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Exploring Imidazole and Its Derivatives : Versatile Agents with Anti-Bacterial and Anti-Viral Capabilities

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KEYWORDS
Imidazole, Heterocyclic compounds, Clinical trials, Anti-microbial

ABSTRACT:
Heterocyclic compounds constitute the largest and most diverse family of organic compounds. Various imidazole-containing compounds have been investigated for their medical potential in clinical trials targeting several disease conditions. The rapid expansion of imidazole-based medicinal chemistry suggests the promising therapeutic value of imidazole-derived compounds for treating incurable diseases. Imidazole is a five-membered heterocyclic moiety composed of three carbon, two nitrogen, four hydrogen atoms, and two double bonds. It is also known as 1,3-diazole. Imidazole compounds exhibit antimicrobial properties by disrupting DNA double-strand helix and inhibiting protein kinase. The introduction of highly functional imidazole has also spurred significant advancements in the field of chemotherapeutic agents. This systematic review aims to facilitate the design and discovery of more potent and efficient imidazole compounds based on previous research, as well as the chemistry and biological activity of imidazole.

Introduction:

Imidazole is an organic compound with the formula $C_3N_2H_4$. It is a white or colorless solid that is soluble in water, producing a mildly alkaline solution. In chemistry, it is an aromatic heterocyclic, classified as a diazole and has non-adjacent nitrogen atoms[1].

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.

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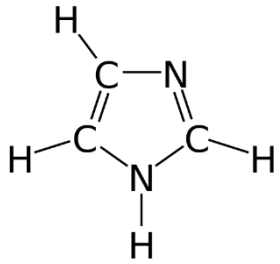

Fig.no.1

Imidazole is a planar 5-membered ring, that exists in two equivalent tautomeric forms because hydrogen can be bound to one or other nitrogen atom. This led to the synthesis of the metronidazole.[2]

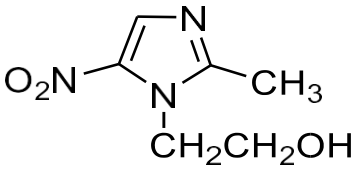

Fig. no. 2

Metronidazole was shown to cure giardiasis, amoebiasis, and *Balantidium infections* and most widely used in the treatment of anaerobic protozoan parasitic infections caused by *Trichomonas vaginalis, Giardia duodenalis,* and *Entamoeba histolytica.*[3] Current therapeutic drugs containing imidazole nucleus having good systemic activity against *Trichomonas vaginalis* infections are metronidazole (2), tinidazole (3),nimorazole (4), panidazole (5), dimetridazole (6), ornidazole(7), secnidazole (8) and carnidazole (9).[4]

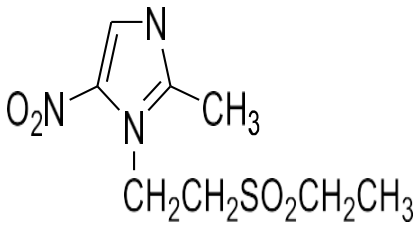

Fig. no. 3

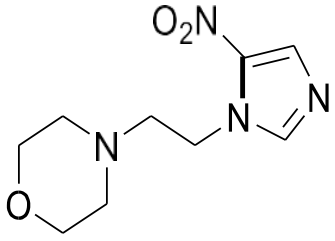

Fig. No. 4

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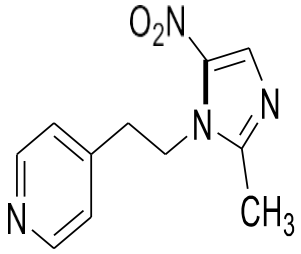

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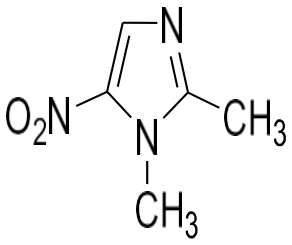
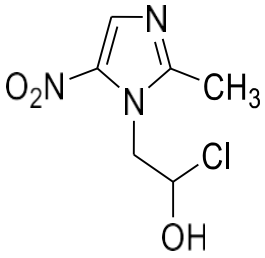


