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IN SILICO CRAFTING OF SCHIFF'S BASE OF QUINOXALINE-2, 3-DIONE DERIVATIVES AS NEXT GEN ANTIBIOTICS

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ABSTRACT

The increasing prevalence of antimicrobial resistance, particularly in Staphylococcus aureus and methicillin-resistant S. aureus (MRSA), necessitates the development of novel therapeutic agents. In this study, an in silico approach was employed to design and evaluate Schiff's base derivatives of quinoxaline-2,3-dione as potential next-generation antibiotics. A total of 41 derivatives were designed using rational drug design principles and assessed for drug-likeness using Lipinski's rule of five, where all compounds demonstrated favorable properties. Molecular docking studies were performed against DNA gyrase (PDB ID: 2XCT) and MRSA protein (PDB ID: 6FTB) using AutoDock4. Several compounds exhibited superior binding affinity compared to standard drugs such as ciprofloxacin and streptomycin, indicating strong potential for antibacterial activity. ADMET analysis revealed that many derivatives showed good human intestinal absorption and acceptable pharmacokinetic profiles, although variations in permeability, metabolic stability, and toxicity were observed. Notably, some compounds demonstrated improved binding and pharmacokinetic characteristics with relatively lower cardiotoxicity risk. However, toxicity parameters such as hepatotoxicity and mutagenicity remain areas of concern. Overall, this study highlights quinoxaline derivatives as promising scaffolds and demonstrates the effectiveness of computer-aided drug design in accelerating the discovery of novel antibacterial agents against resistant pathogens.

KEYWORDS: Quinoxaline derivatives, Schiff base, Molecular docking, Antibacterial activity, ADMET analysis.

1. INTRODUCTION

Drug discovery

The bench-to-bedside journey of a drug costs more than a billion US dollars and takes more than 10 years. The classical approach to identify hit molecules against a disease is high-throughput screening (HTS). HTS involves the screening of hundreds of thousands of small molecules to identify active molecules that can elicit desired biological response. This brute-force approach often fails due to instability, toxicity, or other poor pharmacokinetic/pharmacodynamic properties of hit molecules. Among other approaches, computer-aided drug design (CADD) is effective in reducing the cost, duration, and attrition rate of the drug discovery process. CADD involves predictive algorithms, computing resources, and 3D visualization tools to design, optimize, and develop small molecule therapeutics against diseases. The early detection of undesired molecules reduces the cost and workload of HTS without compromising the success rate.

For example, in a comparative case study, a group performed virtual screening (VS) of small molecules against tyrosine phosphatase-1B, a therapeutic target in diabetes mellitus. They reported 365 compounds, among which 127 (35%) showed an effective inhibition. In parallel, the group performed traditional HTS and among 400,000 compounds tested, only 81 (0.021%) showed effective inhibition. This study showed the power of CADD, which has become an integral part of the drug discovery process.

In contrast to HTS or combinatorial chemistry, CADD involves much more targeted searching and therefore results in higher success rates.

There are three major roles of CADD in pharmaceutical industries:

- The screening of large libraries of molecules to predict minimal best small molecules to further test in actual experiments;
- Lead identification by designing novel small molecules;
- Lead optimization for affinity or pharmacokinetic/pharmacodynamic (PK/PD) properties.[1]

  CADD methods can be broadly classified into two groups, namely structure-based (SB) and ligand-based (LB) drug discovery.[2]

Ligand-based drug discovery (LBDD)

In the absence of any structure information available for the therapeutic target, the alternative approach is LBDD. Unlike SBDD, LBDD does not require a prior knowledge of mechanism of action and only needs structural information and bioactivity data for small molecules. The principle of LBDD is that structurally similar molecules are likely to have similar properties.

The most common LBDD techniques include molecular similarity-based search, quantitative structure-activity relationship (QSAR), and pharmacophore modelling.[1]

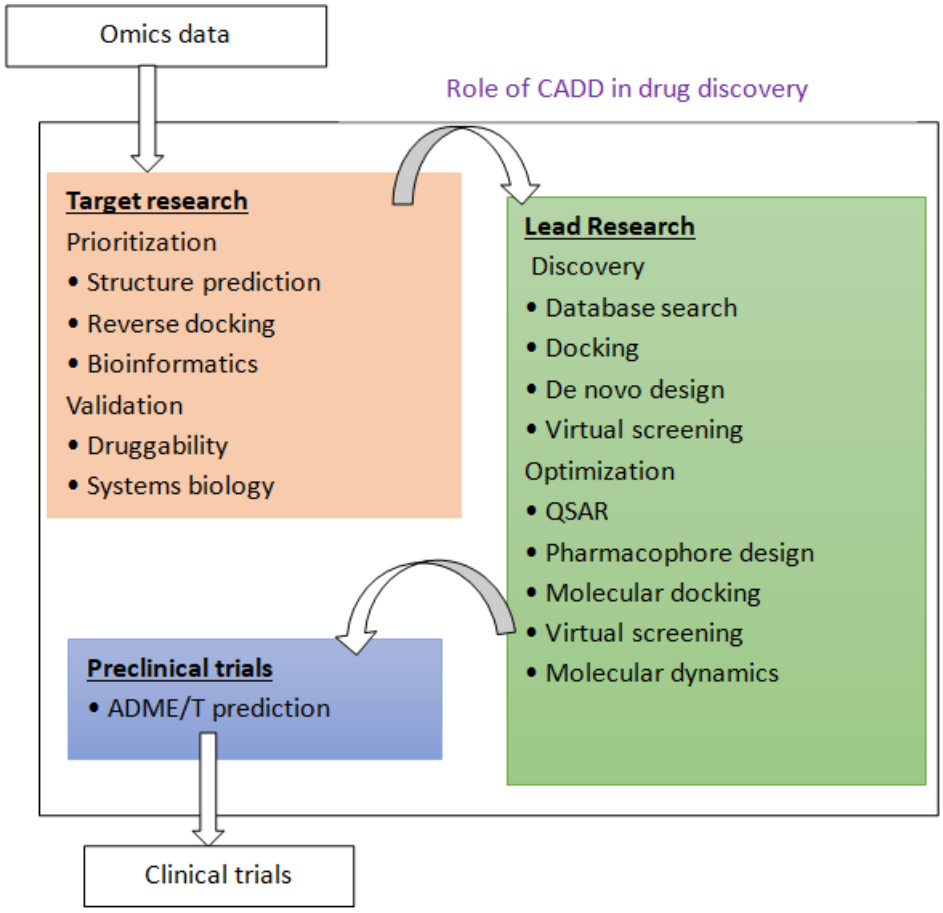


Figure 1: Role of computer-aided drug design (cadd) in drug discovery. ADME/T, Absorption, distribution, metabolism, excretion, and toxicity; QSAR, quantitative structure-activity relationship.[1]

Structure-based drug discovery (SBDD)

If the three-dimensional structure of a disease-related drug target is known, the most commonly used CADD techniques are structure-based. In SBDD the therapeutics are designed based on the knowledge of the target structure. Two commonly used methods in SBDD are molecular docking approaches and de novo ligand (antagonists, agonists, inhibitors, etc. of a target) design. Molecular dynamics (MD) simulations are frequently used in SBDD to give insights into not only how ligands bind with target proteins but also the pathways of interaction and to account for target flexibility. This is especially important when drug targets are membrane proteins where membrane permeability is considered to be important for drugs to be useful.[2]

Quinoxaline 2, 3-dione

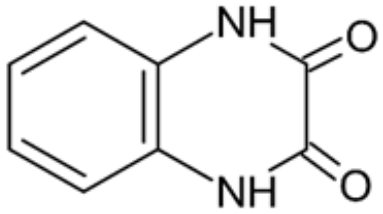


Figure 2: Quinoxaline-2, 3-dione.

Quinoxaline derivatives are an important class of nitrogen containing heterocycles in medicinal chemistry. For example, quinoxalines area part of various antibiotics such as echinomycin, leromycin and actinomycin, which are known to inhibit the growth of Gram-positive bacteria and are also active against various transplantable tumours.4 In addition, they are well known for their application in dyes, efficient electroluminescent materials,6 organic semiconductors,7 building blocks for the synthesis of anion receptors,8 cavitands,9 dehydroannulenes10 and DNA cleaving agents.[3]

Quinoxaline-2,3-dione is a bicyclic heteroaromatic compound with a fused benzene and pyrazine ring system, bearing two adjacent carbonyl groups at positions 2 and 3.

Synthesis

A solution of o-phenylene diamine (0.005 mol) and oxalic acid (0.05 mol) in 4 N HCl (90 ml) was refluxed for 4 h. The mixture was subjected for cooling in the refrigerator overnight to give respective quinoxaline-2, 3-(1H, 4H) – diones. The white solid recovered was filtered and underwent for cold water washing and recrystallized by using ethanol.[3]

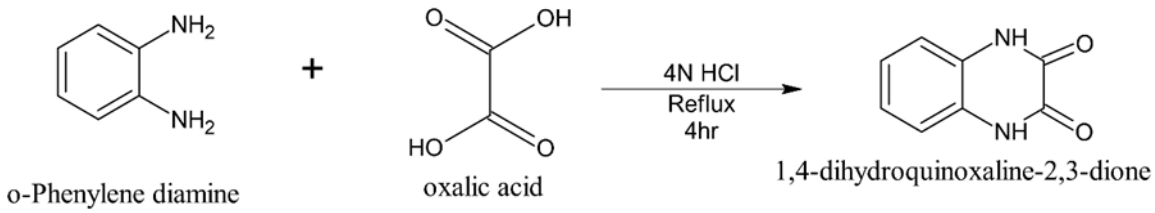


Figure 3: Synthesis.

Antibacterial activity

Staphylococcus aureus (S aureus) causes a wide spectrum of clinical diseases and remains one of the leading sources of bacterial-associated morbidity and mortality worldwide. Infections occur in both community-acquired and hospital-acquired settings, with prevention and treatment complicated by the organism's high transmissibility, extensive pathogenic mechanisms, and growing antimicrobial resistance. S aureus can exist as an innocuous colonizer of skin, mucous membranes, and the gastrointestinal tract.

Despite its ability to exist as a benign colonizer, S aureus can also produce severe, life-threatening infections. The organism frequently exchanges mobile genetic elements with both pathogenic and nonpathogenic bacteria, enhancing its adaptability and virulence. Through these genetic exchanges, S aureus has acquired the capacity to invade tissues, produce toxins, resist antimicrobial therapies, and evade host immune defenses. This overview discusses the pathogenesis of S aureus infections, with particular attention to the evaluation and management of bacteremia.[4]

S. aureus is a Gram-positive coccoid bacterium. It is ubiquitous, and 30-40% of adults are asymptomatic carriers. It is also a major pathogen of humans and can cause various infections, from mild skin infections and food poisoning to life-threatening infections.[13-18] Resistance to methicillin by S. aureus was initially observed in 1961, shortly after the antibacterial agent was introduced clinically. Since then, there has been a global epidemic of Methicillin-resistant Staphylococcus aureus (MRSA) in healthcare and community settings.[19-21] S.aureus is widely spread in the human population, with many asymptomatic carriers. It can also cause life-threatening infections, and its strains have evolved into MRSA and strains with reduced vancomycin susceptibility.[5]

Here we investigated the potential of derivatives as antibacterial and as anti MRSA agents through computational docking and validation studies.

