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A Study on Deuterium: An Isotope of Hydrogen for Drug Development

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ABSTRACT

The review mentions the isotopic form of Hydrogen-Deuterium: a Hydrogen-2 atom or heavy hydrogen containing one proton and one neutron in its nucleus. The study determines the strategy of substitution of a hydrogen atom with deuterium to get a more intense medicinal effect of drugs for effective onset action and pharmacological action. A carbon-deuterium bond is more stable and effective in the body than a carbon-hydrogen bond. If deuterium is included in the chemical structure of the drug, it can cause better stability to bond with prolonged drug action. The isotopically labeled atom can serve mechanistic probes in chemistry along with characteristic features in medicinal research. The whole review gives a clear distinction for use of deuterium in the advanced form of drug compounds along with clinical factors and development, showing its better kinetic effect.

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INTRODUCTION:

Deuterium (or hydrogen-2, symbol ^{2}H or D, also known as heavy hydrogen), is one of the isotopes of Hydrogen molecule which is termed as deuteron because of one proton and one neutron in its nucleus and also incorporates one electron, which differs in comparison to hydrogen protium which just consists one proton and one electron[1]. Its mass is double time the mass of hydrogen i.e. 2.014 AMU (atomic mass unit) it contributes to around 0.0156% of total naturally hydrogen in nature. It was first discovered by Harold Urey in1931 and he proposed the theory of heavy water made of 2 atoms of deuterium and 1 atom of oxygen[2].

Deuterium is obtained from the natural source of water by the electrolytic method of concentration by differential distillation of liquid hydrogen. When electric current pass it leads to the production of a small fraction of deuterium, 6500 atoms of hydrogen from one part of the deuterium atom[1]. Its dissolving point is - 426°F (- 254°C) and its limit is - 417°F (- 249°C) which are non-radioactive and have properties such as color, odor, taste are as same as those for protium, minor physical property changes have been measured in partially or fully deuterated compounds, which include reduced hydrophobicity[3], decreased acidity of carboxylic acids and phenols, and increased basicity of amines[4]. It is having low toxicity and organism such as single-cell and low org such fishes and tadpoles can survive in the deuterated compound region[5]. Due to the double mass of Deuterium compared with Hydrogen, the C-D bond is much more resistant toward oxidative processes, for example, catalyzed by CYP450 or by other enzymes involved in metabolism (for example; MAO, aldehyde oxidase), and hence might have various pharmacokinetic properties[5]. Deuterium is one of the two stable isotopes of hydrogen. The nucleus of a deuterium molecule, called a deuteron, carries one proton and one neutron, however, the unassailable more normal protium has no neutrons in the nucleus. Deuterium has a consistent wealth in Earth's seas of around one molecule in 6420 of hydrogen.

History of deuterium pharmaceutical compounds

The absolute first instances of deuterium consideration in organically dynamic mixtures are referenced underway of the mid-twentieth century. Two autonomous exploration bunches announced a diminishing in the biotransformation pace of d2-tyramine and d3-morphine contrasted with the parent proton-containing accumulates [6][7]. The time stretch between the distribution of the primary licenses for a deuterium substance and the enlistment of medications dependent on them was about 50 years. Such a model is deutetrabenazine (d6 the

principal enlistment of a deuterium drug is a critical occasion for another bearing of drug store- tetrabenazine) supported by the Food and Drug Administration (FDA) in 2017. Its protium forerunner tetrabenazine was enrolled in the USA in 2008. Beginning around 2018, the medication (trademark Normokineztin) has been remembered for the rundown of indispensable and fundamental medications in the Russian Federation. Artificially, deutetrabenazine is an isotopic isomer of tetrabenazine ("bioisostere"), in which six protium iotas are supplanted by deuterium molecules. An increment in the half-existence of the deuterium drug from the circulation system from 4.8 to 8.6 h and a roughly twofold expansion nearby under the pharmacokinetic bend (AUC) permitted splitting the portion versus tetrabenazine. Along these lines, the new medication is portrayed by a diminished number of day-by-day infusions, and its resistance is worked on contrasted with the parent compound [8]. Signs for the utilization of the medication are equivalent to tetrabenazine, in this way, while enrolling deutetrabenazine, the candidate was given the option to somewhat utilize the enlistment materials of the parent drug[9].

