INSILICO DESIGN AND DOCKING STUDIES OF NOVEL PYRAZOLINE-5-ONE DERIVATIVES OF 2-(1H-INDOL-3-YL)ACETOHYDRAZIDE

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ABSTRACT

Bacterial infections remain a leading cause of mortality worldwide, and the limited availability of effective antibiotics alongside the rapid rise of antimicrobial resistance presents a critical health challenge. Developing novel antimicrobial agents is therefore essential to overcome resistance and improve therapeutic outcomes. Pyrazolones have recently gained attention as potential inhibitors of the bacterial enzyme Mur B and modulators of pathogenic mechanisms. In this research, a succession of novel pyrazoline-5-one analogues of 2-(1H-indol-3-yl)acetohydrazide were designed using ACD / Chem Sketch 12.0, and their physicochemical and drug-likeness properties were assessed with Molinspiration software. Compounds meeting Lipinski's Rule of Five were further evaluated through molecular docking in Autodock vina and Biovia Discovery Studio. Results revealed that compounds 3d,3b,3f and 3h exhibited strong inhibitory potential against 2Q85(the crystal structure of E.coli Mur B bound to a Naphthyl Tetronic acid inhibitor)while compounds 3c, 3e, and 3a and 3f showed notable activity against 14α-demethylase. Docking studies also provided insights into their binding interactions with the target proteins. Overall, the findings highlight pyrazoline-5-one derivatives of 2-(1H-indol-3-yl) acetohydrazide as promising scaffolds for the development of novel antibacterial and antifungal agents with favourable drug-likeness and pharmacokinetic profiles.

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KEYWORDS

Pyrazolone, Indole, Antibacterial ,Antifungal, Docking, Autodock Vina, Biovia Discovery Studio

INTRODUCTION

The drug discovering and developing process is highly intricate, time-consuming, and costly. It often carries significant risks, including potential threats to patient safety. Scientists and physicians are responsible for identifying, designing, and developing treatments for diseases, injuries, and various health conditions. However, this journey typically spans 12 to 15 years and demands an investment of nearly $1 billion. Out of the millions of compounds screened, only a small fraction advance to late-stage clinical trials and eventually reach human testing.(1) Among the various classes of compounds studied in this context, heterocycles are of particular significance. They account for more than half of all known chemical structures and are frequently encountered in natural products, vitamins, biomolecules, and a wide variety of biologically active agents. These include compounds with antitumor, antibiotic, anti-inflammatory, antimalarial, anti-HIV, antimicrobial, antifungal, antiviral, antidiabetic, antidepressant, herbicidal, fungicidal, and insecticidal properties (2). Beyond their natural occurrence, heterocycles also serve as indispensable building blocks in synthetic drugs and agrochemicals.

Structurally, a heterocyclic compound is defined by the presence of at least two different types of atoms within its ring system, with nitrogen, oxygen, and sulphur being the most common heteroatoms. Their presence imparts unique chemical and biological properties, making heterocycles a cornerstone in medicinal and pharmaceutical chemistry.

Drug discovery is a multistage process that involves a series of crucial phases, including(3)

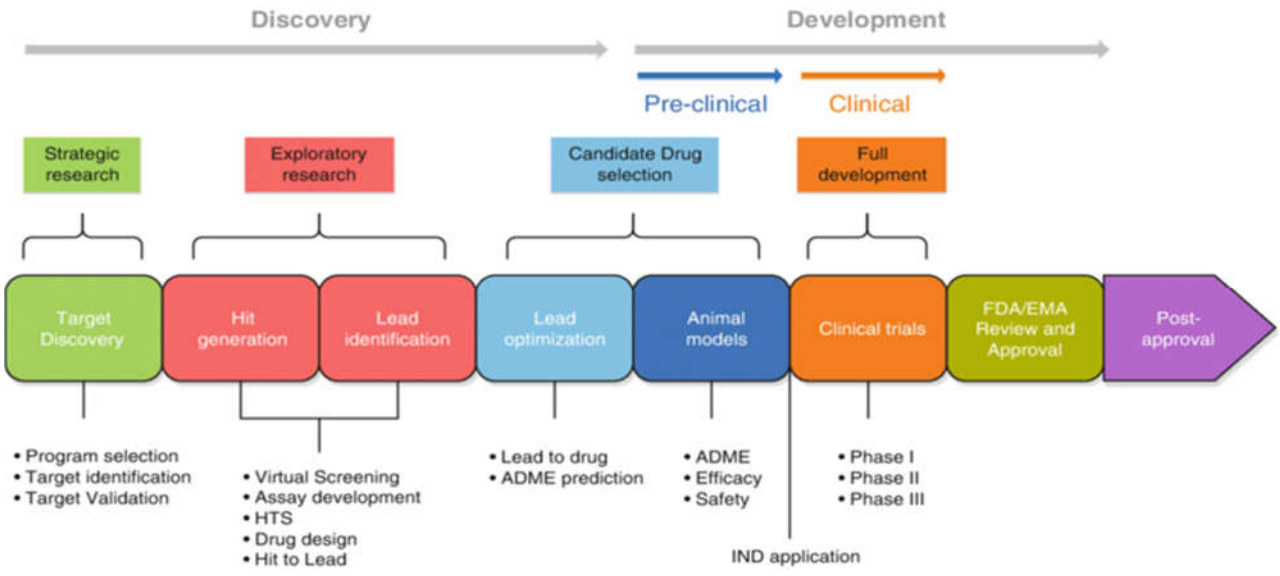
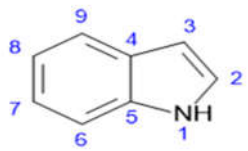


