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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and analgesic activity of monoterpenoid-derived 2-aryl-4,4,7-trimethyl-4a,5,8,8a-tetrahydro-4*H*-benzo[*d*][1,3]dioxin-8-ols

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Abstract A new series of chiral heterocyclic compounds with frameworks of different types were synthesized by reactions of verbenol epoxide with aromatic aldehydes in the presence of montmorillonite clay. The analgesic activity of compounds with frameworks of 2-aryl-4,4,7-trimethyl-4a,5,8,8a-tetrahydro-4*H*-benzo[*d*][1,3]dioxin-8-ol type was studied in vivo. The majority of these compounds showed a significant analgesic activity in the acetic acid-induced writhing test; two compounds also showed analgesic activity in the hot-plate test. ED_{50} in acetic acid-induced writhing test for compound where aryl is 4-chlorophenyl substituent was determined to be 4.5 mg/kg. Compound with 4-nitrophenyl substituent demonstrated high analgesic activity in both tests.

Keywords Terpenoid · Heterocyclic compounds · Benzodioxine · Analgesic activity · Acetic acid-induced writhing test · Hot-plate test

Introduction

Pain is the most frequent cause of patient's recourse for medical assistance. The pain syndrome is the main reason for a decrease in the quality-of-life of patients with the majority of diseases and dominates in the clinical picture, while being the major symptom of the disease. Traditional analgesic and anti-inflammatory agents, such as opiates, steroids, and non-steroidal anti-inflammatory drugs all have serious side effects, particularly at high doses taken by chronic users (Melnikova, 2010; Kinsey *et al*., 2011). The development of highly effective, low-toxic analgesics thus remains a challenge in pharmacology and medicinal chemistry, stimulating studies in this direction (Kankala *et al*., 2013; Deep *et al*., 2012; Nigade *et al*., 2012; Ingale *et al*., 2012; Tolstikova *et al*., 2012).

Recently, we showed that several chiral heterocyclic compounds that formed in reactions of verbenol epoxide **1** with aromatic aldehydes containing three methoxy groups at different positions of the aromatic ring had a considerable analgesic activity (Mikhalchenko *et al*., 2013). Importantly, compounds of different structural types showed activity, due to which it seems promising to perform systematic studies of biological properties for each type of framework.

Earlier, it was shown that epoxide **1** reacted with aldehydes **2a–d** containing various substituents in the *para*-position of the aromatic ring in the presence of montmorillonite clay K10, giving compounds **3a–d** with a benzodioxin framework (Scheme 1) (Il'ina *et al*., 2010). These compounds that formed as a single stereoisomer are promising for studies of their biological activity including the analgesic activity.

The goal of this study was to synthesize heterocyclic compounds of Type **3** with a benzodioxin framework with various substituents in the aromatic ring and study their analgesic activity.

Chemistry

To synthesized new compounds with a benzodioxin framework, we performed the reaction of verbenol epoxide **1**

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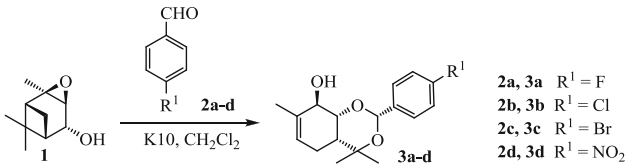


Scheme 1 The interaction of verbenol epoxide **1** with aldehydes **2a–d**

with aromatic aldehydes **2e–h** in the presence of clay K10 (Scheme 2). The choice of substituents (halogen atoms and CF_3 group) in aldehydes was dictated by the necessity of studying the structure–activity relationship and based on our knowledge of the effect of the nature of substituent in the aromatic ring on the structure of the intermolecular products formed in reactions with verbenol epoxide **1**. For example, it was shown that the introduction of oxygen-containing substituents in the aromatic ring of aldehyde led to the formation of compounds with a hexahydro-2*H*-chromene but not benzodioxin type of framework (Mikhalchenko *et al*., 2013; Il'ina *et al*., 2007, 2011).

The reactions were performed in dichloromethane at room temperature. The individual products were isolated by column chromatography on silica gel. The yields of intermolecular products are listed in Table 1. In addition to the products of the reactions of **1** with aldehydes, compounds **4–6**, which are the products of the isomerization of epoxide **1**, formed in all instances.

Earlier, it was shown that the main intermolecular products formed in the reaction of verbenol epoxide **1** with aromatic aldehydes **2a–c** containing a halogen atom in the *para*-position in the presence of clay K10 were products **3a–c** with a benzodioxin framework (Il'ina *et al*., 2010). The displacement of Cl and F atoms from *para*- to *meta*-position led to compounds with a hexahydro-2*H*-chromene framework as the main reaction products (**7e**, **g**). Compounds **3e**, **g** were obtained in minor quantities. When dichlorobenzaldehyde **2f** and 4-(trifluoromethyl)benzaldehyde **2h** were used, compounds **3** and **7** formed in a comparable ratio. The highest yield of intermolecular products was observed in the reaction with dichlorobenzaldehyde **2f**

Table 1 Yields of products in the reaction of (–)-*cis*-verbenol epoxide **1** with aldehydes **2e–h**

Aldehyde		Yields of intermolecular products[a] (%)		
		3	**7** (5*S*:5*R*)	**8**, **9**
2e	$R^1 = H$; $R^2 = Cl$	11	37 (60:40)	3
2f	$R^1 = R^2 = Cl$	29	30 (55:45)	–
2g	$R^1 = H$; $R^2 = F$	10	28 (60:40)	2
2h	$R^1 = CF_3$; $R^2 = H$	21	18 (50:50)	–

[a] The yields of isolated products calculated based on the consumed aldehyde **2**

(59 %). This is a good yield for reactions with such a labile compound as verbenol epoxide **1**.

Compounds **7** formed as a mixture of diastereomers at the C-5 carbon atom (Scheme 2) in comparable amounts.

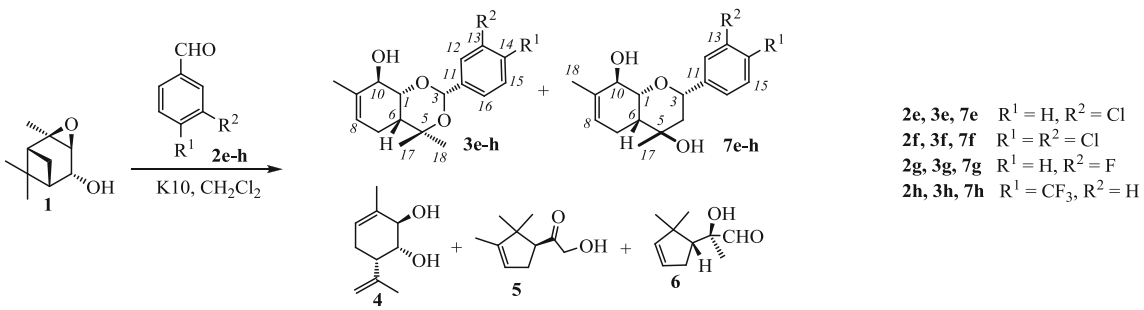
Using aldehydes **2e** and **2g** containing a chlorine and fluorine atom, respectively, at the *meta*-position led to the formation of small amounts of compounds **8e** and **8g**, which are the products of the addition of two aldehyde molecules to monoterpenoid **1**, and to compound **9** evidently formed as a result of dehydration in **7g** (Fig. 1).

