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Deuterium Labelled Compounds by H–D Exchange Using Heavy Water for Improving Pharmacokinetics

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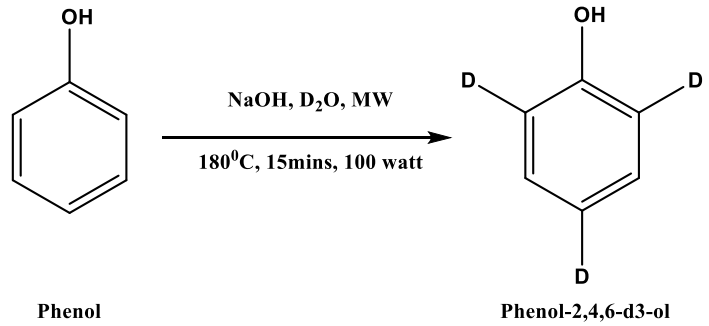
1. Introduction:

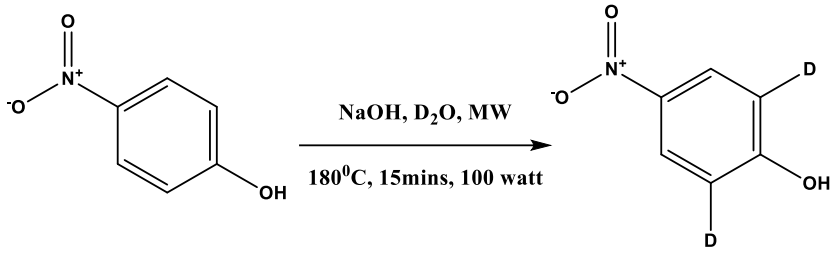
Medicinal chemists use bioisosterism to enhance small-molecule drugs by substituting substructures while maintaining biological activity [1]. Replacing hydrogen with deuterium, a stable isotope, improves metabolic stability and impacts drug efficacy and safety beyond pharmacokinetics (PK) [2]. The FDA-approved deutetrabenazine (2017) demonstrated superior PK properties over tetrabenazine, allowing lower doses and reduced frequency. Deuterium chemistry, primarily through Hydrogen/Deuterium (H/D) exchange, leverages the C-D bond's 6–10 times greater stability, resulting in a kinetic isotope effect (KIE) that optimizes dosing regimens [3].

2. Material and Methods:

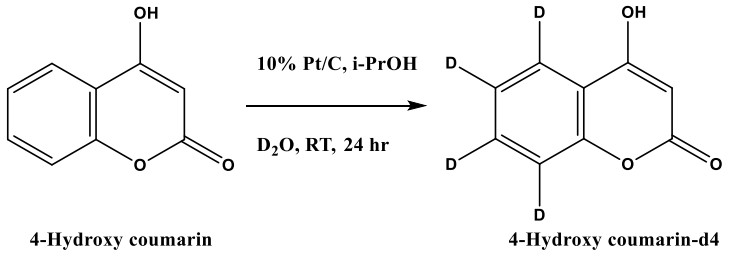
We developed efficient deuteration techniques for various scaffolds, biomolecules, and pharmaceuticals using heavy water (D_2O) with heterogeneous catalysts like Pd/C, Pt/C, Ru/C, Rh/C, and $NaBD_4$. Reactions were performed under thermal or microwave-assisted conditions in an inert nitrogen atmosphere. Deuterium-labeled products were confirmed via LC-MS and ^{1}H-NMR. Synthesized compounds such as phenol-d_3, p-nitrophenol-d_2, 4-hydroxycoumarin-d_3, valproic acid-d_{10}, chalcone-d_1, and uracil-d_1 demonstrate improved metabolic stability. Enhancing their potential utility in various applications. The following schemes were employed for conducting the deuteration reactions.



