17 CB1 Receptor Antagonists in Obesity Treatment: Current Advances and Perspectives

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Abstract

Obesity is becoming a major global issue that requires careful attention. It is estimated that over 650 million people are fat and over 1.9 billion adults are overweight. Unexpectedly, the issue of underweight deaths is less common than obesity and overweight [1]. There may be more deaths related to the lack of pharmacological treatments for treating obesity. Some of the current methods for controlling obesity include diet, exercise, medication, and invasive surgery. Although each of these tactics works, they all have some sort of issue.

Keywords: Obesity, Global Issue, Pharmacological Treatments, Invasive Surgery, Medication.

Introduction

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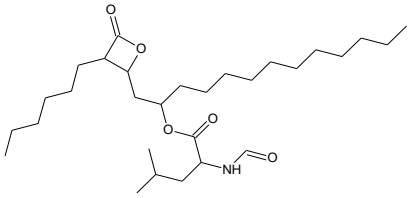
The most recent operation, known as "bariatric arterial embolization," involves blocking the primary artery that supplies blood to the fundus and is thought to offer an alternative to the other regulating approaches. By cutting off the fundus's blood supply, this lowers the release of the peptide hormone ghrelin, which acts on the hypothalamus to decrease appetite [2]. Additionally, a novel gadget that may partially empty the stomach and prevent the body from absorbing calories is being developed. Gastric balloon use is also permitted. To increase the effectiveness of these medications, new formulations with extended-release lorcaserin and low-dose phentermine are being developed. All of these, regrettably, have turned out to be short-term fixes for the ongoing obesity issue [3].

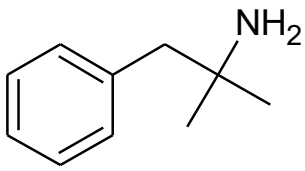
There are now just five authorized medications or formulations available to manage obesity. Although it is known to decrease the absorption of dietary fat, orlistat, a peripherally acting pancreatic lipase inhibitor, has gastrointestinal adverse effects. Qsymia is a mixture of the anticonvulsant topiramate and the appetite-suppressant sympathomimetic amine phentermine. Another medication used to treat addiction is Contrave, which combines naltrexone, an opioid receptor antagonist, with bupropion, an adopamine receptor antagonist and norepinephrine reuptake inhibitor. Finally, liraglutide, a similar to glucagon peptide1 receptor agonist, stimulates 5HT-2c receptors in the brain's appetite regulation center. Lorcaserin is a competitive serotonin 2c (5HT-2c) 4 receptor actuator [4].

Despite being approved for the purpose, these five medications and formulations are not very successful. As a result, efforts are underway to find new anti-obesity drugs with better safety and efficacy profiles.

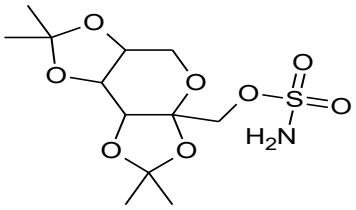
Developed by Sanofi-Aventis (Paris, France), rimonabant is a selective CB1 cannabinoid receptor antagonist. It was first licensed for the European market in 2006 to treat the symptoms of obesity, however it had to be removed within two years because of severe psychiatric side effects. Due to its limited efficacy and elevated risk of adverse cardiovascular events, Abbott Laboratories (IL, USA) stated on October 8, 2010, that it was removing the dual serotonin-norepinephrine transfer inhibitor sibutramine from the US market [5].



Orlistat



Phentermine



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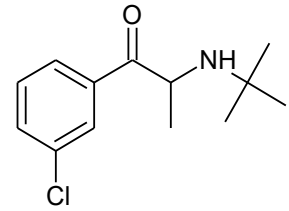
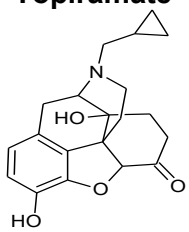
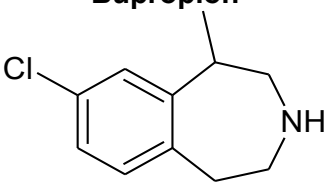


