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A Review on The Chemistry of Nicotinonitriles and Their applications

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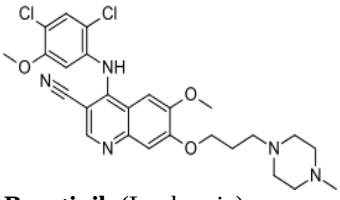
Abstract

Several studies on nicotinonitrile and their derivatives because of their wide range of therapeutic activities have been reported. Many drugs containing nicotinonitrile derivatives are available in market such as *Bosutinib*, *Milrinone*, *Neratinib*, and *Olprinone*. This review article highlights the recently synthesized nicotinonitrile possessing important biological, therapeutic, and medicinal properties.

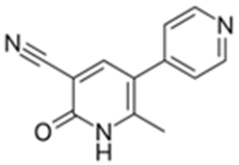
Keyword: Nicotinonitrile, Biological activities, Therapeutic activities, Medicinal properties.

INTRODUCTION

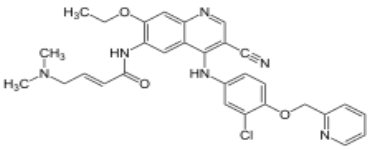
The pyridine ring system is one of the most popular N-heteroaromatics incorporated into the structure of wide range of biologically active compounds. Also it is present in many natural products such as nicotinic acid, nicotinamide, vitamin B6, which play key roles in metabolism. Cyanopyridines (nicotinonitriles) have biological, therapeutic, and medicinal properties such as, antimicrobial [1,2], cardiotonic [3], antioxidant [4,5], anti-inflammatory [6], anti-alzheimer [7], anticonvulsant [8], anti-parkinsonism [9], antitubulin agents [10], antiproliferative [11,12], antiprotozoal agent [13], protein kinases inhibitor [14], active-site inhibitors of sphingosine 1-phosphate lyase [15], non-nucleoside adenosine kinase inhibitor [16], dipeptidyl peptidase IV inhibitor (NVP-DPP-IV) and dipeptidyl peptidase 728 inhibitor (NVP-DPP 728) [17], epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor [18], rearranged during transfection (RET) tyrosine kinase inhibitor [19], check point kinase 1 (CHK1) inhibitor [20], farnesyltransferase inhibitor [21], sodium–calcium exchanger inhibitor [22], glutamate receptor subtype 5 [23], janus kinases (JAKS) inhibitor [24], acetylcholine receptor [25], a2a adenosine receptor antagonists [26], TRPV1 antagonists [27], as androgen receptor antagonists [28]. On the other hand, some nicotinonitrile derivatives are used as electrical materials [29] and optical materials [30]. This review gives an overview of the chemistry and applications of nicotinonitriles. **Scheme 1** shows some of the drugs that contain nicotinonitrile moiety. It is not feasible to discuss the chemistry and applications of all these types in this report, since each type needs and deserves a separate treatment.



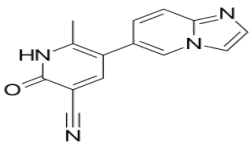
Bosutinib (Leukemia)



Milrinone (Cardiotonic)



Neratinib (Breast cancer)



Olprinone (Cardiotonic)

Scheme 1: Some drugs containing nicotinonitrile moiety

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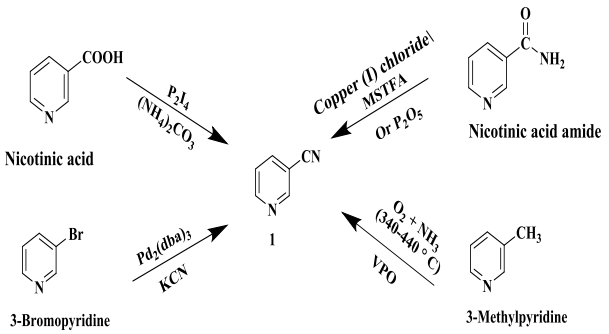
1. Synthetic approaches of 3-cyanopyridine scaffolds

3-Cyanopyridine nucleus **1** can be prepared in a yield of 88% by the reaction of nicotinic acid with diphosphorus tetraiodide / ammonium carbonate. [31] Also, elimination of water from nicotinic acid amide was carried out using copper (I) chloride and the silylating agent MSTFA (N-methyl-N-(trimethylsilyl) trifluoroacetamide) or by means of phosphorus pentoxide to achieve 3-cyanopyridine in 84 % yield. 32-34] Better yield (93%) of 3-nicotinonitrile was obtained by the reaction of 3-bromopyridine with KCN in the presence of organopalladium compound $Pd_2(dba)_3$ [tri (dibenzylideneacetone) dipalladium] at 80 ° C. [35] On industrial scale, 3-methylpyridine or 3-picoline undergoes ammoxidation in the presence of vanadium phosphorous oxide (VPO) as a catalyst to produce 3-cyanopyridine. [36] **(Scheme 2)**



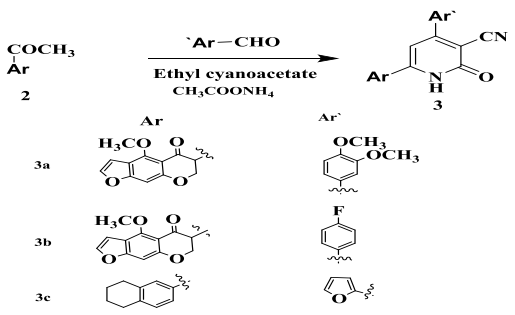
Scheme 2. Different procedures for synthesis of 3-nicotinonitrile scaffolds

2. Synthesis of some 3-cyanopyridine derivatives

2.1. Synthesis of 2-oxo-3-cyanopyridine derivatives

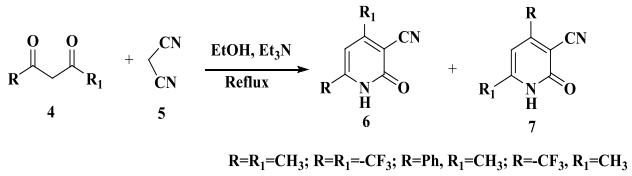
2.1.1. Starting with various substituted ketones

Synthesis of 4-substituted phenyl-6-(3,4-dimethoxyphenyl)-3-cyano-2(1*H*)-pyridinones **3** was carried out through one-pot multi-component reaction of 3,4-dimethoxy-acetophenone (**2**), different aromatic aldehydes, ethyl cyanoacetate, and ammonium acetate in refluxing ethanol in the presence of K_2CO_3 [37a,b] **(Scheme 3)**.



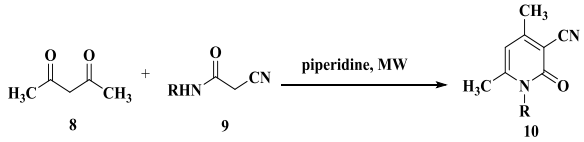
Scheme 3. Synthesis of phenyl-6-(3,4-dimethoxyphenyl)-3-cyano-2(1*H*)-pyridinone derivatives

dicarbonyl derivatives **4**, malononitrile **5** in ethanol containing triethylamine as a catalyst afforded 3-cyano-2-oxopyridine derivatives **6** and **7** [38] **(Scheme 4)**.



Scheme 4. Synthesis of 3-cyano-2-oxopyridine derivatives

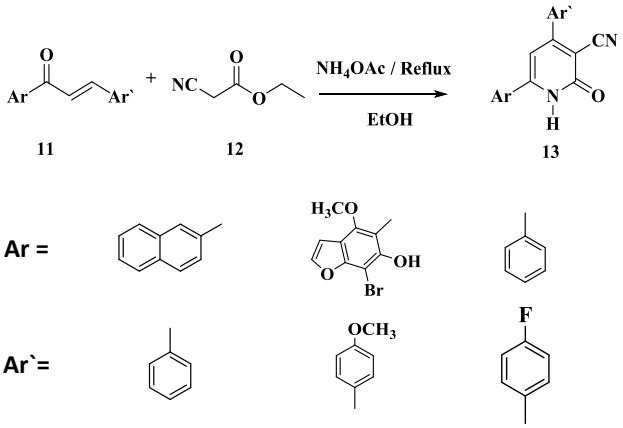
On the other hand, Dušan *et al.*, showed that *N*-substituted 4,6-dimethyl-3-cyano-2-pyridones **10** were obtained by the reaction of acetyl-acetone **(8)** and the corresponding *N*-substituted cyanoacetamide **9** under microwave conditions in the presence of piperidine as a catalyst [39] **(Scheme 5)**.



Scheme 5. Synthesis of 4,6-dimethyl-3-cyano-2-pyridones

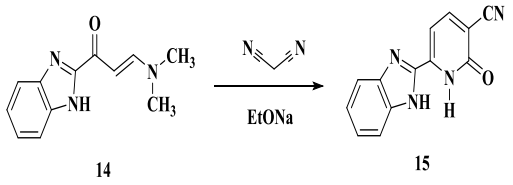
2.1.3. Starting with different chalcones

4,6-Disubstituted-3-cyano-2-pyridones **13** could be obtained by condensation of ethyl cyanoacetate **12** with various substituted α,β-unsaturated ketones **11** in the presence of excess ammonium acetate [40a-c] **(Scheme 6).**



Scheme 6. Synthesis of 4,6-disubstituted-3-cyano-2-pyridones.

6-Substituted-3-cyano-2-pyridones **15** was taken place by the reaction of malononitrile with 1-(1*H*-benzo[d]imidazol-2-yl)-3-(dimethylamino)prop-2-en-1-one **14** in the presence of sodium ethoxide [41] **(Scheme 7)**.

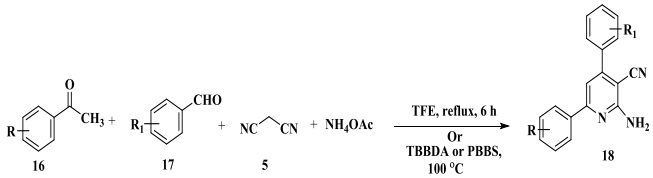


Scheme 7. Synthesis of 6-Substituted-3-cyano-2-pyridones.

