International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Soluble Guanylate Cyclase Stimulators in Heart Failure

Nida Mirza[1], Dr. M. Vijaya Bhargavi[2]

[1]Student, RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad, India
Email: *nmirzaa24[at]gmail.com*

[2]Assistant professor, HOD of Pharmaceutical Chemistry,
Email: *mvijayabhargavi[at]gmail.com*

Abstract: ***Heart failure nowadays has a high degree of morbidity and mortality rates. Various treatments have been introduced but still the prognosis remains poor. This justifies the search of newer agents with the development of soluble cyclase guanylate inhibitors which has been studied through the NO oxide pathway cyclase. Therefore, the development of the sGCs have reduced the risk of hospitalizations with heart failure with reduced ejection fraction that are at a high risk of cardiovascular events. The novel sGC stimulators increase sGC sensitivity to NO and independently stimulate sGC, whereas the sGC activators target oxidized and heme free sGC to stimulate cGMP production. This review will discuss the pathophysiologic basis for sGC stimulator and activator use in HFrEF, review pre-clinical and clinical data, and propose a place in the HFrEF armamentarium for this novel pharmacotherapeutic class***

Keywords: sGCs, cGMP, Heart Failure, HFpEF,HFrEF, PAH, CTEPH

1. Introduction

Soluble cyclase inhibitors are the receptors for the target nitric oxide (NO). NO is usually initiated by the signaling pathway where it is regulated by the activation of the NO synthase in the donor receptor to produce NO molecules. It plays an essential role in the functioning of tissues and cells in body and the deregulation of NO leads to the disturbance in the normal physiological process which leads to various cardiovascular diseases and cardiopulmonary diseases, it not only affects the major organs associated with the cardiac system but also affects the kidneys and brain.

1.1 How do the sGCs work?

NO readily passes across the cellular membrane and binds to the target receptor sGC's which boosts the activity of sGC'sfor the production of cGMP. sGC's is composed of one alpha and one beta sub-unit, both of which contains the homology in their domains and has common domains: N-terminal H-NOX domain, PAS domain and C-terminal catalytic domain. In recent studies in human sGC it has been recognized that sGC is an allosteric enzyme and is composed of three structural modules: sensor module and transducer module and a catalytic module.Endogenous synthase is synthesized in the vasculature by the L-Arginine which is then activated by the enzyme endothelium synthase. Endothelium synthase can also be activated by the ligands such as acetylcholine, adenosine and bradykinin and also sheer stress produced by the blood vessels. This activated NO then binds to the heme group on the sGC enzyme. sGC is an enzyme that catalyzes the conversion of guanosine triphosphate to cGMP and the conversion is mediated by the cGMP targets such as cGMP protein kinases and cGMP regulated ion channels. Phosphodiesterase's breakdown the cGMP, terminating the effects of this pathway.

cGMP downregulates the effects of this pathway such as inhibition of platelet aggregation, subsequent hypotension and inhibition of smooth muscle proliferation. In heart, natriuretic factor leads to the activation of NO-sGC-cGMP pathway .This results in cardioprotective actions such as leads to the increase in dilatory relaxation, improved coronary blood flow, reduced hypertrophy, inflammation and fibrosis.

