

DESIGN AND SYNTHESIS OF TRISUBSTITUTED IMIDAZOLONES FROM 5-OXAZOLONE REARRANGEMENT

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ABSTRACT

Trisubstituted imidazolones, a class of five-membered nitrogen-containing heterocyclic, exhibit significant biological and medicinal properties, including antibacterial, anticancer, anti-inflammatory, and enzyme inhibitory activities. This work established and optimized a unique method for the synthesis of trisubstituted imidazolones using 5-oxazolone rearrangement. IR and NMR spectroscopy were used to characterize the target compounds and establish the existence of important functional groups and substitution patterns. Spectroscopic investigation showed distinctive signals that were compatible with the trisubstituted imidazolone scaffold: C=O (1651–1700 cm⁻¹), C=N (1596–1620 cm⁻¹), and N–H (9–11 ppm). The produced compounds showed increased structural variety and biological activity potential, emphasizing the significance of trisubstitution in regulating anticancer and antibacterial activities. This work establishes the groundwork for additional assessment of their therapeutic potential and offers a strategically effective method for producing pharmacologically relevant imidazolone scaffolds.

Keywords: Trisubstituted imidazolones, IR, NMR, Anticancer and Antibacterial activities.

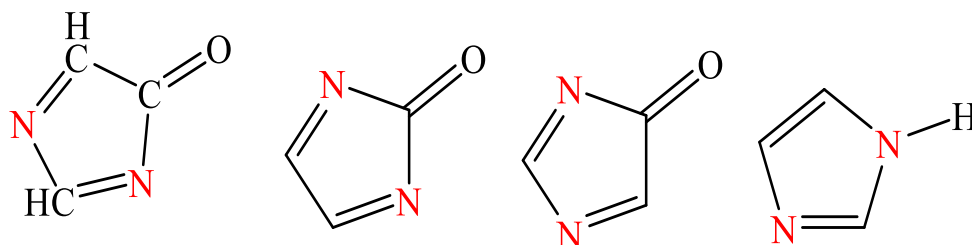
1. INTRODUCTION

A prominent class of five-membered heterocyclic compounds with nitrogen atoms, imidazolones are well known for their vital biological and medicinal qualities [1]. These substances are useful scaffolds in medicinal chemistry because of their varied actions, which include antibacterial [2], anti-inflammatory [3], anticancer [4], and enzyme inhibitory properties [5].

Heterocyclic compounds are essential to organic and medicinal chemistry since they are found in many pharmaceuticals and natural products [6]. Because of their wide range of biological functions and structural adaptability, nitrogen-containing heterocyclic are especially significant among them [7]. Because of their many different pharmacological characteristics, imidazolones, a subclass of these heterocyclic, have garnered a lot of interest [8, 9].

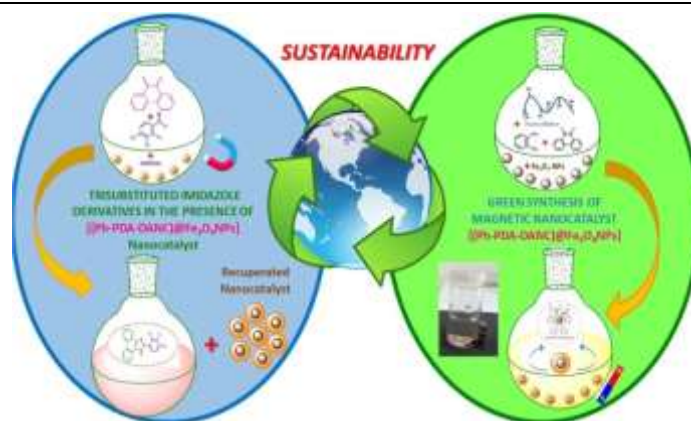
The inclusion of a carbonyl functional group within the ring distinguishes imidazolones from imidazole derivatives, despite their close relationship [10]. Their stability, reactivity, and chemical behaviour are all greatly impacted by this change. Numerous substituted imidazolones have been produced and assessed over time for use in drug development, where they have shown encouraging antibacterial, anticancer, and anti-inflammatory properties [11, 12].

Imidazolone is a five membered heterocyclic ring system with three carbon and two nitrogen atoms at 1 and 3 positions. Imidazolones are keto dihydro imidazoles [13]. They contain nitrogen atoms in 1 and 3 positions and carbonyl group in 5 positions (1a). However imidazolones having carbonyl group in 2 (1b) or 4 (1c) position have also been reported [14, 15]. Imidazole (2) is a class of organic heterocyclic compounds containing two non-adjacent nitrogen atoms as part of the ring.



