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Isoxazole—A Basic Aromatic Heterocycle : Synthesis, Reactivity And Biological Activity

S.S.Rajput[1]*, Dr. S.N.Patel[2], Nilesh B. Jadhav[3]

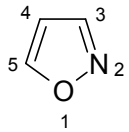
[1]Department of Chemistry, SVS's Dadasaheb Rawal College Dondaicha 425408, Maharashtra, India.
[2]Department of Chemistry, S.P.D.M.College, Shirpur 425405, Maharashtra, India.
[3]Department of Chemistry, S.P.D.M. College, Shirpur425405, Maharashtra, India.

Abstract: This review summarizes the synthetic method , reactions and biological application of isoxazoles and summarizes recent development in their derivatives such as chalcone, 5-isoxazole penicillins,shiff base etc.over the last years.The biological activities of isoxazoles is also briefly discussed .Formation of isoxazoles & fused heterocyclic isoxazoles derivatives constitute an interesting class of heterocycles which have diverse biological activities.
Keywords: Isoxazoles, biological activity, 5-isoxazole penicillin.

1. Introduction

Substituted Isoxazoles are important compounds of many drugs and drug candidates. It is one of the most fundamental objectives of organic and medicinal chemistry is the design and synthesis of molecules having value human therapeutic agents. The diversity of biological activities and pharmaceutical uses have been attributed to them, such as isoxazole is a part of many active molecule possessing activities such as Anti-tubercular[1], Analgesic[2], Antipyretic[2], Anti-inflammatory[2][3], Antiplatelet[4], Anti-HIV[4], Antagonist activity[4], CNS depressant[5], Antifungal[6][7], Antibacterial[6][7][8], Anti-oxidant[7], Anticancer[9][10] .

The Substituted isoxazole moiety 1 appears as an interesting precursor of many biologically active of the above class compounds.



Isoxazole
1

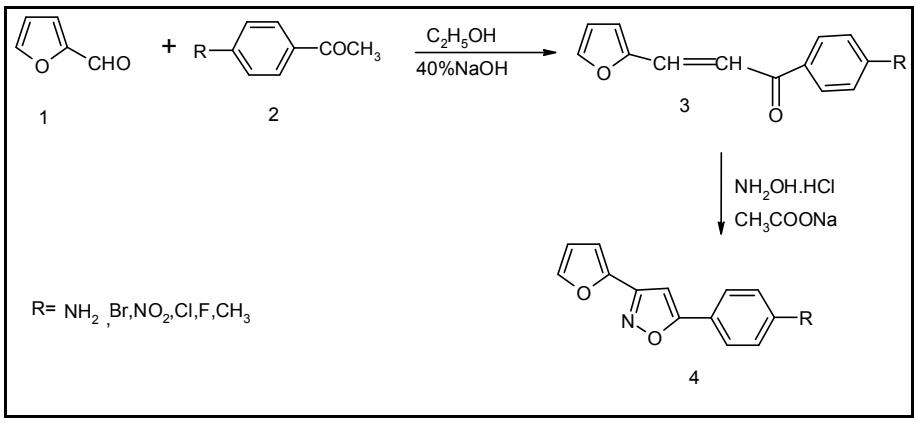
This review provides an overview of the synthesis and reactivity of isoxazole and its derivatives .In first part we intend to outline the general methods by which substituted isoxazole are prepared .The second and third parts are devoted to the chemical reactivity of substituted isoxazoles.

2. Synthetic Methods

There have been a number of practically important routes to synthesize isoxazoles.

2.1 From furfuraldehyde using $NH_2OH.HCl$

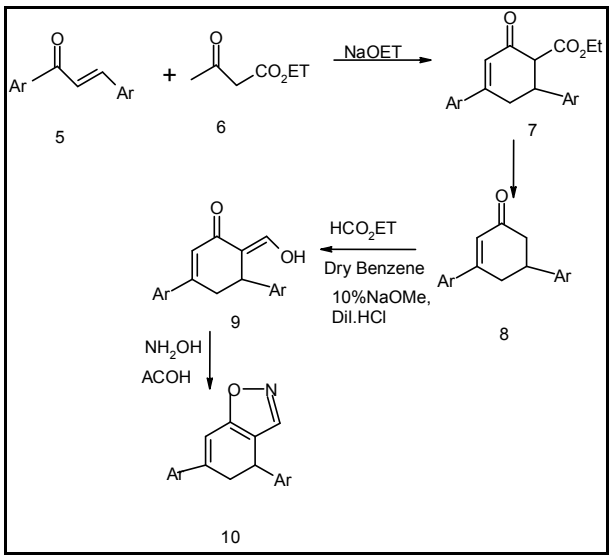
A well established route for the synthesis of substituted isoxazole (**4**) was reported from chalcones by claisen- Schmidt condensation of aldehyde, acetophenone and $NH_2OH{\cdot}HCl$.[Scheme 1][11]



Scheme 1

2.2 By Knoevenagel Condensation using Sod.Ethoxide

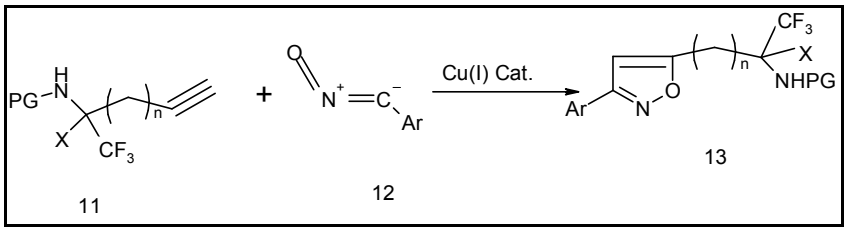
The convenient method was reported for synthesis of substituted isoxazoles in which Knoevenagel condensation of ethyl acetoacetate (6) and 1,3 diaryl -2-propen-1-one(5)using sodium ethoxide took place .The intermediate (8) was react with ethyl formate and sodium ethoxide gives compound (9) which on reaction with NH_2OH in acetic acid afforded substituted isoxazole (10)[Scheme 2][12]



Scheme 2

2.3 Synthesis using Click Chemistry Approach

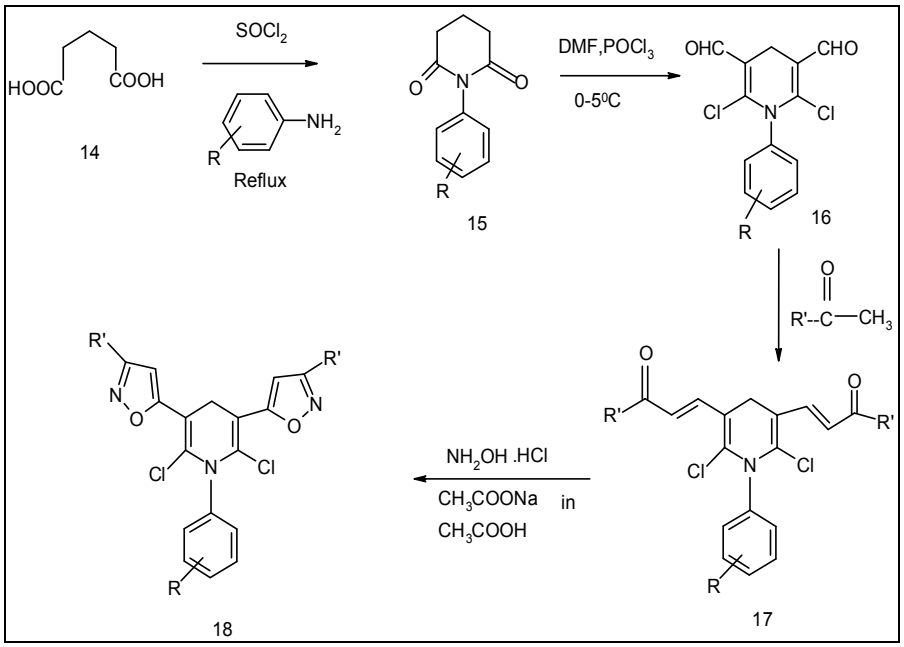
The method includes transition metal catalyzed 1,3-dipolar cycloaddition of nitrile oxides(12) to alkynes (11)gives substituted isoxazoles(13)[Scheme-3][13]



Scheme 3

2.4 From Glutaric acid using $SOCl_2$,DMF/$POCl_3$ and NH_2OH·HCl

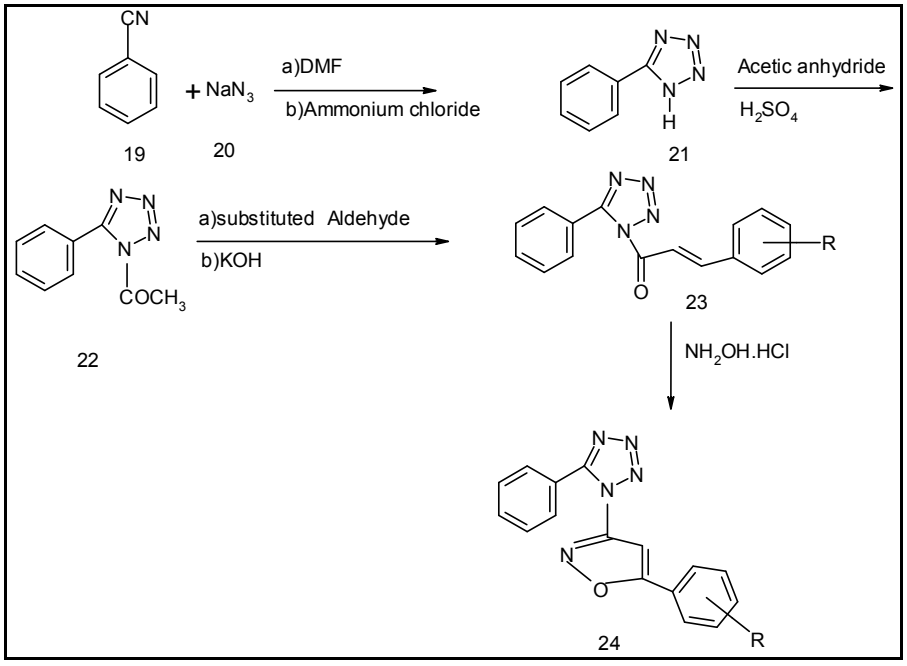
Glutaric acid (14) treated with amine using $SOCl_2$ gives N-substituted phenyl glutarimides(15) which on diformylated using Vilsmeier –Haack Reaction afforded dihalovinyl aldehyde(16).The halovinylaldehyde on condensation with acetophenone gives chalcone (17)which underwent ring closer with $NH_2OH.HCl$ furnished isoxazoles(18)[Scheme-4][14]



