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

Human Journals
Research Article
June 2020 Vol.:18, Issue:3

Synthesis and Evaluation of New Isoxazole Derivative for Their Biological Activity

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

Vijay Pratap*, Manish Singh, Surya Nath Pandey

Department of Pharmacy, J.K Institute of pharmacy & management khurja, Bulandshahr, India.

Department of Pharmacy, SSITM, Aligarh, India.

Department of Pharmacy, J.K Institute of pharmacy & management khurja, Bulandshahr, India.

Submission: 22 May 2020
Accepted: 29 May 2020
Published: 30 June 2020

Keywords: Isoxazole, Heterocyclic ring, Anti-fungal, Antibacterial, Anti-HIV, Anti-inflammatory, Anti-hypertensive

ABSTRACT

Isoxazole is a five-membered heterocyclic ring having a broad spectrum of pharmacological activities like anti-tubercular, anti-cancer, anti-bacterial, anti-fungal, anti-HIV, anti-inflammatory and anti-hypertensive activities. In the present research work, we reported the synthesis of some novel isoxazoles by using various substituted chalcones and screened for their anti-inflammatory activity.

HUMAN JOURNALS
www.ijppr.humanjournals.com

INTRODUCTION

Medicinal chemistry is an interdisciplinary science. It has been stated that "Medicinal chemistry concerns the discovery, the development, the identification and interpretation of the mode of action of biologically active compounds at the molecular level". It touches all branches of chemistry and biology. Medicinal chemistry is also treated under the terms pharmaceutical chemistry, molecular pharmacology, bio-organic chemistry, and selective toxicity. Medicinal chemistry is a chemistry-based discipline, also having aspects of biological, medicinal, and pharmaceutical sciences.

It is concerned with the invention, discovery, design, identification, and preparation of biologically active compounds, the study of their metabolism, the interpretation of their mode of action at the molecular level and construction of structural activity relationships by which can be used as a medicine of the prevention mitigation and treatment of diseases.

The focus is mainly on organic medicinal substances. The organic drugs may be of natural or synthetic origin. The synthetic drugs have resulted in simple or more modification of the structures of the natural drugs, or by pure synthesis. The other areas of collaboration in medicinal chemistry include biology computer-aided drug design (CADD), 3-D QSAR, X-ray crystallography, metabolism pharmacokinetics, legal and regulatory affairs, clinical franchise management, pharmaceutical, and process research chemistry.

Chemists and pharmacologist's concerned with the synthesis and evaluation of new compounds have realized the need for a publication that would provide comprehensive and systemic summaries which stimulate the visualization of new molecular structure and leads to the synthesis and testing of new compounds.

INFLAMMATION:

Inflammation is defined as the local response of living mammalian tissues to injury due to any agent. It is a body defense reaction to eliminate or limit the spread of injurious agents as well as to remove the consequent necrosed cells and tissues.

The agents causing inflammation may be as under:

- Physical agents like heat, cold, radiation, mechanical trauma.

- Chemical agents like organic and inorganic poisons.
- Infective agents like bacteria, viruses, and their toxins.
- Immunological agents like cell-mediated and antigen-antibody reactions.

Inflammation involves two basic processes with some overlapping, *viz.* early inflammatory response, and later followed by healing. Though both these processes generally have a protective role against injurious agents, inflammation and healing may cause considerable harm to the body as well as anaphylaxis to bites by insects or reptiles, drugs, toxins, atherosclerosis, chronic rheumatoid arthritis, fibrous bands and adhesions in intestinal obstruction.

SIGNS OF INFLAMMATION:

- Rubor(redness)
- A tumor (swelling)
- Calor (heat)and
- Dolar(pain)

To these, the fifth sign functional area (loss of function) was later added by Virchow. The word inflammation means burning. This nomenclature had its origin in old times but now we know that burning is only one of the signs of inflammation.

Anti-inflammatory Agents:

- Hetero aryl acetic acid analogs:

  - Indomethacin
  - Tolmetin sodium
  - Zomepiacsodium

- Aryl acetic acid analogs:

  - Sulindac

- Ibufenac
- Diclofenac sodium

- Aryl propionic acid analogs:

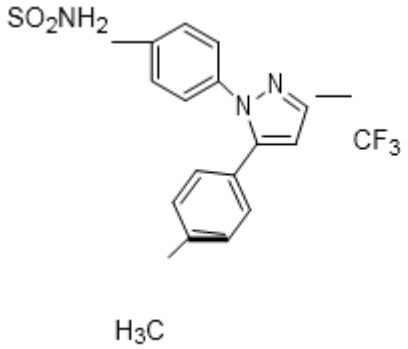
- Ibuprofen
- Flurbiprofen
- Ketoprofen
- Naproxen

- Selective COX-2inhibitors:

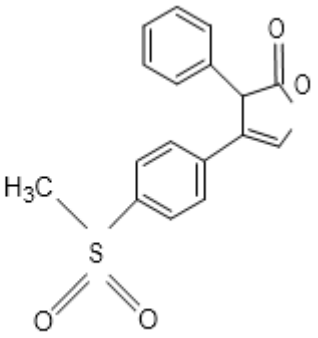
- Celecoxib
- Rofecoxib
- Valdecoxib

Mechanism of action:

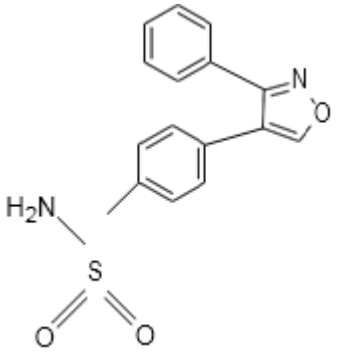
NSAIDs inhibit the Cyclooxygenases, the enzyme that catalyzes the synthesis of cyclic endoperoxides from the Arachidonic acid to form Prostaglandins(PG). The two COX isoenzymes are COX-1 and COX-2. COX-2 is responsible for the production of PGs at the inflammation site. Selective COX-2 inhibitors may eliminate the side effects associated with NSAIDs due to COX-1 inhibition such as gastric and renal effects.



Celecoxib



Rofecoxib



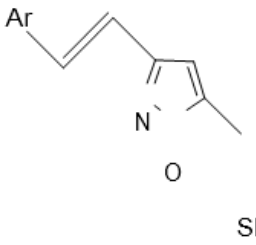
Valdecoxib

ISOXAZOLE:

Isoxazoles are unique in their chemical behavior not only among heterocyclic compounds in general but also among related azoles. This is because isoxazole possesses the typical properties of the aromatic system, which are rather pronounced in these derivatives, together with the high liability of the ring under certain conditions, particularly at the nitrogen-oxygen bond. From a purely formal point of view, isoxazole can be considered as an analog of pyridine just as furan is an analog of benzene. Such a formal analogy is to some extent valid, isoxazole resembles pyridine more than other heterocyclic compounds as far as chemical properties are concerned. It differs from pyridine in undergoing more readily electrophilic substitution reactions and possessing a more liable ring; this relationship thus resembles that between furan and benzene.

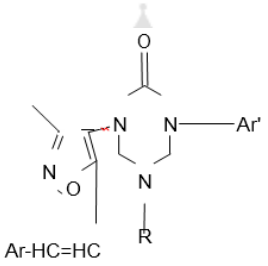
Although isoxazole derivatives have been known for more than 80 years, the investigation of their chemistry commended rather slowly. Earlier studies were mainly devoted to the development of synthetic methods. Recently the attention was focused on the investigation of

chemical properties and in particular on the peculiarities of the behavior of isoxazole derivatives and the elucidation of their physicochemical characteristics. This enabled new data to be obtained that were of considerable importance. The Cyclo condensation of Oxo ketene dithioacetals with either hydroxylamine hydrochloride gives corresponding isoxazole.



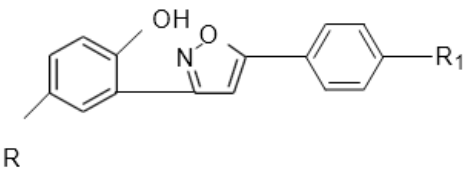
a) Ar = -C_6H_5, b) Ar = -4-CH_3-C_6H_4, c)Ar = -4-Cl-C_6H_4, d)Ar = -2-Cl-C_6H_4

Trimolecular condensation of N-(3-methyl-5-styryl-4-isoxazolyl)-N'-aryl ureas, paraformaldehyde, and primary amines using mononitrile in dry media under microwave irradiation leads to isoxazolyl-[1, 3, 5]-triazinan-2-ones.



a) Ar = -C_6H_5, Ar'= -C_6H_5, R = -CH_3, b) Ar = -C_6H_5, Ar' = 4-CH_3-C_6H_4, R = -CH_3, c) Ar = -C_6H_5, Ar' = -C_6H_5-CH_2, R = -CH_3, d) Ar = -C_6H_5, Ar' = -C_6H_4Cl, R =-CH_3

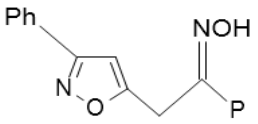
2'- hydroxychalcone bromide with phenyl hydroxylamine hydrochloride gives isoxazole in triethanolamine medium.



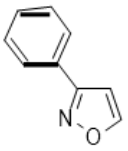
a)R=-CH_3,R_1=-OCH_3,b)RFS=-CH_3,R_1=-H,c)R=-CH_3,R_1=-Cl

The reaction of 1,5-diarylpent-1-yne-3 with hydroxylamine hydrochloride in ethanol leads to

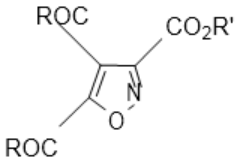
the formation of 5-hydroxy isoxazolines. These isoxazolines with on heating in xylene form isoxazoles.



