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A BRIEF REVIEW ON SYNTHESIS AND BIOLOGICAL ACTIVITY OF RANOLAZINE

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- **ABSTRACT**

Currently approved as a second-line treatment for chronic stable angina pectoris in both the US and Europe, ranolazine is a derivative of Piperazine. Chemically defined as N(6,2dimethylphenyl)-2-(4-2-hydroxy-3-(2-methoxyphenoxy)propyl)piperazin-1-yl)acetamide, ranolazine is a racemic combination. Ranolazine belongs to a group of drugs known as anti-angina drugs. Usually, this medication is taken in combination with other medications. It can be taken either on its alone or in combination with calcium channel blockers, beta-blockers, angiotensin receptor blockers, anti-platelet medications, and nitrates. Many medicinal chemists are interested in investigating the entity's diverse pharmacological and biological potentials. Because of its strong biological action, ranolazine is a key component in medicinal chemistry. The synthetic process utilised to prepare ranolazine last year is revised in this article and has demonstrated biological.

- **KEYWORDS:**

Ranolazine, Synthesis, Anti-anginal, Biological activity, structure

- **Introduction:**

A novel and distinctive antianginal medication called ranolazine has received approval to treat persistent, stable angina pectoris.[1] The drug is administered in a sustained-release formulation. Approvals (FDA 2006, EMA 2008) for chronic angina N-(2,6-dimethylphenyl)-4-(2-hydroxy-3-(2-methoxyphenoxy)propyl), also known as 1-Piperazineacetamide, can be synthesised using a variety of techniques. using its formal name Purification, drying, and milling are all steps in the three-step synthetic process that produces ranolazine.[9]Ranolazine is a solid that ranges from white to off-white and is barely soluble in water. At pH values below 4.4, it is easily soluble in buffered aqueous solutions and soluble in a number of organic solvents. When obtained as a racemic mixture, ranolazine displays a chiral centre and contains equal amounts of the (R) and (S) enantiomers.[2] Sudden chest discomfort, also known as angina pectoris, is brought on by various stresses or when the heart does not receive enough oxygen. Millions of people worldwide suffer from chronic angina, a common cardiovascular ailment that significantly impairs daily activities while also causing significant disability.[3] A well-tolerated piperazine

derivative called ranolazine is used to treat this illness and provide relief from its painful and crippling effects.[18] Ranolazine is a promising anti-anginal medicine with a different mechanism of action from medications used to treat the same illness.[19] It is synergistic with calcium channel blockers, nitrates, antiplatelet therapy, lipid-lowering therapy, ACE inhibitors, and angiotensin receptor blockers.[8] It may also be administered concurrently with these medications. It has been researched as a monotherapy as well as in addition to other drugs used to treat irregular heartbeats,[10] and it is beneficial at preventing atrial fibrillation.

