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MEETING ABSTRACTS

INDAZOLYLKETONES: HIT TO LEAD OPTIMIZATION OF A MULTITARGET DRUGS

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A new family of indazolylketones with a multitarget profile as modulators of cholinergic and BACE-1 enzymes and cannabinoids receptors [1] was designed based on our previous results [2]. We present the synthesis, computational studies and biological evaluation and of a new family of heterocyclic compounds.

Pharmacological evaluation include *in vitro* inhibitory assays in AChE/BuChE enzymes and BACE-1. In addition, functional activity for cannabinoid receptors has been carried out. The results of the pharmacological tests have revealed that some of these derivatives behave as CB2 cannabinoid agonists and simultaneously show BuChE and/or BACE-1 inhibition. Furthermore, studies in human neuroblastoma SH-SY5Y cells and in the lymphoblasts of patients with Alzheimer's disease have shown neuroprotective effects of this family of compounds, as well as their capacity to blunt the abnormal enhanced proliferative activity of AD lymphoblasts. Based on the *in vitro* and functional studies we performed *in vivo* studies of those best compounds employing transgenic mouse (TgAPP) model. The results of the *in vivo* study revealed that some of these compounds could be very promising candidates for the treatment of Alzheimer's disease.

Keywords: Alzheimer's disease; BACE-1 inhibitor; BuChE inhibitor; CB2R agonist; indazolylketone; multitarget drug

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