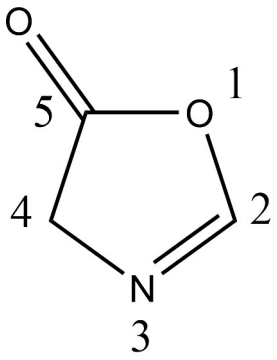
Chapter V
Biologically active Oxazolone derivatives

An efficient synthesis of some novel oxazolone derivatives showing cytotoxicity behaviour

5.1. Introduction

One of the five-membered heterocyclic compounds, oxazolones exists in three isomeric forms: one based on the position of the carbonyl group, and the other two based on the position of the double bond [1,2].



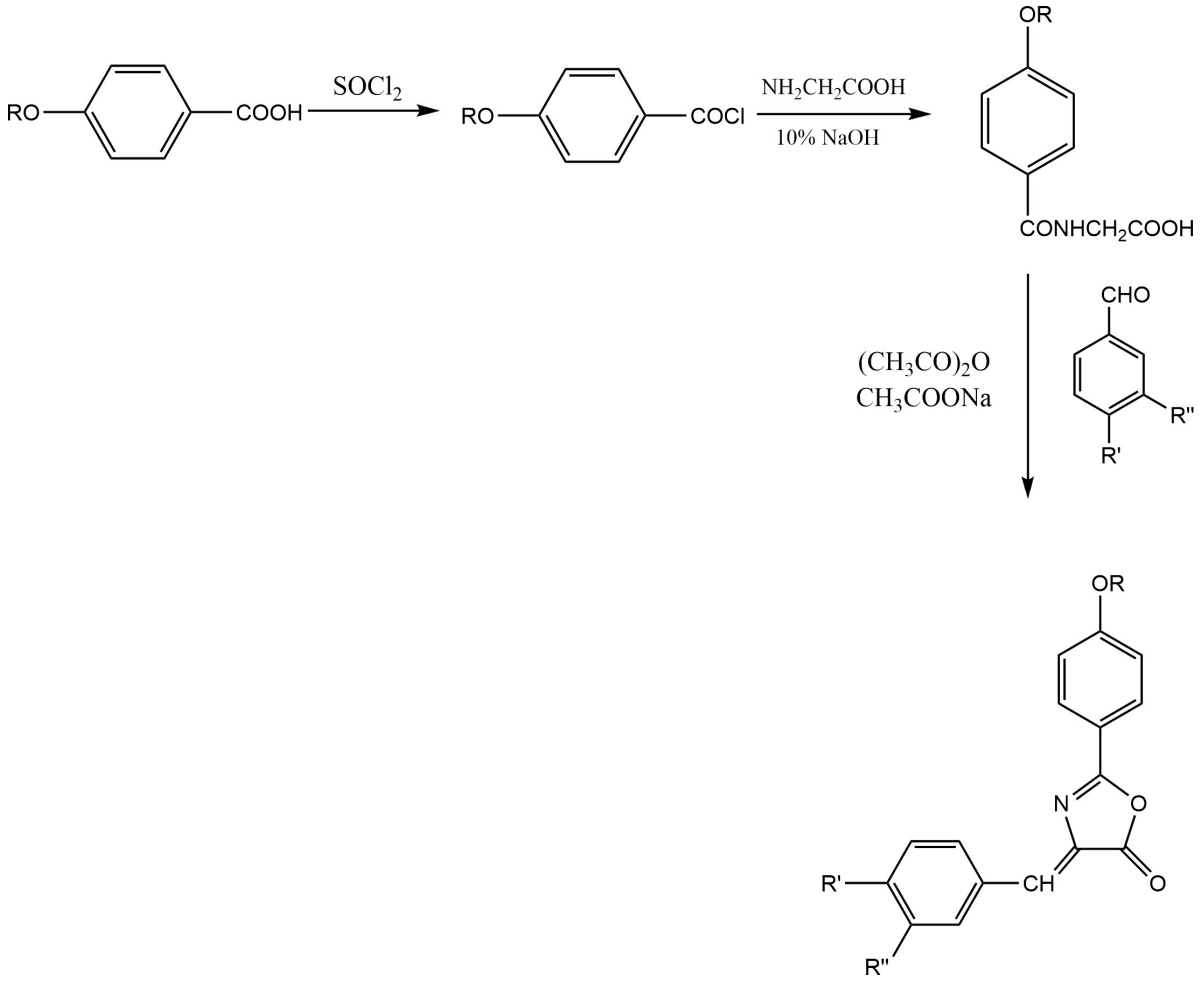
5-(4*H*)-oxazolone

Figure 5.1: Structure of 5-(4*H*)-oxazolone

Oxazolone was synthesized by Plochl in 1883 using benzaldehyde and hippuric acid, with acetic anhydride present [3, 4]. Further, in 1893, Friedrich Gustav Carl Emil Erlenmeyer discovered the first accurate structure of oxazolone by reacting benzaldehyde with N-acetylglycine in the presence of sodium acetate and acetic anhydride. The reaction proceeds via Perkins condensation and initial cyclization of N-acetylglycine, producing Erlenmeyer azlactones [5,6]. From the literature, several methods were employed for the synthesis of oxazolone derivatives but the most efficient method was developed by Erlenmeyer azlactone synthesis [3,5,6]. The glycine moiety is synthesized intramolecularly via condensation in the presence of dehydrating agents such as carbodiimides and acetic anhydride [3,7]. The general mechanism of formation of oxazolone is elucidated in Scheme 5.14 [8]. Several catalysts have been reported to improve yield, including zinc oxide [9,10], antimony pentafluoride [11], dodecatungstophosphoric acid, samarium catalysts, and ruthenium chloride [2], as well as solvent conditions including chloroform, methanol and ethanol, and DMF [12].

The synthesis of 4-benzylidene-2-phenyloxazol-5(4*H*)-one from the starting material was described by Tandel *et al*. (Scheme 5.1). Using 4-substituted benzoic acid, thionyl chloride,

and glycine, 4-substituted benzoyl glycine was formed. The necessary oxazolone derivatives are then formed by adding the proper aldehyde, acetic anhydride, and sodium acetate [13].



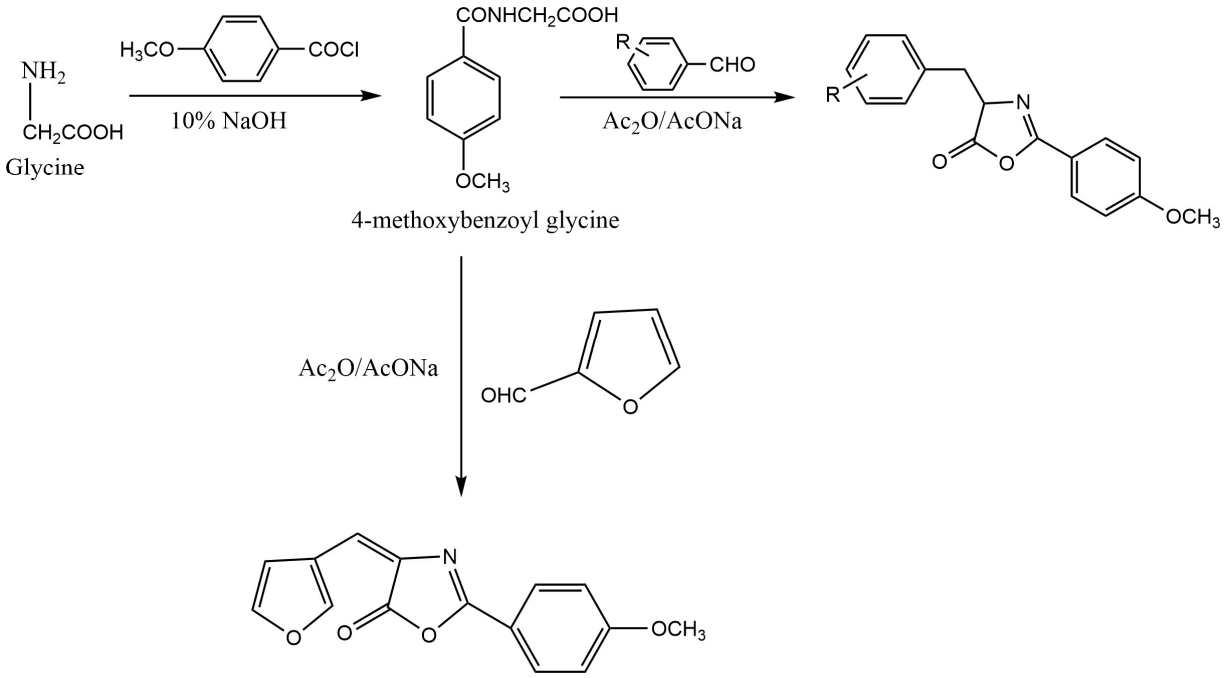
Scheme 5.1: Synthesis of 4-Benzylidene-2-phenyloxazol-5(4*H*)-one

4-arylidine 2-[4-methoxy phenyl] oxazol-5-one derivatives (Scheme 5.2) were synthesized by Mariappan *et al*. First, 4-methoxy benzoyl glycine was formed as the starting material by reacting glycine with 4-methoxy benzoyl chloride in the presence of sodium hydroxide. To form oxazolones, it was subsequently reacted with substituted aromatic aldehydes in the presence of glacial acetic acid and acetic anhydride [14].

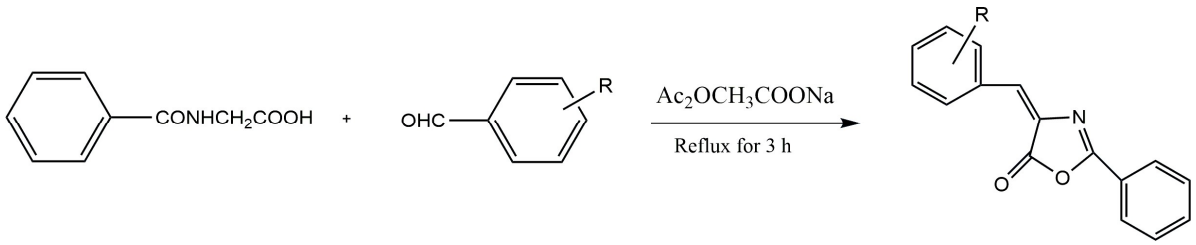
Jat *et al*. reported the derivatives of 4-Benzylidene-2-phenyloxazol-5(4*H*)-one (Scheme 5.3) by refluxing a mixture of anhydrous sodium acetate, hippuric acid, acetic anhydride, and substituted benzaldehyde. After the completion of the reaction, the product was cooled, and ethanol was gradually added and left overnight. The mixture was cleaned using methanol and water before being recrystallized in ethanol [15].

Mekabaty *et al* reported that 2-aryl-4-arylazo-2-oxazoline-5-ones (Scheme 5.4) were formed when aroylglycines were coupled with the proper aryldiazonium salts in acetic anhydride

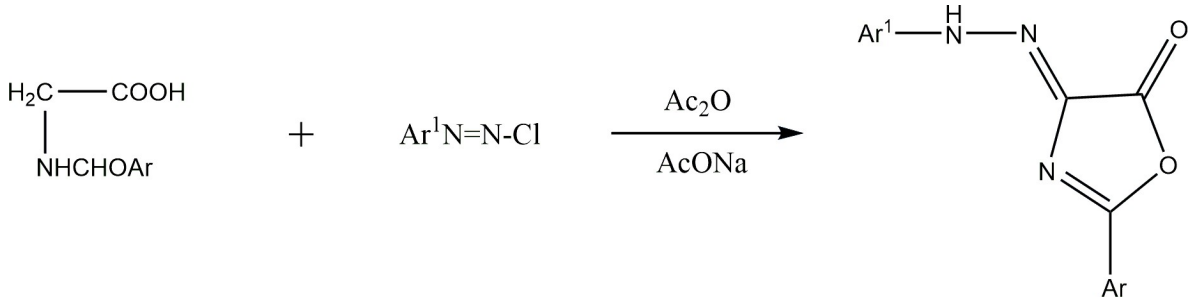
containing newly fused sodium acetate at 0 ºC [16]. Islam M.A. found that condensing phthalic anhydride with hippuric acid yields 2-Aryl-4-phthalidyliden-l,3-oxazolin-5-one [17].



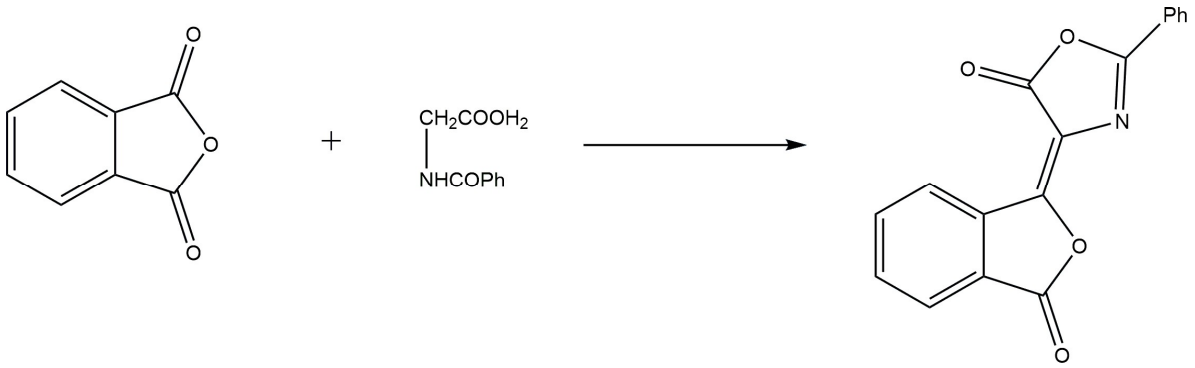
Scheme 5.2: Synthesis of 4-arylidine 2-[4-methoxy phenyl]oxazol-5-one



Scheme 5.3: Synthesis of 4-Benzylidene-2-phenyloxazol-5(4*H*)-one

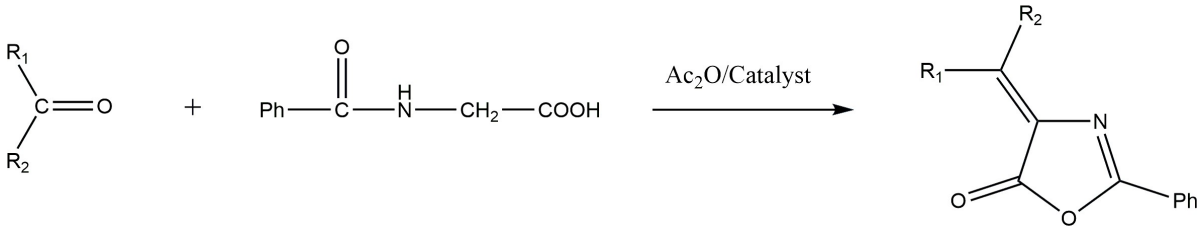


Scheme 5.4: Synthesis of 2-aryl-4-arylazo-2-oxazolin-5-ones



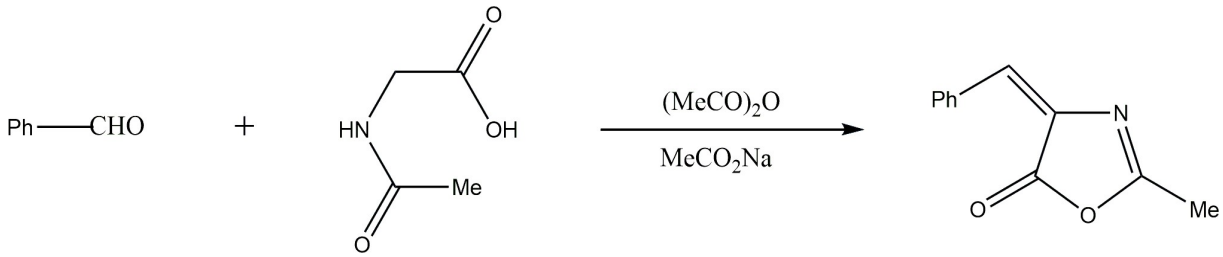
Scheme 5.5: Synthesis of 2-phenyl-4-phthalyl-2-oxazolin-5-one

Tikdari *et al*. reported the synthesis of unsaturated 2-phenyl-5(4*H*)-oxazolone derivatives (Scheme 5.6) by microwave irradiation by the mixture of acetic anhydride, hippuric acid, aldehyde or ketones, and the proper catalyst in a solvent-free environment. Both the rate of reaction and the yield were high [7].



