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The Evolution of Deuterium in the Pharmaceutical Industry and Its Effects on Methods of Deuterium Incorporation

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Abstract

The substitution of deuterium, an isotope of hydrogen containing one proton and one neutron, for a hydrogen has far reaching effects on the behavior of the compound. Scientists have been utilizing the effects of deuterium since 1961[1]. The primary purpose for deuterium has been concentrated in the development of internal standards for NMR and mass spectrometers, due to their relative 'silence' in these studies, allowing scientists to elucidate mechanisms and trace a compound's movement throughout the body. However, recently, in addition to the use of deuterium as a standard, it has been added to developing or previously created pharmaceutical compounds with the intent to stabilize the drug. This stabilization can take many forms, including decreasing the rate of metabolic breakdown, decreasing enantiomeric switching, and, in some cases, decreasing toxicity. With this more widespread application, a resurgence of studies have been completed to develop new methods of deuterating a wide variety of molecules, with a focus on common functional groups found within pharmaceutical compounds and mild reaction conditions.

Pharmaceutical Applications

General Effects

Pharmaceuticals are generally analyzed according to several different features: absorption, distribution, metabolism, and excretion (ADME)[2] through isotopic labeling. The heavier than normal element allows scientists to track the drug as it moves throughout the body. However, deuterium has an additional effect on the compound known as the kinetic isotope effect (KIE)[2,3,]. Deuterium changes the pharmacokinetics of the compound, or how the drug moves throughout the body[2]. Though the difference in bond enthalpies of C-D and C-H is just

1.8 kJ*mol^{-1} [4], the addition of deuterium decreases the rate of metabolism[3]. This allows for a decrease in both the dosage and frequency of dosage which in turn lessens the negative side effects[5].

Deuterium can also be utilized in pharmaceutical compounds in order to stabilize stereocenters[5]. The addition of deuterium on a chiral center allows the emergence of one, more common, enantiomer[6]. This, in turn, allows for the development of a medicine with more beneficial effects. Moreover, this stabilization is important as some compounds have a toxic enantiomer and isolation of the beneficial enantiomer was previously impossible due to the chiral environment of the body. While the deuterated compounds may not be entirely stable, it is up to five times more stable than its deuterium-lacking counterpart[5].

Deuterium Containing Drugs in Development (or Approved)

A drug in clinical development goes through four distinct phases. The first phase involves 15-50 patients and aims to determine whether or not a drug is safe; it is given increasingly large doses to determine the magnitude of negative side effects. Phase II involves a larger sample study and begins to determine the effectiveness of a drug, whether or not it will produce the desired outcome. Often, this stage also involves testing the compatibility of the drug in development to other medications used to treat the disease. In the third phase, the developing drug is compared to the current standard of care drug. In this phase, participants are chosen randomly and are not told whether or not the drug that they are receiving is experimental or the standard. Moreover, each patient is watched carefully for side effects. This last phase tests the drug after it is approved by the FDA in several thousands of patients and studies both long and short term effects. This stage can also involve testing for compatibility with other drugs[7].

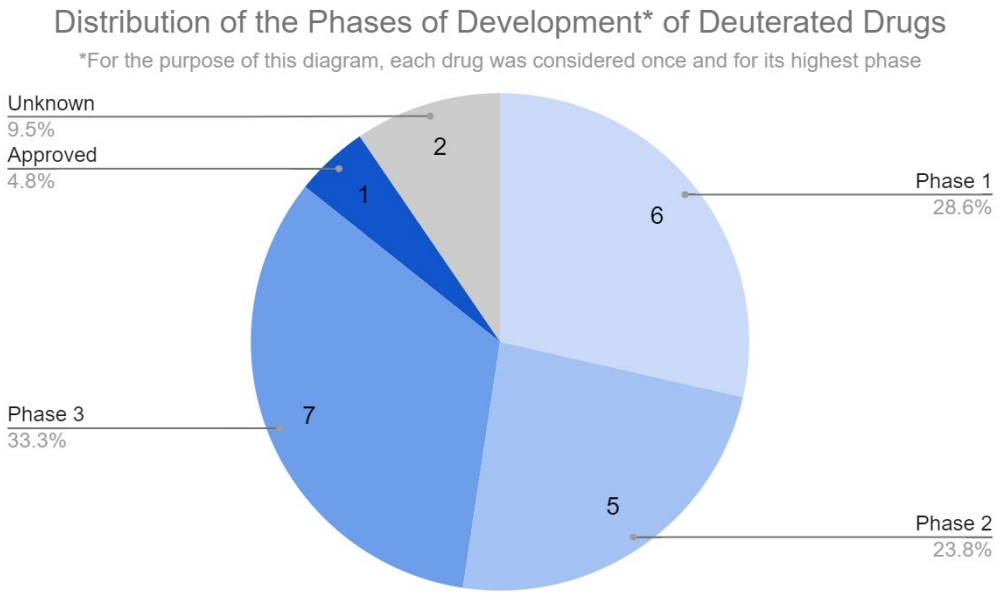


Figure 1: A pie chart detailing the distribution of the phases of development of the deuterated drugs. The raw data can be found in Appendix A and was simplified so each drug is only represented once.

