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Preliminary communication

2,6-Bis-arylmethyloxy-5-hydroxychromones with antiviral activity against both hepatitis C virus (HCV) and SARS-associated coronavirus (SCV)

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ABSTRACT

In this study, as a bioisosteric alternative scaffold of the antiviral aryl diketoacids (ADKs), we used 5-hydroxychromone on which two arylmethyloxy substituents were installed. The 5-hydroxychromones (**5b**–**5g**) thus prepared showed anti-HCV activity and, depending on the aromatic substituents on the 2-arylmethyloxy moiety, some of the derivatives (**5b**–**5f**) were also active against SCV. In addition, unlike the ADKs which showed selective inhibition against the helicase activity of the SCV NTPase/helicase, the 5-hydroxychromones (**5b**–**5f**) were active against both NTPase and helicase activities of the target enzyme. Among those, 3-iodobenzyloxy-substituted derivative **5e** showed the most potent activity against HCV ($EC_{50} = 4$ μM) as well as SCV ($IC_{50} = 4$ μM for ATPase activity, 11 μM for helicase activity) and this might be used as a platform structure for future development of the multi-target or broad-spectrum antivirals.

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1. Introduction

Aryl diketoacid (ADK) has previously been identified to inhibit HIV-1 (human immunodeficiency virus) integrase [1] and RNA-dependent RNA polymerase (RdRp) of hepatitis C virus (HCV) [2,3]. In our previous communications, we reported the ADKs with an arylmethyloxy or arylmethylamino substituent attached at the 2-, 3-, or 4-position of an aromatic ring (**1**, Fig. 1) as inhibitors of the HCV RdRp activity [4] as well as NTPase/helicase activity of SARS-associated coronavirus (SARS-CoV, SCV) [5]. Inhibition of the two different viral enzymes, HCV RdRp and SCV NTPase/helicase, by the same class of compounds was noteworthy because novel multi-target or broad-spectrum antivirals might be developed from this structure. Later, in order to improve unfavorable physicochemical as well as pharmacokinetic properties associated with the diketoacid moiety [6], bioisosteric replacement of pharmacophoric diketoacid core structure (thick line in **1**, Fig. 1) with a β-hydroxyketone moiety (thick line in **2**, Fig. 1) of 5-hydroxyflavone scaffold was attempted. Compared with the ADKs, the 5-hydroxyflavone scaffold provides additional advantage because both sides of the central β-hydroxyketone moiety can be substituted (R_1–R_3 in **2**, Fig. 1) to allow extensive structure–activity relationship study. In our recent proof-of-concept study, the key pharmacophoric arylmethyloxy group of the antiviral ADKs was introduced on opposite sides (3- and 7-positions) of the 5-hydroxyflavone core structure to give the corresponding galangin derivatives, 3-*O*-arylmethyloxygalangins (**3**) [7] and 7-*O*-arylmethyloxygalangins (**4**) [8], and significant anti-HCV activities were observed from both derivatives. However, unlike the ADKs with arylmethyloxy substituents (**1**) which showed inhibitory activity against both HCV RdRp and SCV NTPase/helicase, the galangin derivatives (**3** and **4**) lacked anti-SCV activity [9]. This result suggests that the HCV RdRp might have a binding site specific for the 5-hydroxyflavone scaffold around which two hydrophobic sites with similar shapes are located. It can also be assumed that the SCV NTPase/helicase might not be able to accommodate a 2-phenyl group of the galangin scaffold. Thus, in order to confirm this rationale, we intended to use 5-hydroxychromone instead of 5-hydroxyflavone as a platform structure on which two arylmethyloxy substituents were attached at the same time (**5′**, Fig. 1). However, due to synthetic difficulties associated with synthesis of **5′**, we flipped a core AC ring system of the chromone scaffold and

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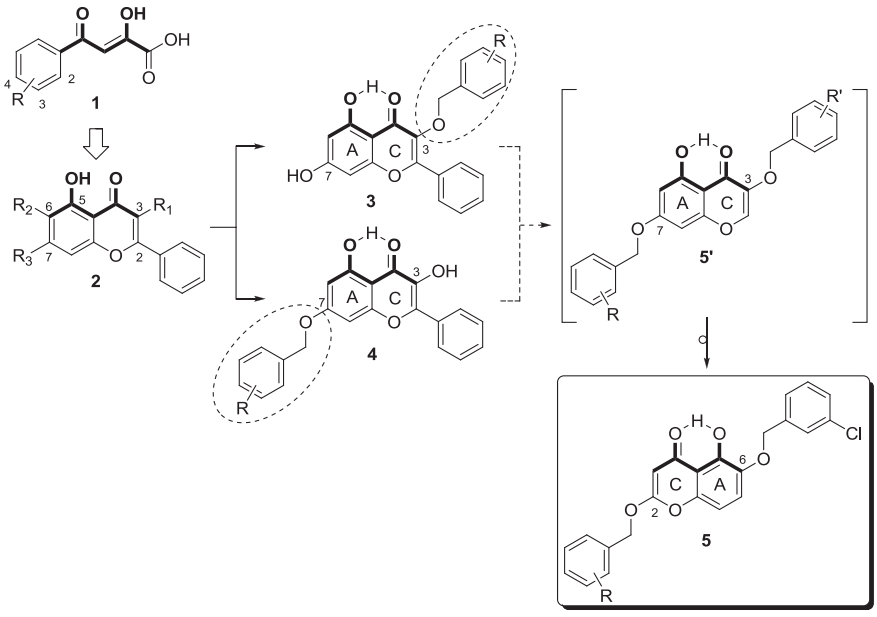


