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Metallaphotoredox Aryl and Alkyl Radiomethylation for PET Ligand Discovery

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Abstract

Positron emission tomography (PET) radioligands are highly enabling tracers which facilitate in vivo characterization of central nervous system (CNS) drug candidates, neurodegenerative diseases, and numerous oncology targets[1]. While both tritium and carbon-11 radioisotopologs are generally necessary for in vitro and in vivo characterization of radioligands[2], there exist few radiolabeling protocols for the synthesis of either, inhibiting the development of PET radioligands. Here, we report a broadly useful metallaphotoredox-catalyzed method for late-stage installation of both tritium and carbon-11 via methylation of pharmaceutical precursors bearing aryl and alkyl bromides, simplifying radioligand discovery. To demonstrate the breadth of applicability of this technology, the rapid synthesis of 20 tritiated and 10 carbon-11-labeled complex pharmaceuticals and PET radioligands has been conducted, including a one-step radiosynthesis of clinically utilized [^{11}C]UCB-J and [^{11}C]PHNO. We have further outlined the direct utility of this protocol for preclinical PET imaging and its translation to automated radiosynthesis for routine radiotracer

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Ethical Approval: All rhesus monkey PET imaging studies were approved by the West Point Institutional Animal Care and Use Committee at Merck Research Laboratories and conducted under the principles established by the American Physiological Society and the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.

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production in human clinical imaging. Last, this protocol has been expanded to the installation of other diverse isotopes, including carbon-14, carbon-13, and deuterium, an enabling feature for the development of pharmaceutical programs.

The incorporation of radioactive nuclides into bioactive molecules has revolutionized the field of pharmaceutical research and development[3-5]. Among known radiolabeling applications, positron emission tomography (PET) is an invaluable clinical tool that enables minimally invasive visualization of PET radioligands, in vivo[1]. These isotope-enriched ligands serve as informative biomarkers for oncology[6] and neurological disorders[7], as well as critical tools for studying brain target occupancy relationships for central nervous system (CNS) drug development[8-11]. At the present time, small molecule PET imaging primarily relies on the use of fluorine-18 (^{18}F, $t_{1/2}$ = 110 minutes) and carbon-11 (^{11}C, $t_{1/2}$ = 20 minutes). However, the systematic incorporation of carbon-11 radionuclides into organic architectures remains a long-standing synthetic problem due to a series of chemical and operational challenges. For example the translation of non-radioactive ^{12}C chemistry to ^{11}C radiolabeling is broadly hampered by: a) the short 20 minute half-life of carbon-11, rendering most synthetic protocols outside the realm of operational utility with respect to experimental timeframes, b) availability of ^{11}C-precursor starting materials, c) carbon-11 generation in low nanomole quantities while non-radioactive reaction components are used in vast super-stoichiometric excess, necessitating clean reaction profiles and experimental miniaturization, and d) the requirement for operationally simple and robust protocols that are insensitive to air and moisture[4,12,13]. Indeed, while a litany of methods for ^{12}C-installation have been invented throughout the history of organic chemistry, the vast majority are unsuited to the challenges of radioisotopic ^{11}C labeling.

While the incorporation of carbon-11 is a necessity for in vivo PET imaging studies, the development of these radioligands generally requires additional in vitro characterization, such as tissue-based radioligand binding assays and in vitro autoradiography (Fig. 1a). These characterization methods are the touchstone for optimizing affinity and selectivity for a target, respectively[2]. In this context, it has long been established that tritium (^{3}H or T) is the most attractive radioisotope for such in vitro studies, given its long half-life ($t_{1/2}$ = 12 years). However, a major challenge of tritium labeling in these applications is the need for high incorporation of 2–4 tritium atoms per molecule (molar activities of 50–100 Ci mmol $^{-1}$), a requirement which has been met with limited success using modern hydrogen isotope exchange strategies and instead is often achieved with tritiodehalogenation or alkene reduction via substrate resynthesis[3,14]. Indeed, while both tritium and carbon-11 isotopologs of any pharmaceutical are critical for PET radioligand discovery, the radiosynthesis of such ligands remains a fundamental limitation in drug discovery. As such, a radiolabeling strategy that allows the incorporation of both tritium and carbon-11 would dramatically impact radioligand design in the context of therapeutic targets of neurological disorders as well as enabling biomarker discovery for cancer and neurodegenerative diseases.