Mode of Action:

Hydrogen is a chemical element in which the atomic number is 1 and H has only one proton and one electron. Deuterium is the heavier normally happening, non-radioactive, stable isotope of hydrogen. Deuterium was founded by Harold Urey in 1931, for which he got the Nobel Prize in 1934. The deuterium isotope effect has become an important tool in the clarification of the mechanism of chemical reactions[10]. Deuterium has involved one electron, one proton, and a neutron, successfully doubling the mass of the deuterium isotope without changing its properties notably. Although, the C–D bond is a bit shorter, as it has reduced electronic polarizability and less hyper conjugative stabilization of adjacent bonds, forming an anti-bonding orbital as part of the newly-formed bond. This can probably result in weaker Van Der Waals stabilization; furthermore, can create different changes in properties that are hard to anticipate, remembering changes for the intramolecular volume and the progress state volume [8]. Subbing deuterium for hydrogen permits in deuterated intensifies that are comparative in size and shape to hydrogen-based mixtures.

What is Deuterium Kinetic Isotope Effect?

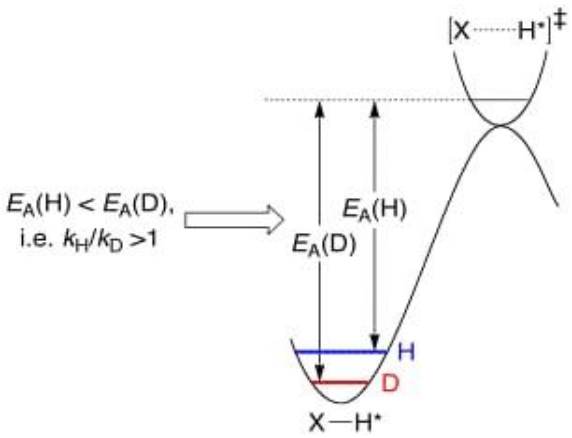

Figure No. 1: primary equilibrium isotope effects (EIEs) may be either normal (KH/KD > 1) or inverse (KH/KD < 1), with a value that is dictated by deuterium preferring to be located in the highest frequency oscillator [11]

Kinetic Isotope Effects (KIEs) are used to conclude reaction parts by concluding rate confining advances and change states and are typically assessed using NMR to perceive isotope region or GC/MS to recognize mass changes [12]. In a KIE test, a particle is supplanted by its isotope and the adjustment of the pace of the response is noticed. An extremely normal isotope replacement is when hydrogen is supplanted by deuterium. This is known as a deuterium impact also is communicated by the proportion kH/kD (as clarified above). Typical KIEs for the deuterium impact are around 1 to 7 or 8. Enormous impacts are seen in the light of the fact that the rate of mass change between hydrogen also deuterium is extraordinary. Significant molecule isotope impacts incorporate the substitution of carbon, oxygen, nitrogen, sulfur, and bromine, with impacts that are a lot more modest and are typically between 1.02 also 1.10. The distinction in KIE size is straightforwardly identified with the rate change in mass. Enormous impacts are seen when hydrogen is supplanted with deuterium because the rate of mass change is extremely enormous (mass is being multiplied) while more modest percent mass changes are available at the point when particle-like sulfur is supplanted with its isotope (expanded by two mass units)[13].

Example:

Think about the bromination of acetone: active studies have been played out that show the pace of this response is free of the focus of bromine. To decide the rate deciding step and system of this response the replacement of deuterium for hydrogen can be made.

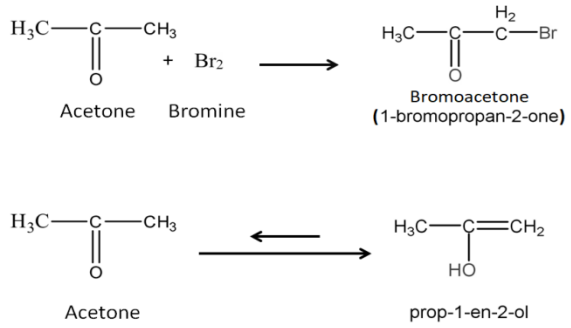

Figure No. 2: Bromination of acetone[14]

At the point when hydrogen was supplanted with deuterium in this response, a kH/kD of 7 was found. Therefore, the rate deciding advance is the tautomerization of CH3)2CO and includes the breaking of a C-H bond. Since the breaking of a C-H bond is involved, a generous isotope impact is normal.

