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Greener One-pot Synthesis of Chromeno Oxazin and Oxazin Quinoline Derivatives and their Antibacterial Activity

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Abstract**—** *An efficient green method for the synthesis of oxazino quinoline-2-amine derivatives, oxazino quinoline derivatives and chromeno oxazin-5-one derivatives have been synthesized through cyclization of aromatic aldehyde, ammonium acetate, substituted amides and 8-hydroxy-quinoline or 4-hydroxy coumarin by one-pot condensation method is described. The synthesized compounds are characterized by FT-IR, ^{1}H NMR and MASS* spectral techniques *and are screened further for biological activities against Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Bacillus subtilis using cup plate method and disc diffusion method.*

Keywords — One-pot Synthesis, Biological activity, Chromeno oxazin-5-one derivatives, Oxazino quinoline-2-amine derivatives and Oxazino quinoline derivative.

I. INTRODUCTION

One pot synthesis through multi-component reactions [MCRs] has a great role in organic synthesis. These are one step reactions, where the reactants are subjected into a single reactor to form a desired product with high yields without any intermediate formation. Its importance lies mainly in the synthesis of medicinally potent compounds and its convenient preparation than the conventional methods, thereby having great advantage over convergent and conventional synthesis [1-3].

The compounds consisting of quinoline moiety have broad range of applications with biological activity such as anti-malarial, anti-asthmatic, anti-inflammatory and anti-bacterial properties [4,5]. On the other hand, oxazinone derivatives have a considerable property as a non-nucleoside reverse transcriptase inhibitor to fight against HIV virus which is approved by FDA [6]. Heterocyclic compounds having coumarin nuclei have aroused wide range of biological activities [7, 8] such as antibacterial, anticoagulant, antiviral, antifungal, anticancer and anti-inflammatory properties [9]. Coumarins acts as urease inhibitors [10], corrosion inhibitors [11], optical brighteners [12], dispersed fluorescent and laser dyes [13] used in Dye Sensitized Solar Cells (DSSCs)[14-21]. The main importance lies in the functionally substituted chromenes in the field of medicinal chemistry [22-23] as natural fruit and plant extract in Ammi Visnaga as visnadine [25] and in Phlojodicarpus sibiricus as Khellactone [26]. These have perfect vasodilatory properties.

Chromene is the privileged structural component for various natural products consisting of photochemical properties. It is the backbone of many polyphenols found mostly in alkaloids, flavanoids, tocopherols and anthocyanins [27]. The chromene derivatives are potential anticancer agents [28]. Earlier several methods are reported for the synthesis of oxazino quinolines, from aromatic aldehydes, 6-quinolinol and urea under solvent-free conditions using *p*-toluene sulfonic acid at 150 °C [6], 6-quinolinol, benzaldehyde and methylcarbamate using H_2O/ Triethylbenzylammonium- chloride using water as solvent [29] and quinoline, dimethyl acetylenedicarboxylate zwitterions and aldehydes using toluene as solvent [30], 8-hydroxyquinoline, thiourea and formaldehyde by condensation method using *N, N*-Dimethylformamide medium as solvent [31].

In this a novel preparation of oxazino quinolines using different reactants is reported. The main objective of our research is synthesis of active heterocyclic compounds, which involves greener procedures, shorter reaction times, lower temperature conditions, higher yields, and economically desirable processes.

Now we report an efficient greener synthesis of oxazino quinoline-2-amine derivatives, oxazino quinoline derivatives and chromeno oxazin-5-one derivatives through cyclization of aromatic aldehyde, ammonium acetate, amide and 8-hydroxy quinoline ("Fig.1") or 4-hydroxy coumarin ("Fig.2") through one pot condensation method without catalyst.

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II. EXPERIMENTAL

2.1. Chemicals and Apparatus:

All chemicals used in this process are of AR grade fine chemicals, without any further purification. The synthesized oxazino quinoline-2-amine, oxazino quinoline derivatives and chromeno oxazin-5-one derivatives were characterized by FT-IR, ^{1}H NMR and MASS spectral techniques. FT-IR spectra recorded on a (Perkin Elmer Spectra-880) spectrophotometer by using KBr pellets in the region 400 - 4500 cm^{-1} and ^{1}H NMR spectra was characterized by 400 MHz-(Bruker Avance) in $CDCl_3$ solvent and MASS spectra was recorded at 70 eV (MASPEC low resolution mass spectrometer).

