Category

Innovative Drug Discovery and Development

Key words

drug binding kinetics

residence time

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Synfact of the Month

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Indazole to 2-Cyanoindole Scaffold Progression for Mycobacterial Lipoamide Dehydrogenase Inhibitors Achieves Extended Target Residence Time and Improved Antibacterial Activity

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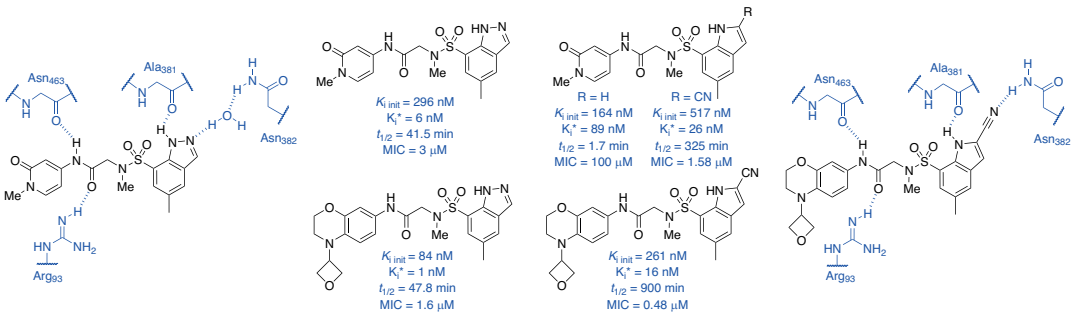
Displacement of a Water Molecule Enhances Drug Residence Time



Significance: Displacement of a water molecule that mediates a drug-target interaction has been exploited as an approach to enhancing potency. The introduction of a substituent that displaces a water molecule and engages the protein target directly can confer significant potency advantage if constructed correctly. In this example, replacement of an indazole heterocycle that engages mycobacterial lipoamide dehydrogenase (LDH) via a water molecule with a 2-cyanoindole that H-bonds directly to the side chain NH of Asn_{382} conferred only modestly enhanced potency toward both the enzyme (K_i) and mycobacterium in cell culture (MIC). However, the 2-cyanaindole derivatives exhibited significantly extended target residence times by 8- and 18-fold in the two examples depicted, an important facet of the biochemical pharmacology of series that correlated with mycobacterial inhibition. In the matched molecular pair comparison, the introduction of the cyano substituent conferred significant mycobacterium inhibition in cell culture compared to the unsubstituted indole.

Comment: Indazole-based LDH inhibitors demonstrated potent and time-dependent inhibition of the mycobacterial enzyme with dissociation $t_{1/2}$ values of 40–50 minutes, in contrast to the rapid dissociation kinetics from the mammalian homologue which conferred selectivity. Attempts to enhance potency by molecular edits to the substituents resulted in only modest increases in potency although the survey identified a benzo[*b*][1,4]oxazine as a suitable bioisostere of the pyridone moiety. A co-crystal structure of the indazole bound to LDH revealed a water molecule mediating the interaction between the heterocyclic N atom and the side chain NH_2 of Asn_{382}. WaterMap analysis showed that the bridging water molecule was of highly unfavorable free energy (9.27 kcal/mol) indicating that it was weakly bound. The 2-cyanoindole analogue demonstrated potent enzyme inhibition that was 2-fold enhanced over the unsubstituted indole. However, the dissociation $t_{1/2}$ for the 2-cyanoindole was almost 200-fold longer than for the unsubstituted progenitor and 8-fold longer than the indazole prototype. A cryo-EM structure of LDH with the benzo[*b*][1,4]oxazine analogue confirmed the drug design principle.

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