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Review

Innovative piperidone derivatives: a new horizon in Potent anticancer therapeutics

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Abstract

Recent advancements in the synthesis and evaluation of piperidone derivatives have unveiled their remarkable potential as potent anticancer agents. This review highlights the innovative approaches and significant findings in the development of novel piperidone-based compounds, showcasing their efficacy against various cancer cell lines. Among the noteworthy compounds, dissymmetric 3,5-bis(arylidene)-4-piperidones (BAPs) have demonstrated selective cytotoxicity with minimal impact on normal cells. Further, modifications involving N-benzoylation, N-benzenesulfonylation and N-acryloylation have enhanced the cytotoxic profiles of these derivatives, revealing significant activity against carcinoma, leukaemia, and colon cancer cell lines. QSAR studies and computer docking simulations have provided insights into the structural requirements for optimizing anticancer potency and selectivity. In vivo studies confirm the therapeutic potential of key compounds, demonstrating tumour growth inhibition with minimal toxicity. This comprehensive review underscores the transformative potential of piperidone derivatives, paving the way for their development as next-generation anticancer therapeutics.

Keywords: Piperidones, cytotoxicity, anticancer, Qualitative structure activity relationship.

INTRODUCTION

Cancer is a complex and multifaceted disease characterized by the uncontrolled growth and spread of abnormal cells in the body. It arises when the regulatory mechanisms that normally control cell proliferation and death becomes disrupted, leading to the formation of malignant tumours. These tumours can invade surrounding tissues and metastasize to distant organs, posing a significant threat to health and life.

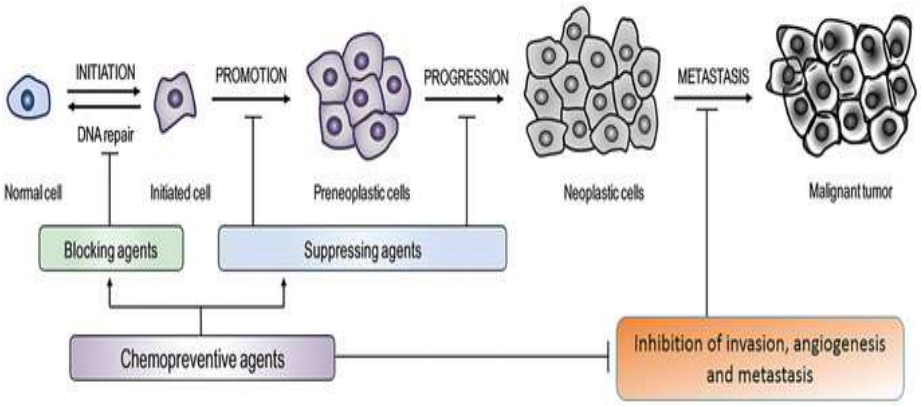


Fig 1: Multistep Carcinogenesis [1]

The development of cancer is typically a multistep process involving genetic mutations and alterations in cellular pathways. [as shown in Figure 1] These changes can result from various risk factors [as shown in Figure 2], including exposure to carcinogens (such as tobacco smoke, radiation, and certain chemicals), genetic predisposition, lifestyle factors (such as diet and physical activity), and infections with certain viruses and bacteria.

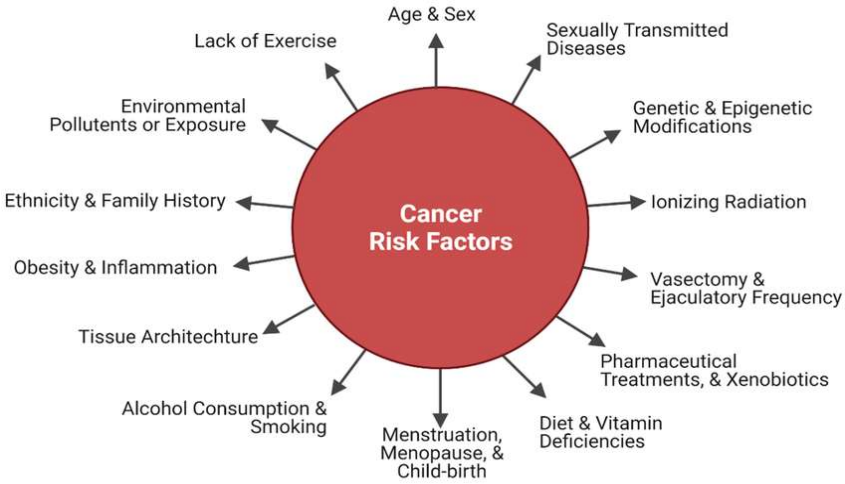


Fig 2: Risk factors of Cancer [2]

