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Pyridine heterocycles: Compiling the anticancer capabilities

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Abstract
Pyridine, a heterocyclic molecule featuring a nitrogen atom, exhibits a natural presence and vital roles within living systems. This nitrogen-rich compound serves as a prosthetic group, actively engaging in redox processes within biological systems. This involvement is pivotal, as it drives the functions of numerous enzymes. Beyond its natural functions, pyridine assumes a critical role in pharmacology and drug development.

As a pharmacophore and a foundational scaffold, pyridine holds a distinguished position in drug development due to its versatile applications. Particularly in the realm of anticancer research, pyridine's efficacy is noteworthy. Its potent interaction with significant receptors renders it a valuable asset in the fight against cancer. Notably, pyridine forms the fundamental structure of various existing medications.

In the battle against cancer, pyridine derivatives have proven their mettle by inhibiting key targets such as kinases, androgen receptors, tubulin polymerization, topoisomerase enzymes, and human carbonic anhydrase. These inhibitory actions showcase the diverse capabilities of pyridine derivatives against multiple cancer-associated pathways. This versatility has spurred researchers to channel their efforts into crafting novel pyridine-based compounds.

The synthesis of pyridine derivatives, coupled with their subsequent biological exploration, has yielded insights into their binding sites and receptor interactions. By delving into the intricate details of these interactions, researchers aim to refine and amplify the therapeutic potential of pyridine derivatives. This concerted effort has resulted in the design of novel entities, wherein pyridine is intricately linked with other moieties to enhance its effectiveness in cancer therapy.

In essence, this section delves into the synthesis of pyridine derivatives, their expansive biological applications, and the specific receptors they target. Through this exploration, the scientific community endeavors to unravel the full potential of pyridine derivatives in the pursuit of more effective cancer therapies.

Keywords: Pyridine derivatives, cancer therapies, receptors, biological applications

Introduction

The term "pyridine" finds its origins in the Greek language, where it stems from the fusion of two words: "pyr," signifying fire, and "idine," denoting aromatic bases [1]. This compound is a nitrogen-containing heterocycle characterized by its six-membered, aromatic structure, and its significance in the realm of medicinal chemistry is profound [2, 3]. In this context, pyridine assumes a pivotal role.

Cancer, a diverse collection of over 100 distinct diseases, can manifest in various regions of the body. The factors contributing to the development of cancer are multifaceted, encompassing both host variables and environmental influences [4]. Host variables span genetics, epigenetics, the microbiome, age, gender, metabolic state, inflammatory condition, and immune function. Simultaneously, environmental factors like food contamination, viral infections, UV radiation, environmental carcinogens, and lifestyle choices including diet, nutrients, phytochemicals, energy intake, alcohol consumption, physical activity, and smoking contribute to cancer development [5].

Within the purview of potential drug candidates, specific derivatives of the pyridine nucleus have garnered attention. Examples such as streptonigrin, streptonigrone, and lavendamycin have been documented in the literature as promising candidates [6]. Certain pyridine derivatives exhibit selectivity toward topoisomerase inhibitors, further highlighting their potential therapeutic utility [7].

The landscape broadens with pyridine-conjugated derivatives, which have demonstrated varied functionalities.

These encompass inhibitors of diverse targets like PIM-1 kinase [8], human carbonic anhydrase [9], proto-oncogene tyrosine-protein kinase (ROS), ALK/ROS1 dual inhibitors, receptor tyrosine kinase (RTK) c-Met, epidermal growth factor receptor (EGFR), HER-2 kinase inhibitors, cyclin-dependent kinase (CDK) inhibitors [11, 12], VEGFR-2 inhibitors, topoisomerases, phosphoinositide 3-kinase, maternal embryonic leucine zipper kinase (MELK), and NF-κB [13], among others.

Given the wealth of information, the exploration of these heterocycles emerges as a crucial endeavor in the quest to develop potential candidates for anticancer drugs. By comprehending and harnessing the diverse capabilities of pyridine derivatives, the scientific community seeks to advance the frontier of cancer treatment options.

Diverse pyridine derivatives: A multifaceted approach to anticancer efficacy

A study led by Shudo and colleagues [14] encompassed the development of pyridine derivatives, which underwent evaluation for their ability to counteract reverse drug resistance in a multidrug-resistant human carcinoma cell line known as KB-C2. Within the spectrum of synthesized derivatives, a standout candidate emerged in the form of compound 1, showcasing remarkable efficacy in reversing multidrug resistance. This particular compound surpassed the potency of established substances such as verapamil, cepharanthine, nimodipine, and nicardipine.

What's particularly noteworthy is that several of the newly synthesized pyridine derivatives exhibited not only reduced calcium channel blocking activity but also exhibited heightened efficacy in reversing resistance when compared to other calcium channel blockers. This dual characteristic of lowered calcium channel inhibition and enhanced resistance-reversing activity points to the potential of these derivatives to effectively combat drug resistance in cancer cells.