2. REVIEW OF LITERATURE

- Suresh Kumar Suthar, Narendra Singh Chundawat, Girdhar Pal Singh, Jose M. Padron et al. (2020) Reviewed the recent pharmacological advancements of quinoxaline derivatives in medicinal chemistry over the period 2010–2020. The authors discussed various modern synthetic approaches, including green protocols, multicomponent reactions and one-pot synthesis methods for the development of quinoxaline analogues. The review emphasized diverse pharmacological activities, structure–activity relationships and bioavailability aspects of quinoxaline derivatives. The study concluded that quinoxaline remains a versatile and promising scaffold for the development of novel therapeutic agents.[6]
- Carta A, Loriga M, Zanetti S, and Sechi LA (2010) reviewed the antimicrobial potential of quinoxaline derivatives and discussed their importance as bioactive heterocyclic compounds. The authors summarized various synthetic modifications of the quinoxaline nucleus and highlighted their significant antibacterial, antifungal, and antitubercular activities. The study emphasized that substitution at different positions of the quinoxaline ring plays a crucial role in enhancing antimicrobial potency. Their findings suggest that quinoxaline derivatives represent promising scaffolds for the development of new antimicrobial agents.[7]
- Ghadage RV and Shirote PJ (2011) reported the synthesis and anticonvulsant evaluation of novel Schiff's bases of quinoxalin-2(1H)-one derivatives. The compounds were synthesized using both conventional and microwave-assisted methods and characterized by IR and ^1H NMR spectroscopy. The anticonvulsant activity was evaluated using the pentylenetetrazole (PTZ)-induced seizure model in mice. Among the synthesized derivatives, compounds IIIb and IIIc showed significant anticonvulsant activity compared to the standard drug diazepam. The study suggests that Schiff's base modification of quinoxaline may enhance anticonvulsant potential.[8]
- Meng XY, Zhang HX, Mezei M, and Cui M (2011) reviewed the principles and applications of molecular docking in structure-based drug design. The authors discussed different docking algorithms, scoring functions, and methods used to predict ligand–protein interactions. They highlighted the importance of molecular docking in identifying binding modes, estimating binding affinity, and accelerating virtual screening in drug discovery. The review emphasized that docking plays a crucial role in modern pharmaceutical research by reducing experimental cost and time during lead identification and optimization.[9]
- Gollapalli Naga Raju, Ramayanam Lakshmi Madhuri, Pattan Shaheena and Nadendla Ramarao(2015)Reviewed the diverse biological activities of quinoxaline derivatives and highlighted their broad pharmacological potential, including antibacterial, antifungal, anticancer and antitubercular properties. The authors discussed various synthetic modifications of the quinoxaline nucleus and their impact on biological activity. The review concluded that quinoxaline derivatives are promising lead molecules for developing new therapeutic agents.[10]
- Challa Siva Shankar Reddy, V. Hari Baskar and M. Gobinath (2017) Synthesized a series of quinoxaline-2,3-dione derivatives incorporating thiazolidinone and azetidinone moieties and evaluated their antimicrobial and antifungal activities. The compounds were characterized by IR and ^{1}H NMR spectroscopy and screened against various gram-positive and gram-negative bacteria as well as fungal strains. Several derivatives, particularly those with chloro, bromo and fluoro substitutions, showed significant antibacterial and antifungal activity compared to standard

drugs. The study concluded that structural modification of the quinoxaline nucleus enhances biological potential and may lead to promising antimicrobial agents.[11]

- M. J. Birajdar, Y. P. Kulkarni, S. M. Sonwane, K. L. Satpute, G. V. Lohiya and B. Rajeeva (2022) Synthesized novel quinoxaline derivatives containing piperazine and Schiff base moieties and evaluated their antimicrobial activity. The compounds were characterized by elemental analysis, IR, NMR and mass spectroscopy. Antibacterial and antifungal activities were assessed by the disc diffusion method against selected bacterial and fungal strains using ciprofloxacin and clotrimazole as standards. Fluoro and trimethoxy substituted derivatives showed promising activity, particularly against Pseudomonas aeruginosa, while some compounds exhibited moderate antimicrobial effects.[12]
- Ameen Ali Abu-Hashem (2015) Reviewed the synthesis, reactions and biological activities of quinoxaline derivatives. The author discussed various synthetic strategies for quinoxaline preparation, including oxidation, nitration, diazotization, alkylation, addition, condensation, cyclization and substitution reactions, mainly involving o-phenylenediamine as a key precursor. The review also highlighted the diverse pharmacological properties of quinoxaline and fused ring systems, emphasizing their importance as biologically active heterocyclic compounds.[13]
- Dhansay Dewangan, Kartik Nakhate, Achal Mishra, Alok Singh Thakur, Harish Rajak, Jaya Dwivedi, Swapnil Sharma and Sarvesh Paliwal (2018) Designed and synthesized a series of quinoxalinone derivatives starting from o-phenylenediamine and characterized them using IR, NMR and mass spectral analysis. The synthesized compounds were evaluated for antimicrobial activity, where derivatives 4c, 4d and 4i showed significant inhibitory effects compared to ciprofloxacin. Molecular docking studies against dihydrofolate reductase (PDB ID: 4XE6) revealed good binding affinities, with compound 4c exhibiting the highest docking score. The study concluded that these quinoxaline derivatives possess promising antimicrobial potential supported by both in vitro and in silico results.[14]
- Marc Montana, Vincent Montero, Omar Khoumeri and Patrice Vanelle (2021) Reviewed the potential of the quinoxaline moiety as a scaffold for the development of new antitubercular agents against Mycobacterium tuberculosis. The authors analyzed 23 studies published between 2011 and 2021, focusing on quinoxaline and quinoxaline-1,4-di-N-oxide derivatives and their structure–activity relationships. The review highlighted that several derivatives exhibited promising antimycobacterial activity and emphasized the growing interest in this scaffold for tuberculosis drug development. The authors concluded that quinoxaline derivatives represent encouraging candidates for further investigation as novel antitubercular agents.[15]
- Honnegowdanahalli Shivabasappa Nagendra Prasad, Navyatha Prashanth Gaonkar, Agasanapura Puttaswamy Ananda, Amogh Mukarambi et al. (2022) Synthesized and characterized a Schiff-based piperazine derivative and evaluated its antibacterial activity against methicillin-resistant Staphylococcus aureus (MRSA). The compound was analyzed using spectral techniques and further studied through DFT, ADME, BBB, PASS prediction and molecular docking approaches. In vitro findings showed potent antibacterial activity, supported by SEM analysis and fatty acid profile studies indicating membrane disassembly. The study concluded that Schiff-based piperazine represents a promising antibacterial candidate against MRSA.[16]
- Hamada H. H. Mohammed, Doaa Mohamed Elroby Ali, Mohamed Badr, Ahmed G. K. Habib et al. (2022) Synthesized new N-4 piperazinyl ciprofloxacin hybrids, including urea-tethered ciprofloxacin-chalcone and thioacetyl-linked ciprofloxacin-pyrimidine derivatives, and evaluated their antimicrobial activity. Several

compounds exhibited broad-spectrum antibacterial activity with low MIC values against Gram-positive and Gram-negative strains, while some derivatives also showed notable antifungal activity against Candida albicans. Selected hybrids demonstrated significant DNA gyrase inhibitory activity, supported by molecular docking studies confirming stable binding interactions with the enzyme. The study concluded that these ciprofloxacin hybrids are promising antimicrobial DNA gyrase inhibitors.[17]

3. AIM & OBJECTIVE

Aim

- To design and evaluate novel Schiff's base of quinoxaline-2,3-dione derivatives as promising antibiotic candidates using in silico tools.
- To explore the antibacterial activity of selected ligands against Staphylococcus aureus and Methicillin-resistant Staphylococcus aureus using computational docking.

OBJECTIVE

- To design a series of structurally diverse Schiff's base of quinoxaline-2,3-dione derivatives using rational drug design principles.
- To perform molecular docking studies to evaluate the binding affinity and interaction profiles of the designed ligands with selected bacterial target protein.
- To predict the pharmacokinetic behaviour and toxicity profiles of the proposed compounds using in silico ADMET analysis, ensuring their suitability as potential antibiotic agents.

Plan of work

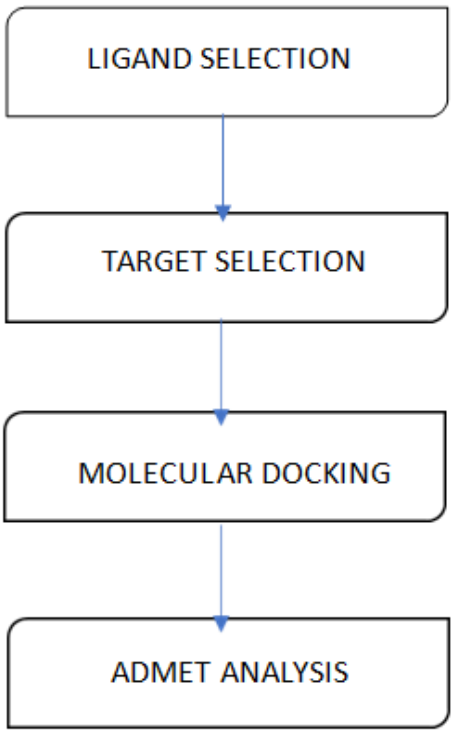


Figure 4: Plan of work.

4. MATERIALS & METHODS

A series of computational tools were employed to design, optimize, and evaluate Schiff's base derivatives of quinoxaline-2,3-dione. Each software served a distinct role in the workflow, ranging from ligand construction and preprocessing to protein preparation, docking simulations, visualization, and pharmacokinetic profiling.

Table 4: Softwares used & their usage.

SL.NO	SOFTWARES USED	USAGE
1	CHEMSKETCH	To draw 2D structures
2	MOLINSPIRATION	To calculate drug likeliness property
3	NOVOPRO	Convert ligand Smiles into 3D structures
4	PDB	Database for downloading proteins
5	UCSF ChimeraX	Protein preprocessing
6	Avogadro	Ligand preprocessing
7	AutoDock4	Docking
8	Biodiscovery Studio	Visualizing
9	ADMETlab 3.0	Pharmacokinetic evaluation

ACD/ChemSketch

A chemical drawing and visualization program that allows researchers to create 2D and 3D molecular structures, generate systematic names, and calculate basic properties. It is widely used for preparing figures and chemical documentation.

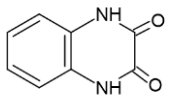


Figure 5: ChemSketch.

Molinspiration

A web-based cheminformatics platform that calculates molecular descriptors and predicts bioactivity. It is commonly applied in drug discovery to evaluate drug-likeness and estimate biological potential of compounds. All the designed compounds were evaluated using Lipinski's Rule of Five (also known as the Pfizer rule), a guideline proposed by Christopher A. Lipinski to assess drug-likeness and oral bioavailability.

The Lipinski rule of five states that an orally active drug should obey:

1. Not more than 5 hydrogen bond donors
2. Not more than 10 hydrogen bond acceptors
3. n octanol-water partition coefficient or log P not greater than 5
4. Molecular weight not more than 500 Dalton
5. Not more than 5 rotatable bonds.

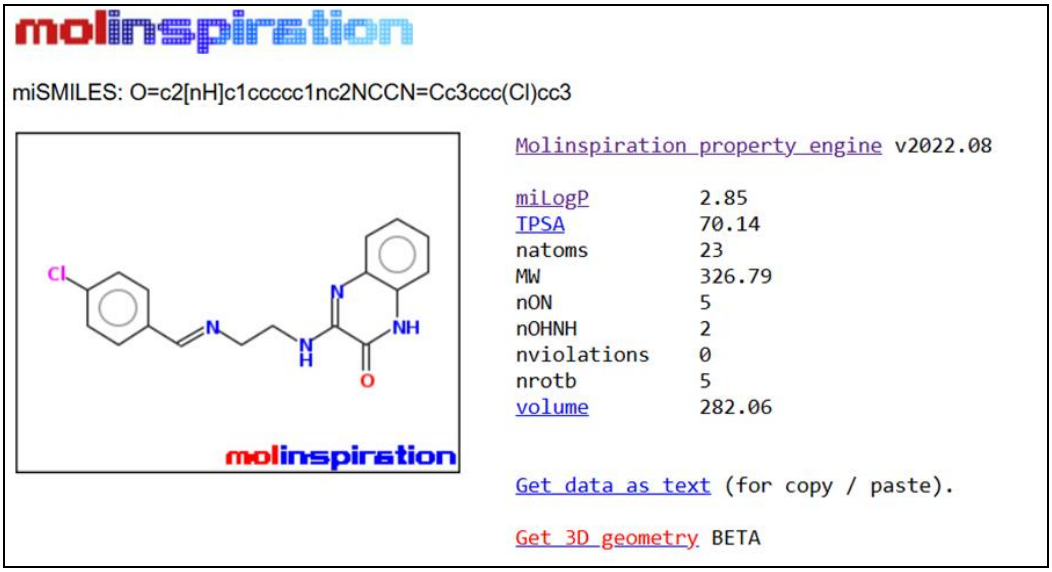


Figure 6: Molinspiration.

