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REVIEW ARTICLE

Deuterium - A Natural Isotope to Combat Microbial Resistance

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Abstract

Deuterated medicinal chemistry is an attempt to introduce deuterium into existing drug molecules through the replacement of hydrogen atoms (-H) with deuterium (-D). The process of deuteration is to reduce the rates of breaking the carbon-hydrogen bond. If the carbon-hydrogen bond breaking is the rate-determining step in the biotransformation of the drug, the deuterated drug may show improved pharmacokinetic characteristics, such as a longer half-life, hence lowering the need for frequent dosing. In this review, we discuss the improvement in the drug's pharmacokinetic profile with deuterium. Further, this Deuterium exchange chemistry can reduce toxicity and be safe for human use. Also, the drugs experimented with using deuterium are discussed as how deuterated chemistry can help fight antimicrobial resistance. Beyond all, still, the design and development of a successful deuterated drug with acceptable efficacy is hence a challenge. The translation of hypotheses from laboratory experiments to clinical application and further to real-time practice is unpredictable. Also, long-term drug stability and toxicity studies for individual drugs are to be studied which may vary from patient to patient.

Keywords: Antimicrobial Resistance, Deuterium, Metronidazole, Pharmacokinetic Property

1. Introduction

Deuterated medicinal chemistry is an attempt to introduce deuterium into existing drug molecules through the replacement of hydrogen atoms (-H) with deuterium (-D). It is a stable, non-radioactive, naturally occurring hydrogen isotope[1]. Hydrogen is comprised of one proton and one electron and has a mass of 1.008 AMU, but deuterium consists of only a single neutron and has 2.014 Atomic Mass Units (AMU). Due to deuterium's natural abundance, which is around 1 part in 6400 or 0.015 per cent, huge amounts of deuterium can be extracted as heavy water (D_2O) with extremely high isotopic purity[2]. Deuterium contains a two-fold higher mass than Hydrogen, Carbon–Deuterium bond has lower ground state energy. The activation energy required for bond cleavage is greater for C-D than C-H and hence rate is slower (kH > kD)[3]. D_2O serves as a direct or indirect source of deuterium and upon requirement on specific sites, deuterium from D_2O can be exchanged directly into drug molecules or into reagents that are used in the synthesizing of drug molecules.

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The Carbon-Deuterium bond is shorter than the Carbon-Hydrogen bond. The Carbon-Deuterium bond exhibits diminished electronic polarizability, lessened hyper conjugative stabilization of neighbouring bonds, possibly poorer van der Waals stabilization, and modifications that are difficult to predict, such as variations in intramolecular volume and transition state volume[4]. In place of the C-H bond, the C-D diatomic pair is nonradioactive, bio-isotopic, and bio-isoelectronic. The Carbon-Deuterium bond (C-D) is hard and is found to be 10 times less reactive than C-H. Due to this, the breaking of bonds is tough and hence results in a metabolic effect called as Kinetic Isotope Effect (KIE). To oxidative reactions, the C-D bonds are more robust because of the Deuterium Kinetic Isotope Effect (DKIE) due to its distinctively higher potential magnitude. This becomes an advantage for deuterated drugs in metabolism or biotransformation. The ADMET property has been altered in wide ranges[5,6].

2. Deuterium Substitution

Compared to protium, Deuterium has a smaller molar volume (by 0.140 cm^3/mol per atom), is less lipophilic (Δlog Poct = −0.006), and has a small variation in the pKa values. The C-D bonds have a shorter length (by 0.005) and are often more robust to oxidative reactions[3,7]. In most cases, while oxidizing pharmaceuticals, cytochromes operate as an electron acceptor instead of oxygen in a conventional oxidase or NAD+ in a typical dehydrogenase. By attaching handles to molecules in phase II conjugation, these cytochromes provide a service by changing the hydrophobic into the hydrophilic. Therefore, oxidizing a C-H bond in a drug produces hydrophilic alcohol, which is excreted more quickly[8].

3. Effect of Deuterium on Drugs

3.1 Pharmacokinetic Profile of the Drug

The process of deuteration is to reduce the rates of breaking the Carbon-Hydrogen bond. If the Carbon-Hydrogen bond breaking is the rate-determining step in the biotransformation of a drug, the deuterated drug may show improved pharmacokinetic characteristics, such as a longer half-life, hence lowering the need for frequent dosing. If a toxic metabolite or reactive intermediate is produced when the Carbon-Hydrogen bond is broken, then deuteration of the drug can reduce the unwanted side effects of the drugs. The Carbon-Hydrogen bond breaking is playing a key role in changing the chirality of a molecule. When comparing the properties of partially or completely deuterated substances with their hydrogen counterparts, only slight physical changes can be seen. These changes may have a reduction in hydrophobicity and altered pKa if the nearest groups are ionizable. These variations are so slight that there haven't been any reports of non-covalent drugs changing in terms of biochemical potency or selectivity to important pharmacological targets[9].

