Review Article

A Systemic Review on Pyridine Derivative Against Cancer and Tumor Cell-Line

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Received: 10-05-2023; **Revised:** 20-07-2023; **Accepted:** 26-07-2023; **Published on:** 15-08-2023.

ABSTRACT

Heterocyclic chemistry is a most important part in organic chemistry. Heterocyclic system containing one or more than one heteroatom like oxygen, sulphur, nitrogen etc. Pyridine is an important example of six-membered heterocyclics consist of five carbon atom and one nitrogen atom. It is unsaturated in nature due to presence of double bond in the ring system. It occupies a major position as a source of clinically useful agent in the field of medical research. Pyridine moiety is present in many drugs like antimicrobial agent, antiviral agent, anti-malarial agent etc. It has potent anti- tumour and anti-cancer property and used in the treatment of myeloid leukaemia, liver cancer, breast cancer etc.

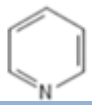
Keywords: Heterocyclic system, Pyridine, medical research, anti-tumour, anti-cancer, leukaemia.

INTRODUCTION

Cancer, may described as a harmful disease in which some abnormal cells grow uncontrollably, have ability to spread and destroy normal body tissue. It is most harmful health problem and cause of mortality throughout the world after cardio vascular disease[1].Till now this one of the most challenging and complex disease to treat infront of the whole world[2,3]. Each and every day a large number of cancer cases are diagnosed. Among them the number of lung cancer is highly identified. In female breast cancer is the most notable cause of death due to cancer[4,5]. The number of stomach and colorectal cancer is also high.

Pyridine is a most significant heterocyclic compound which is basic in nature and exhibit a wide range of medicinal activities. In new medical era pyridine plays a principal role in anti-cancer activity with diverse biological activities[6,7]. Some example molecules approved as anti-cancer properties are vismodegib III, crizotinib IV, sorafenib I [8,9,10].

Table 1: Properties of Pyridine[11,12,13]

Structure	
Molecular formula	C_5H_5N
Molar mass	79.10 g mol^{-1}
Appearance	Colourless Liquid
Density	0.9819 g/cm^3
Boiling point	115.2° C
Melting point	-41.6° C
solubility	Miscible in water
Vapour pressure	18 mm Hg
Refractive index	1.5093
viscosity	0.88cP
Dipole moment	2.2 D

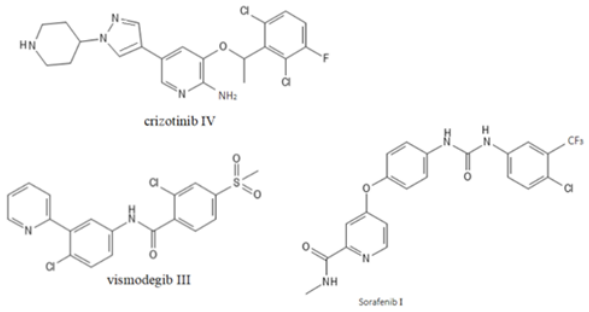


Figure 1: Molecules approved as anti-cancer properties

Pyridine derivatives as anticancer and anti- tumour agent[18]

A large number of synthetic drugs are available as chemotherapeutic agents. Many novel compounds or derivatives which show their anticancer and anti-tumour properties which are synthesized from Pyridine.

- **Pyridine derivatives in cell cycle management:**

Some newly synthesized drugs show a variety of medicinal properties. Such of this are show cytotoxic action for malignant cell lines like HCT-15 (human colon cancer cell line), NCL-H460 (hypotriploid human cell line), HT-29(colon adenocarcinoma cell line), A549 (lung carcinoma). 11-(1-Benzyl-1H-indol-3-y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoline show cytotoxic action over A549 (lung cancer cell line) and it is a potent anti-cancer agent also. Some fused pyridine derivatives are exhibiting anti-cancer activity over cancer cell line. N-hydroxy-5-(2-(2-phenylbutanoyl)amino)pyridyl)acrylami is highly effective against leukemia cells and also displayed anti-proliferative activity[18,19].

