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TOPS-MODE model of multiplexing neuroprotective effects of drugs and experimental-theoretic study of new 1,3-rasagiline derivatives potentially useful in neurodegenerative diseases

Feng Luan [a,b,*], M. Natália D. S. Cordeiro [b,*], Nerea Alonso [c], Xerardo García-Mera [c], Olga Caamaño [c], Francisco J. Romero-Duran [c], Matilde Yañez [d], Humberto González-Díaz [e,f]

[a] Department of Applied Chemistry, Yantai University, Yantai 264005, People's Republic of China
[b] REQUIMTE, Department of Chemistry and Biochemistry, University of Porto, 4169-007 Porto, Portugal
[c] Department of Organic Chemistry, Faculty of Pharmacy, University of Santiago de Compostela (USC), 15782 Santiago de Compostela, Spain
[d] Department of Pharmacology, Faculty of Pharmacy, USC, 15782 Santiago de Compostela, Spain
[e] Departament of Organic Chemistry II, Faculty of Science and Technology, University of the Basque Country (UPV/EHU), 48940 Leioa, Bizkaia, Spain
[f] IKERBASQUE, Basque Foundation for Science, 48011 Bilbao, Spain

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ABSTRACT

The interest on computational techniques for the discovery of neuroprotective drugs has increased due to recent fail of important clinical trials. In fact, there is a huge amount of data accumulated in public databases like CHEMBL with respect to structurally heterogeneous series of drugs, multiple assays, drug targets, and model organisms. However, there are no reports of multi-target or multiplexing Quantitative Structure–Property Relationships (mt-QSAR/mx-QSAR) models of these multiplexing assay outcomes reported in CHEMBL for neurotoxicity/neuroprotective effects of drugs. Accordingly, in this paper we develop the first mx-QSAR model for multiplexing assays of neurotoxicity/neuroprotective effects of drugs. We used the method TOPS-MODE to calculate the structural parameters of drugs. The best model found correctly classified 4393 out of 4915 total cases in both training and validation. This is representative of overall train and validation Accuracy, Sensitivity, and Specificity values near to 90%, 98%, and 80%, respectively. This dataset includes multiplexing assay endpoints of 2217 compounds. Every one compound was assayed in at least one out of 338 assays, which involved 148 molecular or cellular targets and 35 standard type measures in 11 model organisms (including human). The second aim of this work is the exemplification of the use of the new mx-QSAR model with a practical case of study. To this end, we obtained again by organic synthesis and reported, by the first time, experimental assays of the new 1,3-rasagiline derivatives 3 different tests: assay (1) in absence of neurotoxic agents, (2) in the presence of glutamate, and (3) in the presence of H_2O_2. The higher neuroprotective effects found for each one of these assays were for the stereoisomers of compound **7**: compound **7b** with protection = 23.4% in assay (1) and protection = 15.2% in assay (2); and for compound **7a** with protection = 46.2% in assay (3). Interestingly, almost all compounds show protection values >10% in assay (3) but not in the other 2 assays. After that, we used the mx-QSAR model to predict the more probable response of the new compounds in 559 unique pharmacological tests not carried out experimentally. The results obtained are very significant because they complement the pharmacological studies of these promising rasagiline derivatives. This work paves the way for further developments in the multi-target/multiplexing screening of large libraries of compounds potentially useful in the treatment of neurodegenerative diseases.

1. Introduction

Neuroprotective strategy has evolved in the last two decades from targeting a signal pathway in neurons to protect all neurovascular components.[1] According to Xing et al.[2] an understanding of the common signals and substrates involved in the different process in the neurovascular unit may reveal useful paradigms in this area. Nevertheless, regardless of the growing knowledge of the physiological mechanisms of the ischemic penumbra, no effective neuroprotective therapy has been found so far.[1] Indeed, recent failed clinical trials have reduced fervour for the discovery of neuroprotective drugs.[3] In any case, there is a huge amount of information in public datasets about structurally heterogeneous drugs as well as multiple assays, biochemical pathways, and drug targets,

* Corresponding authors.
E-mail addresses: fluan@sina.com (F. Luan), ncordeir@fc.up.pt (M. Natália D.S. Cordeiro).

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which should be taken into consideration towards the development of drugs with neuroprotective effects. In fact, Xing et al.[4] have summarized many pathophysiologic cascades involved in ischemic stroke. For instance, Capettini et al.,[5] have updated very recently the evidence on different cannabinoid-triggered avenues to reduce inflammation and neuronal injury in acute ischemic stroke. In a recent review, Dudas and Semeniken,[6] discussed that the mechanism by which the glycosaminoglycans exhibit neuroprotective properties may involve their impact on amyloidogenesis and in the apoptotic pathway. Another example is Cerebrolysin, a peptide preparation that mimics the pleiotropic effects of neurotrophic factors, which are indispensable for survival, differentiation, and protection against damage under pathologic conditions of developing neurons. Allegri and Guekht,[7] reviewed very recently several clinical trials investigating the therapeutic efficacy of Cerebrolysin in Alzheimer's Disease (AD) and Vascular Dementia (VD). In a last example, Yañez et al.,[8] demonstrated that Resveratrol has neuroprotective effects in patients suffering Amyotrophic Lateral Sclerosis (ALS).

On the other hand, the large number of experimental results reported by different groups worldwide has led to the accumulation of huge amounts of information in large databases. This determines, in turn, the necessity of new algorithms to perform data mining of these databases. CHEMBL is more probably the largest public database containing Binding (B), Functional (F), and ADMET (A) information for a large number of drug-like bioactive compounds. Access is available through a web-based interface, data downloads and web services at: https://www.ebi.ac.uk/chembldb.[9] Currently, CHEMBL contains >5.4 million assay outcomes for >1 million of compounds and 5200 protein targets. Nonetheless, the database describes only some selected tests for almost all drugs with respect to the huge number of assays reported. Consequently, multi-target/multiplexing techniques useful to measure or predict neurotoxicity/neuroprotective profiles of drugs are highly desired in order to increase the safety and efficacy of compounds potentially active against neurodegenerative diseases.[10] In fact, Mok and Brenk[11] postulated the data mining of CHEMBL using different computational tools as a very interesting source of new knowledge for drug discovery. Regrettably, almost current Quantitative Structure–Activity Relationships (QSAR) techniques are able to predict new outcomes only for one specific assay. In our opinion, we can evade this problem developing new Multi-target/Multiplexing QSAR models (mt-QSAR/mx-QSAR). These methods are especially powerful when we need to process very large collections of compounds assayed against multiple molecular or cellular targets in different assay conditions (m_j) as is the case of CHEMBL.[12,13] This step may be of the major relevance for the future of QSAR.

Notably, mt-QSAR models are able to predict the results of the assay of different drugs for multiple targets. However, mt-QSAR models are unable to predict different results for a given series of targets when we change the set of specific assay conditions for each target. Fortunately, the new class of mx-QSAR models applies not only to different targets but also to different multiplexing assay conditions (m_j) for all targets. Specifically, we have reported the first mx-QSAR model for multiplexing assays of anti-Alzheimer, anti-parasitic, anti-fungi, and anti-bacterial activity of GSK-3 inhibitors in vitro, in vivo, and in different cellular lines.[14] In a first step, we need to calculate the molecular descriptors using D_i of a given ith compound using one or more software for generation of molecular descriptors. In a second step, we expand the raw dataset of molecular descriptors adding new variables $\Delta D_{ij} = D_i - \langle D_i(m_j)\rangle$. These deviation-like parameters ΔD_{ij} are inspired in the idea of moving averages used in time series analysis.[15] In any case, $\langle D_i(m_j)\rangle$ is the average of the D_i of compounds active in an assay carry out under the set of conditions m_j and does not quantify an interval of time like in time series. These additional terms express the deviation of the value of one molecular descriptor of one compound from the average $\langle D_j\rangle$ of these values for compounds that give a positive result in the same assay conditions m_j. Next, we upload this preprocessed data to one Statistics or Machine Learning software to seek the model. In the particular case of a linear model, the mx-QSAR equation based on moving averages has the following general form:

$$S_i(m_j) = a_0 + \sum_i^m b_i \cdot D_i + \sum_i^m c_i \cdot \Delta D_i = a_0 + \sum_i^m b_i \cdot D_i + \sum_i^m c_i \cdot (D_i - \langle D_j\rangle) \quad (1)$$

where, $S_i(m_j)$ is a numerical score of the biological activity of the ith compound measured under the jth assay defined by the set of conditions m_j. In the case when m_j refer only to different targets, we are in the presence of a mt-QSAR model based on moving averages.[16] In a more general picture, we are in the presence of a mx-QSAR model when m_j refers to different multiplexing assay conditions, for example, targets, assays, cellular lines, organisms, organs, etc. See also the excellent works published after Speck-Planche et al.[17–22] on different ways to seek similar mt-QSAR/mx-QSAR models. We illustrate the general workflow of the mx-QSAR procedure in Figure 1.