The first deuterated drug that was approved by the Food and Drug Administration (FDA) was Austedo, deutetrabenazine, deuterated benzoquinoline, or d_6-tetrabenazine, developed by Teva Pharmaceuticals[5,8]. It should be noted that in addition to this drug being approved by the FDA, it received a patent as a New Molecular Entity (NME)[9]. This drug is used to treat chorea (tremors) caused by Huntington's disease which are caused by reducing dopamine and serotonin production[8]. As previously mentioned, the main effect of deuterium in this compound is the decrease in the metabolic breakdown by 69-87%[9]. This allows the drug to be administered only twice a day leading to a decrease in negative side effects such as sleepiness, depression, and anxiety[8]. Currently, there are twenty different pharmaceutical compounds in various stages of testing that contain deuterium[5]. Of these, sixteen compounds are deuterium containing analogs to already approved and administered drugs, two are deuterated forms of nutritional compounds,

and two do not have a non-deuterated counterpart, meaning deuterium was utilized from the beginning stages of development[5].

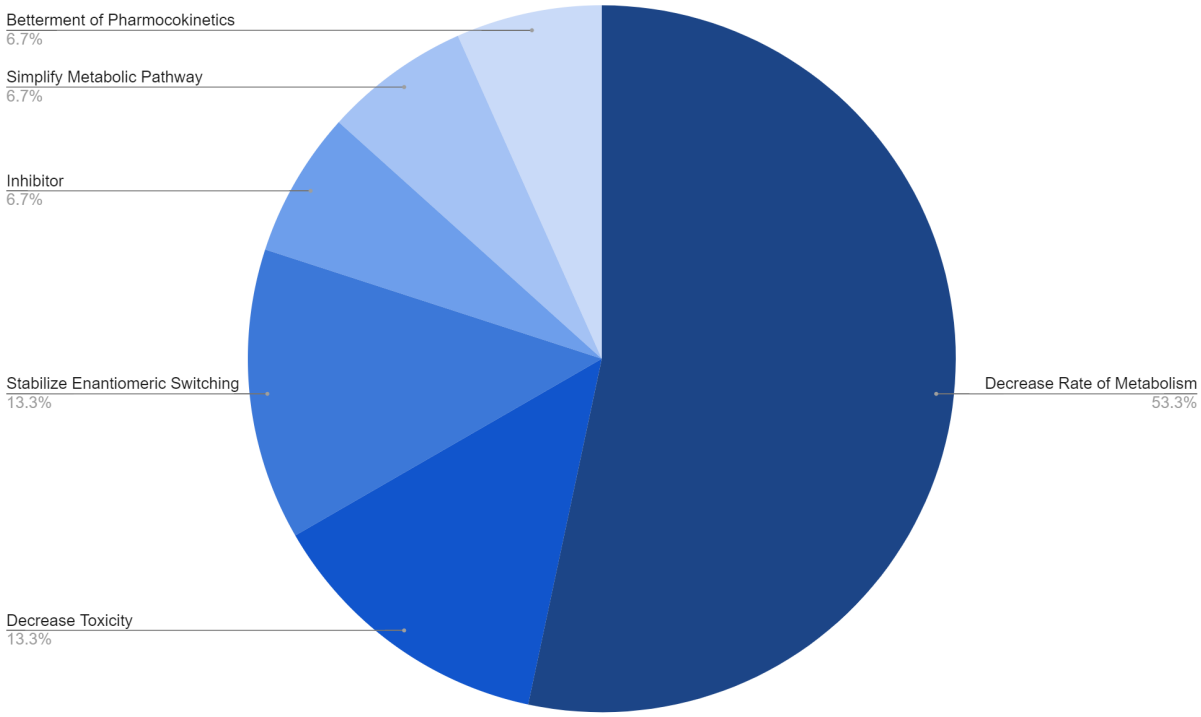


Figure 2: A pie chart detailing the different effects that the addition of deuterium has on already known drugs.

Aldehyde Oxidase and Metabolism

A study on the development of a heroin "vaccine" provides further evidence that the body can differentiate between hydrogen and deuterium[30]. This vaccine is a heroin haptinn that would elicit an immune response from the body which in turn would prevent heroin and heroin metabolites from entering the brain. Heroin breaks down first into 6-monoacetylmorphine (6AM) and then morphine; it is morphine that causes the negative side effects of heroin. The deuterated vaccine for heroin bonded more closely to heroin than the non-deuterated vaccine. The reason for this tighter bonding is not fully known and most likely has to do with "different T-cell

dependent B-cell receptor activation populations". This difference however clearly indicates that the immune system can differentiate between deuterium and hydrogen. Furthermore, the deuterated vaccine also allowed for an increase in 6AM as the breakdown was no longer subject to P450; the deuterated compound slowed the rate of metabolism allowing for a decrease in the metabolite causing undesired effects[30].

The addition of deuterium to slow the metabolism of a drug was utilized in the development of HC-1144[28]. The phosphorylation and activation of Vascular endothelial growth factor receptors (VEGFR) leads to the creation of new tumors. Tivozanib is a VEFGR inhibitor with a longer progression-free survival. However, there was a large increase in both hypertension (34% to 44%) and dysphonia (5% to 21%) compared to sorafenib, a less effective VEFGR inhibitor. The deuterated analog of Tivozanib (HC-1144) was as effective in vitro as Tivozanib itself. HC-1144 was synthesized through the deuteration of an early reactant and had a 69% yield. HC-1144 had a larger half-life, a larger max concentration (C_{max}, meaning smaller doses could be given), a 1.5 times larger AUC (an integral of the change in concentration over time, meaning that the compound stayed in the body for a longer period of time) and a similar peak time (meaning the release of the drug was not further delayed) [28].

