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# Systematic scientific study of 1, 3-oxazole derivatives as a useful lead for pharmaceuticals: A review

**Sweta Joshi, Ajay Singh Bisht and Divya Juyal**

**Abstract**
Oxazole contain an oxygen atom and a pyridine type nitrogen atom at the 1 and 3 positions of the ring and like pyridine, oxazole are weekly basic substances. Oxazole be considered as derived from furan by the replacement of –CH= (methane group) from the position-3 by the azomethine nitrogen (-N=) group. Oxazole is a heterocyclic compound and exhibits a wide variety of pharmacological activities such as analgesics, anti-inflammatory, antimicrobial, anticancer, antidepressants, antidiabetic and antiobesity, anticonvulsant, diuretics and anticancer. Differently substituted oxazole moieties have different activity. In this article we discussed about oxazole chemistry, properties, naturally occurring oxazoles, synthesis, reactions and several pharmacological activities.

**Keywords:** Oxazole, azoles, synthesis, reactions, pharmacological activity

## Introduction
Azoles are a class contain five member ring, nitrogen heterocyclic ring compound containing at least one other heteroatom (or non-carbon atom) of nitrogen, sulfur or oxygen and are considered to be derived from pyrrole, furan and thiophene by substitution of methane groups (—CH=) by pyridine type nitrogen (—N=) atoms from the different positions. Azole mainly consists of:
(i) Oxygen is referred as oxazole
(ii) Sulphur is referred as thiazole and
(iii) Nitrogen is referred as pyrazole, imidazoles or imidazolines [1].

## Oxazole
The chemistry of oxazole began in 1876 with the synthesis of 2-methyloxazole, while parent oxazole was synthesized in 1962. The chemistry of oxazole was come in concern during the world war when penicillin was considered to contain the oxazole ring system, but the invention of oxazoles as dienes in Diels-Alder reaction and in 1, 3-dipolar cycloaddition reaction of mesoionic heterocycles give idea for advance of oxazole chemistry. Oxazole contain an oxygen atom and a pyridine type nitrogen atom at the 1 and 3 positions of the ring and like pyridine, oxazole are weekly basic substances. Oxazole be considered as derived from furan by the replacement of –CH= (methane group) from the position-3 by the azomethine nitrogen (-N=) group [2]. Oxazole ring is numbered as follows:

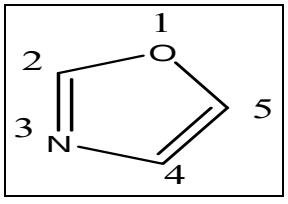



**Fig 1:** Numbering of oxazole

## Activities
Oxazole shows potential photophysical and photochemical activities, so they are used in semiconductor devices like electrophotographic photoreceptors and in non-linear optical materials. Oxazole has cyclooxygenase-2 inhibitory property and tyrosinase inhibitory property. Oxazoles shows resemblance as same in structure and chemistry of penicillin.

They are used in polymerization and condensation primary to homopolymers, peptides, condensation reagents, telomers, herbicides, pesticides, fungicides and agrochemical intermediates [3].

Oxazoles play a fundamental role in the synthesis of numerous biologically active drugs such as analgesics, anti-inflammatory, antimicrobial, anticancer, antidepressants, antidiabetic and antiobesity. Spirocyclopropyl oxazolones is the novel class of inhibitor of herpes protease. Phenacyl oxazolone involves the intermolecular Diels-Alder reaction, ensuing in synthesis of anti-cancer drugs, pancratistantin and a phenanthrene alkaloid [4].

**Chemistry**

At C-4 and C-2 position of oxazolone if substitution of functional group is occur it plays a vital role in the activity. Substitutions of p-nitro group in exocyclic phenyl group at C-4 in oxazolone moiety greatly influence the immunosuppressive activity. Cinnamoyl residue at C-4of oxazolone moiety and substitution of functional group at C-4 and C-2 positions of oxazolone are fundamental for tyrosinase inhibitory activity. Addition double bond at C-4 position and phenyl ring present in C-2 position plays an imperative role in oxazolone ring. Oxazolone ring-operating reaction decreased with an increase of the electron donating properties of the substituent of the phenyl ring at C-2 position [12]. Exocyclic double bond act as dienophile and N-substituted oxazolone participate in intermolecular Diels-Alder reaction. Activation of Lewis acid of the carbonyl group of unsaturated oxazolones gives electrophilic character to the β carbon [5].

Oxazoles [15] contain a distinctive structure and varied application for variety of, pharmaceuticals, natural products and bioactive compounds. For example, the Diazonamide and phorboxazoles families, oxazole containing bioactive natural products, show evidence of anticancer activity.