Notably, cancer is an illness that includes several diseases. Based on the research, more than 100 distinct kinds of cancer have been reported. Researcher's label each type of cancer with regard to the cell line or organ in which it spreads. They also collect kinds of cancer in broad divisions [3][4][5]. Some of the most common types include breast cancer, lung cancer, prostate cancer, colorectal cancer, and skin cancer.

The impact of cancer on global health is profound, making it one of the leading causes of morbidity and mortality worldwide. Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, in 2018. According to the studies, cancer is one instance of the un-controlled divisions of atypical cells, and invasions of the rest tissues. In fact, the cancer cells may penetrate other parts of the body via the lymph, and blood systems.[6] The burden of cancer is expected to rise due to factors such as aging populations, increasing prevalence of risk factors, and improved diagnostic techniques.

Efforts to combat cancer involve a multifaceted approach, including prevention, early detection, and treatment. Prevention strategies focus on reducing exposure to risk factors and promoting healthy lifestyles. Early detection through screening programs aims to identify cancer at an early stage when it is most treatable. Treatment options vary depending on the type and stage of cancer and may include surgery, radiation therapy, chemotherapy, targeted therapy, immunotherapy, and hormone therapy.

Advancements in research and technology have led to significant progress in understanding the molecular and genetic basis of cancer. This knowledge has paved the way for the development of novel therapies

and personalized medicine approaches, which tailor treatments to the individual characteristics of each patient's cancer.

Despite these advancements, challenges remain in the fight against cancer, including the need for more effective treatments, overcoming drug resistance, and addressing disparities in cancer care access and outcomes. Ongoing research and collaboration among scientists, healthcare professionals, and policymakers are essential to continue making strides in cancer prevention, diagnosis, and treatment, ultimately aiming to reduce the global burden of this disease.

Anticancer agents are a diverse group of substances used to prevent, halt, or reverse the progression of cancer by targeting and destroying cancer cells or inhibiting their growth. These agents can be broadly categorized into several classes [as shown in Figure 3], each with distinct mechanisms of action and therapeutic applications. The primary goal of anticancer agents is to eradicate cancer cells while minimizing damage to normal, healthy cells.

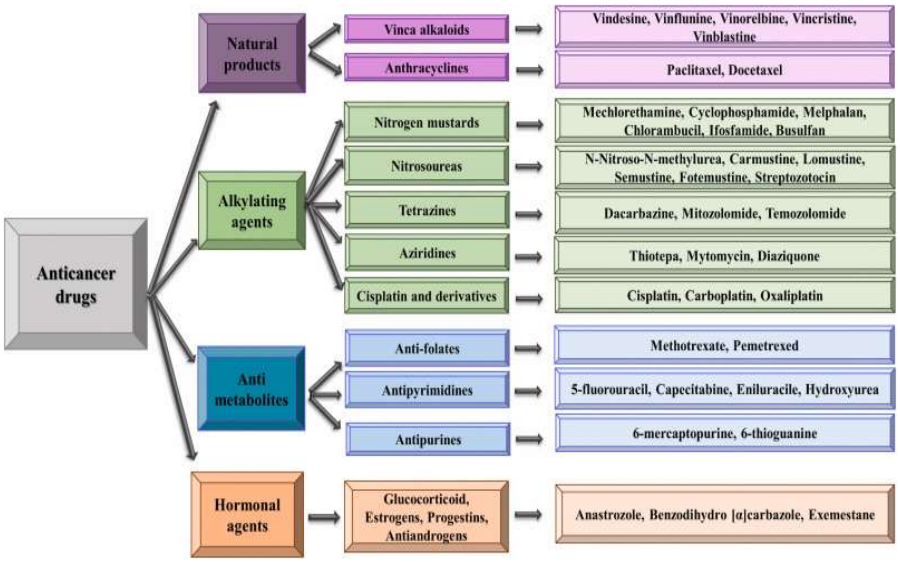


Fig 3: General Classification of Anti-cancer drugs [7]

