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Syntheses, radiolabelings and in vitro evaluations of fluorinated PET radioligands of 5-HT$_6$ serotoninergic receptors.

Julie Colomb,[#,‡] Guillaume Becker,[§,‡,†] Sylvain Fieux, [§,‡] Luc Zimmer, [§,‡,†] Thierry Billard[*,#,‡]

[#] Institute of Chemistry and Biochemistry (ICBMS-UMR CNRS 5246), University of Lyon, University Lyon 1, CNRS, 43 Boulevard du 11 Novembre 1918, 69622 Lyon (France).

[§] Lyon Neuroscience Research Center (UMR 5292, U 1028), University of Lyon, University Lyon 1, CNRS, INSERM, 59 Boulevard Pinel, 69003 Lyon (France).

[‡] CERMEP-In vivo Imaging, Groupement Hospitalier Est, 59 Boulevard Pinel, 69003 Lyon (France).

[†] Hospices Civils de Lyon, Lyon, France.

KEYWORDS *5-HT$_6$, fluorine-18, quinoline, serotonin, PET.*

ABSTRACT: The 5-HT$_6$ receptors are potent therapeutic targets for psychiatric and neurological diseases (schizophrenia, Alzheimer's disease, etc.). However, in lack of specific radiopharmaceuticals, their pharmacology is still incomplete and their exploration is limited to animal models. In this context, we have designed a fluorinated PET radiotracer, **[^{18}F]2FNQ1P**, which possesses a high affinity and selectivity for 5-HT$_6$. In vitro PET autoradiographies in rat brain sections with this radiotracer were in accordance with the 5-HT$_6$ distribution pattern.

Introduction.

The 5-HT$_6$ receptor is one of the most recently discovered of the serotonin family of receptors. It was discovered by two independent groups using molecular cloning technologies and was first isolated from rat striatum.[1-2] Three years later, the human homolog was discovered by Kohen et al.[3] It is known that 5-HT$_6$ receptor density is particularly high in striatal areas in rats and humans. The first autoradiographic visualizations of 5-HT$_6$ receptor distribution used the 5-HT$_6$ receptor antagonists [^{3}H]4-amino-*N*-[2,6-bis(methylamino)pyridin-4-yl] benzenesulfonamide (**[^{3}H]Ro-63-0563**) and **[^{125}I]30**, in various species.[4-5] These studies consistently revealed heterogeneous binding throughout the brain, with the high levels in striatum, moderate levels in cerebral cortex and low levels in cerebellum. Cross-species comparison showed similar distribution patterns between rats and non-human primates and humans.[6] At that stage, however, the role of the 5-HT$_6$ receptor in the brain was not yet clearly understood. Its specific brain localization, particularly in the basal ganglia and limbic regions, and the high affinity shown by several atypical antipsychotics suggested involvement in the serotonergic control of motor function, mood-dependent behavior and related diseases. Recent studies identified 5-HT$_6$ receptors as promising targets for cognitive improvement in psychiatric or neurodegenerative diseases and for anti-obesity drugs.[7-8]

If in vitro imaging (e.g., autoradiography) allows postmortem visualization and accurate delineation of receptors in animal models and humans,[9] but in vivo imaging (e.g., positron emission tomography (PET)) is essential to the development of the preclinical and clinical pharmacology[10] and of directed brain drug candidates,[11] and to assess directly the involvement of serotonin 5-HT$_6$ receptors in neuropsychiatric diseases and possible therapies. This requires a PET radiotracer labeling 5-HT$_6$ receptors with high affinity, high selectivity, high signal-to-noise ratio, lipophilicity sufficient to penetrate the blood brain barrier, relatively slow clearance and a low level of labeled metabolites in the brain.[12]

Although several selective 5-HT$_6$ antagonists exist,[7,13-17] few have been radiolabeled for successful use in PET imaging (Figure 1).