2.2. Synthesis of 2-amino-3-cyanopyridine derivatives

2.2.1. Starting with various substituted ketones

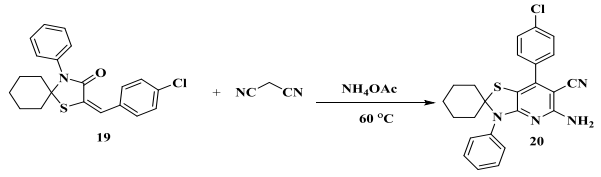
It has been reported that condensation of the four-components synthetic protocol; different substituted acetophenones **16**, different substituted benzaldehydes **17**, malononitrile 5, and ammonium acetate in refluxing trifluoroethanol (TFE) for 6 h afforded the corresponding 2-aminocyanopyridine derivatives **18** [42]. Furthermore, heating a mixture of an aldehyde, substituted acetophenone, malononitrile, ammonium acetate and TBBDA (tetra-bromobenzene-1, 3-disulfonamide) or PBBS (poly(N-bromo-N-ethylbenzene-1,3-disulfonamide)) under stirring at 100 ◦C for appropriate times led to the formation of 2-aminocyanopyridine derivatives **18** [43] **(Scheme 8).**



Scheme 8. Synthesis of 2-amino-3-cyanopyridine derivatives

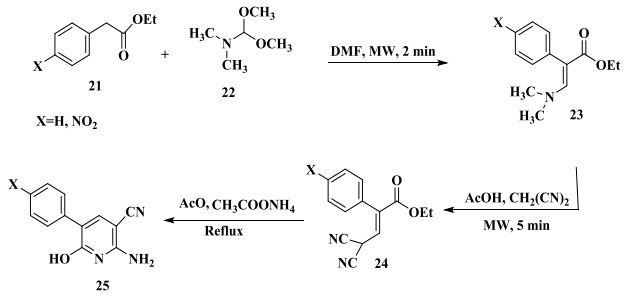
2.2.2. Starting with various substituted chalcones

Reaction of chalcones 19 with malononitrile and ammonium acetate at 60 oC gave corresponding thiazolo[4,5-b]pyridine-6-carbonitrile derivative **20** [44] (Scheme 9).



Scheme 9. Synthesis of substituted 2-amino-3-cyanopyridines

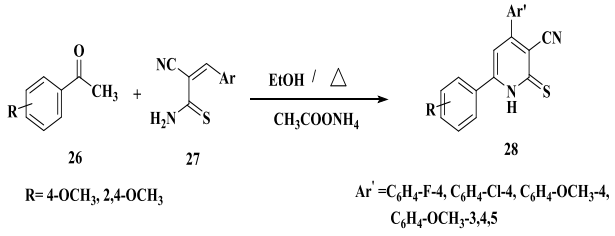
It has been documented that irradiation of a mixture of ethyl phenyl (nitrophenyl) acetate **21** and N,N-dimethylformamide-dimethyl acetal (DMF-DMA) **22** in DMF under microwave conditions for 2 min gave the corresponding enaminoesters **23**, which were allowed to react with malononitrile in acetic acid under microwave conditions for 5 min to afford the dicyanoethyl ester derivatives **24**. Refluxing of compounds **24** with acetic acid and CH_3COONH_4 yielded the corresponding 6-hydroxy-2-amino-3-cyanopyridine derivatives **25** [33] **(Scheme 10)**.



Scheme 10. Synthesis of substituted 6-hydroxy-2-aminocyanopyridines

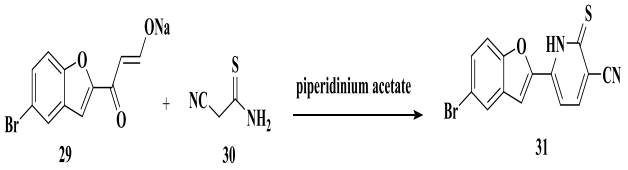
2.3. Synthesis of 2-thioxo-3-cyanopyridine derivatives

Dawoud has exhibited that 4,6-diaryl-2-thioxo-1,2-dihydropyridine-3-carbonitriles **28** were synthesized by one-pot reaction of substituted acetophenones (4-methoxyacetophenone and/or 2,4-dimethoxyacetophenone) **26** with α-arylidene-cyanothioacetamide **27** and ammonium acetate in boiling ethanol [46] **(Scheme 11).**



Scheme 11. Synthesis of 2-thioxo-1,2-dihydropyridine-3-carbonitriles

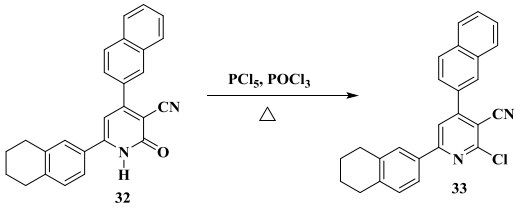
Meanwhile, treatment of sodium 3-(5-bromobenzofuran-2-yl)-3-oxoprop-1-en-1-olate (**29**) with 2-cyanothioacetamide (**30**) in the presence of piperidinium acetate gave 6-(5-bromobenzofuran-2-yl)-2-thioxo-1,2-dihydropyridine-3-carbonitrile derivative **31** [47] **(Scheme 12).**



Scheme 12. Synthesis of 2-thioxo-1,2-dihydrpyridine-3-carbonitriles

2.4.1. 2-Chloro-derivatives

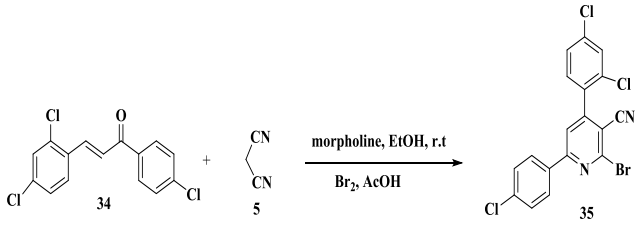
Different studies showed that 2-chloro-3-nicotinonitrile derivative **33** was prepared by heating 2-oxo-3-nicotinonitrile precursor **32** with PCl_5 and $POCl_3$ on a water bath [48] **(Scheme 13)**.



Scheme 13. Synthesis of 2-chloro-3-nicotinonitrile

2.4.2. 2-Bromo-derivatives

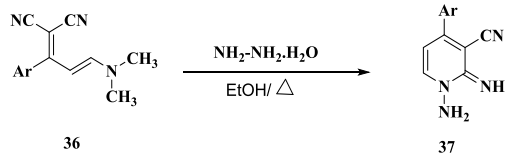
It has been reported that the reaction of 1-(4-chlorophenyl)-3-(2,4-dichlorophenyl)-2-propen-1-one **34** with malononitrile **5** in absolute ethanol in the presence of few drops of morpholine at room temperature, then dropwise addition of a solution of bromine in glacial acetic acid led to the formation of the corresponding 2-bromo-6-(4-chlorophenyl)-4-(2,4-dichlorophenyl)-3-pyridinecarbonitrile derivative **35** [49] **(Scheme 14)**.



Scheme 14. Synthesis of 2-bromo-3-nicotinonitrile derivative

2.5. Synthesis of 1-amino-2-imino-3-cyanopyridine derivatives

Synthesis of 1-amino-2-imino-3-cyanopyridine derivatives **37** was carried out through reaction of enaminonitrile derivatives **36** with hydrazine hydrate in refluxing ethanol [50] **(Scheme 15).**

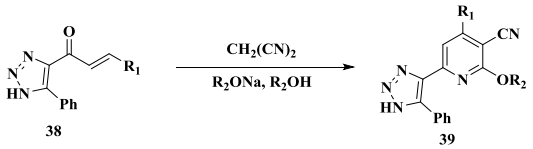


Ar= C_6H_5; *p*-MeC_6H_4; *p*-$MeOC_6H_4$; *p*-ClC_6H_4

Scheme 15. Synthesis of 1-amino-2-imino-3-cyanopyridine derivative

2.6. Synthesis of 2- alkoxy -3-cyanopyridine derivatives

A three-component condensation of 1,2,3-triazole chalcones **38**, malononitrile, and sodium alkoxides afforded 2-alkoxy-4-phenyl-6-(5-phenyl-1H-1,2,3-



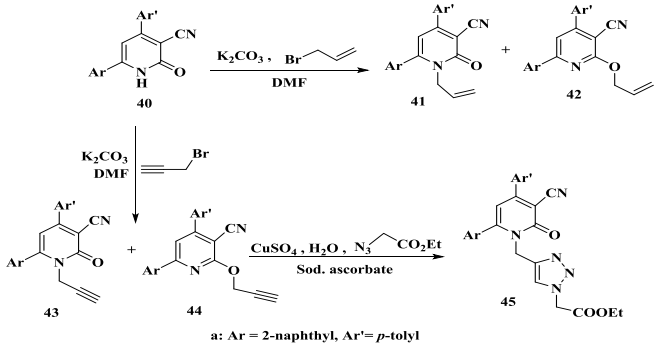
	R_1	R_2
a	Ph	Me
b	4-$MeOC_6H_4$	Me
c	4-$Me_2NC_6H_4$	Me
d	4-ClC_6H_4	Me
e	4-ClC_6H_4	$EtOCH_2CH_2$

Scheme 16. Synthesis of 2- alkoxy-3-cyanopyridine derivatives

3. Reaction of 3-cyanopyridine derivatives

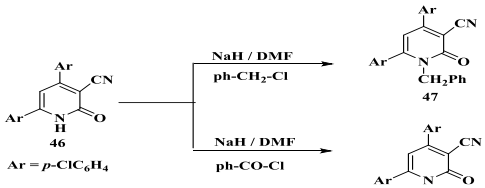
3.1. Reaction of 2-oxo-3-cyanopyridine derivatives

El-Sayed *et al.*, revealed that alkylation of 3-nicotinonitriles **40** with allyl bromide and propargyl bromide in a basic medium produced *N*- and *O*-alkylated nicotinonitrile derivatives **41-44**. Reaction of compound **44** with ethyl-2-azidoacetate in $CuSO_4$ and sodium ascorbate gave 1,4-disubstituted triazole **45** [52] **(Scheme 17)**.



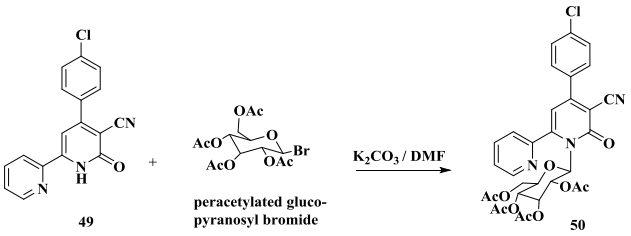
Scheme 17. Preparation of N- / O- alkylated nicotinonitrile derivatives

Furthermore, compound **46** was allowed to react with benzyl chloride or benzoyl chloride in DMF and sodium hydride to afford compounds **47** and 48 [53,54**] (Scheme 18).**



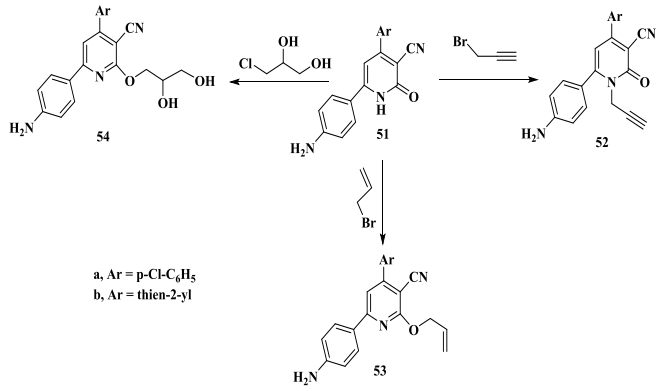
Scheme 18. Preparation of N-benzyl/benzoyl nicotinonitrile derivatives

Also, Abou-Elkhai *et al*. had coupled the 2-oxonicotinonitrile derivative **49** with peracetylated glucopyranosyl bromide in DMF containing K2CO3 to afford the corresponding nucleoside **50** [55] **(Scheme 19)**.



