ejpmr, 2023, 10(10), 141-147

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

SYNTHESIS AND PHARMACOLOGICAL APPLICATIONS OF CYANOPYRIDINE DERIVATIVES: A REVIEW

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Article Received on 25/07/2023 **Article Revised on 15/08/2023** **Article Accepted on 04/09/2023**

ABSTRACT

Heterocyclic compounds, especially pyridine derivatives, play a vital role in the development of pharmaceutical drugs due to their significant impact on various activities such as antimicrobial, antifungal, anti-inflammatory, antioxidant, antiviral, and anticancer properties. A lot of researchers and scientists have explored the diverse biological effects of cyanopyridines, a type of pyridine derivative. As a result, researchers are now focusing on developing a synthetic plan for cyanopyridine derivatives and evaluating their biological activity. During this brief review, our focus has been on the latest advancements in the synthesis of cyanopyridine derivatives and the various pharmacological properties associated with this compound. This review could be useful for medicinal chemists conducting research on cyanopyridine in the future.

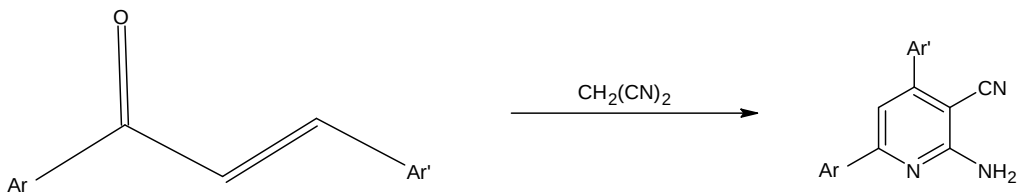
KEYWORDS: Cyanopyridine, synthesis, anticancer activity.

INTRODUCTION

The chemistry of heterocyclic molecules is one of the most fascinating branches of the pharmaceutical field. These compounds are widely distributed in nature and are of considerable value to industry. The majority of drugs currently available on the market are heterocyclic in nature. Cyanopyridines are one of the most versatile synthetic intermediates that finds extensive usage in pharmaceutical industries. These compounds exhibit significant biological and pharmacological activities. Cyanopyridines have become more important in organic synthesis in the last few years. Many fused cyanopyridines have wide-spectrum biological activities. Cyanopyridines, a pyridine derivative, attract attention because many of its derivatives exhibit different pharmacological activities. They are used in the industrial production of nicotinamide, nicotinic acid and isonicotinic acid, intermediates to pharmaceuticals such as pirenzepine. Cyanopyridines also serve as the intermediate in many organic syntheses. It is worth noting that fused cyanopyridines exhibit a vast array of pharmacological effects. They possess antiviral, antibacterial, and fungicidal activities.[1,2] 2-Amino- 3-cyanopyridine derivatives were also reported as novel IKK-β inhibitors[3], A2A adenosine receptor antagonists[4], potent inhibitor of HIV-1 integrase[5], and other activities. Cyanopyridines also exhibit anthelmintic, anti-inflammatory, anticonvulsant, and anti-tubercular activity.[6-8] In this short review, we have focused on the recent developments in the synthesis of cyanopyridine derivatives and all possible activities reported for this compound. This review may be helpful for medicinal chemists conducting research on cyanopyridine in the future.

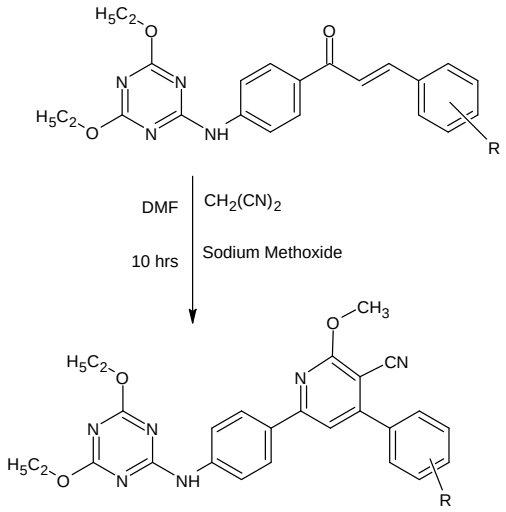
SYNTHESIS

Various preparation methods for Cyanopyridine derivatives have been reported. The common method used in the preparation of cyanopyridine is the condensation of chalcone or carbonyl compound with malononitrile and ammonium acetate by conventional heating between 5 to 12 hours in the presence of ethyl alcohol as a solvent.[9-21]