Figure 1 :Drug Discovery and development process(3)

Identification and confirmation of the target,lead identification and assembly development,optimization of leads, development of preclinical trials, Clinical development (phase I,phaseII,phase III), regulatory sanction, management of life cycle etc. Advances in in-silico techniques have provided pharmaceutical industries with remarkable opportunities to accelerate drug discovery by identifying novel therapeutic targets. These computational strategies not only influence the efficiency of target identification but also significantly reduce the time and cost associated with clinical trials(4) .Through bioinformatics tools, in-silico approaches enable the exploration of potential drug targets, structural analysis of binding sites, and the generation of candidate molecules. Such methods also facilitate the evaluation of drug-likeness, molecular docking studies to assess binding affinities, ranking of compounds, and subsequent optimization to enhance their pharmacological properties.

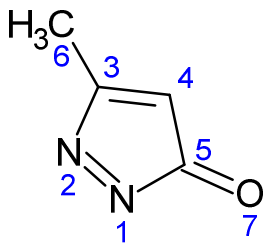
Indole is a benzo pyrrole compound having the molecular formula C8H7N.It is a white or slightly off white solid with the melting point of 52.50c. Indole is a white solid with pleasant smell at higher concentration. Indole is recognised as a multifunctional pharmacodynamic moiety and a highly valuable heterocyclic framework, displaying multiple pharmacological significance encompassing antibacterial,anticonvulsant,anti-inflammatory,anti-malarial,and anticancer activity(5).several clinically approved anticancer agents-including Sunitinib,Nintedanib,Vinblastine,and Vincristine incorporate the indole ring in structure(5) This makes the indole scaffold a critical pharmacophore and an essential structural component in designing novel therapeutic agents. Indole holds significant importance in medicinal chemistry, partly due to its natural presence in amino acid tryptophan and its role in forming the basis of many pharmacologically active molecules such as anti-inflammatory drug indomethacin and plant derived alkaloids like strychnine and LSD.so the inclusion of indole ring endows compounds with diverse biological properties(6).



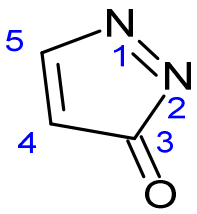
1*H* Indole

Pyrazolones ($C_3H_4N_2O$)are derivative of pyrazole nucleus, defined by the presence of two contiguous nitrogen atom within a five membered ring structure and an additional carbonyl moiety. They are commonly found as crystalline solids and shows wide range of chemical

reactivity, particularly in the synthesis of dyes and pigments The physical properties of pyrazolones can differs depends on the types of substituents in the ring structure and the dominant tautomeric form it adopts.3-pyrazolone and 5-pyrazolone are the most prominent categories in the pharmaceutical field due to its significant biological properties(7).Molecules featuring the pyrazolone nucleus have various pharmacological activities like muscle relaxant,anti convulsant and anti depressant ,analgesic, anti-inflammatory and antipyretic properties. In addition to these certain substituted pyrazolines possess antitumor, antibacterial, antifungal and antitubercular activities(8).Pyrazolones are appeared as white or off white crystalline solids.molecular weight of pyrazolones are 84.08 g/ml.They are soluble in ethanol and other polar solvents(9) and stable at room temperature at dry condition but sensitive to light and moisture over time.



5-pyrazolone



3-pyrazolone

In the present work, a series of novel 5-pyrazolin-5-one derivative of indol-3-acetohydrazide were designed and assessed as potential antimicrobial agents through in-silico analysis using Biovia Discovery Studio 2020.

MATERIALS AND METHODS

ACD/Chem Sketch

Chemical compounds, such as newly synthesized organic, organometallic, polymeric, Markush-structured, and peptide compounds, can be drawn using a free tool called Chem sketch. Other aspects consist of the capacity to identify structures with fewer than 50 atoms and three rings, compute parameters, inspect and clean 2D and 3D structures, and forecast log P (a lipophilicity metric). The following essential characteristics are present in ACD/Chem Sketch since they enable:

The structure mode makes it easier to calculate chemical properties and draw chemical structures.

Text and image processing methods are carried out in Draw Mode.

Molecular property computations are used to automatically estimate formula weight, density, polarizability, molar volume, molar refractivity, dielectric constant, and percentage composition all have additional use(10).

