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"Exploring Pyridine-Quinoline Hybrids: Efficient Synthesis and Their Promising Antimicrobial Properties"

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ABSTRACT:
The main focus of the current research is on the substituted aldehydes that are produced from the reaction of 4-ethoxy acetanilide, DMF, and $POCl_3$. To synthesize a range of substituted quinoline-chalcone conjugates, 2-chloro-6-ethoxyquinoline-3-carbaldehyde reacts with substituted acetophenone(i-iv), and their nucleolytic activity is evaluated. Afterward, substituted chalcone interacts with glacial acetic acid containing ammonium acetate in the presence of malononitrile and Ethylcyanoacetate. Pyridine is a crucial pharmacophore in drug studies, and a preferred scaffold and an exceptional heterocyclic system that offers numerous options for examining and studying this moiety as an antibacterial and antifungal agent by targeting several crucial receptors. In addition, pyridine derivatives have been produced by sealing the chalcone ring.
Keyword: Synthesis, Hetero cycles, Pyridine, Characterization, Biological activity

I. INTRODUCTION:

Quinolines are aromatic compounds that are made up of a pyridine heterocyclic system fused to a benzene ring. With one nitrogen atom in one benzene ring and none in the other ring or at the ring junction, quinolines are also known as benzo[b]pyridine and 1-azanaphthalene. Nitrogen-containing heterocycles have remarkable and fascinating medical and pharmacological capabilities(1).

It has been shown that the Vilsmeier-Haack reagent is a variable reagent that can carry out a wide range of synthetic transformations. It is used in the processes of ring annulation, cyclohaloaddition, formylation, and cyclization.With the aid of the Vilsmeier-Haack reagent ($DMF+POCl_3$) and 4-ethoxy acetanilide, substituted quinolines are very easily, effectively, and conveniently synthesized in a short period and high yield with less amount of raw material under mild conditions. Quinolines are known to have a variety of biological effects. Quinoline derivatives are now a practical starting point for numerous additional substituted quinolines. Heterocyclic compounds can be formylated by heating them in the presence of the Vilsmeier reagent(2).

Edible plants contain large amounts of chalcones, which are thought to be the precursor to flavonoids and isoflavonoids. They are made up of open-chain flavonoids with a three-carbon,α, β-unsaturated carbonyl system connecting the two aromatic rings.In chalcones, two aromatic rings are linked by an aliphatic three-carbon chain. Chalcone bears a very good synthon so that variety of novel heterocycles with good pharmaceutical profiles can bedesigned. Chalcones are unsaturated ketone containing the reactive ketoethylenic group –CO-CH=CH-. These are colored compounds because of the presence of the chromophore -CO-CH=CH-, which depends in the presence of other auxochromes. Different methods are available for the preparation of Chalcones. The most convenient method is the Claisen-Schimdt condensation of equimolar quantities of arylmethylketone with aryl aldehyde in the presence of alcoholic alkali (3).

Chalcones and their synthetic analogs have a variety of therapeutic effects, including anti-cancer, anti-bacterial, anti-fungal, antioxidant, antidepressant, anti-inflammatory, and anti-malarial effects. Due to its abilities as an antioxidant, cytotoxin, and apoptosis inducer, chalcones are regarded as a promising chemical for chemopreventive medications. The main driving force behind the activities of chalcones is the existence ofα, β-unsaturatedcarbonyl bridge.A class of diseases known as cancer is defined by the fast, unchecked, and pathological expansion of aberrant cells. Based on predictions, there were 9.6 million cancer deaths and up to 18.1 million new cancer diagnoses globally in 2018. Some of the leading

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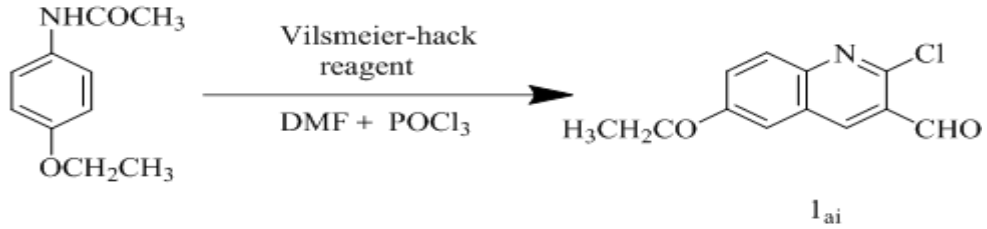
causes of cancer-related mortality are breast cancer, colorectal cancer, and cervical cancer. Despite advancements in cancer chemotherapy, a significant issue still exists about the lack of selectivity needed to prevent the spread of cancer cells while having the least possible impact on healthy cells. Therefore, one of the main goals of medicinal chemistry is to find novel anticancer drugs (4).

One of the core concepts in organic chemistry is the synthesis of pyridine derivatives, which has important applications in the disciplines of materials science, agrochemicals, medicines, and the creation of functional molecules from organic substances. Pyridine is a heterocyclic aromatic molecule with six members that has a nitrogen atom inside of its ring structure. The pyridine ring can be functionalized and modified by adding different substituents, which makes it an adaptable scaffold for making compounds with a wide range of characteristics and uses(5).

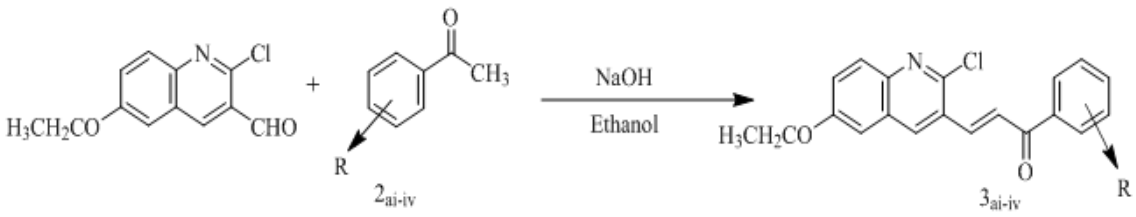
Pyridine derivatives are useful in the search and development of new drugs because of their diverse biological and pharmacological properties. They are the fundamental building blocks of many medications, such as antipsychotics, anti-inflammatory medicines, and anti-infectives. Furthermore, because pyridine derivatives can target particular pests and pathogens, they are commonly used in herbicides and pesticides (6). A significant class of azaheterocycles, pyridine derivatives are present in a wide range of natural products, active medications, and useful materials(7).Many techniques, such as heterocyclization reactions, ring-closure reactions, reductive cyclizations, transition metal-catalyzed reactions, and reactions with pyridine N-oxides, can be used to synthesize pyridine derivatives. The particular derivative of interest and the accessibility of starting materials determine which synthetic process is best. These techniques each present a unique way of adding substituents to the pyridine ring (8).