The 1,3-dipolar cyclo-addition of nitrile oxides with vinyl acetate yields 3-phenyl- 5-acetoxy-Δ^2-isoxazoline. These compounds are readily converted into 3-phenyl isoxazole by the removal of acetic acid.

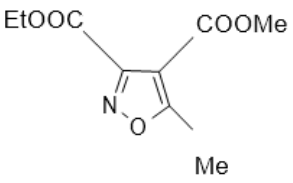


The reaction of dialkyl acetyl carboxylates with alkyl-2-niroethanoates in presence of tri-pheynlphosphine leads to functionalized isoxazoles.

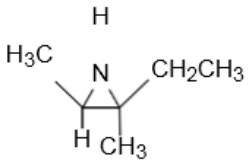


a) R = -OCH_3, R' = -CH_3, b)R = -OCH_3, R' = -CH_2-CH_3

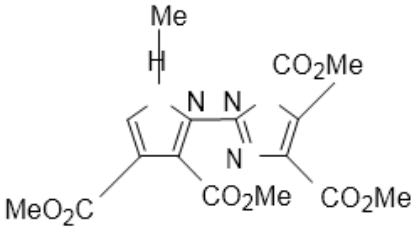
β-Alkyl carbonyl-β-enaminoketoesters react with hydroxylamine hydrochloride to give isoxazoles.



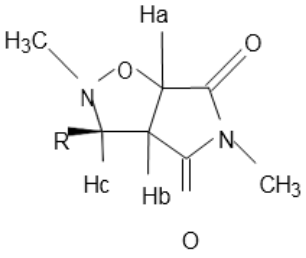
3,4,5-trimethyl isoxazole on reduction with lithium aluminum hydride gives 2,3- dimethyl-3-β- hydoxyethylhydrazine.



The imidazole [4,5-c] isoxazole when treated with dimethyl acetylene dicarboxylateinboilingdrytoluenegives2-pyrrol-2-yl-imidazole.

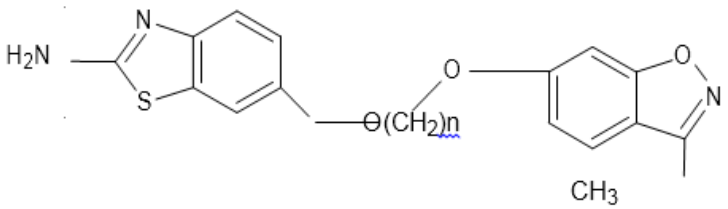


2/3,5-substituted perhydropyrolo [3,4-d] isoxazoles-4-6-diones were synthesized. Compounds were screened for antibacterial activity against *E.faecalis* and *S.aureus*. The following compounds showed effective against the growth of bacteria.

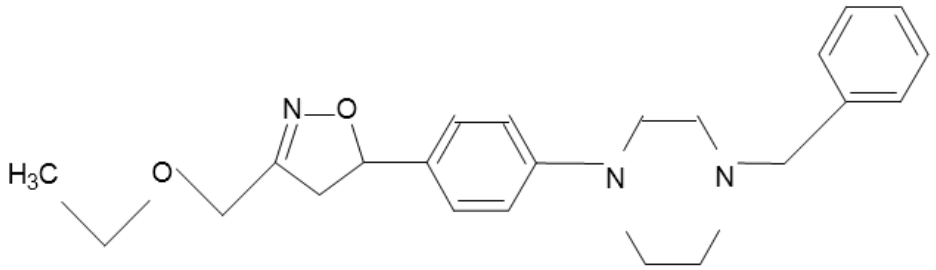


a) R = -p-(C2H5)2-N-C6H4, b) R = -p-(CH3)2N-C6H4, c) R = -p-(OCH3)-C6H4, d) R = - 4-Bzo-3-(OCH3)-C6H3, e) R = -p-CH3-C6H4.

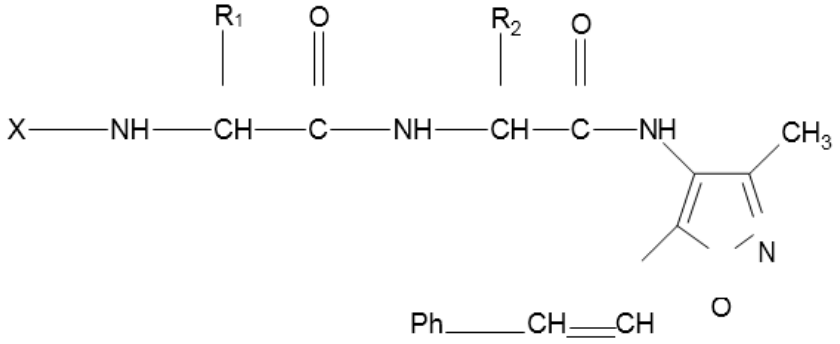
2-amino-5/6-hydroxybenzothiazole,6-hydroxy-3-methyl-1,2-benzisoxazolewere synthesized and screened for anti-bacterial and anti-fungal activity. Following Compound showed good anti-bacterial and anti-fungal activity.



Isoxazoline linked nitrofurans were synthesized and screened for anti-tubercular activity. The following compound showed better anti-tubercular activity.



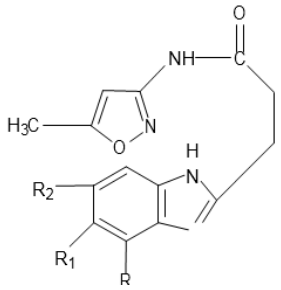
N-protected amino acid/peptide isoxazoles were synthesized and screened for their ability to inhibit the growth of gram-negative bacteria. The following compounds showed high antibacterial activity when compared to the standard drug.



(a) X= -Boc, R1= -CH2-C6H5, R2= -CH2-CH-(CH3)2 (Boc-D-Phe-D-leu),

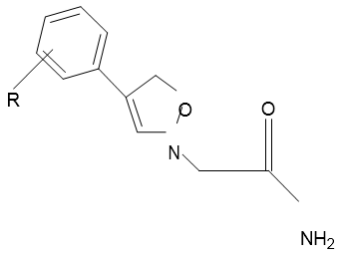
(b) X= -Boc, R1= -CH3, R2=-H-(Boc-D-Ala-Gly)

2/3-(1H-benzimidazole-2-yl)-N-(5-methyl-3-isoxazolyl)-benzamides were synthesized and screened for antibacterial activity against gram-negative bacteria. The following compounds showed good antibacterial activity compared to the standard drug.



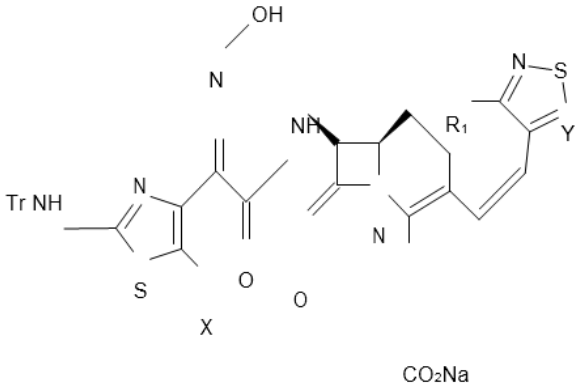
(a) R, R1, R2= -H, (b) R= -NO2, R1&R2= -H, (c) R= -H, R1&R2= -Cl

Benzoisoxazolines and isoxazolines substituted at 4thposition provided isoxazolines with much-improved gram-positive and gram-negative anti-bacterial activity.



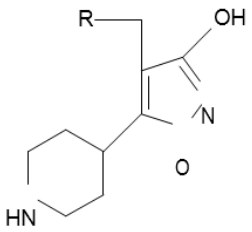
(a) R= -H, (b) R=3-F, (c) R=3-Cl, (d) R= 3-CH3, (e) R= 4-F

3- isoxazolyl-vinyl cephalosporins were synthesized and screened for antibacterial activity. In a series of compounds, few showed antibacterial activity against gram-negative bacteria.



(a) X= -Cl, Y= -N, R1= -H, (b) X= -H, Y= -C, R1= -CH3

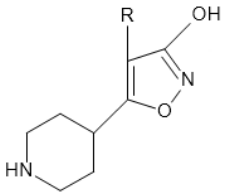
A potent 4-aryl or 4-alkyl aryl-substituted 3-isoxazolyl introduction of chloro, fluoro, cyano, methyl, thio, or phenyl substituents in the position of the 2-naphthyl methyl ring system showed good Gamma Amino Butyric Acid (GABA) activity.



(a) R=1-Bromo-2-naphthyl, (b) R=8-Bromo-2-naphthyl, (c) R=1- Fluoro-2-naphthyl

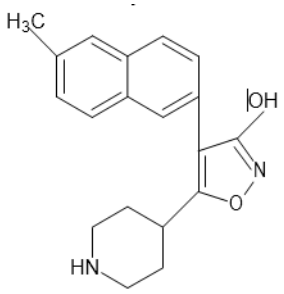
(d) R=1-Chloro-2-naphthyl.

4-aryl-5-(4-piperidyl)-3-isoxazoles were synthesized, the meta phenyl substituted compounds and para phenoxy substituted compounds displayed significant Gamma Amino Butyric Acid antagonistic activity.

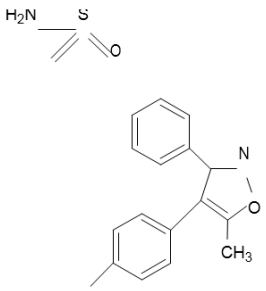


(a) R=3-Chlorophenyl, (b) R=3-pyridyl, (c) R=3-thienyl, (d) R=4-biphenyl.