2.2. General Procedure for the synthesis of oxazino quinoline-2-amine and oxazino quinoline derivatives and chromeno oxazin-5-one derivatives:

The one pot synthesis of oxazino quinoline-2-amine and oxazino quinoline derivatives and chromeno oxazin-5-one derivatives was carried out in 250 mL round bottomed flask by taking equimolar quantities of aromatic aldehydes (10 mmol), ammonium acetate(10 mmol), substituted amides (10 mmol), 8-hydoxyquinoline or 4-hydroxy coumarin (10 mmol) and 15 mL of ethanol were mixed together in a round bottomed flask and the flask was placed in an oil bath over a hotplate consisting of magnetic stirrer and kept for reflux at 80 °C for one hour. The progress of the reaction was monitored by TLC using mobile phase (n-Hexane:ethyl acetate 3:1). The excel solvent from product mixture was removed under rotatory evaporator to obtain the solid product, which was then recrystalized from hot ethanol, to get the pure products and they are characterized and compared by FT-IR, ^{1}H NMR and MASS spectral techniques which are presented in 3.2 spectral data.

III. RESULTS AND DISCUSSION

The procedure involves the cyclization of aromatic aldehyde, ammonium acetate, 8-hydroxy-quinoline and substituted amides to form oxazino quinoline-2-amine and oxazino quinoline derivatives is described as model reaction shown in "Fig.1" and cyclization of aromatic aldehyde, ammonium acetate, 4-hydroxy coumarin and substituted amides to form chromeno oxazin-5-one derivatives is described as model reaction shown in "Fig.2". The attainability of formation of these derivatives and the reaction conditions are tabulated in "Table 1".

3.1 Plausible Mechanism for the synthesis of oxazino quinoline-2-amine and oxazino quinoline derivatives and chromeno oxazin-5-one derivatives:

In this reaction 8-hyroxy quinoline or 4-hydroxy coumarin, benzaldehyde, ammonium acetate and substituted amides are taken as reactants to run the process. Initially aromatic aldehydes undergo nucleophillic addition with 8-hydroxy quinoline or 4-hydroxy coumarin through Knovenegal condensation reaction to form the intermediate Knovenegal product (1). In the second step, ammonium acetate and substituted amides undergo enolisation. The formed enol product reacts with Knovenegal product to form the highly stabilized product smoothly shown in "Fig.3". In this mechanism 8-hydroxy quinoline or 4-hydroxy coumarin consists of same OH groups and the reaction mechanism is same.

3.2. Spectral and physical data for the synthesized compounds:

2-methyl-4-phenyl-4a,10b-dihydro-4H-[1,3]oxazino[5,6-h]quinoline(4a):

IR (KBr, υ_{max} cm^{-1}): 3056(CH str), 1515(-C=C str), 1274(-C=N str), 1104(-C-O-C str); ^{1}H NMR (400 MHz, $CDCl_3$ δ / ppm): 7.914 - 7.898 (m, Ar-H), 7.894 – 7.838 (m, Ar-H), 7.830 -7.818 (m, Ar-H), 7.813-7.869 (m, Ar-H), 7.564-7.556 (m, Ar-H), 7.559 -7.549(m, Ar-H), 7.543 – 7.532 (m, Ar-H), 7.529-7.519 (m, Ar-H), 7.516 – 7.470 (m, Ar-H), 7.320 – 7.260 (m, Ar-H), 4.04 (s,1H), 1.9 (s, methyl proton); ESMS:275.1 [M+1].

2,4-diphenyl-4a,10b-dihydro-4H-[1,3]oxazino[5,6-h]quinoline(4b):

IR (KBr, υ_{max} cm^{-1}): 3172(CH str), 1624(-C=Cstr), 1250(-C=N str), 1150(-C-O-C str); ^{1}H NMR (400 MHz, $CDCl_3$ δ / ppm): 8.898 (m, Ar-H), 7.835 – 7.829 (m, Ar-H), 7.827 -7.823 (m, Ar-H), 7.814-7.809 (m, Ar-H), 7.805-7.559 (m, Ar-H), 7.556 -7.553(m, Ar-H), 7.543 – 7.537(m, Ar-H), 7.532-7.522 (m, Ar-H), 7.519 – 7.516 (m, Ar-H), 7.473 (m, Ar-H), 7.453 (m, Ar-H), 7.439 (m, Ar-H), 7.435 (m, Ar-H), 7.260 (m, Ar-H), 6.11 (m, Ar-H), 5.897 (s,1H); ESMS: 337.2 [M+1].