A uniquely valuable yet versatile architectural element within organic radiolabeling, the —CH_3 or methyl group allows both hydrogen and carbon isotopes to be readily installed into drug molecules. For example, the installation of —CT_3 enables three tritium atoms to

be simultaneously incorporated, allowing rapid access to radioligands with significant molar activities. At the present time, however, the state-of-the-art technology for radiosynthesis remains the classical S_N2 mechanism between phenols or related *N*-nucleophiles with methyl electrophiles (i.e. ^{11}C- or ^{3}H-methyl halides)[15,16]. While this simple alkylation protocol has long been exploited for radioligand development, it has traditionally suffered from the issue of selectivity in drug molecule functionalization. For example, drugs that bear multiple nitrogen sites can often participate in serial methylation or quaternization, a chemoselectivity problem which must be suppressed via lengthy protecting group strategies (which further diminish the likelihood for success of radioisotopic labeling).

As of 2018, more than 65% of top-selling small molecule therapeutics possess one or more —CH_3 groups *bound to another carbon position* (Fig. 1b)[17]. Moreover, as methyl groups are among the most prevalent structural elements found in bioactive molecules, it is surprising that no general technology exists that allows methyl radiolabels to be installed onto aryl or alkyl groups within drug molecules. Given that long established C—C cross-coupling technologies (e.g. Stille, Suzuki, and Negishi couplings) that allow methyl group installation have become a mainstay technology within pharmaceutical discovery, it is remarkable to consider that such approaches have been largely forgone in radioisotopic labeling. While palladium-mediated methods have been developed for aryl and alkyl ^{11}C-methylation with [^{11}C]-iodomethane, the challenging synthesis of organometallic precursors (e.g., aryl stannanes, boronic acids, and alkyl-BBNs), the high reaction temperatures, and strategic protecting group manipulations hamper adaptation of these technologies[16]. More critically, these protocols are not broadly translatable to tritiation due to the volatility and facile radiolysis of [CT_3]iodomethane[18-20]. To bridge this gap, we recognized that the late-stage, functional group-tolerant radioisotopic aryl and alkyl methylation of a stable and easily accessible precursor would be particularly attractive. This methodology would enable the rapid radiosynthesis and discovery of PET radioligands for CNS therapeutic development. Furthermore, the development of an alkyl ^{11}C-methylation strategy would be highly enabling for studying previously inaccessible, novel radioligands.

Metallaphotoredox catalysis has emerged as a powerful platform for facilitating difficult C—C bond-forming reactions[21]. Recently, we reported a metallaphotoredox cross-electrophile coupling strategy mediated by silyl radical activation of alkyl halides[22,23]. This transformation is enabled by the merger of nickel catalysis, photoredox catalysis, and a photocatalytically-generated supersilyl radical intermediate. As this transformation is performed under exceptionally mild conditions and exhibits a broad substrate scope, we sought to develop a general approach to tritium and carbon-11 labeling via a metallaphotoredox-catalyzed cross-electrophile methylation of aryl and alkyl bromides (Fig. 1c).

We first aimed to develop a tritium labeling methodology using the model substrate Celebrex-Br (**2**), which upon methylation would furnish the tritiated pharmaceutical, [^{3}H]Celebrex (**[^{3}H]3**) (Fig. 2). To support sub-nanomolar ligand binding studies and in vitro autoradiography for PET radioligand development programs (requiring molar activities greater than 50 Ci mmol^{-1}), we sought to obtain greater than 10% radiochemical yield (RCY)[3]. The tritritiomethyl source was selected as the limiting reagent due to safety and

