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Article

Rational Design of Multifunctional Ferulic Acid Derivatives Aimed for Alzheimer's and Parkinson's Diseases

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Abstract: Ferulic acid has numerous beneficial effects for human health, which are frequently attributed to its antioxidant behavior. In this report many of them are reviewed and 185 new ferulic acid derivatives are computationally designed, using the CADMA-Chem protocol. For the later, the chemical space was sampled and evaluated. To that purpose selection and elimination scores were used, which are built from a set of descriptors accounting for ADME properties, toxicity, and synthetic accessibility. After the first screening, 12 derivatives were selected and further investigated. Their potential role as antioxidants was predicted from reactivity indexes, directed related with the formal hydrogen atom transfer and the single electron transfer mechanisms. The best performing molecules were identified by comparisons with the parent molecule and two references: Trolox and ⍵-tocopherol. Their potential as polygenic neuroprotectors was investigated through the interactions with enzymes directed related with the etiologies of Parkinson's and Alzheimer's diseases. They are acetylcholinesterase, catechol-O-methyltransferase, and monoamine oxidase B. Based on the obtained results, the most promising candidates (FA-26, FA-118, and FA-138) are proposed as multifunctional antioxidants with potential neuroprotective effects. The findings derived from this investigation are encouraging and might promote further investigations on these molecules.

Keywords: rational design; antioxidants; electron transfer; hydrogen transfer; neuroprotection; AChE; COMT; MAOB

1. Introduction

Oxidative stress (OS) is a harmful multifaceted phenomenon. It is often referred to as the "chemical silent killer" since no manifest symptoms are associated with it. Till today, there is no available test to detect it. Thus its damaging effects can evolve without any advice to the affected person. Currently, OS represents a major concern linked to the onset and development of hundred illnesses, including neurodegenerative disorders such as Alzheimer's[1-20] and Parkinson's[1, 19, 21-34] diseases. OS arises from the imbalance between the production and consumption of oxidants in living organisms. Free radicals, in particular reactive oxygen species (ROS) became toxic in high concentrations and are likely to react with important biomolecules jeopardizing its chemical integrity and functions.

Among the strategies to lessen OS risks to human health, chemical protection by antioxidant molecules is one of the most effective and studied approaches. Antioxidants can be seen as sacrifice compounds that prevent oxidants from reaching biomolecules. In fact, numerous reports have been devoted to these compounds and their capacity to ameliorate the harmful effects of OS.[28, 35-80] Recently, multifunctional antioxidants have arisen as promising candidates to deal with OS-related complex diseases. This kind of antioxidants can scavenge free radicals, chelate metals and inhibit the

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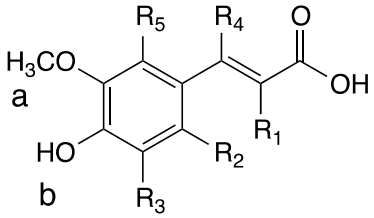
OH production, repair oxidatively damaged biomolecules, and inhibit enzymes involved in the development of health disorders.[81-83]

Antioxidants are produced endogenously by the human body and can be acquired through the intake of food and diet supplements. Phytochemicals have been proven to be beneficial in the treatment of several diseases.[84-110] Phenolic compounds, in particular, which are highly abundant in nature, have attracted great deal of interest due to their diverse health benefits and its proficiency to reduce OS effects.[111-129]

Ferulic acid (4-hydroxy-3-methoxy cinnamic acid, FA, Scheme 1) is one of these valuable molecules. It is found in whole grains, grapes, parsley, rhubarb, spinach, cereal seeds, artichoke, and coffee, among many other natural sources.[130] It is a versatile molecule. There are numerous reports on its antioxidant activity [131-143] as well as on its anti-inflammatory,[144, 145] antibacterial,[146-149] antiviral,[150] anti-thrombotic,[151, 152] anti-ageing, [153-155] and antitumoral effects.[156-170] It also acts as cardio protector,[171-177] neuroprotector,[178-188] antihypertensive,[189-192] antidepressant, [180, 193-198] hepatoprotector,[199-210] and has beneficial effects on diabetes[211-217] and gentamicin-induced nephrotoxicity.[218]



Scheme 1. Ferulic acid (FA) structure and site numbering used in this work.

Thus, it is not surprising that many efforts have been devoted to develop FA derivatives.[150, 156, 158, 219-264] Some of their relevant structural modification and properties are summarized in Table 1. Their bioactivities are diverse including antioxidant, anticancer, anti-inflammatory, and neuroprotective effects. According to the gathered data, it becomes evident that the ferulic acid molecular framework is a promising choice for developing new molecules with health benefits.

Table 1. Structural modifications and properties of some FA derivatives.

Functionalization	Bioactivity	Ref.
3-n-butylphthalide + glucose	Anti-ischemic.	[252]
Alkyl esters	β-amyloid aggregation inhibition.	[253]
Amide	Antiviral	[256]
Amide	Antioxidant, inflammatory, mitophagy enhancing.	[255]
Amide	β-amyloid oligomerization and fibrillization inhibition.	[232]
Amide	Antioxidant, anticancer.	[156]
Amide + pyrazole	Antioxidant, and myocardial cell hypoxia reoxygenation.	[262]
Amino acid	Anti-inflammatory, antioxidant.	[239]
Aniline	Antimicrobial.	[230]
Azetidine-2-one	Anti-inflammatory, antioxidant.	[225, 226]

