STRUCTURE-ACTIVITY RELATIONSHIPS AND COMPUTATIONAL STUDIES ON PDE$_4$ INHIBITORS

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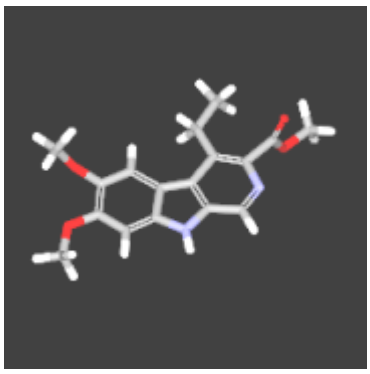
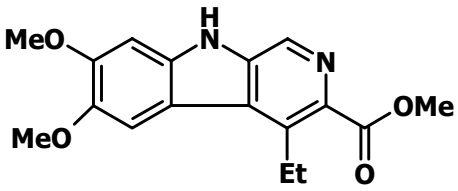
Cyclic AMP controls a wide variety of cellular functions. As the only means of degrading this second messenger is through the action of cyclic nucleotide phosphodiesterases (PDEs), these enzymes provide a key regulatory system [1]. Interest in the potential use of isoenzyme selective phosphodiesterase inhibitors has increased in recent years. In particular, the type 4 family of phosphodiesterases (PDE 4) is comprised of enzymes characterized by their specificity for cAMP hydrolysis [2]. The aim of this present work is to clarify the binding mode of PDE inhibitors by computational studies of new derivatives structurally related to DMCM. Infact a successful synthesis of various β-carboline was carried out and appear to be very attractive models for new PDE 4 inhibitors, with potential uses in the treatment of asthma, chronic pulmonary obstructive disease and some autoimmune disease [3]. In order to identify how selective inhibitors with different chemical structures bind to the similar catalytic pockets of PDEs we performed specific studies to try to define the binding site of the protein, the position and shape of which was used in docking calculations. Some of these synthesized compounds were selected for further biological and pharmacological evaluations of autoimmune and inflammatory diseases.





DMCM

[1] S.H. Soderling, J.A Beavo, Regualtion of cAMP and cGMP signaling: new phosphodiesterases and new functions. *Curr. Opin. Cell. Biol.* 12, 174-179, 2000.
[2] Qing Huai, Huanchen Wang, Yingjie Sun, Hwa-young kim, Yudong Liu, e Hengming ke,Three-dimensional structures of PDE4D in complex with roliprams and implication on inhibitor selectivity, *Structure*, vol. 11, 865–873, 2003.
[3] Barnette MS and Underwood DC (2000), New phosphodiesterase inhibitors as therapeutics for the treatment of chronic lung disease. *Curr. Opin. Pulm. Ed*. 6: 164-169.