In April 2017, FDA approved the first deuterated drug Deutetrabenazine which was developed by Teva Pharmaceuticals[10,11] (Figure 1). Chemically, Deutetrabenazine is an isotopic isomer of tetrabenazine which is used in the treatment of chorea associated with Huntington's disease. This drug, when compared to tetrabenazine's non-deuterated version, has a longer $t_{1/2}$ (half-life)[12,13].

Similarly, Deuteration of the gamma-aminobutyric acid type-A(GABAA)-agonist sleep drug indiplon, in which the N-CH_3 was changed to N-CD_3, led to a reduction in in-vitro metabolism in both rats and Human Liver Microsomes (HLM)[14]. Indiplon Deuterium Individual oral dosing in Drug Discovery and Development demonstrated a clear PK advantage for the deuterated molecule due to its longer $t_{1/2}$ (>2) and higher Area Under Curve (>2) values. The deuteration of indiplon did not alter the pharmacological activity of the drug. The doubling of $t_{1/2}$ in rats suggests that indiplon may be a better agent for sleep maintenance in human beings, as the $t_{1/2}$ for indiplon in humans is roughly 1.3 hour[15].

Deuterated rofecoxib analog shows improved pharmacokinetics in rats that have been reported[16]. Inhibitory actions of rofecoxib and its deuterated counterpart for Cyclooxygenase (COX1) in platelets of humans were evaluated, and identical IC50 values of 169 and 173 nm, respectively, were found. When rofecoxib and deuterated rofecoxib were administered to rats at individual oral doses, the pharmacokinetic parameters AUC (Area Under the Curve, plasma exposure) and Cmax (peak plasma concentration) were increased by 1.5 and 1.6 times, respectively. However, the deuterated form of rofecoxib showed no increase in $t_{1/2}$.

Another illustration is the enhanced in vivo PK of linezolid in primates once it is deuterated. When linezolid