Stabilization of Chiral Center

The isolation of the beneficial enantiomer (eutomer) from the undesired enantiomer (distomer) first arose around the 1990s, allowing for the creation of drugs such as Nexium, Lexapro, Lunesta, and Xopenex [31]. However, some compounds, such as those with hydrogen at the chiral center, could not be isolated due to enantiomeric switching in vivo. This switching can be stabilized through deuterium labeling. For example, (S)-D lenalidomide is ten times

more potent than racemic lenalidomide and (-)-D avadomide was 20 times more potent than its racemic mixture [31]. Furthermore, the deuterated analog had a reduction in degradation rate as well. The addition of deuterium at the chiral center pioglitazone, creating the drug DRX-065 which is used to treat diabetes, allowed for the a reduction in PPARɣ agonist activity which causes weight gain, edema (swelling), and bone fracture as it is caused solely by the S enantiomer [10]. However, it should be noted that deuteration did not affect the stability of inolitazone [31].

Intellectual Property Laws

While deuterated compounds do possess beneficial side effects, there is some controversy surrounding these drugs due to intellectual property laws[5]. Determination of whether or not a deuterated form of a pre-existing compound can be considered a new compound, and thus be eligible for a new patent, is done on a case by case basis. Some believe that scientists are using deuterated forms of their compounds as merely a way to extend their patent without fully developing a new product[5].

However, this is not to say that the intention of all scientists behind the development of deuterated drugs are less than pure. At least two drugs containing deuterium are currently in development that do not have an analog. This suggests that deuterium is becoming more prominent in methods of drug design. Furthermore, deutetrabenazine was approved as a NME, rather than as an extension of tetrabenazine, suggesting that sometimes the KIE can be large enough to have a significant, patentable effect[10]. Moreover, the process of deuterating a drug is complex. One would have to determine exactly which hydrogen atoms should be exchanged and

then study the effects of the drug. This study is complicated by the fact that sometimes while drugs are beneficial in vitro they are not in vivo[5].

The issue of patentability has large monetary importance, increasing its importance. The intellectual property rights for a deuterated version of lenalidomide, with the addition of deuterium decreasing the rate of racemization, was sold from Deuteria Pharmaceuticals to Celegene for 42 billion dollars[11]. This sale occurred *before* the drug was fully developed. On a much larger scale, Teva Pharmaceuticals paid 3.5 billion dollars to acquire Auspex, the company reasonable for the development of Austedo.

Patentability would become even more difficult if the rights to the deuterated drug were owned by a different company than the one that sells the non-deuterated drug. Because there can never be one-hundred percent deuterium incorporation, some of the deuterated drug would be sold with its deuterium-lacking counterpart—a complication that could lead to lawsuits. To counteract this possibility, many companies, such as Celegene, are purchasing or patenting any deuterated analogs.

Toxicity and Cost Concerns

Deuterium does not only have positive effects on the compound, however. In some instances, the metabolites of the deuterated compound are toxic, while the metabolites of the undeuterated compound are not[5]. It should be noted that generally, this is not the case and deuterium is relatively non-toxic. Deuterium would need to be present in 20% of a humans total body water before it reached toxic levels and even then this toxicity is reversible [9, 10]. However, in some instances, such as with JNJ-38877605 and HC-1119, the toxicity could decrease[12]. In this way, deuterium could be used to ‘save’ already developed drugs that proved too toxic to pass

phase one clinical trials. Therefore, it is essential to study the toxicity at all stages when developing new drugs, even if the only new aspect is the addition of deuterium.

Another concern is the cost of deuteration. While strides have been made in the field, many reactions still involve precious metals such as gold or deuterated solvents, both of which increase the cost of production. Though this cost could be partially mitigated by the decrease in dosage size and the relatively small amount of deuterium needed, it still may remain too high for some. Due to cost and selectivity issues of deuteration as well as limited KIE, Cargnin et. al. suggests that less than 10% of the drugs currently on the market are good candidates for deuteration[12]. Nevertheless, an increasing number of drugs containing deuterium are produced, with several sources comparing deuterium's potential to that of fluorine.

Comparison with Fluorine

Fluorine, beginning in the 1970s, began to be added to more drugs for stability. While originally fluorine was only in 2% of drugs, it is now in around 50%[5]. Several articles draw the parallel between deuterium labeling and the addition of a fluorine group [12,5]. Furthermore, the addition of a deuterium atom can, in some cases, be more beneficial than the addition of fluorine. Most notable this occurs when changes in electronegativity and steric hindrance cannot be tolerated. One example of this is the recent study on how to best improve Celecoxib.

Celecoxib is an anti-inflammatory, pain relieving, antipyretic drug that belongs to a class of cyclooxygenase-2 (COX-2) inhibitors. These drugs currently lack a radiotracer as current tracers lack either specific binding, metabolic stability, or ability to demonstrate COX-2 binding in vivo. This study focuses on increasing the metabolic stability of methylsulfonyl-substituted celecoxib through the addition of deuterium or fluorine. Deuterium was added through the

reduction of an intermediate with $LiAlD_4$, rather than $LiAlH_4$. Deuterium was found to not change the COX-2 inhibitory potency but lengthening the fluoroethyl chain decreased both the inhibitory potency and selectivity. While the two variations had similar pharmacokinetic patterns, the deuterium substituted variation was more intact after 60 minutes (52% remaining vs 28% remaining). Deuteration enhances metabolic stability both in vitro and in vivo the most; it has a greater positive effect than the addition of fluorine[29].

Deuterium was also chosen over fluorine in the development of JNJ-38877605 [12]. While fluorine was the first instinct of the developers to stabilize this drug, it could not be used as it would affect the ability of the compound to bond with the residue of kinase as it needs to do [12].

A Comprehensive List of Deuterated Drugs?

