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A patent update on cannabinoid receptor 1 antagonists (2015-2018)

George Amato, Nayaab Khan, and Rangan Maitra

Center for Drug Discovery, RTI International, Research Triangle Park, NC, USA

Abstract

Introduction: The endocannabinoid system is an important regulator of various physiological processes. Preclinical and clinical studies indicate that attenuation of the endocannabinoid system via antagonism of the type 1 cannabinoid receptor (CB1) is an excellent strategy to treat obesity, metabolic syndrome and associated disorders. However, centrally acting antagonists of CB1 also produce adverse effects like depression and anxiety. Current efforts are geared towards discovery and optimization of antagonists and modulators of CB1 that have limited brain penetration.

Areas Covered: Several recent publications and patent applications support the development of peripherally acting CB1 receptor antagonists and modulators. In this review, recent patents and applications (2015 – 2018) are summarized and discussed.

Expert Opinion: Approximately 30 new inventions have been reported since 2015, along with 3 recent commercial deals, highlighting the importance of this class of therapeutics. Taken together, peripherally acting CB1 receptor antagonists and modulators are an emerging class of drugs for metabolic syndrome, non-alcoholic steatohepatitis (NASH) and other important disorders where this receptor has been implicated.

Keywords

CB1; cannabinoid; peripheral; antagonist; metabolic syndrome; NASH; obesity; endocannabinoid

1. Introduction

Selective modulation of the endocannabinoid (EC) system comprised of endocannabinoids, receptors, transporters and enzymes, can be useful in the treatment of several important medical conditions.^{1–6} Cannabinoid receptors CB1 and CB2 are G protein-coupled receptors (GPCRs) whose primary function is to activate G proteins ($G_{i/o}$). CB1 receptors are ubiquitous, but highly expressed in the central nervous system (CNS). Selective inhibition of

Corresponding author: Rangan Maitra, Center for Drug Discovery, RTI International, 3040 East Cornwallis Rd., Research Triangle Park, NC 27709-2194, USA, rmaitra@rti.org, Tel: +1 919-485-2668.

Declaration of interest

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CB1 receptor activity is a validated approach for treating obesity, diabetes, metabolic syndrome, dyslipidemias and liver diseases.^{4, 7–11}

Rimonabant (**1**, Figure 1), a CNS penetrating CB1 receptor inverse agonist developed by Sanofi-Aventis, was clinically approved in 2006 for the treatment of obesity in Europe, but was withdrawn in 2008 because of an increase in psychiatric disorders associated with antagonism of CB1 receptors in the CNS.¹² The adverse side effects seen with **1** precipitated the withdrawal of other CNS-penetrating CB1 receptor inverse agonists from clinical development, including otenabant (**2**, Figure 1); a compound developed by Pfizer. To avoid side effects associated with CNS activity, efforts are underway to develop compounds that selectively target the CB1 receptors in the periphery.^{10, 13–15} These compounds by design have little to no brain penetration. An example of this class of compounds is TM38837, an analog of **1**, which was tested in humans and demonstrated to have limited brain penetration.¹⁶ Other approaches are also being explored, including development of neutral antagonists and negative allosteric modulators.^{17, 18}

2. Recent patent activity

This update is focused on patents with claims for CB1 antagonists in the years 2015–2018. Included are claims for inverse agonists, neutral antagonists and negative allosteric modulators. A review of earlier patent activity is published.¹⁸ Table 1 provides a compilation of patents with a focus on priority dates of 2015–2018, but also includes patents with earlier priority dates when there are US, EP or WO publications that occurred during this time frame. The rows are organized by the assignee (alphabetical). Each row contains the most recent US, EP and WO patent activity, along with publication dates.