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Benzyl, and phenylethyl esters	Anticancer.	[158]
Benzylamino, and carbamyl	β-amyloid aggregation inhibition, antioxidant, AChE inhibition.	[234]
Cyclized	Antiviral.	[263]
Different rings	Improvement of scopolamine-induced memory deficit in mice.	[245]
Dimer	Neuroprotection.	[229]
Dimethylthiazol + diphenyltetrazolium bromide	Anticancer.	[258]
Ester	Antibacterial.	[242, 243]
Ester	Antifungal.	[260]
Ester	Antithrombotic.	[259]
Ester	Anticancer.	[236]
Ester	Xanthine oxidase inhibition.	[250]
Ester, and amide	Anticancer.	[247]
Ester and amide	Antioxidant.	[219]
Glycerol, and diglycerol	β-amyloid aggregation inhibition.	[231]
Heterocyclic	Anticancer.	[238]
Isopentyl	Anticonvulsant.	[264]
N-Hydroxy-N-Propargylamide	Free radical scavenging, AChE inhibition, Cu(II) quelation.	[221]
O-alkylamines	Antioxidant, butyrylcholinesterase inhibition.	[244]
OH + OMe group + amide	Neuraminidase inhibition.	[223]
Phthalate, and maleate	Hepatoprotection.	[220]
Piperazine	Antiviral.	[257]
Tributyltin(IV)	Anticancer.	[261]

In this work, a systematic and rational search for FA derivatives is presented. To that purpose a computer-assisted protocol, known as CADMA-Chem,[81] was used. The aim of the search is to find candidates that behave as multifunctional antioxidants, with potential as neuroprotectors against Parkinson's and Alzheimer diseases. In pursuit this goal, the FA framework was modified through the inclusion of different functional groups at all R1 to R5 sites (Scheme 1). Absorption, distribution, metabolism and excretion (ADME) properties were evaluated, as well as toxicity and synthetic accessibility (SA). Antioxidant activity trough electron and H donation was predicted. The polygenic protection was explored by the interaction with enzymes linked to the target diseases. Namely: acetylcholinesterase (AChE), monoamine oxidase type B (MAOB), and cathecol-O-methyltranferase (COMT). The inhibition of the first one has been shown to help with Alzheimer's,[265-267] while the inhibition of the other two is beneficial for Parkinson's.[268-275] The obtained results are encouraging and might promote further investigations on the molecules identified as the most promising candidates.

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2. Computational Details

2.1. Molecular Properties

For all the designed ferulic acid derivatives (Table S1), physicochemical parameters related to absorption, distribution, metabolism and excretion (ADME) were evaluated (Table S2) with the Molinspiration Property Calculation Service[276] and DruLiTo software.[277] The computed parameters are employed to confirm if the designed derivatives satisfy the Lipinski's, Ghose's, and Veber rules.[278-280] Compounds violating more than one of Lipinski's or Veber's rules are assumed to have difficulties with bioavailability, while those violating Ghose's may present absorption problems or low permeation. Viable medical drugs need also to fulfill other vital requirements, such as synthetic accessibility (SA) and safety. The SA of the designed compounds was determined with the SYLVIA-XT 1.4 program (Molecular Networks, Erlangen, Germany).[281, 282] It estimate a value between 1 and 10. The smaller the value, the more easier to synthesize is the compound. LD_{50} and Ames mutagenicity (M) were employed to assess the toxicity of FA and its derivatives. The Toxicity Estimation Software Tool (T.E.S.T.), version 4.1,[283] was employed to that purpose. Selection and elimination scores (Tables S2 and S3), expressed in terms of toxicity, manufacturability and ADME properties were used for sampling the molecular space. A reference set of molecules, which have been used (to some extent) as neuroprotectors was used for comparison purposes (Table S4).

2.2. Reactivity Indexes

Gaussian 09 package of programs was employed for electronic structure calculations.[284] The M05-2X/6-311+G(d,p) level of theory was used for geometry optimizations and frequency calculations. The solvation model density (SMD)[285] was used for solvent effects, using water as solvent. Local minima were identified by the absence of imaginary frequencies and unrestricted calculations were used for open shell systems. M05-2X is a wide-spectrum functional with good performance for noncovalent interactions, thermochemistry and kinetics.[286] In addition, it has been recommended for modeling open-shell systems.[287] M05-2X functional has also been successfully used to estimate bond dissociation energies (BDE), pKa values, and the free radical scavenging activity of diverse antioxidants.[288-292].

The electron propagator theory (EPT)[293, 294] was used to calculate ionization energies (IE) and electron affinities (EA). The partial third-order quasiparticle theory (P3)[112] was chosen, within the EPT framework, because it produces lower mean errors than other approaches.[295] Pole strength (PS) values were checked to larger than 0.80-0.85 (Table S5), which validates the obtained results.[296]

For the estimation of BDEs, all sites likely to act as H atom donors were considered, i.e., the -CH_3 in the ether moiety of FA, and the phenolic OH (sites *a* and *b*, Scheme 1) and the new groups arising from functionalization of R1 to R5 sites.

Acid constants, expressed as pKa, were calculated with the Marvin suite.[297] This property is of crucial importance for medical drugs since it governs the proportion of neutral species at a particular pH, and these are the species most likely to passively cross biological barriers.

2.3. Enzymatic Interactions

The structures of COMT (PDB ID: 3S68), MAO-B (PDB ID: 2V5Z) and AChE (PDB ID: 4EY7) co-crystallized with recognized neuroprotector drugs, tolcapone, safinamide and donepezil, respectively, were obtained from protein data bank.[298-300] Missing loop regions were fixed using Modeller web service.[301] Water molecules, and species without biological interest were removed with Discovery Studio software.[302] All structures were modelled considering *p*H=7.4. For ligands, atomic charges estimated by NBO protocol as single point calculations with DFT (M05-2X/6-311+G(d,p)) methodology. Docking simulations were carried out using AutoDock Vina software.[303] A gradient optimization algorithm was performed inside of the active site centered at x: -13.50, y: 37.69, z: 61.63 and grid size of 15 x 15 x 15 $Å^3$ for COMT, x: 51.81, y: 156.34, z: 28.15 and grid size of 13 x 13 x 13 $Å^3$ for MAO-B and x: -18.80, y: -43.83, z: 27.67 and grid size of 17 x 13 x 13 $Å^3$

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for AChE. Docking scores (DG_B^W) were reported for the best docked pose and weighted according to the abundance (molar fraction) of the acid-base species at physiological pH. The best conformation was analyzed and drawn with Pymol 2.5.4 software.[304]

The redocking RMSD values 1.8, 1.6 and 2.8 Å respectively and redocking scores (7.65, 10.10 and 10.86 kcal/mol) founded for tolcapone (COMT), safinamide (MAO-B) and donepezil (AChE) respectively, agrees with experimental findings. These results confirm the suitability of docking methodology. Redocking conformations are obtained with Chimera software[305] and they can be founded in Figure S1.

