Therapeutic modulators of the serotonin 5-HT4 receptor: a patent review (2014-present)

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Article highlights

- The interest of 5-HT$_4$R modulators have been explored in several pathologies and approved by the FDA.
- The progress in the development of 5-HT$_4$R modulators patented between 2014 and 2019 is reviewed.
- The exploration of multiple chemical scaffolds has led to the discovery of several potent and selective 5-HT$_4$R modulators.
- Several 5-HT$_4$R modulators are currently being evaluated in clinical trials.
- The potential therapeutic interest of 5-HT$_4$R modulators in combination with other drugs could lead to synergistic combined therapies.

Abstract

Introduction: Numerous chemotypes have been described over time in order to generate potent and selective 5-HT$_4$R ligands. Both agonists and antagonists have demonstrated their interest in several disease models. This culminates with the FDA approval of Tegaserod and Prucalopride in the recent years.

Areas covered: This review summarizes the patent applications from 2014 to present, dedicated to the use or the description of novel 5-HT$_4$R modulators. Several novel ligands and scaffolds have been industrially protected mainly in the field of central nervous system (CNS) pathologies as well as gastrointestinal disorders, including the combination with other drugs or for veterinary uses.

Expert opinion: The therapeutic potential of 5-HT$_4$R modulators has been explored for several years in animal models, but also linked to potential safety issues with initial ligands. The current use of Prucalopride in human demonstrates that its toxicity is not linked to the target and that 5-HT$_4$R modulators are safe in human. Therefore, an important number of studies and patents has continued in the recent years to expand the use of 5-HT$_4$R modulators, not only to treat gastrointestinal disorders, but also for CNS pathologies. This article details current efforts in this development.

Keywords: serotonin, 5-HT_4 receptor, central nervous system, Alzheimer, depression, gastrointestinal disorders

1 Introduction

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) plays an important role in several physiological processes in the periphery but also in the Central Nervous System (CNS) by interacting with seventeen different 5-HT receptors (5-HT_{1-7}R subtypes). Further, the modulation of 5-HTR activity has been connected to different human pathologies, including migraine, depression or schizophrenia and several drugs, today in use, have been developed to interact with 5-HTRs or with the serotonin transporter (SERT). The Serotonin subtype 4 receptor (5-HT_4R) was discovered in 1988 [1]. It is a Gs protein-coupled receptor (GPCR), producing Cyclic Adenosine MonoPhosphate (cAMP) by stimulation of guanylyl cyclase [2]. 5-HT_4Rs are localized in the CNS throughout the brain but also in the periphery, mainly in the heart, intestine, bladder and adrenal cortex. Based on this localization, intense research in the last decades have been conducted in order to develop 5-HT_4Rs ligands to treat memory disorders or gastrointestinal disorders.

If selective 5-HT_4R antagonists have been proposed to treat atrial fibrillation or irritable bowel syndrome (IBS) [3], most of the efforts were put to develop agonists. Agonists display potent prokinetic properties, enhance intestinal peristalsis and gastric emptying and decrease esophageal reflux, but were often linked to non-target mediated toxicity [4]. Among them, Cisapride **1** was known to interact with hERG channels (Table 1) [5]. This derivative is representative of the aminobenzamide scaffold which has been explored in a number of other compounds presented in the manuscript. Tegaserod **2** was firstly approved by the FDA in 2002 to treat the constipation associated to IBS in women [6]. Tegaserod was however withdrawn in 2007 due to cardiac adverse effects linked to prolonged QT interval. Conversely, a large cohort study "*found no evidence for an increased risk of cardiovascular ischemic events in Tegaserod users*" [7]. Tegaserod was then reintroduced in March 2019 after a complete safety review by the FDA [8]. Prucalopride **3**, a highly selective 5-HT_4R agonist, approved by the FDA in 2018 to treat chronic idiopathic constipation by enhancing colon peristalsis and increasing bowel motility, appears also to be devoid of cardiac risk [9]. This is also the case for Minesapride **4** (Fig 1) that was also proved to be devoid of any QT prolongation [10].

In the CNS, the 5-HT_4Rs are located in caudate nucleus, putamen, nucleus accumbens, globus pallidus, as well as substantia nigra [11]. Interestingly, the expression of the receptors is reduced in patients suffering from Alzheimer's disease (AD), while it seems not affected in other neurodegenerative diseases like Parkinson's disease (PD) [12]. This decrease has suggested the implication of 5 HT_4R in cognitive learning and memory processes. The procognitive effects, linked to acute administration of 5-HT_4R agonists, have been attested for a long time. The latter are thought to be mediated by modulation of neurotransmitters's release as 5 HT_4R activation increases the release of acetylcholine (ACh) [13,14], dopamine (D) [15,16] and 5-HT [17]. Moreover, 5 HT_4R agonists, such as BIMU-1 **5** and RS 67333 **6** (Fig 1), are able to promote the "non-amyloidogenic" cleavage of the amyloid protein precursor (APP) by an α-secretase, inducing the decrease in Aβ production in primary neurons [18,19], the release of soluble and neuroprotective sAPPα protein [20], and the *in vivo* improvement of memory in rat [21]. Two 5-HT_4R agonists, SL 65.0155 **7** [22] and PRX 03140 (also named VRX 03011) **8** [23], have already reached the clinical phase IIb for the treatment of AD (Table 1) and several candidates are today under investigation in the field of neurodegenerative diseases.

Interestingly the 5-HT_4R-mediated intracellular signaling, including cAMP release and phosphorylation of CREB, has proved to yield antidepressant-like effects [24]. The use of 5-HT_4R PET radiotracers has recently demonstrated a lower striatal 5-HT_4R binding in familial major depressive disorders [25]. Therefore, the interest of 5-HT_4R agonist have been investigated to treat depressive disorders [26]. Despite first negative results regarding prucolopride anti-depressant effects [27] several 5-HT_4R ligands are still investigated in clinical trials including prucalopride **3**, Revexepride **10** and PF- 04995274 **17** [26].

