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TO STUDY THE ANTIFUNGAL ACTIVITY OF ISAVUCONAZOLE

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ABSTRACT: :

A novel broad-spectrum triazole that is effective against molds, yeasts, and dimorphic fungi is called isavuconazole. In vitro, isavuconazole exhibits efficacy against the majority of medically significant fungus, such as species of Aspergillus, Candida, and Cryptococcus. This triazole has several benefits, such as an IV water-soluble formulation (which does not include cyclodextrin), good oral dosage form bioavailability, and consistent human pharmacokinetics. The US Food and Drug Administration has approved isavuconazole as a prodrug of isavuconazim, a more recent second-generation triazole antifungal. authorized for the management of invasive mucormycosis and aspergillosis. The activity spectrum of isavuconazole, is similar to the one of the polyene amphotericin B. However, because of these medications' inconsistent absorption, severe adverse effects, important drug interactions, and tendency toward bone resistance, their usage is frequently restricted. When treating invasive fungal infections, iavuconazole is a desirable alternative due to its outstanding pharmacokinetic qualities and safety.Their pharmacology, the field of chemistry, in vitro sensitivity, pharmacodynamics/pharmacokinetics, clinical efficacy, safety, tolerability, dosage, and administration are all summarized in this review.

KEYWORDS: Isavuconazole, Invasive fungal infections,Antifungal,Triazoles.

INTRODUCTION:

2015 saw the approval of isavuconazole (ISA), a novel triazole antifungal medication, for the treatment of insavie mucormycosis (IM) and invasive aspergillosis (IA) (1). In individuals with severe impairments and impaired immune systems, invasive fungal infections are the most common cause of morbidity and mortality (2). While all fungi have the capacity to produce invasive infections, Aspergillus and candida species are the most significant pathogens in regards to incidence and death. Both oral and intravenous forms of isavuconazole are available. Its characteristics include extensive tissue distribution, high (>99%) protein binding, and slow elimination, which permits once-daily treatment (3).The most often reported adverse effects are minor and confined in nature, and they include increased liver function tests, nausea, and diarrhea (4). Its potential for medication interactions seems to be smaller than that of voriconazole, although

it is comparable to other azole antifungals (5). There are currently ongoing or recently concluded comparative studies regarding the treatment of uncommon mold infections, invasive candidiasis, aspergillosis, and candidemia (6).Isavuconazole is a triazole antifungal of the second generation that exhibits strong in vitro action against a variety of invasive fungal species and opportunistic infections (7).Isavucinazole is presently being studied in phase 3 studies to treat IFIs caused by uncommon molds, as well as systemic candidiasis and aspergillosis (8).

Research has demonstrated that oral ISA can be administered in place of posaconazole (POS) in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) or at high risk for hematological disorders to prevent invasive fungal disease (IFD)(9).Furthermore, voriconazole (VOR) and ISA oral medicine or intravenously sequential oral delivery are equally effective in treating IA.Similarly, liposomal Aphotericin B (L-AmB) and its effectiveness in treating IM are similar in this regard (10).Antifungal drugs that are currently on the market towards the treatment of IFIs include flucytosine, azoles, polyenes, and enchinocandins (11).Among the azole class, the systemic application Triazoles, as opposed to polyenes, have a better side effect profile and are more tolerant, making them some of the most widely used antifungal medications (12).

Compared to voriconazole, isavuconazole has a wider range of activity, which includes most mucormycetes (13). It also has a once-daily dosing after the loading dose, linear pharmacokinetics, lower interpatient variability in exposure, water solubility (which eliminates the necessity for cyclodextrin in the through an IV formulation), and, lastly, fewer drug-drug interactions mediated by CYP enzymes (14).Isavuconazole is a mild inhibitor of CYP3A4 and is eliminated by it.Drug interactions or the CYP2C9 or CYP2C19 genotype do not affect exposure (15).

