

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

Abstract

This review discusses how we use the most 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 fused pyridines interesting medical and pharmaceutical importance. Many synthetic approaches were used for the preparation of target heterocyclic systems such as cyclocondensation reactions, ring opening-ring closure, cycloaddition, acid- or base-catalyzed reaction, intermolecular cyclization and self-condensation have been reviewed in this paper. Also, the antimicrobial activity carried out on some newly selected synthesized pyridines and their fused derivatives were reported.

Key words

Active methylene, pyridines, thiazolopyridines, indopyridines, pyridopyrimidines, pyridotriazines, pyridotriazepines, antimicrobial activity.

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 medicinal scaffolds and investigations into their pharmacological properties [1]. Benzopyridines specially quinolinones 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 utility of active methylene compounds and heterocycles bearing active methyl or having an active methine in their structures in heterocyclization of five-, six-, and seven-membered heterocyclic systems of important applications in many fields such as medicine, agriculture, pharmacology and pharmaceutical. consequently, we recently publish some reviews [3-6] and this review summarized our work

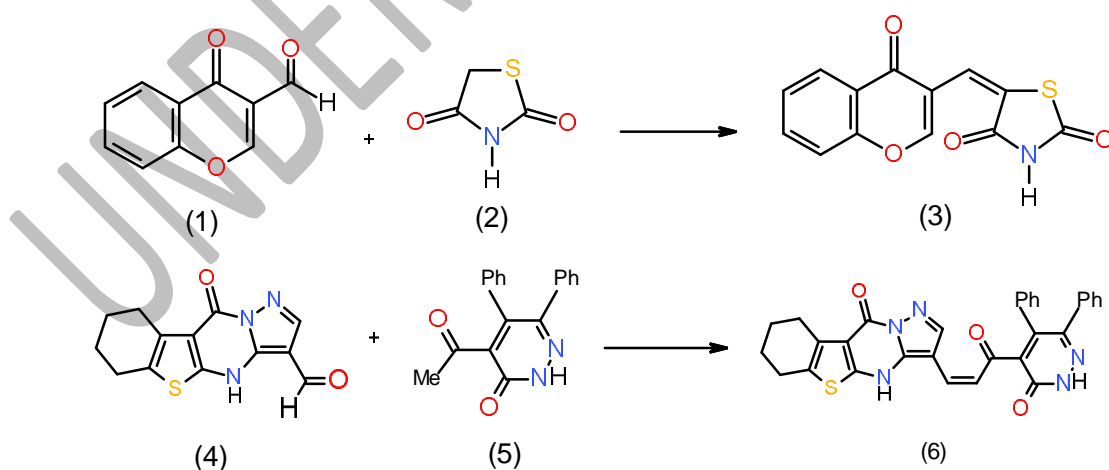
done in the last three decades and it involves the methods developed for the syntheses of substituted and fused pyridine derivatives using the titled compounds and reported the antimicrobial activity of some selected synthesized compounds.

1. Formation of substituted pyridines

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

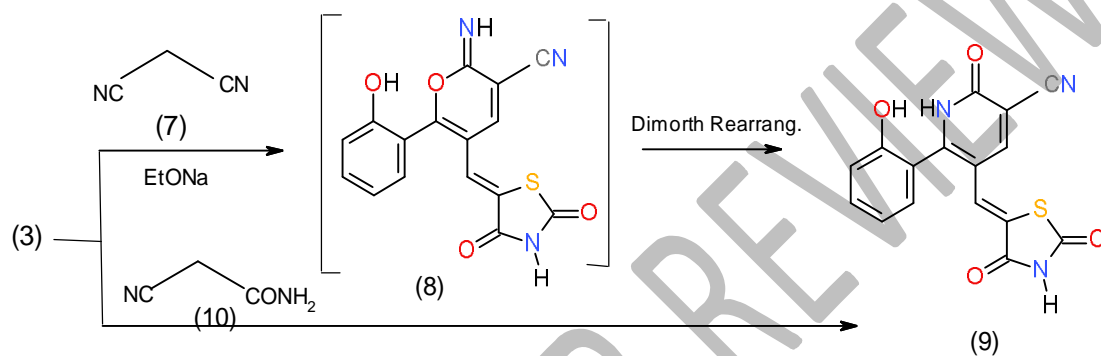
1.1. Using synthesized enones

α, β -Unsaturated ketones are called chalcones or enones and 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 renders the enones susceptible to the cycloaddition reaction forming the target pyridines. The preparation of a novel pyridine bearing substituted heterocyclic systems requires the formation of bi-heterocyclic enones such as the enone (3), which was synthesized via Knoevenagel condensation of 3-formylchromone (1) with thiazolidene-2,4-dione (2) having an active cyclic methylene group [7]. Whereas, the bi-heterocyclic enone 6 was performed by condensation of a formyl derivative of pyrazolobenzothienopyrimidindione (4) with 4-acetylpyridazinone (5) having an active methyl group [8] (Scheme 1).



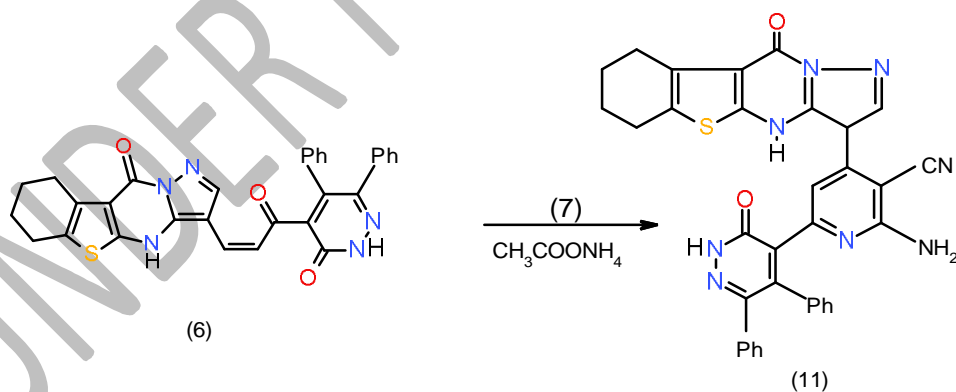
Scheme 1: Formation of bi-heterocyclic enones

The action of malonitrile (**7**) upon the two 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 α -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).



Scheme 2: Formation of oxopyridinecarbonitrile

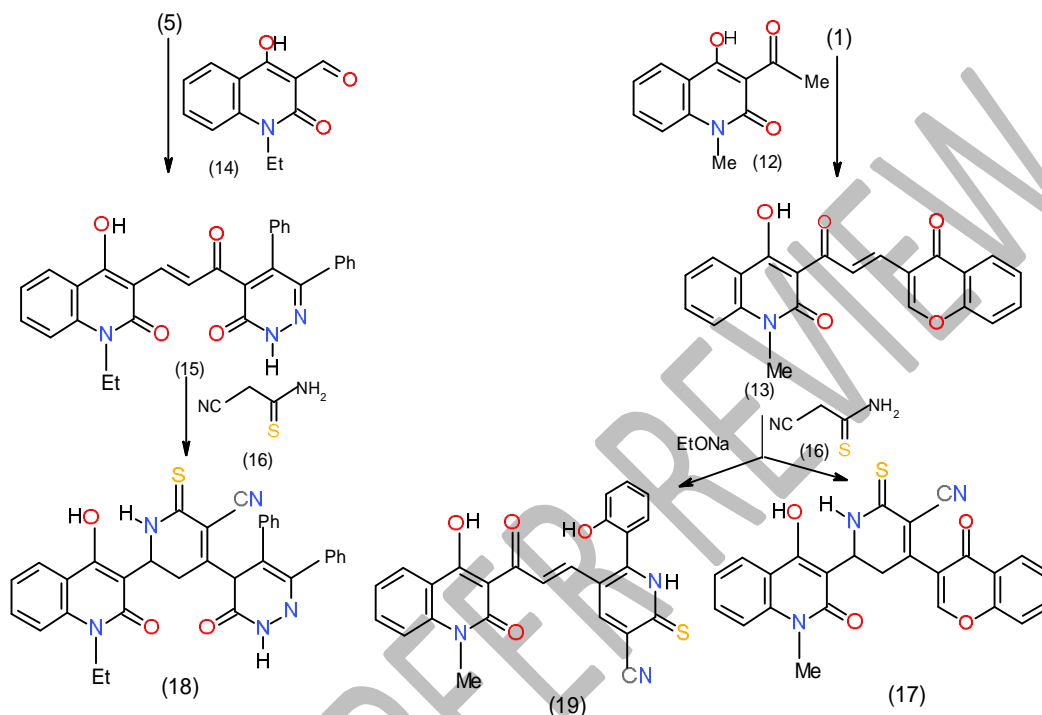
When biheterocyclic enone **6** was subjected to react with malonitrile (**7**) in boiling ethanol containing ammonium acetate, cyclocondensation took place at α,β -unsaturated carbonyl part yielding 4,6-diheterocyclypyridinecarbonitrile **11** [8] (Scheme 3).