- **Structure:**

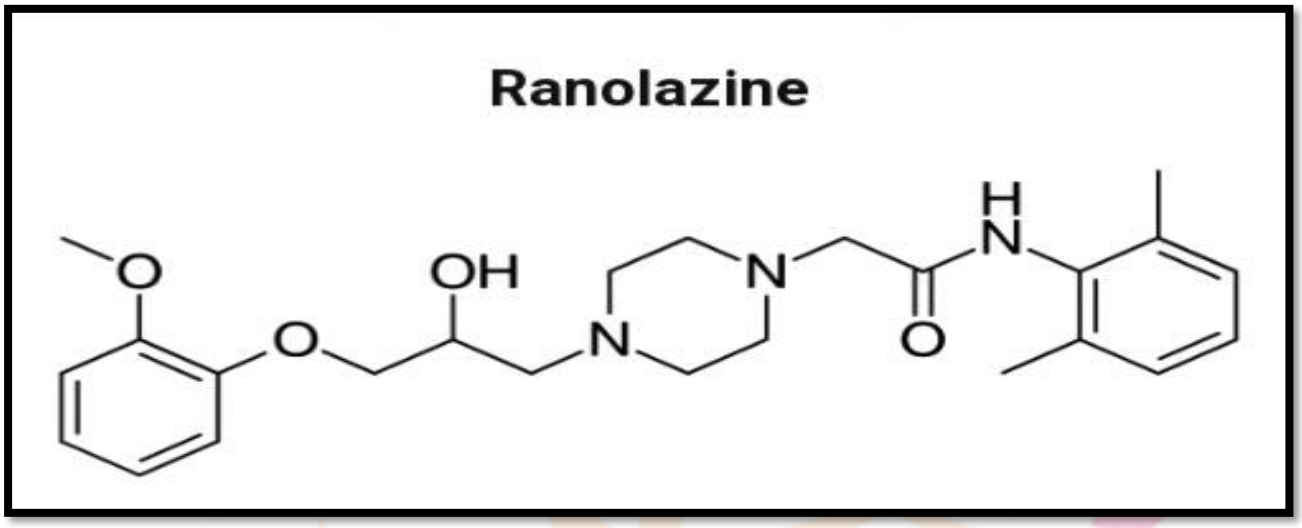


Fig.1 chemical structure of Ranolazine

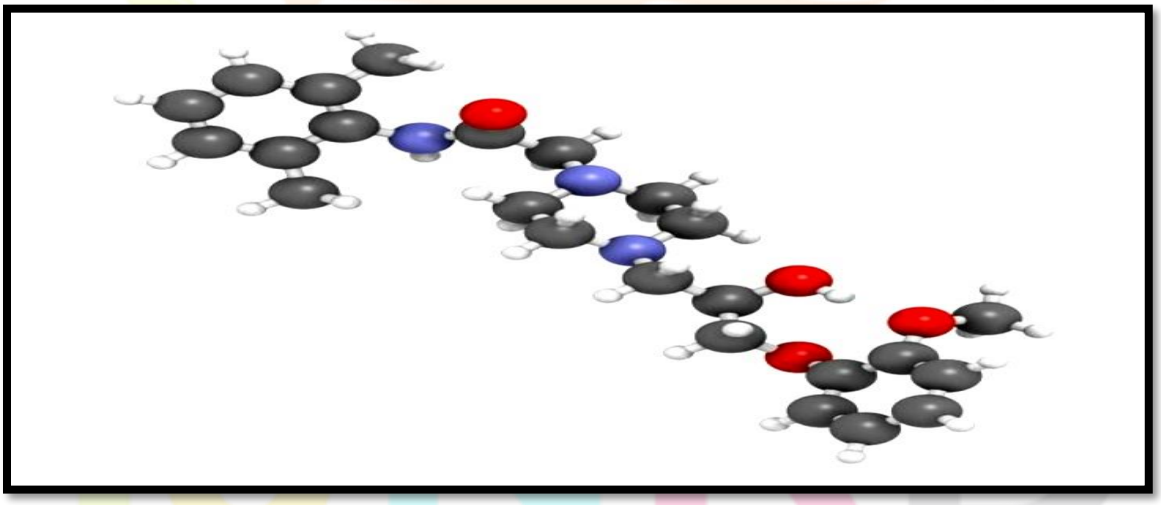


Fig.2 3D structure of Ranolazine

- **Physical and chemical properties:**
- IUPAC Name:N-(2,6-Dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy)-propyl is its IUPAC name.1-yl piperazine]Acetic acid
- Chemical Formula:C24H33N304
- Molar mass: 427.545 g mol−1
- Colour: off-white to white
- Point of boiling: 624.1°C
- Melting point: 166–166 °C
- Solubility: Its main solvents are methanol and dichloromethane. Very poorly soluble substances include Tetrahydrofuran, ethanol, acetonitrile, and acetone.[17] Only very weakly soluble substances include water, ethyl ether, isopropanol, toluene, and ethyl acetate.[3]

- Chirality: racemic mixture
- **Medicinal Use:**

Angina pectoris is treated with ranolazine.[13] It has the potential to be used in conjunction with β blockers, nitrates, calcium channel blockers, ACE inhibitors, lipid-lowering medication, antiplatelet therapy, and angiotensin receptor blockers.[4]

