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SHORT COMMUNICATION article

Design of pyrrolidine-2, 5-dione Schiff's base derivatives as $GABA_A$ inhibitors for antiepileptic activity

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***Keywords*:** Anti-epileptic agent, $GABA_A$ receptor, molecular docking, Schiff's base

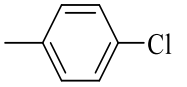
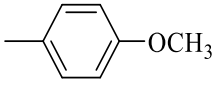
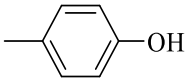
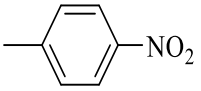
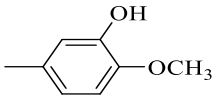
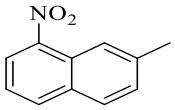
Abstract: Succinimide derivatives are an essential class of compounds with diverse pharmacological applications. Different derivatives of succinimide as Schiff's base were designed for good inhibitory activity against the human $GABA_A$ receptor. Compounds that inhibit $GABA_A$ are effective as anti-epileptic agents. Virtual screening methods, such as chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties, play key roles in drug discovery and development, and molecular docking was used. ADMET properties and drug likeliness of all investigated compounds were predicted by Swiss ADMET software. A higher binding affinity and interactions have been observed with the designed compounds compared to the standard compounds (phenobarbital and flumazenil).

Introduction

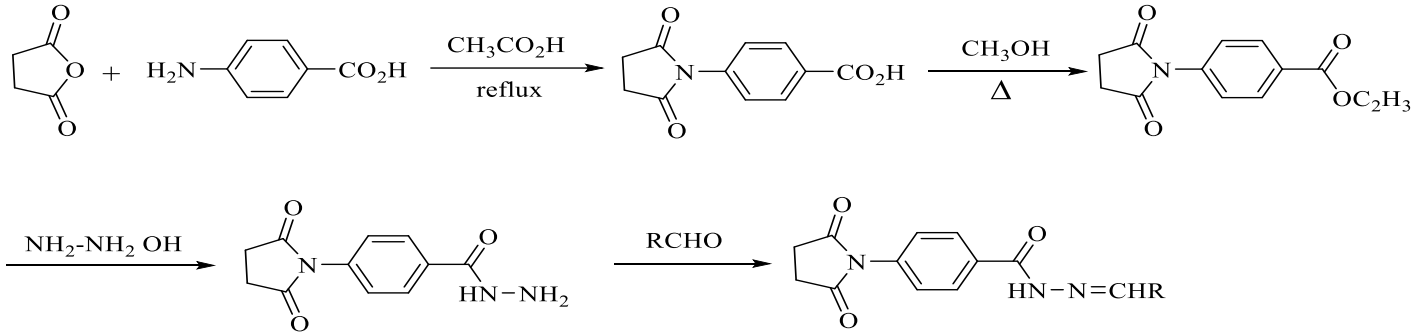
Substituted succinimides are important compounds of many drugs and drug candidates. One of the most fundamental objectives of organic and medicinal chemistry is the design and synthesis of molecules having value as human therapeutic agents. Cyclic imides and their derivatives contain an imide ring and the general structure of –CO–N(R)–CO–, so they cross biological membranes *in vivo* [1]. There are several approved drugs with a cyclic imide structure. Substituted succinimide moiety appears as an interesting precursor of many biologically active such as CNS depressant [2], analgesic [3], antitumor and cytostatic [4, 5], anorectic [6], nerve conduction blocking antispasmodic [7], bacteriostatic [8], muscle relaxant and hypotensive [9], antibacterial [10], antifungal [11], anti-epileptic [12], and anti-tubercular [13, 14].

Although cyclic imide derivatives show a wide range of biological properties, the multidirectional activity of succinimide and its *N*-substituted derivatives prompted us to design several pyrrolidine-2, 5-dione Schiff's base derivatives (**Table 1**). Different methods have been reported for the synthesis of succinimide derivatives [15, 16] (**Scheme 1**). The designed compounds were used to study their binding interaction with the $GABA_A$ receptor as antiepileptic agents by using the molecular docking technique (PyRx software). Evaluate their physicochemical properties, such as water solubility and lipophilicity, also predicting their pharmacokinetic parameters using the Swiss ADMET (chemical absorption, distribution, metabolism, excretion, and toxicity) software.