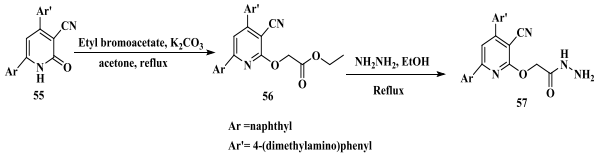
Scheme 19. Preparation of carbonitrile-nucleoside derivative

Alkylation of the 2-pyridone derivatives **51** with different alkylating agents namely; (allyl / propargyl bromides, 3-chloro-1,2-propandiol) in dry DMF afforded the corresponding *N*-alkylated derivatives **52** and *O*-alkylated derivatives **53** and **54** [56] **(Scheme 20)**.



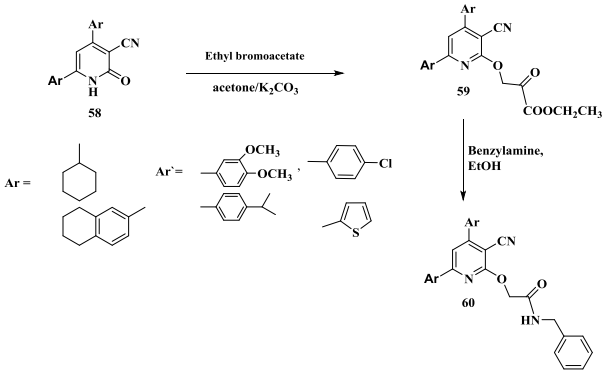
Scheme 20. Preparation of O- / N-alkylated nicotinonitrile compounds

On the other hand, the treatment of the nicotinonitrile derivative 55 with ethyl bromoacetate in dry acetone gave the corresponding ethyl-2-(3-cyano-4-[4-(dimethylamino)phenyl]-6-naphthalen-2-yl)pyridin-2-yloxy)-acetate (56). The latter compound was refluxed with hydrazine hydrate in ethanol to accomplish 2-(3-(Cyano-4-[4-(dimethylamino) phenyl]-6-(naphthalen-2-yl)pyridin-2-yloxy)aceto-hydr azide (**57**) [57a,b] **(Scheme 21).**



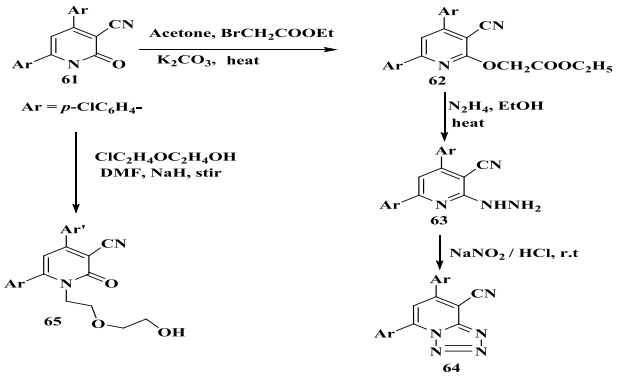
Scheme 21. Preparation of nicotinonitrile-acetohydrazide

Other studies showed that the treatment the 3-cyanopyridones **58** with ethyl bromoacetate yielded the ester derivatives **59** which were refluxed with benzylamine to give the acetamides **60** [58] **(Scheme 22)**.



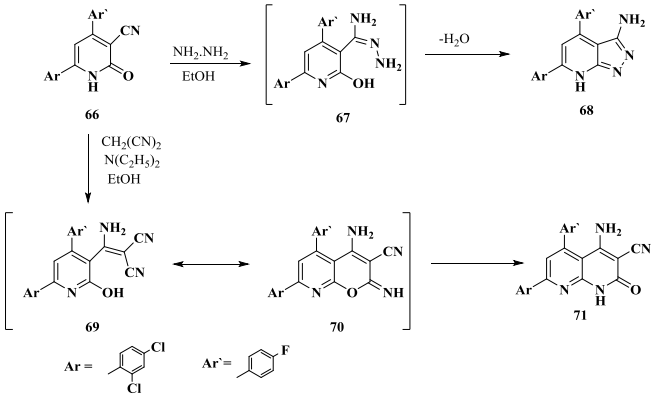
Scheme 22. Preparation of tetralin-nicotinonitrile hybrids

Meanwhile, treatment of the nicotinonitrile derivative **61** with ethyl bromoacetate, in the presence of anhydrous potassium carbonate produced the ethyl ester derivative **62**, which was treated with hydrazine hydrate to form the hydrazine derivative **63**. Nitrozation of compound **63** gave the corresponding 5,7- bis(4- chlorophenyl)- tetrazolo [1,5- *a*]pyridine- 8- carbonitrile **64**. Furthermore, stirring of **61** with chloroethoxyethanol in DMF and NaH led to the formation of the *N*-hydroxyethoxyethyl derivative **65** [53] **(Scheme 23)**.



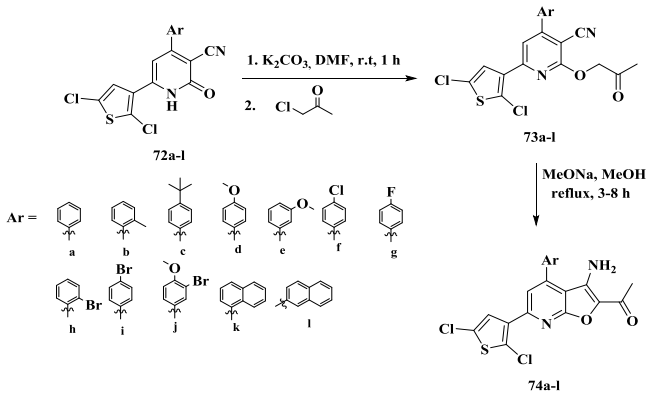
Scheme 23. Preparation of tetrazolo [1,5- a]pyridine- 8- carbonitrile

Hydrazinolysis of pyridin-3-carbonitrile **66** with hydrazine hydrate in absolute ethanol affords the corresponding pyrazolo[3,4-b]pyridin-3-amine derivative **68** through the elimination of a water molecule from the intermediate **67**. Compound **66** was also refluxed with malononitrile to afford 4-amino-7-(2,4-dichlorophenyl)-5-(4-fluorophenyl)-2-oxo-1,2-dihydro-1,8-naphthyridine-3-carbonitrile (**71**) *via* the intermediates **69** and **70** [57] **(Scheme 24)**.



Scheme 24. Preparation of pyrazolo[3,4-b]pyridine and 1,8-naphthyridine

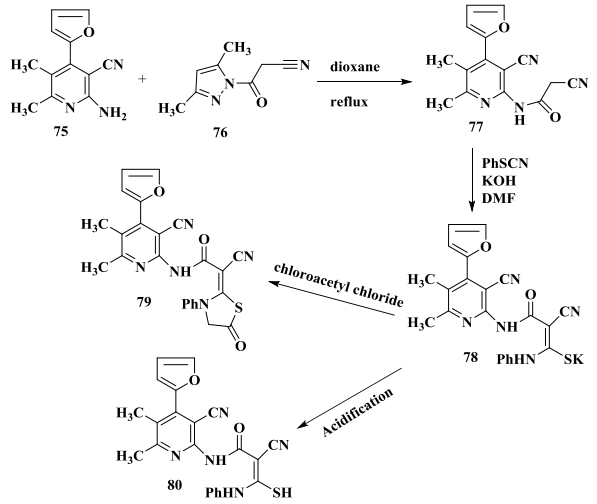
Furo[2,3-b]pyridine derivatives **74** were synthesized in two steps, where, the cyano-(2H)-pyridones **72a-l** were converted to the corresponding nicotinonitriles 73a-l, followed by the Thorpe-Ziegler ring cyclization to the furo[2,3-b]pyridine derivatives **74a-l** [59] **(Scheme 25).**



Scheme 25. Preparation of furo[2,3-b]pyridine derivatives derivatives

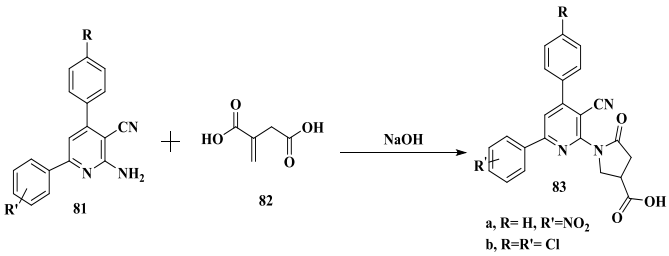
3.2. Reaction of 2-amino-3-cyanopyridine derivatives

cyanoacetylation of 2-amino-4-(furan-2-yl)-5,6-dimethylnicotinonitrile **75** with 3-(3,5-dimethyl-1*H*-pyrazol-1-yl)-3-oxopropanenitrile **76** in dioxane led to the formation of 3-cyano(-*N*-3-cyano-4-furan-2-yl)-5,6-dimethylpyridine-2-yl)-acetamide **77**, which in turn was allowed to react with phenyl isothiocyanate to form the corresponding derivative **78.** Upon treatment of compound **78** with chloroacetyl chloride afforded 2-(5-oxothiazolidinone)cyanoacetamido derivative **79**, while its acidification led to the liberation the of corresponding thiocarbamoyl derivative **80** [4] **(Scheme 26)**.



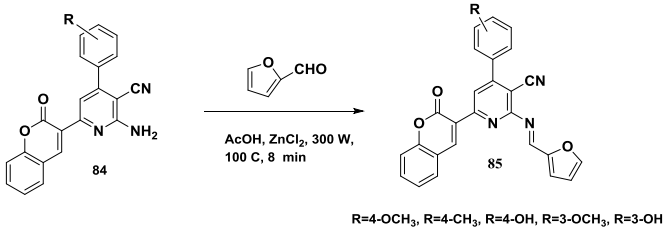
Scheme 26. Preparation of nicotinonitrile-substituted acetamido derivatives

On the other hand, refluxing the nicotinonitriles **81** with itaconic acid **82** in water gave 1-[3-cyano-6-(4-nitrophenyl)-4-phenyl-pyridin-2-yl]-5-oxopyrrolidine-3-carboxylic acid and 1-[4,6-bis-(4-chlorophenyl)-3-cyano-pyridin-2-yl]-5-oxopyrrolidine-3-carboxylic acid (**83a,b**) [60] **(Scheme 27)**.