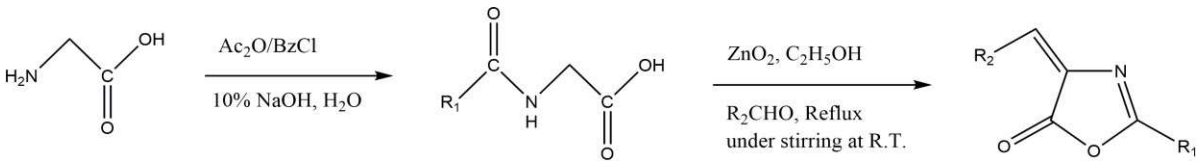
Scheme 5.6: Synthesis of 2-Phenyl-5(4*H*)-oxazolone derivative

Furniss *et al*. reported that 4-Benzylidene-2-Methyloxazol-5-one (Scheme 5.7) by synthesizing a warm mixture of acetyl glycine, benzaldehyde, anhydrous sodium acetate, and acetic anhydride in a water bath, boiling the resulting solution for one hour, cool and left overnight in the refrigerator the resulting solid is wash with cold water and purification was done by recrystallization method using carbon tetrachloride or ethyl-acetate light petroleum as a solvent [18].



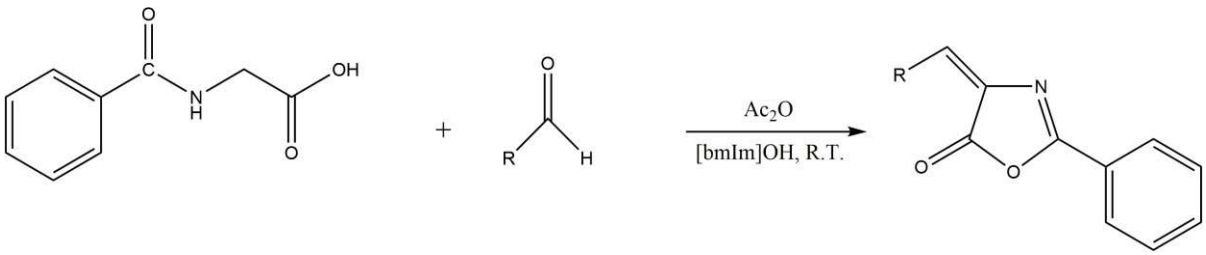
Scheme 5.7: Synthesis of 4-Benzylidene-2-methyloxazol-5-one

By using zinc oxide as a catalyst and acetic anhydride, Fareed *et al*. reported a series of 4-(arylmethylidene)-2-phenyl/methyl-5(4*H*) oxazolone derivatives (Scheme 5.8) by condensing aldehydes with N-benzoyl/N-acetyl glycine at room temperature in ethanol [19].



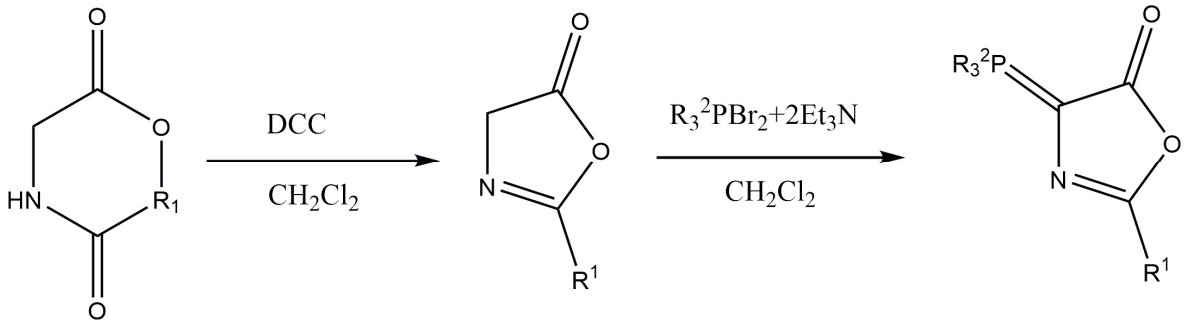
Scheme 5.8: Synthesis of 4-(arylmethylidene)-2-phenyl/methyl-5(4*H*) oxazolone

The synthesis of 4-(4-Benzylidene)-2-phenyl-5-(4*H*) oxazolone (Scheme 5.9) was reported by Patil G.S. using acetic anhydride, benzaldehyde, and hippuric acid in the presence of a basic ionic liquid. 1-n-Butyl-3-methylimidazolium hydroxide as a catalyst in a solvent-free environment at ambient temperature [20].



Scheme 5.9: Synthesis of 4-(4-Benzylidene)-2-phenyl-5-(4*H*) oxazolone

An efficient method for the formation of 4-phosphoranylidene-5(4*H*)-oxazolones (Scheme 5.10) from N-acylglycine was reported by Mazurkiewicz *et al*. The process involves converting N-acylated glycine into the appropriate 5(4*H*)-oxazolone, which is then phosphorylated in situ with either dibromotriphenylphosphorane or dibromotributylphosphorane when triethylamine is present [21].

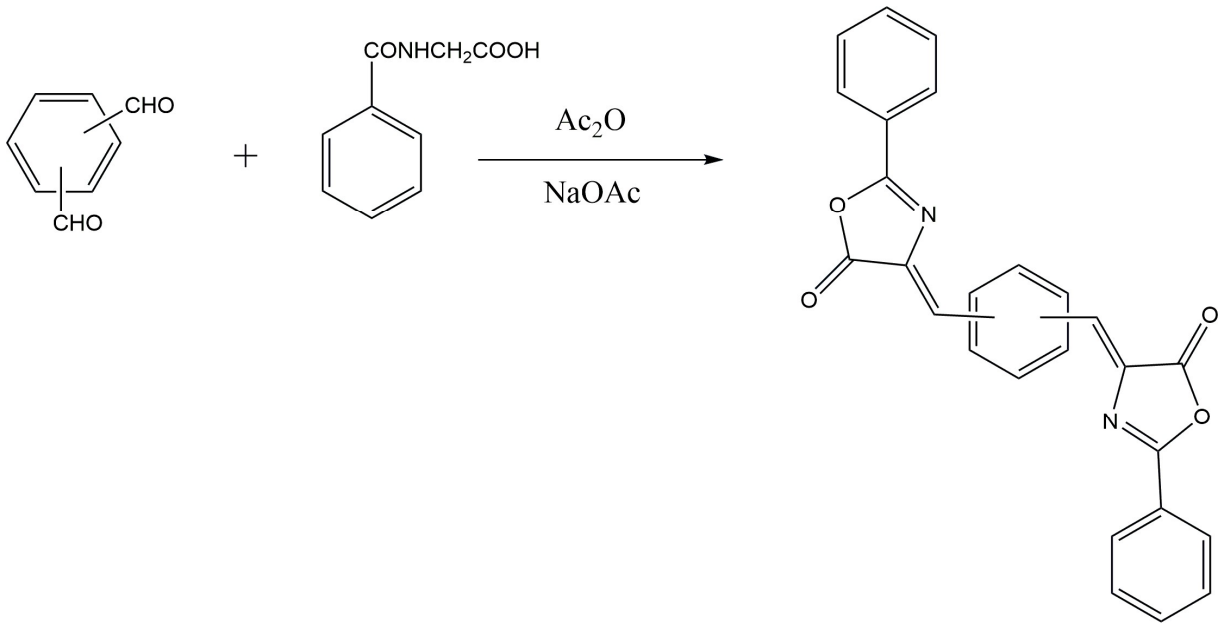


Scheme 5.10: Synthesis of 4-phosphoranylidene-5(4*H*)-oxazolone derivatives

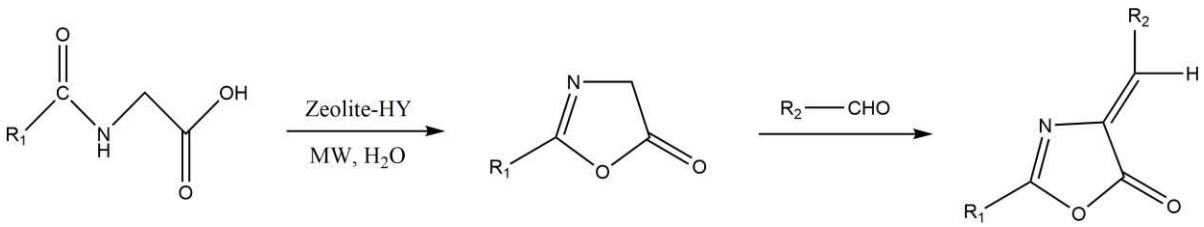
Unsaturated 4,4'-bis-[5(4*H*)-oxazolones] (Scheme 5.11) were reported by Roiban *et al*. by heating a solution of Benzene-1,2-dicarboxaldehyde, N-benzoylglycine, anhydrous sodium acetate, and acetic anhydride. The resulting precipitate was then cleaned with ethanol and recrystallized using the same solvent [22].

Using zeolite and microwave radiation, Sandhu *et al*. discovered an effective process for azlactonization by cyclodehydration that forms 4,5-dihydrooxazol-5-ones (2-oxazolin-5-ones) (Scheme 5.12) [23].

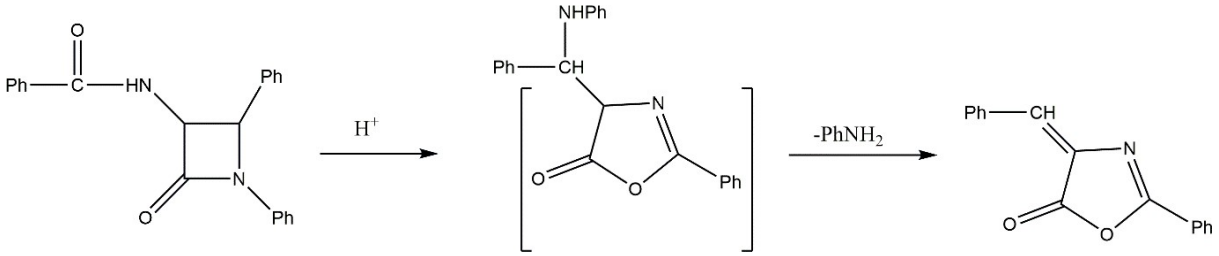
4-ethoxymethylene-2-[1]-naphthyl-5(4*H*) -oxazolone was reported by Koczan *et al*. via a reaction between 1-naphthoyl-glycine, acetic anhydride, and triethylorthoformate in ethyl acetate [24].



Scheme 5.11: Synthesis of Unsaturated 4,4'-bis-[5(4*H*)-oxazolones]



Scheme 5.12: Synthesis of 4,5-Dihydrooxazol-5-ones



Scheme 5.13: Synthesis of 4-benzylidene-2-oxazolin-5-one

The transformation of 3-benzamido-1,4-diphenyl-2-azetidinone into 4-benzylidene-2-phenyl-2-oxazolin-5-one (Scheme 5.13) was reported by Bird *et al*. using an acid catalyst [25].

Diversified Oxazolone Synthesis

1) Amino Acid: Oxazolone is an important compound used in the synthesis of derivatives of amino acids. The following processes lead to the formation of amino acids: the dynamic kinetic resolution of oxazolones formed enantiomerically pure non-quaternary amino acids [26], the nucleophilic ring opening of the quaternary substituted oxazolone moiety results in quaternary substituted amino acids as reported in the Steglich reaction [27], the arylation and alkylation of oxazolone at the C-4 position yields novel amino acids [28, 29], and the intermolecular reaction at the C-4 position produces amino acids [30].
2) Oxazole: Biologically active molecules contain a wide diversity of oxazole moiety. Numerous methods for generating oxazole from oxazolone have already been established; a Friedel-Crafts/Robinson-Gabriel synthesis carried out in one pot yields highly substituted oxazole, while a Friedel-Crafts reaction can be used to form 2-acylamino ketones from oxazolones [31].
3) β–lactams: The β-lactams moiety exhibits antibacterial properties. Huisgen and Funke have shown that imines react with oxazolones to produce the β-lactam molecule. Under basic conditions, Cremonesi *et al.* reported the formation of β-lactam using bicyclic methylamines with imines [32]. They also reported that the yield of trans-β-lactam is increased when imines contain species that donate electrons [33].
4) Pyrroles: The moiety of pyrroles is determined by 1,3-dipolar cycloaddition with oxazolones [34], where cycloaddition is enhanced when the oxazolone is in its munchnone form. Moreover, pyrroles can be synthesized by decarboxylative cycloaddition [35], which combines the reaction of munchnones with alkynes to produce pyrroles [36]. Pyrrole derivatives are formed when the oxazolone ring cleaves at position 2 due to weak nucleophiles that are unable to attack the carbon atom at position 4 of the ring [37].

5) Imidazole: Oxazolones have been used to form imidazole moiety by reacting with the proper nitriles or nitrile equivalents. Imidazole was formed by Huisgen *et al*. [38], Consonni *et al.* [39], and Bilodeau *et al.* [40] using the oxazolone moiety.
6) Pyrrolines: Gotthardt, Huisgen, and Schaefer synthesized the pyrroline moieties by cycloadditionally reacting oxazolones with alkenes to form D2-pyrroline. To obtain a D1-pyrroline in a diastereoselective manner, Maryanoff *et al*. used oxazolone [41].
7) Imidazolines: Oxazolones can be diastereoselectively added to imines via a silicon-mediated 1,3-dipolar cycloaddition, yielding imidazolines with a four-point variety [42].

5.2. Experimental Section

5.2.1 Materials and Measurements

All of the chemicals utilized in the synthesis were received from SD Fine Chemicals Ltd in Mumbai, India, and were of the AR grade. On a Nikon Optical Polarizing microscope equipped with a Mettler heating stage, melting points were noted. The mesomorphic thermal behavior and optical textures of several heterocyclic compounds were investigated using a polarising optical microscope (POM) made up of a Nikon DM 50X camera.

To confirm the separation of Novel heterocyclic compounds and to know the quantity and nature of the components of a mixture present in the novel heterocyclic compounds. TLC can also be used to monitor the progress of the reaction. This method is also used to determine the purity of organic compounds. FT-IR spectra were recorded on Perkin Elmer Spectrum Two as KBr Pellets. FT-IR is used for the identification of chemical substances or the presence of different functional groups in the synthesized novel heterocyclic compounds. To characterize unknown and known samples, the FT-IR spectrum is used. ^{1}H-NMR is an instrument used to identify the no. of hydrogen atoms present in a molecule. It is also used to determine the structure of molecules of a given compound. ^{13}C-NMR is used to identify the no. of carbon atoms present in a molecule. The no. of signals obtained indicates how many different carbons or sets of equivalent carbon are present in the molecule. Proton Nuclear Magnetic Resonance were taken on Bruker spectrometer, at 400 MHz for the proton (^{1}H). Chemical shifts are given in ppm from tetramethylsilane (TMS) as an internal standard in deuterated chloroform ($CDCl_3$). All the reactions were confirmed by thin-layer chromatography (TLC).

5.2.2 Synthesis and Characterization

5.2.2.1 Synthesis of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-alkoxyphenyl) oxazol-5-one [Scheme 5.14]

5.2.2.1.1 Synthesis of 4-n-(alkyloxy)benzoic acid [43]

In 40 mL of ethanol, p-hydroxybenzoic acid (0.1 mol), an alkyl halide (0.12 mol), and KOH were dissolved. Reflux was carried out for 4-5 h. To hydrolyze the ester produced, 10% aqueous KOH solution (25 mL) was added and reflux was carried out for 2 h. To precipitate the formed acid, the prepared solution was cooled and acidified with 1:1 dil. HCl. By the addition of the proper solvent and the recrystallization process, 4-n-alkoxy acids were purified until constant transition temperatures were attained. Table 5.1 illustrates the transition temperatures.

5.2.2.1.2 Synthesis of 4-n-(alkyloxy)benzoyl chloride [43]

4-n-alkoxybenzoic acid obtained in the above step was treated with thionyl chloride and pyridine to obtain 4-n-alkoxybenzoyl chloride.

