The therapeutic potential of 5-HT1A receptors: a patent review

Enza Lacivita, Pantaleo Di Pilato, Paola De Giorgio, Nicola A Colalufo, Francesco Berardi, Roberto Perrone & Marcello Leopoldo†
†Dipartimento Farmaco-Chimico, Università degli Studi di Bari “A. Moro”, Bari, Italy

Introduction: The 5-HT1A receptors are implicated in mood disorders (anxiety, depression), in cognition, and in modulation of pain. Nearly 30 years of research in this field, there is still interest in developing new chemical entities capable of 5-HT1A receptor activation or blockade.

Areas covered: This review article will highlight and review the research advances published in the patent literature between January 2007 and December 2011, giving emphasis to the medicinal chemist’s standpoint. Literature search methodology included search in Scifinder and PubMed Databases and browsing clinicaltrials.gov website.

Expert opinion: Almost no new therapeutic applications have been proposed for molecules targeting the 5-HT1A receptor, during the years covered by the present review. The discovery that stimulation of 5-HT1A receptor can promote neurogenesis will likely renew the interest for selective 5-HT1A receptor agonists as therapeutics to replace neural populations damaged by disease or injury.

Keywords: anxiety, central nervous system, depression, G-protein-coupled receptors, medicinal chemistry, neurogenesis, pain, Parkinson’s disease, schizophrenia, serotonin 5-HT1A receptor, structure–activity relationships

1. Introduction

Serotonin (5-HT, Figure 1) mediates a plethora of physiological effects through at least 14 different receptor subtypes: 13 belong to the G-protein-coupled or seven transmembrane-spanning receptor family and only one is a ligand-gated ion channel. Defined on the basis of molecular, pharmacological, and functional criteria, 5-HT receptors have been classified into seven discrete families (5-HT1-7). The 5-HT1A receptor was the first 5-HT receptor to be fully sequenced and the human gene encoding this receptor has been localized to chromosome 5 (5q11.2-q13) [1]. In the mammalian brain, 5-HT1A receptors are located either pre- and postsynaptically. The 5-HT1A autoreceptors are located on the soma and dendrites of serotonergic neurons in the raphe nucleus [2-4]. Instead, the 5-HT1A heteroreceptors are located postsynaptically on non-serotonergic neurons, primarily of the limbic areas on: the dendrites and soma of glutamatergic pyramidal neurons [4]; axon terminals of GABAergic [5,6] and cholinergic [7] neurons. Activation of 5-HT1A autoreceptors suppresses firing of serotonergic neurons and, thus, reduces activity-dependent serotonin release [8], whereas activation of 5-HT1A heteroreceptors reduces neuronal excitability and firing [9]. The heteroreceptors are highly expressed in the hippocampus (stratum radiatum of CA1, the granule cell layer of the dentate gyrus), entorhinal cortex, frontal cortex, and lateral septum [2,3]. 5-HT1A heteroreceptors are also expressed in moderate levels in the CA3 area of the hippocampus, amygdala, interpeduncular nucleus, piriform cortex, and superior colliculus, and also in several hypothalamic and thalamic nuclei [2,3].
5-HT<sub>1A</sub> receptors couple the inhibitory G-protein-regulated signaling pathway (Gi/o). Experiments in rodent hippocampal membranes demonstrated that 5-HT inhibited forskolin-stimulated cAMP accumulation through 5-HT<sub>1A</sub> receptors [10]. The same effect was also observed in cortical and hippocampal neuron cultures [11], and in cells heterologously expressing the 5-HT<sub>1A</sub> receptor gene [9,12]. 5-HT<sub>1A</sub> receptor stimulation also activates G-protein-coupled inward rectifying potassium channels (GIRKs) in the hippocampus and in the dorsal raphe nucleus [13].

Increasing evidences indicate that 5-HT<sub>1A</sub> receptors are also linked to MAPK and Akt signaling pathways that are associated with neuronal development and survival [14]. The MAPK family includes extracellular signal-regulated kinases 1 and 2 (ERK1/2), p38-MAPK, and c-Jun N-terminal kinase [15]. 5-HT<sub>1A</sub> receptors were first reported to activate ERK by phosphorylation in non-neuronal cells expressing 5-HT<sub>1A</sub> receptors. Despite consistent findings in cells heterologously expressing 5-HT<sub>1A</sub> receptors, effects of 5-HT<sub>1A</sub> receptors on ERK activity vary in cells of neuronal origin. In fact, activation of ERK by 5-HT<sub>1A</sub> receptor stimulation is not a universal response in the brain. Further investigations of the role of ERK in mediating 5-HT<sub>1A</sub> receptor-regulated neuronal activity are needed to define the specific function of MAPK signaling pathway in the brain, especially in view of the brain region-selective effect on ERK. Also, the PI3K and Akt pathway can be regulated by 5-HT<sub>1A</sub> receptors. 5-HT<sub>1A</sub> receptor agonists have shown to increase Akt phosphorylation (that represents the active state of Akt) in either non-neuronal and neuronal cells.

Over the years, a huge number of 5-HT<sub>1A</sub> receptor selective full agonists to partial agonists and antagonists have been developed. The chemical structures of the most representative compounds are shown in Figure 1.

### 2. The Therapeutic Potential of Targeting 5-HT<sub>1A</sub> Receptors

5-HT<sub>1A</sub> receptors have long been implicated in the pathogenesis and treatment of anxiety and depressive disorders. Recently, several lines of studies have revealed that the 5-HT<sub>1A</sub> receptors are a promising target for alleviating extra-pyramidal side effects (EPS) and cognitive/affective disorders caused by either antipsychotic or Parkinson’s disease therapy. Emerging therapeutic applications of 5-HT<sub>1A</sub> drugs are also for alleviating pain or cognitive dysfunction in neurodegenerative diseases.