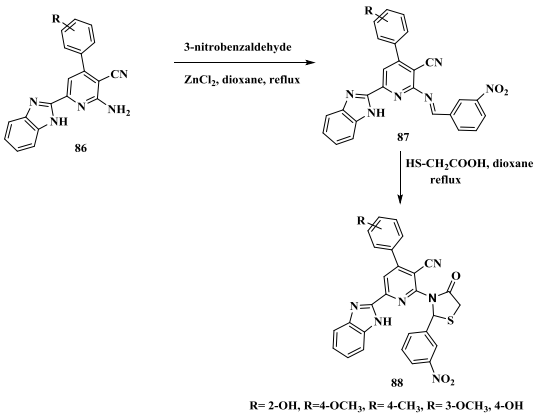
Scheme 27. Preparation of substituted 5-oxopyrrolidine-nicotinonitrile

Synthesis of coumarin derivatives containing cyanopyridine nucleus was carried out via microwave-irradiation, by Desai and coworkers [61]. Whereas a mixture of **84**, 2-furfuraldehyde, acetic acid and catalytic amount of $ZnCl_2$ was irradiated to give derivatives **85 (Scheme 28).**



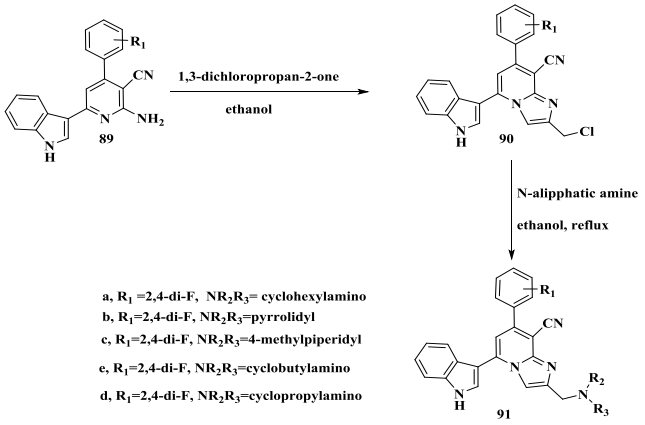
Scheme 28. Preparation of coumarin-cyanopyridine hybrids

In addition, when compound **86** were underwent simple condensation reaction with 3-nitrobenzaldehyde to provide the corresponding Schiff's bases **87** in good yields [74]. Further cyclization of **87** was achieved by their treatment with thioglycolic acid to afford the corresponding substituted 1*H*-benzo[d]imidazol-nicotinonitrile derivatives **88** [62] **(Scheme 29)**.



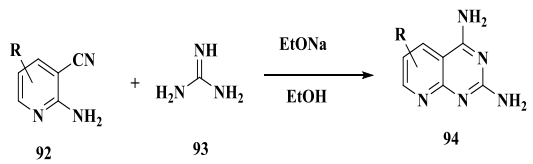
Scheme 29. Preparation of 1*H*-benzo[d]imidazol-nicotinonitriles

On the other hand, compound **89** was reacted with 1,3-dichloropropanone in ethanol affording **90**. Nucleophilic substitution of **90** with appropriate N-aliphatic amines in refluxing ethanol to accomplish the corresponding compounds **91** [10] **(Scheme 30).**



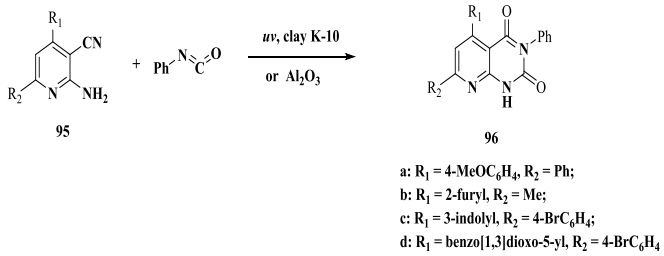
Scheme 30. Preparation of indol-phenylimidazo[1,2-a]pyridine-carbonitriles

Also, 2-amino-3-cyanopyridines **92** rapidly reacted with guanidine (**93**) in sodium ethoxide to form 2,4-diaminopyrido[2,3-d]pyrimidines **94** [63,64] **(Scheme31).**



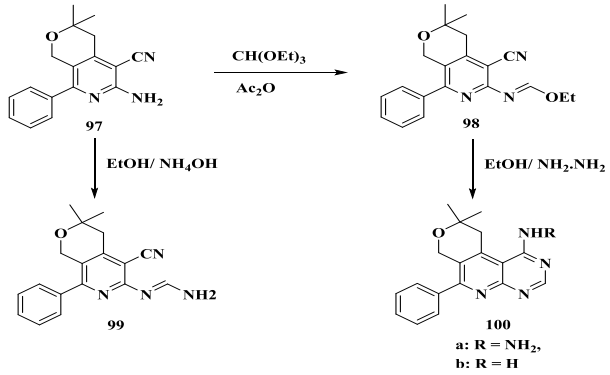
Scheme 31. Preparation of 2,4-diaminopyrido[2,3-d]pyrimidines

2-Amino-3-cyanoperidines derivatives **95** were condensed with phenylisocyanate adsorbed over K-10 monotmorillonite clay or alumina and irradiated under microwaves to afford the final 5,7-disubstituted 3-phenylpyrido[2,3-d]pyrimidine-2,4(1*H*,3*H*)-diones **96** [65] **(Scheme 32).**



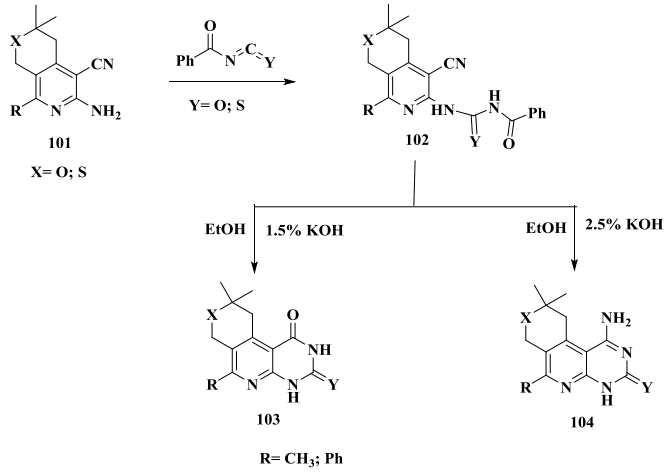
Scheme 32. Preparation of pyrido[2,3-d]pyrimidine-2,4(1*H*,3*H*)-diones

On the other hand, interaction of aminonicotinonitrile **97** with triethylorthoformate in acetic anhydride afforded the imine derivative **98**, which reacted with hydrazine hydrate to afford the hydrazinopyrimidine 100a. Another treatment of **97** with riethylorthoformate in ethanol / ammonia afforded the amino derivative 99, which cyclized under the influence of NaOEt to give the aminopyrimidine **100b** [66] (**Scheme 33).**

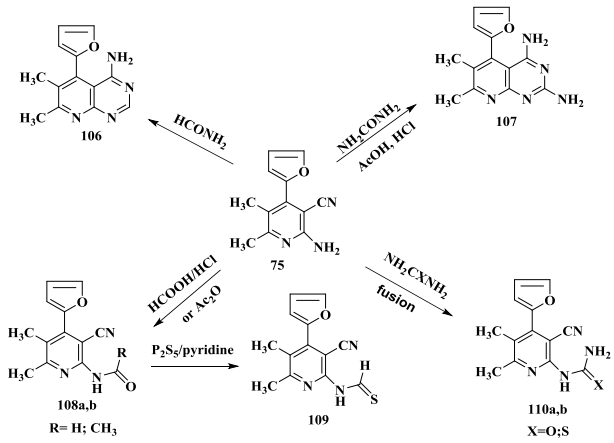


Scheme 33. Preparation of hydrazinopyrimidine and aminopyrimidines

Also, reaction of the aminonitriles **101** with benzoyliso(thio)cynate, followed by cyclization of the resulting N-benzoyluriedo(thiouriedo) derivatives **102** by the action of a base afforded derivatives 103 and 104. When a 1.5% aqueous solution of potassium hydroxide is used, 8,10-dioxo or 10-oxo-8-thio derivatives **103** are formed, whereas with a 2.5% solution of potassium hydroxide in ethanol, the 10-amino-8-oxo derivatives **104** are obtained [66] **(Scheme 34).**

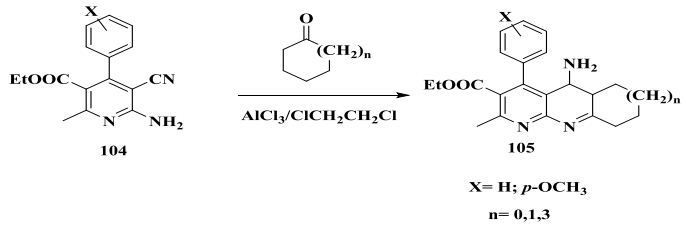


Scheme 34. Preparation of pyrido[2.3-d]pyrimidines

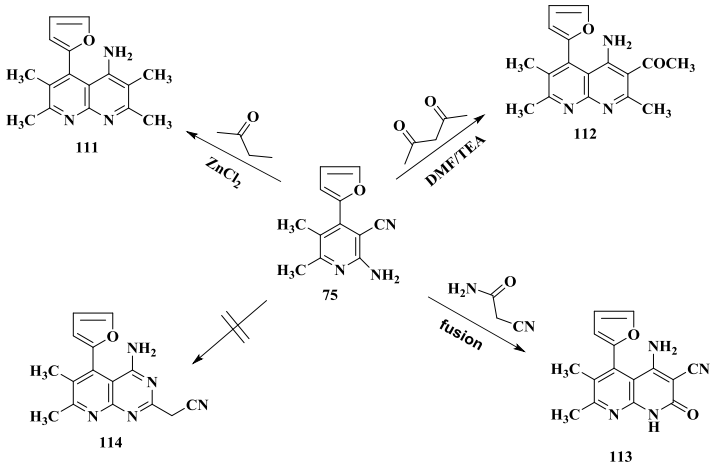


Scheme 36. Preparation of pyrido[2.3-d]pyrimidine derivatives

Cycloanulated[1,8]naphthyridine ring systems **105** were achieved starting from pyridines **104** under standard Friedlander reaction conditions, with cyclopentanone, cyclohexanone, or cycloheptanone[67] **(Scheme 35).**