Methods of Deuterium Incorporation:

1) Using Nanoparticles and Nanosheets

Various current responses use either nanosheets or nanoparticles, however not really of a similar component. Notwithstanding, while various components can be utilized to catalyze these responses, one normal component used is cadmium[15]. Cadmium selenide is utilized in tests because of a few of its electrochemical properties, for example, its bandgap which permits it to ingest sun-based energy, and its conduction band edge which permits it to lessen water, which loans itself toward single electron move (SET) responses as it structures D+ particles, which later become deuterium radicals. At the point when CdSe is created in permeable nanosheets, more synergist locales become accessible to the substrate, taking into consideration more responses to happen in a similar range of time[16]. While a few articles found great deuterium consolidation with any halogen not set in stone because of both bond enthalpies and decrease possibilities, the best outcomes happen when iodine is used[17]. In light of the gentle response conditions, delicate gatherings like cyan, ester, amino, hydroxyl, aldehyde, and ketones were not affected. This denotes a huge improvement over other halogens/deuterium trades which usually utilize solid bases and along these lines do not have a similar level of adaptability. However, drug compounds were not straightforwardly incorporated utilizing this strategy, it stays a significant stage in the blend of deuterium drug compounds. Deuterium intermediates that would somehow or another stay blocked off because of their delicacy, like alkynes, boric corrosive, and alkene compounds, following

Suzuki coupling or security inclusion to form wanted products. A moderate for deuterium nicotinic corrosive, an enemy of hypercholesterolemia drug, was combined through this strategy before going through additional ester hydrolysis [18]. Ruthenium is one of the nanocatalysts that has been utilized for the longest timeframe in the field of deuterium naming and as it were, prepared for the previously mentioned elements. Ruthenium, comparatively to palladium, actuates the CH bond, permitting the remainder of the response to occur. As this progression is the rate deciding advance, it is critical to take note that the nanoparticle idea of the ruthenium atoms declines the initiation energy 1 [19].

2) Radical Pathways:

The palladium nanosheet referenced has an extreme pathway. Palladium works with the photocatalyst, glasslike polymeric carbon nitrides (CPCN). While the CPCN makes the extreme deuterium, the palladium nanosheet traps the extreme that makes the HAT occur [19]. Cadmium sulfide, or CdS, has a marginally unique extremist pathway. These are used with gold to deuterate aryl halides13. The gold deliveries an electron which is then moved to first the CdS nanowire and afterward the aryl halide. The halide then, at that point, tumbles off of the aryl halide anion leaving an aryl extremist, which is then deuterium by D_2O_{13}. Another extreme pathway happens in the improvement of deuterium silanes. In this response, the impetus, 4CzIPN, turns into an extremist. This revolutionary is then extinguished by HAT through SET to Martinez 14 make a thiylradical. It is this thiyl extremist that both recovers the photocatalyst and structures the silane radical. Once the silane is revolutionary, it can burglarize the deuterated thiol of its deuterium atoms and become deuterated[20].

3) Photocatalytic Reactions:

Because of the current interest and demand for green science, various responses including both noticeable and UV light have been explored[21]. These responses benefit from friendlier conditions, as many don't need solid acids or bases, however, some still do. This absence of solid acids by and large prompts a higher resilience of utilitarian gatherings. Besides, it takes into consideration the improvement of deuterium drug compounds, a significant number of which are not tolerant to very essential or incredibly acidic arrangements. Notwithstanding, these advantages don't infer that there are no issues with photocatalytic responses[22].

However much research has been finished in regards to photoredox reactions, the best photocatalyst is as yet discussed[23]. While a few, like gold, take into consideration a more

noteworthy detachment of charge and assimilation of light in the noticeable range and may have a great, others are essentially more affordable however sacrifice some useful gathering resilience and inconstancy. Still, others don't need a photocatalyst however just work on one sort of atom. Inside the local area, nonetheless, it is noticed that the photocatalyst CdSe permeable nanosheets denoted a huge defining moment in the capacity to name compounds.

4) Deuterium Pharmaceutical Compounds (miscellaneous):

Deuterium destinations that are processed are a successful technique to slow the disintegration of a compound. "Digestion happens on pyridines and diazines by molybdenum-containing chemicals like aldehyde oxidases (AOs)". As of now, the medication VX-984, including deuterium that eases back this AO digestion, is being developed. Koniarczyk fostered a strategy for deuterium pyridines and diazines by first changing them into phosphonium salts and afterward responding to these salts with D_2O and K_2CO_3. This response considers the hydrogen at carbon position 4 to be deuterium with high regioselectivity. This is as opposed to a few different techniques, including one found by Chirk that for a similar compound (loratadine) deuterated at positions 2 and 3. At the point when this position is impeded the compound is deuterium at position 2. Pyridines with 3,5-substituents form deuterium with complete regioselectivity when this substituent is a halogen [24].