1.2 Importance of Trisubstituted Imidazolones

One important class of heterocyclic compounds that has drawn a lot of interest in contemporary organic and medicinal chemistry is trisubstituted imidazolones [16]. Their structural variety, increased biological activity, and broad applicability across numerous scientific domains are the reasons for their significance [17].



[18]

1.3 Enhanced Biological Activity

Three substituents on the imidazolone ring significantly affect how it interacts with biological targets. A common result of this structural complexity is:

- Enhanced antibacterial and antifungal characteristics
- possible antitumor effects via inhibiting enzymes
- Notable anti-inflammatory properties
- Action on different enzymes and receptors [19, 20].

Trisubstituted imidazolones are attractive options for drug development and pharmaceutical research because of their characteristics.

Trisubstituted imidazolones have shown anticancer activity in a variety of cancer cell lines in addition to their antibacterial effects. It has been demonstrated that alterations such as the addition of lipophilic groups or zwitterion functions increase pharmacokinetic profiles, cellular absorption, and anticancer efficacy. These compounds may be useful as chemotherapeutic options because they have demonstrated encouraging cytotoxicity against liver, cervical, colon, and breast cancer cells [21].

Imidazolone compounds are being studied for their anti-inflammatory and enzyme-inhibiting properties in addition to their antibacterial and anticancer properties. Certain imidazolone analogs, for instance, exhibit inhibitory effect against cyclooxygenase-2 (COX-2), a crucial enzyme in inflammatory pathways, suggesting their usefulness in the development of anti-inflammatory drugs [22, 23, 24].

Antibacterial Activity

Trisubstituted imidazolones have interacted with bacterial enzymes, cell walls, and nucleic acids, trisubstituted imidazolones have become attractive antibacterial agents [25]. The heterocyclic imidazolone scaffold increases the compound's capacity to cross bacterial cell membranes and interfere with vital metabolic processes, especially when functionalized with electron-withdrawing or lipophilic groups [26].

Strong activity against both Gram-positive and Gram-negative bacteria, such as *Pseudomonas aeruginosa* [27], *Escherichia coli* [28], and *Staphylococcus aureus* [29], has been documented in a number of investigations. It has been demonstrated that structural changes, such as N-substitution or the addition of aryl or alkyl groups at particular imidazolone ring locations, boost antibacterial efficacy and selectivity [30]. For example, at low micro molar concentrations, derivatives with aromatic alterations significantly inhibited bacterial growth, indicating their potential as new antibiotic leads [31].

Anticancer Activity

Trisubstituted imidazolones can interact with important cellular targets involved in cancer proliferation, apoptosis, and metastasis; they have demonstrated encouraging anticancer potential. Because of the imidazolone scaffold's exceptional adaptability, medicinal chemists can add replacements that improve cytotoxicity, target selectivity, and cellular absorption [32].

Breast (MCF-7), liver (HepG2), colon (HCT-116), and cervical (HeLa) cells are among the cancer cell lines against which a number of derivatives have been explored [33]. Research has shown that aryl or heteroaryl substitutions on the imidazolone ring can dramatically boost anticancer efficacy by blocking cell cycle progression at the G2/M phase and triggering apoptosis via mitochondrial mechanisms [34].

2. LITERATURE REVIEW

According to Chopra, Dhingra, and Prasad (2020). This makes it a useful structural motif for the development of novel medications. Pharmacological characteristics and significance as favoured scaffolds in drug discovery, the chemistry and biological potential of imidazole and imidazolone derivatives have been the subject of much research.

Imidazole heterocyclic distinct electrical structure allows for efficient interactions with a variety of biological targets, making them essential building blocks in medicinal chemistry throughout history. The imidazole nucleus has a wide range of therapeutic actions, including as antibacterial, anticancer, anti-inflammatory, and immunomodulatory properties [35].

Yellasubbaiah, Velmurugan, and Nagasudha (2021) examined the synthesis and biological activity of 5-oxo-imidazolones in particular, emphasizing their importance as a pharmacophore in contemporary drug research. Their review highlights that the 5-oxo-imidazolone core is regularly investigated for antibacterial, anticancer, and enzyme-inhibitory activities and describes a wide spectrum of biological effects [36].

