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Design, Synthesis, Chemistry and Biological Evaluation of Some Polyfunctional Heterocyclic Nitrogen Systems—Overview

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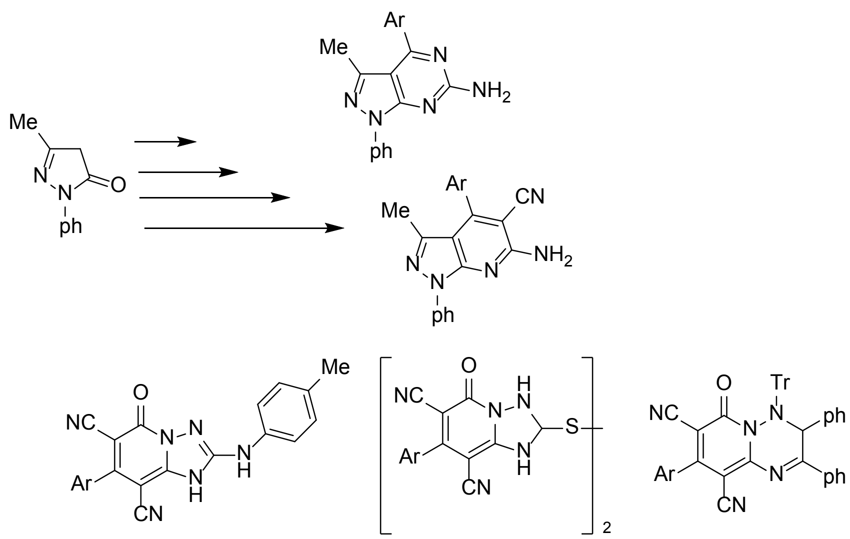
Abstract

The synthesis, preparation, chemical reactivities and biological activity of simple heterocyclic and heteropolycyclic nitrogen systems as small units as functional pyrazoles, pyridine and pyrimidine, and the related fused systems are reviewed. Among the various possible routes to the formation, isomeric structures have been cited because of patented reaching advanced phases of clinical trials, from 2000 to 2020.

Graph Abstract



Some compounds evaluated as antimicrobial agents

Keywords

Pyrazolo[3,4-b]pyridine, Simple Heterocyclic Nitrogen, Biological Properties, Edaravone Drug, Synthetic Strategies

1. Introduction

Recently, heterocyclic nitrogen systems containing polyfunctional groups have developed into the most active and promising research areas of chemical science. Presence of polyfunctional organizations internal the structure of heterocyclic nitrogen systems, increase of net electronegativities over all the amenities of the compounds which adorn and enhance their physical, chemical and biochemical residences as dielectric content, distribution probes and/or the hydrophobic action [1].

The World Health Organization titled a recent study on the synthesis, chemical reactivity and biological activities of Polyfunctional Heterocyclic Nitrogen Systems [2] [3] [4] [5] [6].

One of the important targets is to use as antibiotics, drugs, and bioactive systems, polyfunctional pyrazoles, pyridine, and then fused/condensed polyheterocyclic nitrogen systems [7] [8] [9] [10].

2. Synthesis and Chemical Reactivities of a Polyfunctional Pyrazole [Edaravone Drug] as Base Unties

Edaravone drug and their analogs synthesized from the fusion of arylhydrazine with ethyl acetoacetate (**Scheme 1**) [11] [12].

Edaravone (**1**) for example exhibits two functional groups, active methylene, ketonic and/or enolic as tautomeric start [13] [14] (**Figure 1**)

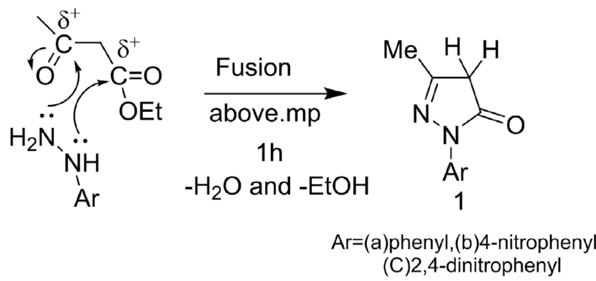
Abdel-Rahman *et al.* [15] reported the synthesis of condensed heteropolycyclic nitrogen systems derived from the Edaravone drug (**Scheme 2**).

Fluoroacylation and/or fluorobenzoylation of Edaravone **1** an afforded 4-trifluoroacetyl-4,5-dihydro-3-methyl-1-phenylpyrazol-5-one (**2**) and/or 4-(4'-fluorobenzoyl)-hydro-3-methyl-1-phenylpyrazol-5-one (**3**) respectively. Ring closure reaction of both **2** and **3** with thiourea afforded the pyrazolopyrimidine-6-thiones **4** and **5** respectively (**Scheme 2**) [15].

A simple nucleophilic attack of -SH groups of **4** and **5** with primary aliphatic amine as ethanolamine in refluxing EtOH, produced the corresponds N-substituted ethanol amines **6** and **7**, which upon dehydration by refluxing with Ac_2O yielded 7,8-tetrahydro-[4,3:6,5]imidazolines **8** and **9** respectively (**Scheme 3**) [15].

Also, the interaction between compounds **4** and **5** with primary aromatic amines in refluxing DMF afforded N-aryl-N-pyrazolopyrimidine amines **10** and **11** respectively (**Scheme 4**), while when using piperazine as the secondary amine in boiling EtOH, produced N, N-di hetero arylpiperazines **12** and **13** respectively (**Scheme 5**) [4].

All the compounds obtained evaluated as antifungal agents, where the activity



Scheme 1. Synthesis of edaravone drug and their analogies.

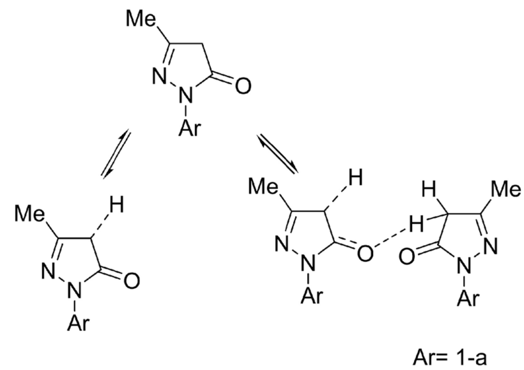
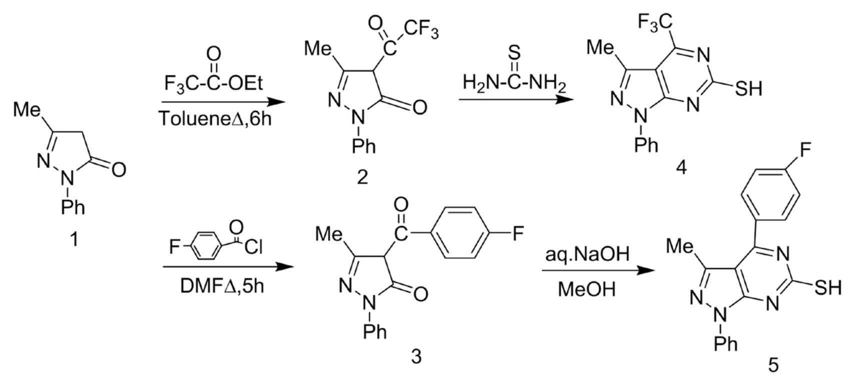
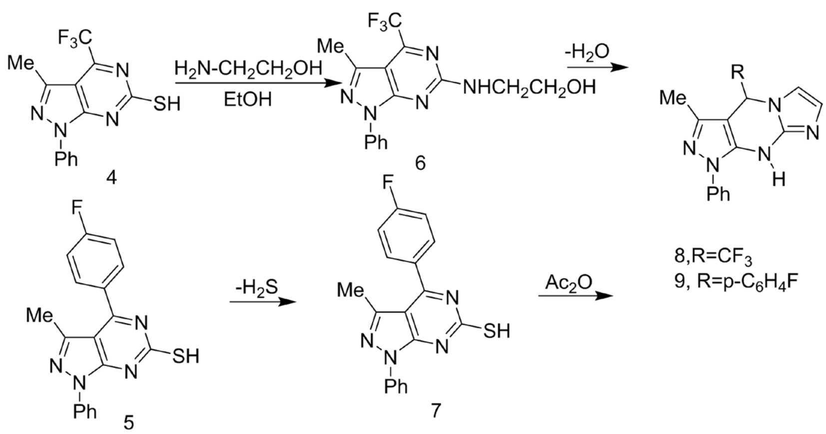


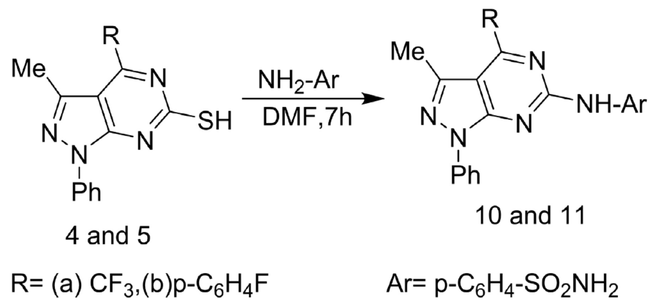
Figure 1. Formation of edaravone **1** as two isomers.



