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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Discovery of highly potent analgesic activity of isopulegol-derived (2*R*,4a*R*,7*R*,8a*R*)-4,7-dimethyl-2-(thiophen-2-yl)octahydro-2*H*-chromen-4-ol

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Abstract A large set of chiral heterocyclic compounds with the octahydro-2*H*-chromene scaffold was first obtained by a reaction of (−)-isopulegol and (+)-neoisopulegol with furan-2-carbaldehyde, thiophene-2-carbaldehyde and their derivatives and isomers in the presence of montmorillonite K10 clay. Most of the (−)-isopulegol-derived compounds exhibited a significant analgesic activity in the acetic acid-induced writhing test. Compound **3b** obtained by a reaction of (−)-isopulegol with thiophene-2-carbaldehyde demonstrated a significant analgesic effect in this test within 15 min after oral administration at the dose of 1 mg/kg and retains the effect for at least 24 h. Compound **3b** exhibited analgesic activity in the hot plate test also. A change in the sulfur atom position in the aromatic ring was found to lead to the effect reversal in the hot plate test.

Keywords Terpene · Chromene · Isopulegol · Analgesic activity · Acetic acid-induced writhing test · Hot plate test

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Introduction

Although pain is the most common symptom for which patients seek medical attention (Wolff *et al.*, 2011), the treatment of pain is still inadequate and continues to be a substantial worldwide public health concern, especially in the case of cancer-related pain (Juniper *et al.*, 2009) and chronic non-cancer pain (Reinecke *et al.*, 2015). Therefore, the development of effective analgesic compounds of novel structural types for pain relief is required.

Recently, we have found that several heterocyclic compounds **1** (Scheme 1) with the hexahydro-2*H*-chromene scaffold that were synthesized by reactions of monoterpenoid **2** with aromatic aldehydes in the presence of montmorillonite K10 clay exhibit a pronounced analgesic activity in in vivo tests (Mikhalchenko *et al.*, 2013a, b; Il'ina *et al.*, 2014; Pavlova *et al.*, 2015). Compound **2** can be obtained from a monoterpenoid (−)-verbenone in three stages, which is not a trivial task due to the formation of a complex reaction mixture at the last stage (Ardashov *et al.*, 2007; Stekrova *et al.*, 2013).

It is known that compounds with the octahydro-2*H*-chromene scaffold **3** which are similar to **1** can be synthesized in one stage via a reaction of commercially available (−)-isopulegol **4** with aldehydes using various catalytic systems, including *para*-toluenesulfonic acid placed onto silica gel (Macedo *et al.*, 2010), I_2 (Silva and Quintiliano, 2009) and montmorillonite clays (Baishya *et al.*, 2013; Anikeev *et al.*, 2013; Timofeeva *et al.*, 2015).

The aim of the present study was to synthesize compound **3** containing heteroaromatic furan and thiophene substituents and investigate their analgesic activity. The choice of this type of substituents was based on the presence of furan and thiophene moieties in a number of compounds with a significant analgesic activity (Nelson

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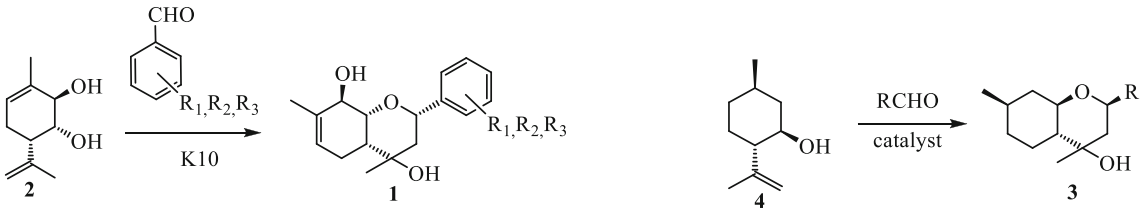


Scheme 1 Synthesis of compounds **1** and **3**

et al., 2012; Thur *et al.*, 2012; Guerrero *et al.*, 2009; Joshi *et al.*, 2009; Sarigol *et al.*, 2015). Moreover, the products with these substituents can be considered as the analogs of earlier synthesized compounds with pronounced analgesic activity which contain hydroxy or methoxy groups in the aromatic ring (Il'ina *et al.*, 2014; Pavlova *et al.*, 2015).

Chemistry

Previously, the synthesis of compounds **3a** and **3b** containing non-substituted furan and thiophene rings (Scheme 2) was performed in a study (Baishya *et al.*, 2013) through a reaction of (−)-isopulegol **4** with aldehydes **5a** and **5b** using montmorillonite K10 clay as a catalyst under microwave irradiation with the yield of 56 and 50 %, respectively. Compounds **3a** and **3b** were formed as mixtures of two diastereomers differing in the fourth position (Scheme 2), with the predominance of the (*R*)-isomer.

We found that conducting these reactions in the presence of K10 clay at room temperature without microwave irradiation requires slightly more time but significantly increases the yield of products **3a** and **3b**, which amounted to 86 and 78 %, respectively. The reactions were carried out without solvent; complete conversion of isopulegol was achieved within 1 h (Table 1); the products were isolated by column chromatography on silica gel.

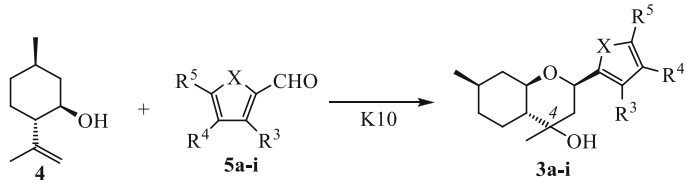
Introduction of a methyl group (**3c**, **3e**, **3f**) or bromine (**3g**, **3h**) into the aldehyde aromatic ring led to an increase in the reaction time to 1.5–2 h. When nitro-substituted aldehydes **3d** and **3i** were used as reactants, the reaction rate was equal to that observed for unsubstituted aldehydes **3a** and **3c**.

Usually, the (4*R*)-diastereomer predominated in the reaction mixtures, except a reaction with 5-nitrofuran-2-carbaldehyde **3d** where the (4*S*)-isomer was the major product (Table 1). Given the lack of an explicit dependence of the stereoisomer ratio on the donor–acceptor properties of substituents, it may be supposed that the isomer ratio is mainly affected by steric factors.

In some cases, we were able to isolate individual (4*R*)- and/or (4*S*)-diastereomers. In particular, we obtained the (4*R*)- and (4*S*)-isomers **3d** and **3g** as well as the (4*R*)-isomer **3b**.

According to GC–MS analysis of reaction mixtures, in almost all cases, the formation of several minor products with molecular weights corresponding to those of compound **3**, but with the loss of a water molecule, was detected. We could not separate these compounds with a purity required to determine their structure. To confirm the structure of these compounds, we searched for a catalyst system that would lead to their preferable formation. These compounds appeared to form with a high yield during the reaction in the presence of TsOH and 4Å molecular sieves in refluxing toluene. After production and subsequent isolation by column chromatography, we obtained a mixture of double-bond position isomers **6** and **7** (Scheme 3) at the 9:1 ratio that were minor products of the reaction conducted in the presence of K10 clay.

A possible mechanism for the formation of compounds **3**, **6** and **7** is depicted in Scheme 4 and includes the attack of a protonated aldehyde group on the alcohol group of (−)-isopulegol **4**, followed by carbocyclization with involvement of an isopropylene double bond. The resulting intermediate can further either interact with a water



3a, 5a	X=O; R^3=R^4=R^5=H
3b, 5b	X=S; R^3=R^4=R^5=H
3c, 5c	X=O; R^3=R^4=H; R^5=Me
3d, 5d	X=O; R^3=R^4=H; R^5=NO_2
3e, 5e	X=S; R^3=R^4=H; R^5=Me
3f, 5f	X=S; R^3=Me; R^4=R^5=H
3g, 5g	X=S; R^3=R^4=H; R^5=Br
3h, 5h	X=S; R^3=R^5=H; R^4=Br
3i, 5i	X=S; R^3=R^4=H; R^5=NO_2

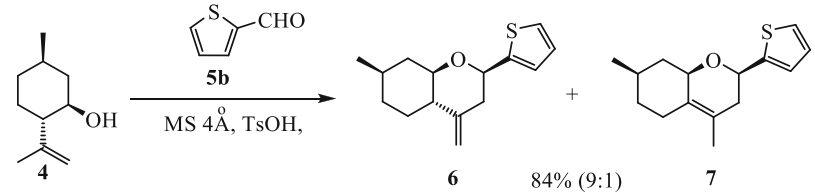
Scheme 2 Synthesis of compounds **3a–i**

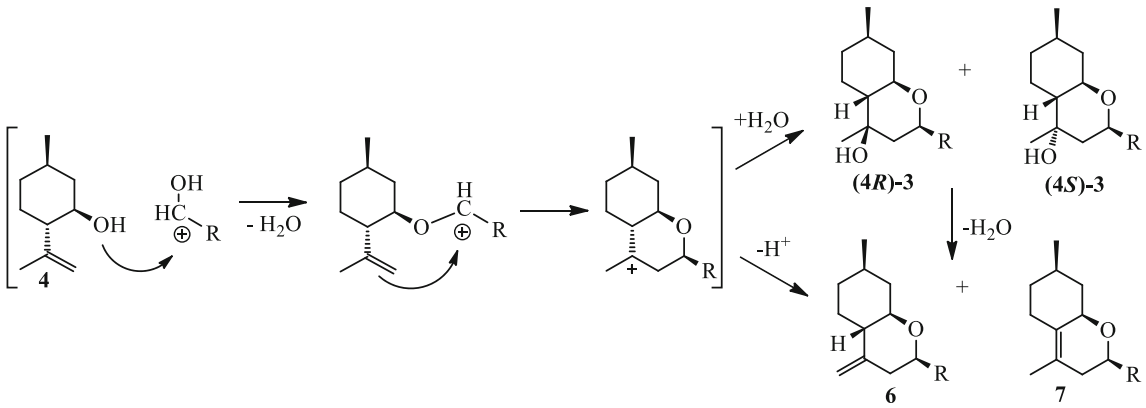
Table 1 Synthesis of compounds **3a–i** via interaction of (−)-isopulegol **4** with different aldehydes

Entry	Aldehyde	Reaction time (min)	Product (yield, %)	Ratio of 4*R*/4*S*[a]
1	**5a**; X = O; $R^3 = R^4 = R^5 = H$	60	**3a** (86)	3:1
2	**5b**; X = S; $R^3 = R^4 = R^5 = H$	60	**3b** (78)	5:1
3	**5c**; X = O; $R^3 = R^4 = H$; $R^5 = Me$	90	**3c** (65)	3.5:1
4	**5d**; X = O; $R^3 = R^4 = H$; $R^5 = NO_2$	60	**3d** (54)	1:1.5
5	**5e**; X = S; $R^3 = R^4 = H$; $R^5 = Me$	120	**3e** (80)	4.5:1
6	**5f**; X = S; $R^3 = Me$; $R^4 = R^5 = H$	120	**3f** (69)	10:1
7	**5g**; X = S; $R^3 = R^4 = H$; $R^5 = Br$	120	**3g** (76)	6.5:1
8	**5h**; X = S; $R^3 = R^5 = H$; $R^4 = Br$	120	**3h** (74)	3:1
9	**5i**; X = S; $R^3 = R^4 = H$; $R^5 = NO_2$	60	**3i** (50)	1:1

[a] The ratio of diastereomers (*S*)/(*R*) for products of type **3** was determined from the ^{1}H NMR spectrum of corresponding reaction mixture

Scheme 3 Synthesis of compounds **6** and **7**

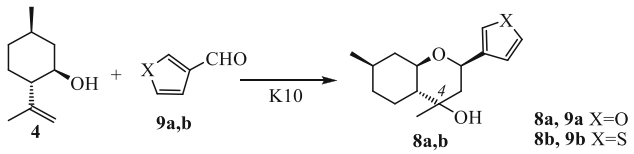




Scheme 4 Possible mechanism of formation of compounds **3**, **6** and **7**

molecule to form diastereomers (4*R*(*S*))-**3** or undergo deprotonation to form compounds **6** and **7**.

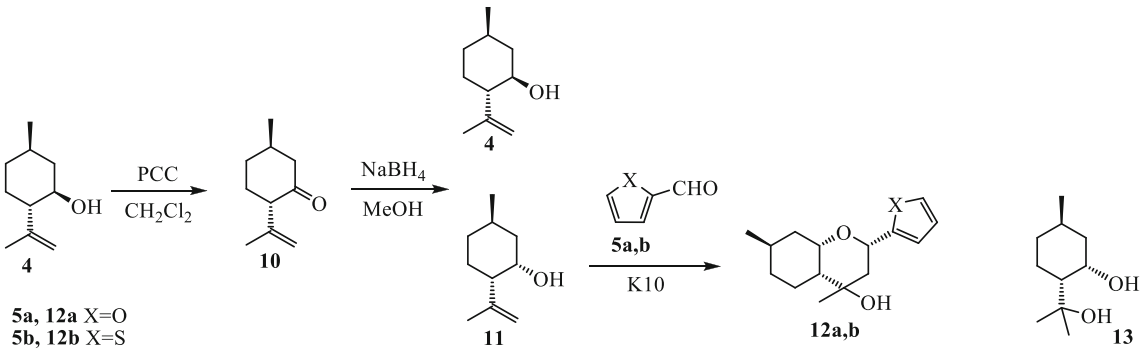
Compounds **8a** and **8b**, which are isomers of compounds **3a** and **3b** differing in the heteroatom position in an aromatic substituent, were synthesized by reacting (−)-isopulegol **4** with aldehydes **9a** and **9b** (Scheme 5). The



Scheme 5 Synthesis of compounds **8a,b**

reaction time was 60 min, and the yields were 61 and 63 %, respectively. It should be noted that the yields in both cases were slightly lower than those upon the use of isomeric aldehydes **3a** and **3b**.