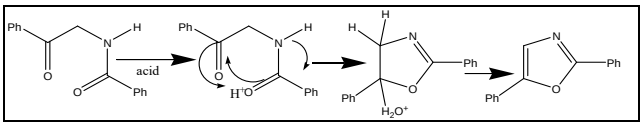
The synthesis, chemistry and application of oxazole were first covered in 1986 by I.J. Turchi. The number of synthetic strategy heading directed for oxazole assembly as well as the use of these versetile heterocycles as intermediates, catalytic ligands and pharmaceutical building blocks vastly increased. Oxazole scaffolds and its heterocyclic analogues posses diversified biological activities such as antitubercular, antihyperglycemic, antibacterial, antifungal, anti-inflammatory and anti-proliferate [1, 6].

**Properties**

Chemistry of heterocyclic compounds is one of the foremost lines of investigation in the organic chemistry. Nitrogen, sulphur and oxygen containing five member heterocyclic compounds have occupied enormous importance in the field of drug discovery process. Oxazole is a weekly basic aromatic compound with three potential points of substitution, C2, C4 and C5**.** Oxazoles are numbered around the ring starting at the oxygen atom and are designated as 1, 3- oxazoles to designate the position of heteroatoms in the ring. The reactivity of oxazoles shows that the acidity of a hydrogen atom decreases in the order C (2) > C (5) > C (4). The acidity of the hydrogen at C(2) was predicted to be pKa 20 while for oxazole itself the pKb is reported to be pKb 1.17, Oxazoles exhibit distinctive resonances in both 1H NMR and 13C NMR spectra. The parent compound displays resonances between 7.00 and 8.00 in the 1H NMR spectrum, and the existence of substituents can change the chemical shift by up to 1 ppm. The 13C NMR of oxazole displays characteristic aromatic resonances. The shielding or deshielding effect of C (2) substitution on the C (4) and C (5) resonances is usually < 2 ppm. The IR spectrum of oxazole shows absorbance at 1537, 1498, 1326 (ring stretch), 1257 (C-H in plane deformation), 1143, 1080 (ring breathing), and 1045 cm _1.23–26. In the UV, the l max of oxazoles depends highly on the substitution pattern. In methanol, the parent ring system indicates the absorption maximum at l max ¼ 205 nm [6, 7].

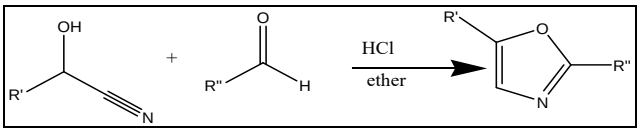
**Synthetic Methods of Oxazoles**

- **Robinson-Gabriel synthesis [8]-** Formation of oxazole by dehydration of 2-acylaminoketones.



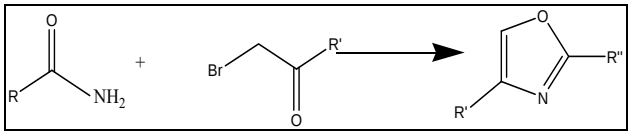

**Scheme 1:** Robinson-Gabriel synthesis

- **The Fisher oxazole synthesis** – synthesis of oxazole from condensation of cyanohydrin and aldehyde.



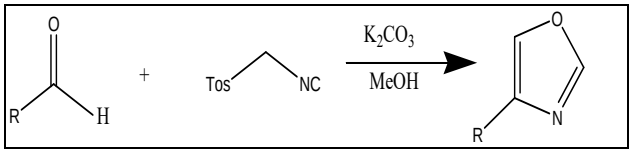

**Scheme 2:** The Fisher oxazole synthesis

- **The Bredereck reaction between α-haloketones and formamide give oxazole [9].**



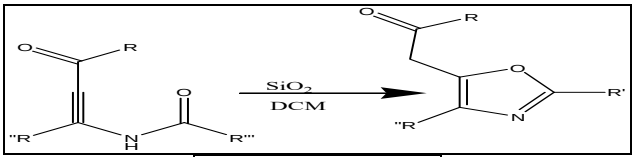

**Scheme 3:** Bredereck reaction for oxazole synthesis

- **The Van Leusen reaction is used for oxazole synthesis by reacting with aldehyde and TosMIC [10].**



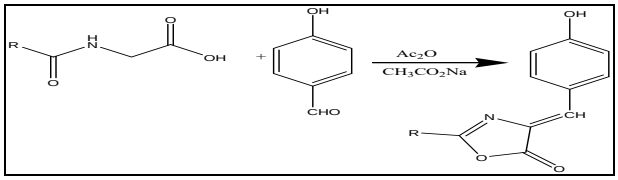

**Scheme 4:** Van Leusen reaction for oxazole synthesis

- **Oxazole synthesis by cycloisomerization of certain propargyl amides.**



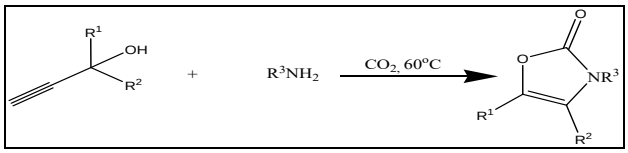

**Scheme 5:** Oxazole synthesis by cycloisomerization of certain propargyl amides.

- **Erlenmeyer- Polchl reaction [11]-** synthesis of oxazole by condensation of aldehyde and hippuric acid in dry acetic anhydride catalyzed by acetate anion.



