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Synthesis of ethyl 6-amino-5-cyano-1,4-dihydro-2-methyl-4-phenyl-1-(pyridin-2-yl)pyridine-3-carboxylate Derivative via a one-pot four component reaction.

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Abstract:

A novel series of substituted ethyl 2-acetyl-4,4-dicyano-3-phenylbutanoate synthesized by using malonitrile, ethyl acetoacetate and various substituted benzaldehyde in ethanol reflux for 1-2 hour via one pot four component reaction. These newly synthesized compounds monitored on TLC plate and confirmed on spectral analysis such as FT-IR, NMR spectroscopy and Mass spectrometry.

Introduction:

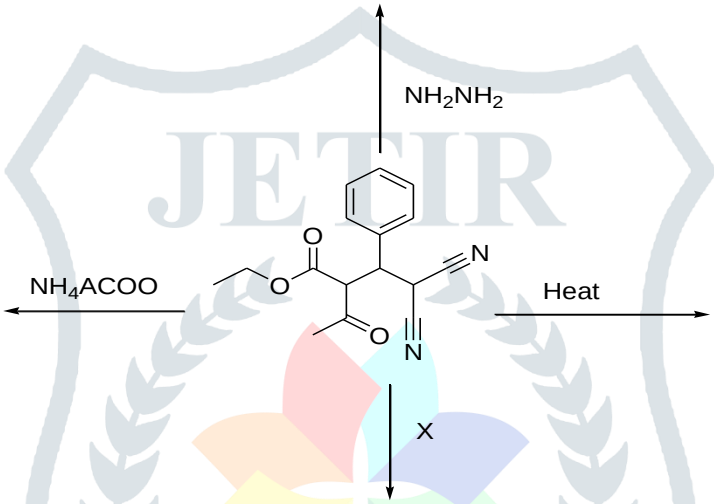
Green chemistry, also called sustainable chemistry, is a philosophy of chemical research and engineering that encourages the design of products and processes that minimize the use and generation of hazardous substances. Whereas environmental chemistry is the chemistry of the natural environment, and of pollutant chemicals in nature, green chemistry seeks to reduce and prevent pollution at its source. So by considering this we were synthesizedethyl 6-amino-5-cyano-1,4-dihydro-2-methyl-4-phenyl-1-(pyridin-2-yl)pyridine-3-carboxylateDerivative via a one-pot three component reaction.

A major challenge of modern drug discovery is the design ofhighly efficient chemical reaction sequences that provide themaximum structural complexity and diversity with a minimumnumber of synthetic steps to assemble compounds with interestingproperties.[1] One of the ways to fulfil these goals is the development of Multicomponent reactions (MCRs).[2] MCRs areimportant for generating high levels of diversity because theyallow more than two building blocks to be combined in a practical,timesaving, one-pot operation to give rise to complex structuresby simultaneous formation of two or more bonds. So developing a new environmentally benign MCR has been recognizedas one of the most important topics of green chemistry.[3]Asuccessful process of this kind will generate considerable savings towards solvent, and waste disposal, as well as time consumedduring work-ups and purifications. This can often beaccomplished by careful substrate and cascade sequence design as well as delicate reaction condition control. In the context of

our medicinal chemistry efforts, we aimed to construct structurally complex scaffolds by merging compatible reactions in cascade manner, which may provide great opportunities for the development of novel synthetic routes to natural products and drug candidates with remarkable synthetic efficiency. Herein wereport our efforts towards developing a cascade strategy to generate ethyl 2-acetyl-4,4-dicyano-3-phenylbutanoate Derivative via a one-pot three component reaction