The relative and absolute configurations of monoterpenoids and their derivatives are well known to be capable of exerting a decisive influence on their biological activity (Pavlova *et al.*, 2013; Ardashov *et al.*, 2011). To obtain other diastereomers of compounds **3a** and **3b**, we synthesized a mixture of (+)-neoisopulegol **11** and (−)-isopulegol **4** by oxidation of (−)-isopulegol **4** to isopulegone **10** followed by reduction (Scheme 6). Compound **11** was isolated from the epimer mixture by column chromatography. A reaction of (+)-neoisopulegol **11** with furan-2-



Scheme 6 Synthesis of (+)-neoisopulegol **11** and its interaction with aldehydes **5a,b**

carbaldehyde **5a** in the presence of K10 clay resulted in the formation of compound with the octahydrochromene scaffold **12a** (41 %, 4*R*:4*S* = 1:1.5) and monoterpenoid diol **13** (19 %) obviously formed by the reaction of **11** with water. Analogous interaction with thiophene-2-carboxaldehyde **5b** led to formation of **12b** in 75 % yield (4*R*:4*S* = 1:1). Complete conversion of monoterpenoid **11** in both cases was achieved in 60 min.

Thus, we first synthesized a large set of chiral heterocyclic compounds with the octahydro-2*H*-chromene scaffold, containing heteroaromatic substituents.

Biology

The analgesic activity of the compounds in a dose of 10.0 mg/kg (oral administration) was studied in the standard experimental pain models, namely in the acetic acid-induced writhing (0.75 % acetic acid, 0.1 ml for one animal, intraperitoneally) and hot plate (thermal stimulation, $T = 54 \pm 0.5$ °C) tests (Koster *et al.*, 1959; Eddy and Leimbach, 1953). Agents were administered 1 h before testing. Diclofenac sodium in the dose of 10.0 mg/kg was used as a reference drug. The mixtures of diastereomers at the carbon atom bonded with the methyl and hydroxyl groups were used without separation. We also tested the individual stereoisomers in cases we obtained them. Table 2 presents the analgesic activity data.

Compound **3a** obtained by interaction of isopulegol **4** with furfural **5a** exhibited no analgesic activity. Compound **3c** with a methyl substituent at the fifth position also had no activity. At the same time, the replacement of a methyl group by a nitro group in the case of compound **3d** led to a significant analgesic effect in the acetic acid-induced writhing test, with both diastereomers being effective.

Unlike compound **3a**, its sulfur-containing analog **3b** had a statistically significant analgesic effect in both used models. Interestingly, the individual (4*R*)-**3b** stereoisomer was somewhat less effective than the 5:1 original mixture of (4*R*)- and (4*S*)-isomers in acid-induced writhing test, and the effect observed in the hot plate test for (4*R*)-**3b** was not statistically significant.

Compounds **3e** and **3f** containing a methyl group at the fifth and the third positions of the thiophene ring, respectively, exhibited the analgesic activity in the acetic acid-induced writhing test only. Analgesic activity in this test was also found in the (4*R*)-diastereomer of 5-bromo-substituted compound **3g**. In the case of the (4*S*)-diastereomer, the observed effect appeared not to be statistically significant. Compound **3h** with a bromine atom at the fourth position of the aromatic ring was significantly more effective in acid-induced writhing test, but it did not have a statistically significant analgesic effect in the hot plate test. Nitro-containing compound **3i** exhibited analgesic effect in acid-induced writhing test.

Therefore, most of the compounds prepared by interaction of (−)-isopulegol **4** with furan-2-carbaldehyde, thiophene-2-carbaldehyde and their derivatives exhibited a potent analgesic activity in the acetic acid-induced writhing test. In all cases when the activity of individual diastereomers was tested, their analgesic effect was comparable. Only compound **3b** exhibited analgesic activity in both used animal models: in acid-induced writhing and in the hot plate test.

Compound **8a**, like its isomer differing in the heteroatom position in the aromatic ring **3a**, had no analgesic activity (Table 2). The result of testing compound **8b**, an isomer of the most active compound **3b**, was unexpected. Instead of the analgesic effect previously observed for compound **3b** in the hot plate test, the use of compound **8b** led to statistically significant manifestation of hyperalgesia in this test. Thus, a change in the sulfur atom position in the aromatic ring appeared to lead to the effect reversal in the hot plate test. Compound **8b** did not influence on the numbers of writhing induced by acetic acid administration.

Compounds **12a** and **12b** derived from (+)-neoisopulegol **11** exhibited no analgesic activity in both tests

Table 2 Analgesic activity of compounds **3a–i**, **8a,b**, **12a,b** and sodium diclofenac (10 mg/kg dose)

Compound	Acetic acid-induced writhing test		Hot plate test	
	Control	Mean ± SD (pain inhibition, %)[a]	Control	Mean ± SD (protection, %)[b]
3a	11.1 ± 0.6	9.8 ± 1.3	14.4 ± 1.7	19.9 ± 2.5
3b	9.6 ± 0.9	4.3 ± 1.1 (55)[#]	9.8 ± 0.8	13.1 ± 1.2 (34)*
(4*R*)-**3b**	8.9 ± 0.7	5.6 ± 0.8 (37)*	11.5 ± 1.1	15.1 ± 2.0
3c	9.8 ± 0.5	8.1 ± 1.2	13.3 ± 1.4	16.0 ± 2.2
(4*S*)-**3d**	11.1 ± 0.7	4.8 ± 1.2 (57)[§]	12.1 ± 1.3	15.1 ± 1.2
(4*R*)-**3d**	11.1 ± 0.7	6.4 ± 1.5 (42)*	12.1 ± 1.3	17.9 ± 2.3
3e	10.9 ± 0.5	6.6 ± 0.5 (39)[§]	18.4 ± 2.1	17.4 ± 2.4
3f	10.9 ± 0.5	7.0 ± 0.6 (36)[§]	18.4 ± 2.1	12.8 ± 1.7
(4*R*)-**3g**	10.0 ± 0.7	7.4 ± 0.6 (26)*	13.4 ± 1.8	20.3 ± 3.8
(4*S*)-**3g**	10.0 ± 0.7	6.6 ± 1.4	13.4 ± 1.8	14.5 ± 2.3
3h	9.6 ± 0.9	3.6 ± 1.5 (63)[#]	9.8 ± 0.8	13.6 ± 1.7
3i	11.1 ± 0.7	7.5 ± 1.2 (32)*	12.1 ± 1.3	14.5 ± 1.6
8a	7.9 ± 1.1	7.3 ± 0.9	19.4 ± 2.7	13.9 ± 1.0
8b	7.9 ± 1.1	8.9 ± 0.9	19.4 ± 2.7	10.5 ± 1.0 (−46)[#]
12a	8.4 ± 1.5	5.3 ± 1.7	14.0 ± 1.2	17.5 ± 2.1
12b	8.1 ± 0.5	7.6 ± 1.1	13.4 ± 1.6	11.5 ± 0.9
Diclofenac sodium	10.1 ± 1.9	5.0 ± 1.1 (50)[§]	9.6 ± 1.6	15.6 ± 2.4 (62)[#]

* $p < 0.05$; [#] $p < 0.01$; [§] $p < 0.001$ in comparison with control

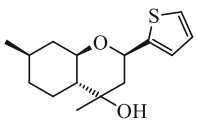
[a] % of pain inhibition = $(t_{control} - t_{exp})/t_{control} \times 100$ %

[b] % of protection = $(t_{exp} - t_{control})/t_{control} \times 100$ %

(Table 2), indicating importance of the *trans*-junction of rings for the analgesic effect in compound **3b**.

Compound **3b** (Fig. 1) that demonstrated the analgesic activity in both tests was studied for the effect–dose dependence (Table 3). As seen from the presented data, compound **3b** at doses of 1, 5 and 10 mg/kg has a comparable analgesic effect in both tests. Further lowering the dose to 0.5 mg/kg results in the disappearance of the analgesic effect. Based on these data, we may conclude that the optimal dose for **3b** is 1 mg/kg.

Fig. 1 Structure of the most promising compound **3b**



3b

Acute toxicity of compound **3b** was investigated at single intragastric administration in mice at a doses of 500, 1000, 2500 and 4500 mg/kg. Doses of 500, 1000 and 2500 mg/kg did not influence behavior and physiological state of animals. Administration of 4500 mg/kg of the studied compound caused the labored breathing and movement in animals in the first day. Two animals were died on the second and third day (33 % of total number of animals). Therefore, the LD_{50} for compound **3b** was found

Table 3 Analgesic activity of compound **3b** in various doses

Dose (mg/kg)	Acetic acid-induced writhing test		Hot plate test	
	Control	Mean ± SD (pain inhibition, %)[a]	Control	Mean ± SD (protection, %)[b]
0.5	10.1 ± 0.7	7.4 ± 1.3	15.8 ± 1.6	20.3 ± 2.2
1	8.4 ± 0.6	2.4 ± 0.8 (71)[§]	10.4 ± 1.2	16.5 ± 1.9 (59)*
5	8.4 ± 0.6	4.9 ± 1.0 (42)[#]	10.4 ± 1.2	16.3 ± 1.6 (57)*
10	9.6 ± 0.9	4.3 ± 1.1 (55)[#]	9.8 ± 0.8	13.1 ± 1.2 (34)*

* $p < 0.05$; [#] $p < 0.01$; [§] $p < 0.001$ in comparison with control

[a] % of pain inhibition = $(t_{control} - t_{exp})/t_{control} \times 100$ %

[b] % of protection = $(t_{exp} - t_{control})/t_{control} \times 100$ %

Table 4 Time-dependent analgesic effect of compound **3b** in 1 mg/kg dose in acetic acid-induced writhing test

Time	Control	Mean ± SD (pain inhibition, %)[a]
15 min	10.0 ± 0.3	4.1 ± 1.4 (59)[§]
30 min	10.0 ± 0.3	7.3 ± 0.7 (27)[#]
60 min	10.0 ± 0.3	5.3 ± 1.3 (47)[#]
2 h	10.0 ± 0.3	5.6 ± 0.8 (44)[§]
3 h	10.1 ± 0.7	7.3 ± 0.5 (28)[#]
4 h	10.1 ± 0.7	5.0 ± 1.4 (50)[#]
5 h	10.1 ± 0.7	4.0 ± 0.9 (60)[§]
24 h	10.1 ± 0.7	5.6 ± 1.0 (45)[#]

* $p < 0.05$; [#] $p < 0.01$; [§] $p < 0.001$ in comparison with control

[a] % of pain inhibition = $(t_{control} - t_{exp})/t_{control} \times 100$ %

[b] % of protection = $(t_{exp} - t_{control})/t_{control} \times 100$ %

to exceed 4500 mg/kg, indicating a low acute toxicity of the compound. For comparison, the LD_{50} of diclofenac sodium is 370 mg/kg (Syubaev *et al.*, 1986).

The next step of the research was to study the time-dependent analgesic effect of compound **3b** at the dose of 1 mg/kg. A significant analgesic effect was observed as soon as 15 min after oral administration of the agent and was retained for at least 24 h (Table 4). Importantly, compound **3b**, in contrast to opioid analgesics (Bihel *et al.*, 2015), has no signs of hyperalgesia throughout the experiment.

Conclusion

In summary, a large set of chiral heterocyclic compounds with the octahydro-2*H*-chromene scaffold, containing heteroaromatic substituents, was first synthesized by interaction of (−)-isopulegol **4** with furan-2-carbaldehyde **5a**, thiophene-2-carbaldehyde **5b** and their derivatives and isomers in the presence of montmorillonite K10 clay. Two more products with the octahydro-2*H*-chromene scaffold but with another ring junction were obtained by reactions of (+)-neoisopulegol **11** with aldehydes **5a** and **5b.**

Most of the (−)-isopulegol **4** derived compounds exhibited a potent analgesic activity in the acetic acid-induced writhing test, but only compound **3b** that was obtained by the reaction with thiophene-2-carbaldehyde **5b** exhibited a potent analgesic activity in hot plate test too. A change in the sulfur atom position in the aromatic ring upon transition from **3b** to **8b** leads to the effect reversal in the hot plate test. Compounds **12a** and **12b** synthesized from (+)-neoisopulegol **11** had no analgesic activity in both tests.

The minimum dose at which compound **3b** retained a high efficacy in both tests was found to be 1 mg/kg. Given a low acute toxicity ($LD_{50} > 4500$ mg/kg), compound **3b** exhibits a wide therapeutic index, which is unique for analgesic medications. Compound **3b** exhibits the analgesic activity in the acetic acid-induced writhing test within 15 min after oral administration at the dose of 1 mg/kg, with the effect being retained for at least 24 h.

Experimental

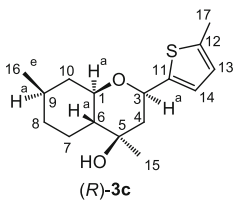
Chemistry

All the chemicals and reagents were of commercial grade. As the catalyst, we used K10 clay (*Aldrich*). The clay was calcined at 105 °C for 3 h immediately before use. CH_2Cl_2 was passed through calcined Al_2O_3. (−)-Isopulegol ($[\alpha]_D^{31}$ − 49.1 (c = 2.6, $CHCl_3$)) was purchased from Aldrich.