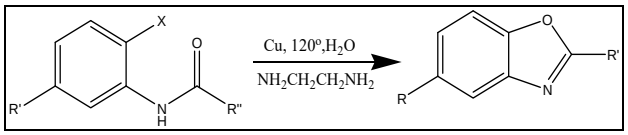
**Scheme 6:** Erlenmeyer- Polchl reaction

- **N- Substituted oxazolone synthesis by the cycloaddition reaction of propargylic alcohols and amines in the presence of carbon dioxide.**



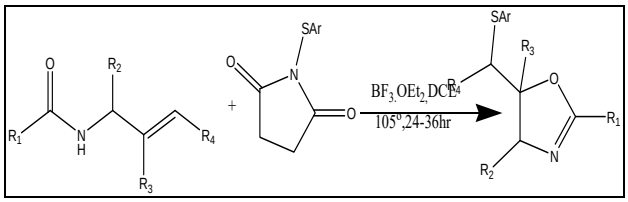
**Scheme 7:** oxazolone synthesis by the cycloaddition reaction of propargylic alcohols and amines

- **Intermolecular cyclization of oxazole- benoxazole is synthesized from intermolecular *O*-arylation of haloanilides**.



**Scheme 8:** cyclization of oxazole

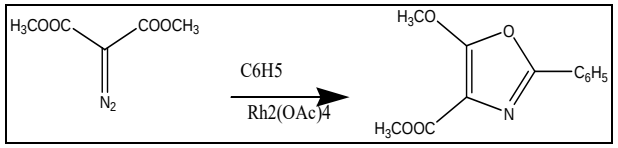
- **Boron-Catalyzed Arylthiooxygination of *N*-Allylamide: Synthesis of (Arylsulfanyl)oxazolines [4, 5, 12]**



**Scheme 9:** synthesis of Arylsulfanyl oxazolines

- **Organometallic reaction-**

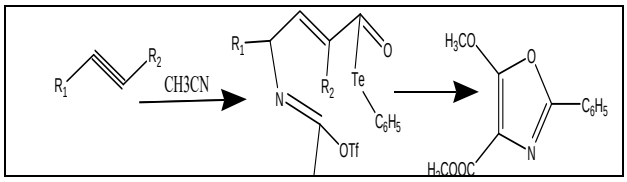
(a) **Rhodium carbene addition-** Nitrile reacts with diazocarbonyl compound in the presence of lewis acid catalyst.



**Scheme 10:** Synthesis of oxazole derivatives

**(b) Organotellurium reagent**

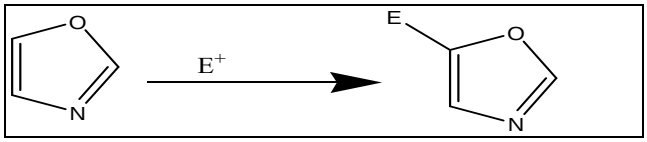
Synthesis of 4, 5-disubstituted-2-methyloxazole from attempted amido tellurinylation of internal acetylenes [12].



**Scheme 11:** 4, 5-disubstituted-2-methyloxazole

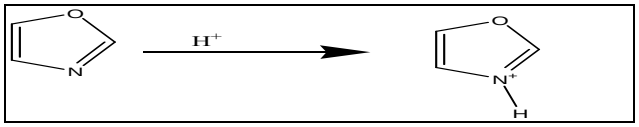
**Reactivity of Oxazole**

**1. Electrophilic substitution:** The preferred action in 1, 3-azoles is takes place at position-5. Electrophilic attack occurs readily when the ring is activated by electron-donating substituent.



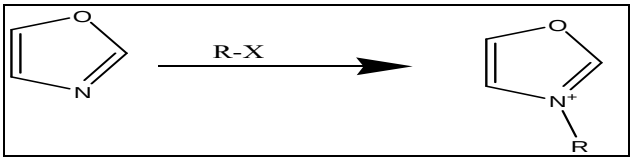
**Scheme 12:** Electrophilic substitution on oxazole

**2. Deprtonation of oxazole [1]:** The deprotection of oxazole takes place in 3rd position, containing nitrogen heteroatom.