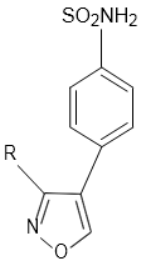
Novel classes of potent-3-isoxazolyl Gamma Amino Butyric Acid antagonists were synthesized. In the series of compounds extension of the aromatic system from phenyl to naphthyl group gave markedly increased affinity.



4-[5-methyl-3-phenylisoxazol-4-yl]-benzene sulfonamide was synthesized. In the series of compounds, the following compound showed a highly selective and potent inhibitor of COX-2 in human whole blood and against the recombinant human enzyme.

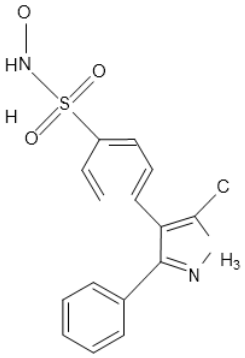


Novel 3, 4-diarylisoxazole analogs of valdecoxib were synthesized and screened for anti-inflammatory activity. Among the synthesized compounds a, b, and c are showed good anti-inflammatory activity compared to the standard drug.

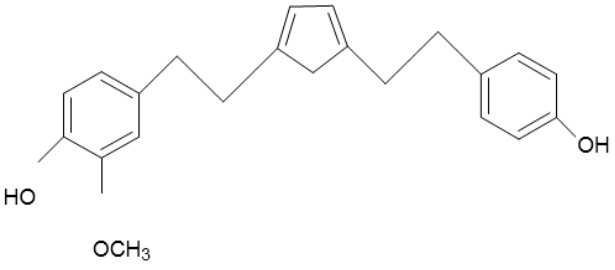


(a) R=phenyl, (b) R=5-chloro-2-furyl, (c)R=3-chloro-2,4,6-trimethoxyphenol

N-hydroxyvaldecoxib analogs were synthesized, in these compounds, N- hydroxy 4-[5-methyl-3-phenyl isoxazolyl -4- yl] benzenesulfonamide primary metabolite of the highly selective COX-2 inhibitor showed potent anti-inflammatory activity in carrageenan-induced rat paw edema in chronic and acute pain models.



Curcuminoids from Curcuma longa and their isoxazole analogs were synthesized and evaluated for anti-inflammatory activity. The following compound showed good anti-inflammatory activities in the carrageenan-induced rat paw edema method.



OBJECTIVES

Compounds containing isoxazole nucleus find a unique place in medicinal chemistry and play a significant role as they are associated with immense biological activity. Isoxazole is reported to show some interesting pharmacological properties like anti-bacterial, fungicidal, insecticidal, anti-tumor, anti-inflammatory, anti-hypertensive, and anti-tubercular.

Isoxazole derivatives have attracted considerable attention owing to their effective biological activity and extensive use. There are several methods available in the literature for the synthesis of isoxazole. However, some of these methods suffer from disadvantages such as poor solubility, lower yield, the requirement of severe conditions, and using strong or toxic or costly reagents. Therefore, the synthesis of new derivatives with greater efficacy and better yield is still desirables.

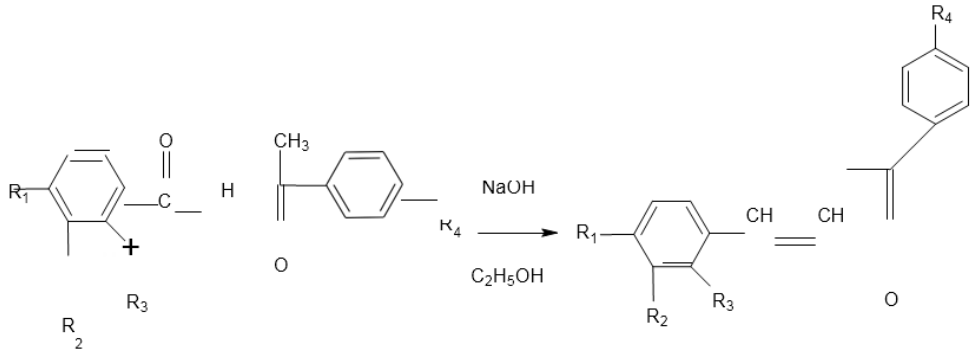
THE MAIN OBJECTIVES OF THE PROPOSED WORK IS:

- To synthesize novel isoxazole derivatives.
- To characterize newly synthesized compounds by M.P, TLC, FT-IR, H^1NMR, and Mass Spectroscopic techniques.
- To screen the newly synthesized compounds for their Anti-inflammatory activity using Wister Albino rats.

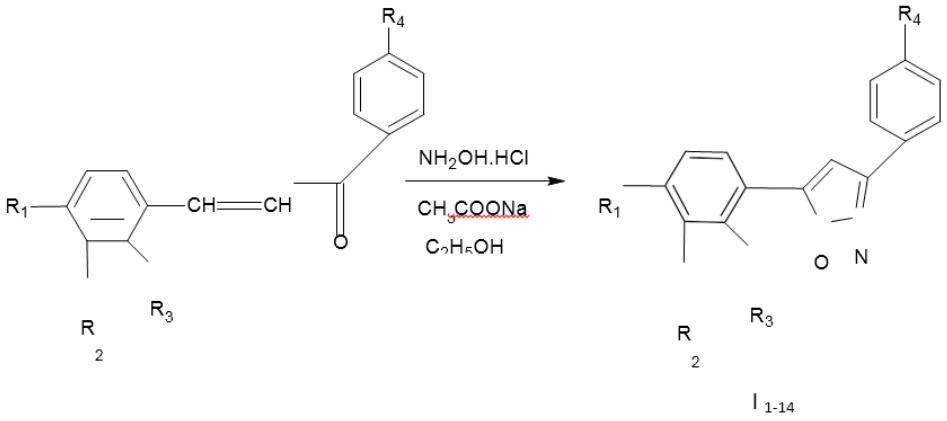
METHODOLOGY

SCHEME:

STEP-I:



STEP-2:



SUBSTITUTION:

Compound	R1	R2	R3	R4
I1	OH	OCH3	H	OH
I2	Cl	H	H	OH
I3	H	NO2	H	OH
I4	H	H	Cl	OH
I5	H	H	OH	OH
I6	OCH3	H	H	OH
I7	H	H	H	OH
I8	OH	OCH3	H	H
I9	Cl	H	H	H
I10	H	H	Cl	H
I11	H	H	OH	H
I12	H	H	H	H

GENERAL PROCEDURE FOR SYNTHESIS OFCHALCONES:

Equimolar quantities of different substituted aromatic benzaldehydes(0.01 mol) and substituted aromatic acetophenones(0.01 mol) were dissolved in 25 mL of alcohol. Sodium hydroxide solution (0.02 mol) was added slowly and the mixture stirred for 12 hr. until the entire mixture becomes very cloud. Then the mixture was poured slowly into 400 mL of water with constant stirring and kept refrigerator for 24 hr. Then precipitate obtained was filtered, washed, and recrystallized from ethanol.

GENERAL PROCEDURE FOR CYCLISATION OF CHALCONES:

0.015 mol of chalcone, 0.015 mol of hydroxyl ammonium hydrochloride, and sodium acetate 0.015 mol in 25 mL of ethanol were refluxed for 6 hr. The mixture was concentrated by

distilling out the solvent under reduced pressure and poured into ice water. The precipitate obtained was filtered, washed, and recrystallized from acetone.

TABLE No. 1: PHYSICAL CHARACTERIZATION DATA OF COMPOUND C1

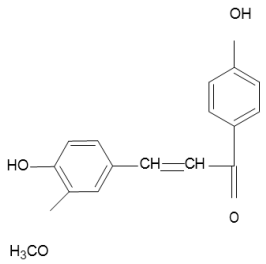
Structure	
Molecular Formula	$C_{16}H_{14}O_4$
Physical state	Red amorphous
Molecular Weight	270
%Yield	41%
TLC solvent system	Chloroform: acetone (8:2) Rfvalue 0.84

TABLE No. 2: PHYSICAL CHARACTERIZATION DATA OF COMPOUND C2

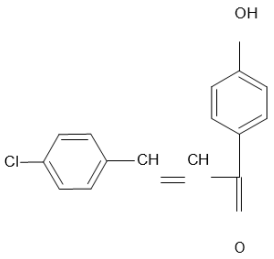
Structure	
Molecular Formula	$C_{15}H_{11}ClO_2$
Physical state	Yellow amorphous
Molecular Weight	258.5
%Yield	40%
TLC solvent system	Chloroform: acetone (8:2) Rfvalue 0.87

TABLE No. 3: PHYSICAL CHARACTERIZATION DATA OF COMPOUND C3

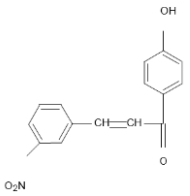
Structure	
Molecular Formula	$C_{14}H_{11}NO_4$
Physical state	white amorphous
Molecular Weight	257
%Yield	42.2%
TLC solvent system	Chloroform: acetone (8:2) Rfvalue 0.75

TABLE No. 4: PHYSICAL CHARACTERIZATION DATA OF COMPOUND C4

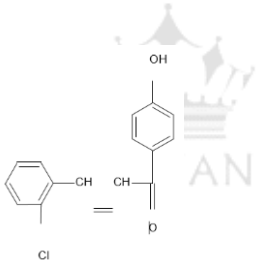
Structure	
Molecular Formula	$C_{15}H_{11}ClO_2$
Physical state	Yellow amorphous
Molecular Weight	258.5
%Yield	41.9%
TLC solvent system	Chloroform: acetone (8:2) Rfvalue 0.84

