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REVIEW ON DRUG DISCOVERY AND QSAR STUDY OF PYRAZOLE DERIVATIVES

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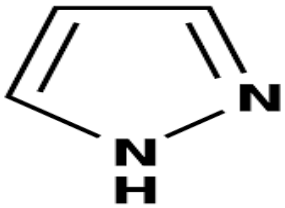
ABSTRACT :

This article reviews the role of pyrazole derivatives in modern drug discovery using QSAR, molecular docking, and ADME prediction. Pyrazole, a five-membered heterocycle, serves as a privileged scaffold for a range of therapeutics due to its broad pharmacological properties. The study highlights synthetic methodologies, physicochemical profiling, in silico modeling, and docking simulations to illustrate the potential of sulfinpyrazone in medicinal chemistry.

Key words:QSAR,pyrazole,docking studies

INTRODUCTION

Pyrazole is a five-membered heterocyclic moiety with two adjacent nitrogen atoms. Since its introduction by Ludwig Knorr in 1883, it has gained prominence due to its broad spectrum of pharmacological activities. Pyrazole derivatives are widely used in anti-inflammatory, analgesic, antitumor, antimicrobial, antiviral, and other therapeutic applications.



The systematic IUPAC name for pyrazole is 1,2-diazacyclopenta-2,4-diene. Other names include 1,2-diazole and 1H-pyrazole.

PHYSICOCHEMICAL PROPERTIES

CHEMICAL PROPERTIES OF PYRAZOLE

- *Basicity*: Weakly basic due to aromatic nitrogen atoms.
- *Aromaticity*: Aromatic 5-membered ring; stable and planar.
- *Reactivity*: Electron-rich; undergoes electrophilic substitution.
- *Acid Reaction*: Forms pyrazolium salts with strong acids.
- *Electrophilic Substitution*: Occurs mainly at C-5 position.
- *Halogenation*: Forms 3-halogenated derivatives with halogens.
- *Reduction*: Reduces to pyrazoline/pyrazolines using hydrogen catalysts.

PHYSICAL PROPERTIES OF PYRAZOLE

- *Appearance*: Colorless to pale yellow liquid or solid.
- *Boiling Point*: ~157°C
- *Melting Point*: ~70–72°C
- *Solubility*: Soluble in water, ethanol, ether, chloroform.
- *Density*: ~1.03 g/cm³
- *Odour*: Faint, characteristic smell.

DRUG AND DRUG DISCOVERY

Drugs are chemical substances used for diagnosis, treatment, or prevention of diseases. Drug discovery involves identifying new bioactive compounds through computational and experimental methods. The multi-step process includes target identification, validation, hit discovery, lead optimization, preclinical testing, and clinical trials.

