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

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***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 it's 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 reflects the action of a vasodilatory agents and the hemodyamic response to riociguat correlated with riociguat exposure in patients with PAH/CTEH 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 it's 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)

***IndexTerms*** **– Tablets,soluble guanylate cyclase,pulmonary hypertension,Pharmacokinetics.**

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## INTRODUCTION:

Pulmonary arterial hypertension (PAH) is a progressive condition of multi factorial etiology.PHi 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 subsyrups 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 episomiology 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

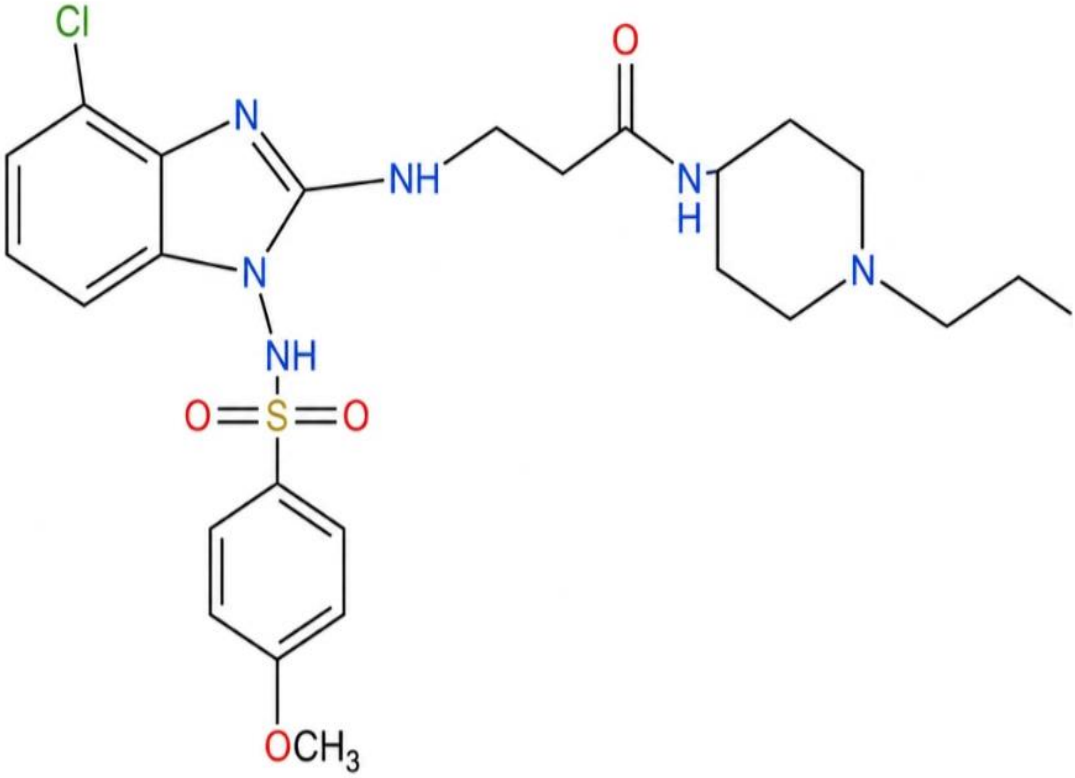
Chemical classification: soluble guanylate cyclase (SGC)
Molecular Formula :C20H19FN8O2 . (3)
Molecular weight :422.42 g/mol (3)
Core scaffold : pyrazole (3,4—b) pyridine(3)
Important functinal groups
pyrazolopyridine nucleus
pyrimidine ring
fluorobenzyl substituent
carbamate functionality (3)(Riociguat _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 odfff 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 substitutents (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 #x2019;s 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)