In 2005, a pharmaceutical company patented a new generation of 5-HT$_6$ receptor antagonists based on the 3-benzenesulfonyl-8-piperazine-1-yl-quinoline scaffold.[18] Within this scaffold, a *N*-methyl derivative, **1**, presented high binding affinity for 5-HT$_6$ (K_i = 0.16 nM). **[^{11}C]1** was then prepared by *N*-methylation of the corresponding desmethyl precursor with [^{11}C]MeOTf.[19] This radioligand readily entered the brain of anesthetized pigs, with a distribution consistent with reported 5-HT$_6$ receptor density patterns.[19-20] Selectivity, however, was by no means optimal, since **[^{11}C]1** also showed non-negligible affinity toward 5-HT$_{2A}$ receptors (K_i = 0.79 nM), a different serotoninergic receptor known to be colocalized with 5-HT$_6$ receptors, particularly in the striatum.[21] Nevertheless, and because of the lack of other 5-HT$_6$ PET radiotracers, evaluation was pursued in pigs, nonhuman primates and finally in humans.[22] More recently, another compound, **2**, was radiolabelled with carbon-11. Despite sub-nanomolar 5-HT$_6$ affinity (K_i = 0.78 nM) and straightforward radiolabeling, **[^{11}C]2** showed poor brain entry, limiting its usefulness for in vivo imaging of 5-HT$_6$ receptors.[23] In the same year, another group proposed various candidate 5-HT$_6$ PET ligands, of which **[^{11}C]3** appeared to be the most promising but was abandoned because of its poor radiopharmacological properties.[24] Very recently, a structural modification of **[^{11}C]1** was patented (**[^{11}C]4**) as a potential PET radiotracer with sub-nanomolar affinity for 5-HT$_6$ receptor (K_i = 0.22 nM) and good selectivity

toward 5-HT_{2A} receptors (K_i = 123 nM).[25-26] Nevertheless, and despite the interest of several of these radiotracers, the fact that they are radiolabeled using carbon-11 is a drawback for further development, due to its short radioactive half-life ($T_{½}$ = 20 min.). Fluorine-18 is the radionuclide of choice in PET, because of its longer half-life ($T_{½}$ = 110 min.), facilitating transfer between PET imaging centers if it can be successfully developed as a radiopharmaceutical. This last point justifies research for fluorinated candidates.

In 2007, we reported a fluorine-18 labeled ligand (**[^{18}F]5**) presenting in vitro affinity toward the 5-HT_6 receptor (4 nM); it showed a good brain penetration, but no specific binding to 5-HT_6 receptors.[27] A new PET radiotracer, with greater specificity and selectivity for 5-HT_6 receptors and, ideally, with fluorine-18 radiolabelling, therefore remains an objective. This article presents the first developments in a new series of fluorinated 5-HT_6 tracer-candidates, and the emergence of a potent 5-HT_6 radiotracer.

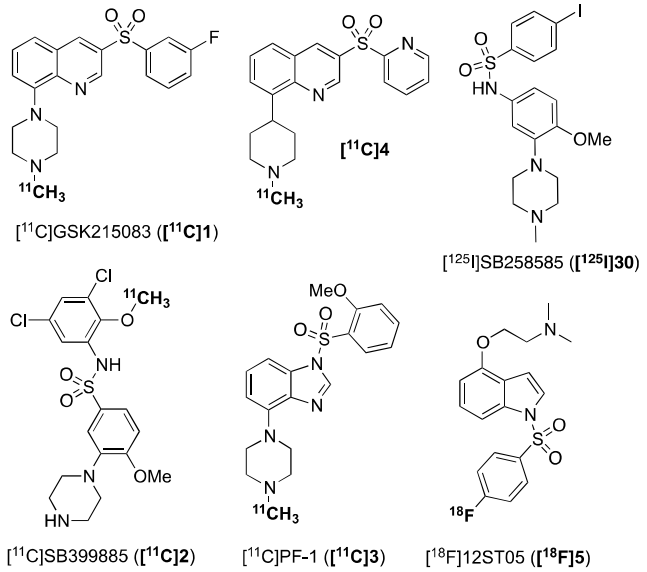


Figure 1. Published 5-HT_6 receptor radioligands.

Results and discussion.