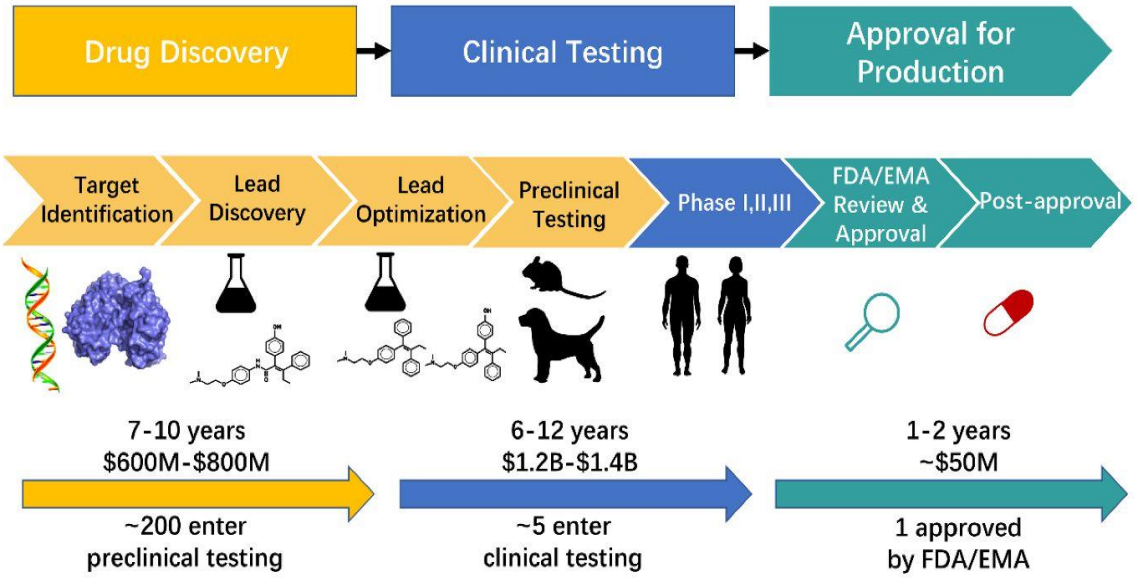


Figure 1; Drug discovery process

DRUG DISCOVERY OF PYRAZOLE DERIVATIVES

PYRAZOLE AS A PRIVILEGED SCAFFOLD

- Five-membered aromatic ring with two nitrogen atoms.
- Found in FDA-approved drugs for cancer, HIV, PH, and ED.
- Active against MRSA and VRE infections.

PYRAZOLE-CONTAINING ANTICANCER DRUGS

- *Crizotinib*: ALK/ROS1 inhibitor; used in NSCLC.
- *Lorlatinib*: Advanced/resistant NSCLC (ALK/ROS1).
- *Ruxolitinib*: JAK1/JAK2 inhibitor; treats myelofibrosis, polycythemia vera.
- *Pyrazofurin*: Inhibits nucleotide biosynthesis; explored for leukemia.

HIV TREATMENT

- *Celecoxib*: Selective COX-2 inhibitor (NSAID); anti-inflammatory and pain relief.
- *Crizotinib*: Kinase inhibitor with antiviral implications.

ERECTILE DYSFUNCTION & PULMONARY HYPERTENSION

- *Sildenafil*:
  - PDE5 inhibitor.
  - Treats ED and PH.
  - Brand names: Viagra (ED), Revatio (PH).
  - Origin: Originally developed for angina.

WITHDRAWN/OTHER USES

- *Rimonabant*:
  - Anti-obesity drug.
  - Withdrawn due to psychiatric side effects.
- *Lonafarnib*:
  - Farnesyltransferase inhibitor.
  - Treats progeria and cancers.

INNOVATIVE PYRAZOLE DERIVATIVES

1. Pyrazole Hybrids

- Combines pyrazole with other pharmacophores.
- Enhances therapeutic effect.
- Promising for antibacterial, anticancer, and antidiabetic treatments.

2. Synthesis & Evaluation

- Pyrazole derivatives show:
  - Antimicrobial
  - Antifungal
  - Antituberculosis
  - Anti-inflammatory activities

3. Advanced Synthesis Techniques

- Techniques include:
  - Microwave-assisted synthesis
  - Ultrasound
  - Mechanochemistry
- Benefits: Faster, greener, higher yield.

4. Amino-Pyrazoles

- Known for anticancer and anti-inflammatory effects.
- *Pirtobrutinib*: Recently approved amino-pyrazole drug.

DRUG DESIGN

Drug design is the innovative process of designing molecules with specific interactions with biological targets. It includes Ligand-Based Drug Design (QSAR, pharmacophore modeling) and Structure-Based Drug Design (SBDD), which utilizes protein structures to develop inhibitors or modulators.

