antioxidants

Article

Quinoline derivatives strategically. Estimation of its antioxidant and neuroprotective activity.

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Abstract: Quinoline has been proposed as a privileged molecular framework in medicinal chemistry. Although by itself it has very few applications, its derivatives have diverse biological activities. In this work, 8536 quinoline derivatives strategically designed using the CADMA-Chem protocol are presented. This large chemical space was sampled, analyzed and reducing using selection and elimination scores that represent their properties of bioavailability, toxicity and manufacturability in a single score. After applying the above filters, 25 derivatives were selected to investigate their acid-base, antioxidant and neuroprotective properties. The antioxidant activity was predicted based on the ionization potential and the bond dissociation energy, parameters directly related to the transfer of hydrogen atoms and of a single electron, respectively. These two mechanisms are typical in the radical scavenging process. The antioxidant efficiency was compared with reference reducers and the compounds were found to be more efficient than Trolox but less efficient than ascorbate. In addition, based on molecular docking simulations, some derivatives are expected to act as inhibitors of catechol-O methyltransferase (COMT), acetylcholinesterase (AChE) and monoamine oxidase type B (MAO-B) enzymes. Some structural insights about the compounds were found to cand enhance or decrease the neuroprotection activity. Given the results, four quinoline derivatives are proposed as candidates to act as multifunctional antioxidants against Alzheimer's (AD) and Parkinson's (PD) diseases.

Keywords: Rational design, quinoline derivatives, antioxidants, neuroprotection, Alzheimer and Parkinson diseases.

1. Introduction

In an oxidative stress (OS) condition, there is an excess of pro-oxidants that cannot be counteracted by the antioxidant systems [1]. Under pathological situation, there is a state of chronic OS where cellular metabolism increases the production of free radicals and reactive oxygen species (ROS) [2-5]. The brain consumes large amounts of oxygen to carry out its physiological functions, and therefore generates a high number of free radicals. Some factors make the brain susceptible to ROS attack, such as the lack of antioxidant mechanisms, its particularly rich fatty acid composition [6], and the low permeability of the blood-brain barrier [7-9], which reduces the passage of many antioxidants such as vitamin E. Due to this, OS has been studied mainly in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), among others [10,11]. OS situations have been observed in these diseases, even in early stages, indicating that ROS and other free radicals could be related to their etiology [12,13].

Several lines of research have implicated the OS and free radical damage in the origin and pathogenesis of AD [12,14-17]. This damage includes energy metabolism and overcompensation of antioxidant enzymes [17]. Despite the extensive literature regarding OS in AD, the sources of increased free radicals responsible for initiating such damage remain unclear. However, some candidates could be activated microglia [18], ß-amyloid protein deposits [19], modified lipoxidation advanced proteins [20] and the increase in the concentration of metals such as iron and copper [21-25]. In the case of PD, evidence suggests

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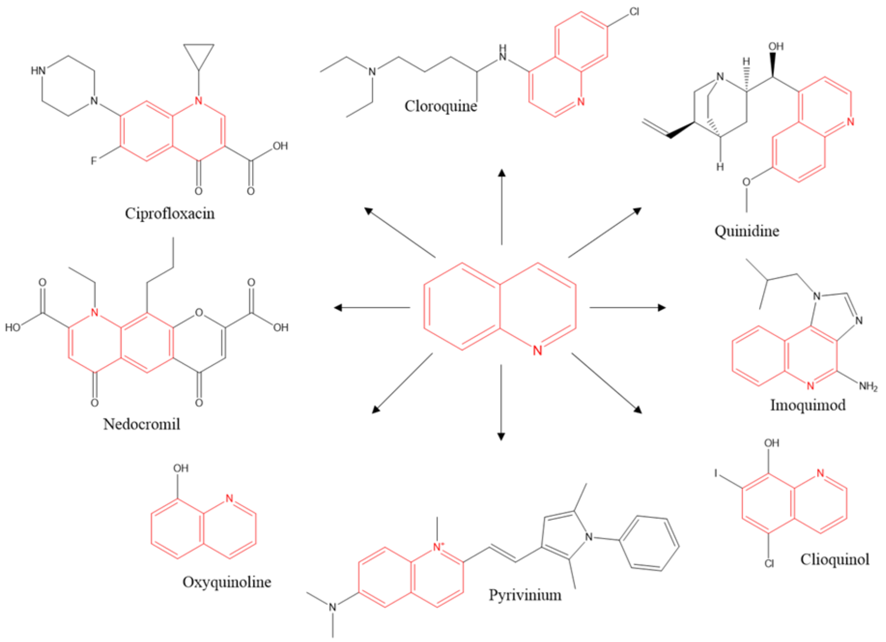
that deficiencies in mitochondrial function, increased oxidative stress, apoptosis and inflammation [26-29] are part of the processes that eventually result in neurodegeneration. Also, the ROS generated by the oxidation of dopamine have been implicated in the destruction of neurons related to age and other neurodegenerative processes such as PD [30-32]. Two enzymes are involved in the dopamine oxidation process, monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT), whose reactions produce considerable quantities of superoxide and hydroxyl radicals, as well as hydrogen peroxide [33-35].

Quinolines are aromatic heterocycles formed by the fusion of a benzene nucleus with a pyridine ring. Quinoline as such has few applications, but it is considered a privileged structure [36-40] from which derivatives are built that are useful in various fields [41-44], mainly medicinal chemistry. A prominent example of these derivatives is quinine, an alkaloid found in plants that has long been the main choice in the treatment of malaria [45]. More than 200 biologically active quinoline alkaloids have been identified [46]. The primary use of this compound is as a precursor to 8-hydroxyquinoline, a versatile chelating agent and pesticide precursor [47]. The interest to study the quinoline derivatives has increased since these are of great importance for the pharmaceutical industry. This interest has driven the development of simple and eco-friendly synthesis methods that represents an advantage over other molecular scaffolds [48-52].

