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Synthesis and bioactivity of 1-substituted tetrahydroisoquinolines derived from phenolic aldehydes

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Abstract: Phenolic aldehydes and their derivatives found in nature are well-known for their potential biological activity. In this study, four 1-substituted 1,2,3,4-tetrahydroisoquinolines (THIQs) derived from phenolic aldehydes were synthesized by phosphate buffer mediated Pictet-Spengler reaction. All derivatives were chemically and structurally characterized by elemental CHN analysis and spectroscopic methods (IR, HR-ESI-MS, ^{1}H- and ^{13}C-NMR). 1-Substituted THIQs derived from 3,4-dihydroxybenzaldehyde and 4-hydroxy-3-methoxybenzaldehyde were described for the first time. In order to cover the diversity of the mechanistic approach, but also to establish the relationship between structure and activity, antioxidant activity was examined by five different *in vitro* methods, namely: neutralization and reduction of stable free radicals 2,2-diphenyl-1-picrylhydrazyl and radical cation derived from [(2,2´-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)], ferric reducing antioxidant power, oxygen radical absorbance capacity, and ability to chelate Fe(II) ions. *In vitro* inhibition of acetylcholinesterase (AChE) was examined by the Ellman's colorimetric method, while computer-simulated docking was used to reveal the preferred binding site and major interaction between AChE and THIQs. Antibacterial testing was examined using the agar well method and results were presented in the form of zones of inhibition (mm).

Keywords: Synthesis; bioactivity; 1-substituted tetrahydroisoquinolines; phenolic aldehydes;

1. Introduction

Phenolic compounds, from the aspect of secondary metabolites, are classified into subgroups depending on the structural details present[1]. One of these categories consists of hydroxybenzaldehydes, which show a wide range of positive biological effects (antioxidant, antimicrobial, anti-inflammatory, antithrombotic, anticancer, as well as inhibitory action against some

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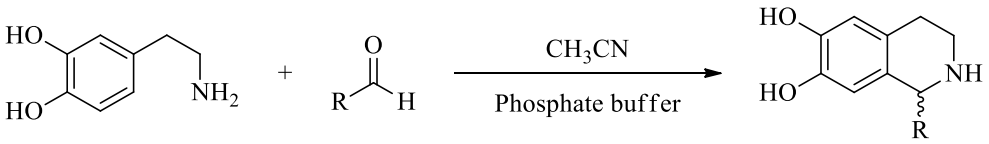
cytotoxic enzymes such as NO synthetase, cyclooxygenase-2, …)[2,3]. Also, they have unique toxicological and pharmacokinetic properties. Absorption and excretion are very fast, so that in 5-10 minutes they can be detected in the plasma, and in 90 minutes they are excreted through urine or feces. These properties reduce their toxicity, make them interesting for pharmacological use[4,5], but also as precursors for the synthesis of a large number of bioactive derivatives[6-8]. Heterocycles, which are widespread among natural alkaloids and possess a wide range of therapeutic activity, including antitumor, antibacterial, antiviral, anticoagulant, anti-inflammatory, anticonvulsant, and enzyme-inhibitory[9,10]. The tetrahydroisoquinoline (THIQ) skeleton is present in several clinically useful drugs, the most important of which are those that act on the central nervous system[11]. Previous studies described THIQ derivatives derived from dopamine, which is the most important neurotransmitter of the catecholamine structure in the central nervous system of mammals. It participates in various motor and mental functions of the organism, such as complex motor behavior, emotional and motivational aspects of behavior, cognitive functions and neuroendocrine regulation[12]. In addition, dopamine can also act as an endogenous antioxidant, which has been proven by *in vitro* and *in vivo* experiments on neuronal cell lines[13-15].

2. Background

Hydroxybenzaldehydes with β-phenylethylamines do not form imines, but the resulting iminium salt undergoes intramolecular Pictet-Spengler cyclization resulting in the formation of 1-substituted THIQs[16]. Often these reactions require harsh conditions such as high temperature and the use of strong acid or superacid[17,18]. On the other hand, unstable aldehydes and amines do not allow the use of such harsh conditions, and therefore, Pesnot et al. (2011), describes the use of mild conditions with phosphate as a catalyst in these reactions (Scheme 1)[19].



