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Utilities of Active Methylene Compounds and Heterocycles Bearing Active Methyl or having an Active Methine in the Formation of Heterocyclyl and Heterocyclopyridines (Part III)

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

This review discusses the work done in the last three decades in our laboratory which describes the use of some common and novel synthesized active methylene compounds as well as heterocycles having active methyl or methine in the syntheses of a wide variety of substituted and condensed pyridines. The used synthetic approaches involves cyclocondensation reactions, ring opening-ring closure, cycloaddition, acid- or base-catalyzed reaction, intermolecular cyclization and self-condensation have been reviewed in this paper. Also, antimicrobial activities of some reported pyridines were discussed.

Keywords: Active methylene; pyridines; thiazolopyridines; indolopyridines; pyridopyrimidines; pyridotriazines; pyridotriazepines; antimicrobial activities.

1. INTRODUCTION

Pyridine derivatives are important heterocyclic systems whose preparation, reactivity, and properties are of continuing interest. The biological activity associated with naturally occurring and synthetic pyridines has led to the development of pyridine-containing

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medicinal scaffolds and investigations into their pharmacological properties [1]. Benzopyridines specially quinolones are the effective moiety in a large number of natural and synthetic heterocyclic compounds that exhibit significant antibiotic activity with a wide variety of significant medicinal, pharmacological, and industrial applications [2]. In continuation to our recent target in setting on some heterocyclic reviews discuss the utility of active methylene compounds and heterocycles bearing active methyl or having an active methine in their structures in heterocyclization of somefive-, six-, and seven-membered heterocyclic systems of important applications in many fields suc has medicine, agriculture, pharmacology and pharmaceutical. Consequently, we recently publish some reviews [3-6] summarized our work done in our laboratory in the last three decades. Herein this review involves the methods developed for the syntheses of substituted and condensed pyridine derivatives using the titled compounds and reported the antimicrobial activity of some selected synthesized pyridines.

2. FORMATION OF HETROCYCLYL-PYRIDINES

Some active methylene compounds such as malononitrile, cyanoacetohydrazide, caynoacet-amide, cyanothioacetamide, and an enaminone were used for the synthesis of some pyridines bearing heterocyclic substituents and tested their biological activities.

2.1 Using Synthesized Enones

α, β- Unsaturated ketones are called chalcones or enones were synthesized via the interaction of aromatic aldehydes with compounds having active methylene or methyl groups in their structures. The activated influence of the carbonyl group on the exocyclic double bond render the enones susceptible to the cycloaddition reaction forming the target heterocyclylpyridines. The preparation of a novel pyridines bearing substituted heterocyclic systems requires the formation of biheterocycli cenones. The enone 3 was synthesized via Knoevenagel condensation of 3-formylchromone (1) with the active cyclic methylene group ofthiazolidene-2,4-dione (2) [7]. Whereas, the biheterocycli cenone 6 performed by condensation of formyl group of pyrazolo-benzothienopyrimidine derivative (4) with the active methyl group of 4-acetylpyridazinone 5 [8] (Scheme 1).

The action of malonitrile (7) upon the two synthesized enones 3 and 6 showed two different behaviors. The presence of chromone with an active methine at C2 in the enone 3 facilitate the attack by the carbanion at C2 causing ring-opening of the ϒ-pyron ring followed by ring closure producing the target pyridine. Thus, the reaction of chromenylthiazolidine derivative 3 with malonitrile (7) in basic medium afforded the intermediate 8, which underwent Dimorth rearrangement under the reaction condition to yield oxopyridinecarbonitrile 9. Compound 9 also obtained directly by the action of cyanoacetamide (10) upon biheterocyclic enone 3 [7] (Scheme 2).

When biheterocyclic enone 6 was subjected to react with malononitrile (7) in boiling ethanol containing ammonium acetate, cyclocondensa-tion took place at α,β-unsaturated carbonyl part yielding 4,6-diheterocyclylpyridinecarbonitrile 11 [8] (Scheme 3).

Similarly, another two synthesized enones having quinolone in their structures were prepared, the enone 13 was obtained by condensation of formylchromone (1) with the active methyl group of acetylquinolone (12), while the enone 15 formed through the condensation of formylquinolone (14) with the active methyl group of acetylpyridazinone (5).When the reaction between cyanothio-acetamide (16) and the enones13 and 15 was carried out in ethanol containing piperidinium acetate, the respective 4,6-diheterocyclyl-pyridines 17 and 18, were obtained. But when the reaction between 13 and 16 took place in sodium ethoxide, ring opening of ϒ-pyrone ring followed by ring closure took place giving rise to the thioxopyridinecarbonitrile19 [9,10] (Scheme 4).

Moreover, acylation of 2-aminopyrimidinecarbo-nitrile (20) using acetic anhydride yielded 2-acetamidopyrimidinecarbonitrile (21), which underwent condensation with benzaldehyde in ethanolic sodium hydroxide gave 2-(N-cinnamoyl- amino)pyrimidinecarbonitrile (22). As reported for α,β-unsaturated ketones, the interaction of compound 22 with active methylene compounds afforded the substituted pyridines. Accordingly, when compound 22 was allowed to react with malononitrile (7) and ethyl cyanoacetate in the presence of ammonium acetate afforded 2-amino-6-

pyrimidylaminopyridinecarbonitrile (23) and 3-cyano-6-pyrimidylaminopyridine (24), respectively [11] (Scheme 5).

2.2 Using Acetylpyridazine

In addition to the use of acetylpyridazine (5) in the formation of some enones, it could be converted into a new active methylene compound or enaminone, which were used in the synthesis of pyridine. Accordingly, synthesized active methylene compound namely, pyridazinylbutan-1,3-dione 27 which obtained from the reaction of 4-acetylpyridazinone 5 with ethyl acetate (25) under clasein condensation [12]. Whereas, the enaminone 28 was formed via the condensation of 5 with dimethylformamide dimethylacetal,DMFDMA, (26) in non-polar solvent [9]. Cyclocondensation of cyanoacetamide (10) with compound 27 in refluxing ethanol containing catalytic amount of triethyl amine afforded 4-pyridinylpyridazinone 29 [8]. Whereas, 2-pyridinyl 4-pyridazinyl ketone (30) synthesized on refluxing the enaminone 28 in acetic acid containing ammonium acetate [13] (Scheme 6).

2.3 Using Arylidene Malononitriles

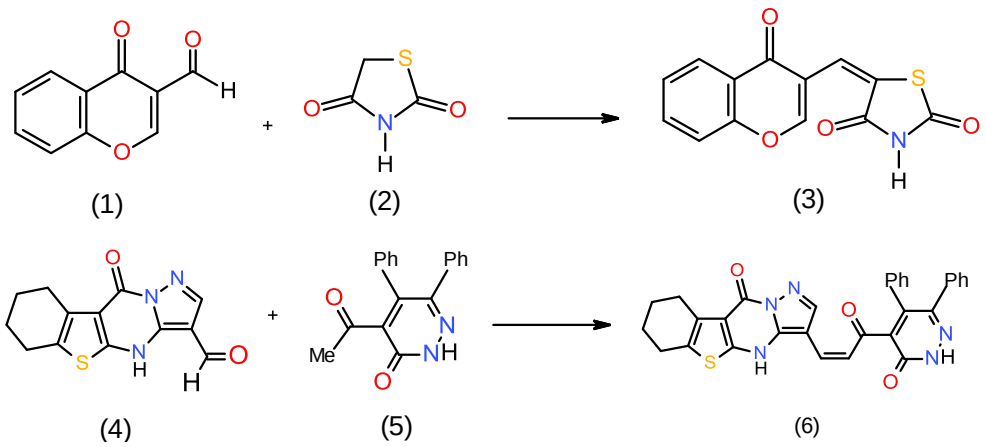
Condensation of malononitrile (**7**) with each of p-chlorobenzaldehyde (31), formyl derivative (4) and 3-formyl-6-methylchromone (32) afforded the respective arylidenemalononitriles 33a-c. In refluxing dimethyl formamide containing catalytic amount of piperidine the cyanoaceticacid-hydrazide (35) - the product of hydrazonolsis of ethyl cyanoacetate, (34) - was added to arylidenemalononitriles 33a-c, and yielded the corresponding 1,6-diamino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles (36a-c) [14,15] (Scheme 7). Compound 36 was considered as a suitable synthon for many condensed pyridines.

