Computational Design of Rasagiline Derivatives: Searching for Enhanced Antioxidant Capability

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Abstract

A set of new rasagiline derivatives is presented. They were designed to be antioxidant compounds with the potential to be used for treating neurodegenerative disorders. They are expected to be multifunctional molecules that can help reduce oxidative stress, which is thought to contribute to neurodegenerative disorders. The CADMA-Chem computational protocol was used to produce rasagiline derivatives and to evaluate their likeliness as oral drugs and antioxidants. Three of them were identified as the most promising ones. They are proposed to be better free radical scavengers than rasagiline. In addition, they are expected to keep the parent's molecule neuroprotective capability. Hopefully, the results presented here would promote further experimental and theoretical investigations on these compounds.

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Abstract

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Keywords : rasagiline; 1-(R)-aminoindan; DFT; ADME; computer-aided design, free radical scavenger, oxidative stress; toxicity; synthetic accessibility.

Introduction

Neurodegenerative disorders (ND); including Parkinson's[1, 2], Alzheimer's,[3, 4] and other neural diseases;[5] have been described to involve the gradual loss of particular neuronal cell population. Although numerous investigations have been devoted to the elucidation of the ND pathologies, their primary causes continue elusive. Some interrelated crucial aspects on the progression of these disorders are proteopathy[6-8], metal ion dyshomeostasis[9-32], environmental pollutants,[33-47] and neurotransmitter deficiencies. A chemical phenomenom shared by all these diseases is oxidative stress (OS). It could be accountable for the dysfunction or death of neuronal cells that conduces to disease pathogenesis.[48-65]

OS arises due to unregulated production and consumption of free radicals, primarily reactive oxygen species (ROS).[66-78] ROS are produced from molecular oxygen in the mitochondrial respiratory chain. Some partially reduced O_2 intermediates are formed in low amounts, including the highly reactive hydroxyl radical ($^*OH$) and the superoxide anion (O_2^{*-}), among others[66, 74, 75, 78-84]. Neurons are particularly vulnerable to ROS-induced damage because of their high oxygen consumption, relatively low antioxidant defense, low regenerative capacity, and high polyunsaturated fatty acid content.[78, 85-87] Thus, ROS overproduction in brain tissue imposes a very harmful threat. One possible therapeutic strategy is to prevent and/or diminish OS using free radical scavengers. In fact, a variety of neuroprotective drug agents are used because of their antioxidant capability[88-97].

Rasagiline (N-propargyl-1-(R)-aminoindan; Azilect$^{(r)}$) is an anti-Parkinson, selective irreversible monoamine oxidase (MAO-B) inhibitor drug. It is currently accepted by the US Food and Drug Administration, and has demonstrated to show neuroprotective and neurorestorative activities in *in vitro* and *in vivo* models[98-114]. Rasagiline benefits patients with both early and late Parkinson's disease as monotherapy or as an assistant to levodopa.[115-117] From a chemical point of view, rasagiline is a secondary cyclic benzylamine and indane derivative, in which the acetylenic group provides hydrophobicity and steric volume.

Rasagiline can act as a hydrogen bond donor, enabling an additional interaction with monoamine oxidase B enzyme. Youdim et al. reported that the S-isomer of rasagiline, TVP1022, is thousands times less potent as a MAO-B inhibitor[118-120] than selegiline. Nevertheless, both compounds present similar molecular mechanisms, suggesting that the neuroprotective effect of rasagiline is not depending on MAO-B inhibition, but to some extent is related to the N-propargyl moiety.
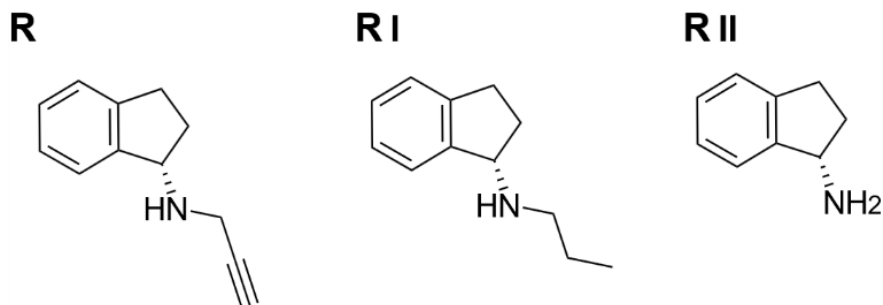
Rasagiline is mainly metabolized by hepatic cytochrome P-450. Its major metabolite, 1-(R)-aminoindan, is a weak reversible MAO-B inhibitor and a non-amphetamine compound with antioxidant and neuroprotective capabilities[121]. 1-(R)-aminoindan has reversed behavioral asymmetry and restored striatal catecholamine levels and neurons protection from hydrogen peroxide-induced oxidative stress *in vivo* models of Parkinson's disease.[122, 123] 5-hydroxy-1-(R)-aminoindan is the major metabolite of Ladostigil [(N-propargyl-(3R) aminoindan-5yl)-ethyl methyl carbamate], an anti-Parkinson drug. It *in vitro* neuroprotective capabilities are similar to those of 1-(R)-aminoindan. These findings suggest that 1-(R)-aminoindan and 5-hydroxy-1-(R)-aminoindan contribute to the overall neuroprotective activity of its parental compounds and are also neuro-active compounds.[124, 125] So, is the N-propargyl moiety a key feature to design novel derivatives with potent antioxidant behavior?