In essence, the work of Shudo and collaborators unveiled a set of pyridine derivatives, with compound 1 emerging as a frontrunner due to its superior ability to counteract multidrug resistance. Moreover, the study highlighted the intriguing phenomenon where certain derivatives displayed dual capabilities of reduced calcium channel blocking alongside heightened resistance-reversing potential, setting the stage for potential breakthroughs in the realm of drug resistance modulation.

In a study conducted by Temple Jr. and his team [15], they documented their efforts in synthesizing pyridine derivatives and conducting structure-activity investigations aimed at assessing their cytotoxic effects on lymphoid leukemia L1210 cells. The outcomes of their study illuminated that these compounds exert their effects through diverse mechanisms.

Notably, the data indicated that compound 3 displayed a primary mode of action involving the inhibition of pyrimidine nucleoside incorporation into both DNA and RNA. This suggests that compound 3 interferes with the fundamental processes of DNA and RNA synthesis, thereby impeding the cell's ability to replicate and propagate. On the other hand, two other compounds, 4 and 5, exhibited a distinct mode of action centered around the inhibition of tubulin polymerization.

The findings from this study collectively underscore the multifaceted nature of these pyridine derivatives' actions. These compounds manifest their cytotoxic effects through a variety of pathways, including interfering with nucleoside incorporation as well as disrupting tubulin polymerization. This intricate understanding of their mechanisms of action provides a foundation for potentially harnessing these derivatives in therapeutic strategies targeting lymphoid leukemia L1210 cells.

In their study, Liu and colleagues [16] detailed the synthesis of pyridine-2-carboxaldehyde thiosemicarbazone derivatives. These compounds were subjected to evaluation for their potential anti-neoplastic effects in mice carrying L1210 leukemia. Notably, the 3-amino derivative compounds, namely 6 and 7, demonstrated comparable effectiveness in combating L1210 leukemia. Similarly, the 5-amino derivatives, 8 and 9, along with the 5-hydroxy amino derivative 10, exhibited efficacy similar to that of the 5-HP anti-neoplastic agents.

Following this initial assessment, the focus was narrowed to the lead molecules featuring solely amino groups. These selected compounds, specifically 6–7 and 8–9, were subjected to further scrutiny and screened against L1210 leukemia-bearing CD2F1 female mice. Remarkably, compounds 6–7 and 8–9 emerged as the most potent in countering L1210 leukemia, highlighting their significant potential in the realm of anticancer therapeutics.

Another research group embarked on enhancing the effectiveness of pyridine-2-carboxaldehyde thiosemicarbazone derivatives. However, their efforts revealed a significant hindrance: the introduction of cytidine into DNA through ribonucleotide reductase was markedly impeded. Consequently, there was a notable reduction in the creation of [14C] deoxyribonucleotides from radioactive cytidine within the acid-soluble fraction of L1210 cells treated with compounds 6 and 7.

This inhibition pattern aligns with the process of DNA replication. At lower concentrations, the cells exhibited a tendency to accumulate in the S-phase of the cell cycle, while at higher concentrations of compounds 6 and 7, a distinct shift was observed. Specifically, a decrease in the S-phase population was noted, accompanied by an accumulation of cells at the G0/G1 phase of the cell cycle.

These findings underscore the potential of these compounds for further advancement. Notably, compounds 6 and 7 emerge as promising contenders for drug development due to their demonstrated ability to disrupt DNA replication and influence cell cycle progression. This robust evidence lends substantial support to the trajectory of harnessing these compounds, particularly 6 and 7, as prospective drug candidates for clinical applications in cancer treatment [17].

Jew and colleagues undertook the synthesis of a derivative known as 6-formyl-pyridine-2-carboxylate [18]. The primary aim was to assess the telomerase inhibitory potential of these molecules. Within this series, compound 11 surfaced as the frontrunner, displaying potent telomerase inhibitory activity. Notably, a majority of thioester derivatives showcased even greater activity compared to the reference compound. Intriguingly, the position of the halide on the aromatic ring led to a wide spectrum of activity variation. Specifically, the para chloro derivative exhibited heightened potency in contrast to the meta- and ortho-substituted counterparts. Interestingly, the activity did not seem to correlate directly with the number of chlorides on the ring. Upon *in vivo* assays, the researchers further examined the *in vitro* activity using various cancer cell lines (HT-29, Caki-2, A549, HEC-1-B, and HL-60), with camptothecin as a benchmark. The results revealed that the lead molecules, although potent in telomerase inhibition, did not manifest the same effectiveness

in *in vitro* assays. This suggests that their antitumor mechanism differs from mere cytotoxicity.

