International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

Heart Failure Treatment for New Drug - Vericiguat: An Overview

D.Nagavalli*[1], P.Nanthagopal[2]

[1*]*M.Pharm, Ph.D., Professor & H.O.D,Department of Pharmaceutical Chemistry, Adhiparasakthi College of Pharmacy,Melmaruvathur,Tamil Nadu,India.*

[2,]*Department of Pharmaceutical Chemistry, Adhiparasakthi College of Pharmacy,Melmaruvathur, Kancheepuram Distric, The Tamilnadu Dr.M.G.R Medical university Chennai-28,Melmaruvathur-603319,Tamil Nadu,India.*

Submitted: 15-05-2023 Accepted: 30-05-2023

ABSTRACT:

Despite recent advances in heart failure (HF) management, the risk of death and hospitalizations remains high in the long term. HF is characterized by endothelial dysfunction, inflammation and increased oxidative stress, due to a reduction in the activity of the **nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) s**ignaling pathway. All these factors contribute to direct damage at the myocardial, vascular and renal level. **Vericiguat restores** the deficiency in this signaling pathway, through stimulation and activation of sGC, aiming to increase cGMP levels, with a reduction in HF-related oxidative stress and endothelial dysfunction**. Vericiguat** is a drug that stimulates the cyclic guanosine monophosphate (cGMP) pathway through direct and indirect stimulation of soluble guanylate cyclase (sGC).The downstream effects of this stimulation pathway are smooth muscle cell relaxation, reduction in hypertrophy, inflammation and fibrosis. Vericiguat is a soluble guanylate cyclase stimulator used to reduce heart failure-related hospitalization and cardiovascular death in patients with chronic systolic heart failure.

Keywords: Heart Failure(HF), Vericiguat, soluble guanylate cyclase(SGC)

I. INTRODUCTION:

Heart failure (HF) is a major global heart pathology, affecting an average of 64.3 million people worldwide. Moreover, its prevalence is increasing due to aging of the general population and better outcomes after acute cardiovascular events. Although new therapies and management strategies have reduced mortality and morbidity, the prognosis for these patients remains poor. It is estimated that only 50% of patients survive after 5 years from their initial diagnosis. Moreover, repeated hospitalizations and the need for supplemental parenteral therapy during frequent exacerbations indicate an impaired quality of life and worse prognosis.The increase in hospitalization rate and mortality associated to the initial diagnosis of HF justifies the research of new therapeutic agents. Many treatment options are now available for the management of HF with reduced ejection fraction (HFrEF), based on large randomized controlled trials and accessible in the American Heart Association/ American College of Cardiology and the European Society of Cardiology guidelines. The milestones of drug treatment for HfrEF are angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers and mineralocorticoid receptor antagonists (MRAs) with a Class I recommendation. Furthermore, sacubitril /valsartan, an angiotensin receptor neprilysin inhibitor (ARNI), and the sodium-glucose cotransporter 2 inhibitors (SGLT2i) empagliflozin and dapagliflozin have been added to the list of disease modifying therapies.

OBJECTIVE:

Vericiguat is currently considered a second step of treatment in patients who remained symptomatic despite optimized medical therapy (OMT), to improve outcomes in HFrEF(Heart Faliure reduced ejection fraction)

Describe the indications of vericiguat as a novel agent for heart failure with a reduced ejection fraction.

Review the potential adverse effects associated with the use of vericiguat.

Explain the mechanism of action of vericiguat.

Outline the dose of administering vericiguat and explain the importance of monitoring vitals after administration of the drug by the interprofessional team to help titration and decide the dose.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

Fig: (vericiguat)Active substance structure

Physico -Chemical Properties of Vericiguat
Chemical Name:
Methyl[4,6-diamino-2-[5-fluoro-1-(2-fluorobenzyl)-1h-pyrazolo[3,4b]pyridine-3-yl]pyrimidin-5-yl}carbomate.

Physical State	Solid
Appearance	White to Yellowish powder
Molecular Formula	$C_{19}H_{16}F_2N_8O_2$
Molecular Weight	426.39 g/mol
Log P	2.99
pKa (Strongest Acidic)	11.84
pKa (Strongest Basic)	3.53
Hydrogen Acceptor Count	8
Hydrogen Donor Count	3
Polar Surface Area	146.86 Å2
Rotatable Bond Count	5
Refractivity	132.35 m3·mol-1
Polarizability	40.69 Å3
Number of Rings	4

Solubility: Freely soluble in Dimethyl Sulfoxide, Slightly soluble in Acetone, Very slightly soluble in ethanol, Acetonitrile, Methanol, Ethyl acetate, Practically insoluble in Isopropanol.

Storage: Stored at 20°C to 25°C(68°F to 77°F)

Mechanism of Drug Action (Vericiguat)
Vericiguat is a drug that **stimulates the cyclic guanosine monophosphate (cGMP)** pathway through direct and indirect **stimulation of soluble guanylate cyclase** (sGC). The downstream effects of this stimulation pathway are **smooth muscle cell relaxation, reduction in hypertrophy, inflammation and fibrosis.**
The nitric oxide (NO)-sGC-cGMP pathway begins with NO production by vascular endothelial cells**. NO** is synthesized from L-arginine by three nitric oxide synthases, among **which endothelial nitric oxide synthase (eNOS) plays a major role.** NO diffuses rapidly into vessel smooth muscle cells, binds to the heme subunit of sGC and catalyzes the conversion of guanosine triphosphate (GTP) into the second intracellular messenger, cGMP .

CGMP interacts with three types of intracellular proteins: **cGMP-dependent protein kinases,cGMP-regulated ion channels and phosphodiesterases (PDEs)** Subsequently, these transduction cascades mediate various physiological and tissue-protective effects, including smooth muscle relaxation**, inhibition of smooth muscle** proliferation, leukocyte recruitment and platelet function.

In HFrEF, tissue hypoperfusion caused by a reduction in cardiac output induces inflammation and oxidative stress, leading to a decrease in NO bioavailability and decreased activity of cGMP. Reduced sGC activity is associated with coronary microvascular dysfunction, cardiomyocyte stiffness and interstitial fibrosis, fundamental elements that lead to the progression of myocardial dysfunction.Therefore, sGC stimulators, such as **vericiguat,** may be particularly effective in this condition, counteracting endothelial dysfunction and increased oxidative stress through cGMP elevation by a double pathway for enzyme activation.

CGMP is also enhanced by others signaling pathways. The natriuretic peptides (NPs, atrial natriuretic peptide and the B-type natriuretic peptide) increase cGMP through activation of membrane-bound guanylate cyclase (particularly guanylate cyclase, pGC) Some therapeutic strategies, which act in the NP-pGC-cGMP pathway, have been evaluated, such as synthetic NPs and NP analogs (nesiritide, ularitide) and ARNI (sacubitril/ valsartan), that increase NPs through inhibition of neprilysin. In clinical trials, the use of sacubritil/valsartan has been shown to significantly improve outcomes in HF Degradation of cGMP in GMP is catalyzed by seven, differentially expressed PDE families . PDE

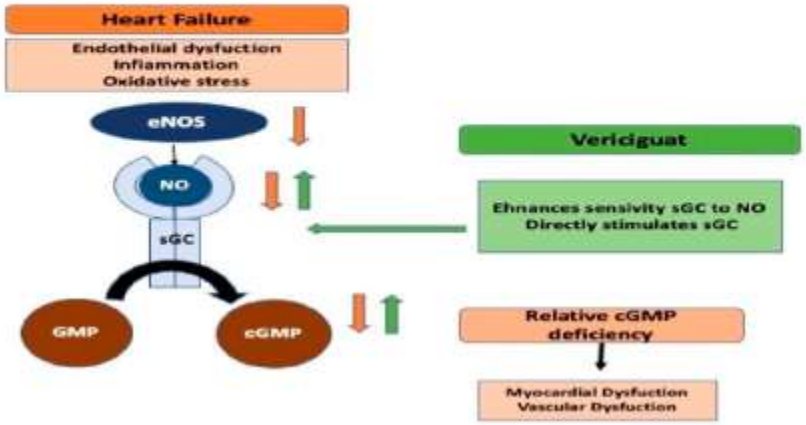
International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

inhibitors, such as milrinone and enoximone (PDE-3 inhibitors) and sildenafil (PDE-5 inhibitors), have also been evaluated as therapeutic strategies in the context of HF. PDE-5 inhibitors improve contractile function in systolic HF and reduce remodeling of the left ventricle. However, to date, no randomized clinical trials demonstrated an improved outcome in HF with the use of PDE inhibitors.