Scheme 1. Phosphate-catalyzed synthesis of THIQs.

We used the described mild synthesis conditions and extended the use of aldehydes, and synthesized two compounds that were described for the first time. In addition, we developed a simple procedure for the isolation of THIQ derivatives from a synthetic mixture.

3. Experimental

Synthesis of 1-Substituted THIQs

The reaction mixture containing dopamine hydrochloride (2 mmol) and phenolic aldehyde (2.2 mmol) in 10 mL of the mixture CH_3CN and phosphate buffer (0.1 M, pH 6.5) was incubated at 50°C for 12 hours[20]. After removal of CH_3CN under reduced pressure, the THIQs were extracted with *n*-BuOH (3×15 mL). The organic extract was washed with water (3×5 mL), dried over anhydrous K_2CO_3 and evaporated to dryness. The solid residue was washed with Et_2O and recrystallized from 1M HCl at 4°C. The purity of prepared THIQs was checked by chromatography on a thin layer of silica gel 60 F_{254} (*n*-BuOH-HOAc-H_2O, 4:1:1). The antioxidant capacity activity, anticholinesterase activity and antibacterial activity assays together with docking studies were carried out based on formerly reported methods in the literature[21-24]. (See supporting information for details of the methods)

4. Present Study

1-Substituted THIQs were synthesized by the Pictet-Spengler 6-endo-trig cyclization of phenolic aldehydes and dopamine. The synthesis reaction was carried out in a mixed solvent of acetonitrile/water in the presence of a catalytic amount of phosphate[19,20]. After extraction with *n*-BuOH, the solid residue was recrystallized from 1M HCl, and the THIQs were isolated as the hydrochloride salts (Figure 1).

1-(3-Hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride ***(1)***: Beige solid; MP. 204°C; Yield: 363 mg, 62%; R_f 0.51 (*n*-BuOH-HOAc-H_2O, 4:1:1); IR ν_{max} (KBr): 3466, 3400, 3231, 2560, 1590, 1522, 1274, 1196 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H: 9.71 (s, 1H), 9.11 (s, 1H), 8.95 (s, 1H), 7.24 (t, *J* = 7.8 Hz, 1H), 6.84 (ddd, *J* = 7.8, 4.2, 1.9 Hz, 2H), 6.76 (t, *J* = 2.0 Hz, 1H), 6.63 (s, 1H), 6.11 (s, 1H), 5.43 (s, 1H), 3.27 (q, *J* = 5.8 Hz, 2H), 3.07 (dt, *J* = 14.8, 7.1 Hz, 1H), 2.84 (dt, *J* = 16.8, 5.2 Hz, 1H); ^{13}C-NMR (125 MHz, D_2O) δ_C: 156.0, 144.3, 143.0, 137.8, 130.6, 124.5, 122.6, 121.6, 116.8, 116.5, 115.4, 114.9, 58.7, 39.5, 23.9; HR-ESI-MS: *m*/*z* 258.1124 $[M+H]^+$ (calcd. 258.1125 for $C_{15}H_{16}NO_3$); Anal. calcd. for $C_{15}H_{16}ClNO_3$: C, 61.33, H, 5.49, N, 4.77, Found: C, 61.38, H, 5.47, N, 4.79.