cost considerations. We identified commercially available methylating reagent [CT_3]methyl 1-naphthalenesulfonate (CT_3ONp, **1**) as a suitable methylating reagent which, due to its stability and non-volatility compared to [CT_3]iodomethane or tritium gas, allows for broader use in research laboratories[24]. A lithium bromide additive was employed to generate CT_3Br in situ via a Finkelstein-like reaction from CT_3ONp as well as to promote silyl radical formation (Fig. S1) and a polar solvent system, dimethylacetamide (DMA)/toluene, was chosen in order to solubilize complex pharmaceuticals (Fig. S2). As the reaction needs to be performed on a micromole scale, our protocol was developed to work under dilute conditions (0.01M) such that an appreciable volume of delivered the tritiated products in good yields (33–49% yield). In these cases, additional lithium bromide was necessary to reduce the formation of oxidized byproducts, potentially through the preferential oxidation of bromide over amines. Heteroaryl bromides such as bromopyrazines (**[^{3}H]14**) and 2- or 3-bromopyridines (**[^{3}H]12**, **[^{3}H]13**, and **[^{3}H]15**) coupled in synthetically useful yields (28–68% yield). For more activated aryl bromide substrates where rapid consumption of the haloarene was observed (**[^{3}H]11**, **[^{3}H]14**, **[^{3}H]15**), using acetone as solvent and solvent (125 μL) could be used for ease of handling. After 12 hours of blue light irradiation in the integrated photoreactor[25] under the optimized reaction conditions (see Supplementary Materials for details), [^{3}H]Celebrex was isolated in 62% RCY. As hypothesized, the molar activity of the starting CT_3ONp reagent (78.6 Ci mmol^{-1}) was faithfully incorporated into the target drug, affording [^{3}H]Celebrex (**[^{3}H]3**) with a high molar activity of 78.9 Ci mmol^{-1}. Additionally, control reactions conducted with unlabeled CH_3ONp showed that all reaction components were necessary (Fig. S3, S4).

With the optimized conditions in hand, we sought to evaluate the generality of the silyl radical-mediated CT_3-labeling protocol by synthesizing a variety of tritiated pharmaceuticals from their aryl bromide precursors (Fig. 2). A broad range of electronically differentiated aryl bromides coupled efficiently in this protocol (**[^{3}H]4**, **[^{3}H]5**, **[^{3}H]6**, and **[^{3}H]7**, 50–68% yield). Protic functionality such as amides (**[^{3}H]4**, **[^{3}H]11**, **[^{3}H]13**, and **[^{3}H]14**), sulfonyl ureas (**[^{3}H]7**, **[^{3}H]8**), phenols (**[^{3}H]9**), and free benzoic acids (**[^{3}H]13**), as well as ortho substituents (**[^{3}H]4**, **[^{3}H]11**, **[^{3}H]13**, and **[^{3}H]14**), are well tolerated. Perhaps most notably, substrates possessing tertiary amines (**[^{3}H]9**, **[^{3}H]10**, **[^{3}H]12**), traditionally challenging functional groups for photoredox catalysis given their low oxidation potential (E_{pa} [Et_3N / $Et_3N^{\bullet+}$] = +0.78 V vs saturated calomel electrode (SCE) in CH_3CN)[26], lithium iodide in lieu of lithium bromide was beneficial through generation of the more reactive CT_3I and consequent matching of the consumption rates of the two coupling partners. Gratifyingly, we found that tritiated analogs of reported PET radioligands could be synthesized in high molar activity using this coupling manifold (**[^{3}H]16**, **[^{3}H]17**, and **[^{3}H]18**, 42–62% yield).

Given the recently demonstrated silyl radical-mediated C_{sp^3}–C_{sp^3} coupling of alkyl bromides[23], we questioned whether —CT_3 groups could be introduced at aliphatic positions of pharmaceuticals. Excitingly, we found primary (**[^{3}H]20**) and secondary alkyl bromides (**[^{3}H]19** and **[^{3}H]21**) to be competent coupling partners under these reaction conditions (8–28% yield), demonstrating, to the best of our knowledge, the first example of tritium labeling via an alkyl–alkyl cross-coupling strategy.

From the outset, we recognized the different challenges associated with carbon-11 labeling compared to tritium chemistry. Namely, the short half-life of carbon-11 (20 minutes) necessitates a rapid reaction with a simple purification procedure for a synthesis time under 60 minutes. Furthermore, the limited pool of radiolabeled starting materials required the use of simple reagents such as [^{11}C]MeI or [^{11}C]MeOTf. With the same Celebrex-Br precursor (**2**), we evaluated the feasibility of carbon-11 labeling with [^{11}C]iodomethane (**22**) (Fig. 3a). Through optimization, we found that introducing tetrabutylammonium iodide increased the reaction efficiency potentially by suppressing formation of the less reactive [^{11}C]bromomethane mediated by bromide anion generated during the course of the reaction (Fig. S5, S6). The labeling was performed by bubbling [^{11}C] iodomethane in a stream of helium gas through the reaction mixture containing all other reaction components. Conducting the reaction with 130–165 mCi (4.81–6.11 GBq) of [^{11}C]iodomethane for 5 minutes under blue light irradiation followed by HPLC purification afforded [^{11}C]Celebrex (**[^{11}C]3**) after 22.7 minutes in 48 ± 4% (n = 3) decay-corrected yield (dc) (22% non-decay-corrected, ndc) (see Supplementary Materials for experimental details). We attribute this shorter reaction time to the super-stoichiometric excess of reagents relative to the nanomole quantities of [^{11}C]MeI, resulting in pseudo-first order reaction kinetics.

