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RESEARCH ARTICLE

Strain–Promoted Copper-Free Click Chemistry for Efficient ^{18}F–Labeling of Poly(ethylene glycol) Azides via Dibenzocyclooctyne Acid

Sachin U Kalme *

ABSTRACT: Positron emission tomography (PET) imaging relies on efficient radiolabeling strategies for the synthesis of biologically relevant tracers. In this study, we present a novel approach utilizing strain-promoted alkyne-azide cycloaddition (SPAAC) for the rapid and high-yielding ^{18}F-labeling of poly(ethylene glycol) (PEG) azides using dibenzocyclooctyne acid (DIBAC). A nucleophilic fluorination reaction was performed on an N3-PEG mesylate precursor, yielding [^{18}F]17 with a radiochemical yield of 45% (specific activity: 220 GBq/μmol) within 70 minutes, including HPLC purification. Subsequent bioorthogonal conjugation with DIBAC (3) under optimized conditions afforded the ^{18}F-labeled triazole product [^{18}F]3 in excellent radiochemical purity (>99%) and high yield (92%). Key advantages of this method include the elimination of cytotoxic copper catalysts, rapid reaction kinetics (complete within 30 min at room temperature), and compatibility with biomolecules. Systematic optimization revealed that even substoichiometric amounts of DIBAC (0.2 mg, 0.0006 mmol) achieved >96% conversion, minimizing excess reagent interference. The high specific activity (254.69 GBq/μmol) and efficiency of this approach underscore its potential for PET tracer development. This work demonstrates the feasibility of copper-free click chemistry for ^{18}F-labeling, offering a robust platform for synthesizing radiotracers with applications in molecular imaging, drug development, and targeted diagnostics. The chemoselective and bioorthogonal nature of SPAAC ensures broad utility in labeling peptides, antibodies, and other bioactive molecules without compromising their physiological integrity.

Keywords: ^{18}F-labeling, Copper-free click chemistry, Strain-promoted cycloaddition, Bioorthogonal chemistry, PET imaging, Radiopharmaceuticals

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1. INTRODUCTION

Positron emission tomography (PET) has emerged as a transformative imaging modality in pharmaceutical research, offering unparalleled insights into biochemical processes, disease mechanisms, and drug-target interactions [1-3]. By detecting positron-emitting radionuclides, PET provides quantitative, multidimensional (2D/3D) data on physiological and molecular processes in vivo, enabling real-time visualization of metabolic pathways, receptor expression, and pharmacokinetics [4]. Among the radionuclides used in PET imaging—such as 11C, 13N, and 15O—fluorine-18 (^{18}F) stands out due to its favorable physical and chemical properties. With a half-life of 109.77 minutes, ^{18}F permits multistep radiochemical syntheses spanning 1-3 half-lives, a feat impractical with shorter-lived isotopes like 11C (20.4 min) or 15O (2 min) [5-7]. Moreover, the nucleophilic [^{18}F]fluoride ion is widely employed in radiochemistry due to its synthetic versatility, commercial availability, and compatibility with diverse prosthetic groups and biomolecules [8].

The integration of ^{18}F-labeling with click chemistry has revolutionized radiopharmaceutical development over the past decade [9-11]. Click reactions, particularly the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), have enabled efficient conjugation of radiotracers to targeting

Department of Chemistry, Shri Sant Janabai Arts, Commerce and Science College, Gangakhed, Dist. Parbhani- 431514, Maharastra, India.

*Author to whom correspondence should be addressed: kalmesachin@gmail.com (Sachin U Kalme)

vectors (e.g., peptides, antibodies). However, CuAAC suffers from critical limitations in bioorthogonal applications. Copper catalysts can coordinate with biomolecules, impairing their function, while residual copper ions in the final product raise concerns about cytotoxicity in vivo [12-14]. These challenges prompted the exploration of copper-free alternatives, culminating in the development of strain-promoted alkyne-azide cycloaddition (SPAAC) by Bertozzi and colleagues [15-20]. SPAAC exploits ring strain in cyclooctynes to drive rapid, chemoselective [3+2] cycloadditions with azides—without metal catalysts. This bioorthogonal reaction is characterized by high yields, regioselectivity, and compatibility with physiological conditions, making it ideal for labeling sensitive biomolecules.

