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Synthesis of Fluorine-Containing Phosphodiesterase 10A (PDE10A) Inhibitors and the In Vivo Evaluation of F-18 Labeled PDE10A PET Tracers in Rodent and Nonhuman Primate

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Abstract

A series of fluorine-containing PDE10A inhibitors were designed and synthesized to improve the metabolic stability of [¹¹C]MP-10. Twenty of the 22 new analogues had high potency and selectivity for PDE10A: **18a–j**, **19d–j**, **20a–b**, and **21b** had IC_{50} values <5 nM for PDE10A. Seven F-18 labeled compounds [¹⁸F]**18a–e**, [¹⁸F]**18g**, and [¹⁸F]**20a** were radiosynthesized by ¹⁸F-introduction onto the quinoline rather than the pyrazole moiety of the MP-10 pharmacophore and performed in vivo evaluation. Biodistribution studies in rats showed ~2-fold higher activity in the PDE10A-enriched striatum than nontarget brain regions; this ratio increased from 5 to 30 min postinjection, particularly for [¹⁸F]**18a–d** and [¹⁸F]**20a**. Micro-PET studies of [¹⁸F]**18d** and [¹⁸F]**20a** in nonhuman primates provided clear visualization of striatum with suitable equilibrium kinetics and favorable metabolic stability. These results suggest this strategy may identify a ¹⁸F-

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Notes

The authors declare no competing financial interest.

Supporting Information

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General chemistry methods. Synthesis of intermediate compounds: **6a–j**, **9**, **11**, **12**, **14**, **15a–d**, and **16a–n**. Synthesis of radiolabeling precursors **23a–e**, **23g** and **24a** and intermediate compounds (PDF)

Molecular formula strings of final products and IC_{50} values for PDEs (CSV)

labeled PET tracer for quantifying the levels of PDE10A in patients with CNS disorders including Huntington's disease and schizophrenia.

INTRODUCTION

Phosphodiesterase 10A (PDE10A) is a dual-specificity phosphodiesterase enzyme that is able to hydrolyze both cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) to AMP and GMP, respectively.^{1–3} PDE10A mRNA is highly expressed in the brain; expression in peripheral tissues, with the exception of the testis, is low.⁴ Both PDE10A mRNA and protein are specifically enriched in the medium spiny neurons (MSNs) of the striatum.⁵ Abnormal striatal levels of PDE10A play a major role in schizophrenia, Huntington's disease, addiction, and other neuropsychiatric disorders.^{6–8}

Positron emission tomography (PET) is a preclinical molecular imaging technique which permits quantitative noninvasive measurement of drug disposition and localization in animal models of human disease and an important tool for clinical studies. PDE10A inhibitors have shown promise as therapeutics in preclinical models of human disease; several have progressed to clinical trials.^{7,9–16} The highly potent ($IC_{50} = 0.37$ nM) and highly selective (>100-fold) PDE10A inhibitor 2-[4-(1-methyl-4-pyridin-4-yl-1*H*-pyrazol-3-yl)-phoxymethyl]-quinoline (MP-10)¹⁷ has been extensively evaluated as a therapeutic inhibitor of PDE10A and has completed several clinical trials in human subjects.¹⁸ [¹¹C]MP-10 (Figure 1) was independently investigated by several groups as a PET tracer for quantifying PDE10A in vivo. Although variable success and significant species differences have been reported in preclinical studies,^{19–21} [¹¹C]MP-10 remains a potentially viable PET tracer for clinical studies. Numerous other ¹¹C- and ¹⁸F-labeled PDE10A inhibitors have been evaluated in preclinical rodent models, and although several candidate tracers have proceeded to studies in nonhuman primates and human subjects, the search for a PET tracer with ideal pharmacological properties is ongoing.^{22–31}

Although [¹¹C]MP-10 provides a clear anatomic image of the brain with high accumulation in the striatum of nonhuman primates (NHP), tissue time-activity curves in macaques revealed an increasing trend of radioactivity accumulation in both the target region (striatum) and the reference region (cerebellum) which may limit its utility.¹⁹ Our metabolite analysis of [¹¹C]MP-10 suggested that a brain penetrant radiometabolite was formed by *O*-dealkylation of the pyrazole moiety of [¹¹C]MP-10.¹⁹ An additional consideration in the search for an improved PET tracer is that the longer half-life of ¹⁸F places fewer time constraints on production and permits longer scan sessions that usually result in improved target:nontarget ratios and higher quality images. Although a potent and selective quinoline analogue of MP-10 was formed by introducing a [¹⁸F]fluoroethyl group on the *N*-atom of the pyrazole moiety ([¹⁸F]JNJ41510417, Figure 1),^{32,33} slow equilibrium kinetics were reported in rodents and NHPs, possibly due to brain-penetrant radioactive metabolites that accumulate nonspecifically in the brain. To overcome this potential liability, we recently ¹¹C-labeled the quinoline moiety instead of the pyrazole moiety of several new PDE10A inhibitors ([¹¹C]1–4, Figure 1).³⁴ We hypothesized that this strategy might lead to the identification of a new analogue with (i) increased in vivo metabolic stability, and/or (ii)

a metabolic pathway which generates radioactive metabolites that do not cross the blood-brain barrier (BBB). Our earlier structure–activity relationship (SAR) study explored the introduction of a methoxy group ($-\text{OCH}_3$) in the 3-, 4-, or 6-position of the 2-methylquinoline moiety of the MP-10 pharmacophore and the regioisomers of the new analogues. The most potent and selective compounds were the 3- and 4-methoxy substituted quinolines with an O atom bridge linkage; little difference was seen in the in vitro biological activity of regioisomers.³⁵ Subsequent evaluation of the ^{11}C -labeled lead tracers showed prolonged favorable target:background ratios in rats for the 3- and 4-methoxy substituted quinolines with high selectivity in the target region versus nontarget region and promising kinetic behavior in both the target region (striatum) and the reference regions of the NHP brain.³⁴

We have continued our exploration of ^{18}F -labeled PET radiotracers for PDE10A by introducing fluoro-, fluoromethyl, fluoropropyl, or triazole fluoroethyl groups into the quinoline moiety of MP-10. We also explored the introduction of a short fluoroPEGylated (FPEG) unit. Incorporation of a short FPEG unit has been shown to (i) enable facile ^{18}F -labeling of the target compound; (ii) improve the in vivo pharmacokinetics of molecules interacting with biologically interesting proteins or peptides;^{36,37} (iii) decrease the lipophilicity of molecules, which enhances their ability to cross the BBB.³⁸ Radiolabeling of [^{11}C]MP-10 also yielded the regioisomer ([^{11}C]isoMP-10 Figure 1),¹⁹ a slightly less potent PDE10A inhibitor reported in the discovery of MP-10;¹⁷ [^{11}C]isoMP-10 also showed selective binding in the rat striatum, though initial brain uptake was significantly lower than that of [^{11}C]MP-10.²⁸ We further expanded our synthetic efforts to include modification of the pyrazole moiety to generate regioisomers of the new fluorine-containing MP-10 quinoline analogues: this permitted expanded SAR studies. Here we report (i) the synthesis and screening of new analogues which allow ^{18}F -labeling in the quinoline moiety rather than the pyrazole moiety; (ii) ^{18}F -labeling of the potent and selective candidates and the in vivo evaluation of their suitability as PDE10A PET imaging agents using rats and macaques.

RESULTS AND DISCUSSION

Chemistry

The syntheses of target new PDE10A analogues was accomplished by a Mitsunobu reaction³⁹ of benzyl alcohols on the quinoline moiety coupled with substituted phenols on pyrazole moiety **17a–b**, or a *O*-alkylation of substituted methyl bromide on quinoline moiety with substituted phenols **17a–b**.

Following the above strategy, quinoline fragments of molecules including fluorine-containing intermediates **6a–j** and **15a** were first synthesized as shown in Scheme 1. Different approaches were used for the synthesis of compounds **6a–j** and **15a**: (i) aniline **5** was converted to the aryl fluoride **6a** via diazonium fluoroborates under the Balz-Schiemann conditions;⁴⁰ (ii) the alcohol **7** was converted directly into **6b** by treatment with diethylaminosulfur trifluoride (DAST); (iii) treatment of compound **8** with 1,1,1-trifluoro-*N*-phenyl-*N*-((trifluoromethyl)sulfonyl)methane-sulfonamide afforded the triflate; stille reaction^{41–43} of the triflate with allyltributyltin in the presence of tetrakis triphenylphosphine palladium and lithium bromide generated compound **9**; hydroboration–

oxidation of **9** to afford the alcohol, followed by fluorination generated compound **6c**; (iv) alkylation of commercially available **10** (ethyl 4-hydroxy quinoline-2-carboxylate) with 2-fluoroethyl bromide afforded ethyl 4-(2-fluoroethoxy)-quinoline-2-carboxylate (**6d**) in 60% yield; (v) alkylation of the phenol group of **10** with either a –Cl atom or –OTs group afforded the corresponding alcohols which were converted using DAST to the corresponding fluoroPEGylated intermediates **6e–g** in modest yields (60–71%); (vi) alkylation of (2-methylquinolin-4-yl)methanol **7** with 2-fluoroethyl bromide under basic conditions afforded 4-((2-fluoroethoxy)methyl)-2-methylquinoline **6h**; (vii) the aniline group of **5** was protected using di-*tert*-butyl dicarbonate to form the Boc-protected compound **11**, subsequent *N*-alkylation using 2-fluoroethyl bromide afforded **6i**; (viii) **10** was brominated using POBr₃ to afford ethyl 4-bromoquinoline-2-carboxylate **12**, which was converted to the azide compound and subjected to click reaction conditions,⁴⁴ followed by DAST fluorination to afford compound **6j**; (ix) using Friedlander synthesis,⁴⁵ 2-amino-benzaldehyde **13** reacted with 1-methoxypropan-2-one afforded the 3-methoxy-2-methylquinoline,⁴⁶ subsequent demethylation utilizing BBr₃ followed by *O*-alkylation afforded compound **15a**.

The synthesis of intermediate compounds **16a–n** was accomplished using strategies shown in Scheme 2: (i) bromination of **6a** or **15d** using NBS afforded compound **16a** and **16n**, respectively (Scheme 2, Method 1); (ii) the methylquinoline derivatives **6b–c**, **6h–i**, and **15a–c** were oxidized using selenium dioxide (SeO₂), followed by NaBH₄ reduction, while the ethyl quinoline-2-carboxylates **6d–g**, **6j** were reduced using NaBH₄ to afford the corresponding alcohols **16b–m** (Scheme 2, Methods 2–3). The detailed methods for synthesis of intermediates are provided in the Supporting Information.

The synthesis of final compounds **18a–j**, **19d–j**, **20a–d**, and **21b** was accomplished as shown in Scheme 3. Substituted phenols **17a–b** were prepared as previously published (Scheme 3).³⁵ **16b–m** were coupled with the phenol **17a** or **17b** with a Mitsunobu reaction³⁹ to afford **18b–j**, **20a–c**, **19d–j**, and **21b**. Compounds **18a** and **20d** were made by *O*-alkylation of the substituted phenol **17a** with substituted methyl bromide **16a** or **16n**.