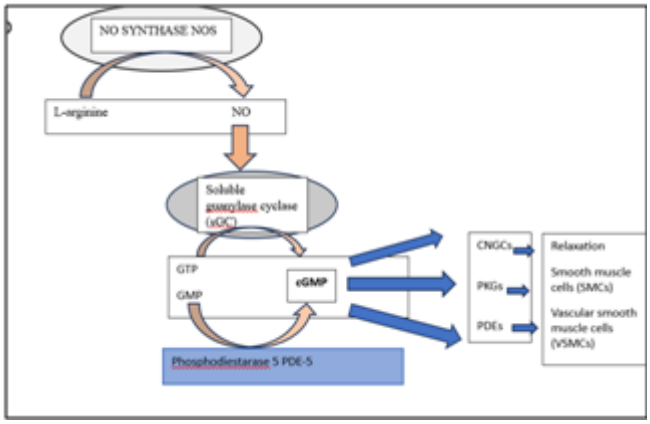


Figure 1: NO-sGC-cGMP pathway
cGMP: cyclic guanosine monophosphate: CNGC: cyclic nucleoside gated-ion channels;
GMP: guanosine monophosphate; GTP: guanosine triphosphate;
NO: nitric oxide; NOS: nitric oxide synthase; PDE: phosphodiesterase;
PKG: protein kinase G; sGC: soluble guanylate cyclase

HF pathology itself can also cause endothelial dysfunction. Elevated levels of tumor necrosis factor-α (TNF-α), a common finding in heart failure, have been identified as a possible factor in eNOS impairment. Decreased NO production may also contribute to reduced exercise because NO has a significant impact on limb. blood. flow during exercise. Impaired exercise capacity can lead to a sedentary lifestyle, which can further increase ROS levels and reduce

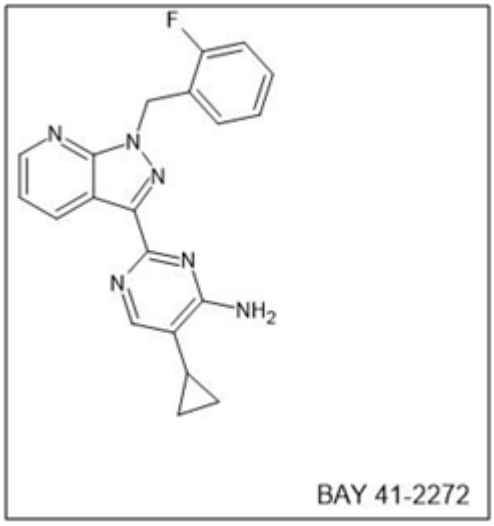
eNOS activity due to reduced shear stress due to lower heart rates. afterload and disorders of regulation of both renal and coronary blood flows

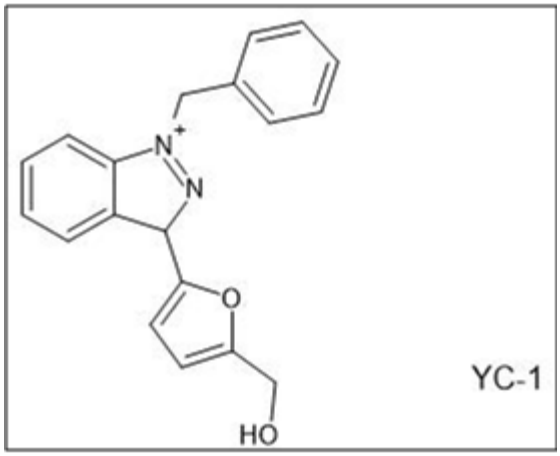
Endothelial dysfunction is one of the independent factor found mostly in the patients afflicted with heart failure. This may also occur as a part of other comorbid diseases such as diabetes, hyperlipidemia, and hypertension. However, the studies has also been done on the NO-cGMP-sGCs pathway where it was found that isosorbide dinitrate reduced mortality in patients given with a standard therapy and it usually requires multiple dosing a day with the concomitant use of hydralazine to reduce the nitrate tolerance. Randomized trials didn't show any improvement with the use of PDE 5 inhibitors and showed no efficacy whereas when low bioavailability of cGMP in endothelial dysfunction may limit the efficacy of PDE 5 inhibitors. Therefore meta analysis was found effective in showing the clinical outcomes in patients with endothelial dysfunction with the utilization of PDE 5.

