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Synthesis, antioxidant and anticholinesterase activities of novel quinoline-aminophosphonate derivatives

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Abstract

A series of 20 novel α-aminophosphonate derivatives bearing quinoline or quinolone moiety was designed and synthesized *via* Kabachnik-Fields reaction in the presence of triethylammonium acetate as a solvent and catalyst under ultrasound irradiation. This procedure affords products in high yields and short reaction times. Molecular structures of the synthesized compounds **4a-g** and **5a-m** were confirmed using various spectroscopic methods. The antioxidant activity of these compounds was evaluated by eight complementary *in vitro* tests. The anticholinesterase activity (AChE, BChE) of these compounds were also evaluated. In addition, theoretical calculations of all compounds were investigated as corrosion inhibitors using density functional theory (DFT). The results revealed that 16 of these compounds exhibited high levels of antioxidant activities depending on the assay and that most compounds showed more potent inhibitory activities against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE).

1 | INTRODUCTION

Currently, chemical researchers are striving for new safely agents to prevent major health problems related to oxidative stress. These problems including Alzheimer's diseases affecting a large portion of the world population. From this point, the development of new treatment strategies for these diseases is one of the most remarkable topics in the scientific area.[1,2] An antioxidant agent is defined as a molecule that protects a biological target against oxidative damage which causes many diseases. As a result, many diseases have been treated with antioxidants to prevent oxidative damage[3]; also, these antioxidant agents have a great effect to minimize the progress of Alzheimer's disease[4,5] by reacting with reactive oxygen species (ROS).[6–9] In addition to their potential beneficial effects, there has been an increasing research in pharmaceutical, cosmetic and food industries for the discovery of antioxidants to compare the bioactivities above mentioned with those of commercial antioxidants, such as BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), TBHQ (tertbutyl hydroquinone), PG (gallate), galantamine and kojik acid which are commonly used in the food and pharmaceutical industries.

α-aminophosphonate constitutes a class of important motifs among the organophosphorus compounds with variety of interesting and useful properties in medicinal chemistry. compounds bearing this moiety have seen huge development due to their expansive range of biological and pharmaceutical properties,[10] such as catalyst inhibitors,[11] antitumor, antimicrobial,[12] anti-inflammatory, anticancer,[13] antimalarial,[14] peptidomimetics,[15] antioxidant,[16] and inhibitors of protein tyrosine.[17]

On the other hand, quinoline and its analogs represent privileged moieties with numerous derivatives widely distributed in nature.[18] Quinoline plays an important role in the field of synthetic and medicinal chemistry, illustrated by their extensive application as biologically and pharmacologically active compounds,[19,20] such as antitumor,[21] anti-parasitic, antimalarial,[22] anti-hepatitis, antifungals, antimicrobial,[23] anti-arrythmic,[24] antioxidant,[25] anti-inflammatory[26] and anticancer properties.[27]

In order to increase the activity of these moieties, we attempt to introduce the quinoline scaffold onto α-aminophosphonate, using 2-chloro-3-formylquinoline derivatives as starting material via simple and effective procedure under ultrasound irradiation. In particular, the objectives of this study were the investigation of the ability of compounds 4a-g and 5a-m to inhibit AChE and BChE enzymes and the determination of the antioxidant properties by using eight complementary *in vitro* tests, such as β-carotene-linoleic acid, DPPH scavenging, ABTS scavenging, reducing power, cupric-reducing antioxidant capacity (CUPRAC), hydroxyl radical-scavenging, phenanthroline and galvinoxyl scavenging assays, followed by the assessment of theoretical antiradical activity using DFT calculations. The theoretical part of this study relates to the calculation of some thermodynamic molecular descriptors of tested molecules, with the density functional theory (DFT).

It appears that the presence of 2-oxo-quinoline in the scaffold lead to potent antioxidant activities according literature works[28]. It is thus to expect that the combination of 2-oxo-quinoline derivatives and α-aminophosphonate groups may lead to good antioxidant agents.

2 | RESULTS AND DISCUSSION

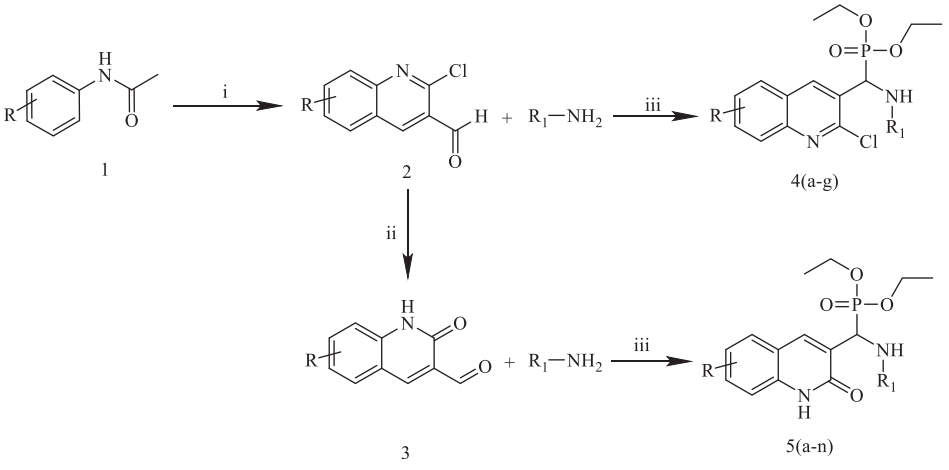
2.1 | Synthesis and identification

Series of 20 novel α-aminophosphonates **4a-g** and **5a-m** containing quinoline or quinolone moiety was designed and synthesized under ultrasound irradiation. A simple, rapid, facile and highly efficient method has been employed for the synthesis of α-aminophosphonate derivatives *via* Kabachnik-Fields reaction starting from quinoline or quinolone carbaldehyde and functionalized amine using ionic liquid [TEAA] as a solvent and catalysts.

Firstly, 2-chloro-quinoline-3-carbaldehyde derivatives (2) were obtained *via* Meth-Cohn[29] reaction, which included the condensation of acetanilide derivatives (1) with Vilsmeir-Haack reagent. 2-Oxoquinoline 3-carbaldehyde derivatives (3) were then obtained in good yields by the hydrolytic reaction of (2) in the presence of 70% acetic acid.[30] The target compounds **4a-g** and **5a-m** were synthesized *via* Kabachnik-Fields reaction, under ultrasound irradiation in the presence of ionic liquid [TEAA], using aminophenol or aminopyridine as starting materials (Scheme 1). This method offers several advantages including the easy, work-up reaction and giving pure product without chromatography purification and high yield in short reaction time. The structures of target compounds **4a-g** and **5a-m** were confirmed using various spectroscopic methods, including ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, HSQC, HMBC, COSY, ESI-MS and elemental analysis.

