Chinese Chemical Letters xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

Synthesis and antiviral bioactivity of novel chalcone derivatives containing purine moiety

Yan-Jiao Wang, Da-Gui Zhou, Fang-Cheng He, Ji-Xiang Chen, Yong-Zhong Chen, Xiu-Hai Gan, De-Yu Hu*, Bao-An Song*

State Key Laboratory Breeding Base of Green Pesticide and Agricultural Bioengineering, Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Research and Development Center for Fine Chemicals, Guizhou University, Guiyang 550025, China

ARTICLE INFO

Article history:
Received 9 April 2017
Received in revised form 17 May 2017
Accepted 5 July 2017
Available online xxx

Keywords:
Chalcone derivatives
6-Chloro-purine
Antiviral activity
Cucumber mosaic virus
Tobacco mosaic virus
Interaction mechanisms

ABSTRACT

A series of novel chalcone derivatives containing purine moiety was designed and synthesized, and their antiviral activities against cucumber mosaic virus (CMV) and tobacco mosaic virus (TMV) were evaluated *in vivo*. Bioactivity assays indicated that some compounds showed good antiviral activities against CMV and TMV. It is worth mentioning that compounds **3o**, **3s**, **3w**, and **3x** exhibited excellent curative activity against CMV, with EC_{50} values of 301.1 μg/mL, 315.7 μg/mL, 282.3 μg/mL, 230.5 μg/mL, respectively, which were better than that of Dufulin (373.7 μg/mL) and Ribavirin (726.3 μg/mL). In addition, the fluorescence spectroscopy experiment results showed that compound **3o** showed strong combining capacity to tobacco mosaic virus coat protein.

Cucumbermosaic virus (CMV) and tobacco mosaic virus (TMV) are two important plant viruses, which can cause serious plant disease in plants and can cause considerable damage to agriculturewith those parasitic[1,2]. Up to now, only a few antiviral agents can be widely used to prevent and control CMV and TMV, such as Dufulin and Ribavirin. However, their inhibitory activities were from 40% to 50% at 500 μg/mL [3,4] and it is difficult to effectively control the spread of the virus in the field. Therefore, it is imperative to vigorously develop the new, high-efficiency and low toxicity antiviral agents. As positive-sense single-stranded RNA virus, TMV can infect a wide range of plants, especially tobacco, vegetable and other members of the Solanaceae family. This virus is globally ubiquitous and unmanageable, which can cause great crop loss [1] and was named “plant cancer”. Ningnanmycin was found to be more effective in the treatment of TMV. However, it was not used in field trials because of unstable and expensive [2,3]. Therefore, the development of stable, natural product-based, and economical antiviral agents is a challenge in pesticide science [4].

Chalcone, as a natural flavonoids, widely exist in medicinal plants [5] with broad-spectrum bioactivity, such as antifungal [6], anticancer [7,8], antibacterial [9], insecticidal [10,11], and antiviral [12] activities. Some reports indicated that these bioactivity is due to their molecular flexibility and their ability to bind to different receptors [13,14]. In our previous study, a number of chalcone derivatives containing malonate (Fig. 1A and B) and quinazoline (Fig. 1C) groups have been designed and synthesized, and these compounds exhibited potent antiviral activities against CMV and TMV [15–17].

Meanwhile, purine is an important heterocyclic compounds, which has been widely used as antiviral agent in medicine [18], such as ganciclovir [19], abacavir [20], famciclovir [21] and so on. Additionally, purine and its derivatives possess well others pharmacological properties, including anticancer [22], anticonvulsant [23], antimicrobial [24], herbicidal activity [25], and growth regulating effects [26]. However, the application of purine and its derivatives in pesticide field was extremely rare, especially in controlling plant virus disease aspect. Our group found that a series of purine derivatives containing 1,4-pentadien-3-one moiety (Fig. 1D) exhibited potential antiviral activities against CMV [27].