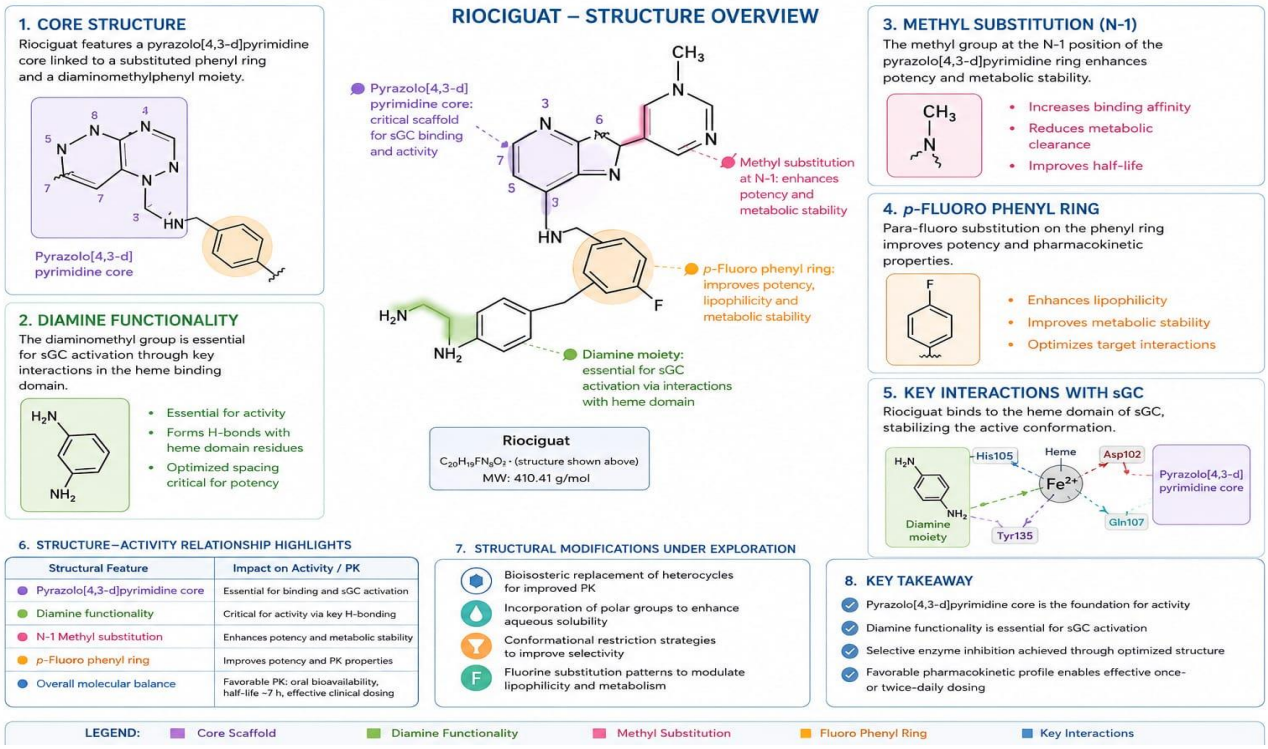
Enhanced hydrogen bonding with the sGC enzyme active site(3)

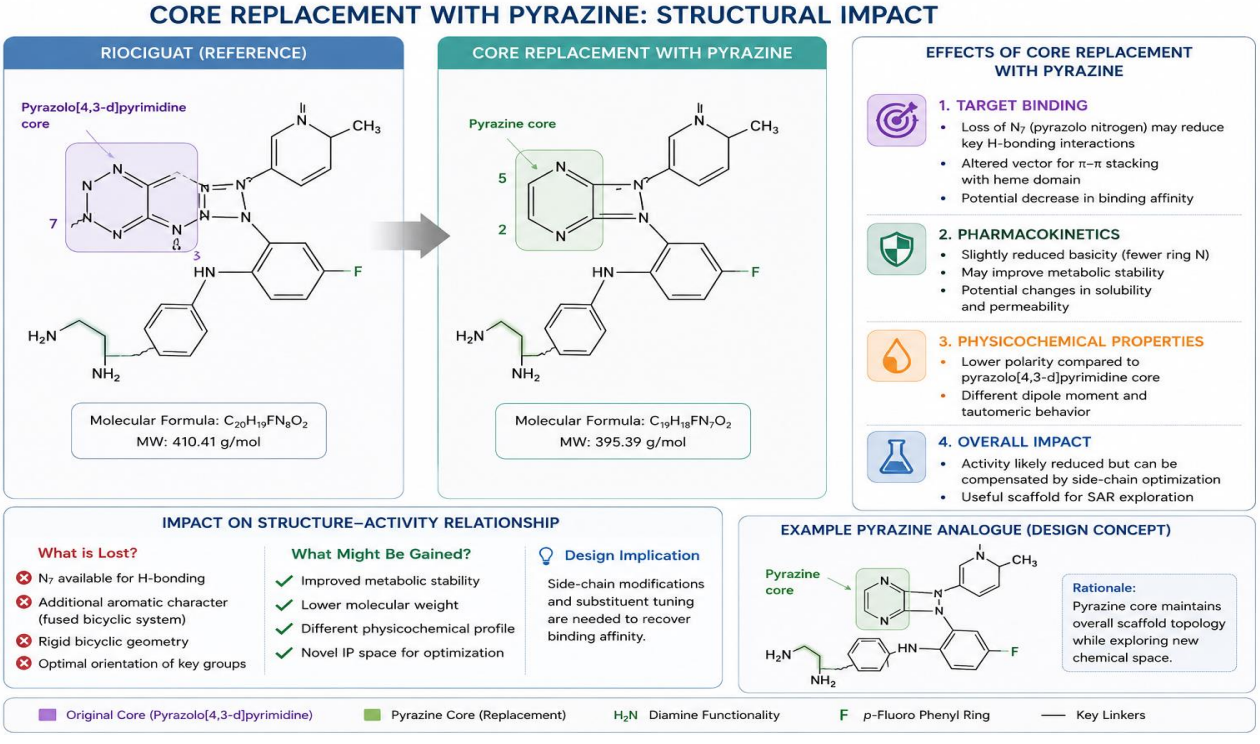
Decreased lipophilicity improving solubility profiles (3)