(a): DMF, $POCl_3$ (3/7), 70°C, (b): CH_3COOH (70%), reflux, (c): $PO(OEt)_3$, *IL*[TEAA], ultrasound irradiation.

It was found that ionic liquid [TEAA] has a large effect on the rate of the reaction and yields of products; the rates of the reaction were remarkable slowed without



SCHEME 1 One-pot synthesis of novel *α*-aminophosphonate derivatives under ultrasound irradiations

ionic liquid, and the yields were very low (about 30%). The results were listed in Table 1. The great improvement of the yield was achieved to afford α-aminophosphonates containing quinolone moiety in the yield of 81-93% in short reaction time; the obtained results were summarized in Table 2.

2.2 | Biological evaluation

Antioxidant capacity of all synthesized compounds was evaluated by using eight complementary tests. These tests were based on different mechanisms of action. It is important to use many assays to prove the effectiveness of each product and their mechanisms like the reductive capacity and radical scavenging, prevention of chain initiation, decomposition of peroxides, prevention of continued hydrogen abstraction.[31] Moreover, inhibition potential against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) key enzymes involved in common human pathologies neurodegenerative disorders[32] was also evaluated.

TABLE 1 Effect of *IL* (TEAA) on the yield of **4a**, **4b**, **4c**

Compound	Yield without *IL*	Yield With *IL*[a]
4a	30	76
4b	25	85
4c	28	82

[a]1 mL *IL* (triethylammonium acetate): 1 mmol substrate.

2.2.1 | Determination of the antioxidant activity

In this study, the antioxidant activity of 20 novel synthesized compounds was tested using eight complementary *in vitro* tests; namely, β-carotene-linoleic acid assay according to the method of Marco[33] with slight modifications. Free radical-scavenging activity by DPPH scavenging assay according to the method described by Blois 1958[34]. ABTS scavenging assay according to the method of Re et al.[35] with slight modifications. Cupric-reducing antioxidant capacity (CUPRAC) was determined according to the method of Apak et al.[36]. The reducing power assay was carried out as described by Oyaizu[37] with slight modifications. Measurement of the hydroxyl radical-scavenging activity of the compounds was based on the method described by Smirnoff and Cumbes[38].

TABLE 2 Synthesis of novel α-aminophosphonate under ultrasound irradiation

Entry	R	Amine	Time (min)	Yield%	mp°C
4a	H	2-aminophenol	12	76	177-178
4b	6-Me	2-aminophenol	16	85	190-191
4c	6-OMe	2-aminophenol	14	82	166-167
4d	7-Me	2-aminophenol	15	74	184-185
4e	8-Me	2-aminophenol	16	77	198-199
4f	6-OMe	4-aminophenol	17	86	203-204
4g	6-OMe	3-aminopyridine	19	79	179-179.8
5a	H	2-aminophenol	10	92	133-134
5b	6Me	2-aminophenol	11	87	170-170.7
5c	6OMe	2-aminophenol	9	84	163-164.2
5d	7Me	2-aminophenol	11	88	116-117
5e	8Me	2-aminophenol	10	92	221-222
5f	H	4-aminophenol	13	75	222-223
5g	6Me	4-aminophenol	12	81	216-217
5h	6OMe	4-aminophenol	11	89	124-125
5i	7Me	4-aminophenol	10	78	200-201
5j	8Me	4-aminophenol	12	71	229-230
5k	6Me	3-aminopyridine	14	83	198-199
5l	7Me	3-aminopyridine	13	93	127-128
5m	8Me	3-aminopyridine	11	79	311-313

Note: Conditions: aldehyde (1 mmol), amine (1 mmol), triethylphosphite (1 mmol), *LI*, 40 kHz.

TABLE 3 IC_{50} and $A_{0.50}$ values of antioxidant activity of compounds 4a-g and 5a-m by eight complementary tests

Compound	Antioxidant activity[a]							
	DPPH˙ assay	ABTS˙+ assay	Galvinoxyl assay	OH˙ assay	β-carotene assay	Reducing power assay	CUPRAC assay	Phenantroline assay
	IC_{50} (μM)					$A_{0.50}$ (μM)		
4a	22.19 ± 0.07	6.55 ± 0.06	14.66 ± 0.35	355.70 ± 1.15	4.77 ± 0.21	119.05 ± 1.60	19.01 ± 0.09	1.99 ± 0.20
4b	13.82 ± 0.10	6.30 ± 0.08	9.34 ± 0.05	222.43 ± 2.18	2.37 ± 0.02	14.32 ± 0.06	13.36 ± 0.02	3.61 ± 0.05
4c	15.52 ± 0.05	7.43 ± 0.14	10.11 ± 0.04	248.01 ± 1.53	3.01 ± 0.08	13.30 ± 0.18	14.21 ± 0.12	1.84 ± 0.81
4d	18.02 ± 074.	6.64 ± 0.35	7.79 ± 0.19	169.66 ± 0.53	12.53 ± 0.34	13.06 ± 0.04	13.77 ± 0.33	4.36 ± 0.75
4e	10.07 ± 0.18	6.32 ± 0.06	10.71 ± 0,13	957.08 ± 0.89	5.08 ± 0.46	333.44 ± 0.03	12.73 ± 0.03	8.96 ± 0.19
4f	2.01 ± 0.02	2.61 ± 0.56	3.74 ± 0.03	N.T	1.88 ± 0.11	26.63 ± 0.79	1.86 ± 0.01	2.87 ± 0,16
4g	>100	>50	>50	N.A	>100	>200	>100	>100
5a	18.66 ± 0.13	7.70 ± 0.01	13.07 ± 0.11	363.92 ± 1.56	6.03 ± 0.03	26.78 ± 1.07	22.41 ± 0.63	6.90 ± 0.09
5b	20.94 ± 0.16	6.48 ± 0.04	10.83 ± 0.52	1322.39 ± 0.45	5.71 ± 0.08	24.44 ± 2.23	28.19 ± 1.24	9.77 ± 0.71
5c	20.58 ± 0.05	6.66 ± 0.05	19.65 ± 019.	644.61 ± 1.51	6.17 ± 0.15	34.98 ± 1.61	23.14 ± 0.28	6.66 ± 0.45
5d	50.74 ± 0.95	10.90 ± 0.11	23.53 ± 0.08	1818.49 ± 1.44	7.27 ± 0.08	16.18 ± 0.64	39.93 ± 0.29	20.96 ± 0.03
5e	13.40 ± 003.	18.49 ± 0.09	12.91 ± 0.46	428.49 ± 2.41	3.79 ± 0.09	69.37 ± 0.39	24.63 ± 0.31	22.88 ± 0.94
5f	8.15 ± 0.18	7.67 ± 0.19	9.69 ± 0.27	496.40 ± 1.51	5.61 ± 0.08	20.30 ± 0.14	21.42 ± 0.08	86.16 ± 0.89
5g	34.14 ± 0.14	12.55 ± 0.05	14.50 ± 0,17	426.02 ± 1.85	7.18 ± 0.06	18.85 ± 0.30	31.57 ± 1.18	42.24 ± 0.92
5h	24.99 ± 015.	9.11 ± 0.02	7.70 ± 0.22	N.A	6.10 ± 0.04	16.95 ± 0.36	28.29 ± 0.33	50.52 ± 0.1
5i	18.94 ± 0,17	7.85 ± 0.15	4.73 ± 0,08	449.82 ± 2.89	3.26 ± 0.07	47.45 ± 0.25	19.11 ± 0.08	37.36 ± 1.27
5j	5.64 ± 0.01	3.29 ± 0.03	7.39 ± 0.51	N.A	3.29 ± 0.53	32.05 ± 0.48	2.37 ± 0.03	21.94 ± 0.75
5k	>100	>50	>50	N.A	>100	>200	>100	>100
5l	>100	>50	>50	N.A	>100	>200	>100	>100
5m	>100	>50	>50	N.A	91.55 ± 0.72	>200	>100	>100
BHT[b]	29.72 ± 0.59	5.35 ± 0.01	15.06 ± 0.18	N.T	5.62 ± 0.00	40.70 ± 3.94	43.65 ± 0.87	10.16 ± 0.17
BHA[b]	87.32 ± 0.47	13.31 ± 0.03	29.84 ± 0.06	N.T	6.99 ± 0.00	29.68 ± 0.71	20.19 ± 0.19	5.15 ± 0.07
Ascorbic acid[b]	N.T	N.T	N.T	32.33 ± 1.17	N.T	N.T	N.T	N.T

