Chapter

Anticancer Functions of Pyridine Heterocycles

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Abstract

Pyridine is a heterocyclic molecule with a nitrogen atom that is often found in nature. As a prosthetic group taking part in redox processes in the biological system, it plays an important function in many enzymes of the living system. Pyridine is an important pharmacophore, a privileged scaffold, and a superior heterocyclic system in drug development, with various applications in anticancer research because of its ability to work on significant receptors. Typically, it is the core of several currently available medicines. In the fight against cancer, many pyridine derivatives have been shown to inhibit kinases, androgen receptors, tubulin polymerization, topoisomerase enzyme, human carbonic anhydrase, and several other targets. Researchers are now concentrating on developing pyridine novel entities with other moieties for cancer therapy. This section presents pyridine derivative synthesis and biological expansions, as well as their target receptor sites.

Keywords: synthesis, leukemia, tumor, anticancer, *N*-containing heterocycles, pyridine

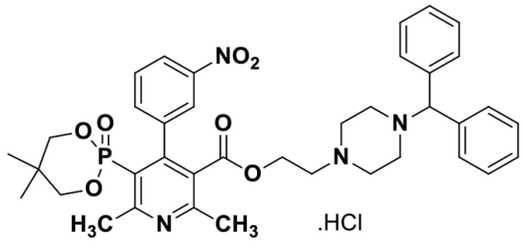
1. Introduction

The name pyridine is derived from the Greek word and is a combination of two words: pyr means fire and idine is used for aromatic bases [1]. It is nitrogen-containing heterocycle [2], six-membered and aromatic, and it plays a vital role in the field of medicinal chemistry [3]. Cancer is a group of more than 100 different diseases. It can progress almost anywhere in the body. The causes of cancers are host variables such as genetics, epigenetics, microbiome, age, gender, metabolic state, inflammatory state, and immune function [4]. Environmental factors such as food contamination, viruses, UV radiation, carcinogens from the environment, and diet/lifestyle factors such as nutrients, energy consumption, phytochemicals, other food ingredients, alcohol, physical activity, and smoking [5]. Some of the derivatives of pyridine nucleus containing molecules that are potential drug candidates are streptonigrin, streptonigrone, and lavendamycin, which were reported in the literature [6]. Some of the reported pyridine molecules are selective toward topoisomerase inhibitors [7]. Some of the pyridine-conjugated derivatives were PIM-1 kinase inhibitors [8], human carbonic anhydrase inhibitors [9], proto-oncogene tyrosine-protein kinase (ROS) [10],

ALK/ROS1 dual inhibitors, receptor tyrosine kinase (RTK) c-Met, epidermal growth factor receptor [11], EGFR and HER-2 kinase inhibitors, cyclin-dependent kinase (CDK) inhibitors [12], VEGFR-2 inhibitors [12], topoisomerases, phosphoinositide 3-kinase, maternal embryonic leucine zipper kinase (MELK), NF-κB inhibitors [13], etc. Considering all this information, exploration of these heterocycles is very important for the development of potential anticancer drug candidates. Hence, we covered all the reports related to the pyridine moiety in this book chapter.

2. Anticancer efficacy of diverse pyridine derivatives

Shudo and group developed pyridine derivatives [14] and these were tested for their reverse drug resistance in a multidrug-resistant human carcinoma cell line, KB-C2. Among the synthesized derivatives, compound **1** was the most active in reversing multidrug resistance. Its activity is higher than that of verapamil, cepharanthine, nimodipine, and nicardipine. Few of the synthesized pyridine derivatives displayed lower calcium channel blocking activity and more potent resistance-reversing activity than other calcium channel blockers.



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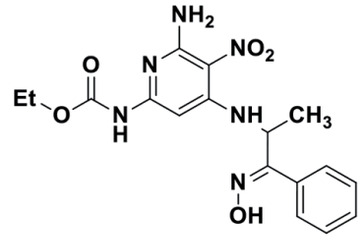

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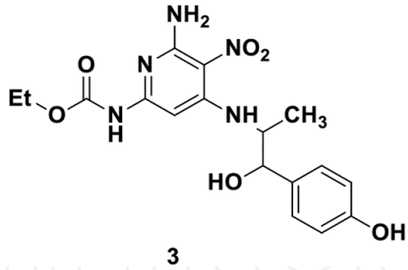

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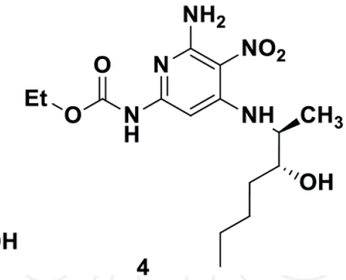

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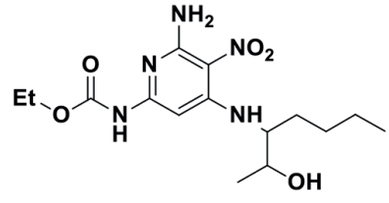

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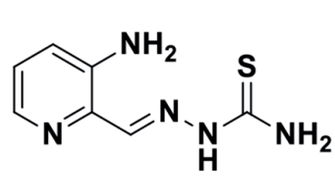
Temple Jr. and his group reported [15] the synthesis and structure-activity studies of some pyridine derivatives and cytotoxic activity against lymphoid leukemia L1210 cells. From the results, it was confirmed that compounds act by multiple modes of action. The primary mode of action of compound **3** might be through the inhibition of the incorporation of pyrimidine nucleosides into DNA and RNA. However, there were two other compounds, **4** and **5**, whose primary mode of action was tubulin polymerization inhibition.