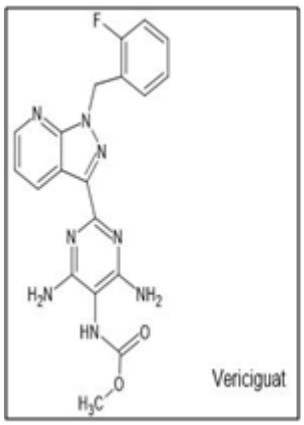
Two novel classes of medications i.e., sGC stimulators and activators are the main criteria for the treatment in HF pharmacotherapy. sGC activators such as cinaciguat, can activate both the oxidized haem and stimulate the production of cGMP by mimicking the haem group. The sGCactvators also prevent the degradation of sGC's and increase sGC protein levels. Whereas sGC stimulators such as riociguat and vericiguat require a reduced haem to stimulate the production of cGMP independent of NO. They are also found to have synergistic affects to activate the sGCin its active configuration.

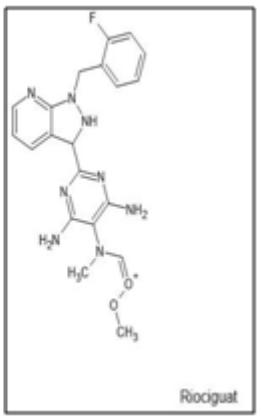
2. sGC agonists in cardiovascular, cardiopulmonary and cardiorenal diseases

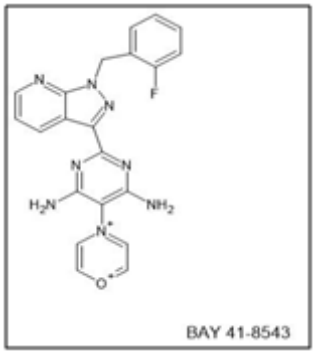
In accordance with the well-established mode of action of cGMP, the chemical patent applications addressed the full spectrum of cardiovascular, cardiopulmonary, and cardiorenal problems, as well as illnesses of the heart, lung, and kidney. While the sGC stimulator praliguat recently finished phase 2 clinical development for both HFpEF(A study of the effect of IW-1973 on the exercise capacity of patients with heart failure with preserved ejection fraction) and diabetic nephropathy, the sGC stimulator vericiguat completed late-stage phase 3 clinical development for Heart Failure (HFrEF) and phase 2 for HFpEF. Riociguat, also known as Dempas®, is an authorized sGC stimulant for the treatment of PAH (Pulmonary arterial hypotension) and CTEPH (Chronic Thromboembolic Pulmonary Hypertension). Thus combinations of sGC agonists with PDE5 inhibitors with neprilysin inhibitors with mineralocorticoid receptors antagonists or with lipid lowering drugs were identified.











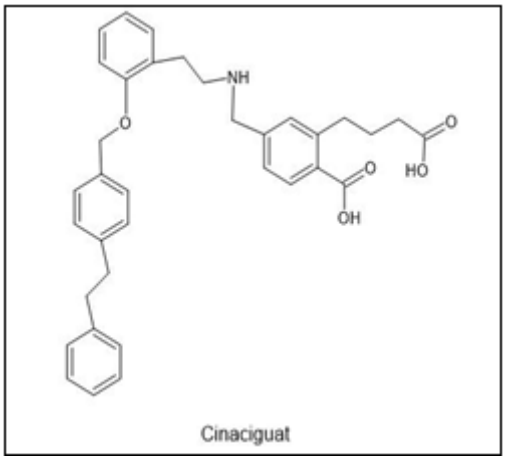
2.1sGC stimulators: Discovery, mode of action, and pre clinical profiling of their therapeutic potential