Deuterium safety and medicinal effect:

The impacts of deuterium have been broadly investigated since adequate amounts of deuterium-containing compounds opened up. In general, deuterium has remarkably low fundamental maliciousness. Single-celled organisms can frequently be filled in states of full deuteration. Lower creatures including fish and fledglings get by in something like 30% D_2O. Mice and canines don't show noticeable impacts from long haul substitution of somewhere around 10-15 percent of body liquid hydrogen with deuterium, even though fixations over 25% are extensively poisonous to those species. People can tolerate undeniable levels of deuterium in body liquids. Intense openness levels of 15-23 percent deuterium substitution in entire body plasma have been accounted for with no clear antagonistic impacts. Deuterated water is renally released by individuals with a half-presence of around 10 days. Because of the KIE, deuteration can bring about adjusted digestion designs. We are not mindful of instances of deuteration coming about in the development of exceptional metabolites in creatures that were not created by the all-hydrogen simple. Be that as it may, decreased paces

of digestion and metabolic shunting, where the proportion of metabolites is changed, have been accounted for [25]. Albeit seldom detailed in the writing, we have likewise noticed a few situations where particular deuteration builds the pace of metabolic leeway *in vitro*. We have felt that it is useful to conceptualize the pharmacological effects of deuteration in three critical orders. Therefore, the biological half-existence of the compound is expanded. Potential medication advantages could incorporate a decrease in measurements and the capacity to keep up with comparable foundational openness with diminished pinnacle levels and expanded box levels. This could result in a lower occurrence of secondary effects and upgraded viability, contingent upon the specific medication's pharmacokinetic/pharmacodynamic relationship. The subsequent board represents a transcendently pre foundational impact of deuteration, which we have seen on various occasions. In these cases, decreased paces of (typically oxidative) digestion in the gut divider and additionally liver outcome in a bigger level of the unmetabolized drug coming to fundamental stream, as a rule, the pace of fundamental freedom is unaltered. Deuterated drugs showing this impact might have decreased dosing necessities and produced lower metabolite loads. Since gastrointestinal aggravation has been identified with the measure of dosed compound rather than blood concentration for certain meds, this effect could permit upgraded respectability and also the ability to achieve a higher most noteworthy suffered segment. The third board represents metabolic shunting. Many medications are processed in complex examples, once in a while shaping both dynamic and harmless metabolites. We and others have shown that the deuterium KIE can bring about decreased development of harmful or responsive metabolites; just as expanded arrangement of desirable active metabolites. Clear likely advantages as far as human prescriptions are obvious.

Deuterium in drug discovery

Bio isosterism Replacement of valuable get-togethers having relative properties is known as Bioisosteric replacement. Bioisosteres are particles having substance and physical properties which deliver extensively comparative organic properties. Molecules are generally appointed based on the quantity of valence electrons of an atom or a gathering of atoms rather than on the complete number of orbital electrons. BIOISOSTERES OF HYDROGEN Monovalent bioisosteres F, Cl, I, Br, OH, NH_2, CH_3, SH, CF_3.

Differentiation between C-H Bond and C-D Bond: C−D bond is to some degree more restricted, reduced electronic polarizability Lesser Hyper conjugative adjustment of

contiguous bonds and Weaker Van der Waals adjustment. Intramolecular volume besides change state volume is difficult to predict.

Deuterium the Best Bio isosteres of Hydrogen:

Ordinary C−H replacement is C−F in drug revelation. Produce contrasts in so many properties similar to hydrogen. Fluorine has a van der Waals volume practically 100% bigger than hydrogen, Electronegative, Hydrogen bond acceptor. The fluorinated drug is diverse in each way. A few boundaries might change by a C-F substitution.

•Mechanism of activity, • Target restricting fondness, • PK/PD relationship, • Solubility in all vehicles, • Protein restricting/ serum limiting, • CNS decency, • Porousness, • BBB entrance, • GI decency. C-D supplanted items are indistinct from its protium simple, • *In vitro* pharmacodynamics (PD), •Physicochemical properties, • Biological properties: The C−D bonds, more steady to oxidative cycles due to the active isotope result.