#### 2.1 Anxiety and Depression

The 5-HT<sub>1A</sub> receptor has been implicated in the modulation of anxiety processes, mainly via pharmacological experiments. Buspirone (Figure 1), the prototype of 5-HT<sub>1A</sub> receptor partial agonists, was originally developed as an antipsychotic drug but it was not found effective for the treatment of schizophrenia. Instead, it showed anxiolytic actions [17]. Thereafter, a number of 5-HT<sub>1A</sub> agonists have shown anxiolytic activities in various animal models, such as Vogel’s or Geffen-Seifert conflict test and elevated-plus maze, light-dark and conditioned-fear paradigms, anti-marble burying behavior test. Although the involvement of presynaptic 5-HT<sub>1A</sub> receptors cannot be completely ruled out, the crucial role of postsynaptic 5-HT<sub>1A</sub> receptors in the limbic areas (hippocampus, amygdala, and lateral septum) in regulating anxiety has been supported by a number of studies. Hippocampus and amygdala are the major sites that control psychomotorial functions, including anxiogenesis and stress reactions [18,19], and lateral septum is a relay nucleus that transfers the neural outputs from the limbic system to the hypothalamus, which is the center of control for the autonomic nervous system [18,20]. 5-HT<sub>1A</sub> agonists inhibit the activity of both hippocampal and lateral septal neurons probably through activation of GIRK channels [21-24]. Therefore, it is believable that 5-HT<sub>1A</sub> agonists alleviate anxiety by inhibiting anxiogenesis in the limbic areas and its propagation from the lateral septum to the hypothalamus.

5-HT<sub>1A</sub> agonists such as buspirone, gepirone, and tandospirone (Figure 1) show a significant antidepressant activity in various animal models such as tail suspension test and forced swimming test [25]. Although the precise mechanism responsible for the antidepressant action of 5-HT<sub>1A</sub> agonists is still uncertain, desensitization or downregulation of presynaptic 5-HT<sub>1A</sub> receptors has been implicated in the antidepressant actions of 5-HT<sub>1A</sub> agonists [26]. Specifically, repeated treatment with a 5-HT<sub>1A</sub> receptor agonist desensitizes presynaptic 5-HT<sub>1A</sub> receptors in the raphe nuclei, which disengages 5-HT neurons from the autoreceptor-mediated inhibition [26-28].

As a consequence, 5-HT neurons are activated by chronic treatment with 5-HT<sub>1A</sub> agonists and this counteracts the 5-HT deficit in depression.

It has been proposed that the combination therapy of a 5-HT<sub>1A</sub> agonist or antagonist would be expected to speed up
The effect of serotonin reuptake inhibitors (SSRIs) which represent the first-line treatment of depression. In particular, a 5-HT$_{1A}$ receptor antagonist can improve the efficacy of SSRIs by blocking inhibitory 5-HT$_{1A}$ autoreceptors. Likewise, 5-HT$_{1A}$ agonists could have antidepressant-like activity by acting at postsynaptic 5-HT$_{1A}$ receptors and/or by producing a faster desensitization of 5-HT$_{1A}$ autoreceptors. There is also evidence that 5-HT$_{1A}$ partial agonism, combined with serotonin reuptake inhibition, can produce antidepressant-like effects. As example, vilazodone (Figure 1), the prototype of SSRI/5-HT$_{1A}$ partial agonist, has been approved in 2011 by the FDA for use in the United States to treat major depressive disorder [29].

Researchers at Pierre Fabre Medicament have studied a novel series of 2-pyridinemethylamine derivatives with...
unprecedented selectivity and efficacy for the 5-HT1A receptor subtype which culminated with the identification of F-13640 (besifradol) (Figure 1), which entered clinical trials for the treatment of chronic pains (see paragraph 2.5.), and F-15599 (Figure 1), which showed potent antidepressant activity in several animal models of depression. Further research efforts have led to the identification of a novel family of potent and selective 5-HT1A agonists where the 5-methylpyrimidin-2-yl ring of F-15599 was replaced by the 3,4-dihydro-2H-1,4-benzoxazine nucleus [30]. This basic motif has been extensively used to develop 5-HT1A ligands since 1988 starting from the seminal work by Hibert et al. [31].

The antidepressant activity of compound (-)-1 (Figure 2) was evaluated in the rat-forced swimming test in comparison with buspirone. (-)-1 exhibited remarkable antidepressant properties after oral administration, being able to reduce animal immobility in a dose-dependent manner (ED50 = 0.08 mg/kg), whereas buspirone had no effect on animal immobility even at 40 mg/kg dose.

Following a me-too approach, researchers at Friederich-Alexander Universitet [32] developed a series of 5-HT1A agonists structurally related to F-13640 (Figure 1), where the phenyl ring linked to the aminomethylpiperidin-1-ylmethanone moiety was replaced by a five-membered heteroaryl ring (general formula I, Figure 2). Among all the studied compounds, 2- and 3-thiophene derivatives showed good 5-HT1A affinity (Ki ≤ 50 nM) and at least 10-fold selectivity over α1 and α2-adrenoceptor, serotonergic 5-HT2 and dopaminergic D2-like receptors. The compounds behaved as potent agonists at 5-HT1A receptors (efficacy>75%, EC50 ≤ 50 nM). No in vivo data are described in the patent application. The compounds were claimed as useful for the treatment of those pathologies related to 5-HT1A receptors, such as depression, anxiety, pain, psychosis, and addiction.

N1-substituted N4-arylpiperazines (the so-called “long-chain” arylpiperazines) have been extensively studied as 5-HT1A receptor ligands. The general formula of these compounds presents an 1-arylpiperazine linked through an alkyl chain of variable length to a terminal fragment (imides, amides, alkyl, arylalkyl or heteroaryalkyl derivatives and tetralins) [33]. Researchers at SK Holding disclosed a series of 1-phenylpiperazine derivatives with general formula II (Figure 2), in which the terminal fragment is a substituted phenoxy ring [34]. Different aza-heterocycles have been introduced on the phenoxy ring in 4- and 3-position as well as different substituted aryl groups, already reported for 5-HT1A ligands, have been linked to the piperazine ring. 5-HT1A affinity was assessed as percentage of radioligand displacement at 10 nM concentration of test compound. Among the tested compounds, 1-(2-methoxyphenyl)piperazine derivatives showed the highest displacement percentage (> 70%), whereas the 4-position was preferred for the introduction of the aza-heterocycles. Selected compounds have been tested in vivo in mice in the tail suspension test: all the compounds were able to reduce immobility at 1 mg/kg dose whereas fluoxetine showed the same effect at 30 mg/kg dose. In the mice anti-marble burying behavior test, all the tested compounds demonstrated anxiolytic activity since they were able to reduce the number of marbles buried at lower doses (1 – 7.5 mg/kg) than buspirone (20 mg/kg).

