Bioorganic & Medicinal Chemistry Letters 28 (2018) 2061–2067

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Highly potent activity of isopulegol-derived substituted octahydro-2*H*-chromen-4-ols against influenza A and B viruses

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ARTICLE INFO

Article history:
Received 14 March 2018
Revised 19 April 2018
Accepted 23 April 2018
Available online 24 April 2018

Keywords:
Influenza
Antiviral
Monoterpene
Chromene
Montmorillonite K10

ABSTRACT

A set of (−)-isopulegol derived octahydro-2*H*-chromen-4-ols was synthesized and evaluated *in vitro* for antiviral activity against panel of reference influenza virus strains differing in subtype, origin (human or avian) and drug resistance. Compound (4*R*)-**11a** produced via one-pot synthesis by interaction between (−)-isopulegol and acetone was found to exhibit an outstanding activity against a number of H1N1 and H2N2 influenza virus strains with selectivity index more than 1500. (4*R*)-**11a** was shown to be most potent at early stages of viral cycle. Good correlation between anti-viral activity and calculated binding energy to hemagglutinin TBHQ active site was demonstrated.

Development of novel drugs for therapy and prevention of viral infections remains a first-level priority problem of modern pharmacology and medicinal chemistry. Influenza is the most common human infectious disease, with 9% of the world population (20% in USA alone) affected annually.[1] The influenza virus causes recurrent epidemic outbreaks characterized by mass morbidity and high mortality rates associated with influenza complications.[2] Alongside vaccination, chemotherapy is the key method to prevent and treat viral diseases, especially during the pandemics when a new virus spreads much faster than the practical medicine can produce vaccine and immunize the epidemically significant population cohort.

The high variability of the influenza virus allows it to become resistant to the few currently used anti-influenza drugs (neuraminidase inhibitors (oseltamivir and zanamivir) and M2 channel blockers (amantadine and rimantadine).[3] The development of drug-resistant influenza virus mutants can be prevented by using a combination of two or more agents with different mechanisms of action.[4] Hence, it is necessary to search for novel anti-influenza agents belonging to new structural types, including those whose targets and mechanisms of action differ from the currently used ones.

Natural compounds, including monoterpenoids that are components of natural essential oils exhibiting antiviral activity, are a promising source of novel anti-influenza agents.[5,6] For example, (+)-α-pinene-derived compounds pinanamine (Fig. 1)[7] and its derivative **1**[8] were found to be more active than amantadine with respect to influenza A M2 channel inhibition. Several imines based on natural (+)-camphor were shown to be promising antiviral agents. Thus, camphecene (Fig. 1) exhibits a high level and a broad range of inhibiting activity against influenza viruses including viruses A of H1N1, H3N2 and H5N2 subtypes and influenza B.[9,10] Its activity is supposed to be based on inhibition of viral hemagglutinin.[13] Substituted 1-norbornylamine **2** (Fig. 1) synthesized from (±)-camphor also exhibited high activity against influenza virus A.[11]

Interesting group of compounds exhibiting activity against the influenza virus H1N1 was derived from monoterpenoid diol **3** (Fig. 1), which is synthesized from a monoterpenoid (−)-verbenone

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https://doi.org/10.1016/j.bmcl.2018.04.057
0960-894X/

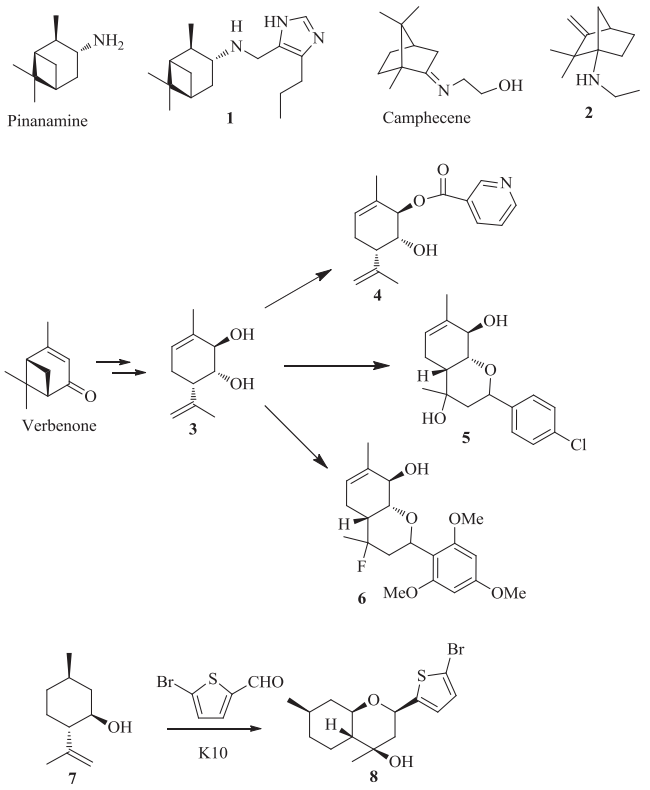


Fig. 1. Structure of monoterpene-derived compounds with anti-influenza activity.

in three stages.[12] Thus, anti-influenza activity was observed for mononicotinate **4**,[13] compound **5** with the hexahydro-2*H*-chromene framework synthesized via interaction between monoterpenoid **3** and *p*-chlorobenzaldehyde in the presence of *K*10 clay, and fluorine-containing compound **6** produced using $BF_3 * Et_2O$ as a catalyst and a reagent.[14] Compound **6** seems to be the most promising one among these compounds combining high antiviral potency (IC_{50} = 5 μM) and low cytotoxicity with the selectivity index SI (the ratio of the 50% cytotoxic concentration to the 50% inhibitory concentration) value of 55.