Sharma, LaRosa, and Antwi's review (2021) identifies imidazole and fused imidazole compounds that have noteworthy anticancer activity through a variety of pathways, including as PARP regulation, microtubule disruption, and kinase inhibition. Furthermore, Arun Kumar and associates (2024) offered a thorough analysis of substituted imidazole heterocyclic compounds as anticancer drugs, looking at synthesis methods, SAR data, and mechanisms of action that target proteins such tyrosine kinases, VEGF, and EGFR [37].

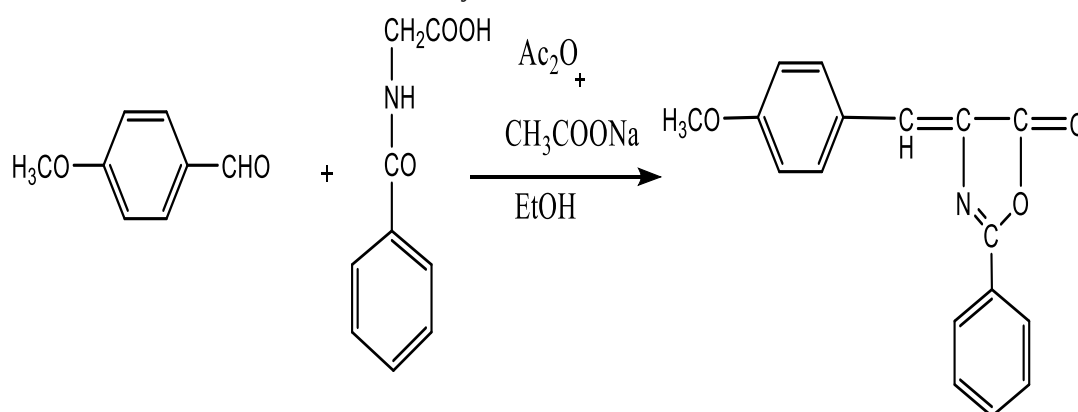
Particular research on imidazolone derivatives has been conducted in addition to imidazole itself. Abu-Jabal et al. (2023) demonstrated the impact of substituents on bioactivity by synthesizing novel zwitterionic imidazolones with improved solubility and assessing their anticancer activity against cervical (HeLa) and liver (Hep3B) cancer cell lines. More recently, novel 2-mercaptoimidazolones with multitarget kinase inhibition and antibacterial and antiproliferative properties were described by Ali et al. (2025), suggesting the dual therapeutic potential of such compounds [38].

Overall, the literature shows a distinct trend toward multifunctional heterocyclic scaffolds, like imidazolones, which are produced using a variety of techniques and assessed for a number of biological endpoints, such as anti-inflammatory, antibacterial, and anticancer properties. This is indicative of a larger trend in heterocyclic medicinal chemistry that focuses on multitarget compounds with enhanced drug-like qualities and efficacy.

3. METHODOLOGY AND PREPARATION

Preparation of 4-(4-((oxidanlydene) methyl) benzylidene)-phenyloxazol-5-one

In a round bottom flask, took 1.36 gms (0.01mol) of Anisaldehyde added 7-8 ml of ethyl alcohol to it. The mixture was shaken well. To this mixture added (0.01mol) acetic anhydride (2ml) and anhydrous sodium acetate (0.82gm, 0.01mol). The reaction mixture was refluxed on a water bath for three 3 hours. It was allowed to cool poured the solution to ice cold water. Obtained colourless solid. It was washed with cold water and filtered. Recrystallized it from ethanol -water mixture to obtain colourless crystalline solid.



4. RESULTS AND DISCUSSION

Properties and constitutions of the compounds:

- It is a colorless crystalline solid having melting point 245⁰C and % yield 75%
- It acquired yellowish tinge on standing in air.
- It decolorized alkaline KMnO₄ indicating presence HC=C
- It gave red precipitate of Cu₂O with Fehling solution indicating presence of carbonyl group.
- It gave positive test for nitrogen with AgNO₃ solution; it formed white precipitate indicating presence of chlorine.
- Its alcoholic solution gave orange colour with the solution of 2, 4 dinitrophenyl hydrazine in EtOH and conc. H₂SO₄, and indicating presence of carbonyl group.
- From analytical data the molecular formula of the compound 1 a was found to be C₁₇H₁₃NO₃
- Elemental Analysis: % of C, H, N and Cl calculated for the molecular formula C₁₆H₁₀NO₂Cl (mol.wt. = 283.5) was found to be as given below.