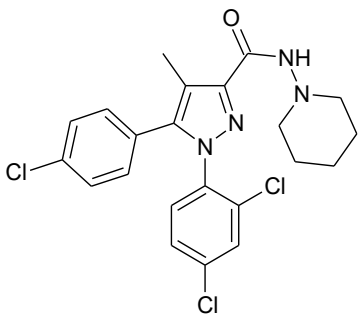
Bupropion



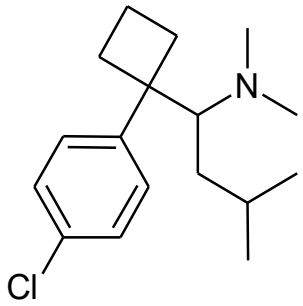
Naltrexone



Lorcaserin



Rimonabant



Sibutramine

Cannabinoid 1 Receptor: A Target For The Treatment Of Obesity

The endocannabinoid system is involved in regulating metabolism and energy homeostasis [6]. Cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors are members of the super family of G-protein-coupled receptors [7]. Central CB1 receptors are well distributed in the hypothalamus. Orexigenic/anorexigenic signals are regulated by Energy balance and metabolism are regulated by the endocannabinoid system [6]. The superfamily of G-protein-coupled receptors includes the cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors [7]. The hypothalamus has a good distribution of central CB1 receptors. Central CB1 receptors regulate orexigenic/anorexigenic signals, which in turn alter energy balance or feeding behavior, which in turn governs food intake. Peripheral organs such as the stomach, liver, hepatocytes, even white adipose tissues additionally contain CB1 receptors. Additionally, the CB1 receptor facilitates neurotransmitter release and regulates a number of cognitive, motor, affective, and sensory processes [8]. peripheral CB1 receptors in the gut are also implicated in obesity, as evidenced by the observation that diet-induced obesity is caused by fatty acid production, which is started by hepatic CB1 receptor activation [9]. Central CB1 receptors, which in turn affects feeding behavior and energy balance, which in turn regulates food intake. Peripheral organs such as the stomach, liver, hepatocytes, and white adipose tissues also contain CB1 receptors. Additionally, the CB1 receptor facilitates neurotransmitter release and regulates a number of cognitive, motor, affective, and sensory processes [8]. Peripheral CB1 receptors have been linked in obesity, as evidenced by the observation that diet-induced obesity is caused by fatty acid production, which is started by hepatic CB1 receptor activation [9].

Designing of Safe CB1 Receptor Antagonists

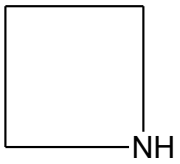
Research on the development of new rimonabant-derived CB1 receptor antagonists suffered when rimonabant was withdrawn because of its psychiatric side effects. This pattern has recently shifted, and scientists are now concentrating on creating CB1 receptor antagonists that have little to no capacity to pass through the

barrier between the brain and [10]. A substance must be made to be less hydrophobic and many more polar in order to be impermeable into the central nervous system (CNS) and limited to peripheral tissues in order to prevent negative mental effects [11–13]. AM6545, a neutral antagonist, and JD5037, a CB1R inverse agonist, are intriguing substances since they have no central side effects and are peripherally restricted while still reducing obesity.

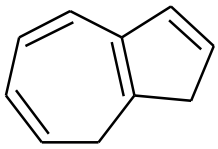
It has been discovered that long-term administration of JD5037, which does not penetrate the brain, is more effective compared to AM6545 at reducing food intake, body weight, and adiposity. Because of this, JD5037 is a perfect anti-obesity drug that lowers the risk of cardiometabolic disease. The primary factors influencing a molecule's passive diffusion across the blood–brain barrier are its polar the area of surface and hydrophobicity. The blood–brain barrier could be readily crossed by substances with a polar surface area of less than 60˚. In order to limit a molecule to the peripheral area and eliminate CNS side effects, attempts are being made to create compounds with a larger polar surface area [5].