Scheme 3: Formation of aminopyridinecarbonitrile

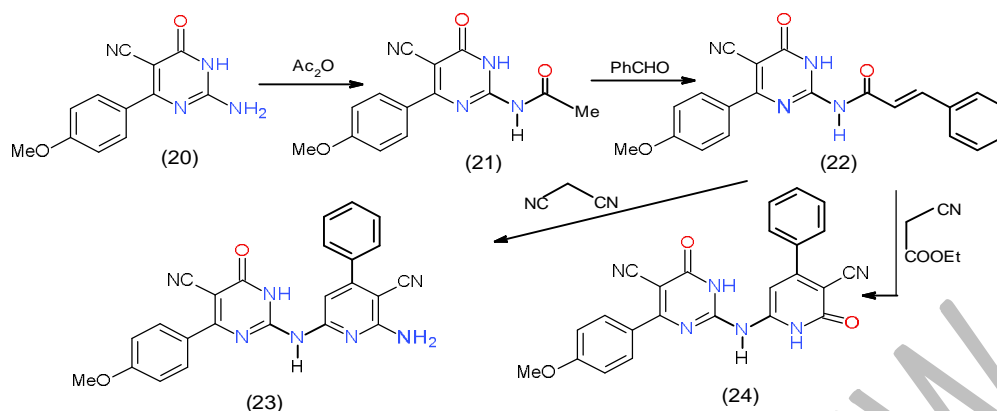
Similarly, another two synthesized enones having quinolone in their structures was prepared, the enone **13** obtained by condensation of formylchromone (**1**) with acetylquinolone (**12**) while the enone **15** formed through the condensation of formylquinolone (**14**) with acetylpyridazinone (**5**). When the reaction between cyanothioacetamide (**16**) and the enones **13** and **15** was carried

out in ethanol containing piperidinium acetate, the respective 4,6-diheterocyclpyridines **17** and **18**, was obtained. But when the reaction between **13** and **16** took place in sodium ethoxide, ring opening of α -pyrone ring followed by ring closure took place giving rise to the thioxopyridinecarbonitrile **19** [9, 10] (Scheme 4).



Scheme 4: cyanothioacetamide in the formation of thioxopyridinecarbonitriles

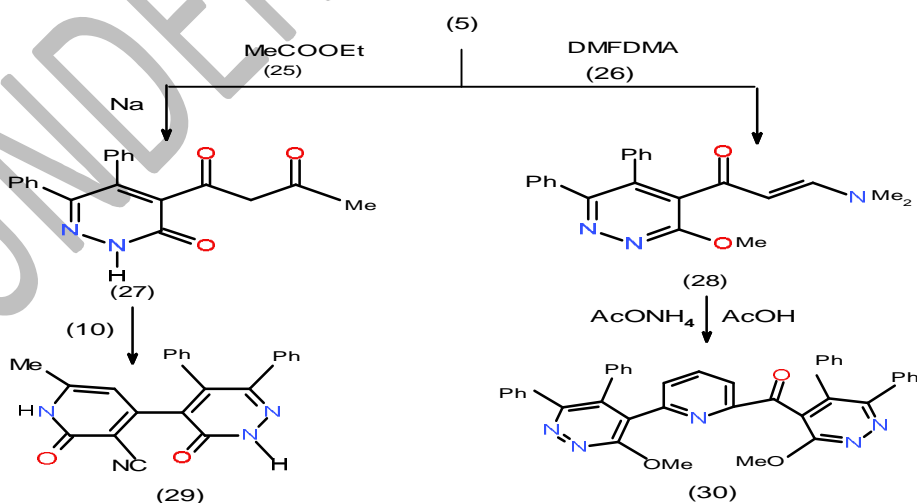
Moreover, acylation of 2-aminopyrimidinecarbonitrile (**20**) using acetic anhydride yielded 2-acetamidopyrimidinecarbonitrile (**21**), which underwent condensation with benzaldehyde in ethanolic sodium hydroxide giving 2-(N-cinnamoylamino)pyrimidinecarbonitrile (**22**). As reported for α , β -unsaturated ketones, the interaction of compound **22** with active methylene compounds afforded the substituted pyridine. Accordingly, when compound **22** was allowed to react with malononitrile (**7**) and ethyl cyanoacetate in the presence of ammonium acetate afforded 2-amino-6-pyrimidinylaminopyridinecarbonitrile (**23**) and 3-cyano-6-pyrimidinylaminopyridone (**24**), respectively [11] (Scheme 5).



Scheme 5: Formation of pyrimidinylaminopyridines

1.2. Using acetylpyridazine

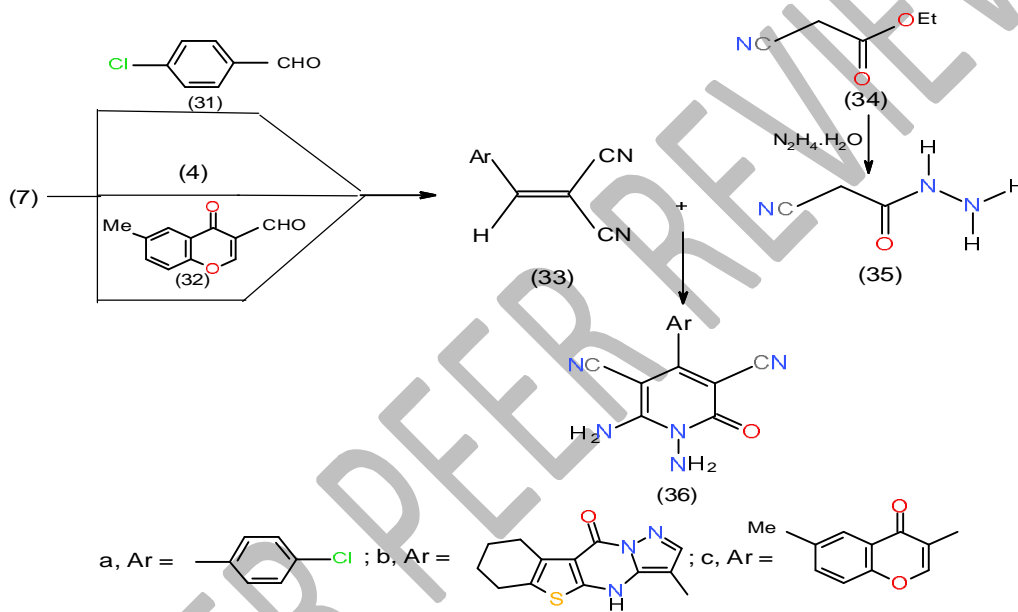
In addition to the use of acetylpyridazine (**5**) in the formation of some enones, it could be converted into a new active methylene compound or enaminone and used them in the synthesis of pyridine. Accordingly, synthesized active methylene compound namely, pyridazinylbutan-1,3-dione **27** obtained from the reaction of 4-acetylpyridazinone **5** with ethyl acetate (**25**) under claisen condensation[12]. Whereas, the enaminons **28** formed through condensation of **5** with dimethyl- formamide 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 in the presence of ammonium acetate [13] (Scheme 6).



Scheme 6: Formation of pyridazinylpyridines

1.3.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 cyanoacetic acid-hydrazide (35), the product of hydrazonolysis 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 fused pyridines.



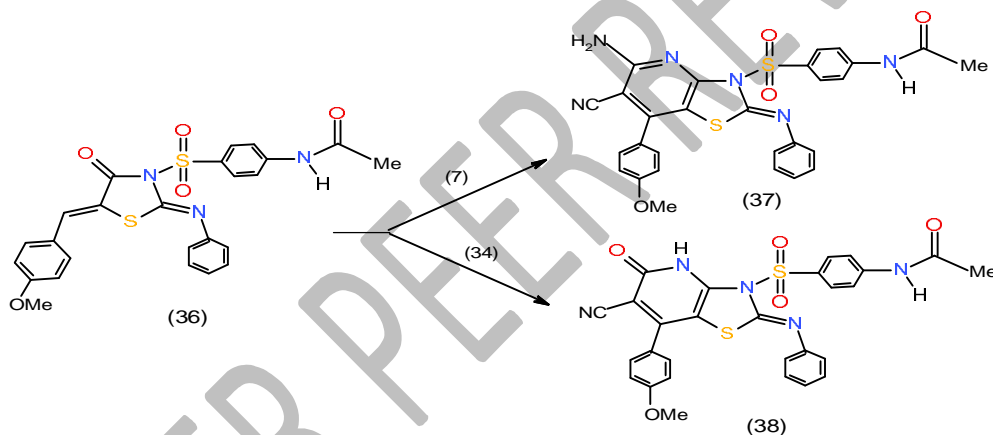
Scheme 7: Formation of diaminopyridinedicarbonitrile

2. Formation of fused pyridines

Incorporating pyridine with other heterocyclic systems such as thiazole, indole, pyrimidine, triazine and triazepines in one molecular framework enhance the biological activities of the produced condensed pyridine derivatives. Synthesis of fused pyridine 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 diaminogroups as in compound 36.

2.1. Synthesis of thiazolopyridines

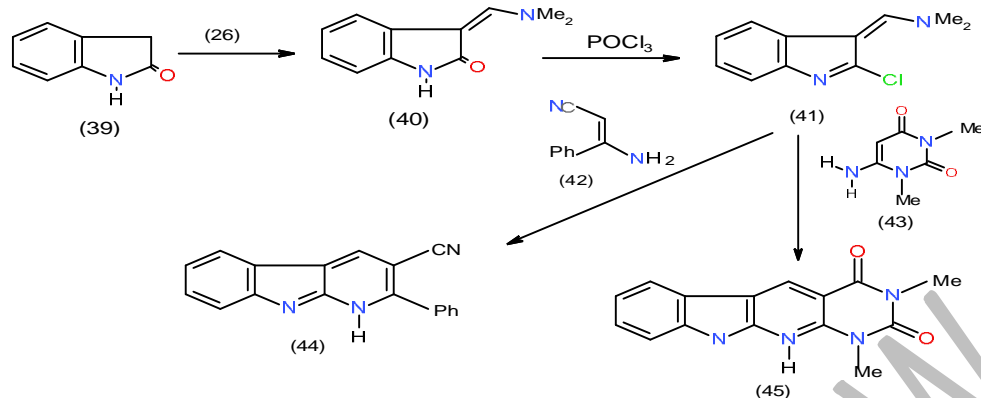
A number of methods to prepare thiazolopyridines have been documented in the literature. For example, methods that construct the bicycle by formation of a thiazole ring, include condensations of 3-amino-2-halopyridine, or 3-amino-2-pyridone derivatives, with thiocyanates, thioamides, or thioesters, condensations 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 pyridineone thiazolidinone 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 8: Formation of thiazolopyrimidines

