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A SYSTAMIC REVIEW ON SYNTHESIS OF VERICIGUAT & IT'S PHARMACOLOGICAL ACTION

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ABSTRACT

Synthesis of **VERICIGUAT(**methyl N-[4,6-diamino-2-[5-fluoro-1-[(2-fluorophenyl)methyl]pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl]carbamate**)** which is used in heart failure disease because the significant morbidity and mortality in cases with heart failure HF), specially in the most advanced forms of the complaint, justify the need for new remedial options. In the last time, the soluble guanylate cyclase(sGC) stimulator, vericiguat, has accentuate the medical profession following the report of reduced clinical issues in cases with worsening habitual HF(WCHF)

KEY WORDS

Soluble guanylate cyclase (SGC), Heart failure, Vericiguat, Nitro oxide

INTRODUCTION

Vericiguat is a pyrazolopyridine that is 5-fluoro-1H-pyrazolo[3,4-b]pyridine in which at the position 1 amino hydrogen has been substituted by a 2-fluorobenzyl group and the hydrogen at position 3 position has been substituted by a 4,6-diamino-5-[(methoxycarbonyl)amino]pyrimidin-2-yl group. [15] Vericiguat is a soluble guanylate cyclase (SGC) direct stimulant that is used to treat systolic heart failure and lower mortality and hospitalization rates. SGC enzymes are intracellular enzymes present in vascular smooth muscle cells (among other cell types) that catalyze the synthesis of cyclic guanosine monophosphate (cGMP) in response to activation by nitric oxide (NO), and are an important part of the NO-SGC-cGMP signaling pathway that helps to regulate the cardiovascular system. These diverse cellular effects have linked deficiencies in cyclic GMP production (primarily due to insufficient NO bioavailability) to the pathogenesis of various cardiovascular diseases. Cyclic GMP functions as a second messenger, activating a number of downstream signaling cascades that elicit a broad variety of effects.[15]