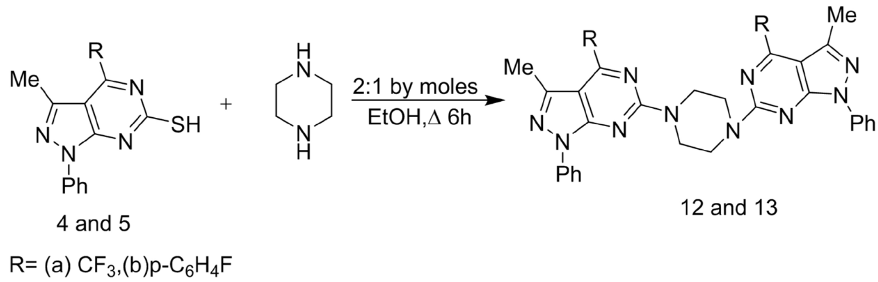
Scheme 2. Fluoroacylation and fluorobenzoylation of edaravone **1**.



Scheme 3. Synthesis of imidazolines **8** - **9**.



Scheme 4. Formation of compounds **10** - **11** from **4** - **5**.



Scheme 5. Formation of **12** - **13** from **4** - **5**.

in the order **12** > **10a** > **10b** > **4** > **6** > **8**. Only compound **12** exhibits a highly affect a cellobiose activity produced by *Aspergillus Nodulins* Fungi at 1000 and 100 μg/ml as biodynamic agent [15].

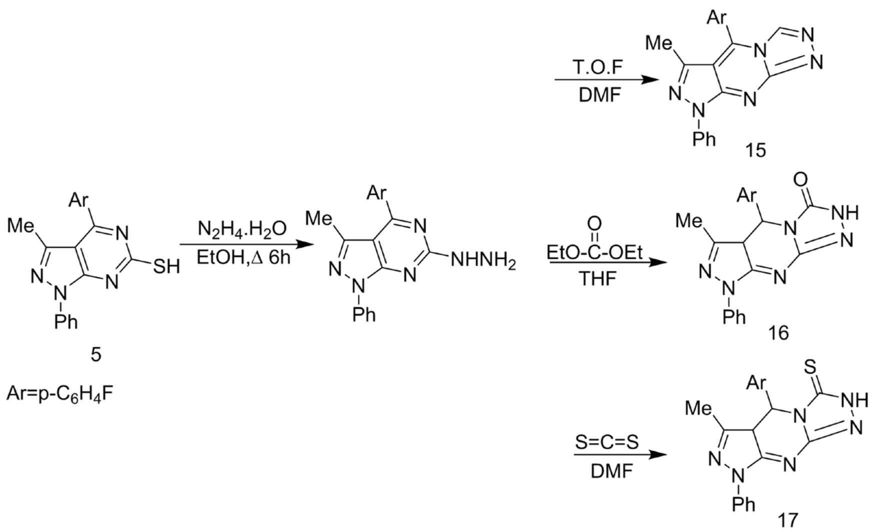
The hydrazino-groups when bonded to heterocyclic nitrogen systems, improve that possible activity to formation various heteropolycyclic systems characterized with biological, pharmacological and medicinal properties [16] [17] [18]. Thus, hydrazinolysis of compound **5** by refluxing with hydrazine hydrate in EtOH, yielded the corresponding hydrazine derivative **14** [19]. Ring closure reactions of compound **14** by refluxing with T.O.F (DMF); diethyl carbonate (THF) and/or carbon disulfide (DMF), produced the 1,2,4-triazolo pyrimido pyrazole derivatives **15** - **17** (**Scheme 6**) [20].

Fused heteropolycyclic nitrogen systems **19** and **20** obtained from refluxing compound **5** with benzoic acid hydrazide (DMF) and/or isonicotinic acid hydrazide (EtOH) (**Scheme 7**) [20].

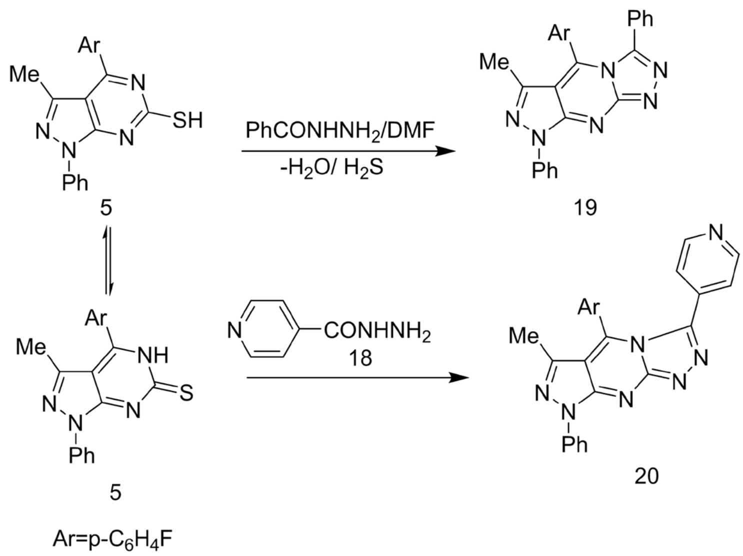
On the other hand, the interaction between compound **5** with dithioic formic acid hydrazide in refluxing DMF led to the direct formation of compound **17** (**Scheme 8**) [20].

It is known that hydrazo and azo aromatic compounds exhibit an important in dust rate ant attention due to its application in the industrial chemistry and agriculture fields [21] [22]. Thus, the interaction between compound **5** and **14** (1:1 by moles) in refluxing isopropyl alcohol, the hydrazo-compound **21**, which upon simple oxidation by warming with sulfur-in dry C_6H_6, yielded the azo-compound **22** (**Scheme 9**) [20].

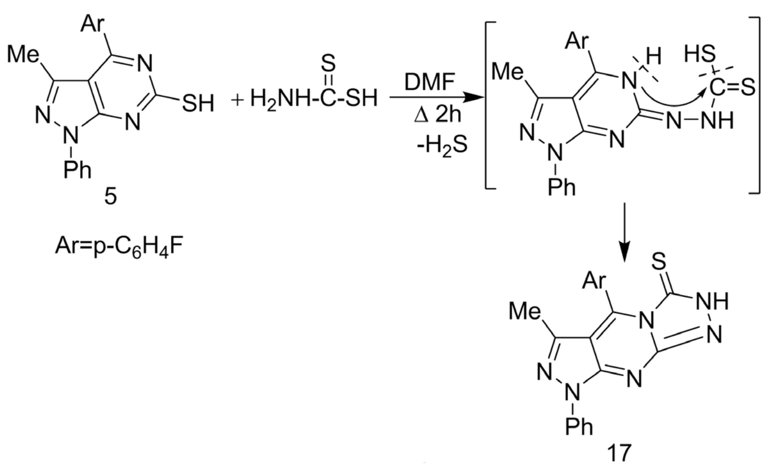
All the obtained compounds, evaluated as enzymatic affects the cellobiose activity of *Aspergillus Nodulins* fungi, were the activity increases in the order of



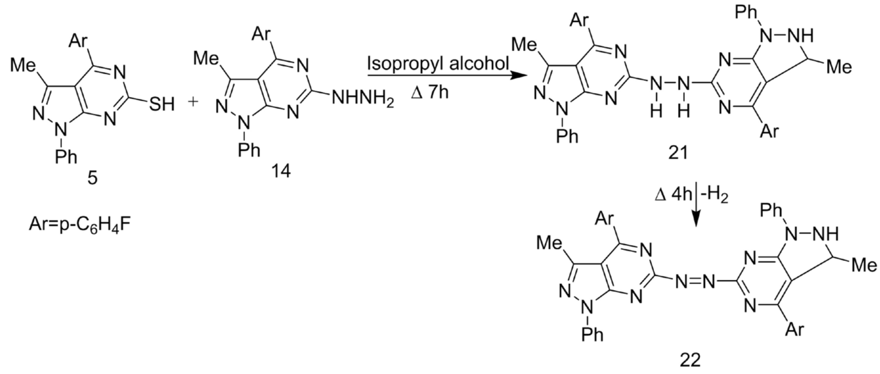
Scheme 6. Formation of 1,2,4-triazolo pyrimido pyrazole derivatives **15** - **17**.



Scheme 7. Formation of compounds **19** - **20** from **5**.



Scheme 8. Formation of compound **17** from **5**.



Scheme 9. Formation of azo-compound **22**.

22 > **21** > **14** > **16** > **19** and a highly bioactive are compounds **22** and **21** Respectively [20].

Polyfunctional nitrogen compounds substituted guanidine **25**, obtained from the condensation of Edaravone **1** with an aromatic aldehyde in warming with EtOH/piperidine produced the 5-arylidine derivative **23** which upon cycloaddition with guanidine.

HCl in refluxing EtOH-piperidine, yielded 6-amino-4-(4'-fluorophenyl)-1-phenyl-3-methyl pyrazolo [3,4-d] pyrimidine (**24**). The addition of cyanamide to **24** in refluxing ethanol-piperidine, yielded the compound **25** (Scheme 10) [23].

