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Address for correspondence:
R.N Gaikwad
Department of chemistry shree V.R College, Sawana Dist.Yavtmal (MS)
Email:
rahulgaikwad955276@gmail.com

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In Silico Molecular Descriptor Assessment and Target Rationale for a Benzodioxole Trifluoromethyl Pyrazoline Derivative

R.N Gaikwad[1], R.N Ingole[2]
[1,2]Department of chemistry shree V.R College, Sawana Dist.Yavtmal (MS)

Abstract

The present study reports an in silico molecular descriptor assessment of 5-(1,3-benzodioxol-5-yl)-1-methyl-3-[2-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrazole, a nitrogen-containing pyrazoline derivative bearing benzodioxole and trifluoromethyl-substituted aryl groups. The molecular structure was represented using a chemically consistent molecular graph and evaluated using RDKit molecular descriptors. The molecular formula was determined as C18H15F3N2O2 with a molecular mass of 348.32 g mol−1. The calculated topological polar surface area (TPSA) was 34.06 Å², the Crippen estimated logP was 4.22, the hydrogen-bond acceptor count was 4, the hydrogen-bond donor count was 0, and the rotatable-bond count was 2. These values describe a relatively compact molecule with moderate calculated lipophilicity and a limited polar surface. JAK2 was considered as a biologically relevant target for future structure-based investigation because experimentally determined inhibitor-bound kinase structures are available, while JAK1 provides a logical comparator for any future selectivity study. No molecular docking, binding-affinity prediction, ADMET prediction, chemical synthesis, spectral measurement, or biological assay was performed as part of the present work. Accordingly, no docking score, pIC50, binding energy, ADMET value, or biological activity is reported. The study provides a reproducible molecular-property baseline and a clearly defined framework for subsequent experimental and computational validation.

Keywords: *pyrazoline; benzodioxole; trifluoromethyl; JAK2; JAK1; molecular descriptors; RDKit; computational chemistry*

Introduction

Pyrazolines, also known as 4,5-dihydro-1H-pyrazoles, are five-membered nitrogen-containing heterocycles that have received considerable attention in synthetic and medicinal chemistry. Their structural flexibility allows substitution at different positions and provides opportunities to tune molecular polarity, lipophilicity, conformation, and biological recognition. Pyrazoline derivatives have been investigated for antimicrobial, antifungal, anti-inflammatory, analgesic, anticonvulsant, antioxidant, anticancer, and other pharmacological properties. [1–5] Recent reviews have also emphasized continued development of pyrazoline synthesis and structure–activity relationships, including approaches based on chalcones and hydrazine derivatives. [6–8].The biological and physicochemical behavior of pyrazoline derivatives is influenced by the nature and position of substituents. Aromatic and heteroatom-containing groups can modify electronic distribution and molecular recognition, while fluorinated substituents may affect lipophilicity and binding interactions. [9,10] The benzodioxole moiety is an oxygen-containing aromatic unit encountered in bioactive small molecules, whereas a trifluoromethyl group is widely used in medicinal chemistry to modulate physicochemical properties. These considerations support preliminary computational evaluation of appropriately designed pyrazoline structures without assuming biological activity.Janus kinases (JAKs) are non-receptor tyrosine kinases involved in cytokine and growth-factor signaling. JAK2 contains a catalytic JH1 kinase domain that is an important target for small-molecule inhibitor development. Structural investigations have demonstrated that interactions within and around the ATP-binding region can influence potency and isoform selectivity. [11–13] Experimentally determined JAK2 structures therefore provide a rational basis for subsequent structure-based assessment. Recent work on JAK inhibitor selectivity further emphasizes the importance of distinguishing kinase inhibition from true isoform selectivity. [14,15].In the present work, 5-(1,3-benzodioxol-5-yl)-1-methyl-3-[2-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrazole was evaluated using a chemically consistent molecular representation and calculated molecular descriptors. The objective was to establish its basic physicochemical profile and provide a transparent rationale for future JAK2/JAK1 structure-based investigations. The study does not claim experimental synthesis, docking, binding affinity, ADMET performance, or biological activity; such conclusions require corresponding experimental or validated computational evidence.

