Discovery of *N*-{(1*S*,2*S*)-2-(3-Cyanophenyl)-3-[4-(2-[^{18}F]fluoroethoxy)phenyl]-1-methylpropyl}-2-methyl-2-[(5-methylpyridin-2-yl)oxy]propanamide, a Cannabinoid-1 Receptor Positron Emission Tomography Tracer Suitable for Clinical Use

Ping Liu,*,† Linus S. Lin,† Terence G. Hamill,‡ James P. Jewell,†,# Thomas J. Lanza, Jr,† Raymond E. Gibson,‡ Stephen M. Krause,‡ Christine Ryan,‡ Waisi Eng,‡ Sandra Sanabria,‡ Xinchun Tong,† Junying Wang,† Dorothy A. Levorse,† Karen A. Owens,† Tung M. Fong,§ Chun-Pyn Shen,§ Julie Lao,§ Sanjeev Kumar,|| Wenji Yin,|| Joseph F. Payack,∞ Shawn A. Springfield,∞ Richard Hargreaves,‡ H. Donald Burns,‡ Mark T. Goulet,†,# and William K. Hagmann†

Departments of Medicinal Chemistry, Metabolic Disorders, Drug Metabolism, and Process Research, Merck Research Laboratories, Rahway, New Jersey 07065, and Department of Imaging Research, Merck Research Laboratories, West Point, Pennsylvania 19486

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Abstract: The discovery of a structurally distinct cannabinoid-1 receptor (CB1R) positron emission tomography tracer is described. Starting from an acyclic amide CB1R inverse agonist (**1**) as the lead compound, an efficient route to introduce ^{18}F to the molecule was developed. Further optimization focused on reducing the lipophilicity and increasing the CB1R affinity. These efforts led to the identification of [^{18}F]-**16** that exhibited good brain uptake and an excellent signal-to-noise ratio in rhesus monkeys.

Cannabinoid receptors belong to the superfamily of G-protein-coupled receptors. Cannabinoid-1 receptors (CB1R) are mainly located within the central nervous system, and cannabinoid-2 receptors (CB2R) are mainly associated with cells of the immune system.[1] Cannabinoid receptors are recognized for mediating their biological effects through exposure to agonists, antagonists, or inverse agonists. While CB1R agonists are known to be beneficial for the treatment of pain, chemotherapy-induced nausea, and emesis,[2] CB1R antagonists or inverse agonists may be beneficial for the treatment of smoking cessation,[3] appetite control,[3] and other central nervous system disorders.[4] Currently, rimonabant, a selective CB1R inverse agonist from Sanofi-Aventis, has been approved in the European Union and is under FDA review as a novel treatment for obesity. To better understand CB1R biology and assist in the design and testing of promising drug candidates targeting this receptor, a suitable CB1R positron emission tomography (PET) or single photon emission computed tomography (SPECT) radioligand is highly desirable that would allow CB1R imaging studies in the living human and animal brain under normal physiological and diseased conditions. In general, a successful PET ligand should provide a good specific signal (total/nonspecific, ≥2:1) to allow quantitative mapping of a receptor of interest. Ideally, a brain PET ligand needs to have a good affinity with $B_{max}/K_d \geq 10$ and reasonable lipophilicity with log *P* or log *D* ≈ 1−3.5 for adequate brain penetration and optimum specific to nonspecific ratio.[5,6] Much effort has been devoted to the search for suitable CB1R PET and SPECT ligands. Most of the reported radioligands are variations of alkylindoles[7] or 1,5-diaryl-3-carboxypyrrazoles, for example, [^{18}F]-AM694,[8] [^{123}I]-AM281,[9] and [^{11}C]-JHU75528[10] (Figure 1). Although progress has been made in this area, PET imaging studies of CB1R have been unsatisfactory presumably because of low affinity and/or high lipophilicity of the previous ligands. Herein, we report the discovery of a novel CB1R PET tracer (MK-9470) that has proven suitable for clinical application.[11]

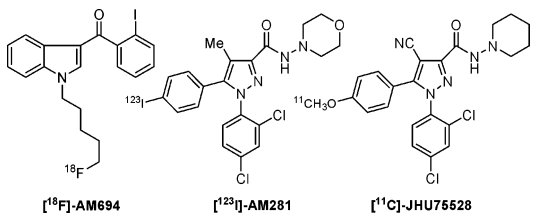
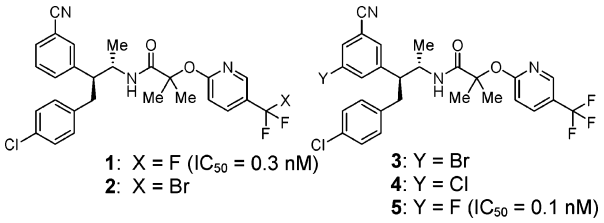
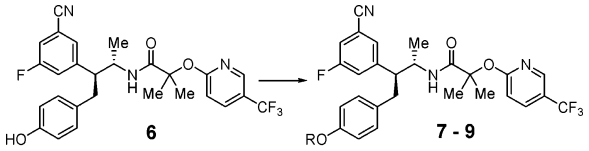


Figure 1. Representative examples of CB1R PET or SPECT tracers.