Most of the CB1 antagonist patent activity during the past four years involves small molecule peripherally selective compounds that act on the orthosteric binding site, but a small amount of patent activity falls into other categories: antibodies, negative allosteric modulators, neutral antagonists, new uses for existing compounds and biased CB1 modulators. The highlights of these disclosures are discussed below with an emphasis on in vivo data when provided. The discussion is divided into three sections: peripherally restricted orthosteric CB1 antagonists or inverse agonists (Section 3), neutral antagonists, CB1 receptor negative allosteric and biased agonists (Section 4), and CB1 receptor antibodies, covalent antagonists and new uses for existing compounds (Section 5). Each section is organized alphabetically by the patent assignee.

3. Peripherally restricted orthosteric CB1 antagonists or inverse agonists

Pyrazoles, similar to **1**, are claimed in patent activity by the Beijing Institute et al.¹⁹ The focus is on 1,5-diaryl-4-methyl pyrazoles with a urea in the three position, as exemplified by compound **3** (Figure 2). Compound **3** and several others were shown to be peripherally restricted using pharmacokinetic (PK) studies in rodents. In vivo efficacy data were not provided in the patent, but **3** is the subject of a 2017 publication.¹⁰ Compound **3**, designated TXX-522 in the paper, was shown to be an orally bioavailable neutral antagonist which reduced body weight gain and improved insulin resistance in a diet induced obesity (DIO)

mouse model of metabolic syndrome. It was noted that food intake was not reduced by this compound, a feature often seen with centrally acting inverse agonists.

Pyrazolines are claimed in patent activity by Hanmi Pharmaceutical.²⁰ The focus is on 1,5-diaryl pyrazolines, substituted in the three position with carboximidamides, as exemplified in compound **4** (Figure 2). In DIO mice, **4** was shown to be peripherally restricted (low brain levels) and effective at reducing body weight. The company's pipeline on its website does not include a compound from this patent.²¹

Janssen Pharmaceutica has published multiple patents focused on applying a particular structural motif to a variety of cores.^{22–35} These are discussed below. Published in 2018, is a US approved patent on benzimidazoles with a focus on compounds that contain a 6-diarylmethyl group, a 2-alkyl group and a variety of groups in the one position, as exemplified by compound **5** (Figure 2).³⁵ Compound **5** was shown to be peripherally selective in mouse PK studies. In DIO mice, compound **5** reduced body weight and improved insulin tolerance. A US approved patent on cinnolines, published in 2017, has a focus on compounds containing a 6-diarylmethyl group and a variety of groups in the four position, as exemplified by compound **6** (Figure 2).²⁸ This patent did not contain in vivo data. A US approved patent on indazoles, published in 2017, has a focus on compounds containing a 5-diarylmethyl group and a variety of groups in the three position, as exemplified by compound **7** (Figure 2).²⁹ Compound **7**, peripherally selective in mouse PK studies, was shown to reduce body weight and improve insulin tolerance in DIO mice. A pair of patents on quinolines and quinolones were disclosed and approved in the US in 2016.^{24, 25} These patents focus on compounds containing a 6-diarylmethyl group and a variety of groups in the four position, as exemplified by the quinolone **8** (Figure 2). In DIO mice, **8** was shown to be a peripherally selective compound (low brain levels) that reduced body weight and improved insulin tolerance. In a recent publication, however, increasing brain levels of compound **8** was found upon repeat dosing.³⁶ A 2017 US approved patent publication on quinolines and quinolones has a focus on compounds containing a 6-diarylmethyl group, a variety of groups in the four position, and a polar polymeric group to establish peripheral restriction.³⁰ The quinoline **9** and the quinolone **10** are specified examples (Figure 2), but in vivo data are not provided. In 2017, a US approved patent on quinazolines with a focus on compounds containing a 6-diarylmethyl group and a variety of groups in the four position was published.³¹ In some cases, a polar group is present at the two position. Compound **11** (Figure 2) is an example, which was shown to be peripherally selective in mouse PK studies, but in vivo efficacy data were not provided. The Janssen Pharmaceutica website currently does not list a peripheral CB1 antagonist as part of its late stage clinical pipeline.³⁷

