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Molecular Docking Of New Acetaminophen Derivatives As Inhibitors Of Carbonic Anhydrase Enzyme with A Computational Evaluation Of Their Pharmacokinetic And Drug-Likeness Properties

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Abstract
This study explores the design and computational evaluation of novel acetaminophen derivatives as potential inhibitors of carbonic anhydrase II (CA II), an enzyme implicated in various physiological and pathological processes, including glaucoma, epilepsy, and cancer. Given the limitations and side effects associated with traditional sulfonamide-based CA inhibitors, there is a pressing need for more selective and safer alternatives. Utilizing molecular docking techniques, the binding affinities and interaction modes of these derivatives within the CA II active site were assessed, with compounds A and B exhibiting promising binding energies (-6.67 and -6.47 kcal/mol, respectively) and favorable interactions with key residues such as Zn262, Asn67, and Trp5. Complementary ADMET profiling via SwissADME predicted satisfactory pharmacokinetic properties, including solubility, permeability, and drug-likeness, aligning with Lipinski's rule. The integration of docking scores with pharmacokinetic predictions underscores the potential of these derivatives as lead candidates for further experimental validation. This computational framework highlights the feasibility of repurposing acetaminophen scaffolds for CA II inhibition, offering a strategic pathway toward the development of selective, efficacious, and safer CA inhibitors for therapeutic applications. The findings lay the groundwork for subsequent synthesis and in vitro testing, aiming to contribute to the advancement of targeted treatments with minimized adverse effects.

Key words: Molecular docking, Acetaminophen derivatives, Carbonic anhydrase, ADME study

1. Introduction

Carbonic anhydrases (CAs) are a group of zinc metalloenzymes, which catalyze the reversible hydration of carbon dioxide (CO_2), and are involved in the pH homeostasis, respiration, production of cerebrospinal fluid as well as bone resorption [1]. From 15 isoforms of human CAs, the role of CA II is prominent due to its elevated catalytic efficiency as well as its widespread distribution in the body, which makes it an ideal drug target in the treatment of glaucoma, epilepsy and cancers [2]. Carbonic anhydrase inhibitors (CAIs) have been a focus of interest; the sulphonamide acetazolamide is commonly used clinically [3]. Nonetheless, side effects such as metabolic acidosis and hypokalemia may limit their use, which has prompted the development of new selective and safer inhibitors [4]
Acetaminophen, also known as paracetamol, serves primarily as an analgesic and antipyretic. Recent investigations have revealed its modest inhibitory effects on carbonic anhydrases (CAs), indicating its potential as a lead compound for the development of new carbonic anhydrase inhibitors (CAIs). Advances in computational drug design facilitate the rapid identification and refinement of drug candidates, thereby accelerating the drug discovery process. Among these methodologies, molecular docking has emerged as a crucial technique for elucidating ligand-receptor interactions and binding affinities. Additionally, computational profiles of absorption, distribution, metabolism, excretion, and toxicity (ADMET) enable the prioritization of compounds with advantageous pharmacokinetic characteristics. This study centers on the in-silico design and analysis of novel acetaminophen derivatives aimed at inhibiting carbonic anhydrase II. Through molecular docking, we evaluate the binding interactions of these derivatives and predict their pharmacokinetic and drug-likeness properties, ultimately identifying candidates for experimental validation and the advancement of more effective CAIs.

1.1. Carbonic Anhydrase as a Therapeutic Target

CAs are involved in numerous physiological and pathological processes, making them attractive targets for drug development [8]. CA II, in particular, is highly expressed in tissues such as the eyes, kidneys, and brain, where its inhibition can modulate intraocular pressure, electrolyte balance, and neuronal excitability [9]. Traditional sulfonamide-based inhibitors, while effective, often lack isoform selectivity, leading to off-target effects [10]. Recent efforts have focused on identifying non-sulfonamide inhibitors, including coumarins, phenols, and polyamines, to overcome these limitations [11].

Acetaminophen, a well-known analgesic, has been shown to weakly inhibit CA activity, suggesting that its derivatives could be optimized for enhanced binding affinity [12]. Structural modifications of the acetaminophen scaffold, such as halogenation or incorporation of heterocyclic moieties, may improve interactions with the CA active site while maintaining favorable drug-like properties [13]. Computational approaches provide an efficient means of exploring these modifications before synthetic efforts are undertaken.

1.2. Computational Approaches in CA Inhibitor Design

1.2.1. Molecular Docking for Binding Affinity Prediction

Molecular docking is a widely used computational technique to predict the binding orientation and affinity of small molecules within a protein's active site [14]. Recent studies have successfully employed docking to identify novel CA inhibitors, including natural products and synthetic derivatives [15]. By simulating the interaction between acetaminophen derivatives and CA II, we can prioritize compounds with the highest predicted binding energies and favorable interaction patterns (e.g., zinc coordination, hydrogen bonding with key residues like Thr199 and His94) [16].

1.2.2. ADMET and Drug-Likeness Profiling

A major challenge in drug development is ensuring that candidates possess suitable pharmacokinetic properties for clinical use [17]. Computational tools such as SwissADME and pkCSM allow for rapid prediction of key ADMET parameters, including solubility, permeability, cytochrome P450 interactions, and toxicity [18]. Additionally, drug-likeness filters (e.g., Lipinski's Rule of Five, Veber's criteria) help assess oral bioavailability and synthetic feasibility [19]. Integrating these analyses with docking results enables the identification of lead compounds with balanced potency and pharmacokinetic profiles.

Despite the clinical success of sulfonamide-based CAIs, their side effects necessitate the development of alternative inhibitors [20]. Acetaminophen derivatives represent an underexplored class of potential CAIs, and computational screening offers a cost-effective strategy to identify promising candidates before experimental validation.

1.3. Objectives

1.3.1. Molecular Docking Studies

Evaluate the binding modes and affinities of newly designed acetaminophen derivatives against CA II. Compare their docking scores with reference inhibitor (5-(dimethylamino)-1-naphthalenesulfonamide).

1.3.2. Pharmacokinetic and Toxicity Prediction

Assess ADMET properties to identify derivatives with optimal solubility, permeability, and metabolic stability. Apply drug-likeness rules to filter compounds with high oral bioavailability potential.

1.4. Significance of the Study

This study provides a computational framework for the rational design of novel CA inhibitors derived from acetaminophen. By combining molecular docking with ADMET prediction, we aim to identify lead compounds with improved selectivity and drug-like properties, potentially leading to safer and more effective CA-targeting therapies.

2. Materials and methods

2.1. Preparation of the protein crystallographic structure by protein preparation panel

The X-ray crystallographic structure of carbonic anhydrase enzyme was obtained from the protein databank (https://www.rcsb.org/, PDB ID:1OKL). The protein preparation wizard (Schrödinger Suite 2025–1, Glide module) was utilized to correct particular mistakes, such as missing hydrogen atoms from the crystallographic structure of the protein.