- **Pyridine derivatives with anti-tumorigenic action:**

A wide range of Pyridine derivatives show anti-tumorigenic action over cell lines HepG-2, MCF-7. Picolinamide

derivatives acquiring dithiocarbamate and urea moieties are VEGFR-2 kinase inhibitors and also displayed action over malignant cell lines from different sources i.e., HT-29 (human colorectal adenocarcinoma cell line), panc-1 (human pancreatic cancer cell line). In-vitro test of some Pyridine and fused pyridine derivatives exhibit their anti-tumorigenic action over HepG 2(hepatoma) and MCF-7 (breast cancer cell line)[19,20].

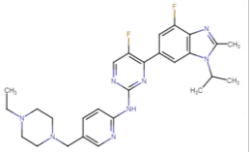
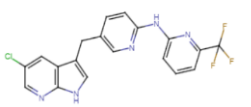
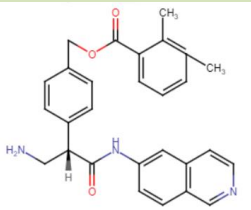
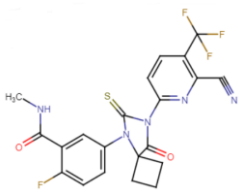
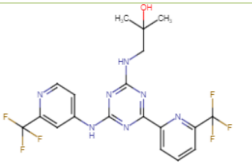
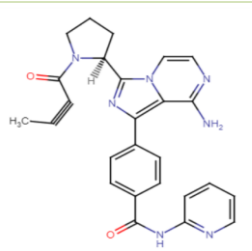
• Synthetic pyridine derivatives show cytotoxicity:

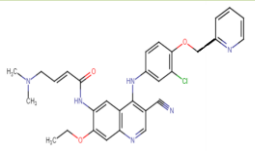
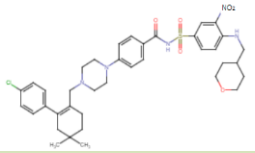
Chalcone linked thiazole-imidazopyridine analogues examined anti-cancer action over some cell line in human like prostate carcinoma, breast carcinoma. Cyanopyridines, pyridopyrazolotriazines are potent against HepG -2 (liver cancer cell line), A-549(lung cancer cell line)[21].

Table 2: Synthetic pyridine derivatives and their anticancer activity[14-17]

Compound	*In vitro* studies	Possible target
Thieno [2,3-b] pyridine analogoues	Anti-tumor activity	Human topoisomerase IIα Targeting ATP binding site VEGFR-2 kinase inhibitors
Pyridine and fused pyridine derivatives	Anti-tumor action	Human topoisomerase IIα Targeting ATP binding site VEGFR-2 kinase inhibitors
Picolinamide derivatives acquiring dithiocarbamate and urea moieties	Anti-tumor action	Human topoisomerase IIα Targeting ATP binding site VEGFR-2 kinase inhibitors
Aza-analogues like the regioisomers from the N-hydroxy-3-(4-(2-phenyl butanoyl)amino)phenyl) acrylamide comprising pyridine nucleus	G_2 stage inhibitor	HDACs
Pyridine-chalcone analogue	G2 /M stage inhibitor, anticancer	Anti-tubulin compound
Pyrazolo[3,4-b]pyridine-bridged derivatives of combretastatin A-4 acquiring 3,4,5-trimethoxylphenyl groups	Anti-proliferative action	Tubulin polymerization inhibitor
Chalcone linked thiazole-imidazopyridine analogues library	cytotoxicity	—
Cyanopyridines, pyridopyrazolotriazines and pyridopyrazolopyrimidines	cytotoxicity	—
11-(1-Benzyl-1H-indol-3-y1)-2, 3, 4, 11-tetrahydro-1H-pyrido[2,1-b] quinazoline	Cytotoxic, anti-clonogenic; G0/G1 cell cycle phase inhibitor	EGFR kinase

Table 3: List of some anti-cancer drugs containing pyridine[22]

