Semiconductor Photoredox Catalysis to Engineering Deuterated *N*-Alkyl Pharmaceuticals

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'Deuterium switch' in therapeutic molecules is widely used to study and alter the absorption, distribution, metabolism and excretion of pharmaceuticals. In 2017, the first deuterium-labeled drug, deutetrabenazine, was approved by the FDA, ushering a new era of deuterated clinical drug development. "Among the myriad of commercial drugs, over 50% of the top-selling drugs contain *N*-alkyl amine units and *N*-dealkylation by cytochrome P450 (CYP450) is a very common metabolic pathway in such *N*-alkyl drugs," said Professor Chenliang Su (Shenzhen University, P. R. of China). "Thus, deuterium substitution of *N*-alkyl groups in *N*-alkyl drug molecules could impact their pharmacodynamic properties by slowing down the N–C bond cleavage. In this regard, the precision synthesis of drug analogues with deuterated *N*-alkyl amine units holds great promise but is still a challenging endeavor from the chemistry viewpoint." Traditional approaches to these *N*-alkyl drugs generally rely on N-alkylation with deuterated alkyl halides such as CD_3I or reduction of N–CO_2R moieties with $LiAlD_4$. "The substitution is of interest as these deuterated reagents are often highly toxic, carcinogenic and/or volatile, the latter generally causing high costs and waste production," added Professor Su.

Professor Su's group had previously developed a controllable deuteration of halides and alkenes via semiconductor-promoted photocatalytic D_2O splitting (*Nat. Commun.* **2018**, *9*, 80; *Adv. Sci.* **2019**, *6*, 1801403). In this new article, they developed a groundbreaking semiconductor photoredox catalysis to achieve mild and controllable deuterium-labeling in N-alkylated pharmaceuticals via D_2O splitting coupled with isotopic alkanol oxidation. "With the goal of achieving controllable isotope-labeling in N-alkylated amines, in this work we rationally designed photocatalytic water-splitting to furnish [H] or [D] by photogenerated electron-induced reduction; meanwhile, photogenerated electron-holes with appropriate oxidative ability are utilized to selectively oxidize isotopically labelled alkanols, furnishing the corresponding aldehydes for aldehyde-amine condensation to afford isotopically labelled imine intermediates. These imines could be subsequently reduced by [H]/[D] from water splitting, producing the corresponding *N*-alkyl chemicals and drugs," said Professor Su, who continued: "Benefitting from this unique design, low-cost and sustainable isotopic water and alkanols are proposed as a combined deuterated alkylation reagent for the first time. More importantly, precise control of the number of deuterium atoms (i.e., *N*-CD_3, *N*-CD_2H and *N*-CDH_2) at the potential metabolic position of *N*-methyl drugs is enabled by simply tuning the deuteration of isotopic water and methanol." Gratifyingly, the group found that this photocatalytic strategy exhibited a broad reaction scope, good functional group tolerance, high selectivity and excellent deuterium incorporation. "Substrates including primary amines, secondary amines, amino acid derivatives and heterocyclic amines readily underwent N-trideuteromethylation reactions, furnishing the corresponding products with high deuterium incorporation (up to 98%) and excellent yields (up to 94%). Sensitive substrates with alkyl chiral centers were compatible and unperturbed," explained Professor Su. "Late-stage functionalization of various commercial pharmaceuticals such as flutamide, nimesulide, fluoxetine, tetracaine, atomoxetine, sertraline, paroxetine and vortioxetine was successfully demonstrated. Impressively, this mild and general process enables access to site-specifically labeled drugs in a single step," he added. Professor Su continued by explaining that deuterated *N*-alkyl pharmaceuticals, including imipramine-d_3, loxapine-d_3, alverine-d_5 and dofetilide-d_3, were successfully obtained and gram-scale synthesis could be easily achieved. "Last but not least, this protocol has been nicely applied for the facile synthesis of *N*-CD_3, *N*-CD_2H and *N*-CDH_2 nimesulide derivatives, butenafines-d_3, d_2 and d_1, loxapines-d_3, d_2 and d_1 and imipramines-d_3, d_2 and d_1, with high yields and uniformly high D-incorporation (> 95%)," he said.