Researchers at Wyeth disclosed a series of 1-arylpiperazine derivatives which combined a SSRI and 5-HT1A antagonist profile as potential antidepressants with faster onset of therapeutic action (Table 1) [35]. Several rigid analogs were also prepared by inserting a cyclohexane ring between the benzofuran nucleus and the piperazine. The reported data showed that 5-HT1A affinity depended upon the position and the nature of the electron-withdrawing group on the quinoline nucleus and upon the length of the alkyl chain, being a two-carbon linker preferred. The length and the nature of the alkyl spacer were also important for SERT activity. In fact, the insertion of the rigid cyclohexane ring led to a decrease of both affinity and potency of the compounds for the serotonin transporter. It is interesting to note that the cis-cyclohexyl derivatives demonstrated higher affinity for 5-HT1A receptor than their trans-counterparts, showing a different trend as compared to other arylpiperazine-based 5-HT1A ligands that shared the same structural framework [36]. In another patent application, Wyeth described a class of 3-aminochroman derivatives with dual SSRI/5-HT1A affinity (general formula III, Figure 2) [37]. The compounds were designed by using the “overlapping approach” [38]. In particular, a 3-aminochromane nucleus, which is responsible of the 5-HT1A receptor affinity, was linked to an aminooalkylindole moiety, which is known to be a SSRI pharmacophore. The reported data showed that affinity for both targets depended upon the size of the substituent on the basic nitrogen. In particular, cyclobutyl, propyl, and cyclopropymethyl substituents led to an increase of affinity for SERT and 5-HT1A receptors, whereas the presence of a trifluoropropyl group resulted in a loss of biological activity for both targets. The nature of the substituent on the basic nitrogen influenced also the intrinsic activity at 5-HT1A receptors: the compounds bearing a cyclobutyl or cyclopropymethyl group were antagonists, whereas propyl-substituted compounds were agonists. The replacement of the 8-methoxy group on the chromane nucleus with other substituents (methyl, ethyl) led to an increase of 5-HT1A receptor affinity and switched the activity from antagonism to agonism. Wyeth developed a third class of mixed 5-HT1A/SERT agents (general formula IV, Figure 2) [39]. Certain indole alkyl derivatives of heterocycle-fused benzodioxan methylamines were reported as SSRI as well as high-affinity 5-HT1A receptor ligands. On such basis, several tetrahydroquinolines and dihydroidolines derivatives were disclosed. The structural modifications were performed on the “right side” of the molecule and had marginal effects on affinity and potency at 5-HT1A receptors. SERT affinity, as well as the ability to block the 5-HT reuptake, depended on the nature and the presence of an electron-withdrawing group on the heterocyclic nucleus, being the...
The therapeutic potential of 5-HT$_{1A}$ receptors: a patent review

Figure 2. 5-HT$_{1A}$ agents developed as anxiolytics and/or antidepressants.
6- or 7-F-3,4-dihydroquinoline derivatives the most potent compounds.

Pfizer Inc. described a series of phenoxy-pyridyl derivatives possessing norepinephrine reuptake inhibition and 5-HT1A partial agonist properties useful in treatment of disorders wherein the modulation of monoamine neurotransmission is required, including cognitive and behavioral disorders associated with depression [40]. In the patent application, it is claimed that combination of 5-HT1A partial agonism and norepinephrine reuptake inhibition can increase extracellular levels of both norepinephrine and dopamine within the prefrontal cortex, a brain region important for attention and executive functions. Instead, this combination should not affect the extracellular monoamine levels within the nucleus accumbens, a brain region associated with reward behavior and abuse liability. General formula V (Figure 2) exemplifies the structural framework used to obtain the above mixed activity. Most of the compounds were able to displace > 60% of the specific radioligand from NET (10 µM) and 5-HT1A sites (1 µM). The compounds also behaved as partial agonists at 5-HT1A receptor. Piperazine derivatives proved to be more potent than their piperidine counterparts, showing lower EC50 values. No in vivo data that might support the initial hypothesis were reported.

The synergistic effect on the monoamine systems can be obtained also by co-administration of drugs acting specifically on different targets. The General Hospital Corporation has filed a patent application claiming that the co-administration of bupropion with a 5-HT1A partial agonist, such as buspirone, provides synergistic effects for treating major depressive disorders, dysthymic disorder, bipolar disorder, or minor depressive disorder [41]. Bupropion is an FDA-approved drug for treatment of major depressive disorders. Its antidepressant action is elicited through blocking the reuptake of dopamine and norepinephrine. On the other hand, buspirone exerts its anxiolytic and antidepressant activity acting at both pre- and postsynaptic 5-HT1A receptors. Therefore, the combined effects of the two agents on the dopamine, norepinephrine, and serotonin systems are responsible for the synergistic effect on depressive disorders.

### Table 1. Compounds developed by Wyeth [35].

<table>
<thead>
<tr>
<th>Compd.</th>
<th>R</th>
<th>R1</th>
<th>X</th>
<th>spacer</th>
<th>5-HT1A</th>
<th>RB-5-HT transporter*</th>
<th>HC-5-HT transporter‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>H</td>
<td>6-F</td>
<td>O</td>
<td>CH₂CH₂</td>
<td>1.94</td>
<td>6.50</td>
<td>25.30</td>
</tr>
<tr>
<td>3</td>
<td>6-Cl</td>
<td>H</td>
<td>O</td>
<td>CH₂CH₂</td>
<td>0.73</td>
<td>31</td>
<td>1.6</td>
</tr>
<tr>
<td>4</td>
<td>7-OCH3</td>
<td>H</td>
<td>O</td>
<td>CH₂CH₂</td>
<td>0.11</td>
<td>0.65</td>
<td>9.46</td>
</tr>
<tr>
<td>5</td>
<td>7-OCH₃</td>
<td>H</td>
<td>O</td>
<td>CH₂CH₂CH₂</td>
<td>0.91</td>
<td>4.17</td>
<td>9.53</td>
</tr>
<tr>
<td>6</td>
<td>5-OCH₃</td>
<td>6-Cl</td>
<td>O</td>
<td>CH(CH₂)CH₂</td>
<td>0.34</td>
<td>5.50</td>
<td>40.10</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>6-F</td>
<td>O</td>
<td></td>
<td>0.11</td>
<td>116</td>
<td>471</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>6-F</td>
<td>O</td>
<td></td>
<td>16.58</td>
<td>77</td>
<td>337</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>6-Cl</td>
<td>S</td>
<td></td>
<td>2.25</td>
<td>65</td>
<td>338</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>6-Cl</td>
<td>S</td>
<td></td>
<td>140.5</td>
<td>157</td>
<td>184</td>
</tr>
<tr>
<td>11</td>
<td>7-OCH₃</td>
<td>5-F</td>
<td>O</td>
<td></td>
<td>0.40</td>
<td>163</td>
<td>3040</td>
</tr>
<tr>
<td>12</td>
<td>7-OCH₃</td>
<td>5-F</td>
<td>O</td>
<td></td>
<td>21.06</td>
<td>34</td>
<td>272</td>
</tr>
</tbody>
</table>