Scheme 35. Preparation of pyridoquinoline derivatives

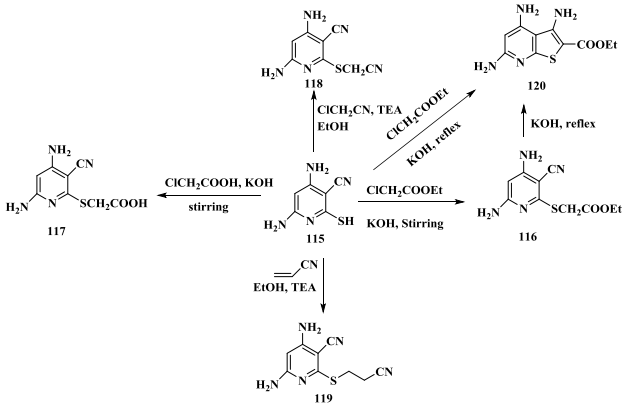


Scheme 37. Preparation of 1,8-naphthyridine derivatives

Furthermore, refluxing of compound **75** with formamide and urea in glacial acetic acid gave the pyrido[2,3-d]pyrimidine **106** and **107**, respectively. On the other hand, heating of **75** with formic acid and acetic anhydride afforded the anilide derivatives **108a,b** respectively. Refluxing of the anilide **108a** with P_2S_5 in pyridine afforded the thioanilide derivative **109**. Moreover, condensation of compound **75** with urea and thiourea afforded the ureado and thioureado **110a,b** derivatives, respectively [68] **(Scheme 36).** The 1,8-naphthyridine derivatives **111** and **112** were furnished via the reaction of compound **75** with butanone and acetylacetone, respectively. On the other hand, fusion of **75** with cyanoacetamide afforded the 2-oxo-1,8- naphthyridine derivative **113** instead of the pyrido[2,3-d]pyrimidine-2-yl derivative **114** [68**] (Scheme 37).**

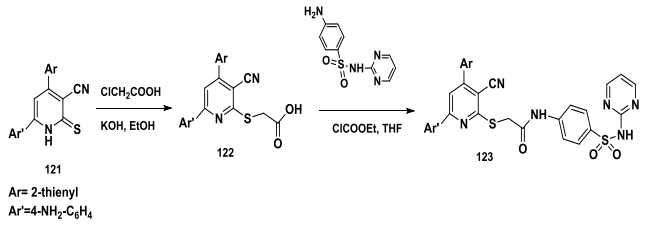
3.3. Reaction of 2-thioxo -3-cyanopyridine derivatives

Studies showed that the reaction of 4,6-diamino-2-thioxo-nicotinonitrile **115** with different halo compounds (ethyl chloroacetate, chloroacetic acid, chloroacetonitrile) and acrylonitrile in EtOH in the presence of TEA as catalyst produced the corresponding S-alkyl derivatives **116-119**, respectively. Thienopyridine derivatives **120** was furnished by heating of S-alkyl derivative **116** in hot KOH solution or by reaction of compound **115** with appropriate halo compound directly in hot KOH solution [69] **(Scheme 38)**.



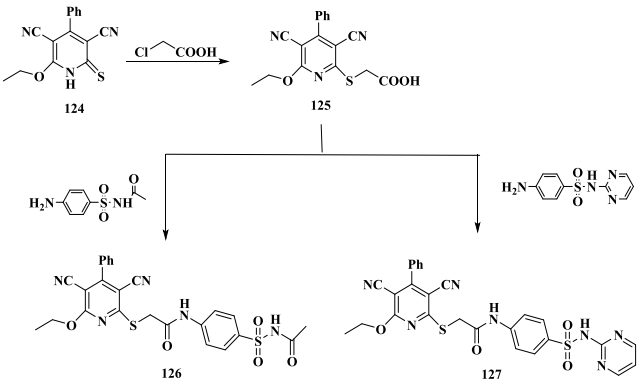
Scheme 38. Preparation of S-alkylated nicotinonitriles

Other researches showed that refluxing of 4,6-diaryl-3-cyanopyridine-2-thione **121** with KOH and chloroacetic in ethanol for 15 h yielded 2-(4-(4-aminophenyl)-3-cyano-6-(thiophen-2-yl)pyridin-2-ylthio)acetic acid (**122**). A solution of **122** in THF was cooled to -10 oC and stirred with ethyl chloroformate and sulphadiazine to give **123** [56] **(Scheme 39)**.



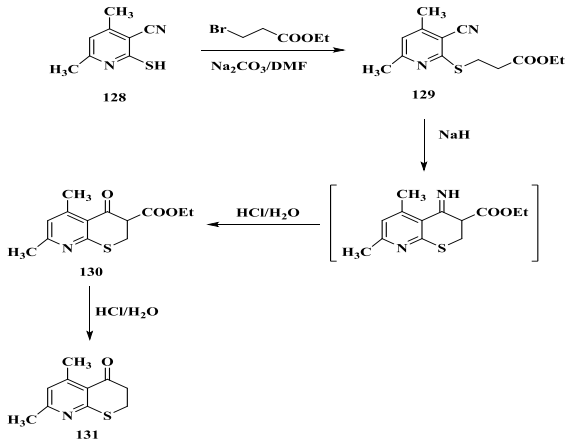
Scheme 39. Preparation of the nicotinonitrile-sulfa derivatives

The S-alkylated pyridine **125** was obtained by the reaction of nicotinonitrile-2-thione derivative **124** with chloroacetic acid in ethanolic NaOH. Reaction of acid derivative **125** with sulfa drugs such as sulfa acetamide and sulfa diazine in the presence of triethylorthoformate/triethylamine in THF gave the sulfonamide derivatives **126** and **127**, respectively [70] **(Scheme 40)**.



Scheme 40. Preparation of nicotinonitrile-sulfonamide derivatives

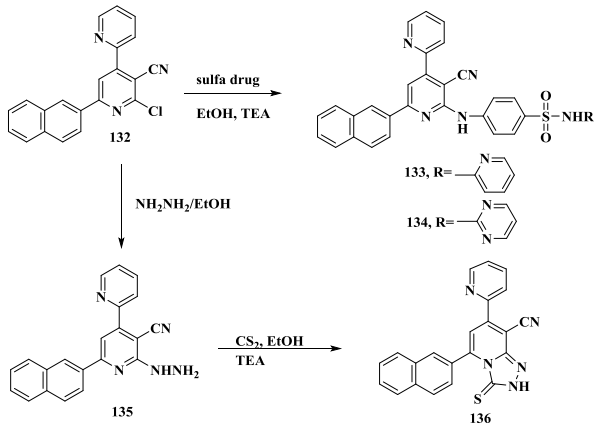
On the other hand, refluxing of the thione derivative **128** with ethyl 3-bromopropanoate in DMF as a solvent and sodium carbonate afforded the S-alkylated derivative **129**. Cyclization of **129** by sodium hydride in tetrahydrofuran as a solvent, followed by an acidic hydrolysis for the imine intermediate produced the corresponding thiopyrano[2,3-b]pyridine **130** in quantitative yield. The acidic hydrolysis of **130** led to the formation of the cyclic ketone **131** as a target precursor to synthesize the new thiopyranopyridines of pharmaceutical interest [71] **(Scheme 41**).



Scheme 41. Preparation of thiopyrano[2,3-b]pyridine derivatives

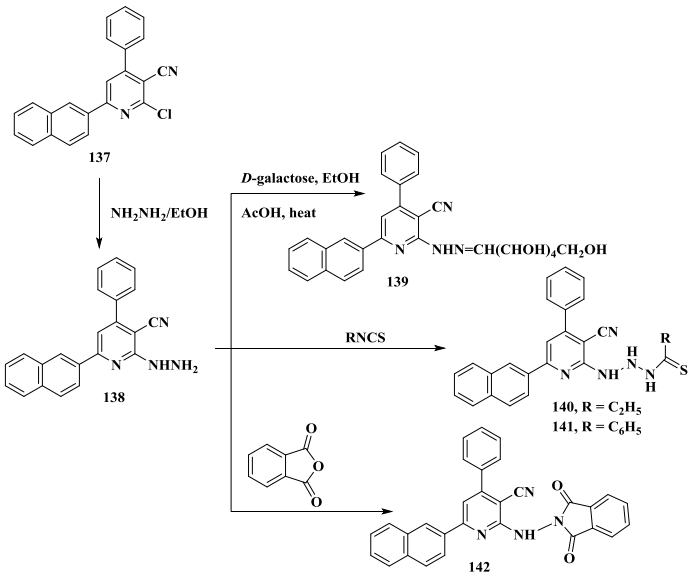
3.4. Reaction of 2-halo-3-cyanopyridine derivatives

Kotb *et al*., showed that condensation of 2-chloro 3-cyanopyridine derivative **132** with sulfa drugs gave the sulfonamide derivatives **133** and **134**. Refluxing compound **132** with hydrazine hydrate in ethanol gave the hydrazide **135**, which was cyclocondensed with carbon disulphide in ethanol and triethylamine to afford 3-thioxo triazolopyridine **136** [72] **(Scheme 42)**.



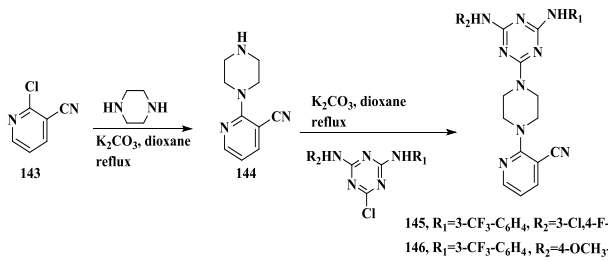
Scheme 42. Preparation of nicotinonitrile-sulfoneamides and triazolopyridines

Also, treatment the chloro-derivative **137** with excess hydrazine hydrate in refluxing ethanol afforded **138**, which was reacted with D-galactose in ethanol containing drops of glacial acetic acid, to yield hydrazone **139**. Condensation of **138** with ethyl (phenyl) isothiocyanate in dry DMF and drops of TEA afforded the thiosemicarbazides **140** and **141**. Reaction of the hydrazinyl derivative **138** with phthalic anhydride in acetic acid gave the derivative **142** [73] **(Scheme 43)**.



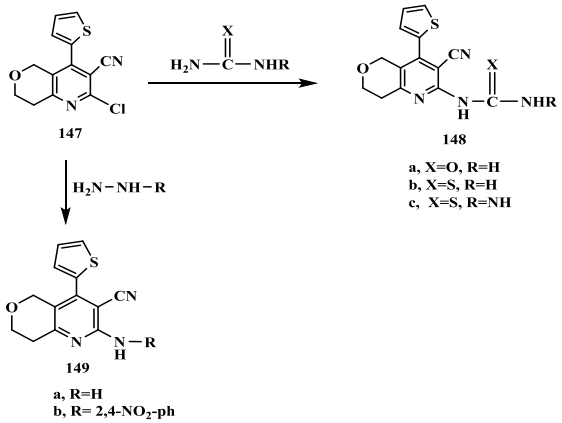
Scheme 43. Preparation of nicotinonitrile derivatives

A series of cyanopyridine triazines **145** and **146** was prepared by Maqbool et al. via reaction of 2-chloronicotinonitrile (**143**) with piperazine in dioxane to yield 2-(piperazin-1-yl)nicotinonitrile **144** which was refluxed with different trisubstituted triazines to afford the desired compounds [74] **(Scheme 44)**.



