ORGANIC CHEMISTRY

Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds

Yong Yao Loh,[1]* Kazunori Nagao,[1]* Andrew J. Hoover,[2] David Hesk,[2] Nelo R. Rivera,[2] Steven L. Colletti,[3] Ian W. Davies,[1,2] David W. C. MacMillan[1]†

Deuterium- and tritium-labeled pharmaceutical compounds are pivotal diagnostic tools in drug discovery research, providing vital information about the biological fate of drugs and drug metabolites. Herein we demonstrate that a photoredox-mediated hydrogen atom transfer protocol can efficiently and selectively install deuterium (D) and tritium (T) at α-amino sp^3 carbon-hydrogen bonds in a single step, using isotopically labeled water (D_2O or T_2O) as the source of hydrogen isotope. In this context, we also report a convenient synthesis of T_2O from T_2, providing access to high-specific-activity T_2O. This protocol has been successfully applied to the high incorporation of deuterium and tritium in 18 drug molecules, which meet the requirements for use in ligand-binding assays and absorption, distribution, metabolism, and excretion studies.

An essential component of the drug discovery and development process is the thorough elucidation of a drug molecule's action and toxicity (*1*–*9*). Despite rapid advancements in analytical techniques over the past 20 years, the introduction of isotopic labels, which integrates a distinguishing signal into a molecule without drastically altering its function, remains the most effective method to detect and quantify drugs and drug metabolites both in vivo and in vitro (*1*–*6*). Recently, the ability to introduce hydrogen isotopes at nonlabile C–H moieties has led to the emergence of deuterium (^{2}H, D) and tritium (^{3}H, T) as cheaper and more readily accessible alternatives to ^{13}C and ^{14}C for the synthesis of isotopically labeled drug analogs, especially when high isotopic incorporation is desired (*1*–*6*). In particular, highly deuterated analogs of drug molecules are used in absorption, distribution, metabolism, and excretion (ADME) studies, where they are ideal internal standards for mass spectrometry–based quantification in animal and human samples, because they negate matrix effects that can interfere with accurate quantification (*10*, *11*). High-specific-activity tritium analogs are critical for accurate quantification in nanomolar ligand-binding affinity studies, as well as the imaging of in vivo compound distribution by autoradiography (*7*–*9*).

A large majority of deuterium- and tritium-labeled pharmaceutical compounds are synthesized in multistep procedures involving the reduction of halogenated or unsaturated drug precursors (*1*–*6*). However, advances in transition metal–catalyzed C–H activation have allowed for direct hydrogen isotope exchange (HIE) at C–H bonds for deuterium or tritium, enabling the synthesis of labeled compounds in a single step without the need for resynthesis (*12*–*14*). This straightforward approach has recently found widespread application in the pharmaceutical industry, where the increasing impact of early-stage ligand-binding assays and ADME studies on drug discovery has led to a rising demand for the efficient synthesis of isotopically labeled pharmaceutical compounds (*2*).

Transition metal–catalyzed HIE reactions at aromatic C(sp^2)–H moieties are well established (Fig. 1A). For example, cationic iridium(I) complexes have long been used to selectively label sites ortho to directing groups on aromatic rings (*12*, *13*). More recently, Chirik and co-workers reported the use of an iron catalyst for the deuteration and tritiation of pharmaceutical drugs at aromatic C–H moieties without the need for a directing group, enabling orthogonal site selectivity relative to the iridium catalyst (*14*). In contrast, the direct HIE at aliphatic C(sp^3)–H moieties remains a challenge in the field (*15*–*20*). With more than 50% of the top-selling commercial drugs containing at least one alkyl amine moiety (*21*), the development of a HIE reaction targeting α-amino C(sp^3)–H bonds could potentially provide a general method for the isotopic labeling of the aliphatic positions of a drug molecule. The site of the isotopic label can be of vital importance, depending on the nature of the study and the metabolic pathways of the substrate of interest (*1*–*6*). In addition, the inherently larger number of exchangeable hydrogens at α-amino C–H moieties relative to aromatic C–H moieties enables high incorporation of the desired isotopic label, which is often necessary for the labeled compound to be of practical use in pharmaceutical studies. Therefore, the development of a mild and efficient HIE reaction targeting α-amino C(sp^3)–H bonds is particularly attractive for the pharmaceutical industry.

Visible light–mediated photoredox catalysis has emerged in recent years as an enabling platform to access new organic transformations through single-electron transfer events (*22*–*24*). In particular, our laboratory and others have demonstrated that tertiary amines can be activated by single-electron oxidation to give an amine radical cation, which can undergo facile α-deprotonation to yield carbon-centered α-amino radicals. The synthetic utility of α-amino radicals has been showcased by its ability to couple with various electrophilic partners (*25*–*27*). On this basis, we questioned whether we could exploit α-amino radicals to access α-deuterated or α-tritiated products (Fig. 1B). Specifically, we hypothesized that, instead of trapping the α-amino radical with a carbon electrophile, the use of an appropriate hydrogen atom transfer (HAT) catalyst in equilibrium with D_2O or T_2O could facilitate the abstraction of deuterium or tritium to yield labeled products. We recognized that the choice of the HAT catalyst would be heavily influenced by thermodynamic factors, particularly the bond dissociation energy (BDE) relative to that of the α-amino C–H bond, as well as its pK_a (where K_a is the acid dissociation constant) relative to water (Fig. 1B) (*28*–*30*). With these considerations in mind, we postulated that thiols, which have been demonstrated to be good hydrogen atom donors (*31*), would be suitable HAT catalysts for this transformation. Herein we describe direct HIE at α-amino C(sp^3)–H bonds mediated by the synergistic merger of photoredox and HAT catalysis. This methodology was readily applied to the program-scale deuteration (*32*) and high-specific-activity tritiation of 18 representative drugs and drug candidates.