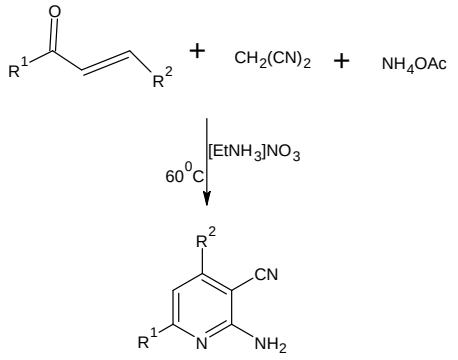


The same method was done by using microwave irradiation[22]or ultrasound irradiation[23-24]

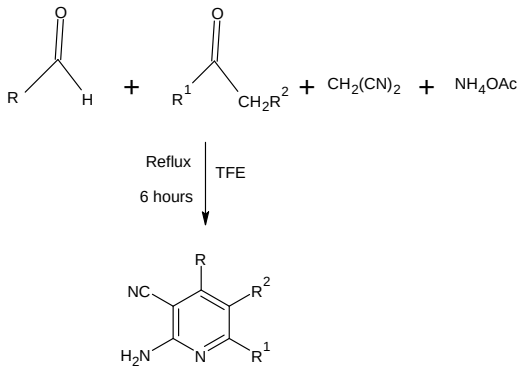
Cyano pyridine derivatives are also obtained by the condensation of chalcone derivatives with malononitrile and sodium Methoxide[25-26]



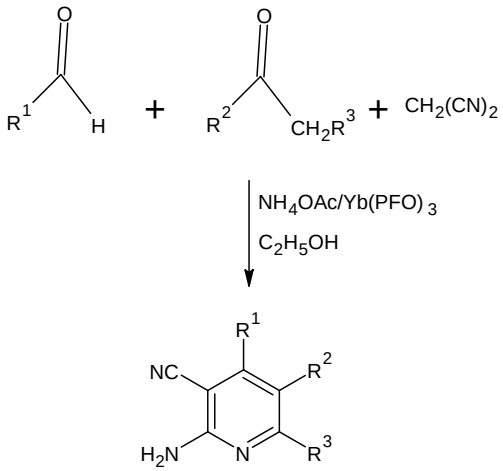
2-amino-3-cyanopyridine derivatives are prepared by the reaction of chalcone with malononitrile and ammonium acetate in presence of ethylammoniumnitrate at 60^0C. This process gives a good yield.[27]



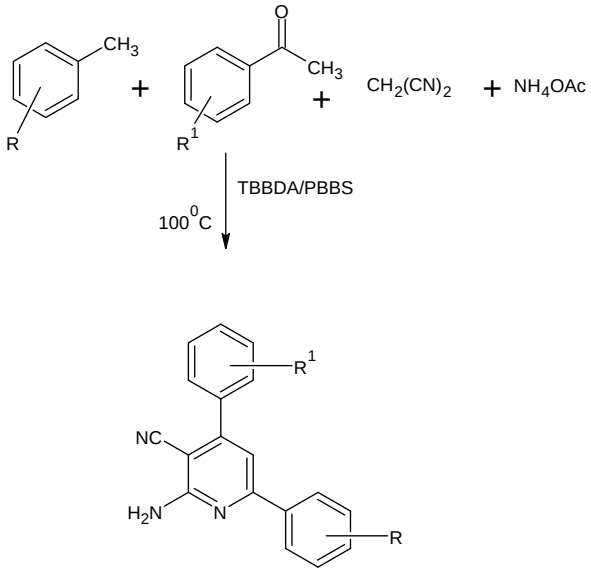
Khaksar S and Yaghoobi M have reported that Four-component condensation of benzaldehyde, acetophenone, malononitrile, and ammonium acetate in trifluoroethanol at refluxing temperature for 6 h results in the formation of 2-amino-3-cyanopyridine.[28]



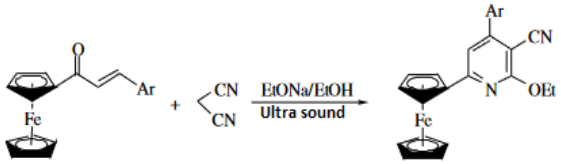
Tang J et al. reported the one-pot reaction for the synthesis of 2-amino-3-carbonitrile by taking a mixture of benzaldehyde, acetophenone, malononitrile, ammonium acetate, and of $Yb(PFO)_3$, in ethanol at refluxing temperature for 12 hours yielded the crude product in 92%.[29]



