IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
June 2019 Vol.:15, Issue:3

Synthesis and Antimicrobial Screening of Modified Isoxazoles: A Short Review

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

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Submission: 26 May 2019
Accepted: 31 May 2019
Published: 30 June 2019

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Isoxazole, chalcone, cycloaddition, antimicrobial activity, antitubercular activity

ABSTRACT

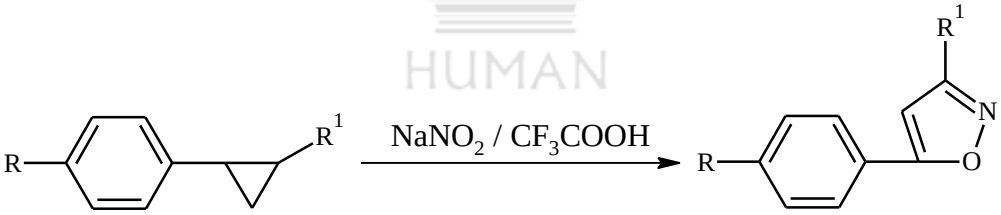
Isoxazoles are 5 membered heterocyclic compounds with promising biological activities. The marketed drugs such as valdecoxib and cloxacillin used as antibiotics have proven the efficacy of the isoxazole containing moiety. The substituted isoxazole derivatives displayed antimicrobial, antitubercular, anti-viral, anti-inflammatory, hypoglycaemic, antioxidant and anticancer activities. This mini-review describes the reported strategies to synthesize and evaluate the antibacterial, antifungal and antitubercular activities of some of the substituted isoxazole derivatives.

INTRODUCTION

Heterocyclic compounds are widely distributed in nature which is essential for various biological activities. Nitrogen containing heterocyclic compounds are important building blocks in both organic and medicinal chemistry[1]. One of the major 5 membered heterocyclic compound isoxazole is an azole with an oxygen atom next to the nitrogen atom. Isoxazole exhibits a broad spectrum of biological activities and also forms a basis of several bioactive agents[2]. The substituted isoxazole derivatives displayed antibacterial[3], antifungal[4], antiviral[5], anti-inflammatory, hypoglycemic[6] and anticancer activities[7]. Isoxazole derivatives such as sulfamethoxazole, sulfisoxazole, cloxacillin, cycloserine, acivicin have been in commercial use for many years. The synthetic androgenic steroid, danazol also possess an isoxazole ring. Due to these activities, isoxazole containing drugs have been used as a prominent pharmaceutical agent.