Review of Literature:-

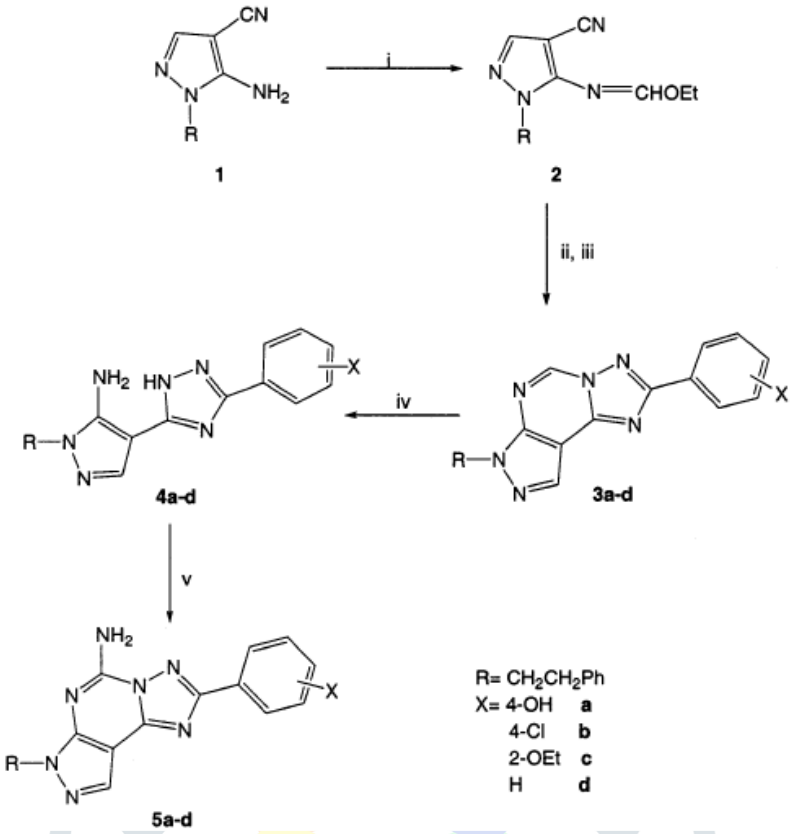
There are many synthesis having combination of various name reactions in this synthesis there are two name reactions are involved that is Mannich reaction followed by Knovengael condensation are also important tools in the synthesis of various heterocycles synthesis. We were synthesized a reagent which is useful in synthesis of heterocycles.



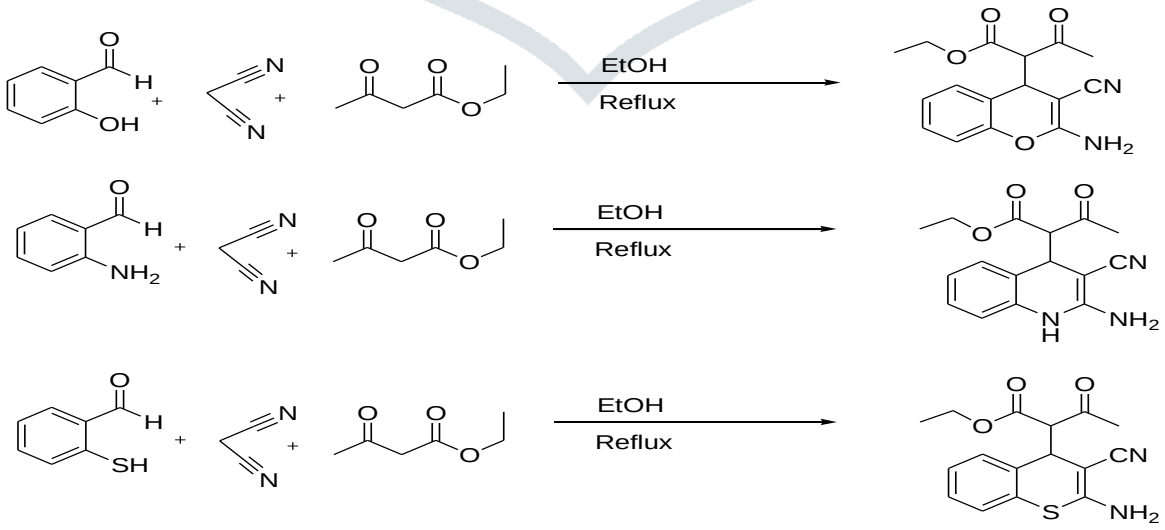
Diverse biological activities are encountered in fused heterocyclic systems containing the pyridine fused heterobicyclic systems which are likely to show enhanced biocidal effect. Pyridine is considered to be important chemical synthons of various physiological significances and pharmaceutical utilities. They possess a variety of biological effects, including antihypertensive, antimicrobial, antihyperlipidemic, antiinflammatory, and anticonvulsant activities. So we were synthesized.

These pyridine derivatives heterocycles attracted attention because of their applications as bioactive compounds for example as a promising class of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs),as antibacterial, antifungal and cardiotonic agents. Moreover, such derivatives have recently become important due to their structural similarity to nucleosides. Also, pyridines derivatives were used as ligands for the late 3d-metals.Thus, the development of novel methods for the synthesis of the pyridine ring is of topical interest Diverse biological activities are encountered infused heterocyclic systems containing the pyridine fused heterocyclic ring showenhancedbiocidal effect. The heterocyclic ring containing 2-amino,3-Cyano group is useful for the development of A2A and A3 adenosine receptor antagonists which led to the synthesis of SCH58261 (5-amino-7-(2-phenylethyl)-2-(2furyl)pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine, potent and very selective at the A2Areceptor subtype, and N8-substituted-pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidines-N5-urea or amide , very selective at the human A3 adenosine receptor subtype. The introduction of the cycloaminomethyl function by Mannich reaction at the 5¢ position of the furanyl ring of and the C9-substituted compound(5-amino-8-methyl-9-methylsulfanyl-2-(2-furyl)-pyrazolo[4,3-*e*]-1,2,4-triazolo[1,5 *c*]pyrimidine) resulted in complete water

solubility substitutions at the furanyl ring are not allowed and the introduction of asubstituent at the 9-position of the core pyrazolo-triazolo-pyrimidine structure caused a severeloss of selectivity, probably due to an increased steric hindrance of the radical introduced.



