(1*R*, 2*R*, 6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol derivatives as promising compounds for anti-Parkinsonian activity.

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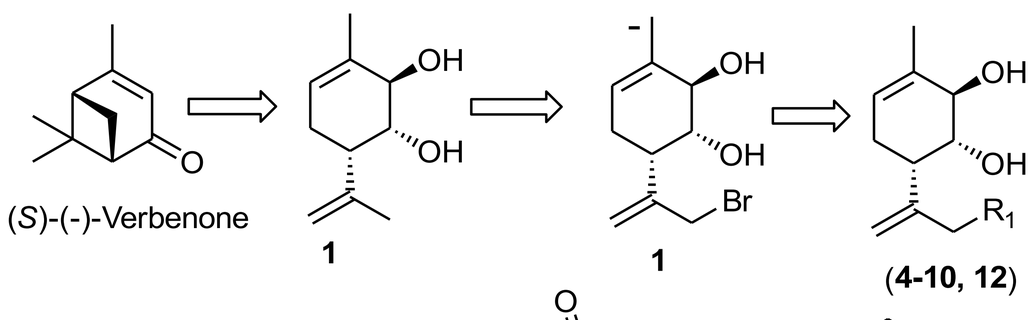
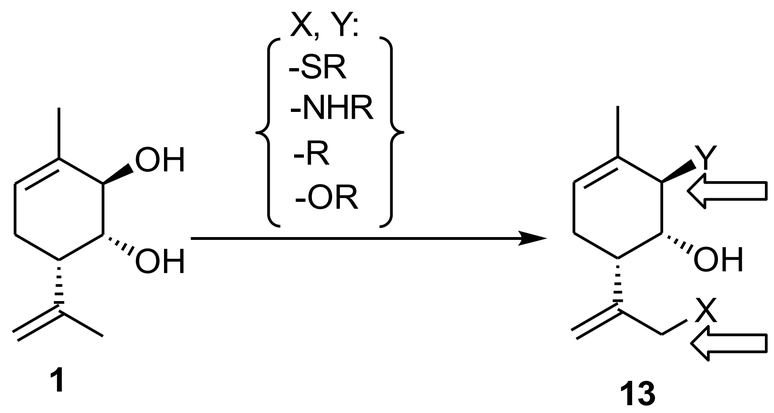
Introduction

- Parkinson's disease is a progressive neurodegenerative disorder.
- Levodopa, the main drug for Parkinson's disease treatment, has serious side effects.
- We have investigated that monoterpenoid (1*R*, 2*R*, 6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol (**1**) demonstrated high anti-Parkinsonian activity[1].
- Now we report on the obtained derivatives of compound **1**, modified at different allylic positions.

Synthesis of **1** and it's derivatives[1,2]



Synthesis of compound **1** derivaties, modified at different allylic positions



Results:

Previous research showed that interpose in molecule of (1*R*, 2*R*, 6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol different substitutes (hydroxyl group (**4**), amino group (**5**), phthalimide (**6**), morpholine (**7**), a derivative of 2-aminoadamantane (**8**), 1,1-Dimethylethylenediamine (**9**), butyl (**10**) and propylthio (**12**)) led to decrease in activity, a few new compounds demonstrated promising anti-Parkinsonian activity. The butyl and thiopropyl derivatives **10** and **12** were the most active among the synthesized 9-derivatives of compound **1** , 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**[2]. (Table 1)

At current research we have synthesized compounds **13** with several modifications at different sites were carried out. Although most modifications led to decrease in activity, a few new compounds demonstrated promising anti-Parkinsonian activity.

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.

Acknowledgements:

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Reference:

(1)Ardashov, O.V., et al. Highly Potent Activity of (1R,2R,6S)-3-Methyl-6-(prop-1-en-2-yl)cyclohex3-ene-1,2-diol in Animal Models of Parkinson's Disease. J. Med. Chem 2011;54: 3866-3874.

(2)Ardashov, O.V., et al. 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