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Review

Radiotracers for the Central Serotonergic System

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Abstract: This review lists the most important radiotracers described so far for imaging the central serotonergic system. Single-photon emission computed tomography and positron emission tomography radiotracers are reviewed and critically discussed for each receptor.

Keywords: serotonin; GPCR; radiotracer; PET; SPECT

1. Introduction

In recent decades, the serotonergic system constituting serotonin (5-HT) and its receptors (5-HTR) has become a promising target in neuroscience. The many studies carried out have shown its involvement in many brain functions and neuropsychiatric disorders such as Alzheimer's disease, Parkinson's disease, schizophrenia, or depression [1].

Among the G protein-coupled receptors (GPCR), 5-HTRs appear to be the largest family of receptors. Indeed, the physiological action of serotonin is carried by at least 14 subtypes of receptors: 5-HT_{1A,B,D,E,F}, 5-HT_{2A-C}, 5-HT₃, 5-HT₄, 5-HT_{5A}, 5-HT₆, and 5-HT₇ [2,3]. This classification (IUPHAR) is based on their signal transduction pathways, pharmacological effects, and molecular structures.

The significant variability of these receptors has led to the development of new tools, allowing the selective *in vivo* exploration of each of them. This exploration is based in particular on the use of medical imaging techniques such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET). These non-invasive imaging techniques are commonly used by researchers and clinicians to perform the mapping of neurotransmitter systems in the living brain in healthy and sick patients. Thanks to the development and use of new radiolabeled molecules (radiotracers or radiopharmaceuticals), the precise quantification of the density of these receptors within different brain areas is possible. Radiotracers, which are molecular scaffold containing a radioactive isotope, must fulfill several criteria to be effective brain receptor imaging agents: a high selectivity and high affinity (nM range) for the target receptor, a low or moderate lipophilicity (logD = 1–3) for blood–brain barrier penetration and to avoid excessive nonspecific binding to brain tissue, a slow metabolism (or non-interfering radioactive metabolites), and a high specific activity to visualize weakly abundant biological targets.

In this review, for each 5-HTR subtype, we will focus on the central radiotracers of interest mentioned in the literature, sorted by chemical families. Their interesting properties will be discussed, and their uses in clinical or preclinical trials will be specified. Moreover, the radiotracers used for the detection and quantification of 5-HT reuptake transporters (SERTs) will be described as well. The SERT does not belong to the 5-HTR family, but its involvement in the regulation of the serotonin concentration in the inter-synaptic space makes it an important target in neuroscience and therapeutics [4].



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2. 5-HT₁ Receptors

5-HT₁R receptors are involved in many biological and physiological processes and constitute a large family of receptors. Five different isoforms (5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}) exist, all coupled to a G α i/o protein which inhibits cAMP synthesis and therefore potentially inhibits signal transduction. In the current classification, we can note the absence of 5-HT_{1C} because the latter has been reclassified as 5-HT_{2c} following numerous discoveries for GPCRs and their sequence homology with the 5-HT₂R family [5]. To date, the description of efficient radiotracers of the 5-HT₁R family have been restricted to the 5-HT_{1A}R and 5-HT_{1B}R subtypes.

2.1. 5-HT_{1A} Receptors

Among the 5-HTRs, 5-HT_{1A}R is the first to have been cloned and characterized. In 1987, its gene (G-21) was cloned and identified as a GPCR by structural homology with the β 2-adrenergic receptor [6]. However, this is the work of Fargin et al., which determined that G-21 coded for 5-HT_{1A}R [7]. In the mammalian brain, 5-HT_{1A}Rs are divided into two distinct populations based on their location, including (1) presynaptic 5-HT_{1A}R (autoreceptors) located in the soma and dendrites of serotonergic neurons in the raphe nucleus [8,9], where their activation leads to a reduction in nerve impulses (G α i/o), resulting in a decrease in the release of 5-HT in the inter-synaptic space [10,11], and (2) postsynaptic 5-HT_{1A}R (heteroreceptors) localized in non-serotonergic neurons, mainly in limbic areas such as on the dendrites and soma of glutamatergic neurons, the terminal axons of GABAergic neurons, or on cholinergic neurons [12]. Their action is inhibitory and extends to the many areas of the brain innervated by the serotonergic system. It has to be noted that 5-HT_{1A}R heteroreceptors are expressed in a high density in the hippocampus (zone CA1, CA2, and serrated gyrus), the septum pellucidum, layers II and VI of the frontal cortex, the lateral and medial septum, and more moderately in the amygdala, the inferior colliculus, and in the thalamic and hypothalamic nuclei [8]. The wide distribution of 5-HT_{1A}R suggests that they have a great variety of functions in the brain. Indeed, they are distinguished by their influence in the phenomena of neurogenesis, neuroprotection, neuronal plasticity, memorization, and learning, but also by their involvement in various behavioral disorders such as anxiety and depression [13–15]. They are currently a target of choice in medical therapy, research, and medical imaging via the development of antagonists, agonists, and radiotracers specific to this target.

Many 5-HT_{1A} receptor (5-HT_{1A}R) radiotracers are described in the literature, but very few of them are currently used in human studies [16]. Indeed, there is a significant bias between the in vitro results and the different models (rodent, non-rodent, monkey, etc.) used in pre-clinical trials due to a difference in the distribution of 5-HT_{1A}R in the cerebral areas of the species studied, the intensity of the signal collected compared with the background noise, and the metabolization or distribution phenomena limiting the contact between the radiotracer and its target.

2.2. N-Acetamide Pyridine Series: WAY-100635 Derivatives

[¹¹C]WAY-100635 (Figure 1) is the first radioligand described as a potent antagonist, presenting good affinity for 5-HT_{1A}R ($K_D = 0.2\text{--}0.4$ nM) [17]. This radioligand has shown a partial selectivity, albeit it is also known as a dopamine D4 receptor agonist ($K_D = 2.4$ nM). This lack of selectivity is not really a problem because the 5-HT_{1A}R receptor density in the brain is significantly greater than the population of D4 receptors. Studies carried out on this radiotracer have shown good correlation between the distribution of receptors compared to that obtained previously using agonists and antagonists on human tissues (postmortem) [18]. The [*O*-methyl-¹¹C]WAY-100635 analogous has been the first radioligand to be synthesized for PET purposes, which led to 5-HT_{1A}R images in rodents, monkeys, and humans [19,20]. However, a high level of nonspecific radioactivity has been detected in the brain due to the easy crossing of BBB by radiometabolites. Then, [carbonyl-¹¹C]WAY-100635 was synthesized, which was degraded into polar radioactive metabolites that did not cross the BBB [21,22]. Since

its first synthesis, [carbonyl- ^{11}C]WAY-100635 has become a reference radioligand, allowing several studies to be performed first on healthy patients and then on patients presenting several psychiatric conditions such as depression, anxiety, or anorexia [22–25]. Nevertheless, several pharmacomodulations have been performed in order to mainly reduce its metabolization, leading to the preparation of carbon-11 and fluorine-18 radioligands.

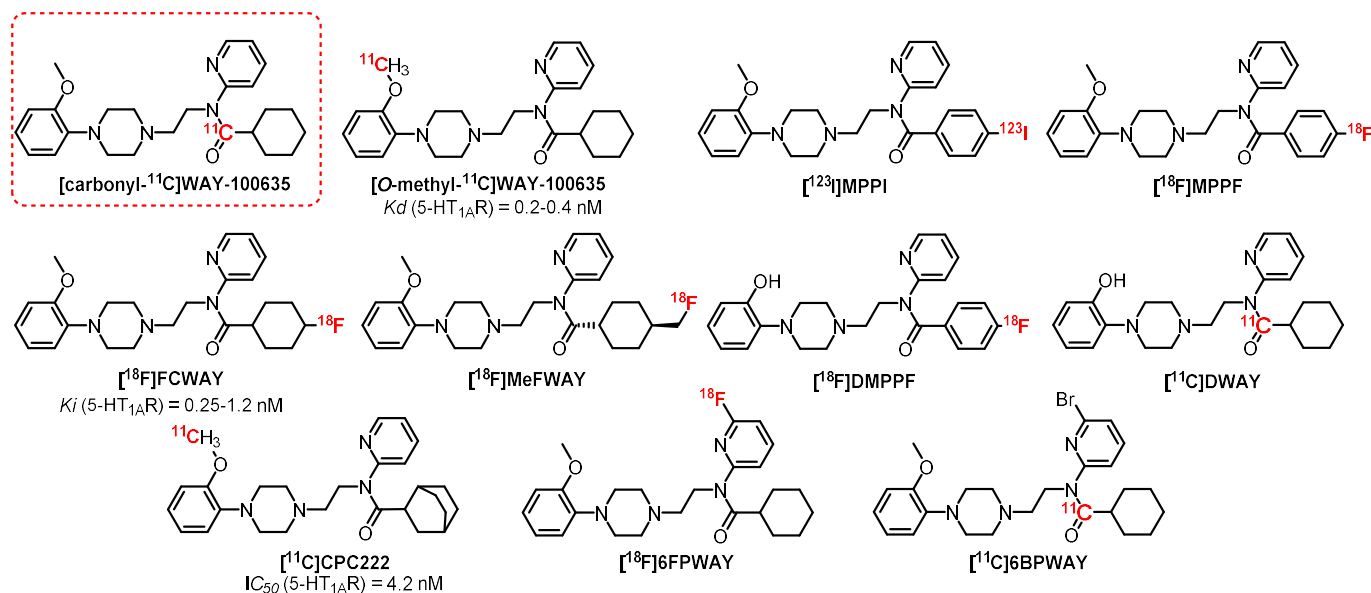


Figure 1. WAY-100365 derivatives.

[^{123}I]MPPI, an iodinated analogous of [^{11}C]WAY-100635, was prepared in 1994 by Kung [26]. Nevertheless, due to the instability of the C-I bond *in vivo*, this compound was radiolabeled with fluorine-18, as the C-F bond is known to be less metabolized. Then, in 1997, the same group prepared [^{18}F]MPPF, which has been proven to be a valuable 5-HT_{1A}R radiotracer in monkeys [27]. [^{18}F]MPPF is a selective antagonist of 5-HT_{1A}R used to measure the evolution of serotonin levels *in vivo* [28]. Studies realized in rodents, cats, monkeys, and dogs led to a selective labeling of 5-HT_{1A}R-rich cerebral regions (hippocampus, entorhinal cortex, and raphe nuclei) [29,30]. [^{18}F]MPPF has also been tested on healthy patients [31] as well as patients presenting Alzheimer's disease [32], depression, and temporal lobe epilepsy [33,34].

[^{18}F]FCWAY is a fluorinated analogue of WAY-100635 developed by Lang [35]. Its *trans* isomer, [4-*trans*- ^{18}F]FCWAY, exhibits a 0.25 nM affinity toward 5-HT_{1A}R, and its *cis* isomer, [4-*cis*- ^{18}F]FCWAY, has a slightly weaker affinity of 1.2 nM. However, [4-*trans*- ^{18}F]FCWAY showed the best pharmacological and pharmacokinetic properties, leading to the measurement of the 5-HT_{1A}R density in the hippocampus and cerebellum. [^{18}F]FCWAY has also been used to quantify 5-HT_{1A}R in patients with behavioral disorders such as epilepsy, post-traumatic stress, or panic attacks [36–38]. However, the accumulation of radiofluorine in bones due to the metabolism of the radiotracer decreases the resolution of brain imaging. The use of disulfiram, a cytochrome P450 isozyme 2E1 inhibitor which decreases defluorination, limited this phenomenon and improved the visualization of these receptors, but it was not sufficient to justify its use or its marketing [39].

[^{18}F]MeFWAY is a derivative of [^{18}F]FCWAY, possessing a fluoromethyl group at cyclohexane's position 4, thus limiting metabolization issues. *In vivo* assays in rodents and primates showed that the [*trans*- ^{18}F]MeFWAY isomer presented good affinity and specificity for 5-HT_{1A}R and was suitable for *in vivo* imaging [40,41]. In 2014, the first assays on six healthy volunteers allowed obtaining preliminary evidences of its potential as a radiopharmaceutical [42]. In 2015, Choi et al. confirmed this conclusion by using a comparative study with [^{18}F]FCWAY associated with disulfiram [43]. Nevertheless, to date, there is no publication demonstrating its usefulness in sick patients.

[¹⁸F]DMPPF is the demethylated analogue of [¹⁸F]MPPF. This pharmacomodulation was performed in order to increase the PET signal by improving the cerebral uptake of the compound. [¹⁸F]DMPPF was crossing the BBB and leading to an efficient imaging contrast with a lower clearance in rats than [¹⁸F]MPPF [44]. Despite this encouraging first result, this radiotracer has not been used, probably due to the great interest of the community in [¹¹C]WAY-100635.

[¹¹C]DWAY is a putative metabolite of [¹¹C]WAY-100635 which presents similar characteristics but provides a twofold higher brain uptake than [¹¹C]WAY-100635 in the human brain [45]. However, despite these interesting results, this radiotracer has not been investigated so far.

[¹¹C]CPC-222 is a WAY-100635 analogue with good 5-HT_{1A}R affinity (IC₅₀ = 4.2 nM) which crosses the BBB [46]. However, this molecule has not been used because of its too weak signal-to-noise ratio.

[¹⁸F]6FPWAY and [¹¹C]6BPWAY are halogenated (fluorinated and brominated, respectively) analogues of WAY-100635 [47]. Halogen atoms have been introduced on this scaffold in order to decrease the metabolism of the compound while allowing further radiolabeling with fluorine-18 or bromine-76. [¹⁸F]6FPWAY was initially synthesized and tested as [¹¹C]6FPWAY in monkeys and then was prepared while incorporating fluorine-18 [48]. Assays have shown a moderate interest in these ligands due to faster metabolism of the compound compared with [*O*-methyl-¹¹C]WAY-100635. This phenomenon is probably due to faster degradation of the amide bond of the 6-fluoropyridine group [49]. [¹⁸F]6FPWAY and [¹¹C]6BPWAY have not been further studied so far.

2.3. 1,2,4-Triazine-3,5-Dione Series: CUMI-101 Derivatives

[¹¹C]CUMI-101 and its derivative [¹¹C]FECUMI-101 are 5-HT_{1A}R agonists (Figure 2). Agonists are good candidates for estimating the level of 5-HT receptors present in the synaptic cleft, the receptor's occupancy, and the determination of the internalization of autoreceptors after administration of the serotonin transporter's (SERT) inhibitors, which are used to treat depressive states. [¹¹C]CUMI-101, also called [¹¹C]MMP, is a 2-methoxyphenyl analogous of a previous radiotracer (MPT) described by the same authors in 2006. This former radiotracer has shown a promising agonist profile with good affinity for 5-HT_{1A}R (K_i = 1.36 nM) in baboons [50], but slow washout kinetics prompted the authors to perform structure–activity relationship studies, leading to the preparation of [¹¹C]CUMI-101. This compound has been demonstrated to be a potent (K_i = 0.15 nM) and selective 5-HT_{1A}R agonist ligand, with a high uptake in 5-HT_{1A}R-rich areas in baboons [51]. Used in healthy volunteers, [¹¹C]CUMI-101 led to determination of the distribution and quantification of central and peripheral 5-HT_{1A}R [52,53]. Notably, this radiotracer shows interesting properties, as its metabolites are not crossing the BBB. In 2011, Hendry et al. investigated the pharmacological profile determination of [¹¹C]CUMI-101 in rat brain tissue and demonstrated that, while acting as an 5-HT_{1A}R agonist in humans, it behaves as an antagonist in the rat cortex and rat hippocampal tissue [54]. Thus, this compound may act as a partial agonist, leading to interpretation difficulties from one model to another. In 2020, [¹¹C]CUMI was also used to assess the 5-HT_{1A}R occupancies of brexpiprazole in adult subjects with schizophrenia [55].

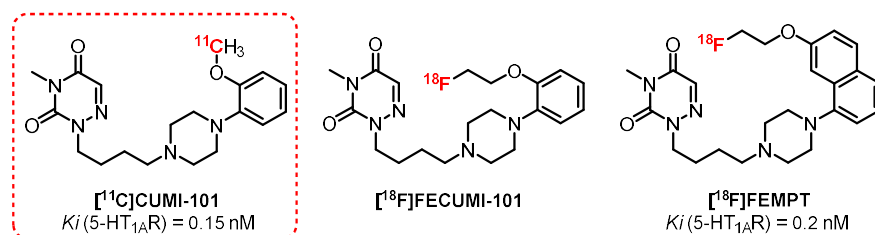


Figure 2. CUMI-101 derivatives.

[¹⁸F]FECUMI-101 is the ethylfluorinated analogue of [¹¹C] CUMI-101 synthesized in 2013 by Kumar [56]. Studies carried out in baboons showed that this radiotracer crosses the

BBB with good distribution of the radiotracer in the 5-HT_{1A}R-rich brain regions, with the exception of the thalamus. In 2016, autoradiographic studies carried out on human brain sections confirmed this specific binding, along with some binding with α 1 receptors [57]. A possible explanation is the difference in the concentration of α 1 receptors in different species in this brain region or a specific binding on an unknown target. In addition, competition experiments in the presence of **WAY-100635** have shown a binding blockade of [¹⁸F]FECUMI-101 on the receptors present in the cerebellum, limiting its use as a reference for in vivo PET applications.

[¹⁸F]FEMPT is a radiotracer synthesized in 2017 by Collier et al. via a continuous flow microfluidic method [58]. The advantage of this technique lies mainly in the saving of time and the reagent, allowing one to increase and optimize the parameters and the yield of reactions for radiolabeling with fluorine-18. The first in vitro assays carried out with this compound showed a strong affinity of [¹⁸F]FEMPT toward 5-HT_{1A}R (K_i = 0.2 nM). In addition, the affinity for α 1 adrenergic receptors (K_i = 180 nM) was much lower than that observed for [¹¹C]CUMI-101. These initial results are very encouraging, and preclinical studies are currently being carried out on this new radiotracer.

2.4. 2-Pyridinemethylamine Series: F15599 Derivatives

F15599 (Figure 3) is the first 5-HT_{1A}R ligand described in the 2-pyridinemethylamine series, presenting a strong affinity and very high specificity for 5-HT_{1A}R. In vitro and in vivo studies led to assessing its particular affinity for the postsynaptic 5-HT_{1A}R present in the cortical areas of the brain [44]. In vivo imaging with [¹⁸F]F15599 in rats and cats demonstrated a rapid accumulation of this radioligand in the brain, suggesting good BBB passage as well as good distribution in brain areas such as the raphe nucleus, the hippocampus, and the side bridge [45]. However, the labeling intensity was considered insufficient for further investigations as a radiopharmaceutical, probably due to its relatively low affinity (K_i = 2.24 nM) [16]. Efforts have been therefore focused on pharmacomodulations of [¹⁸F]F15599.

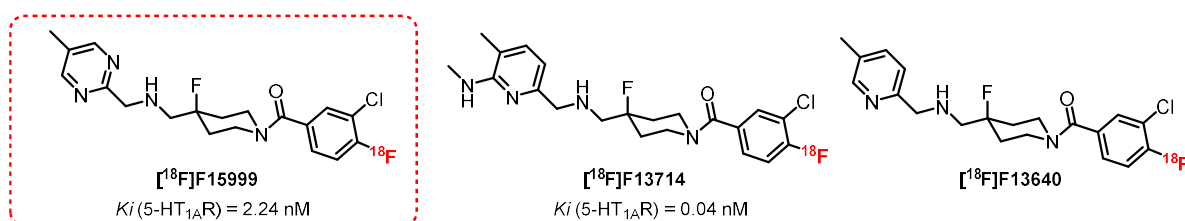


Figure 3. F15999 derivatives.

[¹⁸F]F13714, a 2-pyridinemethylamine analogue of [¹⁸F]F15999, presented a particularly strong affinity for recombinant human 5-HT_{1A}R (K_i = 0.04 nM) [59,60]. In vitro autoradiography carried out on rats revealed significant radioactivity in the targeted brain areas [61]. In addition, [¹⁸F]F13714 was shown to have very good resistance to metabolism. Specific binding of this radiotracer in 5-HT_{1A}R-dense areas was observed in in vivo PET imaging (cats), with a particular tropism for the cortex compared with the hippocampus. In 2016, Yokoyama et al. published a comparative study between [¹⁸F]F13714 and [¹⁸F]MPPF in awake and anesthetized marmosets, demonstrating the strong influence of anesthesia on functional 5-HT_{1A}R and therefore suggesting that caution is necessary when interpreting results from agonists in PET imaging [62]. Although the results were encouraging, [¹⁸F]F13714 was not optimal for in vivo imaging because of its irreversible binding.

F13640 (also known as **befiradol** or **NLX-112**) is a 5-HT_{1A}R ligand that has recently been investigated from the same series, presenting selectivity and efficacy for 5-HT_{1A}R along with strong analgesic properties [63]. Demonstrated on a large panel of animal models presenting physiological or pathological acute pain, and in comparison with a large intake of opioids, its analgesic action led to the development of a reverse tolerance [64]. In 2018, Zimmer et al. carried out the first in vivo imaging assays in rats, cats, and primates [65].

[¹⁸F]F13640 has been proven to cross the BBB (without formation of radioactive metabolites), and its distribution has been observed in 5-HT_{1A}R-rich areas, with notable differences in comparison with the distribution observed using antagonist radiotracers so far. In addition, [¹⁸F]F13640 has been used to determine the evolution of the number of these receptors in the hippocampus in the prodromal stage of Alzheimer's disease (post mortem) [66]. In 2019, [¹⁸F]F13640 was used in vivo in healthy humans, affording promising results since the visualized distribution correlated with that of functional 5-HT_{1A}R receptors [67]. [¹⁸F]F13640 is the first radiopharmaceutical that enables in vivo investigation of functional 5-HT_{1A}R that is likely to be altered in pathological conditions such as neuro-degenerative diseases or psychiatric disorders. Indeed, in 2021, [¹⁸F]F13640 was proven to be a valuable tool to explore neurological or neuropsychiatric pathologies involving fluctuations in extracellular serotonin. Indeed, Zimmer et al. have shown its sensitivity to detecting in vivo 5-HT concentration fluctuations [68].

2.5. 5-HT_{1B} Receptors

Like 5-HT_{1A}R, 5-HT_{1B}R exists at the pre- and postsynaptic level. However, their locations are different; presynaptic 5-HT_{1A}R is localized mainly in the cell body and the dendrites of the serotonergic neurons, while 5-HT_{1B}R is expressed at the axonal endings. The 5-HT_{1B}R has an important influence in the regulation of the concentration of 5-HT in the intersynaptic space and induces a negative feedback limiting 5-HT's release (homoreceptors). All postsynaptic 5-HT_{1B}R (heteroreceptors) receptors are located on the terminal axons of non-serotonergic neurons (GABAergic, muscarinic, or dopaminergic) and will influence the release of their neurotransmitters. There is a great homology between the receptors present in humans and rats, with the only difference being a replacement of a threonine by an asparagine on the seventh transmembrane domain. However, this slight difference is responsible for significant variations during pharmacological studies. The 5-HT_{1B}R receptors are present in a high density in different brain locations, such as the globus pallidus, substance nigra, ventral pallidum, or dorsal subiculum and more moderately in the cortex, the hippocampus, and the putamen [69]. The 5-HT_{1B}R receptors are involved in learning and memorization phenomena. Thus, the injection of antagonists into knockout mice allowed the observation of an improvement in their cognitive performance, with a probable involvement of the cholinergic system [70]. In addition, pharmacological studies have demonstrated the interest of 5-HT_{1B}R in aggression phenomena, with a decrease of the latter in the presence of agonists [71].

2.6. Chromen-4-One Series: AZ10419369 Derivatives

[¹¹C]AZ10419369 (Figure 4) is a partial 5-HT_{1B}R agonist (K_D = 0.37 nM). This compound is considered a reference radiotracer for these receptors and has been used on numerous occasions to assess the influence of 5-HT_{1B}R in healthy volunteers as well as in neuropsychiatric disorders. In 2008, Pierson et al. carried out the first studies in macaques and observed a specific radiolabeling of 5-HT_{1B}R-rich areas through a competitive method in the presence of a reference antagonist: AR-A000002 [72]. In addition, the interesting potential of this compound has been confirmed thanks to the intensity of the collected signal and the absence of detection of any radiometabolite. In this same study, [¹¹C]AZ10419369 was tested in two human subjects, and good correlation in the receptor's distribution in both macaques and human brains was observed, as well as those obtained previously by autoradiogram in guinea pig brains [73]. From 2010 to 2020, many studies used [¹¹C]AZ10419369 as a reference in PET imaging [74,75]. Used in patients with depressive disorders and Parkinson's disease, a decrease in 5-HT_{1B}R in the targeted areas of the brain was observed [76,77]. Very recently, pharmacomodulations of [¹¹C]AZ10419369 have been performed by Lindberg et al. in order to replace carbon-11 with the longer half-life fluorine-18, allowing them to increase the acquisition time in imaging [78,79]. Among the described radiotracers, [¹⁸F]AZ10419096, a radiotracer published in 2019 by Lindberg et al. [80], revealed interesting properties. This compound is an antagonist of

5-HT_{1B}R presenting very good affinity ($K_i = 0.13$ nM). The first in vivo tests in monkeys demonstrated a specific binding of this compound to 5-HT_{1B}R-rich brain areas (e.g., the occipital cortex or globus pallidus). Approximately 80% of this binding is inhibited in the presence of a reference antagonist (pretreatment with AR-A000002). In addition, the main metabolites of [¹⁸F]AZ10419096 seemed to be too polar to cross the BBB. The only drawback of this compound lies in its synthesis, since the yield of radiolabeling from the boronic precursor is very low (<5%) and needs to be optimized.

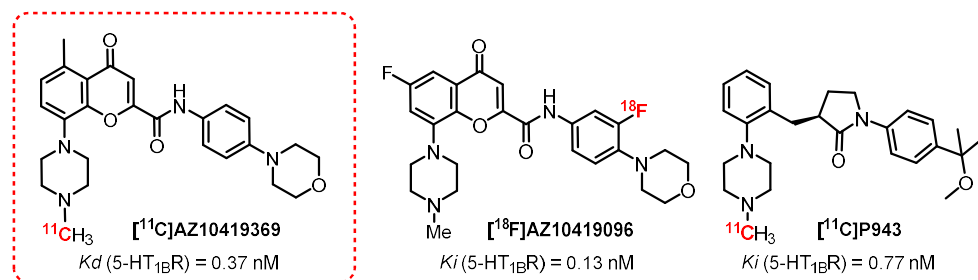


Figure 4. AZ10419369 derivatives.

