Bioorganic & Medicinal Chemistry 21 (2013) 1082–1087

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Antiparkinsonian activity of some 9-N-, O-, S- and C-derivatives of 3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol

Oleg V. Ardashov, Alla V. Pavlova, Dina V. Korchagina, Konstantin P. Volcho *, Tat'yana G. Tolstikova, Nariman F. Salakhutdinov

N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Lavrentjev Avenue 9, 630090 Novosibirsk, Russian Federation

ARTICLE INFO

Article history:
Received 31 October 2012
Revised 24 December 2012
Accepted 3 January 2013
Available online 11 January 2013

Keywords:
(1*R*,2*R*,6*S*)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol
Monoterpenoid
Derivatives
Antiparkinsonian activity
MPTP model
Mice

ABSTRACT

Earlier it was found, that (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (**1**) possess high antiparkinsonian activity. The N-, O-, S- and C-derivatives at the C-9 position of diol **1** were synthesized in this work. The antiparkinsonian activity of these compounds was studied in MPTP mice models. As a rule, the introduction of substituents containing nitrogen atoms at the C-9 position led to a considerable decrease or loss of antiparkinsonian activity. A derivative of 2-aminoadamantane **8** significantly decreased the locomotor activity time, thus enhancing the symptoms of the parkinsonian syndrome. However the introduction of butyl or propylthio substituents at the C-9 position of diol **1** did not diminish the antiparkinsonian activity comparing to parent compound. This information is important when choosing a route for immobilization of compound **1** to find possible targets.

1. Introduction

Parkinson's disease (PD) is the second most common progressive, neurodegenerative disorder, affecting approximately four million people worldwide, and this is expected to double by 2030.[1,2] PD is an age-related neurodegenerative disease, being primarily a disease of elderly persons.[3–5] Thus, about 2% of people over 65 years of age and 4–5% of people over 85 are sufferers of PD.[3] This is an incurable disease with extensive involvement of motor behavior as well as widespread cognitive, emotional and mood disturbances.[6] The major clinical diagnostic criteria for PD are tremor, rigidity, akinesia, postural instability, and bradyphrenia.[5,7,8] Currently, the only therapies approved for the treatment of PD are agents that attenuate the symptoms of the disease. PD treatment focuses on the replacement of lost dopamine (DA) with L-DOPA therapy, DA agonists, treatment with monoamine oxidase (MAO) B and catechol-*O*-methyltransferase inhibitors, and amantadine, thereby normalizing the patient symptomatically.[3,6,9] Nevertheless L-DOPA (L-3,4-dihydroxyphenylalanine) continues to be the most effective pharmacological treatment strategy, which counteracts most of the major motor symptoms of PD. L-DOPA therapy often has to be curtailed, because of the development of debilitating, treatment-limiting adverse effects, including 'wearing-off' phenomena and other motor complications such as dyskinesia.[2]

Recently,[10,11] we found that (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol **1** displayed a potent antiparkinsonian activity in animal MPTP and haloperidol models of PD. The compound possessed low acute toxicity, its LD_{50} being 4250 mg/kg.[10] It was found that a pronounced antiparkinsonian effect of **1** could be only achieved if it contained all the four functional groups (two hydroxy groups and two double bonds).[12] While studying the effect of chemical modification on the antiparkinsonian activity, therefore, we decided to leave the hydroxyl groups and double bonds of molecule **1** intact, using methyl groups as modification sites. The goal of this work was to synthesize and investigate the antiparkinsonian activity of the derivatives of diol **1** modified at the C-9 position. Modification of the compound at this position can substantially affect its pharmacological activity and stimulate the development of approaches to immobilization of **1** without loss of activity for identification of possible targets.

Abbreviations: CC, column chromatography; DMF, dimethylformamide; DMSO, dimethylsulfoxide; L-DOPA, L-3,4-dihydrophenylalanine; MAO, monoamine oxidase; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NBS, *N*-bromosuccinimide; PD, Parkinson's disease; r.t., room temperature.

* Corresponding author. Tel.: +7 3833308870; fax: +7 3833309752.
E-mail address: volcho@nioch.nsc.ru (K.P. Volcho).

0968-0896/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmc.2013.01.003

2. Results and discussion

2.1. Chemistry

Compound **1** has ten allylic protons, which substantially hinder the choice of selective methods. One of the widely used methods for modification of natural compounds at the allylic positions is their oxidation with SeO_2.[13–15] It appeared, however, that for diol **1** oxidation with SeO_2 was not selective; according to GLC data, the reaction mixture contained four major products in approximately equal amounts and a set of minor products.

Allylic bromination of diol **1** was more selective probably for steric reasons. The reaction of **1** with NBS in CCl_4 in the presence of $(t\text{-BuO})_2$ under reflux for 3 h followed by the application of the mixture to a SiO_2 column (without water treatment) and chromatography gave bromide **2** with a 34% yield (Scheme 1). For comparison, after the standard treatment of the reaction mixture (washing with a Na_2SO_3 solution, drying of the organic phase, subsequent concentration, and separation by column chromatography) the yield of bromide **2** was only 10%. Note that using 1,2-diacetate instead of diol **1** in allylic bromination led to lower selectivity and to the formation of a complex mixture of products.

The reaction of bromide **2** with NaOAc in aqueous DMSO gave acetate **3** with a 72% yield. Saponification of acetate **3** with an aqueous methanol solution of NaOH led to the formation of triol **4** with a 76% yield. The overall yield of triol **4** based on the starting diol **1** was 19% in three steps (Scheme 1).

The amino derivative **5** was synthesized by Gabriel's procedure[16] via the corresponding phthalimide **6**. The reaction of bromide **2** with potassium phthalimide in DMF for 1 day gave compound **6** with a 78% yield after column chromatography. Attempts to convert this product into amino derivative **5** by the standard procedure[17] failed even when using a large excess of the commonly used reagent $N_2H_4 \times H_2O$ which gave only the starting compound **6** in all cases. We showed that ethylenediamine is an effective reagent for removing the phthalate group. The reflux of compound **6** with ethylenediamine in a $CHCl_3$/EtOH (2:1) for 4 h gave the desired product **5** with a 93% yield (Scheme 1).

The reaction of bromide **2** with morpholine in $CHCl_3$ for 2 days led to compound **7** with a 63% yield (Scheme 1). Compound **8** was obtained by the reaction of bromide **2** with 2-aminoadamantane hydrochloride in $CHCl_3$ for 4 days. NEt_3 was used as a base. The preparative yield of **8** was 76%. One more N-derivative **9** was obtained by the reaction of **2** with N^1,N^1-dimethylethane-1,2-diamine in 27% yield. The yield was less than in the cases of compounds **7** and **8** due to competitive alkylation of tertiary N-atom in the reagent and in the product **9**.

Further, when *n*-BuLi was used as a reagent, the reaction in THF performed for 1 day gave the corresponding butyl derivative **10** with a 18% yield and heterocyclization product **11** with a 15% yield (Scheme 1).