2-(5-Bromothiophen-2-yl)octahydro-2*H*-chromen-4-ol **8** (SI value of 25) synthesized via interaction between monoterpenoid (−)-isopulegol **7** and 5-bromothiophene-2-carbaldehyde (Fig. 1) has recently been shown to exhibit antiviral activity.[15] Although chromenes derived from compound **7** had a less pronounced anti-influenza activity than compounds synthesized from diol **3**, it is preferential from a practical perspective to search for novel antiviral compounds among polyhydro-2*H*-chromenes synthesized from (−)-isopulegol **7** rather than from diol **3**. The reason is that (−)-isopulegol **7** is a commercially available compound, while **3** is produced via multi-stage synthesis.[12] Furthermore, (−)-isopulegol **7** shows higher activity in reacting with carbonyl compounds than monoterpenoid **3** does; heterocyclic compounds with the octahydro-2*H*-chromene framework are the only products in these reactions, while the interaction between compound **3** and aldehydes often yields complex reaction mixtures.[16,17]

Since the products obtained via interaction between isopulegol **7** and aldehydes exhibited only moderate antiviral activity, the aim of this study was to search for novel anti-influenza agents with the octahydro-2*H*-chromene framework synthesized via interaction between isopulegol **7** and ketones.

The key method for stereoselective synthesis of chiral compounds with the octahydro-2*H*-chromene framework is the interaction between (−)-isopulegol **7** and carbonyl compounds (usually aldehydes) in the presence of various catalysts, including montmorillonite clays,[18–22] zeolites and mesoporous materials,[23,24] Lewis acids,[20] and iodine[25] (Scheme 1). (*R*)-Citronellal **9**[20] can also be used as a starting compound as it is converted to (−)-isopulegol **7** during the reaction. However, compound **9** is more expensive that isopulegol **7** and the catalyst $Sc(OTf)_3$ employed in this reaction is also quite expensive. Based on these findings, we selected (−)-isopulegol **7** as a starting agent to synthesize compounds with the octahydro-2*H*-chromene framework; montmorillonite clay, which is most often used for these processes, was chosen as a catalyst.

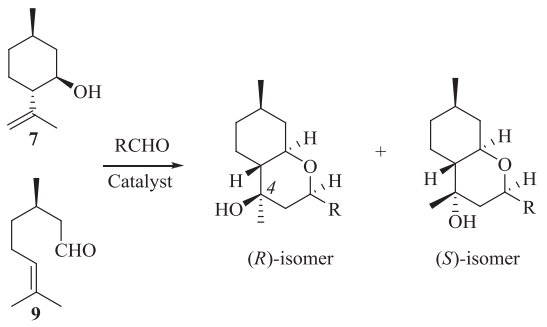
We started our research with studying the reaction between (−)-isopulegol **7** and acetone **10a** (Scheme 2). Iodine in dichloromethane was previously used to catalyze this reaction;[25] the only diastereomer (4*S*)-**11a**, which was mistakenly assigned by authors[25] as (4*R*)-**11a** (for details, see Suppl. data), was produced with 49% yield.

We used K10 montmorillonite clay as a catalyst. The reaction was carried out in the absence of solvent at room temperature for 1 h; i.e., under the conditions used previously when studying the interaction between alcohol **7** and hetaryl aldehydes.[18] As a result, the heterocyclic compounds (4*R*)- and (4*S*)-**11a** (Scheme 2) with the octahydro-2*H*-chromene framework (a mixture of two isomers with respect to the relative position of the methyl and hydroxyl groups at the C(4) position) were obtained with the total yield of 21% (the (4*R*)/(4*S*) ratio being equal to 9:1). In addition, other three compounds were formed during the reaction; according to the GC-MS data, they are the products of dehydration of chromenes **11a** (*m*/*z* = 194) and apparently contain a double bond (**12**–**14**) similar to what was observed in the reactions between (−)-isopulegol **7** and hetaryl aldehydes.[18] The total yield of the dehydration products was 23%.

We managed to isolate individual compounds (4*R*)-**11a** and (4*S*)-**11a**, while the isomeric compounds **12**–**14** could not be separated by column chromatography with SiO_2 adsorbent used for product separation. Hence, both diastereomers were produced using K10 clay to catalyze the reaction between isopulegol **7** and acetone for further research on their biological activity.

We have attempted to select reaction conditions that would reduce the contents of **12**–**14** and increase the yield of **11a**. Earlier,[19] H^+-K10 montmorillonite clay produced by treating K10 clay with 1 M HCl was successfully applied for Prins cyclization reactions of isopulegol with aldehydes. We found that when using H^+-K10 montmorillonite clay to catalyze the reaction between (−)-isopulegol **7** and acetone **10a** and conducting the reaction at room temperature for 2.5 h, the total yield of **11a** increased from 21% to 57% (the (4*R*)/(4*S*) ratio being equal to 3:1), while the total yield of **12**–**14** was 24%.

Based on these results, all the subsequent reactions between (−)-isopulegol **7** and ketones were carried out using H^+-K10 clay at room temperature for 2 h, with the catalyst quantity varied in



Scheme 1. Synthesis of chiral compounds with octahydro-2*H*-chromene framework.