JOURNAL OF PHARMA INSIGHTS AND RESEARCH

REVIEW ARTICLE

The Re-emergence of Deuterated Drugs in 21st Century

Adhi Kesava Naidu Neelam [1 *], Vijaya Durga N [2], Ajay Ratnam Mulaparthi [3], Esther Puli[4], Pallavi Badarala [5]

[1] *Student, B. Pharmacy, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, Andhra Pradesh, India*
[2] *Asst. Professor, B. Pharmacy, AKRG College of Pharmacy, Nallajerla, Andhra Pradesh, India*
[3] *Asst. Professor, B. Pharmacy, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, Andhra Pradesh, India*
[4] *Asst. Professor, B. Pharmacy, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, Andhra Pradesh, India*
[5] *Assist. Professor, B. Pharmacy, Sri Vasavi Institute of Pharmaceutical Sciences, Tadepalligudem, Andhra Pradesh, India*

Article DOI: 10.5281/zenodo.10039260
Publication history: Received on 3 Sep 2023; Revised on 18 Oct 2023; Accepted on 23 Oct 2023

Abstract: The idea of substituting hydrogen isotope atoms with a deuterium isotope is an illustration of bio-isosteres, in which the biological effects of a recognized medicine are synthesized in an analog that is intended to have superior qualities. The Food and Drug Administration's clearance of the first drug with a deuterium label highlights the recent growth in the employment of deuteration in medicinal chemistry. When faced with issues including metabolism-mediated toxicity, drug interactions, and poor bioactivation, precision deuteration goes beyond the basic improvement of a medication's pharmacokinetic properties and may present an opportunity. Deuterium is used in even more diverse ways, allowing for the possibility of lowering epimerization levels, lowering co-administered booster doses, and finding molecules whose mechanisms of action are based on deuterium. However, creating, synthesizing, and producing an effective deuterated medicine and studying its toxic effects is far from simple, and the transition from idea to reality is frequently unexpected. Deuterated compounds often have advantages over their non-deuterated counterparts, usually due to changes in clearance. Deuteration may also reroute metabolic pathways to minimize toxicity. Additional deuterated chemicals may soon be approved. Practitioners will need to be knowledgeable about the dosage, effectiveness, potential adverse effects, and particular metabolic profiles of these novel substances.

Keywords: Deuterated drugs; Bio-isosteres; Synthesis; Toxicity; Metabolism

1. Introduction

Isotopes are atoms with an equal number of protons but differing numbers of neutrons. They differ in mass, which affects their physical qualities even if their chemical characteristics are nearly the same. Isotopes exist that are unstable and release radiation and steady isotopes that don't. The latter are renowned as radioisotopes.

The quantity of protons in nuclei of an element's atoms, or the element's atomic number, defines it. Furthermore, the number of neutrons in the nucleus of some elements' atoms could vary. These are known as isotopes, and they can be found in specific elements. Radioisotopes and stable isotopes both have the potential to spontaneously disintegrate. Between 2 and 10 stable isotopes make up about two-thirds of all the elements [1]

The abundance of the lighter isotopes is frequently greater than that of the heavier ones; for instance, the carbon isotopes 12C and 13C are abundant at 98.89 atom% and 1.11 atom%, respectively; the nitrogen isotopes 14N and 15N are abundant at 99.63 atom% and 0.37 atom%, respectively; and the oxygen isotopes 16O, 17O, and 18O are abundant at 99.759 atom%, 0.037 atom%, and 0.204 atom%, respectively; Moreover, the percentages of hydrogen isotopes 1H and 2H (D) are 99.985 atom% and 0.015 atom%, respectively. [2].

When it comes to drug research and development, medicinal chemists employ a variety of strategies to maximize the safety and effectiveness of small-molecule compounds. One of these is bioisosterism, in which a substructure is swapped out for a new one to enhance a compound's characteristics while maintaining its biological activity1. For instance, the tiniest conceivable chemical alteration, substituting deuterium for hydrogen, might significantly affect a range of pharmacological properties. Originally, deuterium insertion was thought to just improve a compound's metabolic stability. It has since been demonstrated, moreover, that this modification might have a significant influence on both pharmacological effectiveness and safety, going well beyond straightforward pharmacokinetic (PK) benefits

* Corresponding author: Adhi Kesava Naidu Neelam

2. Deuterated Compounds

2.1. Discovery

Deuterium was discovered by Harold Urey, among the finest scientists of the 20th century. Even without having an in-depth understanding of isotope, he nevertheless comprehended the significance of his work well enough to foresee a large portion of what's transpired to deuterium science as a consequence. Tens of thousands of scientific articles have included this isotope. And when it comes to valuing and using deuterium, Perhaps the nuclear industry comes in second to the pharmaceutical industry. The incorporation of the isotope into the finished product will be the next development in this expanding connection [3] [4].