Table 5.1: The transition temperatures of the 4-n-alkoxybenzoic acids

Sr. No.	n-alkyl group	Transition temp. (°C)		
		Smectic	Nematic	Isotropic
1	$-C_6H_{13}$	-	105.1	153.2
2	$-C_8H_{17}$	101.2	108.3	149.4
3	$-C_{10}H_{21}$	97.5	122.2	142.2
4	$-C_{12}H_{25}$	95.2	124.5	137.5
5	$-C_{14}H_{29}$	94.1	135.6	136.6

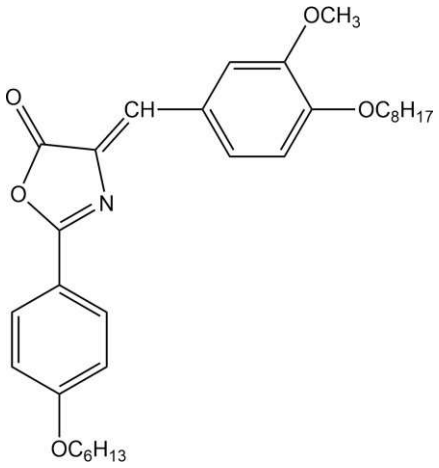
5.2.2.1.3 Synthesis of (4-n-(alkyloxy)benzoyl) glycine [44]

Glycine (0.1 mol) should be dissolved in 25 mL of 10% sodium hydroxide before being added to a solution of 4-n-alkoxybenzoyl chloride. Stir for 20 min. To precipitate the product at a pH of 6 to 7, add 1:1 HCl. Utilizing the proper solvent and the recrystallization process, the product was purified. The melting point closely follows the literature.

5.2.2.1.1 Synthesis of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-alkoxyphenyl) oxazol-5-one [44]

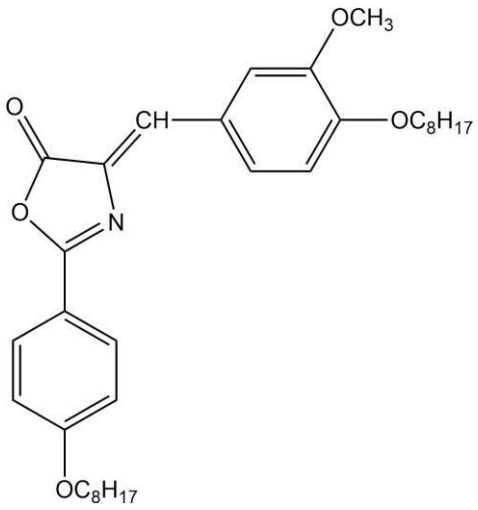
Anhydrous sodium acetate (0.25 mol), substituted aromatic aldehyde (0.25 mol), 4-alkoxy benzoyl glycine (0.25 mol), and 2 mL acetic anhydride (0.75 mol) were mixed and refluxed for 1 h with continuous stirring. After the reaction, the product was cooled, filtered, water-washed, and refined using the recrystallization process and the proper solvent. An optical polarizing microscope was used to record the compound's melting point in Table 5.2. The yield obtained was between 64-75%.

4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-hexyloxyphenyl) oxazol-5-one (1)



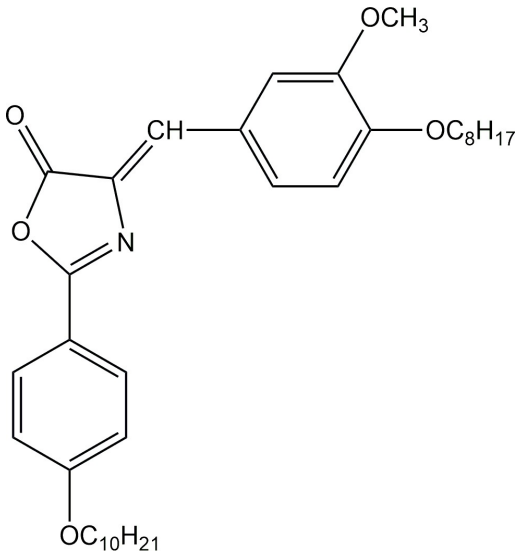
M.P.: 153.2 °C, yield 70%. **FT-IR**: 2920, 2819 (CH_2, CH_3), 1722 (C=O lactone), 1689 (C=N), 1581, 1511 (C-C), 1257 (C-N aryl), 1211, 1025, 1069 (C-O ether), 848 (Ar-H). **^{1}H NMR** (400 MHz, $CDCl_3$): 8.12-8.13 (d, 2H, J = 2Hz, Ar-H), 7.84 (s, 1H, -C=CH-), 7.45-7.46 (d, 1H, J = 4.8Hz, Ar-H), 7.03-7.04 (d, 2H, J = 2Hz, Ar-H), 7.01-7.02 (d, 2H, J = 2Hz, Ar-H), 4.08-4.1 (t, 4H, Ar-O-CH_2-), 4.07 (s, 3H, -OCH_3), 1.38-1.88 (m, 16H, -CH_2-CH_2-), 1.36-1.37 (m, 4H, -CH_2-CH_3), 0.93-0.97 (t, 6H, -CH_3). Anal. Calc. for $C_{31}H_{41}NO_5$ (507.30): C, 73.34; H, 8.14; N, 2.76. found: C, 73.30; H, 8.10; N, 2.80%.

4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-octyloxyphenyl) oxazol-5-one (2)



M.P.: 140.6 °C, yield 74%. **FT-IR**: 2930, 2851 (CH_2, CH_3), 1722 (C=O lactone), 1685 (C=N), 1606, 1507 (C-C), 1257 (C-N aryl), 1170, 1067, 1026 (C-O ether), 947, 846 (Ar-H). **^{1}H NMR** (400 MHz, $CDCl_3$): 8.19 (d, 2H, J = 2Hz, Ar-H), 8.02-8.03 (d, 2H, J = 4.8Hz, Ar-H), 7.94 (s, 1H, Ar-H), 7.41-7.42 (d, 1H, J = 4.8Hz, Ar-H), 7.00-7.01 (d, 2H, J = 2Hz, Ar-H), 4.08-4.10 (t, 4H, Ar-O-CH_2-), 1.36-1.87 (m, 20H, -CH_2-CH_2-), 1.34-1.35 (m, 4H, -CH_2-CH_3), 0.91-0.95 (t, 6H, -CH_3). Anal. Calc. for $C_{33}H_{45}NO_5$ (535.73): C, 73.99; H, 8.47; N, 2.61. found: C, 73.95; H, 8.50; N, 2.58%.

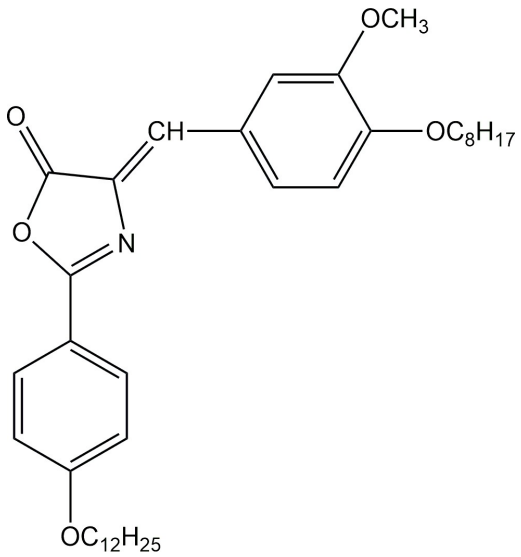
4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-decyloxyphenyl) oxazol-5-one (3)



M.P.: 138.2 °C, yield 68%. **FT-IR**: 2940, 2837 (CH_2, CH_3), 1728 (C=O lactone), 1656 (C=N), 1600, 1509 (C-C), 1256 (C-N aryl), 1165, 1066, 1027 (C-O ether), 842, 825 (Ar-H). **^{1}H NMR**

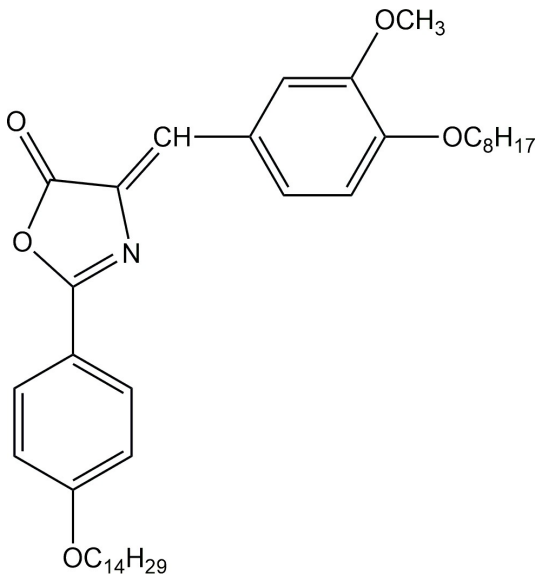
(400 MHz, $CDCl_3$): 8.12-8.14 (d, 2H, J = 8Hz, Ar-H), 7.95 (s, 1H, Ar-CH-), 7.25-7.28 (d, 2H, J = 10.4Hz, Ar-H), 7.20 (s, 1H, Ar-H), 7.02-7.04 (d, 2H, J = 8Hz, Ar-H), 4.10-4.40 (t, 4H, Ar-O-CH_2-), 1.47-1.72 (m, 24H, -CH_2-CH_2-), 1.30 (m, 4H, -CH_2-CH_3), 0.88 (t, 6H, -CH_3). Anal. Calc. for $C_{35}H_{49}NO_5$ (563.78): C, 74.57; H, 8.76; N, 2.48. found: C, 74.60; H, 8.70; N, 2.42%.

4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-dodecyloxyphenyl) oxazol-5-one (4)



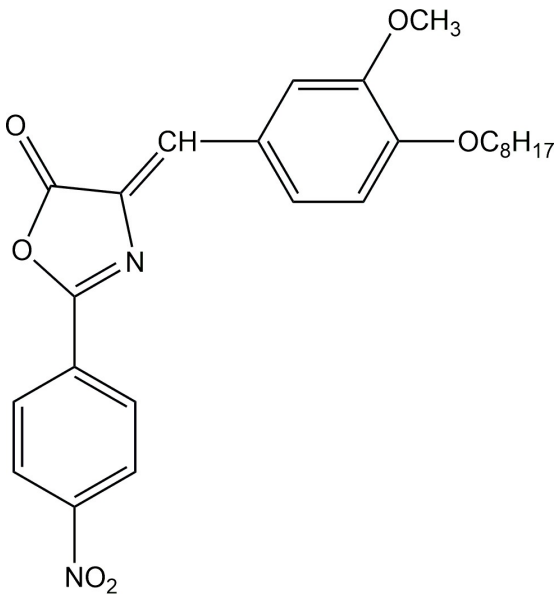
M.P.: 144.6 °C, yield 75%. **FT-IR**: 2957, 2871 (CH_2, CH_3), 1728 (C=O lactone), 1651 (C=N), 1600, 1507 (C-C), 1254 (C-N aryl), 1167, 1064, 1028 (C-O ether), 843 (Ar-H). **^{1}H NMR** (400 MHz, $CDCl_3$): 8.01-8.03 (d, 2H, J = 9.2Hz, Ar-H), 7.80 (s, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 7.01-7.03 (d, 2H, J = 8.4Hz, Ar-H), 6.94-6.98 (d, 2H, J = 8.8Hz, Ar-H), 3.89 (s, 3H, Ar-O-CH_3), 3.92-4.10 (t, 4H, Ar-O-CH_2-), 1.30-1.79 (m, 28H, -CH_2-CH_2-), 1.26-1.28 (m, 4H, -CH_2-CH_3-), 0.91-0.92 (t, 6H, -CH_3). Anal. Calc. for $C_{37}H_{53}NO_5$ (591.83): C, 75.09; H, 9.03; N, 2.37. found: C, 75.12; H, 9.05; N, 2.40%.

4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-tetradecyloxyphenyl) oxazol-5-one (5)



M.P.: 148.8 °C, yield 64%. **FT-IR**: 2921, 2849 (CH_2, CH_3), 1757 (C=O lactone), 1657 (C=N), 1604, 1554, 1507 (C-C), 1253 (C-N aryl), 1209, 1169, 1125, 1100, 1031 (C-O ether), 987, 881, 861, 844 (Ar-H). **^{1}H NMR** (400 MHz, $CDCl_3$): 8.06-8.08 (d, 2H, J = 6.8Hz, Ar-H), 7.87 (s, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.01-7.02 (d, 2H, J = 5.2Hz, Ar-H), 6.94-6.96 (d, 2H, J = 2.4Hz, Ar-H), 4.02-4.17 (t, 4H, Ar-O-CH_2-), 3.90 (s, 3H, Ar-O-CH_3), 1.37-1.84 (m, 32H, -CH_2-CH_2-), 1.28-1.35 (m, 4H, -CH_2-CH_3-), 0.88-0.92 (t, 6H, -CH_3). Anal. Calc. for $C_{39}H_{57}NO_5$ (619.89): C, 75.57; H, 9.27; N, 2.26. found: C, 75.60; H, 9.21; N, 2.30%.

4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-nitrophenyl) oxazol-5-one (6)



M.P.: 172 °C, yield 66%. **FT-IR**: 2925, 2850 (CH_2, CH_3), 1752 (C=O lactone), 1665 (C=N), 1600, 1550 (-NO_2), 1500 (C-C), 1255, 1260 (C-N aryl), 1170, 1128, 1100, 1031 (C-O ether), 989, 861, 844 (Ar-H). **^{1}H NMR** (400 MHz, $CDCl_3$): 8.06-8.13 (d, 4H, J = 8.4Hz, Ar-H), 7.61 (s, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 6.99-7.01 (d, 2H, J = 8.8Hz, Ar-H), 4.04 (t, 2H, Ar-O-CH_2-), 3.96 (s, 3H, Ar-O-CH_3), 1.45-1.82 (m, 10H, -CH_2-CH_2-), 1.26 (m, 2H, -CH_2-CH_3-), 0.89 (t, 3H, -CH_3). Anal. Calc. for $C_{25}H_{28}N_2O_6$ (452.51): C, 66.36; H, 6.24; N, 6.19. found: C, 66.40; H, 6.28; N, 6.25%.

5.2.2.2 Synthesis of (4-((2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene)methyl)phenyl4-methoxybenzoate [Scheme 5.15]

The primary three steps of the reaction are the same as described in Scheme 5.14.

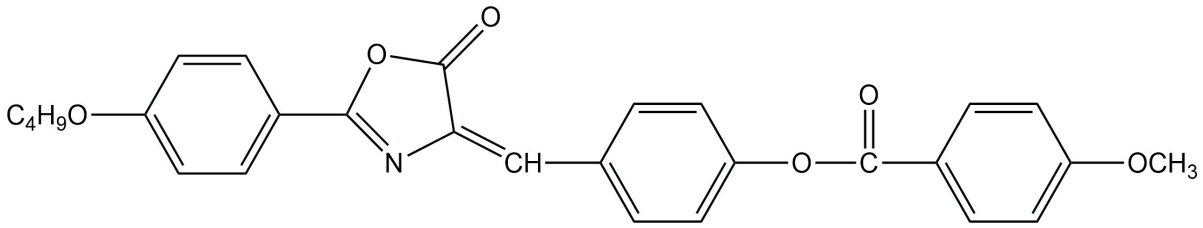
5.2.2.2.1 Synthesis of 4-formyl phenyl 4-(alkoxy)benzoate

Refluxing a mixture of 4-(alkoxy)benzoyl chloride and 4-hydroxybenzaldehyde for 1 h to obtain an intermediate product, 4-formylphenyl-(alkoxy)benzoate, which was employed in the reaction's final step without further purification.

5.2.2.2.1 Synthesis of (4-(2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene) methyl)phenyl 4'-(alkoxy)benzoate

In a round-bottomed flask, a mixture of 4-n-alkoxybenzoyl glycine (0.25 mol), 4-formyl phenyl 4-(alkoxy)benzoate (0.25 mol), 2 mL of acetic anhydride (0.75 mol), and anhydrous sodium acetate (0.25 mol) was added. A liquid mixture was heated for 2 h. After that, 30 mL of ethanol was slowly added and kept overnight. Filter the end product, and the recrystallization process was carried out to purify the compound. Yield: 60-65%.