Table 1: Succinimide Schiff's base derivatives

No	R			No	R
1		3		5	
2		4		6	

General procedure for the synthesis of succinimide Schiff's base derivatives



Scheme 1: Synthesis of pyrrolidine-2,5-dione Schiff's base derivatives

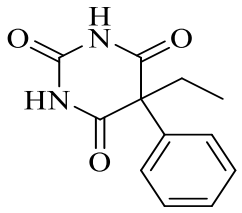
Materials and methods

Molecular docking: The docking studies of the designed (not synthesized) pyrrolidine-2, 5-dione Schiff's base derivatives have been carried out to predict the most possible type of interaction, the binding affinities, and the orientations of the docked ligands at the active site of the target proteins (gamma-aminobutyric acid, $GABA_A$). The starting geometry of the pyrrolidine-2, 5-dione Schiff base derivatives was constructed using chem3D Ultra software (version 12.0, Cambridge Soft Com, USA). The optimized geometry of pyrrolidine-2, 5-dione Schiff's base derivatives with the lowest energy was used for molecular docking. Molecular docking was accomplished by Discovery Studio Visualizer overview 0.56. The crystal structures of the human $GABA_A$ receptor alpha1-beta2-gamma2 subtype in complex with GABA and flumazenil (6D6T) and human $GABA_A$ receptor alpha1-beta2-gamma2 subtype in complex with GABA plus phenobarbital (6X3W) were downloaded from the Protein Data Bank (http://www.rcsb.org/pdb). The crystal structures of the $GABA_A$ receptor (6D6T and 6X3W) were set up by cleaning the ligand and water molecules and saved as protein data bank (PDB) format through Discovery Studio (DS) software. Molecular docking was performed using PyRx software, with flumazenil and phenobarbital as $GABA_A$ receptor control compounds. The polar hydrogen atoms were added to protein molecules. Then, partial atomic charges of the $GABA_A$ receptor and designed compounds derivatives **1 - 6** molecules were calculated using Kollman methods. In the process of molecular docking, the grid maps of dimensions: (135.11Å X 121.58Å X 126.57 Å) and (94.06 Å X 112.79 Å X 110.56 Å) for 6D6T and 6X3 W, respectively. DS software was used to analyze the docking results.

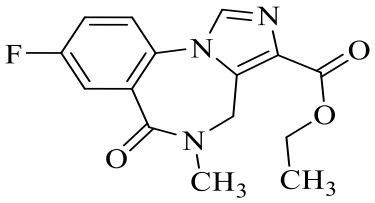
Results and discussion

Molecular docking analysis: Computer-aided drug designing, especially the molecular docking method, is an efficient technique to study the affinity and binding energy of a ligand with a studied receptor protein. The binding affinity and energy of designed pyrrolidine-2, 5-dione Schiff's base derivatives with the $GABA_A$ receptor were obtained by using a molecular docking strategy [18 - 20].

According to the medical subject headings (MeSH) classification, phenobarbital and flumazenil are classified as GABA modulators, where they thought that $GABA_A$ receptors have at least three allosteric sites at which these medications act [17, 21]. The docking energies of the reference compounds were utilized to compare the binding affinities of the tested compounds (**Table 2**). Three hydrogen bonds were observed between flumazenil with active sites by THR B: 122, LEU B: 128, and LYS B: 42. A single hydrogen bond was noticed between phenobarbital and the $GABA_A$ receptor at the active site by THR B: 207. Other interactions of flumazenil and phenobarbital were found with the $GABA_A$ receptor, such as π-π stacking and π-π -T-shaped interactions (**Figure 1**).



