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

Gabriele Murineddu, a Christian Dessì, b Caterina Murruzzu, a Stefania Ruju, b Amedeo Pau, a Paolo Lazzari, b Giorgio Chelucci, c Roberta Reali, b Gérard A. Pinna, a and Luca Pani b, d

a Dipartimento Farmaco Chimico Tossicologico, Università di Sassari, Via F. Muroni 23/A, 07100 Sassari; 
b Neuroscienze PharmaNess S.c.a r.l., c/o POLARIS, Edificio 5, Loc. Piscinamanna, 09010 Pula (CA); 
c Dipartimento di Chimica, Università di Sassari, Via Vienna 2, 07100 Sassari; 
d C.N.R. Istituto di Tecnologie Biomediche, Sezione di Cagliari, c/o Neuroscienze PharmaNess S.c.a r.l.

Cannabinoid receptors 1 CB1 and CB2, 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.

![Structure](image)

We also have presented structure-affinity relationships of 1,4-dihydroindeno[1,2-c]pyrazoles (1A), 4,5-dihydro-1H-benzo[g]indazoles (1B) and 1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-c]pyrazoles (1C) for CB1 and CB2 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 CB₁ affinity and CB₂/CB₁ 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-1H-6-oxa-cyclohepta[1,2-c]pyrazoles 1Cb-l variously substituted in position 3.


