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Synthesis and Evaluation of Pyrazolone and Oxazolone Derivatives for Therapeutic Applications

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Abstract: Novel pyrazolone and oxazolone compounds are synthesised and their biological assessment is the focus of this work. The pharmacological potential of these heterocyclic compounds is highly promising, as they exhibit significant anti-inflammatory, antibacterial, and anticancer properties. To emphasise their potential as medication candidates, we talk about different synthesis processes, structure-activity connections, in vitro and in vivo assessments, and so on.

Keywords: Synthesis, Evaluation, Pyrazolone, Oxazolone Derivatives, Therapeutic Applications

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INTRODUCTION

Because of their versatility in pharmacology, heterocyclic compounds, especially pyrazolones and oxazolones, have been the subject of much research. Novel derivatives and their assessment in various therapeutic domains are the primary foci of this study.

Because of their wide range of biological effects, quinazoline derivatives have a special role in medicinal chemistry [1]. Take metolazone as an example; it's a medication for hypertension and congestive heart failure. The volume of blood drops and urine rises because it reduces the quantity of water the kidneys reabsorb into the bloodstream in an indirect way [2]. Sedative and muscle relaxant effects are caused by the agonist action of the quinazoline family GABAergic medications afloqualone and cloroqualone at the β-subtype of the GABA receptor [3-4]. One medication that helps with migraines is selurampanel, which is a member of the quinoxalinedione family of drugs and a competitive antagonist of the AMPA and kainite receptors [5]. Pneumocystis pneumonia has been treated with trimetrexate and leucovorin, two dihydrofolate reductase inhibitors. It is an analogue of methotrexate (MTX) that is effective against tumour cells that have developed resistance to methotrexate, whether that resistance is acquired or inherent [6]. In cases of cutaneous lymphoma, trimetrexate is also prescribed. [7]

Recent research has led to the development of many quinazoline derivatives for use in cancer treatment, including erlotinib, gefitinib, lapatinib, cancertinib, and vandetanib [8]. Many different kinds of tumours may be treated with erlotinib, a reversible tyrosine kinase inhibitor [9]. This includes pancreatic cancer, non-small cell lung cancer, and others. One of the main ways that gefitinib treats cancers like lung and breast is by blocking signalling in cells that have the epidermal growth factor receptor (EGFR) [10]. When administered to patients with certain thyroid cancers, the kinase inhibitor vadetanib inhibits the activity of

many cell receptors, including VEGFR, EGFR, and the RET-tyrosine kinase [11]. Lapatinib ditosylate is an oral medication that is effective against solid tumours. It blocks the pathways for both the HER2/neu and the epidermal growth factor receptor (EGFR), making it a dual tyrosine kinase inhibitor. Patients with advanced or metastatic breast cancer whose tumours overexpress HER2 (ErbB2) and those with HER2-positive breast cancer are treated with it in combination therapy. [12]

METHODOLOGY

In this experimental work, pyrazolone and oxazolone compounds will be synthesised, characterised, and their medicinal potential evaluated. The pharmacological applications were evaluated using a mix of computational, synthetic, and biological screening approaches. Chemical reagents and solvents of analytical grade and high purity will be used in the synthesis of oxazolone and pyrazolone derivatives. The compounds were produced by the optimisation of reaction parameters including temperature, duration, and catalysts during traditional and microwave-assisted organic synthesis processes. Chromatography and recrystallisation will be used to purify the substance.

We used nuclear magnetic resonance (1H and 13C), Fourier transform infrared spectroscopy, mass spectrometry, and FTIR to characterise and confirm the structures of the synthesised compounds. When necessary, X-ray diffraction (XRD) was used to determine crystal structures, and elemental analysis (CHN analysis) was used to confirm composition and purity. In order to predict the binding affinity of the synthetic compounds with target proteins, computational studies were conducted. These studies included molecular docking, ADMET studies to evaluate the drug-likeness and pharmacokinetic properties, and Density Functional Theory (DFT) calculations for electronic structure analysis and reactivity assessment.

In vivo and in vitro investigations were used to conduct biological assessments. Disc diffusion antimicrobial activity testing against bacterial and fungal strains, DPPH and ABTS radical scavenging activity assays for antioxidants, and MTT assays for cytotoxicity on cancer and normal cell lines will all be part of the in vitro research that will be conducted to assess the therapeutic potential. With proper ethical approval in place, we will undertake pharmacological evaluations of drugs that show promise in vitro utilising standard animal models in our in vivo research. The statistical analysis, which will be conducted using ANOVA and other relevant methods, will employ a significance threshold of $p < 0.05$ and will display the results as the mean ± standard deviation (SD).