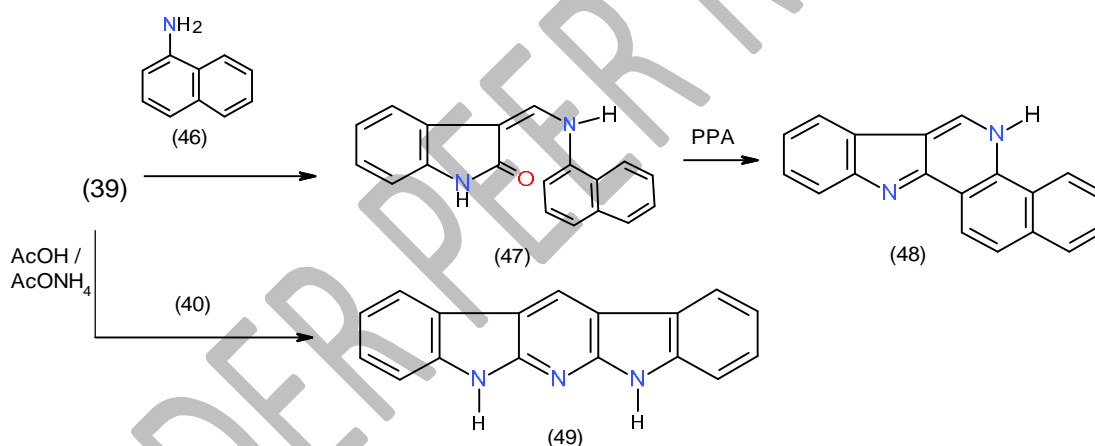
2.2. Synthesis of indolopyridines

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**) was studied. 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 methinesite in their structures such as, enaminonitrile **42** and 6-aminoaminouracil **43**, afforded the indolopyridine carbonitrile **44** and indolopyridopyrimidinedione **45**, respectively [18] (Scheme 9).



Scheme 9: Formation of indolopyridine derivatives

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

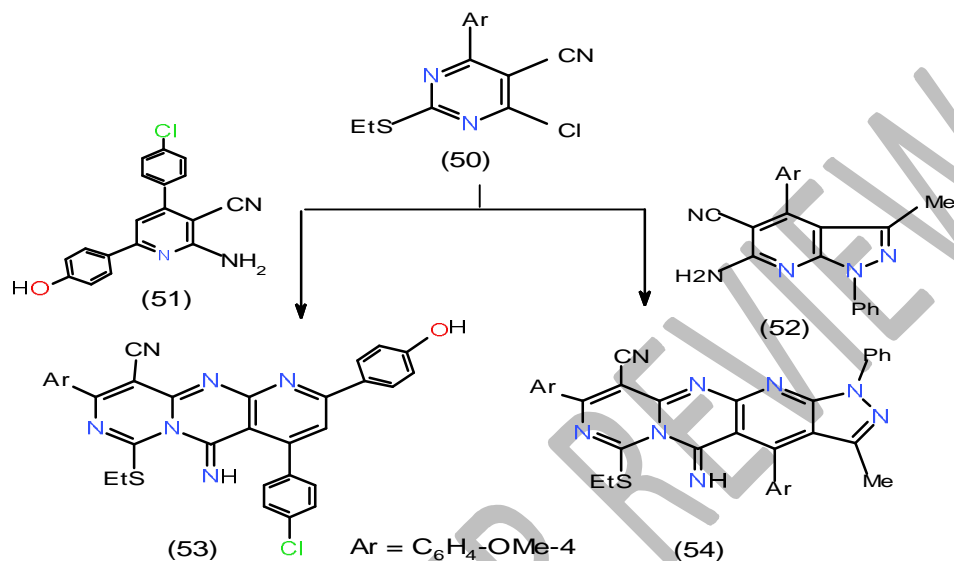


Scheme 10: Formation of poly cyclic system having pyridine

2.3. Formation of pyridopyrimidine derivatives

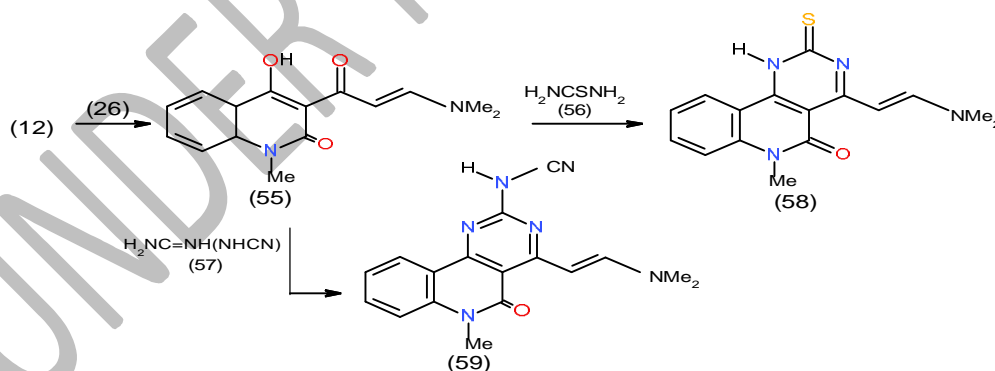
Pyridopyrimidine derivatives are a privileged bicyclic ring system. Due to its potent and significant biological activities it has great pharmaceutical importance; synthesis of these compounds is considerable interest. The development of a practical method for the synthesis of various pyrido- pyrimidines, in view of their structure relation with pteridine, is of interest in the field of medicinal chemistry [19]. Most preparation of pyridopyrimidines centered on ring closure reactions of either pyridine or pyrimidine nucleus having appropriate substituents.

Accordingly, chloropyrimidinecarbonitrile **50** reacted with some heterocycles having vicinal amino-cyano groups such as 2-aminopyrimidinecarbonitrile **51** and 3-aminopyrazolopyrimidinecarbonitrile **52** to afford the respective polycyclic systems **53** and **54** having pyridolopyrimidines in their structures [20] (Scheme 11).



Scheme 11: Formation of pyridolopyrimidine derivatives

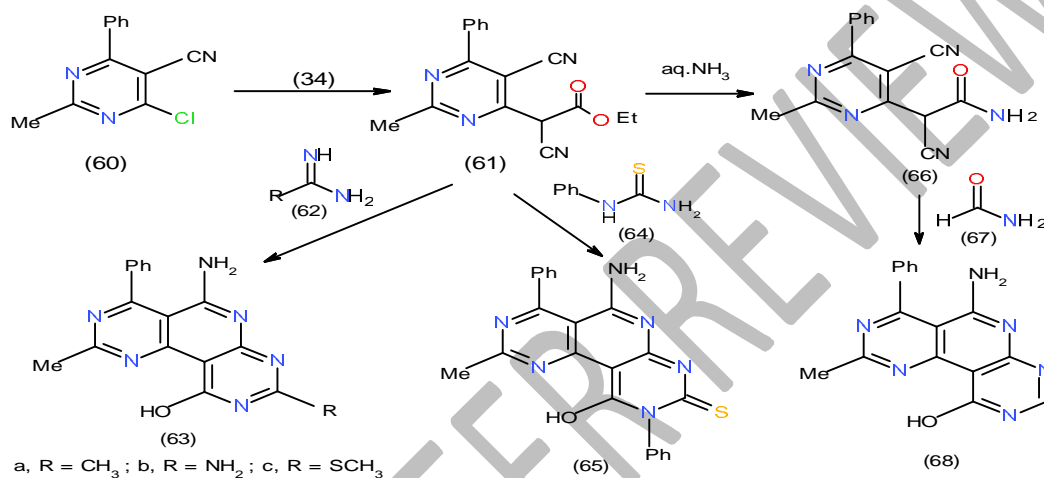
On the other hand, Condensation of 3-acetyl quinolinone **12** with DMFDMA (**26**) yielded the enaminone **55**. The reaction of thiourea (**56**) and cyanoguanidine (**57**) upon the enaminone **55** gave rise to pyrimidoquinolinones **58** and **59**, respectively [21] (Scheme 12).



Scheme 12: Formation of pyrimidoquinolinones

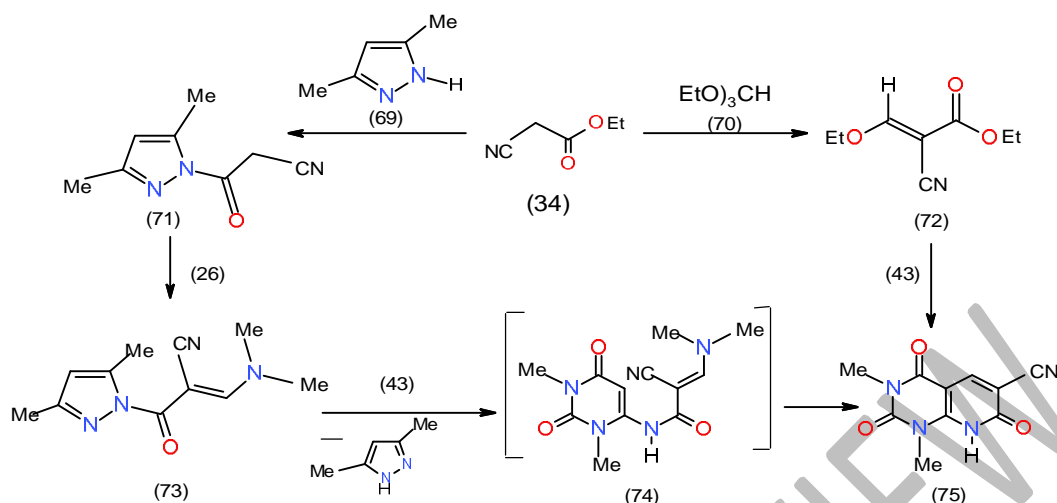
Nucleophilic substitution of the chlorine atom in chloropyrimidinecarbonitrile (**60**) using ethyl cyanoacetate (**34**) under basic condition afforded pyrimidinyl cyanoacetate derivative (**61**). Compound **61** is considered a good synthon for some interesting tri-nitrogenous heterocyclic systems 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 pyrimidopyridopyrimidinethione **65**. Moreover, treatment of **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).



