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Synthesis, Characterization And Biological Activity Of Isoxazole Derivatives

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Abstract: Isoxazole nucleus is a very important system in the field of new drug discovery, especially in the area of antimicrobials and antibiotics. Isoxazoles have been repeatedly shown as useful synthons in organic synthesis. Literature survey revealed that several substituted isoxazoles had been prepared from numerous synthetic routes like routes for the synthesis of 3,5 disubstituted isoxazole, 3,4,5 trisubstituted isoxazole etc. Isoxazole derivatives are a fascinating class of heterocyclic compounds known for a broad range of biological and pharmacological activities including antistress, anticancer, antiageing, antidepressant, antiviral, antinflammatory, antitubercular etc. Characterization of isoxazole derivatives is essential to confirm their chemical structure, purity, and functional groups. Most reliable methods of characterization includes Nuclear Magnetic Resonance (NMR), Mass, infrared Spectroscopy, Elemental analysis, melting point determination, X-Ray Crystallography etc.

Keywords: Isoxazole, Isoxazole derivatives, Biological activity, Structure, Synthesis

1. Introduction

Isoxazole nucleus is a very important system in the field of new drug discovery, especially in the area of antimicrobials and antibiotics. Isoxazoles have been repeatedly shown as useful synthons in organic synthesis(1).

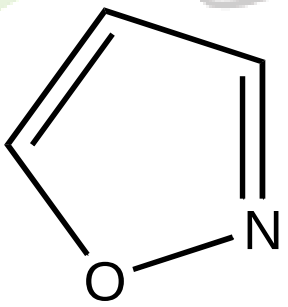

Fig. 1 Structure of Isoxazole

Among the isoxazole sulphanilamides, 5-methyl-3-isoxazolyl sulphanilamide under the trade name-sulphamethoxazole, is being widely used against a variety of bacterial infections(2).

The Penicillin derivative, consisting 3-(o-chlorophenyl) -5-methyl-isoxazolyl-4-carboxamide group known as “Cloxacillin” is used as a powerful antibiotic(3).

5-Methylisoxazole derivatives are found to possess antibacterial and plant growth regulative activities(4). Isoxazole containing orally active cephalosporin esters are reported to possess antibiotic activity(5) . A large number of isoxazole derivatives exhibited antibacterial, antifungal(6) , anticonvulsant(7) , analgesic(8), and anticancer (9, 10) activities.

Heterocycles play a vital role in pharmacological, agricultural and synthetic fields(11) . Consequently the development of methodologies useful for the assembly of molecules containing heterocyclic templates continues to attract the attention of both the academic and industrial communities. Isoxazole unit constitutes an easily accessible nucleus that is present in a number of natural and pharmacological compounds(12-17) and display a wide range of biological activity. Survey of literature revealed that when one biodynamic heterocyclic system was coupled with another, a molecule with enhanced biological activity(18) was produced.

The chemistry of these linked heterocyclics has been a fascinating field of investigation in medicinal chemistry, as they have been found to exhibit enhanced biological profile(19).

1.1 General Synthetic scheme of Isoxazole

Isoxazoles can be synthesized *via* different pathways using both homogeneous as well as heterogeneous catalysts. Nevertheless, the most broadly researched and reported synthesis of isoxazole derivative is through the (3 + 2) cycloaddition reaction of an alkyne that acts as a dipolarophile and nitrile oxide as the dipole.

Two predicted mechanisms have been reported for the 1,3-dipolar cycloaddition reaction.firstly, pericyclic cycloaddition reaction *via* concerted mechanismand secondly, *via* a step-by-step mechanism through diradical intermediate formation. Subsequently, the first proposed idea has been accepted, *i.e.*, concerted pathway, *via* the reaction of the dipole and the dipolarophile (Fig. 2). In 2001, Sharpless and his co-workers described this kind of cycloaddition reaction as 'Click Chemistry' for the regioselective synthesis of disubstituted triazoles(20).