*[^3H]-paroxetine binding at 5-HT transporter in rat frontal cortical membrane preparation; ^[^3H]-5-HT reuptake inhibition in human Jar cell line.

6- or 7-F-3,4-dihydroquinoline derivatives the most potent compounds.
2.2 Schizophrenia

Schizophrenia is characterized by diverse symptoms including positive symptoms (e.g., delusion, excitation, and hallucinations), negative symptoms (e.g., apathy, emotional, and social withdrawal), cognitive impairments, and affective disorders (e.g., anxiety and depression). Typical antipsychotics (e.g., butyrophenone, benzamide, and phenothiazine derivatives) exert their therapeutic action by blocking dopamine D2 receptors and effectively improve positive symptoms. Atypical antipsychotics (such as clozapine, olanzapine, perospirone, quetiapine, risperidone, and ziprasidone) exert their therapeutic action by blocking either dopamine D2 and serotonin 5-HT2A receptors [19]. These atypical antipsychotics, differently from the typical ones, relieve both positive and negative symptoms and display reduced EPS incidence. However, the second-generation antipsychotics do not show significant advantages in the treatment of neurocognitive effects associated with schizophrenia over the first-generation antipsychotics [42]. Therefore, there is still clinical demand of newer antipsychotic drugs against positive and negative symptoms, cognitive impairments, and affective disorders. It has been proposed that 5-HT1A agonists can alleviate antipsychotic-induced EPS by stimulating postsynaptic 5-HT1A receptors in the striatum and cerebral cortex [43], probably through non-dopaminergic mechanisms. Moreover, it has been suggested that 5-HT1A receptor antagonists can enhance cognition by blocking postsynaptic 5-HT1A receptors located in the medial septum and/or diagonal band of Broca, where 5-HT1A receptors inhibit neuronal activity of acetylcholine and/or glutamate neurons [44-47]. Thus, 5-HT1A antagonism potentiates activities of the septo-hippocampal/cortical acetylcholinergic and/or glutamatergic neurons and ultimately improves cognitive functions.

Pharmaceutical companies have focused their efforts on the development of drugs combining dopamine D2 receptor antagonism with 5-HT1A activity. As example, bifeprunox, a partial dopamine D2 and serotonin 5-HT1A agonist, designed to stabilize dopamine function in the brain, has been studied in more than 2,500 patients with schizophrenia [48]. However, after initial clinical Phase III trial program, H. Lundbeck A/S and Solvay Pharmaceuticals stopped all joint researches because efficacy data did not support pursuing the development of stabilization of non-acute patients with schizophrenia using bifeprunox [49]. Indeed, other pharmaceutical companies continued pursuing the same pharmacological strategy.

Researchers at NeuroSearch A/S disclosed a series of classical long-chain arylpiperazines (or homopiperazines) bearing a terminal quinolinylamide fragment that were able to modulate dopamine and serotonin receptors (general formula VI, Figure 3) [50-52]. The affinity of the compounds for dopamine D2 and D3, serotonin 5-HT1A and 5-HT2A receptors was assessed by radioligand binding assays. The antipsychotic potential of the compounds was evaluated in the MK-801 (dizocilpine) hyperactivity model. The administration of MK-801 in rodents and humans elicits schizophrenia-like symptoms characterized by hyperlocomotion and stereotyped behavior which was reverted by antipsychotic drugs. Selected compounds were able to significantly reduce MK-801-induced hyperactivity at minimal effective dose (MED) of 10 mg/kg.

The activity profile of the 11-piperazin-1-ylidibenzo[b,f][1,4]thiazepine (13) (Figure 3), the circulating metabolite of quetiapine, has been studied by researchers at Astra Zeneca [53]. Quetiapine is an atypical antipsychotic drug efficacious in the treatment of both positive and negative symptoms of schizophrenia with a reduction in hostility and aggression. Moreover, quetiapine is associated with fewer side effects, such as EPS, acute dystonia, acute and tardive dyskinesia, as compared to classical antipsychotics. Positron emission tomography studies evidenced that 13 was able to reach the brain and to occupy dopamine D1, D2, serotonin 5-HT2A, 5-HT1A receptors and 5-HT transporter. Although the activity profile of 13 at D2 and 5-HT2A receptors would be predictive for an atypical antipsychotic action, 13 failed to be efficacious in two animal models of antipsychotic activity (standard amphetamine swim test and D-amphetamine locomotor activity test). On the other hand, 13 showed 5-HT1A partial agonist activity and in vivo efficacy in animal model for anxiety (Geller-Seifter conflict test) and for depression (forced swim test). Therefore, it was suggested that compounds structurally related to 13 could be used for the treatment of anxiety and mood disorders related to psychosis.

With the aim to develop new antipsychotic drugs with improved off-target pharmacology and pharmacokinetics, that are responsible for most of the adverse side-effects associated with the atypical antipsychotics, researchers at Reviva Pharmaceuticals disclosed a series of 1-arylpiperazine derivatives structurally related to aripiprazole (Figure 3), approved by the FDA in November 2002 for the treatment of schizophrenia [54-56]. The most representative compounds are listed in Table 2. The compounds were designed to improve resistance to CYP-oxidative metabolism or to afford metabolites devoid of CNS activity. Tested compounds showed high affinity for dopamine D2 receptor and for serotonin 5-HT1A and 5-HT2A receptors. In particular, the 3-oxo-3,4-dihydro-2H-benzo[b][1,4]oxazine derivatives had a better affinity profile for the target receptors than the 2-oxo-1,2,3,4-tetrahydroquinoline counterparts. Compound 18 showed nanomolar affinity for all the target receptors. To improve pharmacokinetics, ester functions were introduced in the molecules to allow fast hydrolysis by seric esterases. This modification had limited impact on D2 and 5-HT1A affinity whereas it led to a marked decrease in 5-HT2A receptor affinity. However, neither pharmacokinetic data nor in vivo data were disclosed in the patent applications.