Fig.no. 6



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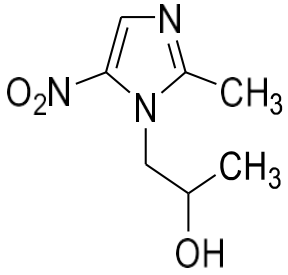

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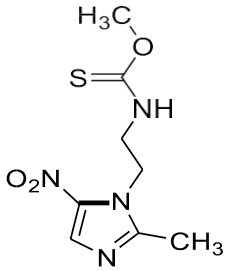

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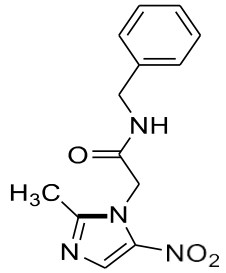

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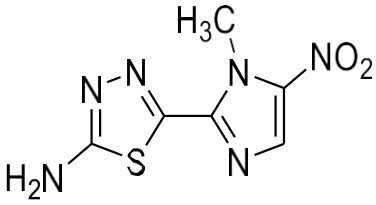

Fig. no. 11

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These drugs have both intestinal and systemic action and is characterized by high tissue penetration, which affects the extra intestinal stages of *Entamoeba histolytica* to a high degree than the lumen stages. In clinical use these drugs easily penetrate various tissues such as bones, joints and CNS where they achieve clinically effective concentration.[6]

Benznidazole (10) has been found mutagenic in *Salmonella*, but it is active against several strains of *Trypanosoma cruzi* of diverse sensitivity. It has a potential role in treatment of Chagas disease.[4] The nitroimidazole-thiadiazole derivative 5-nitromegazol (11) has a pronounced trypanocidal activity.[5]

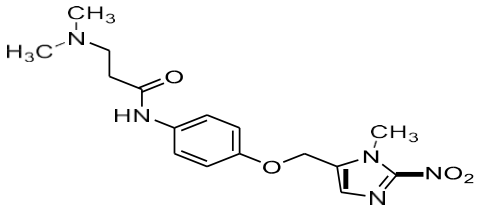

Fig. no. 12

RO 150216 (12), nitroimidazole derivative, has been shown to be effective in inhibiting the culture growth of different strains of the African trypanosome, and is also active *in vivo* that has been studied using various animal models.[7]

APPLICATION:

Imidazole derivatives have gained attractions round the globe due to its flexibility in the widespread application. The widespread use integrates the metallurgical industries in one end as a corrosion inhibitor and on the other hand to the pharmaceutical industry as a potent drug with admirable versatile applications. These imidazoles also have other interesting biological activities of therapeutic potential such as, radio sensitizers in treatment of cancer,[9-10] control of fertility,[11] antitubercular therapy[12] and antiepileptic agents.[13] 2-nitroimidazoles play an important role as bio reductive markers for tumour hypoxia, as radiosensitizers[14-15] and some also display anti-protozoal activity.[16]

The substituted imidazole derivatives are significant in treatment of numerous systemic fungal infections. Imidazole (l) is a part or the theophylline atom found in tea leaves and coffee beans, which animates the central nervous system[17]. Imidazole (I) has been used extensively as a corrosion inhibitor on certain transition metals, such as copper, preventing copper corrosion is important especially in aqueous systems. Imidazole can also be found in various compounds that are used for photography and electronics[18].