Liu and coworkers [16] reported the synthesis of pyridine-2-carboxaldehyde thiosemicarbozone derivatives. The above molecules were evaluated for anti-neoplastic activity in mice containing L1210 leukemia. The 3-amino derivative compounds **6** and **7** were comparable in their antitumor efficacy against L1210 leukemia. The 5-amino derivatives **8**, **9,** and 5-hydroxy amino derivatives **10** were comparable to the 5-HP anti-neoplastic agents. The above lead molecules containing only amino groups

were selected for further studies and screened against L1210 leukemia-bearing CD_2F_1 female mice. Compounds **6–7** and **8–9** were found to be the most active against L1210 leukemia.



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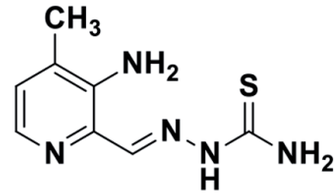

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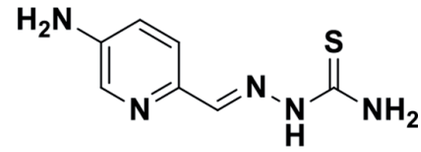

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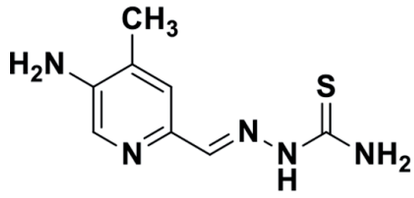

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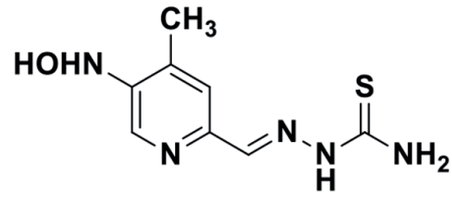

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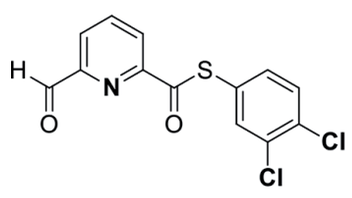
One more research group tried to improve the efficacy of pyridine-2-carboxaldehyde thiosemicarbozone derivatives. However, the incorporation of cytidine into DNA *via* ribonucleotide reductase was inhibited markedly. Thus, a pronounced decrease in the formation of [^{14}C] deoxy ribonucleotides from radioactive cytidine occurred in the acid-soluble fraction of compounds **6** and **7** treated L1210 cells. And it is consistent with DNA replication that at lower concentrations, cells generally accumulate in the S-phase of the cell cycle at higher concentrations of compounds **6** and **7**. Cells at the G0/G1 phase of the cell cycle are observed with a loss of S phase population. The above results provide more support for the development of HCTs. Specifically, compounds **6** and **7** are potential drug candidates for clinical use in the treatment of cancer [17].

Jew and coworkers synthesized [18] a 6-formyl-pyridine-2-carboxylate derivative, and these molecules were tested for telomerase inhibitory activity. Among the series, compound **11** was identified as the lead molecule, and most of the thioester derivatives showed higher activity than the reference compound. A wide variation in the activity was observed based on the position of the halide on the aromatic ring. From the results, it was evident that the *para* chloro derivative showed higher potency than the *meta*- and *ortho*-substituted derivatives. The number of chlorides on the ring is not directly affected by activity. Following the *in vivo* assay, the authors investigated the *in vitro* activity using cancer cell lines HT-29, Caki-2, A549, HEC-1-B, and HL-60, with camptothecin serving as a positive control. From the *in vitro* results, it was confirmed that lead molecules are not that effective in *in vitro* assays. Hence, the antitumor mechanism is different from cytotoxicity.

In the year 2006, Amr and group reported pyridine, [19] pyran, and pyrimidine derivatives. *In vitro* activity of the above-synthesized molecules was performed using 59 different cancer cell lines. Among the series, several active molecules showed higher activity, but our topic of interest is pyridine; hence, compound **12** is identified as a lead molecule and it is selective toward leukemia cell lines. Structure-activity relationship studies of the above series indicate that the presence of nitrile in the molecules enhances the activity. Onnis and group reported [20] the synthesis

of trifluoromethyl pyridine derivatives and their *in vitro* cytotoxicity assays using diverse cancer cell lines. Among the series, compound **13** emerged as a potent molecule and gave activity at nanomolar concentration. And because it is free from animal toxicity, the given lead molecule was further evaluated for *in vivo* assay.