4-phenyl-4a,10b-dihydro-4H-[1,3]oxazino[5,6-h]quinolin-2-amine(4c):

IR (KBr, υ_{max} cm^{-1}): 3072(CH str), 1508 (-C=C str), 1275 (-C=N str), 1103(-C-O-C str); ^{1}H NMR (400 MHz, $CDCl_3$ δ / ppm): 7.91 - 7.897 (m, Ar-H), 7.651 – 7.568 (m, Ar-H), 7.549-7.531 (m, Ar-H), 7.506-7.487 (m, Ar-H), 7.357-7.329 (m, Ar-H), 7.311 -7.290(m, Ar-H), 7.260 – 7.126 (m, Ar-H), 7.107 (m, Ar-H), 7.089 (m, Ar-H), 5.862 (m, Ar-H), 4.01 (s,1H), 2.191(s, NH_2 proton); ESMS: 276.2 [M+1].

2,4-diphenylchromeno[3,4-e] [1,3]oxazin-5(4H)-one(4d):

IR (KBr, υ_{max} cm^{-1}): 3090(CH str), 1590(-C=C str), 1200(-C=N str), 1050(-C-O-C str); ^{1}H NMR (400 MHz, $CDCl_3$ δ / ppm): 8.184(m, Ar-H), 8.163 (m, Ar-H), 7.487(m, Ar-H), 7.466(m, Ar-H), 7.454 (m, Ar-H),

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7.447(m, Ar-H), 7.434(m, Ar-H), 7.532-7.522 (m, Ar-H), 7.355 (m, Ar-H), 7.353 (m, Ar-H), 7.334 (m, Ar-H), 7.332(m, Ar-H), 7.260 (m, Ar-H), 7.260 (m, Ar-H), 206(m, Ar-H), 7.187 (m, Ar-H) 5.01 (s,1H); ESMS: 354.2 [M+1].

2-methyl-4-phenylchromeno[3,4-e][1,3]oxazin-5(4H)-one(4e):

IR (KBr, υ_{max} cm^{-1}): 3100(CH str), 1650(-C=C str), 1350(-C=N str), 1050(-C-O-C str); ^{1}H NMR (400 MHz, $CDCl_3$ δ / ppm): 7.504 (m, Ar-H), 7.485 (m, Ar-H), 7.334 (m, Ar-H), 7.315 (m, Ar-H), 7.295 (m, Ar-H), 7.260(m, Ar-H), 7.122 (m, Ar-H), 7.104 (m, Ar-H), 7.085 (m, Ar-H), 3.35 (s,1H), 1.5 (s, methyl proton); ESMS: 291.1 [M+1]

IV. BIOLOGICAL ACTIVITY

The antibiotic potency can be determined using the microbial assays. The basic principle of microbial assay lies in comparison of the inhibition of growth of bacteria by measuring concentration of the product to be investigated with that produced by known concentration of the antibiotic having a known activity.

The methods used for assay are cup plate method and disc diffusion method. The cup plate method is based on the diffusion of an antibiotic from a cavity through the solidified agar layer of a Petri-dish. Growth of inoculated microbe is inhibited entirely in a circular zone around a cavity containing a solution of the antibiotics. Antimicrobial activity of synthesized compounds was screened against 4 human pathogenic bacteria, two gram positive and two gram negative bacteria. Their respective MTCCNO numbers are, *Escherichia coli (Gram-negativeve_(2692), Pseudomonas aeruginosa (Gram-negative)_(2453), Staphylococcus aureus (Gram-positive)_(902), Bacillus subtilis (Gram-positive)_(441).* The activities of the drug samples against 4 human pathogenic bacteria are tabulated in "Table 2". The antibacterial activity of the samples is assessed using the different concentration of the sample i.e., low, intermediate, high. The present investigation reveals that the zone of inhibition increased as the concentration of the sample increased. This is seen in case of the compounds 4a and 4c. Hence the MIC (Minimum Inhibitory Concentration) of these samples that can inhibit bacterial growth is 10µl, 20µl and 30µl respectively. Thus the above samples are able to show antibacterial activity on *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Bacillus subtilis*.

The standard drug streptomycin is found to be very effective anti-microbial agent. Here it is found that the standard drug show antibacterial activity on both gram-positive and gram–negative bacteria and it is found that the zone of inhibition increased as the concentration of the sample increased.