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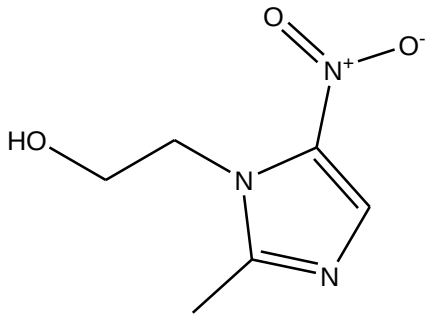
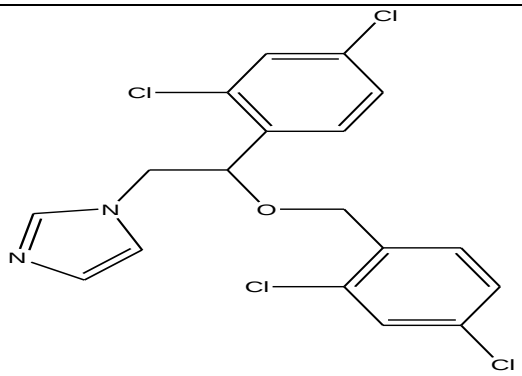
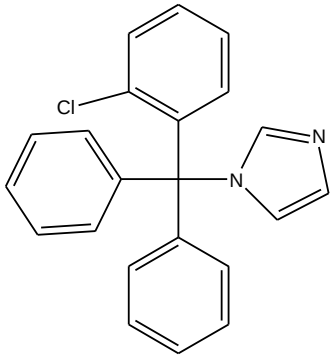
Table no. 1 representing imidazole derivative which work as anti-bacterial & anti-fungal:

S No.	Name	Figures	Function
1	Metronidazole		Antibacterial and antiprotozoal
2	Miconazole		Antifungal
3	Clotrimazole		Antifungal

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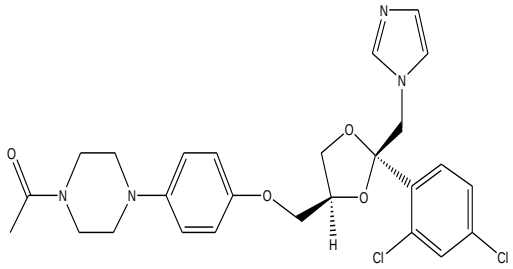
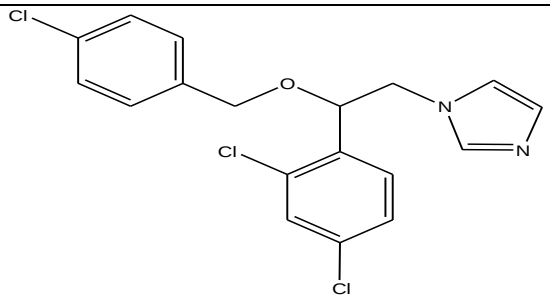
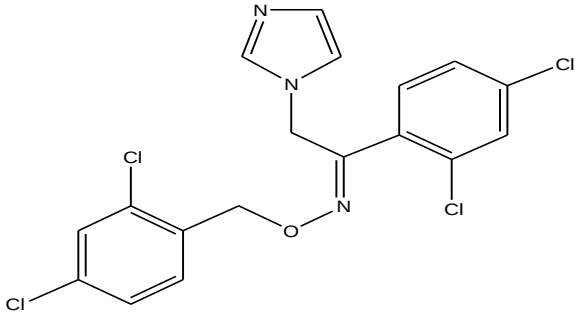
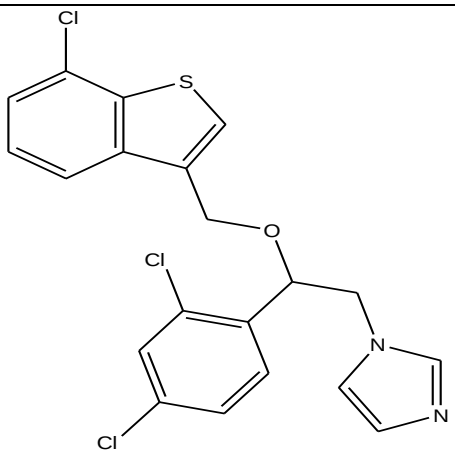
4	Ketoconazole		Antifungal
5	Econazole		Antifungal
6	Oxiconazole		Antibacterial
7	Sertaconazole		Antiviral

