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], dipetidyl 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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
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<tbody>
<tr>
<td>Bosutinib</td>
<td>Leukemia</td>
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<tr>
<td>Milrinone</td>
<td>Cardiotonic</td>
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<tr>
<td>Neratinib</td>
<td>Breast cancer</td>
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<tr>
<td>Olprinone</td>
<td>Cardiotonic</td>
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Scheme 1: Some drugs containing nicotinonitrile moiety
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(dibenzyldieneacetone) 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(1H)-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$_2$CO$_3$ [37a,b] (Scheme 3).

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

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

![Scheme 7](https://example.com/scheme7.png)

**Scheme 7.** Synthesis of 6-Substituted-3-cyan-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-aminoacypyriddyne derivatives 18 [42]. Furthermore, heating a mixture of an aldehyde, substituted acetophenone, malononitrile, ammonium acetate and TBBDA (tetrabromobenzofuran-1,3-disulfonylamine) or PBBS (poly(N-bromo-N-ethylbenzene-1,3-disulfonylamine)) under stirring at 100 °C for appropriate times led to the formation of 2-aminoacypyriddyne derivatives 18 [43] (Scheme 8).

![Scheme 8](https://example.com/scheme8.png)

**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 °C gave corresponding thiazolo[4,5-b]pyridine-6-carbonitrile derivative 20 [44] (Scheme 9).

![Scheme 9](https://example.com/scheme9.png)

**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 CH₃COONH₄ yielded the corresponding 6-hydroxy-2-amino-3-cyanopyridine derivatives 25 [33] (Scheme 10).

![Scheme 10](https://example.com/scheme10.png)

**Scheme 10.** Synthesis of substituted 6-hydroxy-2-aminoacypyriddyne derivatives

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

Dawod 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) with α-arylidene-cyanothioacetamide 27 and ammonium acetate in boiling ethanol [46] (Scheme 11).

![Scheme 11](https://example.com/scheme11.png)

**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](https://example.com/scheme12.png)

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

_Egypt. J. Chem._ **64**, No. 8 (2021)
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 PCl₃ and POCl₃ on a water bath [48] (Scheme 13).

![Scheme 13. Synthesis of 2-chloro-3-nicotinonitrile](image)

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](image)

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 enaminoitrile derivatives 36 with hydrazine hydrate in refluxing ethanol [50] (Scheme 15).

![Scheme 15. Synthesis of 1-amino-2-imino-3-cyanopyridine derivatives](image)

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-

![Scheme 16. Synthesis of 2-alkoxy-3-cyanopyridine derivatives](image)

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 CuSO₄ and sodium ascorbate gave 1,4-disubstituted triazole 45 [52] (Scheme 17).

![Scheme 17. Preparation of N-/O-alkylated nicotinonitrile derivatives](image)

Furthermore, compound 46 was allowed to react with benzyl chloride or benzyol 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](image)
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](image)

Alkylation of the 2-pyridone derivatives 51 with different alkylation 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](image)

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-hydrazide (57) [57a,b] (Scheme 21).

![Scheme 21. Preparation of nicotinonitrile-aceto-hydrazide](image)

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](image)

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](image)

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).
Furo[2,3-b]pyridine derivatives 74 were synthesized in two steps, where, the cyano-(2H)-pyridones 72a-1 were converted to the corresponding nicotinonitriles 73a-1, followed by the Thorpe-Ziegler ring cyclization to the furo[2,3-b]pyridine derivatives 74a-1 [59] (Scheme 25).

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

\[
\begin{align*}
\text{Ar} = & \text{C} & \text{Ar} = & \text{Ar} \\
\text{HOCN} + & \text{NH}_2\text{CN} & \text{HOCN} + & \text{NH}_2\text{CN} \\
\text{KOH} & & \text{KOH} & \\
\text{H}_2\text{O} & & \text{H}_2\text{O} & \\
\text{MeOH} & & \text{MeOH} & \\
\text{MeCN} & & \text{MeCN} & \\
\end{align*}
\]

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

\[
\begin{align*}
\text{Ar} = & \text{C} & \text{Ar} = & \text{Ar} \\
\text{HOCN} + & \text{NH}_2\text{CN} & \text{HOCN} + & \text{NH}_2\text{CN} \\
\text{KOH} & & \text{KOH} & \\
\text{H}_2\text{O} & & \text{H}_2\text{O} & \\
\text{MeOH} & & \text{MeOH} & \\
\text{MeCN} & & \text{MeCN} & \\
\end{align*}
\]

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-1H-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

\[
\begin{align*}
\text{Ar} = & \text{C} & \text{Ar} = & \text{Ar} \\
\text{HOCN} + & \text{NH}_2\text{CN} & \text{HOCN} + & \text{NH}_2\text{CN} \\
\text{KOH} & & \text{KOH} & \\
\text{H}_2\text{O} & & \text{H}_2\text{O} & \\
\text{MeOH} & & \text{MeOH} & \\
\text{MeCN} & & \text{MeCN} & \\
\end{align*}
\]

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 27. Preparation of substituted 5-oxopyrrolidine-nicotinonitrile

\[
\begin{align*}
\text{Ar} = & \text{C} & \text{Ar} = & \text{Ar} \\
\text{HOCN} + & \text{NH}_2\text{CN} & \text{HOCN} + & \text{NH}_2\text{CN} \\
\text{KOH} & & \text{KOH} & \\
\text{H}_2\text{O} & & \text{H}_2\text{O} & \\
\text{MeOH} & & \text{MeOH} & \\
\text{MeCN} & & \text{MeCN} & \\
\end{align*}
\]

