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MERCAPTOIMIDAZOLE ANALOGS AS POTENTIAL THERAPEUTIC AGENT

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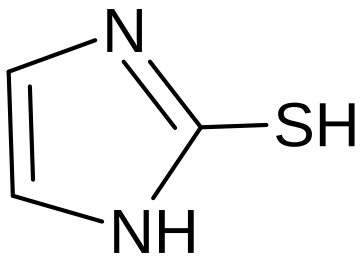
ABSTRACT
Mercaptoimidazoles have occupied a unique position in heterocyclic chemistry, and its derivatives have attracted considerable interests in recent years for their versatile properties in chemistry and pharmacology. Mercaptoimidazole is nitrogen and Sulphur containing heterocyclic ring which possesses biological and pharmaceutical importance. Thus, Mercaptoimidazole compounds have been an interesting source for researchers for more than a century. There are several methods used for the synthesis of Mercaptoimidazole-containing compounds, and also their various structure reactions offer enormous scope in the field of medicinal chemistry. The imidazole derivatives possess extensive spectrum of biological activities such as antibacterial, antifungal, analgesic, and anti-HIV activities. This paper aims to review the important biological activities of Mercaptoimidazole during the past years.

KEYWORDS: Mercaptoimidazole, Antimicrobial, Antibacterial, Anti-HIV, Antifungal.

INTRODUCTION

Heterocycles containing nitrogen and sulfur have long been used in the fields of biological and pharmaceutical chemistry.[1-2] The nitrogen and sulfur derivatives exhibit biological activities that include phosphodiesterase inhibition, anti-tubercular, analgesic, anti-inflammatory, antibacterial, antiallergic, antitumor, and anthelmintic properties. Mercaptoimidazole also called as imidazole-2-thione, having empirical formula C3H4N2S is one such compound.[3]



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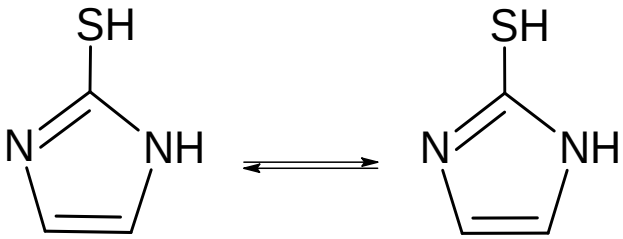


R=H,alkyl or aryl group
Figure: 2.

Based on a calculation using density-functional theory, imidazole-2-thione exhibits the tautomerism of thione and thiol, where thione's existence is greater than thiol's and is more stable than thiol.[4] There are several medications with strong biological effects that include imidazole-2-thione skeletons. We present the synthesis of a new series together with its biological activity here, based on an evaluation of the above-mentioned facts.

Pharmacological activities of Mercaptoimidazole Derivatives

Mercaptoimidazole derivatives exhibit a range of biological activities, including antimicrobial, antioxidant, anti-inflammatory, and anticancer properties. These compounds are often synthesized and evaluated for their potential as therapeutic agents. certain mercaptoimidazole derivatives have been investigated for their potential to inhibit enzymes linked to cancer cell growth.

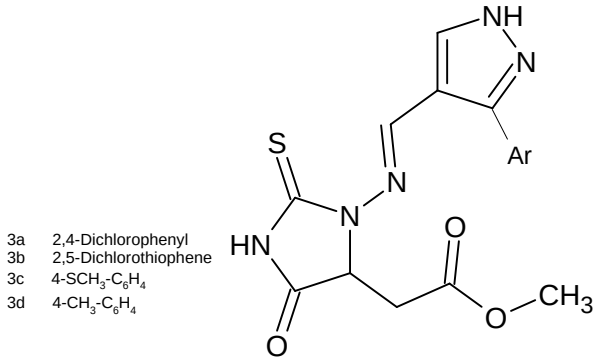
Antimicrobial

Mercaptoimidazole derivatives have shown promising antimicrobial activity against various bacterial and fungal pathogens. These compounds often target critical enzymes in microbes, such as DNA gyrase and topoisomerase IV, which are essential for bacterial DNA replication and cell division.

