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Anti-influenza activity of monoterpene-containing substituted coumarins

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ABSTRACT

Compounds simultaneously carrying the monoterpene and coumarin moieties have been tested for cytotoxicity and inhibition of activity against influenza virus A/California/07/09 (H1N1)pdm09. The structure of substituents in the coumarin framework, as well as the structure and the absolute configuration of the monoterpenoid moiety, are shown to significantly influence the anti-influenza activity and cytotoxicity of the compounds under study. The compounds with a bicyclic pinane framework exhibit the highest selectivity indices (the ratios between the cytotoxicity and the active dose). The derivative of (−)-myrtenol **15c**, which is characterized by promising activity, low cytotoxicity, and synthetic accessibility, has the greatest potential among this group of compounds. It exhibited the highest activity when added to the infected cell culture at early stages of viral reproduction.

Influenza A virus is the major cause of seasonal or pandemic influenza worldwide. These annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths.[1] New influenza viruses are constantly evolving by mutation or by reassortment, giving rise to new strains that can infect people who are immune only to the pre-existing influenza strains.[2] Although vaccination against the virus is quite effective, low-molecular anti-influenza drugs are the first line of protection against the virus during an epidemic outbreak, since an effective vaccine for the circulating strains usually takes at least 6 months to be developed.[3] The ability of the influenza virus to develop resistance to the available drugs is a serious problem[4,5] that necessitates designing new structural types of drugs with novel targets, improved antiviral effects, higher safety, and increased tolerability.

An important area in searching for novel antiviral agents is using natural compounds, including marine natural products,[6] monoterpenoid derivatives,[7–13] phenylethanoid glycosides,[14] etc., as starting compounds. Natural coumarins and their derivatives are attracting significant attention as lead structures to search for orally bioavailable antiviral agents.[15] Thus, it has recently been suggested using the pharmacophore-based virtual screening of the library of natural compounds taken from the Princeton database that some coumarin derivatives, for example **1** (Fig. 1), may act as novel neuraminidase inhibitors.[16] Coumarin derivative **2** was identified as a promising anti-influenza agent by cell-based high-throughput screening of 20,000 compounds.[17] The detailed studies focused on structure–activity relationship revealed that BPR2-D2 (Fig. 1) exhibits an excellent antiviral efficacy against the oseltamivir-resistant virus.[18] virus. BPR2-D2 may target viral ribonucleoproteins that are responsible for viral RNA synthesis. A promising group of sesquiterpene coumarins with anti-influenza activity was isolated from *Ferula assafoetida*.[19] The structure of one of these compounds (**3**) is presented in Fig. 1. This compound contains a set of functional groups with fixed stereoconfiguration; synthesizing this compound is very challenging. We supposed that replacement of the sesquiterpene moiety with a monoterpene might give rise to new synthetically accessible compounds with anti-influenza activity. Hence, this study was aimed at searching for novel agents that would possess activity against H1N1 influenza virus among synthetic coumarin derivatives containing a monoterpenoid moiety.

