Chapter

Azoles as Potent Antimicrobial Agents

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Abstract

Imidazole analogs have proved to be a very good source of medicinal agents. The various activities associated with these moieties include antibacterial, antifungal, anthelmintic, Anti HIV activity, anticancer, antihypertensive, analgesic, anti-inflammatory, anticonvulsant, sedative and other pharmacological activities.

Keywords: imidazole, antibacterial, antifungal and antiviral

1. Introduction

Azoles are basically five member heterocyclic compounds containing one or more different hetero atom out of which at least one must be nitrogen and other heterocyclic may be nitrogen or other than nitrogen like sulfur or oxygen.

Some of the common five member azoles which consist the nitrogen hetero atom only are as follows as imidazole (1), pyrazole (2), 1,2,3-triazole (3), 1,2,4-triazole (4), tetrazole (5) and pentazole (6).

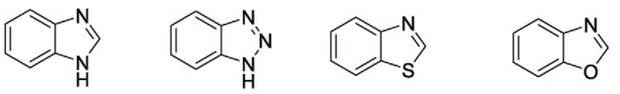
(1) (2) (3) (4) (5) (6)

Some of the five member azoles which consist sulfur and oxygen as hetero atom along with nitrogen atom such as thiazole (7), isothiazole (8), 1,2,3-thiadiazole (9), 1,2,4-thiadiazole (10), 1,2,5-thiadiazole (11), 1,3,4-thiadiazole (12), oxazole (13), isoxazole (14), 1,2,3-oxadiazole (15), 1,2,4-oxadiazole (16), 1,2,5-oxadiazole (17) and 1,3,4-oxadiazole (18).

(7) (8) (9) (10) (11) (12)

(13) (14) (15) (16) (17) (18)

Some of the heterocyclic azoles are fused with benzene ring to form bicyclic azole derivatives such as benzimidazole (19), benzotriazole (20), benzothiazole (21) and benzoxazole (22).



(19) (20) (21) (22)

Among above mentioned class of azoles a brief review is presented focused on imidazoles and benzotriazoles as given below.

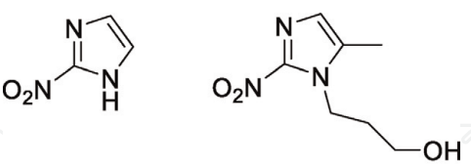
2. Imidazole analogs and their significance

In various oxidation states (23 and 24) imidazole has shown a number of interesting biological activities, like antiviral [1, 2], antibacterial [3] antifungal [4, 5], antiprotozoal [6, 7], antihypertensive [8, 9], antihistaminic [10], alpha-adrenergic agonist [11], alpha adrenergic blocking [12] and other activities [13, 14].

(23) (24)

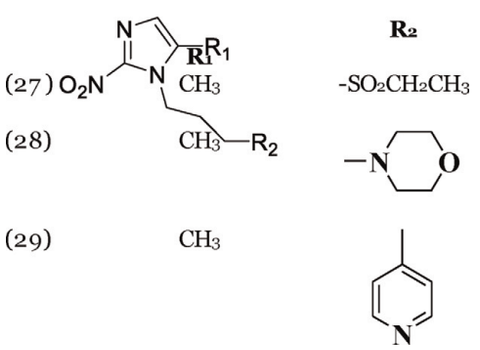
2.1 Antiprotozoals

Nitroimidazoles (25) with antitrichomonas activity were reported in year 1961 and then in 1966. Metronidazole (26) was among these compounds, it exhibited broad antiprotozoal activity and has found wide use in treating trichomoniasis orally.

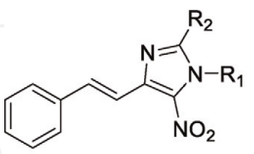


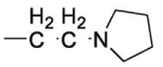
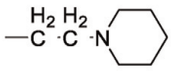
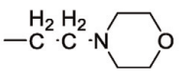
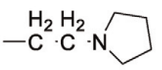
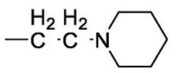
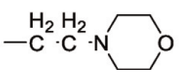
(25) (26)

Structural variation of Metronidazole (26), mainly to improve trichomonacidal activity led to the discovery of Tinidazole (27), Nimorazole (28), and Panidazole (29). Tinadazole (27) is most potent towards *Entamoeba histolytica*, *in vitro*, cecal amoebiasis and hepatic amoebiasis in experimental animals [6–8].



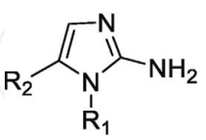
Giraldi et al. [15] in year 1967, synthesized a series of 1-aminoalkyl and 1-aminoalkyl-2-methyl-5(4)-nitro-4(5)-styrylimidazoles (30–37) and these compounds were tested to check the potency of synthesized compounds against various non-pathogenic bacteria and fungi.



	R_1	R_2
(30)	$CH_2CH_2N(C_2H_5)_2$	H
(31)		H
(32)		H
(33)		H
(34)	$CH_2CH_2N(C_2H_5)_2$	CH_3
(35)		CH_3
(36)		CH_3
(37)		CH_3

In vitro activity against *Trichomonas vaginalis* of the compounds was found to be very potential, moderate against *Entamoeba histolytica* and least active against *Candida albicans*. It was found that those 5-nitroimidazoles in which the fourth position is free showed higher activity against *Trichomonas vaginalis*, whereas substituents at imidazole follow the order pyrrolidine > piperidine > diethylamine > morpholine.

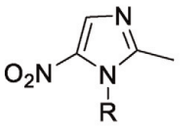
In the year 1969, Lancini et al. [16] synthesized a various number of 1,5-disubstituted 2-nitro imidazoles (38–44) through diazotization reaction or Gattermann reaction.