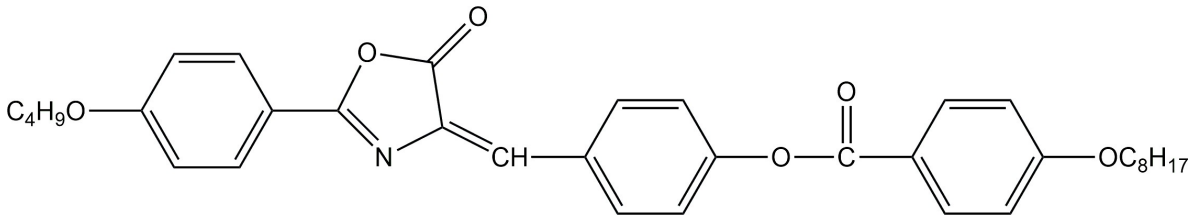
(4-(2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene) methyl)phenyl 4'-methoxybenzoate (1')



M.P.: 92.1 °C, yield 60%. **FT-IR**: 2956, 2870 (CH_2, CH_3), 1786 (C=O lactone), 1648 (C=N), 1604, 1508 (C-C), 1259 (C-N aryl), 1211, 1163 (C-C-(O)-C esters), 1038 (C-O ether), 851, 842

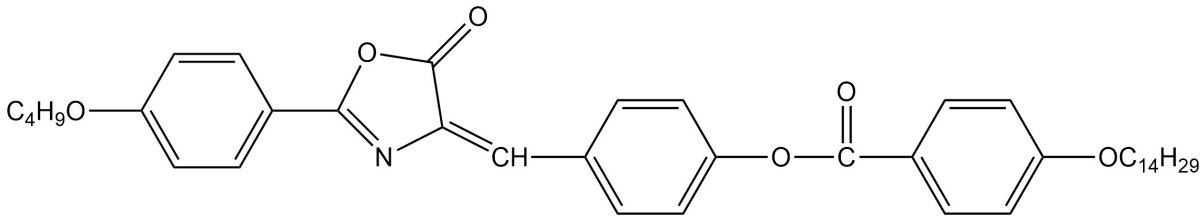
(Ar-H). **^{1}H NMR** (400 MHz, $CDCl_3$): 8.16-8.15 (d, 2H, J = 2.4 Hz, Ar-H), 8.14-8.15 (d, 2H, J = 2.8 Hz, Ar-H), 7.97-7.98 (d, 2H, J = 2Hz, Ar-H), 7.85-7.86 (d, 2H, J = 2Hz, Ar-H), 7.83-7.84 (d, 2H, J = 2Hz, Ar-H), 7.40 (s, 1H, -C=CH-), 7.01-7.02 (d, 2H, J = 2.8 Hz, Ar-H), 4.03 (t, 2H, Ar-O-CH_2-), 1.80 (m, 2H, -CH_2-CH_2-), 1.46 (m, 2H, -CH_2-CH_3), 0.89-0.93 (t, 6H, -CH_3). Anal. Calc. for $C_{28}H_{25}NO_6$ (471.51): C, 71.33; H, 5.34; N, 2.97. found: C, 71.25; H, 5.28; N, 2.88%.

(4-(2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene) methyl)phenyl 4'-(octyloxy)benzoate (2')



M.P.: 72.5 °C, yield 65%. **FT-IR**: 2951, 2886 (CH_2, CH_3), 1763 (C=O lactone), 1653 (C=N), 1571, 1527 (C-C), 1310 (C-N aryl), 1110 (C-C-(O)-C esters), 1036 (C-O ether), 932, 921 (Ar-H). **^{1}H NMR** (400 MHz, $CDCl_3$): 8.16-8.17 (d, 2H, J = 4Hz, Ar-H), 8.14-8.16 (d, 2H, J = 9.2Hz, Ar-H), 8.13-8.14 (d, 2H, J = 2.4Hz, Ar-H), 7.37 (s, 1H, -C=CH-), 7.03-7.05 (d, 2H, J = 8.8Hz, Ar-H), 7.02-7.03 (d, 2H, J = 2.8Hz, Ar-H), 7.00-7.02 (d, 2H, Ar-H), 4.06-4.11 (t, 4H, Ar-O-CH_2-), 1.37-1.87 (m, 12H, -CH_2-CH_2-), 1.33-1.35 (m, 4H, -CH_2-CH_3), 0.91 (t, 6H, -CH_3). Anal. Calc. for $C_{35}H_{39}NO_6$ (569.70): C, 73.79; H, 6.90; N, 2.46. found: C, 73.72; H, 6.85; N, 2.51%.

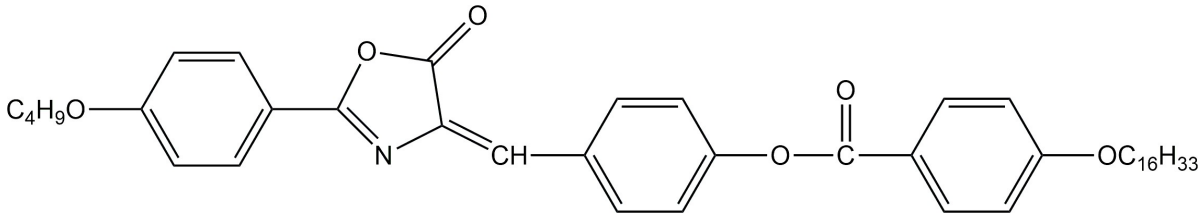
(4-(2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene) methyl)phenyl 4'-(tetradecyloxy)benzoate (3')



M.P.: 65.4 °C, yield 64%. **FT-IR**: 2920, 2857 (CH_2, CH_3), 1762 (C=O lactone), 1682 (C=N), 1597, 1568 (C-C), 1300 (C-N aryl), 1158 (C-C-(O)-C esters), 1038 (C-O ether), 967, 931 (Ar-H). **^{1}H NMR** (400 MHz, $CDCl_3$): 8.17-8.18 (d, 2H, J = 2Hz, Ar-H), 8.04-8.05 (d, 2H, J = 2Hz, Ar-H), 7.53-7.54 (d, 2H, J = 2Hz, Ar-H), 7.37 (s, 1H, -C=CH-), 7.35 (d, 2H, J = 2Hz, Ar-H), 7.02-7.03 (d, 2H, J = 2Hz, Ar-H), 7.01-7.02 (d, 2H, J = 4.8Hz, Ar-H), 4.02-4.05 (t, 4H, Ar-O-CH_2-), 1.25-1.46 (m, 4H, -CH_2-CH_3-), 1.26-1.86 (m, 24H, -CH_2-CH_2-), 0.88-0.91 (t, 6H, -CH_3).

Anal. Calc. for $C_{41}H_{51}NO_6$ (653.86): C, 75.31; H, 7.86; N, 2.14. found: C, 75.25; H, 7.82; N, 2.20%.

(4-(2-(4-butoxyphenyl)-5-oxooxazol-4(5H)-ylidene) methyl)phenyl 4'-(hexadecyloxy)benzoate (4')



M.P.: 60.6 °C, yield 62%. **FT-IR**: 2953 (CH_2, CH_3), 1764 (C=O lactone), 1653 (C=N), 1532 (C-C), 1302 (C-N aryl), 1112 (C-C-(O)-C esters), 1037 (C-O ether), 922, 892 (Ar-H). **^{1}H NMR** (400 MHz, $CDCl_3$): 8.19-8.20 (d, 2H, J = 4Hz, Ar-H), 8.17-8.19 (d, 2H, J = 11.6Hz, Ar-H), 8.16-8.17 (d, 2H, J = 4Hz, Ar-H), 7.03-7.05 (d, 2H, J = 8.8 Hz, Ar-H), 7.02-7.03 (d, 2H, J = 2.8Hz, Ar-H), 7.00-7.02 (d, 2H, J = 8.8Hz, Ar-H), 4.06-4.10 (t, 4H, Ar-O-CH_2-), 1.50-1.89 (m, 28H, -CH_2-CH_2-), 1.29-1.49 (m, 4H, -CH_2-CH_3), 0.89-0.90 (t, 6H, -CH_3). Anal. Calc. for $C_{43}H_{55}NO_6$ (681.40): C, 75.74; H, 8.13; N, 2.05. found: C, 75.71; H, 8.09; N, 2.10%.

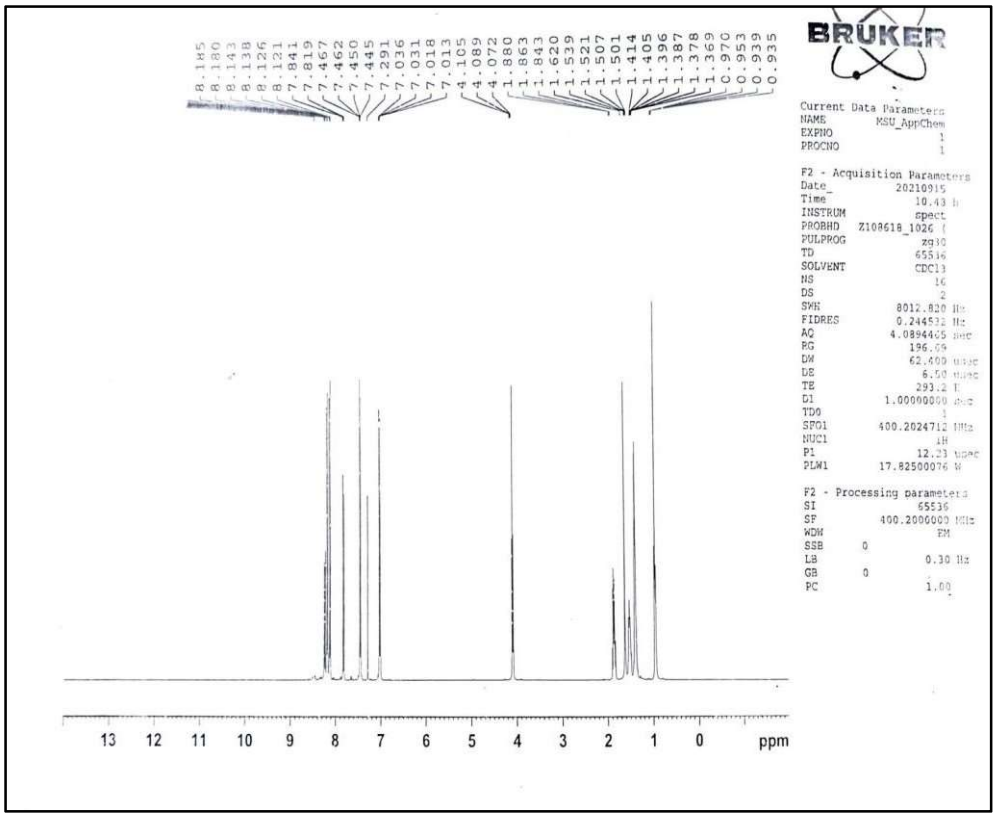


Figure 5.2: ^{1}H NMR of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-hexyloxyphenyl) oxazol-5-one (1) [Scheme 5.14]

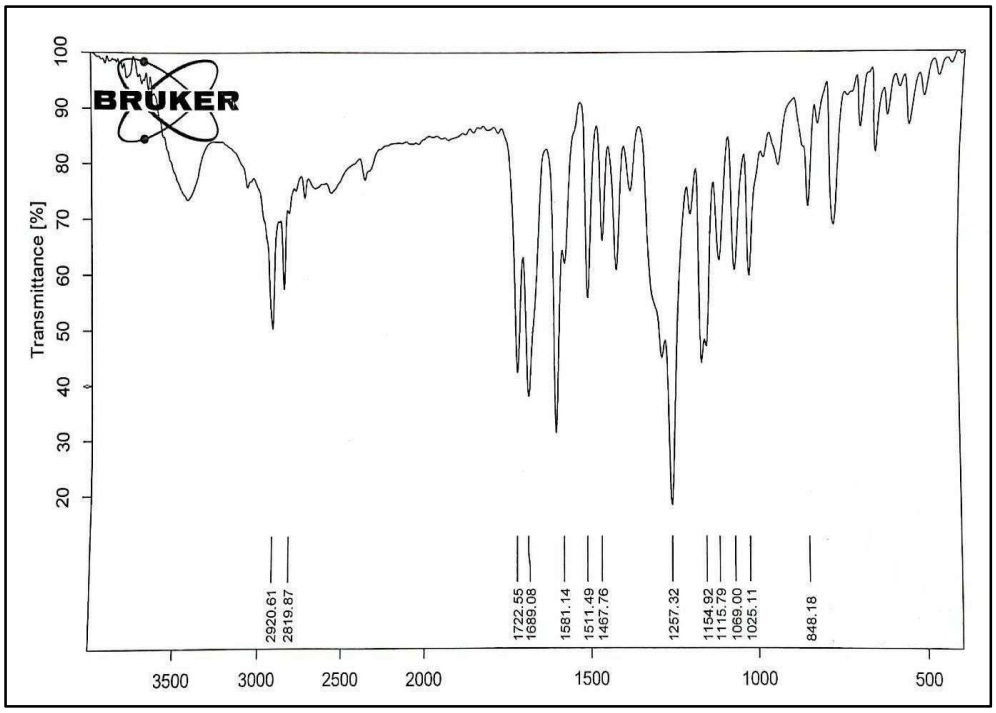


Figure 5.3: FT-IR of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-hexyloxyphenyl) oxazol-5-one (1) [Scheme 5.14]

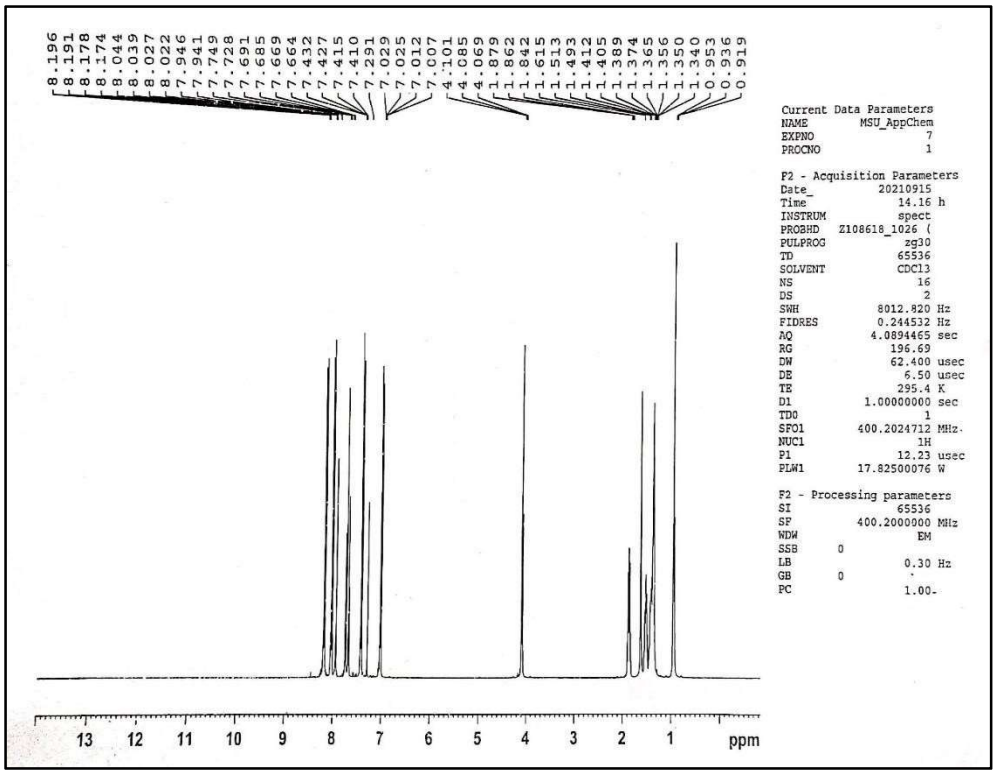


Figure 5.4: [1]H NMR of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-octyloxyphenyl) oxazol-5-one (2) [Scheme 5.14]

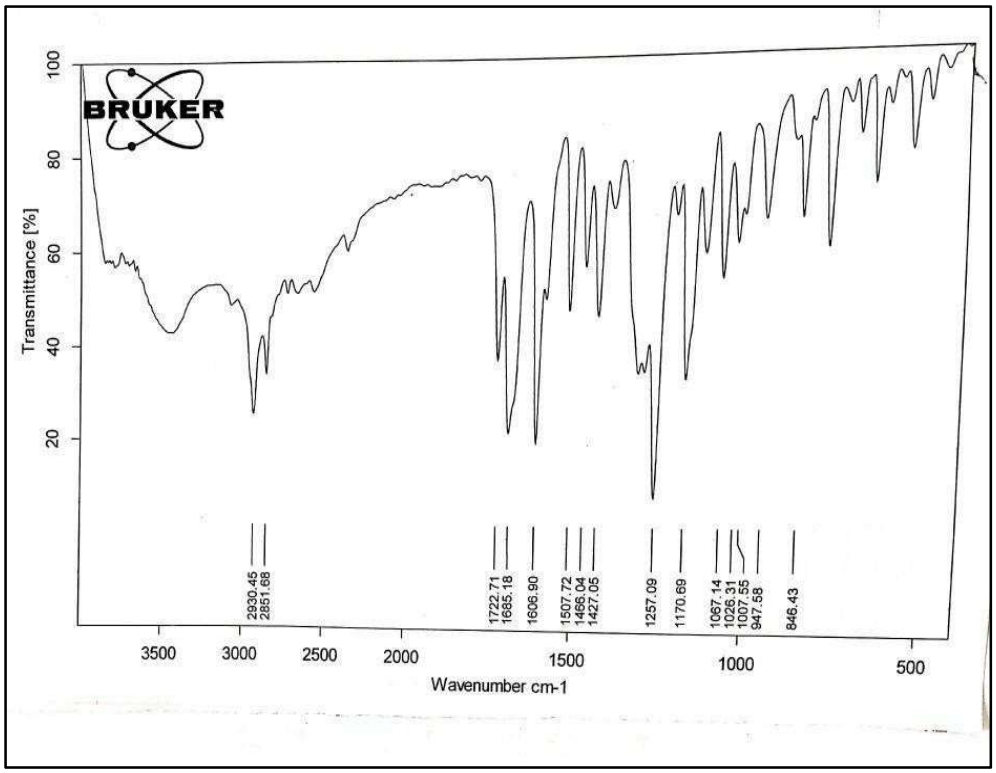


Figure 5.5: FT-IR of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-octyloxyphenyl) oxazol-5-one (2) [Scheme 5.14]

