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Short Note

(1*R*,2*R*,6*S*)-2(4-(4-Isopropylbenzyl)piperazin-1-yl)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-enol

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder mainly characterized by movement dysfunction. 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 (Prottremin) demonstrated antiparkinsonian activity in vivo on different animal models of PD. The paper presents synthesis of new Prottremin derivative, (1*R*,2*R*,6*S*)-2(4-(4-isopropylbenzyl)piperazin-1-yl)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-enol. The derivative was obtained by epoxide ring opening reaction with 1-(4-isopropylbenzyl)piperazine. The product yield was 48% after purification.

Keywords: monoterpene; epoxide cycle opening; tertiary amine

1. Introduction

Parkinson's disease (PD) is one of the most common age-related movement disorders characterized by progressive death of nigrostriatal dopamine neurons, which leads to classical symptoms of PD including tremors, rigidity, and bradykinesia. [1]. Currently, therapy against PD is aimed at relieving symptoms for a long time. Levodopa, a direct metabolic precursor of dopamine, is the gold standard of PD treatment. Unfortunately, the drug is most effective only in the first few years of administration. Additionally, the "on-off" syndrome has been found in patients with PD taking Levodopa. During the "off" period the symptoms of PD return [2].

Earlier, it was demonstrated that Prottremin ((1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol) possessed potent antiparkinsonian activity in vivo on MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), rotenone, 6-hydroxydopamine (6-OHDA), and haloperidol models of PD on mice and rats at a dose of 20 mg/kg [3,4]. Further investigations showed that change in Prottremin configuration or removal of one of its functional groups (double bonds or alcohol groups) diminishes or decreases activity [3,5]. However, the addition of thiopropyl and butyl fragment to the Prottremin molecule at position 9 allows one to obtain compounds **2** and **3** with high antiparkinsonian activity [6]. In addition, epoxydiol **4**, an active metabolite of Prottremin, was synthesized. It was shown that epoxydiol **4** protected cultured dopamine neurons [7]. Recently, it was found that Prottremin derivative **PA96** alleviated symptoms of haloperidol-induced PD model at dose 1 mg/kg (active dose of Prottremin is 20 mg/kg) and protected cultured dopamine neurons against spontaneous and toxin-induced death of dopamine neurons [8]. Thus, the synthesis of new derivatives and analogues of Prottremin is an important task. Here, the synthesis of new derivative of Prottremin, (1*R*,2*R*,6*S*)-2-(4-(4-isopropylbenzyl)piperazin-1-yl)-3-methyl-6-(prop-1-en-2-yl) cyclohex-3-en-1-ol **1**, is presented (Figure 1).

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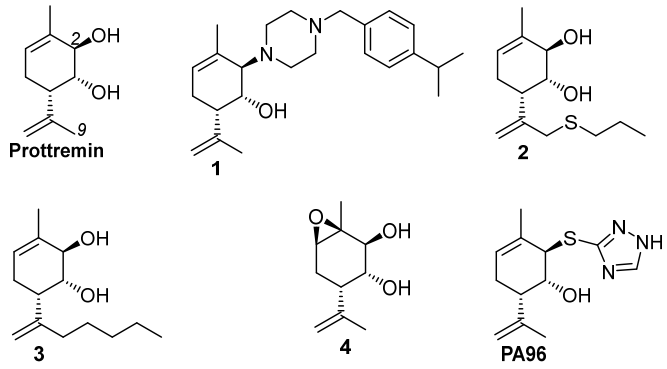
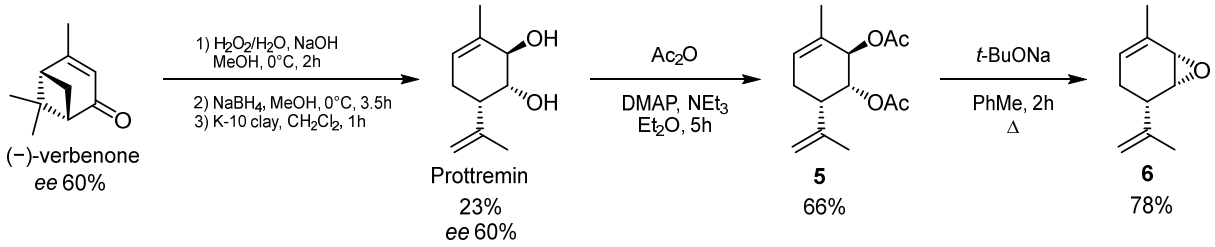


Figure 1. Prottremin and its derivatives.

