

# ADME and In Silico Profiling of Conjugated Schiff Bases to Assess Their Potential as a Human Carbonic Anhydrase II IX XII Inhibitor

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**Abstract:** The present study investigates the ADME properties and in silico inhibitory potential of a series of conjugated Schiff bases (L1–L11) against human carbonic anhydrase isoforms II, IX, and XII, using acetazolamide, SLC-0111 (PubChem CID: 49836916), and U-104 (PubChem CID: 9813825) as reference drugs. Molecular docking using CB-Dock and AutoDock Vina revealed that ligand L5 exhibited the strongest binding affinities (−8.3, −9.0, and −9.8 kcal/mol, respectively), outperforming the reference inhibitors. ADME profiling using SwissADME indicated that all ligands complied with Lipinski's Rule of Five, with molecular weights below 500 Da, moderate LogP values, and high gastrointestinal absorption. The synthetic accessibility scores (2.32–3.34) suggested ease of laboratory synthesis. Overall, these results highlight ligand L5 as a promising human carbonic anhydrase inhibitor with favorable pharmacokinetic properties, warranting further in vitro and in vivo evaluation, particularly for isoform-specific inhibition and therapeutic potential.

**Keywords:** conjugated Schiff bases; human carbonic anhydrase inhibitors; molecular docking; ADME profiling; Lipinski's rule of five; pharmacokinetics; acetazolamide; synthetic accessibility.

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## 1. Introduction

Carbonic anhydrases (CAs) are ubiquitous metalloenzymes that catalyze the reversible hydration of carbon dioxide to bicarbonate and protons, a fundamental reaction essential for maintaining acid–base balance, CO<sub>2</sub> transport, and ion regulation in biological systems. Among the 15 human isoforms identified so far, CA II, CA IX, and CA XII have received considerable attention because of their distinct physiological and pathological roles [1]. CA II is one of the most active and widely distributed cytosolic isoforms, and its inhibition has proven beneficial in the management of glaucoma and epilepsy [2]. By decreasing aqueous humor formation, CA II inhibitors effectively reduce intraocular pressure, while in the central nervous system, they modulate neuronal excitability to control seizures.

In contrast, the membrane-associated isoforms CA IX and CA XII are overexpressed in several types of hypoxic tumors, where they regulate extracellular pH and support tumor proliferation, metastasis, and therapy resistance. Consequently, selectively inhibiting these isoforms is an attractive therapeutic strategy in oncology, as it can disrupt the acidic tumor microenvironment that facilitates cancer progression and treatment resistance.

Despite the clinical success of classical inhibitors such as acetazolamide and methazolamide, their lack of isoform selectivity frequently results in undesirable adverse effects, including metabolic acidosis, electrolyte imbalance, and taste alteration, which restrict their long-term application [3]. The high structural similarity among CA isoforms makes it particularly challenging to design inhibitors that selectively target tumor-associated isoforms such as CA IX and CA XII while sparing physiologically essential isoforms like CA I and CA II [4]. Therefore, the design of isoform-selective CA inhibitors with optimized pharmacokinetic and pharmacodynamic properties remains a critical research focus in medicinal chemistry.

Schiff bases, characterized by their azomethine ( $-C=N-$ ) linkage, represent a versatile and widely studied class of organic compounds with notable biological and pharmacological potential. Their ability to form stable coordination complexes with transition metals and engage in multiple non-covalent interactions within enzyme active sites enhances their therapeutic relevance. Schiff bases are also recognized for their favorable physicochemical and pharmacophoric properties, which contribute to improved bioavailability and drug-likeness. Several studies have reported Schiff base derivatives as potent CA inhibitors, yet detailed exploration of conjugated aromatic heterocyclic Schiff bases against multiple CA isoforms remains limited [5].

In this context, the present study investigates the *in silico* inhibitory potential and ADME characteristics of a new series of conjugated Schiff bases (L1–L11) against human CA II, CA IX, and CA XII, using well-known inhibitors as reference compounds [6]. The study aims to identify novel lead molecules exhibiting high binding affinity, favorable pharmacokinetic profiles, and isoform selectivity, providing a rational basis for subsequent *in vitro* and *in vivo* evaluation toward the development of selective carbonic anhydrase inhibitors [7,8].

## 2. Materials and Methods

### 2.1. Retrieval of protein structures and ligand preparation.

The three-dimensional (3D) crystal structures of human carbonic anhydrase (CA) isoforms—CA II (PDB ID: 1CA2), CA IX catalytic domain (PDB ID: 3IAI), and CA XII (PDB ID: 1JD0)—were retrieved in PDB format from the Protein Data Bank [9]. Reference inhibitors—acetazolamide (AZM) (PubChem CID: 1986) for CA II, SLC-0111 (PubChem CID: 49836916) for CA IX, and U-104 (PubChem CID: 9813825), an analog of SLC-0111, for CA XII—were obtained from the PubChem database [10].

A series of Schiff base ligands (L1–L13) was designed using ChemDraw Ultra 12.0 (CambridgeSoft Corporation, USA) (in Table 1). The corresponding SMILES strings were generated, and molecular structures were exported in *.mol* format for subsequent docking and pharmacokinetic analysis. Ligands were energy-minimized using Open Babel 3.1.1, employing the MMFF94 force field with a convergence criterion of  $10^{-6}$  kcal/mol·Å, ensuring geometrical and conformational stability [11]. Optimized structures were saved as *.pdbqt* and *.sdf* files for docking and SwissADME input [12]. All computational steps were performed on a Windows 11 64-bit system with an Intel i7 processor and 16 GB RAM to ensure reproducibility and consistent computational conditions.

**Table 1.** Chemical names and structures of the ligands (L1-L11) utilized in this study.

| Ligand                                                                           | Chemical Structure |
|----------------------------------------------------------------------------------|--------------------|
| L1<br>4-amino-N-[(3Z)-2-oxo-1,2-dihydro-3H-indol-3-ylidene]benzene-1-sulfonamide |                    |
| L2<br>6-(4-chloroanilino)indolizine-1,2(3H,5H)-dione                             |                    |
| L3<br>(3E)-3-[(2-nitrophenyl)imino]-1,3-dihydro-2H-indol-2-one                   |                    |
| L4<br>(3E)-3-[(3-chlorophenyl)imino]-1,3-dihydro-2H-indol-2-one                  |                    |
| L5<br>3-[(1E)-3-oxo-3-phenylprop-1-en-1-yl]-2H-1-benzopyran-2-one                |                    |

## 2.2. Assessment of ADME profiles and drug-likeness evaluation.

The ADME (absorption, distribution, metabolism, and excretion) characteristics of the ligands were predicted using the SwissADME web server. Physicochemical descriptors, lipophilicity (iLOGP, XLOGP3, WLOGP), water solubility (ESOL), pharmacokinetics (GI absorption, BBB permeability, and CYP inhibition), and medicinal chemistry filters were calculated (in Table 2).

Drug-likeness was assessed according to Lipinski's Rule of Five [13,14]. Compounds meeting these criteria were considered potentially drug-like. GI absorption was categorized as high ( $\geq 85\%$ ), moderate (60–84%), or low ( $< 60\%$ ). BOILED-Egg analysis was used to visualize predicted BBB permeability, where compounds in the yolk region indicate CNS accessibility.

**Table 2.** ADME properties of ligands (L1-L11).

| Ligand | Physicochemical properties                                                                                                                                            | Lipophilicity               | Water solubility                                                                | Pharmacokinetic properties                                                                                                                                                      | Drug likeness                                                                                                                              | Medicinal Chemistry                                                                             |
|--------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| L1     | MF=C <sub>14</sub> H <sub>13</sub> N <sub>4</sub> O <sub>3</sub> S<br>MW= 317.34<br>Da<br>nHA=22<br>nArHA= 12<br>Fraction (Csp <sup>3</sup> )=0.07<br>nRB=2<br>nHBA=5 | iLOGP= -3.04<br>XLOGP=31.05 | ESOL Log S=-2.74<br>ESOL Solubility (mg/ml)= 5.77E-01<br><br>ESOL Class=Soluble | GI absorption= High<br>BBB permeant=No<br>Pgp substrate=Yes<br>CYP1A2 inhibitor=No<br>CYP2C19 inhibitor=No<br>CYP2C9 inhibitor=No<br>CYP2D6 inhibitor=No<br>CYP3A4 inhibitor=No | Lipinski Violations=0<br>Ghose violations=0<br>Veber violations=0<br>Egan violations=1<br>Muegge violation=0<br>Bioavailability Score=0.55 | PAINS alerts=1<br>Brenk alerts=1<br>Lead likeness violations=0<br>Synthetic Accessibility= 2.75 |
| L2     | MF=C <sub>15</sub> H <sub>11</sub><br>CIN <sub>2</sub> O MW=270.71<br>nHA=19                                                                                          | iLOGP=2.53<br>XLOGP=33.24   | ESOL Log S=3.96                                                                 | GI absorption= High<br>BBB permeant=Yes<br>Pgp substrate=No                                                                                                                     | Lipinski violations=0                                                                                                                      | PAINS alerts=0                                                                                  |