In vitro inhibition assays identified candidate potent and selective analogues for radiolabeling: **18a–e**, **18g**, and **20a**. Schemes 4 and 5 outline the synthesis of the precursors for radiolabeling; the detailed methods for their synthesis are provided in the Supporting Information. Scheme 4 outlines the synthesis of precursors **23a**, **23d**, and **24a**. The method described above for synthesis of **16d** from **6d** was used for the synthesis of **23a**. A methoxymethyl ether (MOM) group was used to protect phenols **10** and **24b** under basic conditions; the protected intermediates were reacted with the substituted phenol **17a** under Mitsunobu reaction conditions to afford **27a–b**. The MOM ether functional group was easily deprotected by TFA to afford precursors **23d** and **24a**.

The precursors **23b–c**, **23e**, and **23g** were obtained by following Scheme 5. Commercially available *tert*-butyldimethyl-silyl (TBS) chloride was used as a silylation agent to protect alcohols **28a–d**. The use of 1.7 equiv imidazole as base with 1.7 equiv of TBSCl and DMF as solvent proved effective and resulted in TBS-ethers **29a–d** in high yield. Compounds **29a–d** were converted to the respective alcohols **30a–d**, which were coupled with the phenol

17a or **17b** in the presence of Ph_3P and di-*tert*-butyl azodicarboxylate (DBAD) via a Mitsunobu *O*-alkylation³⁹ to afford compounds **31a–d**. The TBS-ethers **31a–d** were easily deprotected with a catalytic amount of tetrabutyl ammonium fluoride (TBAF); the intermediate alcohol was then chlorinated or sulfonated as indicated in Scheme 5 to afford precursors **23b–c**, **23e**, and **23g**.

Radiochemistry

An overview of the radiolabeling of [^{18}F] **18a–e**, [^{18}F] **18g**, and [^{18}F] **20a** is shown in Scheme 6. These tracers were labeled by the following strategies: (i) a one-step direct nucleophilic halogen exchange was used for labeling [^{18}F] **18a** and [^{18}F] **18b**; (ii) a one-step direct nucleophilic aliphatic substitution with a tosylate (Ts) or mesylate (Ms) leaving group was used for labeling [^{18}F] **18c**, [^{18}F] **18e**, and [^{18}F] **18g**; (iii) a two-step strategy was used for labeling [^{18}F] **18d** and [^{18}F] **20a** using the 2- ^{18}F fluoroethyl tosylate **34** as a secondary labeling agent. The structures of the new fluorine-containing PDE10A inhibitors [^{18}F] **18a–e**, [^{18}F] **18g**, and [^{18}F] **20a** are shown in Figure 2.

Scheme 6 shows the conditions used for the successful radiolabeling of [^{18}F] **18a–e**, [^{18}F] **18g**, and [^{18}F] **20a**. Labeling of [^{18}F] **18b** was initially planned by a direct nucleophilic aliphatic substitution using a tosylate (Ts) or mesylate (Ms) leaving group. However, because heating the precursor with $^{18}\text{F}^-$ at 85 °C for 15 min yielded only a trace of [^{18}F] **18b**, an alternative strategy of halogen exchange reaction was pursued; this was successfully performed using the chloride precursor **23b**. As shown in Scheme 6, a one-step displacement reaction using mesylate and tosylate leaving groups was employed for radiolabeling [^{18}F] **18b**, [^{18}F] **18c**, [^{18}F] **18e**, and [^{18}F] **18g**. A two-step strategy was used for the radiosynthesis of [^{18}F] **18d** and [^{18}F] **20a** using the tosylate [^{18}F] **34** as a secondary labeling agent. First, [^{18}F]KF/4,7,13,16,21,24-Hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (Kryptofix 2.2.2.) was substituted into the ditosylate **33**. Second, the resulting 2- ^{18}F fluoroethyl tosylate, [^{18}F] **34**, was directly used in a nucleophilic substitution by reaction with the precursors to afford [^{18}F] **18d** and [^{18}F] **20a**. Details are provided in the Experimental Section. All tracers were obtained with high specific activity (SA), and with a radiochemical yield sufficient for in vivo studies. The radiochemical purity of each tracer was >99% and the chemical purity was >95%. Details of the radiosynthesis for each ^{18}F -labeled compound are provided in the Experimental Section.

In Vitro Assays

We previously reported that the introduction of a 3- or 4-methoxy group on the quinoline fragment of MP-10 and isoMP-10 yielded potent and PDE10A selective analogues.³⁵ Here we report our continued exploration of fluorine-containing quinoline analogues as PDE10A inhibitors. In vitro potency and selectivity of the new substituted quinoline analogues as PDE10A inhibitors are shown in Table 1; the top section of the table contains analogs of MP-10 while the lower section contains select corresponding regioisomers which are analogues of isoMP-10. Comparison of the in vitro assay results for MP-10 analogues **18d–j** and **20b**, with the regioisomers **19d–j** and **21b** showed no significant difference for paired regioisomers, although the slightly lower IC_{50} values for the analogues based on MP-10 suggest they may be modestly more potent. New analogues with a fluorine-containing group

into the 4-position of the quinoline moiety of the MP-10 pharmacophore (**18a–j**, **19d–j**) had high potency for PDE10A with IC₅₀ values <3 nM, particularly **18a–b**, **18d–i**, and **19f–i** with IC₅₀ values <1 nM. These results are consistent with the SAR we reported for the methoxy-substituted quinolone analogues.³⁵

We also explored substitution at the 3- and 6-positions. Compound **20a** (3-fluoroethoxy substitution) demonstrated high PDE10A inhibition (IC₅₀ = 0.26 nM). Replacement of the hydrogen atom at the 6-position of the quinoline moiety with fluoride(-F) yielded regioisomers **20b** and **21b** which demonstrated high potency with IC₅₀ values of 0.29 and 0.76 nM, respectively; however, replacement of the hydrogen at 6-position using larger fluorine-containing groups resulted in analogues with low potency (**20c**, -CH₂F, IC₅₀ > 76 nM; **20d**, -OCH₂CH₂F, IC₅₀ = 33.5 ± 0.08 nM).

Selectivity of a PET ligand for PDE10A over the other subtypes is also an important consideration. Inhibition of PDE3A/B has been associated with arrhythmia and increased mortality,^{47,48} while PDE4 is widely expressed in the central nervous system.^{49,50} The potent new PDE10A inhibitors (20 compounds, PDE10A IC₅₀ < 5 nM) were also evaluated for inhibition of PDE3A/B and PDE4A/B. The results for final compounds **18a–j**, **19d–j**, **20a–d**, and **21b** (Table 1) revealed that almost all compounds had very low potency for inhibiting PDE3A/B and PDE4A/B with the IC₅₀ value >750 nM, except **18c** which had slight potency for inhibiting PDE4A/B (IC₅₀ 460 nM for PDE4A and 380 nM for PDE4B). All of the new compounds, including **18c**, had >210-fold selectivity ratios for PDE10A vs PDE3A/B and PDE4A/B. This suggests that **18a–j**, **19d–j**, **20a,b**, and **21b** are both potent and selective inhibitors of PDE10A.

Based on these screening results and our previous experience with the ¹¹C-labeled regioisomers, seven analogues of MP-10 were identified as candidate ligands for ¹⁸F-labeling: -F (**18a**), -(CH₂)_n F (**18b**, **18c**), -OCH₂CH₂F (**18d**), -CH₂OCH₂CH₂F (**18e**), and -FPEG (**18g**, **20a**). The precursors were synthesized (details are provided in the Supporting Information) for the subsequent radiolabeling and the in vivo evaluation as PET tracers for quantification of PDE10A in rodents and nonhuman primates.

Biodistribution

The biodistribution of [¹⁸F]**18a–e**, [¹⁸F] **18g**, and [¹⁸F]**20a** was evaluated in normal adult male Sprague–Dawley rats at 5, 30, and 60 min postinjection (p.i.) Table 2 shows the uptake and washout in peripheral organs and whole brain for each of the seven tracers. The initial brain uptake values were 0.410 ± 0.063, 0.128 ± 0.012, 0.114 ± 0.015, 0.118 ± 0.012, 0.213 ± 0.039, 0.353 ± 0.052, and 0.092 ± 0.011%ID/g for [¹⁸F]**18a**, [¹⁸F]**18b**, [¹⁸F]**18c**, [¹⁸F]**18d**, [¹⁸F]**18e**, [¹⁸F]**18g**, and [¹⁸F]**20a**, respectively. At 5, 30, and 60 min p.i., brain uptake of each of the tracers was comparable to or higher than [¹¹C]MP-10 (0.162 ± 0.025, 0.066 ± 0.008, and 0.056 ± 0.006%ID/g 5, 30, and 60 min p.i.).¹⁹ Modest but progressive accumulation of radioactivity in bone was observed for [¹⁸F]**18a**, [¹⁸F]**18b**, and [¹⁸F]**18c**: bone activity increased from 0.522 ± 0.116, 0.421 ± 0.063, and 0.222 ± 0.014%ID/g at 5 min to 6.300 ± 0.314, 5.620 ± 1.132, and 2.037 ± 0.303%ID/g at 60 min p.i., respectively. This progressive increase in bone activity was most likely the result of metabolic

defluorination. These results suggest that functional groups including -F (**18a**), -CH₂F (**18b**), and -CH₂CH₂CH₂F (**18c**) on the quinoline fragment of MP-10 undergo in vivo metabolic defluorination in rodents. In contrast, [¹⁸F]**18d**, [¹⁸F]**18e**, [¹⁸F] **18g**, and [¹⁸F]**20a** appeared more stable to in vivo defluorination.

The cerebellum and cortex are accepted reference (non-target) regions in kinetic modeling of PDE10A PET tracers.²⁹ Therefore, in addition to high striatal uptake and retention, a candidate tracer for clinical imaging should show low uptake and rapid washout in the cerebellum and cortex; this will facilitate high target:nontarget ratios and yield high quality images. The new radiotracers displayed generally heterogeneous regional brain distribution with the highest uptake observed in the striatum; by 30 min p.i., the ratio of activity in the striatum versus nontarget brain regions was >2-fold for [¹⁸F]**18a**, [¹⁸F]**18b**, [¹⁸F]**18c**, [¹⁸F]**18d**, and [¹⁸F]**20a** (Figure 3). Between 5 and 30 min p.i., the striatum:cerebellum and striatum:cortex ratios increased for the five tracers, which suggests that they were rapidly cleared from nontarget regions and displayed specific binding within the PDE10A-enriched-striatum.

Taken together, the rodent biodistribution and regional brain uptake and washout data identified 4-fluoroethoxy [¹⁸F]**18d** and 3-fluoroethoxy [¹⁸F]**20a** as the more promising candidates for further evaluation in nonhuman primates. Both tracers appeared stable to metabolic defluorination and showed favorable ratios in the striatum versus nontarget brain regions.