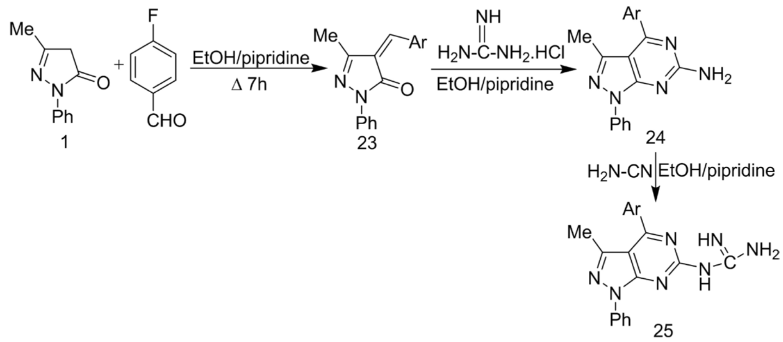
The course of orientation cyclization reactions, is very important to obtain a type of isomeric structure [24]. Thus, refluxing compound **25** with 4-nitrobenzoyl isothiocyanate in non-polar solvent (dioxane) gave 1-heteroaryl-2-imino-6-aryl-1,3,5-triazin-6(5H) thione (**26**), while that reaction when carried in polar solvent (EtOH/pipridine) produced1-heteroaryl-2-imino-4-aryl-1,3,5-triazin-6(5H)thione (**27**) respectively (Scheme 11) [23].

It is an interest that interaction between compound **25** as polynuclophilic agents with π-e acceptors bearing a carbon triple group as unsaturated carbonitriles (**A**) and/or (**B**) in polar solvent as EtOH/piperidine as catalyst led to the direct formation of polyfunctional hetero polycyclic systems **28** and **29** respectively (Scheme 12) [23].

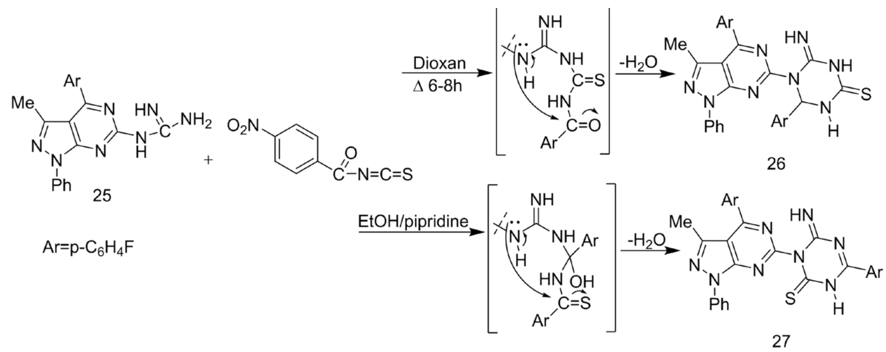
Also, cycloaddition reaction of compound **25** with 1-phenyl-3-methyl-4-arylidene-pyrazol-5-one (**23**) in refluxing EtOH-piperidine afforded the diheteroarylamine derivative **30** (Scheme 13) [23].

Recently, reported that [25]-[30], the introduction of fluorine atoms to heterocyclic nitrogen systems often improves then physical, chemical and biological properties [25]-[30]. Thus, cyclo condensation of compound **25** with fluorinated acetylacetone in refluxing EtOH, afforded N-(heteroaryl-2-imino-4,6-di(trifluoromethyl) pyrimidine (**31**) (Scheme 14 & Scheme 15) [23].

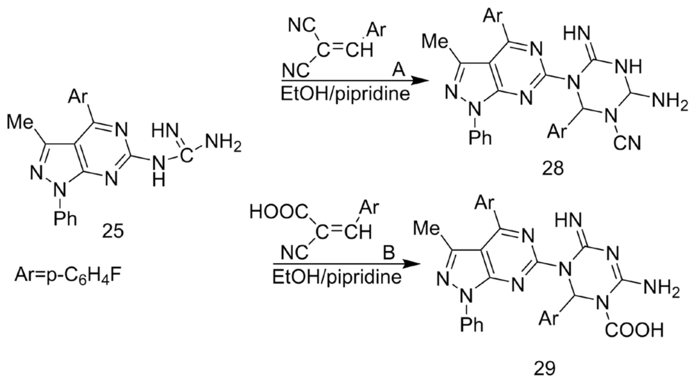
Some full fused heteropolycyclic nitrogen systems bearing various functional groups **32** - **39** were obtained from the interaction between 6-amino-4-(4'-fluorophenyl)-1-phenyl-3-methyl pyrazolo [3,4-d]pyrimidine (**24**) 23, with *α*, *β*-bifunctional reagents via a ring closure reaction (heterocization systems) [31].



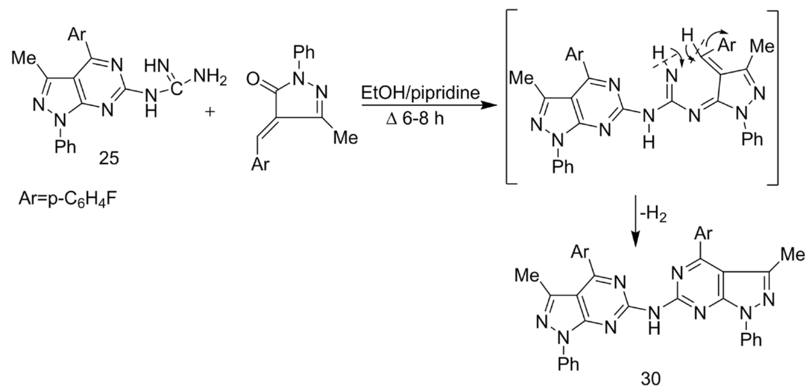
Scheme 10. Synthesis of pyrazolo[3,4-d]pyrimidine **25**.



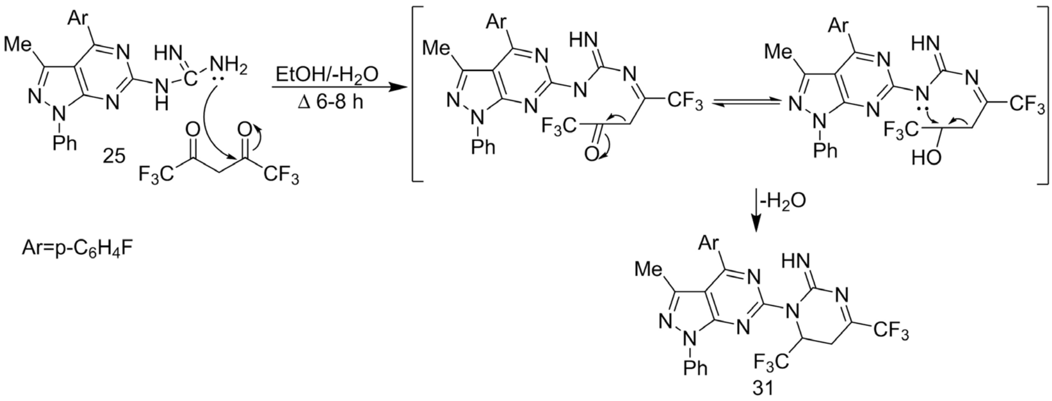
Scheme 11. Synthesis of 1,3,5-triazin 6(5H)thione derivatives **26** - **27**.



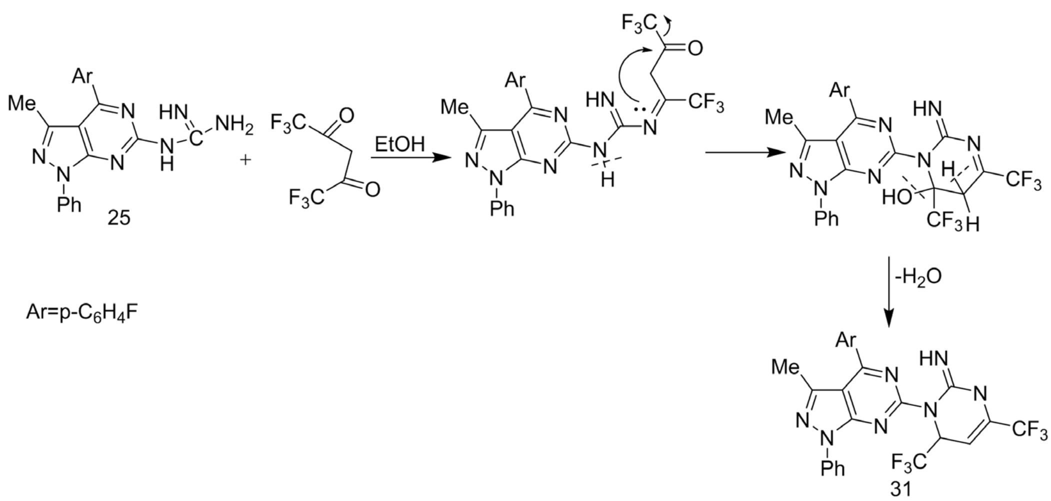
Scheme 12. Formation of **28** - **29** from **25**.



Scheme 13. Synthesis of dihetero aryl amine derivative **30**.



Scheme 14. Formation **31** from **25**.