Employing Deuterium in the Design and the investigation of New Medicines:

Deuteration will upgrade medication's pharmacokinetic, pharmacodynamic, or toxicological properties. Instances of clinically tried deuterated drugs D1 Halothane is an unstable sedative is known to cause hepatotoxicity. Acyl chloride is the responsive widely appealing at risk for outlining DNA adducts and conceivable various adducts, in the liver.

1) D1-halothane was created, and an emotional decrease in DNA adducts.

2) FLUDALANINE: The anti-microbial fludalanine is expansive and has strong antibacterial movement, created by Merck, the most widely examined deuterated drug candidate.

3) D6-NIFEDIPINE (2-deutero-3-fluoro-D-alanine) one of the objectives of deuteration was to increment the half-life, work on tolerant consistency, and subsequently both adequacy and security by implication. Longer half-life should prompt diminished "withdrawal impacts" in numerous specialists, again a wellbeing improvement. D6-NIFEDIPINE deuterated Nifedipine led to a 34% increment inadequacy in rodents.

4) NEVIRAPIN: Nevirapine is a non-nucleoside turn-around transcriptase inhibitor for the treatment of HIV contamination. ADR-high frequency of skin rash also causes hepatotoxicity. The hepatotoxicity and skin rash is because of CYP digestion. Deuterated Nevirapine diminishes covalent limiting to hepatic proteins, and produces less hydroxy

metabolite which diminished the recurrence and earnestness of the rashes in both mouse and rat models.

Clinical Trials of Deuterated Drugs:

1) CTP-499 for Diabetic Nephropathy CTP- 499 is a medication competitor of Concert drugs for diabetic nephropathy in type 2 diabetics. CTP-499 is a simple of Lisofylline a functioning metabolite of Pentoxifylline hydrogen atoms with deuterium.

2) Pentoxifylline Lisofylline CTP-499

3) CTP-347: Deuterium Modification of Paroxetine CTP-347, a specifically deuterated simple of paroxetine. CTP-347 was intended to dispose of the irreversible restraint of the processing compound (CYP2D6).

4) AVP-786: deuterated dextromethorphan AVP- 786 is a blend of deuterated dextromethorphan and super low portion quinidine, created by Avanir Pharmaceuticals in major depressive disorder.

5) SD-254 SD-254 is deuterated simple of the energizer venlafaxine created by Auspex drugs. SD-254 Phase I showed a pharmacokinetic profile better than venlafaxine".

6) DEUTERATED BENZOPYRAN Deuterated benzopyran analogs as new COX-2 inhibitors. The new particles formed have improved pharmacokinetic actions in rodents contrasted with their non-deuterated analogs.

Deuterium compounds in clinical development:

As currently referenced, the main deuterium compound that has entered clinical practice is deutetrabenazine for the treatment of the two chores related to Huntington's illness and tardive dyskinesia. This achievement has given industry certainty to put resources into the improvement of deuterium drugs, and accordingly, in excess of 20 deuterium drugs are at present in the clinical turn of events[26]. Considering that such harmfulness was viewed as portion reliant, a deuterium procedure was applied to further develop enzalutamide's PK properties and conceivably limit after effects. Since enzalutamide is used to N-demethylenzalutamide for the most part by CYP2C8 and CYP3A4/5, the N-CH_3 moiety was snubbed by N-CD3 to weaken the N-demethylation pathway. Therefore, HC-1119 was

displayed to have an enhanced PK profile and a higher security edge contrasted and its nondeuterium partner in various in vivo models[27].

Regardless of whether GA and Stargardt's infection are perceived as particular issues, they share the gathering of lipofuscin granules in the retinal color epithelium as one of the super pathogenic components. Concerning Stargardt's illness, there is no treatment approved for GA, and ALK-001 was speculated to address an expected response to neglected remedial requirements in GA. The fruition date of the clinical preliminary on GA is relied upon to be on 2022 and, as pronounced by the Sponsor, ALK001 will be tried likewise in other ophthalmological messes, including the middle of the road dry-AMD, autosomal latent retinitis pigmentosa, and autosomal passive cone-pole dystrophy (18).

