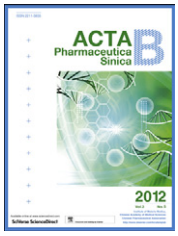
Acta Pharmaceutica Sinica B 2012;2(6):575–580

Institute of Materia Medica, Chinese Academy of Medical Sciences
Chinese Pharmaceutical Association

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



ORIGINAL ARTICLE

Synthesis and antiviral activities of a novel class of thioflavone and flavonoid analogues

Dajun Zhang[†], Xingyue Ji[†], Rongmei Gao, Huiqiang Wang, Shuai Meng, Zhaojin Zhong[*], Yuhuan Li[*], Jiandong Jiang, Zhuorong Li

Institute of Medicinal Biotechnology, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100050, China

Received 12 July 2012; revised 12 September 2012; accepted 9 October 2012

KEY WORDS

Thioflavones;
Antiviral activity;
Coxsackievirus;
Enterovirus

Abstract A novel class of thioflavone and flavonoid derivatives has been prepared and their antiviral activities against enterovirus 71 (EV71) and the coxsackievirus B3 (CVB3) and B6 (CVB6) were evaluated. Compounds **7d** and **9b** showed potent antiviral activities against EV71 with IC_{50} values of 8.27 and 5.48 μM, respectively. Compound **7f**, which has been synthesized for the first time in this work, showed the highest level of inhibitory activity against both CVB3 and CVB6 with an IC_{50} value of 0.62 and 0.87 μM. Compounds **4b**, **7a**, **9c** and **9e** also showed strong inhibitory activities against both the CVB3 and CVB6 at low concentrations (IC_{50} = 1.42−7.15 μM), whereas compounds **4d**, **7c**, **7e** and **7g** showed strong activity against CVB6 (IC_{50} = 2.91–3.77 μM) together with low levels of activity against CVB3. Compound **7d** exhibited stronger inhibitory activity against CVB3 (IC_{50} = 6.44 μM) than CVB6 (IC_{50} > 8.29 μM). The thioflavone derivatives **7a**, **7c**, **7d**, **7e**, **7f** and **7g**, represent a new class of lead compounds for the development of novel antiviral agents.

© 2012 Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association. Production and hosting by Elsevier B.V. All rights reserved.

[*]Corresponding authors. Tel.: +86 10 63010984 (Yuhuan Li), +86 10 63150581 (Zhaojin Zhong).
E-mail addresses: zhongzhaojin@imb.pumc.edu.cn (Zhaojin Zhong), yuhuanlibj@126.com (Yuhuan Li).
[†]These authors contributed equally to this work.

Peer review under responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.

2211-3835 © 2012 Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association. Production and hosting by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.apsb.2012.10.005

1. Introduction

The prevention and treatment of viral infectious diseases has become a global public health problem. The emergence of drug-resistant and unknown viral infections has made the development of new antiviral agents with new mechanisms of action and broad-spectrum levels of activity even more important. Notably, the number of enterovirus 71 (EV71) outbreaks in the Asia-Pacific region has increased significantly in recent years, and group B coxsackieviruses (CVB) are known to be associated with a variety of the acute and chronic forms of several different diseases.

Human enteroviruses are small, single-stranded, positive-sense RNA viruses which belongs to the enteroviruses genus of the picornaviridae family. Like other types of enteroviral infections, EV71 infections may be asymptomatic or may cause diarrhea, rashes, vesicular lesions on the hands, feet, and oral mucosa (hand–foot-and-mouth disease), herpangina, aseptic meningitis, encephalitis, myocarditis, or a combination of these conditions. EV71 infections in children have recently become a significant public health problem in China[1,2]. CVBs are known to be associated with a variety of acute and chronic forms of several different diseases, including myocarditis, meningitis and pancreatitis, especially in neonates, young children and immune-compromised adult patients. Cardiac infection with CVB3 can result in acute myocarditis that spontaneously resolves or chronic myocarditis with prolonged viral persistence[3].

