Development of a highly-specific $^{18}$F-labeled irreversible positron emission tomography tracer for monoacylglycerol lipase mapping

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Abstract As a serine hydrolase, monoacylglycerol lipase (MAGL) is principally responsible for the metabolism of 2-arachidonoylglycerol (2-AG) in the central nervous system (CNS), leading to the formation of arachidonic acid (AA). Dysfunction of MAGL has been associated with multiple CNS disorders and symptoms, including neuroinflammation, cognitive impairment, epileptogenesis, nociception and neurodegenerative diseases. Inhibition of MAGL provides a promising therapeutic direction for the treatment of these conditions, and a MAGL positron emission tomography (PET) probe would greatly facilitate preclinical and clinical development of MAGL inhibitors. Herein, we design and synthesize a small...
1. Introduction

As a serine hydrolase, monoaoylglycerol lipase (MAGL) exerts a vital role in the endocannabinoid and eicosanoid signalling systems\(^1\)\(^-\)\(^3\). MAGL is widespready distributed in the body with particularly high expression in the brain. In the central nervous system (CNS), MAGL catalyses the metabolism of the endocannabinoid 2-arachidonylglycerol (2-AG) to arachidonic acid (AA), approximately constituting 50% AA production, which not only serves as a proinflammatory eicosanoid precursor, but also constitutes inflammatory signals\(^6\)\(^-\)\(^10\). In this case, simultaneous regulation of both endocannabinoid and eicosanoid system constitutes the dual-function of MAGL in the CNS. Recent studies have indicated that dysfunction of MAGL is associated with multiple disorders such as neuroinflammation, cognitive impairment, epileptogenesis, nociception, neurodegenerative diseases, and cancer pathogenesis\(^11\)\(^-\)\(^23\). Inhibition of MAGL not only reduces the production of pro-inflammatory eicosanoids, but also increases 2-AG signaling, thereby providing a promising therapeutic direction for the treatment of heterogeneous radio activity accumulation in various brain regions, which was consistent with MAGL expression profile in regions, which was consistent with MAGL expression profile in the brain. This work may serve as a roadmap for PET imaging translation in higher species and guideline for further design of potent \(^18\)F-labeled MAGL PET tracers.

Complementary to routine clinical diagnostic application, positron emission tomography (PET) is a well-characterized noninvasive nuclear imaging tool, which has emerged to be invaluable for target engagement and phase 0 studies in the discovery of CNS drugs\(^25\)\(^-\)\(^38\). Our interest focuses on the discovery of highly MAGL-specific (PET) tracers to enable preclinical and clinical drug development. A MAGL PET tracer would not only allow a deep understanding of biology \textit{in vivo} such as target expression/distribution and relationship with multiple diseases, but also enable a facile clinical translation of MAGL inhibitors. So far, our group\(^35\)\(^-\)\(^36\) and others\(^43\)\(^-\)\(^46\) have reported several first-in-class \(^11\)C-labeled MAGL PET probes with favorable brain permeability and target specificity, such as \[^{11}\text{C}]\text{SAR127303}, \[^{11}\text{C}]\text{MA-PB-1}, \[^{11}\text{C}]\text{MAGL-0519}, \[^{11}\text{C}]\text{MAGL-2-11} \text{ and } \[^{11}\text{C}]\text{PF06809247}. \) However, the short half-life of carbon-11 \(t_{1/2} = 20.4 \text{ min}\) requires on site tracer preparation. To synthesize irreversible MAGL inhibitors \(^14\)\(^-\)\(^17\) containing 3-azabicyclo[3.1.0]hexane core unit, we took advantage of a general strategy shown in Scheme 1 with tert-butyloxy carbonyl (Boc)-protected 3-azabicyclo[3.1.0]hexane-6-carboxylic acid \(1\) as the starting material. Briefly, the coupling of \(1\) with \(N,O\)-dimethylhydroxylamine hydrochloride (NHMeOMe-HCl) occurred smoothly to deliver the Weinreb amide \(2\). Subsequent Grignard addition converted \(2\) to the corresponding ketone \(3\) in 99% yield over two steps. Ketone \(3\) was then transformed into pyrazole \(5\) via enamine formation and cyclization with hydrazine in 97% total yield. Copper-mediated cross-coupling reaction of pyridyl boronic acid or direct nucleophilic \(S_nAr\) substitution of 2-fluoropyridine derivatives with \(5\) provided compounds \(6\)\(^-\)\(^9\) in 8%\(-\)52% yield. TFA-triggered removal of the Boc group in \(6\)\(^-\)\(^9\) followed by coupling with an activated carbonate \textit{in situ} generated from \((R)-1,1,1\)-trifluoro-3-(4-methoxybenzyloxy)propan-2-ol readily proceeded to provide carbamates \(10\)\(^-\)\(^13\) in moderate yields.