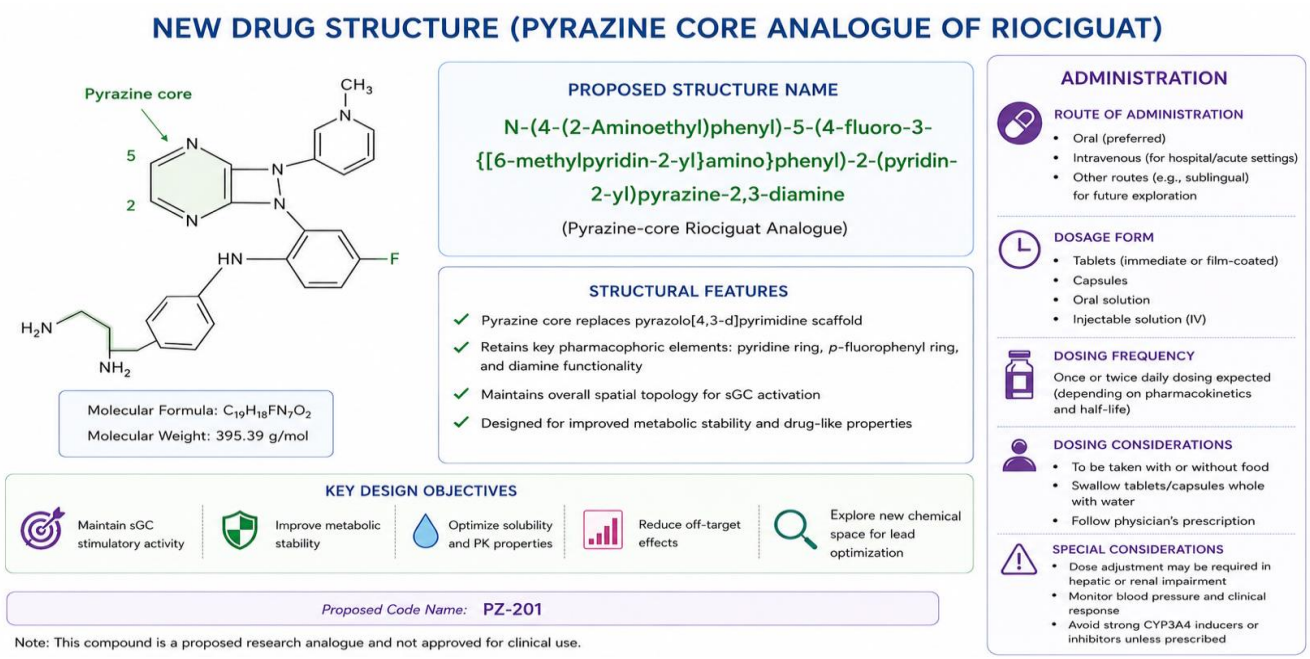
Position dependent effects on metabolic stability (3)
Acetylation or methylation of hydroxyl groups reduced potency (3)

### 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 $CH_5N$ | Activity loss (≥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 potency; improved stability |






USES
Improve metabolic stability
Reduce molecular complexity
Alter hydrogen bonding pattern
Reduced SGC binding potency unless other substitutents 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)

Confimatinal 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 #x2019;s 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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