1-(4-Hydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride ***(2)***: Beige solid; MP. 212°C; Yield: 316 mg, 54%; R_f 0.63 (*n*-BuOH-HOAc-H_2O, 4:1:1); IR ν_{max} (KBr): 3548, 3368, 3024, 1605, 1510, 1279, 1171 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H: 8.73 (s, 3H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.70 – 6.65 (m, 2H), 6.43 (s, 1H), 6.00 (s, 1H), 4.69 (s, 1H), 3.02 (dt, *J* = 11.5, 4.7 Hz, 2H), 2.80 (ddd, *J* = 11.6, 9.2, 4.2 Hz, 1H), 2.70 (ddd, *J* = 14.9, 9.2, 5.4 Hz, 1H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ_C: 156.7, 143.9, 143.3, 136.6, 130.3, 130.2, 126.1, 116.9, 115.7, 115.1, 115.0, 60.9, 42.6, 29.1; HR-ESI-MS: *m*/*z* 258.1129 $[M+H]^+$ (calcd. 258.1125 for $C_{15}H_{16}NO_3$); Anal. calcd. for $C_{15}H_{16}ClNO_3$: C, 61.33, H, 5.49, N, 4.77, Found: C, 61.72, H, 5.37, N, 4.31.

1-(3,4-Dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride ***(3)***: Beige solid; MP. 208°C; Yield: 278 mg, 45%; R_f 0.61 (*n*-BuOH-HOAc-H_2O, 4:1:1); IR ν_{max} (KBr): 3536, 3399, 3014, 1611, 1524, 1290, 1119 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H: 9.33 (s, 1H), 9.17 (s, 1H), 9.13 (s, 1H), 8.97 (s, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 6.67 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.62 (s, 1H), 6.13 (s, 1H), 5.34 (dd, *J* = 7.5, 3.3 Hz, 1H), 3.26 (tt, *J* = 13.9, 6.3 Hz, 2H), 3.04 (ddd, *J* = 15.1, 8.5, 6.1 Hz, 1H), 2.82 (dt, *J* = 16.8, 5.3 Hz, 1H); ^{13}C-NMR (125 MHz, D_2O) δ_C: 145.3, 144.2, 144.2, 143.0, 128.5, 124.5, 123.0, 122.5, 117.1, 116.2, 115.3, 114.9, 58.5, 39.2, 23.9; HR-ESI-MS: *m*/*z* 274.1069 $[M+H]^+$ (calcd. 273.0997 for $C_{15}H_{15}NO_4$); Anal. calcd. for $C_{15}H_{16}ClNO_4$: 58.16; H, 5.21; N, 4.52; Found: C, 58.38; H, 5.47; N, 4.79.

1-(4-Hydroxy-3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-6,7-diol hydrochloride ***(4)***: Light brown solid; MP. 199°C; Yield: 459 mg, 71%; R_f 0.56 (*n*-BuOH-HOAc-H_2O, 4:1:1); IR ν_{max} (KBr): 3119, 2351, 1603, 1512, 1285, 1034 cm^{-1}; ^{1}H-NMR (500 MHz, DMSO-d_6) δ_H: 9.37 (s, 1H), 9.13 (s, 1H), 8.95 (s, 1H), 7.09 (d, *J* = 2.1 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.73 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.62 (s, 1H), 6.12 (s, 1H), 5.43 – 5.38 (m, 1H), 3.76 (s, 3H), 3.31 (dt, *J* = 10.6, 5.8 Hz, 1H), 3.27 – 3.22 (m, 1H), 3.12 (ddd, *J* = 15.5, 9.1, 6.1 Hz, 1H), 2.83 (dt, *J* = 16.7, 5.1 Hz, 1H); ^{13}C-NMR (125 MHz, D_2O) δ_C: 147.6, 146.1, 144.3, 143.1, 128.5, 124.5, 123.2, 123.0, 115.5, 115.4, 114.9, 113.3, 58.9, 55.8, 39.4, 23.9; HR-ESI-MS: *m*/*z* 288.1223 $[M+H]^+$ (calcd. 288.1217 for $C_{16}H_{17}NO_4$); Anal. calcd. for $C_{15}H_{16}ClNO_4$: C, 59.35; H, 5.60; N, 4.33; Found: C, 59.64; H, 5.97; N, 4.15.