Patented CB1 Receptor Antagonists

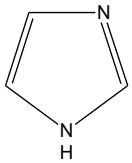
Astra Zeneca AB (UK), Jenrin Discovery Therapeutics (PA, USA), Sanofi-Aventis, Solvay Pharmaceuticals, Inc. Green Cross The Corporation (South Korea), the Japanese company Mitsubishi Tanabe Pharma (Japan), the pharmaceutical firm Merck (NJ, USA), the US subsidiary of Merck & Dohme Corp., 7TM Pharma (Denmark), Eli Lilly and Associates (IN, USA), Schering Corp. (NJ, USA), Northwestern University in Connecticut (CT, United States), A more pacific Corporation (Seoul, South Korea), and 7TM Pharma (Denmark) are among the companies that have patented CB1 receptor antagonists. Azetidine, azulene, imidazole, imidazolines, morpholine, piperazine, pyrrole, pyrazole, pyrazolines, pyrrolidine, pyridine, pyrimidine, purine, thiophene, and triazole scaffolds are among the patented compounds that belong to these families [5,10]. The following sections highlight a few key chemicals from each category.



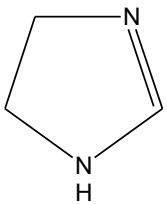
Azetidine



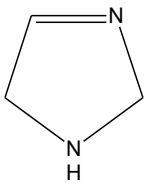
Azulene



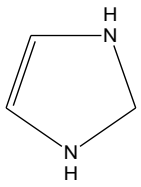
Imidazole



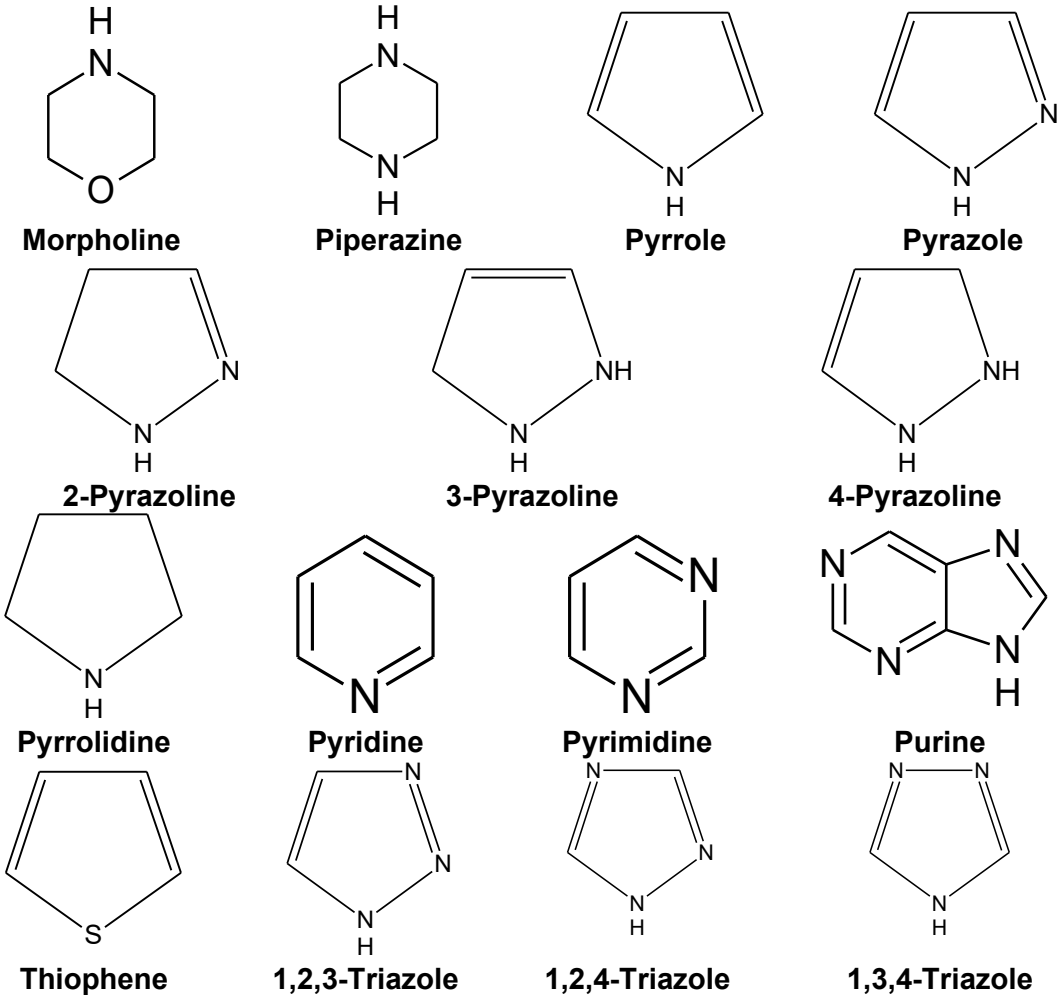
2-Imidazoline



3-Imidazoline



4-Imidazoline



Jenrin Discovery, a US-based company, has a lengthy history of finding CB1 receptor antagonists that are peripherally confined. This company has filed the most patents pertaining to CB1 receptor antagonists, including diastereomeric pyrazoline derivatives in three separate patents (WO2014018695A1, US8680131B2, and US20140031404A1), substituted N-phenyl-5-phenyl-pyrazolin-3-yl amides in patent US2009/0286758A1, novel sulfonamide and carboxamide containing pyrazoline derivatives in patent US2007/0259934A1, and compounds of the pyrazole series in patent WO2009/033125A1. Patents US20100041650A1 and US8252791B2 also contain claims for novel purine derivatives. According to patent US20110160179A1, substituted amino azetidines are peripherally acting CB1 receptor antagonists with negligible or no central nervous system adverse effects.