Novoprolabs

It is used to convert SMILES of a chemical structure into its 3D conformer. The 3D structure can be downloaded in any one of the desired format like pdb, mol, sdf.

PDB (Protein Data Bank)

The Protein Data Bank (PDB) is a global archive of 3D structural data for proteins, nucleic acids, and other biological macromolecules. It serves as a freely accessible resource for scientists, educators, and students worldwide.

Figure 7: - 3D image of 6FTB.

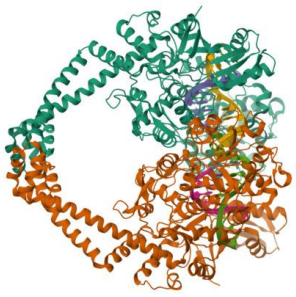


Figure 8: - 3D image of 2XCT.

UCSF ChimeraX

An advanced molecular visualization tool designed for interactive exploration of macromolecular structures, cryo-EM maps, and docking results.

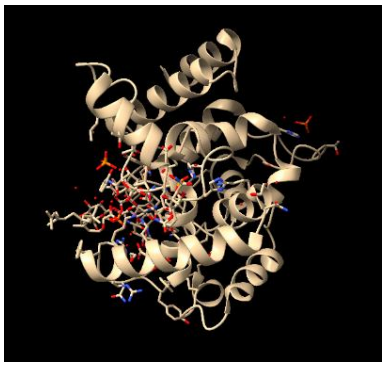


Figure 9: - UCSF ChimeraX.

Avogadro

An open-source molecular builder and editor that supports 3D visualization, geometry optimization, and file conversion.

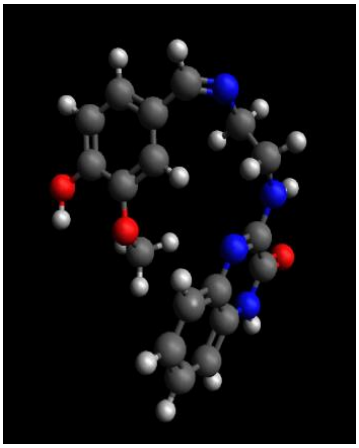


Figure 10: Avogadro.

AutoDock4

A molecular docking software that predicts how small molecules bind to protein targets. It is extensively used in drug discovery to evaluate binding affinities and ligand–receptor interactions.

Steps involved in docking

1. Protein preparation
2. Ligand preparation
3. Grid map setting
4. Run autogrid & autodock

Protein preparation

Protein preparation is necessary after downloading a structure from the PDB because raw PDB files are not directly suitable for docking or molecular studies. They often contain unnecessary molecules such as water, ions, or solvents, lack hydrogen atoms, have missing residues, and may not have correct charge or protonation states. These issues can affect ligand binding and lead to inaccurate results. Preparing the protein helps remove unwanted components, add missing hydrogens, assign proper charges, fix structural errors, and optimize geometry, making the structure more realistic and reliable for computational analysis.

The target protein structure was downloaded from the Protein Data Bank (PDB) and initially processed in UCSF ChimeraX. The prepared structure was then imported into AutoDock 4, where water molecules were deleted, hydrogens were added, non-polar hydrogens were merged, Kollman charges were assigned, and AutoDock 4 atom types were defined to generate the final docking-ready protein file.

Ligand preparation

The ligand structure was initially constructed using Avogadro molecular editor. Hydrogen atoms were added to ensure proper valency and to complete the molecular framework. Following this, the geometry of the ligand was optimized using Avogadro's built-in energy minimization algorithms, thereby reducing steric clashes and achieving a stable conformation suitable for docking studies. The optimized ligand file was then exported in the required format and subsequently imported into AutoDock 4 for molecular docking simulations.

Biodiscovery Studio

A commercial suite for molecular modeling and drug design, integrating visualization, simulation, and analysis tools. After docking studies were completed, the best conformer of each ligand was further analyzed using BIOVIA Discovery Studio. The ligand–receptor interactions were carefully visualized, and their 2D interaction diagrams were obtained to provide a clear representation of hydrogen bonds, hydrophobic contacts, and other non-covalent interactions between the selected quinoxaline derivatives and the target proteins.

ADMETlab 3.0

The pharmacokinetic and toxicity properties of the quinoxaline derivatives were evaluated using ADMETlab 3.0, an advanced computational platform for absorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction.

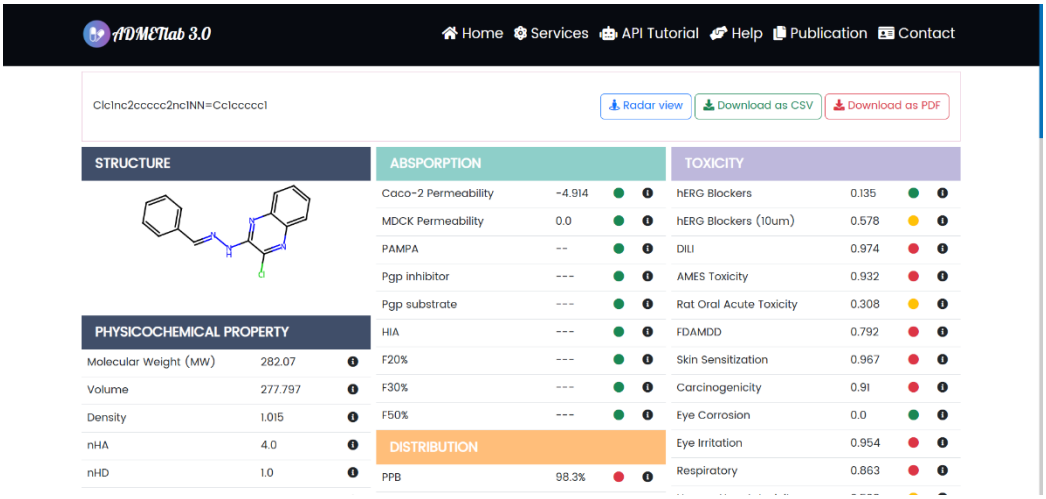
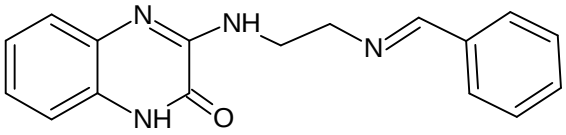
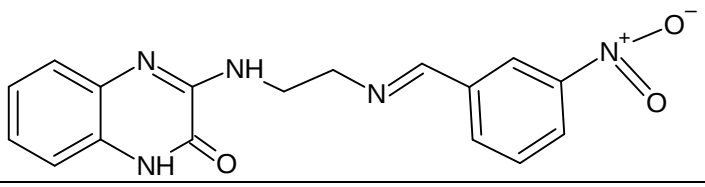
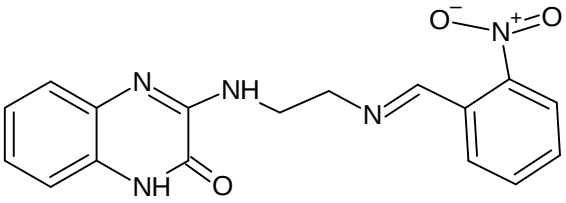
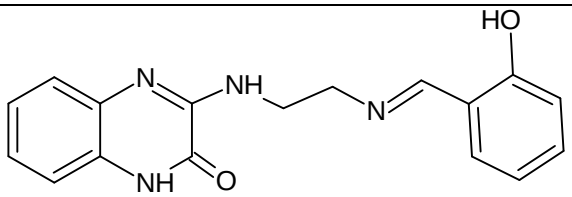
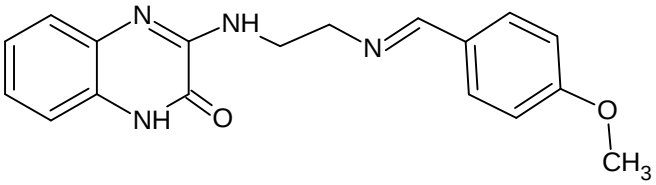
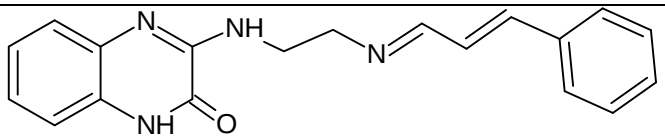
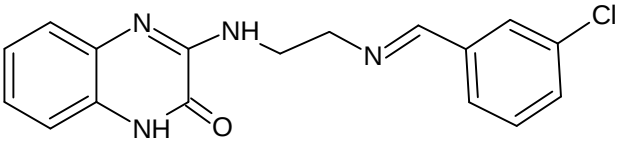
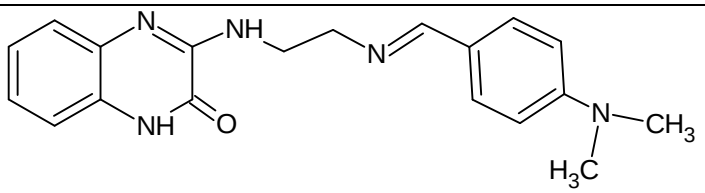
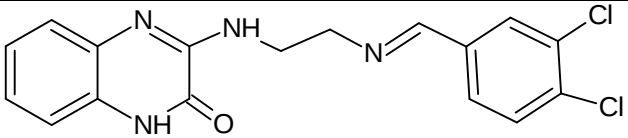
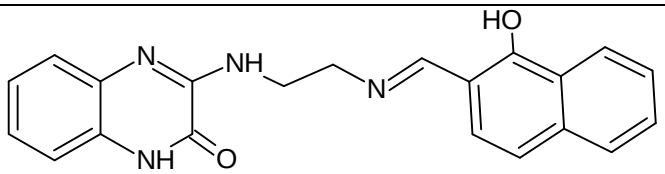


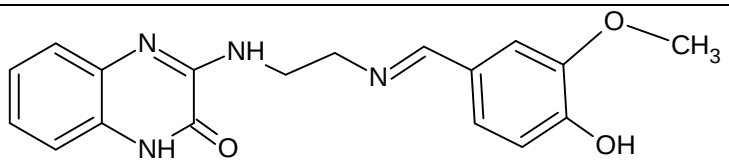
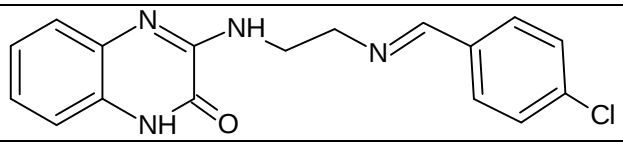
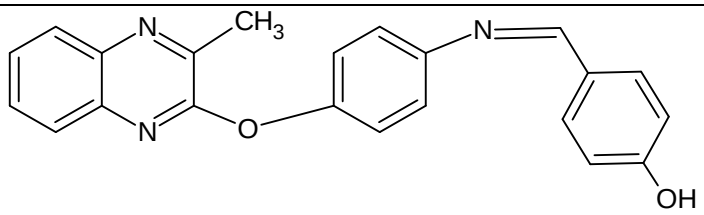
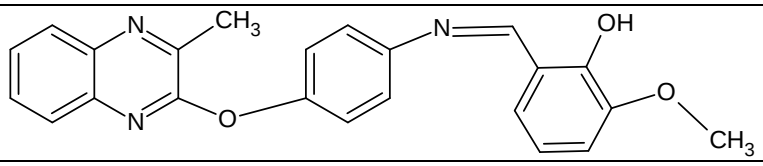
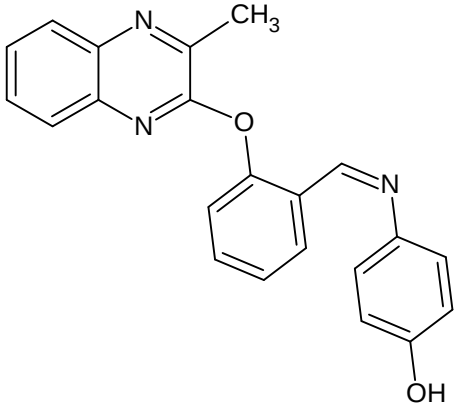
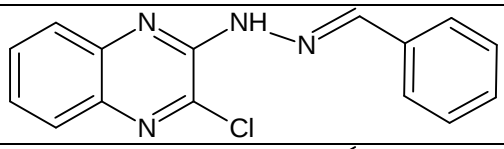
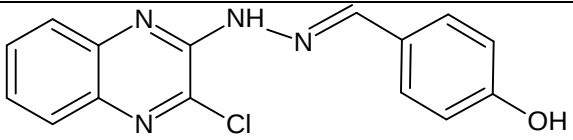
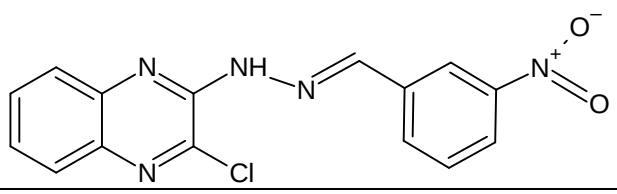
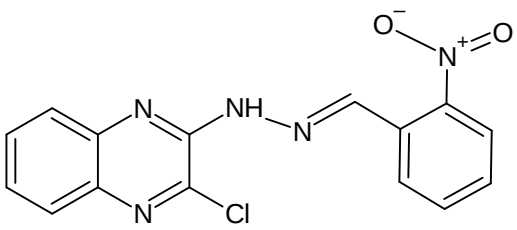
Figure 11: ADMETlab 3.0

