Received: 30 June 2017 | Revised: 22 August 2017 | Accepted: 23 August 2017

DOI: 10.1002/jlcr.3557

RESEARCH ARTICLE

WILEY Journal of Labelled Compounds and Radiopharmaceuticals

Synthesis, radiofluorination, and preliminary evaluation of the potential 5-HT_{2A} receptor agonists [^{18}F]Cimbi-92 and [^{18}F]Cimbi-150

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An agonist PET tracer is of key interest for the imaging of the 5-HT_{2A} receptor, as exemplified by the previously reported success of [^{11}C]Cimbi-36. Fluorine-18 holds several advantages over carbon-11, making it the radionuclide of choice for clinical purposes. In this respect, an ^{18}F-labelled agonist 5-HT_{2A} receptor (5-HT_{2A}R) tracer is highly sought after. Herein, we report a 2-step, 1-pot labelling methodology of 2 tracer candidates. Both ligands display high in vitro affinities for the 5-HT_{2A}R. The compounds were synthesised from easily accessible labelling precursors, and radiolabelled in acceptable radiochemical yields, sufficient for in vivo studies in domestic pigs. PET images partially conformed to the expected brain distribution of the 5-HT_{2A}R; a notable exception however being significant uptake in the striatum and thalamus. Additionally, a within-scan displacement challenge with a 5-HT_{2A}R antagonist was unsuccessful, indicating that the tracers cannot be considered optimal for neuroimaging of the 5-HT_{2A}R.

KEYWORDS
[^{18}F]Cimbi-150, [^{18}F]Cimbi-92, 5-HT_{2A} antagonist, PET, radiofluorination, reductive amination

1 | INTRODUCTION

The serotonin-2A receptor (5-HT_{2A}R) has been identified to be involved in the pathophysiology of psychiatric disorders, including schizophrenia and depression.[1,2] Pharmacological intervention with 5-HT_{2A}R acting compounds suggests that the receptor could be a target for several different purposes, eg, hypnotics such as trazodone requiring 5-HT_{2A}R antagonism for therapeutic action.[3-7] Additionally, the 5-HT_{2A}R is a key target for second-generation neuroleptics, with drugs (eg clozapine) again relying on the antagonism of the receptor.[8] Positron emission tomography (PET) is a powerful tool for molecular imaging allowing in vivo studies and visualisation of human physiology.[9] Among its many applications, it allows for receptor distribution characterisation, receptor quantification, and determination of receptor occupancy of small molecule ligands.[10] Several 5-HT_{2A}R tracers have been developed, including (R)-[^{18}F]MH.MZ, [^{18}F]altanserin, and [^{11}C]MDL 100907 (Figure 1); however, they are all antagonists.[11,12,19,20]

According to the extended ternary complex model hypothesis, antagonists bind to receptors in both their inactive and active states, therefore allowing the quantification of the full receptor population.[14,21,22] By contrast, agonist tracers should only bind to the active receptor pool and may thus provide additional information regarding neurotransmission.[23] In this respect, agonists should be more sensitive to endogenous serotonin,