Pyrazolines are claimed in patent activity by Jenrin Discovery.^{38–40} A US approved patent, published in 2016, is focused on 3,4-diaryl pyrazolines substituted at the one position with carboximidamides, as exemplified by compound **12** (Figure 2).⁴⁰ A US approved patent that focusses on valine deuterated versions of **12** was published in 2018.³⁸ In vivo data are not provided in these patents, but in a 2012 publication, compound **12** was shown to be a peripherally restricted CB1 antagonist in mouse PK studies. A closely related compound (hydrogen in place of isopropyl group) was shown to reduce triglyceride levels, reduce liver

weights and improve glucose tolerance and insulin sensitivity in DIO mice.⁴¹ In 2017, a Jenrin Discovery press release stated that **12** (JD5037) was cleared for clinical trials, to be developed as a treatment for NASH.⁴² In 2018, Corbus Pharmaceuticals acquired the rights to the Jenrin portfolio of CB1 receptor antagonists and they are planning a 2019 phase one clinical trial of a second-generation compound, CRB-4001 (structure not disclosed).⁴³

Purines, similar to **2**, are claimed in patent activity by the Research Triangle Institute.^{44–46} A US approved patent, published in 2016, is focused on 8,9-diaryl purines with a variety of groups in the six position.⁴⁴ Compound **13** (Figure 2) is an example which was shown to be peripherally restricted in rat PK studies. Published in 2017, is a US application which broadens the scope of the groups covered in the six position.⁴⁵ Compound **14** (Figure 2) was shown to be a peripherally restricted CB1 antagonist in mouse PK studies. Compound **14** reduced liver lipid accumulation in a mouse model of alcoholic steatosis.

Azetidinones are claimed in patent activity by the Universite de Nantes et al.^{47–49} A US patent application, published in 2018, is focused on 1,4-di-(4-methylthiophenyl)azetidine-2-ones with a variety of groups at the three position.⁴⁸ Compound **15** (Figure 2) was shown to be a CB1 inverse agonist with protective effects on the livers of DIO mice.

Pyrazolines are claimed in patent activity by the US department of HHS.^{50–59} US patent applications that are focused on 3,4-diaryl pyrazolines, substituted at the one position with carboximidamides were published in 2018.^{56–58} The patent claims include peripheral CB1 antagonists with dual activity as either inhibitors of inducible nitric oxide synthase (iNOS) or activators of adenosine monophosphate kinase (AMPK), governed by the type of group in the one position. Compound **16** (Figure 2) is an example of a CB1 antagonist which is also an inhibitor of iNOS. Low brain levels were observed in mouse PK studies. In DIO mice, this compound showed positive effects, including body weight reduction and improved insulin tolerance. Positive effects were also shown in the Zucker diabetic fatty rat model and the carbon tetrachloride induced liver fibrosis mouse model.

4. Neutral antagonists, negative allosteric modulators and biased agonists of CB1 receptor

During the years 2015–2018, there was patent activity involving negative allosteric modulators (NAMs) of the CB1 receptor. Patent activity by Northeastern University was published in 2018 and includes a granted US patent.^{60, 61} These patents claim diaryl ureas, oxadiazoles and 3,4-diaminocyclobut-3-ene-1,2-diones as NAMs of the CB1 receptor. Compound **17** (Figure 3) is an example from this patent which was shown to reduce alcohol preference in mice.

A patent application by Research Triangle Institute was published in 2018, claiming diaryl ureas as CB1 NAMs.^{62, 63} Compound **18** (Figure 3) is an example of a NAM which was shown to reduce cocaine seeking behavior in a rat model of drug abuse.

A granted US patent by Universite de Bordeaux and INSERM was published in 2018, claiming steroids that inhibit CB1 activity without blocking the orthosteric binding site.⁶⁴ In

DIO mice, pregnenolone (**19**, Figure 3) was shown to reduce body weight without affecting food intake. Analogs of pregnenolone with improved metabolic stability are claimed in that patent.