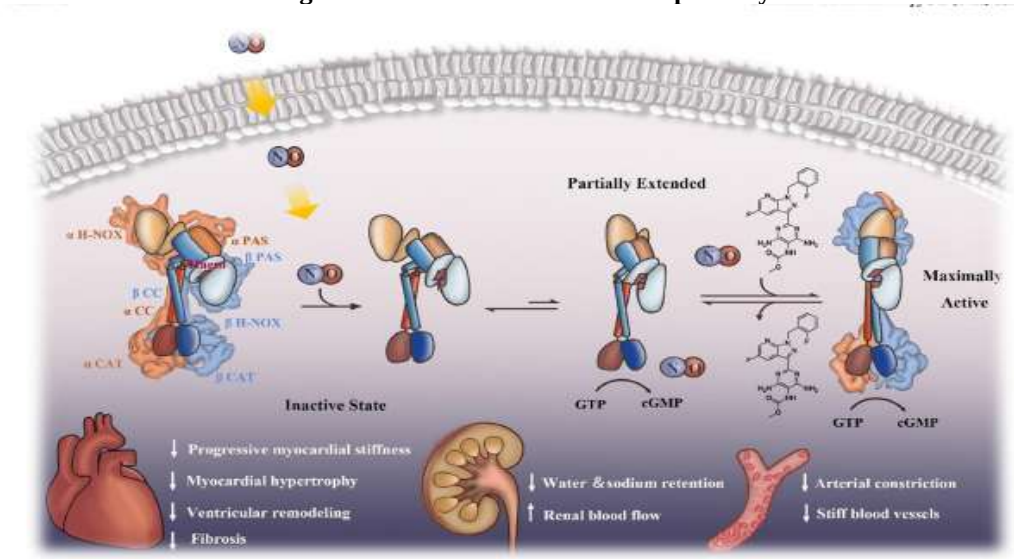
Mechanisms of action of vericiguat. cGMP= cyclic guanosine monophosphate; eNOS = endothelial nitric oxide synthase; GMP = guanosine monophosphate; NO = nitric oxide; sGC = soluble guanylate cyclase.

Category:
Congestive Heart Failure, Cardiovascular Disease, Preventive Heart Faliure.

In patients with heart failure (HF), one of the pathophysiologic features that follows endothelial dysfunction, inflammation, and increased oxidative stress is reduced activity of the guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway, which is associated with myocardial dysfunction and altered vascular regulation. Vericiguat stimulates sGC both in a direct, NO-independent manner and indirectly, through increasing the sensitivity of the enzyme to endogenous NO, with an increasing production of cGMP levels.



Vericiguat acts on the NO-sGC-cGMP pathway.



Pharmacological Proprieties of Vericiguat

Vericiguat is a weakly basic drug with a low water solubility and high intestinal permeability (class II according to the Biopharmaceutics Classification System) In six phase I studies, analysis on healthy volunteers, carried out with the aim of evaluating the safety, tolerability, pharmacodynamic and pharmacokinetic of vericiguat demonstrated that its chemical structure exhibits an excellent oral bioavailability (93%)

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

with a long half‐life (18–22 h) that allows oral administration once daily. It also has a high pharmacokinetic stability and a lower variability after administration with food. Vericiguat is a low‐clearance drug (1.6 L/h in healthy volunteers and 1.3 L/h in patients with HFrEF) with a plasma protein binding of approximately 98%, serum albumin being the main binding component without alterations in the case of renal or hepatic impairment.

In healthy subjects, after an oral administration of vericiguat, about 53% of the dose is excreted in the urine and 45% is excreted in the feces. For this reason, as demonstrated in phase I clinical trials during the titration regimen (from 0.5 mg to 15 mg daily), the drug can be administered without dose adjustments in patients with renal impairment up to an estimated glomerular filtration rate (eGFR) of 15 mL/min/1.73 m2 or with moderate liver disease.

Vericiguat is mainly metabolized by glucuronidation through uridine diphosphate glucuronosyl transferase to N‐glucuronide M‐1, which is pharmacologically inactive against sGC. A small part of the drug (<5%) is metabolized by the CYP clearance pathway . In vitro studies in phase I drug–drug interaction studies revealed that vericiguat shows a low potential for pharmacological interactions: the main molecule and its N-glucuronide metabolite do not act as inhibitors of major CYP isoforms,

Pharmacodynamics:

By directly stimulating the increased production of intracellular cyclic guanosine monophosphate (cGMP), vericiguat causes the relaxation of vascular smooth muscle and vasodilation. Vericiguat has a relatively long half-life (~30h) that allows for once-daily dosing.

Absorption

Following the administration of 10mg of vericiguat by mouth once daily, the average steady-state Cmax and AUC in patients with heart failure is 350 mcg/L and 6,680 mcg•h/L, respectively, with a Tmax of 1 hour. The absolute bioavailability of orally-administered vericiguat is approximately 93% when taken with food - co-administration with meals has been shown to reduce pharmacokinetic variability, increase Tmax to roughly 4 hours, and increase Cmax and AUC by 41% and 44%, respectively.

Protein binding

Vericiguat is extensively (~98%) protein-bound in plasma, primarily to serum albumin.

Metabolism:

Vericiguat is primarily metabolized via phase II conjugation reactions, with CYP-mediated oxidative metabolism comprising a small (<5%) portion of its overall biotransformation. The major inactive metabolite, vericiguat N-glucuronide (M1), is formed by UGT1A9 and, to a lesser extent, UGT1A1.5 Other identified metabolites include a denbenzylated compound1 and an M15 metabolite thought to be the result of oxidative metabolism,3 although these metabolites are poorly characterized.

Vericiguat ------ Vericiguat N-glucuronide --------Vericiguat debenzylated (metabolite)

Route of elimination

Following the oral administration of radiolabeled vericiguat, approximately 53% of the administered radioactivity was recovered in the urine and 45% in the feces.A human mass balance study found that the portion recovered in the urine comprised approximately 40.8% N-glucuronide metabolite, 7.7% other metabolites, and 9% unchanged parent drug, while virtually the entire portion recovered in the feces comprised unchanged vericiguat.

Half-life : In patients with heart failure, the half-life of vericiguat is 30 hours.

Clearance

Vericiguat is a low-clearance drug, with an observed plasma clearance of 1.6 L/h in healthy volunteers and 1.3 L/h in patients with systolic heart failure.

Toxicity

Data regarding over dosage with vericiguat are unavailable. Doses of up to 15mg once daily (50% greater than the recommended maintenance dose) have been studied and found to be well-tolerated. Symptoms of overdose are likely to be consistent with the adverse effect profile of vericiguat and may therefore involve significant hypotension for which symptomatic and supportive measures should be provided. Dialysis is unlikely

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

to be of benefit in vericiguat overdose given its high degree of protein binding.

Animal Study:

Animal reproduction studies have demonstrated the potential for embryo-fetal toxicity when vericiguat is administered to pregnant females - defects in major vessel and heart formation, as well as spontaneous abortions/resorptions, were observed when vericiguat was administered to pregnant rabbits during organogenesis. The possibility of pregnancy should be excluded prior to beginning therapy with vericiguat, and adequate contraception should be used throughout therapy and for one month following cessation of treatment.

Dosage forms and Strengths

Vericiguat -2.5mg –Film coated tablet.

Vericiguat -10 mg – Yellow orange film coated tablet

Vericiguat - 5 mg- Brown-red film coated tablet

Dose

Recommended Dose:

Starting dose of (Vericiguat)- 2.5mg orally once daily with food.

Double Dose of Vericiguat approximately every 2 weeks to reach target maintaince dose of 10mg once daily.

Use in Specific Patient Population:

Patients with Hepatic Impairment: No dosage adjustment of vericiguat is advised in patients with mild hepatic impairment(Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). Use of vericiguat should be avoided in severe hepatic impairment(Child-Pugh C) as there are no studies conducted in these patient populations.

Patients with Renal Impairment: No dosage adjustment of vericiguat is suggested in patients with eGFR ≥15 mL/min/1.73m2. However, the use of vericiguat has not been investigated in patients with eGFR <15 mL/min/1.73m2 or on dialysis.

Breastfeeding Considerations: Vericiguat has the potential cause for serious adverse reactions in breastfed infants. Hence, breastfeeding is not recommended during treatment with vericiguat.

Pregnancy Considerations: Due to concerns for embryo-fetal toxicity and substantial fetal harm to the fetus, vericiguat should not be administered to pregnant women or currently planning for pregnancy.

Adverse drug reactions:

1) Hypotension,
2) syncope, and anemia
3) Headache and postural dizziness
4) Diarrhea, nausea, and abdominal discomfort
5) Symptomatic hypotension,
6) Orthostatic hypotension
7) Baroreflex due to vasodilation and blood pressure reduction.