3. FORMATION OF FUSED PYRIDINES

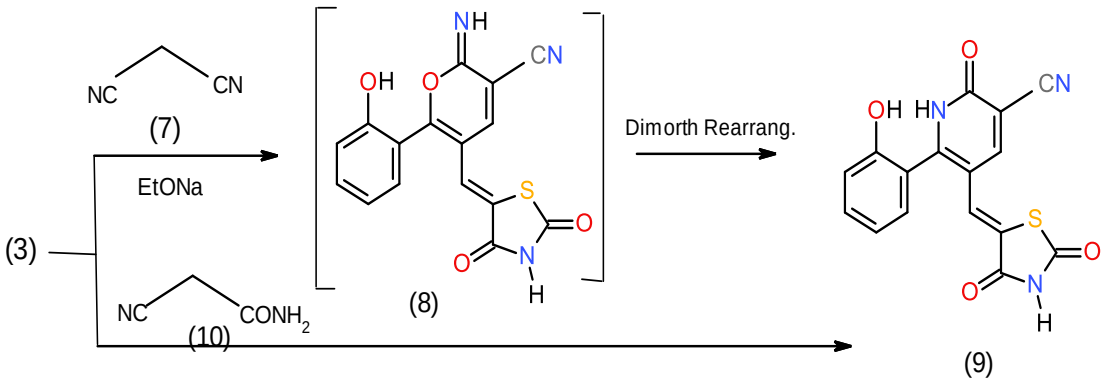
Incorporating pyridine with other heterocyclic systems such as thiazole, indole, pyrimidine, triazine and triazepines in one molecular frame-work enhance the biological activities of the produced condensed pyridine derivatives. Synthesis of heterocyclopyridines could be carried out using some heterocyclic systems having active methylene such as thiazolidinones, 2-indolinone or heterocycles have active methine like 6-amino-1,3-dimethyluracil and with a heterocycle with a vicinal diamino groups as in compound 36.

3.1 Synthesis of Thiazolopyridines

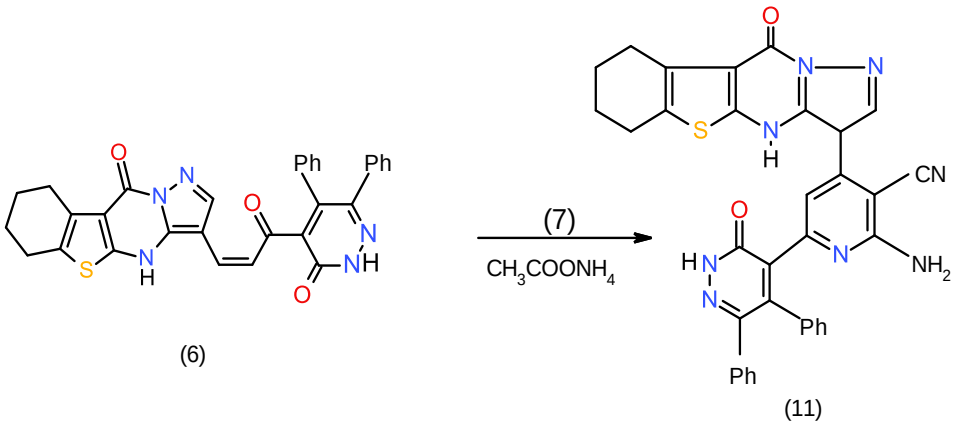
A number of methods to prepare thiazolopyridines have been documented in the literature. For example, methods that construct the bicycle by formation of a thiazole ring, include condensation of 3-amino-2-halopyridine, or 3-amino-2-pyridone derivatives, with thiocyanates, thioamides, or thioesters; condensation with 3-aminopyridin-2-thiones, and reactions of N-(2-pyridone-3-yl)acetamides with phosphorous pentasulfide, the oxidative ring-closure of 3-aminopyridine-thioamides or thioureas [16]. In our work, we annulated pyridine on thiazolidnone derivative using active methylene compounds. Thus, cyclocondensation of 5-arylidene thiazolidinone 36 with malononitrile (7) and ethyl cyanoacetate (34) in the presence of ammonium acetate yielded thiazolopyridine 37 and thiazolopyridone 38, respectively [17] (Scheme 8).



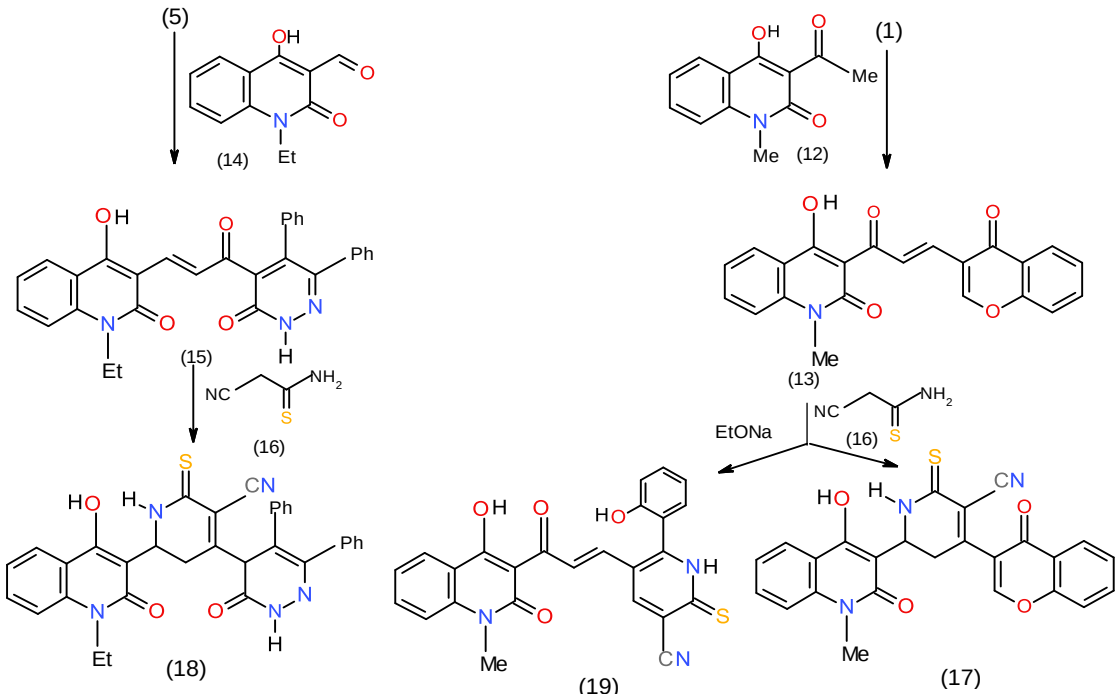
Scheme 1. Formation of bi-heterocyclic enones



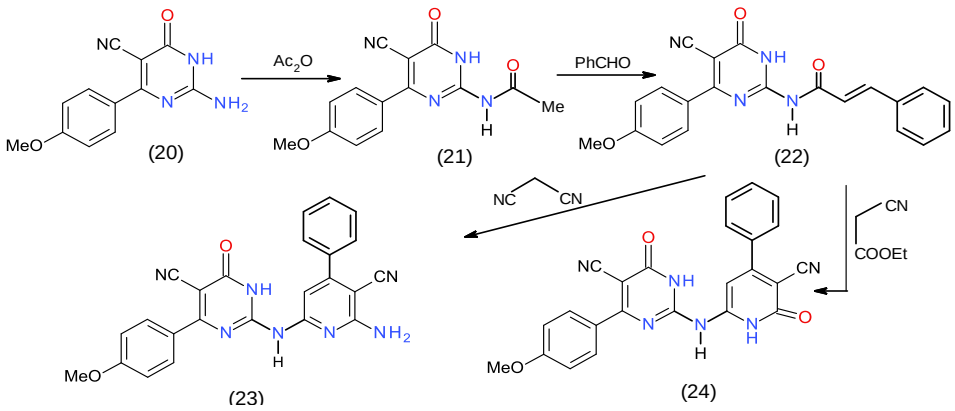
Scheme 2. Formation of oxopridinecarbonitrie



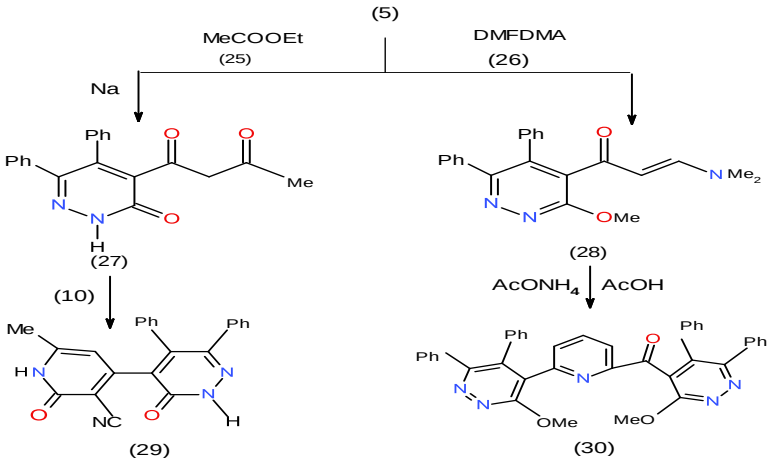
Scheme 3. Formation of aminopyridinecarbonitrie