A proposed mechanism for the photoredox- and HAT-catalyzed HIE of α-amino C(sp^3)–H bonds is shown in Fig. 2A (*33*). Initial photoexcitation of the iridium(III) photocatalyst Ir(F-Meppy)$_2$(dtbbpy)PF$_6$ [F-Meppy, 2-(4-fluorophenyl)-5-(methyl)pyridine; dtbbpy, 4,4′-di-*tert*-butyl-2,2′-bipyridine] (**1**) would generate the long-lived (lifetime τ = 1.1 μs) triplet-excited-state Ir^{III} complex **2** (*34*). This species is a strong single-electron oxidant [reduction potential $E_{1/2}^{red}(*Ir^{III}/Ir^{II})$ = +0.94 V versus saturated calomel electrode (SCE) in acetonitrile] (*34*) and can oxidize amine **3**, which undergoes facile deprotonation at the α-position to give α-amino radical **4**. At the same time, a thiol HAT catalyst (**6**) would undergo exchange with T_2O to give the tritiated thiol **7**, which would serve as the source of tritium. In addition to the reported BDE for typical α-amino C–H and thiol S–H bonds, we reasoned that HAT can proceed between the polarity-matched (*35*) nucleophilic α-amino radical **4** and tritiated thiol **7**, which would furnish α-tritiated amine product **8** and the electrophilic thiol radical **9** [α-amino C–H BDE = 93.0 kcal mol^{-1} (*36*) versus S–H BDE = 87.0 kcal mol^{-1} (*37*)]. Both catalytic cycles can then converge to undergo a second single-electron transfer between **5** and **9** to regenerate photocatalyst **1** and

[1]Merck Center for Catalysis at Princeton University, Princeton, NJ 08544, USA. [2]Labeled Compound Synthesis Group, Department of Process R&D, Merck Research Laboratories (MRL), Merck & Co., Inc., Rahway, NJ 07065, USA. [3]Department of Discovery Chemistry, MRL, Merck & Co., Inc., Kenilworth, NJ 07033, USA.
*These authors contributed equally to this work.
†Corresponding author. Email: dmacmill@princeton.edu

tritiated thiol **7** through protonation of thiol anion **10** [$E_{1/2}^{red}(Ir^{III}/Ir^{II})$ = –1.50 V versus SCE in acetonitrile (*31*); $E_{1/2}^{red}$(thiol) = –0.85 V versus SCE for cysteine] (*38*).

We began our investigations into the proposed isotopic-labeling protocol by first examining the deuteration of clomipramine (**11**) hydrochloride (Anafranil), a commercially available antidepressant. For the application of deuterated compounds as internal standards in pharmaceutical studies, each compound should ideally have an isotopic incorporation of more than 4.0 deuteriums per molecule, with less than 0.1% of the unlabeled compound remaining, so as to avoid peak overlaps on the mass spectrum and allow for accurate quantification (*11*). In addition, to facilitate long-term studies, the program-scale synthesis of a uniformly deuterated batch of compound is also highly desirable (Fig. 2B, left). A variety of photoredox and thiol catalysts and their respective loadings were evaluated, using *N*-methyl-2-pyrrolidone (NMP) as the solvent (figs. S1 and S2). In our preliminary studies conducted at a 0.1-mmol scale, we observed that the use of 2 mol % of organic photocatalyst 4Cz-IPN (**12**) [1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene; excited-state τ = 5.1 μs; $E_{1/2}^{red}$(*4Cz-IPN/4Cz-IPN$^-$) = +1.35 V; $E_{1/2}^{red}$(4Cz-IPN$^-$/4Cz-IPN) = +1.21 V] (*39*) and 30 mol % triisopropylsilanethiol (**13**), along with 1.2 equivalents of lithium carbonate, afforded the corresponding deuterated product in 79% yield, with 9.2 deuteriums incorporated per molecule and less than 0.1% of unlabeled compound remaining. Scaling the reaction up resulted in a comparable efficiency of deuterium incorporation, enabling the program-scale synthesis of **[^{2}H]11** with 7.2 deuteriums per molecule, no detectable unlabeled compound remaining, and an isolated yield of 76% as its HCl salt (1.06 g) (Fig. 2B, left). The use of the sterically hindered triisopropylsilanethiol was critical to prevent a deleterious thiol-substrate coupling pathway (fig. S2). Control experiments also revealed that light, photoredox catalyst, and thiol are all essential for deuteration to proceed (table S1).