Because of this peculiarity, it has entered the clinical improvement in 2015 for Friedrich's ataxia, an uncommon acquired neurodegenerative issue related to an expansion in lipid peroxidation and described by areflexia, dysarthria, and sensory deficits (NCT02445794). After three years, a Phase II/III planned open-mark study was started to evaluate the viability and wellbeing of RT001 in patients impacted by puerile neuroaxonal dystrophy, an uncommon deadly neurodegenerative issue portrayed by an ever-evolving loss of motor functions. Based on empowering results found in two Expanded Access patients, in February 2019 the Committee for Orphan Medical Products of the European Medicines Agency allowed the Sponsor demand for vagrant restorative item assignment for the therapy of juvenile neuroaxonal dystrophy with RT00[28].

Synthetic utilities of the deuterium methodology:

To additionally show the manufactured utility of this procedure, we inspected the feasibility of huge scope amalgamation utilizing nonstop stream miniature tubing reactors. the change was amiable to increase with 100 grams of beginning triethyl silane helped by a functionally straightforward consistent stream arrangement, which brought about the deuterium of triethyl silane with amazing D-fuse (95%) and great unrefined yield (89% dependent on examination of the rough 1H NMR spectra). 61.5 grams of unadulterated deuterium triethyl silane was disengaged by cautious refining of the unrefined item blend, featuring the potential for huge scope union. Prominently, contrasted with the bunch amalgamation, the prerequisites of photocatalyst (4CzIPN), HAT impetus (triisopropylsilanethiol), and D_2O to accomplish a productive change were all drastically diminished in constant stream miniature tubing

reactors, from 2 mol%, 10 mol%, and 50 counterparts to 0.2 mol%, 2 mol%, and 30 reciprocals, individually. The home time was abbreviated to 3 h rather than the 12 h needed in the cluster response. This gives a significantly more monetary pathway for the blend of deuterium silanes [29][30] highlighting the predominance of miniature tubing stream reactors in photochemical synthesis. We imagined that there may be a chance to get to enantioenriched deuterium silanes beginning from chiral organosilanes through the memory of chirality[31]. Even though the non-cyclic chiral silane managed racemic item, the chirality of cyclic chiral silane was safeguarded in item generally by means of the photograph deuterium convention [32].