Amin and his group reported [21] a series of tetralin-6-ylpyridines. These molecules were evaluated for *in vitro* antiproliferative activity using two cell lines, HepG2 and MCF-7 cell lines. From the results, it was confirmed that compound **14** was selected for liver cancer and compound **15** was selective for breast cancer. Elgemeie and his group reported [22] the pyridine thioglycosides as anticancer agents. The *in vitro* antiproliferative activity was conducted using four different cancer cell lines such as HepG2, H460, MCF-7, U251, and the animal cell line EAC cells. These molecules displayed good cytotoxicity against four cell lines and the animal cell line EAC. Flow cytometric analysis of the aforementioned derivatives against U251 and HepG2 cell lines later revealed that cell cycle arrest occurred in the S phase. This mechanism is almost the same as the antimetabolite cell cycle arrest.



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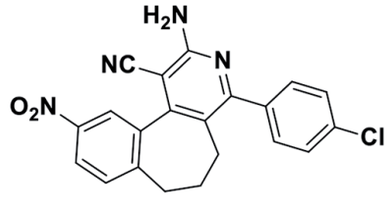

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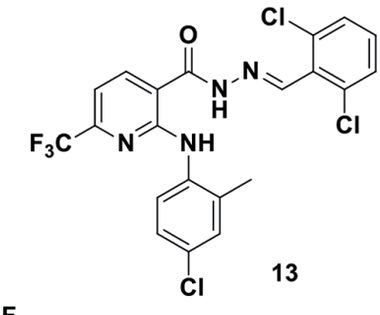

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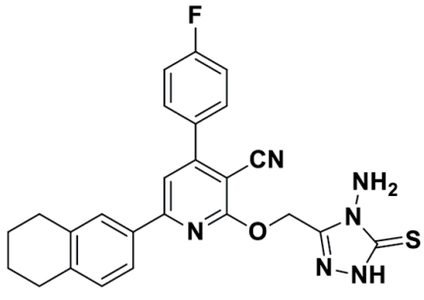

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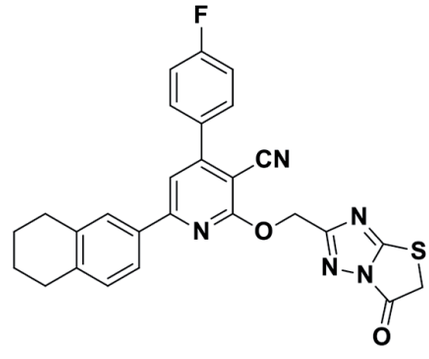

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Elzahabi reported [23] the pyridine-conjugated benzimidazoles as anticancer agents. These were tested for *in vitro* antiproliferative activity using 41 different panel cancer cell lines. It was confirmed that compounds **16** and **17** are lead molecules in most of the cell lines they tested. The structure-activity relationship of the above synthesized derivatives gave some information. The *para*-substituted chloro group and methoxy group greatly enhanced the activity.

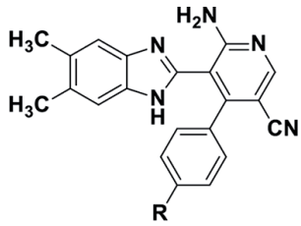
Liu and coworkers developed a series of benzo[5,6]cyclohepta[1,2-*b*]pyridine containing thiourea derivatives as anticancer agents. *In vitro* activity is performed using MCF-7, MDA-MB 231, and HT-29 cancer cell lines using 5-fluorouracil as a positive control. In an *in vitro* assay, the results showed that the activities of the molecules were comparable to those of 5-fluorouracil [24].

Bassyouni and coworkers [25] developed a series of pyridine conjugates, and after synthesis, the above derivatives were tested for anticancer activity. *In vitro* activity of the above compounds was performed using the liver cancer cell line HepG2 and

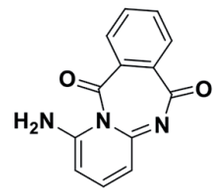
5-fluorouracil and doxorubicin as positive controls. Among the synthesized derivatives, compounds **18–23** displayed better activity than the positive control.

In the year 2014, one more group reported [26] the quinoline pyrazole pyridine hybrids as anticancer agents. All the synthesized derivatives were tested for EGFR kinase and antiproliferative activity against cell lines such as A549 and HepG2 cell lines using erlotinib as a positive control. From the results, it was confirmed that compounds **24** and **25** were identified as lead molecules against EGFR and other cell lines. Zheng and group reported [27] the synthesis of a series of pyridine bridged analogs of combretastatin-A4. The above-synthesized derivatives were tested for *in vitro* antiproliferative activity using three different cell lines: MDA-MB-231, A549, and HeLa. The three-atom linker containing nitrogen emerged as the more favorable structure. Among the synthesized molecules, compounds **26**, **27,** and **28** were identified as lead molecules. These molecules inhibit cell survival and growth and arrest the cell cycle. The competitive binding assay confirms the binding posture of CA-4, **26**, and **27**, which is very similar to CA-4.

Lu and coworkers developed [28] a series of sulfonyl groups containing pyridine derivatives as potential anticancer agents. The above-synthesized derivatives were tested for their *in vitro* activity using A2780, MCF-7, and HCT-116, and here, ON01910 is used as a positive control. After *in vitro* analysis, lead molecules were identified, that is, compounds **29–32**. Later, these molecules are tested on a panel of cancer cell lines. Of the four compounds, **30** and **31** gave better antitumor activity in an *in vivo* assay.



