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Methods for synthesis of Oxazolones: A Review

Suman Bala*, Minaxi Saini and Sunil Kamboj

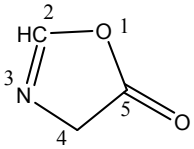
M.M. College of Pharmacy, Maharishi Markandeshwar University, Mullana, Ambala, Haryana-133203,India.

***Corres.author: sumankmj7@gmail.com**
Phone no: +08059930163.

Abstract: Oxazolones are five membered heterocyclic compounds containing nitrogen and oxygen as hetero atoms. The C-2 and C-4 positions of the oxazolone are crucial for their various biological activities. N-substituted oxazolones also participated in variety of intermolecular reactions. Considering these properties, various research workers have shown a keen interest in this small heterocyclic moiety as target structure for evaluation of many pharmacological activities. This review includes various synthetic routes and guidelines for the development of new oxazolones.
Keywords: Erlenmeyer-Plochl reaction, Intramolecular Diels-Alder reaction, Photosensitive, Carbodiimide.

INTRODUCTION

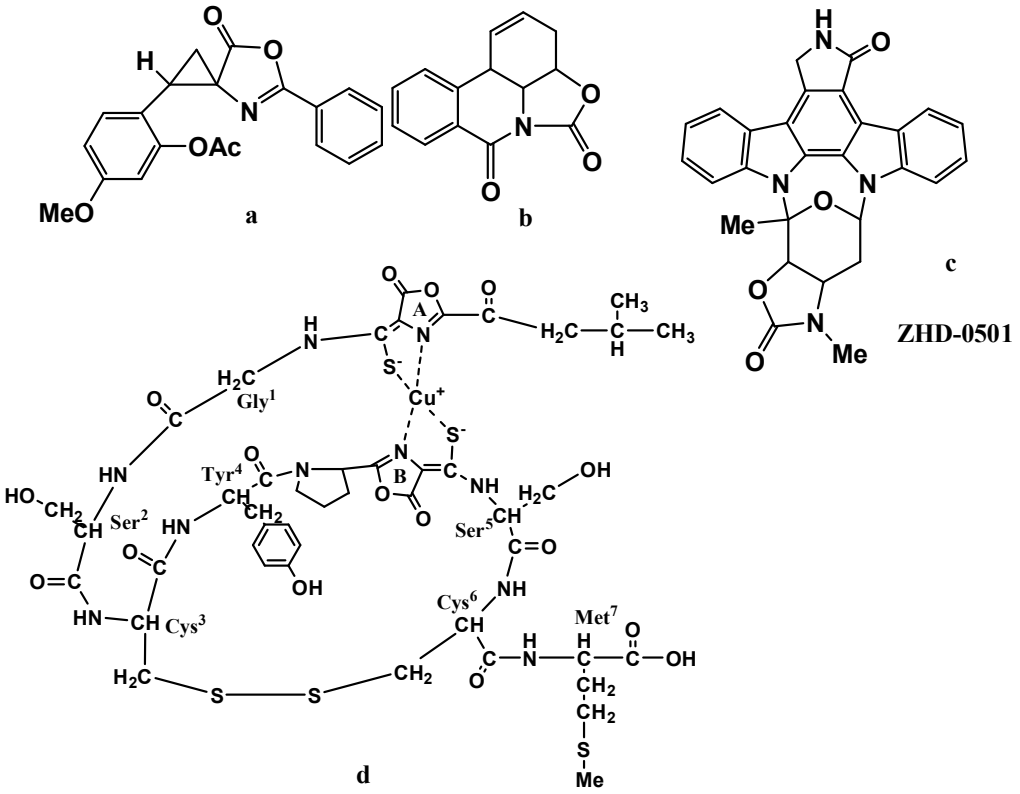
Since many decades, active heterocyclic compounds are one of the main topic of interest for the medicinal chemists as it displays a number of pharmacological activities. Nitrogen, sulphur, oxygen containing five and six membered heterocyclic compounds have occupied enormous significance in the field of medicinal chemistry.[1] Oxazolones are heterocyclic compounds which perform an important role in the synthesis of several organic molecules including amino acids,[2] amino alcohols, thiamine,[3]amides,[4] peptides[5,6,7] and polyfunctional compounds.[8] Certain natural and synthetic oxazolone also including benzoxazolone[9,10,11,12,13] derivatives possess important biological activities; such as antimicrobial,[14,15,16] anti-inflammatory,[10,17,18] anticancer,[19,20] anti-HIV,[21,22,23] antiangiogenic,[24] anticonvulsant,[25] antitumor, antagonistic, sedative[26,27,28] and cardiotonic activity.[12,29] These are used as synthons for the construction of various alkaloid skeletons, immunomodulators and biosensors[26,30,31,32] or photosensitive composition devices for proteins.[12,27,28]



Oxazol-5-one

Oxazolones exhibited promising photophysical and photochemical activities,[5,31,33] so they are used in semiconductor devices such as electrophotographic photoreceptors and in non-linear optical materials.[34,35,36] Oxazolone has cyclooxygenase-2 inhibitory property[10,11,37] and tyrosinase inhibitory property.[17] AG 50 Peptaibol,[38] endothiopeptides[39] and 24-membered cyclic depsipeptide were formed by "azirine/oxazolone" method which incorporate the Aib (α-aminoisobutyric) acid units for cyclization of the linear peptides.[40,41] Oxazol-5(4H)-ones,