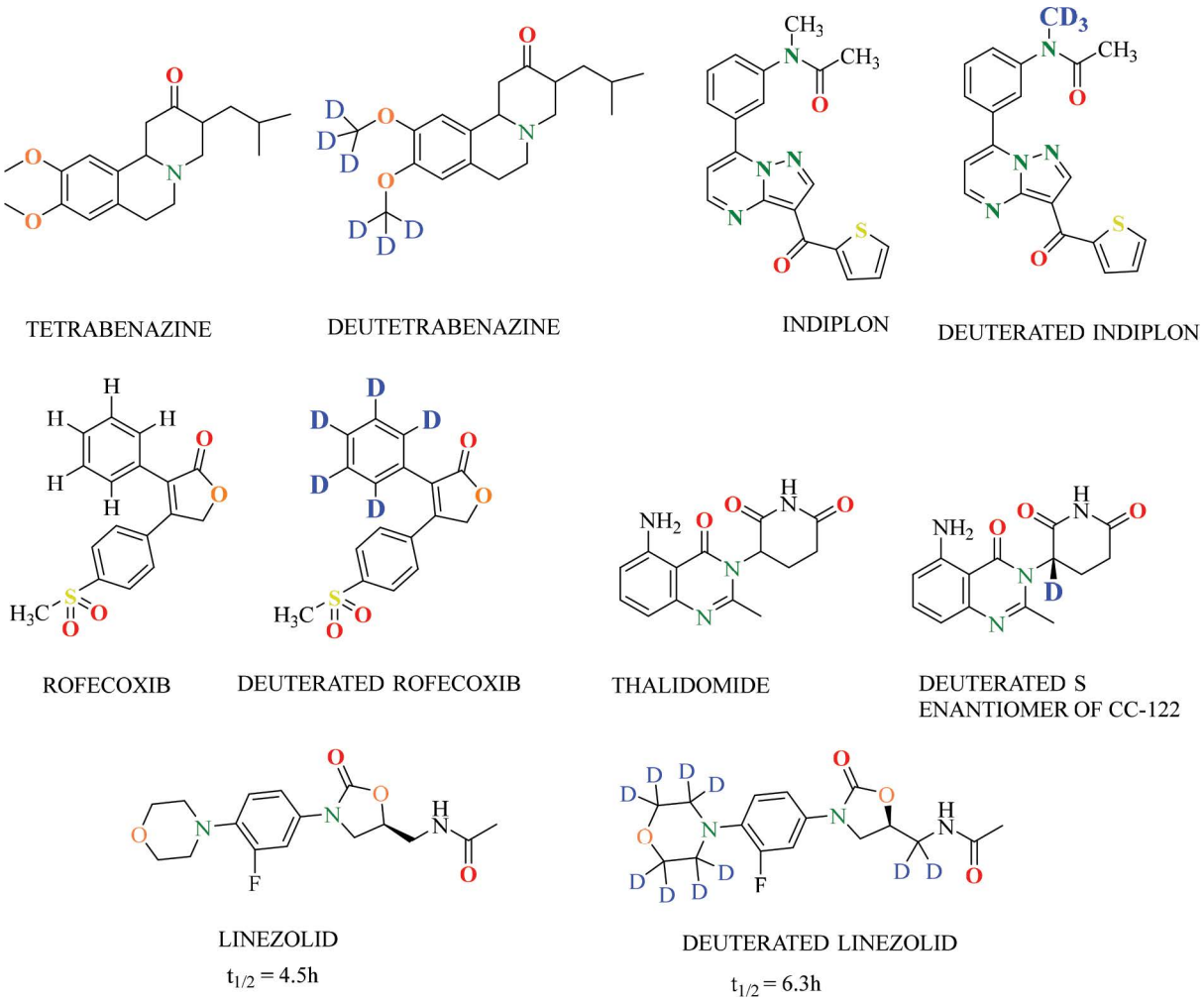

Figure 1. List of deuterated drugs under trials.

and deuterated linezolid were administered together (IV; 1:1), the $t_{1/2}$ values were 6.3 and 4.5 hours, respectively. Deuterated linezolid may be administered to humans once a day due to the enhanced PK seen in primates[17].

3.2 Reduction of Toxicity

Thalidomide is a racemic drug that has teratogenic effects, incorporation of deuterium by "chiral switching" can stabilize the chiral centres changing the drug from a racemate to a single enantiomer. The effect of deuterating, a stereo-genic centre to stabilize enantiomerization was illustrated with analogs of thalidomide[18,19]. Generally, the two enantiomers of racemic compounds exist as 50:50 ratios and this can separate for its examination to identify. In Thalidomide analogs, each enantiomer cannot be studied pharmacologically because of the fairly rapid interconversion of one form into another in solution and *in vivo*. For analog CC-122, deuterium substitution at the stereo centre slowed down this interconversion rate and allowed each enantiomer to study independently for anti-inflammatory and antitumor pharmacology. The (−)-enantiomer of CC-122 is opposed to its (+)-enantiomer activity. Hence there are possibilities for reducing the toxicity and improving the efficacy of the drugs by introducing deuterium into it[20].

3.3 Chemical Stability

A 1:1 combination of two interconvertible enantiomers makes up pioglitazone. DeuteRx used deuterium to stabilize these enantiomers (Figure 2). Different mechanistic characteristics are present in the