Scheme 4

2.5 From Tetrazole derivative

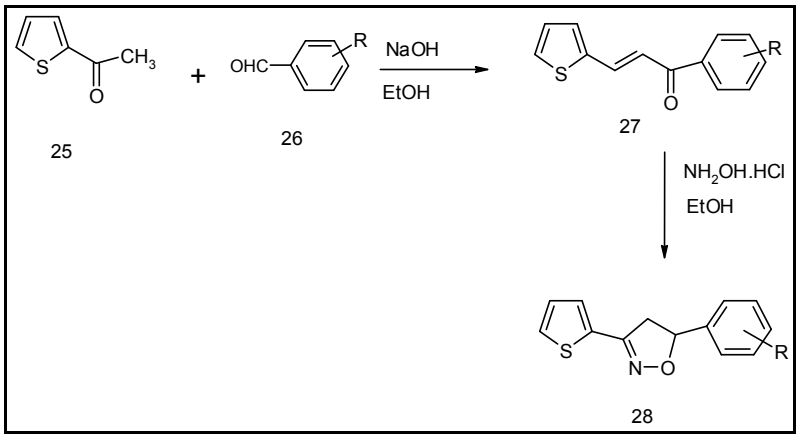
Treatment of Benzonitrile (19), sodium azide (20) in presence of DMF & Ammonium chloride furnished 5- phenyl tetrazole(21) .5-phenyl tetrazole treated with acetic anhydride resulting in the formation of acetyl tetrazole(22) which was condensed with substituted aldehydes followed by cyclization using $NH_2OH.HCl$ furnished isoxazoles(24) which exhibited anticancer activity.[Scheme-5][15]



Scheme 5

2.6 Using 2-acetyl thiophene

A convenient route for the substituted Isoxazole (28) is achieved by refluxing $NH_2OH.HCl$ with chalcone (27) in presence of ethanol.[Scheme-6][16].

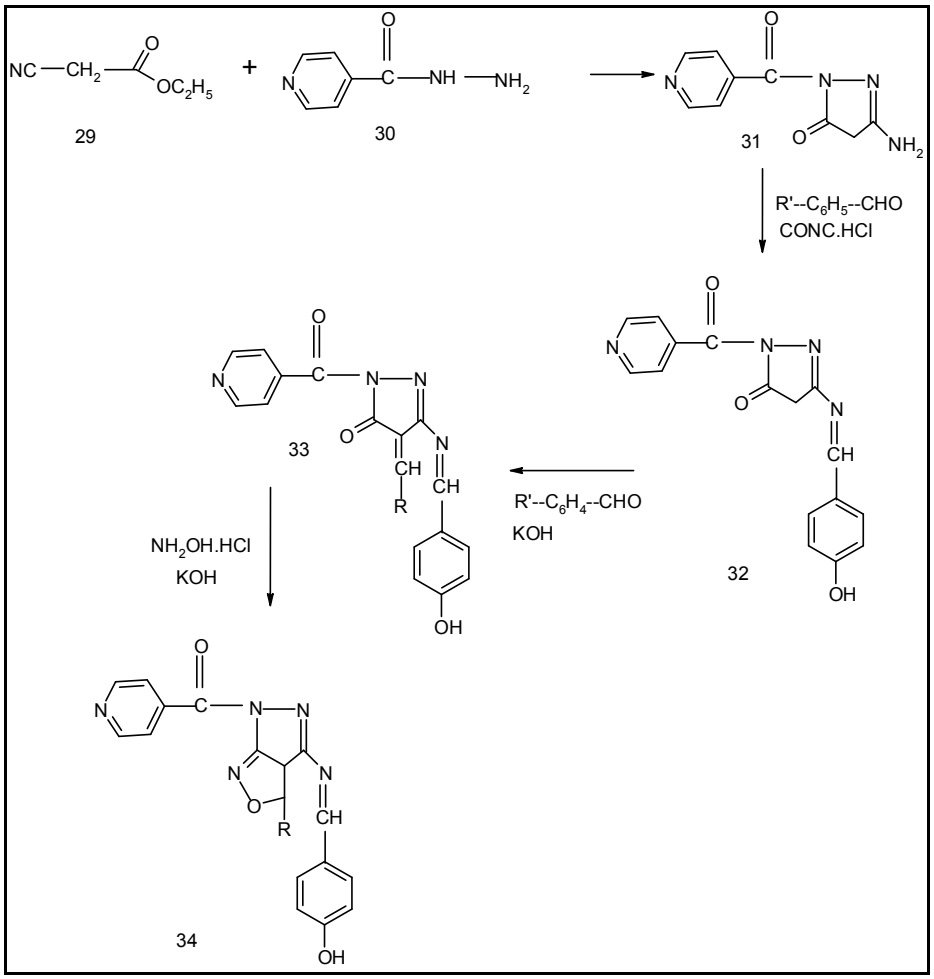


25 26 27 28

Scheme 6

2.7 Microwave assisted synthesis of Isoxazole

Microwave assisted synthesis of isoxazole (34) reported by author Kumudini Bhanat,Bharat Parashar and V.K.Sharma from Irradiation of Chalcone (33) with $NH_2OH{\cdot}HCl$.[Scheme-7][17]

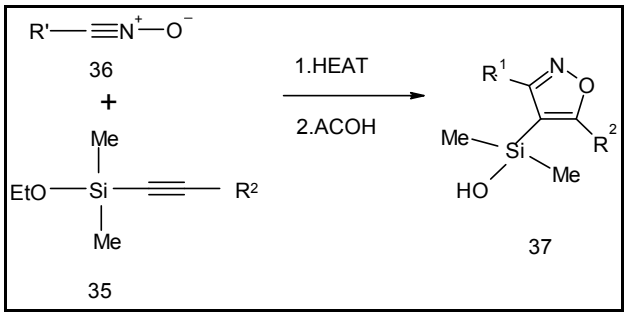


29 30 31 32 33 34

Scheme 7

2.8 Synthesis via [3+2] cycloaddition

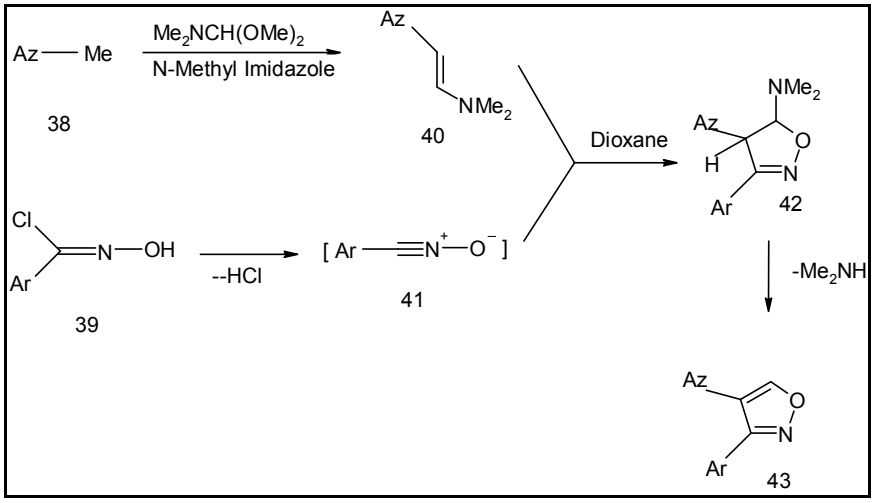
The [3+2] cycloaddition reaction between alkynyl dimethyl silyl ethers (35) and aryl or alkyl nitrile oxide (36) gives isoxazolyl silanols (37).[Scheme-8][18]



Scheme 8

2.9 From cycloaddition of Azolylacetylenes to nitrile oxides

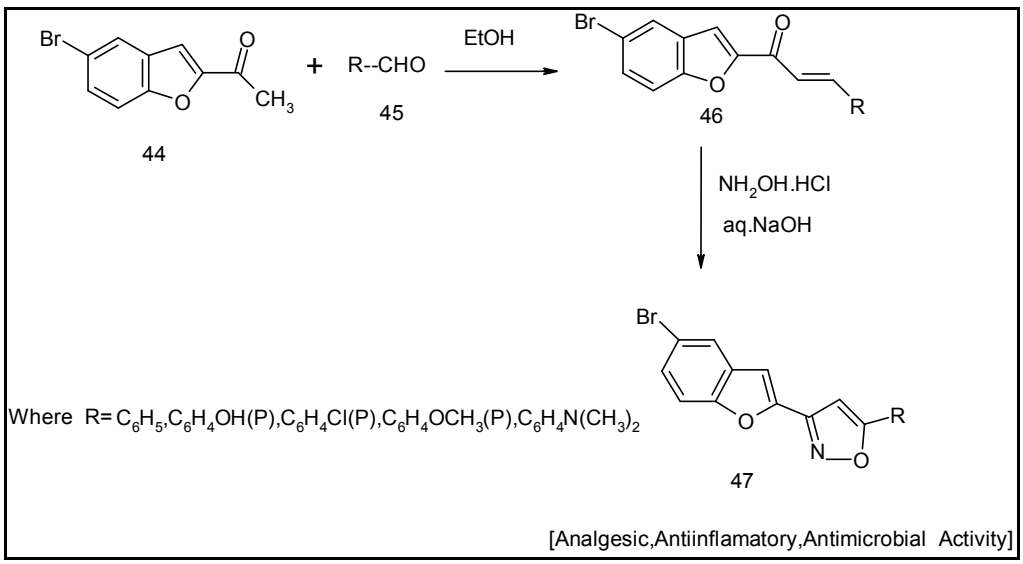
Isoxazoles (43) have been synthesized from cycloaddition of enamines (40) with nitrile oxide (41) through the intermediate (42) [Scheme-9][19]