2.2. Deuterium Isotopes in Medicinal Chemistry

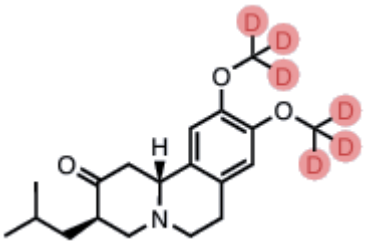
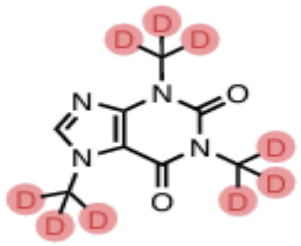
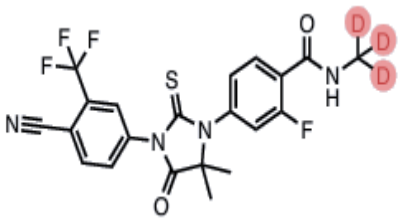
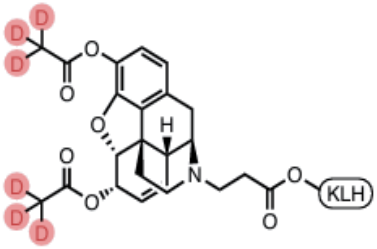
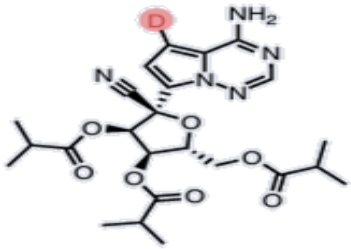
As a part of active medicinal compounds, deuterium is becoming increasingly valued and used. The potency and selectivity of a chemical that has been deuterium modified or deuterated remains intact. The deuterium isotope effect has the potential to drastically alter medication metabolism in some circumstances, it might positively impact the safety, tolerability, or efficacy of medication characteristics. Long-term research has been conducted on deuterated medications, however, it has taken them thus long to reach the final stages of clinical testing [5] [6] [7]. This is particularly significant since deutetrabenazine, the first medication containing deuterium was granted approval by the US FDA in 2017. While keeping comparatively similar steric properties, the carbon-deuterium (C-D) bond is significantly more resistant to oxidative activities, such as those catalyzed by CYP450 or other metabolism-related enzymes (for example, MAO, and aldehyde oxidase). This is because Compared to H, D is twice as massive. The presence of such resistance has endured to be demonstrated empirically, individually, as it depends more on the circumstances surrounding the enzyme's catalysis, which is particularly noticeable in circumstances when the phase that supposedly controls the rate is C-H bond breaking. Consequently, the Hydrogen-Deuterium (H-D) isosteric substitution by an oxidizable soft spot often maintains the pharmacodynamics while enhancing the way that pharmacokinetics of medication with an effect on the half-life, the area under the curve, and, ultimately, dosage and/or dosing schedule [8].

2.3. Deuterated Drug Synthesis

The advantages of deuterated medications and the researchers' interest in them led to their synthesis. The deuterated medicine allowed the whole pharmaceutical industry to concentrate on ways to replace the hydrogen isotope with the deuterium isotope. There are just a few successful strategies and ways to do this.