A granted US patent by The University of Arkansas and The University of Kansas was published in 2016, claiming indoles as neutral CB1 receptor antagonists.⁶⁵ Compound **20** (Figure 3) is an example of a compound that was claimed as a neutral CB1 antagonist with CB2 agonist activity. It was shown to decrease alcohol self-administration in a mouse model of alcohol abuse.

Patent activity by The University of North Carolina (Greensboro), including a granted US patent published in 2018, is focused on 2-substituted indoles that are agonists of the CB1 receptor with a bias for the β -arrestin pathway.^{66, 67} Compound **21** (Figure 3) is an example of this class. In vivo efficacy data were not provided. Theoretically, these compounds might induce receptor desensitization, resulting in functional antagonism of the CB1 receptor in a chronic dosing situation.

5. CB1 receptor antibodies, covalent antagonists and new uses for existing compounds

In the 2015–2018-time frame, there was patent activity involving antibodies of the CB1 receptor. Patent activity by Amgen, including a granted EP patent published in 2018, claims coverage of all diseases involving antagonism of the CB1 receptor by an antibody.^{68, 69} Amgen has an antibody for obesity in phase one trials, but the target is not disclosed.⁷⁰ US patent applications by Bird Rock Bio, including one published in 2018, claim coverage of all diseases involving antagonism the CB1 receptor by an antibody.^{71, 72} In 2017, Janssen struck a deal with Bird Rock Bio and is now evaluating Namacizumab (RYI-018 or JNJ-2463), a negative allosteric modulating CB1 antibody, in liver disease (phase one clinical trial).⁷³ Patent activity by Icahn School of Medicine, including a US granted patent published in 2018, claim antibodies of CB1 receptor heteromers to treat liver diseases.^{74, 75} Reductions in liver fibrosis were observed in animal models of liver disease.

Patent activity by Northeastern University, including a granted US patent published in 2017, claim nitrate esters.^{76, 77} The claims include nabilone analogs such as compound **22** (Figure 3), which covalently bind the CB1 receptor. Compound **22** was shown to covalently bind the rat CB1 receptor and to have an antinociceptive effect in mice.

New uses for existing CB1 receptor antagonists were claimed in recent patent activity. A granted US patent by FUHNPAIIN was published in 2017, claiming the treatment of fatigue associated with spinal cord lesions or with Parkinson's disease.⁷⁸ Using rimonabant, an increase in resistance to fatigue was demonstrated in normal rats and rats with spinal cord lesions. Patent activity by Universitat Pompeu Fabra, including a granted US patent published in 2017, claim the treatment of neuronal dendritic diseases, including Down syndrome.^{79, 80} Rimonabant was shown to improve the spine density and morphology of CA1 pyramidal neurons in Fragile X mental retardation 1 gene knockout mice. A patent application by The University of Texas was published in 2018, claiming the use of

rimonabant to treat synthetic cannabinoid toxicity.⁸¹ In monkeys, rimonabant was shown to reduce the toxic effects of centrally acting CB1 agonists.

6. Conclusions

There has been a recent uptick in commercial activity around the development of peripherally restricted CB1 receptor regulators. The clinical experience with 1 presented a rather curious case wherein adverse effects were noted in only a small subset of patients. The reasons behind this are still unclear. Unfortunately, 1 was approved as an anti-obesity agent. Therefore, while these adverse effects were only noted in a limited number of users, the benefit to risk ratio of use was not deemed adequate for continued use of this drug. However, over the last decade, it has become abundantly clear that the beneficial effects of CB1 antagonism or negative regulation extends beyond the CNS and into the periphery. Along with many publications from various research programs across the globe, development of second generation peripherally restricted compounds have led to a resurgence of CB1 as a target for many diseases. In tandem, substantial patent related activities and commercial developments have also been noted. Taken together, CB1 has re-emerged as an important drug target for metabolic, endocrine, fibrotic and cardiovascular disorders.