[a] IC_{50} and $A_{0.50}$ values are expressed as means ± SD of three parallel measurements ($P < 0.05$).

[b] Reference compounds: BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; N.T: not tested; N.A: not active.

Phenanthroline activity was evaluated by the method of Szydlowska-Czerniaka[39] and galvinoxyl scavenging (GOR) assay was determined as previously method described by Shi et al.[40]. BHA and BHT were used as positive standards for comparison of the activity. The tests were performed at different concentrations to calculate the IC_{50} and $A_{0.50}$ values. Results were statistically significant ($P < 0.05$) when compared with those of controls in each test.

The results of all the tests expressed in term of IC_{50} or $A_{0.50}$ presented in Table 3. The effectiveness of antioxidant properties is inversely correlated with their IC_{50} values. The product concentration providing 50% antioxidant activity (IC_{50}) was calculated from the graph of antioxidant activity percentage against product concentration. The sample concentration producing 0.50 absorbance ($A_{0.50}$) was calculated from the graph of the absorbance against the sample concentration.

In general, the all tested compounds exhibited potent antioxidant activity, except compounds **4g**, **5k**, **5l**, **5m** which showed weak antioxidant activity with all tests. In the DPPH and ABTS assays, all compounds except **5g** and **5d** showed stronger antioxidant activities than BHT. The highest DPPH activity was observed in the compound **4f** ($IC_{50} = 2.01 \pm 0.02$ μM) followed by **5j** ($IC_{50} = 5.64 \pm 0.01$ μM) and **5f** ($IC_{50} = 8.15 \pm 0.18$ μM), evidently, the same derivatives **4f** ($IC_{50} = 2.61 \pm 0.56$ μM) and **5j** ($IC_{50} = 3.29 \pm 0.03$ μM), exhibited the best ABTS radical scavenging activity. For Galvinoxyl assay, all selected compounds showed a very high antioxidant activity with IC_{50} values lower than 23.53 ± 0.08 μM. All these compounds except **5c**, **5d** have a higher antioxidant capacity than that of BHT ($IC_{50} = 15.06 \pm 0.18$ μM). The highest inhibitory effect was respectively exhibited by the derivatives **4f, 5i, 5j, 5h** and **4d** ($IC_{50} = 3.74 \pm 0.03$, 4.73 ± 0.08; 7.39 ± 0.51; 7.70 ± 0.22; 7.79 ± 0.19 μM), their IC_{50} values about three times lower than that of BHA ($IC_{50} = 29.84 \pm 0.06$ μM). In the hydroxyl radical scavenging assay, the obtained results demonstrate that all compounds except **4g**, **5h**, **5j**, **5k**, **5l**, **5m** had a moderate activity translated by a high values of IC_{50} (169.66 ± 0.53-1818.49 ± 1.44 μM) which was still much more than that of ascorbic acid ($IC_{50} = 32.33 \pm 1.17$ μM).

Cupric reducing antioxidant capacity (CUPRAC) of all compounds was also assayed. The results were given as absorbance. In this method, copper (I) and neocupronine give a stable complex, the formation of this complex is carried out by reduction of copper (II) in the presence of neocupronine. The results demonstrated that all compounds exhibited higher antioxidant activity than BHT ($A_{0.50} = 43.65 \pm 0.87$ μM) with $A_{0.50}$ lower than 31.57 ± 1.18 μM. Unfortunately, since these compounds, cupric reducing antioxidant capacity of **4f** ($A_{0.50} = 1.86 \pm 0.01$ μM), **5j** ($A_{0.50} = 2.37 \pm 0.03$ μM), **4e** ($A_{0.50} = 12.73 \pm 0.03$ μM) and **4b** ≈ **4d** ($A_{0.50} = 13.36 \pm 0.02$, 13.77 ± 0.33 μM), respectively, were very higher than that of both BHT ($A_{0.50} = 43.65 \pm 0.87$ μM) and BHA ($A_{0.50} = 20.19 \pm 0.19$ μM). In the β-carotene-linoleic acid assay, the antioxidants scavenge singlet oxygen causing radicals in lipids. The results suggested that all the selected compounds showed remarkable lipid peroxidation inhibition with IC_{50} values less than 12.6 μM. All these compounds except **5g**, **5d**, **4d**, **5m** have a higher antioxidant capacity than BHA ($IC_{50} = 6.99 \pm 0.00$ μM). In this method, oxidation of linoleic acid was effectively inhibited by **4f**, **5b**, **4c** ≈ **5i** ≈ **5j** ≈ **5e** (5.61 ± 0.08; 5.71 ± 0.08; 3.01 ± 0.08; 3.26 ± 0.07; 3.29 ± 0.53; 3.79 ± 0.09), respectively. On the other hand, the best results were obtained for compounds **4d** ($A_{0.50} = 13.06 \pm 0.04$ μM), **4c** ($A_{0.50} = 13.30 \pm 0.18$ μM), **4b** ($A_{0.50} = 14.32 \pm 0.06$ μM) and **5d** ($A_{0.50} = 16.18 \pm 0.64$ μM), respectively, with reducing power assay. These derivatives have a higher antioxidant capacity than the standard BHA ($A_{0.50} = 20.19 \pm 0.19$ μM) and about three times higher than BHT ($A_{0.50} = 40.70 \pm 3.94$ μM). In phenantroline assay, the derivatives bearing a quinoline moiety exhibited a very high antioxidant capacity translated by their low values of $A_{0.50}$. The derivatives **4c** ($A_{0.50} = 1.84 \pm 0.81$ μM), **4a** ($A_{0.50} = 1.99 \pm 0.20$ μM), **4f** ($A_{0.50} = 2.87 \pm 0.16$ μM), **4b** ($A_{0.50} = 3.61 \pm 0.05$ μM), **4d** ($A_{0.50} = 4.36 \pm 0.75$ μM), respectively, have a higher antioxidant capacity than the standard BHA ($A_{0.50} = 5.15 \pm 0.07$ μM) and BHT ($A_{0.50} = 10.16 \pm 0.17$ μM).

