GPR17 receptor modulators and their therapeutic implications: review of recent patents

Gabriella Marucci, Diego Dal Ben, Catia Lambertucci, Aleix Martí Navia, Andrea Spinaci, Rosaria Volpini & Michela Buccioni

To cite this article: Gabriella Marucci, Diego Dal Ben, Catia Lambertucci, Aleix Martí Navia, Andrea Spinaci, Rosaria Volpini & Michela Buccioni (2019): GPR17 receptor modulators and their therapeutic implications: review of recent patents, Expert Opinion on Therapeutic Patents, DOI: 10.1080/13543776.2019.1568990

To link to this article: https://doi.org/10.1080/13543776.2019.1568990

Accepted author version posted online: 14 Jan 2019.
Publisher: Taylor & Francis

Journal: Expert Opinion on Therapeutic Patents

DOI: 10.1080/13543776.2019.1568990

Review

GPR17 receptor modulators and their therapeutic implications: review of recent patents
Gabriella Marucci, Diego Dal Ben, Catia Lambertucci, Aleix Martí Navia, Andrea Spinaci, Rosaria Volpini, and Michela Buccioni

1School of Pharmacy, Medicinal Chemistry Unit, University of Camerino

* Corresponding Author: Michela Buccioni, School of Pharmacy, Medicinal Chemistry Unit, University of Camerino, via S. Agostino 1, 62032 Camerino, Italy
email: michela.buccioni@unicam.it
Abstract

Introduction: The GPR17 receptor, phylogenetically related to both purinergic P2Y and CysLT receptors, is mainly expressed in the CNS and, in general, in organs that can typically undergo ischemic damage. This receptor is involved in various pathologies including stroke, brain and spinal cord trauma, multiple sclerosis and in all diseases characterized by neuronal and myelin dysfunction. Therefore, there is a strong need to identify molecules capable of binding specifically to GPR17 receptors.

Areas covered: The review provides a summary of patents, published between 2009 and 2018, on chemicals and biologics and their clinical use. In this work, information is reported about the representative structures and biological activity of recently developed GPR17 receptor ligands.

Expert opinion: The GPR17 receptor is an enigmatic receptor and an interesting therapeutic target in a variety of brain disorders and demyelinating diseases such as multiple sclerosis, stroke, schizophrenia and depression. The modulation of this receptor could also be potentially useful in obesity treatment. Unfortunately, so far, there are no compounds under investigation in clinical trials but many researchers and companies are investing in the discovery of future potential GPR17 receptor drugs.

Keywords: GPR17 receptor, leukotrienes, nucleotides, oligodendrocytes myelination, patent.
1. Introduction

G protein-coupled receptors (GPCRs) is a superfamily representing the largest and most diverse cell surface receptors. More than 140 GPCRs are so-called orphan receptors with a not yet known endogenous ligand [1-3]. Orphan GPCRs are assumed to represent promising drug targets, which may allow for the development of innovative pharmaceuticals [2]. Among them, a GPCR receptor phylogenetically related to both purinergic P2Y and Cysteinyl-Leukotrienes (CysLT) receptors, named GPR17 receptor, is mainly expressed in the Central Nervous System (CNS) and, in general, in organs that can typically undergo to ischemic damage. It is well known that this receptor is involved in the neuronal cell differentiation, the myelination process, and the repair mechanisms following a brain insult. GPR17 receptor has been proposed as a potential pharmacological target for the treatment of multiple sclerosis (MS) and traumatic brain injury in humans. Raport et al. [4] that isolated the GPR17 gene, which they called R12, discovered this receptor in 1996. In addition, [5] they used RT-PCR to identify novel P2 nucleotide (P2Y) GPCRs and to isolate GPR17 cDNA. It was “deorphanized” as a GPCR and it is located at intermediate phylogenetic position between known purinergic P2Y and CysLTS receptors. This receptor responds to two unrelated families of endogenous ligands: nucleotide sugars (UDP, UDP-galactose, and UDP-glucose) and cysteinyl leukotrienes (LTD4, LTC4, and LTE4), with significant affinity at micromolar and nanomolar concentrations, respectively [6-8].

The activation of GPR17 receptor by cysteinyl-leukotriene and purinergic ligands (UDP, UDP-gal, UDPglc, LTC4, and LTD4) is still controversially discussed. In fact, some researchers could not reproduce GPR17 activation by either ligand type in various assay systems [9-11]. Nevertheless, Buccioni et al. [12] as well as Eberini et al. [13] showed that this receptor was activated by UDP analogue PUP 2 and the ATP derivatives differently modified in N6 and in 2-position and it is coupled with a Gαi protein [12,14,15]. Structurally, GPR17 receptor belongs to GPCR superfamily. The C-terminus (intracellular domain) has a PDZ-1-like region (X-S-X-Ø) that participates in the interaction of signaling proteins with the receptor in the internalization and recycling processes. TM3, TM6, and TM7 almost completely overlap in human GPR17 (hGPR17) and murine (mGPR17) and rat (rGPR17) forms with a similarity of 90% among all these three species. Based on N-terminus length two GPR17 receptor isoforms have been identified: the short and long GPR17 isoforms. The first one encodes a 339 amino acid-residue protein with typical rhodopsin type-seven trans-membrane loop. The long isoform encodes a receptor with a 28 amino acid longer N-terminus [5].