3. Results and Discussion

3.1. Derivatives and Properties

By inserting -OH, -NH_2, -SH and -COOH groups in sites R_1 to R_5, 185 new FA derivatives were built (Table S1). Twenty of them with one functional group, 160 with any possible combination of two functional groups, and 5 with three functional groups. The latter were constructed from the most promising bi-functionalized species.

A selection score (S^S) was computed. It is meant to identify the FA derivatives with the most likely drug-like behavior and corresponds to that included in the CADMA-Chem protocol.[81-83, 306-308] The associated equations are provided in Table S6. The higher the value of S^S the more likely the drug-like behavior. S^S takes into account eight ADME properties: water/octanol partition coefficient (logP), topological polar surface area (PSA), number of heavy atoms (^{X}At), molecular weight (MW), number of H-bond acceptors (HB^A), number of H-bond donors (HB^D), rotatable bonds (RB), and molar refractivity (^{M}R); two toxicity descriptors: oral rat 50 percent lethal dose (LD_{50}) and Ames' mutagenicity (M); and the synthetic accessibility (SA).

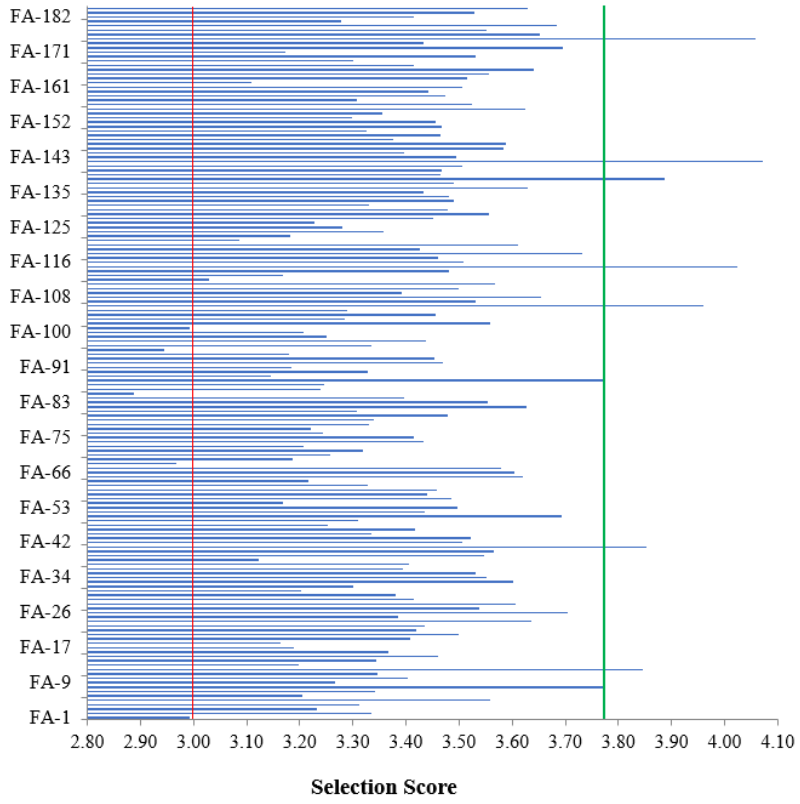

Figure 1. Selection score (S^S) for the FA derivatives designed in this work. Vertical lines mark the arithmetic mean of the reference set (red) and the value for the parent molecule (FA, green).

The S^S for all the designed FA derivatives is presented in Figure 1. The parent molecule and the average S^S value for the reference set are included for comparison purposes. The individual values of

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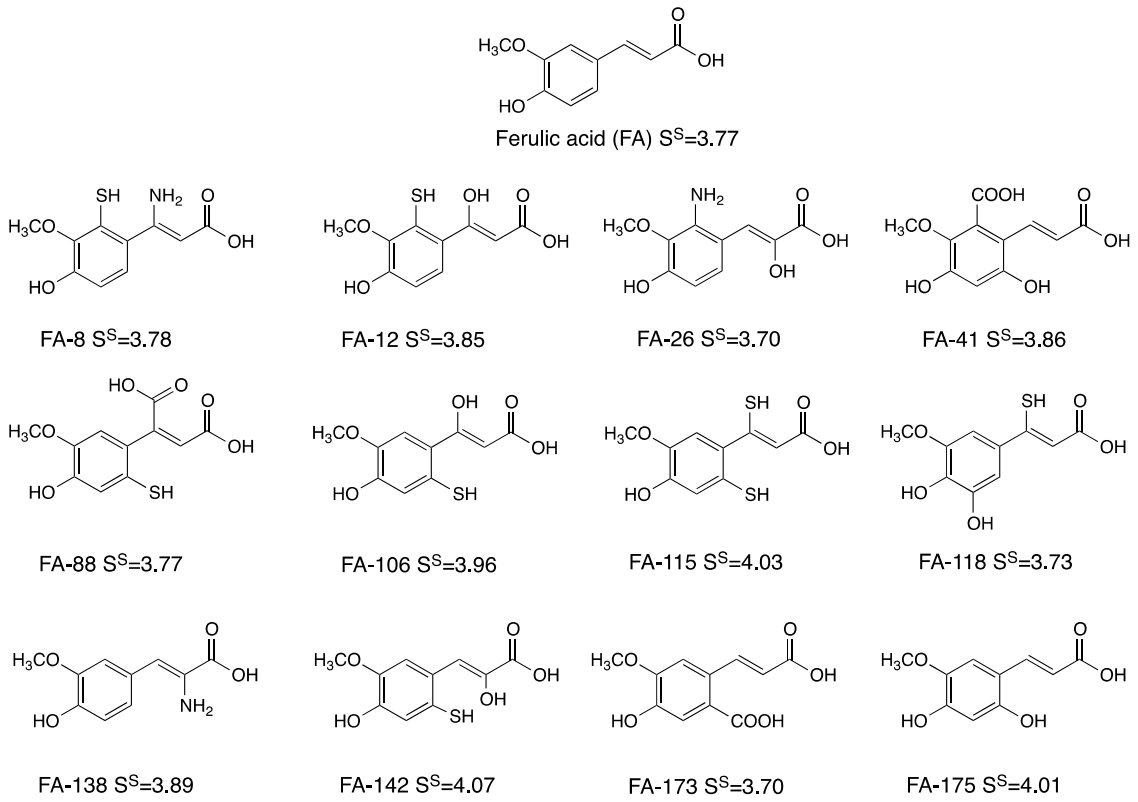
all the FA derivatives are reported in Table S2, together with those of the above-mentioned descriptors. Higher values of S^S suggest better drug-like behavior, lower toxicity, and easier synthesis. The first screening was based on this score, and twelve FA derivatives were selected. However, before moving them forward to the next stage of the investigation (Scheme 2) a double-check analysis was performed using exclusion scores (S^E), which allows verifying if any of the selected molecules significantly deviates (in any of its properties) from the average value of the reference set.



