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# Multi-Target Prediction of Neuroprotective Drugs, Synthesis, Assay, and Theoretical Study of Rasagiline Carbamates

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**Abstract:** In this work, we developed a multi-target model for neuroprotective compounds reported in the CHEMBL database. The model predicted correctly >8300 experimental outcomes with Accuracy, Specificity, and Sensitivity above 80-90% in training and external validation series. This is model can different outcomes for >30 experimental measures in >400 different experimental protocols and related to >150 molecular and cellular targets present in 11 different organisms (including human). After that, we reported by the first time, the synthesis, characterization, and experimental assays of new series of chiral 1,2-rasagiline carbamate derivatives; not reported in previous works. This work is a synopsis of the results presented in our previous paper: Int J Mol Sci. 2014 Sep 24;15(9):17035-64. doi: 10.3390/ijms150917035.

**Keywords:** CHEMBL; Neuroprotective agents; Rasagiline derivatives; Asymmetric synthesis

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## 1. Introduction

The discovery of new drugs for the treatment of neurodegenerative diseases such as Alzheimer's, Parkison's, and Huntington's diseases, Friedreich ataxia and others an important goals of medicinal chemistry [1-4]. In order to develop such computational models we need to use modeling techniques to process chemical information from public databases. These databases have accumulated immense datasets of experimental results of pharmacological trials for many compounds. For instance, CHEMBL[5, 6], https://www.ebi.ac.uk/chembldb, is one of the biggest with more than 11,420,000 activity data

for >1,295,500 compounds, and 9,844 targets. In our previous work, we reported the first multi-target, multi-output, and multi-scale ALMA model for CHEMBL data of neuroprotective / neuro-toxic effect of drugs. After that, we reported by the first time, the synthesis, characterization, and experimental assays of new series rasagiline carbamate derivatives; not reported in previous works.

## RESULTS AND DISCUSSION

### 1.1. Development of New Model for Prediction of Drug-Target Networks

**Model training and validation.** We report a model to predict when the $i^{th}$ compound may present a high ($L_{ij}(c_q) = 1$) or not ($L_{ij}(c_q) = 0$) value of the experimental parameter used to characterize interaction with a molecular or cellular target involved in neuroprotective/neurodegenerative process. The output $S_{ij}(c_q)$ of our multi-output model depend on both chemical structure of the $i^{th}$ drug $d_i$ and the set of conditions selected to perform the biological assay ($c_q$) including the $j^{th}$ target, of course. In consonance, the ALMA model should predict different probabilities if we change the organisms ($c_1$), the biological assays ($c_2$), the molecular / cellular target ($c_3$), or the standard experimental parameter measured ($c_4$), for the same compound [7]. The best ALMA-entropy model found in this work was:

$$S_{ij}(c_q) = 1.1396 - 0.4039 \cdot p(c_l)?\theta_1^i + 0.1993 \cdot \Delta\theta_1^i(s_x) + 0.4349 \cdot \Delta\theta_1^i(a_u) \quad (4)$$
$$- 0.0202 \cdot \Delta\theta_1^i(o_t) - 0.0017 \cdot \Delta\theta_1^i(t_e)$$
$$N = 2661 \quad R_c = 0.72 \quad \chi^2 = 1913.007 \quad p < 0.005$$

The statistical parameters for the above equation in training are: Number of cases used to train the model (N), Canonical Regression Coefficient (Rc), Chi-square ($\chi^2$), and p-level [8]. The probability cut-off for this LDA model is ${}^{i}p_1(c_q) > 0.5 \Rightarrow L_{ij}(c_q) = 1$. It means that the drug $d_i$ predicted by the model with probability > 0.5 are expected to give a positive outcome in the $q^{th}$ assays carry out under the given set of conditions $c_q$. This ALMA-entropy model present excellent performance in both training and external validation series with Sensitivity (Sn), Specificity (Sp), and Accuracy (Ac) > 80%. Values higher than 75% are acceptable for LDA-QSAR models, according to previous reports [9-13].

### 1.2. Experimental and Theoretical Study of New Compounds

**Synthesis and experimental assay of new 1,2-rasagiline derivatives.** The compounds **2**, **3**, **4**, **5**, **6**, **7**, **8** and **9** were synthesized according to the strategy given in **Figure 2**. As shown in this scheme, they were synthesized from the aminoalcohol **1** [(1*R*,2*S*)-(+)-1-amino-2-indanol], a commercial product. The alkylation of **1** with propargyl bromide and potassium carbonate in hot acetonitrile provided, in a global yield of 92%, a mixture of the corresponding mono- and dipropargylated derivatives (**2** and **3**), which were separated by flash column chromatography using hexane/EtOAc (3:1) as eluent. Compound **3** was converted to the corresponding acetate (**4**) and benzoate (**5**) by treatment with acetic anhydride or benzoyl chloride, $Et_3N$ and catalytic amounts of DMAP in MeCN. The carbamate derivatives (**6**, **7**, **8** and **9)** were synthesized, from the hidroxy mono- or dipropargylaminoindans (**2** and **3**), by reaction with the corresponding dialkylcarbamyl chloride in NaH and acetonitrile following the procedure described in the literature [14].