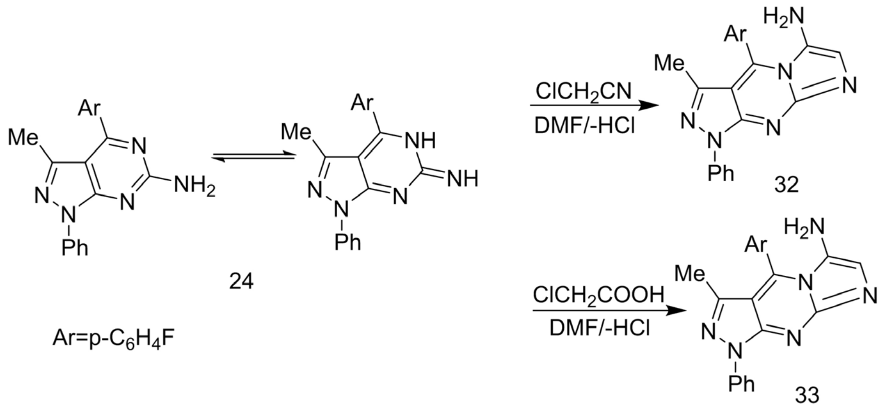
Scheme 15. Formation of **31** from **25**.

Thus, refluxing of compound **24** with chloroacetonitrile and/or monochloroacetic acid in boiling DMF for 4 h, yielded the imidazo [3,2-a]pyrimido [4,3-d]pyrazoles **32** and **33** respectively (Scheme 16) [31].

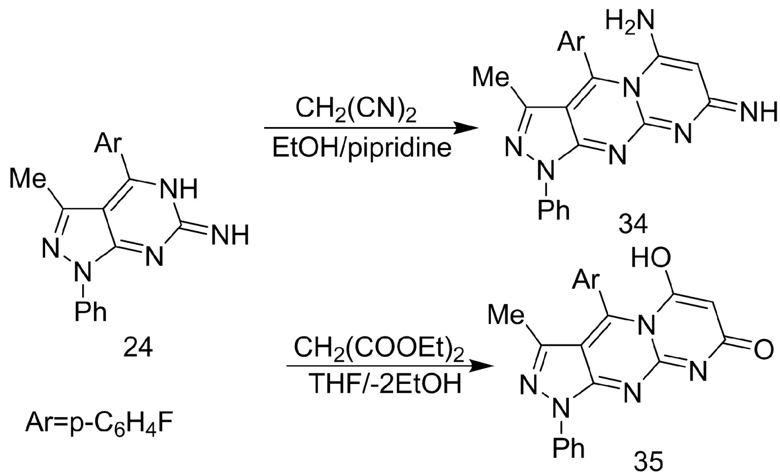
The interaction between compound **24** and the active methylene reagents as malononitrile (EtOH/piperidine) and/or diethyl malonate (THF) under refluxing Δ/6h, resulted in pyrimido [3,1-a]pyrimido [5,4-d]pyrazole (**34** and **35**) respectively (Scheme 17) [31].

The behaviour of compounds **32** and **35** as nucleophilic agents towards Pph_3 as electrophilic agents also evaluated in boiling CH_3CN, led to the direct formation of triphenylphosphine derivatives imino **36** and **37** respectively (Scheme 18) [31]. Formation of compound **36** as shown in Figure 2.

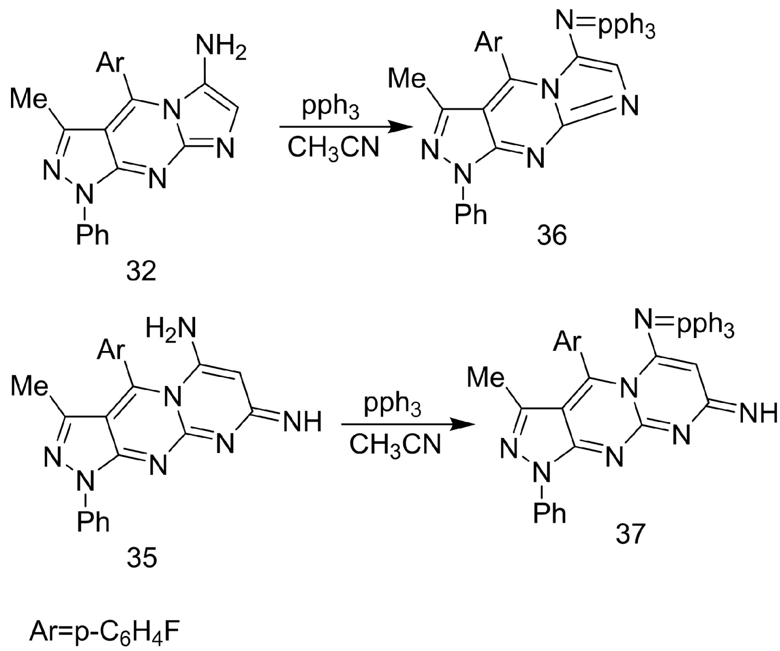
On other hand, refluxing compound **24** with 4-nitrobenzoyl isothiocyanate in non-polar solvent (dioxane or THF) and/or in polar solvent (EtOH/piperidine) also, afforded 2-aryl-4-thioxo-6-(4'-fluorophenyl)-7-methyl-9-phenyl-1,3,5-triazino [5,4-a]pyrimido[5,4-d]pyrazole (**38**) and/or 2-thioxo-4-(aryl)-6-(4'-flourophenyl-7-methyl-9-phenyl-1,3,5-triazino[5,4-a]pyrimido[5,4-d]pyrazole (**39**) respectively (Scheme 19) [31].



Scheme 16. Synthesis of imidazo[3,2-a]pyrimido[4,3-d]pyrazoles **32** - **33**.



Scheme 17. Formation of **34** - **35** from **24**.



Scheme 18. Treatment of **35** and **32** with pph_3 and CH_3CN.

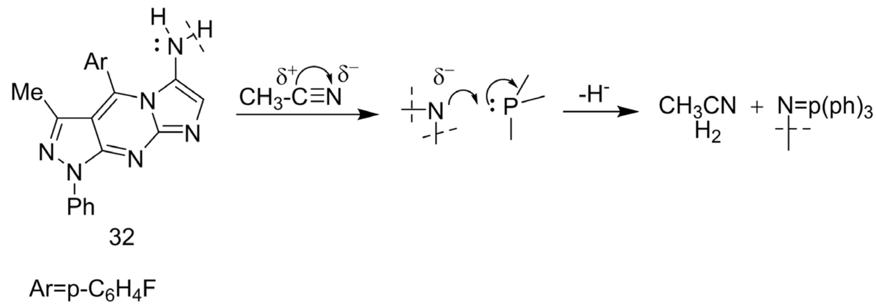
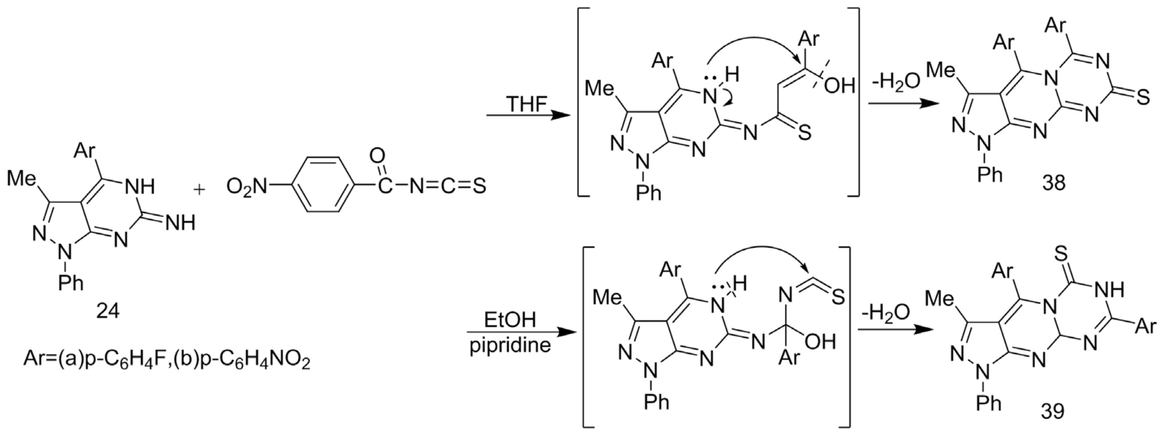


Figure 2. Formation of phosphinimino **36**.



Scheme 19. Formation of **38** - **39** from **24**.

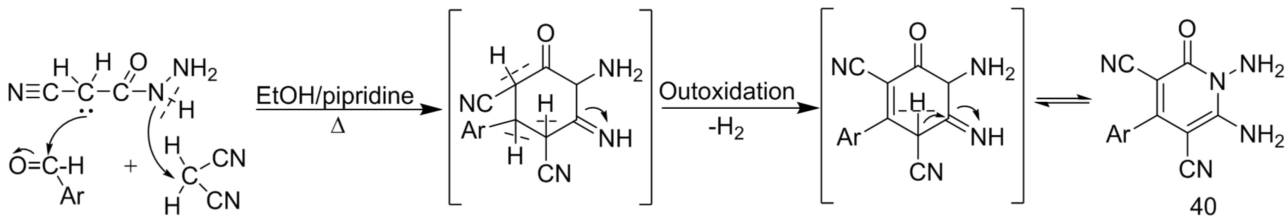
3. Synthesis and Chemical Reactivities of a Polyfunctional Pyridine Systems (1,6-Diamino-2-oxo-4-(aryl)-1,2-dihydropyridine-3,5-dicarbonitrile)

A general method to obtain 4-aryl-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **40** includes the interaction between cyanoacetic acid hydrazide, malononitrile and aromatic aldehyde in refluxing absolute EtOH with drops of piperidine (Scheme 20) [32].