The large literature on the synthesis of quinoline and its derivatives has encouraged researchers to explore this molecular framework for potential drugs. Quinoline is a characteristic structural motif of many drugs used in the clinic for the treatment of various diseases, its main application being antimalarial drugs [18]. Since heterocyclic molecules are used as the set of bases for drug discovery and development, the quinoline ring is a framework with different advantages and representing a wide variety of potential benefits. Its derivatives have been studied as possible antibacterial, antifungal, antimycobacterial, antiviral, antiprotozoal, antimalarial, anticarcinogenic, antioxidant, anticonvulsant, analgesic, anti-inflammatory, anthelmintic agents, as well as beneficial against diseases of the nervous system such as cardiovascular and other biological activities [53-70]. In the Scheme 1 are presented some quinoline contain approved drugs.



Scheme 1. Quinoline approved drugs

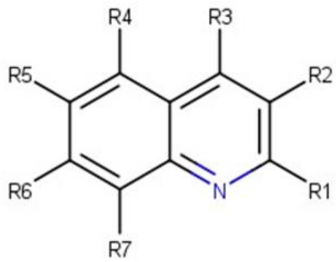
A strategical, systematic, and rational search for quinoline derivatives with antioxidant and neuroprotector activities has been performed using the CADMA-Chem protocol

[71]. Bioavailability, toxicity, synthetic availability, electron, and hydrogen atom donating capabilities, and the potential for inhibiting COMT, AChE, and MAO-B enzymes were explored. According to the obtained results, the promising candidates were identified and proposed for further investigations.

2. Materials and Methods

2.1. Construction of derivatives and estimation of molecular properties.

Quinoline derivatives (Q1, Scheme 2) were systematically designed. For this, Smile-it tool was used, it was developed in the working group of the research team and is available at (https://agalano.com/Smile-It/). The seven possible sites of the scaffold were substituted. The mono, di, and tri-substituted compounds with six functional groups (-OH, -NH_2, -SH, -COH, -$COCH_3$ and -$COOCH_3$) were analyzed. According to this, 8356 dQ derivatives were designed.



Scheme 2. Quinoline (R1-R7=H) and their derivatives (dQ)

For all the derivatives designed, the parameters of absorption, distribution, metabolism and excretion (ADME) were estimated with the open source chemoinformatics tools RDKit [72]. These parameters were used to confirm whether the derivatives satisfy the rules of Lipinski, Ghose, Veber, Egan and Muegge [73-77]. Compounds that violate more than one of these rules have difficulties with bioavailability and could present permeation problems. Its difficulty of synthesis was also evaluated by means of the synthetic accessibility (SA) parameter calculated with the AMBIT-SA software specialized in organic molecules [78]. A value between 0 and 100 is estimated. The higher the value, the easier the compound is to synthesize. The safety of the compounds was estimated by four parameters, using the Toxicity Estimation Computer Tool (T.E.S.T.), version 5.1.2 [79]. Rodent median lethal dose (LD_{50}), Ames mutagenicity (M), developmental toxicity (DT), and bioaccumulation factor (BF) were used to assess the toxicity of quinoline and its derivatives. The significance of each parameter and the criteria used is defined in Table S1.

To select samples from the constructed chemical space, selection and elimination scores were used as expressed in terms of the parameters described above [80,81]. For comparison purposes, a set of reference molecules was used, which have been used as neuroprotectors or are being investigated in advanced clinical phases with this same activity (Table S2).

2.2. DFT calculations.

Electronic structure calculations were performed with density functional theory (DFT) using Gaussian 16 [82] software. Geometric optimizations and frequency calculations were performed using a M05-2X/6-311+G(d,p) protocol, no imaginary frequencies were obtained, ensuring that the structures are minimal on the potential energy surface. Solvation effects were simulated using the universal solvation model (SMD) [83], using water as solvent. M05-2X has popular functionalities for various databases and its performance in various difficult cases is accurate. The tests include barrier heights, conformational energy and the trend in bond dissociation energies [84], it is recommended to model open shell systems [84]. This functional has been successfully used to determine the bond dissociation energies (BDE) and the radical scavenging capacity of several antioxidants [85-89].

Electron propagator theory (EPT)[90] was used to calculate ionization energies (IE). For the estimation of BDE, all the probable sites for the donation of H atoms were considered, that is, the $-CH_3$ in the quinoline ester fraction, and the phenolic OH in the different functionalization sites, from R1 to R7 (Scheme 1).

Deprotonation route was predicted with Marvin suite [91] and the pKa values were refined with DFT fitted parameters procedure [92]. 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. This method of prediction and calculation of pKa values has been tested before, offering results comparable to those reported experimentally [93].

2.3. Protein-ligand docking details.

The structures of enzymes were obtained from protein data bank. The data are summarized in the Table 1.

Table 1. Data of proteins used in the docking simulations.

Enzyme	Co-crystallized inhibitor	Substrate
COMT	Tolcapone [94]	Dopamine
MAOB	Safinamide [95]	Phenylethylamine
AChE	Donopezil [96]	Acetylcholine

AChE misplaced loop regions (256-261 and 493-496 residues) were fixed using Modeller [97]. Water and solvent molecules, chloride ions and non-relevant species were removed with Autodock Tools [98]. Protein ionizable residues were considered at physiological pH, i. e., the protonation state of lateral chains for D, E were considered as deprotonated species and R, K and H as protonated amino acids. For quinolines, natural substrates and inhibitors atomic charges estimated by NBO protocol with DFT (M05-2X/6-311+G(d,p)) methodology. Docking simulations were carried out using AutoDock Vina 1.2.0 software [99]. 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 Å3 for COMT, x: 51.81, y: 156.34, z: 28.15 and grid size of 15 x 15 x 15 Å3 for MAO-B and x: -16.30, y: -43.83, z: 30.17 and grid size of 21 x 21 x 21 Å3 for AChE. Docking scores (ΔGB) were reported for the best docked pose and then this score was weighted according to the fractions of each relevant specie at pH= .4. For the five most stable complexes, the conformation protein-ligand was analyzed and drawn with Discovery Studio software [100]. Redocking simulations were carried out and the RMSD values for inhibitors 1.8, 1.6 and 2.8 Å and the scores 7.6, 10.0 and 12.0 kcal/mol were founded for tolcapone, safinamide and donepezil respectively, agrees with experimental IC_{50}, Ki or ΔG_B findings [95,96,101]. These results confirm the suitability of our docking methodology.

