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1,2-Benzisothiazol-3-one derivatives as a novel class of small-molecule caspase-3 inhibitors

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ABSTRACT

A novel series of 1,2-benzisothiazol-3-one derivatives was synthesized and their biological activities were evaluated for inhibiting caspase-3 and -7 activities, in which some of them showed low nanomolar potency against caspase-3 in vitro and significant protection against apoptosis in a camptothecin-induced Jurkat T cells system. Among the tested compounds, compound **5i** exhibited the most potent caspase-3 inhibitory activity (IC_{50} = 1.15 nM). The molecular docking predicted the interactions and binding modes of the synthesized inhibitor in the caspase-3 active site.

1. Introduction

Apoptosis, or programmed cell death, is an essential physiological process of tissue development and homeostasis.[1] Disregulation of apoptosis is involved in a wide variety of diseases, such as cancer, neurodegenerative and developmental defects, atherosclerosis, autoimmune and cardiovascular diseases including Alzheimer's, Parkinson's and Huntington's diseases.[2] Thus, key apoptosis factors serve as attractive molecular targets for designing specific pharmaceuticals for apoptosis diseases.[3]

Caspases, constituting a family of Cys-dependent Asp-specific proteinases, play critical roles in initiation and execution of apoptosis.[4] The caspase family consists of two different classes of enzymes involved in apoptosis: initiator caspases and executioner caspases. The former, which includes caspase-2, -8, -9, and -10, are located upstream of the signaling cascade and primarily function to activate the executioner caspases (i.e., caspase-3, -6, and -7).[5] Caspase-3, a member of a class of effector caspases, has been found to be activated in nearly every model of apoptosis encompassing several different signaling pathways. Therefore, caspase-3 is a potential therapeutic target for the treatment of diseases involving disregulated apoptosis.[6]

Our strategy was to identify a potent inhibitor for this enzyme, and thus we have recently identified 1,2-benzisothiazol-3-one **1** was an important core as an inhibitor of caspase-3 through a high throughput screening, and then we reported a new series of 1,2-benzisothiazol-3-one derivatives which showed moderate to high affinity at caspase-3 (Fig. 1).[7] Within the active compounds, compound **2** (Fig. 1) presented the best activity with an IC_{50} value of 31 nM. The docking studies (Fig. 2) indicated that the carbonyl of benzoisothiazol-3-one in compound **2** could be generating two hydrogen bonds with H121 and G122 within the S1 pocket. The carbonyl of urea group also formed one hydrogen bond in the S2

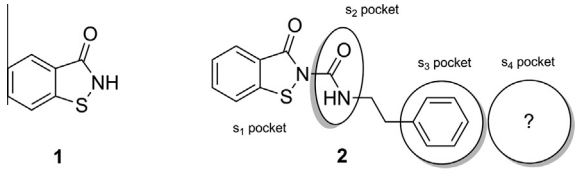

Figure 1. Structures of the hit compounds **1** and **2**.

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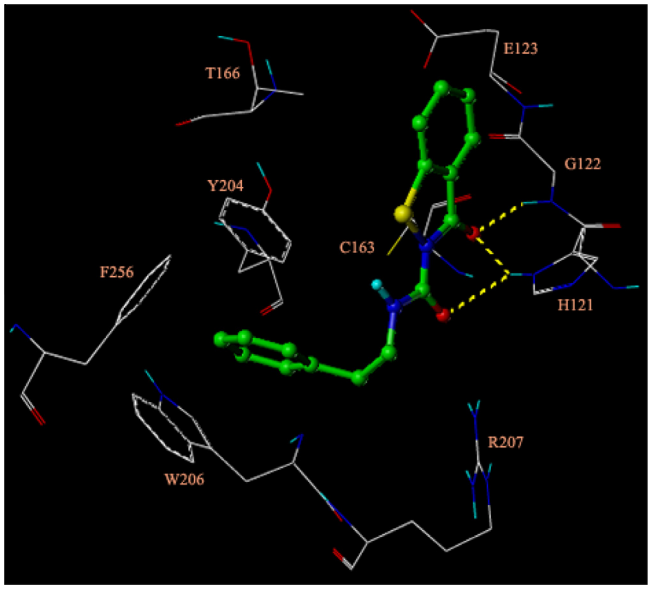


Figure 2. The complex structure of inhibitor **2** (green) and caspase-3 from docking study.[7]

pocket. The benzene ring of **2** plunged into the hydrophobic part S3 and generated hydrophobic interactions, but there are not hydrophobic interactions between **2** and the part S4. However, the phenoxy of co-crystallized inhibitor[8] (IC_{50} = 7 nM) could generate the hydrophobic interactions with S4 pocket of caspase-3. Hence, we inferred that the inhibitory activity of the compounds could be improved through extending the length of the molecule and a better combination of the compound with the protein pocket would be obtained.