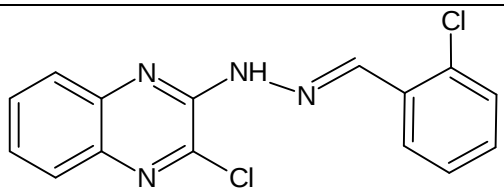
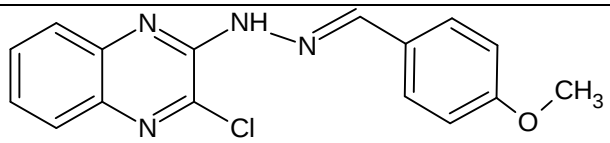
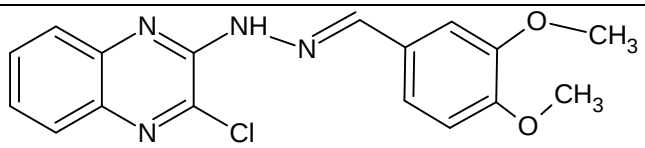
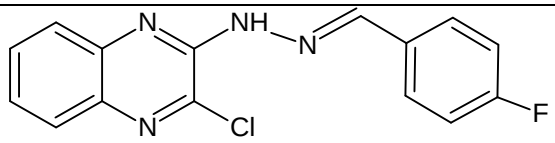
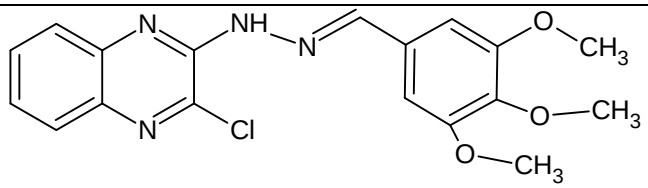
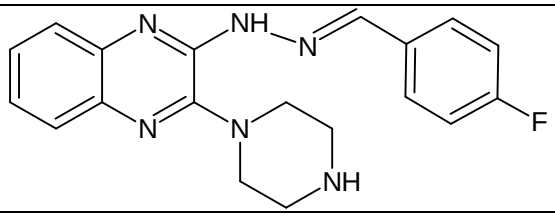
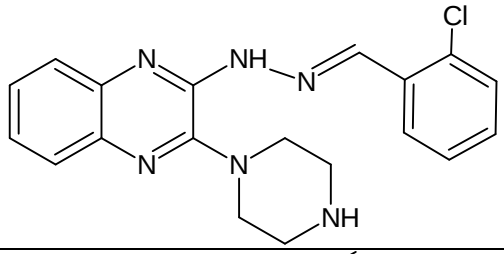
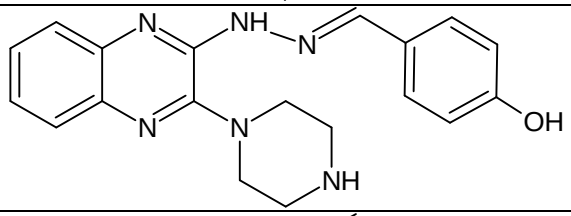
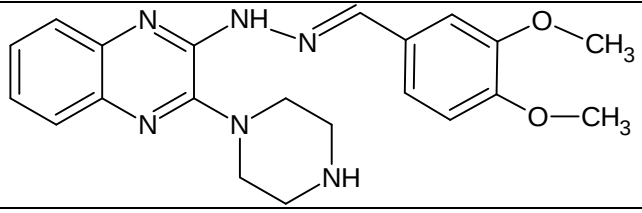
Selected derivatives

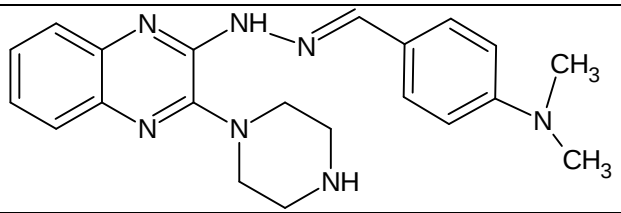
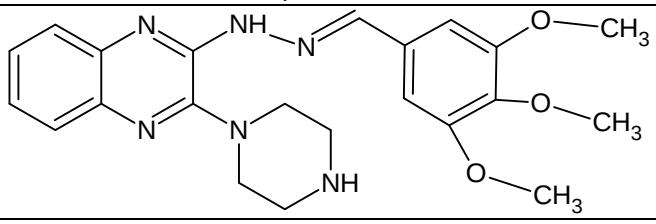
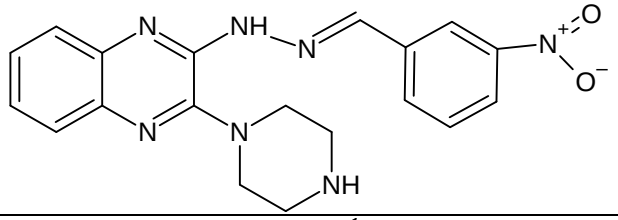
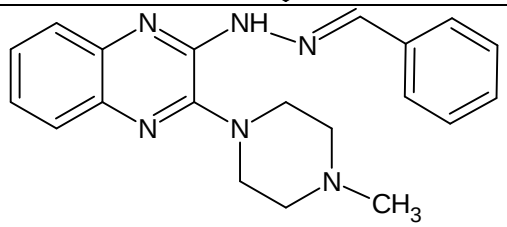
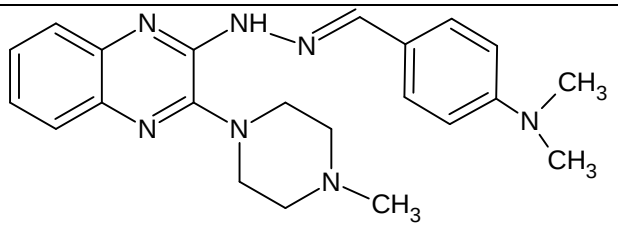
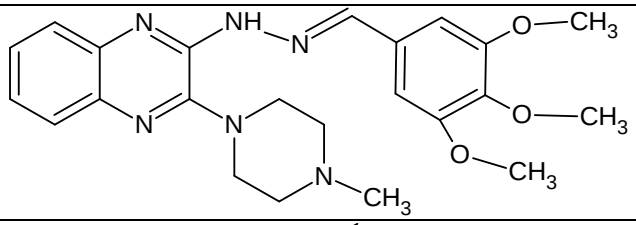
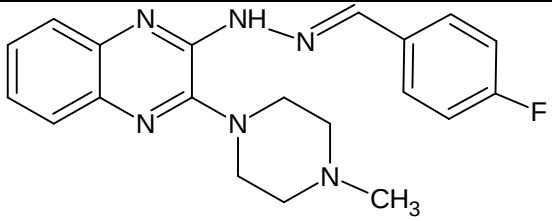
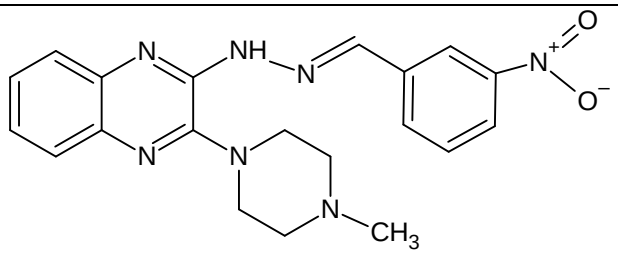
The derivatives selected from various literature are given here.

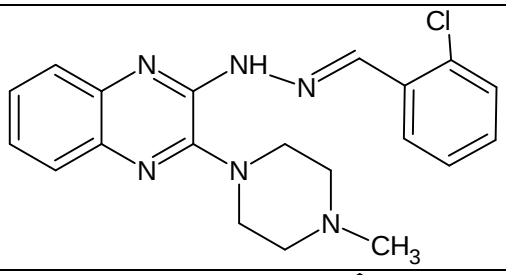
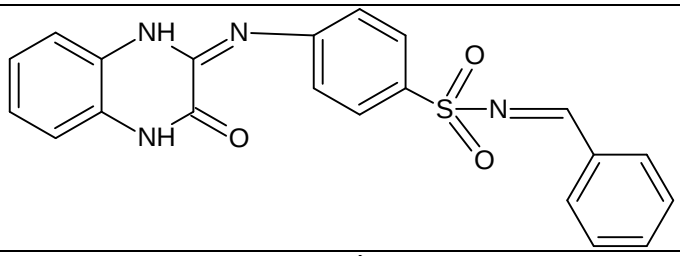
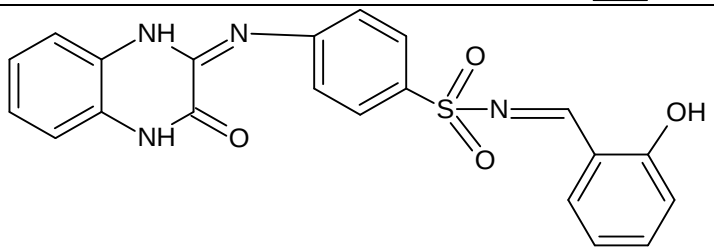
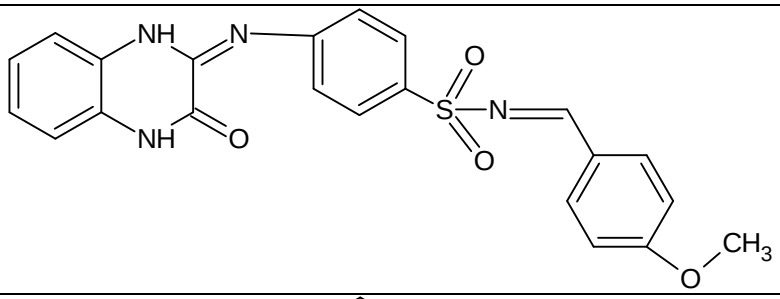
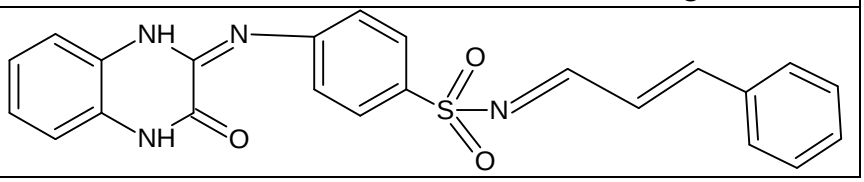
Table 2: Selected derivatives.