3. Results and discussion

3.1. Screening the chemical space. Selection and elimination scores

Due to the substitution of -OH, -NH2, -SH, -COH, -COCH3 and -COOCH3 groups in the R1 to R7 sites and the study the mono-, di- and tri-substituted compounds 8359 quinoline derivatives were built. Forty-two of them are monosubstituted compound, seven hundred fifty-six are disubstituted and seven thousand five hundred sixty are trisubstituted compounds. Since some toxicity values for 2033 derivatives could not be estimated, they were eliminated in a first screening. All designed compounds investigated were reported in the supporting information file 1 (SIF1.pdf).

The selection score (SS) was the indicator applied to sample the generated chemical space. The values obtained for this selection parameter oscillate between 2.36 and 3.54. The selection score considers the bioavailability of the compounds through the estimation of the ADME properties, it also contemplates the toxicity and the ease with which the compounds should be synthesized. According to the values obtained, the derivatives that beat the performance of the parent molecule (SS=2.83) and the average of the reference set (SS=3.00) are five hundred and thirty compounds.

This scoring system considers the averages of the variables (ADME, toxicity, and synthetic accessibility) and may mask flaws in some property. To overcome this obstacle, an elimination function (SE) was developed that indicates the deviations of the values of each property with respect to the reference set. This function can be analyzed as a whole or by individual property, which is more useful. Furthermore, SE works as an additional filter to choose the most promising derivatives. The elimination function contains all deviations from each property and is a sum of the individual elimination coefficients. The details about the SS and SE calculations can be founded in the supporting information.

Using this exclusion score, further evaluation was achieved. At this point, 25 derivatives were chosen. The structures of the best-scoring derivatives and the molecular framework (dQ1) are presented in Figure 1.

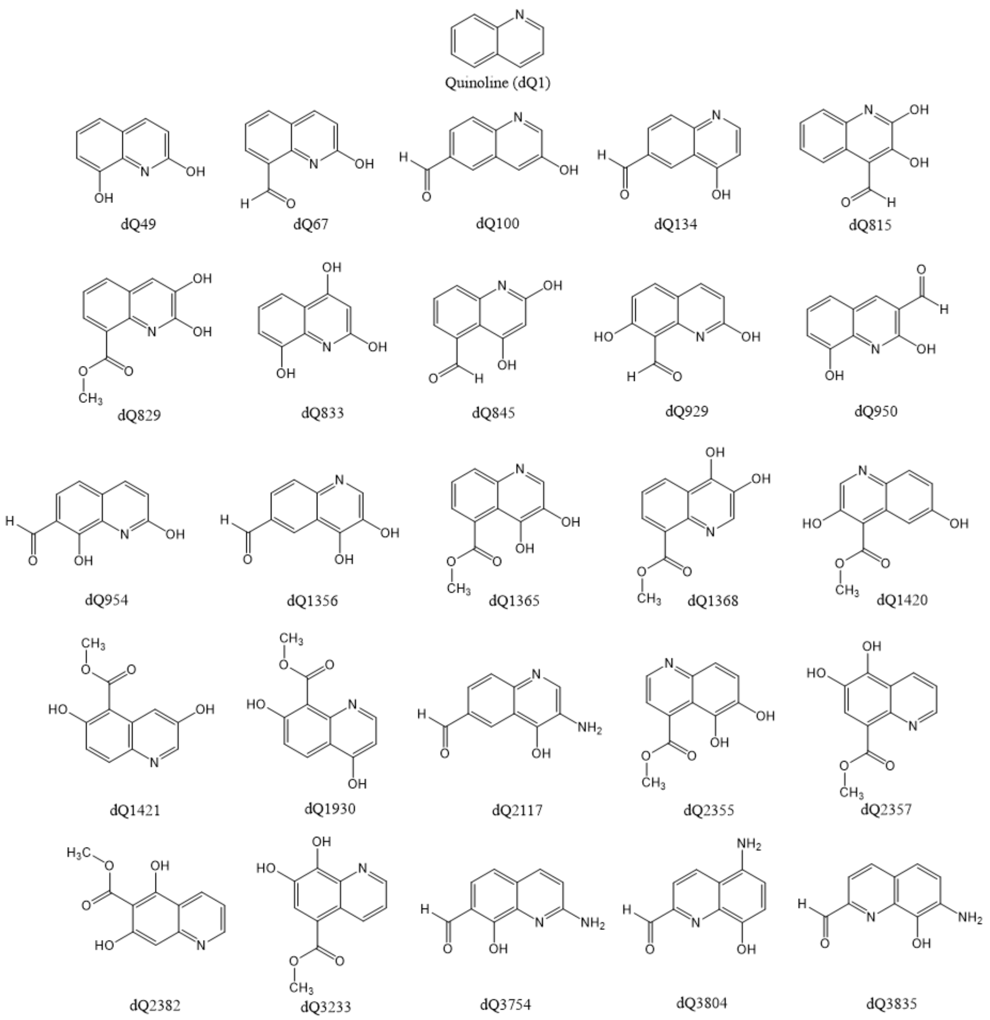


Figure 1. 2D Structures of the best scored (SS y SE) quinoline derivatives.

Due to the large number of studied compounds, only the S^S and S^E plots (in Figures 2 and 3 respectively) are presented for the twenty-five most promising derivatives.