In principle, we can use any one of the existing software for calculation molecular descriptors to seek mt-QSAR or mx-QSAR models. Some of the more used nowadays are: DRAGON,[23,24] MOE,[25] TOMOCOMD,[26,27] CODESSA[28–30] and MARCH-INSIDE.[31–33] Specially, the method TOPS-MODE implemented by Estrada et al. in the computer program MODESLAB, is one of the more widely used techniques for both QSAR and mt-QSAR studies. Very recently,

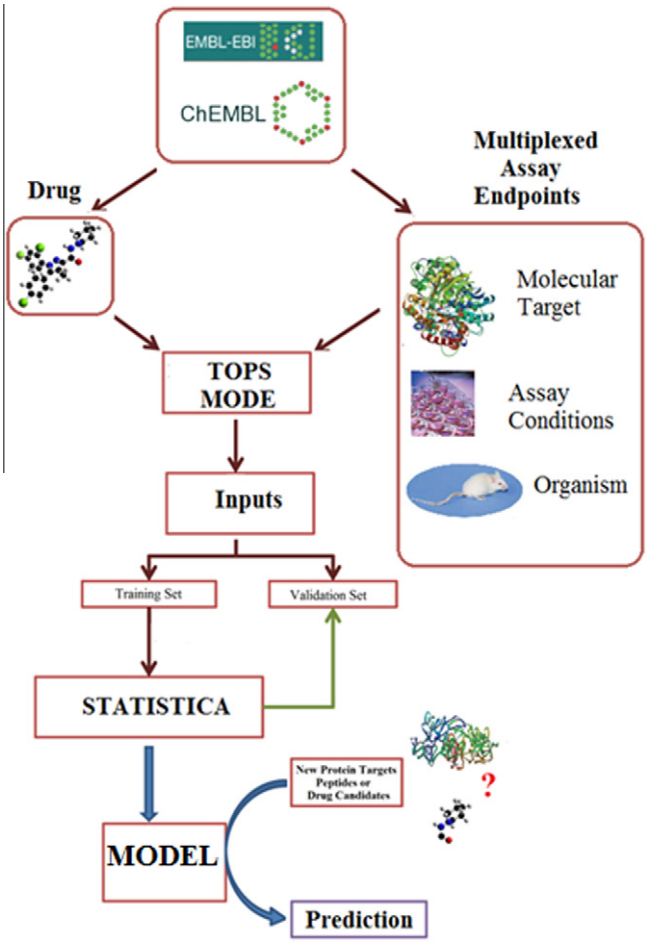


Figure 1. Workflow of the mx-QSAR study.

Tenorio-Borroto et al.[34] upgraded the method TOPS-MODE to carry out mx-QSAR studies using the MAD methodology. For instance, the mx-QSAR model developed by our group recently correctly classifies 8258 out of 9000 (Accuracy = 91.76%) multiplexing assay endpoints of 7903 drugs (including both train and test series). Each endpoint correspond to one out of 1418 assays, 36 molecular and cellular targets, 46 standard type measures, in two possible organisms (human and mouse).[34] However, there is no report of mx-QSAR analysis of multiplexing assay outcomes reported in CHEMBL for neurotoxicity/neuroprotective effects of drugs, until the best of our knowledge. Accordingly, in this paper we develop the first mx-QSAR model for multiplexing assays of neurotoxicity/neuroprotective effects of drugs. We used the method TOPS-MODE to calculate the structural parameters of drugs. The second aim of this work is the exemplification of the use of the new mx-QSAR model with a practical case of study. To this end, we obtained again by organic synthesis and report by the first time, the biological assay of new 2,3-rasgiline derivatives in three different tests for neuroprotective effect. Rasagiline is a promising drug for treatment of Parkison's disease with an interesting inhibition effect selective for MAO-B.[35,36] After that, we used the mx-QSAR model to predict the most probable results for this compound in a large number of assays not carried out experimentally in this work.

2. Results and discussion

2.1. TOPS-MODE multiplexing model of drug neuroprotective effects

The outcome of multiplexing neuroprotective assays depend both on drug structure and the set of assay conditions selected (m_j).[37] In this work, we report the first mx-QSAR model capable of predict whether a drug with a determined molecular structure may give or not a positive result in different multiplexing assay conditions m_j. These models are expected to give different classification probabilities of the compound for different: organisms (o_t), biological assays (a_u), molecular or cellular targets (t_e), or standard type of activity measure (s_x). It is also desirable to use an algorithm that takes into consideration the different degrees of accuracy or level of curation (c_l) in the experimental data. The best mx-QSAR model found was:

$$S_i(m_j) = -7.01\cdot10^{-4}\cdot\mu^i_5 - 7.84\cdot10^{-4}\cdot\Delta\mu^i_5(s) - 2.93\cdot10^{-4}\cdot\Delta\mu^i_5(a) + 1.16\cdot10^{-4}\cdot\Delta\mu^i_5(o) + 2.84\cdot10^{-4}\cdot\Delta\mu^i_5(t) + 4.198684$$
$$N = 3683\ \mathrm{Rc} = 0.7\ \mathrm{Sn} = 98.0\ \mathrm{Sp} = 81.3\ \mathrm{Ac} = 89.5 \quad (2)$$

$S(m_j) = S(d_i, a_u, c_l, o_t, t_e, s_x)$ is a real-valued variable that scores the propensity of the drug to be active in multiplex pharmacological assays of the drug d_i carried out on the conditions selected $m_j \geqslant a_u, c_l, o_t, t_e$, and s_x. The statistical parameters for the above equation in training are: Number of cases used to train the model (N), Canonical Regression Coefficient (Rc), Sensitivity (Sn), Specificity (Sp), and Accuracy (Ac).[15] The probability cut-off for this LDA model is ${}^ip_1(m_j) > 0.5 \geqslant C_i(m_j) = 1$. It means that the ith drug (d_i) predicted by the model with probability >0.5 is expected to give a positive outcome in the jth assays carry out under the given set of conditions m_j. This linear equation presented good results both in training and external validation series with overall Accuracy in training series above 90% (see Table 1). According to previous reports[38–46] values accuracy higher than 75% are acceptable for LDA-QSAR models. The reader should be aware that N here is not number of compounds but number of statistical cases. One compound may lead to 1 or more statistical cases because it may give different outcomes for alternative biological assays carried out in diverse sets of multiplex conditions defined by the ontology $m_j \geqslant (a_u, c_l, o_t, t_e, s_x)$. This type of ontology allows a clear definition of the multiplex conditions for one assay in our dataset following the same line of thinking used for other ontology-like datasets in the literature.[47]

Table 1
Overall results of the mx-QSAR classification model

Sub-set	Statistics[a]	%	Groups	$C_i(m_j)_{pred} = 0$	$C_i(m_j)_{pred} = 1$
Train	Specificity	81.3	$C_i(m_j)_{obs} = 0$	**1533**	352
	Sensitivity	98.0	$C_i(m_j)_{obs} = 1$	36	**1762**
	Accuracy	89.5	Total		
CV	Specificity	81.0	$C_i(m_j)_{obs} = 0$	**513**	120
	Sensitivity	97.7	$C_i(m_j)_{obs} = 1$	14	**585**
	Accuracy	89.1	Total		

[a] Sensitivity = Sn = positive correct/positive total; specificity = Sp = negative correct/negative total; accuracy = Ac = total correct/overall total.

The first parameter $\mu^i_5 = p(c)\cdot{}^{dip}\mu^i_5$ codifies the influence of the chemical structure of the compound on the biological activity. It is known that the spectral moment of order 5 codifies information about all types of structural fragments with five or less bonds in the molecule. In addition to the topological information, ${}^w\mu^i_5$ also codifies information about the physicochemical properties of the atoms and bonds in the molecule. It depends on the type of atomic or bond weights w_{ij} used. In our equation, we set w_{ij} equal to the values of standard bond dipole moments (dip) in order to incorporate both geometrical and electronic charge information.[33–37] Consequently, ${}^*\mu^i_5$ codifies the effect of the drug structure on the biological activity, but depending on the confidence of assays reported in CHEMBL. In this sense, we have pre-multiplied μ^i_5 by the parameter $p(c_l)$. The parameter $p(c_l)$ is a probability (a priori) of confidence for a given data value into the CHEMBL dataset studied. Next, we have defined $p(c) = 1, 0.75$, or 0.5 for data values reported as being curated at expert, intermediate, or auto-curation level, respectively.