2. GPR17 in diseases

It is worthwhile to note that these endogenous signaling molecules and their receptors mediate immune responses and ischemic/inflammatory conditions, including stroke and several currently incurable neurodegenerative diseases [16]. For these reasons, GPR17 receptor could be a target for a new chemical entity useful in stroke, brain and spinal cord trauma, MS and in all diseases characterized by neuronal and myelin dysfunction [7, 17, and 18]. In addition, it is well known that mature oligodendrocytes are able to restore the damaged myelin envelope enwrapping neuronal axons. GPR17 receptor is involved in the transition from oligodendrocyte precursors to mature oligodendrocytes expressing a myelinating phenotype [7, 18-20]. Consequently, GPR17 receptor can direct the neural precursor cells to the neuronal lineage [21]. Since the MS, a chronic progressive disorder, is characterized by a damage of fatty myelin sheaths around the axons of the brain and spinal cord, related with a broad spectrum of signs and symptoms, GPR17 receptor plays an important role in this pathology. The pharmacological treatments currently available are symptomatic and are not able to counteract MS progression. For these reasons, there is the real exigency to identify molecules capable to bind specifically GPR17 receptor. Since it responds to two distinct classes of ligands, chemical entities able to interact on both the CysLT and nucleotide component of this receptor, may prove extremely more effective in preventing brain damage. Thus, it can open up to entirely new therapeutic strategies for all diseases in which GPR17 is involved. Furthermore, there are evidences that GPR17 is an effector of FOXO1 orexigenic signals in agouti-related peptide (AgRP) neurons and it is involved in food intake [22-24], suggesting that pharmacological modulation of this receptor can be potentially useful in obesity treatment.

Obesity and overweight are widely recognized as the largest and fastest growing public health problem in the developed and developing countries [25] so that in 2013 American Medical Association classified it as a
disease, defined by a body mass index (BMI) $\geq 30$ Kg/m$^2$ [26]. Obesity is a risk factor for a range of chronic conditions and pathologies, such as ischemic heart disease, stroke, arterial hypertension, type 2 diabetes, and some types of cancer i.e. uterine body, colon and breast. A study including 2.88 millions of individuals with different obesity grades has shown a significant increase in mortality rate [27].

Food intake is regulate by hypothalamic neurons expressing agouti-related peptide (AgRP). In particular, this peptide regulates eating and glucose metabolism. There are evidences that the ablation of FOXO1 in AgRP neurons reduced food intake, leads to slimming, improve glucose homeostasis, and increase sensitivity to insulin and leptin. GPR17 receptor is an effector of FOXO1 orexigenic signals in AgRP neurons. In fact, intra cerebro-ventricular injection of GPR17 receptor agonists induces food intake, while the GPR17 receptor antagonist, Cangrelor, curtails it. In addition, in AgRP-FOXO1 knockout mice these effects are absent suggesting that GPR17 pharmacological modulation has therapeutic potential to treat obesity [22-24]. Accili et al. [28-30] made the first patent that identified GPR17 receptor as a new pathway involved in appetite and weight control. It was proved a strict correlation between AgRP-FOXO1 and GPR17 receptor. This observation allowed finding new methods of treating or preventing obesity and/or reducing appetite by administering a treatment able to reduce GPR17 receptor biological activity or its expression by a GPR17 receptor antagonist or inhibitory oligonucleotide of siRNA, respectively. The inhibition of GPR17 receptor activity could be used in a subject having impaired glucose tolerance or low insulin sensitivity because this increases glucose tolerance and/or insulin sensitivity. On the other hand, by GPR17 receptor activating could be treated eating disorders such as anorexia that are associated with abnormal weight loss.

3. Patents: biologics

Recent studies have recognized GPR17 receptor as an important regulator of oligodendrocyte development and remyelination [21,31-34]. The GPR17 activation is still controversially discussed but some patents, focused on the finding that GPR17 receptor responds to two distinct classes of ligands, were based on methods for the identification of GPR17 receptor modulators. Abbracchio et al. in the patent US 2009/0156521 [35] provide a method for the identification of GPR17 receptor modulators other than the leukotrienes or analogues thereof. This method is based on $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ assay and its set-up on GPR17 receptor allowed the study of agents able to modify or block GPR17 receptor activity.