Researchers at Schwarz Pharma have filed a patent application describing a series of arylpiperazine-based indolizine compounds as a new class of atypical antipsychotics.
The compounds were screened at dopamine D2-like and at serotonin 5-HT1A and 5-HT2A receptors. The disclosed data indicated that the 1-(2,3-dichlorophenyl)piperazine derivatives had a better affinity profile toward all the target receptors (especially for the 5-HT2A receptor) than the other substituted arylpiperazine derivatives. On the other hand, the different position of the insertion of the alkyl chain on the distal indolizine nucleus had limited impact on dopamine D2, D3 and D4 and on serotonin 5-HT1A receptor affinities whereas it had a more marked influence on 5-HT2A receptor affinity. The intrinsic activity at D2 receptors was assessed for selected compounds which behaved as full antagonists or partial agonists. No in vivo data were reported.

Figure 3. 5-HT1A agents studied as antipsychotics.
A series of isosters of aripiprazole was developed by Pfizer Inc. (general formula VIII, Figure 3). The compounds displayed an in vitro pharmacological profile comparable with that of aripiprazole [58].

2.3 Parkinson’s disease

Dopamine D2 and serotonin 5-HT1A receptor dual agonist profile has attracted interest in terms of the paradigm of developing new anti-Parkinson’s disease (PD) therapeutics with less troublesome motor fluctuations and dyskinesias [59]. Sarizotan [60] and pardoprunox [61] (Figure 4) are the most studied D2 and 5-HT1A receptor dual agonists. In a “proof-of-concept” study in patients with moderate to advanced PD, sarizotan significantly reduced the level of L-DOPA-induced dyskinesia [62]. In a double-blind study, pardoprunox significantly improved motor functions in patients with early PD. This compound currently has progressed to Phase III clinical trials as a new anti-PD treatment [61].

5-HT1A receptor agonism is believed to be beneficial for alleviating motor complications associated with L-DOPA treatment on the basis of several experimental evidences: i) L-DOPA is also taken into the serotonin nervous system, where it is converted to dopamine and released; ii) there is a high possibility that the release of dopamine from the serotonin nervous system is controlled (or inhibited) by 5-HT1A receptor agonists in the same way as 5-HT [59].

Researchers at Asubio Pharma proposed piclozotan (Figure 4) and related compounds as new therapeutic agents able to improve motor complications associated with L-DOPA therapy [63]. In the patent application WO09069828 piclozotan, sarizotan, and 23 (Figure 4), previously described in the patent application JP298402 [64], have been comparatively studied in in vitro and in vivo models of PD. The affinity and intrinsic activity profile showed that piclozotan and 23 behaved as partial agonists at serotonin 5-HT1A receptor and as full agonists at dopamine D3 receptors, a feature that is predictive of a neuroprotective and neurorestoring activity on dopaminergic neurons, whereas sarizotan and 23 showed a strong antagonistic activity at dopamine D2 receptors, differently from piclozotan. Therefore, piclozotan was selected for further in vivo studies. Brain microdialysis experiments demonstrated that, after intraperitoneal administration, piclozotan (3 and 10 mg/kg) was able to modulate L-DOPA-induced striatal dopamine release, that is responsible for wearing-off phenomena of PD. Moreover, in rats with unilateral nigrostriatal dopamine nerve destruction, a widely used animal model of PD, piclozotan was able to alleviate dyskinesia and to delay the onset of motor complications accompanying long-term administration of L-DOPA. Finally, piclozotan showed antidepressant activity in the forced swimming test: this activity might improve mood disorders, the biggest factor impairing the quality of life of PD patients.

Table 2. Compounds developed by Reviva Pharmaceuticals [54-57].

<table>
<thead>
<tr>
<th>Compd.</th>
<th>X</th>
<th>A</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Ki,n M</th>
<th>D2</th>
<th>5-HT1A</th>
<th>5-HT2A</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>CH2</td>
<td>OCH2</td>
<td></td>
<td>H</td>
<td>H</td>
<td>1.69</td>
<td>3.93</td>
<td>239</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>CH2</td>
<td>COO</td>
<td>Cl</td>
<td>Cl</td>
<td>H</td>
<td>17</td>
<td>16</td>
<td>147</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>CH2</td>
<td>CH2OOCO</td>
<td>Cl</td>
<td>Cl</td>
<td>H</td>
<td>12.80</td>
<td>48.50</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>O</td>
<td>OCH2</td>
<td>OCH3</td>
<td>Cl</td>
<td>H</td>
<td>0.30</td>
<td>0.65</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>O</td>
<td>OCH2</td>
<td>Cl</td>
<td>Cl</td>
<td>H</td>
<td>0.61</td>
<td>1.50</td>
<td>58.5</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>O</td>
<td>OCH2</td>
<td></td>
<td>H</td>
<td>H</td>
<td>6.77</td>
<td>10.22</td>
<td>282</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>O</td>
<td>OCH2</td>
<td></td>
<td>H</td>
<td>H</td>
<td>50.20</td>
<td>3.30</td>
<td>3.40</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>O</td>
<td>OCH2</td>
<td></td>
<td>H</td>
<td>H</td>
<td>2.09</td>
<td>2.67</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>O</td>
<td>OCH2</td>
<td>Cl</td>
<td>Cl</td>
<td>O</td>
<td>15.50</td>
<td>2.96</td>
<td>106</td>
<td></td>
</tr>
</tbody>
</table>
In the patent application US20249621 has been reported that the co-administration of 8-OH-DPAT (Figure 1) and L-DOPA improved motor coordination in hemi-lesioned 6-hydroxydopamine (6-OHDA)-treated rat model as compared to the administration of L-DOPA alone [65]. Moreover, the repeated co-administration of 8-OH-DPAT and SKF-38393 (a dopamine D1 agonist) or quinpirole (a dopamine D2 agonist) improved dyskinetic behavior and this effect is blocked by the pre-treatment with WAY-100635 (Figure 1).