All product yields are given for isolated compounds. Column chromatography (CC): silica gel (SiO_2; 60–200 μ; *Macherey–Nagel*); hexane/EtOAc 100:0 → 0:100; *Agilent 7890A* gas chromatograph equipped with a quadrupole mass spectrometer *Agilent 5975C* as a detector; quartz column HP-5MS (copolymer 5 % diphenyl–95 % dimethylsiloxane) of length 30 m, internal diameter 0.25 mm and stationary phase film thickness 0.25 μm was used for the analysis; optical rotation: *polAAr 3005* spectrometer, $CHCl_3$ soln; HR-MS: *DFS-Thermo-Scientific* spectrometer in a full scan mode (15–500 *m/z*, 70 eV electron-impact ionization, direct sample introduction); ^1H and ^{13}C NMR: *Bruker DRX-500* apparatus at 500.13 MHz (^1H) and 125.76 MHz (^{13}C), *J* in Hz; and structure determinations by analyzing the ^1H NMR spectra, including ^1H–^1H double resonance spectra and ^1H–^1H 2D homonuclear correlation, *J*-modulated ^{13}C NMR spectra (JMOD) and ^{13}C–^1H 2D heteronuclear correlation with one-bond and long-range spin–spin coupling constants (C–H COSY, $^1J(C,H) = 160$ Hz, COLOC, $^{2,3}J(C,H) = 10$ Hz).

Numeration for carbon atoms used for assignment in NMR spectra is presented in Fig. 2 with compound (*R*)-**3c** as an example.

Fig. 2 Numeration for NMR spectra



(*R*)-**3c**

Reaction of isopulegol 4 with aldehydes on clay K10: general procedure

An appropriate aldehyde was added to a suspension of clay K10 in CH_2Cl_2 (10 ml), and then, a solution of isopulegol **4** in CH_2Cl_2 (10 ml) was added. The solvent was distilled off. The mixture was stored at r.t. for the required period of time. Then ethyl acetate (15 ml) was added. The catalyst was filtered off, the solvent was distilled off, and the residue was separated on a SiO_2 column.

Reactions of isopulegol 4 with aldehydes 5a–i and 9a,b on clay K10

*(2R,4R(S),4aR,7R,8aR)-2-(Furan-2-yl)-4,7-dimethyloctahydro-2H-chromen-4-ol (**3a**)* The reaction of isopulegol **4** (0.400 g) and furan-2-carbaldehyde **5a** (0.250 g) in the presence of clay K10 (1.3 g) for 60 min led to compound **3a** ((*R*):(*S*) = 3:1) (0.558 g, 86 %).

(*R*)-**3a**. ^{1}H NMR ($CDCl_3$): 0.85–0.94 (m, 1H, H_a-8); 0.90 (d, *J*(16,9) = 6.6 Hz, 3H, H-16); 0.97–1.06 (m, 1H, H_a-7); 1.07 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 10.8 Hz, 1H, H_a-10); 1.23 (d, *J*(15,4a) = 0.6 Hz, 3H, H-15); 1.28 (ddd, *J*(6a,7a) = 12.2 Hz, *J*(6a,1a) = 10.2 Hz, *J*(6a,7e) = 3.2 Hz, 1H, H_a-6); 1.38–1.48 (m, 1H, H_a-9); 1.70 (dm, *J*(8e,8a) = 13.0 Hz, 1H, H_e-8); 1.92 (dd, *J*(4e,4a) = 12.8 Hz, *J*(4e,3a) = 2.4 Hz, 1H, H_e-4); 1.92 (dm, *J*(7e,7a) = 13.0 Hz, 1H, H_e-7); 1.95–2.02 (m, 2H, H_a-4, H_e-10); 3.24 (ddd, *J*(1a,10a) = 10.8 Hz, *J*(1a, 6a) = 10.2 Hz, *J*(1a, 10e) = 4.3 Hz, 1H, H_a-1); 4.49 (dd, *J*(3a,4a) = 11.8 Hz, *J*(3a,4e) = 2.4 Hz, 1H, H_a-3); 6.24 (dd, *J*(14,13) = 3.3 Hz, *J*(14,12) = 0.7 Hz, 1H, H-14); 6.28 (dd, *J*(13,14) = 3.3 Hz, *J*(13,12) = 1.8 Hz, 1H, H-13); 7.33 (dd, *J*(12,13) = 1.8 Hz, *J*(12,14) = 0.7 Hz, H-12). ^{13}C NMR ($CDCl_3$): 77.34 (d, C-1); 70.00 (d, C-3); 45.70 (t, C-4); 70.44 (s, C-5); 51.84 (d, C-6); 22.87 (t, C-7); 34.17 (t, C-8); 31.31 (d, C-9); 41.22 (t, C-10); 154.21 (s, C-11); 141.98 (d, C-12); 109.90 (d, C-13); 106.43 (d, C-14); 21.03 (q, C-15); 21.98 (q, C-16). HR-MS: 250.1559 (M^+, $C_{15}H_{22}O_3^+$; calc. 250.1563).

(*S*)-**3a**. ^{1}H NMR ($CDCl_3$): 0.84–0.94 (m, 1H, H_a-8); 0.89 (d, *J*(16,9) = 6.6 Hz, 3H, H-16); 1.04 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 11.2 Hz, 1H, H_a-10); 1.10–1.22 (m, 2H, H_a-6, H_a-7); 1.23 (s, 3H, H-15); 1.40–1.50 (m, 1H, H_a-9); 1.67–1.74 (m, 1H, H_e-8); 1.75–1.83 (m, 2H, H_e-4, H_e-7); 1.94–2.02 (m, 2H, H_a-4, H_e-10); 3.55 (ddd, *J*(1a,10a) = 11.2 Hz, *J*(1a,6a) = 9.7 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 4.83 (dd, *J*(3a,4a) = 12.0 Hz, *J*(3a,4e) = 2.2 Hz, 1H, H_a-3); 6.22 (dd, *J*(14,13) = 3.3 Hz, *J*(14,12) = 0.7 Hz, 1H, H-14); 6.27 (dd, *J*(13,14) = 3.3 Hz, *J*(13,12) = 1.8 Hz, 1H, H-13); 7.33 (dd, *J*(12,13) = 1.8 Hz, *J*(12,14) = 0.7 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 75.45 (d, C-1); 68.12 (d, C-3); 43.73 (t, C-4); 69.00 (s, C-5); 49.21 (d, C-6); 22.38 (t, C-7); 34.24 (t, C-8); 31.13 (d, C-9); 41.03 (t, C-10); 154.72 (s, C-11); 141.91 (d, C-12); 109.81 (d, C-13); 106.40 (d, C-14); 28.09 (q, C-15); 22.05 (q, C-16). HR-MS: 250.1559 (M^+, $C_{15}H_{22}O_3^+$; calc. 250.1563).

*(2R,4R(S),4aR,7R,8aR)-4,7-Dimethyl-2-(thiophen-2-yl)octahydro-2H-chromen-4-ol (**3b**)* The reaction of isopulegol **4** (0.400 g) and thiophene-2-carbaldehyde **5b** (0.290 g) in the presence of clay K10 (1.3 g) for 60 min led to compound **3b** ((*R*):(*S*) = 5:1) (0.543 g, 78 %).

(*R*)-**3b**. ^{1}H NMR ($CDCl_3$): 0.87–0.96 (m, 1H, H_a-8); 0.93 (d, *J*(16,9) = 6.7 Hz, 3H, H-16); 1.03 (dddd, *J*(7a,7e) = *J*(7a,8a) = 12.8 Hz, *J*(7a,6a) = 12.2 Hz, *J*(7a,8e) = 3.3 Hz, 1H, H_a-7); 1.11 (ddd, *J*(10a,10e) = 12.2 Hz, *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 10.8 Hz, 1H, H_a-10); 1.26 (d, *J*(15,4a) = 0.8 Hz, 3H, H-15); 1.30 (ddd, *J*(6a,7a) = 12.2 Hz, *J*(6a,1a) = 10.2 Hz, *J*(6a,7e) = 3.3 Hz, 1H, H_a-6); 1.40–1.52 (m, 1H, H_a-9); 1.72 (ddddd, *J*(8e,8a) = 12.8 Hz, *J*(8e,7a) = *J*(8e,9a) = *J*(8e,7e) = 3.3 Hz, *J*(8e,10e) = 2.0 Hz, 1H, H_e-8); 1.89 (ddq, *J*(4a,4e) = 12.7 Hz, *J*(4a,3a) = 11.8 Hz, *J*(4a,15) = 0.8 Hz, 1H, H_a-4); 1.93 (dm, *J*(7e,7a) = 12.8 Hz, 1H, H_e-7); 2.01 (ddm, *J*(10e,10a) = 12.2 Hz, *J*(10e,1a) = 4.3 Hz, 1H, H_e-10); 2.05 (dd, *J*(4e,4a) = 12.7 Hz, *J*(4e,3a) = 2.2 Hz, 1H, H_e-4); 3.27 (ddd, *J*(1a,10a) = 10.8 Hz, *J*(1a, 6a) = 10.2 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 4.69 (ddd, *J*(3a,4a) = 11.8 Hz, *J*(3a,4e) = 2.2 Hz, *J*(3a,14) = 0.7 Hz, 1H, H_a-3); 6.93 (dd, *J*(13,12) = 5.0 Hz, *J*(13,14) = 3.5 Hz, 1H, H-13); 6.95 (ddd, *J*(14,13) = 3.5 Hz, *J*(14,12) = 1.2 Hz, *J*(14, 3a) = 0.7 Hz, 1H, H-14); 7.21 (dd, *J*(12,13) = 5.0 Hz, *J*(12,14) = 1.2 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 77.51 (d, C-1); 72.39 (d, C-3); 49.76 (t, C-4); 70.61 (s, C-5); 51.83 (d, C-6); 22.89 (t, C-7); 34.21 (t, C-8); 31.34 (d, C-9); 41.27 (t, C-10); 145.37 (s, C-11); 124.47 (d, C-12); 126.24 (d, C-13); 123.45 (d, C-14); 21.13 (q, C-15); 22.02 (q, C-16). HR-MS: 266.1332 (M^+, $C_{15}H_{22}O_2S^+$; calc. 266.1335).

(*S*)-**3b**. ^{1}H NMR ($CDCl_3$): 0.92 (d, *J*(16,9a) = 6.7 Hz, 3H, H-16); 1.06–1.22 (m, 3H, H_a-6, H_a-7, H_a-10); 1.23 (s, 3H, H-15); 1.83 (dd, *J*(4a,4e) = 13.7 Hz, *J*(4a,3a) = 11.5 Hz, 1H, H_a-4); 1.77–1.85 (m, 1H, H_e-7); 3.59 (ddd, *J*(1a,10a) = 11.2 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 5.04 (ddd, *J*(3a,4a) = 11.5 Hz, *J*(3a,4e) = 2.4 Hz, *J*(3a,14) = 0.7 Hz, 1H, H_a-3); 7.19 (dd, *J*(12,13) = 5.0 Hz, *J*(12,14) = 1.2 Hz, 1H, H-12). Other signals in ^{1}H NMR spectrum of minor isomer (*S*)-**3b** were overlapped with the signals of (*R*)-**3b**. ^{13}C NMR ($CDCl_3$): 75.66 (d, C-1); 70.59 (d, C-3); 47.87 (t, C-4); 69.29 (s, C-5); 49.20 (d, C-6); 22.39 (t, C-7); 34.28 (t, C-8); 31.16 (d, C-9); 41.09 (t, C-10); 146.06 (s, C-11); 124.17 (d, C-12); 126.22 (d, C-13); 123.31 (d, C-14); 28.08 (q, C-15); 22.08 (q, C-16). HR-MS: 266.1332 (M^+, $C_{15}H_{22}O_2S^+$; calc. 266.1335).

*(2R,4R(S),4aR,7R,8aR)-4,7-Dimethyl-2-(5-methylfuran-2-yl)octahydro-2H-chromen-4-ol (**3c**)* The reaction of isopulegol **4** (0.300 g) and 5-methylfuran-2-carbaldehyde **5c** (0.210 g) in the presence of clay K10 (1.0 g) for 90 min gave rise starting isopulegol **4** (0.020 g) and compound **3c** ((*R*):(*S*) = 3.5:1) (0.312 g, 65 %). Yield is calculated based on converted **4**.

(*R*)-**3c**. ^{1}H NMR ($CDCl_3$): 0.86–0.95 (m, 1H, H_a-8); 0.91 (d, *J*(16, 9) = 6.5 Hz, 3H, H-16); 1.02 (dddd, *J*(7a,7e) = *J*(7a,8a) = 12.8 Hz, *J*(7a,6a) = 12.2 Hz, *J*(7a,8e) = 3.2 Hz, 1H, H_a-7); 1.08 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 10.8 Hz, 1H, H_a-10); 1.23 (d, *J*(15,4a) = 0.8 Hz, 3H, H-15); 1.29 (ddd, *J*(6a,7a) = 12.2 Hz, *J*(6a,1a) = 10.2 Hz, *J*(6a,7e) = 3.3 Hz, 1H, H_a-6); 1.38–1.50 (m, 1H, H_a-9); 1.71–1.74 (dm, *J*(8e,8a) = 12.8 Hz, 1H, H_e-8); 1.90–1.95 (m, 1H, H_e-7); 1.91 (dd, *J*(4e,4a) = 12.8 Hz, *J*(4e,3a) = 2.2 Hz, 1H, H_e-4); 1.95–2.02 (m, 1H, H_e-10); 1.99 (ddq, *J*(4a,4e) = 12.8 Hz, *J*(4a,3a) = 11.8 Hz, *J*(4a,15) = 0.8 Hz, 1H, H_a-4); 2.25 (d, *J*(17,13) = 1.0 Hz, 3H, H-17); 3.24 (ddd, *J*(1a,10a) = 10.8 Hz, *J*(1a,6a) = 10.2 Hz, *J*(1a,10e) = 4.2 Hz, 1H, H_a-1); 4.43 (dd, *J*(3a,4a) = 11.8 Hz, *J*(3a,4e) = 2.2 Hz, 1H, H_a-3); 5.87 (dq, *J*(13,14) = 3.1 Hz, *J*(13,17) = 1.0 Hz, 1H, H-13); 6.13 (d, *J*(14,13) = 3.1 Hz, 1H, H-14). ^{13}C NMR ($CDCl_3$): 77.34 (d, C-1); 70.08 (d, C-3); 45.66 (t, C-4); 70.62 (s, C-5); 51.94 (d, C-6); 22.96 (t, C-7); 34.25 (t, C-8); 31.40 (d, C-9); 41.35 (t, C-10); 152.48 (s, C-11); 151.84 (s, C-12); 105.95 (d, C-13); 107.51 (d, C-14); 21.14 (q, C-15); 22.04 (q, C-16); 13.47 (q, C-17). HR-MS: 264.1722 (M^+, $C_{16}H_{24}O_3^+$; calc. 264.1720).