The most potent compound among the patented purine derivatives is N- (2-(8-(2-chlorophenyl)-9 purin-6-yl) piperidin-4-yl acetamide, which has a selectivity (CB1/CB2) ratio of 1223 and a Ki value of 0.00193μM. However, a research group

from Research Triangle, the Institute has also trademarked peripherally restricted diphenyl purine derivatives in WO2013/123335A1.
After Jenrin Discovery, the French multinational pharmaceutical corporation Sanofi, formerly known as Sanofi–Aventis, holds the second-highest number of patents for CB1 receptor antagonists. In patent US2011/0183960A1, the Sanofi team has claimed a number of new thiophene-2-carboxamide derivatives, with the most potent being 1-({4-(2,4-dichlorophenyl)-5-[4-(3-hydroxypropoxy)phenyl]-2-thienyl}carbonyl)-4-phenylpiperidine-4carboxamide, which has an IC50 value of 0.5 μM.

WO2009/141532A2, the aforementioned US2011/0144157A1, US2011/0152320A1, US8383666B2, and US8680102B2 were the patents for pyrrole derivatives. 1-[4-(2-chlorophenyl)-5-[4-(3-hydroxypropoxy)phenyl]-1-methyl-1H-pyrrole-2-carbonyl]-4-(4-fluoro benzyl amino) piperidine-4-carboxamide was the most active of the pyrrole-containing derivatives, with an IC50 value of 0.5μM. Sanofi-Aventis filed patent US2011/0053908A1 on August 26, 2010, and it was published on March 3, 2011. The most potent molecule in this patent was 4-[N'-1(bis(4-chlorophenyl) methylazetidine-3-yl)-N'-(methanesulphonyl)amino)- N-(1,3-dihydroxy-2-methylpropan-2-yl)benzamide, which was produced from azetidine and had an IC50 value of 0.006μM. Sanofi-Aventis also patented substituted imidazoline-2,4-diones as a peripherally acting CB1 receptor antagonist in US20110112097A1. Compound 4-[3-(2-benzylbenzyl)-4,4-dimethyl-2,5-dioxoimidazolidin-1-yl]-2-trifluoromethyl benzonitrile exhibited the highest activity in the substituted imidazoline-2,4-dione series, with a Ki value of 0.002 μM.