Phenobarbital



Flumazenil

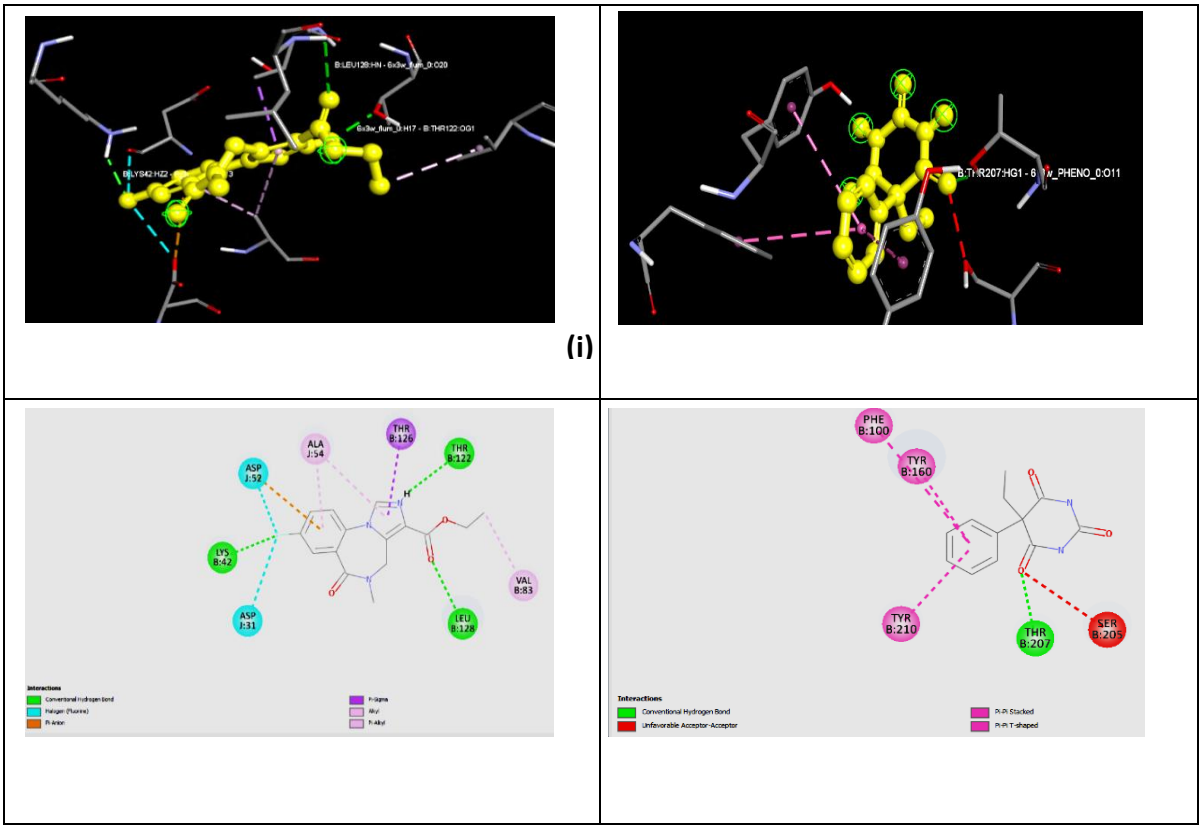


Figure 1: (i) Localization of flumazenil and phenobarbital (yellow shape) at active sites at GABA A (ii) 2D interactions of drugs with amino acid residues

The molecular docking calculations tested compounds showed good binding affinity to the $GABA_A$ receptor compared to the reference compounds (**Table 2**). Different bonds were observed in the binding of tested compounds **1 - 6**, the $GABA_A$ receptor, such as H-bonding, Van der well forces, and electrostatic attraction. The observed interaction was between the aromatic ring of compounds **1 - 6** with Val 8: 292, ALA B: 328, LEU: 332, and LYS B: 71.

Compound **6** exhibited stronger interactions with active sites and with the highest binding affinities scores of the series $GABA_A$ receptor (-9.1 and -8.0 Kcal/mol) for 6X3W and 6D6T, compared to standards (phenobarbital and flumazenil) with their binding affinity scores of -6.3 and -6.5 kcal/mol, -5.8 and -7.5 kcal/mol, respectively. The strength of binding is attributed to H-bonding with arginine amino acid 102 and more hydrophobic binding from the naphthyl group.

Compounds (**3** and **5**) with electron-donating groups (-OCH3, -OH) show similar binding energies (-8.0 kcal/mol). The binding affinity of compound **2** to 6D6T (-7.7 kcal/mol) is higher than that of compounds **3** and **5**, with electron-donating groups. Introduction of a chlorine atom at the *p*-position on the aromatic ring has the same binding energy as compounds (**3** and **5**) with electron-donating groups.

