Since 1987
REVIEW OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS, INTERNATIONAL EDITION | 38 (Sup2): 47-50 (2024) Rcpp

Received: 22 January 2024 | **Accepted**: 5 February 2024 | **Published**: 5 May 2024

Open Access | Research

Theoretical calculations and molecular design of novel dioxoisoindoline derivatives as anticonvulsant agents

Rawaa Mohammed Ahmed[1], Mohammed Oday Ezzat[2,*]

[1]Department of Chemistry, College of Education for Pure Sciences, University of Anbar, Ramadi, Anbar, Iraq
[2]Department of Chemistry, College of Education for Women, University of Anbar, Ramadi, Anbar, Iraq

***Corresponding author:** Mohammed Oday Ezzat, Department of Chemistry, College of Education for Women, University of Anbar, Ramadi, Anbar, Iraq; Tel.: +964-(0)7733760080
E-mail: edw.mohamed-oday@uoanbar.edu.iq

Abstract

Our study discusses the need for the development of alternative treatments for antiepileptic drugs. It proposes a theoretical chemical study using dioxoisoindoline derivatives and molecular docking in order to find potential alternative drugs. Three compounds (S1, S3, and S4) exhibited distinct activity against specific proteins related to epilepsy treatment. Our study also describes a DFT study that analysed the energy levels of the derivatives. Furthermore, we employed Lipinski's rule and drug likeness predictions in order to assess the suitability of the derivatives as medicines. The results indicate that the molecular mass, log P, hydrogen bonding donors, and acceptors of the compounds fall within acceptable ranges. Overall, our study emphasizes the importance of finding new treatments for epilepsy, and presents a preliminary investigation into the potential of dioxoisoindoline derivatives.

KEYWORDS

dioxoisoindoline derivatives, anticonvulsant, molecular docking, DFT study, ADME

How to cite: Ahmed R. M., Ezzat M. O. Theoretical calculations and molecular design of novel dioxoisoindoline derivatives as anticonvulsant agents. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed.* 38 (Sup2): 47-50 (2024).
https://doi.org/10.61873/ANKG7670

Publisher note: PHARMAKON-Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. INTRODUCTION

Epilepsy is a neurological condition that is marked by rapid, irregular, or excessive neuronal excitation in the grey matter of the brain due to the brain's high excitability, and manifests symptomatically as seizures [1]. Epileptic seizures arise due to an imbalance between excitatory and inhibitory neurotransmitters in the brain. The excessive neuronal firing results from functional issues caused by macromolecules involved in excitatory and inhibitory communications, leading to the development of epilepsy [2]. Neuronal membrane and molecular channel alterations in ionic conduction are another mechanism [3]. The membrane potential is typically polarized and maintained by ion pumps and channels. When the membrane depolarizes, it creates an action potential that stimulates muscle cells. Neurotransmitters at the axon tip transmit this action potential to the next cell, thereby leading to neuronal activation. After depolarization, the membrane hyperpolarizes, reaching a voltage

lower than the resting potential [4]. In a healthy neural tissue, this is a reaction that prevents excessive excitability brought on by repeated firings, and the membrane quickly returns to the resting phase (polarization). As a result, repeated synchronized sub-threshold excitatory stimuli, increased excitatory synaptic neurotransmission, reduced inhibitory synaptic neurotransmission, a change in ion concentration on both sides of the membrane, or severe excitability occur [5].

While there are many effective drugs available for the treatment of epilepsy, some of them have toxic side effects and can interact with other medications. As a result, there is still a demand for new antiepileptic drugs that can better manage seizures without these drawbacks. Quantitative structure-activity relationship methods (QSAR and 3D-QSAR) have been widely employed in the design and effectiveness of novel compounds as well as in resolving the mechanisms of action of existing antiepileptic drugs. These methods support the identification of novel compounds with lower side-effect profiles as well as the prediction and enhancement of the activities of various compounds [6,7]. In this study, six dioxoisoindoline derivatives were designed and evaluated as potential alternative drugs for epilepsy. The study aimed to determine if these derivatives have a strong binding affinity (ΔG) with specific proteins in the brain. This research is part of an ongoing investigation into the synthesis of novel dioxoisoindolines with potential anticonvulsant activity.