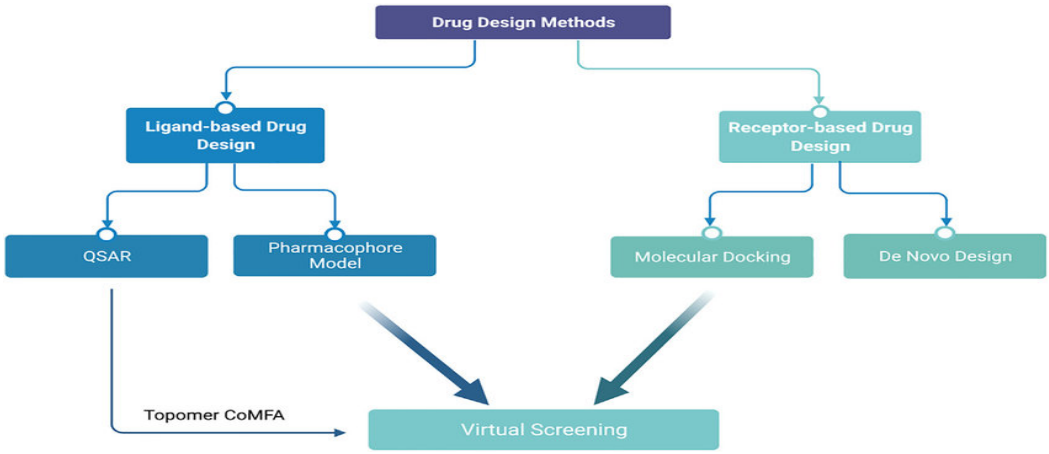


Figure 2; Types of drug design

PYRAZOLE: STRUCTURE AND IMPORTANCE

Pyrazole contains three carbon atoms and two nitrogen atoms in a five-membered aromatic ring. It exhibits tautomerism, aromaticity, and moderate basicity. It is the core structure in many clinically successful drugs like Celecoxib, Sildenafil, and Rimonabant.

SYNTHESIS OF PYRAZOLE DERIVATIVES

Various synthetic routes such as Knorr synthesis, Pechmann synthesis, and reactions of α,β-unsaturated aldehydes with hydrazine are employed to generate pyrazole compounds efficiently.

