In searching of the magic bullet: The role of heme oxygenase-1 in cancer

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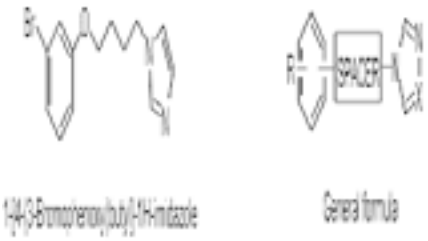
Heme Oxygenases (HO) are family of microsomial enzymes that catalyze heme regiospecific catabolism. HO-1 overexpression is detected in many cancers and its selective inhibition is acknowledged as a new therapeutic opportunity. The first generation of HO-1 inhibitors were soon discontinued due to their pharmacological profile. In the search of HO-1 inhibitors with novel chemical structure, proprietary azole-based compounds were reconsidered as HO-1 inhibitors. Basing on virtual screening results, we tested a compound library possessing two key-features: a N-3 imidazole nitrogen able to coordinate heme ferrous iron and a hydrophobic moiety (Fig. 1). Biological assays revealed high inhibitory activity towards HO-1 and, for some derivatives towards HO-2. Chemical optimization of azole-based derivatives was performed, and most potent compounds were studied for their antitumor properties in different cancer cell lines (imatinib-resistant LAMA-84 R, DU-145, PC3, LnCap, MDA-MB-231, and MCF-7) with highly promising results. Some compounds were able to restore imatinib sensitivity in LAMA-84 R cells. Preliminary results of in vivo studies will be presented. Moreover, new potent and specific ligands for HO-1 and/or HO-2 have been identified. Formulation strategies including nanoparticles have been used to improve pharmacological profile of some selected derivatives and will be the object of the present talk. Finally, elucidation of HO-1 inhibition role in tumor will guarantee useful therapeutic applications in cancer therapy.



1-[4-(3-Bromopropoxy)butyl]-1H-imidazole — General formula

Biography

Valeria Pittalà has completed her MSc in CTF, PhD in Pharmaceutical Sciences at the University of Catania (Italy), and joined Pharmacia Corporation. There she has worked as Member of Combinatorial Chemistry Group, contributed to the discovery of Danusertib, currently under clinical investigation, being Co-Inventor of Bicyclopyrazoles class. Subsequently, she has returned to the University of Catania as Medicinal Chemistry Professor. She is highly motivated drug discovery Scientist and project Leader with proven leadership capability, interpersonal skill, and independence in achieving given objectives. She has published over 60 patents and peer-reviewed papers in reputed journals and has been serving as an Editorial Board Member of repute.

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