Scheme 9

2.10 From Benzofuran

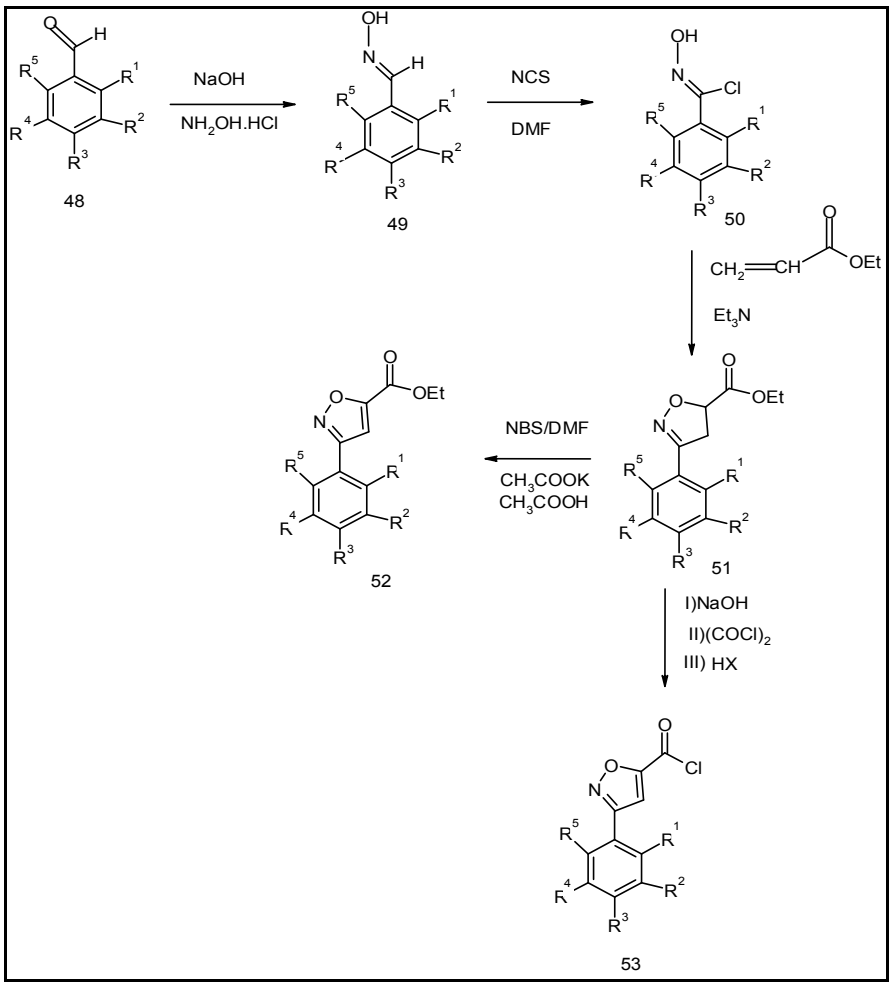
The reaction of 5-bromo-2-acetyl Benzofuran (44) with a different aromatic aldehydes (45) in presence of alkali gives chalcones (46) which on treatment with hydroxylamine hydrochloride afforded Isoxazole derivatives of Benzofuran(47)[Scheme-10][20]



Scheme 10

2.11 Synthesis via 1,3 dipolar cycloaddition of α,β unsaturated ester & nitrile oxides

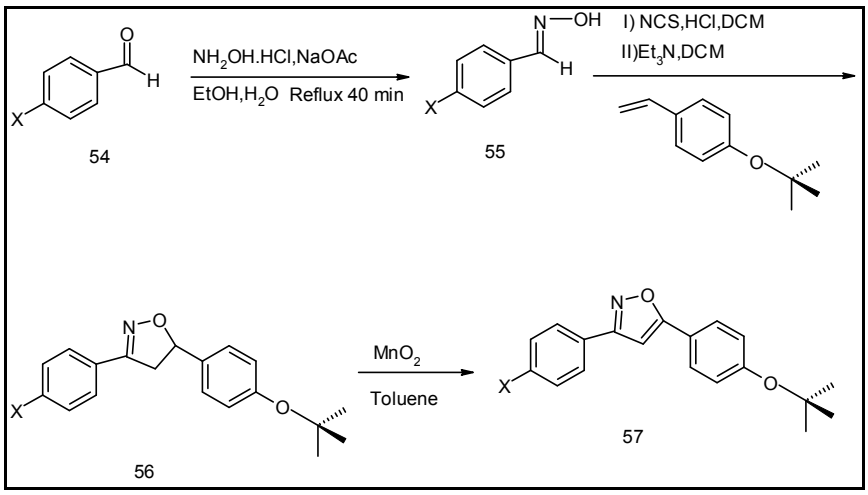
The multistep synthesis of isoxazole (52)(53) have been reported via 1,3 dipolar cycloaddition of α,β unsaturated ester and nitriles oxide by author W.Marek GOLEBIEWSKI .[Scheme-11][21]



Scheme 11

2.12 Synthesis from oxime using NCS, HCl, DCM & Et_3N, DCM Reagents

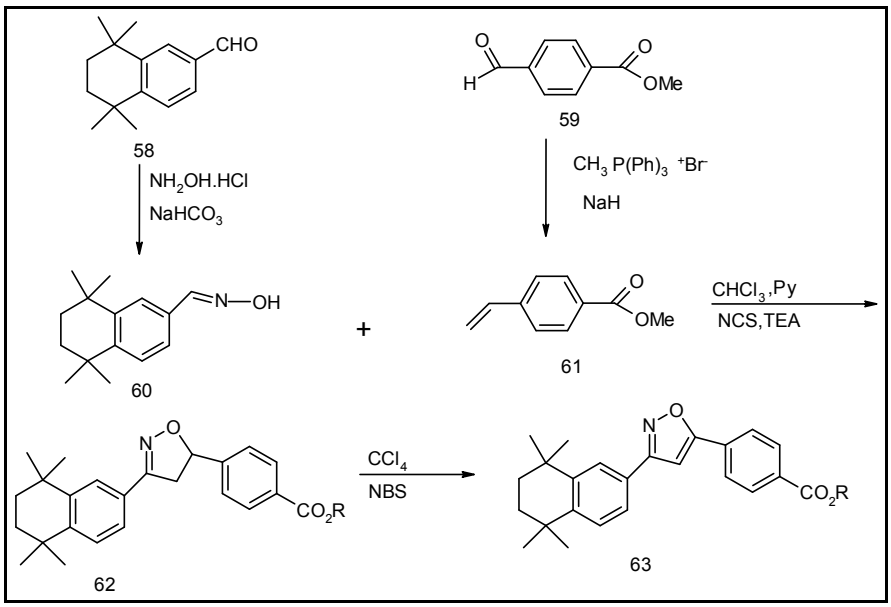
The substituted aromatic aldehyde (54) treated with $NH_2OH.HCl$, NaOAc gives oxime(55) which undergoes [3+2] cycloaddition with other chiral compound gives isoxazoline intermediate (56) which on oxidation with MnO_2 gives isoxazole derivatives (57)[Scheme-12][22]



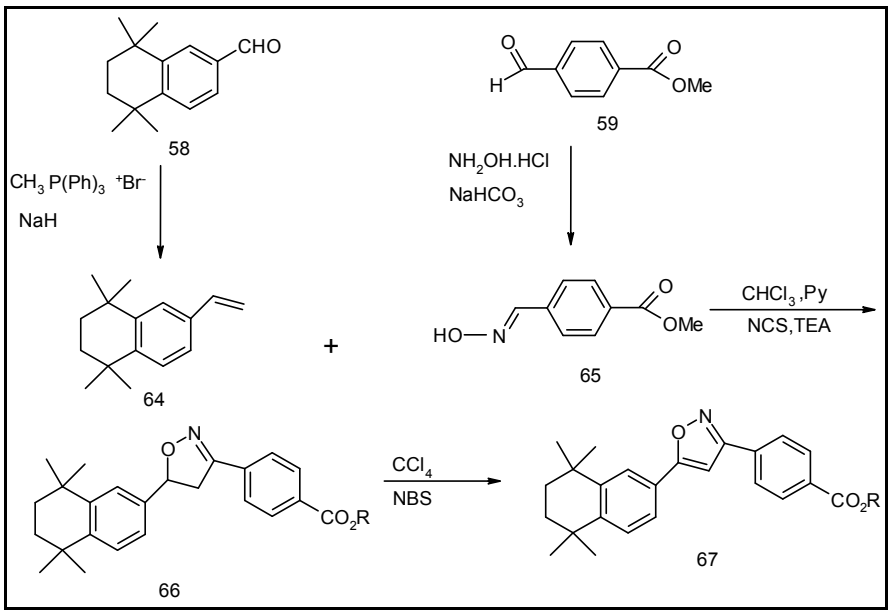
Scheme 12

2.13 Synthesis from different oxime with different olefins

An alternative , fast & clean method was reported for the synthesis of substituted isoxazole(63) & (67) from aromatic aldehyde (58) and carbomethoxy benzaldehyde (59).[Scheme-13][Scheme-14][23]



