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Brief Article

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Synthesis and Evaluation of Three Structurally Related ^{18}F-Labeled Orvinols of Different Intrinsic Activities: 6-*O*-[^{18}F]Fluoroethyl-diprenorphine ([^{18}F]FDPN), 6-*O*-[^{18}F]Fluoroethyl-buprenorphine ([^{18}F]FBPN), and 6-*O*-[^{18}F]Fluoroethyl-phenethyl-orvinol ([^{18}F]FPEO)

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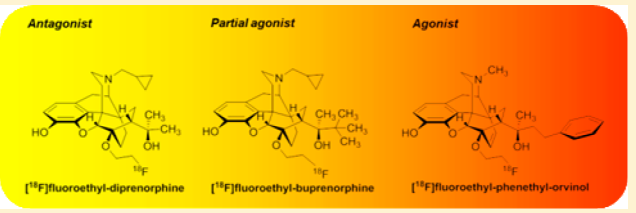
Supporting Information

ABSTRACT: We report the synthesis and biological evaluation of a triplet of 6-*O*-^{18}F-fluoroethylated derivatives of structurally related orvinols that span across the full range of intrinsic activities, the antagonist diprenorphine, the partial agonist buprenorphine, and the full agonist phenethyl-orvinol. [^{18}F]-fluoroethyl-diprenorphine, [^{18}F]fluoroethyl-buprenorphine, and [^{18}F]fluoroethyl-phenethyl-orvinol were prepared in high yields and quality from their 6-*O*-desmethyl-precursors. The results indicate suitable properties of the three 6-*O*-^{18}F-fluoroethylated derivatives as functional analogues to the native carbon-11 labeled versions with similar pharmacological properties.



INTRODUCTION

Positron emission tomography (PET) imaging of opioid receptors (OR) with the nonselective antagonist [^{11}C]-diprenorphine ([^{11}C]**1a**) has a long history in measuring OR and its functions in brain.[1] A large variety of PET studies for detecting OR occupancy with [^{11}C]**1a** and [^{18}F]fluoroethyl-diprenorphine ([^{18}F]**5a**) are reported, e.g., within measurements on conditions of experimental pain and emotional physiological states like euphoria.[2−4] Variable sensitivities have been reported for the measurements of OR occupancy caused by the release of endogenous endorphin peptides. On the other hand, consequently low sensitivity is reported from studies in detecting changes to the availability of ORs from competition and OR occupation from exogenous potent opioid.[5,6]

Current tracer design of opioid receptor tracers for use in PET aims at optimizing the sensitivity of the tracer for detecting changes to the availability of receptors from physiological, physical, or pharmacological stimuli relative to control conditions. The effects of tracer affinity and subclass selectivity on the tracer sensitivity toward endogenous and exogenous opioid receptor binding compounds have been addressed.[5,6] In contrast, the effects of the tracer agonist or antagonist properties, the intrinsic activity of the tracer, have so far not been systematically studied on these parameters.

The ORs belong to the super family of G protein-coupled receptors that exist in two different conformational states, corresponding to the coupled or high affinity state and uncoupled or low affinity state. This suggests that agonists preferentially bind with higher affinity to the receptor when in the coupled state, while antagonists bind with the same affinity to both, independent of the coupling status as reported for dopamine receptors.[7] Current available OR PET tracers possessing different intrinsic activity originate from different compound classes. Investigations on the effects of intrinsic activity by these tracers could be difficult because tracers with different structures are likely to have different binding pattern toward the receptor pocket which potentially could shade for apparent binding selectivity toward OR coupling states. Investigations with structurally related PET tracers possessing different intrinsic activity could clarify these relations and be useful in optimizing PET tracers selectivity to obtain more

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specific physiological information about the presence of OR states by PET imaging.