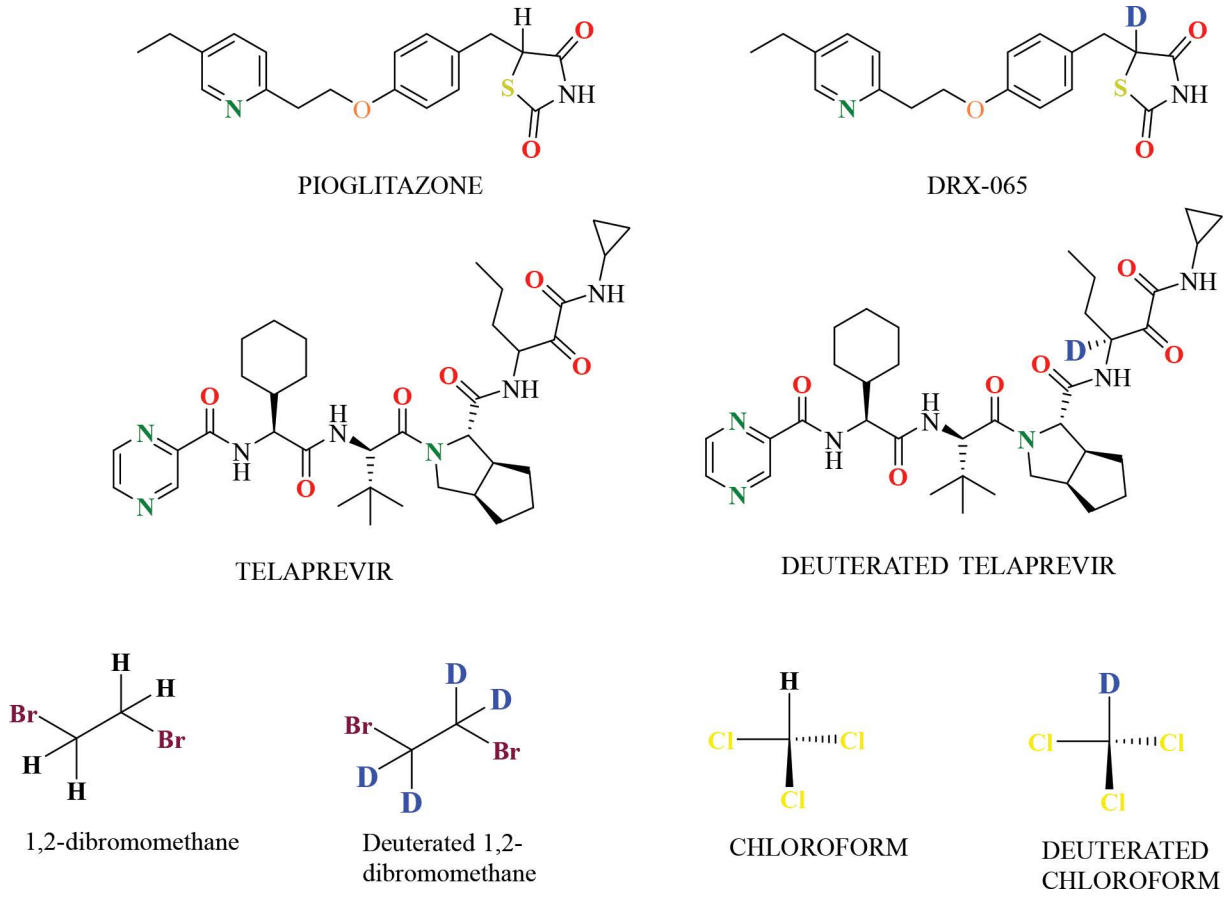

Figure 2. Deuterated antimicrobial drugs.

deuterated enantiomer. In contrast to the (R)-enantiomer, which showed modification of mitochondrial activity and anti-inflammatory benefits, the (S)-enantiomer is a PPARγ agonist with the adverse effects of weight gain and edema. When compared to the (S)-enantiomer in mouse models, the (R)-enantiomer does not cause weight gain. The benefits of pioglitazone found in animal and/or human research for indications like Alzheimer's disease and COPD are probably due to the (R)-enantiomer. In the liver, the deuterated DRX-065 has demonstrated comparable or superior action to pioglitazone for indicators of steatosis, inflammation, triglycerides, free fatty acids, and cholesterol[21]. The S-chirality is present in Telaprevir's core, which is close to the ketoamide moiety. They are found to have 30-fold less activity as a protease inhibitor and epimerize using an enol intermediate in vivo to the R-diastereomer, which circulates as the main metabolite in plasma. There was no epimerization into the R-diastereomer because the deuteration of this chiral hydrogen in telaprevir reduced the rate of conversion to the enol form[22]. The deuterated version of linoleic acid reduces oxidative stress in mitochondria and boosts ATP generation by slowing the rate of lipid peroxidation[23,24].

3.4 Safety

Humans through renal excrete deuterated water with a half-life of about 10 days. In humans, it is generally thought to be harmless and regarded as a typical physiological component unless extremely high doses (over 20 per cent of the total body water) are provided and allowed to accumulate[25]. Healthy people, including newborns and pregnant women, have received significant amounts of deuterated water without any negative side effects being noted[26–29]. For instance, 1,2-dibromoethane damages DNA more severely than its Deuterium-labeled analog, showing that deuterium substitution results in a slower metabolism and lengthens the half-life of the DNA-alkylating molecule[30]. Another example is Deuteron Chloroform

($CDCl_3$) is up to 70% less harmful to rodents than conventional Chloroform ($CHCl_3$) because it produces less nephrotoxic phosgene due to its lower metabolic rate[31].

4. Deuterium- A Solution to Antimicrobial Resistance

Deuteration of the medication leads to reduced van der Waals stability and other major changes in many molecular characteristics, which are exceedingly difficult to anticipate. Especially, molecular descriptors like intramolecular volume and the volume of transition state are quite difficult to predict which considerably depends on the position of deuterium in the drug molecules. In the year 1970, Merck and Co attempted to discover a deuterated antimicrobial on fludalanine, (Known as 3-fluoro-2-deutero-d-alanine). But this molecule was found to be brain toxic, therefore it was rejected in Phase IIb trials. Later, the toxicity was proven that it was unrelated to the deuterium. In addition, till today, the *in-silico* drug design tools are not reliable to predict the significance of deuterium regarding the expected biological efficacy and toxicity.