Mechanisms of Action

Anticancer agents exert their effects through various mechanisms, including:

- **DNA Damage and Repair Inhibition**: Inducing DNA damage that cancer cells cannot repair
- **Inhibition of Cell Division**: Disrupting processes essential for cell division, leading to apoptosis (programmed cell death).
- **Angiogenesis Inhibition**: Preventing the formation of new blood vessels that supply tumours.
- **Immune Modulation**: Enhancing the immune system's ability to recognize and destroy cancer cells.

Challenges and Considerations

- **Resistance**: Cancer cells can develop resistance to anticancer agents through various mechanisms, such as drug efflux, mutations, and alterations in drug targets.
- **Side Effects**: Many anticancer agents have significant side effects due to their toxicity to normal cells. Managing these side effects is crucial for patient care.
- **Personalized Medicine**: The effectiveness of anticancer agents can vary widely among patients. Personalized medicine aims to tailor treatments based on the genetic and molecular profile of the individual's cancer.

Anticancer agents are critical tools in the fight against cancer, offering a range of therapeutic strategies to target and eliminate cancer cells. Ongoing research and development are focused on improving the efficacy and safety of these agents, overcoming resistance, and developing personalized approaches to cancer treatment. Through these efforts, the goal is to achieve better outcomes and improve the quality of life for patients with cancer.

Despite the rising number of cancer-related complications, it is imperative to discover therapeutic medicines with distinct mechanisms of action. It was demonstrated that the number of α, β-unsaturated ketones exhibited anticancer and cytotoxic properties.[8][9] In many of the articles, it was demonstrated that many 3,5-bis(benzylidene)-4-piperidones 1 possess promising cytotoxic potencies.[10][11][12]

Piperidones as anticancer agents: An Overview

Piperidones are a class of organic compounds characterized by a six-membered ring containing nitrogen and a carbonyl group. These compounds have attracted significant attention in medicinal chemistry due to their diverse biological activities, particularly as anticancer agents.

The interest in piperidones as anticancer agents stems from their ability to modulate various biological pathways critical to cancer cell survival and proliferation. Research has shown that piperidones can interfere with cell cycle progression, induce apoptosis (programmed cell death), and inhibit angiogenesis (the formation of new blood vessels that supply tumours). These mechanisms make piperidones promising candidates for the development of new anticancer therapies.

Several studies have reported the synthesis of novel piperidone derivatives with enhanced anticancer activity. These derivatives are often designed to improve their pharmacokinetic properties, target specificity, and reduce potential side effects. The versatility of the piperidone scaffold allows for the introduction of various functional groups, enabling the fine-tuning of their biological activities and the development of more effective anticancer agents.

Moreover, piperidones have shown potential in overcoming drug resistance, a major challenge in cancer treatment. By targeting multiple signalling pathways simultaneously, piperidones can effectively combat resistant cancer cell lines that no longer respond to conventional therapies.

Mechanisms of Action

The anticancer properties of piperidones are attributed to their ability to interfere with multiple cellular processes crucial for cancer cell survival and proliferation:

1. **Cell Cycle Arrest**: Piperidones can induce cell cycle arrest at various phases, preventing cancer cells from progressing through the cell division cycle. This halts the proliferation of cancer cells and can lead to apoptosis.
2. **Apoptosis Induction**: Many piperidone derivatives have been shown to activate apoptotic pathways. This programmed cell death is essential for eliminating cancer cells and reducing tumour size.
3. **Inhibition of Angiogenesis**: Piperidones can inhibit the formation of new blood vessels, a process known as angiogenesis. By preventing the supply of nutrients and oxygen to the tumour, these agents can starve the cancer cells and inhibit tumour growth.
4. **Interference with Signalling Pathways**: Piperidones can disrupt various signalling pathways that are often dysregulated in cancer cells. For instance, they may inhibit pathways like PI3K/Akt, MAPK, and NF-κB, which are involved in cell survival, proliferation, and metastasis.