(*S*)-**3c**. ^{1}H NMR ($CDCl_3$): 0.86–0.95 (m, 1H, H_a-8); 0.90 (d, *J*(16,9) = 6.5 Hz, 3H, H-16); 1.01–1.09 (m, 1H, H_a-10); 1.11–1.21 (m, 2H, H_a-6, H_a-7); 1.24 (s, 3H, H-15); 1.38–1.50 (m, 1H, H_a-9); 1.68–1.74 (m, 1H, H_e-8); 1.78 (dd, *J*(4e,4a) = 13.7 Hz, *J*(4e,3a) = 2.2 Hz, 1H, H_e-4); 1.78–1.83 (m, 1H, H_e-7); 1.95–2.02 (m, 2H, H_a-4, H_e-10); 2.25 (s, 3H, H-17); 3.55 (ddd, *J*(1a,10a) = 11.2 Hz, *J*(1a,6a) = 9.7 Hz, *J*(1a,10e) = 4.2 Hz, 1H, H_a-1); 4.77 (dd, *J*(3a,4a) = 12.0 Hz, *J*(3a,4e) = 2.2 Hz, 1H, H_a-3); 5.86 (dq, (*J*(13,14) = 3.1 Hz, *J*(13,17) = 1.0 Hz, 1H, H-13); 6.11 (d, *J*(14,13) = 3.1 Hz, 1H, H-14). ^{13}C NMR ($CDCl_3$): 75.48 (d, C-1); 68.21 (d, C-3); 43.72 (t, C-4); 69.17 (s, C-5); 49.23 (d, C-6); 22.47 (t, C-7); 34.32 (t, C-8); 31.22 (d, C-9); 41.16 (t, C-10); 152.98 (s, C-11); 151.74 (s, C-12); 105.86 (d, C-13); 107.51 (d, C-14); 28.21 (q, C-15); 22.11 (q, C-16); 13.50 (q, C-17). HR-MS: 264.1722 (M^+, $C_{16}H_{24}O_3^+$; calc. 264.1720).

*(2R,4R(S),4aR,7R,8aR)-4,7-Dimethyl-2-(5-nitrofuran-2-yl) octahydro-2H-chromen-4-ol (**3d**)* The reaction of isopulegol **4** (0.300 g) and 5-nitrofuran-2-carbaldehyde **5d** (0.280 g) in the presence of clay K10 (1.2 g) for 60 min led to compound **3d** (0.120 g of (*R*)-isomer and 0.188 g of mixture (*R*):(*S*) = 1:11; 54 %).

(*R*)-**3d**. $[\alpha]_D^{27.1}$ + 27.2 (*c* 0.272, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.87–0.95 (m, 1H, H_a-8); 0.92 (d, *J*(16, 9) = 6.5 Hz, 3H, H-16); 1.02 (dddd, *J*(7a,7e) = *J*(7a,8a) = 13.0 Hz, *J*(7a,6a) = 12.2 Hz, *J*(7a,8e) = 3.3 Hz, 1H, H_a-7); 1.07 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 10.9 Hz, 1H, H_a-10); 1.26 (d, *J*(15,4a) = 0.7 Hz, 3H, H-15); 1.31 (ddd, *J*(6a,7a) = 12.2 Hz, *J*(6a,1a) = 10.3 Hz, *J*(6a,7e) = 3.3 Hz, 1H, H_a-6); 1.39–1.50 (m, 1H, H_a-9); 1.72 (ddddd, *J*(8e,8a) = 13.0 Hz, *J*(8e,7a) = *J*(8e,9a) = *J*(8e, 7e) = 3.3 Hz, *J*(8e,10e) = 2.0 Hz, 1H, H_e-8); 1.89 (ddq, *J*(4a,4e) = 12.7 Hz, *J*(4a, 3a) = 12.1 Hz, *J*(4a,15) = 0.7 Hz, 1H, H_a-4); 1.93 (dm, *J*(7e,7a) = 13.0 Hz, others $J \leq 3.5$ Hz, 1H, H_e-7); 1.98 (dddd, *J*(10e,10a) = 12.2 Hz, *J*(10e,1a) = 4.3 Hz, *J*(10e,9a) = 3.7 Hz, *J*(10e,8e) = 2.0 Hz, 1H, H_e-10); 2.03 (dd, *J*(4e,4a) = 12.7 Hz, *J*(4e,3a) = 2.2 Hz, 1H, H_e-4); 3.26 (ddd, *J*(1a,10a) = 10.9 Hz, *J*(1a,6a) = 10.3 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 4.55 (dd, *J*(3a,4a) = 12.1 Hz, *J*(3a,4e) = 2.2 Hz, 1H, H_a-3); 6.49 (dd, *J*(14,13) = 3.8 Hz, *J*(14,3a) = 0.7 Hz, 1H, H-14); 7.24 (d, *J*(13,14) = 3.8 Hz, 1H, H-13). ^{13}C NMR ($CDCl_3$): 77.85 (d, C-1); 69.98 (d, C-3); 45.70 (t, C-4); 70.19 (s, C-5); 51.76 (d, C-6); 22.83 (t, C-7); 34.11 (t, C-8); 31.30 (d, C-9); 41.10 (t, C-10); 157.90 (s, C-11); 151.47 (s, C-12); 112.17 (d, C-13); 109.48 (d, C-14); 20.99 (q, C-15): 21.97 (q, C-16). HR-MS: 295.1428 (M^+, $C_{15}H_{21}O_5N^+$; calc. 295.1414).

(*S*)-**3d**. $[\alpha]_D^{27.3}$ + 57.6 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.87–0.96 (m, 1H, H_a-8); 0.90 (d, *J*(16,9) = 6.6 Hz, 3H, H-16); 1.02 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.1 Hz, *J*(10a,1a) = 11.2 Hz, 1H, H_a-10); 1.10–1.21 (m, 2H, H_a-6, H_a-7); 1.25 (s, 3H, H-15); 1.41–1.51 (m, 1H, H_a-9); 1.72 (dm, *J*(8e,8a) = 13.0 Hz, others $J \leq 4.0$ Hz, 1H, H_e-8); 1.77–1.82 (m, 1H, H_e-7); 1.86 (dd, *J*(4a,4e) = 13.6 Hz, *J*(4a,3a) = 11.3 Hz, 1H, H_a-4); 1.91 (dd, *J*(4e,4a) = 13.6 Hz, *J*(4e,3a) = 3.0 Hz, 1H, H_e-4); 1.94 (dddd, *J*(10e,10a) = 12.1 Hz, *J*(10e,1a) = 4.2 Hz, *J*(10e,9a) = 3.7 Hz, *J*(10e,8e) = 2.0 Hz, 1H, H_e-10); 3.57 (ddd, *J*(1a,10a) = 11.2 Hz, *J*(1a,6a) = 9.6 Hz, *J*(1a,10e) = 4.2 Hz, 1H, H_a-1); 4.91 (dd, *J*(3a,4a) = 11.3 Hz, *J*(3a,4e) = 3.0 Hz, 1H, H_a-3); 6.47 (dd, *J*(14,13) = 3.7 Hz, *J*(14,3a) = 0.6 Hz, 1H, H-14); 7.23 (d, *J*(13,14) = 3.7 Hz, 1H, H-13). ^{13}C NMR ($CDCl_3$): 75.88 (d, C-1); 68.25 (d, C-3); 43.69 (t, C-4); 68.74 (s, C-5); 49.18 (d, C-6); 22.32 (t, C-7); 34.17 (t, C-8); 31.11 (d, C-9); 40.89 (t, C-10); 158.72 (s, C-11); 151.50 (s, C-12); 112.21 (d, C-13); 109.54 (d, C-14); 27.97 (q, C-15); 22.01 (q, C-16). HR-MS: 295.1428 (M^+, $C_{15}H_{21}O_5N^+$; calc. 295.1414).

*(2R,4R(S),4aR,7R,8aR)-4,7-Dimethyl-2-(5-methylthiophen-2-yl)octahydro-2H-chromen-4-ol (**3e**)* The reaction of isopulegol **4** (0.300 g) and 5-methylthiophene-2-carbaldehyde **5e** (0.250 g) in the presence of clay K10 (1.1 g) for 120 min gave rise to starting isopulegol **4** (0.034 g) and compound **3e** ((*R*):(*S*) = 4.5:1) (0.386 g, 80 %). Yield is calculated based on converted **4**.

(*R*)-**3e**. ^{1}H NMR ($CDCl_3$): 0.87–0.96 (m, 1H, H_a-8); 0.92 (d, *J*(16,9a) = 6.6 Hz, 3H, H-16); 1.02 (dddd, *J*(7a,7e) = *J*(7a,8a) = 12.8 Hz, *J*(7a,6a) = 12.2 Hz, *J*(7a,8e) = 3.3 Hz, 1H, H_a-7); 1.09 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.3 Hz, *J*(10a,1a) = 10.8 Hz, 1H, H_a-10); 1.25 (d, *J*(15,4a) = 0.8 Hz, 3H, H-15); 1.28 (ddd, *J*(6a,7a) = 12.2 Hz, *J*(6a,1a) = 10.2 Hz, *J*(6a,7e) = 3.3 Hz, 1H, H_a-6); 1.39–1.52 (m, 2H, H_a-9, OH); 1.72 (ddddd, *J*(8e,8a) = 12.8 Hz, *J*(8e,7a) = *J*(8e,9a) = *J*(8e,7e) = 3.3 Hz, *J*(8e,10e) = 2.0 Hz, 1H, H_e-8); 1.86 (ddq, *J*(4a,4e) = 12.7 Hz, *J*(4a,3a) = 11.7 Hz, *J*(4a,15) = 0.8 Hz, 1H, H_a-4); 1.93 (dddd, *J*(7e,7a) = 12.8 Hz, *J*(7e,6a) = *J*(7e,8a) = *J*(7e,8e) = 3.3 Hz, 1H, H_e-7); 1.99 (dm, *J*(10e,10a) = 12.3 Hz, 1H, H_e-10); 2.01 (dd, *J*(4e,4a) = 12.7 Hz, *J*(4e,3a) = 2.2 Hz, 1H, H_e-4); 2.42 (d, *J*(17,13) = 1.1 Hz, 3H, H-17); 3.24 (ddd, *J*(1a,10a) = 10.8 Hz, *J*(1a,6a) = 10.2 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 4.59 (dd, *J*(3a,4a) = 11.7 Hz, *J*(3a,4e) = 2.2 Hz, 1H, H_a-3); 6.56 (dq, *J*(13,14) = 3.4 Hz, *J*(13,17) = 1.1 Hz, 1H, H-13); 6.73 (d, *J*(14,13) = 3.4 Hz, 1H, H-14). ^{13}C NMR ($CDCl_3$): 77.43 (d, C-1); 72.54 (d, C-3); 49.58 (t, C-4); 70.69 (s, C-5); 51.89 (d, C-6); 22.93 (t, C-7); 34.26 (t, C-8); 31.38 (d, C-9); 41.35 (t, C-10); 142.89 (s, C-11); 139.12 (s, C-12); 124.26 (d, C-13); 123.50 (d, C-14); 21.17 (q, C-15); 22.04 (q, C-16); 15.16 (q, C-17). HR-MS: 280.1491 (M^+, $C_{16}H_{24}O_2S^+$; calc. 280.1492).

(*S*)-**3e**. ^{1}H NMR ($CDCl_3$): 0.86–0.97 (m, 1H, H_a-8); 0.91 (d, *J*(16,9a) = 6.5 Hz, 3H, H-16); 1.05 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 11.2 Hz, 1H, H_a-10); 1.11–1.20 (m, 2H, H_a-6, H_a-7); 1.23 (s, 3H, H-15); 1.41–1.52 (m, 1H, H_a-9); 1.72 (dm, *J*(8e,8a) = 13.1 Hz, 1H, H_e-8); 1.76–1.84 (m, 1H, H_e-7); 1.80 (dd, *J*(4a,4e) = 13.7 Hz, *J*(4a,3a) = 11.5 Hz, 1H, H_a-4); 1.90 (dd, *J*(4e,4a) = 13.7 Hz, *J*(4e,3a) = 2.4 Hz, 1H, H_e-4); 1.98 (dddd, *J*(10e,10a) = 12.2 Hz, *J*(10e,1a) = 4.2 Hz, *J*(10e,9a) = 3.3 Hz, *J*(10e,8e) = 2.0 Hz, 1H, H_e-10); 2.41 (d, *J*(17,13) = 1.1 Hz, 3H, H-17); 3.55 (ddd, *J*(1a,10a) = 11.2 Hz, *J*(1a,6a) = 9.7 Hz, *J*(1a,10e) = 4.2 Hz, 1H, H_a-1); 4.93 (dd, *J*(3a,4a) = 11.5 Hz, *J*(3a,4e) = 2.4 Hz, 1H, H_a-3); 6.55 (dq, *J*(13,14) = 3.4 Hz, *J*(13,17) = 1.1 Hz, 1H, H-13); 6.72 (d, *J*(14,13) = 3.4 Hz, 1H, H-14). ^{13}C NMR ($CDCl_3$): 75.57 (d, C-1); 70.68 (d, C-3); 47.66 (t, C-4); 69.34 (s, C-5); 49.22 (d, C-6); 22.40 (t, C-7); 34.31 (t, C-8); 31.17 (d, C-9); 41.14 (t, C-10); 143.54 (s, C-11); 138.74 (s, C-12); 124.22 (d, C-13); 123.36 (d, C-14); 28.08 (q, C-15); 22.08 (q, C-16); 15.13 (q, C-17). HR-MS: 280.1491 (M^+, $C_{16}H_{24}O_2S^+$; calc. 280.1492).