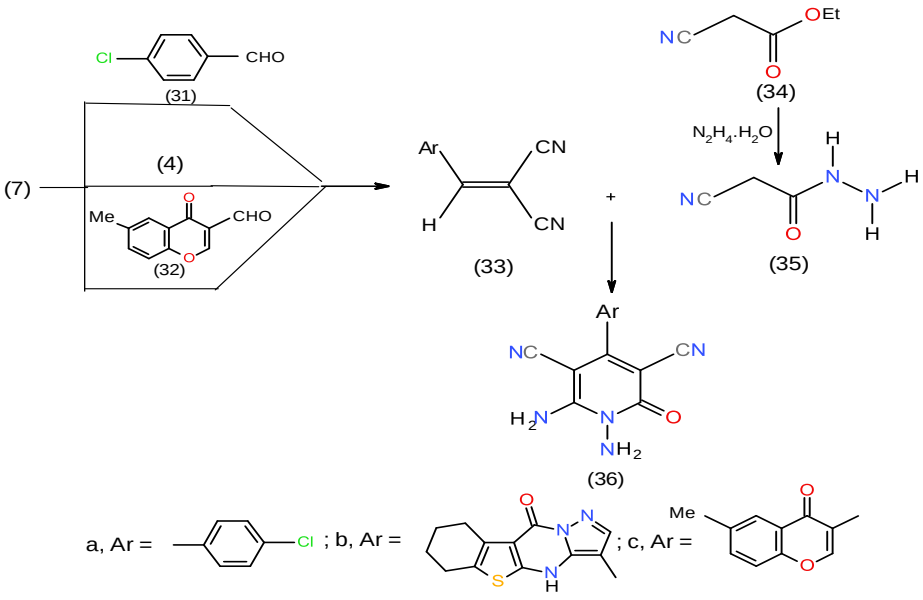
Scheme 4. Cyanothioacetamide in the formation of thioxopyridinecarbonitries



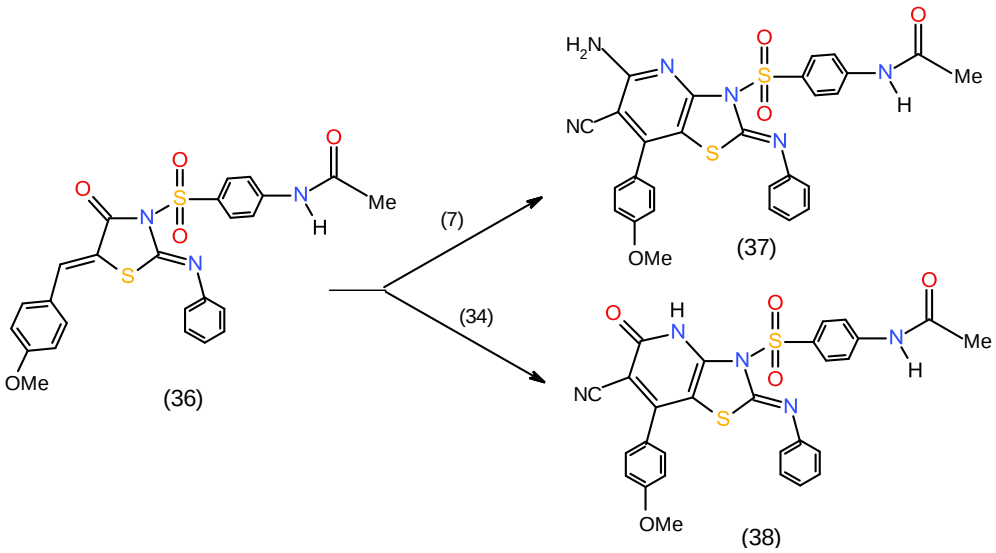
Scheme 5. Formation of pyrimidylaminopyridines



Scheme 6. Formation of pyridazinylpyridines



Scheme 7. Formation of diaminopyridinedicarbonitriles



Scheme 8. Formation of thiazolopyridines

3.2 Synthesis of Indolopyridines

In the last 30 years, hundreds of indoloquinoline analogues were synthesized and their biological activities evaluated as scaffolds for drug discovery. This fact aroused us to synthesize some bioactive indolopyridines starting with 2-indolinone (39), which having cyclic active methylene. Thus, condensation of 2-indolinone (39) with DMFDMA (26) afforded the respective enaminone 40, which on treating with $POCl_3$ gave 2-chloroindole derivative 41. Cyclocondensation of 41 with two compounds having active methine site in their structures such as, enaminonitrile 42 and 6-aminouracil 43, afforded the indolopyridine- carbonitrile 44 and indolopyridopyrimidinedione45, respectively [18] (Scheme 9).

On the other hand, treatment the enaminone 40 with 1-naphthylamine (46) yielded 3-N-naphthyl-amino derivative 47, which on boiling in polyphosphoric acid (PPA), dehydration took place giving rise to indolobenzoquinoline 48. Heating of 2-indolinone (39) with enaminone 40 in acetic acid and ammonium acetate mixture furnished indolopyridoindole (49) [18] (Scheme 10).

3.3 Formation of Pyridopyrimidine Derivatives

Pyridopyrimidine derivatives are a privileged bicyclic ring system. Due to its potent and significant biological activities it has great pharmaceutical importance; synthesis of these compounds is considerable interest. The development of a practical method for the synthesis of various pyridopyrimidines, in view of their structure relation with peteridine, is of interest in the field of medicinal chemistry [19]. Most preparation of pyridopyrimidines concentered on ring closure reactions of either pyridine or pyrimidine nucleus having appropriate substituents. Accordingly, chloropyridine-carbonitrile 50 reacted with some heterocycles having vicinal amino-cyano groups such as 2-aminopyridinecarbonitrile 51 and 3-amino-pyrazolopyridinecarbonitrile 52 to afford the respective polycyclic systems 53 and 54 having pyridopyrimidine moiety in their structures [20] (Scheme11).

On the other hand, Condensation the active methyl group of 3-acetylquinolinone 12 with DMFDMA (26) in non-polar solvent yielded the enaminone 55. The action of thiourea (56) and cyanoguanidine (57) upon the enaminone 55 gave rise to pyrimidoquinolinones 58 and 59, respectively [21] (Scheme 12).

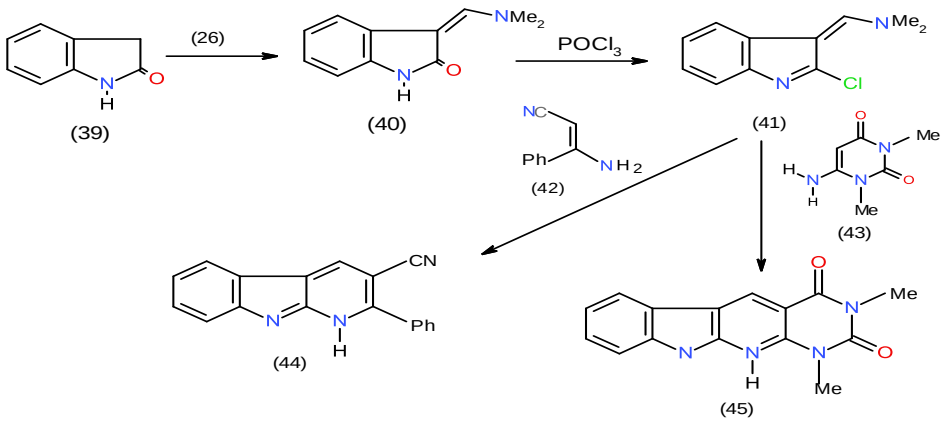
Nucleophilic substitution of the chlorine atom in chloropyrimidinecarbonitrile (60) using ethyl cyanoacetate (34) under basic condition afforded pyrimidinylcyanoacetate derivative (61). Compound 61 is considered a good synthon for some interesting tri-nitrogenous heterocyclic systems having pyridine nucleus in their structures. Thus, cyclocondensation of 61 with acetamidine hydrochloride (62a), guanidine hydrochloride (62b) and S-methylthiourea-sulphate (62c) in sodium ethoxide solution

furnished substituted pyrimidopyridopyrimidines 63a-c, respectively. Similar behavior was observed when compound 61 also reacted with N-phenylthiourea (64) to afford pyrimidopyrido-pyrimidinethione 65. Moreover, treatment of pyrimidinylcyanoacetate derivative 61 with aqueous ammonia at room temperature gave the corresponding amide 66, which reacted with formamide (67) in DMF to yield the substituted pyrimidopyridopyrimidines 68 [22] (Scheme 13).

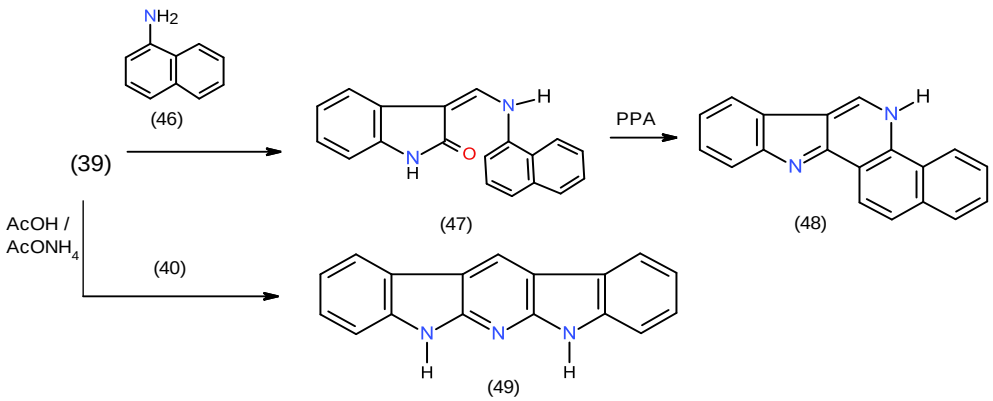
Recently, an analogous method for the synthesis of pyridopyrimidines was proposed via the reaction of 6-amino-2-thiouracil with activated olefinic system possessing a leaving group such as dimethylamino [23]. Motivated by this fact, we allowed ethyl cyanoacetate (34) to react with both 3,5-dimethylpyrazole (69) and tiethylorthoformate (70) to afford 3,5-dimethylpyrazol-1-yloxo) acetonitrile (71) and ethyl ethoxymethylene- cyanoacetate (72), respectively. Treatment of 71 with DMFDMA (26) yielded the enaminone 73, which reacted with 6-aminouracil 43 to give the pyridopyrimidine 75 via non-separable intermediate 74. Compound 75 was also obtained from the reaction of 6-aminouracil 43 with compound 72 [24] (Scheme 14).