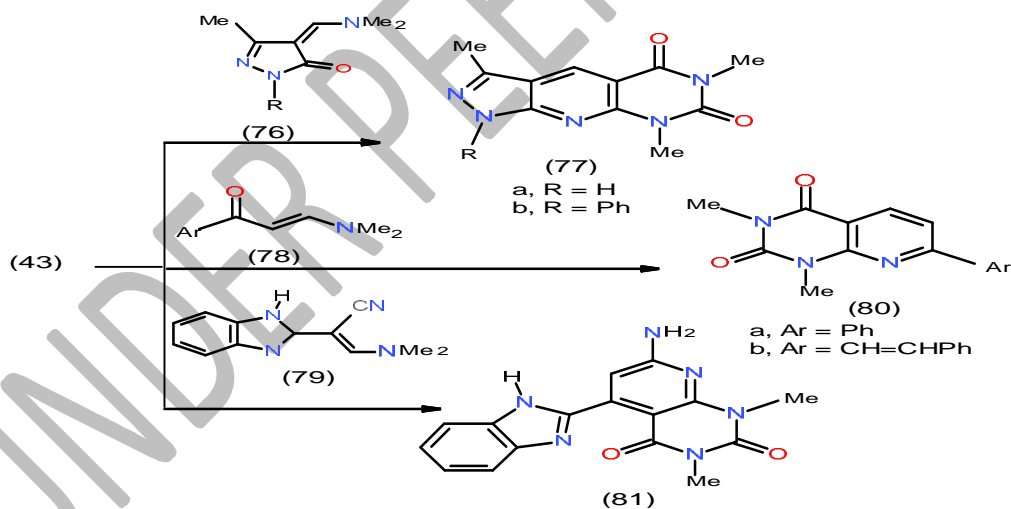
Scheme 13: Formation of pyrimidopyridopyrimidines

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 tiethyl orthoformate (**70**) to afford 3,5-dimethylpyrazol-1-yl-oxo) acetonitrile (**71**) and ethyl ethoxymethylenecyanoacetate (**72**), respectively. Treatment of **71** with DMFDMA (**26**) yielded the enaminone **73**, which reacted with 6-aminouracil **43** to give the pyrimidopyrimidine **75** via non-separable intermediate **74**. Compound **75** was also obtained from the reaction of 6-aminouracil **43** with compound **72**[24] (Scheme 14).



Scheme 14: Formation of pyrimidopyridines

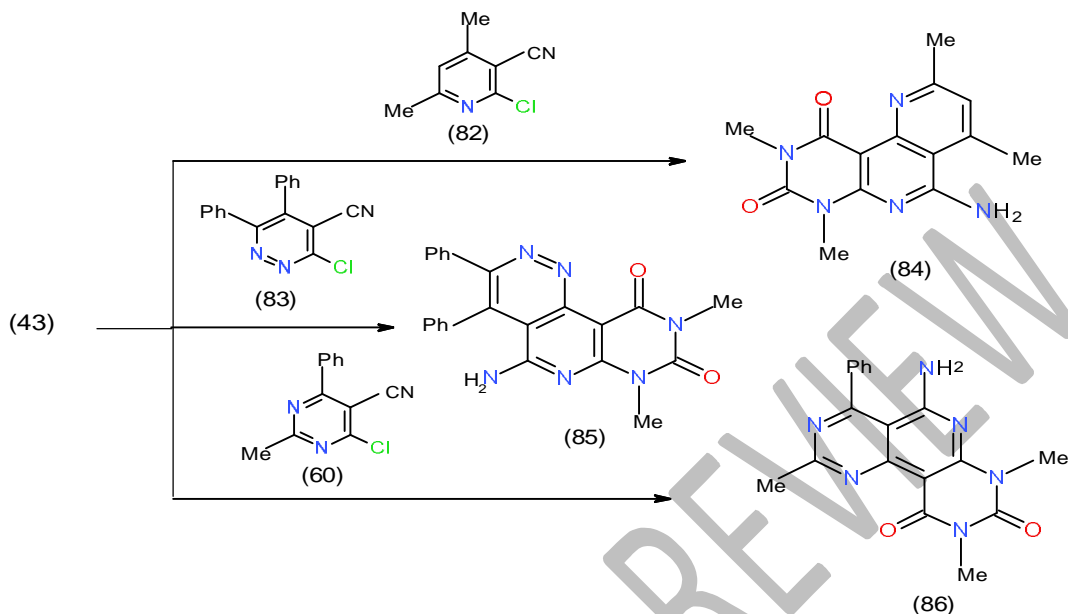
In conjunction to our interest in the chemistry of the enaminones, pyrazolopyrido-pyrimidindiones **77a, b** synthesized on treatment of 6-amino-uracil **43** with the cyclic enaminones **76a, b**, while the pyridopyrimidinediones **80a, b** and benzimidazolypyridopyrimidinedione **81** obtained from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



Scheme 15: Formation of pyridopyrimidinediones

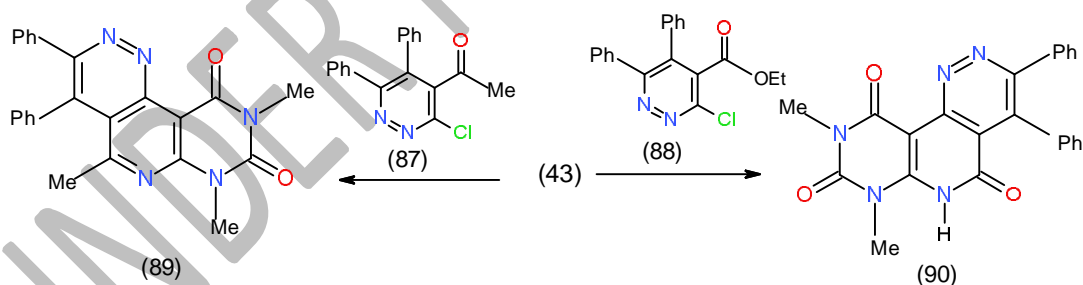
Moreover, 6-amino-1,3-dimethyluracil (**43**) having an active methine group at position-5, reacted with some bifunctional heterocyclic systems having vicinal chloro-cyano groups in their structures such as 2-chloropyridinecarbonitrile **82**, 3-chloropyridazinecarbonitrile **83** and 4-

chloropyrimidinecarbonitrile **60** and afforded the novel triheterocyclic systems having pyridopyrimidines in their structures **84-86**, respectively [25] (Scheme 16).



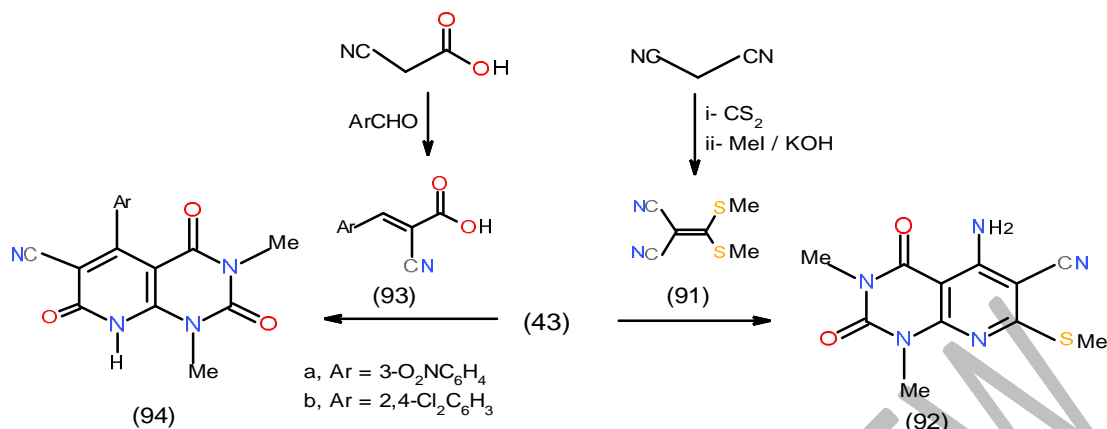
Scheme 16: Formation of pyridine in triheterocyclic systems

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



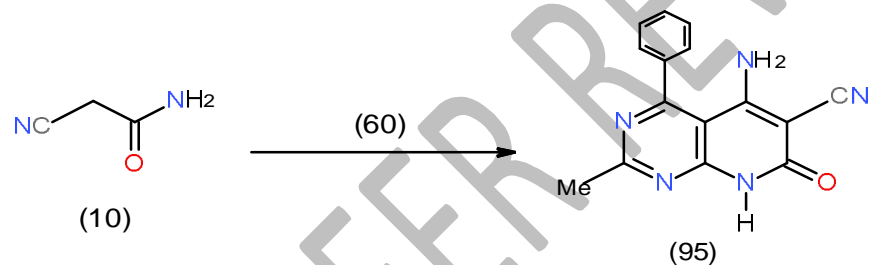
Scheme 17: Formation of pyrimidopyridopyridazines

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 yield pyrimidopyrimidinedione derivative **92** while, the reaction of **43** with arylidene cyanoacetic acids **93a, b**, obtained from the condensation of cyanoacetic acid with aromatic aldehydes afforded pyridopyrimidinetrienes **94a, b** [20] (Scheme 18).



