

Structure Activity Relationship (Sar) Studies Of Riociguat: A Comprehensive Review

¹Navya Manavala, ² G.Bhargavi,³Dr.Dharmapuri Sasasvi,

⁴Dr. Chandrasekhara Rao Baru

¹Assistant Professor, ²Student, ³Assistant Professor, ⁴Principal

¹Pharmaceutical Analysis,

¹Chilkur Balaji College of Pharmacy in Hyderabad ,India

Abstract : Oral riociguat is a soluble guanylate cyclase (SGC) stimulator that targets the nitric oxide (NO)-SGC-cyclic guanosine monophosphate pathway with a dual mode of action: directly by stimulating SGC, and indirectly by increasing the sensitivity of SGC, to NO(1). It is rapidly absorbed, displays almost complete bioavailability (94.3%), and can be taken with or without food and as crushed or whole tablets. Riociguat exposure shows pronounced interindividual (60%) and low intraindividual (30%) variability in patients with pulmonary hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) and is therefore administered using an individual dose-adjustment scheme at treatment initiation. The half life of riociguat is approximately 12h in patients and approximately 7h in healthy individuals. Riociguat and its metabolites are excreted via both renal (33-45%) and biliary routes (48-59%) and dose adjustment should be performed with particular care in patients with moderate hepatic impairment or mild to severe renal impairment (no data exist for patients with severe hepatic impairment). The pharmacodynamic effects of riociguat reflect the action of a vasodilatory agent and the hemodynamic response to riociguat correlated with riociguat exposure in patients with PAH/CTEPH in phase 3 population. Pharmacokinetics/pharmacodynamic analyses. Riociguat has a low risk of clinically relevant drug interactions due to its clearance by multiple cytochrome p450 (cyp) enzymes and its lack of effect on major cyp isoforms and transporter proteins at therapeutic levels. Riociguat has been approved for the treatment of PAH and CTEPH that is inoperable or persistent/recurrent after surgical treatment. (Clinical pharmacokinetics and pharmacodynamic profile of riociguat)

Index Terms – Tablets, soluble guanylate cyclase, pulmonary hypertension, Pharmacokinetics.

INTRODUCTION:

Pulmonary arterial hypertension (PAH) is a progressive condition of multi factorial etiology. PH is associated with markedly decreased exercise capacity and reduced quality of life(2). Despite the availability of treatments, the natural history and prognosis are variable and patient's with PH may progress to right heart failure and death(2). Five groups have been defined for clinical classification that categories PH based on the underlying cause of elevated pulmonary pressures(2). PAH represents group 1 and includes the following subgroups: idiopathic, heritable, drug and toxin-induced, persistent PH of the newborn and associated PAH most recently, 2 additional subgroups have been added to group 1 to account for differences in treatment considerations -PAH long term responders to calcium channel blockers and PAH with overt features of venous involvement(2). PH due to pulmonary artery obstruction represents group 4 and includes chronic thromboembolic pulmonary hypertension (CTEPH)(2). This article reviews the epidemiology and pathophysiology of these 2 groups -PAH and CTEPH -as well as the pharmacology, pharmacokinetics, dosing and clinical efficacy and safety of riociguat; the utilisation of riociguat in treating patients with PH; and the role of the pharmacist in the appropriate and safe use of therapies for PAH and CTEPH (PUBMED central)(2)

CHEMICAL STRUCTURE

Chemical classification: soluble guanylate cyclase (SGC)

Molecular Formula : C₂₀H₁₉N₈O₂ . (3)

Molecular weight : 422.42 g/mol (3)

Core scaffold : pyrazole (3,4-b) pyridine(3)

Important functional groups

pyrazolopyridine nucleus

pyrimidine ring

fluorobenzyl substituent

carbamate functionality (3)(Riociguat _sar_ Documentation.docx)

CORE HETEROCYCLE OPTIMIZATION

Initial SAR efforts examined various heterocyclic core as SGC stimulators.(3). The pyrazole [4,3-d] pyrimidine scaffold was selected as optimal due to:(3)