The antagonist [^{11}C]**1a** belongs to the class of orvinols established by Bentley and his associates at the company Reckitt and Colman in the 1960s.[8−10] Previously, together with the earlier established partial antagonist [^{11}C]buprenorphine ([^{11}C]**1b**),[11] we completed the spectrum of structurally related orvinol PET tracers possessing all intrinsic activities by the provision of the agonist [^{11}C]phenethyl-orvinol ([^{11}C]**1c**).[12]

The availability and flexibility to design PET imaging protocol with this orvinol triplet could benefit from a shift from the short-lived carbon-11 label ($t_{1/2}$ = 20.3 min) to the longer lived fluoride-18 ($t_{1/2}$ = 109.7 min). Recently, we reported the production of 6-*O*-[^{18}F]fluoroethyl-diprenorphine ([^{18}F]**5a**) based on a new method for fully automated provision of high quality 2-[^{18}F]fluoroethyl-tosylate.[13] With 6-*O*-[^{18}F]-fluoroethyl-phenethyl-orvinol ([^{18}F]**5c**) and [^{18}F]**5a** previously reported with different production protocols,[14−16] we here aimed for production of 6-*O*-[^{18}F]fluoroethyl-buprenorphine ([^{18}F]**5b**), not previously reported, and to provide the triplet of orvinols ([^{11}C]**1a−c**) as fluoride-18 versions ([^{18}F]**5a−c**) with a single production protocol (Figure 1).

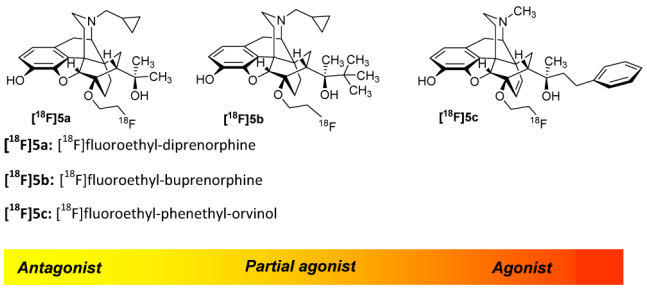


Figure 1. Three 6-*O*-^{18}F-fluoroethylated orvinol PET tracers with different intrinsic activity.

RESULTS AND DISCUSSION

The starting materials for the synthesis of the reference standards and precursor compounds (Scheme 1) DPN (**1a**), BPN (**1b**), and PEO (**1c**), are available by the original method of Bentley[8,9] and more recently developed procedures.[12,17−20] 6-*O*-Desmethyl derivatives DDPN (**2a**), DBPN (**2b**), and DPEO (**2c**) and the 3-*O*-trityl protected precursor compounds TDDPN (**3a**), TDBPN (**3b**), and TDPEO (**3c**) were prepared according to the method of Luthra et al.[11] previously used to provide precursor compounds for production of the [6-*O*-methyl-^{11}C]labeled versions of PEO, BPN, and DPN.

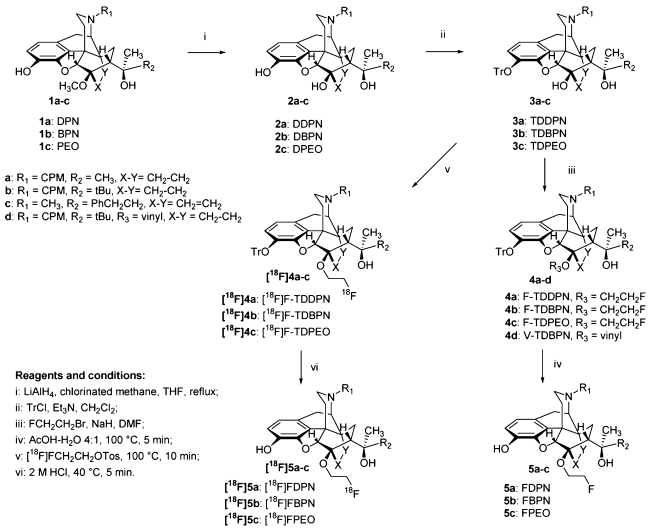
For provision of 6-*O*-fluoroethylated orvinol reference standards (**5a−c**), the 3-*O*-trityl-protected-6-*O*-desmethyl precursors (**3a−c**) were treated with fluorethyl bromide (Scheme 1). Selective 6-*O*-alkylation was accomplished using 2.33 equiv of 2-fluoroethyl-bromide in the presence of 10 equiv of sodium hydride in DMF at room temperature.