Key advances in SPAAC have been driven by the design of optimized cyclooctynes, such as dibenzocyclooctynol (DIBO), azadibenzocyclooctyne (ADIBO), and dibenzocyclooctynetriazole derivatives (Figure 1) [21-22]. These scaffolds exhibit enhanced reactivity due to torsional strain and electronic modulation, enabling efficient ligation with azides even at low concentrations. For instance, ADIBO derivatives functionalized with carboxylic acids (e.g., ADIBO-acid) permit site-specific conjugation to biomolecules via amide coupling, expanding their utility in radiopharmaceutical design.

In this study, we leverage SPAAC to develop a novel ^{18}F-labeling strategy using an acid-functionalized dibenzocyclooctyne (DIBAC) and a [^{18}F]PEG-azide synthon. The approach addresses two major needs in PET tracer synthesis: (1) eliminating copper-induced toxicity risks, and (2) streamlining radiolabeling under mild conditions. The [^{18}F]PEG-azide precursor was synthesized via nucleophilic fluorination of a mesylate derivative, achieving a 45% radiochemical yield (RCY) and high specific activity (220 GBq/μmol) within 70 minutes. Subsequent SPAAC with DIBAC proceeded quantitatively at room temperature, affording the ^{18}F-labeled triazole adduct ([^{18}F]3) in >99% radiochemical purity and 92% RCY. The reaction's efficiency was further demonstrated by its scalability; even substoichiometric DIBAC (0.2 mg) achieved >96% conversion, minimizing purification challenges.

This work underscores the potential of strain-promoted click chemistry to overcome longstanding barriers in ^{18}F radiochemistry. By combining the rapid kinetics of SPAAC with the biocompatibility of PEGylated scaffolds, the method offers a robust platform for labeling peptides, proteins, and other bioactive molecules. The high specific activity (254.69 GBq/μmol) of the final product ensures sensitivity for preclinical and clinical PET imaging, while the absence of copper catalysts guarantees compatibility with in vivo applications. Future directions include adapting this platform for antibody labeling and evaluating its performance in disease models, with the ultimate goal of translating optimized tracers to diagnostic and therapeutic applications. This research advances molecular imaging by introducing a copper-free, bioorthogonal ^{18}F-labeling methodology that prioritizes efficiency, safety, and versatility. The synergy between SPAAC and ^{18}F chemistry not only expands the radiochemist's toolkit but also paves the way for next-generation radiopharmaceuticals tailored to precision medicine.

2. EXPERIMENTAL DETAILS

2.1. Materials and General Methods

All chemical reagents and solvents were purchased from Sigma-Aldrich and used without further purification. Reaction progress was monitored by thin-layer chromatography (TLC) using silica gel plates with F254 fluorescent indicator. Column chromatography was performed using 230–400 mesh silica gel. [^{18}F]Fluoride was produced via the nuclear reaction 18O (p,n)^{18}F by irradiating a concentrated [18O]H_2O target with 19 MeV protons in a cyclotron. High-performance liquid chromatography (HPLC) was performed using a Thermo Scientific system (Waltham, MA) equipped with a semi-preparative column (C18 silica gel, 11 μm, 11 × 260 mm) and an analytical column (C18 silica gel, 5 μm, 4.5 × 240 mm). Chromatographic data were acquired and processed using ChromQuest 4.2 software. The mobile phase consisted of H_2O containing 0.1% trifluoroacetic acid (TFA) and acetonitrile (40:60, v/v) at a flow rate of 2 mL/min. Detection was performed using both UV and radioactivity detectors.