Based on the findings, more research into clinical applications and mechanistic investigations is recommended, however the paper does note that there may be limits in the sample size and biological applicability. The methodology guarantees a thorough evaluation of the therapeutic potential of pyrazolone and oxazolone molecules using computational and experimental methods.

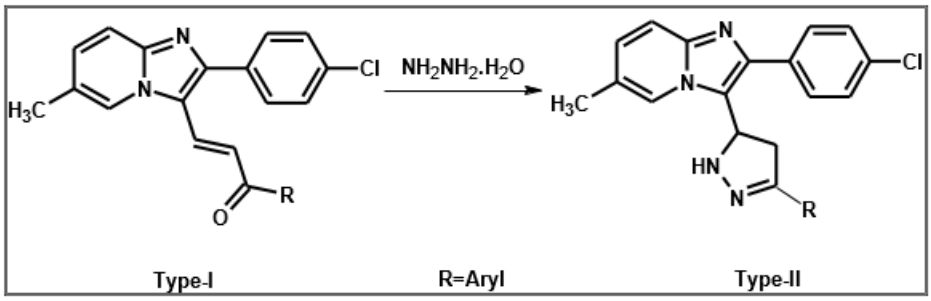
RESULTS AND DISCUSSION

Studies on Pyrazolines

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-(4'-CHLOROPHENYL) –6 – METHYL – 3 - (3" - ARYL - 4", 5" – DIHYDRO -1"H-PYRAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINES.

There is a vast spectrum of pharmacological actions shown for the pyrazoline nucleus. These findings

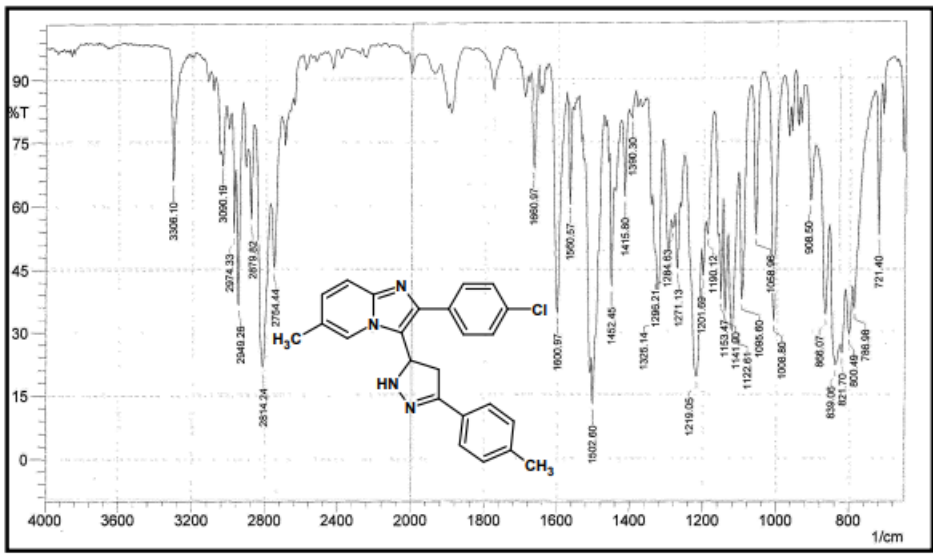
inspired new 2-(4'-chlorophenyl) pyrazoline compounds 2. ((3-aryl-4, 5-dihydro-1-H-pyrazol-5-yl)) By means of condensation, Type II pyridines of the 2-(4'-chlorophenyl)imidazo[1, 2-a] variety have been synthesised. 3 methyl-3-[1"-aryl-2"-propene-1"-one-3-yl] a methanol solution of -hydrazine hydrate and -imidazo [1,2-a]pyridine of type (I).



Element analyses, infrared, 1H nuclear magnetic resonance spectroscopy, mass spectroscopy, and thin-layer chromatography have all been used to characterise the synthesised compounds' composition.

At a dose of 50 µg/ml, all of the products were tested for their in vitro biological testing, which included antibacterial activity against Gramme positive and Gramme negative bacterial strains and antifungal activity against Aspergillus niger. We compared the synthetic chemicals' biological activity to those of conventional pharmaceuticals.

