Alloxan derivatives as inhibitors of matrix metalloproteinase-2: theoretical calculations and experimental results

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Motivation

Matrix metalloproteinases (MMPs) are a family of structurally related zinc-containing endopeptidases involved in tissue remodelling and degradation of the extracellular matrix. The failure of common synthetic inhibitors makes the design of new selective and potent MMP inhibitors an extreme challenge in health care for the treatment of various pathological states such as inflammation, arthritis, and cancer. In this view, an over-expression of MMP-2 is supposed to be responsible for the occurrence of many different human tumours and inflammatory processes involving the hydrolysis of the type IV collagen, the main component of the basement membrane. A series of studies focused on the design of new potential inhibitors biased towards MMP-2.

Methods

Campaigns of molecular virtual screening of several large chemical libraries resulted in a number of attractive hits. Interestingly, a shortlist of alloxan-like structures was selected with inhibition constants in the nM range. In this respect, we investigated a series of complexes of MMP-2 with alloxan inhibitors by thermodynamic integration in all atoms molecular dynamics simulations.

Results

We obtained quantitative differences in binding free energies for a list of alloxan compounds. On this basis, we were able to elucidate the molecular rationale for the remarkable inhibition exerted by these compounds with the ultimate aim of driving the synthesis of new more potent and selective derivatives that are at present awaiting for further experimental investigations through enzymatic assays.

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