7. Expert opinion

Recent patent activity shows that there continues to be strong interest in developing compounds that attenuate CB1 activation. The main disease targets are metabolic with a focus on liver diseases and diabetes, which are of growing concern and have limited treatment options. Other metabolic diseases being targeted include obesity and metabolic syndrome. Additional areas of interest include treatment of alcohol and drug abuse, pain, Parkinson's disease and Down syndrome. The assignees for these patents were mostly small companies and academic/research/non-profit institutions. Patents from Janssen, however, along with their acquisition of Bird Rock Bio's Namacizumab (RYI-018 or JNJ-2463), a negative allosteric modulating CB1 antibody, shows that larger pharmaceutical companies might retain an interest in this target.

Patent activity in the years 2015–2018 is focused on small molecule peripherally restricted CB1 antagonists as a means of attaining efficacy while avoiding side effects associated with antagonizing CB1 receptors in the CNS. Animal models indicate that these compounds should be effective in treating metabolic diseases. Developing such compounds that have good oral pharmacokinetics is a difficult, but achievable task that has been ongoing for several years. The success of these compounds will depend on how well they get to the desired peripheral targets without triggering CNS related side effects and the translation of efficacy noted in animal models to humans. The clinical profile of compound 3 would be of particular interest, since this is a peripherally restricted analog of rimonabant.

Neutral antagonists and negative allosteric modulators are gaining attention as potential means for achieving efficacy while avoiding side effects by eliminating the change in CB1 basal tone observed with inverse agonists. The limited patent activity for these types of

compounds may reflect the increased difficulty in identifying suitable compounds. It would be of interest to clinically test both peripherally selective and unselective compounds for their efficacy and side effect profiles. It has been suggested that CNS-penetrant neutral antagonists might not pose the same risks as inverse agonists, but concrete data in this regard are lacking. Although rimonabant was reported to produce anxiolytic effects in patients, testing for depression and anxiety in animal models is particularly challenging for this class of compounds.

Biased agonists of CB1 receptors is a relatively novel idea that may provide unique pharmacological tools and strategies. Activation of the β -arrestin pathway results in internalization of most GPCRs, including the CB1 receptor. Biased CB1 agonists that target this pathway over the $G\alpha_i$ pathway may effectively reduce CB1 activity and provide functional antagonism. Development of structure-activity relationships for these types of compounds is still in the early stages.

Antibodies of the CB1 receptor are also of interest, as evidenced by recent patent and commercial activity. Clinical development of antibodies for acute treatments often lead the development of small molecules for chronic treatments. Bird Rock Bio's Namacizumab (RYI-018 or JNJ-2463), a negative allosteric modulating CB1 antibody, is the class leader, currently in clinical trials for liver disease. The success or failure of Namacizumab, will likely affect the interest in funding the advancement of small molecule negative allosteric modulators. Recombinant proteins do have certain drawbacks as therapeutics. Chronic treatment with neutralizing antibodies, often results in diminished efficacy. Antibodies are typically injected, which require expert training for administration. Biologics also tend to be more expensive than small molecules due to increased production costs. On the other hand, many antibodies have long half-lives, which might be advantageous in some patient populations where adherence to a dosing regimen is challenging. Additionally, antibodies do not penetrate into the CNS. Therefore, accumulation in the CNS upon repeat dosing and related adverse reactions are unlikely with this class of agents.

The complexity of metabolic diseases may favor combination therapy for more robust efficacy. Indeed, CB1 antagonists that have an added target such as iNOS were claimed in recent patents. However, it is unclear whether this particular strategy is more advantageous over using a combination therapy with two separate agents. Although, reduced potential for drug-drug interaction and the PK profile of a single agent with two targets might be perceived as advantages over combination therapy.

