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Research paper

Design, synthesis and biological evaluation of peptidomimetic benzothiazolyl ketones as 3CL^{pro} inhibitors against SARS-CoV-2

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ABSTRACT

A series of peptidomimetic compounds containing benzothiazolyl ketone and [2.2.1] azabicyclic ring was designed, synthesized and evaluated in the hope of obtaining potent oral 3CL^{pro} inhibitors with improved pharmacokinetic properties. Among the target compounds, **11b** had the best enzymatic potency (IC_{50} = 0.110 μM) and **11e** had the best microsomal stability ($t_{1/2}$ > 120 min) and good enzyme activity (IC_{50} = 0.868 μM). Therefore, compounds **11b** and **11e** were chosen for further evaluation of pharmacokinetics in ICR mice. The results exhibited that the $AUC_{(0-t)}$ of **11e** was 5143 h*ng/mL following single-dose oral administration of 20 mg/kg, and the F was 67.98%. Further structural modification was made to obtain compounds **11g**-**11j** based on **11e**. Among them, **11j** exhibited the best enzyme inhibition activity against SARS-CoV-2 3CL^{pro} (IC_{50} = 1.646 μM), the $AUC_{(0-t)}$ was 32473 h*ng/mL (20 mg/kg, po), and the F was 48.1%. In addition, **11j** displayed significant anti-SARS-CoV-2 activity (EC_{50} = 0.18 μM) and low cytotoxicity (CC_{50} > 50 μM) in Vero E6 cells. All of the above results suggested that compound **11j** was a promising lead compound in the development of oral 3CL^{pro} inhibitors and deserved further research.

1. Introduction

COVID-19 is an acute respiratory infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which has engendered a huge threat to the global economy and public health [1,2]. The ORF1a and ORF1b genes account for about 2/3 of the total length of the SARS-CoV-2 genome and encode two polyproteins [3,4]. The two polyproteins can be cleaved by 3C-like protease (3CL^{pro}) and Papain-like protease (PL^{pro}) to form sixteen functional proteins [5,6]. It is worth mentioning that 3CL^{pro} is responsible for the cleavage of 11 sites on polyproteins and plays an essential role in viral replication and propagation [7,8]. Besides, it has been proven that the catalytic domains of different coronaviruses 3CL^{pro} are highly conservative, thus 3CL^{pro} inhibitors may have a broad spectrum of anti-coronaviral activities [9,10]. In addition, no human protease has high structural homology with the 3CL^{pro} of SARS-CoV-2 [11,12]. Therefore, given the indispensable role of 3CL^{pro} in the viral life cycle [13], the highly conserved structure [14], and the less related homologous protein in humans [15], 3CL^{pro} is an important target for COVID-19 drugs development.

Many covalent peptidomimetics have been reported as 3CL^{pro}

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