IR SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4"'-METHYLPHENYL)-4",5"-DIHYDRO-1"H-PYRAZOL-5"-YL] IMIDAZO [1, 2-a] PYRIDINE.

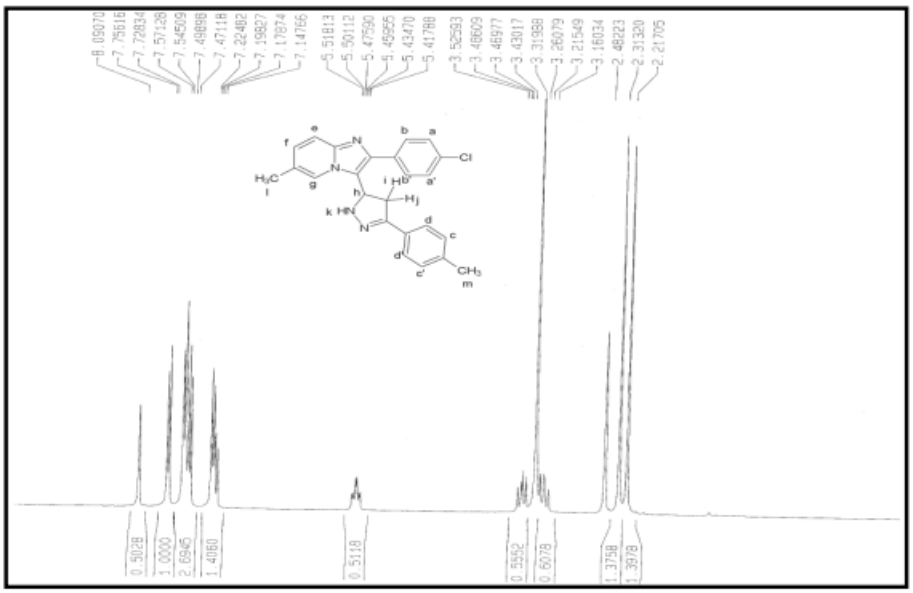


Instrument: SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1}(KBr disc).

Type	Alkane	Aromatic	Pyrazoline	Imidazo[1,2-a] pyridine	Halide

Vibretion mode		C-H str. (asym.)	C-H str. (sym.)	C-H def. (asym.)	C-H def. (sym.)	C-H str.	C=C str	C-H i.p. (def.)	C-N str	C=N str	N-H str	-CH-$(CH)_2$ str.	C-N str.	C=N str.	C-Cl str.
Frequency in cm^{-1}	**Observd**	2949	2879	1452	1390	3090	1502	1122	1095	1560	3306	2754	1058	1600	721
	Reported	2990-2850	2880-2860	1470-1435	1390-1370	3090-3030	1600-1450	1300-1100	1230-1020	1650-1550	3320-3140	2850-1790	1220-1020	1612-1593	800-600
Ref.		648	"	"	"	"	"	"	649	"	"	"	"	"	"

NMR SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4"'-METHYLPHENYL]4",5"-DIHYDRO-1"H-PYRAZOL-5"-YL) IMIDAZO [1, 2-a] PYRIDINE.