2. MATERIALS AND METHODS

The online application SwissDock was utilized in order to predict the potential molecular interactions between a target protein and a small molecule. The proteins 1OHV (4-aminobutyrate-aminotransferase; from pig), 3F8E (coumarins as suicide carbonic anhydrase inhibitors), and 6KZP (calcium channel-ligand) were docked with six dioxoisoindoline derivatives proposed for the protein active site. In ChemOffice (ChemDraw version 20.0), the chemical structures were designed with the appropriate 2D orientation. MM2 energy minimization was performed for each structure so as to estimate the potential energy surface, including factors such as steric energy and thermal energy. The resulting conformations of the models were obtained [8]. Theory at the molecular level was employed. The energy-minimized ligand molecules were then treated with quantum mechanics using the B3LYP/6-31G++ (d,p) level of theory for frequency calculation and geometry optimization. The assessed compounds of residues ARG_{192}, GLY_{191}, HIS_{190}, PHE_{189}, ASN_{140}, GLU_{265}, *etc*. in the case of 1OHV, of residues PHE_{131}, THR_{200}, ASN_{62}, TRP_{5}, HIE_{64}, HIS_{94}, *etc*. in the case of 3F8E, and of residues ILE_{379}, LEU_{353}, SER_{383}, PHE_{384}, THR_{1777}, and GLN_{1816} in the case of 6KZP (Table 1). The three most prevalent interactions (between the assessed proteins and the assessed compounds) with residue involvement were chelation bonding, H-bonding, and pi–pi stacking. SwissDock was fed the density-functional theory (DFT)-optimized structures as input. The receptor molecule's crystal structures were obtained from the Protein Data Bank.

3. RESULTS AND DISCUSSION

Molecular docking: A molecular modelling theory called "docking" describes how two or more ligands and proteins fit into one another; it is determined by "ΔG". A greater negative ΔG indicates a better fit between the chemical compound and the protein [9]. Our study employed the molecular level theory and quantum mechanics calculations in order to analyse the interaction of various compounds with proteins involved in anticonvulsant activity. The compounds S3, S1, and S4 showed promising anticonvulsant action (Table 1). Compound S3 exhibited the highest affinity for the protein 1OHV, with a ΔG value of -4.833, while compound S1 had the highest association with the protein 3F8E (ΔG=-3.817) and compound S4 showed the strongest interaction with the protein 6KZP (ΔG=-6.665). Furthermore, it was found that ligand PLP (pyridoxal 5-phosphate) had the strongest affinity with the protein 1OHV (ΔG=-6.773), ligand TE1 had the highest association with the protein 3F8E (ΔG=-5.417), and ligand PLP showed the strongest interaction with the protein 6KZP (ΔG=-6.709). These ligands exhibited higher ΔG values than any of the compounds, thereby indicating their potential as effective drugs across a wider range of compounds. In conclusion, compound S3, with its interaction with protein 1OHV, showed the most promising anticonvulsant activity, while compounds S1 and S4, interacting with proteins 3F8E and 6KZP, respectively, also exhibited potential. Ligands PLP, TE1, and PLP were identified as the most effective ligands for the respective proteins. These findings suggest that these compounds and ligands may serve as potential candidates for the development of anticonvulsant drugs.