| Ligand | Physicochemical properties                                                                         | Lipophilicity               | Water solubility                                                                                     | Pharmacokinetic properties                                                                                                                                                             | Drug likeness                                                                                                                                                  | Medicinal Chemistry                                                                                  |
|--------|----------------------------------------------------------------------------------------------------|-----------------------------|------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
|        | nArHA= 12<br>Fraction<br>Csp3=0.07<br>nRB=1<br>nHBA= 2                                             |                             | ESOL<br>Solubility<br>(mg/ml)=2.96<br>E-02<br><br>ESOL<br>Class=Soluble                              | CYP1A2inhibitor=Yes<br>CYP2C19<br>inhibitor=Yes<br>CYP2C9 inhibitor= No<br>CYP2D6 inhibitor=No<br>CYP3A4 inhibitor=No                                                                  | Ghose<br>violations=0<br>Veber<br>violations=0<br>Egan<br>violations=0<br>Muegge<br>violations=0<br>Bioavailability<br>Score=0.55                              | Brenk alerts=1<br>Lead likeness<br>violations=0<br>Synthetic<br>Accessibility=<br>2.59               |
| L3     | MF=<br>C14H10CIN2O<br>MW=257.69<br>nHA==18<br>nArHA= 12<br>Fraction Csp3=0.07<br>nRB= 1<br>nHBA= 2 | iLOGP= - 1.41<br>XLOGP=33.8 | ESOL Log S=- 4.26<br>ESOL Solubility<br>(mg/ml)=1.42 E-02<br><br>ESOL<br>Class=Moderately<br>soluble | GI absorption=High<br>BBB permeant=Yes<br>Pgp substrate=Yes<br>CYP1A2<br>inhibitor=Yes<br>CYP2C19<br>inhibitor=No CYP2C9<br>inhibitor=No CYP2D6<br>inhibitor=No CYP3A4<br>inhibitor=No | Lipinski<br>violations=0<br>Ghose<br>violations =0<br>Veber<br>violations=0<br>Egan<br>violations=0<br>Muegge<br>violations=0<br>Bioavailability<br>Score=0.55 | PAINS alerts=1<br>Brenk alerts=0<br>Lead likeness<br>violations=1<br>Synthetic<br>Accessibility=2.32 |
| L4     | MF=<br>C14H10N3O3<br>MW=268.25<br>nHA= 20<br>nArHA=12<br>Fraction Csp3=0.07<br>nRB= 2<br>nHBA= 4   | iLOGP= - 1.78<br>XLOGP=33   | ESOL Log S=- 3.71<br>ESOL Solubility<br>(mg/ml)=5.29 E-02<br><br>ESOL<br>Class=Soluble               | GI absorption= High<br>BBB permeant=No<br>Pgp substrate=Yes<br>CYP1A2inhibitor=Yes<br>CYP2C19inhibitor=No<br>CYP2C9 inhibitor=No<br>CYP2D6 inhibitor=No<br>CYP3A4 inhibitor=No         | Lipinski<br>violations=0<br>Ghose<br>violations=0<br>Veber<br>violations=0<br>Egan<br>violations=0<br>Muegge<br>violation=0<br>Bioavailability<br>Score=0.5 5  | PAINS alerts=1<br>Brenk alerts=2<br>Lead likeness<br>violations=0<br>Synthetic<br>Accessibility=2.61 |
| L5     | MF=C18H12O3<br>MW=276.29<br>nHA= 21<br>nArHA=16<br>Fraction Csp3=0<br>nRB= 3<br>nHBA= 3            | iLOGP=2.62<br>XLOGP=33.32   | ESOL Log S=-4.01<br>ESOL Solubility<br>(mg/ml)=2.70E<br>-02<br><br>ESOL<br>Class=Soluble             | GI absorption=High<br>BBB permeant=Yes<br>Pgp substrate=No<br>CYP1A2<br>inhibitor=Yes<br>CYP2C19inhibitor=No<br>CYP2C9 inhibitor=No<br>CYP2D6 inhibitor=No<br>CYP3A4 inhibitor=No      | Lipinski<br>violations=0<br>Ghose<br>violations=0<br>Veber<br>violations=0<br>Egan<br>violations= 0<br>Muegge<br>violation=0<br>Bioavailability<br>Score=0.55  | PAINS alerts=0<br>Brenk alerts=1<br>Lead likeness<br>violations=0<br>Synthetic<br>Accessibility=3.34 |
| L6     | MF=C13H13N2O2S<br>MW=261.32<br>nHA=18<br>nArHA= 12<br>Fraction Csp3=0<br>nRB=3<br>nHBA=3           | iLOGP - 2.61<br>XLOGP3=2.13 | ESOL Log S=-3.1<br>ESOLSolubility<br>(mg/ml)=2.09 E-01<br><br>ESOL Class=Soluble                     | GI absorption=High<br>BBB permeant=No<br>Pgp substrate=Yes<br>CYP1A2inhibitor=No<br>CYP2C19inhibitor=No<br>CYP2C9 inhibitor=No<br>CYP2D6inhibitor=No<br>CYP3A4inhibitor=No             | Lipinski<br>violations=0<br>Ghose<br>violations=0<br>Veber<br>violations=0<br>Egan<br>violations=0<br>Muegge<br>violation=0<br>Bioavailability<br>Score=0.55   | PAINS alerts=0<br>Brenk alerts=1<br>Lead likeness<br>violations=0<br>Synthetic<br>Accessibility=2.82 |
| L7     | MF=C13H12CIN<br>2O2S<br>MW=295.76<br>nHA=19<br>nArHA=12<br>Fraction Csp3=0<br>nRB= 3<br>nHBA= 3    | iLOGP=- 2.8<br>XLOGP=32.76  | ESOL Log S=-3.68<br>ESOL Solubility<br>(mg/ml)= 6.15E-02<br><br>ESOL Class=Soluble                   | GIabsorption=High<br>BBBpermeant=No<br>Pgp substrate=Yes<br>CYP1A2 inhibitor=No<br>CYP2C19<br>inhibitor=No CYP2C9<br>inhibitor=No CYP2D6<br>inhibitor=No CYP3A4<br>inhibitor=No        | Lipinski<br>violations=0<br>Ghose<br>violations=0<br>Veber<br>violations=0<br>Egan<br>violations=0<br>Muegge<br>violation=0                                    | PAINS alerts=0<br>Brenk alerts=1<br>Lead likeness<br>violations=0<br>Synthetic<br>Accessibility=2.9  |

| Ligand | Physicochemical properties                                                                   | Lipophilicity             | Water solubility                                                               | Pharmacokinetic properties                                                                                                                                                        | Drug likeness                                                                                                                              | Medicinal Chemistry                                                                            |
|--------|----------------------------------------------------------------------------------------------|---------------------------|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
|        |                                                                                              |                           |                                                                                |                                                                                                                                                                                   | Bioavailability Score=0.55                                                                                                                 |                                                                                                |
| L8     | MF=C13H11ClN2O2S<br>MW=294.76<br>nHA=19<br>nArHA=12<br>Fraction Csp3=0<br>nRB= 3<br>nHBA= 4  | iLOGP=2.02<br>XLOGP=32.41 | ESOL Log S=-3.46<br>ESOL Solubility (mg/ml)=1.03E-01<br><br>ESOL Class=Soluble | GI Absorption=High<br>BBB permeant=No<br>Pgp substrate=No<br>CYP1A2 inhibitor=Yes<br>CYP2C19 inhibitor=Yes<br>CYP2C9 inhibitor=Yes<br>CYP2D6 inhibitor=No<br>CYP3A4 inhibitor=Yes | Lipinski violations=0<br>Ghose violations=0<br>Veber violations=0<br>Egan violations=0<br>Muegge violation=0<br>Bioavailability Score=0.55 | PAINS alerts=0<br>Brenk alerts=1<br>Lead likeness violations=0<br>Synthetic Accessibility=2.47 |
| L9     | MF=C13H12N2O3S<br>MW=276.31<br>nHA= 19<br>nArHA=12<br>Fraction Csp3=0<br>nRB= 3<br>nHBA= 5   | iLOGP=1.41<br>XLOGP=31.65 | ESOL Log S=-2.86<br>ESOL Solubility (mg/ml)=3.80E-01<br><br>ESOL Class=Soluble | GI absorption=High<br>BBB permeant=No<br>Pgp substrate=No<br>CYP1A2 inhibitor=No<br>CYP2C19 inhibitor=No<br>CYP2C9 inhibitor=No<br>CYP2D6 inhibitor=No<br>CYP3A4 inhibitor=No     | Lipinski violations=0<br>Ghose violations=0<br>Veber violations=0<br>Egan violations=0<br>Muegge violation=0<br>Bioavailability Score=0.55 | PAINS alerts=0<br>Brenk alerts=1<br>Lead likeness violations=0<br>Synthetic Accessibility=2.51 |
| L10    | MF=C14H14N2O3S<br>MW=290.34<br>nHA=20<br>nArHA=12<br>Fraction Csp3=0.07<br>nRB= 4<br>nHBA= 5 | iLOGP=1.62<br>XLOGP=31.77 | ESOL Log S=-2.94<br>ESOL Solubility (mg/ml)=3.37E-01<br><br>ESOL Class=Soluble | GI Absorption=High<br>BBB permeant=No<br>Pgp substrate=No<br>CYP1A2 inhibitor=No<br>CYP2C19 inhibitor=No                                                                          | Lipinski violations=0<br>Ghose violations=0<br>Veber violations=0<br>Egan violations=0<br>Muegge violation=0<br>Bioavailability Score=0.55 | PAINS alerts=0<br>Brenk alerts=1<br>Lead likeness violations=0<br>Synthetic Accessibility=2.45 |
| L11    | MF=C14H14N2O4S<br>MW=306.34<br>nHA=21<br>nArHA=12<br>Fraction Csp3=0.07<br>nRB= 4<br>nHBA=6  | iLOGP=1.9<br>XLOGP=31.61  | ESOL Log S=-2.91<br>ESOL Solubility (mg/ml)=3.75E-01<br><br>ESOL Class=Soluble | GI Absorption=High<br>BBB permeant=No<br>Pgp substrate=No<br>CYP1A2 inhibitor=No<br>CYP2C19 inhibitor=No<br>CYP2C9 inhibitor=Yes<br>CYP2D6 inhibitor=No<br>CYP3A4 inhibitor=Yes   | Lipinski violations=0<br>Ghose violations=0<br>Veber violations=0<br>Egan violations=0<br>Muegge violation=0<br>Bioavailability Score=0.55 | PAINS alerts=0<br>Brenk alerts=1<br>Lead likeness violations=0<br>Synthetic Accessibility=2.58 |