TABLE No. 5: PHYSICAL CHARACTERIZATION DATA OF COMPOUND C5

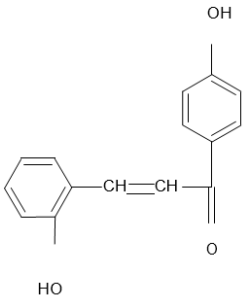
Structure	
Molecular Formula	$C_{15}H_{12}O_3$
Physical state	White amorphous
Molecular Weight	240
%Yield	47.5%
TLC solvent system	Chloroform: acetone (8:2) Rfvalue 0.71

TABLE No. 6: PHYSICAL CHARACTERIZATION DATA OF COMPOUND C6

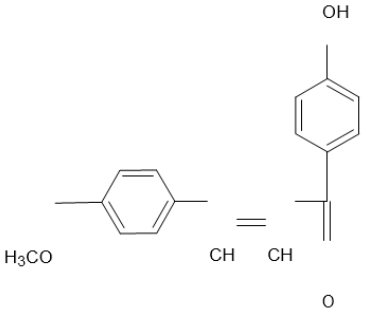
Structure	
Molecular Formula	$C_{16}H_{14}O_3$
Physical state	Yellow amorphous
Molecular Weight	254
%Yield	43.81%
TLC solvent system	Chloroform: acetone (8:2) Rfvalue 0.78

TABLE No. 7: PHYSICAL CHARACTERIZATION DATA OF COMPOUND C7

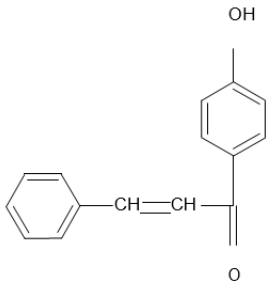
Structure	
Molecular Formula	$C_{16}H_{14}O_3$
Physical state	white amorphous
Molecular Weight	255
%Yield	43.47%
TLC solvent system	Chloroform: acetone (8:2) Rfvalue 0.77

TABLE No. 8: PHYSICAL CHARACTERIZATION DATA OF COMPOUND C8

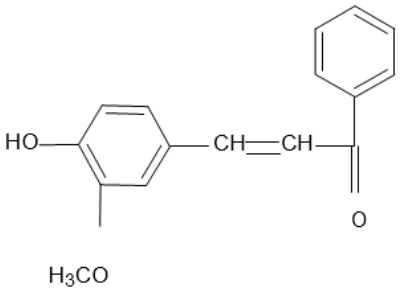
Structure	
Molecular Formula	$C_{16}H_{13}O_2$
Physical state	Red amorphous
Molecular Weight	253
%Yield	44.34%
TLC solvent system	Chloroform: acetone (8:2) Rfvalue 0.77

TABLE No. 9: PHYSICAL CHARACTERIZATION DATA OF COMPOUND C9

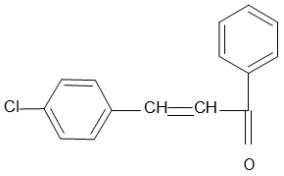
Structure	
Molecular Formula	$C_{16}H_{12}ClO$
Physical state	Yellow amorphous
Molecular Weight	241.5
%Yield	44.93%
TLC solvent system	Chloroform: acetone (8:2) Rfvalue 0.72

TABLE No. 10: PHYSICAL CHARACTERIZATION DATA OF COMPOUND C10

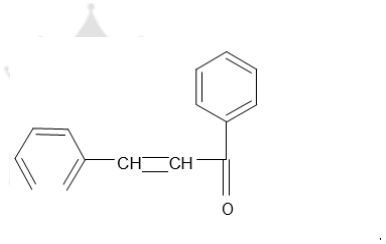
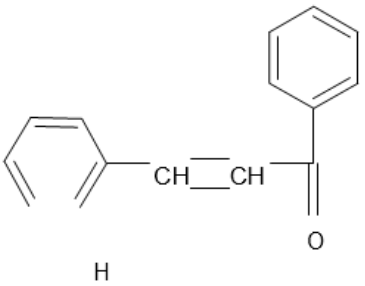
Structure	
Molecular Formula	$C_{16}H_{12}ClO$
Physical state	Yellow amorphous
Molecular Weight	241.5
% Yield	40.32%
TLC solvent system	Chloroform: acetone (8: 2)
Rf value	0.8

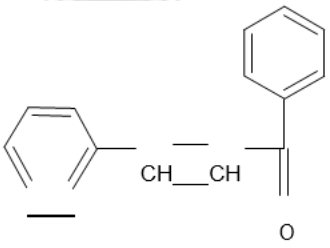
TABLE No. 11: PHYSICAL CHARACTERIZATION DATA OF COMPOUND C11



Structure

Molecular Formula	$C_{15}H_{11}O_2$
Physical state	White amorphous
Molecular Weight	223
% Yield	46.13%
TLC solvent system	Chloroform : acetone (8 : 2)
Rf value	0.68

TABLE No. 12:PHYSICALCHARACTERIZATIONDATAOFCOMPOUNDC12



Structure

Molecular Formula	$C_{15}H_{12}O_1$
Physical state	White amorphous
Molecular Weight	207
% Yield	40.32%
TLC solvent system	Chloroform : acetone (8 :2)
Rf value	0.74

TABLE No. 13: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I1

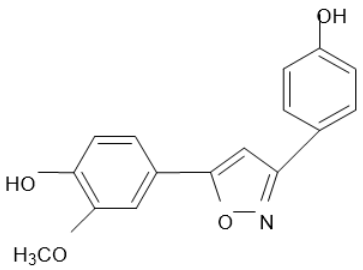
Structure	
Name	oxyphenyl)isoxazol-5-yl]-2- methoxyphenol
Physical state	Brown Crystals
Solubility	DMSO
Molecular Formula	$C_{16}H_{13}NO_4$
Molecular Weight	283
% Yield	43%
Melting point	81˚C
TLC Solvent System	Chloroform: acetone (8 : 2)
R_f value	0.92
Composition	C-67.84%,H-4.63%,N-4.94%,O-22.59%

TABLE No. 14: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I2

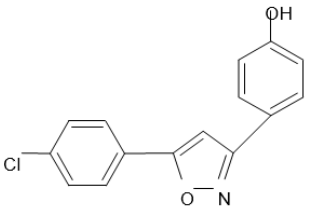
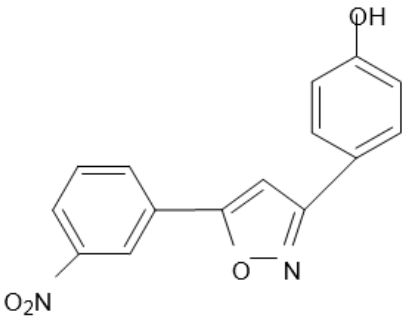
Structure	
Name	4-[5-(4-chlorophenyl) isoxazol-3-yl] phenol
Physical State	Colourless Crystals
Solubility	DMSO
Molecular Formula	$C_{15}H_{10}ClNO_2$
Molecular Weight	271
% Yield	36.58%
Melting point	88°C
TLC Solvent System	Chloroform : acetone (8 : 2)
Rf value	0.92
Composition	C-66.31%,H-3.71%,Cl-13.05%, N-5.16%,O-22.59%

TABLE No. 15: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I3

Structure	
Name	4-[5-(3-nitrophenyl) isoxazol-3-yl] phenol
Physical State	Colour less Crystals
Solubility	DMSO
Molecular Formula	$C_{15}H_{10}N_2O_4$
Molecular Weight	282
% Yield	40.28%
Melting point	86°C

TLC Solvent system	Chloroform : acetone (8 : 2)
R_f value	0.88
Composition	C-66.83%,H-3.57%,N-9.92%,O-22.67%

TABLE No. 16: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I4

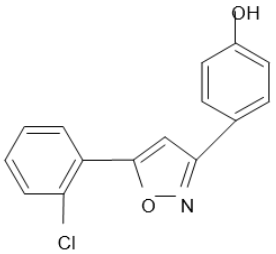
Structure	
Name	4-[5-(2-chlorophenyl) isoxazol-3- yl]phenol
Physical state	Colourless Crystals
Solubility	DMSO
Molecular Formula	$C_{15}H_{10}ClNO_2$
Molecular Weight	271
% Yield	39.4%
Melting point	87°C
TLC Solvent system	Chloroform : acetone (8 : 2)
Rf value	0.9
Composition	C-66.31%,H-3.71%,Cl-13.05%, N-5.16%,O-11.78%

TABLE No. 17: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I5

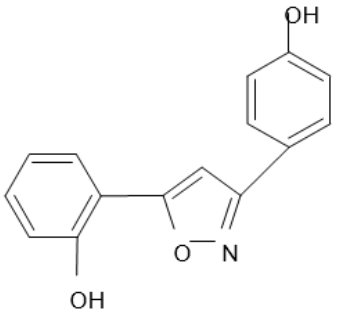
Structure	
Name	2-[3-(4-hydroxyphenyl) isoxazol-5-yl] phenol
Physical state	Colourless crystals
Solubility	DMSO
Molecular Formula	$C_{15}H_{11}NO_3$
Molecular Weight	253
% Yield	46.29%
Melting point	84°C
TLC Solvent system	Chloroform : acetone (8 : 2)
R_f value	0.88
Composition	C-71.14%,H-4.38%,N-5.53%,O-18.95%

