Trends in Peptide and Protein Sciences
Volume 7 (2022): e11

DOI: http://dx.doi.org/10.22037/tpps.v7i0.40074

Original Article

Electrosynthesis, *in Silico* Ligand-Protein Interaction and Pharmacokinetic Studies of Some Aryl Sulfone Derivatives as Potential Acetylcholinesterase Inhibitors

Omid Ghanbarzadeh[a], Farzad Kobarfard[a], Salimeh Amidi [a,b*]

[a] *Department of Medicinal Chemistry, Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*
[b] *Protein Technology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

Article history:
Received: 26 November 2022
Accepted: 21 December 2022

Keywords:
Acetylcholinesterase inhibitor
Aryl sulfone derivatives
Catechol
Molecular docking
Physicochemical properties

HIGHLIGHTS

- Aryl sulfone derivatives with catechol rings were synthesized by electrochemical method.
- Molecular docking studies of the compounds revealed good binding affinities against acetylcholinesterase.
- All of the synthesized compounds obey Lipinski's rule of five which suggests them as good oral drug candidates.

ABSTRACT

Acetylcholinesterase (AChE) is an enzyme that catalyzes the hydrolysis of acetylcholine. Acetylcholine plays an essential role in learning and memory. Since acetylcholine deficiency is related to the pathogenesis of Alzheimer's disease, obtaining acetylcholinesterase inhibitors is of great interest. Here, a group of aryl sulfone derivatives with a catechol ring was synthesized by the electrochemical method. The structure of compounds was confirmed by ^{1}HNMR and ESI-MS. Molecular docking studies of the synthesized compounds with AChE were performed and the results showed that all of the compounds have good theoretical affinities for the target enzyme, AChE. Moreover, the physicochemical properties and ADME parameters of synthesized compounds were predicted, which revealed that they have acceptable features as drug candidates.

Cite this article as: Ghanbarzadeh, O., Kobarfard, F. and S. Amidi, (2022). Electrosynthesis, *in silico* ligand-protein interaction and pharmacokinetic studies of some aryl sulfone derivatives as potential acetylcholinesterase inhibitors. *Trends Pept. Protein Sci.*, **7**: e11.

Introduction

About 55 million people suffer from dementia around the world according to World Health Organization (WHO) report. This number is estimated to reach 75 million by 2030. Alzheimer's disease (AD) is

O. Ghanbarzadeh: https://orcid.org/0000-0002-3663-9928
S. Amidi: https://orcid.org/0000-0002-6032-3237
*Corresponding Author:
Email: s.amidi@sbmu.ac.ir (S. Amidi)

responsible for 60-70% of all forms of dementia (WHO, 2017). Because of the complicated and unclear pathogenesis of AD, there are various hypotheses about AD such as the cholinergic neuron damage hypothesis, Tau hypothesis, amyloid β (Aβ) hypothesis, oxidative stress hypothesis, inflammation, etc. (Du et al., 2018; Pasieka et al., 2020), and these hypotheses are considered for the development of AD drugs. One of the most important hypotheses is the ‘‘cholinergic hypothesis”. Cholinergic neurons are the source of acetylcholine (Ach) and Ach activity is terminated by acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) which hydrolyzes Ach into choline and acetate. Because acetylcholine is involved in physiological processes, such as learning and memory, reducing acetylcholine levels as a result of neuronal damage can play a role in AD. Therefore, inhibition of acetylcholinesterase has been considered one of the treatment strategies for AD. Donepezil, rivastigmine, and galantamine are some of the currently FDA-approved AChE inhibitors used for the treatment of symptoms of AD (Du et al., 2018).

Aryl sulfones and sulfonamides are widely used as active molecules and they are considered important building blocks in medicinal chemistry (Wang et al., 2022). Aryl sulfones are found in the structure of some drugs, such as rofecoxib, the selective cyclooxygenase-2 (COX-2) inhibitor, and dapsone the antibacterial compound (Chen and Waser, 2015). A group of (*E*)-3,4-dihydroxystyryl alkyl sulfones were synthesized as compounds with antioxidant and anti-inflammatory activities, as well as, enhanced neuroprotective effects (Chen et al., 2019). Taha *et al.* reported the preparation and evaluation of indole-base sulfonamide analogs as AChE inhibitors (Taha et al., 2021). Soyer *et al.* synthesized a group of 4-phthalimidobenzenesulfonamide and evaluated their inhibitory potential against AChE and BuChE (Soyer et al., 2017). Moreover, sulfonylbis(acylhydrazones) have been synthesized and their anticholinesterase activity is reported by Ibrahim *et al.* (Ibrahim et al., 2022).