In this assay the steps are:
1) in vitro contacting GPR17 receptor with a compound under study,
2) determining the receptor response.

The screening method may be applied to the identification of agonists, antagonists, inverse- or partial-agonists. In addition, some agonists (UDP, UDP-glucose, UNP-galactose, LTD, and LTC) and antagonist (AR-C69931MX, Montelukast, and Pranlukast) were validated to interact with GPR17 receptor.

Kostenis et al. [36] set up some assays to determine the compounds ability to modify the biological activity of GPR17 receptor. These assays include the measure of $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ binding increase to the heterotrimeric G proteins activated by the receptor, the inhibition of cyclic adenosine monophosphate (cAMP) formation and/or the release of calcium from intra cellular calcium stores, the increase in inositol phosphates (IP), and/or the recruitment of cytoplasmic $\beta$-arrestin proteins. The cell lines transfected with GPR17 receptor were CHO cells, astrocytoma cells, COS7 cells or HEK293 cells, or membrane fractions thereof, or native tissues.

The screenings were performed using some kits available on the market providing:

a) methods for determining calcium release from intracellular deposits associated with activation of GPR17 receptor with a measurable fluorescence or luminescence signal;
b) methods to determine GTPS binding to heterotrimeric G proteins by radioactivity;
c) methods for determining the inhibition of cAMP formation after a stimulation of the adenylyl cyclase (e.g. forskolin) or its increase associated with GPR17 receptor activation with a suitable cAMP indicator system;
d) methods for determining the increase in IP, quantified as IP1, e.g. a suitable IP1 detector system;
e) methods for determining the recruitment cytoplasmic $\beta$-arrestin proteins by fluorescence or bioluminescence resonance energy transfer.

Another pathology, in which GPR17 receptor is involved, is obesity. It is caused by an imbalance between energy intake and expenditure that leads to an excessive accumulation of white adipose tissue.
4. Patents: chemical agents

The modulation of GPR17 receptor activity by active and selective compounds improved the capability to understand the diseases and disorders where this receptor is involved. In particular, these compounds could be used in neuroprotective and/or reparatory purposes in cerebral, cardiac and renal ischemia, in traumatic brain injury and in demyelinating diseases such as MS, schizophrenia, depression, Alzheimer's disease, Alzheimer-like dementia, Parkinson's disease, Huntington's chorea, amyotrophic lateral sclerosis (ALS) and all other neuro-inflammatory disorders. Beyond all the previous diseases, these molecules have therapeutic potential to treat obesity. The only molecules currently on the market, able to activate GPR17 receptor, are LTD4 and LTC4, two natural ligands of CysLT receptor, and UDP (nucleotide diphosphate), UDP-glucose and UDP-galactose (nucleotide diphosphate sugars) agonists of some P2Y receptors. CysLT receptor antagonists, marketed as anti-asthma agents, are able to inhibit GPR17 receptor activity (i.e. Montelukast, Pranlukast and Zafirlukast). An adenosine triphosphate derivative antagonist of some P2Y, Cangrelor, which was developed as a platelet aggregation inhibitor, also inhibits the GPR17 receptor. A novel platelet aggregation inhibitor, Ticagrelor was approved (2 December 2010) by the European Medicines Agency (EMA) and the US Food and Drug Administration (20 July 2011).

The crystallographic structure of GPR17 receptor is not available since it was deorphanized only some years ago. However, the crystallographic structure of CXCR4, a G protein-coupled chemokine receptor, is known and it was demonstrated to be phylogenetically and structurally very close to GPR17 receptor [37].

Abbracchio et al. [38] identified, by in silico experimental procedure based on a comparative chimeric modelling method, developed by the inventors [13], a series of new GPR17 receptor compounds. These compounds, not structurally correlated with the known ligands, showed high affinity/activity (nanomolar, subnanomolar, picomolar IC50/EC50) for GPR17 receptor. The affinity/activity is significantly superior to known ligands able to interact with GPR17 receptor. These compounds, which can be a salt, an isomer, a single enantiomer, a racemate or a tautomer, are represented in the following molecular structures (I – V) (Figure 1). The affinity/activity of these compounds is shown in Table 1.

Comparing CXCR4 crystallographic structure with the in silico model of GPR17 receptor [39], in which the extracellular loops of the receptor were modeled referring of all the class GPCRs crystallized so far [13], it resulted that CXCR4 crystallographic structure is the best template to model each domain of GPR17 receptor. On this base, was discovered a homodimer in which are present the helices V and VI that may be involved in signal regulation [37]. This peculiarity makes it different from other GPCRs such as GPR17 receptor. GPR17 receptor A3-D molecular model was obtained by fixing it in a phospholipids bilayer and by molecular dynamics simulations was refined [40]. These studies showed that in GPR17 receptor nucleotide binding pocket only one of the three basic residues (Arg255), present in other P2Y receptors that usually interact with ligand, are conserved. Based on this model, Abbracchio et al. [41,42] proposed new chemical compounds and their pharmaceutical salts that selectively act on GPR17 receptor and could be useful in the treatment or amelioration of chronic and/or acute diseases in which GPR17 receptor is involved. The first class of molecules shows the following formula (VI) (Figure 2).