Generally, it should be mentioned that α-aminophosphonate derivatives exhibited good antioxidant activity, and it is worth noting that the presence of quinoline and quinolone moiety significantly increases their antioxidant activity[41]. In all studied methods, all novel compounds showed excellent antioxidant activity except **4g**, **5k**, **5l** and **5m**. It was observed that the most effective compounds are those containing phenol due to their power to give more atoms to stabilize free radicals[42,43]. This explains the low antioxidant activity of **4g**, **5k**, **5l** and **5m**, which have a pyridine moiety replacing a phenol groups in its structure.

2.2.2 | DFT calculations

A molecular descriptors calculation was carried out on all of our synthesized compounds, using the density functional theory (DFT). Their structures geometries were optimized at the B3LYP/6-311G++(d,p) level of the DFT

theory. Solvation effects were considered using the IEFPCM model[44]. Vibrational frequencies' calculations were performed to check if the optimized geometries are located at the minimum point of the corresponding potential surface. All calculations were made with GAUSSIAN 09 software[45], whereas GaussView 5.0.9[46] was used for results visualization and analysis. Chem3D Ultra software (version 8.0) was used to conduct a preliminary molecular dynamics calculation with the molecular mechanics force field MM2 (ChemOffice 2003, Cambridge Soft Corporation). The calculated molecular descriptors are: the bond dissociation enthalpy (BDE), the ionisation potential (IP), the proton dissociation enthalpy (PDE), the proton affinity (PA) of the anion and the electron transfer enthalpy (ETE). The three possible radical scavenging mechanisms, that may coexist are: hydrogen atom transfer (HAT), single electron transfer-proton transfer (SET-PT) and sequential proton loss electron transfer (SPLET)[47,48]. Each of these mechanisms is distinguished by one or more molecular descriptors, as illustrated in Equations (1) to (3). Therefore, BDE, IP and PA are the three determinant molecular descriptors of the thermodynamically preferred antiradical mechanism. The higher is the scavenging activity, the lower are their values[49] and the smallest descriptor corresponds to the favored mechanism.

$$\mathbf{HAT}: \mathrm{RX-H} \rightarrow \mathrm{H^{\cdot}} + \mathrm{RX^{\cdot}}\ [\mathbf{BDE} = \mathrm{H(RX^{\cdot})} + \mathrm{H(H^{\cdot})} - \mathrm{H(RX-H)}], \quad (1)$$

$$\mathbf{SET-PT}: \begin{cases} \mathrm{RX-H} \rightarrow (\mathrm{RX-H})^{+\cdot} + \mathrm{e^-}\ \left[\mathbf{IP} = \mathrm{H}\left((\mathrm{RX-H})^{+\cdot}\right) + \mathrm{H(e^-)} - \mathrm{H(RX-H)}\right] \\ (\mathrm{RX-H})^{+\cdot} \rightarrow \mathrm{RX^{\cdot}} + \mathrm{H^+}\ \left[\mathbf{PDE} = \mathrm{H(RX^{\cdot})} + \mathrm{H(H^+)} - \mathrm{H}\left((\mathrm{RX-H})^{+\cdot}\right)\right], \end{cases} \quad (2)$$

$$\mathbf{SPLET}: \begin{cases} \mathrm{RX-H} \rightarrow \mathrm{RX^-} + \mathrm{H^+}\ [\mathbf{PA} = \mathrm{H(RX^-)} + \mathrm{H(H^+)} - \mathrm{H(RX-H)}] \\ \mathrm{RX^-} \rightarrow \mathrm{RX^{\cdot}} + \mathrm{e^-}\ [\mathbf{ETE} = \mathrm{H(RX^{\cdot})} + \mathrm{H(e^-)} - \mathrm{H(RX^-)}]. \end{cases} \quad (3)$$

For the generated radicals (RX• and RX-H^+•), the unrestricted open shell level UB3LYP/6-311G++(d,p) was used to calculate their vibrational frequencies and no significant change was noted when subjected to a geometry optimization. Molecular descriptors are calculated at 298.15 K and 1 atm. The enthalpy values of hydrogen atom (H•), proton (H^+) and electron (e^-) in ethanol are equal to −1307.479[50], −1012.303 and −102.154 kJ/mol, respectively. The two last values were obtained from the corresponding solvation enthalpies[51].

The geometries of the studied molecules were optimized. The vibrational frequencies' calculations exhibited no negative value, indicating indeed that the optimized geometries are located on the global minimum point of its potential energy surface. When comparing the determinant molecular descriptors' values (Table 4), for each molecule, it was found that PA was the lowest one. Which mean that SPLET is thermodynamically the most favored mechanism for the radical scavenging activity of all studied molecules. However, a difference in the origin of the transferred proton is noted between the tested compounds. Some prefer to release the proton from the hydroxyl group (**4a**, **4b**, **4c**, **4d**, **4e**, **4f**, **5f**, **5i** and **5h**) while others favor the departure of the proton from the N-H bond (**5a**, **5b**, **5c**, **5d**, **5e**, **5g**, **5j**, **5k**, **5l**, **5m** and **4g**). Notice that a number of molecules have two N-H bonds (two labile protons H_a and H_b), as shown in Figure 1. In this case, the H_a proton transfer is always preferred to the H_b one. Thus, molecules having a single N-H bond (**4a**, **4b**, **4c**, **4d**, **4e**, **4f**) prefer the transfer of the O-H proton. For molecules having two N-H bonds (**5a**, **5b**, **5c**, **5d**, **5e**), the transfer of the H_a proton is preferred. The same thing is observed for molecules having no O-H bond (**5k**, **5l**, **5m**, **4g**). The rest of molecules show very close values of PA with a slight preference to transfer the H_a proton, for **5g** and **5j**, and to transfer the O-H proton, for **5f, 5i** and **5h**.

A good correlation between the experimental results of the DPPH scavenging activity (IC_{50}) and the relevant descriptors (PA)[52] is also observed (Figure 1).

