ZITA MEDICAL MANAGEMENT

www.hsmc.gr/en/pharmakeftiki-journal/

PHARMAKEFTIKI, 37, 2S, 2025 | 72-76 RESEARCH

https://doi.org/10.60988/p.v37i2S.145

Design, molecular docking, and DFT analysis of dioxoisoindoline derivatives as potential anticonvulsant agents targeting epilepsy-associated proteins

Reem Safi Ali[1,*], Mohammed Oday Ezzat[2]

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

KEY WORDS:
dioxoisoindoline derivatives; anticonvulsants; theoretical calculations; molecular docking; DFT study

ARTICLE INFO:
Received: October 14, 2024
Revised: November 01, 2024
Accepted: November 09, 2024
Available online: October 10, 2025

ABSTRACT

This study attempts to address the necessity of developing substitute therapies for antiepileptic medications. It suggests utilizing molecular docking and dioxoisoindoline derivatives in a theoretical chemical investigation to identify possible substitute medications that could be used in the treatment of epilepsy. In this study five compounds show different activities against particular proteins related to epilepsy treatment; especially compound R3 shows high negative values when it is associated with the three studied proteins. A density functional theory (DFT) approach was employed in order to identify the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) for the five herein studied compounds; it was also used in order to calculate the gap between HOMO and LUMO, the ionization potential, the electron affinity, the electronegativity, as well as the softness and hardness of the molecules, among other chemical characteristics. Overall, this study highlights the need of developing efficient epilepsy treatments and provides a preliminary analysis of possible drugs.

*** CORRESPONDING AUTHOR:**
Reem Safi Ali, Department of Chemistry, College of Education for Pure Sciences, University of Anbar, Ramadi, Iraq; e-mail: ree23u4012@uoanbar.edu.iq

1. Introduction

Epilepsy is a neurological disease characterized by rapid, irregular, or excessive neuronal excitation in the brain's grey matter. It is characterized by recurring episodes of uncontrollable movements, which can affect one or more parts of the body. In different areas of the brain,

PHARMAKEFTIKI, 37, 2S, 2025 | 72-76

a group of cells can be exposed to severe electrical discharge during epileptic seizures. These seizures may be mild (in the form of muscle spasms and loss of concentration) or severe (including spasms for long periods). The occurrence of these seizures ranges from once a year to many times per day[1]. Treatment is carried out after the accurate diagnosis of the condition. Medications with regular follow-up can be used in order to control epilepsy in most of the cases; the surgical procedure is the last option allowing us to control seizures that cannot be treated with medications[2]. Several methods of examination techniques are used in order to diagnose epileptic seizures, such as blood tests, computed tomography, clinical examination, and magnetic resonance imaging[3]. In the majority of the cases, these tests are not crucial for the diagnosis of epilepsy, but they reveal the key causes of these seizures and they define the most effective treatment approach for them[4].

As far as the epilepsy treatment is concerned, the classification of epilepsy is one of the most important steps when assessing the patient's condition. It has an impact on every clinical consultation, but it also has a significant impact on basic and clinical epilepsy research as well as the development of new treatments. A framework for comprehending the type of seizures the patient has, the additional seizure types that are more likely to develop in that person, the potential triggers for their seizures as well as, frequently, their prognosis, are all defined by classification. In addition, classification provides information on the risks associated with comorbidities such as learning disabilities, intellectual disabilities, mental health conditions (such as the autism spectrum disorder), and mortality risks (such as sudden unexpected death in epilepsy). For the development of effective compounds in the treatment of epileptic seizures, many studies have employed quantitative structure-activity relationship (QSAR and 3D-QSAR) methodologies that have contributed to the anticipating that the activities of the new components would have fewer side effects[5]. Five dioxoisoindoline derivatives were designed and assessed in this study as possible substitute medications for epilepsy. The purpose of the study was to ascertain whether these derivatives have a high binding affinity (ΔG) for particular brain proteins related to epilepsy. We should note that his study is a component of a larger research effort to synthesize new dioxoisoindolines that may have anticonvulsant properties.