Advantages of Piperidones

- **Versatile Chemical Structure**: The piperidone scaffold allows for extensive chemical modifications, enabling the design of derivatives with improved anticancer activity and selectivity.
- **Broad Spectrum of Activity**: Piperidones have shown efficacy against a wide range of cancer types, including breast cancer, lung cancer, prostate cancer, and leukaemia.
- **Potential for Combination Therapy**: Piperidones can be used in combination with other anticancer agents to enhance therapeutic efficacy and overcome drug resistance.

Research and Development

Significant research has been dedicated to synthesizing novel piperidone derivatives and evaluating their anticancer potential. Studies have demonstrated that these compounds can exhibit potent cytotoxic effects against cancer cell lines while sparing normal cells. This selective toxicity is a crucial attribute for any effective anticancer agent.

Examples of Piperidone Derivatives

- **Piperidone-Thiosemicarbazones**: These derivatives have shown promising anticancer activity by targeting multiple cellular pathways and inducing apoptosis in cancer cells.
- **Spiro-Piperidones**: The spiro derivatives of piperidones have been reported to possess strong anticancer properties, potentially due to their ability to interact with DNA and inhibit topoisomerase enzymes.

Challenges and Future Directions

While piperidones hold great promise as anticancer agents, several challenges need to be addressed:

- **Optimization of Pharmacokinetics**: Enhancing the bioavailability, stability, and distribution of piperidone derivatives in the body is essential for their effective use in cancer therapy.
- **Minimizing Side Effects**: Although piperidones are designed to selectively target cancer cells, minimizing potential side effects on normal cells remains a critical goal.
- **Clinical Trials**: Advancing piperidone derivatives from preclinical studies to clinical trials is necessary to validate their safety and efficacy in humans.

Biological applications of piperidones

Piperidones are a class of compounds known for their versatile chemical structure, which allows for a wide range of modifications and the development of derivatives with diverse biological activities. These compounds have been extensively studied for various therapeutic applications beyond their well-documented anticancer properties. Here are some of the notable biological applications of piperidones:

1. Antimicrobial Activity

Piperidone derivatives have demonstrated significant antimicrobial properties, including antibacterial, antifungal, and antiviral activities.

- **Antibacterial**: Certain piperidones have been effective against a variety of bacterial strains, including both Gram-positive and Gram-negative bacteria. They can act by disrupting bacterial cell wall synthesis or interfering with essential bacterial enzymes.
- **Antifungal**: Piperidone compounds have shown efficacy against fungal pathogens, making them potential candidates for treating fungal infections.
- **Antiviral**: Some piperidone derivatives possess antiviral properties, inhibiting the replication of viruses and potentially offering therapeutic options for viral infections.

2. Antioxidant Activity

Piperidones have been studied for their antioxidant properties, which are crucial in protecting cells from oxidative stress and damage caused by free radicals. This activity is beneficial in preventing various diseases associated with oxidative stress, including neurodegenerative diseases, cardiovascular diseases, and aging-related conditions.

3. Anti-Inflammatory Activity

Inflammation is a key component of many chronic diseases. Piperidone derivatives have shown anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines and mediators. This makes them potential candidates for treating inflammatory conditions such as arthritis, asthma, and inflammatory bowel disease.

4. Anticonvulsant Activity

Some piperidone derivatives have been found to possess anticonvulsant properties, making them useful in the management of epilepsy and other seizure disorders. They can modulate neuronal excitability and neurotransmitter release, thereby preventing the onset of seizures.

5. Analgesic Activity

Piperidones have also been explored for their analgesic (pain-relieving) effects. By interacting with specific pain pathways and receptors, these compounds can alleviate pain, offering potential therapeutic options for conditions such as chronic pain, neuropathic pain, and postoperative pain.

6. Antidiabetic Activity

Certain piperidone derivatives have shown potential in managing diabetes by modulating glucose metabolism and enhancing insulin sensitivity. These compounds can be explored further for developing new treatments for diabetes and its complications.

7. Antidepressant and Anxiolytic Activity

Piperidone compounds have been investigated for their effects on the central nervous system, particularly in the treatment of depression and anxiety disorders. They may act by modulating neurotransmitter levels and receptor activities, providing therapeutic benefits for mental health conditions.