R is H, a linear or branched alkyl, a linear or branched alkyl phenyl optionally substituted, a phenyl optionally substituted; R2 is H, a linear or branched alkyl, a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S; R3 is H, a linear or branched alkyl or NHC(O)R4, wherein R1 is a linear or branched alkyl, a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S. The length of the carbon chain present in different positions (R-R3) were in ranges from 1 to 4 carbon atoms.

A second class of the molecules was also obtained (VII) (Figure 3).
R is H, a linear or branched alkyl phenyl optionally substituted, a un- or saturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S. R2 can be an H, a linear or branched alkyl, a linear or branched alkyl phenyl that can be substituted, a saturated or unsaturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S. R and R2 can be H, a linear or branched alkyl phenyl optionally substituted, a un- or saturated mono, bi or tricycle having from 3 to 16 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S. In addition, R2 can be a linear or branched alkyl too.

The length of the carbon chain present in different positions (R-R2) were in ranges from 1 to 4 carbon atoms (VIII) (Figure 4).

R1 and R2 can be an H or an optionally substituted phenyl, or R1 or R2 are able to form with N (to which are linked) a 1,2,3,4-tetrahydroquinoline, a 1,2,3,4-tetrahydroisoquinoline, a piperidine, a piperazine or a piperazine optionally substituted; A is C and the 6 membered ring is an aromatic ring; Z forms a bicycle with said 6 membered ring by closing on A, wherein said second ring formed by Z is a 5 member ring open to fusion, preferably said 5 membered ring is fused with and optionally substituted phenyl creating a tricycle, preferably said tricycle is a 5H-[1,2,4]triazino[5,6–b]indole optionally substituted.

In a preferred embodiment, wherein A is a band and said ring containing 3 N is a 5 membered ring, said compounds of formula (VIII) (Figure 4) are selected from the group of formula (VIIIa) (Figure 4).

The length of the carbon chain present in different positions (R) were in ranges from 1 to 4 carbon atoms wherein R1 is H and R2 is an optionally substituted phenyl, or R1 and R2 are able to form with the N to which are attached a piperidine, a phenothiazine, a pyridine, a piperidine, morpholine, indoline pyrazole, isoquinoline, furyl, pyrrolidine, and others suitable rings all these appropriately substituted with different alkyl chains, carboxyl esters, carboxylic acids, carbox-amide-N-phenyl, halogens, sulphonils and others opportune substituents.

Furthermore, R1 and R2 are closed to form with the N to which are linked an indoline, a 1,2,3,4-tetrahydroisoquinoline, a 1,2,3,4-tetrahydroquinoline, a piperidine, a piperazine; R is H, optionally substituted with benzyl or-CH2C(O)N; R4 is H; R5 is an optionally substituted phenyl or an optionally substituted cycloexane or R4 and R5 form with the nitrogen to which they are attached a pyrrolidine; R6 and R7 are independently H or an optionally substituted phenyl, or R6 and R7 close to form a saturated or unsaturated cycle having from 3 to 8 members optionally substituted and eventually containing from 1 to 4 heteroatoms selected from N, O, S. In a preferred embodiment, R6 and R7 are closed in a cycle forming a tricycle.

Kostenis et al. [36], in the same patent that set up several assays to determine the compounds ability to modify the biological activity of GPR17 receptor, reported new agonists for this receptor. In particular, compound RA-II-150 (Figure 5), its derivatives, and their salts can activate GPR17 receptor expressed in different cell lines such as 1321N1 astrocytoma cells, human embryonic kidney HEK293 cells, and Chinese hamster ovary (CHO) cells (Table 2 and 3).

It is worthwhile to note that none of these identified GPR17 receptor agonists display activity in native cells that lack GPR17 receptor. Moreover, in this patent small molecules were identified with the ability to activate GPR17 receptor that show high specificity and potency significantly greater over other GPR17 receptor agonists.
These indole-2-carboxylic acids are all potent agonists and are not suited to down-regulate GPR17 receptor activity as needed in the treatment of myelination disorders such as MS. In addition, this new indole-2-carboxylic acids able to activate GPR17 receptor does not sufficiently pass the blood-brain barrier due to their carboxyl groups that are easily ionizable, for this reason they are no suitable as lead compounds to develop negative GPR17 receptor modulators [43,44]. For these reasons, it is necessary to identify powerful negative modulators of the GPR17 receptor able to reduce its activity.