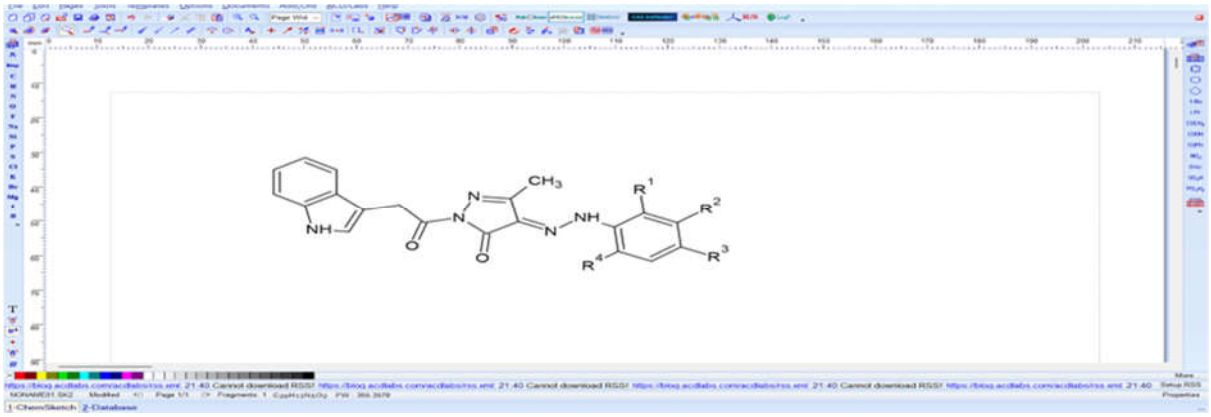


Figure 2 :Chem sketch window

Molinspiration

An independent research group called "Molinspiration" is dedicated to the advancement and utilization of contemporary cheminformatics methods, particularly as they relate to the internet. A broad variety of cheminformatics software applications that support molecules are available. Modification and processing, such as converting SMILES and SD files, normalizing molecules, creating tautomer, fragmenting molecules, calculating different molecular properties required for QSAR, drug design and molecular modelling, higher quality molecule representation, and molecular database tools that support pharmacophore similarity search and substructure search or similarity(11).

Lipinski Rule of Five

Lipinski rule of five provides a general protocol in evaluating the drug -likeness of chemical entities (11),indicating their potential to act as orally active medications. Lipinski's rule outlines the fundamental molecular features—namely absorption, distribution, metabolism, and excretion—that significantly influence the pharmacokinetic profile of a drug within the human body (11).

Drug development involves the stepwise modification of a bioactive lead molecule to achieve better efficacy, specificity, and desirable drug-like features, as suggested by Lipinski's rule(12).

The molecular alteration that drugs with additional rings, rotatable bonds, lipophilicity, and molecular weight are frequently the result of structure.

Poor absorption or penetration of medications taken orally tends to occur when

1) Exceeding five Hydrogen bond donors (represented by combined count of -OHs and -NHs), according to "Rule of 5"(11)

2) There are over 500 Daltons in the molecular weight.

3) The log P value exceeds 5.

4) Sum of the Ns with Os indicates the H-bond acceptors exceeded ten.

5) Substance groups that function as biological transporter substrates are exempt from

the regulation.

The regulations have led to numerous extensions in order to adequately assess drug similarity.

Log P (partition coefficient)within the span of -0.4 to +5.6 ,molecular mass lies from 160 to 500,molar refractivity values span from 40 to 130,number of atoms from 20 to70 includes both hydrogen bond donors and hydrogen bond acceptors,Polar surface area not exceeds 140 Å.