Sl no	Drug	Target	Structure
1	Abemaciclib	Kinase inhibitor	
2	Pexidartinib	Kinase inhibitor	
3	Netarsudil	Rho Kinase inhibitor	
4	Apalutamide	Androgen receptor inhibitor	
5	Enasidenib	IDH2 inhibitor	
6	Acalabrutinib	Kinase inhibitor	

7	Neratinib	Kinase inhibitor	
8	Venetoclax	BCL-2 inhibitor	

Kinase Inhibitors

Kinase inhibitors plays a vital role in the treatment of cancer. Kinases are one kind of enzyme which helps to transfer a phosphate group to a protein. Some recent advance studies elucidated a critical role of kinase in the metastases of various cancer cells. Abemaciclib, Neratinib are kinase inhibitor[23,24]. Kinase helps in control some important functions like cell division, metabolism etc. In some cancer cells, certain kinases are much active. By inhibiting kinase, the growth of certain cancer cells may decrease. They also inhibit the growth of new blood vessels that tumors need to grow[25].

A series of imidazo[1,2-a]pyridine derivatives was designed and estimated by Yu et al. which is effective for tumor therapy[26].

pyridine-pyrazole-benzenethiourea and pyridine-pyrazole-benzenesulfonamide moiety plays a vital role in advanced cancer treatment for their inhibitory effect on pyrophosphatase /phosphodiesterase and ENPP3 isoenzymes[27].

Androgen receptor (AR) inhibitor

Apalutamide, enzalutamide are example of androgen receptor antagonist. Androgen receptor exist in family of steroid hormone receptor. Androgen mainly produced in testes and also by adrenal glands. AR stimulate the development of prostate cancer and metastasis by modulating the expression of gene involve in growth of tumor cells[28,29].

Steroidal pyridine derivatives evaluated for their anti-proliferative action against cancer cell lines. They inhibit the apoptosis of prostate cancer cell via mitochondria-mediated apoptotic pathway. SARs analyse displayed that extra pyridine ring at para position (figure-2) plays good activity against cancer cells, prostate cancer cell line (PC-3)[30].

B-cell lymphoma 2 (bcl-2) inhibitors

Apoptosis is a process of cell suicide (programmed cell death). It plays vital role in many physiological and pathological process like elimination of unnecessary or damaged cell to protect organs from destruction.BCL-2 is a protein which is responsible for regulation of cell death[31]. Many studied examined that blockage of apoptosis is a critical carcinogenic procedure. Over expression of BCL-2 is a common outcome of lymphomas and leukemia. So, for the treatment of hematological carcinoma a large number of antagonists of anti-apoptotic BCL-2 have been improved[32,33].

A series of Hydroxypyrazoline and Oxadiazole derivatives exhibit remarkable anticancer and antiproliferative action. They reduce the growth of human breast cancer cell line (MDA-MB-231) and human colorectal adenocarcinoma cell line (HT-29). They are the inhibitor of cyclic-dependent kinase 2/cell division kinase 2 (CDK2) which is an enzyme encoded by CDK2 gene[34,35].Nesapidil is a derivative of Oxadiazole with antiproliferative property[36](Figure-2).

Novel 3-cyanopyridine derivatives was assessed for their targeting surviving and cytotoxic action against cancer cell lines prostate cancer(PC-3), breast cancer(MDA-MB-231). Some derivatives show cytotoxicity against cancer cell lines more effective than 5-FU which is a standard anticancer drug[37].

Cytochromes P450 (cyps) inhibition

Cytochromes P450 is a superfamily of hemoprotein which plays a vital role in metabolism of endogenic compounds and detoxification of xenobiotics. It is mainly takes part in oxidation reaction of phase 1 biotransformation reaction [38]. 18 CYP gene families along with 50 enzymes are found in human[39]. 50% of clinically used drugs metabolized by CYP3A4 and CYP2D6[40].

Several studies described the enzyme inhibition and anticancer action of 3-substituted 1H-pyrrole[2,3-b]pyridine derivative. Some of them show moderate action against such subtype of cytochrome P450[41].