Fig. 1. Structures of ADK with an arylmethyloxy or arylmethylamino substituent (**1**), 5-hydroxyflavone (**2**), 3-*O*-arylmethylgalangins (**3**), 7-*O*-arylmethylgalangins (**4**), 3,7-bis-*O*-arylmethyl-5-hydroxychromone (**5′**), and the title compound of this study [2-arylmethyloxy-6-(3-chlorobenzyloxy)-5-hydroxychromone, **5**].

introduced the substituents on both 2- and 6-positions. As an enol–keto arrangement on a flat fused AC ring system forming an intramolecular hydrogen bond is believed as a key pharmacophoric element of the flavones as well as the chromones, it was fair to assume that flipping the AC ring system to a keto–enol form (CA ring system) would not affect the pharmacophore of the chromone scaffold. As shown in Fig. 1, the 2,6-bis-*O*-arylmethyloxy substituents attached to the flipped fused ring system in **5** are superimposable to those at the 3- and 7-positions of **5′**. The arylmethyloxy substituent at 6-position was fixed with a 3-chlorobenzyloxy group because it provided the 3-*O*-arylmethyloxygalangin derivatives (**3**) with the most potent inhibitory activity against the HCV RdRp ($IC_{50} = 0.1$ μM) [7]. In contrast, as the anti-HCV activity of the 7-*O*-arylmethylgalangin derivatives (**4**) was found to be critically dependent upon size and position of a hydrophobic aromatic substituent in the arylmethyloxy group [8], the aromatic substituent of the 2-arylmethyloxy group was varied with Cl-, I-, and CN- at 3-, 4-, and 5-positions of the aromatic ring. Herein we report synthesis and evaluation of anti-HCV as well as anti-SCV activity of novel 2-arylmethyloxy-6-(3-chlorobenzyloxy)-5-hydroxychromones **5** (Fig. 1).

2. Results and discussion

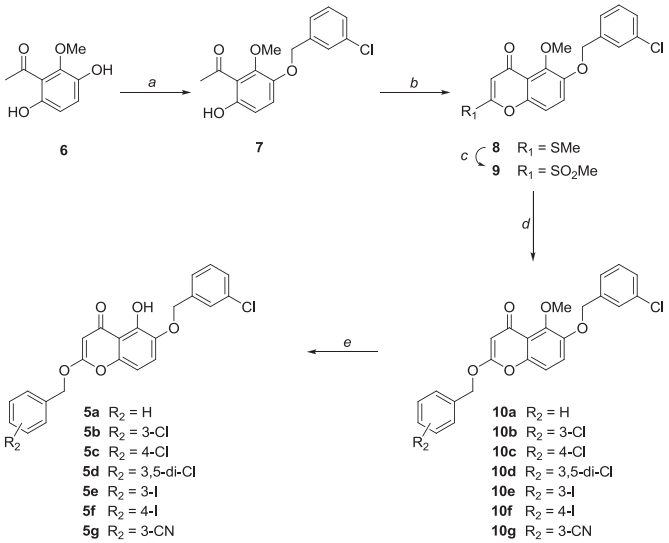
2.1. Chemistry

Synthesis of the title compounds, 2-arylmethyloxy-6-(3-chlorobenzyloxy)-5-hydroxychromone (**5a**–**5g**) is summarized in Scheme 1.

Following literature methods [10], 2,5-dihydroxy-6-methoxyacetophenone (**6**) was prepared from commercially available 2,5-dihydroxyacetophenone. Due to intramolecular hydrogen bonding, the 5-OH group of **6** selectively reacted with 3-$ClPhCH_2Br$ in the presence of K_2CO_3 to provide the alkylated product **7** in 58% yield. Treatment of **7** with LiHMDS, CS_2, and MeI in THF provided the corresponding ketene dithioacetal, which was then cyclized under basic conditions to give 2-methylthiochromone **8** in 51% yield [11]. The sulfide **8** was oxidized by *m*CPBA to **9**, whose methylsulfonyl group was then successfully displaced with sodium salt of variously substituted benzyl alcohols to furnish 2,6-bis-arylmethyloxy-5-hydroxychromone derivatives (**10a**–**10g**) in 47–71% yield [12]. Final Lewis acid-mediated demethylation of **10** to **5** necessitated careful control of the reaction conditions because of concurrent loss of the arylmethyl moiety. Thus, after optimization of Lewis acid as well as the reaction conditions, use of less than one equivalent (~0.89) of $AlCl_3$ in CH_2Cl_2 was found to be the method of choice to provide the desired 2-arylmethyloxy-6-(3-chlorobenzyloxy)-5-hydroxychromones (**5a**–**5g**) in moderate (43–57%) yield.

2.2. Biological activity

In this study, we combined the pharmacophoric arylmethyloxy group of 3-*O*-arylmethylgalangins (**3**) and 7-*O*-arylmethylgalangins (**4**) on the 5-hydroxychromone scaffold to prepare 7 derivatives of 2,6-bis-arylmethyloxy-5-hydroxychromones (**5a**–**5g**). The



Reagents and conditions: (a) 3-$ClPhCH_2Br$, K_2CO_3, Acetone; (b) i) LiHMDS, CS_2, MeI; ii) 10N KOH, THF; (c) mCPBA, toluene; (d) R_2PhCH_2OH, NaH, THF; (e) $AlCl_3$, CH_2Cl_2

Scheme 1. Synthesis of the title compounds (**5a**–**5g**).

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