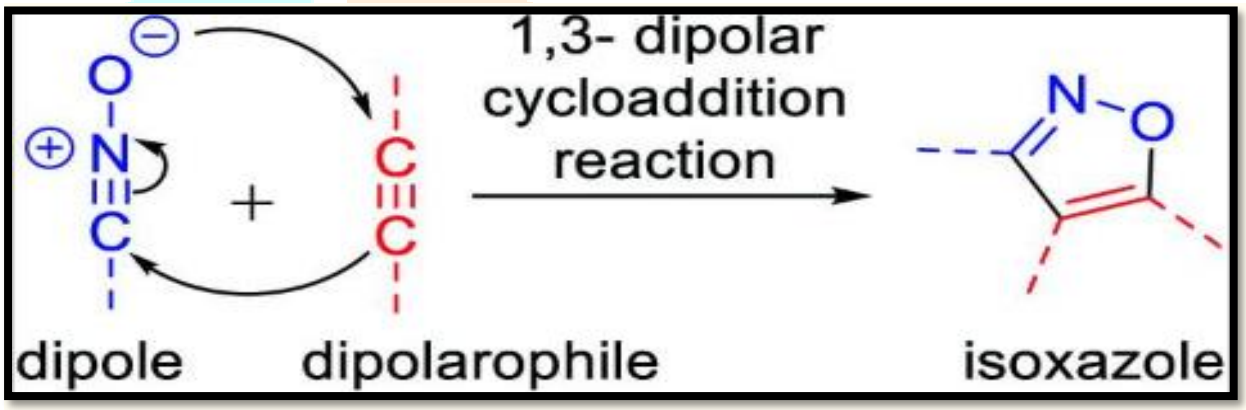

Fig. 2 Mechanism of 1,3-dipolar cycloaddition reaction.

2. Synthesis of Isoxazole Derivatives

Literature survey revealed that several substituted isoxazoles had been prepared from numerous synthetic routes. The first contribution to the chemistry of isoxazoles was made by Claisen in 1903, when he synthesized the first compound of series, isoxazole, by oximation of propargylaldehyde acetal (21).

2. 1. Routes for the synthesis of 3,5 disubstituted isoxazole

A regioselective, experimentally convenient one-pot copper(I)-catalyzed procedure was developed for the rapid synthesis of 3,5-disubstituted isoxazoles (Fig. 2) by reacting in situ generated nitrile oxides and terminal acetylenes (22).

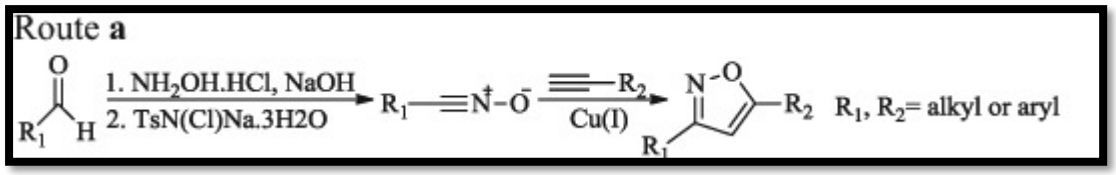

Fig.2

2.2 Routes for the synthesis of 3,4,5 trisubstituted isoxazole

Various methods have been reported to prepare isoxazoles with a variety of substituents at 3, 4, and 5 positions. Denmark and Kallemeyn (23) first synthesized isoxazolylsilanols by [3+2] cycloaddition reaction between alkynyldimethylsilyl ethers and aryl and alkyl nitrile oxides (Fig.3).