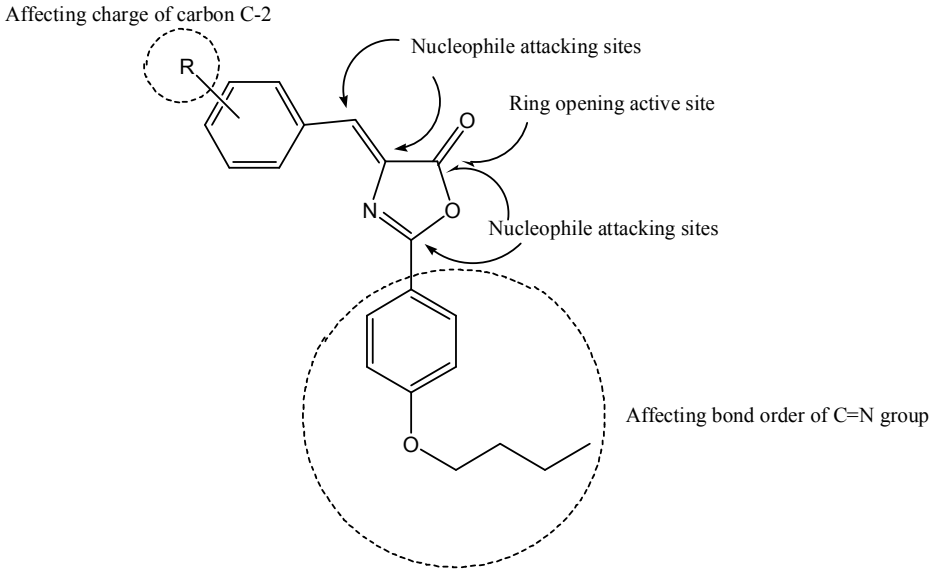
also known as azlactones, are readily prepared from N-protected amino acids by dehydration.[6,7] Ring-opening of oxazolone leading to an enantiomerically enriched N-protected phenylalanine esters[6,42] and peptido-alcohols.[38,43] Oxazolone linked to the structure and chemistry of penicillin, has also been described in the literature.[14,44,45] Oxazolone show interesting behaviour towards polymerization and condensation leading to homopolymers, telomers, condensation reagents,[8] peptides, herbicides[46], fungicides, pesticides[17] and agrochemical intermediates. Oxazolone plays very vital role in the manufacturing of various biologically active drug as analgesic, anti-inflammatory, antidepressant, anti-cancer, anti-microbial, anti-diabetic and antiobesity.[47,48] Formation of b_2 ions in mass spectrometery from protonated peptides arising for affording the protonated and deprotonated oxazolones.[49,50,51] Spirocyclopropyl oxazolone **a**, is the new class of inhibitors of herpes proteases.[21,22] Phenacyl oxazolone involves the intramolecular Diels-Alder reaction, resulting in the synthesis of anti-cancer drug, pancratistatin **b**, a phenanthrene alkaloid.[20] Deflazacort, an oxazolone derived from prednisone, has anti-inflammatory and immunosuppressive effects.[52] ZHD-0501 **c**, is a metabolite of staurosporine (STA) analog with an oxazolone ring which inhibit the proliferation of several human and murine cancer cell lines.[19] The proposed structure of methanobactin **d**, containing oxazolone rings **A** and **B** play an integral role in the global carbon cycle.[53]



CHEMISTRY

Substitution of functional group at C-4 and C-2 position plays a vital role in the activity of oxazolone.[17] Substituted (*p*-nitro) exocyclic phenyl group at C-4 in oxazolone moiety greatly influences the immunosuppressive activity.[28] Cinnamoyl residue at C-4 of oxazolone moiety and substitution of functional group at C-4 and C-2 positions of oxazolone are crucial for tyrosinase inhibitory activity. An extension of conjugation through an aliphatic double bond present at C-4 position of oxazolone moiety and a phenyl ring present at C-2 play a pivotal role in activity.[26] The rate of the oxazolone ring-opening reaction decreased with an increase of the electron donating properties of the substituent of the phenyl ring at C-2 position.[54] Exocyclic double bond can operate as a dienophile and N-substituted oxazolone participates in intermolecular Diels–Alder reactions.[30]

Lewis acid activation of the carbonyl group of unsaturated oxazolones give electrophilic character to the ß-carbon.[55] In the structure of (4Z)-4-benzylidene-2-phenyl-1,3-oxazol-5(4H)-ones **e** have multiple electrophilic reaction centres for an attack of the nucleophile. Mostly they attack the carbonyl group often leading to a ring opening.

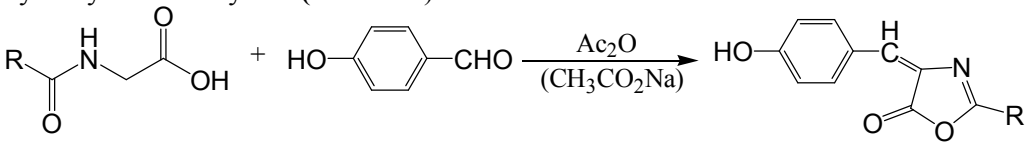


e

The positive charge of carbon C-2 increases by *m*-NO_2 group which may be easily attacked by any nucleophile. An alkoxy group at the *para* position of the phenyl ring decreases the negative effect of the nitro group and the electron withdrawing effect of this group may support the attack of the C=N group. The bond order of the C=N group decreases by the presence of *m*-NO_2 group at the benzylidene ring.[5,56]

SYNTHESIS

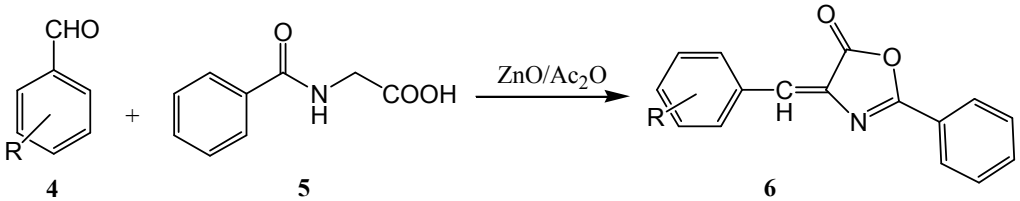
Vijay Taile et al reported the preparation of 5-oxazolones by the Erlenmeyer-Polchl reaction, a cyclodehydration-condensation of the appropriate aldehyde and hippuric acid in dry acetic anhydride catalyzed by acetate anion.[44,48] Compound 4-(4-hydroxybenzylidene)-2-substituted oxazol-5-ones **3** were synthesized from acetylglycine **1** and *p*-hydroxy benzaldehyde **2 (**Scheme 1).[48]



1 **2** **3**

Scheme 1: Synthesis of 4-(4-hydroxybenzylidene)-2-substituted oxazol-5-ones using glycine and benzaldehyde

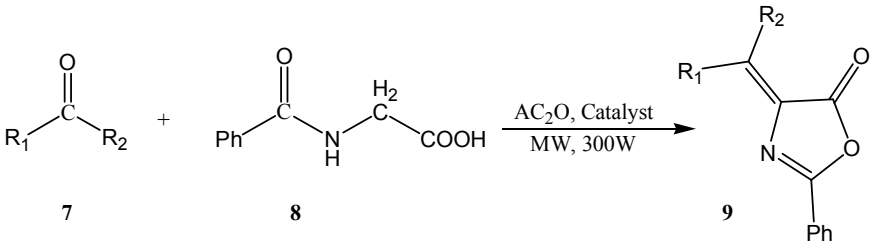
M.A. Pasha et al reported the synthesis of 4-arylmethylidene-2-aryl-5(4H)-oxazolones **6** by stirred suspension of subtituted benzaldehyde **4**, hippuric acid **5**, ZnO (catalyst) and acetic anhydride. It was reported that the reaction was completed at room temperature in a short duration of time with good yield of oxazolone **6** (Scheme 2).[12]



