International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395-0056
Volume: 11 Issue: 06 | Jun 2024 www.irjet.net p-ISSN: 2395-0072

Recent Studies of Pyridine derivatives as an anticancer agent: Mini review

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Abstract- *The class of heterocyclic nitrogen compounds with the greatest biological activity includes cyanopyridine and pyridines, which are utilized in the development of anticancer drugs. These artificial sources are a powerful class of chemicals used in the treatment of idiopathic pulmonary fibrosis, pancreatic cancer, liver cancer, prostate cancer and, breast cancer among other cancers. The outcomes of recently published articles are compiled in this review. Important tests in the development of anticancer drugs, pyridine and cyanopyridine derivatives with their different anticancer properties are described, and their potential anticancer activity is proved in vitro, in vivo, or through in silico research. This study discusses recent developments in pyridine and cyanopyridine compounds, which are grabbing prospects for cancer therapy.*

Key Words: **Cancer, Tumor, Pyridine, Cells, Heterocyclic Compounds.**

1. INTRODUCTION

Prostate and breast cancer, which primarily affect men and women and have a high incidence and fatality rate, have affected the majority of people worldwide in this century. The most widespread cancer in the men is prostate cancer, which is tailed by lung cancer [1-3]. This growing tumor, which usually first appears in people over 50, is caused by aberrant cells found in the prostate tissue. It can spread to surrounding tissues, lymph nodes, and even bones if left untreated. Similarly, aside from skin cancer, breast cancer is also the highest frequent cancer in females [4-6]. Current therapeutic approaches include radiation, chemotherapy, and surgery; nevertheless, these drugs have drawbacks and side effects. Thus, it is crucial to continue studying and creating novel small-molecule medications to treat prostate cancer. Numerous small-molecule medications have demonstrated therapeutic benefits in the medication of breast and prostate cancer in recent years [7]. In order to support the development of more potent and cutting-edge medications for the efficient control of prostate and breast cancer, this study purposes to deliver a thorough analysis of the clinical applications and synthetic techniques of numerous noteworthy small molecule drugs that have been approved to treat these two cancers.

Finding novel compounds for the treatment of cancer is an enticing prospect thanks to heterocyclic blocks containing heteroatoms. Systematically, heterocycles, or compounds comprising a heterocycle molecule, account for roughly 85% of all molecules exhibiting biological activity. Most often, the involved structures of heterocycles have nitrogen as a backbone. These attributes are highlighting the critical role that heterocycles play in the discovery and design of novel drugs [8]. The most common forms of heterocyclic compounds containing nitrogen are found in antibiotics, vitamins, and hormones.

N-containing heterocycles make up 60% of small molecular medications, according to FDA databases, demonstrating the structural significance of the nitrogen-bearing heterocyclic molecules in therapeutic innovation and development. The nitrogen atoms of heterocyclic compounds are easily bound to DNA by hydrogen bonding. The N atom's hydrogen bonding affinity for DNA is the source of the anticancer or antitumor action. Moreover, pyridine derivatives and cyanopyridine serve as prospective anti-cancer drugs in the field of anti-cancer research. A multitude of biological activities, including the development of cancer, have been connected to these cyanopyridine and pyridine backbone configurations. Current medical research has focused a great deal of interest on pyridine and cyanopyridine derivatives because of their potential to treat a number of malignant illnesses, including myeloid leukemia, idiopathic pulmonary fibrosis, prostate cancer, and breast cancer [10]. Among the authorized medications having pyridine moiety are Sorafenib, Vismodegib, Crizotinib, and Regorafenib.

The pharmacological and therapeutic qualities of pyridine and its derivatives have led to their development and a significant space in synthetic organic chemistry. There are already over 7,000 medications with pyridine as their main ingredient. In contrast, it is anticipated that compounds related to agriculture and pharmaceuticals will require

cyanopyridine derivatives [11-13]. Cyanopyridines are deeply involved in effective treatment for a vast collection of illnesses. Many remarkable biological properties, like antifungal, anticancer, and antifungal activity, antimicrobial activity, were produced by cyanopyridine derivatives. This review highlights the potential of pyridine and cyanopyridine derivatives in the development of anticancer medicines by summarizing the findings of several studies on these compounds [14].