Recent studies suggest that the kinetic isotope effect in deuterated drug molecules has reduced the rate of metabolism which implied that the deuterated drug is more stable. Still, the chemical stability of multiple deuterated drugs is not much investigated. There are possibilities these multiple deuterated drugs may produce residual drugs which still need to be investigated. For example, dextromethorphan-d6 may be converted into dextromethorphan-d5 or dextromethorphan-d5, or dextromethorphan-d3. Still, the detection of these impurities required highly sophisticated techniques LC-HR-MS, and the existing chromatography techniques like LC-UV or LC-PDA are not suitable. Deuteration increases the heat stability of macromolecules. But it lowers cellular heat stability which results in the inhibition of chaperonin protein formation. Chaperonins are proteins that create ideal circumstances for proper protein folding, preventing aggregation. They stop proteins from misfolding, which stops disorders like Mad Cow Disease. Thus, could be the space for extrapolating the deuteration in the discovery of newer antimicrobials.

The inclusion of deuterium in metabolites perturbs the metabolism of some bacteria. The deuterium antibiotics from microbes will have modified physicochemical properties disrupting enzyme substrates recognition processes. The biodegradation of the antibiotic by the resistant bacterial strain is one of the most common mechanisms of drug resistance. This is especially true for the aminoglycosides and ß lactam antibiotics, two of the most clinically significant medication groups[32]. One of the assumptions is that the deuterated drugs can be designed in such a way that the drug may be resistant to the bacterial enzyme, so there is a possibility for enhancing the intracellular concentration of antibiotics inside the cytoplasm. For example, the CO-NH can be converted into CO-ND, so the amide cleavage by bacterial enzymes may be retarded. Same way, the -OH group can be converted into –OD, so the drug inactivation by bacterial acetylase may be retarded.

5. Deuterated Molecules

5.1 Benzylpenicillin

The solvent deuterium oxide is involved in the production of benzylpenicillin, and a highly deuterated form of the antibiotic was isolated and characterized by Crespi *et al.*, in 1973. The phenyl-acetyl group, the C-3 position of the thiazolidine ring, and the C-6 position of the j3-lactam ring all exhibit complete replacement by 2H. 64 per cent of the C-5 position of the j3-lactam ring and methyl groups at the C-2 position of the thiazolidine ring show partial substitution. Further investigation was carried out to find the comparative antibacterial efficacy of H-benzylpenicillin and this highly deuterated benzylpenicillin. The protio analog was found to be slightly more potent than the fully deuterated analog, although there was no difference in activity between the two. Laskar and Mrtek[33] synthesized deuteriobenzyl-chloropenicillin and the biological activity of the protio- and deuterioanalogs' N-ethylpiperidine salts were compared; a H/D ratio of 1.25, There were signs that the deutero-efficacy analogs had decreased. Fisher and Jardetzky[34] and Katz and Crespi[35] It was discovered that the benzylpenicillin molecule's phenyl group was what caused it to bind to serum protein albumin. When compared to IH-benzylpenicillin, the binding strength of heavily deuterated benzylpenicillin should be lower if the phenyl group helps benzylpenicillin bind to the enzyme. The highly deuterated benzylpenicillin's potency would

decrease because the acylation of the compound to the enzyme would be slowed. The overall result indicates that the deuteration of penicillin at any point has little effect on its biological efficacy.

5.2 Bedaquiline[36]

The United States Food and Drug Administration (FDA) approved bedaquiline, a diarylquinoline (Figure 3), in 2012 as part of the accelerated-approval program for the treatment of Multidrug-Resistant Pulmonary Tuberculosis (MDR-TB) in adults who had no other treatment alternatives[37]. So, utilizing deuterated Bedaquiline as the internal standard, the goal of this study was to establish a straightforward and reliable LC-MS/MS approach without involving considerable sample processing to measure the serum levels of M2 and bedaquiline in individuals with MDR-TB. Bedaquiline had an average retention time of 1.9 minutes. Bedaquiline-D6 had a mean retention time of 1.9 min as well, and M2 had a mean retention time of 1.8 min, in any of the six different batches of human serum, no peaks were affecting endogenous substances at the retention period of bedaquiline or M2, demonstrating the analytical method's selectivity.