4 **5** **6**

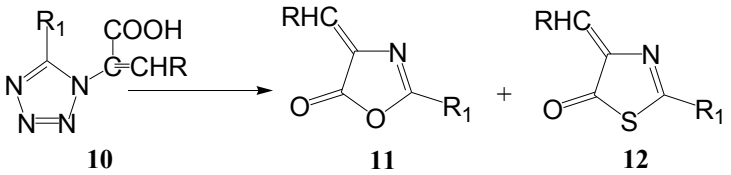
Scheme 2: Synthesis of 4-arylmethylidene-2-aryl-5(4H)-oxazolones using ZnO as catalyst

Ahmad Momeni Tikdari et al reported the synthesis of 2-phenyl-5(4H)-oxazolone **9** by microwave irradiation from the mixture of hippuric acid **8** and aldehydes or ketones **7**, in the presence of acetic anhydride and corresponding catalysts (dodecatungstophosphoric acid, samarium and ruthenium(III) chloride). The rate of the reaction was very fast and leads to good yield of oxazolone **9** (Scheme 3).[27]



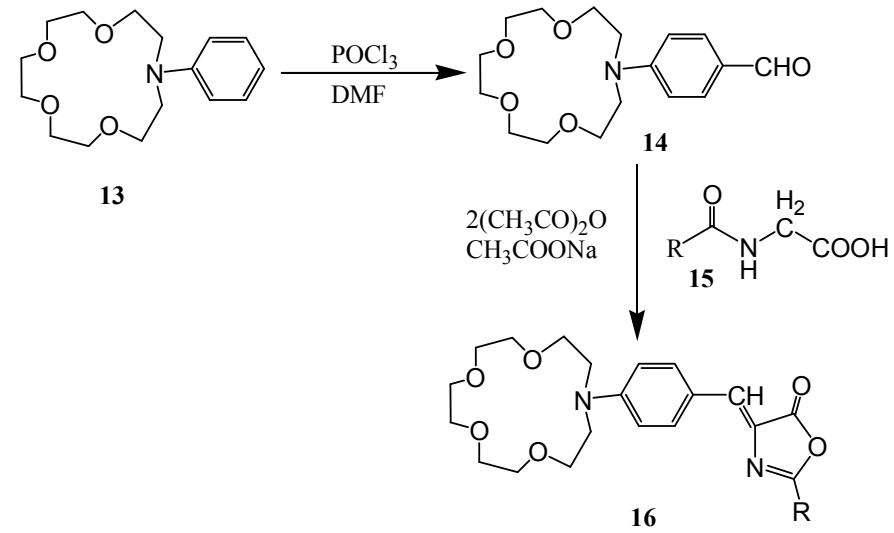
Scheme 3: Synthesis of 2-phenyl-5(4H)-oxazolone from dodecatungstophosphoric acid, samarium and ruthenium(III) chloride as catalyst

Jytte Lykkeberg et al synthesised some unsaturated 5-oxazolones **11** by the decarboxylation of the ß-substituted α-(1-tetrazollyl) acrylic acids **10**. They reported that compound **11** was produced with the combination of thiazolone **12** and further this oxazolone **11** responsible for the formation of imidazolones and amides (Scheme 4).[57]



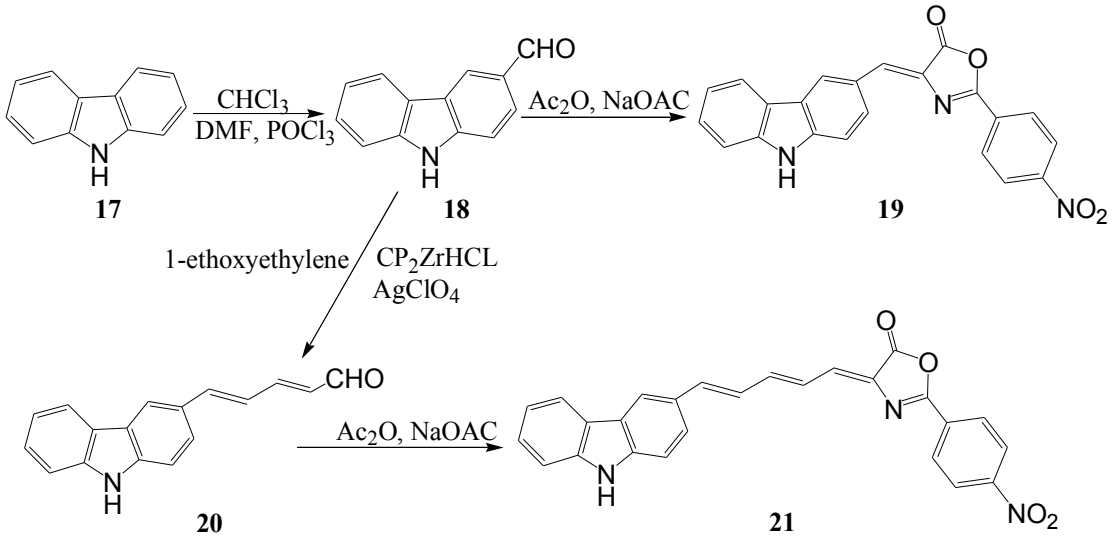
Scheme 4: Synthesis of 4H-5-oxazolone ß-substituted α-(1-tetrazollyl) acrylic acids

Gulsiye Ozturk et al reported that the treatment of N-phenyl-(aza-15-crown-5) **13** with $POCl_3$ in dimethylformamide led to the formation of 2-aryl-4-[4-(1,4,7,10-tetraoxa-13-azacyclopentadecyl)-benzylidene]-5-oxazolone **16** dyes. They reported the cyclization of 4-(1,4,7,10-tetraoxa-13-azacyclopentadecyl)benzaldehyde **14** with benzoylglycine derivative **15** in the presence of acetic anhydride gave reasonable oxazolone **16** (Scheme 5).[34]