STRUCTURE OF ISAVUCONAZOLE:

As a prodrug of isavuconazole (BAL4815), isavuconazonium (BAL 8557) is soluble in water and has an ester moiety that connects it to isavuconazole via an N-(3-acetoxypropyl)-N-methylamino carboxymethyl group. The chemical name for isavuconazole is C22H17F25OS. When administered orally or intravenously, isavuconazonium rapidly cleaves into the active ingredient (isavuconazole) along with an inactive prodrug breakage product (BAL 8728).

Figure 1 shows the chemical structures of the prodrug, active drug, and cleavage product.

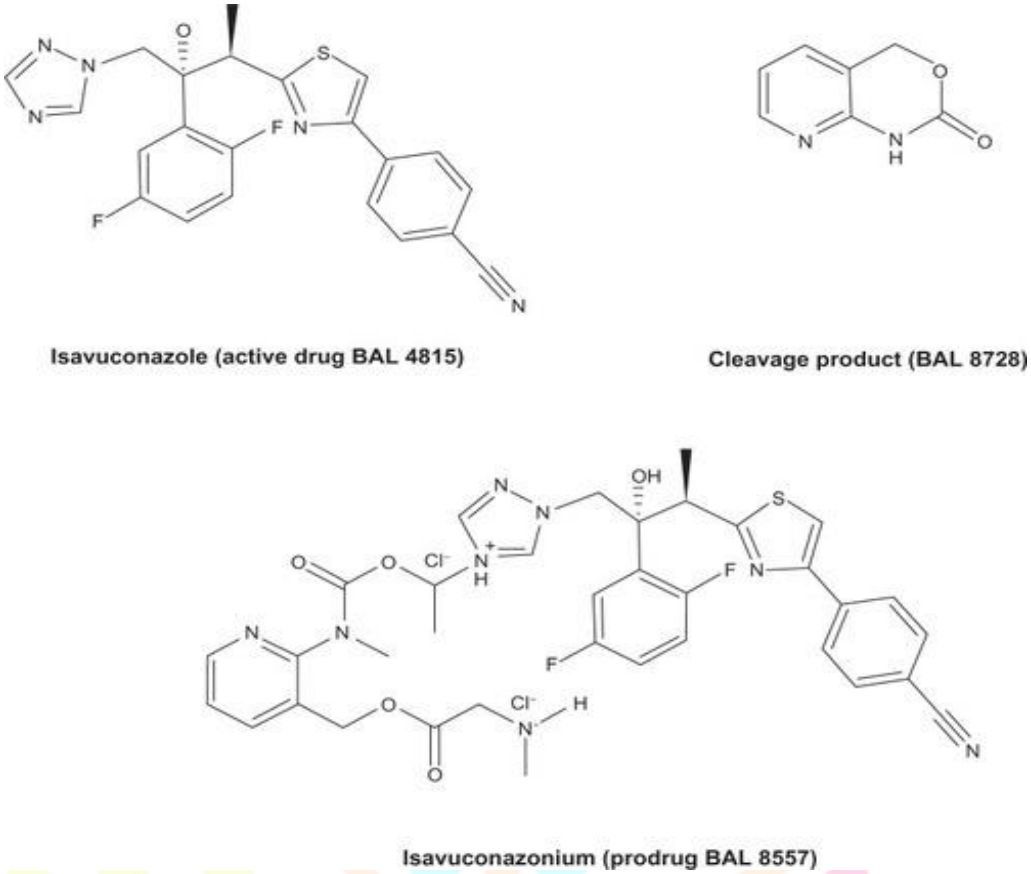


Fig 1:Chemical composition of the prodrug, active drug and cleavage product of isavuconazole