Studies on striatal signaling evidenced a correlation between 5-HT1A agonist administration with the ΔFosB levels. ΔFosB is a truncated splice variant of FosB, a transcription factor mediating long-term effects of synaptic plasticity. ΔFosB has been shown to be upregulated in PD patients as well as in lesioned 6-OHDA-treated rodents. The administration of the 5-HT1A agonist prevented the rise in ΔFosB in striatal neurons.

Atir Holding has reported on a series of piperazine, piperidine, and tetrahydropyridine derivatives as potential agents for the treatment of PD [66]. The compounds showed high affinity for 5-HT1A receptor along with affinity for D2-like receptors. Compound 24 (Figure 4) was tested in lesioned 6-OHDA-treated rats showing strong anti-dyskinetic effect at daily dose of 2 mg/kg.

2.4 Cognitive dysfunction
It has been proposed that 5-HT1A receptor antagonists may improve cognition by removing the inhibitory effects of endogenous 5-HT on pyramidal neurons and thus enhance glutamatergic activation and ensuing signal transduction [67,68]. As example, the 5-HT1A antagonist WAY-100635 can alleviate cognitive deficits induced by both glutamatergic dysfunction (dizocilpine-induced cognitive deficits) and cholinergic dysfunction (fornix transaction surgery) in primates [69,70].

Lecozotan (Figure 5) is a potent and silent antagonist of the 5-HT1A receptor currently under development by Wyeth Research for the symptomatic treatment of mild-to-moderate Alzheimer’s disease [71]. An evaluation of the neurochemical effects of lecozotan on glutamate and acetylcholine levels evidenced that the compound can significantly potentiate the potassium chloride-stimulated release of glutamate and acetylcholine in the hippocampus. This would suggest that 5-HT1A antagonism results in secondary potentiation of cholinergic and glutamergic transmission [72].

Lundbeck has filed several patent applications relating to the therapeutic use of compounds showing a combined SSRI, 5-HT3 and 5-HT1A activity in the treatment of cognitive deficits [73-75]. It is known that 5-HT1A and/or 5-HT3 receptors...
The therapeutic potential of 5-HT<sub>1A</sub> receptors: a patent review

Affect the cholinergic system and, therefore, compounds acting on 5-HT<sub>1A</sub> and/or 5-HT<sub>3</sub> receptor may be useful in the treatment of cognitive disorders. Moreover, a compound acting also on SERT would be particularly useful for the treatment of cognitive impairment in depressed patients as such compound would also provide a fast onset of the treatment of the depression. The compounds developed by Lundbeck, exemplified by LU AA21004 (Figure 5) which entered clinical trials [76] behaved as SERT inhibitors, 5-HT<sub>1A</sub> partial agonists, and 5-HT<sub>3</sub> receptor antagonists. When administered in rats, LU AA21004 determined an increase of the extracellular level of acetylcholine in the prefrontal cortex and the ventral hippocampus that is considered predictive of a pro-cognitive effect in vivo. Moreover, LU AA21004 enhanced contextual memory in rats without inducing anxiety. Therefore, compounds with a pharmacological profile similar to that of LU AA21004 were claimed as useful in the treatment of cognitive impairments associated with several CNS diseases (depression, schizophrenia, and ADHD) [77].

Astra Zeneca has developed a series of 2-carboxamide-7-piperazinylbenzofuran derivatives as cognition enhancers starting from the experimental observation that 5-HT<sub>1A</sub>/5-HT<sub>1B</sub> receptor antagonists can enhance acetylcholine levels in brain areas, such as frontal cortex and hippocampus [78]. The most interesting compounds were 25, 26, 27 (Figure 5) that showed subnanomolar affinities for both target receptors. Other structural modifications were performed on the carboxamide moiety and N-substituent on the piperazine ring. These modifications had limited impact on 5-HT<sub>1A</sub> receptor affinity, whereas greatly affected 5-HT<sub>1B</sub> receptor affinity. No data on the intrinsic activities were reported nor on in vivo experiments.

Wyeth filed a patent application describing the improvement of cognitive performances in two rat models of cognition by co-administration of subtherapeutic doses of donepezil, an acetylcholinesterase inhibitor, and of a 5-HT<sub>1A</sub> antagonist [79]. Current therapies for cognitive dysfunctions exhibit undesired side-effect profiles, as liver damage, gastrointestinal problems, that may not be sustained over a long duration therapy. Therefore, there is the need to identify new compounds or therapeutic regimens that have a lower risk of side-effects occurrence. In particular, the synergistic effect was studied in the novel object.
recognition rat model. The combined administration of donepezil (0.5 mg/kg) and of 5-HT1A antagonist 28 or 29 (0.1 mg/kg) (Figure 5) produced a positive effect on recognition memory as demonstrated by the rats spending significantly more time exploring the novel object than the familiar one. The effect was not elicited by separate administration of the same dose of the drugs.

2.5 Other

Starting from early 1990s, researchers at Pierre Fabre developed the concept that in nociceptive systems any input causes two effects that are opposite in sign. Activation of opioid receptors produces analgesia as “first-order” effect and hyperalgesia as “second-order” effect. The chronic treatment with opioids attenuates the first-order effect, while strengthens the second-order hyperalgesia. This concept offered a description of the neuroadaptive tolerance and sensitization caused by opioid therapy. According to this concept, it was proposed that 5-HT1A receptor activation has two effects that are opposite to those produced by opioids: stimulation of peripheral nociceptors would initially produce pain as a first-order effect, but also hypoalgesia as a second-order effect; with chronicity, this second-order hypoalgesia counteracts the first-order pain and remarkably develops into increasingly powerful analgesia [80]. The identification of the highly selective and efficacious 5-HT1A agonist F-13640 (Figure 1) allowed proof-of-concept studies that proved that 5-HT1A receptor activation initially produces hyperalgesia followed by hypoalgesia, i.e. repeated treatment with F-13640 caused hypoalgesia and tolerance to its pro-algesic effect. Thus, high efficacy 5-HT1A receptor stimulation was proposed as a new molecular and neuroadaptive approach to the treatment of acute and chronic, nociceptive and neuropathic pain states. The concept has been extended to a larger series of compounds exemplified by (-)1 (Figure 2) [30]. This compound showed broad analgesic activity: in rats in the formol test of physiological pain (-)1 showed an ED50 = 0.05 mg/kg, whereas in the oxaliplatine test of pathological pain (-)1 produced full analgesia at 0.04 mg/kg dose. In both tests, the analgesic effects elicited by (-)1 were higher than those elicited by buspirone.