In conjunction to our interest in the chemistry of the enaminones, pyrazolopyridopyrimidinediones 77a, b synthesized on treatment of 6-aminouracil 43 with the cyclic enaminones 76a, b, while the pyridopyrimidinediones 80a, b and benzimid-azolylpyridopyrimidinedione 81 obtained from the reaction of compound 43 with two enaminones 78a, b and with enamine 79, respectively [25] (Scheme 15).

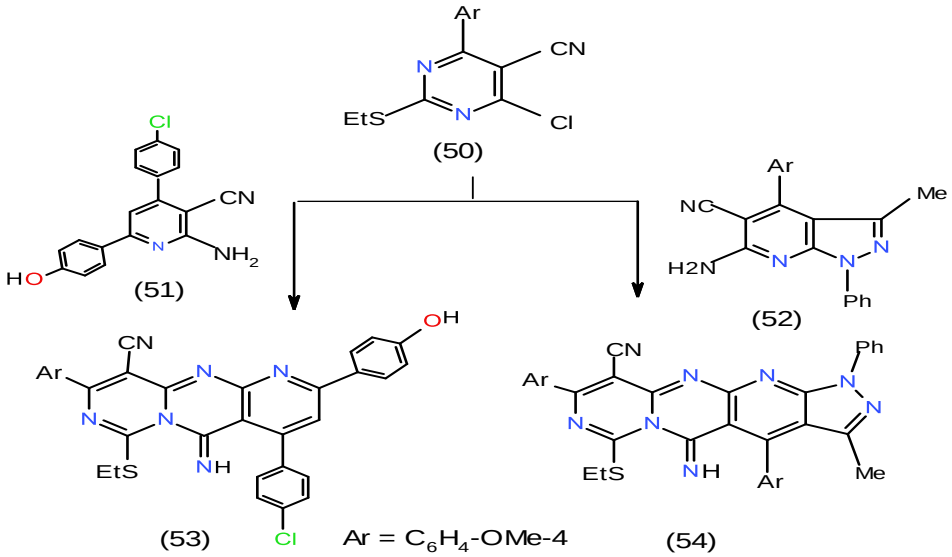
Moreover, 6-amino-1,3-dimethyluracil (43) having an active methine group at position-5, reacted with some bifunctional heterocyclic systems having vicinal chloro-cyano groups in their structures such as 2-chloropyridinecarbonitrile 82, 3-chloropyridazinecarbonitrile 83 and 4-chloro- pyrimidinecarbonitrile 60 and afforded the novel triheterocyclic systems having pyridopyrimidine moiety in their structures 84-86, respectively [25] (Scheme 16).



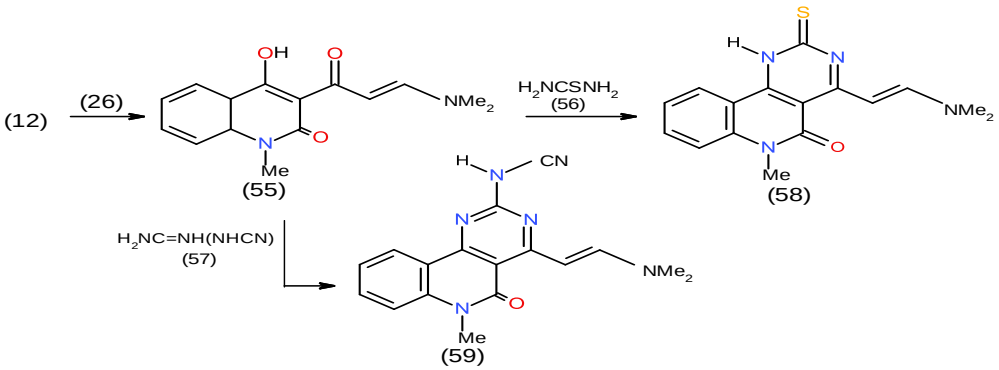
Scheme 9. Formation of indolopyridine derivatives



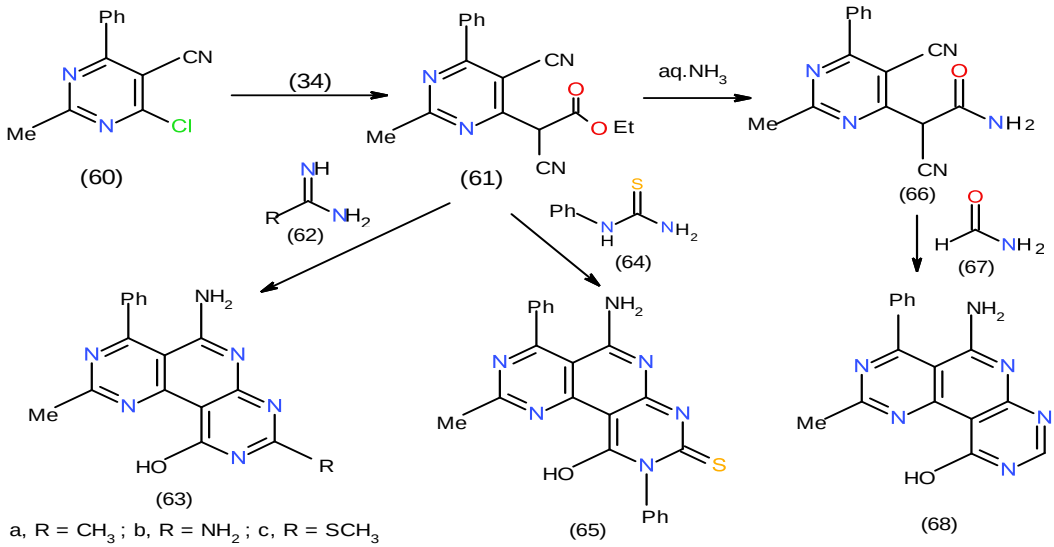
Scheme 10. Formation of polycyclic system having pyridine



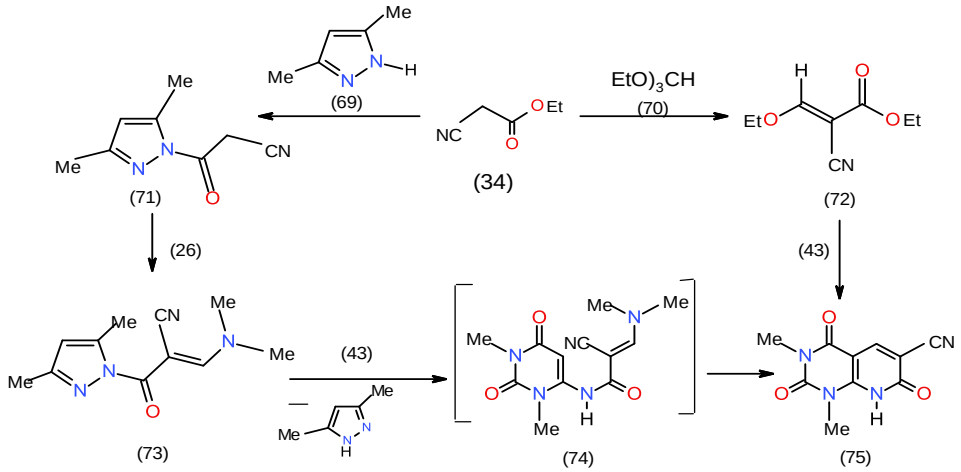
Scheme 11. Formation of pyridopyrimidopyrimidine derivatives



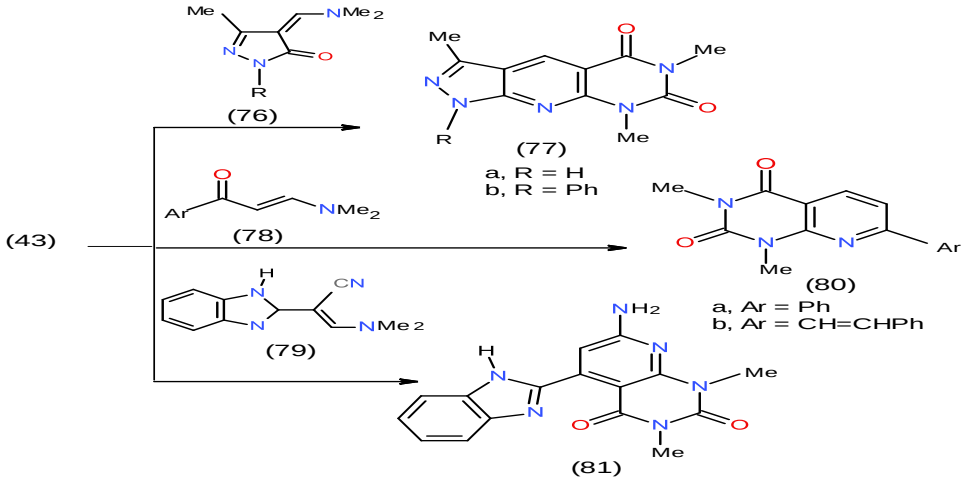
Scheme 12. Formation of pyrimidoquinolones