Based on the above-discussed information, the aims of this study are:

-To performe a rational search of molecules derived from the rasagiline framework, using a computer-assisted design protocol.

-To analyze the importance of the rasagiline triple bond and of the 1-(R)-aminoindan moiety in their drug-like behaviour and antioxidant potential.

-To propose rasagiline derivatives with high probabilities of being multipurpose antioxidants capable of lowering OS.

To accomplish that, the rasagiline structure was systematically modified in two different ways: (i) By inserting different functional groups in all the possible positions of the aromatic ring. (ii) By replacing the triple bond of rasagiline with a methyl group or a hydrogen atom (Scheme 1).

The reported results are expected to encourage further theoretical and experimental investigations on these molecules.

Scheme 1 . Structure of compounds under study (rasagiline (R), N-(propanyl)-2,3-dihydroinden-1-amine (R_I) and 1-(R)-aminoindan (R_{II}).

Computational details

Numerous physicochemical parameters for absorption, distribution, metabolism and excretion (ADME) were evaluated for all the designed R, R_I and R_{II} frameworks employing Molinspiration Property Calculation Service[126] and DruLiTo software.[127] The computed parameters were employed to confirm if the designed derivatives satisfy the Lipinski's rule of five, the Ghose's rule, and the Veber criteria.[128-131] Compounds violating more than one of Lipinski's rules might have difficulties with bioavailability. Those violating Ghose's rules could show absorption problems or low permeation; and those following Veber criteria may have better chances of suitable oral bioavailability.

Since all these conditions are general rules and not rigorous regulations, viable drugs have also to fulfill other vital requirements, such as synthetic accessibility (SA) and safety.[132-135] The SA of the designed compounds was determined with the SYLVIA-XT 1.4 program (Molecular Networks, Erlangen, Germany).[136] It delivers a value between 1 and 10. The smaller the value the easier to synthesize is the compound. The SYLVIA program has been certified for ranking virtual compounds during drug discovery processes[137]. Additionally, LD_{50} and Ames mutagenicity (M) were employed in this work to assess the toxicity of R, R_I and R_{II} and its derivatives. The Toxicity Estimation Software Tool (T.E.S.T.), version 4.1, was employed to obtain these parameters.[138] This software constructs predictions based on quantitative structure-activity relationships (QSAR), which are envisioned for screening new compounds. The LD_{50} and M descriptors were determined with the consensus method, which makes predictions as the average of the toxicities obtained with several QSAR methodologies.[139] There is a general understanding that the consensus method commonly offers higher accuracy and coverage than other protocols. Selection and elimination scores, expressed in terms of toxicity, manufacturability and ADME properties were used to make the first selection of derivatives.[140-142]

Gaussian 09 package was employed for electronic structure calculations[143]. Geometry optimizations and frequency calculations were carried out using the Density Functional Theory (DFT). The M05-2X approach was used in conjunction with 6-311+G(d,p) basis set and the solvation model density (SMD) using water to mimic a polar environment.[144] Local minima were identified by the absence of imaginary frequencies. Unrestricted calculations were used for open shell systems. M05-2X is a global hybrid exchange-correlation general gradient approximations functional designed for noncovalent interactions, kinetics and thermochemistry.[145] It has also been recommended for calculating reaction energies involving free radicals[146]. Furthermore, the M05-2X functional has been widely used for estimating pKa values, bonding dissociation energies, and the free radical scavenging activity of numerous antioxidant molecules[147-151].

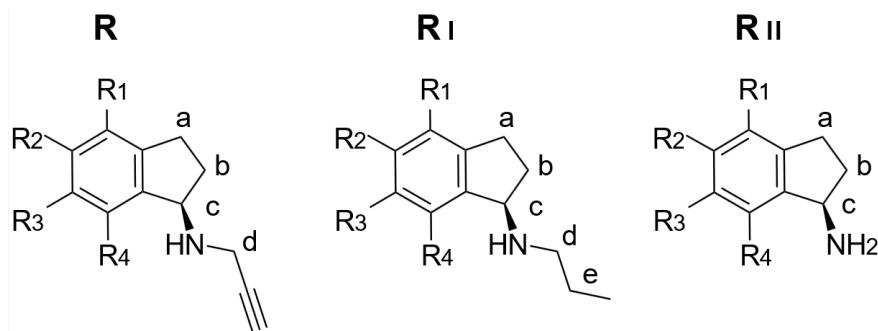Ionization energies (IE) and electron affinities (EA) were calculated in the framework of the electron propagator theory (EPT),[152, 153] which usually delivers values closer to those derived from experimental results than other methodologies. The partial third-order quasiparticle theory (P3)[154] was chosen since it has been

3

reported to have lower mean errors, compared to other methods.[155] However, for the EPT approximations (including P3) to be valid, pole strength (PS) values are needed to be larger than 0.80-0.85 [156] Electrophilicity, ω, was also estimated for electron transfer reactions[157-159]to analyze the chemical behavior of the designed R, R_I and R_{II} derivatives. In a chemical reaction, involving two molecules, that with the higher ω is expected to act as the electrophile, while the other will behave as the nucleophile. This index was calculated following the equation:

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For the computation of bond dissociation energies (BDE), all sites that are likely to act as H donors were considered (Scheme 2). They correspond to those already present in the rasagiline framework (sites a , b , c and d), and the new possibilities arising from incorporating functional groups (-OH, -NH$_2$, -SH and -COOH) in sites R_1 to R_4. These four groups were chosen because they can enhance the antioxidant behaviour and modify the acid-base ratio. Two rasagiline analogs were used to analyze the effects of the terminal alkyne group in physicochemical parameters, toxicity, synthetic accessibility, and the global reactivity indexes. They are: N-(propanyl)-2,3-dihydroinden-1-amine (R_I), which present a terminal methyl group instead of the corresponding rasagiline terminal alkyne; and 1-(R)-aminoindan (R_{II}) that present no alkyl chain. The derived comparisons could be interesting since no rational studies comparing these molecules have been carried out. Because of this structural modification, the e site in R_I was included, while d site in R_{II} was not considered, for BDE calculations.

Scheme 2 . Sites considered in the BDE calculations for R, R_I and R_{II}.

The proportion of neutral vs. charged species for molecules with acid-base bahaviour is ruled by the pKa-pH relationship. Thus, acid constants, expressed as pKa, were calculated for the subset of the most promising R, R_I and R_{II} derivatives. A fitted parameters approach (FPA) was used for that, because it was already proven as reliable.[160, 161] The calculated data was compared with a reference set of molecules, previously used for similar purposes.[142] The computational protocol described here is known as CADMA-Chem.[140]

Results and discussion

The data on the compounds used as references are reported in Table S1 and Table S2, Supporting Information. The data on the designed rasagiline derivatives are provided in Table S3, and their estimated properties in Table S4.

Three central matters were addressed in this investigation:

- building the candidate molecules,
- sampling the search space in a suitable maner, and
- assessing their potential for the intended purpose.

Following the CADMA-Chem protocol, above-explained; -OH, -NH$_2$, -SH and -COOH functional groups were inserted in sites R$_1$ to R$_4$ of R, R$_I$ and R$_{II}$. This led to 361 rasagiline derivatives. and are considered as the first two rasagiline derivatives, 48 compounds have only one functional group insertion (all possible species within the used scheme), 288 compounds have two functional groups substituted using any possible combination, and 23 have three added functional groups. The latter were built from the most promising bi-functionalized species.

ADME properties, toxicity values, and synthetic accessibility (Table S4) are used in the selection score (S^S), as previously described[140-142]. The higher the value of S^S (Table S5) the more probable that a rasagiline derivative presents a drug-like behavior. Equations on how S^S has been constructed considering ADME (absorption, distribution, metabolism, excretion) properties, toxicity (T), and synthetic accessibility (SA) can be found in Appendix S1.