[¹¹C]P943, obtained through a structural simplification of [¹¹C]AZ10419369, is a 5-HT_{1B}R antagonist presenting a very strong affinity and specificity for these receptors ($K_i = 0.77$ nM). A complete pharmacokinetic study was performed in baboons (*Papio anubis*) in order to determine the BBB crossing, the presence of metabolites, and its affinity for 5-HT_{1B}R. The specificity of [¹¹C]P943 for 5-HT_{1B}R was revealed by blocking the receptors with a specific 5-HT_{1B}R antagonist (SB-616234-S), while no significant change was observed using a 5-HT_{1D}R antagonist (SB-714786) [81]. Thanks to this radiotracer, the implication of 5-HT_{1B}R was evaluated in patients with various pathologies (e.g., depression or post-traumatic stress) or drug addiction (cocaine), where a decrease in the binding of [¹¹C]P943 to 5-HT_{1B}R was observed compared with the healthy patients [82,83]. This phenomenon is reversed in people with alcohol addiction, where an increase in binding was observed, especially in the ventral striatum [84].

3. 5-HT₂ Receptors

5-HT₂R receptors are among the first serotonergic receptors to be identified with 5-HT_{1A}R. Their identification was possible thanks to genetic cloning, allowing for distinguishing three different subtypes (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}). Structural variations in these 3 isomers with 471 amino acids for 5-HT_{2A}R, 481 for 5-HT_{2B}R, and 458 for 5-HT_{2C}R (in humans) can be noted. This variation in structure is not surprising, since each of them is encoded by different genes carried on three distinct chromosomes (chromosomes 13, 2, and X, respectively). These receptors possess a wide area of localization and are mainly involved in cell development and migration processes [85]. All these receptors are coupled to a G_{q/11} protein, and their activation regulates an enzymatic cascade involving the phospholipase C. This enzyme leads to the hydrolysis of membrane phosphatidylinositol biphosphate into two intracellular secondary messengers: diacylglycerol and inositol-1,4,5-triphosphate (IP₃). IP₃ plays an important role in the release of calcium ions by binding to the IP₃ receptors on the membrane of the endoplasmic reticulum. This increase in Ca²⁺ ions in the cytosol is completed by the action of ion pumps (allowing the passage of extracellular Ca²⁺ ions) which are activated by protein kinases C, themselves activated by the diacylglycerols synthesized beforehand [86]. Currently, there are no potent and selective radioligands commonly used in clinic or research facilities to quantify and characterize 5-HT_{2B}R and 5-HT_{2C}R. It is nevertheless interesting to note the recent development of promising new molecules that are affine and selective for 5-HT_{2C}R, specifically marking the choroid plexus (cerebral area rich in 5-HT_{2C}R) (Figure 5) [87,88]. These molecules could be the subject of future clinical studies and could enhance the interest shown in these receptors via PET and SPECT imaging.

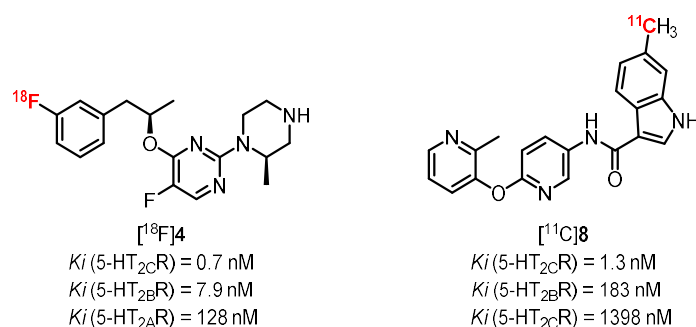


Figure 5. 5-HT_{2C}R selective radioligands.

Conversely, numerous studies involving 5-HT_{2A}R radioligands have been described in the literature. In humans, 5-HT_{2A}R was identified and cloned for the first time by Branchek et al. in 1990 [89]. It quickly aroused the particular interest of the scientific community because of its role in certain behavioral disorders and its psychomimetic effects when taking psychotropic substances such as lysergic acid diethylamide (LSD), mescaline, or psilocybin [90]. Human 5-HT_{2A}R radioligands are located mainly in the cortex and in a lower density in the central brain structures such as the hippocampus or the caudate nucleus. In the cortex, they are found mainly in layers II–III but also in lesser quantities in layers V and VI [91]. At the cellular level, they are mainly postsynaptic receptors and are expressed in non-serotonergic (cholinergic or GABAergic) neurons with the result of increasing cellular hyperexcitability and promoting nerve impulses [92]. 5-HT_{2A}R has been at the center of many studies on the one hand for its involvement in many neuropsychiatric disorders such as depression, anxiety, schizophrenia, and psychosis and on the other hand because it is the target of second-generation antipsychotics (D1/D2 and 5-HT_{2A} antagonists) such as Clozapine, Olanzapine, or Risperidone [93]. To date, many efficient 5-HT_{2A}R radiotracers have been developed in several chemical series both for SPECT and PET.

3.1. Quinazoline-2,4-Dione and Thiazolo [3,2-*a*]Pyrimidin-5-One Series: *Ketanserin* Derivatives

The first evaluations of 5-HT_{2R} radiotracers were carried out in 1985 using a very affine and selective antagonist (in vitro and in vivo in rats): [¹¹C]Ketanserin [94]. In humans, a too rapid metabolism along with nonspecific binding rapidly stopped the development of this molecule as a 5-HT_{2R} radiotracer. However, these first trials were the starting point for more specific studies of 5-HT_{2A}R in PET imaging through the development of ketanserin analogues (Figure 6).

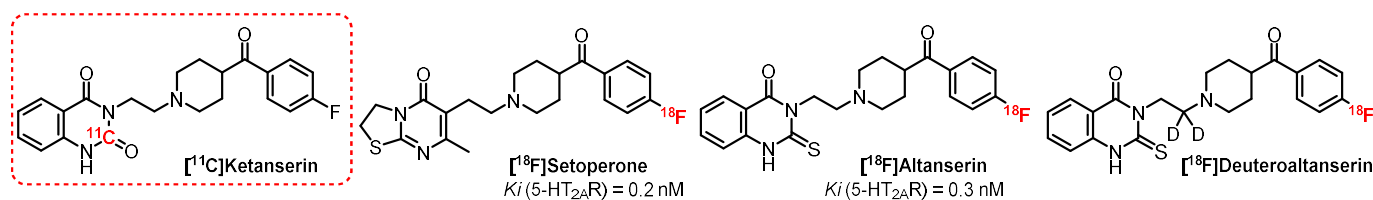


Figure 6. Ketanserin analogues as 5-HT_{2A}R radiotracers.

[¹⁸F]Setoperone is one of the reference radioligands for 5-HT_{2A}R. It is a very potent antagonist of these receptors (K_i = 0.2 nM) along with relative specificity since in baboons, it also interacts with the dopaminergic D2 receptors present in the striatum [95]. Despite this specificity issue, it has been used regularly as a radiotracer for 5-HT_{2A}R in PET imaging, especially in healthy subjects or subjects with various pathologies such as depression, migraines, or Alzheimer's disease [96–100]. [¹⁸F]Setoperone is not used anymore in human studies due to the discovery of [¹⁸F]Altanserin, which has demonstrated a higher potential in animal and human studies.

As a 5-HT_{2A}R antagonist (K_i = 0.3 nM), [¹⁸F]Altanserin was first evaluated in rats in 1991 by Lemaire et al., and an important signal in the frontal cortex along with a more moderate one in the striatum were detected [101]. The specificity of the signal was determined by prior blocking of the receptors in the presence of 5-HT_{2A}R ligands (ketanserin, pipampone, and methylsergide) and D2 receptor ligands (sulpiride and halopemide). Subsequently, [¹⁸F]Altanserin was tested in healthy volunteers, and good distribution of the radioligand was found despite the presence of nonspecific binding, particularly in the cerebellum [102]. This off-target labeling was later attributed to the in vivo production of radiometabolites [103,104]. A more recent study on 52 healthy volunteers demonstrated the absence of a significant difference in [¹⁸F]Altanserin binding between the male and female genders and a significant decrease in 5-HT_{2A}R in the elderly and in patients with high body mass indexes [105]. [¹⁸F]Altanserin has also been used to determine the density of 5-HT_{2A}R in subjects with various CNS-related disorders such as anorexia, schizophrenia, obsessive-compulsive disorder, depression, and Alzheimer's disease [105–109]. In light of all these characteristics, numerous pharmacomodulations of [¹⁸F]Altanserin were considered in order to increase the resolution of PET imaging by limiting nonspecific binding and by decreasing the production of lipophilic radioactive metabolites.

In 2001, in order to reduce metabolite production, a deuterated analogue was considered: [¹⁸F]Deuteroaltanserin. The main objective was to maintain the pharmacological and pharmacokinetic properties while delaying the metabolization by inserting an isotope of hydrogen: deuterium. Initially, a study was carried out in baboons and did not allow observing any significant difference between the two radioligands (neither for radiolabeling nor metabolization) [110]. Subsequently, a study on a healthy man was conducted and allowed the observation of good distribution of the radiotracer as well as a modest decrease in the production of radiometabolites in the plasma [111,112]. In 2009, Santhosh et al. carried out a study with [¹⁸F]Deuteroaltanserin on nine subjects affected by Alzheimer's disease and concluded that there was a significant reduction in the binding of the radiotracer to 5-HT_{2A}R, mainly in the anterior, frontal, medial, parietal, and temporal cingulate cortex [113]. Despite these promising results, no study has referred to [¹⁸F]Deuteroaltanserin since then.

3.2. Piperidin-4-Ylmethanol Series: Volinanserin Derivatives

[¹¹C]Volinanserin, or [¹¹C]MDL100907 or [¹¹C]MDL100,907 (Figure 7), is a very selective and potent 5-HT_{2A}R antagonist (K_i = 0.2 nM) [114]. Its interesting pharmacokinetic properties, such as its moderate lipophilicity (logP = 2.7), allowed [¹¹C]Volinanserin to become a reference radiotracer in the study of the distribution of 5-HT_{2A}R. First, its tritiated analogue [³H]MDL10090 has been used in animals (rats and monkeys) to assess its strong specificity, allowing the visualization, quantification, and direct characterization of these receptors by autoradiography [115,116]. The monkey studies were enlarged to the use of [¹¹C]Volinanserin in PET imaging by Lundkvist et al. [117] and permitted the observation of specific labeling of the frontal, temporal, and visual cortex through competition with ketanserin. In 1998, Ito et al. confirmed these results in healthy humans (three volunteers), where a specific labeling of the neocortex (occipital, frontal, and temporal cortex) with moderate nonspecific labeling was observed [114]. In 2012, a comparative study on a large cohort of healthy volunteers consolidated the interest in [¹¹C]Volinanserin since, in addition to obtaining good distribution of labeling of 5-HT_{2A}R receptors, a decline in this population with age for 5-HT_{2A}R expression was evidenced. In addition, the analyses carried out demonstrated a slow metabolization of the radiotracer limiting the presence of radiometabolites, the main drawback encountered with ketanserin derivatives [118]. [¹¹C]Volinanserin represents a reference ¹¹C-radiotracer for the study of 5-HT_{2A}R receptors and has been used in numerous studies on humans and animals in order to observe the influence of 5-HT_{2A}R in various pathologies, such as depression, Huntington's disease, Asperger's syndrome, as well as in obsessive-compulsive disorders [119–121]. Interesting fluorinated analogues of Volinanserin have also been evaluated recently. [¹⁸F]MDL100907

is a **Volinanserin** analogue labeled with fluorine-18 instead of carbon-11, and it was considered mainly for the benefit represented by the longer half-life of fluorine-18 compared with carbon-11. Few publications refer to this radiotracer, mainly because of the difficulty in achieving an efficient radiofluorination of **Volinanserin** [122]. In 2014, a study carried out by Ren et al. identified a new method for obtaining [^{18}F]MDL100907 using a nickel-mediated fluorination strategy. In nonhuman primates, a comparison of binding results between [^{18}F]MDL100907 and [^{11}C]Volinanserin concluded that [^{18}F]MDL100907 was able to provide a better 5HT $_2\text{A}$ R distribution and density through PET imaging [123]. (*R*)-[^{18}F]MH-MZ is an ethylfluorinated analogue of [^{11}C]Volinanserin which exhibits very good affinity and specificity for 5-HT $_2\text{A}$ R ($K_i = 0.72$ nM), along with easier radiosynthetic access compared with [^{18}F]MDL100907. In rats, the (*R*)-[^{18}F]MH-MZ enantiomer showed the best radiolabeling results, as the affinity of the racemic mixture [^{18}F]MH-MZ was quite lower ($K_i = 3.0$ nM) [124,125]. The comparative study between [^{18}F]MH-MZ and [^{18}F]Altanserin demonstrated a more specific labeling of areas rich in 5-HT $_2\text{A}$ R by [^{18}F]MH-MZ. In addition, it revealed a low level of radiometabolites in the cortex extracts compared with the plasma levels, thus confirming that the latter cannot pass the BBB [126]. Despite these encouraging results, to date, no publication refers to the use of this radiotracer in humans.

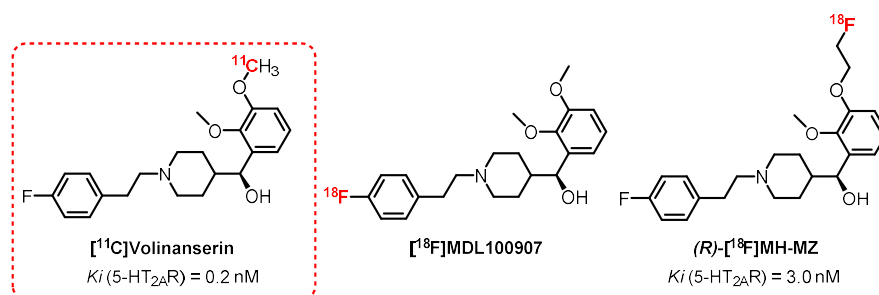


Figure 7. Volinanserin analogues as 5-HT $_2\text{A}$ R radiotracers.

3.3. *N*-Benzylphenethylamine Series: CIMBI-5 Derivatives

The vast majority of radiotracers synthesized to radiolabel 5-HT $_2\text{A}$ R are antagonists of these receptors. However, the development of a series of agonist compounds constitutes a major interest, allowing for distinguishing the functional receptors involved in various brain pathologies. It is in this context that [^{11}C]CIMBI-5 was synthesized (Figure 8). In 2010, Ettrup et al. carried out the first studies on this compound, which revealed that it was indeed a potent 5-HT $_2\text{A}$ R agonist with moderate specificity for these receptors (K_i (5-HT $_2\text{A}$ R) = 2.2 nM; K_i (5-HT $_2\text{B}$ R) = 2,3 nM; K_i (5-HT $_2\text{C}$ R) = 7.0 nM) [127]. The *ex vivo* study carried out on rat brains showed absorption of the radiotracer mainly in the frontal cortex equivalent to that obtained with [^{18}F]Altanserin. This binding is specific to 5-HT $_2\text{A}$ R, as proven by a significant displacement of the radiotracer in the presence of **ketanserin**. *In vivo* (pigs) imaging revealed significant cortical absorption as well as more moderate absorption in the thalamic and striatal regions, thus evidencing the interest in evaluating [^{11}C]CIMBI-5 in humans. In 2019, additional tests carried out on nonhuman primates (two baboons and two vervet monkeys) allowed observing a radiolabeling in correlation with those obtained previously but with a lower intensity compared with [^{11}C]Volinanserin [128].

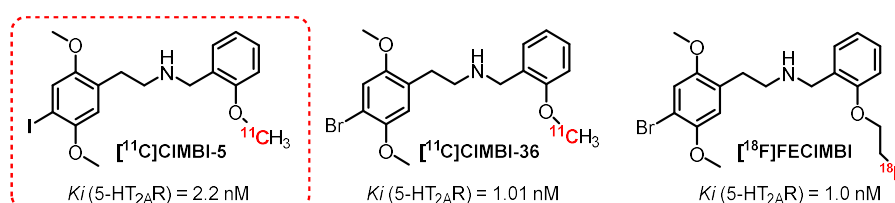


Figure 8. CIMBI-5 analogues as 5-HT $_2\text{A}$ R radiotracers.

Many derivatives of [^{11}C]CIMBI-5 were synthesized and tested, with widely varying radiolabeling results [129]. Among them, [^{11}C]CIMBI-36, the brominated analogue of [^{11}C]CIMBI-5, demonstrated the most interesting results. [^{11}C]CIMBI-36 possesses a strong affinity and specificity toward 5-HT $_2\text{A}$ R ($K_i = 1.01$ nM) and afforded an intense radiolabeling of the cerebral cortex in pigs [129]. In 2014, [^{11}C]CIMBI-36 was evaluated against a cohort of 29 healthy volunteers, and good distribution of the radiotracer was demonstrated, particularly in the neocortex and the sensory cortex. The study suggested a weak plasmatic stability of [^{11}C]CIMBI-36, with a 50% decrease in plasma 10 min after injection. This metabolism issue was not evidenced in the pig brain tissue but was the subject of additional research [130,131]. Finally, in the presence of ketanserin, radiolabelling was significantly reduced in the neocortex, confirming the binding selectivity toward 5-HT $_2\text{A}$ R. Additional studies were carried out on humans and animals with the aim of observing the changes induced by the administration of substances that interact with the serotonergic system [132–134]. The study on pigs and monkeys revealed a decrease in the uptake of [^{11}C]CIMBI-36 (46%) in the presence of a significant increase in 5-HT. In humans, [^{11}C]CIMBI-36 allowed assessing a decrease in radioemission in areas rich in 5-HT $_2\text{A}$ R in the presence of D-amphetamine, thus evidencing the interest in this radiotracer as a potential new tool for the evaluation of neuropathologies such as depression [135]. Finally, in 2016, a study by Ettrup et al. revealed a probable binding of [^{11}C]CIMBI-36 to 5-HT $_2\text{C}$ R detected by radiolabeling of the hippocampus and choroid plexus greater than that in the presence of [^{18}F]Altanserin [136].

[^{18}F]FECIMBI, an ethylfluorinated analogue of [^{11}C]CIMBI-36, exhibited interesting binding properties toward 5-HT $_2$ Rs (K_i (5-HT $_2\text{A}$ R) = 1 nM; K_i (5-HT $_2\text{C}$ R) = 1.7 nM) and an agonist profile. [^{18}F]FECIMBI was synthesized by Prabhakaran et al. in 2015 and was able to radiolabel the temporal cortex, the hippocampus, and the choroidal plexus (an area rich in 5-HT $_2\text{C}$ R) by autoradiography [137]. In 2017, a complementary study in monkeys showed insufficient cerebral absorption and an insufficient volume of distribution for the development of an in vivo quantification tool [138].

3.4. Miscellaneous Derivatives as SPECT Imaging Tracers

Over the past few decades, many SPECT radiotracers with an affinity for 5-HT $_2\text{A}$ R have been synthesized (Figure 9). However, due to moderate selectivity, the presence of radiometabolites interfering with imaging and signals that are too weak, very few of them are currently used to quantify 5-HT $_2\text{A}$ R in humans. Discovered in the 1970s, [^{123}I]DOI is a mixed agonist of 5-HT $_2\text{A}$ R and 5-HT $_2\text{C}$ R which allowed the first scintigraphic explorations of the brain even before the emergence of SPECT and PET imaging techniques [139]. [^{123}I]DOI was previously used in its racemic form, in particular in rats ($K_i = 2.8$ nM) [140]. In 1989, Nazarali et al. published a comparative study highlighting the interest of (R)-[^{125}I]DOI ($K_d = 1.2$ nM) in its enantiomer (S)-[^{125}I]DOI ($K_d = 2.1$ nM) [141]. Finally, the results obtained for baboons did not conclude favorably with regard to its use as a specific radiotracer for 5-HT $_2\text{A}$ R and 5-HT $_2\text{C}$ R [142].

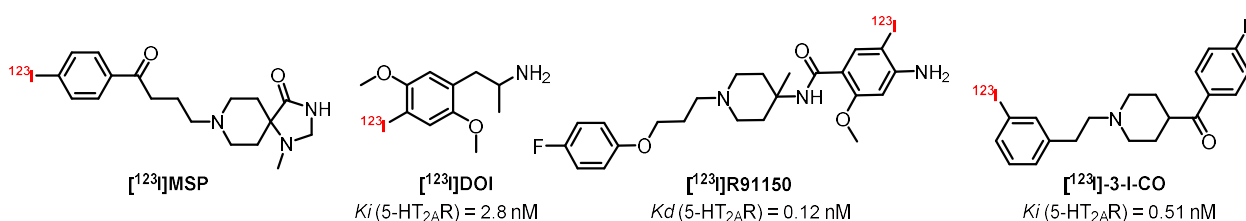


Figure 9. Miscellaneous 5-HT $_2\text{A}$ R SPECT imaging tracers.

[^{123}I]R91150 or [^{123}I]R93274 are the most popular radiotracers used to quantify and characterize 5-HT $_2\text{A}$ R by SPECT imaging. [^{123}I]R91150 is a potent ($K_d = 0.12$ nM) and selective antagonist of 5-HT $_2\text{A}$ R which demonstrated its effectiveness through pronounced radiolabeling of the frontal cortex (FC) compared with the cerebellum (CER, nonspecific),

with an FC/CER ratio greater than 10 in rats (in vivo) [143]. In 1997, Abi-Dargham et al. published the first complete preclinical study carried out on baboons and observed a specific radiolabeling of the occipital and temporal cortex (reversible in the presence of **ketanserin**) with a lower FC/CER ratio (1.5). The plasma study revealed a rapid metabolism of [^{123}I]R91150 (75% metabolized 3 h after the injection) with the presence of a less lipophilic metabolic fraction which did not cross the BBB [144]. These observations were confirmed by studies carried out on healthy volunteers who did not question the usefulness of this radiotracer for the quantification and characterization of cerebral 5-HT_{2A}R [145,146]. In 1998, [^{123}I]R91150 was tested on a larger cohort of healthy volunteers (13 women and 13 men) and confirmed the results obtained with [^{18}F]Altanserin (i.e., the absence of a significant difference between genders and the significant decrease in 5-HT_{2A}R with aging) [147]. During the last two decades, [^{123}I]R91150 was used on numerous occasions to study various neuropathologies such as Alzheimer's disease, Parkinson's disease, or schizophrenia [148–150]. [^{123}I]R91150 became a reference for evaluating the distribution and the quantification of 5-HT_{2A}R in subjects (humans and animals) presenting neuropsychiatric disorders (with or without treatment) such as depression, anxiety, anorexia, or having suicidal behaviors [151–157]. In 2009, a fluorinated analogue usable in PET imaging was synthesized: [^{18}F]R91150. Despite encouraging results, the difficulty of obtaining the radiotracer did not encourage its development for further studies [158].

[^{123}I]MSP is an iodinated derivative of **spiperone**, an atypical antipsychotic drug belonging to the butyrophenone family used as a treatment for schizophrenia. [^{123}I]MSP was designed to maintain the affinity for 5-HT_{2A}R of **spiperone** while decreasing its affinity toward dopaminergic D2 and D3 receptors. The study carried out with [^{123}I]MSP evidenced a strong affinity and selectivity for 5-HT_{2A}R, with a radiolabeling distribution in correlation with those obtained with the reference radiotracers (intense labeling of the mouse frontal cortex) [159]. Despite promising results, [^{123}I]MSP has not been the subject of recent studies.

[^{123}I]-3-I-CO is a potent ($K_i = 0.51$ nM) and selective antagonist of 5-HT_{2A}R which was developed by Fu et al. in 2002. In 2008, a study on rodents showed good distribution of the radiotracer with a moderate intensity and poorly specific signal. In addition, [^{123}I]-3-I-CO was the target of efflux mechanisms at the BBB level, demonstrated by a significant increase in the intensity of the radiosignal after prior administration of a P-glycoprotein inhibitor (cyclosporine A) [160]. The potential of this radioligand was therefore limited for clinical development and was simply abandoned.

4. 5-HT₃ Receptors

Among the 14 serotonin receptor subtypes, 5-HT₃R is the only ionotropic receptor which belongs to the pentameric ligand-gated ion channel (LGIC) superfamily [161]. In humans, there are five 5-HT₃R subtypes, from 5-HT_{3A} to 5-HT_{3E}. The subunits are encoded by the HTR₃ genes located on chromosome 11q23 (HTR_{3A} and HTR_{3B}) and 3q27 (HTR_{3C}, HTR_{3D}, and HTR_{3E}) [162]. 5-HT₃R is found in both the CNS and peripheral nervous system. It is mainly located in the dorsal vagal complex of the brainstem, regions involved in the vomiting reflex, and in low levels in many forebrain areas, including the hippocampus, amygdala, nucleus accumbens, putamen, and caudate nucleus [163,164]. The 5-HT₃Rs are involved in many physiological processes and neuropsychiatric disorders such as schizophrenia, depression, bulimia, anxiety, pain, autism, bipolarity, and learning and memory disorders [165–167]. A class of high-affinity 5-HT₃R antagonists named “setrons” has been established as antiemetic drugs, resulting from chemo- and radiotherapy and general anesthesia [166,168]. Moreover, many selective agonists and antagonists are described, thereby facilitating the development of promising radioprobes. However, to date, no radiotracers have demonstrated useful applications in humans.

4.1. Tropane Series: MDL7222 Derivatives

First, several antagonists labeled with carbon-11 (Figure 10) were designed as potential PET radiotracers [169]. Thus, MDL7222, a selective 5-HT₃R antagonist, was radiolabeled with carbon-11 and further evaluated in rats and baboons. Despite [¹¹C]MDL7222 quickly crossing the BBB in preliminary studies, a heterogeneous diffusion in the brain was observed, probably due to its high lipophilicity and low specificity [170]. A closely related analogue of MDL7222 was radiolabeled by Ishiwata et al. for PET imaging: [¹¹C]KF17643. Nevertheless, [¹¹C]KF17643 displayed nonspecific binding [171].

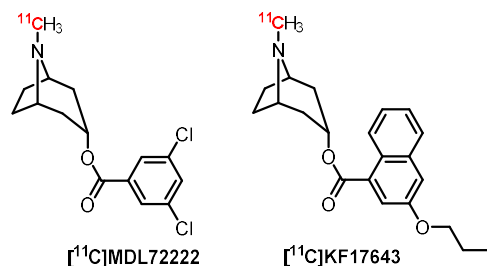


Figure 10. [¹¹C]MDL7222 and [¹¹C]KF17643.