Scheme 2. Structure and S^S values of FA and the derivatives selected for the next stage of the investigation.

Four exclusion scores were analyzed ($S^{E,ADME2}$, $S^{E,ADME8}$, $S^{E,ADMET}$ and $S^{E,ADMETSA}$). Their equations are provided Table S7. $S^{E,ADME8}$, $S^{E,ADMET}$ and $S^{E,ADMETSA}$ are extensions of the well-known $S^{E,ADME2}$, based on two descriptors (logP and MW).[309, 310] $S^{E,ADME8}$ uses the same kind of strategy as $S^{E,ADME2}$, but includes six additional terms (PSA, XAt, HB^A, HB^D, RB, and ^MR). $S^{E,ADMET}$ and $S^{E,ADMETSA}$ also include toxicity (LD_{50} and M) and synthetic accessibility (SA) descriptors.

$S^{E,ADME2}$ values were previously estimated to be between 1.2 and 1.5 for 1791, 152 and 35 oral drugs.[309, 310] For the 12 selected FA derivatives the average $S^{E,ADME2}$ value was found to be 1.06, with individual values ranging from 0.56 to 1.42 (Table S4). The estimated average values for the other elimination scores were found to be: $S^{E,ADME8}$ = 4.86 (ranging from 2.59 to 7.34). $S^{E,ADMET}$ = 8.13 (ranging from 4.53 to 11.54), and $S^{E,ADMETSA}$ = 9.59 (ranging from 5.50 to 12.52). It seems worthwhile mentioning that high values of the exclusion scores might result from either worse or better behavior than the average of the reference drugs. Thus, a detailed analysis is required to determine if any particular candidate should be removed from the selection or not.

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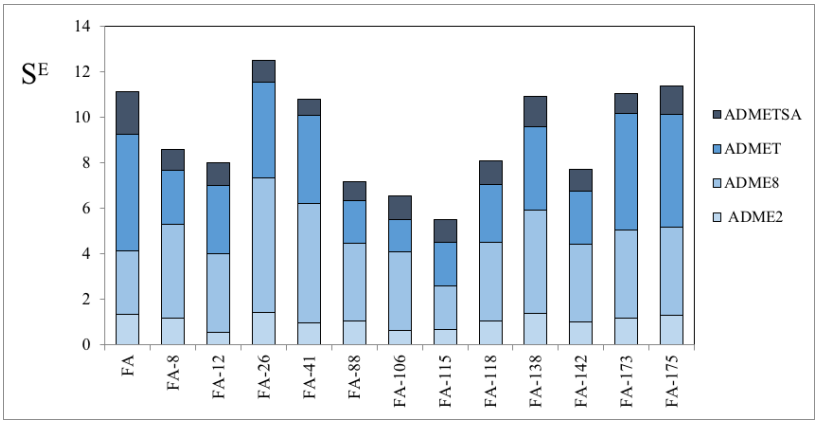

Figure 2. Elimination score (S^E) for the most promising FA derivatives, according to S^S. Columns are divided to show the influence of the new contributions included in each score, with respect to the previous one.

According to the gathered results (Figure 2), toxicity is responsible for the largest deviation. Regarding ADME, the six additional descriptors lead to largest deviation than logP and MW. Synthetic accessibility also has rather small influence on the deviations from the reference molecules. A more detailed examination, considering the individual contribution of all the investigated descriptors is presented in Figure 3.

The more important deviations arise from LD_{50}, followed by M, PSA and HB^D. the FA derivatives with the largest LD_{50} deviations from the reference set are FA, FA-173, FA-175 and FA-26. However, they correspond to a lower toxicity to rats than the reference average (LD_{50} = 960.8), with values 4742.7, 4471.9, 4040.7, and 3635.2, respectively. Regarding Ames mutagenicity, a similar trend was found. The FA derivatives predicted as the least mutagenic are just those that deviate the most from the reference set average (M = 0.41). They are FA-88, FA-106, FA-115 and FA-142, all with M = 0.01. Thus, these deviations imply that the above-mentioned derivatives have a more desirable behavior than that of the reference set. Accordingly, they were not excluded from the chosen subset.