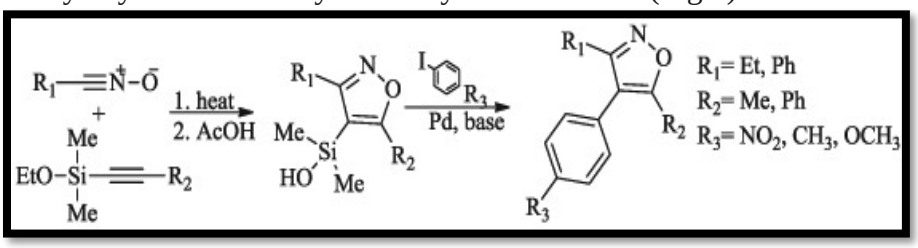

Fig.3

2. 3. Routes for the synthesis of aminoisoxazole

Different methods have been reported for the synthesis of aminoisoxazoles. Treatment of β-ketonitriles with hydroxylamine in aqueous ethanol (Fig. 4) gives 3-aminoisoxazoles (24).

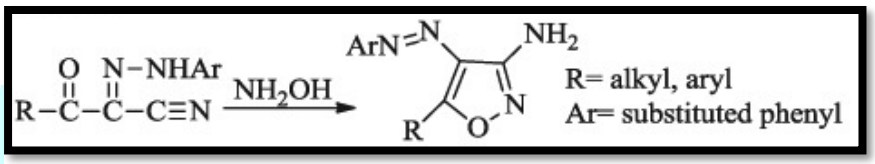

Fig.4

2. 4. Routes for the synthesis of Miscellaneous Isoxazole

3-substituted isoxazoles-4-carbaldehyde (Fig. 5) can be prepared by condensation reaction of nitroalkanes with 3-oxetanone (25).

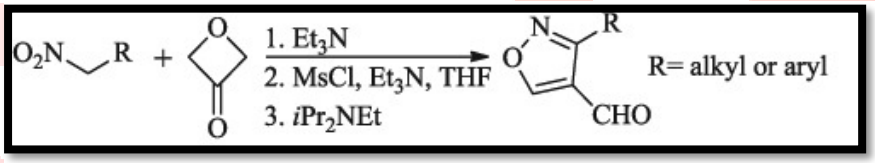

Fig.5

3. Biological Activities of isoxazole derivatives

3. 1. Antistress activity

Badru et al. synthesized a series of pyrrolo-isoxazole derivatives via 1,3-dipolar cycloaddition of azomethine N-oxides with N-(α-naphthyl)maleimide. Compound 1 (Fig. 6) exhibited significant anti-stress activity in immobilization stress-induced increase in non-social behavior(26).

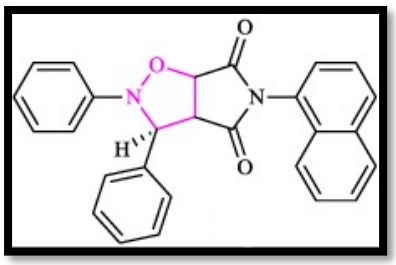

Fig.6 Compound showing Antistress activity

3.2. Antioxidant/antiageing activity

Padmaja et al. prepared bis heterocycles-oxazolyl/thiazolylsulfonylmethyl isoxazoles (Fig. 7) and evaluated for antioxidant activity. It was observed that the compounds having isoxazole in combination with oxazoline exhibited high antioxidant activity. The presence of electron donating substituent on the aromatic ring enhanced the activity (27).

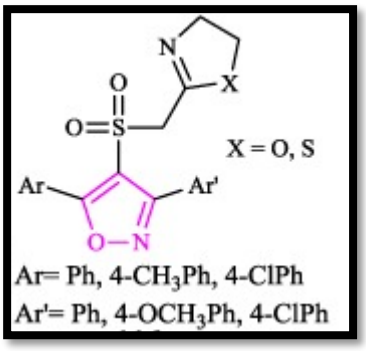

Fig.7 Compound showing Antioxodant activity

3.3. Dopamine transporter inhibitory activity

Carroll et al. synthesized several 3β-(substituted phenyl)-2β-(3-substituted isoxazol-5-yl)tropanes and evaluated for their ability to inhibit radioligand binding at the monoamine (dopamine, serotonin and norepinephrine) transporters for the treatment of cocaine abuse. Most of the analogs were dopamine transporter selective, increase locomotor activity with slow onset and long duration of action. But the high dopamine transporter selective compound (Fig. 8) surprisingly did not increase the locomotor activity that could be due to lack of brain penetration(28).