There are many reactions related to synthesis of chromen,[3] thiochromen[4] and same as dihydroquinoline synthesis.[5]By using active methylene group having malononitrile, Ethyl acetoacetate and salicyaldehyde as,



A protocol described for the synthesis of certain 2-amino-4-aryl-3-cyanopyridines was considered. The attractiveness of this synthetic choice lies in the fact that itconsists of a *one pot* procedure, involving the

condensation of malononitrile with aromaticaldehydes and alkyl ketones in the presence of ammonium acetate. To the best of our knowledge,no*N*-substituted-4-piperidones have been tested under these conditions (Equation 1). Regarding our interest in obtaining 2-amino-4-phenyl-5,6,7,8-tetrahydro-1,6-naphthyridine-3-carbonitriles,we decided to study the scope of the above mentioned method.[6] The cyclization occurred to give substituted (4*H*-pyrido[1,2-*a*]pyrimidin-3-yl)thiazole-5-carboxylates.[7] Literature survey revealed number of reports describing synthesis of 5,6,7,8-tetrahydroquinoline-3-carbonitriles. Several reports describe the synthesis of 2-amino-5,6,7,8-tetrahydroquinoline-3-carbonitriles by the reaction of arylidene malononitrile with cyclohexanone and ammonium acetate. The same compounds were obtained by the reaction of 3-amino-2-cyclohexen-1-one(enaminone) with arylidene malononitriles in better yields. Reaction of arylidenecyanoacetate with cyclohexanone in excess of ammonium acetate yielded 2-oxo-5,6,7,8-tetrahydroquinoline-3-carbonitriles . One pot synthesis from aldehyde, ethyl cyanoacetate, cyclohexanone and ammonium acetate is also reported yielding same compounds.[9] Synthesis of 4-alkyl/aryl-3-cyano-5,6,7,8-tetrahydroquinoline-2(1H)-thionesisalso reported using different methods viz. cyclocondensation of arylmethylenecyclohexanoneswithcyanothioacetamide, reaction of cyclohexanone or its enamine with arylmethylenecyanothioacetamides. Three componentcondensation of cyanothioacetamide with aliphatic aldehydes and enamine is reportedto give 4-alkyl-3-cyano-5,6,7,8-tetrahydroquinoline-2(1*H*)-thiones.[10]

Recyclization of 3-cyanopyridinium salts by theaction of alkali can occur with participation of thecyano group in the formation of new pyridine ring orwithout it. When hydroxide ion is covalently bound to the α-carbon atom of the pyridine ring in the *ortho*position with respect to the cyano group, the latter isinvolved in the recyclization. When hydroxide ionadds at the *para* position with respect to the cyanogroup, the recyclization occurs without its participationbut involves ester moiety to afford the corresponding pyridinone.[11]

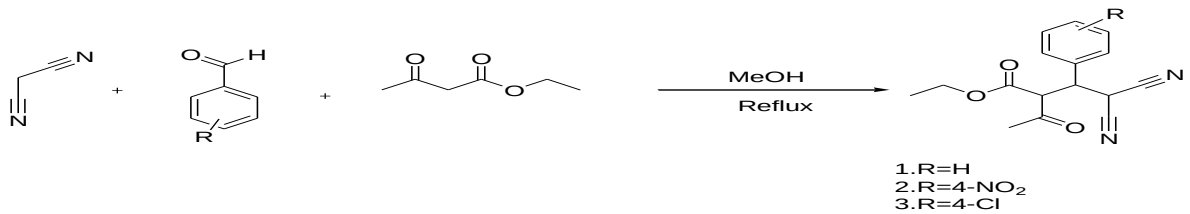
Malononitrilewas reacted with ethyl acetoacetate in the presence of piperidine as reported in somepaperto yield in 67 % yields. Repeating the reaction in water afforded in much lower yield (24 %) while in water and piperidine the product was formed in 45 % yield. In presence of chitosan/water, the product was formed in 43 % yield. Utilizing chitosan in ethanol afforded the product in 59 % yield.[12]

Experimental:

Various substituted ethyl 2-acetyl-4,4-dicyano-3-phenylbutanoate synthesized by using malonitrile, ethyl acetoacetate and various substituted benzaldehyde in ethanol reflux for 1-2 hour. Then stop the heating cool the reaction mixture after this stop the reaction by addition of crushed ice. Filter the reaction mixture we get solid product. In this reaction we observed that without basic condition there were formation of only ethyl 2-acetyl-4,4-dicyano-3-phenylbutanoate. Recrystallization the product using ethanol. Reaction is afforded by any basic or acidic or any other catalyst.