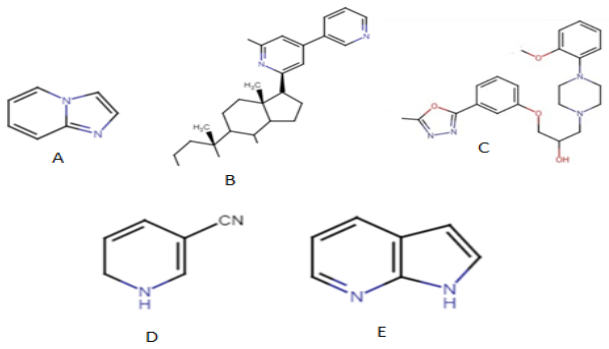


Figure -2

A: Structure of imidazo[1,2-a]pyridine , **B**: Structure of Steroidal pyridine derivative,

C: Structure of nesapidil, **D**: Structure of 3-cyanopyridine scaffold, **E**: Structure of 1H-pyrrole[2,3-b]pyridine scaffold.

A novel class of hetero steroids are potent and exhibit cytotoxicity against liver cancer cell line (HepG2 and Huh-7) and A549 cell line[42]. Moreover, molecular simulation further reveals the action of tested compounds against four proteins CDK2, CYP19, janus kinase 2 and BCL2 which highly concerned with cancer regulation.

Aldo-keto reductase (akr) inhibitors:

Aldo-keto reductases are group of NAD(P)H dependent protein enzymes which present in wide range of

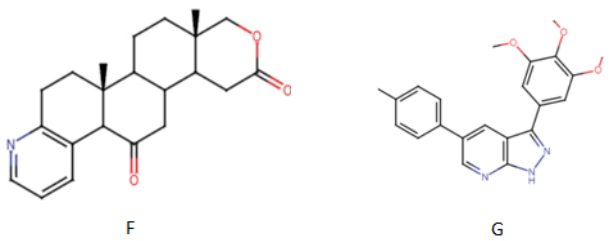
organisms[43]. Some of them demonstrate multiple functions like reduction of steroid double bond and carbonyl group [44]. It consists of various genes among them AKR1C4 and AKR1C3 mostly involve in liver and prostate cancer. AKR1C2 identified in colorectal cancer, breast cancer [45,46].

A ring pyridine fused androstanes in 17a-homo-17-oxa (D-homo lactone), 17 α-picolyl or 17(E)-picolinylidene synthesized for their action as anti-tumor agent against human cancer cell line[47]. Sar study explained that fusion of pyridine at 3 and 4 position of a ring profoundly enhance the affinity of 17 α-picolyl for CYP 17 while rovidingselective anti- proliferative property against prostate cancer cell (PC-3). Fusion of andopyridine to the D-homo lactone androstanes results a potent starting component for the synthesis of a new inhibitor of AKR1C3. One a pyridine fused D- lactone steroid(figure-3) shows selective anti-proliferative action against HT-29 human colon cancer cell lines[48].

Tubulin polymerization inhibitors:

Tubulin is an important protein which plays vital role in maintaining cellular function and facilitating cell growth, cell division[49]. The drugs which disturb the dynamics of microtubule are mainly used in chemotherapy [50,51]. Microtubules are made up of alpha and beta tubulin heterodimers [(52)]. Microtubule targeting agents interact with tubulin via different binding sites like vinca alkaloid, colchicine, laulimalide, taxane[53]. By disturbing the dynamics of microtubule, they block the cell cycle which results cell death[54,55].

Twenty-six novel pyrazolo[3,4-b]pyridine-bridged analogues of combretastatin A-4 possessing 3,4,5-trimethoxyphenyl groups , were evaluated for their tubulin polymerization inhibition action and antiproliferative activity[56,57]. Some of them exhibit significant effect against MCF-7,MDA-MB-231(human breast cancer cell line), HeLa and Kysel150 (esophegeal squamous carcinoma cell lline).