Molecular Identity

Parameter	Value
Compound	5-(1,3-Benzodioxol-5-yl)-1-methyl-3-[2-(trifluoromethyl)phenyl]-4,5-dihydro-1H-pyrazole
Molecular formula	C18H15F3N2O2
Molecular mass	348.32 g mol−1
Canonical SMILES	CN1N=C(c2ccccc2C(F)(F)F)CC1c1ccc2c(c1)OCO2
Chemical class	1-Methylpyrazoline / 4,5-dihydro-1H-pyrazole derivative

Computational Methods

1 Molecular Structure Representation

The compound was represented by the canonical SMILES CN1N=C(c2ccccc2C(F)(F)F)CC1c1ccc2c(c1)OCO2. The molecular graph was checked for chemically consistent atom connectivity and valence. The resulting formula was C18H15F3N2O2.

2 Molecular Descriptor Calculation

Molecular descriptors were calculated with RDKit version 2025.09.4. The evaluated descriptors were molecular weight, topological polar surface area (TPSA), Crippen estimated logP, hydrogen-bond donor count, hydrogen-bond acceptor count, and rotatable-bond count. These descriptors were selected as a first-pass assessment of molecular size, polarity, hydrogen-bonding capacity, and calculated lipophilicity.

3 Target Rationale

JAK2 structure 8BX6 was selected as a candidate receptor for future docking because it is an experimentally determined X-ray structure of the JAK2 JH1 kinase domain in complex with cerdulatinib at 1.50 Å resolution. JAK1 structure 3EYH is a suitable comparative structural reference for a future JAK1/JAK2 analysis. These structures were used only to establish target rationale; no docking calculation was performed in the present study.

4 Proposed Future Docking Validation

A future docking study should use the co-crystallized ligand to define the ATP-binding region and should document receptor preparation, ligand preparation, protonation and charge assignment, treatment of crystallographic waters, grid center and dimensions, search parameters, number of poses, and software version. The crystallographic ligand should first be redocked to evaluate whether the protocol reproduces the experimental binding mode. The same validated protocol should then be applied to the test compound against JAK2 and JAK1. Docking scores should be treated only as computational ranking metrics and should not be presented as experimental IC50, Kd, or binding free-energy measurements. AutoDock Vina is one suitable documented docking engine for such a future study.

5 Proposed Future ADMET Assessment

A subsequent ADMET assessment may use documented tools such as SwissADME or pkCSM. The exact input structure, software or web-tool version, prediction endpoints, and output should be archived with the study. Such predictions should be described as computational estimates and should not substitute for experimental pharmacokinetic or toxicity data.

Results and Discussion

1 Calculated Molecular Descriptors

Descriptor	Calculated value	Interpretation
Molecular mass	348.32 g mol−1	Moderate molecular size
TPSA	34.06 Å²	Limited polar surface
Crippen estimated logP	4.22	Moderate-to-high calculated lipophilicity
H-bond acceptors	4	Potential acceptor sites are present
H-bond donors	0	No donor group is present
Rotatable bonds	2	Relatively compact framework

The calculated molecular mass of 348.32 g mol−1 places the molecule within a size range commonly encountered in small-molecule medicinal chemistry. The TPSA of 34.06 Å² reflects the contribution of the two benzodioxole oxygen atoms and two pyrazoline nitrogen atoms. The molecule contains no hydrogen-bond donor according to the descriptor calculation. The Crippen estimated logP of 4.22 indicates appreciable calculated lipophilicity; this descriptor may be relevant to membrane partitioning and protein hydrophobic interactions but can also be associated with solubility and nonspecific-binding considerations. The two rotatable bonds indicate a comparatively compact scaffold, although conformational sampling would still be relevant in a docking study.