Scheme 18: Aminouracil in the formation of pyrimidopyridines

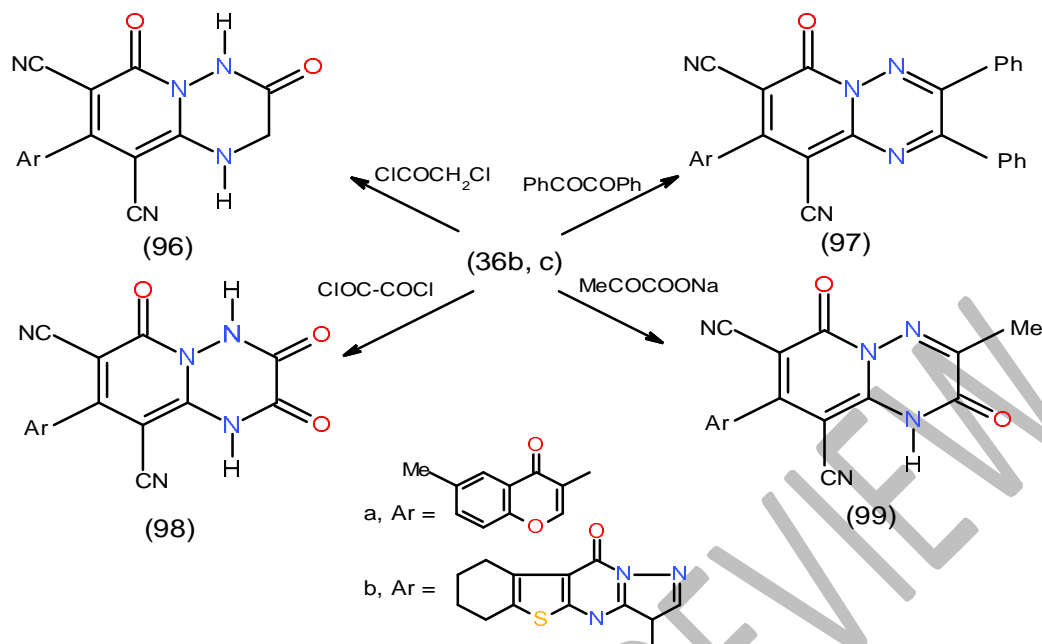
Also, the reaction of 4-chloropyrimidinecarbonitrile **60** with cyanoacetamide (**10**) in boiling dimethyl formamide gave aminopyridopyrimidinecarbonitrile **95** [27] (Scheme 19).



Scheme 19: Formation of aminopyridopyrimidinecarbonitrile

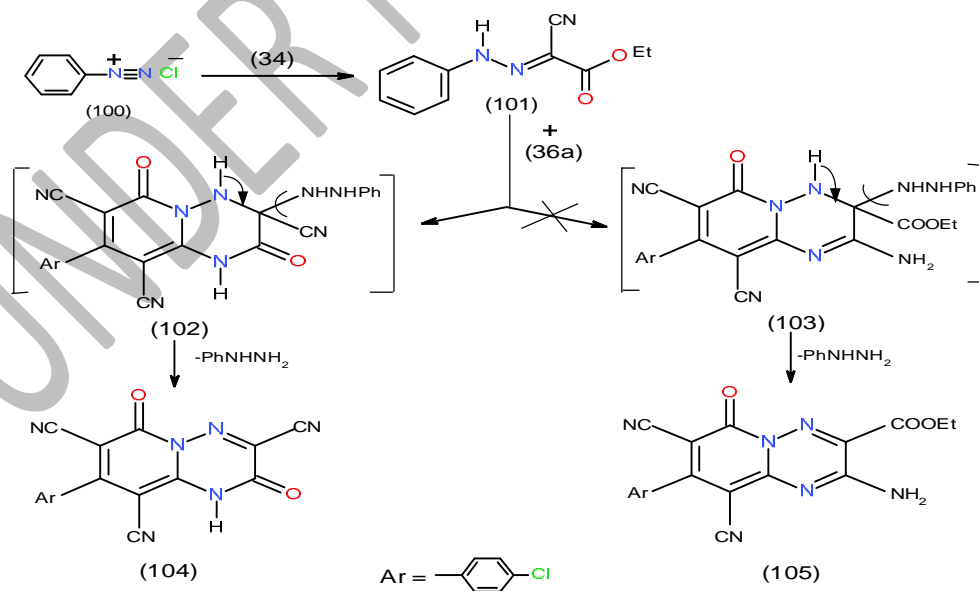
2.4. Formation of pyridotriazines derivatives

The bicyclic heterocycles 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-dicarbonitriles (**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).



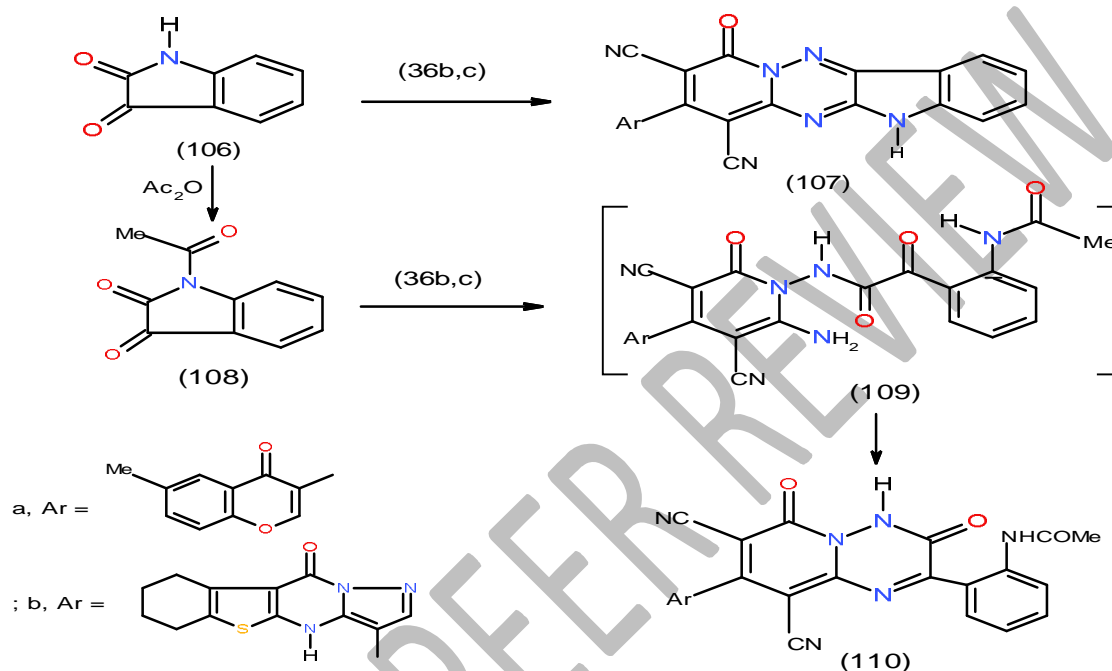
Scheme 20: Formation of pyrido1,2,4-triazinones

Moreover, the action of ethyl α -cyano- α -phenylazoacetate **101**, obtained via the condensation of ethyl cyanoacetate (**34**) with benzenediazonium chloride **100** upon diaminopyridinedicarbonitrile **36a** 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).



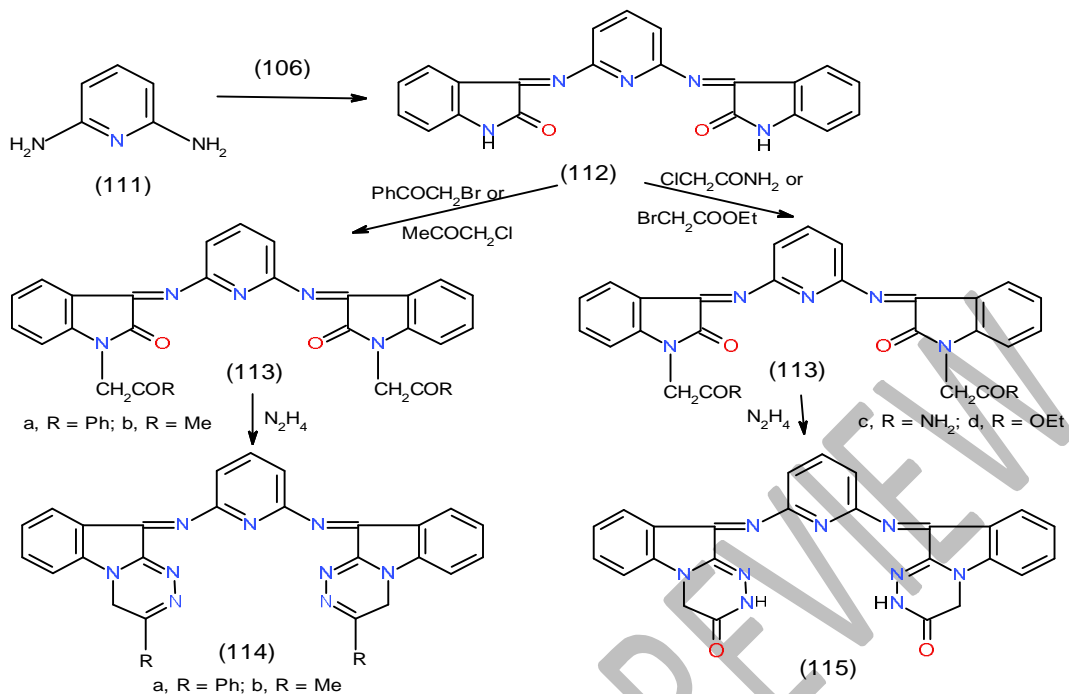
Scheme 21: Formation of pyrido1,2,4-triazinone

Also, condensation of 2,3-indole-1-one (isatin) (**106**) with diaminopyridone-dicarbonitrile **36b, c** in glacial acetic acid containing freshly fused sodium acetate afforded indolopyridotriazine derivative **107a, b**. Whereas, a different behavior was observed on treating **36b, c** with N-acetyl isatin **108** in glacial acetic acid as it furnished pyridotriazinone **110a, b**. The formation of **110** took place via the intermediate **109** [14] (Scheme 22).