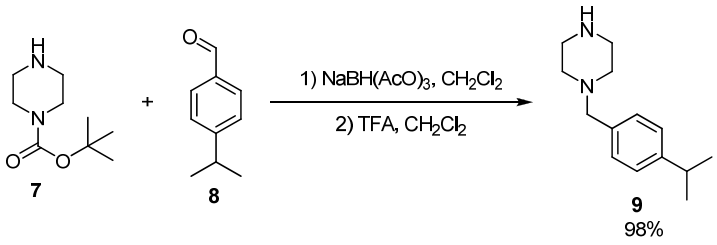
2. Results and Discussion

The synthesis of (1*R*,2*R*,6*S*)-2-(4-(4-isopropylbenzyl)piperazin-1-yl)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-en-1-ol **1** began with the preparation of Prottremin according to the method [3] from (−)-verbenone. The total yield of Prottremin over three stages was 23%. Thereafter, the reaction of Prottremin with acetic anhydride gave diacetate **5** [9]. After purification, diacetate **5** was refluxed with sodium *tert*-butoxide in toluene for 2 h affording the epoxide **6** at a 78% yield [8] (Scheme 1).



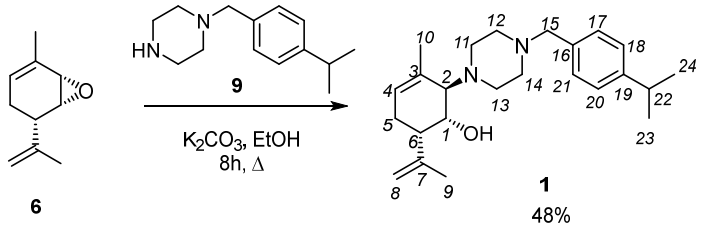
Scheme 1. Synthesis of (1*S*,5*S*,6*R*)-2-methyl-5-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]hept-2-ene **6**.

1-(4-Isopropylbenzyl)piperazine **9** was used for the modification of Prottremin and prepared according to [10]. This molecule contains fragments of monoterpene *p*-cymene demonstrating various pharmacological properties [11]. Piperazine is a versatile linker and pharmacophore for the construction of biologically active compounds [12]. At the first stage, 4-isopropylbenzaldehyde **8** reacted with *tert*-butyl piperazine-1-carboxylate **7** and 30 min sodium triacetoxyborohydride was added. After the work up of the reaction mixture, organic residue was involved in the reaction with trifluoroacetic acid for Boc-deprotection. The yield of product **9** was 98% (Scheme 2).



Scheme 2. Synthesis of 1-(4-isopropylbenzyl)piperazine **9**.

Reaction of epoxide **6** with 1-(4-isopropylbenzyl)piperazine **9** in the presence of potassium carbonate was carried out in ethanol. The reaction mixture was refluxed for 8 h. After purification by column chromatography on SiO_2, compound **1** was isolated with 48% yield (Scheme 3).



Scheme 3. Synthesis of (1*R*,2*R*,6*S*)-2-(4-(4-isopropylbenzyl)piperazin-1-yl)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-en-1-ol **1**.