DFT analysis: Highest occupied molecular orbitals HOMOs) are the highest in DFT; an atomistic (simulation that calculates a variety of significant features. The least unoccupied molecular orbitals (LUMOs) are the next highest energy orbitals that are empty, while the HOMO–LUMO gap is their

Table 1. Binding affinity (ΔG) and 1OHV, 3F8E, and 6KZP protein residues surrounding the assessed compounds. Amino-acid abbreviations used: ALA, alanine; ARG, arginine; ASN, asparagine; ASP, aspartic acid; CYS, cysteine; GLU, glutamic acid; GLN, glutamine; GLY, glycine; HIE, histidine with hydrogen on the epsilon nitrogen; HIS, histidine; ILE, isoleucine; LEU, leucine; LYS, lysine; MET, methionine; PHE, phenylalanine; PRO, proline; SER, serine; THR, threonine; TRP, tryptophan; TYR, tyrosine; VAL, valine.

Compound	ΔG	1OHV protein residues surrounding the compounds	Residues with interferences
S1	-4.402	ARG_{192}, GLY_{191}, GLY_{136}, HIS_{190}, PHE_{189}, ASP_{298}, GLU_{265}, GLU_{270}, VAL_{300}, GLN_{301}, ASN_{140}, SER_{137}, SER_{269}, SER_{328}, CYS_{135}, LYS_{329}	GLU_{265}, GLY_{136} (H-bonding); PHE_{189} (pi–pi stacking)
S2	-3.703	ARG_{192}, GLY_{191}, GLY_{136}, HIS_{190}, PHE_{189}, GLN_{301}, VAL_{300}, ASP_{298}, GLU_{270}, GLU_{265}, SER_{269}, SER_{137}, SER_{328}, ASN_{140}, CYS_{135}, LYS_{329}	GLY_{136} (H-bonding); PHE_{189} (pi–pi stacking)
S3	-4.833	ARG_{192}, GLY_{191}, GLY_{136}, HIS_{190}, PHE_{189}, ASN_{140}, SER_{137}, SER_{269}, GLY_{136}, CYS_{135}, GLU_{265}, ASP_{298}, VAL_{300}, GLN_{301}, LYS_{329}	SER_{137} (H-bonding); PHE_{189} (pi–pi stacking)
S4	-3.866	PRO_{76}, ILE_{75}, SER_{74}, SER_{328}, SER_{137}, LYS_{360}, LYS_{329}, MET_{332}, CYS_{135}, GLY_{136}, GLY_{191}, PHE_{189}, ARG_{192}, VAL_{300}	LYS_{329}, SER_{328}, GLY_{136} (H-bonding)
S5	-2.491	ARG_{192}, GLY_{191}, GLY_{136}, HIS_{190}, PHE_{189}, GLU_{270}, GLU_{265}, GLU_{299}, SER_{269}, SER_{328}, SER_{137}, ASP_{298}, VAL_{300}, GLN_{301}, THR_{302}, ASN_{140}, CYS_{135}, LYS_{329}	GLY_{136} (H-bonding); PHE_{189} (pi–pi stacking)
S6	-4.164	ARG_{192}, GLY_{191}, GLY_{136}, HIS_{190}, PHE_{189}, GLN_{301}, VAL_{300}, GLU_{265}, GLU_{270}, ASP_{298}, ASN_{140}, SER_{137}, SER_{269}, SER_{328}, CYS_{135}, LYS_{329}	GLU_{265}, GLY_{136} (H-bonding); PHE_{189} (pi–pi stacking)
Compound	**ΔG**	**3F8E protein residues surrounding the compounds**	**Residues with interferences**