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inhibitors. To approach the MAGL binding site, thereby being good MAGL promise of compounds formed H-bonding interactions. These results suggested great 14 AG. In these binding poses, the carbonyl oxygen of candidates oriented towards the Ser122-His269-Asp239 catalytic triad of MAGL, which is a crucial functional unit for the catabolism of 2-AG. In these experiments an excellent selectivity profile was demonstrated with no significant inhibition of serine hydrolase activity of these off-targets (Fig. 3B). To evaluate the reversibility of inhibition, a time-dependent ABPP study was carried out with compound 14 and a known reversible MAGL inhibitor, FEPAD59, which served as a positive control (Fig. 3C). In this assay, MAGL activity recovered rapidly over time in FEPAD-treated samples, whereas MAGL activity only slowly increased in compound 14-treated samples, indicating irreversible binding. Furthermore, no direct agonism or antagonism was found for compound 14 with the cannabinoid receptors CB1 and CB2 (Fig. 3D–G). An off-target pharmacological screening in major CNS targets, including common GPCRs, enzymes, ion channels and transporters was further carried out for compound 14 at a testing concentration of 10 μmol/L. As illustrated in Supporting Information Fig. S2A, only norepinephrine transporter (NET) was identified with greater than 50% target activity at 10 μmol/L of compound 14, and a follow-up NET binding assay using [3H]nisoxetine showed the Ki value of 14 to be 4.08 μmol/L (Fig. S2B), indicating more than 400-fold selectivity towards MAGL among other CNS targets tested.

2.3. Pharmacology

To probe the potency and selectivity, compounds 14–17 were evaluated in vitro in mouse brain lysates by activity-based protein profiling (ABPP) with the serine hydrolase directed probe FP-rhodamine57. As shown in Fig. 3A, compounds 14–16 demonstrated excellent inhibitory activity towards MAGL with single-digit nanomolar IC50 values (8.5 nmol/L for 14, 7.5 nmol/L for 15 and 7.1 nmol/L for 16). Considering the unique 2-fluoropyridine scaffold in 14, which enables facile synthesis of the precursor and radiolabeling with fluorine-18, we prioritized this probe for further pharmacological evaluation. As such, the selectivity of compound 14 for inhibition of MAGL over other serine hydrolases, e.g., FAAH, ABHD6, ABHD12 and KIAA1363, was determined by ABPP in mouse brain lysates. In these experiments an excellent selectivity profile was demonstrated with no significant inhibition of serine hydrolase activity of these off-targets (Fig. 3B). To evaluate the reversibility of inhibition, a time-dependent ABPP study was carried out with compound 14 and a known reversible MAGL inhibitor, FEPAD59, which served as a positive control (Fig. 3C). In this assay, MAGL activity recovered rapidly over time in FEPAD-treated samples, whereas MAGL activity only slowly increased in compound 14-treated samples, indicating irreversible binding. Furthermore, no direct agonism or antagonism was found for compound 14 with the cannabinoid receptors CB1 and CB2 (Fig. 3D–G). An off-target pharmacological screening in major CNS targets, including common GPCRs, enzymes, ion channels and transporters was further carried out for compound 14 at a testing concentration of 10 μmol/L. As illustrated in Supporting Information Fig. S2A, only norepinephrine transporter (NET) was identified with greater than 50% target activity at 10 μmol/L of compound 14, and a follow-up NET binding assay using [3H]nisoxetine showed the Ki value of 14 to be 4.08 μmol/L (Fig. S2B), indicating more than 400-fold selectivity towards MAGL among other CNS targets tested.

