KINURENAMINES AS A NEW TYPE OF POTENT nNOS INHIBITORS.

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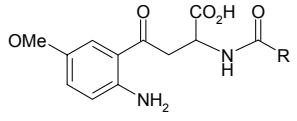
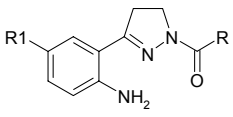
We have recently synthesized and evaluated a series of kynurenine and 4,5-dihydro-1H-pyrazole derivatives of general formulae **1** and **2,** respectively, as neuroprotective agents**.** Such compounds show a significant nNOS inhibitory activity [1,2,3], are inactive againts KYN3OH and consequently, their neuroprotective properties are due to the inhibition of the first enzyme.

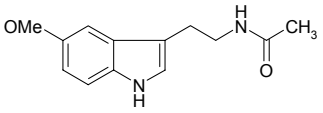
The side chain conformational mobility in kynurenine compounds is restricted by the formation of an intramolecular hydrogen bond between both the 2-NH_2 and the carbonyl groups, and as a consequence of this restriction, the kynurenine derivative can mimic the active conformation of melatonin **3** when it interacts with its biological target [2]. 4,5-dihydro-1H-pyrazole derivatives **2** are more rigid compounds that interact with nNOs in a similar manner to compounds **1** and **3.** A model for the interaction can be drawn on comparing both types of compounds[3].



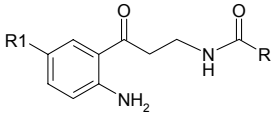
1, R = Me, Pr



2, R_1 = H, Cl, OMe
R = Me, Et, Pr, etc.



3



4, R_1 = H, Cl, OMe
R = Me, Et, Pr, etc.

We present in this communication our previous results on the inhibition of nNOS by a new type of kynurenamines derivatives **4**, that are well suited to our interaction model described for the nNOS inhibition [3].

[1] J. León, F. Vives, E. Crespo, M.E. Camacho, A. Espinosa, M.A. Gallo, G. Escames, D. Acuña-Castroviejo. Modification of Nitric Oxide Synthase Activity and Neuronal Response in Rat Striatum by Melatonin and Kynurenine Derivates. *J. Neuroendocrinol*. **1998**, *10*, 297-302.

[2] M.E. Camacho, J. León, M.D. Carrión, A. Entrena, G. Escames, H. Khaldy, D. Acuña-Castroviejo, M. A. Gallo, A. Espinosa. Inhibition of nNOS Activity in Rat Brain by Synthetic Kynurenines: Structure-Activity Dependence. J. Med. Chem. **2002**, *45*, 263-274.

[3] M.E. Camacho, J. León, A. Entrena, G. Velasco, M.D. Carrión, G. Escames, A. Vivó, D. Acuña-Castroviejo, M.A. Gallo, A. Espinosa. 4,5-Dihydro-1H-pyrazole Derivatives with Inhibitory nNOS Activity in Rat Brain: Synthesis and Structure-Activity Relationships. *J. Med. Chem.* **2004**, *47*, 5641-5650