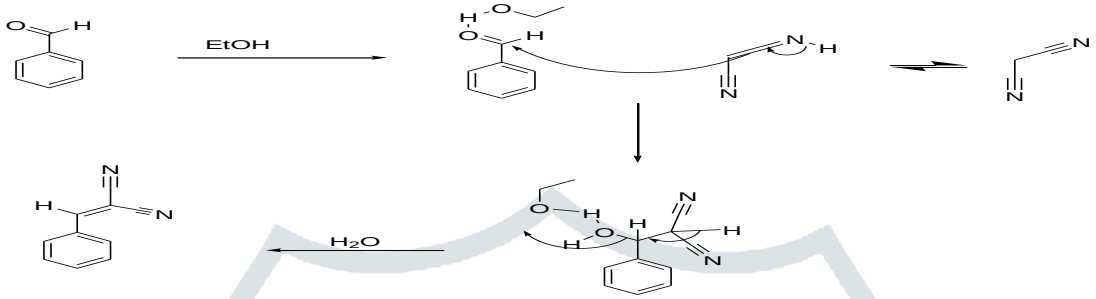
The results are presented in table one.

Scheme 1 :



Mechanism:

Step I- Knovengael Condensation



Step II- Michael Addition:

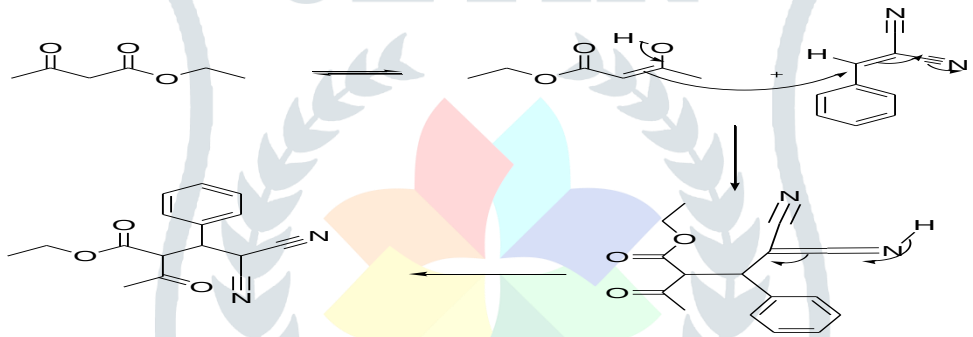


Table No.1:

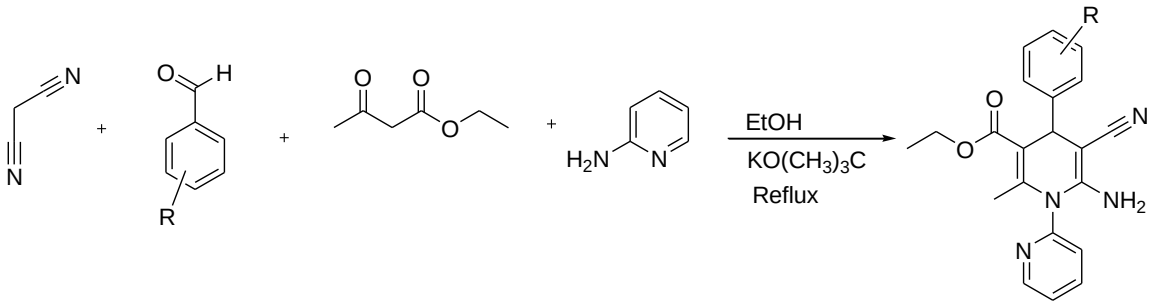
Preparation of ethyl 2-acetyl-4,4-dicyano-3-phenylbutanoate derivatives

Sr. No.	Substrate	Yield(%)	Reaction Time(hr)	MP(^{0}C)
1	4-Nitrobenzaldehyde	65	4	240
2	Benzaldehyde	63	4	212
3	3-Nitrobenzaldehyde	50	4.5	220
4	4-Chlorobenzaldehyde	55	5	170
5	4-Hydroxybenzaldehyde	67	3	225
6	2-Nitrobenzaldehyde	70	4	185
7	Vanillin	67	5	160