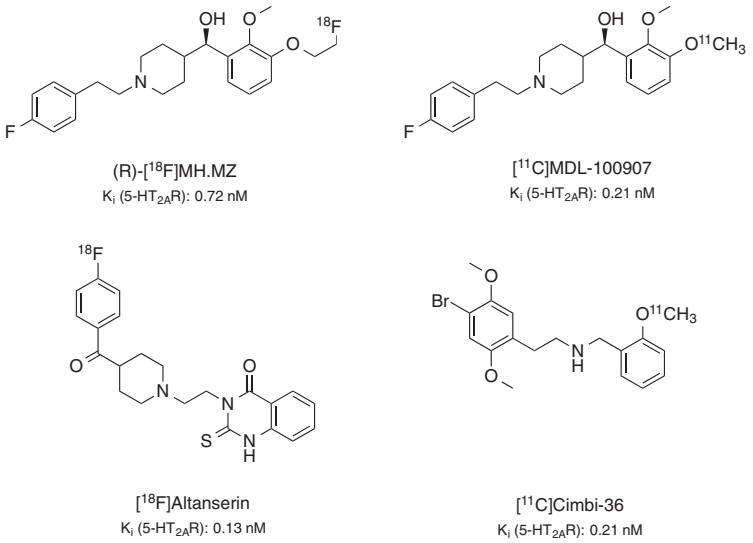
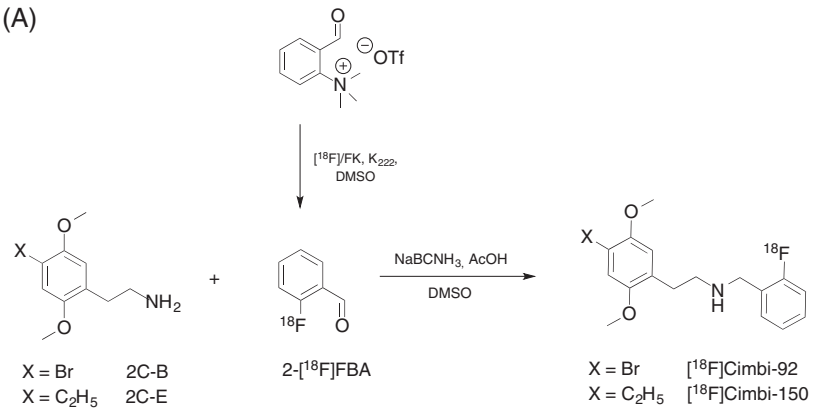


FIGURE 1 Successfully applied 5-HT_{2A}R PET ligands[11-18]

and as a consequence agonists could serve as a tool to quantify endogenous serotonin concentrations within the synaptic cleft.[24,25] Furthermore, agonist tracers should provide a better estimate of receptor occupancy levels of receptor activating therapeutic drugs.[26] Access to a 5-HT_{2A}R agonist PET tracer could provide insights into therapeutic mechanism of action, the effects on neurobiology and potentially help determine effective doses of similar drugs. Currently, [^{11}C]Cimbi-36 is the only validated 5-HT_{2A}R agonist PET tracer in the human brain (Figure 1).[27,28] However, for clinical applications, the PET radionuclide fluorine-18 has several advantages over carbon-11: (1) its longer half-life of 109.8 minutes allows for range of distribution, thus marketability, (2) the lower β^+-energy of fluorine-18 allows for higher resolution, and (3) higher radioactivity amounts can be produced.[11,29] Accordingly, an ^{18}F-labelled agonist 5-HT_{2A}R PET tracer would be beneficial, and there have been several unsuccessful attempts to develop such a tracer.[13,14,30]

The aim of this study is to extend these efforts, and ^{18}F-label recently developed and promising 5-HT_{2A}R agonist ligands.[18] Cimbi-92 and Cimbi-150 show a similar selectivity profile as Cimbi-36,[27] and they can be labelled using a similar labelling strategy that we have recently published (Figure 2).[9,13,14,20] Despite some affinity for the 5-HT_{2B} receptor, Cimbi-92 and Cimbi-150 appeared to be a suitable candidate to develop an ^{18}F-labelled Cimbi-36 derivative for 5-HT_{2A}R PET imaging. This is due to the 5-HT_{2B} receptors only being present in low



(B)

	Affinity data [nM]						
	5-HT_{2A}	5-HT_{2B}	5-HT_{2C}	5-HT_{1A}	5-HT_{1e}	5-HT_6	5-HT_7
Cimbil-36	0.8	0.5	1.7	1255	>10000	n.d.	4720
Cimbi-92	2.7	5.9	18.6	826	1245	378	2088
Cimbi-150	2.4	20	26.1	n.d.	n.d.	742	n.d.

