Since 1987
REVIEW OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS, INTERNATIONAL EDITION | 38 (Sup2):109-112 (2024) Rcpp

Received: 7 February 2024 | **Accepted**: 12 February 2024 | **Published**: 5 May 2024

Open Access | Research

Theoretical calculations and molecular modelling of isoindoline compounds as anticonvulsant agents

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Abstract

The lack of safe and effective antiepileptic drugs is a persistent issue that could be addressed through the repurposing or further development of commonly available drugs. Due to high accuracy, low effort, and high cost, it is best to begin the search for alternative treatments with a theoretical chemical study. Isoindoline derivatives, their ΔG, and their molecular docking were subjected to the molecular level theory. Having a ΔG of -4.9, compound A1 demonstrated a unique activity against protein 1OHV (4-aminobutyrate-aminotransferase; from pig), while the same compound demonstrated distinct activity against protein 3F8E (coumarins as suicide carbonic anhydrase inhibitors) with a ΔG of -4.533. Moreover, compound A3 exhibited a unique activity against protein 6KZP (calcium channel-ligand) with a ΔG of -7.597. The undertaken DFT analysis determined the highest occupied molecular orbital (HOMO), the least unoccupied molecular orbital (LUMO), and the HOMO-LUMO gap values for the studied derivatives (compound A1: -0.202, -0.091, and -0.111 eV; compound A3: -0.228, -0.102, and -0.126 eV, respectively). The ionization potential, the softness, the hardness, and other chemical properties of these compounds were subsequently computed. Drug likeness predictions were employed in order to show that the compounds adhered to Lipinski's rule. Our results indicate that the molecular mass, log P, as well as the hydrogen bonding donors and acceptors of the herein assessed isoindoline compounds fall within acceptable ranges.

KEYWORDS
isoindoline derivatives, anticonvulsant, molecular docking, DFT study, ADME

How to cite: Chalawi R. H., Ezzat M. O. Theoretical calculations and molecular modelling of isoindoline compounds as anticonvulsant agents. *Rev. Clin. Pharmacol. Pharmacokinet. Int. Ed.* 38 (Sup2): 109-112 (2024).
https://doi.org/10.61873/AFGH8682

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1. INTRODUCTION

Behind Alzheimer disease and stroke, epilepsy is the third most prevalent neurological condition. During the previous three decades, a number of third-generation antiepileptic medications have improved the treatment of epilepsy. However, the need for novel medications or approaches to the treatment of epilepsy became urgent due to the patients' intolerance and resistance to antiepileptic medications in 20–30% of the cases [1]. Daily medication is typically used to treat epilepsy once a second seizure has manifested. In individuals who are at high risk of having more seizures, medication may even be initiated after the first seizure [2]. Moreover, several other treatment options, such as special diets, neurosurgery, or the implan-

tation of a neurostimulator, may be considered in drug-resistant cases [3].

The aim of this study was to identify the highest binding affinity (ΔG) value for isoindoline derivatives that have a significant association with specific proteins in the brain. When the ΔG value of isoindoline derivatives bound to the protein is higher than the ΔG value of the drug available as an anticonvulsant, this means that the derivative could be highly effective and reliable as an anticonvulsant drug.

2. MATERIALS AND METHODS

SwissDock is a protein ligand docking server that is based on the EADock dihedral space sampling (DSS). This server is intended to provide protein-ligand docking to a global scientific community [4]. The Swiss Institute of Bioinformatics offers SwissDock as a web service. The following proteins were docked using a standard protocol: 1OHV (4-aminobutyrate-aminotransferase; from pig), 3F8E (coumarins as suicide carbonic anhydrase inhibitors), and 6KZP (calcium channel-ligand). Five isoindoline derivatives have been suggested for the proteins' active sites. Every chemical structure was generated with the correct 2D orientation in ChemOffice (ChemDraw version 20.0). MM2 energy minimization was estimated for each structure, so as to estimate the potential energy surface (including factors such as steric energy and thermal energy).

