

Metallaphotoredox aryl and alkyl radiomethylation for PET ligand discovery

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Positron emission tomography (PET) radioligands (radioactively labelled tracer compounds) are extremely useful for in vivo characterization of central nervous system drug candidates, neurodegenerative diseases and numerous oncology targets¹. Both tritium and carbon-11 radioisotopologues are generally necessary for in vitro and in vivo characterization of radioligands², yet there exist few radiolabelling protocols for the synthesis of either, inhibiting the development of PET radioligands. The synthesis of such radioligands also needs to be very rapid owing to the short half-life of carbon-11. Here we report a versatile and rapid metallaphotoredox-catalysed method for late-stage installation of both tritium and carbon-11 into the desired compounds via methylation of pharmaceutical precursors bearing aryl and alkyl bromides. Methyl groups are among the most prevalent structural elements found in bioactive molecules, and so this synthetic approach simplifies the discovery of radioligands. To demonstrate the breadth of applicability of this technique, we perform rapid synthesis of 20 tritiated and 10 carbon-11-labelled complex pharmaceuticals and PET radioligands, including a one-step radiosynthesis of the clinically used compounds [¹¹C]UCB-J and [¹¹C]PHNO. We further outline the direct utility of this protocol for preclinical PET imaging and its translation to automated radiosynthesis for routine radiotracer production in human clinical imaging. We also demonstrate this protocol for the installation of other diverse and pharmaceutically useful isotopes, including carbon-14, carbon-13 and deuterium.

The incorporation of radioactive nuclides into bioactive molecules has revolutionized the field of pharmaceutical research and development^{3–5}. Among known radiolabelling applications, PET is an invaluable clinical tool that enables minimally invasive visualization of PET radioligands, in vivo¹. These isotope-enriched ligands serve as informative biomarkers for oncology⁶ and neurological disorders⁷, as well as critical tools for studying brain target occupancy relationships for central nervous system drug development^{8–11}. At present, small-molecule PET imaging primarily relies on the use of fluorine-18 (¹⁸F, *t*_{1/2} = 110 min) and carbon-11 (¹¹C, *t*_{1/2} = 20 min). However, the systematic incorporation of carbon-11 radionuclides into organic architectures remains a long-standing synthetic problem owing to a series of chemical and operational challenges. For example, the translation of non-radioactive ¹²C chemistry to ¹¹C radiolabelling is broadly hampered by: (1) the short 20-min half-life of carbon-11, rendering most synthetic protocols outside the realm of operational utility with respect to experimental timeframes, (2) the availability of ¹¹C-precursor starting materials, (3) 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 (4) the requirement for operationally simple and robust protocols

that are insensitive to air and moisture^{4,12,13}. Indeed, although many methods for ¹²C-installation have been invented throughout the history of organic chemistry, most are unfortunately unsuited to the challenges of radioisotopic ¹¹C labelling.

Although the incorporation of carbon-11 is a necessity for in vivo PET imaging studies, the development of these PET 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, respectively². In this context, it has long been established that tritium (³H 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 labelling in these applications is the need to incorporate 2–4 tritium atoms per molecule (molar activities of 50–100 Ci mmol^{−1}), a requirement that 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, although both tritium and carbon-11 isotopologues of any pharmaceutical are critical for the discovery of PET radioligands, the radiosynthesis of such ligands remains a fundamental challenge, limiting drug discovery. As such, a radiolabelling