Over the last years, a wide variety of 5-HT_4R ligands have been evaluated in clinical trials as summar

As depicted by the different structures presented above, 5-HT_4R ligands share common structural features which could be illustrated by the pharmacophore presented below on Cisapride **1** (Fig 2). Indeed, all the structures are possessing an aromatic or heteroaromatic ring core, linked by a hydrogen bond acceptor goup as linker to a basic center. This basic center, generally featuring a cyclic amine, is finally substituted by a hydrophobic scaffold of large diversity.

In this review, we will discuss about the new patents published between 2014 and 2019 on 5-HT_4R ligands, based on new indications, new structures or novel associations of compounds.

2 Patents on new 5-HT_4R ligands (2014-2019)

2.1 New indications (or therapeutical areas)

2.1.1 Repurposing

Due to the wide variety of localizations of 5-HT_4Rs in the body, it is not surprising to find repurposing of well-known 5-HT_4R agonists from gastrointestinal to neurological areas. Ishii Toshiaki *et al.*, from Obihiro Chikusan University, Japan, reported in 2018 on JP2018168072 [28] the use of known 5-HT_4R agonists (Prucalopride **3**, Naronapride **9** and Velusetrag **14**) as therapeutic agents for cognitive dysfunction accompanying PD. The inventors completed the present invention by elucidating the onset mechanism of cognitive impairment associated with PD and newly discovering that 5-HT_4R agonists can be useful therapeutics for cognitive impairments associated to PD. They used PD model mice and showed that the intraperitoneal administration (IP) of Prucalopride reduced the freezing behavior, but could also improve hippocampal cAMP reduction.

Revexepride **10** (currently in clinical trial phase 2b against GERD [29,30]) and its dihydrofuran derivative were patented in 2014 [31] as neuroprotective compounds in combination with an Acetylcholinesterase (AChE) inhibitor or any other procognitive compounds, such as 5-HT_6R antagonists. Those partial agonists appear to show higher procognitive effects on an animal model in working, fear and spatial motivated memory tests than the reference Prucalopride **3**

and a lower effect on the peripheral 5-HT_4R. This makes them particularly interesting for the treatment of neurodegenerative diseases.

To repurpose finding of 5-HT_4R agonists, Pfizer Japan patented in 2015 a trifluoroethoxy benzisoxazole derivative (RQ-10) **16** and all its salts in gastroparesis and as prokinetic agents [32–34]. This compound was previously described in 2011 with other benzisoxazole 5-HT_4R agonists that include their lead compound PF-04995274 **17** [35]. The latter was tested in clinical trial against cognitive impairment in AD [36]. During its development, it has been shown that this new trifluoroethoxy compound only showed moderate CNS permeation, but could be interesting in the peripheral system.

2.1.2 New indications

Even if the two main indications of 5-HT_4R ligands are the gastrointestinal diseases or cognitive impairments due to neurodegenerative diseases, some new indications seem to be investigated in the literature, as shown by the previously described clinical trial of Prucalopride **3** as an antidepressant or Tegaserod **2** for cardiac failure. On the other hand, Alisi *et al.* patented their new pyrroloquinolines as useful 5-HT_4R ligands to treat neuropathic pain (US8686147). They already patented indazole derivatives for that indication in 2006 (US7638534) [37,38]. In order to demonstrate the activity of their compounds in the treatment of chronic pain, they tested some of them (compound **18**; Figure) on the inducement of allodynia induced by ligature of the sciatic nerve in rats. It appears that the rats which received the compound could handle twice more pressure in their paw of the left hind leg than the group who receive only the vehicle, showing that those rats could handle more pain.

2.1.3 Potential Ameliorated pharmacokinetics

Dhanoa *et al.* patented deuterated derivatives of PRX 03140 **8** in US20150080377 [39]. According to the patent, suitable modifications of certain carbon-hydrogen bonds into carbon-deuterium bonds can generate novel substituted pyridinone carboxamides with unexpected and non-obvious improvements of pharmacological, pharmacokinetic and toxicological properties in comparison to the non-isotopically enriched 5-HT_4R agonists, full agonists, inverse agonists

or antagonists. The authors patented the introduction of deuterium in the compound at each available position (where there is usually a Hydrogen), and that this transformation could have a huge impact on the parameters previously cited. However they did not performed any pharmacokinetic studies to confirm this hypothesis. [23,39–41].

2.1.4 New species

Mosapride is a 5-HT_4R agonist that acts as a prokinetic agent and is used for the treatment of gastritis, GERD, functional dyspepsia and IBS. In the veterinary field, Mosapride citrate has already been marketed as a drug for improving upper gastrointestinal motility in dogs, and an application for an approval has been filed for the improvement and reduction of gastrointestinal motility in equine constipation. In 2017, Mikami *et al.* patented the use of Mosapride for bovine digestive disease in JP2017014113 [42]. This study opens the possibility of using 5-HT_4R agonists for bovine species.

2.2 Design of new 5-HT_4R ligands

As seen in the introduction, almost all 5-HT_4R ligands follow the same general structure with first an aromatic core, connected with a linker to a basic center, then a substituent (Fig 2). The description of the new patented scaffold will be presented according to the different possibilities.

2.2.1 New scaffolds – Aromatic core

One of the main aromatic cores is the chloro-aniline one that is already well known to confer a 5-HT_4R agonist activity to compounds such as Cisapride **1** and Mosapride **19**. Therefore, it was not surprising to find patents from different companies and nationalities that explored this aromatic ring [42–45].