3. Materials and Methods

3.1. General

All reagents and solvents are commercially available and used as supplied. Spectral and analytical measurements were obtained at the Multi-Access Chemical Research Center SB RAS (Novosibirsk, Russia). Column chromatography (CC): silica gel (SiO_2; 60–200 μ; *Macherey-Nagel*); hexane/EtOAc 100:0 → 0:100 and MeOH/CH_2Cl_2 (1:1). GC/MS (purity control and products analysis): Agilent 7890A (Agilent Technologies, Santa Clara, CA, USA) with a quadrupole mass spectrometer Agilent 5975C as a detector, HP-5MS quartz column, 30,000 × 0.25 mm, He (1 atm) as carrier gas. Optical rotation: *polAAr 3005* spectrometer (Optical Activity LTD, Huntingdon, UK), $CHCl_3$ soln. HR-MS: *DFS-Thermo-Scientific* spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) in a full scan mode (15–500 *m*/*z*, 70 eV electron-impact ionization, direct sample introduction) and Agilent 7200 Accurate Mass Q-TOF GC/MS (Agilent Technologies, Santa Clara, CA, USA) (70 eV, electron-impact ionization).^{1}H- and ^{13}C-NMR: *Bruker* Avance-III 600 (Bruker Corporation, Karlsruhe, Germany) apparatus at 600.30 MHz (^{1}H) and 150.95 MHz (^{13}C) and *Bruker* Avance 400 (Bruker Corporation, Karlsruhe, Germany) apparatus 400.13 MHz (^{1}H) and 100.61 MHz (^{13}C) in $CDCl_3$; chemical shifts δ in ppm rel. to residual $CHCl_3$ (δ (H) 7.24, δ (C) 76.90 ppm), *J* in Hz. Structure determinations: by analyzing the ^{1}H NMR spectra, including ^{1}H-^{1}H 2D homonuclear correlation (COSY); 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) = 135 Hz; HSQC, ^1J(C,H) = 145 Hz; HMBC, $^{2,3}J$(C,H) = 7 Hz). All the target compounds reported in this paper have a purity of at least 95%. Prottremin was synthesized according to [3] from (−)-verbenone (*Aldrich*).

(1*R*,2*R*,6*S*)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diacetate **5** was synthesized according to [9]. (1*S*,5*S*,6*R*)-2-Methyl-5-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]hept-2-ene **6** was synthesized from diacetate **5** according to [8].

*3.2. Synthesis of 1-(4-Isopropylbenzyl)piperazine **9***

4-Isopropylbenzaldehyde **8** (1.0 g, 6.75 mmol, 1 eq.) was added to the solution of *tert*-butyl piperazine-1-carboxylate **7** (1.26 g, 6.75 mmol, 1 eq.) in CH_2Cl_2 (50 mL). The reaction mixture was stirred for 30 min, and $NaBH(AcO)_3$ (2.0 g, 9.45 mmol) was added in small portions. After 1 h the reaction mixture was washed with a saturated solution of $NaHCO_3$ (3 × 20 mL). The organic layer was dried over Na_2SO_4. The desiccant was filtered off, the solvent was distilled off, the residue was dissolved in CH_2Cl_2 (10 mL), and TFA (3 mL) was added dropwise. The reaction mixture was stirred for 2 h, then washed with a saturated solution of K_2CO_3 (3 × 20 mL). The organic layer was dried over Na_2SO_4. The desiccant was filtered off, and the solvent was distilled off. The residue was purified by column chromatography on SiO_2 with CH_2Cl_2/MeOH (50%) as eluent, and the product (1.4 g, 98%) was obtained as slightly yellow oil. ^{1}H and ^{13}C spectra are consistent with the previous results [10]. HR-MS: 218.1777 ([M^+], $C_{14}H_{22}N_2$; calcd 218.1778).

3.3. Synthesis of (1R,2R,6S)-2-(4-(4-Isopropylbenzyl)piperazin-1-yl)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-en-1-ol ***1***