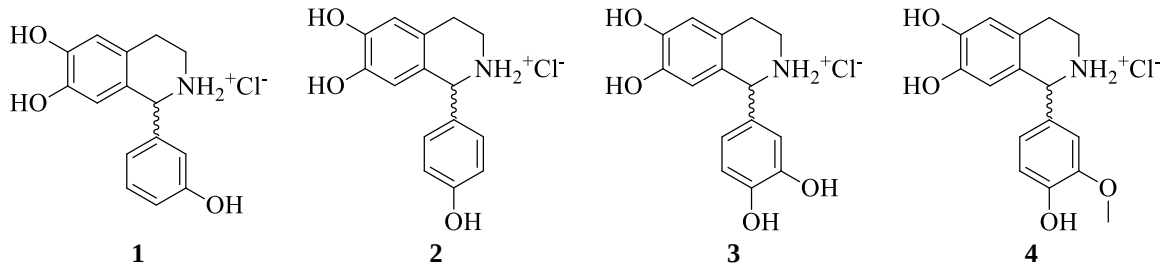


Figure 1. Structures of compounds **1**-**4**.

The results of the ability to neutralize free radicals and reduce/chelate transition metals are presented in the Table 1.

Table 1. Antioxidant activity of synthesized THIQs

Compund	DPPH$^{\bullet}$ IC_{50} (μM)	ABTS$^{\bullet+}$ IC_{50} (μM)	FRAP *AAE* (μmol$_{AA}$/mmol)	ORAC *TE* (μmol$_T$/μmol)	Fe(II)-FZ IC_{50} (μM)
1	28.71 ± 0.82	1.42 ± 0.07	516.19 ± 15.56	0.42 ± 0.02	0.93 ± 0.04
2	29.62 ± 0.94	1.02 ± 0.04	520.37 ± 13.29	0.35 ± 0.02	2.25 ± 0.10
3	11.14 ± 0.39	0.76 ± 0.02	654.64 ± 10.18	1.56 ± 0.07	3.62 ± 0.16
4	18.37 ± 0.57	1.35 ± 0.06	600.74 ± 14.69	1.10 ± 0.04	1.36 ± 0.08
Ascorbic acid	1.14 ± 0.03	0.11 ± 0.00	-	0.48 ± 0.04	-
Na_2EDTA	-	-	-	-	0.01 ± 0.00

There is a noticeable trend that compound **3** shows the most significant antioxidant activity, apart from the ability to chelate Fe(II). Such a low IC_{50} and high *AAE* and *TE* values are most likely due to the catechol arrangement in their structures (one on the 3,4-dihydroxybenzaldehyde residue and one on the dopamine unit). At the same time, the weaker antioxidant activity of compound **4** can be explained by additional alkylation of phenolic groups at C3 positions. Also, a significant decrease in the antioxidant activity of THIQ derivatives derived from 3- and 4-hydroxybenzaldehyde is visible, as a result of the loss of the second substituent on the aromatic nucleus (OH and/or OCH_3). Namely, regardless of the impossibility of homolytic cleavage, the OCH_3 group in the *ortho* position lowers the oxidation potential, but also acts as an electron-donating group and thus facilitates the stabilization of phenoxy radicals. Taking into account all the above, it is clear that in the case of THIQ derivatives, the antioxidant activity can be attributed both to the structural parts of the phenolic compound and to the dopamine unit. Like dopamine, phenolic aldehydes, in this case 3,4-dihydroxybenzaldehyde with a catecholic arrangement of phenolic groups, give *o*-quinone as an oxidation product. However, by reducing the degree of hydroxylation, mechanistic studies proved the formation of *p*-quinone through a one-electron mechanism[25,26]. The direct reaction of antioxidants with free radicals is not the only mechanism by which free radical species are inactivated. There is another mechanism by which antioxidants do not convert free radicals into less reactive species, but instead slow down the rate of the oxidation reaction through several mechanisms. The most important mechanism of secondary antioxidants is the chelation of proactive metal ions[27]. To investigate this, we used the method of competitive chelation of Fe(II) with ferrozine and the test compounds. Compound **1** showed the highest ability to bind Fe(II) ions with an associated IC_{50} value of 0.93 μM. At the same time, an IC_{50} value of 1.36 μM was determined for compound **4**. These two derivatives can act as *O*,*N*-donor ligands, as a consequence of the arrangement of the phenolic/methoxy group and the amine nitrogen.