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

11	
12	
13	
14	
15	
16	
17	
18	
19	

20	
21	
22	
23	
24	
25	
26	
27	
28	

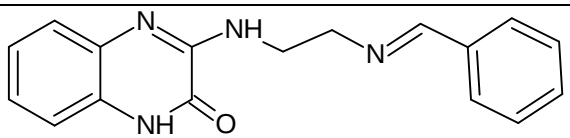
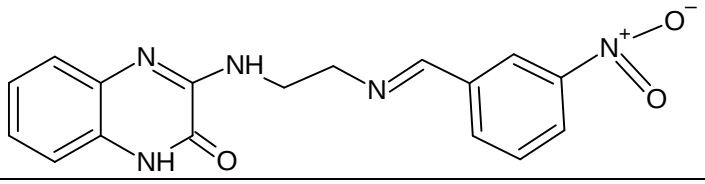
29	
30	
31	
32	
33	
34	
35	
36	

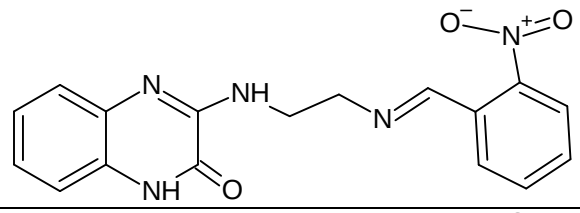
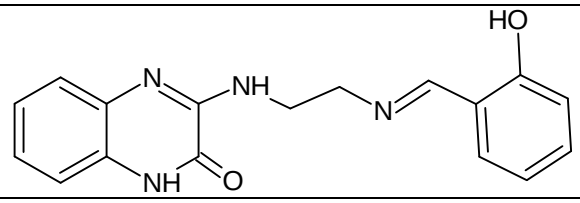
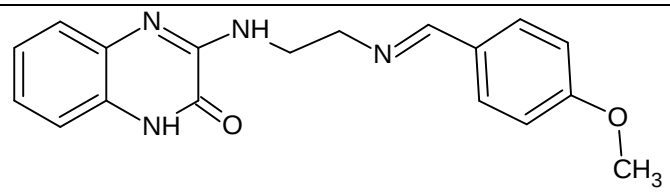
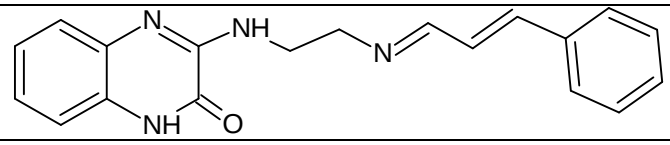
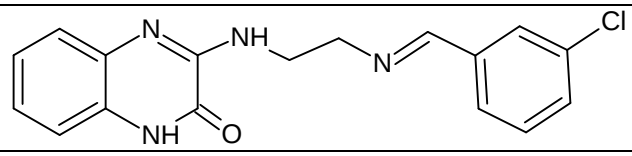
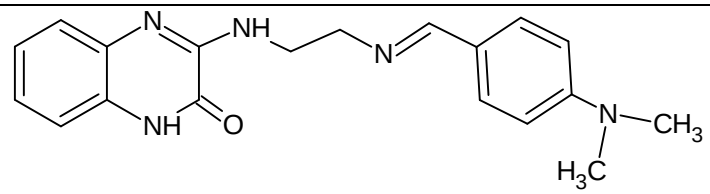
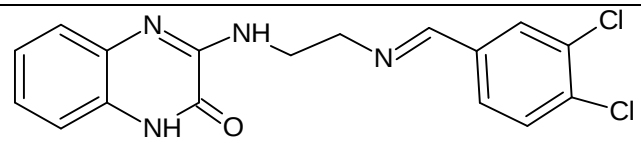
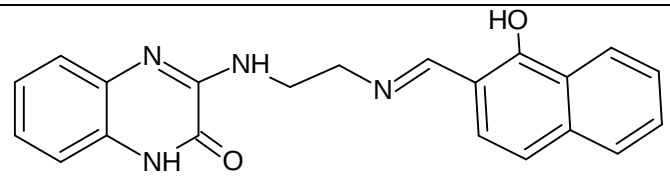
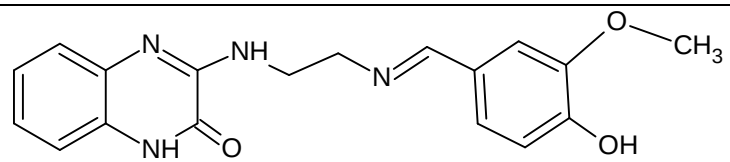
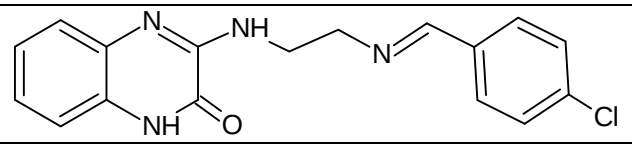
37	
38	
39	
40	
41	

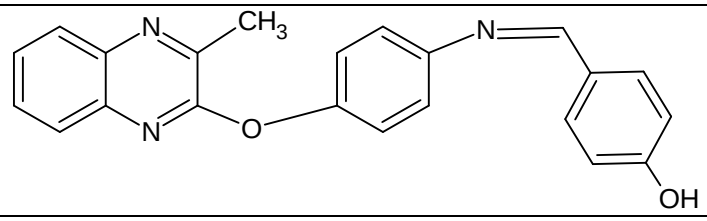
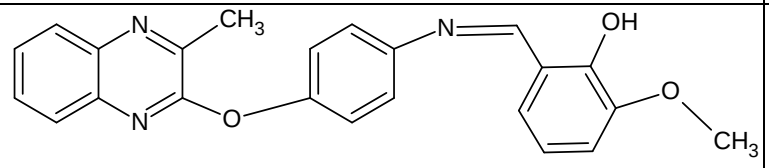
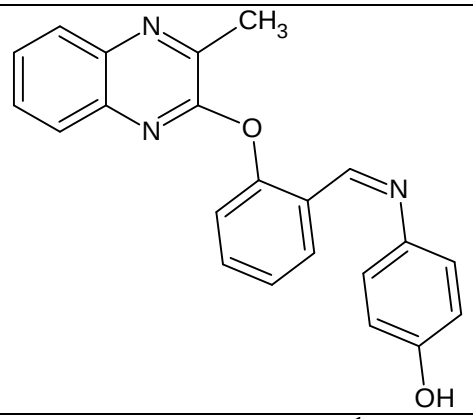
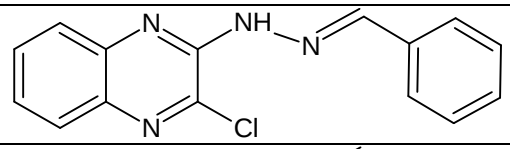
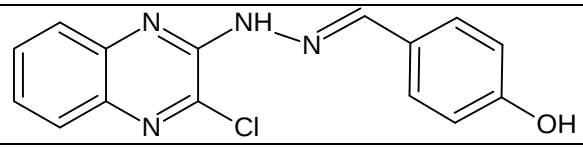
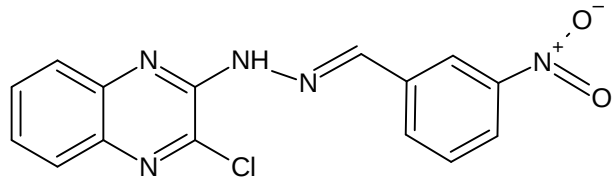
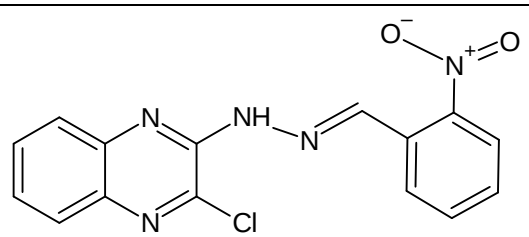
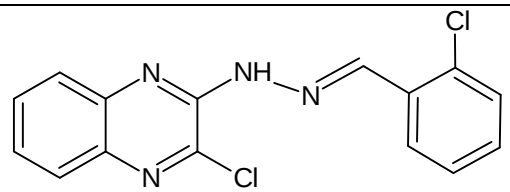
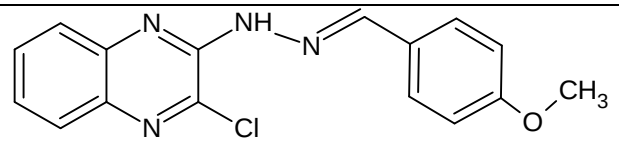
5. RESULTS & DISCUSSION

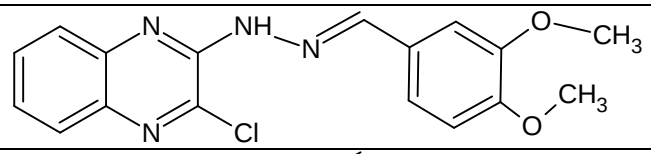
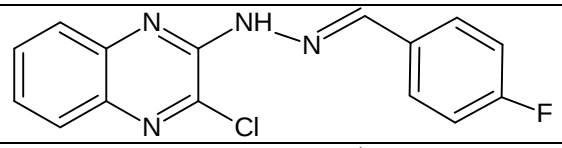
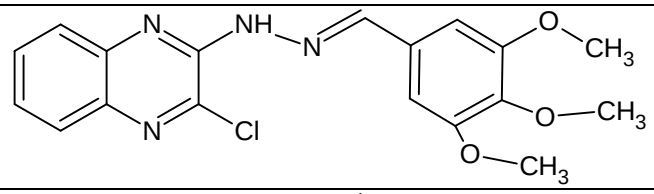
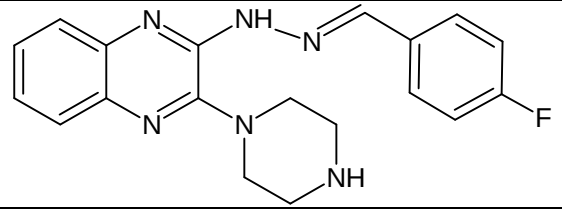
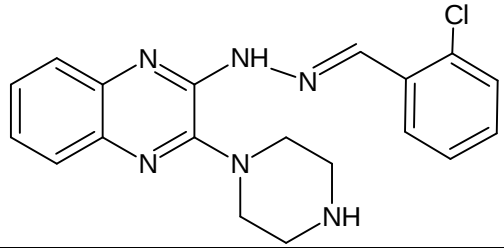
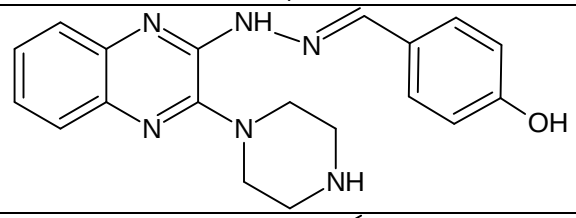
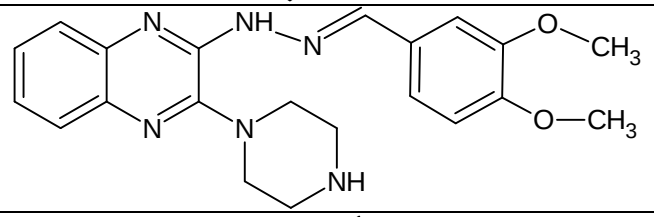
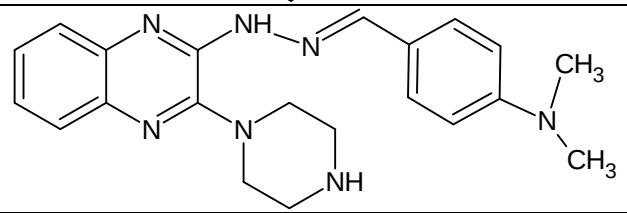
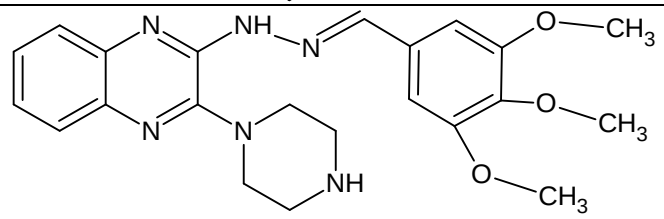
The SMILES & IUPAC names of all derivatives were obtained using ACD/Chemsketch.