Currently, there are twenty different pharmaceutical compounds in various stages of testing that contain deuterium[5]. Of these, sixteen compounds are deuterium containing analogs to already approved and administered drugs, two are deuterated forms of nutritional compounds, and two do not have a non-deuterated counterpart, meaning deuterium was utilized from the beginning stages of development[5].

A full list of drugs currently in development and accessible through a search on clincialtrials.gov can be found in Appendix A. However, it should be noted that this list is not fully comprehensive as some individual companies advertise the development of deuterium containing drugs that do not appear in the aforementioned database. Furthermore, many companies are reluctant to advertise the composition of drugs under development. In May of 2015 when Teva purchased Auspex it was estimated that over 60 deuterated drug candidates

were being studied[11]. Currently many companies, including Pfzier, Teva, Concert, Avanir, and DeuteRx are all researching, or at least patenting, deuterated analogs of drugs in development.

Methods of Deuterium Labeling

Using Nanoparticles and Nanosheets

A number of modern reactions use either nanosheets or nanoparticles, though not necessarily of the same element. However, while multiple elements can be used to catalyze these reactions, one common element utilized is cadmium [13,14,15]. Cadmium selenide is used in experiments due to several of its electrochemical properties, such as its bandgap which allows it to absorb solar energy and its conduction band edge which allows it to reduce water, which lends itself toward single electron transfer (SET) reactions as it forms D^+ ions, which later become deuterium radicals.[15]. When CdSe is developed in porous nanosheets, more catalytic sites become available to the substrate, allowing for more reactions to occur in the same span of time[14,15]. Nanowire cadmium sulfide is used for much of the same reasons[13].

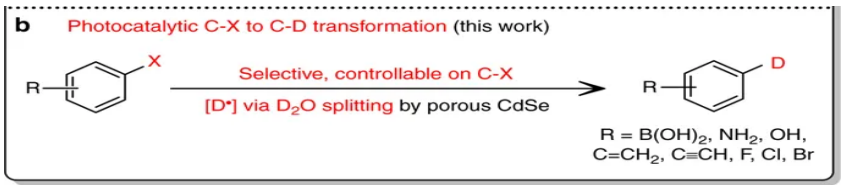


Figure 3: A reaction scheme for photocatalytic deuterium labeling with CdSe nanosheets[15]

While some articles found good deuterium incorporation with any halogen[13,14], it was determined that due to both bond enthalpies and reduction potentials, the best results occur when iodine is used[15]. Because of the mild reaction conditions, sensitive groups such as cyan, ester, amaino, hydroxyl, aldehyde, and ketones were not affected[15]. This marks a significant improvement over other halogen/deuterium exchanges which commonly use strong bases and

therefore lack the same degree of flexibility. Though pharmaceutical compounds were not directly synthesized using this technique, it remains an important step in the synthesis of deuterated pharmaceutical compounds. Deuterated intermediates that would otherwise remain inaccessible due to their fragility, such as alkynes, boric acid, and alkene-containing compounds, can undergo Suzuki coupling or bond insertion in order to form desired products[15]. An intermediate for deuterated nicotinic acid, an anti-hypercholesterolemia drug, was synthesized through this technique before undergoing further ester hydrolysis[15].

Palladium, Pd, is another element that, when in nanosheets, is used for reactions in which an aryl chloride is replaced with a deuterium atom[16]. Palladium serves as the catalyst to both activate the C-Cl bond and to replace the chloride atom with a deuterium atom[16]. Furthermore, the nanosheet structure of this reagent allows it to collect the electrons released when the deuterium source, in this case D_2O, breaks down as well as regenerate the sacrificial agent[16].

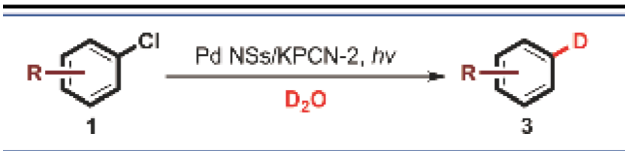
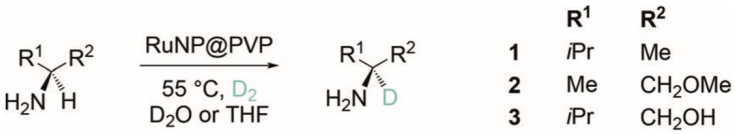


Figure 4: A reaction scheme for the replacement of a chloride atom with a deuterium atom through the use of a palladium nanosheet [16].

Ruthenium is one of nanocatalysts that has been used for the longest period of time in the field of deuterium labeling and in a way, paved the way for the aforementioned elements[17]. Ruthenium, similarly to palladium, activates the CH bond, allowing the rest of the reaction to occur[17]. As this step is the rate determining step, it is important to note that the nanoparticle nature of the ruthenium atoms decrease the activation energy[17]. Therefore, while ruthenium is the catalyst, the innovation of using a nanocluster allows the reaction to proceed faster and with less energy. Ruthenium nanoparticles, along with D_2O, were able to deuterate the α position of the

nitrogen atom of an amine through the activation of a C(sp3)-H bond. This reaction occurred enantiospecifically for amino acids with aliphatic, amide, and nitrogen containing side chains[17]. Molecules containing multiple good ruthenium coordination units, such as carboxylic acids, amines, and aromatic rings, had a lower deuterium incorporation due to decrease in flexibility of the molecule. Notably, these reaction conditions were able to selectively deuterate the C_α carbon atom of the N-terminal group amino acid of several peptides—a modification of interest in the field of drug development.