In 2006, Amr and his team reported a comprehensive exploration involving pyridine, pyran, and pyrimidine derivatives [19]. The scope of their study encompassed *in vitro* evaluations across 59 distinct cancer cell lines. Among these derivatives, compound 12, belonging to the pyridine series, emerged as a lead molecule. Notably, this compound demonstrated selectivity towards leukemia cell lines. The analysis of structure-activity relationships revealed that the presence of a nitrile group in the molecules notably enhanced their activity.

Onnis and collaborators contributed to the field through the synthesis of trifluoromethyl pyridine derivatives, subsequently subjecting them to *in vitro* cytotoxicity assessments across diverse cancer cell lines [20]. Among this series, compound 13 emerged as a particularly potent molecule, exerting its effects at nanomolar concentrations. The added advantage of minimal animal toxicity prompted further evaluation of this lead molecule through *in vivo* assays.

Amin and his research group conducted an investigation involving a series of tetralin-6-ylpyridines [21]. The purpose was to evaluate their potential as antiproliferative agents through *in vitro* assessments on two distinct cell lines: HepG2 and MCF-7. The outcomes pinpointed compound 14 as particularly effective against liver cancer, while compound 15 exhibited a selective action against breast cancer cells.

Elgemeie and colleagues contributed to the field with their research on pyridine thioglycosides as potential anticancer agents [22]. Their study involved evaluating *in vitro* antiproliferative activity across a range of cancer cell lines, including HepG2, H460, MCF-7, U251, and the animal cell line EAC. Impressively, these molecules demonstrated robust cytotoxic effects on all four human cell lines and the EAC animal cell line. Further analysis through flow cytometry of U251 and HepG2 cell lines unveiled a compelling mechanism: cell cycle arrest in the S phase. This arrest mechanism bears resemblance to the mode of action of antimetabolite-induced cell cycle arrest.

In essence, these studies by Amin's and Elgemeie's groups contribute valuable insights into the potential of distinct pyridine derivatives as antiproliferative agents against various cancer types. The findings underscore the specificity of certain compounds towards particular cancer cell lines and highlight intriguing mechanisms of action that could pave the way for novel treatment strategies.

Elzahabi's study [23] delved into pyridine-conjugated benzimidazoles as potential anticancer agents. With testing encompassing 41 different cancer cell lines, compounds 16 and 17 emerged as leading contenders across the majority of the tested cell lines. The structural features of these synthesized derivatives provided insights, revealing that the presence of para-substituted chloro and methoxy groups significantly heightened their activity.

Liu and collaborators undertook the development of benzo[5,6]cyclohepta[1,2-b]pyridine-containing thiourea derivatives with anticancer potential. These derivatives underwent *in vitro* testing on cancer cell lines MCF-7, MDA-MB 231, and HT-29, utilizing 5-fluorouracil as a benchmark. The results showcased that the activities of these derivatives were on par with that of 5-fluorouracil, demonstrating their potential as effective anticancer agents [24].

Bassyouni and colleagues [25] designed a series of pyridine conjugates, which were then subjected to *in vitro* anticancer activity assessment using the HepG2 liver cancer cell line. In comparison to the positive controls, 5-fluorouracil and doxorubicin, compounds 18–23 exhibited superior activity, hinting at their potential utility in cancer treatment.

In 2014, another group reported [26] quinoline pyrazole pyridine hybrids as potential anticancer agents. Rigorously tested against A549 and HepG2 cell lines, compounds 24 and 25 emerged as lead molecules with pronounced activity against EGFR and other cell lines.

Zheng and co-researchers [27] synthesized a series of pyridine-bridged analogs of combretastatin-A4, which were then subjected to *in vitro* antiproliferative assessments across MDA-MB-231, A549, and HeLa cell lines. A three-atom linker containing nitrogen proved optimal, and among the synthesized molecules, compounds 26, 27, and 28 were identified as potent agents capable of inhibiting cell survival and growth, as well as inducing cell cycle arrest.

Lu and his team developed [28] a series of pyridine derivatives containing sulfonyl groups as potential anticancer agents. *In vitro* testing on A2780, MCF-7, and HCT-116 cell lines identified compounds 29–32 as lead molecules. Subsequent analysis on a panel of cancer cell lines revealed that compounds 30 and 31 exhibited notable antitumor activity in *in vivo* assays.

Collectively, these studies highlight the diverse avenues explored in the search for potent pyridine derivatives with anticancer potential. The results underscore the significance of structural modifications and in-depth evaluations in identifying lead molecules for further development as effective anticancer agents.