### 2.3. Molecular docking studies.

Docking simulations were conducted using the CB-Dock server [15]. CB-Dock employs a curvature-based cavity detection algorithm coupled with AutoDock Vina to calculate binding energies ( $\Delta G$ , kcal/mol) and identify favorable binding poses (in Table 3)

Default cavity detection parameters were applied with an automatically generated grid box (typical dimensions:  $20 \times 20 \times 20 \text{ \AA}^3$ ) centered on the predicted binding pocket. The exhaustiveness parameter was set to 8, ensuring balanced computational efficiency and accuracy.

Validation of docking reliability was achieved by re-docking the co-crystallized ligand (acetazolamide) into the CA II binding site. The reproduced docking pose showed an RMSD

< 2.0 Å compared to the crystal structure, confirming the reproducibility and reliability of the docking protocol.

Visualization and interaction mapping were performed using Discovery Studio Visualizer 2021 (Dassault Systèmes BIOVIA, USA) [16] and PyMOL 2.5 [17] (Schrödinger LLC, USA). Key hydrogen bonds, hydrophobic contacts, and  $\pi$ – $\pi$  stacking interactions with catalytic residues were analyzed to interpret structure–activity correlations.

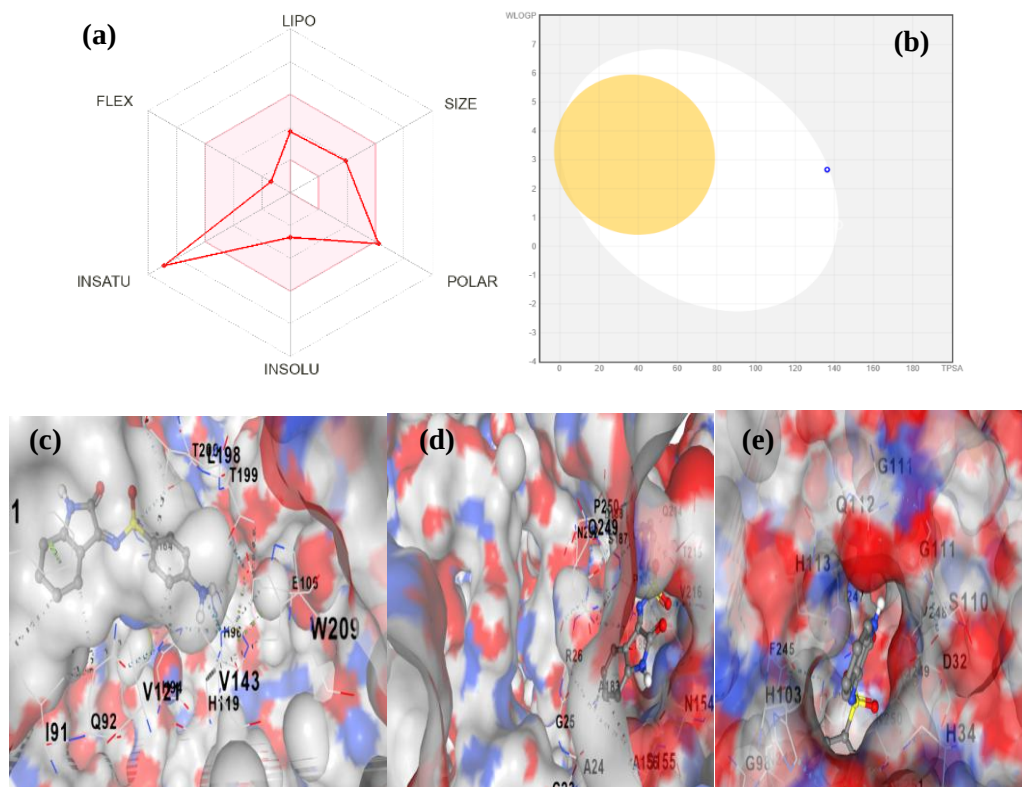
**Table 3.** Cavity-detection guided blind docking-predicted biological characteristics of ligands L1- L11.

| S.No. | Ligand                             | hCA-II | hCA-IX | hCA-XII |
|-------|------------------------------------|--------|--------|---------|
| 1     | L1                                 | -7.5   | -8.6   | -9.5    |
| 2     | L2                                 | -7.2   | -8.1   | -8.9    |
| 3     | L3                                 | -7.3   | -8.2   | -8.6    |
| 4     | L4                                 | -7     | -8.5   | -8      |
| 5     | L5                                 | -8.3   | -9     | -9.8    |
| 6     | L6                                 | -7.3   | -7.3   | -7.6    |
| 7     | L7                                 | -7.1   | -7.8   | -7.6    |
| 8     | L8                                 | -7.9   | -7.8   | -8.8    |
| 9     | L9                                 | -7.9   | -8.1   | -8.8    |
| 10    | L10                                | -7.7   | -7.7   | -8.8    |
| 11    | L11                                | -7.5   | -8     | -8.2    |
| 12    | *Acetazolamide                     | -6.5   | -6.6   | -7.2    |
| 13    | *SLC-0 111 (PubChem CID: 49836916) | ---    | -9.8   | -----   |
| 14    | *U-104 (PubChem CID: 9813825)      | ---    | -----  | -6.1    |

\*Standard or Reference drug according to several studies.

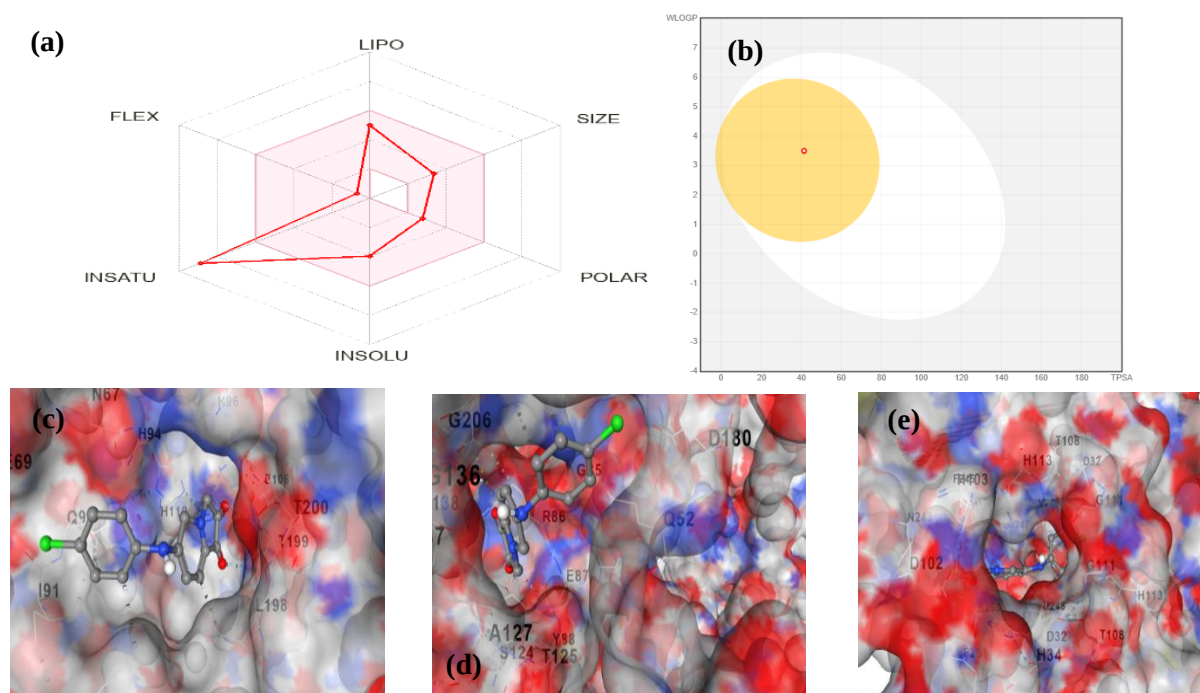
#### 2.4. Target prediction and visualization of ADME properties.