	R1	**R2**
(38)	CH_3	CH_3
(39)	CH_3	C_2H_5
(40)	CH_3	n-C_3H_7
(41)	CH_3	t-C_3H_7
(42)	CH_3	n-C_4H_9
(43)	C_2H_5	C_2H_5
(44)	C_2H_5	CH_3

All the synthesized compounds showed moderate *In vitro* activity against *Trichomonas vaginalis*.

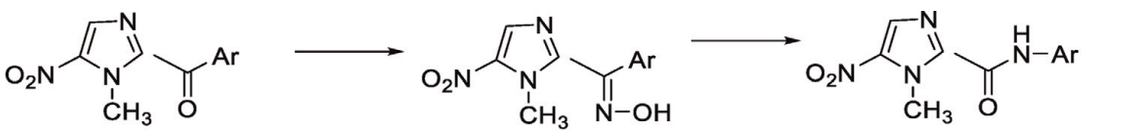
Miller et al. [17] in the year 1970, synthesized a novel series of 2-methyl-5-nitroimidazoles (45–49) and evaluated their antiprotozoal activity. This series bore an aliphatic side chain incorporated with electronegative group. *In vitro* and *In vivo* evaluations were carried out against *Trichomonas foetus* and *Trichomonas vaginalis* as well as against *Entamoeba histolytica*.



	R
(45)	$(CH_2)_2SO_2CH_2CH_3$
(46)	$(CH_2)_2SO_2CH_2(CH_3)_2$
(47)	$(CH_2)SO_2(CH_2)_2CH_3$
(48)	$(CH_2)_2SO_2CH_3$
(49)	$(CH_2)SO_2(CH_2)_3CH_3$

All the synthesized compounds showed mild activity against *Entamoeba histolytica* when compared to standard Tinidazole (27).

Nair et al. [18] in the year 1982, performed an acrylation of 1-methyl-5-nitroimidazole (50–58) with aroyl chlorides to form 2-aroyl-1-methyl-5-nitroimidazole through Beckmann rearrangement and yielded corresponding oximes and anilides as Beckmann product.

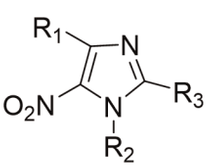


(50) Ar = C_6H_5,
(51) Ar = $C_6H_4Cl(p)$
(52) Ar = 2-theonyl

(53) Ar = C_6H_5,
(54) Ar = $C_6H_4Cl(p)$
(55) Ar = 2-theonyl

(56) Ar = C_6H_5,
(57) Ar = $C_6H_4Cl(p)$
(58) Ar = 2-theonyl

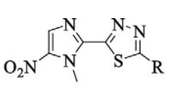
Walsh et al. [19] in the year 1986, synthesized a library of 5-nitroimidazole derivatives (59–65) which had ability to cause mutagenicity and these were also evaluated for their antitrichomonal activity.

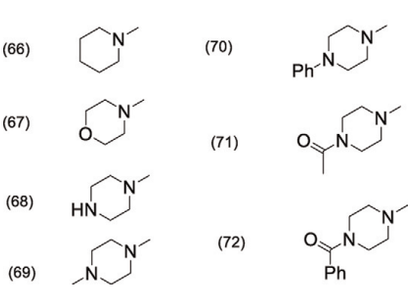


	R_1	R_2	R_3
(59)	CH_3	CH_3	CH_2OCONH_2
(60)	CH_3	CH_3	4-F-Ph
(61)	CH_3	CH_3CH_2OH	CH_3
(62)	CH_3	CH_3	CH_3
(63)	CH_3CH_2OH	CH_3	CH_3
(64)	CH_3CH_2OH	CH_3	CH_3
(65)	CH_3CH_2OH	CH_3	CH_3CH_2OH

Compounds 64 and 65 showed very less mutagenicity in comparison to standard drug ronidazole.

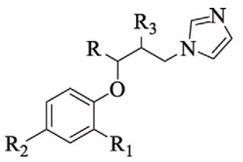
Foroumadi et al. [20] in the year 2005, synthesized a series of 2-(1-methyl-5-nitro imidazol-2-yl)-5-(1-piperazinyl, 1-piperidinyl and 1-morpholinyl)-1,3,4-thiadiazoles and estimated the antileishmanicidal activity for the synthesized compounds (77–83).



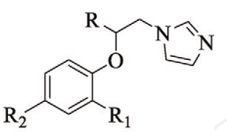


All compounds exhibited better activity against *Leishmania major* (IC_{50} < 1.744 μM).

Bhandari et al. [21] in the year 2010, synthesized a series of various substituted alkyl/aryl imidazoles (73–91) and estimated their activity against *Leishmania donovani* as antileishmanial agents.



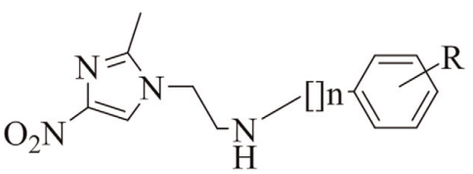
	R	R_1	R_2	R_3
(73)	Ph	H	CF_3	H
(74)	Ph	H	NO_2	H
(75)	Ph	NO_2	H	H
(76)	Ph	F	NO_2	H
(77)	Ph	H	CF_3	CH_3
(78)	Ph	NO_2	H	CH_3
(79)	CH_3	H	CF_3	H
(80)	CH_3	H	NO_2	H
(81)	CH_3	F	NO_2	H
(82)	CH_3	NO_2	H	H
(83)	CH_3	CF_3	NO_2	H



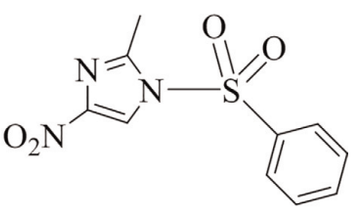
	R	R_1	R_2
(84)	Ph	H	CF_3
(85)	Ph	H	NO_2
(86)	Ph	F	NO_2
(87)	Ph	NO_2	H
(88)	$PhOCH_2$	H	NO_2
(89)	$PhOCH_2$	H	CF_3
(90)	$PhOCH_2$	F	NO_2
(91)	$PhOCH_2$	NO_2	H

Most of the synthesized compounds exhibited very significant activity up to 84–91% inhibition at the concentration of 10 μg/ml while some compounds showed high IC_{50} values ranging from 0.47–4.85 μg/ml against amastigotes.