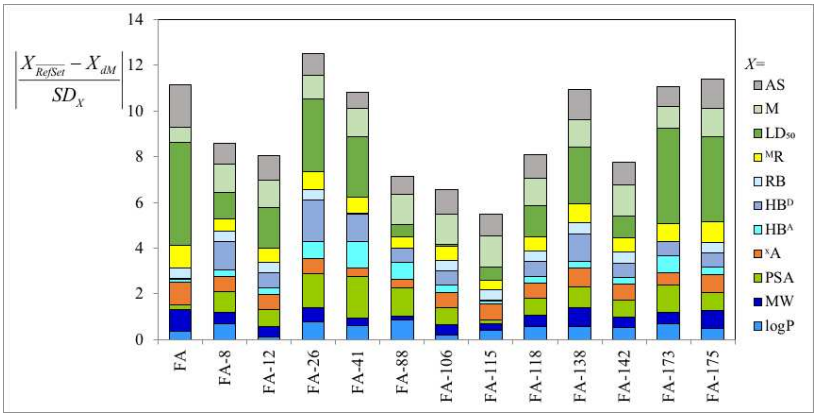

Figure 3. Individual contributions to the elimination score (S^E), for the most promising FA derivatives.

The largest PSA deviation were found for FA-41, FA-26, FA-88 and FA-173 (124.3, 113.0, 104.1 and 104.1 Å^2, respectively). However, their PSA values are all below the Veber's limit: 140 Å^2. Thus, these derivatives were also kept in the chosen subset. The largest deviations for HB^D correspond to FA-26 with HB^D = 5 and FA-8, FA-41 and FA-138 with HB^D = 4. Since they do not represent violations of the Lipinski's rule, these candidates were not eliminated.

After carefully examining elimination scores for the 12 FA derivatives with the highest S^S values, none of them were excluded from the selection. Thus, they move forward to the next stage, which is the investigation of the antioxidant capacity through electron and H-atom donation. This detailed

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analysis is important since it allows interpreting deviations for all the used descriptors, and prevents from excluding suitable candidates for no good reason.

3.2. pKa and Antioxidant Activity

As previously mentioned, acid-base equilibria are crucial for medical drugs intended to passively cross biological barriers. The *p*Ka values and molar fractions (^{M}f), at physiological *p*H, were estimated for the 12 FA derivatives chosen in the first stage of the investigation as those with the best drug-like behavior (Table 2). Additionally, the corresponding deprotonation routes and distribution diagrams are provided in Figures S2 and S3.

Table 2. Estimated *p*Ka values and molar fractions, $^{M}f_{(q)}$, at *p*H=7.4. The (q) in the acronym represents the charge of the acid base species.

	pKa_1	pKa_2	pKa_3	pKa_4	$^{M}f_{(+1)}$	$^{M}f_{(0)}$	$^{M}f_{(-1)}$	$^{M}f_{(-2)}$	$^{M}f_{(-3)}$	$^{M}f_{(-4)}$
FA	4.0	10.0	-	-	-	4×10^{-4}	0.997	0.003	-	-
FA-8	3.1	4.4	5.8	10.8	$<10^{-4}$	0.023	0.976	4×10^{-4}	-	-
FA-12	3.7	5.6	10.3	11.3	-	$<10^{-4}$	0.015	0.984	0.001	$<10^{-4}$
FA-26	2.5	3.9	10.1	11.8	$<10^{-4}$	3×10^{-4}	0.998	0.002	$<10^{-4}$	-
FA-41	2.7	4.4	9.7	11.1	-	$<10^{-4}$	0.001	0.994	0.005	$<10^{-4}$
FA-88	1.9	5.2	5.9	10.5	-	$<10^{-4}$	2×10^{-4}	0.033	0.966	0.001
FA-106	3.7	5.7	10.3	11.2	-	$<10^{-4}$	0.019	0.980	0.001	$<10^{-4}$
FA-115	3.8	5.8	8.6	10.9	-	$<10^{-4}$	0.023	0.918	0.059	$<10^{-4}$
FA-118	3.6	8.5	9.5	13.0	-	1×10^{-4}	0.921	0.078	0.001	$<10^{-4}$
FA-138	4.0	7.6	9.9	-	2×10^{-4}	0.596	0.403	0.001	-	-
FA-142	3.1	5.8	10.4	12.2	-	$<10^{-4}$	0.022	0.977	0.001	$<10^{-4}$
FA-173	3.6	4.2	10.0	-	-	$<10^{-4}$	0.001	0.997	0.003	-
FA-175	3.8	9.6	11.0	-	-	3×10^{-4}	0.994	0.006	$<10^{-4}$	-

The calculated molar fractions (Table 2) revealed that 7 of the 12 derivatives, selected based on the S^S value, would have negligible population ($<10^{-4}$) at physiological pH, i.e., at pH=7.4. Thus, they were excluded as viable candidates. Albeit the $^{M}f_{(0)}$ for other 3 (FA-26, FA-118, and FA-175) are rather small, they are very similar to that of FA. Since there is abundant data on the biological activities of FA (Table 1), it can be inferred that such fractions are enough. Consequently, 5 derivatives (FA-8, FA-26, FA-118, FA-138, and FA-175) were further investigated. Among the studied derivatives, FA-138 is the only one that is predicted to have similar fractions of neutral (q= 0) and anionic (q= -1) species. This feature might be relevant to its possible use as multifunctional antioxidant. The rather large neutral fraction (59.0%) is expected to promote passive crossing through biological membranes, while the anionic fraction (40.3%) is likely to be the key one for the free radical scavenging activity as it is the case for many phenolic compounds.

The ionization energies (IE), electron affinities (EA), and the lowest bond dissociation energies (BDE) for the acid-base species with non-negligible population ($^{M}f_{(q)} \geq 10^{-4}$) of FA and its derivatives, at *p*H=7.4, are reported in Table 3. The complete set of BDEs, i.e., considering all viable H-donating sites, is provided as Supplementary Materials (Table S8). IE and BDE reactivity indexes are related to the viability of electron and H atom donation. Thus, they were used to compare the efficiency of the derivatives with that of reference antioxidants, as free radical scavengers via single electron transfer (SET) and formal hydrogen atom transfer (HAT) mechanisms, respectively.