Quercetin is a flavonoid containing a catechol ring with high antioxidant properties. Several biological effects have been reported for quercetin, such as anti-inflammatory, anti-carcinogenic, and antiplatelet activities. The neuroprotective effects of quercetin have been disclosed in many studies (Khan et al., 2019). Since AD is also associated with oxidative processes, the inclusion of scaffolds with antioxidant properties in the design of anti-Alzheimer's compounds can be valuable.

The use of various electrochemical methods in the synthesis of organic compounds has been of great interest in recent decades (Möhle et al., 2018). Several studies on the electrochemical oxidation of catechol ring into *o*-quinone in presence of different nucleophiles are reported (Nematollahi and Rafiee, 2004; Motin et al., 2017; Kärkäs, 2018; Toghan et al., 2019). Therefore, in this study six aryl sulfone compounds containing a catechol ring were synthesized by electrochemical method (Fig. 1). The *in silico* studies and molecular docking of synthesized compounds were performed on AChE.

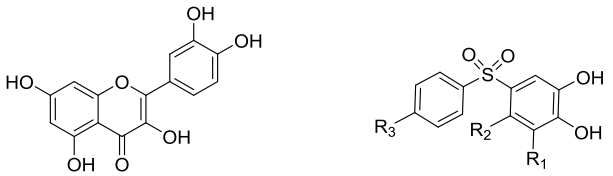

Figure 1. Chemical structures of quercetin and synthesized compounds.

Materials and Methods

Chemicals and instruments

All the chemicals and reagents were reagent-grade purchased from Merck and Sigma. Electrochemical synthesis of compounds was carried out using BHP2050 potentiostat/ galvanostat (Corrtest Instrument Corp., China) in the presence of Ag/AgCl/KCl (3M), platinum wire, and carbon rods (8 mm diameter and 6 cm length) as reference electrode, a counter electrode, and working electrode respectively. An Agilent 6410 triple quadrupole mass spectrometer (Agilent, USA) and spectrometer (400 MHz) (Bruker, USA) were used to prepare positive ESI-MS mass spectra and ^{1}HNMR spectra. IR spectra were obtained by IR spectrophotometer (PerkinElmer, USA) as KBr discs. An Electrothermal melting point apparatus was used to determine the melting points of the compounds.

General procedures for the electro-organic synthesis of 4a-4f

The electro-organic synthesis of compounds was performed according to previously reported methods (Nematollahi and Rahchamani, 2002a). Briefly, catechol derivatives (1 mmol) and sodium benzenesulfinate derivatives (1 mmol) were added to the electrochemical cell containing acetate buffer (c= 0.2 M, pH = 4.6) which was pre-electrolyzed at 0.5 V. The electrolysis process

was interrupted many times, when the current reached 5% of the starting value, to wash and reactivate the electrode. The precipitated products were filtered off and washed with water (Nematollahi and Rahchamani, 2002b).

Chemistry

- 4-(phenylsulfonyl) benzene-1,2-diol (*4a*) (Nematollahi and Rahchamani, 2002b; Habibi et al., 2017):

Yield: 85%; mp: 116-117°C; ^{1}H-NMR (DMSO-d6, δ, ppm): 10.13 (s, 1H, -OH), 9.76 (s, 1H, -OH),7.85 (d, J = 8 Hz, 2H, H-2' and H-6'), 7.57-7.67 (m, 3H, H-3', H-5' and H-6), 7.22-7.27 (m, 2H, H-2 and H-4'), 6.89 (d, J = 8Hz, 1H, H-5). ESI-MS (m/z): $[M+Na]^+$=273.

- 4-tosylbenzene-1,2-diol (*4b*) (Habibi et al., 2017):

Yield: 80%; mp: 100-102°C, ^{1}H-NMR (DMSO-d6, δ, ppm): 10.10 (s, 1H, -OH), 9.75 (s, 1H, -OH),7.72 (d, J = 8 Hz, 2H, H-2' and H-6'), 7.39 (d, J = 8 Hz, 2H, H-3'and H-5'), 7.20-7.24(m, 2H, H-2 and H-6), 6.88 (d, J =8 Hz, 1H, H-5), 2.35 (s, 3H, -CH3). ESI-MS (m/z): $[M+Na]^+$= 287, $[2M+Na]^+$=551.