The other three terms in the equation express the structural dissimilarity between one specific compound and a group of active compounds that have been assayed in specific multiplex conditions defined by the sub-ontology $m_j \geqslant (o_t, t_e, s_x)$. We have quantified this effect in terms of the deviation $\Delta\mu^i_5(m_j) = {}^{dip}\mu^i_5 - p_1(m_j)\cdot\langle{}^{dip}\mu^i_5(m_j)\rangle$. In general, we have defined $p_1(m_j) = n_1(m_j)/n_{tot}(m_j)$; where $n_1(m_j)$ and $n_{tot}(m_j)$ are the number of positive or total results for compounds assayed in the jth condition in the CHEMBL dataset. These moving average or deviation terms represent the hypothesis: H_0 the structural dissimilarity between one compound, with respect to the average of all compounds in a group, predicts the final behavior of the compound. For instance, $\Delta\mu^i_5(o_t) = {}^{std}\mu^i_5 - p_1(o_t)\langle{}^{std}\mu^i_5(o_t)\rangle$ measures the deviation from the average value $\langle\mu^i_5(t_e)\rangle$ of μ^i_5 for all active compounds ($C = 1$) assayed in the organism $o_t \geqslant t = 1, 2, \ldots$ for Human, or other organisms, respectively. This type of model able to model/interpret cross-species activity is of major importance in order to reduce assays in humans.[38] By analogy, $\Delta\mu^i_5(t_e) = {}^{std}\mu^i_5 - \langle{}^{std}\mu^i_5(t_e)\rangle$ is the dissimilarity between the structure of compound ith (expressed by ${}^{std}\mu^i_5$) with respect to all compounds active against the molecular or cellular target t_e. In Table 2 we give some examples of average values for the different targets, organisms, or standard measure types. Online Supplementary data files contain detailed lists of values of these parameters.

2.2. Experimental-theoretical study of new neuroprotective drugs

2.2.1. Experimental assay of neuroprotective effects of new 1,3-rasagilines

The second aim of this work is the exemplification of the use of the new mx-QSAR model with a practical case of study. To this end, we obtained again by organic synthesis and reported by the first

Table 2
Selected examples of average values for different targets, measures, and organisms

CHEMBLID	$\langle\mu_5(m_j)\rangle$	Name or units	CHEMBLID	$\langle\mu_5(m_j)\rangle$	Name or units
Protein targets			*Protein targets*		
3599	4888.44	Acetylcholine receptor protein alpha chain	1907608	7569.51	Glutamate NMDA receptor
3916	5304.48	Acetylcholine receptor protein delta chain	384	5731.6	HT-29 (Colon adenocarcinoma cells)
319	6020.28	Alpha-1a adrenergic receptor	614585	7436.96	IMR-32 (Neuroblastoma cells)
315	8533.75	Alpha-1b adrenergic receptor	3772	7395.55	Metabotropic glutamate receptor 1
1867	5316.33	Alpha-2a adrenergic receptor	1907609	6108.82	Muscarinic acetylcholine receptor
1942	5234.11	Alpha-2b adrenergic receptor	4573	5542.08	Neurokinin 1 receptor
249	6982.89	Beta-1 adrenergic receptor	4980	5161.98	Neuronal acetylcholine receptor protein alpha-7
3715	7518.82	Betaine transporter	1907592	6023.39	Neuronal acetylcholine receptor; alpha2/beta2
4801	14682.75	Caspase-1	4802	4874.72	Nitric-oxide synthase, endothelial
5037	7333.74	Caspase-10	614205	3838.14	NT2 (Teratocarcinoma cells)
1843	6480.94	DOPA decarboxylase	612556	7046.1	PC-12 (Adrenal phaeochromacytoma cells)
5102	7956.01	Dopamine D2 receptor	612405	9075.71	SCG (Superior cervical ganglion neurones)
2799	5233.51	Dopamine transporter	1899	7502.62	Serotonin 3a (5-HT3a) receptor
4054	4098.58	GABA transporter 1	4906	4329.83	Sodium channel protein type I alpha
5208	8841.88	GABA transporter 3	2752	9118.42	Sodium channel protein type VIII alpha
5102	5383.23	Vanilloid receptor	2863	7273.42	Transient receptor potential cation channel V2
Organisms			*Organisms*		
Organism-01	5775.6	*Homo sapiens*	Organism-07	6006.98	*Rattus norvegicus*
Organism-03	4932.01	*Caenorhabditis elegans*	Organism-08	16162.12	*Heliothis virescens*
Organism-04	5680.88	*Cavia porcellus*	Organism-09	7775.19	*Mus musculus*
Organism-06	7534.91	*Felis catus*	Organism-10	8776.43	*Tropedo californica*
Standard type measures			*Standard type measures*		
Activity	7208.42	nM	Ratio	4211.43	nM
Decrease	6334.59	%	Inhibition	3862.29	nM
nNOS activity	6514.67	%	Concentration	2781.19	% dose g^{-1}
Dopamine release	4584.1	%	Activity	11283.7	%
ED_{50}	4753.33	μg ml^{-1}	%max	14405.49	%
Efficacy	5779.68	%	ED_{50}	11160.96	nM
ED_{50}	8002.48	μg kg^{-1}	Morbidity	11419.52	%
K_i	5524.2	nM	Survived	8060.06	%
EC_{50}	4077.11	nM	Inhibition	6031.43	%

time, experimental measures of the Neuroprotection capacity (NP) of the new 2,3-rasagiline derivatives in 3 different assays: assay (1) in absence of neurotoxic agents, (2) in the presence of glutamate, and (3) in the presence of H_2O_2. In general, the synthesized compounds (**7a**, **7b**, **8a**, **8**b, **9a**, **9b**, **10a**, and **10b**) were subjected to an initial study to determine their neuroprotective capacity in both the absence and presence of neurotoxic agents, using the reduction method bromide 3-(4,5-dimethyl-2-thiazoyl)-2,5-difeniltetrazólico (MTT) method used to determine cell viability, given by the number of cells present in culture. The ability of cells to reduce MTT is an indicator of mitochondrial integrity and its functional activity is interpreted as a measure of cell viability. There were three types of assays in cultured neurons of embryonic motor cortex of Sprague–Dawley rats of 19 days. All results are expressed as mean ± SEM of at least three independent experiments (Table 3). First, assay (1), we studied the ability to induce a neuroprotective effect in the absence of any neurotoxic stimulus. Secondly, in assay (2), the neuroprotective effect was studied in the presence of glutamate excitotoxicity compound that causes a pathological process in which the neurons are damaged sobreactivarse receptors (NMDA and AMPA/kainate) the excitatory neurotransmitter glutamate, ultimately leading to apoptosis. Finally, in assay (3), we examined the ability of the compounds synthesized to protect neurons from damage caused by H_2O_2 neuronal death caused by oxidative stress. The results indicate that all compounds prepared, except **10b**, have a high neuroprotective capacity against damage caused by H_2O_2, assay (3). Especially the compound **7a** highlights with a NP = 46.2%, with the remainder of compounds level average NP = 16.5%. Moreover, the compound **7b** showed a high neuroprotective capacity in all three types of assays performed with values of NP = 23.4% in assay (1), and NP = 15.2% in assay (2), and NP = 14.5% in assay (3), see Table 3.

2.2.2. Prediction of multiplexing outcomes of new neuroprotective drugs in other assays

After that, we used the mx-QSAR model to predict the more probable results for all these compounds in >500 assays not carried out experimentally in this work. Notably, the mx-QSAR model has predicted a very high probability $p_1(m_j)$ of activity for compound **7** (both isomers **7a** and **7b**) against different receptors related to glutamate (see Table 4). This result may be in coincidence with the experimental value of protection = 46.2% for **7a** in the presence of glutamate. Nuritova and Frenguelli,[48] a novel neuroprotective strategy involving retrograde release of glutamate.