	R1	R2
1	*i*Pr	Me
2	Me	CH_2OMe
3	*i*Pr	CH_2OH

Figure 5: A reaction scheme for a HAT reaction using ruthenium nanoparticle as a catalyst[17].

Radical Pathways

The palladium nanosheet previously mentioned has a radical pathway. Palladium works with the photocatalyst which is, in this reaction, crystalline polymeric carbon nitrides (CPCN)[16]. While the CPCN creates the radical deuterium, the palladium nanosheet traps the radical that causes the HAT to occur[16].

Cadmium sulfide, or CdS, has a slightly different radical pathway. It works with gold to deuterate aryl halides[13]. The gold releases an electron which is then transferred to first the CdS nanowire and then the aryl halide[13]. The halide then falls off of the aryl halide anion leaving an aryl radical, which is then deuterated by D_2O[13].

Another radical pathway occurs in the development of deuterated silanes. In this reaction, the catalyst, 4CzIPN, becomes a radical[18]. This radical is then quenched by HAT through SET to

make a thiyl radical[18]. It is this thiyl radical that both regenerates the photocatalyst and forms the silane radical[18]. Once the silane is a radical, it can rob the deuterated thiol of its deuterium atom and become deuterated[18].

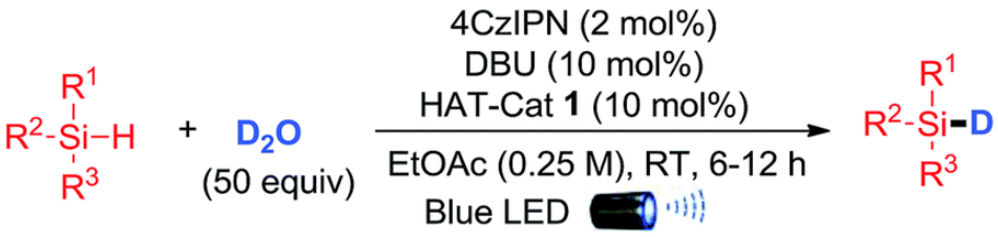


Figure 6: A reaction scheme for the deuteration of silanes through the use of the photocatalyst CzIPN[18].

A very similar mechanism occurs with iridium, Ir, as the photocatalyst. However, in this reaction, amines, rather than silanes, are deuterated and several intermediate steps are eliminated. This reaction starts when the 'excited' iridium atom oxidizes an amine, forming an amino radical at the alpha position[19]. This amino radical is then deuterated with the same deuterium donor as the previous reaction, deuterated thiol.

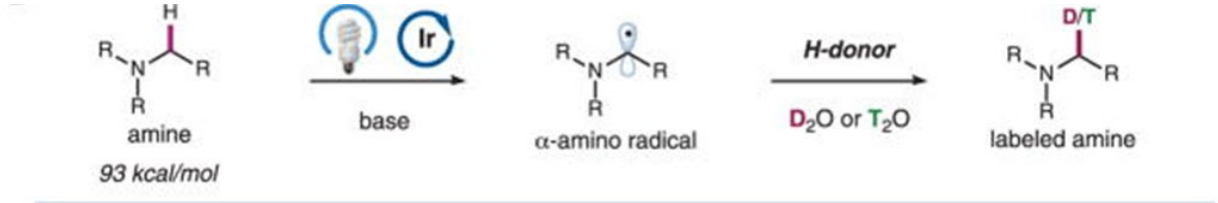


Figure 7: A reaction scheme for the deuteration of α-amines through the use of the photocatalyst iridium[19].

Some mechanisms, unlike those previously mentioned, do not require a catalyst. Instead, light can immediately activate a bond, such as the S-N bond in arylazo sulfones, forming an aryl radical[20]. The weakest CH bond on the ring then undergoes HAT with either deuterated isopropanol or deuterated THF as the deuterium donor[20].

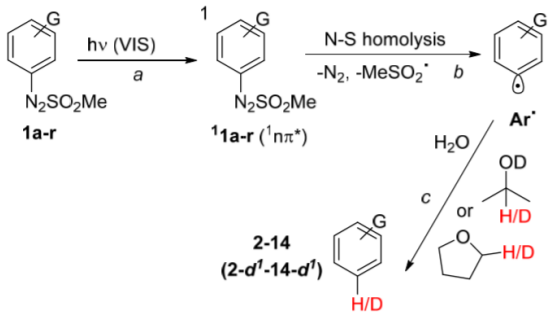


Figure 8: A reaction scheme for an arylazo sulfane undergoing deuteration without the use of a photocatalyst[20].

Though there are many different individual radical pathways, most follow a similar pattern. First, the substrate must be radicalized, though this may occur through an intermediate[16,18], due to a photocatalyst [13,16,18,19], or independently[20]. The substrate then becomes quenched with the addition of a deuterium atom with the donor changing depending on the reaction. In some cases, this reaction can be nearly infinite[18] while most others are limited by the amount of reagent.

Photocatalytic Reactions

Due to the current interest and demand for green chemistry, a number of reactions involving both visible and UV light have been researched [13-16,18-21]. These reactions benefit from conditions that are less harsh, as many do not require strong acids or bases, though some[21] still do. This lack of strong acids generally leads to a higher tolerance of functional groups. Moreover, it allows for the development of deuterated pharmaceutical compounds, many of which are not tolerant to extremely basic or extremely acidic solutions. However, these benefits do not imply that there are no issues with photocatalytic reactions.