- 3-methyl-5-(phenylsulfonyl) benzene-1,2-diol (*4c*) (Habibi et al., 2017):

Yield: 78%; mp: 164-166°C, ^{1}H-NMR (DMSO-d6, δ, ppm): 7.82 (d, J = 6.8 Hz, 2H, H-2' and H-6'), 7.55-7.62 (m, 3H, H-3', H-4'and H-5'), 7.13 (d, J = 1.6 Hz, 1H, H-6), 7.07 (d, J = 2 Hz, 1H, H-2), 2.11 (s, 3H, -CH3). ESI-MS (m/z): $[M+Na]^+$=287, $[2M+Na]^+$=551.

- 3-methyl-5-tosylbenzene-1,2-diol (*4d*) (Habibi et al., 2017):

Yield: 84%; mp: 141-143°C, ^{1}H-NMR (DMSO-d6, δ, ppm): 7.68 (d, J = 8.4 Hz, 2H, H-2' and H-6'), 7.35 (d, J = 8 Hz, 2H, H-3'and H-5'), 7.05(d, J = 1.6 Hz, 1H, H-6), 6.98 (d, J = 2 Hz, 1H, H-2), 2.34 (s, 3H, -CH3), 2.08 (s, 3H, -CH3). ESI-MS (m/z): $[M+Na]^+$=301, $[2M+Na]^+$=579.

- 4-methyl-5-(phenylsulfonyl) benzene-1,2-diol (*4e*)

Yield: 85%; mp: 117-119°C, ^{1}H-NMR (DMSO-d6, δ, ppm): 7.75 (d, J = 7.6 Hz, 2H, H-2' and H-6'), 7.67 (t, J = 8 Hz, 1H, H-4'), 7.58-7.61(m, 2H, H-3' and H-5'), 7.50 (s, 1H, H-6), 6.64 (s, 1H, H-3), 2.15 (s, 3H, -CH3). ESI-MS (m/z): $[M+H]^+$ =265, $[M+Na]^+$= 287, $[2M+Na]^+$=551.

- 4-methyl-5-tosylbenzene-1,2-diol (*4f*)

Yield: 81%; mp: 136-138°C, ^{1}H-NMR (DMSO-d6, δ, ppm): 8.32 (s, 2H, OH), 7.63 (d, J = 8 Hz, 2H, H-2' and H-6'), 7.47 (s, 1H, H-6),7.38(m, 2H, H-3' and H-5'), 6.62 (s, 1H, H-3), 2.36 (s, 3H, -CH3), 2.15 (s, 3H, -CH3). ESI-MS (m/z): $[M+Na]^+$ =301, $[2M+Na]^+$=579.

Ligand-protein interaction study

Hyperchem software was used for sketching and minimizing the structures of compounds Downloaded Acetylcholinesterase structure (PDB ID: IEVE) (Kryger et al., 1999) from the RCSB Protein Data Bank was prepared as a receptor according to protocols (Boittier et al., 2020), by AutoDockTools (Morris et al., 2009). Docking studies were performed by Autodock Vina. The center of the cocrystal ligand in the active site of IEVE was used as the center of the grid box with a dimension of 20 × 20 × 20 Å. Interactions of docked compounds with amino acids of the active site were studied by using Discovery Studio Visualizer Software (BIOVIA Dassault Systemes, 2016). The images were prepared by UCSF Chimera 1.16 (Pettersen et al., 2004).

In silico studies

The physicochemical properties of the compounds were calculated by SwissADME online tool (Daina et al., 2017) and DataWarrior v.4.5.1 software (Sander et al., 2015). Estimation of pharmacokinetic properties such as plasma protein binding (%) and human intestinal absorption (HIA, %) was done using the PreADMET online tool (https://preadmet.qsarhub.com/). The ability of a compound to cross the blood-brain barrier (BBB) was predicted by the BBB predictor using the support vector machine (SVM) (http://www.cbligand.org/BBB/) (Liu et al., 2014).

Results and Discussion

Electro-organic synthesis

The sulfone compounds (*4a-4f*) were synthesized by the reaction of catechol derivatives and benzenesulfinate via an electrochemical method (Fig. 2). In this reaction, catechol was oxidized to *o*-quinone, and as a Michael acceptor, it could be attacked by benzenesulfinate (Nematollahi and Rahchamani, 2002a). In the case of the synthesis of compounds with a methyl group at C-3 of the catechol ring (*4c* and *4d*), the ^{1}HNMR results showed two peaks at 6.98–7.13 ppm related to aromatic protons of the catechol ring. The coupling constant (*J*) of these peaks confirmed that the hydrogens of catechol rings were in meta position, so benzenesulfinate has attacked the carbon with less steric hindrance (C_β) (Fig. 3). This finding is consistent with the results reported in previous studies (Nematollahi and Rahchamani, 2002a; Habibi et al., 2017).

