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IMIDAZOLE DERIVATIVES AND ITS PHARMACOLOGICAL ACTIVITIES

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ABSTRACT: Imidazole is a planer five-member heterocyclic ring with 3C and 2N atom and in ring N is present in 1st and 3rd positions. The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. Being a polar and ionisable aromatic compound, it improves pharmacokinetic characteristics of lead molecules and thus used as a remedy to optimize solubility and bioavailability parameters of proposed poorly soluble lead molecules. Imidazole derivatives have occupied a unique place in the field of medicinal chemistry. The incorporation of the imidazole nucleus is an important synthetic strategy in drug discovery. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. This articles aims to review the work reported, their chemistry and biological activities of imidazole during past years.

Key words- Imidazole, antibacterial, antifungal, heterocyclic, biological active

INTRODUCTION

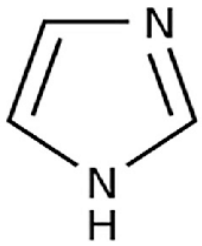
Imidazole is a five-member heterocyclic aromatic compound in which two Nitrogen atoms are present both Nitrogen atom are sp2 hybridized. Imidazole ring contains two types of lone-pair one is delocalized and second is non-delocalized (Non-Huckle-lone pair) due to this both Nitrogen has different pka. The Nitrogen has delocalized lone-pair has pka=7 and other nitrogen which has non- delocalized lone-pair has pka=14.9. Hence Imidazole is amphoteric in nature i.e., it work as both acid and base, susceptible to nucleophile and electrophilic attack[1].

Imidazole generally is colorless or pale yellow solid, has amine like order, it is an aromatic heterocyclic categorized as a diazole and as an alkaloid. It is water soluble and other polar solvents. It occurs in two equivalent tautomeric forms because the hydrogen atom can be located on either of the two nitrogen atoms.

The melting point imidazole is 88.9°C and the boiling point is 267.8°C. Imidazole is polar in nature and its dipole moment is 4.8 Debye, The molecular formula is C3 H4 N2 and the structural formula[2,3].

Imidazoles are a class of heterocycles with five-member ring structure, but variable substituents. This ring system is present in significant biological skeleton, like histidine and the associated hormone histamine. Imidazole can serve as a weak acid as well as base. Many drugs have an imidazole ring, like Nitro imidazole and antifungal drugs[4].

Heterocyclic compounds are also having utility in agriculture and pharmacy. Analysis of research manuscript in the last ten decades exposed that there is an overall trend in research for novel drugs involving modified of existing biologically vigorous matrices and molecular strategy of the structures of compounds.



The imidazole nucleus is a significant synthetic technique in drug discovery. Imidazole derivatives show anti-inflammatory, anticancer, antimicrobial, analgesic, and anti-tubercular activity. One of the most vital features of imidazole derivatives is their use as material for action of denture stomatities. The high beneficial properties of the imidazole associated drugs have encouraged the medicinal chemists to prepare a large number of new chemotherapeutic materials. Imidazole drugs have wide scope in pharmaceutical field.

Medicinal characteristics of imidazoles include anti-coagulants, anti-cancer, anti-fungal, anti-inflammatory, antibacterial, anti-viral, anti-diabetic, anti-malarial and anti-tubercular[5,6]. Imidazole derivatives are reported to be pharmacologically and physiologically active and it is used in the treatment of several diseases. The basic site is N-3. Synthesis Several types of 2-imidazolines are pharmaceutically and biologically very indispensable,

Imidazole's are synthetically indispensable due to their use as a synthetic intermediates, catalysts, chiral catalysts, chiral auxiliaries, and ligands for asymmetric catalysis in different synthetic reactions.