TABLE 4 Molecular descriptors (kJ/mol) calculated at the B3LYP/6-311G++(d,p) level of the DFT theory. Solvation effects (ethanol) were considered using the IEFPCM model

Molecule	BDE(OH)	BDE(NH)	IP	PDE	PA(OH)	PA(NH)	ETE(OH)	ETE(NH)
4a	410.86	411.70	482.14	121.74	288.69	320.82	315.19	283.90
4b	409.17	411.75	480.39	121.80	287.69	321.93	314.50	282.84
4c	395.03	399.25	474.83	113.22	280.53	323.72	307.52	268.56
4d	395.75	418.74	499.71	89.06	262.47	317.51	326.30	294.25
4e	347.47	347.47	465.34	75.16	227.01	313.35	313.48	227.14
4f	344.42	374.11	434.16	103.28	242.96	321.37	294.48	245.76
4g	No OH	390.09	483.02	No OH	No OH	298.73	No OH	284.39
5a	381.48	435.07[a]	462.27	112.23	269.83	222.32[a]	304.67	405.77[a]
		915.31[b]				340.40[b]		767.93[b]
5b	427.27	420.63[a]	467.36	152.93	323.21	241.15[a]	297.08	372.50[a]
		390.23[b]				325.06[b]		258.19[b]
5c	380.25	413.26[a]	458.78	114.49	321.61	224.40[a]	251.66	381.88[a]
		384.48[b]				334.76[b]		242.74[b]
5d	394.34	429.15[a]	465.37	121.98	289.33	236.61[a]	298.02	385.56[a]
		416.72[b]				344.63[b]		265.11[b]
5e	381.03	426.02[a]	463.04	91.97	270.64	254.02[a]	284.36	365.02[a]
		387.12[b]				358.97[b]		221.17[b]
5f	337.54	387.19[a]	414.75	115.80	245.55	237.60[a]	285.01	242.61[a]
		386.06[b]				345.76[b]		233.31[b]
5g	336.01	416.17[a]	411.87	117.17	244.72	233.59[a]	284.31	375.60[a]
		379.04[b]				338.64[b]		233.42[b]
5h	339.59	408.67[a]	423.60	109.01	242.32	242.89[a]	290.29	358.81[a]
		876.26[b]				314.86[b]		754.42[b]
5i	343.21	428.66[a]	428.71	107.52	238.79	240.85[a]	297.44	380.83[a]
		386.58[b]				342.92[b]		236.68[b]
5j	343.58	424.78[a]	430.16	106.44	240.82	236.25[a]	295.78	381.55[a]
		390.32[b]				351.57[b]		231.77[b]
5k	No OH	423.97[a]	463.56	No OH	No OH	232.81[a]	No OH	384.18[a]
		423.98[b]				313.07[b]		303.93[b]
5l	No OH	431.44[a]	466.62	No OH	No OH	231.19[a]	No OH	393.27[a]
		399.29[b]				320.61[b]		271.70[b]
5m	No OH	425.33[a]	478.58	No OH	No OH	236.70[a]	No OH	381.65[a]
		381.42[b]				294.13[b]		280.31[b]

[a]N-H_a
[b]N-H_b

2.2.3 | Determination of cholinesterase (AChE, BChE) inhibitory activity

Inhibitors of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) are the most investigated and commonly strategy used for the treatment of Alzheimer's disease[53–55]. In this context, we evaluated the anticholinesterase activity of all synthesized products which can lead to their possible uses as effect enzyme inhibitors. Cholinesterase (ChE) inhibitory activity was measured using Ellman's method, as previously reported[56] with slight modification.

The IC_{50} values of all tested compounds against BChE and AChE were summarized in Table 5. The obtained

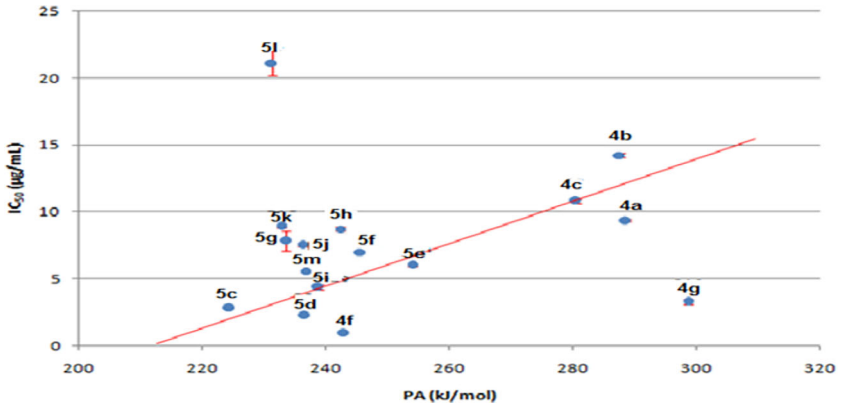


FIGURE 1 Correlation curve between the IC_{50} of the DPPH scavenging activity and the determinant molecular descriptor, PA in our case, for the most active molecules

TABLE 5 IC_{50} values of (AChE, BChE) inhibitory activity of compounds 4(a-g) and 5(a-m)

Compound	IC_{50} (µM)[a]	
	AChE	BChE
4a	70.49 ± 0.70	>500
4b	28.42 ± 0.02	73.38 ± 1.99
4c	38.39 ± 0.89	186.79 ± 1.99
4d	107.37 ± 1.12	65.30 ± 1.42
4e	105.32 ± 1.25	169.40 ± 1.99
4f	67.20 ± 1.12	79.22 ± 1.86
4g	>500	429.55 ± 2.01
5a	55.23 ± 0.38	29.35 ± 0.86
5b	>500	55.27 ± 1.25
5c	141.57 ± 1.16	43.46 ± 1.35
5d	191.15 ± 0.69	24.56 ± 1.20
5e	52.55 ± 1.07	>500
5f	>500	256.72 ± 1.44
5g	>500	97.61 ± 0.58
5h	>500	33.49 ± 2.25
5i	67.39 ± 2.01	61.94 ± 2.35
5j	>500	180.82 ± 1.15
5k	91.73 ± 0.49	>500
5l	>500	>500
5m	96.92 ± 1.12	>500
Galantamine[b]	21.81 ± 1.15	120.93 ± 1.99

[a]Values expressed are means ± SD of three parallel measurements.
[b]Reference compounds.

IC_{50} values revealed that all tested compounds except **5b**, **5f**, **5g**, **5i**, **5h**, **5l**, **4g** (IC_{50} > 500 µM) showed moderate inhibitory activity against AChE (IC_{50} = 28.42 ± 0.02-191.15 ± 0.96 µM). The highest inhibitory activity against AChE was observed with derivatives **4b** (IC_{50} = 28.42 ± 0.02 µM), **4c** (IC_{50} = 38.39 ± 0.89 µM), **5e** (IC_{50} = 52.55 ± 1.07 µM) and **5a** (IC_{50} = 55.23 ± 0.38 µM), respectively, compared with Galantamine standard (IC_{50} = 21.81 ± 1.15 µM). In term of anti-BChE activity, all tested compounds except **4a**, **5e**, **5l**, **5k**, **5m** (IC_{50} > 500 µM), showed good activities. The derivatives **5d**, **5a**, **5h**, **5c** and **5b** (IC_{50} = 24.56 ± 1.20; 29.35 ± 0.86; 33.49 ± 2.25; 43.46 ± 1.35-55.27 ± 1.25 µM) respectively, were the most potent compounds against BChE compared with Galantamine standard (IC_{50} = 120.93 ± 1.99 µM).