2. Methodology

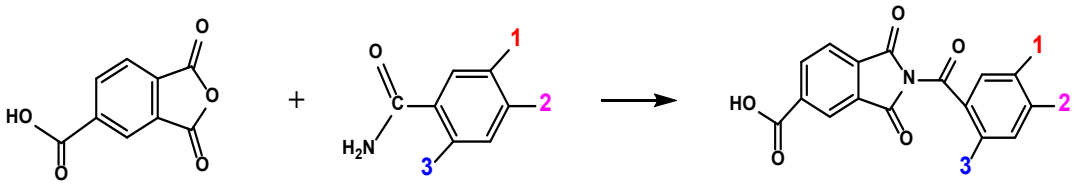
CB-Dock was used in order to predict the possible molecular interactions between the target proteins and the small chemicals. We have, herein, docked five dioxoisoindoline compounds (R1–R5) against the protein active sites of the proteins 1OHV (4-aminobutyrate-aminotransferase; pig), 3F8E (coumarins as suicide carbonic anhydrase inhibitors), and 6KZP (calcium channel ligand), and have obtained the crystal structures of the receptor molecules from the Protein Data Bank. The chemical structures were built with the proper 2D-orientation in ChemOffice (ChemDraw version 20.0). For every structure, MM2 energy minimization was carried out in order to determine the potential energy surface, taking into account elements like thermal and steric energy. The models' final conformations were identified[6]. Moreover, by utilizing the Gaussian program and the density functional theory (DFT), the three most prevalent interactions (between the assessed proteins and the assessed compounds) with residue involvement were found to be the chelation bonding, the H-bonding, and the pi–pi stacking. The five compounds' efficacies were also determined (Table 1).

3. Results and Discussion

Molecular docking is a theory of molecular modelling that explains the fit between two or more proteins and ligands, which is dictated by "ΔG". A better match between the chemical molecule and the protein is indicated by a larger negative ΔG value[7]. This study has used quantum mechanical computations and molecular level theory to examine how different substances interact with anticonvulsant-active proteins (Table 1). When comparing the obtained results with those of the antiepileptic medication phenytoin (ΔG = -8.3 kJ/mol), it is evident that the five assessed

PHARMAKEFTIKI, 37, 2S, 2025 | 72-76

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; HG, mercury (Hg) atom; 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.



Compounds	**1**	**2**	**3**
R1	CHOH	H	H
R2	H	H	OH
R3	CF_3	H	H
R4	H	CN	H
R5	H	C_4H_9	H