The THIQs were tested for their ability to inhibit acetylcholinesterase (AChE) from *Electrophorus electricus* by a spectrophotometrically assay based on an Ellman method (Figure 2).

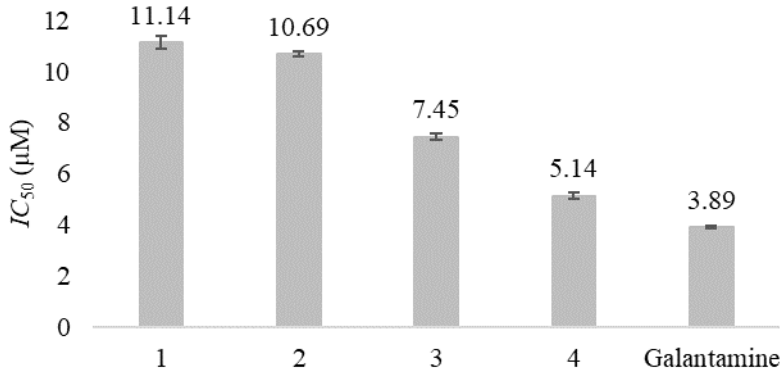


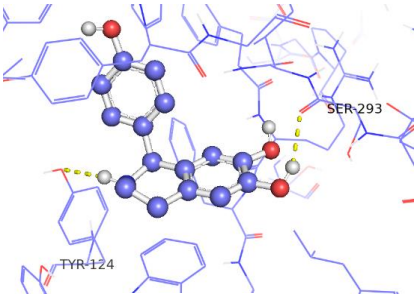
Figure 2. AChE-inhibitory activity of synthesized THIQs

From the obtained results, it is clear that the reduction of the degree of hydroxylation and the introduction of the Me group at the C3 position in the case of compound **4** causes a superior inhibitory activity over the unmethylated one (**3**). This trend of behavior has already been described in the literature, and is explained by a decrease in polarity and an increase in the possibility of interaction

between the peripheral anionic subunit of AChE and the non-polar amino acid Trp[28]. In the case of derivatives of monosubstituted benzaldehydes (**1** and **2**), the activity is additionally suppressed by reducing the degree of substitution. This trend is a consequence of the reduced possibility of interactions (especially the possibility of realizing H-bonds) with the active sites of AChE. To support the experimental results obtained by AChE inhibition, computer-simulated docking was used to reveal the preferred binding site and major interaction between AChE and THIQs (Table 2).

Table 2. H-bonds in AChE interaction with synthesized THIQs

Sample	Affinity (kcal/mol)	Bonding in AChE / Distance (Å)
1	-9.1	***H*** [C6-OH] → ***O***-Ser^{293} / 2.8 Å ***H*** [C7-OH] → ***O***-Ser^{293} / 2.8 Å ***H*** [C3'-OH] → ***O***-Phe^{338} / 2.6 Å
2	-8.6	***H*** [C6-OH] → ***O***-Ser^{293} / 2.3 Å ***H*** [N-H] → ***O***-Tyr^{124} / 2.4 Å
3	-7.7	***H***-Ser^{293} → ***O***-[C4'-OH] / 2.5 Å ***H***-Phe^{295} → ***O***-[C7-OH] / 2.4 Å ***H***-Arg^{296} → ***O***-[C7-OH] / 2.1 Å
4	-8.4	***H*** [C7-OH] → ***O***-Tyr^{124} / 2.8 Å ***H*** [N-H] → ***O***-Arg^{296} / 2.1 Å
Galantamine	-8.1	***H***-[C6-OH] → ***O***-Arg^{296} / 2.0 Å ***H***-Arg^{296} → ***O***-[C6-OH] / 2.2 Å ***H***-Phe^{295} → ***O***-[C6-OH] / 2.2 Å