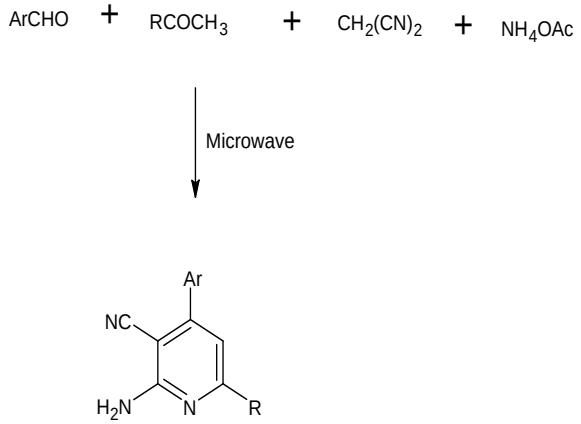
A mixture of aldehyde, substituted acetophenone, malononitrile, ammonium acetate and TBBDA (Tetra-bromobenzene-1, 3-disulfonamide) or PBBS (Poly(N-bromo-N-ethylbenzene-1,3-dis-ulfonamide)) was heated under stirring at 100^0C for appropriate time yields cyanopyridines.[30]



Shun-Jun Ji et al reported an efficient synthesis of ferrocenyl substituted 3-cyanopyridine derivatives under ultrasound irradiation A mixture of ferrocenyl-substituted chalcone and malononitrile in a freshly prepared sodium alkoxide solution was immersed into the water bath of an ultrasonic cleaner at 50–60 °C. At the end of the reaction, the solvent was removed under reduced pressure, then the residue was purified by column chromatography over a silica gel column using ethyl acetate–petroleum ether as eluent to give the products.[31]



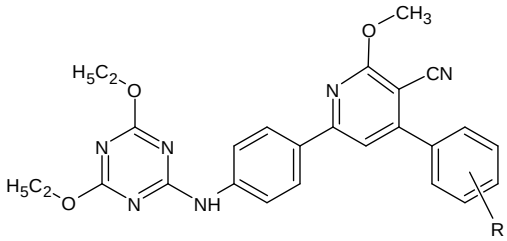
A series of 2-amino-3-cyanopyridine derivatives have been prepared by one-pot condensation from malononitrile, aromatic aldehyde, methyl ketone and ammonium acetate under microwave (the reactions were almost completed in 7-9 min.) irradiation without solvent. This method has the advantage of short routine, high yields (72-86%) and being environmental-friendly.[22]



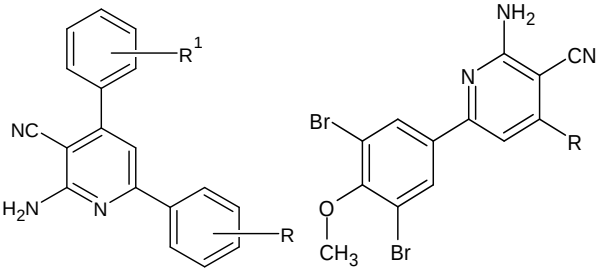
ACTIVITY

Antimicrobial activity[20]

Shantilal D. Rathod et al synthesised 6-(4-(4,6-diethoxy-1,3,5-triazin-2-ylamino)phenyl)-4-(substituted phenyl)-2-methoxypyridine -3-carbonitrile and tested for anti-bacterial activity using species E. coli, Salmonella typhi and Staphylococcus aureus by disc diffusion method using Penicilline as a standard drug and anti-fungal activity using species like Aspergillus niger, Aspergillus flavus, Penicillium chrysogenum by poison plate method using Griseofulvin as reference standard and DMSO as a control solvent. From the results of Anti-Bacterial and Anti-Fungal Activity; it can be concluded that compounds having chloro and Methoxy groups shows significant activity than other compounds They showed good anti-bacterial and anti-fungal activity.[25]

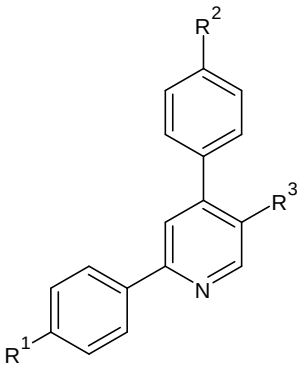


Vyas et al reported the synthesis of some new cyanopyridine derivatives and their screening against M. tuberculosis and other microorganism. Anti-tubercular data was compared to the rifampin. Antimicrobial activities of the compounds were compared with norfloxacin, griseofulvin, benzyl penicillin, amoxicillin and ampicillin against various bacterial strain, Bacillus subtillis, Bacillus megaterium, E. coli, Proteus Vulgaris, and Aspergillus niger. Few derivatives have shown promising Antimicrobial and Antitubercular activity.[16]

