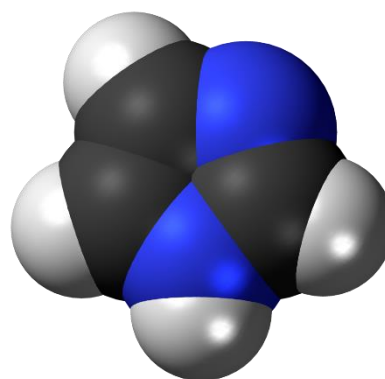
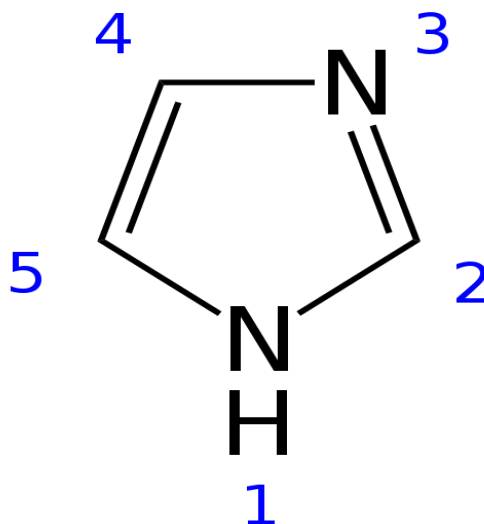
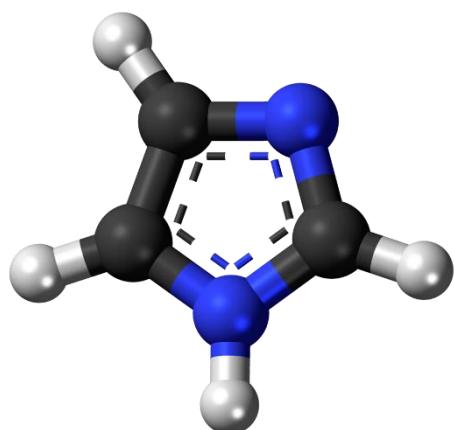
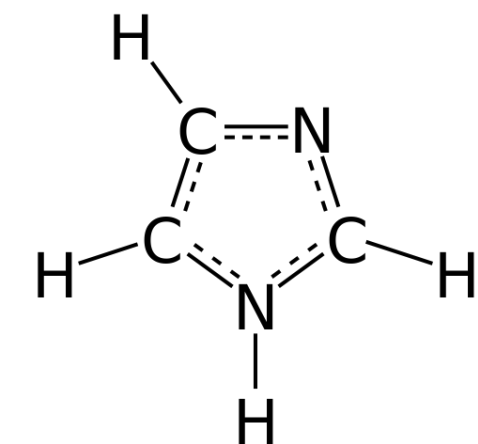




IMIDAZOLES

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Imidazole is an organic compound with the formula $C_3N_2H_4$. It is a white or colourless solid that is soluble in water, producing a mildly alkaline solution. In chemistry, it is an aromatic heterocycle, classified as a diazole, and has non-adjacent nitrogen atoms.

Many natural products, especially alkaloids, contain the imidazole ring. These imidazoles share the 1,3- C_3N_2 ring but feature varied substituents. This ring system is present in important biological building blocks, such as histidine and the related hormone histamine. Many drugs contain an imidazole ring, such as certain antifungal drugs, the nitroimidazole series of antibiotics, and the sedative midazolam.

When fused to a pyrimidine ring, it forms purine, which is the most widely occurring nitrogen-containing heterocycle in nature.

The name "imidazole" was coined in 1887 by the German chemist Arthur Rudolf Hantzsch.

Imidazoles may have antibacterial, antifungal, antiprotozoal, and anthelmintic activity. Several distinct phenylimidazoles are therapeutically useful antifungal agents with wide spectra against yeasts and filamentous fungi responsible for either superficial or systemic infections. The anthelmintic thiabendazole is also an imidazole with antifungal properties. Clotrimazole, miconazole, econazole, ketoconazole, itraconazole, and fluconazole are the most clinically important members of this group. Posaconazole and voriconazole are among the newer drugs; voriconazole is approved for use in people to treat aspergillosis.