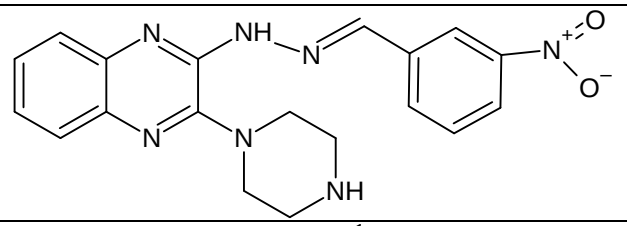
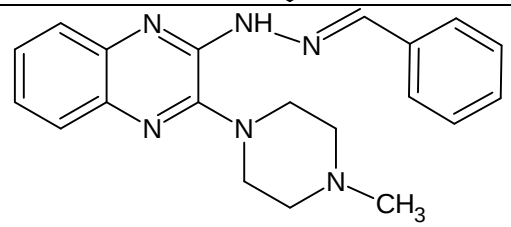
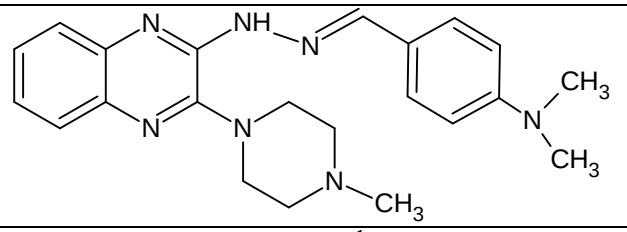
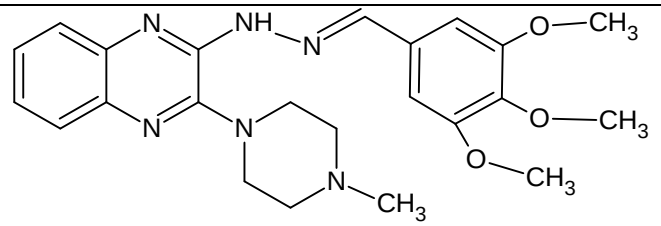
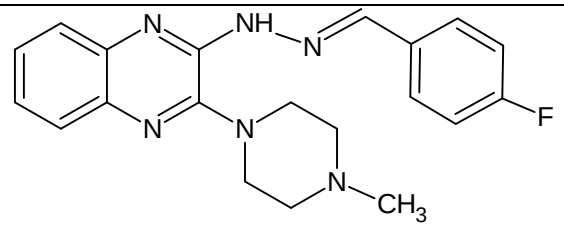
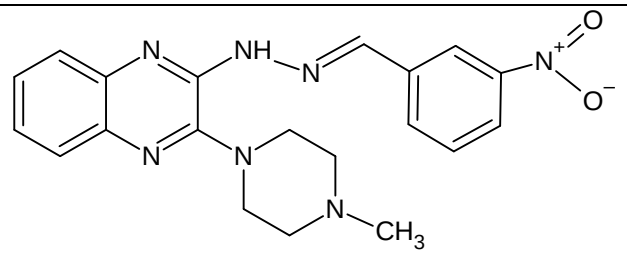
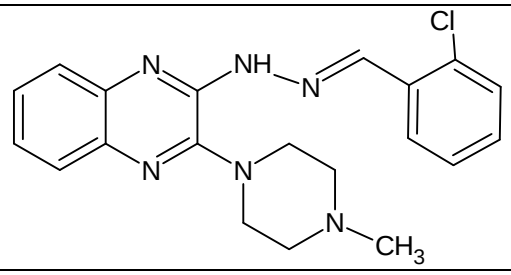
Table 3: SMILES & IUPAC names of all derivatives.

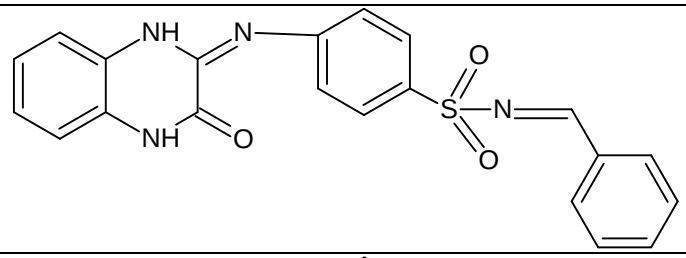
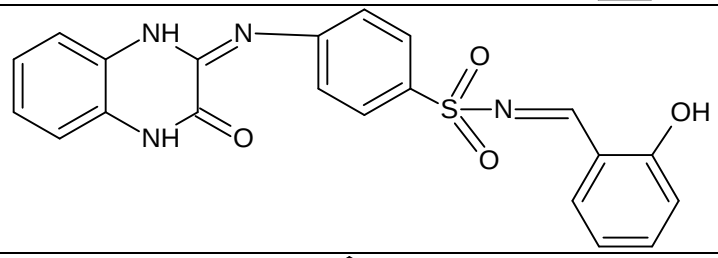
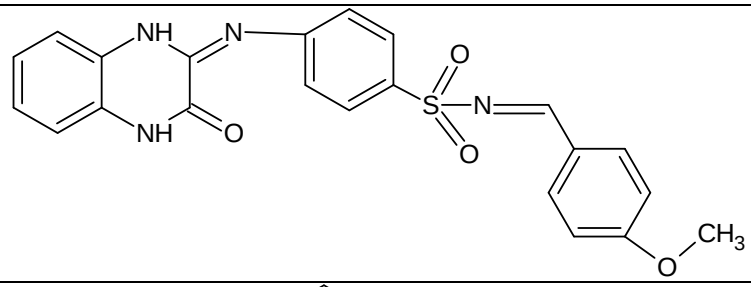
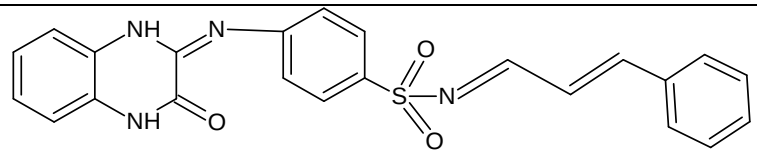
SL. NO	LIGANDS	SMILES	IUPAC NAME
1		O=c2[nH]c1ccccc1nc2NCCN=Cc3ccccc3	3-({2-[(E)-benzylideneamino]ethyl}amino)quinoxalin-2(1H)-one
2		O=c2[nH]c1ccccc1nc2NCCN=Cc3cccc(N(=O)=O)c3	3-[(2-{(E)-[(3-nitrophenyl)methylidene]amino}ethyl)amino]quinoxalin-2(1H)-one

3		O=c2[nH]c1ccccc1nc2NCCN=Cc3ccccc3N(=O)=O	3-[(2-{(E)-[(2-nitrophenyl)methylidene]amino}ethyl)amino]quinoxalin-2(1H)-one
4		O=c2[nH]c1ccccc1nc2NCCN=Cc3ccccc3O	3-[(2-{(E)-[(2-hydroxyphenyl)methylidene]amino}ethyl)amino]quinoxalin-2(1H)-one
5		COc3ccc(C=NCCNc2nc1ccccc1[nH]c2=O)cc3	3-[(2-{(E)-[(4-methoxyphenyl)methylidene]amino}ethyl)amino]quinoxalin-2(1H)-one
6		O=c2[nH]c1ccccc1nc2NCCN=CC=Cc3ccccc3	3-[(2-{(E)-[(2E)-3-phenylprop-2-en-1-ylidene]amino}ethyl)amino]quinoxalin-2(1H)-one
7		O=c2[nH]c1ccccc1nc2NCCN=Cc3cccc(Cl)c3	3-[(2-{(E)-[(3-chlorophenyl)methylidene]amino}ethyl)amino]quinoxalin-2(1H)-one
8		CN(C)c3ccc(C=NCCNc2nc1ccccc1[nH]c2=O)cc3	3-({2-[(E)-{[4-(dimethylamino)phenyl]methylidene}amino]ethyl}amino)quinoxalin-2(1H)-one
9		O=c2[nH]c1ccccc1nc2NCCN=Cc3ccc(Cl)c(Cl)c3	3-[(2-{(E)-[(3,4-dichlorophenyl)methylidene]amino}ethyl)amino]quinoxalin-2(1H)-one
10		O=c2[nH]c1ccccc1nc2NCCN=Cc4ccc3ccccc3c4O	3-[(2-{(E)-[(1-hydroxynaphthalen-2-yl)methylidene]amino}ethyl)amino]quinoxalin-2(1H)-one
11		COc3cc(C=NCCNc2nc1ccccc1[nH]c2=O)ccc3O	3-[(2-{(E)-[(4-hydroxy-3-methoxyphenyl)methylidene]amino}ethyl)amino]quinoxalin-2(1H)-one
12		O=c2[nH]c1ccccc1nc2NCCN=Cc3ccc(Cl)cc3	3-[(2-{(E)-[(4-chlorophenyl)methylidene]amino}ethyl)amino]quinoxalin-2(1H)-one

13		Cc2nc1ccccc1nc2Oc4ccc(N=Cc3ccc(O)cc3)cc4	4-[(Z)-({4-[(3-methylquinoxalin-2-yl)oxy]phenyl}imino)methyl]phenol
14		COc4cccc(C=Nc3ccc(Oc2nc1ccccc1nc2C)cc3)1c4O	2-methoxy-6-[(Z)-({4-[(3-methylquinoxalin-2-yl)oxy]phenyl}imino)methyl]phenol
15		Cc2nc1ccccc1nc2Oc3ccccc3C=Nc4ccc(O)cc4	4-[(Z)-({2-[(3-methylquinoxalin-2-yl)oxy]phenyl}methylidene)amino]phenol
16		Clc2nc1ccccc1nc2NN=Cc3ccccc3	2-[(2E)-2-benzylidenehydrazin-1-yl]-3-chloroquinoxaline
17		Oc3ccc(C=NNc2nc1ccccc1nc2Cl)cc3	4-{(E)-[2-(3-chloroquinoxalin-2-yl)hydrazinylidene]methyl}phenol
18		O=N(=O)c3cccc(C=NNc2nc1ccccc1nc2Cl)c3	2-chloro-3-{(2E)-2-[(3-nitrophenyl)methylidene]hydrazin-1-yl}quinoxaline
19		O=N(=O)c1ccccc1C=NNc3nc2ccccc2nc3Cl	2-chloro-3-{(2E)-2-[(2-nitrophenyl)methylidene]hydrazin-1-yl}quinoxaline
20		Clc1ccccc1C=NNc3nc2ccccc2nc3Cl	2-chloro-3-{(2E)-2-[(2-chlorophenyl)methylidene]hydrazin-1-yl}quinoxaline
21		COc3ccc(C=NNc2nc1ccccc1nc2Cl)cc3	2-chloro-3-{(2E)-2-[(4-methoxyphenyl)methylidene]hydrazin-1-yl}quinoxaline

22		COc3ccc(C=NNc2nc1ccccc1nc2Cl)cc3OC	2-chloro-3-{(2E)-2-[(3,4-dimethoxyphenyl)methylidene]hydrazin-1-yl}quinoxaline
23		Fc3ccc(C=NNc2nc1ccccc1nc2Cl)cc3	2-chloro-3-{(2E)-2-[(4-fluorophenyl)methylidene]hydrazin-1-yl}quinoxaline
24		COc3cc(C=NNc2nc1ccccc1nc2Cl)cc(OC)c3OC	2-chloro-3-{(2E)-2-[(3,4,5-trimethoxyphenyl)methylidene]hydrazin-1-yl}quinoxaline
25		Fc4ccc(C=NNc2nc1ccccc1nc2N3CCNCC3)cc4	2-{(2E)-2-[(4-fluorophenyl)methylidene]hydrazin-1-yl}-3-(piperazin-1-yl)quinoxaline
26		Clc1ccccc1C=NNc3nc2ccccc2nc3N4CCNCC4	2-{(2E)-2-[(2-chlorophenyl)methylidene]hydrazin-1-yl}-3-(piperazin-1-yl)quinoxaline
27		Oc4ccc(C=NNc2nc1ccccc1nc2N3CCNCC3)cc4	4-[(E)-{2-[3-(piperazin-1-yl)quinoxalin-2-yl]hydrazinylidene}methyl]phenol
28		COc4ccc(C=NNc2nc1ccccc1nc2N3CCNCC3)cc4OC	2-[2-(3,4-dimethoxybenzylidene)hydrazinyl]-3-(piperazin-1-yl)quinoxaline
29		CN(C)c4ccc(C=NNc2nc1ccccc1nc2N3CCNCC3)cc4	2-[2-(4-(dimethylamino)benzylidene)hydrazinyl]-3-(piperazin-1-yl)quinoxaline
30		COc4cc(C=NNc2nc1ccccc1nc2N3CCNCC3)cc(OC)c4OC	2-[2-(3,4,5-trimethoxybenzylidene)hydrazinyl]-3-(piperazin-1-yl)quinoxaline