The South Korean company Amorepacific Corp. asserted novel pyrazolo[1,5-a]pyrimidine derivatives as peripherally acting CB1 receptor antagonists in the patents WO2012/030170A3 and US2013/0158025A1.((S)-1-(3-(4-chlorophenyl)-7-(3-fluorophenyl)-2-(methoxymethyl) pyrazolo[1,5-a] pyrimidin-5-yl] pyrrolidin-2-yl) methanol had an IC50 value of 0.004 μM among the series that were reported. A Spanish research team at Laboratorios Del DrEsteve has patented 4-methyl-4,5-dihydro-1H-pyrazole-3-carboxamide as a cannabinoid CB1 neutral antagonist in two separate patents, WO2009/124950A2 and US2011/0028517A1. Benzimidazole derivatives were patented as CB1 antagonists in 2007 by Sweden-based AstraZeneca AB under the registration number WO2007/145563A1.

The molecule with the highest activity among the reported series was 1-(2-tert-butyl-1-[(4,4 cyclo hexyl) methyl]- 1H-benzimidazol-5-yl}carbonyl)-N-cyclopropyl piperi-dine-3-carboxamide, with a Ki value of 0.01917 μM. 1,5-diphenylpyrrolidin-2-ones are patented by a group from Eli Lilly & Co. under patents the following names: WO2009/131815A1, US2011/0034484A1, US8168659B2, and US8420654B2. The compound with the highest activity, compound (3R,5R)-3-[1-methyl-1-(6-trifluoromethyl-pyridin-3-yl)-ethyl amino]-5-[3- (1,1,2,2-tetra fluoro ethoxy) phenyl]-1-

(4-chloro phenyl)-pyrrolidin-2-one, with a selectivity (CB1/CB2) ratio of over 15,000 and a Ki value of 0.00091 μM.

Through WO2008/039023A1, US2008/0081812A1, WO2009/078498A1. WO2010/035915A, US7875647B2, and US8309584B2, Green Cross Corporation, a South Korean biopharmaceutical company, has patented a number of pyrazole-containing compounds as CB1 receptor inverse agonists/antagonists for the treatment of obesity and metabolic disorders associated with obesity.

An IC50 value of 0.87nM was demonstrated by the most effective molecule, 2-(2-(2-chloropheyl)-3-(4-chlorophenyl)-4-(methylsulfonyl)-2H-pyrazol-5-yl)-5-(1-trifluoro methyl cyclo butyl)-1,3,4-thiadiazole. The same group also patented some hetero-aryl imidazole derivatives as CB1 agonists antagonists in 2008 under patent WO2008/105607A1. The most potent compound, 1-((2-(2,4-Di chloro phenyl)-1-(4 chloro phenyl)-8- (5-(1-(tri fluoro methyl) cyclo propyl)-1,3,4- diazol-2-yl)-1H-imidazol-5-yl)methyl)-1H-1,2,4-triazole, had an IC50 value of 1.114nM. In 2014, Hanmi Pharm. Co., another South Korean company, received a patent for some new 1,5-diaryl-4,5-dihydro-1H-pyrazole-3-carboxamine derivatives. The developed compounds demonstrated CB1 receptor antagonist action with great selectivity for the peripheral tissues, according to patent WO2014/208939. An IC50 value of 3 nM was demonstrated by compound (2S)-1-(4-chlorophenyl)-N'((4-chlorophenyl)sulfonyl)-5-(2-thiophenyl-4,5-dihydro-1H-pyrazole-3-car-boximidamido)-3-methylbutanamide.

Tetra hydro-lH-1,2,6-triazaazulenes were patented as CB1 receptor antagonists in patent US8012957B2 by the Belgian company Janssen Pharmaceutica NV (now known as Janssen Research & Development), a division of Johnson & Johnson Pharmacy Research and Development). Compound (8E)-1-(2,4-dichloro-phenyl)-8-(4-fluoro benzylidene)-3-(piperidin-1-yl carbamoyl)-4,5,7,8-tetra hydro-1H-1,2,6- triaza-azulene-6-carboxylic acid tert-butyl ester showed 52% inhibition at a concentration of 0.2 μM.

