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Abstract

Synthesis of 4-acetamido-octahydrochromene Derivatives Based on (–)-Isopulegol—Promising Analgesic Agents †

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Abstract: Selective modification of natural compounds is one of the most important ways to develop and search for new biologically active substances of various structural types. It was found earlier that some compounds with octahydro-2*H*-chromene scaffolds synthesized from monoterpenoid (–)-isopulegol demonstrated promising biological activity, e.g., analgesic, and antiviral activities, inhibitory activity against DNA repair enzyme Tdp1. The flexible method for the synthesis of octahydro-2*H*-chromenes derivatives is the Prins cyclization. This reaction could serve also as an initiator of a three-component tandem reaction. For example, the sequence of the Prins and Ritter reactions is one of the best synthetic methods to efficiently build six-membered fragment of 4-amidotetrahydropyran in a one-pot single step reaction. In this work we have developed a method for synthesis of chiral 4-acetamido-octahydro-2*H*-chromenes. We used tandem Prins-Ritter reaction between (–)-isopulegol and a set of ketones in acetonitrile. Desired products were formed as a mixture of 4*R*/4*S* diastereomers, where 4*S* one is a major isomer. Development of new analgesic agents with high activity and low toxicity is important task. It is known that the heterocyclic compounds synthesized from (–)-isopulegol exhibit analgesic activity. In the study of the analgesic activity of the synthesized compounds in vivo, we found that a number of derivatives showed high analgesic activity reliably and not inferior in efficiency to the reference drug sodium diclofenac administered at a similar dose.

Keywords: (–)-isopulegol; cascade reaction; octahydrochromene; analgesia

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