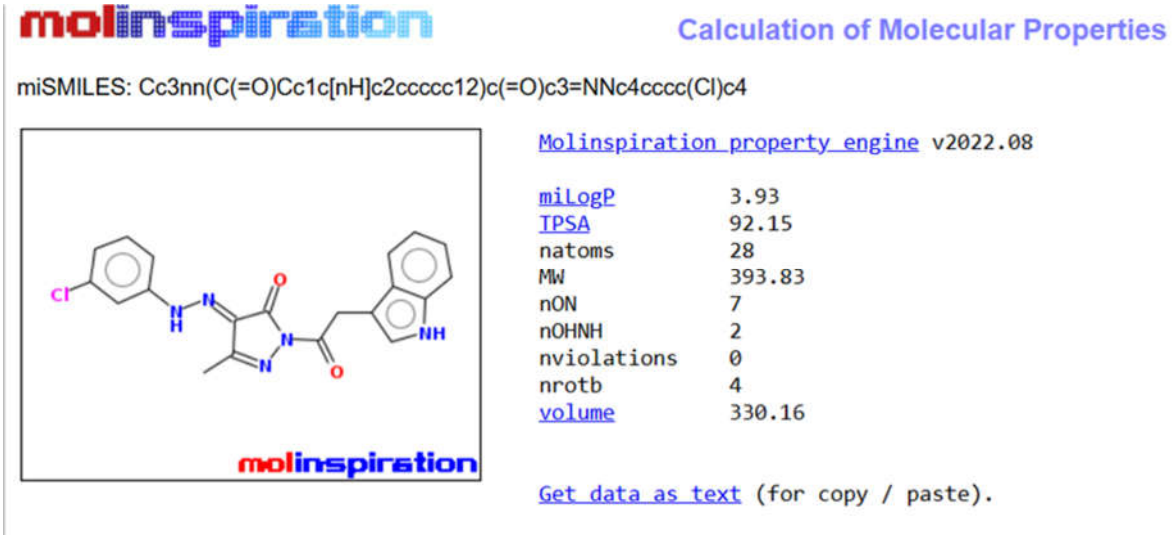


Figure 3: Molinspiration window

Molecular Docking Studies

Molecular docking ,a computational method designed to simulate and aticipate the formation of the receptor–ligand complexes. , The ligand may be a small organic molecule or a protein, whereas the receptor can be a protein or a nucleic acid (DNA or RNA).This method is applied to predict the structural composition of the resulting intermolecular complex, approximating the ligand's position within a predicted or predetermined binding site.The goal is to optimize the relative orientation and conformation of ligand and protein so as to reduce the free energy of the complete system. The ligand, a tiny molecule, typically interacts with the binding site of proteins(13).Binding sites are the areas of proteins which are active in complex formation with ligands. Binding can happen in a number of different mutual conformations. They are frequently referred as binding techniques. Additionally, it forecasts the complex's energy, the binding strength, the kinds of signals that are generated, and, by utilizing scoring algorithms, determines the binding affinity between two molecules. The search stage of molecular docking sets up a specific number of potential bindings between a given protein and ligand, and the scoring stage calculates its binding affinity of a given protein, ligand, posture, and conformation

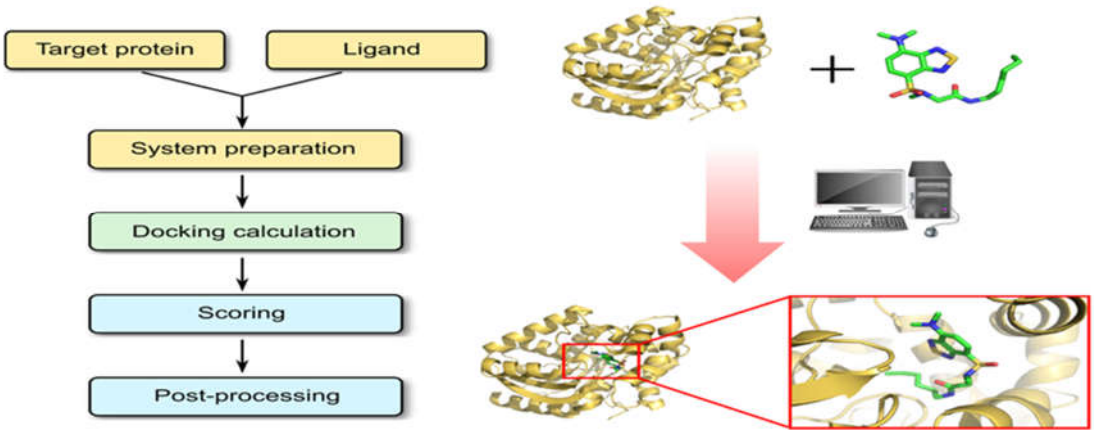


Figure 4 :molecular docking process

Docking Types

Two forms of docking are

1.Rigid docking

2.Flexible docking

Lock and key (Rigid docking) is one of the most often used docking methods.This type of docking is carried out when both internal geometry of receptor and ligand is maintained Constant.. Flexible docking (induced fit docking) is the next type.Here the rotations of one

molecule typically the smaller one are carried out. The energy and pocket occupancy are computed for each rotation, and the most optimal position is then chosen

Docking steps

Step I : Constructing Receptor ,Step II: Locating Active Site , Step III: Preparing the Ligand

Step IV: Docking .

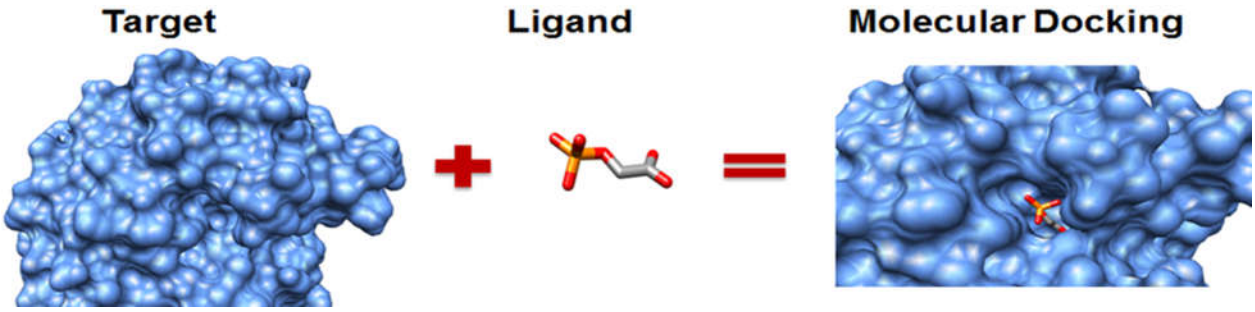


Figure 5 :ligand binding to the target site

Methodology of docking

Docking has been done with Autodock vina (rapid) and biovia discovery studio 2.0

1.Ligand preparation

Zinc database-substances-browse-download as. sdf format, Draw ligand using chemsketch-save in .mol format, Open structure in.mol format in Drug discovery studio-add hydrogens-save as protein data bank file (PDB).