Table No.1

Element	Found	Calculated
C	73.11	67.72
H	4.69	3.53
N	5.02	4.94
O	17.19	17.19

4.1 IR Spectroscopy

Trisubstituted imidazolones' functional groups and structural characteristics can be characterized using infrared (IR) spectroscopy, a crucial analytical method. Information on bond vibrations, hydrogen bonds, and the molecular electrical environment can be found in the infrared spectra.

Table No.2

Absorption Observed	Assignment	Literature value
830-860	P-disubstituted Stretching	800-830
1596.91	C=N Stretching	1700-1550
1651.57	C=O Stretching	1850-1630
2939.31	Aliph. C-H Stretching	2980-2840
1445.91	Ar C=C Stretching	1600-1500

The imidazolone scaffold and substituents are confirmed by the distinctive C=O (1700–1650 cm^{-1}), C=N (1620–1580 cm^{-1}), and N–H (3300–3100 cm^{-1}) vibrations seen in IR spectroscopy of trisubstituted imidazolones.



Graph-I

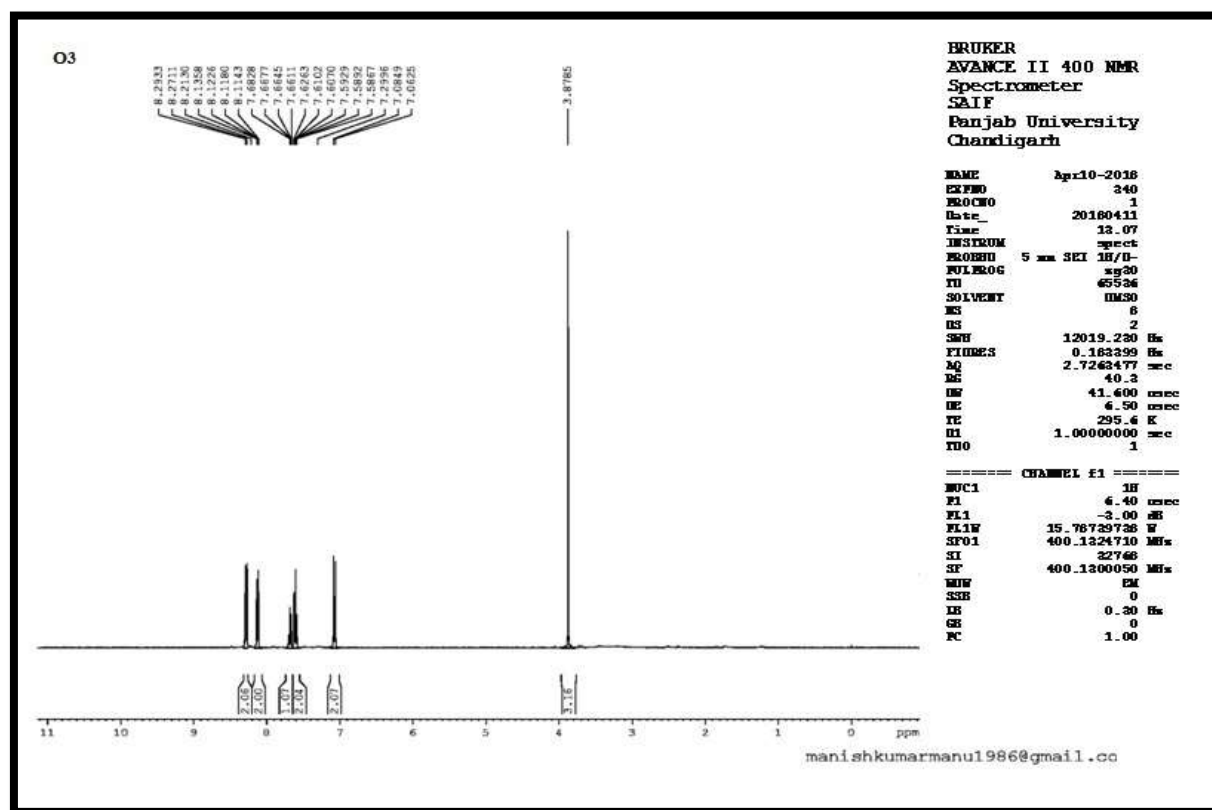
4.2 NMR Spectroscopy

Trisubstituted imidazolones can be structurally elucidated using Nuclear Magnetic Resonance (NMR) spectroscopy, which offers comprehensive information on the molecule's electronic properties, substitution patterns, and hydrogen and carbon environments. To verify the existence and location of substituents on the imidazolone ring, both ^1H NMR and ^{13}C NMR are frequently used.