CHEMICAL STRUCTURE

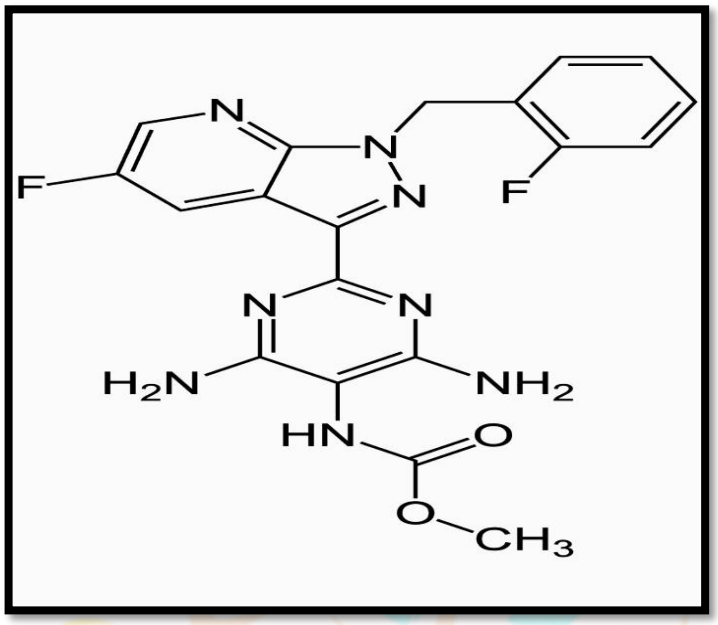

Fig. 1. Structure of vericiguat

3D STRUCTURE:-

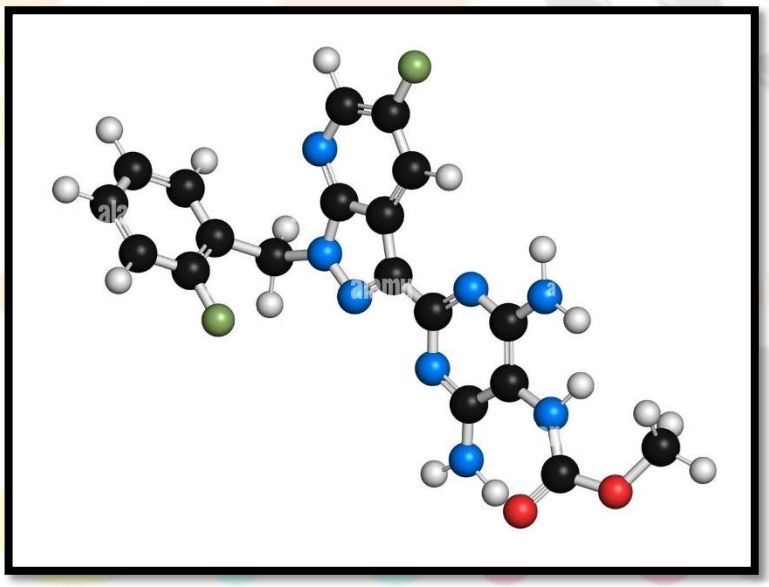

Fig. 2. 3D structure of vericiguat

PHYSICOCHEMICAL PROPERTIES

Vericiguat, a white to yellowish powder, is practically insoluble in 2-propanol but is freely soluble in dimethyl sulfoxide, marginally soluble in acetone, very little soluble in ethanol, acetonitrile, methanol, and ethyl acetate.[5]

Vericiguat 2.5 mg, 5 mg, or 10 mg film-coated tablets for oral administration are offered under the brand name VERQUVOTM.[5]

Croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate are among the inactive components found in tablets.

Titanium dioxide, talc, and hypromellose are ingredients in the film coating. Ferric oxide red is also present in the tablet's film coating, which contains 5 mg of VERQUVO. Ferric oxide yellow is also present in the film coating of VERQUVO 10 mg tablets.[5]

- IUPAC NAME:- methylN-[4,6-diamino-2-[5-fluoro-1-[(2-fluorophenyl)methyl]pyrazolo[3,4-b]pyridin-3-yl]pyrimidin-5-yl]carbamate.
- MOLECULAR FORMULA:- $C_{19}H_{16}F_2N_8O_2$
- MOLECULAR WEIGHT:- 426.38
- MONOISOTOPIC MASS:- 426.136414 Da
- MELTING POINT:- 250~260 ℃. 255 ℃.
- BOILING POINT:- 535.9±50.0 °C at 760 mmHg
- DENSITY:- 1.6±0.1 g/cm^3
- VAPOUR PRESSURE:- 0.0±1.4 mmHg at 25°C
- INDEX OF REFRACTION:- 1.736
- MOLAR REFRACTIVITY:- 104.8±0.5 cm3
- ENTHALPY OF VAPORIZATION:- 81.2±3.0 kJ/mol
- #H BOND ACCEPTORS:- 10
- #H BOND DONORS:- 5
- #FREELY ROTATING BONDS:5

SYNTHESIS OF VERICIGUAT:-

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.