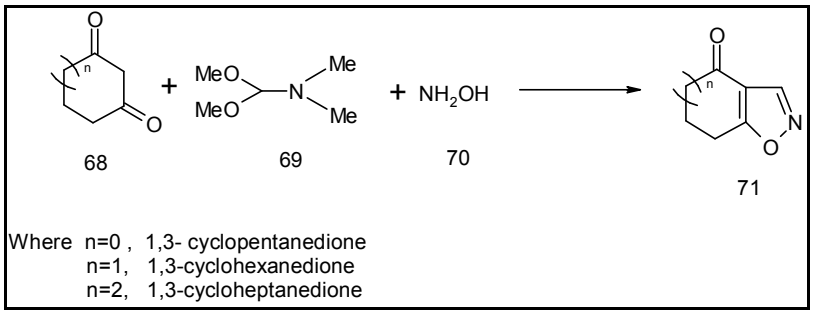
Scheme 13



Scheme 14

2.14 Aqueous one pot synthesis of isoxazole

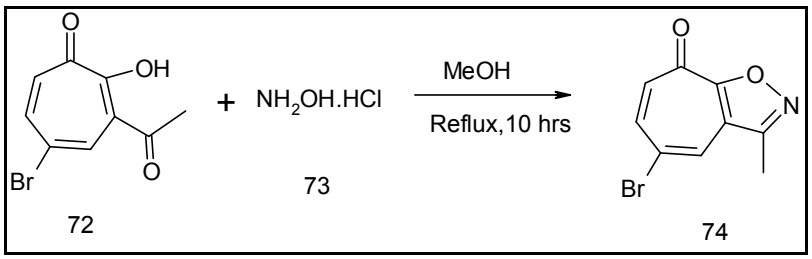
A novel one pot synthesis of isoxazoles (71) has been accomplished under microwave irradiation of three component reaction of 1,3 diketone (68) dimethyl formamide dimethyl acetal (69) and $NH_2OH.HCl$ (70). [Scheme-15][24]



Scheme 15

2.15 Synthesis from tropolone

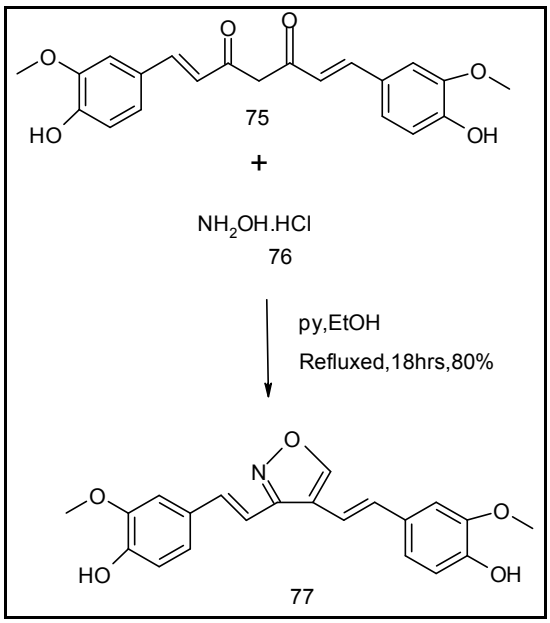
A mixture of 3-acetyl-5-bromo tropolone (72) and hydroxyl amine hydrochloride (73) in methanol and promoter was refluxed for 10 hrs to obtain isoxazole(74)[Scheme-16][25]



Scheme 16

2.16 Synthesis from Curcumin using NH2OH.HCl

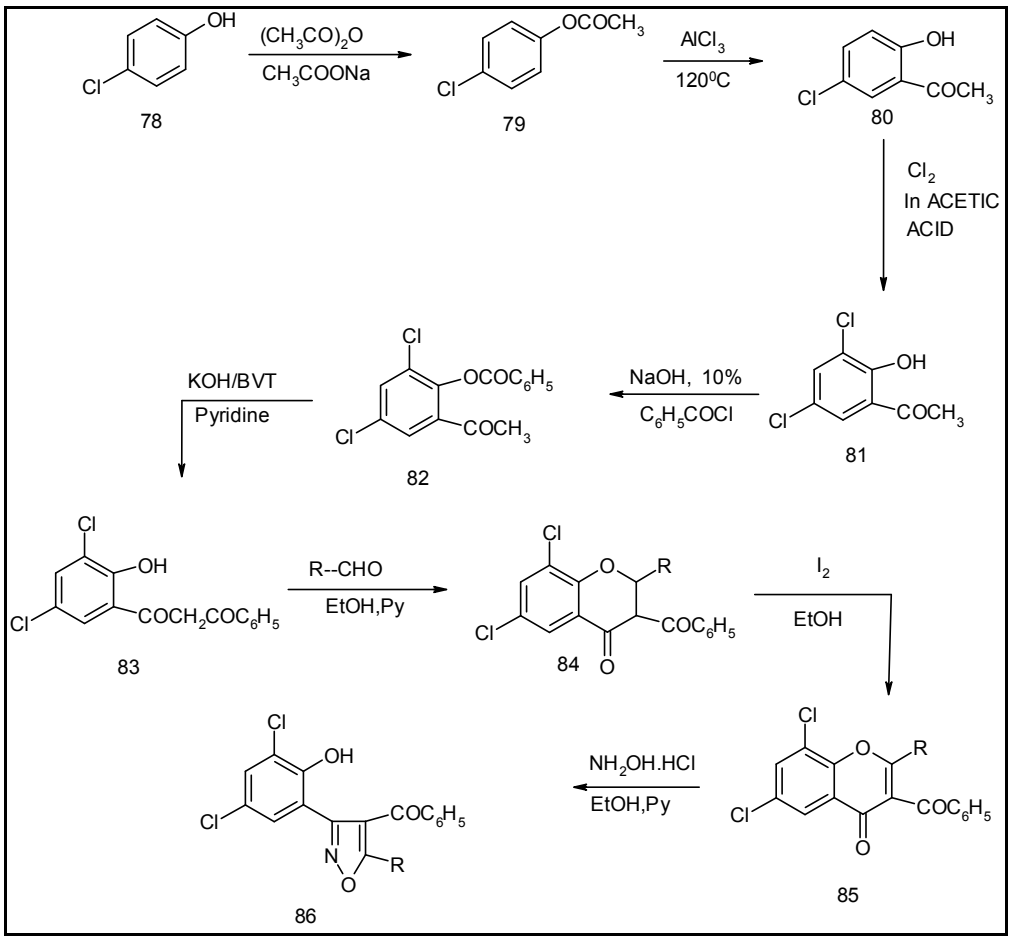
A novel one spot synthesis of isoxazole (77) was reported by refluxing a mixture of Curcumin (75), $NH_2OH.HCl$ (76) with catalytic amount of pyridine in ethanol. [Scheme-17][26]



Scheme 17

2.17 Synthesis using p- chloro phenol

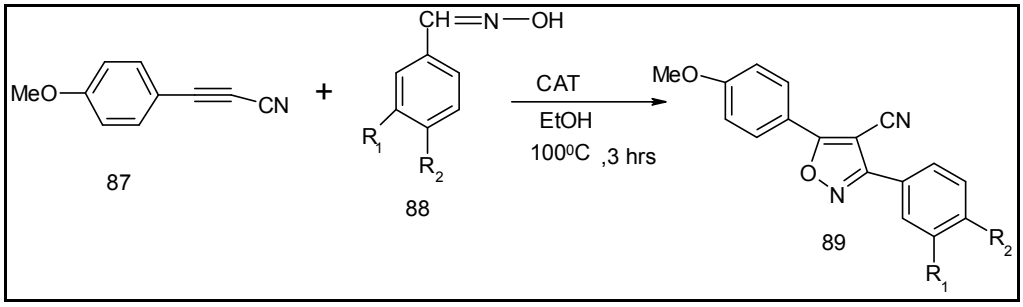
Multistep reaction on p-chloro phenol (78) provides the intermediate (85). The intermediate on treatment with hydroxyl amine hydrochloride afforded isoxazole (86) in good yield.[Scheme-18][27]



Scheme 18

2.18 Using Cycloaddition reaction of Aromatic aldoximes & propiolonitrile

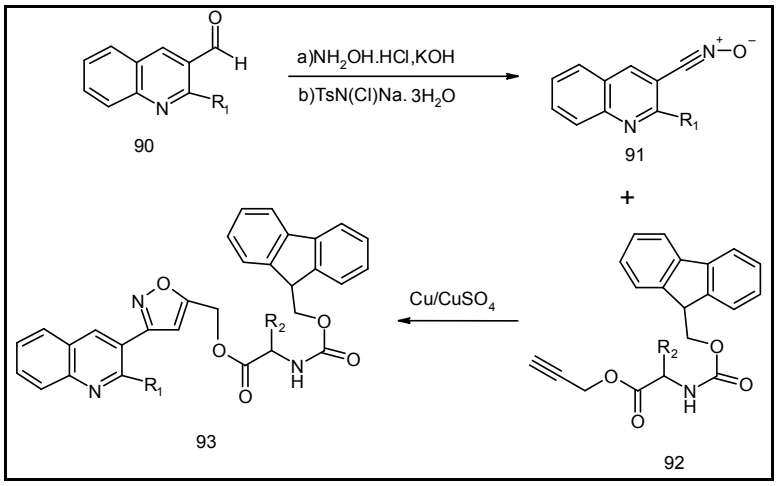
A mixture of aromatic aldoximes (88),3-(4-methoxy phenyl)propiolonitrile(87) and chloramine –T in ethyl alcohol was refluxed afforded isoxazole derivatives (89)[Scheme-19][28]