FIGURE 2 A, synthesis strategy for ^{18}F-label Cimbi-92 and [^{18}F]Cimbi-150; B, selectivity profile of Cimbi-36, Cimbi-92, and Cimbi-150[27]

abundance in relevant brain regions for the imaging of the 5-HT_{2A}R, for example in cortical structures.[31-33]

2 | RESULTS AND DISCUSSION

[^{18}F]Cimbi-92 was successfully radiolabelled in a 2-step reaction sequence. First 2-[^{18}F]fluorobenzaldehyde was labelled and subsequently reacted with 2C-B (Figure 2). A n.d.c. RCY of 1.7% resulting in 311 ± 54 MBq (n = 3) was isolated in a total synthesis time of 75 minutes. Radio-chemical purity was found to be >97% and chemical purity was determined to be >99%. A molar activity of 78 ± 23 GBq/μmol (n = 3) was obtained. [^{18}F]Cimbi-150 was synthesised using the same labelling strategy. 2C-E was alkylated using 2-[^{18}F]fluorobenzaldehyde in a n.d.c. RCY of 4%. The total synthesis time was 75 minutes and 456 ± 54 MBq (n = 3) was isolated. Radiochemical purity was found to be >98%, and chemical purity was determined to be >99%. A molar activity of 358 ± 41 GBq/μmol (n = 3) could be obtained.

Subsequent PET scans of [^{18}F]Cimbi-92 and [^{18}F]Cimbi-150 were performed in Danish Landrace pigs. Both ligands exhibited good brain uptake and reversible binding (Figure 3). For both compounds, the highest uptake was observed in striatum and thalamus, followed by neocortical, and low cerebellar uptake. High striatal and thalamic uptake are not in accordance with the known 5-HT_{2A}R distribution in the pig brain.[27] The binding pattern could be explained by off-target binding not included in our initial selectivity screen. To test whether this is the case, a displacement study with the known 5-HT_{2A}R antagonist ketanserin was conducted. The experimental setup used within this study has previously been successfully applied in the same animal model for [^{11}C]Cimbi-36 or [^{18}F]MH.MZ.[28,34] The displacement study was performed after 90 minutes. No significant decrease in binding was seen (Figure 3) showing that neither [^{18}F]Cimbi-92 or [^{18}F]Cimbi-150 shows displaceable 5-HT_{2A}R binding, at least not in a within-scan displacement study. This observation is incompatible with the features of suitable 5-HT_{2A}R PET tracers.

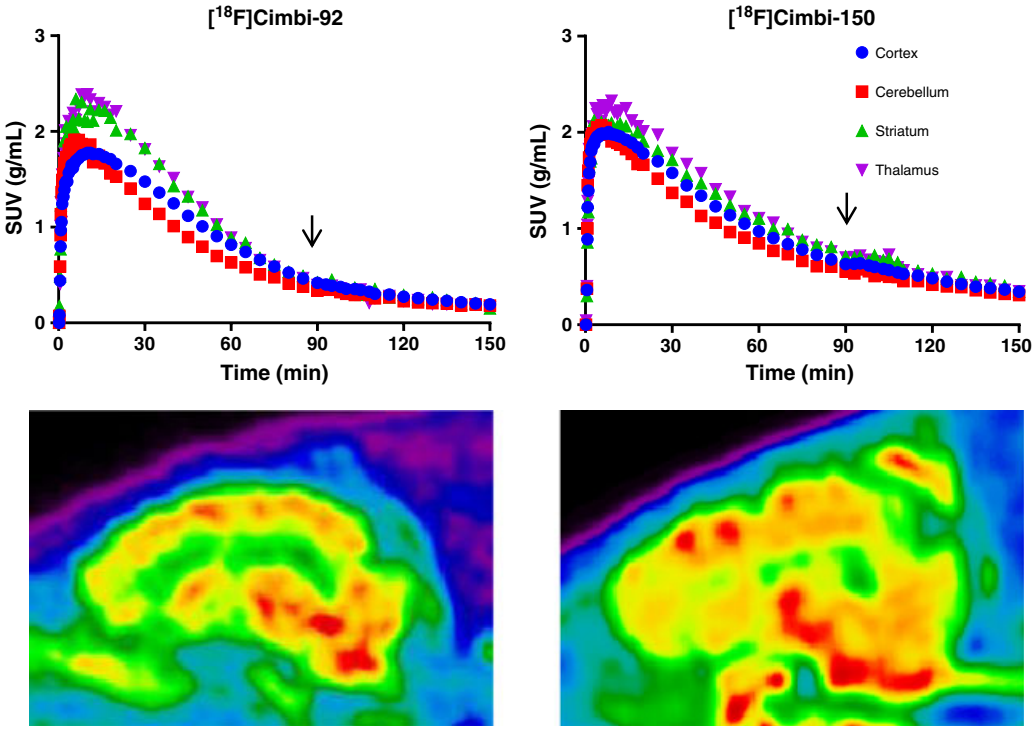
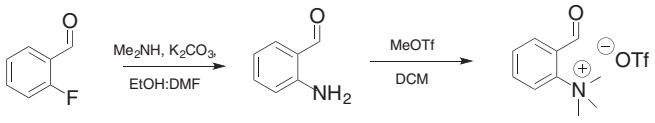


