Structural profile of collagenase inhibitors

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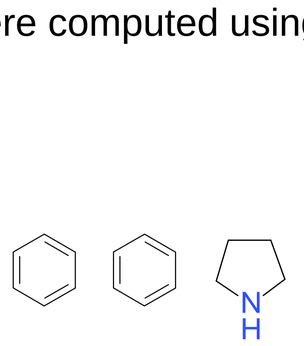
Objectives

The collagenases are metalloproteinases that are involved in the degradation of animal cells, due to their ability to digest collagen. The bacterial collagenolytic proteases are important virulence factors in a variety of pathogenic bacteria due to their capacity to accelerate the bacterial dissemination through digestion of the protein components of the extracellular matrix. The pharmacological inhibition of these enzymes can block the bacterial invasion of the host tissues without killing the bacteria, and therefore limiting the risk of selecting resistant bacteria.

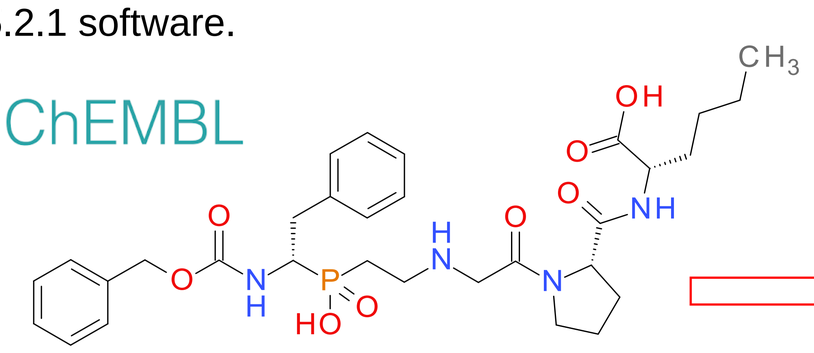
The purpose of this research was to identify the structural profile of the collagenase inhibitors in order to use it for in silico screenings for new potential anti-virulence solutions.

Material and methods

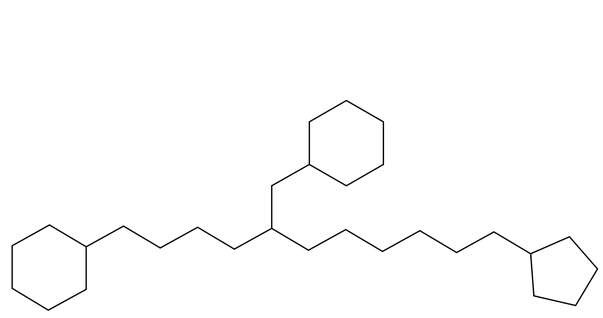
In order to determine the structural profile of the bacterial collagenase inhibitors, we used as a model the collagenase of *Clostridium perfringens* (strain 13/Type A), enzyme coded CHEMBL2802 in the ChEMBL database of the European Institute of Bioinformatics (EMBL-EBI). The results were curated to possess an exact values of the Ki parameter (pKi), as quantitative measure for the inhibitory potency. This collection of compounds was analyzed to reveal relevant structural features and to develop predictive relationships between chemical structure and inhibitory potency on collagenase, as measured by the Ki parameter. A series of molecular descriptors and Bemis-Murcko scaffolds were computed using Data Warrior 5.2.1 software.



Plain rings



CHEMBL2115242

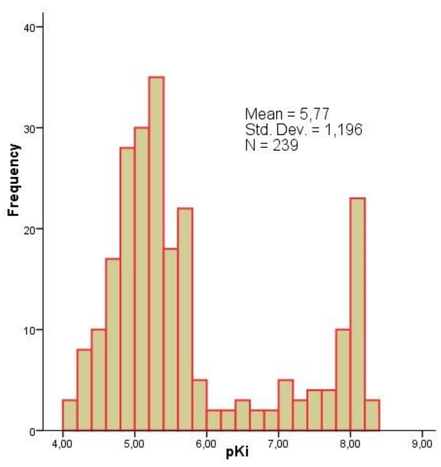


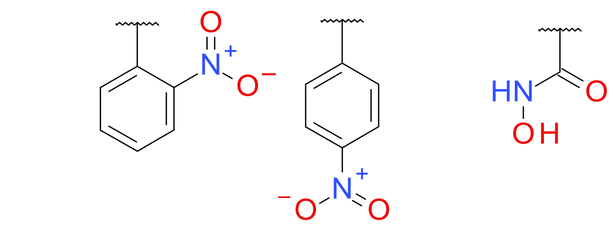
Bemis-Murcko scaffold

Results

All the compounds analysed contain at least 1 donor and at least 8 hydrogen bond acceptors and at least one aromatic ring, which is very often a benzene. The molecule's size doesn't seem to directly influence the potency of the inhibition. A series of pharmacophore groups were identified and discuss: o-nitrobenzene, p-nitrobenzene, hydroxamic acid, sulphonamide. Although hydroxamic acid is an important pharmacophore (41.4%) its presence is not sufficient for a strong inhibitory effect, a number of 49 compounds containing this element have pKi values below 5.5. The additional presence of an o-nitrobenzene structure is a determinant for a higher potency inhibitory effect. The two pharmacophore elements are joined in a N-o-nitrobenzyl-alanine structure.

At the base of the structures of the 239 collagenase inhibitors are 23 types of Bemis-Murcko skeletons consisting of 1 to 4 cyclic structures. Most inhibitors are based on two aromatic structures, either two benzene rings or a benzene nucleus and a naphthalene nucleus, joined by a bridge of at least 3 atoms. Analysis of the types of cyclic structures in the structure of collagenase inhibitors indicated 483 records for 17 types of individual rings, the most common being benzene (85.3%), thiadiazoline (5.6%) and naphthalene (3.9%).

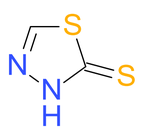




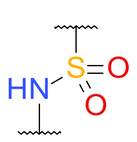
average pKi 6.62

average pKi 5.14

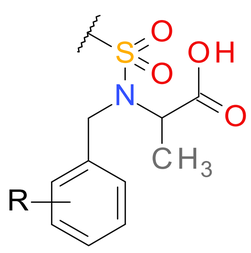
average pKi 5.14

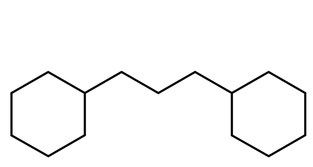


average pKi 4.97

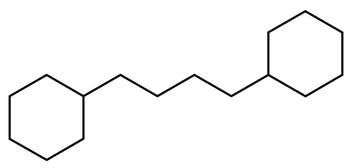


average pKi 5.75



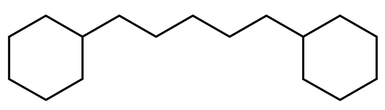


N= 104
average pKi: 5.89

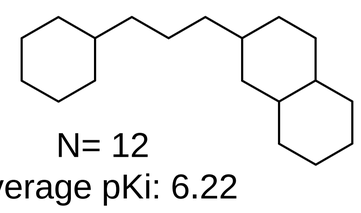


N= 24
average pKi: 5.69

N= 24
average pKi: 5.57



N= 22
average pKi: 6.17



N= 12
average pKi: 6.22

Conclusions

The highlighted structural elements are very specific, making it difficult to identify new candidates as collagenase inhibitors. The observation of bioisosterism relationships between certain structural fragments may allow the application of isosteric analogy changes to the design of new collagenase inhibitors.

Acknowledgement

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