3 | CONCLUSION

In conclusion, we reported the synthesis, identification and evaluation of antioxidant and anticholinesterase activities of novel α-aminophosphonates derivatives. A good correlation between the experimental results of the DPPH scavenging activity (IC_{50}) and the relevant descriptors (PA) is also observed using DFT calculation.

The results suggested a potent antioxidant activity with all tests of most products and showed a middle inhibitory against AChE and important inhibition of BChE, which may find the application of these novel molecules as potential antioxidant agents and may be useful as a moderate anticholinesterase agent, for treatment of Alzheimer's diseases.

4 | EXPERIMENTAL SECTION

4.1 | General information

All starting materials and reagents used for synthesis were obtained commercially from commercial sources Aldrich and Acros and were used without purification. Sonication was performed in a FUNGILAB ultrasonic bath with a frequency of 40 kHz and an output power of 250 W. Melting points were measured using Buchi

Melting Point B-545. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm Merck silica gel plates (60F-254) using ultraviolet light (254 nm) as the visualizing agent and ninhydrine solution as developing agents. ^{1}H NMR and ^{13}C NMR spectra were recorded at 30°C on a Bruker spectrometers (400 MHz for ^{1}H, 101 MHz for ^{13}C and 162 MHz for ^{31}P) using TMS as internal standard and $CDCl_3$ or $DMSO_{d\text{-}6}$ as solvent. Mass spectra were recorded with a MicrOTOF-Q Bruker spectrometer using electrospray ionization (ESI) analysis. All reagents used for biological activities were purchased from Sigma-Aldrich Co., S**t** Lowis, M**O**. Measurements and calculations of the antiradical activity were carried out on a 96-well microplate reader, Perkin Elmer Multimode Plate Reader EnSpire.

4.2 | *General procedure for the preparation of quinoline derivatives*

Place dimethyl formamide (DMF)(3 eq) in a flask equipped with a drying tube cooled to 0°C temperature, then $POCl_3$(Phosphorousoxychloride) (7 eq) was added dropwise with stirring to it. To this solution add acetanilide (1 mmol). After few minutes the reaction mixture was refluxed for 6-8 h. After completion of requiring time reaction, the mixture was cooled and poured in ice-cold water and stirred about half an hour then filtered to offer powder of compound.

2-Chloro-3-formyl-6-méthylquinoline: $C_{10}H_7NO_2$; MW = 173.17; TLC R_f = 0.35 (CH_2Cl_2); yellow powder; 96% yield; IR ν_{max} (KBr) (cm^{-1}) = 1645 (CO). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57(s, 1H, CHO), 8.58 (s, 1H, H_4), 7.97 (d, J = 7.7, 1H, H_8), 7.75 (d, J = 2.3, 1H, H_5), 7.74 (dd, J = 7.7, 2.4, 1H, H_7), 2.57 (s, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, DMSO-d_6) δ 189.3, 149.2, 148.1, 139.5, 138.4, 135.9, 128.3, 128.1, 126.5, 126.2, 21.5 ppm.

4.3 | *General procedure for the preparation of compounds 3a-f*

2-Chloro-3-formyl quinoline derivatives were treated with 70% acetic acid aqueous solution (200 mL) at 95°C for 10 h and then the solution was cooled to room temperature to offer needle crystals of compounds **3a-f**.

2-oxo-1,2-dihydroquinoline-3-carbaldehyde (3a): $C_{10}H_7NO_2$; MW = 173.17; TLC R_f = 0.35 (CH_2Cl_2); yellow powder; 96% yield; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (s, 1H, NH), 10.25 (s, 1H, CHO), 8.50-8.45 (m, 1HAr,H_7), 7.90 (dd, J_{ortho} = 7.9, J_{metha} = 1.4 Hz, 1HAr,H_3), 7.65 (ddd, J_{ortho} = 8.5, 7.2, J_{metha} = 1.5 Hz, 1HAr,H_1), 7.37 (dd, J_{ortho} = 8.5, J_{metha} = 1.1 Hz, 1HAr,H_6), 7.25 (td, J_{ortho} = 8.1, 7.2, J_{metha} = 1.1 Hz, 1HAr,H_2). ^{13}C NMR (101 MHz, DMSO-d_6) δ 190.18, 190.15, 142.87, 134.08, 134.05, 131.29, 123.09, 123.07, 118.60, 115.89 ppm.

4.4 | *General procedure for the preparation of α-aminophosphonate*

In a 10 mL round-bottom flask, a mixture of amine (1 mmol) and aldehyde (1 mmol) was taken with 1 mL of ionic liquid at room temperature and then triethyl phosphite (1 mmol) was added. The reaction mixture was subjected to the ultrasonication for appropriate time. After completion of the reaction, as indicated by TLC, distilled water was added. The product was finally filtered and dried and it was purified by recrystallization using chloroform/diethyl ether to yield pure α-aminophosphonate.

diethyl(((2-hydroxyphenyl)amino)(−2-oxo-1,-2-dihydroquinolin 3yl)methyl)phosphonate **5a**: $C_{20}H_{23}N_2O_5P$; TLC R_f = 0.48 (CH_2Cl_2); yellow powder; 92% yield; ^{1}H NMR (400 MHz, Chloroform-d_6) δ 11.75 (s, 1H, OH), 9.74 (s, 1H, NH), 7.70 (d, $J_{H\text{-}P}$ = 3.5 Hz, 1H Ar, H_7), 7.10-7.00 (m, 2H Ar, H_1, H_3,), 6.93 (dd, J_{ortho} = 8.2, J_{metha} = 1.5 Hz, 1H Ar, H_6), 6.88 (dd, J_{ortho} = 7.8, J_{metha} = 1.4 Hz, 1H Ar, H_{17}), 6.72 (td, J_{ortho} = 7.7, J_{metha} = 1.9 Hz, 1H Ar, H_2), 6.54 (td, J_{ortho} = 7.6, J_{metha} = 1.4 Hz, 1H Ar, H_{18}), 6.50 (dd, J_{ortho} = 8.4, J_{metha} = 3.6 Hz, 1H Ar, H_{16}), 5.92(d, J = 11.6 Hz, 1H, NH), 5.89(dd, J_{ortho} = 7.8, J_{metha} = 1.7 Hz, 1H, H_{15}), 5.77 (dd, $J_{H\text{-}P}$ = 25.0, 11.6 Hz, 1H, H_{12}), 4.46-4.33 (m, 2H, H_{27}), 4.16-3.91 (m, 2H, H_{24}), 1.20 (t, J = 7.0 Hz, 3H Ar, H_{25}), 1.09 (t, J = 7.1 Hz, 3H, H_{29}) ppm. ^{13}C NMR (101 MHz, Chloroform-d_6) δ 163.10 (d, $J_{C\text{-}P}$ = 6.4 Hz), 145.22, 138.96, 137.17, 135.09 (d, $J_{C\text{-}P}$ = 16.2 Hz), 130.38, 128.53, 127.54, 122.05, 120.38, 119.39, 119.03, 115.16, 115.03, 112.35, 64.65 (d, $J_{C\text{-}P}$ = 6.8 Hz), 63.75 (d, $J_{C\text{-}P}$ = 7.5 Hz), 45.46, 16.51 (d, $J_{C\text{-}P}$ = 5.8 Hz), 16.21 (d, $J_{C\text{-}P}$ = 5.6 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.04 ppm. ESI-MS (m/z): 403.59 ($M + H^+$). Anal. Calcd for $C_{20}H_{23}N_2O_5P$ (402.39): C, 59.70; H, 5.76; N, 6.96; O, 19.88; P, 7.70. Found: C, 59.75; H, 5.78; N, 6.92; O, 19.81; P, 6.90%.