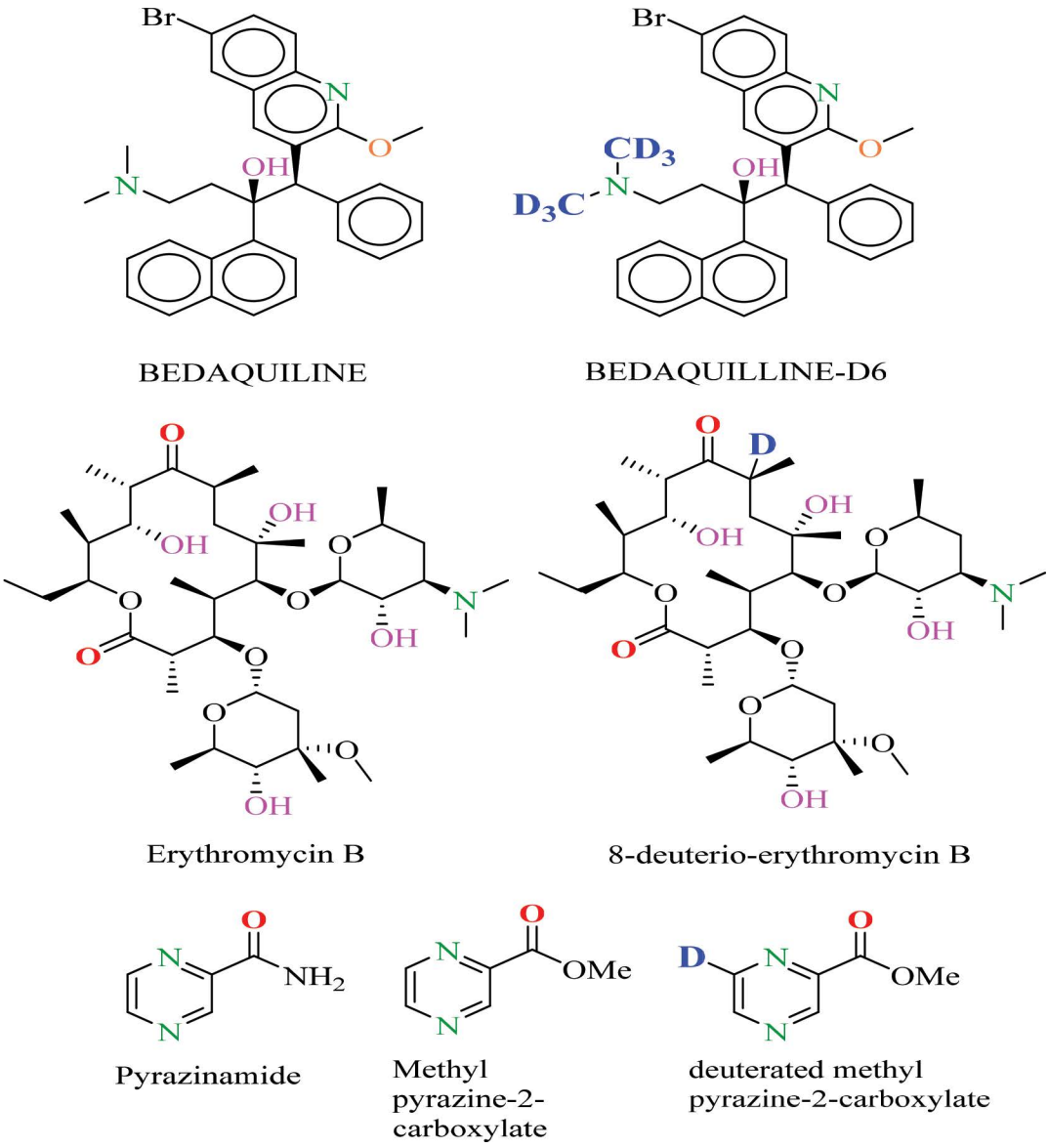

Figure 3. Drugs and their deuterated analogs tested.

5.3 8-Deuterio-Erythromycin[38]

The deuterated version was developed in an attempt to avoid erythromycin from breaking down in an acidic environment. In the beginning, 8-d-erythromycin B was used to challenge four Gram-negative (-) and four Gram-positive (+) microorganisms in a straightforward diffusion assay. They focused on the main theory, which claimed that erythromycin B's deuteration at its Carbon-8 position would restrict the production of erythromycin B enol ether in an aqueous, particularly acidic solution, after demonstrating that deuteriation has no negative effects on either ribosomal binding or antibacterial activities. It was expected that erythromycin B concentration would drop, and 5-Odesosaminyl erythronolide B would accumulate due to the synthesis of erythromycin B enol ether and the loss of cladinose sugar. The half-life and the rate constant were then determined by calculating the intensities versus time. It was clear that complex kinetics were used in the breakdown of erythromycin B. The generation of the intermediate erythromycin B enol ether was suggested to be the consequence of this.

From erythromycin-B, the synthesis of 8-d-erythromycin B successfully was achieved in 87% yield which had no apparent racemization. Predictably, in a variety of biochemical and microbiological assays, this substance reacted quite similarly to erythromycin B. The effectiveness of the medication does not seem to be affected by deuteration. The earlier work by Mordi *et al.*, had shown a very strong inhibition of enol ether production in a D2O-based medium, the concentration of enol ether in acid peaked at 15% but was nearly completely suppressed by deuteriation at C-8. Solvent isotope effects played a role in that actual result. According to recent research, 8-d-erythromycin B may be more effective than erythromycin B alone in vivo, particularly when used over an extended period. According to recent studies revealed that 8-d-erythromycin B may have more in vivo efficacy than erythromycin B alone, especially when taken over a prolonged period. Although it is reported that pure enol ethers are 10 times more potent than erythromycins. Since the preparation of 8-d-erythromycin B is very straightforward, even benefits to small numbers of patients would make the drug enol ether production has been partially suppressed.