Next, we turned to examine the generality of the silyl radical-mediated carbon-11 labeling using selected examples from the tritiation scope (Fig. 3a). Substrates for which the corresponding organostannanes would be unstable or challenging to synthesize, such as complex molecule **[^{11}C]11** and 2-methylpyridine-containing **[^{11}C]15**, are methylated with [^{11}C]iodomethane in sufficient yields to support in vivo PET imaging or biodistribution studies (26% and 44% yield, respectively). The previous synthesis of **[^{11}C]16** relies on methylation of the corresponding bis-protected arylstannane in 19% yield (dc); however, no product was observed with the unprotected purine ring[27]. Under our protocol, however, methylation directly from the unprotected aryl bromide affords **[^{11}C]16** in 21% yield, avoiding time-consuming protecting group strategies. Additionally, **[^{11}C]17** and [^{11}C]UCB-J (**[^{11}C]18**) are generated in excellent yields (44% and 58% yield, respectively)[28,29].

Carbon-11 methylation at alkyl positions through cross-coupling has been a particularly underdeveloped field, only having been demonstrated with primary 9-BBN reagents[30]. By using DMA as solvent and without added tetrabutylammonium iodide, a variety of alkyl bromides were coupled efficiently (**[^{11}C]19**, **[^{11}C]20**, and **[^{11}C]21**, 13–36% yield). Notably, free phenols were tolerated in our transformation by virtue of the mild reaction conditions (**[^{11}C]20** and **[^{11}C]21**). To highlight the utility of this approach, we aimed to develop an improved synthesis of [^{11}C]PHNO (**[^{11}C]20**), a well-studied PET tracer previously prepared in three radiochemical steps employing protecting group manipulations and pyrophoric reagents[31]. In one step from a stable alkyl bromide precursor, [^{11}C]PHNO was conveniently prepared in sufficient yields for in vivo imaging studies (13 ± 2% yield). Lastly, SB-269970, a specific 5-HT$_7$ antagonist which previously required derivatization to introduce a handle for fluorine-18 labeling[32], was successfully carbon-11-labeled (**[^{11}C]21**).

To demonstrate the utility of this carbon-11 labeling protocol for in vivo PET imaging applications, a non-human primate PET study was conducted with [^{11}C]UCB-J (**[^{11}C]18**), an investigational PET radioligand for measuring synaptic density in neurodegenerative

disorders (Fig. 3b, S12, and S13). To ensure reproducibility of this method, our ^{11}C-labeling protocol was independently performed by Siemens Molecular Imaging Biomarker Research in North Wales, PA with a robotic, remote-controlled radiosynthetic setup for the preparation of [^{11}C]UCB-J. The procedure was validated, yielding 72 ± 10% RCY (dc) and 19 ± 2% RCY (ndc) (n = 4) of the radioligand. Remarkably, up to 140 mCi (5.18 GBq) of isolated **[^{11}C]18** could be synthesized using this operationally simple reaction protocol with molar activities ranging 1.03–3.00 Ci μmol^{-1} (Fig. 3b), activities well above the threshold required to perform human PET studies (10 mCi, 1 Ci μmol^{-1})[12,33]. Consistent with preclinical data in rhesus monkeys[28], baseline PET scans with 11.8 mCi (437 MBq) of [^{11}C]UCB-J showed rapid uptake into the brain, peaking at 10–30 minutes and with moderate washout of the radiotracer by the end of the 90-minute scan (Fig. S12, and S13). Importantly, these results demonstrate the robustness of the radiolabeling procedure in the hands of multiple practitioners and its utility in pre-clinical PET imaging.