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
A1	-4.9	CYS_{135}, GLY_{136}, GLY_{191}, SER_{137}, SER_{328}, SER_{269}, LYS_{329}, ASN_{140}, ASP_{298}, GLU_{265}, GLU_{270}, VAL_{300}, GLN_{301}, PHE_{189}, HIS_{190}, ARG_{192}	GLY_{136}, GLN_{301} (H-bonding); PHE_{189} (pi–pi stacking)
A2	-4.081	ARG_{192}, GLY_{191}, GLY_{136}, PHE_{189}, SER_{137}, SER_{328}, SER_{74}, CYS_{135}, ALA_{134}, VAL_{300}, LYS_{329}, MET_{332}	GLY_{136}, SER_{328}, CYS_{135} (H-bonding)
A3	-4.458	SER_{74}, SER_{328}, SER_{137}, MET_{332}, LYS_{329}, CYS_{135}, GLY_{136}, GLY_{191}, VAL_{300}, ASN_{140}, PHE_{189}, HIS_{190}, ARG_{192}	SER_{328}, GLY_{136} (H-bonding)
A4	-3.986	CYS_{135}, GLY_{136}, GLY_{191}, SER_{137}, SER_{328}, LYS_{329}, ASN_{140}, GLU_{265}, ASP_{298}, VAL_{300}, GLN_{301}, PHE_{189}, HIS_{190}, ARG_{192}	GLY_{136} (H-bonding); PHE_{189} (pi–pi stacking)
A5	-0.275	CYS_{135}, GLY_{136}, GLY_{191}, SER_{137}, SER_{328}, SER_{269}, LYS_{329}, ASN_{140}, ASP_{298}, GLU_{299}, GLU_{265}, GLU_{270}, VAL_{300}, GLN_{301}, THR_{302}, PHE_{189}, HIS_{190}, ARG_{192}	GLY_{136} (H-bonding); PHE_{189} (pi–pi stacking)
Compound	**ΔG**	**3F8E protein residues surrounding the compounds**	**Residues with interferences**
A1	-4.533	ASN_{62}, ASN_{67}, HIE_{64}, GLN_{92}, HIS_{94}, TRP_{5}, THR_{200}, PRO_{201}, PRO_{202}	H_2O, ASN_{62} (H-bonding); HIE_{64} (pi–pi stacking)
A2	-3.92	TRP_{5}, PRO_{202}, PRO_{201}, THR_{200}, ASN_{62}, ASN_{67}, HIE_{64}, GLU_{69}, GLN_{92}, ILE_{91}, PHE_{131}	H_2O (H-bonding); PHE_{131} (pi–pi stacking)
A3	-3.907	PHE_{131}, PRO_{202}, PRO_{201}, THR_{200}, TRP_{5}, ASN_{62}, ASN_{67}, HIE_{64}, HIS_{94}, GLN_{92}, ILE_{91}	H_2O (H-bonding); PHE_{131} (pi–pi stacking)
A4	-3.27	PHE_{131}, ILE_{91}, GLN_{92}, ASN_{62}, ASN_{67}, HIE_{64}, THR_{200}	H_2O, HIE_{64} (H-bonding)
A5	-2.861	PRO_{202}, PRO_{201}, THR_{200}, TRP_{5}, ASN_{62}, ASN_{67}, HIE_{64}, GLU_{69}, PHE_{70}, ASP_{71}, ASP_{72}, LEU_{57}, PHE_{131}, ILE_{91}, GLN_{92}	H_2O (H-bonding)
Compound	**ΔG**	**6KZP protein residues surrounding the compounds**	**Residues with interferences**
A1	-6.524	PHE_{917}, PHE_{956}, LEU_{920}, LEU_{872}, LEU_{1499}, THR_{921}, GLN_{922}, LYS_{1462}, ILE_{876}, GLY_{951}, ASN_{952}	ASN_{952}, LYS_{1462} (H-bonding); PHE_{956} (pi–pi stacking)
A2	-5.49	GLN_{922}, THR_{921}, LEU_{920}, LEU_{872}, LEU_{1499}, ASN_{952}, GLY_{951}, PHE_{956}, PHE_{868}, ALA_{1502}, LYS_{1462}	ASN_{952}, LYS_{1462} (H-bonding)
A3	-7.597	THR_{921}, LEU_{920}, LEU_{872}, LEU_{959}, LEU_{1499}, LEU_{1506}, PHE_{917}, PHE_{868}, PHE_{956}, PHE_{1503}, ILE_{876}, CYS_{869}, VAL_{865}, ALA_{1502}, LYS_{1462}	H_2O (H-bonding); PHE_{131} (pi–pi stacking)
A4	-6.203	PHE_{917}, PHE_{956}, LEU_{920}, LEU_{1499}, LEU_{872}, THR_{921}, GLN_{922}, LYS_{1462}, TYR_{953}, ASN_{952}, GLY_{951}, ILE_{876}	ASN_{952}, LYS_{1462} (H-bonding); PHE_{956} (pi–pi stacking)
A5	-6.653	PHE_{917}, PHE_{956}, LEU_{920}, LEU_{1499}, LEU_{872}, LEU_{391}, THR_{921}, GLN_{922}, LYS_{1462}, TYR_{953}, ASN_{952}, GLY_{951}, ILE_{876}, ILE_{387}	ASN_{952}, LYS_{1462} (H-bonding); PHE_{956} (pi–pi stacking)