When this work started, the best radioligand so far described and fully validated was **[^{11}C]1**. Consequently, inspired by this structure, various structural modifications around the quinoline core were envisaged, by taking care that the envisaged structural modifications fit always with the 5-HT_6 receptor pharmacophore.[13, 28] The priority was for all these new structures to also be able to be radiolabeled with the fluoride anion fluorine-18, which is the only radioisotope source which can be introduced onto organic compounds by nucleophilic substitution. For our purposes of aromatic radiolabeling, the fluorine atom must be placed in the ortho- or para-position of an electron-withdrawing group to favor such a reaction.

The first envisaged modification concerned only the position of the fluorine atom in ortho or para position on the benzenesulfonyl core of **1**, to determine a possible "fluorine position" effect (**6-7**, Scheme 1). These molecules have been previously described in literature, however their 5-HT_6 activities have not been described.[29] Some replacements of the sulfonyl hydrogen acceptor part by bioisosteres, such as the sulfoxide (**8**) and sulfonamide (**9-10**) groups, were also considered.[30] Modifications to the piperazine substituent was also envisaged, in accordance with the pharmacophore. Consequently, the fluorobenzenesulfonyl group, which can be radiolabeled, could substitute for the methyl substituent (**11-12**). A combination of these modifications was also designed, modifying both sulfonamide and the substituent (**13-14**). Finally, the moving of the fluorobenzenesulfonyl part from the quinoline position 3 to the position 5 was also envisaged (**15**).

From a retrosynthetic point of view, compounds **6-14** can be obtained via two coupling reactions from 3-iodo-8-chloro quinoline (**17**), easily obtained from the commercially available 8-chloro-quinoline (**16**), which then constitutes the common starting material (Scheme 1).

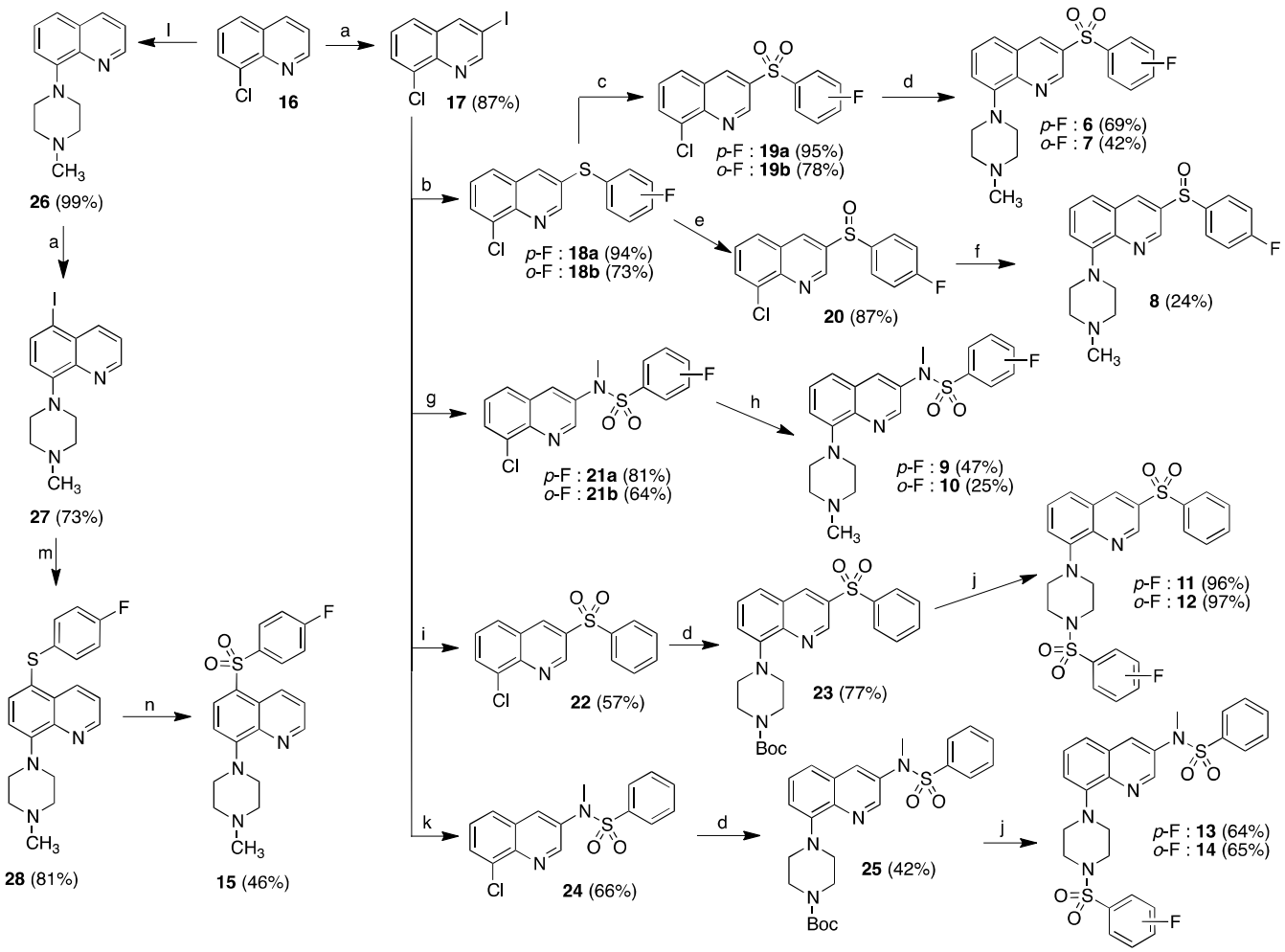
The 8-chloro-quinoline (**16**) was regioselectively iodinated to furnish **17** with good yield.[18] Despite various attempts at direct sulfonylation of **17**,[31-34] no efficient methods proved effective, leading sometimes to desulfitative coupling.[35] Consequently, a two step strategy was adopted: the corresponding fluorobenzene thiols were first introduced by chemoselective copper-catalyzed coupling reaction[36] and the resulting sulfides (**18**) were then oxidized with MMPP (magnesium monoperoxyphthalate) into the expected sulfones (**19**). Buchwald previously demonstrated that the biphenylphosphine DavePhos facilitated the coupling reaction of chlorinated aromatic rings with various amino groups, such as piperazine.[37] In the case of **19**, satisfactory yields were obtained with *N*-methylpiperazine to afford the expected ligands **6-7**. A similar synthetic pathway was applied to obtain **8**. More moderate oxidation conditions (mCPBA) were used to stop at the sulfoxide **20**, which was then coupled to *N*-methylpiperazine. In this last coupling reaction, XPhos is preferable to DavePhos to obtain the expected product **8** in moderate yield (Scheme 1).[38]