The development of new innovative aromatic cores led to the discovery of several bicyclic compounds possessing a benzyl ring linked to a 5 membered heterocycle (analog of the indole ring of 5-HT). Raqualia, on the model of BIMU-1 **5** [46] and PF-04995274 **17** [47], developed a new benzimidazolone compound in US8980922 [48]. Even if they described a wide variety of 5-HT_4R agonist moieties, they only claimed the compound **20** as promising compound with

combining activities as ACh inducement, β-amyloid (A)β production's decrease and selective 5-HT_4R agonism (over others 5-HT receptors) in mammalian subjects. They showed that direct injection of their compound into rat hip could increase ACh concentration up to 187%. The Aβreduction was shown in Tg2576 mice according to the method described by Kawarabayashi *et al.* [49] and compound **20** decreased from 25% to 36% the $A_{04-1}\beta$ and $A_{24-1}\beta$levels.

Dainippon Sumimoto Pharm patented in 2014 in WO2014092104 a lot of hetero aromatic bicyclic cores, including known indazoles and benzisoxazoles (already explored by Pfizer for example in PF-04995274) [47], but also some new innovative fragments like benzothiazoles [50].

Suven Life Science was also really active. The company patented a large variety of different indazoles compounds as seen on Table 2. They also investigated the benzofuran (from Prucalopride **3** or Revexepride **10**) as a bicyclic core. They succeeded to give to those well-known scaffolds a renew by modifying the rest of the molecule, leading to innovative compounds [40,51–53]. They were the only ones to patent, from 2014 to 2019, bicyclic 6-membered rings in US9079894 [52] and WO2016128990 [54] as chromane and dihydrobenzodioxine (also found in SL65.0155 – Sanofi 2002) [22]. They also described a new 5-aminoquinoline moiety with interesting series of compounds with more than 40 compounds out of 50 possesing nanomolar EC_{50} on 5-HT_4R. Several compounds like **21** (Fig 3) were successfully tested in *in vivo* rodent models (rat mostly) for neurodegenerative disease (Aβreduction, ACh release, brain permeation study, cortical sAPP α levels…) even if they were also patented for gastrointestinal diseases.

Concerning the tricyclic core, only Alisi *et al.* in US8686147 described their new pyrrolo quinoline compounds, such as **18** (Fig 3), as useful 5-HT_4R ligands [37]. To date, only Tegaserod possesses a tricyclic "aromatic core". It is thus an under-represented scaffold that could be further investigated.

2.2.2 New linkers

To obtain a good affinity towards 5-HT_4R, the aromatic core is important but the linker could also play an important role by rigidifying the whole structure and thus allows a stronger interaction and a better affinity toward the receptor.

In literature, most of the time, the linker in 5-HT_4R agonists is an amide group. But some new linkers appeared in the last years as shown in the Table 3. Inspired by RS 67333 **6**, Dallemagne *et al.* were the only ones to patent a ketone linker between 2014 and 2019. Proving that the amide link is not necessary to get good activity toward 5-HT_4R, this work led to the discovery of Donecopride **23**, a dual 5-HT_4R agonist/AChE inhibitor that is in preclinical study against AD [44,55].

Among the linear linkers, we can also notice the ether group patented by Pfizer or Raqualia for PF-04995274 **17** or RQ-10 **16** (Fig 3) in WO2015174098 and WO2015178020, respectively. But Also by Alisi et *al.* in US8686147 [32,34,37].

The oxadiazolinone linker present in Capeserod **7** was a precursor cyclic linker. Since, research teams have focused their attention on finding new cyclic linkers. As such examples, Suven Life Science and Dainippon Sumimoto Pharma have described new oxadiazole links that keep the affinity toward 5-HT_4R [50–53].

One of the compound of Suven Life Science that possesses an 1,3,4-oxadiazole, SUVN-D4010 **13** is currently in clinical trial for cognitive impairment. The same company dedicated a whole patent in 2015 to those oxadiazole derivatives, as for example compound **23** (Fig 3) that has an EC_{50} of 1.3 nM toward 5-HT_4R and good response in *in vivo* experiment in rat, such as novel object recognition task model or radial arm maze [52].

Dainippon Sumimoto Pharm developped a new series of 1,2,4-oxadiazole on his part, with compound **24** (Fig 3) as a promising agonist toward 5-HT_4R with an EC_{50} of 5.8 nM and an activation rate of 77%. The company patented it to treat all diseases linked to 5-HT_4R, but no *in vivo* assay was described that could indicate if they planned to use this compound predominantly in neurological or gastroenterological area. [50]

2.2.3 Modulation of the basic center

The basic center of these scaffolds is an important part of the molecules. Its size, basicity and bulkiness were evaluated as well as the presence in the ring of an extra oxygen atom or its

substitution by various atoms or groups. Piperidine is the basic core that is present in the large majority of the 5-HT_4R ligands described in the literature and especially in the 5-HT_4R drugs currently on the market or in clinical trial, as seen on Table 4. The distance between this basic center from the aromatic ring could play a role in the profile toward the receptor as some studies showed it [4].

Chemists have thus tried to find a potent bioisostere moiety of piperidine to diversify their structures. Cisapride **1** possesses a methoxypiperidine and Mosapride **19** has a morpholine ring. Suven Life Science, in this respect, especially described a lot of compounds with different 6-membered amino rings including piperidinol, halogeno piperidine **25** or azabicyclohexane **26** (Fig 3) [51–54].

Dainippon Sumimoto Pharm patented a lot of different basic centers of different size, from 5-membered ring such as pyrrolidine **27** (Fig 3) to 7-membered ring such as oxazepane [50]. The pyrrolidine scaffold is not often described in the literature but can be found in old patents from Yamaguchi Pharm or Kyoshin Pharm [56,57].

2.2.4 Substituents

Due to the wide variety of substituents found in the literature and in the patents, we only focused our attention on the more important ones.The substituent can be an alkyl chain from 1 to 12 carbon linked at the end to an aromatic or a non-aromatic cycle, like a cyclohexane found in compound **22** (Fig 3). In this example, the use of cyclohexane was also designed in order to target AChE as well as maintaining a good affinity toward 5-HT_4R [55].