Though much research has been done regarding photoredox reactions[22], the best photocatalyst is still debated. While some, such as gold, allow for a greater separation of charge and absorption of light in the visible spectrum[13] and may have a high quality, others are a significantly less expensive [18,21] but sacrifice some functional group tolerance and variability. Still others do not require a photocatalyst[20] but only work on one type of molecule. Within the community, however, it is noted that the photocatalyst CdSe porous nanosheets [14,15] marked a significant turning point in the ability to label compounds.

A study completed by Kuang et. al. focuses on the direct H/D exchange between D_2O (used at 50 equiv) and molecules containing either formyl C-H or hydriodic C(sp3)-H bonds using tetra-n-butylammonium decatungstate (TBADT)(2%mol) and 2,4,6-triisopropyl benzenethiol(10% mol) as HAT photocatalysts[25]. The direct H/D is preferred because while halogen/deuterium exchange and reductive deuteration both require precursors, H/D exchange can be done directly on the compound of interest. The average reaction time was 4-8 hours under 390nm light, though some substrates, such as the hydric C(sp3)-H bonds that occurred in the same molecule as an aldehyde group and 4-acetoxybenzaldehyde required either a longer reaction time (48hr) or higher energy light (365nm).

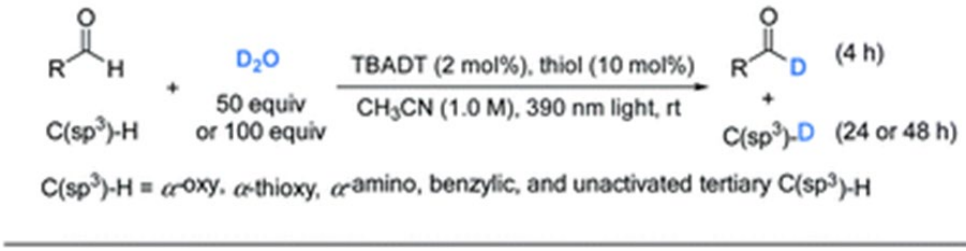


Figure 9: A reaction scheme for the deuteration of aldehydes through the addition of the photocatalyst TBADT[25].

Aromatic aldehydes, aldehyde with an electron withdrawing group (ie halides, trifluoromethyl, cyanide, boronate ester), and aldehydes with electron donating substituents (ie amides, phenols, ethers) were all able to be deuterated with no lower than 89% deuterium incorporation. These reaction conditions also allow for selective deuteration for if the reaction continued for 48hours, the secondary groups (α-oxy,α-thioxy, benzylic C(sp3)-H bonds) could be deuterated as well. The more hydridic C-H bonds underwent deuteration to a greater extent. Those molecules with hydridic C(sp3)-H bonds without an aldehyde could be selectively deuterated as well. However, for these substrates, more TBADT was necessary.

Several pharmaceutical compounds could be deuterated using this method including ibuprofen, gemfibrozil, heterocyclic drugs (fomepizole, edaravone, pirfenidone) at only the benzylic C-H bonds, mexiletine, and chloroxylenol. Notably, drugs in the adamantane family (amantadine, memantine) were deuterated with more than 5 deuterium atoms per molecule and less than 0.1% unlabeled molecule remaining, allowing them to be used as internal standards in ADME-Tox biostudies. Several precursors for drugs were also deuterated. However, the deuteration mainly occurred at the benzylic position, rather than all of the required positions (missing phenyl methoxy groups and α-carbonyl).

Figure 10: Structures and percent incorporation of deuterium for drugs in the adamantane family through the use of the TBADT catalyst[25].

This reaction proceeds through a radical pathway. A carbon radical is generated through HAT between the substrate and photo-excited TBADT. The deuterated thiol is made due to the

presence of excessive D_2O. The carbon radical then reacts with the deuterated thiol to make the deuterated product and a thiyl radical. The thiyl radical interacts with $[W_{10}O_{32}]^{5-}H^+$ to remake TBADT and deuterated thiol[25].

For the deuteration of aldehydes, Garg et. al. focused on using N-heterocyclic carbenes (NHC). The NHC condensed on the aldehyde forming a Breslow intermediate, which then underwent deuteration, forming the desired product[26]. Different catalysts were necessary for varying aldehydes with varying functional groups. Aryl aldehydes were deuterated using an imidazolium catalyst, while enal aldehydes used triazolium catalysts[26].

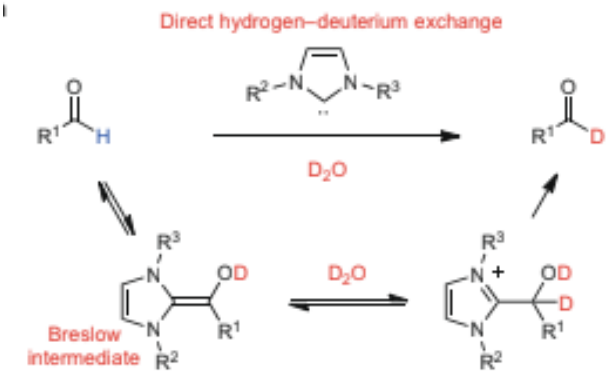


Figure 11: A reaction scheme for the deuteration of aldehydes through the addition of NHC[26].

Deuterating Pharmaceutical Compounds (miscellaneous)

Deuterating sites that are metabolized is an effective method to slow the deterioration of a compound. "Metabolism occurs on pyridines and diazines by molybdenum-containing enzymes such as aldehyde oxidases (AOs)"[27]. Currently, the drug VX-984, involving a deuteration that slows this AO metabolism, is in development. Koniarczyk et. al. developed a method for deuterating pyridines and diazines by first transforming them into phosphonium salts and then reacting these salts with D_2O and K_2CO_3[27]. This reaction allows for the hydrogen at

carbon position 4 to be deuterated with high regioselectivity. This is in contrast to several other methods, including one discovered by Chirk, that for the same compound (loratadine) deuterated at positions 2 and 3. When this position is blocked the compound is deuterated at position 2. Pyridines with 3,5-substituents are deuterated with complete regioselectivity, even when this substituent is a halogen.