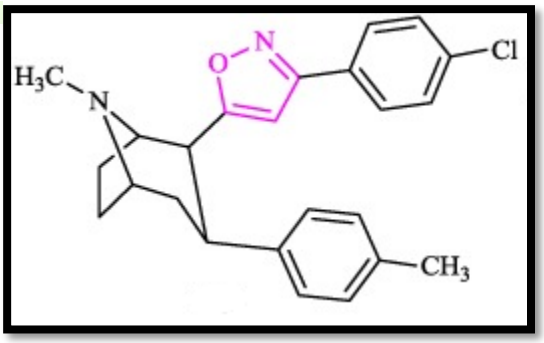

Fig.8 Compound showing Dopamine transporter inhibitory activity activity

3.4. Antihyperglycemic, antiobesity, or hypolipidemic activity

Kafle and co-workers synthesized a series of isoxazolones to develop a potent inhibitor of PTP1B as an antiobesity and antihyperglycemic agent. PTP1B inhibition leads to prolongation of tyrosine phosphorylated stats of insulin and leptin receptors resulting in suppression of weight gain and augmentation of insulin

sensitivity(29,30). Among them, compound (Fig. 9) was the most potent and selective inhibitor of PTP1B with an IC_{50} of 2.3 μM and can be considered as a promising lead compound for the control of obesity and hyperglycemia.

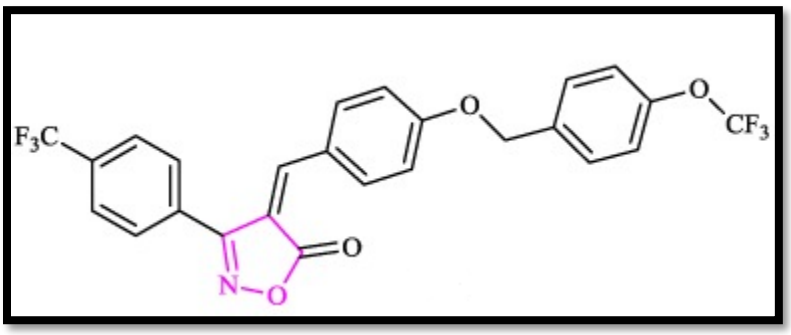

Fig.9 Compound showing Antiobesity activity

3. 5. Immunosuppressant activity

Agonism of $S1P_1$, in particular, has been shown to play a significant role in lymphocyte trafficking from the thymus and secondary lymphoid organs, resulting in immunosuppression. Watterson et al. (31) synthesized a series of isoxazoles derived from isoxazole-3-carboxylic acids and isoxazole-5-carboxylic acids to develop selective $S1P_1$ selective agonists. Compound in Fig. 10 was emerged as a lead compound with good efficacy when administered orally in a rat model of arthritis (ED_{50} 0.05 mg/Kg) and a mouse experimental autoimmune encephalomyelitis model of multiple sclerosis (ED_{50} 0.05 mg/Kg). EPACs are involved in regulating a wide variety of intracellular physiological and pathophysiological processes like T-cell mediated immunosuppression (32).

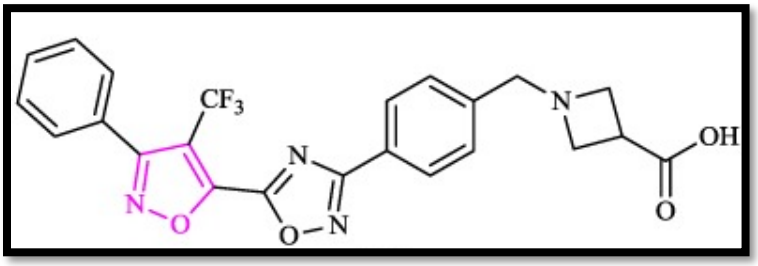

Fig.10 Compound showing Immunosuppressant activity

3.6. Anticancer Activity

Eid *et al.*, synthesized and evaluated the biological performance of new isoxazole–amide analogues. As a result of the anticancer evaluation, these derivatives were tested against HeLa, Hep3B, and MCF-7 cell lines, their IC_{50} (half-maximal inhibitory concentration) values were compared with that of doxorubicin. It was

