Synthesis of new 1-substituted isoquinolines with potential anti-Parkinson activity

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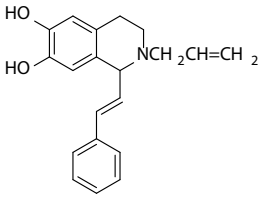
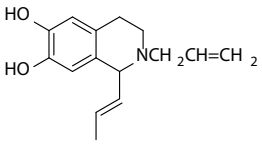
Introduction/Objectives: Dopaminergic ligands can bind to D_1-like (D_1 and D_5) and D_2-like (D_2, D_3 and D_4) dopamine receptors (DR) to "restore" the dopaminergic pathway. Agonists can be useful in the treatment of Parkinson's disease. Tetrahydroisoquinolines (THIQs) display important pharmacological activities including DR binding. Therefore, the aim of this study was to obtain new 1-substituted THIQs with dopaminergic activity. **Material/Methods**: (*E*)-1-Styryl-THIQs and (*E*)-1-(propenyl)-THIQs were synthesized *via* Bischler–Napieralski cyclization, and tested *in vitro* for their affinity towards DR in rat striatum. Functional assays to agonist activity was performed by measuring inhibition of forskolin-estimulated cyclic AMP production in CHO-K1 cells stably expressing human D_2 receptors. Cytotoxicity studies were carried out in both human neutrophils and HUVEC by MTT assay. Molecular modeling studies (MM) on DRs were performed to determine ligand/receptor complex interactions. **Results**: 1-Substituted IQs were synthesized bearing 1-styryl or 1-propene substituent. Catecholic IQs displayed affinity towards D_1-DR and D_2-DR at μM and nM concentrations, respectively. *N*-methyl or *N*-allyl groups improved considerably the affinity towards D_2-like DR. The most active compounds, **1e** and **2e**, also showed high selectivity (K_i= 41 nM and 18 nM; K_i D_1/D_2 ratio= 147 and 95, respectively). The cAMP assays indicated that **1e** and **2e** behaved as full agonist (EC_{50} = 500 nM and 555 nM, respectively) with maximal efficacy values similar to quinpirole at 10 μM. None of these THIQs displayed relevant cytotoxicity in human cells. In agreement with the experimental data, MM studies on DRs revealed stronger molecular interactions with D_2-DR than with D_1-DR. **Conclusions**: The catechol group and *N*-substitution at the IQ nucleus improved the affinity towards D_2-DR. Therefore, **1e** and **2e**, are potential candidates to be used in the treatment of PD.



1-(Styryl)-THIQ **1e**
(*series 1*)



1-(Prop-1-en-yl)-THIQ **2e**
(*series 2*)

Key words: Tetrahydroisoquinolines; synthesis; dopamine receptors; Parkinson disease