The corresponding sulfonamide compounds **9-10** were prepared by two successive palladium-catalyzed coupling reactions. Sulfonamides **21** were obtained by the chemoselective reaction of **17** with the corresponding fluorobenzenesulfonamide in good yields. A second coupling reaction with *N*-methylpiperazine, under conditions similar to those described above, led to the expected ligands **9-10** with satisfactory yields (Scheme 1).

Similar strategies were applied to the synthesis of **11-14** (Scheme 1). After a first coupling between **17** and benzenesulfinate (Cu-catalyzed) or benzenesulfonamide (Pd-catalyzed), compounds **22** and **24** were respectively obtained with satisfactory yields. Then a second coupling reaction with *N*-Boc-piperazine afforded **23** and **25** with moderate to good yields. Finally, Boc deprotection, followed by sulfonylation with the corresponding fluorobenzenesulfonyl chloride, led to the expected ligands **11-14**.

The final targeting ligand **15** was synthesized by inverting the steps of quinoline iodination and coupling with piperazine. After introduction, mediated by palladium, of *N*-Methylpiperazine in position 8, regioselective iodination gave rise to compound **27**, which was then coupled to fluorobenzenethiol with copper-catalysis, and the resultant sulfide **28** was oxidized into the expected sulfone **15** (Scheme 1).

