Pyrazolo[4,3-e][1,2,4]Triazolo[1,5-c]Pyrimidine Template: Organic and Medicinal Chemistry Approach

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Abstract:

Here we report our medicinal chemistry approach on the synthesis of the pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidines and related compounds that have permitted us to complete the SAR analyses on this class of chemical molecules. Evaluating their pharmacological profiles, we planned several structural modifications to modulate the biological activity versus the different adenosine receptor subtypes. Efforts made by our research group led to the discovery of a variety of selective antagonists for the A2A and A3 receptors, performing modifications at the N7, N8, N5, C9, C2-position of the pyrazolo-triazolo-pyrimidine core and by the replacement of the 2-(2-furyl)[1,2,4]triazole molecular part with substituted 2-thioxotriazole, dioxotriazine, oxotriazine, and 1,2,4-triazepine moieties. Modifications at the N7-pyrazole performed by the introduction of different alkyl or arylalkyl chains, led us to the discovery of very potent and selective A2A receptor antagonists, whereas, functionalisations at the N5-position together with the modulation of the pattern of substitution on the N8-pyrazole nitrogen revealed new A3 antagonists (40, 41) suitable to represent candidate for the pharmacological and clinical investigations. Other modifications performed to the tricyclic nucleus, such as the introduction at the C9-position of thioethyl, aminoalkyl and (cyclo)alkylamino radicals (compounds 50-66) and the replacement of the 2-furyl moiety with substituted aromatic rings (compounds 48 a-f and 49a, b) led to a diminished receptor affinity. Also the replacement of the 2-(2-furyl)triazolo template with new heterocycles revealed inactive molecules but allowed us to real understand what structural modifications introduced on the pyrazolo-triazolo-pyrimidine structure played an important role on ligand-receptor interaction. In this way, we notice what position of the heterocyclic structure is not allowed to be modified and, on the contrary, what position is susceptible of modifications or functionalizations.

Keywords:

adenosine receptor subtypes; pyrazolotriazolo-pyrimidines; pyrazole nitrogen; ethylchloroformate; hexamethyldisilazane; 5-N-ethylcarboxamidoadenosine

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