Routine clinical production of carbon-11 PET-imaging agents is carried out on automated radiosynthesis modules within a cGMP environment. To demonstrate the feasibility of applying this method within a relevant context, we adapted a Synthra MeIplus module with the integrated photoreactor and conducted a fully automated production of [^{11}C]Celebrex (**[^{11}C]3**). Under identical reaction conditions, the fully automated radiosynthesis of [^{11}C]Celebrex (**[^{11}C]3**) from Celebrex-Br was complete in 29 minutes in 35% RCY (dc, n = 1), yielding 43.2 mCi of **[^{11}C]3** with high molar activity (2.237 Ci μmol^{-1}) (Fig. 3c). Furthermore, ICP-MS (inductively coupled plasma mass spectrometry) analysis of the isolated radioligand **[^{11}C]18** indicated a nickel and iridium content of 33 ppb and 1 ppb respectively, in line with international recommendations of elemental impurities for samples injected into humans[34]. Taken together, this data strongly supports the feasibility of utilizing this labeling methodology for clinical imaging in humans.

To further underscore the utility and generality of this cross-coupling manifold, we endeavored to incorporate all medicinally-relevant carbon and hydrogen isotopes into a given pharmaceutical agent (Fig. 4). Each of these isotopologs serves a unique purpose in the drug development process. Carbon-14-labeled compounds are valuable for tracking the fate of a chemical compound through ADME (absorption-distribution-metabolism-excretion) studies[35], benzylic deuteration allows for slowed metabolism of pharmaceutical agents[36], and incorporation of $^{13}CD_3$ groups generates [M+4] mass compounds which are particularly useful as mass spectrometry standards[37]. As demonstrated with the anti-diabetic medication Glipizide, these isotopologs, including the tritiated and carbon-11 analogs, are accessed in excellent yields using the same general coupling strategy (**[^{3}H]23**, **[^{2}H]23**, **[^{13}C^{2}H]23**, **[^{14}C]23**, and **[^{11}C]23**).

In summary, we have developed a broadly useful radioisotopic methylation protocol allowing access to novel radioligands from easily accessibly organobromide precursors. Furthermore, we have demonstrated this methodology is amenable to preclinical PET imaging and have provided support for potential translation to human clinical imaging through automated radiosynthesis. We anticipate that this powerful platform will enable a more rapid discovery of PET radiotracers for addressing unmet clinical needs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

The data supporting the findings of this study are available within the paper and its Supplementary Information.

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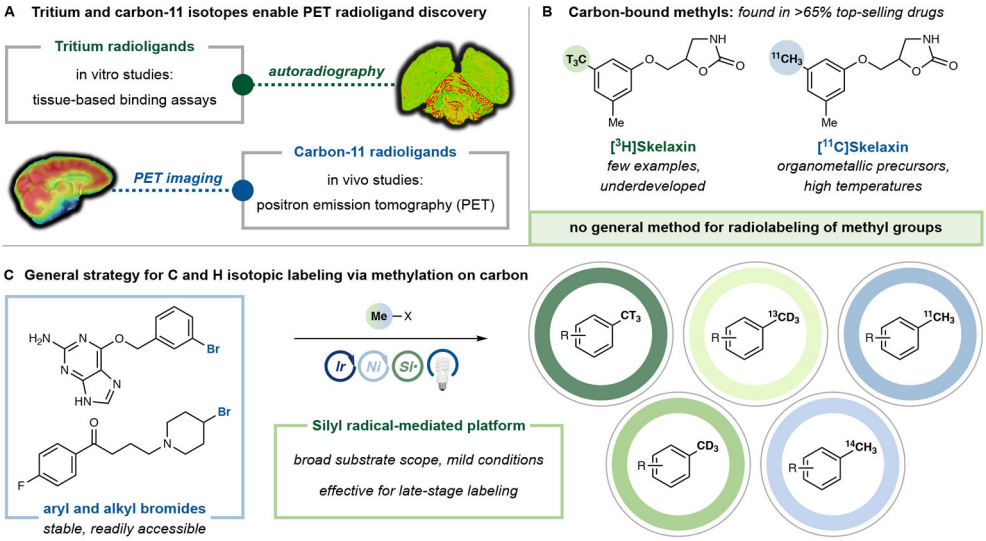

Fig. 1 |. General approach to radioligand synthesis.

(**A**) Tritium and carbon-11 isotopologs are critical for assessing in vitro and in vivo radioligand properties. (**B**) Strategies for tritiation and carbon-11 labeling at methyl groups bound to carbon are limited despite their prevalence in bioactive molecules. (**C**) Proposed approach to radioligand synthesis from aryl or alkyl bromides using metallaphotoredox catalysis. Me, methyl; X, heteroatom.