R = Cl, **16**
R = OCH_3, **17**



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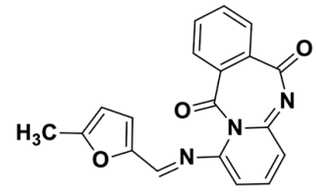

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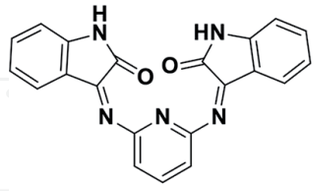

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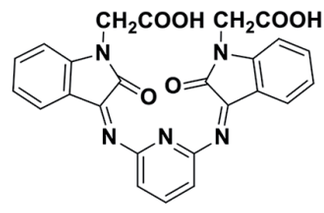

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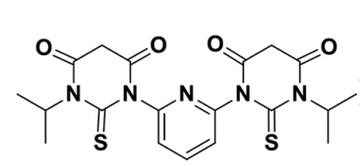

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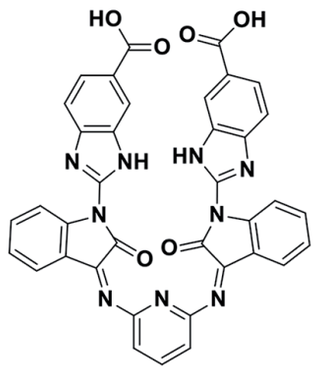

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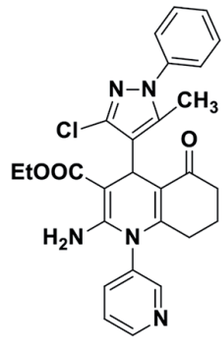

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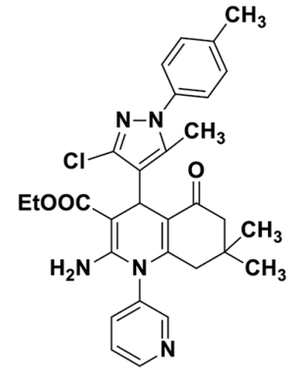

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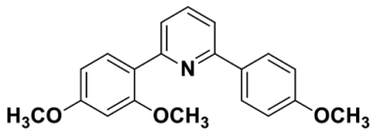
Eldehna and his group reported [29] the isatin-pyridine derivatives as antiproliferative agents, with *in vitro* activity being performed using HepG2, A549, and MCF-7 cancer cell lines. Among the isatin derivatives, compound **33** was found to be more active against HepG2 cancer cell lines than the reference compound doxorubicin, while compound **34** was found to be active against A549 and MCF-7 cell lines.

Previously reported tetraindole derivatives had some disadvantages; hence, to overcome that, Fu and coworkers [30] reported a series of tetraindole derivatives. The synthesized derivatives were evaluated against triple-negative breast cancer cell lines and adenocarcinoma cell lines. Among the synthesized derivatives, compound **35** displayed selective cytotoxicity against breast cancer cell lines over normal cell lines. In addition, its mode of action is shown to involve the G2/M phase of cell cycle arrest and also blocks cancer cell metastasis effectively.



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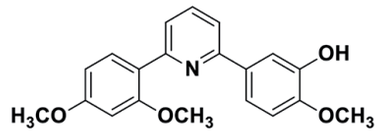

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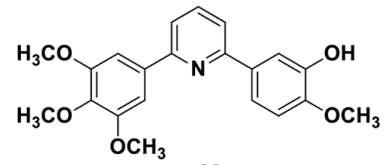

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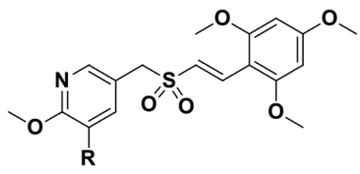
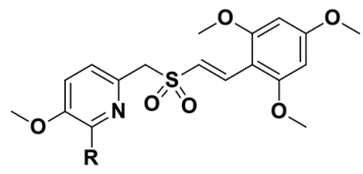
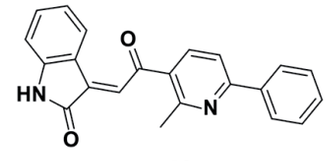


R = NH_2, **29**
R = $NHSO_2Me$, **30**



R = NH_2, **31**
R = $NHSO_2Me$, **32**



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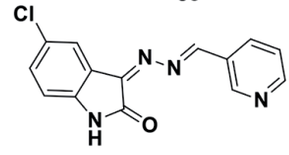

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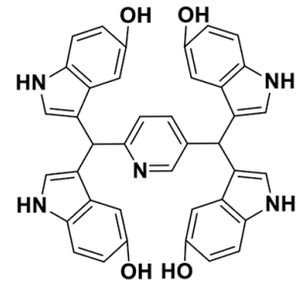
One more research group [31], in the same year, reported a 1,2,4-triazine group containing derivatives. Synthesized derivatives were tested for *in vitro* antiproliferative activity using different cancer cell lines. Among the series, compound **36** was identified as the lead molecule. This compound also showed prominent activity in *in vivo* activity. Abbas and his group reported [32] the synthesis of an imidazole group containing pyridine derivatives. The above-synthesized derivatives were evaluated for anticancer activity. *In vitro* antiproliferative studies were conducted using MCF-7 and HepG2 cell lines using doxorubicin as a positive control. Among the synthesized derivatives, compound **37** is identified as the lead molecule in both cell lines.