According to an examination of the methods used to produce advanced deuterated candidates, the most popular way to utilize deuterated APIs is by using currently both accessible and traditional deuterated chemicals, sometimes known as "deuterated pool," such as CD3I, CD3OD, and D6-acetone [9] and as evidenced by the commercially available methods created for the drugs deutivacaftor and deucravacitinib [10] Regretfully, it's not always practical to use deuterated building blocks. Although severe Conditions for the experiment are often as a replacement for the target chemical or a late step, hydrogen isotope exchange (HIE) can be carried out selectively and quantitatively, but D enrichment is particularly difficult. Another alternative is the reductive deuteration of the carbonyls with the existence of deuterated metallic hydrides like NaBD4 or LiAlD4, or of alkenes using D2 gas and a catalyst, or very intricate processes. It has recently been revealed that the enantiospecific insertion of D at stereocenters may be achieved using biocatalytic reductive deuteration of multiple double bonds. [11] In the aftermath of a groundbreaking effort by MacMillan and colleagues describing photoredox methods to deuterate the α-position of pharmaceuticals based on N-alkyl amines [12] Photocatalysis [13] electrochemistry and radical chemistry [14], rapidly to offer approaches that will appeal to the pharmaceutical sector in the deuteration field. Notably, A lot of focus has been placed on the course of synthesizing per-deuterated methyl groups due to their significant significance in enhancing pharmacological profile although Nowadays, methods exist for mono-deuterating alkyl locations. This will open the door for future research on a characteristic that is now unknown: the impact of one D atom on the oxidative metabolism of a drug.

Table 1 Some instances of deuterated compounds

SN.	Structure	Therapeutic use (mechanism of action)	Deuterium incorporation's advantages
1	 Deutetrabenazine(d6-tetrabenazine)	Tardive dyskinesia and Huntington chorea (VMAT2 inhibitor)	enhanced interaction with active metabolites
2	 d9-caffeine	premature birth apnoea; analgesic drug interactions with painkillers (adenosine receptor antagonist)	Reduced oral absorption and elevated PK parameters (extended $t_{1/2}$, higher AUC)
3	 Deutenzalutamide (d3-enzalutamide, HC-1119)	Prostate cancer resistant to castration (androgen receptor antagonist)	PK improvement; decreased metabolite production linked to adverse consequences
4	 Heroin vaccine	Addiction to opioids	boosted defence against illness
5	 VV116 (JT001)	COVID-19 and RSV (RNA-dependent RNA polymerase inhibitor)	involvement in the transition of oral medication from intravenous

The structure of deuterated compounds is shown in the table.

3. Pharmacological role

Deutetrabenazine, applied to treat both choreas related to Huntington's disease and tardive dyskinesia, earliest deuterated substance to be used in therapeutic settings. Over 20 deuterated drugs are currently undergoing clinical development; six of these (BMS-986165, AVP-786, RT001, ALK-001, donafenib, and HC-1119) have initiated Phase III clinical trials as a result of their success in

encouraging industry funding for the development of deuterated drugs [15]. Deuterated medication clinical testing has advanced significantly during the past six months, and there is undoubtedly a stir in the industry. A brand-new deuterated medication called HC-1119 officially entered the field of medicines deuterated under clinical research in December 2018. Enzalutamide, the two-generation androgen receptor competitive antagonist that is successful in treating metastatic prostate cancer resistant to castration (mCRPC), has an analog of deuterium called HC-1119. Enzalutamide users had a greater probability of having seizures even if it was proven to enhance overall survival in individuals with mCRPC substantially in comparison to placebo [16]. A deuteration technique was used to enhance the PK characteristics of enzalutamide and perhaps reduce side effects because it was discovered that this sort of toxicity was dosage-dependent. The N-CH_3 moiety was switched to N-CD_3 to reduce the N-demethylation pathway, as CYP2C8 and CYP3A4/5 metabolize enzalutamide primarily to N-demethylenzalutamide. In several in vivo models, it was discovered that HC-1119 had an enhanced profile of PK together with an increased safety cushion than its nondeuterated equivalent [17].

Currently, Clinicaltrials.gov lists five clinical studies for HC-1119. Three Phase I, open-label clinical trials are being conducted to assess the pharmacokinetics of HC-1119 in individuals with mCRPC (NCT03778047) and healthy subjects (NCT03776968). The pair ongoing Phase III multicenter randomized double-blind clinical trials investigations that compare oral HC-1119 to placebo or oral enzalutamide concerning their effectiveness and patient safety with mCRPC. (NCT03851640 and NCT03850795, respectively). It is crucial to remember that using enzalutamide as an obvious comparison allows for an extremely informative research design since it gives the opportunity to accurately determine the benefit of deuteration. According to reports, the completion dates for Phase III research will occur in 2021. Deuterated chemicals are the subject of an increasing number of clinical trials, this is a direct outcome of the pharmaceutical industry's attempts to understand their medicinal potential. However, it has to be acknowledged that from the standpoint of a medicinal chemist, clinical research feeds information back far too slowly, with effectiveness and safety data anxiously awaited to determine whether to follow this tactic more frequently. Particularly instructive trials are those that compare deuterated and non-deuterated substances.