2.4. Radiochemistry

With promising pharmacology results, we commenced with the labeling of compound 14 with fluorine-18. The synthesis of bromopyridine precursor 19 was obtained as per the general strategy depicted in Scheme 2. Beginning with pyrazole derivative 5, 2-bromopyridyl moiety was successfully incorporated via a copper-promoted cross-coupling reaction with (6-bromopyridyl-3-yl)bromonic acid. Deprotection of the Boc group was achieved with TFA, and the corresponding amine intermediate readily underwent alkoxyl-carbonylation reaction with (R)-1,1,1-trifluoro-3-(4-methoxybenzyl)oxy)propan-2-ol and 1,1'-[carbonylbis(oxy)]dipyrrolidine-2,5-dione, thus providing precursor 19 in 54% yield over 2 steps.

With the precursor 19 in hand, we performed its radiolabeling with fluorine-18 to synthesize MAGL PET tracer [18F]14. As illustrated in Scheme 3A, SbAr reaction of 19 with fluorine-18 was achieved by use of K2CO3/K222 (0.53 mg/9.4 mg) in DMSO at 150 °C for 10 min (entry 1). Increase of the amount of K2CO3 or use of other base such as tetraethylammonium bicarbonate (TEAB) failed to improve this reaction (entries 2 and 3). Complete deprotection of the PMB group was achieved by use of 6 mol/L HCl at 100 °C for 4 min, thus providing an access to radioligand [18F]14.
This protocol features several merits such as reasonable radiochemical yield (11% RCY, decay-corrected), good molar activity (up to 210 GBq/mmol) and high radiochemical purity (>99%) at end of synthesis. Of note, no radiolysis was observed up to 5 h in ethanol-containing saline (5%), which implicated excellent formulation stability for radioligand [18F]1 (Scheme 3B). In addition, in the discovery of CNS PET tracers, favorable physicochemical property is crucial to increase the likelihood of the passive blood–brain barrier (BBB) permeability and decrease the risk of non-specific binding. In this case, the lipophilicity of ligand [18F]1 was determined by the ‘shake flask method’, also well-characterized as liquid–liquid partition between n-octanol and PBS, the value of which was aligned within the favorable space (1.0–3.5) of PET CNS tracers.

2.5. Preliminary PET imaging and whole-body biodistribution studies of [18F]14

Radioligand [18F]14 was then advanced to PET imaging evaluation. Dynamic rat brain PET images were collected under baseline and blocking conditions for 90 min post intravenous administration of [18F]14 to Sprague–Dawley (SD) rats. Fig. 4 illustrated the co-registration of summed PET images (0–20, 20–50 and 50–90 min) with magnetic resonance imaging (MRI).
The baseline scan demonstrated good BBB penetration ability for \(^{18}\text{F}\)14 (Fig. 4A), and the maximum brain uptake was achieved at 1.5 min post tracer injection with the standard uptake value (SUV) of 1.3, as indicated by the whole-brain TAC (Fig. 4D). In addition, radioligand \(^{18}\text{F}\)14 also implicated a heterogeneous distribution pattern, and high radioactivity were accumulated in the striatum, hippocampus and cerebral cortex, whereas pons exhibited low radioactivity accumulation. Of note, the slow elimination of \(^{18}\text{F}\)14 from rat brain over time is possibly attributed to a slow hydrolysis of the inhibitor \(-\text{MAGL adduct}, \) which was also observed in the ABPP studies. Following a 30 min pretreatment with KML29 under a dose of 0.3 mg/kg, a well-characterized MAGL inhibitor, the uptake of \(^{18}\text{F}\)14 in various brain regions all reduced significantly, thereby leading to the abolishment of heterogeneous distribution pattern in baseline scans (Supporting Information Fig. S3). Of note, increasing the dose of KML29 to 3 mg/kg could further enhanced this radioactivity reduction in all brain regions with a robust attenuation of the whole-brain uptake by 57% as per the area under the curve (AUC), which suggested high in vivo binding specificity and a dose-dependent blocking of the binding of \(^{18}\text{F}\)14 in rat brains (Fig. 4B, E and Fig. S3). To further assess the in vivo specificity of \(^{18}\text{F}\)14, we then carried out another pretreatment experiment with PF06795071 (3 mg/kg), a potent MAGL inhibitor disclosed by Pfizer.31 As expected, a robust blocking was seen in the rat brain images and the corresponding TAC (45% reduction of whole-brain uptake as per AUC, Fig. 4C and E). Motivated by these promising results, we then conducted whole-body biodistribution studies aiming to further examine in vivo uptake and washout of \(^{18}\text{F}\)14 in peripheral organs of rodents. As illustrated in Fig. 5 and Supporting Information Table S1, CD-1 mice were used as objects and four time points (5, 15, 30 and 60 min) was selected post injection of \(^{18}\text{F}\)14. Radioactivity was robustly accumulated in multiple peripheral organs of CD-1 mice, such as the heart, liver kidneys, lungs, small intestine, and pancreas with levels of higher than 5% ID/g (injected dose per gram of wet tissue) at 5 min post tracer injection. Following initial high uptake, the radioactivity of \(^{18}\text{F}\)14 in the kidneys and liver slowly washed out, and high radioactivity level was observed in the small intestine at 60 min after injecting \(^{18}\text{F}\)14, which implicated a possible hepatobiliary and urinary elimination pathway for \(^{18}\text{F}\)14. To further showcase the pharmacokinetic properties of \(^{18}\text{F}\)14, we performed whole-body PET imaging studies in mice. As