Scheme 19

2.19 Synthesis using copper catalyst

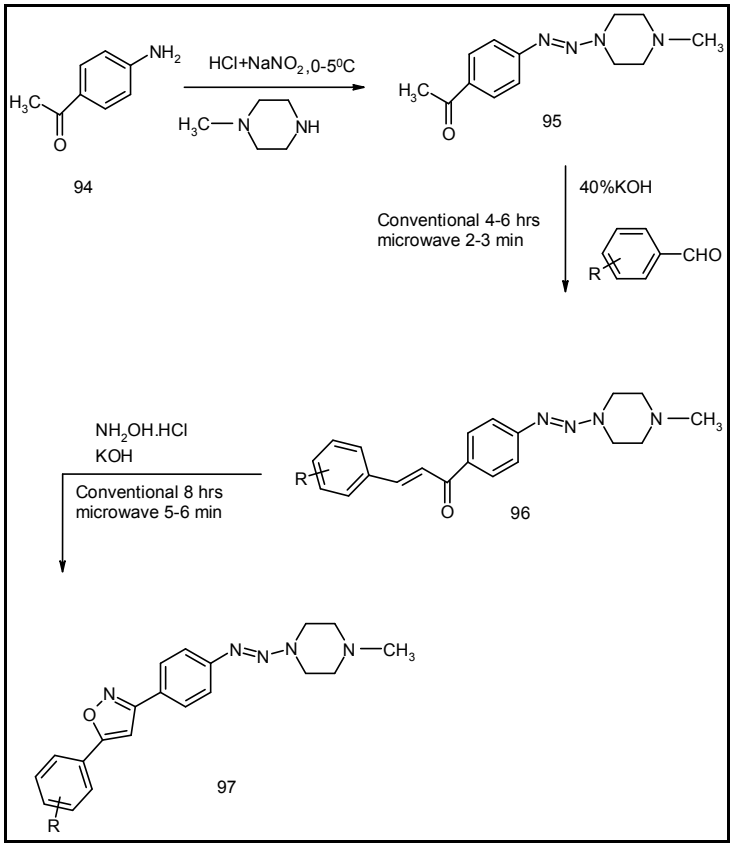
The quinolene carbaldehyde (90) is mixed with $NH_2OH.HCl$ & chloramine-T trihydrate is catalyzed by $CuSO_4$ with copper turnings afforded isoxazole derivatives(93)[Scheme-20][29]



Scheme 20

2.20 Microwave induced synthesis of isoxazole

The p-amino acetophenone (94) on diazotization and coupling with N-methyl piperazine yield (95).In which Substituted aldehyde were added gives intermediate (96) which cyclised with hydroxylamine hydrochloride furnished isoxazole derivatives (97) by microwave assisted reaction.[Sheme-21][30]

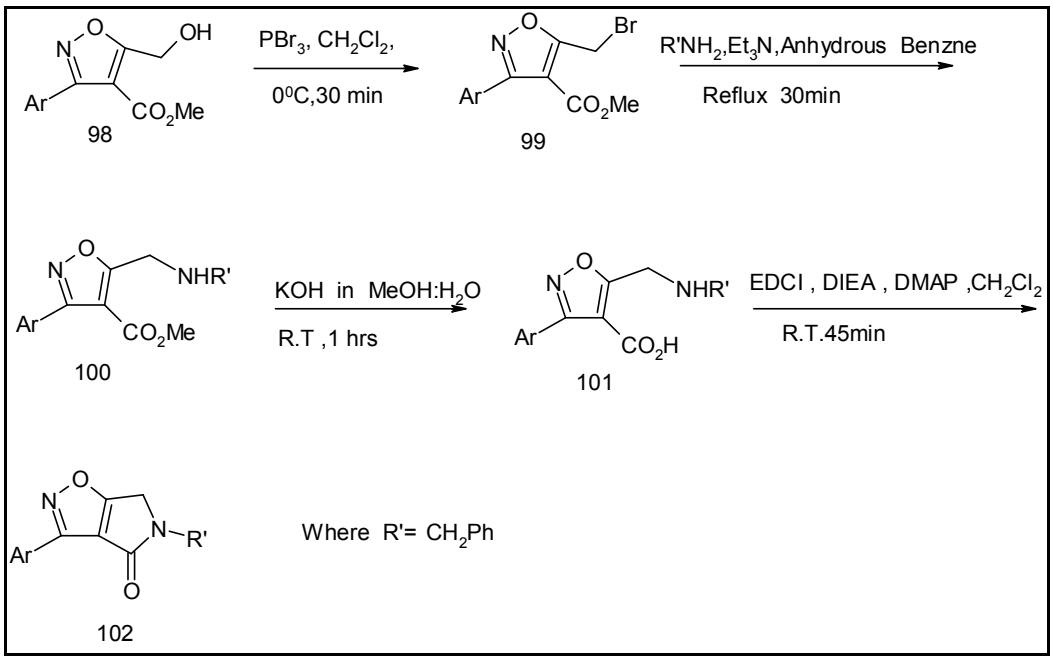


Scheme 21

3. Chemical Reactions

3.1 Synthesis of bicyclic lactum of Isoxazoles

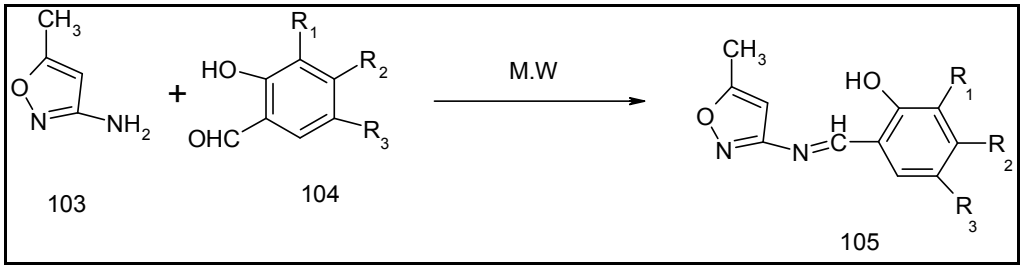
The synthesis of bicyclic lactum of isoxazoles (102) were reported by using alcohols of isoxazole (98) which on bromination , amination and by EDCI,DIEA , DMAP.[Scheme-22][31]



Scheme 22

3.2 Microwave assisted synthesis of Schiff base

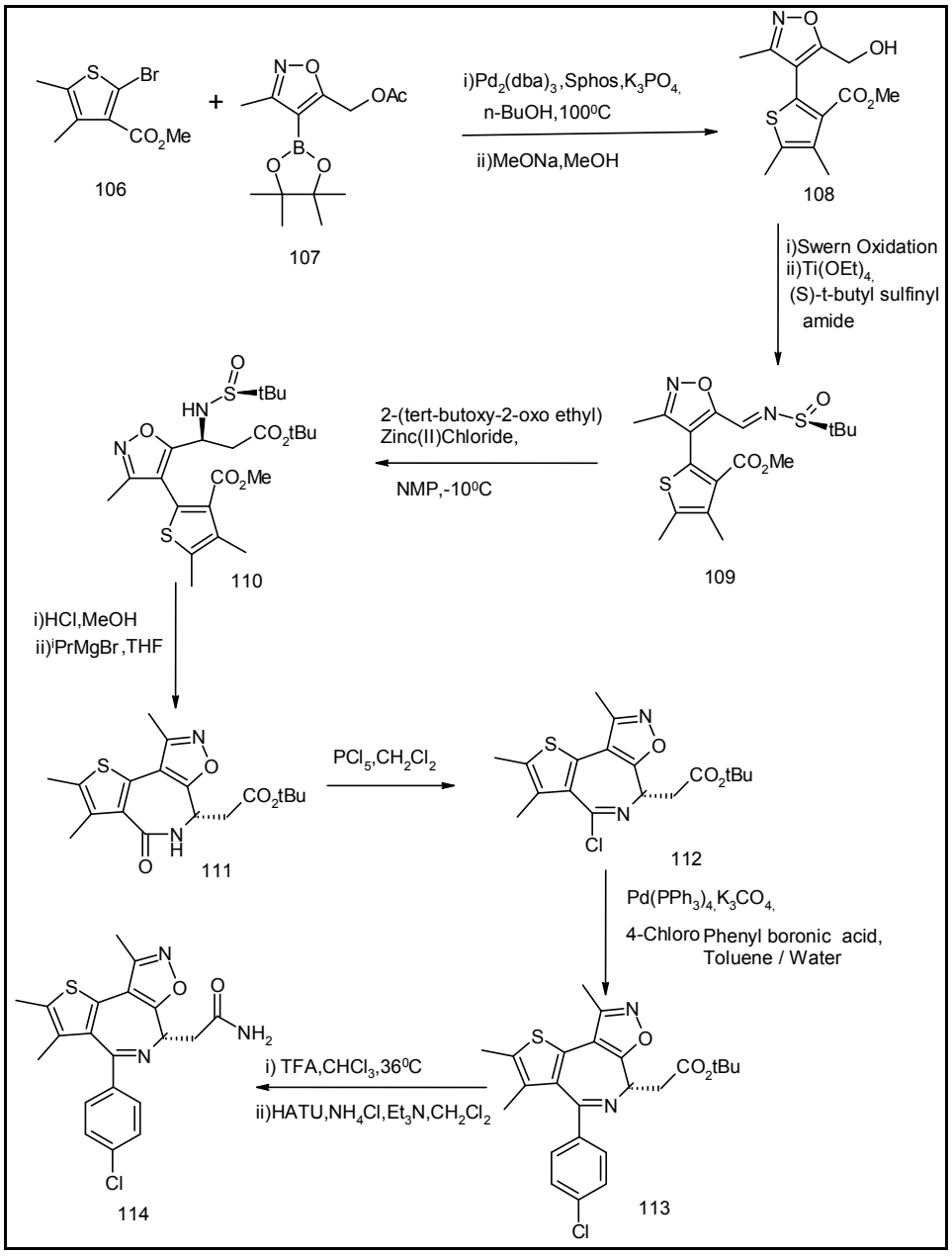
Isoxazole Schiff bases (105) obtained from 3-amino-5-methyl isoxazole (103) with substituted salicylaldehyde (104) using microwave assisted method [Scheme-23][32]