Antibacterial activity

Vijesh et al. carried out the invitro antibacterial activity of newly synthesized compounds 1a–d. *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Salmonella typhimvrium*, *Clostridium perfringens*, and *Pseudomonas aeruginosa* were used to investigate the activity. The

antibacterial screening revealed that some of the tested compounds showed good inhibition against various tested microbial strains.3c showed excellent activity against *P. aeruginosa* and *C. perfringens* compared to standard drug streptomycin.[5]



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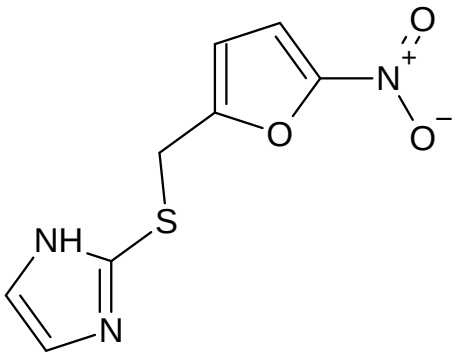


Figure: 4.

Tweit and associates created a number of substituted imidazole's, as well as their 5- and 4-nitro counterparts, having alkyl and aralkyl Sulphur groups at position 2. Using the serial dilution approach, the antibacterial efficacy of each synthesized derivative was measured against *B. subtilis, E. coli, Salmonella Para typhi A*, and *Erwinia spp*.[6]

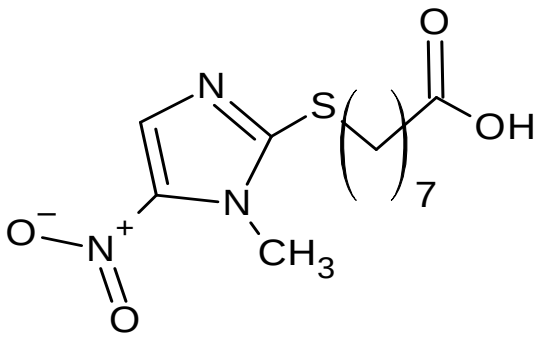


Figure:5.

Robert C *et al*. synthesized Nitroimidazoles which show interesting activity against the bacterium, *Neisseria gonorrhoeae*, in addition to the activities usually shown by nitroimidazoles against protozoa and anaerobic bacteria. The compounds were prepared by alkylation of l-methyl-2-mercaptoimidazole, followed by nitration. Optimum activity occurs with a 5-nitro group and a free carboxyl at the end of the group attached to the Sulphur.[7]

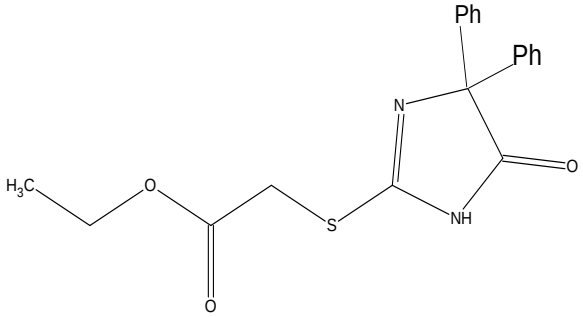


Figure: 6.

In another study, 2-(4,5-dihydro-5-oxo-4,4 (diphenyl-1H-imidazole-2-yl) thioacetic acid (6) was shown to have a modest level of antibacterial activity against *S. aureus, P. aeruginosa, and B. subtilis*. On the other hand, the side chain's cyclization boosted activity.[8]

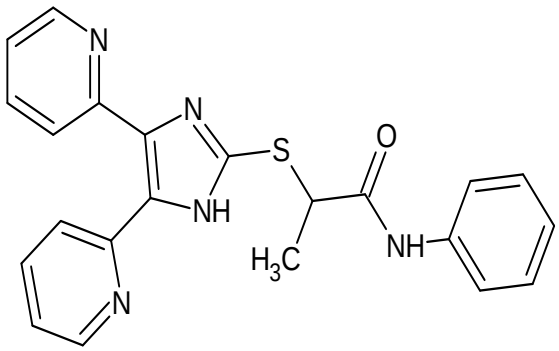
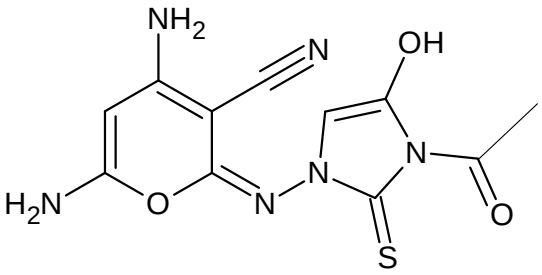


Figure: 7.