![Scheme 2](image)

**Scheme 2** Synthesis of precursor 19 and its radiolabeling en route to MAGL PET tracer 20 (\(^{18}\text{F}\)14). Conditions: (i) (6-bromopyridin-3-yl)boronic acid, Cu(OAc)$_2$, pyridine, 4 Å molecular sieves, CH$_2$Cl$_2$, 30 °C, 30 h; 9% yield; (ii) TFA, rt, 1 h; (iii) Et$_3$N, 1,1′-[carbonylbis(oxy)]dipyrrrolidine-2,5-dione, (R)-1,1,1-trifluoro-3-(4-methoxybenzyl)oxy)pro-pan-2-ol, CH$_2$Cl$_2$, 30 °C, 30 h; 54% yield over two steps. TFA = trifluoroacetic acid; PMB = \(\rho\)-methoxybenzyl.
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3. Conclusions

We have successfully designed and synthesized a focused library of fluoropyridyl-containing MAGL inhibitor candidates on the basis of unique azabicyclo[3.1.0]hexane scaffold. The molecular interaction between these candidates and MAGL binding pocket was predicted by molecular docking studies. Pharmacological assessment by ABPP in mouse brain lysates identified 14 as a potent and selective lead compound. The radioligand [18F]14 (also called [18F]MAGL-1902) was achieved via a facile SnAr reaction on the 2-fluoropyridine scaffold with reasonable radiochemical yield, favorable molar activity and high radiochemical purity. Good BBB permeability, characteristic heterogeneous brain distribution and high in vivo binding specificity were demonstrated by PET studies. To further showcase the translation value of this [18F]14, comprehensive PET imaging studies in mouse models of MAGL deficiency and higher species with kinetic modeling is necessary in the future work. This work may provide a roadmap and guideline for further design of potent 18F-labeled MAGL PET tracers and translation into higher species, such as nonhuman primates and human subjects.

4. Experimental

4.1. General information

The experimental procedures used in this work were slightly modified from literatures. All the chemicals used in the synthesis of MAGL inhibitors and the corresponding precursor were directly acquired from commercial vendors without any purification. Silica gel was used for the purification of synthetic compounds by column chromatography and 0.25 mm silica gel plates were used as indicator for TLC. To obtain the NMR spectra of synthetic compounds, a 300 MHz Bruker spectrometer was used. “ppm” was used to indicate the chemical shifts (δ) and “Hz” was the unit of coupling constants. The abbreviations of multiplicities for peaks in HNMR and FNMR spectra were described as follows: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiple), and br (broad signal). For the measurement of mass spectrometer, Agilent 6430 Triple Quad LC/MS was adopted with ESI as the ionization approach. No promiscuity was observed in the assay of PAINS (Pan Assay Interference Compounds) for all candidate compounds 14—17 with two in silico filters (http://zinc15.docking.org/patterns/home and http://www.swissadme.ch/index.php). High purity (>95%) was also determined for lead compound 14 by a reverse-phase HPLC (Agilent 5 μm, Eclipse plus C18 column (100 mm × 4.6 mm). Unless noted otherwise, molar activity was determined at the end of synthesis. All animal studies were carried out following the ethical rules of Massachusetts General Hospital and National Institute of Radiological Sciences. CD-1 mice (female, 22—24 g, 7 weeks), SD rats (male, 210—230 g, 7 weeks) were fed ad libitum with food and water under a condition of 12 h light/12 h dark cycle.