Thus we obtained the desired set of chiral heterocyclic compounds **3a–h** with a benzodioxin framework, which allowed us to pass to studies of their biological activity.

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 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). Sodium diclofenac in the same dose was used as a reference drug.

According to the data of Table 2, among *para*-halogen-substituted compounds **3a–c**, compound **3b** containing a chlorine atom showed the highest analgesic activity in a



Scheme 2 The interaction of verbenol epoxide **1** with aldehydes **2e–h**

Fig. 1 Structures of compounds **8e**, **g**, and **9**

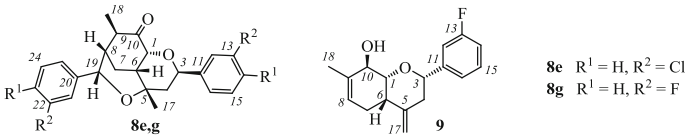


Table 2 Analgesic activity of compounds **3a–h**, **7e** and sodium diclofenac in the acetic acid-induced writhing test (10 mg/kg dose)

Compound	Substituents	Mean ± SD	Saline	Pain inhibition (%)
3a	$R^1 = F$; $R^2 = H$	5.5 ± 1.1	9.1 ± 0.7	40*
3b	$R^1 = Cl$; $R^2 = H$	1.0 ± 0.1	8.4 ± 0.8	88#
3c	$R^1 = Br$; $R^2 = H$	5.6 ± 0.8	8.4 ± 0.8	33
3d	$R^1 = NO_2$; $R^2 = H$	2.9 ± 1.2	8.4 ± 0.8	65#
3e	$R^1 = H$; $R^2 = Cl$	9.6 ± 0.3	13.2 ± 0.6	27*
3f	$R^1 = R^2 = Cl$	11.4 ± 0.7	13.2 ± 0.6	14
3g	$R^1 = H$; $R^2 = F$	6.8 ± 1.0	11.3 ± 0.5	40*
3h	$R^1 = CF_3$; $R^2 = H$	6.3 ± 1.1	13.2 ± 0.6	52#
7e	$R^1 = H$; $R^2 = Cl$	8.4 ± 0.7	11.3 ± 0.5	26*
Diclofenac sodium		0.8 ± 0.4	8.4 ± 0.8	90#

% Of pain inhibition = $(t_{exp} - t_{saline})/t_{saline} \times 100$ %

* $P < 0.01$; # $P < 0.001$ in comparison with saline

dose of 10 mg/kg in the acetic acid-induced writhing test. In this test, compound **3b** was almost equal to the sodium diclofenac reference. A displacement of the chlorine atom to the *meta*-position on passing to compound **3e** led to considerable decrease in the analgesic effect, and dichloro derivative **3f** did not show any reliable degree of analgesic activity at all. At the same time, the position of the fluorine atom (**3a** and **3g**) did not affect the analgesic activity of these compounds which are both effective. Using bromo derivative **3c** did not reveal any reliable analgesic effect. According to (Tolstikova *et al*., 2011), LD_{50} exceeds 1,000 mg/kg for **3a** and is 350 mg/kg for sodium diclofenac (Syubaev *et al*., 1986).

Compound **3d** containing a nitro group showed a pronounced analgesic effect, while its analog **3h** with a CF_3 group was slightly less effective.

For **3b**, which showed the highest analgesic activity in the acetic acid-induced writhing test, ED_{50} (the ''median effective dose'' is a dose that produces 50 % protection) was determined to be 4.5 mg/kg. For comparison, ED_{50} was 5 mg/kg for sodium diclofenac and 155 mg/kg for aspirin in this test (Syubaev *et al*., 1986). Note that, an appreciable analgesic activity in compounds of this structural type was found for the first time.

In the hot plate test, reliable analgesic activity was found in compounds **3d** and **3e** in a dose of 10 mg/kg (Table 3). Compound **3d** containing a nitro group exhibited more pronounced analgesic activity than the sodium diclofenac reference. It had a considerable analgesic activity in both the acetic acid-induced writhing and hot plate tests. Compound **3e** showed less pronounced activity.

We also studied the analgesic activity of the compound **7e** with a hexahydro-2*H*-chromene framework, which formed in the highest yield among compounds of this structural type. In the acetic acid-induced writhing test, compound **7e** was equal to **3e** having a benzodioxin framework in efficiency (Table 2), but proved inactive in the hot plate test (in contrast to **3e**) (Table 3).

Table 3 Analgesic activity of compounds **3a–h** and sodium diclofenac in the hot plate test (10 mg/kg dose)

Compound	Substituents	Mean ± SD	Saline	Protection (%)
3a	$R^1 = F$; $R^2 = H$	19.5 ± 2.1	19.3 ± 3.8	0
3b	$R^1 = Cl$; $R^2 = H$	22.0 ± 2.6	20.4 ± 2.2	8
3c	$R^1 = Br$; $R^2 = H$	27.2 ± 1.2	20.4 ± 2.2	33
3d	$R^1 = NO_2$; $R^2 = H$	37.5 ± 4.1	20.4 ± 2.2	84#
3e	$R^1 = H$; $R^2 = Cl$	17.5 ± 1.4	12.9 ± 1.0	36*
3f	$R^1 = R^2 = Cl$	17.6 ± 2.6	12.9 ± 1.0	36
3g	$R^1 = H$; $R^2 = F$	16.3 ± 1.6	16.4 ± 1.6	0
3h	$R^1 = CF_3$; $R^2 = H$	16.8 ± 1.7	12.9 ± 1.0	30
7e	$R^1 = H$; $R^2 = Cl$	19.0 ± 1.9	16.4 ± 1.6	14
Diclofenac sodium		33.4 ± 2.3	20.4 ± 2.2	64*

* $P < 0.01$; # $P < 0.001$ in comparison with saline

Conclusion

The reactions of verbenol epoxide **1** with aromatic aldehydes containing a halogen atom or a CF_3 group in the presence of clay K10 gave a set of new chiral heterocyclic compounds **3**, **7**–**9** with frameworks of different types. The structure and position of substituents in the aromatic ring produced a considerable effect on the yield and distribution of heterocyclic products.

For compounds **3e**–**h** with a benzodioxin framework and previously prepared compounds **3a**–**d**, the analgesic activity was studied on models in the acetic acid-induced writhing test and hot plate test.