Scheme 1. Substrates for Attempted Fluoride Exchange



Scheme 2. Alkylation of Phenol **6**[a]



Compd. No.	R	CB1 (IC_{50}, nM)[a]	log D[b]
1		0. 3 ± 0.1	5.2± 0.1
7	CH_3	0.9 ± 0.2	4.8 ± 0.1
8	FCH_2	2.0 ± 0.8	4.7 ± 0.1
9	FCH_2CH_2	0.9 ± 0.5	4.6 ± 0.1

[a] Inhibition of binding (mean ± SD, $n \geq 4$ independent experiments) of [^{3}H]CP-55940 to recombinant human CB1 receptors expressed on Chinese hamster ovary cells.[13] [b] HPLC log *D* (pH 7.3).

The medicinal chemistry efforts began with taranabant (MK-0364), a potent CB1R inverse agonist (**1**) that had been selected for clinical evaluation to treat obesity.[12] Compound **1** has an HPLC log *D* value of 5.2 and human CB1R IC_{50} of 0.3 nM. Although the lipophilicity of **1** is higher than desired, we were encouraged by its excellent CB1R affinity. We decided to direct our initial effort to finding a reliable route to introduce a radiolabel before addressing the lipopholicity issue of the lead.

Exchange of a fluorine atom of the trifluoromethyl group in **1** with ^{18}F was first attempted. However, the substrate **1** and the bromo precursor **2**[14] (Scheme 1) failed to produce the high specific activity required for a receptor based PET tracer.

Introduction of ^{18}F onto one of the phenyl rings was then investigated because labeling of a 3-fluorobenzonitrile was

* To whom correspondence should be addressed. Phone 732-594-0321. Fax 732-594-5966. E-mail: ping_liu2@merck.com.
† Department of Medicinal Chemistry, Merck, NJ.
‡ Department of Imaging Research, Merck, PA.
# Current affiliation: MRL Boston.
§ Department of Metabolic Disorders, Merck, NJ.
|| Department of Drug Metabolism, Merck, NJ.
∞ Department of Process Research, Merck, NJ.

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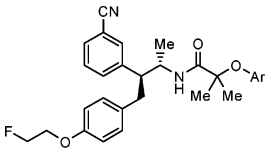
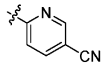
Table 1. Inhibition of CB1R (IC_{50}, nM)[a] and HPLC log D of Fluoroethyl Analogues



Compd. No.	Ar	CB1 (IC_{50}, nM)[a]	log D[b]
10		0.9 ± 0.6	4.4 ± 0.1
11		0.77, 1.5	4.6 ± 0.1
12		1.3, 1.4	3.7 ± 0.1
13		0.8 ± 0.3	4.2 ± 0.1
14		1.8, 2.0	3.3 ± 0.1
15		0.47, 1.6	4.1 ± 0.1
16		0.7 ± 0.4	4.0 ± 0.1
17		1.8, 3.8	3.9 ± 0.1

[a] Inhibition of binding (mean ± SD if $n \geq 4$ independent experiments; individual values if $n = 2$).[13] [b] HPLC log *D* (pH 7.3).

successful in a previous program.[15] The SAR study suggested that the Y position of the top phenyl ring (Scheme 1) could be substituted by fluorine because the fluoro analogue exhibited a very high human CB1R binding affinity (IC_{50} = 0.1 nM). However, when the bromo or chloro precursor **3** or **4** was subjected to nucleophilic substitution with fluoride, no desired product was observed presumably because of insufficient activation of the phenyl ring by the nitrile group.

Finally, alkylation of a phenolic precursor with radiolabeled electrophiles was evaluated. Palladium catalyzed boronation of aryl chloride **5** afforded a boronic ester that was subsequently oxidized to phenol **6**.[16] The appropriate electrophile was reacted with **6** to afford the ethers **7**−**9** (Scheme 2). On the basis of the CB1R binding data, the methoxy analogue **7** and the fluoroethoxy analogue **9** were potential candidates as PET ligands. Furthermore, of the three analogues, the fluoroethoxy analogue **9** seemed to be the least lipophilic with the lowest log *D*. For the radiolabeled **9** where R is $^{18}FCH_2CH_2$, specific activity of >1000 Ci/mmol was achieved.[11a] Therefore, further exploration of the physical properties of **9** was pursued with the objective of lowering lipophilicity while maintaining potency.