diethyl(((2-hydroxyphenyl)amino)(6-methyl-2-oxo-1,-2-dihydroquinolin-3yl)methyl)phosphonate **5b**: $C_{21}H_{25}N_2O_5P$; TLC R_f = 0.43 (CH_2Cl_2);yellow powder; 87% yield; ^{1}H NMR (400 MHz, Chloroform-d_6) δ 10.99 (s, 1H, OH), 9.76 (s, 1H, NH), 7.52 (d, $J_{H\text{-}P}$ = 3.6 Hz, 1HAr, H_7), 6.95 (d, J_{ortho} = 7.7 Hz, 1HAr, H_6), 6.85 (dd, J_{ortho} = 7.8, J_{metha} = 1.4 Hz, 1HAr, H_1), 6.81 (m, 3HAr, H_{15}, $H_{18,}$ H_3), 6.75 (td, J_{ortho} = 7.1, J_{metha} = 1.2 Hz, 1HAr, H_{16}), 6.53 (td, J_{ortho} = 7.6, J_{metha} = 1.4 Hz, 1HAr, H_{17}), 5.95 (dd,

$J_{H\text{-}H}$ = 12.2, $J_{H\text{-}P}$ = 6.3 Hz,1H, NH), 5.78 (dd, $J_{H\text{-}P}$ = = 25.2, $J_{H12\text{-}H13}$ = 12.1 Hz, 1H, H_{12}), 5.13 (s, 1H, H_7), 4.54-4.36 (m, 2H), 4.20-4.01 (m, 2H), 1.44 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, Chloroform-d_6) δ 162.68, 145.29, 138.68, 135.19, 135.10 (d, $J_{C\text{-}P}$ = 18.7 Hz), 131.56, 128.39, 127.16, 120.50, 119.17, 115.07, 113.96, 112.50, 77.33, 77.02, 76.70, 64.82, 63.90 (d, $J_{C\text{-}P}$ = 7.3 Hz), 19.98, 16.54 (d, $J_{C\text{-}P}$ = 5.8 Hz), 16.22 (d, $J_{C\text{-}P}$ = 5.7 Hz) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 24.26 ppm. ESI-MS m/z: 417.35 ($M + H^+$). Anal. Calcd for $C_{21}H_{25}N_2O_5P$ (416,41): C, 59.70; H, 5.76; N, 6.96; O, 19.88; P, 7.70. Found: C, 59.80; H, 5.81; N, 6.88; O, 19.74; P, 6.86%.