The majority of the compounds under study exhibited pronounced analgesic activity in the acetic acid-induced writhing test in a dose of 10 mg/kg. Compound **3b** containing a chlorine atom in the *para*-position of the aromatic ring showed the highest pain inhibition characteristics. The ED_{50} of this compound was 4.5 mg/kg.

In the hot plate test, **3d** and **3e** showed the analgesic activity; compound **3d** was more effective that the sodium diclofenac taken in the same dose. Only compound **3d** showed considerable analgesic activity in both tests.

Thus we have found analgesics **3b** and **3d** of a new structural type, which are very promising for further studies.

Experimental

Chemistry

General

All the chemicals reagents were of commercial grade. As catalyst, we used K10 clay (*Fluka*). The clay was calcinated at 110 °C for 3 h immediately before use. CH_2Cl_2 was passed through calcined alumina. (**–**)-*cis*-Verbenol epoxide (**1**) ($[\alpha]_{580}^{20} = -60$ ($c = 0.41$, $CHCl_3$)) was synthesized according to (Il'ina *et al.*, 2007) from (**–**)-verbenone (*Aldrich*), the content of the main substance was not less than 98.0 %. All product yields are given for pure compounds isolated by column chromatography. Column chromatography: silica gel (SiO_2; 60–200 μ; Macherey–Nagel), 15 g per 1 g of reaction mixture; eluent hexane/EtOAc 100/0 → 0/100, acetone. GC/MS (purity control and products analysis): *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, $CHCl_3$ or MeOH soln., conc. g/100 ml. HR-MS: *DFS-Thermo-Scientific* spectrometer in a full scan mode (15–500 *m/z*, 70 eV electron-impact ionization, direct sample introduction). ^{1}H- and ^{13}C-NMR: *Bruker DRX-500* apparatus at 500.13 MHz (^{1}H) and 125.76 MHz (^{13}C) in $CDCl_3$ or $CDCl_3$ + CD_3OD (10:1, v/v); chemical shifts in ppm relative to residual $CHCl_3$ ((H) 7.24, (C) 76.90 ppm), *J* in Hz; structure determinations by analyzing the ^{1}H NMR spectra, including ^{1}H–^{1}H double resonance spectra and ^{1}H–^{1}H 2D homonuclear correlation, *J*-modulated ^{13}C-NMR spectra (JMOD), and ^{13}C–^{1}H 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).

General procedure for synthesis of (2S,4aR,8R,8aR)-2-(3-Aryl)-4,4,7-trimethyl-4a,5,8,8a-tetrahydro-4H-benzo[d][1,3]dioxin-8-ols

An appropriate aldehyde (4.2 μmol) was added to a suspension of clay K10 (4 g) in CH_2Cl_2 (25 ml). A solution of epoxide **1** (0.700 g, 4.2 μmol) in CH_2Cl_2 (10 ml) was added dropwise with stirring and the reaction mixture was stirred for 1.5 h at r.t. (20–25 °C). Then mixture of ethyl acetate (20 ml) and acetone (20 ml) was added. The catalyst was filtered off, the solvent was distilled off, and the residue was separated on a SiO_2 column. The yields of the intermolecular products were calculated based on the consumed aldehyde.

*With 3-chlorobenzaldehyde **2e*** The following compounds were isolated: unreacted aldehyde **2e** (0.270 g, conversion 54 %); intermolecular reaction products **3e** (0.073 g, 11 %), **7e** (*S*:*R* = 60:40) (0.253 g, 37 %) and **8e** (0.260 g, 15 %); and isomerization products (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol **4** (0.129 g, 18 %), (*S*)-2-hydroxy-1-(2,2,3-trimethylcyclopent-3-enyl)ethanone **5** (0.066 g, 9 %), and (*R*)-2-((*R*)-2,2-dimethylcyclopent-3-enyl)-2-hydroxypropanal **6** (0.010 g, 1 %). The spectral data of **4**, **5**, and **6** coincided with those reported in the literature (Il'ina *et al.*, 2007, 2012; Ardashov *et al.*, 2007).

*(2S,4aR,8R,8aR)-2-(3-Chlorophenyl)-4,4,7-trimethyl-4a,5,8,8a-tetrahydro-4H-benzo[d][1,3]dioxin-8-ol **3e*** ^{1}H NMR ($CDCl_3$): 1.26 (s, 3H, H-18); 1.51 (s, 3H, H-17); 1.53 (ddd, J(6a,7a) = 10.8 Hz, J(6a,7e) = 6.0 Hz, J(6a,1e) = 2.0 Hz, 1H, H_a-6); 1.80 (ddd, J(19,7a) = 2.5 Hz, J(19,7e) = 1.5 Hz, J(19,8) = 1.5 Hz, 3H, H-19); 2.07 (dddq, J(7e,7a) = 17.8 Hz, J(7e,6a) = 6.0 Hz, J(7e,8) = 5.3 Hz, J(7e,19) = 1.5 Hz, 1H, H_e-7); 2.42 (dddqd, J(7a,7e) = 17.8 Hz, J(7a,6a) = 10.8 Hz, J(7a,8) = 2.5 Hz, J(7a,19) = 2.5 Hz, J(7a,10e) = 1.2 Hz, 1H, H_a-7); 3.88 (br.s, 1H, H_e-10); 4.34 (dd, J(1e,10e) = 2.3 Hz, J(1e,6a) = 2.0 Hz, 1H, H_e-1); 5.65 (dm, J(8,7e) = 5.3 Hz,

another $J \leq 2.5$ Hz, 1H, H-8); 5.75 (s, 1H, H-3); 7.23–7.28 (m, 2H, H-14, H-15); 7.31 (ddd, $J(16,15) = 6.7$ Hz, $J(16,14) = 2.1$ Hz, $J(16,12) = 1.8$ Hz, 1H, H-16); 7.45 (dd, $J(12,14) = 2.1$ Hz, $J(12,16) = 1.8$ Hz, 1H, H-12). ^{13}C-NMR ($CDCl_3$): 75.16 (d, C-1); 95.06 (d, C-3); 74.84 (s, C-5); 34.00 (d, C-6); 22.95 (t, C-7); 125.40 (d, C-8); 130.71 (s, C-9); 70.43 (d, C-10); 140.74 (s, C-11); 126.58 (d, C-12); 134.08 (s, C-13); 128.80 (d, C-14); 129.44 (d, C-15); 124.60 (d, C-16); 22.66 (q, C-17); 27.14 (q, C-18); 20.49 (q, C-19). $[\alpha]_D^{25} = -115.0$ ($c = 0.67$, MeOH); HR-MS: 308.1169 (M^+, $C_{17}H_{21}ClO_3^+$; calc. 308.1174).