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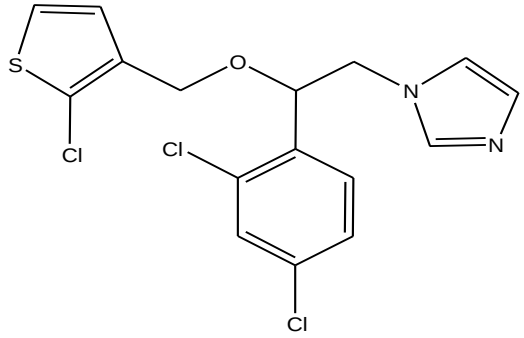
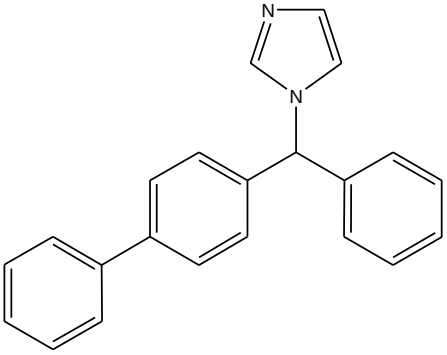
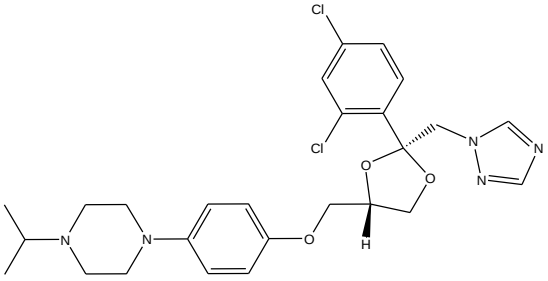
8	Tioconazole		Antibacterial
9	Bifonazole		Antifungal
10	Terconazole		Antibacterial

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Antiprotozoal Agents

In the year 2018, Lohidashan *et al*[19] reported the synthesis of nitroimidazole derivatives using Michael addition, which were evaluated for anti-malarial activity.

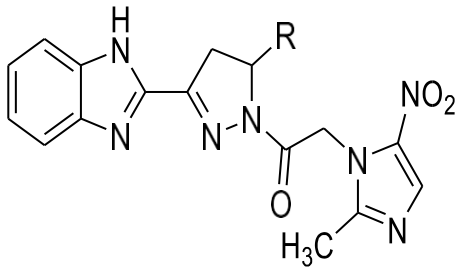

Fig. no. 13

Table no.2 depicting substitution on 'R' group

Compounds	**R**
13a	2-chlorophenyl
13b	4-fluorophenyl
13c	4-hydroxyphenyl
13d	5-styryl

Compound (13c) was found to be the most active and potent among the other synthesized compounds, as it showed good results on *in vitro* anti-malarial screening among the other synthesized compounds.

Antibacterial agents

Miller *et al* in the year 1970 reported the synthesis and biological activity of N- substituted-2-methyl-5-nitroimidazole. Among these, two compounds (14a) and (14b) were reported to possess activity comparable to metronidazole (2). Introduction of a sulfone moiety yielded compounds (14c) to (14h), which were more or equally effective in their activity as compared to metronidazole[18] (2).

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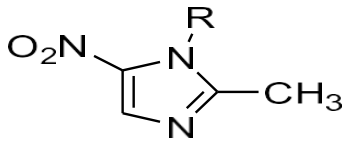
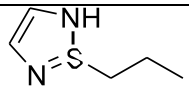


Fig. no.14

Table no.3 depicting substitution on 'R' group

Compounds	R
14a	$-CH_2CH_2I$
14b	
14c	$(CH_2)_2SO_2CH(CH_3)_2$
14d	$-(CH_2)_2SO_2(CH_2)_2CH_3$
14e	$-(CH_2)_2SO_2CH_3$
14f	$(CH_2)_2SO_2(CH_2)_3CH_3$
14g	$-(CH_2)_3SO_2CH_3$
14h	$-(CH_2)_3SO_2Ph$
14i	$-CHC(CH_2)_2$

Hoffer and Grunberg[20] in the year 1974 have reported the synthesis and antitrichomonal activity of compounds having a 3 carbon chain at position N-1, of which compounds (15a-c) were found to be active but at the same time more toxic than metronidazole (2).

