New *N*-arylsulfonyl and *N*-methylaryl-iminodiacetic-monohydroxamic acid derivatives as potent and selective MMPs ihibitors

Sérgio Marques[1], Armando Rossello[2], Paolo Carelli[2] and M. Amélia Santos[1]*

[1] *Centro de Química Estrutural, Instituto Superior Técnico, Lisboa, Portugal;* [2] *Dipartimento di Scienze Farmaceutiche, Università degli Studi di Pisa, Pisa, Italy.*

**email to: masantos@ist.utl.pt*

The synthetic inhibitors of certain matrix metalloproteinases (MMPs) which are over-expressed during tumor progression, namely MMP-2, MMP-9 and MT-1MMP (MMP-14), are target molecules under intensive research, as potential antimetastatic and antiangiogenic drugs. We have developed a series of new peptide-mimetic hydroxamic acids, having the iminodiacetic-monohydroxamic acid as scaffold and different *N*-attached lipophilic moieties. Besides the hydroxamic acid, as the zinc-binding group, the lipophilic residue is of high importance for a convenient interaction with the S1' hydrophobic pocket in the enzymes and it can be a major key in finding good selectivity for these targeted MMPs. On the other hand, in these inhibitor molecules, the carboxylic group has the specific role of interacting with hydrophilic residues.

Therefore, based on the known importance of sulfonamide groups in MMP inhibitors and on preliminary docking simulation studies, several arylsulfonyl groups were chosen as lipophilic moieties, such as *p*-methoxybenzenesulfonyl, biphenylsulfonyl and biphenylether-sulfonyl. In order to check the importance of sulfonyl groups on the interaction with the enzymes, another set of analogues was studied, in which a methylene group substituted the SO_2 group of those sulfonamides derivatives. Herein we report the study of this series of MMP inhibitors, namely the results of docking simulations, the synthesis strategy and the inhibitory activity against MMP-2,
-7, -9 and -14. The sulfonamide analogs showed in general high inhibitory activity (*ca* nanomolar order), some of them presenting very high selectivity for MMP-2 (subnanomolar order). One the other hand, the non-sulfonamide analogues proved to be *ca* one thousand-fold less potent than the sulfonamide-based inhibitors, thus confirming the importance of the SO_2 group in the accommodation and binding of the inhibitor to the enzyme hydrophobic subset.