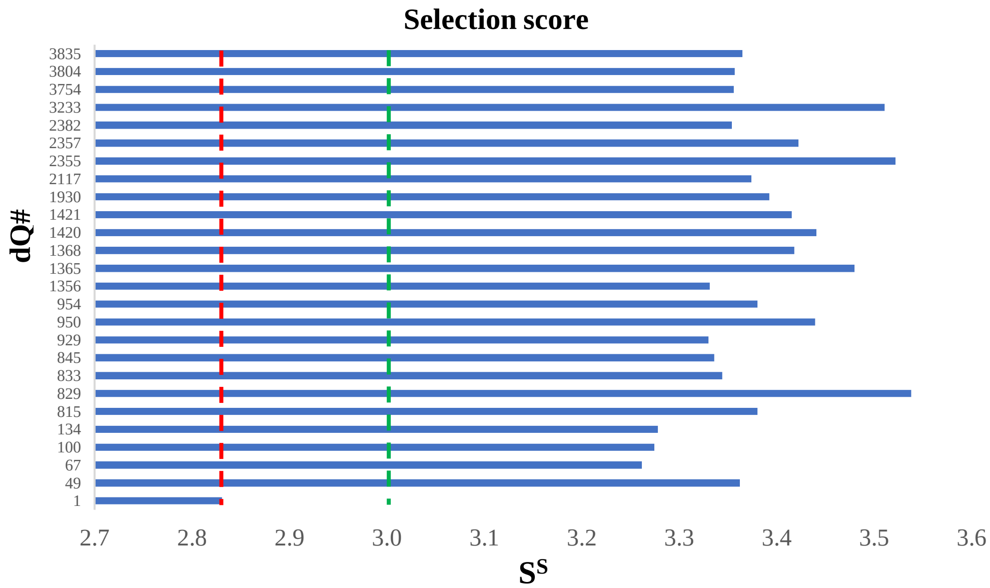


Figure 2. Selection score SS for the best quinoline derivatives. Red line is the estimated value for quinoline scaffold and green line represents the average selection score for reference set.

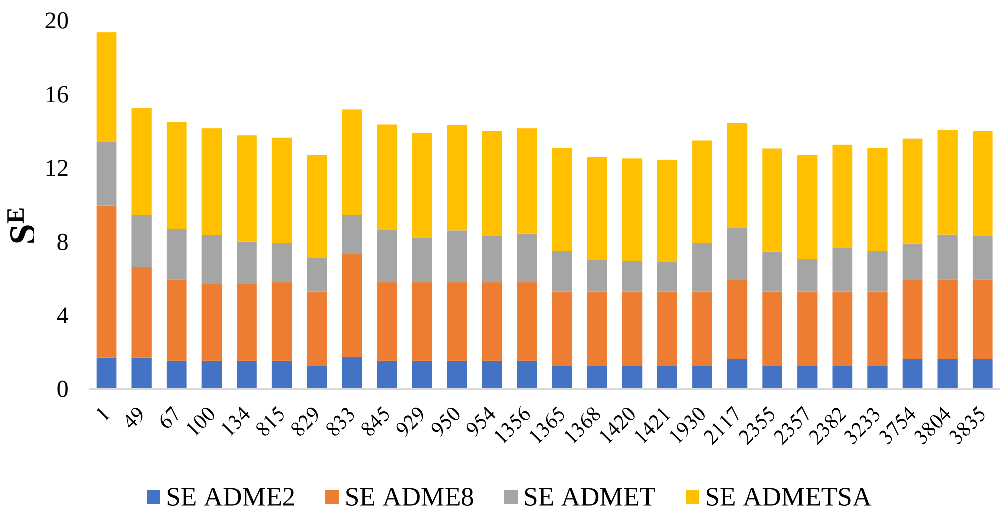


Figure 3. Elimination score (S^E) by set of properties for the most promising quinoline derivatives. The size of the segments represents the deviations from the estimated values for the reference set.

In general, molecules with higher S^S values are expected to have lower toxicity, easier synthesis, and better bioavailability, i.e., they would have all the desirable aspects for a good oral drug. In the case of S^E, the values ranging from 12.5 to 19.4, the highest value being that obtained for the parent molecule. In the Figure 3, are presented the plot of S^E values for a set of properties, SADME2, SADME8, SADMET and SADMETSA. These plot show that the major deviations (with respect to the reference set) are the ADME properties and the synthetic accessibility. In the first case the ADME properties presents a negative variation since the derivatives are significantly smaller that the reference set molecules. On the other hand, the synthetic accessibility of our derivatives represents a serious advantage is an advantage over the recognized neuroprotectors. Finally, this plot is not enough to analyze the deviations of toxicity parameters, to analyze that an individual contribution plot are presents in the Figure 4.

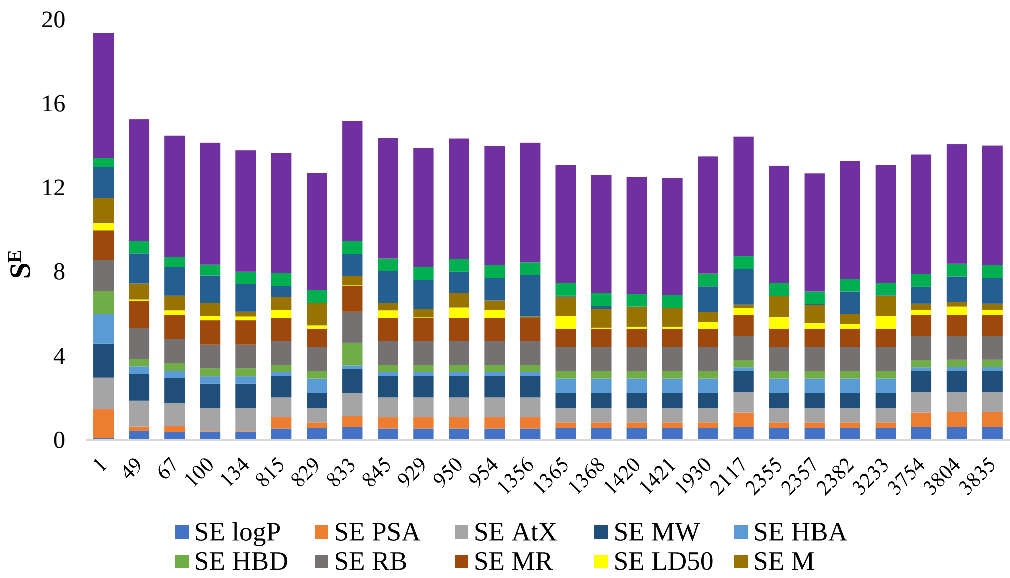


Figure 4. Individual contributions to the elimination score (SE) for the most promising quinoline derivatives.