Eldehna and his team's research [29] centered on isatin-pyridine derivatives as potential antiproliferative agents. Their *in vitro* testing encompassed HepG2, A549, and MCF-7 cancer cell lines. Within the scope of isatin derivatives, compound 33 demonstrated heightened activity against HepG2 cancer cell lines, surpassing the reference compound doxorubicin. On the other hand, compound 34 exhibited efficacy against A549 and MCF-7 cell lines.

In an endeavor to overcome the limitations of previously reported tetraindole derivatives, Fu and collaborators introduced a series of tetraindole derivatives [30]. These newly synthesized compounds underwent evaluation against triple-negative breast cancer cell lines and adenocarcinoma cell lines. Notably, compound 35 emerged as a standout contender, displaying selective cytotoxicity against breast cancer cell lines while sparing normal cell lines. The mode of action of compound 35 involved arresting the G2/M phase of the cell cycle and effectively inhibiting cancer cell metastasis, highlighting its potential as a multifaceted therapeutic agent.

In the same year, an additional research team [31] contributed to the field by introducing derivatives containing a 1,2,4-triazine group. These newly synthesized compounds underwent rigorous *in vitro* antiproliferative testing across various cancer cell lines. Within this series, compound 36 emerged as the lead molecule, demonstrating potent activity. Impressively, the efficacy of this compound extended to *in vivo* activity, reinforcing its potential therapeutic value.

Abbas and colleagues [32] embarked on the synthesis of pyridine derivatives containing an imidazole group, followed by their assessment for anticancer activity. The *in vitro* antiproliferative evaluations involved MCF-7 and HepG2 cell lines, utilizing doxorubicin as a benchmark. Compound 37, among the synthesized derivatives, took the spotlight as the

lead molecule, displaying exceptional activity across both cell lines.

Abdelazem and his team [33] contributed a series of diarylamides containing the pyrimidinyl pyridine group. These derivatives underwent comprehensive evaluation for *in vitro* antiproliferative activity across a diverse spectrum of 60 cancer cell lines. Among all the synthesized compounds, compound 38 stood out, exhibiting highly promising results. This particular compound displayed activity in the micromolar concentration range across nine different cancer types, with its most notable impact observed against melanoma cell lines.

Collectively, these studies reflect the dynamic landscape of research focused on pyridine derivatives as potential anticancer agents. The diverse range of structures and mechanisms explored underscores the ongoing efforts to identify effective therapeutic candidates to combat various forms of cancer.

Naresh Kumar and his team [34] undertook the design and synthesis of oxadiazolo pyridine derivatives. Through *in vitro* antiproliferative assays on cell lines such as HeLa, DU145, HepG2, and MBA-MB-231, with 5-fluorouracil as a reference, compounds 36–41 showcased notable activity specifically against DU145 and HepG2 cancer cell lines.

In a separate study, Wu and colleagues [35] developed benzimidazole propyl ketone derivatives. Post-synthesis, these compounds underwent *in vitro* cytotoxicity assays utilizing HCT-116, MCF-7, and HepG2 cell lines, with 5-fluorouracil and paclitaxel as controls. Among the molecules, compound 42, featuring a pyridine ring, stood out with substantial activity. *In vivo* investigations further underscored the promising nature of these compounds, with compound 42 emerging as a particularly potent candidate. This heterocyclic core, represented by compound 42, holds promise as a potential drug candidate.

The work by Zhou and collaborators [36] revolved around the design and synthesis of pyridine analogs of curcumin, aiming to inhibit human prostate cancer. Evaluations were conducted on the human prostate cancer cell line CWR-22Rvl. Among the synthesized derivatives, compounds 45-48 were identified as lead molecules. To assess their inhibitory effects, an androgen receptor-linked luciferase assay was employed, revealing that compounds 46–48 displayed the most robust inhibitory effects.

These studies collectively highlight the continued exploration of pyridine derivatives as potential anticancer agents across diverse cancer types. The diversity in molecular structures and their corresponding activities underscores the intricate interplay between chemical design and biological effects, guiding the search for promising candidates in the fight against cancer.

Gu and colleagues [37] contributed to the field through the synthesis of fluoro phenoxy pyridine derivatives. Their focus lay on dual c-Met/VEGFR-2 targeting. Initial *in vitro* assays involving both c-Met and VEGFR-2 revealed that compounds 49–51 displayed exceptionally high inhibitory potency. Further confirmation came from *in vitro* enzyme assays, where compound 51 emerged as the lead molecule. Molecular docking studies fortified these findings, solidifying compound 51's potential as a viable candidate for cancer treatment.

Abdelaziz and his team [38] designed and synthesized a series of pyridine analogs, subjecting these derivatives to evaluation for anticancer PIM-1 kinase activity. Comprehensive testing across 60 different cancer cell lines led to the identification of compounds 52–55 as lead molecules. Subsequent selection focused on active molecules, revealing impressive PIM-1 kinase inhibitory activity that correlated with their activity in the *in vitro* assays.