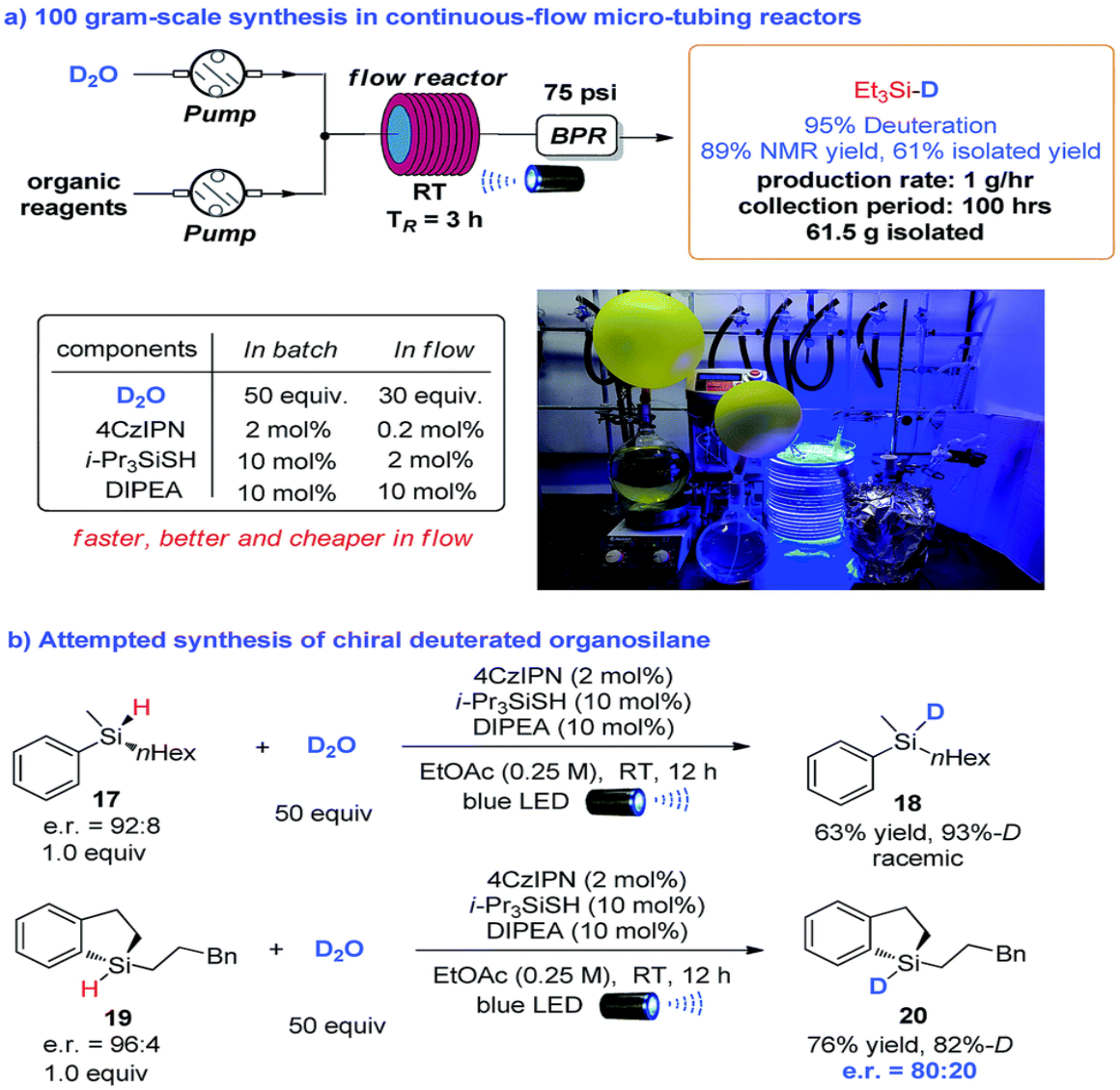

Figure No. 3: Reaction scaling up in continuous-flow reactors and synthesis of chiral deuterated silanes [29]

Stabilization of stereoisomers at deuteration:

Synthetic deuteration includes deuterating entire particles or building blocks for the union of an ideal particle by presenting them to heavy water (deuterium oxide) at high temperatures and tensions within the sight of a catalyst [33].

To reduce the symptoms of optically dynamic drug substances, enantiopure drugs have been created starting around 1992. This innovatively troublesome methodology made it conceivable to enlist more compelling enantiomers, eutomers, as new medications [34][35][36]. This methodology, known as "chiral switch", finished in the business availability of unadulterated enantiomers [37][38].

At the same time, for various optically active substances, the chiral change is unthinkable because of the quick interconversion of stereoisomers in vitro or potentially *in vivo*. Supplanting protium with deuterium in the chiral focal point of one of the stereoisomers can settle the stereoisomer.

The teratogenic impact of thalidomide (see table 4) relates basically to the S(+)- enantiomer [39]. The organization of just the R (-)- enantiomer doesn't forestall the indication of teratogenicity because of a huge and quick epimerization in physiological conditions.

It was shown that the deuteration to some degree defeats this inconvenience d1-thalidomide is multiple times steadier to epimerization in different cushion arrangements than its protium simple. The impact of deuterium on the motor impacts of biotransformation of drug substances isn't restricted to the models given. Increasingly more deuterium compounds are portrayed as promising substances for conceivable use as medications [40][41][42].

Deuterium in Drug Development:

Disclosure Process: The cycle by which one more medication is brought to showcase. Time burning-through Expensive Understanding the sickness Target distinguishing proof target approval Lead distinguishing proof Lead enhancement Drug advancement Preclinical and clinical examinations. Postmarketing observation.

Deuterium consolidates Lead advancement:

DCE Platform - More Efficient and Pharmaceuticals Less Expensive Deuterated Compound Entity Platform is the exchange sign of Show.

The traditional techniques for drug discovery involve extensive cycles with high disappointment rates. Empower drug revelation and clinical turn of events more productive and more affordable than ordinary medication innovative work. Deuterium in drug discovery and clinical improvement gives way to tritium in drug revelation. Deuterium used in bio-engineering. PATENTABILITY- The patentability of this approach is grounded, with more than 100 USPTO-in all actuality licenses straightforwardly covering deuterium subbed variants of supported medications.

Challenges in Deuterium Incorporation:

Deuterium/ Hydrogen trade inside the physiological Environment. Deuterium impedes digestion at one site. ("Metabolic exchanging") Suppression of one metabolic pathway advances digestion at another site.

CONCLUSION:

Deuterium incorporates:

- Patentable new medications.
- Holds biochemical strength and selectivity enable PK/PD.
- Hazard decreased the way to deal with making new substance element drugs.
- New medications.

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