For compounds **3a** and **3c**, the 6-*O*-fluoroethylated products F-TDDPN (**4a**) and F-TDPEO (**4c**) were isolated in good yields (65% and 64%) with no formation of orvinol side products. Under identical conditions, a 6-*O*-vinyl byproduct, V-TDBPN (**4d**), was formed in 20% yield during the alkylation of TDBPN (**3b**) with 2-fluoroethyl-bromide.

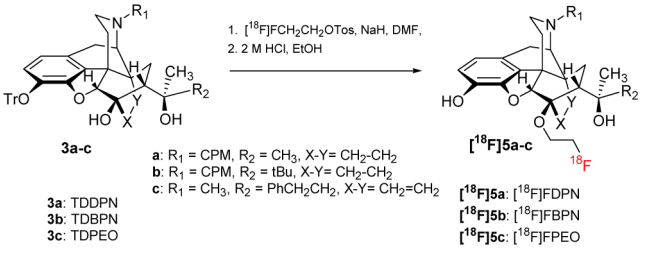
Finally, the reference substances 6-*O*-fluoroethyl-DPN (FDPN, **5a**), 6-*O*-fluoroethyl-BPN (FBPN, **5b**), and 6-*O*-fluoroethyl-PEO (FPEO, **5c**) were achieved by deprotection of the corresponding 3-*O*-trityl derivatives (**4a−c**) using boiling aqueous acetic acid.[21]

The radiosynthesis of [^{18}F]**5a−c** was accomplished by ^{18}F-fluoralkylation of the 6-*O*-desmethyl 3-*O*-trityl protected orvinol precursors (**3a−c**) with 2-[^{18}F]fluoroethyl-tosylate ([^{18}F]FETos) in a two-pot, three-step synthesis. In this work, we used the same method (Scheme 2) and set up for the automated production of the three 6-*O*-[^{18}F]fluoroethylated orvinols as previously described for the production of [^{18}F]**5a**.[13]

Scheme 1. Synthesis of Orvinol Precursors and Fluorine-18 and Fluorine-19 Labeled Orvinol Drivatives



Scheme 2. Preparation of ^{18}F-Labeled Orvinols by Three-Step, Two-Pot ^{18}F-Fluoroalkylation



The set up for the automated synthesis of the ^{18}F-labeled orvinols comprised the following processes: (1) fixation, wash, and release of [^{18}F]fluoride from target water on strong-anion exchange SPE cartridge before (2) drying and formation of the [K+ ⊂ 2.2.2]^{18}F- complex, (3) synthesis of [^{18}F]FETos, (4) isolation and drying of [^{18}F]FETos, (5) ^{18}F-fluoro-ethylation and (6) deprotection of the 3-*O*-trityl moiety from the ^{18}F-fluorethylated intermediates ([^{18}F]**4a−c**), and finally (7) isolation by means of preparative HPLC of [^{18}F]**5a−c** before SPE fixation, release with EtOH, and finally formulation in PBS.

Preparative isolated yield of [^{18}F]FETos was >45% with >99% in radiochemical purity (TLC and HPLC). ^{18}F-Fluoralkylation of **3a−c** provided >90% in radiochemical yield (based on [^{18}F]FETos) with >99% in yield for the following deprotection (TLC/HPLC). Starting from 10 to 30 GBq of [^{18}F]fluoride, the decay corrected formulated product yield was 26% ± 8% for all three products (n > 90). The total radiosynthesis was completed in a synthesis time of ∼100 min.