To extend our study, 1,4-pentadien-3-one moiety was replaced with chalcone structure, and a series of novel chalcone derivatives containing purine group (Scheme 1) were designed and their antiviral activities against CMV and TMV were evaluated *in vivo*. Moreover, the interaction between the target compounds and the tobacco mosaic virus coat protein (TMV-CP) was tested by means of the fluorescence titration

* Corresponding authors.
E-mail addresses: dyhu@gzu.eud.cn (D.-Y. Hu), basong@gzu.edu.cn (B.-A. Song).

http://dx.doi.org/10.1016/j.cclet.2017.07.006

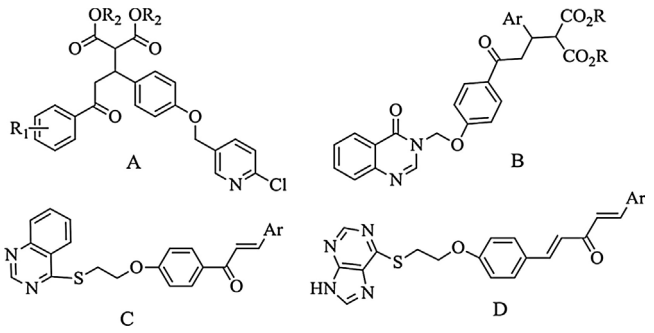
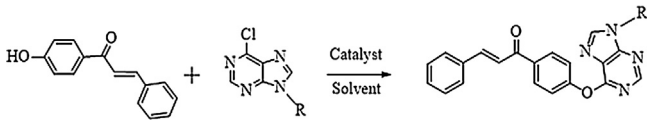


Fig. 1. Chemical structures of known antiviral molecules.

The synthetic route of the target compounds was depicted in Scheme 1. Based on reported method [28,29], intermediates **1** and **2** were prepared. Then, a mixture of intermediates **1** (1.1 mmol) and potassium carbonate (1.8 mmol) in acetonitrile was stirred for 1 h, and 9-substituted-6-chloro-9*H*-purine (1 mmol) was added and refluxed for 8 h. The solvent was evaporated *in vacuo*, and the residue was isolated by column chromatography on silica gel using petroleum ether/ethyl acetate (2:1, v/v) to obtain the title compounds (**3a**–**3z**). Their antiviral activities against CMV and TMV *in vivo* were evaluated by literature methods [27,30], with Dufulin and Ribavirin as controls. Meanwhile, the interaction between the target compound and TMV-CP was test by fluorescence spectroscopy titration [16].

During the synthesis of the target compounds, it is worth mentioning that the corresponding target compounds were not obtained in most reaction conditions when the 9-position of 6-chloropurine was hydrogen including different solvent, catalyst, and temperature (Table 1). However, it is exciting that the target product was obtained successfully when the 9-position was substituted with alkyl, in order to obtain the target compounds with high yields, the reaction conditions of compound **3a** were optimized. The results showed that the maximum yield of **3a** up to 67.3% was achieved when solvent, catalyst and temperature was CH_3CN, K_2CO_3 and 75 °C, respectively (Table 1). Under these conditions, other target compounds were synthesized with corresponding chaclone and 6-chloro-9-substitued-9*H*-purine. The structures of target compounds were identified by ^{1}H NMR, ^{13}C NMR and HRMS. These data were collected in the Supporting information. Take compound **3e** as an example, the two single peaks at δ 8.53, 8.07 in the ^{1}H NMR spectra indicated the presence

Table 1
Effect of different conditions for synthesis of title compounds.[a]

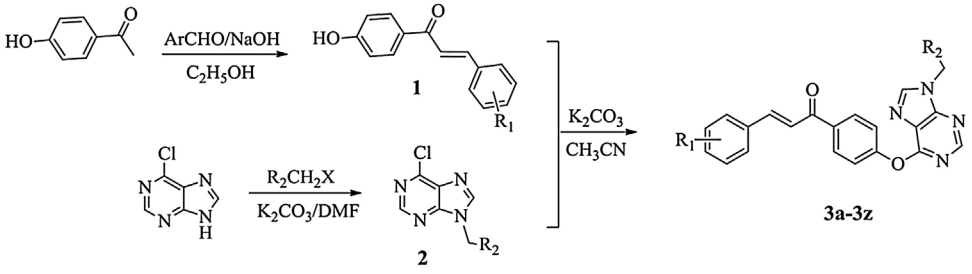


Entry	R	Solvent	Catalyst	T (°C)	Yield[b]
1	H	DMF	K_2CO_3	65	0
2	H	DMF	KOH	80	0
3	H	Acetone	KOH/KI	50	0
4	H	CH_3OH	KOH	65	0
5	H	CH_3CN	DBU[c]	80	0
6[d]	H	DMSO	KOH	180	0
7	CH_3	DMF	K_2CO_3	25	20.8
8	CH_3	DMSO	K_2CO_3	25	45.7
9	CH_3	CH_3CN	K_2CO_3	25	48.3
10	CH_3	CH_3CN	K_2CO_3	75	67.3