Scheme 1. Synthesis of fluorinated ligands 6-15[a]



[a]Reagents and conditions: (a) NIS, AcOH, 80°C; (b) CuI (2.5%), Cs_2CO_3, thiol, DMF, 100°C; (c) MMPP (2.25 eq.), CH_2Cl_2/MeOH; (d) Pd_2dba_3 (5%), DavePhos (10%), *t*BuONa (1.4 eq.), *N*-Methyl piperazine, Toluene, 110°C; (e) mCPBA (1.1 eq.), CH_2Cl_2; (f) Pd_2dba_3 (5%), XPhos (10%), *t*BuONa (1.4 eq.), *N*-Methyl piperazine, Toluene, 110°C; (g) Pd_2dba_3 (5%), XPhos (10%), Cs_2CO_3 (1.4 eq.), *N*-Methyl sulfonamide, Toluene, 110°C; (h) Pd_2dba_3 (5%), XPhos (10%), Cs_2CO_3 (1.4 eq.), *N*-Methyl piperazine, Toluene, 110°C; (i) $PhSO_2Na$, CuI (10%), DMEDA (20%), DMSO, 110°C; (j) 1) TFA, CH_2Cl_2; 2) $ArSO_2Cl$, Et_3N; (k) Pd_2dba_3 (5%), XPhos (10%), Cs_2CO_3 (1.4 eq.), $PhSO_2NHMe$, Toluene, 110°C; (l) Pd_2dba_3 (5%), DavePhos (10%), *t*BuONa (1.4 eq.), *N*-Methyl piperazine, Dioxane, 110°C; (m) CuI (20%), Cs_2CO_3, thiol, DMF, 100°C; (n) Oxone (2.05 eq.), MeOH/H_2O:1/1.

Affinities of these ligands for 5-HT_6 receptors were determined by binding assays on human recombinant receptors expressed in CHO cells. 5-HT_6 receptor affinity results varied according to the compound (Table 1). It thus appeared that replacing the sulfonyl group by the sulfonamide moiety was not deleterious for the affinity, confirming the bioisostery between SO_2 and $NHMeSO_2$ (**6-7** *vs* **9-10**) for 5-HT_6 receptor. 5-HT_6 receptor affinities decreased with increasing of steric hindrance onto piperazine (**11-12**). However, excessive hindrance is highly deleterious for the affinity with K_i > 1µM (**13-14**). The drop in the basicity of the piperazine nitrogen substituted by the sulfonyl group can also contribute to the lost in binding for 5-HT_6 receptor. Finally, modifying geometry by changing the substituent positions also reduces affinity (**15**).

The second receptor-target which held our attention was the 5-HT_{2A} receptor, since it is known that this family is the closest to 5-HT_6 receptors, ranging between 33% and 40% in sequence homology.[39] Only molecules with K_i(5-HT_6) < 5 nM were selected: i.e., **6, 7, 8, 10** (Table 1).

As expected, only modifying the position of the fluorine atom onto the benzenesulfonyl part (**6-7**) did not bring significantly improved affinity or selectivity in comparison to the parent compound **1**. A simple change in the oxidation state of the sulfur atom (**8**) decreased 5-HT_6 receptor affinity and did not improve 5-HT_{2A} receptor selectivity. Finally, bioisosteric replacement of sulfone by sulfonamide (**10**) led to subnanomolar 5-HT_6 receptor affinity and very low affinity for 5-HT_{2A} receptor. Because lipophilicity and molecular polar surface (PSA) could be predictive of blood-brain-barrier penetration,[40-42] the lipophilicity (logD) and PSA of compounds **6-8, 10** were also calculated with the ACD/Labs and Marvin software applications (Table 1). PSA values were lower than 70 Å^2, predicting good brain penetration.[42] The logD values at physiological pH were also compatible with good brain permeation.

Table 1. Lipophilicity, PSA, 5-HT$_7$ and 5-HT$_{2A}$ affinities (K$_i$) of compounds 6-15

Ligand	K$_i$ 5-HT$_6$ (nM) [a]	K$_i$ 5-HT$_{2A}$ (nM) [a]	5-HT$_{2A}$ / 5-HT$_6$	Log D (pH=7.4)[b]	PSA (pH = 7.4) (Å^2) [c]
6	0.26	1.7	6.5	3.01	61.89
7	0.10	14	140	2.33	61.89
8	4.4	54	12.3	2.00	56.85
9	27				
10	0.9	> 1µM	> 1000	1.86	66.33
11	7.6				
12	30				
13	> 1µM				
14	> 1µM				
15	53				

[a] determined on CHO cells

[b] calculated with ACD/Labs, version 7.09, Advanced Chemistry Development, Inc., Toronto, On, Canada, www.acdlabs.com, 2014.