TABLE No. 18: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I6

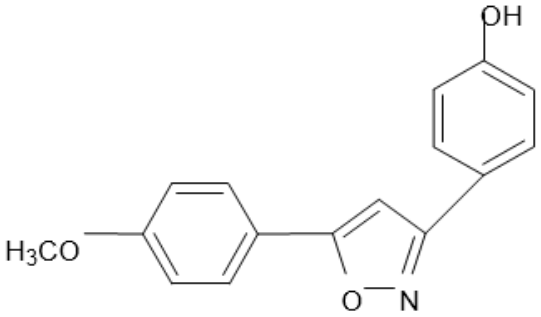
Structure	
Name	4-[5-(4-methoxyphenyl) isoxazol-3-yl] phenol
Physical state	Colourless Crystals
Solubility	DMSO
Molecular Formula	$C_{15}H_{13}NO_3$
Molecular Weight	255
% Yield	46.29%
Melting point	82°C
TLC Solvent system	Chloroform : acetone (8 : 2)
R_f value	0.86
Composition	C-71.90%,H-4.90%,N-5.24%,O-17.96%

TABLE No. 19: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I7

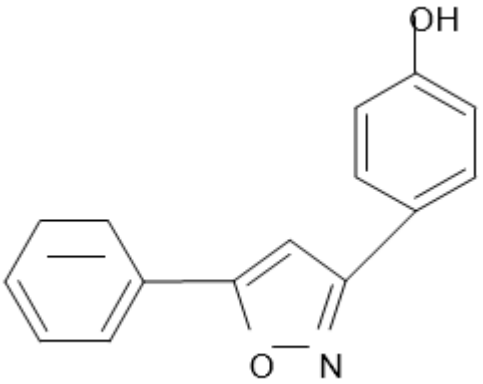
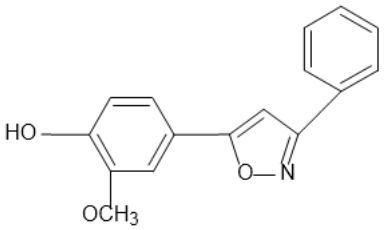
Structure	
Name	4-(5-phenylisoxazol-3-yl) phenol
Physical state	Colourless crystals
Solubility	DMSO
Molecular Formula	$C_{15}H_{11}NO_2$
Molecular Weight	237
% Yield	46.29%
Melting point	89°C

TABLE No. 20: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I8

Structure	
Name	2-methoxy-4-(3-phenylisoxazol-5-yl) phenol

Physical state	Brown crystals
Solubility	DMSO
Molecular Formula	$C_{16}H_1NO_2$
Molecular Weight	267
%Yield	34.28%
Melting point	80°C
TLC Solvent system	Chloroform: acetone (8:2)
Rfvalue	0.89
Composition	C-75.94%,H-4.67%,N-5.90%,O-13.49%

TABLE No. 21: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I9

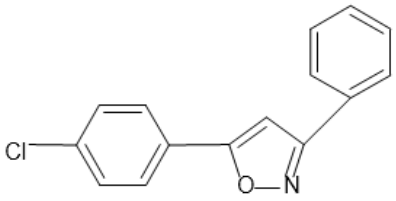
Structure	
Name	5-(4-chlorophenyl)-3-phenylisoxazole
Physical state	Colourless crystals
Solubility	DMSO
Molecular Formula	C15H10 ClNO
Molecular Weight	255.5
%Yield	36.84%
Melting point	98ºC
TLC Solvent system	Chloroform: acetone (8:2)
Rf value	0.80
Composition	C-70.46%,H-3.94%,Cl-13.87%, N-5.90%,O-13.49%

TABLE No. 22: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I10

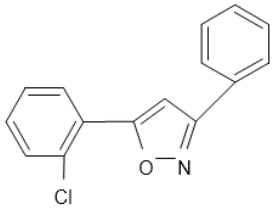
Structure	
Name	5-(2-chlorophenyl)-3-phenylisoxazole
Physical state	Colourless crystals
Solubility	DMSO
Molecular Formula	$C_{15}H_{10}ClNO$
Molecular Weight	255.5
% Yield	44.73%
Melting point	106ºC
TLC Solvent system	Chloroform: acetone (8:2)
Rf value	0.92
Composition	C-70.43%,H-3.94%,Cl-13.87%,

TABLE No. 23: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I11

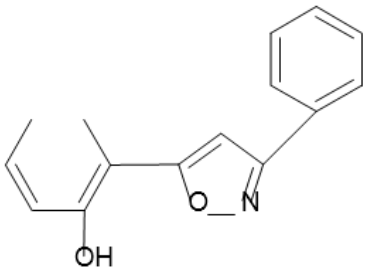
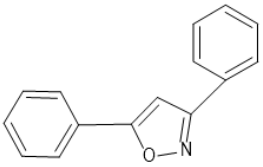
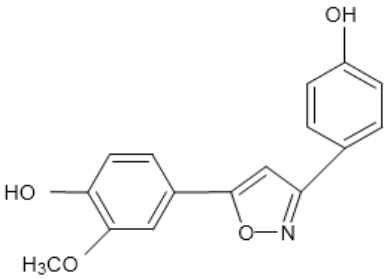
Structure	
Name	2-(3-phenylisoxazol-5-yl) phenol
Physical state	Colourless crystals
Solubility	DMSO
Molecular Formula	$C_{15}H_{11}NO_2$
Molecular Weight	237
% Yield	44.73%
Melting point	88ºC
TLC Solvent system	Chloroform : acetone (8 : 2)
Rf value	0.96
Composition	C-75.94%,H-4.67%,N-5.90%,O-13.49%

TABLE No. 24: PHYSICAL CHARACTERIZATION DATA OF COMPOUND I12

Structure	
Name	3,5-diphenylisoxazole
Physical state	Colourless
crystals Solubility	DMSO
Molecular Formula	$C_{15}H_{11}NO$
Molecular Weight	221
% Yield	36.36%
Melting point	92ºC

TLC Solvent system	Chloroform: acetone (8:2)
Rfvalue	0.90
Composition	C-81.43%,H-5.01%,N-6.33%,O-7.23%

CHEMICAL CHARACTERIZATION DATA OF COMPOUND-I1



IR Data:

Functional group	**Frequency in cm^{-1}**
OH stretching	3366.50
C=N stretching	1504.68
C-O stretching (OCH3)	1037.49
C-O stretching	1091.87

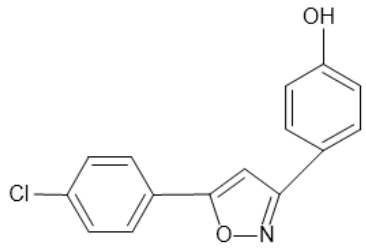
^{1}H NMR Data:

Protons		**δ in ppm**
OCH3	s(3.8)	
CH	s(6.3)	
Ar-H		m(6.8-7.6)
OH		s(9.4-9.5)

MASS Data:

Molecular Weight	**Fragmentation**
283.58	283.58 (55)
	268.58 (50)
	241.44(15)
	105.25 (100)
	77.23(50)
	57.22 (25)

CHEMICAL CHARACTERIZATION DATA OF COMPOUND-I2



IR Data:

Functional group	Frequency in cm^{-1}
OH stretching	3333.50
C=N stretching	1504.68
C-O stretching	1243.98

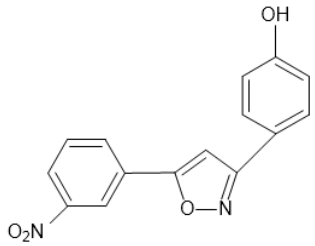
^{1}H NMR Data:

Protons	δ in ppm
CH	s(6.3)
OH	s(9.5)
Ar-H	m(6.7-7.6)

MASS Data:

Molecular Weight	Fragmentation
271.23	271.23(55)
	268.38(50)
	241.42(15)
	206.39(20)
	105.25 (100)
	77.58 (50)
	57.24(25)

CHEMICAL CHARACTERIZATION DATA OF COMPOUND-I3



IR Data:

Functional group	Frequency in cm^{-1}
OH stretching	3081.50
C=N stretching	1504.68
NO_2 aromatic stretching	1243.93
C-O stretching	1037.49

MASS Data:

Molecular Weight	Fragmentation
281.59	281.59(55)
	268.38(50)
	241.42(15)
	206.39(20)
	105.25 (100)
	77.58 (50)
	57.24(25)

CHEMICAL CHARACTERIZATION DATA OF COMPOUND-I4

IR Data:

Functional group	Frequency in cm^{-1}
OH stretching	3081.50
C=N stretching	1521.24
C-O stretching	1168.92

^{1}H NMR Data:

Protons	δ in ppm
CH	s(6.3)
OH	s(8.9)

Ar-H	m(6.5-8.1)

MASS Data:

Molecular Weight	**Fragmentation**
271.49	271.49(60)
	268.38(55)
	241.42(15)
	206.39(20)
	105.25 (100)
	77.58 (50)

BIOLOGICAL ACTIVITY

Anti-inflammatory activity:

The various *in vivo* and *in vitro* models for evaluation for anti-inflammatory agents.

The *in vitro* models:

- Inhibition of Nitric Oxide production Induced by IFN-γ.
- Measurement of NO production in mouse macrophages.
- Mass celled gradation.
- Adhesion assays.

The *in vivo* models:

- UV-B Inducederythema.
- Carrageenan induced paw edema model.
- Pleuralexudation.
- Cotton pellet induced granuloma.
- Zymosan induced arthritis.

***In vitro* Methods:**

Inhibition of NO production induced by IFN-γ:

In this method ability of test drug to inhibit the nitric oxide, which is one of the key mediators of inflammation, is evaluated. Hydrocortisone, a well-known steroidal anti-inflammatory drug is used as a positive control for such experiments and potential candidates are compared against hydrocortisone for efficacy measurement. Inhibitory test compounds dissolved in DMSO before addition to cell cultures; final concentrations of DMSO are kept at 0.1% or less than that. Controls with DMSO alone are also run a long side the test drugs.