found that, compound(a) **(fig.11)** was most active against HeLa cell line with IC_{50} value of $15:48 \pm 0:89$ µg ml^{-1}. However, compound **(b)** was considerably active against HeLa showing IC_{50} value of $18:62 \pm 0:79$ µg ml^{-1}. Compounds **(a)** and **(c)** showed anticancer activity against Hep3B cell line with IC_{50} $23:98 \pm 1:83$ µg ml^{-1} and $23:44 \pm 1:99$ µg ml^{-1}, respectively(33).

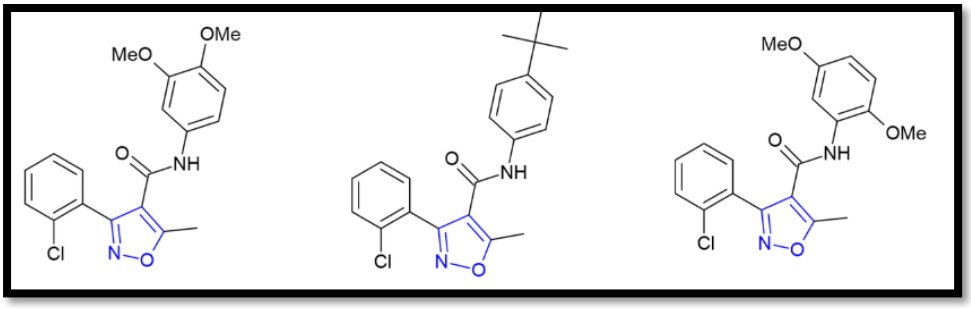

Fig. 11 (a,b,c) Compounds showing Anticancer activity

3.7. Antitubercular Activity

Mycobacterium tuberculosis causes Tuberculosis, an air-borne lung infection *i.e.*, contagious in nature(34).*Mycobacterium tuberculosis* falls under the three major classes of the genus *Mycobacterium* that cause tuberculosis, leprosy and other non-tuberculous mycobacteria(35,36,37). Thus, many compounds were developed to treat tuberculosis among which isoxazole containing molecules have gained great attention and importance. Quinoline–isoxazole containing compounds have been widely studied and some of these include compounds **fig**.12