Professor Su concluded: "This study not only paves the way to the precision deuterium-labeling at potential metabolic sites of *N*-alkyl pharmaceuticals, which may provide a reliable shortcut for the discovery of new deuterated drugs, but also reveals the potential of semiconductor photocatalysts in artificial photosynthesis of pharmaceuticals with water and organics."

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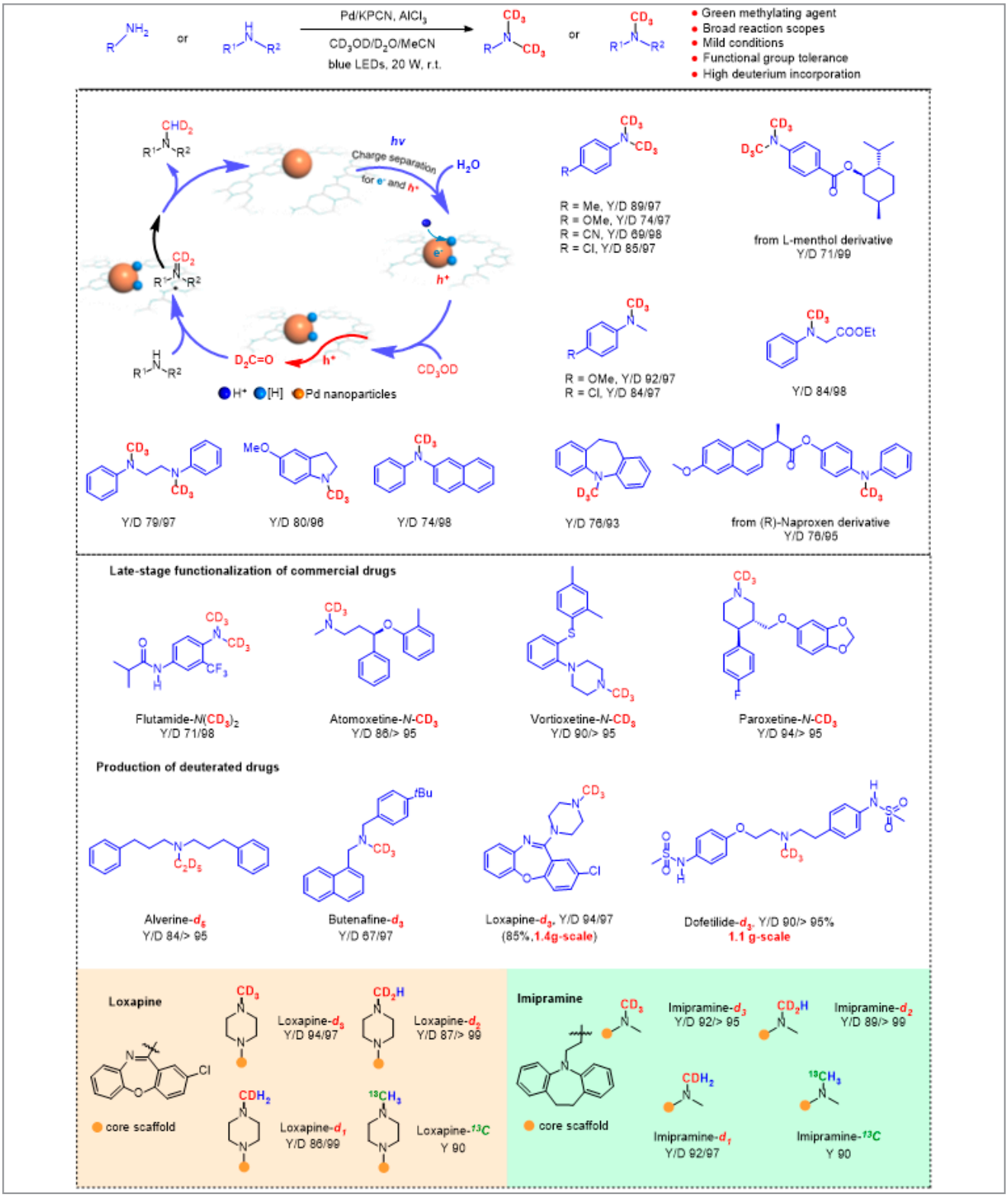

Scheme 1 Selected examples of controllable D-labeled N-alkylation of pharmaceutical-related amines by semiconductor photoredox catalysis

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