Salama and Almotabacani found 2-mercaptoimidazoles to possess some antibacterial activity. The authors created two mercaptoimidazoles and used the cup plate method to test their antibacterial efficacy in order to confirm. The most active chemical in the series, compound 7, was shown to be sensitive to all tested strains, including *B. subtilis, S. aureus, E. Coli*, and *P. mirabilis*.[9]



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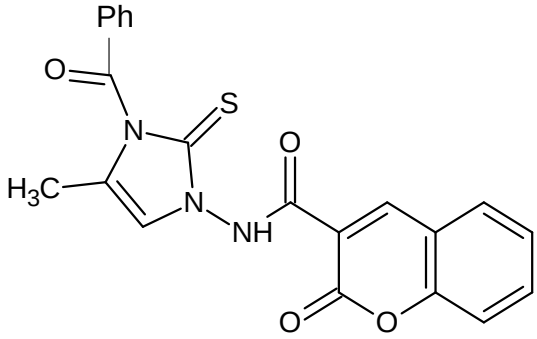
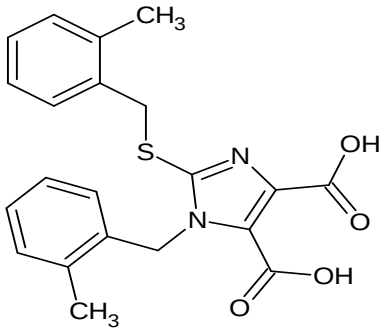


Figure: 9.

An imidazole conjugated systems based on cyanoacetic 2-[(benzoylamino) thioxomethyl] hydrazides were developed as a result of further research. The majority of the synthesized systems showed appreciable antibiotic activity against *X. citri* and *E. coli*, according to an evaluation of their antibacterial efficacy. Compounds 8 and 9 showed high inhibitory activity against both bacteria, according to analysis and evaluation of the antimicrobial spectra of the synthesized systems.[10]



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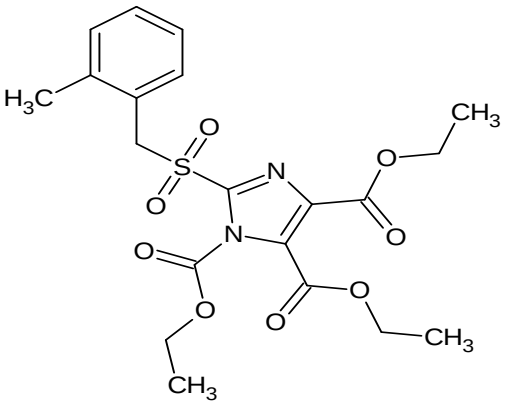


Figure: 11.

Additionally, the antibacterial activity of 2-benzylthio- and 2-benzylsulfonyl-1H-imidazoles was assessed against *S. aureus*, *B. subtilis*, *P. vulgaris*, and *K. pneumonia* in an effort to create a more potent chemotherapeutic drug. At a dosage of 100 g/ml, compounds 10 and 11 demonstrated outstanding inhibitory action against all tested bacteria.[11]

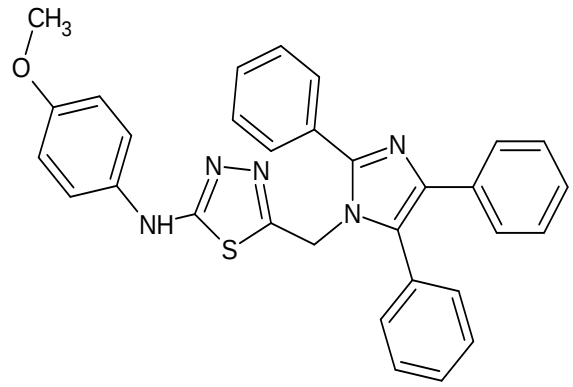


Figure. 12.

Amir *et al*. synthesized a new set of azole derivatives containing a 2,4,5-triphenylimidazole moiety, and used the agar diffusion method to test them for antibacterial activity. With an 80.6% and 78.6% inhibition against *E. coli* and *S. aureus*, respectively, at a concentration of 100 g/ml, compound 12 was shown to be the most powerful chemical based on early analytical data.[12]

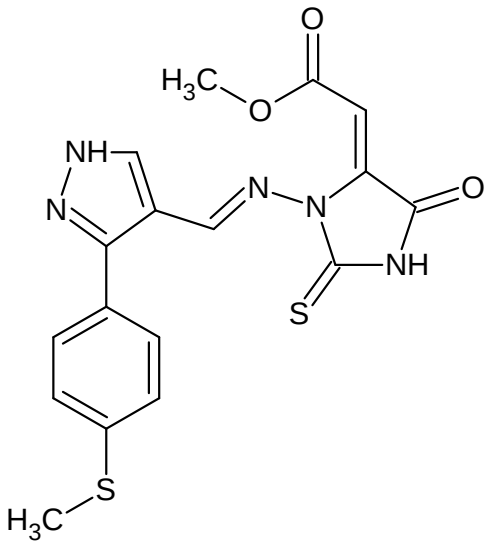


Figure: 13.