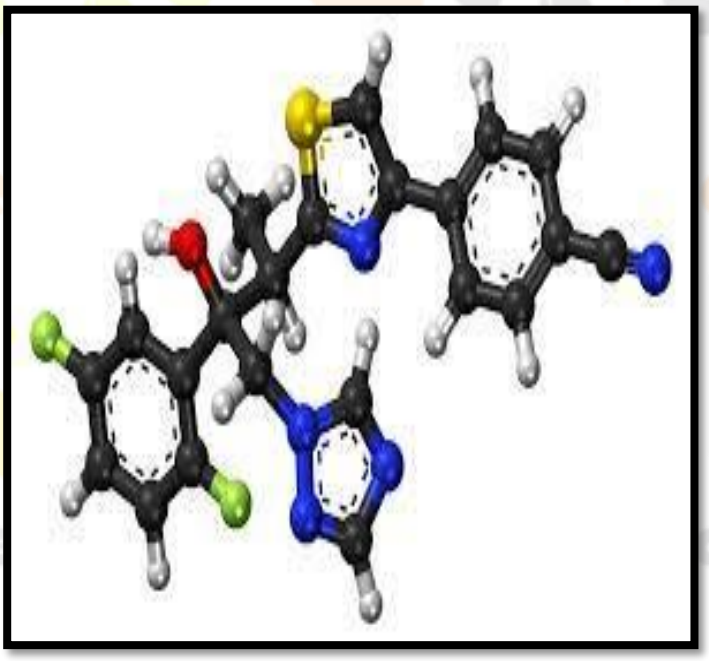
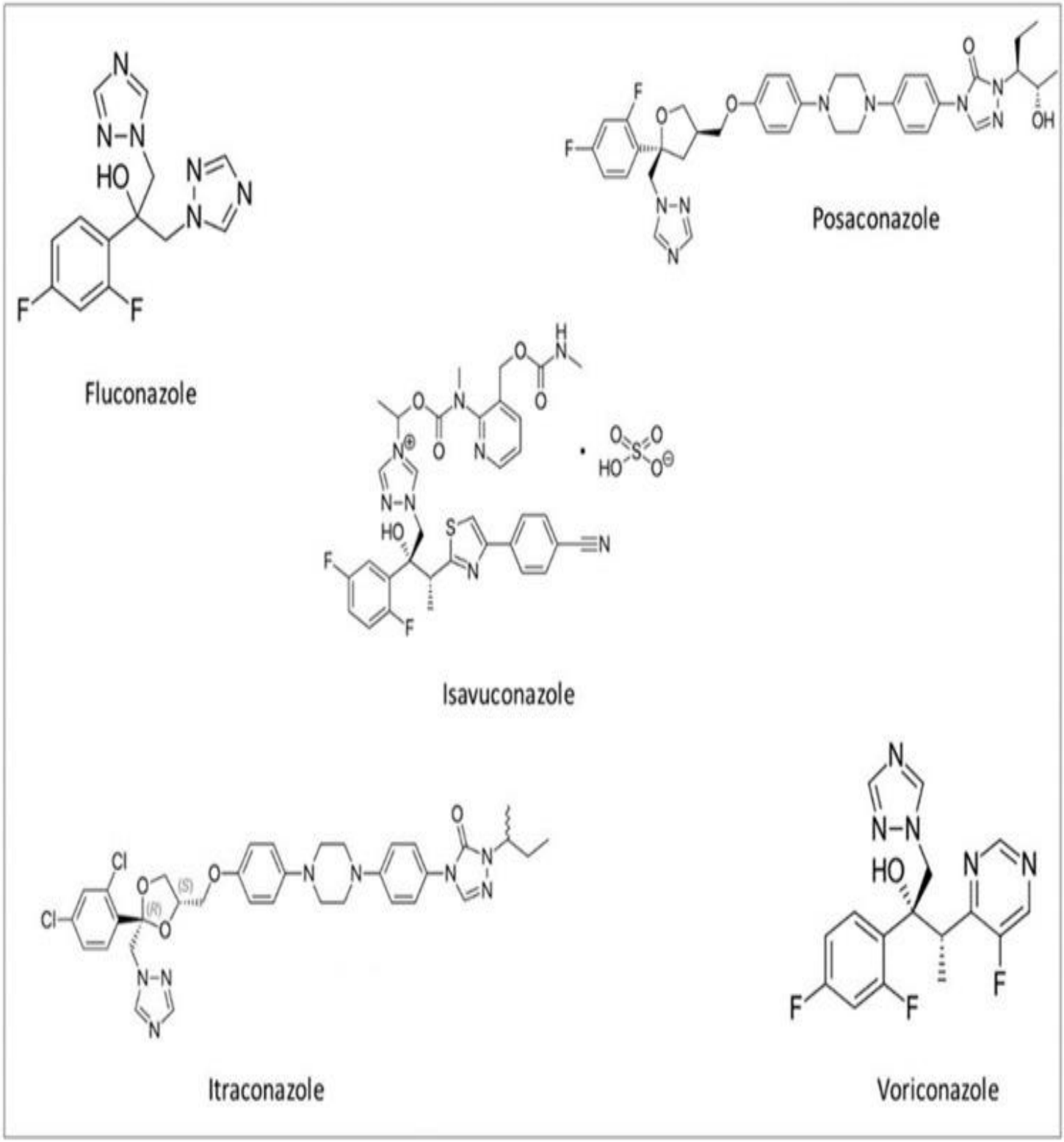