Finally, S-derivative **12** was obtained by the reaction with *n*-PrSNa in EtOH in 58% yield.

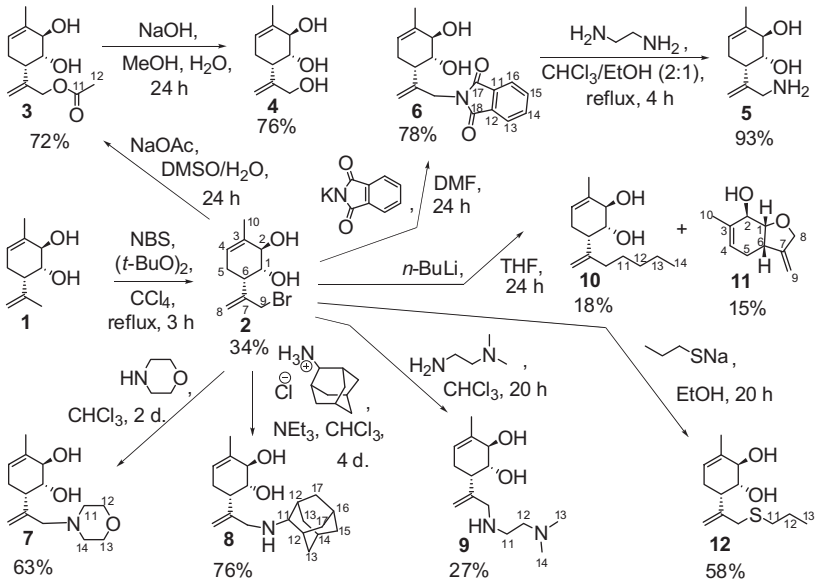
Analogous reaction of bromide **2** with *n*-PrONa in dioxane led only to the formation of **11** with the 55% yield. Of course the protection groups may be used in this case but the use of sequence 'protection–deprotection' is not convenient for immobilization procedure.

Thus a series of N-, O-, C-, and S-derivatives of diol **1** at the C-9 position were synthesized for the first time.

2.2. Pharmacology

In animal studies, neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is commonly used to create experimental model of PD, which may be used to model certain aspects of the disease, such as catalepsy, motor imbalance, and slowing of movement.[18] MPTP produces a statistically significant different and reproducible lesion of the nigrostriatal dopaminergic pathway after its systemic administration and is the only known dopaminergic neurotoxin capable of causing a clinical picture in humans indistinguishable from PD.[19]

We studied the antiparkinsonian activity of the compounds **1**, **4–12** (Scheme 1) in accordance with MPTP mouse model of Parkinson's disease published in Nature protocols.[19] It involves one injection of MPTP (20 mg/kg per dose) to mice of C57Bl/6 line every 2 h for a total of 4 doses over a 6 h period in 1 day. The studied agents were administered per os 24 h after the last injection of MPTP in a dose of 20 mg/kg. The main markers of the locomotor activity were measured 2 h after the administration of the agent with the 'Open



Scheme 1. Synthesis of compounds **2–12**.

Table 1
Study of the antiparkinsonian activity of compounds **1**, **4–12** in C57Bl/6 mice

Group	Time of locomotor activity (s)	Movement distance (cm)	Movement speed (cm/s)	Immobility time (s)
Saline	72.4 ± 2.6	372.1 ± 27.2	3.1 ± 0.2	47.6 ± 2.6
MPTP	56.2 ± 3.2**	241.1 ± 20.7**	2.0 ± 0.2**	63.8 ± 3.2**
MPTP and **1**	69.2 ± 4.2#	302.0 ± 17.4#	2.6 ± 0.1#	50.8 ± 4.2#
MPTP and **5**	53.5 ± 7.1	248.6 ± 36.8	2.0 ± 0.3	66.5 ± 7.1
MPTP and **6**	58.3 ± 4.4	280.0 ± 32.4	2.3 ± 0.3	61.7 ± 4.4
MPTP and **7**	48.5 ± 6.7	215.3 ± 34.5	1.7 ± 0.3	71.5 ± 6.8
MPTP and **8**	34.8 ± 9.0#	149.7 ± 42.8	1.2 ± 0.4	85.2 ± 9.0#
MPTP and **10**	63.2 ± 2.6	335.2 ± 29.5#	2.7 ± 0.3#	56.8 ± 2.7
MPTP and **11**	46.6 ± 6.5	214.0 ± 38.5	1.7 ± 0.3	73.4 ± 6.5
Saline	68.1 ± 2.3	337.5 ± 16.5	2.8 ± 0.1	51.9 ± 2.3
MPTP	26.1 ± 8.0***	106.0 ± 37.0***	0.8 ± 0.3***	93.9 ± 7.9***
MPTP and **4**	37.2 ± 10.7	182.1 ± 55.2	1.5 ± 0.5	80.0 ± 1.2
Saline	66.9 ± 5.1	343.7 ± 43.7	2.8 ± 0.4	53.1 ± 5.1
MPTP	37.3 ± 6.2**	145.0 ± 26.8**	1.2 ± 0.2**	82.7 ± 6.2**
MPTP and **9**	51.2 ± 3.3	225.0 ± 20.9#	1.8 ± 0.2#	68.8 ± 3.3
MPTP and **12**	61.4 ± 3.5##	317.6 ± 26.6###	2.6 ± 0.2###	58.6 ± 3.5##

*P <0.05.
** P <0.01.
*** P <0.001 statistically significant different in comparison with saline group.
# P <0.05.
P <0.01.
P <0.001 statistically significant different in comparison with MPTP group.

field' test for 2 min. The effectiveness of the studied medication was evaluated according to its ability to reduce the symptoms of hypokinesia induced by MPTP.

Four administrations of MPTP led to a considerable effect on the locomotor activity of animals (Table 1): the locomotor activity time, the movement distance and the movement speed decreased, while the immobility time increased. The administration of **1** along with MPTP neurotoxin injections led to a significant recovery of the parameters of the locomotor activity of animals. Compounds **4**, **9** and **12** were studied in other series of experiments; data for the saline treated and MPTP groups for these compounds are given separately in the Table 1.

When amino derivative **5** was administrated, none of the given locomotor activity parameters deviated from those in the MPTP group. Similar results were obtained for phthalimide **6**. An insignificant difference was an increase in the mean of movement distance, but differences from the MPTP group were not statistically significant different. For compound **7**, having a morpholine substituent, all the four markers of the locomotor activity were worse than those in the MPTP group, but the differences were not statistically significant different again.

Compound **8** (a derivative of 2-aminoadamantane) produced a more significant effect. This compound considerably decreased the locomotor activity time, thus enhancing the symptoms of the parkinsonian syndrome. The distance and the movement speed decreased markedly, through not statistically significant different.

Another nitrogen containing derivative, compound **9**, markedly increased movement distance and speed of the animals but the values were far from the ones in the saline treated group.

Administration of compound **10** statistically significant different increased the distance and movement speed of animals almost to the level exhibited by saline treated animals. The locomotor activity time was also increased, although changes in this parameter was not statistically significant different.