The substituted pyrido[2,3-d]pyrimidine derivatives were claimed by Merck and Co. Inc. in the patents US2010/0029697A1 and US2010/0063032A1. 2-tert-butyl-7-(2-chlorophenyl)-6-(4-chlorophenyl)-4-(4-fluorophenyl)pyrido[2,3-d]pyrimidine, the series' most powerful chemical, has an IC50 value of 0.0006 μM. Another patent, WO2008/094476A1, claims substituted pyrano[2,3-b]pyridines. Additionally, US20070123505A1 and US7906652B2 are patents that show central action for substituted 3-alkyl azetidine compounds.

Compound 3-[(S)-(4-chloro benzene) (3-{(1S)-2-fluoro-1-[3-fluoro-5-(5-oxo-4,5-di hydro-1,3,4-oxadiazol-2-yl) phenyl]-2-methyl propyl] azetidin-1-yl) methylation] benzo-nitrile demonstrated a 100-fold selectivity and an IC50 value of less than 1μM. Azetidine carboxamide derivatives were also patented in 2009 by Vernalis Research Ltd., a UK-based company, under the patent EP1620395B1. A Ki value of 0.0006μM

was demonstrated by compound 3-[2-(trifluoromethyl)-4'-chlorobenzhydryloxy]-N-(tert-butyl)azetidine-1-carboxamide in the series. In the patent US2009/0247499A1, Merck and Co. Inc. also asserted that sulfonylated piperazines are cannabinoid-l receptor modulators. 4-(4-trifluoromethylphenyl-acetyl)-1-((3-cyclopropyl-5-trifluoromethyl-phenyl)sulfonyl)piperazine was the most effective compound, with an IC50 value of 0.00124 μM. In patent EP2146997B1, a group from the pharmaceutical company Merck Sharp and Do Corp. (previously Schering Corporation), a division of Merck & Co. Inc., has asserted certain substituted furo[2,3-b]pyridines. An IC50 value of 0.4nM was determined for the most effective molecule, N-(6-(2-chloro-4-(1,2,4-oxadiazol-3-yl)phenyl)-5-(4-chlorophenyl)- 2-(2,2-dimethylpropanoyl)furo[2,3b]pyridine-3-yl)-2-hydroxyacetamide.

In its patents WO2008/059207A1, US8173680B2, US2010/0292273A1, WO2008/074982A1, and US8124634 B, the Danish biotech company 7TMN Pharma A/S described cannabinoid receptor modulators having a pyrazole scaffold as peripherally acting substances. With a selectivity ratio ranging from 22 to 480 for the CB1 receptors and a Ki value of 0.35 nM, 1-(2,4-dichlorophenyl)-5-(4-(4-cyanobut-1-ynyl)phenyl)-4-mercapto-N-(piperidin-1-yl)1H-pyrazole-3-carboxamide was the most potent of these compounds. In their 2010 patent, US20100144734A1, National Tsing Hua University researchers claimed that 1,2,3-triazole compounds were novel cannabinoid-1 receptor antagonists.With an IC50 value of 11.6 nM and a notable selectivity for CB1 over CB2, 2-(4,5-Bis(2,4-dichlorophenyl-2H-1,2,3-triazol-2-yl)-N-(4-fluorobenzyl)acetamide had the strongest activity in the series.

In the patent EP1542678B1, a consortium of Belgian businesses called Solvay Pharmaceuticals BV asserted that 1H-1,2,4-triazole-3-carboxamide derivatives are CB1 receptor antagonists. Derivatives of 1,3,5-trisubstituted 4,5-dihydro-1H-pyrazole in EP1713475B1, 3,4-diaryl-(1H)-pyrazole-1-carboxamide in WO2010/012797A2, and (5R)-1,5-diaryl-4,5-dihydro-1H-pyrazole-3-carboxamidine in US2011/0053983A1 have also been claimed as CB1 receptor antagonists by the same group. With an IC50 value of 7.52 nM, the most active of these compounds was (4S,5S)-(2,4-dichlorophenyl)-5-(4-chlorophenyl)-4,5-dihydro-4-mercapto-N-(2,6-dimethylpiperidin-1-yl)-1H-pyrazole-3-carboxamide. Additionally, Solvay Pharmaceuticals Sa has asserted imidazoline derivatives with CB1-antagonistic action in its patents US7495108B2 and EP1725536B1. 1-(4-chloro phenyl)-2-(2,4-di chloro phenyl)-N-cyclo the hexyl-4,5-di hydro-1H-imidazole-4-carboxamide, the most powerful molecule, exhibited an apA2 value of 7.7.