One of the relatively new substituents that appeared in the literature after 2010, is the oxanol moiety that can be found in PF04995274 **17** or RQ-10 **16** (Pfizer and Raqualia) or in compound **20, 25** [48,54].

Futhermore, at the image of Minesapride **4** developped by Dainippon Sumimoto Pharm, some patents decribed basic cores linked to an other basic one which is itself substituted by an oxane or a benzyle moiety, as seens in compound **27** [50] from the same company and compound **29** from Suven Life Science [54].

The aromatic benzyl or analogue derivatives are also found in most of the patents as they can carry a large amount of different substituents, like halogen for example in Mosapride **19**, but also nitro group, carboxylic acid like in compound **18** or esther in compound **27** [37,42,50]. Among the aromatic group found in that position, we can also notice the presence of, pyridine in compound **24**, triazole, tetrazole, imidazole or pyrrole rings [50,58]. As shown in patent US9221790 [43], the indole derivative **28**, for example, has an IC_{50} toward the receptor of 0.002 nM and, since the reported derivatives are supposed to be used for gastroenterology purpose, they were evaluated for gastric emptying, following the method developed by Iwanaga *et al*. [59]. Compound **28** appears to improve gastric emptying of more than 10% compared to the control.

2.2.5 New structural $5HT_4R$ ligands

While most of the ligand for 5-HT_4R in the literature follow the same pharmacophore as described in Fig 2, Yuhan Corporation however succeeded in developing innovative pyrimidine derivatives, with a first patent in 2014 (WO2014189331) [60] where was described a series of novel bicyclic compounds containing a pyrimidine ring. Thirty compounds were described with EC_{50} below 0.1 nM, showing excellent properties as agonists toward 5-HT_4R with, for example, compound **30** (EC_{50} = 0.95 pM) (Fig 4). The latter was patented for a gastroenterological purpose but without any *in vitro* or *in vivo* study that could support this indication. In 2019, the company also patented a new process to prepare a diaminopyrimidine derivative that was previously described in patent WO2012115480A2 with an EC_{50} of 4.7 pM on 5-HT4R [61-62].

In 2017, YH12852 was described as a novel 5- HT_4R agonist with high *in vitro* potency (EC_{50} = 4.8 pm) and selectivity (>200-19,000- fold) over other 5-HTRs, other receptors, ion channels, enzymes and transporters [63]. The structure of this new potent agonist, was however not disclosed, we herein suppose that YH12852 is the compound **31** (Fig 4) that is described for optimized synthesis in the patent previously cited [62]. This compound is also patented for gastrointestinal problems, specially for the prevention or treatment of gastrointestinal dysmotility, and other diseases of the digestive system, such as GERD, constipation, IBS, indigestion, post-operative ileus, delayed gastric emptying, gastroparesis, intestinal pseudo-obstruction, drug-induced delayed transit, diabetic gastroparesis…

3 Conclusion

Over the last years, an intense research activity was ongoing in the development of 5-HT_4R ligands with more than 100 patents registered in the field since 2014. As described above, most of the patents deal with generic structure extension in order to protect the use of 5-HT_4R modulators to treat CNS disorders, mainly neurodegenerative diseases, but also gastrointestinal pathologies. In this context, Suven Life Science, Pfizer and Dainippon Sumimoto Pharm were particularly active to extend the protection of known structures after modulation of the aromatic core, the linker between the basic amine and its substituents. The nature of the aromatic moiety is crucial in order to maintain a good affinity but also the optimal partial agonist profile needed for the therapeutic application of these ligands [64]. A limited number of aromatic cores (monocyclic or bicyclic) were explored, including aminochlorobenzamide, indole and indazole, benzimidazolone, benzofurane or quinolone or benzisoxazole. The discovery of novel aromatic scaffolds remains a challenge in order to generate novel chemical diversity with optimal biological properties and drugability. New opportunities in terms of patentability will rely on the discovery of such innovative compromises, such as YH12852 [63].

The modulation of the other parts of the structure was also particularly explored in the recent years. The nature of the linker (amide, ketone or heteroaromatic cycle), the amine (mosty cyclic amine) and the substituents, appear particularly important in order to optimize physicochemical properties of the ligand and then their PK/PD properties. Indeed, most of the derivatives developed for gastrointestinal purpose are based on the presence of an amide linker present in the structure of Tegaserod or Cisapride (Table 1). The replacement of the amide by a ketone or an oxadiazole ring appears as an interesting strategy in order to optimize the central distribution of 5-HT_4R ligand for treatment of CNS pathologies [65,66]. It is also worth to note that novelty in terms of structures could rely in the introduction of deuterium atom in place of hydrogen on known ligands and could finally lead to an improvement in metabolic stability [39]. This active research activity would certainly lead in the next years to an increase in the number of clinical trials investigating the effect of 5-HT_4R modulators.

4 Expert opinion

The approval of 5-HT_4R ligands, Tegaserod and Prucalopride, by the FDA is of particular importance to treat chronic idiopathic constipation in patients. It offers also great opportunity to confirm their use as safe therapeutic strategies, devoid of the suspected cardiac toxicity wrongly associated to 5-HT_4R ligand in the past [9] This situation is at the origin of an active research field attested by a large number of patents in the recent years. If 5-HT_4R agonists have been approved to treat gastrointestinal disorders, we have to mention an important number of ongoing clinical trials in the field of CNS disorders. The development of novel derivatives particularly in the field of neurodegenerative diseases, and more particularly AD, will be one of the most interesting challenges in the next years. In the difficult context of AD clinical trials, clear evidence of target engagement will be necessary. This could be possible through the identification of relevant biomarkers, such as sAPPα [67], or the development of innovative imaging agents [68].