The complex AChE-**2**

According to the results, **1** shows the strongest affinity and binds with three H-bonds with AChE. Compounds **2** and **4** show binding to the central hydrophobic region of the protein gorge (Trp^{86}, Tyr^{124}, and Tyr^{337}) to the hydroxyl group of Tyr^{124}. The predicted binding sites are already proven binding and transport sites of bioactive compounds in the case of some AChE inhibitors, such as heterocyclic substituted alkyl and cycloalkyl propargyl amine[29]. However, the *in vitro* and docking results obtained are not fully correlated in terms of IC_{50} values and affinity. This behavior is well known and described in the literature[30,31]. However, what is noticeable is that compounds **3**, **4** and galantamine interact with Arg^{296} on the active site and are bound deeper in the binding pocket.

All synthesized THIQs were tested for antibacterial activity toward *Staphylococcus aureus* (ATCC 6538), Methicillin resistant *Staphylococcus aureus* (ATCC 33591), *Pseudomonas aeruginosa* (ATCC 10145) and *Escherichia coli* (ATCC 14169) (Table 3).

Table 3. Antibacterial activity of synthesized THIQs.

Compound	Zone of inhibition (mm)			
	S. aureus	***MRSA***	***P. aeruginosa***	***E. coli***
1	11.00 ± 1.00	-	17.00 ± 0.00	-
2	10.67 ± 0.58	-	-	-
3	11.00 ± 1.00	-	-	-
4	9.33 ± 0.58	-	28.33 ± 0.58	-
Ampicillin	12.33 ± 0.33	-	11.33 ± 0.33	20.67 ± 0.58

Of the tested compounds, only compounds **1** and **4** show significant antibacterial activity against the gram-negative *P. aeruginosa* strain. In all other cases, the compounds had moderate or no antibacterial activity.

5. Conclusion

Using mild conditions and in the presence of a catalytic amount of phosphate, four THIQ derivatives derived from dopamine and phenolic aldehydes were successfully synthesized. The procedure for their simple isolation and purification, without the use of instrumental techniques, is also described. Among all, **3** and **4** are described for the first time. Compound **3** showed the most significant antioxidant activity in all applied methods based on the hydrogen atom and electron

transfer mechanism, while compounds **3** and **4** showed the most significant AChE inhibition compared to galantamine, which was used as a standard. Excluding compounds **1** and **4** that showed significant antibacterial activity against the gram-negative *P. aeruginosa* strain, all other tested compounds showed moderate or no antibacterial activity.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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References