1.1 Pyridine as an anticancer agent

Pyridines belong to a class of nitrogenous heterocycles that can be synthesized using various methods to produce new compounds with anticancer and antitumor characteristics. Many synthetic medications work incredibly well as chemotherapeutics. Pyridines are a type of heterocycles carrying nitrogen that can be synthesized by a variety of methods to produce new compounds with anticancer and antitumor characteristics [15]. On the other hand, numerous artificial derivatives are ready for the pyridines.

Al-Majid et al. (2019) synthesized N,N'-malonamide derivatives via Michael addition reaction shows various anticancer activities. The synthesized compounds tested against certain cancer cell lines, with, MCF-7, SAS, MDA-MB-231, PC-3, HuH-7, HepG2 and CT-116 cells Thirteen derivatives were described, and six of these compounds shown remarkable anticancer activity toward MDA-MB-231 ([IC50 = 5 ± 0.5 μM], IC50 = 5 ± 0.25 μM, , [IC50 = 7 ± 1.12 μM], [IC50 = 45 ± 3 μM]), and [IC50 = 18 ± 0.87 μM]. The substituted chloropyridine and p-trifluoromethylphenyl demonstrated considerable toxicity (IC50 = 4.5 ± 0.3 μM) in contradiction of Huh7 cells from liver tumor and effective influence (IC50 = 6 ± 0.78 μM) compared to HCT116 human colorectal cancer cells. Al-Majid et al. (2019) used OpenEye Modeling to carry out successful molecular docking investigations.

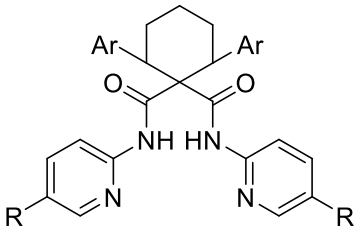

Fig.1 N,N'-malonamide derivatives

Using the MTT colorimetric assay and using standard reference of etoposide drug, Sharmila Rani et al. (2021) described the combination of a novel series of amide containing imidazo[1,2-a]pyridine products and the anticancer activities against breast cancer cell lines (MDAMB 231 and MCF7), prostate cancer cell lines (DU 145) and lung cancer cell lines (A549). The compounds containing 0.021 ± 0.0012 μM, 0.091 ± 0.0053 μM, 0.24 ± 0.032 μM, and 0.95 ± 0.039 μM, IC50 values correspondingly, demonstrated the maximum efficacy in antitumour behaviour hostile to DU 145, MCF-7, A549, and MDA-MB-231 cell lines. These compounds were functionalized with imidazo[1,2-a] pyridine derivatives.

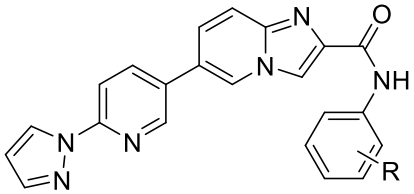

Fig. 2 Amide functionalized imidazo[1,2-a] pyridine derivatives

El-Naggar et al. (2018) created effective anticancer drugs using compounds of pyridine and urea. The compounds based on pyridine-urea were assessed in vitro for their ability to suppress the proliferation of the breast cancer cell line (MCF 7). The furthermost active congeners against MCF-7 cells were compounds containing -Cl, -CF3, and -OCH3 (IC50 value is 1.88 μM 0.22 and after 48 h therapy, 0.80 μM and 0.11 after 72 h treatment, correspondingly), by higher activity when associated to the reference drug doxorubicin (IC50 value is 1.93 μM) medication.

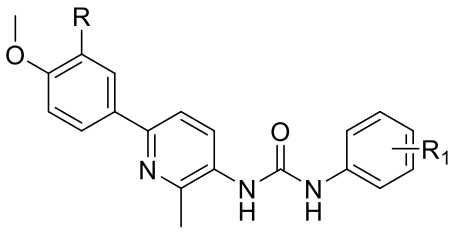

Fig. 3 Pyridine-urea derivatives

The fusion complexes of pyridine-coumarin/attached pyridine was developed and produced by Fayed et al. (2019). They were experimented against the human being cancer cell lines HepG 2, HCT 116, A549, and MCF 7, to determine their anticancer activities. Methyl, pyridine, and cyano substituted compounds exhibited the extremely growing repressive effects critical of the MCF 7 cell line, with IC50 values ranging from 1.1 to 2.4 μM. These substances caused cell cycle detention in the G2/M stage, followed by the apoptotic cell death, according to flow cytometric examination. The caspase 3 activity in the MCF 7 cells also been confirmed these results by means of testing.