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REFERENCES

[1] S. Saha, R. Verma, *Pharm. Biol.* **2012**, *50*, 326.
[2] J. Xiao, R. Tundis, *J. Pharm. Pharmacol.* **2013**, *65*, 1679.
[3] B. Halliwell, J. M. C. Gutteridge, *Free Radicals in Biology and Medicine*, 4th ed., Clarendon, Oxford **2007**.
[4] M. I. C. Atta-ur-Rahman, *Pure Appl. Chem.* **2001**, *73*, 555.
[5] C. Derabli, I. Boualia, A. B. Abdelwahab, R. Boulcina, C. Bensouici, G. Kirsch, A. Debache **2018**; *28*(14), 2481
[6] D. Trachootham, J. Alexandre, P. Huang, *Nat. Rev. Drug Discov.* **2009**, *8*, 579.
[7] R. W. Moss, *Antioxidants Against Cancer*, New York, NY, Equinox Press **2000**.
[8] M. L. Cornish, D. J. Garbary, *Algae* **2010**, *25*, 155.
[9] P. Gao, H. H. Zhang, R. Dinavahi, F. Li, Y. Xiang, V. Raman, Z. M. Bhujwalla, D. W. Felsher, L. Z. Cheng, J. Pevsner, G. L. Semenza, C. V. Dang, *Cancer Cell* **2007**, *12*, 230.
[10] F. R. Atherton, C. H. Hassall, R. W. Lambert, *J. Med. Chem.* **1986**, *29*, 29.
[11] a) M. C. Allen, W. Fuhrer, B. Yuck, R. Wade, J. M. Wood, *J. Med. Chem.* **1989**, *32*, 1652. b) E. W. Logusch, D. M. Walker, J. F. McDonald, G. C. Leo, J. E. Franz, *J. Org. Chem.* **1988**, *53*, 4069. c) P. P. Giannousis, P. A. Bartlett, *J. Med. Chem.* **1987**, *30*, 1603.
[12] M. V. N. Reddy, S. Annar, A. Balakrishna, G. C. S. Reddy, C. S. Reddy, *Org. Commun.* **2010**, *3*, 39.
[13] a) Y. C. Guo, J. Li, J. L. Ma, Z. R. Yu, H. W. Wang, W. J. Zhu, X. C. Liao, Y. F. Zhao, *Chin. Chem. Lett.* **2015**, *26*, 755. b) X. C. Huang, M. Wang, Y. M. Pan, X. Y. Tian, H. S. Wang, Y. Zhang, *Bio. Org. Med. Chem. Lett.* **2013**, *23*, 5283. c) A. K. Bhattacharya, D. S. Raut, K. C. Rana, I. K. Polankia, M. S. Khan, S. Iramb, *Eur. J. Med. Chem.* **2013**, *66*, 146.
[14] S. Bhagat, P. Shah, S. Mishra, P. K. Kaur, S. Singh, A. K. Chakraborti, *Med. Chem. Commun.* **2014**, *5*, 665.
[15] P. Kafarski, B. Lejczak, *Sulfur Silicon Relat. Elem.* **1991**, *63*, 1993.
[16] K. U. M. Rao, S. Swapna, D. M. Mahidhar, K. M. K. Reddy, C. S. Reddy, *Phosphorus, Sulfur Silicon Relat. Elem.* **2015**, *98*, 232.
[17] Q. Wang, M. Zhu, R. Zhu, L. Lu, C. Yuan, S. Xing, Y. Mei, Q. Hang, *Eur. J. Med. Chem.* **2012**, *49*, 354.
[18] K. C. Majumdar, S. K. Chattopadhyay, *Heterocycles in Natural Product Synthesis*; Wiley-VCH: Weinheim; **2011**, p. 1.
[19] E. M. El-Sheref, A. A. Aly, A. F. E. Mourad, A. B. Brown, S. Bräse, M. E. M. Bakheet, *Chem. Pap.* **2017**, *72*(1), 181.
[20] E. Polo, N. Ibarra-Arellano, L. Prent-Peñaloza, A. Morales-Bayuelo, J. Henao, A. Galdámez, M. Gutiérrez, *Bioorg. Chem.* **2019**, *90*, 103034.
[21] N. M. Sukhova, M. Lidak, A. Zidermane, I. S. Pelevina, S. S. Voronia, *Khim-Farm. Zh.* **1989**, *23*, 1226.
[22] J. C. Craig, P. E. J. Person, *Med. Chem.* **1971**, *14*, 1221.
[23] H. V. Patel, K. V. Vyas, P. S. Fernandes, *Indian J. Chem.* **1990**, *29*(B), 836.
[24] N. L. Allinger, M. P. Cava, C. Don, C. R. De Jong, N. A. Johnson, C. A. Lebel, *Chimie Organique*, Edscience/Mc Graw-Hill: United States, **1975**, p. 774.
[25] K. Laalaoui, D. Bendjeddou, H. Menasra, A. Belfaitah, S. Rhouati, D. Satta, J. Egypt, *Ger. Soc. Zool.* **2003**, *41A*, 255.
[26] R. D. Dillard, D. E. Pavey, D. N. J. Benslay, *Med. Chem.* **1973**, *16*, 251.
[27] F. Dorvault, *L'Officine*, XXIe ed., Vigot, Paris **1982**, p. 1725.
[28] Z. C. Liu, B. D. Wang, Z. Y. Yang, Y. Li, D. D. Qin, T. R. Li, *Eur. J. Med. Chem.* **2009**, *44*, 4477.
[29] a) O. Meth-Cohn, B. Narine, B. Tarnowsky, *J. Chem. Soc. Perkin Trans. 1*, **1981**, 1520. b) O. Meth-Cohn, *Heterocycle* **1993**, *35*, 539. (c) O. Meth-Cohn, D. L. Taylor, *Tetrahedron. Lett.* **1995**, *51*, 1287. https://doi.org/10.1039/p19810001520
[30] T. Tilakraj, S. Y. J. Ambekar, *Indian J. Chem.* **1985**, *62*, 251.
[31] H. B. Li, C. C. Wong, K. W. Cheng, F. Chen, *Lebens-Wizs Techonologie* **2008**, *41*, 385.
[32] I. Boualia, C. Derabli, R. Boulcina, C. Bensouici, M. Yildirim, A. Birinci Yildirim, A. Debache, *Arch. Der Pharm.* **2019**, *352*, 1900027.
[33] G. J. Marco, *J. Am. Oil Chem. Soc.* **1968**, *45*, 594.
[34] R. Re, N. Pellegrini, A. Proteggente, A. Pannala, M. Yang, C. Rice-Evans, *Free Radical Bio. Med.* **1999**, *26*, 1231.
[35] R. Apak, K. Guclu, M. Ozyurek, S. E. Karademir, *J. Agric. Food Chem.* **2004**, *52*, 7970.
[36] M. Oyaizu, *Jpn. J. Nutr.* **1986**, *44*, 307.
[37] N. Smirnoff, Q. J. Cumbes, *Phytochemistry* **1989**, *28*, 1057.
[38] A. Szydlowska-Czerniaka, C. Dianoczki, K. Recseg, G. Karlovits, E. Szlyk, *Talanta* **2008**, *76*, 899.
[39] H. Shi, N. Noguchi, E. Niki, *Methods Enzymol.* **2001**, *335*, 157.
[40] J. Xiao, R. Tundis, *J. Pharm Pharmacol.* **2013**, *65*, 1679.
[41] K. Laalaoui, D. Bendjeddou, H. Menasra, A. Belfaitah, S. Rhouati, D. Satta, J. Egypt, *Ger. Soc. Zool.* **2003**, *41A*, 255.
[42] A. Seyoum, K. Asres, F. K. El-Fiky, *Phytochemistry* **2006**, *67*, 2058.

[43] T. A. De Pinedo, P. Pen Alver, J. C. Morales, *Food Chem.* **2007**, *103*, 55.
[44] E. Cancès, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032.
[45] R. Dennington, T. A. Keith, J. M. Millam, *GaussView, Version 5.0.9.*, Semichem, Shawnee Mission, KS **2016**.
[46] *Gaussian 09, Revision E.02*, Gaussian, Wallingford, CT **2016**.
[47] M. Leopoldini, N. Russo, M. Toscano, *Food Chem.* **2011**, *125*, 288.
[48] M. Musialik, G. Litwinienko, *Org Lett.* **2005**, *7*, 4951.
[49] J. J. Fifen, M. Nsangou, Z. Dhaouadi, O. Motapon, N. Jaidane, *Comput. Theor. Chem.* **2011**, *966*, 232.
[50] L. Bamonti, T. Hosoya, K. F. Pirker, S. Böhmdorfer, F. Mazzini, F. Galli, T. Netscher, T. Rosenau, L. Gille, *Bioorg. Med. Chem.* **2013**, *21*, 5039.
[51] J. Tošović, S. Marković, D. Milenković, Z. Marković, *J. Serb. Soc. Comput. Mech.* **2016**, *10*, 66.
[52] R. Bensegueni, M. Guergouri, C. Bensouici, M. Bencharif, *SN Appl. Sci.* **2018**, *1*(1) https://doi.org/10.1007/s42452-018-0085-9.
[53] S. Stepankova, K. Komers, *Curr. Enzym. Inhib.* **2008**, *4*, 160.
[54] F. Mao, J. Li, H. Wei, L. Huang, X. Li, *J. Enzyme Inhib. Med. Chem.* **2015**, *30*(6), 995.
[55] a) S. Saha, R. Verma, *Pharm. Biol.* **2012**, *50*, 326. b) S. Saha, R. Verma, J. Enzyme Inhib, *Med. Chem.* **2015**, *30*, 995.
[56] G. L. Ellman, K. D. Courtney, V. Andres, R. M. Featherston, *Biochem. Pharmacol.* **1961**, *7*, 88.

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