- **Synthesis of Ranolazine:**

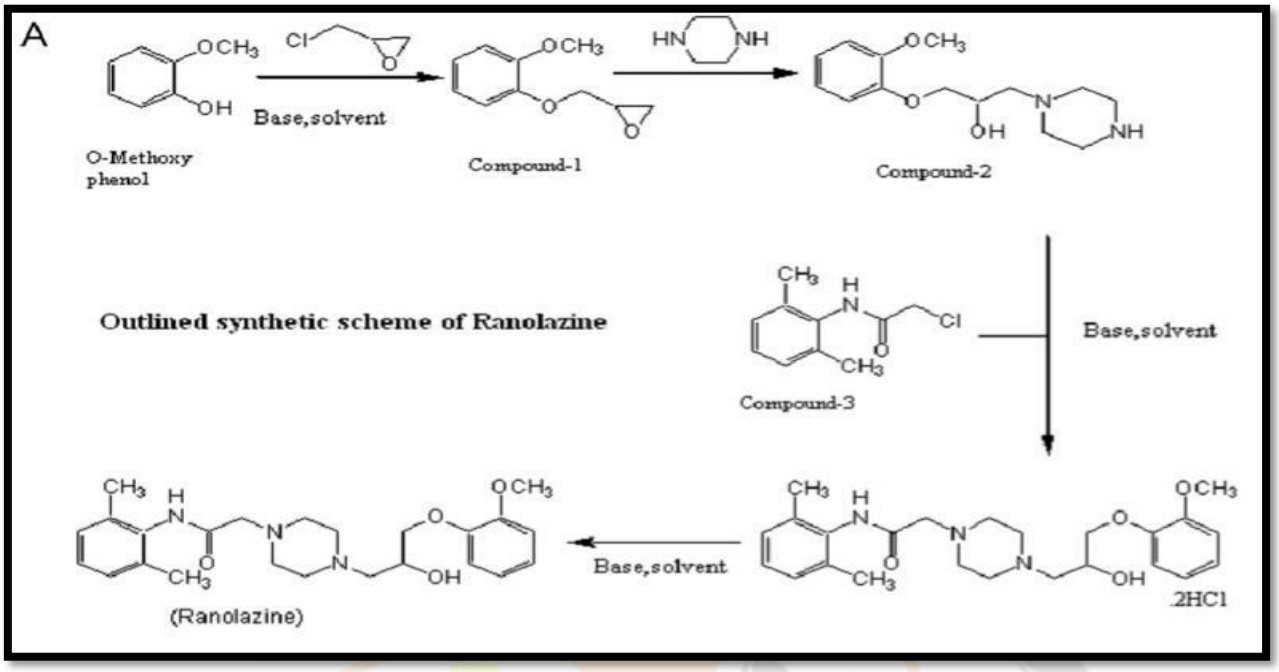


Fig.3 Synthesis of Ranolazine

Compound 1: 1-cyclopropoxy-2-methoxybenzene

Compound 2: 1-(2-methoxyphenoxy)-3-(piperazin-1-yl)-2ol

Compound 3:N –(2,6,2dimethylphenyl)-2-(4-(2-4-2-hydroxy-3 (2-methoxyphenoxy)propyl)piperazin-1-yl) acetamide

- **General Method of Preparation:**

Filled the R.B. flask with 1000 ml of water. Once added, 109 g of piperazine were dissolved by stirring. O-phosphoric acid was used to bring the pH between 5.0 and 5.5 after one to two hours of room-temperature stirring. After the reaction mass was filtered, the piperazine monophosphate monohydrate solid was separated and added to an R.B. flask holding 1000 ml of water. After adding 100 g of [(2,6-dimethylphenyl)-amino carbonyl methyl]chloride, the reaction mixture was heated for 7-8 hours at reflux temperature.[16] The reaction mixture was cooled to a temperature of 25–30°C, and a diluted sodium hydroxide solution was filtered to bring the pH down to 5.5–6.0. The filter was cleaned. Using 500 ml x 3 methylene chloride for extraction, and then further basified with a diluted sodium hydroxide solution. Washing the combined organic layer.[5]