*(2S,4S,4aR,8R,8aR)-2-(3-Chlorophenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2H-chromene-4,8-diol ((S)-**7e**)* ^{1}H NMR ($CDCl_3$): 1.51 (s, 3H, H-17); 1.67 (ddd, $J(4e,4a) = 13.4$ Hz, $J(4e,3a) = 2.7$ Hz, $J(4e,6) = 1.1$ Hz; 1H, H_e-4); 1.77–1.85 (m, 1H, H_a-6); 1.81 (m, all $J \leq 2.5$ Hz, 3H, H-18); 1.83 (dd, $J(4a,4e) = 13.4$ Hz, $J(4a,3a) = 12.0$ Hz, 1H, H_a-4); 2.12–2.18 (m, 2H, H-7); 3.79 (dd, $J(1e,10e) = 2.4$ Hz, $J(1e,6a) = 2.2$ Hz, 1H, H_e-1); 3.90 (br.s, 1H, H_e-10); 4.39 (dd, $J(3a,4a) = 12.0$ Hz, $J(3a,4e) = 2.7$ Hz, 1H, H_a-3); 5.63-5.66 (m, 1H, H-8); 7.15 (ddd, $J(16,15) = 6.7$ Hz, $J(16,14) = 2.2$ Hz, $J(16,12) = 1.8$ Hz, 1H, H-16); 7.17–7.22 (m, 2H, H-14, H-15); 7.27–7.30 (m, 1H, H-12). ^{13}C-NMR ($CDCl_3$): 77.67 (d, C-1); 76.80 (d, C-3); 43.08 (t, C-4); 70.97 (s, C-5); 38.25 (d, C-6); 22.61 (t, C-7); 124.55 (d, C-8); 131.34 (s, C-9); 70.45 (d, C-10); 143.90 (s, C-11); 125.91 (d, C-12); 134.14 (s, C-13); 127.57 (d, C-14); 129.53 (d, C-15); 123.83 (d, C-16); 26.96 (q, C-17); 20.67 (q, C-18). HR-MS: 308.1171 (M^+, $C_{17}H_{21}ClO_3^+$; calc. 308.1174).

*(2S,4R,4aR,8R,8aR)-2-(3-Chlorophenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2H-chromene-4,8-diol ((R)-**7e**)* ^{1}H NMR ($CDCl_3$): 1.22 (s, 3H, H-17); 1.63 (ddd, $J(4e,4a) = 14.2$ Hz, $J(4e,3a) = 3.5$ Hz, $J(4e,6) = 1.3$ Hz, 1H, H_e-4); 1.66–1.72 (m, 2H, H_a-4, H_a-6); 1.81 (m, all $J \leq 2.5$ Hz, 3H, H-18); 1.95–2.02 (m, 2H, H-7); 3.92 (br.s, 1H, H_e-10); 4.23 (dd, $J(1e,10e) = 2.3$ Hz, $J(1e,6a) = 2.1$ Hz, 1H, H_e-1); 4.75 (dd, $J(3a,4a) = 11.0$ Hz, $J((3a,4e) = 3.5$ Hz, 1H, H_a-3); 5.56–5.60 (m, 1H, H-8); 7.15 (ddd, $J(16,15) = 6.7$ Hz, $J(16,14) = 2.2$ Hz, $J(16,12) = 1.8$ Hz, 1H, H-16); 7.17–7.24 (m, 2H, H-14, H-15); 7.27–7.30 (m, 1H, H-12). ^{13}C-NMR ($CDCl_3$): 75.16 (d, C-1); 75.09 (d, C-3); 42.00 (t, C-4); 70.71 (s, C-5); 37.99 (d, C-6); 24.48 (t, C-7); 123.94 (d, C-8); 131.80 (s, C-9); 70.45 (d, C-10); 144.65 (s, C-11); 125.85 (d, C-12); 134.09 (s, C-13); 127.31 (d, C-14); 129.45 (d, C-15); 123.88 (d, C-16); 28.27 (q, C-17); 20.77 (q, C-18).

*(2R,4S,4aR,6S,7R,8aR,9S)-2,9-Bis(3-Chlorophenyl)-4,7-dimethyl hexahydro-2H-4,6-(epoxymethano)chromen-8(5H)-one **8e*** ^{1}H NMR ($CDCl_3$): 1.12 (d, $J(18,9) = 7.5$ Hz, 3H, H-18); 1.48 (s, 3H, H-17); 1.95 (dd, $J(4e,4a) = 14.9$ Hz, $J(4e,3a) = 2.6$ Hz, 1H, H_e-4); 1.94–1.97 (m, all $J \leq 3.5$ Hz, 1H, H_e-8); 2.19 (dd, $J(4a,4e) = 14.9$ Hz, $J(4a,3a) = 13.2$ Hz, 1H, H_a-4); 2.39–2.42 (m; 2H, H-7); 2.43 (br.q, $J(9e,18) = 7.5$ Hz, 1H, H_e-9); 2.57–2.61 (m, all $J \leq 5.2$ Hz, 1H, H_e-6); 4.54 (d, $J(1a,6e) = 5.2$ Hz, 1H, H_a-1); 4.75 (dd, $J(3a,4a) = 13.2$ Hz, $J(3a,4e) = 2.6$ Hz, 1H, H_a-3); 4.79 (br.s, 1H, H-19); 7.15 (br. d, $J(25,24) = 7.6$ Hz, 1H, H-25); 7.18–7.28 (m, 4H, H-14, H-21, H-23, H-24); 7.29 (t, $J(15,14(16)) = 7.6$ Hz, 1H, H-15); 7.52 (ddd, $J(16,15) = 7.6$ Hz, $J(16,14) \approx 1.5$ Hz, $J(16,12) \approx 1.5$ Hz, 1H, H-16); 7.58 (dd, $J(12,14) = 2.0$ Hz, $J(12,16) \approx 1.5$ Hz, 1H, H-12). ^{13}C-NMR ($CDCl_3$): 76.32 (d, C-1); 71.63 (d, C-3); 48.13 (t, C-4); 73.13 (s, C-5); 39.01 (d, C-6); 24.40 (t, C-7); 43.30 (d, C-8); 42.60 (d, C-9); 211.43 (s, C-10); 144.01 (s, C-11); 126.72 (d, C-12); 134.13 (s, C-13); 127.88 (d, C-14); 129.67 (d, C-15); 124.75 (d, C-16); 23.16 (q, C-17); 17.70 (q, C-18); 74.97 (d, C-19); 142.25 (s, C-20); 125.81 (d, C-21); 134.07 (s, C-22); 127.28 (d, C-23); 129.50 (d, C-24); 123.93 (d, C-25). $[\alpha]_D^{25} = -56.7$ ($c = 0.53$, MeOH); HR-MS: 430.1091 (M+, $C_{24H24}Cl_2O_3^+$; calc. 430.1097).

*With 3,4-dichlorobenzaldehyde **2f*** The following compounds were isolated: unreacted aldehyde **2f** (0.433 g, conversion 41 %); intermolecular reaction products **3f** (0.169 g, 29 %) and **7f** (S:R = 55:45) (0.180 g, 30 %); and isomerization products **4** (0.079 g, 11 %), **5** (0.124 g, 18 %), and **6** (0.049 g, 7 %).