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The identity of [^{18}F]**5a−c** was confirmed by coelution with the respective authentic reference **5a−c** by means of HPLC. Final quality control of [^{18}F]**5a−c** revealed a specific activity in the range 50−300 GBq/μmol (HPLC) depending on the starting specific activity.

Animal PET. In vivo brain imaging with PET was performed with [^{18}F]**5a−c** in rats together with naloxone for blocking of each tracer. Figure 2 shows the measured uptake kinetics for all

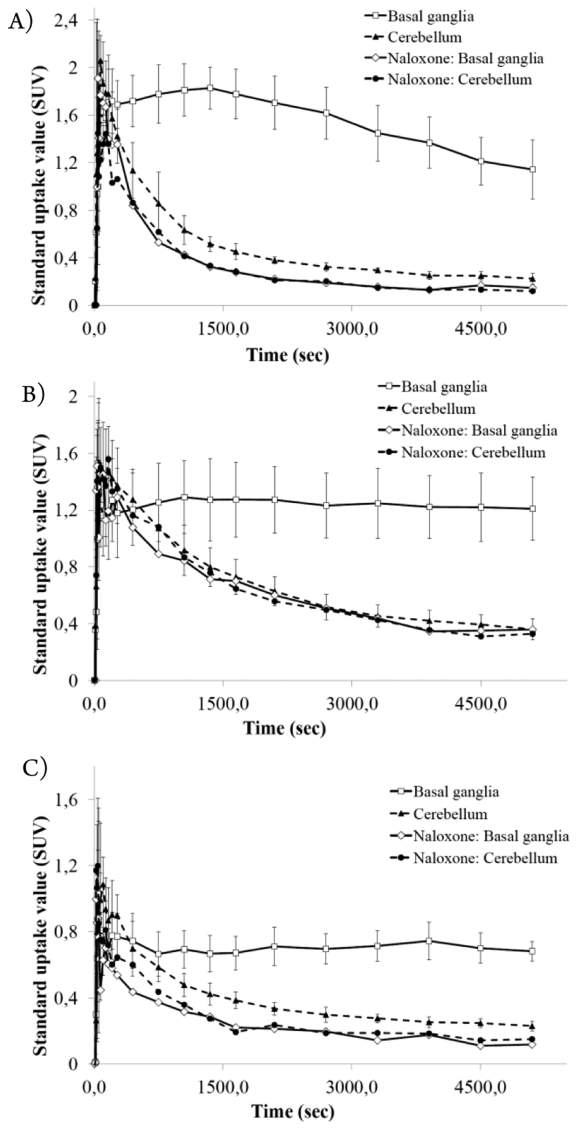

Figure 2. Regional time−activity curve of [^{18}F]**5a** (A), [^{18}F]**5b** (B), and [^{18}F]**5c** (C) with number (n) of rats: n = 4, 8, and 6, respectively. For Naloxone n = 1.

tracers of the μ-OR high density region, the basal ganglia, and the μ-OR low density region, the cerebellum. All data (mean ± SD) are normalized for injected dose and body weight. [^{18}F]**5a−c** showed fast brain uptake and specific accumulation in basal ganglia. The measured uptake kinetics of [^{18}F]**5b−c** (Figure 2B,C) shows a plateau after ∼3 min as previously observed with [^{11}C]**1c**[12] and in accordance with [^{11}C]**1b** in baboon.[21] In contrast, [^{18}F]**5a** shows a pronounced washout of activity from basal ganglia after reaching maximum at about 10 min as previously reported with [^{11}C]**1a** and [^{18}F]**5a** in mice.[14]

In separate experiments, we investigated the effect of blocking the ORs with the nonselective antagonist naloxone, which was injected 15 min prior to the three fluoride-18 labeled orvinol tracers (Figure 2A−2C). The measurement of activity in brain revealed the same fast and high initial uptake of all three tracers as seen without any pretreatment, followed by a fast washout of activity from all brain regions. The uptake of all three tracers in basal ganglia approached that of cerebellum, indicating that the binding of the tracers is specifically to opioid receptors.