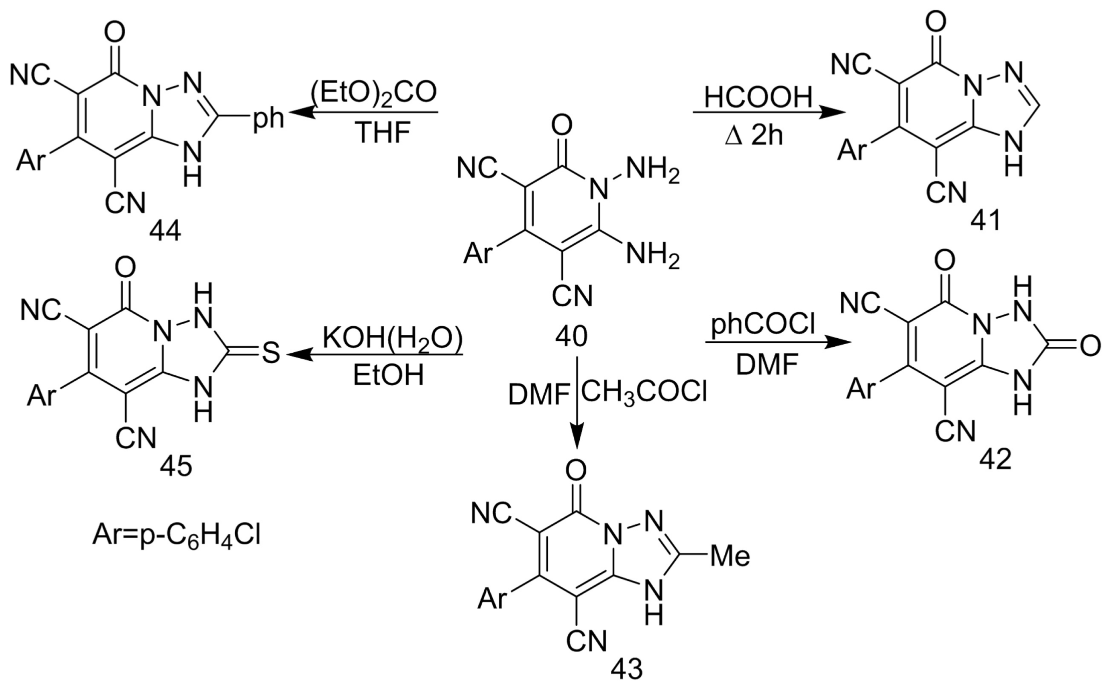
Abdel-Monem [33] reported the synthesis of fused heterobicyclic nitrogen systems as 1,2,4-triazolopyridinone **41** - **50** derived from compounds $\mathbf{40}_a$ and $\mathbf{40}_b$ with α, β-bifluorodional oxygen and halo-oxo compounds in different media (Scheme 21 & Scheme 22). Also, fused pyrido-1,2,4-triazine **53** - **60** have been obtained from treatment of 3-mercapto-5,6-diphenyl-1,2,4-triazine **51** with compound **40** to give the substituted aminopyridinone **52** (Scheme 21 & Scheme 22) [33].

It is the interest that, compound **52** on alkylated and/or cyclocendened with an alkyl halide (Base) and/or hydroxy/halo ketones afforded the pyrido-1,2,4-triazine derivatives **53** - **60** (Scheme 23 & Scheme 24) [33].

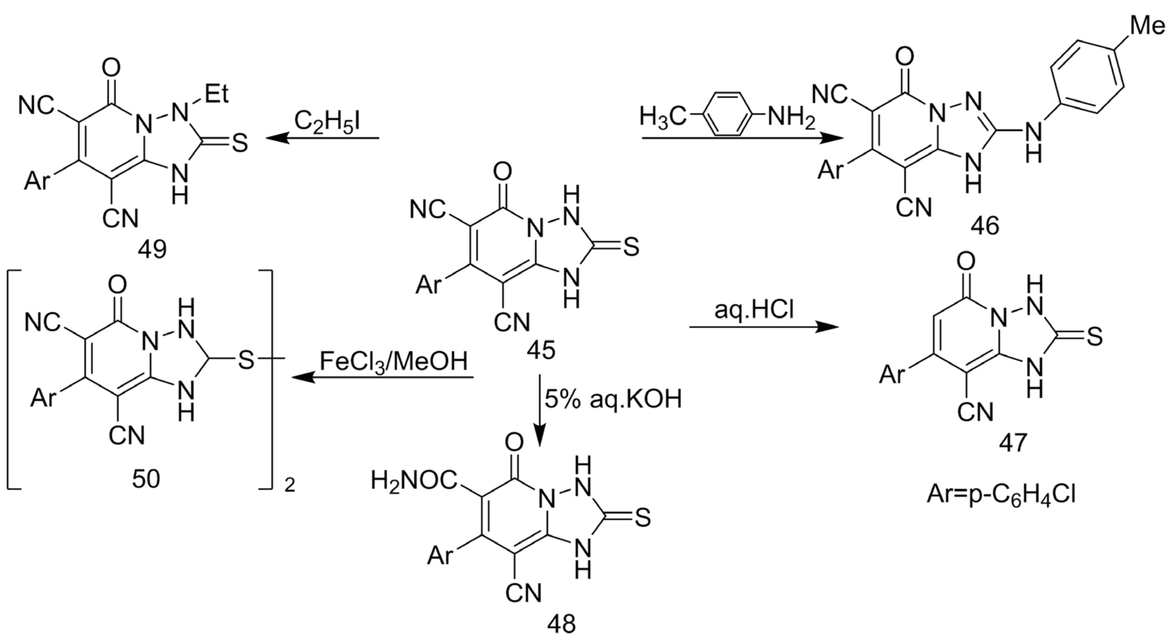
All the obtained compounds evaluated as antimicrobial agents (some Bacteria and fungi); were the compounds exhibit good to moderate activities in the order of **54**, **47**, **45** as bactericidal and the compounds **46**, **50**, **58** exhibit a fungicidal activity [33].



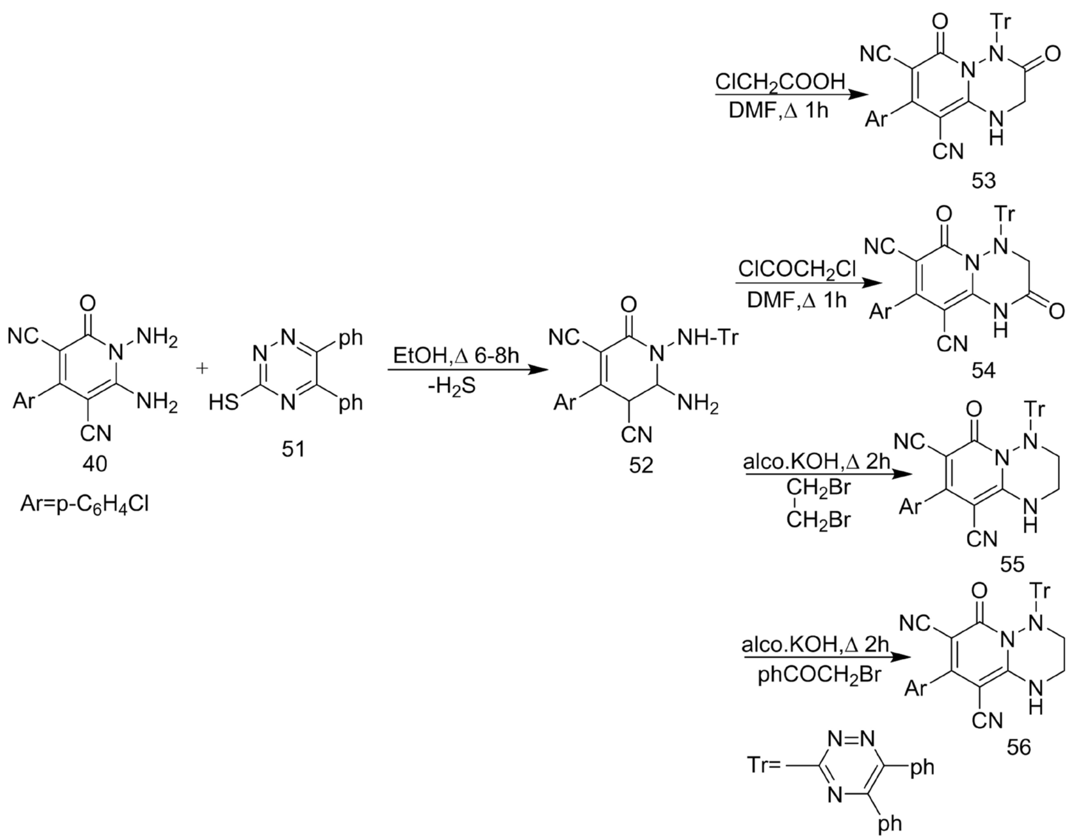
Scheme 20. Formation of pyridine derivative **40**.