*(2R,4R(S),4aR,7R,8aR)-4,7-Dimethyl-2-(3-methylthiophen-2-yl)octahydro-2H-chromen-4-ol (**3f**)* The reaction of isopulegol **4** (0.300 g) and 3-methylthiophene-2-carbaldehyde **5f** (0.250 g) in the presence of clay K10 (1.1 g) for 120 min led to compound **3f** ((*R*):(*S*) = 10:1) (0.381 g, 69 %).

(*R*)-**3f**. ^{1}H NMR ($CDCl_3$): 0.88–0.97 (m, 1H, H_a-8); 0.92 (d, *J*(16,9a) = 6.6 Hz, 3H, H-16); 1.03 (dddd, *J*(7a,7e) = *J*(7a,8a) = 12.8 Hz, *J*(7a,6a) = 12.1 Hz, *J*(7a,8e) = 3.3 Hz, 1H, H_a-7); 1.11 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 10.8 Hz, 1H, H_a-10); 1.28 (d, *J*(15,4a) = 0.7 Hz, 3H, H-15); 1.31 (ddd, *J*(6a,7a) = 12.1 Hz, *J*(6a,1a) = 10.2 Hz, *J*(6a,7e) = 3.3 Hz, 1H, H_a-6); 1.40–1.53 (m, 2H, H_a-9, OH); 1.72 (ddddd, *J*(8e,8a) = 12.9 Hz, *J*(8e,7a) = *J*(8e,9a) = -*J*(8e,7e) = 3.3 Hz, *J*(8e,10e) = 2.0 Hz, 1H, H_e-8); 1.85 (ddq, *J*(4a,4e) = 12.7 Hz, *J*(4a,3a) = 11.7 Hz, *J*(4a,15) = 0.7 Hz, 1H, H_a-4); 1.91–1.97 (m, 1H, H_e-7); 1.95 (dd, *J*(4e,4a) = 12.7 Hz, *J*(4e,3a) = 2.4 Hz, 1H, H_e-4); 1.99 (dm, *J*(10e,10a) = 12.2 Hz, 1H, H_e-10); 2.19 (s, 3H, H-17); 3.26 (ddd, *J*(1a,10a) = 10.8 Hz, *J*(1a,6a) = 10.2 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 4.71 (dd, *J*(3a,4a) = 11.7 Hz, *J*(3a,4e) = 2.4 Hz, 1H, H_a-3); 6.75 (d, *J*(13,12) = 5.0 Hz, 1H, H-13); 7.09 (d, *J*(12,13) = 5.0 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 77.63 (d, C-1); 71.09 (d, C-3); 49.70 (t, C-4); 70.64 (s, C-5); 51.91 (d, C-6); 22.94 (t, C-7); 34.26 (d, C-9); 41.32 (t, C-10); 138.34 (s, C-11); 122.92 (d, C-12); 129.72 (d, C-13); 133.29 (s, C-14); 21.09 (q, C-15); 22.03 (q, C-16); 13.63 (q, C-17). HR-MS: 280.1488 (M^+, $C_{16}H_{24}O_2S^+$; calc. 280.1492).

(*S*)-**3f**. ^{1}H NMR ($CDCl_3$): 0.91 (d, *J*(16,9a) = 6.6 Hz, 3H, H-16); 1.16–1.21 (m, 1H, H_a-6); 1.23 (s, 3H, H-15); 2.21 (s, 3H, H-17); 3.58 (ddd, *J*(1a,10a) = 11.3 Hz, *J*(1a,6a) = 9.7 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 5.07 (dd, *J*(3a,4a) = 10.8 Hz, *J*(3a,4e) = 3.1 Hz, 1H, H_a-3); 7.08 (d, *J*(12,13) = 5.0 Hz, 1H, H-12). Other signals in ^{1}H NMR spectrum of minor isomer (*S*)-**3f** were overlapped with the signals of (*R*)-**3f**. ^{13}C NMR ($CDCl_3$): 75.76 (d, C-1); 69.10 (d, C-3); 47.64 (t, C-4); 69.39 (s, C-5); 49.23 (d, C-6); 22.45 (t, C-7); 34.33 (t, C-8); 31.21 (d, C-9); 41.15 (t, C-10); 138.92 (s, C-11); 122.69 (d, C-12); 126.03 (d, C-13); 133.43 (s, C-14); 28.09 (q, C-15); 22.09 (q, C-16), 13.63 (q, C-17). HR-MS: 280.1488 (M^+, $C_{16}H_{24}O_2S^+$; calc. 280.1492).

*(2R,4R(S),4aR,7R,8aR)-2-(5-Bromothiophen-2-yl)-4,7-dimethyloctahydro-2H-chromen-4-ol (**3g**)* The reaction of isopulegol **4** (0.300 g) and 5-bromothiophene-2-carbaldehyde **5g** (0.370 g) in the presence of clay K10

(1.4 g) for 120 min led to compound **3g** (0.443 g of (*R*)-isomer and 0.069 g of (*S*)-isomer; (*R*):(*S*) = 6.4:1; 76 %).

(*R*)-**3g**. $[\alpha]_D^{26.9}$ − 65.2 (*c* 0.276, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.87–0.96 (m, 1H, H_a-8); 0.92 (d, *J*(16,9a) = 6.6 Hz, 3H, H-16); 1.02 (dddd, *J*(7a,7e) = *J*(7a,8a) = 12.8 Hz, *J*(7a,6a) = 12.2 Hz, *J*(7a,8e) = 3.3 Hz, 1H, H_a-7); 1.09 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 10.8 Hz, 1H, H_a-10); 1.25 (d, *J*(15,4a) = 0.8 Hz, 3H, H-15); 1.28 (ddd, *J*(6a,7a) = 12.2 Hz, *J*(6a,1a) = 10.2 Hz, *J*(6a,7e) = 3.3 Hz, 1H, H_a-6); 1.37–1.50 (m, 2H, H_a-9, OH); 1.72 (dm, *J*(8e,8a) = 12.8 Hz, others $J < 3.5$ Hz, 1H, H_e-8); 1.81 (ddq, *J*(4a,4e) = 12.7 Hz, *J*(4a,3a) = 11.8 Hz, *J*(4a,15) = 0.8 Hz, 1H, H_a-4); 1.92 (dddd, *J*(7e,7a) = 12.8 Hz, *J*(7e,6a) = *J*(7e,8a) = *J*(7e,8e) = 3.3 Hz, 1H, H_e-7); 1.98 (dddd, *J*(10e,10a) = 12.2 Hz, *J*(10e,1a) = 4.3 Hz, *J*(10e,9a) = 3.7 Hz, *J*(10e,8e) = 2.0 Hz, 1H, H_e-10); 2.01 (dd, *J*(4e,4a) = 12.7 Hz, *J*(4e,3a) = 2.2 Hz, 1H, H_e-4); 3.24 (ddd, *J*(1a,10a) = 10.8 Hz, *J*(1a,6a) = 10.2 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 4.59 (ddd, *J*(3a,4a) = 11.8 Hz, *J*(3a,4e) = 2.2 Hz, *J*(3a,14) = 0.8 Hz, 1H, H_a-3); 6.68 (dd, *J*(14,13) = 3.8 Hz, *J*(14,3a) = 0.8 Hz, 1H, H-14); 6.86 (d, *J*(13,14) = 3.8 Hz, 1H, H-13). ^{13}C NMR ($CDCl_3$): 77.58 (d, C-1); 72.53 (d, C-3); 49.42 (t, C-4); 70.54 (s, C-5); 51.84 (d, C-6); 22.89 (t, C-7); 34.20 (t, C-8); 31.35 (d, C-9); 41.23 (t, C-10); 147.17 (s, C-11); 111.45 (s, C-12); 129.01 (d, C-13); 123.55 (d, C-14); 21.16 (q, C-15); 22.02 (q, C-16); HR-MS: 345.0442 (M^+, $C_{15}H_{21}O_2SBr^+$; calc. 345.0440).

(*S*)-**3g**. $[\alpha]_D^{27.0}$ + 36.5 (*c* 0.768, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.87–0.97 (m, 1H, H_a-8); 0.91 (d, *J*(16,9a) = 6.6 Hz, 3H, H-16); 1.04 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 11.2 Hz, 1H, H_a-10); 1.08–1.19 (m, 2H, H_a-6, H_a-7); 1.22 (s, 3H, H-15); 1.41–1.51 (m, 1H, H_a-9); 1.74 (dd, *J*(4a,4e) = 13.5 Hz, *J*(4a,3a) = 11.6 Hz, 1H, H_a-4); 1.69–1.75 (m, 1H, H_e-8); 1.77–1.83 (m, 1H, H_e-7); 1.90 (dd, *J*(4e,4a) = 13.5 Hz, *J*(4e,3a) = 2.4 Hz, 1H, H_e-4); 1.97 (dddd, *J*(10e,10a) = 12.2 Hz, *J*(10e,1a) = 4.2 Hz, *J*(10e,9a) = 3.8 Hz, *J*(10e,8e) = 2.0 Hz, 1H, H_e-10); 3.55 (ddd, *J*(1a,10a) = 11.2 Hz, *J*(1a,6a) = 9.7 Hz, *J*(1a,10e) = 4.2 Hz, 1H, H_a-1); 4.94 (ddd, *J*(3a,4a) = 11.6 Hz, *J*(3a,4e) = 2.4 Hz, *J*(3a,14) = 0.8 Hz, 1H, H_a-3); 6.66 (dd, *J*(14,13) = 3.8 Hz, *J*(14,3a) = 0.8 Hz, 1H, H-14); 6.85 (d, *J*(13,14) = 3.8 Hz, 1H, H-13). ^{13}C NMR ($CDCl_3$): 75.69 (d, C-1); 70.75 (d, C-3); 47.50 (t, C-4); 69.21 (s, C-5); 49.18 (d, C-6); 22.37 (t, C-7); 34.25 (t, C-8); 31.15 (d, C-9); 41.02 (t, C-10); 147.92 (s, C-11); 111.02 (s, C-12); 128.96 (d, C-13); 123.38 (d, C-14); 28.07 (q, C-15); 22.06 (q, C-16). HR-MS: 345.0442 (M^+, $C_{15}H_{21}O_2SBr^+$; calc. 345.0440).

*(2R,4R(S),4aR,7R,8aR)-2-(4-Bromothiophen-2-yl)-4,7-dimethyloctahydro-2H-chromen-4-ol (**3h**)* The reaction of isopulegol **4** (0.300 g) and 4-bromothiophene-2-carbaldehyde **5h** (0.370 g) in the presence of clay K10 (1.4 g) for 120 min led to compound **3h** ((*R*):(*S*) = 3:1) (0.499 g, 74 %).

(*R*)-**3h**. ^{1}H NMR ($CDCl_3$): 0.87–0.96 (m, 1H, H_a-8); 0.93 (d, *J*(16,9a) = 6.6 Hz, 3H, H-16); 1.02 (dddd, *J*(7a,7e) = *J*(7a,8a) = 12.8 Hz, *J*(7a,6a) = 12.1 Hz, *J*(7a,8e) = 3.2 Hz, 1H, H_a-7); 1.10 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 11.1 Hz, 1H, H_a-10); 1.26 (d, *J*(15,4a) = 0.7 Hz, 3H, H-15); 1.29 (ddd, *J*(6a,7a) = 12.1 Hz, *J*(6a,1a) = 10.1 Hz, *J*(6a,7e) = 3.2 Hz, 1H, H_a-6); 1.39–1.50 (m, 1H, H_a-9); 1.56 (br.s, OH); 1.72 (dm, *J*(8e,8a) = 12.8 Hz, others $J < 3.5$ Hz, 1H, H_e-8); 1.82 (ddq, *J*(4a,4e) = 12.7 Hz, *J*(4a,3a) = 11.7 Hz, *J*(4a,15) = 0.7 Hz, 1H, H_a-4); 1.93 (dddd, *J*(7e,7a) = 12.8 Hz, *J*(7e,6a) = *J*(7e,8a) = *J*(7e,8e) = 3.2 Hz, 1H, H_e-7); 1.99 (dddd, *J*(10e,10a) = 12.8 Hz, *J*(10e,1a) = 4.3 Hz, *J*(10e,9a) = 3.7 Hz, *J*(10e,8e) = 2.0 Hz, 1H, H_e-10); 2.01 (dd, *J*(4e,4a) = 12.7 Hz, *J*(4e,3a) = 2.2 Hz, 1H, H_e-4); 3.26 (ddd, *J*(1a,10a) = 11.1 Hz, *J*(1a,6a) = 10.1 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 4.62 (ddd, *J*(3a,4a) = 11.7 Hz, *J*(3a,4e) = 2.2 Hz, *J*(3a,14) = 0.8 Hz, 1H, H_a-3); 6.86 (dd, *J*(14,12) = 1.5 Hz, *J*(14,3a) = 0.8 Hz, 1H, H-14); 7.11 (d, *J*(12,14) = 1.5 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 77.65 (d, C-1); 72.07 (d, C-3); 49.54 (t, C-4); 70.52 (s, C-5); 51.82 (d, C-6); 22.89 (t, C-7); 34.20 (t, C-8); 31.36 (d, C-9); 41.22 (t, C-10); 146.74 (s, C-11); 121.72 (d, C-12); 108.88 (s, C-13); 126.11 (d, C-14); 21.16 (q, C-15); 22.02 (q, C-16). HR-MS: 345.0445 (M^+, $C_{15}H_{21}O_2SBr^+$; calc. 345.0440).