### Scheme 28. Preparation of coumarin-cyanopyridine hybrids

\[
\begin{align*}
\text{Ar} = & \text{C} & \text{Ar} = & \text{Ar} \\
\text{HOCN} + & \text{NH}_2\text{CN} & \text{HOCN} + & \text{NH}_2\text{CN} \\
\text{KOH} & & \text{KOH} & \\
\text{H}_2\text{O} & & \text{H}_2\text{O} & \\
\text{MeOH} & & \text{MeOH} & \\
\text{MeCN} & & \text{MeCN} & \\
\end{align*}
\]
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 1H-benzo[d]imidazolonicotinonitrile derivatives 88 [62] (Scheme 29).

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

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

Also, reaction of the aminonitriles 101 with benzoyliso(thio)cyinate, 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).

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] (Scheme 31).

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

Furthermore, refluxing of compound with formamide and urea in glacial acetic acid gave the pyrido[2,3-d]pyrimidine and respectively. Refluxing of the anilide with P2S5 in pyridine afforded the thioanilide derivative. Moreover, condensation of compound with butanone and acetylacetone, respectively. On the other hand, fusion of with cyanoacetamide afforded the 2-oxo-1,8- naphthyridine derivative instead of the pyrido[2,3-d]pyrimidine-2-yl derivative [68] (Scheme 37).

3.3. Reaction of 2-thioxo -3-cyanopyridine derivatives
Studies showed that the reaction of 4,6-diamino-2-thioxo-nicotinonitrile 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 respectively. Thienopyridine derivatives was furnished by heating of S-alkyl derivative directly in hot KOH solution (Scheme 38).
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 \(-10\) °C and stirred with ethyl chloroformate and sulfa diazine to give \(123\) \[56\] (Scheme 39).

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 triethylorthofomrate/triethylamine in THF gave the sulfonamide derivatives \(126\) and \(127\), respectively \[70\] (Scheme 40).

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).

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 thiopyrano[2,3-b]pyridines of pharmaceutical interest \[71\] (Scheme 41).
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-carbonitriles.

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 pyranopyridine-3-carbonitriles.

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

Egypt. J. Chem. 64, No. 8 (2021)
3.5. Reaction of 1-amino-2-imino-3-cyanopyridine derivatives

The reaction of 1-amino-2-imino-pyridine derivative with carboxylic acids (as a solvent and reactant) to form the triazolo[1,5-a]pyridin-carbonitriles have been detected. Moreover, when the diethyl oxalate allowed to react with 1-amino-2-iminopyridines using 5 equiv. of acetic acid in ethanol under microwave irradiation, the products were received in excellent yields.

Further studies revealed that when tested against Human hepato-cellular, Human breast adenocarcinoma, Human cervical epithelioid carcinoma and Human prostate cancer cell lines showed moderate activities [79] (Scheme 50).

4. Biological Potentials of Nicotinonitriles:

4.1. Nicotinonitriles as anticancer agents:

When various substituted nicotinonitriles 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).

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).

Other study showed that, benzo[f]chromen-3-one-nicotinonitrile hybrid 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).
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 nM, showed good cytotoxicity activities against the tested cell lines [52] (Scheme 53).

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).

Also, nicotinonitrile-acetylbenzohydrazide 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).

Furthermore, nicotinonitrile-acetohydrazide and nicotinonitrile-malononitrile derivatives as anticancer agents

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

Also, nicotinonitrile-mannich derivatives 172a-c were evaluated against colon (HT-29), 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 53. N- and O- alkylated nicotinonitrile derivatives as anticancer agents

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

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

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

Scheme 57. Dimethoxyphenyl-nicotinonitrile-acetohydrazide as anticancer agents

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).

4.2. Nicotinonitriles as antioxidants:

It has been reported that 2-(1-(4-(3-cyano-4,6-dimethylpyridin-2-yl)amino)-phenylethylidene)-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] (Scheme 60).

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).

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).

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).
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).

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

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

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

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).

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).

4.7. Nicotinonitriles as anti-Alzheimer agents:

A new series of cyanopyridine 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).

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

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).

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).

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).

3-Cyanopyridine-β-pinene (192) exhibited the best antimicrobial activity against overall strains (K. pneumonia, E. aerogenes, S. aureus, S. epidermidis, P. aeruginosa, and E. coli).
C. albicans) comparable to the references Kanamycin and Rifampicin [91] (Scheme 77).

\[
\text{Scheme 77. Cyanopyridine-β-pinene as anti-microbial agents}
\]

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).

\[
\text{Scheme 78. Benzenesulfonamide-nicotinonitriles as anti-microbial agents}
\]

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 comparable to the reference drugs Chloramphenicol and Ketoconazole [62] (Scheme 79).

\[
\text{Scheme 79. Benzo[d]imidazol-nicotinonitriles as anti-microbial agents}
\]

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).

\[
\text{Scheme 80. Nicotinonitrile-sulfonamide derivatives as anti-microbial agents.}
\]

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).

\[
\text{Scheme 81. Tetrazol-nicotinonitrile derivatives as anti-ulcer agents}
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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
A REVIEW ON THE CHEMISTRY OF NICOTINONITRILES AND THEIR APPLICATIONS

4525

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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