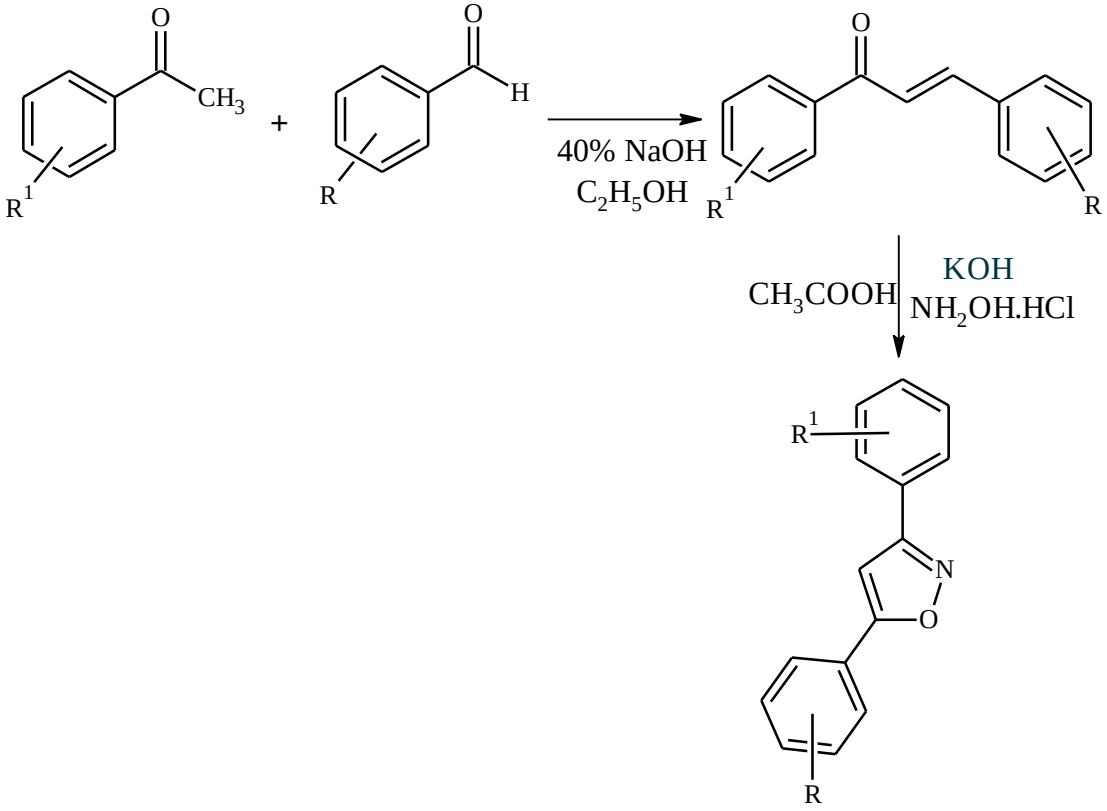
SYNTHESIS OF ISOXAZOLE DERIVATIVES

1. 3-Alkyl, 5-aryl isoxazoles can be synthesized from aryl cyclopropanes with $NaNO_2$ in CF_3COOH[8] (Scheme 1).



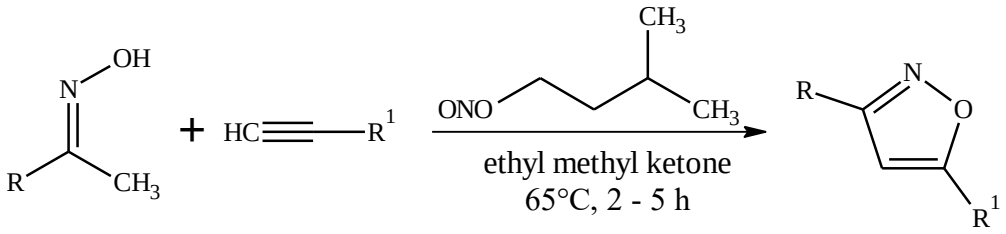
Scheme 1

2. Claisen-Schmidt condensation of substituted acetophenone and aromatic aldehyde yields chalcones which on treatment with hydroxylamine hydrochloride and in presence of alkali affords respective isoxazoles[9] (Scheme 2).



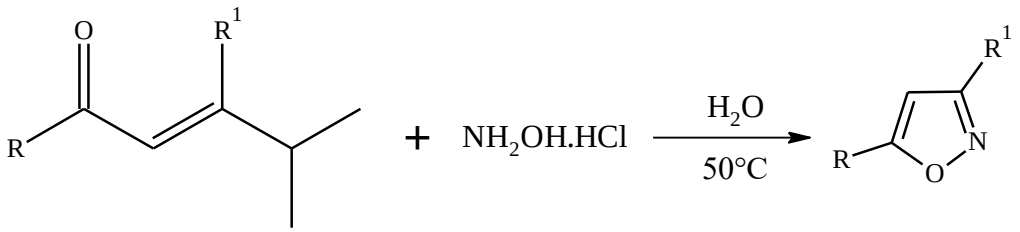
Scheme 2

3. In the presence of isoamyl nitrite or tert-butyl nitrite provides the one-pot synthesis of 3,5-disubstituted isoxazoles from substituted aldoximes and alkynes[10](Scheme 3).