Abdelazem and coworkers reported [33] a series of diary amides with the pyrimidinyl pyridine group. These were evaluated for *in vitro* antiproliferative activity using 60 different cancer cell lines. Among all the prepared derivatives, compound **38** gave very good results. This compound showed activity in micromolar concentration in all nine cancer types, but it was the highest against melanoma cell lines.



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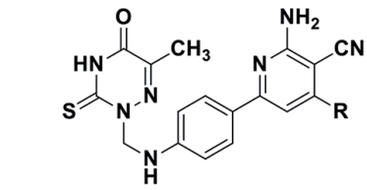

R = 2,4-dimethoxy-5H-furo[3,2g] chromen-5-one

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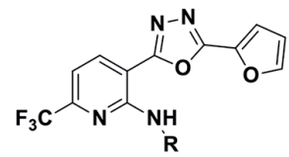
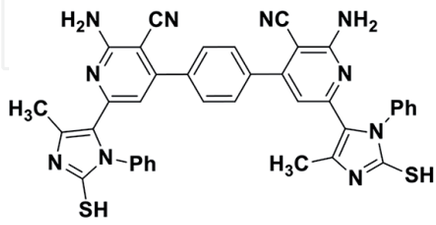


R = 2-methyl furyl **39**
R = C_3H_7 **40**



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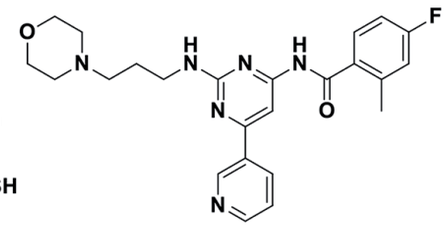

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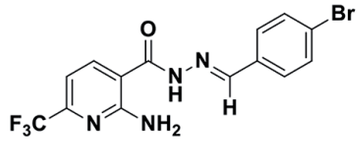

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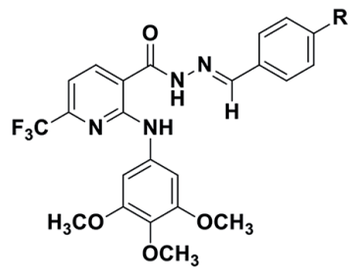
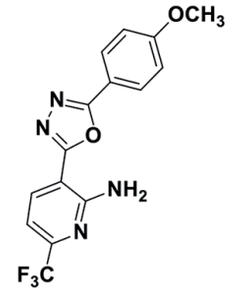


R = 4-OH **42**
R = H, **43**

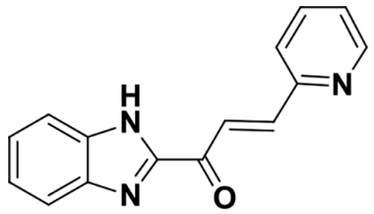


44

Naresh kumar and group designed [34] and synthesized oxadiazolo pyridine derivatives. *In vitro* antiproliferative assay was carried out for the cell lines such as HeLa, DU145, HepG2, and MBA-MB-231 cell lines; here, 5-fluoro uracil is used as a positive control. Among the synthesized derivatives, compounds **36–41** showed better activity against DU145 and HepG2 cancer cell lines only.

Wu and coworkers developed [35] benzimidazole propyl ketone derivatives; after synthesis, these molecules are evaluate for *in vitro* cytotoxicity assay, using cell lines such as HCT-116, MCF-7, and HepG2 cell lines. Here, 5-fluoro uracil and paclitaxel are used as positive control. From the *in vitro* studies, it was evident that some of the molecules exhibited better activity than others, but the topic of interest was pyridine. Hence, compound **42** is the only molecule containing a pyridine ring that displayed good activity. *In vivo* studies of these compounds showed promising activity. Compound **42** displayed better activity; hence, this heterocyclic core is considered a promising drug candidate.

Zhou and group designed [36] and prepared a series of pyridine analogs of curcumin as human prostate cancer inhibitors. Effects of curcumin analogs are on the human prostate cancer cell line CWR-22Rvl. Among the synthesized derivatives, compounds **45–48** were identified as lead molecules. The inhibitory effects of these compounds were tested by using an androgen receptor-linked luciferase assay. Results suggest that compounds **46–48** had the strongest inhibitory effect.