Table 2: Binding energy of compounds **1** - **6** with $GABA_A$ receptors

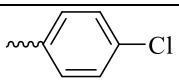
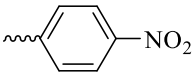
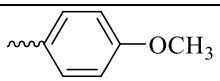
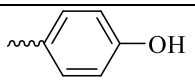
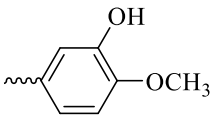
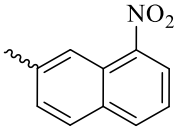
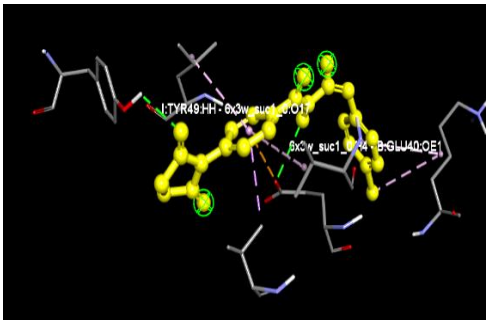
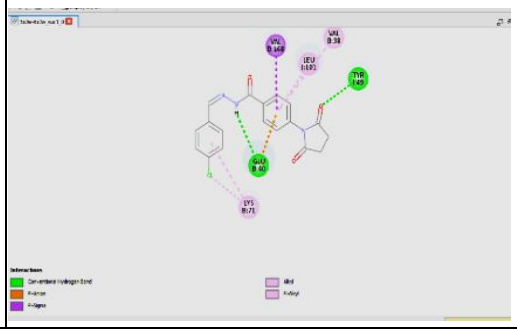
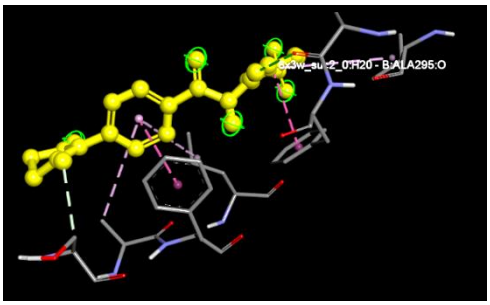
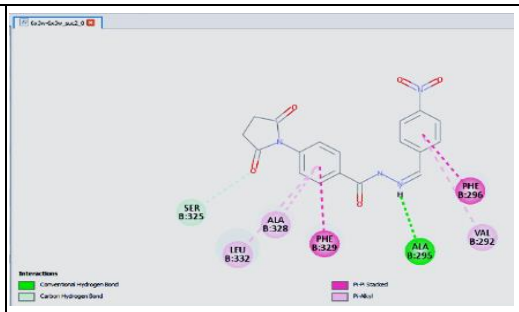
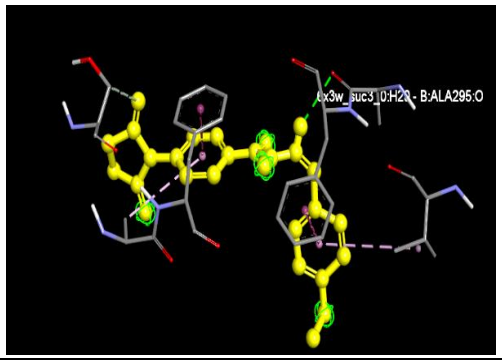
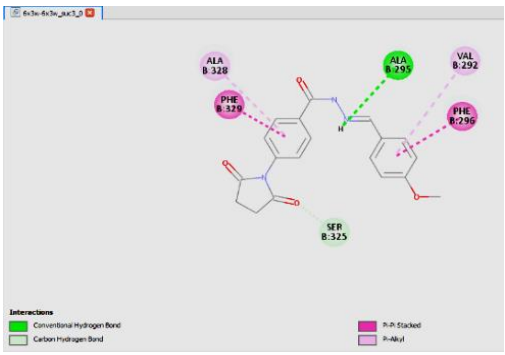
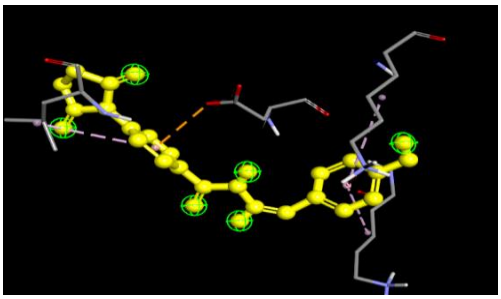
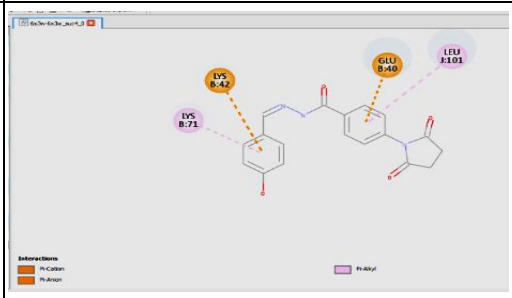
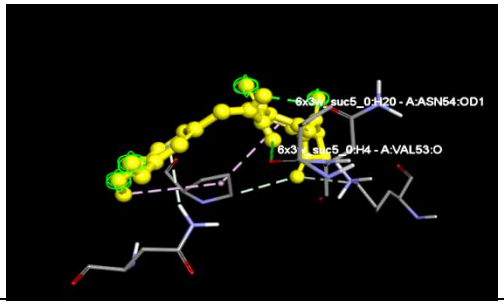
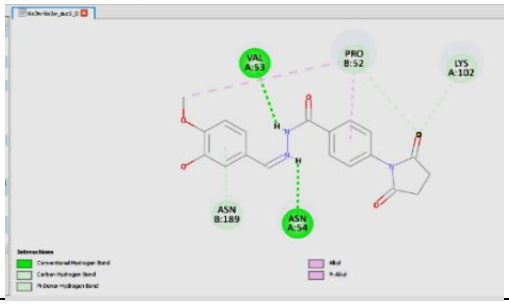
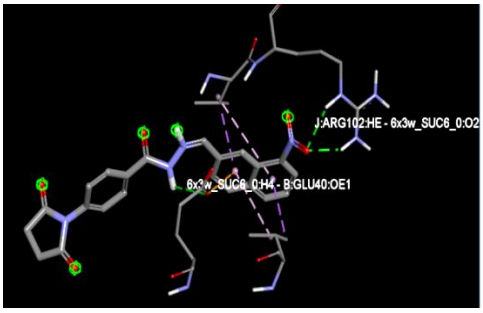
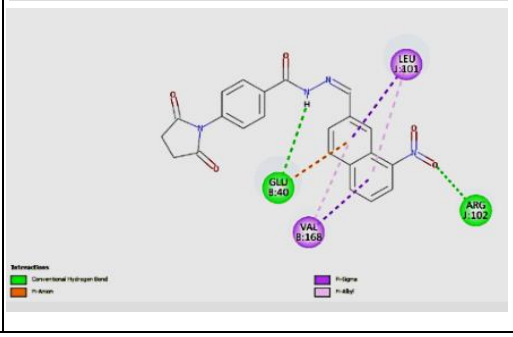
Compound	R	M. Wt	Docking energy (kcal/mol)	
			6x3 w	6D6T
Phenobarbital			-6.5	-6.3
Flumazenil			-7.3	-5.8
1		355.78	-8.1	-7.1
2		366.33	-8.1	-7.7
3		351.36	-8.0	--7.0
4		337.33	-8.0	-7.2
5		367.36	-7.7	-7.3
6		416.39	-9.1	-8.0