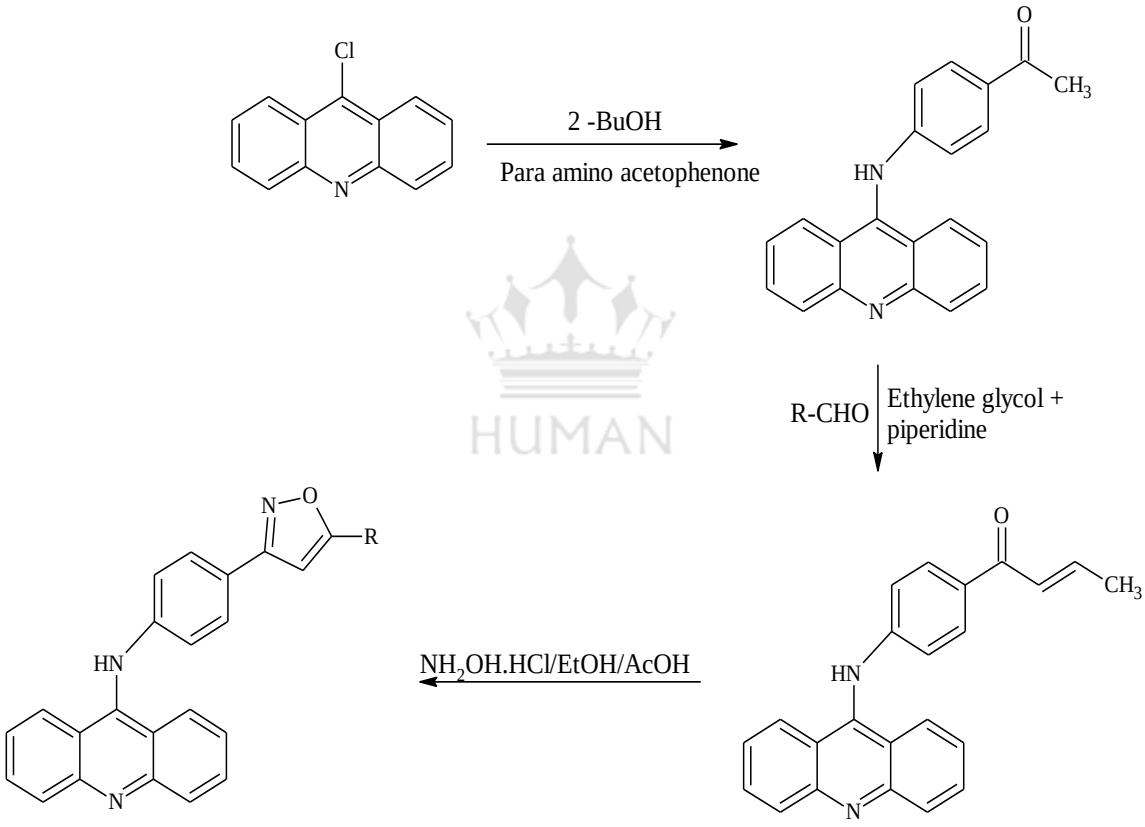
Scheme 3

4. An equivalent mixture of 3-(dimethylamino)-1-arylprop-2-en-1-one derivative and hydroxylamine hydrochloride was stirred at 50 °C in aqueous media to obtain 5-arylisoxazole derivatives in good yield[11] (Scheme 4).



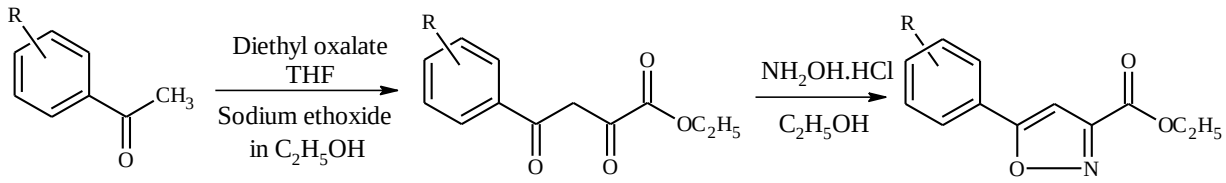
Scheme 4

5. 9-chloro acridine on reflux with para amino acetophenone affords 1-(4-acridine 9-ylamino) phenyl ethanone and reacted with various aldehyde to yield chalcone substituted 9-anilino acridines. Substituted chalcones cyclized with hydroxylamine hydrochloride yields corresponding isoxazole substituted 9-anilino acridines[12] (Scheme 5).



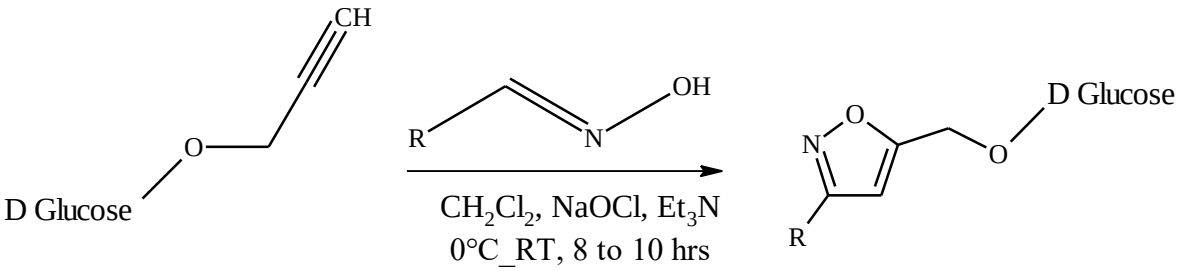
Scheme 5

6. Various substituted acetophenones reacted with diethyl oxalate in the presence of sodium ethoxide to form 2, 4-diketo esters which on treatment with hydroxylamine hydrochloride furnishes substituted 3-isoxazole esters[13](Scheme 6).