4.2. Pyrrolo[1,2-*a*]Pyrazine Series: S21007 Derivatives

S21007 is a 5-HT₃R partial agonist (Figure 11) which has also been evaluated as a potential PET ligand in rats and baboons because of its strong affinity ($K_i = 1.4$ nM), selectivity, and high brain uptake. However, [¹¹C]S21007 was unable to detect the 5-HT₃R via a specific binding signal, as [¹¹C]S21007 did not displace unlabeled S21007 in the brain areas with 5-HT₃ receptors, suggesting a lack of specific binding [172]. This series was further investigated with the synthesis of [¹⁸F]MR18445, another pyrrolo[1,2-*a*]pyrazine derivative radiolabeled with fluorine-18. Autoradiography and PET studies showed rapid uptake in both rat and baboon brains, but no specific binding in 5-HT₃R-rich brain regions was detected with [¹⁸F]MR18445, probably due to its high lipophilicity [173]. All these compounds were not successfully used for selective binding to 5-HT₃R in vivo.

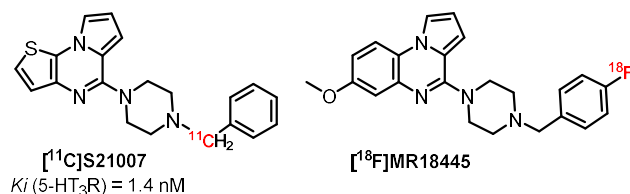


Figure 11. [¹¹C]MDL7222 and [¹¹C]KF17643.

4.3. (*S*)-Quinuclidin-3-Amine Series: Zacopride Derivatives

Zacopride, a 3-aminoquinuclidinyl derivative, is a well-known mixed 5-HT₃R antagonist and 5-HT₄R agonist [174]. A series of Zacopride derivatives was developed by Ebert et al. (Figure 12) [175,176]. [¹²⁵I]DAIZAC exhibited high affinity ($K_i = 0.19$ nM) and enhanced selectivity for the 5-HT₃R. Autoradiographic studies also demonstrated the usefulness of this ligand, but to date, despite these promising characteristics, the ligand has not yet been further developed for SPECT imaging [176]. Highly selective and potent antagonists, such as granisetron and palonosetron, belong to a family of drugs (the “setrons”) that is well established for clinical use, especially because of their effects on Chemotherapy-Induced Nausea and Vomiting (CINV). Among them, [¹⁸F]Fesetron was designed based on the model of [¹²⁵I]MIZAC, a potent and selective radioligand of 5-HT₃R [175]. [¹⁸F]Fesetron was shown to display a binding profile to rat brain regions known to contain a high density of 5-HT₃R. However, the in vivo rat brain uptake of [¹⁸F]Fesetron was low, and a significant amount of activity was unable to cross the BBB. This lack of brain permeability, which could be explained by low lipophilicity, limits the usefulness of [¹⁸F]Fesetron as a PET radiotracer in this animal model [177].

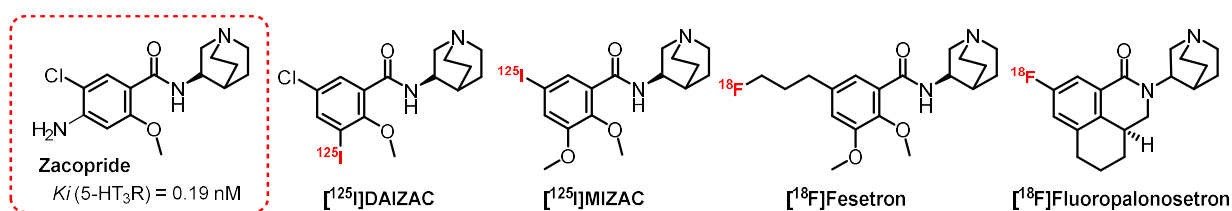


Figure 12. Zacopride derivatives as 5-HT₃R radiotracers.

The second “setron” drug developed in 2016 was a fluorine analogue of the clinically used **palonosetron** which also contained the 3-aminoquinuclidinyl moiety. In vitro autoradiography showed specific labeling in rodent brain slices, but in vivo PET studies in rats with $[^{18}\text{F}]$ Fluoropalonosetron gave low and homogeneous radiotracer signals [178]. This could be related to the low expression of 5-HT₃R in the brain combined with the low lipophilicity of the radioligand and could explain why $[^{18}\text{F}]$ Fluoropalonosetron is not suitable for in vivo PET imaging of 5-HT₃ receptors.

4.4. Miscellaneous Derivatives as 5-HT₃R Radiotracers

In 1995, $[^{11}\text{C}]$ YM060 was labeled with carbon-11 through *N*-methylation of indole and revealed poor brain uptake in mice (Figure 13) [179]. *N*-methylquipazine (NMQ, (2-[1-(4-methyl)-piperazinyl]quinoline) is an agonist with good affinity and selectivity for 5-HT₃R ($\text{IC}_{50} = 4.7 \text{ nM}$). Its biodistribution has been evaluated in vivo in rats and nonhuman primates using PET imaging [180]. The imaging results indicate that its uptake was observed in structures known to contain 5-HT₃R, although the radiotracer also interacted with non-5-HT₃R sites. In 2008, Gao et al. designed a new carbon-11-labeled benzisoxazole derivative for PET imaging of 5-HT₃ receptors [181]. These partial agonists exhibited high binding affinity and could be promising for future in vivo biological evaluation.

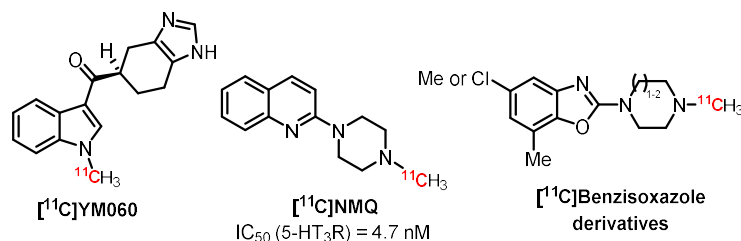


Figure 13. Miscellaneous derivatives as 5-HT₃R radiotracers.

5. 5-HT₄ Receptors

5-HT₄R receptors were first described by Dumuis et al. in 1988 [182]. They are GPCRs positively coupled to adenylyl cyclase and induce cyclic adenosine monophosphate (cAMP) production [183]. 5-HT₄R are located in the peripheral nervous system (PNS), mainly being found in the heart, gastrointestinal tract, and enteric nervous system [184], as well as in the CNS, where they are highly expressed in different brain regions like the hippocampus, amygdala, and cerebral cortex, suggesting the involvement of the receptor in brain physiological functions [185] such as learning and memory [186–188], eating disorders [189], and mood behavior [190]. In order to further specify in vivo the 5-HT₄R physiological or pathological role, selective radioligands able to target 5-HT₄R have been developed for SPECT and PET applications.

5.1. Benzodioxane Series: SB207710 Derivatives

Kaumann et al. [191] reported on **SB207710**, a selective high-affinity benzodioxane antagonist for 5-HT₄R (Figure 14). Autoradiographic experiments on humans [192] and on rat brains with its radiolabeled analogue, $[^{125}\text{I}]$ SB207710, confirmed its potency and selectivity [193] and led Pike et al. to characterize its efficacy in vivo as a SPECT radioligand [194]. A good brain uptake in rats was observed for $[^{125}\text{I}]$ SB207710, and the study

revealed specific radiolabeling of regions rich in 5-HT₄R (striatum, frontal, and temporal cortex). [¹²³I]SB207710 was then examined by SPECT imaging in nonhuman primates. The radiotracer readily accumulated in 5-HT₄R-rich areas. The specificity of this radiolabeling was underlined through pretreatment with a selective 5-HT₄R antagonist, SB204070, which reduced the radioactivity in all brain regions. Even if [¹²³I]SB207710 entered the brain, its signal quickly disappeared in SPECT, thus proving rapid clearance. Since then, no further investigations for SPECT studies in humans have been reported. Nevertheless, the use of [¹²³I]SB207710 in SPECT imaging provided the first demonstration of 5-HT₄R imaging in primate brains in vivo [194]. The antagonist SB207145 (K_i = 0.3 nM), structurally related to SB207710, was radiolabeled with carbon-11 by Gee et al. in 2008 [195], and its potential as a PET radioligand was evaluated for 5-HT₄R imaging. The preliminary data in a few healthy subjects indicated that [¹¹C]SB207145 was distributed in the brain according to the known 5-HT₄R distribution. It was then successfully used for in vivo studies in animals to evaluate the metabolism and binding kinetics in a minipig brain [196] and human subjects [195,197–199]. To date, [¹¹C]SB207145 remains the only 5-HT₄R radiotracer that has been evaluated in human studies [200–203]. However, the short half-life of the radioisotope (t_{1/2} = 20.4 min) significantly restricted its use for more advanced clinical trials.

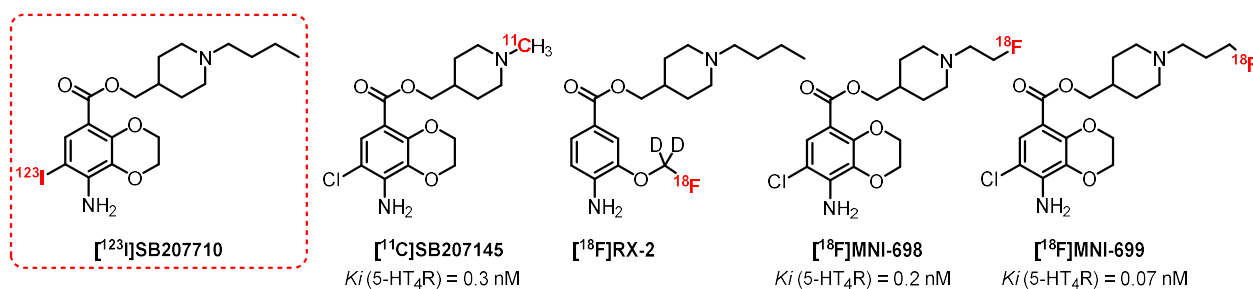


Figure 14. SB207710 derivatives as 5-HT₄R radioligands.

In 2010, Xu et al. reported the first fluorine-18-radiolabeled 5-HT₄R radiotracer [¹⁸F]RX-2 [204] in which deuterium was incorporated to provide greater in vivo resistance to defluorination [205]. PET studies with [¹⁸F]RX-2 were performed on monkeys in 2014 and showed a high brain uptake, quantifiable distribution, and insignificant radiometabolite detection [206]. The mild but stable 5-HT₄R-specific signal validated the potential use of [¹⁸F]RX-2 for mapping 5-HT₄R, but no transposition to human PET studies were published to date.

More recently, [¹⁸F]MNI-698 and [¹⁸F]MNI-699, two fluorinated analogues of SB207145 containing fluorine-18 in the terminal piperidine alkyl chain, were described [207]. These radioligands have been shown to be affine with 5-HT₄R (K_i = 0.2 nM and 0.07 nM, respectively). In vivo PET studies on adult rhesus monkeys established that both radioligands displayed suitable brain penetration and brain distribution consistent with the known 5HT₄R densities. The whole-body biodistribution and dosimetry of [¹⁸F]MNI-698 were then investigated and supported that this radioligand could be used for investigation in humans [208,209]. All these ligands belong to the same family of compounds and contain an ester function which can generate short metabolic stability. Other chemical series deprived of ester functions have been explored recently, such as azaphenanthrene derivatives [210].

5.2. 5-HT₅ Receptors

Two subtypes of 5-HT₅R are known—5-HT_{5A}R and 5-HT_{5B}R—but only 5-HT_{5A}R is expressed in the human brain. Because of the lack of a selective and potent ligand described for this receptor to date, no potent radiotracer or even radioligand has been described.

5.3. 5-HT₆ Receptors

The 5-HT₆ receptor is one of the most recently identified members of the 5-HT receptor family. First cloned in a rat, the 5-HT₆R gene encodes a 438-aminoacid protein [211,212]

which is well-conserved in humans [213], and 5-HT₆R is a G_{αs}-coupled receptor (GPCR) that is almost exclusively expressed in the CNS and is abundant in the brain regions involved in cognitive functions, such as the prefrontal cortex, hippocampus, striatum, and nucleus accubens [214–216]. Similar distribution patterns between rats, nonhuman primates, and humans have been established [217,218]. In addition to the adenylyl cyclase signaling pathway [219], 5-HT₆R has been linked to cellular signaling cascades involved in cognitive processes and neurogenesis, such as the mammalian target of the rapamycin (mTOR) pathway [220]. Thus, 5-HT₆R has emerged as a promising target for cognitive enhancement in neurodegenerative or in psychiatric diseases and for antiobesity drugs [187,221–225].

5.4. Benzene Sulfonamide Derivatives: SB258585 Derivatives

Selective radioligands for in vitro autoradiographic studies are available, such as [¹²⁵I]SB258585 (K_i = 1 nM), but their development as in vivo imaging tools was restricted due to poor brain uptake (Figure 15) [226]. Tang et al. [227] developed a series of 4-(2-aminoethoxy)-*N*-(phenylsulfonyl)indoles based on the selective 5-HT₆R antagonist SB271046 [228]. This study led to the design of [¹⁸F]12ST05, presenting good affinity for 5-HT₆R (K_i = 4 nM). Ex vivo autoradiographic studies in rat brain slices established high labeling in regions known to contain 5-HT₆R. In vivo studies in cats failed to show the specific binding of [¹⁸F]12ST05 to 5-HT₆R in the cerebral regions, and hence, further investigations were not undertaken for [¹⁸F]12ST05 as a PET radioligand.

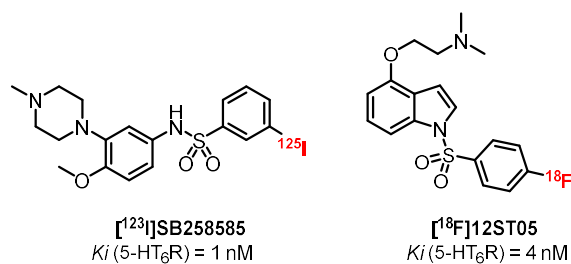


Figure 15. [¹²⁵I]SB258585 and [¹⁸F]12ST05.

5.5. 5-(Piperazin-1-yl)Quinolone Derivatives: GSK215083 Derivatives

In 2012, Parker et al. published an interesting study presenting the in vivo evaluation of [¹¹C]GSK215083 (K_i (5-HT₆R) = 0.16 nM and K_i (5-HT_{2A}R) = 0.79 nM) in pigs, nonhuman primates, and humans (4 healthy volunteers) (Figure 16). They revealed a significant binding of the radiotracer on the striatum and frontal cortex in correlation with the autoradiograms carried out previously on cats. Two additional studies confirmed the interest shown in this radiotracer and revealed a decrease in 5-HT₆R with age. Moreover, its mixed action (5-HT₆R and 5-HT_{2A}R) was effective in the study of neuropsychiatric diseases such as AD and schizophrenia [229,230].

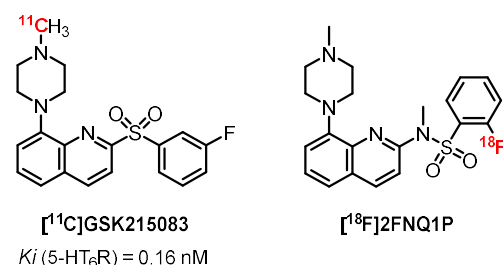


Figure 16. [¹¹C]GSK215083 and [¹⁸F]2FNQ1P.

In 2014, Rosse designed radiolabeled quinolone derivatives structurally related to GSK215083 as 5-HT₆R PET ligands [231]. In 2014, Colomb et al. developed a new chemical series of compounds inspired by GSK215083 in order to maintain a strong affinity toward 5-HT₆R and to optimize its specificity. The bioisosteric replacement of the sulfonyl part

by sulfonamide led to a new ligand, **2FNQ1P**, with high affinity and selectivity for 5-HT₆ receptors [232]. The distribution of [¹⁸F]**2FNQ1P** in 5-HT₆R-dense regions (i.e., the cortex and striatum) was assessed by semiquantitative autoradiography in rat brains. Furthermore, the addition of **SB2258585** (a specific 5-HT₆R antagonist) displaced the binding of [¹⁸F]**2FNQ1P** in a concentration-dependent manner, confirming its excellent specificity for 5-HT₆R [233]. The cerebral distribution of [¹⁸F]**2FNQ1P** was then studied in vivo in various animal models, from rodents to nonhuman primates. The in vivo evaluation in rats using microPET exhibited reduced brain uptake of [¹⁸F]**2FNQ1P**. By contrast, in vivo PET imaging with [¹⁸F]**2FNQ1P** in feline and primate models showed high uptake and distribution in the striatal regions particularly rich in 5-HT₆R, suggesting that [¹⁸F]**2FNQ1P** could be a suitable 5-HT₆R PET tracer for quantification of the brain 5-HT₆R in primates. A recent in vitro study demonstrates a decrease in the caudate nucleus 5-HT₆R density with [¹⁸F]**2FNQ1P** in human brain tissue from patients with different stages of Alzheimer's disease [233]. Future in vivo exploration should be carried out to establish the relevance of [¹⁸F]**2FNQ1P** to confirm an early decline in 5-HT₆R expression during the progression of the disease.

5.6. 5-HT₇ Receptors

In 1993, 5-HT₇R was independently cloned and discovered by several scientific teams in different species including mice, rats, and humans [212,234,235]. In human, the protein is encoded by the HTR₇ gene located on the long arm of chromosome 10 (10q23.31), comprising 3 introns involved in alternative splicing phenomena. Splicing of intron 2 and 3 is responsible for the existence of 3 distinct isoforms—5-HT_{7A}, 5-HT_{7B} and 5-HT_{7D}—showing no pharmacological difference. The 5-HT₇R receptors are GPCRs (coupled to a G_s protein) that will diffuse nerve impulses through the activation of adenylate cyclase and the production of the secondary messenger: cAMP. In human CNS, 5-HT₇R are localized mainly in the anterior thalamus and in the dentate gyrus. The hypothalamus, anterior cingulate gyrus, hippocampus, and amygdala constitute other human brain regions containing substantial amounts of 5-HT₇R [236].

The 5-HT₇R receptors are involved in the phenomena of learning and memorization as well as in the regulation of temperature and circadian rhythm. In addition, they play a decisive role in the development of certain pathologies such as schizophrenia, migraines, and Alzheimer's disease [237]. Among the 14 known serotonergic receptors, 5-HT₇R is the most recently discovered and explored one. Its implication in the genesis of certain pathologies such as depression, anxiety, and epilepsy make it a target of choice for the development of curative and diagnostic tools [238]. The development of radiotracers allowing their visualization and quantification has become a major axis of research in medicinal chemistry.

5.7. Oxindoles Series: **DR4004** Derivatives

DR4004 (Figure 17) is a selective and potent antagonist of 5-HT₇ receptors (K_i = 2 nM) discovered in 1999 by Kikuchi et al. [239]. In 2002, the same group proposed a N-methylated analogue, **DR4446**, while maintaining the affinity and selectivity toward 5-HT₇R (K_i = 9.7 nM) [240]. Radiolabeling through [¹¹C]N-methylation, performed by Zhang et al., allowed obtaining the first imaging study with the 5-HT₇R antagonist radiotracer [241]. [¹¹C]**DR4446** showed good diffusion through the BBB in vivo (rhesus monkeys), with a high brain uptake especially in the 5-HT₇R-rich region: the thalamus. However, this study did not allow a favorable transfer to human experiments due to the impossibility to observe a blocking effect in a self-block study, probably due to off-target labeling of other CNS receptors.

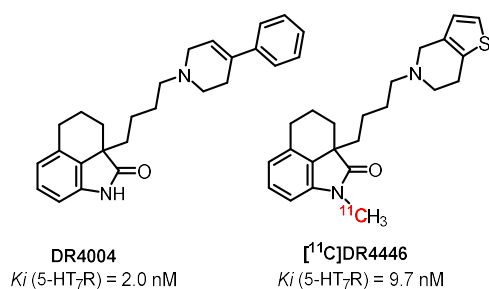


Figure 17. DR4004 and [¹¹C]DR4446.

CIMBI-717 and **CIMBI-712** (Figure 18) are potent 5-HT₇R antagonists (K_i = 2.6 nM and 1.1 nM, respectively) discovered in 2012 by Herth et al. [242]. In 2014, both of these ligands, after radiolabeling with carbon-11, were evaluated in vivo (pigs) as 5-HT₇R tracers by Knudsen et al. A high brain uptake was observed for both [¹¹C]CIMBI-712 and [¹¹C]CIMBI-717. Their specificity was demonstrated through blocking studies after the injection of **SB-269970**, a 5-HT₇R antagonist [243]. For [¹¹C]CIMBI-717, a radiolabeling of the thalamus, the striatum, the hippocampus, and the cortex in correlation with the in vitro autoradiographs determined beforehand with [³H]SB-269970 was also observed. Despite these encouraging results, no recent publication mentions its use in humans. However, in the same series, Herth et al. proposed in 2019 a closely related analogue of **CIMBI-717** and **CIMBI-712**: **ENL10** [244] while overcoming the problematic short half-life of carbon-11 through fluorine-18 labeling. [¹⁸F]ENL10, a potent and selective 5-HT₇R antagonist (K_i = 5.6 nM) demonstrated in vivo (rats) a very modest passage across the BBB due to the efflux phenomena induced by a significant expression of the transporter P-gp in rats. In the presence of **Elacridar** (P-gp inhibitor) and **SB-269970**, the study revealed specific radiolabeling of 5-HT₇R-rich areas, making this compound a serious candidate for possible application of these tests to other species (e.g., pigs or nonhuman primates). This suggestion is motivated mainly by recent observations, indicating a lower expression of P-gp in non-rodents and making the use of **Elacridar** probably obsolete for these species.

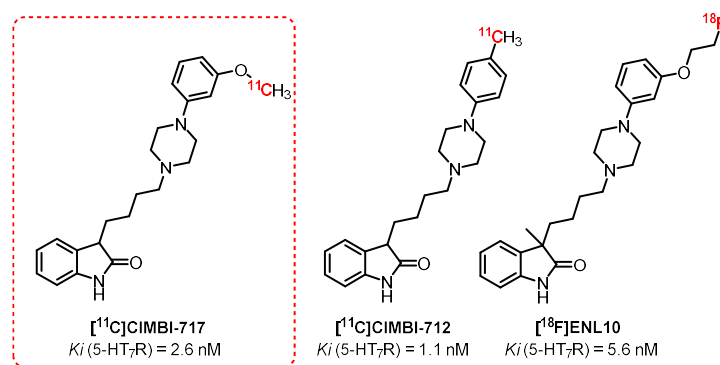


Figure 18. [¹¹C]CIMBI-717, [¹¹C]CIMBI-712, and [¹⁸F]ENL10.

5.8. N-Sulfonyrrolidine Series: **SB-269970** Derivatives

In 2011, Zimmer et al. developed a new chemical series of compounds inspired by the N-sulfonyrrolidine structure from a 5-HT₇R antagonist: **SB-269970** [243] (Figure 19). Among this first generation of radioligands, [¹⁸F]2FP3 proved to be the most promising. Indeed, [¹⁸F]4FP3, [¹⁸F]4FPMP, and [¹⁸F]2FPMP exhibited nonspecific radiolabeling in the presence of a reference antagonist (**SB269970**) in rats (ex vivo and in vivo). [¹⁸F]2FP3 is an affine and selective 5-HT₇R antagonist (K_D = 8.4 nM) which was previously tested in rats (ex vivo autoradiography) and in cats (in vivo) [243]. The first results were very promising, since selective radiolabeling of the hippocampus, cingulate cortex, and thalamus was observed. In addition, 95% of the collected signal was assigned to [¹⁸F]2FP3 and not from a radiometabolite. In 2019, a complementary study on pigs and nonhuman primates was carried out [245]. Partial

specificity of [^{18}F]2FP3 for the cerebellum (in monkeys) was revealed, clearly reflecting the difficulties in translating the results from one species to another. In addition, [^{18}F]2FP3 was found to be rapidly metabolized in pigs (50% metabolized 10 min after injection) and more moderately in primates (50% in 60 min). This study did not provide a favorable conclusion for its use in humans. This first approach was further completed by the evaluation of a second generation of radioligands, where additional carbon between the pyrrole and the piperidine or the piperazine was inserted [246]. These radioligands were optimized in terms of radiolabeling specificity for 5-HT $_7$ R, but additional pharmacomodulations will be necessary in order to improve the biodistribution and passage of the BBB.

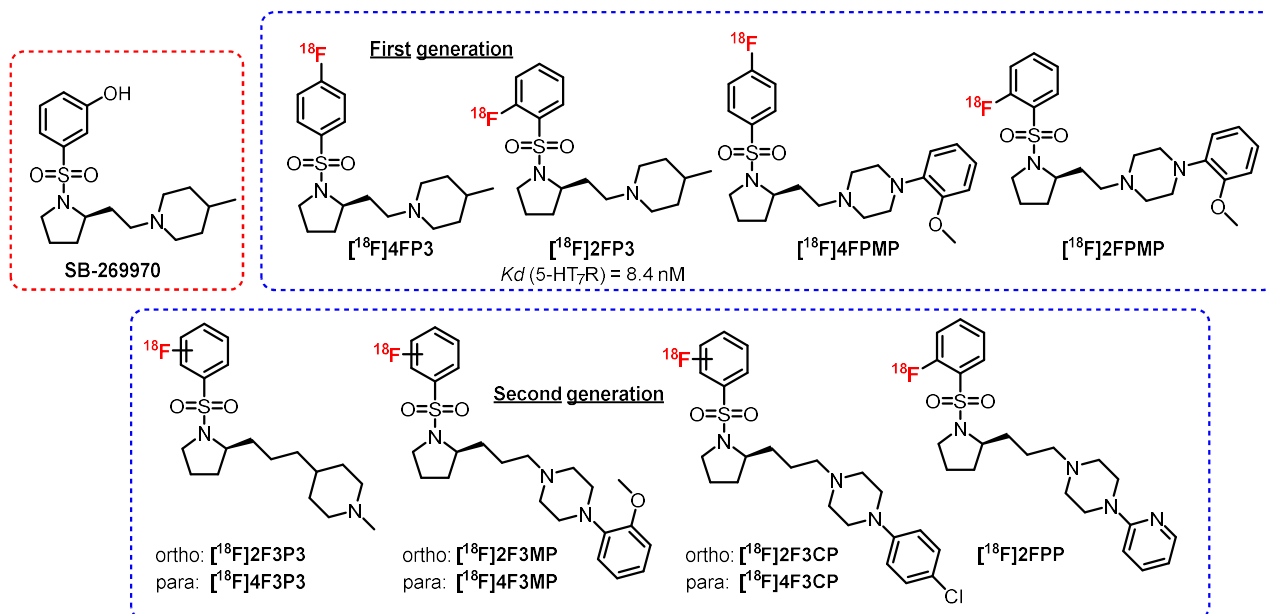


Figure 19. Radiolabeled SB-269970 derivatives.