Drug-Drug Interaction

omeprazole with vericiguat reduced the absorption of vericiguat.

Magnesium hydroxide and aluminum hydroxide also decreased the absorption of vericiguat.

Drug-drug interaction study indicates that vericiguat is a suitable drug for managing patients with heart failure with multiple comorbidities requiring poly pharmacy.

Manufacture, characterisation and process controls

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

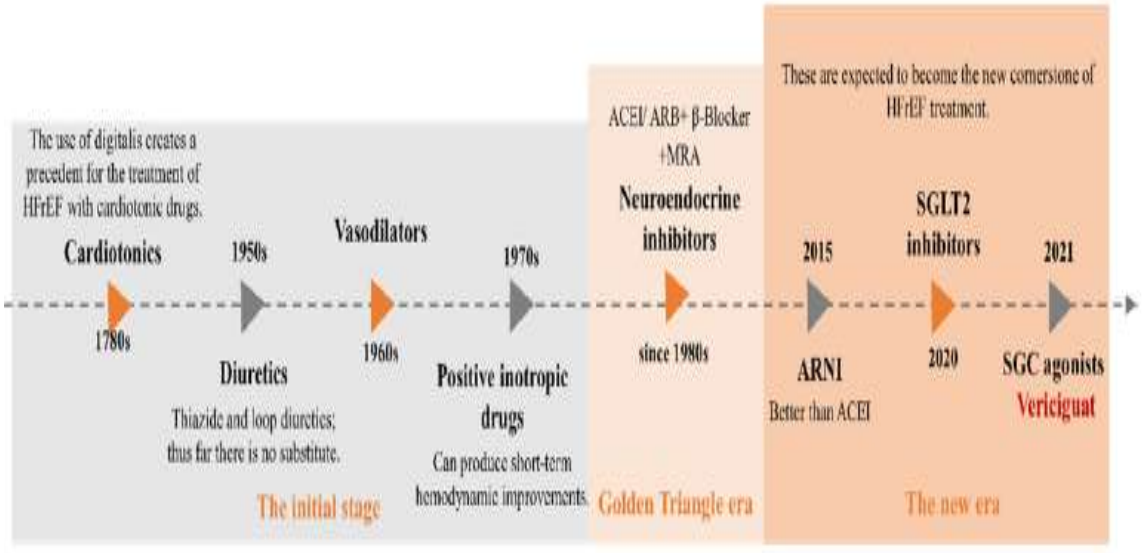
Vericiguat is synthesized at one site in 3 main synthetic steps using well-defined starting materials with acceptable specifications and is subsequently micronized at a second site. The starting materials are considered acceptable, following submission of additional data on impurities in response to a major objection. This data had previously been stated to be necessary as part of a scientific advice procedure.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Proven acceptable ranges are defined for the stoichiometry of input materials for some steps and these have been adequately justified. No design space is claimed.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Fate and purge data were provided which demonstrates that the process as described provides active substance of suitable purity.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Development of HFrEF drugs. (Vericiguat)



Soluble guanylate cyclase stimulator development and SAR study

Development of vericiguat. From YC-1 to riociguat In 1994, Bayer began a search for drugs that could target sGC [48]. The sGC-inducing activity of nearly 20,000 compounds was tested in primary endothelial cell cultures, and it was found that 5-substituted-2-furaldehyde-hydrazone derivatives could directly act on sGC and increase cGMP production [49]. In the same year, researchers from National Taiwan University and Yongshan Pharmaceuticals discovered that a benzyl indazole compound synthesized in 1978 for antithrombotic therapy could stimulate cGMP; they named this compound YC-1 [50]. Lei Chen et al. performed molecular docking between **YC-1** and NO-activated sGC (PDB ID: 6JT2), and the results showed that the compound mainly acts on β subunits sandwiched between β H-NOX and CC domains. This also further verified the effect of vericiguat on sGC at the molecular level. Specifically, including stacking of the side chain of β TYR112 with the terminal benzene ring of **YC-1**, vericiguat also forms hydrophobic interactions with the side chains of TYR2, PHE4 and haem. The central indazole part of YC-1 interacts with TYR83 and PHE77 in the H-NOX domain. The furan group of **YC-1** interacts with β ARG40. The above two compounds, with obvious structural similarity, were the starting point for the development of sGC

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

drugs [52,53]. Unfortunately, because of their poor vasodilation effects, low selectivity for mentioned compounds have not been further clinically developed . Subsequently, **CFM-1571** was produced, but its sGC-stimulating activity (concentration required for 50% of maximal effect, EC50 =5.5 μM) and oral bioavailability were relatively low (12%) [57]. In addition to the aminopyrimidine compounds shown in blue, early sGC stimulators also included arylacrylamides (shown in orange). However, this class of compounds was mainly focused on enhancing erectile function, so it is not discussed here. Notably, Bayer's research on sGC stimulators did not stop there. To develop next-generation stimulators, Bayer chemically optimized 2000 newly synthesized compounds to obtain **BAY 41–2272**, which was modified by substituting the benzyl indazole moiety of **YC-1** with (2-fluorobenzyl)pyrazolopyridine and replacing the (hydroxymethyl) furan moiety with 5-substituted 4-aminopyrimidine. Compared with **YC-1**, **BAY 41–2272** had higher stimulating potency and selectivity for sGC. However, **BAY 41–2272** is clinically limited due to its strong inhibitory and inducing effects on cytochrome P450 (CYP) enzymes. The pyrimidine ring of **BAY 41–2272** was further modified to obtain a stronger sGC-stimulating effect and the specific 4,6-diamino-5-morpholine derivative **BAY 41–8543**. However, further clinical use of **BAY 41–8543** was also hindered due to the high blood clearance (CLb) and the effect of dose nonlinearity. After structure-activity relationship (SAR) analyses, researchers found that the above two problems were mainly concentrated at the C5 position on the pyrimidine ring. To further develop sGC drugs, Bayer began to further screen and optimize pyrimidine derivatives and finally identified **BAY 63–2521** (riociguat) from the screening of over 1000 compounds (Fig. 5). Riociguat exhibited good metabolic stability and oral bioavailability and caused no CYP side effects [67–69]. **BAY41–2272**, **BAY41–8543** and riociguat all combine with sGC in a manner similar to that of **YC-1**. The newly introduced diaminopyrimidine group produces additional polar interactions with β SER81 and VAL39, making riociguat more potent than **YC-1**

From riociguat to vericiguat

Although riociguat had a satisfactory sGC-stimulating effect, clinical studies of HF treatment showed that its half-life was short [70]. A series of structural optimizations of riociguat to reduce the CLb and increase the half-life led to the development of vericiguat (**BAY 102-1189**, **MK-1242**).As shown in the modification process involved carbamate optimization and central skeleton replacement) .

Carbamate optimization

To ensure the effect of riociguat (minimum effective concentration (MEC)= 0.03 μM) and increase its CLb from 0.2 L/h/kg, structural optimization of the 5-carbamate on the pyrimidine ring was first performed. Compounds **1a-1 g** were carbamates with 7 different N-substituents. As a result, the introduction of ethyl groups (**1a**), hydroxyethyl groups (**1b**), blocking group fluorine atoms (**1c–d**), and fluorobenzyl compounds (**1e–f**) failed to improve CLb Fig. 8. In 2015, researchers discovered compound **2a** with reduced CLb among the metabolites of riociguat . To improve the stability, structural modification was conducted for the terminal methyl group,while the N remained unsubstituted. These research ideas are similar to those of compounds **1a-1 g**, including the introduction of increased steric hindrance (**2b–d**) and the groups that could change metabolism (**2e–f**), but the results were not satisfactory. Notably, the stimulating effect of compound **2d** (MEC=2.3 μM) on sGC is nearly 8 times higher than that of **2a**, but due to its low ability to permeate the Caco-2 cell monolayer and high outflow rate , **2d** was not further developed. Finally, a series of compounds in which oxazolidinone (**3a–c**) derivatives replace carbamates have also been studied, but they were also ineffective with respect to in vitro clearance. Since then, research on the optimization of carbamate groups has been halted. Therefore, the focus of the optimization shifted from carbamate to the central skeleton based on the most promising compound: N-unsubstituted carbamate **2a**.