Ansari and coworkers [9] ventured into pyridine thiazolidinones as potential anticancer agents, specifically targeting human carbonic anhydrase IX. Among the synthesized derivatives, compounds 56 and 57 demonstrated potent enzyme inhibitory activity. Docking studies aligned with these results, indicating robust interaction and hydrogen bonding within the active pocket site. Further testing against three cancer cell lines (HEK-293, MCF-7, and HepG2) showcased that compounds 56 and 57 outperformed the reference doxorubicin in *in vitro* activity, specifically with MCF-7 and HepG2 cell lines.

Durgapal and his collaborators [39] engaged in the design and synthesis of 3-amino methyl pyridine derivatives, evaluating them for *in vitro* antiproliferative studies and DNA binding activity. Their investigations included two cancer cell lines, A549 and MCF-7, with 5-fluorouracil as a positive control. Compound 58 emerged as the lead molecule, surpassing the activity of 5-fluorouracil. Moreover, the compound's efficacy was evident in subsequent DNA binding assays, showcasing it to be twofold more active than compound 59. Further tests confirmed compound 59's efficiency.

These studies collectively contribute to the expanding knowledge of pyridine derivatives' potential as anticancer agents. The varied approaches, molecular designs, and mechanisms explored highlight the multifaceted nature of this research, aiming to identify effective strategies for combatting cancer.

Gomha and his research team [40] embarked on the development of a series of thiadiazolo pyridine derivatives. The synthesized compounds underwent rigorous anticancer activity assessment across two cancer cell lines, A549 and HepG2, employing cisplatin as a reference. Notably, compound 60 emerged as the lead molecule within the HepG2 cell line and displayed significant activity in the A549 cell line.

Another group directed their focus towards pyridine analogues with anticancer potential, specifically targeting G-Quadruplex [41]. Their strategy involved utilizing the FLET melting assay to confirm the selectivity of compounds for G-4 over duplexes. Subsequently, the most active G-4 ligands were subjected to antiproliferative activity testing using HL60 and K562 cell lines. Compound 61 was identified as the lead molecule through this assessment.

In 2018, another research team [42] contributed to the field by developing pyridine urea derivatives as potential anticancer agents. Initial *in vitro* activity evaluations targeted the MCF-7 cancer cell line. Active molecules were then subjected to *in vitro* assessment across a range of cell lines. Among the results, compounds 62 and 63 emerged as potent molecules. Further evaluation against VEGFR-2 indicated their good activity at micromolar concentrations.

Androutsopoulos and colleagues [43] reported on the synthesis and biological evaluation of pyridine molecules. Their investigations commenced with *in vitro* assays employing HepG2 and MCF-7 cell lines. Compound 65 showcased greater activity compared to compound 64, and interestingly, HepG2 cells demonstrated heightened sensitivity. Additional insights revealed G2/M phase arrest induction, down-regulation of cyclin D1, and up-regulation of cell cycle inhibitors p53 and p21. These results collectively positioned these molecules as promising candidates for cancer treatment.

Fayed and his team [44] investigated pyridine analogs containing the coumarin group. Through *in vitro* antiproliferative assays across HCT-116, MCF-7, HepG2, and A549 cell lines, compounds 66–68 emerged as lead molecules. Further exploration into their effects unveiled G2/M phase cell cycle arrest and apoptosis induction, with an increase in caspase-3 activity.

Eldehna and coworkers [45] engaged in the synthesis of pyridine phenyl urea derivatives, followed by *in vivo* activity assessment. Utilizing A549 and HCT-116 cancer cell lines, with doxorubicin as a benchmark, compound 69 emerged as the lead molecule in both cell lines. Deeper investigations demonstrated that this lead molecule induced apoptosis in HCT-116 cells, leading to altered protein expression. Furthermore, active molecules disrupted the cell cycle by arresting the G2/M phase. Additional apoptosis confirmation was derived from the annexin V-FITC/propidium iodide assay, revealing a substantial increase in positive annexin V-FITC apoptotic cells.

These comprehensive studies collectively contribute rich insights into the potential of pyridine derivatives as impactful anticancer agents. The diversity in molecular design, target specificity, and mode of action underscores the multifaceted approach taken by researchers in the pursuit of effective cancer treatments.

Muruguvel and colleagues [46] contributed to the field with their investigation into the biological potential of thiophene-containing triazole and pyridine structures. Their initial focus encompassed *in vitro* activity assessments using human cancer cell lines, including A549, PC-3, and MDAMB-231, with doxorubicin as a benchmark. Among these compounds, pyridine derivative 70 emerged as particularly potent against breast cancer (MDAMB-231) cell lines compared to others.