A class of chemical compounds identified as pyridine derivatives is structurally related to pyridine, a heterocyclic aromatic ring with six members and one nitrogen atom. The fundamental organic compound pyridine has many uses in chemistry and industry. Its derivatives are crucial for the manufacture of numerous medications, agrochemicals, dyes, and other significant goods. (9). Due to the presence of at least one heteroatom (nitrogen) in the ring, pyridine derivatives are heterocyclic compounds with special reactivity and characteristics. (10).A broad range of functional groups, including aryl, alkyl, and other chemical groups, as well as other functional substituents, can be found in pyridine derivatives. The chemical and biological characteristics of the molecules can be influenced by these functional groups. (11).



1_{ai}

SCHEME 1 Synthesis of 2-chloro-6-ethoxyquinoline-3-carbaldehyde **(1_{ai-iv})**



2_{ai-iv} 3_{ai-iv}

	R
2_{ai}	4-Br
2_{aii}	4-F
2_{aiii}	4-OCH_3
2_{iv}	2,4-Cl

	R
3_{ai}	4-Br
3_{aii}	4-F
3_{aiii}	4-OCH_3
3_{iv}	2,4-Cl

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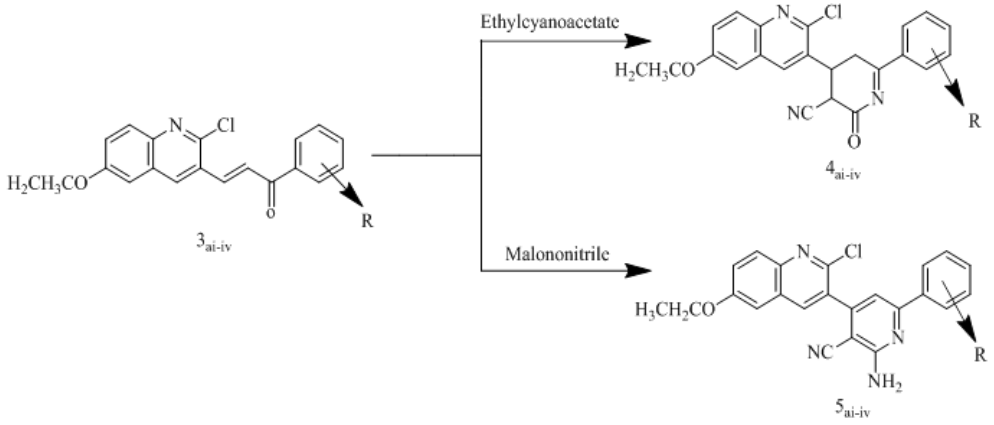
SCHEME 2 Synthesis of substituted chalcone **(3_{ai-iv})**



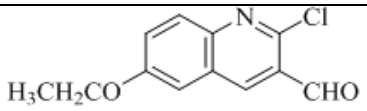
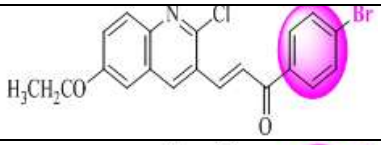
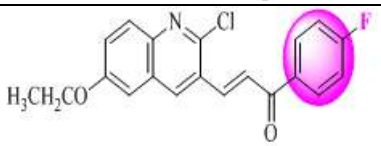
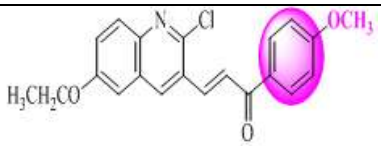
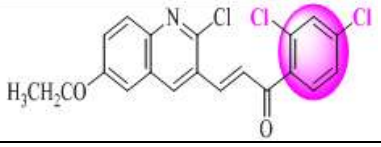
	R
3_{ai}	4-Br
3_{aii}	4-F
3_{aiii}	4-OCH_3
3_{iv}	2,4-Cl

	R
4_{ai}	4-Br
4_{aii}	4-F
4_{aiii}	4-OCH_3
4_{iv}	2,4-Cl

	R
5_{ai}	4-Br
5_{aii}	4-F
5_{aiii}	4-OCH_3
5_{iv}	2,4-Cl

SCHEME 3 Synthesis of Pyridine derivative **(4_{ai-iv} and 5_{ai-iv})**

TABLE 1 Description, molecular formula, Mwt,and m.p., of the synthesized compounds

Compound No.	R	Yield%	M.P. (℃)	M.F	Mwt
1_{ai}		66.82%	213.72℃	$C_{12}H_{10}O_2ClN$	235.67
3_{ai}		63.32%	405.47℃	$C_{20}H_{15}O_2BrClN$	416.70
3_{aii}		72.65%	346.26℃	$C_{20}H_{15}O_2ClFN$	355.79
3_{aiii}		66.67%	379.17℃	$C_{21}H_{18}O_3ClN$	367.83
3_{aiv}		69.94%	418.03℃	$C_{20}H_{14}O_2Cl_3N$	406.69