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Table 3. First ionization energy (IE, eV), electron affinities (EA, eV), and lowest bond dissociation energies (BDE, kcal/mol) for FA and the selected subset of derivatives.

	IE	EA	BDE	BDE-site*
q= 1				
FA-138	11.64	3.54	89.30	b (OH)
q= 0				
FA	8.36	-0.28	85.15	b (OH)
FA-8	8.75	-0.13	80.24	R5 (SH)
FA-26	8.35	0.34	83.06	R1 (OH)
FA-118	8.31	-0.95	80.18	b (OH)
FA-138	8.58	0.29	83.97	b (OH)
FA-175	8.12	-0.23	80.09	R2 (OH)
q= -1				
FA	4.85	-2.95	82.48	b (OH)
FA-8	3.75	-2.95	77.44	R5 (SH)
FA-26	4.33	-3.12	77.29	R1 (OH)
FA-118	4.43	-2.98	78.79	b (OH)
FA-138	3.89	-3.11	74.88	b (OH)
FA-175	4.66	-3.05	78.54	b (OH)
q= -2				
FA	-0.06	-6.00	96.96	a (OCH_3)
FA-8	0.20	-5.58	82.04	b (OH)
FA-26	-0.34	-6.04	71.30	b (OH)
FA-118	-1.09	-4.97	74.87	b (OH)
FA-138	-0.55	-5.77	97.02	a (OCH_3)
FA-175	-0.31	-5.32	75.90	b (OH)
q= -3				
FA-118	-3.78	-7.59	71.01	b (OH)

*The labels correspond to those shown in Scheme 1.

IE and BDE values were used to build the electron and hydrogen donating ability map for antioxidants (eH-DAMA, Figure 4). This graphical tool has been recently proposed to simultaneously accounting for the likeliness of molecules as H donors (formal HAT reaction route) and electron donors (SET reaction route).[92,93] The dominant acid-base species of the investigated FA derivatives, at physiological pH, were included in this map; as well as two antioxidant references (Trolox and α-tocopherol), the parent molecule, and the $H_2O_2/O_2^{\bullet-}$. This pair represents the potential oxidant target. The best radical scavengers are expected to be located at the bottom left, i.e., lower IE and lower BDE. The species in this region are likely to simultaneously act as electron and H-atom donors.

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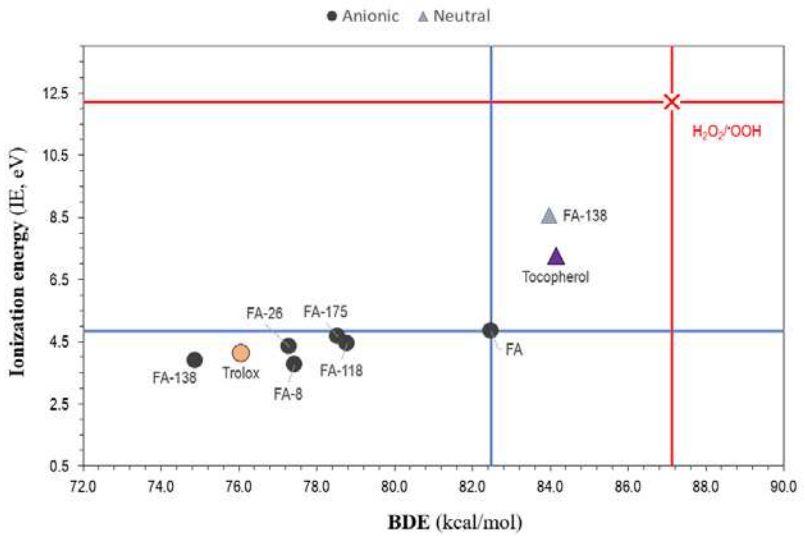

Figure 4. The electron and hydrogen donating ability map for antioxidants (eH-DAMA), including the dominant acid-base species of FA derivatives, the parent molecule, Trolox, α-tocopherol, and the $H_2O_2/O_2^{\bullet-}$ oxidant pair.

Based on the eH-DAMA (Figure 4) it is predicted that the five FA derivatives included in it should be efficient for scavenging peroxyl radicals through both mechanisms, SET and *f*-HAT. Their efficient for that purpose is expected to surpass that of α-tocopherol and ferulic acid. On the contrary, only the anionic form of FA-138 is predicted to be more efficient than Trolox for that purpose. FA-8 may be better electron donor than Trolox, but not as good for donating H-atoms. However, further investigation dealing with other aspects of antioxidant activity, kinetics in particular, are still needed to confirm of refute the foreseen trends.

3.3. Polygenic Activity

The possible neuroprotection activity of the ferulic acid derivatives was investigated using molecular docking studies. Only the compounds with a significant molar fraction of the neutral specie, at physiological pH, were studied. To evaluate the general neuroprotection activity, a polygenic score (S_P) was developed. S_P is a measure of the tested compounds capacity to bind to the enzymes compared with natural substrates (COMT: dopamine (dopa), MAO-B phenylethylamine (pea) and AChE: acetylcholine (ACh). It was defined according to our previously reports [81, 82] as:

$$S_P = \frac{\Delta G^W_{B,COMT}}{\Delta G_{B,dopa}} + \frac{\Delta G^W_{B,MAO-B}}{\Delta G_{B,pea}} + \frac{\Delta G^W_{B,AChE}}{\Delta G_{B,\ ACh}}$$

The scoring values are presented in the Table 4. When the values of S_P are examined, it can be predicted that the compounds exhibit neuroprotection activity since their scores are higher than the those of the corresponding natural substrates (S_P= 3.00), i.e., the investigated ferulic acid derivatives may present stronger affinities towards the enzymes. Among the studied compounds, the FA-26 analog is expected to have the best neuroprotection activity. Interestingly, according with the docking results, the parent molecule (ferulic acid) is also likely act as a neuroprotector.