Receptor crystal structures can aid the development of potent and selective compounds with good physical properties. Only recently, in 2016 and 2017, did crystal structures of the human CB1 receptor become available.^{82–84} This has led to a better understanding of how orthosteric ligands interact with the receptor and where the opportunities are for making modifications to favor potent, selective compounds with desirable physical properties. Crystal structures with allosteric ligands are not available but would be of significant interest to developers of these compounds.

Advancement of programs focused on modulators of the cannabinergic system including that of CB1 antagonists can hinge on availability of funding for IND-enabling studies and clinical research. Public and scientific interest in products that modulate the cannabinergic system are currently high due to the recent US approval of Epidiolex, a cannabidiol product for epilepsy, and an increased use of hemp and legalized marijuana products. The clinical failures of centrally acting CB1 inverse agonists due to side effects and CB2 agonists due to a lack of efficacy had resulted in a temporary decrease of interest in developing modulators of the cannabinergic system. The recent uptick in licensing activities suggest that interest in this class of compounds is once again on the rise. This will likely provide a near term benefit to advancing late stage preclinical and early stage clinical programs. Large pharmaceutical companies might also become more interested in funding these programs after positive early phase clinical trials.

In summary, there is a lot of interest in the regulation of CB1 activity to treat a variety of diseases. Clinical trials of peripherally restricted compounds, antibodies and neutral antagonists are still in the early stages. The utility of such compounds as stand-alone therapies or combination therapies will emerge in the near future.

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“ *of considerable interest*

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Article highlights

- This update is focused on patents with claims for CB1 antagonists in the years 2015–2018. Included are claims for inverse agonists, neutral antagonists and negative allosteric modulators.
- A substantial amount of patent activity was identified, a summary of which is provided in Table 1.
- A wide variety of structures are patented. Examples of key compounds are provided in Figures 2–3.
- Most of the patent activity is focused on small molecule CB1 inverse agonists or neutral antagonists that are peripherally restricted.
- There is a focus on targeting metabolic diseases, most notably liver diseases and diabetes.

Figure 1.
Examples of clinical CNS penetrating CB1 antagonists.

Figure 2.
Examples of molecules from recent patent publications discussed in Section 3, compounds 3–16.

Figure 3.
Examples of molecules from recent patent publications discussed in Section 4 and 5, compounds **17–22**.

Table 1.

Summary of patent activity from 2015 to 2018.