The heterocyclic analog of triol **4**, compound **11**, produced an opposite effect, reducing the locomotor activity of animals substantially, though not statistically significant different.

Finally, the best results were achieved when using compound **12**, which is the sulfur containing derivative of diol **1**. Administration of compound **12** led to the restoration of all the four markers of the locomotor activity of the mice.

Thus the introduction of a substituent at the C-9 position differently affected the antiparkinsonian activity of the agents. Almost all of the nitrogen-containing derivatives synthesized in this study, namely, the amino derivative (**5**) and the derivatives of morpholine (**7**) and phthalimide (**6**), did not exhibit statistically significant different results for any of the given activity parameters. An exception were dinitrogen containing compound **9**, which partly restored the locomotor activity, and the derivative of 2-aminoadamantane **8**, which caused an increase of the neurotoxin action.

The introduction of a hydroxyl group at the C-9 position of diol **1** led to a significant decrease in the antiparkinsonian activity in comparison with parent compound **1**. Moreover, heterocyclization product **11** worked in the opposite direction, appreciably decreasing the locomotor activity of animals. This confirms the importance for diol **1** to contain hydroxy group in the 1st position, found earlier.[12]

The *n*-Bu and *n*-PrS derivatives **10** and **12** were the most active among the synthesized 9-derivatives of diol **1**. According to Table 1, the compounds substantially increased the distance and the movement rate, restoring all locomotor activity markers at the level close to that of saline treated animals and showing nearly the same level of efficiency as diol **1**.

From the data obtained it may be supposed that the interaction of bromide **2** with thiol with long aliphatic chain may be used for immobilization of diol **1** without lost of the antiparkinsonian activity.

3. Conclusion

As a result of our studies, we elaborated a procedure for selective modification of (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (**1**) at the C-9 position, which allowed us to synthesize a series of N-, O-, S- and C-derivatives of diol **1**. Studies of the antiparkinsonian activity of the resulting compounds on mice using the MPTP model showed that the introduction of substituents containing heteroatoms at the C-9 position led to a loss of the antiparkinsonian activity except triol **4** and containing two nitrogen atoms compound **9** which partly restored motion markers of the animals. At the same time, this compound retained its high antiparkinsonian activity when an aliphatic or thioaliphatic substituent was introduced at the C-9 position of diol **1**. This information

is extremely important for choosing the route for immobilization of compound **1** to find possible targets.

4. Experimental section

4.1. General chemical methods

Reagents and solvents were purchased from commercial suppliers and used as received. Dry solvents were obtained according to the standard procedures. GC: 7820A gas chromatograph (Agilent Tech., USA); flame-ionization detector; HP-5 capillary column (0.25 mmol Ø × 30 m × 0.25 μm), He as carrier gas (flow rate 2 ml/min, flow division 99:1). Optical rotation: polAAr 3005 spectrometer; $CHCl_3$ soln. ^1H and ^{13}C NMR spectra/Bruker DRX-500 apparatus at 500.13 MHz (^1H) and 125.76 MHz (^{13}C) in $CCl_4/CDCl_3$ 1:1 (v/v), $CDCl_3$ or $CDCl_3 + CD_3OD$ (~10:1); chemical shifts δ in ppm rel to residual $CHCl_3$ [δ(H) 7.24, δ(C) 76.90 ppm], J in Hz. The structure of the products was determined by analyzing the ^1H and ^{13}C NMR spectra, $^1H,^1H$ double-resonance spectra and $^{13}C,^1H$-type 2D-COSY (J(C,H) = 160 Hz). HR-MS: DFS Thermo Scientific spectrometer in a full scan mode (15–500 m/z, 70 eV electron impact ionization, direct sample administration). Spectral and analytical investigations were carried out at Collective Chemical Service center of Siberian Branch of Russian Academy of Sciences. Column chromatography (CC) was performed on silica gel (60–200 μ, Macherey-Nagel). The purity of the target compounds was determined by gas chromatography methods. All of the target compounds reported in this paper have a purity of no less then 95%.

(1*R*,2*R*,6*S*)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (**1**) ($[\alpha]_D^{31}$ −49.1 (*c* 2.6, $CHCl_3$)) was synthesized from (−)-verbenone (Aldrich) ($[\alpha]_D^{25}$ −210.5 (*c* 0.77, $CHCl_3$)) according to previously described procedure.[20,21]

4.2. (1*R*,2*R*,6*S*)-6-(3-Bromoprop-1-en-2-yl)-3-methylcyclohex-3-ene-1,2-diol (2)

Freshly recrystallized *N*-bromosuccinimide (0.992 g, 5.57 mmol) and (*t*-BuO)$_2$ (80 μl, 0.44 mmol) were added to a solution of (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (**1**) (0.757 g, 4.51 mmol) in CCl_4 (20 ml) (distilled and passed through a column with calcinated Al_2O_3). The reaction mixture was boiled for 2 h, then diluted with CCl_4 (15 ml), and applied without treatment on a column with silica gel (17 g). The mixture was chromatographed using hexane solutions of ether and chloroform as eluent (0–100% gradient). Compound **2** (0.383 g, 1.55 mmol, 34%) was isolated. $[\alpha]_D^{27}$ −28.4 (*c* 2.10, $CHCl_3$). ^1H NMR ($CDCl_3 + CCl_4$ (1: 1), δ_H): 1.77 (3H, m; all $J \leqslant 2.5$ Hz, H-10), 2.09 (1H, dddq; ^2J 17.7, $J_{5e,6a}$ 5.3, $J_{5e,4}$ 4.7, $J_{5e,10}$ 1.5 Hz, H-5e), 2.20 (1H, dddqd; ^{2}J 17.7, $J_{5a,6a}$ 9.8, $J_{5a,4}$ 2.8, $J_{5a,10}$ 2.5, $J_{5a,2e}$ 1.1 Hz, H-5a), 2.47 (2H, br s; 2 OH), 2.74 (1H, ddddd; $J_{6a,5a}$ 9.8, $J_{6a,5e}$ 5.3, $J_{6a,1e}$ 2.2, $J_{6a,8}$ 1.1, $J_{6a,8'}$ 0.7 Hz, H-6a), 3.78 (1H, br d; $J_{2e,1e}$ 3.7 Hz, H-2e), 3.88 (1H, dd; $J_{1e,2e}$ 3.7, $J_{1e,6a}$ 2.2 Hz, H-1e), 3.99 (1H, d; ^2J 10.2 Hz, H-9), 4.11 (1H, d; ^2J 10.2 Hz, H-9′), 5.13 (1H, br s; H-8), 5.34 (1H, br s; H-8′), 5.58 (1H, ddq; $J_{4,5e}$ 4.7, $J_{4,5a}$ 2.8, $J_{4,10}$ 1.4 Hz, H-4). ^{13}C NMR, δ_C:71.86 (d; C-1), 72.25 (d; C-2), 132.08 (s; C-3), 124.63 (d; C-4), 25.92 (t; C-5), 36.91 (d; C-6), 145.90 (s; C-7), 116.74 (t; C-8), 36.65 (t; C-9), 20.55 (q; C-10). HR-MS: 229.0211 (M^+-OH, $C_{10}H_{14}OBr$; Calc. 229.0228).