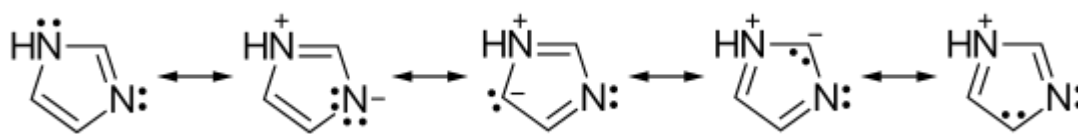
Antimicrobial Spectra :

The antifungal imidazoles also have some antibacterial action but are rarely used for this purpose. Miconazole has a wide antifungal spectrum against most fungi and yeasts of veterinary interest. Sensitive organisms include *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *Histoplasma capsulatum*, *Candida* spp, *Coccidioides immitis*, *Cryptococcus neoformans*, and *Aspergillus fumigatus*. Some *Aspergillus* and *Madurella* spp are only marginally sensitive.

Ketoconazole has an antifungal spectrum similar to that of miconazole, but it is more effective against *C. immitis* and some other yeasts and fungi. Itraconazole and fluconazole are the most active of the antifungal imidazoles. Their spectrum includes dimorphic fungal organisms and dermatophytes. They are also effective against some cases of aspergillosis (60%–70%) and cutaneous sporotrichosis. Clotrimazole and econazole are used for superficial mycoses (dermatophytosis and candidiasis); econazole also has been used for oculomycosis. Thiabendazole is effective against *Aspergillus* and *Penicillium* spp, but its use has largely been replaced by the more effective imidazoles. Voriconazole is approved for human use in treatment of *Aspergillus* but is effective against many other fungal organisms. Posaconazole may be more effective than itraconazole or fluconazole but may be associated with more adverse effects.

Structure and properties :

Imidazole is a planar 5-membered ring. It exists in two equivalent tautomeric forms, because hydrogen can be bound to one or the other nitrogen atom. Imidazole is a highly polar compound, as evidenced by its electric dipole moment of 3.67 D . It is highly soluble in water. The compound is classified as aromatic due to the presence of a planar ring containing 6 π -electrons (a pair of electrons from the protonated nitrogen atom and one from each of the remaining four atoms of the ring). Some resonance structures of imidazole are shown below:

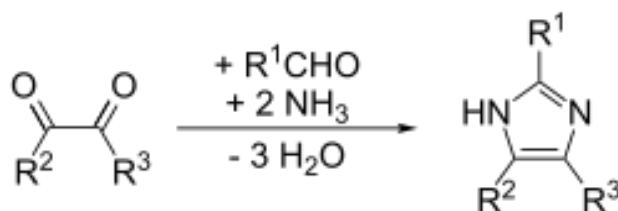


Amphoterism :

Imidazole is amphoteric. That is, it can function as both an acid and as a base. As an acid, the pK_a of imidazole is 14.5, making it less acidic than carboxylic acids, phenols, and imides, but slightly more acidic than alcohols. The acidic proton is the one bound to nitrogen. Deprotonation gives the imidazole anion, which is symmetrical. As a base, the pK_a of the conjugate acid (cited as pK_{BH^+} to avoid confusion between the two) is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic site is the nitrogen with the lone pair (and not bound to hydrogen). Protonation gives the imidazolium cation, which is symmetrical.

Preparation :

Imidazole was first reported in 1858 by the German-British chemist Heinrich Debus, although various imidazole derivatives had been discovered as early as the 1840s. It was shown that glyoxal, formaldehyde, and ammonia condense to form imidazole (glyoxaline, as it was originally named). This synthesis, while producing relatively low yields, is still used for generating C-substituted imidazoles.

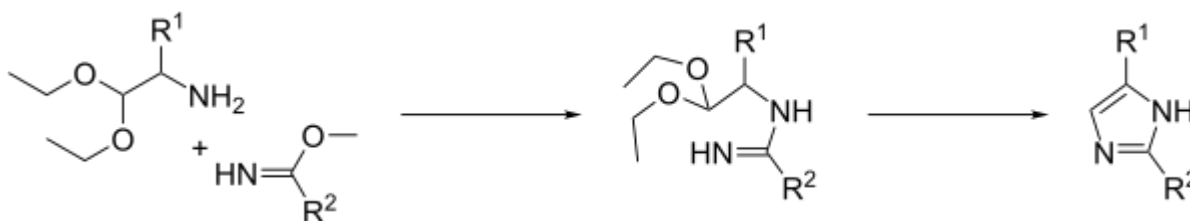


In one microwave modification, the reactants are benzil, benzaldehyde and ammonia in glacial acetic acid, forming 2,4,5-triphenylimidazole.