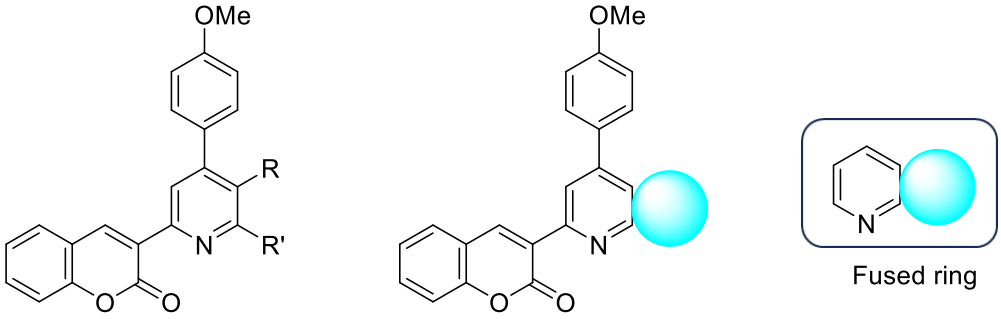

Fig. 4 Coumarin-pyridine/fused pyridine hybrid derivatives

Kutlu and colleagues [Kutlu et al. (2022)] produced a new series of platinum complexes with pyridine derivatives, and they also examined their anticancer effectiveness in contradiction of human cancer cell lines. The IC 50 values for the amine- and fluorine-substituted pyridine platinum complexes were determined to be 52.45 μM and 25.79 μM, respectively. The most likely molecular structure for the most stable complexes was identified by Kutlu and associates. Finding the most likely molecular structure for the most stable compounds using the DFT/MPW1PW91 technique with LanL2DZ basis. Calculations were also performed for the molecule lowest occupied molecular orbital, electrostatic potential, and highest occupied molecular orbital. Using a combination DTA/TG system, the complexes' thermal breakdown processes were examined. The FWO and KAS methods were used to calculate the decomposition kinetics.

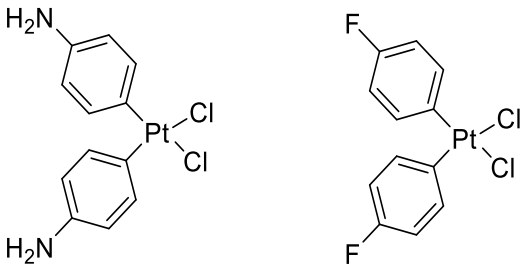

Fig. 5 Pyridine derivative platinum complexes

Naphthalene and furan moieties were found in pyridine derivatives reported by Ahmed et al. (2019). The anti-proliferative properties of each newly synthesized chemical were examined in vitro in contradiction of the HePG 2 and MCF7 cell lines. When compared to the common medication doxorubicin, the compounds showed a promising growth inhibitory effect on the two cell lines. Cyanoamine derivatives demonstrated a positive effect on MCF-7 (IC50 = 5.52 ± 0.3) and HePG-2 (IC50 =

6.93 ± 0.4). An imimine derivative exhibited remarkable cytotoxic properties against MCF-7 (IC50 = 7.26 ± 0.8) and HePG-2 (IC50 = 8.98 ± 0.9).

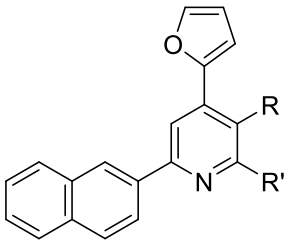

Fig. 6 Pyridine derivatives bearing naphthalene and furan moieties

In 2019, Abdallah et al. reported by means of multi component reactions (MCR), in basic conditions containing a variety of aromatic aldehydes, amino tetrahydro benzo thiophene derivatives reacted with various active methylene reagents, like ethyl malononitrile and cyanoacetate to prepare and illustrate thiazole and thiazole pyridine derivatives. Additionally, the purpose of this study is to assess the synthetic compounds' in vitro cytotoxic activity in contradiction of cancer cell lines. Altogether the synthesized compounds showed significant activity when related to the standard drug. When applied to the six cancer cell lines, several pyrano thiazole and thiazolo[4,5-b] compounds exhibited the strongest anticancer activity. Furthermost effective (IC50 > 10μM) at inhibiting Pim-1 activity were amine and cyano derivatives, with IC50 range of 0.39 and 0.26μM, correspondingly. In the assay, SGI1776 was utilized as a optimistic control, with an IC50 of 0.048μM.