Measurement of NO production:

Nitric accumulation is used as an indicator of NO production in the medium and is assayed by the Griess reaction. Griess reagent is added to 100 µL of each supernatant from IFN-γ or inhibitory test compound-treated cells in triplicate. The protein determination is performed by brad ford protein assay. The plates are read at 550 nm against a standard curve of sodium nitrite.

Mast cell degranulation:

Tyrodes solution is injected into the peritoneal cavity of the exsanguinated rat. After the abdominal massage, the cells in the peritoneal fluid are harvested and then separated through 38% bovine serum albumin. Cells are washed and suspended in a tyrodes solution with 0.1%BSA at (1-15) x 10^6 cells/mL. The cell suspension is preincubated with test drugs at 37ºC for 3 min. Fifteen minutes after the addition of compound 48/80, glucuronidase and histamine in the supernatant are determined.

Adhesion assays:

Platelet-neutrophil adhesion:

Thrombin-activated human platelets are incubated with the drug (10^7-10^{-4}) at 20ºC for 10 min and mixed with neutrophils at a ratio of 10:1. Neutrophils with two or more and one or no adherent platelets are counted as an index of activity. The test drug blocks the adhesion concerning controls.

Neutrophils adhesion to hypoxia-stimulated porcine aortae:

Fresh porcine aortae are stimulated by placing them into PBS gassed with N_2 and fixed between a Teflon block and a stainless steel plate with drilled holes. Neutrophils and the test drug (10^{-5} to 10^{-7}) are added onto the luminal side for 90 min. Adhesion is blocked by test drug and the adherent cells are lysed to assess the myeloperoxidase activity photometrically.

***In vivo* Methods:**

UV-B Induced erythema:

Erythema is the earliest sign of inflammation, not yet accomplished by plasma exudation and edema. Guinea pigs are the frequently used animals to study the anti-inflammatory activity of drugs in this model. In Albino guinea pigs, the pure erythema reaction appears in 2 hr. after exposure of the depilated skin to UV radiation from UV lamp that emits the radiation in the wavelength of 180-200 nm. This model can be used as a pure measure of the vasodilatory phase of inflammatory reaction. The test suffers from the drawback that shaving skin is required before the application of irritants and it also depends on skin thickness and intensity of erythema. It is difficult also and requires a skilled investigator.

Carrageenan induced paw edema model:

To study the acute and sub-acute phases of inflammation on rodents carrageenan is a widely used phlogistic agent. Chemically, it initiates a cascade of events leading to the formation of exudates. A 1% w/v suspension of carrageenan is prepared freshly in normal saline and injected in the sub-plantar region of the left hind paw. In control group animals, the only vehicle is injected. The drug is usually administered in orally or intraperitoneally, according to bodyweight immediately or half an hr. or one hr. before the experiment. A mark is made to the ankle joint is measured in drug-treated and untreated groups before and after 3 hr. after the carrageenan challenge using a plethysmograph filled with mercury. Paw edema in rats has been measured beyond 3 hr. also after the carrageenan challenge. The sophisticated electronic devices are also used nowadays to record the paw volume of rodents.

Pleural exudation method:

In this model, it is easy to measure the volume of exudates and to determine the amounts of protein, mediators, and leucocytes in the exudates. Pleurisy can be induced in rats by

intraperitoneal injection of carrageenan, turpentine, even's blue, Arabic gum, microbes, mast cell degranulation, *etc.* this model not only allows quantitation of the anti-inflammatory activity but also allows for investigating the mechanism underlying the action of new test drugs. The method is suitable for the detection of both steroidal and non-steroidal anti-inflammatory drugs. It is produced by injection of 0.1 mL of turpentine into right pleural space in rats under light ether anesthesia as described by Spector. The test drugs are decapitated intraperitoneally in graded doses 1hr. before turpentine injection. Threats are decapitated and pleural exudate collected half an hr. after turpentine treatment. The exudate is removed preferably by washing the pleural cavity with a known volume of Hank's solution to ensure complete recovery of the exudate and integrity of the cells. Volume of the exudate is measured as an index activity of the test drug.

Cotton pellet induced granuloma:

This method is used to study the exudative and proliferative of inflammation. Sterile cotton pellets (5mg), each impregnated with 0.4mL of 5% aqueous solution of ampicillin are used. Under ether anesthesia, pellets are inserted subcutaneously through a skin incision in the back of the animal. Drug treatment is started 2 hr. after cotton pellet implantation and continued for 5 consecutive days. Vehicle treated animals received saline for the same duration as the drug. On the 5^{th}day animals are sacrificed granulomas are removed, dried for 24 hr. 60ºC and dry weights determined. The final dry weight of cotton pellets and % protection by the drug can be calculated.

Zymosan induced edema arthritis in mice:

In the early phase, after intra-articular zymosan stimulation edema formation is accomplished by a massive neutrophil infiltration in synovial tissues and fluids of inflamed joints. In the late phase, the chronic response is characterized by macrophage and lymphocyte accumulation. Articular inflammation is characterized by the generation of TNF-α, interleukin-1β, and prostaglandin E2 in the synovial space clinically and in animal models. In zymosan method arthritis induced in mice by intra-articular injection of zymosan in 25 µL of sterile saline, into one knee joint under light ether anesthesia and the control knee injected with the same volume of the vehicle to serve as a control. Zymosan intra-articular injection induced a significant increase in knee joint diameter within 6 hr, peaked within 24 hr. and remained above control values for 20 days. An increase in TNF-α, IL-βandIL-8 levels were detected in the synovial

extracts.

MATERIALS AND METHODS:

Animals:

Albino Wister rats weighing 150-200gm were taken and kept under standard conditions in the central animal house at the college and animal ethical committee clearance was obtained for experimenting. They were housed in the pharmacology department of the college for 7 days for acclimatization in the air-conditioned atmosphere 20ºc. Before the experiment, all the animals fasted overnight with water *ad libitum.*

Chemicals: Tween-80, Diclofenac sodium, Isoxazole derivatives.

Anti-inflammatory Activity:

Thirty-six Albino Wister Rats (male) weighing between 150-200 gm was divided into six groups. (n=6).

- Group I received carrageenan (1%s.p.) and served as control.
- Group II received Diclofenac sodium (s.p.)25mg/kg and served as standard.
- Group III, Group IV, Group V, and Group VI received the synthesized isoxazole derivatives as dose of 25 mg/kg suspended in tween-80 (orally).
- One hr. after the administration, 0.1 mL of 1% carrageenan solution was injected beneath the sub-plantar surface of the right hind paw of all animals. For the assessment of the anti-inflammatory activity, the volume of the paw was measured with the help of mercury Plethysmometer at 0 hr. and 1 hr. the interval for a period of three hr. after the carrageenan treatment. The results are tabulated in **Table-25.**

Table No. 25: Anti-inflammatory activity of compounds I1-I12

Sr. No.	Group	0 hr	1hr	2hr	3hr	4hr
1	**Control**	1.466± 0.1212	1.616± 0.079	1.633± 0.250	1.676± 0.074	1.75± 0.061[a]
2	**Standard**	1.616±0. 0793	1.45± 0.067	1.35± 0.151	1.45± 0.099	1.283± 0.060
3	**I1**	1.55± 0.042	0.983± 0.074[a**]	0.816± 0.147[a***]	1.066± 0.042[a**]	0.816± 0.047[a,***]
4	**I2**	1.45± 0.056	1.016± 0.074[a*]	1.016± 0.183[a*]	0.966± 0.066[a***]	0.866± 0.066[a,***]
5	**I3**	1.533± 0.055	1.366± 0.071	0.916± 0.231[a*]	1.116± 0.060[a*]	0.933± 0.055[a**]
6	**I4**	1.5± 0.093	1.366± 0.084	0.933± 0.186[a*]	1.066± 0.049[a**]	0.883± 0.047[a***]
7	**I5**	1.5± 0.093	0.983± 0.074[a**]	0.866± 0.150[a**]	1.1± 0.063[a*]	0.933± 0.055[a**]
8	**I6**	1.5± 0.0774	1.05± 0.067[a*]	0.833± 0.150[a,**]	1.2± 0.051[a]	1.000± 0.036[a*]
9	**I7**	1.616± 0.83	0.975± 0.083[a**]	0.85± 0.164[a**]	1.083± 0.047[a**]	0.833± 0.033[a***]
10	**I8**	1.616± 0.94	1.433± 0.0988	0.883± 0.194[a**]	1.083± 0.0792[a**]	0.95± 0.076[a**]
11	**I9**	1.583± 0.011	1±0.103[a*]	1±0.253[a*]	1.1± 0.056[a*]	0.883± 0.060[a***]
12	**I10**	1.133± 0.088	0.966± 0.080[a**]	0.966± 0.196[a**]	1.083± 0.060[a**]	0.866± 0.066[a***]
13	**I11**	1.65± 0.076	1.466± 0.666	0.85± 0.242[a**]	1.116± 0.060[a*]	0.916± 0.060[a**]
14	**I12**	1.55± 0.076	1.4±0.816	0.783± 0.116[a***]	1.083± 0.060[a**]	0.9± 0.057[a***]

All values are expressed as mean ± SEMs.

[a]$p<0.001$ Vs. Control.

[***]$p<0.001$, [**]$p<0.05$, [*]$p<0.01$ Vs Standard.

RESULTS AND DISCUSSION

Isoxazole derivatives were synthesized screened for their anti-inflammatory activity by in vivo method on rats. The action of synthesized compounds was done on the paw of Wister albino rats. The physical characterizations of twelve derivatives were presented in **Table no 13-24.** All the compounds are recrystallized with acetone. The IR, ^{1}H-NMR and Mass spectral data showed the presence of major functional groups in the compounds.

