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3-Cyano-2-oxa-pyridines: a promising template for diverse pharmacological activities

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Abstract

Pyridines have occupied a unique place in medicinal chemistry as it is widely profound as natural products and formed the integral backbone of great number of drugs in the market. In particular, 3-cyano-2-oxa-pyridines showed diverse biological and pharmacological activities such as cardiotonic, antimicrobial, antidepressant, and anticancer activity. 3-Cyano-2-oxa-pyridine derivatives have elevated importance for modern medicinal applications especially in cancer therapy. This article shed light on the general chemical synthetic approaches of 3-cyano-2-oxa-pyridines and summarized their various biological activities and pharmacological uses. This article may be helpful in the future to direct attention towards utilization of 3-cyano-2-oxa-pyridine template in the design of new molecules with enhanced biological properties such as PIM1 kinase, tubulin polymerase and survivin inhibitors for cancer therapy or new AMPK activator for diabetes and obesity control or cardiotonic agents.

Key words

Cyanopyridines; PIM-1 kinase inhibitors; Survivin inhibitors; AMPK activators

1. Introduction

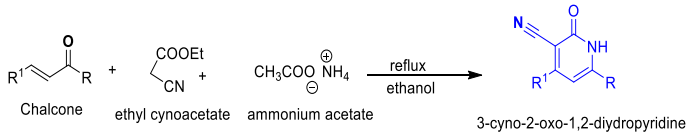
A diversified and highly functionalized nitrogen-containing heterocyclic compounds are core structural units in several natural products and synthetic drugs. These natural products and synthetic molecules possess tremendous applications in drug discovery and useful functional materials [1-3]. This encouraged the synthesis of biologically active heterocyclic compounds such pyridine derivatives [4-7]. Furthermore, pyridine derivatives are one of the important heterocyclic compounds that possess medicinal and functional properties with attractive applications as pharmaceuticals as well as general synthetic building blocks [8-11]. The pyridine nucleus is an integral part of anti-inflammatory and anticancer agents [12-14]. Pyridine derivatives containing various groups such as streptonigrone, streptonigrin, and lavendamycin are reported as anticancer drugs, and cerivastatin is reported as the HMG-CoA reductase enzyme inhibitor [15]. Moreover, substituted pyridines are reported as leukotriene B-4 antagonists [16, 17]. On the other hand, cyanopyridine derivatives have shown to possess promising antimicrobial [18-20], antioxidant [21-23], antibiotic [24-26], anti-inflammatory [27, 28], analgesic [29], anticonvulsant [30] and anticancer [31-33] properties. In particular, 3-cyano-2-pyridones are known to have diverse biological and pharmacological activity, particularly antimicrobial [19, 34-36], antidepressant [37], cardiotonic [6, 38], and anticancer activity [33, 35, 39, 40]. There is much interest in the anticancer activity of these compounds owing to different types of biological targets they might interfere with for this effect to occur e.g. PIM1 Kinase [40-44], tubulin [45], PDE3 [10, 40, 46-49] and Survivin protein [33, 40, 50-53]. In this context, due to the great significance of 3-cyano-2-oxa-pyridines and the interest in further development of new routes in their synthesis, we focus on their reported pharmacological activities and the general different methods involved in their synthesis.

2. General methods for synthesis of 3-cyano-2-oxa-pyridines

Several synthetic methods for preparation of 3-cyano-2-oxa-pyridines were reported; herein we have stated the general methods for their synthesis.

2.1. From chalcones (α,β-unsaturated ketones)

Condensation of chalcone with ethyl cyanoacetate and excess of ammonium acetate in ethanol (reflux) gave 3-cyano-2-oxo-1,2-dihydropyridines but in poor yield and consume time(yield about 60-70%, 2 steps more than 24 hours)[50,54-57], **Scheme1**.



Scheme 1: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines from chalcones.