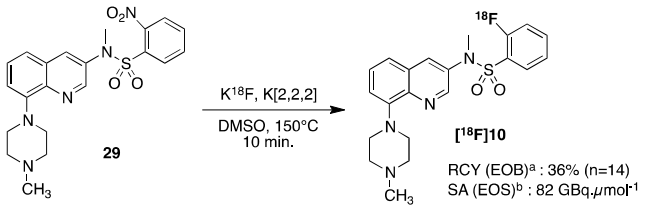
[c] Calculator Plugins were used for structure property prediction and calculation, Marvin 6.0.3, 2013, ChemAxon (http://www.chemaxon.com)

Consequently, radiolabeling of **10** was envisaged to obtain the corresponding ^{18}F analogs. In order to obtain the nitro-precursor (**29**), strategy similar to this described above (Scheme 1) was applied, with some adjustments probably required due to the presence of the highly electron-withdrawing nitro substituent, which would tend to modify substrate reactivity. In particular, triflate of quinoline had to be used to enable the final coupling step with *N*-methylpiperazine (see Supporting Informations).

The nitro-precursor **29** has been obtained with an overall yield of 13% and has been labeled by nucleophilic aromatic substitution of the nitro group, in classical conditions at 150°C, in dimethylsulfoxide (DMSO) and in presence of kryptofix® (Scheme 2).[43-45]

The radiolabeled compound **[^{18}F]10** was produced with good radiochemical yield, chemical and radiochemical purity > 90% and with good specific activity of 82 GBq.µmol^{-1}.

Scheme 2. Radiolabeling of 29



[a] RCY: Radiochemical yield. Based on the fluorine-18 activity recovered from the resin (EOB: end of bombardment). Mean of radiochemical yields of several radiolabelings (in brackets, number of radiolabeling experiments).

[b] SA: specific activity (EOS: End of synthesis).

Distributions of **[^{18}F]10** were assessed by semi-quantitative autoradiography in rat brain (Figure 3). Autoradiograms obtained after incubation with a constant in vitro radiotracer concentration demonstrated the presence of structures able to concentrate radioactivity (i.e., cortex and striatum). These binding areas corresponded to those described as rich in 5-HT$_6$ receptors.[5] **[^{18}F]10** radioactivity levels were markedly reduced after addition of their respective cold molecules (1 µM). Furthermore, the binding level of **[^{18}F]10** decreased significantly after addition of 1 µM of **30**, a 5-HT$_6$ antagonist.[46] These preliminary biological results demonstrated the favorable properties of **[^{18}F]10** as a 5-HT$_6$ radiotracer.

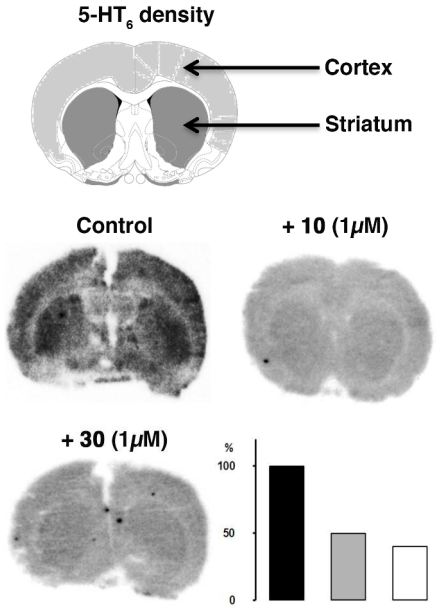


Figure 3. In vitro autoradiograms of rat brain sections incubated with **[^{18}F]10** and after competition with cold compound (**10**) or 5-HT$_6$ antagonist **30** (both at 1 µM). The corresponding anatomic slice shows 5-HT$_6$ receptor locations and density (proportional to gray level) in cortex and striatum. Histogram: decrease of **[^{18}F]10** binding after cold compound or 5-HT$_6$ antagonist addition (grey and white bars *versus* the control black bar).