Potential biological targets were predicted using Swiss Target Prediction [18] based on 2D/3D similarity to known ligands [19-23].

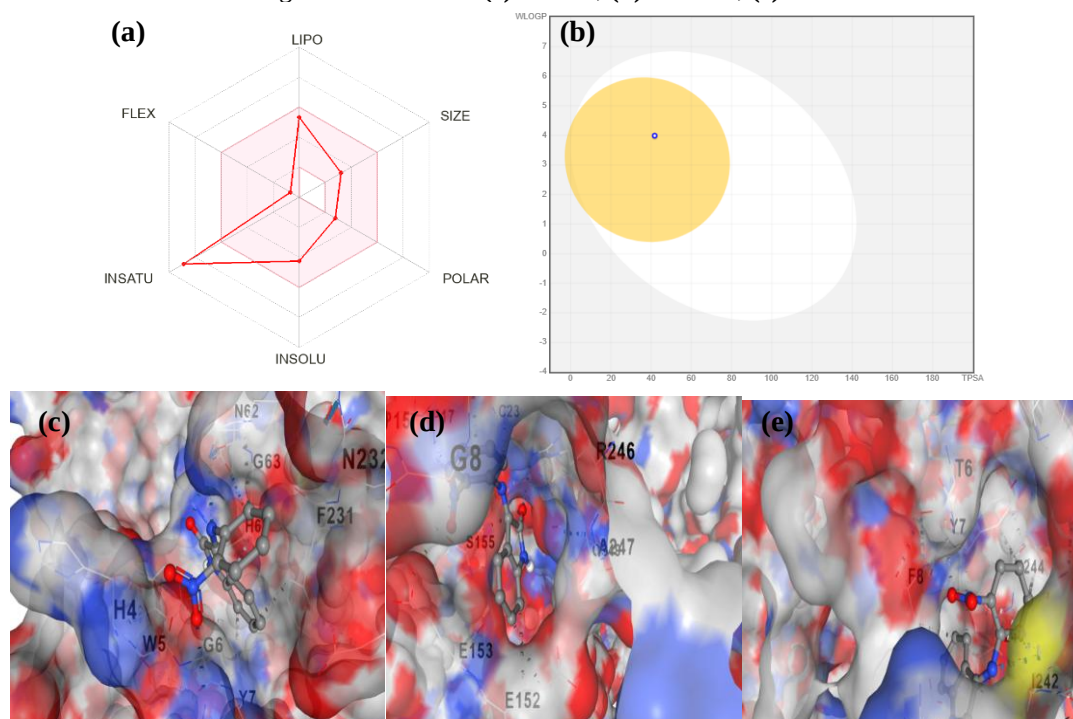


**Figure 1.** (a) SwissADME Bioavailability Radar depicting the physicochemical property space of Compound L1; (b) BOILED-Egg diagram illustrating gastrointestinal absorption and blood–brain barrier permeability prediction for compound L1. The blue dot indicates high GI absorption and non-BBB penetration; Molecular docking studies of L1 for (c) hCA-II; (d) hCA-IX; (e) hCA-XII.

ADME visualization was performed using the Bioavailability Radar of SwissADME, summarizing six key pharmacokinetic parameters—lipophilicity (LIPO), size, polarity (POLAR), insolubility (INSOLU), insaturation (INSATU), and flexibility (FLEX). The fraction of  $sp^3$ -hybridized carbons ( $F_{sp^3}$ ) was computed to estimate molecular complexity, an important determinant of drug-likeness.

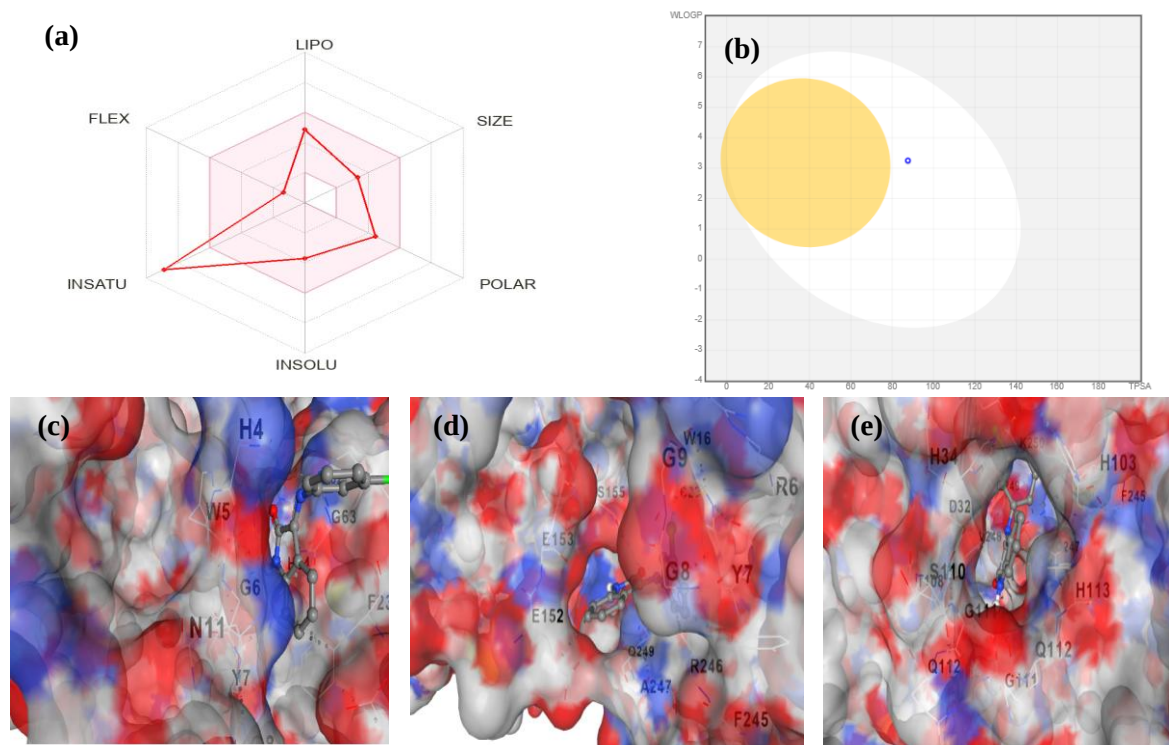


**Figure 2.** (a) SwissADME Bioavailability Radar depicting the physicochemical property space of Compound L2; (b) BOILED-Egg diagram illustrating gastrointestinal absorption and blood–brain barrier permeability prediction for compound L2. The blue dot indicates high GI absorption and non-BBB penetration. Molecular docking studies of L2 for (c) hCA-II; (d) hCA-IX; (e) hCA-XII.

