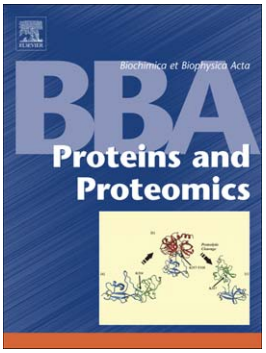

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Modeling Covalent-Modifier Drugs

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Abstract

In this review, we present a summary of how computer modeling has been used in the development of covalent modifier drugs. Covalent modifier drugs bind by forming a chemical bond with their target. This covalent binding can improve the selectivity of the drug for a target with complementary reactivity and result in increased binding affinities due to the strength of the covalent bond formed. In some cases, this results in irreversible inhibition of the target, but some targeted covalent inhibitor (TCI) drugs bind covalently but reversibly. Computer modeling is widely used in drug discovery, but different computational methods must be used to model covalent modifiers because of the chemical bonds formed. Structural and bioinformatic analysis has identified sites of modification that could yield selectivity for a chosen target. Docking methods, which are used to rank binding poses of large sets of inhibitors, have been augmented to support the formation of protein–ligand bonds and are now capable of predicting the binding pose of covalent modifiers accurately. The pK_a's of amino acids can be calculated in order to assess their reactivity towards electrophiles. QM/MM methods have been used to model the reaction mechanisms of covalent modification. The continued development of these tools will allow computation to aid in the development of new covalent modifier drugs.

Keywords: review, covalent modifiers, irreversible inhibition, computer modeling, docking, QM/MM, bioinformatics, pK_a, cysteine, Michael addition, kinase

1. Introduction

The general mechanism for the inhibition of an enzyme or receptor by a small molecule drug is for the drug to bind to the protein, attenuating