molbank

MDPI

Short Note

(1*R*,2*R*,6*S*)-3-Methyl-6-(3-(4-phenylpiperidin-1-yl)prop-1-en-2-yl)cyclohex-3-ene-1,2-diol

Alexandra V. Podturkina, Nikolai S. Li-Zhulanov *, Tatyana V. Rybalova, Konstantin P. Volcho and Nariman F. Salakhutdinov

N. N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Lavrentiev Avenue 9, 630090 Novosibirsk, Russia; volcho@nioch.nsc.ru (K.P.V.)
* Correspondence: lizhulan@nioch.nsc.ru; Tel.: +7-(383)-330-8870

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder whose primary manifestation is motor dysfunction. Previous research showed that (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (Prottremine) exhibits potent antiparkinsonian activity in animal models of PD, with an efficacy comparable to levodopa. Herein, we report the synthesis of a new Prottremine derivative, (1*R*,2*R*,6*S*)-3-methyl-6-(3-(4-phenylpiperidin-1-yl)prop-1-en-2-yl)cyclohex-3-ene-1,2-diol. The compound was fully characterized and its structure was confirmed through single-crystal X-ray diffraction analysis.

Keywords: monoterpenoids; prottremine; piperidine; antiparkinsonian activity

1. Introduction

Parkinson's disease (PD) is a severe neurodegenerative disorder causing hypokinesia, tremors, and rigidity [1–3]. Although most common in the elderly, it can also manifest in younger individuals [4,5]. The key pathological features include the loss of dopaminergic neurons in the *substantia nigra*, leading to dopamine deficiency, and the accumulation of α-synuclein in Lewy bodies, which drive disease progression [6,7]. Currently, there is no cure for PD, and the medications used to manage its symptoms are not always effective while often causing problematic side effects [8,9]. For instance, while levodopa, a dopamine precursor, is the most effective treatment for PD's symptoms, its long-term use can cause patients to experience rapid onsets of immobility following periods of normal movement [10,11].

Previously it was shown that Prottremine (Scheme 1) exhibited antiparkinsonian efficacy comparable to levodopa in vivo in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, 6-hydroxydopamine (6-OHDA), and haloperidol models of Parkinson's disease in mice and rats at a dose of 20 mg/kg [12,13]. It should be noted that Prottremine demonstrated low acute toxicity in mice (LD_{50} = 4250 mg/kg) [12]. Subsequent studies showed that modifying the C-10 position of the isopropenyl fragment in the Prottremine molecule yielded new active derivatives. In particular, compounds containing thiopropyl and butyl substituents demonstrated pronounced antiparkinsonian effect [14]. We designed a new derivative of Prottremine incorporating a phenylpiperidine fragment, a structural motif similar to one present in MPTP. We hypothesize that this modification might influence the interaction with dopamine transporters and, potentially, the antiparkinsonian activity.

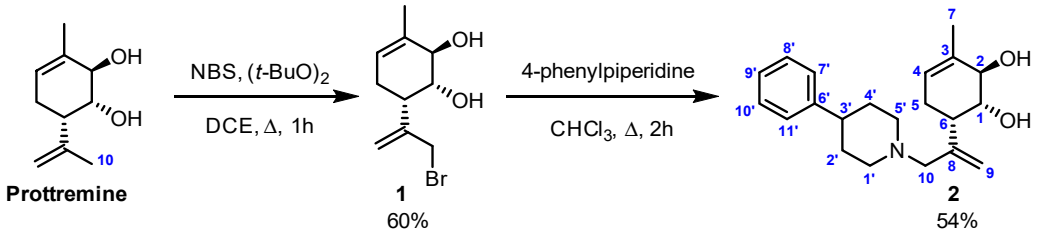
check for updates

Academic Editor: R. Alan Aitken

Received: 29 October 2025
Revised: 7 November 2025
Accepted: 11 November 2025
Published: 12 November 2025

Citation: Podturkina, A.V.; Li-Zhulanov, N.S.; Rybalova, T.V.; Volcho, K.P.; Salakhutdinov, N.F. (1*R*,2*R*,6*S*)-3-Methyl-6-(3-(4-phenylpiperidin-1-yl)prop-1-en-2-yl)cyclohex-3-ene-1,2-diol. *Molbank* **2025**, *2025*, M2088. https://doi.org/10.3390/M2088