8. Antitumor and Chemopreventive Activity

Beyond their direct anticancer properties, some piperidone derivatives exhibit chemopreventive effects by preventing the initiation, promotion, and progression of tumours. They can modulate signalling pathways and gene expression involved in tumorigenesis, offering potential in cancer prevention.

Thus, piperidones are a remarkably versatile class of compounds with a broad spectrum of biological activities. Their ability to modulate various biological processes and pathways makes them valuable candidates for the development of new therapeutic agents across different medical fields. Ongoing research into their mechanisms of action and optimization of their pharmacological properties will continue to uncover new applications and enhance their therapeutic potential.

Recent developments in piperidones as potent anti-cancer agents

Ning Li et al synthesized 35 new dissymmetric 3,5-bis(arylidene)-4-piperidone derivatives (BAPs; 6a-h, 7a-h, 8a-g, 9a-g, and 10a-e) and their cytotoxicity was assessed. BAPs 6d((3E,5E)-3-(2-fluorobenzylidene)-5-(3,4,5-trimethoxybenzylidene)-1-methylpiperidin4-one),7h((3E,5E)-3-(3,4,5-trimethoxybenzylidene)-5-(3,5-dimethoxybenzylidene)-1-methylpiperidin-4-one),8g((3E,5E)-3-(3,4,5-trimethoxybenzylidene)-5-(4cyanobenzylidene)-1-methylpiperidin4-one),and9g((3E,5E)-3-(3-nitrobenzylidene)-5-(4-(trifluoromethyl)benzylidene)-1-methylpiperidin -4-one) showed the lowest cytotoxicity toward LO2 but the greatest potential inhibitory effects against HepG2 and THP-1. In HepG2 cells, 6d((3E,5E)-3-(2-fluorobenzylidene)-5-(3,4,5-trimethoxy benzylidene)-1-methylpiperidin4-one),7h((3E,5E)-3-(3,4,5-trimethoxybenzylidene)-5-(3,5-dimethoxy benzylidene)-1-methylpiperidin-4-one),8g((3E,5E)-3-(3,4,5-trimethoxybenzylidene)-5-(4-cyano benzylidene)-1-methylpiperidin4-one), and 9g((3E,5E)-3-(3-nitrobenzylidene)-5-(4-(trifluoromethyl) benzylidene)-1-methylpiperidin-4-one) can successfully up-regulate BAX expression and down-regulate Bcl-2 expression in vitro. Molecular docking modes demonstrated that they could plausibly bind to the Bcl-2 protein's active site. Using flow cytometry, the most potent BAP 6d ((3E,5E)-3-(2-fluorobenzylidene)-5-(3,4,5-trimethoxybenzylidene)-1-methylpiperidin4-one) caused HepG2 cells to undergo apoptosis in a dose-dependent manner. Using confocal laser scanning microscopy (CLSM), the cellular uptake of HepG2 cells revealed that 6d ((3E,5E)-3-(2-fluorobenzylidene)-5-(3,4,5-trimethoxybenzylidene)-1-methylpiperidin4-one)mostly accumulated inside the nucleus. 6d ((3E,5E)-3-(2-fluorobenzylidene)-5-(3,4,5-trimethoxybenzylidene)-1-methylpiperidin4-one) was relatively harmless to mice and inhibited the growth of HepG2 xenografts in nude mice when used in vivo. These results suggest that 6d ((3E,5E)-3-(2-fluorobenzylidene)-5-(3,4,5-trimethoxybenzylidene)-1-methylpiperidin4-one) could be therapeutically beneficial as potential therapeutic agent for the early clinical treatment of liver cancers.[13]