Table 3: Distribution within the active site of the $GABA_A$ receptor (A) and predicted formed bonds with the $GABA_A$ receptor (B)

Comp	A	B
1		

2		
3		
4		
5		
6		

Prediction of ADMIT properties and drug-likeliness

In-Silico ADMET prediction: To verify drug-likeliness, canonical SMILES format of the designed compounds **1** - **6** were used in Swiss ADME (http://www.swissadme.ch/index.php) [22, 23]. The main bioavailability parameters were molecular weight (g/mol), lipophilicity (XlogP3), solubility (log S), polarity (Topological Polar Surface Area - TPSA in Å^2), saturation (fraction of carbon atoms in Sp3 hybridization-Csp3), and flexibility (No

of rotatable bonds). Absorption parameters such as human intestinal absorption, blood-brain barrier, P-glycoprotein interaction (substrate or inhibitor), and metabolism (inhibitor or substrate) of the bio-active molecules with different cytochrome P450 enzymes, QSAR data for prediction of absorption, distribution, metabolism, excretion, and toxicity (ADMET) [24, 25].

Drug-like molecules, considering Ghose, Veber, Egan, Muegge, and Lipinski rules and good ADMET properties, were chosen as ligands in a subsequent molecular docking procedure. Molecular weight ≤ 500, hydrogen bond acceptor ≤ 10, hydrogen bond donor ≤ 5, Log P ≤ 5, Molar refractivity ≤ 140, comply with Lipinski's Rule of five and then log p o/w range between -2 to 6.5, polar surface area range between 7 to 200, log S (Silicos-it) range lie above -4 and the drug score value above 0.5 is accepted one for designed compounds.

