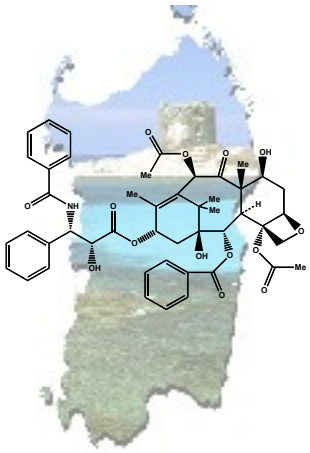
SardiniaChem2008

GIORNATA DI STUDIO DEDICATA ALLA CHIMICA ORGANICA DELLE MOLECOLE BIOLOGICAMENTE ATTIVE

30 Maggio 2008, Aula Magna della Facoltà di Scienze – Sassari



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TRICYCLIC PYRAZOLES. SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL 4,5-DIHYDROBENZO-1H-6-OXA-CYCLOHEPTA[1,2-*C*] PYRAZOLE-BASED ANALOGUES OF THE CANNABINOID ANTAGONIST NESS 0327

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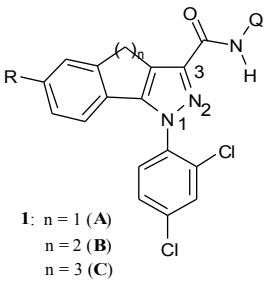
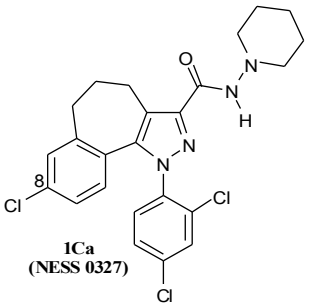
Cannabinoid receptors[1] CB_1 and CB_2, are part of the endocannabinoid system (ECS). This system consists of cannabinoid receptors, endogenous ligands, and several proteins responsible for their synthesis and degradation. Emerging evidences suggest that ECS seems to have modulatory roles in cognition, reward, appetite, pain perception and neuroexcitability, to name just few putative physiological functions. Thus, it appears that dysfunction of the ECS contributes to several pathophysiological conditions that have been associated with the above mentioned biological processes[2].

Previously[3-6], we have described the synthesis of novel tricyclic compounds of general structure **1**.



1: n = 1 (**A**)
n = 2 (**B**)
n = 3 (**C**)



1Ca
(NESS 0327)

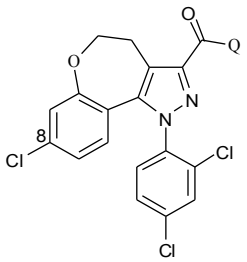
K_i (CB_1) = 0.00035 ± 0.000005 nM
K_i (CB_2) = 21 ± 0.5 nM
CB_1 selectivity = K_i CB_2/K_i CB_1 = >60·000

We also have presented structure-affinity relationships of 1,4-dihydroindeno[1,2-*c*]pyrazoles (**1A**), 4,5-dihydro-1*H*-benzo[*g*]indazoles (**1B**) and 1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazoles (**1C**) for CB_1 and CB_2 receptors.

Compound with the piperidine carbamoyl group in position 3 of the 1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-c]pyrazole ring system, **1Ca**, displayed very high CB_1 affinity and CB_2/CB_1 selectivity.

In order to acquire new insights into structure-affinity relationship of **1Ca**, we decided to replace the methylene in position 6 of the lead with an oxygen atom.

We report in this poster the synthesis and *in vitro* evaluation of novel 4,5-dihydrobenzo-1*H*-6-oxa-cyclohepta[1,2-*c*]pyrazoles **1Cb-l** variously substituted in position 3.



Q = different substituents

1CBb-l

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