Except for quinoline, all the derivatives present a slightly higher LD50 (yellow segment), the same case occurs with mutagenicity (gold segment) but the deviation is more pronounced. For all derivatives, the bioaccumulation factor (light green bar) is lower than the average of the reference set, however this parameter shows a very large dispersion in these compounds, which makes this elimination score small. The most significant case is developmental toxicity (aqua bar), quinoline and its derivatives are less toxic than the reference set, in some cases the deviation is remarkable, such as compounds dq845, dQ1356 and dQ2117. Since the twenty-five compounds have acceptable bioavailability (no violations of the Lopinski, Egan, Muegge, Ghose and Veber rules), low toxicity and easier manufacturability (than the reference set), all compounds were kept in the next stage of the investigation to evaluate their potential antioxidant and neuroprotective activity.

3.2. Acid-base equilibria and antioxidant activity.

In potential drugs, the study of the acid-base balance is crucial to find out if the molecules can cross biological barriers by passive diffusion. Deprotonation pathways and estimated pka values are found in Figure S1. Molar fractions (represented as percentage X%) at biological pH are found in Table 2.

In most of the compounds the neutral species (X%dQ) predominates at pH= 7.4, however, there are several derivatives that present an important anionic fraction (X%H-1dQ-), in the case of dQ833 and dQ2382, the cationic species (X%HdQ+) has a significant percentage (>1.0%) and for dQ1421 the dianionic form has a little amount. Among the analyzed derivatives dQ829, dQ833, dQ954, dQ1365, dQ1368, dQ1930, dQ2355, dQ2357 have an important amount of both neutral and anionic species. According to the portion of neutral form, these compounds should not present problems to cross the barriers passively and additionally, and according to the group's experience, the antioxidant activity can be enriched by the presence of a significant amount of the charged species.

Table 2. Estimated percentage fractions of the dQ acid-base species at pH= 7.4

dQ	$X_{\%}H_2dQ^{2+}$	$X_{\%}HdQ^{+}$	$X_{\%}dQ$	$X_{\%}H_{-1}dQ^{-}$	$X_{\%}H_{-2}dQ^{2-}$	$X_{\%}$ $H_{-3}dQ^{3-}$
1	---	0.0	100.0	---	---	---
49	---	0.0	79.6	29.4	0.0	---
67	---	0.0	98.7	1.3	---	---
100	---	0.0	84.9	15.1	---	---
134	---	0.0	100.0	0.0	---	---
815	---	0.0	92.4	7.6	0.0	---
829	---	0.0	30.9	69.1	0.0	---
833	---	1.1	63.3	35.6	0.0	0.0
845	---	0.0	98.7	1.3	0.0	---
929	---	0.0	88.6	11.4	0.0	---
950	---	0.0	98.8	1.2	0.0	---
954	---	0.0	59.7	40.3	0.0	---
1356	---	0.0	97.7	2.3	0.0	---
1365	---	0.0	68.1	31.2	0.0	---
1368	---	0.0	31.4	68.6	0.0	---
1420	---	0.3	28.4	71.3	0.0	---
1421	---	0.1	80.1	18.8	1.0	---
1930	---	0.0	56.8	43.2	0.0	---
2117	---	0.1	99.9	0.0	---	---
2355	---	0.0	56.3	43.7	0.0	---
2357	---	0.0	68.6	31.4	0.0	---
2382	---	4.3	92.8	2.9	---	---
3233	---	0.1	54.0	46.0	---	---
3754	---	0.0	98.0	2.0	---	---
3804	0.0	0.0	98.0	2.0	---	---
3835	0.0	0.0	98.8	1.2	---	---

Ionization potential (IP) and bond dissociation energies (BDE) were calculated for the acid-base species with non-negligible fraction (X%dQ ≥1%), the whole results are presented in the Table S3. The sp3 hydrogens were considered as potential H-donating sites, i.e., phenol, amine and methyl groups, in this order, quinoline was not considered since it does not contain H-atoms like those mentioned above. BDE and IP are related with the capability of the compounds to the donate H-atoms and electron respectively. Then, these parameters were used to evaluate the efficacy of the ascorbate derivatives as free radical scavengers via single electron transfer (SET) and hydrogen atom transfer mechanisms (HAT), respectively, comparing them with some reference antioxidants such as Trolox, α-tocopherol and ascorbate and with the latent oxidant target H_2O_2/$^{\bullet}OOH$. To analyze the scavenging efficiency, the electron and hydrogen atom donation map for antioxidants (eH-DAMA) was constructed with IP and BDE, this map is presented in the Figure 5.

According to the eH-DAMA, anionic species are the most efficient. Almost all compounds will be capable of scavenging hydroxyl radicals, likewise most species are more efficient than a-tocopherol. The most powerful antioxidants are those with a greater antioxidant potential than Trolox, among them are derivatives dQ49, dQ829, dQ950, dQ1356, dQ1368, dQ2355 and dQ2357. dQ49 has better H-atom dative behavior than Trolox and is as strong an electron donor as this antioxidant. The results suggest that the remaining compounds would be better radical scavengers via both SET and HAT mechanisms than Trolox. Finally, five compounds have better radical scavenging performance via the HAT mechanism than ascorbate (vit. C) but are less efficient via the SET mechanism. At this point it is worth noting that vitamin C is one of the antioxidants present in the biological environment [102].