Figure 1 presents the selection score (S^S) of rasagiline derivatives designed in this work. The values of individual properties used to assess S^S are presented in Table S4, while the reference values to compare with are those reported in Tables S1 and S2. In general, the molecules with higher S^S values are likely to have lower toxicity, improved synthetic accessibility, and enhanced ADME properties. Based on this criterion, sixteen rasagiline derivatives (Scheme 3) were chosen for the next stage, i.e., to determine their potential as antioxidants based on electronic structure calculations. Additionally, even though 1-(R)-aminoindan does not present a selection score value high enough to belong to the subset group, it has been included for comparison purposes on its own subfamily of derivatives.
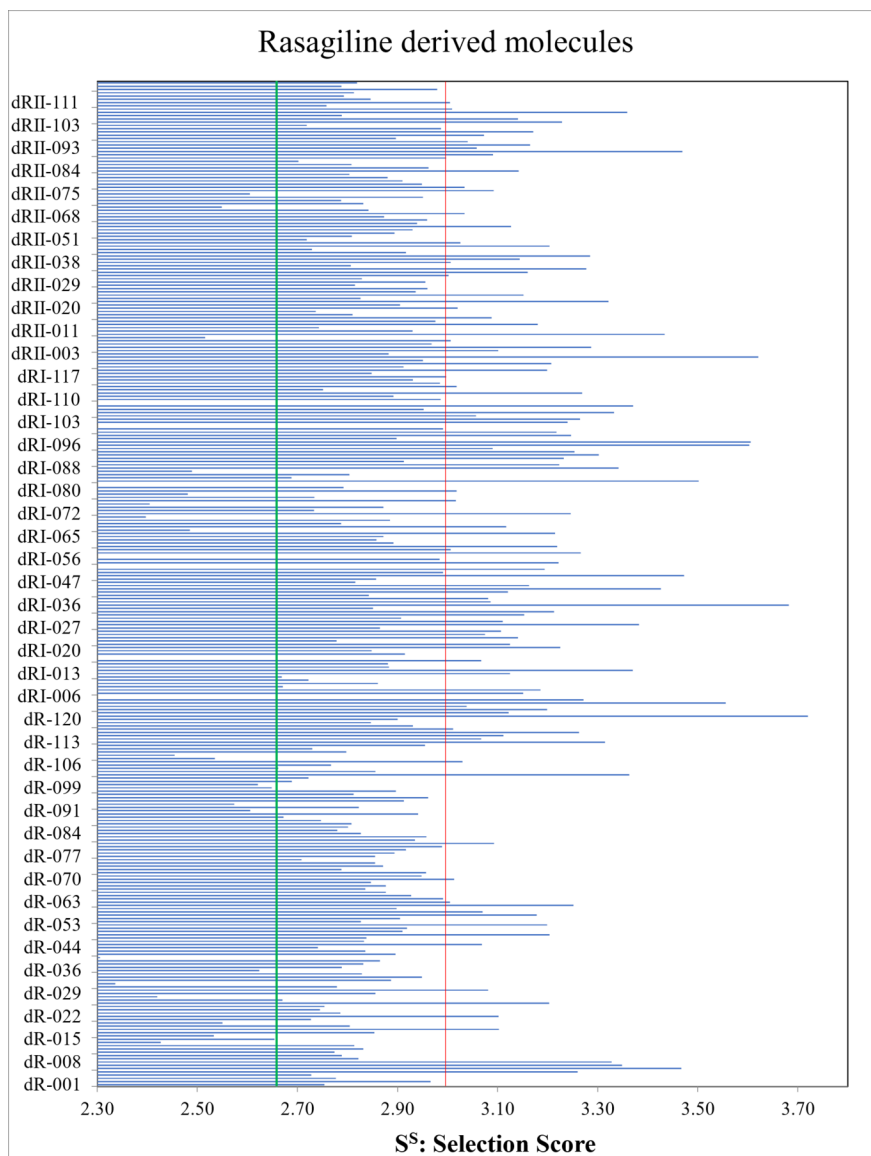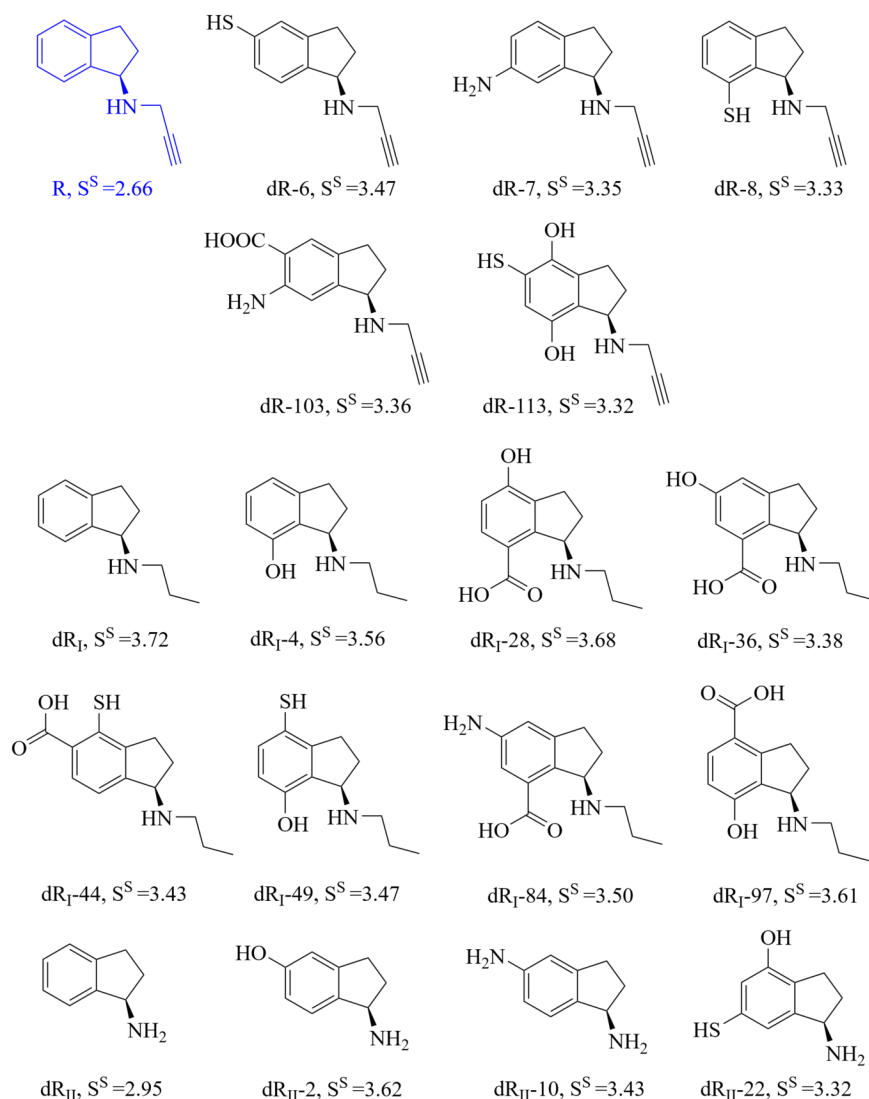
Figure 1 . Selection score (S^S) for the rasagiline derivatives designed in this work. Vertical lines mark the arithmetic mean of the reference set (red) and the value for the parent molecule (rasagiline, green).

Scheme 3 . Structure and S^S values of rasagiline and the derivatives selected for the next stage of the investigation.

