ZITA MEDICAL MANAGEMENT

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

PHARMAKEFTIKI, 37, 2S, 2025 | 278-281 RESEARCH

https://doi.org/10.60988/p.v37i2S.209

Molecular design and theoretical calculations of new 1,3-dioxoisoindoline derivatives as potential antiepileptic drugs

Khalid Mushtaq Hashim[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; molecular docking; DFT study; epilepsy; antiepileptic drugs

ARTICLE INFO:
Received: December 03, 2024
Revised: January 22, 2025
Accepted: February 07, 2025
Available online: October 10, 2025

ABSTRACT

This study aimed at identifying alternative therapeutic agents for epilepsy syndromes, with a focus on compounds that may attenuate seizure activity. A theoretical chemical approach was employed in order to assess the potential of dioxoisoindoline derivatives, by utilizing molecular docking techniques so as to explore ligand–protein interactions relevant to epileptogenesis. Several derivatives have demonstrated notable binding affinities toward proteins implicated in the pathophysiology of the disorder. Density functional theory (DFT) calculations were conducted in order to evaluate the electronic properties of the candidate molecules, particularly those derivatives subject to structural constraints or regulatory bans. Additionally, the suitability of these compounds as drug candidates was assessed by using Lipinski's Rule of Five and predictive similarity metrics. The resulting data indicate that the molecular weight, the partition coefficient (log P), the hydrogen bond donors, and the hydrogen bond acceptors of the evaluated molecules fall within acceptable pharmacokinetic thresholds. Taken together, these findings underscore the need for novel antiepileptic therapies and offer a preliminary appraisal of dioxoisoindoline derivatives as promising candidates for further investigation.

*** CORRESPONDING AUTHOR:**
Khalid Mushtaq Hashim, Department of Chemistry, College of Education for Pure Sciences, University of Anbar, Ramadi, Iraq; e-mail: kha23u4010@uoanbar.edu.iq

1. Introduction

For more than fifty years, epilepsy syndromes have been recognized as distinct electroclinical phenotypes with implications for prognosis and therapeutic strategy. However, there is no formally established classification system for epilepsy syndromes endorsed by the Inter-

PHARMAKEFTIKI, 37, 2S, 2025 | 278-281

national League Against Epilepsy (ILAE)[1]. Approximately one-third of individuals with epilepsy are considered drug-resistant, although prevalence varies based on the syndrome type, underlying aetiology, age at seizure onset, and presence of comorbid neurological impairments[2]. Nonetheless, treatment outcomes and quality of life have improved, driven by an expanded understanding of the syndrome-specific drug efficacy and an increased caution regarding medications with severe cognitive side effects or polytherapy burdens[3]. Epileptic seizures result from a dysregulation in the balance between excitatory and inhibitory neurotransmitters[4]. Abnormal neuronal hyperexcitability may arise from dysfunctional macromolecules involved in neural signalling, contributing to epileptogenesis.

In the present study, eight dioxoisoindoline derivatives were synthesized and evaluated as candidate antiepileptic compounds. The objective was to investigate their binding affinity (ΔG) toward selected brain proteins implicated in epilepsy[5]. This study is part of an ongoing effort to develop dioxoisoindoline-based molecules with potential anticonvulsant properties.

2. Methodology

In an attempt to predict molecular interactions between candidate compounds and target proteins, blind docking simulations were performed by using the Cavity Detection Guide Blind Docking platform (CB-DOCK). The following proteins were selected for docking studies: 1OHV (4-aminobutyrate aminotransferase; *Sus scrofa*), 3F8E (coumarins acting as suicide inhibitors of carbonic anhydrase), and 6KZP (calcium channel-ligand complex). Each of the eight dioxoisoindoline compounds was docked into the predicted active sites of these proteins.

Chemical structures were generated in ChemOffice (ChemDraw version 23.1.1) and optimized using MM2 energy minimization, considering steric and thermal parameters. The final conformations of the molecules were identified[6]. Quantum mechanical optimization of these energy-minimized ligands was subsequently performed using the B3LYP/6-31G++(d,p) level of theory for vibrational analysis and geometry refinement.

The residue-level interactions for each protein were as follows: (i) 1OHV (GLY_{136}, GLY_{191}, ASN_{140}, VAL_{300}, PHE_{189}, HIS_{190}, ARG_{192}), (ii) 3F8E (HIE_{64}, TRP_{5}, PRO_{201}, PRO_{202}, THR_{200}, GLN_{92}, ILE_{91}), and (iii) 6KZP (THR_{921}, GLN_{922}, ASN_{952}, GLY_{951}, LYS_{1462}, ALA_{1502}). The predominant interaction modes observed were π–π stacking, hydrogen bonding, and chelation bonding. All density functional theory (DFT)-optimized ligand structures were used as input for CB-DOCK. Protein crystal structures were obtained from the Protein Data Bank (PDB).

3. Results and Discussion

Molecular docking theory describes a ligand–protein fit by using the Gibbs free energy of binding (ΔG), where greater negative values indicate a stronger binding affinity[7]. In this study, docking simulations and quantum mechanical modelling were used in order to assess compound interactions with proteins of known anticonvulsant relevance[8]. The inhibitory potential of compounds A4, A1, and A3 appeared promising[9].

Compound A4 exhibited the strongest affinities: ΔG = -8.6 with 1OHV and ΔG = -7.2 with 3F8E. Compounds A1 and A3 showed strong binding to 6KZP (ΔG = -8.2). Phenytoin (5,5-diphenylimidazolidine-2,4-dione) exhibited a ΔG = -7.9 for 1OHV, a ΔG = -7.4 for 3F8E, and a ΔG = -7.8 for 6KZP. Phenytoin consistently displayed higher binding affinities than other compounds, thereby suggesting a broad potential as a reference or benchmark compound. In summary, compound A4 demonstrated the most robust potential anticonvulsant activity *via* interactions with 1OHV and 3F8E. Compounds A1 and A3 showed promising interactions with 6KZP. Phenytoin was validated as the optimal ligand across all protein targets. These data highlight the inhibitory potential of the studied compounds and support their further evaluation as anticonvulsant drug candidates[10].