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

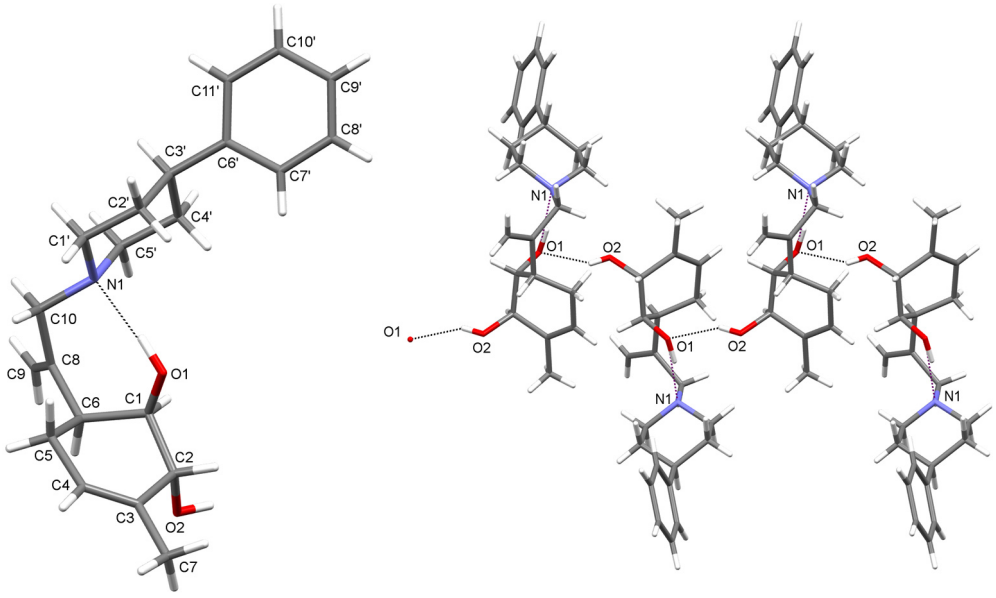


Scheme 1. Synthesis of (1*R*,2*R*,6*S*)-3-methyl-6-(3-(4-phenylpiperidin-1-yl)prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (**2**).

2. Results and Discussion

The synthesis of (1*R*,2*R*,6*S*)-3-methyl-6-(3-(4-phenylpiperidin-1-yl)prop-1-en-2-yl)cyclohex-3-ene-1,2-diol began with the preparation of bromide **1** which was synthesized following an improved procedure by boiling Prottremine and *N*-bromosuccinimide (NBS) in the presence of $(t\text{-BuO})_2$ in 1,2-dichloroethane, the product yield being 60% [15]. Reaction of bromide **1** with phenylpiperidine was carried out in chloroform by refluxing for 2 h. After purification by column chromatography on SiO_2 product **2** was isolated with 54% yield (Scheme 1).

The structure of product **2** was determined via 1D and 2D NMR experiments (HSQC, HMBC, and COSY) and HRMS. Moreover, we successfully isolated crystals of compound **2** through recrystallization from ethyl acetate and confirmed the structure via an X-ray diffraction analysis (Figure 1).



(**a**) (**b**)

Figure 1. Molecular structure (**a**) and fragment of H-bonded 1D-motif in crystals of compound **2** (**b**).

The piperidine cycle has a chair conformation with sp^3-hybridizied nitrogen atom which deviates from the plane C10C1′C5′ by 0.454(3) Å. Phenyl substituent on C3′ lays in axial position to piperidine cycle and is oriented with torsional angle C2′C3′C6′C7′ equaling to 75°. The hexene cycle adopts half-chair conformation, atoms C2–C5 lay in common plane in the limits of ±0.003(3)Å while atoms C1 and C6 deviate from this plane by 0.388(4) and 0.398(4) Å correspondently. Both hydroxy groups on cyclohexene ring are axial and oriented along intramolecular O1-H. . .N1 (Figure 1a) and intermolecular O2-H. . .O1 (Figure 1b) H-bonds. The strong intramolecular H-bond O1-H. . .N1 between the nitrogen atom of the piperidine ring and the hydroxyl group at position 1 restricts