4.2. Radiosynthesis of [18F]14

[18F]F− was generated by the 18O(p,n)18F reaction performed in the cyclotron using 18 MeV protons and >98% enriched H218O (ROTEM Industries, Arava, Israel). An automated synthetic module was used in this work. The [18F]F− generated from the cyclotron was purified from H218O by use of an anion-exchange cartridge (Sep-Pak QMA Plus Light cartridge; Waters). The elution of [18F]F− from the cartridge was achieved with a solution of K2CO3 (0.53 mg) and Kryptofix 222 (9.4 mg) in water (250 μL) and acetonitrile (250 μL). The eluted [18F]F− solution was then

![Scheme 3](image-url)
transferred to a reaction vessel and dried at 110°C with a helium flow. Then a solution of bromopyridine precursor 19 (1.5 mg) in dry-DMSO (300 µL) was added, and the reaction vial containing precursor and dry [18F]F was heated at 150°C for 10 min before cooling to 60°C. Then 6 mol/L HCl (500 µL) was added and heated at 100°C (4 min) to remove the PMB group. After cooling to room temperature, 6 mol/L NaOH (500 µL) was added and the resulting mixture was purified through a semi-preparative HPLC (CAPCELL PAK C18 UG80, 5 µm L, 250 mm x 10 mm) with an eluent of CH3CN/H2O (45/55, v/v) at a flow rate of 5.0 mL/min. A wavelength of 254 nm was used for the UV monitor. The radioactive [18F] fraction with a retention time of 9.5 min was collected with a flask containing ethanol (300 µL), Tween 80 (75 µL), and 25% ascorbic acid aqueous solution (0.1 mL). The mixture was then concentrated in vacuo and redissolved in 3 mL of saline containing 5% ethanol to obtain [18F]14. The chemical and radiochemical purity were measured by use of an analytical HPLC (OOF-4454-YO, Gemini 5 µm, 150 mm x 3 mm) with an eluent of CH3CN/H2O (40/60, v/v) at a flow rate of 1.0 mL/min. The retention time of [18F]14 was 5.2 min. The decay-corrected radiochemical yield of [18F]14 was determined to be 11% with good molar activity (up to 210 GBq/mmol) and high radiochemical purity (>99%).

4.3. Molecular docking studies

The procedure for molecular docking studies in this work was slightly modified from literature. We first downloaded the crystal structure of soluble human MAGL with a resolution of 1.35 Å (PDB ID: 3PE6). The original ligand was re-docked into the binding site, and its binding pose from Autodock Vina exhibited a good overlapping with the original one. Compounds 14–17 were then docked into the aforementioned 3PE6 structure.

4.4. Activity-based protein profiling (ABPP)

The procedure of ABPP assay in this work was slightly modified from literatures. In brief, 1 mg/mL membrane proteomes from mouse brain were first incubated at 37°C together with a candidate MAGL inhibitor or DMSO as negative control for 30 min. FP-rhodamine was then added to give a final concentration of 0.5 µmol/L. After incubating at room temperature for another 15 min, 4 × SDS loading buffer was introduced to stop the reaction and the reaction mixture was separated with SDS–PAGE. A ChemiDoc MP system was used to visualize the samples by in-gel fluorescence scanning. For time-dependent studies, the membrane proteomes are preincubated at 37°C with 1 µmol/L compound 14 for 30 min before incubation with FP-Rh at room temperature for different time (1–160 min) with a final concentration of 0.5 µmol/L. Herein the reversible MAGL inhibitor

Figure 4: Summed PET images and representative time–activity curves (TACs) of [18F]14 in rat brains under (A) Baseline conditions; (B) Pretreatment conditions with KML29 (3 mg/kg); (C) Pretreatment conditions with PF06795071 (3 mg/kg). (D) Whole-brain TACs; (E) Area under curves. **P ≤ 0.01, ***P ≤ 0.001, and ****P ≤ 0.0001.

Figure 5: Ex vivo whole-body biodistribution studies. The statistical significance was expressed with asterisks: *P < 0.05, **P < 0.01, and ***P < 0.001.
FEPAD\textsuperscript{40} was used as the positive control. Three parallel experiments were carried out and the data was indicated as an average of 3 runs. The intensity of DMSO-treated proteomes was normalized to 100\% and the relative intensity of candidate MAGL inhibitors was acquired by comparison.

