Enzyme Ribonucleotide Reductase. The paradigm of enzyme inhibition by furanone derivatives. Nuno M. F.S.A. Cerqueira, Pedro A. Fernandes and Maria João Ramos
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Ribonucleotide Reductase (RNR) is the enzyme responsible for the physiological reduction of all four ribonucleotides to 2'-deoxyribonucleotides. The activity of this enzyme is therefore essential for the stability and survival of the cell, since it is directly involved in DNA synthesis and repair. This key role makes it an attractive target for anti-tumor, anti-viral and anti-bacterial therapies, having been largely studied for the past few years[1-4]. Several 2'-substituted-2'-deoxyribonucleotides are potent inactivators of the enzyme ribonucleotide reductase (RNR), that destroy the essential tyrosil radical located in subunit R2 or/and add covalently to subunit R1. In the absence of reductors the inactivation of the former is related with the alquilation of a furanone derivative that is detected in solution by UV spectroscopy. The furanone is a degradation product of a keto-deoxyribonucleotide that is an intermediate of the inhibitory mechanism of a wide group of 2'-substituted inhibitors. Interestingly the same keto-deoxyribonucleotide is also a proposed intermediate of the natural substrate during the reduction mechanism but, by some reason it does not dissociates from the active site and does not inactivate the enzyme [5]. This study was dedicated to this paradigm and allowed to evaluate the interaction between the enzyme and this keto-deoxyribonucleotide. A model containing a complete R1 subunit was used to model the desire minimums and to deal with such a big system a QM/MM method was employed. The results allowed to conclude that the release of the keto-deoxyribonucleotide is dependent on the charged/neutral nature of the atoms/group that is/are attached to carbon C-2' of the deoxyribonucleotide and their tendency to dissociate through solution.

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