The methodology employed in this work has been formerly elucidated [21]. The bond order was determined, and any potentially absent hydrogen atoms in the crystallographic structure were included. In addition, disulfide bonds were formed between two adjacent sulfur atoms, but the remaining choices were kept at their usual settings. The final refining stage was performing full energetic optimization using the OPLS3 force field, with a heavy atom RMSD set at 0.3 Å [22].

2.2. Preparation of Ligands

Using a 2D sketcher, the investigated compounds (A-I) were created and then uploaded to the Schrödinger suite's Maestro software workspace. For every two-dimensional structure, low-energy 3D conformers with appropriate bond lengths and angles were produced. [23]. For every ligand structure, the potential ionization states were produced at a physiological pH of 7.2 ± 0.2. An optimum potential liquid simulation (OPLS3) force field was used to minimize the ligands, with all other settings being set to default [24].

2.3. Generation of the Grid

By selecting the co-crystallized ligand at the protein's active site at random, the receptor grid generating panel produced the glide grid file, which automatically revealed the x, y, and z coordinates. Glide determines a default center and default size for the region for which grids will be calculated based on the position and size of the ligand.

2.4. Molecular docking studies

Molecular docking was performed using the ligand docking panel. The glide gride and the prepared ligands files were chosen. The run was conducted using XP docking mode. Finally, the docking scores in kcal/mole and the visualization images were recorded [25, 26].

2.5. ADME study

The Swiss ADME server virtually identified the pharmacokinetic characteristics of gastrointestinal absorption, systemic distribution, metabolism, excretion, and drug-likeness factors. The Mrvin SJ panel sketched the compounds under study and converted them into SMILES. The run sequence was completed, and the outcomes were captured as pictures.

Result and discussion

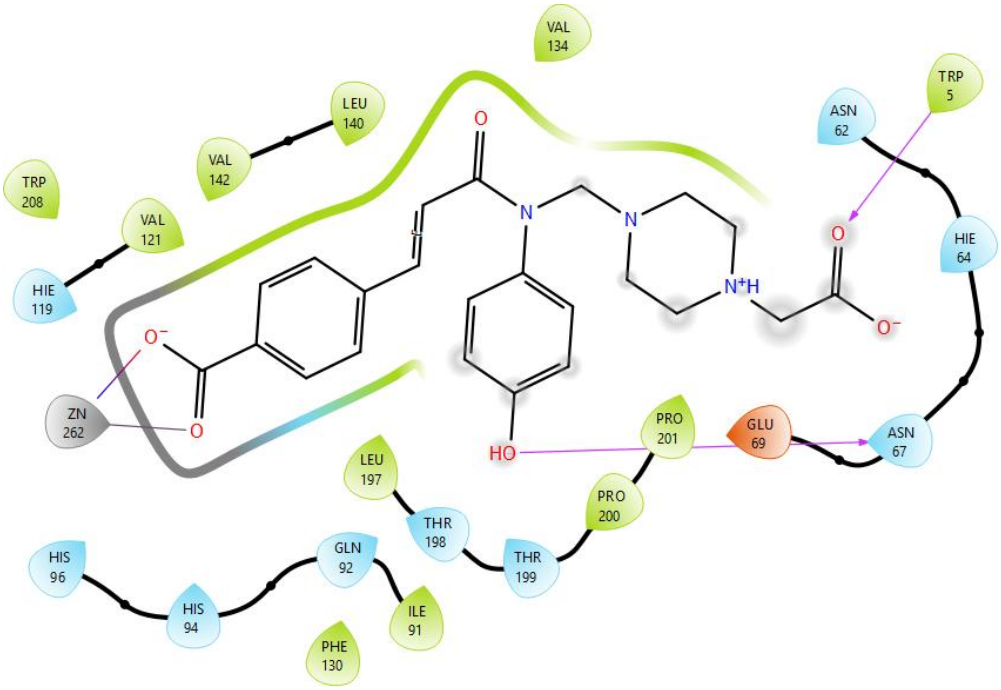
3.1. Molecular docking results of the investigated compounds in the carbonic anhydrase enzyme active site

The docking study was used to estimate the suggested binding interaction, affinity, and preferred orientation for each docking pose, and the binding interaction energy (ΔG) of the investigated compounds with histone deacetylase enzyme, **Table 1**. In addition, **Figure 3.1**. Show the calculated interaction energies for the hit compounds examined were all consistent with the reported results, suggesting that compounds A and B may have effective inhibitory activities against carbonic anhydrase enzyme.

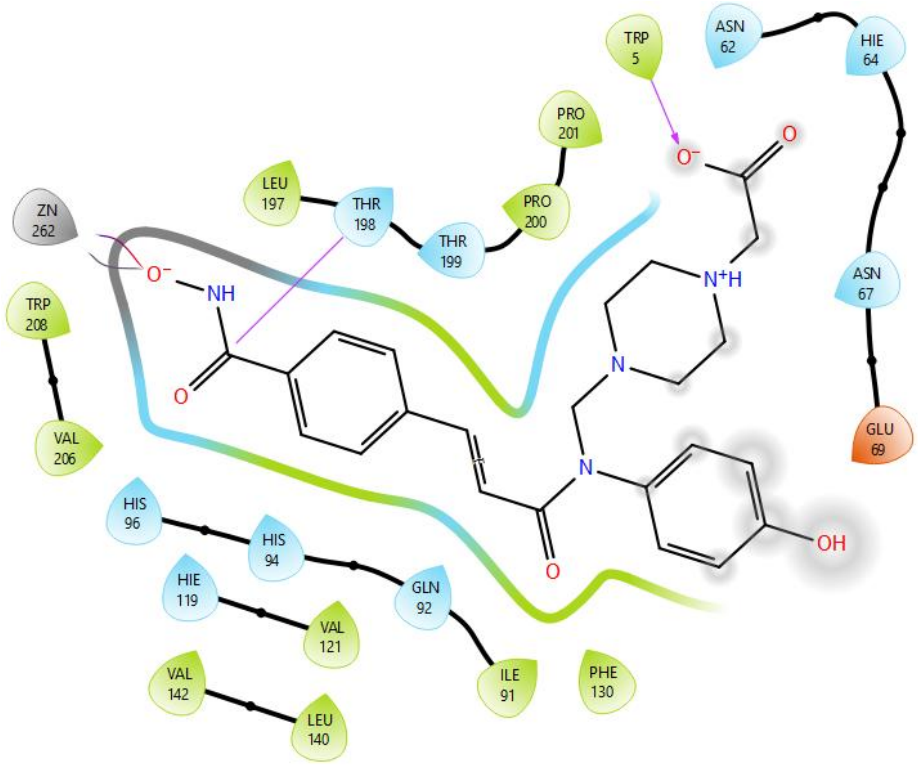
Table 3.1 Docking scores in Kcal/mol and amino acid residues involved in ligand-receptor interaction (PDB ID: 1OKL).