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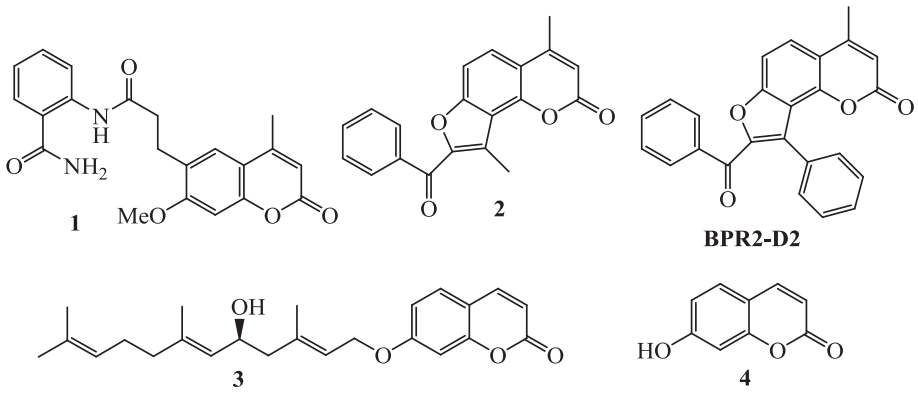
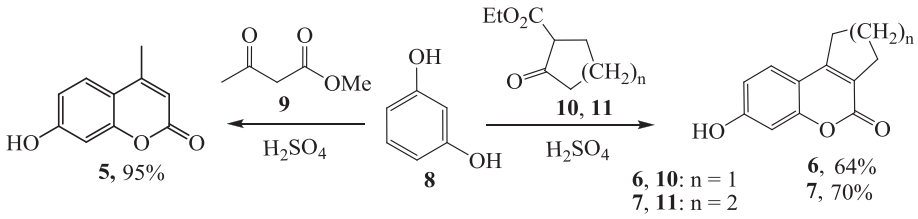
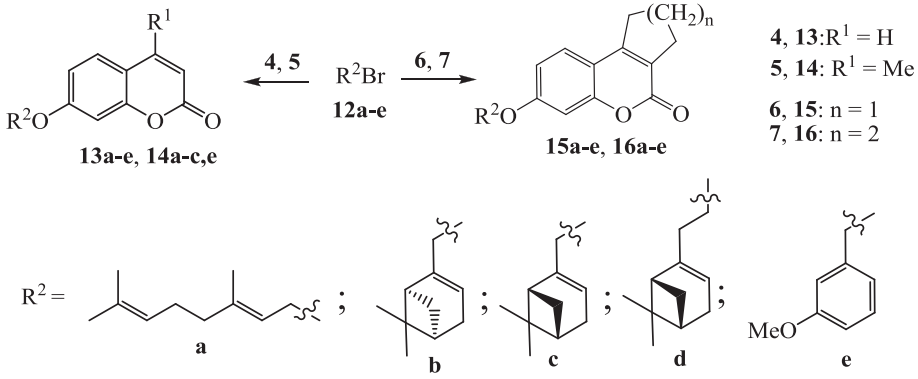


Fig. 1. Structures of anti-influenza active coumarin derivatives and umbelliferone.



Scheme 1. Synthesis of coumarins **5–7** and their yields.



Scheme 2. Synthesis of substituted coumarins.

The commercially available umbelliferone **4** (Fig. 1) and its analogues **5–7** synthesized *via* interaction between resorcin **8** and esters of the corresponding β-keto acids **9–11** (Scheme 1) as described previously[20,21] were used as a coumarin component.

Aurapten **13a** and its analogues **13b–e** (Scheme 2) were obtained by interaction of umbelliferone **4** with monoterpenoid bromides **12a–d** and, for the sake of comparison, with aryl bromide **12e** using DBU in DMF.[22] Bromides **12a**, **12b**, **12c**, **12d** and **12e** were synthesized by interaction between the corresponding alcohols and PBr_3 with the yields of 91%, 55%, 60%, 24% and 65%, respectively.[23] Compound **12d** obtained by interaction between nopol and PBr_3 was insufficiently pure, thus making it necessary to use column chromatography for purification and abruptly decreasing its yield.

In a similar manner, compounds **14a–c**,**e**, **15a–e**, and **16a–e** were prepared as described previously[21] using K_2CO_3, ethanol, and coumarins **5–7** as phenol components.[24] The products were purified by recrystallization or column chromatography (the yields of 29–56%). the reaction of nopyl bromide **12d** with methylcoumarin **14** was not successful due to the formation of a complex reaction mixture with high level of resinification.

The water/octanol partition coefficient (Log P)) is often considered to be an important molecular descriptor as it is linked to toxicity issues and oral bioavailability. The Calculated Log P (cLog P) data are presented in Table 1. Although cLog P of all the compounds carrying the monoterpene and coumarin moieties exceeds the Lipinski's cLog P = 5 limit,[25] most of them are within the known drug chemical space according to this criterion ($cLogP \leq 6.5$).[26]

The antiviral activity of the synthesized compounds was studied[27] against the pandemic influenza virus A/California/07/09 (H1N1)pdm09 cultivated in cell culture by the technique described earlier.[28] Cytotoxicity of the compounds was evaluated[29] in uninfected MDCK cells as described previously.[30]The selectivity index was calculated for each derivative based on the data obtained. The compounds with SI = 10 and higher were regarded as active. The test results are summarized in Table 1. Rimantadine was taken as a reference drug due to its polycyclic structure being close to the pinane scaffold used in the study.