4.3. 2-((1*S*,5*R*,6*R*)-5,6-Dihydroxy-4-methylcyclohex-3-enyl)allyl acetate (3)

A 1 M solution (7.5 ml) of NaOAc (7.5 mmol) was added to a solution of (1*R*,2*R*,6*S*)-6-(3-bromoprop-1-en-2-yl)-3-methylcyclohex-3-ene-1,2-diol (**2**) (0.124 g, 0.502 mmol) in DMSO (9 ml). The reaction mixture was stirred for 24 h at rt and then transferred to a saturated NaCl solution (150 ml). The product was extracted with ethylacetate (4 × 30 ml). The combined extracts were dried over Na_2SO_4. The solvent was evaporated. The residue was purified by CC on silica gel (4.5 g) using 0–100% ethylacetate gradient in hexane as eluent. This gave **3** (0.075 g, 0.36 mmol, 72%). $[\alpha]_D^{18}$ −50.6 (*c* 0.77, $CHCl_3$). ^1H NMR ($CDCl_3 + CCl_4$ (1:1), δ_H): 1.74 (3H, m; all $J \leqslant 2.5$ Hz, H-10), 1.99 (1H, dddq; ^2J 17.5, $J_{5e,6a}$ 5.3, $J_{5e,4}$ 4.5, $J_{5e,10}$ 1.5 Hz, H-5e), 2.04 (3H, s; H-12), 2.22 (1H, dddqd; ^2J 17.5, $J_{5a,6a}$ 10.0, $J_{5a,4}$ 2.8, $J_{5a,10}$ 2.5, $J_{5a,2e}$ 1.1 Hz, H-5a), 2.50 (1H, dddd; $J_{6a,5a}$ 10.0, $J_{6a,5e}$ 5.3, $J_{6a,1e}$ 2.1, $J_{6a,8}$ 0.7 Hz, H-6a), 2.53 and 2.85 (2H, br s; 2 OH), 3.76 (1H, br d; $J_{2e,1e}$ 3.3 Hz, H-2e), 3.81 (1H, dd; $J_{1e,2e}$ 3.3, $J_{1e,6a}$ 2.1 Hz, H-1e), 4.55 (1H, d; ^2J 13.6 Hz, H-9) and 4.60 (1H, d; ^2J 13.6 Hz, H-9′)—AB-system, 5.06 (1H, br s; H-8), 5.13 (1H, br s; H-8′), 5.55 (1H, ddq; $J_{4,5e}$ 4.5, $J_{4,5a}$ 2.8, $J_{4,10}$ 1.4 Hz, H-4). ^{13}C NMR, δ_C:71.95 (d; C-1), 72.03 (d; C-2), 132.11 (s; C-3), 124.43 (d; C-4), 25.21 (t; C-5), 36.95 (d; C-6), 144.42 (s; C-7), 113.27 (t; C-8), 66.33 (t; C-9), 20.59 (q; C-10), 170.67 (s; C-11), 20.79 (q; C-12). HR-MS: 208.1096 (M^+, $C_{12}H_{16}O_3$; Calc. 208.1094).

4.4. (1*R*,2*R*,6*S*)-6-(3-Hydroxyprop-1-en-2-yl)-3-methylcyclohex-3-ene-1,2-diol (4)

A mixture of acetate **3** (0.052 g, 0.25 mmol), NaOH (0.146 g, 3.65 mmol), H_2O (0.5 ml), and MeOH (5 ml) was stirred for 1 day at rt. The reaction mixture was diluted with H_2O (10 ml). MeOH was evaporated under reduce pressure. The residual water phase was saturated with NaCl. The product was extracted with ethylacetate (5 × 10 ml). The combined extracts were dried over Na_2SO_4. The solvent was distilled off. The residue was purified by CC on silica gel (4.5 g) using 0–100% ethylacetate gradient in hexane as eluent. This gave **4** (0.035 g, 0.19 mmol, 76%). $[\alpha]_D^{38}$ −38.6 (*c* 0.43, $CHCl_3$). ^1H NMR ($CDCl_3$, δ_H): 1.76 (3H, m; all $J \leqslant 2.5$ Hz, H-10), 2.02 (1H, dddq; ^2J 17.7, $J_{5e,6a}$ 5.3, $J_{5e,4}$ 4.5, $J_{5e,10}$ 1.5 Hz, H-5e), 2.26 (1H, dddq; ^2J 17.7, $J_{5a,6a}$ 9.8, $J_{5a,4}$ 2.8, $J_{5a,10}$ 2.5 Hz, H-5a), 2.64 (1H, dddd; $J_{6a,5a}$ 9.8, $J_{6a,5e}$ 5.3, $J_{6a,1e}$ 2.1, $J_{6a,8}$ 0.7 Hz, H-6a), 3.32 (1H, br s; OH) and 3.92 (2H, br s; 2 OH), 3.81 (1H, br d; $J_{2e,1e}$ 3.8 Hz, H-2e), 3.83 (1H, dd; $J_{1e,2e}$ 3.8, $J_{1e,6a}$ 2.1 Hz, H-1e), 4.04 (1H, d; ^2J 12.6 Hz, H-9), 4.11 (1H, d; ^2J 12.6 Hz, H-9′), 5.04 (1H, br s; H-8), 5.13 (1H, br s; H-8′), 5.59 (1H, ddq; $J_{4,5e}$ 4.5, $J_{4,5a}$ 2.8, $J_{4,10}$ 1.4 Hz, H-4). ^{13}C NMR, δ_C: 72.78 (d; C-1), 72.12 (d; C-2), 132.00 (s; C-3), 124.58 (d; C-4), 25.78 (t; C-5), 38.42 (d; C-6), 148.65 (s; C-7), 114.55 (t; C-8), 65.39 (t; C-9), 20.42 (q; C-10). HR-MS: 166.0986 (M^+-H_2O, $C_{10}H_{14}O_2$; calcd 166.0988).