*(2S,4aR,8R,8aR)-2-(3,4-Dichlorophenyl)-4,4,7-trimethyl-4a,5,8,8a-tetrahydro-4H-benzo[d][1,3]dioxin-8-ol **3f*** ^{1}H NMR ($CDCl_3$): 1.25 (s, 3H, H-18); 1.50 (s, 3H, H-17); 1.52 (ddd, $J(6a,7a) = 10.8$ Hz, $J(6a,7e) = 6.2$ Hz, $J(6a,1e) = 2.1$ Hz, 1H, H_a-6); 1.80 (br.s, 3H, H-19); 2.06 (dddq, $J(7e,7a) = 17.7$ Hz, $J(7e,6a) = 6.2$ Hz, $J(7e,8) = 5.3$ Hz, $J(7e,19) = 1.5$ Hz, 1H, H_e-7); 2.38 (dddqd, $J(7a,7e) = 17.7$ Hz, $J(7a,6a) = 10.8$ Hz, $J(7a,8) = 2.5$ Hz, $J(7a,19) = 2.5$ Hz, $J(7a,10e) = 1.3$ Hz, 1H, H_a-7); 3.86 (br.s, 1H, H_e-10); 4.32 (dd, $J(1e,10e) = 2.4$ Hz, $J(1e,6a) = 2.1$ Hz, 1H, H_e-1); 5.63 (ddq, $J(8,7e) = 5.3$ Hz, $J(8,7a) = 2.5$ Hz, $J(8,19) = 1.5$ Hz, 1H, H-8); 5.72 (s, 1H, H-3); 7.26 (dd, $J(16,15) = 8.2$ Hz, $J(16,12) = 1.8$ Hz, 1H, H-16); 7.38 (d, $J(15,16) = 8.2$ Hz, 1H, H-15); 7.53 (d, $J(12,16) = 1.8$ Hz, 1H, H-12). ^{13}C-NMR ($CDCl_3$): 75.15 (d, C-1); 94.33 (d, C-3); 74.96 (s, C-5); 33.94 (d, C-6); 22.90 (t, C-7); 125.28 (d, C-8); 130.69 (s, C-9); 70.34 (d, C-10), 139.00 (s, C-11); 128.45 (d, C-12); 132.23 and 132.56 (2 s, C-13, C-14); 130.07 (d, C-15); 125.74 (d, C-16); 22.62 (q, C-17); 27.07 (q, C-18); 20.46 (q, C-19). $[\alpha]_D^{25} = -101.5$ ($c = 0.40$, MeOH); HR-MS: 342.0782 (M^+, $C_{17}H_{20}Cl_2O_3^+$; calc. 342.0784).

(2S,4S,4aR,8R,8aR)-2-(3,4-Dichlorophenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2H-chromene-4,8-diol ((S)-

7f) ^{1}H NMR ($CDCl_3$ + CD_3OD): 1.51 (s, 3H, H-17); 1.63–1.68 (m, 1H, H_e-4); 1.82 (br.s, 3H, H-18); 1.80–1.89 (m, 2H, H_a-4, H_a-6); 2.11–2.18 (m, 2H, H-7); 3.80 (dd, J(1e,10e) = 2.3 Hz, J(1e,6a) = 2.1 Hz, 1H, H_e-1); 3.85 (br.s, 1H, H_e-10); 4.43 (dd, J(3a,4a) = 12.0 Hz, J(3a,4e) = 2.7 Hz, 1H, H_a-3); 5.63–5.67 (m, 1H, H-8); 7.16 (dd, J(16,15) = 8.2 Hz, J(16,12) = 2.0 Hz, 1H, H-16); 7.39 (d, J(15,16) = 8.2 Hz, 1H, H-15); 7.42 (d, J(12,16) = 2.0 Hz, 1H, H-12). ^{13}C-NMR ($CDCl_3$ + CD_3OD): 77.71 (d, C-1); 75.72 (d, C-3); 41.95 (t, C-4); 69.84 (s, C-5); 37.77 (d, C-6); 22.21 (t, C-7); 123.80 (d, C-8); 130.78 (s, C-9); 69.57 (d, C-10); 142.25 (s, C-11); 127.33 (d, C-12); 130.35 and 131.73 (2 s, C-13, C-14); 129.70 (d, C-15); 124.77 (d, C-16); 25.87 (q, C-17); 19.91 (q, C-18). HR-MS: 342.0788 (M^+, $C_{17}H_{20}Cl_2O_3^+$; calc. 342.0784).

*(2S,4R,4aR,8R,8aR)-2-(3,4-Dichlorophenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2H-chromene-4,8-diol ((R)-**7f**)* ^{1}H NMR ($CDCl_3$): 1.23 (s, 3H, H-17); 1.59–1.67 (m, 2H, H-4), 1.70 (ddd, J(6a,7a) = 10.8 Hz, J(6a,7e) = 6.2 Hz, J(6a,1e) = 2.1 Hz, 1H, H_a-6); 1.82 (br.s, 3H, H-18); 1.88–1.98 (m, 2H, H-7); 3.91 (br.s, 1H, H_e-10); 4.23 (dd, J(1e,10e) = 2.3 Hz, J(1e,6a) = 2.1 Hz, 1H, H_e-1); 4.74 (dd, J(3a,4a) = 9.4 Hz, J(3a,4e) = 5.0 Hz, 1H, H_a-3); 5.57–5.60 (m, 1H, H-8); 7.10 (dd, J(16,15) = 8.2 Hz, J(16,12) = 2.0 Hz, 1H, H-16); 7.34 (d, J(15,16) = 8.2 Hz, 1H, H-15); 7.38 (d, J(12,16) = 2.0 Hz, 1H, H-12). ^{13}C-NMR ($CDCl_3$): 75.21 (d, C-1); 74.51 (d, C-3); 41.89 (t, C-4); 70.70 (s, C-5); 38.02 (d, C-6); 24.49 (t, C-7); 123.91 (d, C-8); 131.85 (s, C-9); 70.43 (d, C-10); 142.89 (s, C-11); 127.74 (d, C-12); 130.99 and 132.27 (2 s, C-13, C-14); 130.12 (d, C-15); 125.10 (d, C-16); 28.30 (q, C-17); 20.77 (q, C-18).

*With 3-fluorobenzaldehyde **2g*** The following compounds were isolated: unreacted aldehyde **2g** (0.145 g, conversion 72 %); intermolecular reaction products **3g** (0.085 g, 10 %), **7g** (*S*:*R* = 60:40) (0.247 g, 28 %), **8g** (0.007 g, 0.5 %), and **9** (0.012 g, 1.5 %); and isomerization products **4** (0.062 g, 9 %), **5** (0.069 g, 10 %), and **6** (0.012 g, 2 %).