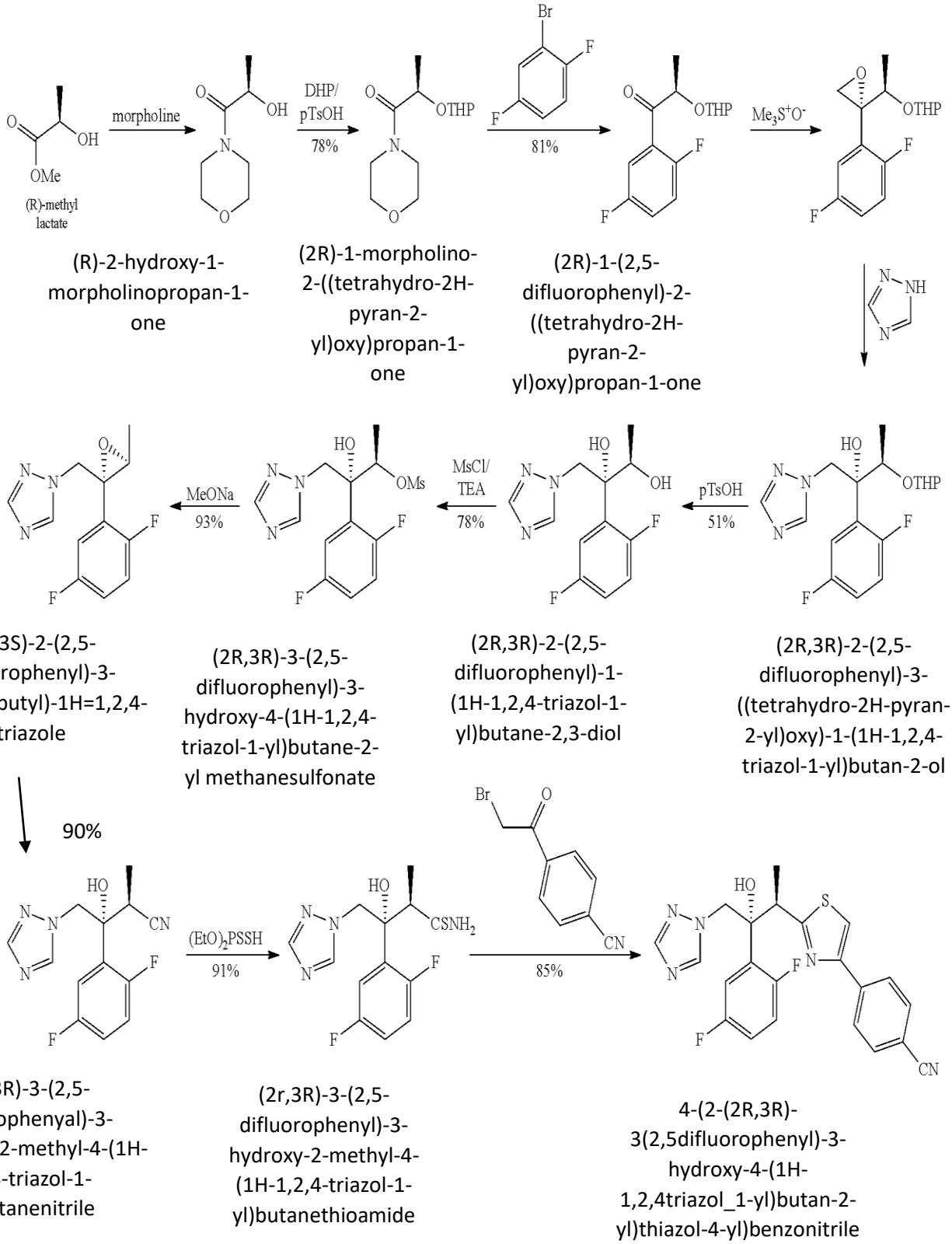
Fig2:3D structure of 4-{2-[(1R,2R)-(2,5-Difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-1,3-thiazol-4-yl}benzonitrile