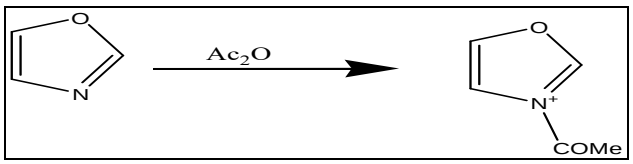
**Scheme 13:** Deprotonation of oxazole

**3. N-Alkylation of oxazole:** Alkylation of oxazole occur in 3-position, showing high affinity for alkylation.



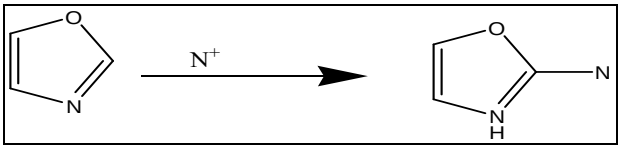
**Scheme 14:** alkylation of oxazole

**4. N- Acylation of oxazole [13]:** Acyl group attack in 3-position, the 3-positon shows high reactivity towards acylation of oxazoles.



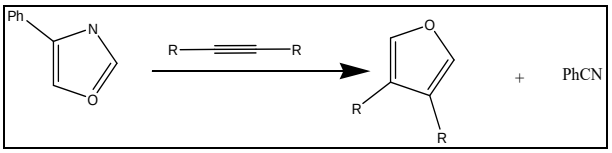
**Scheme 15:** Acylation of oxazole

**5. Nucleophilic substitution of oxazole:** Nucleophilic substitution reactions on the oxazole ring is uncommon. The ease of displacement of halogens on the oxazole ring is C-2>>C-4>C-5.



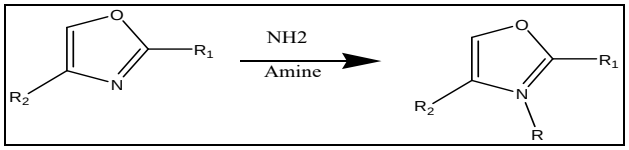
**Scheme 16:** Nucleophilic substitution of oxazole

### 6. Cycloaddition [14]



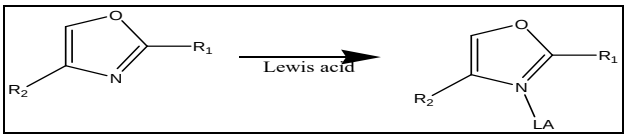

**Scheme 17:** cycloaddition on oxazole

### 7. Amination



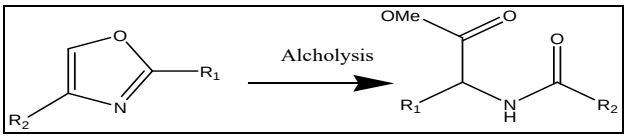

**Scheme 18:** Amination of oxazole

### 8. Lewis acids




**Scheme 19:** oxazole reaction through lewis acid

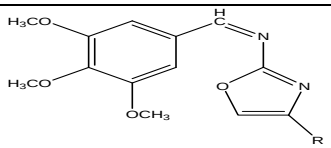
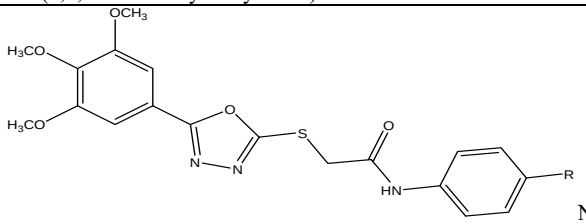
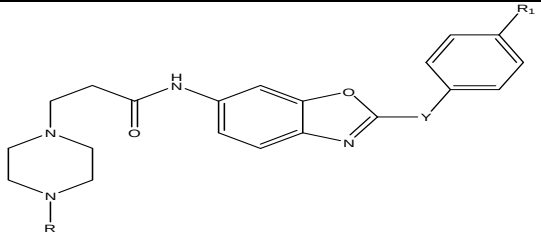
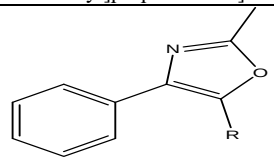
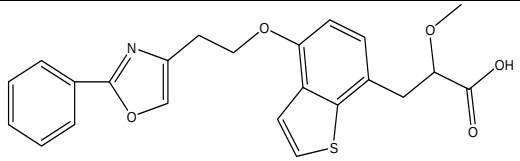
### 9. Alcholysis [15]