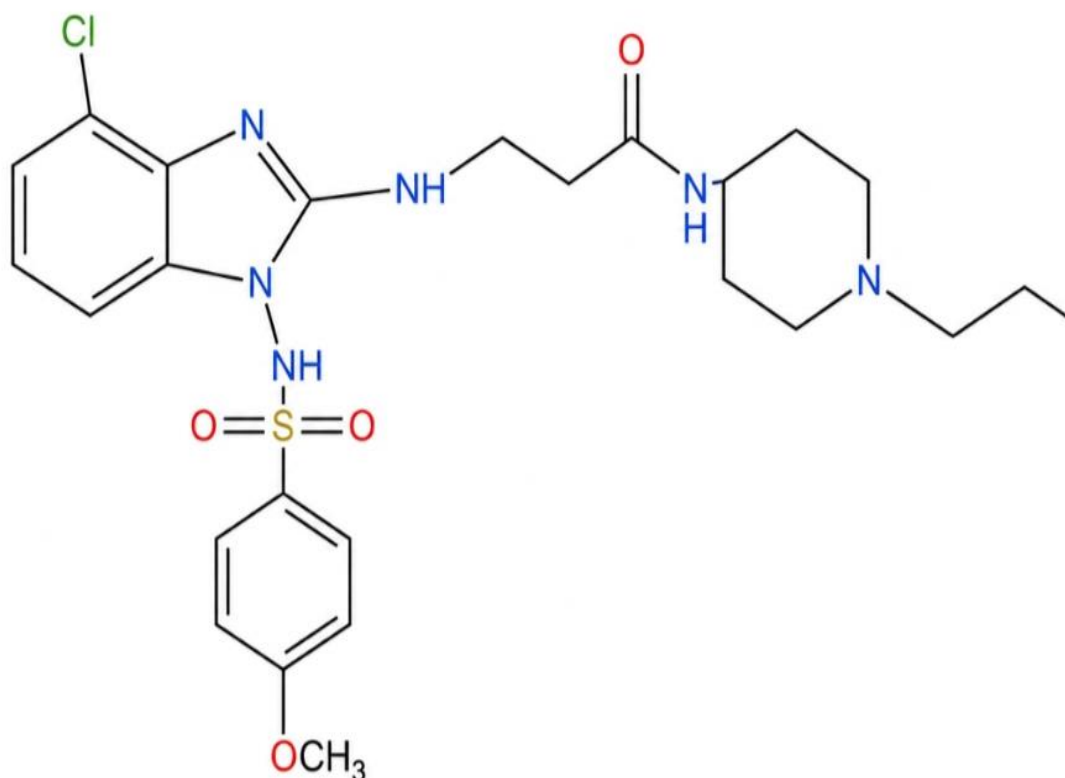
Superior binding affinity to the sGC enzyme (3)

Reduced off-target activities compared to alternative scaffolds(3)

Enhanced metabolic stability (3)

Favorable physicochemical properties for oral absorption(3)

Riociguat (soluble guanylate cyclase stimulator)



STRUCTURE ACTIVITY RELATIONSHIP (SAR) studies

POSITION 4 AND 6 SUBSTITUENTS (DIAMINOPYRIDINE CORE)

The diamine functionality at positions 4 and 6 of the pyrimidine ring is critical for sGC recognition binding SAR studies demonstrated(3)

Amino groups maintain essential hydrogen bonding interactions with sGC(3)

Replacement with other functional groups (Ketones, methylamines) significantly reduced potency(3)

N-methylation of these amines decreased activity, emphasizing the importance of free NH functionality (3)

POSITION 3 METHYL SUBSTITUTION

The methyl group at position 3 of the pyrazole ring contributes:(3)

Lipophilicity and cell membrane permeability(3)

Protein binding characteristics (3)

Metabolic stability through protection against enzymatic hydroxylation(3)

Sar studies showed that removal of this methyl group or replacement with larger alkyl groups reduced potency (3)

PHENYL RING SUBSTITUTION PATTERN

The phenyl ring directly attached to the pyrazole core underwent extensive sar analysis. key findings: chlorine substituents (3)

Chlorine atom presence was essential for potency (3)

Position dependent effects observed when chlorine was moved or replaced(3)