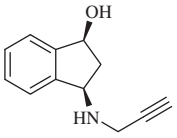
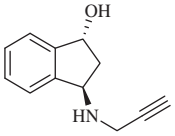
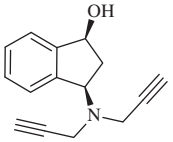
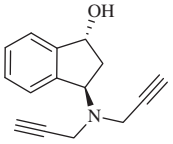
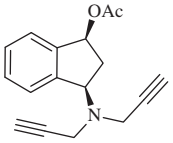
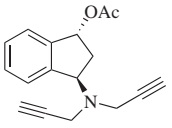
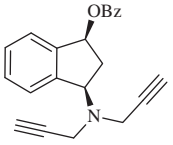
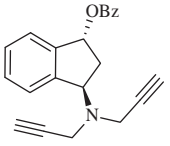
3. Materials and methods

3.1. Computational methods

3.1.1. CHEMBL dataset

This dataset includes $N_d = 2217$ unique drugs and/or organic compounds previously assayed in different multiplexing assay conditions (m_j). We assigned a value of the observed (obs) class variable $C_i(m_j)_{obs} = 1$ (active compound) or $C_i(m_j)_{obs} = 0$ (non-active compounds) to every ith drug biologically assayed in different m_j conditions. One compound may lead to 1 or more statistical cases because it may give different outcomes (statistical cases) for alternative biological assays carried out in diverse sets of multiplex conditions. In this work, we defined m_j according to the ontology $m_j \geqslant (a_u, c_l, o_t, t_e, s_x)$. A general data set composed of >10,000 multiplexing assay endpoints was downloaded from the public database CHEMBL.[9,49] In any case, after a carefully curation of the dataset we retain 4915 multiplexing assay endpoints (statistical cases) after elimination of all cases with missing information or very low representation. The different conditions that may change in the dataset are the following: organisms (o_t), biological assays

Table 3
Neuroprotective ability of the new 1,3-rasagiline derivatives tested in the absence of neurotoxic agents, in the presence of glutamate and in the presence of H_2O_2[a]

Compound	Formula	Protection[b] (%)	e.s.m.	Glutamate[c] (%)	e.s.m.	H_2O_2[d] (%)	e.s.m.
7a		0	3.8	0	4.0	**46**.2	5.6
7b		**23.4**	4.6	**15.2**	2.0	**14.5**	2.1
8a		−5	6.2	0	3.0	**17.8**	4.8
8b		−1	4.3	−0.5	4.0	**19.6**	2.6
9a		0	4.6	−1.5	2.0	**18.2**	3.1
9b		0	3.9	−0.5	1.8	**12.3**	2.9
10a		−5.1	5.6	1.6	4.0	**16.4**	5.2
10b		6.9	8.0	−1.3	4.7	−5.8	3.0

[a] Highest neuroprotective ability is highlighted in bold.
[b] % Protection (compd 5 μM).
[c] % Protection (compd 5 μM) against Glutamate 100 μM.
[d] % Protection (compd 5 μM) against H_2O_2 100 μM.

(a_u), molecular or cellular targets (t_e), or standard type of activity measure (s_x). In closing, we analyzed N = 4915 statistical cases conformed by the above-mentioned N_d = 2217 drugs; which have been assayed each one in at least one out of N_a = 338 possible assays. For each one of these assays the dataset studied present for each drug at least one out of N_s = 35 standard types of biological activity measures in turn carried out in at least one out of N_t = 148 molecular or cellular targets. We withdrawn these values from CHEMBL as results of experiments carried out on at least 1 out of 11 model organisms and with 3 different levels of data curation N_c = 3 (expert, intermediate, or auto-curation level). Please, see details on the assignation of cases to different classes in Section 2.

3.1.2. The moving averages model

In order to seek the mx-QSAR model we used the technique LDA implemented in the software package STASTICA 6.0.[50] The LDA model studied here based on the concept of moving averages has the following general form:

$$S_i(m_j) = b_0 + b_1 \cdot \mu^i_5 + \sum_{j=2}^{4} b_j \cdot \Delta\mu^i_5(m_j) = b_0 + b_1 \cdot \mu^i_5 + \sum_{j=2}^{4} b_j \cdot (\mu^i_5 - p_1(m_j) \cdot \langle \mu^i_5(m_j) \rangle) \quad (3)$$

Where, $S(m_j) = S(d_i, a_u, c_l, o_t, t_e, s_x)$ is a real-valued variable that scores the propensity of the drug to be active in multiplex pharmacological assays of the drug depending on the conditions selected m_j. The statistical parameters used to corroborate the model were: Number of cases in training (N), and overall values of Specificity (Sp), Sensitivity (Sn), and Accuracy (Ac).[15] In this model, ${}^{std}\mu_5{}^i$ is the spectral moment or order k = 5 calculated with Modeslab. In this study, we used only standard bond distance as entries of the main diagonal of the bond adjacency matrix. The parameter $p_1(m_j)$ is a probability, calculated a priori, with which any drug is expected to give a positive results, $C_i(m_j)$ = 1, in the test carried out under the m_j conditions. The parameter $p(c_l)$ is a probability, calculated a priori, of confidence for a given data value into the CHEMBL dataset studied. The structural deviation terms $\Delta\mu^i{}_5(m_j) = \mu^i{}_5 - p_1(m_j) \cdot \langle \mu^i{}_5(m_j) \rangle$ represent the hypothesis H_0.

Table 4
Prediction of endpoints in multiplexing assays for compound **7**

Assay ID	Target name[a]	$p_1(m_j)$[b]	Measure (U)	Cutoff[c]	Organism
715720	MGluR 5	0.9999	Activity (nM)	100,000	*H. sapiens*
715721	MGluR 5	1.0000	Activity (nM)	17,000	*H. sapiens*
715722	MGluR 5	1.0000	Activity (nM)	100,000	*H. sapiens*
712468	MGluR 8	1.0000	Activity (nM)	45,000	*H. sapiens*
712469	MGluR 8	0.9998	Activity (nM)	100,000	*H. sapiens*
835748	Glu[NMDA]R 3B	0.9502	Selectivity ratio	158	*R. norvegicus*
835748	Glu[NMDA]R epsilon 4	0.9294	Selectivity ratio	15.3	*R. norvegicus*
835748	Glu[NMDA]R zeta 1	0.9344	Selectivity ratio	158	*R. norvegicus*
835748	Glu[NMDA] 3A	0.9489	Selectivity ratio	1774	*R. norvegicus*
835748	Glu[NMDA] epsilon 3	0.9294	Selectivity ratio	15.3	*R. norvegicus*
872629	MGluR 8	0.9939	EC_{50} (nM)	31	*R. norvegicus*
714496	MGluR 4	0.9999	EC_{50} (nM)	320	*R. norvegicus*
713191	MGluR 2	0.9715	EC_{50} (nM)	300	*R. norvegicus*
717250	MGluR 3	1.0000	EC_{50} (nM)	600	*R. norvegicus*
682643	GABA receptor gamma-2	0.9950	K_i (nM)	10,000	*H. sapiens*
876081	GABA receptor gamma-2	0.9651	K_i (nM)	10,000	*H. sapiens*
859484	NAChR protein alpha-2	0.9448	Activity (%)	7	*H. sapiens*
866501	NAChR protein alpha-2	0.9446	Activity (%)	3	*H. sapiens*
911164	NAChR protein alpha-2	0.9925	Inhibition (%)	30	*H. sapiens*
748592	MAChR M4	0.9958	K_i (nM)	501	*H. sapiens*
617201	Serotonin 2b (5-HT2b) receptor	0.9764	K_i (nM)	18	*H. sapiens*
669461	DOPA decarboxylase	0.9796	Inhibition (%)	100	*H. sapiens*
682643	GABA receptor beta-3	0.9568	K_i (nM)	10,000	*H. sapiens*
876081	GABA receptor beta-3	0.9497	K_i (nM)	10,000	*H. sapiens*
748592	MAChR M3	0.9934	K_i (nM)	501	*H. sapiens*
874089	Alpha-2a adrenergic receptor	0.9819	K_i (nM)	783	*H. sapiens*
859484	NAChR protein alpha-4	1.0000	Activity (%)	7	*H. sapiens*
866501	NAChR protein alpha-4	0.9571	Activity (%)	3	*H. sapiens*
911164	NAChR protein alpha-4	0.9925	Inhibition (%)	30	*H. sapiens*
752536	NAChR protein beta-2	1.0000	K_i (nM)	1990	*H. sapiens*
859484	NAChR protein beta-2	0.9949	Activity (%)	7	*H. sapiens*
866501	NAChR protein beta-2	1.0000	Activity (%)	3	*H. sapiens*
911164	NAChR protein beta-2	0.9573	Inhibition (%)	30	*H. sapiens*
874089	Alpha-2c adrenergic receptor	0.9776	K_i (nM)	783	*H. sapiens*
682643	GABA receptor beta-2	0.9994	K_i (nM)	10,000	*H. sapiens*
876081	GABA receptor beta-2	0.9418	K_i (nM)	10,000	*H. sapiens*
874089	Alpha-2b adrenergic receptor	0.9711	K_i (nM)	263	*H. sapiens*
682643	GABA receptor alpha-1	0.9995	K_i (nM)	10,000	*H. sapiens*
876081	GABA receptor alpha-1	0.9497	K_i (nM)	10,000	*H. sapiens*
748592	MAChR M5	0.9974	K_i (nM)	501	*H. sapiens*
859484	NAChR protein alpha-9	0.9584	Activity (%)	7	*H. sapiens*
866501	NAChR protein alpha-9	1.0000	Activity (%)	3	*H. sapiens*
911164	NAChR protein alpha-9	0.9874	Inhibition (%)	30	*H. sapiens*
682643	GABA receptor alpha-4	0.9991	K_i (nM)	10,000	*H. sapiens*
859484	NAChR protein alpha-7	0.9584	Activity (%)	7	*H. sapiens*
682643	GABA receptor gamma-3	0.9249	K_i (nM)	10,000	*H. sapiens*
876081	GABA receptor gamma-3	0.9418	K_i (nM)	10000	*H. sapiens*
682643	GABA receptor theta	0.9925	K_i (nM)	10,000	*H. sapiens*
876081	GABA receptor theta	0.9418	K_i (nM)	10,000	*H. sapiens*
682643	GABA receptor alpha-3	0.9925	K_i (nM)	10,000	*H. sapiens*
876081	GABA receptor alpha-3	0.9497	K_i (nM)	10,000	*H. sapiens*
752536	NAChR protein alpha-3	0.9866	K_i (nM)	22.5	*H. sapiens*
859484	NAChR protein alpha-3	1.0000	Activity (%)	7	*H. sapiens*
866501	NAChR protein alpha-3	0.9571	Activity (%)	3	*H. sapiens*
911164	NAChR protein alpha-3	0.9329	Inhibition (%)	30	*H. sapiens*
1613870	Nuclear factor NF-kappa-B p105	0.9824	EC_{50} (nM)	346	*H. sapiens*
682643	GABA receptor pi	0.9991	K_i (nM)	10,000	*H. sapiens*
876081	GABA receptor pi	0.9497	K_i (nM)	10,000	*H. sapiens*
679291	Nitric-oxide synthase, brain	0.9937	Selectivity	10	*H. sapiens*
751927	Nitric-oxide synthase, brain	0.9901	K_i (nM)	1250	*H. sapiens*
755291	Neurokinin 1 receptor	0.9998	EC_{50} (nM)	4	*H. sapiens*
883402	Neurokinin 1 receptor	0.9838	EC_{50} (nM)	1300	*H. sapiens*
671419	Dopamine D2 receptor	0.9232	K_i (nM)	20	*H. sapiens*
617201	Serotonin 2a (5-HT2a) receptor	0.9428	K_i (nM)	112	*H. sapiens*
682643	GABA receptor alpha-5	0.9992	K_i (nM)	10,000	*H. sapiens*
876081	GABA receptor alpha-5	0.9368	K_i (nM)	10,000	*H. sapiens*