Novel opportunities will also be offered in the exploration and identification of novel chemical scaffolds of orthosteric ligands, as well as allosteric modulators which have not been explored for the moment. The effect of those novel tools on signal transduction should be clearly defined. First, the role of the six different splice variants present in human is not yet fully understood [69]. Second, if the activation of 5-HT_4R leads ultimately to an increase of cAMP and protein kinase A (PKA) levels, it could also be followed by G-protein independent activation pathways [70]. The complete characterization of the known ligands is still needed. Finally, an increasing body of evidences confirms that 5-HT_4R activation stimulates the liberation of neuronal plasticity related proteins including AKT, CREB and BDNF and could therefore has a positive impact on neurogenesis [71].

According to this discovery, new opportunities will be offered in the application of 5-HT_4Rs agonists to treat novel deficiencies, including memory disorders, as well as cognition deficits [72]. Such compounds might also have a positive impact on neurogenesis in hippocampus and finally could be considered to treat depression [24]. In this case again, the development of a 5-HT_4R agonist, with optimal brain distribution, will be a major advance in the future. This possible effect on neuroregeneration offers also novel opportunities to use 5-HT_4Rs in combination with other drugs in order to obtain a synergy of action. Such drugs could include those which could have an impact on neurotransmitter concentration such as AChE inhibitors [73]. One challenge will remain however in the evaluation of such a combination earlier in the development, in preclinical but also in clinical trials and will surely focus the attention in the next 5 to 10 years. Finally, some opportunities will rely on the discovery of single molecules

able to act simultaneously on different targets and better known as MTDL. The first examples of these pleiotropic compounds have already been identified and patented with the conjugation of 5-HT_4R activation and AChE inhibition in a unique structure [55]. Several other examples have been also disclosed with antagonist properties for 5-HT_6R [74], antioxidant properties [75] but also multiple targets [76].

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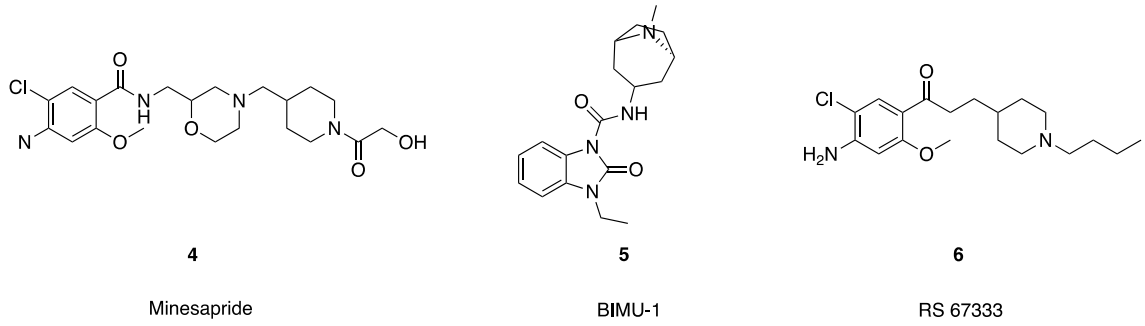


4 Minesapride

5 BIMU-1

6 RS 67333

Figure 1- Structure of 5-HT_4R agonists

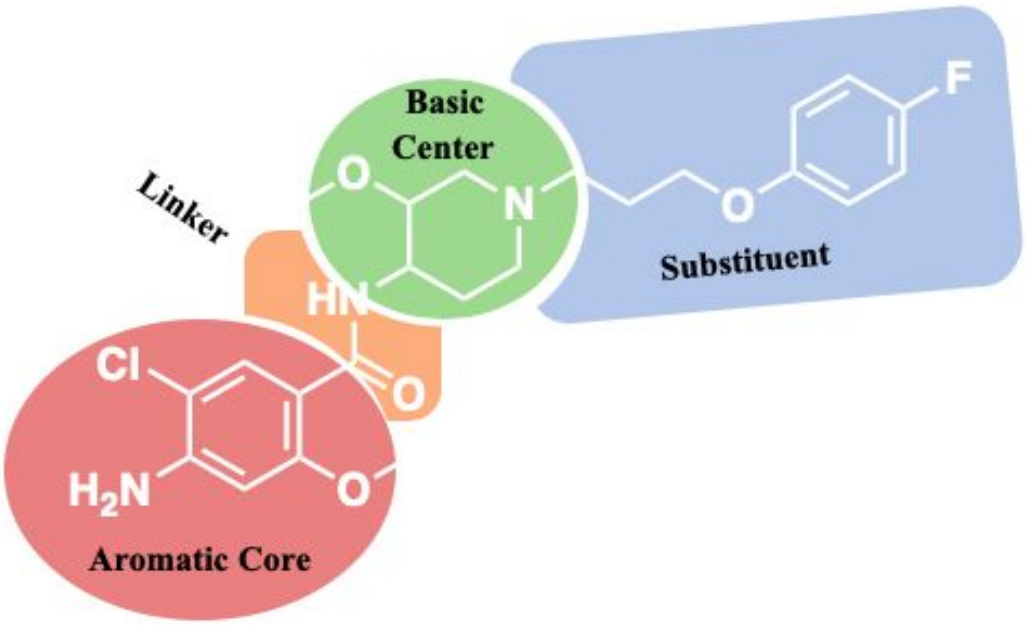
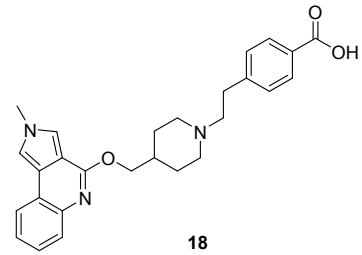


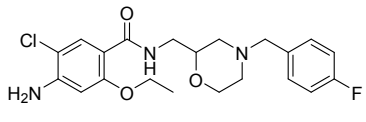
Figure 2: General structure of the 5-HT_4R ligands that entered clinical trials