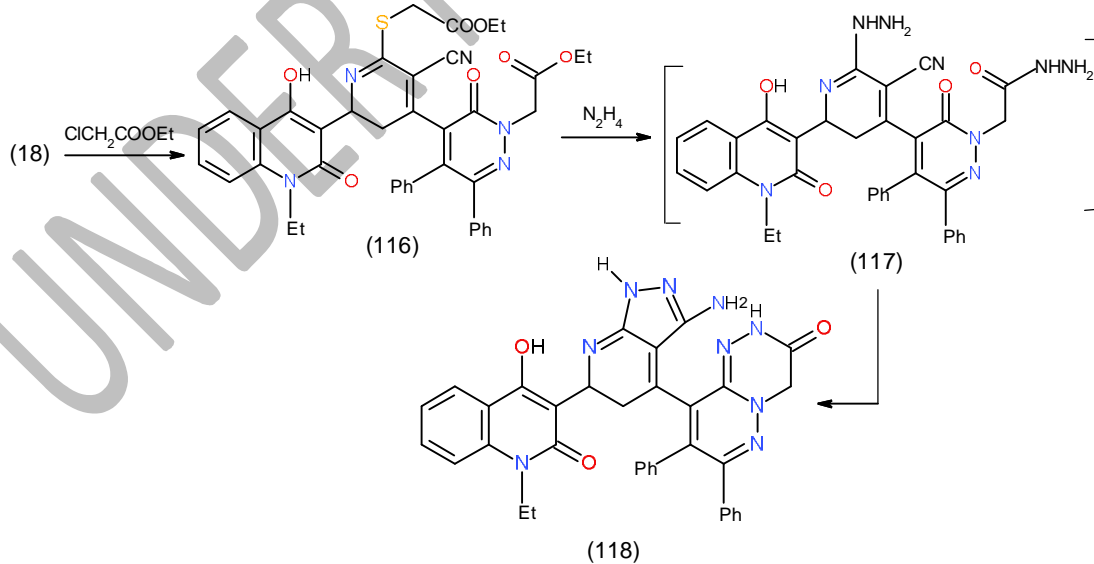
Scheme 22: Formation of pyrido1,2,4-triazinone derivatives

On the other hand, for the preparation of pyridine bearing indotriazine we carried out the condensation of 2,6-diaminopyridine (**111**) with 2,3-indole-1-one (**106**) afforded 2,6-bis(indol-3-ylidene)pyridine (**112**). Alkylation of **112** with phenacyl bromide and chloro acetone gave 2,6-bis(1-substitutedindol-3-ylidene)pyridine (**113a, b**), respectively. Hydrazinolysis of **113a, b** with hydrazine hydrate yielded the respective 2,6-bis(1,2,4-triazinoindol-3-ylidene)pyridine **114a, b**, whereas, alkylation of **112** with chloroacetamide and ethyl bromoacetate furnished 2,6-bis(1-substitutedindol-3-ylidene)pyridine (**113c, d**), which on fusion with hydrazine hydrate produced 2,6-bis(1,2,4-triazinoindol-3-ylidene)pyridinone **115** [29] (Scheme 23).



Scheme 23: Formation of bis indolo1,2,4-triazinone

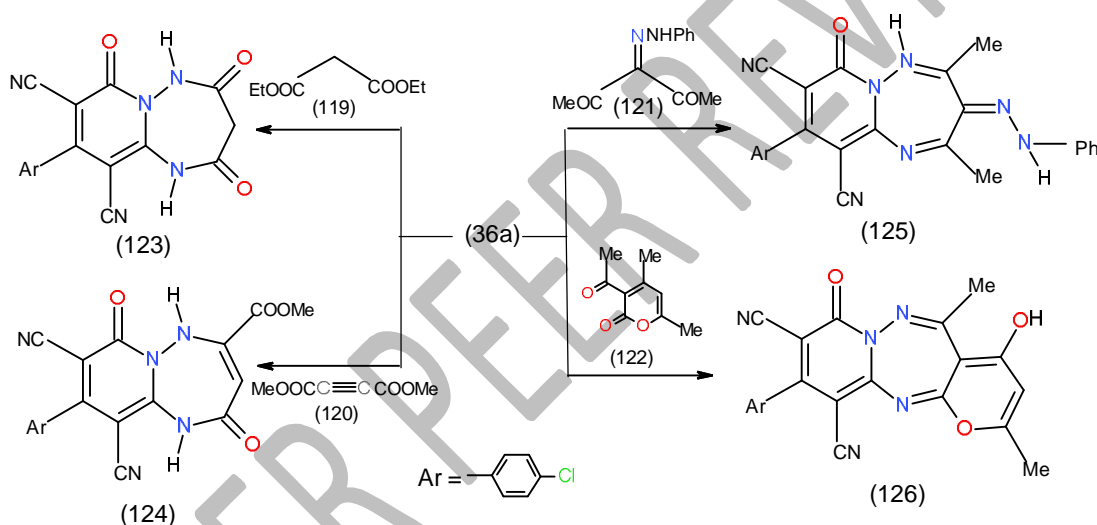
Moreover, the formation of pyrazolopyridine in addition to pyridazinotriazine in one molecular frame was carried out by alkylation of compound **18** with ethyl chloroacetate to afford S- and N- alkylated product **116**. Treatment of **116** with hydrazine hydrate produced pyridazino1,2,4-triazinone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



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

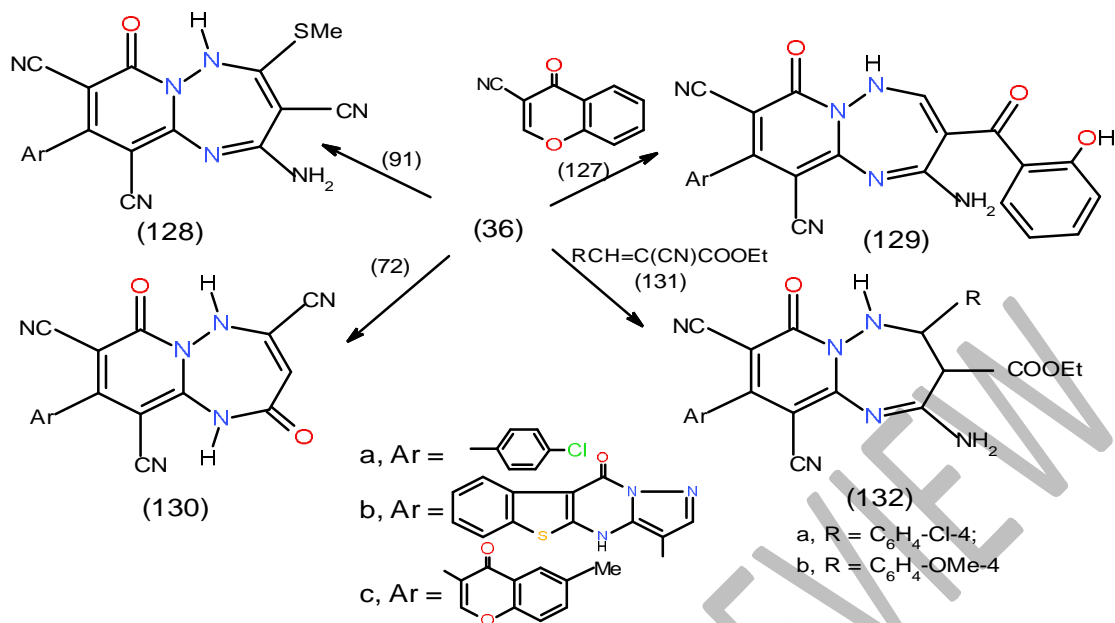
1.5. Formation of pyrido1,2,4- triazepines

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 is designed to utilize of 1,6-diamino-4-aryl-2-oxopyridine-3,5-dicarbonitrile **36a** 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).



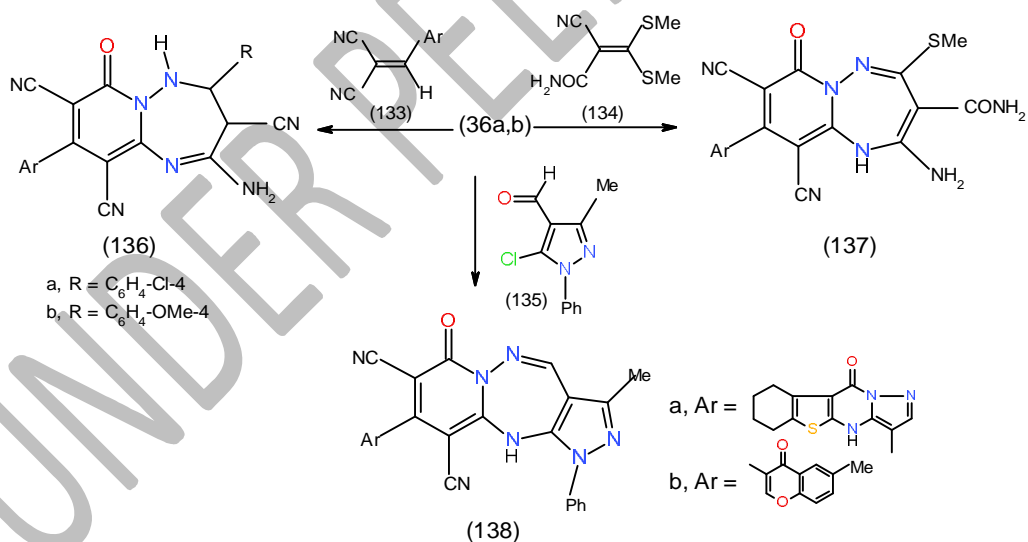
Scheme 25: Formation of pyridotriazepine derivatives

Moreover, the action of 2-cyano-3,3-bis(methylthio)acrylonitrile (**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 pyrido1,2,4-triazepine-tricarbonitriles **130** while, the reaction of **36b, c** with arylidene cyanoacetate (**131**) produced aminopyrido1,2,4-triazepinedicarbonitriles **132a, b**, respectively [14-31] (Scheme 26).