(*S*)-**3h**. Some signals in ^{1}H NMR spectrum of minor isomer (*S*)-**3h** were overlapped with the signals of (*R*)-**3h**. ^{1}H NMR ($CDCl_3$): 0.88–0.97 (m, 1H, H_a-8); 0.92 (d, *J*(16,9a) = 6.6 Hz, 3H, H-16); 1.01–1.21 (m, 3H, H_a-10, H_a-6, H_a-7); 1.24 (s, 3H, H-15); 1.40–1.51 (m, 1H, H_a-9); 1.75 (dd, *J*(4a,4e) = 13.6 Hz, *J*(4a,3a) = 11.6 Hz, 1H, H_a-4); 1.70–1.83 (m, 2H, H_e-8, H_e-7); 1.90–2.02 (m, 2H, H_e-4, H_e-10); 3.57 (ddd, *J*(1a,10a) = 11.1 Hz, *J*(1a,6a) = 9.7 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 4.97 (ddd, *J*(3a,4a) = 11.6 Hz, *J*(3a,4e) = 2.3 Hz, *J*(3a,14) = 0.8 Hz, 1H, H_a-3); 6.85 (dd, *J*(14,12) = 1.5 Hz, *J*(14,3a) = 0.8 Hz, 1H, H-14); 7.09 (d, *J*(12,14) = 1.5 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 75.79 (d, C-1); 70.29 (d, C-3); 47.57 (t, C-4); 69.26 (s, C-5); 49.21 (d, C-6); 22.40 (t, C-7); 34.27 (t, C-8); 31.19 (d, C-9); 41.03 (t, C-10); 147.49 (s, C-11); 121.45 (d, C-12); 108.85 (s, C-13); 125.89 (d, C-14); 28.11 (q, C-15); 22.08 (q, C-16). HR-MS: 345.0445 (M^+, $C_{15}H_{21}O_2SBr^+$; calc. 345.0440).

*(2R,4R(S),4aR,7R,8aR)-4,7-Dimethyl-2-(5-nitrothiophen-2-yl)octahydro-2H-chromen-4-ol (**3i**)* The reaction of isopulegol **4** (0.400 g) and 5-nitrothiophene-2-

carbaldehyde **5i** (0.410 g) for 60 min in the presence of clay K10 (1.6 g) led to compound **3i** (0.167 g of (*R*)-isomer, 0.233 g of mixture (*R*):(*S*) = 1:6; 50 %).

(*R*)-**3i**. $[\alpha]_D^{27.3}$ + 17.9 (*c* 0.312, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.86–0.95 (m, 1H, H_a-8); 0.93 (d, *J*(16,9a) = 6.6 Hz, 3H, H-16); 1.01 (dddd, *J*(7a,7e) = *J*(7a,8a) = 12.8 Hz, *J*(7a,6a) = 12.1 Hz, *J*(7a,8e) = 3.4 Hz, 1H, H_a-7); 1.09 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 10.9 Hz, 1H, H_a-10); 1.26 (d, *J*(15,4a) = 0.7 Hz, 3H, H-15); 1.29 (ddd, *J*(6a,7a) = 12.1 Hz, *J*(6a,1a) = 10.2 Hz, *J*(6a,7e) = 3.2 Hz, 1H, H_a-6); 1.39–1.50 (m, 1H, H_a-9); 1.72 (dm, *J*(8e,8a) = 12.8 Hz, others $J < 3.5$ Hz, 1H, H_e-8); 1.75 (ddq, *J*(4a,4e) = 12.8 Hz, *J*(4a,3a) = 11.9 Hz, *J*(4a,15) = 0.7 Hz, 1H, H_a-4); 1.92 (dddd, *J*(7e,7a) = 12.8 Hz, *J*(7e,6a) = *J*(7e,8a) = *J*(7e,8e) = 3.2 Hz, 1H, H_e-7); 1.99 (dddd, *J*(10e,10a) = 12.2 Hz, *J*(10e,1a) = 4.3 Hz, *J*(10e,9a) = 3.7 Hz, *J*(10e,8e) = 1.9 Hz, 1H, H_e-10); 2.04 (dd, *J*(4e,4a) = 12.8 Hz, *J*(4e,3a) = 2.2 Hz, 1H, H_e-4); 3.27 (ddd, *J*(1a,10a) = 10.9 Hz, *J*(1a,6a) = 10.2 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 4.65 (ddd, *J*(3a,4a) = 11.9 Hz, *J*(3a,4e) = 2.2 Hz, *J*(3a,14) = 0.9 Hz, 1H, H_a-3); 6.82 (dd, *J*(14,13) = 4.2 Hz, *J*(14,3a) = 0.9 Hz, 1H, H-14); 7.75 (d, *J*(13,14) = 4.2 Hz, 1H, H-13). ^{13}C NMR ($CDCl_3$): 77.81 (d, C-1); 72.38 (d, C-3); 49.42 (t, C-4); 70.25 (s, C-5); 51.68 (d, C-6); 22.78 (t, C-7); 34.09 (t, C-8); 31.25 (d, C-9); 41.04 (t, C-10); 154.79 (s, C-11); 150.56 (s, C-12); 128.17 (d, C-13); 121.75 (d, C-14); 21.01 (q, C-15); 21.95 (q, C-16). HR-MS: 311.1185 (M^+, $C_{15}H_{21}O_2SBr^+$; calc. 311.1186).

(*S*)-**3i**. ^{1}H NMR ($CDCl_3$): 0.88–0.97 (m, 1H, H_a-8); 0.92 (d, *J*(16,9a) = 6.5 Hz, 3H, H-16); 1.05 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.1 Hz, *J*(10a,1a) = 11.2 Hz, 1H, H_a-10); 1.09–1.20 (m, 2H, H_a-6, H_a-7); 1.24 (s, 3H, H-15); 1.41–1.52 (m, 1H, H_a-9); 1.67 (dd, *J*(4a,4e) = 13.4 Hz, *J*(4a,3a) = 11.6 Hz, 1H, H_a-4); 1.72 (dm, *J*(8e,8a) = 13.1 Hz, others $J < 3.5$ Hz, 1H, H_e-8); 1.77–1.83 (m, 1H, H_e-7); 1.95 (dd, *J*(4e,4a) = 13.4 Hz, *J*(4e,3a) = 2.4 Hz, 1H, H_e-4); 1.97 (dm, *J*(10e,10a) = 12.1 Hz, others $J < 4.5$ Hz, 1H, H_e-10); 3.58 (ddd, *J*(1a,10a) = 11.2 Hz, *J*(1a,6a) = 9.7 Hz, *J*(1a,10e) = 4.2 Hz, 1H, H_a-1); 5.01 (ddd, *J*(3a,4a) = 11.6 Hz, *J*(3a,4e) = 2.4 Hz, *J*(3a,14) = 1.0 Hz, 1H, H_a-3); 6.81 (dd, *J*(14,13) = 4.2 Hz, *J*(14,3a) = 1.0 Hz, 1H, H-14); 7.74 (d, *J*(13,14) = 4.2 Hz, 1H, H-13). ^{13}C NMR ($CDCl_3$): 75.89 (d, C-1); 70.73 (d, C-3); 47.54 (t, C-4); 69.98 (s, C-5); 49.12 (d, C-6); 22.28 (t, C-7); 34.14 (t, C-8); 31.08 (d, C-9); 40.83 (t, C-10); 155.99 (s, C-11); 150.31 (s, C-12); 128.26 (d, C-13); 121.60 (d, C-14); 27.91 (q, C-15); 22.00 (q, C-16). HR-MS: 311.1185 (M^+, $C_{15}H_{21}O_2SBr^+$; calc. 311.1186).

*(2R,4R(S),4aR,7R,8aR)-2-(Furan-3-yl)-4,7-dimethyloctahydro-2H-chromen-4-ol (**8a**)* The reaction of isopulegol **4** (0.300 g) and furan-3-carbaldehyde **9a** (0.190 g) in the presence of clay K10 (1.0 g) for 60 min led to compound **8a** (0.178 g of (*R*)-isomer, 0.050 g of (*S*)-isomer and 0.072 g of mixture (*R*):(*S*) = 8:1; 61 %).

(*R*)-**8a**. $[\alpha]_D^{26.4}$ + 4.3 (*c* 0.326, MeOH). ^{1}H NMR ($CDCl_3$): 0.87–0.96 (m, 1H, H_a-8); 0.92 (d, *J*(16,9) = 6.5 Hz, 3H, H-16); 1.03 (dddd, *J*(7a,7e) = *J*(7a,8a) = 13.0 Hz, *J*(7a,6a) = 12.2 Hz, *J*(7a,8e) = 3.2 Hz, 1H, H_a-7); 1.07 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 10.8 Hz, 1H, H_a-10); 1.25 (d, *J*(15,4a) = 0.7 Hz, 3H, H-15); 1.27 (ddd, *J*(6a,7a) = 12.2 Hz, *J*(6a,1a) = 10.2 Hz, *J*(6a,7e) = 3.2 Hz, 1H, H_a-6); 1.39–1.50 (m, 1H, H_a-9); 1.72 (dm, *J*(8e,8a) = 13.0 Hz, others $J \leq 3.5$ Hz, 1H, H_e-8); 1.79 (ddq, *J*(4a,4e) = 12.7 Hz, *J*(4a,3a) = 11.8 Hz, *J*(4a,15) = 0.7 Hz, 1H, H_a-4); 1.91 (dd, *J*(4e,4a) = 12.7 Hz, *J*(4e,3a) = 2.2 Hz, 1H, H_e-4); 1.92 (dm, *J*(7e,7a) = 13.0 Hz, others $J \leq 3.5$ Hz, 1H, H_e-7); 1.98 (dddd, *J*(10e,10a) = 12.2 Hz, *J*(10e,1a) = 4.3 Hz, *J*(10e,9a) = 3.7 Hz, *J*(10e,8e) = 2.0 Hz, 1H, H_e-10); 3.22 (ddd, *J*(1a,10a) = 10.8 Hz, *J*(1a,6a) = 10.2 Hz, *J*(1a,10e) = 4.3 Hz, 1H, H_a-1); 4.42 (dd, *J*(3a,4a) = 11.8 Hz, *J*(3a,4e) = 2.2 Hz, 1H, H_a-3); 6.38 (dd, *J*(14,13) = 1.8 Hz, *J*(14,12) = 0.8 Hz, 1H, H-14); 7.34 (dd, *J*(13,14) = 1.8 Hz, *J*(13,12) = 1.5 Hz, 1H, H-13); 7.37 (ddd, *J*(12,13) = 1.5 Hz, *J*(12,14) = 0.8 Hz, *J*(12,3a) = 0.5 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 77.26 (d, C-1); 69.42 (d, C-3); 48.43 (t, C-4); 70.58 (s, C-5); 51.97 (d, C-6); 22.94 (t, C-7); 34.27 (t, C-8); 31.37 (d, C-9); 41.38 (t, C-10); 126.72 (s, C-11); 139.03 (d, C-12); 142.93 (d, C-13); 108.79 (d, C-14); 21.19 (q, C-15); 22.06 (q, C-16). HR-MS: 250.1561 (M^+, $C_{15}H_{22}O_3^+$; calc. 250.1563).

(*S*)-**8a**. $[\alpha]_D^{26.3}$ + 10.3 (*c* 0.812, MeOH). ^{1}H NMR ($CDCl_3$): 0.87–0.96 (m, 1H, H_a-8); 0.91 (d,, *J*(16,9) = 6.5 Hz, 3H, H-16); 1.03 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.1 Hz, *J*(10a,1a) = 11.2 Hz, 1H, H_a-10); 1.08–1.20 (m, 2H, H_a-6, H_a-7); 1.22 (s, 3H, H-15); 1.41–1.52 (m, 1H, H_a-9); 1.72 (dm, *J*(8e,8a) = 13.0 Hz, 1H, H_e-8); 1.73 (dd, *J*(4a,4e) = 13.6 Hz, *J*(4a,3a) = 11.5 Hz, 1H, H_a-4); 1.78–1.83 (m, 1H, H_e-7); 1.80 (dd, *J*(4e,4a) = 13.6 Hz, *J*(4e,3a) = 2.5 Hz, 1H, H_e-4); 1.96 (dddd, *J*(10e,10a) = 12.1 Hz, *J*(10e,1a) = 4.2 Hz, *J*(10e,9a) = 3.7 Hz, *J*(10e,8e) = 2.0 Hz, 1H, H_e-10); 3.52 (ddd, *J*(1a,10a) = 11.2 Hz, *J*(1a,6a) = 9.6 Hz, *J*(1a,10e) = 4.2 Hz, 1H, H_a-1); 4.75 (dd, *J*(3a,4a) = 11.5 Hz, *J*(3a,4e) = 2.5 Hz, 1H, H_a-3); 6.38 (dd, *J*(14,13) = 1.8 Hz, *J*(14,12) = 0.8 Hz, 1H, H-14); 7.33 (dd, *J*(13,14) = 1.8 Hz, *J*(13,12) = 1.5 Hz, 1H, H-13); 7.36 (ddd, *J*(12,13) = 1.5 Hz, *J*(12,14) = 0.8 Hz, *J*(12,3a) = 0.5 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 75.36 (d, C-1); 67.48 (d, C-3); 46.43 (t, C-4); 69.20 (s, C-5); 49.33 (d, C-6); 22.42 (t, C-7); 34.32 (t, C-8); 31.18 (d, C-9); 41.19 (t, C-10); 127.04 (s, C-11); 138.96 (d, C-12); 142.78 (d, C-13); 108.82 (d, C-14); 28.14

(q, C-15); 22.11 (q, C-16). HR-MS: 250.1561 (M^+, $C_{15}H_{22}O_3^+$; calc. 250.1563).