Müller et al. [45] presented a class of sulfonamide compounds, pharmaceutically acceptable salts, solvates, isotopes and co-crystals as negative GPR17 receptor modulators. These compounds have a general structure according to formula IX (Figure 6).

Usually X₁₋₃ corresponds to NH and/or N and/or S and/or O and/or C and all possible combinations. When X₃ is C, a substitute (R₇) is present.

R₄ is selected from hydrogen, methoxy and halogen;
R₅ is selected from hydrogen, halogen, cyano, alkyl, alkenyl, alkynyl, alkoxy, alkylcarbonyl, alkoxycarbonyl, alky lsulfinyl, and alky lsulfonyl;
R₆ is selected from hydrogen, hydroxy, halogen, cyano, azido, nitro, alkyl, alkenyl, alkylnyl, alkoxy, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, phenyl, heteroaryl, heterocyclyl, -ORₓ, -SRₓ, -SORₓ, SO₂Rx, -pentafluorosulfanyl, NRYRₓz, -NRYCORₓ, -NRyCO₂Rx, -N-RₓCONRᵧRz, -N-RySORₓ, -N-RySO₂Rx, -CORₓ, -C₀₂Rx, -CONRᵧRz;
R₇, if present, is selected from hydrogen, halogen, cyano, azido, nitro, amino, alkyl, alkoxy, alkenyl, alkynyl, alkylcarbonyl, alkoxy carbonyl, alky lsulfonyl, alkyl sulfinyl, alkyl thio, alkyl carbonylamino, alkylaminocarbonyl, dialkylaminocarbonyl, cycloalkyl, cycloalkoxy, heterocycloalkyl, heterocycloalkenyl, phenyl, phenyl ox y, phenylalkyl, phenylalkoxy, phenyl sulfonyl, phenyl sulfinyl, heteroaryl, hetero aryl, hetero aryl, alkyl, cyclo alkyl, cyclo alkyl alkoxy, heterocycloalkyl, heterocycloalkyl alkxy, heterocycloalkyl alkxy, hetero cyclo alkyl alkxy;
R₈ is selected from hydrogen, alkyl, alkenyl, alkylnyl, alkoxy, alkyl sulfonyl, alkyl sulfinyl, alkyl thio, cyano, and halogen;
R₉ is selected from hydrogen, halogen, cyano, azido, alkyl, alkoxy, alkenyl, alkynyl halogen;
R₁₀ is selected from hydrogen, halogen, alkyl, alkoxy, alkenyl, alkynyl, cyano, cyano alkyl, cyano alk oxy, alkyl carbonyl, alkoxycarbonyl, alkyl sulfonyl, alkyl sulfinyl, alkyl thio, cycloalkyl, cycloalk oxy, hetero cycloalkyl, heterocycloalkyl ox y, amin o, azido, pentafluorosulfanyl, nitro, alkyl carbonylamino, alkylaminocarbonyl, dialkylaminocarbonyl, dialkyl sulfinyl and alkyl sulfonyl;
R₁₁ is selected from hydrogen, halogen, cyano, alkyl, alkoxy, alkyl carbonyl, alkoxy carbonyl, alkyl sulfonyl, and alkyl sulfinyl, alkenyl, and alkynyl;
R₁₂, if present, is selected from hydrogen, alkyl, alkoxy and halogen, wherein each alkyl or alkoxy can be unsubstituted or substituted with one or more substituents selected from halogen and halogenated preferably fluorinated or unsubstituted alkoxy.

The length of the carbon chain present in different positions (R₄-R₁₂) were in ranges from 1 to 6 carbon atoms.

In a further example, the compounds of the present invention are represented by one of the following structures (Xₐ – Xₐ) (Figure 7).

n is any number from 0 to 4,
m is 0 or 1,
p is any number from 0 to 3,
and any Y is an independently selected substitution selected from the group consisting of halogen, hydroxy, cyano, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkoxy, heterocycloalkyl, alkoxy, and alkoxy alkyl wherein each alkyl or alkoxy can be unsubstituted or substituted with one or more substituents selected from halogen and alkoxy,
R₄, R₅, X₃, R₈, R₉, R₁₀, R₁₁ and R₁₂ are as described in the compounds with structure X,
Moreover, the compounds were added with at least one isotope selected from $^{123}$I, $^{124}$I, $^{125}$I, $^{131}$I, $^{11}$C, $^{14}$C, $^{13}$N, $^{15}$O, $^{18}$F, $^{76}$Br, $^2$H and $^3$H in an amount suitable for PET and/or SPECT imaging, in diagnosis and/or in PET or SPECT imaging. Compounds were tested with cAMP and Ca$^{2+}$ assays and the data are expressed in pA$_2$ and pIC$_{50}$, respectively. The compounds activity range was $7.5 \leq X \leq 8.5$.