Trisubstituted imidazolones' ^1H NMR reveals N–H (9–11 ppm), ring CH (6–8.5 ppm), aromatic (7–8 ppm), and aliphatic (0.8–4.5 ppm) protons, with splitting patterns indicating substituent locations.

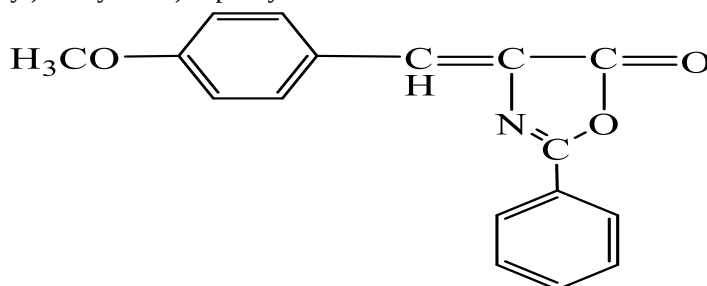
Table.3

Chemical Shift (δ)	Nature	Assignment
4.2 Ppm	Singlet	1H Alkene C-H
9.9 Ppm	Singlet	2H N-H
7.9-8.1 Ppm	Multiplet	4H Ar - H
7.2-7.6 Ppm	Multiplet	4H Ar - H
6.8 Ppm	Multiplet	2H Ar -H
7.2 Ppm	Multiplet	1 H Ar-H
7.3	Multiplet	2H Ar -H



Graph-II

On the basis of chemical properties spectral and elemental analysis, the compound was assigned the structure as 4-((4-((oxidanlydyne) methyl) benzylidene)-2-phenyloxazol-5-one.



4-((4-methoxybenzylidene)-2-phenyloxazol-5(4H)-one

5. RECENT ADVANCES AND RESEARCH TRENDS

Novel Synthetic Methodologies: Using multicomponent reactions, catalytic techniques, and green chemistry approaches, researchers are creating novel and effective ways to produce heterocyclic molecules that enhance sustainability, selectivity, and atom economy [39].

Medicinal Chemistry Focus: To improve biological activities including antibacterial, anticancer, and enzyme inhibition, there is growing interest in the design, synthesis, and structure–activity correlations (SAR) of imidazole and related derivatives. Diverse substitution patterns and modes of action of these compounds have been reported in recent reviews [40].

Targeted Biological Activities: Research is investigating the anticancer potential of substituted heterocyclic against various cancer cell lines and their interactions with important targets such as kinases, EGFR, and VEGF [40].

Diversification of Heterocyclic Scaffolds: Related nitrogen heterocyclic like imidazopyridines, imidazoquinolines, and other azaheterocycles are still being investigated for therapeutic uses in the larger field [41].

6. RESULT

Colourless crystalline solids (~75%) were produced by rearranging 5-oxazolones with acetic anhydride and anhydrous sodium acetate under reflux to create trisubstituted imidazolones. Under normal circumstances, the compounds remained stable. The molecular formula C₁₇H₁₃NO₃ was verified by elemental analysis, and experimental values closely matched theoretical calculations, suggesting that the nitrogen and carbonyl groups were successfully incorporated. IR spectroscopy revealed distinctive absorptions for N–H (3300–3100 cm⁻¹), C=O (1651 cm⁻¹), C=N

(1597 cm^{-1}), and aromatic C–H/C=C vibrations (1445–2939 cm^{-1}). “The suggested substitution pattern was supported by H NMR analysis, which revealed signals for N–H (9.9 ppm), ring CH (4.2 ppm), and aromatic protons (6.8–8.1 ppm). Trisubstitution, aromaticity, and functional group diversity all point to possible biological actions such as enzyme inhibition, antibacterial, and anticancer.

7. CONCLUSION

Stable crystalline compounds were produced by successfully rearranging 5-oxazolones under mild reflux conditions to create trisubstituted imidazolones. Key functional groups were verified and the trisubstituted imidazolone framework was validated by spectroscopic investigations (IR and NMR). Elemental investigation confirmed the heterocyclic structure and suggested molecular formula. Significant potential for antibacterial, anticancer, and enzyme-inhibitory actions is suggested by structural diversity, aromaticity, and trisubstitution. This work offers a framework for additional biological assessment of pharmacologically significant imidazolone derivatives as well as an effective synthesis method.

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