To confirm the potential of **[^{18}F]10** as a PET radiotracer, affinities toward other receptors were explored in vitro: serotoninergic 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C} and 5-HT_4, adrenergic α_{1B} and dopaminergic D_2 and D_3 receptors were selected because of their shared location in the target brain area, the striatum.[47] Compound **10** presented very low affinity toward the main receptors located in the striatal region and toward other 5-HT_2 family receptors, confirming its excellent selectivity for the 5-HT_6 receptor (Table 2).

Table 2. In vitro selectivity of compound 10.

Receptor	K_i[a]	Receptor	K_i[a]
5-HT_6	0.9 nM	5-HT_4	$>10^{-6}$ M
5-HT_{1B}	$>10^{-6}$ M	α_{1B}	$>10^{-6}$ M
5-HT_{2A}	$>10^{-6}$ M	D_2	$>10^{-6}$ M
5-HT_{2B}	260 nM	D_3	$>10^{-6}$ M
5-HT_{2C}	$>10^{-6}$ M		

[a] determined on CHO cells

Conclusion

To our knowledge, this is the first report of a promising fluorinated PET radioligand for in vivo imaging of the serotonin 5-HT_6 receptor. We synthesized ten compounds according to a quinoline-based scaffold. Four of these were selected for their 5-HT_6 receptor affinity and selectivity toward 5-HT_{2A} receptor. These non-radioactive fluorinated ligands and their radiolabeling precursors were obtained from a bis-functionalized quinoline core followed by coupling reactions in three steps. Radiolabeling used ^{18}F-nucleophilic aromatic substitution. Three presented high in vitro binding in the striatum (an area rich in 5-HT_6 receptors), but only one, **10**, specifically presented favorable in vitro binding for 5-HT_6 receptors versus striatal 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_4, α_{1B}, D_2 and D_3 receptors. In vitro PET autoradiographies in rat brain sections confirmed the 5-HT_6 distribution pattern of **[^{18}F]10**. In conclusion, this study enabled selection of a fluorinated radiotracer-candidate with suitable characteristics for PET imaging of 5-HT_6 receptors, justifying further radiopharmacological evaluation in animal models before considering human brain imaging. For the following studies, this promising molecule will be named **2FNQ1P**.

Experimental section

Chemistry. The purity of the tested compounds and their nitro-precursors was assessed by RP-HPLC and elemental analysis. All compounds reported are at least 95% pure.

2-Fluoro-*N*-methyl-*N*-[8-(4-methylpiperazin-1-yl)quinolin-3-yl]benzenesulfonamide (10). Obtained with 25 % yield. Brown oil. ^{1}H NMR: δ 8.76 (d, J = 2.6 Hz, 1H), 7.91 (d, J = 2.6 Hz, 1H), 7.69 (ddd, J = 7.6 Hz, J = 7.6 Hz, J = 1.7 Hz, 1H), 7.57 (m, 1H), 7.43 (m, 1H), 7.35 (dd, J = 8.2 Hz, J = 1.2 Hz, 1H), 7.23-7.12 (m, 3H), 3.49-3.45 (m, 7H), 2.86 (m, 4H), 2.47 (s, 3H). ^{13}C NMR: δ 159.28 (d, J = 256.6 Hz), 149.4, 146.9, 141.2, 135.9 (d, J = 8.3 Hz), 134.7, 132.9, 131.9, 129.6, 128.1, 126.1 (d, J = 14.6 Hz), 124.9 (d, J = 3.9 Hz), 122.2, 117.7 (d, J = 21.6 Hz), 117.0, 55.4, 51.9, 46.2, 38.9. ^{19}F NMR: δ -107.64 (m). Calcd for $C_{21}H_{23}FN_4O_2S$ C, 60.85 ; H, 5.59 ; N, 13.52 ; found C, 61.03 ; H, 5.67 ; N, 13.69.