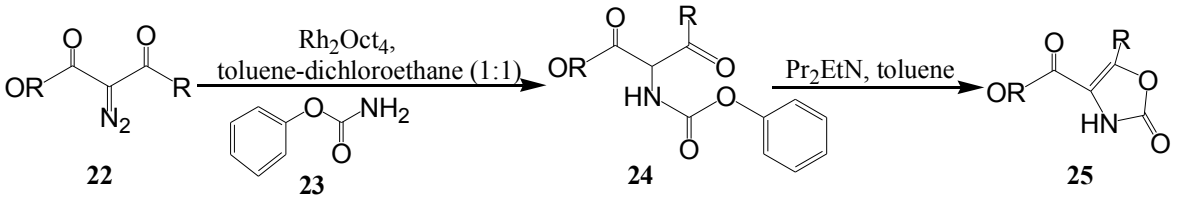
Scheme 5: Synthesis of 2-aryl-4-[4-(1,4,7,10-tetraoxa-13-azacyclopentadecyl)-benzylidene]-5-oxazolone dyes from N-phenyl-(aza-15-crown-5)

Jose Luis Dıaz et al reported the preparation of new compound carbazole-oxazolone (Cz-OXA) chromophores **19** from carbazole **17** via an intermediate compound 9-methyl-9H-3- carbazolecarbaldehyde **18**. They reported that compound **18** in the presence of 2-(4-nitrophenylcarboxamido)acetic acid gave oxazolone **19** and 4-[5-(9-methyl)-9H-3-carbazolyl)-2,4-pentadienylidene]-2-(4-nitrophenyl)-4,5-dihydro-1,3-oxazol-5-one **21**. They reported, hydrozirconation of two-carbon homologation reaction of compound **18** by an $AgClO_4$-catalyzed addition of zirconocene chloride gave an intermediate compound 5-(9-methyl)-9H-3-carbazolyl)-2,4-pentadienal **20.** It has been reported that Erlenmeyer reaction gave the reasonable compound **21** (60%), where the carbonyl group of the oxazolone ring and the nitrophenyl group act as acceptors in different directions, the oxazolone chromophore to be considered as a two-dimensional (2D) chromophore (Scheme 6).[58]



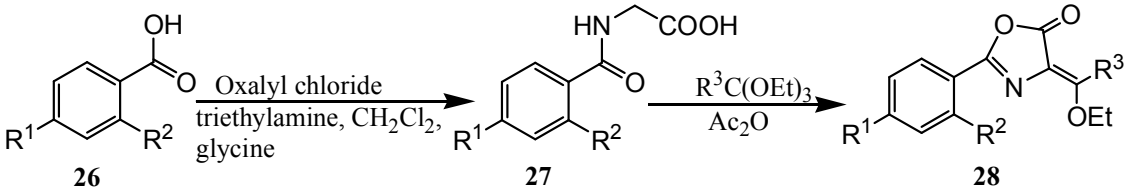
Scheme 6: Synthesis of carbazole-oxazolone from carbazole

Makoto Yamashita et al reported that solid-phase synthetic methodology used for preparing various heterocycles. They found that phenylcarbamate **23** reacted with diazocarbonyls **22** and rhodium octanoate catalyst. It gives to the N–H insertion products **24**. Further they treat this intermediate **24** with mild base Pr_2EtN afforded the ring-closed oxazolone products **25**. (Scheme 7).[59]



Scheme 7: Synthesis of oxazolone from diazocarbonyls and phenylcarbamate

Manish Tandon et al reported that the treament of aromatic carboxylic acids **26** with glycine gave glycine amides **27** and cyclization of intermediate **27** with a tri-substituted orthoformate in acetic anhydride at elevated temperature gave 4-ethoxy-5-oxazolones **28 (**Scheme 8).[60]