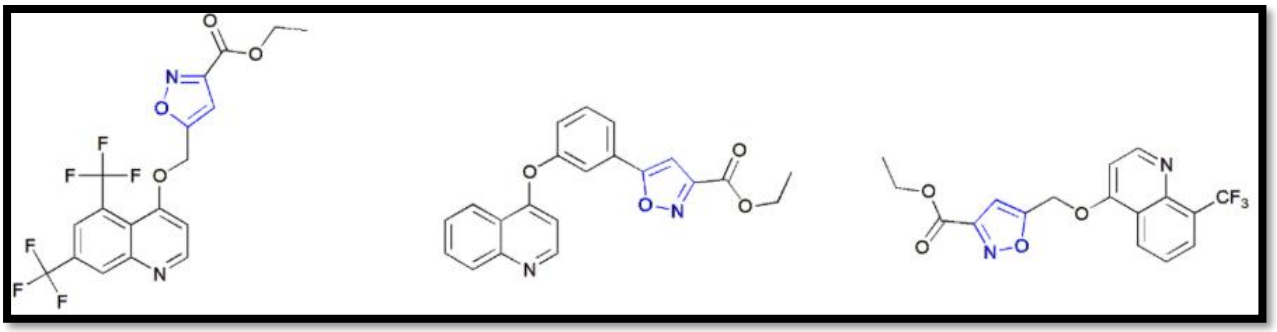

Fig. 12 Compounds showing Antitubercular Activity

3. 8. Anti-inflammatory Activity

Isoxazoles are reported to have good anti-inflammatory activities and they control inflammation as there is a great need to reduce or treat edema. Normally, they follow two pathways namely, the cyclooxygenase (COX) and lipoxygenase (LOX) pathways(38). Rajanarendar et al. (39) synthesized some 6-methyl isoxazolo[5,4-*d*]isoxazol-3-yl aryl methanones, assessed them for molecular properties prediction, drug-likeness, lipophilicity and solubility parameters, evaluated for in vitro COX inhibitory activity and screened for anti-inflammatory activity using carrageenan induced paw edema method. The compounds with chloro or bromo substitutions on phenyl ring (**1**; Fig. 13**)** exhibited significant anti-inflammatory activity and were more selective towards COX-2 enzyme.

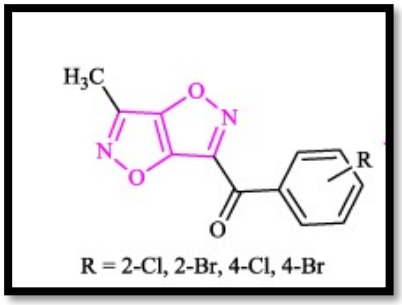

Fig.13 Compounds showing Antiinflammatory Activity

3. 9. Antimicrobial activity

Srinivas et al. (40) synthesized an another series of methylene-bis-tetrahydro[1,3]thiazolo[4,5-*c*]isoxazole and evaluated for their antifungal activity against *C. albicans*, *A. fumigatus*, *T. rubrum*, and *T. mentagrophytes* and further for nematicidal activity against *D. myceliophagus* and *C. elegans*. The compound **in** (Fig. 14) showed good activity against all the tested fungi, as well as significant nematicidal activity.

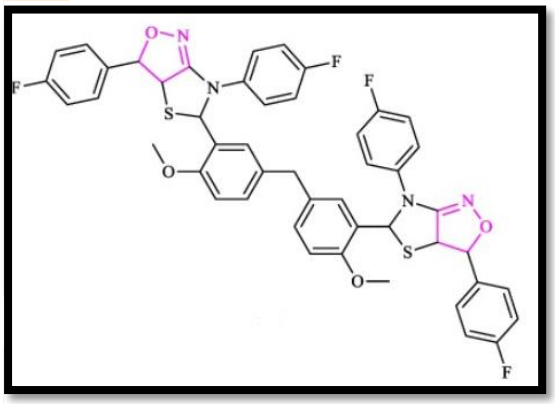

Fig. 14 Compounds showing Antimicrobial Activity

3.10. Antiviral Activity

Deng et al. (41) synthesized a series of alkenyldiarylmethanes with a benzo[*d*]isoxazole ring in place of metabolically unstable methyl ester moiety and screened for anti-HIV activity. All the compounds were found to inhibit HIV-1 Reverse Transcriptase but the compound **in** (Fig. 15) was most promising and a good alternative to hydrolytically unstable methyl esters.

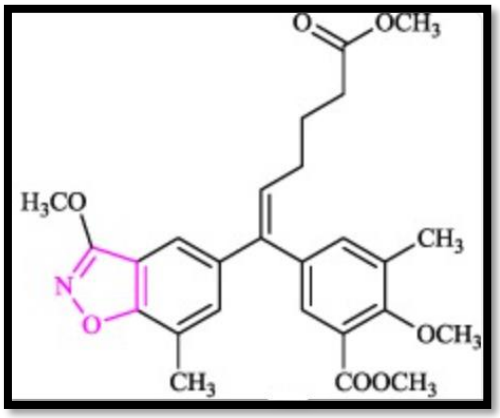

Fig.15 Compounds Showing Antiviral Activity

The biological profile of Isoxazole Derrivatives is summarized in Table 1.