Central skeleton replacement

The in vitro CLb values of the 6 compounds (**4a–b**) obtained by replacing the central skeleton were all ≤ 0.1 L/h/kg [80]. Fig. 9 shows the in vivo CLb in rats. **4a–b** are adjustments to the pyrazole structure, of which **4a** exhibited a significant increase in sGC stimulating activity (MEC=1.2 μM); however, it was rapidly metabolized. The 6-fluoro derivative **4b** also had good sGC-stimulating ability and low CLb and was thus a good candidate. However, through metabolic studies, it was found that pyridine was not metabolized. To continue to pursue the discovery

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

of a better structure, 1H-pyrazolo[3,4-c] pyridazine **4c**, imidazo[1,5-a] pyrimidine **4d**, imidazo[1,5-b] pyridazine **4e** and 1H-pyrazolo [3,4-b] pyridine vericiguat derivatives were synthesized. Finally, a further cross-species study was carried out on the three preferred compounds, **4b**, **4e**, and vericiguat, with riociguat. The results showed that vericiguat had the best overall pharmacokinetic characteristics. Vericiguat had low CLb in rats and dogs, a long half-life, and high oral bioavailability. The half-life of vericiguat in patients was 30 h. As shown in Fig. 10, during the optimization process from riociguat to vericiguat, we found that the pink-shaded central skeleton of vericiguat is the core of its sGC-stimulating property and prolonged metabolism. 1H-indazole, 1H-benzopyrazole, imidazo[1,5-b]pyridazine 4e and 1H-pyrazolo[3,4-b]pyridine are all preferred backbone fragments. Another fragment that can be modified in this class of compounds is the purple-shaded carbamate moiety. The introduction of polar fragments to this structure to reduce lipid solubility and the introduction of F atoms to block metabolic sites and increase steric hindrance could slightly improve sGC activity but had few or even adverse effects on reducing clearance. At the same time, ensuring that the N atom on the carbamate is not substituted and that the terminal methyl group is unchanged can delay metabolism.

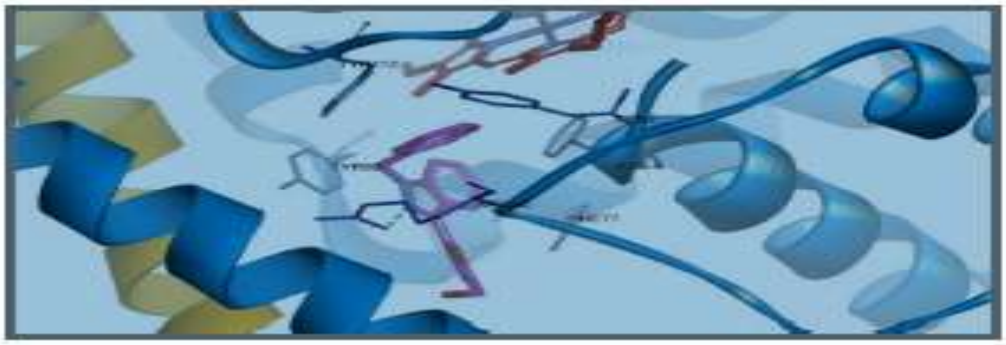
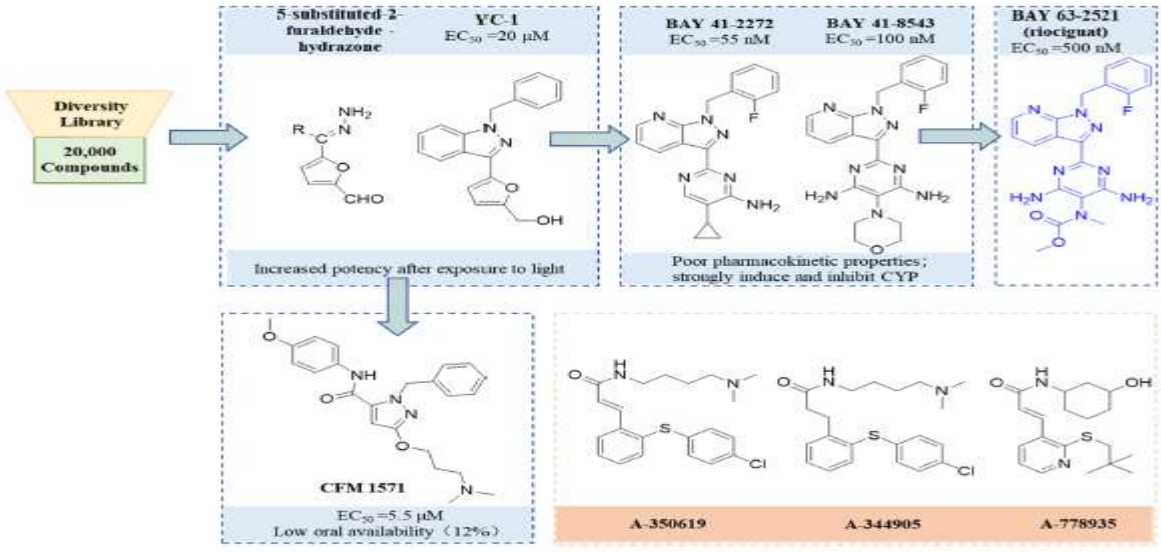


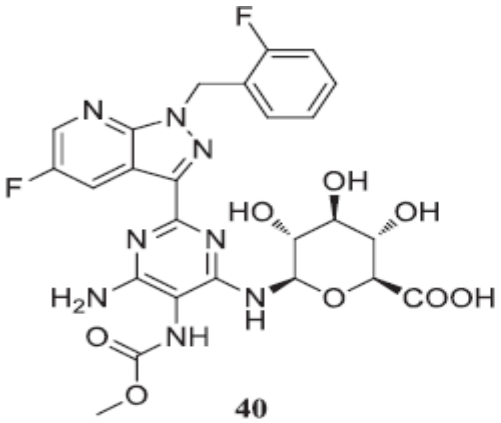
Fig. The interactions between YC-1 and sGC (α and β homologous subunits and residues are shown in yellow and blue, respectively). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Discovery of Riociguat.

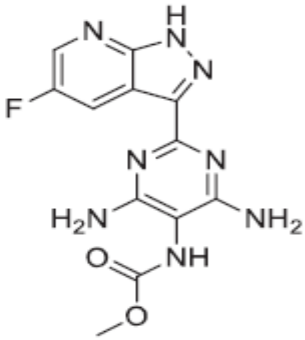


Vericiguat metabolites in human hepatocytes.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781



40



41

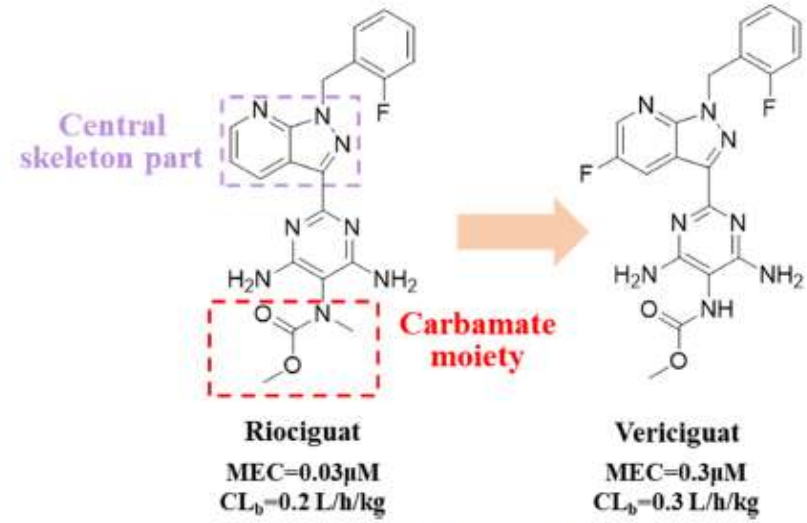
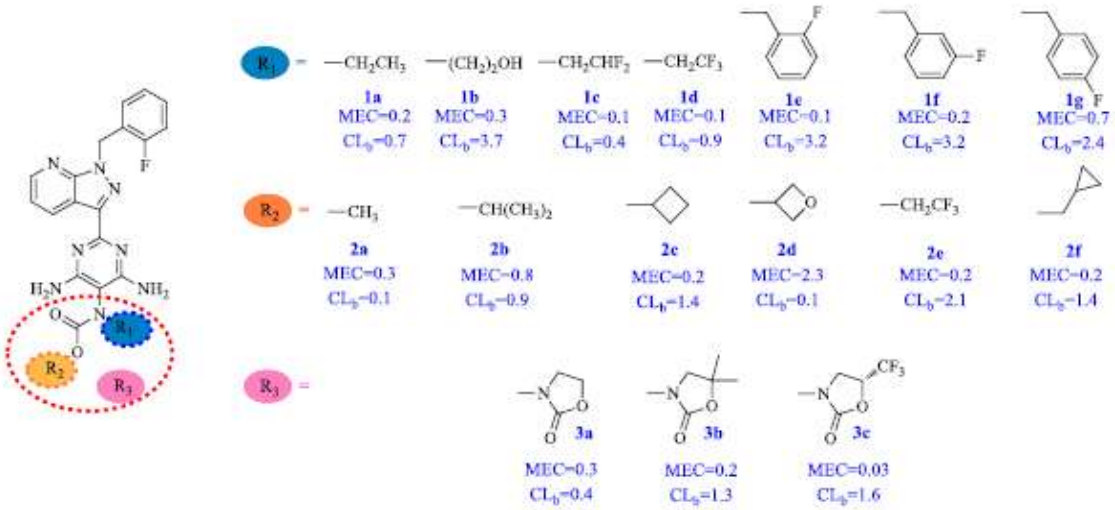


Fig. 7. The evolution of riociguat to vericiguat.