Ratios between basal ganglia and cerebellum uptake (Table 1) revealed the highest standard uptake values (SUV) ratio for

Table 1. Binding Ratios with Test Retest for [^{18}F]5a−c in Rat Brain (Mean ± SD)[a]

orvinol	binding ratio	test/retest
[^{18}F]**5a**	5.03 ± 0.30	4.64/4.97
[^{18}F]**5b**	3.01 ± 0.26	3.19/3.24
[^{18}F]**5c**	2.82 ± 0.15	2.78/2.83

[a]Left column shows binding ratio between basal ganglia and cerebellum for [^{18}F]**5a−c** with average SUV and SD from 55 to 85 min post injection (n = 4−8).

[^{18}F]**5a**, followed by that of [^{18}F]**5b** and of [^{18}F]**5c**. Also, intrasubject variability of SUV is interestingly low (CoV (%): 6.0%, 8.6%, and 5.3% for [^{18}F]**5a−c**, respectively).

Test retest measurement was performed by injection of [^{18}F]**5a−c** to the same animal with minimum 7 days apart for investigating the reproduction of ratios of measured SUV of basal ganglia and cerebellum. The results revealed a high degree of reproducibility within subject for all three tracers.

Characterization. For characterization and biological evaluation of [^{18}F]**5a−c**, and to compare physiochemical properties and structure−activity relations (SAR) caused by altering the structure of the native 6-*O*-methylated orvinol by a 6-*O*-fluoroethylation, [^{18}F]**5a−c** and **5a−c** were investigated in different in vitro and in vivo assays.

The octanol/PBS partition coefficient (log *P* octanol/PBS) of [^{18}F]**5a−c** was measured to determine the apparent lipophilicity. log *P* for [^{18}F]**5a−c** was measured to be 2.20 ± 0.03, 3.08 ± 0.07, and 2.92 ± 0.15, respectively. The measured log *P* for [^{18}F]**5c** represented an 22% increase in value compared to the earlier measured value for the native drivative [^{11}C]**1c**. The observed increase in lipophilicity for [^{18}F]**5c** is in accordance with the effect of an extended alkyl moiety from the substitution of 6-*O*-methyl with a 6-*O*-fluoroethyl group. All measured log *P* values are within the range of optimal lipophilicity for PET tracers (log *P* optimal range =2.0−3.5) for crossing the blood−brain barrier which is a prerequisite to reach OR targets in the CNS.[22]

In Vitro Receptor Binding Assay. The opioid receptor affinities of all three fluoroethylated orvinols (**5a−c**) toward μ, δ, and κ-ORs were determined in radioligand binding assay in vitro using human cloned receptors stably expressed on CHO cells (μ- and δ-OR) and HEK-293 (κ-OR) according to published procedures. The results are given in Table 2 as K_i values (nM), together with literature values for the native 6-*O*-methyl orvinol versions.

The results from the in vitro binding study in Table 2 revealed similar high affinities for human cloned μ-OR to κ-OR for the native and the 6-*O*-fluoroethylated orvinol triplet. **5c** was found to possess similar high affinity binding to human

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Table 2. Binding Affinity (K_i in nM) of 6-*O*-Methylated and 6-*O*-Fluoroethylated Orvinol Triplet towards Human Cloned Opioid Receptors

orvinol	μ-OR (nM)	δ-OR (nM)	κ-OR (nM)
1a[a]/**5a**	0.07/0.24	0.23/8.00	0.02/0.2
1b[b]/**5b**	0.09/0.24	1.15/2.10	0.07/0.12
1c[c]/**5c**	0.18/0.10	5.1/0.49	0.12/0.08

[a]Values from Raynor et al. 1994.[23] [b]Values from Romero et al. 1999.[24] [c]Previous study, Marton et al. 2009.[12]

cloned μ-OR and to κ-OR with a lowered affinity for δ-OR. The measured affinities to μ- and κ-OR are close to affinities previously reported for **1c**. The affinity to δ-OR was increased for **5c** over that of **1c** by a factor of 10. In contrast, both **5a** and **5b** revealed a slight decrease in affinity toward δ-OR relative to their native versions by a factor of 35 and 2, respectively.