1. **KNORR PYRAZOLE SYNTHESIS**

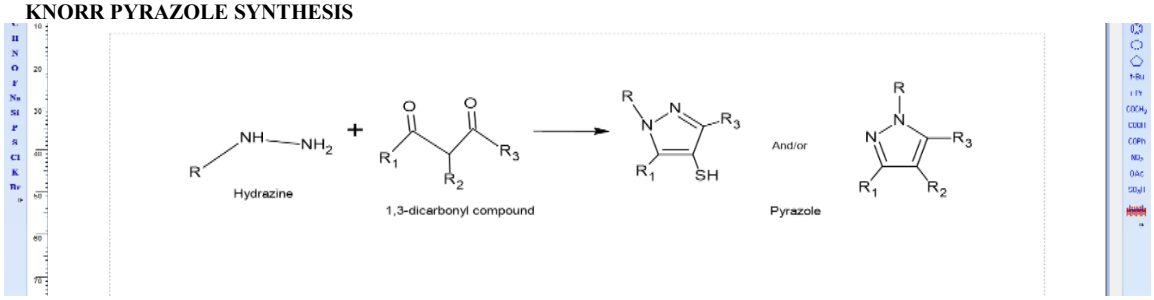


Figure 3; Knorr pyrazole synthesis by chemsketch

2. **PECHMANN PYRAZOLE SYNTHESIS**

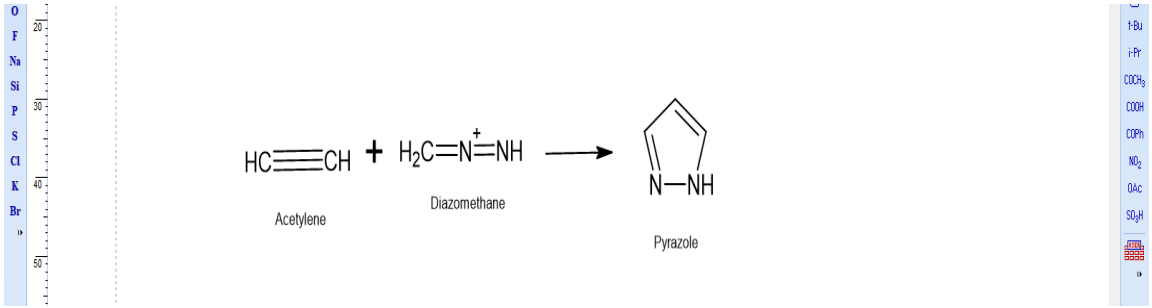


Figure 4; pechman synthesis of pyrazole by chemsketch

3. **FROM α,β UNSATURATE ALDEHYDE WITH HYDRAZINE**

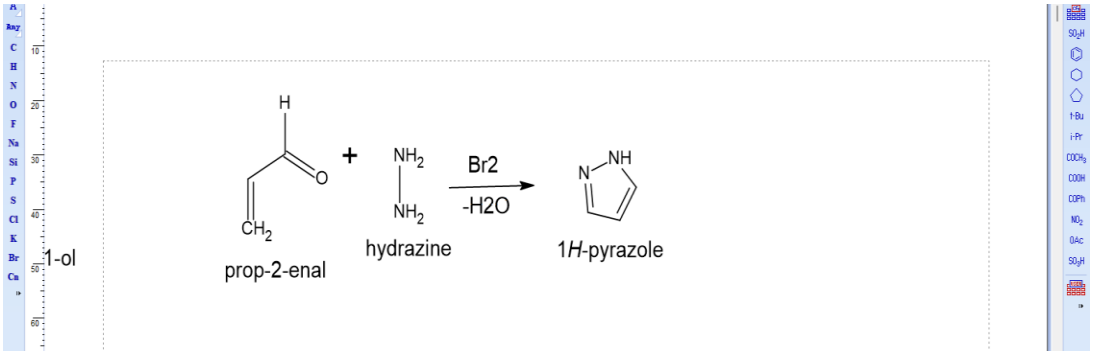


Figure 5; from α,β unsaturate aldehyde with hydrazine

QSAR STUDIES OF PYRAZOLE

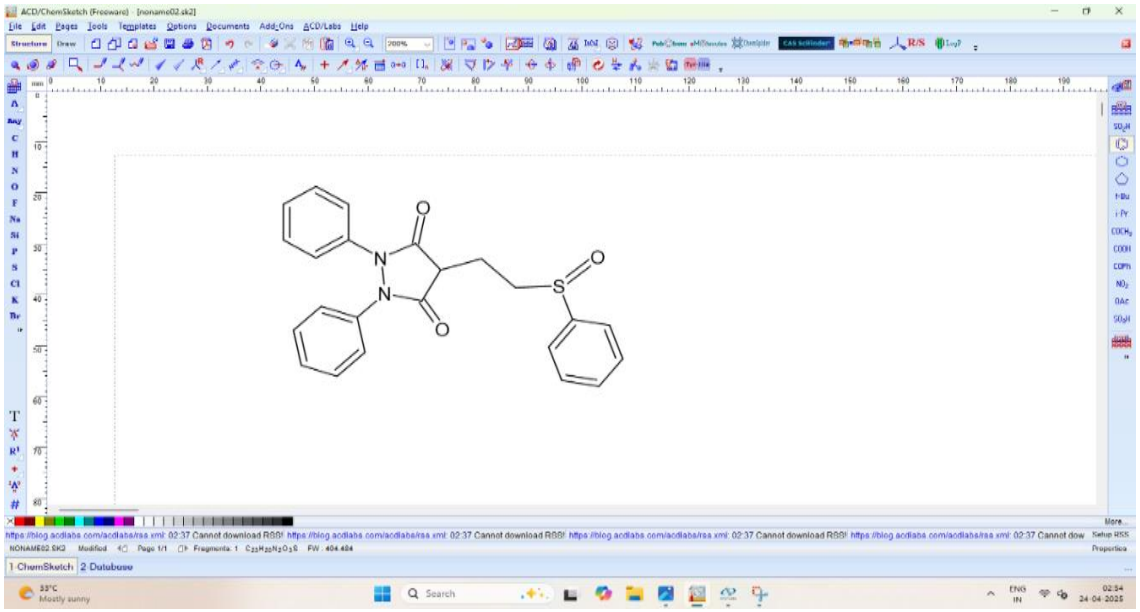
QSAR helps correlate the structural properties of pyrazole derivatives with biological activity. 3D-QSAR, CoMFA, and CoMSIA are advanced methods used to optimize anticancer and anti-inflammatory activity.

CHEMICAL MODELING TOOLS

ChemSketch, Molinspiration, and SwissADME were used to draw and analyze sulfinpyrazone. These tools predict logP, H-bond donors/acceptors, bioavailability, and drug-likeness.