MicroPET Imaging Studies of Cynomolgus Macaques

The two fluoroethoxy lead PET radioligands for imaging PDE10A, [¹⁸F]**18d** and [¹⁸F]**20a**, underwent PET imaging studies (*n* = 3 for each tracer) in male cynomolgus monkeys (Figure 4) using a microPET Focus 220 scanner. The representative summed images from 0 to 180 min were coregistered with MRI images to accurately identify the anatomical regions of interest (ROI's) are shown in Figure 4. MicroPET studies of both [¹⁸F]**18d** and [¹⁸F]**20a** gave clear visualization of the PDE10A-enriched striatum. Both the caudate and putamen striatal regions had high uptake of [¹⁸F]**18d** and [¹⁸F]**20a**; the ratios of uptake in the striatum vs nontarget brain regions were >3-fold by 40 min p.i. In particular, for [¹⁸F]**20a**, target:nontarget ratios reached >5-fold by 70 min p.i. More importantly, although the two tracers showed differences in striatal clearance, tissue time-activity curves of both [¹⁸F]**18d** and [¹⁸F]**20a** demonstrated improved washout kinetics from both target and nontarget regions compared with [¹¹C]MP-10. The improved washout kinetics suggest that the strategy of ¹⁸F-labeling the quinoline rather than the pyrazole moiety reduced the formation of radioactive metabolites that cross the BBB.

Metabolite Studies in Cynomolgus Macaques

Initial NHP brain imaging of [¹⁸F]**18d** and [¹⁸F]**20a** showed improved kinetics over previously published PET tracers for PDE10A. To further investigate the in vivo metabolic stability of these tracers, HPLC analysis was performed to identify the percentage of parent compound versus radiometabolites in solvent extracts of NHP plasma obtained during microPET imaging studies of [¹⁸F]**18d** and [¹⁸F]**20a**. NHP arterial blood was obtained from

cynomolgus macaques 5, 15, 30, 60, and 90 min p.i. for [^{18}F]**18d** and [^{18}F]**20a**. Plasma was separated from packed red cells; ~65–75% of the radioactivity was in the plasma. Following solvent extraction and deproteination, ~90% of the plasma activity was in the supernatant and only 10% of the activity was in the protein pellet. The solvent extract was injected onto an HPLC to quantify the percentage of the radioactivity for the parent compound versus radiolabeled metabolites based on the different retention times. As shown in Table 3, HPLC analysis of NHP plasma revealed good metabolic stability for both [^{18}F]**18d** and [^{18}F]**20a**. Particularly, at 30 min p.i., solvent extracts of arterial blood contained ~90% parent compound for [^{18}F]**18d**. The major radioactive metabolite of [^{18}F]**18d** was more polar (retention time ~3.5 min) than the parent compound (retention time ~10.5 min), negligible amounts of a minor radioactive metabolite (retention time ~7.5 min) were also observed. For [^{18}F]**20a**, solvent extracts of arterial blood contained >90% parent compound 15 min p.i., 73% parent remained 30 min p.i. The major radioactive metabolite was more polar (retention time ~3.5 min) than the parent compound (retention time ~10.5 min). The minor radioactive metabolite was <14% of the recovered activity 90 min p.i. (retention time ~7.5 min). The results of the metabolite analysis confirmed that our new strategy of ^{18}F -labeling the quinoline rather than the pyrazole moiety resulted in significant metabolic stability in NHP blood.

CONCLUSION

In the present study, we optimized the structure of MP-10 to identify new compounds that can be ^{18}F -labeled in the quinoline moiety instead of the pyrazole moiety. As a result, the 20 highly potent compounds **18a–j**, **19d–j**, **20a–b**, and **21b** ($\text{IC}_{50} < 5 \text{ nM}$) were identified which also displayed high selectivity for PDE10A against PDE3A/B and PDE4A/B. Among these potent compounds, **18a–e**, **18g**, and **20a** were evaluated as potential PET radioligands for quantifying the level of PDE10A. [^{18}F]**18a**, [^{18}F]**18b**, [^{18}F]**18c**, [^{18}F]**18d**, [^{18}F]**18e**, [^{18}F]**18g**, and [^{18}F]**20a** are, to our knowledge, the first MP-10 analogues successfully ^{18}F -labeled in the quinoline instead of the pyrazole moiety. Rat biodistribution indicated [^{18}F]**18a**, [^{18}F]**18b**, [^{18}F]**18c**, [^{18}F]**18d**, [^{18}F]**18e**, [^{18}F]**18g**, and [^{18}F]**20a** can cross the blood-brain-barrier and accumulate in the PDE10A-enriched striatum. [^{18}F]**18d** and [^{18}F]**20a** proceeded to further evaluation in NHPs. The preliminary microPET imaging studies in NHPs demonstrated that [^{18}F]**18d** and [^{18}F]**20a** provided very clear visualization of striatum. Although different patterns of striatal clearance were observed, both tracers showed rapid clearance from nontarget brain regions. Compared with [^{11}C]MP-10, [^{18}F]**18d** and [^{18}F]**20a** displayed more suitable washout kinetics in NHP brain. In addition, both tracers displayed favorable in vivo metabolic stability based on HPLC analysis of NHP plasma. These promising preliminary results suggest that our strategy has a high probability of identifying a clinical PET tracer for quantifying PDE10A in the human brain. Future NHP microPET imaging studies with [^{18}F]**18d** and [^{18}F]**20a** will explore the specificity of the tracer uptake.

In summary, the strategy of introducing fluorine-containing group in a suitable position of the 2-methylquinoline moiety of MP-10 identified new potent and selective PD10A inhibitors; this approach will help guide the design of potent and selective ligands with

suitable lipophilicity as candidates for treating schizophrenia and other CNS diseases using PDE10A enzyme inhibition strategies. Further validation of these new analogues is ongoing to determine if either is a suitable PET tracer to quantify the level of PDE10A in the human brain.

EXPERIMENTAL SECTION

General

All reagents and chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. All anhydrous reactions were carried out in oven-dried glassware under an inert nitrogen atmosphere unless otherwise stated. When reactions involved extraction with DCM (CH_2Cl_2), chloroform (CHCl_3), or ethyl acetate (EtOAc), the organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Free bases were converted into the corresponding oxalate salt by addition of oxalic acid for all final compounds. Melting points of salts were determined on the MEL-TEMP 3.0 apparatus and left uncorrected. ^1H NMR spectra were recorded at 400 MHz on a Varian Mercury-VX spectrometer with CDCl_3 as solvents and tetramethylsilane (TMS) was used as the internal standard. Elemental analyses (C, H, N) were determined by Atlantic Microlab, Inc. Synthesis of starting materials and intermediates are shown in Supporting Information.

General Method for Synthesis of 18a–j, 19d–j, 20a–d, and 21b

4-Fluoro-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)-phenoxy)methyl)quinoline (18a): Sodium hydride (31 mg, 1.3 mmol) was added to a solution of **16a** (251 mg, 1.00 mmol) in anhydrous DMF (20 mL) at 0 °C. After 30 min, **17a** (238 mg, 1.00 mmol) was added to the reaction mixture which was stirred overnight at rt. The reaction mixture was then diluted with water (30 mL), extracted with DCM (3×60 mL), washed with 1 N NaOH (30 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography using MeOH:DCM (1:30, v/v) to afford **18a** as a light yellow solid (205 mg, 50%). ^1H NMR (CDCl_3) δ 8.48–8.45 (m, 2H), 8.09–8.07 (m, 2H), 7.80–7.76 (m, 1H), 7.61–7.57 (m, 2H), 7.41–7.38 (m, 3H), 7.18–7.16 (m, 2H), 7.01–6.99 (m, 2H), 5.37 (s, 2H), 3.96 (s, 3H). mp: 176.2–177.2 °C. Anal. ($\text{C}_{25}\text{H}_{19}\text{FN}_4\text{O} \cdot 2\text{H}_2\text{C}_2\text{O}_4$) C, H, N: Calcd C: 58.98, H: 3.93, N: 9.49. Found C: 58.78, H: 3.84, N: 9.26.

4-(Fluoromethyl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy) methyl) quinoline (18b): Triphenylphosphine (84 mg, 0.32 mmol) and DBAD (73 mg, 0.32 mmol) were added to a solution of **17a** (50 mg, 0.26 mmol) and **16b** (50 mg, 0.28 mmol) in 1,4-dioxane (2 mL) and heated at 60 °C for 18 h. The reaction mixture was quenched with 1 N NaOH (50 mL), extracted DCM (3×50 mL), dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using MeOH: DCM (1:30, v/v) to afford **18b** as a yellow solid (55 mg, 65%). ^1H NMR (CDCl_3) δ 8.55–8.37 (m, 2H), 8.22–8.00 (m, 1H), 7.86 (d, $J = 8.3$ Hz, 1H), 7.80–7.70 (m, 2H), 7.63–7.53 (m, 2H), 7.43–7.33 (m, 2H), 7.20–7.11 (m, 2H), 7.08–6.93 (m, 2H), 5.94 (s, 1H), 5.83 (s, 1H), 5.39 (s, 2H), 3.95 (s, 3H). mp: 174.4–174.5 °C. Anal.

(C₂₆H₂₁FN₄O·2H₂C₂O₄) C, H, N: Calcd C: 59.60, H: 4.17, N: 9.27. Found C: 59.89, H: 4.36, N: 9.15.

4-(3-Fluoropropyl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinoline (18c): Compound **16c** was used as the starting material following the procedure described above for the preparation of **18b** to synthesize **18c** as a yellow solid (40 mg, 49%). ¹H NMR (CDCl₃): δ 8.45 (d, *J* = 5.0 Hz, 2H), 8.05 (m, 2H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.55 (dd, *J* = 14.5, 7.1 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.24 (s, 1H), 7.14 (d, *J* = 5.0 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 5.35 (s, 2H), 4.56 (t, *J* = 5.6 Hz, 1H), 4.44 (t, *J* = 5.5 Hz, 1H), 3.95 (s, 3H), 3.22 (t, *J* = 7.7 Hz, 2H), 2.25–2.05 (m, 2H). mp: 125.3–125.5 °C. Anal. (C₂₈H₂₅FN₄O·2H₂C₂O₄) C, H, N: Calcd C: 60.76, H: 4.62, N: 8.86. Found C: 60.86, H: 4.51, N: 8.63.

4-(2-Fluoroethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinoline (18d): Compound **16d** was used as the starting material following the procedure described above for the preparation of **18b** to synthesize **18d** as a white solid (82 mg, 67%). ¹H NMR (CDCl₃): δ 8.46 (s, 2H), 8.24 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 6.7 Hz, 1H), 7.71 (s, 1H), 7.64–7.46 (m, *J* = 22.3 Hz, 2H), 7.38 (d, *J* = 6.6 Hz, 2H), 7.15 (s, 2H), 7.00 (s, 3H), 5.33 (s, 2H), 4.89 (d, *J* = 47.9 Hz, 2H), 4.43 (d, *J* = 26.9 Hz, 2H), 3.95 (s, 3H). mp: 126.2–126.3 °C. Anal. (C₂₇H₂₃FN₄O₂·2H₂C₂O₄) C, H, N: Calcd C: 58.68, H: 4.29, N: 8.83. Found C: 58.98, H: 4.19, N: 8.91.