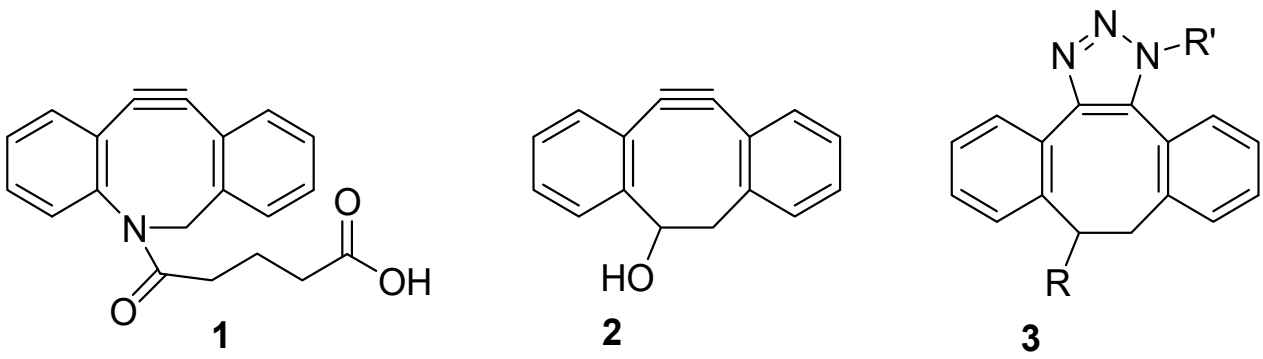
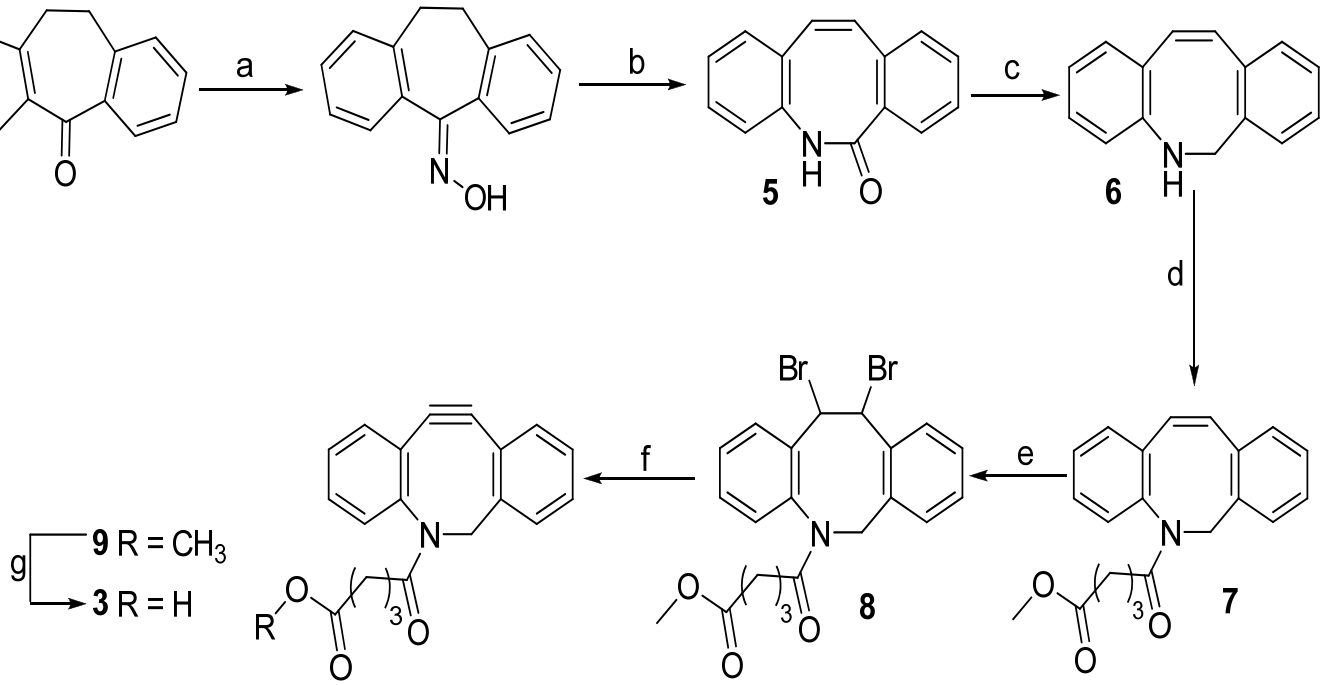


Fig. 1. Cyclooctynes complexes for metal-free click reactions.