An example of the molecules presented in this patent was reported below (I-14, I-73, I-272) (Figure 8).

5. Conclusions

In the past decade, some novel compound series were patented even though any of these compounds are able to interact with the double binding site. Some structures were discovered by molecular modeling studies. The affinity/activity of these compounds for GPR17 receptor, not structurally correlated with the known ligands, is in the nanomolar, subnanomolar, picomolar range. In addition, a class of sulfonamide compounds behaving as antagonists of GPR17 receptor, with an affinity expressed in pA$_2$ and pIC$_{50}$ in the range 7.5-8.5, was synthesized. Unfortunately, any clinical trials are not still started with new GPR17 receptor ligands.

6. Expert opinion

GPR17, a member of G protein-coupled receptors phylogenetically related to both purinergic P2Y and CysLT receptors, was deorphanized only few years ago. Despite this, the activation of GPR17 receptor by purinergic and cysteiny-leukotriene ligands is still controversially discussed in academia. Numerous studies demonstrate that GPR17 signaling plays a critical and pivotal role in many different physiological processes, including inflammation, neurodegeneration, MS, and obesity. GPR17 receptor is a sensor of brain damage and plays a crucial role in lesion remodeling and/or repair. In particular, GPR17 receptor is also involved in the cell death of irreversibly damaged neurons, in activation of microglia and in macrophages remodeling the lesion, and in activation and proliferation of multipotent parenchymal progenitors starting repair processes. Accordingly, GPR17 receptor is considered an orchestrator of central nervous system in remodeling/repair brain after a stroke. Pharmaceutical industries are currently focusing in brain repair after a stroke but until now, they did not develop ligands that interact with GPR17 receptor. On the other hand, academia is very active in this field and produced many compounds, included in patents, which are able to interact with GPR17 receptor. In fact, molecules with triazol-phenylpropanamide structures were projected by in silico experimental procedure based on a comparative chimeric modelling method, as agonists of GPR17 receptor [38]. In addition, comparing CXCR4 crystallographic structure with the in silico modeling of GPR17 receptor [39], others GPR17 receptor ligands bearing a triazolidine structure otherwise substituted were constructed [41,42]. The last compounds showed an antagonistic behavior for GPR17 receptor. What is more, a series of indole-2-carboxylic acids were synthesized as agonist of GPR17 receptor [36]. Lastly, a series of sulfonamide compounds was projected and synthesized as antagonists of GPR17 receptor [45].

On the light of the foregoing, the clinical trials and the availability in the market of these different classes of molecules could represent a therapeutic strategy for the treatment of neurodegenerative diseases in which, until now, only palliative remedies are helpful. It is important to note that neurodegenerative diseases constitute a category that the World Health Organization calculates will become the world’s second leading cause of death by the year 2040, overtaking cancer. Neurodegenerative diseases are thus destined to become the next great health crusade over the next several decades.

In general, for neurodegenerative diseases, social and economic costs represent an enormous burden due to disease long duration, the loss of patients' productivity, the need for assistance in activities of daily living and the use of costly treatments and multidisciplinary health care.
By addressing the basic dysfunction of neurogenesis in these diseases and by utilizing the new compounds reported in this review, as therapeutic drugs, it will eventually improve the health of citizens and contribute to the health crusade against neurodegenerative diseases. In conclusion, much remains to be discovered about pharmacology and biochemistry of this GPR17 receptor but all these new molecules discovered, that can act as agonists or antagonists of it, can only augment the rate of translation of this interesting drug target receptor.

Article highlights
- GPR17 receptor is a promising target to cure neurodegenerative diseases.
- The come to light of new molecule classes able to interact with GPR17 receptor opened a new perspective in the pharmacotherapy, in particular for multiple sclerosis.
- Unfortunately, until now, no clinical trial is started with the new GPR17 receptor ligands.
- Until now only academia is focused on the discovery of new ligands for GPR17 receptor.

Funding
This paper was not funded.

Declaration of interest
The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures
Peer reviewers on this manuscript have no relevant financial or other relationships to disclose
References

Articles or patents of special interest have been highlighted as either of interest (*) or of considerable interest (**) to readers.

3. Civelli, O. GPCR deorphanizations: the novel, the known and the unexpected transmitters. In Trends in pharmacological sciences 2005; 26: 15–19. *This article explains the importance of orphan GPCR and how beneficial can be the deorphanization.


28. Accili D, Ren H. G protein-coupled purinergic receptor GPR17 mediates orexigenic effects of foxo1 in AgRP neurons US9309514 B2 (2016). * This patent explains the implication of orexigenics effects on Foxo1 in AgRP neurons.