4-((2-Fluoroethoxy)methyl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinoline (18e): Compound **16h** was used as the starting material following the procedure described above for the preparation of **18b** to synthesize **18e** as a white solid (69 mg, 69%). ¹H NMR (CDCl₃): δ 8.45 (dd, *J* = 4.6, 1.5 Hz, 2H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.78–7.67 (m, 2H), 7.61–7.50 (m, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.14 (dd, *J* = 4.6, 1.6 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.37 (s, 2H), 5.06 (s, 2H), 4.71–4.61 (m, 1H), 4.58–4.49 (m, 1H), 3.94 (s, 3H), 3.87–3.81 (m, 1H), 3.80–3.74 (m, 1H). mp: 126.8–127.4 °C. Anal. (C₂₈H₂₅FN₄O₂·2H₂C₂O₄) C, H, N: Calcd C: 59.26, H: 4.51, N: 8.64. Found C: 58.09, H: 4.77, N: 8.88.

4-(2-(2-Fluoroethoxy)ethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinoline (18f): Compound **16e** was used as the starting material following the procedure described above for the preparation of **18b** to synthesize **18f** as a white solid (64 mg, 68%). ¹H NMR (CDCl₃): δ 8.50–8.42 (m, 2H), 8.20 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.56 (s, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 5.8 Hz, 2H), 7.04–6.95 (m, 3H), 5.33 (s, 2H), 4.68–4.61 (m, 1H), 4.58–4.50 (m, 1H), 4.40–4.32 (m, 2H), 4.06–3.99 (m, 2H), 3.95 (s, 3H), 3.92–3.86 (m, 1H), 3.85–3.79 (m, 1H). mp: 170.1–170.3 °C. Anal. (C₂₉H₂₇FN₄O₃·2H₂C₂O₄) C, H, N: C: 58.41, H: 4.60, N: 8.26. Found C: 58.70, H: 4.81, N: 8.45.

4-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinoline (18g): Compound **16f** was used as the starting material following the procedure described above for the preparation of **18b** to synthesize **18g** as a

white solid (55 mg, 63%). ^1H NMR (CDCl_3): δ 8.47 (d, J = 5.8 Hz, 2H), 8.22 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.57 (s, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.6 Hz, 2H), 7.16 (d, J = 5.9 Hz, 2H), 7.07–6.96 (m, 3H), 5.33 (s, 2H), 4.63–4.56 (m, 1H), 4.51–4.44 (m, 1H), 4.41–4.31 (m, 2H), 4.01 (t, J = 4.6 Hz, 2H), 3.96 (s, 3H), 3.83–3.71 (m, 6H). mp: 166.0–166.2 °C. Anal. ($\text{C}_{31}\text{H}_{31}\text{FN}_4\text{O}_4 \cdot 2\text{H}_2\text{C}_2\text{O}_4$) C, H, N: Calcd C: 58.17, H: 4.88, N: 7.75. Found C: 58.33, H: 4.98, N: 7.94.

4-(2-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)ethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinoline (18h): Compound **16g** was used as the starting material following the procedure described above for the preparation of **18b** to synthesize **18h** as a white solid (48 mg, 59%). ^1H NMR (CDCl_3): δ 8.46 (d, J = 5.9 Hz, 2H), 8.21 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.56 (s, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.15 (d, J = 5.9 Hz, 2H), 7.05–6.95 (m, 3H), 5.32 (s, 2H), 4.61–4.55 (m, 1H), 4.49–4.42 (m, 1H), 4.35 (t, J = 4.6 Hz, 2H), 4.00 (t, J = 4.6 Hz, 2H), 3.95 (s, 3H), 3.82–3.62 (m, 10H). mp: 128.4–129.0 °C. Anal. ($\text{C}_{33}\text{H}_{35}\text{FN}_4\text{O}_5 \cdot 2\text{H}_2\text{C}_2\text{O}_4$) C, H, N: Calcd C: 57.96, H: 5.13, N: 7.31. Found C: 58.06, H: 5.31, N: 7.50.

N-(2-Fluoroethyl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinolin-4-amine (18i): Compound **16i** was used as the starting material following the procedure described above for the preparation of **18b**, then used TFA for deprotection to afford **18i** as a light yellow solid (42 mg, 63%). ^1H NMR (CDCl_3): δ 8.47 (d, J = 4.0 Hz, 2H), 7.99 (d, J = 4.4 Hz, 1H), 7.86–7.83 (m, 1H), 7.64–7.61 (m, 1H), 7.57 (s, 1H), 7.42–7.37 (m, 3H), 7.17–7.15 (m, 2H), 7.03–7.01 (m, 2H), 6.63 (s, 1H), 5.33 (s, 2H), 4.82–4.79 (m, 1H), 4.70–4.67 (m, 1H), 3.96 (s, 3H), 3.76–3.69 (m, 2H). mp: 210.6–210.7 °C. Anal. ($\text{C}_{27}\text{H}_{24}\text{FN}_5\text{O} \cdot 2\text{H}_2\text{C}_2\text{O}_4$) C, H, N: Calcd C: 58.77, H: 4.45, N: 11.05. Found C: 58.98, H: 4.34, N: 11.23.

4-(4-(2-Fluoroethyl)-1H-1,2,3-triazol-1-yl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinoline (18j): Compound **16j** was used as the starting material following the procedure described above for the preparation of **18b** to synthesize **18j** as a light yellow solid (59 mg, 64%). ^1H NMR (CDCl_3): δ 8.52–8.44 (m, 2H), 8.23–8.17 (m, 1H), 8.02–7.96 (m, 1H), 7.96–7.93 (m, 1H), 7.88–7.80 (m, 2H), 7.65–7.63 (m, 1H), 7.57 (s, 1H), 7.44–7.37 (m, 2H), 7.19–7.13 (m, 2H), 7.07–6.99 (m, 2H), 5.45 (s, 2H), 4.89 (t, J = 5.9 Hz, 1H), 4.77 (t, J = 5.9 Hz, 1H), 3.97 (s, 3H), 3.35 (t, J = 5.9 Hz, 1H), 3.28 (t, J = 5.9 Hz, 1H). mp: 214.2–214.6 °C. Anal. ($\text{C}_{29}\text{H}_{24}\text{FN}_7\text{O} \cdot 2\text{H}_2\text{C}_2\text{O}_4$) C, H, N: Calcd C: 57.81, H: 4.12, N: 14.30. Found C: 57.97, H: 4.01, N: 14.42.

4-(2-Fluoroethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinoline (19d): Compound **16d** with **17b** (in place of **17a**) were used as the starting materials following the procedure described above for the preparation of **18b** to synthesize **19d** as a white solid (86 mg, 70%). ^1H NMR (CDCl_3): δ 8.38 (d, J = 2.4 Hz, 2H), 8.29–8.27 (m, 1H), 8.03–8.01 (m, 1H), 7.82 (s, 1H), 7.75 (m, 1H), 7.57–7.53 (m, 1H), 7.26–7.22 (m, 3H), 7.16–7.14 (m, 2H), 7.06–7.03 (m, 3H), 5.38 (s, 2H), 5.00 (s, 1H), 4.86 (s, 1H), 4.55 (s, 1H), 4.45 (s, 1H), 3.75 (s, 3H). mp: 189.1–189.3 °C. Anal.

(C₂₇H₂₃FN₄O₂·2H₂C₂O₄) C, H, N: Calcd C: 58.68, H: 4.29, N: 8.83. Found C: 58.58, H: 4.49, N: 9.01.

4-((2-Fluoroethoxy)methyl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinoline (19e): Compound **16h** with **17b** (in place of **17a**) were used as the starting materials following the procedure described above for the preparation of **18b** to synthesize **19e** as a white solid (62 mg, 69%). ¹H NMR (CDCl₃) δ 8.39–8.38 (m, 2H), 8.14–8.12 (m, 1H), 8.02–8.00 (m, 1H), 7.82 (s, 2H), 7.77–7.74 (m, 1H), 7.62–7.58 (m, 1H), 7.26–7.23 (m, 2H), 7.18–7.16 (m, 2H), 7.05–7.04 (m, 2H), 5.43 (s, 2H), 5.12 (s, 2H), 4.73–4.71 (m, 1H), 4.61–4.59 (m, 1H), 3.94–3.92 (m, 1H), 3.87–3.85 (m, 1H), 3.75 (s, 3H). mp: 121.3–121.8 °C. Anal. (C₂₈H₂₅FN₄O₂·2H₂C₂O₄) C, H, N: Calcd C: 59.26, H: 4.51, N: 8.64. Found C: 59.45, H: 4.31, N: 8.51.

4-(2-(2-Fluoroethoxy)ethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinoline (19f): Compound **16e** with **17b** (in place of **17a**) were used as the starting materials following the procedure described above for the preparation of **18b** to synthesize **19f** as a white solid (58 mg, 62%). ¹H NMR (CDCl₃): δ 8.39–8.38 (m, 2H), 8.24 (d, *J* = 4.0 Hz, 1H), 8.01 (d, *J* = 4.3 Hz, 1H), 7.81 (s, 1H), 7.73 (m, 1H), 7.52 (m, 1H), 7.26–7.04 (m, 7H), 5.38 (s, 2H), 4.69 (m, 1H), 4.53 (m, 1H), 4.41 (m, 2H), 4.06 (m, 2H), 3.94–3.93 (m, 1H), 3.85–3.83 (m, 1H), 3.75 (m, 3H). mp: 109.6–109.7 °C. Anal. (C₂₉H₂₇FN₄O₃·2H₂C₂O₄) C, H, N: Calcd C: 58.41, H: 4.60, N: 8.26. Found C: 58.63, H: 4.79, N: 8.45.

4-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinoline (19g): Compound **16f** with **17b** (in place of **17a**) were used as the starting materials following the procedure described above for the preparation of **18b** to synthesize **19g** as a white solid (52 mg, 60%). ¹H NMR (CDCl₃): δ 8.39–8.38 (m, 2H), 8.25 (d, *J* = 4.0 Hz, 1H), 8.01 (d, *J* = 4.3 Hz, 1H), 7.82 (s, 1H), 7.75–7.70 (m, 1H), 7.54–7.49 (m, 1H), 7.26–7.03 (m, 7H), 5.38 (s, 2H), 4.63 (m, 1H), 4.47–4.40 (m, 3H), 4.06–4.04 (m, 2H), 3.82–3.72 (m, 9H). mp: 82.0–82.1 °C. Anal. (C₃₁H₃₁FN₄O₄·2H₂C₂O₄) C, H, N: Calcd C: 58.17, H: 4.88, N: 7.75. Found C: 58.35, H: 4.99, N: 7.62.