Design strategy, chemical structure, MEC and CLb for carbamate optimization.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

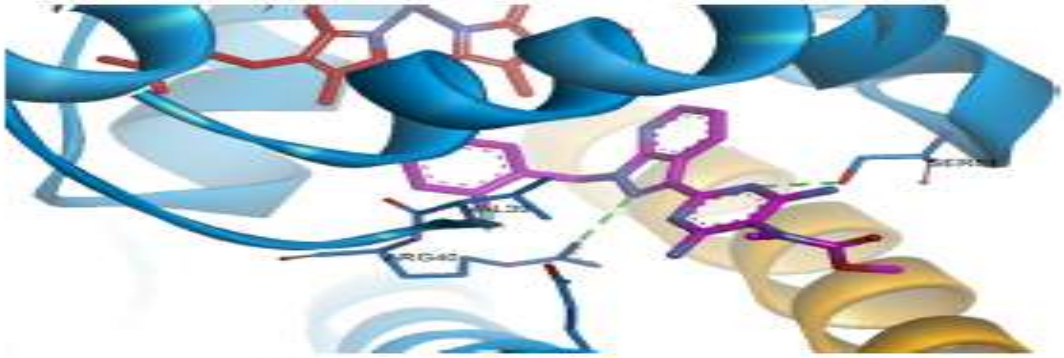


Fig. 6. Combination of riociguat and sGC.

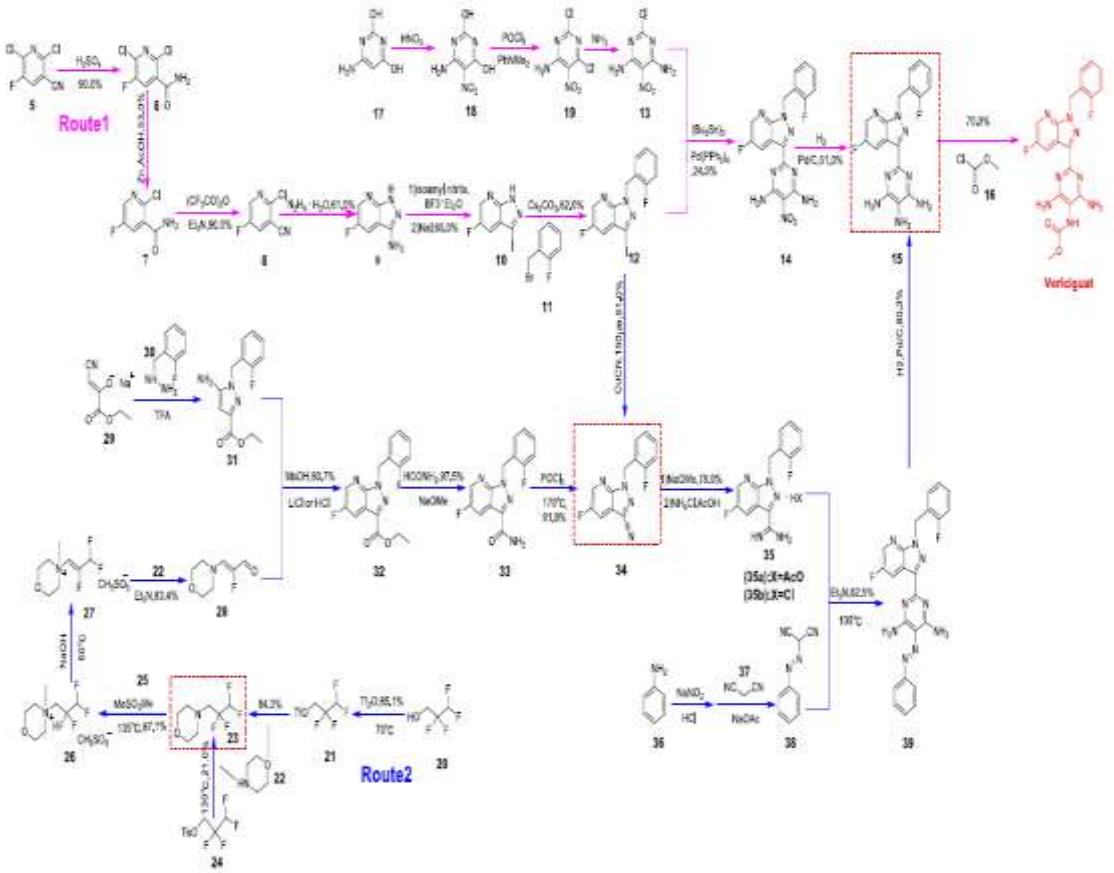
Synthesis of vericiguat :

The synthesis of vericiguat can be classified into two routes, which are outlined Route 1 Partial hydrolysis of 2,6-dichloro-5-fluoronicotinonitrile with H2SO4 at 63 ◦C yields 2,6-dichloro-5-fluoronicotinamide, which upon partial dechlorination using Zn and AcOH in MeOH yields 2- chloro-5-fluoronicotinamide. The dehydration of intermediate by means of (CF3CO)2O and Et3N in CH2Cl2 provides 2-chloro-5-fluoronicotinonitrile, which upon cyclization with N2H4·H2O in refluxing 1,2-ethanediol leads to 5-fluoropyrazolo[3,4-b] pyridin-3-amine. The diazotization of intermediate with isoamyl nitrite and BF3·Et2O in THF, followed by iodination with NaI in acetone, provides 5-fluoro-3- iodopyrazolo[3,4-b] pyridine (**10**), which is then N-alkylated with 2-fluorobenzyl bromide (**11**) in the presence of Cs2CO3 in dimethylformamide (DMF) to yield 5-fluoro-1-(2-fluorobenzyl)-3-iodopyrazolo[3,4-b] pyridine (**12**). The reaction of intermediate (**12**) with (Bu3Sn)2, followed by Stille coupling with 2-chloro-5-nitropyrimidine-4,6-diamine (**13**) in the presence of Pd (PPh3)4 in refluxing dioxane affords intermediate (**14**). Nitro reduction of intermediate (**14**) with H2 over Pd/C in pyridine yields the triaminopyrimidine derivative (**15**), which is finally condensed with methyl chloroformate (**16**) in pyridine/CH2Cl2 to afford the vericiguat[81,82]. The synthesis of intermediate (**13**) involves the initial nitration of 6-aminouracil (**17**) with HNO3, yielding 6-amino-5-nitrouracil (**18**), which upon chlorination with POCl3 and PhNMe2 yields 2,6-dichloro-5-nitropyrimidin-4-amine (**19**). The amination of intermediate (**14**) with ethanolic NH3 in ether provides 2-chloro-5-nitropyrimidine-4,6-diamine (**13**) [83]. The sulfonylation of 2,2,3,3-tetrafluoropropan-1-ol (**20**) with Tf2O at 70 ◦C gives the corresponding sulfonate (**21**), which is then condensed with morpholine (**22**) in CH2Cl2 to yield 4-(2,2,3,3-tetrafluoropropyl) morpholine (**23**) (2,3) [80]. This compound can be alternatively obtained by the coupling of 2,2,3,3-tetrafluoropropyltosylate (**24**) with morpholine (**22**) at 130 ◦C (7). N-Alkylation of intermediate (**23**) with methyl mesylate (**25**) at 135 ◦C provides 4-methyl-4-(2,2,3,3-tetrafluoropropyl) morpholin-4-ium mesylate (**26**), which is dehydrogenated with NaOH in H2O to provide 4-methyl-4-[2,3,3-trifluoro-1(E)-propenyl] morpholin-4-ium mesylate (**27**) [80,84]. The demethylation of intermediate (**27**) using morpholine and Et3N in H2O/CH2Cl2 at 75 ◦C leads to 2 (E)-fluoro-3-(4-morpholinyl) acrylaldehyde (**28**). The cyclization of this compound (**28**) with ethyl 5-amino-1-(2-fluorobenzyl) pyrazole-3- carboxylate (**31**) (prepared by the cyclization of ethyl cyanopyruvate sodium salt (**29**) with (2-fluorobenzyl) hydrazine (**30**) using trifluoroacetic acid (TFA) in refluxing dioxane) in the presence of MsOH and LiCl or HCl in refluxing EtOH affords a pyrazolo[3,4-b] pyridine derivative (**32**) [85,86]. The reaction of ester (**32**) with HCONH2 and NaOMe in MeOH yields carboxamide (**33**), which is dehydrated with POCl3 in sulfolane/acetonitrile to furnish intermediate (**34**) (2,3). Compound **36** can also be prepared by the substitution of 5-fluoro-1-(2-fluorobenzyl)-3-iodopyrazolo[3,4-b] pyridine (**12**) with CuCN in DMSO at 150 ◦C. 5-Fluoro-1-(2-fluorobenzyl) pyrazolo[3,4-b] pyridine-3-carbonitrile (**34**), upon reaction with NaOMe in MeOH and subsequent treatment with NH4Cl, optionally in the presence of AcOH, yields 5-fluoro-1-(2-fluorobenzyl) pyrazolo[3,4-b] pyridine-3-carboximidamide acetate (**35a**) or hydrochloride salt (**35b**). The cyclization of intermediates (**35a**) or (**35b**) with [(E)-phenyldiazenyl] malononitrile (**38**) (obtained by the diazotization of aniline (**36**) with NaNO2 and HCl in H2O, followed by