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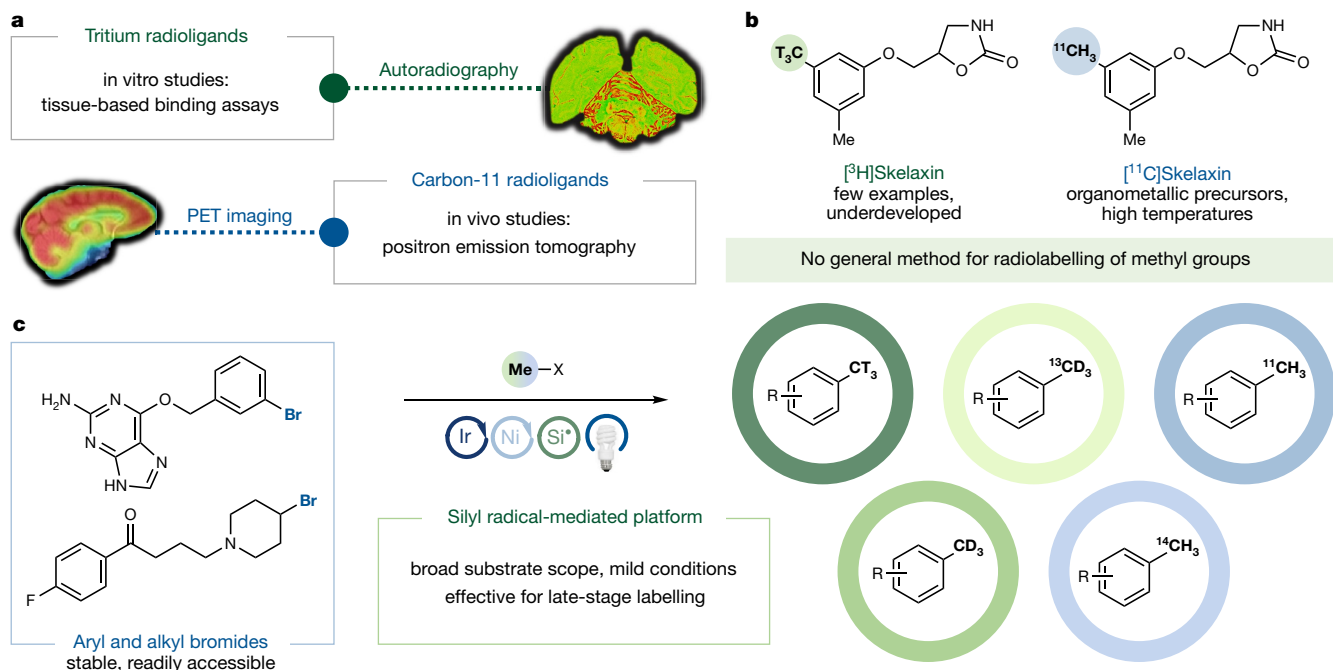


Fig. 1 | General approach to radioligand synthesis. **a**, Tritium and carbon-11 isotopologues are critical for assessing in vitro and in vivo radioligand properties and enable PET radioligand discovery. **b**, Carbon-bound methyls are found in more than 65% of top-selling drugs, such as Skelaxin. Strategies for

tritiation and carbon-11 labelling at methyl groups bound to carbon are limited despite their prevalence in bioactive molecules. **c**, Proposed general approach for C and H isotopic labelling from aryl or alkyl bromides using metallaphotoredox catalysis. Me, methyl; X, heteroatom.

strategy that allows the incorporation of both tritium and carbon-11 would dramatically affect radioligand design in the context of the therapeutic targets of neurological disorders as well as enabling biomarker discovery for cancer and neurodegenerative diseases.

A valuable yet versatile architectural element within organic radiolabelling, 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 high molar activities. At present, however, the state-of-the-art technology for radiosynthesis remains the classical S_N2 mechanism between phenols or related *N*-nucleophiles with methyl electrophiles (that is, ^{11}C - or 3H -methyl halides)^{15,16}. This simple alkylation protocol has long been exploited for radioligand development, but 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 that must be suppressed via lengthy protecting-group strategies (which further diminish the likelihood of success in radioisotopic labelling).

As of 2018, more than 65% of top-selling small-molecule therapeutics possess one or more $-CH_3$ groups bound to another carbon position¹⁷ (Fig. 1b). 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 (for example, Stille, Suzuki and Negishi couplings) that allow methyl group installation have become a mainstay technique within pharmaceutical discovery, it is remarkable to consider that such approaches have been little used in radioisotopic labelling. Although palladium-mediated methods have been developed for aryl and alkyl ^{11}C -methylation with $[^{11}C]$ iodomethane, the challenging synthesis of organometallic precursors (for example, aryl stannanes, boronic acids and alkyl-BBNs), and the high reaction temperatures and strategic protecting-group manipulations required hamper adaptation of these technologies¹⁶. More critically,

these protocols are not broadly translatable to tritiation owing 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 central nervous system therapeutic development. Furthermore, the development of an alkyl ^{11}C -methylation strategy would enable the study of previously inaccessible radioligands.