(2-(2-(2-(2-Fluoroethoxy)ethoxy)ethoxy)ethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinoline (19h): Compound **16g** with **17b** (in place of **17a**) were used as the starting materials following the procedure described above for the preparation of **18b** to synthesize **19h** as a white solid (46 mg, 57%). ¹H NMR (CDCl₃): δ 8.39–8.37 (m, 2H), 8.24 (d, *J* = 4.0 Hz, 1H), 8.00 (d, *J* = 4.3 Hz, 1H), 7.81 (s, 1H), 7.74–7.70 (m, 1H), 7.53–7.49 (m, 1H), 7.24–7.22 (m, 2H), 7.16–7.13 (m, 2H), 7.05–7.03 (m, 3H), 5.37 (s, 2H), 4.50–4.58 (m, 1H), 4.48–4.46 (m, 1H), 4.40–4.38 (m, 2H), 4.40–4.38 (m, 2H), 3.81–3.67 (m, 13H). mp: 108.8–108.9 °C. Anal. (C₃₃H₃₅FN₄O₅·2H₂C₂O₄) C, H, N: Calcd C: 57.96, H: 5.13, N: 7.31. Found C: 57.71, H: 5.33, N: 7.47.

N-(2-Fluoroethyl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinolin-4-amine (19i): Compound **16i** with **17b** (in place of **17a**) were used as the starting materials following the procedure described above for the preparation of **18b**, then

deprotection with TFA afforded **19i** as a yellow solid (40 mg, 60%). ^1H NMR (CDCl_3): δ 8.37 (d, J = 3.0 Hz, 2H), 7.99 (d, J = 4.2 Hz, 1H), 7.81–7.77 (m, 2H), 7.71–7.67 (m, 1H), 7.50–7.46 (m, 1H), 7.23–7.21 (m, 2H), 7.15–7.13 (m, 2H), 7.05–7.03 (m, 2H), 6.75 (s, 1H), 5.33 (s, 2H), 4.82–4.79 (m, 1H), 4.70–4.67 (m, 1H), 3.76–3.69 (m, 5H). mp: 206.5–206.7 °C. Anal. ($\text{C}_{27}\text{H}_{24}\text{FN}_5\text{O}\cdot 2\text{H}_2\text{C}_2\text{O}_4$) C, H, N: Calcd C: 58.77, H: 4.45, N: 11.05. Found C: 58.53, H: 4.71, N: 11.22.

4-(4-(2-Fluoroethyl)-1H-1,2,3-triazol-1-yl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)phenoxy)methyl)quinoline (19j): Compound **16j** with **17b** (in place of **17a**) were used as the starting materials following the procedure described above for the preparation of **18b** to synthesize **19j** as a light yellow solid (62 mg, 67%). ^1H NMR (CDCl_3) δ 8.38–8.36 (m, 2H), 8.22–8.20 (m, 1H), 7.99–7.97 (m, 2H), 7.87–7.84 (m, 2H), 7.80 (s, 1H), 7.68–7.64 (m, 1H), 7.26–7.23 (m, 2H), 7.16–7.14 (m, 2H), 7.04–7.02 (m, 2H), 5.48 (s, 2H), 4.89 (t, J = 5.8 Hz, 1H), 4.77 (t, J = 5.8 Hz, 1H), 3.74 (s, 3H), 3.35 (t, J = 5.8 Hz, 1H), 3.28 (t, J = 5.8 Hz, 1H). mp: 172.3–172.7 °C. Anal. ($\text{C}_{29}\text{H}_{24}\text{FN}_7\text{O}\cdot 2\text{H}_2\text{C}_2\text{O}_4$) C, H, N: Calcd C: 57.81, H: 4.12, N: 14.30. Found C: 58.01, H: 4.02, N: 14.52.

3-(2-Fluoroethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinoline (20a): Compound **16k** was used as the starting material following the procedure described above for the preparation of **18b** to synthesize **20a** as a light yellow solid (60 mg, 67%). ^1H NMR (CDCl_3) δ 8.44 (d, J = 4.9 Hz, 2H), 8.07 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.60–7.46 (m, 3H), 7.43 (s, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.19–7.11 (m, 2H), 7.05 (d, J = 8.5 Hz, 2H), 5.43 (s, 2H), 4.85 (d, J = 3.8 Hz, 1H), 4.73 (d, J = 3.9 Hz, 1H), 4.40 (d, J = 3.7 Hz, 1H), 4.33 (d, J = 3.6 Hz, 1H), 3.96 (s, 3H). mp: 191.4–191.7 °C. Anal. ($\text{C}_{27}\text{H}_{23}\text{FN}_4\text{O}_2\cdot 2\text{H}_2\text{C}_2\text{O}_4$) C, H, N: Calcd C: 58.68, H: 4.29, N: 8.83. Found C: 58.73, H: 4.48, N: 8.99.

6-Fluoro-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)-phenoxy)methyl)quinoline (20b): Compound **16l** was used as the starting material following the procedure described above for the preparation of **18b** to synthesize **20b** as a white solid (56 mg, 69%). ^1H NMR (CDCl_3) δ 8.52–8.42 (m, 2H), 8.14 (d, J = 8.6 Hz, 1H), 8.07 (dd, J = 9.3, 5.3 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.57 (s, 1H), 7.55–7.42 (m, 2H), 7.43–7.35 (m, 2H), 7.20–7.12 (m, 2H), 7.04–6.97 (m, 2H), 5.38 (s, 2H), 3.97 (s, 3H). mp: 213.3–213.5 °C. Anal. ($\text{C}_{25}\text{H}_{19}\text{FN}_4\text{O}\cdot 2\text{H}_2\text{C}_2\text{O}_4$) C, H, N: Calcd C: 58.98, H: 3.93, N: 9.49. Found C: 59.09, H: 3.71, N: 9.57.

6-(Fluoromethyl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinoline (20c): Compound **16m** was used as the starting material following the procedure described above for the preparation of **18b** to synthesize **20c** as a light solid (50 mg, 61%). ^1H NMR (CDCl_3) δ 8.51–8.34 (m, 2H), 8.16 (d, J = 8.5 Hz, 1H), 8.07 (d, J = 8.7 Hz, 1H), 7.79 (t, J = 2.2 Hz, 1H), 7.74–7.64 (m, 2H), 7.53 (s, 1H), 7.43–7.32 (m, 2H), 7.22–7.09 (m, 2H), 7.02–6.90 (m, 2H), 5.59 (s, 1H), 5.47 (s, 1H), 5.37 (s, 2H), 3.96 (s, 3H). mp: 220.7–220.8 °C. Anal. ($\text{C}_{26}\text{H}_{21}\text{FN}_4\text{O}\cdot 2\text{H}_2\text{C}_2\text{O}_4$) C, H, N: Calcd C: 59.60, H: 4.17, N: 9.27. Found C: 59.78, H: 4.29, N: 9.15.

6-(2-Fluoroethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-

yl)phenoxy)methyl)quinoline (20d): Compound **16n** was used as the starting material following the procedure described above for the preparation of **18a** to synthesize **20d** as a light yellow solid (290 mg, 61%). ¹H NMR (CDCl₃): δ 8.48–8.46 (m, 2H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.64–7.62 (m, 1H), 7.57 (s, 1H), 7.43–7.37 (m, 3H), 7.16–7.14 (m, 2H), 7.09–7.08 (m, 1H), 7.01–6.99 (m, 2H), 5.35 (s, 2H), 4.90–4.88 (m, 1H), 4.78–4.76 (m, 1H), 4.38–4.36 (m, 1H), 4.31–4.29 (m, 1H), 3.96 (s, 3H). mp: 228.8–228.9 °C. Anal. (C₂₇H₂₃FN₄O₂·2H₂C₂O₄) C, H, N: Calcd C: 58.68, H: 4.29, N: 8.83. Found C: 58.83, H: 4.56, N: 8.73.

6-Fluoro-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-5-yl)-phenoxy)methyl)quinoline

(21b): 6-Fluoroquinolin-2-yl)methanol (**16l**) with **17b** (in place of **17a**) were used as the starting materials following the procedure described above for the preparation of **18b** to synthesize **21b** as a white solid (53 mg, 65%). ¹H NMR (CDCl₃) δ 8.39 (dd, *J* = 4.7, 1.4 Hz, 2H), 8.19 (d, *J* = 8.5 Hz, 1H), 8.09 (dd, *J* = 9.2, 5.3 Hz, 1H), 7.82 (s, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.58–7.42 (m, 2H), 7.30–7.21 (m, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.07–7.00 (m, 2H), 5.42 (s, 2H), 3.75 (s, 3H). mp: 220.8–220.9 °C. Anal. (C₂₅H₁₉FN₄O·2H₂C₂O₄) C, H, N: Calcd C: 58.98, H: 3.93, N: 9.49. Found C: 58.85, H: 4.11, N: 9.68.

General Radiochemistry

We used both one- and two-step approaches for radiolabeling; methods for each are described below. [¹⁸F]Fluoride is produced by a ¹⁸O(p, n)¹⁸F reaction through proton irradiation of enriched ¹⁸O water (95%) using Washington University's RDS-111 cyclotron (Siemens/CTI Molecular Imaging, Knoxville, TN, USA). [¹⁸F]Fluoride is first passed through an ion-exchange resin then eluted with 0.02 M potassium carbonate (K₂CO₃) solution.

Following the one- or two-step incorporation of [¹⁸F]Fluoride, the reaction mixture was purified using a semipreparative HPLC system which contains a 5 mL injection loop, a semipreparative column, UV detector at 254 nm, and an in-line radioactivity detector which is used to identify the desired product for collection in a vial containing 50 mL sterile water. The diluted eluent was trapped on a C-18 Plus Sep-Pak cartridge, which was then rinsed with 10 mL sterile water; the product was eluted with 0.6 mL ethanol followed by 5.4 mL saline. After the diluted radiotracer was sterile-filtered through a 0.22 μm syringe filter into a sterile glass vial, an aliquot was removed for QC testing. The total synthesis time was ~2 h for one-step labeling and ~3 h for two-step labeling. Quality control was conducted on an analytical HPLC system with UV detection at 254 nm. The radioactive dose was authenticated by coinjection with the nonradioactive reference compound.

Synthesis of [¹⁸F]18a: A One-Step General Procedure for Radiosynthesis of [¹⁸F]18a, [¹⁸F]18b, [¹⁸F]18c, [¹⁸F]18e, and [¹⁸F]18g**4-(Fluoro-¹⁸F)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-**

yl)phenoxy)methyl)quinoline ([¹⁸F]18a): A sample of ~7.40 GBq [¹⁸F]/fluoride/K₂CO₃ was added to a reaction vessel containing Kryptofix [222] (6.5–7.0 mg), and dried by azeotropic distillation at 110 °C using MeCN (3 × 1 mL) under a gentle flow of nitrogen.