Xu and his team [47] undertook the development of chalcone pyridine analogues as anti-tubulin agents. Notably, compound 71 displayed remarkable potency, effectively inhibiting tubulin polymerization reactions through its binding to the colchicine site of tubulin. Further investigations into its cellular mechanism highlighted cell cycle arrest at the G2/M phase. Impressively, compound 71's *in vivo* efficacy surpassed that of CA-4, reinforcing its potential as a promising candidate in the realm of cancer therapeutics.

Conclusion

This comprehensive review compiles the findings from various research endeavors exploring the anticancer potential of pyridine derivatives, shedding light on the promising role of the pyridine nucleus in the development of novel anticancer drugs. The versatility of the pyridine nucleus in driving diverse pharmacological activities is clearly evident through the spectrum of biological actions exhibited by its derivatives. These investigations underscore the extensive utilization of pyridine-based compounds in the realm of anticancer therapeutics. This multifaceted nature positions the pyridine nucleus as a potential panacea, holding promise for addressing a wide range of medical conditions.

References

1. Allais C, Grassot J-M, Rodriguez J, Constantieux T. Metal-free multicomponent syntheses of pyridines. Chemical Reviews. 2014;114(21):10829-10868.
2. 2.Narasimhamurthy KH, Sajith AM, Joy MN, Rangappa KS. An overview of recent developments in the synthesis of substituted thiazoles. Chemistry Select. 2020;5(19):5629-5656.
3. Oehninger L, Rubbiani R, Ott I. N-Heterocyclic carbene metal complexes in medicinal chemistry. Dalton Transactions. 2013;42(10):3269-3284.
4. Lynn DJ, Benson SC, Lynn MA, Pulendran B. Modulation of immune responses to vaccination by the microbiota: Implications and potential mechanisms. Nature Reviews Immunology. 2022;22(1):33-46.
5. Hoffman R, Gerber M. The Mediterranean diet: Health and science. Wiley-Blackwell. 2013.
6. Rashdan HR, Shehadi IA, Abdelmonsef AH. Synthesis, anticancer evaluation, computer-aided docking studies, and ADMET prediction of 1, 2, 3-triazolyl-pyridine hybrids as human aurora B kinase inhibitors. ACS Omega. 2021;6(2):1445-1455.
7. Liang X, Wu Q , Luan S, Yin Z, He C, Yin L, *et al*. A comprehensive review of topoisomerase inhibitors as anticancer agents in the past decade. European Journal of Medicinal Chemistry. 2019;171:129-168.
8. Naguib BH, El-Nassan HB. Synthesis of new thieno [2, 3-b] pyridine derivatives as pim-1 inhibitors. Journal of Enzyme Inhibition and Medicinal Chemistry. 2016;31(6):1718-1725.
9. Ansari MF, Idrees D, Hassan MI, Ahmad K, Avecilla F, Azam A. Design, synthesis and biological evaluation of novel pyridine-thiazolidinone derivatives as anticancer agents: Targeting human carbonic anhydrase IX. European Journal of Medicinal Chemistry. 2018;144:544-556.
10. Lawson M, Rodrigo J, Baratte B, Robert T, Delehouze C, Lozach O, *et al*. Synthesis, biological evaluation and molecular modeling studies of imidazo [1, 2-a] pyridines derivatives as protein kinase inhibitors. European Journal of Medicinal Chemistry. 2016;123:105-114
11. Lin R, Johnson SG, Connolly PJ, Wetter SK, Binnun E, Hughes TV, *et al*. Synthesis and evaluation of 2, 7-diamino-thiazolo [4, 5-d] pyrimidine analogues as anti-tumor epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. Bioorganic & Medicinal Chemistry Letters. 2009;19(8):2333-2337.
12. Misra RN, Rawlins DB, Xiao H-Y, Shan W, Bursuker I, Kellar KA, *et al*. 1H-Pyrazolo [3, 4-b] pyridine inhibitors of cyclin-dependent kinases. Bioorganic & Medicinal Chemistry Letters. 2003;13(6):1133-1136.
13. Han JG, Gupta SC, Prasad S, Aggarwal BB. Piperlongumine chemosensitizes tumor cells through interaction with cysteine 179 of IκBα kinase, leading to suppression of NF-κB–regulated gene products. Molecular Cancer Therapeutics. 2014;13(10):2422-2435.
14. Shudo N, Mizoguchi T, Kiyosue T, Arita M, Yoshimura A, Seto K, *et al*. Two pyridine analogues with more effective ability to reverse multidrug resistance and with lower calcium channel blocking activity than their dihydropyridine counterparts. Cancer Research. 1990;50(10):3055-3061.
15. Temple C, Rener GA, Waud WR, Noker PE. Antimitotic agents: Structure-activity studies with some pyridine derivatives. Journal of Medicinal Chemistry. 1992;35(20):3686-3690.
16. Liu MC, Lin TC, Sartorelli AC. Synthesis and antitumor activity of amino derivatives of pyridine-2-carboxaldehyde thiose micarbazone. Journal of Medicinal Chemistry. 1992;35(20):3672-3677. DOI: 10.1021/jm00098a012
17. Cory JG, Cory AH, Rappa G, Lorico A, Mao-Chin L, Tai-Shun L, Sartorelli AC. Inhibitors of ribonucleotide