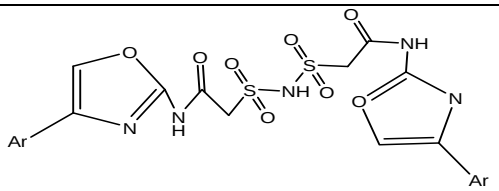
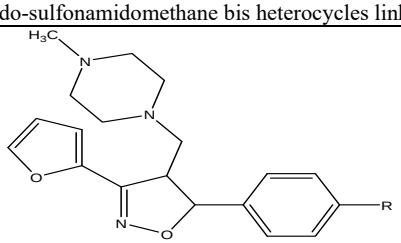
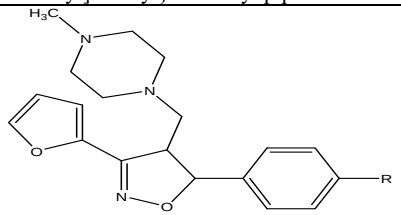
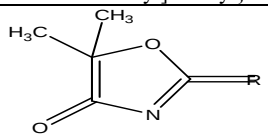
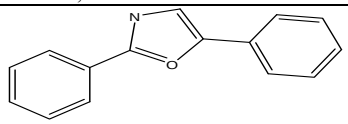
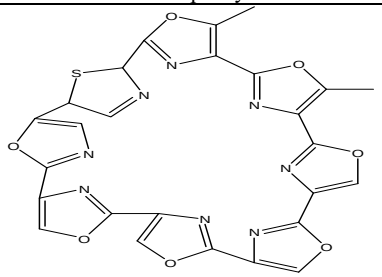
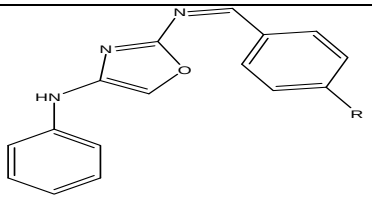
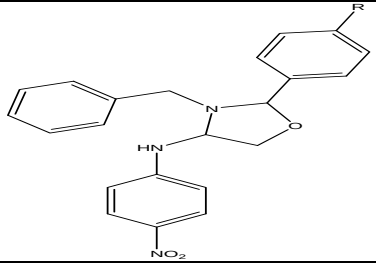


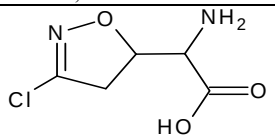
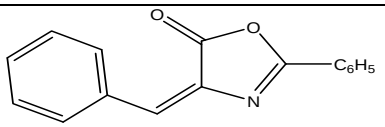
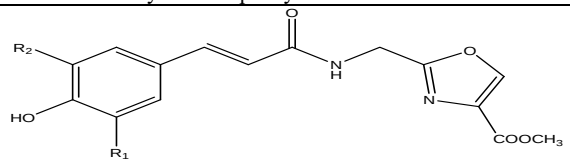
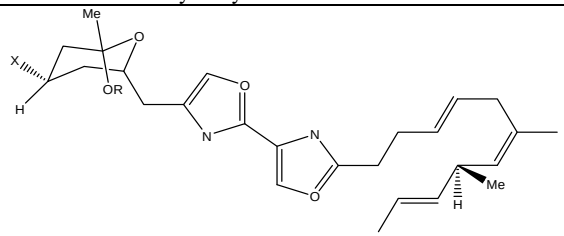
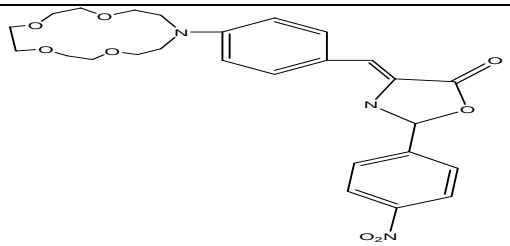
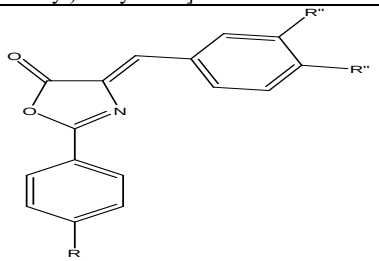
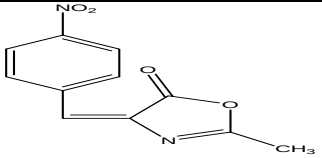
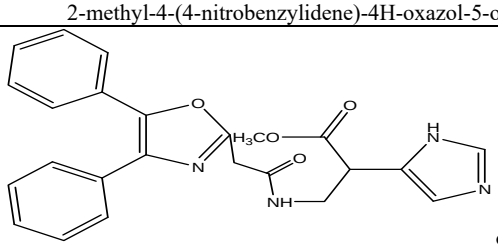