Still in the *N*-sulfoyrrolidine series, two radioligands were synthesized and tested by Herth et al.: [^{18}F]ENL30 [247] and [^{11}C]CIMBI-701 [248] (Figure 20). These compounds exhibited mixed labeling of the 5-HT $_7$ R and σ -receptors and added to a moderate signal in the brain (probably linked to the mechanisms of efflux (P-gp substrate)), thus limiting their use in humans.

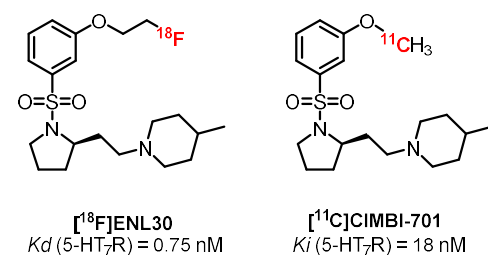


Figure 20. [^{18}F]ENL30 and [^{11}C]CIMBI-701.

6. Serotonin Transporter

A serotonin transporter (SERT) is not a serotonergic receptor per se. However, it is heavily involved in the regulation of 5-HT. The development of radioligands that are affine and selective for these transporters constitutes an interesting axis of development in clinical research.

SERTs are proteins consisting of 12 transmembrane helices whose main role is to regulate the concentration of 5-HT in the inter-synaptic space. The reuptake of 5-HT results from a complex catalytic reaction incorporating both symporter and antiporter transport involving three distinct ions: Na $^+$, Cl $^-$, and K $^+$. This transport takes place in four

successive stages [249]. (1) A conformation change of SERTs, resulting in exposure of the binding sites to the intracellular medium, takes place due to the extracellular stoichiometric binding of 5-HT, Na^+ ions, and Cl^- ions. (2) The 5-HT, Na^+ , and Cl^- ions are released in the intracellular medium. (3) Intracellular binding of K^+ ions leads to a conformational modification of the SERT, which regains its original conformation. (4) K^+ ions are released into the extracellular medium. SERT expression is tightly regulated by the concentration of 5-HT in the intersynaptic space. In the presence of an increased amount of 5-HT, there is a decrease in the internalization of the transporter, resulting in an increase in its density on the presynaptic membrane. On the contrary, SERTs are downregulated in the presence of a small amount of 5-HT. In this context, a large panel of compounds has been developed with the main objective of blocking the reuptake of serotonin by inhibiting these transporters. The serotonin reuptake inhibitors (SSRI drug class), including **fluoxetine** (Prozac[®]), **sertraline** (Zoloft[®]), and **citalopram** (Celexa[®]), are mainly prescribed to treat major depressive disorders as well as obsessive-compulsive disorders.

During the last three decades, the development of new potent and selective radiotracers of SERTs has become a major axis of development in clinical and preclinical research. Indeed, their expression fluctuations, dependent on the endogenous 5-HT level, are an interesting marker in various pathologies such as depression, bipolarity, and eating disorders. In addition, these studies could allow assessing the impact of regular administration of SSRIs on the serotonergic system, thus allowing a better understanding of their mode of action.

6.1. Isoquinoline Series: McN5652 Derivatives

McN5652 is the first SERT ligand evaluated as a radiotracer. The two evaluated diastereomers of **McN5652**—(+)-[¹¹C]McN5652 and (−)-[¹¹C]McN5655—present significant differences in terms of affinity toward SERTs at K_i of 0.4 nM and 58.4 nM, respectively (Figure 21) [250]. Preliminary studies carried out on mice allowed appreciating the difference in radiolabeling between the two enantiomers, with clearly more interesting results for the (+) enantiomer. In 1995, a study on baboon brains revealed significant absorption of the radiotracer in the midbrain, hypothalamus, thalamus, and striatum. This distribution correlates with the results obtained for brain section autoradiography with [³H]paroxetine [251]. In 2000, Parsey et al. carried out a study on six healthy male volunteers and confirmed the interest in (+)-[¹¹C]McN5652 as a radiotracer, allowing the quantification of SERTs in the limbic, striatal, and thalamic regions. However, the study revealed major limitations to its use, in particular with the presence of a non-selective labeling in the neocortex area and a specific or nonspecific binding ratio (satisfactory after 115 min) not being in adequacy with the use of carbon-11 ($t_{1/2} = 20.4$ min) [251,252]. Nevertheless, (+)-[¹¹C]McN5652 has been used on numerous occasions to assess SERT biodistribution in various pathological conditions such as depression and obsessive-compulsive and mood disorders [253–255].

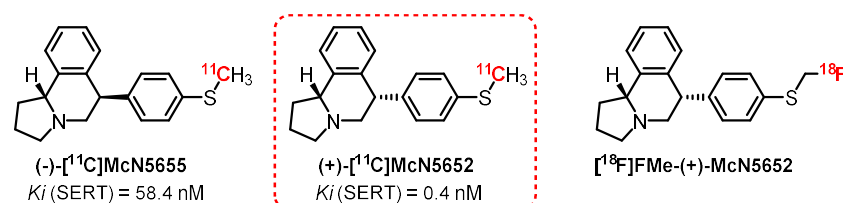


Figure 21. (−)-[¹¹C]McN5655, (+)-[¹¹C]McN5652, and [¹⁸F]FMe-(+)-McN5652.

In order to improve its properties, a methylfluorinated analogue of (+)-[¹¹C]McN5652 was synthesized: [¹⁸F]FMe-(+)-McN5652. Preliminary evaluations in a rat (ex vivo) revealed intense and specific radiolabeling (competitive tests in the presence of **fluoxetine**, **nisoxetine**, and **GBR12909**) of the amygdala, hypothalamus, raphe nuclei, thalamus, and locus coeruleus compared with the cerebellum (nonspecific binding) [256]. A complementary study on a pig (in vivo) allowed concluding favorably regarding the use of this radiotracer as an alternative to (+)-[¹¹C]McN5652 [257]. However, as its affinity for SERTs

was found to be more moderate ($K_i = 2.3$ nM) than (+)-[^{11}C]McN5652, its binding parameters were estimated to be less reliable [258]. Despite promising results, no publication to date mentions the use of this tracer in humans.

6.2. Diarylthioether Series: [^{123}I]IDAM Derivatives

[^{11}C]DASB is probably the most used radiotracer to explore the distribution of SERTs at the CNS level. This radiotracer was synthesized in the early 2000s as an analogue of [^{123}I]IDAM, the first radiotracer to be synthesized and evaluated in the diarylthioether series [259], but quickly abandoned in favor of its analogues (Figure 22). [^{11}C]DASB is very affine and selective toward SERT ($K_i = 1.1$ nM) [260]. The first human study (nine healthy volunteers) was performed by Wilson et al. and allowed observing an intense assimilation of [^{11}C]DASB in the midbrain, the thalamus, the hypothalamus, and the striatum [261]. The specificity was confirmed by a prior oral intake of **citalopram**, decreasing the radioactivity of these cerebral areas to equivalent values to those obtained in the cerebellum (nonspecific labeling). In addition, comparative tests with (+)-[^{11}C]McN5652 indicated a much more interesting specific or nonspecific binding ratio for [^{11}C]DASB [262,263]. Between 2002 and 2004, several studies were carried out on animals (rats, cats, and baboons), allowing for evaluating the general distribution of [^{11}C]DASB, and concluded favorably regarding its use to determine the influence of SERTs in various psychiatric and neurological disorders [264–266]. Thus, [^{11}C]DASB was used on numerous occasions in patients presenting various pathologies such as depression, schizophrenia, obsessive-compulsive disorder, Parkinson's disease, alcoholism, and bipolarity [267–273]. To date, [^{11}C]DASB constitutes a reference in the quantification and characterization of SERTs at the cerebral level.

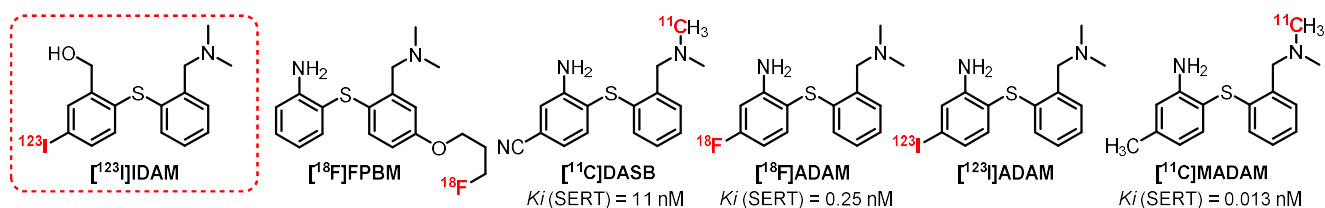


Figure 22. [^{123}I]IDAM derivatives.

In 2001, [^{11}C]MADAM, a methylated analogue of [^{11}C]DASB exhibiting a very strong affinity and specificity for SERTs ($K_i = 0.013$ nM), was described [274]. The first baboon studies indicated consistent radiolabeling of SERT-rich areas of the brain [275]. In 2005, imaging studies on healthy humans (nine volunteers) confirmed the previous observations, with a major absorption of [^{11}C]MADAM in the raphe nuclei, the putamen, the hippocampus, and more moderately in the frontal and cingulate cortex [276,277]. Finally, [^{11}C]MADAM has been used more recently to study the density of brain SERTs in people with eating disorders and gambling addiction [278].

In 2000, the discovery of [^{123}I]ADAM offered the possibility to perform human imaging exploration of SERTs using SPECT imaging [279]. [^{123}I]ADAM was first tested in mice, rats, rabbits, and nonhuman primates and allowed observing intense and specific radiolabeling of the midbrain [280–283]. In 2003 and 2004, two preliminary studies evaluated the biodistribution of [^{123}I]ADAM in humans (7 and 11 healthy volunteers) and allowed observing the specific labeling of the midbrain [284,285]. These results were confirmed by several additional studies which demonstrated a specific and reproducible labeling in the midbrain, the thalamus, and the striatum, particularly in people with an SERT polymorphism [286–288]. Finally, a double-blind trial was carried out (12 healthy men volunteers) in order to visualize the differences in radiolabeling with an administration of **paroxetine** versus a placebo [289]. [^{123}I]ADAM allows exploration of the variations of SERTs, particularly in the presence of various pathologies such as depression, Parkinson's disease, and eating disorders [289–294]. In 2003, [^{18}F]ADAM, a fluorinated analogue of [^{123}I]ADAM with good affinity and selectivity toward SERTs ($K_i = 4.8$ nM), was described [295,296].

[¹⁸F]ADAM was first tested on monkeys and allowed observing an intense radiolabeling of the striatum, thalamus, and midbrain. The selectivity was confirmed in the presence of increasing doses of **fluoxetine**, allowing visualization of the displacement of the radioligand [297]. [¹⁸F]ADAM was then further studied in humans with major depressive disorders and allowed the observation of a significant decrease in radiolabeling in the midbrain and the striatum in those who had attempted suicide recently. These contradictory results are probably linked to a recent administration of an SSRI, which can induce a decrease in the central SERTs [298,299]. The results obtained with [¹⁸F]ADAM are very encouraging and place it as a future radiotracer for exploring and quantifying the central SERTs using PET. A closely related analogue of [¹⁸F]ADAM was described in 2009 by Wang et al., exhibiting high affinity and selectivity toward SERTs ($K_i = 0.25$ nM): [¹⁸F]FPBM [300]. The first studies in animals (rats) revealed specific labeling of the midbrain, cortex, striatum, and thalamus. [¹⁸F]FPBM evaluation was recently supplemented by tests on monkeys, which confirmed the interest of this compound as a new PET tracer of central SERTs [301].

6.3. Tropane Series: β -[¹²³I]CIT Derivatives

β -[¹²³I]CIT (Figure 23) is one of the first radiotracers to be synthesized and tested for SPECT imaging in humans [302–304]. β -[¹²³I]CIT has a mixed affinity for serotonergic and dopaminergic transporters, which is not a major drawback since there is a different distribution within the brain for these two targets. However, its demethylated counterpart **Nor- β -[¹²³I]CIT** has an affinity 10 times higher for SERTs and has allowed the observation in humans of a very strong accumulation of radioactivity in the midbrain and the striatum [305]. Since then, β -[¹²³I]CIT and **Nor- β -[¹²³I]CIT** have been used repeatedly to determine the evolution of the SERT density in the presence of pathologies such as depression and autism and in people with obsessive-compulsive disorders [306–308]. Recently, compounds exhibiting similar structures have been synthesized, particularly [¹¹C]NS9762 and [¹¹C]NS6417, which could provide promising alternatives in the coming years [309].

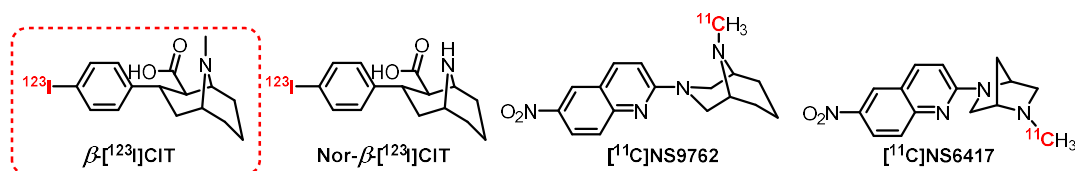


Figure 23. SERT tracer in the tropane series.

7. Conclusions

As described in this review, several potent and selective radiotracers for 5-HT_{1A}R and SERTs have been developed in recent decades. Three radiotracers with good affinity to 5-HT_{1A}R are commonly used in clinical trials: [¹¹C]WAY100635, [¹⁸F]MPPF, and [¹⁸F]FCWAY. The characterization and distribution of 5-HT_{2A}R is frequently performed by [¹²³I]5-I-R91150 in SPECT imaging, with that of [¹⁸F]Setoperone, [¹⁸F]Altanserine, and [¹¹C]MDL100907 performed in PET imaging. Moreover, the utilization of [¹²³I]ADAM, [¹¹C]DASB, and [¹¹C]MADAM has improved the exploration of SERTs. These radiotracers have greatly contributed to facilitating the characterization, localization, and biological implication of the brain serotonin system in normal and pathological conditions. Indeed, in vivo PET and SPECT studies carried out on humans and animals allowed the observation of brain areas rich in 5-HT_{1A}R by precise detection of radioactive emission. The signal specificities were confirmed via radiotracer displacement methods in the presence of reference ligands. Furthermore, these studies have shown the importance of multiparametric approaches to designing a new radiotracer, since a lack of selectivity, insufficient passage through the BBB, and fast metabolism can significantly decrease its effectiveness. In addition, these investigations also revealed the difficult transposition of the results from one species to another due to the interspecies variation of 5-HT_{1A}R distribution, which could lead to misinterpretation. Overall, despite interesting results during clinical trials, none of these radiotracers are approved as diagnostic tools for neuropsychiatric

disorders in clinics. New radiolabel-capable, potent, and selective ligands of the 5-HT_{1A} receptors allowing exploration of brain functions are thus still needed to fully understand the role of these receptors in either healthy or sick individuals.

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References

1. Švob Štrac, D.; Pivac, N.; Mück-Šeler, D. The serotonergic system and cognitive function. *Transl. Neurosci.* **2016**, *7*, 35–49. [[CrossRef](#)] [[PubMed](#)]
2. Nichols, D.E.; Nichols, C.D. Serotonin receptors. *Chem. Rev.* **2008**, *108*, 1614–1641. [[CrossRef](#)] [[PubMed](#)]
3. Hoyer, D. Serotonin receptors nomenclature. In *The Serotonin System*; Elsevier: Amsterdam, The Netherlands, 2019; pp. 63–93; ISBN 9780128133231.
4. Homberg, J.R.; Schubert, D.; Gaspar, P. New perspectives on the neurodevelopmental effects of SSRIs. *Trends Pharmacol. Sci.* **2010**, *31*, 60–65. [[CrossRef](#)] [[PubMed](#)]
5. Humphrey, P.P.A.; Hartig, P.; Hoyer, D. A proposed new nomenclature for 5-HT receptors. *Trends Pharmacol. Sci.* **1993**, *14*, 233–236. [[CrossRef](#)]
6. Kobilka, B.K.; Frielle, T.; Collins, S.; Yang-Feng, T.; Kobilka, T.S.; Francke, U.; Lefkowitz, R.J.; Caron, M.G. An intronless gene encoding a potential member of the family of receptors coupled to guanine nucleotide regulatory proteins. *Nature* **1987**, *329*, 75–79. [[CrossRef](#)] [[PubMed](#)]
7. Fargin, A.; Raymond, J.R.; Lohse, M.J.; Kobilka, B.K.; Caron, M.G.; Lefkowitz, R.J. The genomic clone G-21 which resembles a β -adrenergic receptor sequence encodes the 5-HT_{1A} receptor. *Nature* **1988**, *335*, 358–360. [[CrossRef](#)]
8. Zhou, F.C.; Patel, T.D.; Swartz, D.; Xu, Y.; Kelley, M.R. Production and characterization of an anti-serotonin 1A receptor antibody which detects functional 5-HT_{1A} binding sites. *Mol. Brain Res.* **1999**, *69*, 186–201. [[CrossRef](#)]
9. Pompeiano, M.; Palacios, J.M.; Mengod, G. Distribution and cellular localization of mRNA coding for 5-HT_{1A} receptor in the rat brain: Correlation with receptor binding. *J. Neurosci.* **1992**, *12*, 440–453. [[CrossRef](#)]
10. Richardson-Jones, J.W.; Craige, C.P.; Guiard, B.P.; Stephen, A.; Metzger, K.L.; Kung, H.F.; Gardier, A.M.; Dranovsky, A.; David, D.J.; Beck, S.G.; et al. 5-HT_{1A} Autoreceptor Levels Determine Vulnerability to Stress and Response to Antidepressants. *Neuron* **2010**, *65*, 40–52. [[CrossRef](#)]
11. Sprouse, J.S.; Aghajanian, G.K. Electrophysiological responses of serotonergic dorsal raphe neurons to 5-HT_{1A} and 5-HT_{1B} agonists. *Synapse* **1987**, *1*, 3–9. [[CrossRef](#)]
12. Riad, M.; Garcia, S.; Watkins, K.C.; Jodoin, N.; Doucet, E.; Langlois, X.; El Mestikawy, S.; Hamon, M.; Descarries, L. Somatodendritic localization of 5-HT_{1A} and preterminal axonal localization of 5-HT_{1B} serotonin receptors in adult rat brain. *J. Comp. Neurol.* **2000**, *417*, 181–194. [[CrossRef](#)]
13. Maier, S.F.; Grahm, R.E.; Watkins, L.R. 8-OH-DPAT microinjected in the region of the dorsal raphe nucleus blocks and reverses the enhancement of fear conditioning and interference with escape produced by exposure to inescapable shock. *Behav. Neurosci.* **1995**, *109*, 404–412. [[CrossRef](#)] [[PubMed](#)]
14. Mendelson, S.D.; Quartermain, D.; Francisco, T.; Shemer, A. 5-HT_{1A} receptor agonists induce anterograde amnesia in mice through a postsynaptic mechanism. *Eur. J. Pharmacol.* **1993**, *236*, 177–182. [[CrossRef](#)]
15. Zhuang, X.; Gross, C.; Santarelli, L.; Compan, V.; Trillat, A.C.; Hen, R. Altered emotional states in knockout mice lacking 5-HT_{1A} or 5-HT_{1B} receptors. *Neuropsychopharmacology* **1999**, *21*, 525–60S. [[CrossRef](#)]
16. Billard, T.; Bars, D.; Zimmer, L. PET Radiotracers for Molecular Imaging of Serotonin 5-HT_{1A} Receptors. *Curr. Med. Chem.* **2014**, *21*, 70–81. [[CrossRef](#)]
17. Forster, E.A.; Cliffe, I.A.; Bill, D.J.; Dover, G.M.; Jones, D.; Reilly, Y.; Fletcher, A. A pharmacological profile of the selective silent 5-HT_{1A} receptor antagonist, WAY-100635. *Eur. J. Pharmacol.* **1995**, *281*, 81–88. [[CrossRef](#)]
18. Hall, H.; Lundkvist, C.; Halldin, C.; Farde, L.; Pike, V.W.; McCarron, J.A.; Fletcher, A.; Cliffe, I.A.; Barf, T.; Wikström, H.; et al. Autoradiographic localization of 5-HT_{1A} receptors in the post-mortem human brain using [³H]WAY-100635. *Brain Res.* **1997**, *745*, 96–108. [[CrossRef](#)]

19. Mathis, C.A.; Simpson, N.R.; Mahmood, K.; Kinahan, P.E.; Mintun, M.A. [11C]WAY 100635: A radioligand for imaging 5-HT1A receptors with positron emission tomography. *Life Sci.* **1994**, *55*, PL403–PL407. [[CrossRef](#)]
20. Pike, V.W.; McCarron, J.A.; Lammerstma, A.A.; Hume, S.P.; Poole, K.; Grasby, P.M.; Malizia, A.; Cliffe, I.A.; Fletcher, A.; Bench, C.J. First delineation of 5-HT1A receptors in human brain with PET and [11C]WAY-100635. *Eur. J. Pharmacol.* **1995**, *283*, 3–5. [[CrossRef](#)]
21. Hwang, D.R.; Simpson, N.R.; Montoya, J.; Mann, J.J.; Laruelle, M. An improved one-pot procedure for the preparation of [11C-carbonyl]-WAY100635. *Nucl. Med. Biol.* **1999**, *26*, 815–819. [[CrossRef](#)]
22. Rabiner, E.A.; Messa, C.; Sargent, P.A.; Husted-Kjaer, K.; Montgomery, A.; Lawrence, A.D.; Bench, C.J.; Gunn, R.N.; Cowen, P.; Grasby, P.M. A database of [11C]WAY-100635 binding to 5-HT1A receptors in normal male volunteers: Normative data and relationship to methodological, demographic, physiological, and behavioral variables. *Neuroimage* **2002**, *15*, 620–632. [[CrossRef](#)] [[PubMed](#)]
23. Sullivan, G.M.; Ogden, R.T.; Oquendo, M.A.; Kumar, J.S.D.; Simpson, N.; Huang, Y.-y.; Mann, J.J.; Parsey, R.V. Positron Emission Tomography Quantification of Serotonin-1A Receptor Binding in Medication-Free Bipolar Depression. *Biol. Psychiatry* **2009**, *66*, 223–230. [[CrossRef](#)] [[PubMed](#)]
24. Penttilä, J.; Hirvonen, J.; Tuominen, L.; Lumme, V.; Ilonen, T.; Nägren, K.; Hietala, J. Verbal memory and 5-HT1A receptors in healthy volunteers—A PET study with [carbonyl-11C]WAY-100635. *Eur. Neuropsychopharmacol.* **2016**, *26*, 570–577. [[CrossRef](#)]
25. Metts, A.V.; Rubin-Falcone, H.; Ogden, R.T.; Lin, X.; Wilner, D.E.; Burke, A.K.; Sublette, M.E.; Oquendo, M.A.; Miller, J.M.; Mann, J.J. Antidepressant medication exposure and 5-HT 1A autoreceptor binding in major depressive disorder. *Synapse* **2019**, *73*, e22089. [[CrossRef](#)] [[PubMed](#)]
26. Zhuang, Z.; Kung, M.-P.; Kung, H.F. Synthesis And Evaluation of 4-(2'-Methoxyphenyl)-1-[2'-[N-(2''-pyridinyl)-p-iodobenzamido]ethyl]piperazine (p-MPPI): A New Iodinated 5-HT1A Ligand. *J. Med. Chem.* **1994**, *37*, 1406–1407. [[CrossRef](#)] [[PubMed](#)]
27. Shiue, C.-Y.; Shiue, G.G.; Mozley, P.D.; Kung, M.-P.; Zhuang, Z.-P.; Kim, H.-J.; Kung, H.F. p-[18F]-MPPF: A potential radioligand for PET studies of 5-HT1A receptors in humans. *Synapse* **1997**, *25*, 147–154. [[CrossRef](#)]
28. Aznavour, N.; Zimmer, L. [18F]MPPF as a tool for the in vivo imaging of 5-HT1A receptors in animal and human brain. *Neuropharmacology* **2007**, *52*, 695–707. [[CrossRef](#)] [[PubMed](#)]
29. Pauwelyn, G.; Vlerick, L.; Dockx, R.; Verhoeven, J.; Dobbeleir, A.; Peremans, K.; Goethals, I.; Bosmans, T.; Vanhove, C.; De Vos, F.; et al. PET quantification of [18F]MPPF in the canine brain using blood input and reference tissue modelling. *PLoS ONE* **2019**, *14*, e0218237. [[CrossRef](#)]
30. Plenevaux, A.; Lemaire, C.; Aerts, J.; Lacan, G.; Rubins, D.; Melega, W.; Brihaye, C.; Degueldre, C.; Fuchs, S.; Salmon, E.; et al. [18F]p-MPPF: A Radiolabeled Antagonist for the Study of 5-HT1A Receptors with PET. *Nucl. Med. Biol.* **2000**, *27*, 467–471. [[CrossRef](#)]
31. Costes, N.; Merlet, I.; Ostrowsky, K.; Faillenot, I.; Lavenne, F.; Zimmer, L.; Ryvlin, P.; Le Bars, D. A 18F-MPPF PET normative database of 5-HT1A receptor binding in men and women over aging. *J. Nucl. Med.* **2005**, *46*, 1980–1989.
32. Kepe, V.; Barrio, J.R.; Huang, S.-C.; Ercoli, L.; Siddarth, P.; Shoghi-Jadid, K.; Cole, G.M.; Satyamurthy, N.; Cummings, J.L.; Small, G.W.; et al. Serotonin 1A receptors in the living brain of Alzheimer's disease patients. *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 702–707. [[CrossRef](#)]
33. Merlet, I.; Ostrowsky, K.; Costes, N.; Ryvlin, P.; Isnard, J.; Faillenot, I.; Lavenne, F.; Dufournel, D.; Le Bars, D.; Mauguière, F. 5-HT1A receptor binding and intracerebral activity in temporal lobe epilepsy: An [18F]MPPF-PET study. *Brain* **2004**, *127*, 900–913. [[CrossRef](#)] [[PubMed](#)]
34. Lothe, A.; Didelot, A.; Hammers, A.; Costes, N.; Saoud, M.; Gilliam, F.; Ryvlin, P. Comorbidity between temporal lobe epilepsy and depression: A [18 F]MPPF PET study. *Brain* **2008**, *131*, 2765–2782. [[CrossRef](#)] [[PubMed](#)]
35. Lang, L.; Jagoda, E.; Schmall, B.; Vuong, B.; Adams, H.R.; Nelson, D.L.; Carson, R.E.; Eckelman, W.C. Development of Fluorine-18-Labeled 5-HT 1A Antagonists. *J. Med. Chem.* **1999**, *42*, 1576–1586. [[CrossRef](#)]
36. Toczek, M.T.; Carson, R.E.; Lang, L.; Ma, Y.; Spanaki, M.V.; Der, M.G.; Fazilat, S.; Kopylev, L.; Herscovitch, P.; Eckelman, W.C.; et al. PET imaging of 5-HT1A receptor binding in patients with temporal lobe epilepsy. *Neurology* **2003**, *60*, 749–756. [[CrossRef](#)] [[PubMed](#)]
37. Neumeister, A.; Bain, E.; Nugent, A.C.; Carson, R.E.; Bonne, O.; Luckenbaugh, D.A.; Eckelman, W.; Herscovitch, P.; Charney, D.S.; Drevets, W.C. Reduced Serotonin Type 1A Receptor Binding in Panic Disorder. *J. Neurosci.* **2004**, *24*, 589–591. [[CrossRef](#)]
38. Bonne, O.; Bain, E.; Neumeister, A.; Nugent, A.C.; Vythilingam, M.; Carson, R.E.; Luckenbaugh, D.A.; Eckelman, W.; Herscovitch, P.; Drevets, W.C.; et al. No Change in Serotonin Type 1A Receptor Binding in Patients with Posttraumatic Stress Disorder. *Am. J. Psychiatry* **2005**, *162*, 383–385. [[CrossRef](#)]
39. Ryu, Y.H.; Liow, J.-S.; Zoghbi, S.; Fujita, M.; Collins, J.; Tipre, D.; Sangare, J.; Hong, J.; Pike, V.W.; Innis, R.B. Disulfiram Inhibits Defluorination of 18F-FCWAY, Reduces Bone Radioactivity, and Enhances Visualization of Radioligand Binding to Serotonin 5-HT1A Receptors in Human Brain. *J. Nucl. Med.* **2007**, *48*, 1154–1161. [[CrossRef](#)]
40. Saigal, N.; Bajwa, A.K.; Faheem, S.S.; Coleman, R.A.; Pandey, S.K.; Constantinescu, C.C.; Fong, V.; Mukherjee, J. Evaluation of serotonin 5-HT 1A receptors in rodent models using [18F]mefway PET. *Synapse* **2013**, *67*, 596–608. [[CrossRef](#)]
41. Wooten, D.W.; Hillmer, A.T.; Moirano, J.M.; Ahlers, E.O.; Slesarev, M.; Barnhart, T.E.; Mukherjee, J.; Schneider, M.L.; Christian, B.T. Measurement of 5-HT 1A receptor density and in-vivo binding parameters of 18Fmefway in the nonhuman primate. *J. Cereb. Blood Flow Metab.* **2012**, *32*, 1546–1558. [[CrossRef](#)]