reductase: Comparative effects of amino- and hydroxy-substituted pyridine-2-carboxaldehydethiosemicarbazones. Biochemical Pharmacology. 1994;48(2):335-344.
18. Jew SS, Park BS, Lim DY, Kim MG, Chung IK, Kim JH, *et al*. Synthesis of 6-formyl-pyridine-2-carboxylate derivatives and their telomerase inhibitory activities. Bioorganic & Medicinal Chemistry Letters. 2003;13(4):609-612.
19. Amr A-GE, Mohamed AM, Mohamed SF, Abdel-Hafez NA, Hammam AE-FG. Anticancer activities of some newly synthesized pyridine, pyrane, and pyrimidine derivatives. Bioorganic & Medicinal Chemistry. 2006;14(16):5481-5488.
20. Onnis V, Cocco MT, Fadda R, Congiu C. Synthesis and evaluation of anticancer activity of 2-arylamino-6-trifluoromethyl-3-(hydrazonocarbonyl)pyridines. Bioorganic & Medicinal Chemistry. 2009;17(17):6158-6165.
21. Amin KM, El-Zahar MI, Anwar MM, Kamel MM, Mohamed MH. Synthesis and anticancer activity of novel tetralin-6-ylpyridine and tetralin-6-ylpyridine derivatives. Acta Poloniae Pharmaceutica-Drug Research. 2009;66(3):279-291
22. Elgemeie GH, Mahdy EM, Elgawish MA, Ahmed MM, Shousha WG, Eldin ME. A new class of antimetabolites: Pyridine thioglycosides as potential anticancer agents. Zeitschrift für Naturforschung C. 2010;65(9-10):577-587.
23. Elzahabi HSA. Synthesis, characterization of some benzazoles bearing pyridine moiety: Search for novel anticancer agents. European Journal of Medicinal Chemistry. 2011;46(9):4025-4034.
24. Liu W, Zhou J, Zhang T, Zhu H, Qian H, Zhang H, *et al*. Design and synthesis of thiourea derivatives containing a benzo[5,6]cyclohepta[1,2-b]pyridine moiety as potential antitumor and anti-inflammatory agents. Bioorganic & Medicinal Chemistry Letters 2012;22(8):2701-2704.
25. Bassyouni FA, Tawfik HA, Soliman AM, Rehim MA. Synthesis and anticancer activity of some new pyridine derivatives. Research on Chemical Intermediates. 2012;38(7):1291-1310.
26. Sangani CB, Makawana JA, Zhang X, Teraiya SB, Lin L, Zhu H-L. Design, synthesis and molecular modeling of pyrazole–quinoline–pyridine hybrids as a new class of antimicrobial and anticancer agents. European Journal of Medicinal Chemistry. 2014;76:549-557.
27. Zheng S, Zhong Q, Mottamal M, Zhang Q, Zhang C, LeMelle E, *et al*. Design, synthesis, and biological evaluation of novel pyridine-bridged analogues of combretastatin-A4 as anticancer agents. Journal of Medicinal Chemistry. 2014;57(8):3369-3381.
28. Lu T, Goh AW, Yu M, Adams J, Lam F, Teo T, *et al*. Discovery of (E)-3-((Styrylsulfonyl)methyl) pyridine and (E)-2-((Styrylsulfonyl)methyl)pyridine derivatives as anticancer agents: Synthesis, structure–Activity relationships, and biological activities. Journal of Medicinal Chemistry. 2014;57(6):2275-2291. DOI: 10.1021/jm4019614
29. Eldehna WM, Altoukhy A, Mahrous H, Abdel-Aziz HA. Design, synthesis and QSAR study of certain isatin-pyridine hybrids as potential anti-proliferative agents. European Journal of Medicinal Chemistry. 2015;90:684-694.
30. Fu C-W, Hsieh Y-J, Chang TT, Chen C-L, Yang C-Y, Liao A, *et al*. Anticancer efficacy of unique pyridine-based tetraindoles. European Journal of Medicinal Chemistry. 2015;104:165-176. DOI: 10.1016/j.ejmech.2015.09.032
31. Abd El-All AS, Osman SA, Roaiah HMF, Abdalla MM, Abd El Aty AA, AbdEl-Hady WH. Potent anticancer and antimicrobial activities of pyrazole, oxazole and pyridine derivatives containing 1,2,4-triazine moiety. Medicinal Chemistry Research. 2015;24(12):4093-4104.
32. Abbas I, Gomha S, Elaasser M, Bauomi M. Synthesis and biological evaluation of new pyridines containing imidazole moiety as antimicrobial and anticancer agents. Turkish Journal of Chemistry. 2015;39:334-346