S1	-3.817	ASP_{72}, GLU_{69}, ASN_{67}, ASN_{62}, ILE_{91}, GLN_{92}, HIS_{94}, HIE_{64}, TRP_{5}, THR_{200}, PHE_{131}	THR_{200}, HIE_{64} (H-bonding)
S2	-3.164	ARG_{58}, GLU_{69}, ASN_{67}, ASN_{62}, HIE_{64}, THR_{200}, PRO_{201}, TRP_{5}, HIS_{94}, GLN_{92}, ILE_{91}	GLU_{69}, H_2O (H-bonding)
S3	-3.15	PRO_{202}, PRO_{201}, THR_{200}, ASN_{62}, ASN_{67}, HIE_{64}, TRP_{5}, GLU_{69}, PHE_{70}, PHE_{131}, ILE_{91}, GLN_{92}, LEU_{57}	H_2O (H-bonding)
S4	-3.099	PRO_{202}, PRO_{201}, THR_{200}, TRP_{5}, ASN_{62}, ASN_{67}, HIE_{64}, ILE_{91}, GLN_{92}, GLU_{69}, PHE_{70}, PHE_{131}, ASP_{71}, ASP_{72}, LEU_{57}	GLU_{69}, H_2O (H-bonding)
S5	-3.422	LEU_{57}, ASP_{72}, ASP_{71}, PHE_{70}, GLU_{69}, ASN_{67}, ASN_{62}, HIE_{64}, TRP_{5}, THR_{200}, PRO_{201}, ILE_{91}, GLN_{92}	
S6	-3.586	ARG_{58}, GLU_{69}, ASN_{67}, ASN_{62}, GLN_{92}, ILE_{91}, HIE_{64}, TRP_{5}, THR_{200}, PRO_{201}	PRO_{201}, H_2O (H-bonding)
Compound	**ΔG**	**6KZP protein residues surrounding the compounds**	**Residues with interferences**
S1	-6.389	LEU_{1499}, LEU_{872}, LEU_{920}, PHE_{868}, PHE_{956}, PHE_{917}, ASN_{952}, THR_{921}, THR_{352}, GLN_{922}, LYS_{1462}	ASN_{952}, LEU_{920}, LYS_{1462}, GLN_{922} (H-bonding)
S2	-5.546	PHE_{917}, PHE_{956}, LEU_{920}, LEU_{1499}, LEU_{872}, LEU_{391}, ILE_{876}, ILE_{387}, THR_{921}, GLN_{922}, LYS_{1462}, ASN_{388}, ASN_{952}, TYR_{953}, GLY_{951}	LYS_{1462}, ASN_{952} (H-bonding)
S3	-5.963	PHE_{917}, PHE_{956}, LEU_{920}, LEU_{1499}, LEU_{872}, LEU_{391}, ILE_{876}, ILE_{387}, LYS_{1462}, THR_{921}, GLN_{922}, ASN_{388}, ASN_{957}, ASN_{952}, TYR_{953}, GLY_{951}	LYS_{1462}, ASN_{952} (H-bonding); PHE_{956} (pi–pi stacking)
S4	-6.665	ILE_{379}, LEU_{353}, LEU_{1819}, LEU_{391}, LEU_{1506}, SER_{383}, SER_{1776}, GLN_{1816}, VAL_{1820}, VAL_{1823}, VAL_{1505}, VAL_{960}, PHE_{1509}, PHE_{956}, PHE_{384}, ASN_{388}, THR_{1777}	ASN_{388}, GLN_{1816} (H-bonding); PHE_{384} (pi–pi stacking)
S5	-6.212	ILE_{387}, ILE_{876}, GLN_{922}, THR_{921}, LYS_{1462}, LEU_{920}, LEU_{1499}, LEU_{872}, ALA_{1502}, PHE_{917}, PHE_{956}, TYR_{953}, ASN_{952}	LYS_{1462}, LEU_{920}, ASN_{952} (H-bonding)
S6	-6.051	ILE_{876}, ILE_{387}, LEU_{872}, LEU_{1499}, LEU_{920}, PHE_{917}, PHE_{956}, LYS_{1462}, THR_{921}, GLN_{922}, TYR_{953}, ASN_{952}, GLY_{951}	LEU_{920}, LYS_{1462}, ASN_{952} (H-bonding); PHE_{956} (pi–pi stacking)