Next, we sought to extend this HIE protocol to the high-specific-activity tritiation of amine-containing drugs with T_2O. In contrast to the deuterium HIE reactions, the analogous tritium HIE reactions are predominantly run on a micromolar scale because (i) the tritium isotope is easily detectable and only a small amount of radioactive product is required, and (ii) safety and cost concerns favor limiting the amount of tritium used to 1.0 Ci (17.2 μmol) per reaction. An additional complication is that commercially available T_2O is typically highly diluted with natural-abundance H_2O to prevent the decomposition of T_2O through autoradiolysis (Fig. 2C) (*3*). To overcome this issue, we set out to establish a convenient process to synthesize high-specific-activity T_2O using only 1 Ci of T_2 gas, which could be performed in a common laboratory setting and used immediately in our tritium HIE reaction. Industrially, neat T_2O is produced in bulk from the reaction between T_2 and PtO_2 before being distilled and diluted (*40*). To facilitate the transfer of micromolar-scale T_2O into our photoredox reaction mixture, we proposed to adapt this procedure for the generation of T_2O in a potential reaction solvent. Among the solvents evaluated, we observed that the use of NMP as the reaction solvent enabled the formation of high-specific-activity tritiated water in 61% yield (0.51 Ci, 8.8 μmol) from 1.0 Ci T_2 gas and PtO_2 (fig. S3).

With this convenient method to access T_2O in hand, we proceeded to optimize the proposed photoredox-HAT–catalyzed tritium-labeling protocol. In general, high-specific-activity tritium–labeled compounds are required to have a specific activity of at least 15 Ci mmol^{-1} (equivalent to an incorporation of 0.5 tritiums per molecule) and are isolated in an appreciable radiochemical yield of at least 10 mCi (Fig. 2B, right). Under the dilute micromolar conditions (using ~4.4 equivalents of T_2O), we observed that the use of **11** in its free base form—along with increased loadings of the photoredox (4 mol %) and thiol (60 mol %) catalysts—and the use of the integrated photoreactor developed at Merck & Co., Inc. (*41*), as the visible light source greatly enhanced the incorporation of tritium, yielding [^{3}H]**11** with a high specific activity of 40.2 Ci mmol^{-1} and an isolated yield of 39.8 mCi (Fig. 2B, right).

Under these optimized conditions, we explored the generality of the photoredox-mediated deuteration and tritiation protocols with a library of commercially available drugs containing a variety of alkyl amine scaffolds. For the deuteration of these substrates (Fig. 3), the best conditions were found to be substrate-dependent, given a choice of two photocatalysts [Ir(F-Meppy)$_2$(dtbbpy)PF$_6$ (**1**) and 4Cz-IPN (**12**)], two thiols (**13** and **14**), and two light sources [a 34-W blue light-emitting diode (LED) or the integrated photoreactor; see the supplementary materials]. Acyclic trialkyl amines (**[^{2}H]15** to **[^{2}H]17**) worked well, as did piperidine (**[^{2}H]18** and **[^{2}H]19**) and piperazine rings (**[^{2}H]20** to **[^{2}H]24**). The reaction also showed good tolerance for a variety of functional groups. Aryl fluoride (**[^{2}H]16**) and aryl chloride (**[^{2}H]18** and **[^{2}H]22**) substituents were well

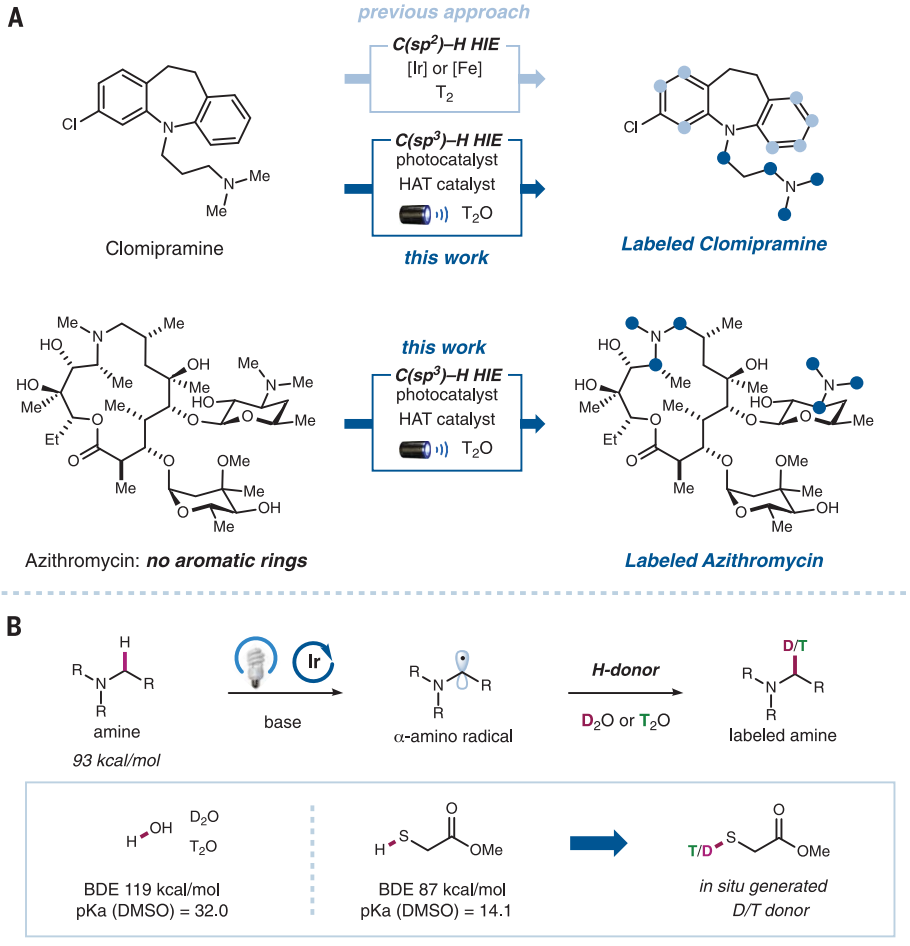

Fig. 1. Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds. (**A**) The merger of photoredox and hydrogen atom transfer (HAT) catalysis enables α-amino C(sp^3)–H selective hydrogen isotope exchange (HIE) of alkyl amine–based drugs. Light and dark blue circles represent the positions of isotopically labeled C(sp^2)–H and C(sp^3)–H bonds, respectively. (**B**) Hypothesis for the proposed photoredox-catalyzed deuteration and tritiation. Me, methyl; Et, ethyl; R, alkyl or aryl group; DMSO, dimethyl sulfoxide; BDE, bond dissociation energy.