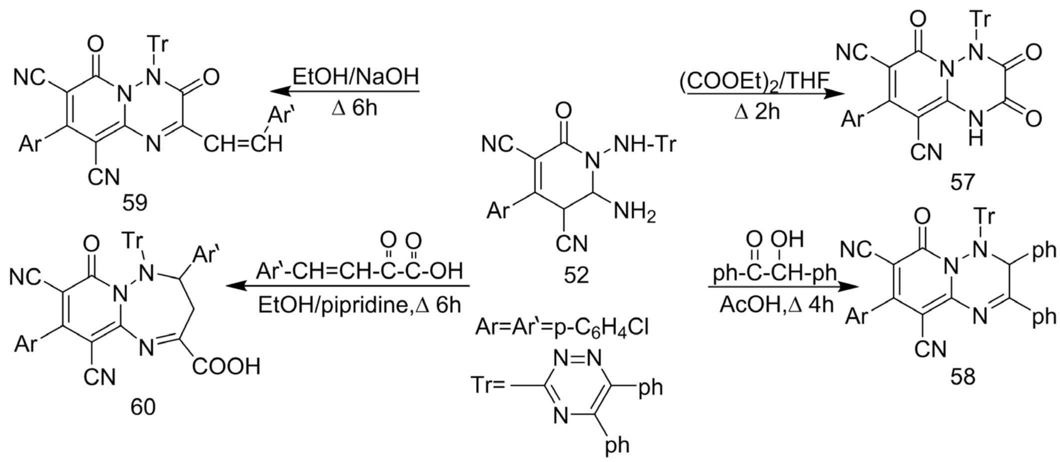
Scheme 21. Formation of 1,2,4-triazolopyridinone **41** - **45**.



Scheme 22. Formation of **46** - **50** from **45**.

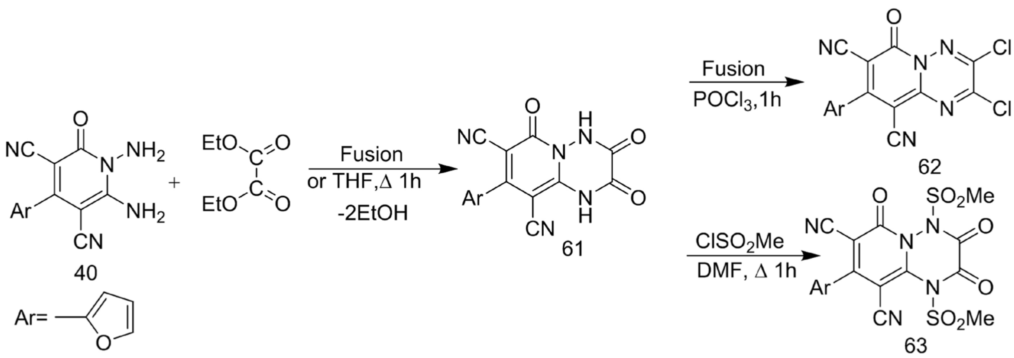


Scheme 23. Formation of **53** - **56** from **40** and **51**.

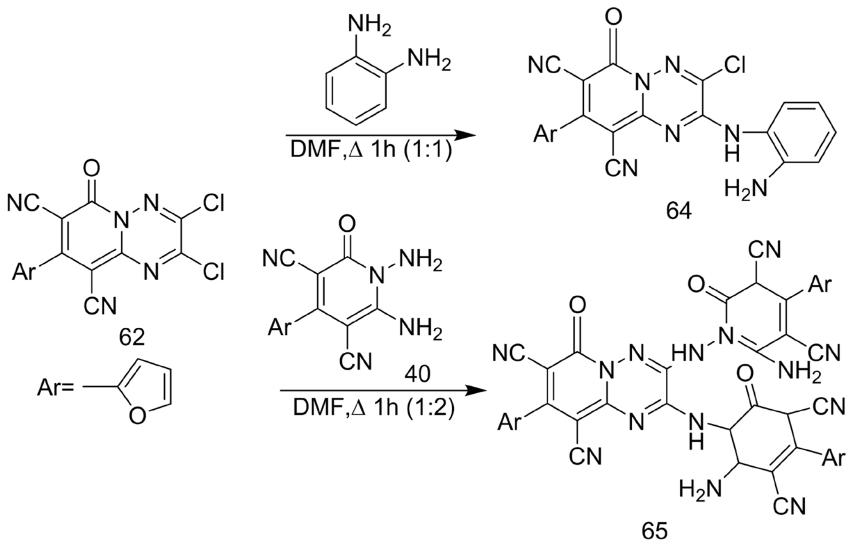


Scheme 24. Formation of **57** - **60** from **40**.

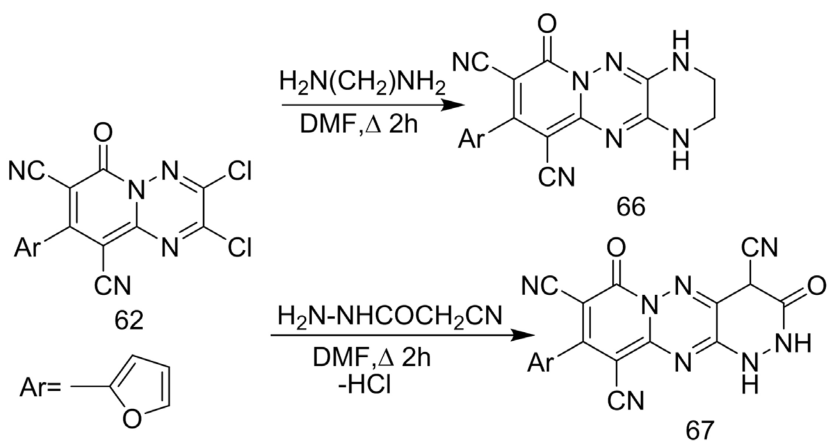
Simitary [34] [35] [36], polyfunctional pyrido-1,2,4-triazine derivatives **61** - **65** and the related fused polyheterocyclic systems **66** and **67** were isolated from the interaction between compound **40** (Ar: -furyl) and *α*, *β*-bifunctional reagents in the differing media (Schemes 25-27). All the obtained compounds showed antimicrobial activity (bacteria & fungi) in comparison with chloramphenicol and terbinafine antibiotics as control [34]. The compounds **64** & **66** are highly active towards staphylococcus, while compounds **66** & **68** against *Bacillus* S.



Scheme 25. Formation of **62** - **63** from **40**.



Scheme 26. Formation of **64** - **65** from **62**.



Scheme 27. Formation of **66** - **67** from **62**.

Most of the compounds **61** - **68** showed towards activity *Staphylococcus*, *Bacillus S.L pseudomonas*, and only the compounds **66** towards *Escherich co*.

On the other hand, the compound, **68** showed a high activity towards Candida albicans fungi. Also, the compounds **61** & **66** exhibit activity towards Aspergillus

F.; **62, 63 & 68** towards penicillium ita; **61 - 68** towards candida alb.

Diamines are very important and safe, active simple substrates for producing of various heterocyclic nitrogen systems [37] [38]. Also, 4-aryl-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles uses for the building of high biologically active nitrogen bridgehead triazole [1,5-a]pyridines [39]; pyrido [1,2-b] [1,2,4]triazines [40] [41] and/or pyrido [1,2-b] [1,2,4]triazepines [42] [43]. Based on, these observations-Kazak *et al.* [44] obtained 4-(4'-methoxyphenyl)-1,6-diamino-2-oxo-1,2-dihydropyridine (**68**) from refluxing ethyl cyanoacetate, arylaldehyde, malononitrile; hydrazine hydrate in EtOH with a few drops of pipe-rdine (**Scheme 28**) [44], and uses to obtaining various fused polyheterocyclic nitrogen systems **69** - **73** as antimicrobial agents (**Schemes 28-30**) [44]. All the compounds obtained evaluated as antimicrobial agents, were the highly active compounds in the order **73** > **72** towards *Bacillus bacterial S.L* towards *candida a.* (fungi strain) [44].

The formation of compound **67** may be as shown in **Figure 3**.

Diamines are very important and safe, active simple substrates for producing of various hetero cyclic nitrogen systems [37] [38]. Also, 4-aryl-1,6-diamino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles uses for the building of high biologically active nitrogen bridgehead triazolo [1,5-a] pyridines [39]. Pyrido [1,2-b] [1,2,4]triazines [40] [41] and/orpyrido [1,2b] [1,2,4]triazepines [42] [43].

Based on, these observations, El-Kazak *et al.* 44 prepared 4-(4'-methoxyphenyl)-1,6-diamino-2-oxo-1,2-dihydropyridine (**68**) from refluxing ethyl cyanoacetate, aryl aldehyde, malononitrile, hydrazine hydrate in EtOH with a few drops of piperidine (**Scheme 28**) [44], and uses to obtaining various fused polyheterocyclic nitrogen systems **69** - **73** as antimicrobial agents (**Schemes 28-30**) [44].