Open Auto dock Tools

Ligand>input>open>select//Ligand>torsion tree>detect root//Ligand>tortion tree>choose tortions//Ligand >output>save as PDBQT

2.Protein Preparation

Download protein from PDB website in.pdb format-open in DS-delete water-ligand attributes-delete ligand-add hydrogen-change name and savein.pdb format

Auto dock tools-dashboard-all molecules-read molecules-select the pdb file

Edit>misc>check for missing atom >select all residues-dismiss

Edit>misc>repair missing atoms>save as 2 sets-dismiss

Edit-charges-add kollmann charges

Select grid-macromolecules-choose selected molecules-save as pdbqt(14)

Running Vina

Windows search-type cmd-change the prompt to directory C:> D:,D:cd directory

Command to run vina.exe-config.txt-log log.txt

Analysis of results

Open pymol,//File-open-working folder-ligand_out.pdbq,t//File-open-working folder-receptor.pdb,//Open result in discovery studio 2021

.**Determination of quantitative structure activity relationship parameters**

The physicochemical properties like electronic (polarizability),steric feature(molar volume)and hydrophobicity (log p) were determined for the newly synthesised compounds using ACD Chem sketch 12.5.7

Electronic properties:

The distribution of electrons within a drug molecule significantly influences its pharmacological activity and overall disposition. Since a drug must traverse multiple biological membranes to reach its target site, its ionization state plays a crucial role. Typically, non-ionized polar and non-polar molecules cross membranes more readily compared to their ionized counterparts. Moreover, the electron density within the drug structure determines the types of interactions it can establish with the target at the site of action, thereby impacting its biological efficacy.

Steric factors:

The molecular dimensions—such as size, shape, and bulkiness—affect a drug's interaction with its receptor or binding site. Large substituents may hinder or block optimal binding, while in some cases, bulky groups may assist in orienting the molecule properly, leading to enhanced binding affinity and activity. Unlike electronic or hydrophobic parameters, steric properties are more complex to quantify.

Lipophilicity:

Lipophilicity is one of the most extensively studied physicochemical features of drug molecules. It is often assessed using the partition coefficient, which reflects the drug's ability to distribute between aqueous and organic phases. A higher partition coefficient generally

facilitates passive diffusion across biological membranes. However, extreme values—either too low or too high—make compounds unsuitable for controlled oral drug delivery systems. Drugs with low coefficients poorly penetrate membranes, while those with excessively high values also present formulation challenges (15)

For the newly designed derivatives, physicochemical descriptors such as electronic properties (polarizability), steric properties (molar volume), and lipophilicity (log P) were computed using ACD Lab ChemSketch (version 12.0).

RESULTS AND DISCUSSION

Using the program ACD Lab chemsketch 12.0 numerous novel pyrazoline-5-one derivatives of 2-(1H indol-3-yl)acetohydrazide were designed. Using molinspiration software, the fifteen created analogues were first examined against rule of five.From that 10 are selected for further synthesis.

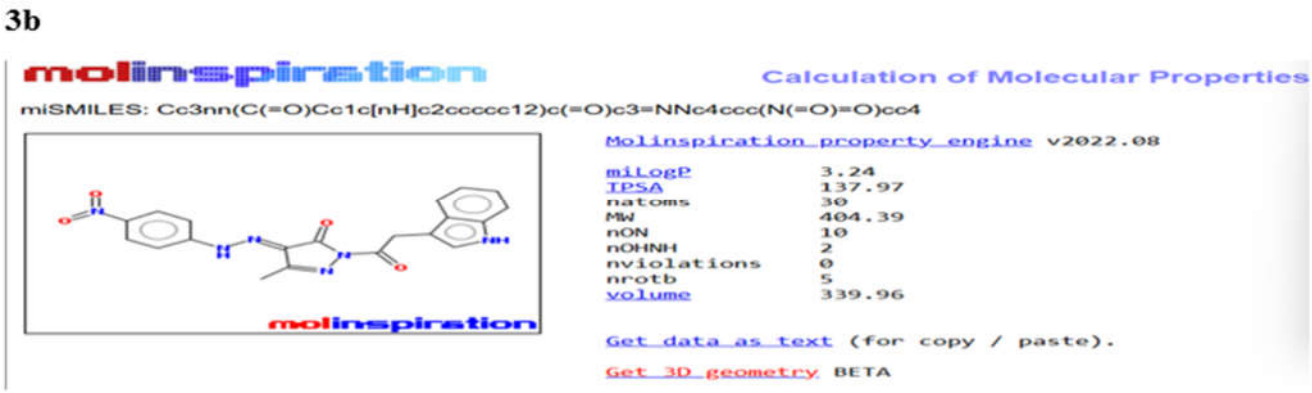
Compounds were chosen for more research based on the Lipinski rule analysis results because they adhere to the Lipinski rule study.

Molinspiration study

Figure 6 (3a-3j): Lipinski rule analysis of newly synthesised compound

3a

3b



3c

molinspiration Calculation of Molecular Properties

miSMILES: Cc3nn(C(=O)Cc1c[nH]c2ccccc12)c(=O)c3=NNc4ccccc4Cl

Molinspiration property engine v2022.08

miLogP	3.91
TPSA	92.15
natoms	28
MW	393.83
nON	7
nOHNH	2
nviolations	0
nrotb	4
volume	330.16

Get data as text (for copy / paste).