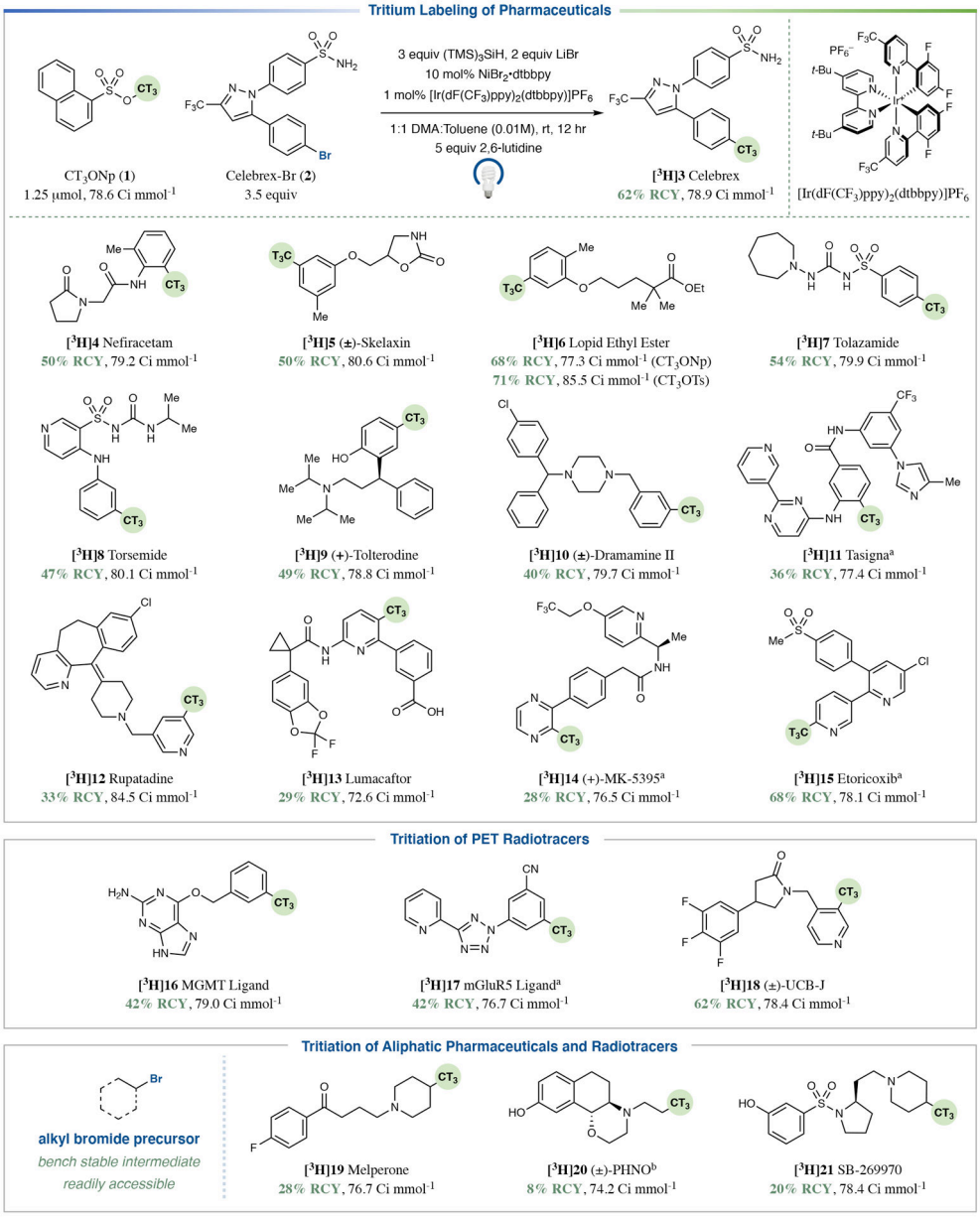

Fig. 2 | Scope of high molar activity tritiation.

