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Molecular design of new aggrecanases-2 inhibitors

Zhi Jie Shan, Hong Lin Zhai *, Xiao Yan Huang, Li Na Li, Xiao Yun Zhang

College of Chemistry & Chemical Engineering, Lanzhou University, Lanzhou 730000, PR China

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ABSTRACT

Aggrecanases-2 is a very important potential drug target for the treatment of osteoarthritis. In this study, a series of known aggrecanases-2 inhibitors was analyzed by the technologies of three-dimensional quantitative structure–activity relationships (3D-QSAR) and molecular docking. Two 3D-QSAR models, which based on comparative molecular field analysis (CoMFA) and comparative molecular similarity analysis (CoMSIA) methods, were established. Molecular docking was employed to explore the details of the interaction between inhibitors and aggrecanases-2 protein. According to the analyses for these models, several new potential inhibitors with higher activity predicted were designed, and were supported by the simulation of molecular docking. This work propose the fast and effective approach to design and prediction for new potential inhibitors, and the study of the interaction mechanism provide a better understanding for the inhibitors binding into the target protein, which will be useful for the structure-based drug design and modifications.

Osteoarthritis (OA) is the most common form of arthritis, which is a disease of entire joints, involving the cartilage, joint lining, ligaments and bone. The exacerbation of OA leads to mechanical damages and culminates in the failure of these structures.[1] Aggrecan is a large proteoglycan containing numerous chondroitin sulphate and keratan sulphate glycosaminoglycan moieties, and the degradation of aggrecan is an early event in the development of OA and become to the central of OA pathology.[2] Aggrecanases, the homologous enzyme family with thrombospondin motifs (ADAMTS), are potential drug targets because that they can degrade aggrecan,[3,4] and aggrecanase-2 (also named ADAMTS-5, a member of this family) is a more important potential target owing to its highest activity of degradation.[5,6] Therefore, the design of aggrecanases-2 inhibitors with higher activity is significant. Several synthesized 1-sulfonylaminocyclopropanecarboxylates had been reported as aggrecanases-2 inhibitors,[7] and the pharmacophore models were used to analyze and predict the activity of aggrecanases-2 inhibitors.[8,9] Although these inhibitors have been discovered, the binding mode or interaction mechanism between inhibitors and aggrecanases-2 is still unclear.

It is well known that the biochemical behaviors of molecules are closely associated with their chemical structures and properties. As one of powerful techniques, quantitative structure–activity relationships (QSARs) have been widely applied in the design of molecule and the prediction of activity.[10–12] QSAR models reveal the relationship between the molecular structures of compounds and their biological activity, which can be used to predict the biological activity of new compounds. And some significant information for the mechanistic interpretation of biochemical interaction could also be obtained from the established QSAR models. Three-dimensional (3D) QSAR methods including comparative molecular field analysis (CoMFA) and comparative molecular similarity analysis (CoMSIA) have been applied in drug discovery, and gained delectable successes.[10,12,13] In CoMFA study, small molecules are set in the 3D space of steric or electrostatic field, and the difference of their physical or chemical properties is relative to the increase or decrease of the biological activity. The same grid constructed in CoMFA is also adopted for CoMSIA analysis, in which five fields (steric, electrostatic, hydrophobic, hydrogen-bond acceptor and donor properties) are calculated and used to analyze the biological activity of small molecules.

In this study, the data set was derived from the published literature,[14] in which amount to 41 compounds were collected, and their activity values were converted into the negative logarithmic 50% inhibitory growth concentration ($pIGC_{50}$). Their common skeleton is shown in Figure 1a, and the number of atoms in molecule is shown as Figure 1b. The molecular structures are listed in Table 1.

The data set was separated into two subsets randomly: the training set with 27 compounds was used to establish QSAR models, and the test set contained 14 compounds (marked with * in Table 1) was employed to evaluate the prediction ability of these models. As the independent samples, test set did not take part in the establishing of models.