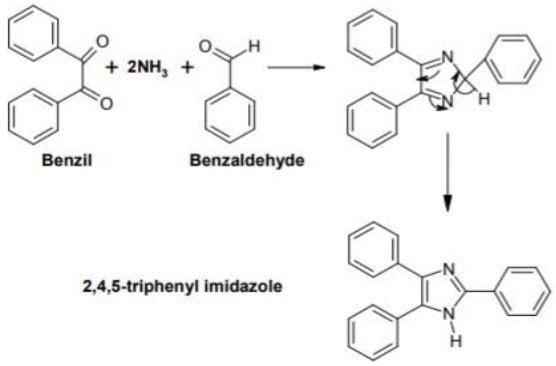
SYNTHESIS OF IMIDAZOLE:

Imidazoles were prepared in 1858 from glyoxal and ammonia. Several approaches are available for synthesis of Imidazole's as, Radiszewski synthesis, dehydrogenation of imidazolines, from alpha halo ketones, Wallach Synthesis, from aminonitrile and aldehyde and Marckwald synthesis. Details of the synthetic procedures are given below:

1).RADISZEWSKI

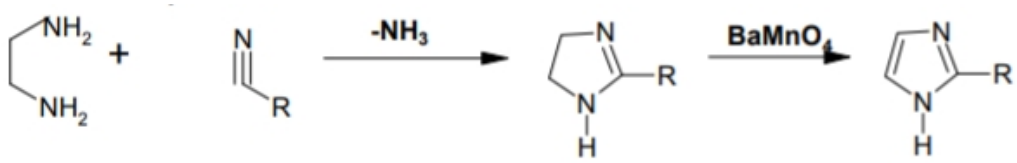
SYNTHESIS:

It consist of condensing a dicarbonyl compound such as glyoxal, a- keto aldehyde or a- diketones with an Aldehyde in the presence of ammonia, benzyl for instance, with benzaldehyde and two molecule of ammonia react To yield 2,4,5-triphenylimidazole. Formamide often proves a convenient substitute for ammonia[7].



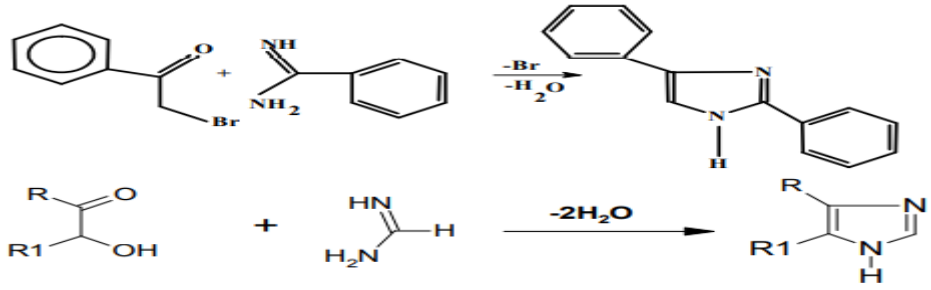
2).DEHYDROGENATION OF IMIDAZOLINE:

Knapp and coworkers[8] have reported a milder reagent barium managanate for the conversion of imidazolines to Imidazoles in presence of sulphur. Imidazolines obtained from alkyl nitriles and 1, 2 ethanediamine on reaction With BaMnO4 yield 2-substituted imidazoles.



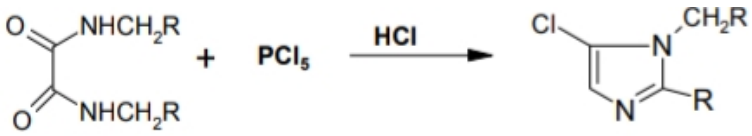
3).FROM a- HALO KETONE:

This reaction involves an interaction between an imidine and alpha halo ketones. This method has been applied Successfully for the synthesis of 2, 4- or 2, 5- biphenyl imidazole phenacyl bromide and benzimidine according to This method afford 2,4-diphenyl imidazole. Similarly, amidine reacts with acyloin or alpha halo ketones to yield Imidazoles[8].



4).WALLACH SYNTHESIS:

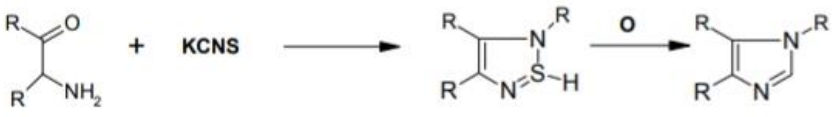
When N, N′ -dimethyloxamide is treated with phosphorus pentachloride, a chlorine containing compound isobtained which on reduction with hydroiodic acid give N- methyl imidazole. Under the same condition N, N′ -diethyloxamide is converted to a chlorine compound, which on reduction gives 1- ethyl –2- methyl imidazole. The chlorine compound has been shown to be 5- chloral imidazole[8,9].