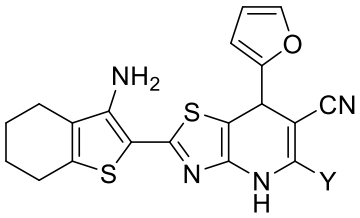

Fig. 7 Pyran thiazole & thiazole pyridine products

According to Altay et al. (2019), $Ag_2(\mu\text{-mef})_2(2\text{-pymet})_2$ is one of two Ag(I) complexes. $[Ag_2(\mu\text{-mef})_2(2\text{-pyet})_2]$, Using elemental, SCXRD, FT-IR, thermal, and analytical methods, 2-pyridinemethanol, 2-pyridineethanol, and mefenamic acid were synthesized and characterized. While mefenamic acid complex was produced as a microcrystalline powder, 2-pyridineethanol complex was created as a single crystal. There is a binuclear structure in complex 1. The small Ag-Ag distance (2.8710(10) Å) between silver(I) ions causes the argentophilic interaction. The binuclear metal core is formed by a carboxylato oxygen-bridge connecting two Ag(I) centers. The comparable structures of both complexes were verified by thermal analysis investigations and FT-IR spectra. The two complexes' in vitro antiproliferative activity was assessed in contradiction of the cancer cell lines HepG2, HT29, and MCF7. Using flow cytometry analysis, intracellular ROS production and the apoptotic effects from both compounds was examined in the MCF7 cell line. Both complexes demonstrated considerable antiproliferative activity with stronger selectivity for cancer cells other than the normal cells, according to the results of the XTT and LDH experiments. Furthermore, the assay using Annexin V and propidium iodide demonstrated that the amount of apoptotic cells in MCF7 cells rose as Ag(I) complex concentrations increased. Additionally, both complexes significantly improved the synthesis of reactive oxygen species (ROS) in MCF7 cells, indicating a potential prooxidant function of the newly produced Ag(I) complexes. When combined, these results offer strong evidence for the potential value of Ag(I) complexes as innovative anticancer medicines in contradiction of various forms of carcinogenesis.

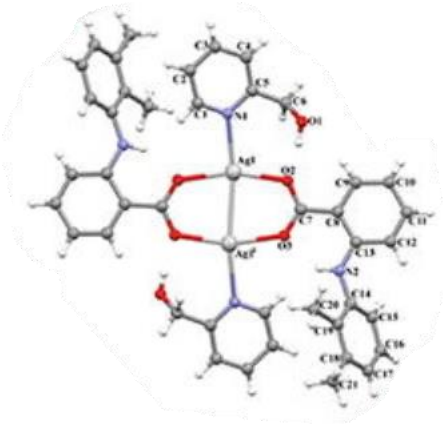

Fig. 8 Single crystal XRD structure of Ag(I) complexe

2019's Gangireddy et al. created, manufactured, and assessed the in vitro cytotoxicity of a quantity of new imidazole pyridine derivatives. Compounds containing fluorine, such as 2-fluorophenyl Methanone, pyridinyl imidazo pyridinyl) piperazine derivative, and (3-fluorophenyl). The effective cytotoxic profile of pyridinyl imidazo pyridinyl) piperazine derivative was observed against MDA MB231, HeLa, and HepG2. Comparing complexes (IC50 value is 0.8 μM) and (IC50 value is 3.5 μM) against HeLa, they were shown to be more potent than the control complex Paclitaxel (IC50 value is 2.8 μM). Comparing Compound 7h to Paclitaxel (IC50= 0.56 μM; IC50= 1.9 μM, HepG2, MDAMB-231) it was also discovered to be effective against MDAMB-231 (IC50= 6.9 μM) and HepG2 (IC50 value is 2.0 μM) correspondingly. It was also discovered that compound 7e was effective opposed to HepG2 (IC50 value is 9.8 μM) cell lines. In comparison to reported imidazole pyrimidine derivatives, synthesized piperazine substituted pyridine derivatives (IC50 value is 3.5μM) and (IC50 value is 5.8 μM) demonstrated 1.8-fold and 1.4-fold rise in anti-proliferative activity. Against Hela cell lines, imidazole pyrimidine diazepanyl methanone (IC50 value is 6.54 μM) and Fluorophenyl imidazole methanone (10f, IC50 value is 6.12 μM) were tested. The proposed complexes were able to attach with several targets, as evidenced by molecular docking studies showing that they occupied the active sites of the colchicine and estrogen receptor. These compounds' biological activity suggests that they may be used in treatment protocols.