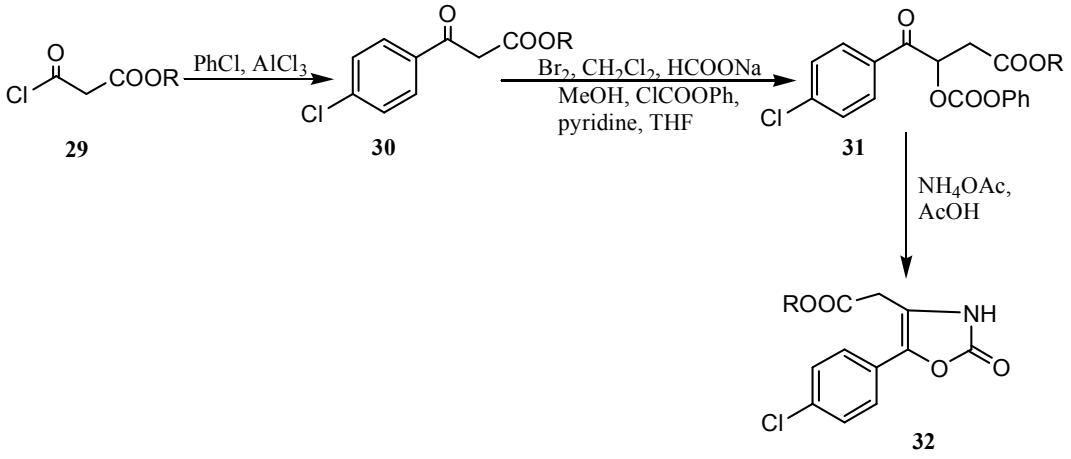


26 **27** **28**

Scheme 8: Synthesis of 4-ethoxy-5-oxazolones from aromatic carboxylic acids

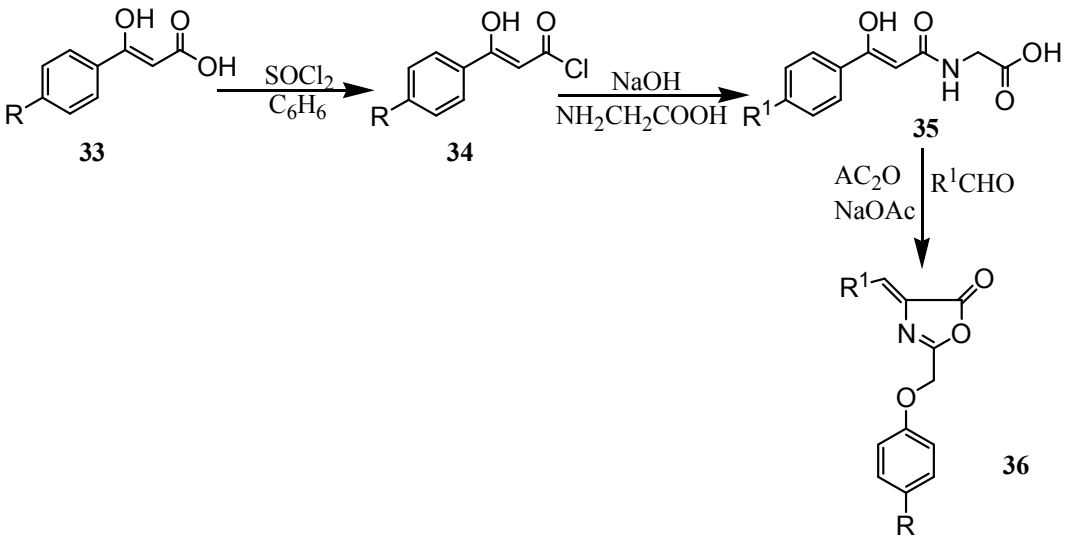
Tsuyoshi Maekawa et al reported Friedel–Crafts reaction of acyl chlorides **29** with chlorobenzene afforded ω-(4-chlorobenzoyl)alkanoic acid esters **30**. Further they performed the bromination of **30** followed by treatment with sodium formate in methanol gave the corresponding α-hydroxyketones. Formation of α-phenoxycarbonyl -oxyketones **31** by the introduction of a phenoxycarbonyl moiety to the hydroxyl group of α-hydroxyketones in the presence of pyridine and THF. Further cyclization of **31** leads to 4-(4-chlorophenyl)-oxazolones **32** by the reaction of ammonium acetate in acetic acid. They found that the compound **32** is responsible for the formation of 5-(ω-aryloxyalkyl)oxazole which is clinically useful in the treatment of diabetic neuropathy (Scheme 9).[61]

M. J. Aaglawe et al reported the conversion of phenoxy acetic acid **33** to acid chloride **34** on reflux with thionyl chloride and benzene. They further react phenoxy-acetyl chloride **34** with glycine which gave phenoxy-acetyl-amino acetic acid **35** and reaction with aldehyde led to the formation of 2,4-substituted phenloxy methyl 4-oxazol-5-one **36** by 4h reflux in the presence of acetic anhydride and sodium acetate (Scheme 10).[1]



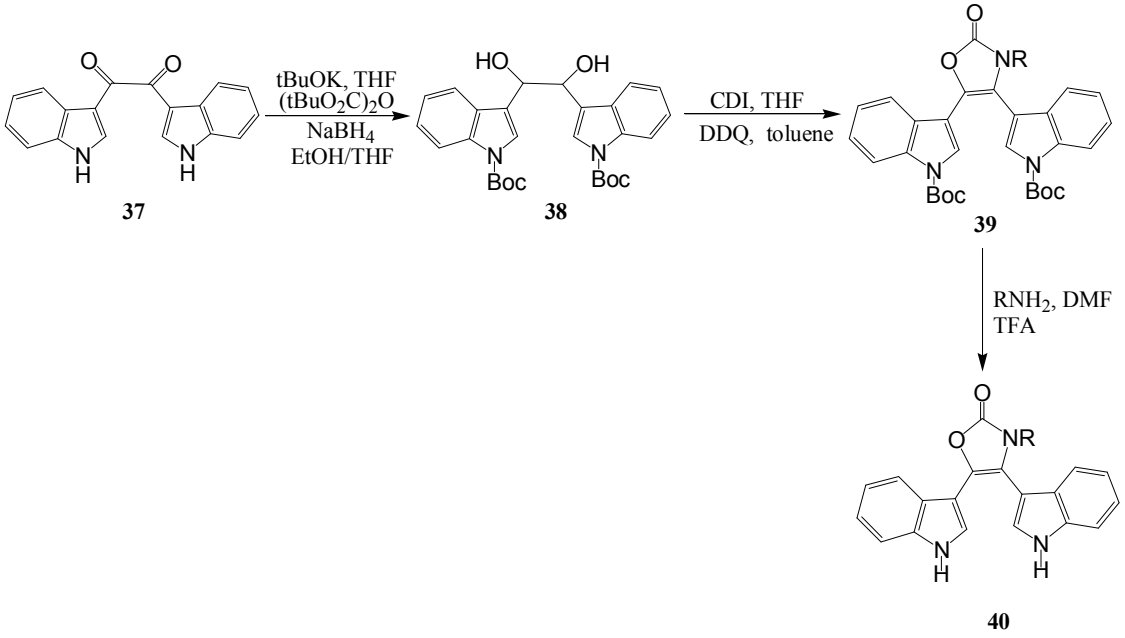
29 **30** **31** **32**

Scheme 9: Synthesis of 4-(4-chlorophenyl)-oxazolones from acyl chlorides



Scheme 10: Synthesis of 2,4-substituted phenloxy methyl 4-oxazol-5-one using thionyl chloride

Elisabete Rodrigues Pereira et al reported the synthesis of oxazol-2-ones **40** have been achieved by the reaction of cyclic carbonates **39** with primary amines. Carbonate **39** was easily accomplished through four steps from 1,2-bis-(1H-indol-3-yl)-ethane-1,2-dione **37**. The indole nitrogens of α-diketone **37** protected with Boc (tert-butyloxycarbonyl) groups when refluxing with tBuOK and THF for 1h. The reduction of α-diol done by refluxing it with ethanol and THF for 5h at room temperature using sodium borohydride that afforded the mixture of stereoisomers **38** (Scheme 11).[62]



Scheme 11: Synthesis of N-substituted-oxazol-2-ones from α-diketone

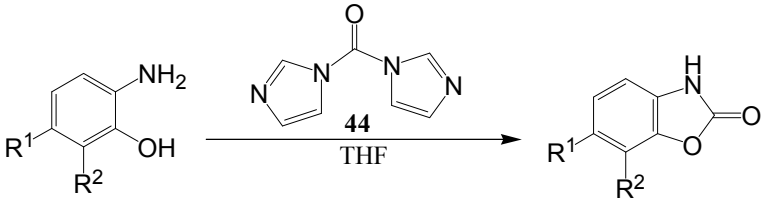
Further cyclisation of the isomeric mixture to cis and trans carbonates using carbonyldiimidazole (CDI) and THF was done by refluxing at room temperature for 12h. The oxidation of the cis isomer to carbonate **39** was reported by refluxing 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in toluene for 6h. Further the reflux of carbonate **39** with primary amines gave N-substituted-oxazol-2-ones **40** in the presence of DMF and TFA (Scheme 11).[62]