**Scheme 20:** alcholysis of oxazole

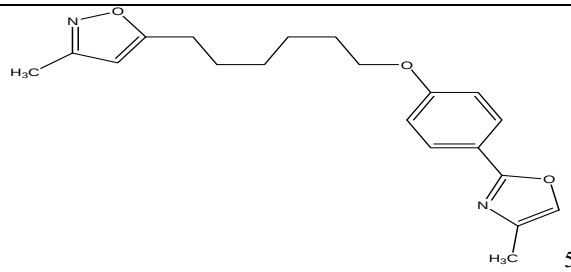
### Pharmacological Activity

**Table 1:** Some pharmacological active compounds and their structure

| S. No. | Chemical Structure/ Name | Activity | Author Name /Year | Active compound |
|---|---|---|---|---|
| 1 |  N-(3,4,5-trimethoxybenzylidene)-4-substituted oxazol-2-amine | Antibacterial, Antifungal, Antihelmenthic | Rawat B.S [7] *et al* (2016) | R=H, $C_6H_5$, $C_6H_4Cl$, $C_6H_4F$, $C_6H_4NO_2$ |
| 2 |  N-Phenyl-2-{[5-(3, 4, 5-tri-methoxy phenyl)-1, 3, 4-o-diazol-2-yl) sulfanyl} acetamide | Antibacterial and Antifungal | Maharishi [16] B.S *et al* (2016) | R=F, Cl, $CH_3$, H |
| 3 |  2-(p-substitutedphenyl/benzyl)-5-[3-[4-[p-chlorophenyl-1-yl]propionamido]-benzoxazole | Antibacterial | Mustafa [17] A. *et al* (2016) | X=$CH_2CH_2$, Y=$CH_2$, $R_1$=p-Cl, R=Cl and X=$CH_2CH_2$, Y=$CH_2$, $R_1$=p-Cl, R=$CH_3$ |
| 4 |  R= Substitued phenyl or heteroaryl 5-substituted aryl (or heteroaryl)-2-methyl-4-phenyloxazole | Antimalarial, antibacterial, antifungal | Singh R.K. [8] *et al* (2016) | R=4-F-Phenyl, R=3-$CF_3$ Phenyl |
| 5 |  Aleglitazar | Type2 diabetes mellitus | Lincoff A.M [18] *et al* (2014) | R=OH, R'=H |

| | | | | |
|---|---|---|---|---|
| 6 |  <br>Amido-sulfonamidomethane bis heterocycles linkage | Antimicrobial, anticancer | Chokkappagari P. [19] *et al* (2014) | R=Ar |
| 7 |  <br>1-{[3-(furan-2-yl)-5-substituted phenyl-4, 5-dihydro-1, 2-oxazol-4- yl] methyl}-4-methyl piperazine | Antianxiety | Kumar J. [20] *et al* (2013) | R= H,OH, Cl. |
| 8 |  <br>1-{[3-(furan-2-yl)-5-substitutedphenyl-4,5-dihydro-1, 2-oxazol-4-yl] methyl}-4-methyl piperazine | Antidepressant | Jagdish K. [20] *et al* (2013) | R=H, 4-$CH_3$, 2-Cl, 4-Br, 4-Cl, 4-OH, 4-$OCH_3$ |
| 9 |  <br>1, 3-oxazoline-2-thiones | Anti-depressant, anticancer | Purohit S.S. [21] *et al* (2013) | R=S |
| 10 |  <br>Biphenyl oxazole | Anti-tubercular | Moura C.G Kelly [22] *et al* (2012) | R=H |
| 11 |  <br>Telomestatin | Anticancer | Dougal R.J [23] *et al* (2012) | R=R'=$CH_3$ |
| 12 |  <br>*N*-phenyl-*N*-[(*Z*)-phenylmethylidene]-1,3-oxazole-2, 4-diamine. | Antileprotic | Niraimathi [24] V. (2011) | R=$CH_3$, Cl, $OCH_3$, $N(CH_3)_2$ |
| 13 |  | Anticonvulsant,Analgesics, Antiinflammatory and Anti-tumor | Selvam T.P [25] *et al (*2011) | R=H,OH,Cl. |

| | | | | |
|---|---|---|---|---|
| | 3-benzyl-2-(4'-substitutedphenyl)-4(5H)-(4''-nitrophenyl amino)-1, 3-oxazolidines | | | |
| 14 |  Acivicin | Used in leukemias,ovarian carcinoma, and the human breast tumor xenograft. | Ghosh A.[26] *et al* (2010) | R=O |
| 15 |  4-Benzylidene-2-phenyl-4H-oxazole-5-one | Pesticidal | Abdel aty [27] *et al* (2009) | R=H,F |
| 16 |  Hydroxycinnamic acid amides | Antioxidant | Ivanka S. [28] *et al* (2009) | R=$OCH_3$, OH |
| 17 |  Henzoxazole | Antiherpes | Delia H. [29] *et al* (2008) | R=H,$CH_3$ |
| 18 |  2-(4-nitro-phenyl)-4-[4-(1,4,7,10-tetraoxa-13-aza-cyclopentadec-13-yl)benzylidene]-4H-oxazol-5-one | Photophysical properties | Ozturk G [30] *et al* (2008) | R=O, $OCH_3$ |
| 19 |  4-Benzylidene-2-phenyloxazol-5-one | Antibacterial, Antifungal, Anticytotoxic | Tandel R.C [31] *et al* (2008) | R=R'=R''=H, R=R'=OH,R''=H |
| 20 |  2-methyl-4-(4-nitrobenzylidene)-4H-oxazol-5-one | Immunomodulator | Mesaik M.A [32]. *et al* (2004) | R=$NO_2$ R'=$CH_3$ |
| 21 |  oxaprozin | Antiulcer | Kachwaha [33] S.J *et al* (2002) | R=$OCH_3$ |

| | | | | |
|---|---|---|---|---|
| 22 |  5-methyl-2-thienylketopolymethylene oxyphenyl 4,5-dihydro-2-(alkyl)oxazoles | Anti-human picornavirus activity | A.Mar [34] *et al* | 1996 |