*(2R,4R(S),4aR,7R,8aR)-4,7-Dimethyl-2-(thiophen-3-yl)octahydro-2H-chromen-4-ol (**8b**)* The reaction of isopulegol **4** (0.300 g) and thiophene-3-carbaldehyde **9b** (0.220 g) in the presence of clay K10 (1.1 g) for 60 min led to compound **8b** (0.216 g of (*R*)-isomer and 0.112 g of mixture (*R*):(*S*) = 1.5:1; 63 %).

(*R*)-**8b**. $[\alpha]_D^{26.4}$ + 18.0 (*c* 0.412, MeOH). ^{1}H NMR ($CDCl_3$): 0.88–0.97 (m, 1H, H_a-8); 0.93 (d, *J*(16,9) = 6.6 Hz, 3H, H-16); 1.04 (dddd, *J*(7a,7e) = *J*(7a,8a) = 12.9 Hz, *J*(7a,6a) = 12.2 Hz, *J*(7a,8e) = 3.3 Hz, 1H, H_a-7); 1.10 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 10.8 Hz, 1H, H_a-10); 1.27 (d, *J*(15,4a) = 0.8 Hz, 3H, H-15); 1.29 (ddd, *J*(6a,7a) = 12.2 Hz, *J*(6a,1a) = 10.2 Hz, *J*(6a,7e) = 3.3 Hz, 1H, H_a-6); 1.40–1.52 (m, 1H, H_a-9); 1.73 (ddddd, *J*(8e,8a) = 12.9 Hz, *J*(8e,7a) = *J*(8e,9a) = *J*(8e,7e) = 3.3 Hz, *J*(8e,10e) = 2.0 Hz, 1H, H_e-8); 1.81 (ddq, *J*(4a,4e) = 12.8 Hz, *J*(4a,3a) = 11.8 Hz, *J*(4a,15) = 0.8 Hz, 1H, H_a-4); 1.93 (dddd, *J*(7e,7a) = 12.9 Hz, *J*(7e,6a) = *J*(7e,8a) = *J*(7e,8e) = 3.3 Hz, 1H, H_e-7); 1.97 (dd, *J*(4e,4a) = 12.8 Hz, *J*(4e,3a) = 2.2 Hz, 1H, H_e-4); 2.00 (dddd, *J*(10e,10a) = 12.2 Hz, *J*(10e,1a) = 4.2 Hz, *J*(10e,9a) = 3.7 Hz, *J*(10e,8e) = 2.0 Hz, 1H, H_e-10); 3.25 (ddd, *J*(1a,10a) = 10.8 Hz, *J*(1a,6a) = 10.2 Hz, *J*(1a,10e) = 4.2 Hz, 1H, H_a-1); 4.53 (dd, *J*(3a,4a) = 11.8 Hz, *J*(3a,4e) = 2.2 Hz, 1H, H_a-3); 7.06 (dd, *J*(14,13) = 5.0 Hz, *J*(14,12) = 1.2 Hz, 1H, H-14); 7.18 (ddd, *J*(12,13) = 3.0 Hz, *J*(12,14) = 1.2 Hz, *J*(12,3a) = 0.8 Hz, 1H, H-12); 7.25 (dd, *J*(13,14) = 5.0 Hz, *J*(13,12) = 3.0 Hz, 1H, H-13). ^{13}C NMR ($CDCl_3$): 77.36 (d, C-1); 72.84 (d, C-3); 49.16 (t, C-4); 70.71 (s, C-5); 52.04 (d, C-6); 22.97 (t, C-7); 34.31 (t, C-8); 31.39 (d, C-9); 41.42 (t, C-10); 143.36 (s, C-11); 120.78 (d, C-12); 125.61 (d, C-13); 125.87 (d, C-14); 21.21 (q, C-15); 22.08 (q, C-16). HR-MS: 266.1337 (M^+, $C_{15}H_{22}O_2S^+$; calc. 266.1335).

(*S*)-**8b**. ^{1}H NMR ($CDCl_3$): 0.88–0.97 (m, 1H, H_a-8); 0.92 (d, *J*(16,9) = 6.6 Hz, 3H, H-16); 1.06 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.1 Hz, *J*(10a,1a) = 11.2 Hz, 1H, H_a-10); 1.12–1.21 (m, 2H, H_a-6, H_a-7); 1.23 (s, 3H, H-15); 1.41–1.53 (m, 1H, H_a-9); 1.74 (dd, *J*(4a,4e) = 13.7 Hz, *J*(4a,3a) = 11.7 Hz, 1H, H_a-4); 1.78–1.84 (m, 1H, H_e-7); 1.70–1.76 (m, 1H, H_e-8); 1.88 (dd, *J*(4e,4a) = 13.7 Hz, *J*(4e,3a) = 2.5 Hz, 1H, H_e-4); 1.97–2.01 (m, 1H, H_e-10); 3.55 (ddd, *J*(1a,10a) = 11.2 Hz, *J*(1a,6a) = 9.6 Hz, *J*(1a,10e) = 4.2 Hz, 1H, H_a-1); 4.87 (dd, *J*(3a,4a) = 11.7 Hz, *J*(3a,4e) = 2.5 Hz, 1H, H_a-3); 7.06 (dd, *J*(14,13) = 5.0 Hz, *J*(14,12) = 1.3 Hz, 1H, H-14); 7.17 (ddd, *J*(12,13) = 3.0 Hz, *J*(12,14) = 1.3 Hz, *J*(12,3a) = 0.8 Hz, 1H, H-12); 7.24 (dd, *J*(13,14) = 5.0 Hz, *J*(13,12) = 3.0 Hz, 1H, H-13). ^{13}C NMR ($CDCl_3$): 75.49 (d, C-1); 71.01 (d, C-3); 47.19 (t, C-4); 69.34 (s, C-5); 49.41 (d, C-6); 22.47 (t, C-7); 34.38 (t, C-8); 31.23 (d, C-9); 41.26 (t, C-10); 143.98 (s, C-11); 120.52 (d, C-12); 125.45 (d, C-13); 125.89 (d, C-14); 28.20 (q, C-15); 22.14 (q, C-16). HR-MS: 266.1337 (M^+, $C_{15}H_{22}O_2S^+$; calc. 266.1335).

Synthesis of compounds 6 and 7

A solution of TsOH (0.032 g) in toluene (5 ml) was added to a solution of aldehyde **5b** in toluene (10 ml). Then a solution of isopulegol **4** (0.300 g) in toluene (10 ml) and molecular sieves 4Å (30 pieces) were added. The mixture was refluxed for 60 min. The sieves were filtered off, the solvent was distilled off, and the residue was separated on a SiO_2 column. The mixture of compounds **6** and **7** (0.407 g, 9:1; 84 %) was obtained.

*(2R,4aS,7R,8aR)-7-Methyl-4-methylene-2-(thiophen-2-yl)octahydro-2H-chromene (**6**)* ^{1}H NMR ($CDCl_3$): 0.95 (d, *J*(16,9a) = 6.5 Hz, 3H, H-16); 1.00 (dddd, *J*(8a,8e) = 13.0 Hz, *J*(8a,7a) = 13.0 Hz, *J*(8a,9a) = 12.2 Hz, *J*(8a,7e) = 3.7 Hz, 1H, H_a-8); 1.20 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 11.0 Hz, 1H, H_a-10); 1.27 (dddd, *J*(7a,7e) = *J*(7a,8a) = 13.0 Hz, *J*(7a,6a) = 11.7 Hz, *J*(7a,8e) = 3.7 Hz, 1H, H_a-7); 1.44–1.55 (m, 1H, H_a-9); 1.74 (dddd, *J*(8e,8a) = 13.0 Hz, *J*(8e,7a) = 3.7 Hz, *J*(8e,7e) = 3.3 Hz, *J*(8e,10e) = 2.0 Hz, 1H, H_e-8); 1.81–1.88 (m, 1H, H_a-6); 1.90 (dddd, *J*(7e,7a) = 13.0 Hz, *J*(7e,8a) = *J*(7e,6a) = 3.7 Hz, *J*(7e,8e) = 3.3 Hz, 1H, H_e-7); 2.01 (dddd, *J*(10e,10a) = 12.2 Hz, *J*(10e,1a) = *J*(10e,9a) = 4.1 Hz, *J*(10e,8e) = 2.0 Hz, 1H, H_e-10); 2.50 (ddm, *J*(4a,4e) = 13.1 Hz, *J*(4a,3a) = 11.4 Hz, 1H, H_a-4); 2.61 (dd, *J*(4e,4a) = 13.1 Hz, *J*(4e,3a) = 2.6 Hz, 1H, H_e-4); 3.13 (ddd, *J*(1a,10a) = 11.0 Hz, *J*(1a,6a) = 9.8 Hz, *J*(1a,10e) = 4.1 Hz, 1H, H_a-1); 4.63 (ddd, *J*(3a,4a) = 11.4 Hz, *J*(3a,4e) = 2.6 Hz, *J*(3a,14) = 0,7 Hz, 1H, H_a-3); 4.69, 4.81 (2 m, all $J \leq 2.2$ Hz, 2H, H-15); 6.95 (dd, *J*(13,12) = 5.0 Hz, *J*(13,14) = 3.5 Hz, 1H, H-13); 6.98 (ddd, *J*(14,13) = 3.5 Hz, *J*(14,12) = 1.3 Hz, *J*(14,3a) = 0.7 Hz, 1H, H-14); 7.22 (dd, *J*(12,13) = 5.0 Hz, *J*(12,14) = 1.3 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 81.96 (d, C-1); 76.35 (d, C-3); 44.24 (t, C-4); 145.59 (s, C-5); 46.24 (d, C-6); 25.97 (t, C-7); 34.02 (t, C-8); 31.38 (d, C-9); 41.28 (t, C-10); 147.54 (s, C-11); 124.41 (d, C-12); 126.28 (d, C-13); 123.40 (d, C-14); 105.99 (t, C-15); 22.11 (q, C-16). HR-MS: 248.1230 (M^+, $C_{15}H_{20}OS^+$; calc. 248.1229).

*(2R,7R,8aR)-4,7-Dimethyl-2-(thiophen-2-yl)-3,5,6,7,8,8a-hexahydro-2H-chromene (**7**)* ^{1}H NMR ($CDCl_3$): 0.83–0.95 (m, 1H, H_a-8); 0.92 (d, *J*(16,9a) = 6.6 Hz, 3H, H-16); 1.04 (ddd, *J*(10a,10e) = *J*(10a,9a) = 12.2 Hz, *J*(10a,1a) = 11.2 Hz, 1H, H_a-10); 1.54–1.73 (m, 3H, H_a-7, H_e-8, H_a-9); 1.69 (m, all $J \leq 2.5$ Hz, 3H, H-15); 2.07–2.16 (m, 2H, H_e-4, H_e-10); 2.49 (ddm, *J*(4a,4e) = 16.5 Hz,

J(4a,3a) = 10.8 Hz, 1H, H_a-4); 2.67–2.74 (m, 1H, H_e-7); 4.12–4.18 (m, 1H, H_a-1); 4.77 (ddd, J(ddd, J(3a,4a) = 10.8 Hz, J(3a,4e) = 3.2 Hz, J(3a,14) = 0.7 Hz, 1H, H_a-3); 6.94 (dd, J(13,12) = 5.0 Hz, J(13,14) = 3.5 Hz, 1H, H-13); 6.98 (ddd, J(14,13) = 3.5 Hz, J(14,12) = 1.2 Hz, J(14,3a) = 0.7 Hz, 1H, H-14); 7.21 (dd, J(12,13) = 5.0 Hz, J(12,14) = 1.2 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 76.45 (d, C-1); 71.13 (d, C-3); 39.19 (t, C-4); 121.46 (s, C-5); 131.39 (s, C-6); 26.43 (t, C-7); 34.95 (t, C-8); 30.91 (d, C-9); 42.65 (t, C-10); 146.08 (s, C-11); 124.34 (d, C-12); 126.30 (d, C-13); 123.45 (d, C-14); 18.05 (q, C-15); 21.87 (q, C-16).

Synthesis of (+)-neoisopulegol 11

A solution of (−)-isopulegol **4** (3.47 g) in CH_2Cl_2 (10 ml) was added dropwise during 10 min to a slurry of PCC (pyridinium chlorochromate, 11.26 g) in CH_2Cl_2 (50 ml). The mixture was stirred for 5 h at r.t.; then Et_2O (60 ml) was added, the sediment was filtered through the column with SiO_2, and the solvent was distilled off. Isopulegone **10** (2.70 g, 79 %) was obtained.

$NaBH_4$ (1.34 g) was added to a solution of **10** (2.70 g) in MeOH (10 ml). The mixture was stirred at r.t. for 2.5 h, and then, 3.5 % HCl was added before pH 3 was reached. MeOH was distilled off, and then water (5 ml) was added. The product was extracted by Et_2O. The solution was dried over Na_2SO_4. The solvent was distilled off which gave rise to 2.39 g (87 %) mixture of (−)-isopulegol **4** and (+)-neoisopulegol **11** (1.7:1). (+)-Neoisopulegol **11** (0.73 g, 21 %; $[\alpha]_D^{30,6}$ + 28.5 (c 0.498, C_6H_{14})) was isolated by column chromatography on SiO_2, and (−)-isopulegol **4** (1.32 g) was also obtained. The ^{1}H and ^{13}C NMR spectra of (+)-neoisopulegol **11** coincided with the literature data (Moreira and Correa 2003).

Reaction of (+)-neoisopulegol 11 with aldehydes 5a,b on clay K10: general procedure

An appropriate aldehyde was added to a suspension of clay K10 in CH_2Cl_2 (10 ml); then, a solution of neoisopulegol **11** in CH_2Cl_2 (10 ml) was added. The solvent was distilled off. The mixture was stored at r.t. for 60 min. Then ethyl acetate (15 ml) was added. The catalyst was filtered off, the solvent was distilled off, and the residue was separated on a SiO_2 column.