42. Hillmer, A.T.; Wooten, D.W.; Bajwa, A.K.; Higgins, A.T.; Lao, P.J.; Betthausen, T.J.; Barnhart, T.E.; Rowley, H.A.; Stone, C.K.; Johnson, S.C.; et al. First-in-Human Evaluation of ¹⁸F-Mefway, a PET Radioligand Specific to Serotonin-1A Receptors. *J. Nucl. Med.* **2014**, *55*, 1973–1979. [[CrossRef](#)] [[PubMed](#)]
43. Choi, J.Y.; Lyoo, C.H.; Kim, J.S.; Kim, K.M.; Kang, J.H.; Choi, S.-H.; Kim, J.-J.; Ryu, Y.H. ¹⁸F-Mefway PET Imaging of Serotonin 1A Receptors in Humans: A Comparison with ¹⁸F-FCWAY. *PLoS ONE* **2015**, *10*, e0121342. [[CrossRef](#)]
44. Defraiteur, C.; Lemaire, C.; Luxen, A.; Plenevaux, A. Radiochemical synthesis and tissue distribution of p-[¹⁸F]DMPPF, a new 5-HT_{1A} ligand for PET, in rats. *Nucl. Med. Biol.* **2006**, *33*, 667–675. [[CrossRef](#)] [[PubMed](#)]
45. Andrée, B.; Halldin, C.; Pike, V.W.; Gunn, R.N.; Olsson, H.; Farde, L. The PET radioligand [carbonyl-(¹¹C)]desmethyl-WAY-100635 binds to 5-HT(1A) receptors and provides a higher radioactive signal than [carbonyl-(¹¹C)]WAY-100635 in the human brain. *J. Nucl. Med.* **2002**, *43*, 292–303.
46. Houle, S.; Wilson, A.A.; Inaba, T.; Fisher, N.; Dasilva, J.N. Imaging 5-HT_{1A} receptors with positron emission tomography initial human studies with [¹¹C]cpc-222. *Nucl. Med. Commun.* **1997**, *18*, 1130–1134. [[CrossRef](#)]
47. Sandell, J.; Halldin, C.; Pike, V.W.; Chou, Y.H.; Varnäs, K.; Hall, H.; Marchais, S.; Nowick, B.; Wikström, H.V.; Swahn, C.G.; et al. New halogenated [¹¹C]WAY analogues, [¹¹C]6FPWAY and [¹¹C]6BPWAY—Radiosynthesis and assessment as radioligands for the study of brain 5-HT_{1A} receptors in living monkey. *Nucl. Med. Biol.* **2001**, *28*, 177–185. [[CrossRef](#)]
48. Karramkam, M.; Hinnen, F.; Berrehouma, M.; Hlavacek, C.; Vaufrey, F.; Halldin, C.; McCarron, J.A.; Pike, V.W.; Dollé, F. Synthesis of a [6-Pyridinyl-¹⁸F]-labelled fluoro derivative of WAY-100635 as a candidate radioligand for brain 5-HT_{1A} receptor imaging with PET. *Bioorg. Med. Chem.* **2003**, *11*, 2769–2782. [[CrossRef](#)]
49. McCarron, J. The Pyridinyl-6 Position of WAY-100635 as a site for radiofluorination—Effect on 5-HT_{1A} receptor radioligand behavior in vivo. *Mol. Imaging Biol.* **2004**, *6*, 17–26. [[CrossRef](#)]
50. Kumar, J.S.D.; Majo, V.J.; Hsiung, S.; Millak, M.S.; Liu, K.; Tamir, H.; Prabhakaran, J.; Simpson, N.R.; Van Heertum, R.L.; Mann, J.J.; et al. Synthesis and in Vivo Validation of [O-Methyl-¹¹C]2-{4-[4-(7-methoxynaphthalen-1-yl)piperazin-1-yl]butyl}-4-methyl-2H-[1,2,4]triazine-3,5-dione: A Novel 5-HT_{1A} Receptor Agonist Positron Emission Tomography Ligand. *J. Med. Chem.* **2006**, *49*, 125–134. [[CrossRef](#)]
51. Kumar, J.S.D.; Prabhakaran, J.; Majo, V.J.; Milak, M.S.; Hsiung, S.-C.; Tamir, H.; Simpson, N.R.; Van Heertum, R.L.; Mann, J.J.; Parsey, R.V. Synthesis and in vivo evaluation of a novel 5-HT_{1A} receptor agonist radioligand [O-methyl-¹¹C]2-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2H,4H)dione in nonhuman primates. *Eur. J. Nucl. Med. Mol. Imaging* **2007**, *34*, 1050–1060. [[CrossRef](#)]
52. Milak, M.S.; DeLorenzo, C.; Zanderigo, F.; Prabhakaran, J.; Kumar, J.S.D.; Majo, V.J.; Mann, J.J.; Parsey, R.V. In Vivo Quantification of Human Serotonin 1A Receptor Using ¹¹C-CUMI-101, an Agonist PET Radiotracer. *J. Nucl. Med.* **2010**, *51*, 1892–1900. [[CrossRef](#)] [[PubMed](#)]
53. Hines, C.S.; Liow, J.-S.; Zanotti-Fregonara, P.; Hirvonen, J.; Morse, C.; Pike, V.W.; Innis, R.B. Human Biodistribution and Dosimetry of ¹¹C-CUMI-101, an Agonist Radioligand for Serotonin-1A Receptors in Brain. *PLoS ONE* **2011**, *6*, e25309. [[CrossRef](#)] [[PubMed](#)]
54. Hendry, N.; Christie, I.; Rabiner, E.A.; Laruelle, M.; Watson, J. In vitro assessment of the agonist properties of the novel 5-HT_{1A} receptor ligand, CUMI-101 (MMP), in rat brain tissue. *Nucl. Med. Biol.* **2011**, *38*, 273–277. [[CrossRef](#)] [[PubMed](#)]
55. Girgis, R.R.; Forbes, A.; Abi-Dargham, A.; Slifstein, M. A positron emission tomography occupancy study of brexpiprazole at dopamine D₂ and D₃ and serotonin 5-HT_{1A} and 5-HT_{2A} receptors, and serotonin reuptake transporters in subjects with schizophrenia. *Neuropsychopharmacology* **2020**, *45*, 786–792. [[CrossRef](#)]
56. Majo, V.J.; Milak, M.S.; Prabhakaran, J.; Mali, P.; Savenkova, L.; Simpson, N.R.; Mann, J.J.; Parsey, R.V.; Kumar, J.S.D. Synthesis and in vivo evaluation of [¹⁸F]2-(4-(4-(2-(2-fluoroethoxy)phenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2H,4H)-dione ([¹⁸F]FECUMI-101) as an imaging probe for 5-HT_{1A} receptor agonist in nonhuman primates. *Bioorg. Med. Chem.* **2013**, *21*, 5598–5604. [[CrossRef](#)]
57. Kumar, J.S.D.; Underwood, M.D.; Simpson, N.R.; Kassir, S.A.; Prabhakaran, J.; Majo, V.J.; Bakalian, M.J.; Parsey, R.V.; Mann, J.J.; Arango, V. Autoradiographic Evaluation of [¹⁸F]FECUMI-101, a High Affinity 5-HT_{1A} Receptor Ligand in Human Brain. *ACS Med. Chem. Lett.* **2016**, *7*, 482–486. [[CrossRef](#)]
58. Collier, T.L.; Liang, S.H.; Mann, J.J.; Vasdev, N.; Kumar, J.S.D. Microfluidic radiosynthesis of [¹⁸F]FEMPT, a high affinity PET radiotracer for imaging serotonin receptors. *Beilstein J. Org. Chem.* **2017**, *13*, 2922–2927. [[CrossRef](#)]
59. Vacher, B.; Bonnaud, B.; Funes, P.; Jubault, N.; Koek, W.; Assié, M.B.; Cosi, C.; Kleven, M. Novel derivatives of 2-pyridinemethylamine as selective, potent, and orally active agonists at 5-HT(1A) receptors. *J. Med. Chem.* **1999**, *42*, 1648–1660. [[CrossRef](#)]
60. Koek, W.; Vacher, B.; Cosi, C.; Assié, M.B.; Patoiseau, J.F.; Pauwels, P.J.; Colpaert, F.C. 5-HT_{1A} receptor activation and antidepressant-like effects: F 13714 has high efficacy and marked antidepressant potential. *Eur. J. Pharmacol.* **2001**, *420*, 103–112. [[CrossRef](#)]
61. Lemoine, L.; Becker, G.; Vacher, B.; Billard, T.; Lancelot, S.; Newman-Tancredi, A.; Zimmer, L. Radiosynthesis and Preclinical Evaluation of ¹⁸F-F13714 as a Fluorinated 5-HT_{1A} Receptor Agonist Radioligand for PET Neuroimaging. *J. Nucl. Med.* **2012**, *53*, 969–976. [[CrossRef](#)]
62. Yokoyama, C.; Mawatari, A.; Kawasaki, A.; Takeda, C.; Onoe, K.; Doi, H.; Newman-Tancredi, A.; Zimmer, L.; Onoe, H. Marmoset Serotonin 5-HT_{1A} Receptor Mapping with a Biased Agonist PET Probe ¹⁸F-F13714: Comparison with an Antagonist Tracer ¹⁸F-MPPF in Awake and Anesthetized States. *Int. J. Neuropsychopharmacol.* **2016**, *19*, pyw079. [[CrossRef](#)] [[PubMed](#)]

63. Heusler, P.; Palmier, C.; Tardif, S.; Bernois, S.; Colpaert, F.C.; Cussac, D. [3H]-F13640, a novel, selective and high-efficacy serotonin 5-HT1A receptor agonist radioligand. *Naunyn Schmiedebergs Arch. Pharmacol.* **2010**, *382*, 321–330. [[CrossRef](#)] [[PubMed](#)]
64. Xu, X.-J.; Colpaert, F.; Wiesenfeld-Hallin, Z. Opioid hyperalgesia and tolerance versus 5-HT1A receptor-mediated inverse tolerance. *Trends Pharmacol. Sci.* **2003**, *24*, 634–639. [[CrossRef](#)]
65. Vidal, B.; Fieux, S.; Colom, M.; Billard, T.; Bouillot, C.; Barret, O.; Constantinescu, C.; Tamagnan, G.; Newman-Tancredi, A.; Zimmer, L. 18F-F13640 preclinical evaluation in rodent, cat and primate as a 5-HT1A receptor agonist for PET neuroimaging. *Brain Struct. Funct.* **2018**, *223*, 2973–2988. [[CrossRef](#)] [[PubMed](#)]
66. Vidal, B.; Sebti, J.; Verdurand, M.; Fieux, S.; Billard, T.; Streichenberger, N.; Troakes, C.; Newman-Tancredi, A.; Zimmer, L. Agonist and antagonist bind differently to 5-HT1A receptors during Alzheimer’s disease: A post-mortem study with PET radiopharmaceuticals. *Neuropharmacology* **2016**, *109*, 88–95. [[CrossRef](#)]
67. Colom, M.; Costes, N.; Redouté, J.; Dailler, F.; Gobert, F.; Le Bars, D.; Billard, T.; Newman-Tancredi, A.; Zimmer, L. 18F-F13640 PET imaging of functional receptors in humans. *Eur. J. Nucl. Med. Mol. Imaging* **2020**, *47*, 220–221. [[CrossRef](#)]
68. Colom, M.; Vidal, B.; Fieux, S.; Redoute, J.; Costes, N.; Lavenne, F.; Mérida, I.; Irace, Z.; Iecker, T.; Bouillot, C.; et al. [18F]F13640, a 5-HT1A Receptor Radiopharmaceutical Sensitive to Brain Serotonin Fluctuations. *Front. Neurosci.* **2021**, *15*, 622423. [[CrossRef](#)]
69. Sari, Y. Serotonin receptors: From protein to physiological function and behavior. *Neurosci. Biobehav. Rev.* **2004**, *28*, 565–582. [[CrossRef](#)]
70. Rutz, S.; Riegert, C.; Rothmaier, A.K.; Buhot, M.C.; Cassel, J.C.; Jackisch, R. Presynaptic serotonergic modulation of 5-HT and acetylcholine release in the hippocampus and the cortex of 5-HT1B-receptor knockout mice. *Brain Res. Bull.* **2006**, *70*, 81–93. [[CrossRef](#)]
71. Olivier, B.; van Oorschot, R. 5-HT1B receptors and aggression: A review. *Eur. J. Pharmacol.* **2005**, *526*, 207–217. [[CrossRef](#)]
72. Pierson, M.E.; Andersson, J.; Nyberg, S.; McCarthy, D.J.; Finnema, S.J.; Varnäs, K.; Takano, A.; Karlsson, P.; Gulyás, B.; Medd, A.M.; et al. [11C]AZ10419369: A selective 5-HT1B receptor radioligand suitable for positron emission tomography (PET). Characterization in the primate brain. *Neuroimage* **2008**, *41*, 1075–1085. [[CrossRef](#)] [[PubMed](#)]
73. Maier, D.L.; Sobotka-Briner, C.; Ding, M.; Powell, M.E.; Jiang, Q.; Hill, G.; Heys, J.R.; Elmore, C.S.; Pierson, M.E.; Mrzljak, L. [N-methyl-3H3]AZ10419369 binding to the 5-HT 1B receptor: In vitro characterization and in vivo receptor occupancy. *J. Pharmacol. Exp. Ther.* **2009**, *330*, 342–351. [[CrossRef](#)] [[PubMed](#)]
74. Varnäs, K.; Nyberg, S.; Halldin, C.; Varrone, A.; Takano, A.; Karlsson, P.; Andersson, J.; McCarthy, D.; Smith, M.; Pierson, M.E.; et al. Quantitative Analysis of [11C]AZ10419369 Binding to 5-HT 1B Receptors in Human Brain. *J. Cereb. Blood Flow Metab.* **2011**, *31*, 113–123. [[CrossRef](#)]
75. Nord, M.; Finnema, S.J.; Schain, M.; Halldin, C.; Farde, L. Test–retest reliability of [11C]AZ10419369 binding to 5-HT1B receptors in human brain. *Eur. J. Nucl. Med. Mol. Imaging* **2014**, *41*, 301–307. [[CrossRef](#)] [[PubMed](#)]
76. Tiger, M.; Farde, L.; Rück, C.; Varrone, A.; Forsberg, A.; Lindfors, N.; Halldin, C.; Lundberg, J. Low serotonin1B receptor binding potential in the anterior cingulate cortex in drug-free patients with recurrent major depressive disorder. *Psychiatry Res. Neuroimaging* **2016**, *253*, 36–42. [[CrossRef](#)] [[PubMed](#)]
77. Varrone, A.; Svenningsson, P.; Forsberg, A.; Varnäs, K.; Tiger, M.; Nakao, R.; Halldin, C.; Nilsson, L.-G.; Farde, L. Positron emission tomography imaging of 5-hydroxytryptamine1B receptors in Parkinson’s disease. *Neurobiol. Aging* **2014**, *35*, 867–875. [[CrossRef](#)]
78. Lindberg, A.; Nag, S.; Schou, M.; Takano, A.; Matsumoto, J.; Amini, N.; Elmore, C.S.; Farde, L.; Pike, V.W.; Halldin, C. [11C]AZ10419096—A full antagonist PET radioligand for imaging brain 5-HT1B receptors. *Nucl. Med. Biol.* **2017**, *54*, 34–40. [[CrossRef](#)]
79. Lindberg, A.; Arakawa, R.; Nogami, T.; Nag, S.; Schou, M.; Elmore, C.S.; Farde, L.; Pike, V.W.; Halldin, C. Potential for imaging the high-affinity state of the 5-HT1B receptor: A comparison of three PET radioligands with differing intrinsic activity. *EJNMMI Res.* **2019**, *9*, 100. [[CrossRef](#)]
80. Lindberg, A.; Nag, S.; Schou, M.; Arakawa, R.; Nogami, T.; Moein, M.M.; Elmore, C.S.; Pike, V.W.; Halldin, C. Development of a 18F-labeled PET radioligand for imaging 5-HT1B receptors: [18F]AZ10419096. *Nucl. Med. Biol.* **2019**, *78–79*, 11–16. [[CrossRef](#)]
81. Ridler, K.; Plisson, C.; Rabiner, E.A.; Gunn, R.N.; Easwaramoorthy, B.; Abi-Dargham, A.; Laruelle, M.; Slifstein, M. Characterization of in vivo pharmacological properties and sensitivity to endogenous serotonin of [11C] P943: A positron emission tomography study in *Papio anubis*. *Synapse* **2011**, *65*, 1119–1127. [[CrossRef](#)]
82. Murrough, J.W.; Henry, S.; Hu, J.; Gallezot, J.-D.; Planeta-Wilson, B.; Neumaier, J.F.; Neumeister, A. Reduced ventral striatal/ventral pallidal serotonin1B receptor binding potential in major depressive disorder. *Psychopharmacology* **2011**, *213*, 547–553. [[CrossRef](#)] [[PubMed](#)]
83. Matuskey, D.; Bhagwagar, Z.; Planeta, B.; Pittman, B.; Gallezot, J.-D.; Chen, J.; Wanyiri, J.; Najafzadeh, S.; Ropchan, J.; Geha, P.; et al. Reductions in Brain 5-HT1B Receptor Availability in Primarily Cocaine-Dependent Humans. *Biol. Psychiatry* **2014**, *76*, 816–822. [[CrossRef](#)] [[PubMed](#)]
84. Hu, J.; Henry, S.; Gallezot, J.D.; Ropchan, J.; Neumaier, J.F.; Potenza, M.N.; Sinha, R.; Krystal, J.H.; Huang, Y.; Ding, Y.S.; et al. Serotonin 1B Receptor Imaging in Alcohol Dependence. *Biol. Psychiatry* **2010**, *67*, 800–803. [[CrossRef](#)]
85. Leysen, J.E. 5-HT2 receptors. *Curr. Drug Targets CNS Neurol. Disord.* **2004**, *3*, 11–26. [[CrossRef](#)]
86. Conn, P.J.; Sanders-Bush, E. Selective 5ht-2 antagonists inhibit serotonin stimulated phosphatidylinositol metabolism in cerebral cortex. *Neuropharmacology* **1984**, *23*, 993–996. [[CrossRef](#)]

87. Kim, J.; Moon, B.S.; Lee, B.C.; Lee, H.Y.; Kim, H.J.; Choo, H.; Pae, A.N.; Cho, Y.S.; Min, S.J. A Potential PET Radiotracer for the 5-HT_{2C} Receptor: Synthesis and in Vivo Evaluation of 4-(3-[¹⁸F]fluorophenethoxy)pyrimidine. *ACS Chem. Neurosci.* **2017**, *8*, 996–1003. [[CrossRef](#)] [[PubMed](#)]
88. Zeng, F.; Nye, J.A.; Voll, R.J.; Howell, L.; Goodman, M.M. Synthesis and Evaluation of Pyridyloxypyridyl Indole Carboxamides as Potential PET Imaging Agents for 5-HT_{2C} Receptors. *ACS Med. Chem. Lett.* **2018**, *9*, 188–192. [[CrossRef](#)]
89. Brancheck, T.; Adham, N.; Macchi, M.; Kao, H.T.; Hartig, P.R. [³H]-DOB(4-bromo-2,5-dimethoxyphenylisopropylamine) and [³H]ketanserin label two affinity states of the cloned human 5-hydroxytryptamine₂ receptor. *Mol. Pharmacol.* **1990**, *38*, 604–609.
90. Nichols, D.E. Hallucinogens. *Pharmacol. Ther.* **2004**, *101*, 131–181. [[CrossRef](#)]
91. Hall, H.; Farde, L.; Halldin, C.; Lundkvist, C.; Sedvall, G. Autoradiographic localization of 5-HT(2A) receptors in the human brain using [³H]M100907 and [¹¹C]M100907. *Synapse* **2000**, *38*, 421–431. [[CrossRef](#)]
92. Hasuo, H.; Matsuoaka, T.; Akasu, T. Activation of presynaptic 5-hydroxytryptamine 2A receptors facilitates excitatory synaptic transmission via protein kinase C in the dorsolateral septal nucleus. *J. Neurosci.* **2002**, *22*, 7509–7517. [[CrossRef](#)] [[PubMed](#)]
93. Gijssman, H.J.; Verkes, R.J.; Schouten-Verhagen, J.C.M.; Schoemaker, R.C.; Van Gerven, J.M.A.; De Rijk, R.H.; Van Kempen, G.M.J. A review of the role of serotonin receptors in psychiatric disorders. *Hum. Psychopharmacol.* **2000**, *15*, 397–415. [[CrossRef](#)]
94. Berridge, M.; Comar, D.; Crouzel, C.; Baron, J.-C. ¹¹C-Labeled ketanserin: A selective serotonin S₂ antagonist. *J. Label. Compd. Radiopharm.* **1983**, *20*, 73–78. [[CrossRef](#)]
95. Blin, J.; Pappata, S.; Kiyosawa, M.; Crouzel, C.; Baron, J.C. [¹⁸F]Setoperone: A new high-affinity ligand for positron emission tomography study of the serotonin-2 receptors in baboon brain in vivo. *Eur. J. Pharmacol.* **1988**, *147*, 73–82. [[CrossRef](#)]
96. Blin, J.; Sette, G.; Fiorelli, M.; Bletry, O.; Elghozi, J.L.; Crouzel, C.; Baron, J.C. A Method for the In Vivo Investigation of the Serotonergic 5-HT₂ Receptors in the Human Cerebral Cortex Using Positron Emission Tomography and ¹⁸F-Labeled Setoperone. *J. Neurochem.* **1990**, *54*, 1744–1754. [[CrossRef](#)]
97. Meyer, J.H.; Kapur, S.; Houle, S.; DaSilva, J.; Owczarek, B.; Brown, G.M.; Wilson, A.A.; Kennedy, S.H. Prefrontal cortex 5-HT₂ receptors in depression: An [¹⁸F]setoperone PET imaging study. *Am. J. Psychiatry* **1999**, *156*, 1029–1034. [[CrossRef](#)]
98. Massou, J.M.; Trichard, C.; Attar-Levy, D.; Feline, A.; Corruble, E.; Beaufile, B.; Martinot, J.L. Frontal 5-HT(2A) receptors studied in depressive patients during chronic treatment by selective serotonin reuptake inhibitors. *Psychopharmacology* **1997**, *133*, 99–101. [[CrossRef](#)]
99. Chabriat, H.; Vera, P.; Samson, Y.; Pappata, S.; Boullais, N.; Tehindrazanarivelo, A.; Bousser, M. 5HT₂ receptors in cerebral cortex of migraineurs studied using PET and ¹⁸F-fluorosetoperone. *Cephalalgia* **1995**, *15*, 104–108. [[CrossRef](#)]
100. Blin, J.; Baron, J.C.; Dubois, B.; Crouzel, C.; Fiorelli, M.; Attar-Lévy, D.; Pillon, B.; Fournier, D.; Vidailhet, M.; Agid, Y. Loss of brain 5-HT₂ receptors in Alzheimer’s disease. *Brain* **1993**, *116*, 497–510. [[CrossRef](#)]
101. Lemaire, C.; Cantineau, R.; Guillaume, M.; Plenevaux, A.; Christiaens, L. Fluorine-18-altanserin: A radioligand for the study of serotonin receptors with PET: Radiolabeling and in vivo biologic behavior in rats. *J. Nucl. Med.* **1991**, *32*, 2266–2272.
102. Biver, F.; Goldman, S.; Luxen, A.; Monclus, M.; Forestini, M.; Mendlewicz, J.; Lotstra, F. Multicompartmental study of fluorine-18 altanserin binding to brain 5HT₂ receptors in humans using positron emission tomography. *Eur. J. Nucl. Med.* **1994**, *21*, 937–946. [[CrossRef](#)] [[PubMed](#)]
103. Price, J.C.; Lopresti, B.J.; Mason, N.S.; Holt, D.P.; Huang, Y.; Mathis, C.A. Analyses of [¹⁸F]altanserin bolus injection PET data. I: Consideration of radiolabeled metabolites in baboons. *Synapse* **2001**, *41*, 1–10. [[CrossRef](#)] [[PubMed](#)]
104. Tan, P.Z.; Baldwin, R.M.; Van Dyck, C.H.; Al-Tikriti, M.; Roth, B.; Khan, N.; Charney, D.S.; Innis, R.B. Characterization of radioactive metabolites of 5-HT(2A) receptor PET ligand [¹⁸F]altanserin in human and rodent. *Nucl. Med. Biol.* **1999**, *26*, 601–608. [[CrossRef](#)]
105. Adams, K.H.; Pinborg, L.H.; Svarer, C.; Hasselbalch, S.G.; Holm, S.; Haugbøl, S.; Madsen, K.; Frøkjær, V.; Martiny, L.; Paulson, O.B.; et al. A database of [¹⁸F]-altanserin binding to 5-HT_{2A} receptors in normal volunteers: Normative data and relationship to physiological and demographic variables. *Neuroimage* **2004**, *21*, 1105–1113. [[CrossRef](#)] [[PubMed](#)]
106. Frank, G.K.; Kaye, W.H.; Meltzer, C.C.; Price, J.C.; Greer, P.; McConaha, C.; Skovira, K. Reduced 5-HT_{2A} receptor binding after recovery from anorexia nervosa. *Biol. Psychiatry* **2002**, *52*, 896–906. [[CrossRef](#)]
107. Rasmussen, H.; Frøkjær, V.G.; Hilker, R.W.; Madsen, J.; Anhøj, S.; Oranje, B.; Pinborg, L.H.; Glenthøj, B.; Knudsen, G.M. Low frontal serotonin 2A receptor binding is a state marker for schizophrenia? *Eur. Neuropsychopharmacol.* **2016**, *26*, 1248–1250. [[CrossRef](#)]
108. Mintun, M.A.; Sheline, Y.I.; Moerlein, S.M.; Vlassenko, A.G.; Huang, Y.; Snyder, A.Z. Decreased hippocampal 5-HT_{2A} receptor binding in major depressive disorder: In vivo measurement with [¹⁸F]altanserin positron emission tomography. *Biol. Psychiatry* **2004**, *55*, 217–224. [[CrossRef](#)]
109. Marnier, L.; Frøkjær, V.G.; Kalbitzer, J.; Lehel, S.; Madsen, K.; Baaré, W.F.C.; Knudsen, G.M.; Hasselbalch, S.G. Loss of serotonin 2A receptors exceeds loss of serotonergic projections in early Alzheimer’s disease: A combined [¹¹C]DASB and [¹⁸F]altanserin-PET study. *Neurobiol. Aging* **2012**, *33*, 479–487. [[CrossRef](#)]
110. Staley, J.K.; Van Dyck, C.H.; Tan, P.Z.; Al Tikriti, M.; Ramsby, Q.; Klump, H.; Ng, C.; Garg, P.; Soufer, R.; Baldwin, R.M.; et al. Comparison of [¹⁸F]altanserin and [¹⁸F]deuteroaltanserin for PET imaging of serotonin_{2A} receptors in baboon brain: Pharmacological studies. *Nucl. Med. Biol.* **2001**, *28*, 271–279. [[CrossRef](#)]