Imidazole can be synthesized by numerous methods besides the Debus method. Many of these syntheses can also be applied to substituted imidazoles by varying the functional groups on the reactants. These methods are commonly categorized by the number of reacting components.

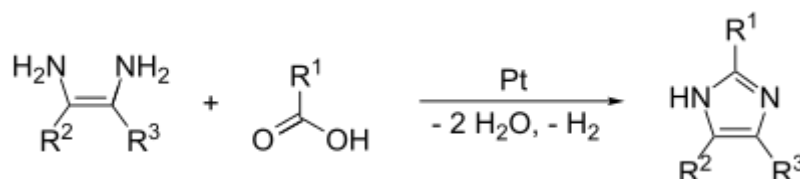
One component

The (1,5) or (3,4) bond can be formed by the reaction of an imide and an α -aminoaldehyde or α -aminoacetal. The example below applies to imidazole when $\text{R}_1 = \text{R}_2 = \text{hydrogen}$.



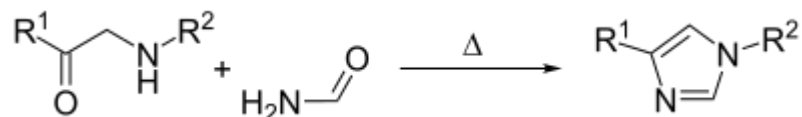
Two component

The (1,2) and (2,3) bonds can be formed by treating a 1,2-diaminoalkane, at high temperatures, with an alcohol, aldehyde, or carboxylic acid. A dehydrogenating catalyst, such as platinum on alumina, is required.



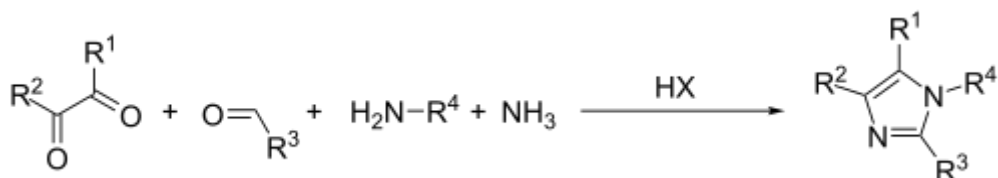
The (1,2) and (3,4) bonds can also be formed from *N*-substituted α -aminoketones and formamide with heat. The product will be a 1,4-disubstituted imidazole, but here

since $R_1 = R_2 = \text{hydrogen}$, imidazole itself is the product. The yield of this reaction is moderate, but it seems to be the most effective method of making the 1,4 substitution.



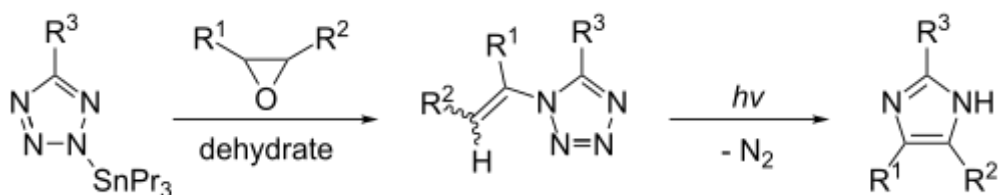
Three component

This method proceeds in good yields for substituted imidazoles. An adaptation of the Debus method, it is called the Debus-Radziszewski imidazole synthesis. The starting materials are substituted glyoxal, aldehyde, amine, and ammonia or an ammonium salt.



Formation from other heterocycles

Imidazole can be synthesized by the photolysis of 1-vinyltetrazole. This reaction will give substantial yields only if the 1-vinyltetrazole is made efficiently from an organotin compound, such as 2-tributylstannyltetrazole. The reaction, shown below, produces imidazole when $R_1 = R_2 = R_3 = \text{hydrogen}$.



Imidazole can also be formed in a vapor-phase reaction. The reaction occurs with formamide, ethylenediamine, and hydrogen over platinum on alumina, and it must take place between 340 and 480 °C. This forms a very pure imidazole product.