Other derivatives of ISAVUCONAZOLE:



SYNTHESIS OF ISAVUCONAZOLE:

Scheme 1:



(R)-2-hydroxy-1-morpholinopropan-1-one

(2R)-1-morpholino-2-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-one

(2R)-1-(2,5-difluorophenyl)-2-((tetrahydro-2H-pyran-2-yl)oxy)propan-1-one

(2R,3R)-2-(2,5-difluorophenyl)-3-((tetrahydro-2H-pyran-2-yl)oxy)-1-(1H-1,2,4-triazol-1-yl)butan-2-ol

(2R,3R)-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)butane-2,3-diol

(2R,3R)-3-(2,5-difluorophenyl)-3-hydroxy-4-(1H-1,2,4-triazol-1-yl)butane-2-yl methanesulfonate

1-((3S)-2-(2,5-difluorophenyl)-3-methoxybutyl)-1H=1,2,4-triazole

(2S,3R)-3-(2,5-difluorophenyal)-3-hydroxy-2-2-methyl-4-(1H-1,2,4-triazol-1-yl)butanenitrile

(2r,3R)-3-(2,5-difluorophenyl)-3-hydroxy-2-methyl-4-(1H-1,2,4-triazol-1-yl)butanethioamide

4-(2-(2R,3R)-3(2,5difluorophenyl)-3-hydroxy-4-(1H-1,2,4triazol_1-yl)butan-2-yl)thiazol-4-yl)benzonitrile

PREPARATION METHODS OF ISAVUCONAZOLE :

(A) Isavuconazole preparation in an amorphous form :

Charged ethanol (250 ml), thioamide compound (25.0 gm), and 4-cyano phenacyl bromide (18.4 gm) in a flask with a circular bottom while stirring (16). At 70 °C, the reaction mixture was heated. After the reaction was finished, the solvent was extracted using vacuum distillation, and the reaction mass was then supplemented with 250 ml of water and 350 ml of ethyl acetate. After stirring the reaction mixture, a 10% sodium bicarbonate solution was added to bring the pH down to between 7.5 and 7. The organic layer was concentrated under vacuum to extract residue after the aqueous layer was discarded and cleaned with a 100 ml saturated sodium chloride solution. After the mixture used for the reaction was heated to 40°C to create uniform crystals, the residue was suspended in 250 milliliters of methyl tert-butyl ether. The reaction mass was then cooled to room temperature, filtered, and cleaned by using methyl tert-butyl ether. The product was separated and dried to produce a solid, pale yellowish product.

(B) Crystalline Isavuconazole Base Preparation:

250 millilitres of charged methylene dichloride and 25.0 grams of formula-II isavuconazole hydrobromide compound were added to a 1.0 litre flask and swirled. To obtain a clear solution, add a water-soluble solution of sodium bicarbonate to the reaction mass. After the layers were separated, the organic layer was cleaned using a saturated sodium chloride solution and a diluted hydrochloric acid solution. Ultimately, a vacuum was used to concentrate the organic layer to create the final product.

(C) Crystalline Isavuconazole Hydrobromide Preparation:

Indicted isopropanol alcohol (250 ml), 4-cyano phenacyl bromide (18.4 gm), and thioamide compound (25.0 gm) were added to a 1.0 L flask. Following the stirring and heating of the reaction mixture to 50 degrees Celsius, the resulted in material was passed through filters and washed with 25 milliliters of isopropanol alcohol. The off-white solid product is obtained by vacuum-drying the wet cake at 40°C for four to five hours.