Flavonoids are a group of low molecular weight phenyl benzopyrones that possess a variety of different pharmacological properties, including antioxidant, anticancer, antiviral and anti-inflammatory activities[4–6]. Some naturally occurring and modified flavonoid compounds have been reported to exhibit a broad spectrum of antiviral activity against picornavirus[7,8]. These compounds were reported to interfere with picornavirus replication by preventing the decapsidation of the viral particles and RNA release within the cells. 3-Hydroxyflavone was reported to exhibit antiviral activity against human rhinovirus (HRV)-1B and HRV-14, with IC_{50} values of 1.3 and 2.1 μM, respectively. Although the molecular mechanism of action for flavonoids remains unclear, it has been attributed to interference with the early stages of viral infection, probably represented by viral RNA synthesis.

Thioflavone derivatives are the thio analogues of the flavonoid derivatives, and some thioflavone compounds have been reported to exhibit antimicrobial activities[9]. For example, compounds A and B (Fig. 1) have been reported to exhibit inhibitory activities against *Trichophyton rubrum* IFO5467, with MIC values of 0.19 and 0.05 μg/mL, respectively.

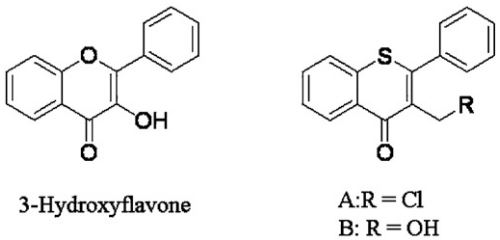


Figure 1 Structures of several known flavone and thioflavone analogues.

However, there have been no reports concerning their antiviral activities.

There are currently no effective antiviral drugs in the clinic for the treatment of EV17 and CVB infections. Treatments for acute EV71 infections with neurological manifestations are principally intended to alleviate the symptoms. With this in mind, herein we describe the synthesis of a series of thioflavone analogues and the subsequent *in vitro* evaluation of their activities against EV71, CVB3 and CVB6. According to the principle of bioisosterism, we synthesized a series of compounds (**7a**–**i**) in which the oxygen atom at position 1 of the flavonoids was replaced with a sulfur atom. To investigate the effects of methoxyl and hydroxyl groups on the activity of these compounds, we obtained compounds **8a**–**c** *via* demethylation of the methoxyl group of **7a**–**c**. Furthermore, several flavonol derivatives were also synthesized in an attempt to improve their antiviral potency and to systemically investigate their antiviral structure activity relationships.

2. Results and discussion

2.1. Chemistry

With the exception of compounds **9a**–**h**, which were purchased from J&K Scientific, all of the target compounds described in this paper were synthesized according to well-established literature procedures[10–12]. The synthetic schemes are discribed below (Schemes 1 and 2).

As shown in Scheme 1, compounds **4a**–**d** were successfully synthesized *via* the condensation reaction of 2-hydroxy acetophenone (**1**) with a variety of substituted benzaldehydes (**2**) in a mixture of MeOH and KOH. The resulting intermediate compounds **3a**–**d** were then reacted with hydrogen peroxide (H_2O_2) in a mixture of MeOH and KOH at 0–5 °C to provide the target compounds **4a**–**d**.

4-Methoxybenzenethiol (**5**) was used as the starting material for the synthesis of the thiochromen-4-one derivatives (**7** and **8**). Compound **5** was condensed with the appropriately substituted ethyl 3-oxopropionates (**6**) in polyphosphoric acid to afford compounds **7a**–**i**, according to a published procedure[10]. These compounds were then treated with boron tribromide in dichloromethane to affect the ether cleavage to generate the substituted thioflavones **8a**–**c**.

2.2. Biological results and discussion

The antiviral activities of the flavonoids against EV71 (SZ-98), CVB3 and CVB6 were evaluated using African green monkey kidney cells (Vero cell) as the virus host. The results are summarized in Table 1.

As shown in Table 1, compounds **7d** and **9b** clearly exhibited the highest levels of inhibitory activity of all of the compounds tested against EV71, with IC_{50} values of 8.27 and 5.48 μM, respectively. Unfortunately, they were not as potent as the reference drug pirodavir, which gave an IC_{50} of 0.32 μM. Compounds **4b** and **7i** showed moderate inhibitory activity against EV71 with IC_{50} values of 16.90 and 39.63 μM, respectively, whereas the remaining compounds showed little to no activity against EV71 under the conditions tested.

The tested compounds showed strong levels of activity against coxsackieviruses. Compound **4a**, for example, showed

Download English Version:

https://daneshyari.com/en/article/2474701

Download Persian Version:

https://daneshyari.com/article/2474701

Daneshyari.com