4.5. 2-(2-((1*S*,5*R*,6*R*)-5,6-Dihydroxy-4-methylcyclohex-3-enyl)allyl)isoindoline-1,3-dione (6)

Potassium phthalimide was obtained from phthalimide and KOH by the procedure.[22] Potassium phthalimide (0.105 g, 0.568 mmol) was added to a solution of **2** (0.118 g, 0.480 mmol) in DMF (6 ml). The reaction mixture was stirred for 1 day at rt. Then H_2O (10 ml) was added and DMF was distilled off at reduced pressure with a water azeotrope, for which we added another portion of H_2O (3 × 5 ml). The solid residue was extracted with ethylacetate (3 × 5 ml) and filtered off through a silica gel layer to remove phthalimide. The solvent was distilled off. The product was purified by CC on silica gel (4.5 g) using 0–100% ethylacetate gradient in hexane as eluent. The product was **6** (0.117 g, 0.373 mmol, 78%). $[\alpha]_D^{24}$ −45.8 (*c* 1.83, $CHCl_3$). ^1H NMR ($CDCl_3 + CCl_4$ (1:1), δ_H): 1.75 (3H, m; all $J \leqslant 2.5$ Hz, H-10), 2.01 (1H, dddq; ^2J 17.7, $J_{5e,6a}$ 5.3, $J_{5e,4}$ 4.6, $J_{5e,10}$ 1.5 Hz, H-5e), 2.28 (1H, dddqd; ^2J 17.7, $J_{5a,6a}$ 9.8, $J_{5a,4}$ 2.6, $J_{5a,10}$ 2.5, $J_{5a,2e}$ 1.1 Hz, H-5a), 2.54 (1H, dddd; $J_{6a,5a}$ 9.8, $J_{6a,5e}$ 5.3, $J_{6a,1e}$ 2.0, $J_{6a,8'}$ 0.7 Hz, H-6a), 2.81 (1H, br s; OH), 2.88 (1H, br s; OH), 3.86 (1H, br d; $J_{2e,1e}$ 3.4 Hz, H-2e), 4.01 (1H, br t; $J_{1e,2e}$ 3.4, $J_{1e,6a}$ 2.0 Hz, H-1e), 4.25 (1H, d; ^2J 16.3 Hz, H-9), 4.34 (1H, br d; ^2J

16.3 Hz, H-9′), 4.90 (1H, br s; H-8′), 5.01 (1H, br s; H-8), 5.54 (1H, m; all $J < 5.0$ Hz, H-4), 7.63–7.68 (2H, m; H-14, H-15) and 7.75–7.80 (2H, m; H-13, H-16)—A_2B_2-system. ^{13}C NMR, δ_C: 71.90 (d; C-1), 72.16 (d; C-2), 132.27 (s; C-3), 124.28 (d; C-4), 25.34 (t; C-5), 37.97 (d; C-6), 143.90 (s; C-7), 111.96 (t; C-8), 41.63 (t; C-9), 20.57 (q; C-10), 131.97 (s; C-11, C-12), 123.30 (d; C-13, C-16), 133.84 (d; C-14, C-15), 167.94 (s; C-17, C-18). HR-MS: 313.1311 (M^+, $C_{18}H_{19}O_4N$; calcd 313.1309).

4.6. (1*R*,2*R*,6*S*)-6-(3-Aminoprop-1-en-2-yl)-3-methylcyclohex-3-ene-1,2-diol (5)

A mixture of **6** (0.045 g, 0.14 mmol), ethylenediamine (0.043 g, 0.72 mmol), $CHCl_3$ (10 ml), and EtOH (5 ml) was boiled for 4 h (GLC control). The solvent was evaporated. The residue was separated by CC on silica gel (4.5 g) using 0–100% chloroform gradient in hexane with a 0.5% NEt_3 addition as eluent. This procedure gave **5** (0.024 g, 0.13 mmol, 93%). $[\alpha]_D^{28}$ −35.0 (*c* 0.60, EtOH). ^{1}H NMR ($CDCl_3$ + CD_3OD (~10:1), δ_H): 1.73 (3H, m; all $J \leqslant 2.5$ Hz, H-10), 1.93 (1H, dddq; ^2J 17.7, $J_{5e,6a}$ 5.4, $J_{5e,4}$ 4.5, $J_{5e,10}$ 1.5 Hz, H-5e), 2.22 (1H, dddqd; ^2J 17.7, $J_{5a,6a}$ 9.8, $J_{5a,4}$ 2.8, $J_{5a,10}$ 2.5, $J_{5a,2e}$ 1.1 Hz, H-5a), 2.62 (1H, dddd; $J_{6a,5a}$ 9.8, $J_{6a,5e}$ 5.4, $J_{6a,1e}$ 2.2, $J_{6a,8'}$ 0.7 Hz, H-6a), 3.29 (1H, dd; ^2J 13.2, $J_{9,8}$ 0.8 Hz, H-9), 3.31 (1H, dd; ^2J 13.2, $J_{9',8'}$ 1.1 Hz, H-9′), 3.71 (1H, dd; $J_{1e,2e}$ 3.8, $J_{1e,6a}$ 2.2 Hz, H-1e), 3.77 (1H, br d; $J_{2e,1e}$ 3.8 Hz, H-2e), 5.00 (1H, dd; ^2J 1.4, $J_{8,9}$ 0.8 Hz, H-8), 5.03 (1H, ddd; ^2J 1.4, $J_{8',9'}$ 1.1, $J_{8',6a}$ 0.7 Hz, H-8′), 5.53 (1H, ddq; $J_{4,5e}$ 4.5, $J_{4,5a}$ 2.8, $J_{4,10}$ 1.4 Hz, H-4). ^{13}C NMR, δ_C: 72.87 (d; C-1), 72.01 (d; C-2), 132.48 (s; C-3), 123.86 (d; C-4), 26.09 (t; C-5), 40.80 (d; C-6), 148.10 (s; C-7), 116.04 (t; C-8), 44.55 (t; C-9), 20.35 (q; C-10). HR-MS: 183.1255 (M^+, $C_{10}H_{17}O_2N$; calcd 183.1254).

4.7. (1*R*,2*R*,6*S*)-3-Methyl-6-(3-morpholinoprop-1-en-2-yl)cyclohex-3-ene-1,2-diol (7)

A mixture of **2** (0.073 g, 0.30 mmol) and morpholine (0.068 g, 0.78 mmol) in $CHCl_3$ (10 ml) was allowed to stay for 2 days at rt. Then a solution of $NaHCO_3$ (1 g) and NaCl (1 g) in H_2O (20 ml) was added. The organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (3 × 10 ml). The combined organic phases were dried over Na_2SO_4. The solvent was evaporated. The residue was separated by CC on silica gel (4.5 g) using 0–100% chloroform gradient in hexane with a 0.5% NEt_3 addition as eluent. This gave **7** (0.049 g, 0.19 mmol, 63%). $[\alpha]_D^{28}$ −18.6 (*c* 1.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$ + CCl_4 (1:1), δ_H): 1.78 (3H, m; all $J \leqslant 2.5$ Hz, H-10), 1.90 (1H, dddq; ^2J 17.6, $J_{5e,6a}$ 5.2, $J_{5e,4}$ 4.8, $J_{5e,10}$ 1.5 Hz, H-5e), 2.27 (1H, dddqd; ^2J 17.6, $J_{5a,6a}$ 10.6, $J_{5a,4}$ 2.5, $J_{5a,10}$ 2.5, $J_{5a,2e}$ 1.1 Hz, H-5a), 2.35–2.47 (2H, m) and 2.54–2.66 (2H, m; H-11, H-14), 2.72 (1H, ddd; $J_{6a,5a}$ 10.6, $J_{6a,5e}$ 5.2, $J_{6a,1e}$ 2.0 Hz, H-6a), 2.73 (1H, d; ^2J 12.4 Hz, H-9), 3.17 (1H, d; ^2J 12.4 Hz, H-9′), 3.67 (1H, dd; $J_{1e,2e}$ 3.4, $J_{1e,6a}$ 2.0 Hz, H-1e), 3.68–3.74 (4H, m; H-12, H-13), 3.82 (1H, br d; $J_{2e,1e}$ 3.4 Hz, H-2e), 4.95 (1H, br s; H-8), 5.16 (1H, d; ^2J 1.9 Hz, H-8′), 5.58 (1H, ddq; $J_{4,5e}$ 4.8, $J_{4,5a}$ 2.5, $J_{4,10}$ 1.4 Hz, H-4). ^{13}C NMR, δ_C: 73.63 (d; C-1), 72.24 (d; C-2), 132.42 (s; C-3), 124.13 (d; C-4), 25.96 (t; C-5), 42.31 (d; C-6), 145.06 (s; C-7), 119.71 (t; C-8), 62.15 (t; C-9), 20.68 (q; C-10), 52.85 (t; C-11, C-14), 66.16 (t; C-12, C-13). HR-MS: 253.1684 (M^+, $C_{14}H_{23}O_3N$; calcd 253.1672).