Compounds	**ΔG** (kJ/mol)	**1OHV protein residues surrounding the compounds**	**Residues with interferences**
R1	-8.7	ARG_{192}, GLY_{191}, GLY_{132}, HIS_{190}, PHE_{189}, GLU_{265}, GLU_{270}, ASN_{140}, SER_{137}, SER_{328}, SER_{269}, ILE_{72}, CYS_{135}, LYS_{329}, ASP_{298}, VAL_{300}, GLN_{301}, THR_{302}	PHE_{189} (pi–pi stacking); GLY_{136}, GLU_{265} (H-bonding)
R2	-9	CYS_{135}, GLY_{136}, GLY_{191}, SER_{137}, SER_{269}, SER_{328}, ASN_{140}, GLU_{265}, GLU_{270}, PHE_{189}, HIS_{190}, ARG_{192}, ASB_{298}, VAL_{300}, GLN_{301}	PHE_{189} (pi–pi stacking); GLY_{136}, ASP_{298} (H-bonding)
R3	-9.3	ARG_{192}, GLY_{191}, GLY_{136}, HIS_{190}, PHE_{189}, ASN_{140}, SER_{137}, SER_{328}, SER_{74}, CYS_{135}, LYS_{329}, ILE_{72}, GLN_{71}, VAL_{300}	HIS_{190}, GLY_{136}, SER_{328} (H-bonding)
R4	-8.9	ARG_{192}, GLY_{191}, GLY_{136}, HIS_{190}, PHE_{189}, GLN_{301}, VAL_{300}, ASP_{298}, ASN_{140}, SER_{137}, SER_{269}, SER_{328}, CYS_{135}, Glu_{270}, Glu_{265}	PHE_{189} (pi–pi stacking); GLY_{136} (H-bonding)
R5	-8.9	CYS_{135}, GLY_{136}, GLY_{191}, SER_{137}, SER_{269}, SER_{328}, ASN_{140}, GLN_{301}, GLU_{270}, GLU_{265}, VAL_{300}, ASP_{298}, ARG_{192}, ARG_{445}, HIS_{190}, PHE_{189}, LYS_{329}, MET_{332}, THR_{333}	PHE_{189} (pi–pi stacking); SER_{137}, LYS_{329}, MET_{332} (H-bonding)
Compounds	**ΔG** (kJ/mol)	**3F8E protein residues surrounding the compounds**	**Residues with interferences**
R1	-7.8	TRP_5, HIE_4, HIE_{64}, HG_{264}, LYS_{170}, ASN_{62}, ASN_{67}, ALA_{65}, GLN_{92}, HIS_{94}, THR_{200}, PRO_{201}, PRO_{202}	TRP_5 (pi–pi stacking); H_2O (H-bonding)
R2	-7.4	PRO_{201}, PRO_{202}, TRP_5, ASN_{62}, ASN_{67}, HIE_{64}, ILE_{91}, GLN_{92}, VAL_{121}, PHE_{131}	PRO_{201}, HIE_{64}, GLN_{92}, H_2O (H-bonding)
R3	-8	PRO_{202}, PRO_{201}, THR_{200}, TRP_5, ASN_{62}, ASN_{67}, HIE_{64}, GLU_{69}, PHE_{131}, ILE_{91}, GLN_{92}, VAL_{121}	PRO_{201}, HIE_{64} (H-bonding)
R4	-7.3	GLU_{69}, ASN_{67}, ASN_{62}, HIE_{64}, LEU_{60}, ARG_{58}, GLN_{92}, ILE_{91}, THR_{200}, PRO_{201}, TRP_5	GLN_{92}, GLU_{69}, H_2O (H-bonding)
R5	-6.7	TRP_5, PRO_{201}, THR_{200}, ASN_{62}, ASN_{67}, HIE_{64}, GLU_{69}, PHE_{70}, PHE_{131}, ASP_{71}, ASP_{72}, GLN_{92}, ILE_{91}, LEU_{57}	HIE_{64}, TRP_5 (H-bonding)
Compounds	**ΔG** (kJ/mol)	**6KZP protein residues surrounding the compounds**	**Residues with interferences**
R1	-8	LEU_{391}, LEU_{1819}, LEU_{1506}, LEU_{353}, ASN_{388}, ILE_{387}, ILE_{351}, PHE_{384}, PHE_{956}, PHE_{1509}, SER_{383}, THR_{352}, GLN_{922}, TYR_{953}, VAL_{1505}, VAL_{1823}, VAL_{1820}	ASN_{388}, GLN_{922} (H-bonding)
R2	-8	GLN_{922}, THR_{921}, LEU_{920}, LEU_{1499}, LEU_{872}, LEU_{955}, PHE_{917}, LEU_{868}, PHE_{956}, ASN_{952}, GLY_{951}, LYS_{1462}	PHE_{956} (pi–pi stacking); ASN_{952}, LYS_{1462} (H-bonding)
R3	-9	PHE_{956}, PHE_{868}, LEU_{955}, LEU_{872}, LEU_{920}, TYR_{953}, ASN_{952}, GLY_{951}, ILE_{387}, ILE_{876}, LYS_{1462}, GLN_{922}, THR_{921}, ALA_{1502}	PHE_{956} (pi–pi stacking); ASN_{952}, LYS_{1462} (H-bonding)
R4	-8.2	ASN_{952}, ASN_{957}, TYR_{953}, PHE_{956}, PHE_{868}, PHE_{917}, LEU_{959}, LEU_{920}, LEU_{872}, LEU_{1499}, THR_{921}, LYS_{1462}, ILE_{876}, ALA_{1502}	ASN_{952}, LYS_{1462} (H-bonding)
R5	-8.4	GLN_{922}, THR_{921}, LEU_{920}, LEU_{1499}, LEU_{872}, LEU_{959}, PHE_{917}, PHE_{956}, PHE_{868}, PHE_{1503}, ALA_{1505}, LYS_{1462}, VAL_{865}, CYS_{869}, ILE_{876}, ASN_{952}, GLY_{951}	GLN_{922}, ASN_{952} (H-bonding)