Determination of pharmacological potency of **5a**−**c** was performed in a separate experiment by agonist stimulation of [^{35}S]GTPγS. The measured agonist stimulation of [^{35}S]GTPγS toward the different OR subtypes are given in Table 3 for **5a**−**c**

Table 3. [^{35}S]GTPγS Stimulation by 5a−c at 1 nM, Pharmacological Potency (% Relative Agonist Response)

orvinol	μ-OR (%)	δ-OR (%)	κ-OR (%)
5a	12	22	70
5b	55	9	43
5c	97	92	95

as % agonist response relative to the maximum stimulation by standards: the full μ-agonist DAMGO, the δ-agonist DPDPE, and the full κ-agonist U69593 at 1 nM concentration of the ligand in question.

The assay revealed high potency for **5c** to all three receptor subtypes as previously reported for the native version **1c**.[12] Less agonist response was observed for **5a** and **5b** toward all OR subtypes as expected from properties of the native versions.

Protein Binding Assay. Protein binding properties of [^{18}F]**5a**−**c** were investigated by an in vitro assay in full blood from rats (n = 3). After separating the red blood cell fractions, only 14, 16, and 6% of the total radioactivity was measured in the serum fraction for [^{18}F]**5a**−**c**, respectively. After filtering off the proteins, 68, 96, and 94% of the activity measured in serum remained in the protein fractions.

The observed high binding of radioactivity to the red blood cell and the protein fraction in the in vitro assay limited the method relevance for preparation of serum samples to be analyzed for tracer stability and integrity toward metabolism. Therefore, we aimed for a method to increase the total activity amount in serum after removing the proteins. The method was changed by adding a washing step for the red blood cell fraction by use of PBS followed by the use of acetonitrile to precipitate proteins from serum. The changed method was applied in an assay with in vivo incubation. Blood samples were collected 5, 20, and 40 min (n = 3) after iv injection of [^{18}F]**5a**−**c** in male Sprague−Dawley rats. The combined serum and PBS fraction revealed a content 48 ± 13%, 60 ± 8%, and 48 ± 6% of the total activity after 5 min in vivo incubation of [^{18}F]**5a**−**c**, respectively. In samples, 40 min post injection showed a slight reduction of activity in serum to 29 ± 14%, 50 ± 1%, and 46 ± 7% (mean % value, SD).

Measurements of proteins precipitated with acetonitrile showed for all time points a stable protein bound radioactivity fraction of 9 ± 3%, 11 ± 2%, and 11 ± 2% (mean, SD) relative to radioactivity in serum for [^{18}F]**5a**−**c**, respectively. Compared to the protein filtering method, washing the red blood cell fraction resulted alone in a 10% increase in recovery of activity while precipitating the proteins from the serum with acetonitrile represented a significant increase in work-up of radioactivity from the full blood samples.

Metabolite Assay. The metabolic fate of the three tracers was assessed from samples worked up in the in vivo protein binding assay by use of the above-described method for washing the red blood cell and the protein fraction. Intact tracers were determined by radio-TLC measurements analyzed by exposure of phosphor imaging plate before digital readout.