rotation around single bonds of N1C10C8C6 moiety, thus forming six-membered cycle C10C8C6C1O1(H)...N1 which adopts a distorted chair conformation with absolute values of torsion angles being in the range from 41 to 76°. Due to the intermolecular O2-H...O1 hydrogen bond, the molecules in crystals are organized to hydrogen-bonded chains along axis a with head-to-tail orientation of neighboring molecules (Figure 1b). The parameters of these bonds are as follows: distances O-H—0.89(4) and 0.85(5), H...O—1.85(4) and 2.12(5) and O...N/O—2.714(3) and 2.907(3)Å, angles O-H...N/O 164(4) and 154(4)° for O1-H...N1 and O2-H...O1, respectively. There are no other significant intermolecular short contacts or interactions affecting the crystal packing.

3. Materials and Methods

General Information: 4-phenylpiperidine 97% (Macklin, Shanghai, China), *N*-bromosuccinimide 99% (Alfa Aesar, Haverhill, MA, USA), di-*tert*-butyl peroxide 98% (Sigma Aldrich, St. Louis, MO, USA). 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. 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. Melting points were determined using a Mettler Toledo FP900 Thermosystem (Greifensee, Switzerland). 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). ^{1}H- and ^{13}C-NMR: Bruker Avance 400 (Bruker Corporation, Karlsruhe, Germany) apparatus at 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%. Prottremine was synthesized according to [12] from (1*S*)-(–)-verbenone (Sigma Aldrich, St. Louis, MO, USA). Bromide **1** was synthesized from Prottremine according to [15].

The X-ray diffraction experiment was carried out on a Bruker KAPPA APEX II (Madison, WI, USA) diffractometer at 296 K (graphite-monochromated Mo Kα radiation). Reflection intensities were corrected for absorption by *SADABS*2016/2 program [16,17]. The structures were solved by direct methods using the *SHELXT*2014/5 [18] and refined by anisotropic (isotropic for all H atoms) full-matrix least-squares method against F^2 of all reflections by *SHELXL*2018/3 [19]. The positions of the hydrogen atoms were calculated geometrically and refined in riding model, while the hydroxyl hydrogen were localized from density difference map and refined independently. Molecular structures of compounds are drawn in Figure 1.

*Synthesis of (1R,2R,6S)-3-Methyl-6-(3-(4-phenylpiperidin-1-yl)prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (***2***)*

4-Phenylpiperidine (127 mg, 0.79 mmol) was added to the solution of bromide **1** (163.2 mg, 0.66 mmol) in $CHCl_3$ (15 mL). The reaction mixture was refluxed for 2 h, 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%). Compound **2** (116.5 mg, 54%) was obtained as slightly yellow powder. Melting point: 132.3 °C (EtOAc) with subsequent decomposition. $[\alpha]_D^{22.7}$ − 21.4 (c 0.42, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$ δ, ppm): 7.29–7.23 (2H, m, H-7′, H-11′), 7.21–7.14 (3H, m, H-8′, H-9′, H-10′), 5.64–5.60 (1H, m, H-4), 5.15 (1H, d, *J* = 2.1 Hz, H-9), 4.94 (1H, s, H-9), 3.89 (1H, d, *J* = 3.4 Hz, H-2), 3.71 (1H, dd, *J* = 3.4, 1.8 Hz, H-1), 3.22–3.14 (2H, m, H-10, H-1′ or H-5′), 3.06–2.99 (1H, m, H-1′ or H-5′), 2.76–2.70 (2H, m, H-10, H-6), 2.55–2.45 (1H, m, H-3′), 2.40–2.29 (1H, m, H-5), 2.26–2.18 (1H, m, H-1′ or H-5′), 2.01–1.92 (1H, m, H-5), 1.91–1.85 (1H, m, H-1′ or H-5′), 1.85–1.74 (7H, m, H-2′, H-4′, H-7).