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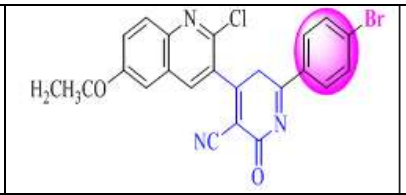
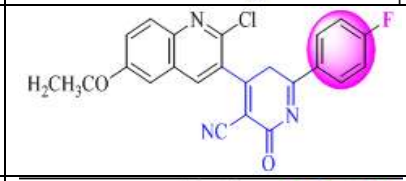
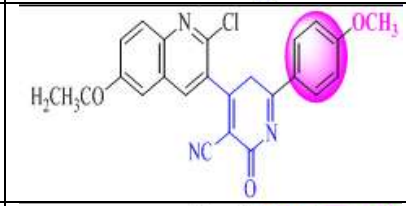
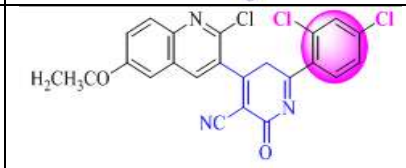
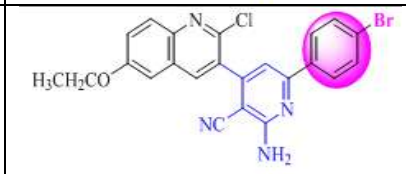
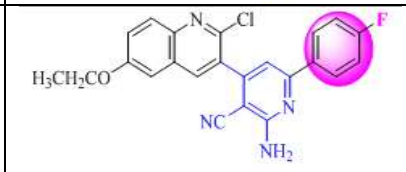
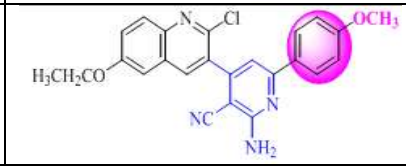
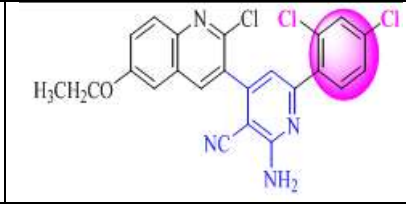
4_{ai}		72.56%	649.88℃	$C_{23}H_{15}O_2BrClN_3$	480.75
4_{aii}		69.94%	590.67℃	$C_{23}H_{15}O_2ClFN_3$	419.84
4_{aiii}		70.22%	623.58℃	$C_{24}H_{18}O_3ClN_3$	431.88
4_{aiv}		65.31%	628.16℃	$C_{23}H_{14}O_2Cl_3N_3$	470.73
5_{ai}		67.88%	678.2℃	$C_{23}H_{16}OBrClN_4$	479.76
5_{aii}		69.92%	618.99℃	$C_{23}H_{16}OClFN_4$	418.86
5_{aiii}		66.66%	651.9℃	$C_{24}H_{19}O_2ClN_4$	430.89
5_{aiv}		69.35%	690.76℃	$C_{23}H_{15}OCl_3N_4$	469.75

II. RESULTS AND DISCUSSION

2.1 | Chemistry

Analytical-grade chemicals produced by Sigma Aldrich and S.D. Fine Chem. Limited were all utilized. The melting point device has determined each melting point. Thin layer chromatography, or TLC, was used to monitor the progress of each process involving the generated molecule. Hexane, ethyl acetate (7:3), and aluminum sheets were the materials utilized for TLC. The TLC plate is submerged in a solvent combination of hexane and ethyl acetate, let to dry, and then placed in a UV transmitter. The Shimadzu ATR-FTIR Spectrophotometer (ώ, cm^{-1}) was used for the spectroscopic investigation of the infrared

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(IR). The synthesized compounds' carbon (^{13}C NMR) and proton (^{1}H NMR) spectra were acquired using a BRUKER apparatus running at 500MHz, respectively. Tetramethyl silane was used as the internal standard, and the chemical shift was indicated by the symbol δ=ppm. DMSOd6 was the solvent that was used. Scheme 1, Scheme 2 and scheme 3 shows the route of synthesis, while the description, molecular formula, Mwt, m.p. of the synthesized compounds are summarized in Table 1.

2.2 | Biological evaluation

2.2.1 | In vitro antimicrobial activity

Evaluation techniques

➢ To evaluate antimicrobial activity, certain requirements must be met:

1. The drug and test organisms must have close contact.
2. Conditions for microbes to flourish must be created.
3. The study should be conducted under identical conditions.
4. Maintaining a sterile and aseptic atmosphere is crucial.

➢ Several techniques can be used to evaluate antibacterial activity:

1. Turbidometric technique
2. Agar dilution technique
3. Serial dilution process
4. Agar Diffusion Method

➢ The agar diffusion method can be applied using the following techniques:

1. Agar Cup technique
2. Paper Disc technique

3. Agar Ditch method

We utilized the Borth Dilution Method to assess the antibacterial activity. This method is a non-automated in vitro bacterial susceptibility test that provides a quantitative result for the amount of antimicrobial agents required to inhibit the growth of specific microorganisms. The test is conducted in tubes and can also be performed using plastic trays in a microdilution format.

Determination of minimal inhibition concentrations by micro broth dilution method

Please take note of the following information:

➢ Materials and methods:

1. All synthesized drugs were used for antibacterial test procedures.
2. All necessary controls were included:

- Drug Control
- Vehicle Control
- Agar Control
- Organism Control
- Known Antibacterial Drugs Control
- All MTCC cultures were tested against the above-mentioned known and unknown drugs.
- Mueller Hinton Broth was used as a nutrient to grow and dilute the drug suspension for the test bacteria.
- The inoculum size for the test strain was adjusted to 10^8 CFU (Colony Forming Unit) per milliliter by comparing the turbidity.
- Common standard strains procured from the Institute of Microbial Technology, Chandigarh were used for screening antibacterial and antifungal activities.

E.coli	P.aeruginosa	S.aureus	S. pyogenus
MTCC443	MTCC1688	MTCC96	MTCC442

C.albicans	A.niger
MTCC227	MTCC282

- DMSO was used as a diluent or vehicle to achieve the desired concentration of drugs to test upon standard bacterial strains.
- The median inhibitory concentration (IC50) value was determined.
- The percentage (%) of bacterial growth inhibition is calculated as [(Ac-At)/Ac] × 100, where Ac is an average of six replicates of light absorption values at wavelength - nm of the negative controls, and At is an average of six replicated light absorption values at wavelength - nm of the samples.
- The IC50 value is calculated using the linear relation between the inhibitory probability and concentration logarithm according to the method of Sakuma. The IC50 value is expressed as the mean ± standard deviation of three independent experiments.