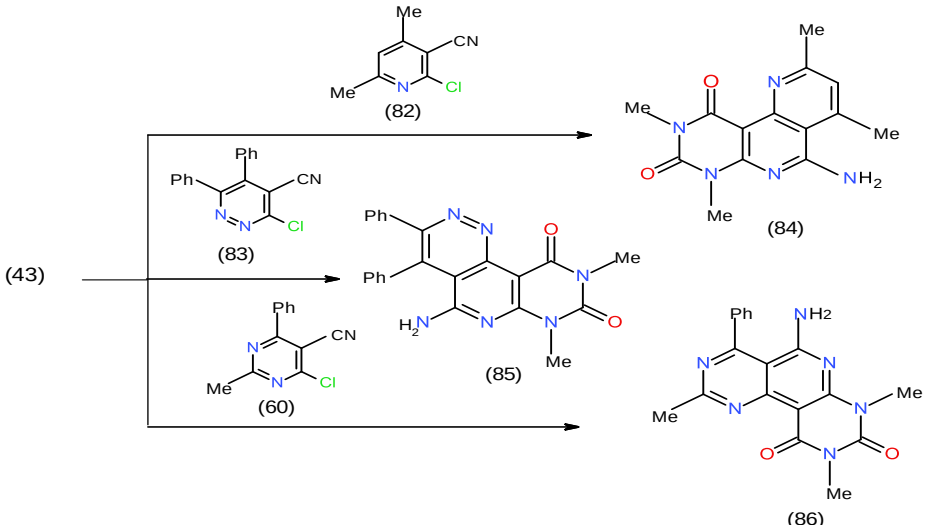
Scheme 13. Formation of pyrimidopyridopyrimidines



Scheme 14. Formation of pyrimidopyridines



Scheme 15. Formation of pyridopyrimidinediones



Scheme 16. Formation of pyridine in triheterocyclic systems

Furthermore, bifunctional heterocyclic system having vicinal chloro-acetyl groups (4-acetyl-3-chloropyridazine 87) or vicinal chloro-ethoxy-carbonyl groups (4-carbethoxy-3-chloropyridazine 88) reacted with 6-amino-1,3-dimethyluracil (43) to yield the corresponding pyrimidopyrido-pyridazines 89 and 90 [25] (Scheme 17).

On the other hand, the reaction of malononitrile (7) with carbon disulphide in basic medium followed by addition of methyl iodide afforded 2-cyano-3,3-bis(methylthio)acrylonitrile (91) [26], which reacted with 43 to yieldpyrido-pyrimidinedione derivative 92 while, the reaction of 43 with arylidenecyanoacetic acids 93a,b, obtained from the condensation of cyanoacetic acid with aromatic aldehydes afforded pyrido-pyrimidinetriones 94a, b [20] (Scheme 18).

Also, the reaction of 4-chloropyrimidinecarbo-nitrile 60 with cyanoacetamide (10) in boiling dimethyl formamide gave aminopyridopyrimidine-carbonitrile 95 [27] (Scheme 19).

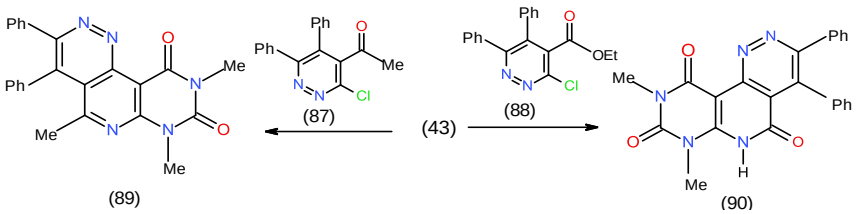
3.4 Formation of Pyridotriazine Derivatives

The bihererocyclic systems such as pyridotriazine and pyridopyridazine are useful for treating cell proliferative disorders, such as cancer, atherosclerosis, restenosis, angiogenesis, diabetic retinopathy, psoriasis and endometriosis and immunological disorders [28].

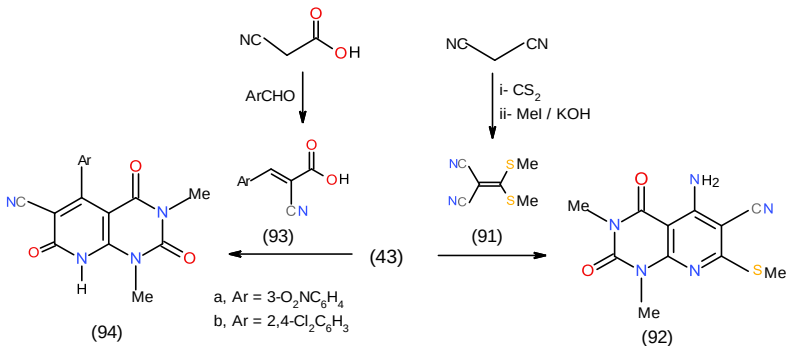
Motivated by these facts we succeeded in the preparation of some pyridotriazines with the help of 1,6-diamino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbo-nitriles (36a-c) as starting intermediate. Thus, the action of α, β-bifunctional electrophilic reagents such as chloroacetyl chloride, benzil, oxalyl chloride and sodium pyruvate upon compounds 36b,c was studied and yielded the corresponding nitrogen bridgehead pyrido1,2,4-triazinones 96a, b - 99a, b, respectively, via cyclocondensation process [14,15] (Scheme 20).

Moreover, the action of ethyl α-cyano-α-phenyl-azoacetate 101, obtained via the condensation of ethyl cyanoacetate (34) with benzenediazonium chloride 100 upon diaminopyridinedicarbo-dicabonitrile 36 a afforded pyrido1,2,4-triazinone 104 instead of aminopyrido1,2,4-triazine 105. The formation of 104 could be explained via non-separable intermediate 102 not 103 [11] (Scheme 21).

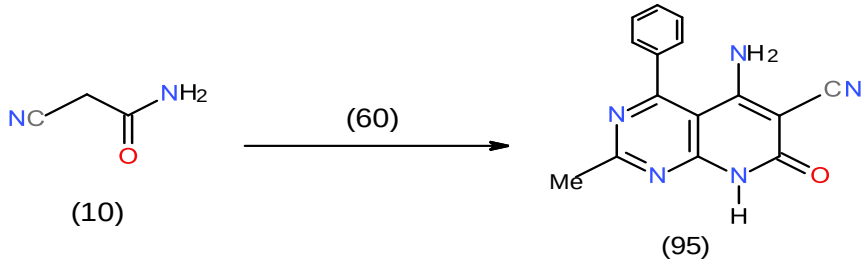
Also, condensation of 2,3-indoledione (isatin) (106) with diaminopyridonedicarbonitriles 36b,c in glacial acetic acid containing freshly fused sodium acetate afforded indolopyridotriazine derivative 107a,b. Whereas, a different behavior was observed on treatment of 36b, c with N-acetylisatin 108 in glacial acetic acid as it furnished pyridotriazinone110a,b. The formation of 110 took place via the intermediate 109 [14] (Scheme 22).



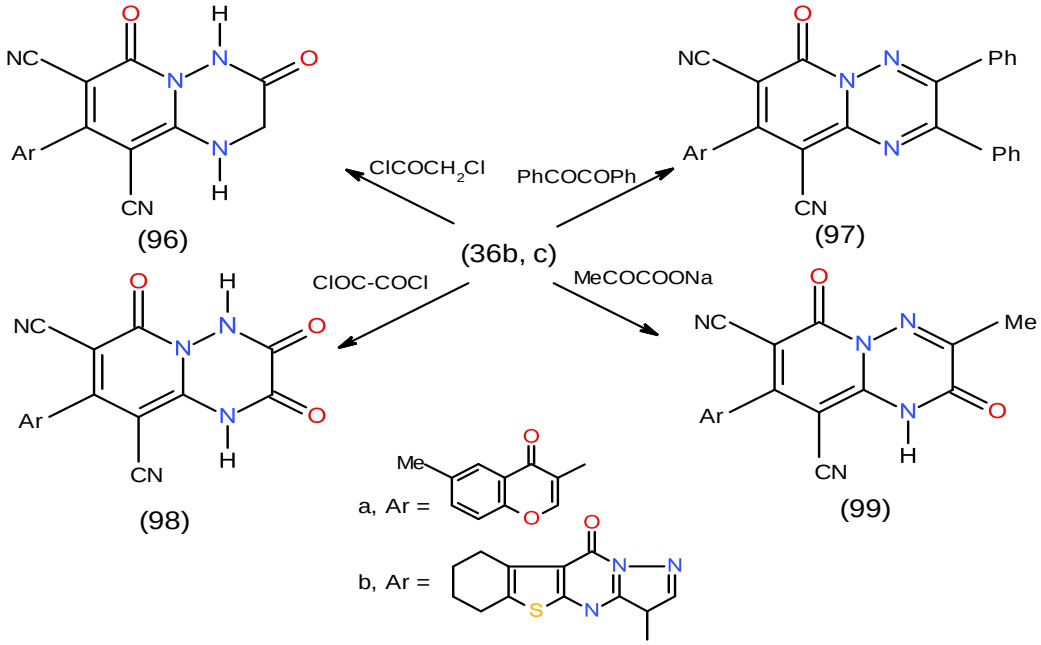
Scheme 17. Formation of pyrimidopyridopyridazines