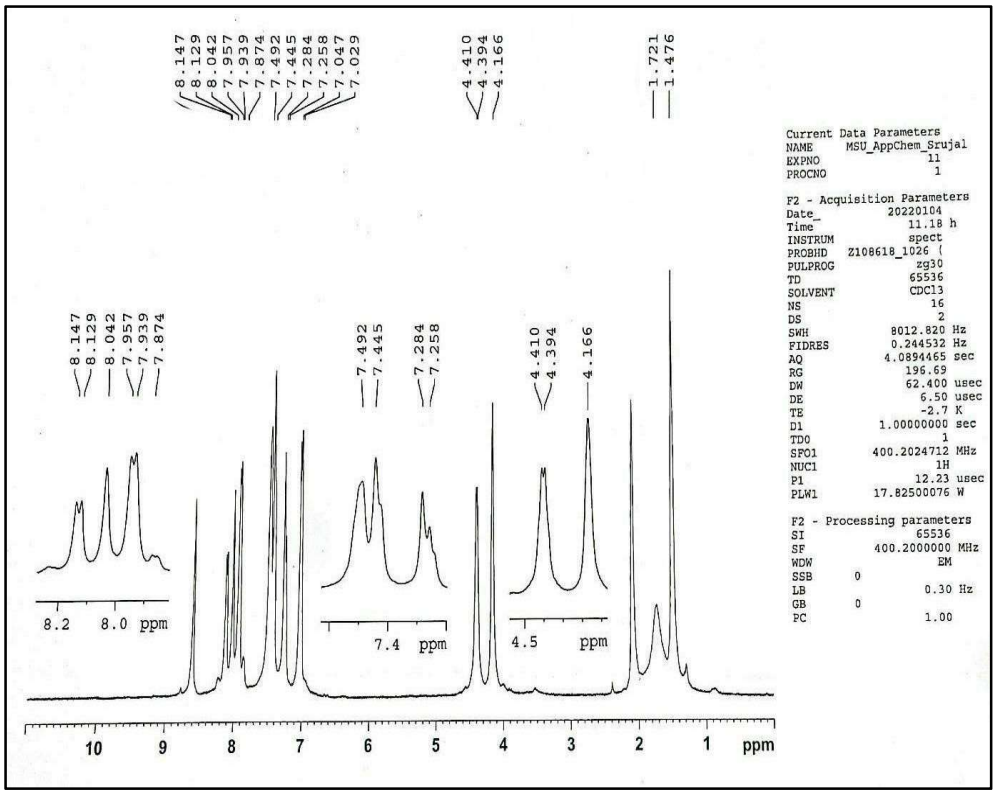


Figure 5.6: [1]H NMR of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-decyloxyphenyl) oxazol-5-one (3) [Scheme 5.14]

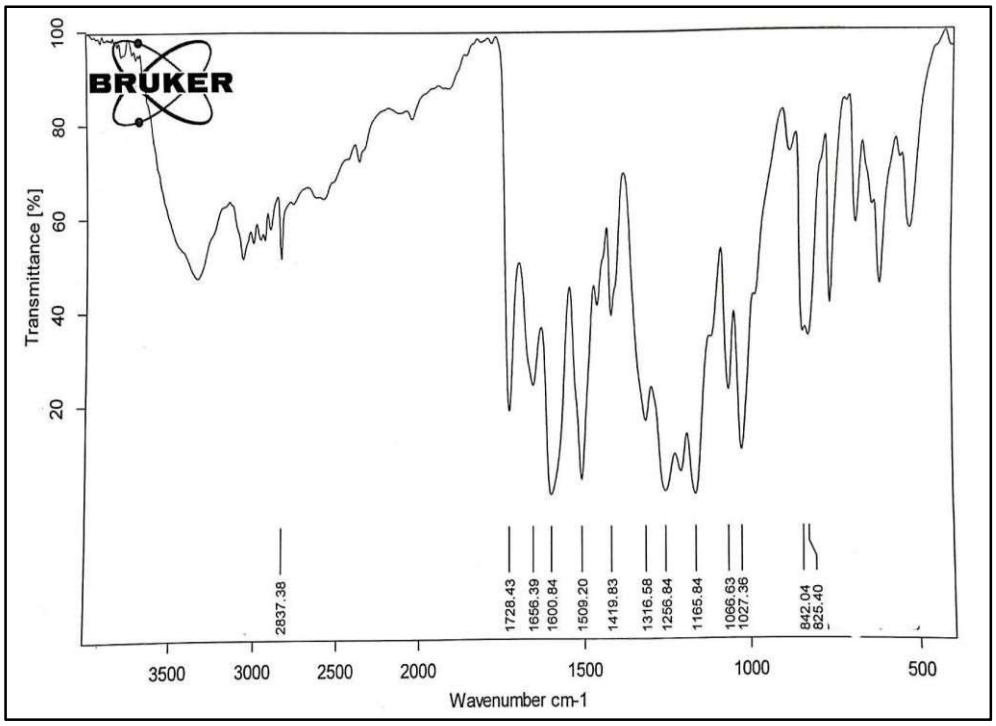


Figure 5.7: FT-IR of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-decyloxyphenyl) oxazol-5-one (3) [Scheme 5.14]

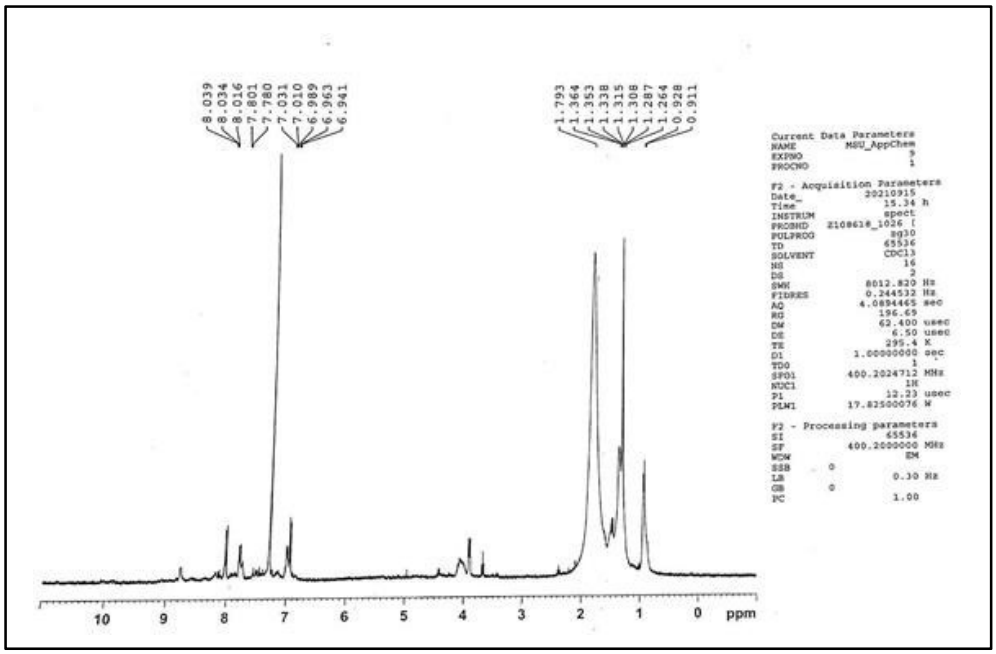


Figure 5.8: ^{1}H NMR of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-dodecyloxyphenyl) oxazol-5-one (4) [Scheme 5.14]

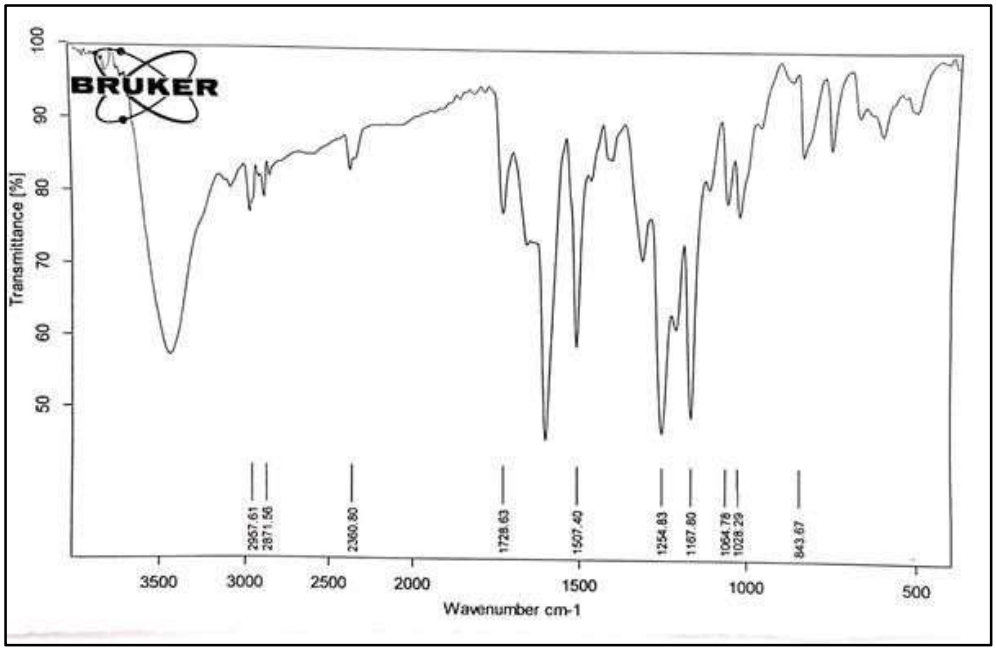


Figure 5.9: FT-IR of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-dodecyloxyphenyl) oxazol-5-one (4) [Scheme 5.14]

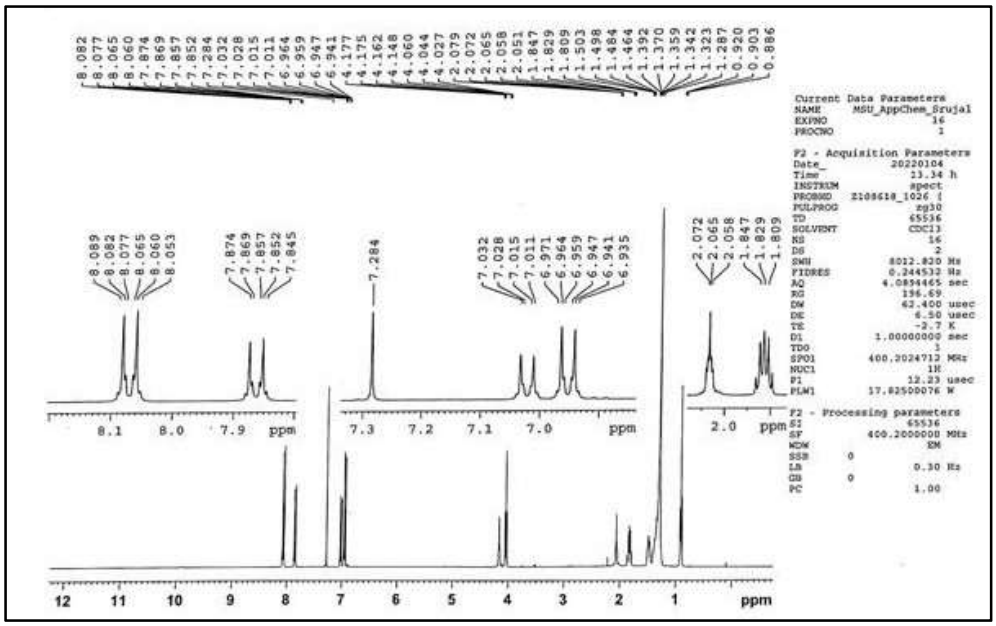


Figure 5.10: ^{1}H NMR of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-tetradecyloxyphenyl) oxazol-5-one (5) [Scheme 5.14]

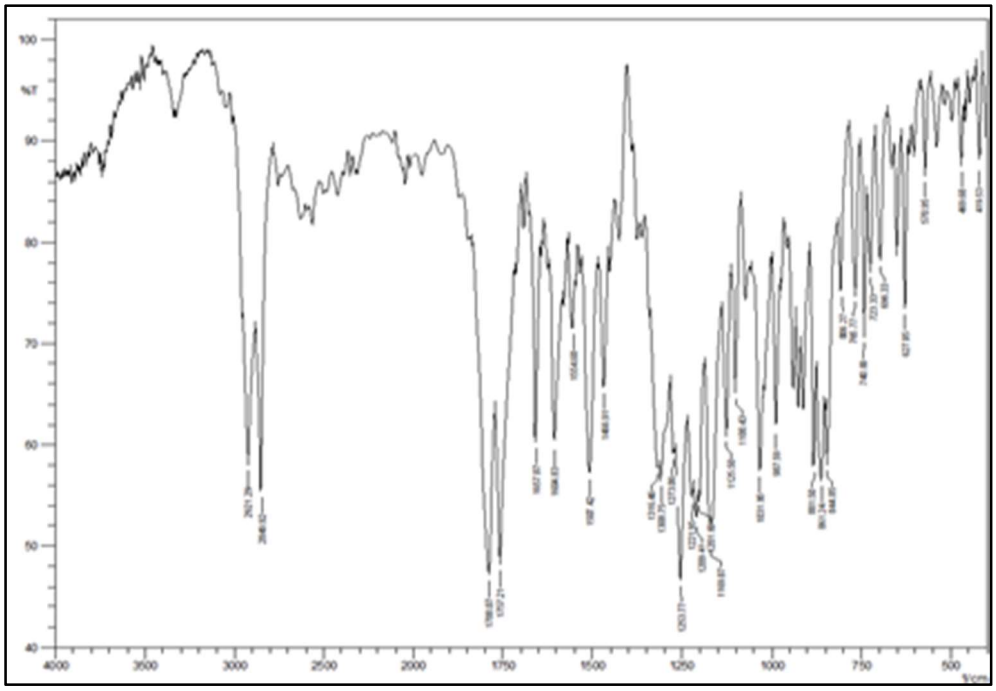


Figure 5.11: FT-IR of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-tetradecyloxyphenyl) oxazol-5-one (5) [Scheme 5.14]

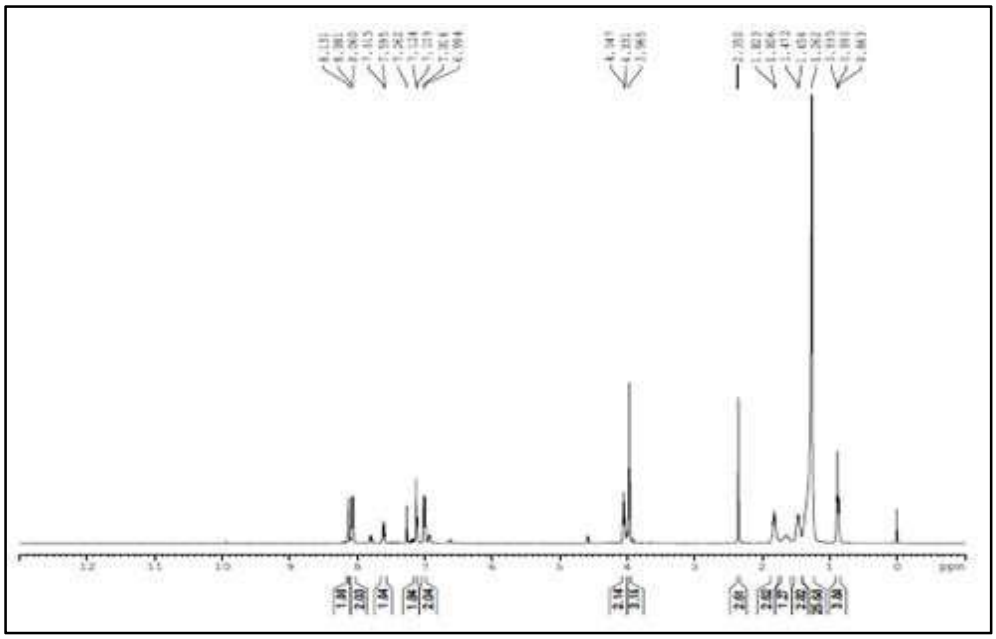


Figure 5.12: ^{1}H NMR of 4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-nitrophenyl) oxazol-5-one (6) [Scheme 5.14]