Assignees	Priority Date	Compounds	Claimed Uses	Patent Number & Date
Amgen	2013 6–26	Antibodies	Obesity, Diabetes & More	US20160145333A1 2016-5-26 EP3013860B1 2018-12-12
Beijing Institute of Pharmacology & Toxicology, Academy of Military Medical Sciences	2015 5–21	Pyrazoles	Obesity & More	WO2016184310A1 2016-11-24
Bird Rock Bio	2015 9–30	Antibodies	Obesity, Diabetes, Liver Disease & More	US20180282406A1 2018-10-4 US20170210797A1 2017-7-27
Fundacion del Hospital Nacional de Paraplejicos Para la Investigacion y la Integracion	2009 1–12	Rimonabant & Others	Parkinson's Disease, Motor Neuron Diseases	US9592237B2 2017-3-14
Hanmi Pharmaceutical	2014 3–31	Pyrazolines	Metabolic Disorders & More	WO2015152550A1 2015-10-8
Icahn School of Medicine at Mount Sinai	2010 1–25	Antibodies	Liver Diseases	US9855290B2 2018-1-2 US20180250322A1 2018-9-6
Janssen Pharmaceutica	2015 8–25	Benzimidazoles	Metabolic Disorders & More	US10118900B2 2018-11-6 WO2017035114A1 2017-3-2
Janssen Pharmaceutica	2015 1–12	Cinnolines	Metabolic Disorders & More	US9732061B2 2017-8-15 WO2016115013A1 2016-7-21
Janssen Pharmaceutica	2015 8–25	Indazoles	Metabolic Disorders & More	US9682940B2 2017-6-20 WO2017034872A1 2017-3-2
Janssen Pharmaceutica	2014 2–27	Quinolines, Quinolones	Metabolic Disorders & More	US9266835B2 2016-2-23 US9464055B2 2016-10-11 WO2015130444A1 2015-9-3 WO2015130445A1 2015-9-3
Janssen Pharmaceutica	2015 8–27	Quinolines, Quinolones	Metabolic Disorders & More	US9815790B2 2017-11-14 WO2017034877A1 2017-3-2
Janssen Pharmaceutica	2014 9–9	Quinazolines	Metabolic Disorders & More	US9682955B2 2017-6-20 WO2016040081A1 2016-3-17
Jenrin Discovery	2012 7–25	Pyrazolines	Metabolic Disorders & More	US9987253B2 2018-6-5 EP2877173A4 2016-3-16 US9517228B2 2016-12-13 EP2877173A4 2016-3-16
Northeastern University	2013 8–22	Ureas, Oxadiazoles, Cyclobutene-diones	Addiction, Metabolic Syndrome, Obesity & More	US9926275B2 2018-3-27 WO2015027160A3 2015-11-5
Northeastern University	2013 2–26	Nitrate Esters	Obesity, Diabetes, & More	US9580400B2 2017-2-28 US20170210728A1 2017-7-27
Research Triangle Institute	2017 5–12	Diaryl Ureas	Metabolic Syndrome, Addiction & More	US2018031977 2018-5-10 WO2018209030A1 2018-11-15
Research Triangle Institute	2016 12–21	Purines	Metabolic Syndrome & More	US2017067602 2017-12-20 WO2018119076A1 2018-6-28
Research Triangle Institute	2012 2–17	Purines	Metabolic Syndrome & More	US9458160B2 2016-10-4
Universitat Pompeu Fabra	2013 3–19	Rimonabant & Others	Down Syndrome, Neuronal Dendritic Diseases	US9662320B2 2017-5-30 EP2976074A1 2016-1-27
Universite de Bordeaux, Institut National de la Sante et de la Recherche Medicale	2011 5–20	Steroids	Metabolic Disorders, Addiction & More	US10040816B2 2018-8-7

Assignees	Priority Date	Compounds	Claimed Uses	Patent Number & Date
Universite de Nantes, Institut National de la Sante et de la Recherche Medicale, Universite de Bourgogne	2015 9–25	Azetidinones	Obesity, Diabetes, Liver Disease & More	US20180265498A1 2018-9-20 EP3353165A1 2018-8-1 WO2017050990A1 2017-3-30
University of Arkansas, University of Kansas	2012 1–9	Indoles	Drug & Alcohol Abuse, Obesity	US9416103B2 2016-8-16
University of North Carolina, Greensboro	2014 6–20	Indoles	Metabolic Syndromes, Liver Disease & More	US10118914B2 2018-11-6 WO2015195486A1 2015-12-23
University of Texas	2017 5–4	Rimonabant	Synthetic Cannabinoid Toxicity	WO2018204689A1 2018-11-8
US Department of Health and Human Services	2015 6–4	Pyrazolines	Obesity, Diabetes, Liver Disease & More	US20180273485A1 2018-9-27 EP3303325A1 2018-4-11 WO2016196646A8 2017-1-5
US Department of Health and Human Services	2014 5–9	Pyrazolines	Obesity, Diabetes, Liver Disease & More	US20180179163A1 2018-6-28 EP3140288A1 2017-3-15 WO2015172059A8 2016-10-27
US Department of Health and Human Services	2012 11–13	Pyrazolines	Obesity, Diabetes, Liver Disease & More	US20180022705A1 2018-1-25 EP2919779A1 2015-9-23 WO2014078309A8 2015-5-21 US20160257654A1 2016-9-8