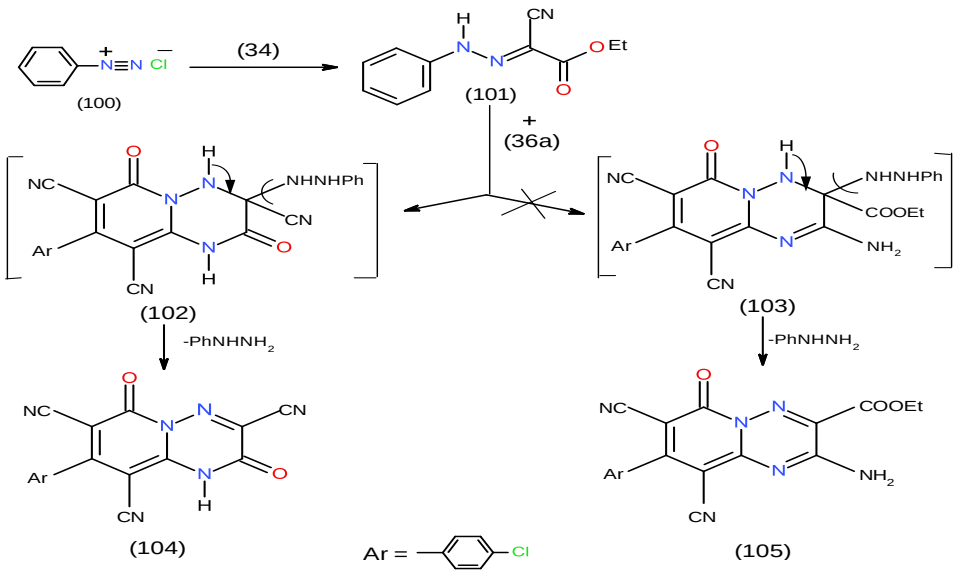
Scheme 18. Aminouracil in the formation of pyrimidopyridines



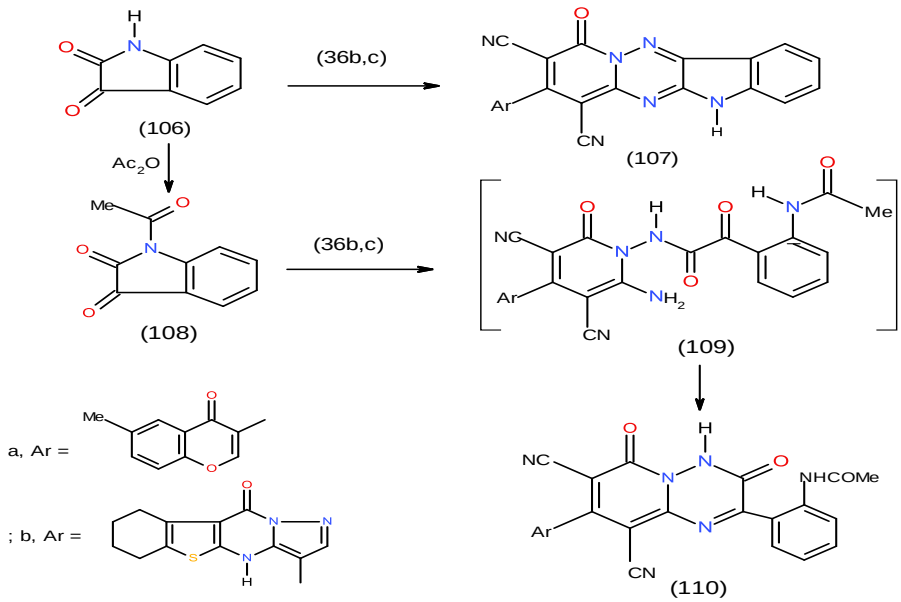
Scheme 19. Formation of aminopyridopyrimidinecarbonitrile



Scheme 20. Formation of pyrido1,2,4-triazinones



Scheme 21. Formation of pyrido1,2,4-triazinones



Scheme 22. Formation of pyrido1,2,4-triazinone derivatives

On the other hand, for the preparation of pyridine bearing indolotriazine, we carried out the condensation of 2,6-diaminopyridine (111) with 2,3-indoledione (106) to afforded 2,6-bis(indol-imino)pyridine (112). Alkylation of 112 with phenacyl bromide and chloroacetone gave 2,6-bis(1-substitutedindolimino)pyridine (113a,b), respectively. Hydrazinolysis of 113a,b with hydrazine hydrate yielded the respective 2,6-bis(1,2,4-triazinoindolimino) pyridines 114a,b, whereas, alkylation of 112 with chloroacetamide and ethyl bromoacetate furnished 2,6-bis(1-substitutedindolimino)pyridine (113c, d), which on fusion with hydrazine hydrate produced 2,6-bis(1,2,4-triazinoindolimino)pyridine 115 [29] (Scheme 23).

Moreover, the formation of pyrazolopyridine in addition to pyridazinotriazine in one molecular frame was carried out by alkylation of compound 18 with ethyl chloroacetate to afford S- and N-alkylated product 116. Treatment of 116 with hydrazine hydrate produced pyridazino1,2,4-triazinone 118 through the non-separable intermediate 117 [9] (Scheme 24).

3.5 Formation of Pyrido1,2,4- Triazepines

The literature survey of 1,2,4-triazepines, synthesis and reactions of monocyclic and fused heterocycles incorporating 1,2,4-triazepines as well as their biological evaluation and synthetic applications was described [30]. As a part of our program directed for the synthesis of new polynuclear bioactive heterocyclic systems, one of our synthetic strategy was utilize the 1,6-diamino-4-aryl-2-oxopyridine-3,5-dicarbonitrile 36a- c as a suitable synthon for the synthesis of nitrogen bridge-head pyrido[1,2,4]-triazepines. Accordingly, treatment of 36a with diethyl malonate (119), diazotized acetylacetone (120), dimethyl acetylenedicarboxylate (121) and dehydroacetic acid (122) furnished substituted pyrido1,2,4-triazepines 123-126, respectively [31] (Scheme 25).

The action of 2-cyano-3,3-bis-(methylthio) (91) and chromone-3-carbonitrile 127 upon 36a-c yielded pyrido1,2,4-triazepines 128a-c and 129a-c, respectively. Also, Treatment of 36a with ethyl exothymethylenecyanoacetate (72) gave pyrido-1,2,4-triazepinetricarbonitriles 130 while, the reaction of 36b,c with arylidenecyanoacetate (131) produced aminopyrido1,2,4-triazepine-dicarbonitriles 132a,b, respectively [14-31] (Scheme 26).

Furthermore, cyclocondensation of 36b,c with arylidedmalonitrile (133),2-cyano-3,3-bis(methyl thio)prop-2-enamide (134) and o-chloroaldehyde derivative 135 gave the corresponding pyrido-1,2,4-triazepines 136a,b, 137a,b and 138a,b, respectively [14,15] (Scheme 27).

On the other hand, the action of 3-formyl-chromone (1) upon 36a and the effect of 2-chloro-3-formylquinoline (139) on 36c were studied and furnished the respective pyrido1,2,4-triazepines 140 and 141 [14,31] (Scheme 28).

4. BIOLOGICAL IMPORTANCE

4.1 Antimicrobial Activities

Some synthesized heterocyclic compounds were tested their antimicrobial activity against some Gram-positive bacteria such as *Bacillus subtilis, Staphylococcus aureus and Bacillus cereus*and some Gram-negative bacteria namely, *Escherichia coli, Salmonella typhimurium, Pseudomonas aeruginosa* and *Proteus vulgaris* and some fungi for examples *Candida albicans, Aspergillus fumigatus*using standardized disc agar diffusion method [32] or Vincent filer paper disc method [33] with taken some antibiotics as reference. Herein we recorded the compounds exhibited strong inhibition effect against a certain microorganism.