Scheme 6

7. Regioselective synthesis via 1, 3-dipolar cycloaddition of aldoxime, sugar alkyne and triethylamine in dichloromethane and sodium hypochlorite affords sugar conjugates of isoxazole[14] (Scheme 7).



Scheme 7

ANTIMICROBIAL AND ANTITUBERCULAR STUDIES

Francis Chevreuil *et.al* synthesized new 2-aryl-1-azol-1-ylpropan-2-olbearing a phenyl substituted 5-membered heterocyclic ring (Fig 1) by 1,3-dipolar cycloaddition and reported the synthesized compounds could be considered as potent broad-spectrum antifungal agents which is capable of overcoming the increased activity of efflux pump required for acquired resistance of azoles. Their antifungal activity was screened against *C. albicans, C. glabrata, A. fumigatus* and an azole-resistant petite mutant of *C. glabrata.* Tioconazole, fluconazole, voriconazole were used as standard drugs. Minimum Inhibitory Concentration (MICs) was determined using a microdilution assay in RPMI-1640 culture medium[15].

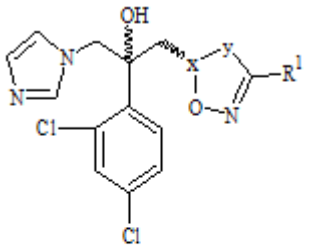


Fig 1

x-y = $CH\text{-}CH_2$

$\mathbf{R^1}$ = CH_3, Pr, Ph

Suryawanshi V.S reported the synthesis of 4,5-dihydro-3-(5-methyl benzofuran -2-yl)-5-arylisoxazole (Fig 2) by the reaction of benzofuran chalcones with hydroxylamine hydrochloride in the presence of potassium hydroxide in ethanol. The synthesized compounds were characterized by IR, ^{1}H NMR and elemental analysis and screened for their antimicrobial activity by cup plate method at the concentration of 500 µg/ml. Antibacterial activity was done against various microbes such as *S. typhi* and *S. aureus.* Antifungal activity was performed against *A. niger* and *C. albicans.* Penicillin and Griseofulvin were used as the standard. The synthesized compounds showed significant antimicrobial activity[16].

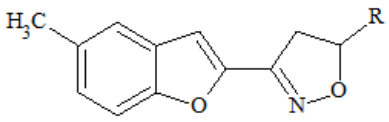


Fig 2

R = 4-Methylphenyl, 4-Hydroxyphenyl, 4-Chlorophenyl, 4-Methoxyphenyl, 4-Fluorophenyl

The synthesis of new isoxazole derivatives carrying 4-thiomethyl moiety was carried out by 2 step synthesis. In the first step, 4-Methylthiobenzaldehyde was condensed with various aryl ketones in the presence of potassium hydroxide to give a series of 1-aryl-3-(4-methylthiophenyl)-2-propene-1-ones. In the second step, the obtained compound was treated with hydroxylamine hydrochloride in the presence of aq. alkali to yield 3,5-diarylisoxazoles (Fig 3). The synthesized compounds were characterized by FT-IR, ^{1}H NMR, mass spectroscopy and compounds possess good antimicrobial activity against *E. coli*, *S. aureus,*

P. aeruginosa and *K. pneumoniae* bacterial strains by a disc diffusion method using ciprofloxacin as standard drug[17].

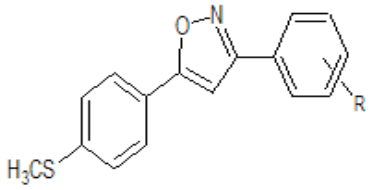


Fig 3

R = 4-CH_3, 4-OCH_3, 4-Cl

4-Br, 4-F, 4-NO_2, 4-C_6H_5

Substituted 2–amino benzothiazoles were prepared from different substituted amines via substituted phenylthiourea. 5-(substituted-benzothiazole-2yl)-amino-3- methyl isoxazole derivatives (Fig 4) have been prepared by the reaction of various synthesized 3-Carboxamido-(substituted benzothiazole-2yl)-propane-2-one and hydroxylamine hydrochloride. The structures of the isoxazole compounds have been confirmed by elemental analysis and spectral analysis. Most of the compounds resulted in prominent antibacterial activity against various gram positive and gram negative organisms by agar plate method using chloramphenicol as standard[18].