Minimal inhibition concentration [MIC]

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The 'Broth Dilution Method' for determining Minimum Inhibitory Concentration (MIC) offers several advantages, one of which is its ability to readily determine the MIC. Here are the steps involved:

1. Prepare serial dilutions for primary and secondary screening.
2. Inoculate the control tube containing no antibiotic by evenly spreading a loopful over a quarter of a medium suitable for the test organism's growth. Incubate the tubes at 37℃ overnight.
3. Read the MIC of the control organism to verify the accuracy of the drug concentrations.
4. Record the lowest concentration that inhibits the growth of the organism as the MIC.
5. Compare the amount of growth from the control tube before incubation (representing the original inoculum).

Methods used for primary and secondary screening: For each synthesized drug, a stock solution was created by diluting it to a concentration of 2000 micrograms/ml.

- In the primary screening, the synthesized drugs were tested at concentrations of 1000 micro/ml, 500 micro/ml, and 250 micro/ml. The active drugs identified in this screening were then further tested at a second set of dilutions against all microorganisms.
- The active drugs from the primary screening were diluted to concentrations of 200 micro/ml, 100 micro/ml, 50 micro/ml, 12.5 micro/ml, and 6.250 micro/ml for the secondary screening.
- The MIC (minimum inhibitory concentration) was determined by identifying the highest dilution that resulted in at least a 99% inhibition zone. It's important to note that the test results can be affected by the size of the inoculum, and the test mixture should contain 10^8 organisms/ml.
- A summary table of the study results is provided below for easy reference and a better understanding of the findings.

TABLE 2 Antimicrobial activity (MICs, µg/mL) of (3_{ai-iv}, 4_{ai-iv}, 5_{ai-iv})

MINIMAL BACTERICIDAL CONCENTRATION (µg/mL)					MINIMAL FUNGICIDAL CONCENTRATION (µg/mL)	
Compound No.	E. coli	P. aeruginosa	S. aureus	S. pyogenus	C. albicans	A.niger
3_{ai}	100	250	100	250	1000	**250**
3_{aii}	**62.5**	100	125	125	1000	1000
3_{aiii}	100	125	250	125	1000	**250**
3_{aiv}	100	125	**62.5**	100	500	1000
4_{ai}	**62.5**	125	100	125	1000	500
4_{aii}	100	100	125	100	>1000	1000
4_{aiii}	125	**62.5**	100	250	>1000	1000
4_{aiv}	**62.5**	100	100	100	500	500
5_{ai}	100	**50**	100	**62.5**	1000	500
5_{aii}	125	250	250	250	1000	500
5_{aiii}	100	100	250	250	500	500
5_{aiv}	125	250	100	100	500	500
Drug	Micromolar (µg/mL)					
Gentamycin	0.05	1	0.25	0.5	-	-
Ampicillin	30	-	40	25	-	-
Chloramphenicol	50	50	50	50	-	-
Ciprofloxacin	25	25	50	50	-	-
Norfloxacin	10	10	10	10	-	-
Nystatin	-	-	-	-	100	100
Griseofulvin	-	-	-	-	500	100

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2.2.2 | Antimicrobial evaluation

The results displayed in Table revealed that most of the tested compounds had varied inhibitory effects on the growth of both Gram-positive and Gram-negative bacterial strains. 4_{aiii} containing pyridine showed good activity compared to Gentamycin against P. Aeruginosa. 3_{aii}, $4_{ai}$and 4_{aiv}containing pyridine showed good activity compared to Gentamycin against E.coli. 3_{aiv} containing pyridine showed good activity compared to Gentamycin against S. aureus. 5_{ai}containing pyridine showed good activity compared to Gentamycin againstS. pyogenusand also showed good activity compared to Chloramphenicol againstP. Aeruginosa.However, the rest of the compounds were either poor or moderately active against all of the organisms with higher MIC values. Additionally, new derivatives were tested as potential antifungal agents. Compound $3_{ai}$and 3_{aiii}containing Pyridinewere found to be as effective as the reference drug Griseofulvin against A. niger. However, other compounds did not show satisfactory results.

III. CONCLUSIONS

In the first step 4-Ethoxyacetanilide raect with DMF and $POCl_3$to give2-chloro-6-ethoxyquinoline-3-carbaldehyde**(1_{ai})**product. In the second step2-chloro-6-ethoxyquinoline-3-carbaldehyde react with substituted acetophenone (4-Fluoroacetophenone, 4-Methoxyacetophenone, 2,4-dichloroacetophenone and 4-fluoroacetophenone) in the preserance of Ethanol and NaOH gives substituted chalcone**(3_{ai-iv})**. In the third step substituted chalcone react with Ethylcyanoacetate and malononiteile in the presence of galcial acetic acid contaning ammonium acetate to give pyridine derivative**(4_{ai-iv} and 5_{ai-iv})**. The structures of the new compounds were confirmed bt different spsctroscopic techniques. Compound3_{aii}, $4_{ai}$and 4_{aiv} demonstrated excellent activity againstE.coli. at a concentration of 62.5µg/mL. Compound 3_{aiv}demonstrated excellent activity againstS. aureus at a concentration of 62.5µg/mL. Compound4_{aiii} exhibited potency againstP. Aeruginosa at a concentration of 62.5µg/mL. Compound5_{ai} demonstrated excellent activity against S. pyogenusat a concentration of 62.5µg/mL also showed activity against P. Aeruginosaat a concentartion of 50µg/mL.While compound $3_{ai}$and 3_{aiii}showed good antifungal activity. These findings suggest that these compounds hold promise for further reserach in the development of novel antimicrobial agents.

