>
<thead>
<tr>
<th>2. MCH-R1 antagonists based on biphenyl scaffolds or isosteric replacements.</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Diagram" /></td>
<td>1. Compound (4)</td>
</tr>
<tr>
<td>2. Schering-Plough</td>
<td>3. Exemplified compound of biaryl ureas as potent and selective MCH-R1 antagonists</td>
</tr>
<tr>
<td><img src="image2" alt="Diagram" /></td>
<td></td>
</tr>
<tr>
<td>1. Compound (5)</td>
<td>2. P&amp;G</td>
</tr>
<tr>
<td>3. Conformationally constrained MCH-R1 antagonist based on the structure of GSK-856464</td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>3. MCH-R1 antagonists based on various structures.</th>
<th>Ref.</th>
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</thead>
<tbody>
<tr>
<td><img src="image3" alt="Diagram" /></td>
<td>1. SNAP-7941</td>
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<tr>
<td>2. Synaptic</td>
<td></td>
</tr>
<tr>
<td>3. A novel, selective and high-affinity MCH-R1 antagonist</td>
<td></td>
</tr>
<tr>
<td>: The first study of behavioral effects of pharmacological MCH-R1 antagonism using this compound</td>
<td></td>
</tr>
<tr>
<td><img src="image4" alt="Diagram" /></td>
<td>1. Compound (6)</td>
</tr>
<tr>
<td>2. Argenta Discovery Ltd.</td>
<td>3. Novel and potent MCH-R1 antagonist found with a virtual screening approach</td>
</tr>
</tbody>
</table>

* 1. Name of compound; 2. Research group; 3. Special features
4.1. Gut hormones that Regulate Food Intake

4.1.1. Glucagon-Like Peptide-1 (GLP-1)

GLP-1 is rapidly released from lower intestinal L-cells in response to food intake, mainly from carbohydrates and fat. GLP-1, peptide-YY (PYY), and oxyntomodulin are believed to be secreted in the postprandial phase to cause satiety, thus promoting meal termination. All three of these L cell peptides are being explored for their potential anti-obesity effects. GLP-1(7-36) is processed from the pre-pro-glucagon precursor by tissue specific enzymes and is rapidly inactivated by dipeptidyl peptidase (DPP)-4. The DPP-4 protease resistant GLP-1 analogue is already being marketed for the treatment of obese type 2 diabetes. The beneficial effects of GLP-1 on diabetes are mediated by stimulating insulin secretion and promoting weight loss through anorexic effects of GLP-1 on diabetes are mediated by stimulating insulin secretion and promoting weight loss through anorexic actions in the hypothalamus. The human homologue of GLP-1, Exendin-4 (exenatide; Byetta® developed by Amylin/ Lilly), which is extracted from the lizard Heloderma suspectum, overcomes the short biological activity of human GLP-1. It was recently approved and marketed for the treatment of obese type 2 diabetes [64].

Concentrations of GLP-1 have been found to be decreased in obese adults and this phenomenon may be a secondary effect of weight gain [65]. A direct intra-cerebro-ventricular infusion of GLP-1 inhibits food intake [66] in animal models by acting on the hypothalamic paraventricular nucleus (PVN). Peripheral infusion of the GLP-1 analogue decreases food intake and GI motility. In contrast to insulin and sulfonylurea, GLP-1 results in a tendency to reduce body weight. These prominent advantages over conventional anti-diabetic drugs provide new support for the use of a GLP-1 analogue in the treatment of obese type 2 diabetes.

4.1.2. Amylin

Amylin is a pancreatic hormone that is co-secreted with insulin in pancreatic beta cells in response to nutrient intake. Experimental animal studies have shown that amylin may have central and peripheral actions associated with food intake and carbohydrate metabolism. Amylin has an anorexigenic effect by modulating its receptors, which are present in the area postrema of the brainstem [67]. In addition, it has potent inhibitory effects on gastric emptying and glucagon secretion, both of which favor glucose control in the management of diabetes [68]. The stimulation of the amylin receptor or use of amylin analogues is emerging as a comprehensive therapeutic approach in the management of diabetes and obesity. Pramlintide, an analogue of amylin, has been studied in type 2 diabetes as an anti-hyperglycemic agent. Clinical studies of pramlintide in subjects with obesity demonstrated that it has significant, sustained, and dose-dependent weight-loss effects [69]. These studies may stimulate the development of amylin analogues for the care of both diabetes and obesity.

4.1.3. Oxyntomodulin

Oxyntomodulin (OXM) is another product of the tissue-specific differential cleavage of proglucagon and is co-secreted with GLP-1 and PYY by intestinal L cells in response to meal ingestion. A human trial using OXM showed that preprandial subcutaneous injection in overweight and obese subjects over a 4-week period resulted in significant weight reduction compared to placebo [70]. In addition, this study demonstrated that OXM is well-tolerated and has beneficial effects on energy usage. OXM is thought to reduce food intake by a central effect via the GLP-1 receptor and also produces a peripheral effect [71]. Because OXM is inactivated by DPP-4 [72], a DPP-4 resistant OXM analogue is currently under development. Long-term clinical trials are now required to measure the beneficial effects on obesity and diabetes.