^{13}C-NMR (101 MHz, $CDCl_3$, δ, ppm): 146.2 (C-8), 145.4 (C-6′), 132.4 (C-3), 128.3 (C-7′, C-11′), 126.7 (C-8′, C-10′), 126.1 (C-9′), 124.4 (C-4), 119.0 (C-9), 73.6 (C-1), 72.5 (C-2), 62.1 (C-10), 54.7, 52.5 (C-1′, C-5′), 42.8 (C-6), 42.3 (C-3′), 32.9, 32.6 (C-2′, C-4′), 26.1 (C-5), 20.8 (C-7). HR-MS: 327.2191 ([M^+], $C_{21}H_{29}NO_2^+$; calcd. 327.2193).

^{1}H NMR, ^{13}C NMR, and mass spectra of compound **2** are presented in Supplementary Materials.

Crystallographic data for **2**: $C_{21}H_{29}NO_2$, *M* = 327.45, orthorhombic, $P2_12_12_1$, *a* = 9.3484(6), *b* = 13.914(1), *c* = 14.484(1) Å, *V* = 1883.9(2) Å^3, *Z* = 4, D_{calcd} = 1.155 g·cm^{-3}, μ(Mo-*K*α) = 0.07 mm^{-1}, F(000) = 712, (θ = 2.6–27.0°, completeness (2θ = 50°) 99.8%), colorless, 1.00 × 0.60 × 0.30 mm^3, transmission 0.855–0.901, 38,409 measured reflections in index range $-11 \leq h \leq 11$, $-17 \leq k \leq 17$, $-18 \leq l \leq 18$, 4115 independent (R_{int} = 0.052), 230 parameters, 0 restraints, R_1 = 0.048 (for 3595 observed $I > 2\sigma(I)$), wR_2 = 0.153 (all data), GOOF = 1.08, largest diff. peak and hole are 0.23 and −0.16 e.A^{-3}.

Crystallographic data for **2** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 2497127. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-12-2333-6033 or e-mail: deposit@ccdc.cam.ac.uk; internet: www.ccdc.cam.ac.uk).

4. Conclusions

The method for preparation of Prottremine derivative with phenyl-piperidine substituent at C-10 position was developed. According to this method, (1*R*,2*R*,6*S*)-3-methyl-6-(3-(4-phenylpiperidin-1-yl)prop-1-en-2-yl)cyclohex-3-ene-1,2-diol **2** was synthesized in 54% yield. Its structure was determined by 1D and 2D NMR experiments (HSQC, HMBC, COSY), HRMS and XRD.

Supplementary Materials: The following supporting information can be downloaded online: Figure S1: ^{1}H NMR spectra of compound **2**; Figure S2: ^{13}C NMR spectrum of compound **2**; Figure S3: HSQC spectrum of compound **2**; Figure S4: HMBC spectrum of compound **2**; Figure S5: HRMS of compound **2**.

Author Contributions: Conceptualization: A.V.P., N.S.L.-Z., K.P.V. and N.F.S.; investigation: A.V.P., T.V.R. and N.S.L.-Z.; writing—original draft preparation: A.V.P., T.V.R. and N.S.L.-Z.; writing—review and editing: K.P.V. and N.F.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Russian Science Foundation (Moscow, Russia) with grant number 24-73-00139.

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

Acknowledgments: The authors would like to acknowledge the Multi-Access Chemical Service Centre SB RAS for spectral and analytical measurements.