Scheme-2

Various substituted ethyl 6-amino-5-cyano-1,4-dihydro-2-methyl-4-phenyl-1-(pyridin-2-yl)pyridine-3-carboxylate synthesized by using malonitrile, ethyl acetoacetate, various substituted benzaldehyde and 2-amino pyridine in ethanol and catalytic amount of base reflux for 4-5 hour. Then stop the heating cool the reaction

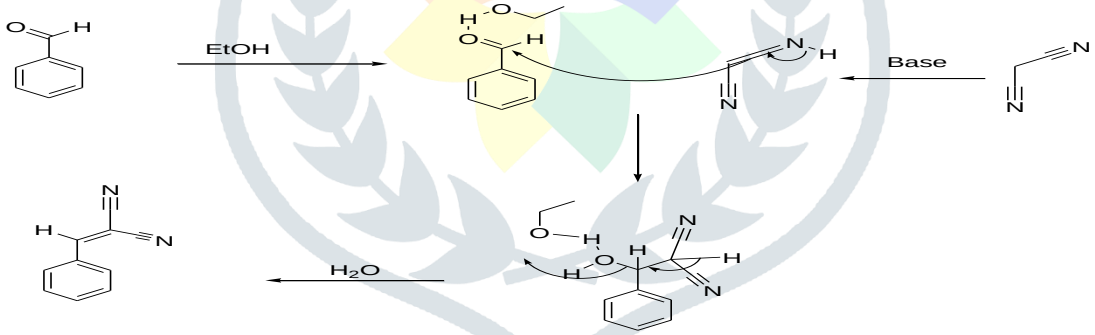
mixture after this stop the reaction by addition of crushed ice. Filter the reaction mixture we get solid product. Recrystallization the product using ethanol. Reaction is afforded catalytic amount of basic condition.



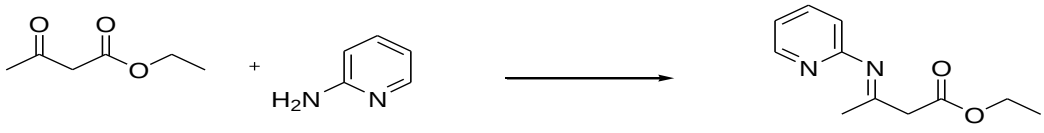
1.R=H
2.R=4-NO_2
3.R=3-NO_2
4.R=4-Cl
5.R=4-OH
6.R=4-Me
7.R=4-OMe
8.R=4-N(Me)$_2$

Mechanism:

Step-IKnovengael Condensation



Step-II Schiffs Base formation:



Step-III Cyclization followed by Michael addition:

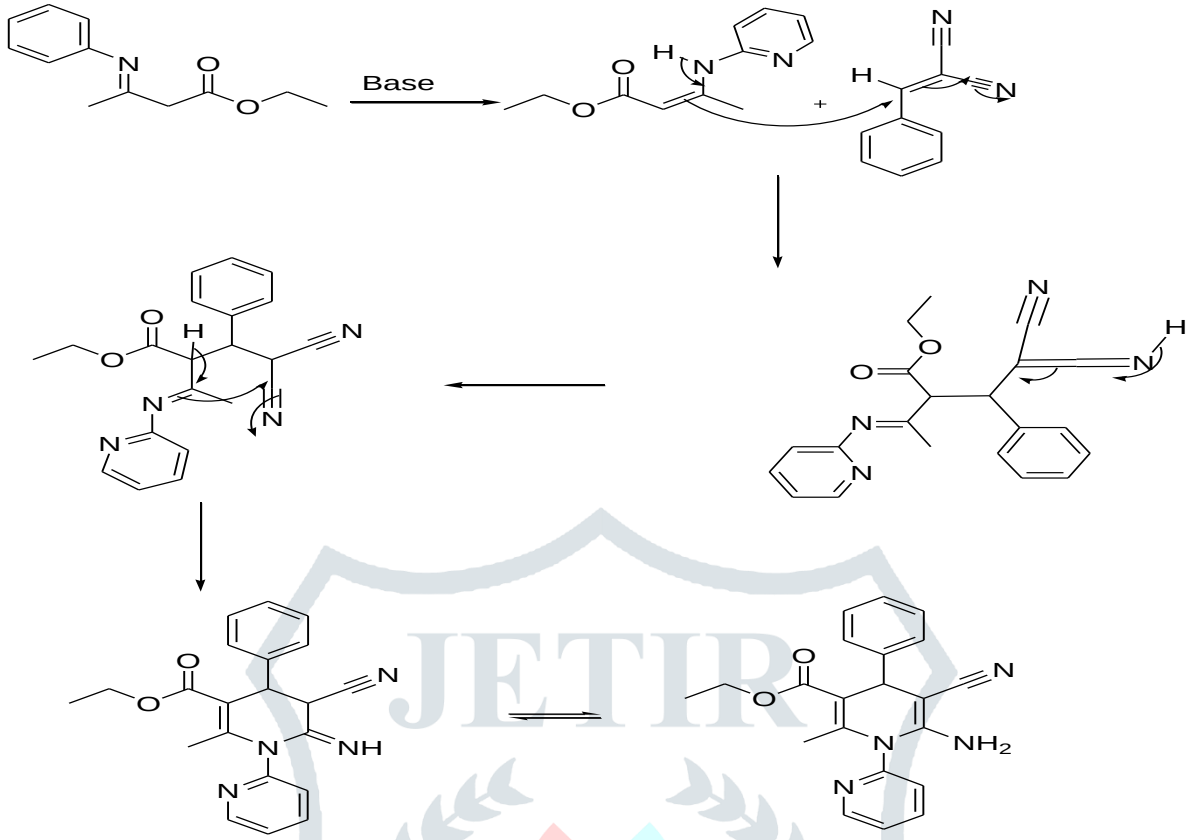
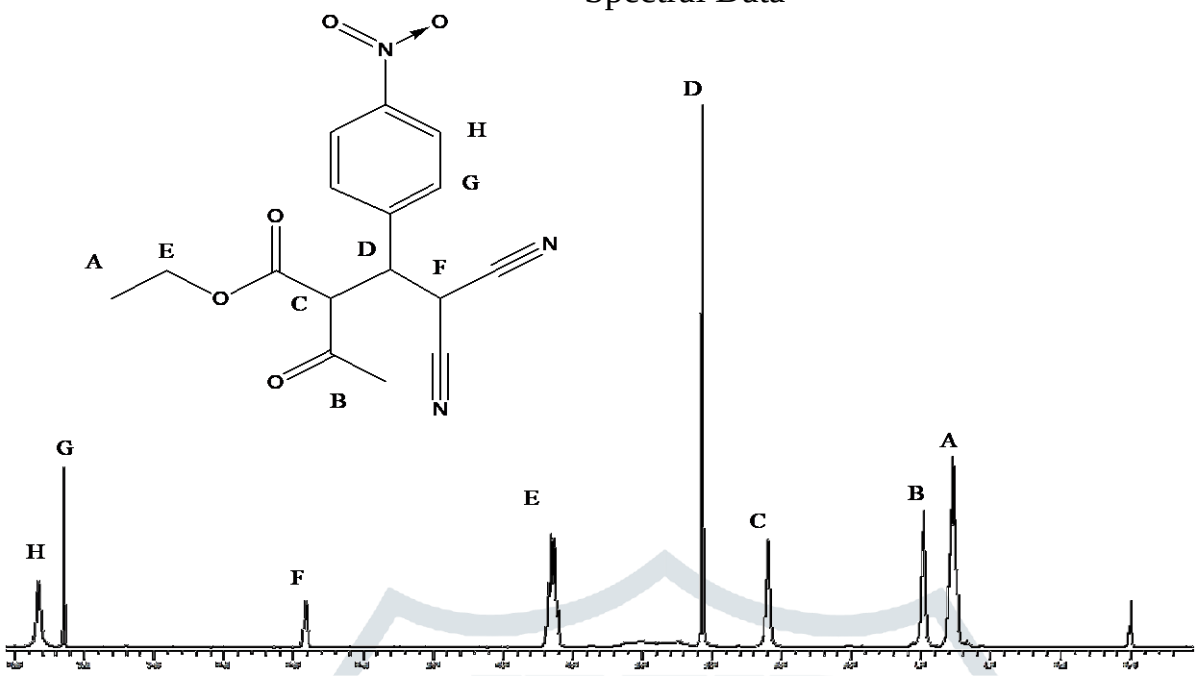