To verify if any molecule in the selected subset considerably diverges (in any of its properties) from the average value of the reference set,[140-142] four exclusion scores (S^E) were also evaluated ($S^{E,ADME2}$, $S^{E,ADME8}$, $S^{E,ADMET}$ and $S^{E,ADMETSA}$). Their equations can be found in Appendix S2 of Supporting Information. $S^{E,ADME2}$ is the same to that formerly reported,[162] and the others use the same kind of scrutiny but including 8 terms for ADME properties, two terms related to toxicity (T), and a term for synthetic accessibility (SA). Thus, the accronyms are self-explanatory. These exclusion scores (Figure 2 and Table S6) measure deviations from the average values of already used oral drugs.

$S^{E,ADME2}$ values have been described to be between 1.2 and 1.5 when studying 1791, 152 and 35 oral drugs, respectively.[140-142, 162] On the other hand, for the rasagiline derivatives with the highest selection scores, average $S^{E,ADME2}$ =1.35, with individual values ranging from 0.6 to 2.9 for the whole set (Table S6, Supporting Information). The average $S^{E,ADME8}$ is 5.9, with individual values ranging from 2.4 to 9.9; the average $S^{E,ADMET}$ was found to be 7.6, with individual values ranging from 3.7 to 12.7; and the average

7

$S^{E,ADMETSA}$ is 7.8, with individual values ranging from 3.8 to 13.3 (Table S6). It is essential to keep in mind, though, that high values of these scores may arise from either worse or better behavior (as oral drug-like species) than the average of the reference set of drugs.
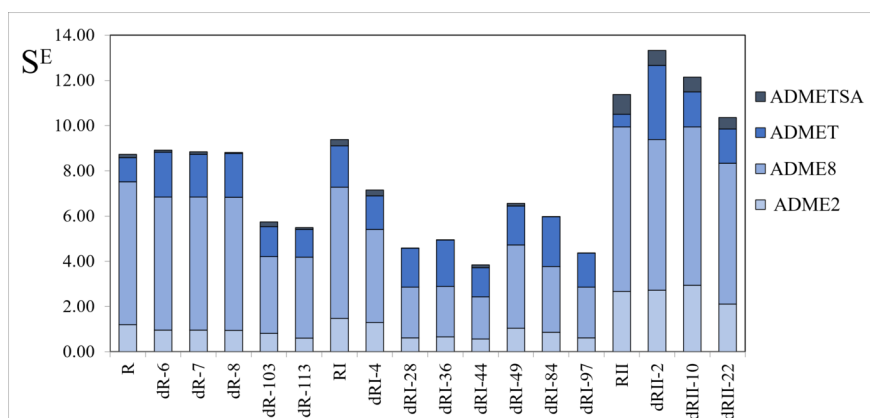

Figure 2 . Elimination score (S^E) for the most promising rasagiline derivatives, according to S^S. Columns are divided to show the influence of the new contributions included in each score, with respect to the previous one.

Figure 2 shows that the new properties included in $S^{E,ADME8}$, and the toxicity indexes have the largest contribution to $S^{E,ADMETSA}$. Thus, the proposed index emphasizes the importance of toxicity in the choice of candidates drugs. Figure 3 shows a more meticulous analysis of the individual contributions of the different parameters to the $S^{E,ADMETSA}$ elimination score.

The largest deviations arise mainly from LD_{50}, M, PSA, MW, HB^A, and HB^D.

Regarding LD_{50}, the rasagiline derivatives deviating the most from the average value (R-8, R_I-36 and R_{II}-2) are less toxic to rats than the reference compounds ($LD_{50} = 960.8$)[140-142]. Their LD_{50} were estimated to be 1970.2, 1613.9, 1882.0, and 2644.1, respectively. Thus, these important deviations imply a more desirable behaviour, compared to the reference set. Therefore, these derivatives were included in the subset selected as the most promising, based on ADMETSA properties. A similar trend was found for the Ames mutagenicity, i.e., the compounds predicted as the least mutagenic are just those that deviate the most from the reference set (M = 0.41)[140-142]. They are R_I, R_I-4, R_I-36, R_I-49, R_I-97, R_{II}-2, and R_{II}-10 all with M [?] 0.03. Consequently, it is essential not only to detect the designed molecules with the largest deviation from the reference set, but also to examine what causes such deviations. Otherwise, promising candidates could be excluded for no good reason.
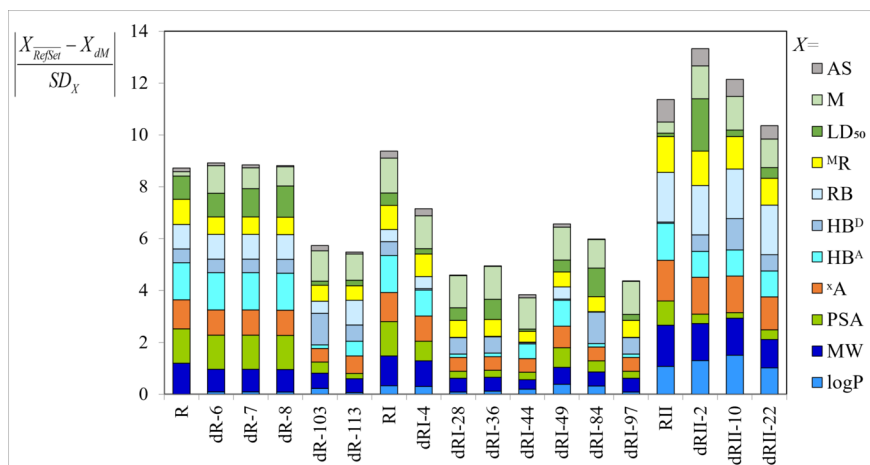
8

Figure 3 . Individual contributions to the elimination score (S^E), for the most promising rasagiline derivatives.