Table 4. Polygenic score (S_P) values for ferulic acid and its derivatives.

Compound	DG_B^W (kcal/mol)			S_P
	COMT	MAO-B	AChE	
Ferulic Acid	-5.28	-7.19	-7.37	3.78
FA-9	-5.14	-6.91	-6.43	3.50
FA-26	-5.09	-7.63	-7.88	3.93

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FA-118	-5.90	-7.09	-6.95	3.79
FA-138	-5.12	-7.17	-7.40	3.76
FA-175	-5.42	-7.02	-7.01	3.70

$DG_{B,\,dopa}$= -5.44 kcal/mol in COMT; $DG_{B,\,pea}$= -6.01 kcal/mol in MAO-B; $DG_{B,\,ACh}$= 4.56 kcal/mol in AChE. For natural substrates S_P=3.00

The examination of individual DG_B^W values reveals that the studied compounds could be better inhibitors for AChE and MAO-B than they are for the COMT enzyme. Negative values of COMT (blue fragment of the bars, in Figure 5) indicates that this enzyme forms more stable complexes with dopamine than with the tested FA derivatives. Only FA-118 shows a slightly higher score than dopamine. Interestingly, this compound has a catechol moiety, which is recognized to exhibit effective COMT inhibition potential.[311] FA-175 presents almost the same score as dopamine (log $DG^W_B/DG_{B,sub}$= - 0.001). On the other hand, for MAO-B and AChE (green and red fragments, respectively, Figure 5), the neuroprotection behavior of FA derivatives was evidenced by their positive values. Between these two enzymes, the inhibitor potential of the studied derivatives is expected to be stronger for AChE, which suggests an improved activity against acetylcholine degradation. The complete set of binding energies can be founded in Table S9, Supplementary Materials.

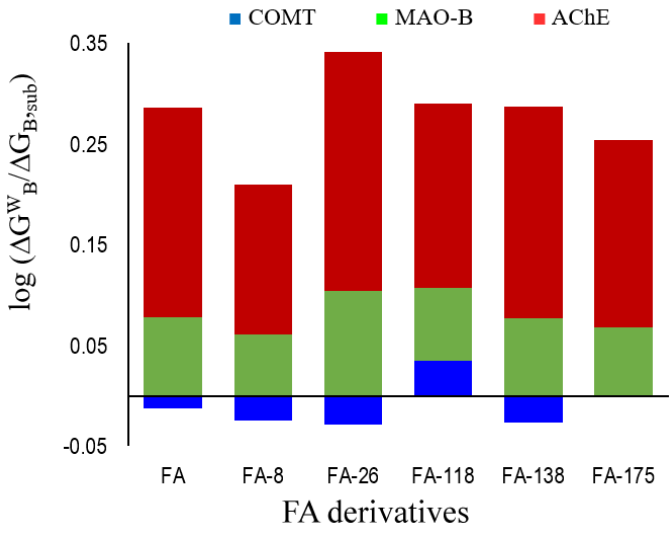

Figure 5. Polygenic scores of the ferulic acid and its derivatives.

The main interactions for the complexes with the highest S_P are shown in Figure 6. They are FA-26 with AChE (left), FA-26 with MAO-B (middle), and FA-118 with COMT (right). For all of them FA-26 is in its anionic form, which is the most abundant species at physiological pH (X~0.97). To understand the interactions formed in the protein-ligand complexes, it is important to know the architecture of the enzymes and the function of the key residues. AChE has a highly specialized structure, which allows it to be one of the fastest known enzymes. The catalytic triad (H447, E334 and S203) is founded at the bottom of the enzyme and surrounded by 14 well conserved aromatic residue.[312] Among them, W83 plays an essential role since it forms a substrate union site, while Y70, Y121, and W279 conform the anionic peripheric site.[312] Additionally, AChE has a high dipole moment with the axis oriented towards the substrate entry site. It has been suggested that this moment may serve to pull down the cationic substrate of AChE. This dipole is controlled mainly by residues D71, E199, and E443.[313]

FA-26 has several H-bond donors and acceptors, and an aromatic ring that contribute to generate intermolecular connections with the AChE key amino acids. In fact, complex FA-26:AChE is formed by several interactions, mainly hydrogen bonds and p-interactions. This derivative is bonded to the active site of AChE through four hydrogen bonds (D71, Y121, F292, and Y338), one p-stacking

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interaction (Y334) and one p-alkyl interaction (W83). The observed interactions suggest that FA-26, although not bonded to the catalytic triad, can inhibit the ACh degradation, blocking the entry and union sites.

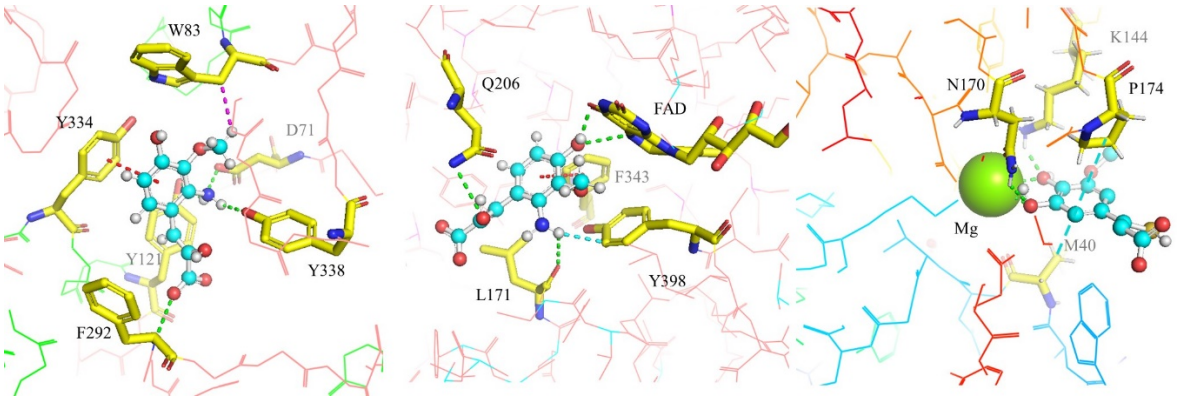

Figure 6. Interactions in FA-26:AChE (left), FA-26:MAOB (middle) and FA-118:COMT complexes. FA-26 and FA-118 are shown using the ball and stick model. Interactions are presented as dotted lines: conventional hydrogen bonds (green), p-stacking (red), p-alkyl (magenta), and C-H non-conventional bond (cyan).