30. Accili D, Ren H. G protein-coupled purinergic receptor GPR17 mediates orexigenic effects of foxol in AgRP neurons. WO2013113032 (2013). * This patent explains the implication of orexigenics effects on Foxo1 in AgRP neurons.


38. Abbracchio MP, Eberini I, Parravicini C, et al. GPR17 modulating compounds, diagnostic and therapeutic uses thereof. WO2012059869 (2012). ** This patent presents compounds that modulate GPR17 in a specific way useful for treatment and diagnosis.


42. Abbracchio MP, Battaglia MA, Eberini I, et al. GPR17 receptor modulators. WO2013167177 (2013). **This patent provides compounds useful in the treatment of chronic and/or acute neurodegenerative diseases, immune system, cardiovascular diseases, and renal diseases.


45. Mueller C, Pegurier C, Deligny ML, et al. (Aza)indole-, benzothiophene-, and benzofuran-3-sulfonamides. WO 2018122232 (2018). **This patent indicates sulfonamide compounds that modulates GPR17 for treating or preventing a variety of CNS and other diseases.

Table and figure legends

**Table 1.** Pharmacological parameters for the compounds according to the invention determined in [35S]GTPyS binding.

**Table 2.** Potencies and efficacies of RA-II-150 and its congeners in the 1321N1-GPR17 receptor and CHO-GPR17 receptor cell systems obtained through calcium mobilization assays.

**Table 3.** Molecular structure of compounds that can be produced using the same synthetic methods of compound RA-II-150 and its congeners.

**Figure 1.** Structures I-V

**Figure 2.** Structure VI

**Figure 3.** Structure VII

**Figure 4.** Structures VIII and VIIIa

**Figure 5.** Structure RA-II-150

**Figure 6.** Structure IX

**Figure 7.** Structures Xa-Xc

**Figure 8.** Structures I-14, I-73 and I-272
Table 1. Pharmacological parameters for the compounds according to the invention determined in $[^{35}\text{S}]\text{GTPyS}$ binding

<table>
<thead>
<tr>
<th>Compound</th>
<th>EC$_{50}$</th>
<th>E$_{max}$</th>
<th>% E$_{max}$ vs standard</th>
<th>IC$_{50}$ Compound vs Cangrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASN06917370</td>
<td>268 ± 9 pM</td>
<td>161.5 ± 2.4</td>
<td>111.5 **</td>
<td>0.78 ± 0.22 nM</td>
</tr>
<tr>
<td>ASN02563583</td>
<td>109 ± 28 pM</td>
<td>145.6 ± 5.7</td>
<td>100.6</td>
<td>0.64 ± 0.19 nM</td>
</tr>
<tr>
<td>ASN04450772</td>
<td>1.18 ± 0.08 nM</td>
<td>129.7 ± 0.7</td>
<td>89.6 ***</td>
<td>0.51 ± 0.04 nM</td>
</tr>
<tr>
<td>ASN04885796</td>
<td>2.27 ± 0.07 nM</td>
<td>1735.5 ± 0.5</td>
<td>119.8 ***</td>
<td>0.48 ± 0.17 nM</td>
</tr>
<tr>
<td>ASN04421891</td>
<td>3.67 ± 0.51 nM</td>
<td>206.8 ± 8.3</td>
<td>142.8 ***</td>
<td>0.71 ± 0.09 nM</td>
</tr>
<tr>
<td>LTC$_{4}$ 100 nM</td>
<td></td>
<td>144.8 ± 0.4</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