Compound	Score in Kcal/mol	Amino acid residues involved in ligand-receptor interaction
Compound A	-6.67	Zn262, Asn67, Tyr5
Compound B	-6.47	Zn262, Trp5
Compound C	-6.20	Zn262, Asn67, Asp72, Phe130
Compound D	-6.08	Zn262, Hie64
Compound E	-6.04	Zn262, Hie64
Compound F	-5.64	Zn262, Thr198, Hie64
Compound G	-5.47	Zn262, Thr198, Gln92, Glu69, Hie64, Arg58
Compound H	-4.76	Zn262, Thr198, Gln92
Compound I	-4.64	Zn262, Thr198
5-(dimethylamino)-1-naphthalenesulfonamide	-6.24	Zn292, Thr198, Thr199

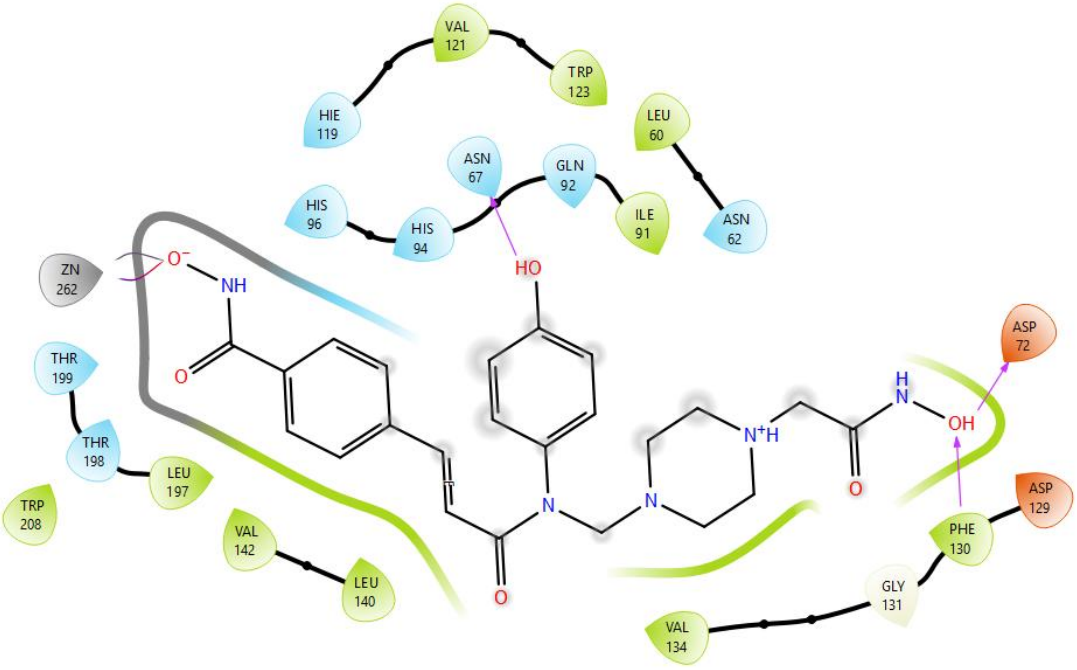
*Red color represents the amino acid residues involved in the interaction between the reference ligand (5-(dimethylamino)-1-naphthalenesulfonamide) and the enzyme