Providing proof of unanticipated ways that deuteration exerts its benefits is an excellent strategy to bolster claims about deuterated versions of already available medications. Deuteration at the precise position of this reaction was regarded sufficiently non-obvious in the instance of the aforementioned deuterated bupropion to cause a decrease in the racemization caused by keto-enol tautomerization. If combined with previous data on the effects of deuteration isotopes on keto-enol tautomerization, this patent might be used as prior art in the future to regulate such racemization [18].

3.1. Biological Effects of Deuterium

Both Urey and G. N. Lewis realized shortly after deuterium's discovery that protium and deuterium's chemical and physical characteristics would be sufficiently dissimilar to produce noticeably distinct biological activity from one another. These predictions have already been verified to the fullest extent, and biological investigations of deuterated systems are now recognized as a crucial new tool in molecular biology. One might say that the field is still young.

Scheraga, Hermans, and Calvin carried out a sample experiment. These researchers looked at how deuteration affected polypeptides, proteins, and enzymes as they changed from helical to random coil structures. The development and breakdown of hydrogen bonds from one amino acid group in the molecule to another is a crucial aspect of these changes, which are of essential biological relevance. We may anticipate a movement in the transition temperature on the order of the % shift in the hydrogen bond strength if the strength of the hydrogen bonds is altered, as would occur if deuterium were substituted for protium in a molecule.

All that goes on in the evaporation of water is the creation and breaking of hydrogen bonds. Protium and deuterium exhibit a 7 % per hydrogen atom variation in vapor pressure for this procedure. Concerning a transition that occurs close to room temperature, one may anticipate a change of 21 °C based on the difference in vapor pressure. Between deuterated and regular polybenzyl glutamate, there is a 12°C difference in transition temperature [19].

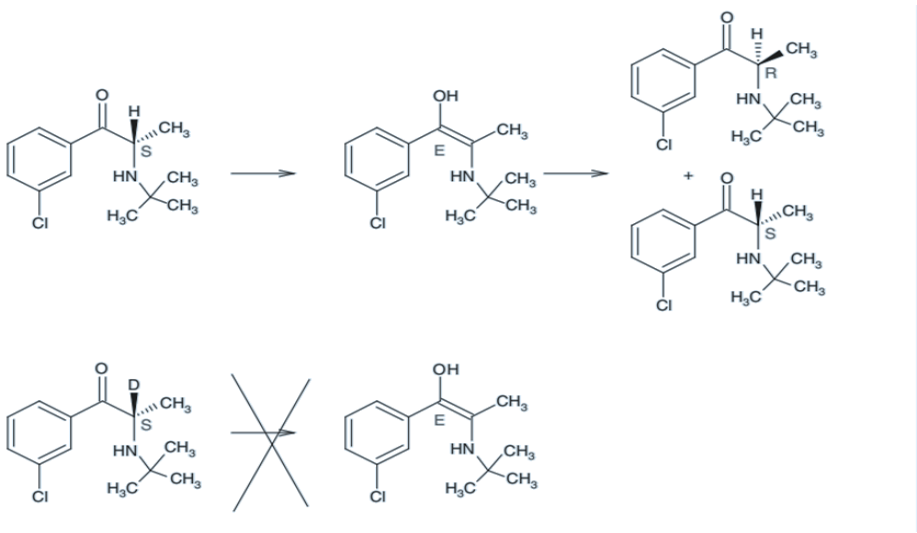


Figure 1 The frequency of bupropion racemization is greatly dropped by specific deuteration.

3.2. Deuterated Drug Safety Margin

Inquiries concerning the underlying toxicity of deuterium in pharmaceuticals are undoubtedly those that are voiced most reluctantly. Depending on where you reside, the natural availability of deuterium ranges from 0.0156% to 0.0175%. A typical-sized human body, like the author's, will therefore constantly have about 1 g of deuterium. All of the biomolecules that normally contain hydrogen atoms will have deuterium scattered throughout the body's water, or DHO, in different proportions at every position. The rise in deuterium load is therefore calculated at 1 g per day for average drug dosages of 100 mg per day, this is not unexpected considering this methodology has the deliberate end objective of redirecting the metabolism separate from the deuterated site. Even after accounting for the buildup in a steady state, this is a 0.1% rise within the deuterium burden. Studies on deuterium oxide-treated animals indicated that frank toxicity can only be observed at dosages of >25% complete replacement of body water, as well as this toxicity is reversible [19]. Deuterium's safety is sufficiently established that, as a matter of course, humans are routinely purposely subjected to this isotope in single- and double-labeled water experiments in a variety of metabolic research.