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

References

1. Balestrino, R.; Schapira, A.H.V. Parkinson disease. *Eur. J. Neurol.* **2020**, *27*, 27–42. [CrossRef] [PubMed]
2. Dejanovic, B.; Sheng, M.; Hanson, J.E. Targeting synapse function and loss for treatment of neurodegenerative diseases. *Nat. Rev. Drug Discov.* **2024**, *23*, 23–42. [CrossRef] [PubMed]
3. Klein, C.; Westenberger, A. Genetics of Parkinson's disease. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a008888. [CrossRef] [PubMed]
4. Tysnes, O.-B.; Storstein, A. Epidemiology of Parkinson's Disease. *J. Neural Transm.* **2017**, *124*, 901–905. [CrossRef] [PubMed]
5. Dorsey, E.R.; Sherer, T.; Okun, M.S.; Bloem, B.R. The Emerging Evidence of the Parkinson Pandemic. *J. Park. dis.* **2018**, *8*, S3–S8. [CrossRef] [PubMed]
6. Del Tredici, K.; Braak, H. Review: Sporadic Parkinson's disease: Development and distribution of α-synuclein pathology. *Neuropathol. Appl. Neurobiol.* **2016**, *42*, 33–50. [CrossRef] [PubMed]
7. Koeglsperger, T.; Rumpf, S.L.; Schließer, P.; Struebing, F.L.; Brendel, M.; Levin, J.; Trenkwalder, C.; Höglinger, G.U.; Herms, J. Neuropathology of incidental Lewy body & prodromal Parkinson's disease. *Mol. Neurodegener.* **2023**, *18*, 32. [CrossRef] [PubMed]
8. Armstrong, M.J.; Okun, M.S. Diagnosis and Treatment of Parkinson Disease A Review. *JAMA* **2020**, *323*, 548–560. [CrossRef] [PubMed]
9. Oertel, W.; Schulz, J.B. Current and experimental treatments of Parkinson disease: A guide for neuroscientists. *J. Neurochem.* **2016**, *139*, 325–337. [CrossRef] [PubMed]
10. Chopade, P.; Chopade, N.; Zhao, Z.; Mitragotri, S.; Liao, R.; Chandran Suja, V. Alzheimer's and Parkinson's disease therapies in the clinic. *Bioeng. Transl. Med.* **2023**, *8*, e10367. [CrossRef] [PubMed]
11. di Biase, L.; Pecoraro, P.M.; Carbone, S.P.; Caminiti, M.L.; Di Lazzaro, V. Levodopa-Induced Dyskinesias in Parkinson's Disease: An Overview on Pathophysiology, Clinical Manifestations, Therapy Management Strategies and Future Directions. *J. Clin. Med.* **2023**, *12*, 4427. [CrossRef] [PubMed]
12. 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. Highly Potent Activity of (1*R*,2*R*,6*S*)-3-Methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol in Animal Models of Parkinson's Disease. *J. Med. Chem.* **2011**, *54*, 3866–3874. [CrossRef] [PubMed]
13. Valdman, E.; Kapitsa, I.; Ivanova, E.; Voronina, T.; Ardashov, O.; Volcho, K.; Khazanov, V.; Salakhutdinov, N. Evolution of anti-parkinsonian activity of monoterpenoid (1*R*,2*R*,6*S*)-3- methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol in various in vivo models. *Eur. J. Pharmacol.* **2017**, *815*, 351–363. [CrossRef] [PubMed]
14. Ardashov, O.V.; Pavlova, A.V.; Korchagina, D.V.; Volcho, K.P.; Tolstikova, T.G.; Salakhutdinov, N.F. 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. *Bioorg. Med. Chem.* **2013**, *21*, 1082–1087. [CrossRef] [PubMed]
15. Podturkina, A.V.; Ardashov, O.V.; Soldatova, Y.V.; Poletaeva, D.A.; Smolina, A.V.; Vasyuchenko, E.P.; Vyatkin, Y.V.; Li-Zhulanov, N.S.; Faingold, I.I.; Salakhutdinov, N.F.; et al. Inhibitory Activity of N- and S-Functionalized Monoterpene Diols Towards Monoamine Oxidases A and B. *Int. J. Mol. Sci.* **2025**, *26*, 97. [CrossRef] [PubMed]
16. *SADABS*, v. 2016-2; Bruker AXS: Madison, WI, USA, 2016.
17. Krause, L.; Herbst-Irmer, R.; Sheldrick, G.M.; Stalke, D.J. Comparison of silver and molybdenum microfocus X-ray sources for single-crystal structure determination. *J. Appl. Cryst.* **2015**, *48*, 3–10. [CrossRef] [PubMed]
18. Sheldrick, G.M. *SHELXT*—Integrated space-group and crystal-structure determination. *Acta Crystallogr. Sect. A* **2015**, *A71*, 3–8. [CrossRef] [PubMed]
19. Sheldrick, G.M. Crystal Structure Refinement with *SHELXL*. *Acta Crystallogr. Sect. C* **2015**, *C71*, 3–8. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.