Scheme 23

3.3 Synthesis of isoxazole Azepine

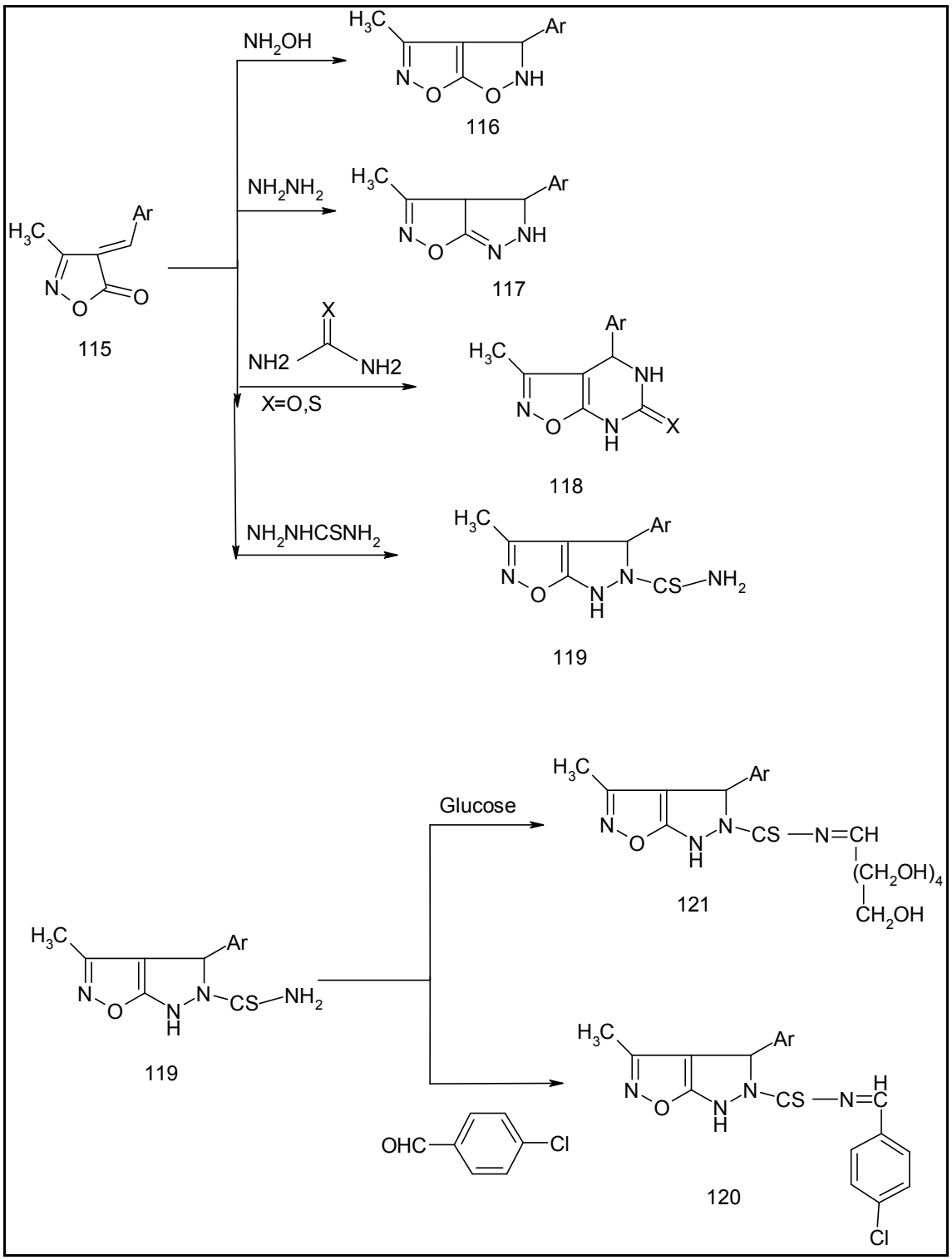
Synthesis of Azepine began with bromothiophene (106) & isoxazole boronic ester(107) condensed via Suzuki reaction & which deprotected to primary alcohol (108) oxidation & imine formation with (s)-tert-butyl sulfinamide formed sulfinyl imine (109) which on addition of enolate of tert-butyl acetate gives sulfinamine (110) which was deprotected in acid condition & treat with ^{i}PrMgBr gives Lactum(111) which on treatment with PCl_5 afforded imidoyl chloride(112) whichwas converted into Azepine(113) on deprotection & amide formation gives desired compound (114).[Scheme-24][33]

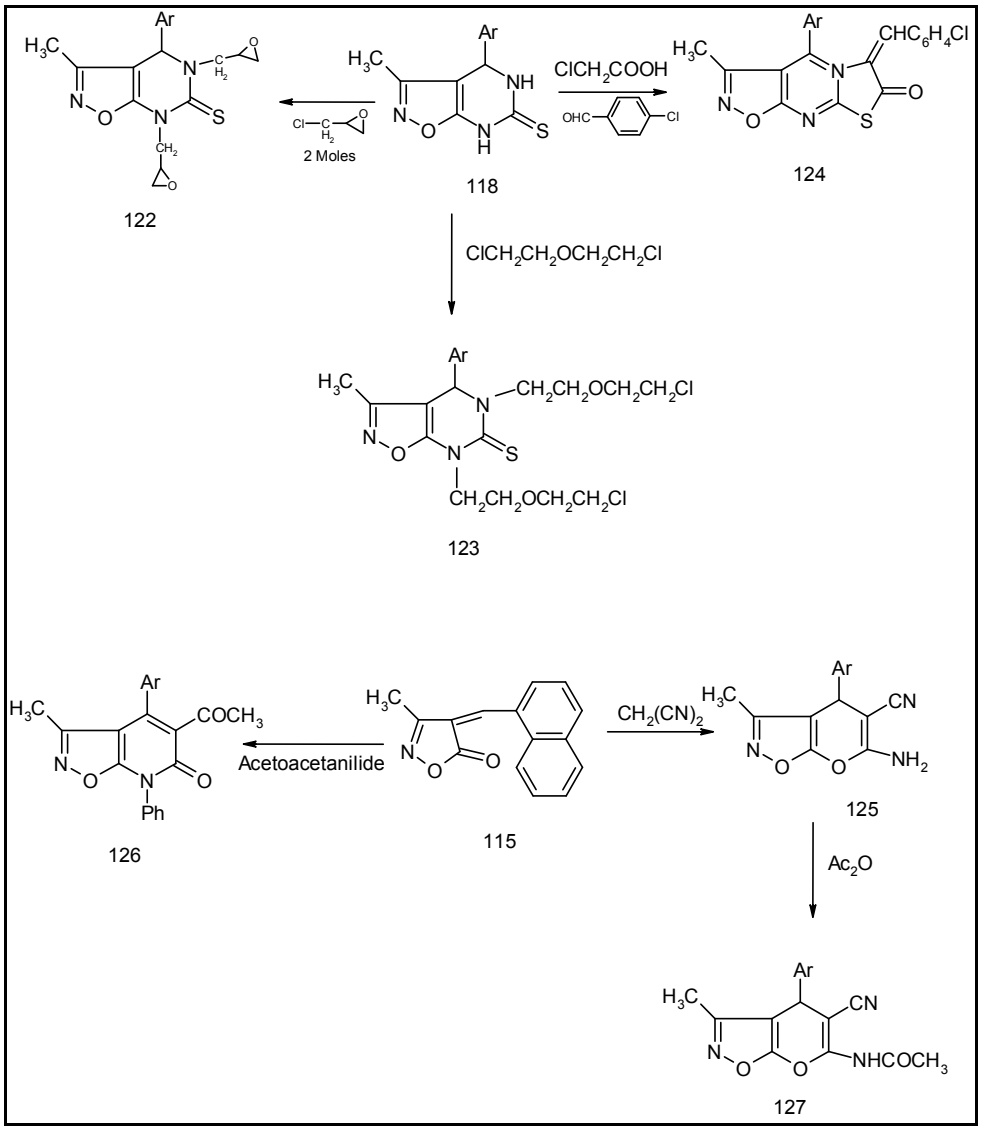


Scheme-24

3.4 Synthesis of Novel Isoxazole derivatives

A Convenient synthesis of some isoxazole have been reported by the reaction of isoxazole derivatives with some reagents such as $NH_2OH.HCl$,hydrazine hydrate,thiosemicarbazide & thiaurea via Michael addition to gives compound (116-119).Compound(119) was reacted with p-chloro benzaldehyde & glucose afforded compound (120,121) while compound (118) react with different halo compounds to gives (122-124).compound(115) reacted with malononitrile and acetoacetanilide to gives compounds(125,126). [Scheme-25][34]

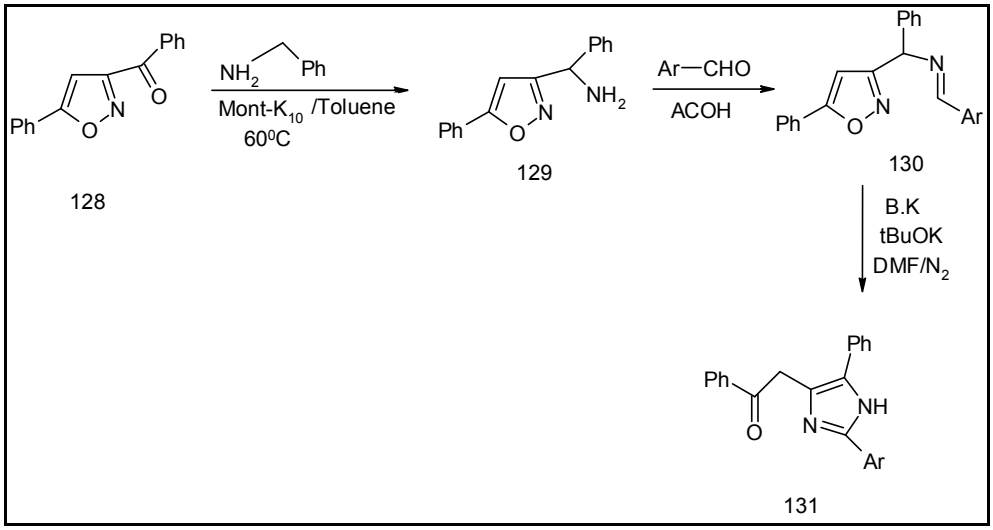

NH2OH
NH2NH2
NH2
X
NH2
X=O,S
NH2NHCSNH2
115
116
117
118
119
Glucose
119
121
120
OHC
Cl
Cl