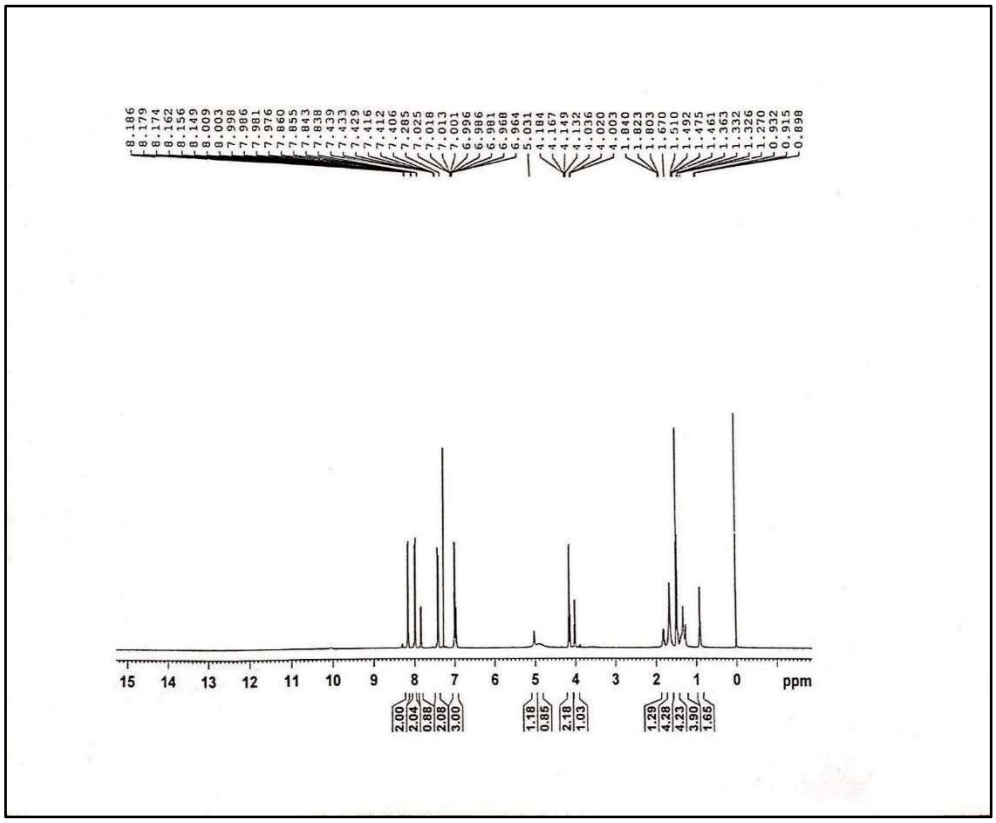


Figure 5.13: ^{1}H NMR of (4-(2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene) methyl)phenyl 4'-methoxybenzoate (1') [Scheme 5.15]

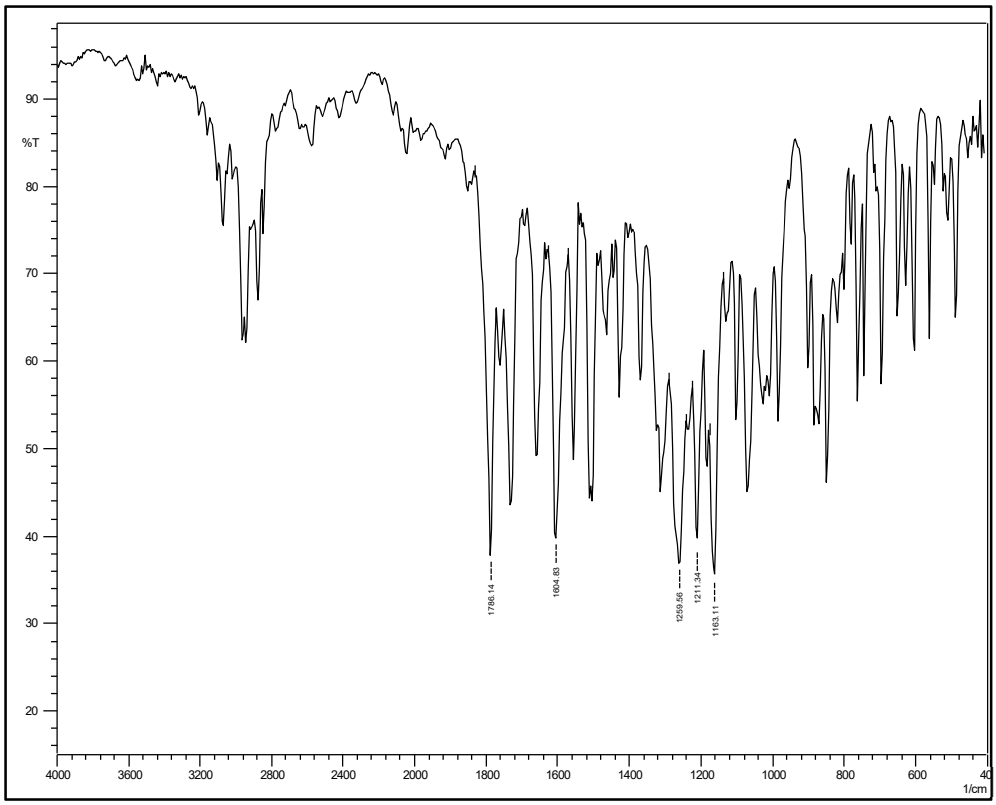


Figure 5.14: FT-IR of (4-(2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene) methyl)phenyl 4'-methoxybenzoate (1') [Scheme 5.15]

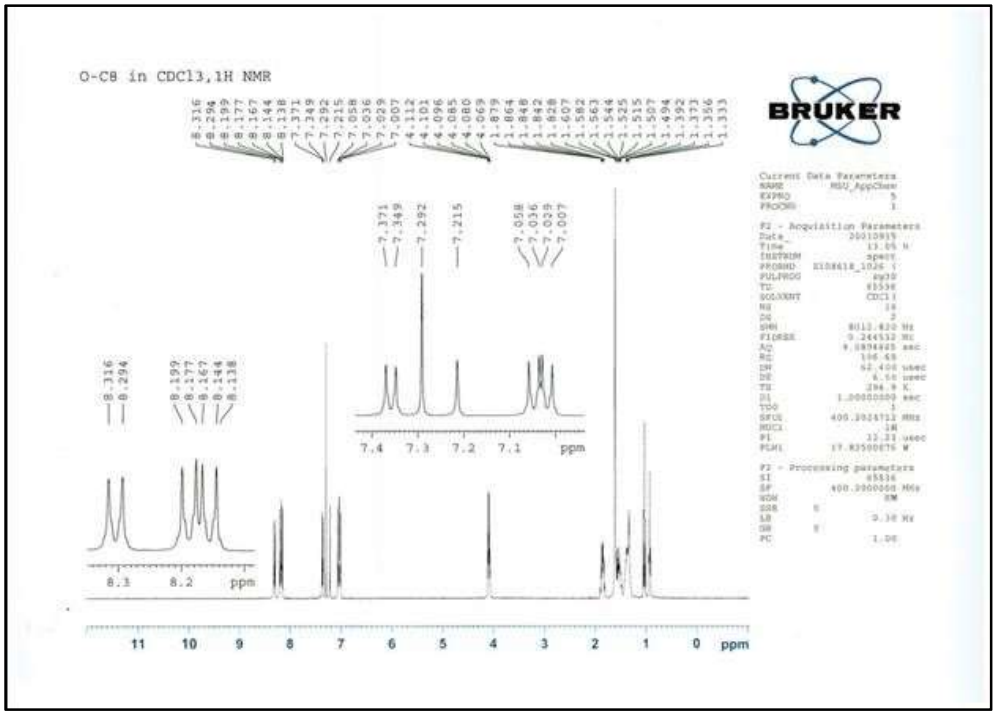


Figure 5.15: ^{1}H NMR of (4-(2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene) methyl)phenyl 4'-(octyloxy)benzoate (2') [Scheme 5.15]

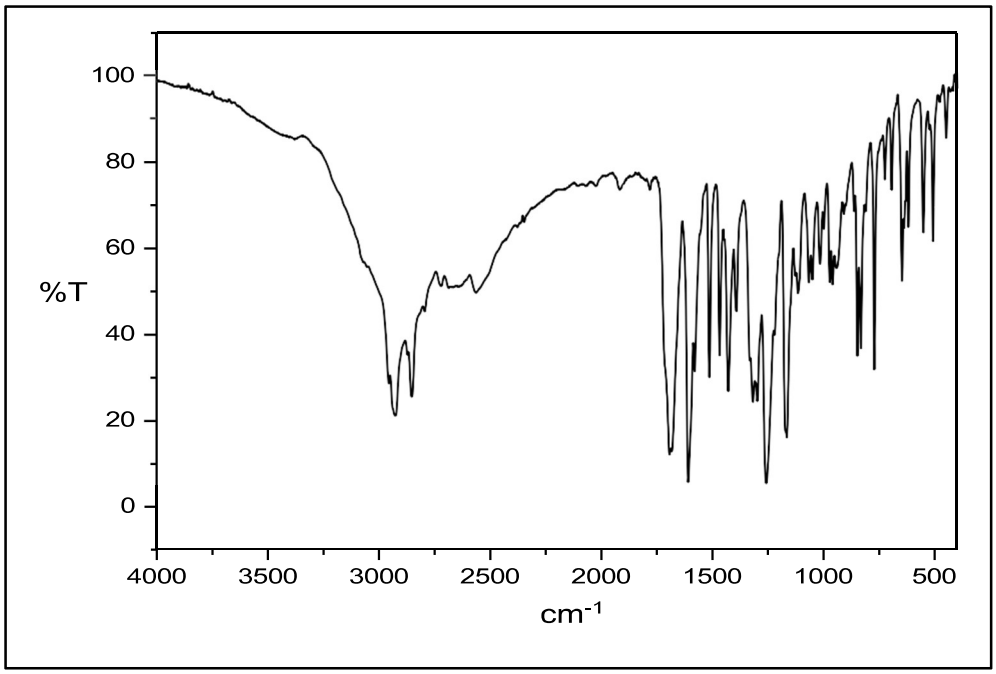


Figure 5.16: FT-IR of (4-(2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene) methyl)phenyl 4'-(octyloxy)benzoate (2') [Scheme 5.15]

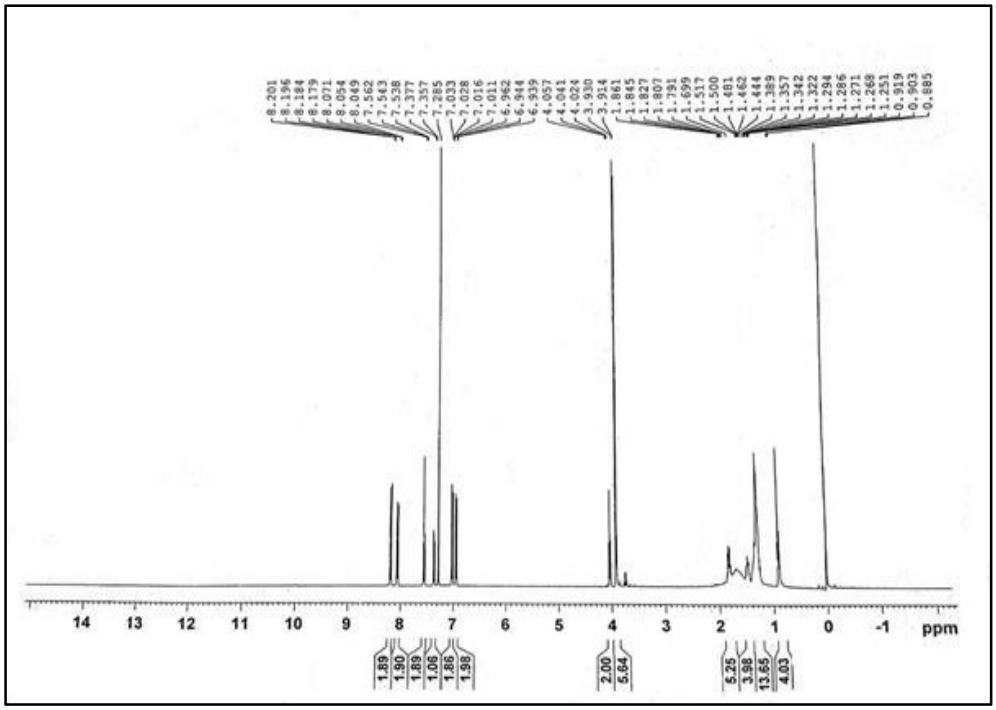


Figure 5.17: ^{1}H NMR of (4-(2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene) methyl)phenyl 4'-(tetradecyloxy)benzoate (3') [Scheme 5.15]

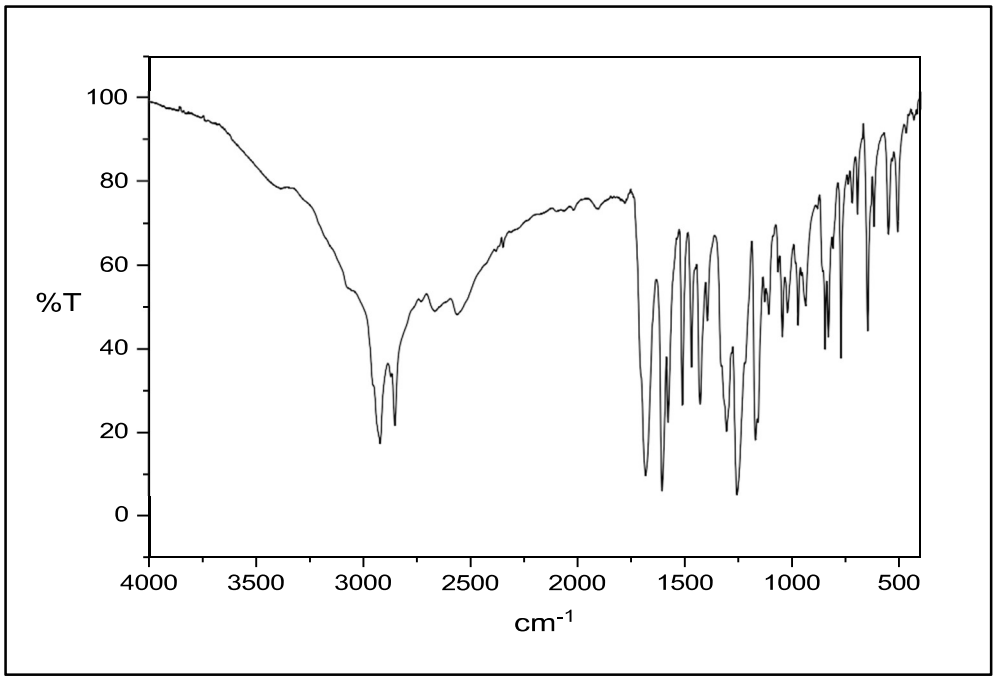


Figure 5.18: FT-IR of (4-(2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene) methyl)phenyl 4'-(tetradecyloxy)benzoate (3') [Scheme 5.15]

5.3. Results and Discussion

5.3.1 Chemistry

In Figure 5.19, the substitution of functional groups at the C-2 and C-4 positions is extremely important for oxazolone's action. The immunosuppressive effect of the oxazolone molecule is enhanced by the exocyclic phenyl group at C-4 [45]. Cinnamoyl residue at C-4 of oxazolone moiety and substitution of a functional group at C-4 and C-2 positions of oxazolone is very essential for tyrosinase inhibitory activity. An extension of conjugation through an aliphatic double bond present at the C-4 position of oxazolone moiety and a phenyl ring present at C-2 plays a very important role in biological activity. The rate of the oxazolone ring-opening process decreases when the substituent at the C-2 position of the phenyl ring exhibits more electron-donating characteristics [46]. Their biological activity is greatly influenced by the phenyl ring at position C-2 and an extension of conjugation through an aliphatic double bond at position C-4 [47].