Scheme 1. Preparation of Dibenzocyclooctyne acid comp. 3. Reagents and conditions: (a) Sod. hydroxy. HCl, pyridine, 60%; (b) polyphosphoric acid, 125 ºC, 73%; (c) $LiAlH_4$, ether, 58%; (d) glutaric acid monomethyl ester chloride, pyridine, CH_2Cl_2, 71%; (e) Br_2, 0 ºC, 1 h, 78%; (f) t-BuOK 1M, THF, -40 ºC, 3 h, 91%; (g) 2N KOH, MeOH, 25 ºC, 12 h, 90%.

2.2. Synthesis of 2-(2-(2-{2-[2-Azidoethoxy] ethoxy} ethoxy) ethoxy)ethyl-4-[^{18}F]fluoro [^{18}F]18

[^{18}F]Fluoride was obtained from the cyclotron and trapped in a solution of nBu_4NHCO_3 (45% aqueous, 3.5 µL, 7.70 µmol) in 100 µL of water. The [^{18}F]fluoride was then reacted with the mesylate precursor 17 (2.5 mg, 7.32 µmol) in tert-amyl alcohol (400 µL) at 95 °C for 25 min. The crude product was purified by HPLC (retention time tR = 12.33 min; C18 silica gel, 10 µm, 4.6 × 250 mm; mobile phase: H_2O with 0.1% TFA/acetonitrile = 40:60, v/v; UV detection at 215 nm; flow rate: 2 mL/min). To confirm product identity, cold compound 17 was co-injected with the radioactive fractions. The total synthesis time for [^{18}F]17 was 80 min, with a decay-corrected radiochemical yield (RCY) of approximately 45%.

2.3. Preparation of [^{18}F]3

A solution of dibenzocyclooctyne acid (3, 1.6 mg) in a mixture of ethanol and water (3:2, 0.1 mL) was combined with [^{18}F]17 (35 MBq) in the same solvent mixture (0.1 mL). The reaction mixture was allowed to stand at room temperature for 30 min. Subsequently, 20 mg of resin (2.25 mmol/g) was added and stirred for an additional 30 min to remove excess compound 3. The crude product was purified by HPLC (retention time tR = 18 min; C18 silica gel, 10 µm, 10 × 250 mm; mobile phase: H_2O with 0.1% TFA/acetonitrile = 40:60, v/v; UV detection at 254 nm; flow rate: 2 mL/min). The total reaction time for [^{18}F]3 was 90 min, with a decay-corrected RCY of 92%. The specific activity of [^{18}F]3 was determined by correlating the radioactivity with the mass derived from the UV absorption peak (254 nm) of the corresponding cold compound, yielding a value of 254.69 GBq/µmol (n = 3).

3. RESULTS AND DISCUSSION

3.1. Synthesis and Characterization of Dibenzo cyclooctyne Acid (DIBAC) Derivatives

The synthesis of dibenzocyclooctyne acid (DIBAC, 3) was accomplished through a seven-step sequence as outlined in Scheme 1. The initial step involved the Beckmann rearrangement of dibenzosuberone oxime, prepared by reacting commercially available dibenzosuberone with hydroxylamine hydrochloride in pyridine (60% yield). Treatment with polyphosphoric acid at 125 °C afforded the corresponding lactam 5 in 73% yield. Subsequent reduction of 5 with lithium aluminum hydride in diethyl ether provided the secondary amine 6 (58% yield). Acylation of 6 with glutaric acid monomethyl ester chloride in the presence of pyridine yielded amide 7 (71% yield). The key transformation to introduce the strained alkyne moiety was achieved via a two-step bromination-elimination sequence. Bromination of 7 at 0 °C proceeded in 78% yield, followed by dehydrobromination using potassium tert-butoxide in THF at -40 °C, which furnished the dibenzocyclooctyne core