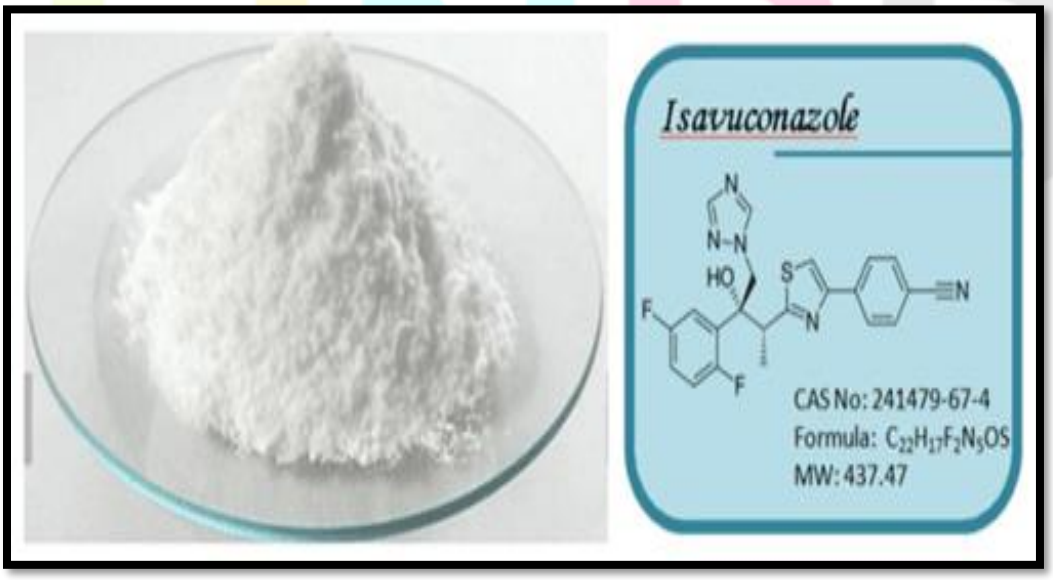


Fig3: powder form of isavuconazole

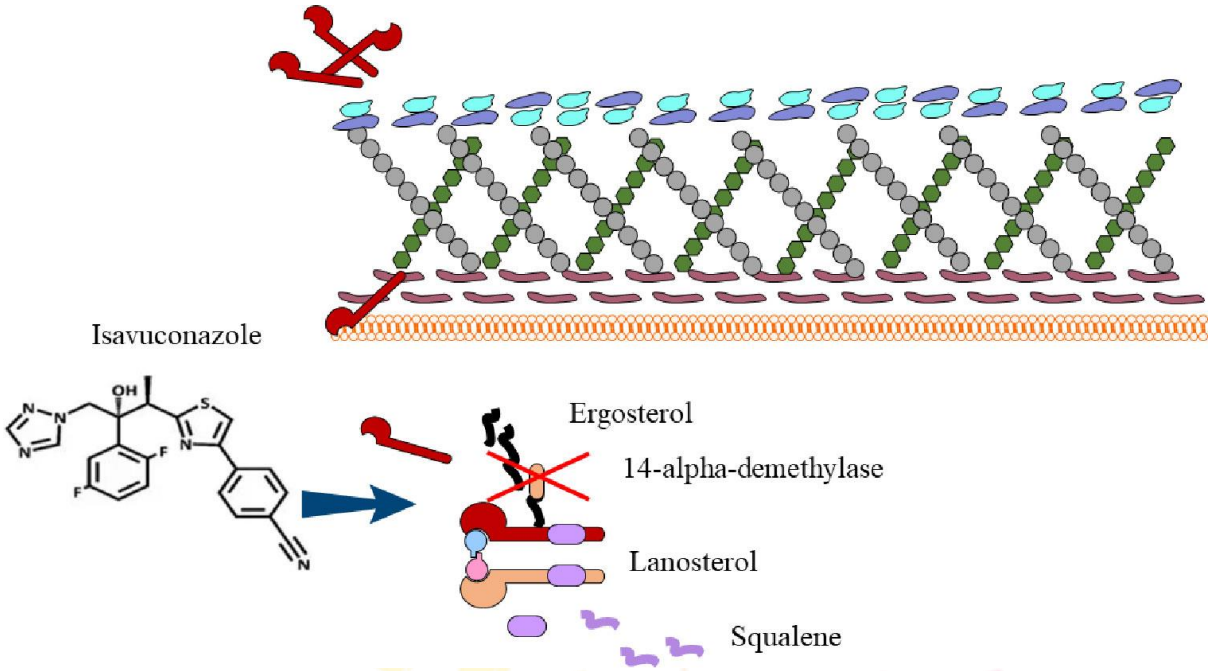
PHYSIOCHEMICAL PROPERTIES OF ISAVUCONAZOLE:

