Synthesis of 4-acetamido-octahydrochromene derivatives based on (-)-isopulegol - promising analgesic agents

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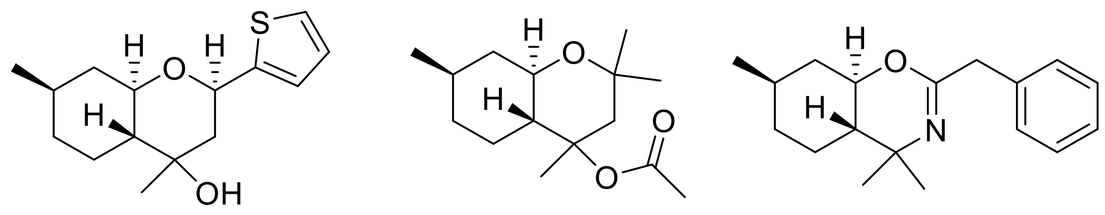
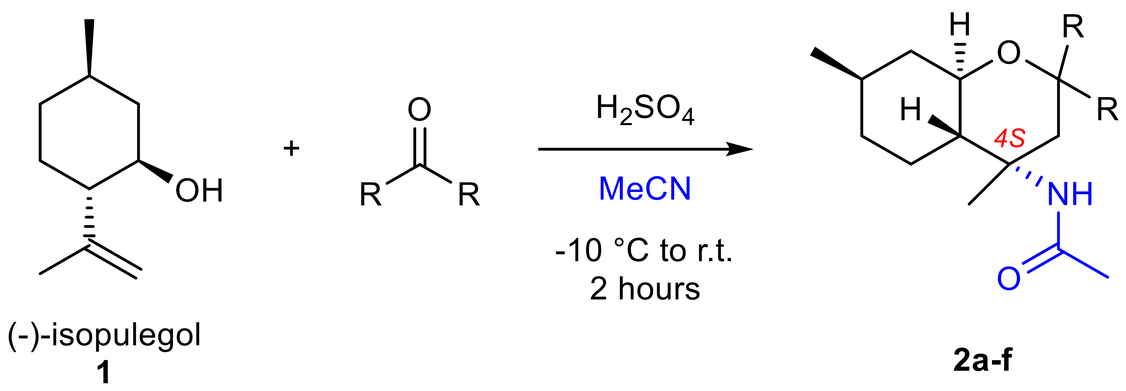
Selective modification of natural compounds is one of the most important ways to develop and search for new biologically active substances of various structural types. It was found earlier that some compounds with octahydro-2*H*-chromene scaffolds synthesized from monoterpenoid (-)-isopulegol demonstrated promising biological activity, e.g., analgesic and antiviral activities, inhibitory activity against DNA repair enzyme Tdp1 [1-3].



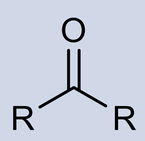
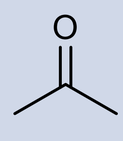
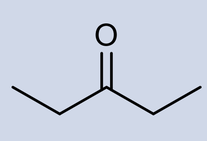
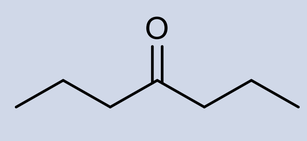
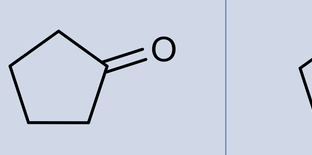
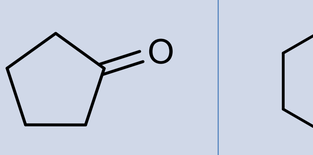
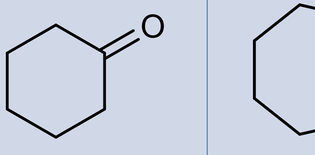
(-)-Isopulegol based compounds with analgesic activity

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 tandem three-component reaction. For example, the sequence of the Prins and Ritter reactions is one of the best synthetic method to build efficiently in a one-pot single step reaction six-membered fragment of 4-amidotetrahydropyran.



(-)-isopulegol **1** **2a-f**

In this work we have developed a method for synthesize of 4-acetamide derivatives of chiral octahydro-2*H*-chromenes. We used one-pot tandem Prins-Ritter reaction between monoterpenoid (-)-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.

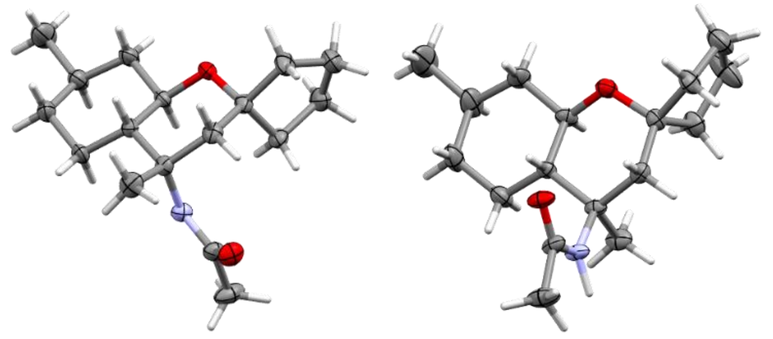
Compound	**2a**	**2b**	**2c**	**(*4S*)-2d**	**(*4R*)-2d**	**2e**	**2f**
							
Yield, %	40	35	25	40	20	30	25

Compound	Acetic acid-induced writhing test, number		Pain inhibition, %
	control	Mean ± SD	
2a	8.5±0.6	3.4±0.7*	60
2b	10.0±0.8	4.4±0.9*	56
2c	10.0±0.8	4.1±0.9*	59
(4S)-2d	8.5±0.6	1.5±0.7*	82
(4R)-2d	9.6±0.8	6.7±0.9*	30
2e	8.2±1.3	5.6±1.0	
2f	10.0±0.8	4.7±0.9*	53
Diclofenac sodium	10.1±1.8	5.0±1.1*	50

*p < 0.05

% of pain inhibition = $(n_{control} - n_{exp})/n_{control} \times 100\%$

Development of new analgesic agents with high activity and low toxicity is very important task. When studying the analgesic activity of the synthesized compounds *in vivo*, it was found that a number of derivatives exhibited high analgesic activity reliably and not inferior in efficiency to the reference drug sodium diclofenac administered at a similar dose. The best pain inhibition (82%) was shown for compound with cyclopentane ring **(*4S*)-2d**. Also, we managed to isolate **(*4R*)-2d** diastereomer from reaction mixture, but it shows less pain inhibition (30%) than 4*S* one.



Molecular structure of **(*4S*)-2d** and **(*4R*)-2d** by X-ray analysis.

1. Nazimova, E.; Pavlova, A.; Mikhalchenko, O.; Il'ina, I.; Korchagina, D.; Tolstikova, T.; Volcho, K.; Salakhutdinov, N.// *Med. Chem. Res*. **2016**, *25*, 1369.
2. I. V. Il'ina, D. V. Korchagina, E. A. Morozova, T. G. Tolstikova, K. P. Volcho, N. F. Salakhutdinov// *Russian Chemical Bulletin*, **2019**, 68(5), 1061-1066
3. N.S. Li-Zhulanov, A.V. Pavlova, D.V. Korchagina, Yu.V. Gatilov, K.P. Volcho, T.G. Tolstikova, N.F. Salakhutdinov // *Chemistry of Heterocyclic Compounds*, **2020**, 56(7), 936-941