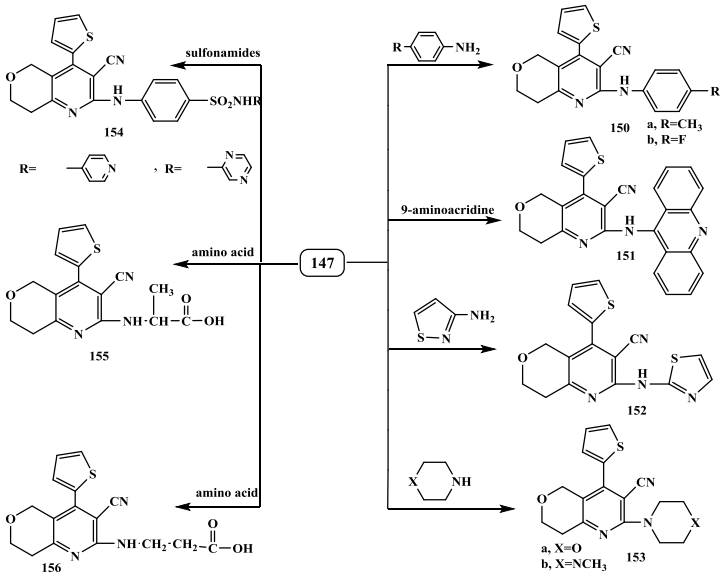
Scheme 44. Preparation of cyanopyridine triazine derivatives.

Mohamed *et al*. prepared the corresponding pyranopyridine-3-carbonitrile derivatives **148a-c** by reacting 2-chloropyranopyridine-3-carbonitrile (**147**) with urea, thiourea and thiosemicarbazide. Furthermore, condensation of **147** with hydrazine hydrate and/or 2,4-dinitrophenyl-hydrazine in ethanol gave the hydrazides **149a,b**[75] **(Scheme 45).**



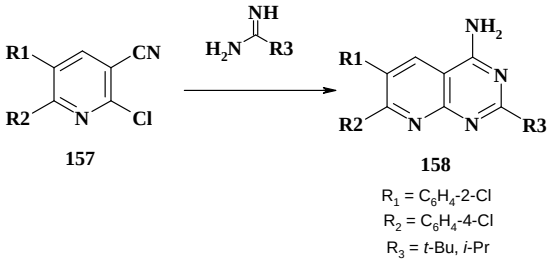
Scheme 45. Preparation of substituted pyranopyridine-3-

While heating compound **147** with different aromatic, heterocyclic and secondary alicyclic amines yielded compounds **150-153**. On the other hand, treatment of **147** with sulfonamides and different amino acids led to the formation of the corresponding sulfonamides **154** and pyranopyridine amino acid derivatives **155**, **156**, respectively [75] **(Scheme 46).**



Scheme 46. Preparation of substituted pyrano[4,3-b]pyridine-3-carbonitriles.

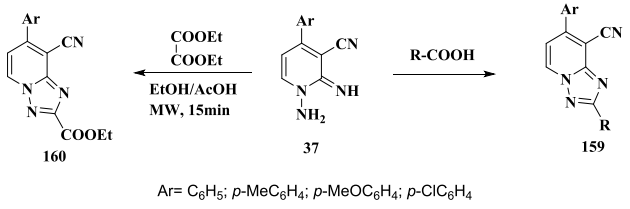
Similarly, addition of amidines to the 2-chloro nicotinonitrile **157** affords the 4-aminopyrido pyrimidine derivatives 158 in high yield [76] **(Scheme 47)**.



Scheme 47. Preparation of 4-aminopyridopyrimidine derivatives

3.5. Reaction of 1-amino-2-imino-3-cyanopyridi derivatives

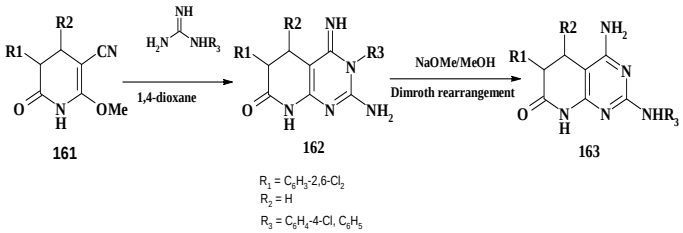
The reaction of 1-amino-2-imino-pyridine derivati **37** with carboxylic acids (as a solvent and reacta the formation of the [1,2,4]triazolo[1,5-a]pyridine carbonitriles **159** have been detected. Moreo when the diethyl oxalate allowed to react with 1-amino-2-iminopyridines **37** using 5 equiv. of acetic acid in ethanol under microwave irradiation, the products **160** were received in excellent yields [50] **(Scheme 48)**.



Scheme 48. Preparation of[1,2,4]triazolo[1,5-a]pyridine-8-carbonitriles

3.6. Reaction of 2- alkoxy-3-cyanopyridine derivatives

Galve *et al*, synthesized 3-N-aryl substituted 2-amino-4-imino-5,6-dihydropyrido[2,3-d]pyrimidin-7(8H)-ones **162**, from treatment of 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles **161** with an aryl substituted guanidine in 1,4-dioxane, which undergoes the Dimroth rearrangement to the 2-arylamino- pyridopyrimidine **163** by heating in NaOMe/MeOH [77] **(Scheme 49)**.

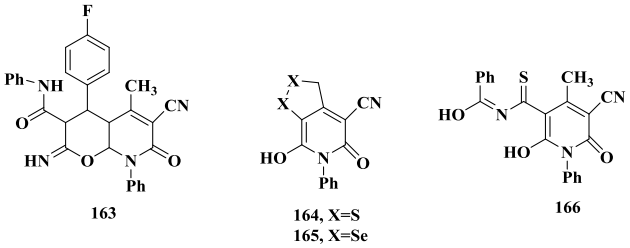


Scheme 49. Preparation of 2-amino-4-imino-pyrido[2,3-d]pyrimidin-7(8H)-ones

4. Biological Potentials of Nicotinonitriles:

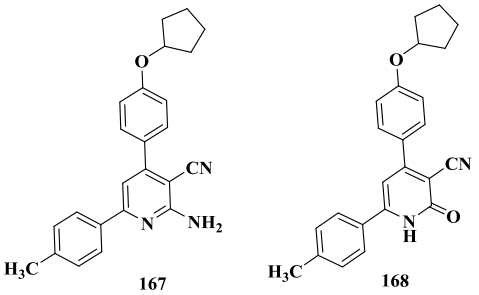
4.1. Nicotinonitriles as anticancer agents:

When various substituted nicotinonitriles **163-166** were tested against three human tumor cell lines, MCF-7, NCI-H460 and SF-268, compounds **163** and **164** showed the highest inhibitory effects, while compounds **165** and **166** showed moderate inhibitory effect compared to the references drug Doxorubicin [78] **(Scheme 50)**.



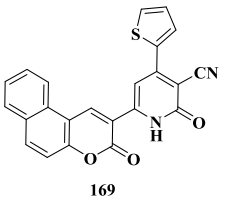
Scheme 50. Substituted nicotinonitriles as anticancer agents

Further studies revealed that 2-amino (2-oxo)-4-(4-(cyclopentyloxy)-phenyl)-6-(p-tolyl)nicotinonitriles, **167** and **168** when tested against Human hepato-cellular, Human breast adenocarcinoma, Human cervical epithelioid carcinoma and Human prostate cancer cell lines showed moderate activities [79] **(Scheme 51)**.



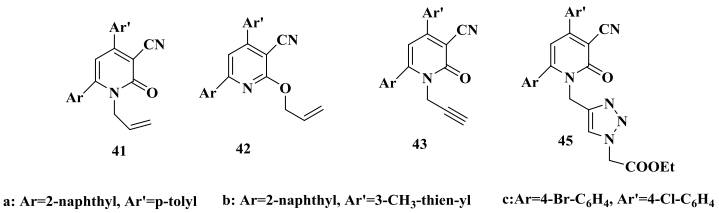
Scheme 51. 2-Amino (2-oxo)-4-(4-(cyclopentyloxy)-phenyl)-6-(p-tolyl)nicotinonitrile derivatives as anticancer agents.

Other study showed that, benzo[f]chromen-3-one-nicotinonitrile hybrid **169** was evaluated against breast (MCF-7), live (HepG2) and colon (HCT-116) cancer cell lines. It showed good antiproliferative activity with relatively low IC50 values [80] **(Scheme 52)**.



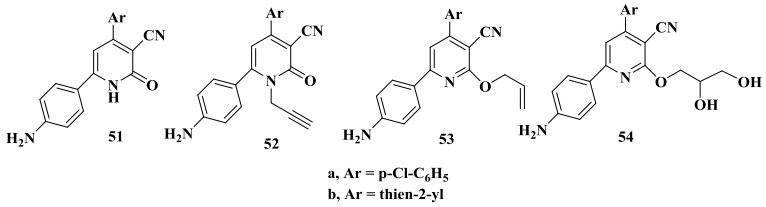
Scheme 52. Benzo[f]chromen-3-one-nicotinonitrile hybrid as anticancer agents.

When *N*- and *O*- alkylated nicotinonitrile derivatives **41-43** and **45** were tested for their anticancer activity against Retinal Pigmented Epithelial Cells Page 1 (RPE-1) and Human Breast Adenocarcinoma Cell Line (MCF-7), at concentration 100□M, showed good cytotoxicity activities against the tested cell lines [52] **(Scheme 53)**.



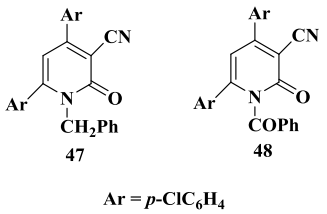
Scheme 53. *N*- and *O*- alkylated nicotinonitrile derivatives as anticancer agents.

Furthermore, compounds **51a,b, 52a, 53b**, and **54b** showed good anticancer activities against cell culture of HepG-2, PC-3 and HCT116 cell lines [56] **(Scheme 54)**.



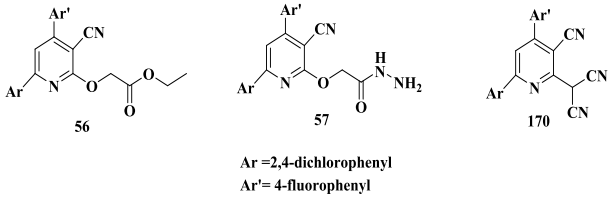
Scheme 54. *N*- and *O*- alkylated nicotinonitrile derivatives as anticancer agents.