Deletion of the fluorine from the phenyl ring of **9** afforded **10** with a slightly lower log *D* (4.4 vs 4.6, Table 1) while retaining the same level of affinity. The amine portion of the molecule was then conserved, and SAR efforts focused on modification of the right-hand portion of the molecule.

As shown in Table 1, moving the CF_3 group from the 5-position to the 4-position (**11**) or replacement of CF_3 with Cl (**13**) did not lead to improvement in log *D* or CB1R potency. A noticeable log *D* reduction was observed when the 5-CF_3 group was replaced with H (**12**) or CN (**14**) or when an additional nitrogen atom was introduced to the pyridine ring to derive the corresponding pyrimidine (**17**). However, some loss of CB1R binding activity was also observed in these cases. Replacement of 5-CF_3 with 5-CH_3 resulted in an improvement over **10** in log *D* and CB1R affinity (**16**). Again, moving 5-CH_3 to 4-CH_3 provided no advantage in potency or lipophilicity (**16** vs **15**). Overall, analogue **16** appeared to offer the best balance of CB1R affinity (IC_{50} = 0.7 nM) and liphophilicity in this series. Therefore, this compound was selected for further characterization.

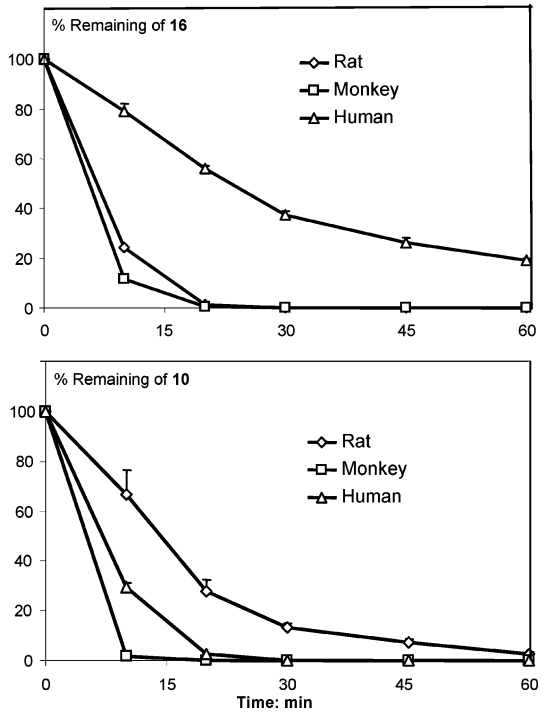


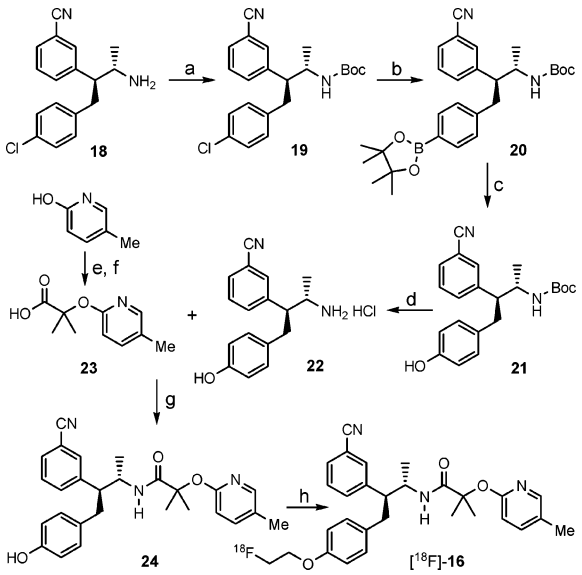
Figure 2. Metabolic stability of **16** (top) and **10** (bottom) in liver microsomes (0.2 mg protein/mL, 1 μM substrate) in rats, monkeys, and humans. Values are the average of three determinations.

Compound **16** is a selective CB1R inverse agonist with human CB2R IC_{50} of 44 nM. Other off-target activities of **16** were evaluated in 168 assays of receptors, enzymes, ion channels, and transporters, and it showed more than 700-fold selectivity over all the targets tested. This compound was not a substrate for mouse (Mdr1a) or human (MDR1) P-glycoprotein in vitro and rapidly penetrated into the brain and achieved a brain-to-plasma concentration ratio of 0.5 at 15 min after a 1 mg/kg iv dose to rats.