2.2. One-pot multi-component reaction

Synthesis of 3-cyano-2-substiuted pyridines might be done *via* one-pot four component reaction of substituted acetophenone, ethyl cyanoacetate or malononitrile, appropriate aldehyde and

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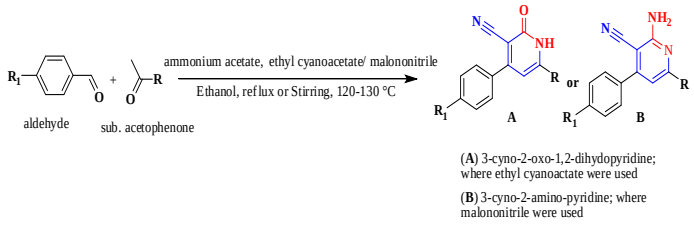
excess of ammonium acetate in various solvents e.g. ethanol, butanol and toluene, but also gave poor yield and consume time (yield about 60%, more than 12 hours) [38, 41, 58-60].(**Scheme 2**)

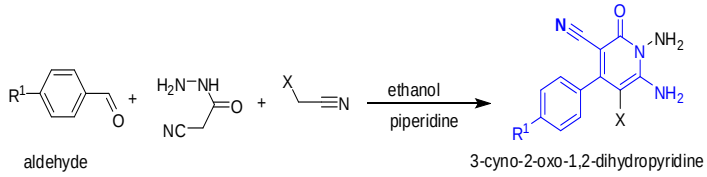
The synthesis can be carried out without solvent through one-pot four component reaction of equal quantity of substituted acetophenone, ethyl cyanoacetate or malononitrile, appropriate aldehyde and ammonium acetate under strong stirring at 120-130 °C, for 10-15 min. the reaction consumed short time and good yield (yield up to 90%,10-15 min.) [61]. (**Scheme 2**)



Scheme 2: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines *via* on-pot reaction with/ without solvent from substituted ketone and aldehyde

2.3. One-pot multi-component reaction using piperidine as a base

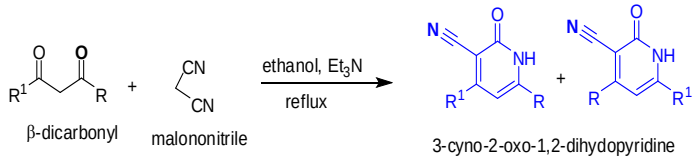
This synthesis method is through one-pot reaction of equal quantity of 2-cyanoacetohydrazide, an activated nitrile, appropriate aldehyde in ethanol using catalytic amount of piperidine to afford 3-cyano-2-oxo-1,2-dihydropyridine [62-65]. (**Scheme3**)



Scheme 3: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines via on-pot reaction using piperidine as catalyst.

2.4. From β-dicarbonyl compounds

This synthetic method involves refluxing equimolar amount of the appropriate β-dicarbonyl compound with malononitrile and triethylamine in ethanol with stirring for 15 min [66, 67]. (**Scheme 4**)



Scheme 4: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines from β-dicarbonyl compound.

3. Biological activity of 3-cyano-2-substituted pyridine

3-Cyano-2-substituted pyridines (particularly; 3-cyano-2-oxa-pyridine) and its derivatives have been showed well known significant role in various biological processes as well as, their pharmacological and chemical importance [68-71],(**Figure 1**). The pharmacophore 2-pyridone is noticeable in several therapeutic agents [72] that can be expanded into cardiotonic agents [73-77], antimicrobial [78], HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) [79, 80], and sedatives [81]. Structural similarity to nucleosides [82-86], has attracted attention of researchers. Researches have also indicated that they were found to be a key precursor in building of complex natural products such as nitroguanidine insecticide Imidacloprid [87].

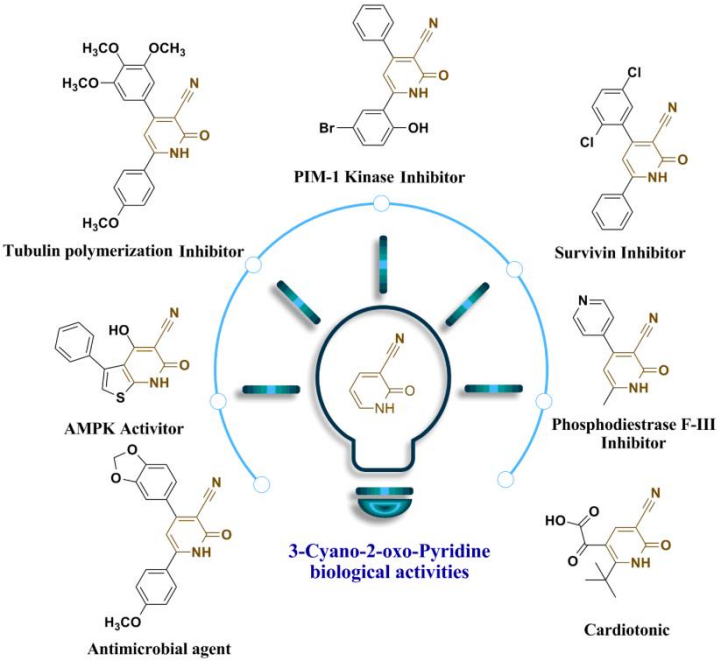


Figure 1: Various biological activities of 3-cyano-2-oxo-pyridine.