Metallaphotoredox catalysis has emerged as a powerful platform for facilitating difficult C–C bond-forming reactions²¹. 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 allows the use of a broad range of substrates, we sought to develop a general approach to tritium and carbon-11 labelling via a metallaphotoredox-catalysed cross-electrophile methylation of aryl and alkyl bromides (Fig. 1c).

We first aimed to develop a tritium-labelling methodology using the model substrate Celebrex-Br (**2**), which upon methylation would furnish the tritiated pharmaceutical, $[^3H]$ Celebrex ($[^3H]$ **3**) (Fig. 2). To support sub-nanomolar ligand-binding studies and in vitro autoradiography for PET radioligand development programmes (requiring molar activities greater than 50 Ci mmol^{-1}), we sought to obtain a radiochemical yield (RCY) greater than 10% (ref. ³). The tritritiomethyl source was selected as the limiting reagent owing to safety and cost considerations. We identified the commercially available methylating reagent $[CT_3]$ methyl 1-naphthalenesulfonate (CT_3ONp , **1**) as a suitable methylating reagent, which, owing to its stability and non-volatility compared to $[CT_3]$ iodomethane or tritium gas, allows for broader use in research laboratories²⁴. 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 (Supplementary Fig. 1) and

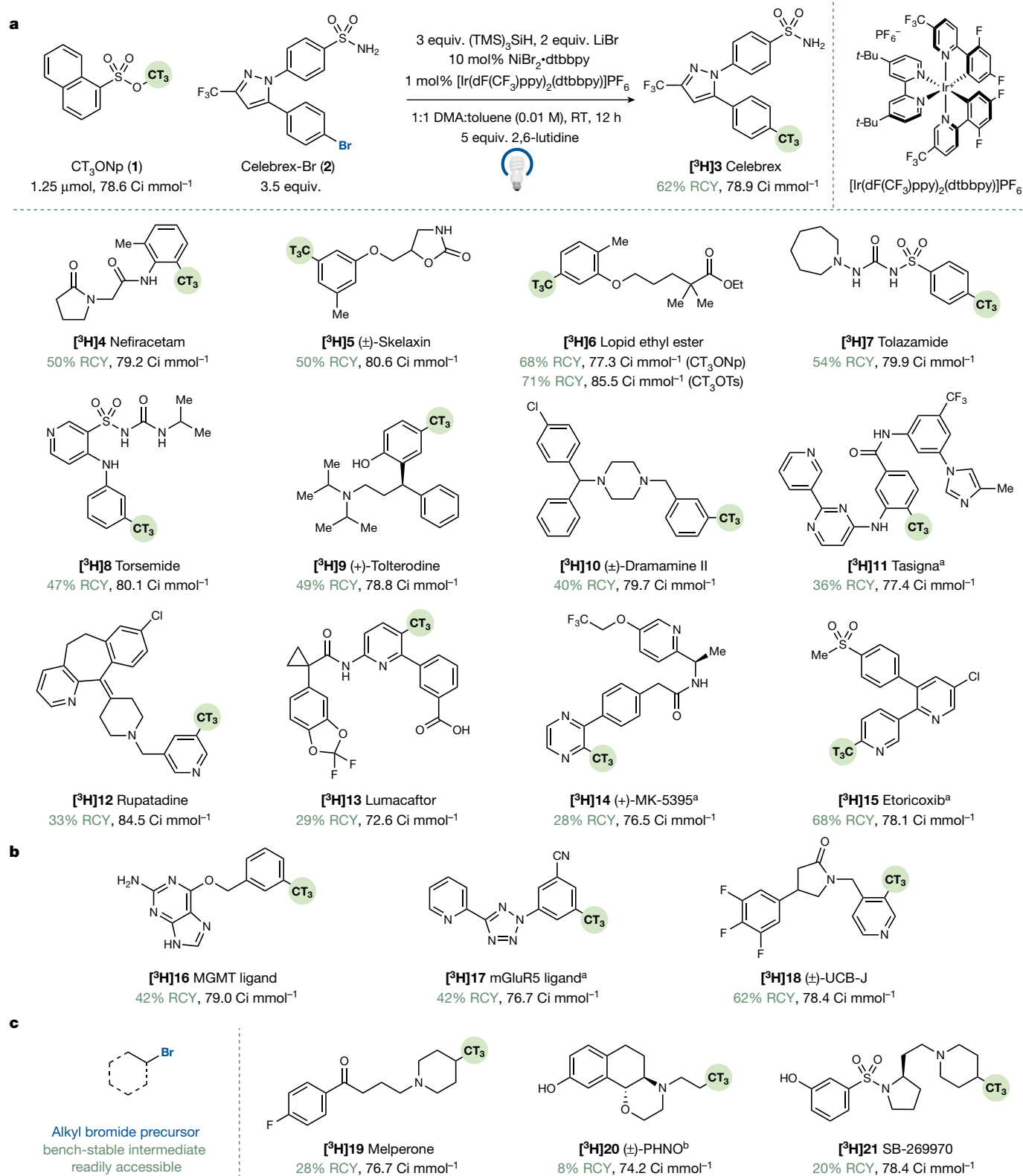


Fig. 2 | Scope of high-molar-activity tritiation. **a**, Tritium labelling of pharmaceuticals. **b**, Tritiation of PET radiotracers. **c**, Tritiation of aliphatic pharmaceuticals and radiotracers. All experiments reflect isolated RCY values with $n = 1$. Reaction conditions: CT₃ONp (100 mCi, 1.25 μmol, 78.6–80.0 Ci mmol⁻¹), lithium bromide (2–20 equiv.), integrated photoreactor (450 nm, 50% intensity), 4–12 h. See the Supplementary Information for experimental details. ^aWith acetone (0.01 M), lithium iodide (5 equiv.), NiBr₂·dtbbpy (40 mol%), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (4 mol%). ^bWith alkyl bromide TFA salt (7 equiv.),

lithium iodide (1 equiv.), NiBr₂·dtbbpy (80 mol%), [Ir(dF(CF₃)ppy)₂(dtbbpy)]PF₆ (8 mol%), supersilane (6 equiv.), 2,6-lutidine (10 equiv.), DMA (5 mM), Me, methyl; Et, ethyl; CT₃-ONp, [CT₃]-methyl 1-naphthalenesulfonate; dF(CF₃)ppy, 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy, 4,4'-di-*tert*-butyl-2,2'-bipyridine; TMS, trimethylsilyl; OTs, 4-toluenesulfonate; MGMT, O⁶-methylguanine DNA methyltransferase; mGluR5, metabotropic glutamate receptor type 5; DMA, dimethylacetamide.