Contrarily, for the other indexes (PSA, HB^A and HB^D) larger S^E values denote that the properties of the examined derivatives deviate from the reference average, although they still fulfill the Lipinski's and Ghose's rules, as well as the Veber criteria. Regarding PSA, the chosen rasagiline derivatives deviating the most from the reference set are dR-6, dR-7, dR-8, and R_I, but their PSA values (12.03 for the first three and 26.02 Å^2 for the last) are below the Veber's limit: 140 Å^2. The largest deviations for HB^A and HB^D correspond to R-6, R-7, R8 and R_I with $HB^A = 1$ and to R_I-84 and R_{II}-10, with $HB^D = 4$, respectively. Once again, they do not represent violations of the Lipinski's rule. Stand on what has been considered, none of the 16 rasagiline derivatives selected as the most promising candidates, following the selection score, was excluded after the exhaustive screening using the elimination scores. Hence, IE, EA, and electrophilicity were estimated and analyzed for all of them.

Since all the rasagiline derivatives selected in the subset may be involved in acid-base equilibria, and such equilibria frequently influences the antioxidant capability, their p Ka values were determined, as well as their molar fractions ($^M f$) at physiological p H (Table 1). Their corresponding deprotonation routes and their distribution diagrams were also elucidated (Scheme S1 and Figure S1 in the Supporting Information). Ionization energies, electron affinities, and electrophilicities for the acid-base species with non-negligible population ($^M f > 0.1\%$) at p H=7.4, are reported in Table 2.

Table 1 . Estimated p Ka values and molar fractions of the diprotonated ($^M f_{\text{diprot}}$), protonated ($^M f_{\text{prot}}$), neutral ($^M f_{\text{neutral}}$), anionic ($^M f_{\text{anion}}$) dianionic ($^M f_{\text{dian}}$) and trianionic ($^M f_{\text{trian}}$) species of rasagiline its derivatives, at p H=7.4.

	$p\text{Ka}_1$	$p\text{Ka}_2$	$p\text{Ka}_3$	$p\text{Ka}_4$	$^M f_{\text{diprot}}$	$^M f_{\text{prot}}$	$^M f_{\text{neutral}}$	$^M f_{\text{anion}}$	$^M f_{\text{dian}}$
R	7.49	-	-	-	-	0.552	0.448	-	-
dR-6	6.25	11.15	-	-	-	0.066	0.934	$<10^{-3}$	-
dR-7	6.12	11.01	-	-	-	0.050	0.950	$<10^{-3}$	
dR-8	2.79	11.06	-	-	-	$<10^{-4}$	≈ 1.00	$<10^{-3}$	
dR-103	0.98	5.80	7.92	-	$<10^{-8}$	0.019	0.754	0.228	-
dR-113	3.94	8.95	10.74	-	-	$<10^{-3}$	0.972	0.027	$<10^{-4}$
dR_I	10.10	-	-	-	-	0.998	0.002	-	-
dR_I-4	8.05	13.04	-	-	-	0.817	0.183	$<10^{-6}$	-
dR_I-28	2.39	8.99	13.54	-	-	$<10^{-5}$	0.975	0.025	$<10^{-7}$
dR_I-36	2.01	9.49	14.03	-	-	$<10^{-5}$	0.992	0.008	$<10^{-8}$

9

	$p\mathrm{Ka_1}$	$p\mathrm{Ka_2}$	$p\mathrm{Ka_3}$	$p\mathrm{Ka_4}$	$^\mathrm{M}f_\mathrm{diprot}$	$^\mathrm{M}f_\mathrm{prot}$	$^\mathrm{M}f_\mathrm{neutral}$	$^\mathrm{M}f_\mathrm{anion}$	$^Mf_\mathrm{dian}$
$\mathrm{dR_I}$-44	3.48	6.57	10.99	-	-	$<10^{-4}$	0.129	0.871	$<10^{-3}$
$\mathrm{dR_I}$-49	6.52	9.50	13.68	-	-	0.116	0.877	0.007	$<10^{-8}$
$\mathrm{dR_I}$-84	1.36	3.65	12.86	-	$<10^{-9}$	$<10^{-3}$	≈1.00	$<10^{-5}$	-
$\mathrm{dR_I}$-97	4.25	7.45	13.19	-	$<10^{-3}$	0.529	0.471	$<10^{-6}$	-
$\mathrm{dR_{II}}$	9.10	-	-	-	-	0.980	0.020	-	-
$\mathrm{dR_{II}}$-2	9.33	10.26	-	-	-	0.988	0.012	$<10^{-4}$	-
$\mathrm{dR_{II}}$-10	3.55	9.91	-	-	$<10^{-3}$	0.997	0.003	-	-
$\mathrm{dR_{II}}$-22	5.86	7.97	10.78	-	-	0.022	0.770	0.207	$<10^{-4}$