Hernandez-Nunez et al. [22] in the year 2009, reported synthesis of novel imidazole derivatives (103–117). These compounds were biologically examined against various parasites namely *Giardia intestinalis*, *Trichomonas vaginalis* and *Entamoeba histolytica*.



	n	R
(92)	1	H
(93)	0	H
(94)	0	4-F
(95)	0	4-Cl
(96)	0	4-CN
(97)	0	4-NO_2
(98)	0	2,4-di-Cl
(99)	0	3-CF_3



	R
(100)	$NHCOCH_3$
(101)	H
(102)	CH_3
(103)	Cl
(104)	F
(105)	NO_2
(106)	OCH_3

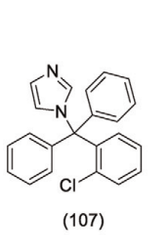
Compounds (100–106) exhibited two fold better activity in comparison to benzimidazole analogs against *Trichomonas* vaginalis and *Giardia intestinalis* and found to be more active analogs against *Entamoeba histolytica*.

2.2 Antibacterial and antifungal agents

During the last 30 years, antifungal azoles [23] such as clotrimazole (107), miconazole (108), ketoconazole (109), butoconazole (110), econazole (111), cloconazole (112), fenticonazole (113), oxiconazole (114) and sulcoconazole (115)

have been introduced. In all these compounds N-1 atom of imidazole is linked to other aromatic rings. The other antimycotic azoles have a five membered ring with three nitrogen atoms.

The antifungal azoles inhibit the cytochrome P-450 which catalyzes the 14-α-demethylation of lanosterol to ergosterol [15]. The azole drugs are relatively of broad spectrum antifungal activity but there may be differences among the individual compounds.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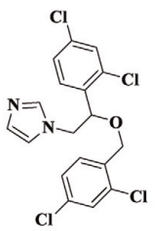
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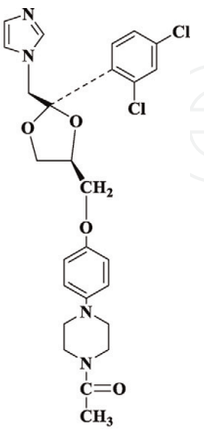
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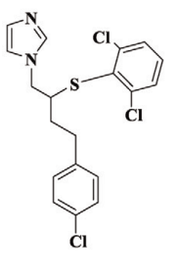
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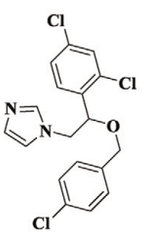
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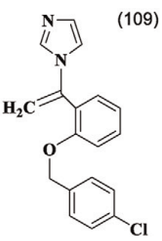
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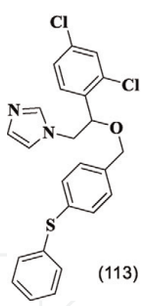
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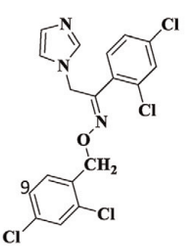
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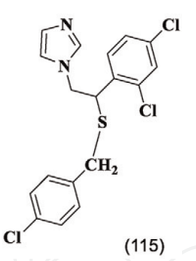
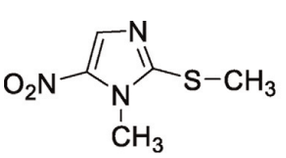

(115)

Castelli et al. [24] in the year 1997, synthesized two new compounds belonging to 5-nitroimidazole family: sulphuridazole and sulphonidazole derivatives (116–119) and compared their minimum inhibitory concentrations with metronidazole (26).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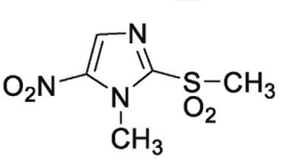
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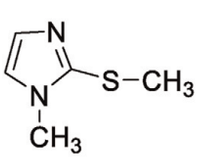
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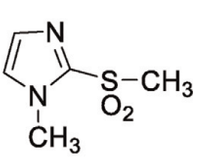
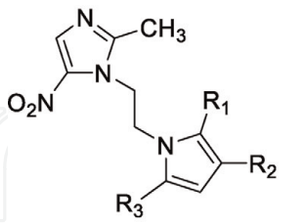
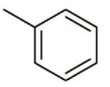
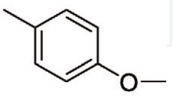
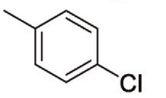
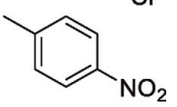

(119)

Sulphonidazole (116–117) showed better activity than sulphuridazole (118–119) against all the bacterial and fungal strains.

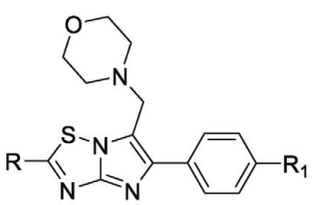
Demirayak et al. [25] in the year 1999, synthesized a novel series of some pyrrole-nitroimidazole clubbed hybrid derivatives (120–125) and evaluated their antifungal activity.