Synthesized twelve compounds were screened for anti-inflammatory activity by the in-vitro method on Wister albino rats. The actions of synthesized compounds were done on paw of Wister albino rats and compared with Diclofenac sodium as a standard drug. The paw volumes are recorded within 1 hr interval time duration and the SEM values are calculated by using SPSS software. The study indicated that compounds **I3, I5, I6,** and **I11** exhibited highly potent anti-inflammatory activity. Other compounds have less significant anti-inflammatory activity. Structural activity studies of the title compounds for anti-inflammatory activity reveal the compounds having OH, NO_2 & OCH_3 groups showing more activity. The above results establish the fact that isoxazoles substituted with aromatic ketones and aromatic substituted aldehydes can be studied further to search for new anti-inflammatory compounds.

CONCLUSION

Isoxazoles are among the most important classes of heterocyclic compounds. These compounds possess the versatile type of biological activities; they have anti-cancer, antitubercular, anti-bacterial, anti-fungal, anti-malarial, anti-inflammatory, anti-helmentic, and anti-hypertensive activities. As expected, isoxazole derivatives exhibited anti-inflammatory activity in which some are good and moderately active like standard employed for comparison. Therefore further a detailed study of toxicity is necessary. There is no such thing as a completely safe drug. Drugs are powerful tools, which alter physiological processes for the better or the worse. A society that wishes to benefit from them will not achieve all the benefits open to it, if it ignores the fact, and seeks for impossible standards of harmlessness. The anti-inflammatory activity testing showed that few compounds have promising anti-inflammatory activity like that of standard drug diclofenac sodium. Further, the detailed structural activity relationship studies are required along with molecular manipulation *i.e.* molecular modeling may give better drugs. Molecules prepared for the biological testing do not always turn out as potential new drugs but may be intended to serve as models for

evaluation of the hypothesis. From the data of anti-inflammatory activity, it is concluded that the synthesized compounds are having good anti-inflammatory activity. The isoxazole moieties are already known for the different pharmacological activities. Here we fused the two moieties (aromatic substituted ketones and aromatic substituted aldehydes) to isoxazole with the view to get good pharmacological activity and less toxicity. When these were screened for anti-inflammatory activity showed a very good result. Isoxazole and condensed isoxazoles show potent cytotoxic and anti-inflammatory activities. Position 2,3,4 is very important for structural activity studies. The above results establish the fact that isoxazole derivatives could be a rich source of exploitation. Therefore, in search of a new generation of active compounds, it may be worthwhile to explore the possibility in this area by fusing and substituting different moieties, which may result in better pharmacological activities. Hence in the present study, the aromatic ketones and aromatic substituted aldehydes when linked with isoxazole moiety showed highly potent, more specific anti-inflammatory activity.

ACKNOWLEDGMENT

I am thankful to the almighty for blessing in the successful completion of the review article. This satisfaction that accompanies the successful completion of any task would be incomplete without mention of the people who made it possible with constant guidance, support, and encouragement that crows all effort with success. I would like to express my appreciation for all the efforts to everyone who have directly or indirectly contributed their ideas and energies to the successful completion of my review article. The completion of this dissertation is not only the fulfillment of my ambition but also the dreams of my parents, who have given all supports in the completion of my higher studies. Firstly, I offer my adoration to God Almighty, who created me, gave me the strength and courage to complete my dissertation.

It gives me immense pleasure to express my deep gratitude, respect, and sincere thanks to **Manish Singh**, who has guided, contributed, in completing my work successfully. I will be Indebted to him throughout my life. I am also extremely thankful to my Director, **Prof. (Dr.) Amar Singh Chaudhary** and I want to give thanks to my dear Yatendra Sharma, Surya Nathpandey, Renu mam, Surya Pratap and Naresh Kumar for his valuable guidance and encouragement to complete this dissertation work successfully.

REFERENCES

1. Harsha Mohan. Essential Pathology for dental students. New Delhi: Jaypee Brothers medical publishers;2007:95-115
2. Ilango K. Valentina P. Textbook of Medicinal Chemistry Vol-1. Chennai: Keerthi Publishers;2007:336-352
3. Ashutosh Kar. Medicinal Chemistry. New Delhi. New Age Publishers; 2007:95-110.
4. Purkayastha ML, Patro B, Junjappa H. Regioselective synthesis of 3 (or 5) – styryl - (4-aryl-1,3,5-hexatrienyl)-5(or3)-(methylthio) isoxazoles and pyrazoles *via* α-oxoketenedithioacetals. J. Hetercycl. Chem. 1991;28:1341- 1349.
5. Rajanarendar E, Afzal Md, Ramu K. Microwaved assisted synthesis of some new isoxazolyl-[1,3,5]-triazinana-2-ones-isoxazolyl-[1,3,5]-oxadiazinan-4- one sindry media.Ind.J.Chem.2005;44B:376-380.
6. Nitin NA, Soni PA. Synthesis of pyrazole and isoxazole in triethanolamine medium. Ind. J. Chem.2007;46B:532-534.
7. Mohamed GM, Reda AG. A new synthesis of 5-hydroxy-2-isoxazolines and theirconversionintoisoxazoles.J.IslamicAca.Sci.1992;5(2):81-85.
8. MicetichRG.Studies in isoxazoles chemistry.II.Isoxazoles from the Δ^2-isoxazolin-5-ols and their acetates. Can. J. Chem. 1969;48:467-476.
9. Yavari I, Loghman M. A synthesis of isoxazoles through the reaction of activated acetylenes and alkyl 2-nitoethanoates in the presence of triphenylphosphine. Tetrahedron Lett.2006;47:1627-1629.
10. Augusto CV, Rosella C, Carlo FM, Chiara BV. A facile synthesis of pyrazole, isoxazole and pyrimidine *ortho*- dicarboxylic acid derivatives. Tetrahedron. 1997;53(42):14497-14506.
11. Khurana AL, Unaru AM. Reduction of some alkyl isoxazoles with lithium aluminium hydride. Can. J. Chem.1975;53:3011-3013.
12. Abutariq T, Alexandra MZ, Slawin, George WW. Reactions of an imidazo [4,5-c] isoxazole-6-carboxylate with eletron deficient acetylenes. Tetrahedron Lett.1999;40:8157-8162.
13. Agribas H, Selahaddin G, Farma B, Sema K, Fatma K, Nathaly S, Vasyl K, Anatholy D. Synthesis and structure anti-bacterial activity relationship investigation of isomeric 2,3,5-substituted perhydropyrrolo [3,4-d] isoxazole- 4,6diones. Bioorg. Med. Chem. Lett.2007;15:2332-2333.
14. Ravindra MK, Ingle VN. Synthesis of novel benzothiazole and benzisoxazole functionalized unsymmetrical alkanes and study of their anti-microbial activity. Ind. J. Chem.2009;48B:996-1000.
15. Rajendra PT, Dianquing S, Rakesh, Nageshwar B, Robin EBL, Anne JML, Bernd M, Richard EL. Discovery of novel isoxazolines as anti-tuberculosis agents. Bioorg. Med. Chem. Lett.2007;17:6638-6642.
16. Rajanarendar E, Mohan G, Kalyanrao E, Siva rami reddy A, Praveen B, Srinivasarao M. Synthesis, anti-microbial and mosquito larvicidal activity of N-protected amino acid/peptide isoxazoles. Ind. J. Chem.2008;47B:781-786.
17. Rajanarendar E, Ramu K, Siva rami reddy A, Firoz PS. Synthesis and invitro study of novel isoxazolylbenzimidazolyl benzamides acrylamides and propionamidesasanti-microbialagents.Ind.J.Chem.2008;47B:1284-1290.
18. Lawrence BS, Zhaoxing M, Robert M, Stanley V, Marinier AD. Discovery of isoxazoline antibacterial agents. Nitrogen a replacement for the stereogenic center found in oxazolidinone antibacterials. Bioorg. Med. Chem. Lett. 2004;14:4735-4739.
19. Nim AP, Jie Eun L, Hyung BK, Hawan JC, Yeon HK. Structural modifications and biological evaluation of 3- isoxazolylvinyl cephalosporins. Tetrahedron. 2000;56:5657-5665.
20. Bente F, Lars SJ, Luca G, Carolina C, Hnerik TV. Potent 4-aryl- or 4-arylalkyl-substituted 3-isoxazolol $GABA_A$ antagonists: synthesis, pharmacology and molecular modelling. J. Med. Chem. 2005;48:427-439.
21. Bente F, Lars SJ, Signe IS, Tine BS, Bjarke E. 4-Aryl-5-(4-piperidyl)-3-isoxazolol $GABA_A$ antagonists: synthesis, pharmacology, and structural activityrelationships.J.Med.Chem.2007;50:1988-1992.
22. Bente F, Lena T, Tommy L, Tine BS, Christine E. A novel class of potent 3-isoxazolol GABAA antagonists: design, synthesis, and pharmacology. J. Med. Chem.2000;43:4930-4933.
23. John JT, David LB, Jeffery SC, Matthew JG, Carol MK. 4-[5-methyl-3- phenylisoxazol-4-yl]-benzene sulfonamide, Valdecoxib: A potent and selective inhibitor of COX-2. J. Med. Chem. 2000;43:775-777.