Researchers at Bayer initiated a screening program in 1994 to find compounds that could boost NO production and accelerate sGC in pig endothelial cells. In these investigations, cGMP levels were measured using RIA. Nearly 20,000 molecules were investigated, resulting in the identification of 5-substituted-2-furaldehyde-hydrazone derivatives as direct, NO-independent sGC stimulators. However, light boosted these compounds' effectiveness in stimulating sGC in vitro and relaxing isolated blood arteries, making them unsuitable for further therapeutic development. In 1994, it was discovered that the synthetic benzyl YC-1 inhibited platelet aggregation mediated by increased intracellular cGMP . YC-1 was profiled because of its structural closeness to our compounds, and it was discovered to directly stimulate isolated sGC in the same NO-independent, but haem-dependent manner. YC-1 was then characterized in several in vitro experiments and had a promising profile in various pharmacological studies. However, it had a poor pharmacokinetic (PK) profile and a lack of selectivity, as it inhibited PDEs and altered several cGMP-independent actions, in addition to its relatively weak sGC-stimulating activity. As a result, additional optimization is required. Therefore, it marked the starting point for the extensive studies of structure-activity relationship by modifying the development of YC-1 inhibitors with the introduction of more than 4000 compounds.

The discovery of BAY 41-2272(a potent activator of soluble guanylyl cyclase) , which demonstrated significantly improved sGC-stimulating potency, was the first breakthrough in terms of improved potency. BAY 41-2272, in contrast to YC-1, is a highly selective sGC stimulator with no significant inhibition of PDEs. Further research resulted in the identification of BAY 41-8543(heme dependent stimulator of sGC), which has a threefold increase in potency.

2.1.1 Discovery of Riociguat

BAY 41-2272 and BAY 41-8543 had limited metabolic stability and oral bioavailability in rats, and BAY 41-2272 inhibited and induced cytochrome P450 (CYP) enzymes. Despite these limitations, these compounds were utilized as instruments in various pharmacological investigations to research this emerging class of medications.



Cinaciguat

BAY 41-2272 and BAY 41-8543 metabolite identification studies revealed oxidative metabolism at the cyclopropyl and morpholino substituents, respectively. In vitro, riociguat potently stimulated purified recombinant sGC and demonstrated the typical profile of sGC stimulators: strong synergistic enzyme stimulation when combined with NO-releasing agents and critical dependency on the presence of the reduced prosthetic haem moiety, thereby bypassing the need for endogenous NO production and increasing cGMP levels via a mechanism distinct from that of PDE5is.

As a result, sGC stimulators like riociguat provide a novel approach to increasing NO-mediated cGMP synthesis for the treatment of cardiopulmonary diseases

2.1.2 Discovery and development of Vericiguat

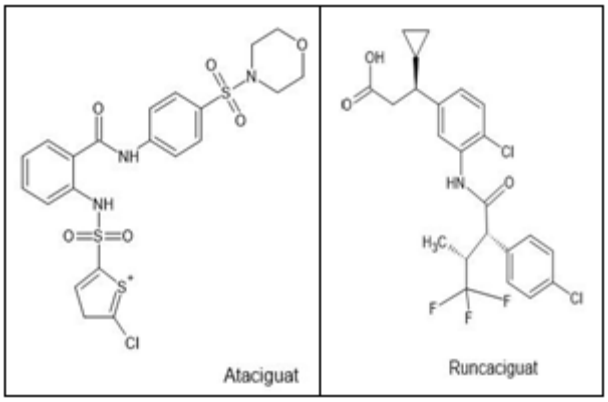
Vericiguat was created to identify orally bioavailable sGC stimulators with a longer duration of action than riociguat to support a profile that allows for once-daily oral dosing and less oxidative metabolism to lower interaction potentials. Riociguat has a moderate half-life in various animal species, which translated into a three-times-daily dosing regimen in patients. The strategy was to improve riociguat's metabolic stability, which is primarily catalyzed by CYP1A1, but also by CYP3A4, CYP3A5, and CYP2J2, and thus reduce blood clearance to achieve a longer half-life while maintaining potency. Vericiguat had the best overall PK profile in these studies, with low clearance and a long half-life in different species, as well as high oral bioavailability. Vericiguat also had no inhibitory effects on major CYP isoforms. Vericiguat was chosen as a clinical candidate after extensive preclinical drug metabolism and pharmacokinetics (DMPK) studies. Vericiguat had pronounced effects on the cardiovascular system ex vivo on blood vessels and the heart due to its mode of action and pharmacological properties. Vericiguat reduced coronary perfusion pressure in an isolated rat heart preparation while not affect heart rate or contractility. Additional research with vericiguat and other sGC stimulators in animal models of hypertension, heart failure, and kidney disease found dose-dependent anti-fibrotic and organ-protective properties consistent with the sGC stimulator mode of action.

