**Novel bicyclic α-iminophosphonate ligands targeting the imidazoline I2 receptor as neuroprotective agents**

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Imidazoline I2 receptors (I2-IR) are not specified molecular identities that can be found in the central nervous system and many other organs such as heart and liver. The modulation of I2-IR by standard ligands evidenced their role in analgesia, inflammation, and human brain disorders, encompassing glial tumors, depression, Alzheimer’s disease (AD) and Parkinson’s disease (PD), amongst others. The chemical structure of I2-IR ligands is restricted to 2-heterocyclic-2-imidazolines in the standards idazoxan, tracizoline, BU224, 2-BFI and BU99008 (clinical candidate, Phase I) or an N1-imidazole

heterocyclic scaffold in CR4056 (clinical candidate, Phase II). We have contributed to the disclosure of the pharmacological role of I2-IR by their modulation with structurally original I2-IR ligands and observing in vivo physiological responses and modifications of molecular AD-biomarkers in treated murine model animals [1,2,3]. Here we report a new family of bicyclic α-phosphoprolines that showed high affinity and selectivity upon I2-IR and good BBB permeation. We evaluated three selected new compounds in dopaminergic neurodegeneration and neuroinflammation cellular models. The good results led us to take the challenge to carry out the first study of I2-IR ligands in Caenorhabditis elegans as an in vivo AD model organism [4].

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