33. Naresh Kumar R, Poornachandra Y, Nagender P, Santhosh Kumar G, Krishna Swaroop D, Ganesh Kumar C, *et al*. Synthesis of novel nicotinohydrazide and (1,3,4-oxadiazol-2-yl)-6-(trifluoromethyl)pyridine derivatives as potential anticancer agents. Bioorganic & Medicinal Chemistry Letters. 2016;26(19):4829-4831.
34. Wu L-t, Jiang Z, Shen J-j, Yi H, Zhan YC, Sha MQ, *et al*. Design, synthesis and biological evaluation of novel benzimidazole-2-substituted phenyl or pyridine propyl ketene derivatives as antitumour agents. European Journal of Medicinal Chemistry. 2016;114:328-336.
35. Zhou DY, Zhao SQ, Du ZY, Zheng X, Zhang K. Pyridine analogues of curcumin exhibit high activity for inhibiting CWR-22Rv1 human prostate cancer cell growth and androgen receptor activation. Oncology Letters. 2016;11(6):4160-4166.
36. Gu W, Dai Y, Qiang H, Shi W, Liao C, Zhao F, *et al*. Discovery of novel 2-substituted-4-(2-fluorophenoxy) pyridine derivatives possessing pyrazolone and triazole moieties as dual c-Met/VEGFR-2 receptor tyrosine kinase inhibitors. Bioorganic Chemistry. 2017;72:116-122.
37. Abdelaziz ME, El-Miligy MMM, Fahmy SM, Mahran MA, Hazzaa AA. Design, synthesis and docking study of pyridine and thieno[2,3-b] pyridine derivatives as anticancer PIM-1 kinase inhibitors. Bioorganic Chemistry. 2018;80:674-692.
38. Durgapal SD, Soni R, Umar S, Suresh B, Soman SS. 3-Aminomethyl pyridine chalcone derivatives: Design, synthesis, DNA binding and cytotoxic studies. Chemical Biology & Drug Design. 2018;92(1):1279-1287.
39. Gomha SM, Muhammad ZA, Abdel-aziz MR, Abdel-aziz HM, Gaber HM, Elaasser MM. One-pot synthesis of new thiadiazolyl-pyridines as anticancer and antioxidant agents. Journal of Heterocyclic Chemistry. 2018;55(2):530-536.
40. Das RN, Chevret E, Desplat V, Rubio S, Mergny J-L, Guillon J. Design, synthesis and biological evaluation of new substituted diquinolinyl-pyridine ligands as anticancer agents by targeting G-quadruplex. Molecules. 2018;23(1):81.
41. El-Naggar M, Almahli H, Ibrahim HS, Eldehna WM, Abdel-Aziz HA. Pyridine-ureas as potential anticancer agents: Synthesis and *in vitro* biological evaluation. Molecules. 2018;23(6):1459
42. Androutsopoulos VP, Spandidos DA. Anticancer pyridines induce G2/M arrest and apoptosis via p53 and JNK upregulation in liver and breast cancer cells. Oncology Reports. 2018;39(2):519-524.
43. Fayed EA, Sabour R, Harras MF, Mehany ABM. Design, synthesis, biological evaluation and molecular modeling of new coumarin derivatives as potent anticancer agents. Medicinal Chemistry Research. 2019;28(8):1284-1297.

44. Eldehna WM, Hassan GS, Al-Rashood ST, Al-Warhi T, Altyar AE, Alkahtani HM, *et al*. Synthesis and *in vitro* anticancer activity of certain novel 1-(2-methyl-6-arylpyridin-3-yl)-3-phenylureas as apoptosis-inducing agents. Journal of Enzyme Inhibition and Medicinal Chemistry. 2019;34(1):322-332.
45. Murugavel S, Ravikumar C, Jaabil G, Alagusundaram P. Synthesis, computational quantum chemical study, in silico ADMET and molecular docking analysis, *in vitro* biological evaluation of a novel sulfur heterocyclic thiophene derivative containing 1,2,3-triazole and pyridine moieties as a potential human topoisomerase IIα inhibiting anticancer agent. Computational Biology and Chemistry. 2019;79:73-82.
46. Xu F, Li W, Shuai W, Yang L, Bi Y, Ma C, *et al*. Design, synthesis and biological evaluation of pyridine-chalcone derivatives as novel microtubule-destabilizing agents. European Journal of Medicinal Chemistry. 2019;173:1-14.