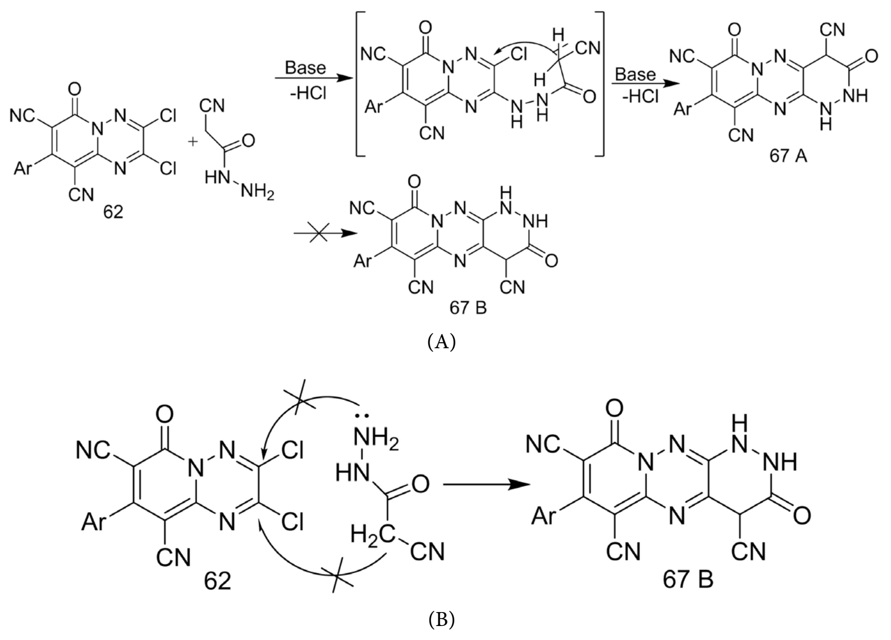
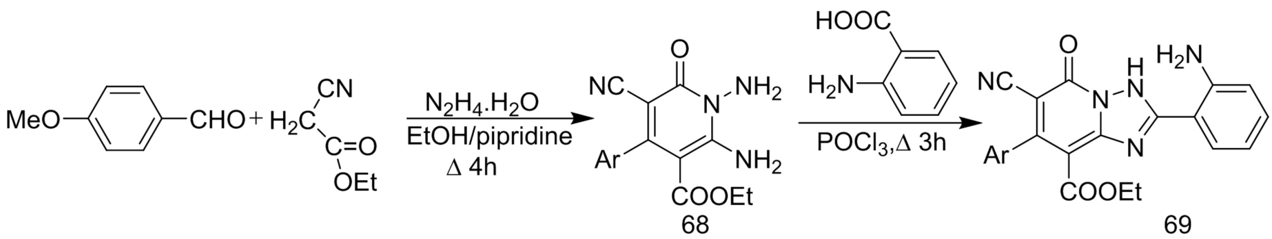
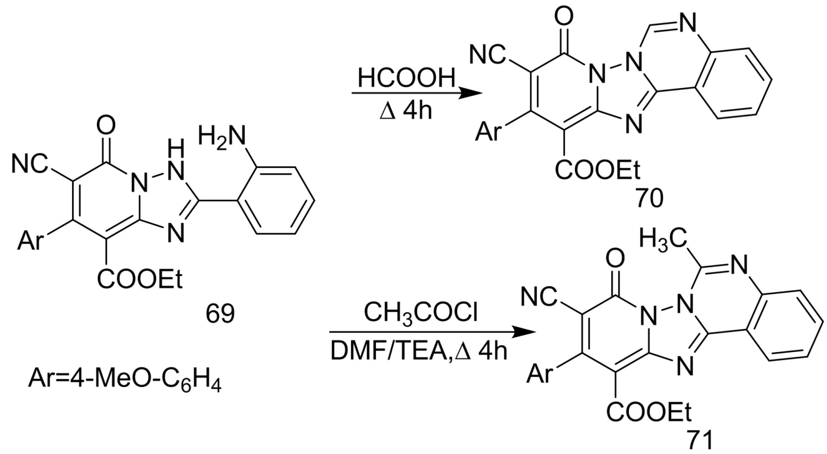


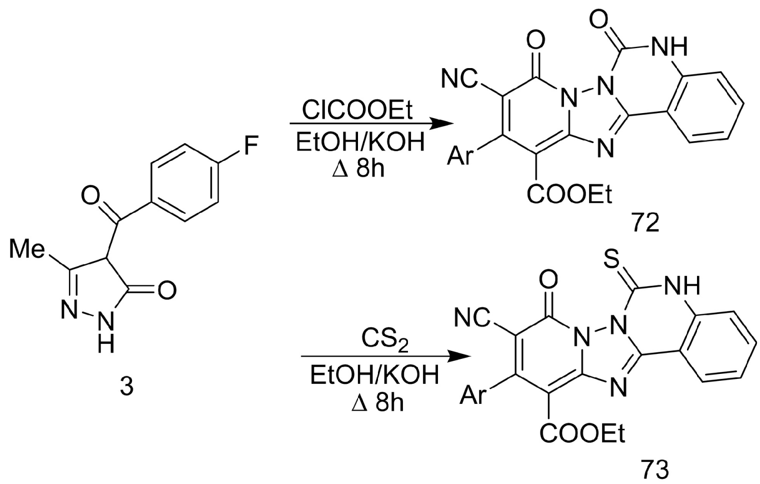
Figure 3. (A) Formation of compound **67A** from **62**; (B) Anot possible formation of compound **67B** from **62**.



Scheme 28. Formation of **69** from 4-methoxybenzaldehyde.



Scheme 29. Formation of **70** - **71** from **69**.



Scheme 30. Formation of **72** - **73** from **3**.

All the compounds obtained evaluated as antimicrobial agents, were the highly active compounds in the order **73** > **72** towards *Bacillus s.* and towards *Candida a.* (fungi strain) [44].

4. Synthesis and Chemical Reactivities of Polyfunctional Pyrazolo-Pyridine Derivatives

Various pyrazolo[3,4-d]pyridine derivatives **76** - **80** have been obtained from the reaction of 3-hydrazino-5,6-diphenyl-1,2,4-triazine (**74**) 46 with ethoxy methylene malononitrile in refluxing EtOH to give 5-amino-1-(5,6-diphenyl-1,2,4-triazine-3-yl)-1H-pyrazole-4-carbonitrile (**75**) which used as starting materials to obtain the targets **76 - 80** (**Schemes 31-33**) [45].

5. Important and Applications

Fused heterocyclic nitrogen systems especially which containing a pyrazole moiety are well known for their wide range of biological, pharmacological and medicinal significance properties [46] [47] [48] [49] [50]. Also, pyrazolo [3,4-b]pyridines have been exhibited the diverse biological and pharmacological fields such as antitubercular, antibacterial, anti-inflammatory, antipyretic, anti-leishmanial and protein Kinase Potential inhibitors agents [51]-[60].

Some pyrazolo[3,4-b]pyridines have been obtained and evaluated for an anti-chagasic activity to establish a structure-activity relationship [61].

A few publications deal with the preparation of pyrazolo [3,4-b]pyridines containing a polyfunctional group [62].

In continuation of the work done on the synthesis and chemistry of pyrazolo [3,4-b]pyridines [63], Maqbool *et al.* 64 prepared a series of ethyl-3-methyl-1-phenyl-6-aryl-1H-pyrazolo[3,4-b]pyridine-4-carboxylates (**82**) by the reaction of 5-amino-3-methyl-1-phenyl-1H-pyrazole (**81**) [64] with various aromatic aldehydes and ethyl pyruvate in warming acetic acid (**Scheme 34**) [65].

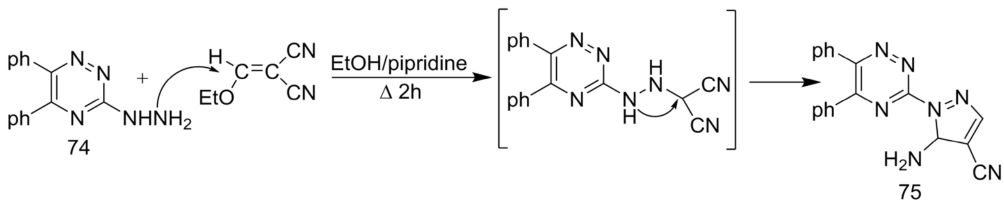
One of the important studies of synthesis, chemistry and biological evaluation of polyfunctional pyrazolo[3,4-b]pyridine-carbonitrile was deduced by El-Assiery *et al.* [66], was the compound 1-phenyl-3-methyl-4-aryl-6-amino pyrazolo [3,4-b] pyridine-5-carbonitriles (**83**) obtained from the cycloaddition of both Edaravone **1**, aromatic aldehydes; malononitrile and ammonium acetate by fusion with a few drops of piperidine within a long time (15 h) (**Scheme 35**) [66].

Also, the chemistry of compound **83** was studied by treatment with polyfunctional reagents, because of their biological evaluation (**Scheme 36** and **Scheme 37**) [66].

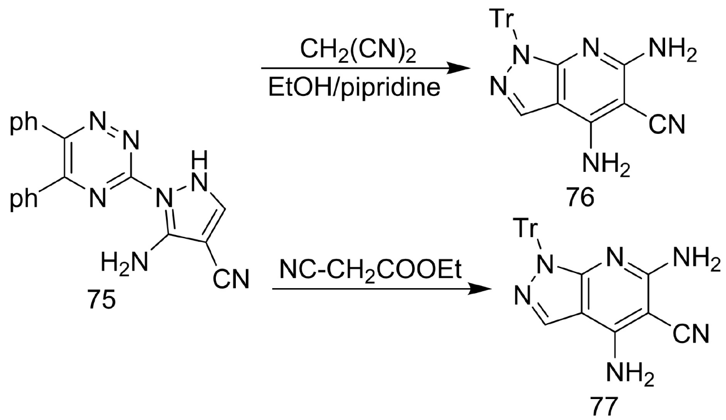
6. Attitudes of the Next New Work

Based upon these observations, the next work tends to synthesize some more new fused heteropolycyclic nitrogen systems containing polyfunctional groups because of their biocidal effects.