18

IC_{50}= 2.24 nM

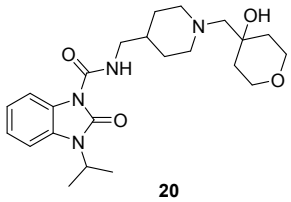
US8686147



19

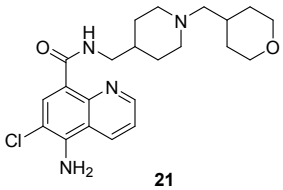
Mosapride

JP2017014113



20

US8980922

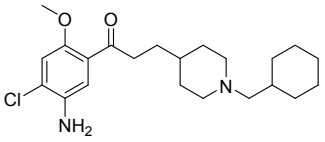


21

EC_{50} = 0.09 nM

E_{Max} = 70%

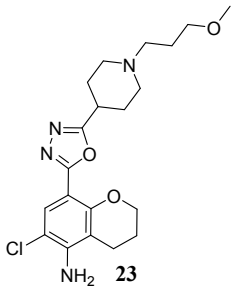
WO2014147636A



22

Donecopride

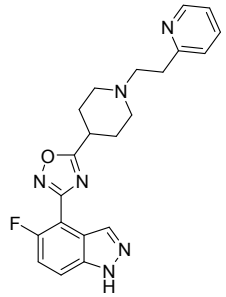
WO2014195593



23

EC_{50} = 1.3 nM

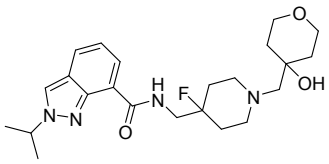
WO2016128990



24

EC_{50} = 5.8 nM

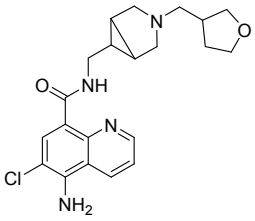
WO2014092104



25

EC_{50} < 1 nM

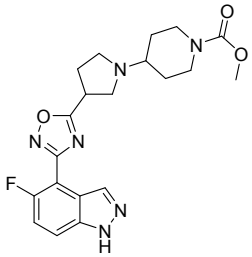
WO2016128990



26

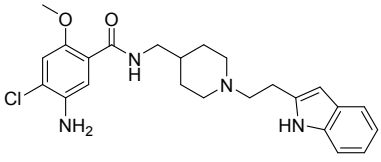
EC_{50} = 0.57 nM

WO2014147636



27

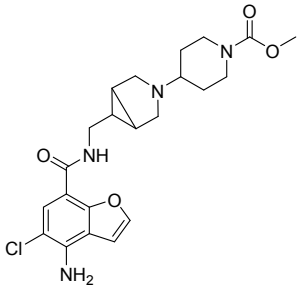
WO2014092104



28

IC_{50} = 0.002 nM

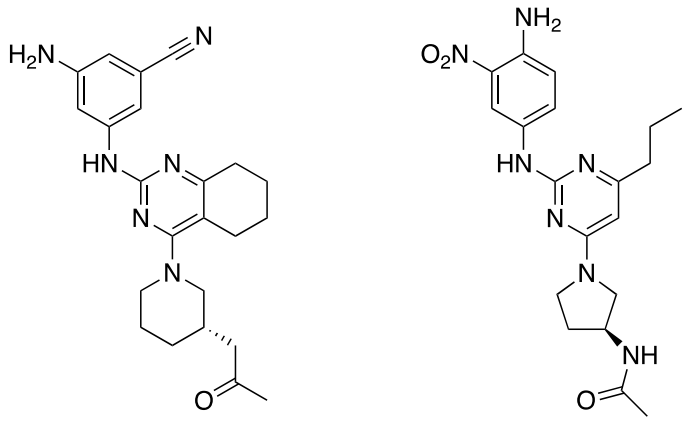
US9221790B2



29

WO2016128990

Figure 3- Structures of the main compounds in recent patents



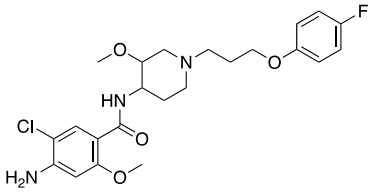
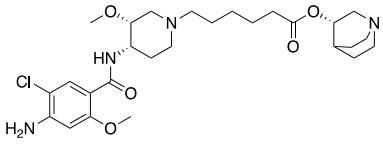
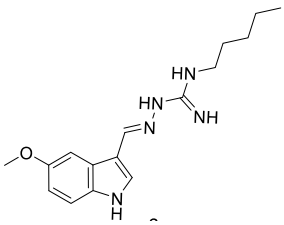
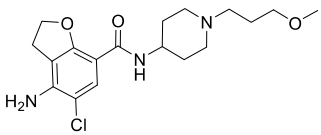
30

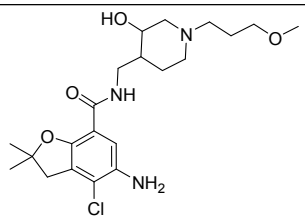
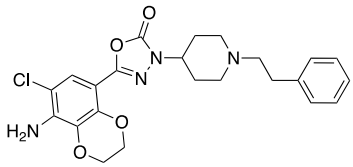
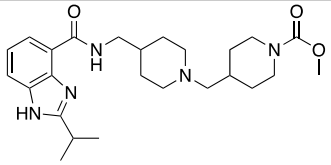
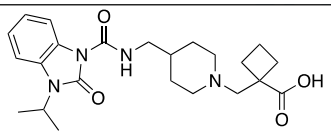
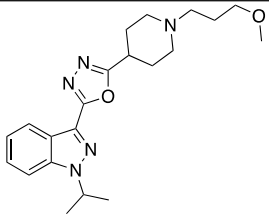
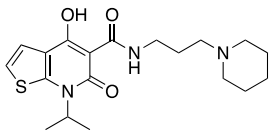
EC_{50}= 0.95 pM

31

EC_{50} = 4.8 pM

Figure 4- Compounds developped by Yuhan Pharm.