Schering Corp. has asserted that substituted piperazines in one patent (WO2009/005645A1) and diaryl morpholine derivatives in two other patents (WO2008/130616A2 and US2010/0197564A1) are CB1 receptor antagonists. With a Ki value of less than or equal to 0.025 μM, the diaryl morpholine equivalents 2-(5-(2,4-

di chloro phenyl)-4-(4-chloro phenyl), morpholin-2-yl)-N- (pyridin ethanamine exhibited the best activity.

Pyrazo[1,5-a]pyrimidine derivatives were revealed as cannabinoid receptor antagonists by Tanabe Seiyaku Co. Ltd., a Japanese firm in patent WO2007/046548A1, and Mitsubishi Tanabe Pharma Corporation in patents US8188097B2, EP2520577A1, WO2008/004698A3, US2009/0258867A1, and EP2035427. The most effective molecule in their ported series has a CB1/CB2 selectivity ratio of over 500 and an IC50 value of less than 0.01μM.

The patent WO2012/117216A1 from the Faculty of Medicine Court of the University of Aberdeen (which is located in the UK) revealed N-(arylalkyl)-1H-indole-2-sulfonic acid amides to work as allosteric modulators of cannabinoid receptors. The IC50 value for the chemical N-((4'-fluorobiphenyl-4-yl)methyl)-1H-indole-2-sulfonamide was 0.001 μM.

In the patent WO2013/106349A1, the University of Arkansas (AR, USA) Board of Trustees asserted that derivatives containing amino alkyl indole were neutral CB1 receptor antagonists. The Ki value of (1-Butyl-7-methoxy-3(naphthalen-1-ylmethyl)-1H-indole was 15.4nM. In their US2015/0266820A1 patent, the University of Arkansas and the the University of Kansas (KS, USA) asserted that certain amino alkyl indoles and similar compounds are neutral CB1 receptor antagonists that can be used to treat obesity. The NIH and Medical Research have claimed several steroidal substances as CB1 receptor antagonists in patent WO2012/160006A1.

As a CB1 receptor antagonist, 17α-Methyl pregnenolone, however, was found to be less harmful than pregnenolone. Two separate patents, US2016/0257654A1 and WO2017/151802A1, have been issued for substituted4,5-dihydro-1H-pyrazole-1-carboximidamide derivatives by the United States, represented by the Secretary, of the Department of Health and Human Services, Bethesda. Among the molecules in the disclosed series, the most powerful derivative had a Ki value of 2.7 nM. Researchers from the University of Connecticut in the United States asserted in the patent US2012/0046280A1 that hetero pyrrole analogs, including imidazoles, thiazoles, oxazoles, and pyrazoles, had the ability to modulate CB1 and/or CB2 cannabinoid receptors. The patented substances acted preferentially on receptors for CB 1 in the peripheral nervous system and were neutral antagonists, were selective for either CB1 or CB2 receptors, and/or were nitric oxide donors.

To summarize, since rimonabant, researchers have leveraged a wide range of heterocyclic scaffolds to develop CB1 receptor antagonists that are secure weight-management medicines, which has resulted in the filing of numerous patent applications. The the surface area of polar of the resultant molecules has been increased to alter CNS permeability, which has improved the test chemicals' concentrations in the serum and brain.

For many of the produced test compounds, the CB1/CB2 selectivity ratio has additionally been enhanced. Sadly, the researchers have yet to find success since just one of their proposed CB1 receptor antagonists have made it to market. However, it will not be long until we can enjoy the results of our laborious study and have a distantly acting CB1 receptor antagonists that works well as an anti-obesity medication.

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