1.0–3.0 mg of the bromide precursor **23a** dissolved in DMSO (200–300 μ L) was then transferred to the reaction vessel which was capped, vortexed, and heated in an oil bath at 170–175 °C for 20 min. After the heat source was removed, the reaction mixture was diluted with 3.0 mL of HPLC mobile phase and purified using an Agilent SB-C18 column with MeCN/0.1 M ammonium formate buffer pH 4.5 (48/52, v/v) as the mobile phase at a flow rate of 4.0 mL/min; the retention time for the desired product was 19–21 min. QC was conducted on a Grace Alltima C-18 column (250 mm $\times$ 4.6 mm), with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 4.5 (62/38, v/v) at 1.8 mL/min. The retention time of [18 F]**18a** was 5.1 min. The radiochemical purity was >99%, the yield was 4.2–4.8% (decay-corrected), and SA was >74 GBq/ μ mol (decay-corrected to EOS).

4-((Fluoro- 18 F)methyl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)

methyl) quinoline ([18 F]18b**):** The chloride precursor **23b** was used for the one-step radiolabeling of [18 F]**18b** as described above for [18 F]**18a**. The reaction temperature was 105–110 °C for 20 min. The reaction mixture was purified using an Agilent SB-C18 column with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 4.5 (40/60, v/v) at 4.0 mL/min; the retention time for the desired product was 24–26 min. QC was performed using a Phenomenex Prodigy C-18 column (250 mm $\times$ 4.6 mm) with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 4.5 (62/38, v/v) at 1.5 mL/min. The retention time of [18 F]**18b** was 4.9 min. The radiochemical purity was >99%, the chemical purity was >95%, the yield was 1.1–1.5% (decay-corrected), and the SA was >74 GBq/ μ mol (decay-corrected to EOS).

4-(3-(Fluoro- 18 F)propyl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-

yl)phenoxy)methyl) quinoline ([18 F]18c**):** The mesylate precursor **23c** was used for the one-step radiolabeling of [18 F]**18c** as described above for [18 F]**18a**. The reaction temperature was 75–80 °C for 20 min. The reaction mixture was purified using an Agilent SB-C18 column with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 4.5 (50/50, v/v) at 4.0 mL/min; the retention time for the desired product was 17–18 min. QC was performed using an Agilent SB-C18 column (250 mm $\times$ 4.6 mm) with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 4.5 (65/35, v/v) at 1.5 mL/min. The retention time of [18 F]**18c** was 4.9 min. The radiochemical purity was >99%, the yield was 10.1–12.2% (decay-corrected) and the SA was >74 GBq/ μ mol (decay-corrected to EOS).

4-((2-(Fluoro- 18 F)ethoxy)methyl)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)

phenoxy)methyl)quinoline ([18 F]18e**):** The mesylate precursor **23e** was used for the one-step radiolabeling of [18 F]**18e** as described above for [18 F]**18a**. The reaction temperature was 85–90 °C for 15 min. The reaction mixture was purified using an Agilent SB-C18 column with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 4.5 (40/60, v/v) at 4.0 mL/min; the retention time was 21.8 min. QC was performed using a Grace Alltima-C18 column (250 mm $\times$ 4.6 mm) with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 4.5 (62/38, v/v) at 1.8 mL/min. The retention time of [18 F]**18e** was 4.4 min. The radiochemical purity was >99%, the chemical purity was >95%, the yield was 15–18% (decay-corrected), and the SA was >74 GBq/ μ mol (decay corrected to EOS).

2-(2-(2-((4-(1-Methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)-phenoxy)methyl)quinolin-4-yl)oxy)ethoxy)-ethoxy)ethyl hypofluorite-¹⁸F ([¹⁸F]18g): The tosylate precursor **23g** was used for the onestep radiolabeling of [¹⁸F]**18g** as described above for [¹⁸F]**18a**. The reaction temperature was 95–100 °C for 15 min. The reaction mixture was purified using an Agilent SB-C18 column with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 6.5 (50/50, v/v) at 3.5 mL/min; the retention time for the desired product was 13 min. QC was performed using an Agilent SB-C18 column (250 mm × 4.6 mm) with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 6.5 (56/44, v/v) at 1.5 mL/min. The retention time of [¹⁸F]**18g** was 4.9 min. The radiochemical purity was >99%, the chemical purity was >95%, the yield was 27–30% (decay-corrected), and the SA was >74 GBq/μmol (decay-corrected to EOS).

Synthesis of [¹⁸F]20a: A Two-Step General Procedure for Radiosynthesis [¹⁸F]20a and [¹⁸F]18d

3-((2-Fluoro-¹⁸F)ethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)-quinoline ([¹⁸F]20a): A sample of ~7.40 GBq [¹⁸F]/fluoride/K₂CO₃ was added to a reaction vessel containing Kryptofix [222] (7.0–8.0 mg). The syringe was washed with 2 × 0.4 mL ethanol, evaporated, and dried by azeotropic distillation at 110 °C using MeCN (3 × 1 mL) under a gentle flow of N₂ gas. After all the water was removed, 5.0–5.5 mg of the ditosylate **33** was dissolved in MeCN (200 μL), mixed, then transferred into the reaction vessel containing [¹⁸F]fluoride/Kryptofix-[222]/K₂CO₃ which was capped, mixed, and heated in an oil bath to 100 °C for 15 min. After the heat source was removed, the reaction mixture was diluted with 3.0 mL of HPLC mobile phase and passed through an alumina Neutral Sep-Pak Plus cartridge. The reaction mixture was then purified with an Agilent SB-C18 column (250 mm × 10 mm) with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 6.5 (50/50, v/v) at 4.0 mL/min; the retention time of the [¹⁸F]fluoroethyl tosylate product was 9.5–10 min. The retention time of the precursor was 23–24 min. The product was diluted with 50 mL sterile water then trapped on a C-18 Sep-Pak Plus cartridge. The trapped product was eluted with diethyl ether (2.5 mL).

The eluted solution formed two phases, the top organic phase was removed and reserved, and the bottom aqueous phase was extracted with 1 mL of ether. The ether extracts were combined and passed through two Sep-Pak Plus dry cartridges in series into a reaction vessel; the ether was evaporated under a stream of nitrogen. 1–2 mg of phenol precursor **24a** was then dissolved in 200 μL DMSO and transferred to a vial containing 2.0 mg Cs₂CO₃ and vortexed for 1 min; this saturated Cs₂CO₃ solution was added to the reaction vessel which was capped, mixed, and heated in an oil bath at 85–90 °C for 15 min. The reaction mixture was diluted with 3.0 mL HPLC mobile phase and purified using an Agilent SB C-18 column with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 4.5 (40/60, v/v) at 4.0 mL/min; the retention time was 21.4 min. QC was performed using an Agilent Zorbax, SB-C18 column (250 mm × 4.6 mm) with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 4.5 (56/44, v/v) at 1.5 mL/min. The retention time of [¹⁸F]**20a** was 4.8 min. The radiochemical purity was >99%, the chemical purity was >95%, the yield was 65–72% (decay-corrected), and the SA was >74 GBq/μmol (decay-corrected to EOS).

4-((2-Fluoro-¹⁸F)ethoxy)-2-((4-(1-methyl-4-(pyridin-4-yl)-1H-pyrazol-3-yl)phenoxy)methyl)quinoline ([¹⁸F]18d): The phenol precursor **23d** was used for the two-step labeling of [¹⁸F]**18d** as described above for [¹⁸F]**20a**. The reaction temperature was 95–100 °C for 15 min. The reaction mixture was purified on an Agilent SB-C18 column with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 4.5 (45/55, v/v) at 4.0 mL/min; the retention time was 16.2 min. QC was performed using an Agilent Zorbax, SB-C18 column (250 mm × 4.6 mm) with a mobile phase of MeCN/0.1 M ammonium formate buffer pH 4.5 (50/50, v/v) at 1.4 mL/min. The retention time of [¹⁸F]**18d** was 7.5 min. The radiochemical purity was >99%, the chemical purity was 95%, the yield was 30–35% (decay-corrected) and the SA was >74 GBq/μmol (decay-corrected to EOS).

In Vitro Assay

The PDE10A in vitro screening assay followed our previously published procedures.³⁵ PDE activity was measured using the Phosphodiesterase [³H]cAMP Scintillation Proximity Assay (SPA) (Cat. #TRKQ7090, PerkinElmer, Waltham, MA) with minor modifications. Recombinant human PDE10A containing catalytic domain of human PDE10A (Swiss-Prot accession number Q9Y233) was purchased from Enzo Life Sciences Inc., Farmingdale, NY. Recombinant human PDE3A and 3B, PDE4A, and PDE4B were purchased from EMD Chemicals, Inc., San Diego, CA. Optimal concentrations of enzymes were tested in the linear range of the enzyme activation curves with substrate. Inhibitor compounds were tested along with compound whose IC₅₀ values are known (e.g., MP-10) as an internal control for each PDE assay. All inhibitors were dissolved in DMSO, and serial dilutions were performed to obtain desired concentrations. Diluted compounds (10 μL/well) were added to a 96-well plate, after addition of 50 μL diluted PDE enzyme in buffer the plate was incubated on ice for 5 min. 50 μL of radiolabeled substrate ([³H]cAMP) at a fixed (1/3 of the *K_m*) concentration of 1.48 kBq/mL was then added to each well and plates were incubated on ice for an additional 20 min to give ~30% substrate turnover before termination of the reaction with 50 μL yttrium silicate SPA beads (8 mg/mL). Plates were allowed to settle for 1.5 h at rt, then counted on a Trilux Micro-Beta Counter (PerkinElmer, Waltham, MA). CPM values for each well were plotted against inhibitor concentration in GraphPad Prism (GraphPad Software, Inc., La Jolla, CA) and inhibitor IC₅₀ values were calculated by nonlinear regression with Prism's one-site receptor competitive binding model. All compounds were independently assayed at least twice and fitting *R*² values were > 90%; results are reported as fitted IC₅₀ ± SD.

Biodistribution and Regional Brain Uptake in Rats

All animal experiments were conducted in compliance with the Guidelines for the Care and Use of Research Animals under protocols approved by the Washington University Animal Studies Committee. For the biodistribution studies, 1.48–2.22 MBq of the radiotracer was injected in the tail vein of mature male Sprague–Dawley rats (250–400 g) under anesthesia (2.5% isoflurane in oxygen). At 5, 30, and 60 min post-injection (p.i.), rats (*n* = 4 per study group) were anesthetized and euthanized. The whole brain was quickly removed and the hippocampus, striatum, cortex, thalamus, brain stem, and cerebellum were separated by gross dissection. The remainder of the brain was collected to determine total brain uptake. Peripheral tissues including blood, lung, heart, liver, kidney, muscle, fat, and bone were also

collected. Samples were weighed and counted in an automated gamma counter (Beckman Gamma 8000 well counter) with a standard of diluted injectate, and the %ID/g was calculated.

