Pentacyclic triterpenoids as potential inhibitors of aldo-keto reductase 1C: virtual screening of a natural product library

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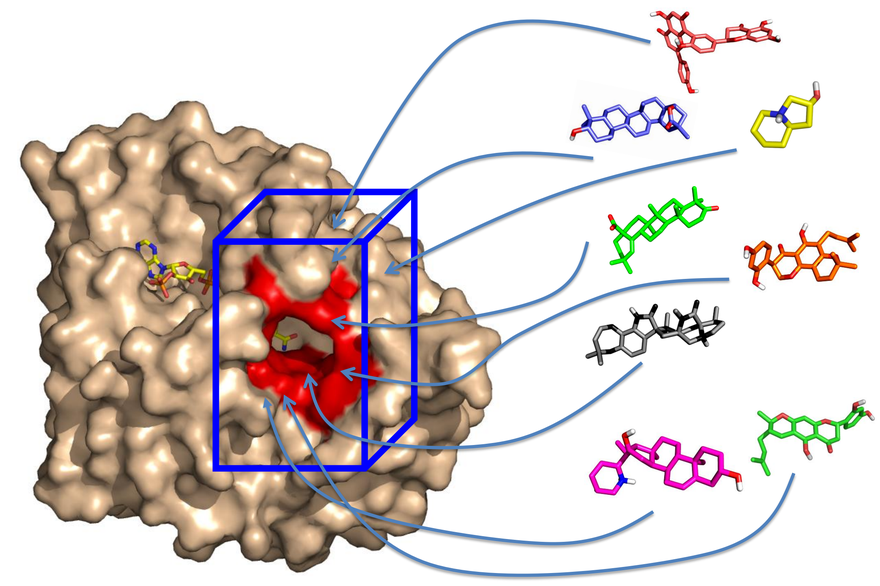
INTRODUCTION

Aldo-keto reductase (AKR) 1C isoforms (AKR1C1-C4) are involved in metabolism of steroid hormones, and are targets for treatment of hormone-dependent breast and prostate cancers; and hormone-independent leukemias. AKR1C enzymes metabolize several chemotherapeutics, reducing their effectiveness. To identify new compounds for experimental testing as AKR1C inhibitors, a virtual library of natural products was screened in silico, for relative binding affinity for AKR1C2. Natural products provide a potent source of compounds with anticancer activities. Over 50% of small-molecule anticancer drugs approved by the U.S. FDA are derived from natural products.

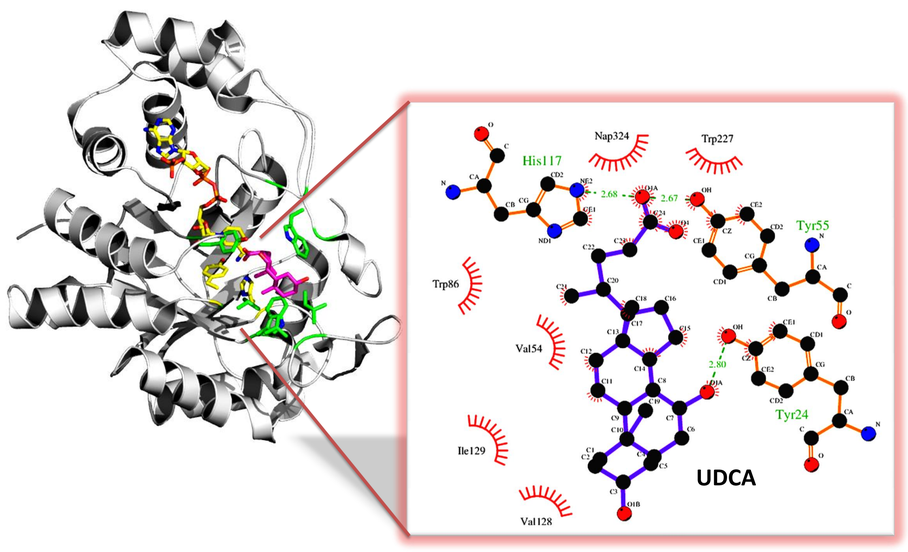
METHODS

A virtual library of 1228 natural products was screened in silico, for relative binding affinity for AKR1C2. Virtual screening was conducted in Autodock Vina using MTiOpenScreen.



Molecular docking of a virtual library of natural products.

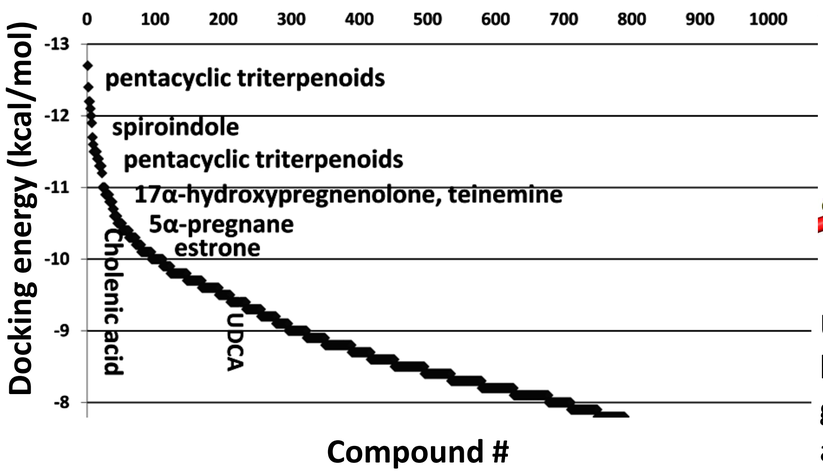
A search space (blue box) of 50x50x50 Å was centered on the active site of AKR1C2 (at x=-1.9, y=36.7, z=23.7). Amino acid residues in the active site of AKR1C2 are highlighted in red.