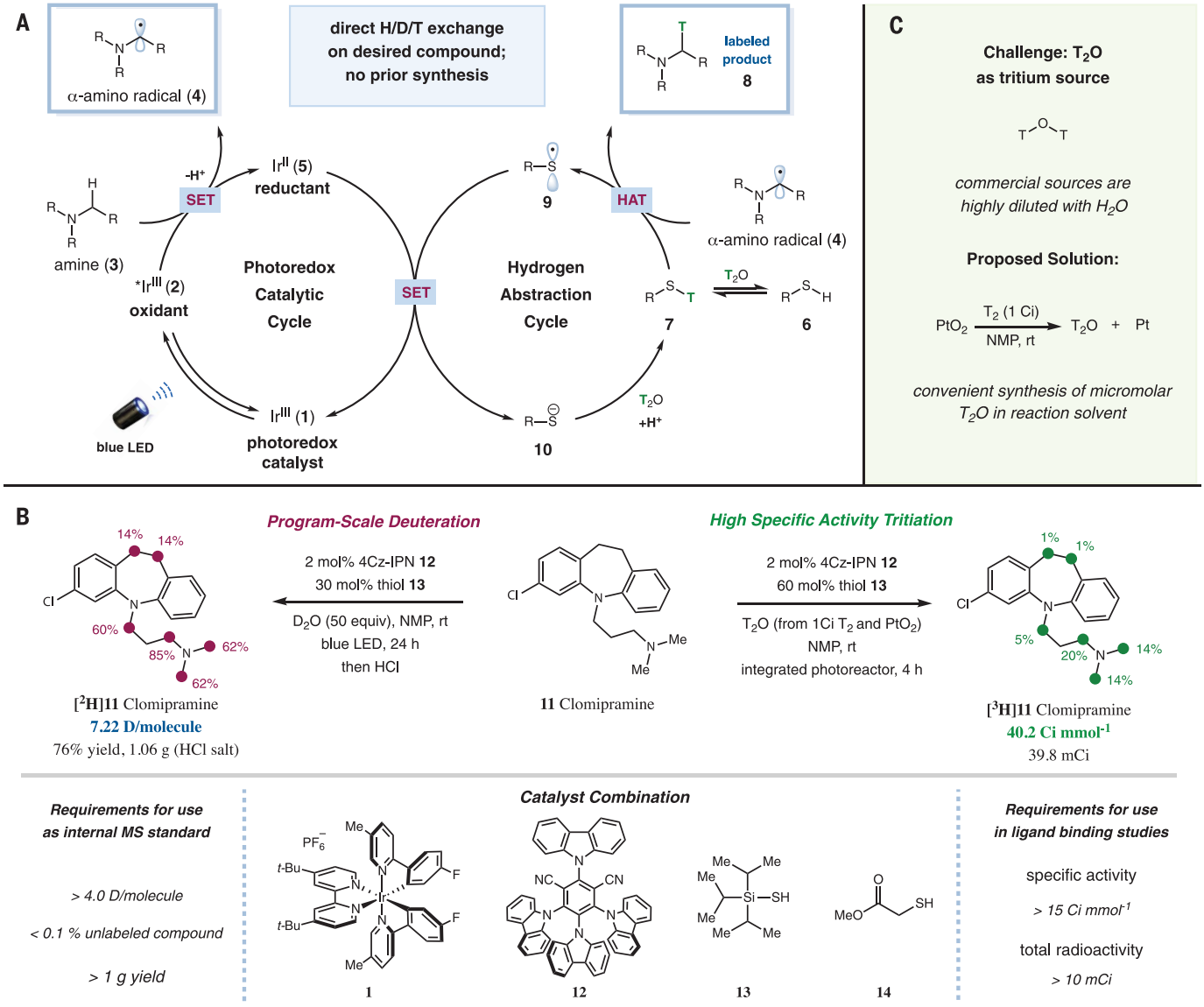

Fig. 2. Reaction development. (**A**) Proposed catalytic cycle for the photoredox-catalyzed HAT protocol. SET, single-electron transfer; LED, light-emitting diode. (**B**) Procedures and requirements for program-scale deuteration and high-specific-activity tritiation. The colored circles (maroon or green) and numbers denote the positions of the C–H bonds that are labeled and the percent incorporation of the hydrogen isotope, respectively. NMP, *N*-methyl-2-pyrrolidone; *t*-Bu, *tert*-butyl group; rt, room temperature; h, hours. (**C**) High-specific-activity T_2O is accessible from T_2 and PtO_2 at a micromolar scale and can be used for photoredox-catalyzed tritiation in a one-pot procedure.