MAO-B function involves two hydrophobic pockets, an entry pocket and an active site pocket with I199 acting as a gatekeeper between two cavities. The catalytic reaction site comprises a redox cofactor, flavin adenosin dinuleotide (FAD). The active site is completed by residues Y398 and Y435, orienting the substrate to the proper position.[314]

Four H-bonds involving Q206, L171, and FAD; a p-stacking (F343); and non-conventional C-H bonds stabilize the complex formation. An important feature of the conformation adopted by FA-26 in the complex is the formation of an H-bond with N5 in the FAD moiety. This atom is required for the redox activity of the cofactor[314] and, hence, for the catalytic function of the enzyme. This conformation could not be achieved without the orientation promoted by the L171 and Y398 residues, which suggests that FA-26 could inhibit some enzymes with the same mechanism of action as MAO (type A) or other flavoenzymes as lactate oxidase.[315] According to these findings, FA-26 is predicted to act as a reversible or non-covalent MAO-B inhibitor as Safinamide o Moclobemide,[299, 316], which are recognized antidepressant drugs. This way of inhibition is preferable since it has been proven to be associated with less toxicity than others.[317]

COMT is a selective enzyme that catalyzes the transfer of methyl groups to the 3-OH position of catecholamines. COMT is a Mg-dependent enzyme, with the metal bound to D141, D169, and N170 residues. This enzyme uses the Mg atom to bind the substrate and make it more easily ionizable.[318] The methyl group is transferred by S-Adenosylmethionine cofactor. The binding substrate site is completed with several hydrophobic residues M40, L198, W143, and the gatekeepers W38 and P174.[318].

FA-118 has a catechol moiety that binds the Mg atom, according to the docking simulations by two metal-donor unions. A hard acid-base interaction (Mg-O) stabilizes the formation of this adduct. In addition, H-bonds between the catechol fragment and the residues K144 and N170 also contribute to the binding energy. Finally, several hydrophobic interactions with key residues of the active site (M40 and P174) complete the stabilization of the FA-118:COMT complex. Such an arrangement explains the good score obtained in the simulations and suggests that FA-118 can be efficient as a COMT inhibitor.

The docking simulations indicate that while all the investigated FA derivatives can act as neuroprotectors of acetylcholine and phenylethylamine (with FA-26 being predicted as the best one for that purpose), only FA-118 would be able to protect dopamine against COMT-induced degradation. Accordingly, FA-118 is proposed as a promising candidate in the context of Alzheimer's and/or anti-anxiety disorders, while FA-26 was identified as the best candidate (among the studied

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molecule) for Parkinson´s. All of them certainly deserve further investigations related to their potential as neuroprotectors.

4. Conclusions

A total of 185 ferulic acid (FA) derivatives were built through a rational *in silico* design, using the CADMA-Chem protocol. The chemical space was sampled using a selection score (S^S) that considers ADME properties, toxicity and synthetic accessibility descriptors. Based on the estimated S^S values, 12 FA derivatives were identified as the candidates with the best drug-like behavior. For this subset, some reactivity indices were computed, as well as their pKa values. According to eH-DAMA results, that takes into account the free radical scavenging behavior through single electron transfer (SET) and formal hydrogen transfer (HAT) mechanisms, FA-138 seems to be the best candidate to scavenge free radicals. However, FA-8, FA-26, FA-118, and FA-175 derivatives are predicted to be better for that purpose than α-tocopherol and the parent molecule.

On the other hand, docking studies suggest that ferulic acid and some of its derivatives can act as inhibitors of AChE and MAO-B enzymes. FA-26 is predicted as the most efficient one for that purpose. This compound is bounded preferably to the entry site of AChE and to the catalytic site of MAO-B, acting as a reversible inhibitor for the latter. On the contrary, FA-118 was the only compound identified as a viable candidate to efficiently inhibit COMT. Accordingly, FA-26 is proposed as the best candidate in the context of Alzheimer's and/or anti-anxiety disorders, and FA-118 for Parkinson's. At least these two compounds certainly deserve further investigation regarding their potential role as neuroprotectors.

Considering the gathered data altogether the FA derivatives proposed to further investigations are FA-26, FA-118, and FA-138.

Supplementary Materials: Table S1: FA derivatives designed in this work. Table S2: Values of the ADME properties, toxicity descriptors, synthetic accessibility, and selection score (S^S) for all designed derivatives. Table S3: Elimination scores for the subset of ferulic acid derivatives chosen as the most promising, according to S^S. Table S4: Reference set of molecules, with some neuroprotective effects. Table S5: Pole strength values for the EPT approximation (P3) used to calculated ionization energies and electron affinities. Table S6: Equations concerning S^S construction. Table S7: Exclusion scores (S^E) equations. Table S8: Complete set of BDEs for ferulic acid and its derivatives. Table S9: Complete set of the binding energies for ferulic acid and its derivatives. Figure S1: Redocking simulation: tolcapone in COMT, Safrinamide in MAO-B, and Donopezil in AChE. Figure S2: Deprotonation routes for the subset of ferulic acid derivatives chosen as the most promising, from their drug-like behavior. Figure S3: Distribution diagram of the acid-base species of ferulic acid derivatives.

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