The purpose of presenting the electrophilicity (ω) and the bonding dissociation energies (Table 2) is to assist in the prediction of the antioxidant behavior, via free radical scavenging chemical activity, especially for by hydrogen atom transfer (HAT) and single electron transfer (SET) mechanisms. Figure 4 presents the eH-DAMA (*e* lectron and *h* ydrogen *d* onating *a* bility *m* ap for *a* ntioxidants) for the rasagiline derivatives. This graphical tool has been recently designed to simultaneously account for the likeliness of molecules as H donors (formal HAT reactions) and electron donors (SET reactions).[82-84] It is constructed taking into account both the bond dissociation energies (related to HAT feasibility), and electrophilicity (related to SET viability). The pole strength (PS) values, arising from the EPT calculations (used to obtain electrophilicities) are all in the recommended range (Table S7). The complete set of BDE values for each species is provided as Supporting Information (Table S8). eH-DAMA employs electrophilicity (ω) over IE, since molecules with very low IE, are actually not expected to be very effective as free radical scavengers acting as electron donors in SET reactions since they are located in the inverted region of the Marcus parabola. In those cases, electrophilicity (ω) should be used instead of IE (Figure S3 and S4).[140-142]

As Figure 4 shows, the most promising acid-base species for deactivating free radicals via SET are the anions. They have the lowest ω values, followed by the neutral and the protonated species, respectively. In Figure 4, the parent molecule and Trolox are also included for comparison purposes, and the $H_2O_2/O_2{}^{*-}$ pair as the potential oxidant target. The latter has been chosen because it is usually harder to scavenge peroxyl radicals than other ROS. In the eH-DAMA, the species with low BDE are likely to be especially competent for scavenging free radicals acting as H donors via formal HAT, while species with low ω are expected to be efficient for scavenging free radicals acting as electron donors via SET. Hence, the species located at the bottom and left side of the eH-DAMA are assumed to act both ways. Thus, they can be considered *a priori* as good antioxidants. dR-113 is likely the most promising antioxidant from rasagiline derivatives followed by the neutral species of R_{II}-22 and R_I-49 which can be efficient as H donors but not perform particularly well for electron transfer reactions.

Table 2 . First ionization energy (IE, eV) and electron affinities (EA, eV), electrophilicity (ω and bond dissociation energies (BDE, kcal/mol) for rasagiline and the selected subset of derivatives.

		IE	IE	EA	EA	ω	ω	BDE	BDE
Protonated	Protonated								
R	R	12.36	12.36	2.69	2.69	2.93	2.93	86.92	86.92
dR-6	dR-6	11.08	11.08	2.72	2.72	2.85	2.85	77.82	77.82
dR-7	dR-7	11.08	11.08	2.72	2.72	2.85	2.85	76.62	76.62
dR-103	dR-103	11.36	11.36	3.31	3.31	3.34	3.34	84.88	84.88
$\mathrm{dR_I}$	$\mathrm{dR_I}$	12.26	12.26	2.48	2.48	2.77	2.77	86.86	86.86
$\mathrm{dR_I}$-4	$\mathrm{dR_I}$-4	11.93	11.93	2.19	2.19	2.56	2.56	86.83	86.83
$\mathrm{dR_I}$-49	$\mathrm{dR_I}$-49	10.85	10.85	2.26	2.26	2.5	2.5	74.73	74.73
$\mathrm{dR_I}$-97	$\mathrm{dR_I}$-97	12.2	12.2	2.35	2.35	2.68	2.68	86.38	86.38
$\mathrm{dR_{II}}$	$\mathrm{dR_{II}}$	12.52	12.52	3.28	3.28	3.38	3.38	86.34	86.34
$\mathrm{dR_{II}}$-2	$\mathrm{dR_{II}}$-2	11.99	11.99	3.28	3.28	3.34	3.34	86.34	86.34