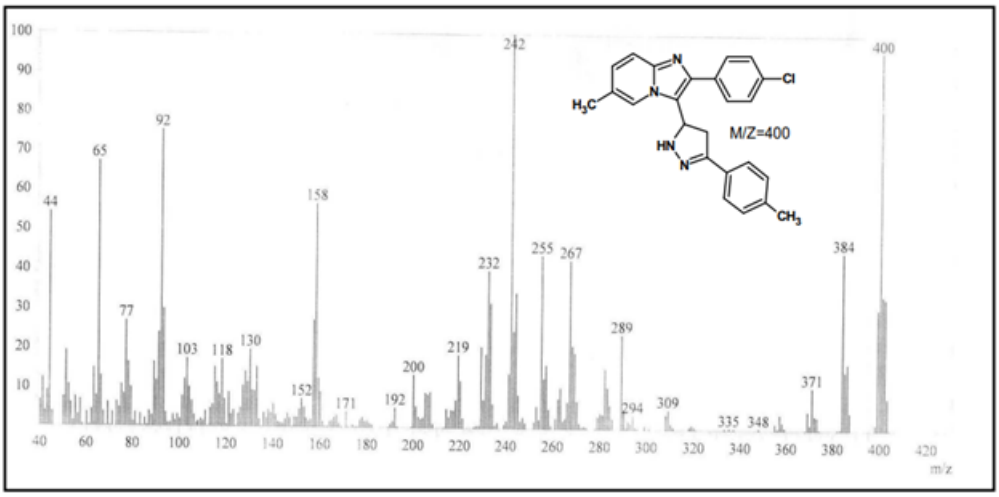


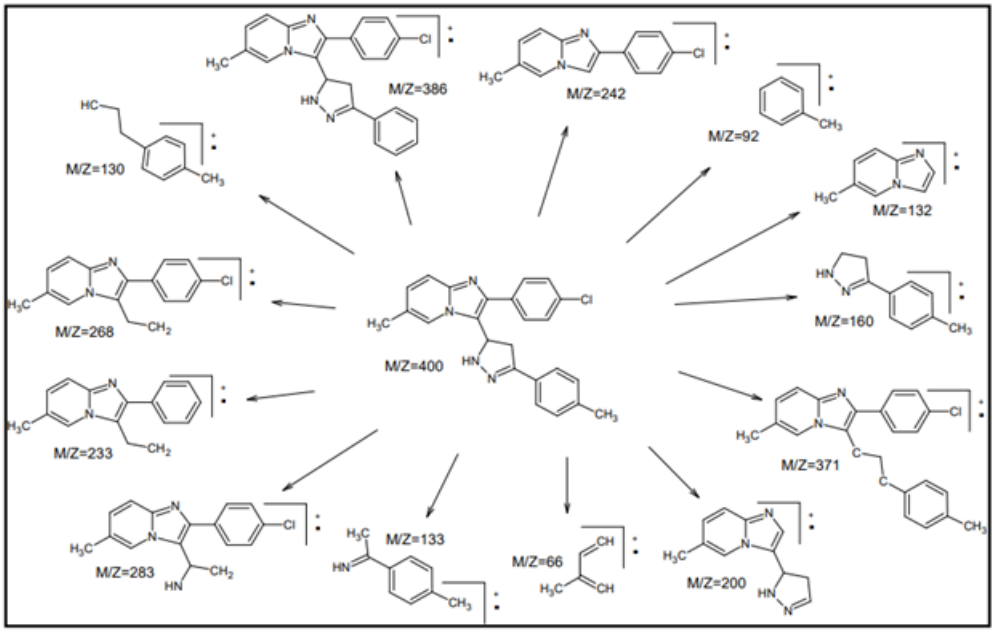
Internal Standard: TMS;Solvent :$CDCl_3$; Instument Bruker Spectometer (300 MHz)

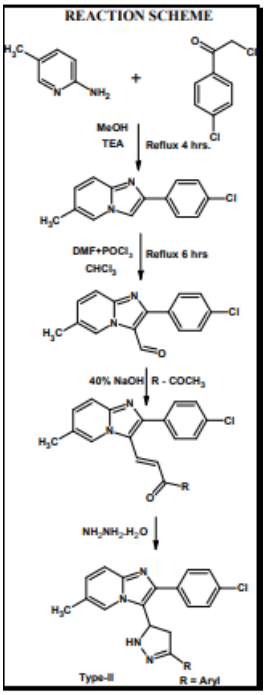
Signal Position (δppm)	Relative No. of protons	Multiplicity	Inference
2.21	3H	Singlet	Ar-CH_3(k)
2.31	3H	Singlet	Ar-CH_3(l)
3.16-3.31	1H	ddoublet	Ar- H(i)

3.43-3.52	1H	ddoublet	Ar-H(j)
5.41-3.51	1H	quatret	Ar-H(h)
7.14-7.17	1H	doublet	Ar-H(f)
7.19-7.22	2H	doublet	Ar-H(cc')
7.47-7.57	5H	multiplate	Ar-H(aa',bb',e)
7.72-7.75	2H	doublet	Ar-H(dd')
8.09	1H	Singlet	Ar-H(g)

MASS SPECTRAL STUDY OF 2-(4'-CHLOROPHENYL)-6-METHYL-3-[3"-(4"'-METHYLPHENYL)-4",5"-DIHYDRO-1"-H- PYRAZOL-5"-YL] IMIDAZO [1, 2-a] PYRIDINE.