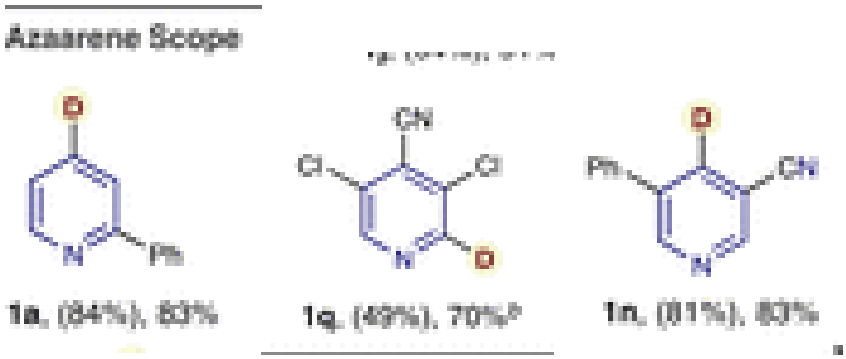


Figure 12: The selective deuteration at position 4, the selective deuteration at position 2 when positive 4 is blocked, and the selective deuteration with 3,5 substituents through the transformation into salts and then deuteration with K_2Co_3[27].

Around 50% of the top-selling pharmaceuticals contain N-alkyl amine groups[23]. Recently, a photoredox method was discovered resulting in the deuteration of α bonds. However, a method for the deuteration of βC-H bonds is slightly more complicated due to their increased stability. Chang et. al. discusses an acid-base reaction containing acetone-d_6 as a deuterium source, $B(C_6F_5)_3$ as a catalyst, and a reaction temperature of 150°C. The product was then filtered through silica gel chromatography. Cyano, ester, amide, and ketone N-alkylaines all gave deuterium products in a yield >95% [23]. Moreover, this reaction was more efficient when the substrate had a hindering group. Some pharmaceutical compounds that were effectively deuterated include piperidine, 1,4-diazepane, piperazine, thiophene, indanone, benzodioxole, benzothiophene, benzimidazole, clopidogrel, prasugrel, and doneprezil[23].

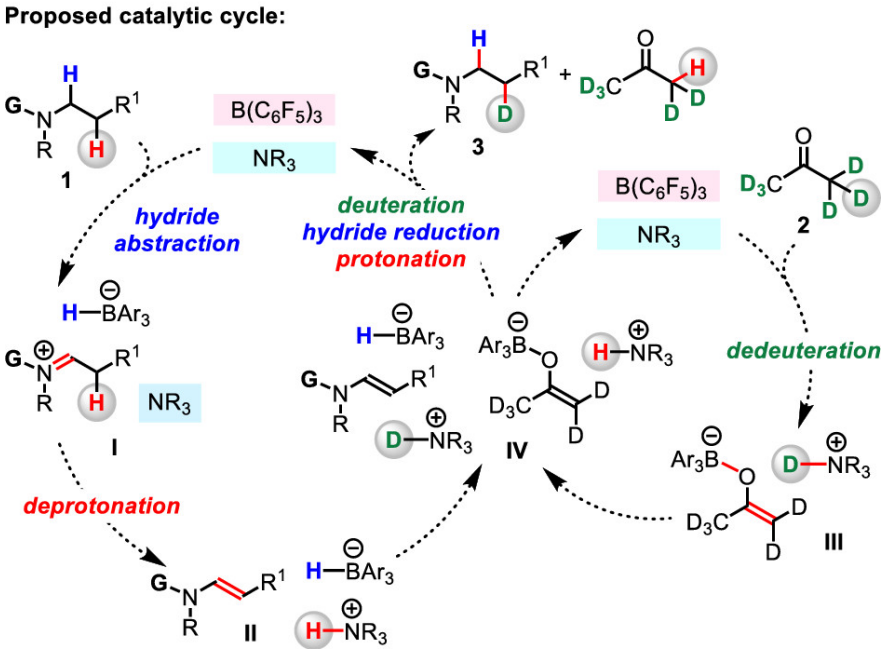


Figure 13: A proposed reaction scheme for the deuteration of the β-CH bonds of amines through the addition of the catalyst $B(C_6F_5)_3$[23].

The same catalyst, utilized by Chang et. al. could be used to deuterated carbonyls at temperatures ranging from 60 to 100°C (with a higher temperature leading to higher levels of deuterium incorporation)[24]. Both acyclic and cyclic bioactive ketones were deuterated, along with compounds containing methoxy theobromine, carboxylic acid, N-alkylamine, and hydroxyl groups. Clopidogrel and risperidone, two pharmaceuticals containing these groups, also showed moderately high (60%) to very high (95%) deuterium incorporation[24]. However, some compounds, such as the drug donepezil which is used to treat Alzheimer's, required up to 12 hours to reach 90% incorporation[24].

Conclusion

The addition of deuterium in pharmaceutical compounds has multiple different effects ranging from a decrease in the rate of metabolism to an increase in stability of a chiral compound. This in turn allows medicinal chemists to develop new drugs or breathe new life back into previously patented drugs, both increasing its effectiveness and decreasing the negative side

effects. While some may have concerns regarding the patentability, toxicity, or cost of these compounds, these worries do not currently serve as a strong enough deterrent to persuade people to *not* study the effects of deuterium incorporation. Deuterium appears to be creating a new wave in the drug development industry, with multiple experts predicting a similar level of incorporations of deuterium across the field as the addition of fluorine that occurred years ago.