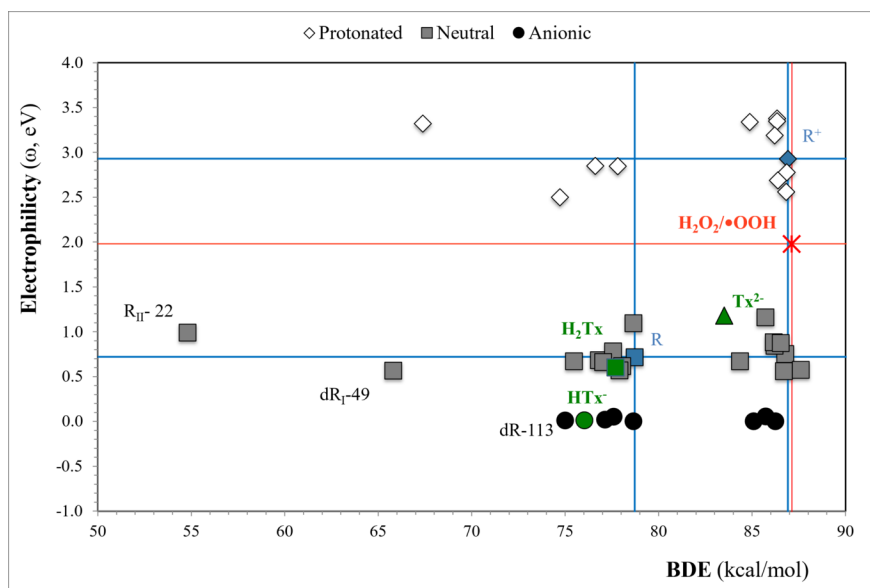|		IE	IE	EA	EA	ω	ω	BDE	BDE
dR$_{II}$-10	dR$_{II}$-10	11.18	11.18	3.14	3.14	3.19	3.19	86.21	86.21
dR$_{II}$-22	dR$_{II}$-22	11.24	11.24	3.29	3.29	3.32	3.32	67.39	67.39
Neutral	Neutral								
R	R	8.70	8.70	-1.18	-1.18	0.72	0.72	78.72	78.72
dR-6	dR-6	4.94	4.94	0.32	0.32	0.75	0.75	86.79	86.79
dR-7	dR-7	4.96	4.96	0.14	0.14	0.67	0.67	84.37	84.37
dR-8	dR-8	6.13	6.13	-0.64	-0.64	0.56	0.56	86.71	86.71
dR-103	dR-103	7.29	7.29	0.60	0.60	1.16	1.16	85.73	85.73
dR-113	dR-113	5.38	5.38	-0.01	-0.01	0.67	0.67	75.49	75.49
dR$_I$	dR$_I$	8.57	8.57	-1.25	-1.25	0.68	0.68	76.82	76.82
dR$_I$-4	dR$_I$-4	6.31	6.31	-0.65	-0.65	0.58	0.58	87.62	87.62
dR$_I$-28	dR$_I$-28	8.29	8.29	-0.56	-0.56	0.84	0.84	86.21	86.21
dR$_I$-36	dR$_I$-36	8.52	8.52	-0.53	-0.53	0.88	0.88	86.17	86.17
dR$_I$-44	dR$_I$-44	7.43	7.43	0.41	0.41	1.09	1.09	78.67	78.67
dR$_I$-49	dR$_I$-49	4.87	4.87	-0.12	-0.12	0.56	0.56	65.82	65.82
dR$_I$-84	dR$_I$-84	7.87	7.87	-0.60	-0.60	0.78	0.78	77.58	77.58
dR$_I$-97	dR$_I$-97	6.68	6.68	0.10	0.10	0.87	0.87	86.54	86.54
dR$_{II}$	dR$_{II}$	8.63	8.63	-1.36	-1.36	0.66	0.66	77.04	77.04
dR$_{II}$-2	dR$_{II}$-2	8.18	8.18	-1.33	-1.33	0.62	0.62	78.06	78.06
dR$_{II}$-10	dR$_{II}$-10	7.61	7.61	-1.26	-1.26	0.57	0.57	77.92	77.92
dR$_{II}$-22	dR$_{II}$-22	5.12	5.12	0.75	0.75	0.99	0.99	54.81	54.81
Anionic	Anionic								
dR-103	dR-103	4.11	4.11	-2.95	-2.95	0.02	0.02	77.14	77.14
dR-113	dR-113	2.50	2.50	-3.17	-3.17	0.01	0.01	75.01	75.01
dR$_I$-28	dR$_I$-28	2.69	2.69	-2.67	-2.67	0.000	0.000	85.09	85.09
dR$_I$-36	dR$_I$-36	2.62	2.62	-2.57	-2.57	0.000	0.000	86.26	86.26
dR$_I$-44	dR$_I$-44	1.79	1.79	-1.63	-1.63	0.001	0.001	78.67	78.67
dR$_I$-49	dR$_I$-49	1.24	1.24	-2.53	-2.53	0.06	0.06	85.74	85.74
dR$_{II}$-22	dR$_{II}$-22	2.06	2.06	-3.51	-3.51	0.05	0.05	77.61	77.61

11

Figure 4 . The electron and hydrogen donating ability map for antioxidants (eH-DAMA), including the acid-base species of rasagiline derivatives, the parent molecule, Trolox and the oxidant the H_2O_2/O_2^{*-} pair.

Conclusions

A systematic rational search for newly designed rasagiline derivatives is presented. It was performed using the CADMA-Chem computer-assisted protocol. A total of 361 derivatives were generated by adding, or modifying, functional groups in the rasagiline molecular framework.

A selection score (S^S) was built to sample the search space, simultaneously considering ADME (absorption, distribution, metabolism, excretion) properties, toxicity, and manufacturability (i.e., synthetic accessibility). It was used to characterize the whole set of designed derivatives and allowed the selection of a reduced subset of ten compounds expected to be the most promising, regarding drug-like behavior.

For this subset, several reactivity indices were estimated, as well as their pKa values. These indices account for electron and H donor capabilities. Thus, they are expected to reflect free radical scavenging behavior through single electron transfer (SET) and formal hydrogen transfer (HAT) mechanisms. According to the gathered data, three rasagiline derivatives were identified as the most likely candidates to act as chemical antioxidants (by directly scavenging free radicals). They are: dR-113, dR_I-49 and dR_{II}-22 in that order. All of them are predicted to be better for that purpose than rasagiline itself. In addition, since the made structural modifications are mild, they are expected to retain the neuroprotection of the parent molecule. The findings from this work are expected to motivate further investigations on these molecules, using both theoretical and experimental approaches.

Acknowledgements

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