5.4 Deuterated Analogues of Pyrazinamide Deuterated Analogs of Pyrazinamide[39]

To increase the level of hyperpolarization, the deuterated analogs of pyrazinamide and methyl pyrazine-2-carboxylate were synthesized. Several derivatives with deuterium were made by reducing the appropriate heteroaryl chlorides under D2 with palladium, followed by transesterification or amidation. Signal Amplification by Reversible Exchange (SABRE) research on methyl pyrazine-2-carboxylate deuterated analogs were studied. The relaxation times of the remaining 1H nuclei were slightly prolonged by deuteration at the 3-position in comparison to methyl pyrazine-2-carboxylate while providing it with equivalent SABRE polarisation levels.

5.5 Deuteration of BTZ043[40]

Nitrobenzothiazone is a potent second-line anti-tb prodrug. A recent article demonstrates how easily deuterium might be included in the electrophilic warhead at the centre of the nitro benzothiazinone BTZ043 and if replacing the ortho and para-H-atoms with the D-atoms within the electrophilic nitro-substituted "warhead" nucleus might increase the lifespan of significant complexes of Meisenheimer hinder progress by re-oxidation process. The Kinetic Isotope Effect (KIE) on reaction rates is caused by increasing deuteration and results in considerable decreases in reaction rates mono-deuteration The KIE on di-deuteration is k_{HH}/k_{DD} = 4.7 0.3, and k_{HH} /k_{HD} = 2.00 ± 0.15. The magnitude of the latter catalyst, the Primary Isotope Effect (KIE) shows up, showing that the Carbon-H bond to the sp^3-hybridized carbon-atom in structure is flawed in the stage that determines the pace of re-aromatization. However, in the mono-deuterated compounds, if there is only a primary isotope effect, the substance interacts much more gradually than anticipated (because on reaction if the primary isotope effect were so significant that only the C-H bond was ever broken, the isotope effect k_{HH}/k_{HD} could only be as high as 2.00). According to the experimental results, the re-aromatization reaction has a primary KIE of 3.2 ± 0.6 and a secondary KIE of 1.46 ± 0.26.

Although primary KIEs have received consideration for influencing pharmacological properties, a compound like BTZ043 in which protium is incorporated in vivo in a critical reactive region that makes the existence of a considerable secondary KIE is potentially interesting. In this case, instead of its primary isotope effect, the secondary isotope effect of deuteration may very well carry the effect of deuteration to a significant level. The original BTZ043 and the final deuterium-enriched sample both showed the expected identical therapeutic potency in whole cell assays when anti-tuberculosis effectiveness was tested on them (0.004 M each in MABA medium and 0.02-0.03 M in GAS media utilizing H37RV cells) (Figure 4).

5.6 Fludalanine[41]

Merck advanced the research and development of fludalanine, one of the deuterated drug candidates to reach clinical trials[42]. A potent and broad-spectrum antibacterial activity is achieved when fludalanine and cycloserine are combined. In the preclinical study, reports suggest that hydrogen analog was converted into L-3-fluorolactate, a toxin that leads to brain vacuolization. Deuteration of fludalanine at the