Jufeng Sun et al. synthesized two series of new N-benzoylated or N-benzenesulfonylated 3,5-bis(arylidene)-4-piperidone derivatives (series 1 and 2) as effective curcumin synthetic analogs and examined their fluorescence and cytotoxic potential. Of these molecules, compounds 1a-1e with electron-withdrawing bromine groups showed a significant amount of cytotoxicity against human carcinoma cell lines; however, because of the bromine groups' electron-withdrawing effects, their fluorescent properties were marginally worse than those of compounds 2a-2e; on the other hand, compounds 2a-2e with electron-rich aromatic heterocyclic thiophen groups showed poor cytotoxicity but slightly better fluorescent properties than those of 1a-1e.All of the compounds for series 1 and 2, however, showed notable fluorescence characteristics overall. Specifically, molecules 1a(3,5-bis((E)-3-bromobenzylidene)piperidine-4-one),1c(3,5-bis(E)-3-bromobenzylidene)-1-tosylpiperidin-4-one),1d(N-(4-((3,5-bis((E)-3-bromobenzylidene)-4-oxopiperidin-1-yl)sulfonyl)phenyl) acetamide) and 1e(3,5-bis((E)-3-bromobenzylidene)-1-((4-nitrophenyl)sulfonyl)piperidine-4-one) showed significant cytotoxic action against human SW1990, MIA PaCa-2, PG-BE1, NCI-H460, and SK-BR-3 cell lines, with average IC50 values of 1.94, 1.11, 1.16, and 0.817 lM, respectively. These compounds have great potential as prospective fluorescent anticancer agents and should be studied further to increase their potencies as helpful templates.[14]

Rahul L. Jadhav et al has revealed that a number of furfurylidene derivatives of piperidin-4-one have promising cytotoxic properties. N-Acrylolylation of the secondary amino group gives compounds 2d((3E,5E)-1-Acryloyl-3,5-bis(furan-2-ylmethylene) piperidin4-one) and 3d((3E,5E)-1-Acryloyl-3,5-bis(furan-2-ylmethylene) -2,6-diphenylpiperidin-4-one), which shows significant increased cytotoxicity. This result is in accordance with the theory of sequential cytotoxicity. But, further optimization of various substitutions is required for development of potent anticancer agents.[15]

Tamas Kalai et al showed that nitroxides or their amine precursors can be used to N-alkylate or acylate the previous DAP compounds, resulting in strong antioxidant moieties. Evaluation of the novel chemicals' cytotoxicity against cancer cell lines have shown that the modified compounds are more effective as anticancer agents but less hazardous to non-cancerous (healthy) cells, as demonstrated by A2780, MCF-7, and H9c2 noncancerous (healthy) cardiac cell line. The acquired empirical evidence is supported by computer docking simulations. Of the substances examined, compound 5c (N-Alkyl-3,5-bis(4-fluorobenzylidene) piperidin-4-one) was selected as the principal chemical for more research. These findings corroborate previous research showing that while nitroxides and their precursors improve the original activity, they do not lessen the modified compounds' anticancer properties.[16]

Umashankar Das et al introduced 1-[4-(2-alkylaminoethoxy) phenyl carbonyl]-3,5-bis(arylidene)-4-piperidones as a new class of cytotoxins. In several bioassays, several of these compounds show noticeably higher potencies than two well-known anticancer medications. The N-acyl group's adherence to the 3,5- bis(arylidene)-4-piperidones 1 to series 3-6 was followed by potency increases in around half of the comparisons with the series 1 analogues. This discovery implies that the N-acyl groups in different members of series 3-6 align with auxiliary binding sites, strengthening the interaction between the 1,5-diaryl-3-oxo-1,4-pentadienyl pharmacophore and a primary binding site.[17]

Swagatika Das et al reveals that in general the dimers in series 7-9 are generally strong cytotoxic agents against colon cancer cells HCT116 and HT29. These compounds generally have a significant potency advantage

over 5-FU or curcumin. Evidence was gathered that revealed the cytotoxic potencies were partly attributed to amidic groups in series 7 and 8. Specifically, 7a(1,2-bis[3,5-bis(Benzylidene)-4-oxo-piperidin-1-yl]ethane-1,2-dione), 7e(1,2-bis[3,5-bis(4-Fluorobenzylidene)-4-oxo-piperidin-1-yl]ethane-1,2-dione) and 8a(1,3-bis-[3,5-bis(Benzylidene)-4-oxo-piperidin-1yl]propane-1,3-dione),8c(1,3-bis-[3,5-bis(4-Chlorobenzylidene)-4-oxo-piperidin-1yl]propane-1,3-dione),8h(1,3-bis-[3,5-bis(3,4,5-Trimethoxybenzylidene)-4-oxo-piperidin-1yl] propane-1,3-dione) were identified as lead compounds for additional research and development. Strong electron withdrawing groups inserted into aryl rings may increase their cytotoxic potencies even further, according to QSAR research. Compound 7f(1,2-bis[3,5-bis(4-Methoxybenzylidene)-4-oxo-piperidin-1-yl] ethane-1,2-dione), a lead representative, caused HCT116 cells to undergo apoptosis. Nonetheless, structural alterations will be necessary to enhance a number of physicochemical characteristics.[18]