3.1. 3-Cyano-2-oxa-pyridine as cardiotonic agents

3-Cyano-2-oxa-pyridine derivatives exhibited potent cardiotonic activity [6, 38]. One of these derivatives, Milrinone **1** was marketed in treatment of congestive heart failure. Moreover, compounds **2-6** showed cardiotonic activities. The mechanism of their action includes inhibition of Phosphodiesterase-3 (PDE-3), resulted in prevention of cAMP degradation that followed by the decrease in Protein kinase A (PKA) amount in cells [73-77]. (**Figure 2**).

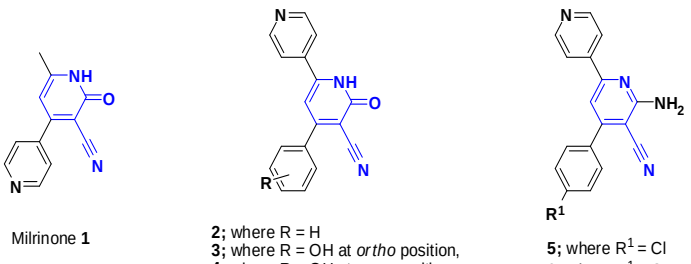
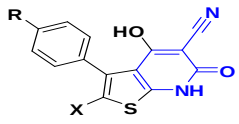


Figure 2: Structures of cardiotonics with 3-cyano-2-substitued-pyridine pharmacophore.

3.2. 3-Cyano-2-oxa-pyridines as an AMPK activator in metabolic syndrome, diabetes, and obesity

Adenosine monophosphate-activated protein kinase "AMPK", a heterotrimeric serine/ threonine kinase, has been found to be as a key sensor and regulator of intracellular and whole-body energy metabolism [88-91]. Its activation modifies the metabolism of carbohydrate and lipid *via* increase glucose uptake and fatty acid oxidation and decrease synthesis of fatty acid and cholesterol. Through its central role in the regulation of glucose and lipid metabolism, AMPK is emerging as an attractive molecular target for the treatment of diabetes, metabolic syndrome, and obesity [92-98]. Some 3-cyano-2-oxo-pyridine derivatives showed AMPK activation [58], (**Figure 3**). Compound **7**, which exhibited modest AMPK activity (rat liver EC_{50}, 38 µM), has been used as starting point to be optimized. The most potent one was compound **10** with more potent AMPK activity (rat liver EC_{50}, 3.7 µM) than **11, 9** and **8** with AMPK activity (rat liver EC_{50} of 5.8, 8 and 20 µM), respectively.



7; where R = H, X = H,
8; where R = OH, X = H,
9; where R = -OCH_2OCH_3, X = H,
10; where R = H, X = Cl,
11; where R = H, X = Br.

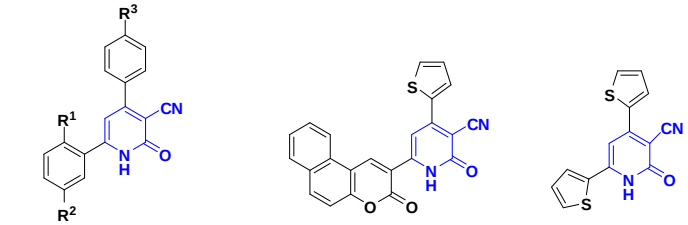
Figure 3: Structure of AMPK activators with 3-cyano-2-oxa-pyridine pharmacophore.

3.3. 3-Cyano-2-oxa-pyridines with anticancer activity

Cancer, the second leading factor of death after cardiovascular diseases, is an abnormal uncontrollable cell cycle disease characterized by the rapid proliferation of normal cells [99]. Several 3-cyano-2-oxa-pyridine derivatives display promising potent anticancer activity [33, 35, 39, 40] against a wide range of cell lines [100-102]. There is much interest in the anticancer activity of these compounds as they might act on different types of biological targets *via* different mechanisms of action.