Fig.4 Powder of Ranolazine

- **Biological activity of Ranolazine:**

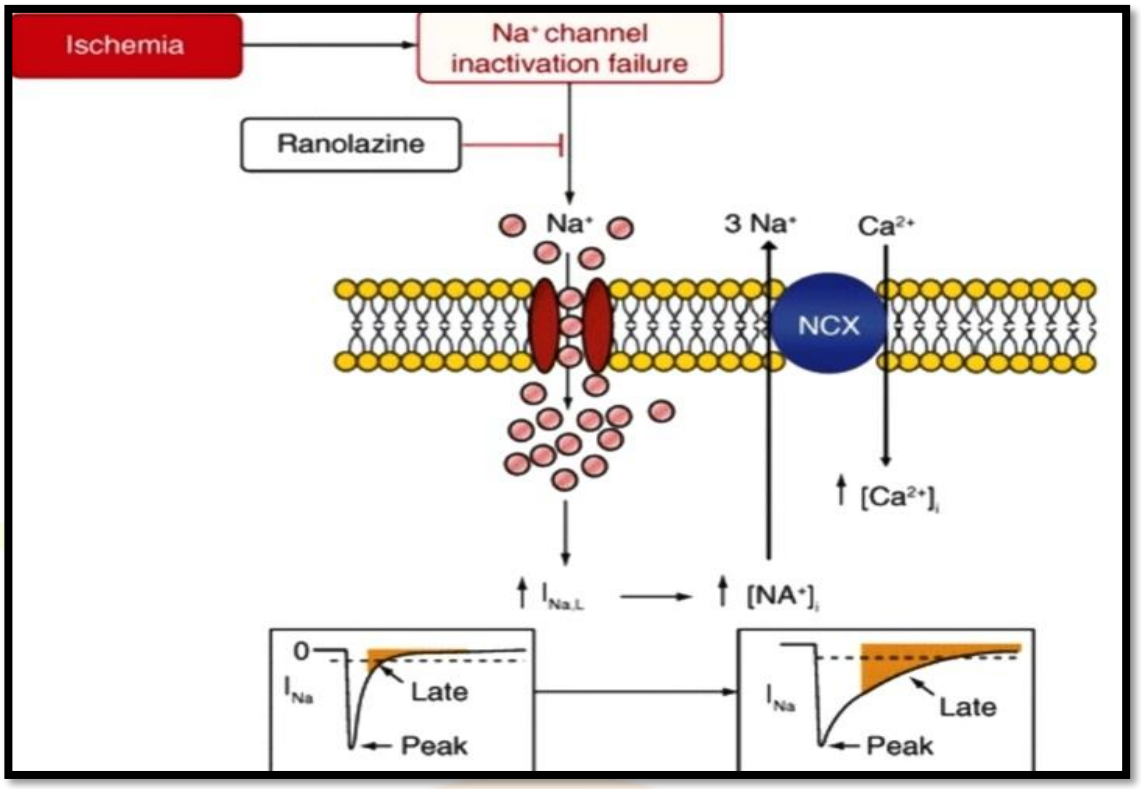
In vitro: It is discovered that ranolazine binds more firmly to the sodium channel's inactivated state than its resting state, with apparent dissociation constants of K(dr)=7.47 mM and K(di)=1.71 mM, respectively, underlying I(NaL). At 5 mM and 10 mM, ranolazine reversibly reduces the length of TCs and eliminates subsequent contracting.[6] In both the absence and presence of IK-blocking medications, ranolazine decreases the late component of INa and reduces the extension of action potential duration when late INa is elevated. The 13.6-fold increase in variability of APD generated by 10 nM ATX-II is reduced by 89% by ranolazine (10 mM).