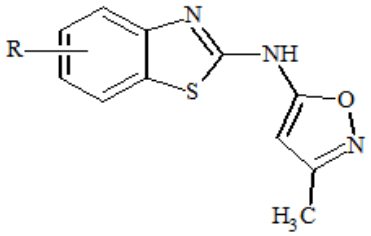


Fig 4

R = H, 4-CH_3, 6- CH_3,

4-Cl, 5-Cl, 6-Cl

Novel 3,4,5-trisubstituted isoxazole derivatives were synthesized by multi-step synthesis. In the first step 3,5-diarylisoxazole-4-carboxamide derivative (Fig 5) and in the second step, 3,5-diaryisoxazole-4-methylamine derivatives (Fig 6) were synthesized. The structures of the newly synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, LC-MS and

screened for their antifungal activity against *A. flavus, F. oxysporum and C. albicans* by the disc diffusion method. Most of the newly synthesized 3,4,5-trisubstituted isoxazole compounds exhibited remarkable antifungal activity[19].

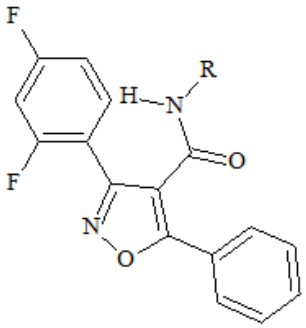


Fig 5

R = $CH_2C_6H_5OCH_3$, $C_6H_5OCH_3$

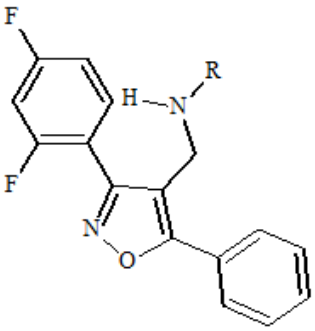


Fig 6

R = $CH_2C_6H_5OCH_3$, C_6H_5Cl

A series of Isoxazole derivatives (Fig 7) were synthesized from chalcones and evaluated for their antimicrobial activities. Chalcones were synthesized by reaction of furan-2-carbaldehyde with various acetophenones by Claisen-Schmidt condensation and chalcones on treatment with hydroxylamine hydrochloride and sodium acetate in ethanol yield isoxazole derivatives. Most of the compounds showed moderate to good antibacterial and antifungal activity (by cup plate method) compared to the standard drugs[20].

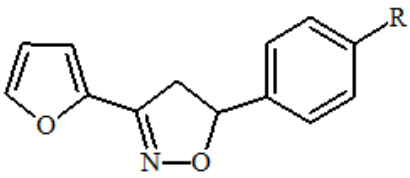


Fig 7

R = NH_2, Br, F, CH_3, NO_2

Kamala Chand Gautam *et.al*, synthesized a series of new chalcones by the reaction of 2-acetyl thiophene and substituted benzaldehydes. These were made to undergo cyclization reaction with hydroxylamine hydrochloride in ethanol to synthesize isoxazole derivatives of thiophene (Fig 8). The synthesized compounds were purified and elucidated with the help of IR and ^{1}H NMR spectroscopy. The compounds were screened for antibacterial activity and antifungal activity by agar plate diffusion method, which suggested that four of the synthesized compounds were moderate to highly active[21].

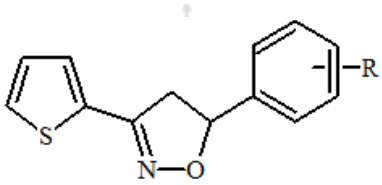


Fig 8

R = 3-NO_2, 4-NO_2, 3-CH_3

3-OCH_3, 4-C_8H_7O, 3-Cl

5-(2,8-Bis (trifluoromethyl)quinolin-4-yloxymethyl) isoxazole-3-carboxylic acid ethyl ester (Fig 9) was reported to have promising antitubercular activity against both replicating and non replicating *Mycobacterium tuberculosis*. The antitubercular activity was specific for organisms of *Mycobacterium tuberculosis* complex and it reduced bacterial numbers in infected macrophages and it may act as a prodrug[22].

