Systematic progression of fragments by linking AI and experiment by robotics

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Abstract

In contrast to the question of fragment screening, which has been vigorously explored for over two decades, the problem of progressing fragment hits to biologically relevant potency does not have the equivalent systematic and well-established best-practice. In real-world projects, the available medicinal chemistry toolbox makes it difficult to discriminate between more potent chemical matter and fragment hits, despite their striking qualitative differences. This question is a focus of the current phase of development of Diamond's XChem facility for crystallographic fragment screening, which since 2016 has annually been supporting 30-40 discovery projects ranging from fully public to fully industrial. We are seeking to develop a formulaic approach that can be routinely applied to any cluster of 3D-observed fragment hits, that categorically establishes or discounts the tractability of targeting any putative binding site. The goal is a defined, limited and inexpensive amount of work, that yields progressable chemical matter of measurable affinity. This talk will present our evidence that this is achievable, spanning Cloud-based web-tools, compound design algorithms that emerged from the COVID Moonshot, capacity upgrades at Diamond, low-cost array robotics and crude reactions mixtures; and outline the remaining gaps and work ahead, including the role of so-called AI.