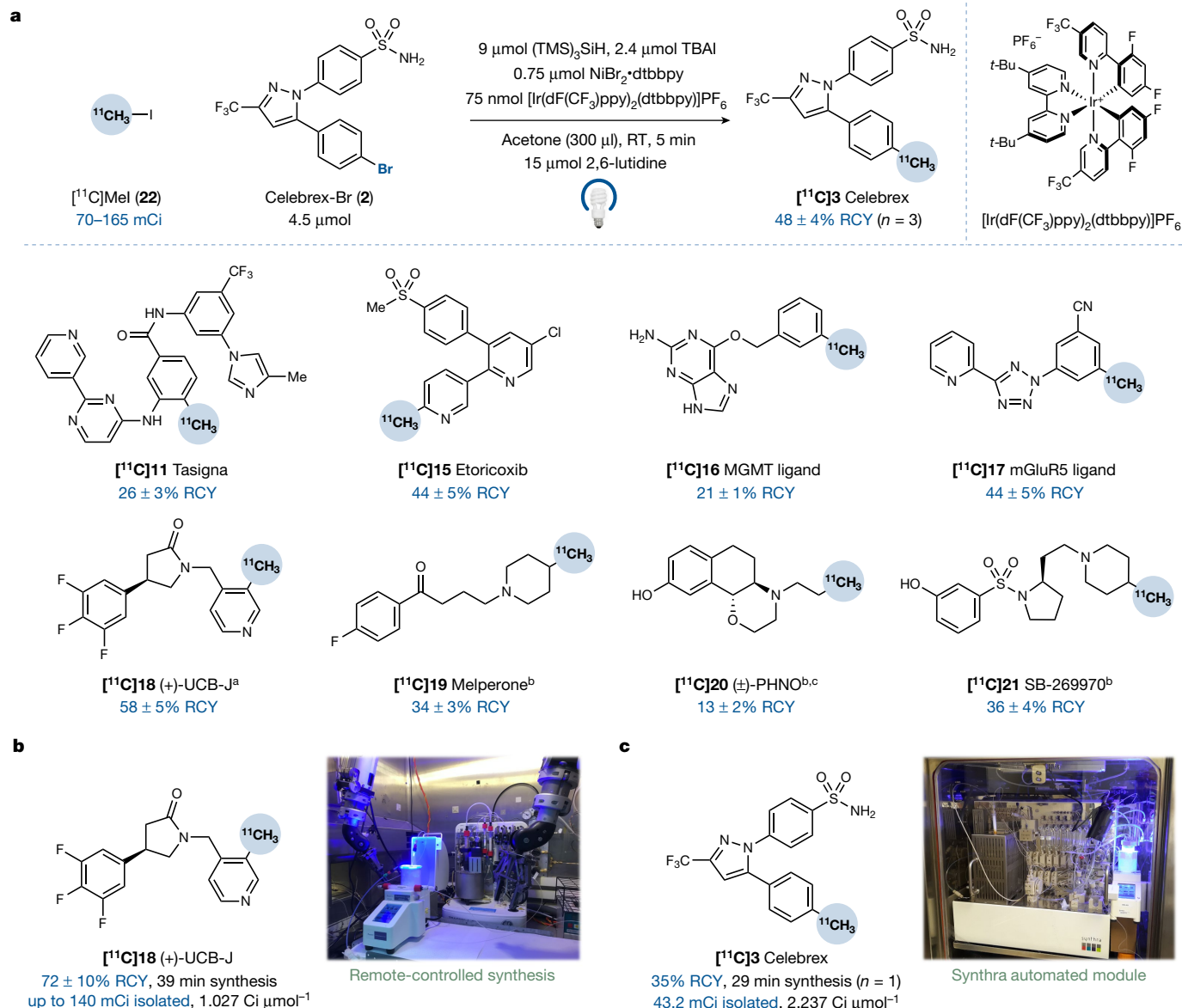


Fig. 3 | Scope of carbon-11 radiolabelling. a, Scope of high-activity carbon-11 labelling of pharmaceuticals and PET radioligands. All RCY values are isolated via semi-preparative HPLC, decay-corrected to starting activity from the end of $[^{11}\text{C}]\text{MeI}$ production, and include standard deviation 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. ^aWith 2.25 μmol aryl bromide. ^bWith DMA as

solvent (300 μl), no TBAI additive. ^cWith 9 μmol alkyl bromide TFA salt, $\text{NiBr}_2 \cdot \text{dtbbpy}$ (1.5 μmol), $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (0.15 μmol). **b**, Scale-up of $[^{11}\text{C}]\text{UCB-J}$ through remote-controlled radiosynthesis for preclinical PET imaging. Synthesis time starts at $[^{11}\text{C}]\text{MeI}$ production and ends at product isolation. **c**, Fully automated radiosynthesis of $[^{11}\text{C}]\text{Celebrex}$ using a Synthra Melplus module combined with the integrated photoreactor. TBAI, tetrabutylammonium iodide.