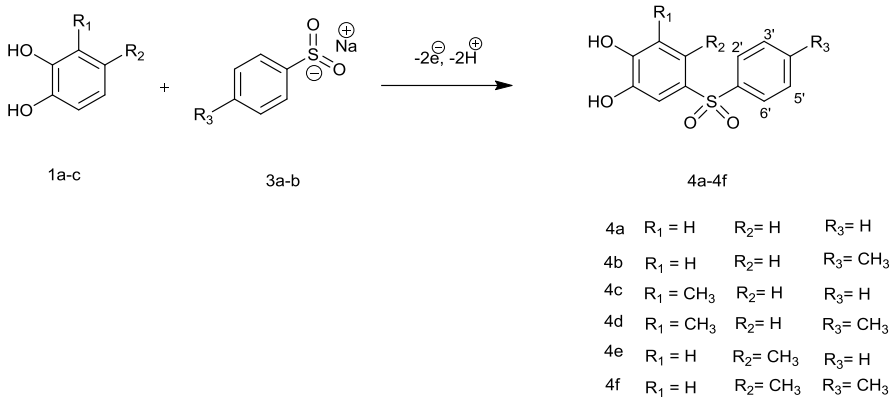

Figure 2. Synthesis route of compounds *4a-4f.*

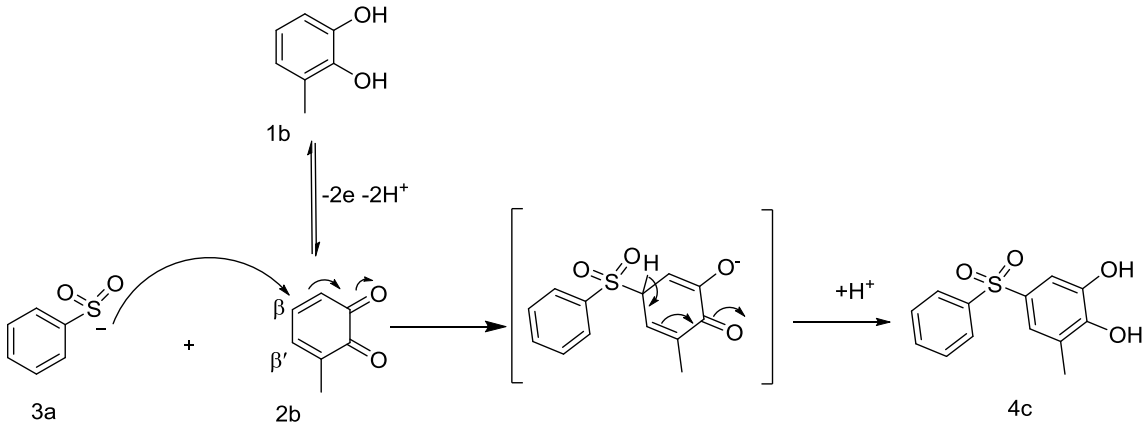

Figure 3. Proposed mechanism for the electrochemical oxidation of catechol in the presence of benzenesulfinate.

Ligand-protein interaction study

Molecular docking was used to predict the interaction of synthesized aryl sulfones in the active site of AChE. In this study, the crystal structure of AChE with donepezil (PDB ID: 1EVE) was used. First re-docking of native ligand was performed and the obtained RMSD value (0.270 Å) was within the acceptable criteria. Molecular docking results showed that all compounds have a docking affinity between -9.2 and -9.8 kcal/mol against AChE (PDB ID: 1EVE) and displayed hydrophobic interactions and hydrogen bonds with active site (Table 1). The standard drug donepezil showed a docking affinity value of -11.2 kcal/mol. The overlaid binding poses of *4a-4f* with donepezil are represented in Fig. 4a. The phenyl ring of compounds *4a-4f* showed interactions with common residues at the AChE active site such as Phe330 and Tyr334. The catechol ring of compounds *4a*, *4b*, *4c*, and *4d* formed π-π stacking interactions with Trp84. These amino acids represent interactions with donepezil. Compound *4d* with a lowest binding energy of -9.8 kcal/mol formed hydrogen bond with Tyr130 through OH of catechol ring (bond length of 2.33 Å). 4-methylphenyl moiety of compound *4d* formed hydrophobic interactions with Phe330, Phe331 and Tyr334. The ligand interaction of the best docking poses of compound *4d* at the active site of the AChE is represented in Fig. 4b. The obtained protein-ligand interactions are consistent with the docking results obtained from previously reported studies (Akrami et al., 2014; Yusufzai et al., 2018).