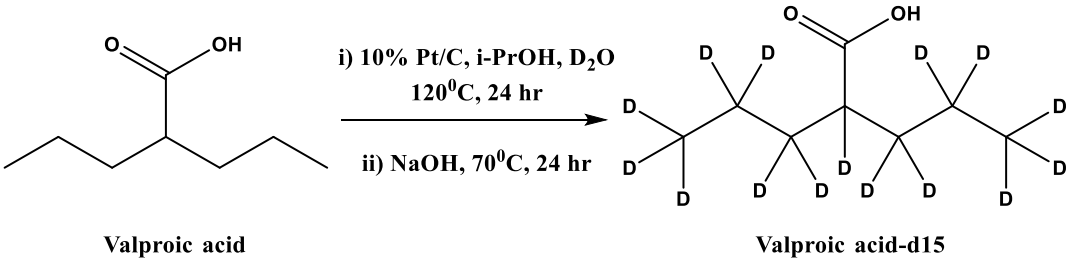
Scheme 1. Schematic representation of deuteration of phenol



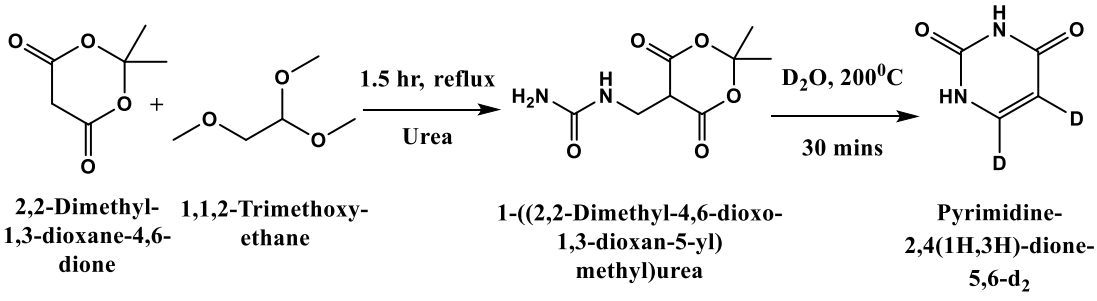
Scheme 2. Schematic representation of deuteration of p-nitrophenol



Scheme 3. Schematic representation of deuteration of 4-hydroxy coumarin



Scheme 4. Schematic representation of deuteration of valproic acid



Scheme 5. Schematic representation of synthesis of deuterated uracil

3. Significant Results and Discussion

In this project, we synthesized deuterium-labeled compounds using both conventional catalytic methods (Pd/C, Pt/C, Ru/C, Rh/C) and microwave-assisted synthesis without catalysts. The microwave method eliminated the need for catalysts and significantly reduced reaction time. Mass and ^{1}H-NMR analysis confirmed successful hydrogen-to-deuterium conversion with D_2O as the deuteration source, achieving a maximum isotopic distribution of 97.37% for d_2 at the ortho position of p-nitrophenol via the microwave method. This approach effectively facilitated aromatic substitution reactions. The developed schemes achieved isotopic purities of phenol-d_3 (80%), p-nitrophenol-d_2 (97%), 4-hydroxycoumarin-d_3 (49%), valproic acid-d_{10} (53%), chalcone-d_1 (37%), and uracil-d_1 (49%).

Table 1. % Deuterium incorporation in synthesized deuterated molecules

Deuterated Compounds	% D Incorporation										
	D0	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**
Phenol	-	-	20.27	**79.72**	NA	NA	NA	NA	NA	NA	NA
p-Nitrophenol	-	2.61	**97.37**	0.02	NA	NA	NA	NA	NA	NA	NA
4-Hydroxy-coumarin	8.71	5.6	4.81	**48.60**	32.12	NA	NA	NA	NA	NA	NA
Valproic acid	29.1	-	1.52	-	-	-	-	3.52	2.8	-	**52.67**
Chalcone	37.05	**37.38**	25.56	NA	NA	NA	NA	NA	NA	NA	NA
Uracil	39.33	**48.95**	11.71	NA	NA	NA	NA	NA	NA	NA	NA

4. Conclusion:

We developed efficient deuteration techniques for medicinal scaffolds, biomolecules, and pharmaceuticals, achieving superior %D incorporation with the microwave method. Deuterium-labeled molecules, confirmed by LC-MS and ^{1}H-NMR, can serve as biomarkers or stable deuterium switches. The microwave method enabled up to 97.37% incorporation and demonstrated a proof of concept for targeting aromatic and aliphatic metabolic soft spots in drug development.

References:

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[3] Pirali, T., Serafini, M., Cargnin, S. & Genazzani, A. Journal of medicinal chemistry 2019, 62(11), 5276–5297.