[a] Reactions were performed with the molar ratio of 6-chloro-9*H*-purine: chalcone: catalyst was 1:1.1:1.8.
[b] Yield of isolated product.
[c] 1, 8-Diazabicyclo[5.4.0]undec-7-ene.
[d] Microwave synthesis method.

of Purine-H. The doublets at δ 7.82 (d, 1H, J = 15.7 Hz) and δ 7.51 (d, 1H, J = 15.7 Hz) indicated the presence of C=CH. The doublets at δ 8.13, 7.55, 7.42, and 7.22 were assigned to the Ar-H protons. Besides, the spectra shown the presence of —N—CH_2— in the form of a quartet at δ 4.36, the triplet at δ 1.59 and the single at δ 2.39 indicated the presence of —N—CH_2CH_3 and —CH_3, respectively. In addition, the ^{13}C NMR spectra showed the presences of —C=O, —N—CH_2—, Ar—CH_3, and —NCH_2CH_3 at δ 189.4, 39.5, 21.7, and 16.5, respectively.

The antiviral activity of the title compounds *in vivo* was tested and shown in Table 2. The results revealed some compounds exhibited obvious inhibitory activities against CMV and TMV at 500 μg/mL. Notably, compounds **3k**, **3o**, **3p**, **3s**, **3w**, and **3x** demonstrated good curative activities against CMV with the values of 52.3%, 58.3%, 51.3%, 52.5%, 53.3%, and 58.7%, respectively, which were better than that of Dufulin (50.6%) and Ribavirin (40.8%). Besides, the protective effects of compounds **3e**, **3k**, **3n**, **3o** and **3t** was 51.9%, 49.0%, 50.5%, 52.4%, and 48.5%, respectively, which were similar to that of Dufulin (51.5%) and Ribavirin (50.5%). Meanwhile, compounds **3d**, **3f**, **3p**, **3u**, **3x**, and **3y** exhibited good curative



3a: R_1 = H, R_2 = H
3b: R_1 = 2-F, R_2 = H
3c: R_1 = 4-Cl, R_2 = H
3d: R_1 = 2-Br, R_2 = H
3e: R_1 = 4-CH_3, R_2 = CH_3
3f: R_1 = 2-OCH_3, R_2 = CH_3
3g: R_1 = H, R_2 = CH_3
3h: R_1 = 2-F, R_2 = CH_3
3i: R_1 = 4-Cl, R_2 = CH_3
3j: R_1 = 4-NO_2, R_2 = CH_3
3k: R_1 = 4-CH_3, R_2 = Ph
3l: R_1 = 2-OCH_3, R_2 = Ph
3m: R_1 = H, R_2 = Ph
3n: R_1 = 2-F, R_2 = Ph
3o: R_1 = 4-Cl, R_2 = Ph
3p: R_1 = 4-NO_2, R_2 = Ph
3q: R_1 = 2-Br, R_2 = Ph
3r: R_1 = 4-F, R_2 = Ph
3s: R_1 = 2,4-diOCH_3, R_2 = Ph
3t: R_1 = 4-CH_3, R_2 = 2-Cl-Py
3u: R_1 = 2-OCH_3, R_2 = 2-Cl-Py
3v: R_1 = H, R_2 = 2-Cl-Py
3w: R_1 = 2-F, R_2 = 2-Cl-Py
3x: R_1 = 4-Cl, R_2 = 2-Cl-Py
3y: R_1 = 4-NO_2, R_2 = 2-Cl-Py
3z: R_1 = 2,4-diCl, R_2 = 2-Cl-Py

Scheme 1. Synthesis route of compounds 3a to 3z.

Please cite this article in press as: Y.-J. Wang, et al., Synthesis and antiviral bioactivity of novel chalcone derivatives containing purine moiety, Chin. Chem. Lett. (2017), http://dx.doi.org/10.1016/j.cclet.2017.07.006