a polar solvent system, dimethylacetamide (DMA)/toluene, was chosen in order to solubilize complex pharmaceuticals (Supplementary Fig. 2). Because the reaction needs to be performed on a micromole scale, our protocol was developed to work under dilute conditions (0.01 M) such that an appreciable volume of solvent (125 μl) could be used for ease of handling. After 12 h of blue light irradiation in the integrated photoreactor²⁵ under the optimized reaction conditions (see Supplementary Information for details), $[^3\text{H}]\text{Celebrex}$ was isolated at 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 $[^3\text{H}]\text{Celebrex}$ ($[^3\text{H}]\text{3}$) with a high molar activity of 78.9 Ci mmol⁻¹. Additionally, control reactions conducted with unlabelled CH_3ONp showed that all reaction components were necessary (Supplementary Figs. 3, 4).

With the optimized conditions established, we sought to evaluate the generality of the silyl radical-mediated CT_3 -labelling 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 ($[^3\text{H}]\text{4}$, $[^3\text{H}]\text{5}$, $[^3\text{H}]\text{6}$ and $[^3\text{H}]\text{7}$, 50%–68% yield). Protic functionality such as amides ($[^3\text{H}]\text{4}$, $[^3\text{H}]\text{11}$, $[^3\text{H}]\text{13}$ and $[^3\text{H}]\text{14}$), sulfonyl ureas ($[^3\text{H}]\text{7}$, $[^3\text{H}]\text{8}$), phenols ($[^3\text{H}]\text{9}$) and free benzoic acids ($[^3\text{H}]\text{13}$), as well as ortho substituents ($[^3\text{H}]\text{4}$, $[^3\text{H}]\text{11}$, $[^3\text{H}]\text{13}$ and $[^3\text{H}]\text{14}$), are well tolerated. Perhaps most notably, substrates possessing tertiary amines ($[^3\text{H}]\text{9}$, $[^3\text{H}]\text{10}$, $[^3\text{H}]\text{12}$), which are traditionally challenging functional groups for photoredox catalysis given their low oxidation potential ($E_{\text{pa}}[\text{Et}_3\text{N}/\text{Et}_3\text{N}^+] = +0.78$ V versus saturated calomel electrode (SCE) in CH_3CN)²⁶, delivered the tritiated products in good yields (33%–49% yield). In these cases, additional

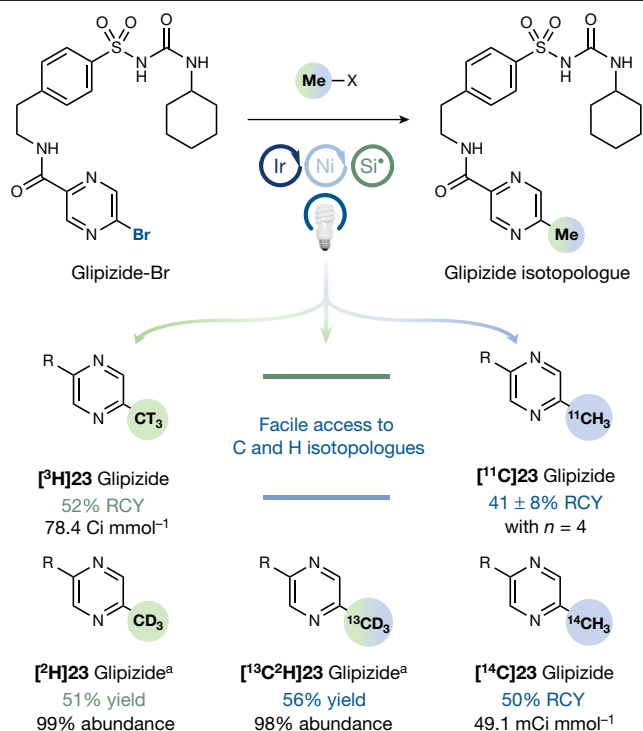


Fig. 4 | Synthesis of various carbon and hydrogen isotopologues.