IV. EXPERIMENTAL

4.1 | Materials and methods

All chemicals used were manufactured by Sigma Aldrich and S.d. Fine Chem. Limited and were of analytical grade. Each melting point has been determined by the melting point apparatus. With the use of TLC, or thin layer chromatography, the development of every reaction involving the produced molecule was tracked. The following materials were used for TLC: Aluminium sheets, Hexane and ethyl acetate (8:2). TLC plate put in the mixture of hexane and ethyl acetate for solvent running and then removed from the mixture then dry and put in the UV transmitter.The Shimadzu ATR-FTIR Spectrophotometer (ώ, cm^{-1}) was used for the spectroscopic investigation of the infrared (IR). The synthesized compounds carbon (^{13}C NMR) and proton (^{1}H NMR) spectra were acquired using a BRUKER apparatus running at 500MHz, respectively. Tetramethyl silane was used as the internal standard, and the chemical shift was indicated by the symbol δ=ppm. $CDCl_3$ was the solvent that was used.

4.2 | Preparation of2-chloro-6-ethoxyquinoline-3-carbaldehyde(1_{ai})

Take 5 ml of dimethyl formamide (DMF), cool it to 0 °C, and place it in a flask with a drying tube. then 18 ml of $POCl_3$ (Phosphorous Oxy Chloride) are dropped into the solution while stirring. Then, add 4 grams of 4-ethoxy acetanilide to this solution. After just a few minutes, the solution of the reaction mixture is refluxed for 6–8 hours using an air condenser and maintaining a temperature of 80–90℃.

After the completion of the necessary time, the reaction mixture is cooled, poured into a 100 ml beaker of ice-cold water, and agitated for about 30 minutes. The quinoline is then filtered, washed with water, dried, and then recrystallized from ethyl acetate (12).

4.2.1| 2-chloro-6-ethoxyquinoline-3-carbaldehyde(1_{ai})

Yield: 66.82%; solid; M.P. 213.72℃; IR ((ύ, cm^{-1}):3064.99 (C-H, aromatic, quinoline ring), 2883.68 (C-H,ethoxy group), 2808.45 (C-H, aldehyde group), 1749.49 (C=O, aldehyde group), 1545.03 (C=C, aromatic, quinoline ring), 1244.13 (C-N, aromatic, quinoline ring),1144.80(C-O, ethoxy group), 744.55 (C-Cl); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm):1.2-1.5 (t, 3H, $-CH_3$), 4.0-4.5 (q, 2H, $-CH_2$), 7-9 (m, 5H, Ar-H), 9.5-10.0 (s, 1H, CHO); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 ($-CH_3$),

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64.6 (-CH_2), 107.4 (Ar-C), 126.3 (Ar-C), 126.9 (Ar-C),129.0 (Ar-C), 130.1 (Ar-C), 141.7 (Ar-C), 142.4 (Ar-C), 148.6 (Ar-C), 158.3 (Ar-C), 189.2 (Ar-C).

4.3 | Preparation ofsubstituted chalcone (3_{ai-iv})

To a stirred mixture of substituted acetophenone (2_{ai-iv}) (0.6 g, 5.2 mmol) and 2-chloro-6-ethoxyquinoline-3-carbaldehyde (1.050 g, 5.2 mmol) dissolved in 10 ml of 95% ethanol was added 2 ml of 2.5 M NaOH. The resulting solution was stirred at room temperature and the mixture was precipitated over five minutes. and after 1 hour the reaction mixture is maintained overnight at 0 to 5°C. The reaction mixture is poured into cold water, filtered and the solids washed with cold ethanol and water. The desired product was prepared by recrystallization of the crude product obtained from MeOH (13).

4.3.1|1-(4-bromophenyl)-3-(2-chloro-6-ethoxyquinoline-3-yl)prop-2-en-1-one(3_{ai})

Yield:63.32%; solid; M.P.405.47°C; IR(ύ, cm^{-1}):3064.99 (C-H, aromatic, quinoline and phenyl rings),2982.05 (C-H, ethoxy group), 1676.20 (C=O, α,β-unsaturated ketone),1585.54 (C=C, conjugated with C=O), 1494.88 (C=C, aromatic, quinoline and phenyl rings), 1230.63 (C-N, aromatic, quinoline ring), 1055.10 (C-O, ethoxy group), 736.83 (C-Cl), 580.59 (C-Br); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.2-1.5 (t, 3H, -CH_3), 4.0-4.5 (q, 2H, -CH_2), 7-9 (m, 10H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm):14.8 (-CH_3), 64.6 (-CH_2), 105.6 (Ar-C), 123.2 (Ar-C), 127.5 (Ar-C), 127.3 (Ar-C), 128.9 (Ar-C), 130.0 (Ar-C), 131.0 (Ar-C), 132.1 (Ar-C), 134.4 (Ar-C), 136.9 (Ar-C), 142.5 (Ar-C), 145.1 (Ar-C), 147.1 (Ar-C), 157.6 (Ar-C), 189.7 (Ar-C).

4.3.2| 3-(2-chloro-6-ethoxyquinoline-3-yl)-1-(4-fluorophenyl)prop-2-en-1-one(3_{aii})

Yield: 72.65%; solid; M.P.346.26°C; IR(ύ, cm^{-1}):3076.56 (C-H, aromatic, quinoline and phenyl rings), 2985.91 (C-H, ethoxy group), 1680.05(C=O, α,β-unsaturated ketone), 1591.33 (C=C, conjugated with C=O), 1498.74(C=C, aromatic, quinoline and phenyl rings), 1232.55 (C-N, aromatic, quinoline ring), 1055.10 (C-O, ethoxy group), 1118.75 (C-F), 789.82(C-Cl); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.2-1.5 (t, 3H, -CH_3), 4.0-4.5 (q, 2H, -CH_2), 7-9 (m, 10H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 (-CH_3), 64.6 (-CH_2), 105.6 (Ar-C), 116.0 (Ar-C), 123.2 (Ar-C), 127.3 (Ar-C), 127.5 (Ar-C), 128.9 (Ar-C), 131.0 (Ar-C), 131.5 (Ar-C), 133.5 (Ar-C), 134.4 (Ar-C), 142.5 (Ar-C), 145.1 (Ar-C), 147.1 (Ar-C), 157.6 (Ar-C), 168.7 (Ar-C), 189.7 (Ar-C).