By means of SYBYL software (v6.9, Tripos Inc.), all the molecular structures were drawn, and their geometrical conformations were optimized using the standard Tripos force field, in which the net atomic charges were calculated with Gasteiger–Huckel method.

* Corresponding author. Tel.: +86 931 8912596; fax: +86 931 8912582.
E-mail address: zhaihl@163.com (H.L. Zhai).

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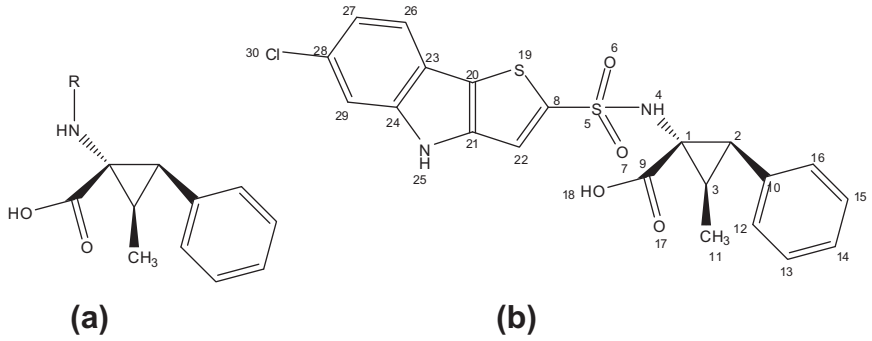
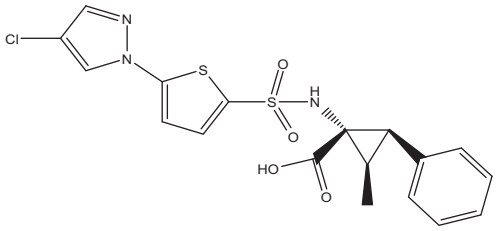
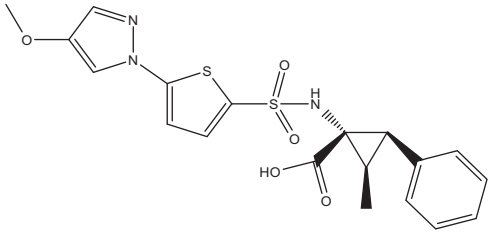
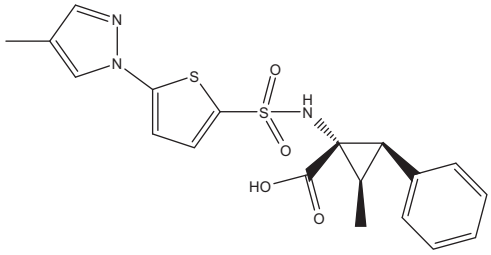
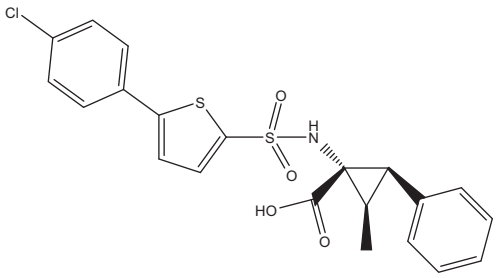
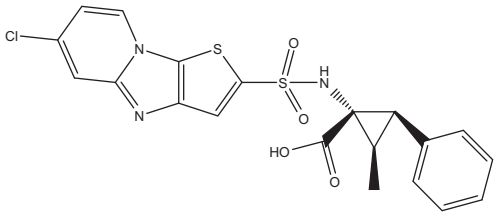


Figure 1. The structural skeleton of the 41 molecules and the number of atoms in molecule.

Table 1
The structures of the 41 compounds and their $pIGC_{50}$ values

Compound No.	Molecular structure	Exp. value[a]	Calcd. value[b]	
			CoMFA model[c]	CoMSIA model[d]
6*		8.131	7.843	7.812
7B		7.770	7.737	7.824
7C		7.721	7.745	7.798
7D*		7.678	8.055	7.915
8A		7.638	7.636	7.428