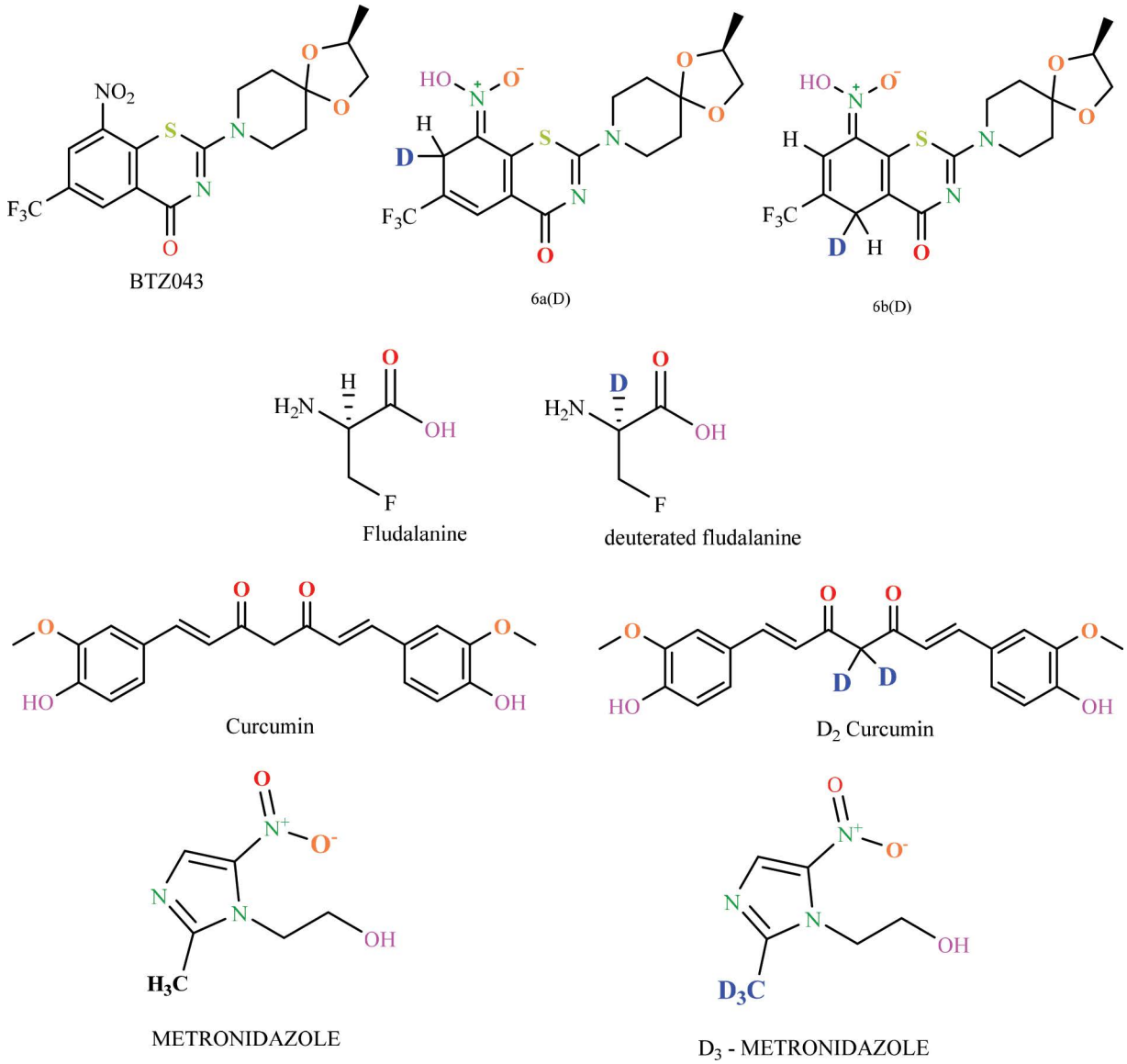

Figure 4. Diverse scaffold and natural product deuteration.

C-2 position reduces toxic metabolite formation. In recent work, Kahan et al reported that the Deuterium Kinetic Isotope Effect (DIE) decreased the production of L-3-fluorolactateto levels that have been considered appropriate in healthy volunteers[43].

5.7 Curcumin[44]

Curcumin's oral bioavailability and water solubility are low, resulting in poor absorption, rapid metabolism, and systemic elimination. To overcome curcumin's drawbacks, we have recently reported H/D exchange in curcumin, which was then characterized and tested for antibacterial, antifungal, and anti-tubercular activities. The deuterated compound showed equipotent antibacterial activity when compared with the non-deuterated compound and had better anti-fungal, anti-tubercular activity compared to its parent compound.

5.8 Metronidazole[45]

In an attempt to check whether the deuterated compounds possessed similar pharmacological activity as that of non-deuterated compounds, we have deuterated metronidazole using deuterium oxide in the presence of benzoic acid under a nitrogen atmosphere. The antitubercular activity of deuterated metronidazole was compared to that of the standard drugs isoniazid and ethambutol, showing activity with MIC of 1.6 µg/ml. Deuterated metronidazole was also shown to have nearly equivalent activity to metronidazole against Gram-positive and Gram-negative aerobic bacterial strains, as well as fungus.

6. Conclusion

Despite the research and development of numerous deuterated drugs, their efficiency, safety, and thorough knowledge of the exact mechanisms of the deuterated drugs remains unaddressed and challenging. Beyond all, still, the design and development of a successful deuterated drug with acceptable efficacy is hence a challenge. The translation of hypotheses from laboratory experiments to clinical application and further to real-time practice is unpredictable. Also, long-term drug stability and toxicity studies for individual drugs are to be studied which may vary from patient to patient. The cost and intellectual property rights of the deuterated drug will also have a great impact on the launch of deuterated drugs. Despite all these challenges, these deuterated drugs give us one more opportunity to combat the antimicrobial resistance problem.

7. Acknowledgement

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