All experiments reflect isolated radiochemical yields (RCY) with n=1. Reaction conditions: CT_3ONp (100 mCi, 1.25 µmol, 78.6–80.0 Ci mmol^{-1}), lithium bromide (2–20 equiv), integrated photoreactor (450 nm, 50% intensity), 4–12 hours. See the supplementary materials for experimental details. [a]With acetone (0.01M), lithium iodide (5 equiv), $NiBr_2$•dtbbpy (40 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (4 mol%). [b]With alkyl bromide TFA salt (7 equiv), lithium iodide (1 equiv), $NiBr_2$•dtbbpy (80 mol%), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (8 mol%), supersilane (6 equiv), 2,6-lutidine (10 equiv), DMA (5mM). Me, methyl; Et, ethyl; CT_3–ONp, [CT_3]-methyl 1-naphthalenesulfonate; $dF(CF_3)ppy$, 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy, 4,4'-di-*tert*-butyl-2,2'-bipyridine; TMS, trimethylsilyl; hr, hours; RCY, radiochemical yield; OTs, 4-

toluenesulfonate; MGMT, O^6-methylguanine DNA methyltransferase; mGluR5, metabotropic glutamate receptor type 5; DMA, dimethylacetamide.

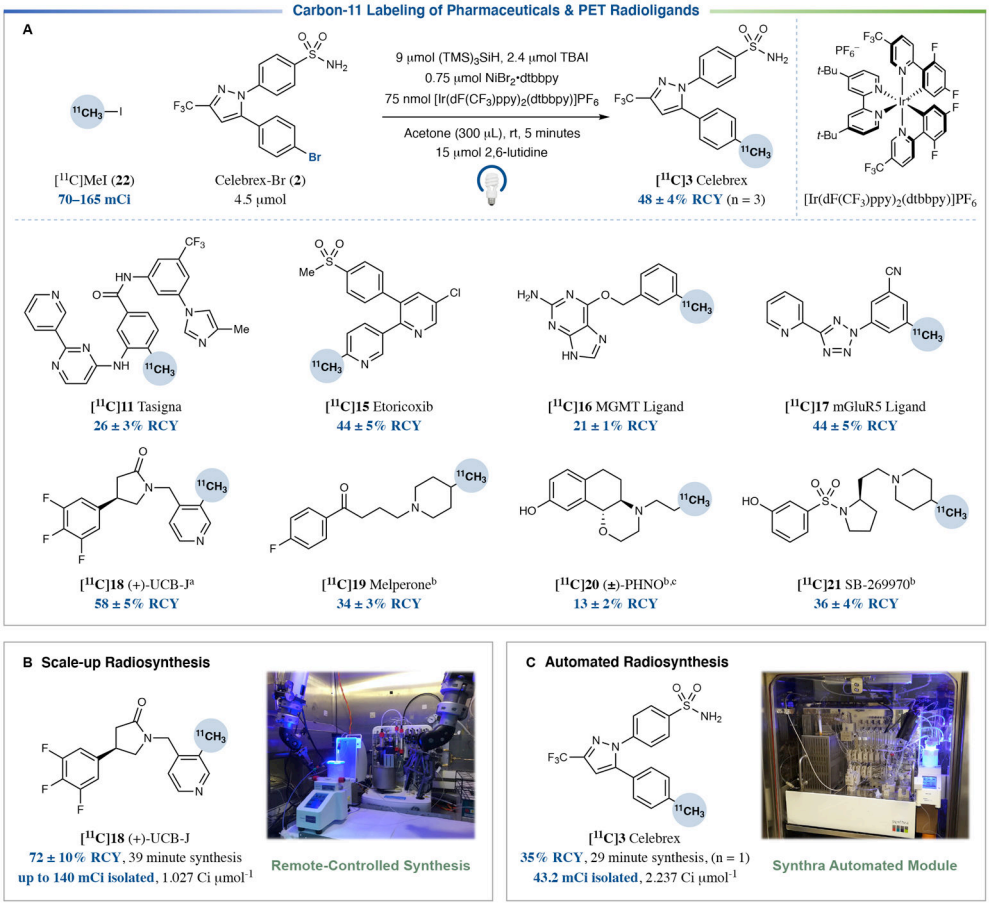

Fig. 3 |. Scope of carbon-11 radiolabeling.

(**A**) Scope of high activity carbon-11 labeling. All radiochemical yields (RCY) are isolated via semi-preparative HPLC, decay-corrected to starting activity from the end of [^{11}C]MeI production, and include standard deviation averaged over 3+ experiments unless otherwise noted. All reactions were conducted using the integrated photoreactor (450 nm, 100% intensity). See the supplementary materials for experimental details. [a]With 2.25 µmol aryl bromide. [b]With DMA as solvent (300 µL), no TBAI additive. [c]With 9 µmol alkyl bromide TFA salt, $NiBr_2$•dtbbpy (1.5 µmol), $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (0.15 µmol). (**B**) Scale-up of [^{11}C]UCB-J through remote-controlled radiosynthesis for preclinical PET imaging. Synthesis time starts at [^{11}C]MeI production and ends at product isolation. (**C**) Fully automated radiosynthesis of [^{11}C]Celebrex using a Synthra MeIplus module combined with the integrated photoreactor. TBAI, tetrabutylammonium iodide.