Get 3D geometry BETA

3d

molinspiration

miSMILES: Cc3nn(C(=O)Cc1c[nH]c2ccccc12)c(=O)c3=NNc4cccc(N(=O)=O)c4

Molinspiration property engine v2022.08

miLogP	3.21
TPSA	137.97
natoms	30
MW	404.39
nON	10
nOHNH	2
nviolations	0
nrotb	5
volume	339.96

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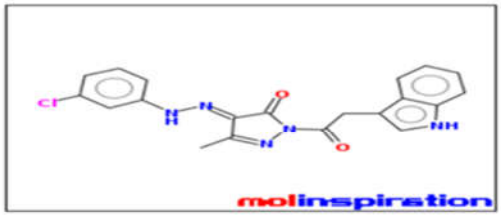
Get 3D geometry BETA

3e

molinspiration Calculation of Molecular Properties

miSMILES: Cc3nn(C(=O)Cc1c[nH]c2ccccc12)c(=O)c3=NNc4cccc(Cl)c4



Molinspiration property engine v2022.08

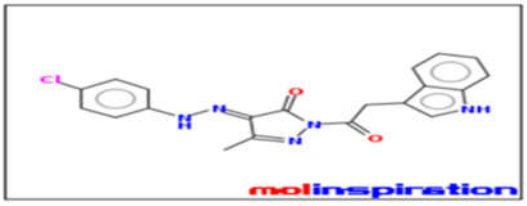
miLogP	3.93
TPSA	92.15
natoms	28
MW	393.83
nON	7
nOHNH	2
nviolations	0
nrotb	4
volume	330.16

Get data as text (for copy / paste).

3f

molinspiration Calculation of Molecular Properties

miSMILES: Cc3nn(C(=O)Cc1c[nH]c2ccccc12)c(=O)c3=NNc4ccc(Cl)cc4



Molinspiration property engine v2022.08

miLogP	3.96
TPSA	92.15
natoms	28
MW	393.83
nON	7
nOHNH	2
nviolations	0
nrotb	4
volume	330.16

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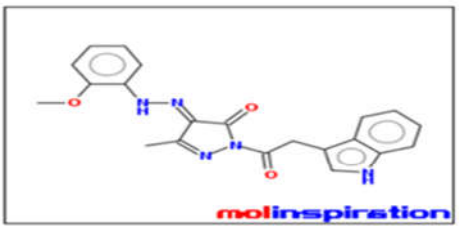
Get 3D geometry BETA

3g

molinspiration Calculation of Molecular Properties

miSMILES: COc1ccccc1NN=c4c(C)nn(C(=O)Cc2c[nH]c3ccccc23)c4=O



Molinspiration property engine v2022.08

miLogP	3.29
TPSA	101.38
natoms	29
MW	389.42
nON	8
nOHNH	2
nviolations	0
nrotb	5
volume	342.17

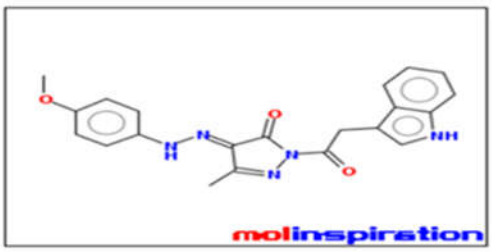
Get data as text (for copy / paste).

Get 3D geometry BETA

3h

molinspiration Calculation of Molecular Properties

miSMILES: COc4ccc(NN=c3c(C)nn(C(=O)Cc1c[nH]c2ccccc12)c3=O)cc4



Molinspiration property engine v2022.08

miLogP	3.34
TPSA	101.38
natoms	29
MW	389.42
nON	8
nOHNH	2
nviolations	0
nrotb	5
volume	342.17

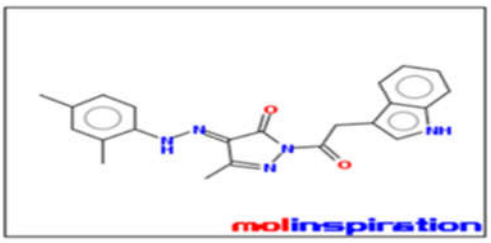
Get data as text (for copy / paste).

Get 3D geometry BETA

3i

molinspiration Calculation of Molecular Properties

miSMILES: Cc4ccc(NN=c3c(C)nn(C(=O)Cc1c[nH]c2ccccc12)c3=O)c(C)c4



Molinspiration property engine v2022.08

miLogP	4.10
TPSA	92.15
natoms	29
MW	387.44
nON	7
nOHNH	2
nviolations	0
nrotb	4
volume	349.75

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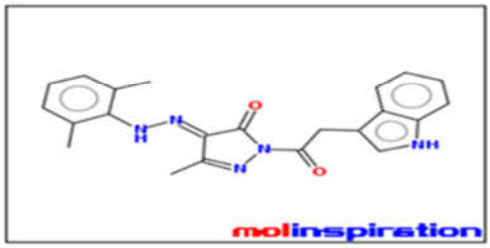
3j

molinspiration Calculation of Molecular Properties

miSMILES: Cc1cccc(C)c1NN=c4c(C)nn(C(=O)Cc2c[nH]c3ccccc23)c4=O



Molinspiration property engine v2022.08

miLogP	4.08
TPSA	92.15
natoms	29
MW	387.44
nON	7
nOHNH	2
nviolations	0
nrotb	4
volume	349.75