4.8. (1*R*,2*R*,6*S*)-6-{1-[(2-Adamantylamino)methyl]vinyl}-3-methylcyclohex-3-ene-1,2-diol (8)

A mixture of **2** (0.042 g, 0.17 mmol), 2-aminoadamantane hydrochloride (0.044 g, 0.24 mmol), NEt_3 (0.060 g, 0.60 mmol), and $CHCl_3$ (7 ml) was stored at rt for 4 days. The solvent was distilled off. The residue was separated by CC on silica gel (4.5 g) using 0–100% chloroform gradient in hexane and 0–100% ethanol in chloroform with a 0.5% NEt_3 addition as eluent. This gave **8** (0.041 g, 0.13 mmol, 76%). $[\alpha]_D^{24}$ −3.25 (*c* 0.80, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ_H): 1.48 (2H, br d; ^2J 12.5 Hz, H-13), 1.77 (3H, m; all $J \leqslant 2.5$ Hz, H-10), 1.87 (1H, dddq; ^2J 17.5, $J_{5e,6a}$ 5.2, $J_{5e,4}$ 4.7, $J_{5e,10}$ 1.5 Hz, H-5e), 1.92 (2H, br d; ^2J 12.5 Hz, H-13′), 2.29 (1H, dddqd; ^2J 17.5, $J_{5a,6a}$ 10.6, $J_{5a,4}$ 2.5, $J_{5a,10}$ 2.5, $J_{5a,2e}$ 1.2 Hz, H-5a), 2.70 (1H, ddd; $J_{6a,5a}$ 10.6, $J_{6a,5e}$ 5.2, $J_{6a,1e}$ 2.0 Hz, H-6a), 2.72 (1H, br. s; H-11), 3.13 (1H, d; ^2J 12.2 Hz, H-9) and 3.14 (1H, d; ^2J 12.2 Hz, H-9′)—AB-system, 3.67 (1H, dd; $J_{1e,2e}$ 3.4, $J_{1e,6a}$ 2.0 Hz, H-1e), 3.83 (1H, br d; $J_{2e,1e}$ 3.4 Hz, H-2e), 4.92 (1H, br d; ^2J 2.0 Hz, H-8), 5.02 (1H, dd; ^2J 2.0, $J_{8',6a}$ 0.7 Hz, H-8′), 5.56 (1H, ddq; $J_{4,5e}$ 4.7, $J_{4,5a}$ 2.5, $J_{4,10}$ 1.4 Hz, H-4), 1.50–1.92 (10 H, m; other protons). ^{13}C NMR, δ_C: 73.82 (d; C-1), 72.17 (d; C-2), 132.54 (s; C-3), 124.06 (d; C-4), 26.04 (t; C-5), 42.32 (d; C-6), 149.19 (s; C-7), 116.94 (t; C-8), 49.81 (t; C-9), 20.72 (q; C-10), 61.27 (d; C-11), 31.15 (d) and 31.25 (d; 2C-12), 30.58 (t; 2C-13), 27.12 (d) and 27.45 (d; C-14, C-16), 37.77 (t; C-15), 37.54 (t; 2C-17). HR-MS: 317.2348 (M^+, $C_{20}H_{31}O_2N$; calcd 317.2349).

4.9. (1*R*,2*R*,6*S*)-6-(3-(2-(Dimethylamino)ethylamino)prop-1-en-2-yl)-3-methylcyclohex-3-ene-1,2-diol (9)

A mixture of **2** (0.070 g, 0.28 mmol) and N^1,N^1-dimethylethane-1,2-diamine (Acros, 0.125 μl, 1.14 mmol) in $CHCl_3$ (20 ml) was allowed to stay for 20 h at rt. Then the reaction mixture was washed with the concentrated solution of $NaHCO_3$ (10 ml) and dried over Na_2SO_4. The solvent was evaporated. The residue (39.4 mg) was separated by CC on silica gel (2 g) using as eluent 25–100% chloroform gradient in hexane and 0–50% ethanol gradient in chloroform (both with a 0.5% NEt_3 addition). This gave **9** (0.019 g, 0.075 mmol, 27%). $[\alpha]_D^{24}$ −14.6 (*c* 0.27, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ_H): 1.79 (3H, m; all $J \leqslant 2.5$ Hz, H-10), 1.93 (1H, dddq; ^2J 17.7, $J_{5e,6a}$ 5.3, $J_{5e,4}$4.7, $J_{5e,10}$ 1.5 Hz, H-5e), 2.21 (6H, s; H-13, H-14), 2.29 (1H, ddm; ^2J 17.7, $J_{5a,6a}$ 10.6, H-5a), 2.44 (2H, t; $J_{12,11}$ 6.0 Hz, H-12), 2.63 (1H, dt; ^2J 12.3, $J_{11,12}$ 6.0 Hz, H-11), 2.69–2.74 (1H, m; H-6a), 2.71 (1H, dt; ^2J 12.3, $J_{11',12}$ 6.0 Hz, H-11′), 3.14 (1H, d; ^2J 12.3 Hz, H-9) and 3.31 (1H, d; ^2J 12.3 Hz, H-9′)—AB-system, 3.71 (1H, dd; $J_{1e,2e}$ 3.7, $J_{1e,6a}$ 2.0 Hz, H-1e), 3.84 (1H, br d; $J_{2e,1e}$ 3.7 Hz, H-2e), 4.21 (3H, br s; 2OH, NH), 4.99 (1H, br s; H-8), 5.07 (1H, br d; ^2J 1.8 Hz, H-8′), 5.53–5.59 (1H, m; all $J \leqslant 4.7$ Hz, H-4). ^{13}C NMR, δ_C: 73.55 (d; C-1), 72.47 (d; C-2), 132.61 (s; C-3), 124.05 (d; C-4), 26.28 (t; C-5), 42.09 (d; C-6), 147.59 (s; C-7), 117.63 (t; C-8), 52.70 (t; C-9), 20.61 (q; C-10), 45.49 (t; C-11), 57.77 (t; C-12), 45.24 (q; C-13, C-14). HR-MS: 254.1984 (M^+, $C_{14}H_{26}O_2N_2$; calcd 254.1989).