Removal of chlorine resulted in 10-50 fold loss of activity (3)

Fluorine substitution showed reduced potency compared to chlorine (3)

ETHOXY SIDE CHAIN

The ethoxy substituted phenyl ring has profound effects on the compound and its profile (3)

Ethoxy group optimization required balance between lipophilicity and aqueous solubility (3)

Methoxy analogs showed similar potency but different pharmacokinetics (3)

Propoxy or larger alkoxy chains resulted in reduced cellular permeability (3)

The ethoxy group serves as a key metabolic site, influencing drug exposure and clearance (3)

HYDROXYL GROUP FUNCTIONALITY

Hydroxyl groups incorporated into the structure demonstrated:(3)

Enhanced hydrogen bonding with the sGC enzyme active site(3)

Decreased lipophilicity improving solubility profiles (3)

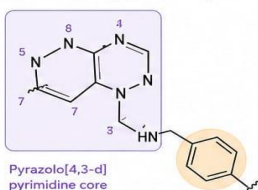
Position dependent effects on metabolic stability (3)
Acetylation or methylation of hydroxyl groups reduced potency (3)

3.6 SAR Summary: Structural Modification Effects

Structural Element	Modification	Effect on Activity
Core Scaffold	Pyrazolo[4,3-d]pyrimidine retained	Reference compound
Position 4,6 Amino	Replaced with C=O or CH ₃ N	Activity loss ($\times 2265/50$-fold)
Position 3 Methyl	Removed or extended to ethyl	Significant reduction in potency
Phenyl Chlorine	Removed or replaced with F/H	10-50 fold loss of activity
Ethoxy Side Chain	Extended to propoxy; reduced to methoxy	Optimal with ethoxy; propoxy too lipophilic
Hydroxyl Groups	Acetylation or methylation	Reduced stability potency; improved stability

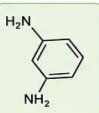
1. CORE STRUCTURE

Riociguat features a pyrazolo[4,3-d]pyrimidine core linked to a substituted phenyl ring and a diaminomethylphenyl moiety.



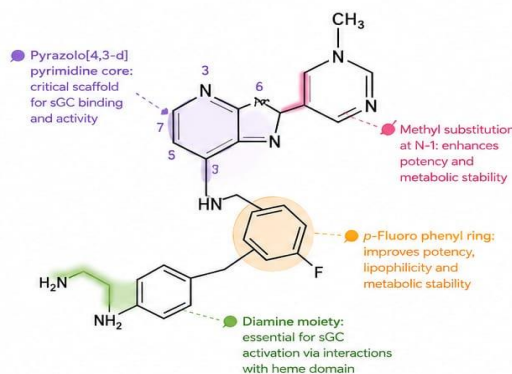
2. DIAMINE FUNCTIONALITY

The diaminomethyl group is essential for sGC activation through key interactions in the heme binding domain.



- Essential for activity
- Forms H-bonds with heme domain residues
- Optimized spacing critical for potency

RIOCIQUAT – STRUCTURE OVERVIEW



Riociguat
C₂₀H₁₉FN₅O₂ (structure shown above)
MW: 410.41 g/mol

3. METHYL SUBSTITUTION (N-1)

The methyl group at the N-1 position of the pyrazolo[4,3-d]pyrimidine ring enhances potency and metabolic stability.



- Increases binding affinity
- Reduces metabolic clearance
- Improves half-life

4. p-FLUORO PHENYL RING

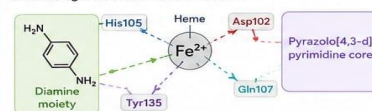
Para-fluoro substitution on the phenyl ring improves potency and pharmacokinetic properties.



- Enhances lipophilicity
- Improves metabolic stability
- Optimizes target interactions

5. KEY INTERACTIONS WITH sGC

Riociguat binds to the heme domain of sGC, stabilizing the active conformation.