tolerated under the reaction conditions. Carboxylic acid (**[^{2}H]21**), ester (**[^{2}H]17**), amide (**[^{2}H]20**, **[^{2}H]22**, and **[^{2}H]24**), and nitrile (**[^{2}H]15** and **[^{2}H]16**) functionalities were also amenable to the photoredox conditions, as were free hydroxyl groups (**[^{2}H]23**, **[^{2}H]25**, and **[^{2}H]26**). In addition, chiral centers away from the reactive sites were unperturbed during the reaction (**[^{2}H]16**, **[^{2}H]17**, and **[^{2}H]21**). Our deuteration protocol was also applicable to macrolide drugs such as azithromycin (**[^{2}H]25**) and clarithromycin (**[^{2}H]26**). These high-molecular-weight macrocycles with no C(sp^2)–H bonds are particularly challenging substrates for HIE through conventional transition metal catalysis. The preparation of deuterated azithromycin would have previously involved a multistep sequence and the use of costly deuterated reagents (*42*). In contrast, our photoredox protocol enables access to **[^{2}H]25** in a single step using D_2O, a readily available source of deuterium. Stereochemistry was retained even when H/D exchange occurred at chiral centers on these macrocycles, likely owing to substrate control in the HAT process. In addition to α-amino positions, benzylic and β-amino positions were also deuterated in certain instances (**[^{2}H]15, [^{2}H]16, [^{2}H]18**, and **[^{2}H]22**; figs. S4 and S5). In summary, all substrates gave excellent deuterium incorporations on a program scale, with incorporations of more than 5.0 deuteriums per molecule and, importantly, less than 0.1% of the unlabeled compound, meeting the minimum requirement for their use as internal standards.

With the same library of 13 pharmaceutical drugs, we demonstrated similar functional group tolerance for the photoredox-mediated tritium HIE protocol (Fig. 4). As with the deuteration reaction, the best conditions were substrate-dependent, and combinations of the two photocatalysts **1** and **12** and the two thiols triisopropylsilanethiol (**13**) and methyl thioglycolate (**14**) were used. Despite the smaller excess of T_2O in the reaction, the presence of acidic hydrogens from carbamate (**[^{3}H]19**), amide (**[^{3}H]22** and **[^{3}H]24**), carboxylic acid (**[^{3}H]21**), and alcohol (**[^{3}H]23**, **[^{3}H]25**, and **[^{3}H]26**) functionalities did not have a major impact on tritium incorporation. Again, we observed high tritium incorporations with the high-molecular-weight macrocycles azithromycin (**[^{3}H]25**) and clarithromycin (**[^{3}H]26**);