Table 1. Binding affinity values and physicochemical properties of aryl sulfone derivatives.

Compounds	Binding affinity (kcal/mol)	Molecular Formula	Lipinski's rule of five (Ro5)				Veber's rule	
			MW[a]	nHBD[b]	nHBA[c]	cLog P	TPSA[d] (A^{o2})	nRB[e]
4a	-9.2	$C_{12}H_{10}O_4S$	250.27	2	4	1.67	82.98	2
4b	-9.5	$C_{13}H_{12}O_4S$	264.3	2	4	2.01	82.98	2
4c	-9.5	$C_{13}H_{12}O_4S$	264.3	2	4	2.01	82.98	2
4d	-9.8	$C_{14}H_{14}O_4S$	278.32	2	4	2.36	82.98	2
4e	-9.3	$C_{13}H_{12}O_4S$	264.3	2	4	2.01	82.98	2
4f	-9.6	$C_{14}H_{14}O_4S$	278.32	2	4	2.36	82.98	2
donepezil	-11.2	$C_{24}H_{29}NO_3$	379.49	0	4	4.21	38.77	6
Acceptable according to rules			≤500	≤5	≤10	≤5	≤140	≤10

[a] Molecular weight, [b] number of hydrogen bond donors, [c] number of hydrogen bond acceptors, [d] total polar surface area, [e] number of rotatable bonds.

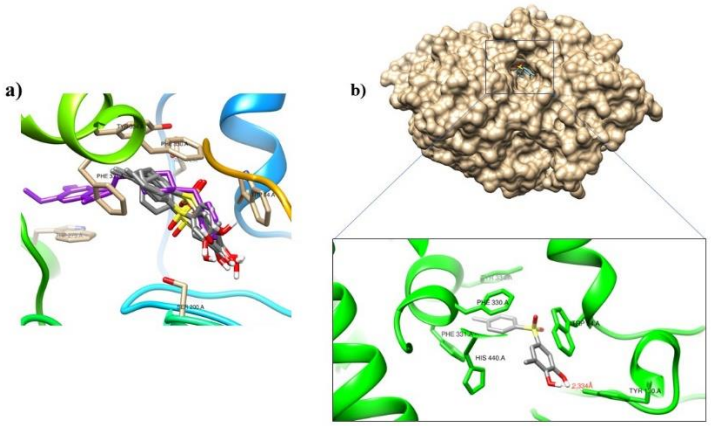

Figure 4. a) Best docking pose of compounds *4a-4f* superimposed on ligand donepezil (purple). b) Interactions of compound *4d* (in gray) with 1EVE (in green). Hydrogen bond is displayed with orange dashed line.

Prediction of physicochemical and pharmacokinetic properties

The calculated physicochemical properties of six aryl sulfone derivatives represented in Table 1, showed no violation of Lipinski's rule of 5 (Ro5) (Lipinski, 2004) and Veber's rules (Veber et al., 2002). Therefore, it is suggested that these compounds would be considered orally active drug candidates. The cLop P values of compounds were within the range of 1.67 to 2.36.

To predict the *in silico* pharmacokinetic properties of the compounds, the aryl sulfone derivatives (*4a-4f*) were screened using an online PreADMET server (https://preadmet.qsarhub.com/) and compared with donepezil (Table 2). Since blood-brain barrier (BBB) permeability is an important factor in the development of neurotherapeutic drugs, this parameter was calculated through an online BBB predictor (Liu et al., 2014).

According to predicted pharmacokinetic parameters, all the compounds showed good human intestinal absorption (93%) this value was 97% for donepezil. All compounds showed strong plasma protein binding (85-95%) compared to 84.61% for donepezil. Based on the obtained results all the synthesized derivatives could inhibit CYP2C9 and CYP3A4. Donepezil did not show any inhibitory effect on CYP2C9 but showed an inhibitory effect on CYP2D6. None of the compounds (*4a-4f*) inhibited glycoprotein, while donepezil was able to inhibit P-glycoprotein (P-gp). All derivatives (*4a-4f*) and donepezil could cross BBB. Regarding the predicted pharmacokinetic parameters of compounds, it could be concluded that derivatives (*4a-4f*) have good pharmacokinetic properties (Lamie et al., 2022; Mahmoud et al., 2022).