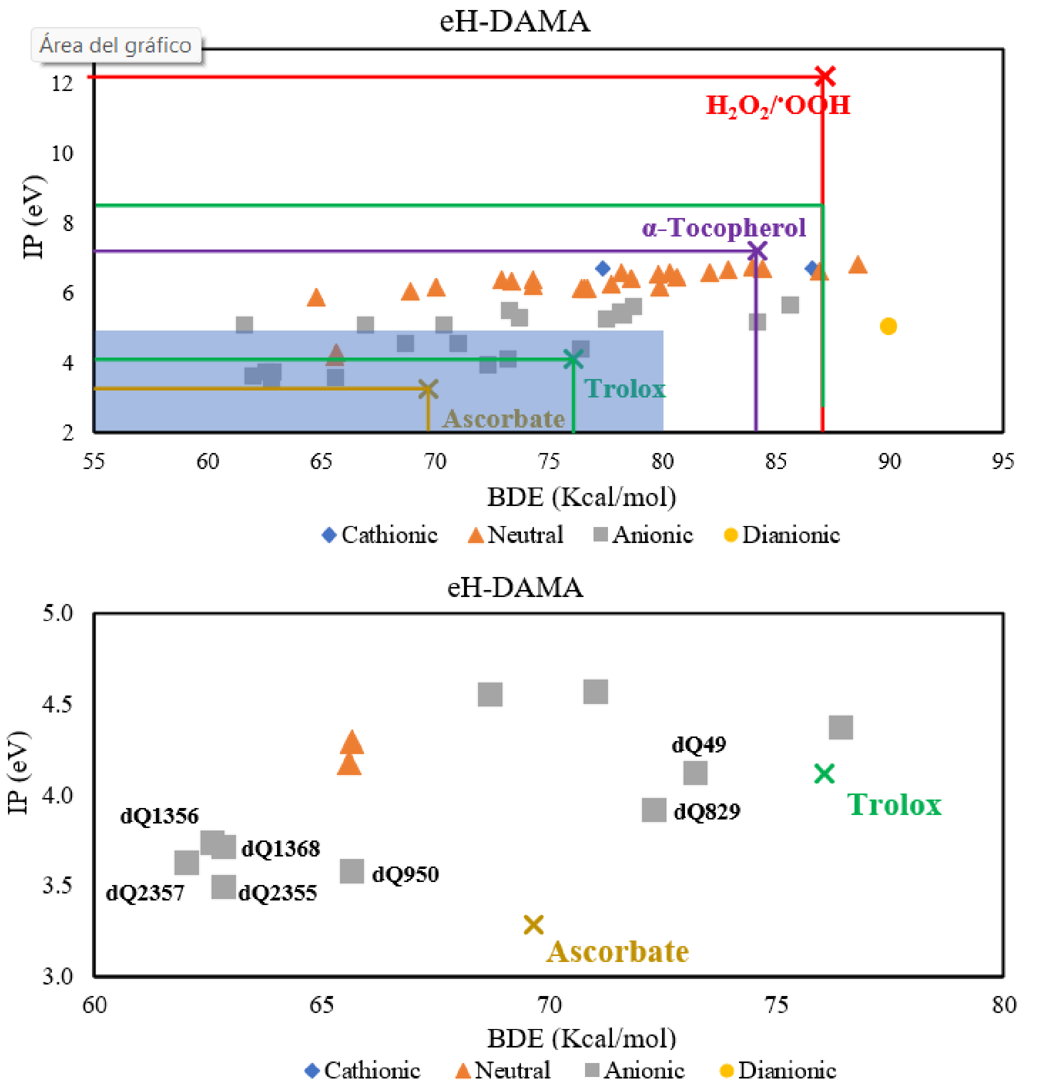


Figure 5. The electron and hydrogen donating ability map for antioxidants (eH-DAMA) for the most promised compounds and their significant species at physiological pH (top). Some typical antioxidants are presented as comparison. Close up to the most promised antioxidants (bottom).

3.3. Neuroprotection assessment.

To assess the neuroprotective activity of quinoline derivatives, the weighted docking scores and polygenic score (SP) of the most promised candidates were reported in the Table 4. The complete set of docking data are in the Table S4. SP is a measure of the affinity of compounds towards enzymes compared to their natural substrates dopamine (COMT), dopamine, phenylethylamine (MAOB) and acetylcholine (AChE) and is defined based on our previous reports [93].

Based on the docking data, quinoline presents less affinity than the natural substrates of COMT and AChE, this is the origin of its lower SP value. As with other properties it seems that the molecular framework by itself lacks chemical or biological interest, they are the functionalized derivatives that present the neuroprotective activity. The SP values suggest that the compounds exhibit neuroprotective activity since the score is magnitude higher than the natural substrates, in a general view, the quinoline derivatives have a good affinity with the enzymes and could inhibit its natural function. Among the compounds studied, it was the analogue dQ929 in which the best neuroprotective efficiency was observed.

Table 4. Scoring values of quinoline derivatives

dQ	ΔG_B^W (kcal/mol)			S^P
	COMT	MAO-B	AChE	
Quinoline	-5.00	-6.90	-3.80	2.85
49	-6.00	-8.34	-8.20	4.18
815	-6.26	-7.91	-9.02	4.11
829	-6.80	-8.41	-8.74	4.44
954	-5.78	-8.16	-8.24	4.11
1368	-5.96	-8.07	-8.24	4.13
2357	-6.29	-8.06	-7.93	4.13

$\Delta G_{B,\ dopamine}$= -5.4 kcal/mol in COMT; $\Delta G_{B,\ phenylethylamine}$= -6.0 kcal/mol in MAO-B; $\Delta G_{B,\ acetylcholine}$= 4.9 kcal/mol in AChE. For natural substrates S^P=3.00

Although most of the compounds presented enhanced S^P values, analysis of individual affinity values can reveal interesting data on the behavior of protein-ligand complexes that can be formed. For this we have designed the polygenic score plot (PSP) found in Figure 6. The colored fragments indicate the affinity for the respective protein and are calculated as the logarithm, the greater the length of the bar, the greater the affinity the compound will present. for the enzyme. On the contrary, if it has a negative magnitude, it means that it does not present neuroprotective activity.

