

Crystal Structures of Mammalian Xanthine Oxidoreductase Bound with Various Inhibitors: Allopurinol, Febuxostat, and FYX-051

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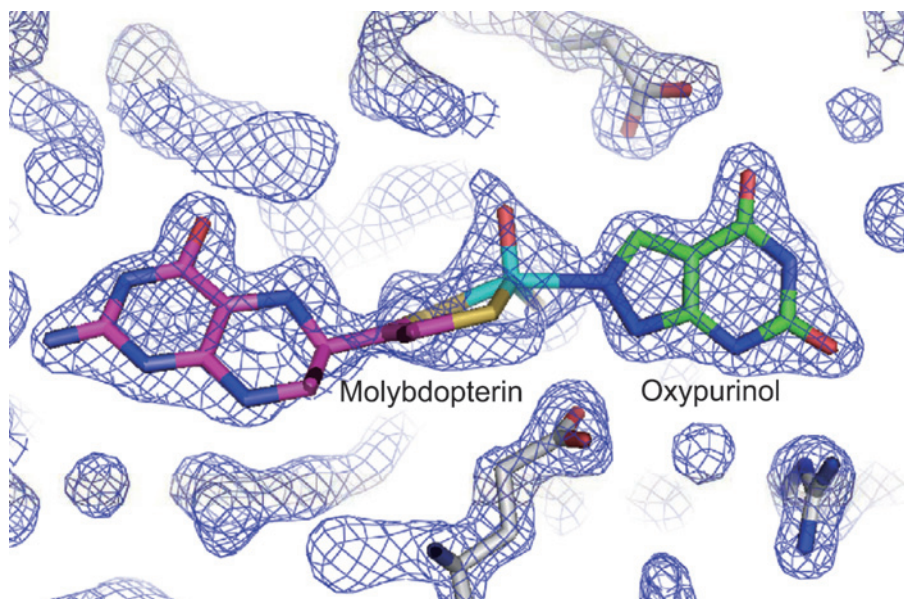


Fig. 1

Abstract

Xanthine oxidoreductase (XOR) catalyzes the reaction of hypoxanthine to xanthine and of xanthine to uric acid. Inhibitors of XOR can thus decrease the concentration of uric acid in serum. Crystal structures of XOR bound with various inhibitors reveal that inhibitors can be categorized into three types, *i.e.* mechanism-based, structure-based, and hybrid types.

Mechanism-based inhibitor

Allopurinol, an analogue of hypoxanthine, has been widely used as an effective remedy for hyperuricemia and gout. Allopurinol is oxidized by XOR itself to oxypurinol, which exhibits weak inhibition ($K_i = 10^{-6}M$) but binds very tightly to the reduced molybdenum during enzyme turnover; thus, oxypurinol is a kind of suicide inhibitor of XOR. The crystal structure (**Fig. 1**) indicates that oxypurinol (green) forms a covalent bond with reduced the molybdenum atom (Mo^{4+}) (light blue) (Modified from the ref. 1)

Structure-based inhibitors

Febuxostat and Y-700 have numerous hydrogen bonds, salt bridges, and hydrophobic interactions with amino acids in the active site (**Fig. 2, left**) and nearly completely fill the narrow channel leading to the molybdenum center of the enzyme (**Fig. 2, right**) (modified from ref. 2, 3).

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Inhibitors XOR

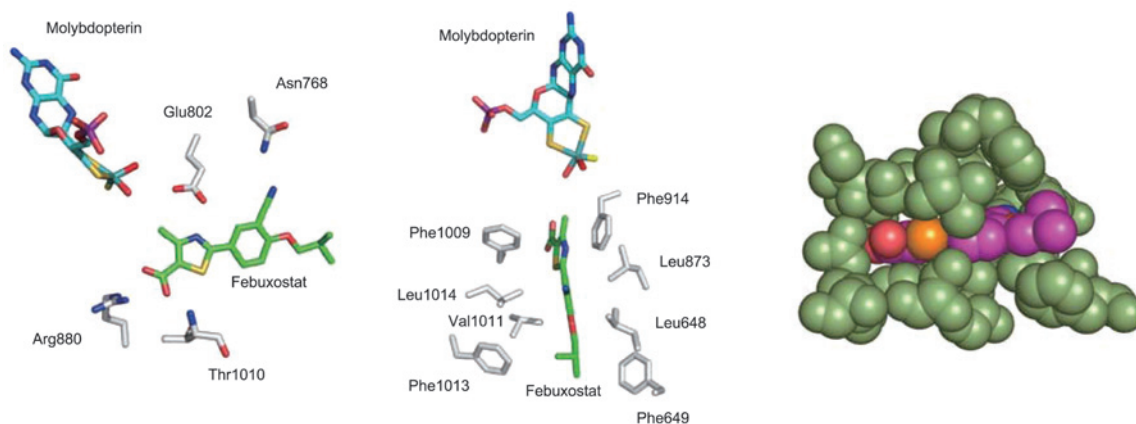


Fig. 2

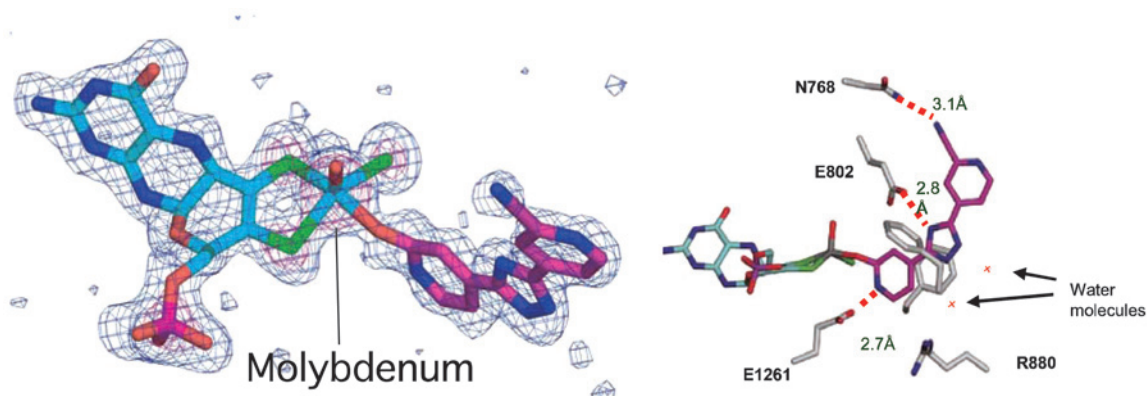


Fig. 3

Hybrid-type inhibitor

FYX-051 has features both a mechanism-based and a structure-based inhibitor. It is a slow substrate of XOR and forms a stable reaction intermediate with the molybdenum atom in the enzyme (**Fig. 3, left**). FYX-051 also has various interactions with amino acid residues at the active site (**Fig. 3, right**) (Modified from ref. 4).

References

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