Furthermore, compounds **47** and **48** exhibited remarkable cytotoxicity activity against breast MCF-7 and liver HepG2 cell lines [53,54] **(Scheme 55)**.



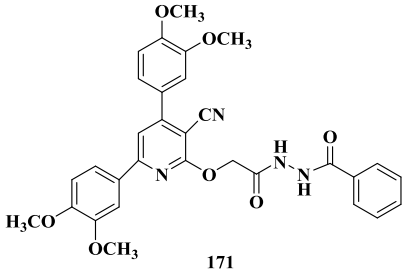
Scheme 55. N-benzyl/benzoyl nicotinonitrile derivatives as anticancer agents

Also, nicotinonitrile-acetohydrazide and nicotinonitrile-malononitrile derivatives **56, 57** and **170** showed high cytotoxic activity against the tested cell lines, SF-268, MCF-7, WI 38, NCI-H460 (IC50 values ranged from 0.01 ± 0.002 to 0.02 ± 0.001 μg /mL). These compounds showed better cytotoxicity against most of cancer cell lines than the reference drug (Doxorubicin) [57] **(Scheme 56)**.



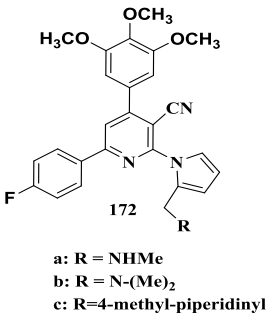
Scheme 56. Nicotinonitrile-acetohydrazide and nicotinonitrile-malononitrile derivatives as anticancer agents

Further researches displayed that the nicotinonitrileacetylbenzohydrazide **171** showed better cytotoxicity against human breast cancer cell line MCF-7 [81] **(Scheme 57)**.



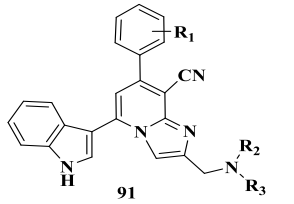
Scheme 57. Dimethoxyphenyl-nicotinonitrile-acetohydrazide as anticancer agents

Also, nicotinonitrile-mannich derivatives **172a-c** were evaluated against colon (HT-29), liver (SMMC-7721), gastric (MKN-45), alveolar (A549) and lung (H460) cancer cell lines and exhibited prominent cytotoxicity with IC50 values from 0.030 to 0.31 μM, which was comparable or superior to the reference drug Crolibulin and CA-4. [82] **(Scheme 58)**.



Scheme 58. Nicotinonitrile-mannich derivatives as anticancer agents

On the other hand, Testing the anticancer activity against cancer cell lines HT-29, H460, A549, MKN-45 and SMMC-772, compounds 91a-e exhibited promising anti-cancer activity with IC50 values in double-digit nanomolar degrees [10] **(Scheme 59)**.

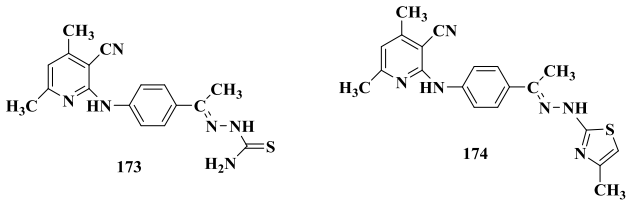


91

a, R_1 =2,4-di-F, NR_2R_3= cyclohexylamino
b, R_1=2,4-di-F, NR_2R_3=pyrrolidyl
c, R_1=2,4-di-F, NR_2R_3=4-methylpiperidyl
d, R_1=2,4-di-F, NR_2R_3=cyclopropylamino
e, R_1=2,4-di-F, NR_2R_3=cyclobutylamino

Scheme 59. Indol-phenylimidazo[1,2-a]pyridine-carbonitrile derivatives as anticancer agents

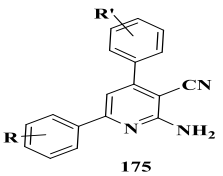
It has been reported that 2-(1-(4-((3-cyano-4,6-dimethylpyridin-2-yl)amino)-phenyl)ethylidene)-hydrazine-1-carbothioamide (**173**) and 4,6-Dimethyl-2-((4-(1-(2-(4-methylthiazol-2-yl)-hydrazono)ethyl) phenyl)amino)-nicotinonitrile (**174**) were tested for their antioxidant activities by using (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) Radical Cation Decolorization Assay [51,52]. They displayed excellent antioxidant property (86.3%) and (80.0%) respectively. They were even very close to the standard inhibitor (L-Ascorbic acid 89.2%) [83]



173 174

Scheme 60. Hydrazine-1-carbothioamide/thiazol-nicotinonitrile derivatives as antioxidants

Furthermore, 2-amino-4,6-diphenyl-nicotinonitrile derivatives **175a-c** showed moderate activity when tested for their antioxidant activities using 2,2-biphenyl-2-picrylhydrazyl (DPPH) method as a free radical scavenging reagent) [84] **(Scheme 61)**.

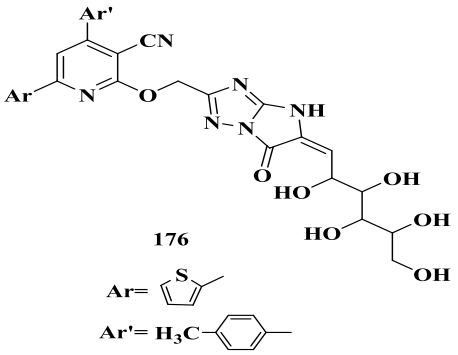


175

a, R= 3-OH, R'= 3-NO_2
b, R= 3-OH, R'= 4-Br
c, R= 4-NO_2, R'=3-OH

Scheme 61. 2-Amino-4,6-diphenyl-nicotinonitrile as antioxidants

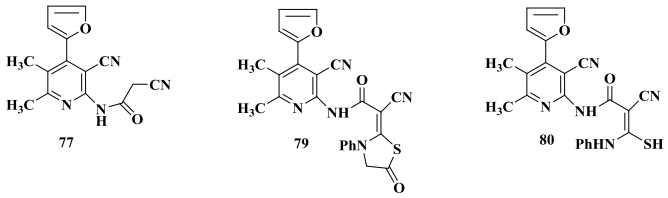
In addition, nicotinonitrile-triazolo derivatives **176** showed the greatest effect against the artificial radical DPPH [85] **(Scheme 62)**.



176

Scheme 62. Nicotinonitrile-triazolo derivatives as antioxidants

antioxidant activities using the ABTS method [4] **(Scheme 63)**.

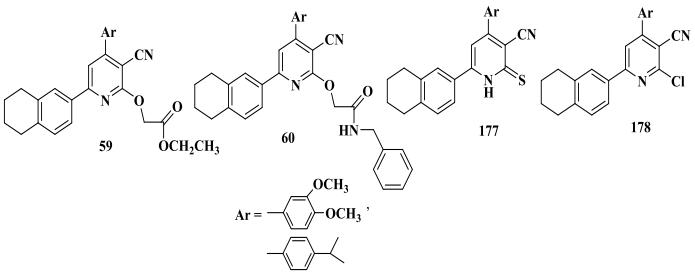


77 79 80

Scheme 63. Nicotinonitrile-substituted acetamido derivatives as antioxidants

4.3. Nicotinonitriles as anti-inflammatory agents:

Some studies showed that various tetralin-nicotinonitrile hybrids showed that the synthesized compounds **59, 60, 177**, and **178** were recognized as promising anti-inflammatory agents [58] **(Scheme 64)**.

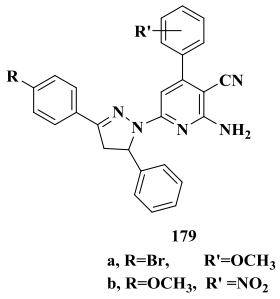


59 60 177 178

Scheme 64. Tetralin-nicotinonitrile hybrids as anti-inflammatory agents

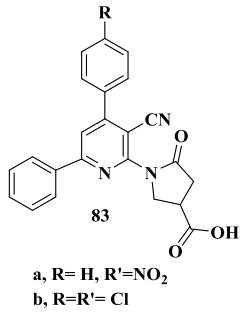
4.4. Nicotinonitriles as anticonvulsants:

Nicotinonitriles **179a,b** showed significant anticonvulsant activity with ED50 values 17.5 and 22.6 mg/kg, respectively, [86] **(Scheme 65)**.



Scheme 65. Nicotinonitrile-pyrazoline derivatives as anticonvulsants

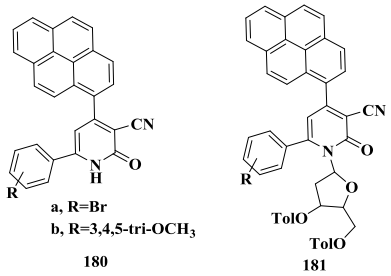
On the other hand, compounds **83a,b** showed anticonvulsant activity with ED50 values of 13.4 and 18.6 mg/kg in electroshock screen comparable to the standard drugs respectively [60] **(Scheme 66)**.



Scheme 66. Nicotinonitrile-5-oxopyrrolidine conjugates as anticonvulsants

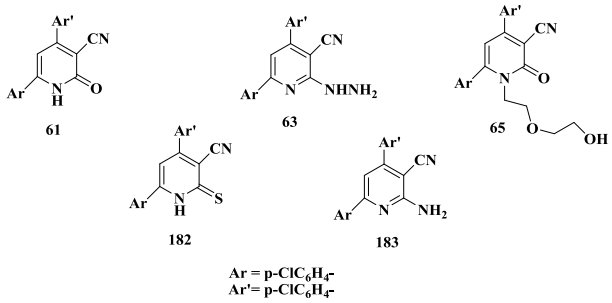
4.5. Nicotinonitriles as antiviral agents:

Various antiviral studies revealed that compounds **180** and **181** prevented the cytopathic effect of HSV-1 (against herpes simplex virus, type 1 (HSV-1),) in Vero cells, at micromolar concentrations, and were minimally toxic to Vero cells resulting in a good selectivity index. The antiviral activity evaluation showed that compound **113b** was the most effective anti-HSV-1 derivative in relation to the reference acyclovir [87] **(Scheme 67)**.



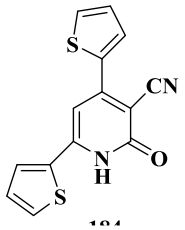
Scheme 67. Pyrene-N-ribosylnicotinonitrile derivatives as antiviral agents

Meanwhile, Compounds **61, 63, 65, 182** and **183** exhibited good anti-Influenza A (H5N1) activities [53] **(Scheme 68)**.