N,N- dimethyloxamide

5).MARKWALD SYNTHESIS:

The preparation of 2- mercaptoimidazoles from alpha-amino ketones or aldehyde and potassium thiocyanate or alkyl Isothiocyanates is a common method for the synthesis of imidazoles. The sulfur can readily be removed by a Variety of oxidative method to give the desired imidazoles. The starting compounds, alpha-amino aldehyde or ketone, Are not readily available, and this is probably the chief limitation of the Marckwald synthesis[8].



alpha-Amino ketone

PHARMACOLOGICAL ACTIVITIES:

Imidazole's are well-known heterocyclic compounds which are common and have an important feature of a variety of medicinal agents. On the basis of various literature surveys, imidazole derivatives show various pharmacological activities:

1. Antifungal activity
2. Anticancer activity
3. Antibacterial activity

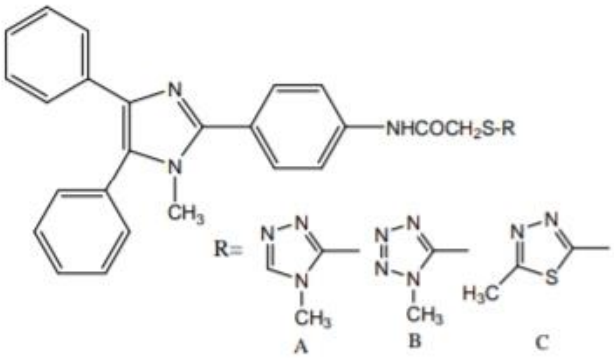
4. Anti- tubercular activity
5. Anti HIV activity
6. Anti -inflammatory and analgesic activity
7. Antiviral activity
8. Anthelmintic activity
9. Antidepressant activity

1).ANTI FUNGAL ACTIVITIES:

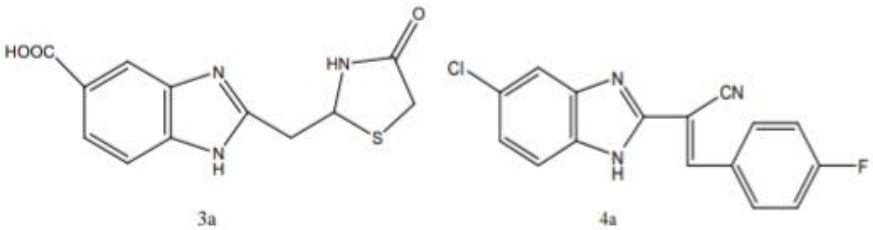
The search for new anti fungal in recent years has concentrated principally on the imidazole and triazole area of chemistry. The group of drug known collectively as the azoles, comprising a number of 1-substituted imidazole and triazole compounds undoubtedly represents the modern approach to both topical and systemic treatment of fungal disease. The imidazole as anti fungal has pronounced pharmacological and biochemical activities. The lipophilic imidazoles such as clotrimazole , econazole and miconazole exhibited poor systemic availability following oral administration due to both poor absorption and extensive first pass metabolism so their use has been limited to topical treatment of superficial fungal infection. Ketoconazole a more polar imidazole introduced into therapy in the late 1970s, represented a break through in the treatment of antifungal disease[10].

2).ANTI CANCER ACTIVITY:

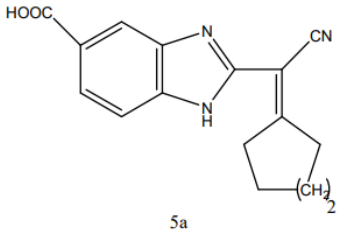
Yusuf Ozkay et al[11] synthesized many novel imidazole-(Benz) azole and imidazole epiperazine derivatives in order to investigate the anticancer activity. Anticancer activity screening results revealed that these were the most active compounds in the series. Cisplatin was used as reference drug.



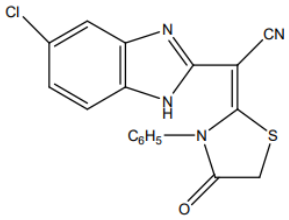
Hanan M. Refaat[12] synthesized various series of 2-substituted benzimidazole. Several of the synthesized products were subjected for anticancer screening which revealed that all the tested compounds exhibited antitumor activity against human hepatocellular carcinoma, breast, adenocarcinoma, and human colon carcinoma. 3a and 4a showed the highest potency against human hepatocellular carcinoma.