4.3.3| 3-(2-chloro-6-ethoxyquinoline-3-yl)-1-(4-methoxyphenyl)prop-2-en-1-one(3_{aiii})

Yield: 66.67%; solid; M.P.379.17°C; IR(ύ, cm^{-1}):3088.85 (C-H, aromatic, quinoline and phenyl rings), 2995.55 (O-CH_3, methoxy group), 2933.83 (C-H, ethoxy group), 1676.20(C=O, α,β-unsaturated ketone), 1589.40 (C=C, conjugated with C=O), 1433.16(C=C, aromatic, quinoline and phenyl rings), 1249.91 (C-N, aromatic, quinoline ring), 1124.54 (C-O, ethoxy group), 1043.52 (C-O, methoxy group), 744.55(C-Cl); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.2-1.5 (t, 3H, -CH_3), 3.5-4.0 (s, 3H, -OCH_3), 4.0-4.5 (q, 2H, -CH_2), 7-9 (m, 10H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 (-CH_3), 55.8 (-OCH_3), 64.6 (-CH_2), 105.6 (Ar-C), 114.8 (Ar-C), 123.2 (Ar-C), 127.3 (Ar-C), 127.5 (Ar-C), 128.9 (Ar-C), 130.2 (Ar-C), 130.9 (Ar-C), 131.0 (Ar-C), 134.4 (Ar-C), 142.5 (Ar-C), 145.1 (Ar-C), 147.1 (Ar-C),157.6 (Ar-C), 166.4 (Ar-C), 189.7 (Ar-C).

4.3.4 | 3-(2-chloro-6-ethoxyquinoline-3-yl)-1-(2,4-dichlorophenyl)prop-2-en-1-one(3_{aiv})

Yield: 69.94%; solid; M.P.418.03°C; IR(ύ, cm^{-1}):3076.56 (C-H, aromatic, quinoline and phenyl rings), 2985.91 (C-H, ethoxy group), 1668.48(C=O, α,β-unsaturated ketone), 1587.47 (C=C, conjugated with C=O), 1494.88(C=C, aromatic, quinoline and phenyl rings), 1230.63 (C-N, aromatic, quinoline ring), 1055.10 (C-O, ethoxy group), 779.27(C-Cl); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.2-1.5 (t, 3H, -CH_3), 4.0-4.5 (q, 2H, -CH_2), 7-9 (m, 10H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 (-CH_3), 64.6 (-CH_2), 105.6 (Ar-C), 123.2 (Ar-C), 127.3 (Ar-C), 127.4 (Ar-C), 127.5 (Ar-C), 128.9 (Ar-C), 129.5 (Ar-C), 131.0 (Ar-C), 131.8 (Ar-C), 132.7 (Ar-C), 134.4 (Ar-C), 135.1 (Ar-C), 142.5 (Ar-C), 145.1 (Ar-C), 146.2 (Ar-C), 147.1 (Ar-C), 157.6 (Ar-C), 189.7 (Ar-C).

4.4 | Preparation of Pyridine derivative (4_{ai-iv} and 5_{ai-iv})

Glacial acetic acid contains ammonium acetate (0.77 g, 10 mmol), mixed with appropriate chalcone (3_{ai-iv}) (10 mmol), Malononitrile (10 mmol) and ethyl cyanoacetate (10 mmol). Acetic acid evaporated under reduced pressure, cooled, and then poured. On the cube of ice, respectively while rotating. To obtain related pyridines, was reinstalled from a solid, dry, and appropriate solvent(14).

4.4.1|6-(4-bromophenyl)-4-(2-chloro-6-ethoxyquinoline-3-yl)-2-oxo-2,5-dihydropyridine-3-carbonitrile(4_{ai})

Yield: 72.56%; solid; M.P.649.88°C; IR(ύ, cm^{-1}): 3066.92 (C-H, aromatic, quinoline and

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phenyl rings), 2210.50 (C≡N, cyanide group), 1720.22 (C=O), 1587.47 (C=C, aromatic, quinoline and phenyl rings), 1232.55 (C-N, aromatic, quinoline ring), 734.90 (C-Cl), 607.80 (C-Br); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.0-2.0 (t, 1H, -CH_3),2.0-3.0 (m, 2H, dihydropyridine ring -CH_2), 3.5-4.5 (q, 2H, ethoxy group -CH_2), 7-9 (m, 8H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 (-CH_3), 37.2 (quinoline ring -CH_2), 64.6 (-CH_2),105.6 (Ar-C),111.1 (Ar-C), 115.8 (Ar-C), 123.2 (Ar-C), 125.4 (Ar-C), 127.5 (Ar-C), 128.6 (Ar-C), 128.9 (Ar-C), 131.0 (Ar-C), 131.7 (Ar-C), 133.0 (Ar-C), 134.4 (Ar-C), 142.5 (Ar-C),147.1 (Ar-C), 157.6 (Ar-C), 164.6 (Ar-C), 165.4 (Ar-C), 173.9 (Ar-C).

4.4.2|4-(2-chloro-6-ethoxyquinoline-3-yl)-6-(4-fluorophenyl)-2-oxo-2,5-dihydropyridine-3-carbonitrile(4_{aii})

Yield: 69.94%; solid; M.P.590.67℃; IR(ύ, cm^{-1}): 3067.93 (C-H, aromatic, quinoline and phenyl rings), 2210.50 (C≡N, cyanide group), 1720.22 (C=O), 1591.33 (C=C, aromatic, quinoline and phenyl rings), 1234.48 (C-N, aromatic, quinoline ring), 1114.89 (C-F), 734.90 (C-Cl); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.0-2.0 (t, 1H, -CH_3),2.0-3.0 (m, 2H, dihydropyridine ring -CH_2), 3.5-4.5 (q, 2H, ethoxy group -CH_2), 7-9 (m, 8H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 (-CH_3), 37.2 (quinoline ring -CH_2), 64.6 (-CH_2), 105.6 (Ar-C),111.1 (Ar-C), 115.6 (Ar-C), 115.8 (Ar-C), 123.2 (Ar-C),127.5 (Ar-C), 128.9 (Ar-C), 129.5 (Ar-C), 129.6 (Ar-C), 131.0 (Ar-C), 134.4 (Ar-C), 142.5 (Ar-C), 147.1 (Ar-C), 157.6 (Ar-C), 164.6 (Ar-C), 165.2 (Ar-C), 165.4 (Ar-C), 173.9 (Ar-C).