V. FIGURES AND TABLES

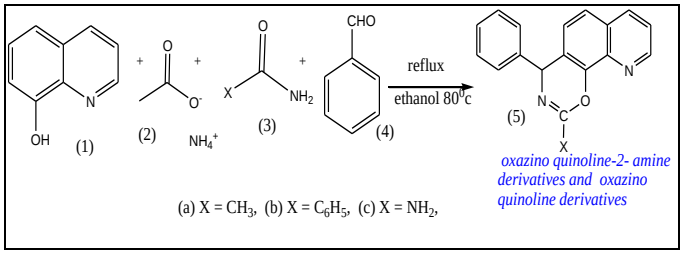

Fig.1: Synthesis of oxazino quinoline-2-amine and oxazino quinoline derivatives

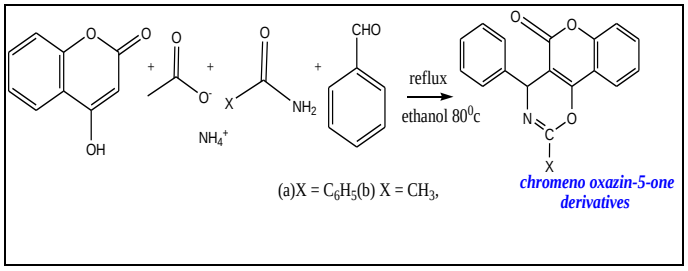

Fig.2: Synthesis of chromeno oxazin-5-one derivatives.

Table.1: Synthesis of oxazino quinoline-2-amine and oxazino quinoline derivatives and chromeno oxazin-5-one derivatives:

S. No	Quinoline/ Coumarin	Amide	Time (min)	Yield %	Product
1	8-hydroxy-quinoline	acetamide	55	96	4a
2	8-hydroxy-quinoline	benzamide	60	92	4b
3	8-hydroxy-quinoline	urea	75	89	4c
4	4- hydroxy coumarin	benzamide	75	85	4d
5	4- hydroxy coumarin	acetamide	70	89	4e

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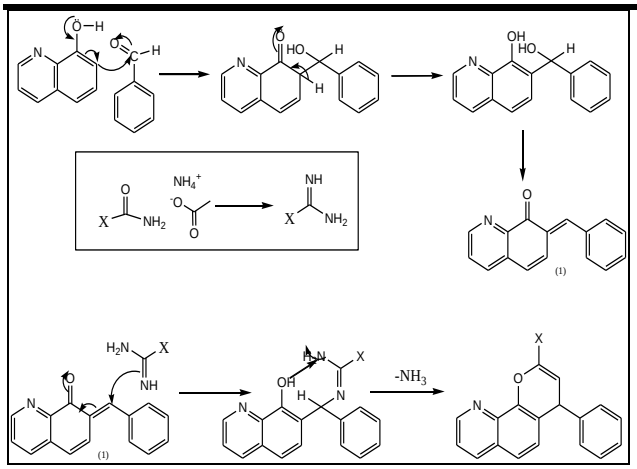

Fig.3: Plausible mechanism for the synthesis of oxazino quinoline-2- amine and oxazino quinoline derivatives

Table.2: Anti-Bacterial activity of drug sample

S.NO	Microorganism	Concentration of the Sample		
		10µl	20µl	30µl
4a	*Escherichia coli*	V3.7	V4.0	V4.7
	Pseudomonas aeruginosa	V3.0	V3.5	V4.0
	Staphylococcus aureus	V2.3	V2.5	V2.7
	Bacillus subtilis	V3.2	V3.5	V3.7
4b	*Escherichia coli*	V1.1	V1.2	V1.4
	Pseudomonas aeruginosa	V	V1.7	V1.9
	Staphylococcus aureus	V2.4	V2.7	V3.2
	Bacillus subtilis	-	-	-
4c	*Escherichia coli*	V3.0	V3.2	V3.5
	Pseudomonas aeruginosa	V2.2	V2.7	V3.5
	Staphylococcus aureus	V2.5	V3.0	V3.5
	Bacillus subtilis	V2.5	V3.6	V4.0
4d	*Escherichia coli*	V1.5	V2.0	V2.5
	Pseudomonas aeruginosa	V1.2	V1.7	V1.9
	Staphylococcus aureus	V1.4	V1.8	V2.0
	Bacillus subtilis	V1.5	V1.7	V2.1
4e	*Escherichia coli*	V2.4	V2.5	V2.9
	Pseudomonas aeruginosa	V1.8	V2.2	V2.5
	Staphylococcus aureus	-	V2.0	V2.3
	Bacillus subtilis	-	-	-

VI. CONCLUSION

In this present study, we report an efficient method for the synthesis of oxazino quinoline-2-amine derivatives, oxazino quinoline derivatives and chromeno oxazin-5-one derivative. This method has advantages like improved yield of products and less reaction times.

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