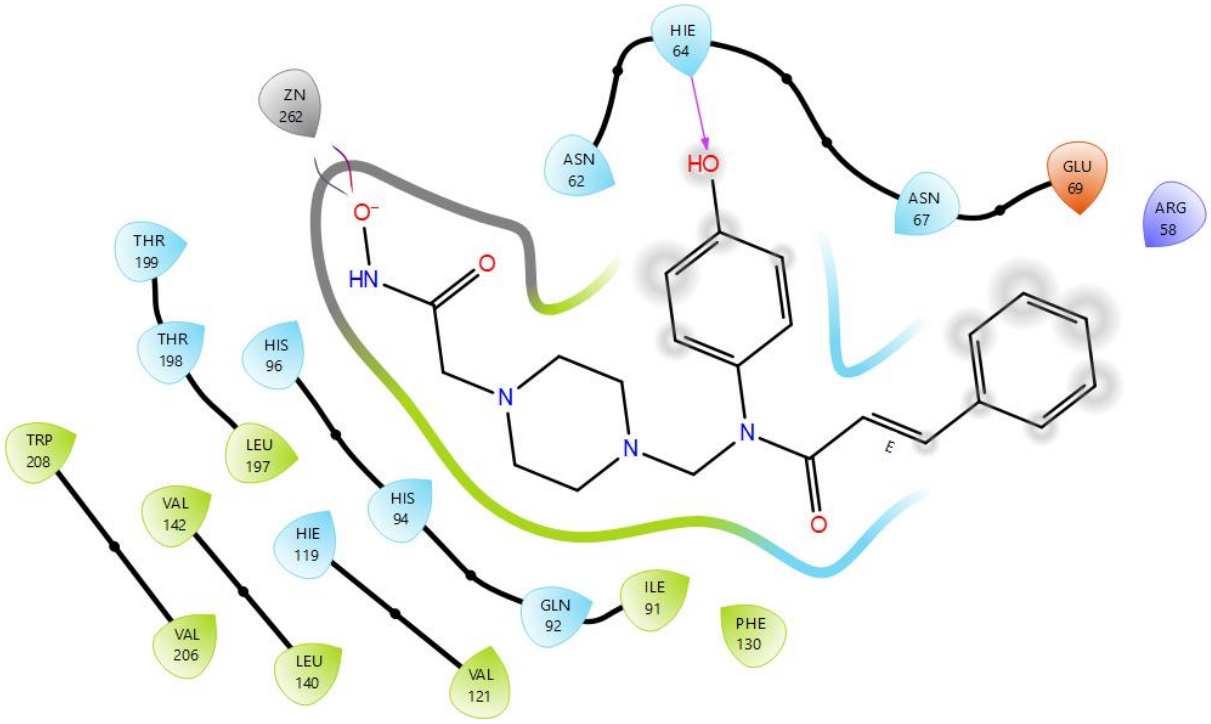
Compound A



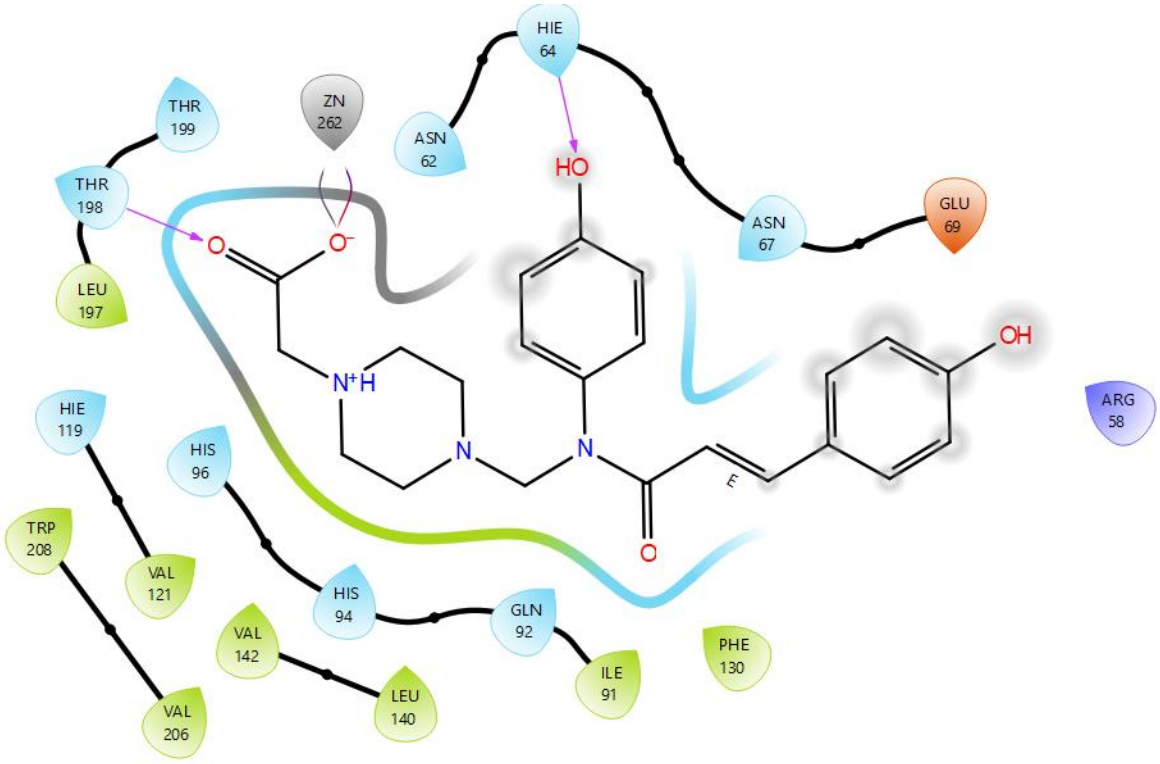
Compound B



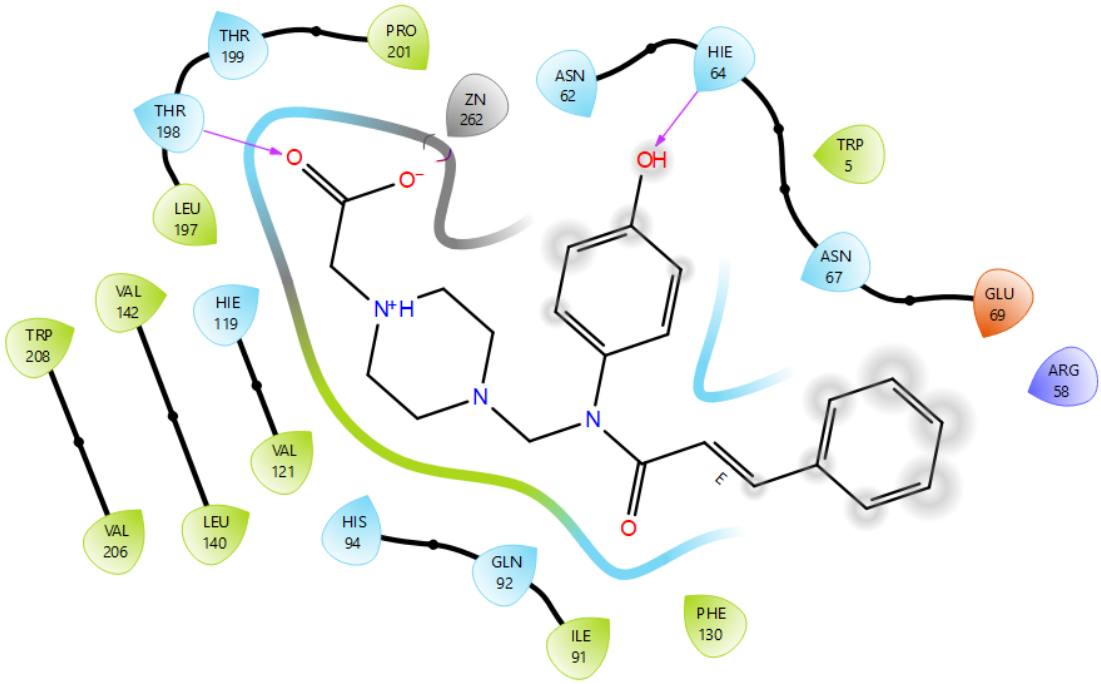
Compound C



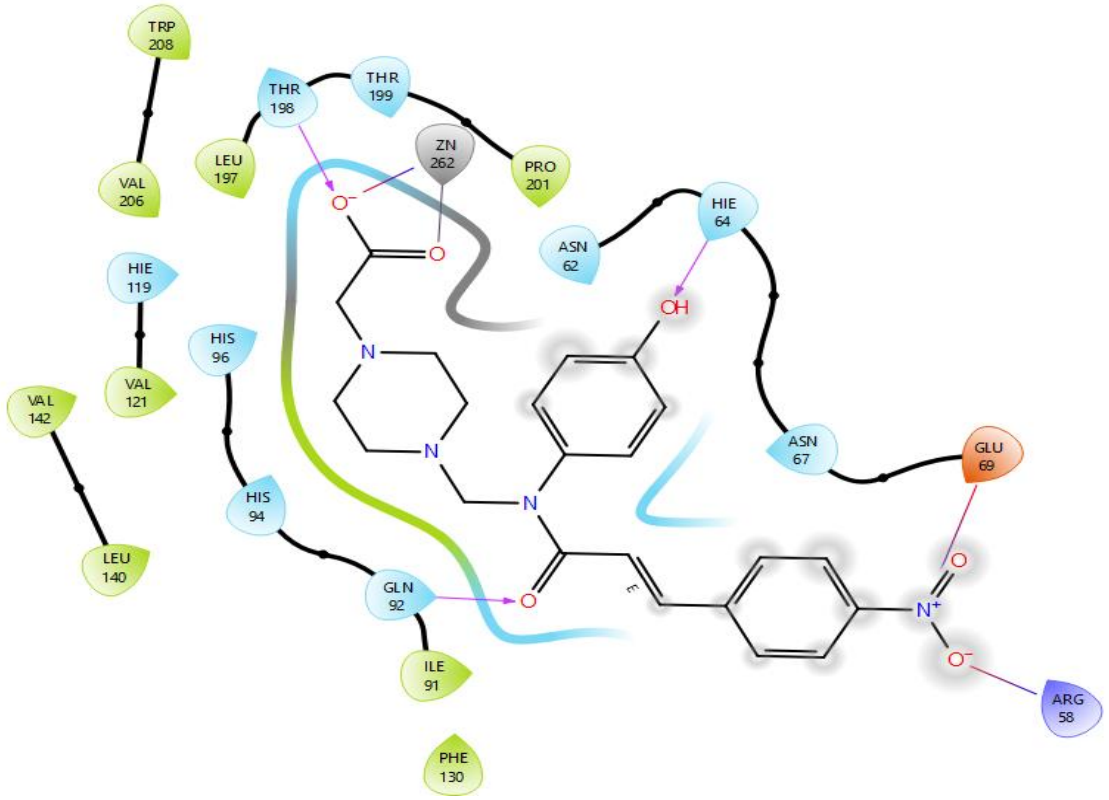
Compound D



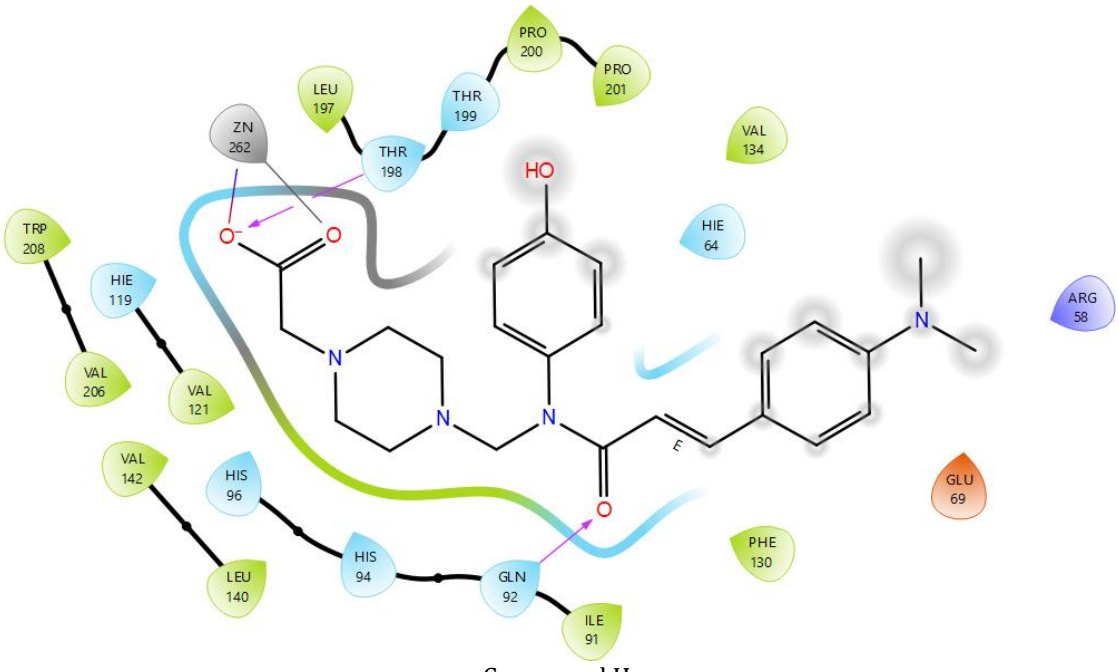
Compound E



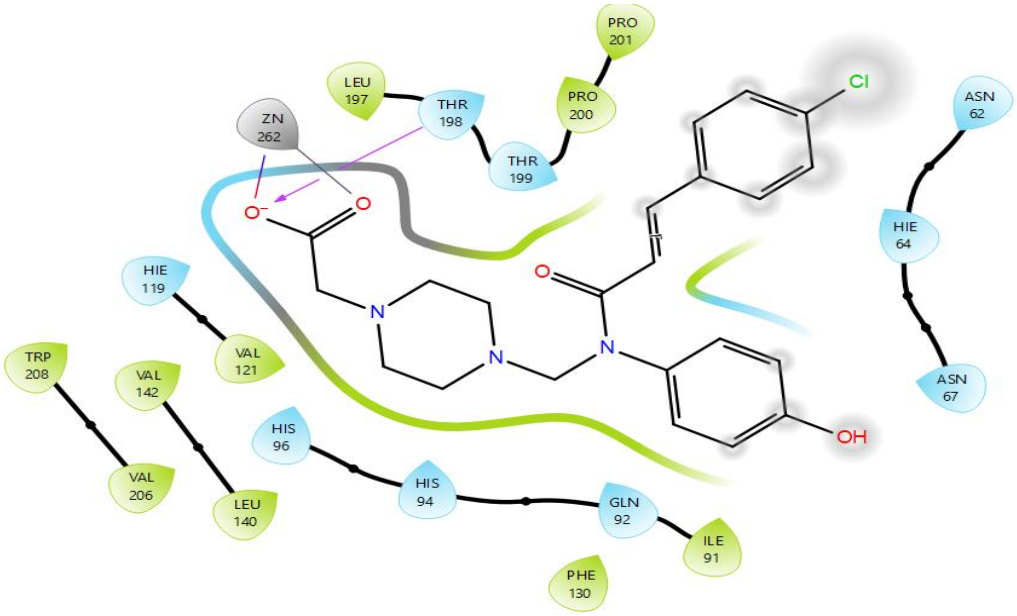
Compound F



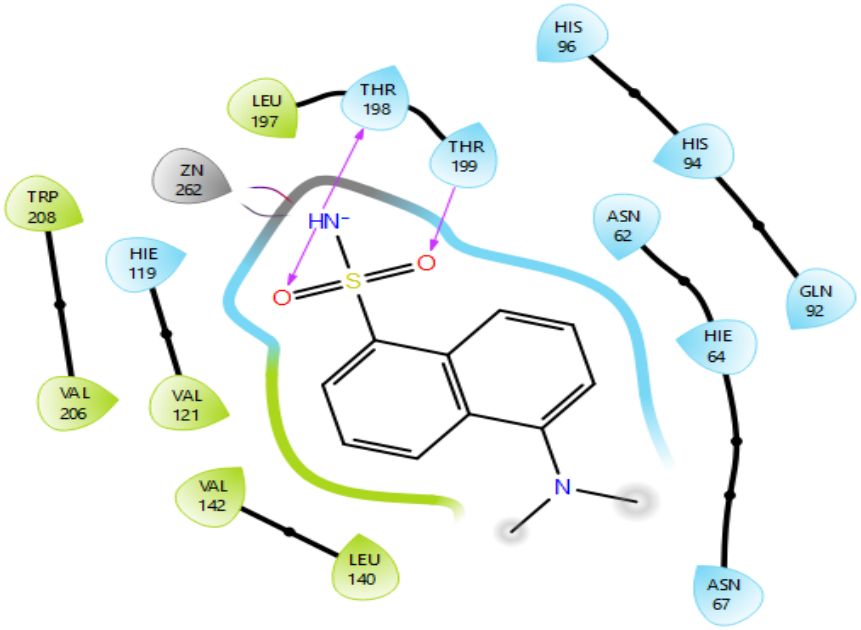
Compound G



Compound H



Compound I

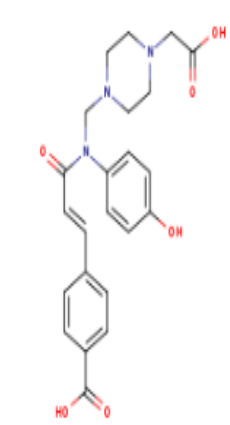


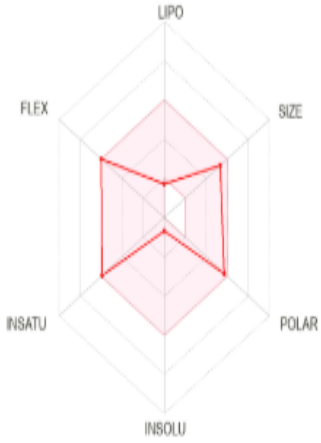
5-(DIMETHYLAMINO)-1-NAPHTHALENESULFONAMIDE

Figure (3.1) The investigated compounds (A-I and 5-(DIMETHYLAMINO)-1-NAPHTHALENESULFONAMIDE) docked in the carbonic anhydrase enzyme (PDB ID: 1OKL)

3.2. ADME evaluation

The Pharmacokinetic properties and drug likeness of compounds (A-I) were evaluated by Swiss ADME server and the predicted results are shown in figure (3.2).