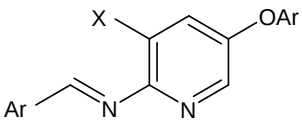


Bhaskar S. Dawane et al synthesized variety of 2-amino-3-cyano-4-aryl-6-(1-napthyl amino)-pyridines and were evaluated for their antibacterial activity by agar well diffusion method against gram-positive Bacillus subtilis, Staphylococcus aureus and gram-negative Escherichia coli and Proteus vulgaris bacteria species. The antibiotic tetracycline (25µg/mL) was used as reference antibacterial substance for comparison. Dimethyl sulphoxide (1%,DMSO) was used a control. The investigation of antibacterial screening data revealed that most of the compounds showed good zone of inhibition.[32]

A new series of Cyanopyridine derivatives were synthesized by T Rajkumar et al by condensing chalcones with malononitrile. The antitubercular and anthelmintic activities of all compounds were tested. From the result it is evident that these cyanopyridine derivatives have biological activities like Anthelmintic, and anti-tubercular and may be a pave for synthesis and characterization of some new derivatives.[14]



Bhatia et al synthesized a series of 5-substituted (arylmethylene) pyridin-2-amine by condensing various 5- substituted pyridyl-2-amines with various aromatic aldehydes. All the compounds were screened for their antibacterial activities. QSAR equation reveled that selected electronic, steric and liphophillic parameters have correlation with their antibacterial activity.[33]



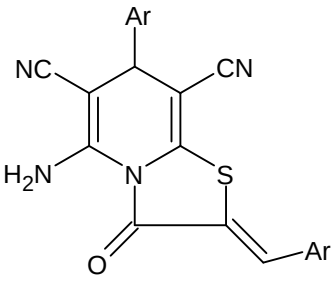
Some new 2-amino-6-(1H-benzimidazol -2-yl)-4- phenyl pyridine -3- carbonitriles have been synthesized and evaluated for antimicrobial activity against K. pneumonae, B. subtilis, E. coli and P. pseudomonas and for antifungal activity against C. albicans and A. niger. All the synthesized compound exhibited moderate antibacterial activities and significant antifungal activities.[34]

Anti-inflammatory activity

Kumar et al has reported eight derivatives of 2- amino-4,6- diphenylpyridine-3-carbonitrile and carried out anti-inflammatory screening in healthy rats using indomethacin as standard. Among them, three derivatives have shown potential anti-inflammatory activity.[35]

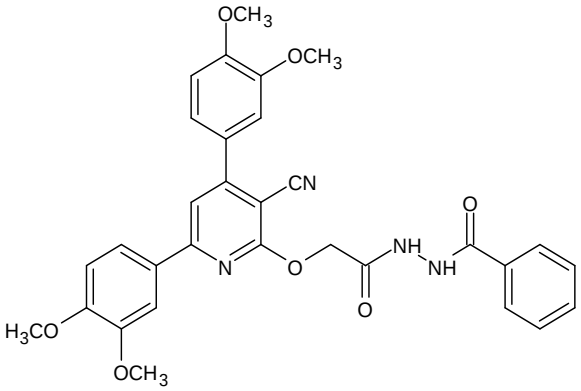
Antioxidant activity

Feng Shi et al synthesized thiazolo[3,2-a]pyridine derivatives, which scavenge free radicals.[36]



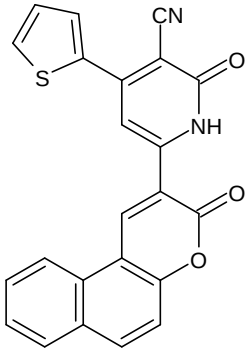
Anti Cancer activity

From the literatures, it has been discovered that 4,6-diaryl-3-cyano-2-pyridone derivatives are a highly effective type of anticancer agent with strong apoptotic properties. .N'-[2-(3-cyano-4,6-bis(3,4-dimethoxyphenyl) pyridin-2-yloxy) acetyl] benzohydrazide, was reported to inhibit the proliferation of MCF-7 cancer cells by inducing apoptosis and arresting the cell cycle at G1 phase via inhibition of CDK2 and CDK4.[37]

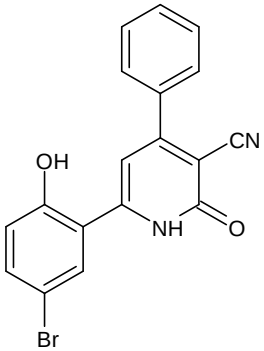


3-Cyano-4,6-diaryl-2-pyridone derivative possess anticancer activity due to its ability to act as surviving inhibitor, which is a unique member of the inhibitors of apoptosis.[38]