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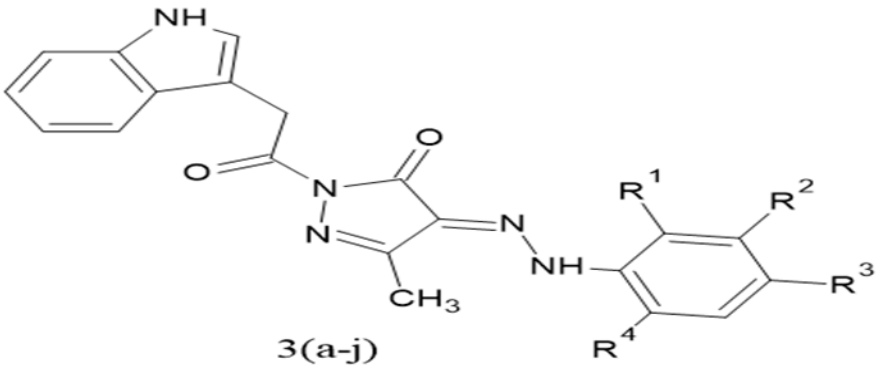

3(a-j)

Compound code	Log p	MW	nON	nOHN	nrotb	N Violation
3a	3.28	359.39	7	2	4	0
3b	3.24	404.39	10	2	5	0
3c	3.91	393.83	7	2	4	0
3d	3.21	404.39	10	2	5	0
3e	3.93	393.83	7	2	4	0
3f	3.96	393.83	7	2	4	0
3g	3.29	389.42	8	2	5	0
3h	3.34	389.42	8	2	5	0
3i	4.10	387.44	7	2	4	0
3j	4.08	387.44	7	2	4	0

Table :1 displays the findings of the Lipinski rule study.

Log P :Partition co-efficient

MW :Molecular Weight

nOHNH : Numbetr of hydrogen bond donors

nON :Number of hydrogen bond acceptors

Molecular docking studies

For anti-bacterial activity ,the crystal structure of E.coli Mur B bound to a Naphthyl Tetronic acid inhibitor (PDB ID :2Q85) were used. For the study of anti fungal activity ,human sterol 14a-deamylase(CYP51) in complex with the substrate lanosterol(PDB ID :6UEZ) was taken.Table :2 -The docking score of newly synthesised compounds

Sl No	Compound code	Binding energy	
		Mur B enzyme(2Q85)	14α -demethylase(6UEZ)
1	3a	-9.9	-10.3
2	3b	-10.5	-10.3
3	3c	-10.1	-10.9
4	3d	-10.8	-10.2
5	3e	-9.8	-10.4
6	3f	-10.5	-10.3
7	3g	-10.1	-7.5
8	3h	-10.3	-7.4
9	3i	-9.9	-6.5
10	3j	-9.8	-6.8
11	Gentamycin	-8.1	-
12	Fluconazole		-7.1

Based on the feasibility and the obtained docking score 10 compounds were selected for the further docking studies

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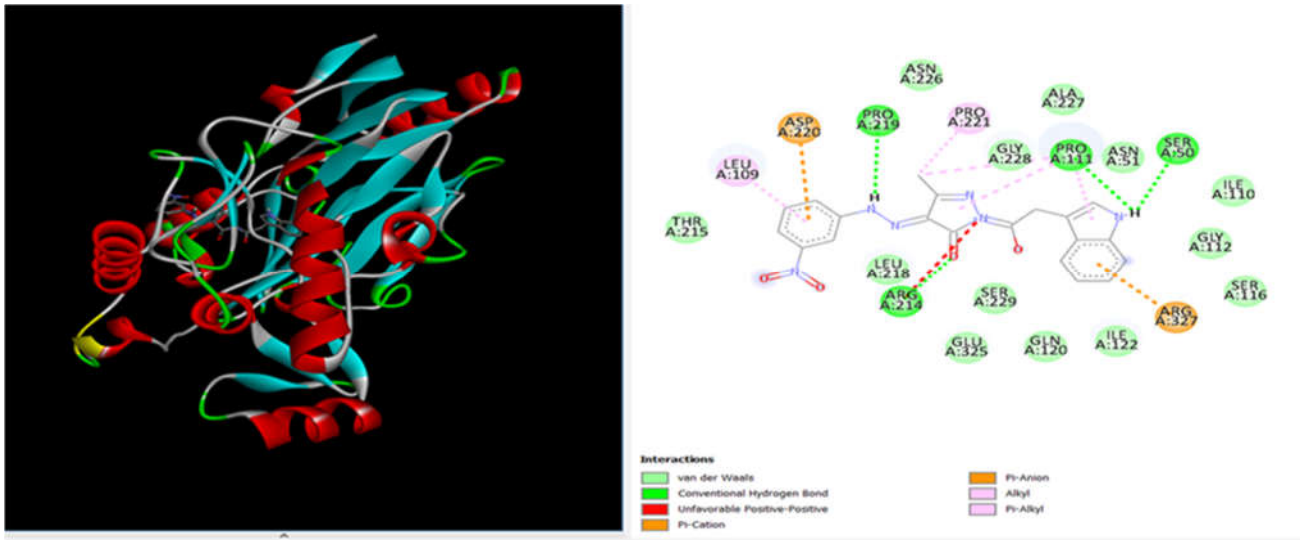