*2S,4aR,8R,8aR)-2-(3-Fluorophenyl)-4,4,7-trimethyl-4a,5,8,8a-tetrahydro-4H-benzo[d][1,3]dioxin-8-ol **3g*** (^{1}H NMR ($CDCl_3$): 1.25 (s, 3H, H-18); 1.51 (s, 3H, H-17); 1.53 (ddd, J(6a,7a) = 10.8 Hz, J(6a,7e) = 6.1 Hz, J(6a,1e) = 2.0 Hz, 1H, H_a-6); 1.79 (m, all $J \leq 2.5$ Hz, 3H, H-19); 2.06 (dddq, J(7e,7a) = 17.7 Hz, J(7e,6a) = 6.1 Hz, J(7e,8) = 5.3 Hz, J(7e,19) = 1.5 Hz, 1H, H_e-7); 2.38–2.47 (m, 1H, H_a-7); 3.87 (br.s, 1H, H_e-10); 4.34 (dd, J(1e,10e) = 2.3 Hz, J(1e,6a) = 2.0 Hz, 1H, H_e-1); 5.64 (dm, J(8,7e) = 5.3 Hz, 1H, H-8); 5.77 (s, 1H, H-3); 6.97 (dddd, J(14,15) = 8.2 Hz, J(14,F) = 8.2 Hz, J(14,16) = 2.5 Hz, J(14,12) = 1.6 Hz, 1H, H-14); 7.17 (ddd, J(12,F) = 9.6 Hz, J(12,14) = 2.5 Hz, J(12,16) = 1.8 Hz, 1H, H-12); 7.21 (br.d, J(16,15) = 7.7 Hz, 1H, H-16); 7.25–7.30 (m, 1H, H-15). ^{13}C-NMR ($CDCl_3$): 75.12 (d, C-1); 95.00 (^4J(C,F) = 2.2 Hz, C-3); 74.77 (s, C-5); 33.98 (d, C-6); 22.93 (t, C-7); 125.31 (d, C-8); 130.71 (s, C-9); 70.39 (d, C-10); 141.28 (^3J(C,F) = 7.1 Hz, C-11); 113.37 (^2J(C,F) = 22.1 Hz, C-12); 162.66 (^1J(C,F) = 245.5 Hz, C-13); 115.52 (^2J(C,F) = 21.2 Hz, C-14); 129.66 (^3J(C,F) = 8.4 Hz, C-15); 122.01 (^4J(C,F) = 3.1 Hz, C-16); 22.64 (q, C-17); 27.12 (q, C-18); 20.47 (q, C-19). $[\alpha]_D^{24} = -90.8$ (c = 0.83, MeOH); HR-MS: 292.1462 (M^+, $C_{17}H_{21}FO_3^+$; calc. 292.1469).

*(2S,4S,4aR,8R,8aR)-2-(3-Fluorophenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2H-chromene-4,8-diol ((S)-**7g**)* ^{1}H NMR ($CDCl_3$): 1.52 (s, 3H, H-17); 1.69 (ddd, J(4e,4a) = 13.4 Hz, J(4e,3a) = 2.8 Hz, J(4e,6a) = 1.1 Hz, 1H, H_e-4); 1.79–1.88 (m, 2H, H_a-4, H_a-6); 1.82 (br.s, 3H, H-18); 2.12–2.19 (m, 2H, H-7); 3.81 (dd, J(1e,10e) = 2.3 Hz, J(1e,6a) = 2.1 Hz, 1H, H_e-1); 3.92 (br.s, 1H, H_e-10); 4.42 (dd, J(3a,4a) = 12.0 Hz, J(3a,4e) = 2.8 Hz, 1H, H_a-3); 5.63-5.67 (m, 1H, H-8); 6.91 (dddd, J(14, 15) = 8.0 Hz, J(14,F) = 8.0 Hz, J(14,16) = 2.5 Hz, J(14,12) = 1.5 Hz, 1H, H-14); 7.00–7.06 (m, 2H, H-12, H-16); 7.25 (ddd, J(15,14) = 8.0 Hz, J(15,16) = 8.0 Hz, J(15,F) = 5.6 Hz, 1H, H-15). ^{13}C-NMR ($CDCl_3$): 77.52 (d, C-1); 76.75 (^4J(C,F) = 1.8 Hz, C-3); 43.06 (t, C-4); 71.01 (s, C-5); 38.19 (d, C-6); 22.60 (t, C-7); 124.56 (d, C-8); 131.31 (s, C-9); 70.42 (d, C-10); 144.42 (^3J(C,F) = 7.1 Hz, C-11); 112.69 (^2J(C,F) = 22.1 Hz, C-12); 162.73 (^1J(C,F) = 245.9 Hz, C-13); 114.28 (^2J(C,F) = 21.2 Hz, C-14); 129.76 (^3J(C,F) = 8.4 Hz, C-15); 121.21 (^4J(C,F) = 3.0 Hz, C-16); 26.96 (q, C-17); 20.70 (q, C-18). HR-MS: 292.1467 (M^+, $C_{17}H_{21}FO_3^+$; calc. 292.1469).

*(2S,4R,4aR,8R,8aR)-2-(3-Fluorophenyl)-4,7-dimethyl-3,4,4a,5,8,8a-hexahydro-2H-chromene-4,8-diol ((R)-**7g**)* ^{1}H NMR ($CDCl_3$): 1.23 (s, 3H, H-17); 1.61-1.73 (m, 3H, 2H-4, H_a-6); 1.82 (br.s, 3H, H-18); 1.95–2.05 (m, 2H, H-7); 3.93 (br.s, 1H, H_e-10); 4.24 (dd, J(1e,10e) = 2.4 Hz, J(1e,6a) = 2.1 Hz, 1H, H_e-1); 4.78 (dd, J(3a,4a) = 11.0 Hz, J(3a,4e) = 3.5 Hz, 1H, H_a-3); 5.57–5.60 (m, 1H, H-8); 6.89 (dddd, J(14,15) = 8.0 Hz, J(14,F) = 8.0 Hz, J(14,16) = 2.5 Hz, J(14,12) = 1.5 Hz, 1H, H-14); 7.00–7.06 (m, 2H, H-12, H-16); 7.25 (ddd, J(15,14) = 8.0 Hz, J(15,16) = 8.0 Hz, J(15,F) = 5.6 Hz, 1H, H-15). ^{13}C-NMR ($CDCl_3$): 75.02 (d, C-1); 75.05 (^4J(C,F) = 1.8 Hz, C-3); 42.00 (t, C-4); 70.75 (s, C-5); 37.96 (d, C-6); 24.49 (t, C-7); 123.95 (d, C-8); 131.76 (s, C-9); 70.42 (d, C-10); 145.19 (^3J(C,F) = 7.1 Hz, C-11); 112.63 (^2J(C,F) = 22.1 Hz, C-12); 162.74 (^1J(C,F) = 245.0 Hz, C-13); 114.00 (^2J(C,F) = 21.2 Hz, C-14); 129.67 (^3J(C,F) = 8.4 Hz,

C-15); 121.22 (^4J(C,F) = 3.0 Hz, C-16); 28.30 (q, C-17); 20.80 (q, C-18).