FIGURE 3 Time-activity curves (TACs) from PET-experiments in pigs for [^{18}F]Cimbi-92 and [^{18}F]Cimbi-150 in cortex, cerebellum, striatum, and thalamus (upper line). The arrows represent the time points for the administration of a ketanserin challenge. Representative summed baseline images for [^{18}F]Cimbi-92 and [^{18}F]Cimbi-150 (lower line); images are averaged from 0 to 90 minutes



SCHEME 1 Synthesis of labelling precursor[14,37]

3 | CONCLUSION

[^{18}F]Cimbi-92 and [^{18}F]Cimbi-150 could successfully be labelled using a 1-pot, 2-step labelling strategy. Subsequent evaluation of both structures revealed brain penetration, but an unexpected binding profile that is only partly in line with the known 5-HT_{2A}R distribution in the pig brain. A displacement study with a known 5-HT_{2A}R antagonist failed for both ligands. Thus, none of the radioligands can be considered suitable for 5-HT_{2A}R PET neuroimaging. In conclusion, further fluorine-based analogues of the lead Cimbi-36 structure must be developed in order to identify future promising candidates.

4 | MATERIALS AND METHODS

4.1 | Chemicals and reagents

Standard chemicals were purchased from Sigma-Aldrich, and all chemicals were used as received. Ketanserin was purchased from Tocris Bioscience, and Sep-Pak C18 columns (Sep-Pak Light) were purchased from (Waters AccellPlus). NMR was conducted on a Bucher 400-MHz NMR spectrometer. Purity was determined by HPLC using a ThermoScientific UltiMate 3000.

4.2 | Reference compound synthesis

The Cimbi-92 and Cimbi-150 reference compounds and precursors were synthesised as previously described.[18,35,36]

4.3 | Precursor synthesis

The labelling precursor was synthesised as previously described.[37] In short, 2-aminobenzaldhyde was synthesised from 2-fluorobenzaldehyde and subsequently reacted with methyl triflate (Scheme 1).[14,37]

4.4 | Radiolabelling of [^{18}F]Cimbi-92 and [^{18}F]Cimbi-150

[^{18}F]Fluoride was produced via the ^{18}O(p, n)^{18}F-reaction on a CTI Siemens Eclipse cyclotron (Rigshospitalet, Denmark), in which ^{18}O-enriched water was irradiated with 11-MeV protons. The aqueous [^{18}F]fluoride solution was passed through an anion exchange resin (Sep-Pak Waters Acell Plus QMA Cartridge), which was washed with ethanol (10 mL) and water (20 mL) and then dried with air prior to use. Afterwards, the trapped [^{18}F]fluoride was eluted with a Kryptofix$_{222}$/K_2CO_3 solution (19 mg K_{222} (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8] hexacosane, 6.6-mg potassium carbonate dissolved in 0.1-mL water and 0.6-mL methanol) from the anion exchange resin. The resulting mixture was then concentrated to dryness by azeotropic drying at 90°C with acetonitrile under a helium-stream for 20 minutes to give no-carrier-added (n.c.a) [^{18}F]KF-K_{222} complex as a yellow residue. A solution of 2-trimethylammonium-benzaldehyde triflate (6 mg, 19 μmol) dissolved in DMSO (0.5 mL) was added to the dried [^{18}F]KF-K_{222} complex, and subsequently heated to 70°C for 10 minutes to yield [^{18}F]2-fluorobenzaldehyde. Thereafter, the respective phenylethylamine (8 mg, 21.7/25.2 μmol) and $NaCNBH_3$ (10 mg, 15.9 mmol) dissolved together in DMSO (0.5 mL) and AcOH (4 μL) were added, and subsequently heated to 130°C for 10 minutes. Afterwards, the reaction mixture was purified via semi-preparative HPLC (Luna 5 μm C_{18}(2) 100 Å, 250 × 10.00 mm; acetonitrile/phosphoric acid in water (0.1%) 50/50, flow rate: 6 mL/min; RT of [^{18}F]2-fluorobenzaldehyde: 5 minutes, RT of [^{18}F]Cimbi-92: 13 minutes, RT of [^{18}F]Cimbi-150: 15 minutes). The fraction (6 mL) containing the product was collected into 200-mL water and then passed through a Sep-Pak C18 column. The column was afterwards washed with an additional 10-mL water and eluted with EtOH.