Table1. Biological Activities of Isoxazole Derrivatives

Serial No.	Compound name	Reported Activity	Conclusion	References
1	3,5-Dimethylisoxazole, 3-(4-Methoxyphenyl)isoxazole, 5-Phenylisoxazole-3-carboxylic acid	Anti-inflammatory	Showed moderate COX-2 inhibition Reduced TNF-α production Selective COX-2 inhibition observed	(42-44)
2	Isoxazole-4-carboxamide derivatives 5-Aryl-3-(2-arylthiazol-4-yl) Isoxazoles 3-(4-Methoxyphenyl)-5-methylisoxazole	Antimicrobial	Potent against *S. aureus.*, Potent anti-infective potential. Inhibited *Staphylococcus aureus* and *E. coli* (MIC 2–4 µg/mL)	(45-47)
3	5-Amino-3-methyl Isoxazole 3-(4-Nitrophenyl)-5-methylisoxazole 3,5-Diphenylisoxazole	Antibacterial	Strong Gram-positive inhibition, Potent MRSA inhibition Inhibited *S. aureus*, *Enterococcus faecium*, MIC 2 µg/mL	(48-50)
4	5-Phenylisoxazole-3-carboxamide 3-(4-hydroxyphenyl)-5-(pyridin-4-yl)isoxazole 5-(4-methylphenyl)-3-(4-nitrophenyl)isoxazole	Antidepressant	Induced antidepressant-like effects in vivo Elevated serotonin and dopamine levels in brain tissue analysis Comparable to imipramine in FST and TST in mice	(51-53)
5	5-Methyl-3-(4-trifluoromethylphenyl)isoxazole 3-(4-chlorophenyl)-5-methylisoxazole 3-(2-pyridyl)-5-(4-hydroxyphenyl)isoxazole	Antiviral	HSV-1 replication strongly inhibited Active against Influenza A virus; IC_{50} = 2.3 µM Inhibits Zika virus replication in vitro	(54-56)
6	5-(3-Pyridyl)isoxazole-3-carboxylic acid 3-(3-Methylthiophen-2-yl)-5-(3,4,5-trimethoxyphenyl)isoxazole 5-(4-Methoxyphenyl)-3-(4-nitrophenyl)isoxazole-4-carbohydrazide	Antiangiogenic	Inhibits VEGF-mediated proliferation Inhibited angiogenesis in EAC mouse model via COX/LOX pathway Potent VEGFR-2 inhibition (IC_{50} = 25.7 nM); inhibited HUVEC proliferation	(57-59)
7	3-(4-Chlorophenyl)-5-methylisoxazole 3-(3-(4-((pyridin-2-yloxy)methyl)benzyl)isoxazol-5-yl)pyridin-2-amine 5-(furan-2-yl)-3-(4-nitrophenyl)isoxazole	Antifungal	Potent activity against *Candida albicans* broad-spectrum activity against Candida spp. and Fusarium spp. MIC = 17.5 µM against *Candida glabrata*	(60-62)
8	5-(4-Fluorophenyl)-3-methylisoxazole 3-(2,4-Dichlorophenyl)-5-methylisoxazole 5-(2-Thienyl)isoxazole-3-carboxylic acid 5-Phenylisoxazole-3-carboxylic acid	Antitubercular	Effective against *Mycobacterium tuberculosis* Effective against resistant TB strains Bioisosteric replacement improved activity Shows good activity against resistant TB	(63-66)

Result:- The results of this study indicate that various isoxazole derivatives exhibit promising biological activities, particularly in the areas of anti-inflammatory, antimicrobial, and anticancer agents. These compounds show potential as lead molecules for further development in drug discovery, with some displaying high potency and selectivity.

Conclusion:- Isoxazole derivatives represent a promising class of compounds with diverse biological activities. The synthesized compounds, particularly those with specific substitutions, have shown potential as anti-inflammatory, antimicrobial, and anticancer agents. Further research and development of these compounds could lead to the discovery of new therapeutic agents for various disease.

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