PHARMAKEFTIKI, 37, 2S, 2025 | 72-76

compounds interact with the protein 1OHV and obtain a larger negative ΔG value; this means that they are more effective than phenytoin and, particularly, this is the case for compound R3 (which has a value of ΔG = -9.3 kJ/mol). Compounds R1 and R3 have exhibited the highest affinity for the protein 3F8E, with a ΔG value of -7.8 and -8 kJ/mol, respectively; these are both higher than the ΔG value of the drug phenytoin with the protein, which is equal to -7.4 kJ/mol. Compound R2 has exhibited the same value ΔG as the drug, while compounds R4 and R5 have scored a lower value than the drug. The binding with the final protein 6KZP has shown that compound R3 has a ΔG value similar to that of the drug (equal to -9 kJ/mol), while the other compounds have a lower ΔG value. Compounds that exhibited more negative values than the drug have the potential to be effective antiepileptic medications. Based on our results, it is clear that compound R3 has the highest negative values for ΔG when interacting with the three proteins, thereby indicating that it is more active and could be used as an anticonvulsant drug. In DFT, an atomistic simulation has computed a range of important features, such as the highest occupied molecular orbital (HOMO) and the lowest lying unoccupied molecular orbital (LUMO). The HOMO values of all compound ranged from -0.268 to -0.232 eV, while the LUMO values were between -0.125 and -0.110 eV; therefore their gap ranged from 0.121 to 0.146 eV. These features were employed in equations in an attempt to identify many molecular properties such as the ionization potential (I) and the electron affinity (EA). The values of the studied compounds ranged from 0.146 to 0.121 for I, from 0.110 to 0.125 for EA, from 0.171 to 0.196 for electronegativity, from 13.612 to 16.467 for softness, and from 0.060 to 0.073 for hardness[8].

4. Conclusion

Our results reveal that most of the assessed compounds (being dioxoisoindoline derivatives) have the potential to display anticonvulsant activity, with the most promising finding resulting from the association of 10HV with compound R3 (ΔG = -9.3 kJ/mol). In addition, this same compound has also exhibited a high ΔG value with the other two proteins: -8 kJ/mol with 3F8E and -9 kJ/mol with 6KZP.

Acknowledgements

The authors express their deep appreciation to the University of Anbar for providing the necessary support and resources, and which significantly contributed to the completion of this study.

Conflicts of interest

None exist.

ORCIDs

0009-0003-0521-0234 (R.S. Ali); 0000-0001-6671-0417 (M.O. Ezzat)

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
2. Milligan T.A. Epilepsy: a clinical overview. *Am. J. Med.* 134(7), 840–847, 2021. DOI: 10.1016/j.amjmed.2021.01.038
3. Sutton F., Barca D., Komoltsev I., Craiu D., Guekht A., von Oertzen T., *et al.* Testing blood and CSF in people with epilepsy: a practical guide. *Epileptic Disord.* 22(4), 381–398, 2020. DOI: 10.1684/epd.2020.1191
4. Shoeibi A., Khodatars M., Ghassemi N., Jafari M., Moridian P., Alizadehsani R., *et al.* Epileptic seizures detection using deep learning techniques: a review. *Int. J. Environ. Res. Public Health* 18(11), 5780, 2021. DOI: 10.3390/ijerph18115780
5. Kumar A., Agarwal P., Rathi E., Kini S.G. Com-

PHARMAKEFTIKI, 37, 2S, 2025 | 72-76

puter-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

6. 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(4*H*)-carbothioamide derivatives: a hybrid pharmacophore approach. *Eur. J. Med. Chem.* 67, 1–13, 2013. DOI: 10.1016/j.ejmech.2013.06.026
7. Shi Y., Szlufarska I. Wear-induced microstructural evolution of nanocrystalline aluminum and the role of zirconium dopants. *Acta Materialia* 200, 432–441, 2020. DOI: 10.1016/j.actamat.2020.09.005
8. Chalawi R.H, Ezzat M.O. Theoretical calculations and molecular modelling of isoindoline compounds as anticonvulsant agents. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed.* 38(s2), 109–112, 2024. DOI: 10.61873/AFGH8682

HOW TO CITE:
Ali R.S., Ezzat M.O. Design, molecular docking, and DFT analysis of dioxoisoindoline derivatives as potential anticonvulsant agents targeting epilepsy-associated proteins. *Pharmakeftiki* 37(2s), 72-76, 2025. https://doi.org/10.60988/p.v37i2S.145