Nachman et al reported the synthesis of benzoxazol-2(3H)-ones **42** from 1-(2-hydroxyphenyl)ureas **41** (Scheme 12).[63]

41 **42**

Scheme 12: Synthesis of benzoxazol-2(3H)-ones from 1-(2-hydroxyphenyl)ureas

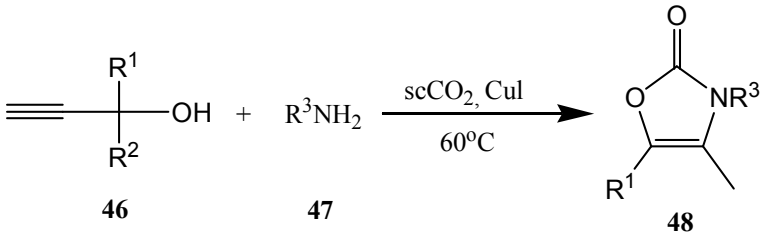
Nachman et al synthesised benzoxazol-2(3H)-ones **45** in excellent yields by refluxing 1,1'-carbonyldiimidazole **44** and 2-aminophenol **43** in dry THF for 4h (Scheme 13).[64]



43 **45**

Scheme 13: Synthesis of benzoxazol-2(3H)-ones from 2-aminophenol

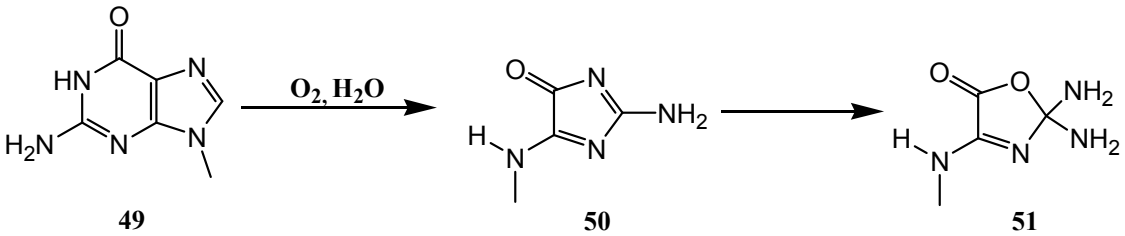
Huanfeng Jiang et al observed that N-substituted oxazolones **48** synthesised by the cycloaddition reactions of propargylic alcohols **46** and amines **47** in the presence of carbon dioxide. They were performed that 4-methyloxazol-2-one **48** obtained under supercritical conditions (Scheme 14).[65]



46 **47** **48**

Scheme 14: Synthesis of 4-methyloxazol-2-one using carbon dioxide

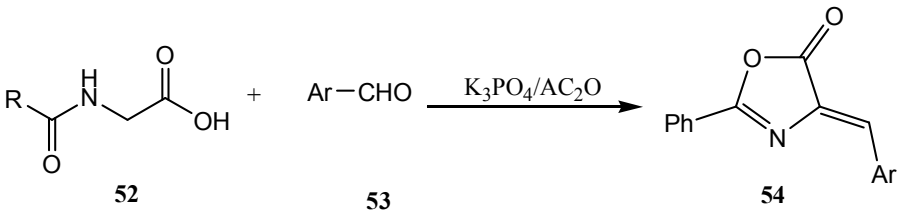
Michele C. Kelly et al reported that highly alkali-labile oxazolone **51** was prepared upon hydrolysis of guanine **49**. Wide variety of oxidation reactions were targeted on the most susceptible DNA which are mediated by OH radicals, singlet oxygen, peroxynitrite and one electron oxidants. In literature, it was found that addition of OH at C-4 (~60%) by oxidation of the purine moiety of 2'-deoxyguanosine **49** led to the formation of 2,2-diamino-4-[(2-deoxy-ß-D-erythro-pentofuranosyl)amino]-5(2H)-oxazolone **51** via 2-amino-5-[(2-deoxy-ß-D-erythro-pento -furanosyl)amino]-4H-imidazol-4-one **50** precursor (Scheme 15).[66]



49 **50** **51**

Scheme 15: Synthesis of oxazolone from guanine using OH radicals

Thomas Cleary et al reported that the Erlenmeyer reaction afforded oxazolone **54** by the reaction of carboxylic acid **52** and benzaldehyde **53**. They used potassium phosphate as a catalyst instead of sodium acetate underwent condensation of aromatic aldehyde **53** by dehydrating agent such as an acetic anhydride (Scheme 16).[67]

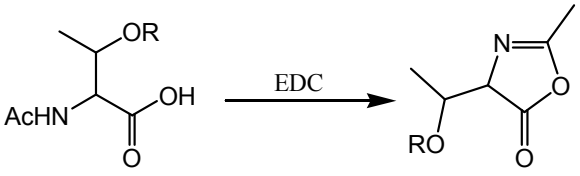


52 **53** **54**

Scheme 16: Synthesis of oxazolone using K_3PO_4 as a catalyst

They found that the rate of reaction depended on the aromatic aldehyde substituents, which is increased by electron withdrawing groups. Further the oxazolone **54** used for the preparation of Z-α-amido-acrylic acid methyl esters by an oxazolone ring opening reaction (Scheme 16).[67]

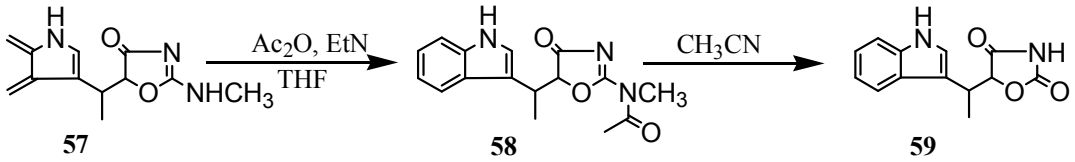
Paul Lloyd-Williams et al reported that the non-proteinogenic D-allo and L-threonine **55** led to the synthesis of oxazolones **56** in the presence of N-ethyl-N'-3-dimethylaminopropyl carbodiimide (EDC). Compound **56** was found to be responsible for the formation of peptides (Scheme 17).[68]