Also LU AA21004 has been tested in the mouse intradermal formalin test: it showed analgesic activity for both nociception and neuropathic pain [74,75].

Several lines of evidence suggest that 5-HT1A receptors are involved in the mechanism of neurogenesis. Understanding the contributions of adult neurogenesis to hippocampal function will provide new insight into the fundamental aspects of brain plasticity, which can be used to guide therapeutic interventions to replace neural populations damaged by disease or injury [81]. As example, it has been reported that stimulation of 5-HT1A receptors in vitro primarily promotes self-renewal of adult neural precursor cells [82]. Also, activation of 5-HT1A receptor by 8-OH-DPAT increases neurogenesis and survival of late differentiating cells in the dentate gyrus and in the olfactory bulb. 8-OH-DPAT also increased gliogenesis (NG2-labeled cells) in the prefrontal cortex and striatum [83].

Researchers at BrainCells have reported that neurogenesis can be stimulated or increased through the administration of drugs acting on different serotonin receptor subtypes such as buspirone or azasetron, a 5-HT3 receptor antagonist [84,85]. The combined administration of buspirone and azasetron determined a synergistic effect on the neural differentiation of human neural stem cells whereas each drug alone elicited the same effect at 10-fold higher dose. The same synergistic effect was observed by co-administering buspirone and modafinil [86].

Anti-anxiety medications, such as diazepam, are not effective in smoking cessation. However, the most commonly tested anti-anxiety medication in smoking cessation has been buspirone. Initial studies by Hilleman and coworkers showed that buspirone ameliorated most of the short-term withdrawal symptoms associated with smoking cessation [87]. However, subsequent studies were unable to demonstrate the efficacy of buspirone in smoking cessation or in the relief of withdrawal symptoms. Farid and Abate suggested a more stringent study design to test the hypothesis (placebo-controlled, randomized trial with a large number of patients, relatively high doses of buspirone, strict abstinence criteria, long-term follow-up, and the inclusion of smokers with general anxiety or anxiety reported in previous quit attempts) [88]. Although at present there are not sufficient evidences to support the usefulness of buspirone as a smoking cessation aid, some patent applications claimed the use of nicotine/ buspirone combination as therapy intervention for smoking cessation [89]. Interestingly, it has been found that buspirone was effective in attenuating the objective and subjective withdrawal symptoms that follow opiate use cessation [90].

3. Expert opinion

Over the last 30 years, intense research efforts have been focused on the development of agonists and antagonists for serotonin 5-HT1A receptor with the aim to identify drugs for the treatment of anxiety, depression, Parkinson’s disease, schizophrenia, cognitive deficits, and pain conditions. A huge number of either selective or multitarget 5-HT1A receptor ligands have been developed so far, and, among them, a good number have been progressed into clinical trials. During the time frame under consideration (2007 – 2011), there has not been the appearance of unprecedentedly studied molecular frameworks capable of binding at 5-HT1A receptor. All the molecules herein reviewed resemble structural motifs already extensively studied (long-chain 1-arylpyperazines and related isosters, 3,4-dihydro-2H-chromen-2-yl-methanamines and related isosters, compounds structurally related to F-13640, violazolone-like compounds). Nevertheless, the structural modulations pursued by the inventors took advantage from the most modern strategies
to develop drug-like molecules [91]. This is largely witnessed by the introduction of electron-withdrawing substituents on the aromatic rings or replacement of phenyl rings with heterocyclic ones in order to improve the pharmacokinetic properties of the target molecules.

In parallel, almost no new therapeutic applications have been proposed for molecules targeting the 5-HT1A receptor. Selective 5-HT1A agonists are investigated as anxiolytics based on the background represented by the marketed drugs buspirone and tandospirone. At the moment, there are no new chemical entities subjected to clinical trials for this application. A possible explanation for this lack of interest is that the newer drugs of this class of compounds actually do not possess a significant degree of novelty that separates them in either efficacy or safety from buspirone. This issue has been excellently addressed in a recent book dedicated to anxiolytics [92]. F-15599, a selective 5-HT1A agonist, has been thoroughly investigated as antidepressant drug [93]. However, it should be noted that any new antidepressant drug must challenge the well established “blockbuster” SSRI drugs, by offering an improved therapeutic potential. It is likely that this discourages pharmaceutical companies to undertake expensive research programs in this area.

Selective 5-HT1A high efficacy agonists such as F-13640 are being developed for the treatment of pain conditions. If the results of the ongoing clinical trial with F-13640 will demonstrate the efficacy of this drug in humans, this therapeutic approach will likely receive renewed interest [94]. Highly selective and silent 5-HT1A receptor antagonists have been proposed as cognition enhancers. Wyeth is being studying lecozotan and SR-444, a compound with undisclosed chemical structure, for the treatment of cognitive deficits in Alzheimer’s disease. The outcomes of the clinical trials that are underway will shed light on this therapeutic avenue.

Targeting 5-HT1A receptor in combination with other receptor/transporter systems has received much attention as well, and turned to be successful in many cases. The introduction in the market of vilazodone (Viibryd®) is of importance because its use in the clinical practice will likely confirm whether targeting SERT and 5-HT1A receptor can give substantial improvement in antidepressant therapy. Another multitargeting molecule, Lu AA21004, has been very recently described as effective in preventing relapse of major depressive disorder [76]. Pardoprunox, a mixed 5-HT1A agonist/dopamine D2 partial agonist, is still under development because pardoprunox was effective in improving motor symptoms in patients with early-stage PD, but further investigation into the dose and titration schedule is required to improve tolerability [95]. On the other hand, the clinical studies on the mixed 5-HT1A agonist/dopamine D2 antagonist sarizotan led Merck KGaA to announce that the development of molecule was discontinued. All in all, the results obtained with the above multitargeting drugs are sufficiently promising to encourage researchers to study new arrays of biological targeting that might benefit from the 5-HT1A receptor component.