Et_3N (125 mg, 1.24 mmol, 1 eq.) was added to the solution of epoxide **6** (186 mg, 1.24 mmol, 1 eq.) and 1-(4-isopropylbenzyl)piperazine **9** (297 mg, 1.36 mmol, 1.1 eq.) in EtOH (10 mL). The reaction mixture was refluxed for 8 h, and then the solvent was evaporated, and the residue was diluted with EtOAc (10 mL) and washed with brine (3 × 10 mL). The organic layer was dried over Na_2SO_4. The desiccant was filtered off, the solvent was distilled off, and the residue was purified by column chromatography on SiO_2 with EtOAc/hexane gradient (0–100%). The compound **1** (222 mg, 48%) was obtained as a slightly yellow oil. $[\alpha]_D^{26} = -27.7$ (*c* 0.39, $CHCl_3$). ^{1}H-NMR ($CDCl_3$, δ_H, ppm, J, Hz): 1.22 (s, 3H, H-23 or H-24), 1.23 (s, 3H, H-23 or H-24), 1.53–1.62 (m, 1H, OH), 1.72 (s, 3H, H-10), 1.82 (s, 3H, H-9), 1.91 (ddm, J = 16.7, 4.6, 1H, H_e-5), 2.10–2.21 (m, 1H, H_a-5), 2.25 (dd, J = 11.3, 4.4, H-6), 2.41 (br. s, 4H, H-12, H-14), 2.53–2.63 (m, 2H, H-11 or H-13), 2.71–2.80 (m, 2H, H-11 or H-13), 2.87 (sept, 1H, H-22), 2.96 (br. s, 1H, H-2), 3.45 (s, 2H, H-15), 4.08 (br. s, 1H, H-1), 4.80 (br. s, 1H, H-8), 4.94 (br. s, 1H, H-8), 5.63–5.68 (m, 1H, H-4), 7.15 (d, J = 8.0, 2H, H-18, H-20), 7.21 (d, J = 8.0, 2H, H-17, H-21). ^{13}C-NMR ($CDCl_3$, δ_C, ppm): 147.42 (s; C-16), 145.99 (s; C-7), 135.23 (s; C-19), 131.15 (s; C-3), 129.11 (d; C-17, C-21), 126.04 (d; C-18, C-20), 124.78 (d; C-4), 110.97 (t; C-9), 67.85 (d; C-2), 64.97 (d; C-1), 62.86 (t; C-15), 54.03 (t; C-12, C-14), 49.10 (t; C-11, C-13), 42.62 (s; C-6), 33.60 (d; C-22), 23.88 (t; C-5), 23.88 (q; C-23, C-24), 22.85 (q; C-8), 21.85 (q; C-10). HR-MS: 368.2826 ([M^+], $C_{24}H_{36}N_2O$; calcd 368.2822).

^{1}H-NMR, ^{13}C-NMR, 2D correlation spectra ^{1}H-^{1}H (COSY), ^{1}H-^{13}C (HSQC, HMBC), and mass spectra of compound **1** are presented in Supplementary Materials.

4. Conclusions

The method for preparation of Prottremin derivative with aryl-piperazine substituent at C-2 position was developed. According to this method, (1*R*,2*R*,6*S*)-2-(4-(4-isopropylbenzyl) piperazin-1-yl)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-en-1-ol **1** was synthesized in 48% yield. Its structure was determined by 1D and 2D NMR experiments (HSQC, HMBC, COSY) and HRMS.

Supplementary Materials: The following supporting information can be downloaded online: Figure S1: ^{1}H NMR spectra of compound **1** ($CDCl_3$, 400 MHz); Figure S2. ^{13}C NMR spectrum of compound **1** ($CDCl_3$, 100 MHz); Figure S3. ^{13}C NMR spectrum (JMOD) of compound **1** ($CDCl_3$, 100 MHz); Figure S4. HSQC spectrum of compound **1** ($CDCl_3$, ^{1}H(400 MHz), ^{13}C(100 MHz)); Figure S5. An expanded view of HSQC spectrum of compound **1** ($CDCl_3$, ^{1}H(400 MHz), ^{13}C(100 MHz)); Figure S6. COSY spectrum of compound **1** ($CDCl_3$, 400 MHz); Figure S7. HMBC spectrum of compound **1** ($CDCl_3$, ^{1}H(400 MHz), ^{13}C(100 MHz)); Figure S8. Mass-spectrum of compound **1**; Figure S9. ^{1}H NMR spectra of compound **6** ($CDCl_3$, 600 MHz). (*-residual solvent); Figure S10. ^{13}C NMR spectrum (JMOD) of compound **6** ($CDCl_3$, 150 MHz). (*-residual solvent) Figure S11. HSQC spectrum of compound **6** ($CDCl_3$, ^{1}H(600 MHz), ^{13}C(150 MHz)); Figure S12. HMBS spectrum of compound **6** ($CDCl_3$, ^{1}H(600 MHz), ^{13}C(150 MHz)); Figure S13. COSY spectrum of compound **6** ($CDCl_3$, 600 MHz); Figure S14. Mass-spectrum of compound **6**.

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

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