4.10. (1*R*,2*R*,6*S*)-6-(Hept-1-en-2-yl)-3-methylcyclohex-3-ene-1,2-diol (10) and (3a*S*,7*R*,7a*R*)-6-methyl-3-methylene-2,3,3a,4,7,7a-hexahydrobenzofuran-7-ol (11)

A 15% solution of *n*-BuLi in hexane (0.40 ml, 0.64 mmol) was added under argon to a solution of **2** (0.063 g, 0.27 mmol) in THF (dried and distilled over sodium) (12 ml). The reaction mixture was stirred for 4 h at rt and allowed to stay overnight. EtOH (0.5 ml) was added dropwise. The solvent was distilled off. Ether (20 ml) was added to the residue. The precipitate was filtered off. The filtrate was evaporated and separated by CC on silica gel (4.5 g) using 0–100% ether gradient in hexane as eluent. This gave **10** (0.011 g, 0.049 mmol, 18%) and **11** (0.007 g, 0.04 mmol, 15%).

Compound **10**. $[\alpha]_D^{26}$ −29.4 (*c* 0.37, $CHCl_3$). ^{1}H NMR ($CDCl_3$ + CCl_4 (1:1), δ_H): 0.89 (3H, t; $J_{14,13}$ 7.0 Hz, H-14), 1.23–1.36 (4H, m; H-12, H-13), 1.38–1.53 (2H, m; H-11), 1.81 (3H, m; all $J \leqslant 2.5$ Hz, H-10), 1.92 (1H, dddq; ^2J 17.7, $J_{5e,6a}$ 5.2, $J_{5e,4}$4.6, $J_{5e,10}$ 1.5 Hz, H-5e), 2.05–2.11 (2H, m; H-9), 2.23 (1H, dddqd; ^2J 17.7, $J_{5a,6a}$ 11.1, $J_{5a,4}$ 2.5, $J_{5a,10}$ 2.5, $J_{5a,2e}$ 1.2 Hz, H-5a), 2.40 (1H, ddd; $J_{6a,5a}$ 11.1, $J_{6a,5e}$ 5.2, $J_{6a,1e}$ 2.2 Hz, H-6a), 3.82 (1H, br t; $J_{1e,2e}$ 3.4, $J_{1e,6a}$ 2.2 Hz, H-1e), 3.85

(1H, br d; $J_{2e,1e}$ 3.4 Hz, H-2e), 4.88 (1H, br s; H-8), 4.95 (1H, m; all $J \leqslant 2.0$ Hz, H-8′), 5.51 (1H, ddq; $J_{4,5e}$ 4.6, $J_{4,5a}$ 2.5, $J_{4,10}$ 1.4 Hz, H-4). ^{13}C NMR, δ_C: 71.13 (d; C-1), 71.82 (d; C-2), 131.77 (s; C-3), 125.35 (d; C-4), 24.84 (t; C-5), 38.44 (d; C-6), 150.03 (s; C-7), 110.37 (t; C-8), 35.99 (t; C-9), 20.86 (q; C-10), 27.78 (t; C-11), 31.64 (t; C-12), 22.58 (t; C-13), 14.11 (q; C-14). HR-MS: 224.1767 (M^+, $C_{14}H_{24}O_2$; calcd 224.1771).

Compound **11**. $[\alpha]_D^{26}$ −69.0 (*c* 0.23, $CHCl_3$). ^{1}H NMR ($CDCl_3$ + CCl_4 (1: 1), δ_H): 1.78 (3H, m; all $J \leqslant 2.5$ Hz, H-10), 2.03 (1H, dddq; ^2J 17.7, $J_{5e,6}$ 6.3, $J_{5e,4}$ 3.3, $J_{5e,10}$ 2.5 Hz, H-5e), 2.38 (1H, dddqd; ^2J 17.7, $J_{5a,6}$ 8.2, $J_{5a,4}$ 5.0, $J_{5a,10}$ 1.5, $J_{5a,2}$ 1.3 Hz, H-5a), 2.79 (1H, dddtdd; $J_{6,5a}$ 8.2, $J_{6,1}$ 6.9, $J_{6,5e}$ 6.3, $J_{6,9}$ 2.3, $J_{6,8'}$ 2.2, $J_{6,8}$ 1.1 Hz, H-6), 3.95 (1H, br. d; $J_{2,1}$ 5.2 Hz, H-2), 3.98 (1H, dd; $J_{1,6}$ 6.9, $J_{1,2}$ 5.2 Hz, H-1), 4.33 (1H, dtd; ^2J 13.2, $J_{8,9}$ 2.2, $J_{8,6}$ 1.1 Hz, H-8), 4.36 (1H, dtd; ^2J 13.2, $J_{8',9}$ 2.2, $J_{8',6}$ 2.2 Hz, H-8′), 4.87–4.92 (2H, m; H-9), 5.43 (1H, dddq; $J_{4,5a}$ 5.0, $J_{4,5e}$ 3.3, $J_{4,2}$ 1.8, $J_{4,10}$ 1.5 Hz, H-4). ^{13}C NMR, δ_C: 84.11 (d; C-1), 69.76 (d; C-2), 134.70 (s; C-3), 121.33 (d; C-4), 26.38 (t; C-5), 38.73 (d; C-6), 151.70 (s; C-7), 69.84 (t; C-8), 103.47 (t; C-9), 19.12 (q; C-10). HR-MS: 151.0755 (M^+-CH_3, $C_9H_{11}O_2$; calcd 151.0759).

4.11. (1*R*,2*R*,6*S*)-3-Methyl-6-(3-(propylthio)prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (12)