(2R,4S,4aR,6S,7R,8aR,9S)-2,9-Bis(3-fluorophenyl)-4,7-dimethylhexahydro-2H-4,6-(epoxymethano)chromen-8(5H)-one ***8g*** ^{1}H NMR ($CDCl_3$): 1.12 (d, J(18,9) = 7.6 Hz, 3H, H-18); 1.48 (s, 3H, H-17); 1.94–1.97 (m, all $J \leq 3.5$ Hz, 1H, H_e-8); 1.97 (dd, J(4e,4a) = 14.9 Hz, J(4e,3a) = 2.6 Hz, 1H, H_e-4); 2.20 (dd, J(4a,4e) = 14.9 Hz, J(4a,3a) = 13.2 Hz, 1H, H_a-4); 2.40–2.47 (m, 3H, H-7, H_e-9); 2.59 (dm, J(6e,1a) = 5.2 Hz, another $J \leq 3.5$ Hz, 1H, H_e-6); 4.55 (d, J(1a,6e) = 5.2 Hz, 1H, H_a-1); 4.77 (dd, J(3a,4a) = 13.2 Hz, J(3a,4e) = 2.6 Hz, 1H, H_a-3); 4.81 (br.s, 1H, H-19); 6.89–6.99 (m, 3H, H-14, H-23; H-12 or H-21); 7.02 (br.d, J(H,H) = 7.7 Hz, 1H, H-16 or H-25); 7.35 (br.d, J(H,H) = 7.7 Hz, 1H, H-25 or H-16); 7.25–7.33 (m, 2H, H-15, H-24); 7.37 (ddd, J(H,F) = 9.8 Hz, J(H,H) = 2.6 Hz, J(H,H) = 1.8 Hz, 1H, H-21 or H-12). ^{13}C-NMR ($CDCl_3$): 76.28 (d, C-1); 71,61 (^4J(C,F) = 2.0 Hz, C-3); 48.19 (d, C-4); 73.05 (s, C-5); 39.04 (d, C-6); 24.34 (t, C-7); 43.34 (d, C-8); 42.63 (d, C-9); 211.51 (s, C-10); 144.59 (^3J(C,F) = 7.1 Hz, C-11); 112.83 (^2J(C,F) = 22.1 Hz), 113.57 (^2J(C,F) = 22.1 Hz), 113.94 (^2J(C,F) = 21.2 Hz) and 114.55 (^2J(C,F) = 21.2 Hz)–C-12, C-14, C-21 and C-23; 162.74 (^1J(C,F) = 245.5 Hz) and 162.79 (^1J(C,F) = 245.5 Hz)–C-13 and C-22; 129.75 (^3J(C,F) = 8.4 Hz, C-15, C-24); 122.01 (^4J(C,F) = 3.1 Hz) and 121.16 (^4J(C,F) = 3.1 Hz)–C-16 and C-25; 23.15 (q, C-17); 17.68 (q, C-18), 74.92 (^4J(C,F) = 2.0 Hz, C-19); 142.83 (^3J(C,F) = 7.1 Hz, C-20). HR-MS: 398.1684 (M^+, $C_{24H24}F_2O_3^+$; calc. 398.1688).

(2S,4aS,8R,8aR)-2-(3-Fluorophenyl)-7-methyl-4-methylene-3,4,4a,5,8,8a-hexahydro-2H-chromen-8-ol ***9*** ^{1}H NMR ($CDCl_3$): 1.83 (br.s, 3H, H-18); 1.96 (dddq, J(7e,7a) = 17.8 Hz, J(7e,6a) = 6.5 Hz, J(7e,8) = 5.2 Hz, J(7e,18) = 1.5 Hz, 1H, H_e-7); 2.27–2.35 (m, 1H, H_a-7); 2.33 (dd, J(4e,4a) = 14.1 Hz, J(4e,3a) = 3.0 Hz, 1H, H_e-4); 2.44 (ddt, J(4a,4e) = 14.1 Hz, J(4a,3a) = 11.5 Hz, J(4a,17) = 2.0 Hz, 1H, H_a-4); 2.54 (ddd, J(6a,7a) = 10.8 Hz, J(6a,7e) = 6.5 Hz, J(6a,1e) = 2.2 Hz, 1H, H_a-6); 3.73 dd, J(1e,10e) = 2.4 Hz, J(1e,6a) = 2.2 Hz, 1H, H_e-1); 3.92 (br.s, 1H, H_e-10); 4.38 (dd, J(3a,4a) = 11.5 Hz, J(3a,4e) = 3.0 Hz, 1H, H_a-3); 4.82 (dd, J(17,17′) = 2.3 Hz, J(17,4a) = 2.0 Hz, 1H, H-17); 4.92 (dd, J(17′,17) = 2.3 Hz, J(17′,4a) = 2.0 Hz, 1H, H-17′); 5.61–5.65 (m, 1H, H-8); 6.93 (dddd, J(14,15) = 8.2 Hz, J(14,F) = 8.2 Hz, J(14,16) = 2.6 Hz, J(14,12) = 1.5 Hz, 1H, H-14); 7.06 (ddd, J(12,F) = 9.5 Hz, J(12,14) = 2.5 Hz, J(12,16) = 1.8 Hz, 1H, H-12); 7.08 (br.d, J(16,15) = 7.5 Hz, 1H, H-16); 7.26 (ddd, J(15,14) = 8.2 Hz, J(15,16) = 7.5 Hz, J(15,F) = 5.6 Hz, 1H, H-15). ^{1}C-NMR ($CDCl_3$): 80.46 (d, C-1); 79.77 (^4J(C,F) = 2.0 Hz, C-3); 38.59 (t, C-4); 146.36 (s, C-5); 36.63 (d, C-6); 26.17 (t, C-7); 124.39 (d, C-8); 131.49 (s, C-9); 70.29 (d, C-10); 144.78 (^3J(C,F) = 7.1 Hz, C-11); 112.66 (^2J(C,F) = 22.1 Hz, C-12); 162.86 (^1J(C,F) = 245.5 Hz, C-13); 114.21 (^2J(C,F) = 21.2 Hz, C-14); 129.71 (^3J(C,F) = 8.4 Hz, C-15); 121.20 (^4J(C,F) = 2.9 Hz, C-16); 110.05 (t, C-17); 20.86 (q, C-18).

With 4-(trifluoromethyl)benzaldehyde ***2h*** The following compounds were isolated: unreacted aldehyde **2h** (0.410 g, conversion 44 %); intermolecular reaction products **3h** (0.131 g, 21 %) and **7h** (*S*:*R* = 50:50) (0.114 g, 18 %); and isomerization products **4** (0.031 g, 4 %), **5** (0.093 g, 13 %), and **6** (0.066 g, 9 %).