Characteristics	ISAVUCONAZOLE:
IUPAC Name	4-(2-(2R,3R)-3(2,5difluorophenyl)-3-hydroxy-4-(1H-1,2,4triazol_1-yl)butan-2-yl)thiazol-4-yl)benzonitrile
Molecular Formula	$C_{22}H_{17}F_2N_5OS$
Molecular Weight	437.2 g/mol
Melting Point	89-91 ^{0}C
Boiling Point	678 ^{0}C
Colour	White to Off White Powder
Solubility	Chloroform, methanol
Percentage Purity	98%
PKa Value	Approximately 3.7
Storage condition	Stored at room temperature between 20-25 ^{0}C
Synonyms	Cresemba, isavuconazonium (Sulfate)

MECHANISM OF ACTION:

Isavuconazole exhibits fungicidal properties by interfering with ergosterol's biosynthesis, a crucial element of the fungal cell membrane. The enzyme lanosterol 14-alpha-demethylase, which is dependent on cytochrome P-450 and facilitates the metabolism of lanosterol to ergosterol, is inhibited by it. By orienting its triazole ring to interact with a hemoglobin moiety at the bottom of the pocket for binding in the fungal CYP51 protein, the side arm of the active isavuconazole molecules facilitates increased affinity for the binding pocket . This clarifies isavuconazole's broad range of antifungal activity as well as any potential resistance cross-res to other triazoles . Toxic methylated sterol precursors including 14-α-methylated lanosterol, 4,14-dimethylzymosterol, and 24-methylenedihydrolanosterol accumulate within the fungal cytoplasm and change the function of the fungal membrane due to lanosterol 14-alpha-demethylase inhibition. Ergosterol depletion in the fungal cell membrane results in impaired fungus cell growth and replication , a reduction in the membrane's structural integrity and function, and ultimately fungal cell death. Isavuconazole inhibition has less of an effect on demethylation in mammalian cells.

Variations to the fungal cyp51A and cyp51B genes, which code to the targeted protein lanosterol 14-alpha-demethylase , result in a resistance mechanism and decreased susceptibility to isavuconazole. There are several other mechanisms that contribute to resistance, such as alterations in the sterol profile and increased fungal efflux pump activity.



PHARMACOLOGY

The active ingredient of isavuconazole, isavuconazonium sulfate, comes in intravenous and oral forms. In both formulations, the dosage strength of 372 mg of isavuconazonium sulfate is equivalent to 200 milligrams of isavuconazole, the active ingredient. There are 186 mg of isavuconazonium sulfate (100 mg isavuconazole) in each capsule. For oral and intravenous formulations, the suggested dosage schedule is 200 mg per day for two days after a loading dose of 600 mg, administered as 200 mg every eight hours .

Following an intravenous injection, the prodrug rapidly degrades into isavuconazole, the active ingredient, as well as an inactive cleavage product. The prodrug and the non-active cleavage product's plasma concentrations in healthy adults are only detectable throughout the infusion through the IV and disappear 30 minutes later. After oral administration, the prodrug and cleavage product are not detectable in plasma; instead, plasma concentrations of the active compound reach their maximum concentrations (Cmax) within two to three hours.