4.1.4. Peptide YY (PYY)

PYY(3-36) is an active circulating form that is cleaved from PYY by DPP-4. Studies on the effects of PYY on energy intake in animal models have disagreements, but a number of reports support that peripheral PYY inhibits food intake and reduces body weight in several animal models. Several routes of administration were studied to observe the anti-obesity effects of PYY. The first clinical study and subsequent studies using intravenous administration showed that PYY produces dose-dependent reductions in appetite and food intake. Two investigational studies of PYY delivery via the intranasal route have completed Phase I clinical trials. Although it had nausea as a significant adverse effect, the intranasal administration of PYY in obese subjects resulted in significant reductions in daily caloric intake, which were sustained over the study period [73]. These small scale clinical trials need to be confirmed by more extensive clinical trials in the future.

4.1.5. Pancreatic Polypeptide (PP)

The PP family of peptides, including PP, PYY and NPY, has common structural features. PP is secreted by specific cells located in the periphery of pancreatic islets after nutrient ingestion. The circulating PP concentration has been reported to be reduced by obesity. PP reduces food intake when administered to rodents and humans via the activation of the PP receptor (Y4) in the brainstem and the arcuate nucleus in the hypothalamus. These findings suggest that PP may act as a circulating factor that regulates food intake. Healthy volunteer studies, which investigated the effect of an intravenous infusion of PP (10 pmol/kg/min) on appetite and food intake, showed that the infusion of PP reduced appetite and decreased the energy intake by 21.8 ± 5.7% (P < 0.01) [74]. TM30338, a synthetic analogue of PP, is under development to target the Y2 and Y4 receptors [6].

4.2. Adipokines

4.2.1. Leptin

The discovery of the ob gene product, leptin, is the first adipose hormone linking the central regulation of metabolism with peripheral adipose fat mass. Leptin suppresses appetite by inhibiting the activity of orexigenic neuropeptides (NPY and AgRP) or stimulating the activity of anorexigenic neuropeptides (α-MSH and CART) in the arcuate nucleus of the hypothalamus. Despite enthusiastic studies for the use of leptin in the treatment of obesity, clinical trials have shown that the administration of leptin has little effect on the body weight of obese subjects [75,76]. The modest anti-obesity effects of the in vivo administration
of leptin are generally believed to be caused by an acquired resistance in the obese patients.

4.2.2. Adiponectin

Adiponectin is secreted from mature adipocyte and its circulating levels are found to be decreased in obese and diabetic patients. Adiponectin improves insulin sensitivity through the activation of AMP kinases, which have been coupled with the adiponectin receptors R1 and R2 in animal models and human studies. Interestingly, anti-diabetic and anti-obesity drugs, such as the PPARγ agonist (thiazolidinediones) and CB1 antagonist (rimonabant), increase the plasma level of adiponectin [77,78]. Therefore, adiponectin and adiponectin receptors could be a therapeutic target to resolve the insulin resistance found in obesity and type 2 diabetes.

4.2.3. Omentin

Omentin is secreted predominantly by stromal-vascular cells in visceral fat tissue rather than adipocytes [79]. Omentin has positive effects on glucose uptake and works as an insulin sensitizer. Interestingly, omentin is produced in considerable amounts in adipose tissues, though the plasma level of omentin in obese people is decreased [80]. The mechanism of action, relevant receptors, and target tissues of omentin remain to be elucidated for its use in anti-obesity therapeutics.

4.2.4. Acylation-Stimulating Protein (ASP)

Acylation-stimulating protein (C3adesArg/ASP) is a 76-amino-acid peptide that is derived from adipocyte and acts on its C5L2 receptor to stimulate triglyceride (TG) synthesis in adipose tissue [81]. The plasma ASP levels are increased in patients with obesity, type 2 diabetes, and cardiovascular disease, whereas exercise or weight loss decreases the ASP levels. Furthermore, an ASP-resistant state has also been proposed to contribute to a disturbed metabolism in adipose tissue and dyslipidemia, which is common to diabetes and cardiovascular disease. It has been suggested that ASP is generated through the activation of complement C3, a precursor of ASP in adipose tissue. A C3 knockout mouse that was obligatory ASP deficient was associated with an anti-adipogenic state [82]. Thus, ASP may provide a target for controlling fat storage.

CONCLUSIONS

As the complexities of the regulation of whole body energy homeostasis continue to be unveiled, the development of novel therapeutics is promising to facilitate more substantial weight reduction without significant side effects. Strategically, new anti-obesity drugs may require properties that act on both appetite regulation and peripheral energy expenditure. Recent studies have demonstrated some possibilities. Several classes of small molecules or peptide hormones have shown both for the inhibition of appetite and the stimulation of energy expenditure. Perhaps the greatest concerns in the development of novel therapeutics involve safety, in the use or misuse of drugs in the treatment of obesity. The side effects of new anti-obesity drugs may be minimized by developing clinical studies, for example, combination therapy. Another important concern in the development of any new anti-obesity drug is whether it has substantial beneficial effects on glucose tolerance, lipid lowering effects, and protection effects against vascular complications, which are the usual causes of morbidity and mortality in obese patients. Investing in a strategy that involves medicinal chemists, biologists, and physicians will open the way to an optimistic era that includes a new class of pharmaceutical adjuncts for the treatment of obesity.

REFERENCES