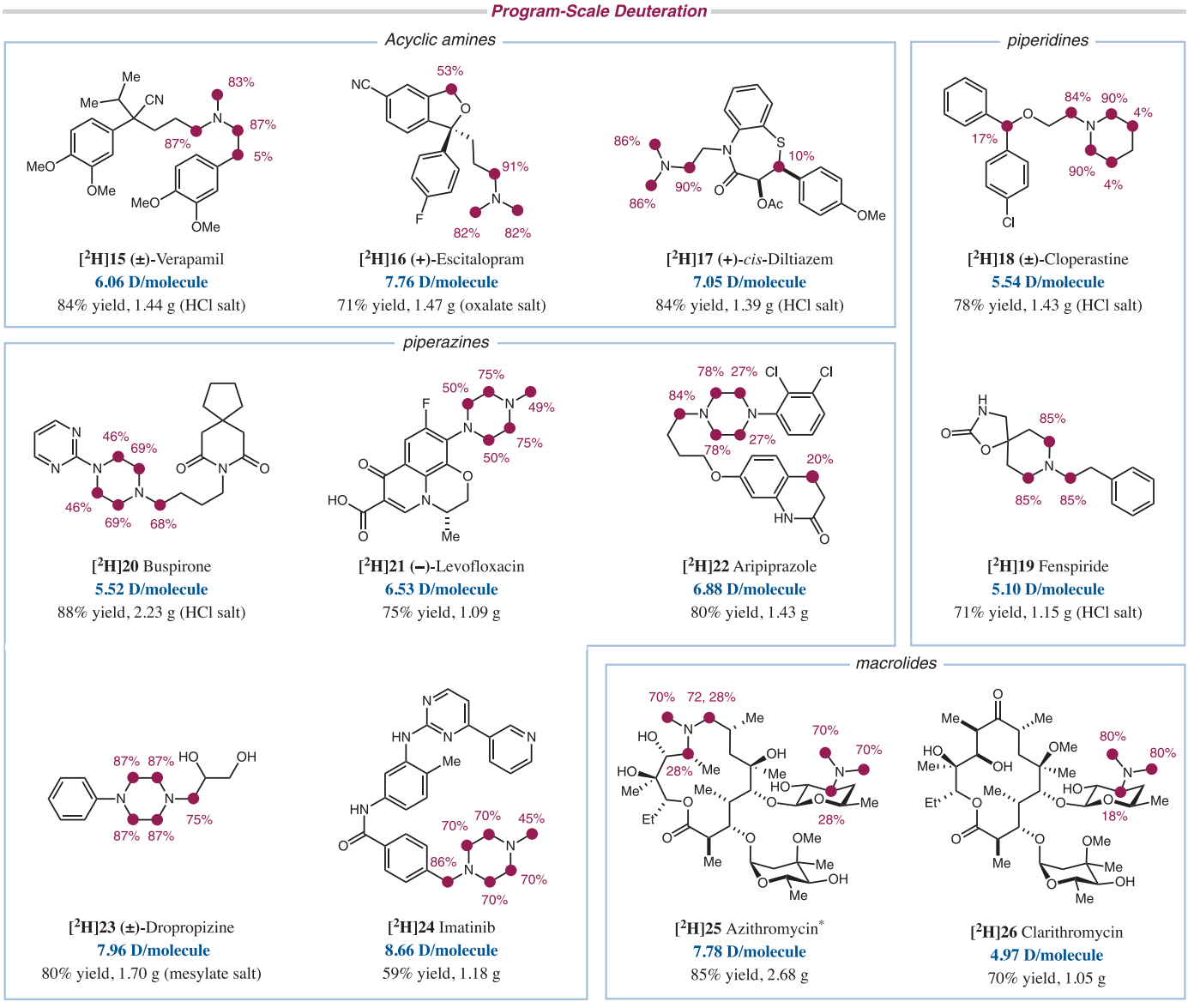

Fig. 3. Scope of program-scale deuteration. Reaction conditions: photoredox catalyst **1** or **12** (2 mol %), triisopropylsilanethiol **13** (30 mol %), D_2O (50 equivalents), Li_2CO_3 (1.2 equivalents, added when substrate is used as its acid salt), NMP, rt, 34-W blue LED or integrated photoreactor. The products were isolated as the appropriate acid salts shown in parentheses. Ac, acetyl group. *The two protons at the α-amino methylene position are diastereotopic and are labeled to different extents.

these substrates have no aromatic rings and cannot be tritiated using existing HIE protocols. For **[^{3}H]22**, when the amount of T_2 gas was increased to 2 Ci, specific activity was boosted from 11.5 to 14.6 Ci mmol^{-1}, with a large increase in yield (8.6 to 19.6 mCi). This demonstrates the tunability of our protocol with respect to the amount of T_2 used, enabling single-step tritiation even for particularly recalcitrant substrates. We achieved high specific activities for all substrates, meeting the typical standards for the preparation of high-specific-activity pharmaceutical drugs in appreciable yield for use in ligand-binding studies.

In addition to the library of commercially available drug molecules, we further evaluated the utility of this photoredox-catalyzed tritiation with a series of potential GPR-40 agonists with positive allosteric modulation (agoPAMs) (Fig. 4) developed in the research laboratories of Merck & Co., Inc. (*43*). The characterization of G protein–coupled receptor allostery is critical to advancing this agoPAM chemical class. Augmentation of binding in the presence of orthosteric ligands has been previously demonstrated using radiolabeled analogs in radioligand-binding assays and subsequently visualized in the GPR-40 ternary crystal structure (*44*). As such, we envision that the radiolabeling methodology described herein might be used to enable metabolite identification both in vitro and in vivo, as well as the elucidation of the extent of covalent protein binding in human hepatocytes to lower the risk of any bioactivation toward reactive electrophiles (*45*).

Initially, we observed photoredox-mediated decarboxylation of the aliphatic carboxylic acid moiety in the drug candidates. However, this was overcome by using a less oxidizing photocatalyst, $Ir(ppy)_2(dtbbpy)PF_6$ [$E_{1/2}^{red}(*Ir^{III}/Ir^{II})$ = +0.66 V versus SCE in acetonitrile] (*34*) or a Lewis acid additive (supplementary materials). We found that sterically hindered amines (**[^{3}H]27** and **[^{3}H]28**) and azetidine rings (**[^{3}H]29**) were also amenable substrates for this protocol. Tritiation was also observed at a C(sp^2)–H moiety in **[^{3}H]27**, possibly owing to conjugation of the benzylic α-amino radical. For **[^{3}H]31**, epimerization likely occurred at the chiral center adjacent to nitrogen as a result of the introduction of tritium (*46*). All five compounds were satisfactorily labeled and