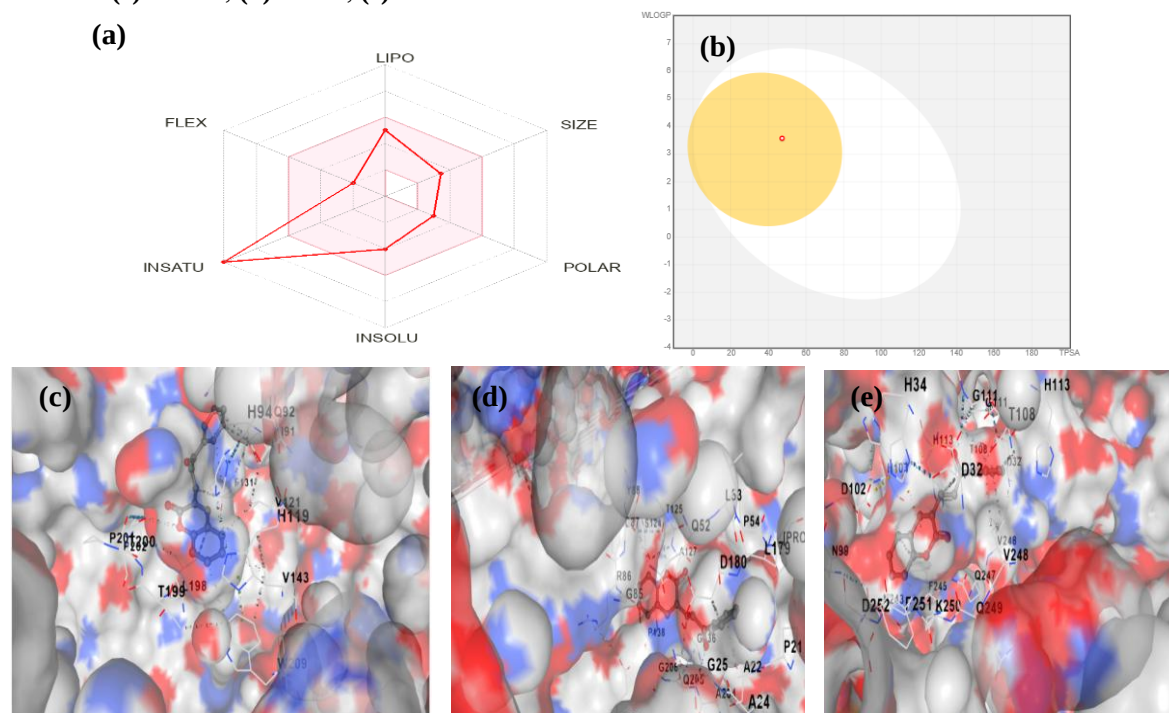


**Figure 3.** (a) SwissADME Bioavailability Radar depicting the physicochemical property space of Compound L3; (b) BOILED-Egg diagram illustrating gastrointestinal absorption and blood–brain barrier permeability prediction for compound L3. The blue dot indicates high GI absorption and non-BBB penetration. Molecular docking studies of L3 for (c) hCA-II; (d) hCA-I; (e) hCA-XII.

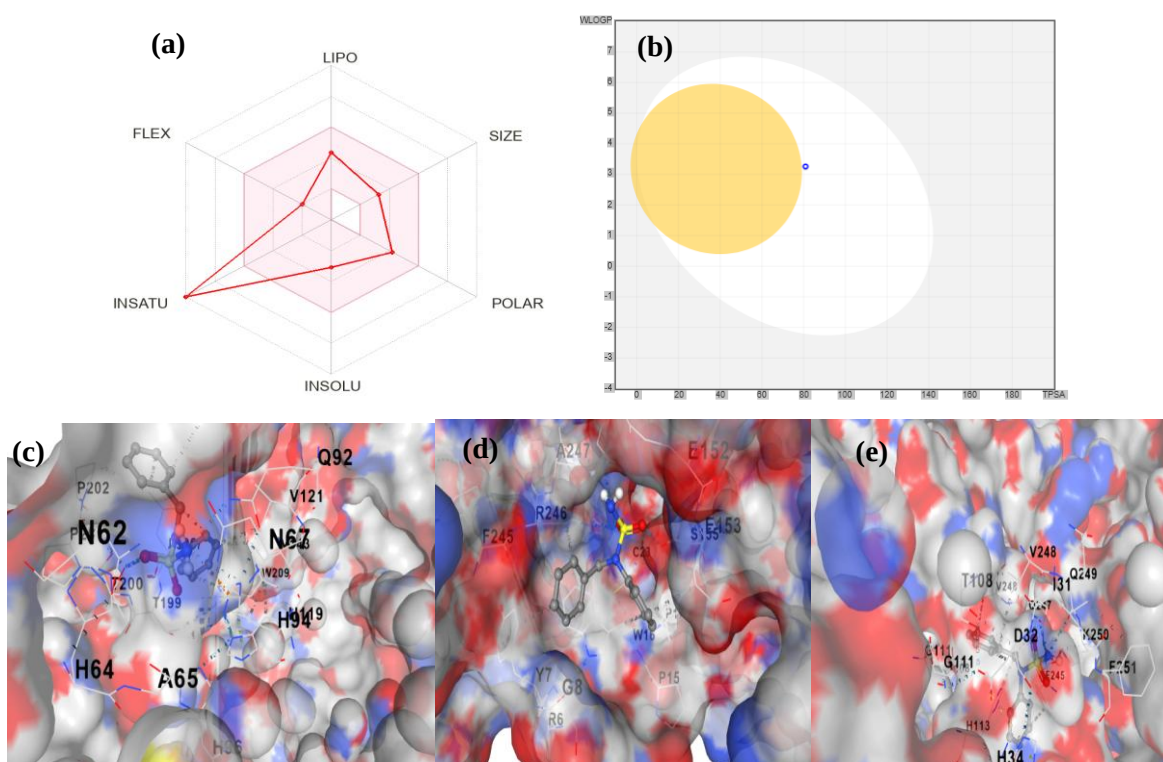
The BOILED-Egg model was again used to graphically assess predicted human intestinal absorption (HIA) and BBB permeability, enabling identification of compounds with favorable oral and CNS availability. All analyses were performed using default software parameters to ensure methodological transparency and reproducibility.



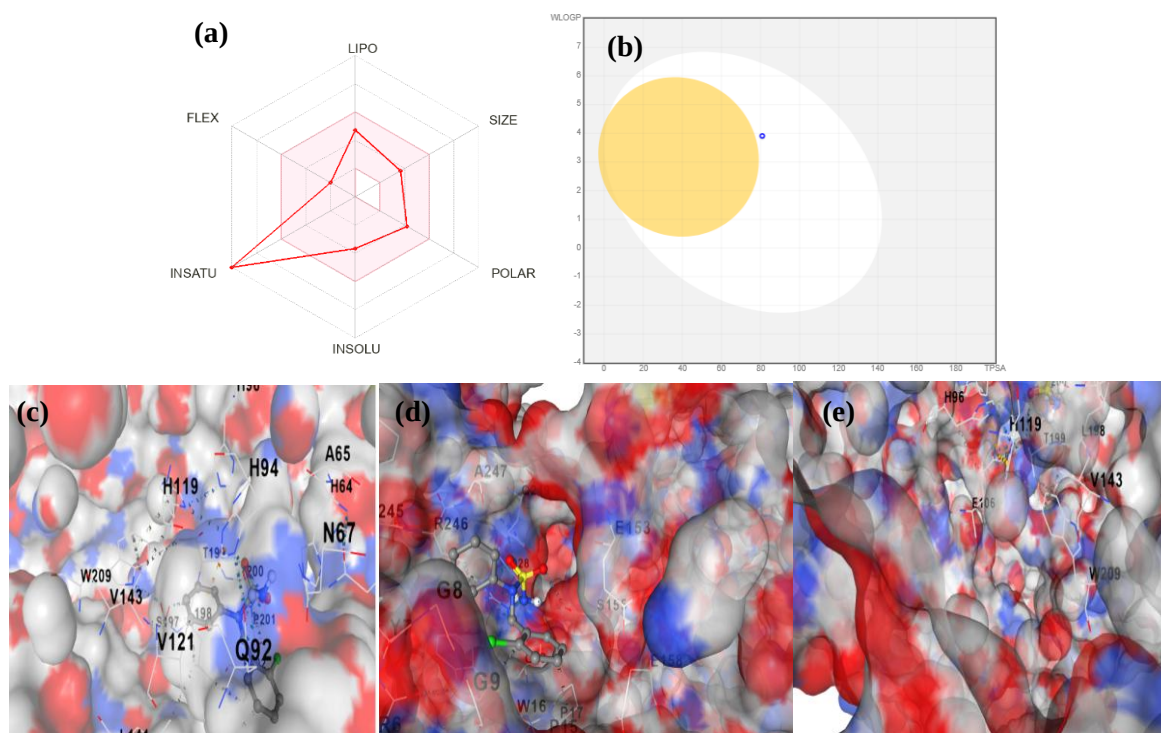
**Figure 4.** (a) SwissADME Bioavailability Radar depicting the physicochemical property space of Compound L4; (b) BOILED-Egg diagram illustrating gastrointestinal absorption and blood–brain barrier permeability prediction for compound L4. The blue dot indicates high GI absorption and non-BBB penetration; Molecular docking studies of L4 for (c) hCA-II; (d) hCA-I; (e) hCA-XII.



