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Abstract

F- and OH-Containing Isopulegol-Derived Octahydro-2*H*-Chromenes as Agents against Influenza A Virus †

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Abstract: Monoterpenes, which have a unique diverse structure and are inexpensive, available and often enantiomerically pure, are an attractive renewable raw material for the development of physiologically active agents. One of the most important methods for the utilization of monoterpenes is their interaction with carbonyl compounds, which produces heterocyclic compounds. Often these products exhibit analgesic, antiviral or neuroprotective properties. Earlier, we discovered the anti-influenza A (H1N1) virus activity of several compounds with a hydro-2*H*-chromene scaffold, which were synthesized by the Prins reaction using *p*-menthane alcohols and carbonyl compounds; montmorillonite K10 or nanosized halloysite catalyst were used as the reaction catalysts [1]. Chromenols produced from an (–)-isopulegol and aliphatic ketones (acetone and cyclopentanone) demonstrated a high activity combined with a low toxicity against the influenza virus [1]. The introduction of the fluorine atom into the molecule is an important strategy in the development of new biologically active compounds, enabling lipophilicity and electrostatic interactions to change and increasing the metabolic stability of compounds, which affects their physiological activity. Here, we synthesized fluoro- and hydroxy-containing octahydro-2*H*-chromenes by the Prins reaction starting from an (–)-isopulegol and a wide range of aromatic aldehydes in the presence of the $BF_3 \cdot Et_2O/H_2O$ system, acting as both an acid catalyst and a fluorine source. The activity of the synthesized compounds against the influenza A/Puerto Rico/8/34 (H1N1) virus was studied. The highest activity was demonstrated by fluoro- and hydroxy-containing 2,4,6-trimethoxybenzaldehyde derivatives. These compounds were supposed to be capable of binding to viral hemagglutinin, which is an agreement with data on the effect of compounds on viral fusogenic activity, as well as with molecular docking studies.

Keywords: influenza; antiviral; fluorine; monoterpene; chromene

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Reference

1. Salakhutdinov, N.; Volcho, K.; Yarovaya, O. Monoterpenes as a renewable source of biologically active compounds. *Pure Appl. Chem.* **2017**, *89*, 1105–1117. [CrossRef]