Compound company	Structure	Indication	Development phase status	Ref
Cisapride	 **1**	Gastro oesophagial reflux (GERD)	Phase 4	NCT01281553 Terminated
ATI-7505 (or Naronapride) Aryx therapeutics	 **9**	Post prandial distress syndrome Chronic constipation GERD	Phase 2 Phase 2 Phase 1	NCT00630370 Terminated NCT00501241 terminated NCT02838797 Completed
Tegaserod Novartis	 **2**	GERDl	Phase 1 and 2	NCT01094821 Completed
Prucalopride Shire	 **3**	GERD Constipation Depression	Phase 3 and 4 Phase 3 Not applicable	NCT03279341 Completed NCT04190173 Recruiting NCT03676374 Recruiting NCT03244553 Recruiting NCT00139568 Completed NCT03572790 Recruiting

SSP-002358 or Revexepride Shire	 **10**	Depression	Not applicable	NCT03863366 completed NCT03572790 recruiting
SL65.0155 (or Capeserod) Sanofi	 **7**	Cognitive impairment	Phase 2	[22] terminated
TD-8954 Theravance pharma	 **11**	Gastrointestinal motility disorder	Phase 1	NCT01644240 Terminated
PF-00885706 Pfizer	 **12**	GERD	Phase 2	NCT00730665 Terminated
SUVN-D4010 Suven Life Science	 **13**	Cognitive impairment	Phase 1	NCT03031574 Completed NCT02575482 Completed
PRX- 03140 Epix Pharmaceuticals	 **8**	AD Chronic constipation	Phase 2 Phase 2	NCT00384423 Completed NCT00693004 terminated NCT00391820 completed

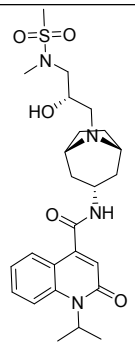
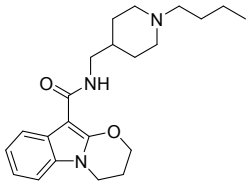
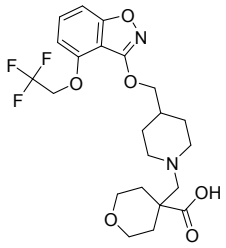
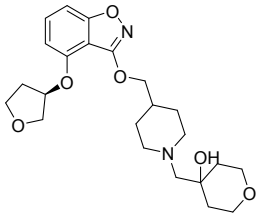
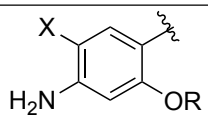
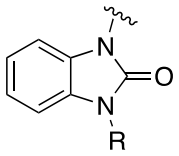
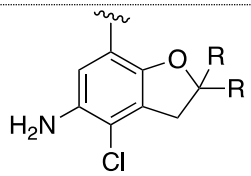
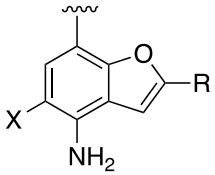
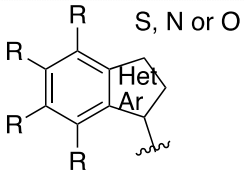
TD-5108 or Velusetrag Theravance Pharma	 **14**	Heart failure	Phase 2	NCT00421746 completed
Piboserod Biomedisinsk Innovasjon	 **15**	GERD	Phase 2b	NCT01472939 completed
RQ-00000010 Raqualia (Pfizer)	 **16**	Cognitive impairement in AD	Phase 1	NCT01173757 completed
PF- 04995274 Pfizer	 **17**	Depression Constipation	Phase 1 Phase 1	NCT03515733 Recruiting NCT03516604 Recruiting NCT03381703 Completed
YH12852 Yuhan corporation	Not disclosed	Gastrointestinal disorder Gastrointestinal disorder Dyspeptia	Phase 1/2 Phase 1 Phase 2	NCT02538367 Completed NCT01870674 NCT02567578 Suspended

Table 1- 5-HT_4R ligands in clinical trials

Aromatic ring			*Patent N°* *Author or company*	*Example*
Monocyclic			**US9221790** [43] *Dong A pharm.* **WO2014195593** [44] *Dallemagne et al.* **JP2017014113** [42] *Mikami et al.* **WO2014043707** [45] *Nektar Therapeutics*	**1** Cisapride* **4** Minesapride **6** RS67333 **9** Naronapride * **19** Mosapride **22** Donecopride **28**
Bicyclic	6-membered ring linked to 5-membered ring		**US8980922** [48] *Raqualia*	**12** PF-00885706 * **20**
			**WO2014083003** [31] *Shire* **US9079894** [52] **WO2016128990** [54] *Suven Life Science*	**3** Prucalopride * **10** Revexepride *
			**WO2016128990** [54] *Suven Life Science*	**29**
			**WO2014092104** [50] *Dainippon Sumimoto Pharm.*	**11** TD-8954* **24** **27**

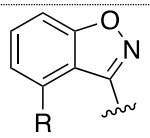
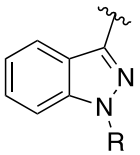
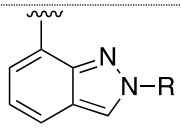
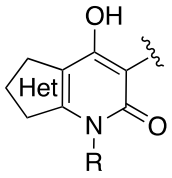
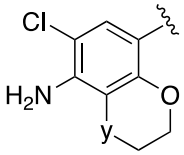
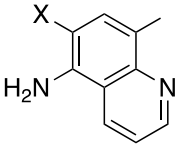
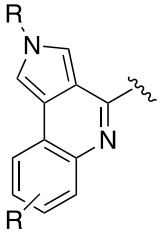
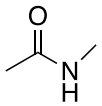
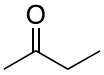
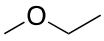
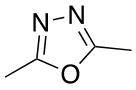
			**WO2015174098** [32] **WO2015178020** [34] *Raqualia* **WO2014092104** [50] *Dainippon Sumimoto Pharm.*	**16** RQ-10* **17** PF- 04995274*
			**WO201627277** [53] **US9079894** [52] *Suven Life Science*	**13** SUVN-D4010*
			**WO2015092804** [51] *Suven Life Science*	**25**
			**US20150080377** [39] *Dhanoa et al.*	**8** PRX- 03140*
	Bicyclic 6-membered rings	 Y = O or CH_2	**US9079894** [52] **WO2016128990** [54] *Suven Life Science*	**7** SL65.0155 * **23**
			**WO2014147636** [58] *Suven Life Science*	**26** **21**
Tricyclic			**US8686147** [*37*] *Alisi et al.*	***18***

