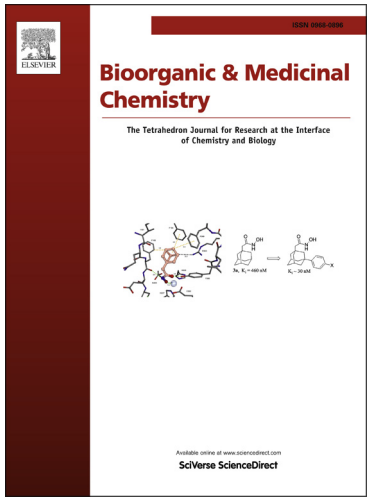

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Discovery of novel series of 6-benzyl substituted 4-aminocarbonyl-1,4-diazepane-2,5-diones as human chymase inhibitors using structure-based drug design

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ABSTRACT

A novel series of 6-benzyl substituted 4-aminocarbonyl-1,4-diazepane-2,5-diones were explored as human chymase inhibitors using structure-based drug design according to the X-ray cocrystal structure of chymase and compound **1**. The optimization focused on the prime site led to the attainment of compounds that showed potent inhibitory activity, and among them, **18R** shows a novel interaction mode.

1. Introduction

Chymase is a chymotrypsin-like serine protease stored in mast cell granules[1] that hydrolyzes a variety of physiological substrates, including angiotensin I.[2] It is known to play a role in the pathogenesis of atopic dermatitis; for example, it has been reported that an intradermal injection of chymase to mouse skin elicits edema as well as inflammatory cell accumulation,[3,4] and a correlation between a particular single nucleotide polymorphism of the chymase gene and incidence of atopic dermatitis has been observed.[5–7] In a previous paper,[8,9] we reported on novel, orally active human chymase inhibitors with a 6-benzyl substituted 4-aminocarbonyl-1,4-diazepane-2,5-dione scaffold, which demonstrated selectivity against other serine proteases. Oral administration of the representative compound SUN13834 reduced skin inflammation in NC/Nga mice[10] that spontaneously develop dermatitis under conventional conditions,[11,12] in addition to significantly decreasing the amount of scratching induced by DNFB challenge in the mouse model.[13] SUN13834 also showed promising results when tested on humans with atopic dermatitis.[14]

In order to increase the chances of successfully launching our chymase inhibitor with lower dosage and/or different pharmacokinetic profile onto the market, a new class of the compound, which showed enhanced inhibitory activity and/or different physical property, was explored using a structure-based drug design approach. Heteroaromatic derivatives and amino acid derivatives were designed by referring to the cocrystal structure of chymase and compound **1** which is SUN13834 series compound (Figure 1). In this paper, the approach used in the design, in addition to the structure activity relationships, is described. In the course of our study, various derivatives were synthesized that showed potent inhibitory activity, comparable to SUN13834.

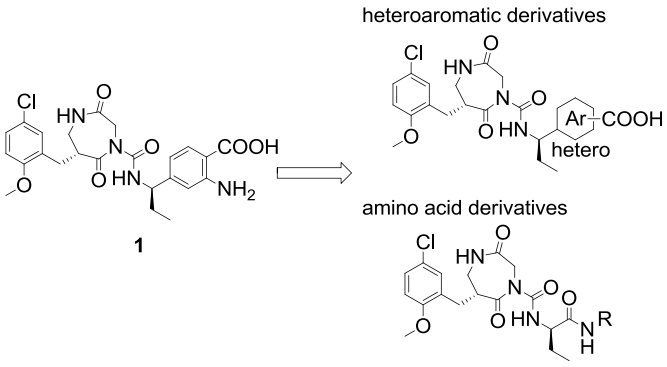

Figure1. Approach to obtaining new inhibitors

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