*(2S,4S(R),4aR,7R,8aS)-2-(Furan-2-yl)-4,7-dimethyloctahydro-2H-chromen-4-ol (**12a**)* The reaction of (+)-neoisopulegol **11** (0.200 g) and furan-2-carbaldehyde **5a** (0.125 g) in the presence of clay K10 (0.7 g) led to compound **12a** ((*S*):(*R*) = 1.5:1) (0.133 g, 41 %) and (1*S*,2*R*,5*R*)-2-(2-hydroxypropan-2-yl)-5-methylcyclohexanol **13** (0.042 g, 19 %). The ^{1}H and ^{13}C NMR spectra of diol **13** coincided with the literature data (Kocovsky *et al.*, 1999).

(*S*)-**12a**. ^{1}H NMR ($CDCl_3$): 0.81 (d, J(16,9) = 6.5 Hz, 3H, H-16); 0.83–0.92 (m, 1H, H_a-8); 1.06 (ddd, J(10a,10e) = 14.0 Hz, J(10a,9a) = 12.3 Hz, J(10a,1e) = 3.0 Hz, 1H, H_a-10); 1.38 (dm, J(6a,7a) = 12.5 Hz, 1H, H_a-6); 1.41 (d, J(15,4a) = 0.8 Hz, 3H, H-15); 1.54–1.63 (m, 1H, H_a-7); 1.63 (ddd, J(4e,4a) = 12.9 Hz, J(4e,3a) = 2.5 Hz, J(4e,6a) = 1.2 Hz, 1H, H_e-4); 1.67–1.79 (m, 3H, H_e-7, H_e-8, H_a-9); 1.97 (dm, J(10e,10a) = 14.0 Hz, others $J \leq$ 4.5 Hz, 1H, H_e-10); 2.07 (ddq, J(4a,4e) = 12.9 Hz, J(4a,3a) = 12.3 Hz, J(4a,15) = 0.8 Hz, 1H, H_a-4); 3.80 (m, all $J \leq$ 3.0 Hz, 1H, H_e-1); 4.46 (dd, J(3a,4a) = 12.3 Hz, J(3a,4e) = 2.5 Hz, 1H, H_a-3); 6.25 (ddd, J(14,13) = 3.2 Hz, J(14,12) = 0.9 Hz, J(14,3a) = 0.7 Hz, 1H, H-14); 6.30 (dd, J(13,14) = 3.2 Hz, J(13,12) = 1.8 Hz, 1H, H-13); 7.35 (dd, J(12,13) = 1.8 Hz, J(12,14) = 0.9 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 73.86 (d, C-1); 70.77 (d, C-3); 39.03 (t, C-4); 71.02 (s, C-5); 46.59 (d, C-6); 21.29 (t, C-7); 34.19 (t, C-8); 26.04 (d, C-9); 40.12 (t, C-10); 154.60 (s, C-11); 142.01 (d, C-12); 109.95 (d, C-13); 106.39 (d, C-14); 27.00 (q, C-15); 22.06 (q, C-16). HR-MS: 250.3335 (M^+, $C_{15}H_{22}O_3^+$; calc. 250.3334).

(*R*)-**12a**. ^{1}H NMR ($CDCl_3$): 0.81 (d, J(16,9) = 6.5 Hz, 3H, H-16); 0.84–0.94 (m, 1H, H_a-8); 1.04 (ddd, J(10a,10e) = 14.0 Hz, J(10a,9a) = 12.3 Hz, J(10a,1e) = 2.9 Hz, 1H, H_a-10); 1.22 (s, 3H, H-15); 1.22–1.27 (m, 1H, H_a-6); 1.47–1.56 (m, 3H, H_e-4, 2H-7); 1.67–1.79 (m, 2H, H_e-8, H_a-9); 1.99 (dd, J(4a,4e) = 13.8 Hz, J(4a,3a) = 12.1 Hz, 1H, H_a-4); 1.97 (dm, J(10e,10a) = 14.0 Hz, 1H, H_e-10); 4.19 (ddd, J(1e,10a) = 2.9 Hz, J(1e,6a) ≈ J(1e,10e) ≈ 2.7 Hz, 1H, H_e-1); 4.80 (dd, J(3a,4a) = 12.1 Hz, J(3a,4e) = 2.5 Hz, 1H, H_a-3); 6.23 (ddd, J(14,13) = 3.2 Hz, J(14,12) = 0.9 Hz, J(14,3a) = 0.7 Hz, 1H, H-14); 6.29 (dd, J(13,14) = 3.2 Hz, J(13,12) = 1.8 Hz, 1H, H-13); 7.34 (dd, J(12,13) = 1.8 Hz, J(12,14) = 0.9 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 71.54 (d, C-1); 68.99 (d, C-3); 38.24 (t, C-4); 71.19 (s, C-5); 46.20 (d, C-6); 23.60 (t, C-7); 34.48 (t, C-8); 25.87 (d, C-9); 39.92 (t, C-10); 155.19 (s, C-11); 141.91 (d, C-12); 109.88 (d, C-13); 106.36 (d, C-14); 28.88 (q, C-15); 22.11 (q, C-16). HR-MS: 250.3335 (M^+, $C_{15}H_{22}O_3^+$; calc. 250.3334).

Compound 13. $[\alpha]_D^{27.5}$ - 10.4 (c 0.154, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.86 (d, J(10,3) = 6.3 Hz, 3H, H-10); 0.87–0.94 (m, 1H, H-4); 1.04 (ddd, J(2a,2e) = 14.1 Hz, J(2a,3a) = 12.4 Hz, J(2a,1e) = 2.3 Hz, 1H, H_a-2); 1.15 (ddd, J(6a,5a) = 11.7 Hz, J(6a,5e) = 4.8 Hz, J(6a,1e) = 2.3 Hz, 1H, H_a-6); 1.21 (s, 3H) and 1.34 (s, 3H)– H-8 and H-9; 1.63–1.71 (m, 2H, H-5); 1.74–1.84 (m, 3H, H_e-2, H_a-3, H'-4); 4.39 (m, all $J \leq$ 3.0 Hz, 1H, H_e-1).

^{13}C NMR ($CDCl_3$): 68.01 (d, C-1); 42.44 (t, C-2); 25.52 (d, C-3); 34.77 (t, C-4); 20.14 (t, C-5); 48.30 (d, C-6); 73.19 (s, C-7); 28.78 and 28.82 (2q, C-8, C-9); 22.07 (q, C-10).

*(2S,4S(R),4aR,7R,8aS)-4,7-Dimethyl-2-(thiophen-2-yl)octahydro-2H-chromen-4-ol (**12b**)* The reaction of (+)-neoisopulegol **11** (0.200 g) and thiophene-2-carbaldehyde **5b** (0.145 g) in the presence of clay K10 (0.7 g) led to compound **12b** ((*S*):(*R*) = 1:1) (0.258 g, 75 %).

(*S*)-**12b**. ^{1}H NMR ($CDCl_3$): 0.84 (d, *J*(16,9) = 6.6 Hz, 3H, H-16); 0.90 (dddd, *J*(8a,8e) = *J*(8a,7a) = *J*(8a,9a) = 12.8 Hz, *J*(8a,7e) = 3.0 Hz, 1H, H_a-8); 1.07 (ddd, *J*(10a,10e) = 13.9 Hz, *J*(10a,9a) = 12.0 Hz, *J*(10a,1e) = 2.9 Hz, 1H, H_a-10); 1.39 (dm, *J*(6a,7a) = 12.8 Hz, others $J \leq 3.5$ Hz, 1H, H_a-6); 1.44 (d, *J*(15,4a) = 0.7 Hz, 3H, H-15); 1.59 (dddd, *J*(7a,7e) = *J*(7a,6a) = *J*(7a,8a) = 12.8 Hz, *J*(7a,8e) = 3.2 Hz, 1H, H_a-7); 1.73 (ddd, *J*(4e,4a) = 13.0 Hz, *J*(4e,3a) = 2.7 Hz, *J*(4e,6a) = 1.2 Hz, 1H, H_e-4); 1.71–1.81 (m, 3H, H_e-7, H_e-8, H_a-9); 1.95 (ddd, *J*(4a,4e) = 13.0 Hz, *J*(4a,3a) = 11.8 Hz, *J*(4a,15) = 0.7 Hz, 1H, H_a-4); 1.98 (dm, *J*(10e,10a) = 13.9 Hz, others $J \leq 4.0$ Hz, 1H, H_e-10); 3.83 (m, all $J \leq 3.0$ Hz, 1H, H_e-1); 4.67 (ddd, *J*(3a,4a) = 11.8 Hz, *J*(3a,4e) = 2.7 Hz, *J*(3a,14) = 0.8 Hz, 1H, H_a-3); 6.93 (dd, *J*(13,12) = 5.0 Hz, *J*(13,14) = 3.5 Hz, 1H, H-13); 6.96 (ddd, *J*(14,13) = 3.5 Hz, *J*(14,12) = 1.3 Hz, *J*(14,3a) = 0.8 Hz, 1H, H-14); 7.21 (dd, *J*(12,13) = 5.0 Hz, *J*(12,14) = 1.3 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 73.92 (d, C-1); 73.24 (d, C-3); 43.58 (t, C-4); 71.13 (s, C-5); 46.42 (d, C-6); 21.36 (t, C-7); 34.21 (t, C-8); 26.10 (d, C-9); 40.20 (t, C-10); 145.92 (s, C-11); 124.36 (d, C-12); 126.24 (d, C-13); 123.33 (d, C-14); 27.02 (q, C-15); 22.10 (q, C-16). HR-MS: 266.1334 (M^+, $C_{15}H_{22}O_2S^+$; calc. 266.1335).

(*R*)-**12b**. ^{1}H NMR ($CDCl_3$): 0.83 (d, *J*(16,9) = 6.6 Hz, 3H, H-16); 0.83–0.95 (m, 1H, H_a-8); 1.05 (ddd, *J*(10a,10e) = 14.0 Hz, *J*(10a,9a) = 12.0 Hz, *J*(10a,1e) = 2.9 Hz, 1H, H_a-10); 1.20 (s, 3H, H-15); 1.23–1.28 (m, 1H, H_a-6); 1.50–1.56 (m, 2H, H-7); 1.65 (ddd, *J*(4e,4a) = 13.9 Hz, *J*(4e,3a) = 2.7 Hz, *J*(4e,6a) = 1.4 Hz, 1H, H_e-4); 1.70–1.80 (m, 2H, H_e-8, H_a-9); 1.84 (dd, *J*(4a,4e) = 13.9 Hz, *J*(4a,3a) = 11.7 Hz, 1H, H_a-4); 1.95–2.10 (m, 1H, H_e-10); 4.22 (ddd, *J*(1e,10a) = 2.9 Hz, *J*(1e,6a) ≈ *J*(1e,10e) ≈ 2.7 Hz, 1H, H_e-1); 5.02 (ddd, *J*(3a,4a) = 11.7 Hz, *J*(3a,4e) = 2.7 Hz, *J*(3a,14) = 0.7 Hz, 1H, H_a-3); 6.92 (dd, *J*(13,12) = 4.9 Hz, *J*(13,14) = 3.5 Hz, 1H, H-13); 6.95 (ddd, *J*(14,13) = 3.5 Hz, *J*(14,12) = 1.3 Hz, *J*(14,3a) = 0.7 Hz, 1H, H-14); 7.19 (dd, *J*(12,13) = 4.9 Hz, *J*(12,14) = 1.3 Hz, 1H, H-12). ^{13}C NMR ($CDCl_3$): 71.63 (d, C-1); 71.54 (d, C-3); 42.85 (t, C-4); 71.44 (s, C-5); 46.12 (d, C-6); 23.69 (t, C-7); 34.50 (t, C-8); 25.93 (d, C-9); 40.01 (t, C-10); 146.67 (s, C-11); 124.09 (d, C-12); 126.24 (d, C-13); 123.20 (d, C-14); 28.78 (q, C-15); 22.16 (q, C-16). HR-MS: 266.1334 (M^+, $C_{15}H_{22}O_2S^+$; calc. 266.1335).

Biology

Animals

All studies were carried out on non-breeding albino mice (male) weighting 20–25 g, 8 animals in each group (SPF-vivarium of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences). Mice were maintained at 22–25 °C on a 12-h light–dark cycle with food and water available ad libitum. All work with animals was performed in strict accordance with the legislation of the Russian Federation, the regulations of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, and the requirements and recommendations of the Guide for the Care and Use of Laboratory Animals.

Analgesic tests

Agents were dissolved in saline containing 0.5 % Tween 80 just before use and were administered per os, 1 h before testing. Saline was administered per os in blank mice (control group), 1 h before testing. Analgesic activity of test agents was assessed using acetic acid-induced writhing test and hot plate test.

In the acetic acid-induced writhing test, the pain reaction was determined by the number of abdominal convulsions, recorded from the 5th to the 8th min following the acetic acid injection (0.75 %, 0.1 ml/mouse) (Koster *et al.*, 1959). The percentage of pain reaction inhibition was calculated according to the following equation: % inhibition = $100 \times (A - B)/A$, where *A* is the mean number of writhes in the control group, and *B* is the mean number of writhes in the test group.

In the hot plate test, animals were placed individually on a metallic plate warmed to 54 ± 0.5 °C, and the time until either licking of the hind paw or jumping occurred was recorded by a stopwatch (Eddy and Leimbach, 1953).

Acute toxicity

Acute toxicity studies were performed on non-breeding albino mice (male) weighting 20–25 g (6 animals in each group). The agent **3b** was dissolved in saline containing 0.5 % Tween 80 just before use and administered per os in doses of 500, 1000, 2500 and 4500 mg/kg. The toxicity was evaluated from the clinical picture of poisoning and survival of animals for 14 days (EPA, 2002).

Statistical data processing was carried out using a Statistica 6.0 program.

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