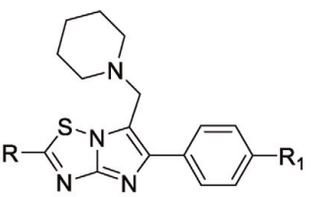
	R_1	R_2	R_3
(120)	H	H	H
(121)	CH_3	H	CH_3
(122)	CH_3	$COOC_2H_5$	
(123)	CH_3	$COOC_2H_5$	
(124)	CH_3	$COOC_2H_5$	
(125)	CH_3	$COOC_2H_5$	

Compounds 120–124 showed excellent activity against *Staphylococcus aureus* at the dose of 8 mg/ml while all the synthesized compounds exhibited excellent activity against fungal strain *Candida albicans*.

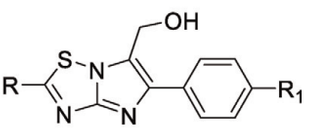
Kolavi et al. [26] in the year 2006, synthesized a library of some imidazo thiadiazole derivatives (126–161) and evaluated their antibacterial activity.



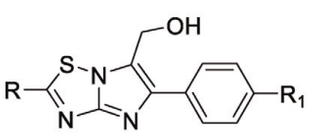
	R	R_1
(126)	Cyclohexyl	H
(127)	Cyclohexyl	Br
(128)	2-furfuryl	H
(129)	2-furfuryl	Br
(130)	2-thienyl	H
(131)	2-thienyl	Br



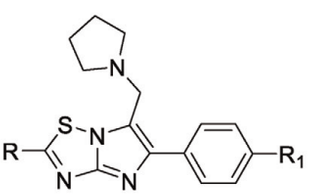
	R	R_1
(132)	Cyclohexyl	H
(133)	Cyclohexyl	Br
(134)	2-furfuryl	H
(135)	2-furfuryl	Br
(136)	2-thienyl	H
(137)	2-thienyl	Br



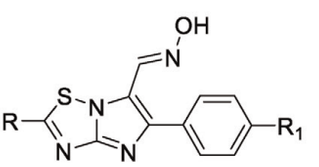
	R	R_1
(138)	Cyclohexyl	H
(139)	Cyclohexyl	Br
(140)	2-furfuryl	H
(141)	2-furfuryl	Br
(142)	2-thienyl	H
(143)	2-thienyl	Br



	R	R_1
(144)	Cyclohexyl	H
(145)	Cyclohexyl	Br
(146)	2-furfuryl	H
(147)	2-furfuryl	Br
(148)	2-thienyl	H
(149)	2-thienyl	Br



	R	R_1
(150)	Cyclohexyl	H
(151)	Cyclohexyl	Br
(152)	2-furfuryl	H
(153)	2-furfuryl	Br
(154)	2-thienyl	H
(155)	2-thienyl	Br

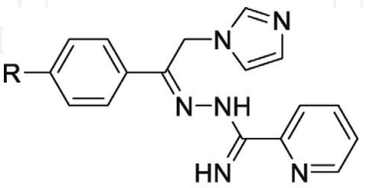


	R	R_1
(156)	Cyclohexyl	H
(157)	Cyclohexyl	Br
(158)	2-furfuryl	H
(159)	2-furfuryl	Br
(160)	2-thienyl	H
(161)	2-thienyl	Br

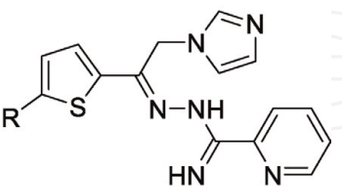
The antibacterial screening revealed that compounds 134 and 140 showed significant activity against *Escherichia coli*. Compounds 126 and 127 showed good inhibition of *Escherichia coli* at a concentration of 100 μg/ml.

The antifungal screening revealed that the compounds 132, 134, 142, 159 and 161, displayed good antifungal activity against *Penicillium wortmannii* and *Aspergillus niger*.

Banfi et al. [27] in the year 2006 synthesized and evaluated new imidazoles (162–166) and (167–171) for antifungal and antimycobacterial activity.



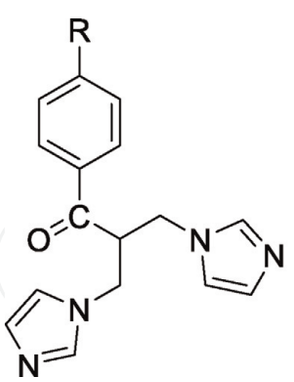
	R
(162)	H
(163)	Br
(164)	Cl
(165)	CH_3
(166)	C_6H_5



	R
(167)	H
(168)	Br
(169)	Cl
(170)	CH_3
(171)	C_6H_5

The results showed that the compounds 166 and 171 showed very good activity, while rest of the derivatives exhibited weak antifungal activity against *Candida* species.

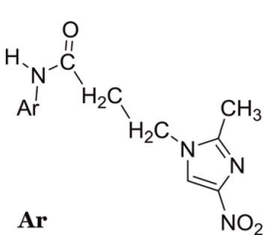
Mamolo et al. [28] in the year 2007, reported the synthesis of novel bis-imidazole derivatives (172–175) and screened their antimycobacterial and antifungal activity.