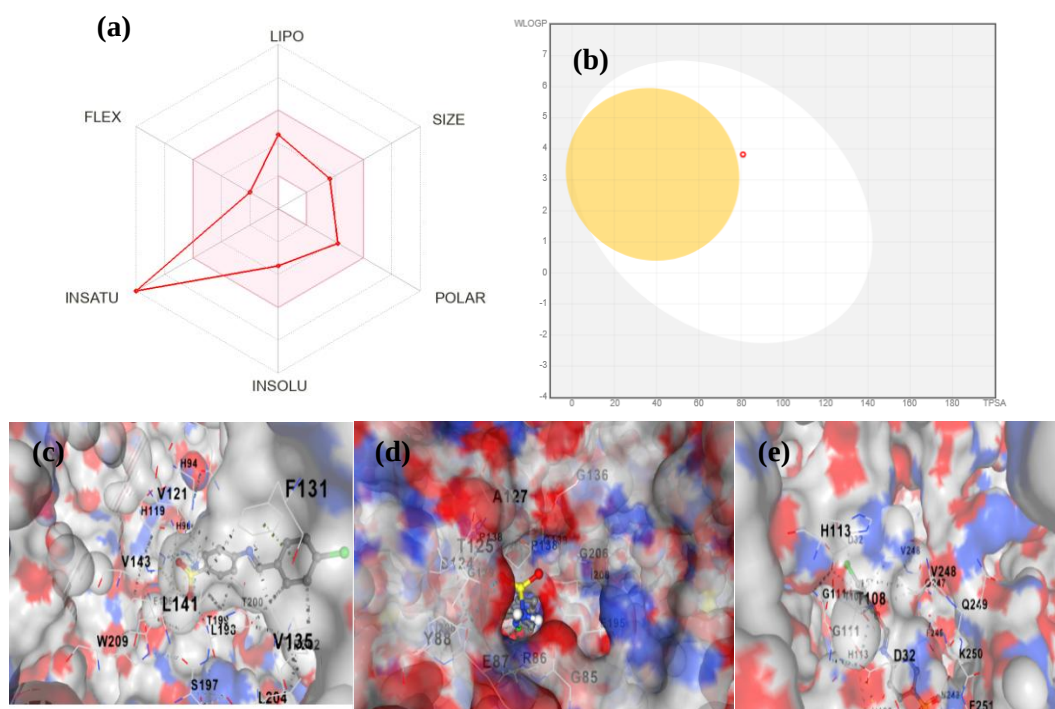
**Figure 5.** (a) SwissADME Bioavailability Radar depicting the physicochemical property space of Compound L5; (b) BOILED-Egg diagram illustrating gastrointestinal absorption and blood–brain barrier permeability prediction for compound L5. The blue dot indicates high GI absorption and non-BBB penetration; Molecular docking studies of L5 for (c) hCA-II; (d) hCA-I; (e) hCA-XII.



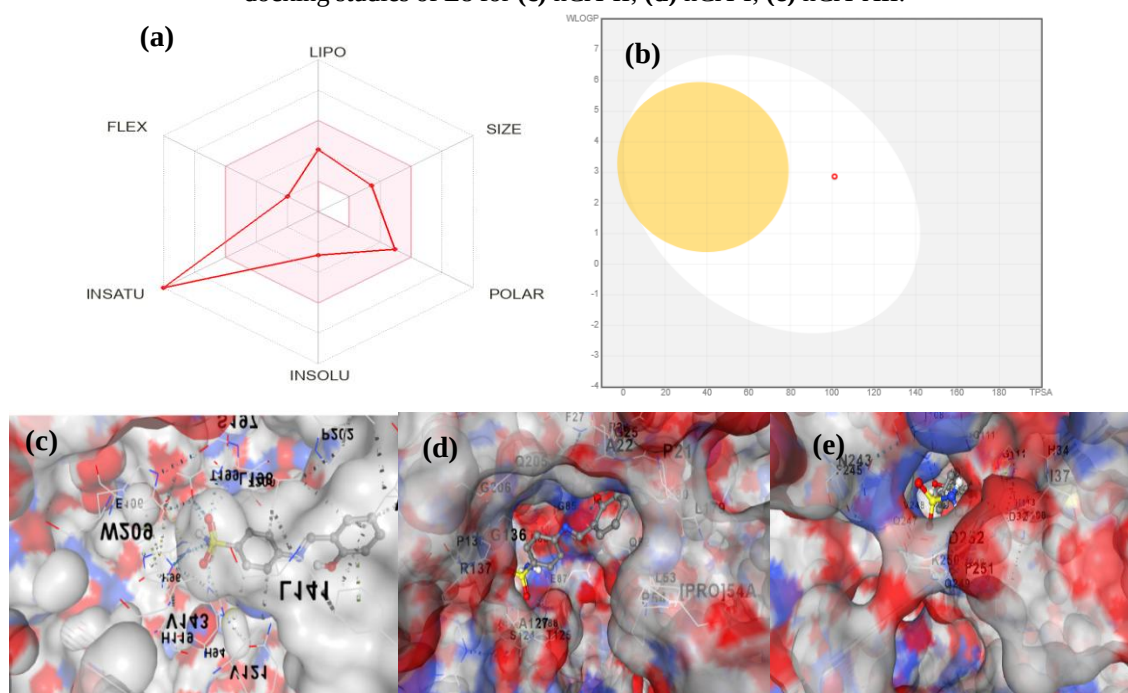
**Figure 6.** (a) SwissADME Bioavailability Radar depicting the physicochemical property space of Compound L6; (b) BOILED-Egg diagram illustrating gastrointestinal absorption and blood–brain barrier permeability prediction for compound L6. The blue dot indicates high GI absorption and non-BBB penetration; Molecular docking studies of L6 for (c) hCA-II; (d) hCA-I; (e) hCA-XII.



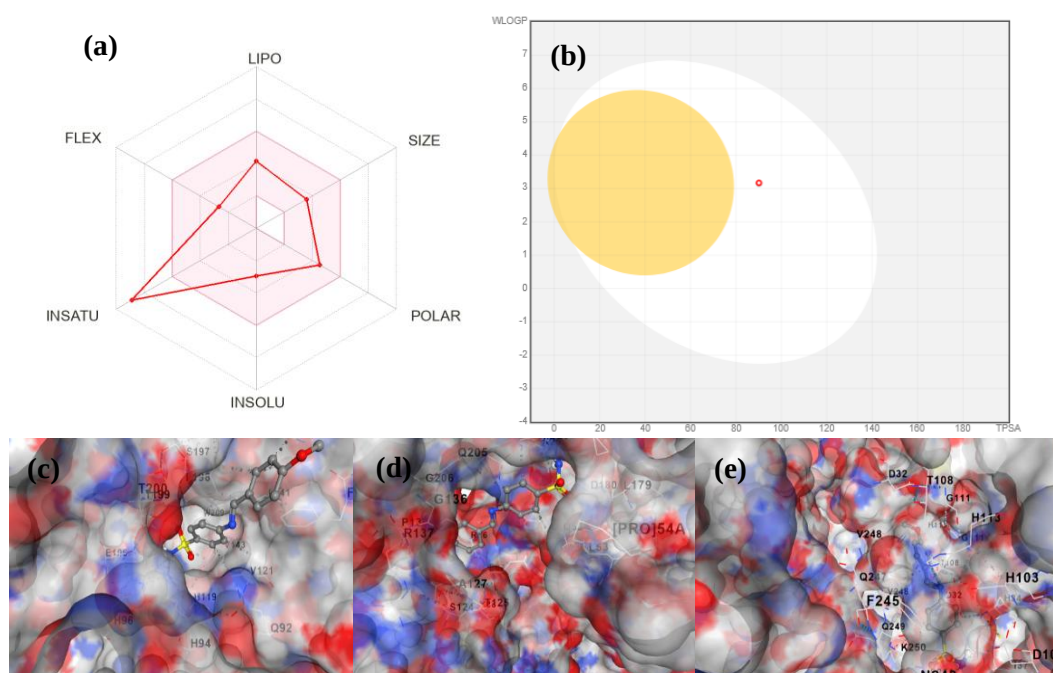
**Figure 7.** (a) SwissADME Bioavailability Radar depicting the physicochemical property space of Compound L7; (b) BOILED-Egg diagram illustrating gastrointestinal absorption and blood–brain barrier permeability prediction for compound L7. The blue dot indicates high GI absorption and non-BBB penetration; Molecular docking studies of L7 for (c) hCA-II; (d) hCA-I; (e) hCA-XII.



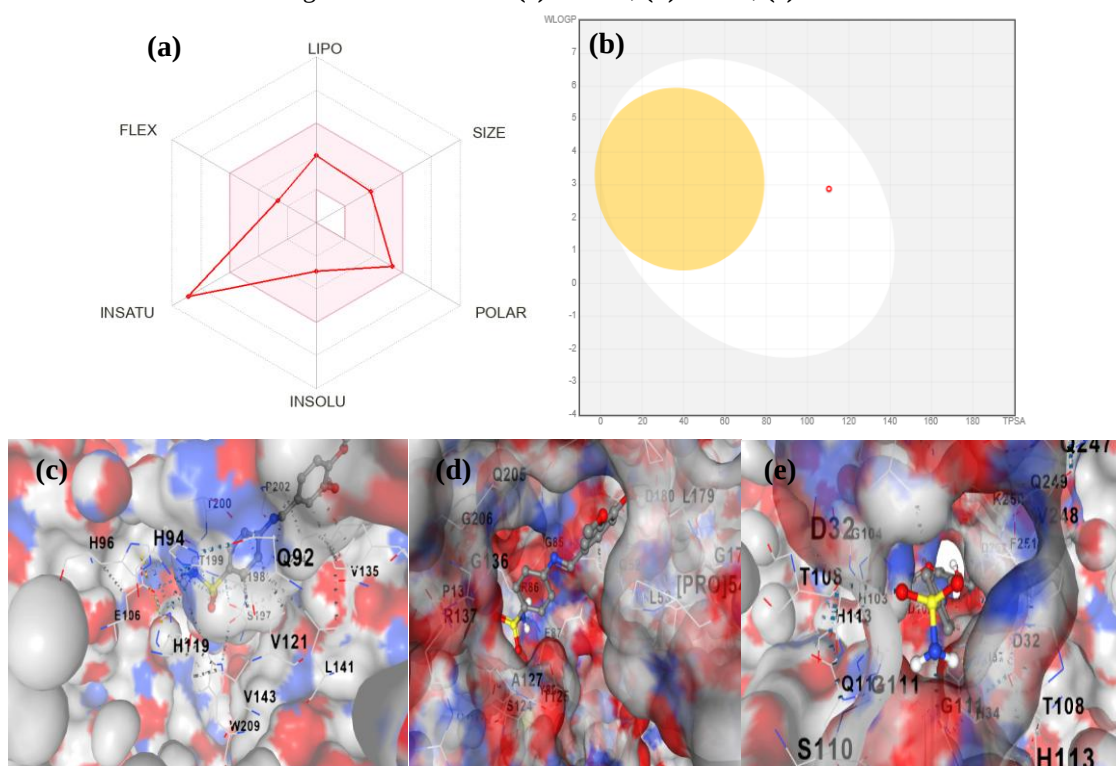
**Figure 8.** (a) SwissADME Bioavailability Radar depicting the physicochemical property space of Compound L8; (b) BOILED-Egg diagram illustrating gastrointestinal absorption and blood–brain barrier permeability prediction for compound L8. The blue dot indicates high GI absorption and non-BBB penetration; Molecular docking studies of L8 for (c) hCA-II; (d) hCA-I; (e) hCA-XII.



