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

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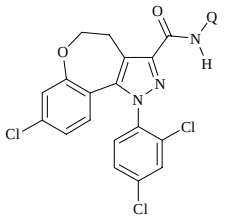
Cannabinoid receptors CB_1 and CB_2, are part of the endocannabinoid system (ECS). This system consists of cannabinoid receptors endogenous ligands and several proteins responsible for their synthesis and degradation. Emerging evidences suggest that ECS seems to have modulatory roles in cognition, reward,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

Previously, we described the synthesis and biological activities of different class of novel tricyclic pyrazole compounds derived from the reference diarylpyrazolic CB_1 antagonist Rimonabant. In particular we showed the highest CB_1 receptor affinity and selectivity for 1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole derivatives with piperidine carbamoyl group at position 3 of pyrazole ring. Among those compounds, 8-Chloro-1-(2',4'-dichlorophenyl)-*N*-piperidin-1-yl-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole-3-carboxamide (NESS 0327) displayed very high CB_1 affinity (K_i CB_1=350 fM) and selectivity (K_i CB_2/ K_i CB_1>60.000).

As a continued effort to further characterize the structure-affinity relationship within the class of tricyclic pyrazole compounds, we replaced the methylene at position 6 of 8-Chloro-1-(2',4'-dichlorophenyl)-1,4,5,6-tetrahydrobenzo[6,7]cyclohepta[1,2-*c*]pyrazole derivatives with an oxygen atom (compounds **I**).



(**I**)

We report in this poster the preparation and preliminary *in vitro* and *in vivo* evaluation of novel 4,5-dihydro-1*H*-6-oxa-cyclohepta[1,2-*c*]pyrazoles (**I**) with a variety of residues "Q" at position 3. Among the new derivates, the coumpond with a piperidine carbamoyl group at position 3, characterized by the highest CB_1 affinity and selectivity, has been investigated through widely recognized *in vivo* models. The results showed that this compound is able to inhibit the agonistic action of WIN 55,212-2 acting as antagonist for CB_1 receptors.