Two novel series of 3- cyano pyridine derivatives were designed as Pim-1 kinase inhibitors. These were tested for their anticancer properties against three different cancer cell lines: HepG2 (liver), HCT-116 (colon), and MCF-7 (breast). The majority of the compounds exhibited good to moderate anti-proliferative activity against HepG2 and HCT-116 cell lines, with only a few compounds demonstrating significant cytotoxic activity against MCF-7 cell line. In addition, the activity of their Pim-1 kinase inhibition was measured and their corresponding IC50 values were documented. 4-Thienyl-6-arylpyridone derivative showed potent antiproliferative activity with high PIM-1 kinase inhibitory activity with IC_{50} value of 0.94 μM, and it was founded to boost the levels of active caspase 3 and BAX and decrease the level of BCL2.[39]

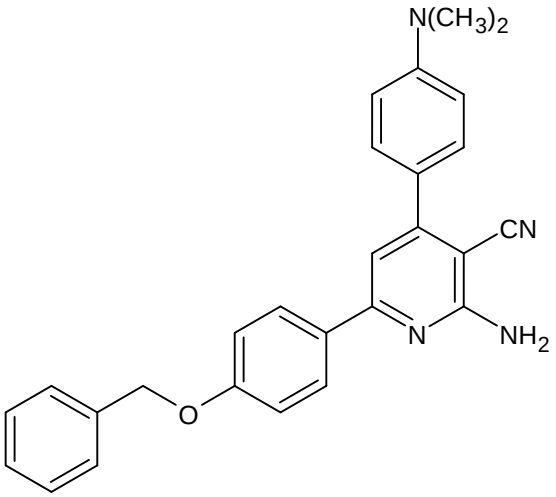


Cheney et al study at 2007, proved that some cyanopyridine derivatives also acted as PIM-1 kinase inhibitors with IC50 of 0.05 μM.[40]



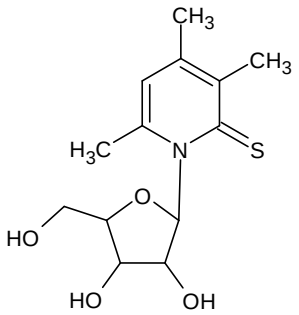
A novel series of cyanopyridines were designed and synthesized for antiproliferative evaluation. 2-Amino-6-(4-(benzyloxy)phenyl)-4-(4-(dimethylamino)phenyl) nicotinonitrile was the most potent inhibitor against the growth of PC-3, and HepG-2cancer cell lines with IC50 values of 2.04 uM (selectivity index, SI = 78.63, 43, respectively). It was safe against the growth of normal human diploid lung fibroblasts cell line (WI-38) with an IC50 value of 160.04 uM. Its analogs, were also active

against the growth of PC-3, and HepG-2 while against MCF-7 cell line, they displayed good cytotoxic activity compared to the reference standard 5-FU. Remarkably, mechanistic studies indicated that these compounds stimulated the level of active caspase 3 and boosted the BAX/BCL2 ratio 20- 95 folds in comparison to the control. Results have also indicated that these compounds exhibited a very potent inhibitory activity against PIM-1 kinase enzyme, where the IC50 values unraveled very potent molecules in the micromolar range (0.47 -1.27 uM). Further investigations have shown that they induced a cell cycle arrest at the G2/M hase.[41]



Antiviral activity:

Attia et al synthesized some pyridine ribosides, used for the treatment of HIV infection diseases. The 1-(β-D-ribofuranosyl)- pyridine-2-thiones (2) were found to be most active anti- HIV agents.[42]



Other activity

2-amino-3- cyanopyridine derivatives are known to have multiple biological activities, such as **A2A Adenosin receptor antagonist[4] IKK-β inhibitory activity**[3] aurora a kinase inhibitor[43] HIV-1 Integrase inhibitor activity[5] Herbicidal[44] anti-tumor properties[45] antiparkinsonism[46] and cardiotonic.

CONCLUSION

Cyanopyridines play an important role in the preparation of various compounds. In this review, we examined the synthesis procedures and biological significance of cyanopyridine derivatives. These derivatives have been found to possess important properties such as antimicrobial, antifungal, anti-inflammatory, antiviral, and anticancer effects, among others. One area of focus was drug development. It has been discovered that cyanopyridine has significant potential as a source for the creation of drugs that can provide clinical benefits with greater efficiency. Further exploration of its various derivatives may lead to the development of such drugs.

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