31		O=N(=O)c4cccc(C=NNc2nc1ccccc1nc2N3CCNCC3)c4	2-{(2E)-2-[(3-nitrophenyl)methylidene]hydrazin-1-yl}-3-(piperazin-1-yl)quinoxaline
32		CN4CCN(c2nc1ccccc1nc2NN=Cc3ccccc3)CC4	2-[(2E)-2-benzylidenehydrazin-1-yl]-3-(4-methylpiperazin-1-yl)quinoxaline
33		CN(C)c4ccc(C=NNc2nc1ccccc1nc2N3CCN(C)CC3)cc4	2-[2-(4-(dimethylamino)benzylidene)hydrazinyl]-3-(4-methylpiperazin-1-yl)quinoxaline
34		COc4cc(C=NNc2nc1ccccc1nc2N3CCN(C)CC3)cc(OC)c4OC	2-[2-(3,4,5-trimethoxybenzylidene)hydrazinyl]-3-(4-methylpiperazin-1-yl)quinoxaline
35		CN4CCN(c2nc1ccccc1nc2NN=Cc3ccc(F)cc3)CC4	2-{(2E)-2-[(4-fluorophenyl)methylidene]hydrazin-1-yl}-3-(4-methylpiperazin-1-yl)quinoxaline
36		CN4CCN(c2nc1ccccc1nc2NN=Cc3cccc(N(=O)=O)c3)CC4	2-(4-methylpiperazin-1-yl)-3-{(2E)-2-[(3-nitrophenyl)methylidene]hydrazin-1-yl}quinoxaline
37		CN4CCN(c2nc1ccccc1nc2NN=Cc3ccccc3Cl)CC4	2-{(2E)-2-[(2-chlorophenyl)methylidene]hydrazin-1-yl}-3-(4-methylpiperazin-1-yl)quinoxaline

38		O=c2[nH]c1ccccc1[nH]c2=Nc4ccc(S(=O)(=O)N=Cc3ccccc3)cc4	(E)-N-(benzylidene)-4-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidenamino)benzenesulfonamide
39		O=c2[nH]c1ccccc1[nH]c2=Nc4ccc(S(=O)(=O)N=Cc3ccccc3O)cc4	(E)-N-(2-hydroxybenzylidene)-4-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidenamino)benzenesulfonamide
40		COc4ccc(C=NS(=O)(=O)c3ccc(N=c2[nH]c1ccccc1[nH]c2=O)cc3)cc4	(E)-N-(4-methoxybenzylidene)-4-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidenamino)benzenesulfonamide
41		O=c2[nH]c1ccccc1[nH]c2=Nc4ccc(S(=O)(=O)N=CC=Cc3ccccc3)cc4	(E)-N-(cinnamylidene)-4-(3-oxo-3,4-dihydroquinoxalin-2(1H)-ylidenamino)benzenesulfonamide

All the proposed derivatives were drawn by using ACD/Chemsketch and SMILES notation and IUPAC names are also generated.

Molinspiration values

The MOLINSPIRATION values depicts whether the molecule follows Lipinski Rule of Five. The drug likeness properties of proposed ligands were shown in table.

Table 4: MOLINSPIRATION values of all derivatives.

SI. No.	COMPOUND CODE	MOLECULAR WEIGHT	No. of H BOND ACCEPTORS	No. of H BOND DONORS	LOG P VALUE	No. of VIOLATIONS
1	Q1	292.34	5	2	2.18	0
2	Q2	337.34	8	2	2.11	0
3	Q3	337.34	8	2	2.09	0
4	Q4	308.34	6	3	2.12	0
5	Q5	322.37	6	2	2.23	0
6	Q6	318.38	5	2	2.93	0
7	Q7	326.79	5	2	2.83	0
8	Q8	335.41	6	2	2.28	0
9	Q9	361.23	5	2	3.46	0
10	Q10	358.40	6	3	3.07	0
11	Q11	338.37	7	3	1.51	0
12	Q12	326.79	5	2	2.85	0
13	Q13	355.40	5	1	4.89	0
14	Q14	385.42	6	1	4.91	0
15	Q15	355.40	5	1	4.84	0

16	Q16	282.73	4	1	3.95	0
17	Q17	298.73	5	2	3.47	0
18	Q18	327.73	7	1	3.89	0
19	Q19	327.73	7	1	3.86	0
20	Q20	317.18	4	1	4.58	0
21	Q21	312.76	5	1	4.01	0
22	Q22	342.79	6	1	3.60	0
23	Q23	300.72	4	1	4.12	0
24	Q24	372.81	7	1	3.58	0
25	Q25	350.40	6	2	2.84	0
26	Q26	366.86	6	2	3.30	0
27	Q27	348.41	7	3	2.19	0
28	Q28	392.46	8	2	2.32	0
29	Q29	375.48	7	2	2.77	0
30	Q30	422.49	9	2	2.30	0
31	Q31	377.41	9	2	2.61	0
32	Q32	346.44	6	1	3.27	0
33	Q33	389.51	7	1	3.37	0
34	Q34	436.52	9	1	2.90	0
35	Q35	364.43	6	1	3.43	0
36	Q36	391.44	9	1	3.20	0
37	Q37	380.88	6	1	3.90	0
38	Q38	404.45	7	2	3.33	0
39	Q39	420.45	8	3	3.27	0
40	Q40	434.48	8	2	3.39	0
41	Q41	430.49	7	2	4.09	0

All the seventy five compounds showed drug likeness properties and obeyed the Lipinski rule of five. The compounds that showed violations were eliminated.

Docking

The derivatives were docked with DNA gyrase and Methicillin resistant protein (PDB ID= 2XCT & 6FTB). The docking score of the analogues are shown in Table 4 and Table 5.

Table 5: Docking scores of all standard and derivatives with protein 2XCT.

SL.NO	LIGANDS	PROTEIN (PDB ID = 2XCT)	DOCKING SCORE
	STANDARD (Ciprofloxacin)	2XCT	-7.14
1	Q1	2XCT	-7.42
2	Q2	2XCT	-8.40
3	Q3	2XCT	-8.52
4	Q4	2XCT	-7.95
5	Q5	2XCT	-7.16
6	Q6	2XCT	-8.56
7	Q7	2XCT	-8.45
8	Q8	2XCT	-7.37
9	Q9	2XCT	-8.28
10	Q10	2XCT	-7.82
11	Q11	2XCT	-6.84
12	Q12	2XCT	-7.57
13	Q13	2XCT	-9.43
14	Q14	2XCT	-7.65
15	Q15	2XCT	-8.04
16	Q16	2XCT	-7.91
17	Q17	2XCT	-8.34
18	Q18	2XCT	-8.95

19	Q19	2XCT	-8.34
20	Q20	2XCT	-8.44
21	Q21	2XCT	-7.92
22	Q22	2XCT	-7.47
23	Q23	2XCT	-7.80
24	Q24	2XCT	-6.78
25	Q25	2XCT	-8.07
26	Q26	2XCT	-7.38
27	Q27	2XCT	-8.11
28	Q28	2XCT	-6.67
29	Q29	2XCT	-9.28
30	Q30	2XCT	-7.61
31	Q31	2XCT	-9.07
32	Q32	2XCT	-7.82
33	Q33	2XCT	-7.68
34	Q34	2XCT	-8.54
35	Q35	2XCT	-7.74
36	Q36	2XCT	-8.47
37	Q37	2XCT	-8.58
38	Q38	2XCT	-9.41
39	Q39	2XCT	-9.49
40	Q40	2XCT	-10.48
41	Q41	2XCT	-9.87

Table 6: Docking scores of all standard and derivatives with protein 6FTB.

SL.NO	LIGANDS	PROTEIN (PDB ID = 6FTB)	DOCKING SCORE
	STANDARD (Streptomycin)	6FTB	-5.19
1	Q1	6FTB	-7.15
2	Q2	6FTB	-7.37
3	Q3	6FTB	-7.75
4	Q4	6FTB	-7.24
5	Q5	6FTB	-6.66
6	Q6	6FTB	-7.40
7	Q7	6FTB	-7.57
8	Q8	6FTB	-7.24
9	Q9	6FTB	-7.66
10	Q10	6FTB	-7.13
11	Q11	6FTB	-5.73
12	Q12	6FTB	-6.64
13	Q13	6FTB	-7.42
14	Q14	6FTB	-6.60
15	Q15	6FTB	-7.67
16	Q16	6FTB	-6.86
17	Q17	6FTB	-7.57
18	Q18	6FTB	-8.24
19	Q19	6FTB	-7.59
20	Q20	6FTB	-7.71
21	Q21	6FTB	-7.11
22	Q22	6FTB	-7.01
23	Q23	6FTB	-7.19
24	Q24	6FTB	-6.62
25	Q25	6FTB	-7.64
26	Q26	6FTB	-7.31
27	Q27	6FTB	-7.52
28	Q28	6FTB	-7.46
29	Q29	6FTB	-6.99
30	Q30	6FTB	-6.71

31	Q31	6FTB	-7.32
32	Q32	6FTB	-7.86
33	Q33	6FTB	-7.40
34	Q34	6FTB	-6.38
35	Q35	6FTB	-7.96
36	Q36	6FTB	-8.65
37	Q37	6FTB	-7.66
38	Q38	6FTB	-8.43
39	Q39	6FTB	-8.02
40	Q40	6FTB	-7.77
41	Q41	6FTB	-8.23

Pharmacokinetic and toxicity evaluation

Absorption

Table 7: Predicted Caco_2 PERMEABILITY [>-5.15: excellent; otherwise: poor] & Human Intestinal Absorption (HIA) [0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor] from ADMETlab 3.0.

Compound code	Caco_2 PERMEABILITY	HIA
Ciprofloxacin (standard)	-5.863	0.002
Q1	-5.153	0.002
Q2	-5.231	0.0
Q3	-5.197	0.001
Q4	-5.309	0.006
Q5	-5.203	0.032
Q6	-5.31	0.006
Q7	-4.921	0.0
Q8	-5.326	0.01
Q9	-4.865	0.0
Q10	-5.301	0.01
Q11	-5.479	0.002
Q12	-4.973	0.001
Q13	-4.874	0.0
Q14	-4.986	0.0
Q15	-4.92	0.0
Q16	-4.914	0.0
Q17	-5.215	0.0
Q18	-5.075	0.0
Q19	-4.942	0.0
Q20	-4.824	0.0
Q21	-4.95	0.0
Q22	-4.862	0.0
Q23	-4.691	0.0
Q24	-4.969	0.0
Q25	-5.207	0.0
Q26	-5.22	0.0
Q27	-5.434	0.0
Q28	-5.544	0.0
Q29	-5.341	0.0
Q30	-5.335	0.0
Q31	-5.263	0.0
Q32	-4.978	0.0
Q33	-4.997	0.0
Q34	-4.867	0.0
Q35	-5.179	0.0
Q36	-5.118	0.0
Q37	-5.174	0.0
Q38	-5.33	0.0

Q39	-5.611	0.0
Q40	-5.522	0.0
Q41	-5.229	0.0

Most of the designed quinoxaline derivatives demonstrated excellent human intestinal absorption (HIA < 0.3), comparable to ciprofloxacin. However, Caco-2 permeability varied significantly among the compounds. Several derivatives such as Q7, Q9, Q13, and Q23 exhibited superior permeability compared to the standard drug, indicating improved membrane penetration potential. Despite some compounds showing poor Caco-2 permeability, their excellent HIA suggests possible involvement of active transport mechanisms. Overall, selected derivatives with both high permeability and absorption could be considered promising candidates for further development.