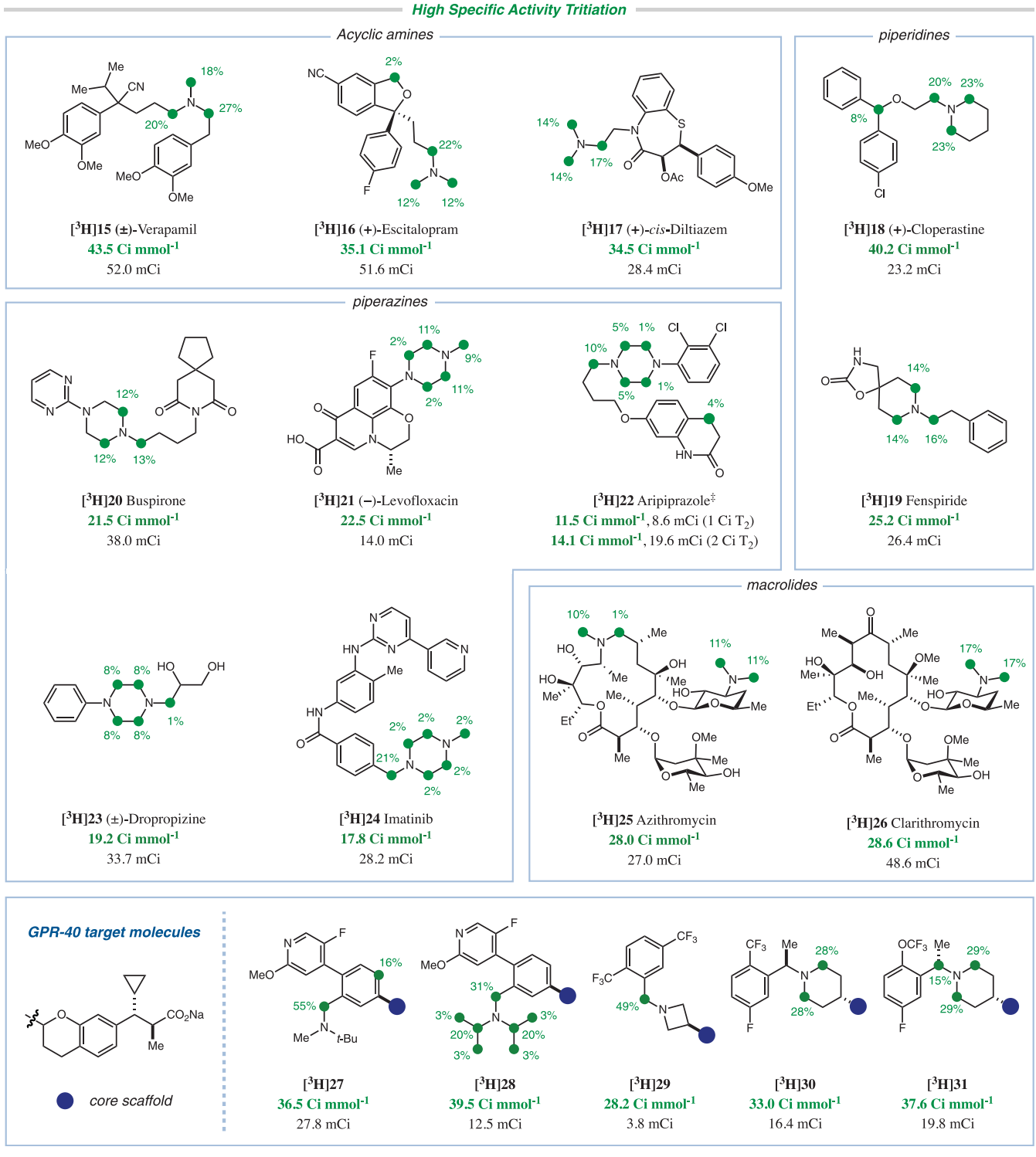

Fig. 4. Scope of high-specific-activity tritiation. Reaction conditions: substrate (2 μmol), photoredox catalyst **1** or **12** (4 mol %), thiol catalyst **13** or **14** (60 mol %), T_2O (preformed from 1 Ci T_2 and PtO_2), NMP, rt, 34-W blue LED or integrated photoreactor. ‡Incorporation depicted is for the 2 Ci reaction with **[^{3}H]22**.

met the requirements for use in preclinical candidate selection studies. We anticipate that facile access to highly deuterated and tritiated compounds based on the method described herein will enable accelerated and broader interrogation of the biological activity of molecules in the pursuit of the development of new molecular therapies.

REFERENCES AND NOTES

1. E. M. Isin, C. S. Elmore, G. N. Nilsson, R. A. Thompson, L. Weidolf, *Chem. Res. Toxicol.* **25**, 532–542 (2012).
2. W. J. S. Lockley, A. McEwen, R. Cooke, *J. Labelled Comp. Radiopharm.* **55**, 235–257 (2012).
3. R. Voges, J. R. Heys, T. Moenius, *Preparation of Compounds Labeled with Tritium and Carbon-14* (John Wiley & Sons, 2009).
4. P. H. Allen, M. J. Hickey, L. P. Kingston, D. J. Wilkinson, *J. Labelled Comp. Radiopharm.* **53**, 731–738 (2010).