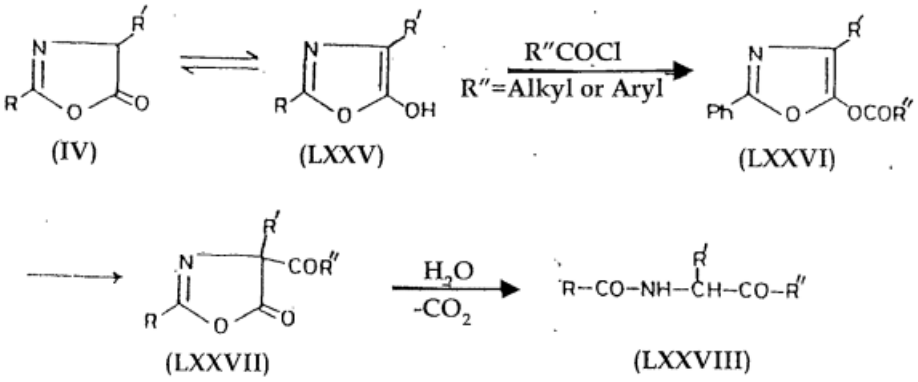




Studies on oxazolone derivatives

Reactions at the C-4 hydrogen atom of 2-oxazolin-5-ones;

Saturated 2-oxazolin-5-ones with C-4 hydrogen atom exhibit tautomerisation and they react as CH-active compounds.



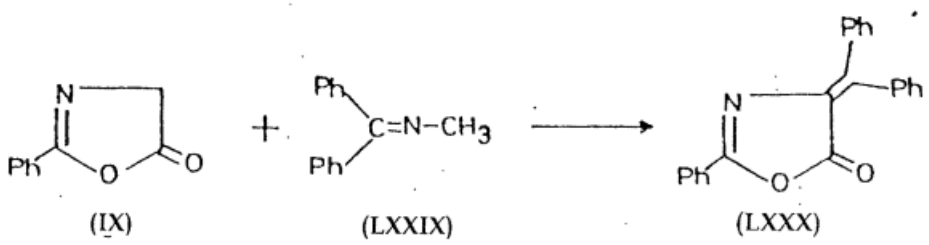
(IV) (LXXV) (LXXVI)

(LXXVII) (LXXVIII)

The hydroxy group of 5-hydroxy oxazoles (LXXV) may be trapped as o-acetyl derivatives, which undergo base-assisted O —C Iransaeylation to provide product(LXXVII). Many oilier valuable compounds, including fiuorinated ketones (LXXVIII, R"= CH2=CHCF2)7'S, have been synthesised using this transition, which is based on the Darkin-West reaction.

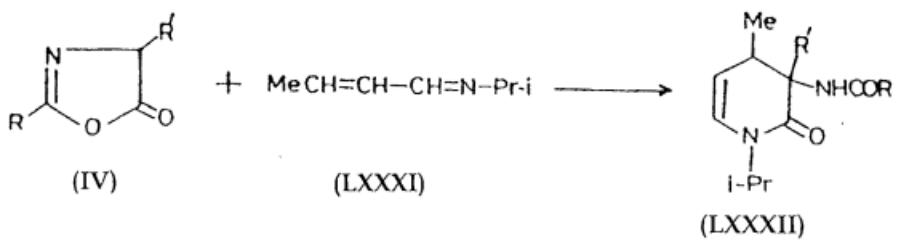
Under phase-transfer conditions, 4-substituted-2-oxazolin-5-ones are C-4 alkylated and arylated; in contrast, 4-unsubstituted 2-oxazolin-5-one(IX) yields unsaturated 2-oxazolin-5-ones when treated with aldehydes, ketones, and amidines; this process has previously been investigated.

Amino pyrimidines and amino pyridazines are sources of various amidines that have found use. It has been discovered that 4-unsubstituted2-oxazolin-5-ones (IX) and N-methyl benzophenone imine (LXXIX) can undergo condensation to produce 4-diphenyl methylene-2-phenyl-2-oxazo!in-5-one (LXXX).