In this paper, we report a new series of 1,2-benzisothiazol-3-one derivatives as caspase-3 inhibitors with improved potency for inhibiting caspase-3 activity in both the in vitro enzyme assay and in camptothecin-induced caspase activation in human Jurkat T cells. In addition, Caspase-7 has often been considered to be analogous to caspase-3, another member of the death trio of executive caspases. However, the role of caspase-7 in non-apoptotic processes is different from caspase-3, such as its role in tissue regeneration, cell fate determination, neural activation and cell differentiation.[9] Hence, it is important to develop the selective inhibitors toward both the highly homologous caspase-3 and -7 active sites, respectively. Here we also evaluate the inhibition of all compounds for caspase-7.

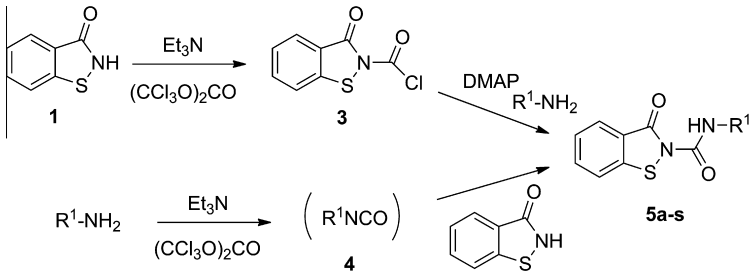
2. Results and discussion

2.1. Chemistry

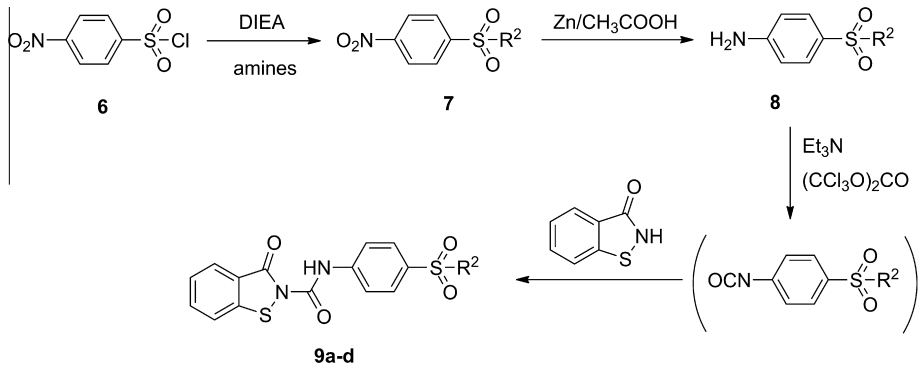
Two approaches for the preparation of *N*-substituted 3-oxobenzo[*d*]isothiazole-2(3*H*)-carboxamides **5** were shown in Scheme 1. Compounds **5a**–**e** were synthesized from acyl chloride **3**, obtained by the reaction of 1,2-benzisothiazol-3-one **1** with triphosgene in the presence of Et_3N, after which a primary amine and DMAP were added into the mixture to obtain **5a**–**e**. The compounds **5f**–**s** were prepared via the reaction of isocyanates **4**, obtained by the reaction of a primary amine with triphosgene and 1,2-benzisothiazol-3-one **1**.[10] Yields for conversion of primary arylamines to isocyanates were quantitative and yields for reactions of the isocyanates with 1,2-benzisothiazol-3-one **1** were typically over 90%.

Scheme 2 showed the synthesis of compounds **9a**–**d**. 4-Nitrobenzene-1-sulfonyl chloride **6** reacted with heterocyclic amines (such as morpholine, 1-methylpiperazine, piperidine and pyrrolidine) to obtain intermediate **7**. Intermediate **7** was reduced to primary amine **8** by reaction with a mixture of Zn and acetic acid. Compounds **9a**–**d** were prepared from **8** by using the similar sequence of reactions described in the synthesis of **5f**–**s**.

Compounds **13a**–**d** were readily synthesized as shown in Scheme 3. Alkylation of 1,2-benzisothiazol-3(2*H*)-one **1** with K_2CO_3/tertbutylbromoacetate followed by cleavage of the *tert*-butyl



Scheme 1. Synthesis of 1,2-benzisothiazol-3-one derivatives **5**.



Scheme 2. Synthesis of 1,2-benzisothiazol-3-one derivatives **9**.