Moreover, 3-substituted-1H pyrazole-4-carbaldehydes were used to create novel imidazole derivatives substituted with pyrazoles. Using the well plate method, the preliminary screening findings showed that compound 13 had good antibacterial activity at 500 g/ml against all tested organisms (*S. aureus*, *B. subtilis*, *C. profingens*, *E. coli*, *S. typhimorium*, and *P. aeruginosa*), with a zone of inhibition extending from 5 to 15 mm.[5]

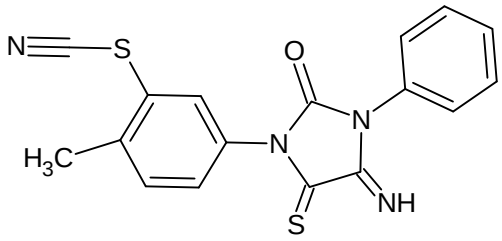


Figure: 14.

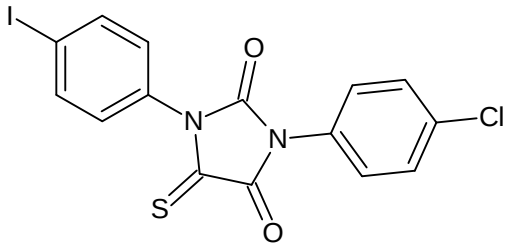


Figure: 15.

Some new imidazolidine derivatives were synthesized by reacting iso(thio)cyanates, aldehydes and dibenzylideneacetone and assayed for antibacterial potency against *B. subtillus*, *S.aureus*, *E. coli and S. typhi*. The compounds 14 and 15 were found to possess high antimicrobial activities.[13]

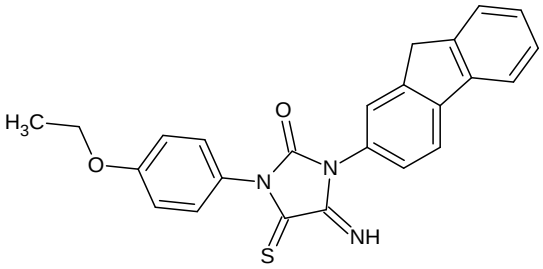


Figure: 16.

El- Sharief and Mousa synthesised and assessed a range of imidazolidine iminodithiones and mono-and bis-imidazolidine-iminothiones against gramme positive (*B. subtilis and S. aureus*) and gramme negative (*E. coli and S. typhi*) bacteria using the disc diffusion method. Considerable antibacterial activity was shown by all of the produced compounds. However, at 100 l concentration, it was discovered that strain 16 had outstanding activity against all strains, with a zone of inhibition spanning from 17 to 19 mm. Additionally, the SAR research showed that the ethoxy group was necessary for function. Absence of activity was caused by substitution with a bromine group.[14]

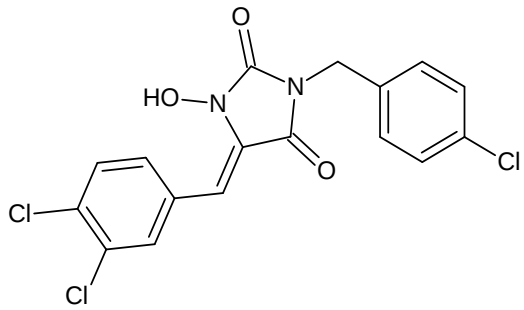
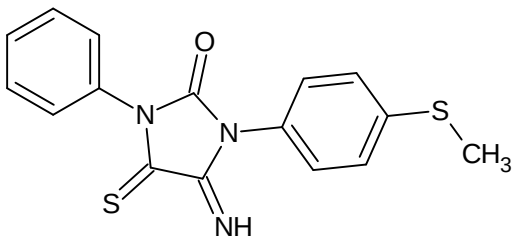


Figure: 17.