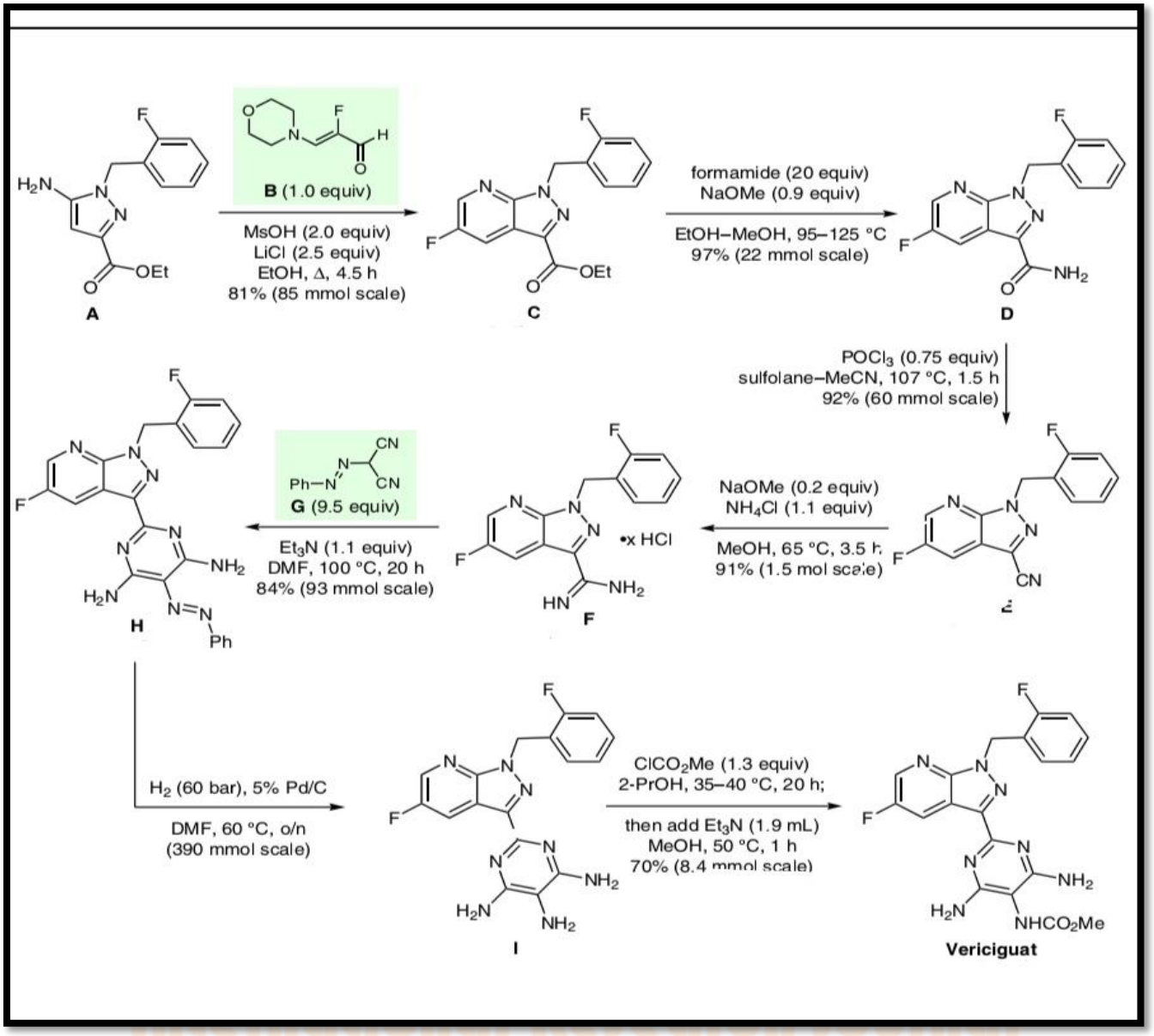

Fig. 3. Synthesis of vericiguat

MECHANISM OF ACTION:-

There are two types of guanylate cyclase: soluble guanylate cyclase (sGC), a receptor for nitric oxide, and transmembrane guanylate cyclase, a receptor for natriuretic peptides. By activating guanosine triphosphate to cyclic guanosine monophosphate (cGMP), nitric oxide and natriuretic peptides indirectly raise phosphokinase G (PKG) levels through sGC. Cellular hyperpolarization and cardiac muscle relaxation are brought on by phosphokinase G. Reactive oxygen species produced by the endothelium lower nitric oxide levels in patients with cardiovascular risk factors and inactivate sGC by eliminating the heme group, which results in decreased PKG and impaired muscle relaxation, which causes stiffness. As a result of the monocytes' production of transforming growth factor-beta, which changed fibroblasts into myofibroblasts, the heart muscle stiffened and formed collagen.[15, 16]

Clinical evidence supports the clinical benefits of using nitric oxide generators to treat heart failure, but tolerance can set in. Additionally, the reactive oxygen species lessen the soluble guanylate cyclase's sensitivity to nitric oxide. **The**

soluble guanylate cyclase stimulators work by increasing soluble guanylate cyclase activity without nitric oxide and by making sGC more sensitive to endogenous nitric oxide. [15, 16]

Without nitric oxide's assistance, vericiguat promotes soluble guanylate cyclase, which then activates the cGMP pathway. Additionally, it stabilizes nitric oxide binding to the binding site, making soluble guanylate cyclase more sensitive to nitric oxide. Vericiguat, in other words, restores cyclic guanosine monophosphate in the presence of oxidative stress and low nitric oxide.[3, 4]