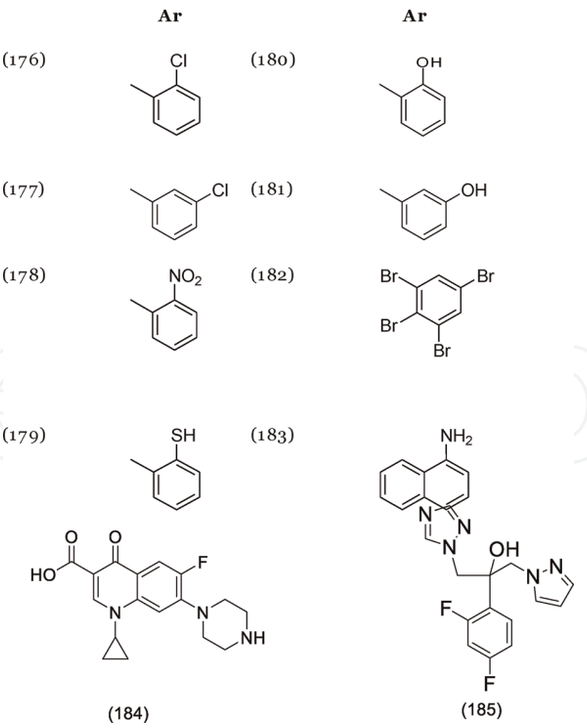
	R
(172)	H
(173)	Cl
(174)	Br
(175)	F

Maximum compounds exhibited weak activity towards *Mycobacterium tuberculosis* and *Candida* species. Compound 175 was considered to be a significant antifungal agent against *Candida* species.

Ganguly et al. [29] in the year 2009, synthesized a few compounds of the type (176–183) and these were evaluated for antibacterial, antifungal and anti-HIV activity.

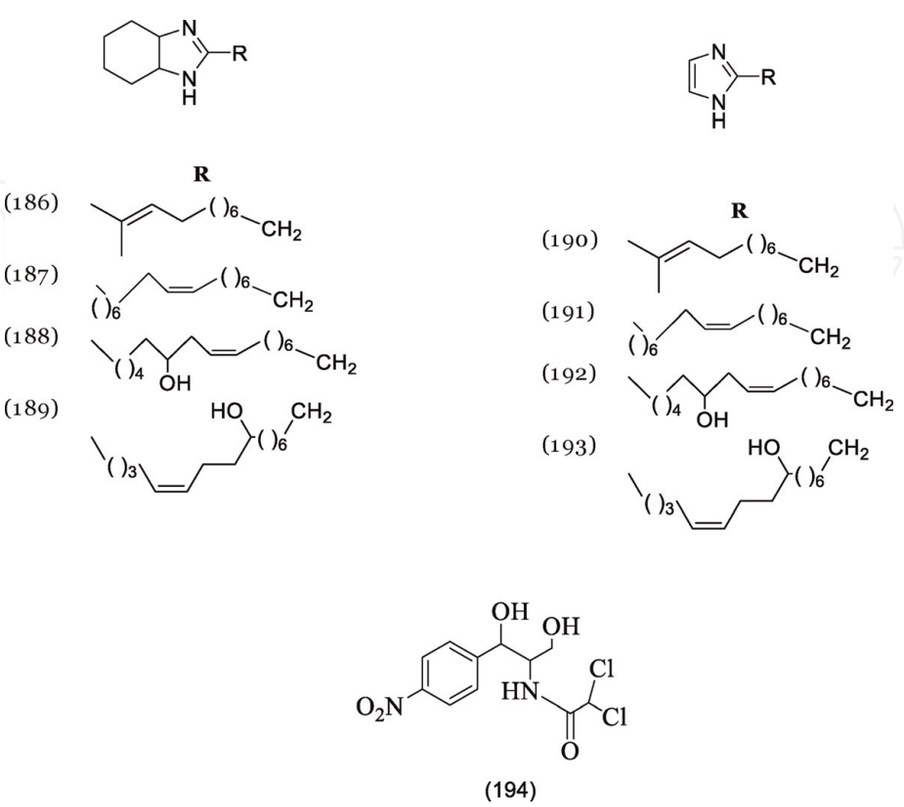


Ar **Ar**



Compound (176) exhibited good activity against *Staphylococcus aureus* whereas compound (178) showed moderate activity towards *Escherichia coli*. However, all the compounds were less active than standard drug ciprofloxacin (184). Compounds (174) and (179) exhibited significant antifungal activities against *Candida albicans* comparable to the standard drug fluconazole (185). None of the compounds had appreciable anti-HIV activity.

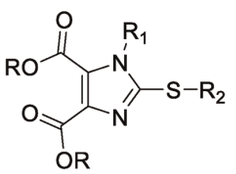
Sharma et al. [30] in the year 2009, synthesized a series of novel 2-substituted benzimidazoles (186–189) and imidazoles (190–193) from long chain alkenoic acids and these were evaluated as antibacterial agents.

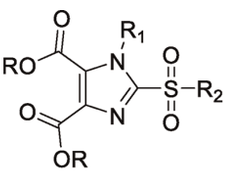


(194)

Compounds (190) and (193) were found to be most active against *Escherichia coli* and *Bacillus subtilis*. Whereas the imidazoles (186–189) exhibited moderate activity against the tested bacterial strains when compared to chloramphenicol (194) as standard.

Wu-Li-Ji et al. [31] in the year 2010, reported the synthesis of 2-benzyl thioimidazoles and 2-benzylthio sulfonyl-1H-imidazoles (195–208) and were evaluated for antibacterial, antifungal and antioxidant activity.



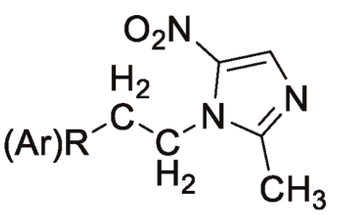


	R	R1	R2
(195)	H	$CH_3CH(CH_3)_2$	o-Me-$CH_3C_3H_4$
(196)	C_2H_5	H	o-Me-$CH_2C_6H_4$
(197)	H	H	$C_{10}H_{11}CH_2$
(198)	H	$COOC_2H_5$	o-Me-$CH_2C_6H_4$
(199)	H	o-Me-$CH_2C_6H_4$	o-Me-$CH_2C_6H_4$
(200)	H	$CH_2C_6H_5$	$CH_2C_6H_5$
(201)	H	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$