Pentasubstituted imidazolidinediones were examined in an additional effort. The findings showed that at 32 g/m, compound 17 was effective against *M. flavus*.[14]



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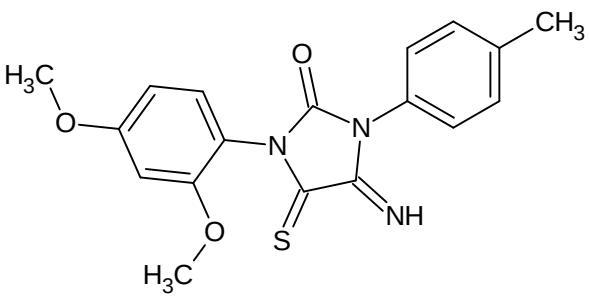


Figure: 19.

The agar diffusion technique was used to examine the antibacterial efficacy of a number of imidazolidineminothiones against *E. Coli*, *Sarcina lutea*, *B. subtilis*, and *S. aureus*. The most active compounds against all tested strains were 18 and 19, according to the bioassay data. A zone of inhibition measuring 22–25 mm was seen by compounds in the series at a concentration of 100 g/ml.[15]

Analgesic Activity

Mercaptoimidazole derivatives have been studied for their analgesic properties and have shown promising results in several in vivo studies. These compounds have

been evaluated for their ability to alleviate pain through various mechanisms, often involving the inhibition of enzymes or receptors related to pain pathways.

Compound	R	Ar
20a	H	4-$OCH_3C_6H_4$
20b	H	4-FC_6H_4
20c	H	4-CNC_6H_4
20d	Br	4-$OCH_3C_6H_4$
20e	Br	4-FC_6H_4
20f	Br	4-CNC_6H_4
20g	OCH_3	4-$OCH_3C_6H_4$
20h	OCH_3	4-FC_6H_4
20i	OCH_3	4-CNC_6H_4
20j	NO_2	4-$OCH_3C_6H_4$
20k	NO_2	4-FC_6H_4
20l	NO_2	4-CNC_6H_4

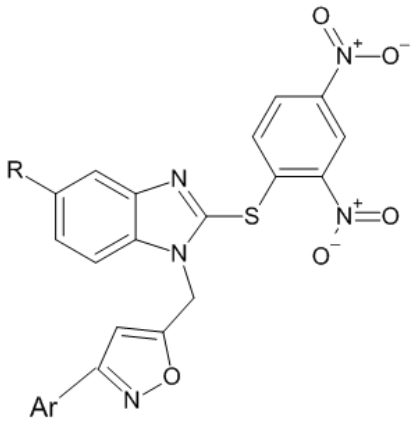


Figure: 20.

According to Kankala *et.al.,* synthesis of isoxazole mercaptobenzimidazole hybrids and the analgesic activity of the synthesized compounds (142a–l) was assessed by hot plate method. Almost all the compounds have shown very potent analgesic activity when compared with standard drug pentazocine. Amongst all the compounds, 20e and 20f with potent analgesic activity, the compounds 142k and 142l have shown moderate activity and were found to be more potent than the standard pentazocine. The remaining compounds 20a–d and 20g–j had shown poor activity.[6]

Compound	R
21a	$C_7H_6O_2$
21b	C_7H_5OBr
21c	C_7H_5OCl
21d	$C_8H_8O_2$
21e	$C_7H_5O_3$
21f	$C_7H_8O_2$
21g	C_7H_6O
21h	C_7H_8O

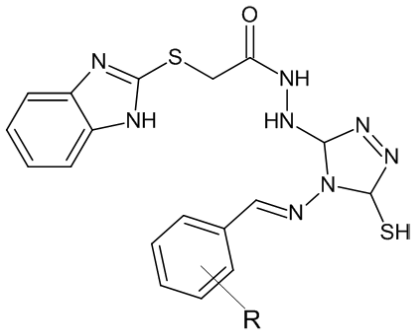


Figure: 21.

Sidram A.Navade *et al*. synthesized mercaptoimidazole derivatives. and conducted analgesis activity by acetic acid induced writhing effect in mice in which compound 2MB1, 2MB4 and 2MB7 have shown good analgesic activity.[17]

22b	n=7
22c	n=8
22d	n=9
22e	n=11

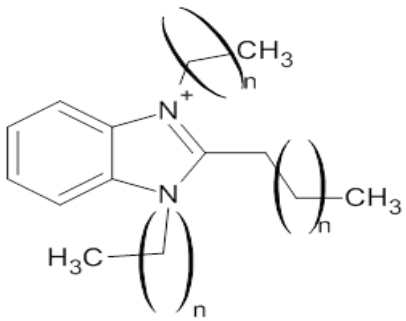


Figure: 22.