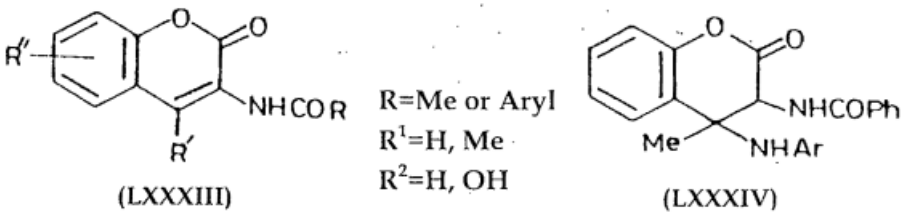
(IX) (LXXIX) (LXXX)

When bis-oxazolones undergo thermal breakdown, the resulting 2,4-DiaryI-2-oxazolin-5-on-4-yI radical reacts with 5-morpholino-4,5- dihydro-4-methyIene-l,2,3-triazoles, and 3-aryl-4,5-d. the equivalent 2,4-diaryl-4-(4-heteromethylene)-2-oxazolin-5-ones from ihydro-4'- methylene-5'-morpholino-isooxazoles.
When CH-active 2-oxazolin-5-ones react with bifunctional compounds that include electrophilic and nucleophilic centres, the result is heterocycles with an expanded ring. An example of this is the formation of tetrahydropyridones (LXXXII) from azadiene (LXXXI) by means of intramolecular aminolysis of the 1,5-bond and Michael addition.



(IV) (LXXXI) (LXXXII)

The equivalent 3-benzoylamino coumarins (LXXXIII, R=Ph) are produced via a similar reaction with salicyldehyde, 2-hydroxy acetophenones, and their imines. The process begins with Naryl-2-hydroxy acetophenone imine as the substrate and ends with dihydrocoumarins (LXXXIV) as an intermediate. It should be mentioned that the main products of the isothiocyanate-mediated condensation of N-acylglycines with salicyldehyde are 3-N-acylaminocoumarins (LXXXIII, R=Me, R'=H).



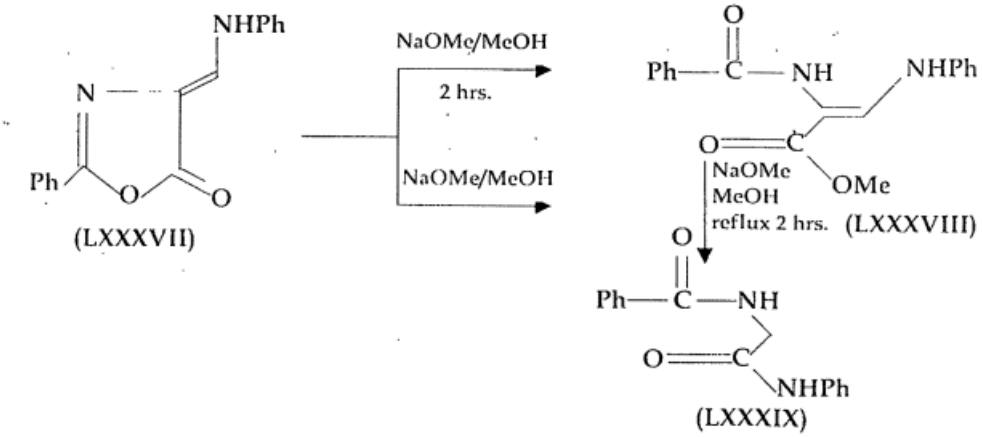
(LXXXIII) (LXXXIV)

In a well-converted reaction between oxazolone (IV) (R=Ph, R'=Me) and imine, 3-lactam (LXXXV) is produced. On the other hand, when 4-unsubstituted 2-(lbenzoylaminostyryl)-2-oxazolin-5-one reacts with N-benzylidene aniline in benzene with glacial acetic acid, 2-(lbenzoylamino styryl)-4-benzylidene-2-oxazolin-5-one (LXXXVI) is produced instead of the desired 3-lactam derivative.

(LXXXV) (LXXXVI)

R = Me, R′ = Alkyl or Aryl

Sodium methoxide in methanol reacts with 4-amilinomethylene-2-phenyl-2-oxazolin-5-one to produce N-benzoylaminoacetamilide (LXXXIX). Additionally, product (LXXXIX) may be obtained from methyl 3-anilino-2-benzoylamino propeonate.