24. Leonardo DN, Paola V, Antonio S, Stefania T, Patrignani P. Novel synthesis of 3,4-diarylisoxazole analogues of valdecoxib: reversal Cyclocoxygenase-2 selectivity by sulfonamide group removal. J. Med.Chem.2004;47:4881-4890.
25. Peter E, Tamas F, Agnes KV, Matyas C, Ankio G. Chemical and biological investigation of N-hydroxy-valdecoxib: an active metanolite of valdecoxib. Bioorg. Med. Chem. Lett.2008;16:5322-5330.
26. Selvam C, Sanjay MJ, Ramasamy T, Chakraborti AK. Design, synthesis, biological evaluation and molecular docking of curcumin analogues as antioxidant, cyclooxygenase inhibitory and anti-inflammatory. Bioorg. Med. Chem. Lett. 2005;15:1793-1797.
27. Yoon-suk lee, Sun Min P, Byeang K. Synthesis of 5-isoxazol-5-yl-2'-deoxy uredines exhibiting anti-viral activity. Bioorg. Med. Chem. Lett. 2009;19:1126-1128.
28. Jae Seok L, Yong SC, Moon HC, Yeong HK, Chung BY. Synthesis and *in vitro* activity of novel isoxazolyl tetrahydro pyridinyl oxazolidinone antibacterial agents. Bioorg. Med. Chem. Lett.2003;13:4117-4120.
29. Kachhadia VV, Patel MR, Joshi HS. Synthesis of isoxazoles and cyanopyridines bearing benzothiophene nucleus as potential anti-tubercular and anti-microbial agents. J. Sci. Islamic Republic of Iran 2004;14:47-51.
30. Naohiko Y, HisaoI, Yukio S. Synthesis and antibacterial activity of triazole andisoxazolederivativesofampicillin.J.Anti-biotics1983;1516-1524.
31. Yoon SL, Byeang HK. Heterocyclic nucleoside analogues: design and synthesis of antiviral, modified nucleosides containing isoxazoles heterocycles. Bioorg. Med. Chem. Lett.2002;12:1395-1397.
32. Sahu SK, Banerjee M, Sahu D, Behera CC, Pradhan GC. Synthesis, analgesic and anti-microbial activities of some novel isoxazoles derivatives. Dhaka University J. Pharm. Sci.2008;7(2):113-118.
33. George BM, Thomas RD, Jerffrey TM, Stanely DA, Richard K. Studies on anti-fungal agents. Novel 3, 5-diphenyl-3-(1H-imidazol-1-ylmethyl)-2- alkylisoxazolidine derivatives. J. Med. Chem.1988;31:2008-2014.
34. Ravindra MK, Ingle VN. Synthesis of novel benzothiazole and benzisoxazole functionalized unsymmetrical alkanes and study of their antimicrobial activity. Ind. J. Chem.2009;48B:996-1000.
35. Erick F, Jens P, Bente F, Brigitte S, Anders B. Selective inhibitors of glial GABA uptake: synthesis, absolute stereochemistry, and pharmacology of the enantiomers of 3-hydroxy-4-amino-4,5,6,7-tetrahydro-1, 2-benzisoxazole (exo-THPO) and analogues. J. Med. Chem.1999;42:5402-5414.
36. Amgad GH, Praveen Rao PN, Edward EK. Design and synthesis of 4,5- diphenyl-4-isoxazolines: novel inhibitors of cyclooxygenase -2 with analgesic and anti-inflammatory activity. J. Med. Chem. 2001;44:2921-2927.
37. Hasse K, Frank AS, Rine BS, Hans BO, Madsen U. Selective antagonists at group I metabotropic glutamate receptors: synthesis and molecular pharmacology of 4-aryl-3-isoxazolol amino acids. J. Med. Chem. 2002;45:988-991.
38. Hisashi S, Syoji O, Tanaka M, Shibata T, Iwao M.Isoxazolidine-3,5-dione and noncyclic 1,3 dicarbonyl compound as hypoglycaemic agents. J. Med. Chem. 1998;41:1927-1933.
39. Nicholas RN, Mark ER, Richard S, David JT, Aleta R. Lipophilic 4- isoxazolyl-1,4-dihydropyridines: synthesis and structure-activity relationships. J. Med. Chem.1999;42:3087-3093.
40. Joseph PY, James SN, Smith DW, Walter GL, John DC. Synthesis and biological evaluation of 1-(1,2-benzisothiazol-3-yl) - and (1,2-benzisoxazol-3- yl-) piperazine derivatives as potential antipsychotic agents. J. Med. Chem. 1986;29:359-369.
41. Hariharan S, Mathur HH, Trivedi GK. Synthesis of polynuclear heterocyclic compounds: part-I synthesis of [1] benzopyrano [4, 3-d] isoxazoles vianitronecyclo addition. Ind. J. Chem.1988;47B:994-996.
42. Donato D, Stefania F, Fabio P, Riccardo RP, Mauro FA. Photoreaction of some 5-alkyldene -2,5-dihyroisoxazoles: facile construction of novel unclassical β-lactam containing heterocycles. Tetrahedron. 2007;63:1583- 1588.
43. Jane EM, Mark WD, Katharine MG, Robert AJW, Joesph PAH. Investigation of the scope of a [3+2] cycloaddition approach to isoxazoleboronic esters. Tetrahedron.2005;61:6707-6714.
44. Chiacchio U, Antonino C, Giuseppe G, Venerado P, Antonio R. Steroselective synthesis of isoxazole and pyrazole annulated sultams via intermolecular 1,3- dipolar cycloaddition reactions. Tetrahedron.1997;53(40):13855-13866.
45. Rajanarendar E, Firoz PS, Siva Rami reddy A. Synthesis of novel isoxazolyl 1,3,5-benzoxadiazocine-4-thiones as possible biodynamic agents. Ind. J. Chem.2008;47B:1753-1758.

46. Venkateswarlu P, Srinivas B. Synthesis and characterization of new isoxazole derived from benzosuberones. Ind. J. Chem. 2006;47B:1753-1755.
47. Suresh babu D, Jianping X, Ashton T, Hamme H. Isoxazoles from 1,1- disubstituted bromoalkenes. Tetrahedron Lett.2007;48:1295-1298.
48. Evdoxia CA, Pygmalion L, Marigoula M, Anestis G, Joanna N. 1,3-dipolar cycloaddition approach to isoxazole, isoxazoline and isoxazolidine analogues of C-nucleosides related to pseudouridine.Tetrahedron.2006;62:1494-1501.
49. Ihsan AS, Richard AG. Mesoionicisoxazolo [2,3-a] pyrimidinediones and 1,3,4-oxadiazolo [3,2-a] pyrimidinediones as potential adenosine antagonists. J. Hetercycl. Chem.1987;24:1291-1295.
50. Trond VH, Peng W, Valrey VF. One-pot copper (I) catalysed synthesis of 3,5- disubstituted isoxazoles. J. Org. Chem.2005;70:7761-7764.
51. Rama Rao K, Nageswar YVD, Sattur PB. 1, 3-dipolar cycloaddition of nitrile oxides to N-vinylcarbazoleRegioselective formation of 5- (9-carabazolyl)- Δ^2-isoxazolines. J. Hetercycl. Chem.1989;26:255-256.
52. Brahmeshwari G, Rajeswar Rao V, Padmanabharao TV. Synthesis of 3- arylnapth [2, 3-d]-isoxazole -4,9diones from law some. Ind. J. Chem. 1995;34B:139-140.
53. Zhou YH, Maio WR, Chen LB. Synthesis and herbicidal activities of 3- (substituted phenyl) isoxazole derivatives. Chin. Chem. Lett. 2003;14(9):897- 900.
54. Chiarino D, Ferrario F, Napoletano M, Sala A. Synthesis of new [[(3- substituted-5-isoxazolyl) - alkyliden] iminoxy] amino propanol derivatives. J. Hetercycl. Chem. 1988;25:1359-1362.
55. Chiarino D, Mauro N, Alberto S. Synthesis of 3-bromo and 3-methoxy-5- isoxazolylglycine derivatives hypothetic precursors of ibotenic acid. J. Hetercycl. Chem.1988;25:1283-1285.
56. Chiarino D, Fantucci M, Sala A, Veneziani C. Synthesis of new isoxazole amino alcohols. J. Hetercycl. Chem.1988;25:337-342.
57. Necdet C, Fatma TT, Ozden OG. Synthesis of di- and cis triaryl-3a,4,5,6- tetrahydroimidazol [1,5-b] isoxazoles and their ring opening reactions. Tetrahedron.2001;57:3413-3417.
58. Chiarino D, Napolitano M, Sala A. Synthesis of 4,7-dihydro-4-isoxazolo [5,4- b] pyridine-5-carboxylic acid derivatives as potential antimicrobial agents. J. Hetercycl. Chem.1988;25:231-233.
59. Kaur J, Singh B, Kewal KS. Huisgen reaction of aldonitrones with N-benzyl maleimideleading to synthesis of 2,3-diaryl-5-benzyl-2H-3,3a,4,5,6,6a- hexahydropyrrolo[3,4-d] isoxazole 4,6=diones. Ind. J. Chem. 2005;44B:1476- 1480.
60. Rajanarendar E, Mohan G, Siva rami reddy A. Synthesis and anti-microbial activity of new isoxazolyl-1, 3-benzoxazines. Ind. J. Chem. 2008;47B:112- 116.
61. Karabasanagouda T, Airody VA, Girisha M. Synthesis of some new pyrazolines and isoxazoles carrying 4-methylthiophenyl moiety as potential analgesic and anti-inflammatory agents.Ind.J.Chem.2009;48B:430-437.
62. Anjani S, Kishor K, Pankit S. Synthesis and characterization of some novel isoxazoles and 1, 5-benzothiazepines bearing s-triazine nucleus. Ind. J. Chem. 2008;47B:473-476.
63. Kalirajan R, Suresh B, Gowramma B, Sivakumar SU. Synthesis and biological evaluation of some new heterocyclic derivatives of some heterocyclic derivatives of chalcones. Int. J. Chem. Res.2009;1:27-34.
64. Gupta SK, Practical pharmacology New Delhi: Jaypee Publications. 2007:480-492.