Scheme 25

3.5 Synthesis of phenacyl - imidazoles

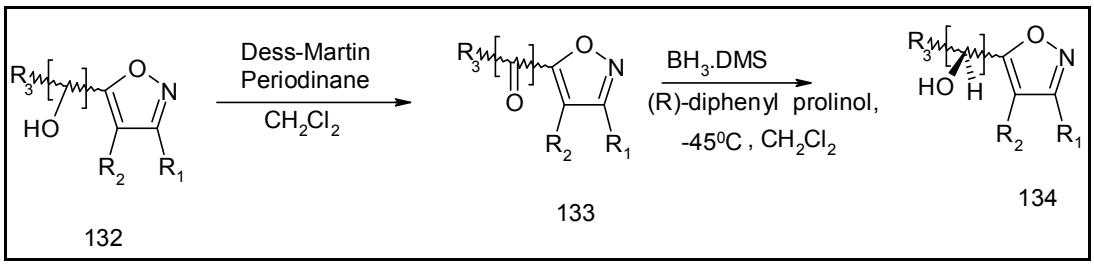
Synthesis of imine (130) by mixture of phenyl (s-phenyl isoxazol -3 -yl) methanamine (129) & aldehyde .Then Boulton-Katritzky rearrangement of imine gives isoxazoles (131).[Scheme-26][35]



Scheme 26

3.6 Reduction

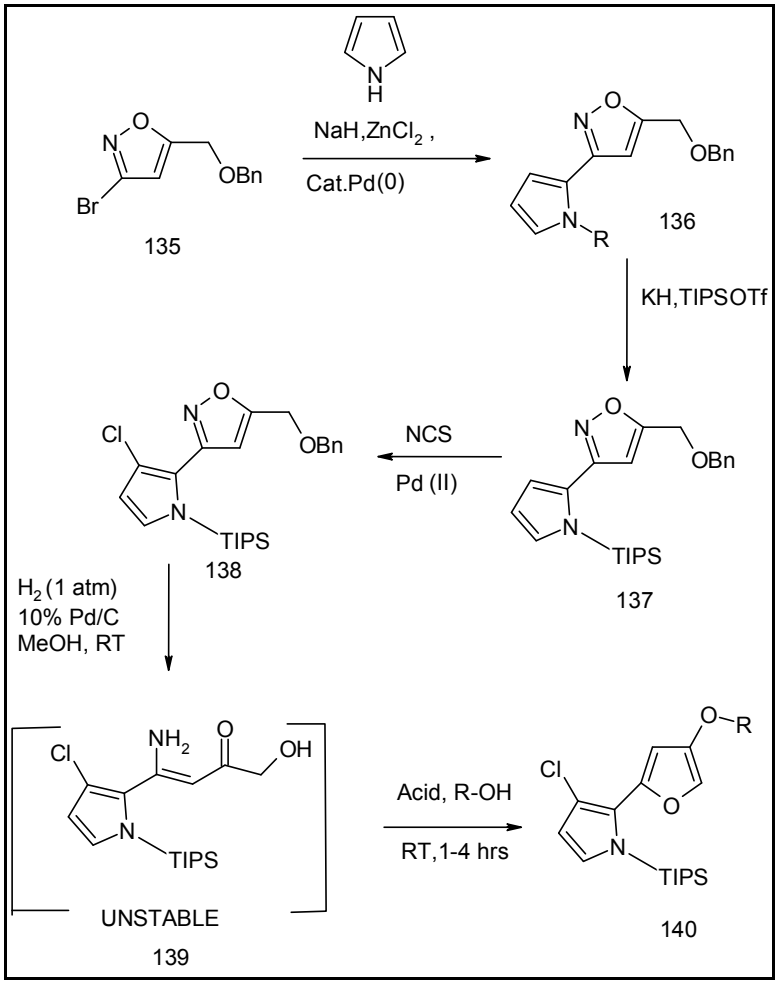
The isoxazole alcohols(132) is oxidized by Dess-Martin Periodinane ,CH_2Cl_2 gives isoxazolyl aryl ketones(133) which on Corey-Bakshi-Shibata reduction using dimethyl sulfide borane furnished chiral isoxazole carbinols(134)[Scheme--27][36]



Scheme 27

3.7 Synthesis of substituted pyrrolyl furans

Synthesis by Sadighi cross-coupling using $ZnCl_2$ of 3-bromo isoxazole(135) gives pyrrolyl isoxazole (136). Which convert in triisopropyl silyl derivatives (137). & treated NCS/$Pd(OAc)_2$ gives chlorinated pyrrol (138) hydrogenolysis of over Pd/C in MeOH gives enaminone (139) which react with acid afforded pyrrolyl furans(140)[Scheme-28][37]

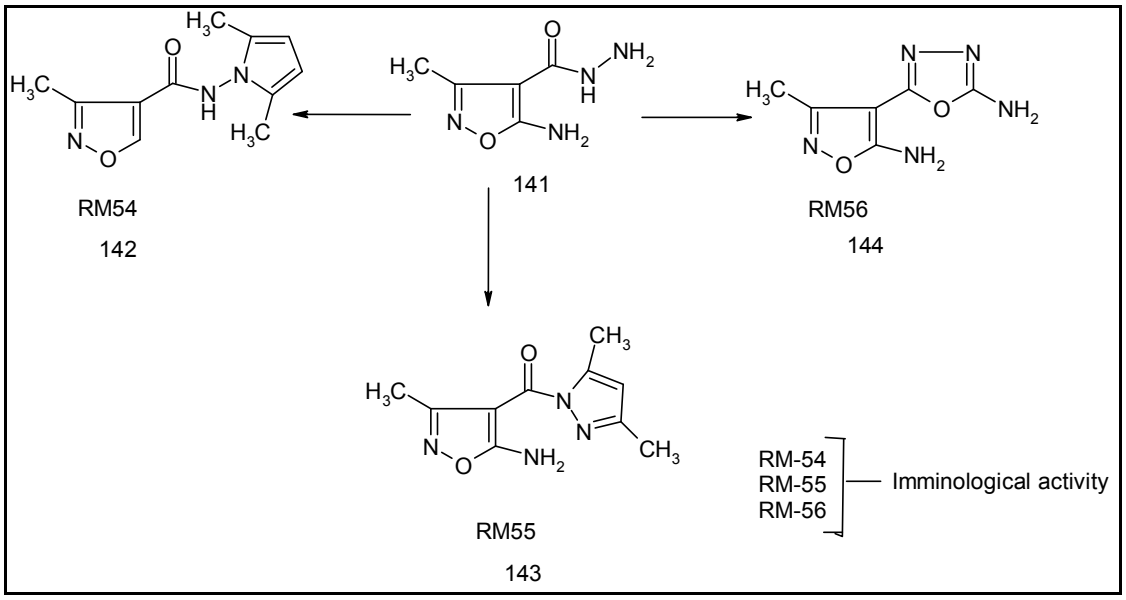


Scheme 28

3.8 Synthesis of new Lead structure in isoxazole

The reaction of 5-amino -3-methyl-4-isoxazole carboxylic acid hydrazide(141) with mixture of

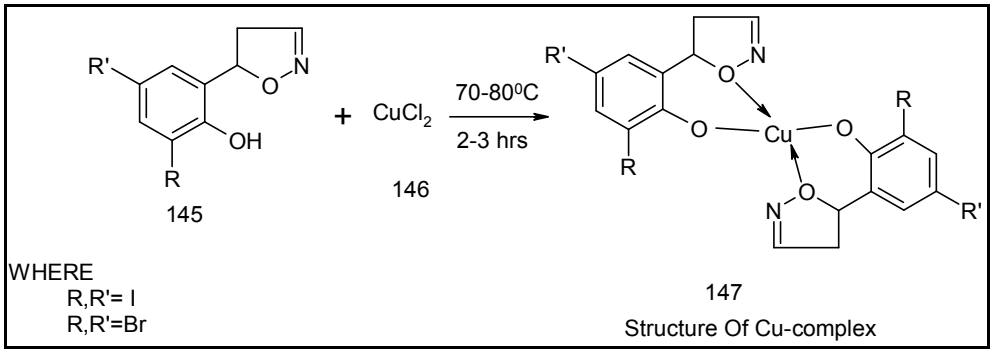
isopropanol & (hexanedione-2,5),(pentanedione2,4) and cyanogen bromide gives new lead structures: 5-amino-3-methyl-4-(2,5-dimethyl pyrrol –amino carbonyl)-Isoxazole RM54(142),5-amino-3-methyl-4-(3,5-dimethyl pyrazole carbonyl)-Isoxazole RM55 (143), & 5-amino – methyl -4-[2-(5-amino-1,3,4-oxadiazole)] – Isoxazole RM56(144)[Scheme-29][38]



Scheme 29

3.9 Synthesis of metal complexes

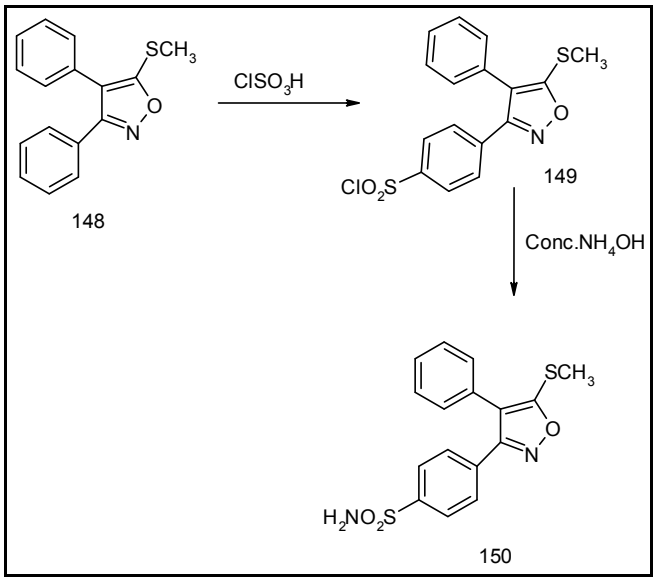
The hot methanolic solution of isoxazole ligand (145) and hot methanolic solution of copper chloride (146) were mixed together and refluxed to afforded Cu-Complex(147).[Scheme-30][39]