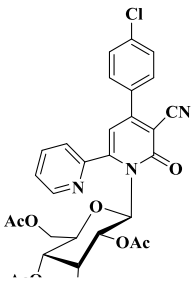
Scheme 68. Nicotinonitrile derivatives as antiviral agents

Furthermore, the thienyl-nicotinonitrile derivative **184** appeared as a strong antiviral candidate against HSV-1 and HSV-2 (EC50 > 12 mM) [88] **(Scheme 69)**.



Scheme 69. Thienyl-nicotinonitrile derivative as antiviral agents

The 4-(4-Chlorophenyl)-1-(-β-D-Ac-glucopyranosyl) -2-oxo-6-(2-pyridyl)nicotine- nitrile (**50**) showed good anti severe acute respiratory syndrome coronavirus (SARS-CoV) and anti-influenza A (H5N1) activities [55] **(Scheme 70)**.

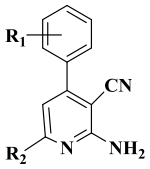


Scheme 70. Glycosylated nicotinonitrile derivative as antiviral agents

4.6. Nicotinonitriles as analgesics:

Atla and coworkers had synthesized the nicotinonitrile: 2-amino-3-cyano-4-(2,4-dichlorophenyl)-6-(4-aminophenyl)pyridine) **185** and 2-amino-3-cyano-4-(4-dimethylaminophenyl)-6-(4-

hydroxyphenyl)pyridine **186**. The analgesic activity was evaluated by tail flick method in which heat is used as a source to induce pain in mice. Dose dependent activity of **185** and **186** showed higher protection at 120 min comparable to the reference standard and exerted their activity in a manner similar to that of Ibuprofen [89] **(Scheme 71)**.

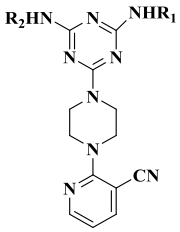


185, R_1= 2,4-Cl_2. R_2= 4-$NH_2C_6H_5$
186, R_1=$N(CH_3)_2$, R_2= OHC_6H_4

Scheme 71. Substituted 2-amino-nicotinonitrile derivatives as analgesics

4.7. Nicotinonitriles as anti-Alzheimer agents:

A new series of cyanpyridine triazines **145** and **146** was prepared by Maqbool *et al*. and screened as multitargeted anti-Alzheimer's agents. Promising inhibitory activity was noticed by **145** and **146** on acetylcholinesterase (IC50 values 0.059 and 0.080 mL) [74] **(Scheme 72)**.

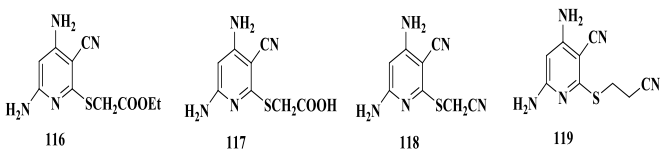


145, R_1=3-CF_3-C_6H_4, R_2=3-Cl,4-F-C_6H_4
146, R_1=3-CF_3-C_6H_4, R_2=4-OCH_3-C_6H_4

Scheme 72. Cyanopyridine triazine derivatives as anti-Alzheimer agents

4.8. Nicotinonitriles as anti-microbial agents:

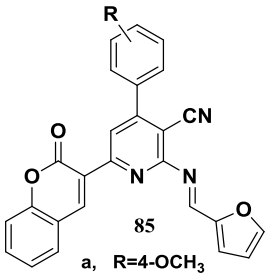
Further studies showed that the compounds **116-119** gave high activities against Gram negative bacteria (Pseudomonas aeruginosa and Escherichia coli) [69] **(Scheme 73)**.



116 117 118 119

Scheme 73. S-alkylated nicotinonitriles as anti-microbial agents

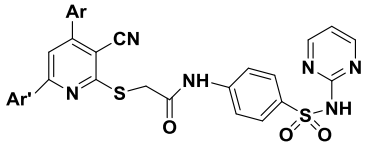
By microwave-irradiation, synthesis of coumarin derivatives **85a-e** containing cyanopyridine nucleus as antimicrobial agents was carried out. High antibacterial activity observed against E. *Coli* and P. *aeruginosa* was reported by these compounds comparable to Ampicillin at 50 mg/ml [61] **(Scheme 74)**.



85
a, R=4-OCH_3
b, R=4-CH_3
c, R=4-OH
d, R=3-OCH_3

Scheme 74. Coumarin-cyanopyridine hybrids as anti-microbial agents

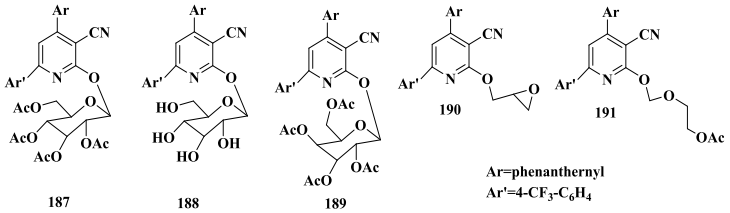
Using cup plate diffusion method, sulfonamide derivative **123** showed the highest antifungal activity against *Candida albicans* [56] **(Scheme 75)**.



123

Scheme 75. Nicotinonitrile-sulfa compound as anti-microbial agents

Compounds **187-191** showed strong activity against S. *aureus* and S. *epidermidis* (Gram +Ve) and P. *aeruginosa* and E. *coli* (Gram –Ve) in comparable to the reference Cefotaxime. Also compounds **190** and **191** showed strong activity against *Candida albicans* and *Aspergillus niger* close to that of the reference Nystatin [90] **(Scheme 76)**.

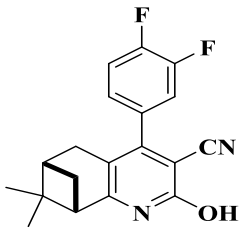


187 188 189

Scheme 76. Glycosylated nicotinonitrile derivatives as anti-microbial agents

3-Cyanopyridine–β-pinene (**192**) exhibited the best antimicrobial activity against overall strains (K. *pneumonia*, E. *aerogenes*, S. *aureus*, S. *epidermidis*,

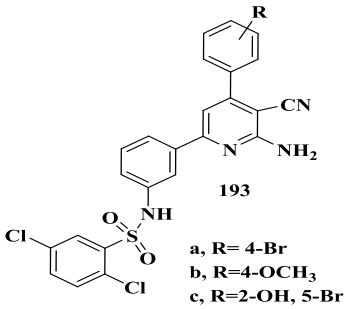
C. *albicans*) comparable to the references Kanamycin and Rifampicin [91] **(Scheme 77)**.



192

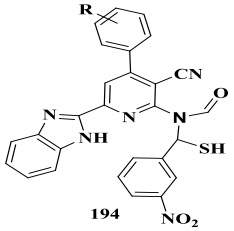
Scheme 77. Cyanopyridine–*β*-pinene as anti-microbial agents

Furthermore, the three benzenesulfonamide-nicotinonitrile derivatives **193a-c** showed good antimicrobial activity against five microbial cell colonies (S. *aureus*, E. *coli*, P. *vulgaris*, B. *mega*, A. *niger*) [92] **(Scheme 78)**.



Scheme 78. Benzenesulfonamide-nicotinonitriles as anti-microbial agents

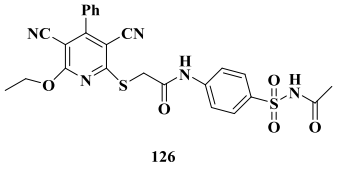
In addition, Ouattara et al. prepared a series of substituted 1H-benzo[d]imidazol-nicotinonitrile derivatives **194a-d** and tested as anti-microbial agents. Compounds **194a-d** exhibited excellent antimicrobial inhibition against S. *pyogenes*, S. *aureus*, P. *aeruginosa*, E. *coli*, C. *albicans*, A. *clavatus* and A. *niger* combarable to the reference drugs Chloramphenicol and Ketoconazole [62] **(Scheme 79)**.



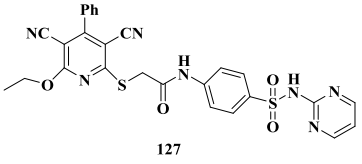
a, R= 2-OH
b. R=4-OCH3
c, R= 4-CH3
d, R= 3-OCH3, 4-OH

Scheme 79. Benzo[d]imidazol-nicotinonitriles as anti-microbial agents

The synthesized compounds **126** and **127** exhibited significant activity against *B. cereus*, *S. aureus*, *P. aeruginosa*, *E. Coli*, *A. flavus*, and *A. niger* [70] **(Scheme 80)**.



126

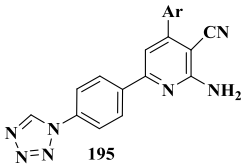


127

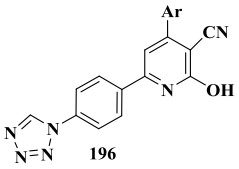
Scheme 80. Nicotinonitrile-sulfonamide derivatives as anti-microbial agents.

4.9. Nicotinonitriles as anti-ulcer agents:

Lamie *et al.*, has tested compounds **195** and **196a-d** as anti-ulcer agents. The latter compounds showed lower ulcer toxicity than indomethacin (UI: 22.50), where the UIs were in the range of 1.25–2.00 [93] **(Scheme 81)**.



Ar= 3,4-(OCH3)2-C6H3



a, Ar= C6H5
b, Ar= 4,4-(CH3)2-N-C6H4
c, Ar= 3,4-(OCH3)2-C6H3
d, Ar= 3,4,5-(OCH3)3-C6H2

Scheme 81. Tetrazol-nicotinonitrile derivatives as anti-ulcer agents

5. Conclusions

Drug discovery field has a pivotal role in the progress of therapeutic chemistry. Significant attention is being diverted to the development of the molecular architecture of heterocyclic compounds in (bio)organic chemistry. In accordance, this review clearly showed that nicotinonitrile compounds play an important role in medicinal chemistry being evaluated against numerous biological targets. It also highlighted an overview of the synthetic methodology used to give polyfunctionalized nicotinonitrile compounds. Several strategies including metal-catalyzed reactions, MW irradiation, and conventional heating methods have been successfully employed to achieve these compounds. This review also exhibited that numerous outstanding achievements revealed that nicotinonitrile compounds possess extensive potential applications as medicinal drugs. Many of these compounds have been successfully developed and extensively used in the clinic in preventing and treating various types of

diseases with low toxicity, high bioavailability, and good biocompatibility and curative effects. Strategy of extensive structure activity relationship studies and further derivatization and structural optimization should be continued on these scaffolds with the aim to obtain novel drugs with various biological activities of high selectivity and potency and devoid of the side effects of the parent drugs.

6. References

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