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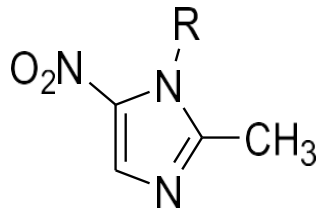
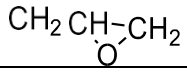


Fig. no. 15

Table no.4 depicting substitution on R

Compounds	**R**
15a	$CH_2CHOHCH_2Cl$
15b	$-CH_2CHClCH_2Cl$
15c	

In the year 1974, Mitra and Pathak reported the synthesis and biological activities of compounds (16) and (17). None of the compounds showed an appreciable activity.

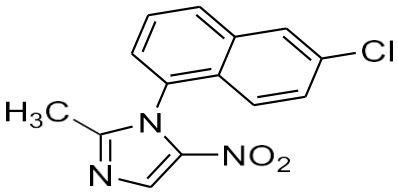


Fig. no. 16

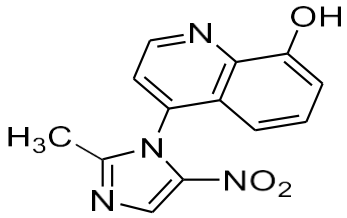


Fig. no. 17

Other N-substituted 2-methyl -5-nitroimidazole compounds with antiprotozoal activity were (18a) and (18b)[21].

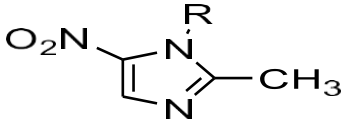


Fig. no. 18

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Table no. 5 Depicting substitution on R group

Compounds	R
18a	$-CH_2CH_2COOH$
18b	$-COOCH_2Ph$

Substitution of styryl group at position 4 in N-1 substituted 2-methyl -5-nitroimidazole have yielded compound (19) which were active against *Trichomonas vaginalis, Entamoeba histolytica* and *Candida albicans.*[21]

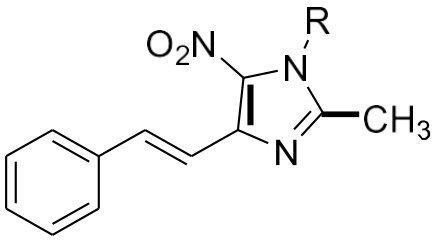
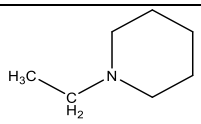
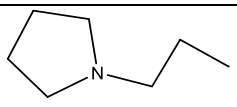
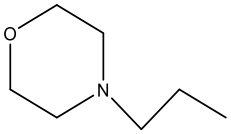


Fig. no. 19

Table no.6 depicting substitution on R group

Compounds	R
19a	$-CH_2CH_2NEt_2$
19b	
19c	
19d	

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Demirayak *et al* in the year 1999 synthesized compounds (20a-f) and (21) and evaluated them for antibacterial activity against *Escherichia coli* and *Streptococcus aureus*[22].

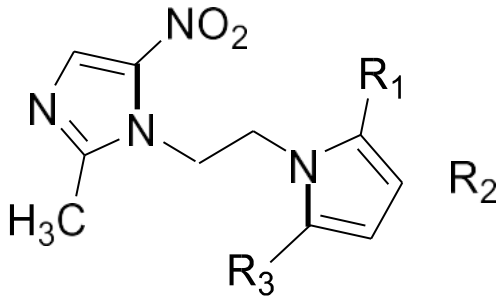

Fig. no. 20

Table no.7 depicting substitution on R group

COMPOUNDS	**R1**	**R2**	**R3**
20a	H	H	H
20b	CH_3	H	CH_3
20c	CH_3	$COOC_2H_5$	C_6H_5
20d	CH_3	$COOC_2H_5$	*p*-$CH_2OC_6H_4$
20e	CH_3	$COOC_2H_5$	*p*-ClC_6H_4
20f	CH_3	$COOC_2H_5$	*p*-$NO_2C_6H_4$

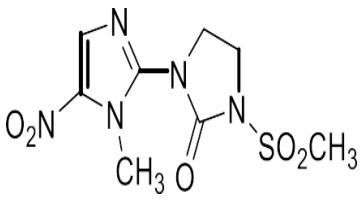

Fig. no. 21

Compound (21) was more active against anaerobic bacteria than metronidazole (2). Substitution of 2-methyl -5-nitroimidazole at position N-1 by lactones, tosylate, haloalkyl acetate, haloalkyl amine, onium salts,