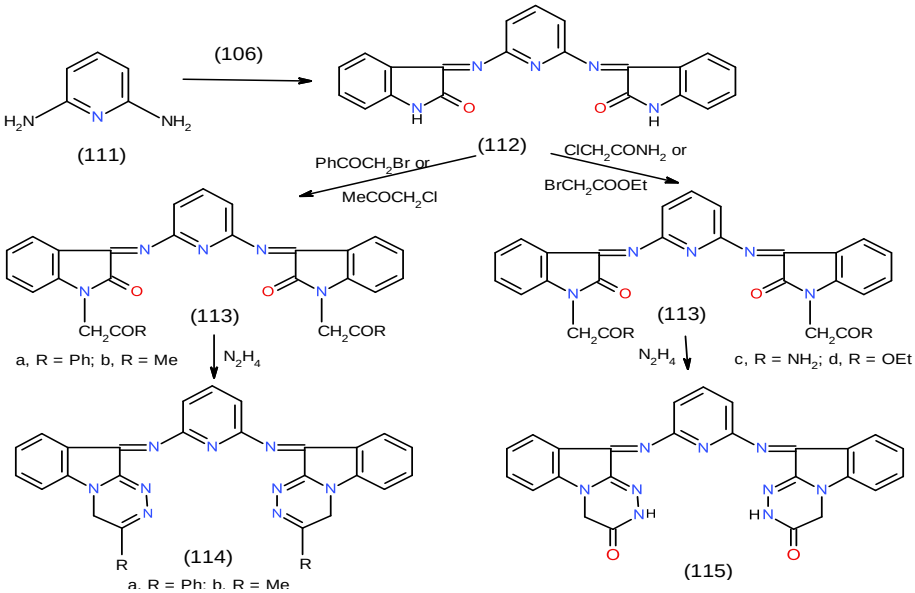
4.2 Action on Gram-Positive Bacteria

Bacillus subtilis: A Gram-positive Bacterium *Bacillus subtilis*, like many microorganisms, can form most of the enzymes needed for the biosynthesis of the amino acid tryptophan. The primary role of tryptophan within living organisms is as a novel residue within many proteins. The efficient production of secreted enzymes B. subtilis is considered a key drivers of the successes in the enzyme industry [34]. The selected synthesized heterocyclic compounds were tested against *Bacillus subtilis*. The results showed that pyrido1,2,4-triazepinetricarbo-nitriles130b, which carrying pyrazolobenzothieno-pyrimidyl nucleus [15] exhibited the highest antimicrobial activity against *Bacillus subtilis*compared with the tested compounds in the study. (Bio-1 scheme).

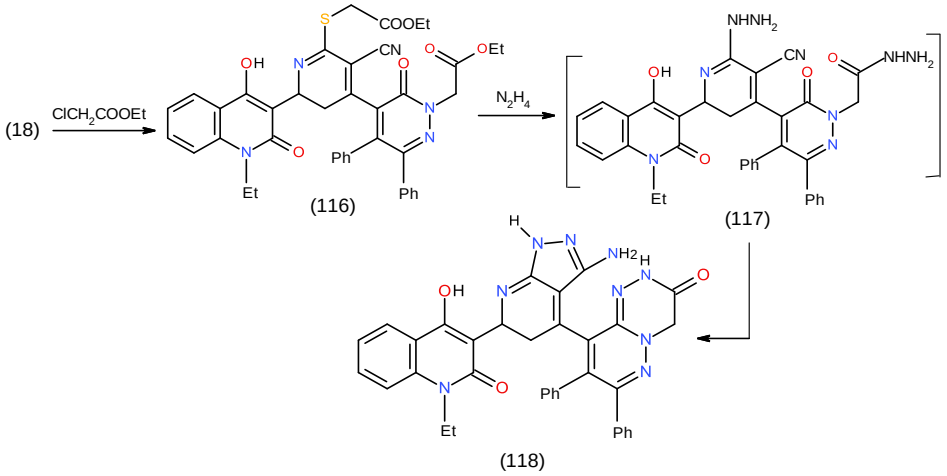
Staphylococcus areus: It is a Gram-positive, omnipresent bacterial pathogen that havethe ability to adapt and live in various states. *S. aureus* is one of the major causes of spreading of the clinical infection such asbacteraemia and infective endocarditis, osteoarticular, skin and soft tissue, pleuropulmonary, and device-related infections [35]. The results showed that pyrazolopyridotroazepine138a, which having pyrazolobenzothienopyrimidinyl moiety exhibited the highest antimicrobial activity against *Staphylococcus areus* [15]. Also, the pyridine carryingthiazolindione nuclei exhibited higher inhibition effect to *Staphylococcus areus* as in oxopyridinecarbonitrile 227 [30] (Bio-2 scheme).

4.3 Action on Gram-Negative Bacteria

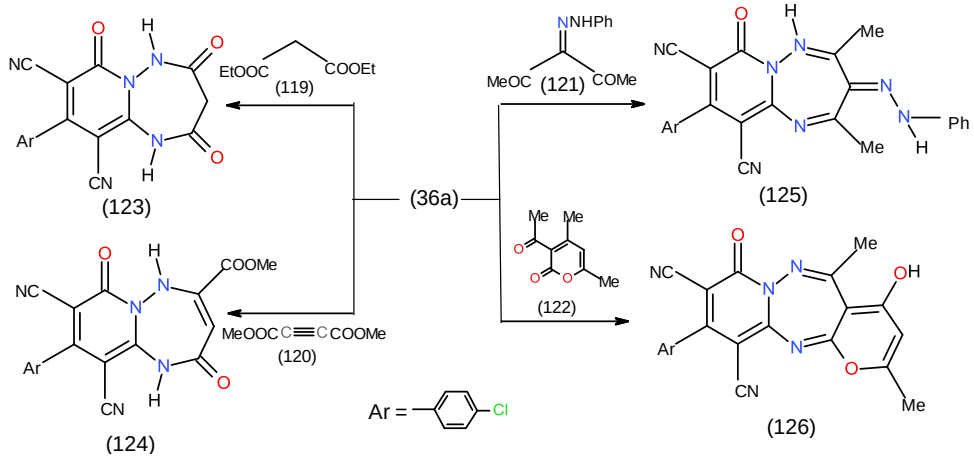
Escherichia coli: *Escherichia coli* is a large and various group of bacteria that is found naturally in the intestines of healthy humans and animals. Most types of *Escherichia coli* are harmless or cause relatively brief diarrhea, but some of the *Escherichia coli* can cause a disease for people which can be done by creating a toxin known as Shiga Toxin [36]. It can be seen clearly that pyridotriazepine128b, which having pyrazolo-benzothienopyrimidinyl moiety exhibited the highest antimicrobial activity against *Escherichia coli* compared with the tested 77 investigated compounds [8] (Bio-3 scheme).



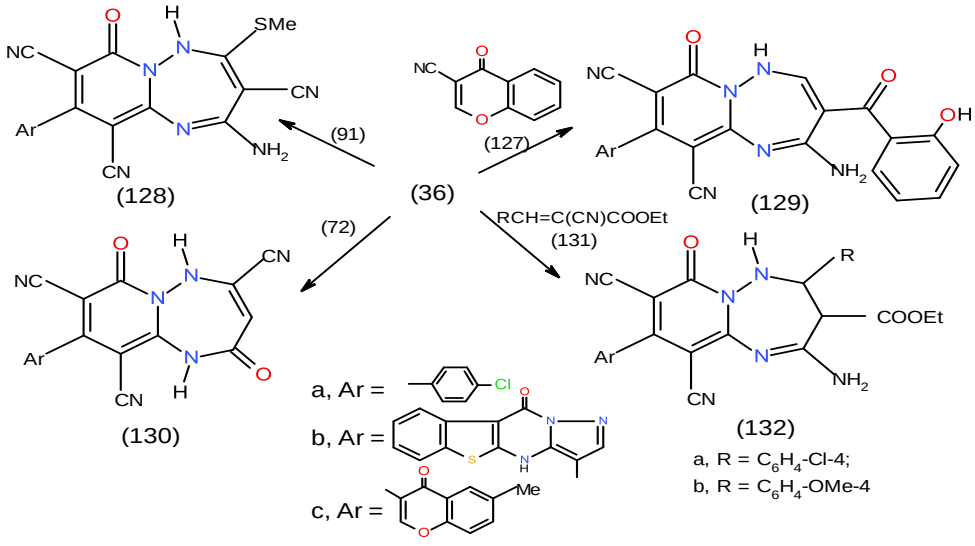
Scheme 23. Formation ofbis indolo1,2,4-triazinone



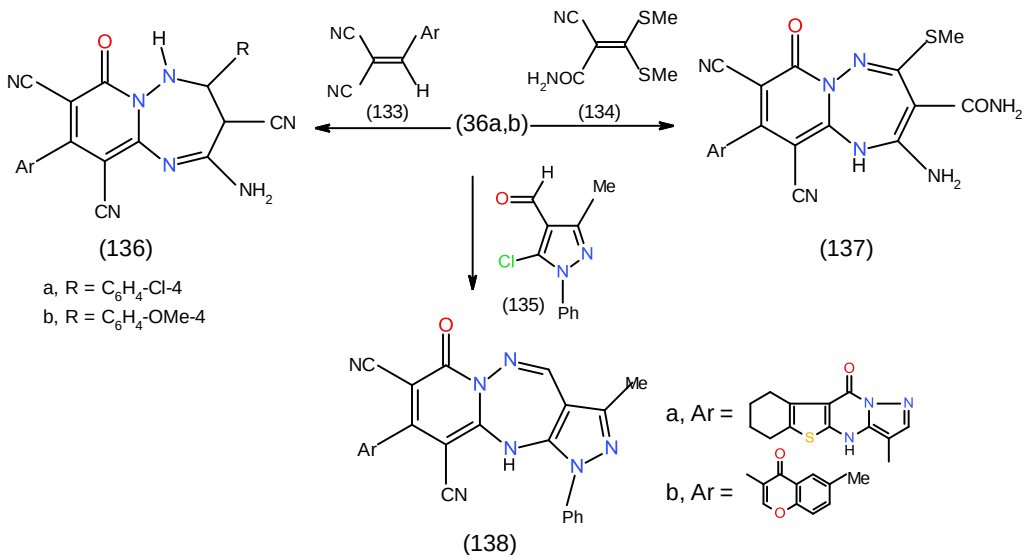
Scheme 24. Formation of and pyridzino1,2,4-triazinones



