Creation of Novel Pharmacological Tools in Heme Oxygenase Research


**Aims:** While great strides have been made in the elucidation of the physiological and pharmacological roles of heme oxygenases (HO) in experimental animals and humans, there is still an enormous potential for further research discoveries and their application in therapeutics. We have identified the need for improved pharmacological tools for Heme Oxygenase research, and have conducted a program to design and test new compounds for their potential as selective inhibitors and activators of HO-1 and HO-2.

**Methods & Results:** Our first undertaking exploited the "hit" compound, (2S,4S)-2-[2-(4-chlorphenyl)ethyl]-2-[(1H-imidazol-1-yl)methyl]-4-[(4-aminophenyl)thio)methyl]-1,3-dioxolane, QC-1. New candidates were designed on the basis of QC-1, and synthesized in our laboratories; they were then tested for HO inhibition using spleen and brain microsomal preparations as sources of HO-1 and HO-2, respectively. Many QC-xx compounds were identified as inhibitors of both HO-1 and HO-2, while a subset were found to be selective for HO-1. X-ray crystallography has revealed that these inhibitors bind to the substrate, heme, in the active site. Subsequently, we screened compound libraries and identified "hits" as candidates for new skeletons in the design of selective inhibitors and activators of HO-2. The latter compounds appear to be selective for HO-2 in that we have observed up to 30-fold activation of HO-2 and no activation of HO-1.

**Conclusions:** The novel compounds that have resulted from this work are being evaluated for their use as tools for the ongoing investigation of heme oxygenases, and their roles in health and disease.

**Key words:** heme oxygenase-1, heme oxygenase-2, inhibitor, activator, QC-xx