ORAL021

A COMPUTATIONAL INSIGHT INTO THE EFFECT OF DEUTERATION ON THE H_2 RECEPTOR HISTAMINE BINDING PROFILE

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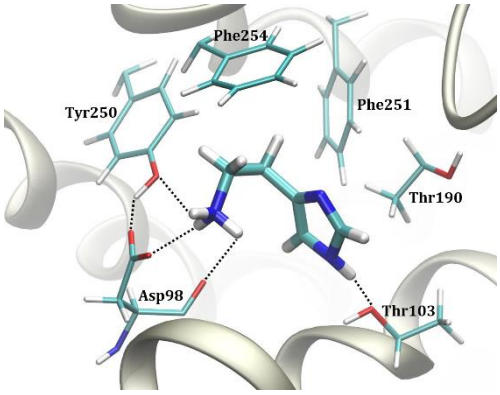
We used a range of computational techniques to reveal an increased histamine affinity for its H_2 receptor upon deuteration, which was interpreted through altered hydrogen bonds within the receptor and the aqueous solution preceding the binding.[1]
Molecular docking identified the area between third and fifth transmembrane α-helices as the likely binding site, with the most favourable binding energy of −7.4 kcal mol^{-1}, closely matching the experimental value of −5.9 kcal mol^{-1}.
The subsequent molecular dynamics simulation recognized Asp98 as the most dominant residue, accounting for 40% of the total binding energy, established through a persistent hydrogen bonding with the histamine $-NH_3^+$ group, which is further stabilised through interaction with Tyr250. Unlike earlier literature proposals, the important role of Thr190 is not evident in hydrogen bonds formed with −OH group, but rather in the C–H···π contacts with the imidazole ring.
Lastly, quantum-chemical calculations within the receptor cluster model and utilizing the empirical quantization of the ionisable X–H bonds (X = N, O, S), supported the deuteration-induced affinity increase. Calculated difference in the binding free energy is −0.85 kcal mol^{-1}, being in excellent agreement with an experimental value of −0.75 kcal mol^{-1}, thus confirming the relevance of hydrogen bonding for the H_2 receptor activation.
The results of this study highlight the importance of deuteration not only for the development of new drugs, as the selective replacement of exchangeable hydrogen atoms with deuterium can increase the duration of action due to their slower decomposition, but in some instances, can result in more beneficial clinical profiles of already marketed pharmaceuticals.



[1] Hok L, Mavri J, Vianello R. *Molecules* 2020, **25**, 6017.