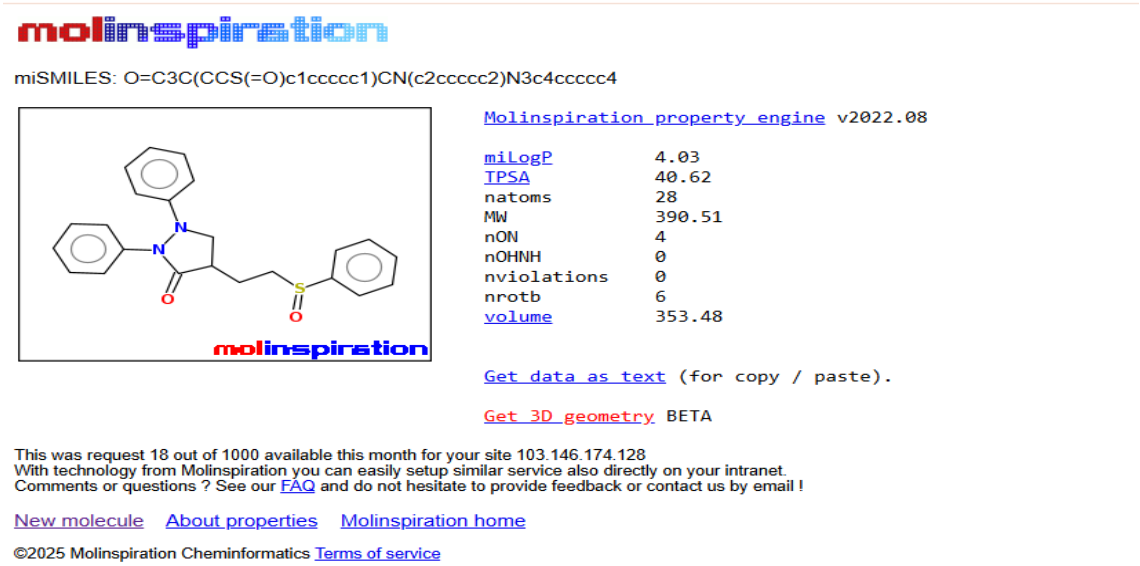
CHEMSKETCH

ACD/ChemSketch Freeware is a drawing package that allows you to draw chemical structure including organics, organometallics, polymers, and Markush structures. It also includes features such as calculation of molecular properties (e.g., molecular weight, density, molar refractivity etc.), 2D and 3D structure cleaning and viewing, functionality for naming structures (fewer than 50 atoms and 3 rings), and prediction of log P



MOLINSPIRATION

MolInspiration offers broad range of cheminformatics software tools supporting molecule manipulation and processing, including SMILES and SD file conversion, normalization of molecules, generation of tautomers, molecule fragmentation, calculation of various molecular properties needed in QSAR, molecular modelling and drug design, high quality molecule depiction, molecular database tools supporting substructure and similarity searches.



SWISS ADME

This website allows you to compute physicochemical descriptors as well as to predict ADME parameters, pharmacokinetic properties, druglike nature and medicinal chemistry friendliness of one or multiple small molecules to support drug discovery. SwissADME web tool that gives free access to a pool of fast yet robust predictive models for physicochemical properties, pharmacokinetics, drug-likeness and medicinal chemistry friendliness, among which in-house proficient methods such as the BOILED-Egg, iLOGP and Bioavailability Radar.