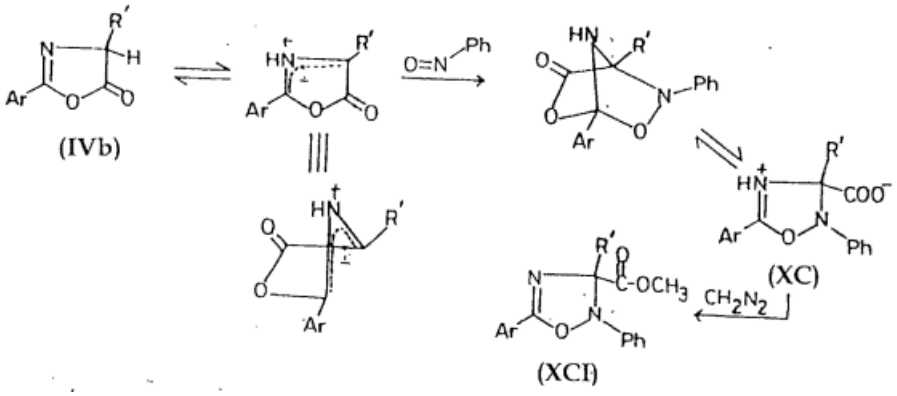
(LXXXVII) (LXXXVIII)

(LXXXIX)

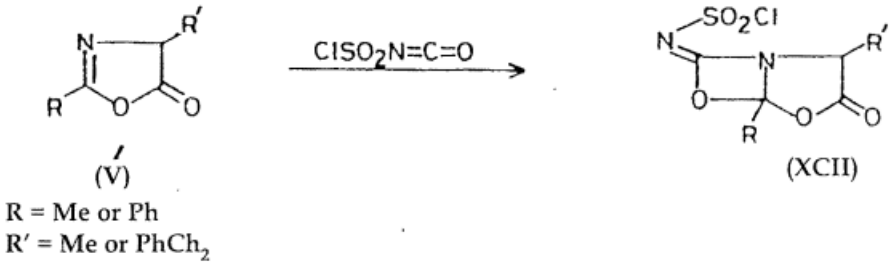
Cycloaddition Reactions:

1,3-dipolar cycloaddition reactions are carried out by 4-substituted-2-oxazolin-5-ones. It has been noted

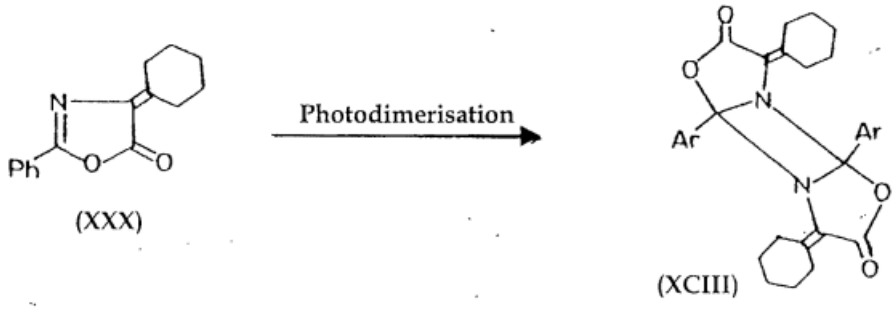
that dimethyl acetylene di-carboxylate can be enhanced with proline-based oxazolone, for instance. It is worth noting that the mesoionic form of oxazolone (IVa) acts as a 1,3-dipole, while the nitroso group acts as a dipolarophile. At room temperature, the 1,3-dipolar cycloaddition of 2-oxazolin-5~one (IVb, R'=Aryl) with nitroso benzene in xylene or dimethyl formamide produces l,2,4-oxadiazol-4-ine-3-carboxoxylic acid (XC) regiospecifically. The XCI is converted to its methyl ester (XCI) through the treatment with diazomethane. Imidazole derivatives are produced by adding mesoionic 2-oxazolin-5-ones generated from amethyl/phenyl N-acylsarcosin to N-benzene sulphonylaldemines.



The cycloadduct(XCII) is a product of the hydrolysis of chlorosulphonylisocyanate and 2-oxazolin-5-one; its structure is based on the creation of a-N-acylamino acid.



The products of the reaction between superoxide and 4-monosubstituted, 4,4-disubstituted, and bis-oxazolin-5-ones in an aprotic solvent are distinct. Oxidation and subsequent alteration provide dibenzamide and tetraphenyl pyrazine, respectively, from 2,4-diphenyl-2-oxazolin-5-one and its biscompound, which in turn create potassium assisted ion radicals. The 1,2 bond of 2-oxazolin-5-ones is the subject of certain uncommon cycloaddition reactions. This means that (XXX) has been solid photodimerized.



CONCLUSION

The pharmacological characteristics of the oxazolone and pyrazolone derivatives that were produced were encouraging. Additional structural alterations and clinical assessments should be the focus of future research to better optimise their therapeutic characteristics.

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