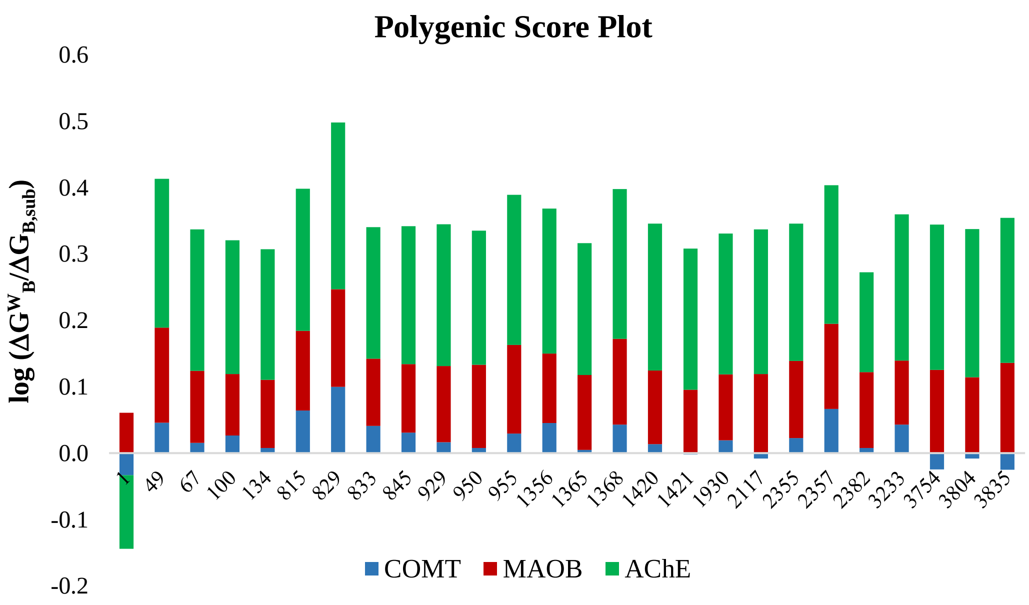


Figure 6. Polygenic score (SP) for the most promised quinoline derivatives. Green bars correspond individual scores.

According to the data in the graph, quinoline derivatives could preferentially inhibit the action of AChE and MAOB enzymes (red and green fragments respectively). In the case of COMT (blue fragments) the behavior of the compounds is heterogeneous, there are compounds that can inhibit the enzyme well (dQ829 and dQ2357), while others have practically the same affinity value as dopamine (dq950 and dQ1421, log=0) and others that have no protective activity (dQ2117, dQ3754, dQ3804, dQ3835). Interestingly, and contrary to what would be expected, it seems that the amino groups do not favor binding to the receptor, since all tested amino compounds presented negative magnitudes. A possible explanation for this observation is that, unlike the substrate, the amino groups of the quinoline derivatives are directly attached to the aromatic rings, whereas in dopamine this group is attached to more accessible and flexible aliphatic chain. On the other hand, the large length of the AChE and MAOB fragments indicate a better activity against the degradation of phenylethylamine and acetylcholine, respectively. Regarding the groups that seem to favor the affinity for the enzyme, there are the aldehyde and ester carbonyl groups, since five of the 6 compounds with the highest affinity present this type of groups. In the case of AChE, the explanation could be the recognition of these groups, since it is in the hydrolysis of esters is the highly specialized function of these enzymes [103]. In the case of MAOB, it would be the great hydrophobic environment of the active site, rich in aromatic amino acids, which would promote the stability of the complex. This would explain the activity of the molecular framework since it was the only enzyme in which it presented considerable neuroprotective activity, presumably because of the hydrophobic interactions it can generate.

In the top of the Figure 7 is presented de 3D diagram of the stabilizing interactions in the complex formed between of the dQ829 with AChE. In the left-bottom of this figure, also can be observed a 2D map that describes in a better way this interaction path. Several H-bonds are originated by the hydroxyl and carboxyl-ester groups and the residues of the pocket of the protein, some of them with key amino acids of ethe active site. The ester moiety was in the anionic site of the enzyme, interacting with Gly121 and Gly122 via two H-bonds at the carbonyl oxygen. This same group seems to mimic the acetylcholine binding, forming an unfavorable bump interaction, blocking catalytic site (Ser203-Glu-Hys447). On the other hand, one of the hydroxyl groups is joined by another H-bond with the residue Tyr124 in the peripheral site. The Trp86 of the acyl site are binding via π-stacking interactions, remaining a recognized reversible AChE inhibitor tacrine [104], which, by the way, has a similar structure to quinoline. Due to this form of interaction, the compound appears to be a pseudo-reversible inhibitor of the AChE enzyme.

The 2D interaction diagram between MAO-B and dQ829 are in the bottom-middle of the Figure 7. The stabilizing interactions of the adduct formed are of a diverse nature. This is reasonable considering the versatility of functional groups that this quinoline derivative contains. Among the most important interactions are those formed between the derivative with the tyrosine fragments, most of them of hydrophobic nature. These residues have a critical role in the maintenance of stable and active conformation of the protein [105]. Likewise, the union of dQ829 with the FAD fragment, via π-forces, would effectively inhibit the action of MAOB, since this is responsible for the oxidation of amines [106].