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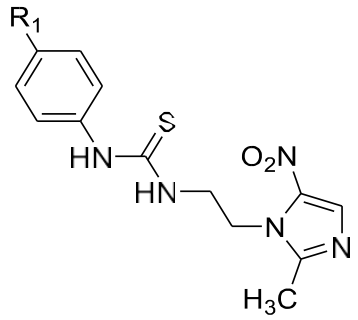
glycosides, haloalkylacetals, haloalkyl sulphides, haloalkyl imidazoles and benzoyl oxiridines have also been reported.

Artico *et al* in the year 2002 reported the synthesis of some compounds mostly having 2-methyl-5-nitroimidazole nucleus. Compounds with methyl group at C-2 and nitro group at C-5 with different substituents at N-1 position are the most effective compounds. A short saturated aliphatic chain is the best choice and the presence of hydroxyl group decreases considerably the toxicity of the product[23].

Benkli*et al*[24] in the 2003 synthesized some new N-substituted nitroimidazole derivatives and evaluated them for antibacterial and antifungal activity. Compound (22a) was found to be most potent amongst others.



(22)

Fig. no. 22

Table no. 8 Depicting substitution on R group

Compounds	**R_1**
22a	H
22b	CH3
22c	OCH3
22d	Cl

Gopalakrishnan[25,26] in the year 2009 synthesised a few compounds of prototype (23) and these were evaluated for antibacterial and antifungal activity.

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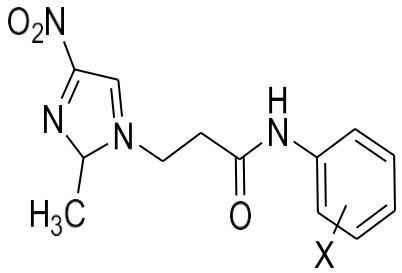

Fig. no. 23

Table no. 9 Depicting substitution on R group

Compounds	R
23a	2-Cl
23b	3-Cl
23c	2-NO_2
23d	2-SH
23e	2-OH
23f	3-OH
23g	2,4,6-tri Bromo

Compounds (23a) and (23d) have shown antifungal activities. Compound (23g) exhibited good antibacterial activity.

Valdez *et al* in the year 2009, synthesized some new 2-ethenyl and 2-ethanyl 5- nitroimidazole derivatives, and noticed that when a bridge which is saturated connects the 5-nitroimidazoles core and a pendant ring system then antigiardial activity increases slightly. Whereas, antigiardial activity increases with a greater extent when olefins with a bridge which is conjugated joins the main ring and a phenyl or heterocyclic ring with substitution without being toxic[27].