Table 2. *In silico* ADME properties of aryl sulfone derivatives.

Properties	Compounds						
	4a	4b	4c	4d	4e	4f	donepezil
HIA(%)[a]	93.52	93.67	93.67	93.79	93.67	93.79	97.95
PPB (%)[b]	89.55	95.08	86.91	92.00	86.53	91.51	84.61
Cross the BBB[c]	+	+	+	+	+	+	+
CYP2C19 inhibition	Non	Non	Non	Non	Non	Non	Non
CYP2C9 inhibition	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Non
CYP2D6 inhibition	Non	Non	Non	Non	Non	Non	Inhibitor
CYP2D6 substrate	Non	Non	Non	Non	Non	Non	Substrate
CYP3A4 inhibition	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Weakly
CYP3A4 substrate	Non	Non	Non	Non	Non	Weakly	Substrate
P-gp inhibition	Non	Non	Non	Non	Non	Non	Inhibitor

[a] Human intestinal absorption, [b] plasma protein binding, [c] blood-brain barrier.

Conclusion

In this study, a group of aryl sulfones with catechol rings were synthesized by electrochemical method. The molecular docking study of the synthesized compounds was performed and all compounds exhibited promising binding affinities. Compound *4d* showed the best binding affinity with AChE. The results of the i*n silico* physicochemical properties and ADME studies showed that all compounds have high intestinal absorption and no inhibitory effect of CYP2D6 and CYP2C19. The compounds may have good oral bioavailability according to Lipinski's rule of five. However, *in vitro* and *in vivo* studies are required to determine the AChE inhibitory activity of the compounds.

Competing Interests

The authors declare no conflict of interest.

Ethical Statement

This study did not contain any animal or human studies. This work was approved by the Ethical Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (approval code: IR.SBMU.PHARMACY.REC.1399.222).

Funding

This project was supported by the Protein Technology Research Center, Shahid Beheshti University of Medical Sciences, which provided the funding for this research (Grant # 25404).

Authors' Contribution

F. Kobarfard supervised the project and edited the manuscript. S. Amidi developed the idea, analyzed the results, and prepared the manuscript. O. Ghanbarzadeh carried out the experiments.

References

Akrami, H, Mirjalili B.F., Khoobi M., Nadri H., Moradi A., Sakhteman A,. Emami S., Foroumadi A. and A. Shafiee, (2014). ″Indolinone-based acetylcholinesterase inhibitors: Synthesis, biological activity and molecular modeling.″ *European Journal of Medicinal Chemistry*, **84**, 375–381. DOI: https://doi.org/10.1016/j.ejmech.2014.01.017.

BIOVIA Dassault Systèmes. Discovery Studio Visulaizer, v4.5.0.15071, San Diego: Dassault Systèmes, CA, USA: 2016.

Boittier, E.D., Tang, Y.Y., Buckley, M.E., Schuurs, Z.P., Richard, D.J. and N.S. Gandhi, (2020). "Assessing molecular docking tools to guide targeted drug discovery of CD38 inhibitors." *International Journal of Molecular Sciences*, **21**(15): 5183. DOI: https://doi.org/10.3390/ijms21155183.

Chen, C.C. and J. Waser, (2015). "One-Pot, three-component arylalkynyl sulfone synthesis." *Organic Letters*, **17**(3): 736–739. DOI: https://doi.org/10.1021/acs.orglett.5b00015.

Chen, Y., Wu, B., Hao, Y., Liu, Y., Zhang, Z., Tian, C., Ning, X., Guo, Y., Liu, J. and X. Wang, (2019). "Structure-activity relationship studies of (E)-3,4-dihydroxystyryl alkyl sulfones as novel neuroprotective agents based on improved antioxidant, anti-inflammatory activities and BBB permeability." *European Journal of Medicinal Chemistry*, **171**: 420–433. DOI: https://doi.org/10.1016/j.ejmech.2019.03.044.

Daina, A., Michielin, O. and V. Zoete, (2017). "SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules." *Scientific Reports*, **7**(1): 42717. DOI: https://doi.org/10.1038/srep42717.