A general approach to methyl isotope labelling as demonstrated with the pharmaceutical glipizide. Carbon-14 labelling was performed with [^{14}C]methyl 2-naphthalenesulfonate (10 mCi, 51 mCi mmol $^{-1}$). ^aWith aryl bromide as limiting reagent. See the Supplementary Information for experimental details.

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 ([^3H]14) and 2- or 3-bromopyridines ([^3H]12, [^3H]13 and [^3H]15) coupled in synthetically useful yields (28–68% yield). For more activated aryl bromide substrates where rapid consumption of the haloarene was observed ([^3H]11, [^3H]14 and [^3H]15), using acetone as solvent and 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 analogues of reported PET radioligands could be synthesized in high molar activity using this coupling manifold ([^3H]16, [^3H]17 and [^3H]18, in 42%–62% yield).

Given the recently demonstrated silyl radical-mediated $\text{C}_{\text{sp}^3}\text{--}\text{C}_{\text{sp}^3}$ coupling of alkyl bromides²³, we questioned whether $-\text{CT}_3$ groups could be introduced at aliphatic positions of pharmaceuticals. Excitingly, we found primary ([^3H]20) and secondary alkyl bromides ([^3H]19 and [^3H]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 labelling via an alkyl–alkyl cross-coupling strategy.

From the outset, we recognized the different challenges associated with carbon-11 labelling compared to tritium chemistry. Namely, the short half-life of carbon-11 (20 min) necessitates a rapid reaction with a simple purification procedure for a synthesis time under 60 min. Furthermore, the limited pool of radiolabelled 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 labelling 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 (Supplementary Figs. 5, 6). The labelling 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 min under blue light irradiation followed by high-performance liquid chromatography (HPLC) purification afforded [^{11}C]Celebrex ([^{11}C]3) after 22.7 min in $48 \pm 4\%$ ($n = 3$) decay-corrected yield (dc) (22% non-decay-corrected, ndc) (see Supplementary Information 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 examined the generality of the silyl radical-mediated carbon-11 labelling using selected examples from tritiation (Fig. 3a). Substrates for which the corresponding organostannanes would be unstable or challenging to synthesize, such as the complex molecule [^{11}C]11 and the 2-methylpyridine-containing [^{11}C]15, are methylated with [^{11}C]iodomethane in sufficient yields to support in vivo PET imaging or biodistribution studies (yields of 26% and 44%, 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 ring²⁷. 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%, 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 reagents³⁰. 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 reagents³¹. In one step from a stable alkyl bromide precursor, [^{11}C]PHNO was conveniently prepared in sufficient yields for in vivo imaging studies ($13 \pm 2\%$ yield). Lastly, SB-269970, a specific 5-HT $_7$ antagonist that previously required derivatization to introduce a handle for fluorine-18 labelling³², was successfully carbon-11-labelled ([^{11}C]21).

To demonstrate the utility of this carbon-11 labelling 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, Supplementary Figs. 12, 13). To ensure reproducibility of this method, our ^{11}C -labelling protocol was independently performed by Siemens Molecular Imaging Biomarker Research in North Wales, Pennsylvania, with a robotic, remote-controlled radiosynthetic setup for the preparation of [^{11}C]UCB-J. The procedure was validated, yielding $72 \pm 10\%$ RCY (dc) and $19 \pm 2\%$ 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 in the range 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 monkeys²⁸, baseline PET scans with 11.8 mCi (437 MBq) of [^{11}C]UCB-J showed rapid uptake into the brain, peaking after 10–30 min and with moderate washout of the radiotracer by the end of the 90-min scan (Supplementary Figs. 12, 13). Importantly, these results demonstrate the robustness of the radiolabelling 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 (current good manufacturing practice) environment. To demonstrate

the feasibility of applying this method within a relevant context, we adapted a Synthra Melplus module with the integrated photoreactor²⁵ and conducted a fully automated production of [¹¹C]Celebrex ([¹¹C]3). Under identical reaction conditions, the fully automated radiosynthesis of [¹¹C]Celebrex ([¹¹C]3) from Celebrex-Br was complete in 29 min in 35% RCY (dc, *n* = 1), yielding 43.2 mCi of [¹¹C]3 with high molar activity (2.237 Ci μmol⁻¹) (Fig. 3c). Furthermore, inductively coupled plasma mass spectrometry (ICP-MS) analysis of the isolated radioligand [¹¹C]18 indicated a nickel and iridium content of 33 parts per billion (ppb) and 1 ppb respectively, in line with international recommendations of elemental impurities for samples injected into humans³⁴. Taken together, this data strongly supports the feasibility of using this labeling methodology for clinical imaging in humans.