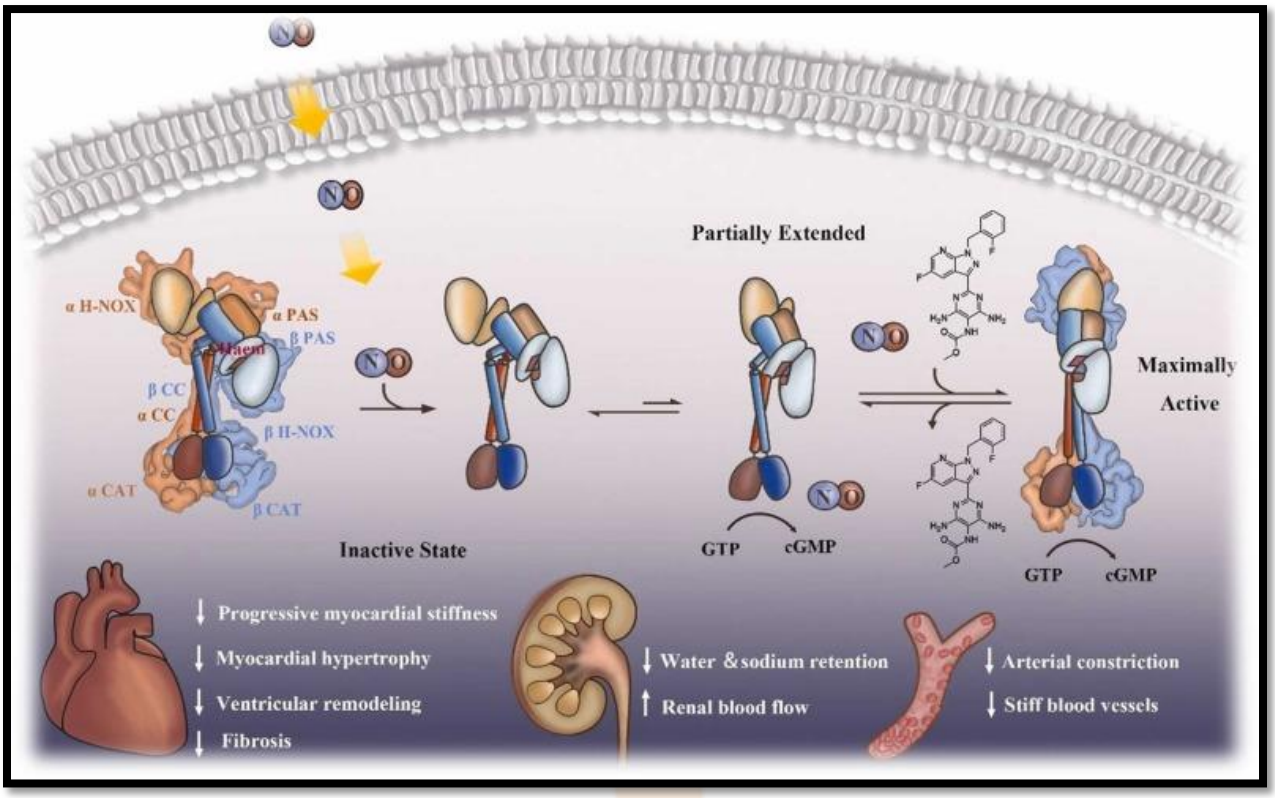

Fig. 4. Mechanism action of vericiguat

PHARMACOKINETIC:-

Vericiguat has a 93% bioavailability rate when taken with meals. Vericiguat's AUC (area under the curve; total drug exposure over time) rises when food is consumed. Vericiguat has a strong affinity for albumin, with a plasma protein binding rate of 98%. The volume of distribution (Vd) is typically 44 liters on average. Vericiguat is predominantly metabolized by the enzymes UGT1A9 (uridinediphosphate-glucuronosyltransferase) and UGT1A1 to an inactive metabolite. 5% of vericiguat's metabolism is carried out by the cytochrome P450 system.[10]

Excretion: In patients with heart failure, the half-life is 30 hours. The clearance rate is about 1.6 L/h. Vericiguat is mostly eliminated in urine (53%) as an inactive metabolite. Additionally, vericiguat is eliminated in the feces (43% of it unaltered).[21]

PHARMACODYNAMIC:-

Vericiguat induces the relaxation of vascular smooth muscle and vasodilation by directly triggering the increased production of intracellular cyclic guanosine monophosphate (cGMP). Vericiguat has a half-life that is rather long (30h), allowing for once-daily dosage. Vericiguat has been used in animal reproduction studies to show the potential for embryo-fetal toxicity when it is administered to pregnant females. When vericiguat was administered to pregnant rabbits during organogenesis, defects in major vessel and heart formation, as well as spontaneous

abortions/resorptions, were observed. Before starting vericiguat therapy, the chance of pregnancy should be ruled out, and appropriate contraception should be used throughout therapy and for a month after treatment ends.[11]

USE:-

Vericiguat is used to lower the risk of hospitalization and death in some adult patients with heart failure. The drug Vericiguat belongs to the group of drugs known as soluble guanylate cyclase (sGC) stimulators. In order to facilitate easy blood flow, it acts by relaxing the blood vessels in the lungs. [8]

CONCLUSION:-

In conclusion, the findings of the four research were consistent. The drug's promising safety and tolerability profile was demonstrated in the two SOCRATES phase II trials.

In addition, the VICTORIA study found a statistically significant 10% decrease in the composite endpoint of CV mortality and HFH in HFrEF patients, which was corroborated by the SOCRATES-REDUCED trial findings. However, vericiguat failed to demonstrate a meaningful difference between the intervention group taking the medication and the placebo group in the studies that included patients with HFpEF (VITALITY and SOCRATES-PRESERVED trials). Accordingly, it is suggested that vericiguat only be used for HFrEF patients whose SOC is insufficient and who consequently experience deterioration based on these (mainly consistent) outcomes.

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