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

condensation with malononitrile (**37**) using NaOAc in H2O/EtOH) in the presence of Et3N at high temperature (100 ◦C) produces the diazo compound (**39**). The reduction of intermediate (**39**) using H2 over Pd/C in DMF affords the triaminopyrimidine intermediate (**15**), which is ultimately condensed with methyl chloroformate (**16**) in pyridine/CH2Cl2 to yield the target compound. In general, there are fewer reaction steps in route 1 than in route 2, which can undoubtedly reduce the cost of reagents, and the reaction conditions are safe and easy to achieve. However, due to the low yields of compounds **13** to **15** in both steps, the route's yield is also limited. Nevertheless, there is still no report on the optimization of processes. In comparison, although route 2 is longer, the conversion rate of each step is high, and the total yield is nearly 10 times higher than that of route 1. The safety of the process from compound **37** to vericiguat has already been proven in the synthesis of riociguat. This part of route 2 can be applied to production on the 100 kg scale [87]. Therefore, this route is also mainstream in actual production applications [88,89]. However, route 2 also uses POCl3 in the dehydration reaction of compounds **33** to **34** at 170 ◦C, which are relatively harsh reaction conditions. Recently, it was discovered that the reaction can also be catalysed by silane using PhSiH3 by using a catalytic amount of fluoride, which is milder and more selective.

Synthesis –Route for Vericiguat



International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

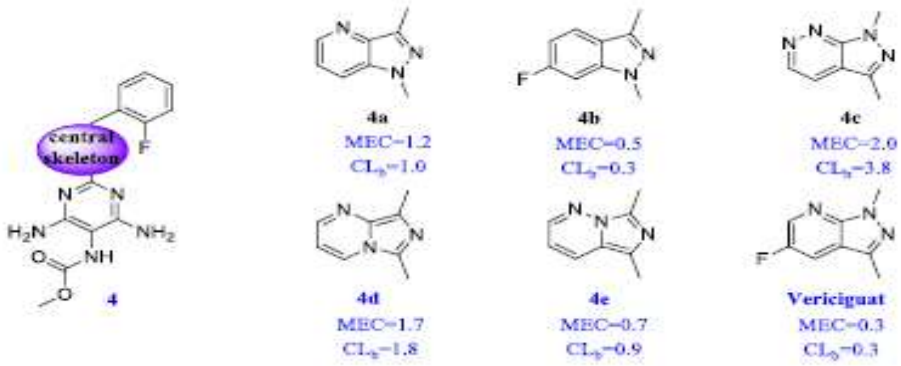


Fig. Riociguat central skeleton changes.

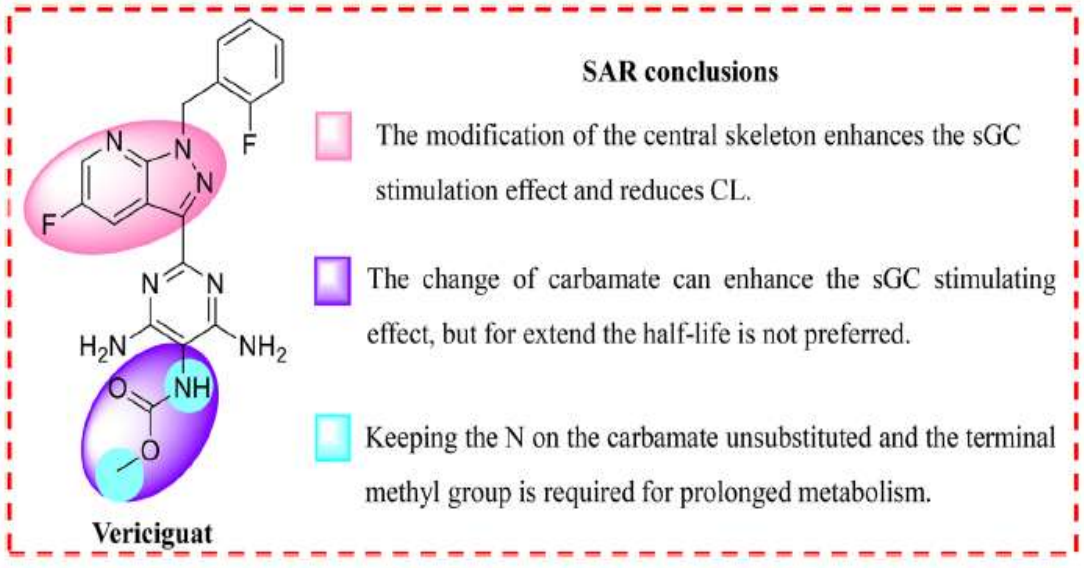


Diagram of vericiguat synthesis(Route)

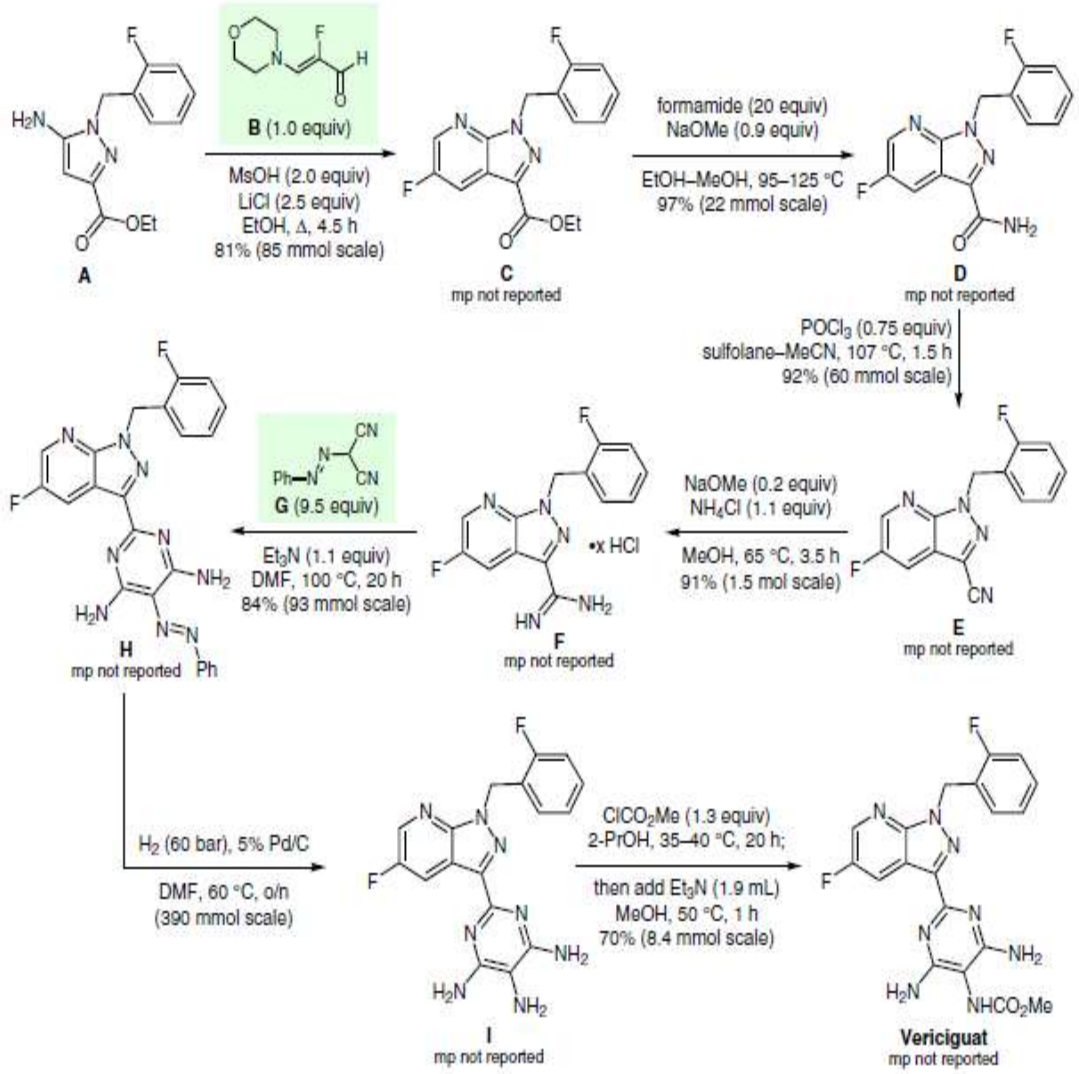
Background Study of Vericiguat:

Vericiguat is a direct stimulator of soluble guanylate cyclase (sGC) used in the management of systolic heart failure to reduce mortality and hospitalizations.5 A key component of the NO-sGC-cGMP signaling pathway that helps to regulate the cardiovascular system, sGC enzymes are intracellular enzymes found in vascular smooth muscle cells (amongst other cell types) that catalyze the synthesis of cyclic guanosine monophosphate (cGMP) in response to activation by nitric oxide (NO).1,4 Cyclic GMP acts as a second messenger, activating a number of downstream signaling cascades that elicit a broad variety of effects, and these diverse cellular effects have implicated deficiencies in its production (primarily due to insufficient NO bioavailability) in the pathogenesis of various cardiovascular diseases. As a direct stimulator of sGC, vericiguat mitigates the need for a functional NO-sGC-cGMP axis and thereby helps to prevent the myocardial and vascular dysfunction associated with decreased sGC activity in heart failure.

\

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

Synthesis of Vericiguat



Vericiguat (BAY 1021189) is an orally available soluble guanylate cyclase (sGC) stimulator that has entered phase-three trials for the once-daily treatment of chronic heart failure. Key steps in the synthesis depicted are **(1)** construction of the 5-fluoro-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-carboxylate **C** by condensation of the 5-amino-1H-pyrazole-3-carboxylate A with the aldehyde **B** and **(2)** construction of the pyrimidine-4,5,6-triamine derivative **H** through reaction of **[(E)-**phenyldiazenyl]malononitrile **(G)** with amidine **F.**

Experimental details are provided for the note worthy **four-step synthesis (**not shown) of the crystalline 2-fluoro-(3-morpholin-4-yl)acrylaldehyde B from commercially available 2,2,3,3- tetrafluoro-1-propanol. The synthesis of pyrazole, A is described in a patent (A. Straub et al. WO 2000/006569 A1). The [(E)-phenyldiazenyl]malononitrile (G) was generated in situ by reaction of phenyldiazonium chloride with malononitrile.

Administration

An increase in cardiac output, an increase in heart rate of 4 to 10 beats per minute, and an increase in the cardiac index are observed in patients who received a single dose of 5 to 15 mg per oral (PO). In addition, systemic vascular

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

resistance has decreased from the baseline, thereby reducing blood pressure. However, the effect was inconsistent and not dose-dependent.

The immediate-release form of the **vericiguat** showed a mean half-life (t1/2) of about 18 to 22 hours. There were no significant differences between single and multiple doses regarding bioavailability, the area under the curve (AUC), and Cmax (maximum concentration). Absorption through percutaneous endoscopic gastrostomy (PEG) is reported to be faster when compared to oral administration. As discussed above, food increases the bioavailability of vericiguat and reduces the variability in the postprandial/fed state; hence medication should be administered with food. A single oral dose of 10 mg was well tolerated by healthy Japanese, Chinese and European subjects.

According to phase III of the VICTORIA Heart Failure with Reduced Ejection Fraction study, the dose of vericiguat can be increased **from 2.5 mg to 10 mg** depending on patient response. Phase II of the VITALITY Heart Failure with Preserved Ejection Fraction study reported that the dose could be titrated up to **15 mg**.

Monitoring

The clinical team should monitor **blood pressure, heart rate, and hemoglobi**n are advised in patients treated with vericiguat.

Monitor BNP or NT-proBNP levels to assess response to the therapy to vericiguat. Monitor fluid intake and output, body weight, and clinical signs and symptoms of congestion and hypoperfusion in patients with heart failure

Heart Failure Vs Vericiguat

Vericiguat was approved by the Food and Drug Administration (FDA) in January 2021. It can serve as an add-on therapy for heart failure with reduced ejection fraction following worsening heart failure. Surprisingly, vericiguat has per patient per month budget impact of fewer than 10 cents, the reason being the reduction in HF hospitalizations and **CV deaths.**

Based on **the phase III VICTORIA (Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction) trial results, the** FDA approved vericiguat for patients with HFrEF. VICTORIA was a multi-centered, randomized, placebo-controlled, double-blind, pivotal phase III trial of the efficacy and safety of the oral soluble guanylate cyclase stimulator vericiguat in subjects with heart failure with reduced ejection fraction. This clinical trial included 5050 patients. The intervention included a single daily dose of **10 mg vericiguat** in addition to heart failure guideline therapy. Patients were followed up for 10.8 months. The primary outcome event was cardiovascular death and first heart failure hospitalization. In the trial conclusion, compared to placebo, vericiguat has a beneficial effect with a hazard ratio of 0.90 (95% CI: 0.82 – 0.98; P=0.02) for either of the primary outcome events in patients with NTproBNP <8000 pg/ml. Also, the risk of primary outcome event in vericiguat compared to placebo in patients aged < 75 and >= 75 years was 0.84 and 1.04, respectively (P value=0.030).

According to ACC/AHA 2022 guidelines, heart failure(HF) has been classified as stage A (at risk of HF), Stage B (Pre-HF), Stage C (Symptomatic HF), and Stage D (advanced HF). Vericiguat should be considered for patients with Stage C HFrEF(Structural heart disease with current or previous symptoms of HF).

Researchers are awaiting the result of an ongoing trial of vericiguat for HFpEF to answer questions like the importance of measuring plasma or urinary cyclic GMP levels or whether atrial natriuretic peptide would be helpful. Assessment of nitric oxide level would be required to assess the best response of vericiguat. An important concern of combining vericiguat and sacubitril-valsartan (soluble guanylyl cyclase and particulate guanylyl cyclase) would have a synergistic effect, and the effect on adverse effect of hypotension or syncope is unanswered.

WARNING:

OVERDOSE:

Limited data is available with regard to overdosage in human patient treated with Vericiguat in doses up to 10mg have been studied. In a study of patients with preserved ejection fraction heart failure (left ventricle ejection fraction >45%) multiple doses 15mg have been studied and were generally well tolerated. In the event an overdose, hypotension may result. Symptomatic treatment should be provide.

Embryo-Fetal toxicity:

Animal study to administered vericiguat to pregnant animal for cause the fetal harm so it influence for human effect for pregnant women.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

Lactation: Advice women not to be Breastfeed during treatment with Vericiguat.

Mutagenesis: Vericiguat was not Genotoxic in the in vitro microbial mutagenicity

Labeling For Vericiguat- Tablet

VERQUVO™ (ver-KYU-voh)
(vericiguat)
tablets

What is the most important information I should know about VERQUVO?
VERQUVO may cause birth defects if taken during pregnancy.

- **Females must not be pregnant when they start taking VERQUVO.**
- Females who are able to get pregnant:
  - Your healthcare provider will do a pregnancy test to make sure that you are not pregnant before you start taking VERQUVO.
  - You must use effective forms of birth control during treatment and for 1 month after you stop treatment with VERQUVO. Talk to your healthcare provider about forms of birth control that you may use to prevent pregnancy during treatment with VERQUVO.
  - Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with VERQUVO.

What is VERQUVO?
VERQUVO is a prescription medicine used in adults who are having symptoms of their chronic (long-lasting) heart failure, who have had a recent hospitalization or the need to receive intravenous (IV) medicines and have an ejection fraction (amount of blood pumped with each heartbeat) of less than 45 percent:

- to reduce the risk of dying and
- to reduce the need to be hospitalized

Heart failure happens when your heart is weak and cannot pump enough blood to your lungs and the rest of your body. It is not known if VERQUVO is safe and effective in children.