The resulting conformations of the models were obtained [5]. Subsequently, the molecular theory was employed. Following energy minimization, the ligand molecules with the participation of residues GLY_{136}, GLN_{301}, ASP_{298}, *etc.* in the case of 1OHV, of residues ASN_{67}, HIE_{64}, ASN_{62}, *etc.* in the case of 3F8E, and of residues LEU_{959}, VAL_{865}, ALA_{1502}, CYS_{869}, *etc.* in the case of 6KZP (Table 1) were subjected to quantum mechanics using the B3LYP/6-31G++ (d,p) level of theory for frequency calculation and geometry optimization. The three most prevalent interactions (between the assessed proteins and the assessed compounds) with residue involvement were found to be chelation bonding, H-bonding, and pi–pi stacking. The optimized by density-functional theory (DFT) structures were then fed into SwissDock. The receptor molecules' crystal structures were obtained from the Protein Data Bank.

3. RESULTS AND DISCUSSION

Molecular docking: A theory of molecular modelling known as "docking" explains the interactions between two or more proteins and ligands. The "ΔG" value makes that determination, where a better fit between the chemical and the protein is indicated by a larger negative ΔG [6]. The five compounds herein assessed were drug-like and could potentially exert an anticonvulsant effect, according to our ΔG calculations (Table 1). Through its interaction with the protein 1OHV, compound A1 exhibited the highest degree of association with the protein (ΔG=-4.9). Compound A1 also exhibited the highest degree of association (ΔG=-4.533) with the protein 3F8E, thereby exhibiting the most promising anticonvulsant activity through its interaction with coumarins; a novel class of suicide carbonic anhydrase inhibitors. Compound A3 exhibited the highest degree of association (ΔG=-7.597) with the protein 6KZP. 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 had the strongest interaction with the protein 6KZP (ΔG=-6.709). Interestingly, compound A3 exhibited a smaller ΔG value than any of the ligands and compounds associated with 6KZP.

DFT analysis: In DFT, an atomistic simulation that computes a range of important features, the highest occupied molecular orbitals (HOMOs) are the highest. The least unoccupied molecular orbitals (LUMOs) are the next highest energy orbitals that are empty, while the HOMO–LUMO gap is their 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. In our study, the HOMO values of the assessed compounds ranged from -0.227 to -0.199 eV, their LUMO values ranged from -0.092 to -0.087 eV, while their 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 as the ionization potential (I) and the electron affinity (EA). The values of the studied compounds ranged from 0.197 to 0.228 in the case of their I, and from 0.081 to 0.102 in the case of their EA. Moreover, their electronegativity (μ) ranged from 0.139 to 0.165, their softness (S) ranged from 15.87 to 18.01, and their hardness (η) ranged from 0.055 to 0.063 [7].

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.

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