ADME PREDICTION BY USING SWISS ADME

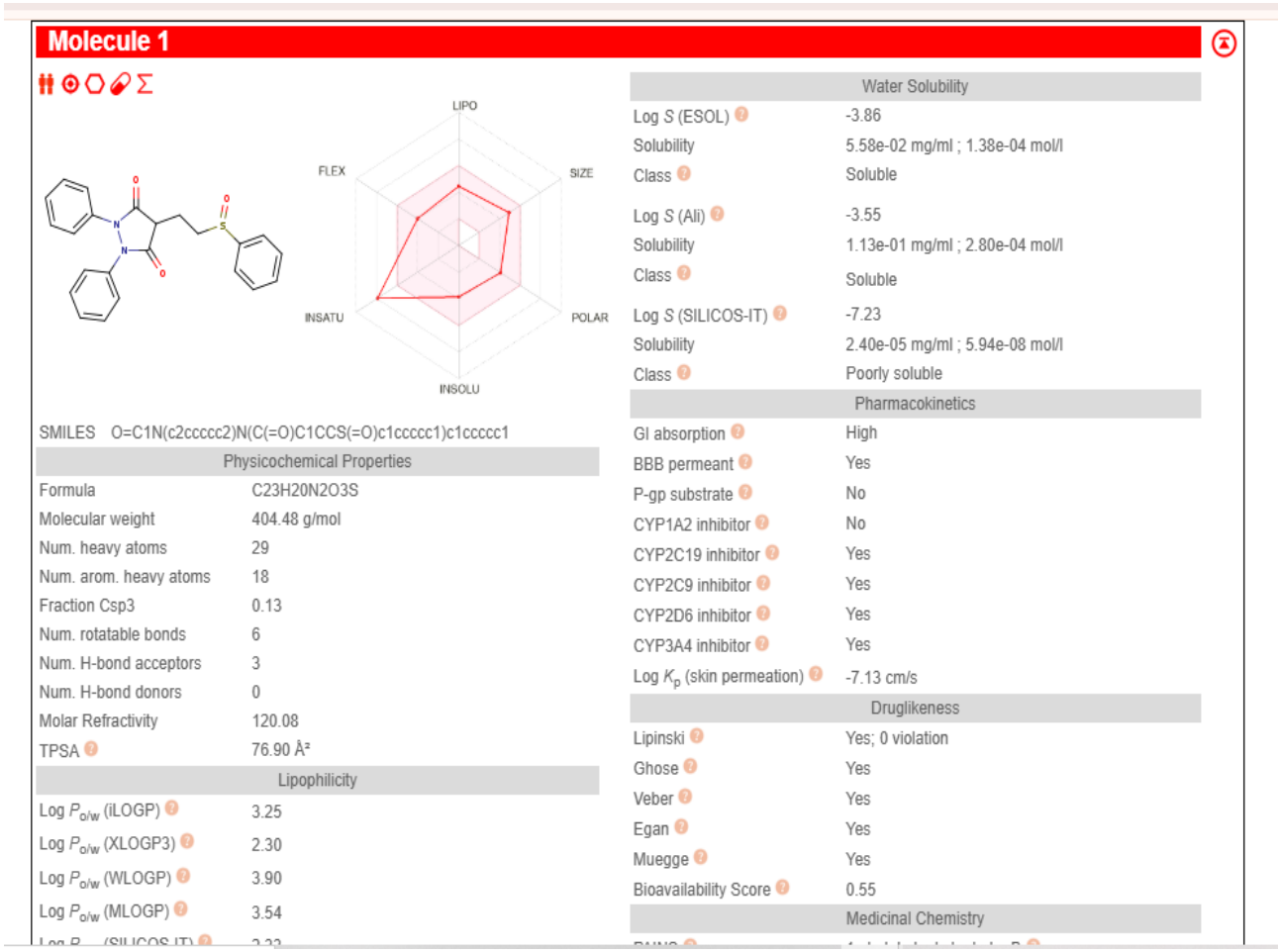


Figure 6; sulfinpyrazone by SWISS ADME

MOLECULAR DOCKING

sulfinpyrazone has long been recognised as a potent uricosuric agent, but has more recently been studied extensively as a platelet inhibitor and antithrombotic agent. Sulfinpyrazone, a pyrazole-based compound, has been investigated for its potential role in treating COVID-19. In preclinical studies, particularly in a Syrian hamster model, sulfinpyrazone demonstrated a 15.6% improvement in lung lesion amelioration when administered at 50 mg/kg twice daily over four days following SARS-CoV-2 infection. This suggests a modest therapeutic effect in reducing viral-induced lung damage.

Docking studies using MOE 2019 suite and molecular dynamics simulation stud is using the Desmond simulation package of Schrodinger LLC were carried out to examine and confirm the binding affinities and modes of the 40 selected FDA-approved NSAIDs against the viral main protease of SARS-CoV-2. The co-crystallized inhibitor (N3) was used as a reference standard.

The tested compounds were downloaded from (https://pubchem.ncbi.nlm.nih.gov/ last accessed on 1 April 2021) website. Their structures and the formal charges on atoms were checked by the 2D depiction, subjected to energy minimization, and the partial charges were automatically calculated.