6. STRUCTURE-ACTIVITY RELATIONSHIP HIGHLIGHTS

Structural Feature	Impact on Activity / PK
Pyrazolo[4,3-d]pyrimidine core	Essential for binding and sGC activation
Diamine functionality	Critical for activity via key H-bonding
N-1 Methyl substitution	Enhances potency and metabolic stability
p-Fluoro phenyl ring	Improves potency and PK properties
Overall molecular balance	Favorable PK: oral bioavailability, half-life ~7 h, effective clinical dosing

7. STRUCTURAL MODIFICATIONS UNDER EXPLORATION

- Bioisosteric replacement of heterocycles for improved PK
- Incorporation of polar groups to enhance aqueous solubility
- Conformational restriction strategies to improve selectivity
- Fluorine substitution patterns to modulate lipophilicity and metabolism

8. KEY TAKEAWAY

- ✓ Pyrazolo[4,3-d]pyrimidine core is the foundation for activity
- ✓ Diamine functionality is essential for sGC activation
- ✓ Selective enzyme inhibition achieved through optimized structure
- ✓ Favorable pharmacokinetic profile enables effective once- or twice-daily dosing

LEGEND: Core Scaffold

Diamine Functionality

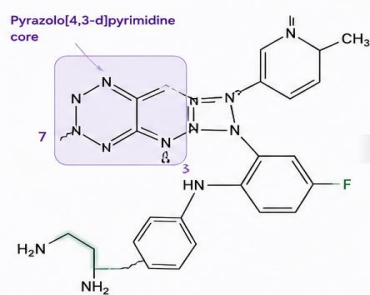
Methyl Substitution

Fluoro Phenyl Ring

Key Interactions

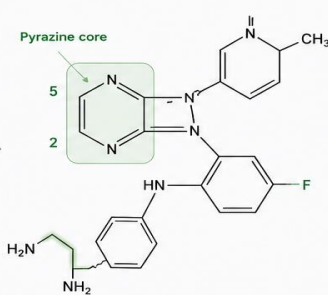
CORE REPLACEMENT WITH PYRAZINE: STRUCTURAL IMPACT

RIOCIQUAT (REFERENCE)



Molecular Formula: C₂₀H₁₉FN₅O₂
MW: 410.41 g/mol

CORE REPLACEMENT WITH PYRAZINE



Molecular Formula: C₁₉H₁₈FN₄O₂
MW: 395.39 g/mol

EFFECTS OF CORE REPLACEMENT WITH PYRAZINE



1. TARGET BINDING

- Loss of N₇ (pyrazolo nitrogen) may reduce key H-bonding interactions
- Altered vector for π - π stacking with heme domain
- Potential decrease in binding affinity



2. PHARMACOKINETICS

- Slightly reduced basicity (fewer ring N)
- May improve metabolic stability
- Potential changes in solubility and permeability



3. PHYSICOCHEMICAL PROPERTIES

- Lower polarity compared to pyrazolo[4,3-d]pyrimidine core
- Different dipole moment and tautomeric behavior



4. OVERALL IMPACT

- Activity likely reduced but can be compensated by side-chain optimization
- Useful scaffold for SAR exploration

IMPACT ON STRUCTURE-ACTIVITY RELATIONSHIP

What is Lost?

- ✗ N₇ available for H-bonding
- ✗ Additional aromatic character (fused bicyclic system)
- ✗ Rigid bicyclic geometry
- ✗ Optimal orientation of key groups

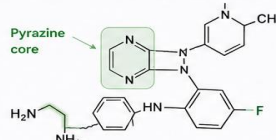
What Might Be Gained?

- ✓ Improved metabolic stability
- ✓ Lower molecular weight
- ✓ Different physicochemical profile
- ✓ Novel IP space for optimization

Design Implication

Side-chain modifications and substituent tuning are needed to recover binding affinity.

EXAMPLE PYRAZINE ANALOGUE (DESIGN CONCEPT)



Rationale:
Pyrazine core maintains overall scaffold topology while exploring new chemical space.