Scheme 30

3.10 Synthesis of Novel Isoxazole Derivatives

Synthesis of novel isoxazole reported by reaction of 5-(methyl thio)-3,4-diphenyl isoxazole(148) with chlorosulfonic acid afforded compound (149) which treated with Conc.NH_4OH furnished compound (150)[Scheme-31][40]

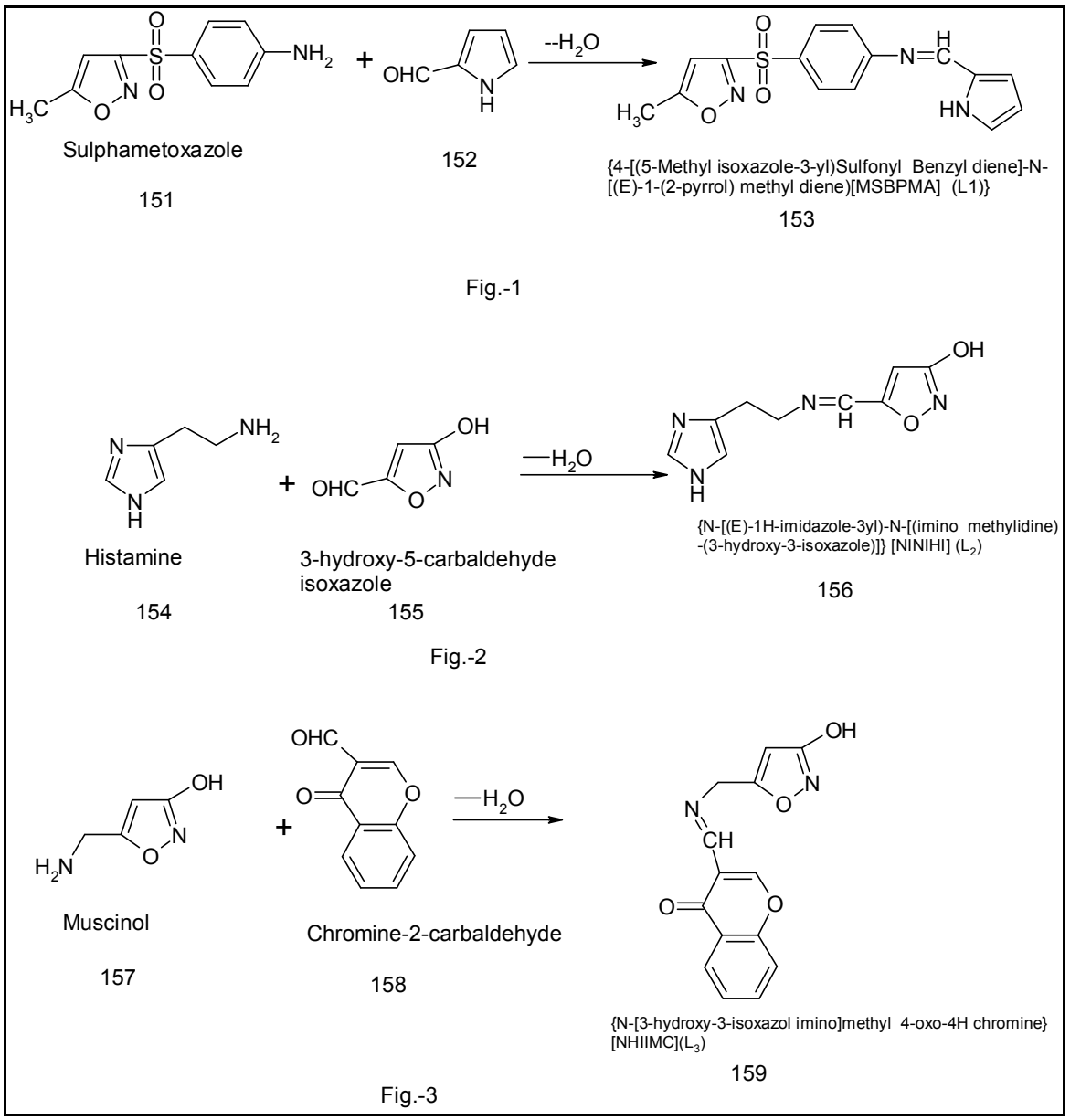


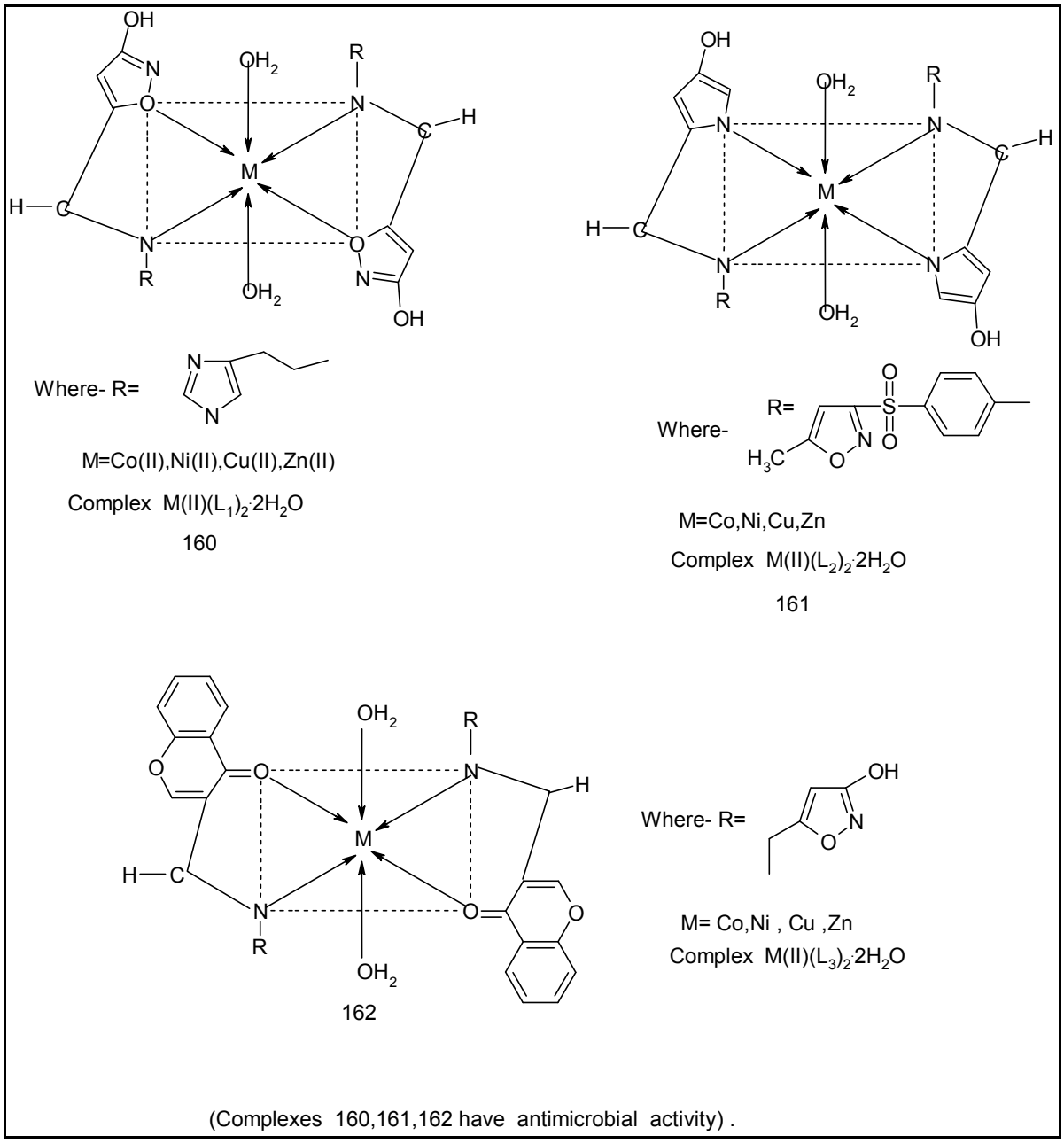
Scheme 31

4. Miscellaneous Reaction

4.1 Synthesis of novel Schiff base ligands and their metal complexes

Schiff bases are excellent ligands which are synthesized from condensation of primary amine with carbonyl group like MSBPMA (153) , NINIHI (156) , NHIIMC (159). The Co(II) , Ni(II) , Cu(II) & Zn(II) metal complexes have been synthesized compounds- (160,161,162)[Scheme-32][41]


--H_2O
Sulphametoxazole
151
152
{4-[(5-Methyl isoxazole-3-yl)Sulfonyl Benzyl diene]-N-[(E)-1-(2-pyrrol) methyl diene)[MSBPMA] (L1)}
153
Fig.-1
Histamine
154
3-hydroxy-5-carbaldehyde isoxazole
155
—H_2O
{N-[(E)-1H-imidazole-3yl)-N-[(imino methylidine) -(3-hydroxy-3-isoxazole)]} [NINIHI] (L_2)
156
Fig.-2
Muscinol
157
Chromine-2-carbaldehyde
158
—H_2O
{N-[3-hydroxy-3-isoxazol imino]methyl 4-oxo-4H chromine} [NHIIMC](L_3)
159
Fig.-3



Scheme 32

Conclusion

Isoxazoles are easily available and have high chemical reactivity. A series of heterocyclic compounds containing a five membered ring consisting of three carbon atoms united to first position oxygen and second position nitrogen atom .Substituted Isoxazoles are important compounds of many drugs & drug candidates .This survey was attempted to summarize the synthetic methods and reactions of isoxazoles.

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