4.4.3|4-(2-chloro-6-ethoxyquinoline-3-yl)-6-(4-methoxyphneyl)-2-oxo-2,5-dihydropyridine-3-carbonitrile(4_{aiii})

Yield: 70.22%; solid; M.P.623.58℃; IR(ύ, cm^{-1}): 3066.92 (C-H, aromatic, quinoline and phenyl rings), 2210.50 (C≡N, cyanide group), 1720.22 (C=O), 1504.53 (C=C, aromatic, quinoline and phenyl rings), 1230.63 (C-N, aromatic, quinoline ring), 1041.60 (C-O, methoxy group), 765.77 (C-Cl); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.0-2.0 (t, 3H, -CH_3),2.0-3.0 (m, 2H, dihydropyridine ring -CH_2), 3.5-4.0 (s, 3H, -OCH_3), 3.5-4.5 (q, 2H, ethoxy group -CH_2), 7-9 (m, 8H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 (-CH_3), 37.2 (quinoline ring -CH_2), 55.8 (-OCH_3), 64.6 (-CH_2), 105.6 (Ar-C),111.1 (Ar-C), 114.4 (Ar-C), 115.8 (Ar-C), 123.2 (Ar-C), 126.3 (Ar-C), 127.5 (Ar-C), 128.7 (Ar-C), 128.9 (Ar-C), 131.0 (Ar-C), 134.4 (Ar-C), 142.5 (Ar-C), 147.1 (Ar-C), 157.6 (Ar-C), 162.9 (Ar-C), 164.6 (Ar-C), 165.4 (Ar-C), 173.9 (Ar-C).

4.4.4|4-(2-chloro-6-ehoxyquinoline-3-yl)-6-(2,4-dichlorophenyl)-2-oxo-2,5-dihydropyridine-3-carbonitrile(4_{aiv})

Yield: 65.31%; solid; M.P.628.16℃; IR(ύ, cm^{-1}): 3050.86 (C-H, aromatic, quinoline and phenyl rings), 2210.50 (C≡N, cyanide group), 1720.22 (C=O), 1575.89 (C=C, aromatic, quinoline and phenyl rings), 1232.55 (C-N, aromatic, quinoline ring), 1055.10 (C-O, ethoxy group),), 785.77 (C-Cl); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.0-2.0 (t, 3H, -CH_3),2.0-3.0 (m, 2H, dihydropyridine ring -CH_2), 3.5-4.5 (q, 2H, ethoxy group -CH_2), 7-9 (m, 7H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 (-CH_3), 36.7 (quinoline ring -CH_2), 64.6 (-CH_2), 105.6 (Ar-C),111.1 (Ar-C), 115.8 (Ar-C), 123.2 (Ar-C), 126.5 (Ar-C),127.5 (Ar-C), 128.3 (Ar-C), 128.9 (Ar-C), 129.1 (Ar-C), 131.0 (Ar-C), 134.4 (Ar-C), 134.6 (Ar-C), 135.3 (Ar-C), 142.5 (Ar-C), 147.1 (Ar-C), 157.6 (Ar-C), 164.6 (Ar-C), 165.4 (Ar-C), 173.9 (Ar-C).

4.4.5| 2-amino-6-(4-bromophenyl)-4-(2-chloro-6-ethoxyquinoline-3-yl)pyridine-3-carbonitrile(5_{ai})

Yield: 67.88%; solid; M.P.678.2℃; IR(ύ, cm^{-1}):3358.25 (N-H, amino group), 3066.92 (C-H, aromatic, quinoline, pyridine and phenyl rings), 2985.91 (C-H, ethoxy group), 2230.50 (C≡N, nitrile group), 1581.68 (C=C, aromatic, quinoline, pyridine and phenyl rings), 1228.70 (C-N, aromatic, quinoline and pyridine rings), 1058.96 (C-O, ethoxy group),), 730.89 (C-Cl), 578.65 (C-Br); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.0-2.0 (t, 3H, -CH_3), 3.5-4.5 (q, 2H,-CH_2), 5-7 (s, 2H, amino), 7-9(m, 12H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 (-CH_3), 64.6 (-CH_2), 86.2 (Ar-C), 105.6 (Ar-C),111.7 (Ar-C), 113.7 (Ar-C), 121.7 (Ar-C), 123.4 (Ar-C),128.4 (Ar-C), 129.3 (Ar-C), 131.2 (Ar-C), 132.1 (Ar-C), 135.2 (Ar-C), 135.6 (Ar-C), 138.0 (Ar-C), 141.4 (Ar-C), 147.7 (Ar-C), 152.2 (Ar-C), 156.2 (Ar-C), 157.4 (Ar-C), 162.0 (Ar-C).

4.4.6| 2-amino-4-(2-chloro-6-ethoxyquinoline-3-yl)-6-(4-fluorophenyl)pyridine-3-carbonitrile(5_{aii})

Yield: 69.92%; solid; M.P.618.99℃; IR(ύ, cm^{-1}): 3446.91 (N-H, amino group), 3066.92 (C-H, aromatic, quinoline, pyridine and phenyl rings), 2985.91 (C-H, ethoxy group), 2210.50 (C≡N, nitrile group), 1593.25 (C=C, aromatic, quinoline, pyridine and phenyl rings), 1228.70 (C-N, aromatic, quinoline and pyridine rings),1166.97 (C-F), 1049.31 (C-O, ethoxy group); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.0-2.0 (t, 3H, -CH_3), 3.5-4.5 (q, 2H, -CH_2), 5-7 (s, 2H, amino), 7-

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9(m, 12H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 (-CH_3), 64.6 (-CH_2), 86.2 (Ar-C), 105.6 (Ar-C), 111.7 (Ar-C), 113.7 (Ar-C), 116.0 (Ar-C), 123.4 (Ar-C), 129.3 (Ar-C), 130.7 (Ar-C), 131.2 (Ar-C), 134.6 (Ar-C), 135.2 (Ar-C), 135.6 (Ar-C), 141.4 (Ar-C), 147.7 (Ar-C), 152.2 (Ar-C), 156.2 (Ar-C), 157.4 (Ar-C), 161.5 (Ar-C), 162.0 (Ar-C).