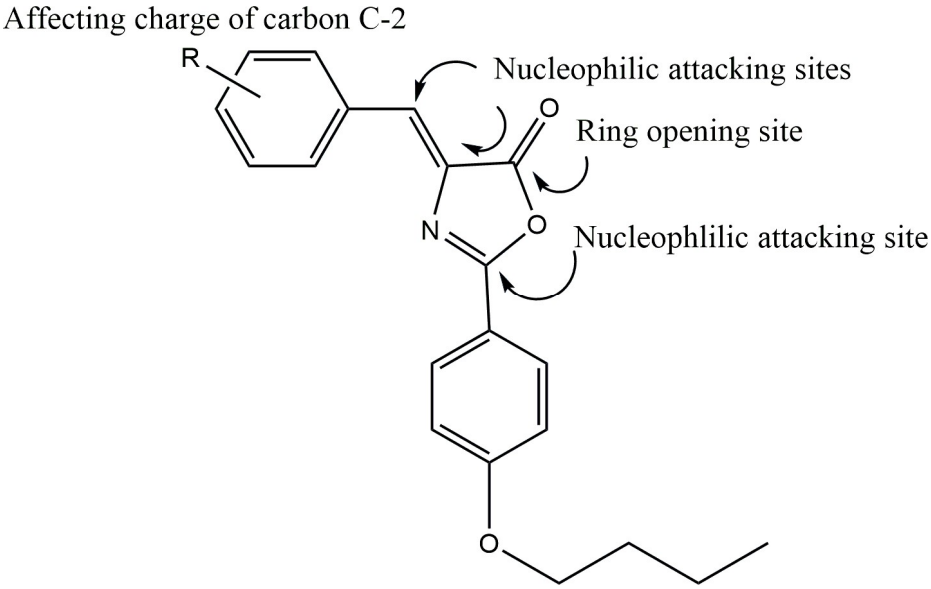


Figure 5.19: Schematic diagram of oxazolone derivative

The most significant chemical process involving oxazolones is the nucleophilic opening of the heterocyclic ring, followed by the hydrolysis and alcoholysis of the compound to form the corresponding esters and amino acids, which can be utilized to form a wide range of novel synthetic amino acids.

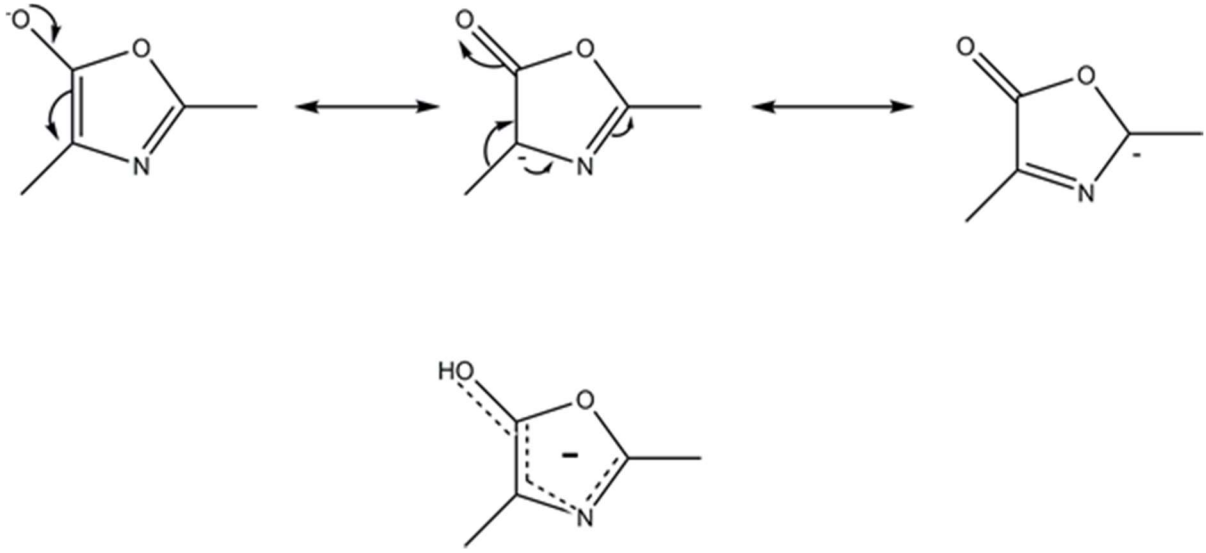
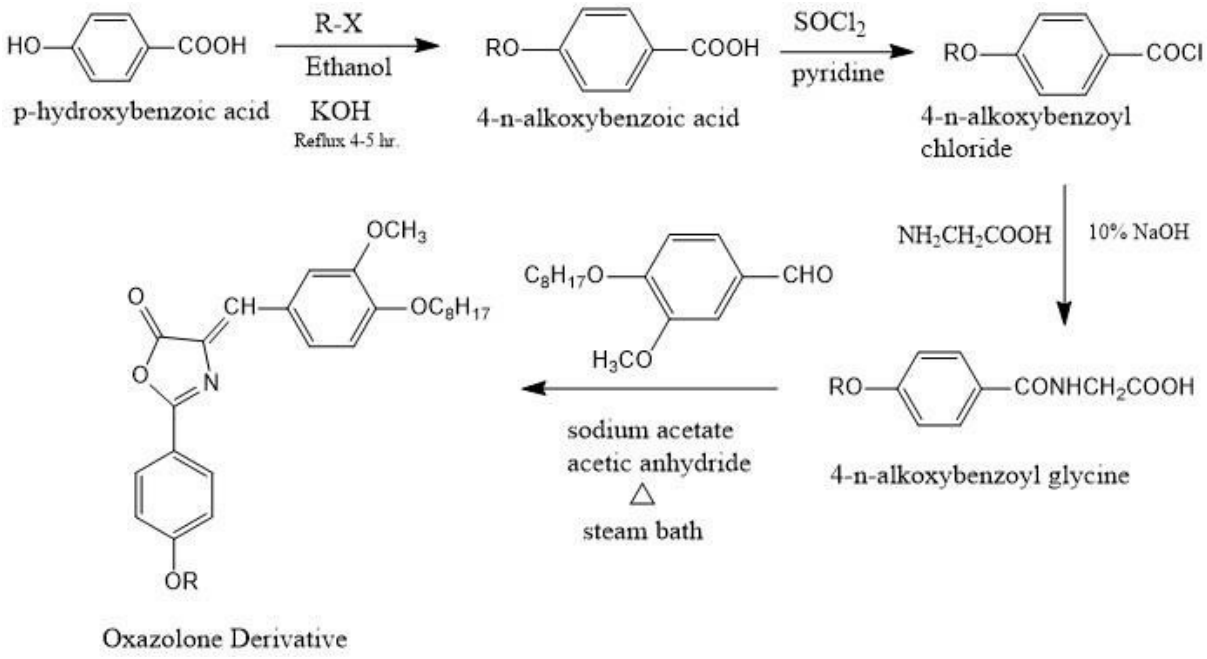


Figure 5.20: Resonance structure of oxazolone structure

4-(3-methoxy-4-octyloxybenzylidene)-2-(4'-alkoxyphenyl)oxazol-5-one (**1-6**) has been synthesized as described in (Scheme 5.14). Firstly, 4-n-alkoxybenzoic acid was formed by the alkylation of p-hydroxybenzoic acid under reflux for 4-5 h. 4-n-alkoxybenzoic acid was treated with $SOCl_2$ to obtain 4-n-alkoxybenzoyl chloride which was further treated with glycine to form 4-n-alkoxy benzoyl glycine. 4-n-alkoxy benzoyl glycine was treated with substituted

aromatic aldehyde, anhydrous sodium acetate, and acetic anhydride and refluxed for 1 h to obtain an oxazolone derivative. The yield obtained was between 64-75%.

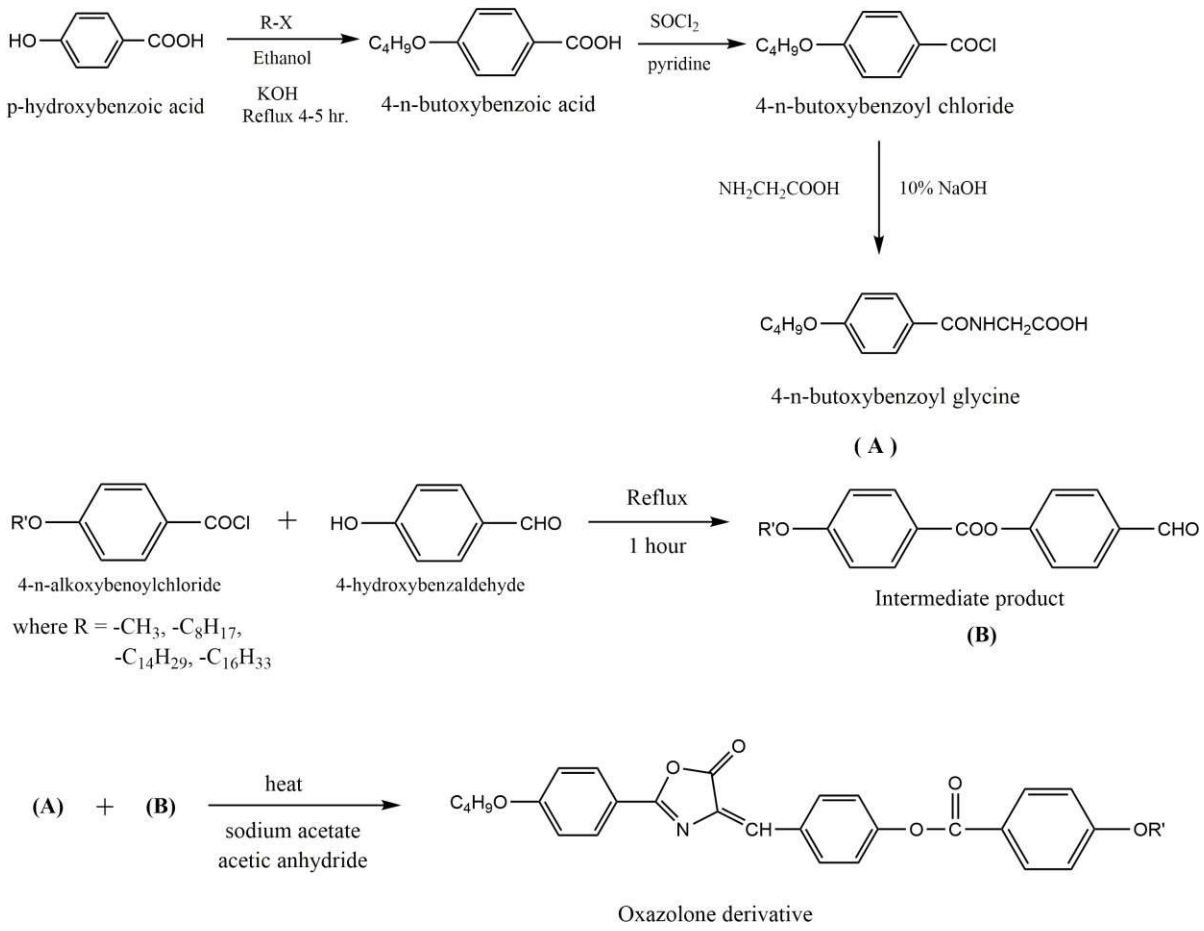
(E)-4-((2-(4-butoxyphenyl)-5-oxooxazol-4(5*H*)-ylidene)methyl)phenyl4'(alkyloxy)benzoate (**1'- 4'**) has been synthesized as described in (Scheme 5.15). A multi-step synthesis was conducted in (Scheme 5.15) to obtain new oxazolone derivatives. The reaction's first three steps are described in (Scheme 5.14). To obtain 4-formyl phenyl-(alkoxy)benzoate, 4-n-alkoxybenzoyl chloride was combined with 4-hydroxybenzaldehyde and refluxed for 1 h. A mixture of 4-n-alkoxy benzoyl glycine and 4-formyl phenyl 4'-(alkoxy)benzoate using acetic anhydride and anhydrous sodium acetate was heated to form oxazolone derivative. The yield obtained was between 60-65%.



Scheme 5.14: Synthesis of Oxazolone derivatives

Table 5.2: Physical Data of Synthesized Compounds

Compound	R	Melting Point(°C)	Yield (%)
1	$-C_6H_{13}$	153.2	70
2	$-C_8H_{17}$	140.6	74
3	$-C_{10}H_{21}$	138.2	68
4	$-C_{12}H_{25}$	144.6	75
5	$-C_{14}H_{29}$	148.8	64
6	$-NO_2$	172.0	66



Scheme 5.15: Synthesis of Oxazolone derivatives

Table 5.3: Physical Data of Synthesized Compounds

Compound	R'	Melting Point(°C)	Yield (%)
1'	$-CH_3$	92.1	60
2'	$-C_8H_{17}$	72.5	65
3'	$-C_{14}H_{29}$	65.4	64
4'	$-C_{16}H_{33}$	60.6	62

5.3.2 Mesomorphic Study of Novel Synthesized Compounds

The melting point of all the novel synthesized compounds (Scheme 5.14 & 5.15) was taken on a Polarizing Optical Microscope. From the Polarizing optical microscopic study of all the novel synthesized compounds of Scheme 5.14, it was observed that none of the compounds exhibit

mesomorphic behavior (Liquid Crystalline Property) due to the hydrogen bonding of amide linkage. In the new class of synthesized compounds containing an oxazolone ring (Scheme 5.14), the $–OCH_3$ is present at a lateral position in the ring which hinders the liquid crystalline property. All the novel synthesized compounds (Scheme 5.14) possess nonlinearity in their molecular structure hence decreasing the mesomorphic nature of the compound. In Scheme 5.15, a new class of compounds was synthesized containing an oxazolone ring by using p-hydroxybenzoic acid as a starting material. The highest terminal cohesions and maximum aromatic nuclear separation are found in the longer chain-length compounds (Scheme 5.15). As a result, it causes the molecule to become less planar and more broader, making the compounds non-mesogenic.

5.3.3 Antibacterial activity

All the compounds were screened for their in vitro antibacterial activity against *Escherichia Coli* and *Micrococcus luteus* which was summarized in Table 5.4. Sterile nutrient agar plates containing about 30 mL nutrient agar (luria agar) and sterile nutrient broth (soft neutral agar) tubes containing 5 mL nutrient broth are prepared under sterile conditions. The bacteria were grown in the nutrient broth under submerged conditions a few hours before the experiment. About 0.1 mL of this culture medium is inoculated on the nutrient agar plate uniformly, once wells are bored using a sterile cork borer. A solution containing 10 mg/0.1 mL was prepared in dimethyl sulfoxide and 0.1 mL of this solution was added to the wells using a micropipette. The plates are incubated at 30 °C for 24 h. The zone of inhibition around the wells is checked and measured.

Table 5.4: Antibacterial activity data of compounds (Scheme-5.14 & 5.15)

Compound code	*Escherichia Coli* (zone in mm)	*Micrococcus Luteus* (zone in mm)
1	10	12
2	11	10
3	12	11
4	07	08
5	09	07
6	08	06
1’	12	11
2’	07	08
3’	09	10
4’	11	12
Standard (Streptomycin)	12	14

The gram-positive bacteria used was Micrococcus luteus while the gram-negative bacteria used was Escherichia Coli.

From the anti-bacterial activity data, it was concluded that all the compounds (Scheme 5.14 & 5.15) show antibacterial activity against E. Coli and Micrococcus luteus as compared to reference standard streptomycin. Amongst all compounds, **2, 3, 1', 4'** shows high antibacterial activity against E. Coli, and **1, 3, 1', 4'** shows the highest activity against Micrococcus luteus.

5.3.4 Seed Infusion Technique (Cytotoxicity)

Using organic solvents like acetone or dichloromethane, bioactive compounds are directly absorbed into seeds in this process. By allowing the bioactive compounds dissolved in the organic solvents to permeate into the seed tissues, these solvents make the seed coverings permeable. This technique involves soaking barley and moong seeds for 1-4 h in a solvent (acetone or dichloromethane) that contains the required solute. The targeted bioactive molecule was absorbed into the seed during these hours. After the infusion procedure, the seeds are taken out of the specific solution and put on a petri dish with filter paper that has been moistened with water to aid in germination. The seeds are kept at a temperature of 25 to 30 °C, and the germination process is seen (Figure 5.21).