Distribution

Table 8: Predicted Plasma protein binding (PPB) [≤ 90%: excellent; otherwise: poor] & volume of distribution at steady state (VDss) [0.04-20: excellent; otherwise: poor] from ADMETlab 3.0.

COMPOUND CODE	PPB	VDss
Ciprofloxacin (standard)	25.515	0.262
Q1	92.113	0.114
Q2	91.229	0.131
Q3	94.378	-0.177
Q4	87.89	-0.053
Q5	93.325	0.139
Q6	94.69	0.014
Q7	97.281	-0.002
Q8	95.928	0.171
Q9	98.188	0.16
Q10	98.804	-0.317
Q11	91.158	-0.166
Q12	97.302	-0.128
Q13	98.273	0.053
Q14	98.681	-0.376
Q15	98.55	-0.119
Q16	98.256	-0.142
Q17	98.061	-0.127
Q18	98.462	-0.085
Q19	99.111	-0.314
Q20	98.292	-0.086
Q21	97.975	0.064
Q22	97.632	0.028
Q23	98.22	-0.048
Q24	98.173	-0.075
Q25	87.738	0.54
Q26	90.037	0.479
Q27	84.484	0.537
Q28	82.203	0.463
Q29	91.587	0.573
Q30	83.729	0.303
Q31	89.554	0.34
Q32	92.73	0.548
Q33	96.0	0.444
Q34	92.161	0.285
Q35	94.1	0.542
Q36	92.145	0.396
Q37	94.182	0.473
Q38	97.914	-0.298

Q39	98.139	-0.539
Q40	97.929	-0.221
Q41	98.375	-0.409

The distribution profile revealed that ciprofloxacin exhibits low plasma protein binding, ensuring a higher fraction of free drug in circulation. In contrast, most synthesized quinoxaline derivatives showed high plasma protein binding (>90%), indicating reduced free drug availability but potentially prolonged duration of action. A few compounds such as Q25, Q27, Q28, Q30, and Q31 demonstrated comparatively lower binding and may offer a better pharmacokinetic balance. All compounds displayed acceptable VDss values, suggesting adequate systemic distribution, although variations indicate differences in tissue penetration. Overall, selected derivatives with moderate PPB and favorable VDss may serve as promising candidates for further studies.

Metabolism

Table 9: Predicted CYP1A2 Inhibitor [Category 0: Non-substrate / Non-inhibitor; Category 1: substrate / inhibitor] & human liver microsomal (HLM) stability [value closer to 1 indicates a higher likelihood of instability. 0-0.3: poor; 0.3-0.7: medium; 0.7-1.0: excellent] from ADMETlab 3.0.

COMPOUND CODE	CYP1A2 Inhibitor	HML stability
Ciprofloxacin (standard)	0.0	0.008
1	0.992	0.074
2	0.998	0.035
3	1.0	0.308
4	1.0	0.191
5	0.997	0.163
6	1.0	0.009
7	1.0	0.044
8	1.0	0.082
9	1.0	0.048
10	1.0	0.206
11	1.0	0.045
12	1.0	0.038
13	0.875	0.046
14	0.967	0.214
15	0.987	0.339
16	1.0	0.312
17	0.999	0.324
18	1.0	0.658
19	0.972	0.741
20	0.998	0.445
21	0.996	0.766
22	0.976	0.538
23	0.999	0.588
24	0.974	0.266
25	0.999	0.712
26	0.998	0.839
27	0.999	0.387
28	0.964	0.879
29	1.0	0.912
30	0.929	0.623
31	0.998	0.434
32	0.344	0.25
33	0.377	0.594
34	0.005	0.29
35	0.178	0.259

36	0.236	0.119
37	0.204	0.431
38	0.522	0.013
39	0.016	0.169
40	0.859	0.081
41	0.982	0.001

The metabolism analysis revealed that ciprofloxacin acts as a non-inhibitor of CYP1A2 with poor metabolic stability. In contrast, most synthesized quinoxaline derivatives were predicted to be CYP1A2 inhibitors, indicating a potential risk for drug–drug interactions. However, several compounds demonstrated improved human liver microsomal stability compared to the standard, suggesting prolonged metabolic persistence. Compounds such as Q19, Q21, Q25, and Q29 showed excellent stability, whereas Q33 and Q37 exhibited a more favourable balance between lower CYP inhibition and moderate stability. Overall, while many derivatives offer improved metabolic stability, their CYP1A2 inhibition profile should be carefully considered during further optimization.

Excretion

Table 10: Predicted Plasma clearance (CL_{plasma}) [>15 ml/min/kg denotes high clearance, 5-15 ml/min/kg signifies moderate clearance, and <5 ml/min/kg indicates low clearance. 0-5: excellent; 5-15: medium; > 15: poor] & half-life ($T_{1/2}$) [$T_{1/2}$ < 1 hour; short half-life drugs: $T_{1/2}$ between 1-4 hours; intermediate short half-life drugs: $T_{1/2}$ between 4-8 hours; long half-life drugs: $T_{1/2}$ > 8 hours. >8: excellent; 1-8: medium; <1: poor] from ADMETlab 3.0.

COMPOUND CODE	Cl plasma	T (½)
Ciprofloxacin (standard)	3.313	1.563
1	7.186	0.889
2	5.643	0.698
3	5.46	0.884
4	8.582	0.845
5	7.858	0.503
6	7.925	0.964
7	6.021	0.657
8	7.754	0.46
9	6.005	0.762
10	5.812	0.64
11	6.006	1.024
12	6.183	0.647
13	3.449	0.735
14	2.958	0.785
15	4.264	0.607
16	4.008	0.841
17	5.434	0.903
18	4.227	0.776
19	3.609	0.907
20	3.88	0.862
21	5.393	0.69
22	4.633	1.196
23	3.878	0.84
24	4.274	0.979
25	3.67	0.675
26	3.837	0.685
27	5.006	0.853
28	4.713	0.926
29	5.426	0.52

30	4.255	0.819
31	4.072	0.703
32	3.114	1.031
33	5.341	0.628
34	3.88	1.201
35	3.074	0.888
36	3.748	0.858
37	3.292	0.909
38	3.096	0.591
39	4.24	0.54
40	4.145	0.444
41	3.719	0.552

The excretion analysis indicated that ciprofloxacin possesses low plasma clearance and a moderate half-life, supporting sustained drug presence in the body. Most of the synthesized quinoxaline derivatives exhibited low plasma clearance, suggesting prolonged retention similar to the standard drug. However, the majority of compounds showed short half-life values (<1 hour), indicating rapid elimination and reduced duration of action. Only a few compounds, such as Q11, Q22, Q32, and Q34, demonstrated moderate half-life comparable to ciprofloxacin. Overall, while clearance profiles were favorable, the short half-life of many derivatives may limit their therapeutic effectiveness and requires further optimization.

Toxicity

Table 11: Predicted human ether-a-go-go related gene(heRG blocker) [0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor], Drug-induced liver injury (DILI) [Category 0: DILI negative; Category 1: DILI positive. 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor], Ames test for mutagenicity [Category 0: Non-AMES Mutagenicity; Category 1: AMES Mutagenicity. 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor], Carcinogenicity [Category 1: carcinogens; Category 0: non-carcinogens 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor] Human hepatotoxicity [Category 0: non-hepatotoxic; Category 1: hepatotoxic. 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor] from ADMETlab 3.0.

COMPOUND CODE	heRG blocker	DILI	AMES Mutagenicity	Carcinogenicity	Human hepatotoxicity
Ciprofloxacin (standard)	0.466	0.996	0.761	0.191	0.983
Q1	0.183	0.782	0.923	0.95	0.616
Q2	0.203	0.971	0.973	0.931	0.636
Q3	0.145	0.927	0.941	0.912	0.591
Q4	0.107	0.534	0.894	0.898	0.559
Q5	0.238	0.775	0.902	0.947	0.57
Q6	0.408	0.568	0.732	0.617	0.538
Q7	0.284	0.878	0.874	0.942	0.662
Q8	0.159	0.812	0.945	0.984	0.485
Q9	0.389	0.888	0.727	0.928	0.546
Q10	0.171	0.651	0.895	0.9	0.588
Q11	0.175	0.658	0.894	0.864	0.782
Q12	0.302	0.871	0.859	0.938	0.617
Q13	0.15	0.927	0.966	0.941	0.83
Q14	0.105	0.942	0.939	0.91	0.774
Q15	0.175	0.658	0.894	0.864	0.782
Q16	0.135	0.974	0.932	0.91	0.538
Q17	0.122	0.945	0.911	0.909	0.523
Q18	0.135	0.997	0.977	0.877	0.628
Q19	0.094	0.991	0.931	0.851	0.583

Q20	0.135	0.975	0.87	0.909	0.58
Q21	0.177	0.981	0.919	0.906	0.529
Q22	0.144	0.974	0.916	0.928	0.496
Q23	0.161	0.954	0.92	0.902	0.576
Q24	0.14	0.968	0.851	0.907	0.494
Q25	0.571	0.989	0.905	0.719	0.943
Q26	0.534	0.994	0.85	0.714	0.937
Q27	0.498	0.986	0.895	0.724	0.928
Q28	0.543	0.994	0.898	0.77	0.926
Q29	0.456	0.997	0.951	0.891	0.914
Q30	0.54	0.993	0.827	0.714	0.927
Q31	0.524	0.999	0.974	0.658	0.953
Q32	0.564	0.977	0.9	0.886	0.878
Q33	0.495	0.989	0.945	0.962	0.855
Q34	0.58	0.978	0.805	0.886	0.875
Q35	0.609	0.967	0.894	0.889	0.902
Q36	0.563	0.998	0.971	0.858	0.919
Q37	0.577	0.982	0.835	0.885	0.893
Q38	0.103	1.0	0.968	0.979	0.97
Q39	0.067	1.0	0.944	0.948	0.945
Q40	0.145	1.0	0.96	0.974	0.959
Q41	0.308	0.996	0.962	0.862	0.92

The toxicity assessment revealed that while many quinoxaline derivatives exhibited low hERG inhibition, indicating reduced cardiotoxic risk compared to ciprofloxacin, most compounds demonstrated high probabilities of drug-induced liver injury, mutagenicity, and carcinogenicity. Additionally, moderate to high hepatotoxicity was observed across the dataset. These findings suggest that despite favorable cardiac safety, the overall toxicity profile of the majority of compounds is concerning. A few derivatives such as Q4, Q8, Q22, and Q24 showed relatively improved safety profiles; however, further structural optimization is necessary to reduce toxicity and enhance drug-likeness.

CONCLUSION

The present study successfully demonstrates the potential of Schiff's base derivatives of quinoxaline-2,3-dione as promising antibacterial agents through an integrated in silico approach. All designed compounds exhibited favorable drug-likeness properties in accordance with Lipinski's rule of five, indicating their suitability for oral drug development. Molecular docking studies against DNA gyrase (2XCT) and MRSA protein (6FTB) revealed that several derivatives showed stronger binding affinities than standard drugs, suggesting significant antibacterial potential.

ADMET analysis further supported the drug candidacy of selected compounds by demonstrating good absorption and acceptable pharmacokinetic profiles. However, variations in permeability, metabolic behavior, and especially toxicity parameters highlight the need for careful optimization. While many compounds showed low cardiotoxicity risk, concerns such as hepatotoxicity, mutagenicity, and carcinogenicity must be addressed in future studies.

Overall, this work underscores the importance of computer-aided drug design in accelerating the identification of novel drug candidates. The findings suggest that quinoxaline-based Schiff's bases can serve as valuable lead compounds for further structural modification, in vitro validation, and in vivo studies aimed at developing effective therapies against resistant bacterial strains such as MRSA.

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