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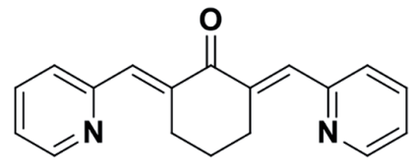

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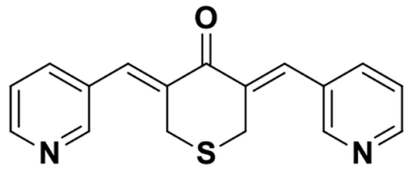

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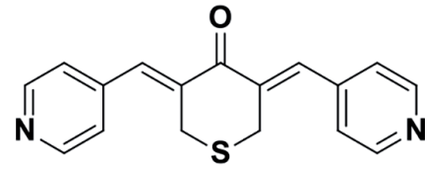


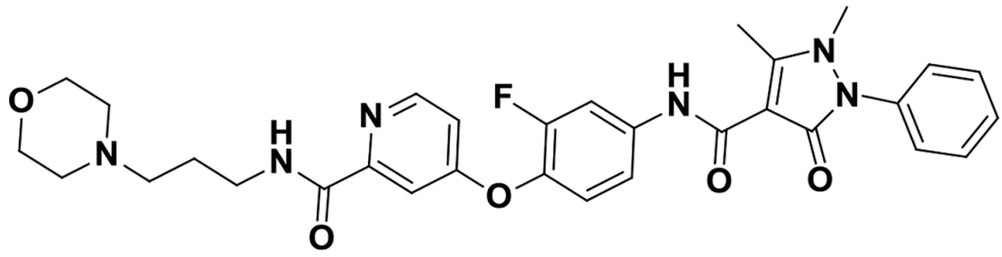
48

Gu and coworkers reported [37] the synthesis of fluoro phenoxy pyridine derivatives. The above-synthesized derivatives were checked for dual c-Met/VEGFR-2 targets. Initially, the above-synthesized derivatives were tested in *in vitro* assays on both c-Met and VEGFR-2. From the results, it was evident that compounds **49–51** showed very high inhibitory potency. Furthermore, an *in vitro* enzyme assay confirmed that compound **51** is the lead molecule. Molecular docking studies also confirmed that compound **51** was a potential compound for cancer treatment.

Abdelaziz and his group designed [38] and synthesized a series of pyridine analogs, and these synthesized derivatives were evaluated for anticancer PIM-I kinase activity. All the synthesized derivatives were evaluated by using 60 different cancer cell lines. From the results, it was confirmed that compounds **52–55** were identified as lead molecules. The active molecules were selected for PIM-1 kinase inhibitory activity. Those molecules that were active in *in vitro* activity displayed very good activity in PIM-1 kinase inhibitory activity.

Ansari and coworkers reported [9] the pyridine thiazolidinones as anticancer agents. Specifically, the above-synthesized derivatives were evaluated for the human carbonic anhydrase IX target. Among the synthesized derivatives, **56** and **57** showed very good enzyme inhibitory activity. Docking studies also supported their findings that the above identified active molecules showed good interaction and hydrogen bonding in the active pocket site. After that, the authors tested these molecules for *in vitro* activity against three cancer cell lines: HEK-293, MCF-7, and HepG2. Compounds **56** and **57** outperformed the reference doxorubicin *in vitro* activity with the cell lines MCF-7 and HepG2.

Durgapal and his group designed [39] and synthesized the 3-amino methyl pyridine derivatives. The above-synthesized derivatives were tested for their *in vitro* antiproliferative studies and DNA binding activity. *In vitro* activity was conducted using two cancer cell lines, that is, A549 and MCF-7, where 5-fluorouracil was used as a positive control. Among the series, compound **58** is identified as a lead molecule, and it is more active than 5-fluorouracil. Then, the further evaluation of this compound toward a DNA binding assay showed that compound **58** is twofold more active than compound **59**. Further evaluation of compound **59** by different tests proved to be efficient.



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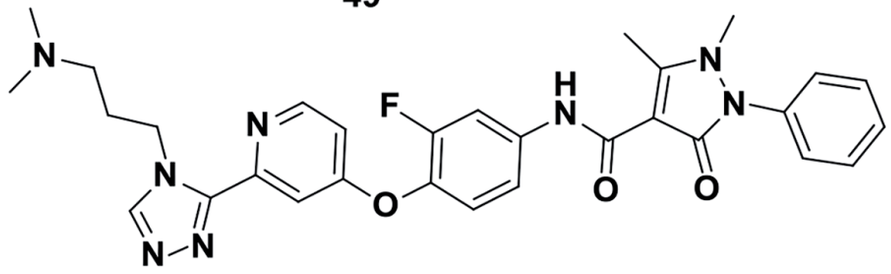

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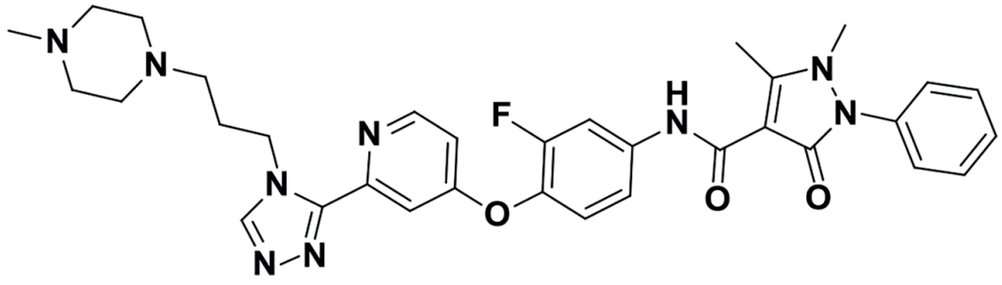