2 Target Rationale for Future JAK2 Investigation

The selected molecule contains two pyrazoline nitrogen atoms, two benzodioxole oxygen atoms, two aromatic rings, and a trifluoromethyl substituent. These features provide a combination of potential hydrogen-bond acceptor sites and hydrophobic surface. Such characteristics provide a reasonable structural hypothesis for protein recognition, but they do not establish JAK2 binding or inhibition.The JAK2 structure 8BX6 was determined by X-ray diffraction at 1.50 Å resolution and contains cerdulatinib in the JH1 kinase domain. Structural work on clinical-stage JAK2 inhibitors has shown that interactions around the ATP-binding region can influence potency and selectivity.

Accordingly, 8BX6 is a rational receptor for a future docking experiment, provided that the protocol is independently validated.

3 JAK1 as a Comparative Target

JAK1 is an appropriate comparator because JAK-family ATP-binding regions share substantial structural similarity. Previous structural analysis of JAK1- and JAK2-specific inhibitors demonstrated that local interactions can contribute to specificity. Therefore, even if a future docking calculation produces a more favorable score for JAK2 than JAK1, such a difference would represent computational prioritization rather than proof of biochemical selectivity.

4 Theoretical Spectral Considerations

The proposed structure does not contain a carbonyl or nitrile group. Expected FT-IR features include aromatic and aliphatic C–H stretching, a pyrazoline C=N-related absorption, benzodioxole C–O–C vibrations, and C–F-associated fingerprint-region absorptions. Expected 1H NMR features include aromatic resonances, a benzodioxole OCH2O signal, an N-methyl signal, and pyrazoline CH/CH2 resonances. These are structural expectations only. No experimental spectral data are claimed in the present manuscript.

5 Explicit Scope of the Present Results

Only molecular descriptors were calculated in the present study. No docking score, docking pose, binding-energy estimate, JAK2 pIC50, JAK1/JAK2 selectivity ratio, ADMET numerical prediction, synthesis result, spectral measurement, or biological assay result is reported. This distinction is intentional and is necessary to keep the manuscript reproducible and consistent with the work actually performed.

Proposed Experimental and Computational Validation

The following activities are proposed as future validation and are not reported as completed experiments:

1. Synthesize the corresponding substituted chalcone from 2-(trifluoromethyl)acetophenone and 1,3-benzodioxole-5-carbaldehyde under a validated condensation procedure.
2. Cyclize the chalcone with methylhydrazine under controlled conditions to obtain the corresponding 1-methylpyrazoline derivative.
3. Purify and characterize the product using FT-IR, 1H NMR, 13C NMR, and mass spectrometry.
4. Validate a docking protocol by redocking the co-crystallized JAK2 ligand and reporting pose RMSD.
5. Dock the test compound to JAK2 and JAK1 using the same validated protocol and report scores and residue-level interactions.
6. Perform computational ADMET assessment using a documented platform and archive the complete outputs.
7. If biological activity is investigated, perform validated biochemical JAK2 and JAK1 assays with appropriate controls before making claims of potency or selectivity.

Limitations

The principal limitation is that the present work is restricted to molecular-descriptor calculations. It does not constitute a completed molecular-docking, ADMET, synthesis, or biological-activity study. The target discussion is therefore a rationale for future investigation rather than evidence of target engagement. In addition, descriptor values are method-dependent and may vary slightly with software implementation and molecular representation. The estimated logP is a model-derived value and should not be interpreted as an experimentally measured partition coefficient.

Conclusion

A chemically consistent benzodioxole–trifluoromethyl pyrazoline derivative was evaluated using reproducible molecular descriptors. The calculated molecular mass was 348.32 g mol−1, TPSA was 34.06 Å², Crippen estimated logP was 4.22, hydrogen-bond acceptor count was 4, hydrogen-bond donor count was 0, and rotatable-bond count was 2. The resulting profile indicates a relatively compact molecule with appreciable calculated lipophilicity and limited polar surface. JAK2 is a rational target for subsequent structure-based investigation because high-resolution inhibitor-bound structures are available, while JAK1 provides a useful comparator for any future selectivity analysis. However, the present study does not establish JAK2 binding, inhibition, selectivity, ADMET performance, or biological activity. Those claims should be made only after the corresponding calculations and experiments have been completed and independently validated.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of thesis paper.

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