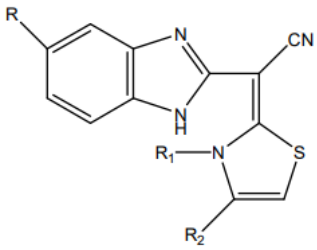
Compounds 5a 6a and 7a were most active against human breast adenocarcinoma.



5a



6a

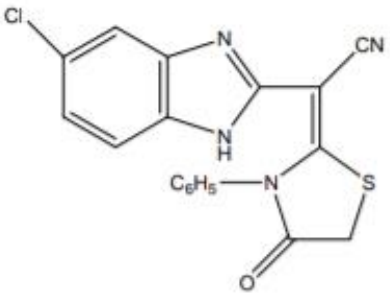


7a

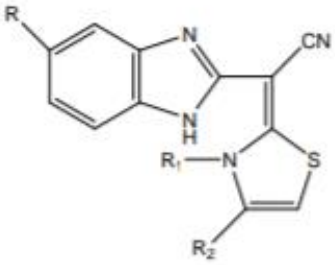
For this compound R=COOH R1=4-Br-C6H4,

R2=2-OCH3 -C6H4

8a and 9a were moderately potent against human colon carcinoma.



8a



9a For this compound R=COOH
R_1=4-Br-C_6H_4
R_2=2-OCH_3-C_6H_4

3).ANTIBACTERIAL ACTIVITY:

Based on the literature review, the next most frequent important pharmacological effect of Imidazole derivatives is the antibacterial effect. Identification of this effect is relevant, because after the identification of almost all groups of important antibiotics (tetracyclines, cephalosporins, aminoglycosides and macrolides), these drugs may lose the effectiveness due to the increased microorganism resistance. Currently, treatment failures, associated with multidrug-resistant bacteria, are the global issue for public health.

For example, antibacterial activity of Imidazole compounds with bactericidal effect in complex with Ag was studied. In 2013, John McGinley et al[13]. (National University of Ireland) synthesized 1-(3-aminopropyl)imidazole and obtained the Schiff base ligands easily coordinated with Ag(I) centers. Studies were carried out against S. aureus, MRSA, E. coli and P. aeruginosa strains. As a result, the most complexes with Ag (I) had the moderate antibacterial activity.

In 2019, Achar G et al[14]. (Jawaharlal Nehru Centre, India) conducted the antibacterial study of benzonitrile hexafluorophosphate and coumarin salts substituted with imidazolium, benzimidazolium and silver complexes against Gram-positive (S. Aureus) and Gram-negative (E. coli) bacteria. Both series of silver complexes showed the antibacterial activity against E. coli, while the antibacterial activity against S. aureus was moderate. Finally, it was concluded that the complex activity is related to the metal center.

4).ANTI-TUBERCULAR ACTIVITY:

Despite the recent progress in the treatment of infectious diseases induced by Mycobacterium, these microorganisms still represent a significant problem in global healthcare and the leading cause of death from infectious diseases in the world. In spite of availability of anti-tuberculosis drugs, tuberculosis is still one of the most common infectious of global concern. The current situation is worsened by HIV epidemic led to the increase in multidrug-resistant tuberculosis prevalence and growth of drug-resistant microorganisms[15]. Taking these facts into consideration, it is required to find new therapeutic agents to combat M. tuberculosis infections.

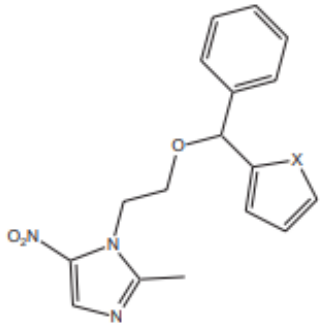
In 2012, Daniel Cvejn, Vera Klimesova, Filip Bures[16] (University of Pardubice, Czech Republic) investigated the antimycobacterial activity of 2-phenylimidazole derivatives obtained from α-amino acids. Among 2-phenylimidazole derivatives, compounds containing a nitro group, had the activity against M. tuberculosis, but this activity was lower than activity of isoniazid. Activity against M. avium and M. kansasii exceeded activity of isoniazid. Availability of nitro group was the essential characteristic affecting the antimycobacterial activity of compounds studied.