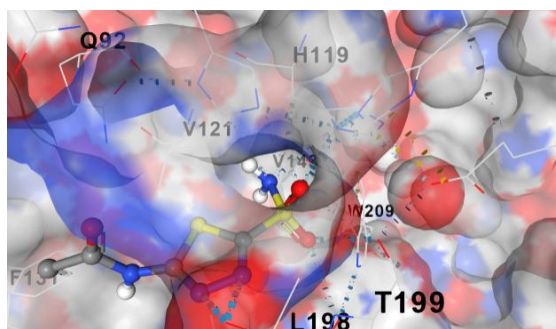
**Figure 9.** (a) SwissADME Bioavailability Radar depicting the physicochemical property space of Compound L9; (b) BOILED-Egg diagram illustrating gastrointestinal absorption and blood–brain barrier permeability prediction for compound L9. The blue dot indicates high GI absorption and non-BBB penetration. Molecular docking studies of L9 for (c) hCA-II; (d) hCA-I; (e) hCA-XII.



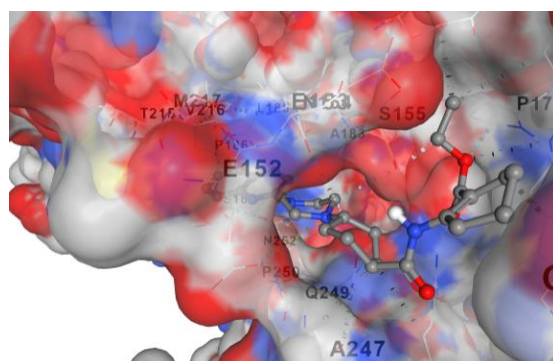
**Figure 10.** (a) SwissADME Bioavailability Radar depicting the physicochemical property space of Compound L10; (b) BOILED-Egg diagram illustrating gastrointestinal absorption and blood–brain barrier permeability prediction for compound L10. The blue dot indicates high GI absorption and non-BBB penetration; Molecular docking studies of L10 for (c) hCA-II; (d) hCA-I; (e) hCA-XII.



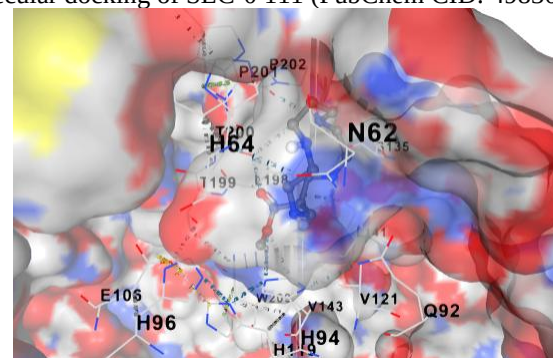
**Figure 11.** (a) SwissADME Bioavailability Radar depicting the physicochemical property space of Compound L11; (b) BOILED-Egg diagram illustrating gastrointestinal absorption and blood–brain barrier permeability prediction for compound L11. The blue dot indicates high GI absorption and non-BBB penetration; Molecular docking studies of L11 (c) hCA-II; (d) hCA-I; (e) hCA-XII.



**Figure 12.** Molecular docking of acetazolamide for hCA-II.



**Figure 13.** Molecular docking of SLC-0 111 (PubChem CID: 49836916) for hCA-IX.



**Figure 14.** Molecular docking of U-104 (PubChem CID: 9813825) for hCA-XII.

The electrostatic surface of hCA II, IX, and XII is shown with the bound Schiff base–coumarin hybrid (L1–L11) represented as a ball-and-stick model. Blue and red regions indicate positively and negatively charged surface potentials, respectively. Hydrogen bonds are shown as green dashed lines. Key interacting residues, including His94, His96, His119, Thr199, Val143, and Glu105, are labeled. A 5 Å scale bar indicates relative dimensions of the binding pocket.

### 3. Results and Discussion

#### 3.1. ADME and physicochemical profiling.

In drug discovery, unfavorable absorption, distribution, metabolism, and excretion (ADME) properties are among the leading causes of attrition in clinical development [24]. Early evaluation of these properties using Computer-Aided Drug Discovery (CADD) tools helps minimize costly late-stage failures and guides rational lead optimization [25].

In the present study, ADME properties of the designed Schiff base ligands (L1–L11) were systematically assessed using SwissADME and compared with the reference inhibitors, acetazolamide, SLC-0111, and U-104, representing standard CA inhibitors.

All ligands adhered to Lipinski's Rule of Five, confirming favorable oral drug-likeness with  $\leq 5$  hydrogen bond donors,  $\leq 10$  acceptors, molecular weight  $< 500$  Da, and  $\text{Log P} < 5$ . The synthetic accessibility (SA) values ranged from 2.32 to 3.34, indicating ease of laboratory synthesis. Predicted high gastrointestinal (GI) absorption across all ligands further highlighted their potential for oral bioavailability (Table 2).

Lipophilicity-dependent variations were notable: L5 and L7 showed higher lipophilicity ( $i\text{LOGP} = 2.62$  and  $2.76$ ;  $\text{XLOGP3} = 3.32$  and  $2.76$ ), suggesting strong membrane permeability and potential blood-brain barrier (BBB) penetration. While such characteristics may be beneficial for central nervous system (CNS)-active agents, they also warrant careful *in vivo* assessment for unintended CNS effects. Conversely, ligands such as L1, L6, and L7 exhibited lower  $i\text{LOGP}$  values ( $-2.61$  to  $-3.04$ ), suggesting hydrophilic tendencies, which enhance aqueous solubility but may limit passive diffusion.

An additional pharmacokinetic insight was the predicted cytochrome P450 (CYP) enzyme inhibition profile. L5 and L7 were predicted to inhibit multiple CYP isoforms (CYP1A2, CYP2C19, and CYP2C9), implying possible drug–drug interaction (DDI) risks if co-administered with other substrates of these enzymes [26]. In contrast, L3, L8, and L10 displayed balanced lipophilicity, minimal CYP inhibition, and favorable synthetic accessibility, marking them as more suitable scaffolds for further optimization.

The SwissADME Bioavailability Radar provided a graphical summary of five essential drug-likeness parameters—lipophilicity (LIPO), polarity (POLAR), insolubility (INSOLU), unsaturation (INSATU), and flexibility (FLEX)—confirming that all ligands lie within the optimal physicochemical space for oral drugs. The Fraction Csp<sup>3</sup> values ( $0.32$ – $0.47$ ) indicated moderate 3D structural complexity, associated with enhanced target engagement and favorable pharmacokinetics. BOILED-Egg analysis predicted high GI absorption for all ligands and BBB permeability, specifically for L5 and L7, correlating well with their higher lipophilicity.

Overall, these computational findings reveal that the designed Schiff base ligands possess drug-like characteristics, satisfactory solubility, and pharmacokinetic profiles consistent with bioavailable small molecules.

### 3.2. Molecular docking studies.

To complement the pharmacokinetic profiling, molecular docking simulations were performed using the CB-Dock platform, which employs a curvature-based cavity detection algorithm integrated with AutoDock Vina for energy minimization and pose ranking [27]. This automated procedure estimates cavity centers, volumes, and docking coordinates within the enzyme's catalytic pocket.