55 **56**

Scheme 17: Synthesis of oxazolone from D-allo and L-threonine

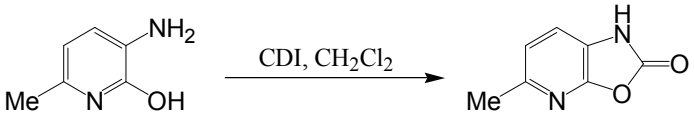
Atsushi Hasuoka et al reported that indolmycin **57** is an anti-*H. pylori* agent led to the formation of oxazolone **59**. They found that the acetylation of methylamino group of indolmycin **57** in the presence of acetic anhydride on refluxing with THF via an intermediate **58** give 5-[1-(1H-Indol-3-yl)-ethyl]-oxazolidine-2,4-dione **59** in good yields (Scheme 18).[69]



57 **58** **59**

Scheme 18: Synthesis of oxazolone from indolmycin

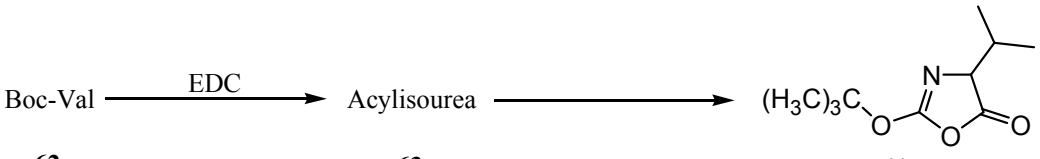
K. Shankaran et al reported that the benzoxazolone **61** prepared from pyridine analogues **60** in the presence of carbonyldiimidazole (CDI) in good yields (Scheme 19).[70]



60 **61**

Scheme 19: Synthesis of benzoxazolones from pyridine analogues

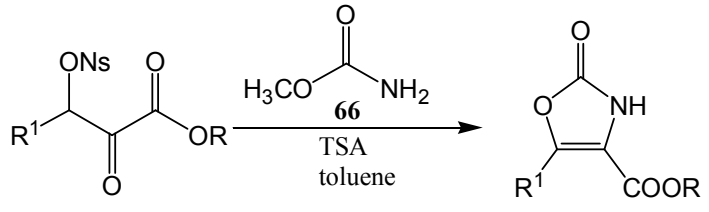
N. Leo Benoiton et al reported the stirring of EDC (N,N'-dicyclohexylcarbodiimide) with N-alkoxycabonylamino acids (Boc-valine) **62** at 0°C for 30 minutes give acylisourea **63**. Further its cyclisation afforded 2-alkoxy-5(4H)-oxazolone **64**. They found that compound **64** reacts with an amino acid ester responsible for obtaining the optically pure peptide even in the presence of salts and tertiary amine. The electronic effects of the 2-alkoxy substituent must also be responsible for the unusually low acidity of the hydrogen (C-2) in compound **64** (Scheme 20).[71]



62 **63** **64**

Scheme 20: Synthesis of oxazolones from Boc-valine

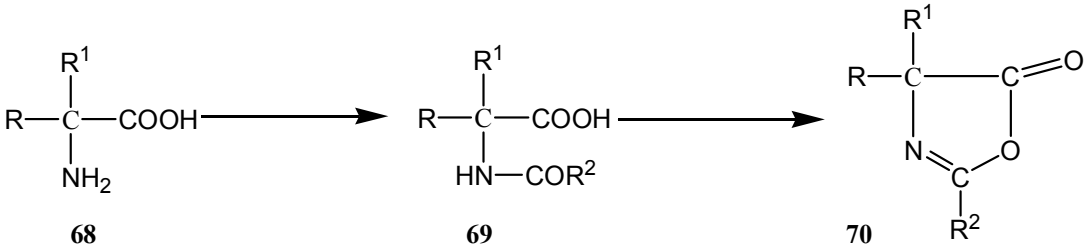
Robert V. Hoffman et al reported the oxazolone **67** in good yields by refluxing of 3-nosyloxy-2-ketoesters **65** with methyl carbamate **66** and TSA (10%) in toluene for 15h. They were found that acid-catalyzed addition of the nitrogen atom of methyl carbamate **66** to the carbonyl group of **65** afforded 4-carboethoxy-4-oxazolin-2-ones **67** (Scheme 21).[72]



65 **67**

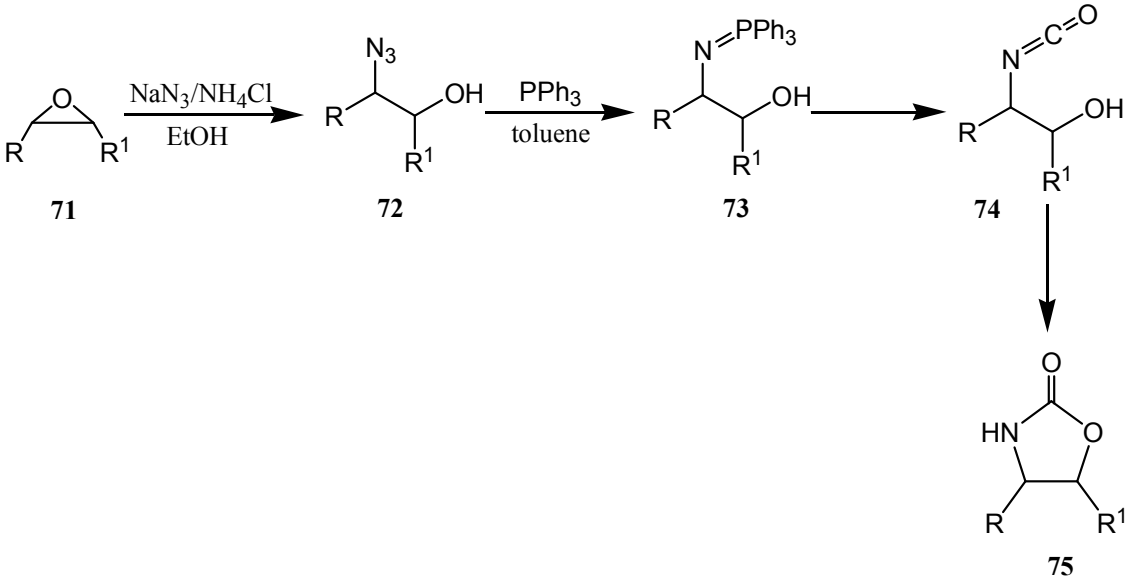
Scheme 21: Synthesis of oxazolones from 3-nosyloxy-2-ketoesters