Two additional therapeutic indications for 5-HT1A drugs come from the studies on flibanserin and GSK958108. Flibanserin has been studied for the treatment of hypoactive sexual desire disorder in postmenopausal women [96]. GSK958108 is a 5HT1A receptor antagonist, which is being investigated by GlaxoSmithKline for the treatment of primary premature ejaculation [97]. However, there are no other agents filed in the patent applications herein reviewed claiming these therapeutic applications.

The discovery that stimulation of 5-HT1A receptor can promote neurogenesis will likely renew the interest for selective 5-HT1A receptor agonists. At present, targeting neurogenesis can be attractive for therapeutic interventions to replace neural populations damaged by disease or injury. However, once the molecular mechanisms responsible for neurogenesis will be elucidated, the new potential drugs will have to be tested in behavioral studies specifically designed to test hypothesis.

**Declaration of interest**

None of the authors have conflict of interest related to the information described in this paper.
Bibliography

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


11. Dumuis A, Sebben M, Bockaert J. Pharmacology of 5-hydroxytryptamine-1A receptors which inhibit cAMP production in hippocampal and cortical neurons in primary culture. Mol Pharmacol 1988;33:178-86


** An exhaustive review on signal transduction pathways regulated by 5-HT1A receptors.


19. Melzer HY, Li Z, Kaneda Y, Ichikawa J. Serotonin receptors: their key role in drugs to treat schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:1159-72


• This paper describes well the rationale behind the design of antidepressants having mixed 5-HT1A/SSRI activity.


29. Citrome L. Vilazodone for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant - what is the number needed to treat, number needed to harm and likelihood to be...


34. SK Holding. Phenylpiperazine compounds, pharmaceutical composition including the same and use thereof. US0298831; 2009

35. Wyeth. Benzofuranaryl- and benzo(b)indol-1-yl)alkylamines. WO0907220; 2009


37. Wyeth. 3-Amino chromane derivatives. WO08080120; 2008


41. The General Hospital Corp. Combination therapy for depression. WO08156749; 2008

42. Newman-Tancredi A, Kleven MS. Comparative pharmacology of antidepressants possessing combined dopamine D2 and serotonin 5-HT1A receptor properties. Psychopharmacology (Berl) 2011;216:451-73


50. NeuroSearch AS. Novel quinolinylamide derivatives useful as modulators of dopamine and serotonin receptors. WO10040808; 2010

51. NeuroSearch AS. Novel arylpiperazine derivatives useful as modulators of dopamine and serotonin receptors. WO09095438; 2009

52. NeuroSearch AS. Novel quinolinylamide derivatives useful as modulators of dopamine and serotonin receptors. WO0609112568; 2009


55. Reviva Pharmaceuticals, Inc. Compositions, synthesis, and methods of using piperazine based antipsychotic agents. US0298819; 2009

56. Reviva Pharmaceuticals, Inc. Composition, synthesis, and methods of utilizing arylpiperazine derivatives. US0216783; 2010

57. Schwarz Pharma AG. Indolizines and aza-analog derivatives thereof as CNS active compounds. WO080155399; 2008

58. Pfizer, Inc. 7-(4-(4-[3-Chloro-2-(trifluoromethyl)phenyl]piperazin-1-yl)butoxy)-[1,8]-naphthyridin-2(1H)-one. US0167319; 2008


63. Asubio Pharma Co. Ltd. Agent for improving motor complications or psychiatric symptoms in Parkinson’s disease. WO0906928; 2009

The therapeutic potential of 5-HT1A receptors: a patent review

The review describes the pharmacological and genetic evidence for 5-HT1A receptor involvement in learning and memory

This review illustrates how compounds exhibiting combined 5-HT1A/5-HT7 properties may be effective in treating a broader range of symptoms of schizophrenia and be better tolerated than existing antipsychotics.
E. Lacivita et al.

64. Sumitomo Pharma. Novel benzoxazolone compounds. JP298402; 2005
65. US. Department of veterans affairs. pharmacological treatment of Parkinson’s disease. US0249621; 2007
66. Air Holding SA. Piperazine, piperidine and tetrahydropyridine derivatives and their pharmaceutical use. WO10137018; 2010
70. Harder JA, Ridley RM. The 5-HT1A antagonist, WAY-100635, alleviates cognitive impairments induced by dicycline (MK-801) in monkeys. Neuropharmacology 2000;39:547-52
73. This study describes the preclinical pharmacological profile of lecozotan as cognition enhancer.
74. Lundbeck AS. Takeda Pharmaceuticals North America, Inc. Therapeutic uses of compounds having combined SERT, 5-HT3, and 5-HT1A activity. WO09062517; 2009
75. Lundbeck AS. Novel therapeutic uses of 1-[2-(2,4-dimethylphenylsulfonyl)phenyl]piperazine. WO0813359; 2008
76. Lundbeck AS. 1-[2-(2,4-dimethylphenylsulfonyl)phenyl]piperazine as a compound with combined serotonin reuptake, 5-HT3 and 5-HT1A activity for the treatment of cognitive impairment. WO07144005; 2007
79. Astra Zeneca AB. 2-carboxamide-7-piperazinyl-benzofuran derivatives. US0331341; 2010
81. Colpaert FC. 5-HT1A receptor activation: new molecular and neuroadaptive mechanisms of pain relief. Curr Opin Investing Drugs 2006;7:40-7
82. This review summarized available the outcomes of the studies conducted with the high-efficacy full agonist F-13640.
86. BrainCells, Inc. 5-HT receptor mediated neurogenesis. US0009983; 2010
87. BrainCells, Inc. 5-HT receptor mediated neurogenesis. WO07134077; 2007
89. Thassin Thomas. Artificial reproduction of pharmaceutical conditions of dependency to tobacco and other addictive drugs (opiateca, psychostimulants, alcohol) by combination of nicotine and a ligand (agonist or antagonist) of 5-HT1A receptors. WO09090556; 2009

Affiliation
Enza Lacivita, Pantaleo Di Pilato, Paola De Giorgio, Nicola A Colabufo, Francesco Berardi, Roberto Perrone & Marcello Leopoldo†
†Author for correspondence
Dipartimento Farmaco-Chimico, Università degli Studi di Bari “A. Moro”, via Orabona, 4, 70125 Bari, Italy
Tel: +39 080 544 2798; Fax: +39 080 544 2231; E-mail: leopoldo@farmchim.uniba.it