Additionally, investigate how the 200 mg/kg dose of this activity affects the results based on moleculesize. Therefore, at the therapeutic dose of 100 mg/kg, 2-mercaptobenzimidazole a had a lesser peripheral analgesic efficacy than acetylsalicylic acid. This product has 26.02 ± 3.96 cramps, while acetylsalicylic acid has 9.60 ± 1.50 cramps. Furthermore, the 1,3-dialkyl-2-alkylthio-1H-benzimidazolium bromides b–e results demonstrate the modest activity of the c–e derivatives at thisdosage.[18]

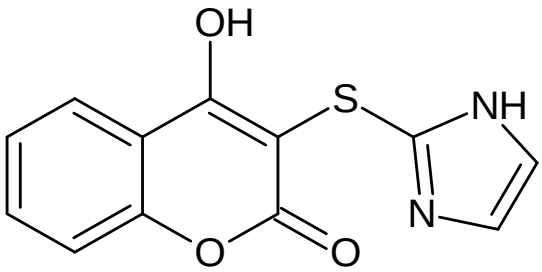


Figure 23.

The study compared the analgesic qualities of test compounds with the activity of aspirin, which was used as a standard medicine. Aspirin had a percentage of protection value of 62.1, while other compound 23, demonstrated a more significant percentage of protection.[19]

Anti-HIV Evaluation

Mercaptoimidazole derivatives have shown potential as anti-HIV drugs. Studies have shown that these drugs can inhibit key enzymes required for HIV replication. For instance, a number of mercaptoimidazole derivatives that were recently synthesised shown significant activity against HIV-1 in vitro, suggesting that they might find application as non-nucleoside reverse transcriptase inhibitors (NNRTIs).

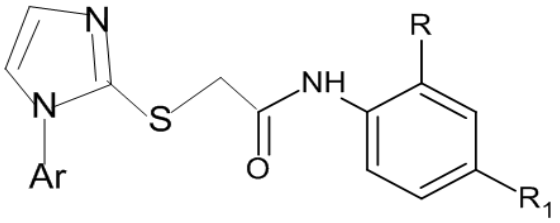


Figure: 24.

Compound	Ar	R	R
24a	Naphthalen-1-yl	F	H
24b	Naphthalen-1-yl	Cl	H
24c	Naphthalen-1-yl	Br	H
24d	Naphthalen-1-yl	Br	Me
24e	Naphthalen-1-yl	NO_2	H
24f	p-Tolyl	NO_2	H

The capacity of a number of imidazole thioacetanilide (ITA) derivatives, specifically 2-(1-aryl-1H-imidazol-2-yl) thioacetamide, to efficiently suppress the human immunodeficiency virus type-1 (HIV-1), was synthesised and evaluated. First, each newly synthesised imidazole thioacetanilide's anti-HIV efficacy was evaluated. 24b and 24e were the most effective inhibitors of HIV-1. The anti-HIV-1 potency of additional compounds, 24c, 24d, 24f, and 24a, was also higher.[20]

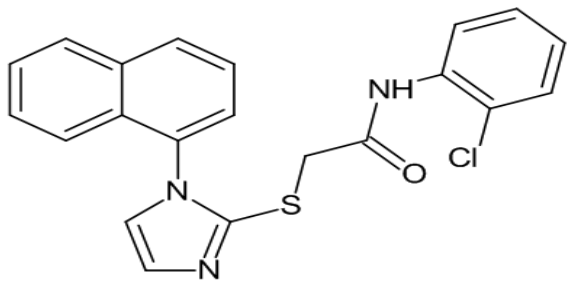


Figure:25.

The number of derivatives of imidazole thioacetanilide (ITA)—2-(1-aryl-1H-imidazol-2-yl)thio acetamide were synthesised and tested for their ability to effectively suppress the human immunodeficiency virus type-1 (HIV-1). The most potent HIV-1 inhibitors among them were 25 (EC50 = 0.20 lM), which outperformed reference medications delavirdine and nevirapine as well as the lead compound L1 (EC50 = 2.053 lM).

Antifungal activity

Compound	Ar
26a	2,4-Dichlorophenyl
26b	2,5-Dichlorothiophen
26c	4-SCH_3-C_6H_4
26d	4-CH_3-C_6H_4

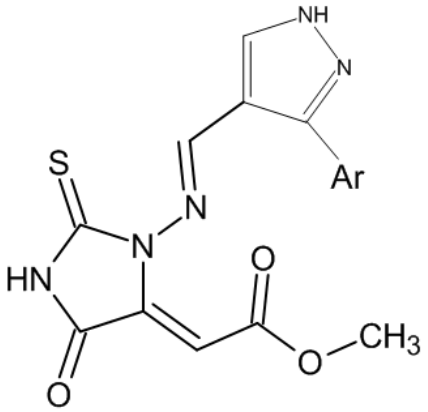


Figure. 26.