4.4.7| 2-amino-4-(2-chloro-6-ethoxyquinoline-3yl)-6-(4-methoxyphenyl)pyridine-3-carbonitrile(5_{aiii})

Yield: 66.66%; solid; M.P.651.9℃; IR(ύ, cm^{-1}): 3446.91 (N-H, amino group), 3066.92 (C-H, aromatic, quinoline, pyridine and phenyl rings), 2985.91 (C-H, ethoxy group), 2210.50 (C≡N, nitrile group), 1502.60 (C=C, aromatic, quinoline, pyridine and phenyl rings), 1246.06 (C-N, aromatic, quinoline and pyridine rings), 1116.82 (C-O, ethoxy group), 1037.73 (C-O, ethoxy group); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.0-2.0 (t, 3H, -CH_3), 3.7-4.0 (s, 3H, -OCH_3),3.5-4.5 (q, 2H, -CH_2), 5-7 (s, 2H, amino), 7-9(m, 12H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 (-CH_3), 55.8 (-OCH_3), 64.6 (-CH_2), 86.2 (Ar-C), 105.6 (Ar-C), 111.7 (Ar-C), 113.7 (Ar-C), 114.8 (Ar-C), 123.4 (Ar-C), 128.6 (Ar-C), 129.3 (Ar-C), 131.2 (Ar-C), 131.3 (Ar-C), 135.2 (Ar-C), 135.6 (Ar-C), 141.4 (Ar-C), 147.7 (Ar-C), 152.2 (Ar-C), 156.2 (Ar-C), 157.4 (Ar-C), 159.2 (Ar-C), 162.0 (Ar-C).

4.4.8| 2-amino-4-(2-chloro-6-ethoxyquinoline-3-yl)-6-(2,4-dichlorophenyl)pyridine-3-carbonitrile(5_{aiv})

Yield: 69.35%; solid; M.P.690.76℃; IR(ύ, cm^{-1}): 3446.91 (N-H, amino group), 3066.92 (C-H, aromatic, quinoline, pyridine and phenyl rings), 2879.82 (C-H, ethoxy group), 2210.50 (C≡N, nitrile group), 1587.47 (C=C, aromatic, quinoline, pyridine and phenyl rings), 1232.55 (C-N, aromatic, quinoline and pyridine rings), 1047.38 (C-O, ethoxy group), 720.50 (C-Cl); ^{1}H NMR(500MHz, $CDCl_3$, δ, ppm): 1.0-2.0 (t, 3H, -CH_3), 3.5-4.5 (q, 2H, -CH_2), 5-7 (s, 2H, amino), 7-9 (m, 8H, Ar-H); ^{13}C NMR (500MHz, $CDCl_3$, δ, ppm): 14.8 (-CH_3), 64.6 (-CH_2), 86.2 (Ar-C), 105.6 (Ar-C), 111.7 (Ar-C), 113.7 (Ar-C), 123.4 (Ar-C), 127.4 (Ar-C), 129.3 (Ar-C), 130.4 (Ar-C), 130.9 (Ar-C), 131.2 (Ar-C), 133.7 (Ar-C), 134.3 (Ar-C), 135.2 (Ar-C), 135.6 (Ar-C), 141.4 (Ar-C), 147.7 (Ar-C), 152.2 (Ar-C), 157.4 (Ar-C), 158.4 (Ar-C), 162.0 (Ar-C).

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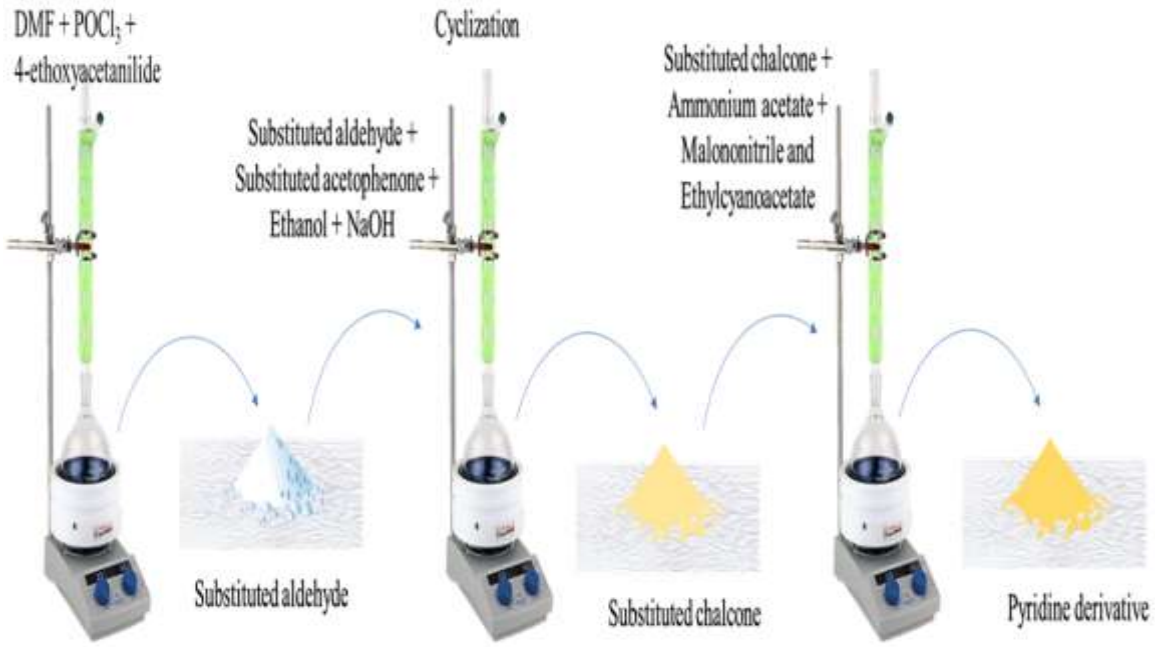
Graphical abstract:



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