SMILES OC(=O)CN1CCN(CC1)CN(c1ccc(cc1)O)C(=O)/C=C/c1ccc(cc1)C(=O)O

Physicochemical Properties	
Formula	C23H25N3O6
Molecular weight	439.46 g/mol
Num. heavy atoms	32
Num. arom. heavy atoms	12
Fraction Csp3	0.26
Num. rotatable bonds	9
Num. H-bond acceptors	8
Num. H-bond donors	3
Molar Refractivity	126.37
TPSA	121.62 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.53
Log $P_{o/w}$ (XLOGP3)	-2.48
Log $P_{o/w}$ (WLOGP)	0.93
Log $P_{o/w}$ (MLOGP)	1.32
Log $P_{o/w}$ (SILICOS-IT)	0.89
Consensus Log $P_{o/w}$	0.64

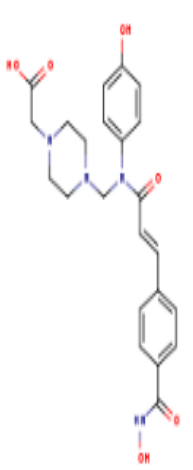
Water Solubility	
Log *S* (ESOL)	-0.69
Solubility	9.06e+01 mg/ml ; 2.06e-01 mol/l
Class	Very soluble
Log *S* (Ali)	0.47
Solubility	1.29e+03 mg/ml ; 2.94e+00 mol/l
Class	Highly soluble
Log *S* (SILICOS-IT)	-2.94
Solubility	5.06e-01 mg/ml ; 1.15e-03 mol/l
Class	Soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-10.74 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	No; 1 violation: XLOGP3<-2
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: michael_acceptor_1
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	3.31

Compound A



SMILES ONC(=O)c1ccc(cc1)/C=C/C(=O)N(c1ccc(cc1)O)CN1CCN(CC1)CC(=O)O

Physicochemical Properties	
Formula	C23H26N4O6
Molecular weight	454.48 g/mol
Num. heavy atoms	33
Num. arom. heavy atoms	12
Fraction Csp3	0.26
Num. rotatable bonds	10
Num. H-bond acceptors	8
Num. H-bond donors	4
Molar Refractivity	128.33
TPSA	133.65 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.32
Log $P_{o/w}$ (XLOGP3)	-0.94
Log $P_{o/w}$ (WLOGP)	0.35
Log $P_{o/w}$ (MLOGP)	0.95
Log $P_{o/w}$ (SILICOS-IT)	0.12
Consensus Log $P_{o/w}$	0.56

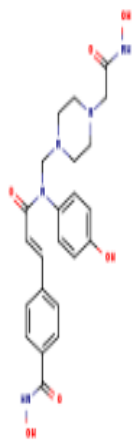
Water Solubility	
Log *S* (ESOL)	-1.67
Solubility	9.61e+00 mg/ml ; 2.12e-02 mol/l
Class	Very soluble
Log *S* (Ali)	-1.38
Solubility	1.88e+01 mg/ml ; 4.15e-02 mol/l
Class	Very soluble
Log *S* (SILICOS-IT)	-2.98
Solubility	4.80e-01 mg/ml ; 1.06e-03 mol/l
Class	Soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-9.74 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	No; 1 violation: TPSA>131.6
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	3 alerts: hydroxamic_acid, michael_acceptor_1, oxygen-nitrogen_single_bond
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	3.43

Compound B



SMILES ONC(=O)CN1CCN(CC1)CN(c1ccc(cc1)O)C(=O)/C=C/c1ccc(cc1)C(=O)NO

Physicochemical Properties	
Formula	C23H27N5O6
Molecular weight	469.49 g/mol
Num. heavy atoms	34
Num. arom. heavy atoms	12
Fraction Csp3	0.26
Num. rotatable bonds	11
Num. H-bond acceptors	8
Num. H-bond donors	5
Molar Refractivity	130.29
TPSA	145.68 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.86
Log $P_{o/w}$ (XLOGP3)	0.60
Log $P_{o/w}$ (WLOGP)	-0.23
Log $P_{o/w}$ (MLOGP)	0.60
Log $P_{o/w}$ (SILICOS-IT)	-0.65
Consensus Log $P_{o/w}$	0.44

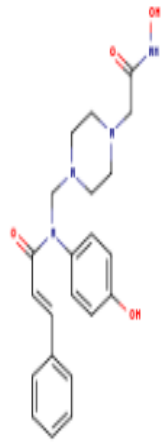
Water Solubility	
Log *S* (ESOL)	-2.66
Solubility	1.02e+00 mg/ml ; 2.17e-03 mol/l
Class	Soluble
Log *S* (Ali)	-3.23
Solubility	2.74e-01 mg/ml ; 5.85e-04 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-3.01
Solubility	4.57e-01 mg/ml ; 9.73e-04 mol/l
Class	Soluble

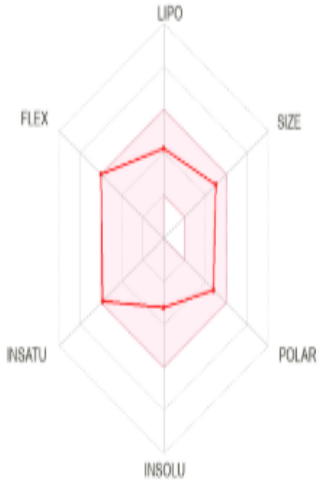
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.74 cm/s

Druglikeness	
Lipinski	Yes; 1 violation: NorO>10
Ghose	No; 1 violation: MR>130
Veber	No; 2 violations: Rotors>10, TPSA>140
Egan	No; 1 violation: TPSA>131.6
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	3 alerts: hydroxamic_acid, michael_acceptor_1, oxygen-nitrogen_single_bond
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	3.58