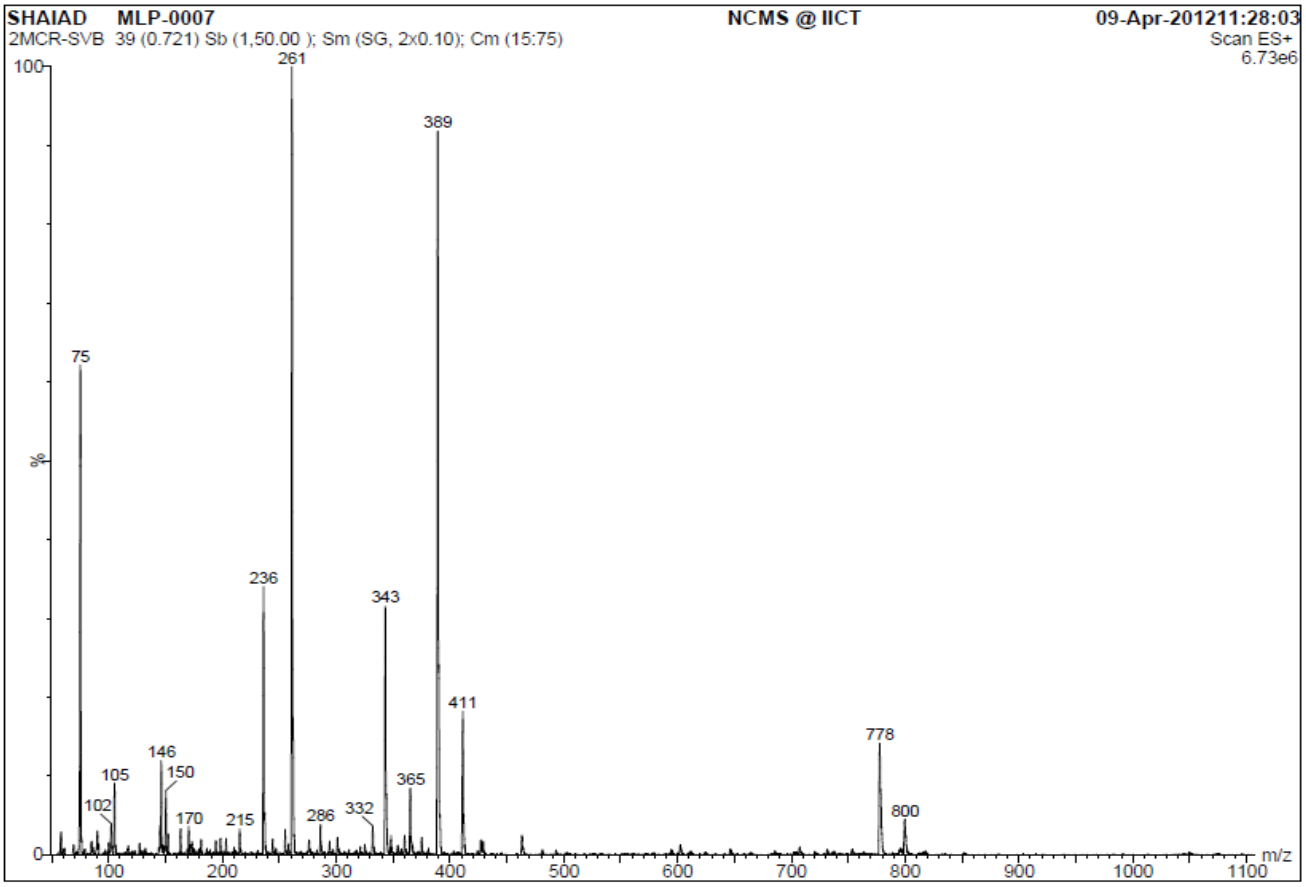
Table-2

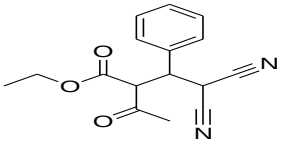
Preparation of ethyl 6-amino-5-cyano-1,4-dihydro-2-methyl-4-phenyl-1-(pyridin-2-yl)pyridine-3-carboxylate derivative

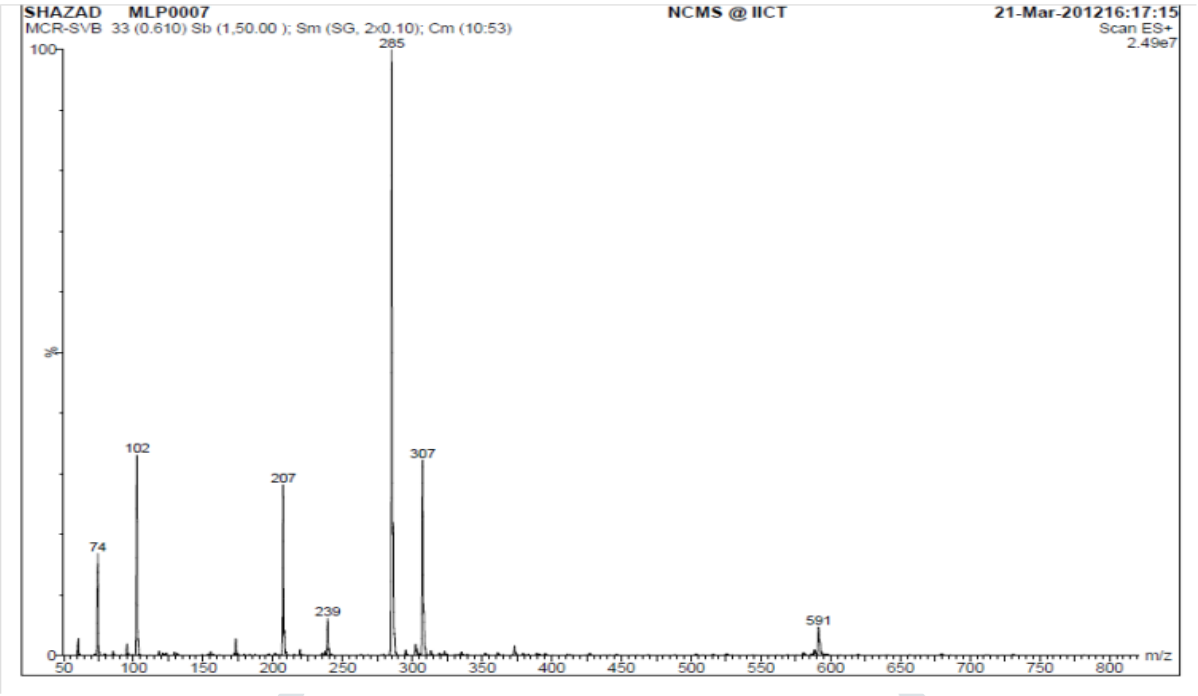
Sr.No.	Substrate	Yield (%)	Time(h)	M. P. (^{0}C)
1	4-Nitrobenzaldehyde	55	3.5	260
2	Benzaldehyde	52	4	227
3	3-Nitrobenzaldehyde	57	4.5	185
4	4-chlorobenzaldehyde	50	4.5	153
5	4-hydroxybenzaldehyde	60	4	179
6	2-nitrobenzaldehyde	58	3	201
7	vanillin	50	4.5	166