**Natural Products Containing Oxazole Moiety**

Natural products are extremely useful for medicinal purpose. From early times natural products are used for the therapeutic function. Numerous bioactive natural products extracted from the sources including bacterial, plants and marine sources containing oxazoles functional groups. They show vital biological activities including antileprotic, analgesics, antifungal, antibacterial, antitubercular, and anti-inflammatory properties. Many medicinal compounds and chemicals contains functionalized polysubstituted oxazole mainly in natural products which contains *N, O*-heterocycles.

**Oxazole isolated from marine sources**

**1. Neopeltolide:** A new marine derived macrolide chosen as neopeltolide was isolated from a deep-water sponge of the family neopeltidae. Neopeltolide is an effective inhibitor of the *in vitro* proliferation of the human lung adenocarcinoma, the human ovarian sarcoma and murine leukemia cell lines.

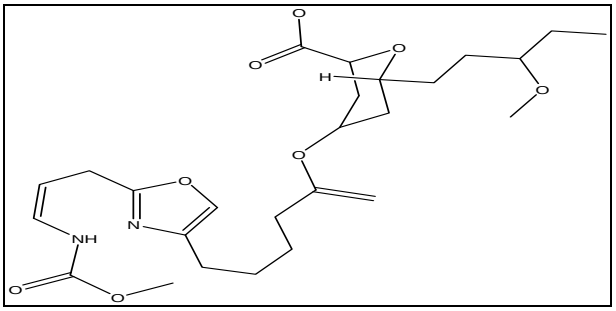


**Fig 2:** Structure of Neopeltolide

**2. Hennoxazole:** Isolated from marine source, it is a potent antiherpese agent and peripheral analgesics contain a bisoxazole unit muscoride [26].

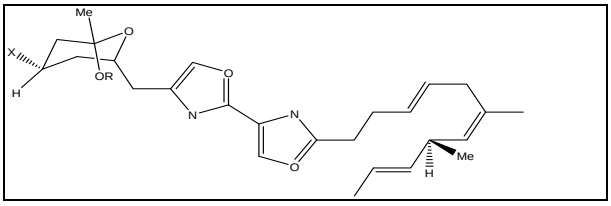


**Fig 3:** Structure of Hennoxazole

**3. Ariakemicins A:** It is an atypical linear hybrid polypeptide or nonribosomal peptide antibiotics, were discovered from the fermentation extract of the marine gliding bacterium Rapidithrix sp

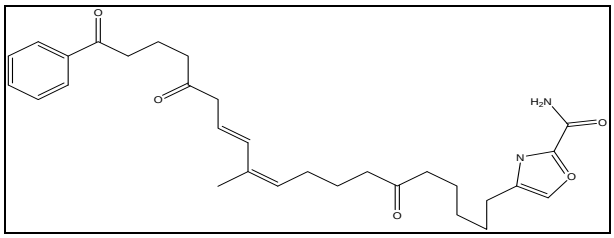


**Fig 4:** Structure of Ariakemicins

**4. Bengazole A, B and E:** The new natural source of bengazole A, B and E is from the bioassay guided fractionation of extract of the sponge *Dorypleres splendens.* The compound shows growth inhibitory activity to seven murine and human cancer cell lines [29].

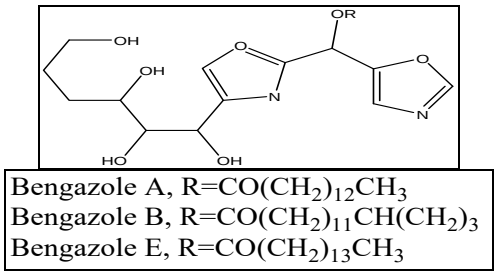



**Fig 5:** Structure of Bengazole

**5. Leucascandrolides:** Leucascandrolides A and B were isolated by Pietra and coworkers in 1996 from a calcareous sponge *leucascandra caveolata* collected from the east coast of New Caledonia, Coral Sea [35].