SOCRATES-REDUCED was a dose-finding study that looked at adding vericiguat to standard HF therapy in adult subjects with CHF and reduced EF (defined as EF 45%) after clinical stabilization after a worsening HF event. The study's goal was to determine the optimal dose of vericiguat for Phase III that could be used in addition to standard HF therapy by characterizing its efficacy, safety, tolerability, and PK/pharmacodynamic (PD) effects and detecting a dose-response relationship.

2.2 sGC Activators: Mode of Action and Development

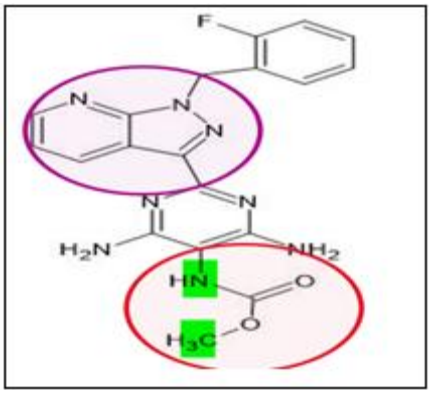
In 1997, ultra-high-throughput screening (uHTS) revealed a distinct class of compounds from sGC stimulators, the NO- and haem-independent sGC activators, as well as an unexpected drug target, the dysfunctional sGC. Cinaciguat is an example of a sGC activator, which was discovered after the first uHTS screening hit, followed by optimisation via chemical synthesis of approximately 1000 compounds. sGC-overexpressing CHO reporter cell line containing

recombinant sGC, a cGMP-sensitive cation channel, and aequorin was used to study uHTS. Activators of sGC bind to the unoccupied haem-binding domain and activate the haem-free oxidised form of sGC, increasing cGMP synthesis. As a result, a new drug target and a new class of compounds were discovered. Cinaciguat (BAY 58-2667) (Figure 4) was used in vitro, in vivo, in healthy volunteers, and in patients with acute decompensated HF (ADHF) to establish this new pharmacological principle. Cinaciguat's efficacy profile was investigated in various in vivo models of MI, chronic renal failure, arterial hypertension and PH, and CHF.



Anthranilic acid derivatives, a novel structural class of compounds, were also found to activate the oxidized and/or haem-free forms of sGC. Ataciguat is one of the best-described examples. The pharmacological efficacy of high-dose ataciguat and S-3448 in various in vivo models of atherosclerosis and peripheral arterial occlusive disease was demonstrated; however, ataciguat demonstrated limitations in early clinical phases, and further development was halted. Bayer also published monocarboxylic acids with novel structural features in order to improve their DMPK profile, as well as lower MW 3-phenylpropionic acid congeners containing the new sGC activator runcaciguat (BAY 1101042).

3. Conclusion



SAR Conclusions
The above structure is of vericiguat.

The modification of the central ring enhances the sGC stimulation effect and reduces CL.

The change of carbamate enhances the sGC stimulating effect, but for extending the half-life is not preferred.

Keeping the N on the carbamate unsubstituted andthe terminal methyl group isrequired for prolonged metabolism.

Acknowledgment
I'm thankful for my lecturer for supporting me to excel in my knowledge research.