111. Van Dyck, C.H.; Soares, J.C.; Tan, P.Z.; Staley, J.K.; Baldwin, R.M.; Amici, L.A.; Fu, X.; Garg, P.K.; Seibyl, J.P.; Charney, D.S.; et al. Equilibrium modeling of 5-HT_{2A} receptors with [18F]deuteroaltanserin and PET: Feasibility of a constant infusion paradigm. *Nucl. Med. Biol.* **2000**, *27*, 715–722. [[CrossRef](#)]
112. Soares, J.C.; Van Dyck, C.H.; Tan, P.Z.; Zoghbi, S.S.; Garg, P.; Soufer, R.; Baldwin, R.M.; Fujita, M.; Staley, J.K.; Fu, X.; et al. Reproducibility of in vivo brain measures of 5-HT_{2A} receptors with PET and [18F]deuteroaltanserin. *Psychiatry Res. Neuroimaging* **2001**, *106*, 81–93. [[CrossRef](#)]
113. Santhosh, L.; Estok, K.M.; Vogel, R.S.; Tamagnan, G.D.; Baldwin, R.M.; Mitsis, E.M.; MacAvoy, M.G.; Staley, J.K.; van Dyck, C.H. Regional distribution and behavioral correlates of 5-HT_{2A} receptors in Alzheimer’s disease with [18F]deuteroaltanserin and PET. *Psychiatry Res. Neuroimaging* **2009**, *173*, 212–217. [[CrossRef](#)] [[PubMed](#)]
114. Ito, H.; Nyberg, S.; Halldin, C.; Lundkvist, C.; Farde, L. PET imaging of central 5-HT(2A) receptors with carbon-11-MDL 100,907. *J. Nucl. Med.* **1998**, *39*, 208–214. [[PubMed](#)]
115. Lopez-Gimenez, J.F.; Vilaro, M.T.; Palacios, M.; Mengod, G. [3H] MDL 100, 907 labels 5-HT 2A serotonin receptors selectively in primate brain. *Neuropharmacology* **1998**, *37*, 1147–1158. [[CrossRef](#)]
116. López-Giménez, J.F.; Mengod, G.; Palacios, J.M.; Vilaró, M.T. Selective visualization of rat brain 5-HT(2A) receptors by autoradiography with [3H]MDL 100,907. *Naunyn Schmiedebergs Arch. Pharmacol.* **1997**, *356*, 446–454. [[CrossRef](#)]
117. Lundkvist, C.; Halldin, C.; Ginovart, N.; Nyberg, S.; Swahn, C.G.; Carr, A.A.; Brunner, F.; Farde, L. [11C]MDL 100907, a radioligand for selective imaging of 5-HT_{2A} receptors with positron emission tomography. *Life Sci.* **1996**, *58*, 187–192. [[CrossRef](#)]
118. Talbot, P.S.; Slifstein, M.; Hwang, D.R.; Huang, Y.; Scher, E.; Abi-Dargham, A.; Laruelle, M. Extended characterisation of the serotonin 2A (5-HT 2A) receptor-selective PET radiotracer 11C-MDL100907 in humans: Quantitative analysis, test-retest reproducibility, and vulnerability to endogenous 5-HT tone. *Neuroimage* **2012**, *59*, 271–285. [[CrossRef](#)]
119. Bhagwagar, Z.; Hinz, R.; Taylor, M.; Fancy, S.; Cowen, P.; Grasby, P. Increased 5-HT_{2A} receptor binding in euthymic, medication-free patients recovered from depression: A positron emission study with [11C]MDL 100,907. *Am. J. Psychiatry* **2006**, *163*, 1580–1587. [[CrossRef](#)]
120. Girgis, R.R.; Slifstein, M.; Xu, X.; Frankle, W.G.; Anagnostou, E.; Wasserman, S.; Pepa, L.; Kolevzon, A.; Abi-Dargham, A.; Laruelle, M.; et al. The 5-HT 2A receptor and serotonin transporter in Asperger’s Disorder: A PET study with [11C]MDL 100907 and [11C]DASB. *Psychiatry Res. Neuroimaging* **2011**, *194*, 230–234. [[CrossRef](#)]
121. Simpson, H.B.; Slifstein, M.; Bender, J.; Xu, X.; Hackett, E.; Maher, M.J.; Abi-Dargham, A. Serotonin 2A receptors in obsessive-compulsive disorder: A positron emission tomography study with [11C]MDL 100907. *Biol. Psychiatry* **2011**, *70*, 897–904. [[CrossRef](#)]
122. Scott, D.O.; Heath, T.G. Investigation of the CNS penetration of a potent 5-HT(2a) receptor antagonist (MDL 100,907) and an active metabolite (MDL 105,725) using in vivo microdialysis sampling in the rat. *J. Pharm. Biomed. Anal.* **1998**, *17*, 17–25. [[CrossRef](#)]
123. Ren, H.; Wey, H.Y.; Strebl, M.; Neelamegam, R.; Ritter, T.; Hooker, J.M. Synthesis and imaging validation of [18F]MDL100907 enabled by Ni-mediated fluorination. *ACS Chem. Neurosci.* **2014**, *5*, 611–615. [[CrossRef](#)] [[PubMed](#)]
124. Herth, M.M.; Piel, M.; Debus, F.; Schmitt, U.; Lüddens, H.; Rösch, F. Preliminary in vivo and ex vivo evaluation of the 5-HT_{2A} imaging probe [18F]MH.MZ. *Nucl. Med. Biol.* **2009**, *36*, 447–454. [[CrossRef](#)] [[PubMed](#)]
125. Debus, F.; Herth, M.M.; Piel, M.; Buchholz, H.G.; Bausbacher, N.; Kramer, V.; Lüddens, H.; Rösch, F. 18F-Labeling and evaluation of novel MDL 100907 derivatives as potential 5-HT_{2A} antagonists for molecular imaging. *Nucl. Med. Biol.* **2010**, *37*, 487–495. [[CrossRef](#)]
126. Hansen, H.D.; Ettrup, A.; Herth, M.M.; Dyssegaard, A.; Ratner, C.; Gillings, N.; Knudsen, G.M. Direct comparison of [18F]MH.MZ and [18F]altanserin for 5-HT_{2A} receptor imaging with PET. *Synapse* **2013**, *67*, 328–337. [[CrossRef](#)]
127. Ettrup, A.; Palner, M.; Gillings, N.; Santini, M.A.; Hansen, M.; Kornum, B.R.; Rasmussen, L.K.; Någren, K.; Madsen, J.; Begtrup, M.; et al. Radiosynthesis and evaluation of [11C]-CIMBI-5 as a 5-HT 2A receptor agonist radioligand for PET. *J. Nucl. Med.* **2010**, *51*, 1763–1770. [[CrossRef](#)]
128. Prabhakaran, J.; DeLorenzo, C.; Zanderigo, F.; Knudsen, G.M.; Gilling, N.; Pratap, M.; Jorgensen, M.J.; Daunais, J.; Kaplan, J.R.; Parsey, R.V.; et al. In vivo PET Imaging of [11C]CIMBI-5, a 5-HT_{2A} Agonist Radiotracer in Nonhuman Primates. *J. Pharm. Pharm. Sci.* **2019**, *22*, 352–364. [[CrossRef](#)]
129. Ettrup, A.; Hansen, M.; Santini, M.A.; Paine, J.; Gillings, N.; Palner, M.; Lehel, S.; Herth, M.M.; Madsen, J.; Kristensen, J.; et al. Radiosynthesis and in vivo evaluation of a series of substituted 11C-phenethylamines as 5-HT_{2A} agonist PET tracers. *Eur. J. Nucl. Med. Mol. Imaging* **2011**, *38*, 681–693. [[CrossRef](#)]
130. Johansen, A.; Hansen, H.D.; Svarer, C.; Lehel, S.; Leth-Petersen, S.; Kristensen, J.L.; Gillings, N.; Knudsen, G.M. The importance of small polar radiometabolites in molecular neuroimaging: A PET study with [11C]Cimbi-36 labeled in two positions. *J. Cereb. Blood Flow Metab.* **2018**, *38*, 659–668. [[CrossRef](#)]
131. Johansen, A.; Holm, S.; Dall, B.; Keller, S.; Kristensen, J.L.; Knudsen, G.M.; Hansen, H.D. Human biodistribution and radiation dosimetry of the 5-HT_{2A} receptor agonist Cimbi-36 labeled with carbon-11 in two positions. *EJNMMI Res.* **2019**, *9*, 71. [[CrossRef](#)]
132. Jørgensen, L.M.; Weikop, P.; Villadsen, J.; Visnapuu, T.; Ettrup, A.; Hansen, H.D.; Baandrup, A.O.; Andersen, F.L.; Bjarkam, C.R.; Thomsen, C.; et al. Cerebral 5-HT release correlates with [11C]Cimbi36 PET measures of 5-HT_{2A} receptor occupancy in the pig brain. *J. Cereb. Blood Flow Metab.* **2017**, *37*, 425–434. [[CrossRef](#)] [[PubMed](#)]

133. Da Cunha-Bang, S.; Ettrup, A.; Mc Mahon, B.; Skibsted, A.P.; Schain, M.; Lehel, S.; Dyssegaard, A.; Jørgensen, L.M.; Møller, K.; Gillings, N.; et al. Measuring endogenous changes in serotonergic neurotransmission with [11C]Cimbi-36 positron emission tomography in humans. *Transl. Psychiatry* **2019**, *9*, 134. [[CrossRef](#)]
134. Yang, K.C.; Stepanov, V.; Martinsson, S.; Ettrup, A.; Takano, A.; Knudsen, G.M.; Halldin, C.; Farde, L.; Finnema, S.J. Fenfluramine Reduces [11C]Cimbi-36 Binding to the 5-HT_{2A} Receptor in the Nonhuman Primate Brain. *Int. J. Neuropsychopharmacol.* **2017**, *20*, 683–691. [[CrossRef](#)] [[PubMed](#)]
135. Erritzoe, D.; Ashok, A.H.; Searle, G.E.; Colasanti, A.; Turton, S.; Lewis, Y.; Huiban, M.; Moz, S.; Passchier, J.; Saleem, A.; et al. Serotonin release measured in the human brain: A PET study with [11C]CIMBI-36 and d-amphetamine challenge. *Neuropsychopharmacology* **2020**, *45*, 804–810. [[CrossRef](#)] [[PubMed](#)]
136. Ettrup, A.; Svarer, C.; McMahon, B.; da Cunha-Bang, S.; Lehel, S.; Møller, K.; Dyssegaard, A.; Ganz, M.; Beliveau, V.; Jørgensen, L.M.; et al. Serotonin 2A receptor agonist binding in the human brain with [11C]Cimbi-36: Test-retest reproducibility and head-to-head comparison with the antagonist [18F]altanserin. *Neuroimage* **2016**, *130*, 167–174. [[CrossRef](#)]
137. Prabhakaran, J.; Underwood, M.D.; Kumar, J.S.D.; Simpson, N.R.; Kassir, S.A.; Bakalian, M.J.; Mann, J.J.; Arango, V. Synthesis and in vitro evaluation of [18F]FECIMBI-36: A potential agonist PET ligand for 5-HT_{2A/2C} receptors. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3933–3936. [[CrossRef](#)]
138. Prabhakaran, J.; Solingapuram Sai, K.K.; Zanderigo, F.; Rubin-Falcone, H.; Jorgensen, M.J.; Kaplan, J.R.; Tooke, K.I.; Mintz, A.; Mann, J.J.; Kumar, J.S.D. In vivo evaluation of [18F]FECIMBI-36, an agonist 5-HT_{2A/2C}receptor PET radioligand in nonhuman primate. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 21–23. [[CrossRef](#)]
139. Sargent, T.; Budinger, T.F.; Braun, G.; Shulgin, A.T.; Braun, U. An iodinated catecholamine congener for brain imaging and metabolic studies. *J. Nucl. Med.* **1978**, *19*, 71–76.
140. Glennon, R.A.; Seggel, M.R.; Soine, W.H.; Herrick-Davis, K.; Lyon, R.A.; Titeler, M. Iodine-125 labeled 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane: An iodinated radioligand that specifically labels the agonist high-affinity state of 5-HT₂ serotonin receptors. *J. Med. Chem.* **1988**, *31*, 5–7. [[CrossRef](#)]
141. Appel, M.; Mitchell, M.; Garlick, R.K.; Glennon, R.A.; Teitler, M.; Souza, B.D.E. Autoradiographic Characterization ([125I]DOI) Binding to 5-HT₂ and 5-HT₁ Receptors in Rat Brain. *J. Pharmacol. Exp. Ther.* **1990**, *233*, 843–857.
142. Zea-Ponce, Y.; Kegeles, L.S.; Guo, N.; Raskin, L.; Bakthavachalam, V.; Laruelle, M. Pharmacokinetics and brain distribution in non human primate of R(-)[¹²³I]DOI, A 5HT_{2A/2C} serotonin agonist. *Nucl. Med. Biol.* **2002**, *29*, 575–583. [[CrossRef](#)]
143. Terriere, D.; Janssen, P.M.; Gommeren, W.; Gysemans, M.; Mertens, J.J.; Leysen, J.E. Evaluation of radioiodo-4-amino-N-[1-[3-(4-fluorophenoxy)-propyl]-4-methyl-4-piperidiny]-5-iodo-2-methoxybenzamide as a potential 5HT₂ receptor tracer for SPE(C)T. *Nucl. Med. Biol.* **1995**, *22*, 1005–1010. [[CrossRef](#)]
144. Abi-Dargham, A.; Zea-Ponce, Y.; Terriere, D.; Al-Tikriti, M.; Baldwin, R.M.; Hoffer, P.; Charney, D.; Leysen, J.E.; Laruelle, M.; Mertens, J.; et al. Preclinical evaluation of [123I]R93274 as a SPECT radiotracer for imaging 5-HT(2A) receptors. *Eur. J. Pharmacol.* **1997**, *321*, 285–293. [[CrossRef](#)]
145. Busatto, G.F.; Pilowsky, L.S.; Costa, D.C.; Mertens, J.; Terriere, D.; Ell, P.J.; Mulligan, R.; Travis, M.J.; Leysen, J.E.; Lui, D.; et al. Initial evaluation of 123I-5-I-R91150, a selective 5-HT_{2A} ligand for single-photon emission tomography, in healthy human subjects. *Eur. J. Nucl. Med.* **1997**, *24*, 119–124. [[CrossRef](#)] [[PubMed](#)]
146. Catafau, A.M.; Danus, M.; Bullich, S.; Llop, J.; Perich, J.; Cunningham, V.J.; Plaza, P.; Penengo, M.M.; Eersels, J.L.H.; Squassante, L.; et al. Characterization of the SPECT 5-HT_{2A} receptor ligand 123I-R91150 in healthy volunteers: Part 1—Pseudoequilibrium interval and quantification methods. *J. Nucl. Med.* **2006**, *47*, 919–928.
147. Baeken, C.; D'haenen, H.; Flamen, P.; Mertens, J.; Terriere, D.; Chavatte, K.; Boumon, R.; Bossuyt, A. 123I-5-I-R91150, a new single-photon emission tomography ligand for 5-HT(2A) receptors: Influence of age and gender in healthy subjects. *Eur. J. Nucl. Med.* **1998**, *25*, 1617–1622. [[CrossRef](#)]
148. Travis, M.J.; Busatto, G.F.; Pilowsky, L.S.; Mulligan, R.; Acton, P.D.; Gacinovic, S.; Mertens, J.; Terrière, D.; Costa, D.C.; Ell, P.J.; et al. 5-HT 2A receptor blockade in patients with schizophrenia treated with risperidone or clozapine. *Br. J. Psychiatry* **1998**, *173*, 236–241. [[CrossRef](#)]
149. Melse, M.; Tan, S.K.H.; Temel, Y.; van Kroonenburgh, M.J.P.G.; Leentjens, A.F.G. Changes in 5-HT_{2A} Receptor Expression in Untreated, de novo Patients with Parkinson's Disease. *J. Parkinsons Dis.* **2014**, *4*, 283–287. [[CrossRef](#)]
150. Versijpt, J.; Van Laere, K.J.; Dumont, F.; Decoo, D.; Vandecapelle, M.; Santens, P.; Goethals, I.; Audenaert, K.; Slegers, G.; Dierckx, R.A.; et al. Imaging of the 5-HT_{2A} system: Age-, gender-, and Alzheimer's disease-related findings. *Neurobiol. Aging* **2003**, *24*, 553–561. [[CrossRef](#)]
151. Baeken, C.; De Raedt, R.; Bossuyt, A.; Van Hove, C.; Mertens, J.; Dobbeleir, A.; Blanckaert, P.; Goethals, I. The impact of HF-rTMS treatment on serotonin_{2A} receptors in unipolar melancholic depression. *Brain Stimul.* **2011**, *4*, 104–111. [[CrossRef](#)]
152. Vermeire, S.T.; Audenaert, K.R.; Dobbeleir, A.A.; De Meester, R.H.; De Vos, F.J.; Peremans, K.Y. Evaluation of the brain 5-HT_{2A} receptor binding index in dogs with anxiety disorders, measured with 123I-5I-R91150 and SPECT. *J. Nucl. Med.* **2009**, *50*, 284–289. [[CrossRef](#)] [[PubMed](#)]
153. Peremans, K.; De Spiegeleer, B.; Buntinx, E.; Dobbeleir, A.; Vermeire, S.; Vandermeulen, E.; De Vos, F.; Megens, A.; Eersels, J.; Audenaert, K. Evaluation of serotonin-2A receptor occupancy with 123I-5-I-R91150 and single-photon emission tomography before and after low-dose pipamperone administration in the canine brain. *Nucl. Med. Commun.* **2008**, *29*, 724–729. [[CrossRef](#)] [[PubMed](#)]

154. Goethals, I.; Vervaet, M.; Audenaert, K.; Jacobs, F.; Ham, H.; Van de Wiele, C.; Vandecapelle, M.; Slegers, G.; Dierckx, R.; van Heeringen, C. Differences of cortical 5-HT_{2A} receptor binding index with SPECT in subtypes of anorexia nervosa: Relationship with personality traits? *J. Psychiatr. Res.* **2007**, *41*, 455–458. [[CrossRef](#)] [[PubMed](#)]
155. Audenaert, K.; Van Laere, K.; Dumont, F.; Vervaet, M.; Goethals, I.; Slegers, G.; Mertens, J.; van Heeringen, C.; Dierckx, R.A. Decreased 5-HT_{2a} receptor binding in patients with anorexia nervosa. *J. Nucl. Med.* **2003**, *44*, 163–169. [[CrossRef](#)] [[PubMed](#)]
156. Van Heeringen, C.; Audenaert, K.; Van Laere, K.; Dumont, F.; Slegers, G.; Mertens, J.; Dierckx, R.A. Prefrontal 5-HT_{2a} receptor binding index, hopelessness and personality characteristics in attempted suicide. *J. Affect. Disord.* **2003**, *74*, 149–158. [[CrossRef](#)]
157. Dumas, N.; Moulin-Sallanon, M.; Ginovart, N.; Tournier, B.B.; Suzanne, P.; Cailly, T.; Fabis, F.; Rault, S.; Charnay, Y.; Millet, P. Small-animal single-photon emission computed tomographic imaging of the brain serotonergic systems in wild-type and Mdr1a knockout rats. *Mol. Imaging* **2014**, *13*, 1–12. [[CrossRef](#)]
158. Mühlhausen, U.; Ermert, J.; Coenen, H.H. Synthesis, labelling and first evaluation of [18F]R91150 as a serotonin 5-HT_{2A} receptor antagonist for PET. *J. Label. Compd. Radiopharm.* **2009**, *52*, 13–22. [[CrossRef](#)]
159. Samnick, S.; Remy, N.; Ametamey, S.; Bader, J.B.; Brandau, W.; Kirsch, C.-M. 123I-MSP and F[1 1C]MSP: New selective 5-HT_{2A} receptor radiopharmaceuticals for in vivo studies of neuronal 5-HT₂ serotonin receptors. Synthesis, in vitro binding study with unlabelled analogues and preliminary in vivo evaluation in mice. *Life Sci.* **1998**, *63*, 2001–2013. [[CrossRef](#)]
160. Blanckaert, P.B.M.; Burvenich, I.; Wyffels, L.; De Bruyne, S.; Moerman, L.; De Vos, F. In vivo evaluation in rodents of [123I]-3-I-CO as a potential SPECT tracer for the serotonin 5-HT_{2A} receptor. *Nucl. Med. Biol.* **2008**, *35*, 861–867. [[CrossRef](#)]
161. Lummis, S.C.R. 5-HT₃ Receptors. *J. Biol. Chem.* **2012**, *287*, 40239–40245. [[CrossRef](#)]
162. Niesler, B.; Kapeller, J.; Hammer, C.; Rappold, G. Serotonin type 3 receptor genes: HTR3A, B, C, D, E. *Pharmacogenomics* **2008**, *9*, 501–504. [[CrossRef](#)] [[PubMed](#)]
163. Kilpatrick, G.J.; Jones, B.J.; Tyers, M.B. Identification and distribution of 5-HT₃ receptors in rat brain using radioligand binding. *Nature* **1987**, *330*, 746–748. [[CrossRef](#)] [[PubMed](#)]
164. Parker, R.M.C.; Barnes, J.M.; Ge, J.; Barber, P.C.; Barnes, N.M. Autoradiographic distribution of [3H]-(S)-zacopride-labelled 5-HT₃ receptors in human brain. *J. Neurol. Sci.* **1996**, *144*, 119–127. [[CrossRef](#)]
165. Thompson, A.J.; Lummis, S.C.R. The 5-HT₃ receptor as a therapeutic target. *Expert Opin. Ther. Targets* **2007**, *11*, 527–540. [[CrossRef](#)] [[PubMed](#)]
166. Walstab, J.; Rappold, G.; Niesler, B. 5-HT₃ receptors: Role in disease and target of drugs. *Pharmacol. Ther.* **2010**, *128*, 146–169. [[CrossRef](#)] [[PubMed](#)]
167. Fakhfour, G.; Rahimian, R.; Dyhrfeld-Johnsen, J.; Zirak, M.R.; Beaulieu, J.M. 5-HT₃ receptor antagonists in neurologic and neuropsychiatric disorders: The iceberg still lies beneath the surface. *Pharmacol. Rev.* **2019**, *71*, 383–412. [[CrossRef](#)] [[PubMed](#)]
168. Thompson, A.J. Recent developments in 5-HT₃ receptor pharmacology. *Trends Pharmacol. Sci.* **2013**, *34*, 100–109. [[CrossRef](#)]
169. Paterson, L.M.; Kornum, B.R.; Nutt, D.J.; Pike, V.W.; Knudsen, G.M. 5-HT radioligands for human brain imaging with PET and SPECT. *Med. Res. Rev.* **2013**, *33*, 54–111. [[CrossRef](#)]
170. Camsonne, R.; Barre, L.; Petit-Taboué, M.C.; Travère, J.M.; Jones, R.; Debruyne, D.; Moulin, M.A.; MacKenzie, E.T.; Baron, J.C. Positron emission tomographic studies of [11C]MDL 72222, a potential 5-HT₃ receptor radioligand: Distribution, kinetics and binding in the brain of the baboon. *Neuropharmacology* **1993**, *32*, 65–71. [[CrossRef](#)]
171. Ishiwata, K.; Saito, N.; Yanagawa, K.; Furuta, R.; Ishii, S.I.; Kiyosawa, M.; Homma, Y.; Ishii, K.; Suzuki, F.; Senda, M. Synthesis and evaluation of 5-HT₃ receptor antagonist [11C]KF17643. *Nucl. Med. Biol.* **1996**, *23*, 285–290. [[CrossRef](#)]
172. Besret, L.; Dauphin, F.; Guillouet, G.; Dhilly, M.; Gourand, F.; Blaizot, X.; Young, A.R.; Petit-taboué, M.C.; Mickala, P.; Barbelivien, A.; et al. [¹¹C] S21007, a Putative Partial Agonist for 5-HT₃ Receptors PET Studies. Rat and Primate in vivo Biological Evaluation. *Life Sci.* **1998**, *62*, 115–129. [[CrossRef](#)]
173. Katounina, T.; Besret, L.; Dhilly, M.; Petit-Taboué, M.C.; Barbelivien, A.; Baron, J.C.; Dauphin, F.; Barré, L. Synthesis and biological investigations of [¹⁸F]MR18445, a 5-HT₃ receptor partial agonist. *Bioorg. Med. Chem.* **1998**, *6*, 789–795. [[CrossRef](#)]
174. Smith, W.W.; Sancilio, L.F.; Owera-Atepo, J.B.; Naylor, R.J.; Lambert, L. Zacopride, a potent 5-HT₃ antagonist. *J. Pharm. Pharmacol.* **1988**, 301–302. [[CrossRef](#)] [[PubMed](#)]
175. Hewlett, W.A.; Fridman, S.; Trivedi, B.L.; Schmidt, D.E.; De Paulis, T.; Ebert, M.H. Characterization of desamino-5-[125I]iodo-3-methoxy-zacopride ([125I]MIZAC) binding to 5-HT₃ receptors in the rat brain. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **1998**, *22*, 397–410. [[CrossRef](#)]
176. Hewlett, W.A.; Trivedi, B.L.; Zhang, Z.; Lovinger, D.M.; Ansari, M.S.I.B.; Ebert, M.H.; Schmidt, D.E. Characterization of (S)-Des-4-amino-3-[125I]iodozacopride ([125I]DAIZAC), a Selective High-Affinity Radioligand for 5-hydroxytryptamine₃ receptors. *J. Pharmacol. Exp. Ther.* **1999**, *288*, 221–231.
177. Pithia, N.K.; Liang, C.; Pan, X.Z.; Pan, M.L.; Mukherjee, J. Synthesis and evaluation of (S)-[18F]fisetron in the rat brain as a potential PET imaging agent for serotonin 5-HT₃ receptors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1919–1924. [[CrossRef](#)]
178. Mu, L.; Müller Herde, A.; Rüefli, P.M.; Sladojevich, F.; Milicevic Sephton, S.; Krämer, S.D.; Thompson, A.J.; Schibli, R.; Ametamey, S.M.; Lochner, M. Synthesis and Pharmacological Evaluation of [11C]Granisetron and [18F]Fluoropalonosetron as PET Probes for 5-HT₃ Receptor Imaging. *ACS Chem. Neurosci.* **2016**, *7*, 1552–1564. [[CrossRef](#)]
179. Ishiwata, K.; Ishii, K.; Ishii, S.I.; Senda, M. Synthesis of 5-HT₃ receptor antagonists, [11C]Y-25130 and [11C]YM060. *Appl. Radiat. Isot.* **1995**, *46*, 907–910. [[CrossRef](#)]