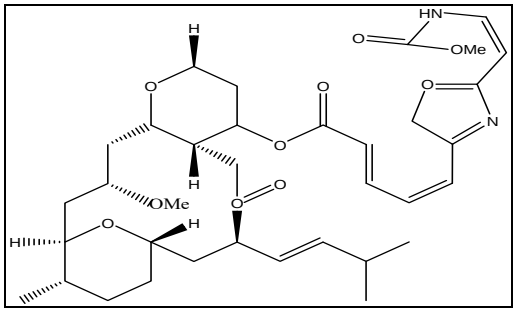


**Fig 6:** Structure of Leucascandrolide A

**6. Diazonamides:** Isolated from the marine ascidian *Diazona* sp. collected in Indonesia. The cytotoxic activity diazonamide A was evaluated against a panel of three human tumor cell lines, including lung (A549), colon (HT29), and breast [36].

**7. Almazole:** Isolated from the red seaweed *Haraldiophylum.* Antibacterial metabolite isolated from red seaweed from the Dakar coast [37].

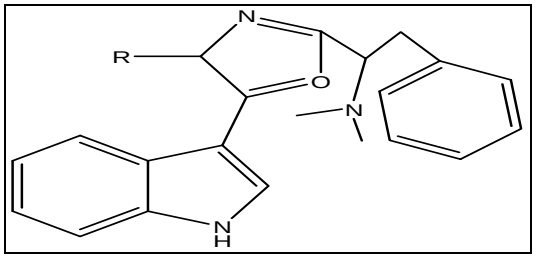
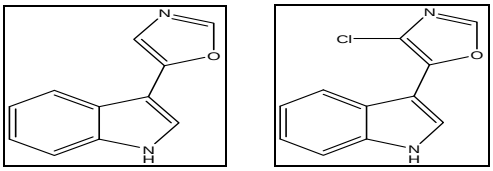


**Fig 7:** Structure of Almazole

**2. Oxazole compounds isolated from microbes**

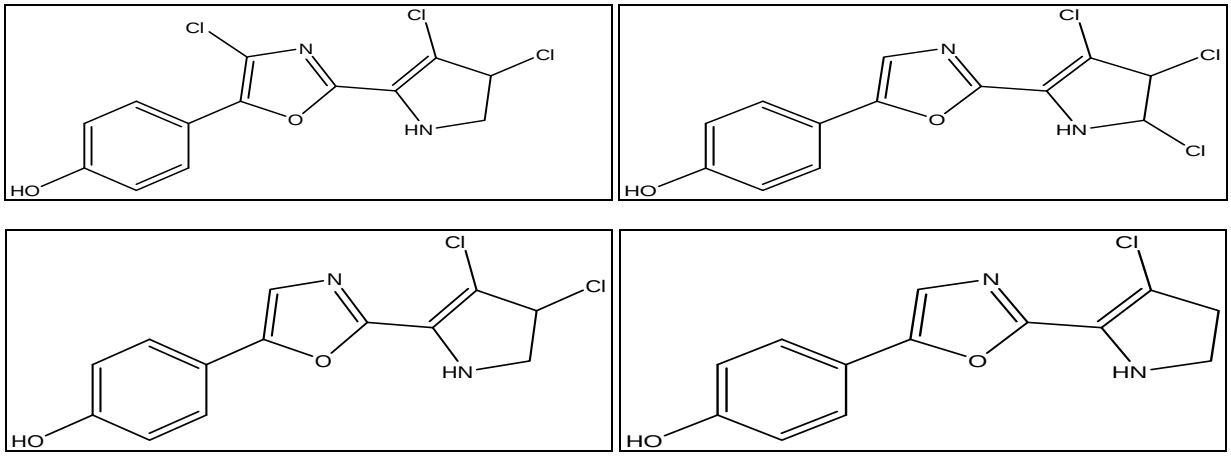
**1. Oxazoles 5-(indol-3-yl) oxazole:** It exist in diversity of natural products ranging from the comparatively simple pimpinine and streptochlorin to the complex diazonamide A. pimprinine has a variety of biological activities, from antibiotics and fungicidal effects to anti-epilepsy effects and monoamide oxidase inhibition. The diazoamides A perform nanomolar activity against HCT-116 human carcinoma and B-16 murine melanoma cell lines.



Pimprinine Streptochlorin

**Fig 8:** Structure of pimprinine and streptochlorin

**2. Pyrrolyl-oxazoles:** The 2-(pyrrole-2-yl) oxazoles is called as phorbaxoles A-D. The phorbazoles are tyrosine- proline dipeptide derivative which are chlorinated on the pyrrole. And phorbazole A, is substituted on the 4-position of the oxazole, similar to the diazonamides [26].



Phorbaxoles A-D

**Fig 9:** Structure of Phorbaxoles A-D

## Conclusion

The present study provides general idea regarding the introduction, synthesis, pharmacology and chemistry of oxazole and its derivatives. The review also provides information about the use of oxazole in diversity oriented synthesis and its pharmacological activity. The review gives the overview of the various synthetic routes used to form a biologically active oxazole moiety, which is helpful for researchers for further novel approaches on oxazole ring for developing better medicinal agents and newer compounds for increasing efficacy and safety of compound.

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