In the DFT analysis undertaken, several key electronic properties were computed, including: (i) the highest occupied molecular orbital (HOMO; -0.211

PHARMAKEFTIKI, 37, 2S, 2025 | 278-281

Table 1. Selected chemical properties of the synthesized compounds. Abbreviations: EA, electron affinity; HOMO, highest occupied molecular orbital; IP, ionization potential; LUMO, lowest unoccupied molecular orbital; S, softness; η, chemical hardness; μ, electronegativity; ω, electrophilicity index.

Properties	A1	A2	A3	A4	A5	A6	A7	A8
LUMO	-0.114	-0.113	-0.112	-0.112	-0.113	-0.107	-0.111	-0.104
HOMO	-0.211	-0.223	-0.218	-0.217	-0.211	-0.181	-0.219	-0.187
HOMO–LUMO gap	0.097	0.11	0.106	0.105	0.098	0.074	0.108	0.083
IP	0.211	0.223	0.218	0.217	0.211	0.181	0.219	0.187
EA	0.114	0.113	0.112	0.112	0.113	0.107	0.111	0.104
μ	0.163	0.168	0.165	0.165	0.162	0.144	0.165	0.146
η	0.049	0.055	0.053	0.052	0.049	0.037	0.054	0.042
S	20.62	18.18	18.87	19.05	20.41	27.03	18.52	24.09
ω	0.271	0.257	0.257	0.262	0.268	0.280	0.252	0.254

to -0.187 eV), (ii) the lowest unoccupied molecular orbital (LUMO; -0.114 to -0.104 eV), and (iii) the HOMO–LUMO gap (0.097 to 0.083 eV). These ranges reflect high kinetic activity and moderate molecular instability. Additional quantum descriptors were calculated: (i) the ionization potential (I; 0.211 to 0.187), (ii) the electron affinity (EA; 0.114 to 0.104), (iii) the chemical hardness (η; 0.049 to 0.042), (iv) the electronegativity (μ; 0.163 to 0.146), and (v) the softness (S; 20.62 to 24.09). These values support the energetic plausibility and reactivity profiles of the candidate compounds (Table 1).

4. Conclusion

Preclinical evidence supports the potential anticonvulsant activity of several studied compounds: compound A4 yielded the most promising ΔG values (-8.6 and -7.2), while compounds A1 and A3 also demonstrated favourable interactions (ΔG = -8.2). Phenytoin was identified as the most effective ligand across all evaluated protein targets. These findings suggest that the tested compounds and ligands hold promise as future anticonvulsant agents.

Acknowledgements

The authors gratefully acknowledge the University of Anbar for providing the facilities necessary to conduct this research.

Conflicts of interest

None exist.

ORCIDs

0009-0003-2744-8390 (K.M. Hashim); 0000-0001-6671-0417 (M.O. Ezzat)

References

1. Wirrell E.C., Nabbout R., Scheffer I.E., Alsaadi T., Bogacz A., French J.A., *et al.* Methodology for classification and definition of epilepsy syndromes with list of syndromes: report of the ILAE Task Force on Nosology and Definitions. *Epilepsia* 63(6), 1333–1348, 2022. DOI: 10.1111/epi.17237
2. Perucca E., Perucca P., White H.S., Wirrell E.C. Drug resistance in epilepsy. *Lancet Neurol.* 22(8), 723–734, 2023. DOI: 10.1016/S1474-4422(23)00151-5
3. Guerrini R. Epilepsy in children. *Lancet*

PHARMAKEFTIKI, 37, 2S, 2025 | 278-281

367(9509), 499–524, 2006. DOI: 10.1016/S0140-6736(06)68182-8

4. 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(s2), 47–50, 2024. DOI: 10.61873/ANKG7670
5. Ezzat M.O., Abd Razik B.M., Shihab W.A. Molecular modelling and theoretical design of novel nirmatrelvir derivatives as SARS-CoV-2 entry inhibitors. *New Mater. Compd. Appl.* 8(2), 178–189, 2024. DOI: 10.62476/nmca82178
6. 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
7. 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
8. Kadhim M.A., Zangana E.K.M., Jawad A.H. Design, synthesis and characterization of a new series of 2,3-dihydroquinazolin-4(1H)-one (DHQZ-1) derivatives and evaluation of antitumor resistant (by Molecule Docking). *Baghdad Sci. J.* 21(7), 2263–2274, 2024. DOI: 10.21123/bsj.2023.8232
9. Arshad A.S.M., Chear N.J.Y., Ezzat M.O., Hanapi N.A., Meesala R., Arshad S., *et al.* Synthesis, characterization and crystal structure of new tetrahydro-β-carboline as acetylcholinesterase inhibitor. *J. Mol. Struct.* 1200, 127070, 2020. DOI: 10.1016/j.molstruc.2019.127070
10. Jamaal M., Ezzat M. A synthesis, characterization and biological activity evaluation of novel quinoline derivatives as antibacterial drug. *Acta Chim. Slov.* 71(2), 319–324, 2024. DOI: 10.17344/acsi.2023.8484

HOW TO CITE:
Hashim K.M., Ezzat M.O. Molecular design and theoretical calculations of new 1,3-dioxoisoindoline derivatives as potential antiepileptic drugs. *Pharmakeftiki* 37(2s), 278-281, 2025. https://doi.org/10.60988/p.v37i2S.209