	R	R1	R2
(202)	H	$CH_3CH(CH3)_2$	o-Me-$CH_3C_3H_4$
(203)	C_2H_5	H	o-Me-$CH_2C_6H_4$
(204)	H	H	$C_{10}H_{11}CH_2$
(205)	H	$COOC_2H_5$	o-Me-$CH_2C_6H_4$
(206)	H	o-Me-$CH_2C_6H_4$	o-Me-$CH_2C_6H_4$
(207)	H	$CH_2C_6H_5$	$CH_2C_6H_5$
(208)	H	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$

All newly reported derivatives exhibited excellent antibacterial activity towards *Proteus vulgaris* and *Klebsiella pneumonia* while exhibiting excellent antifungal activity towards *Penicillium chrysogenum.*

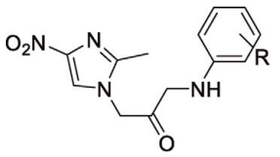
Ganguly et al. [32] in the year 2010, synthesized some novel 2-methyl-5-nitroimidazole analogs (209–211). These were evaluated for antibacterial, antifungal and antidiarrheal activities.



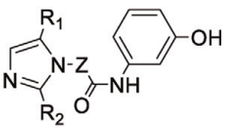
	R	Ar
(209)	-NH-CH_2-CH_2-CH_3	-C_6H_5NH
(210)	-NH-$CH(CH_3)_2$	o-$C_6H_5NHNO_2$
(211)	-N-$[CH(CH_3)_2]_2$	p-$C_6H_5NHNO_2$

Compounds 209–211 showed significant anti-diarrheal activity at a dose of 60 mg/kg body wt. while compound 209 exhibited significant antibacterial activity against *Staphylococcus aureus.*

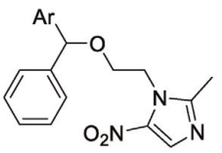
Ganguly et al. [33] in the year 2011, reported some novel imidazole analogs of the type (261–274) and evaluated their antibacterial and anti-HIV activity.

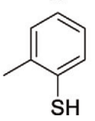


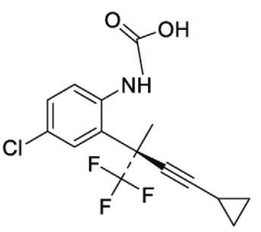
	R
(212)	H
(213)	p-CH3
(214)	p-CH3
(215)	m-Cl
(216)	p-Cl



	R	R1	Z
(217)	CH_3	H	CH_2
(218)	CH_3	H	$CH(CH_3)$
(219)	CH_3	H	CH_2CH_2
(220)	CH_3	NO_2	CH_2
(221)	CH_3	NO_2	$CH(CH_3)$



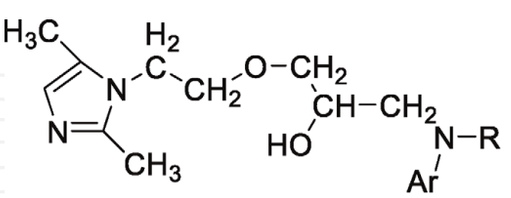
	Ar
(222)	
(223)	
(224)	
(225)	



(226)

Compounds 212, 215 and 220 exhibited moderate activity as antibacterials, however compounds 212, 213 and 215 showed weak anti-HIV activity as compared to the standard efavirenz (226).

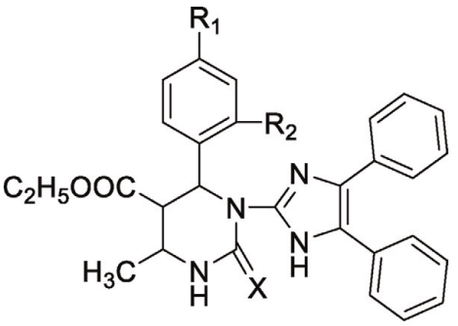
Ganguly et al. [34] in the year 2011 synthesized a few compounds of type (226–232) these were evaluated for antibacterial, antifungal and anti-HIV activity.



	R	Ar
(227)	H	aniline
(228)	H	m-Cl aniline
(229)	H	2,4-di-methyl aniline
(230)	H	1-naphylamine
(231)	H	p-toludine
(232)	H	m-toludine

Compounds 228 exhibited 44% inhibitory activity against HIV-1 RT.

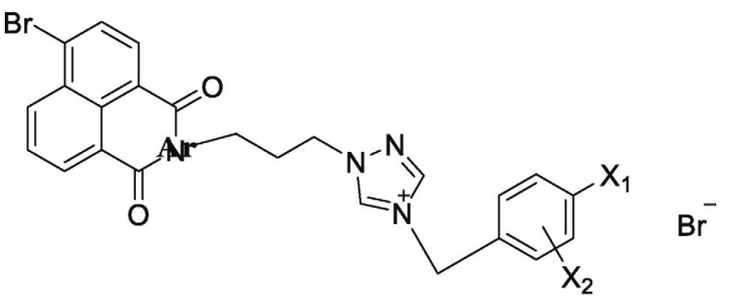
Pathan and Rahatgoankar [35] in the year 2011, synthesized a series of substituted 4,5-diphenyl imidazolyl-pyrimidine hybrids (233–239).



	X	R_1	R_2
(233)	O	H	N
(234)	O	H	NO_2
(235)	O	Cl	H
(236)	O	O	H
(237)	S	H	H
(238)	S	Cl	H
(239)	S	H	NO_2

Compound 236 was found to be most active against *Staphylococcus aureus* among all tested compounds.

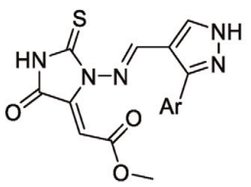
Zhang and Zhou [36] in the year 2011 reported the synthesis of naphthalimide derived azoles (240–248) as novel anti-microbial agents and evaluated their efficiency *in vitro* against bacteria and fungi.