energy difference. According to the simulation, the LUMO, HOMO, and their gap values can define the inclination of molecules to act as bases as opposed to acids. Due to the molecules' high kinetic activity but low stability, the HOMO values of all compounds ranged from -0.227 to -0.199 eV, the LUMO values ranged from -0.092 to -0.087 eV, and the HOMO–LUMO gap values ranged from -0.135 to -0.112 eV. These features were employed in equations that allowed us to identify many molecular properties such the ionization potential (I) and the electron affinity (EA). The values of the studied compounds ranged from 0.199 to 0.227 in the case of their I, and from 0.087 to 0.092 in the case of their EA. Their electronegativity (μ) ranged from 0.143 to 0.159, their softness (S) ranged from 14.81 to 17.85, and their hardness (η) ranged from 0.056 to 0.067.

ACKNOWLEDGEMENTS
The authors are thankful to the University of Anbar for providing the necessary facilities for conducting this research.

CONFLICT OF INTEREST STATEMENT
The authors declare no conflicts of interest.

REFERENCES

1. Perucca P., Bahlo M., Berkovic S.F: The genetics of epilepsy. *Annu. Rev. Genomics Hum. Genet.* 21: 205-230 (2020).
DOI: **10.1146/annurev-genom-120219-074937**
PMID: **32339036**

2. Yuan X., Fu Z., Ji P., Guo L., Al-Ghamdy A.O., Alkandiri A., Habotta O.A., *et al.*: Selenium nanoparticles pre-treatment reverse behavioral, oxidative damage, neuronal loss and neurochemical alterations in pentylenetetrazole-induced epileptic seizures in mice. *Int. J. Nanomedicine* 15: 6339-6353 (2020).
DOI: **10.2147/IJN.S259134**
PMID: **32922005**

3. Barbera N., Ayee M.A.A., Akpa B.S., Levitan I.: Differential effects of sterols on ion channels: stereospecific binding *vs* stereospecific response. *Curr. Top. Membr.* 80: 25-50 (2017).
DOI: **10.1016/bs.ctm.2017.06.001**
PMID: **28863819**

4. Sari, S.: (Arilalkil)Azol yapısında yeni oksim ester türevleri üzerinde çalışmalar: sentez, biyolojik aktivite ve moleküler modlleme. Doktora Tezi, Hacettepes Üniversitesi Sağlık Bilimleri Enstitüsü, Ankara (2018).

5. Vöröslakos M., Takeuchi Y., Brinyiczki K., Zombori T., Oliva A., Fernández-Ruiz A., *et al.*: Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nat. Commun.* 9(1): 483 (2018).
DOI: **10.1038/s41467-018-02928-3**
PMID: **29396478**

6. Kumar A., Agarwal P., Rathi E., Kini S.G.: Computer-aided identification of human carbonic anhydrase isoenzyme VII inhibitors as potential antiepileptic agents. *J. Biomol. Struct. Dyn.* 40(11): 4850-4865 (2022).
DOI: **10.1080/07391102.2020.1862706**
PMID: **33345714**

7. Malik S., Bahare R.S., Khan S.A.: Design, synthesis and anticonvulsant evaluation of N-(benzo[d]thiazol-2-ylcarbamoyl)-2-methyl-4-oxoquinazoline-3(4H)-carbothioamide derivatives: a hybrid pharmacophore approach. *Eur. J. Med. Chem.* 67: 1-13 (2013)
DOI: **10.1016/j.ejmech.2013.06.026**
PMID: **23831504**

8. Shi Y., Szlufarska I.: Wear-induced microstructural evolution of nanocrystalline aluminum and the role of zirconium dopants. *Acta Mater.* 200: 432-441 (2020).
DOI: **10.1016/J.ACTAMAT.2020.09.005**

9. Meng X.Y., Zhang H.X., Mezei M., Cui M.: Molecular docking: a powerful approach for structure-based drug discovery. *Curr. Comput. Aided Drug Des.* 7(2): 146-157 (2011).
DOI: **10.2174/157340911795677602**
PMID: **21534921**