Compound C





SMILES ONC(=O)CN1CCN(CC1)CN(c1ccc(cc1)O)C(=O)/C=C/c1ccccc1

Physicochemical Properties	
Formula	C22H26N4O4
Molecular weight	410.47 g/mol
Num. heavy atoms	30
Num. arom. heavy atoms	12
Fraction Csp3	0.27
Num. rotatable bonds	9
Num. H-bond acceptors	6
Num. H-bond donors	3
Molar Refractivity	121.37
TPSA	96.35 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.97
Log $P_{o/w}$ (XLOGP3)	1.81
Log $P_{o/w}$ (WLOGP)	0.65
Log $P_{o/w}$ (MLOGP)	1.28
Log $P_{o/w}$ (SILICOS-IT)	0.63
Consensus Log $P_{o/w}$	1.27

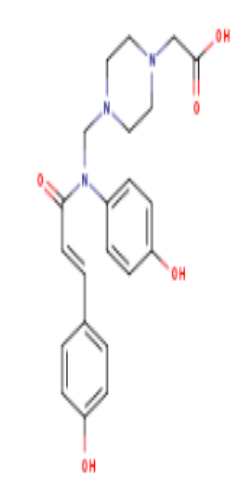
Water Solubility	
Log S (ESOL)	-3.23
Solubility	2.43e-01 mg/ml ; 5.93e-04 mol/l
Class	Soluble
Log S (Ali)	-3.45
Solubility	1.45e-01 mg/ml ; 3.53e-04 mol/l
Class	Soluble
Log S (SILICOS-IT)	-3.64
Solubility	9.32e-02 mg/ml ; 2.27e-04 mol/l
Class	Soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-7.52 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	3 alerts: hydroxamic_acid, michael_acceptor_1, oxygen-nitrogen_single_bond
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	3.41

Compound D



SMILES OC(=O)CN1CCN(CC1)CN(c1ccc(cc1)O)C(=O)/C=C/c1ccc(cc1)O

Physicochemical Properties	
Formula	C22H25N3O5
Molecular weight	411.45 g/mol
Num. heavy atoms	30
Num. arom. heavy atoms	12
Fraction Csp3	0.27
Num. rotatable bonds	8
Num. H-bond acceptors	7
Num. H-bond donors	3
Molar Refractivity	121.44
TPSA	104.55 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.44
Log $P_{o/w}$ (XLOGP3)	-0.08
Log $P_{o/w}$ (WLOGP)	0.93
Log $P_{o/w}$ (MLOGP)	1.14
Log $P_{o/w}$ (SILICOS-IT)	0.93
Consensus Log $P_{o/w}$	1.07

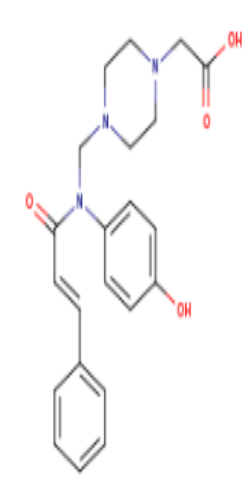
Water Solubility	
Log S (ESOL)	-2.11
Solubility	3.20e+00 mg/ml ; 7.79e-03 mol/l
Class	Soluble
Log S (Ali)	-1.66
Solubility	8.92e+00 mg/ml ; 2.17e-02 mol/l
Class	Very soluble
Log S (SILICOS-IT)	-3.02
Solubility	3.96e-01 mg/ml ; 9.62e-04 mol/l
Class	Soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.87 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: michael_acceptor_1
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	3.23

Compound E



SMILES OC(=O)CN1CCN(CC1)CN(c1ccc(cc1)O)C(=O)/C=C/c1ccccc1

Physicochemical Properties	
Formula	C22H25N3O4
Molecular weight	395.45 g/mol
Num. heavy atoms	29
Num. arom. heavy atoms	12
Fraction Csp3	0.27
Num. rotatable bonds	8
Num. H-bond acceptors	6
Num. H-bond donors	2
Molar Refractivity	119.41
TPSA	84.32 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.90
Log $P_{o/w}$ (XLOGP3)	0.27
Log $P_{o/w}$ (WLOGP)	1.23
Log $P_{o/w}$ (MLOGP)	1.66
Log $P_{o/w}$ (SILICOS-IT)	1.40
Consensus Log $P_{o/w}$	1.49

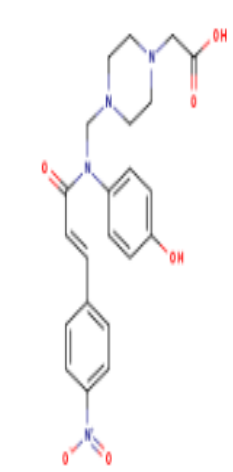
Water Solubility	
Log *S* (ESOL)	-2.24
Solubility	2.28e+00 mg/ml ; 5.75e-03 mol/l
Class	Soluble
Log *S* (Ali)	-1.60
Solubility	9.89e+00 mg/ml ; 2.50e-02 mol/l
Class	Very soluble
Log *S* (SILICOS-IT)	-3.60
Solubility	9.82e-02 mg/ml ; 2.48e-04 mol/l
Class	Soluble

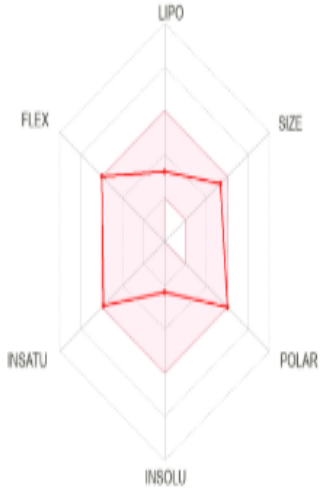
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.52 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	1 alert: michael_acceptor_1
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	3.20

Compound F





SMILES OC(=O)CN1CCN(CC1)CN(c1ccc(cc1)O)C(=O)/C=C/c1ccc(cc1)[N+](=O)[O-]

Physicochemical Properties	
Formula	C22H24N4O6
Molecular weight	440.45 g/mol
Num. heavy atoms	32
Num. arom. heavy atoms	12
Fraction Csp3	0.27
Num. rotatable bonds	9
Num. H-bond acceptors	8
Num. H-bond donors	2
Molar Refractivity	128.23
TPSA	130.14 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	2.14
Log $P_{o/w}$ (XLOGP3)	0.10
Log $P_{o/w}$ (WLOGP)	1.14
Log $P_{o/w}$ (MLOGP)	0.81
Log $P_{o/w}$ (SILICOS-IT)	-0.73
Consensus Log $P_{o/w}$	0.69

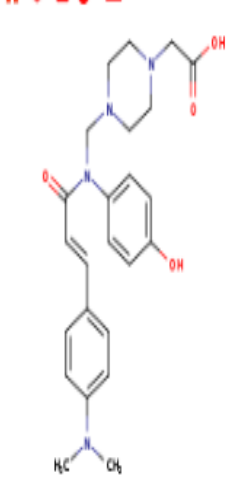
Water Solubility	
Log *S* (ESOL)	-2.32
Solubility	2.12e+00 mg/ml ; 4.82e-03 mol/l
Class	Soluble
Log *S* (Ali)	-2.39
Solubility	1.80e+00 mg/ml ; 4.09e-03 mol/l
Class	Soluble
Log *S* (SILICOS-IT)	-2.94
Solubility	5.01e-01 mg/ml ; 1.14e-03 mol/l
Class	Soluble