1-Propanethiol (0.100 μl, 1.11 mmol) was added to the suspense of NaOH (0.045 g, 1.13 mmol) in 2 ml EtOH. The reaction mixture was stirred for 20 min at rt (NaOH was fully dissolved). Then a solution of **2** (0.181 g, 0.733 mmol) in EtOH (6 ml) was added. The reaction mixture was stirred for 20 h at rt. The solvent was distilled off. The residue (0.288 g) was separated by CC on silica gel (9 g). This procedure gave **12** (0.103 g, 0.426 mmol, 58%). $[\alpha]_D^{26}$ −23.0 (*c* 0.88, $CHCl_3$). ^{1}H NMR ($CDCl_3$, δ_H): 0.93 (3H, t; $J_{13,12}$ 7.3 Hz, H-13), 1.49–1.61 (2H, m; H-12), 1.78 (3H, ddd; $J_{10,5a}$ 2.5, $J_{10,5e}$ 1.5, $J_{10,4}$ 1.3 Hz, H-10), 1.98 (1H, dddq; ^2J 17.6, $J_{5e,6a}$ 5.3, $J_{5e,4}$ 5.3, $J_{5e,10}$ 1.5 Hz, H-5e), 2.22 (1H, dddqd; ^2J 17.6, $J_{5a,6a}$ 11.0, $J_{5a,4}$ 2.5, $J_{5a,10}$ 2.5, $J_{5a,2e}$ 1.2 Hz, H-5a), 2.35 (1H, ddd; ^2J 12.7, $J_{11,12}$ 7.8, $J_{11,12'}$ 6.9, H-11), 2.39 (1H, ddd; ^2J 12.7, $J_{11',12'}$ 7.8, $J_{11',12}$ 6.6, H-11′), 2.71 (1H, dddd; $J_{6a,5a}$ 11.0, $J_{6a,5e}$ 5.3, $J_{6a,1e}$ 2.0, $J_{6a,8}$ 0.7 Hz, H-6a), 3.17 (1H, d; ^2J 13.5 Hz, H-9), 3.19 (1H, d; ^2J 13.5 Hz, H-9′), 3.84 (1H, br d; $J_{2e,1e}$ 3.1 Hz, H-2e), 3.87 (1H, dd; $J_{1e,2e}$ 3.1, $J_{1e,6a}$ 2.0 Hz, H-1e), 5.02 (2H, s; H-8), 5.60 (1H, ddq; $J_{4,5e}$ 5.3, $J_{4,5a}$ 2.5, $J_{4,10}$ 1.3 Hz, H-4). ^{13}C NMR, δ_C: 71.62 (d; C-1), 71.97 (d; C-2), 131.79 (s; C-3), 124.88 (d; C-4), 25.28 (t; C-5), 37.10 (d; C-6), 145.14 (s; C-7), 114.18 (t; C-8), 37.17 (t; C-9), 20.59 (q; C-10), 32.95 (t; C-11), 22.26 (t; C-12), 13.31 (q; C-13). HR-MS: 241.1253 (M^+−H, $C_{13}H_{21}O_2S$; calcd 241.1257).

4.12. Animals

The experiments were performed on C57BL/6 mice (male) weighing 25–30 g (SPF-vivarium of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences). Each experimental group consisted of 8 mice. The animals 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.

4.13. MPTP mouse model of Parkinson's disease[19]

MPTP was injected intraperitoneally to 8-weeks male mice of C57Bl/6 line weighing 22–25 g every 2 h for a total of 4 doses over a 6 h period in 1 day in a dose of 0.12 mmol/kg (20 mg/kg) for a total of 4 doses. The studied agent was administrated per os 24 h after the last injection of MPTP in a dose of 0.12 mmol/kg (20 mg/kg). The effectiveness of the studied medications was evaluated according to their ability to reduce the symptoms of hypokinesia induced by MPTP. Hypokinesia caused by neurotoxin administration was evaluated with the 'Open field' test performed for 2 min using TruScan (U.S.) 2 h after the administration of the studied agent, registering the main markers of the locomotor activity: time of locomotor activity (s), movement distance (cm), movement speed (cm/s) and immobility time (s).

Acknowledgements

The reported study was supported by RFBR, research project No. 12-03-31257.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.01.003.

References and notes

1. Dorsey, E. R.; Constantinescu, R.; Thompson, J. P.; Biglan, K. M.; Holloway, R. G.; Kieburtz, K.; Marshall, F. J.; Ravina, B. M.; Schifitto, G.; Siderowf, A.; Tanner, C. M. *Neurology* **2007**, *68*, 384.
2. Buck, K.; Ferger, B. *Drug Discovery Today* **2010**, *15*, 867.
3. Outeiro, T. F.; Ferreira, J. *Curr. Pharm. Des.* **2009**, *15*, 3968.
4. Obeso, J. A.; Rodriguez-Oroz, M. C.; Goetz, C. G.; Marin, C.; Kordower, J. H.; Rodriguez, M.; Hirsch, E. C.; Farrer, M.; Schapira, A. H. V.; Halliday, G. *Nat. Med.* **2010**, *16*, 653.
5. Hennemann, J.; Schatton, W. Parkinsonism Treatment. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Frankfurt am Main, Germany, 2008; 10.1002/14356007.a19 001.pub2.
6. Esposito, E.; Cuzzocrea, S. *Curr. Med. Chem.* **2010**, *17*, 2764.
7. Duvoisin, R. *Pharmacol. Ther.* **1987**, *32*, 1.
8. Rogers, D.; Lees, A. J.; Smith, E.; Trimble, M.; Stern, G. M. *Brain* **1987**, *110*, 761.
9. Schapira, A.; Bate, G.; Kirkpatrick, P. *Nat. Rev. Drug Disc.* **2005**, *4*, 625.
10. Tolstikova, T. G.; Pavlova, A. V.; Morozova, E. A.; Ardashov, O. V.; Il'ina, I. V.; Volcho, K. P.; Salakhutdinov, N. F.; Tolstikov, G. A. *Dokl. Biol. Sci.* **2010**, *435*, 398.
11. Ardashov, O. V.; Pavlova, A. V.; Il'ina, I. V.; Morozova, E. A.; Korchagina, D. V.; Karpova, E. V.; Volcho, K. P.; Tolstikova, T. G.; Salakhutdinov, N. F. *J. Med. Chem.* **2011**, *54*, 3866.
12. Ardashov, O. V.; Pavlova, A. V.; Korchagina, D. V.; Volcho, K. P.; Tolstikova, T. G.; Salakhutdinov, N. F. *Med. Chem.* **2012**, accepted for publication, Available at: http://www.ncbi.nlm.nih.gov/pubmed/23061568.
13. Sakuda, Y. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3348.
14. Trachtenberg, E. N.; Carver, J. R. *J. Org. Chem.* **1970**, *35*, 1646.
15. Stallcup, W. D.; Hawkins, J. E. *JACS* **1941**, *63*, 3339.
16. Sheehan, J. C.; Bolhofer, W. A. *JACS* **1950**, *72*, 2786.
17. Więcek, M.; Kottke, T.; Ligneau, X.; Schunack, W.; Seifert, R.; Stark, H.; Handzlik, J.; Kiêc-Kononowicz, K. *Bioorg. Med. Chem.* **2011**, *19*, 2850.
18. Speciale, S. G. *Neurotoxicol. Teratol.* **2002**, *24*, 607.
19. Jackson-Lewis, V.; Przeborski, S. *Nat. protocol.* **2007**, *2*, 141.
20. Il'ina, I. V.; Volcho, K. P.; Korchagina, D. V.; Barkhash, V. A.; Salakhutdinov, N. F. *Helv. Chim. Acta* **2007**, *90*, 353.
21. Ardashov, O. V.; Il'ina, I. V.; Korchagina, D. V.; Volcho, K. P.; Salakhutdinov, N. F. *Mendeleev Commun.* **2007**, *17*, 303.
22. Hale, W. J.; Britton, E. C. *JACS* **1919**, *41*, 841.