Following elution of the product, it was subsequently filtered through a sterile filter and collected into a 20-mL vial containing sodium phosphate-buffered saline (9 mL, 100 mM, pH 7), giving a 15-mL solution of the final product with a pH of approximately 7. The final solution was visually inspected for clarity, absences of colour and particles. Chemical and radiochemical purities were also assessed by analytical HPLC analysis (Luna 5 μm C_{18}(2) 100 Å, 150 × 4.6 mm; MeCN/citrate buffer (25mM, pH 4.61) 60/40, flow rate: 1.5 mL/min; RT of [^{18}F]2-fluorobenzaldehyde: 3.2 minutes, RT of [^{18}F]Cimbi-92: 5.5 minutes, RT of [^{18}F]Cimbi-150: 5.7 minutes, RT of 2C-B: 1.1 minutes, RT of 2C-E: 1.3 minutes).

4.5 | Animal procedure

Two female Danish Landrace pigs (weight, 19.4 ± 2 kg; 8 weeks) were used for in vivo PET imaging. Tranquillization, anaesthesia, monitoring, and euthanasia of animals were performed as previously described.[14] All animal procedures were approved by the Danish Council for Animal Ethics (journal no. 2012-15-2934-00156).

4.6 | PET scanning protocol and metabolism study

[^{18}F]Cimbi-92 was given as an intravenous (iv) bolus injection, with an injected dose of 223 MBq. The pigs were subsequently scanned for 150 minutes in list-mode with a high resolution research tomography (HRRT) scanner

(Siemens AG, Munich, Germany), where scanning started at the time of injection (0 minutes). Ninety minutes after the injection of [^{18}F]Cimbi-92, ketanserin was given iv as a within-scan challenge bolus (5.0 mg/kg). Ketanserin was dissolved in 3-mL DMSO and subsequently diluted with saline to a 10% DMSO solution. Radiochemical purity and specific activity of the injected product were measured with HPLC.

4.7 | PET quantification and modelling

List-mode PET data (150 minutes) were reconstructed into 58 dynamic frames of increasing length (6 × 10, 6 × 20, 6 × 30, 6 × 60, 4 × 120, 14× 300, 8 × 150, and 8 × 300 - seconds). Images consisted of 207 planes of 256 × 256 voxels of 1.22 × 1.22 × 1.22 mm. A summed picture of all counts in the 90-minute scan was reconstructed for each pig and used for co-registration to a standardised MRI-based atlas of the Danish Landrace pig brain, similar to that previously published.[38,39] The time-activity curves (TACs) were calculated for the following volumes of interest (VOIs): cerebellum, cortex, hippocampus, lateral and medial thalamus, caudate nucleus, and putamen. Striatum is defined as the mean radioactivity in caudate nucleus and putamen. The activity in thalamus is calculated as the mean radioactivity in the lateral and medial thalamus. Radioactivity in all VOIs was calculated as the average of radioactive concentration (Bq/mL) in the left and right sides. Outcome measure in the time-activity curves (TACs) was calculated as radioactive concentration in VOI (in kBq/mL) normalised to the injected dose corrected for animal weight (in kBq/kg), yielding standardised uptake values (g/mL).

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How to cite this article: Edgar FG, Hansen HD, Leth-Petersen S, et al. Synthesis, radiofluorination, and preliminary evaluation of the potential 5-HT_{2A} receptor agonists [^{18}F]Cimbi-92 and [^{18}F]Cimbi-150. *J Label Compd Radiopharm*. 2017;1–6. https://doi.org/10.1002/jlcr.3557