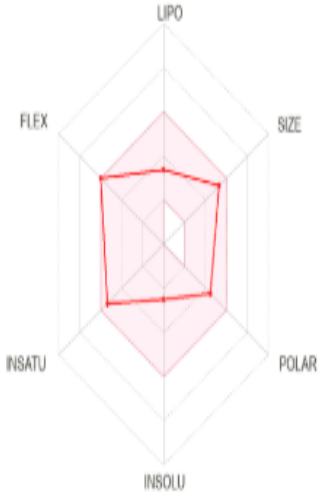
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.92 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	0 alert
Brenk	3 alerts: michael_acceptor_1, nitro_group, oxygen-nitrogen_single_bond
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	3.38

Compound G





SMILES CN(c1ccc(cc1)/C=C/C(=O)N(c1ccc(cc1)O)CN1CCN(CC1)CC(=O)O)C

Physicochemical Properties	
Formula	C24H30N4O4
Molecular weight	438.52 g/mol
Num. heavy atoms	32
Num. arom. heavy atoms	12
Fraction Csp3	0.33
Num. rotatable bonds	9
Num. H-bond acceptors	6
Num. H-bond donors	2
Molar Refractivity	133.62
TPSA	87.56 Å²

Lipophilicity	
Log $P_{o/w}$ (iLOGP)	3.04
Log $P_{o/w}$ (XLOGP3)	0.39
Log $P_{o/w}$ (WLOGP)	1.29
Log $P_{o/w}$ (MLOGP)	1.57
Log $P_{o/w}$ (SILICOS-IT)	1.12
Consensus Log $P_{o/w}$	1.48

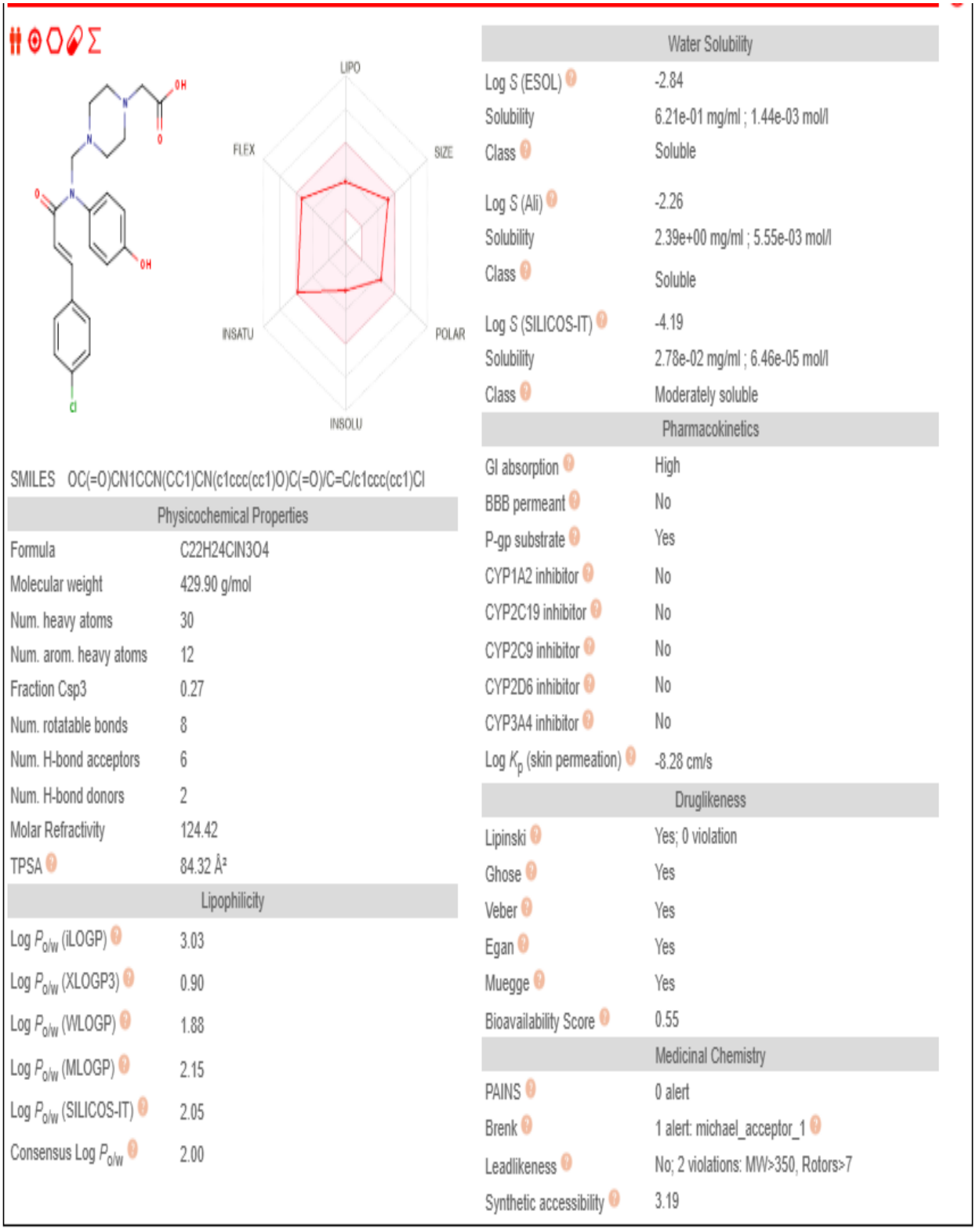
Water Solubility	
Log *S* (ESOL)	-2.49
Solubility	1.43e+00 mg/ml ; 3.25e-03 mol/l
Class	Soluble
Log *S* (Ali)	-1.79
Solubility	7.04e+00 mg/ml ; 1.60e-02 mol/l
Class	Very soluble
Log *S* (SILICOS-IT)	-3.68
Solubility	9.23e-02 mg/ml ; 2.10e-04 mol/l
Class	Soluble

Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-8.70 cm/s

Druglikeness	
Lipinski	Yes; 0 violation
Ghose	No; 1 violation: MR>130
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55

Medicinal Chemistry	
PAINS	1 alert: anil_di_alk_B
Brenk	1 alert: michael_acceptor_1
Leadlikeness	No; 2 violations: MW>350, Rotors>7
Synthetic accessibility	3.51

Compound H



Compound I

Figure (3.2) The predicted results of compounds (A-I) evaluation by Swiss ADME server

All the investigated compounds (A-I) show high GI absorption, no BBB penetration, act as P-gp substrate, no inhibitory activity on CYP enzymes and good druglikness properties.

The results of the investigated compounds were found promising and encouraging for future synthesis and performing a preliminary pharmacological assessment such as in-vitro MTT study against several cell lines.

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