The fractions of intact tracer in the serum samples measured by TLC were used to calculate the extent of total intact tracer in full blood given in Table 4. Measured fractions of intact

Table 4. Intact [^{18}F]5a−c from Blood (n = 3, Mean ± SD)

	[^{18}F]**5a** (%)	[^{18}F]**5b** (%)	[^{18}F]**5c** (%)
5 min	12.5 ± 7.0	39.3 ± 3.5	26.8 ± 8.3
20 min	6.9 ± 1.8	27.4 ± 2.8	17.4 ± 5.6
40 min	4.8 ± 3.2	27.5 ± 1.7	14.3 ± 2.8

tracer was compensated for activity bound to the red blood cell fraction and proteins to achieve the total fraction of available tracer assuming that bound activity is either a metabolite of the tracer in question or irreversibly bound intact tracer.

From the results in Table 4 and measured values for log P, there is a correlation between higher available tracer content in the serum samples for tracers possessing higher lipophilicity (log P: [^{18}F]**5b** > [^{18}F]**5c** > [^{18}F]**5a**).

The integrity of [^{18}F]**5a**−**c** in brain was investigated after collecting whole rat brains at 5, 20, and 40 min after iv injections. Brains were frozen and homogenized before extracting the activity with acetonitrile. Measured average extraction yield remained stable for all time point with 94 ± 3, 92 ± 3, and 93 ± 1% extracted activity for [^{18}F]**5a**−**c**, respectively. Radio TLC on the extracts revealed constantly high content of intact tracer with 94.6 ± 1.3, 98.0 ± 0.7, and 96.9 ± 1.8% (mean ± SD) combined for all time points for [^{18}F]**5a**−**c**, respectively, showing that all three orvinols possess a high integrity toward metabolism in brain. This also indicates that uptake of radioactive metabolites are low and that metabolic species have no accumulation in brain. The measured high tracers integrity in brain is in accordance with earlier report with 80% intact [^{18}F]**5a** after 30 min in mice.

CONCLUSION

The structurally matched orvinol triplet **1a**−**c** is now available as the fluoride-18 version [^{18}F]**5a**−**c** from a fully automated production based on a SPE method by use of a single module with performance and quality suitable for the production of potent OR PET tracers.

PET imaging of [^{18}F]**5a**−**c** in rat brain showed fast brain uptake and selective accumulation in μ-rich regions such as the basal ganglia. Different clearance kinetics from the brain was observed, with a plateau after 3 min for [^{18}F]**5b** and [^{18}F]**5c**, while [^{18}F]**5a** levels decreased constantly after a maximum at 10 min. The in vitro assays revealed that the agonist potency and affinity toward the OR for the fluorine-18 labeled version of

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PEO was conserved except for a slightly higher affinity toward the δ-OR. This first report on the 6-*O*-^{18}F-fluoroethylated version (**5b**) of buprenorphine (**1b**) showed no significant change in subtype selectivity or affinity compared to the native structure.

The results open for continued investigations in characterizing the dependency of agonist and antagonist properties on sensitivity of imaging of OR in different functional states with now available [^{18}F]**5a**−**c**.

EXPERIMENTAL SECTION

Chemistry. The purity of the synthesized compounds was determined by analytical HPLC to be >95%. **3a** and **3b** were produced by ABX Biochemical, Dresden, Germany. Compound **3c** was prepared as reported previously.[12] The syntheses of reference standards **5a** and **5c** are previously reported.[14,15] The method of preparation of **5b** is described in the Supporting Information.

Radiosynthesis. The general method for ^{18}F-fluorethylation of TDDPN (**3a**), TDBPN (**3b**), and TDPEO (**3c**), with subsequent removal of the 3-*O*-trityl-group and preparative HPLC purification of [^{18}F]**5a**−**c**, was performed with modifications to a previously reported method[14] in accordance with the method described earlier.[13] All labeling steps were performed in an automated fashion in a two-pot, three-step reaction on the same synthesis module (Hot-box III, Scintomics GmbH, Fuerstenfeldbruck, Germany).