Mode of Action :

Imidazoles alter the cell membrane permeability of susceptible yeasts and fungi by blocking the synthesis of ergosterol (demethylation of lanosterol is inhibited), the primary cell sterol of fungi. The enzyme targeted is a fungal cytochrome P450 (CYP450). Other enzyme systems are also impaired, such as those required for fatty acid synthesis. Because of the drug-induced changes of oxidative and peroxidative enzyme activities, toxic concentrations of hydrogen peroxide develop intracellularly. The overall effect is cell membrane and internal organelle disruption and cell death. The cholesterol in host cells is not affected by the imidazoles, although some drugs impair synthesis of selected steroids and drug-metabolizing enzymes in the host. Because imidazoles impair synthesis, a lag time to efficacy occurs. This lag time may be prolonged because of the long half-life of these drugs .

Therapeutic Indications and Dose Rates :

The imidazoles are used to treat systemic fungal diseases, dermatophyte infections that have not responded to griseofulvin or topical therapy, *Malassezia* infection in dogs, aspergillosis, and sporotrichosis in animals that cannot tolerate or do not respond to sodium iodide. For serious infections, combination with amphotericin B is strongly recommended. Among the imidazoles, fluconazole may be more likely to distribute into tissues that are tough to penetrate. Both itraconazole and fluconazole are generally preferred to other imidazoles for treatment of systemic fungal infections, including aspergillosis and sporotrichosis. Topically applied imidazoles (clotrimazole, miconazole, econazole) are used for local dermatophytosis. Thiabendazole is included in some otic preparations for treatment of yeast infections.

Enilconazole is an imidazole that can be applied topically for treatment of dermatophytosis and aspergillosis. It has been used safely in cats, dogs, cattle, horses, and chickens and is prepared as a 0.2% solution for treatment of fungal skin infections. When infused into the nasal turbinates of dogs with aspergillosis, enilconazole treated and prevented the recurrence of fungal disease. When applied topically to dog and cat

hairs, enilconazole inhibits fungal growth in 2 rather than 4–8 treatments, as is necessary with other topically administered antifungal agents.

General dosages for the antifungal imidazoles are listed in Dosages of Imidazoles. The dose rate and frequency should be adjusted as needed .

Dosages of Imidazoles :

Enilconazole	10 mg/kg in 5–10 mL, bid for 7–14 days
Fluconazole	5–10 mg/kg, PO, once to twice daily
Itraconazole	5–10 mg/kg, PO, once to twice daily
Ketoconazole	5–20 mg/kg, PO, bid
Thiabendazole	44 mg/kg/day, PO, or 22 mg/kg, PO, bid



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Adverse Effects and Toxicity:

The imidazoles given PO result in few adverse effects, but nausea, vomiting, and hepatic dysfunction can develop. Ketoconazole in particular is associated with hepatotoxicity, especially in cats. Because imidazoles also inhibit CYP450 associated with steroid synthesis, as a result, sex steroids, including testosterone and adrenal steroid (cortisol), metabolism is inhibited. Adrenal responsiveness to adrenocorticotrophic hormone (ACTH) will be decreased, particularly with ketoconazole. Reproductive disorders related to ketoconazole administration may be seen in dogs. Voriconazole is associated with a number of adverse effects in people, including vision disturbances.

Interactions :

Imidazoles, in general, inhibit the metabolism of many drugs. Although ketoconazole has the broadest inhibitory effects, fluconazole followed by itraconazole also inhibit metabolism. Concurrent administration of these drugs with other drugs metabolized by the liver and potentially toxic should be done only with extreme caution. Imidazoles also are substrates for P-glycoprotein transport protein and may compete with other substrates, causing higher concentrations. Many of the substrates for P-glycoprotein are also substrates for CYP450.

Rifampin, which is a P-glycoprotein substrate, decreases serum ketoconazole because of microsomal enzyme induction. The absorption of the imidazoles, except for that of fluconazole, is inhibited by concurrent administration of cimetidine, ranitidine, anticholinergic agents, or gastric antacids. The risk of hepatotoxicity is increased if ketoconazole and griseofulvin are administered together. Imidazoles might be used concurrently with other antifungals to facilitate synergistic efficacy.

Effects on Laboratory Tests :

Treatment with imidazoles increases AST, ALT, plasma bilirubin, and plasma cholesterol. Adrenal responsiveness is altered.