F G

Figure-3

F: pyridine fused D- lactone steroid, G: Pyrazolo[3,4-b] pyridine as tubulin polymerization inhibitor

α, β unsaturated chalcone moieties and quinoline plays a vital and important role as potent anticancer agent[58]. α, β unsaturated chalcone moieties are mainly the precursors of isoflavonoid and flavonoid based components[59]. Chalcones is a precursor of various heterocyclic compounds i.e. pyrazoles, pyrimidine, imidazoles[60,61,62]. Chalcones show various biological activity anti-tumor activity[63-66], anti-tuberculosis[67], analgesic[68], HDAC inhibitors[69], tubulin inhibitior. Some naturally occurring chalcones are plays significant role in medical research. Some of them are butein[70] (anti-cancer agent), cardamonin[71], isoliquirtigenin[72] (anti-cancer, anti-inflammatory), sappanchaclone[73] (anti-inflammatory).

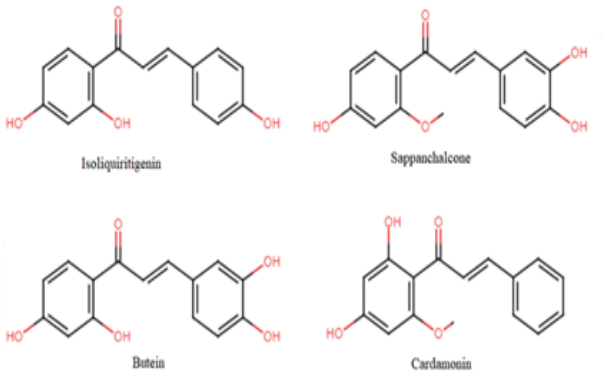


Figure 4: Some naturally occurring chalcones as anti-cancer agent

Quinoline is a N-based heterocyclic compound which is biologically active. Quinoline moieties exhibit a variety of activity like anti-HIV[74], anti- inflammatory [75], antibiotic[76]. Moreover, it an important anticancer drug which is available in market[77,78][Figure -5].

Some molecules which containing quinoline are under clinical trial [78,79] [Figure -5] Quinoline derivatives mainly inhibit tubulin polymerization[80,81,82], arrest cell cycle, induce apoptosis.

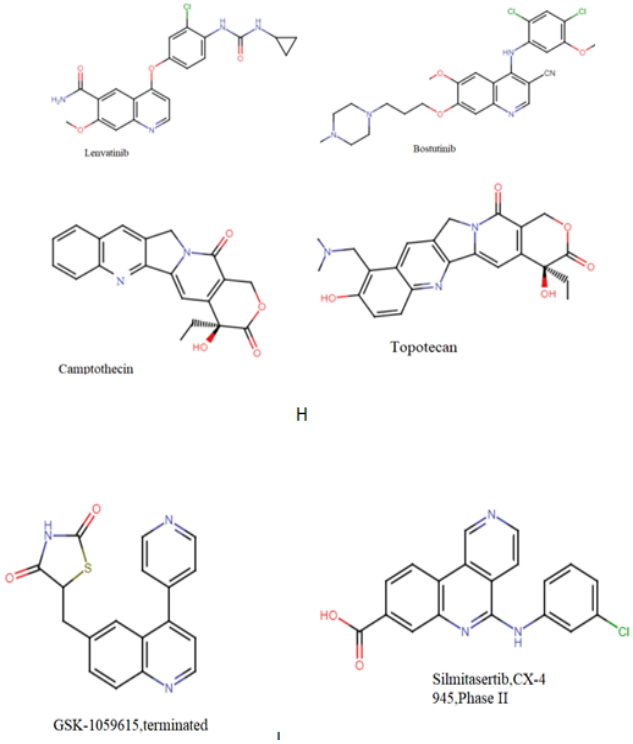


Figure -5

H: Quinoline containing marketed anticancer drug, **I**: Quinoline containing anticancer agents under clinical trials

CONCLUSION

Cancer is now a too much vital and challenging disease infront of the whole world. Though many chemotherapeutic agents are used in the treatment of this disease, the mortality rate increased daily. Many research works is going on for the invention of new drug molecules for healing the disease. Pyridine moiety is one of the most important compounds which is used as anticancer and anti-tumorigenic agent. The above study discussed about different Pyridine derivatives and their role in the field of pharmaceutical and medical science for the treatment of this fatal disease.

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.