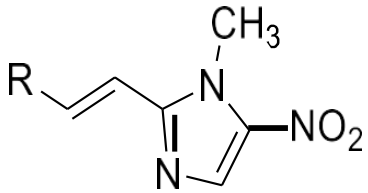

Fig. no. 24

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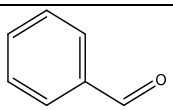
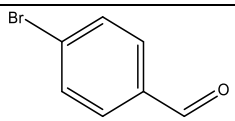
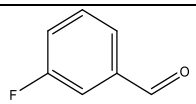
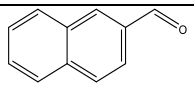
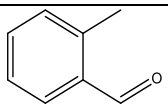
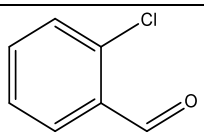
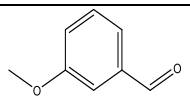
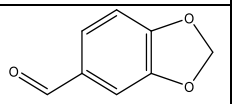
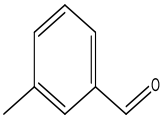
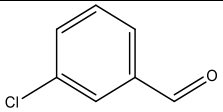
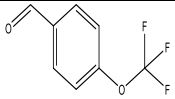
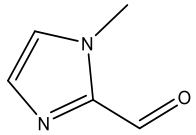
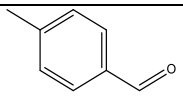
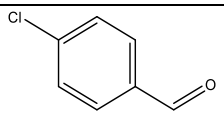
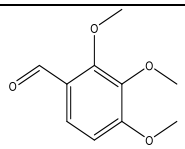
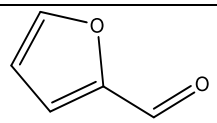
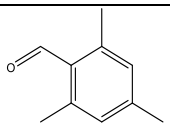
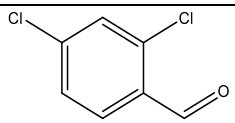
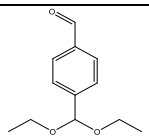
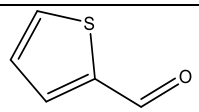
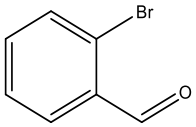
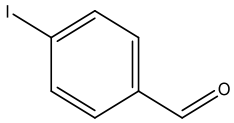
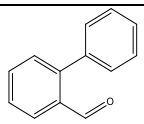
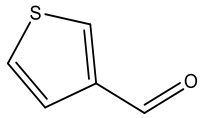
Table no.10 depicting substitution on R group

	R		R		R		R
24a		24g		24m		24s	
24b		24h		24n		24t	
24c		24i		24o		24u	
24d		24j		24p		24v	
24e		24k		24q		24w	
24f		24l		24r		24x	

All of the new 5-nitroimidazole derivatives were more potent than metronidazole (2). Among these compounds, compounds (24e), (24n), (24w), and (24x) caused complete clearance of the infection.

Dubey *et al* in the year 2009, synthesized various novel aliphatic and aromatic esters of metronidazole (2) using prodrug approach and evaluated them for their anaerobic antibacterial activity[28].

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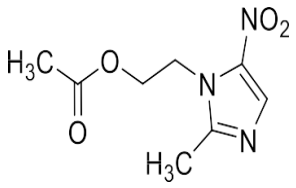


Fig. no. 25

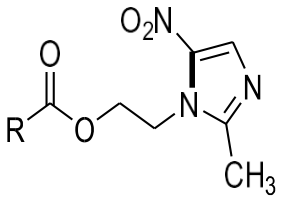
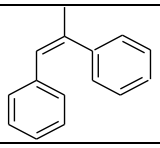


Fig. no. 26

Table no.11 Depicting substitution on R group

Compounds	R
26a	CH_2CH_3
26b	$CH_2CH_2CH_3$
26c	$CH_2CH_2CH_2CH_3$
26d	$CH_2CH_2CH_2CH_2CH_3$
26e	C6H5
26f	

As the carbon chain of esters increased, the antibacterial activity also increased. This indicated that as the lipophilic character increased from 2 to 6-carbon chain length and even more on cyclization of the side chain, it lead to an increase in the antimicrobial property. Further increase in lipophilic character following introduction of biphenyl ring system (increasing the bulk) as in compound (26f) lowered down the activity significantly.

Varshney *et al* in the year 2010 synthesized a series of N-alkylated derivatives of nitroimidazole derivatives with various substituents at N-1 and evaluated them for *in- vitro* antibacterial activity. The compound (27) was the most potent compound of the series[29].

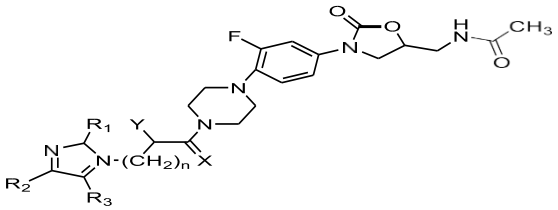


Fig. no. 27

Conclusion:

Imidazole and its derivatives have garnered attention for their distinctive chemical properties, often employed in various applications for their versatility. Recent research has unveiled another dimension to these compounds, revealing their potent antibacterial properties. Imidazole derivatives exhibit a wide spectrum of activity against

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bacteria, coupled with low toxicity levels, making them promising candidates in combating bacterial infections. The ongoing exploration and advancement in this area hold promise for the development of even more effective and safer antibacterial and antiviral agents.

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