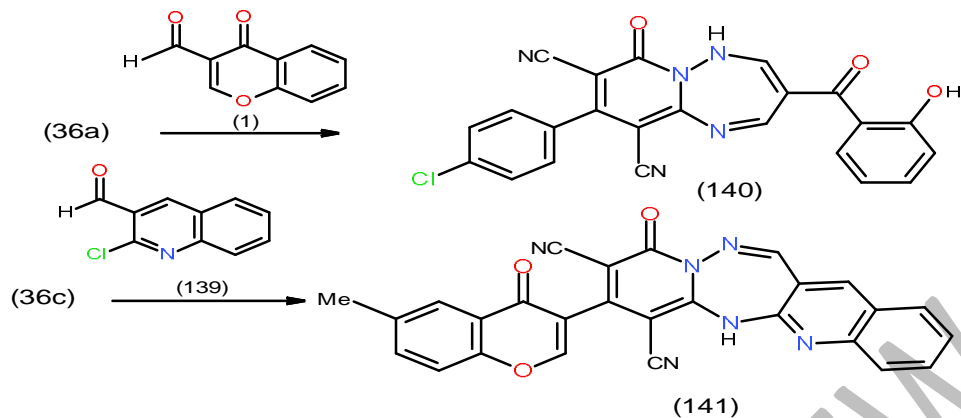
Scheme 26: Formation of substituted pyridotriazepine

Furthermore, cyclocondensation of **36b, c** with arylidenedmalonitrile (**133**), 2-cyano-3,3-bis(methylthio)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).



Scheme 27: Formation of substituted and condensed pyridotriazepines

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



Scheme 28: Formation of pyridoquinolinotriazepine

Biological importance

1. Antimicrobial activities

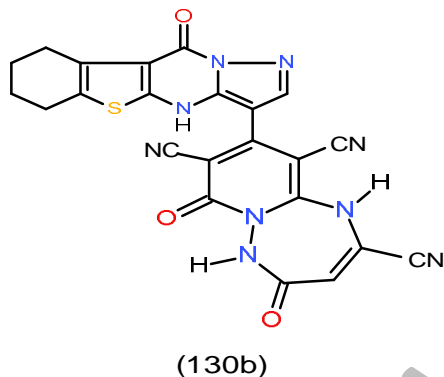
Some synthesized heterocyclic compounds were tested their antimicrobial activity against some Gram-positive bacteria such as *Bacillus subtilis*, *Staphylococcus aureus* and *Bacillus cereus* and some Gram-negative bacteria namely, *Escherichia coli*, *Salmonella typhimurium*, *Pseudomonas aeruginosa*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

1.1. Action on Gram-positive bacteria

1.1.1. *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 akey 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-triazepinetricarbonitriles **130b**,

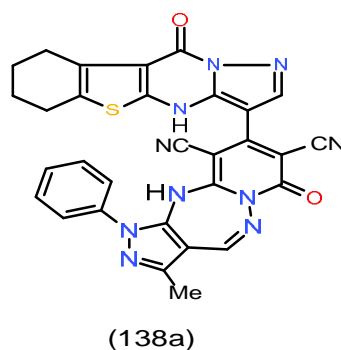
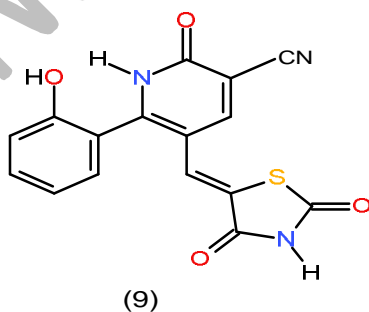
which carrying pyrazolobenzothienopyrimidinyl nucleus [15] exhibited the highest antimicrobial activity against *Bacillus subtilis* compared with the tested compounds in the study. (Bio-1 scheme).



Bio-1 scheme: The highest antimicrobial activity one against *Bacillus subtilis*

1.1.2. *Staphylococcus aureus*

It is a Gram-positive, omnipresent bacterial pathogen that has the ability to adapt and live in various states. *S. aureus* is one of the major causes of spreading of the clinical infection such as bacteraemia and infective endocarditis, osteoarticular, skin and soft tissue, pleuropulmonary, and device-related infections [35]. The results showed that pyrazolopyridotroazepine **138a**, which having pyrazolobenzothienopyrimidinyl moiety exhibited the highest antimicrobial activity against *Staphylococcus aureus* [15]. Also, the pyridine carrying thiazolidione nuclei exhibited higher inhibition effect to *Staphylococcus aureus* as in oxypyridine carbonitrile **227** [30] (Bio-2 scheme).

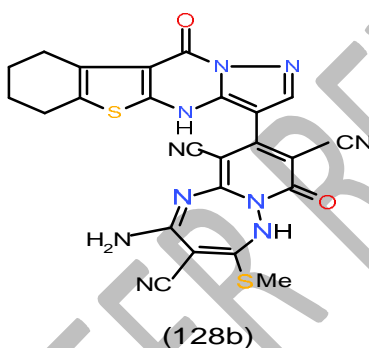


Bio-2 scheme: Compounds could use as antimicrobial agents against *Staphylococcus aureus*

1.2. Action on Gram-negative bacteria

1.2.1. *Escherichia coli*

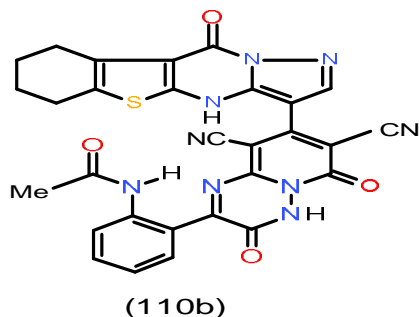
Escherichia coli is a large and various group of bacteria that is found naturally in the intestines of healthy humans and animals. Most types of *Escherichia coli* are harmless or cause relatively brief diarrhea, but some of the *Escherichia coli* can cause a disease for people which can be done by creating a toxin known as Shiga Toxin [36]. It can be seen clearly that pyridotriazepine **128b**, which having pyrazolobenzothienopyrimidinyl moiety exhibited the highest antimicrobial activity against *Escherichia coli* compared with the tested 77 investigated compounds [8]. (Bio-3 scheme).



Bio-3 scheme: The highest antimicrobial activity compound against *Escherichia coli*

1.2.2. *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 pyrazolobenzothienopyrimidinyl moiety exhibited the highest antimicrobial activity against *Salmonella typhimurium* compared with the tested compounds [15] (Bio-4 scheme).

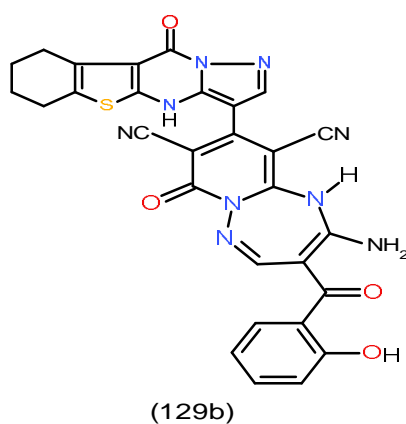
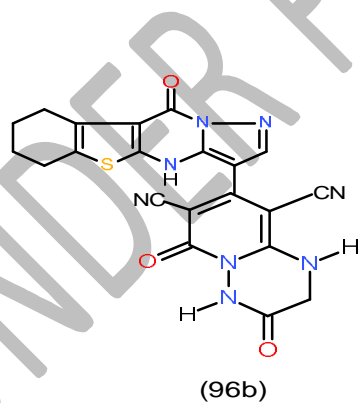


Bio-4 scheme: One of the highest antimicrobial activity against *Salmonella typhimurium*

1.3. Action on Fungi

1.3.1. *Candida albicans*

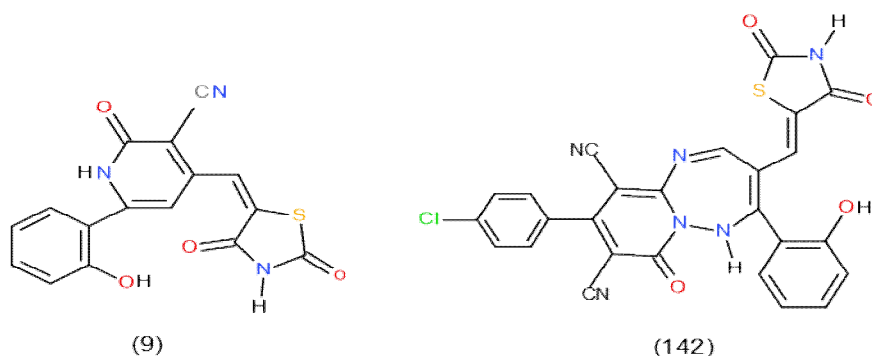
Candida albicans is one of the very few fungal species causing disease in humans—millions of others do not. It is a member of the healthy microbiota, asymptotically colonizing the gastrointestinal (GI) tract, reproductive tract, oral cavity, and skin of most humans [38]. The results showed that pyrido1,2,4-triazinedione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