3.3.1. 3-Cyano-2-substituted pyridine as PIM-1 kinase inhibitor

Proto-oncogenic encodes for serine/ threonine kinase (PIM-1 kinase) has been found to be overexpressed in various cancer cells [103-106], PIM-1 plays an important role in cancer cell survival, differentiation and proliferation [107-109]. Its inhibition resulted in cancer cell arrest and apoptosis [105, 110, 111]. Cheney *et al.*, [44] developed a series of cyanopyridine derivatives (**Figure 4**) that showed potent PIM-1 kinase inhibition. Compound **12** was the most potent inhibitor (IC_{50} = 50 nM). Several recent studies reported different cyanopyridine derivatives as potent PIM-1 kinase inhibitors e.g.: compound **13** (PIM-1 kinase IC_{50} = 0.84 µM), compound **14** (PIM-1 kinase IC_{50} = 0.43 µM), compound **15** (PIM-1 kinase IC_{50} = 0.99 µM) and used 4,6-diaryl-3-cyano-2-substitutedpyridine motif as a template for this purpose [33, 41-43]. These compounds showed potent anticancer activity *via* inhibition for PIM-1 Kinase [40-44].



12; where R^1 = OH, R^2= Br, R^3= H,
13; where R^1 = OH, R^2= H, R^3= OH

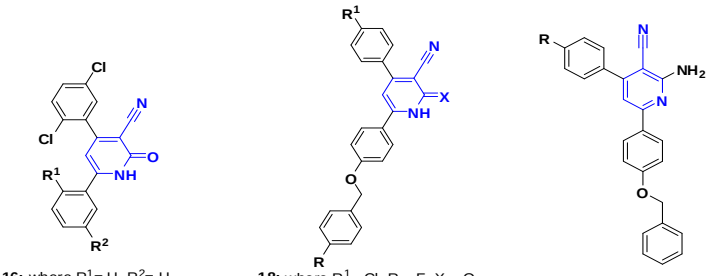
14

15

Figure 4: Structure of PIM-1 kinase inhibitors carrying 3-cyano-2-oxa-pyridine pharmacophore.

3.3.2. 3-Cyano-2-substituted pyridine as Survivin inhibitor

Survivin is an inhibitor of apoptosis family (IAP) [52]. It is encoded protein by the BIRC5 gene in human. Survivin has been found to be highly expressed in various cancer cells and fetal tissue and non-detectable in differentiated adult tissues [53]. Its inhibition resulted in cancer cell arrest and apoptosis. 3-Cyano-2-substituted pyridine derivatives with higher lipophilic properties as compounds **16-23** showed anticancer activity *via* inhibition of surviving protein. The affinity of the nominated compounds to survivin was enhanced by improving the lipophilicity through the introduction of halogen atom to the phenyl at position 4 of the pyridone ring [33, 40, 50-53]. (**Figure 5**).



16; where R^1= H, R^2= H,
17; where R^1= OH, R^2= Br.

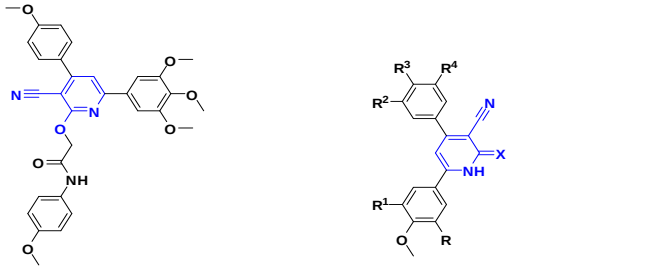
18; where R^1= Cl, R = F, X = O,
19; where R^1= -OCH_3, R = F, X = O,
20; where R^1= Cl, R = H, X= O,
21; where R^1= Cl, R = H, X = S.

22; where R = F,
23; where R = H.

Figure 5: Structures of survivin inhibitors with 3-cyano-2-substituted pyridine pharmacophore.