[a] mGluR = metabotropic glutamate receptor, NAChR = neuronal acetylcholine receptor, MAChR = muscarinic acetylcholine receptor, Glu[NMDA]R = glutamate [NMDA] receptor.
[b] $p_1(m_j)$ is the probability with which the model predict a value of the measure higher than the cutoff for compound **7**.
[c] Cutoff is the threshold value for this assay (average value for all compounds in CHEMBL for this assay).

H_0: the different deviations of the ith drug (d_i) with respect to the average of all positive drugs for different multiplexing assay conditions (m_j) predict the final behavior of the compound. See a detailed discussion of terms and m_j conditions in Section 2 and also in the introductory part. This type of moving average or deviation-like models has been used before to solve different problems.[22,34]

3.2. Experimental methods

3.2.1. General chemistry

The compounds (**7a–b**, **8a–b**, **9a–b** and **10a–b**) were synthesized according to the strategy given in Figure 2. As shown in this Scheme, *N*-(1-oxo-1*H*-3-indanyl)trifluoroacetamide **5** was prepared by intramolecular cyclization of 3-amino-3phenylpropanoic acid, **2**, following procedures previously described in the literature.[51] Compound **2** was prepared by reaction of Rodionow-Johnson of an ethanolic solution of benzaldehyde, malonic acid and ammonium acetate, in 61% yield. After protection of the amino group with trifluoroacetic anhydride at room temperature, and treatment with thionyl chloride, compound **4** was involved in an intramolecular cyclization reaction using excess aluminium chloride in refluxing dichloromethane. After treatment with a saturated solution of $NaHCO_3$, the ketoamide **5** was obtained. The partial reduction of the ketone group and deprotection of amino group of compound **5** were performed simultaneously with $NaBH_4$ in methanol.[52] This reaction affords a mixture of epimers aminoalcohols **6a–6b** (*cis*/*trans* 60:40) in 70% yield. The alkylation of the mixture **6a–6b** with propargyl bromide and potassium carbonate in hot acetonitrile was carried out.[53] It provided in a global yield of 82%, a mixture of the corresponding mono- and dipropargylated derivatives (**7a–7b** and **8a–8b**), which were easily separated by flash column chromatography using hexane/EtOAc (4:1) as eluent.[54] Compounds **8a** and **8b** were converted to the corresponding acetates **10a** and **10b**, in good yields, by treatment with acetic anhydride, Et_3N and catalytic amounts of DMAP, in MeCN.[55] In the same way and using benzoyl chloride instead of acetic anhydride, the corresponding benzoates **11a** and **11b** were prepared.

3.2.2. Synthesis and identification of 1,3-rasagilines

All compounds were obtained again in sufficient amounts for pharmacological assays. Synthesis and characterization was carried out following the know how published in the previous literature.[56] Melting points are uncorrected and were determined in Reichert Kofler Thermopan or in capillary tubes on a Büchi 510 apparatus Infrared spectra, recorded on a Perkin–Elmer 1640-FT spectrophotometer. ^1H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded in a Bruker AMX spectrometer, using TMS as internal reference (chemical shifts in δ values, J in Hz). Mass spectra were recorded on a HP5988A spectrometer. FABMS were obtained using MICROMASS AUTOSPEC mass spectrometer. Microanalyses were performed in a Perkin–Elmer 240B elemental analyzer by the Microanalysis Service of the University of Santiago de Compostela. X-ray diffraction data were collected with an Enraf-Nonius CDAD4 automatic diffractometer using the program CAD4-EXPRESS. We monitored most reactions by TLC on pre-coated silica gel plates (Merck 60 F254, 0.25 mm). Synthesized products were purified by flash column chromatography on silica gel (Merck 60, 230–240 mesh) and crystallized if necessary. Solvents were dried by distillation prior use. Further details such as figures of different spectra are available online in the Supplementary data of our previous work.[56]

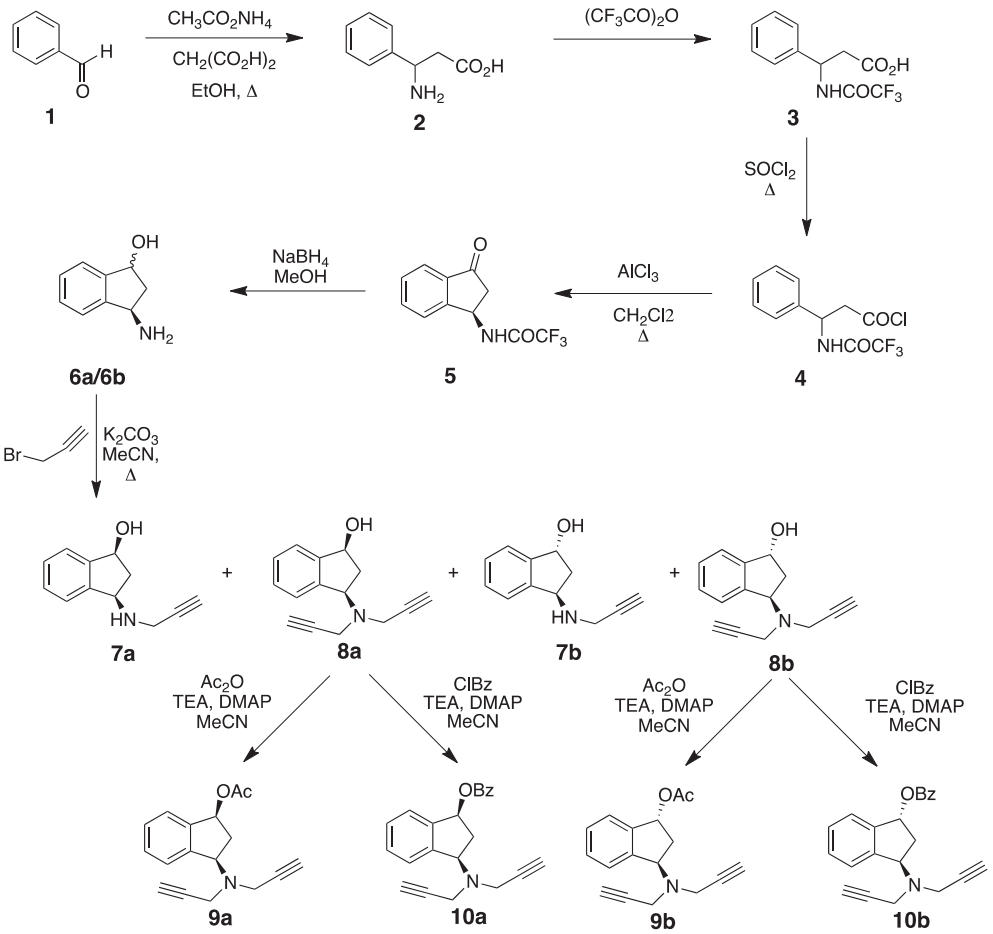


Figure 2. Synthesis of compounds **7a–b**, **8a–b**, **9a–b**, and **10a–b**.