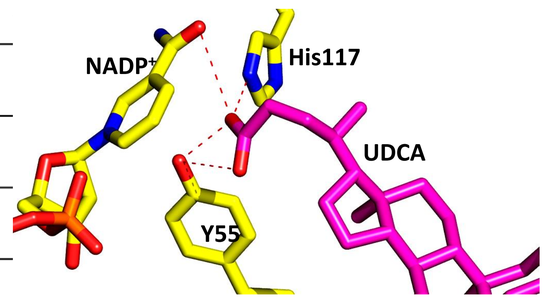


X-ray crystal structure of AKR1C2 in complex with ursodeoxycholate (PDB 1IHI). The structure of AKR1C2 in complex with ursodeoxycholate (UDCA) was used as 'receptor'. For molecular docking simulations. A two dimensional diagram of molecular interactions between inhibitor, UDCA, and AKR1C2 is shown.

RESULTS

Virtual screening identified ~200 compounds with a stronger predicted binding affinity than UDCA, which interact with the catalytic site of AKR1C2.



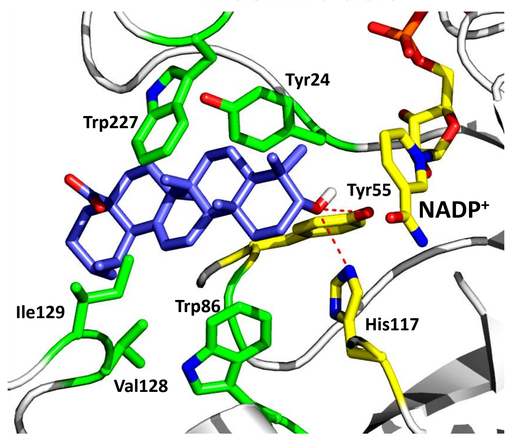


UDCA binds to AKR1C2 via hydrogen bonding between its carboxylate group and catalytic residues (Y55 and H117

Pentacyclic triterpenoid derivatives with similarities to maslinic, oleaonic, ursolic and betulinic acid were among the top 1% of compounds identified. Several of compounds are predicted to form hydrogen bonds with catalytic residues in AKR1C. Previous studies suggest that AKR1C homologs are inhibited by triterpenoids; and we have shown that a pentacyclic steroid derivative inhibits human AKR1C3. Oleaonic acid derivatives were shown to inhibit another member of the AKR1 family of oxidoreductases, AKR1B10, in vitro.

Selected compounds identified by virtual screening against AKR1C2

Maslinic acid



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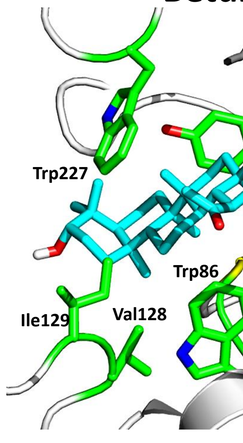
Betulinic acid



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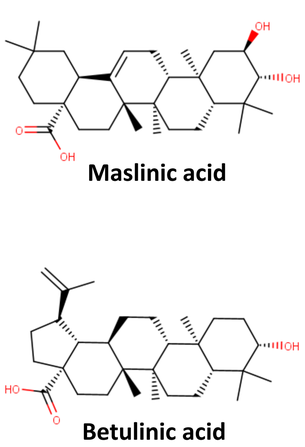
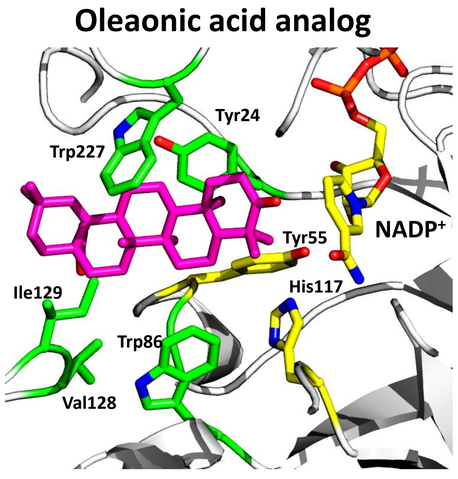


Oleaonic acid analog



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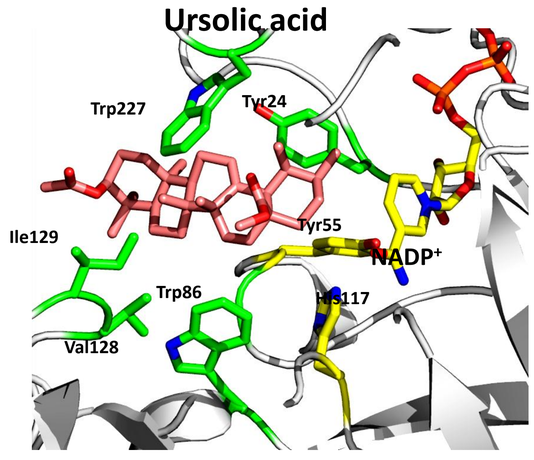
Ursolic acid



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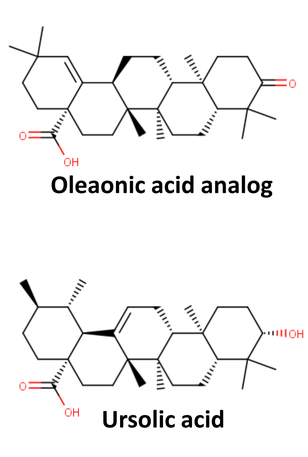

CONCLUSION

The pentacyclic triterpenoid compounds identified in our virtuall screen have been shown to have anticancer properties, and based on the present study represent a new class of compounds for testing as AKR1C inhibitors.

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