180. Thorell, J.O.; Stone-Elander, S.; Eriksson, L.; Ingvar, M. N-methylquipazine: Carbon-11 labelling of the 5-HT₃ agonist and in vivo evaluation of its biodistribution using PET. *Nucl. Med. Biol.* **1997**, *24*, 405–412. [[CrossRef](#)]
181. Gao, M.; Wang, M.; Hutchins, G.D.; Zheng, Q.H. Synthesis of new carbon-11 labeled benzoxazole derivatives for PET imaging of 5-HT₃ receptor. *Eur. J. Med. Chem.* **2008**, *43*, 1570–1574. [[CrossRef](#)]
182. Dumuis, A.; Bouhelal, R.; Sebben, M.; Cory, R.; Bockaert, J. A nonclassical 5-hydroxytryptamine receptor positively coupled with adenylate cyclase in the central nervous system. *Mol. Pharmacol.* **1988**, *34*, 880–887. [[PubMed](#)]
183. Bockaert, J.; Claeysen, S.; Compan, V.; Dumuis, A. 5-HT₄ receptors: History, molecular pharmacology and brain functions. *Neuropharmacology* **2008**, *55*, 922–931. [[CrossRef](#)] [[PubMed](#)]
184. Hegde, S.S.; Eglén, R.M. Peripheral 5-HT₄ receptors. *FASEB J.* **1996**, *10*, 1398–1407. [[CrossRef](#)] [[PubMed](#)]
185. Bockaert, J.; Claeysen, S.; Compan, V.; Dumuis, A. 5-HT₄ receptors, a place in the sun: Act two. *Curr. Opin. Pharmacol.* **2011**, *11*, 87–93. [[CrossRef](#)] [[PubMed](#)]
186. Hagen, H.; Manahan-Vaughan, D. The serotonergic 5-HT₄ receptor: A unique modulator of hippocampal synaptic information processing and cognition. *Neurobiol. Learn. Mem.* **2017**, *138*, 145–153. [[CrossRef](#)]
187. Claeysen, S.; Bockaert, J.; Giannoni, P. Serotonin: A New Hope in Alzheimer's Disease? *ACS Chem. Neurosci.* **2015**, *6*, 940–943. [[CrossRef](#)]
188. Lezoualc'h, F. 5-HT₄ receptor and Alzheimer's disease: The amyloid connection. *Exp. Neurol.* **2007**, *205*, 325–329. [[CrossRef](#)]
189. Jean, A.; Conductier, G.; Manrique, C.; Bouras, C.; Berta, P.; Hen, R.; Charnay, Y.; Bockaert, J.; Compan, V. Anorexia induced by activation of serotonin 5-HT₄ receptors is mediated by increases in CART in the nucleus accumbens. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 16335–16340. [[CrossRef](#)]
190. Lucas, G.; Rymar, V.V.; Du, J.; Mnie-Filali, O.; Bisgaard, C.; Manta, S.; Lambas-Senas, L.; Wiborg, O.; Haddjeri, N.; Piñeyro, G.; et al. Serotonin₄ (5-HT₄) Receptor Agonists Are Putative Antidepressants with a Rapid Onset of Action. *Neuron* **2007**, *55*, 712–725. [[CrossRef](#)]
191. Kaumann, A.J.; Gaster, L.M.; King, F.D.; Brown, A.M. Blockade of human atrial 5-HT₄ receptors by SB 207710, a selective and high affinity 5-HT₄ receptor antagonist. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1994**, *349*, 546–548. [[CrossRef](#)]
192. Varnäs, K.; Halldin, C.; Pike, V.W.; Hall, H. Distribution of 5-HT₄ receptors in the postmortem human brain—An autoradiographic study using [¹²⁵I]SB 207710. *Eur. Neuropsychopharmacol.* **2003**, *13*, 228–234. [[CrossRef](#)]
193. Patel, S.; Roberts, J.; Moorman, J.; Reavill, C. Localization of serotonin-4 receptors in the striatonigral pathway in rat brain. *Neuroscience* **1995**, *69*, 1159–1167. [[CrossRef](#)]
194. Pike, V.W.; Halldin, C.; Nobuhara, K.; Hiltunen, J.; Mulligan, R.S.; Swahn, C.G.; Karlsson, P.; Olsson, H.; Hume, S.P.; Hirani, E.; et al. Radioiodinated SB 207710 as a radioligand in vivo: Imaging of brain 5-HT₄ receptors with SPET. *Eur. J. Nucl. Med. Mol. Imaging* **2003**, *30*, 1520–1528. [[CrossRef](#)] [[PubMed](#)]
195. Gee, A.D.; Martarello, L.; Passchier, J.; Wishart, M.; Parker, C.; Matthews, J.; Comley, R.; Hopper, R.; Gunn, R. Synthesis and evaluation of [¹¹C]SB207145 as the first in vivo serotonin 5-HT₄ receptor radioligand for PET imaging in man. *Curr. Radiopharm.* **2008**, *1*, 110–114. [[CrossRef](#)]
196. Kornum, B.R.; Lind, N.M.; Gillings, N.; Marner, L.; Andersen, F.; Knudsen, G.M. Evaluation of the novel 5-HT₄ receptor PET ligand [¹¹C]SB207145 in the Göttingen minipig. *J. Cereb. Blood Flow Metab.* **2009**, *29*, 186–196. [[CrossRef](#)] [[PubMed](#)]
197. Marner, L.; Gillings, N.; Comley, R.A.; Baaré, W.F.C.; Rabiner, E.A.; Wilson, A.A.; Houle, S.; Hasselbalch, S.G.; Svarer, C.; Gunn, R.N.; et al. Kinetic modeling of [¹¹C]SB207145 binding to 5-HT₄ receptors in the human brain in vivo. *J. Nucl. Med.* **2009**, *50*, 900–908. [[CrossRef](#)] [[PubMed](#)]
198. Marner, L.; Gillings, N.; Madsen, K.; Erritzoe, D.; Baaré, W.F.C.; Svarer, C.; Hasselbalch, S.G.; Knudsen, G.M. Brain imaging of serotonin 4 receptors in humans with [¹¹C]SB207145-PET. *Neuroimage* **2010**, *50*, 855–861. [[CrossRef](#)] [[PubMed](#)]
199. Madsen, K.; Marner, L.; Haahr, M.; Gillings, N.; Knudsen, G.M. Mass dose effects and in vivo affinity in brain PET receptor studies—A study of cerebral 5-HT₄ receptor binding with [¹¹C]SB207145. *Nucl. Med. Biol.* **2011**, *38*, 1085–1091. [[CrossRef](#)]
200. Haahr, M.E.; Fisher, P.M.; Jensen, C.G.; Frokjaer, V.G.; McMahon, B.; Madsen, K.; Baaré, W.F.C.; Lehel, S.; Norremolle, A.; Rabiner, E.A.; et al. Central 5-HT₄ receptor binding as biomarker of serotonergic tone in humans: A [¹¹C]SB207145 PET study. *Mol. Psychiatry* **2014**, *19*, 427–432. [[CrossRef](#)]
201. Perfalk, E.; da Cunha-Bang, S.; Holst, K.K.; Keller, S.; Svarer, C.; Knudsen, G.M.; Frokjaer, V.G. Testosterone levels in healthy men correlate negatively with serotonin 4 receptor binding. *Psychoneuroendocrinology* **2017**, *81*, 22–28. [[CrossRef](#)]
202. Jakobsen, G.R.; Fisher, P.M.; Dyssegaard, A.; McMahon, B.; Holst, K.K.; Lehel, S.; Svarer, C.; Jensen, P.S.; Knudsen, G.M.; Frokjaer, V.G. Brain serotonin 4 receptor binding is associated with the cortisol awakening response. *Psychoneuroendocrinology* **2016**, *67*, 124–132. [[CrossRef](#)] [[PubMed](#)]
203. Deen, M.; Hansen, H.D.; Hougaard, A.; Nørgaard, M.; Eiberg, H.; Lehel, S.; Ashina, M.; Knudsen, G.M. High brain serotonin levels in migraine between attacks: A 5-HT₄ receptor binding PET study. *NeuroImage Clin.* **2018**, *18*, 97–102. [[CrossRef](#)] [[PubMed](#)]
204. Xu, R.; Hong, J.; Morse, C.L.; Pike, V.W. Synthesis, structure-affinity relationships, and radiolabeling of selective high-affinity 5-HT₄ receptor ligands as prospective imaging probes for positron emission tomography. *J. Med. Chem.* **2010**, *53*, 7035–7047. [[CrossRef](#)] [[PubMed](#)]
205. Terry, G.E.; Hirvonen, J.; Liow, J.S.; Zoghbi, S.S.; Gladding, R.; Tauscher, J.T.; Schaus, J.M.; Phebus, L.; Felder, C.C.; Morse, C.L.; et al. Imaging and quantitation of cannabinoid CB₁ receptors in human and monkey brains using 18F-labeled inverse agonist radioligands. *J. Nucl. Med.* **2010**, *51*, 112–120. [[CrossRef](#)]

206. Lohith, T.G.; Xu, R.; Tsujikawa, T.; Morse, C.L.; Anderson, K.B.; Gladding, R.L.; Zoghbi, S.S.; Fujita, M.; Innis, R.B.; Pike, V.W. Evaluation in monkey of two candidate PET radioligands, [11C]RX-1 and [18F]RX-2, for imaging brain 5-HT₄ receptors. *Synapse* **2014**, *68*, 613–623. [[CrossRef](#)]
207. Caillé, F.; Morley, T.J.; Tavares, A.A.S.; Papin, C.; Twardy, N.M.; Alagille, D.; Lee, H.S.; Baldwin, R.M.; Seibyl, J.P.; Barret, O.; et al. Synthesis and biological evaluation of positron emission tomography radiotracers targeting serotonin 4 receptors in brain: [18F]MNI-698 and [18F]MNI-699. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6243–6247. [[CrossRef](#)]
208. Tavares, A.A.S.; Caillé, F.; Barret, O.; Papin, C.; Lee, H.; Morley, T.J.; Fowles, K.; Holden, D.; Seibyl, J.P.; Alagille, D.; et al. Whole-body biodistribution and dosimetry estimates of a novel radiotracer for imaging of serotonin 4 receptors in brain: [18F]MNI-698. *Nucl. Med. Biol.* **2014**, *41*, 432–439. [[CrossRef](#)]
209. Tavares, A.A.S.; Caillé, F.; Barret, O.; Papin, C.; Lee, H.; Morley, T.J.; Fowles, K.; Holden, D.; Seibyl, J.P.; Alagille, D.; et al. In vivo evaluation of 18F-MNI698: An 18F-labeled radiotracer for imaging of serotonin 4 receptors in brain. *J. Nucl. Med.* **2014**, *55*, 858–864. [[CrossRef](#)]
210. Fresneau, N.; Dumas, N.; Tournier, B.B.; Fossey, C.; Ballandonne, C.; Lesnard, A.; Millet, P.; Charnay, Y.; Cailly, T.; Bouillon, J.P.; et al. Design of a serotonin 4 receptor radiotracer with decreased lipophilicity for single photon emission computed tomography. *Eur. J. Med. Chem.* **2015**, *94*, 386–396. [[CrossRef](#)]
211. Monsma, F.J.; Shen, Y.; Ward, R.P.; Hamblin, M.W.; Sibley, D.R. Cloning and expression of a novel serotonin receptor with high affinity for tricyclic psychotropic drugs. *Mol. Pharmacol.* **1993**, *43*, 320–327.
212. Ruat, M.; Traiffort, E.; Leurs, R.; Tardivel-Lacombe, J.; Diaz, J.; Arrang, J.M.; Schwartz, J.C. Molecular cloning, characterization, and localization of a high-affinity serotonin receptor (5-HT₇) activating cAMP formation. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 8547–8551. [[CrossRef](#)]
213. Kohen, R.; Metcalf, M.A.; Khan, N.; Druck, T.; Huebner, K.; Lachowicz, J.E.; Meltzer, H.Y.; Sibley, D.R.; Roth, B.L.; Hamblin, M.W. Cloning, characterization, and chromosomal localization of a human 5-HT₆ serotonin receptor. *J. Neurochem.* **1996**, *66*, 47–56. [[CrossRef](#)] [[PubMed](#)]
214. Yoshioka, M.; Matsumoto, M.; Togashi, H.; Mori, K.; Saito, H. Central distribution and function of 5-HT₆ receptor subtype in the rat brain. *Life Sci.* **1998**, *62*, 1473–1477. [[CrossRef](#)]
215. Ward, R.P.; Hamblin, M.W.; Lachowicz, J.E.; Hoffman, B.J.; Sibley, D.R.; Dorsa, D.M. Localization of serotonin subtype 6 receptor messenger RNA in the rat brain by in situ hybridization histochemistry. *Neuroscience* **1995**, *64*, 1105–1111. [[CrossRef](#)]
216. Gérard, C.; Martres, M.P.; Lefèvre, K.; Miquel, M.C.; Vergé, D.; Lanfumey, L.; Doucet, E.; Hamon, M.; El Mestikawy, S. Immunolocalization of serotonin 5-HT₆ receptor-like material in the rat central nervous system. *Brain Res.* **1997**, *746*, 207–219. [[CrossRef](#)]
217. Roberts, J.C.; Reavill, C.; East, S.Z.; Harrison, P.J.; Patel, S.; Routledge, C.; Leslie, R.A. The distribution of 5-HT₆ receptors in rat brain: An autoradiographic binding study using the radiolabelled 5-HT₆ receptor antagonist [125I]SB-258585. *Brain Res.* **2002**, *934*, 49–57. [[CrossRef](#)]
218. East, S.Z.; Burnet, P.W.J.; Leslie, R.A.; Roberts, J.C.; Harrison, P.J. 5-HT₆ receptor binding sites in schizophrenia and following antipsychotic drug administration: Autoradiographic studies with [125I]SB-258585. *Synapse* **2002**, *45*, 191–199. [[CrossRef](#)]
219. Barnes, N.M.; Ahern, G.P.; Becamel, C.; Bockaert, J.; Camilleri, M.; Chaumont-Dubel, S.; Claeysen, S.; Cunningham, K.A.; Fone, K.C.; Gershon, M.; et al. International union of basic and clinical pharmacology. Cx. Classification of receptors for 5-hydroxytryptamine; pharmacology and function. *Pharmacol. Rev.* **2021**, *73*, 310–520. [[CrossRef](#)]
220. Meffre, J.; Chaumont-Dubel, S.; Mannoury la Cour, C.; Loiseau, F.; Watson, D.J.G.; Dekeyne, A.; Séveno, M.; Rivet, J.M.; Gaven, F.; Déléris, P.; et al. 5-HT₆ receptor recruitment of mTOR as a mechanism for perturbed cognition in schizophrenia. *EMBO Mol. Med.* **2012**, *4*, 1043–1056. [[CrossRef](#)]
221. Karila, D.; Freret, T.; Bouet, V.; Boulouard, M.; Dallemagne, P.; Rochais, C. Therapeutic Potential of 5-HT₆ Receptor Agonists. *J. Med. Chem.* **2015**, *58*, 7901–7912. [[CrossRef](#)]
222. Voigt, J.P.; Fink, H. Serotonin controlling feeding and satiety. *Behav. Brain Res.* **2015**, *277*, 14–31. [[CrossRef](#)] [[PubMed](#)]
223. Andrews, M.; Tousi, B.; Sabbagh, M.N. 5HT₆ Antagonists in the Treatment of Alzheimer’s Dementia: Current Progress. *Neurol. Ther.* **2018**, *7*, 51–58. [[CrossRef](#)] [[PubMed](#)]
224. Khoury, R.; Grysman, N.; Gold, J.; Patel, K.; Grossberg, G.T. The role of 5-HT₆-receptor antagonists in Alzheimer’s disease: An update. *Expert Opin. Investig. Drugs* **2018**, *27*, 523–533. [[CrossRef](#)]
225. Ferrero, H.; Solas, M.; Francis, P.T.; Ramirez, M.J. Serotonin 5-HT₆ Receptor Antagonists in Alzheimer’s Disease: Therapeutic rationale and Current Development Status. *CNS Drugs* **2017**, *31*, 19–32. [[CrossRef](#)] [[PubMed](#)]
226. Hirst, W.D.; Minton, J.A.L.; Bromidge, S.M.; Moss, S.F.; Latter, A.J.; Riley, G.; Routledge, C.; Middlemiss, D.N.; Price, G.W. Characterization of [¹²⁵I]-SB-258585 binding to human recombinant and native 5-HT₆ receptors in rat, pig and human brain tissue. *Br. J. Pharmacol.* **2000**, *130*, 1597–1605. [[CrossRef](#)] [[PubMed](#)]
227. Tang, S.; Verdurand, M.; Joseph, B.; Lemoine, L.; Daoust, A.; Billard, T.; Fournet, G.; Le Bars, D.; Zimmer, L. Synthesis and biological evaluation in rat and cat of [¹⁸F]12ST05 as a potential 5-HT₆ PET radioligand. *Nucl. Med. Biol.* **2007**, *34*, 995–1002. [[CrossRef](#)]
228. Zhou, P.; Yan, Y.; Bernotas, R.; Harrison, B.L.; Huryn, D.; Robichaud, A.J.; Zhang, G.M.; Smith, D.L.; Schechter, L.E. 4-(2-Aminoethoxy)-N-(phenylsulfonyl)indoles as novel 5-HT₆ receptor ligands. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1393–1396. [[CrossRef](#)]

229. Parker, C.A.; Gunn, R.N.; Rabiner, E.A.; Slifstein, M.; Comley, R.; Salinas, C.; Johnson, C.N.; Jakobsen, S.; Houle, S.; Laruelle, M.; et al. Radiosynthesis and characterization of ^{11}C -GSK215083 as a PET radioligand for the 5-HT₆ receptor. *J. Nucl. Med.* **2012**, *53*, 295–303. [[CrossRef](#)]
230. Parker, C.A.; Rabiner, E.A.; Gunn, R.N.; Searle, G.; Martarello, L.; Comley, R.A.; Davy, M.; Wilson, A.A.; Houle, S.; Mizrahi, R.; et al. Human kinetic modeling of the 5HT₆ PET radioligand 11C-GSK215083 and its utility for determining occupancy at both 5HT₆ and 5HT_{2A} receptors by SB742457 as a potential therapeutic mechanism of action in Alzheimer disease. *J. Nucl. Med.* **2015**, *56*, 1901–1909. [[CrossRef](#)]
231. Rosse, G. Quinoline Derivatives as 5-HT₆ Receptor PET Ligands. *ACS Med. Chem. Lett.* **2014**, *5*, 275–276. [[CrossRef](#)]
232. Colomb, J.; Becker, G.; Fieux, S.; Zimmer, L.; Billard, T. Syntheses, radiolabelings, and in vitro evaluations of fluorinated pet radioligands of 5-HT₆ serotonergic receptors. *J. Med. Chem.* **2014**, *57*, 3884–3890. [[CrossRef](#)] [[PubMed](#)]
233. Emery, S.; Fieux, S.; Vidal, B.; Courault, P.; Bouvard, S.; Tourvieille, C.; Jecker, T.; Billard, T.; Zimmer, L.; Lancelot, S. Preclinical validation of [18F]2FNQ1P as a specific PET radiotracer of 5-HT₆ receptors in rat, pig, non-human primate and human brain tissue. *Nucl. Med. Biol.* **2020**, *82–83*, 57–63. [[CrossRef](#)] [[PubMed](#)]
234. Bard, J.A.; Zgombick, J.; Adham, N.; Vaysse, P.; Brancheck, T.A.; Weinshank, R.L. Cloning of a novel human serotonin receptor (5-HT₇) positively linked to adenylate cyclase. *J. Biol. Chem.* **1993**, *268*, 23422–23426. [[CrossRef](#)]
235. Lovenberg, T.W.; Baron, B.M.; de Lecea, L.; Miller, J.D.; Prosser, R.A.; Rea, M.A.; Foye, P.E.; Racke, M.; Slone, A.L.; Siegel, B.W. A novel adenylyl cyclase-activating serotonin receptor (5-HT₇) implicated in the regulation of mammalian circadian rhythms. *Neuron* **1993**, *11*, 449–458. [[CrossRef](#)]
236. Varnäs, K.; Thomas, D.R.; Tupala, E.; Tiihonen, J.; Hall, H. Distribution of 5-HT₇ receptors in the human brain: A preliminary autoradiographic study using [3H]SB-269970. *Neurosci. Lett.* **2004**, *367*, 313–316. [[CrossRef](#)]
237. Cifariello, A.; Pompili, A.; Gasbarri, A. 5-HT₇ receptors in the modulation of cognitive processes. *Behav. Brain Res.* **2008**, *195*, 171–179. [[CrossRef](#)]
238. L'Estrade, E.T.; Erlandsson, M.; Edgar, F.G.; Ohlsson, T.; Knudsen, G.M.; Herth, M.M. Towards selective CNS PET imaging of the 5-HT₇ receptor system: Past, present and future. *Neuropharmacology* **2020**, *172*, 107830–107848. [[CrossRef](#)]
239. Kikuchi, C.; Nagaso, H.; Hiranuma, T.; Koyama, M. Tetrahydrobenzindoles: Selective Antagonists of the 5-HT₇ Receptor. *J. Med. Chem.* **1999**, *42*, 533–535. [[CrossRef](#)]
240. Kikuchi, C.; Hiranuma, T.; Koyama, M. Tetrahydrothienopyridylbutyl-tetrahydrobenzindoles: New selective ligands of the 5-HT₇ receptor. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2549–2552. [[CrossRef](#)]
241. Zhang, M.R.; Haradahira, T.; Maeda, J.; Okauchi, T.; Kida, T.; Obayashi, S.; Suzuki, K.; Suhara, T. Synthesis and preliminary PET study of the 5-HT₇ receptor antagonist [^{11}C]DR4446. *J. Label. Compd. Radiopharm.* **2002**, *45*, 857–866. [[CrossRef](#)]
242. Herth, M.M.; Volk, B.; Pallagi, K.; Kofoed Bech, L.; Antoni, F.A.; Knudsen, G.M.; Kristensen, J.L. Synthesis and in vitro evaluation of oxindole derivatives as potential radioligands for 5-HT₇ receptor imaging with PET. *ACS Chem. Neurosci.* **2012**, *3*, 1002–1007. [[CrossRef](#)] [[PubMed](#)]
243. Lemoine, L.; Andries, J.; Le Bars, D.; Billard, T.; Zimmer, L. Comparison of 4 radiolabeled antagonists for serotonin 5-HT₇ receptor neuroimaging: Toward the first PET radiotracer. *J. Nucl. Med.* **2011**, *52*, 1811–1818. [[CrossRef](#)] [[PubMed](#)]
244. Tampo L'Estrade, E.; Xiong, M.; Shalgunov, V.; Edgar, F.G.; Volk, B.; Baerentzen, S.L.; Palner, M.; Erlandsson, M.; Ohlsson, T.; Knudsen, G.M.; et al. Development and Evaluation of Two Potential 5-HT₇ Receptor PET Tracers: [18F]ENL09 and [18F]ENL10. *ACS Chem. Neurosci.* **2019**, *10*, 3961–3968. [[CrossRef](#)] [[PubMed](#)]
245. Hansen, H.D.; Constantinescu, C.C.; Barret, O.; Herth, M.M.; Magnussen, J.H.; Lehel, S.; Dyssegaard, A.; Colomb, J.; Billard, T.; Zimmer, L.; et al. Evaluation of [18F]2FP3 in pigs and non-human primates. *J. Label. Compd. Radiopharm.* **2019**, *62*, 34–42. [[CrossRef](#)]
246. Colomb, J.; Becker, G.; Forcellini, E.; Meyer, S.; Buisson, L.; Zimmer, L.; Billard, T. Synthesis and pharmacological evaluation of a new series of radiolabeled ligands for 5-HT₇ receptor PET neuroimaging. *Nucl. Med. Biol.* **2014**, *41*, 330–337. [[CrossRef](#)]
247. L'Estrade, E.T.; Edgar, F.G.; Xiong, M.; Shalgunov, V.; Baerentzen, S.L.; Erlandsson, M.; Ohlsson, T.G.; Palner, M.; Knudsen, G.M.; Herth, M.M. Synthesis, Radiolabeling, and in Vitro and in Vivo Evaluation of [18F]ENL30: A Potential PET Radiotracer for the 5-HT₇ Receptor. *ACS Omega* **2019**, *4*, 7344–7353. [[CrossRef](#)]
248. L'Estrade, E.T.; Shalgunov, V.; Edgar, F.G.; Strebl-Bantillo, M.G.; Xiong, M.; Crestey, F.; Neelamegam, R.; Dyssegaard, A.; Lehel, S.; Erlandsson, M.; et al. Radiosynthesis and preclinical evaluation of [11C]Cimbi-701—Towards the imaging of cerebral 5-HT₇ receptors. *J. Label. Compd. Radiopharm.* **2020**, *63*, 46–55. [[CrossRef](#)]
249. Rudnick, G. Serotonin transporters—Structure and function. *J. Membr. Biol.* **2006**, *213*, 101–110. [[CrossRef](#)]
250. Suehiro, M.; Scheffel, U.; Ravert, H.T.; Dannals, R.F.; Wagner, H.N. [11C](+)McN5652 as a radiotracer for imaging serotonin uptake sites with pet. *Life Sci.* **1993**, *53*, 883–892. [[CrossRef](#)]
251. Szabo, Z.; Scheffel, U.; Suehiro, M.; Dannals, R.F.; Kim, S.E.; Ravert, H.T.; Ricaurte, G.A.; Wagner, H.N. Positron emission tomography of 5-HT transporter sites in the baboon brain with [11C]McN5652. *J. Cereb. Blood Flow Metab.* **1995**, *15*, 798–805. [[CrossRef](#)]
252. Parsey, R.V.; Kegeles, L.S.; Hwang, D.R.; Simpson, N.; Abi-Dargham, A.; Mawlawi, O.; Slifstein, M.; Van Heertum, R.L.; Mann, J.J.; Laruelle, M. In vivo quantification of brain serotonin transporters in humans using [11C]McN 5652. *J. Nucl. Med.* **2000**, *41*, 1465–1477. [[PubMed](#)]