Cyclotron produced [^{18}F]fluoride in water was trapped and washed on a QMA-cartridge Sep Pac Light (Waters) before forming the [$K^+ \subset$ 2.2.2]^{18}F complex. Then 7.5 mg of ethylene-ditosylate in 1 mL of acetonitrile was added for reaction in 5 min at 75 °C. Unreacted ethylene-ditosylate precursor was precipitated from the reaction mixture at room temperature by the addition of 3 mL of 0.007 M acetic acid. The precipitate was removed online by means of a 0.45 μm polypropylene filter disk while transferring the mixture to two stacked Sep-Pac Plus C-18 cartridges (Waters). Immobilized [^{18}F]FETos was eluted with 35% (v/v) of methanol/water in the interval 7−17 mL. Subsequent immobilization followed by gas-jet drying on a 30 mg Strata-X column (Phenomenex) and finally eluting [^{18}F]FETos with 200 μL of anhydrous DMF and trapped in a second vial. The ^{18}F-fluoroalkylation of 3-*O*-protected orvinol precursor in question was conducted as follows: 2.0 mg of orvinol precursor, **3a**−**c**, was dissolved in 200 μL of anhydrous DMF and activated with 5 mg of NaH for 5 min. Excess NaH was removed before transfer of activated orvinols precursor to vial containing [^{18}F]FEtos. The reaction was allowed to proceed for 10 min reaction at 100 °C. After cooling to 40 °C, 0.5 mL of 2.0 M HCl in EtOH was added and the mixture allowed reacting for 5 min in order to remove the trityl protecting group. Before product isolation HPLC and work-up, the reaction mixture was brought to pH ∼8 by adding of 0.53 mL of 2.0 M ammonium hydroxide. The product peak was collected from the HPLC (LC, Scintomics GmbH) mobile phase before product immobilization on a Sep-Pak Light C18 cartridge, with subsequent product formulation in physiological phosphate buffer saline and sterile filtering. The purity and specific activity (SA) was determined by HPLC system (Shimadzu) comprising a μ-Bondapak C-18 HPLC column 300 mm length × 4 mm internal diameter (CS Chromatographie GmbH, Germany) fitted with a diode array UV detector (Shimadzu), which was set at 220 nm, coupled in-line with a GABI radioactivity detector (Ray Test, Straubenhardt, Germany). Samples were eluted with 1/1 (v/v) acetonitrile and 0.1 M ammonium formate at 1.5 mL/min. The identity of [^{18}F]**5a**−**c** was confirmed by means of analytical radio-HPLC after coinjection of authentic reference samples.

Yields and physical data of the prepared compounds are collected in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

New compound characterization and procedures for compound synthesis and biological assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS USED

BPN, buprenorphine; CPM, cyclopropylmethyl group; DPN, diprenorphine; DBPN, 6-*O*-desmethyl-buprenorphine; DDPN, 6-*O*-desmethyl-diprenorphine; DPEO, 6-*O*-desmethyl-phenethyl-orvinol; FBPN, 6-*O*-(2-fluoroethyl)-buprenorphine; FDPN, 6-*O*-(2-fluoroethyl)-diprenorphine; F-TDBPN, 6-*O*-(2-fluoroethyl)-3-*O*-trityl-6-*O*-desmethyl-buprenorphine; F-TDDPN, 6-*O*-(2-fluoroethyl)-3-*O*-trityl-6-*O*-desmethyl-diprenorphine; F-TDPEO, 6-*O*-(2-fluoroethyl)-3-*O*-trityl-6-*O*-desmethyl-phenethyl-orvinol; FPEO, 6-*O*-(2-fluoroethyl)-phenethyl-orvinol; PEO, (20*R*)-phenethyl-orvinol; TDDPN, 3-*O*-trityl-6-*O*-desmethyl-diprenorphine; TDBPN, 3-*O*-trityl-6-*O*-desmethyl-buprenorphine; TDPEO, 3-*O*-trityl-6-*O*-desmethyl-phenethyl-orvinol; *t*Bu, *tert*-butyl group; Tr, trityl group = triphenylmethyl group

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