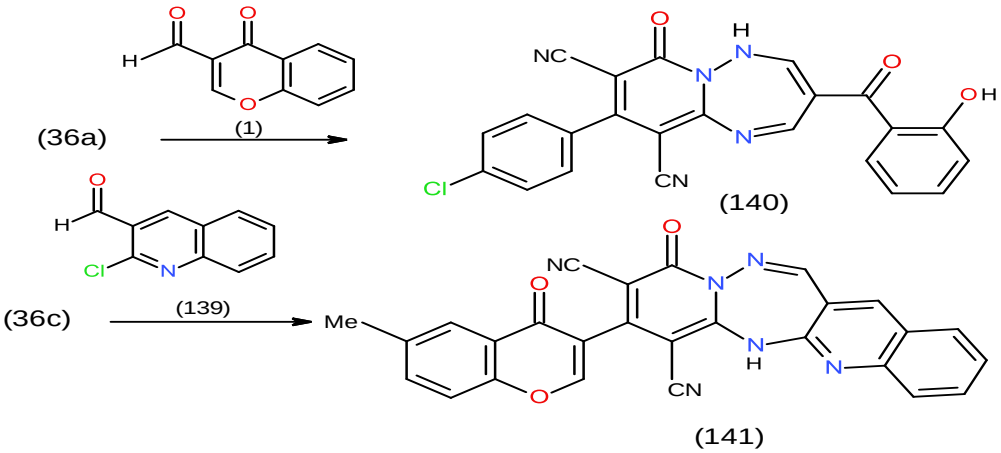
Scheme 25. Formation ofpyridotriazepine derivatives



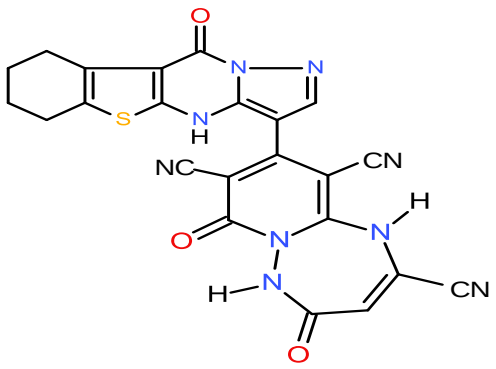
Scheme 26. Formation ofsubstituted pyridotriazepine



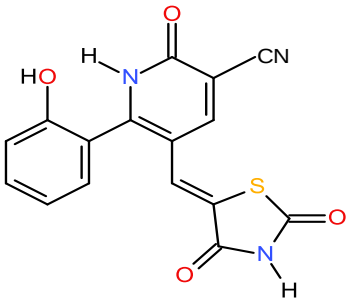
Scheme27. Formation of substituted and condensed pyridotriazepines



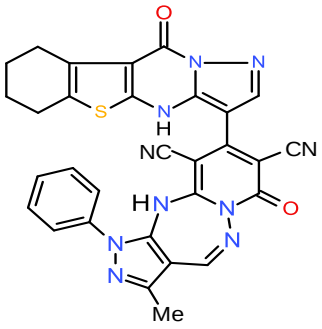
Scheme 28. Formation of pyridoquinolinotriazepine



Bio-1 Scheme. The highest antimicrobial activity one against *Bacillus subtilis*

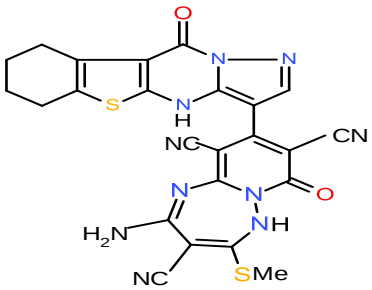


(9)



(138a)

Bio-2 Scheme. Compounds could use as antimicrobial agents against *Staphylococcus aureus*



(128b)

Bio-3 Scheme. The highest antimicrobial activity compound against *Escherichia coli*

Salmonella typhimurium: Infection of humans by the enteric pathogen *Salmonella typhimurium* generally results in severe abdominal cramping and diarrhea. These symptoms may largely result from the mucosal immune response elicited by this pathogen. Specifically, colonization of the human intestine by *S. typhimurium* leads to infiltration of polymorphonuclear leukocytes (PMNs) into the intestinal epithelium culminating in the formation of an intestinal crypt abscess [37]. Results obtained disclosed that pyrido1,2,4-triazinedione 110b [15], which having pyrazolo-benzothienopyrimidinyl moiety exhibited the highest antimicrobial activity against *Salmonella typhimurium* compared with the tested compounds [15] (Bio-4 scheme).

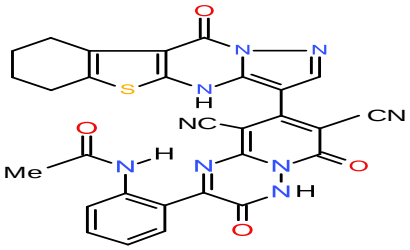
4.4 Action on Fungi

Candida albicans: *Candida albicansis* is one of the very few fungal species causing disease in humans—millions of others do not. It is a member of the healthy microbiota, asymptomatically colonizing the gastrointestinal (GI) tract, reproductive tract, oral cavity, and skin of most humans [38]. The results showed that pyrido1,2,4-triazinedione 96b and aminopyrido1,2,4-triazepine 129b that having pyrazolobenzothienopyrimidinyl moiety in their structures exhibited the highest antimicrobial activity against *Candida albicansis* compared with the tested compounds [15] (Bio-5 Scheme).

Also, the compound carrying thiazolidinedione nucleus in their structures such as pyridinecarbonitrile 9 and pyrido1,2,4-triazepine 142, obtained from reaction of the enone 3 with diaminopyridinedicarbonitrile 36a, may be used as antimicrobial agent against *Candida albicansis* from tested compounds [36] (Bio-6 scheme).

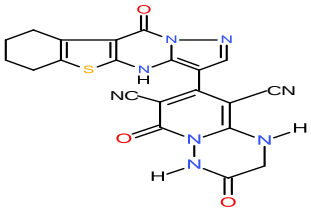
Aspergillus fumigates: *Aspergillus fumigatus* is an opportunistic fungus causing allergic and invasive aspergillosis in humans and animals. It secretes an array of complex biologically active glycoprotein antigens and allergens, which have been implicated in human respiratory allergic disorders [39]. The compounds carrying pyrazolobenzothienopyrimidinyl moiety in their structures such as pyrido1,2,4-triazepine 136a

and pyrazolopyrido1,2,4-triazepine 138a may be used as antimicrobial agent against *Aspergillus fumigatus*as they shown the highest inhibition zones [15] (Bio-7 scheme).

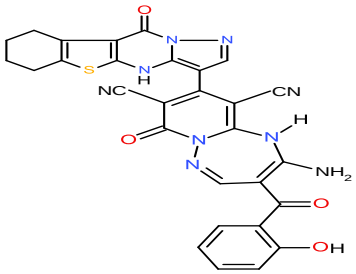


(110b)

Bio-4 Scheme. One of the highest antimicrobial activity against *Salmonella typhimurium*

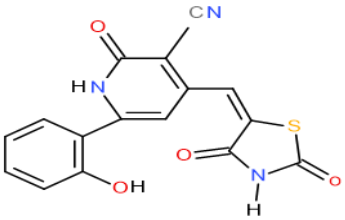


(96b)

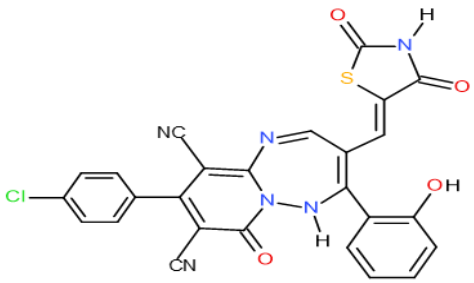


(129b)

Bio-5 Scheme. Compounds with the highest antimicrobial activity against *Candida albicansis*

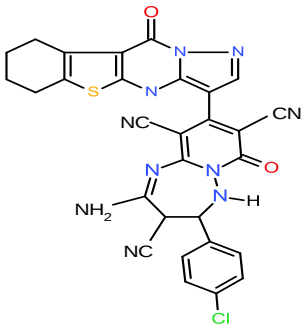


(9)

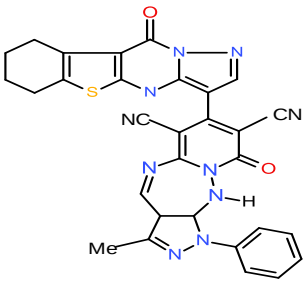


(142)

Bio-6 Scheme. Compounds may be used as antimicrobial agent against *Candida albicansis*



(136a)



(138a)

Bio-7 Scheme. Compounds with the highest antimicrobial activity against *Aspergillus fumigatus*

5. CONCLUSION

In our studies effort done to optimize the synthetic procedures for the preparation of various bioactive pyridines and their condensed systems with the help of active acyclic and cyclic methylene compounds as well as heterocyclic having active methyl or methine sites by their reaction with some synthesizing reagents. This study will help researchers in the fields of organic and medicinal chemistry to design and implement new procedures for the constructions of novel biological components having pyridine nucleus in their structures.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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