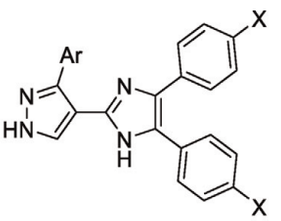


	n	X1	X2
(240)	1	F	2-F
(241)	1	Cl	2-Cl
(242)	1	Cl	3-Cl
(243)	1	H	2-Cl
(244)	1	Cl	H
(245)	1	NO_2	H
(246)	2	F	2-F
(247)	3	F	2-F
(248)	4	F	2-F

It was found that compounds 246–248 with different alkyl linkers were synthesized selectively and gave antibacterial profiles, especially compounds 246 and 247 showed prominent activity against *Pseudomonas aeruginosa* being eight fold more efficient than chloromycin.

Vijesh et al. [37] in the year 2011, synthesized a dual series containing imidazole-pyrazole combined derivatives (249–262).



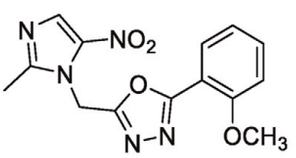


(249)	2,4-dichloro phenyl
(250)	2,5-dichloro thiophene
(251)	4-SCH_3-C_6H_4
(252)	4-SCH_3-C_6H_4

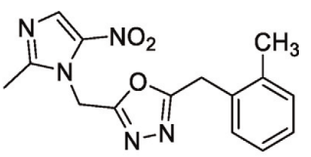
	Ar	X
(253)	4-SCH_3-C_6H_4	H
(254)	2,4-dichlorophenyl	H
(255)	Biphenyl	H
(256)	4-CH_3-C_6H_4	H
(257)	2,5-dichlorothiophene	H
(258)	4-SCH_3-C_6H_4	Br
(259)	2,4-dichlorophenyl	Br
(260)	Biphenyl	Br
(261)	4-CH_3-C_6H_4	Br
(262)	2,5-dichlorothiophene	Br

Among the tested compounds, compound 253 emerged as highly active against *Trychophyton rubrum* compared to standard fluconazole.

Zhu et al. [38] in year 2012 reported the design and synthesized oxadiazole derivatives (263–264) and evaluated their antibacterial activity.



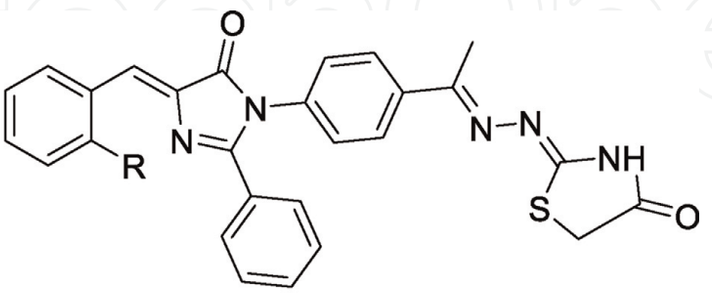
(263)



(264)

Compound 312 with MIC of 1.56–3.13 μg/ml and compound 313 with MIC of 1.56–6.25 μg/ml were the most potent inhibitors of FabH against *Escherichia coli*.

Desai et al. [39] in year 2012 synthesized a series of imidazole analogs (265–269) and reported their activity towards bacterial and fungal species.

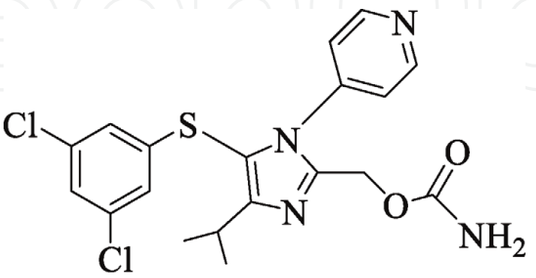


	R		R		R
(265)	H	(319)	2-NO_2	(324)	2-CH_3
(266)	2-Cl	(320)	4-NO_2	(325)	3-CH_3
(267)	4-Cl	(321)	2-OH	(326)	4-CH_3
(268)	2-F	(322)	3-OH	(327)	2-CH_3
(269)	2-F	(323)	4-OH	(328)	2-OCH_3

Compounds (265–269) were evaluated against *Gram-positive bacteria* mainly *Staphylococcus aureus*, *Staphylococcus pyogenes* and Gram-negative *bacteria* mainly *Escherichia coli*, *Pseudomonas aeruginosa* and fungi.

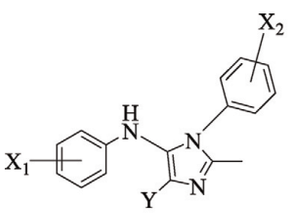
2.3. Antiviral agents

The first report on N-Amino imidazoles as antiHIV agents and particularly as NNRTIs came up with the discovery of Capravirine (S-1153) (270) in the year 2000 [1]. This also retained activity against HIV-1 strains carrying K103N mutation in RT structure.



(270)

After this, anti-viral active N-amino imidazole (271) derivatives were reported by Lagoja et al. [2] in the year 2003, which exhibited considerable antiviral activity.



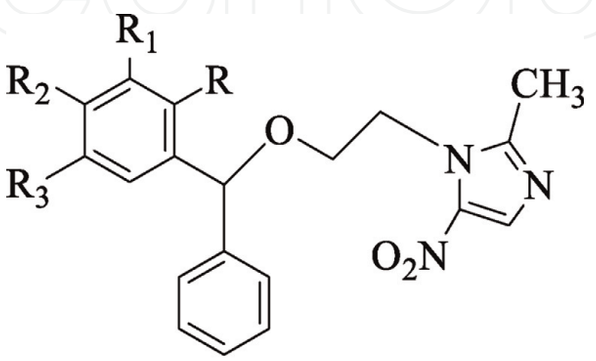
X1 & X2 = Halogen, Alkyl

Y = SH, H

(271)

Methylation or benzoylation on sulfur group may demolish the anti HIV activity of compound, whereas compounds bearing alkyl/aryl substituents at para position to imidazole ring affected the antiHIV activity. Smaller the substituent higher the activity.