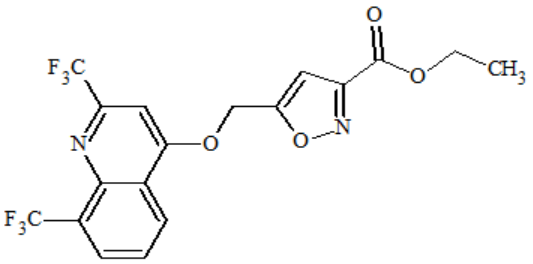


Fig 9

The cyclization of 1-azido-4-methoxy benzene with acetylacetone in the presence of sodium ethoxide furnished 1-(4-methoxyphenyl)-5-methyl-1H-1,2,3-triazole-4-yl) ethanone and the Claisen-Schmidt condensation of the compound with different aromatic aldehydes yield triazolyl Chalcones. This on refluxing with hydroxylamine hydrochloride in glacial acetic acid afford 4-(5-(4-substituted phenyl) isoxazol-3yl) -1- (4-methoxyphenyl) - 5-methyl - 1H-1,2,3-triazoles (Fig 10). Antitubercular activity was performed against $H_{37}RV$ and DKU 156 strain by using broth dilution assay. The results revealed that the synthesized compounds possess antimycobacterial activity[23].

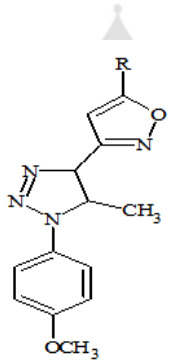


Fig 10

R = 4-C_6H_5Cl, 4-C_6H_5F, 4-$C_6H_5NO_2$

One pot three component condensation reaction involving 4-(4-Nitrophenyl)-thiazol-2-ylamine,benzaldehyde and mercapto acetic acid in the presence of catalyst given 4-(4-Nitrophenyl)-2 phenyl-(2,3)bithiazolyl-4-one, which on reaction with aromatic aldehydes in the presence of CH_3COONa and treatment with hydroxylamine hydrochloride result in isoxazolo-thiazole derivatives (Fig 11). The synthesized compounds were characterized by IR, ^1H NMR, ^{13}C NMR and MS spectra and screened for their antimycobacterial activity against $H_{37}Rv$. Thus the article reported that the synthesized compounds exhibited promising antimicrobial and remarkable anti-TB activity[24].

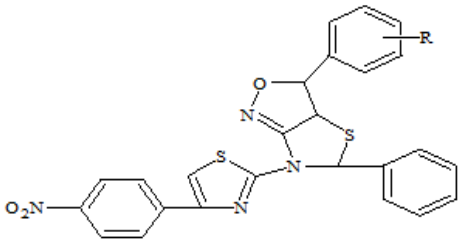


Fig 11

R = H, 4-CH_3, 4-OCH_3

4-Cl, 4-Br, 4-NO_2

Various chalcones were synthesized by the base catalyzed reaction between substituted aromatic ketones and substituted aromatic aldehydes. These chalcones on reaction with hydroxylamine hydrochloride furnished 3,5-disubstituted isoxazole derivatives (Fig 12). All the synthesized compounds were characterized by IR, NMR and mass spectroscopy. Further, these disubstituted compounds were evaluated for their antimicrobial, antifungal and antitubercular activity and thus it was concluded isoxazole derivatives substituted at 3 and 5 position with aromatic rings posses promising activity[25].

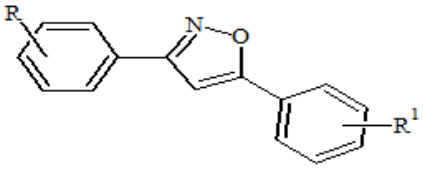


Fig 12

R = 4-OH, $\mathbf{R^1}$ = H

R = H, $\mathbf{R^1}$ = 3-NO_2

R = 4-OH, $\mathbf{R^1}$ = 4-Cl

R = 4-OH, $\mathbf{R^1}$ = 3-NO_2

CONCLUSION

With the emergence of the researcher's interest in synthesis and evaluation of isoxazole derivatives have been emphasized the utility of isoxazole as a broad spectrum antimicrobial agent. Thus the present review describes the enhanced antimicrobial activity is due to the presence of substituents such as 4-methyl, 4-fluoro, 4-methoxy, 4-hydroxy, 4-amino, 4-bromo, 4-nitro, 5-chloro and 6-chloro groups on aromatic ring directly attached to the

isoxazole. Smaller ester substituents such as propyl and butyl esters at position 3 of isoxazole ring favoured for the increased antimycobacterial activity.

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