5).ANTI-HIV ACTIVITY:

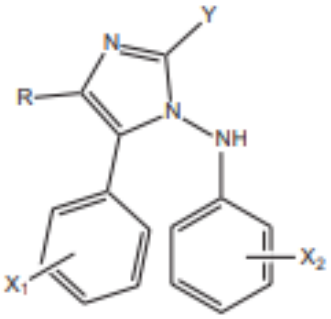
HIV-1 (Human Immunodeficiency Virus Type-1) is a pathogenic retrovirus of the lentivirus family and causative agent of AIDS or AIDS Related Complex (ARC) (1–3). HIV infection targets the monocytes expressing surface CD4 receptors and produces profound defects in cell-mediated immunity.

Overtime infection leads to severe depletion of CD4 T-lymphocytes (T-cells) resulting in opportunistic infections (OIs) such as bacterial, fungal, viral, protozoal and neoplastic diseases and ultimately death[17]. An ideal anti-HIV agent should suppress HIV replication and should also be able to combat other opportunistic infections, like tuberculosis, hepatitis and other bacterial infection.

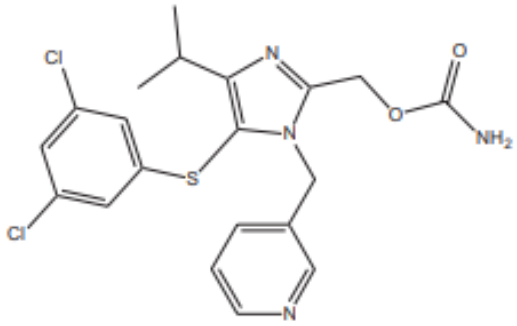
Imidazoles have been known as antiviral agents, one of the examples being capravirine[18]. Silvestri et al[19]. and De Martino et al.[20,21] synthesized a number of 1-2- -(diarylmethoxy)ethyl]-2-methyl-5-nitroimidazole (DAMNI) analogs as novel HIV-1 reverse transcriptase (RT) inhibitory agents active at submicromolar concentration, with the racemic 1-2-[(thiophen-2-yl)phenylmethoxy]ethyl]-2-methyl-5-nitroimidazole (EC50, 0.03 μmol–1) being the most potent among all the analogs (Fig.1), exhibiting higher activity than efavirenz against the viral RT carrying the K103N mutation.



DAMNIs X: S,O



NAIMs X , X : halogen, alkyl R: alkyl, aryl Y:SH,S

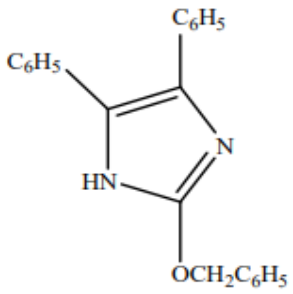


Capravirine

Similarly, N-aminoimidazoles (NAIMs) have also been reported to inhibit replication of the WT virus as well as an HIV-1 strain that contained both the K103N and Y181C mutations.

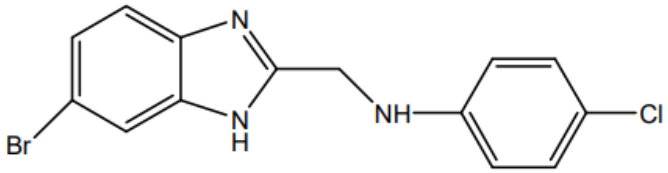
6).ANTI-INFLAMMATORY AND ANALGESIC ACTIVITY:

Puratchikody A.et al[22] studies on 2-substituted-4, 5-diphenyl-1H-imidazoles and checked the anti-inflammatory activity based on Carrageenan-induced paw edema method. This compound shows maximum activity and indomethacin used as reference drug.