Scheme 5.14 Compound codes were attributed as follows:

CO = control, A = Hexa-1, B = Octyl-2, C = Decyl-3, D = Dodecyl-4, E = Nitro-6

Scheme 5.15 Compound codes were attributed as follows:

A = methoxy-1', B = Octyl-2', C = tetradecyl-3', D = Hexadecyl-4'

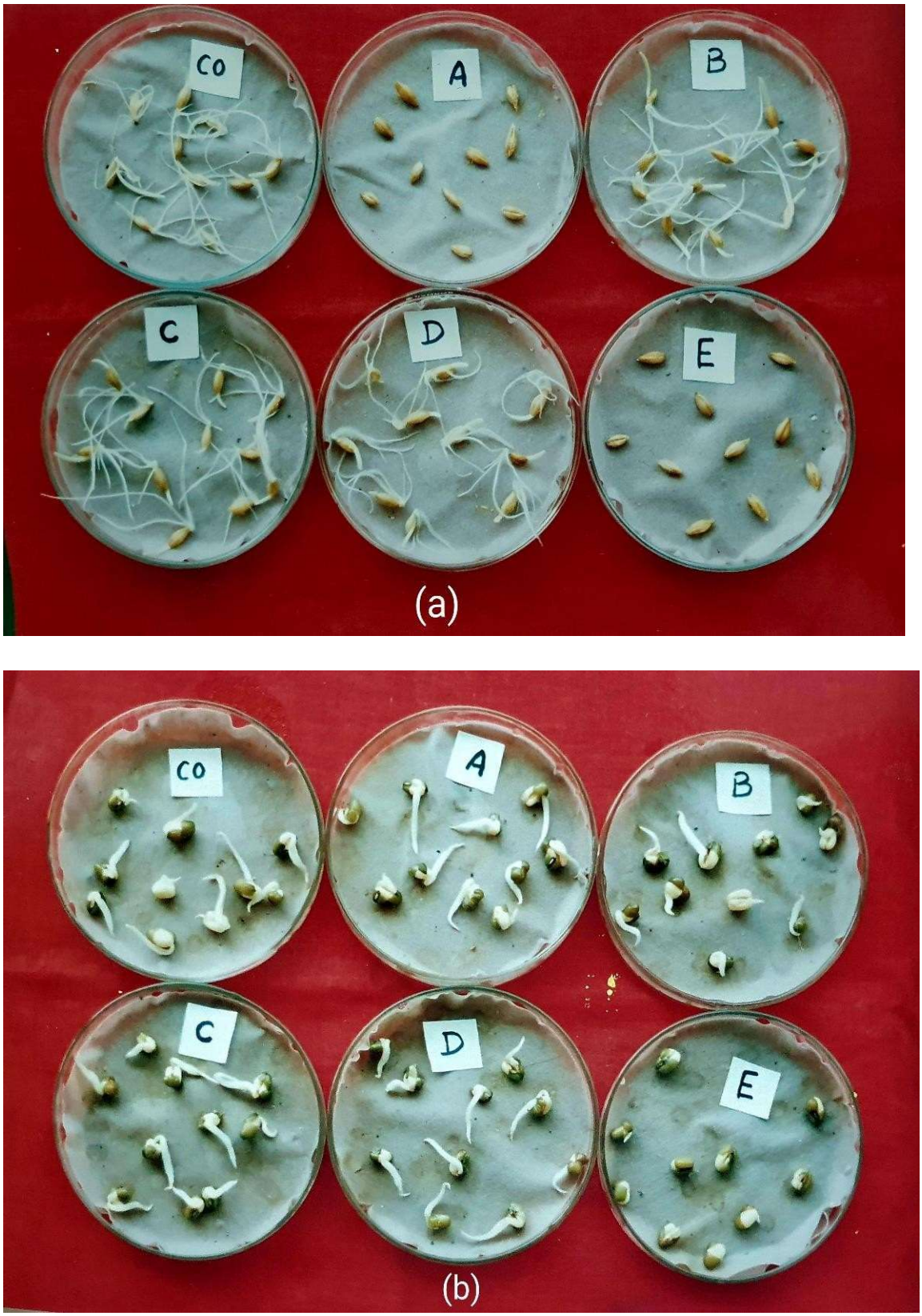


Figure 5.21: (a) Photograph showing the effect of the compounds on Barley seed germination on Scheme 5.14 compounds, (b) Photograph showing the effect of the compounds on Moong seed germination Scheme 5.15 compounds.

Table 5.5: For Barley Seeds

	In Ethyl Acetate			In acetone		
Solution used for seed infusion	**Percentage Germination (%)**	**Average Radicle Length (cm)**	**Average Plumule Length (cm)**	**Percentage Germination (%)**	**Average Radicle Length (cm)**	**Average Plumule Length (cm)**
Hexa-1(A)	-	-	-	94.20	4.68	1.92
Octyl-2(B)	100	1.65	0.58	-	-	-
Decyl-3(C)	100	1.60	0.42	78.45	4.72	2.56
Dodecyl-4(D)	100	1.50	0.60	82.60	4.50	1.92
Nitro-6(E)	-	-	-	-	-	-
Water	100	2.82	0.64	92.75	6.2	2.65
Acetone	-	-	-	86.88	4.46	2.40
Methoxy-1’	-	-	-	91.20	4.50	1.86
Octyl-2’	100	2.92	0.80	89.90	4.80	4.60
Tetradecyl-3’	100	2.75	0.60	79.98	3.75	2.60
Hexadecyl-4’	100	2.20	0.50	80.20	3.02	1.50
Water	100	2.90	0.65	92.80	6.4	2.50
Acetone	-	-	-	86.50	4.42	2.20

Table 5.6: For Moong Seeds

	In Ethyl Acetate		In acetone	
Solution used for seed infusion	**Percentage Germination (%)**	**Average Radicle Length (cm)**	**Percentage Germination (%)**	**Average Radicle Length (cm)**
Hexa-1(A)	90.50	1.40	92.40	1.60
Octyl-2(B)	86.52	0.60	88.50	1.80
Decyl-3(C)	90.42	1.38	74.80	1.20
Dodecyl-4(D)	90.20	1.68	82.80	1.04
Nitro-6(E)	-	-	-	-
Water	88.82	1.40	70.48	3.10
Acetone	-	-	94.86	0.80
Methoxy-1’	90.60	1.50	92.60	1.55
Octyl-2’	88.90	0.88	88.60	1.80
Tetradecyl-3’	90.80	1.55	78.90	1.21
Hexadecyl-4’	90.50	1.65	80.50	1.05
Water	88.50	1.40	70.50	2.90
Acetone	-	-	95.60	0.80

5.4. References

[1] Bala S, Saini M, Kamboj S. Methods for the synthesis of Oxazolones, A Review. International Journal of ChemTech Research CODEN. 2011; **3**(3):1102-1118.

[2] Tikdari MA, Fozooni S, and Hamidian H. Dodecatungstophosphoric Acid (H3PW12O40), Samarium and Ruthenium (III) Chloride Catalyzed Synthesis of Unsaturated 2-Phenyl-5(4H)-oxazolone Derivatives under Solvent-free Conditions. Molecules. 2008; **13**(12):3246-3252.

[3] Fisk SJ, Mosey AR, and Jetze JT. The diverse chemistry of oxazol-5-(4H)-ones. ChemSocRev. 2007; **36**(9):1385–1532.

[4] Jothilakshmi K, Karpagavalli M. Design, synthesis and theoretical studies of 4-(benzylidene)-2-methyloxazol-5(4H)-ones. 2021; **8**(1):235-246.

[5] Mekabaty EA. Erlenmeyer Azlactones: Synthesis, Reactions and Biological Activity. International Journal of Modern Organic Chemistry. 2013; **2**(1):40-66.

[6] Osman MO. et.al. Reactivity of Oxazolone Derivative towards Nitrogen and Carbon Nucleophilic Reagents: Applications to the Synthesis of New Heterocycles. International Journal of Modern Organic Chemistry. 2013; **2**(1):11-25.

[7] Mukherjee AK. Heterocycles. Azlactones: Retrospect and Prospect. 1987; **26**(2):1077-1085.

[8] Grzetic J, Oomens J. Spectroscopic evidence for an oxazolone structure in anionic b-type peptide fragments. J Am Soc Mass Spectrom. 2009; **20**(2):334-339.

[9] Pasha MA, Jayashankara VP, Venugopala KN, and Rao KG. Zinc oxide: An efficient catalyst for the synthesis of 4-arylmethylidene-2-phenyl 5(4H)-oxazolones having Antimicrobial activity. Journal of pharmacology and toxicology. 2007; **2**(3):264-270.

[10] Fareed G, Afza N, Versiani AM, Fareed N, Mughal RU, Kalhoro AM, Iqbal L, and Lateef M. Synthesis, spectroscopic characterization and pharmacological evaluation of oxazolone derivatives. J. Serb. Chem. Soc. 2013; **78**(8):1127–1134.

[11] Hamidian H, and Tikdari MA. Synthesis of Unsaturated 5(4H)-Oxazolone Derivatives in the Presence of Antimony Pentafluoride as Catalyst. Asian Journal of Chemistry. 2007; **19**(2):970-974.

[12] Pereira ER, Sancelme M, Voldoire A, and Prudhomme M. Synthesis and antimicrobial activities of 3-N-substituted-4,5-bis(3- indolyl)oxazo1-2-ones. Bioorganic & Medicinal Chemistry Letters. 1997; **7**(1):2503-2506.

[13] Tandel RC, and Mammen D. Synthesis and study of some compounds containing oxazolone ring showing biological activity. Indian Journal of Chemistry. 2008; **47**(6): 932- 937.

[14] Mariappan G, Saha BP, Datta S, Kumar D, and Haldar KP. Design, synthesis, and antidiabetic evaluation of oxazolone derivatives. J. Chem. Sci, May 2011; **123**(3):335–341.

[15] Jat RL, Mishra R, and Pathak D. Synthesis and anticancer activity of 4-benzylidene-2-phenyloxazol-5(4H)-one derivative. International Journal of Pharmacy and Pharmaceutical Sciences. 2012; **4**(1):378-380.

[16] Mekabaty EA. Erlenmeyer Azlactones: Synthesis, Reactions and Biological Activity. International Journal of Modern Organic Chemistry. 2013; **2**(1):40-66.

[17] Islam MA et al. Synthesis of 2-aryl-4-phthalidyliden-l53-oxazolin-5-ones. Chem. Zvesti. 1974; **28**(5):666-667.

[18] Furniss SB. et al. A textbook of practical organic chemistry, Vogel's fifth edition. 1989; 1155.

[19] Fareed G. et al. Synthesis, spectroscopic characterization and pharmacological evaluation of oxazolone derivatives. J. Serb. Chem. Soc. 2013; **78**(8):1127–1134.

[20] Patil GS, Bagul RR, Kamble VM, and Navale VA. A Green Protocol for Erlenmeyer Plochl Reaction by Using [bmIm]OH. J. Chem. Pharm. Res. 2011; **3**(4):285-290.

[21] Mazurkiewicz R. et al. α-Amino acid derivatives with a Cα-P bond in organic synthesis. ARKIVOC. 2007; **4**(1):193-216.

[22] Roiban DG et al. Unsaturated 4, 4'-bis-[5(4H)-oxazolones]: synthesis and evaluation of their ortho-palladation through C-H bond activation. 2011; **368**(1):247-251.

[23] Romanelli G, Autino JC, Vazquez P, Pizzio L, Blanco M, Caceres C. A suitable synthesis of azlactones (4-benzylidene-2-phenyloxazolin-5-ones and 4-alkylidene-2-phenyloxazolin-5-ones) catalyzed by silica–alumina supported heteropolyacids. 2009; **352**(1):208-213.

[24] Koczan G et al. "Synthesis and characterization of 4-ethoxymethylene-2-[1]-naphthyl-5(4H)-oxazolone and its fluorescent amino acid derivatives". Tetrahedron. 2001; **57**(21):4589-4598.

[25] Bird CW, Twibell JD. Further observations on the rearrangement of 3-acylaminoazetidinones. J.chem. Soc.. 1971; 3155.

[26] Pellissier H. Tetrahedron. Dynamic Kinetic Resolution: A Powerful Approach to Asymmetric Synthesis. 2011; **353**(1):659-676.

[27] Mevridis E, Bermperoglou E, Pontiki E, Dimitra HL. 5-(4H)-oxazolones and their benzamides potential bioactive small molecules. Molecules. 2020; **25**(14):1-20.

[28] Curto MJ, and Kozlowski MC. A-Allyl-α-aryl α-Amino Esters in the Asymmetric Synthesis of Acyclic and Cyclic Amino Acids Derivatives by Alkene Metathesis. J.Org.Chem. 2014; **79**(11):5359-5364.

[29] Liu XX, and Hartwig JF. Palladium-catalyst α-arylation of azlactones to form quaternary amino acid derivatives. Org. Lett. 2003; **5**(11):1915-1918.

[30] Fisk JS, Mosey RA, Tepe JJ. The diverse chemistry of oxazol-5-(4H)-ones. J. Am. Chem. Soc. 2007; **36**(9):1432-1440.

[31] Keni M, and Tepe JJ. One pot Friedal Craft/Robinson-Gabriel Synthesis of Oxazoles using oxazolones templates. J. Org. Chem. 2005; **36**(41):4211-4220.

[32] Hirai K. Recent advances in the field of the β-lactone ring formation reaction from the Aspect of the Synthetic Chemistry. 1980; **38**(2):97-114.

[33] Cremonesi G, Dalla CP, and Rosa La C. [2+2] Cycloaddition Reactions of Imines with Cyclic Ketenes: Synthesis of 1,3-Thiazoline Derived Spiro-β-lactams and Their Transformations. Helv. Chim. Acta. 2005; **88**(6):1580-1588.

[34] Padwa A, and Pearson WH. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products. John Wiley and Sons, Hoboken. 2002; 682–747.

[35] Huisgen R, Gotthard H, Bayer HO, and Schaefer FC. Pyrrole Synthesis. Comprehensive Organic Name Reactions and Reagents, 1970; **103**(1):2611-2622.

[36] Clerici F, Gelmi ML, and Trimarco P. 5(4H)-Oxazolones. Part XI. Cycloaddition reaction of oxazolones and munchnones to triphenylvinylphosponium salts as synthetic equivalents of alkynes. Tetrahedron. 1998; **54**(21):5763-5774.

[37] Kildisheva VO, Linkova GM, Knunyants LI. Structure and properties of oxazolones, Bulletin of the Academy of Sciences of the USSR. Division of chemical science. 1957; **6**(1):737-747.

[38] Buzykin BI. Contemporary Problems in the Chemistry of 1,3-Dipolar Reagents: Definition and Orbital Symmetry of Huisgen 1,3-Dipoles. 2013; **3**(3):207-238.

[39] Bellina F, Silvia C, and Rossi R. Synthesis and biological activity of vicinal diaryl-substituted 1H-imidazoles. Tetrahedron. 2007; **63**:4571-4624.

[40] Katrin I, Nerdinger S, Behenke D, Friedrich C. A novel three component one pot synthesis of 1H-Imidazole-4-yl-pyridine. Organic Lett. 2005; **7**(1):39-42.

[41] Gotthardt H, Huisgen R, and Schaefer FC. The Synthesis of the pyrrole ring. Tetrahedron Lett. 1964; **34**(1):54-113.

[42] Maryanoff CA, Karash CB, Turchi IJ, Corey ER and Maryanoff BE. Characterization of a stable carboxylic acid intermediate from 1,3-dipolar cycloaddition of a munchnone with 1,2-dicyanocyclobutene. J. Org. Chem. 1989; **54**(1):3790-3799.

[43] Morien STM, Arndtsen BA. Chiral Phosphorous-Based 1,3-dipoles: A Modular Approach to Enantioselective 1,3-Dipolar Cycloaddition and Polycyclic 2-Pyrroline Synthesis. Org. Lett. 2014; **16**(4):1056-1059.

[44] Dave JS, and Vora RA. Mesomorphic Behaviour of Biphenyl Esters I: Biphenyl-4-Trans-p-n-akoxycinnamates. Molecular Crystals and Liquid Crystals. 1971; **14**(3-4), 319-327.

[45] Mesaik MA, Rahat S, Khan KM, Zia-Ullah, Choudhary MI, Murad S, Ismail Z, Atta-ur-Rahman, and Ahmad A. Synthesis and immunomodulatory properties of oxazolone derivatives. Bioorg Med Chem. 2004; **12**(9):2049-2057.

[46] Ozturk G, Alp S, and Timur S. Photophysical properties of fluorescent oxazol-5-one derivatives in PVC and their application as biosensors in the detection of ACh and AChE inhibitor: Donepezil. Dyes and Pigments. 2008; **76**(3):792-798.

[47] Khan KM, Mughal UR, Khan MTH, Perveen S, and Choudhary MI. A new class of Tyrosinase inhibitors. Bioorg Med Chem 2006; **14**(17):344-351.