# Drug Discovery, Pharmaceuticals & Cannabis Testing

# Expanding the druggable horizon: Pioneering new covalent medicines with diverse electrophile screening

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***In recent decades, remarkable progress has been made in small molecule drug discovery. This has been driven by significant technological advances in high-throughput screening, medicinal chemistry, and structural biology, which has transformed the treatment landscape for countless diseases and patients. Nevertheless, many disease-causing proteins remain impervious to conventional small molecule drugs. Some of these proteins have been branded as 'undruggable' and are typically characterised by the lack of a well-defined binding pocket.***

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Covalent drugs offer an exciting opportunity to address these challenging protein targets and deliver medicines to those in need. While conventional small molecule drugs bind reversibly to their targets, covalent drugs are equipped with a reactive handle – an electrophile – that irreversibly forms a covalent bond to the protein, affecting its function. In this way, even weak binding interactions can be captured, effectively 'gluing' the drug and its target together. By leveraging these covalent interactions these modalities can not only engage otherwise undruggable proteins, but also confer significantly improved drug potency and duration of action. This translates to lower and less frequent dosing regimens for patients, significantly improving quality of life.

The recent FDA approval of sotorasib, an inhibitor of the cancer- promoting protein KRAS G12C, demonstrates how a covalent medicine can address a therapeutic target that has long been refractory to traditional reversible drug discovery. Mutations of KRAS are regarded as the most common oncogenic drivers across all cancers, particularly those of the lung, pancreas, and bowel. However, the smooth and featureless surface of the protein provides no obvious binding pocket, and consequently, KRAS has resisted more than four decades of drug discovery efforts.

Sotorasib distinguished itself from previous efforts through inclusion of a reactive acrylamide group, an electrophile which forms a covalent bond with a unique cysteine amino acid residue present in the mutant form of the KRAS protein: KRAS-G12C. Sotorasib was granted accelerated FDA approval in 2021 to fill this unmet clinical need. It is currently used for the treatment of non-small cell lung cancer and colorectal cancer harbouring the G12C mutation. In the clinic, sotorasib has significantly improved progression-free survival for patients whose disease has progressed after receiving at least one prior line of therapy. This demonstrates the exciting potential for covalent modalities to deliver innovative medicines to patients.

The success of sotorasib and other covalent drugs has encouraged pharmaceutical companies and academic groups to increasingly screen libraries of covalent compounds against their most challenging targets. A potential limitation of these libraries is that they are frequently biased towards a small number of well-established electrophiles, most notably the acrylamide group, despite the broad diversity of cysteine-reactive electrophiles reported in the chemical literature. This bias is reflected by the strong therapeutic validation of acrylamides, which account for 10 out of the 14 covalent drugs approved in the past decade.

While there is an argument to be made for prioritising electrophiles that have a proven track-record in the clinic, it is also reasonable to conclude that this narrow focus may hamper the identification of covalent medicines for new disease targets. The reactivity and accessibility of a targeted amino acid residue on a protein can be highly dependent on its local environment. To successfully engage it, the properties of the electrophile – its intrinsic reactivity, size, shape, and position – must be a suitable match. Relying heavily on any one electrophile is akin to trying to open many types of locks with only a single type of key. Indeed, there are numerous literature examples where a less traditional electrophile can covalently engage a protein target, where an acrylamide has failed. For these reasons, broadening the scope of electrophiles in covalent screening libraries could provide the platform to unlock novel binding opportunities and expand the reach of drug discovery into territories that are still considered undruggable.

## A Diverse Electrophile Screening Library to Expedite Covalent Drug Discovery

My PhD research, conducted under the collaborative PhD programme between GSK and the University of Strathclyde, aims to overcome this critical gap in covalent drug discovery. In support of this, I have been awarded an Industrial Fellowship by The Royal Commission for the Exhibition of 1851, in recognition of my project's potential to contribute to industry and result in real-world commercial impact. To achieve my goal, I am designing and synthesising a 5000-member covalent screening library, featuring over 20 diverse cysteine-reactive electrophiles which have been selected to explore a wide spectrum of reactivities, mechanisms, and reaction trajectories.

Generating a library of this magnitude is no small feat. In particular, the purification of so many compounds represents a substantial, and potentially insurmountable bottleneck. To circumvent this challenge, I will adopt an innovative 'direct-to-biology', or 'D2B' approach. This method bypasses the need for costly and resource-intensive purification steps by allowing the screening of unpurified reaction products directly against therapeutic targets. The resulting increase in throughput afforded by

such an approach dramatically improves the coverage of chemical space, enabling us to rapidly home in on promising compounds for further development.

Once synthesised, my diverse-electrophile D2B library will be screened against a panel of disease relevant proteins, including those implicated in various cancers and derived from infectious pathogens, to discover new covalent protein modulators. The hit compounds identified may not only be invaluable as molecular probes, allowing researchers to dissect and interrogate the intricate biology of the role of these protein targets in disease, but they could also serve as promising starting points for the development of novel covalent therapeutics.

Beyond hit identification, the rich dataset generated from screening a diverse electrophile library will provide vital insights into reactive groups that are less explored, specifically for their effectiveness against different types of protein targets. These findings will benefit the broader drug discovery community by helping to direct investment in future D2B or purified screening libraries to include the most promising electrophiles.

## Partnerships and early successes

The collaborative framework underpinning this GSK/University of Strathclyde PhD programme has been instrumental to the project's conception and development. As the industrial sponsor, GSK has facilitated access to world-class resources, including a vast chemical collection, state-of-the-art technologies such as liquid handling robots and high-throughput analytical instrumentation, alongside a wealth of expertise across various facets of drug discovery. This is complemented by the academic expertise and cutting-edge, industry-facing research experience provided by the University of Strathclyde, fostering the exchange of new knowledge and ideas between industry and academia to the mutual benefit of all partners.

Through my 1851 Industrial Fellowship, I have received financial support to attend key conferences, where I have learned from, and been inspired by peers and leading experts in the wider scientific community. Furthermore, despite being in my first year of study, I have been able to present my research at four conferences, securing a poster prize at Fragment-Based Lead Discovery 2025 (FBLD). Besides their financial contribution, the Commission has also provided a variety of other development opportunities, such as career workshops, media training, and networking events, which have fostered further collaboration opportunities.

The combined resources and expertise afforded by this unique industry-academia collaboration, supported by the Industrial Fellowship, have enabled significant progress within the project. To date, over a third of the ambitious 5000- member screening library has been successfully synthesised and early screening efforts have identified promising hits from different electrophile classes against a range of disease targets, highlighting the exciting potential for our approach for new discoveries.

Beyond the immediate goal of identifying hit compounds, the D2B compound libraries and methodologies being developed could be applied to any cysteine-containing disease target, thereby facilitating the rapid identification and optimisation of covalent inhibitors. Overall, the knowledge acquired from this project could potentially allow us to expand the 'druggable' proteome, ultimately expediting the discovery and development of new medicines against diseases for which there remains a critical unmet medical need.