University of Leicester

EPSRC DLA Studentship

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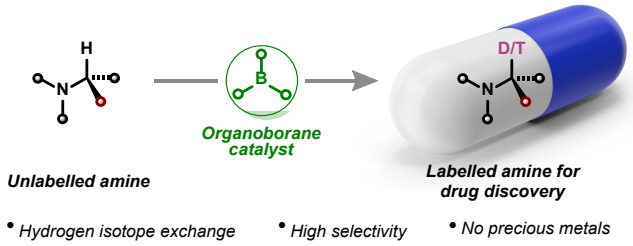
Section 2 – *Project Information*

Project Title	Accessing deuterated amine-based pharmaceuticals through new approaches to hydrogen isotope exchange

Project Summary

Deuterium- and tritium-labelled organic compounds are essential throughout academic and industrial research. They are utilised in the investigation of reaction mechanisms, neutron scattering, and significantly throughout the drug discovery process from target identification to clinical trials. For example: (1) Receptor binding studies rely on the use of tritium-labelled molecules; (2) deuterium-labelled MS standards aid identification of metabolites from animal and human studies; (3) deuterium-labels serve as simple bioisosteres for hydrogen and can alter ADME properties, and; (4) regulatory authorities often require radiolabelled (i.e. tritium) in vivo metabolism studies. Approved deuterium-labelled drugs are increasing in prevalence, and deuterium-derivatives offer the opportunity for new chemical entities, but no clear regulatory framework has yet been established. Therefore, methods that allow for precise control of regio-, chemo- and stereoselectivity in generating deuterium- and tritium-labelled organic compounds at late-stage via direct exchange (ie the direct replacement of hydrogen for deuterium or tritium in a complex molecule which avoids the need for costly and time consuming *de novo* synthesis) will be of strategic importance.



The project will build on the Pulis' group expertise on the application of main group element reactivity,[1-3] and will utilise the unusual and unique ability of organoboranes to activate α-amino C(sp^3)–H bonds in the development of a new approach to late-stage deuterium- and tritium-labelling of amine-containing pharmaceutical compounds. The new methodology will be regioselective and deliver high levels of isotope incorporation that is suitable for a variety of different industrial and academic research applications.

We have exciting preliminary results from which to launch this project. The project will involve organic chemistry and relevant analytical techniques (primarily NMR and MS). To ensure that methodology developed is suitable for industrial applications, we will work closely with established partners from the pharmaceutical industry, including performing late-stage-tritiation at an industrial

site. The final aims, will be to test the deuterated amine-based pharmaceuticals with industrial academic collaborators, leveraging partners who have interests in specific approved drugs (ie patent holders) and/or therapeutic areas.

References

[1] Alvarez-Montoya, Gillions, Winfrey, Hawker, Singh, Ortu, Fu, Li, Pulis, *ACS Catal.* **2024**, *14*, 4856.

[2] Basak, Alvarez-Montoya, Winfrey, Melen, Morrill, Pulis, *ACS Catal*. **2020**, *10*, 4835.

[3] Basak, Winfrey, Kustiana, Melen, Morrill, Pulis, *Chem. Soc. Rev.* **2021**, *50*, 3720.