Compound **16** exhibited high clearance (81 mL min^{-1} kg^{-1}) and short half-life (1.4 h) in rats following a 1 mg/kg iv dose. In vitro metabolism studies of **16** were carried out in liver microsomes from rats, monkeys, and humans. As illustrated in Figure 2, **16** is much more stable in human liver microsomes than in rat and monkey microsomes, which suggested that [^{18}F]-**16** may be cleared more slowly in humans. Interestingly, analogous studies with the CF_3 analogue **10** demonstrated that it is metabolized much more quickly than **16** in human liver microsomes, although they behave similarly in liver microsomes of rats and monkeys.

In general, the CF_3 group is metabolically more stable than the CH_3 group; however replacement of CH_3 with CF_3 in this case did not lead to a more stable structure presumably because of increased lipophilicity and binding to the CYP enzymes.

Scheme 3. Synthesis of the PET Tracer [^{18}F]-**16**[a]



[a] Reagents and conditions: (a) Boc_2O, PhMe, 94%; (b) bis(pinacolato-)diboron, $Pd_2(dba)_3$, PCy_3, KOAc, dioxane, 90−92 °C; (c) Oxone, $NaHCO_3$/NaOH, acetone/THF/H_2O (1:1:1, v/v/v), 0 °C, 95% for two steps; (d) HCl/dioxane, 100%; (e) ethyl 2-bromoisobutyrate, Cs_2CO_3, MeCN, 50 °C; (f) NaOH, H_2O/MeCN, 50 °C, 52% for two steps; (g) EDC, pyridine, MeCN, 50 °C, 85%; (h) [^{18}F]-FCH_2CH_2Br, Cs_2CO_3, DMF, 100 °C.

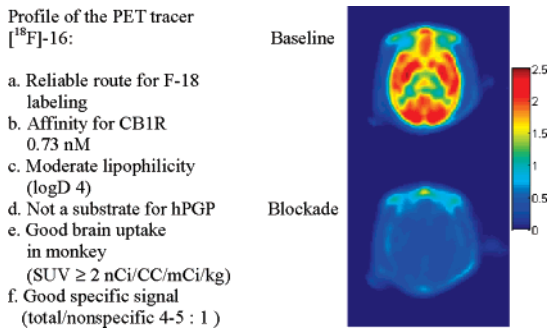


Figure 3. Profile of [^{18}F]-**16** and its in vivo PET images in rhesus monkey brain. Color scale indicates SUV units.

The synthesis of [^{18}F]-**16** is outlined in Scheme 3 and began with the enantiomerically pure amine **18**[12,21] that was reacted with Boc_2O to give Boc-protected amine **19**. The key transformation of this synthetic sequence was the conversion of the chlorobenzene moiety in **19** to the corresponding phenol, which was achieved in an efficient manner (95% yield) through a two-step process: (a) palladium mediated coupling of the aryl chloride with bis(pinacolato)diboron to afford aryl boronic ester **20**[17] and (b) oxone oxidation of the boronic ester to phenol **21**.[18] The Boc group was removed with HCl to give the amine salt **22** that was ready for coupling with acid **23**. Acid **23** was prepared from 2-hydroxy-5-methylpyridine through coupling with ethyl 2-bromoisobutyrate and subsequent hydrolysis. The amide formation between amine **22** and acid **23** was performed at 50 °C with EDC as the coupling reagent that afforded **24** in 85% yield.[19] Finally, phenol **24** was reacted with in situ generated $^{18}FCH_2CH_2Br$,[20] completing the synthesis of PET tracer [^{18}F]-**16**.[11a]

[^{18}F]-**16** was evaluated in propofol-anesthetized rhesus monkeys as a potential PET ligand.[11b] Baseline scans after a single iv (5 mCi) administration revealed that [^{18}F]-**16** rapidly penetrated the blood−brain barrier and accumulated in most gray matter regions (CB1R-rich area; see Figure 3), reaching a maximum signal in ∼2 h. A blockade experiment was also carried out with the CB1R inverse agonist **1** and the total to nonspecific signal ratio was ∼5:1 in one subject and ∼4:1 in another, exceeding the targeted criteria (2:1) for a PET tracer. The properties of this PET tracer are summarized in Figure 3. To our knowledge, [^{18}F]-**16** demonstrated the best profile among the CB1R tracers reported thus far.[22]

In summary, a high-affinity inverse agonist CB1R PET tracer [^{18}F]-**16** was identified by the development of a suitable radiolabeling route and optimization of potency and lipophilicity. This tracer exhibited good brain uptake and an excellent signal-to-noise ratio (total/nonspecific, 4 to 5:1) in rhesus monkey PET studies. The clinical results of [^{18}F]-**16** will be the subject of another publication.[11b]

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Supporting Information Available: Experimental procedures and characterization data for all new compounds; detailed description of pharmacological assays, in vitro metabolism protocol, and rhesus PET imaging studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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