3.2.3. Compound 2

Synthesis and characterization of (±)-3-amino-3-phenylpropanoic acid. To a solution of benzaldehyde (15.00 g, 141.3 mmol) in EtOH (60 mL), ammonium acetate (21.90 g, 283.0 mmol) and malonic acid (14.70 g, 141.3 mmol) were added and the resulting mixture was heated at 82 °C for 15 h. The precipitated was filtered off, washed with hot EtOH (3 × 20 mL), to give **2** (14.02 g, yield 61%) as a white solid. Mp 230–232 °C. IR ν = 2863, 1579, 1509, 1387, 1359 cm^{-1}. ^1H NMR (300 MHz, TFA-*d*): δ = 11.03 (d, 3H, J = 4.1 Hz, D_2O exch., OH + NH_2), 6.96–6.88 (m, 5H, H_{arom}), 4.41-4.38 (m, 1H, CH), 2.95 (ddd, 1H, J = 18.4 Hz, 10.1 Hz, 3.4 Hz, CH_2), 2.7 (dd, 1H, J = 18.4 Hz, 3.8 Hz, CH_2) ppm. ^{13}C NMR (75 MHz, TFA-*d*) δ = 175.07 (CO), 130.68 (C), 129.02, 127.90 and 124.59 (CH_{arom}), 51.84 (CH), 34.27 (CH_2) ppm. MS (EI): *m*/*z* (%): 165 (4) [M^+], 164 (2) [M−1]$^+$, 119 (3) [M^+–COOH], 106 (100), [M^+–CH_2–COOH], 104 (17), 79 (34), 77 (22). Anal. calcd for $C_9H_{11}NO_2$ (165.19): C 65.44, H 6.71, N 8.48; found C 65.59, H 6.51, N 8.42.

3.2.4. Compound 3

Synthesis and characterization of (±)-3-(2,2,2-trifluoroacetamido)-3-phenylpropanoic acid. A solution of **2** (4.00 g, 24.2 mmol) in trifluoroacetic anhydride (15 mL), under argon, was stirred at room temperature for 24 h. After evaporation of solvent and trituration in Et_2O, the white solid obtained was washed with Et_2O (3 × 15 mL), to give **3** (5.35 g, yield 85%) as a white solid. Mp 124–125 °C. IR ν = 3315, 1823, 1695, 1551, 1169, 1029 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d*) δ = 12.41 (br s, 1H, D_2O exch., COOH), 9.92 (d, 1H, J = 8.1 Hz, D_2O exch., NH), 7.35–7.24 (m, 5H, H_{arom}),5.24 (dt, 1H, J = 8.8 Hz, 5.6 Hz, CH), 2.95–2.74 (AB part of an ABM system, 2H, J_{AB} = 16.2 Hz, J_{AM} = 9.4 Hz, J_{BM} = 5.7 Hz, CH2) ppm. ^{13}C NMR (75 MHz, DMSO-*d*) δ = 171.65 (COOH), 156.15 ($COCF_3$), 141.08 (C), 128.78, 127.81 and 126.81 (CH_{arom}), 118.14 ($COCF_3$), 50.67 (CH), 40.05 (CH_2) ppm. MS (EI): *m*/*z* (%): 262 (4) [M+1]$^+$, 261 (3) [M^+], 244 (12) [M^+–OH], 215 (60) [M^+–COOH], 202 (100) [M^+–CH_2COOH], 132 (38), 104 (36), 77 (32). Anal. calcd for $C_{11}H_{10}F_3NO_3$ (261.20): C 50.58, H 3.86, N 5.36; found C 50.43, H 3.97, N 5.39.

3.2.5. Compound 4

Synthesis and characterization of (±)-3-(2,2,2-trifluoroacetamido)-3-phenylpropanoyl chloride. A solution of **3** (3.0 g, 11.5 mmol) in thionyl chloride (15 mL) was heated at 82 °C for 24 h. The resulting mixture was evaporated and the residue obtained was triturated in cyclohexane, to give a brown solid, that was filtered off, washed with cyclohexane (5 × 15 mL), to give **4** (3.15 g, yield 98%) as a yellow solid. Mp 60–62 °C. IR ν = 3306, 1703, 1556, 1275, 1153 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d*) δ = 9.93 (d, 1H, J = 8.1 Hz, D_2O exch., NH), 7.34–7.23 (m, 5H, H_{arom}), 5.23 (dt, 1H, J = 8.8 Hz, 5.8 Hz, CH),), 2.94–2.72 (AB part of an ABM system, 2H, J_{AB} = 16.3 Hz, J_{AM} = 9.4 Hz, J_{BM} = 5.6 Hz, CH_2) ppm ^{13}C NMR (75 MHz, DMSO-*d*) δ = 171.67 (COCl), 156.12 ($COCF_3$), 141.14 (C), 128.88, 127.89 and 126.84 (CH_{arom}), 118.18 ($COCF_3$), 50.69 (CH), 40.07 (CH_2) ppm. MS (EI): *m*/*z* (%): 261(5), 243 (7) [M^+–Cl], 215 (100) [M^+–COCl], 202 (32) [M^+–CH_2–COCl], 146 (24), 104 (40), 79 (43). Anal. calcd for $C_{11}H_9ClF_3NO_2$ (279.64): C 47.25, H 3.24, N 5.01; found C 47.02, H 3.19, N 4.92.

3.2.6. Compound 5

Synthesis and characterization of (±)-*N*-(1-oxo-1*H*-3-indanyl)-2,2,2trifluoroacetamide. A solution of **4** (3.0 g, 10.8 mmol) in Cl_2CH_2 (20 mL) was added, at 0 °C, dropwise and under argon, to a solution of $AlCl_3$ (2.8 g, 21.4 mmol) in Cl_2CH_2 (15 mL), and was heated at 42 °C for 24 h. The excess of solvent was removed to give a brown solid that was triturated in H_2O, filtered off and washed with H_2O (3 × 30 mL). Then, the solid obtained was dispersed in Et_2O and extracted with a saturated solution of $NaHCO_3$ (5 × 20 mL). The combined organic layers were dried (Na_2SO_4). Removal of solvent left **5** (1.6 g, yield 62%) as a white solid. Mp 121–123 °C. IR ν = 3295, 1698, 1551, 1145, 770 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d*) δ = 9.98 (d, 1H, J = 6.4 Hz, D_2O exch., NH), 7.77–7.52 (m, 4H, H_{arom}), 5.57 (t, 1H, J = 7.8 Hz, 3-H), 3.12 (ddd, 1H, J = 18.7 Hz, 8.0 Hz, 2.5 Hz, 2α-H), 2.61 (dt, 1H, J = 18.7 Hz, 3.3 Hz, 2β-H) ppm. ^{13}C NMR (75 MHz, DMSO-*d*) δ = 203.45 (CO), 159.15 ($COCF_3$), 153.10 (C-3a), 136.44 (C-7a), 135.49, 129.20, 125.70 and 122.89 (CH_{arom}), 117.90 ($COCF_3$), 47.64 (CH_2), 42.67 (CH) ppm. MS (EI): *m*/*z* (%): 243 (43) [M^+], 215 (100), 202 (30), 146 (47) [M^+–$COCF_3$], 104 (53), 77 (55). Anal. calcd for $C_{11}H_8F_3NO_2$ (243.2): C 54.33, H 3.32, N 5.76; found C 54.67, H 3.09, N 5.98.