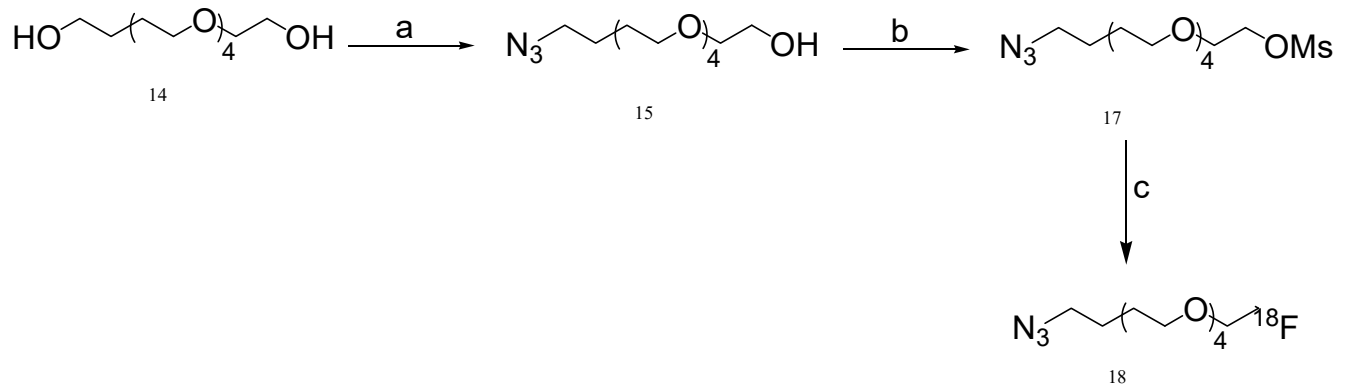
in 91% yield. Final hydrolysis of the methyl ester under basic conditions (2N KOH, methanol, 25 °C) provided the target DIBAC derivative 3 in 90% yield. This synthetic route proved efficient, with an overall yield of approximately 22% over seven steps, and provided sufficient quantities of 3 for subsequent radiolabeling studies [23].

3.2. Radiosynthesis of [^{18}F]PEG-Azide ([^{18}F]17)

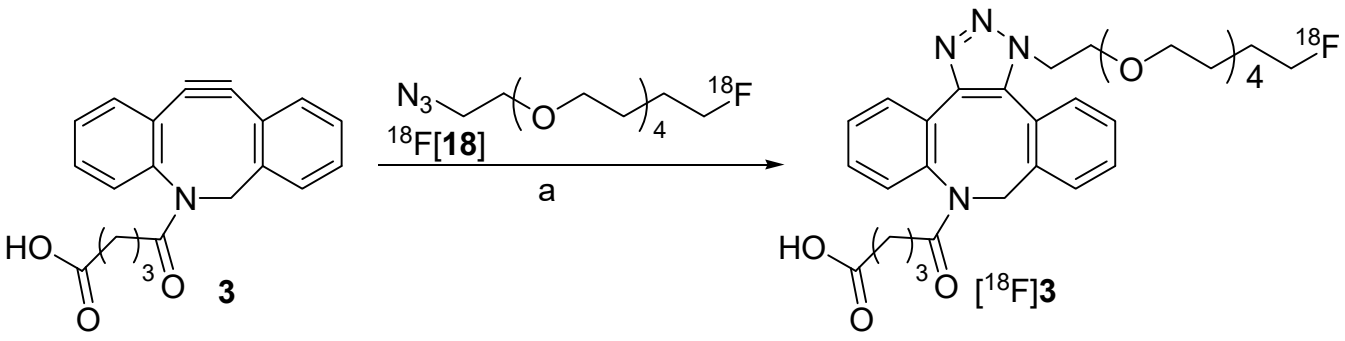
The preparation of the radiolabeled precursor [^{18}F]PEG-azide ([^{18}F]17) was achieved as depicted in Scheme 2. Pentaethylene glycol (14) was first converted to the corresponding monotosylate derivative using p-toluenesulfonyl chloride and triethylamine in dichloromethane (52% yield). Nucleophilic displacement with sodium azide in acetonitrile at 100 °C provided the azido-functionalized PEG derivative 15 in excellent yield (95%). Subsequent mesylation of the terminal hydroxyl group using methanesulfonyl chloride and triethylamine afforded the key precursor 17 in 77% yield. Radiolabeling was accomplished via nucleophilic substitution of the mesylate group with [^{18}F]fluoride, generated by cyclotron irradiation of [18O]H_2O and trapped as [^{18}F]TBAF in aqueous solution. The reaction was performed in tert-amyl alcohol at 95 °C for 25 minutes, followed by HPLC purification (C18 column, 0.1% TFA in H2O/acetonitrile 40:60) to afford [^{18}F]17 in 45% decay-corrected radiochemical yield (RCY) with a specific activity of 220 GBq/µmol. The total synthesis time, including purification, was 80 minutes. Radio-TLC analysis confirmed the high radiochemical purity (>99%) of [^{18}F]17, making it suitable for subsequent click chemistry applications [23-24].

