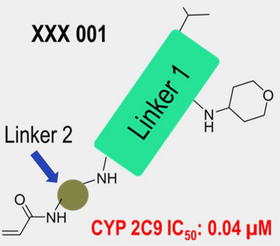
The Problem:

- Active compounds in a project were found to be highly potent inhibitors of CYP 2C9
- The compounds selectively inhibited CYP 2C9 with IC_{50} values <100 nM
- There was no considerable inhibition of the other CYP isoforms

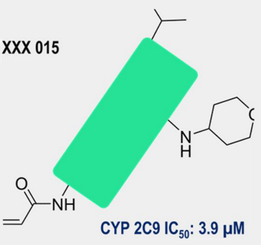


Our Mitigation Approach:

- CYP 2C9 inhibition data was generated for a larger set of compounds with diverse moieties irrespective of their biochemical potency towards the target
- SAR was derived with respect to the CYP 2C9 inhibition

Our Observations:

- Compounds without 'Linker 2' were found to have lower CYP 2C9 inhibition potential
- However, 'Linker 2' was critical for primary activity towards the target

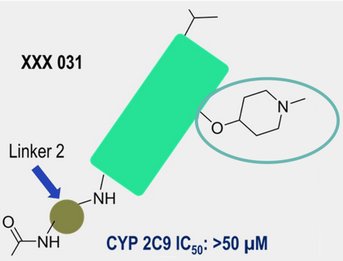


Replacement of the tetrahydropyron with N-methyl piperidine yielded high CYP 2C9 selectivity, while maintaining the potency towards the target

Our Solution:

Understanding the interaction of the inhibitor with CYP 2C9 was important to mitigate this problem

- CYP 2C9 inhibitors are reported to be involved in a key binding interaction with an Arginine (Arg 108), a cationic residue in the active site of the protein
- This binding site is unique to CYP 2C9 and not present in the other CYP isoforms
- It would require an anionic moiety on the molecule to make this interaction with Arg 108 in CYP 2C9
- Systematic SAR was built on this hypothesis by modifying the anionic groups in different regions of the molecule, meanwhile retaining the primary activity



Corroboration:

The in-silico docking studies which followed this project support our above-mentioned finding/hypothesis