To further emphasize the utility and generality of this cross-coupling manifold, we endeavoured to incorporate all medicinally relevant carbon and hydrogen isotopes into a given pharmaceutical agent (Fig. 4). Each of these isotopologues serves a unique purpose in the drug development process. Carbon-14-labelled compounds are valuable for tracking the fate of a chemical compound through absorption–distribution–metabolism–excretion (ADME) studies³⁵, benzylic deuteration allows for slowed metabolism of pharmaceutical agents³⁶, and incorporation of ¹³CD₃ groups generates [M+4] mass compounds that are particularly useful as mass spectrometry standards³⁷. As demonstrated with the anti-diabetic medication Glipizide, these isotopologues, including the tritiated and carbon-11 analogues, are accessed in excellent yields using the same general coupling strategy ([³H]23, [²H]23, [¹³C]23, [¹⁴C]23 and [¹¹C]23).

In summary, we have developed a broadly useful radioisotopic methylation protocol allowing access to novel radioligands from easily accessible organobromide precursors. Furthermore, we have demonstrated that 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.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41586-020-3015-0>.

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Article

Methods

See the Supplementary Information for further methods.

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.

Reporting summary

Further information on research design is available in the Nature Research Reporting Summary linked to this paper.

Data availability

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

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Author contributions P.Z.M., S.R., T.J.A.G., D.H., E.D.H., I.W.D. and D.W.C.M. conceived the work. R.W.P., P.Z.M. and S.R. conducted initial optimization. R.W.P., K.T.S. and S.R. synthesized organobromide precursors. R.W.P. and K.T.S. performed and isolated labelling experiments. R.W.P., K.T.S., S.R. and D.H. developed purification conditions. T.J.A.G., S.V. and E.D.H. provided insight into experimental design. L.G. conducted the non-human primate PET imaging study and T.G.L. performed data analysis. A.S. configured and performed the fully automated radiosynthesis and H.S.L. performed data analysis. R.W.P., K.T.S., T.J.A.G. and D.W.C.M. prepared the manuscript with input from all co-authors.

Competing interests The authors declare no competing interests.

Additional information

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Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

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Data collection Pet Syngo 6.7.3 was used for the non-human primate PET imaging study. SynthraView Version 5.07.037 was used for the automated synthesis module.

Data analysis PMOD 4.004 ATL C was used for the non-human primate PET imaging study.

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Life sciences study design

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Sample size	This study was performed to demonstrate the utility of the developed carbon-11 labeling protocol for in-vivo imaging studies and replicate imaging data from previously published data. A single animal study was deemed sufficient.
Data exclusions	No data were excluded from the study.
Replication	Brain time activity curves were compared to previously published data and were found to be consistent. No further replication was deemed necessary.
Randomization	Randomization was not relevant as this study was used to validate the radiosynthesis of the established [11C]UCB-J ligand for comparison to the many previous [11C]UCB-J studies in the scientific literature.
Blinding	Blinding was not relevant to this study as the PET study was solely performed for comparison to the the many previous [11C]UCB-J studies in the scientific literature.

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Animals and other organisms

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Laboratory animals	Rhesus Macaque, male, 3 yrs old
Wild animals	Study did not involve wild animals
Field-collected samples	Study did not involve field collected samples
Ethics oversight	All monkey PET imaging studies were conducted under the guiding principles of the American Physiological Society and the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH publication no. 85-23, revised 2010) and were reviewed and approved by the IACUC and the Research Laboratories of Merck & Co., Inc. (West Point, PA, USA).

Note that full information on the approval of the study protocol must also be provided in the manuscript.