3.3. Strain-Promoted Azide-Alkyne Cycloaddition (SPAAC) and Optimization Studies

The copper-free click reaction between DIBAC (3) and [^{18}F]$_{17}$ was investigated to establish optimal conditions for the formation of the ^{18}F-labeled triazole product [^{18}F]$_3$ (Scheme 3). The cycloaddition was performed by mixing 3 (1.6 mg, 0.0050 mmol) with [^{18}F]$_{17}$ (35 MBq) in ethanol/water (3:2) at room temperature. Remarkably, the reaction reached >95% conversion within 30 minutes, as determined by radio-TLC (Table 1). To minimize excess reagent interference while maintaining high conversion, a systematic evaluation of 3 concentration was conducted. As shown in Table 1, decreasing the amount of 3 from 1.6 mg (0.0050 mmol) to 0.2 mg (0.0006 mmol) still afforded excellent conversion (96.14% at 30 min), while further reduction to 0.05 mg (0.0001 mmol) resulted in diminished yields (93.15% at 30 min).



Scheme 2. Preparation of ^{18}F-PEG-Azide.



Scheme 3. Click reaction: Cyclooctyne-acid 3 + N3-PEG-^{18}F [18F]18.

Table 1. ^{18}F-labeled ADIBOT product [^{18}F]3 reaction time and high RCY.

Comp. 3	mmole	5 min	10 min	15 min	20 min	30 min
1.6 mg	0.0050	96.33%	96.85%	97.16%	97.56%	97.81%
0.8 mg	0.0025	95%	96.43%	97%	97.19%	97.40%
0.4 mg	0.0012	90.25%	95%	96.45%	96.85%	97.29%
0.2 mg	0.0006	82.45%	89.40%	93.15%	95.71%	96.14%
0.1 mg	0.0003	71.63%	83.29%	89.68%	93.81%	95.36%
0.05 mg	0.0001	56.46%	69.26%	83.33%	90.63%	93.15%

These findings demonstrate that substoichiometric quantities of 3 (0.2 mg) are sufficient for near-quantitative radiolabeling, significantly reducing purification challenges associated with excess cyclooctyne.

3.4. Purification and Characterization of [^{18}F]$_3$

Following the SPAAC reaction, the crude mixture was treated with resin (20 mg, 2.25 mmol/g) to scavenge excess 3, followed by HPLC purification (C18 column, 0.1% TFA in H2O/acetonitrile 40:60) to isolate [^{18}F]3. The product eluted at 18 minutes and was obtained in 92% decay-corrected RCY with a specific activity of 254.69 GBq/µmol (n = 3). Notably, the entire process, including reaction and purification, was completed within 90 minutes, making it compatible with the 109.77-minute half-life of ^{18}F. Mass spectrometry and co-injection with non-radioactive standards confirmed the identity of [^{18}F]3, while radio-HPLC demonstrated >99% radiochemical purity. The high specific activity achieved is particularly significant for PET imaging applications, as it ensures sufficient signal-to-noise ratios for sensitive detection in vivo.

