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DESIGN, SYNTHESIS AND PRELIMINARY BIOLOGICAL EVALUATION OF 3-CYCLOPROPYL-4-PHENOXY-1*H*-PYRAZOLE DERIVATIVES AS SMALL MOLECULAR LIGANDS OF RAGE

Maspero, M.;[a] Fabini, E.;[b] Ruggieri, F.;[a] Tramarin, A.;[b] De Amici, M.;[a] Vistoli, G.;[a] Aldini, G.;[a] Carini, M.;[a] Bartolini, M.;[b] Dallanoce, C.[a]

[a]*Department of Pharmaceutical Sciences, University of Milan, via L. Mangiagalli 25, 20133 Milano, Italy;* [b]*Department of Pharmacy and Biotechnology, Alma Mater Studiorum University of Bologna, Via Belmeloro 6, 40126 Bologna, Italy*

E-mail of the presenting author: clelia.dallanoce@unimi.it

Receptor for advanced glycation end products (RAGE) is a multiligand receptor belonging to the immunoglobulin superfamily and plays a crucial role in the development of many human diseases such as neurodegenerative diseases, diabetes, cardiovascular diseases and cancer.[1] RAGE is involved in a number of cell processes such as neuroinflammation, apoptosis, proliferation and autophagy, and therefore it is of considerable interest as a promising drug target for innovative therapeutic approaches. It consists of an extracellular region, a short hydrophobic transmembrane spanning region, and a highly charged amino acid cytoplasmatic tail. The extracellular region contains a signal peptide, followed by one *N*-terminal V-type immunoglobulin domain and two *C*-type (C1 and C2) immunoglobulin domains.[2] RAGE is able to interact with a large number of pro-inflammatory and regulatory molecules, such as advanced glycation end-products (AGEs), quinolinic acid, beta amyloid (A*β*), high mobility group box 1 (HMGB1), S100/calgranulin family proteins.[3,4] However, due to the structural heterogeneity of these endogenous ligands, little is known about the key pharmacophore elements for ligand-RAGE interaction and the specific mode of binding.

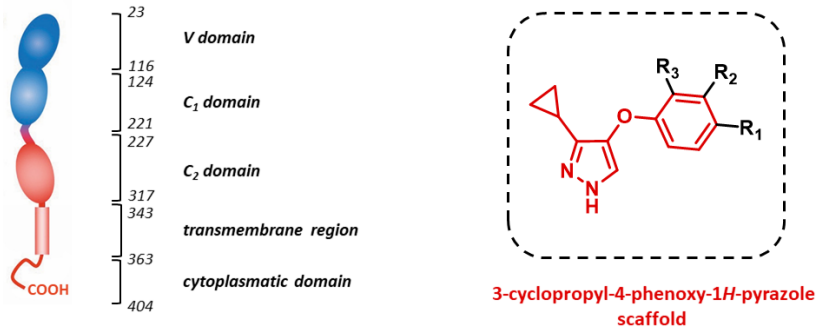

Figure 1. Schematic depiction of RAGE structure and general structure of the new pyrazole-based RAGE ligands.

On these grounds, we aimed at designing new small molecules able to bind the VC1 extracellular domains of RAGE, in order to clarify the structural features that account for RAGE affinity and activation, and to identify new drug-like compounds. Following a process of structural simplification of known pyrazole-5-carboxamide RAGE ligands,[1] we planned a set of novel derivatives characterized by a variously functionalized 3-cyclopropyl-4-phenoxy-1*H*-pyrazole scaffold (Figure 1). The design and synthesis of the new putative RAGE ligands will be presented and discussed, together with the results of their in vitro screening by means of a surface plasmon resonance (SPR)-based assay to estimate their binding ability to the RAGE extracellular domain.

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