3.2.7. Compounds 6a and 6b

Synthesis and characterization of compounds (±)-*cis*- and (±)-*trans*-3-amino-1*H*-indan-1-ol, **6a** and **6b**. To a solution of **5** (1.00 g, 4.11 mmol) in dry MeOH (10 mL), under argon, $NaBH_4$ (0.47 g; 12.33 mmol) was added and stirred at room temperature for 72 h. The excess of solvent was evaporated to give a residue that was triturated in H_2O (20 mL) and extracted with EtOAc (15 × 20 mL). The combined organic layers were dried (Na_2SO_4). The solvent was removed and the yellow oil residue was purified by flash column chromatography using DCM/MeOH (40:1) as eluent, to give a mixture 60:40 of isomers *cis*/*trans* **6a**/**6b** (0.47 g, yield 77%), as a yellow oil. IR ν = 3277, 1686, 1459, 1054, 761 cm^{-1}. ^1H NMR (300 MHz, DMSO-*d*) δ = 7.36–7.16 (m, 8H, $H_{arom(c+t)}$), 5.07 (dd, 1H, J = 6.4 Hz, 3.3 Hz, 1-Ht), 4.82 (t, 1H, J = 7.7 Hz, 1-Hc), 4.36 (t, 1H, J = 6.4 Hz, 3-Ht), 3.91–3.96 (m, 1H, 3-Hc), 3.10 (br s, 6H, D_2O exch., OH + $NH_{2(c+t)}$), 2.67 (dt, 1H, J = 13.7 Hz, 7.0 Hz, 2α-Hc), 2.19 (ddd, 1H, J = 13.2 Hz, 7.0 Hz, 3,5 Hz, 2α-Ht), 1.90–1.81 (m, 1H, 2β-Ht), 1.46–1.36 (m, 1H, 2β-Hc) ppm. ^{13}C NMR (75 MHz, DMSO-*d*) δ = 147.65 (C-7_{ac}), 146.76 (C-7_{at}), 145.63 (C-3_{ac}), 145.21 (C-3_{at}), 127.71, 127.13, 126.92, 126.66, 124.44, 123.80, 123.41 and 123.26 ($CH_{arom(c+t)}$), 72.22 (C-1_c), 71.12 (C-1_t), 54.29 (C-3_c), 52.99 (C-3_t), 47.55 (C-2_c), 46.26 (C-2_t) ppm. MS (EI): *m*/*z* (%): 149 (29) [M^+], 148 (23) [M−1]$^+$, 132 (100) [M^+−H_2O], 117 (18), 104 (98), 77 (19).

3.2.8. Compounds 7a, 7b, 8a, and 8b

Synthesis and characterization of compounds (±)-*cis* and (±)-*trans*-3-(*N*-propargylamino)-1-indanol, **7a** and **7b** and (±)-*cis* and (±)-*trans*-3-(*N*,*N*-dipropargylamino)-1-indanol, **8a** and **8b**. A mixture of **6a**/**6b** (0.50 g, 3.35 mmol), K_2CO_3 (0.46 g, 3.35 mmol) and MeCN (15 mL) was stirred at room temperature under argon for 5 min. A solution of propargyl bromide (0.3 mL, 2.7 mmol) dissolved in MeCN (2 mL) was added dropwise with stirring. After being stirred for 24 h, the solvent was evaporated and the residue was dissolved in EtOAc (20 mL). The organic layer was washed with NaOH 2 N (3 × 25 mL) and dried (Na_2SO_4). The excess of solvent was removed to give a brown oil, that was purified by flash column chromatography using hexane/EtOAc (4:1) as eluent to give, in first place **8a** (80 mg, yield 18%) as a white solid, then **8b** (60 mg, yield 12%) as a yellow solid, in third place **7a** (150 mg, yield 30%) as a brown solid and finally **7b** (110 mg, yield 22%) as a brown oil.

3.2.9. (±)-*cis*-7a

Mp 111–112 °C. IR ν = 3248, 1441, 1332, 1058, 768 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.49–7.27 (m, 4H, H_{arom}), 5.02 (dd, 1H, J = 6.1 Hz, 3.2 Hz, 1-H), 4.35 (dd, 1H, J = 5.9 Hz, 3.2 Hz, 3-H), 3.48 (d, 2H, J = 2.3 Hz, CH_2), 2.55 (dt, 1H, J = 13.5 Hz, 6.5 Hz, 2α-H), 2.40 (br s, 2H, D_2O exch., OH + NH), 2.29 (t, 1H, J = 2.6 Hz, CH), 1.88 (dt, 1H, J = 13.5 Hz, 2.9 Hz, 2β-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.72 (C-7a), 143.24 (C-3a), 128.69, 128.44, 125.07 and 124.70 (CH_{arom}), 81.32 (C≡CH), 74.54 (C-1), 72.40 (C≡CH), 59.04 (C-3), 42.74 (CH_2), 35.92 (C-2) ppm. MS (EI): *m*/*z* (%):186

(5) $[M-1]^+$, 168 (26) $[M^+-H_2O]$, 148 (100) [M^+–propargyl], 130 (71), 116 (72), 77 (80). HRMS (EI): (187): $C_{12}H_{13}NO$ calcd 186.0919, found 186.0921.

3.2.10. (±)-*trans*-7b

IR ν = 3285, 1455, 1332, 1051, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.44–7.31 (m, 4H, H_{arom}), 5.42 (t, 1H, J = 5.9 Hz, 1-H), 4.63–4.59 (m, 1H, 3-H), 3.49 (d, 2H, J = 2.3 Hz, CH_2), 2.32–2.26 (m, 1H, 2α-H), 2.04 (s, 1H, CH), 1.84 (br s, 2H, D_2O exch., OH + NH), 1.26(t, 1H, J = 7.3 Hz, 2β-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.20 (C-7a), 143.52 (C-3a), 128.52, 128.48, 124.67 and 124.60 (CH_{arom}), 81.83 (C≡CH), 74.53 (C-1), 71.89 (C≡CH), 59.37 (C-3), 43.94 (CH_2), 36.12 (C-2) ppm. MS (EI): m/z (%): 186 (6) $[M-1]^+$, 168 (23) $[M^+-H_2O]$, 148 (100) [M^+–propargyl], 130 (63), 116 (49), 103 (70), 77 (67). HRMS (EI): $C_{12}H_{13}NO$ calcd 186.0919, found 186.0920.

3.2.11. (±)-*cis*-8a

Mp 91–92 °C. IR ν = 3283, 3198, 1309, 1123, 1054, 767 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.50–7.31 (m, 4H, H_{arom}), 5.02 (t, 1H, J = 5.4 Hz, 1-H), 4.31 (t, 1H, J = 6.1 Hz, 3-H), 3.63–3.50 (AB system, 2H, J = 16.9 Hz, CH_2), 3.62–3.49 (AB system, 2H, J = 16.9 Hz, CH_2), 2.81 (br s, 1H, D2O exch., OH), 2.56 (dt, 1H, J = 13.7 Hz, 6.1 Hz, 2α-H), 2.26 (t, 2H, J = 2.5 Hz, 2 × CH), 2.13 (dt, 1H, J = 13.4 Hz, 5.0 Hz, 2β-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.35 ($C\text{-}7_a$), 142.03 ($C\text{-}3_a$), 128.58, 128.30, 125.45 and 124.47 (CH_{arom}), 79.85 (2 × C≡CH), 74.01 (C-1), 73.22 (2 × C≡CH), 64.41 (C-3), 39.53 (2 × CH_2), 38.31 (C-2) ppm. MS (EI): m/z (%): 225 (3) [M^+], 224 (4) $[M-1]^+$, 207 (6) $[M^+-H_2O]$, 186 (16) [M^+–propargyl], 141 (7), 116 (88), 92 (100), 77 (30). HRMS (EI): $C_{15}H_{15}NO$ calcd 225.1154; found 225.1152.

3.2.12. (±)-*trans*-8b

Mp 64–65 °C. IR ν = 3271, 2957, 1369, 1137, 1002, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.48–7.30 (m, 4H, H_{arom}), 5.35 (dd, 1H, J = 6.4 Hz, 3.8 Hz, 1-H), 4.73 (dd, 1H, J = 7.0 Hz, 5.1, 3-H), 3.53–3.40 (AB system, 2H, J = 16.9 Hz, CH_2), 3.52–3.39 (AB system, 2H, J = 16.9 Hz, CH_2), 2.60 (ddd, 1H, J = 14.0 Hz, 6.7 Hz, 4.8 Hz, 2α-H), 2.24 (t, 2H, J = 2.5 Hz, 2 × CH), 2.10–2.02 (m, 1H, 2β-H), 1.9 (br s, 1H, D_2O exch., OH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.17 (C-7a), 142.39 (C-3a), 128.73, 128.62, 125.75 and 124.42 (CH_{arom}), 80.09 (2 × C≡CH), 74.58 (C-1), 72.94 (2 × C≡CH), 65.49 (C-3), 39.30 (2 × CH_2), 37.62 (C-2) ppm. MS (EI): m/z (%): 225 (6) [M^+], 224 (4) $[M-1]^+$, 207 (6) $[M^+-H_2O]$, 186 (25) [M^+–propargyl], 141 (9), 116 (94), 92 (100), 77 (51). HRMS (EI): $C_{15}H_{15}NO$ calcd 225.1154; found 225.1148.