(2S,4aR,8R,8aR)-4,4,7-Trimethyl-2-(4-(trifluoromethyl)phenyl)-4a,5,8,8a-tetrahydro-4H-benzo[d][1,3]dioxin-8-ol ***3h*** ^{1}H NMR ($CDCl_3$): 1.26 (s, 3H, H-18); 1.53 (s, 3H, H-17); 1.55 (ddd, J(6a,7a) = 10.8 Hz, J(6a,7e) = 6.1 Hz, J(6a,1e) = 2.0 Hz, 1H, H_a-6); 1.80 (ddd, J(19,7a) = 2.5 Hz, J(19,7e) = 1.5 Hz, J((19,8) = 1.5 Hz, 3H, H-19); 2.08 (dddq, J(7e,7a) = 17.8 Hz, J(7e,6a) = 6.1 Hz, J((7e,8) = 5.2 Hz, J(7e,19) = 1.5 Hz, 1H, H_e-7); 2.42 (dddqd, J(7a,7e) = 17.8 Hz, J(7a,6a) = 10.8 Hz, J(7a,8) = 2.5 Hz, J(7a,19) = 2.5 Hz, J(7a,10e) = 1.2 Hz, 1H, H_a-7); 3.89 (br.s, 1H, H_e-10); 4.37 (dd, J(1e,10e) = 2.3 Hz, J(1e,6a) = 2.0 Hz, 1H, H_e-1); 5.65 (dm, J(8,7e) = 5.2 Hz, 1H, H-8); 5.83 (s, 1H, H-3); 7.54–7.63 (m, 4H, H-12, H-13, H-15, H-16). ^{13}C-NMR ($CDCl_3$): 75.16 (d, C-1); 94.95 (d, C-3); 74.89 (s, C-5); 34.00 (d, C-6); 22.94 (t, C-7); 125.30 (d, C-8); 130.73 (s, C-9); 70.40 (d, C-10); 142.52 (s, C-11); 126.75 (d, C-12, C-16); 125.11 (^3J(C,F) = 4.0 Hz, C-13, C-15); 130.77 (^2J(C,F) = 32.3 Hz, C-14); 22.63 (q, C-17); 27.10 (q, C-18); 20.47 (q, C-19); 121.8 (^1J(C,F) = 272.5 Hz, C-20). $[\alpha]_D^{25} = -80.3$ (c = 0.43, MeOH); HR-MS: 342.1334 (M^+, $C_{18}H_{21}F_3O_3^+$; calc. 342.1437).

(2S,4S,4aR,8R,8aR)-4,7-Dimethyl-2-(4-(trifluoromethyl)phenyl)-3,4,4a,5,8,8a-hexahydro-2H-chromene-4,8-diol ((S) ***7h)*** ^{1}H NMR ($CDCl_3$ + CD_3OD): 1.43 (s, 3H, H-17); 1.59 (dd, J(4e,4a) = 13.4 Hz, J(4e,3a) = 2.7 Hz, 1H, H_e-4); 1.73 (br.s, 3H, H-18); 1.72–1.80 (m, 2H, H_a-4, H_a-6); 2.03–2.12 (m, 2H, H-7); 3.72 (br.t, J(1e,10e) ≈ J(1e,6a) ≈ 2.2 Hz, 1H, H_e-1); 3.78 (br.s, 1H, H_e-10); 4.41 (dd, J(3a,4a) = 12.0 Hz, J(3a,4e) = 2.7 Hz, 1H, H_a-3); 5.55–5.59 (m, 1H, H-8); 7.34 (d, J(12,13) = J(16,15) = 8.2 Hz, 2H, H-12, H-16); 7.47 (d, J(13,12) = J(15,16) = 8.2 Hz, 2H, H-13, H-15). ^{13}C-NMR ($CDCl_3$ + CD_3OD): 77.77 (d, C-1); 76.65 (d, C-3); 42.49 (t, C-4); 70.34 (s, C-5); 38.04 (d, C-6); 22.51 (t, C-7); 124.17 (d, C-8); 131.13 (s, C-9); 69.96 (d, C-10); 145.96 (s, C-11); 125.88 (d, C-12, C-16); 125.01 (^3J(C,F) = 4.0 Hz,

C-13, C-15); 129.43 (^2J(C,F) = 32.3 Hz, C-14); 26.43 (q, C-17); 20.40 (q, C-18); 123.87 (^1J(C,F) = 272.5 Hz, C-19). HR-MS: 342.1442 (M^+, $C_{18}H_{21}F_3O_3^+$; calc. 342.1437).

*(2S,4R,4aR,8R,8aR)-4,7-Dimethyl-2-(4-(trifluoromethyl) phenyl)-3,4,4a,5,8,8a-hexahydro-2H-chromene-4,8-diol ((R)-**7h**)* ^{1}H NMR ($CDCl_3$ + CD_3OD): 1.15 (s, 3H, H-17); 1.60 (d, J(4,3) = 7.3 Hz, 2H, H-4); 1.65 (ddd, J(6a,7a) = 10.8 Hz, J(6a,7e) = 6.3 Hz; J(6a,1e) = 2.1 Hz, 1H, H_a-6); 1.75 (br.s, 3H, H-18); 1.88–2.00 (m, 2H, H-7); 3.82 (br.s, 1H, H_e-10); 4.16 (dd, J(1e,10e) = 2.4 Hz, J(1e,6a) = 2.1 Hz, 1H, H_e-1); 4.78 (t, J(3,4) = 7.3 Hz, 1H, H_a-3); 5.51–5.55 (m, 1H, H-8); 7.35 (d, J(12,13) = J(16,15) = 8.2 Hz, 2H, H-12, H-16); 7.47 (d, J(13,12) = J(15,16) = 8.2 Hz, 2H, H-13, H-15). ^{13}C-NMR ($CDCl_3$ + CD_3OD): 75.17 (d, C-1); 75.09 (d, C-3); 41.74 (t, C-4); 70.08 (s, C-5); 37.54 (d, C-6); 24.36 (t, C-7); 123.57 (d, C-8); 131.72 (s, C-9); 70.00 (d, C-10); 146.71 (s, C-11); 125.84 (d, C-12, C-16); 124.98 (^3J(C,F) = 4.0 Hz, C-13, C-15); 129.20 (^2J(C,F) = 32.3 Hz, C-14); 27.70 (q, C-17); 20.54 (q, C-18); 124.02 (^1J(C,F) = 272.0 Hz, C-19).

Pharmacology

Animals

All studies were carried out on non-breeding albino mice (male) weighting 20–25 g, eight 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 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 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 × ($A-B$)/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).

The results of pharmacological testing were partly presented by us in the patent (Tolstikova *et al.*, 2011).

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

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