Radiosynthesis. Fluorine-18 was produced via the ^{18}O(p,n)^{18}F nuclear reaction (IBA Cyclone 18/9 cyclotron). Nitro/fluoro exchange was performed on a standard Neptis® synthesizer (Ora™): after initial fluoride preparation (collection, drying and kryptofix activation), 1.7-2.5 mg of nitro precursor **29** was introduced in 3 mL of DMSO, and the reaction mixture was heated at 150°C for 10 min. After dilution with 15 mL of water, the reaction mixture was passed through an activated C18 cartridge for pre-purification, and the crude product was eluted from the cartridge with 1.5 mL of methanol. Pure **[^{18}F]10** was obtained after separation on a preparative high-performance liquid chromatography (HPLC) (C18 Symmetry Prep Waters 7 µm 7.8 x 300 mm) eluted with H_2O/CH_3CN/TFA:78/22/0.1% at 3 mL.min^{-1} (λ = 254 nm). For biological use, the radiotracer was formulated via SPE techniques. [48] The product was diluted in 20 mL of sterile water and loaded on a SEP-Pak Light C18 cartridge (Waters, Milford, MA, USA). The loaded cartridge was rinsed with water and eluted with 1 mL of ethanol, and the final product was diluted with isotonic saline and sterilized by filtration (sterile filter Millex-GS, 0.22 mm). The radiochemical purity and specific activity of **[^{18}F]10** were assayed by analytical HPLC (MachereyeNagel EC 250/4.6 Nucleodur 100-5-C18ec C18 column; mobile phase H_3PO_4 20 mM/THF:77/23; flow rate, 0.9 mL.min^{-1}). The identity of **[^{18}F]10** was confirmed by co-injection with an authentic non-radioactive sample.

In vitro affinities. Respective affinities toward 5-HT_6 receptors (K_i) was determined by the CEREP (http://www.cerep.fr).

In vitro rat autoradiographies. All animal experiments were performed in accordance with European guidelines for care of laboratory animals (86/609 EEC) and were approved by the animal use ethics committee of the Université Claude Bernard Lyon 1. After euthanasia by inhaled isoflurane overdose, rat brains were carefully removed and immediately frozen in 2-methylbutane cooled with dry ice (-29 °C). Briefly, coronal sections (30 µm thick) across the hippocampus and cerebellum were cut using a -20°C-cryostat (Leica SM1850), thaw-mounted on glass slides and allowed to air-dry before storage at -80 °C until use. On the day of radiotracer synthesis, the slides were allowed to reach room temperature and then incubated for 20 min in Tris phosphate-buffered saline buffer (138 mM NaCl, 2.7 mM KCl, pH adjusted to 7.6) containing 37 kBq/mL (1 µCi/mL) **[^{18}F]10**. For competition experiments, the slides were placed in the same buffer supplemented with their respective cold compounds (**10** at 1µM) or **30**, a selective 5-HT_6 antagonist (1µM). After incubation, slides were dipped in cold buffer (4°C) for 90 seconds, in distilled cold water (4°C) for 90 sec, and then dried and juxtaposed to a phosphor imaging plate for 60 min (BAS-1800 II, Fujifilm).

ASSOCIATED CONTENT

Supporting Information. Whole experimental data of the syntheses. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* E-mail: Thierry.billard@univ-lyon1.fr. Phone: (+33)472 44 81 29.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

5-HT_6, serotoninergic receptor 6; 5-HT_{1B}, serotoninergic receptor 1B; 5-HT_{2A}, serotoninergic receptor 2A; 5-HT_{2B}, serotoninergic receptor 2B; 5-HT_{2C}, serotoninergic receptor 2C; 5-HT_4, serotoninergic receptor 4; α_{1B}, adrenergic receptor 1B; Boc, tert-butyloxycarbonyl; CHO, Chinese hamster ovary; D_2, dopaminergic receptor 2; D_3, dopaminergic receptor 3; DavePhos, 2-dicyclohexylphosphino-2′-(*N,N*-dimethylamino)biphenyl; EOB, end of bombardment; EOS, end of synthesis; HPLC, high-performance liquid chromatography; mCPBA, *m*-chloroperbenzoic acid; MMPP, magnesium monoperoxyphthalate; NIS, N-iodosuccinimide; PET, positron emission tomography; PSA, polar surface area; RCY, radiochemical yield; RP-HPLC, reverse phase high-performance liquid chromatography; SA, specific activity; S_NAr, nucleophilic aromatic substitution; SPE, solid-phase extraction; XPhos, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

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