Du, X., Wang, X. and M. Geng, (2018). "Alzheimer's disease hypothesis and related therapies." *Translational Neurodegeneration*, **7**(1): 2. DOI: https://doi.org/10.1186/s40035-018-0107-y.

Habibi, D., Rahimi, A., Rostami, A. and S. Moradi, (2017). "Green and mild laccase-catalyzed aerobic oxidative coupling of benzenediol

derivatives with various sodium benzenesulfinates." *Tetrahedron Letters*, **58**(4): 289–293. DOI: https://doi.org/10.1016/j.tetlet.2016.11.119.

Ibrahim, M., Latif, A., Ahmad, M., Ahmad, S., Ali, A., Siddique, A.B., Saadiq, M., Akbar, N., Farooq, U., Khan, A., Al-Harrasi, A. and M. Ali, , (2022). "Sulfonylbis(acylhydrazones) as anticholinesterase inhibitors: Synthesis, in vitro biological evaluation and computational studies." *Journal of Molecular Structure*, **1252**: 132215. DOI: https://doi.org/10.1016/j.molstruc.2021.132215.

Kärkäs, M.D. (2018). "Electrochemical strategies for C–H functionalization and C–N bond formation." *Chemical Society Reviews*, **47**(15): 5786–5865. DOI: https://doi.org/10.1039/C7CS00619E.

Khan, H., Ullah, H., Aschner, M., Cheang, W.S. and E.K. Akkol, (2019). "Neuroprotective effects of quercetin in alzheimer's disease." *Biomolecules*, **10**(1): 59. DOI: https://doi.org/10.3390/biom10010059.

Kryger, G., Silman, I. and J.L. Sussman, (1999). "Structure of acetylcholinesterase complexed with E2020 (Aricept®): implications for the design of new anti-Alzheimer drugs." *Structure*, **7**(3): 297–307. DOI: https://doi.org/10.1016/S0969-2126(99)80040-9.

Lamie P.F., Abdel-Fattah M.M. and J.N. Philoppes, (2022). ″Design and synthesis of new indole drug candidates to treat Alzheimer's disease and targeting neuro-inflammation using a multi-target-directed ligand (MTDL) strategy.″ *Journal of Enzyme Inhibition and Medicinal Chemistry*, **37**(1): 2660–78. DOI: https://doi.org/10.1080/14756366.2022.2126464.

Lipinski, C.A. (2004). "Lead- and drug-like compounds: the rule-of-five revolution." *Drug Discovery Today: Technologies*, **1**(4): 337–341. DOI: https://doi.org/10.1016/j.ddtec.2004.11.007.

Liu, H., Wang, L., Lv, M., Pei, R., Li, P., Pei, Z., Wang, Y., Su, W. and Xie, X.-Q., (2014). "AlzPlatform: An alzheimer's disease domain-specific chemogenomics knowledgebase for polypharmacology and target identification research." *Journal of Chemical Information and Modeling*, **54**(4): 1050–1060. DOI: https://doi.org/10.1021/ci500004h.

Mahmoud Z., Sayed H.S., Mohamed L.W. and K.M. Mohamed, (2022). ″Development of new donepezil analogs: synthesis, biological screening and in silico study rational.″ *Medicinal Chemistry Research*, **31**(10): 1754–1770. DOI: https://doi.org/10.1007/s00044-022-02941-8.

Möhle, S., Zirbes, M., Rodrigo, E., Gieshoff, T., Wiebe, A. and S.R. Waldvogel, (2018). "Modern electrochemical aspects for the synthesis of value-added organic products." *Angewandte Chemie International Edition*, **57**(21): 6018–6041. DOI: https://doi.org/10.1002/anie.201712732.

Morris, G.M., Huey, R., Lindstrom, W., Sanner, M.F., Belew, R.K., Goodsell, D.S. and A.J. Olson, (2009)."AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility." *Journal of Computational Chemistry*, **30**(16): 2785–2791. DOI: https://doi.org/10.1002/jcc.21256.

Motin, M.A., Uddin, M.A., Dhar, P.K., Mia, M.A.H. and M.A. Hashem, (2017). "Study of electrochemical oxidation of catechol in the presence of sulfanilic acid at different pH." *Portugaliae Electrochimica Acta*, **35**(2): 103–116. DOI: https://doi.org/10.4152/pea.201702103.

Nematollahi, D. and M. Rafiee, (2004). "Electrochemical oxidation of catechols in the presence of acetylacetone." *Journal of Electroanalytical Chemistry*, **566**(1): 31–37. DOI: https://doi.org/10.1016/j.jelechem.2003.10.044.