Bio-5 scheme: Compounds with the highest antimicrobial activity against *Candida albicans*

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

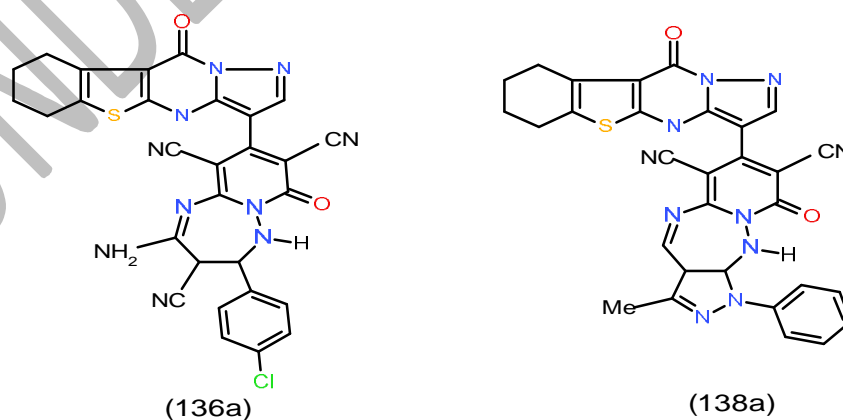
diaminopyridinedicarbonitrile **36a**, may be used as antimicrobial agent against *Candida albicans* from tested compounds [36] (Bio-6 scheme).



Bio-6 scheme: Compounds may be used as antimicrobial agent against *Candida albicans*

1.3.2. *Aspergillus fumigatus*

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, that 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).



Bio-7 scheme: Compounds with the highest antimicrobial activity against *Aspergillus fumigatus*

Conclusion

Pyridine derivatives are very important chemicals with tremendous biological application. In this study effort to optimize the synthetic procedures for the preparation of various bioactive heterocycles. Herein, we explain how active acyclic and cyclic methylene compounds as well as heterocyclic having active methyl or methine sites were used to synthesize wide varieties of pyridines and its fused systems by choosing certain starting materials and different 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.

References

1. Darrin W.Hopper ,Kristina M.K.Kutterer, Aimee L.Crombie and Jeremy J.Clemens ; *progress-in-heterocyclic-chemistry*. **2009**, 20, 289-332.
<https://www.sciencedirect.com/bookseries/progress-in-heterocyclic-chemistry/vol/20>
2. M. Abass, *Heterocycles*,**2005**, 65, 901-965. DOI: 10.3987/REV-04-592
3. Mohamed Abdel-Megid, *J. Synthetic communication*. **2021**, 51(2),191-214. DOI: 10.1080/00397911.2020.1824278.
4. Mohamed Abdel-Megid, *J.Synthetic Communications*, **2020**,50 (23),3563-3591. DOI: 10.1080/00397911.2020.1807570.
5. Mohamed Abdel-Megid, *To Chemistry journal*, **2020**. 7, 74-95.<https://www.purkh.com/to-chemistry-journal.html>
6. Mohamed Abdel-Megid, *J.Synthetic Communication*,**2021**, 51(7), 971-996
DOI: 10.1080/00397911.2020.1865404
7. Magdy A. Ibrahim, M. Abdel-Megid, Naser M. El-Gohary, *J. Braz. Chem, Soc.*, **2011**, 22(6), 1130-1139. DOI:10.1590/S0103-50532011000600019.
8. Kamelia M. El-Mahdy, Azza M. El-Kazak, M. Abdel-Megid, M. Seada, O. Farouk; *J. Advanced in Chemistry*,**2013**, 5(1), 581-591.DOI: [org/10.24297/jac.v5i1.937](https://doi.org/10.24297/jac.v5i1.937)

9. M. Abdel-Megid, M. M. Ismail, *International, J. Chem.*, **2002**, 12(4), 287-296.
<https://www.researchgate.net/publication/272829576>
10. M. Abass, M. Abdel-Megid and M. Hassan; *J. Synthetic communication*, **2007**, 37, 329-352. DOI: doi.org/10.1080/00397910601033930
11. M. Abdel-Megid, M.A. Awas, M. Seada, K. M. El-Mahdy, M. M. El-Sayed; *J. Chemistry & Chemical Engineering, USA.*, **2010**, 4(5), 41-53.
<http://www.davidpublisher.org/Public/uploads/Contribute/55e66bf78f2a6.pdf>
12. M. Abdel-Megid, Y. Gabr, M. A. Awas and N. M. Abdel-Fatah, *Chemistry of Heterocyclic compounds*, **2009**, 45 (11), 1354 -1364. DOI: [org/10.1007/s10593-010-0433-1](https://doi.org/10.1007/s10593-010-0433-1)
13. M. Abdel-Megid, *J. Synthetic communication*, **2007**, 37, 3211-3218.
<https://doi.org/10.1080/00397910701547847>
14. M. Abdel-Megid, M. A. Ibrahim, Y. Gabr, N. M. El-Gohary and E. A. Mohamed; *J. Heterocyclic Chem.*, **2013**, 50, 615. Doi: [org/10.1002/jhet.1608](https://doi.org/10.1002/jhet.1608)
15. M. Abdel-Megid, Azza M. El-kazak, Kamelia M. El-Mahdy, M. Seada, Osama Farouk, *Der Pharma Chemica*, **2017**, 9(20), 86-95.
<https://www.derpharmachemica.com/archive/dpc-volume-9-issue-20-year-2017.html>
16. Kiran P. Sahasrabudhe, M. Angels Estiarte, Darlene tan, Scheilazipfel, Matthew Cox, Donogh J, P, O'Mahony, William T. Edwards and Metthew A. J. Duncton; *J. Heterocyclic Chem.*, **2009**, 46, 1125.
17. M. Seada, M. Abdel-Megid and I.M. El-Deen; *Indian J. Heterocyclic Chem.*, **1993**, 3, 81-86.
18. M. Abdel-Megid, *International J. Chem.*, **2006**, 16(3), 149-157.
<https://www.researchgate.net/publication/272829677>
19. Sahrzad Abdolmohamadi Saeed Blalaie, *International journal of Organic Chem*; **2012**, 2, 7-14 DOI: [10.4236/ijoc.2012.21002](https://doi.org/10.4236/ijoc.2012.21002).

20. K. M. El-Mahdy, A. M. El-Kazak, M. Abdel-Megid, M. Seada and O.Farouk; *Acta Chim Solv.*, **2016**, 63, 18-25. DOI: 10.17344/acsi.2015.1555.
21. M. Abdel-Megid, M. Abass and M. Hassan, *J. Heterocyclic Chem.*, **2007**, 44, 315-322. DOI: org/10.1002/jhet.5570440206.
22. M. Abdel-Megid, *Indian J. Heterocyclic Chemistry*, **1995**, 4 ,269-272.
23. J. Quiroga, B. Insusaty, H. Insusty, R. Absenes, *J. Heterocycl. Chem.*, **2001**, 38,339.
24. M. Seada, M.M. Fawzy, H. Jahine, M. Abdel-Megid, R.R. saad; *J. Chinese Chemical Society*, **1989**, 36, 241-249. DOI: org/10.1002/jccs.198900036.
25. M. Abdel-Megid, *Chem. Heterocycl. Compd.*, **2010**, 3, 405-414.
<https://doi.org/10.1007/s10593-010-0507-0>
26. M. Seada, S.S. Ibrahim, A.M. Abdel-Halim, M. Abdel-Megid; *J. Asian Chem. Soc.* **1992**, 1(1), 19-26.
27. M. Seada, A. M. Abdel-Halim, S. S. Ibrahim, and M. Abdel-Megid; *Asian Journal of Chemistry*, **1992**, 4(3), 544-552.
http://www.asianjournalofchemistry.co.in/User/ViewFreeArticle.aspx?ArticleID=4_3_26
28. James B. Kramer and Howard D. Hollis; **2002**. *Patent application publication* No., US 0061865/ A1.
29. M.seada, R. M. Abdel-Rahman and M. Abdel-Megid, *An, Quim*, **1993**, 89, 16-21.
30. Muylaert Koen, Jatczak Maryna, Mangelinckx Sven and Christain; *Curr. Med. Chem.*, **2016**, 23(42), 4784-4823.
<https://biblio.ugent.be/publication/8509866>
31. M. Abdel-Megid, *J. Chemistry and chemical engineering USA.*, **2010**. 4(2), 32-40.

32. Ahmed El-Mekabaty, M. Monier, Khaled M. Elattar, *Curr. Organic Chem.*, **2018**, 22(5),2419-2443.
33. Rahman A., Choudhary M. I., Thomson W. J., *Bioassay Techniques for drugs Development*, **2001**. Hardwood Academic Publishers, The Netherlands.
34. J. L. Rios, M. C. Recio, R. Villar; Screening methods for natural products with antimicrobial activity A review literature, *J. Ethno pharmacology*, **1988**, 23, 127.
35. Patrick Stragier, *Annu. Rev. Genet.*, **1996**, 30.297-341.
36. Edward J. Bottone, *Clin Microbiol., Rev.*, **2010**, 23, 282-398.
37. Tenailon O, Skurnik D, Picard B, Denamur E. *Nature Reviews. Microbiology*. **2010**, 8(3): 207–217.
38. Mays HadiJabur, Elham Abbas AL- Saedi and Jawad Kadhum Trad, *J. Pure and Applied Sciences*, **2013**, 1 (21),43-56.
39. Clarissa J. Nobile and Alexander D. Johnson, *Annual Review of Microbiology*, **2015**, 69, 71-92.