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Putative *in silico* binding modes of nitrile-based peptoids as cysteine protease inhibitors

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Keywords: Molecular docking, Peptoids, Nitrile warhead, Cysteine protease inhibitors.

Highlights

Covalent docking was used to determine putative binding modes for novel cysteine protease inhibitors.
These chemicals were tested *in vitro* using enzymatic kinetic assays to obtain the constant of inhibition.

Resumo/Abstract

Dipeptidyl nitrile analogs known as peptoids were synthesized as inhibitors of cysteine proteases of the papain superfamily. The new analogs differ from peptides due to the side chains of their P3 position being attached to the peptide backbone's nitrogen atom, not to the α-carbons. These derivatives lack the hydrogen amide at P2-P3 responsible for many of the secondary structural elements in peptides and proteins, making them resistant to proteolysis. The designed peptoids lose a hydrogen bond with the macromolecular targets, decreasing the enzyme's overall affinity. Cross-class cathepsin activity was observed for some of these novel compounds against cruzain and cathepsins B, K, L, and S. Besides, the putative mode of binding was determined using covalent docking, which aided in describing the structure-activity relationship (SAR) for the novel chemicals. Compounds **4a** and **4g** were docked to analyze their mode of binding (MoB) with cruzain. It was concluded that the presence of a methoxy moiety in the P3 position was detrimental to the affinity, corroborating the experimental pKi obtained via enzymatic assays. The same approach was taken to analyze the MoB of compounds 4a and 4d in CatL and compounds **4c** and **4e** in CatK. Interestingly, none of the peptoids inhibited CatB to any appreciable extent. These results provide guidance to identify novel bioactive nitrile-based peptoids for further drug design efforts.

Agradecimentos/Acknowledgments

Authors acknowledge the financial support from the São Paulo Research Foundation (FAPESP projects 2013/18009-4 and 2018/15904-6), the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES - Finance Code 001), and Conselho Nacional de Desenvolvimento Científico (cods 304030/2018-0). Matos, T.K.B. was supported by CNPq (process number 142484/2019-9). Santos, D. A. was granted by FAPESP project 2018/09961-7. Thanks to OpenEye Scientific Software (Santa Fe, NM http://www.eyesopen.com), ChemAxon Ltd. (https://www.chemaxon.com/), and UCSF Chimera (https://www.rbvi.ucsf.edu/chimera/) for providing all pieces of software free of charge.