Revival of covalent inhibitors in drug discovery

- Covalent drugs have proved to be successful therapies for various indications, with nearly 30% of drugs on the market acting via a covalent mechanism of action (CoA). However, largely owing to safety concerns, covalent inhibitors are often shunned by medicinal chemists and toxicologists alike. While the potential risks of covalent inhibition are known, the sustained duration of inhibition offers several advantages:
  (a) Improved biochemical efficiency
  (b) Lower, less frequent dosing reducing the burden on the patient
  (c) Dissociation of pharmacokinetics from pharmacodynamics

Among several reviews published recently highlighting the increased interest in covalent inhibitors, Martin H. Johansson’s paper focuses on reversible Michael additions and describes two major strategies to develop safe and efficient covalently acting drugs:

- **Targeted Covalent Inhibition (TCI)** of less reactive electrophilic functional groups, such as irreversible kinase inhibitors (e.g. EGFR inhibitors) are a classical example for this strategy (Figure 1).
- **Reversible Covalent Inhibition** of more reactive electrophilic groups e.g. aldehydes found in protease inhibitors, boronic acids (e.g. bortezomib), nitro- and Michael acceptors (Figure 2).

As interest in covalent inhibitors continues to grow, the tools to evaluate and characterise a covalent inhibitors will evolve. Herein we would like to present in silico and experimental methods which we evaluated and applied to the optimisation of reversible covalent Usp9x inhibitors.

Michael Acceptors as Reversible Covalent Usp9x Inhibitors

A series of α-cyano acrylamides were previously reported as micromolar inhibitors of the deubiquitinating Usp9x and lead compounds WP1130 and VM030 served as starting point for the optimisation programme (Figure 3).

The medicinal chemistry strategy consisted of a parallel approach to optimise the non-covalent (data not presented) as well as the covalent binding contribution to Usp9x inhibition (Scheme 1). Table 1 describes the in silico descriptors, their trend and the NMR shift of α-hydrogen and Usp9x inhibition (B = constant).

<table>
<thead>
<tr>
<th>Structure</th>
<th>AMI_1HUMO</th>
<th>Hardness</th>
<th>EI</th>
<th>δH (CDCl3, 400 MHz)</th>
<th>Usp9x IC50 (µM)</th>
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| **Figure 2:** Reversibility of Michael acceptor inhibitor optimisation programme.

**Figure 3:** Starting points for Usp9x inhibitor optimisation programme.

In summary, emerging interest to harness the power of covalent inhibitors and the potential of making "undruggable" biological targets "druggable", has led us to strategically establish experimental methods to evaluate covalent binders with the aim to support and drive future medicinal chemistry optimisation strategies. We exemplified the application of - for chemists readily accessible – methods to assess, rank and predict the reactivity of Michael acceptors.

References


Corporative Headquarters: Evotec AG, Mainflingen, Germany. Email: info@eurotech.com. Website: www.eurotech.com