Table 2- Summary of Aromatic core found in the patents. * Compound in clinical trial

Linker		*Patent N°*	*Example*
Linear	Amide 	**US8980922** [48] *Raqualia* **US20150080377** [39] *Dhanoa et al.* **WO2014083003** [31] *Shire* **JP2017014113** [42] *Mikami et al.* **US9221790** [43] *Dong A pharm.* **WO2014147636** [58] **WO2016128990** [54] *Suven Life Science*	**1** Cisapride **3** Prucalopride* **4** Minesapride **5** BIMU-1 **8** PRX- 03140* **9** Naronapride* **10** Revexepride* **11** TD-8954* **12** PF-00885706* **14** Velusetrag* **15** Piboserod* **19** Mosapride **20** **21** **25** **26** **28** **29**
	Ketone 	**WO2014195593** [44] *Dallemagne et al.*	**6** RS 67333 **22** Donecopride
	Ether 	**WO2015174098** [32] **WO2015178020** [34] *Raqualia* **US8686147** [37] *Alisi et al.*	**16** RQ-10* **17** PF- 04995274* **18**
Cycle	1,3,4-oxadiazole, 	**WO2015092804** [51] **WO201627277** [53] **US9079894** [52] *Suven Life Science*	**13** SUVN-D4010 * **23**
	1, 2, 4-oxadiazole	**WO2014092104** [50]	**24**

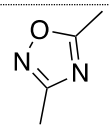
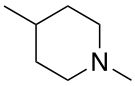
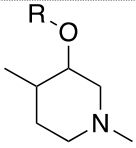
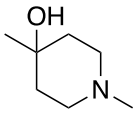
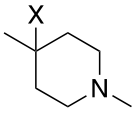
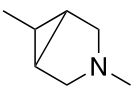
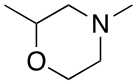
		*Dainippon Sumimoto Pharm.*	**27**

Table 3- Summary of linkers found in patents. * Compound in clinical trial

Basic Core		*Patent N°*	*Example*
6 membered		**US8980922** [48] *Raqualia* **US20150080377** [39] *Dhanoa et al.* **WO2014195593** [44] *Dallemagne et al.* **WO2015174098** [32] *Raqualia* **US9221790** [43] *Dong A pharm.* **US8686147** [37] *Alisi et al.* **WO2015092804** [51] *Suven Life Science* **WO2014092104** [50] *Dainippon Sumimoto Pharm.*	**5** Prucalopride* **6** RS 67333 **7** Capeserod* **8** PRX 03140* **11** TD8954* **12** PF-00885706* **13** SUVN-D4010* **15** Piboserod* **16** RQ-10* **17** PF- 04995274* **18** **20** **21** **22** **23** **24** **28**
		**WO2014083003** [31] *Shire*	**1** Cisapride * **9** Naronapride * **10** Revexepride
		**WO2014147636** [58] **WO2016128990** [54] *Suven Life Science*	
		**WO2016128990** [54] *Suven Life Science*	**25**
		**WO2015092804** [51] **WO2014147636** [58] **WO2016128990** [54] *Suven Life Science*	**26** **29**
		**JP2017014113** [42] *Mikami et al.*	**4** Minesapride

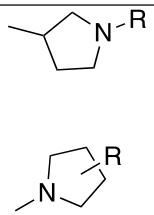
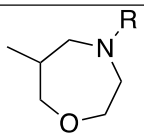
		WO2015092804 [51] *Suven Life Science*	**19** Mosapride
5 membered		**WO2014092104** [50] *Dainippon Sumimoto Pharm.*	**27**
7 membered		**WO2014092104** [50] *Dainippon Sumimoto Pharm.*	

Table 4 – Summary of the different basic center found in patents. * Compound in clinical trial

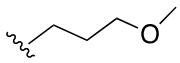
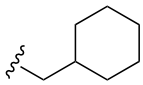
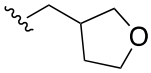
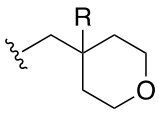
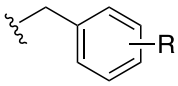
Substituent		*Patent N°*	*Example*
Methoxybutane		**WO2014083003 [**31] *Shire* **WO201627277** [53] *Suven Life Science*	**3** Prucalopride* **13** SUVN D4010* **23**
Cyclo alkyl		**WO2014195593** [44] *Dallemagne et al.*	**22**
Furan		**WO2014147636** [58] *Suven Life Science*	**26**
Oxane	 R= OH,COOH or H	**US8980922** [48] *Raqualia* **WO2015092804** [51] **WO2014147636** [58] *Suven Life Science*	**16** RQ10 * **17** PF-04995274 * **21** **20** **25**
Benzene		**JP2017014113** [42] *Mikami et al.* **US8686147** [37] *Alisi et al.* **WO2015092804** [51] *Suven Life Science*	**1** Cisapride * **7** Capeserod * **18** **19** Mosapride
Hetero aromatic ring	Pyrimidine, triazole, tetrazole, indole , imidazole etc…	**US9221790** [43] *Dong A pharm.*	**24** **28**

Table 5 – Summary of the differents substituent found in patents; * Compound in clinical trial