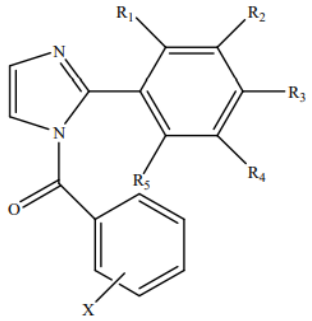
2-(benzyloxy)-4,5-diphenyl-1H-imidazole

Kavitha C.S.et al[23] has synthesized a series of 2-methylaminibenzimidazole derivatives and newly synthesized compounds were screened for analgesic and anti-inflammatory activities. This compound shows analgesic activity and compared with standard nimesulide drug.



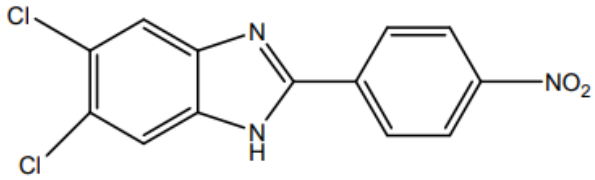
7).ANTIVIRAL ACTIVITY:

Deepika Sharma et al[24] synthesized imidazole derivatives and the antiviral screening of (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-methanones against viral strains indicated that compounds A and B selected as the most potent antiviral agents. Ribavirin was used as standard drug.



For compound A, R1=H,R2=H,R3=Cl,R4=H,R5=H,X=4-NO2

B, R1=H,R2=H,R3=NO2 ,R4=H,R5=H,X=4-NO2



5,6-dichloro-2-(4-nitrophenyl)-1H-benzo[d]imidazole

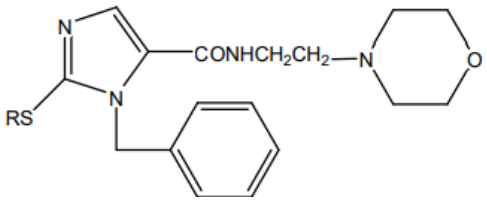
Michele Tonelli et al[25] synthesized seventy six 2-phenylbenzimidazole derivatives and evaluated for cytotoxicity and anti-viral activity against a panel of RNA and DNA viruses. Compound ([56- dichloro-2-(4-nitrophenyl) benzimidazole]) exhibited a high activity resulting more potent than reference drugs smycophenolic acid and 6-azauridine.

8).ANTHELMINTICS ACTIVITY:

It was found that imidazole is less sensitive in extra intestinal parasites particularly intravascular and intestinal dwelling parasites than gastrointestinal parasites. The activity against developing stages is superior to that against arrested or adult stages in comparable habitats. The hatching and larval development are inhibited at doses which are sub- efficacious against adult in vivo.They required to achieve efficacy against nematodes are lower than those used for cestode and trematode control. For cestode or trematode control higher dose of drug or multiple treatments is needed.The member of class (2-alkyl benzimidazole) has been found to remove various species of nematodes and trematodes from different hosts. 4, 5, 6, 7-tetra chloro-2-trifluoromethyl benzimidazole show high activity against the nematodes Ancylostoma caninum, Haemonchus contrtus, ascarissuum and trimatodes Fasciola hepatica several 2-5 disubstituted benzimidazole,- with proven potentials to kill various species of intestinal nematodes have also been found to- posses activity against cestodiasis of man and animal. Mebendazole at the dose of 100 mg/kg cure patient suffering with T. Solium and T. Saginata.

9).ANTIDEPRESSANT ACTIVITY:

Farzin Hadizadeh et al[26] synthesized moclobemide analogues by replacing moclobemide phenylring with substituted imidazole and studied for the antidepressant activity using forced swimming test. Analogues 7a-c was found to be more potent than moclobemide.



For this compound a)R=CH3,

b)R=C2H5,

c)R=CH2C6H

CONCLUSION:

On the basis of various literature survey imidazole derivatives show various activity against antimicrobial, anti-inflammatory, analgesic, antitubercular, anticancer etc. The possible improvements in the activity can be further achieved by slight modifications in the substituents on the basic imidazole nucleus. Having structural similarity with histidine imidazole compound can bind with protein molecules with ease compared to the some other heterocyclic moieties. Thus imidazole offers better pharmacodynamic characteristics. Furthermore, some imidazole drugs, at high concentrations, could exert direct inhibitory effects on membranes, without interference with sterols and sterol esters. Various recent new drugs developments in imidazole derivatives show better effect and less toxicity.

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