** P<0.001 vs LTC$_{4}$ set 100%

*** P<0.001 vs LTC$_{4}$ set 100%
Table 2. Potencies and efficacies of RA-II-150 and its congeners in the 1321N1-GPR17 receptor and CHO-GPR17 receptor cell systems obtained through calcium mobilization assays.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>pEC&lt;sub&gt;50&lt;/sub&gt; (±SEM) 1321N1-GPCR17/CHO-GPCR17</th>
<th>% of response of 30 µM (±SEM) 1321N1-GPCR17/CHO-GPCR17 cells</th>
<th>% of response of 30 µM (±SEM) Native 1321N1 cells/CHO-K1 cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA-II-150</td>
<td>-Cl</td>
<td>-H</td>
<td>-Cl</td>
<td>6.09 (0.06)/8.20 (0.08)</td>
<td>100 (0)/100 (0) (0.3 µM compound)</td>
<td>0 (3)/0 (1) (0.1 µM compound)</td>
</tr>
<tr>
<td>RA-III-40</td>
<td>-Cl</td>
<td>-(CH&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>-Cl</td>
<td>5.28 (0.08)/6.73 (0.12)</td>
<td>80 (6)/85 (5) (1 µM compound)</td>
<td>1 (1)/1 (1) (1 µM compound)</td>
</tr>
<tr>
<td>RA-III-55</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-H</td>
<td>-CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>4.86 (0.10)/6.47 (0.05)</td>
<td>76 (6)/68 (2) (1 µM compound)</td>
<td>1 (1)/1 (1) (1 µM compound)</td>
</tr>
<tr>
<td>KL16-1</td>
<td>-</td>
<td>-H</td>
<td>Cl</td>
<td>5.43 (0.14)/7.69 (0.10)</td>
<td>84 (6)/94 (7) (1 µM compound)</td>
<td>4 (3)/1 (2) (0.3 µM compound)</td>
</tr>
<tr>
<td>KL28</td>
<td>-F</td>
<td>-H</td>
<td>-F</td>
<td>5.13 (0.13)/6.79 (0.10)</td>
<td>77 (2)/97 (5) (3 µM compound)</td>
<td>2 (1)/1 (2) (3 µM compound)</td>
</tr>
<tr>
<td>KL126</td>
<td>-Br</td>
<td>-H</td>
<td>-Br</td>
<td>6.71 (0.01)/7.87 (0.16)</td>
<td>106 (1) (10 µM compound)/89 (2) (0.3 µM compound)</td>
<td>0 (1)/0 (0) (0.3 µM compound)</td>
</tr>
<tr>
<td>SAL006-1</td>
<td>-H</td>
<td>-H</td>
<td>-Br</td>
<td>5.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAL009-1</td>
<td>-H</td>
<td>-H</td>
<td>-I</td>
<td>6.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAL019</td>
<td>-I</td>
<td>-H</td>
<td>-I</td>
<td>5.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAL016</td>
<td>-Ph</td>
<td>-H</td>
<td>-Ph</td>
<td>5.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAL016A</td>
<td>-H</td>
<td>-H</td>
<td>-Ph</td>
<td>6.14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Molecular structure of compounds that can be produced using the same synthetic methods of compound RA-II-150 and its congeners.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R₁</th>
<th>R₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLE12</td>
<td>-H</td>
<td>-Cl</td>
<td>-Cl</td>
</tr>
<tr>
<td>OLE16</td>
<td>-H</td>
<td>-F</td>
<td>-Cl</td>
</tr>
<tr>
<td>OLE33</td>
<td>-H</td>
<td>-F</td>
<td>-Br</td>
</tr>
<tr>
<td>OLE20</td>
<td>-OMe</td>
<td>-H</td>
<td>-OMe</td>
</tr>
<tr>
<td>OLE37</td>
<td>-H</td>
<td>-H</td>
<td></td>
</tr>
<tr>
<td>OLE41</td>
<td>-H</td>
<td>-H</td>
<td></td>
</tr>
<tr>
<td>OLE42</td>
<td>-OH</td>
<td>-H</td>
<td>-OH</td>
</tr>
<tr>
<td>OLE44</td>
<td>-H</td>
<td>-H</td>
<td></td>
</tr>
<tr>
<td>OLE46</td>
<td>-H</td>
<td>-H</td>
<td></td>
</tr>
<tr>
<td>OLE48</td>
<td>-H</td>
<td>-H</td>
<td></td>
</tr>
<tr>
<td>OLE52</td>
<td>-H</td>
<td>-F</td>
<td></td>
</tr>
<tr>
<td>OLE53</td>
<td>-H</td>
<td>-F</td>
<td></td>
</tr>
<tr>
<td>OLE54</td>
<td>-H</td>
<td>-F</td>
<td></td>
</tr>
<tr>
<td>OLE56</td>
<td>-H</td>
<td>-F</td>
<td></td>
</tr>
</tbody>
</table>
I. 2-[[5-(2-methoxyphenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-yl]thio]-N-phenylpropanamide. CAS Registry Number 483283-39-2 (sold by Asinex, code ASN02563583).

II. 6-methoxy-3-[[l-(2-methoxyethyl)-lH-tetrazol-5-yl][2-phenylethyl](phenylmethyl)-amino]methyl]-2(lH)-quinolinone. CAS Registry Number 570365-12-7 (sold by Asinex, code ASN0442 1891)
III. 4-amino-N5-(2-furanylmethyl)-N5-[l-(4-hydroxyphenyl)-2-[[4-methoxyphenyl]-methyl]amino-2-oxoethyl]-3,5-isothiazole dicarboxamide. CAS Registry Number 1032654-1 1-7 (sold by Asinex, code ASN04450772).


V. 4-[3-[(2-chlorophenyl)methyl]-6,7-dihydro-7-oxo-3H-1,2,3-triazole[4,5-d]pyrimidin-5-yl]-N-[4-(trifluoromethyl)phenyl]-l-piperidinecarboxamide. CAS Registry Number 837404-68-9 (sold by Asinex, code ASN069 17370).
Figure 6

Figure 7
Figure 8

I-14

I-73

I-272