4.5. CB\textsubscript{1} and CB\textsubscript{2} binding assays

The profiles for CB\textsubscript{1} and CB\textsubscript{2} binding of 14 were obtained following literatures\textsuperscript{40,41} and the procedures were described on the Website (https://pdspdb.unc.edu/pdspWeb, assay protocol book). This experiment was supported by the National Institute of Mental Health’s Psychoactive Drug Screening Program. In both CB\textsubscript{1} and CB\textsubscript{2} agonist assays, compound CP55940 was adopted as the positive control, while in CB\textsubscript{1} and CB\textsubscript{2} antagonist assays, Rimonabant and SR144528 was adopted as the positive control, respectively. Three to five parallel experiments were carried out and the data was indicated as an average of 3–5 runs.

4.6. Measurement of logD

The procedure for measuring the lipophilicity in this work was slightly modified from literatures\textsuperscript{40,41}. In brief, to obtain the logD values, $[^{18}\text{F}]14$, n-octanol (3 mL) and PBS (0.1 mol/L, 3 mL) was mixed in a centrifugal tube, and vortex was performed for 3 min followed by 5 min’s centrifuge (\(\sim 14,000 \text{rpm}\)). Before use of PBS and n-octanol, pre-saturation with each other needs to be performed. PBS (500 \(\mu\)L) and n-octanol (50 \(\mu\)L) were then aliquoted and weighted. An autogamma counter (Cobra Model 5002/5003) was used to determine the radioactivity. The logD was calculated with Eq. (1):

\[
\text{logD} = \text{Log}\left(\frac{\text{radioactivity}_{\text{n-octanol}}/\text{weight}_{\text{n-octanol}}}{\text{radioactivity}_{\text{PBS}}/\text{weight}_{\text{PBS}}}\right)
\]

Three parallel experiments were carried out and the data was indicated as an average of 3 runs.

4.7. Small-animal PET imaging studies

The procedure for PET imaging studies in this work was slightly modified from literatures\textsuperscript{40,41}. An Inveon PET scanner (Siemens) was used to acquire PET scans and during the scan 1\%–2\% isoflurane/air (v/v) was used to keep the Sprague–Dawley rats under anesthesia. Intravenous injection of radioligand $[^{18}\text{F}]14$ (ca. 0.5 mCi/150 \(\mu\)L) was performed by use of a preinstalled catheter and the dynamic PET images were then collected for 90 min in a 3D mode. For blocking experiments, intravenous injection of KML29 (3 mg/kg) or PF06795071 (3 mg/kg) was carried out 30 min before injecting $[^{18}\text{F}]14$. As we described previously\textsuperscript{40,49,60}, ASIPro VW software was used for the reconstruction of the dynamic PET images and the achievement of the volumes of interest, such as the whole brain and various brain regions. The radioactivity was indicated with SUV as Eq. (2):

\[
\text{SUV} = \frac{\text{Radioactivity per mL tissue}/\text{Injected radioactivity}}{\text{Body weight}}
\]

4.8. Ex vivo whole body biodistribution of $[^{18}\text{F}]14$ in mice

The procedure for biodistribution experiments in this work was slightly modified from literatures\textsuperscript{26,41}. In brief, $[^{18}\text{F}]14$ (20 \(\mu\)Ci/100 \(\mu\)L) was intravenously injected via the tail vein of CD-1 mice. At different time points (5, 15, 30 and 60 min) after injecting $[^{18}\text{F}]14$, the mice were sacrificed and organs of interest were collected and weighted. An autogamma counter (Cobra Model 5002/5003) was used to determine the radioactivity in each organ. All experiments were repeated 4 times and the data was an average of 4 runs indicated as the percentage of injected dose per gram of wet tissue (\%ID/g).

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Author contributions

All the authors contributed to this manuscript and have approved its final version. Zhen Chen and Steven H. Liang designed the study and wrote the manuscript. Zhen Chen, Wakana Mori, Jian Rong, Michael A. Schafroth, Tuo Shao, Richard S. Van, Daisuke Ogasawara, Tomoteru Yamasaki, Atsuto Hiraishi, Akiko Hatori, Jiahui Chen, Yiding Zhang, Kuan Hu, Masayuki Fujinaga, Jiyun Sun and Qingzhen Yu performed experiments. Thomas L. Collier, Yihan Shao, Benjamin F. Cravatt and Lee Josephson designed and guided experiments. Ming-Rong Zhang and Steven H. Liang conceived project and wrote the manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2021.01.021.

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