51

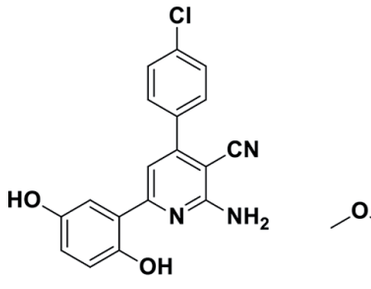
Gomha and his group developed [40] a series of thiadiazolo pyridine derivatives. The above-synthesized derivatives were tested for their anticancer activity using two cancer cell lines, that is, A549 and HepG2 cell lines, using cisplatin as a reference. Among the synthesized molecules, compound **60** emerged as the lead molecule in the HepG2 cell line and the most active molecule in the A549 cell line.

Another group reported some pyridine analogues for anticancer activity targeting G-Quadruplex [41]. Through the FLET melting assay, it was confirmed that compounds were selective for G-4 over duplexes. Most active G-4 ligands were tested for antiproliferative activity by using HL60 and K562 cell lines. Compound **61** is identified as the lead molecule from this assay. In the year 2018, another research group developed pyridine urea derivatives as anticancer agents [42]. Initially, the authors investigated *in vitro* activity against only MCF-7 cancer cell lines. Later, selected molecules were tested for *in vitro* activity against several panels of cell lines. According to the results of the studies, compounds **62** and **63** are potent molecules. Later, active molecules were tested against VEGFR-2. Both compounds exhibited good activity at micromolar concentrations.

Androutsopoulos and his group reported [43] the synthesis and biological evaluation of pyridine molecules. Initially, the authors tested these molecules in *in vitro* assays using HepG2 and MCF-7 cell lines. From the studies, it was confirmed that compound **65** is more active than compound **64** and in these compounds, HepG2 cells showed more sensitivity than other cell lines. From the cell cycle analysis, induction of G2/M phase arrest was observed. Down-regulation of the cell cycle associated protein cyclin D1 was also induced, as was up-regulation of the cell cycle inhibitors p53 and p21. These results indicate that these molecules are promising drug candidates for cancer.

Fayed and group reported [44] that the coumarin group contains pyridine analogs. The above-synthesized derivatives were tested in an *in vitro* antiproliferative assay using four different cancer cell lines, that is, HCT-116, MCF-7, HepG2, and A549 cell lines. From the results, it was evident that compounds **66–68** were identified as lead molecules. Further study of these molecules toward flow cytometric analysis revealed that cell cycle arrest in the G2/M phase is followed by apoptosis. In addition, the caspase-3 activity of lead molecules was confirmed; these compounds increased the caspase-3 activity more than the control group.

Eldehna and coworkers reported [45] a series of pyridine phenyl urea derivatives. The above-prepared derivatives were evaluated for *in vivo* activity. Cancer cell lines such as A549 and HCT-116 are used, and doxorubicin is used as a positive control. Among the phenyl area derivatives, compound **69** is identified as the lead molecule in both cell lines. Later, the activity of this lead molecule was tested against subpanels. The above-mentioned lead molecule causes apoptosis in HCT-116 cells, as evidenced by decreased expression of the anti-apoptotic Bcl-2 protein and increased levels of pro-apoptotic proteins. In addition, active molecules interrupted the cell cycle by arresting the G2/M phase. Later, an annexin V-FITC/propedium iodide assay was performed by treating the lead molecule with HCT-116 cells. An increase in positive annexin V-FITC apoptotic cells was observed, a nearly eightfold increase in comparison with control.



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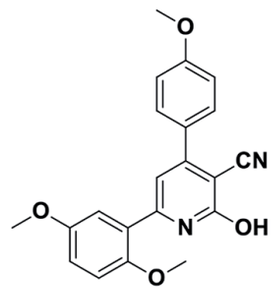

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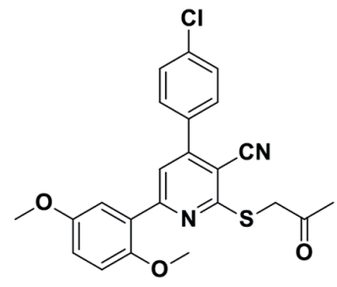

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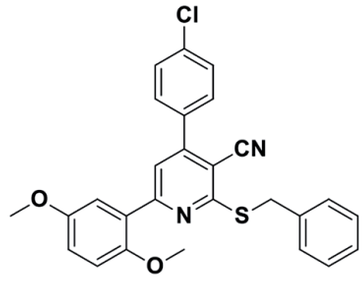

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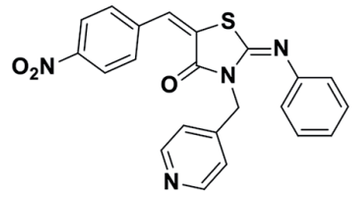

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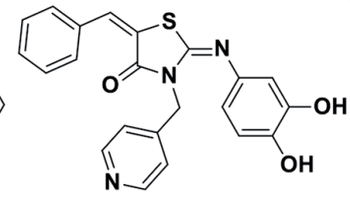