Nematollahi, D. and R. Rahchamani, (2002a). "Electrochemical synthesis of p-tolylsulfonylbenzenediols." *Tetrahedron Letters*, **43**(1): 147–150. DOI: https://doi.org/10.1016/S0040-4039(01)02050-0.

Nematollahi, D. and R. Rahchamani, (2002b). "Electro-oxidation of catechols in the presence of benzenesulfinic acid. Application to electro-organic synthesis of new sulfone derivatives." *Journal of Electroanalytical Chemistry*, **520**(1–2): 145–149. DOI: https://doi.org/10.1016/S0022-0728(02)00654-X.

Pasieka, A., Panek, D. and B. Malawska, (2020). "Multifunctional Ligand Approach: Search for Effective Therapy Against Alzheimer's Disease. In: X. Huang (Ed.), *Alzheimer's Disease: Drug Discovery*. Exon Publications. pp.181–203. DOI: https://doi.org/10.36255/exonpublications.alzheimersdisease.2020.ch11.

Pettersen, E.F., Goddard, T.D., Huang, C.C., Couch, G.S., Greenblatt, D.M., Meng, E.C. and T.E. Ferrin, (2004). "UCSF Chimera--A visualization system for exploratory research and analysis." *Journal of Computational Chemistry*, **25**(13): 1605–1612. DOI: https://doi.org/10.1002/jcc.20084.

Sander, T., Freyss, J., von Korff, M. and C. Rufener, (2015). "DataWarrior: An Open-source program for chemistry aware data visualization and analysis." *Journal of Chemical Information and Modeling*, **55**(2): 460–473. DOI: https://doi.org/10.1021/ci500588j.

Soyer, Z., Uysal, S., Parlar, S., Tarikogullari Dogan, A.H. and V. Alptuzun, (2017). "Synthesis and molecular docking studies of some 4-phthalimidobenzenesulfonamide derivatives as acetylcholinesterase and butyrylcholinesterase inhibitors." *Journal of Enzyme Inhibition and Medicinal Chemistry*, **32**(1): 13–19. DOI: https://doi.org/10.1080/14756366.2016.1226298.

Taha, M., Alshamrani, F.J., Rahim, F., Anouar, E.H., Uddin, N., Chigurupati, S., Almandil, N.B., Farooq, R.K., Iqbal, N., Aldubayan, M., Venugopal, V. and K.M. Khan, (2021). "Synthesis, characterization, biological evaluation, and kinetic study of indole base sulfonamide derivatives as acetylcholinesterase inhibitors in search of potent anti-Alzheimer agent". *Journal of King Saud University - Science*, **33**(3): 101401. DOI: https://doi.org/10.1016/j.jksus.2021.101401.

Toghan, A., Abo-Bakr, A.M., Rageh, H.M. and M. Abd-Elsabour, (2019). "Green electrochemical strategy for one-step synthesis of new catechol derivatives." *RSC Advances*, **9**(23): 13145–13152. DOI: https://doi.org/10.1039/C9RA01206K.

Veber, D.F., Johnson, S.R., Cheng, H.-Y., Smith, B.R., Ward, K.W. and K.D. Kopple, (2002). "Molecular properties that influence the oral bioavailability of drug candidates." *Journal of Medicinal Chemistry*, **45**(12): 2615–2623. DOI: https://doi.org/10.1021/jm020017n.

Wang, Y., Chang, W., Qin, S., Ang, H., Ma, J., Lu, S. and Y. Liang, (2022). "Diversification of aryl sulfonyl compounds through ligand-controlled meta - and para -C−H borylation." *Angewandte Chemie International Edition*, **61**(34): 1-10. DOI: https://doi.org/10.1002/anie.202206797.

World Health Organisation. (2017). "Global action plan on the public health response to dementia." 2017–2025. Retrieved form https://www.who.int/publications-detail-redirect/global-action-plan-on-the-public-health-response-to-dementia-2017---2025.

Yusufzai S.K, Khan M.S., Sulaiman O., Osman H. and D.N. Lamjin, (2018) "Molecular docking studies of coumarin hybrids as potential acetylcholinesterase, butyrylcholinesterase, monoamine oxidase A/B and β-amyloid inhibitors for Alzheimer's disease." *Chemistry Central Journal*, **12**(1): 128. DOI: https://doi.org/10.1186/s13065-018-0497-z.