Vijesh *et al*. synthesized and screened compounds 26a having antifungal activity against Aspergillus flavus, Aspergillus niger, Candida albicans, *Microsporum gypseum*, and *Trichophyton rubrum*. Among the tested compounds, the compound 25c has emerged as active against T. rubrum compared with standard, fluconazole.[5]

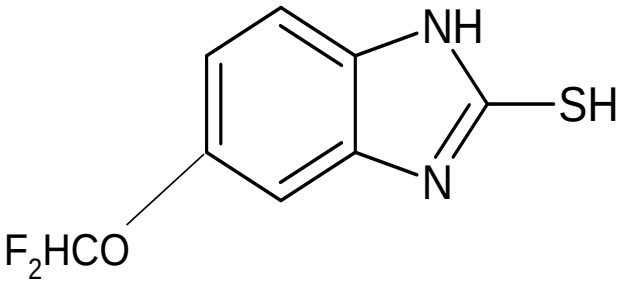


Figure. 27.

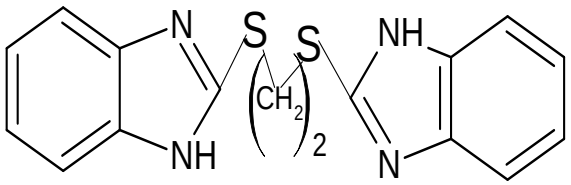


Figure. 28.

According to Srikanth gurrala *et al.* the derivatives are also screened for Antifungal activity using *Candida albicans* by disc diffusion method on nutrient agar media. The standard drug used was Ampicillin for anti-bacterial and Ketoconazole for anti-fungal activity.

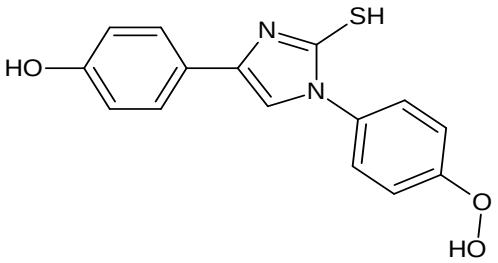


Figure: 29

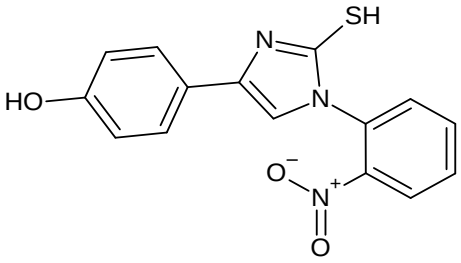


Figure: 30

According to Nidhi rani *et al.* 29 and 30 were found to be most active compounds of the series against fungal strains (C. albicans and P. aeruginosa). In consideration of antibacterial and antifungal property.

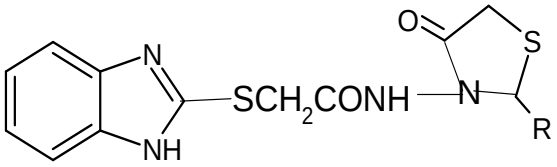


Figure. 31.

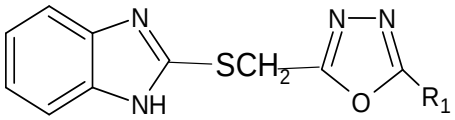
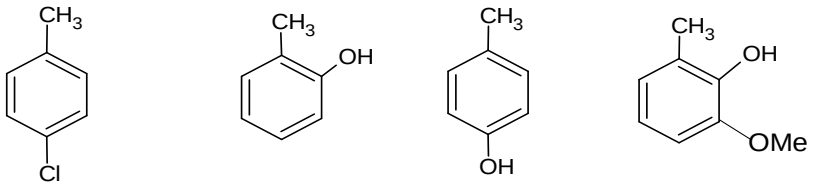


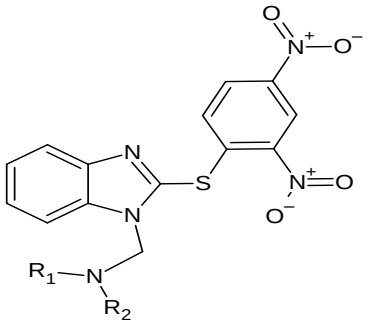
Figure. 32.