[1] Alara, O. R.; Abdurahman, N. H.; Ukaegbu, C. I. Extraction of phenolic compounds: A review. *Curr. Res. Nutr. Food Sci*. **2021**, *4*, 200-214.
[2] Abbaszadeh, H.; Keikhaei, B.; Mottaghi, S. A review of molecular mechanisms involved in anticancer and antiangiogenic effects of natural polyphenolic compounds. *Phytother. Res.* **2019**, *33(8)*, 2002-2014.
[3] Bento-Silva, A.; Koistinen, V. M.; Mena, P.; Bronze, M. R.; Hanhineva, K.; Sahlstrøm, S.; Kitryte, V.; Moco, S.; Aura, A.M. Factors affecting intake, metabolism and health benefits of phenolic acids: do we understand individual variability?. *Eur. J. Nutr.* **2020**, *59*, 1275-1293.
[4] Kasprzak-Drozd, K.; Oniszczuk, T.; Stasiak, M.; Oniszczuk, A. Beneficial effects of phenolic compounds on gut microbiota and metabolic syndrome. *Int. J. Mol. Sci*. **2021**, *22(7)*, 1-24.
[5] Rocchetti, G.; Gregorio, R. P.; Lorenzo, J. M.; Barba, F. J.; Oliveira, P. G.; Prieto, M. A.; Simal-Gandara, J.; Mosele, J. I.; Motilva, M.; Tomas, M.; Patrone, V.; Capanoglu, E.; Lucini, L. Functional implications of bound phenolic compounds and phenolics-food interaction: A review. *Compr. Rev. Food Sci. Food Saf.* **2022**, *21(2)*, 811-842.
[6] Alibi, S.; Crespo, D.; Navas, J. Plant-derivatives small molecules with antibacterial activity. *Antibiot.* **2021**, *10(3)*, 231.
[7] Basyouni, W. M.; Abbas, S. Y.; El-Bayouki, K. A.; Daawod, R. M.; Elawady, M. K. Synthesis and antiviral evaluation of 5-(arylazo)salicylaldehyde thiosemicarbazone derivatives as potent anti-bovine viral diarrhea virus agents. *Synth. Commun.* **2021**, *51(14)*, 2168-2174.
[8] Qiu, Z.; Li, C. J. Transformations of less-activated phenols and phenol derivatives via C–O cleavage. *Chem. Rev.* **2020**, *120(18)*, 10454-10515.
[9] Kumar, B. K.; Sekhar, K. V. G. C.; Chander, S.; Kunjiappan, S.; Murugesan, S. Medicinal chemistry perspectives of 1,2,3,4-tetrahydroisoquinoline analogs-biological activities and SAR studies. *RSC Adv*. **2021**, *11(20)*, 12254-12287.
[10] Kim, A. N.; Ngamnithiporn, A.; Du, E.; Stoltz, B. M. Recent Advances in the total synthesis of the tetrahydroisoquinoline alkaloids (2002–2020). *Chem. Rev*. **2023**, *123(15)*, 9447-9496.
[11] Yang, Y.; Guo, J.; Liu, Z. Progress in the synthesis of analogues of bistetrahdroisoquinoline antitumor alkaloids. *Chin. J. Org. Chem*. **2019**, *39(7)*, 1913-1922.
[12] Pyne, M. E.; Martin, V. J. Microbial synthesis of natural, semisynthetic, and new-to-nature tetrahydroisoquinoline alkaloids. *Curr. Opin. Green Sustain. Chem*. **2022**, *33*, 1-9.
[13] Franco, R.; Reyes-Resina, I.; Navarro, G. Dopamine in health and disease: Much more than a neurotransmitter. *Biomedicines* **2021**, *9(2)*, 1-3.
[14] Mani, A.; Ahamed, A.; Ali, D.; Alarifi, S.; Akbar, I. Dopamine-mediated vanillin multicomponent derivative synthesis via grindstone method: Application of antioxidant, anti-tyrosinase, and cytotoxic activities. *Drug Des. Devel. Ther.* **2021**, *15*, 787-802.

[15] Bandala, C.; Cárdenas-Rodríguez, N.; Mendoza-Torreblanca, J. G.; Contreras-García, I. J.; Martínez-López, V.; Cruz-Hernández, T. R.; Carro-Rodríguez, J.; Vargas-Hernández, M. A.; Ignacio-Mejía, I.; Alfaro-Rodriguez, A.; Lara-Padilla, E. Therapeutic potential of dopamine and related drugs as anti-inflammatories and antioxidants in neuronal and non-neuronal pathologies. *Pharmaceutics* **2023**, *15(2)*, 1-26.

[16] Roddan, R.; Ward, J. M.; Keep, N. H.; Hailes, H. C. Pictet-Spenglerases in alkaloid biosynthesis: Future applications in biocatalysis. *Curr. Opin. Chem. Biol*. **2020**, *55*, 69-76.

[17] Whaley, W. M.; Govindachari, T. R. The Pictet-Spengler synthesis of tetrahydroisoquinolines and related compounds. *Org. React*. **2004**, *6*, 151-190.

[18] Cox, E. D.; Cook, J. M. The Pictet-Spengler condensation: a new direction for an old reaction. *Chem. Rev.* **1995**, *95*(*6*), 1797-1842.