3.3.3. 3-Cyano-2-substituted pyridine as tubulin polymerization inhibitor

Some of 3-cyano-2-substituted pyridine derivatives showed potent cytotoxic activity higher than the combretastatin A4 (CA-4) *via* tubulin polymerization inhibition in sub-micromolar concentrations such as compounds **24-27** [45]. Their β-tubulin polymerization percentage inhibition assay indicates that the antitumor activity of these compounds correlates well with their ability to inhibit β-tubulin polymerization. (**Figure 6**).



24

25; where X = O, R = H, R^1= H, R^2= -OCH_3, R^3= -OCH_3, R^4= -OCH_3,
26; where X = O, R = -OCH_3, R^1= -OCH_3, R^2= -OCH_3,R^3= OH, R^4= H,
27; where X = S, R= -OCH_3, R^1= -OCH_3, R^2= -OCH_3, R^3= OH, R^4= H.

Figure 6: Structures of tubulin polymerization inhibitors carrying 3-cyano-2-substituted pyridine pharmacophore.

4. Structure activity relationship

The reported biological activities of 3-cyano-2-substituted pyridine nucleus seemed to be manipulated with structural variations (**Figure 7**). First of all, and in all cases, the presence of cyano group is essential for all previously reported activities in this review.

1-The presence of phenyl group Ring A and B either substituted or unsubstituted provides PIM-1 kinase inhibitors derivatives as in compounds **12-13**. Replacement of ring A and/or Ring B with thienyl or benzocoumarin-2-one groups retain the PIM-1 kinase inhibitory activity as in compounds **14** and **15**.
2- However, introducing of lipophilic groups such as Cl or F atoms on ring A produces derivatives with high survivin inhibitory activity such as compounds **17-23**.
3- Moreover, adding trimethoxy group to ring A and/or ring B yielded combrestatin analogues with high tubulin polymerization inhibitory activity such as compounds **24-27**. Replacement of O at position 2 with S is also tolerated.
4- Notably, replacement of phenyl group (ring B) with pyridine ring gives derivatives with cardiotonic activity with O > NH_2 > S at position 2 as in **1-6**.
5- Additionally, When the pyridine acquired the aromaticity as in 2-NH_2 substituted derivatives possessed available lone pair of electrons (not available in dihydropyridine derivatives) that can be participated in extra H-bond donating with the targeted enzymes.
6- Finally, fusion of thienyl group with 3-cyano-2-sunstituted pyridine nucleus produces thienopyridin-2-one with enhanced AMPK inhibitory activities as in **7-11**. While replacing the thienyl group with other heterocyclic rings resulted in inactive derivatives.

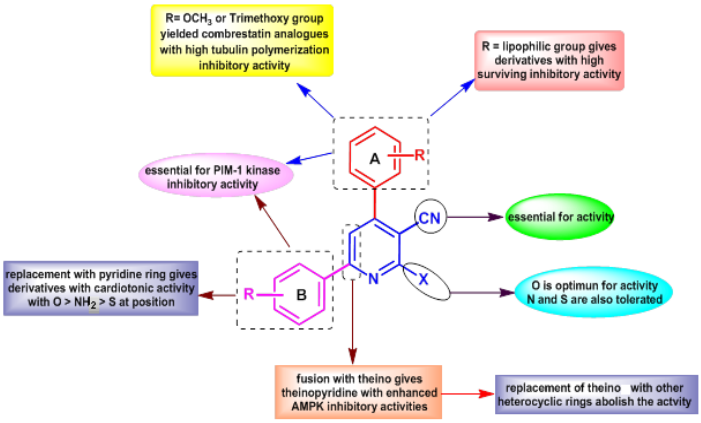


Figure 7: Effects of substitution on biological activity of 3-cyano-2-substituted pyridine.

Conclusion

3-Cyano-2-oxa-pyridine is a potential molecular template for variable biological activities which attracts the attention of many chemists globally to synthesize different compounds carrying this scaffold *via* easily efficient synthetic methods to explore their biological activity and sometimes their molecular drug target. Based on our survey, we could conclude that altering the substitutions on the 3-Cyano-2-oxa-pyridine skeleton is noticed in various pharmacophores for different targets with diverse biological activities. Therefore, this article may be helpful in the future to direct attention towards utilization of this template in the design of new molecules with enhanced biological properties such as PIM1 kinase, tubulin polymerase and survivin inhibitors for cancer therapy or new AMPK activator for diabetes and obesity control or cardiotonic agents as well as ultimately leading to the development of new approaches in the synthesis of their skeleton.

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