Figure 7 : :Docked 3D and 2D diagram of compound 3d with target protein 2Q85

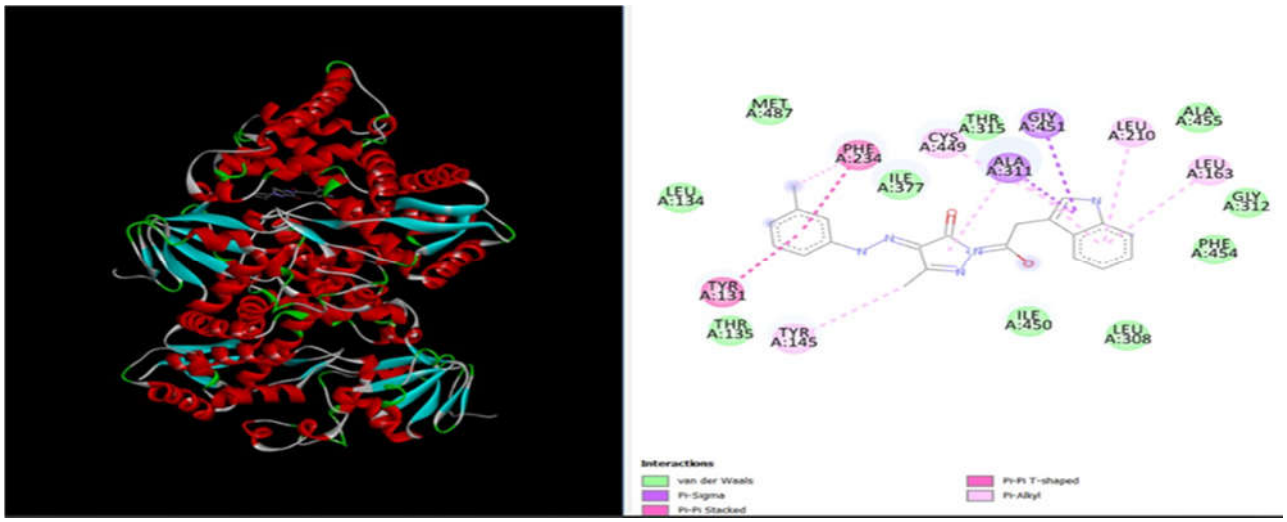

Figure 8 : Docked 3D and 2D images of compound 3e with the target protein 6UEZ

Determination of Physicochemical properties

The anti bacterial activity of compound 3d ,(m-nitrophenyl hyrazono derivative) is superior.The highest docking score for the antifungal activity was showed by the compound 3c,(ortho chlorophenyl hydrozono derivative of pyrazolone)..

Ten analogues selected were evaluated for their physicochemical properties,including solubility(expressed as log P),steric characteristics(molar volume),and electronic properties(polarizability),using ACD/Lab Chem Sketch 12.0 software.The result of 10 pyrazolone derivatives are shown in table 3.

Compound code	R1	R2	R3	R4	Molar volume	Polarisability	Log P
3a	H	H	H	H	190.67cm3/mol	39.097427A^3	3.28
3b	H	H	NO2	H	204.72cm3/mol	40.666553A^3	3.24
3c	H	Cl	H	H	198.82cm3/mol	40.984825A^3	3.91
3d	H	NO2	H	H	204.72cm3/mol	40.666553A^3	3.21
3e	Cl	H	H	H	198.82cm3/mol	40.984825A^3	3.93
3f	H	H	Cl	H	198.82cm3/mol	40.984825A^3	3.96
3g	OCH3	H	H	H	206.05cm3/mol	41.55514A^3	3.26
3h	H	H	OCH3	H	206.05cm3/mol	41.55514A^3	3.34
3i	CH3	H	CH3	H	210.62cm3/mol	42.775345A^3	4.10
3j	CH3	H	H	CH3	210.62cm3/mol	42.775345A^3	4.08

Table 3 : Physicochemical Properties of newly synthesised compound

CONCLUSION

In the present study, twenty novel pyrazoline-5-one derivatives of 2(1H-indol-3-yl)acetohydrazide were designed and evaluated through molecular docking against the antifungal target 14α-demethylase (PDB ID: 6UEZ) and the antibacterial target the crystal structure of E.coli Mur B bound to a Naphthyl Tetronic acid inhibitor (PDB ID :2Q85) . All compounds complied with Lipinski's rule of five, indicating favourable drug-likeness and potential suitability as orally active agents. Docking studies revealed that compounds 3d,3b, 3f and 3h exhibited strong binding affinities toward MurB, with docking scores of -10.8,-10.5,-10.5 and -10.3 respectively, which were comparable to the reference drug gentamicin. Similarly, compounds 3c, 3e, 3a and 3f demonstrated notable activity against 14α-demethylase, with docking scores of -10.9,-10.4,-10.3,-10.3 respectively, comparable to fluconazole. These findings suggest that pyrazoline-5-one derivatives of 2(1H-indol-3-yl)acetohydrazide represent promising scaffolds for the development of new antimicrobial agents with potential therapeutic benefits and reduced side effects.

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