Patented by Shunichi Yamada et al that the acylation of DL-α-alkyl-α-amino acid **68** resulted in the formation of oxazolone **70** *via* dehydration of compound **69** involving the cyclization and subsequent elimination of H_2O from the intermediate compound **69** (Scheme 22).[73]



Scheme 22: Synthesis of oxazolones from DL-α-alkyl-α-amino acid

G. Madhusudhan et al reported a facile one-pot procedure for the synthesis of oxazolone **75**. They found that oxazolone **75** was easily accomplished by the stirring of 1,2-azido alcohols **72** with Ph_3P under mild pressure of CO_2 (5-6psi) at 0°C via two intermediates **73** and **74**. Further 1,2-azido alcohols **72** was formed by ring opening of oxiranes **71** in the presence of NaN_3 and NH_4Cl (Scheme 23).[74]

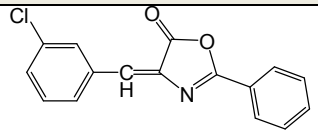
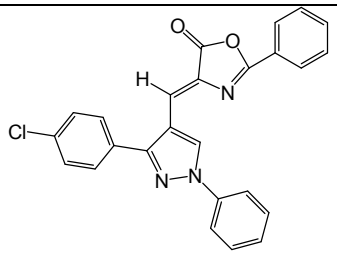
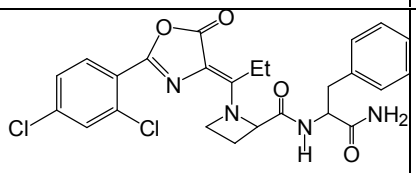
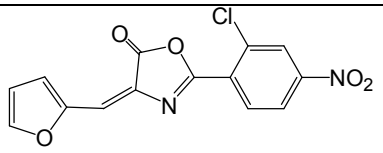
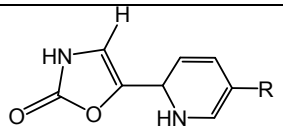
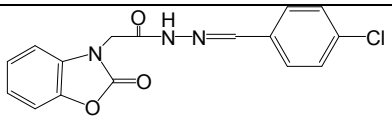
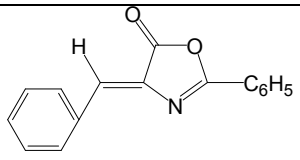
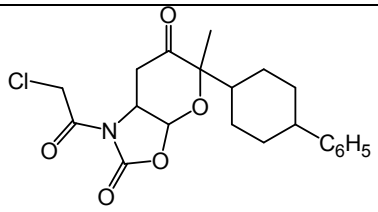
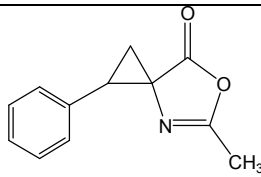


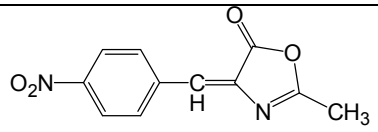
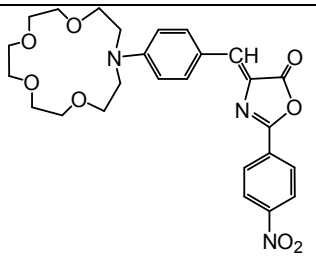
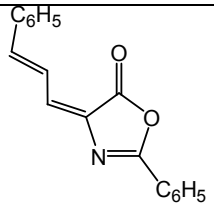
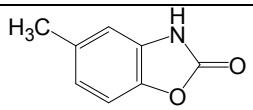
Scheme 23: Synthesis of oxazolones using oxiranes

PHARMACOLOGICAL ACTIVITY

Oxazolone nucleus has various pharmacological activities. Some of which are summarised for exhibitive their potent therapeutics use. Mainly substitutions at the C-4 position and C-2 position in oxazolone ring may affect the activity to a certain extent. N-substituted oxazolones also used as clinical and therapeutic agents.

Table 1: Various pharmacological activities of Oxazolone

S. No.	Chemical Structure	Chemical Name	Activity	Refs.
1.		4-(3-Chloro-benzylidene)-2-phenyl-4H-oxazol-5-one	Antimicrobial	12
2.		4-[3-(4-Chloro-phenyl)-1-phenyl-1H-pyrazol-4-ylmethylene]-2-phenyl-4H-oxazol-5-one	Antimicrobial	18
3.		1-{1-[2-(2,4-Dichloro-phenyl)-5-oxo-oxazol-4-ylidene]-propyl}-azetidine-2-carboxylic acid[1-carbamoyl-2-(4-hydroxy-phenyl)-ethyl]-amide	Antimicrobial	60
4.		2-(2-Chloro-4-nitro-phenyl)-4-furan-2-ylmethylene-4H-oxazol-5-one	Antimicrobial	14
5.		5-Substituted (1,2-Dihydro-pyridin-2-yl)-3H-oxazol-2-one	Cardiotonic	29
6.		(2-Oxo-benzooxazol-3-yl)-acetic acid (4-chloro-benzylidene)-hydrazide	Analgesic, Anti-inflammatory	10
7.		4-Benzylidene-2-phenyl-4H-oxazol-5-one	Pesticidal	17
8.		1-(2-Chloro-acetyl)-5-methyl-5-(4-phenyl-cyclohexyl)-dihydro-pyrano[3,2-d]oxazole-2,6-dione	Antitumor	24
9.		5-Methyl-1-phenyl-6-oxa-4-aza-spiro[2.4]hept-4-en-7-one	Antiviral	22

10.		2-Methyl-4-(4-nitro-benzylidene)-4H-oxazol-5-one	Immunomodulator	28
11.		2-(4-Nitro-phenyl)-4-[4-(1,4,7,10-tetraoxa-13-aza-cyclopentadec-13-yl)-benzylidene]-4H-oxazol-5-one	Photophysical properties	27,32
12.		2-Phenyl-4-(3-phenyl-allylidene)-4H-oxazol-5-one	Tyrosine inhibitory properties	26
13.		5-Methyl-3H-benzooxazol-2-one	Nitric oxide synthase inhibitor	27

CONCLUSION

This review gives an overview of the various synthetic routes used to form a biologically rich oxazolone moiety. This paper proves to be helpful for further research work on the bioactive oxazolone ring and as an important tool for the development of better medicinal agents and newer compounds possessing oxazolone moiety that could be better agents in terms of efficacy and safety.

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