Do not take VERQUVO if you:

- are taking another medicine called a soluble guanylate cyclase stimulator (sGC). Ask your healthcare provider if you are not sure if you are taking an sGC medicine.
- are pregnant. See **"What is the most important information I should know about VERQUVO?"**

Before you take VERQUVO, tell your healthcare provider about all your medical conditions, including if you:

- are breastfeeding or plan to breastfeed. It is not known if VERQUVO passes into your breast milk. **Do not** breastfeed if you take VERQUVO. Talk with your healthcare provider about the best way to feed your baby if you take VERQUVO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Certain other medicines may affect how VERQUVO works.

How should I take VERQUVO?

- Take VERQUVO exactly as your healthcare provider tells you to.
- Take VERQUVO 1 time each day with food.
- Swallow VERQUVO tablets whole. If you are not able to swallow the tablet whole, you may crush VERQUVO tablets and mix with water right before taking your dose.
- Your healthcare provider may change your dose — when you first start taking VERQUVO to find the best dose for you and how well you tolerate VERQUVO.
- If you miss a dose, take the missed dose as soon as you remember on the same day of the missed dose. **Do not** take 2 doses of VERQUVO on the same day to make up for a missed dose.
- If you take too much VERQUVO, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of VERQUVO?
VERQUVO may cause serious side effects, including:
See **"What is the most important information I should know about VERQUVO?"**

The most common side effects of VERQUVO include:

- low blood pressure
- low red blood cells (anemia)

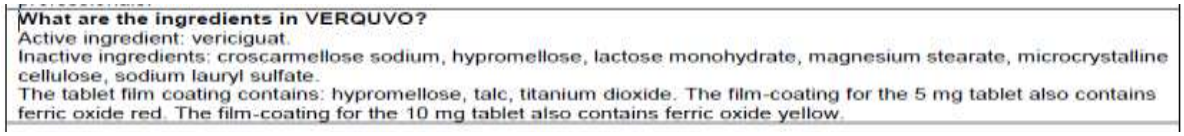
These are not all the possible side effects of VERQUVO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VERQUVO?

- Store VERQUVO at room temperature between 68°F to 77°F (20°C to 25°C).

Keep VERQUVO and all medicines out of the reach of children.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781


What are the ingredients in VERQUVO?
Active ingredient: vericiguat.
Inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate.
The tablet film coating contains: hypromellose, talc, titanium dioxide. The film-coating for the 5 mg tablet also contains ferric oxide red. The film-coating for the 10 mg tablet also contains ferric oxide yellow.

II. CONCLUSIONS:

Despite the improvements achieved in recent years with the current treatments, patients with HF are still at high risk of HFH and death during long follow-up periods. The latest ESC/AHA HF guidelines recommend **vericiguat** as a **second-line treatment** in patients who remain symptomatic despite first-line treatment, manly after a recent decomposition. Based on population characteristics, we believe that this drug could have beneficial effects in chronic stable HF with reduced or mildly reduced ejection fraction, together with the traditional quadruple therapy based on ARNI/ACEi, beta blockers, MRA, SGLT2i and diuretics in those with congestion evidence. **The role of vericiguat in more advanced HF stage and in patients with history of recurrent HFH** has been previously established. If the drug's safety can be confirmed in a larger population, its extensive application may become **a future challenge to reduce adverse events in multiple Heart Failure settings.**

Acknowledgements:
Most Thankful to The principal of Adhiparasakthi College of Pharmacy, Melmaruvathur for providing the necessary ideas in this Review studies.

REFERENCE:

[1]. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, Lam CSP, Ponikowski P, Voors AA, Jia G, McNulty SE, Patel MJ, Roessig L, Koglin J, O'Connor CM., VICTORIA Study Group. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020 May 14;382(20):1883-1893. [PubMed]

[2]. Iacoviello M, Palazzuoli A, Gronda E. Recent advances in pharmacological treatment of heart failure. Eur J Clin Invest. 2021 Nov;51(11):e13624. [PMC free article] [PubMed]

[3]. Alsumali A, Lautsch D, Liu R, Patel D, Nanji S, Djatche LM. Budget Impact Analysis of Vericiguat for the Treatment of Chronic Heart Failure with Reduced Ejection Fraction Following a Worsening Event. Adv Ther. 2021 May;38(5):2631-2643. [PMC free article] [PubMed]

[4]. Ezekowitz JA, O'Connor CM, Troughton RW, Alemayehu WG, Westerhout CM, Voors AA, Butler J, Lam CSP, Ponikowski P, Emdin M, Patel MJ, Pieske B, Roessig L, Hernandez AF, Armstrong PW. N-Terminal Pro-B-Type Natriuretic Peptide and Clinical Outcomes: Vericiguat Heart Failure With Reduced Ejection Fraction Study. JACC Heart Fail. 2020 Nov;8(11):931-939. [PubMed]

[5]. Markham A, Duggan S. Vericiguat: First Approval. Drugs. 2021 Apr;81(6):721-726. [PubMed]

[6]. Burnett JC. Vericiguat - Another Victory for Targeting Cyclic GMP in Heart Failure. N Engl J Med. 2020 May 14;382(20):1952-1953. [PubMed]

[7]. Tsai EJ, Kass DA. Cyclic GMP signaling in cardiovascular pathophysiology and therapeutics. Pharmacol Ther. 2009 Jun;122(3):216-38. [PMC free article] [PubMed]

[8]. Boettcher M, Gerisch M, Lobmeyer M, Besche N, Thomas D, Gerrits M, Lemmen J, Mueck W, Radtke M, Becker C. Metabolism and Pharmacokinetic Drug-Drug Interaction Profile of Vericiguat, A Soluble Guanylate Cyclase Stimulator: Results From Preclinical and Phase I Healthy Volunteer Studies. Clin Pharmacokinet. 2020 Nov;59(11):1407-1418. [PMC free article] [PubMed]

[9]. Murphy SP, Ibrahim NE, Januzzi JL. Heart Failure With Reduced Ejection Fraction: A Review. JAMA. 2020 Aug 04;324(5):488-504. [PubMed]

[10]. Voors AA, Mulder H, Reyes E, Cowie MR, Lassus J, Hernandez AF, Ezekowitz JA, Butler J, O'Connor CM, Koglin J, Lam CSP, Pieske B, Roessig L, Ponikowski P, Anstrom KJ, Armstrong PW., VICTORIA Study Group. Renal function and the effects of vericiguat in patients with worsening heart failure with reduced ejection fraction: insights from the VICTORIA (Vericiguat Global Study in Subjects with HFrEF) trial. Eur J Heart

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 3 May-June 2023, pp: 1544-1560 www.ijprajournal.com ISSN: 2249-7781

Fail. 2021 Aug;23(8):1313-1321. [PMC free article] [PubMed]

[11]. S.S. Suri, S.V. Pamboukian, Optimal diuretic strategies in heart failure, Ann. Transl. Med. 9 (6) (2021) 517.

[12]. C. Cook, G. Cole, P. Asaria, R. Jabbour, D.P. Francis, The annual global economic burden of heart failure, Int. J. Cardiol. 171 (3) (2014) 368–376. [12]

[13]. P. Gouda, J.A. Ezekowitz, Update on the diagnosis and management of acute heart failure, Curr. Opin. Cardiol. 34 (2) (2019) 202–206.

[14]. N. Nair, Epidemiology and pathogenesis of heart failure with preserved ejection fraction, Rev. Cardiovasc. Med. 21 (4) (2020) 531–540.

[15]. E.J. Benjamin, P. Muntner, A. Alonso, M.S. Bittencourt, American Heart Association, Circulation 139 (10)) (2019) 56–528.

[16]. J.J. McMurray, Improving outcomes in heart failure: a personal perspective, Eur. Heart J. 36 (48) (2015) 3467–3470.

[17]. W. Gu, Z. Dong, R. Wang, Compound for Adjusting Activity of NMDA Receptor, and Pharmaceutical Composition and Use Thereof, Beijing Greatway Pharmaceutica lTechnology Co., Ltd., Peop. Rep. China . 2021, 147.

[18]. National Clinical Guideline, National Institute for Health and Clinical Excellence: Guidance, Chronic Heart Failure: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care: Partial Update, Royal College of Physicians (UK)Copyright © 2010,National Clinical Guideline Centre, London, 2010.

[19]. Drug Trials Snapshot: VERQUVO. February 08,2021. 〈 https://www.fda.gov/drug s/drug-approvals-and-databases/drug-trials-snapshot-verquvo 〉 . (Accessed July 2021).

[20]. M. Komajda, M. B¨ohm, J.S. Borer, I. Ford, L. Tavazzi, M. Pannaux, K. Swedberg, Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis, Eur. J. Heart Fail. 20 (9) (2018) 1315–1322.

[21]. M. Metra, August 2017 at a glance: tailored treatment, acute heart failure and cardiac resynchronization, Eur. J. Heart Fail. 19 (8) (2017) 969–970.