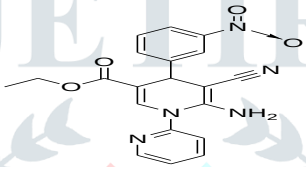
Spectral Data

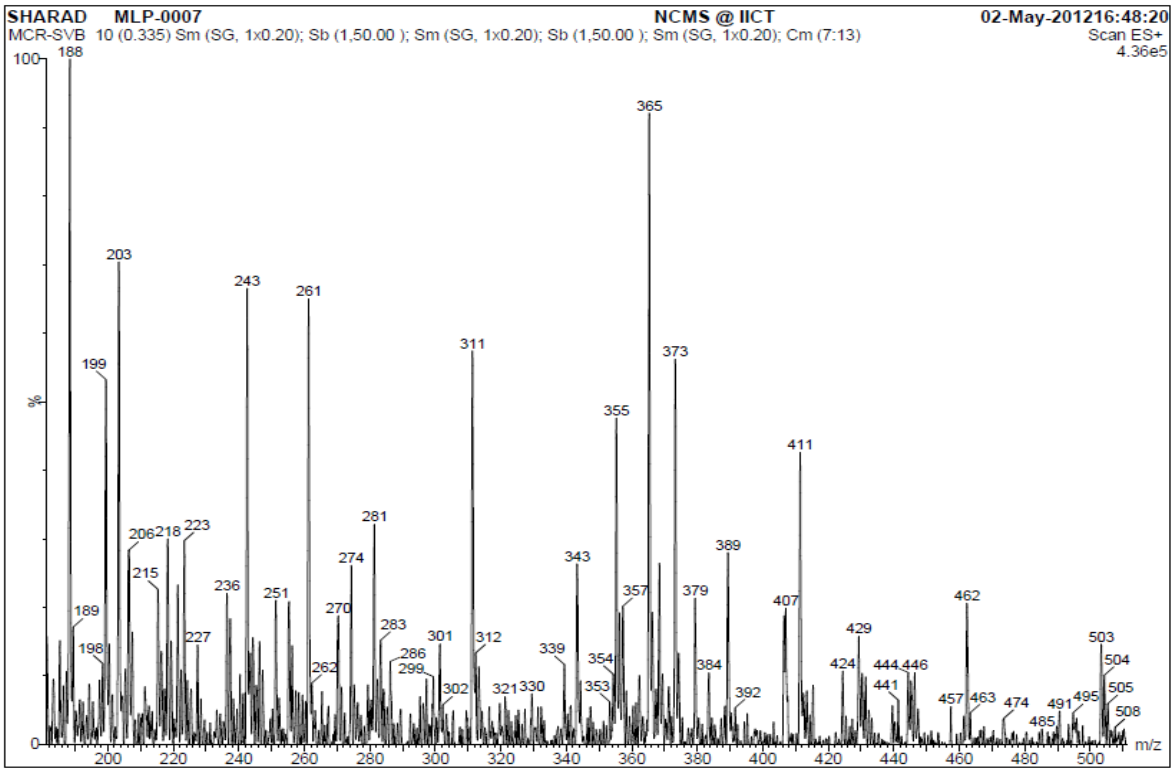












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