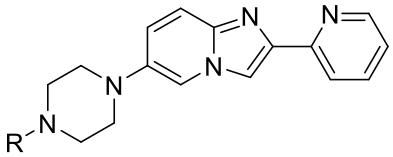

Fig. 9 Pyrano thiazole and thiazolo pyridine derivatives

Ya-Ling Song et al. (2019) demonstrated the antitumor effectiveness of steroidal pyridine derivatives using molecular docking. Several steroidal pyridine derivatives were synthesized using molecular docking software, with a steroid serving as the carrier nucleus and a pyridine heterocycle acting as a pharmacophore on the D-ring. These compounds were then investigated for their potential anticancer effects. The substances were investigated as potential anticancer medicines after being created as small molecule inhibitors. The molecule was created using a single-pot multi-component synthesis, and the in vitro anticancer activity of the resultant compounds was assessed. Prior to treatment, four cancer cell lines that were naturally developing were employed. Out of all the substances that were tested for anticancer activity. The treated cells' morphology showed the most noticeable modifications, according to reports. The corresponding IC50 values for hepg2, skov3, mcf-7, hela, and 12.39 ± 0.14 μM, 5.088 ± 0.05 μM, and 8.81 ± 0.25 μM, respectively, were as follows. In the same way, the values for mcf-7, epg2, hepg2, skov3, and epg2 were 8.457 ± 0.14 μM, 13.84 ± 1.04 μM, 7.025 ± 0.33 μM, and 6.283 ± 0.12 μM accordingly.

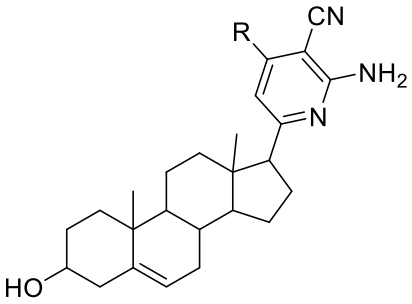

Fig. 10 Steroidal pyridine derivatives

The antitumor efficacy of new pyridine derivatives based on diphenyl ether was reported by Verma et al. (2019). HepG2, A549, and Vero cell lines were used as test subjects to create a variety of distinct 2-amino substituted phenyl nicotinonitriles. The two compounds that showed the greatest activity against the A-549 cell line among those that were examined were -OH substituted diphenyl ether-based pyridine (IC50 16.74±0.45 μM) and -OCH3 substituted diphenyl ether-based pyridine (IC50 10.57±0.54 μM). The 3b- and 3p-induced apoptosis has been further investigated by DNA fragmentation analysis and the AO/EB (ethidium bromide /acridine orange) nuclear staining methodology. Using this method of staining A-549 cells, it was possible to see that the cells treated with -OH and -OCH_3 substituted diphenyl ether-based pyridine had undergone morphological changes that indicated a decrease in cell viability and the beginning of apoptosis. Observations of DNA fragmentation into nucleosomes provided additional evidence that compound 3b-treated cells had undergone cell death. The G2/M phase cell cycle arrest that compound 3b-treated A549 cells underwent was confirmed by flow cytometry studies. Further in in silico investigations verified the medications' in vitro anticancer efficacy, as demonstrated by dock score and binding energy values.

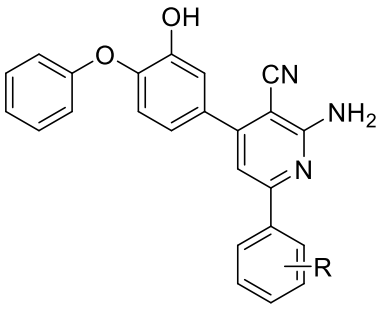

Fig. 11 Diphenyl ether-based pyridine derivatives

Conclusion

Over the past two decades pyridine core molecules plays a vital role in the anti-tumour pharmacopeia field. More than 80% of anti-cancer drugs are based on pyridine core moiety. In the design and synthesis of anticancer drugs the pyridine substituted molecules is getting more fascination to the scientist because of its biological properties. In this review anticancer activity of some of the pyridine derivatives successfully reported.

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