To this end, new methods for adding deuterium to compounds, especially medically relevant compounds, are being developed. The majority of these developments focus on photocatalytic deuterium addition due to its mild reaction conditions which allow for the persistence of sensitive functional groups. Of these reactions, most proceed through a radical pathway and involve nanoparticles or nanosheets of previously well known and utilized catalysts such as ruthenium. Through the utilization of these new reaction conditions, amines, aldehydes, and aryl groups are able to be deuterated, facilitating the development of deuterated drugs.

Research in this field will only increase as the deuterated drugs already undergoing clinical trials become approved and more begin to be created. Further research on methods of activating and deuterating C(sp2)-H bonds is needed and may follow the example of Liu, Yifu, and Dong and their application of porous CdSe nanosheets. However, even this method is not perfect as it requires that the desired drug have an acceptable, halogenated intermediate.

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Appendix A

Drug Name	Therapeutic Indication	Effect of Deuterium	De novo?	Phase	Status
Deutetrabenazine (Austedo)	Chorea from Huntingtons	different ratio metabolites, longer half life	No	*	
JNJ38877605	C-Met inhibitor (neoplasms)	less toxic, less doses	No	1	Terminated (Health Risks)
CC-122	melanoma	stabilize enantiomer switching	No	2	Recruiting
	renal insufficiency		No	1	Unknown
	lymphoma, non-hodgkin		No	1	Active, Not Recruiting
	lymphoma, non-hodgkin		No	1	Active, Not Recruiting
	diffuse B-cell lymphoma		No	1	Active, Not Recruiting
	leukemia, lymphocytic, chronic B-cell		No	1,2	Completed
	lymphoma (non-hodgkin), lymphoma (large B-Cell, diffuse), lymphoma (follicular)		No	1,2	Recruiting
	multiple myeloma, lymphoma, pleiotropic pathway modifier, glioblastoma,		No	1	Active, Not Recruiting
	carcinoma, hepatocellular		No	1	Terminated (No Health Risk)
	carcinoma, hepatocellular		No	1,2	Unknown

HC-1119	prostate cancer metastatic, castration-resistant prostate cancer	less toxic	No	3	Not Yet Recruiting
	metastatic castration resistant prostate cancer		No	3	Recruiting
ALK-001	stargardt disease, stargardt macular degeneration, stargardt macular dystrophy, autosomal recessive stargardt disease 1	inhibitor	No	2	Recruiting
	geographic atrophy, age related macular degeneration, AMD		No	3	Recruiting
RT-001	Friedreich's Ataxia, lipid peroxidation	half life	No	3	Recruiting
	Infantile neuroaxonal dystrophy		No	2,3	Active, Not Recruiting
	lateral canthal lines, crows feet, facial wrinkles		No	2	Completed
BMS-986165	autoimmune (inhibit tyrosine kinase 2) (with rosuvastati)		Yes	1	Completed
	lupus		Yes	2	Recruiting
	ulcerative colitis		Yes	2	Recruiting

	granulomatous colitis, crohn's disease, crohn's enteritis, granulomatous enteritis		Yes	2	Recruiting
	renal impairment		Yes	1	Completed
	active psoriatic arthritis		Yes	2	Active, Not Recruiting
	psoriasis		Yes	3	Recruiting
CTP-543	JAK1 inhibitor, Alopecia areata		No	3	Recruiting
CTP-656	cystic fibrosis	half life	No	2	Completed
SD-1007 (D3-L-DOPA)	Parkinsons	Slows metabolism by slowing AO metabolism	No		
AVP-786	neurobehavioral disinhibition (agitation due to brain injury)	simplify	No	2	Recruiting
	schizophrenia		No	2,3	Recruiting
	agitation in patients with dementia of the alzheimer's type		No	3	Completed
	intermittent explosive disorder		No	2	Terminated (No Health Risk)
	depressive disorder, treatment-resistant		No	2	Completed
HC-1144	Anti tumor	side effects, half life	No		
VX-984	cancer (endometrial)	reduce aldehyde-oxidase (AO) metabolism	Yes	1	Completed

CTP-354	multiple sclerosis (MS), cerebral palsy, amyotrophic lateral sclerosis (ALS), spinal cord injury, and hereditary paraplegia	improved pharmacokinetics (bonding affinity, subunit specificity, pharmacological activity		2	Unknown
CTP-518	HIV		No	1	Completed
JZP-386	narcolepsy, excessive daytime sleepiness		No	1	Completed
CTP-730			No	1	Completed
CTP-499	moderate chronic kidney disease, non dialysis		No	1	Completed
donafenib	thyroid cancer		No	3	recruiting
	metastatic colorectal cancer		No	3	Completed
	advanced hepatocellular carcinoma		No	1,2	Not Yet Recruiting
	advanced gastrointestinal tumors		No	1,2	Not Yet Recruiting
	nasopharyngeal carincoma		No	1,2	Recruiting
	non-small cell lung cancer		No	1	Recruiting
	hcc		No	2,3	Completed
	advanced solid tumor		No	1,2	Not Yet Recruiting
PXL065 (DRX-065)	nonalcoholic steatohepatitis	chiral switching	No	2	Not Yet Recruiting
CTP-692	schizophrenia		No	2	Not Yet Recruiting

* Indicates that the drug has been approved by the FDA

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