Towards the rational design of covalent inhibitors

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Covalent ligands currently experience an intensive renaissance in academic and industrial drug development[1] (Figure 1) because they display several key advantages over their non-covalent counterparts.[2] So far, however, most covalent ligands have been identified serendipitously, since the tools for their rational optimization or *de novo* design are not well established and available methods often fail to decipher the various contributions of the multi-step inhibition processes to the overall potency of a given inhibitor. The latter renders the introduction of new compound classes for covalent inhibitors very tedious or almost impossible as it relies on trial and error strategies. To solve these challenges new approaches are necessary which unravel the various steps of the inhibition processes and which reliably predict the inhibition potency of uncharacterized or even novel compounds.
Such approaches must be able to describe the formation of a covalent bond as well as non-covalent interactions. In the talk, we discuss QM/MM approaches, which are able to elucidate the inhibition mechanisms of covalent ligands[3] and sufficiently accurate to make predictions how the inhibition potencies of a given inhibitor can be influenced.[4]

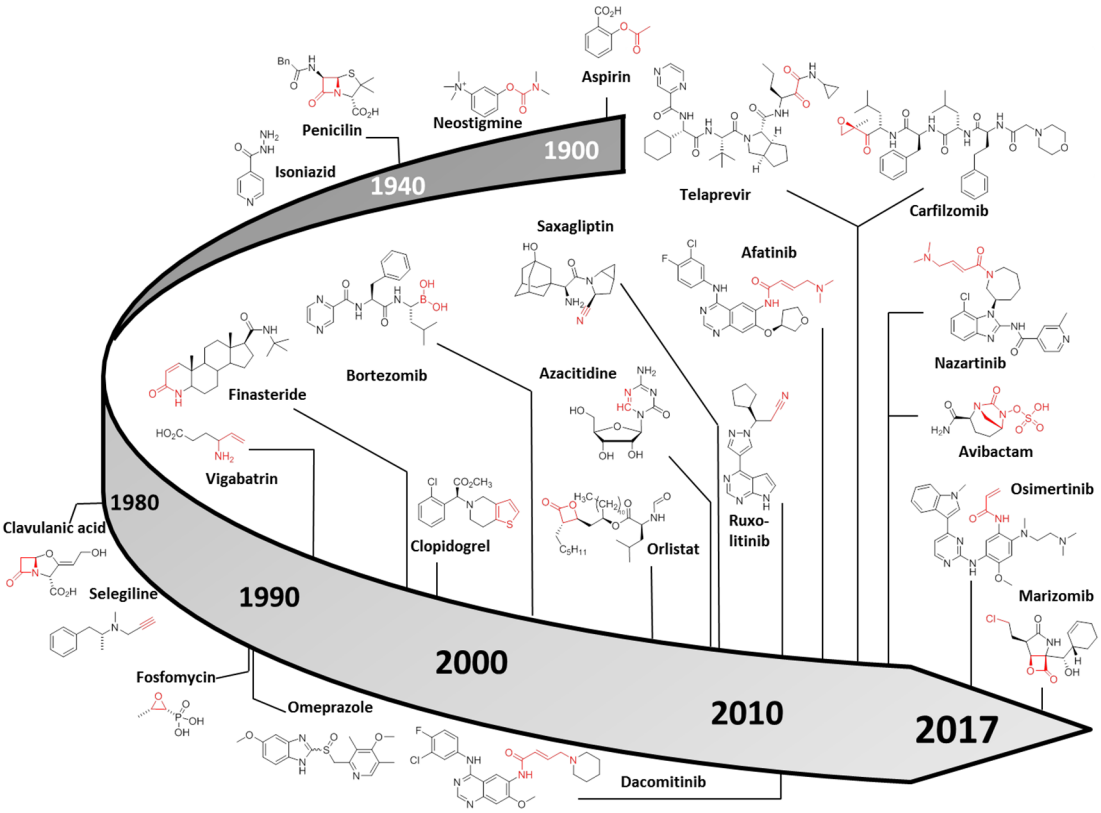

Figure 1: Timeline of selected covalent drugs with approximate dates of discovery.

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