References

[1] Grzegorz Grześk, Adrianna Witczyńska, Magdalena Węglarz, Łukasz Wołowiec, Jacek Nowaczyk, Elżbieta Grześk, Alicja Nowaczyk, Soluble Guanylyl Cyclase Activators—Promising Therapeutic Option in the Pharmacotherapy of Heart Failure and Pulmonary Hypertension, Molecules, 10.3390/molecules28020861, **28**, 2, (861), (2023).

[2] Cordwin DJ, Berei TJ, Pogue KT. The Role of sGC Stimulators and Activators in Heart Failure With Reduced Ejection Fraction. J Cardiovasc Pharmacol Ther. 2021 Nov;26(6):593-600. doi: 10.1177/10742484211042706. Epub 2021 Sep 6. PMID: 34487435.

[3] Kansakar S, Guragain A, Verma D, Sharma P, Dhungana B, Bhattarai B, Yadav S, Gautam N. Soluble Guanylate Cyclase Stimulators in Heart Failure. Cureus. 2021 Sep 6;13(9):e17781. doi: 10.7759/cureus.17781. PMID: 34659992; PMCID: PMC8494752.

[4] 2013 ACCF/AHA guideline for the management of heart failure: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Yancy CW, Jessup M, Bozkurt B, et al. *Circulation.* 2013; 128:1810–1852. [PubMed] [Google Scholar]

[5] 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Ponikowski P, Voors AA, Anker SD, et al. *Eur J Heart Fail.* 2016; 18:891–875. [PubMed] [Google Scholar]

[6] Heart failure with reduced ejection fraction: a review. Murphy SP, Ibrahim NE, Januzzi JL Jr. *JAMA.* 2020; 324:488–504. [PubMed] [Google Scholar]

[7] 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Yancy CW, Jessup M, Bozkurt B, et al. *Circulation.* 2017; 136:0–61. [PubMed] [Google Scholar]

[8] Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. GBD 2017 Disease and Injury Incidence and Prevalence

Collaborators. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC6227754/ *Lancet.* 2018;392:1789–1858. [PMC free article] [PubMed] [Google Scholar]

[9] Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Virani SS, Alonso A, Benjamin EJ, et al. *Circulation.* 2020;141:0–596. [PubMed] [Google Scholar]

[10] Heart failure with preserved, borderline, and reduced ejection fraction: 5-year outcomes. Shah KS, Xu H, Matsouaka RA, et al. *J Am Coll Cardiol.* 2017; 70:2476–2486. [PubMed] [Google Scholar]

[11] 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT) Galiè N, Humbert M, Vachiery JL, et al. *Eur Heart J.* 2016; 37:67–119. [PubMed] [Google Scholar]

[12] cGMPsignalling: from bench to bedside. Conference on cGMP generators, effectors and therapeutic implications. Feil R, Kemp-Harper B. *EMBO Rep.* 2006;7:149–153. [PMC free article] [PubMed] [Google Scholar]

[13] Shattuck lecture. Nitric oxide and cyclic GMP in cell signaling and drug development. Murad F. *N Engl J Med.* 2006;355:2003–2011. [PubMed] [Google Scholar]

[14] From molecules to patients: exploring the therapeutic role of soluble guanylate cyclase stimulators. Sandner P. *Biol Chem.* 2018;399:679–690. [PubMed] [Google Scholar]

[15] The natriuretic peptides system in the pathophysiology of heart failure: from molecular basis to treatment. Volpe M, Carnovali M, Mastromarino V. *Clin Sci (Lond)* 2016;130:57–77. [PMC free article] [PubMed] [Google Scholar]

[16] Physiological activation and deactivation of soluble guanylate cyclase. Horst BG, Marletta MA. *Nitric Oxide.* 2018;77:65–74. [PMC free article] [PubMed] [Google Scholar]

[17] Discovery of stimulator binding to a conserved pocket in the heme domain of soluble guanylyl cyclase. Wales JA, Chen CY, Breci L, et al. *J Biol Chem.* 2018;293:1850–1864. [PMC free article] [PubMed] [Google Scholar]