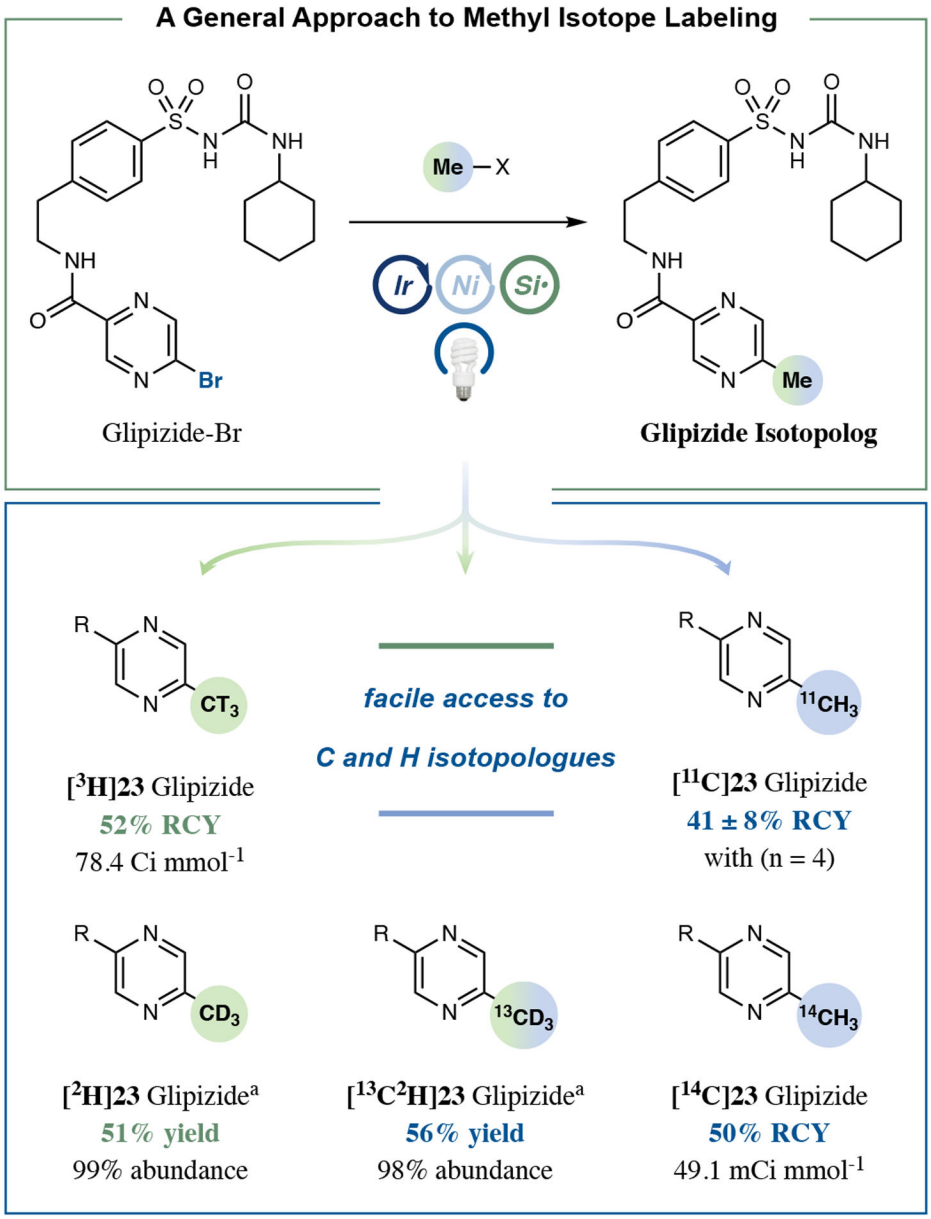

Fig. 4 |. Synthesis of various carbon and hydrogen isotopologs.
With [^{14}C]methyl 2-naphthalenesulfonate (10 mCi, 51 mCi mmol^{-1}). [a]With aryl bromide as limiting reagent. See the supplementary materials for experimental details.