[19] Pesnot, T.; Gershater, M. C.; Ward, J.M.; Hailes, H.C. Phosphate mediated biomimetic synthesis of tetrahydroisoquinoline alkaloids. *ChemComm*. **2011**, *47(11)*, 3242-3244.

[20] Zhao, J.; Méndez-Sánchez, D.; Ward, J. M.; Hailes, H. C. Biomimetic phosphate-catalyzed Pictet-Spengler reaction for the synthesis of 1,1′-disubstituted and spiro-tetrahydroisoquinoline alkaloids. *J. Org. Chem*. **2019**, *84(12)*, 7702-7710.

[21] Čulum, D.; Čopra-Janićijević, A.; Muratović, E.; Siljak-Yakovlev, S.; Maksimović, M.; Vidic, D. Essential oil composition and antioxidant activity of endemic *Achillea lingulata* Waldst. & Kit. compared to common *A. millefolium* L. *Rec. Nat. Prod*. **2021**, *16(4)*, 1-11.

[22] Ellman, G. L.; Courtney, K. D.; Andres, V.; Featherstone, R. M. A new and rapid colorimetric determination of acetylcholinesterase activity. *Biochem. Pharmacol.* **1961**, 7(2), 88-95.

[23] Trott, O.; Olson, A. J. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J. Comput. Chem*. **2010**, *31(2)*, 455-461.

[24] Valgas, C.; Souza, S. M. D.; Smânia, E. F.; Smânia, Jr. A. Screening methods to determine antibacterial activity of natural products. *Braz. J. Microbiol*. **2007**, *38*, 369-380.

[25] Farhoosh, R.; Johnny, S.; Asnaashari, M.; Molaahmadibahraseman, N.; Sharif, A. Structure-antioxidant activity relationships of *o*-hydroxyl, *o*-methoxy, and alkyl ester derivatives of *p*-hydroxybenzoic acid. *Food Chem*. **2016**, *194*, 128-134.

[26] Muñoz, P.; Huenchuguala, S.; Paris, I.; Segura-Aguilar, J. Dopamine oxidation and autophagy. *Parkinsons Dis*. **2012**, *2012*, 1-13.

[27] Csire, G.; Canabady-Rochelle, L.; Averlant-Petit, M. C.; Selmeczi, K.; Stefan, L. Both metal-chelating and free radical-scavenging synthetic pentapeptides as efficient inhibitors of reactive oxygen species generation. *Metallomics* **2020**, *12(8)*, 1220-1229.

[28] Roseiro, L. B.; Rauter, A. P.; Serralheiro, M. L. M. Polyphenols as acetylcholinesterase inhibitors: structural specificity and impact on human disease. *Nutr Aging*. **2012**, *1(2)*, 99-111.

[29] Samadi, A.; De Los Ríos, C.; Bolea, I.; Chioua, M.; Iriepa, I.; Moraleda, I.; Bartolini, M.; Andrisano, V.; Gálvez, E.; Valderas, C.; Unzeta, M.; Marco-Contelles, J. Multipotent MAO and cholinesterase inhibitors for the treatment of Alzheimer's disease: synthesis, pharmacological analysis and molecular modeling of heterocyclic substituted alkyl and cycloalkyl propargyl amine. *Eur. J. Med. Chem.* **2012**, *52*, 251-262.

[30] Mateev, E.; Kondeva-Burdina, M.; Georgieva, M.; Zlatkov, A. Repurposing of FDA-approved drugs as dual-acting MAO-B and AChE inhibitors against Alzheimer's disease: An *in silico* and *in vitro* study. *J. Mol. Graph. Model.* **2023,** *122*, 108471.

[31] Sağlık, B. N.; Levent, S.; Osmaniye, D.; Evren, A. E.; Karaduman, A. B.; Ozkay, Y.; Kaplancıklı, Z. A. Design, Synthesis, and *in vitro* and *in silico* approaches of novel indanone derivatives as multifunctional anti-Alzheimer agents. *ACS Omega* **2022**, *7(50)*, 47378-47404.