Docking results indicated that all Schiff base ligands (L1–L11) displayed substantial binding affinities toward hCA II, hCA IX, and hCA XII, with binding energies ranging from  $-6.1$  to  $-9.2$  kcal/mol (Table 3). For comparison, the reference inhibitors exhibited docking scores of  $-6.7$  kcal/mol (acetazolamide, CA II),  $-8.1$  kcal/mol (SLC-0111, CA IX), and  $-6.1$  kcal/mol (U-104, CA XII).

Among the designed compounds, L5 demonstrated the most favorable binding affinity ( $-9.1$  kcal/mol) toward hCA IX, outperforming SLC-0111, while L7 and L10 also showed strong affinity toward hCA XII. Across isoforms, several Schiff base ligands exhibited comparable or superior binding energies to standard inhibitors, indicating potential efficacy as CA inhibitors.

Binding pose analyses revealed that the active ligands coordinated with the zinc ion ( $\text{Zn}^{2+}$ ) in the CA catalytic site via the imine ( $\text{C}=\text{N}$ ) nitrogen and adjacent carbonyl or hydroxyl groups—mirroring the coordination pattern of classical sulfonamide inhibitors. This coordination was further stabilized by hydrogen bonds with Thr199 and Glu106, along with hydrophobic and  $\pi$ - $\pi$  stacking interactions involving His94, His96, and His119, confirming active-site occupation.

### 3.3. Integrated interpretation of ADME and docking results.

Integrating ADME and molecular docking data provides a holistic understanding of the ligands' pharmacological potential. L5 consistently emerged as the most promising compound, combining strong binding affinity toward hCA IX and favorable pharmacokinetic attributes, including good oral absorption, acceptable solubility, and moderate synthetic accessibility. Its balanced physicochemical profile (moderate polarity and controlled lipophilicity) supports both bioavailability and target specificity.

Ligands L7 and L10 also demonstrated complementary advantages, such as good docking performance and acceptable ADME scores, making them potential secondary leads. However, given the predicted CYP inhibition by L5 and L7, further experimental validation is essential to evaluate enzyme selectivity, off-target effects, and cytotoxicity.

Overall, the combined *in silico* ADME–pharmacokinetic–docking analysis indicates that the Schiff base ligands, particularly L5, represent promising lead candidates rather than confirmed inhibitors [28,29]. Future work should involve enzyme inhibition assays, cell-based cytotoxicity testing, and SAR refinement to confirm the computational predictions and establish their viability as next-generation carbonic anhydrase inhibitors.

## 4. Conclusions

The present *in silico* investigation integrated ADME profiling, pharmacokinetic analysis, and molecular docking to assess a series of Schiff base ligands (L1–L11) as potential carbonic anhydrase (CA) inhibitors. The docking studies indicated that all ligands exhibited favorable binding affinities toward human CA-II, with several compounds also interacting effectively with CA-IX and CA-XII. Among these, L5 demonstrated the most favorable docking energies across all three isoforms, outperforming the reference inhibitors acetazolamide ( $-6.7$  kcal/mol), SLC-0111, and U-104.

The *in silico* predictions further suggest that the ligands possess desirable drug-like physicochemical and pharmacokinetic properties, including acceptable oral bioavailability and synthetic feasibility. Notably, L5 emerged as a promising lead candidate based on its strong predicted binding affinity and favorable ADME characteristics. The Schiff base scaffold, with its potential for efficient zinc ion coordination within the CA catalytic site, provides a rational foundation for future structure–activity relationship (SAR) optimization.

However, it is essential to acknowledge that these findings are derived solely from computational models. Experimental validation—including enzyme inhibition assays, cell-based cytotoxicity studies, and *in vitro* ADME evaluations—is required to substantiate the predicted inhibitory potency, safety, and pharmacological performance. Such investigations will be critical for confirming the therapeutic relevance of L5 and its analogs as potential next-generation carbonic anhydrase inhibitor leads.

## Author Contributions

Conceptualization, B.J.; methodology, B.J.; software, B.J.; validation, B.J.; formal analysis, B.J.; investigation, B.J.; resources, B.J.; data curation, B.J.; writing—original draft preparation, B.J.; writing—review and editing, B.J.; supervision, S.K. All authors have read and agreed to the published version of the manuscript.

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## Informed Consent Statement

Not applicable.

## Data Availability Statement

*Data supporting the findings of this study are available upon reasonable request from the corresponding author.*

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## Conflicts of Interest

The authors declare no conflict of interest.

## Abbreviations

The following abbreviations are used in this manuscript:

| Abbreviation                 | Definition                                                                                                               |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| hCAII                        | Human Carbonic Anhydrase Isoform II                                                                                      |
| hCAIX                        | Human Carbonic Anhydrase Isoform IX                                                                                      |
| hCAXII                       | Human Carbonic Anhydrase Isoform XII                                                                                     |
| CA                           | Carbonic anhydrase                                                                                                       |
| MF                           | Molecular Formula                                                                                                        |
| MW                           | Molecular Weight                                                                                                         |
| nHA                          | Number of Heavy Atoms                                                                                                    |
| nArHA                        | Number of Aromatic Heavy Atoms                                                                                           |
| Fraction (Csp <sup>3</sup> ) | Fraction of sp <sup>3</sup> Hybridized Carbons                                                                           |
| nRB                          | Number of Rotatable Bonds                                                                                                |
| nHBA                         | Number of Hydrogen Bond Acceptors                                                                                        |
| ESOL Log S                   | Estimated Solubility (LogS) – Logarithm of Estimated Solubility in Water Using the ESOL Model (Typically in log mol/L)   |
| ESOL Solubility (mg/mL)      | Estimated Solubility in mg/mL – Quantitative Water Solubility Predicted by ESOL                                          |
| ESOL Class                   | Solubility Classification by ESOL – Indicates Qualitative Solubility Class (e.g., Soluble, Moderately Soluble)           |
| iLOGP                        | In silico Log Partition Coefficient (iLOGP) – Predicts Lipophilicity Based on Physics-based and Chemoinformatics Methods |
| XLOGP                        | Atom Additive Log Partition Coefficient (XLOGP) – Predicts logP Using Atom-based Additive Methods                        |
| GI Absorption                | Gastrointestinal Absorption – Predicts the Likelihood of Compound Absorption in the Gastrointestinal Tract               |

| Abbreviation             | Definition                                                                                                                                                                   |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BBB Permeant             | Blood–Brain Barrier Permeability – Predicts Whether the Compound Can Cross the Blood–Brain Barrier                                                                           |
| Pgp substrate            | P-glycoprotein Substrate – Indicates Whether the Compound is a Substrate for P-glycoprotein (Efflux Transporter)                                                             |
| CYP1A2 inhibitor         | Cytochrome P450 1A2 Inhibition – Predicts the Likelihood of Inhibiting the CYP1A2 Enzyme                                                                                     |
| CYP2C19 inhibitor        | Cytochrome P450 2C19 Inhibition – Predicts the Likelihood of Inhibiting the CYP2C19 Enzyme                                                                                   |
| CYP2C9 inhibitor         | Cytochrome P450 2C9 Inhibition – Predicts the Likelihood of Inhibiting the CYP2C9 Enzyme                                                                                     |
| CYP2D6 inhibitor         | Cytochrome P450 2D6 Inhibition – Predicts the Likelihood of Inhibiting the CYP2D6 Enzyme                                                                                     |
| CYP3A4 inhibitor         | Cytochrome P450 3A4 Inhibition– Predicts the Likelihood of Inhibiting the CYP3A4 Enzyme                                                                                      |
| Lipinski violations      | Lipinski's Rule of Five Violations – Indicates the Number of Violations Against Lipinski's Criteria for Drug-likeness                                                        |
| Ghose violations         | Ghose Filter Violations – Indicates the Number of Violations Against Ghose's Drug-likeness Filter                                                                            |
| Veber violations         | Veber Rule Violations – Indicates the Number of Violations Against Veber's Criteria for Oral Bioavailability.                                                                |
| Egan violations          | Egan Rule Violations – Indicates the Number of Violations Against Egan's Filter for Membrane Permeability                                                                    |
| Muegge violations        | Muegge Filter Violations – Indicates the Number of Violations Against Muegge's Drug-Likeness Filter                                                                          |
| Bioavailability Score    | Predicted Bioavailability Score – Probability Estimates for Oral Bioavailability (Typically Range 0– 1)                                                                      |
| PAINS alerts             | Pan-Assay Interference Structures Alerts– Detects Chemical Substructures Known to Interfere with Biological Assays (False Positives). – 0 = no PAINS Alerts; Favorable       |
| Brenk alerts             | Bren Structural Alerts– Identifies Potentially Toxic or Unstable Substructures. 1 = One Alert Detected; Requires Monitoring During Lead Optimization                         |
| Lead-likeness violations | Lead-Likeness Filter Violations–Checks Molecular Properties Suitable for Lead Compounds (MW<350Da, logP <3.5, ≤7 Rotatable Bonds). 0 = Compliant with Lead-likeness Criteria |
| Synthetic Accessibility  | Predicts Ease of Synthesis on a Scale of 1 (Easy) to 10 (Difficult). 2.59 Indicates Easy Laboratory Synthesis Feasibility                                                    |

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