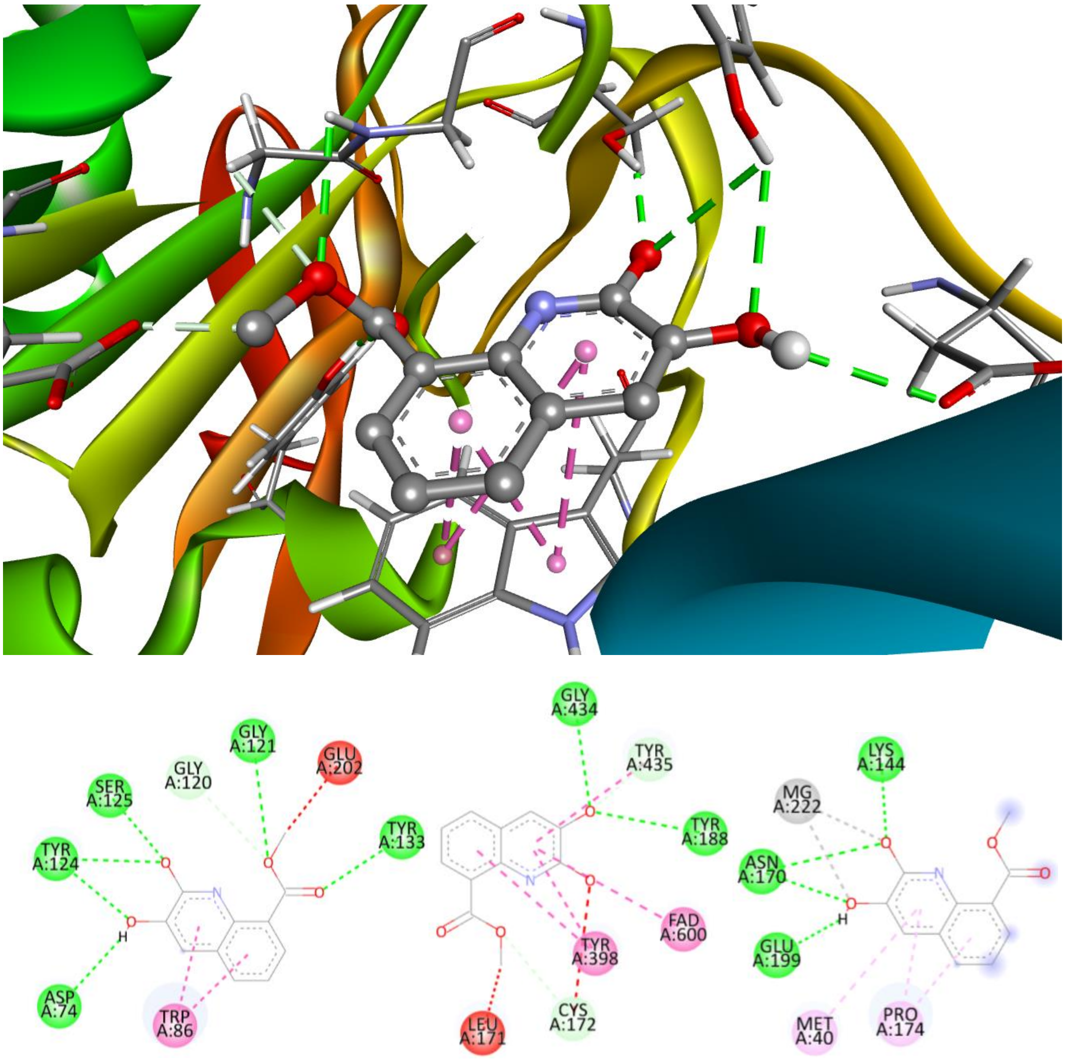


Figure 7. 3D representation of the interactions between dQ829 and the AChE (Top). Bottom: 2D interaction map for the complexes of the quinoline analog with AChE (left), MAOB (middle) and COMT (right). H-bonds are represented in green color, non-conventional C-H bonds are in green light, metal-donor are in gray, π-interactions are in pink and purple, and steric effects are in red.

Finally, the interaction between the active site of COMT and dQ829 is presented in the bottom-right corner of the Figure 8. In this case, the catechol group are the responsible for the stabilization of the adduct. There are several examples in the literature that indicate the inhibition the dopamine degradation by catechol-type compounds [107], in fact Tolcapone is nitro-catechol compound used as therapeutic drug against Parkinson disease. Interestingly the interaction form between the quinoline analog and the Tolcapone with COMT is very similar in several ways. Both compounds present two metal-donor interactions between the Mg^{II} ion and the catechol moiety. These same oxygen atoms forms H-bonds with Lys144, Asn170 and Glu199. The difference arises from the number of H-bonds that each residue can forms whereas tolcapone forms two of these interactions with Glu199 (deprotonated residue), whereas dQ829 makes them the same with Asn170 (neutral residue). Other marked difference is the stabilization provided by the nitro group in Tolcapone that lacks in the quinoline derivative. These last unions seem to make a difference in terms of the stability of the complexes formed, with tolcapone having a higher affinity for COMT than the dQ829 compound. Nevertheless, we must not lose sight that, according to the results of the simulations, this functionalized quinoline has significant neuroprotective activity. Although various catechol compounds were tested, none performed as well as dQ829, the origin of that remains unclear.

Docking simulations indicate that some compounds present high performance in the inhibition of MAO-B and AChE proteins as Tacrine does. In this context, six quinoline derivatives are presented as promising candidates to act against AD and anxiety disorders. According with the results in COMT enzyme, dQ829 is a hopeful molecule to be investigated against PD.

In further studies, it is expected to evaluate the neuroprotective and antioxidant capacity of this quinoline derivatives with more accurately simulations and in a middle-time try to synthesize the most promising compounds in biological tests.

4. Conclusions

Quinoline derivatives represent a privileged molecular scaffold to build derivatives with interesting biological activities. In this sense, the response to two of the most severe problems faced by adults and national health systems, AD and PD, may come from one of these derivatives.

In this work we have created and analyzed a chemical space containing 8356 derivatives adding -OH, -SH, $-NH_2$, -COH, $-COCH_3$ and $-COOCH_3$ to quinoline framework. The compounds were sampling and analyzed using the CADMA-Chem protocol based on the chemical properties of the compounds to find the most promising candidates as antioxidant and at the same time, neuroprotective agents.

Through the selection (S^S) and elimination scores (S^E), the group was reduced to 25 compounds, which according to the results obtained, would present less toxicity, improved bioavailability, and easy manufacturability, all these properties represent advantages for the oral drugs production.

According to eH-DAMA outcomes, dQ49, dQ829, dQ950, dQ1356, dQ1368, dQ2355 and dQ2357 derivatives have the most promising scavenging capability. The enhanced radical scavenging efficiency compared with the reference antioxidants Trolox and α-tocopherol, would come from simple electron transfer (SET) and hydrogen atom transfer (HAT) mechanisms. However, these compounds present a less scavenging activity than ascorbate ion in SET mechanisms but a better antioxidant behavior via HAT process.

On the other hand, the coupling simulations indicate that quinoline only presents neuroprotective activity on the MAOB enzyme. Some of its derivatives can act as inhibitors of this enzyme and the AChE protein. The most efficient compounds for this purpose are dQ49, dQ815, dQ829, dQ954, dQ1368 and dQ2357. Additionally, the derivative dQ829 might have activity by inhibiting the COMT protein by binding in a very similar way like Tolcapone, a drug used to treat PD, does. Evidence of some structural details that favor neuroprotective activity was found. Compounds with amino groups do not favor the neuroprotective activity of dopamine, while, to some extent, catechol groups can enhance it, also, aldehyde and ester groups improve the affinity of the compounds for the AChE enzyme. These insights could be used in future design protocols.

Considering the data obtained as a whole, it is the derivatives dQ49, dQ829, dQ8368 and dQ2357 that represent the best candidates for future research. At least the dQ829 compound certainly they deserve further analysis on their role as neuroprotectors.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1. Properties determined to the Quinoline derivatives, Table S2. ADME, toxicity and synthetic accessibility of the reference set Figure S1. Deprotonation paths and pKa values for the 25 most promising dQ. Table S3. Ionization energy and bond dissociation energy of quinoline derivatives and Table S4. Complete set of docking values.

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