MicroPET Brain Imaging Studies in Male Cynomolgus Monkeys

Three independent PET studies were done on adult male cynomolgus macaques (~4–6 kg) for each tracer with a microPET Focus 220 scanner (Concorde/CTI/Siemens Microsystems, Knoxville, TN). The animal was fasted for 12 h before PET study and initially anesthetized with ketamine (10 mg/kg) and glycopyrrolate (0.13 mg/kg) intramuscularly. Upon arrival at the scanner, the animal was intubated and percutaneous catheters were placed for venous tracer injection and arterial blood sampling. The head was positioned supine in the adjustable head holder with the brain in the center of the field of view. Anesthesia was maintained at 0.75–2.0% isoflurane in oxygen and core temperature maintained at ~37 °C. A 10 min transmission scan was performed to confirm positioning; this was followed by a 45 min transmission scan for attenuation correction. Subsequently, a 3 h dynamic emission scan was acquired after venous injection of 185–259 MBq of [¹⁸F]**18d** or [¹⁸F]**20a**.

MicroPET Image Processing and Analysis

Acquired list mode data were histogrammed into a 3D set of sinograms and binned to the following time frames: 3 × 1 min, 4 × 2 min, 3 × 3 min, and 20 × 5 min. Sinogram data were corrected for attenuation and scatter. Maximum a posteriori (MAP) reconstructions were done with 18 iterations and a β value of 0.004. A 1.5 mm Gaussian filter was applied to smooth each MAP reconstructed image. These images were then coregistered with MRI images to accurately identify the anatomical regions of interest with Amira software (Visage Imaging, Inc., Carlsbad, CA). The 3D regions of interest were manually drawn through all planes of coregistered MRI images for the caudate, putamen, and cerebellum. The regions of interest were then overlaid on all reconstructed PET images to obtain time-activity curves (TACs). Activity measures were standardized to body weight and dose of radioactivity injected to yield standardized uptake value (SUV).

HPLC Metabolite Analysis of NHP Plasma

Arterial blood samples (~1.5 mL) were collected 2, 15, 30, 60, and 90 min p.i. from a percutaneous catheter in a heparinized syringe and 1 mL aliquots were counted in a well counter then centrifuged to separate red blood cells from plasma. Plasma was deproteinated with 2 parts ice-cold methanol and plasma proteins were separated by centrifugation. The solvent extract (200 μ L) was injected on an Agilent SB C-18 analytic HPLC column (250 mm × 4.6 mm, 5 μ m), with a mobile phase of MeCN/0.1 M ammonium formate buffer, pH 4.5 ([¹⁸F]**18d**, 50/50, v/v; [¹⁸F]**20a**, 52/48, v/v), flow rate 0.9 mL/min, mass peaks were detected by UV at 254 nm. HPLC fractions were collected at 1 min intervals for 16 min and counted on a well counter and decay-corrected. The percent parent and percent radiolabeled metabolites for [¹⁸F]**18d** and [¹⁸F]**20a** was calculated by dividing the recovered activity in the respective peaks by the sum of the total recovered off the column and multiplying by 100. The parent compound peaks were authenticated by coinjection with the respective nonradioactive standard.

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ABBREVIATIONS USED

cGMP	cyclic guanosine monophosphate
DAST	diethylaminosulfur trifluoride
DBAD	di- <i>tert</i> -butyl azodicarboxylate
DIEA	<i>N,N</i> -diisopropylethylamine
DMC	dimethyl carbonate
EOS	end of synthesis
EtOH	ethanol
EtOAc	ethyl acetate
FPEG	fluoroPEGylated
MeCN	acetonitrile
MSNs	medium spiny neurons
MOM-Br	bromo(methoxy)methane
MP-10	2-((4-(1-methyl-4-(pyridin-4-yl)-1 <i>H</i> -pyrazol-3-yl)phenoxy)-methyl)quinoline
NHP	nonhuman primate
phenyl triflimide	<i>N</i> -phenyl-bis(trifluoromethane sulfonamide)
PDE3A	phosphodiesterase 3A
PDE3B	phosphodiesterase 3B
PDE4A	phosphodiesterase 4A
PDE4B	phosphodiesterase 4B
PDE10A	phosphodiesterase 10A
p.i	postinjection
QC	quality control
RCY	radiochemical yield
ROI	region of interest
SA	specific activity

TBSCI	<i>tert</i> -butyldimethylsilyl chloride
TEA	triethylamine

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Figure 1. $[^{11}\text{C}]$ MP-10 and previously reported ^{11}C - and ^{18}F -labeled quinoline analogs.

Figure 2.

Structures of new fluorine-containing quinoline analogues: [¹⁸F]**18a**, [¹⁸F]**18b**, [¹⁸F]**18c**, [¹⁸F]**18d**, [¹⁸F]**18e**, [¹⁸F]**18g**, and [¹⁸F] **20a**.

Figure 3.

Ratios of striatum:nontarget brain regions in rats. $[^{18}\text{F}]18\text{a}$, $[^{18}\text{F}]18\text{b}$, $[^{18}\text{F}]18\text{c}$, $[^{18}\text{F}]18\text{d}$, and $[^{18}\text{F}]20\text{a}$ displayed higher target:nontarget ratios than $[^{18}\text{F}]18\text{e}$ and $[^{18}\text{F}]18\text{g}$ at 30 and 60 min p.i. for both striatum:cerebellum (top panel) and striatum:cortex (bottom panel).

Figure 4.

Representative microPET studies of $[^{18}\text{F}]\mathbf{18d}$ and $[^{18}\text{F}]\mathbf{20a}$ in the brain of a male cynomolgus macaque: (a) $[^{18}\text{F}]\mathbf{18d}$: PET image (top left), coregistered image (top middle), MR image (top right); (b) $[^{18}\text{F}]\mathbf{20a}$: PET image (top left), coregistered image (top middle), MR image (top right); (c) brain TACs of $[^{18}\text{F}]\mathbf{18d}$; (d) brain TACs of $[^{18}\text{F}]\mathbf{20a}$. Both $[^{18}\text{F}]\mathbf{18d}$ and $[^{18}\text{F}]\mathbf{20a}$ gave clear visualization of the PDE10A-enriched striatum.

Scheme 1a.

^aReagents and conditions: (a) HBF₄, NaNO₂, -10 °C to rt; (b) DAST, CH₂Cl₂, 0 °C to rt; (c) phenyl triflimide, DIEA, DMF, rt; (d) LiBr, Pd[(C₆H₅)₃P]₄, THF, rt, then allyltributyltin 80 °C; (e) (i) 1.0 M borane THF complex, THF, 0 °C, (ii) NaOH, H₂O₂, sodium ascorbate, DMF, rt; (f) Cs₂CO₃, 1-bromo-2-fluoroethane, DMF, rt; (g) 2-(2-chloroethoxy)ethanol or 2-(2-(2-chloroethoxy)ethoxy)ethanol, K₂CO₃, DMF, 95–100 °C; or tetraethylene glycol *p*-toluenesulfonate, Cs₂CO₃, DMF, 60 °C; (h) 1-bromo-2-fluoroethane, KOH, MeCN, 80 °C; (i) (Boc)₂O, TEA, DMAP, THF, rt; (j) phosphorus(V) oxybromide, K₂CO₃, MeCN, 92 °C; (k) NaN₃, DMF, 90 °C; (l) 3-butyne-1-ol, CuSO₄·5H₂O, sodium ascorbate, DMF, rt; (m) methoxyacetone, ethanolic KOH, ethanol, reflux; (n) BBr₃, DMC, rt.

Method 1

6a, $R^1 = 4\text{-F}$
15d, $R^1 = 6\text{-OCH}_2\text{CH}_2\text{F}$

16a, $R^1 = 4\text{-F}$
16n, $R^1 = 6\text{-OCH}_2\text{CH}_2\text{F}$

Method 2 and 3

6b, $R^2 = \text{CH}_3$, $R^1 = 4\text{-CH}_2\text{F}$
6c, $R^2 = \text{CH}_3$, $R^1 = 4\text{-CH}_2\text{CH}_2\text{CH}_2\text{F}$
6d, $R^2 = \text{COOEt}$, $R^1 = 4\text{-OCH}_2\text{CH}_2\text{F}$
6e, $R^2 = \text{COOEt}$, $R^1 = 4\text{-(OCH}_2\text{CH}_2)_2\text{F}$
6f, $R^2 = \text{COOEt}$, $R^1 = 4\text{-(OCH}_2\text{CH}_2)_3\text{F}$
6g, $R^2 = \text{COOEt}$, $R^1 = 4\text{-(OCH}_2\text{CH}_2)_4\text{F}$
6h, $R^2 = \text{CH}_3$, $R^1 = 4\text{-CH}_2\text{OCH}_2\text{CH}_2\text{F}$
6i, $R^2 = \text{CH}_3$, $R^1 = 4\text{-N(Boc)CH}_2\text{CH}_2\text{F}$
6j, $R^2 = \text{COOEt}$, $R^1 = 4\text{-}$

15a, $R^2 = \text{CH}_3$, $R^1 = 3\text{-OCH}_2\text{CH}_2\text{F}$
15b, $R^2 = \text{CH}_3$, $R^1 = 6\text{-F}$
15c, $R^2 = \text{CH}_3$, $R^1 = 6\text{-CH}_2\text{F}$

16b, $R^1 = 4\text{-CH}_2\text{F}$
16c, $R^1 = 4\text{-CH}_2\text{CH}_2\text{CH}_2\text{F}$
16d, $R^1 = 4\text{-OCH}_2\text{CH}_2\text{F}$
16e, $R^1 = 4\text{-(OCH}_2\text{CH}_2)_2\text{F}$
16f, $R^1 = 4\text{-(OCH}_2\text{CH}_2)_3\text{F}$
16g, $R^1 = 4\text{-(OCH}_2\text{CH}_2)_4\text{F}$
16h, $R^1 = 4\text{-CH}_2\text{OCH}_2\text{CH}_2\text{F}$
16i, $R^1 = 4\text{-N(Boc)CH}_2\text{CH}_2\text{F}$
16j, $R^1 = 4\text{-}$

16k, $R^1 = 3\text{-OCH}_2\text{CH}_2\text{F}$
16l, $R^1 = 6\text{-F}$
16m, $R^1 = 6\text{-CH}_2\text{F}$

Scheme 2a.

^aReagents and conditions: (a) NBS, CCl_4 , reflux; (b) SeO_2 , dioxane, reflux, then NaBH_4 , dioxane, EtOH, rt; (c) NaBH_4 , THF, MeOH, rt.

Scheme 3a.

^aReagents and conditions: (a) **17a**, NaH, DMF, rt; (b) **17a** or **17b**, DBAD, PPh₃, dioxane, 60 °C; (c) **17a** or **17b**, Ph₃P, DBAD, dioxane, 60 °C; then TFA, rt.

Scheme 4a. Synthesis of Precursors (1)

^aReagents and conditions: (a) NaBH_4 , THF: MeOH (20:1), 0 °C to rt; (b) **17a**, DBAD, PPh_3 , dioxane, 60 °C; (c) MOM-Br, DIPEA, CH_2Cl_2 , 0 °C; (d) SeO_2 , dioxane, reflux, then NaBH_4 , dioxane, EtOH, rt; (e) NaBH_4 , THF/MeOH; (f) TFA, DCM.