Table Error! No text of specified style in document.**:** ADME results of designed compounds

Comp.	M. Wt	nHA	nRB	nHBD	nHBA	MR	TPSA (Å²)	Log *Po*/w	Log S (Silicos-IT)
1	355.78	25	5	1	4	97.66	78.84	2.52	-5.80
2	366.33	27	6	1	6	102.41	131.33	0.25	-4.56
3	351.36	26	6	1	5	99.14	88.07	1.95	-5.32
4	337.33	25	5	2	5	94.68	99.07	1.65	-4.62
5	367.36	27	6	2	6	101.17	108.30	1.69	-4.73
6	416.39	31	6	1	6	119.91	131.33	1.37	-6.20

Molecular weight: M.Wt, Number of heavy atom: nHA, Number of aromatic Heavy atom: nAHA, Number of sp3 hybridized carbon out of total carbon count: F. Csp3, Number of rotatable bonds: nRB, Number of H-bond acceptors: nHBA, Number of H-bond donors: nHBD, Molar refractivity: MR, topological polar surface area: TPSA

Pharmacokinetics and drug likeness: All investigated compounds showed high gastrointestinal absorption, indicating suitability for oral bioavailability. Regarding Cytochrome P450 (CYP450) inhibition, compound **1** exhibited inhibitory effects on CYP1A2, CYP2C19, and CYP2C9 isomers, while showing no significant effect on CYP2D6 and CYP3A4. In comparison with compounds **2 - 6**, compound **3** specifically inhibited CYP2C9.

Table 5: Pharmacokinetics parameters of the designed Schiff's base of Succinimide derivatives calculated with Swiss GI absorption

Comp	Absorption	BBB	P-gp Substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 Inhibitor	Log *Kp* (Skin Permeation) (cm/s)
1	high	no	no	yes	yes	yes	no	no	-7.14
2	high	no	yes	no	no	no	no	no	-8.06
3	high	no	no	no	no	yes	no	no	-7.69
4	high	no	no	no	no	no	no	no	-7.46
5	high	no	yes	no	no	no	no	no	-7.67
6	high	no	yes	no	no	no	no	no	-7.48

BBB permeant: P-gp: glycoprotein, CYP: Cytochrome P450 isomer

Drug-likeness prediction: Drug-likeness predictions were conducted based on established criteria, including Lipinski's Rule of Five parameters. According to Lipinski's Rule of Five, which suggests that absorption or permeation is more likely for molecules generally within accepted ranges, all designed compounds (**1 - 6**) met these criteria. Their molecular weights were typically under 500 g/mol. The Lipophilicity values (Log P o/w) for the mono-substituted compounds ranged from 1.37 to 2.52. Furthermore, the compounds exhibited an optimum number of hydrogen bond donors (**1 - 2**) and acceptors (**4 - 6**) (**Table 4)**.

The Ghose filter defines drug-likeness restrictions based on specific physicochemical parameters: a calculated log P value between -7.14 and -8.06, with the molecular weight (M. Wt) between 337.33 and 416.39, a molar refractivity between 97.66 and 119.91, and a total atom range of 25-31. All designed compounds **1 - 6** were found to comply with the established criteria for parameter assessment **(Table 5)**. The Veber rule subjects drug-likeness constraints as follows: a rotatable bond count ≤ 10 and a polar surface area (PSA) ≤ 140. All the designed compounds (**1 - 6**) adhered to these parameters, further supporting their drug-like characteristics. All compounds (**1 - 6**) showed a similar bioavailability score of 0.55 **(Table 6)**.

Table 6: Drug likeness of designed Schiff's base derivatives of succinimide calculated with Swiss ADME database

Comp.	Lipinski	Ghose	Veber	Egan	Muegge	BA. Score
1	Yes	Yes	Yes	Yes	Yes	0.55
2	Yes	Yes	Yes	Yes	Yes	0.56
3	Yes	Yes	Yes	Yes	Yes	0.55
4	Yes	Yes	Yes	Yes	Yes	0.55
5	Yes	Yes	Yes	Yes	Yes	0.55
6	Yes	Yes	Yes	Yes	Yes	0.56

BA.S. Bioavailability score

Conclusion: A series of pyrrolidine-2, 5-dione Schiff base derivatives was designed against the GABA-A receptor. The compound exhibited high binding affinity toward the active site when compared to the reference compounds (flumazenil and phenobarbital). The nitro-substituted compounds (**2** and **6**) exhibited a strong binding affinity. The predicted ADMET properties also indicated acceptable pharmacokinetic and toxicity properties. Based on the integration of molecular docking results, ADMET predictions, and reported biological activity, these pyrrolidine-2, 5-dione Schiff base derivatives represent promising candidates for antiepileptic drug development. In particular, compounds **2** and **6** can be regarded as lead compounds for further structural optimization to enhance binding affinity and therapeutic efficacy toward the GABA-A receptor.

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