Protein Data Bank was used to download the crystal structure of SARS-CoV-2 main protease (Mpro) (PDB code 6LU7, resolution: 2.16 Å). The downloaded protein was prepared as previously described. Briefly, it was protonated and hydrogen atoms were added with their standard 3D geometry. Automatic correction for any errors in the atom's connection and the type was also applied. Docking of the previously prepared database composed of our tested 40 NSAIDs and the co-crystallized inhibitor N3 was performed.

Docking studies showed sulfinpyrazone's strong binding with SARS-CoV-2 Mpro. It formed significant interactions and demonstrated potential antiviral activity. MOE and Desmond were used for simulation and docking, validating interactions using RMSD and energy scoring.

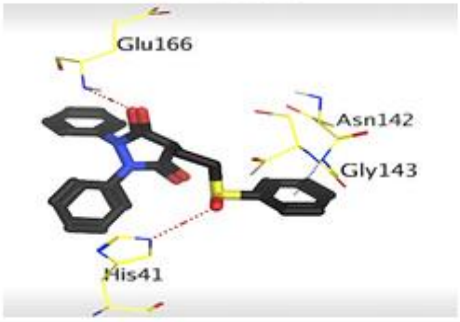
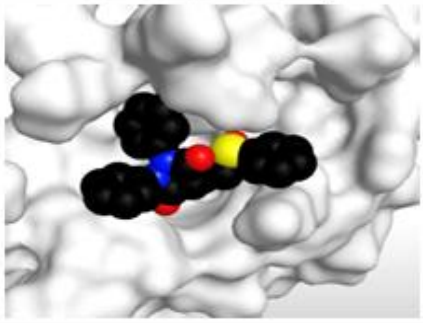
Drug	3 D Interaction	3 D Pocket Positioning
Sulfinpyrazone **2**		

Figure 7:3D Binding Interaction and Pocket Positioning of Sulfinpyrazone

DOCKING SOFTWARE

AutoDock, MOE, Schrodinger, and UCSF Dock were used to simulate binding between pyrazole compounds and protein targets. These tools evaluate orientation, conformation, and binding affinity.

SUMMARY

Pyrazole derivatives exhibit remarkable therapeutic potential due to their structural versatility. Integrated computational tools streamline their development, especially for anticancer and antiviral applications. Sulfinpyrazone is a promising candidate for further development.

CONCLUSION

The review establishes pyrazole as a privileged scaffold in drug discovery. QSAR, docking, and synthetic strategies converge to optimize drug-like molecules. Sulfinpyrazone, as highlighted, exemplifies this potential. Pyrazole stands as a cornerstone in drug discovery due to its versatile heterocyclic structure, enabling diverse therapeutic applications. Its derivatives, such as Celecoxib and Sildenafil, demonstrate significant efficacy in treating inflammation, cancer, infections, and cardiovascular disorders. The integration of *in silico* techniques—like molecular docking and QSAR—has streamlined the design and optimization of pyrazole-based drugs, reducing time and costs in early development. Despite challenges in drug attrition, pyrazole's adaptability and proven clinical success underscore its enduring relevance. Future research should focus on novel hybrid derivatives, improved ADMET profiles, and targeted delivery systems to expand its therapeutic potential. Ultimately, pyrazole continues to bridge innovation and practicality in medicinal chemistry, offering promising solutions for global health challenges.

FUTURE PROSPECTS

1. **Expansion of QSAR Models**: Development of more robust QSAR models incorporating machine learning to predict novel pyrazole derivatives with improved pharmacokinetic properties.
2. **Exploration of New Targets**: Investigation of pyrazole interactions with emerging biological targets (e.g., epigenetic regulators, immune checkpoints) for innovative therapies.
3. **Hybrid Molecule Synthesis**: Design of pyrazole hybrids combining with other pharmacophores to enhance multi-target activity, particularly in complex diseases like cancer and neurodegenerative disorders.
4. **Green Synthesis Methods**: Adoption of eco-friendly synthetic routes to produce pyrazole derivatives sustainably.
5. **Clinical Translation**: Prioritization of pyrazole-based compounds with favourable ADMET profiles for preclinical and clinical trials.

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