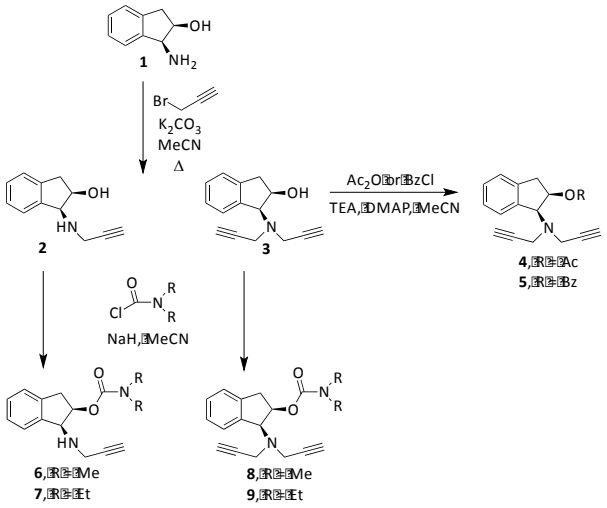


**Figure 1**. Synthesis of compounds **2-9**

The new compounds synthesized in this work (**2**, **3**, **4**, **5**, **6**, **7**, **8**, and **9**) were subjected to an initial study to determinate its neuroprotective ability in both the presence and the absence of neurotoxic agents (ANA). The method of reduction of the 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was used to ascertain the cell viability, given by the number of cells present in the culture. The ability of cells to reduce MTT is an indicator of the integrity of mitochondria, and its functional activity is interpreted as a measure of cell viability [15]. Three assays were conducted in a culture of motor cortex neurons of 19-day-old Sprague-Dawley rat embryos. Firstly, we studied the ability to induce a neuroprotective effect in the absence of any neurotoxic stimulation. Secondly, we studied the neuroprotective effect in the presence of glutamate, a compound that causes a pathological process in which neurons are damaged leading to apoptosis when its receptors such as the NMDA and AMPA are over-activated. Lastly, the ability of the compounds synthesized to protect from damage by $H_2O_2$, that causes neuronal death by Oxidative stress, was analyzed. The results obtained allow to deduce the existence of a moderate neuroprotective effect in the absence of any toxic stimulus, presenting the best results type **6** and **9** carbamate derivatives, with values of 11.5% and 8.4% respectively, followed by the compound **3**, **4**, and **7** with values slightly above 4% (see **Figure 2**).

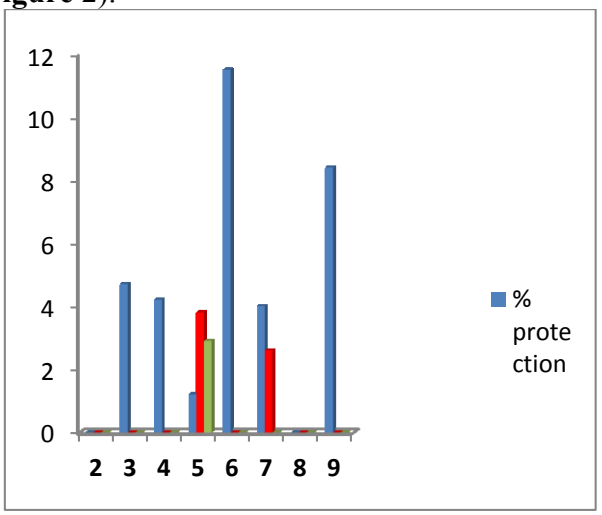


**Figure 2.** Results of the experimental assay of Neuroprotective effect of the new compounds.

**Predict new drugs in other assays**. We used the ALMA-entropy model to predict the more probable results for all the new rasagiline derivatives, synthesized in this work, in >500 assays not carried out experimentally. When the molecular descriptors (entropy indices) of the new rasagiline derivatives were introduced in our model we obtained the probable interaction with different targets. The model predicts that most of them could interact with the subunits A and B of the 5-hidroxy-tryptamine type 3 receptors (5-HT3Rs). These results seem to be consistent with the literature, since the antagonists of 5-HT3Rs have been related to neuroprotective properties *in vitro* and *in vivo* [16].

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**Conflict of Interest**

The authors declare no conflict of interest

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