5. C. S. Elmore, R. A. Bragg, *Bioorg. Med. Chem. Lett.* **25**, 167–171 (2015).
6. C. S. Elmore, *Annu. Rep. Med. Chem.* **44**, 515–534 (2009).
7. E. C. Hulme, M. A. Trevethick, *Br. J. Pharmacol.* **161**, 1219–1237 (2010).
8. C. Meleza *et al.*, *Anal. Biochem.* **511**, 17–23 (2016).
9. W. E. Stumpf, *J. Pharmacol. Toxicol. Methods* **51**, 25–40 (2005).
10. J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, *Angew. Chem. Int. Ed.* **46**, 7744–7765 (2007).
11. V. Derdau, J. Atzrodt, J. Zimmermann, C. Kroll, F. Brückner, *Chemistry* **15**, 10397–10404 (2009).
12. D. Hesk, P. R. Das, B. Evans, *J. Labelled Comp. Radiopharm.* **36**, 497–502 (1995).
13. J. R. Heys, *J. Labelled Comp. Radiopharm.* **50**, 770–778 (2007).
14. R. P. Yu, D. Hesk, N. Rivera, I. Pelczer, P. J. Chirik, *Nature* **529**, 195–199 (2016).
15. For transition metal–catalyzed deuteration of C(sp^3)–H bonds, see (*16*–*19*). For transition metal–catalyzed tritiation of C(sp^3)–H bonds, see (*20*).
16. M. Takahashi, K. Oshima, S. Matsubara, *Chem. Lett.* **34**, 192–193 (2005).
17. L. Neubert *et al.*, *J. Am. Chem. Soc.* **134**, 12239–12244 (2012).
18. G. Pieters *et al.*, *Angew. Chem. Int. Ed.* **53**, 230–234 (2014).
19. L. V. A. Hale, N. K. Szymczak, *J. Am. Chem. Soc.* **138**, 13489–13492 (2016).
20. W. J. S. Lockley, D. Hesk, *J. Labelled Comp. Radiopharm.* **53**, 704–715 (2010).
21. N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **87**, 1348–1349 (2010)
22. C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **113**, 5322–5363 (2013).
23. M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **81**, 6898–6926 (2016).
24. M. D. Kärkäs, J. A. Porco Jr., C. R. J. Stephenson, *Chem. Rev.* **116**, 9683–9747 (2016).
25. A. McNally, C. K. Prier, D. W. C. MacMillan, *Science* **334**, 1114–1117 (2011).
26. A. Noble, D. W. C. MacMillan, *J. Am. Chem. Soc.* **136**, 11602–11605 (2014).
27. C. K. Prier, D. W. C. MacMillan, *Chem. Sci.* **5**, 4173–4178 (2014).
28. S. J. Blanksby, G. B. Ellison, *Acc. Chem. Res.* **36**, 255–263 (2003).
29. W. N. Olmstead, Z. Margolin, F. G. Bordwell, *J. Org. Chem.* **45**, 3295–3299 (1980).
30. H.-Z. Yu, Y.-M. Yang, L. Zhang, Z.-M. Dang, G.-H. Hu, *J. Phys. Chem. A* **118**, 606–622 (2014).
31. S. Escoubet *et al.*, *J. Org. Chem.* **71**, 7288–7292 (2006).
32. A scale that will allow enough material to support a drug discovery program (in this case, more than 1 g of material).
33. Although we favor the mechanism outlined in Fig. 2A, we cannot rule out the possibility that a mechanism similar to that outlined in fig. S4 is a competing pathway. In this instance, thiol radical generated in situ can abstract from α-amino C–H bonds in the substrate to form the key α-amino radical intermediate.
34. M. S. Lowry *et al.*, *Chem. Mater.* **17**, 5712–5719 (2005).
35. C. Le, Y. Liang, R. W. Evans, X. Li, D. W. C. MacMillan, *Nature* **547**, 79–83 (2017).
36. D. D. M. Wayner, K. B. Clark, A. Rauk, D. Yu, D. A. Armstrong, *J. Am. Chem. Soc.* **119**, 8925–8932 (1997).
37. C. M. Hadad, P. R. Rablen, K. B. Wiberg, *J. Org. Chem.* **63**, 8668–8681 (1998).
38. L. G. Shaidarova, S. A. Ziganshina, G. K. Budnikov, *J. Anal. Chem.* **58**, 577–582 (2003).
39. J. Luo, J. Zhang, *ACS Catal.* **6**, 873–877 (2016).
40. H. Morimoto, P. G. Williams, *Fus. Sci. Technol.* **21**, 256–261 (1992).
41. C. C. Le *et al.*, *ACS Cent. Sci.* **3**, 647–653 (2017).
42. A. W. Czarnik, U.S. Patent 20,090,062,220 (2009).
43. C. W. Plummer *et al.*, *ACS Med. Chem. Lett.* **8**, 221–226 (2017).
44. J. Lu *et al.*, *Nat. Struct. Mol. Biol.* **24**, 570–577 (2017).
45. T. A. Baillie, *Chem. Res. Toxicol.* **19**, 889–893 (2006).
46. For the use of tracers or reagents in early in vitro screening, epimerization is less of an issue because the experimental error can be high (>2× in discovery studies for binding or ex vivo occupancy studies). It should be noted that racemic tracers have been used in preclinical and clinical settings (e.g., positron emission tomography).

ACKNOWLEDGMENTS

Research reported in this publication was supported by the National Institutes of Health (NIH) under award number R01 GM103558-04 (D.W.C.M., Y.Y.L., and K.N.). Y.Y.L. thanks the Agency for Science, Technology and Research (A*STAR) for a graduate fellowship. K.N. thanks the Japan Society for the Promotion of Science for an overseas postdoctoral fellowship. Additional funding was provided by kind gifts from Merck, Abbvie, BMS, and Janssen. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Additional data supporting the conclusions are available in the supplementary materials.

SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/358/6367/1182/suppl/DC1
Materials and Methods
Supplementary Text
Figs. S1 to S5
Tables S1 and S2
NMR Spectra
References (*47*–*54*)

14 September 2017; accepted 30 October 2017
Published online 9 November 2017
10.1126/science.aap9674

Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds

Yong Yao Loh, Kazunori Nagao, Andrew J. Hoover, David Hesk, Nelo R. Rivera, Steven L. Colletti, Ian W. Davies and David W. C. MacMillan

Science **358** (6367), 1182-1187.
DOI: 10.1126/science.aap9674originally published online November 9, 2017

Lighting the way to drug labeling

It is important during drug development to study how candidate compounds get absorbed and broken down biologically. One common technique for tracking a drug's fate is to label its molecular framework with heavier isotopes of hydrogen (either deuterium or tritium). Loh *et al.* developed a light-promoted protocol to install these labels on alkyl carbons adjacent to nitrogen. The technique relies on incorporation of the heavy isotope into a thiol from a convenient heavy water source through acid-base chemistry. Next, a photoredox catalyst strips a hydrogen atom equivalent from the carbon, and the thiol engages in radical chemistry to transfer the deuterium or tritium in its place.

Science, this issue p. 1182