R= a b c d



R_1 = a b

Hosamani KM *et al.* synthesized mercaptoimidazole derivatives. In that these compounds 31b, 31c, 31d, 31g, 31i, 32b, and 32i induced markedly anti-fungal activity compared to standard fluconazole against *C. albicans* and *A. fumigatus* compared to control fluconazole with MIC values of 8–2 mg/ml.[24-25]



a : R = H R_1,R_2= CH_3

b: R = CH_3 R_1,R_2= Piperidino

c: R = H R_1,R_2= Pyrrolidino

Figure. 33.

The six phytopathogenic fungus Aspergillus niger, Penicillium notatum, Alternaria alternata, Drechslera avenae, Curvularia lunata, and Fusarium graminearum were used as test subjects for the compounds under investigation. Furthermore, the antifungal activity of the human pathogenic fungus Candida albicans was examined. When the combination compound was compared to the widely used antifungal drug fluconazole, it had a strong antifungal effect. Compounds 33a and 33b demonstrated substantial efficacy against Penicillium notatum and Curvularia sp. Compound 33c with the pyrrolidino substituent showed parity in its efficacy against Curvularia sp. but was unsuccessful against the other fungi. [2-(2,4- Dinitrophenylsulphanyl)-6-methoxybenzimidazol-1-yl methyl] dimethyl amine(33b) was quite efficient against Penicillium notatum and Curvularia sp., but only moderately effective against the other fungi.[26]

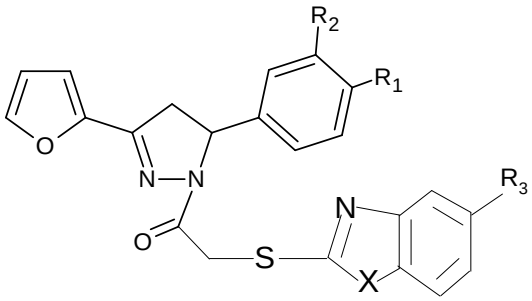


Figure: 34.

Compound	R1	R2	R3	X
34a	Cl	H	H	NH
34b	Cl	H	Cl	NH
34c	Cl	H	CH_3	NH
34d	Cl	H	NO_2	NH
34e	O-CH_2-O		H	NH
34f	O-CH_2-O		Cl	NH
34g	O-CH_2-O		CH_3	NH
34h	O-CH_2-O		NO_2	NH
34i	H	H	H	NH
34j	H	H	Cl	NH
34k	H	H	CH_3	NH
34l	H	H	NO_2	NH

Özdemir A *et al.* showed that all of the compounds were effective against *Candida parapsilosis* when compared to ketoconazole based on their MIC values; compounds 34a, 34b, 34e, 34f, 34g, 34h, 34j, and 34k had particularly significant activity, while compounds 34d, 34i, and 34l demonstrated activity comparable to ketoconazole. The compounds 34e, 34f, and 34g shown efficacy against *C. krusei* as well. Particularly, compounds 34e, 34f, and 34g exhibited potent inhibitory effect against the microbes under test. After then, there was moderate activity in 34a and 34h.[27]

Compound	Molecular formula
35a	$C_{30}H_{26}N_4S_2$
35b	$C_{31}H_{28}N_4S_2$
35c	$C_{28}H_{22}N_4S_2$
35d	$C_{32}H_{29}N_5O_2S_2$
35e	$C_{28}H_{20}C_{l2}N_4S_2$
35f	$C_{32}H_{27}C_{l2}N_5O_2S_2$
35g	$C_{28}H_{20}N_6O_4S_2$
35h	$C_{29}H_{22}N_6O_4S_2$

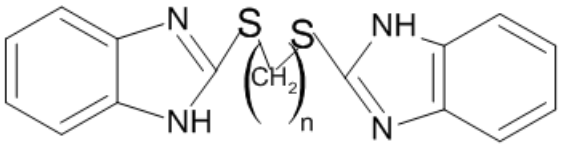


Figure: 35.

Kardile D and Shirsat also showed 35a to 35h is significant and potent antifungal activity against *A. niger* compared with fluconazole.[28]

CONCLUSION

The mercaptoimidazole derivatives studied above represent a large class of heterocyclic compounds. The study's pharmacological activities demonstrated promise, and the compounds intriguing properties included antibacterial, antifungal, analgesic, and anti-HIV properties. Thus far, alterations made to the mercaptoimidazole nucleus have been observed to exhibit encouraging biological activity. Since it is yet unknown and may serve as a model for future research to produce safer and more potent molecules, it will be intriguing to see how many more pharmacological profiles are added to it in the future.

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