Original Core (Pyrazolo[4,3-d]pyrimidine)

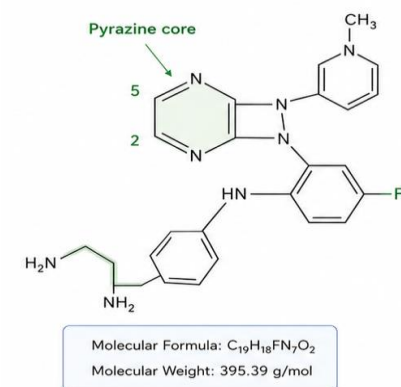
Pyrazine Core (Replacement)

H₂N Diamine Functionality

F p-Fluoro Phenyl Ring

Key Linkers

NEW DRUG STRUCTURE (PYRAZINE CORE ANALOGUE OF RIOCIQUAT)



PROPOSED STRUCTURE NAME

**N-(4-(2-Aminoethyl)phenyl)-5-(4-fluoro-3-
{{6-methylpyridin-2-yl}amino}phenyl)-2-(pyridin-
2-yl)pyrazine-2,3-diamine**
(Pyrazine-core Riociguat Analogue)

STRUCTURAL FEATURES

- ✓ Pyrazine core replaces pyrazolo[4,3-d]pyrimidine scaffold
- ✓ Retains key pharmacophoric elements: pyridine ring, *p*-fluorophenyl ring, and diamine functionality
- ✓ Maintains overall spatial topology for sGC activation
- ✓ Designed for improved metabolic stability and drug-like properties

KEY DESIGN OBJECTIVES



Maintain sGC stimulatory activity



Improve metabolic stability



Optimize solubility and PK properties



Reduce off-target effects



Explore new chemical space for lead optimization

Proposed Code Name: **PZ-201**

Note: This compound is a proposed research analogue and not approved for clinical use.

ADMINISTRATION



ROUTE OF ADMINISTRATION

- Oral (preferred)
- Intravenous (for hospital/acute settings)
- Other routes (e.g., sublingual) for future exploration



DOSAGE FORM

- Tablets (immediate or film-coated)
- Capsules
- Oral solution
- Injectable solution (IV)



DOSING FREQUENCY

Once or twice daily dosing expected (depending on pharmacokinetics and half-life)



DOSING CONSIDERATIONS

- To be taken with or without food
- Swallow tablets/capsules whole with water
- Follow physician's prescription



SPECIAL CONSIDERATIONS

- Dose adjustment may be required in hepatic or renal impairment
- Monitor blood pressure and clinical response
- Avoid strong CYP3A4 inducers or inhibitors unless prescribed

USES

- Improve metabolic stability
- Reduce molecular complexity
- Alter hydrogen bonding pattern
- Reduced SGC binding potency unless other substituents are optimised

6. Comparison with YC-1

Parameter	YC-1	Riociguat
Potency	Moderate	Very high
Selectivity	Lower	Higher
Oral bioavailability	Moderate	Excellent
Metabolic stability	Lower	Improved
Clinical use	Experimental	Approved drug

FUTURE PERSPECTIVE AND SAR Guided Development Next-Generation sGC stimulator

- Sar knowledge from riociguat guides development of improved agents:(3)
- Extended half life agent enabling once or twice daily dosing(3)
- Reduced off target activities through refined selectivity profiles(3)
- Enhanced metabolic stability (3)
- Improved solubility and bioavailability characteristics (3)

STRUCTURAL MODIFICATIONS UNDER EXPLANATION

- Active areas of sar- directed research:(3)
- Biostatistics replacement of heterocycles for improved pk(3)
- Strategic incorporation of polar functionality to enhance aqueous solubility (3)

Confinational restriction strategies to improve selectivity (3)
Fluorine substitution patterns to modulate lipophilicity and metabolism (3)

CONCLUSION

Structure Activity Relationship studies have been fundamental to understanding and optimising riociguat as a therapeutic sGC stimulator.(3) The systemic evaluation of chemical modifications across multiple structural domains has revealed (3)
The critical importance of the pyrazole [4,3-d] pyrimidine core scaffold (3)
Essential roles of the diamine functionality , methyl substitution and
Phenyl ring positioning(3)
Selective enzyme inhibition achieved through optimized structural features (3)
Favorable pharmacokinetics properties enabling effective clinical dosing(3)

The compound and its approval for treatment of
CTEPH treatment validates the sar driven optimization approach.(3) continued structure based design efforts promise next generation sGC stimulator with enhanced therapeutic potential and improved tolerability profile (3)

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