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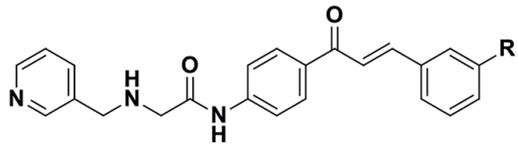
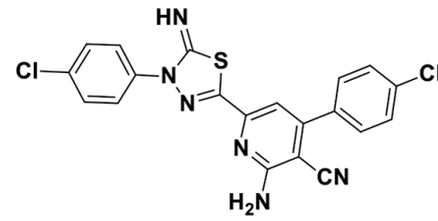
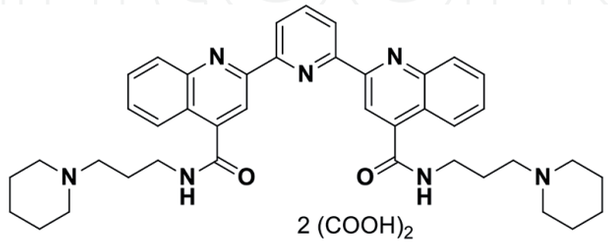


R = OMe **58**
R = Cl **59**



60

Muruguvel and team reported [46] the biological evaluation of the thiophene containing triazole and pyridine structures. Initially, *in vitro* activity of the above moiety was done by using human cancer cell lines such as A549, PC-3, and MDAMB-231 using doxorubicin as a positive control. The above pyridine derivative **70** showed better activity against breast cancer (MDAMB-231) cell lines than others. Xu and his group developed [47] chalcone pyridine analogues as anti-tubulin agents. Compound **71** displayed the most potent activity, and it effectively inhibited tubulin polymerization reactions by binding at colchine site of tubulin. In addition, cellular mechanism studies revealed that cell cycle arrest occurs at the G2/M phase. Notably, the *in vivo* efficacy of compound **71** was more potent than that of CA-4.



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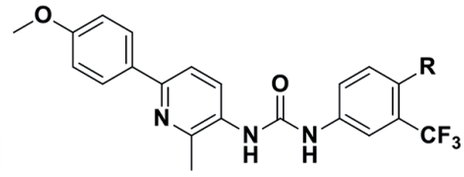
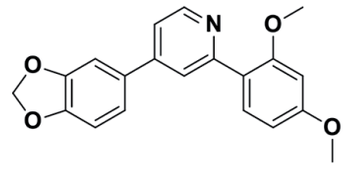


R = H, **62**
R = Cl, **63**



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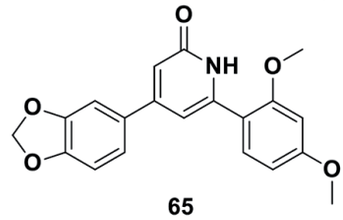

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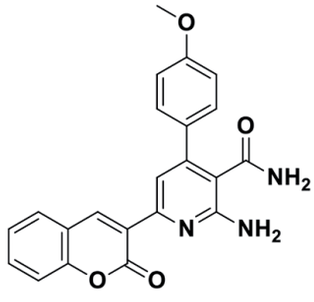

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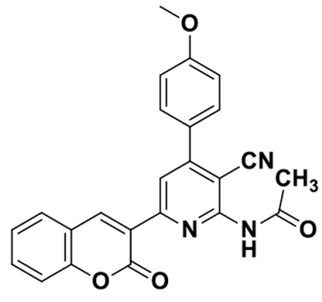

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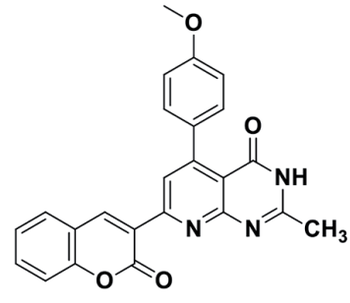

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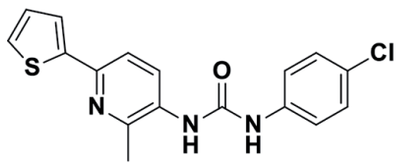

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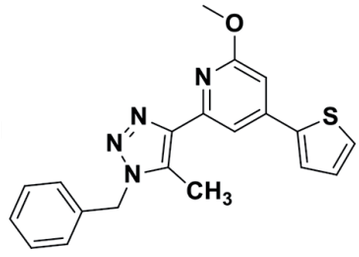

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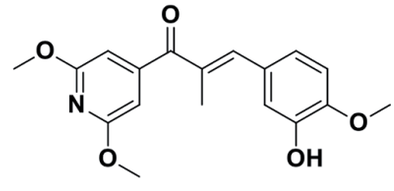

71

3. Conclusion

The results of several investigations into pyridine with anticancer qualities are listed in this review, as well as the prospective function of the pyridine nucleus in the

creation of anticancer drugs. As can be seen from the biological actions of pyridine derivatives, the pyridine nucleus is a very versatile nucleus in the pharmacological sector. Anticancer drugs are frequently utilized with their derivatives. As a result, the pyridine nucleus could be thought of as a cure-all for a variety of ailments.

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Conflict of interest

The authors declare no conflict of interest.

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