IN VIVO: In canine left ventricular myocytes activated at 0.5 or 0.25 Hz, ranolazine dramatically and reversibly shortens the action potential duration (APD) in a concentration-dependent manner. (Source:) When glucose's contribution to total ATP synthesis in the working heart of rats is low (low Ca, high FA, with insulin), high (high Ca, low Fa, with pacing), or intermediate, ranolazine (10 mM) dramatically enhances glucose oxidation by 1.5 to 3 times. Similar increases in glucose oxidation are seen in rats' normoxic Langendorff hearts (high Ca, low FA; 15 mL/min) when exposed to ranolazine (10 mM). In reperfused ischemic working hearts, ranolazine considerably improves functional outcome, which is correlated with considerable increases in glucose oxidation.[6]

- **Mechanism Action Of Ranolazine:**

Ranolazine blocks a range of voltage-gated sodium channels in the cardiac muscle, preventing late or persistent inward sodium current (INa).[7]Reducing that current causes an increase in intracellular calcium levels to decrease. As a result, the heart wall becomes less tense, which lowers the amount of oxygen needed by the muscles.[12] IKr inhibition results in a prolonged ventricular action potential, which is the cause of ranolazine's QT-prolonging effect [8]

Fig.5 mechanism of action



Myocardial ischemia raises the late INa (INa,L) and prevents the cardiac Na+ channels from being inactivated. Through the reverse mode of the Na+-Ca2+ exchange, a rise in INa,L increases intracellular Na+ influx and intracellular Na+ concentration ([Na+]i), which in turn causes an increase in intracellular Ca2+ concentration ([Ca2+]i.trader (NCX). The end result is a rise in [Na+]i. and [Ca2+]i, which directly contributes to the pathophysiology of the anomalies that are evident in the ischemic heart in terms of mechanics, metabolism, and electrical function. It's interesting to note that INa,L also rises in other pathological circumstances (such as atrial fibrillation, type 3 long QT syndrome, left ventricular hypertrophy, and heart failure).Na+i stands for intracellular sodium; INa for inward sodium current; and NCX for sodium-calcium exchanger[17].

- **Contraindications:**

Drug Interactions provides information on several ranolazine contraindications that are associated with the drug's metabolism. Furthermore, ranolazine caused a modest increase in QT interval in certain individuals during clinical trials.[6] The FDA label warns physicians to watch out for this effect in their patients.[8] People with mild to severe liver disease should not use the medication since it increases the QT interval in the condition of liver malfunction.[12]

- **Side Effects:**

Constipation (10.9%) and dizziness (11.8%) are the most frequent adverse effects.[13]] Nausea and headache are among the additional negative effects.[14]

- **Drug Interactions:**

While there are some medications that should never be combined, there are other situations in which two distinct medications can be taken together despite the fact that there may be a risk of interaction.[15] The CYP3A enzyme is primarily responsible for ranolazine metabolism. It also prevents cytochrome CYP2D6, another metabolising enzyme.[8] Because of this, when the same patient takes medications that interact with those enzymes together with ranolazine, the doses of both need to be changed.It is not recommended to combine ranolazine with medications that substantially inhibit CYP3A, such as ketoconazole, clarithromycin, and nelfinavir. Ranolazine doses should be lowered for medications that are moderate CYP3A inhibitors, such as erythromycin, verapamil, and diltiazem. When used with ranolazine, medications that are metabolised by CYP2D6, such as tricyclic antidepressants, may need to be taken at lower dosages.

- **Conclusion:**

Interest in the electro-physiological effects of ranolazine has grown in the last few years. The current data supporting ranolazine's therapeutic role in the treatment of atrial fibrillation is compiled in this article. Arrhythmias of the ventricle in addition to its present antianginal function.Several modest clinical investigations have been conducted on the medication. The MERLIN-TIMI 36 trial provides the only multicenter randomized-control results in favour of its application as an antiarrhythmic medication. However, this study includes limitations relevant to large-scale data mining and was not intended to examine the antiarrhythmic effects of ranolazine; also, only individuals with coronary artery disease were examined. Finding out how well ranolazine works in nonischemic patients as an antiarrhythmic would be interesting. An especially positive fact.

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