3.3. Toxicity

When deuterium is administered in the mass that is anticipated through pharmacological administration, there is concern about its toxicity. Over days to weeks, it has been confirmed that swapping out up to 15% of the body's total hydrogen with deuterium has very minor negative consequences in animals [19]. Additionally, substantial volumes of deuterated water have been given to healthy individuals without any known negative effects, including infants and expectant mothers [20]. Even though there would be very little deuterium administered as part of any pharmaceutical therapy, the effect that deuteration could have on a specific drug molecule is unpredictable, and the PK changes that deuteration produces may have unanticipated unfavorable consequences. Shifting a medicine to a different elimination pathway, for example, may result in a better kinetic profile but may also cause additional toxicity. The actual deuterated metabolites could end up being more difficult to get rid of than anticipated. Deutetrabenazine is the very first deuterated molecule to receive permission for clinical usage among the many deuterated compounds that have undergone development over time, it is significant to highlight.

3.4. Merits and Demerits

Cleaving a C-H bond is simpler than a C-D bond. Steric hindrance and electronic characteristics of H and D are identical. Deuterium is employed in the development of new drugs. Using deuterated examples to prevent patent applicants from entering the market. Numerous tumor cell lines, including the malignant astrocytoma cell line from mice and human digestive organ cell lines, are inhibited by D2O.

Attrition rate from in vitro studies to the clinical setting and variability. From an analytical standpoint, toxicological, and controllable issues, there are currently no set rules from the Food and Drug Administration (FDA) or other regulatory agencies describing the way to deal with isotropic contaminants in deuterated APIs. The Global Alliance for Quality & Innovation in Pharmaceutical Development recently established a task force designed to outline the issue and provide workable solutions.

For numerous reasons, it has become harder to create medications that arise through a deuterium transition. As with other substances, the patentability must be assessed in each case depending on the advancements achieved by the discoveries throughout the development

4. Conclusion

Continued research indicates great promise for using deuteration to improve the pharmacokinetics and/or toxicological properties of already available drugs. Deuterated versions of the novel compounds are now being claimed by the big pharmaceutical corporations in their ongoing patent applications, which makes this evident from the patent literature. Further, with outstanding work from large pharmaceutical corporations like Pfizer now encroaching towards the peer-reviewed press, there's one much better knowledge of the intricate and unpredictable consequences of deuterium substitution on pharmacokinetics and metabolism. It is simple to start the deuterium inclusion process. Additionally, reaching the decision point is typically swift and painless when well-thought-out and educated judgments are made along the route with a properly established assay approach. However, it is also quite simple to overlook significant advancements that are frequently made with this technology due to the lack of tests for unanticipated advantages. It pays to maintain a mind of curiosity and a conscientious analytical approach, even when sometimes things don't work out as expected we might wish. The technology, while still in its infancy in some places, is well-developed in others and offers promise for solving a variety of previously unsolvable issues.

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Author's short biography

Adhi Kesava Naidu Neelam:

Adhi Kesava Naidu Neelam has a lifelong fascination with science. Because of his success in scientific studies in high school, he decided to pursue a degree in pharmacy. He went on to obtain his pharmacy bachelor's degree and worked towards it. Following graduation, he plans to further his education to enhance both public health and pharmacy. With an eye on becoming a pharmacist, he hopes to use his curiosity and drive for self-improvement to further his career

Vijaya Durga Neelam:

Vijaya Durga Neelam completed her master's in Organic Chemistry and now, she is an Asst. Professor of Organic Chemistry, with one year of experience. Her research interests broadly include the facts behind chemical reactions

Ajay Ratnam Mulaparthi:

Ajay Ratnam Mulaparthi completed his M. Pharm in Pharmaceutics and now, he is Asst. Professor of pharmaceutics, with two years of experience

Esther Puli:

Esther Puli completed her M. Pharm in Pharmaceutics and now, she is an Asst. Professor of Pharmaceutics with three years of experience

Pallavi Badarala:

Pallavi Badarala completed her M. Pharm in Pharmaceutical Analysis and she is an Asst. Professor with one year of experience