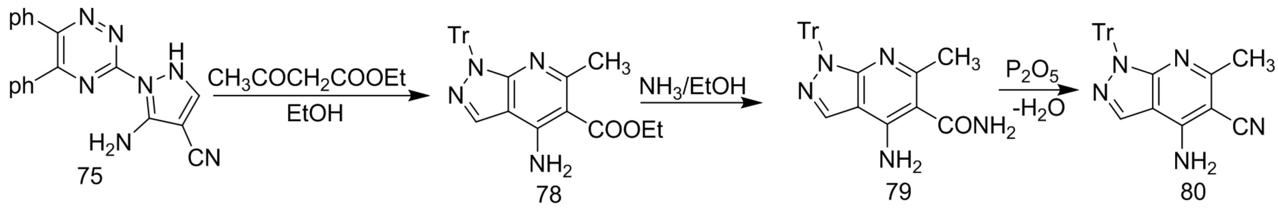
materials to obtain the targets **76-80** (Scheme 31-33)



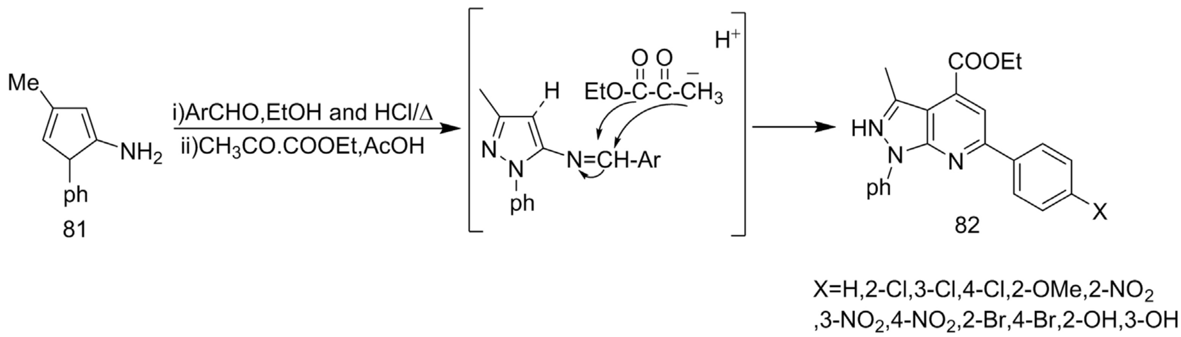
Scheme 31. Reaction of 3-hydrazinotriazine **74** with ethoxymethylene malononitrile.



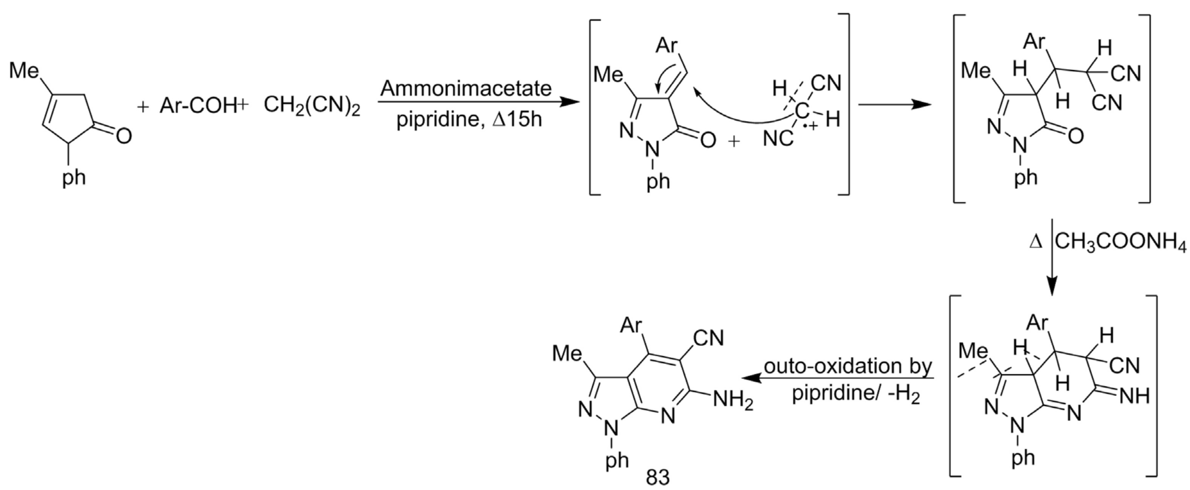
Scheme 32. Formation of **76** - **77** from **75**.



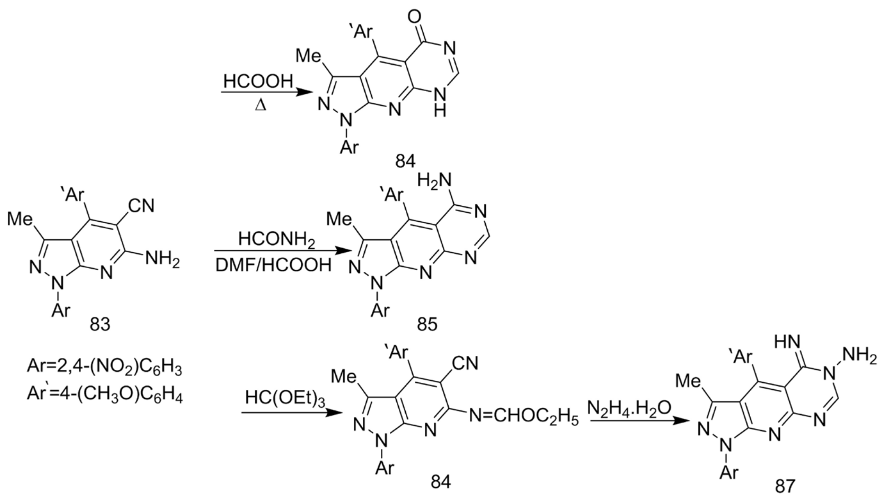
Scheme 33. Synthesis of compound **80**.



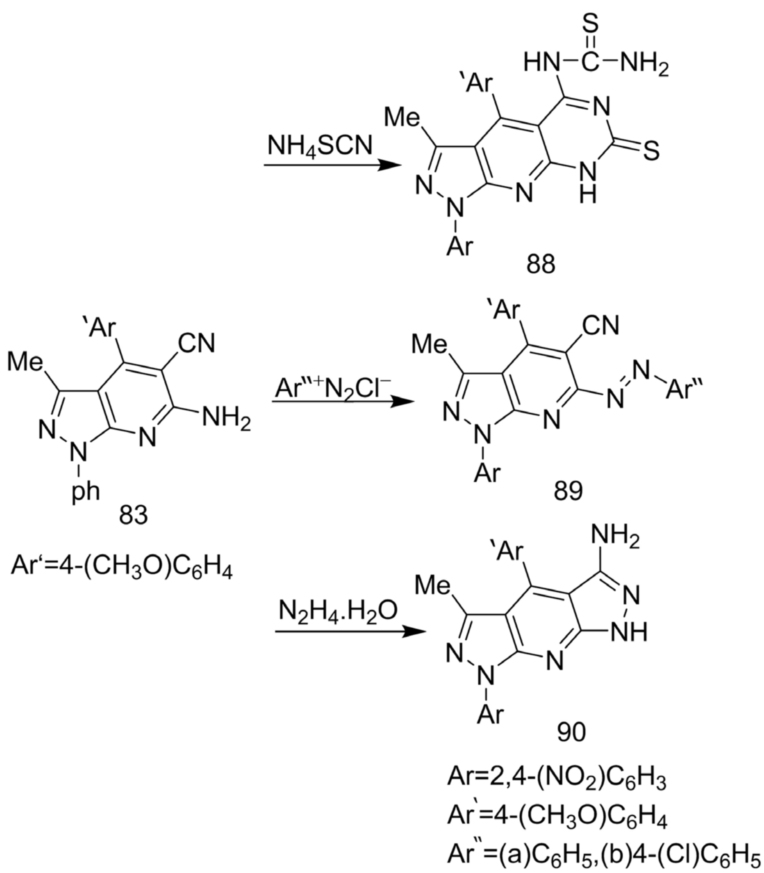
Scheme 34. Synthesis of pyrazolo[3,4-b]pyridine-4-carboxalate **82**.



Scheme 35. Formation of **83** from edaravone **1**.



Scheme 36. Treatment of **83** with polyfunctional reagents.



Scheme 37. Formation of **88** - **90** from **83**.

7. Conclusions

Poly functional heterocyclic nitrogen systems as pyrazole, pyridine, and pyrimidine systems play a vital role in our life due to their biological, pharmacological, and medicinal properties [67] [68] [69] [70].

Based upon these important observations, this overview combines and reports the important attempts to obtain novel small units of heterocyclic systems in view of their biological evaluation which benefits the chemists and scientific researches in the future, from 2000 to 2020 AD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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