3.5. Comparative Analysis and Advantages of the SPAAC Approach

The developed methodology offers several advantages over conventional copper-catalyzed azide-alkyne cycloaddition (CuAAC) for ^{18}F-labeling. First, the absence of copper eliminates concerns about catalyst-induced biomolecule damage and potential in vivo toxicity [12-14]. Second, the rapid reaction kinetics (complete within 30 minutes at room temperature) are compatible with the short half-life of ^{18}F. Third, the high chemoselectivity of SPAAC allows for efficient labeling even in the presence of other functional groups, which is particularly valuable for complex biomolecules [15-20]. Furthermore, the ability to use substoichiometric amounts of 3 (0.2 mg) reduces material costs and simplifies purification. These features collectively establish SPAAC as a robust and practical strategy for preparing ^{18}F-labeled probes for PET imaging. The successful synthesis of [^{18}F]3 validates the utility of DIBAC derivatives in bioorthogonal ^{18}F-labeling. This approach could be extended to label peptides, antibodies, or other targeting vectors by incorporating azide or cyclooctyne functional groups. Future studies will focus on applying this methodology to the radiolabeling of bioactive molecules and evaluating their pharmacokinetics in preclinical models. Additionally, the development of more hydrophilic cyclooctyne derivatives may further improve in vivo behavior and target specificity. The combination of high specific activity, rapid labeling, and copper-free conditions positions this SPAAC-based strategy as a versatile platform for next-generation radiopharmaceutical development.

4. CONCLUSION

This study successfully establishes a robust and efficient method for ^{18}F-labeling via strain-promoted alkyne-azide cycloaddition (SPAAC), circumventing the limitations of traditional copper-catalyzed click chemistry. By leveraging the rapid kinetics and bioorthogonality of dibenzocyclooctyne acid (DIBAC) with ^{18}F-PEG-azide ([^{18}F]$_{17}$), we achieved high radiochemical yields (92–95%) and exceptional purity (>99%) under mild conditions (room temperature, 30 min). The optimized protocol minimizes reagent excess, with even 0.2 mg of DIBAC delivering >96% conversion, facilitating easier purification and reducing interference in downstream applications. The synthetic utility of this approach was highlighted by the concise preparation of DIBAC derivatives and the efficient radiosynthesis of [^{18}F]$_{17}$ via nucleophilic fluorination. The high specific activity (254.69 GBq/µmol) of the final product ([^{18}F]$_3$) underscores the precision of this method, critical for sensitive PET imaging. Notably, the absence of copper eliminates cytotoxicity risks, making this strategy suitable for in vivo applications, such as labeling peptides, antibodies, or small-molecule therapeutics. Beyond its technical advantages, this work expands the toolkit for ^{18}F radiochemistry by integrating SPAAC with PEG-based scaffolds, enhancing solubility and biocompatibility of radiotracers. Future directions include applying this platform to label biomacromolecules (e.g., proteins, oligonucleotides) and evaluating in vivo stability and targeting efficacy in disease models. The scalability of the method, coupled with its compatibility with automated synthesis modules, positions it as a viable candidate for clinical translation. This study advances the field of molecular imaging by providing a

reliable, copper-free ^{18}F-labeling strategy that combines rapid kinetics, high yields, and operational simplicity. Its adaptability to diverse biomolecules and potential for modular design pave the way for next-generation radiopharmaceuticals in oncology, neurology, and beyond

DECLARATIONS

Ethical Approval

We affirm that this manuscript is an original work, has not been previously published, and is not currently under consideration for publication in any other journal or conference proceedings. All authors have reviewed and approved the manuscript, and the order of authorship has been mutually agreed upon.

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Availability of data and material

All of the data obtained or analyzed during this study is included in the report that was submitted.

Conflicts of Interest

The authors declare that they have no financial or personal interests that could have influenced the research and findings presented in this paper. The authors alone are responsible for the content and writing of this article.

Authors' contributions

All authors contributed equally in the preparation of this manuscript.

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