[18] Mechanisms of nitric oxide independent activation of soluble guanylyl cyclase. Schmidt P, Schramm M, Schröder H, Stasch JP. *Eur J Pharmacol.* 2003; 468:167–174. [PubMed] [Google Scholar]

[19] Oxidative stress and inflammation in the evolution of heart failure: from pathophysiology to therapeutic strategies. Aimo A, Castiglione V, Borrelli C, et al. *Eur J Prev Cardiol.* 2020; 27:494–510. [PubMed] [Google Scholar]

[20] Nitric oxide and peroxynitrite in health and disease. Pacher P, Beckman JS, Liaudet L. *Physiol Rev.* 2007;87:315–424. [PMC free article] [PubMed] [Google Scholar]

[21] Angiotensin-neprilysin inhibition versus enalapril in heart failure. McMurray JJ, Packer M, Desai AS, et al. *N Engl J Med.* 2014;371:993–1004. [PubMed] [Google Scholar]

[22] Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. Cuffe MS, Califf RM, Adams KF Jr, et al. *JAMA.* 2002; 287:1541–1547. [PubMed] [Google Scholar]

[23] Effects of low-dose oral enoximone administration on mortality, morbidity, and exercise capacity in patients with advanced heart failure: the randomized, double-blind, placebo-controlled, parallel group ESSENTIAL trials. Metra M, Eichhorn E, Abraham WT, et al. *Eur Heart J.* 2009;30:3015–3026. [PMC free article] [PubMed] [Google Scholar]

[24] Effect of nesiritide in patients with acute decompensated heart failure. O'Connor CM, Starling RC, Hernandez AF, et al. *N Engl J Med.* 2011;365:32–43. [PubMed] [Google Scholar]

[25] Acute hemodynamic effects of riociguat in patients with pulmonary hypertension associated with diastolic heart failure(DILATE-1): a randomized, double-blind, placebo-controlled, single-dose study. Bonderman D, Pretsch I, Steringer-Mascherbauer R, et al. *Chest.* 2014;146:1274–1285. [PMC free article] [PubMed] [Google Scholar]

[26] Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction: the SOCRATES-REDUCED randomized trial. Gheorghiade M, Greene SJ, Butler J, et al. *JAMA.* 2015;314:2251–2262. [PubMed] [Google Scholar]

[27] Vericiguat in patients with worsening chronic heart failure and preserved ejection fraction: results of the soluble guanylate cyclase stimulator in heart failure patients with preserved EF (SOCRATES-PRESERVED) study. Pieske B, Maggioni AP, Lam CS, et al. *Eur Heart J.* 2017;38:1119–1127. [PMC free article] [PubMed] [Google Scholar]

[28] Effect of vericiguat vs placebo on quality of life in patients with heart failure and preserved ejection fraction: the VITALITY-HFpEF randomized clinical trial. Armstrong PW, Lam CS, Anstrom KJ, et al. *JAMA.* 2020;324:1512–1521. [PMC free article] [PubMed] [Google Scholar]

[29] Effect of praliciguat on peak rate of oxygen consumption in patients with heart failure with preserved ejection fraction: the CAPACITY HFpEF randomized clinical trial. Udelson JE, Lewis GD, Shah SJ, et al. *JAMA.* 2020; 324:1522–1531. [PMC free article] [PubMed] [Google Scholar]

[30] Vericiguat in patients with heart failure and reduced ejection fraction. Armstrong PW, Pieske B, Anstrom KJ, et al. *N Engl J Med.* 2020;382:1883–1893. [PubMed] [Google Scholar]

Author Profile

Nida Mirza, StudentI'm interested in QSAR studies of medicinal compounds and gaining profound knowledge regarding the synthesis of compounds.

Dr. M. Vijaya Bhargavi, Assistant Professor**,** Interested in Insilico screening, Molecular Docking, Synthesis of Novel Heterocyclic Compounds.