Silvestri et al. [40] in the year 2002 synthesized a novel series of 1-{2-(diarylmethoxy)ethyl]-2-methyl-5-nitroimidazoles (272) and evaluated their antiHIV activity.

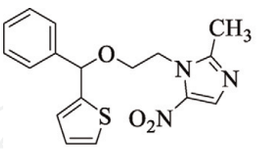


(272)

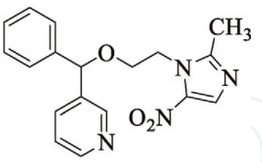
Substitution at meta position to the phenyl ring exhibited better anti-HIV activity while substituents like fluoro, chloro or methyl substituent enhances the activity than its prototype.

It was observed that substitution at meta position facilitates better activity rather than substitution at *ortho* and *para* position. Fluorine at meta position exhibited maximum potency among all derivatives.

De Martino et al. [40] replaced one phenyl ring of 1-[2-diarylmethoxy] ethyl) 2-methyl-5-nitroimidazoles (DAMNIs) with heterocyclic rings, such as 2-thienyl (273) or 3-pyridinyl ring (274), leading to novel DAMNIs with increased activity.



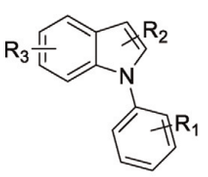
(273)



(274)

N-Alkylation of imidazole, 2-methyl imidazole and 2-methyl-4-nitroimidazole has been carried to achieve effective antiHIV agents.

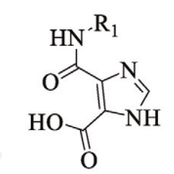
Xu et al. [41] in the year 2008 synthesized some novel derivatives of N-arylindoles (275–282) and evaluated as HIV integrase inhibitors for first time.



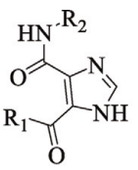
	R_1	R_2	R_3
(275)	p-NO_2	H	H
(276)	o-NO_2	H	H
(277)	o-CN	H	H
(278)	p-NO_2	H	5-NO_2
(279)	o-NO_2	H	5-NO_2
(280)	o-NO_2	H	7-CH_3
(281)	p-NO_2	CH_3	H
(282)	o-NO_2	CH_3	H

Among all synthesized compounds, 276, 279 and 282 exhibited very significant anti HIV-1 integrase inhibitory activity. Especially, compound 277 showed highest activity with EC_{50} value 7.88 μg/ml and therapeutic index 24.61.

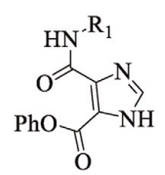
Serrao et al. [42] in the year 2013, reported a novel series of 5-carbonyl-1H-imidazole-4-carboxamides (283–299) capable of inhibiting HIV-1 integrase–LEDGF/p75 interaction.



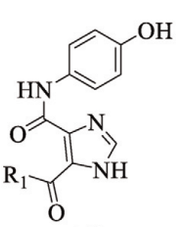
	R1
(283)	p-F-ph
(284)	p-F-Benzyl
(285)	Pyridine
(286)	p-NO_2-Ph
(287)	p-NH_2-Ph



	R1	R2
(288)	Morpholine	Py
(289)	4-OH-pipreidine	Py
(290)	Piperazine	Py
(291)	$NHNH_2$	p-Me-ph
(292)	$NHNH_2$	Py
(293)	MeNH	Py



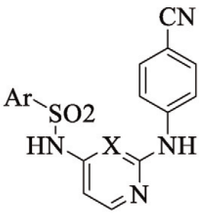
	R1
(294)	Py
(295)	p-Me-ph
(296)	2(Benzyloxy)phenyl



	R1
(297)	Morpholine
(298)	4-OH-pipreidine
(299)	Piperazine

All the synthesized compounds showed almost equivalent activity as their MTT/MT-4 (CC_{50} and EC_{50}) values were same.

Huang et al. [43] in the year 2017, synthesized a series of diarylpyrimidines (300–310) and indolylarylsulphones (311–321) hybrids and showed their activity against HIV1-IIIB strain.



X=CH (300-310)
X=N (311-321)

	Ar
(300)	4-CH_3-Ph
(301)	4-CN-Ph
(302)	4-(tert-butyl)-Ph
(303)	4-F-Ph
(304)	4-CF_3-Ph
(305)	3,5-di-CH_3-Ph
(306)	3,5-di-F-Ph
(307)	3,5-di-CF_3-Ph
(308)	2,4,6-tri-CH_3-Ph
(309)	2,4,6-tri-isopropyl-Ph
(310)	Napth-2-yl

	Ar
(311)	4-CH_3-Ph
(312)	4-CN-Ph
(313)	4-(tert-butyl)-Ph
(314)	4-F-Ph
(315)	4-CF_3-Ph
(316)	3,5-di-CH_3-Ph
(317)	3,5-di-F-Ph
(318)	3,5-di-CF_3-Ph
(319)	2,4,6-tri-CH_3-Ph
(320)	2,4,6-tri-isopropyl-Ph
(321)	Napth-2-yl

Compound 311 exhibited favorable selectivity index (SI = 80) which was the maximum above all synthesized compounds and determined by MTT method.

3. Conclusion

Compounds containing azole derivatives, exhibit a wide variety of activities such as antibacterial, antifungal, anthelmintic, antiprotozoal, antiviral, anticancer, antihistaminic, antiulcer, antipsychotic and various other biological activities.

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