3.2.13. Compound 9a

Synthesis and characterization of (±)-*cis*-3-(*N*,*N*-dipropargylamino)-1-indanyl acetate. A mixture of **8a** (0.08 g, 0.36 mmol), acetic anhydride (69 μL, 0.72 mmol), Et_3N (100 μL, 0.72 mmol), DMAP (a catalytic amount) in MeCN (5 mL), under argon, was stirred at room temperature for 3 h. The solvent was removed and the residue was partitioned between EtOAc and H_2O, and the organic layer was washed with a saturated solution of NaCl (3 × 15 mL), dried (Na_2SO_4) and evaporated, to give **9a** (0.092 g, yield 96%) as a white solid. Mp 72–73 °C. IR ν = 3266, 2917, 1728, 1235, 1031, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.48–7.32 (m, 4H, H_{arom}), 6.06 (t, 1H, J = 13.5 Hz, 1-H), 4.58 (t, 1H, J = 14.5 Hz, 3-H), 3.58–3.44 (AB system, 2H, J = 16.8 Hz, CH_2), 3.57–3.43 (AB system, 2H, J = 16.8 Hz, CH_2), 2.81 (dt, 1H, J = 15.2 Hz, 7.4 Hz, 2α-H), 2.24 (t, 2H, J = 2.5 Hz, 2 × CH), 2.19–2.13 (m, 4H, 2β-H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.01 ($COCH_3$), 142.84 (C-7a), 140.65 (C-3a), 129.16, 128.50, 125.10 and 124.88 (CH_{arom}), 80.39 (2 × C≡CH), 75.26 (C-1), 72.81 (2 × C≡CH), 64.91 (C-3), 39.03 (2 × CH_2), 33.12 (C-2), 21.24 (CH_3) ppm. MS (FAB): m/z (%): 268 (26) $[M+1]^+$, 225 (2) [M^+–acetyl], 208 (5), 171 (5), 154 (91), 137 (100). Anal. calcd for $C_{17}H_{17}NO_2$ (267.3): C 76.38, H 6.41, N 5.24; found C 76.65, H 6.12, N 5.02.

3.2.14. Compound 10a

Synthesis and characterization of (±)-*cis*-3-(*N*,*N*-dipropargylamino)-1-indanyl benzoate. To a solution of **8a** (0.08 g, 0.36 mmol), DMAP (a catalytic amount) in MeCN (5 mL), at 0 °C and under argon, was added dropwise a solution of benzoyl chloride (82 μL, 0.72 mmol) and Et_3N (100 μL, 0.72 mmol). The mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 (10 mL). The layer organic was washed with a saturated solution of NaCl (3 × 10 mL), dried (Na_2SO_4) and evaporated, to give a yellow oil that was purified by flash column chromatography using hexane/EtOAc/CH_2Cl_2 (30:1:1) as eluent to give **10a** (0.065 g, yield 65%) as a clear oil. IR ν = 3291, 1711, 1265, 1108, 1069, 769 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.10–8.07 (m, 2H, 2′-H, 3′-H), 7.60–7.32 (m, 7H, 4′-H, 5′-H, 6′-H, 4 × H_{arom}), 6.33 (t, 1H, J = 7.0 Hz, 1-H), 4.66 (t, 1H, J = 7.1 Hz, 3-H), 3.64–3.50 (AB system, 2H, J = 17.0 Hz, CH_2), 3.63–3.49 (AB system, 2H, J = 17.0 Hz, CH_2), 2.93 (dt, 1H, J = 14.9 Hz, 7.6 Hz, 2α-H), 2.13 (dt, 1H, J = 14.1 Hz, 6.7 Hz, 2β-H), 2.24 (t, 2H, J = 2.3 Hz, 2 × CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.69 (CO), 143.23 (C-7a), 140.97 (C-3a), 133.29 (C′-4), 130.49 (C′-1), 129.96, 129.46, 128.77, 128.62, 125.39 and 125.32 (4 × CH_{arom}, 4 × C′-H), 80.65 (2 × C≡CH), 76.05 (C-1), 73.08 (2 × C≡CH), 65.28 (C-3), 39.31 (2 × CH_2), 33.52 (C-2) ppm. MS (FAB): m/z (%): 331 (12) $[M+2]^+$, 330 (37) $[M+1]^+$, 231 (59), 186 (5), 154 (92), 137 (100), 105 (34). Anal. calcd for $C_{22}H_{19}NO_2$ (329.39): C 80.22, H 5.81, N 4.25; found C 80.56, H 5.45, N 4.39.

3.2.15. Compound 9b

Synthesis and characterization of (±)-*trans*-3-(*N*,*N*-dipropargylamino)-1-indanyl acetate. The same procedure as described for **9a** was used to prepare compound **9b** from **8b** by reaction with acetic anhydride, Et_3N, DMAP in MeCN; yield: 67%. Mp 70–71 °C. IR ν = 3284, 3252, 1720, 1243, 1134 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.47–7.28 (m, 4H, H_{arom}), 6.24 (d, 1H, J = 4.4 Hz, 1-H), 4.84 (t, 1H, J = 6.4 Hz, 3-H), 3.57–3.41 (AB system, 2H, J = 16.9 Hz, CH_2), 3.56–3.40 (AB system, 2H, J = 16.7 Hz, CH_2), 2.64–2.55 (m, 1H, 2α-H), 2.25–2.21 (m, 3H, 2β-H, 2 × CH), 2.04 (s, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.01 ($COCH_3$), 143.96 (C-7a), 140.84 (C-3a), 129.42, 128.46, 125.88 and 125.22 (CH_{arom}), 80.18 (2 × C≡CH), 76.55 (C-1), 72.91 (2 × C≡CH), 66.06 (C-3), 38.98 (2 × CH_2), 33.63 (C-2), 21.25 (CH_3) ppm. MS (FAB): m/z (%): 269 (2) $[M+2]^+$, 268 (9) $[M+1]^+$, 230 (70), 186 (5), 154 (100), 137 (97). Anal. calcd for $C_{17}H_{17}NO_2$ (267.3): C 76.38, H 6.41, N 5.24; found C 76.01, H 6.83, N 5.11.

3.2.16. Compound 10b

Synthesis and characterization of (±)-*trans*-3-(*N*,*N*-dipropargylamino)-1-indanyl benzoate. The same procedure as described for **10a** was used to prepare compound **10b** from **8b** by reaction with benzoyl chloride, Et_3N, DMAP in MeCN; yield: 65%. Mp 74–75 °C, IR ν = 3281, 3248, 1700, 1267, 1109, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 8.03–8.00 (m, 2H, 2′-H, 3′-H), 7.57–7.31 (m, 7H, 4′-H, 5′-H, 6′-H, 4 × H_{arom}), 6.51 (dd, 1H, J = 7.0 Hz, 3.2 Hz, 1-H), 4.92 (t, 1H, J = 6.7 Hz, 3-H), 3.61–3.46 (AB system, 2H, J = 16.7 Hz, CH_2), 3.60–3.45 (AB system, 2H, J = 16.7 Hz, CH_2), 2.76 (dt, 1H, J = 14.4 Hz, J = 6.7 Hz, 2α-H), 2.58 (ddd, 1H, J = 14.4 Hz, 7.1 Hz, 2.9 Hz, 2β-H), 2.27 (t, 2H, J = 2.3 Hz, 2 × CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.56 (CO), 143.95 (C-7a), 141.00 (C-3a), 132.95 (C′-4), 130.29 (C′-1), 129.66, 129.46, 128.56, 128.29, 126.02 and 125.35 (4 × CH_{arom}, 4 × C′-H), 80.17 (2 × C≡CH), 77.27 (C-1), 72.98 (2 × C≡CH), 66.13 (C-3), 39.07 (2 × CH_2), 33.85 (C-2) ppm. MS (FAB): m/z (%): 331 (12) $[M+2]^+$,

330 (48) $[M+1]^+$, 230 (62), 186 (5), 154 (99), 137 (100), 105 (23). Anal. calcd for $C_{22}H_{19}NO_2$ (329.39): C 80.22, H 5.81, N 4.25; found C 80.45, H 5.32, N 4.60.

3.2.17. Biological assay of neuroprotective effects of 1,3-rasagilines

The compounds were evaluated in this work following essentially the same protocol reported in a previous work by Yañez et al.[8]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2013.01.035.

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