253. Ichimiya, T.; Suhara, T.; Sudo, Y.; Okubo, Y.; Nakayama, K.; Nankai, M.; Inoue, M.; Yasuno, F.; Takano, A.; Maeda, J.; et al. Serotonin transporter binding in patients with mood disorders: A PET study with [¹¹C](+)-McN5652. *Biol. Psychiatry* **2002**, *51*, 715–722. [[CrossRef](#)]
254. Simpson, H.B.; Lombardo, I.; Slifstein, M.; Huang, H.Y.; Hwang, D.R.; Abi-Dargham, A.; Liebowitz, M.R.; Laruelle, M. Serotonin transporters in obsessive-compulsive disorder: A positron emission tomography study with [¹¹C]McN 5652. *Biol. Psychiatry* **2003**, *54*, 1414–1421. [[CrossRef](#)]
255. Reivich, M.; Amsterdam, J.D.; Brunswick, D.J.; Yann Shiue, C. PET brain imaging with [¹¹C](+)-McN5652 shows increased serotonin transporter availability in major depression. *J. Affect. Disord.* **2004**, *82*, 321–327. [[CrossRef](#)] [[PubMed](#)]
256. Marjamäki, P.; Zessin, J.; Eskola, O.; Grönroos, T.; Haaparanta, M.; Bergman, J.; Lehtikoinen, P.; Forsback, S.; Brust, P.; Steinbach, J.; et al. S-[¹⁸F]fluoromethyl-(+)-McN5652, a PET tracer for the serotonin transporter: Evaluation in rats. *Synapse* **2003**, *47*, 45–53. [[CrossRef](#)]
257. Brust, P.; Zessin, J.; Kuwabara, H.; Pawelke, B.; Kretschmar, M.; Hinz, R.; Bergman, J.; Eskola, O.; Solin, O.; Steinbach, J.; et al. Positron emission tomography imaging of the serotonin transporter in the pig brain using [¹¹C](+)-McN5652 and S-([¹⁸F]fluoromethyl)-(+)-McN5652. *Synapse* **2003**, *47*, 143–151. [[CrossRef](#)]
258. Brust, P.; Hinz, R.; Kuwabara, H.; Hesse, S.; Zessin, J.; Pawelke, B.; Stephan, H.; Bergmann, R.; Steinbach, J.; Sabri, O. In vivo Measurement of the Serotonin Transporter with (S)-([¹⁸F]fluoromethyl)-(+)-McN5652. *Neuropsychopharmacology* **2003**, *28*, 2010–2019. [[CrossRef](#)]
259. Oya, S.; Kung, M.P.; Acton, P.D.; Mu, M.; Hou, C.; Kung, H.F. A new single-photon emission computed tomography imaging agent for serotonin transporters: [123I]IDAM, 5-Iodo-2-((2-((dimethylamino)methyl)phenyl)thio)benzyl alcohol. *J. Med. Chem.* **1999**, *42*, 333–335. [[CrossRef](#)]
260. Wilson, A.A.; Ginovart, N.; Schmidt, M.; Meyer, J.H.; Threlkeld, P.G.; Houle, S. Novel radiotracers for imaging the serotonin transporter by positron emission tomography: Synthesis, radiosynthesis, and in vitro and ex vivo evaluation of ¹¹C-labeled 2-(phenylthio)araalkylamines. *J. Med. Chem.* **2000**, *43*, 3103–3110. [[CrossRef](#)]
261. Houle, S.; Ginovart, N.; Hussey, D.; Meyer, J.H.; Wilson, A.A. Imaging the serotonin transporter with positron emission tomography: Initial human studies with [¹¹C]DAPP and [¹¹C]DASB. *Eur. J. Nucl. Med.* **2000**, *27*, 1719–1722. [[CrossRef](#)]
262. Szabo, Z.; McCann, U.D.; Wilson, A.A.; Scheffel, U.; Owonikoko, T.; Mathews, W.B.; Ravert, H.T.; Hilton, J.; Dannals, R.F.; Ricaurte, G.A. Comparison of (+)-¹¹C-McN5652 and ¹¹C-DASB as serotonin transporter radioligands under various experimental conditions. *J. Nucl. Med.* **2002**, *43*, 678–692. [[PubMed](#)]
263. Frankle, W.G.; Huang, Y.; Hwang, D.R.; Talbot, P.S.; Slifstein, M.; Van Heertum, R.; Abi-Dargham, A.; Laruelle, M. Comparative evaluation of serotonin transporter radioligands ¹¹C-DASB and ¹¹C-McN 5652 in healthy humans. *J. Nucl. Med.* **2004**, *45*, 682–694. [[CrossRef](#)] [[PubMed](#)]
264. Bélanger, M.J.; Simpson, N.R.; Wang, T.; Van Heertum, R.L.; Mann, J.J.; Parsey, R.V. Biodistribution and radiation dosimetry of [¹¹C]DASB in baboons. *Nucl. Med. Biol.* **2004**, *31*, 1097–1102. [[CrossRef](#)]
265. Wilson, A.A.; Ginovart, N.; Hussey, D.; Meyer, J.; Houle, S. In vitro and in vivo characterisation of [¹¹C]-DASB: A probe for in vivo measurements of the serotonin transporter by positron emission tomography. *Nucl. Med. Biol.* **2004**, *31*, 1097–1102. [[CrossRef](#)]
266. Ginovart, N.; Wilson, A.A.; Meyer, J.H.; Hussey, D.; Houle, S. [¹¹C]-DASB, a tool for in vivo measurement of SSRI-induced occupancy of the serotonin transporter: PET characterization and evaluation in cats. *Synapse* **2003**, *47*, 123–133. [[CrossRef](#)]
267. Meyer, J.H.; Wilson, A.A.; Ginovart, N.; Goulding, V.; Hussey, D.; Hood, K.; Houle, S. Occupancy of serotonin transporters by paroxetine and citalopram during treatment of depression: A [¹¹C]DASB PET imaging study. *Am. J. Psychiatry* **2001**, *158*, 1843–1849. [[CrossRef](#)]
268. Cannon, D.M.; Ichise, M.; Rollis, D.; Klaver, J.M.; Gandhi, S.K.; Charney, D.S.; Manji, H.K.; Drevets, W.C. Elevated Serotonin Transporter Binding in Major Depressive Disorder Assessed Using Positron Emission Tomography and [¹¹C]DASB; Comparison with Bipolar Disorder. *Biol. Psychiatry* **2007**, *62*, 870–877. [[CrossRef](#)]
269. Brown, A.K.; George, D.T.; Fujita, M.; Liow, J.S.; Ichise, M.; Hibbeln, J.; Ghose, S.; Sangare, J.; Hommer, D.; Innis, R.B. PET [¹¹C]DASB imaging of serotonin transporters in patients with alcoholism. *Alcohol. Clin. Exp. Res.* **2007**, *31*, 28–32. [[CrossRef](#)]
270. Matsumoto, R.; Ichise, M.; Ito, H.; Ando, T.; Takahashi, H.; Ikoma, Y.; Kosaka, J.; Arakawa, R.; Fujimura, Y.; Ota, M.; et al. Reduced serotonin transporter binding in the insular cortex in patients with obsessive-compulsive disorder: A [¹¹C]DASB PET study. *Neuroimage* **2010**, *49*, 121–126. [[CrossRef](#)]
271. Politis, M.; Wu, K.; Loane, C.; Kiferle, L.; Molloy, S.; Brooks, D.J.; Piccini, P. Staging of serotonergic dysfunction in Parkinson's Disease: An in vivo ¹¹C-DASB PET study. *Neurobiol. Dis.* **2010**, *40*, 216–221. [[CrossRef](#)]
272. Kim, J.H.; Son, Y.D.; Kim, J.H.; Choi, E.J.; Lee, S.Y.; Lee, J.E.; Cho, Z.H.; Kim, Y.B. Serotonin transporter availability in thalamic subregions in schizophrenia: A study using 7.0-T MRI with [¹¹C]DASB high-resolution PET. *Psychiatry Res. Neuroimaging* **2015**, *231*, 50–57. [[CrossRef](#)] [[PubMed](#)]
273. Lee, J.; Kim, B.H.; Kim, E.; Howes, O.D.; Cho, K.I.K.; Yoon, Y.B.; Kwon, J.S. Higher serotonin transporter availability in early-onset obsessive-compulsive disorder patients undergoing escitalopram treatment: A [¹¹C]DASB PET study. *Hum. Psychopharmacol.* **2018**, *33*, 2–7. [[CrossRef](#)]
274. Christensen, J.B.; Bechgaard, K.; Paquignon, G. Carbon-11 labelling of MADAM in two different positions: A highly selective PET radioligand for the serotonin transporter. *J. Label. Compd. Radiopharm.* **2001**, *44*, 1013–1023. [[CrossRef](#)]

275. Halldin, C.; Lundberg, J.; Sóvágó, J.; Gulyás, B.; Guilloteau, D.; Vercouillie, J.; Emond, P.; Chalon, S.; Tarkiainen, J.; Hiltunen, J.; et al. [11C]MADAM, a new serotonin transporter radioligand characterized in the monkey brain by PET. *Synapse* **2005**, *58*, 173–183. [[CrossRef](#)] [[PubMed](#)]
276. Lundberg, J.; Odano, I.; Olsson, H.; Halldin, C.; Farde, L. Quantification of 11C-MADAM binding to the serotonin transporter in the human brain. *J. Nucl. Med.* **2005**, *46*, 1505–1515. [[PubMed](#)]
277. Lundberg, J.; Halldin, C.; Farde, L. Measurement of serotonin transporter binding with PET and [11C]MADAM: A test-retest reproducibility study. *Synapse* **2006**, *60*, 256–263. [[CrossRef](#)]
278. Majuri, J.; Joutsa, J.; Johansson, J.; Voon, V.; Parkkola, R.; Alho, H.; Arponen, E.; Kaasinen, V. Serotonin transporter density in binge eating disorder and pathological gambling: A PET study with [11C]MADAM. *Eur. Neuropsychopharmacol.* **2017**, *27*, 1281–1288. [[CrossRef](#)]
279. Oya, S.; Choi, S.R.; Hou, C.; Mu, M.; Kung, M.P.; Acton, P.D.; Siciliano, M.; Kung, H.F. 2-((2-((Dimethylamino)methyl)phenylthio)-5-iodophenylamine (ADAM): An improved serotonin transporter ligand. *Nucl. Med. Biol.* **2000**, *27*, 249–254. [[CrossRef](#)]
280. Lin, K.J.; Ye, X.X.; Yen, T.C.; Wey, S.P.; Tzen, K.Y.; Ting, G.; Hwang, J.J. Biodistribution study of [123I] ADAM in mice: Correlation with whole body autoradiography. *Nucl. Med. Biol.* **2002**, *29*, 643–650. [[CrossRef](#)]
281. Itti, E.; Klein, G.; Rosso, J.; Evangelista, E.; Monin, J.L.; Gueret, P.; Meignan, M.; Thirion, J.P. Assessment of myocardial reperfusion after myocardial infarction using automatic 3-dimensional quantification and template matching. *J. Nucl. Med.* **2004**, *45*, 1981–1988.
282. Lin, K.J.; Yen, T.C.; Wey, S.P.; Hwang, J.J.; Ye, X.X.; Tzen, K.Y.; Fu, Y.K.; Chen, J.C. Characterization of the binding sites for 123I-ADAM and the relationship to the serotonin transporter in rat and mouse brains using quantitative autoradiography. *J. Nucl. Med.* **2004**, *45*, 673–681. [[PubMed](#)]
283. Ye, X.X.; Hwang, J.J.; Hsieh, J.F.; Chen, J.C.; Chou, Y.T.; Tu, K.Y.; Wey, S.P.; Ting, G. In vivo quantification by SPECT of [123I] ADAM bound to serotonin transporters in the brains of rabbits. *Nucl. Med. Biol.* **2004**, *31*, 995–1003. [[CrossRef](#)] [[PubMed](#)]
284. Kauppinen, T.A.; Bergström, K.A.; Heikman, P.; Hiltunen, J.; Ahonen, A.K. Biodistribution and radiation dosimetry of [123I]ADAM in healthy human subjects: Preliminary results. *Eur. J. Nucl. Med. Mol. Imaging* **2003**, *30*, 132–136. [[CrossRef](#)] [[PubMed](#)]
285. Newberg, A.B.; Plössl, K.; Mozley, P.D.; Stubbs, J.B.; Wintering, N.; Udeshi, M.; Alavi, A.; Kauppinen, T.; Kung, H.F. Biodistribution and imaging with 123I-ADAM: A serotonin transporter imaging agent. *J. Nucl. Med.* **2004**, *45*, 834–841.
286. Catafau, A.M.; Pérez, V.; Penengo, M.M.; Bullich, S.; Danús, M.; Puigdemont, D.; Pascual, J.C.; Corripio, I.; Llop, J.; Perich, J.; et al. SPECT of serotonin transporters using 123I-ADAM: Optimal imaging time after bolus injection and long-term test-retest in healthy volunteers. *J. Nucl. Med.* **2005**, *46*, 1301–1309. [[PubMed](#)]
287. Frokjaer, V.G.; Pinborg, L.H.; Madsen, J.; De Nijs, R.; Svarer, C.; Wagner, A.; Knudsen, G.M. Evaluation of the serotonin transporter ligand 123I-ADAM for SPECT studies on humans. *J. Nucl. Med.* **2008**, *49*, 247–254. [[CrossRef](#)] [[PubMed](#)]
288. Ma, K.H.; Huang, W.S.; Huang, S.Y.; Cheng, C.Y.; Chen, C.Y.; Shen, L.H.; Liu, J.C.; Fu, Y.K. Imaging serotonin transporters using [123I]ADAM SPECT in a parkinsonian primate model. *Appl. Radiat. Isot.* **2008**, *66*, 1799–1803. [[CrossRef](#)]
289. Van De Giessen, E.; Booij, J. The SPECT tracer [123I]ADAM binds selectively to serotonin transporters: A double-blind, placebo-controlled study in healthy young men. *Eur. J. Nucl. Med. Mol. Imaging* **2010**, *37*, 1507–1511. [[CrossRef](#)]
290. Catafau, A.M.; Perez, V.; Plaza, P.; Pascual, J.C.; Bullich, S.; Suarez, M.; Penengo, M.M.; Corripio, I.; Puigdemont, D.; Danus, M.; et al. Serotonin transporter occupancy induced by paroxetine in patients with major depression disorder: A 123I-ADAM SPECT study. *Psychopharmacology* **2006**, *189*, 145–153. [[CrossRef](#)]
291. Herold, N.; Uebelhack, K.; Franke, L.; Amthauer, H.; Luedemann, L.; Bruhn, H.; Felix, R.; Uebelhack, R.; Plotkin, M. Imaging of serotonin transporters and its blockade by citalopram in patients with major depression using a novel SPECT ligand [123I]-ADAM. *J. Neural Transm.* **2006**, *113*, 659–670. [[CrossRef](#)]
292. Lundgren, J.D.; Newberg, A.B.; Allison, K.C.; Wintering, N.A.; Ploessl, K.; Stunkard, A.J. 123I-ADAM SPECT imaging of serotonin transporter binding in patients with Night Eating Syndrome: A preliminary report. *Psychiatry Res. Neuroimaging* **2008**, *162*, 214–220. [[CrossRef](#)] [[PubMed](#)]
293. Amsterdam, J.D.; Newberg, A.B.; Newman, C.F.; Shults, J.; Wintering, N.; Soeller, I. Change over time in brain serotonin transporter binding in major depression: Effects of therapy measured with [123I]-ADAM SPECT. *J. Neuroimaging* **2013**, *23*, 469–476. [[CrossRef](#)] [[PubMed](#)]
294. Wu, C.H.; Chang, C.S.; Yang, Y.K.; Shen, L.H.; Yao, W.J. Comparison of brain serotonin transporter using [I-123]-ADAM between obese and nonobese young adults without an eating disorder. *PLoS ONE* **2017**, *12*, e0170886. [[CrossRef](#)]
295. Shiue, G.G.; Fang, P.; Shiue, C.Y. Synthesis of N,N-dimethyl-2-(2-amino-4-[18F]fluorophenylthio)benzylamine as a serotonin transporter imaging agent. *Appl. Radiat. Isot.* **2003**, *58*, 183–191. [[CrossRef](#)]
296. Shiue, G.G.; Choi, S.R.; Fang, P.; Hou, C.; Acton, P.D.; Cardi, C.; Saffer, J.R.; Greenberg, J.H.; Karp, J.S.; Kung, H.F.; et al. N,N-dimethyl-2-(2-amino-4-18F-fluorophenylthio)-benzylamine (4-18F-ADAM): An improved PET radioligand for serotonin transporters. *J. Nucl. Med.* **2003**, *44*, 1890–1897. [[PubMed](#)]
297. Chen, Y.A.; Huang, W.S.; Lin, Y.S.; Cheng, C.Y.; Liu, R.S.; Wang, S.J.; Li, I.H.; Huang, S.Y.; Shiue, C.Y.; Chen, C.Y.; et al. Characterization of 4-[18F]-ADAM as an imaging agent for SERT in non-human primate brain using PET: A dynamic study. *Nucl. Med. Biol.* **2012**, *39*, 279–285. [[CrossRef](#)]

298. Yeh, Y.W.; Ho, P.S.; Chen, C.Y.; Kuo, S.C.; Liang, C.S.; Ma, K.H.; Shiue, C.Y.; Huang, W.S.; Cheng, C.Y.; Wang, T.Y.; et al. Incongruent reduction of serotonin transporter associated with suicide attempts in patients with major depressive disorder: A positron emission tomography study with 4-[18F]-ADAM. *Int. J. Neuropsychopharmacol.* **2015**, *18*, pyu065. [[CrossRef](#)] [[PubMed](#)]
299. Yeh, Y.W.; Ho, P.S.; Kuo, S.C.; Chen, C.Y.; Liang, C.S.; Yen, C.H.; Huang, C.C.; Ma, K.H.; Shiue, C.Y.; Huang, W.S.; et al. Disproportionate reduction of serotonin transporter may predict the response and adherence to antidepressants in patients with major depressive disorder: A positron emission tomography study with 4-[18F]-ADAM. *Int. J. Neuropsychopharmacol.* **2015**, *18*, pyu120. [[CrossRef](#)]
300. Wang, J.L.; Parhi, A.K.; Oya, S.; Lieberman, B.; Kung, H.F. In vivo characterization of a series of 18F-diaryl sulfides (18F-2-(2'-(dimethylamino)methyl)-4'-(fluoroalkoxy) phenylthio)benzenamine) for PET imaging of the serotonin transporter. *J. Nucl. Med.* **2009**, *50*, 1509–1517. [[CrossRef](#)]
301. Qiao, H.; Zhang, Y.; Wu, Z.; Zhu, L.; Choi, S.R.; Ploessl, K.; Kung, H.F. One-step preparation of [18F]FPBM for PET imaging of serotonin transporter (SERT) in the brain. *Nucl. Med. Biol.* **2016**, *43*, 470–477. [[CrossRef](#)]
302. Innis, R.; Baldwin, R.; Sybirska, E.; Zea, Y.; Laruelle, M.; Al-Tikriti, M.; Charney, D.; Zoghbi, S.; Smith, E.; Wisniewski, G.; et al. Single photon emission computed tomography imaging of monoamine reuptake sites in primate brain with [¹²³I]CIT. *Eur. J. Pharmacol.* **1991**, *200*, 369–370. [[CrossRef](#)]
303. Neumeyer, J.L.; Wang, S.; Milius, R.A.; Baldwin, R.M.; Zea-Ponce, Y.; Hoffer, P.B.; Sybirska, E.; Al-Tikriti, M.; Charney, D.S. [123I]-2.beta.-carbomethoxy-3.beta.-(4-iodophenyl)tropane: High-affinity SPECT (single photon emission computed tomography) radiotracer of monoamine reuptake sites in brain. *J. Med. Chem.* **1991**, *34*, 3144–3146. [[CrossRef](#)] [[PubMed](#)]
304. Kuikka, J.T.; Åkerman, K.; Bergström, K.A.; Karhu, J.; Hiltunen, J.; Haukka, J.; Heikkinen, J.; Tiihonen, J.; Wang, S.; Neumeyer, J.L. Iodine-123 labelled N-(2-fluoroethyl)-2-β-carbomethoxy-3-β-(4-iodophenyl)nortropane for dopamine transporter imaging in the living human brain. *Eur. J. Nucl. Med.* **1995**, *22*, 682–686. [[CrossRef](#)] [[PubMed](#)]
305. Hiltunen, J.; Åkerman, K.K.; Kuikka, J.T.; Bergström, K.A.; Halldin, C.; Nikula, T.; Räsänen, P.; Tiihonen, J.; Vauhkonen, M.; Karhu, J.; et al. Iodine-123 labeled nor-β-CIT as a potential tracer for serotonin transporter imaging in the human brain with single-photon emission tomography. *Eur. J. Nucl. Med.* **1998**, *25*, 19–23. [[CrossRef](#)] [[PubMed](#)]
306. Zitterl, W.; Aigner, M.; Stompe, T.; Zitterl-Eglseer, K.; Gutierrez-Lobos, K.; Wenzel, T.; Zettinig, G.; Hornik, K.; Pirker, W.; Thau, K. Changes in thalamus-hypothalamus serotonin transporter availability during clomipramine administration in patients with obsessive-compulsive disorder. *Neuropsychopharmacology* **2008**, *33*, 3126–3134. [[CrossRef](#)] [[PubMed](#)]
307. Makkonen, I.; Riikonen, R.; Kokki, H.; Airaksinen, M.M.; Kuikka, J.T. Serotonin and dopamine transporter binding in children with autism determined by SPECT. *Dev. Med. Child Neurol.* **2008**, *50*, 593–597. [[CrossRef](#)]
308. Lehto, S.M.; Tolmunen, T.; Kuikka, J.; Valkonen-Korhonen, M.; Joensuu, M.; Saarinen, P.I.; Vanninen, R.; Ahola, P.; Tiihonen, J.; Lehtonen, J. Midbrain serotonin and striatum dopamine transporter binding in double depression: A one-year follow-up study. *Neurosci. Lett.* **2008**, *441*, 291–295. [[CrossRef](#)]
309. Dam, J.H.; Bender, D.; Peters, D.; Nägren, K. [¹¹C]NS9531, [¹¹C]NS9762 and [¹¹C]NS6417, specific SERT tracers: Pre-clinical evaluation in pigs and optimization of synthesis conditions using [¹¹C]methyl triflate. *Nucl. Med. Biol.* **2016**, *43*, 42–51. [[CrossRef](#)]