Pharmacokinetics of isavuconazole show both dose-proportional and linear behavior in healthy adult volunteers. Isavuconazole has an oral bioavailability of 98%. Eating has no effect on isavuconazole absorption. Isavuconazole serum concentrations exhibit low intersubject variability along with excellent bioavailability. At steady state, the Cmax in healthy volunteers was 2.5 ± 1.0 µg/mL. Similarly pharmacokinetic properties profiles for intravenous isavuconazole were observed in a small number of patients with neutropenia and acute myeloid leukemia.

Isavuconazole is >99% protein bound, has a long terminals half-life of 100–130 hours, and a wide volume of distribution. Tissue levels continue long after plasma levels are no longer detectable, which is consistent with this lengthy terminal elimination half-life. Although the human elimination route is unknown, research on animals has indicated that excretion mostly happens through feces. Isavuconazole is hardly excreted in urine, so treating urinary tract infections with this medication is unlikely to be beneficial.

DRUG-DRUG INTERACTION:

1. Warfarin

   In healthy adults, a phase I study assessed the pharmacokinetic properties and pharmacodynamic interactions between isavuconazole and warfarin [46]. In both the presence and absence of single doses of oral warfarin sodium 20 mg, multiple doses of the oral prodrug isavuconazonium sulfate (372 mg three times per day for a 2-day loading dose, and then 372 mg once daily thereafter; Clinical Pharmacokinetics and Pharmacodynamics is of Isavuconazole equivalent to isavuconazole 200 mg) were administered. When isavuconazole was administered in addition to warfarin, the mean AUC increased while the mean Cmax decreased. Isavuconazole slightly decreased the average warfarin area under the prothrombin time curve. Given that the international normalized ratio remains unaffected, these findings imply that co-administration of isavuconazole has no medically major impact on warfarin PK or PD.

2. Immunosuppressants

   Pharmacokinetic interactions between isavuconazole and immunosuppressants such as cyclosporine, mycophenolic acid, prednisolone, sirolimus for and tacrolimus in healthy adults have been assessed in phase I studies [48]. The AUCs of mycophenolic acid and prednisolone increased by 35 and 8%, respectively, and the AUCs of tacrolimus, sirolimus, and cyclosporine by 125, 84, and 29%, respectively, when co-administered with isavuconazole. The immunosuppressants had little effect on isavuconazole PK, but the findings indicate that isavuconazole inhibits the metabolism of mycophenolic acid, tacrolimus, sirolimus, and cyclosporine. When prescribing isavuconazole, physicians should consider its inhibitory impact on multiple immunosuppressants, as it is likely to be taken in combination with these medications.

3. Antiretroviral Interactions

   The drug-drug interactions between isavuconazole and antiretroviral medications have not been extensively studied in randomized trials. In healthy adults, a phase I open-label study assessed the pharmacokinetic impacts of isavuconazole in combination with lopinavir/ritonavir as an antiretroviral . The results indicate that combined administration of lopinavir/ritonavir with isavuconazole may reduce the exposure of lopinavir/ritonavir and increase the exposure of isavuconazole. The mean AUCs and Cmax of lopinavir were 27 and 23% lower, and the mean an area under the curve and Cmax of ritonavir were 31 and 33% lower in the presence (vs. absence) of isavuconazole. When the medications are taken together, there is no need to adjust the dosage of isavuconazole or lopinavir/ritonavir; however, patients should be closely watched for signs of decreased antiviral efficacy to guarantee proper treatment.

SIDE EFFECTS OF ISAVUCONAZOLE :

- Sore throat
- Hives

- burning eyes
- lightheadedness
- difficulty breathing
- loss of appetite
- constipation

- low blood potassium (hypokalemia),
- anxiety

CONCLUSION :

Isavuconazole is at least as successful as voriconazole, currently the standard of care for the treatment of aspergillosis that is invasive, even among individuals who are most at risk for mortality, as shown by the data now available. Additionally, isavuconazole's exceptional success in clinical trials supports its use as a salve and front-line treatment for mucormycosis, a rare and potentially fatal fungal disease with few therapeutic choices. Isavuconazole's role in treating invasive mold infections is still largely unknown based on phase IV experience, but its wide range of activity, low safety risks, and track record of success make it a valuable addition to the antifungal arsenal.

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