Scheme 5a. Synthesis of Precursors (2)

^aReagents and conditions: (a) imidazole, TBSCl, DMF, 80 °C; (b) SeO₂, dioxane, reflux, then NaBH₄, dioxane, EtOH, rt; (c) NaBH₄, THF, MeOH, rt; (d) **17a**, Ph₃P, DBAD, dioxane, 60 °C; (e) TBAF, THF, rt; (f) SOCl₂, chloroform, 0 °C; (g) MsCl, TEA, CH₂Cl₂; (h) Ts-Cl, DMAP, DIEA, CH₂Cl₂.

Scheme 6.
Radiosynthesis

Table 1

PDE10A, PDE3A/B, and PDE4A/B Potency (IC₅₀) of Fluorinated MP-10 Analogues ^a

Compd.	R ¹	PDE10A (nM)	PDE3A (nM x 10 ³)	PDE3B (nM x 10 ³)	PDE4A (nM x 10 ³)	PDE4B (nM x 10 ³)	LogD (7.4) ^c
18a	4-F	0.71 ± 0.12	199 ± 16.0	103 ± 10.0	8.35 ± 0.60	6.42 ± 0.27	3.47
18b	4-CH ₂ F	0.68 ± 0.02	7.71 ± 0.30	5.68 ± 0.25	4.09 ± 0.25	3.80 ± 0.15	3.75
18c	4-CH ₂ CH ₂ CH ₂ F	1.80 ± 0.09	21.9 ± 1.60	19.1 ± 3.0	0.46 ± 0.03	0.38 ± 0.03	4.43
18d	4-OCH ₂ CH ₂ F	0.32 ± 0.18	29.5 ± 0.23	7.76 ± 0.11	1.01 ± 0.14	1.77 ± 0.16	4.02
18e	4-CH ₂ OCH ₂ CH ₂ F	0.65 ± 0.02	4.07 ± 0.36	4.55 ± 0.23	2.22 ± 0.08	1.77 ± 0.13	3.49
18f	4-(OCH ₂ CH ₂) ₂ F	0.27 ± 0.10	22.9 ± 2.10	16.2 ± 0.93	1.44 ± 0.09	0.90 ± 0.05	3.62
18g	4-(OCH ₂ CH ₂) ₃ F	0.24 ± 0.04	116 ± 10.0	61.9 ± 4.60	1.57 ± 0.07	1.58 ± 0.08	3.26
18h	4-(OCH ₂ CH ₂) ₄ F	0.33 ± 0.07	144.4 ± 27	29.6 ± 0.27	9.89 ± 0.23	10.3 ± 0.47	2.90
18i	4-NHCH ₂ CH ₂ F	0.52 ± 0.24	3.74 ± 0.18	3.48 ± 0.66	5.97 ± 0.28	4.80 ± 0.34	3.98
18j		3.07 ± 0.27	4.51 ± 0.24	3.56 ± 0.86	1.57 ± 0.14	18.3 ± 1.7	3.37
20a	3-OCH ₂ CH ₂ F	0.26 ± 0.01	25.9 ± 3.20	19.9 ± 4.50	1.76 ± 0.11	1.04 ± 0.09	4.10
20b	6-F	0.29 ± 0.01	38.5 ± 12.0	23.9 ± 5.10	2.33 ± 0.39	2.55 ± 0.26	3.60
20c	6-CH ₂ F	>76	ND ^b	ND ^b	ND ^b	ND ^b	3.75
20d	6-OCH ₂ CH ₂ F	33.5 ± 0.81	ND ^b	ND ^b	ND ^b	ND ^b	3.84

Compd.	R ²	PDE10A (nM)	PDE3A (nM x10 ³)	PDE3B (nM x10 ³)	PDE4A (nM x10 ³)	PDE4B (nM x10 ³)	LogD (7.4) ^c
19d	4-OCH ₂ CH ₂ F	1.16 ±0.43	3.77 ±0.36	5.61 ±3.10	3.72 ±0.45	1.02 ±0.06	4.01
19e	4-CH ₂ OCH ₂ CH ₂ F	1.12±0.51	306 ± 36	>1000	4.77 ±0.16	4.24 ± 0.20	3.49
19f	4-(OCH ₂ CH ₂) ₂ F	0.36 ±0.15	66.4 ± 4.40	50.1 ±3.00	12.3 ±0.70	11.6 ±0.67	3.62
19g	4-(OCH ₂ CH ₂) ₃ F	0.47 ± 0.09	62.2 ±5.30	51.8 ±4.00	8.36 ±0.03	7.31 ±0.32	3.26
19h	4-(OCH ₂ CH ₂) ₄ F	0.30 ±0.03	58.71 ±2.0	28.13 ±1.9	15.0 ±2.80	1.73 ±0.18	2.90
19i	4-NHCH ₂ CH ₂ F	0.37 ±0.09	78.8 ±15.0	38.3 ±6.0	12.4 ± 2.40	1.59 ±0.19	3.98
19j		4.98 ± 0.45	0.81 ±0.01	16.2 ±8.00	1.86 ±0.32	0.90 ± 0.09	3.37
21b	6-F	0.76 ±0.12	111 ± 38.0	151 ±37	9.73 ±1.50	0.76 ± 0.07	3.60

^a [C₅₀] is defined as the concentration of the inhibitor required to reduce the [³H]c-AMP hydrolysis of recombinant human PED10A, PDE3A/3B, or PDE4A/4B by 50% in a scintillation proximity assay.

^b Not determined.

^c Calculated Log D value at pH 7.4, ACD/I-Lab v 7.0 (Advanced Chemistry Development, Inc. Toronto, Ontario, Canada).

Table 2

Biodistribution of [^{18}F]18a, [^{18}F]18b, [^{18}F]18c, [^{18}F]18d, [^{18}F]18e, [^{18}F]18g, and [^{18}F]20a in Male Sprague Dawley Rats^a

organ	5 min	30 min	60 min	5 min	30 min	60 min
[^{18}F]18a						
blood	0.353 ± 0.063	0.376 ± 0.033	0.150 ± 0.021	0.471 ± 0.040	0.416 ± 0.062	0.201 ± 0.026
liver	6.87 ± 1.27	3.00 ± 0.91	1.60 ± 0.87	10.16 ± 1.86	4.01 ± 1.34	3.10 ± 0.61
kidney	1.887 ± 0.296	1.034 ± 0.131	0.533 ± 0.119	1.799 ± 0.207	1.351 ± 0.216	0.573 ± 0.134
muscle	0.339 ± 0.053	0.236 ± 0.019	0.092 ± 0.010	0.227 ± 0.042	0.174 ± 0.042	0.107 ± 0.032
fat	0.404 ± 0.102	0.576 ± 0.154	0.477 ± 0.099	0.343 ± 0.153	0.352 ± 0.081	0.222 ± 0.029
bone	0.522 ± 0.116	4.035 ± 0.153	6.300 ± 0.314	0.421 ± 0.063	4.055 ± 1.305	5.620 ± 1.132
brain	0.410 ± 0.063	0.191 ± 0.036	0.125 ± 0.009	0.128 ± 0.012	0.094 ± 0.023	0.069 ± 0.008
[^{18}F]18c						
blood	0.459 ± 0.049	0.345 ± 0.043	0.345 ± 0.043	0.362 ± 0.048	0.226 ± 0.073	0.215 ± 0.008
liver	9.99 ± 1.27	5.67 ± 0.73	6.79 ± 2.49	6.88 ± 1.15	6.98 ± 0.99	3.29 ± 0.56
kidney	2.471 ± 0.487	1.364 ± 0.077	1.216 ± 0.180	2.200 ± 0.158	1.055 ± 0.218	0.765 ± 0.153
muscle	0.223 ± 0.067	0.178 ± 0.016	0.103 ± 0.030	0.247 ± 0.031	0.134 ± 0.019	0.132 ± 0.011
fat	0.220 ± 0.100	0.491 ± 0.035	0.368 ± 0.077	0.213 ± 0.007	0.302 ± 0.033	0.259 ± 0.025
bone	0.222 ± 0.014	1.418 ± 0.182	2.037 ± 0.303	0.189 ± 0.004	0.091 ± 0.012	0.142 ± 0.001
brain	0.114 ± 0.015	0.046 ± 0.006	0.026 ± 0.005	0.118 ± 0.012	0.078 ± 0.009	0.101 ± 0.002
[^{18}F]18e						
blood	0.440 ± 0.038	0.424 ± 0.074	0.401 ± 0.029	0.699 ± 0.090	0.771 ± 0.061	0.646 ± 0.045
liver	3.99 ± 0.82	0.987 ± 0.038	0.554 ± 0.064	4.74 ± 1.10	1.53 ± 0.49	0.527 ± 0.068
kidney	0.981 ± 0.163	0.632 ± 0.123	0.485 ± 0.045	5.969 ± 0.744	1.793 ± 0.291	1.037 ± 0.170
muscle	0.155 ± 0.040	0.265 ± 0.117	0.228 ± 0.058	0.419 ± 0.090	0.488 ± 0.086	0.379 ± 0.027
fat	0.139 ± 0.031	0.139 ± 0.037	0.066 ± 0.018	0.225 ± 0.086	0.254 ± 0.051	0.123 ± 0.021
bone	0.133 ± 0.028	0.170 ± 0.030	0.337 ± 0.072	0.487 ± 0.044	0.441 ± 0.049	0.490 ± 0.035
brain	0.213 ± 0.039	0.353 ± 0.021	0.343 ± 0.033	0.353 ± 0.052	0.509 ± 0.038	0.421 ± 0.028
[^{18}F]20a						
blood	0.343 ± 0.061	0.306 ± 0.016	0.287 ± 0.010			
liver	4.24 ± 0.74	3.17 ± 0.55	1.80 ± 0.62			
kidney	1.789 ± 0.332	1.022 ± 0.103	0.841 ± 0.087			

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organ	5 min	30 min	60 min	5 min	30 min	60 min
muscle	0.166 ± 0.017	0.156 ± 0.014	0.134 ± 0.009			
fat	0.119 ± 0.021	0.202 ± 0.023	0.124 ± 0.011			
bone	0.182 ± 0.003	0.144 ± 0.006	0.224 ± 0.015			
brain	0.092 ± 0.011	0.129 ± 0.005	0.149 ± 0.013			

^a %ID/g values (mean ± SD) with *n* = 4 rats per group.

Table 3HPLC Analysis of NHP Plasma for [^{18}F]18d and [^{18}F]20a

tracer	time p.i. (min)	% peak 1 ^a	% peak 2 ^b	% parent
[^{18}F]18d	2	1	0	98
	15	4	0	93
	30	7	1	90
	60	19	5	75
	90	32	9	57
[^{18}F]20a	2	0	0	99
	15	6	2	90
	30	15	8	73
	60	29	14	55
	90	39	14	45

^aPeak 1 (radiometabolite) retention time ~3.5 min.^bPeak 2 (radiometabolite) retention time ~7.5 min.