Aruna Chikkara et al., synthesized two new series of unsymmetrical 3,5-bis(benzylidene)-4 piperidones, designated 2a–f and 3a–e, as potential antineoplastic agents. These substances exhibit strong cytotoxicity against multiple oral squamous cell carcinomas and two colon malignancies. These compounds are less harmful to several non-cancerous cells producing high selectivity index (SI) values. Several of the compounds are also cytotoxic to HL-60 leukaemia cells and CEM lymphoma cells. Their potencies outweigh those of proven anticancer drugs in multiple cases. Representative compounds induced apoptotic cell death characterized by caspase-3 activation and subG1 accumulation in some OSCC cells, as well as the depolarization of the mitochondrial membrane potential in CEM cells. A further line of inquiry was directed to finding if the SI values are correlated with the atomic charges on the olefinic carbon atoms. The potential of these compounds as antineoplastic agents was enhanced by an ADME (absorption, distribution, metabolism, and excretion) evaluation of five lead molecules, which revealed no violations.[19]

According to Swagatika Das et al., Series 2 and 3 are strong cytotoxins that are more harmful to certain neoplasms than to a variety of non-malignant cells. The compounds 2a, 2b, 2g, 3a, 3b, and 3g are lead molecules in terms of potency whereas 2f and 3b have the greatest SI values. Potency and SI figures are taken into account when calculating PSE values, which show that the 4-fluoro analogs 2b (1,2-bis(3,5-bis((E)-4-fluorobenzylidene)-4-oxopiperidin-1-yl)ethane-1,2-dione) and 3b (1,3-bis(3,5-bis((E)-4-fluorobenzylidene)-4-oxopiperidin-1-yl)propane-1,3-dione), which are lead compounds, have the highest PSE values. Future research should include hydrophilic, electron-donating substituents in the aryl rings to boost potency, according to a QSAR analysis. This evaluation is somewhat consistent with the ADME result, which implies that smaller hydrophilic molecules might have more favourable absorption properties. Numerous mechanisms by which the lead chemical 3b exerts its cytotoxic effects were identified by multiple mode of action studies.[20]

Larissa M Nunes et al revealed that two novel piperidones, 2a(1-(2-methoxyethylthio-propionyl)-3,5-bis(benzylidene)-4-piperidone)and(3,5-bis(4-fluorobenzylidene)-1-[3-(2-methoxyethylsulfiny l)-propionyl]-4-piperidone), exert potent and selective cytotoxicity towards human leukaemia Nalm-6, CEM and Jurkat cells. Additionally, the T-lymphocyte leukaemia Jurkat cell line exhibited increased sensitivity to the two compounds subsequent to 24 and 48 h of exposure. Examination of the cell death mechanism that was involved in the observed cytotoxicity revealed that 2a and 3e elicited PS externalization, depolarization of the mitochondrial membrane potential and activation of caspase-3 on Jurkat cells. A key result of the present study is that the novel 2a and 3e piperidones are promising experimental anti-leukaemia cytotoxins. The piperidones primarily cause programmed cell death in human T-lymphocyte leukemic cells via the intrinsic/mitochondrial/caspase-3 apoptotic pathway, indicating that additional studies regarding these compounds are necessary. Future research on the drugs discussed in this study may involve the development of novel piperidone-derived analogues based on the structure of the aforementioned two lead compounds, with the aim of improving potency and selective cytotoxicity against malignant cells in anti-cancer drug design strategies.[21]

Roayapalley Praveen K. et al. prepared a novel series of 1-[3-{3,5-bis(benzylidene)-4-oxo-1-piperidino}-3-oxopropyl]-4-piperidone oximes 3a–h and related quaternary ammonium salts 4a–h as potential anti-tumour agents. Assessment against neoplastic Ca9-22, HSC-2, and HSC-4 cells demonstrated that the compounds in series 3 and 4 are almost always sub micromolar CC50 values, making them strong cytotoxins. However, the compounds demonstrated their tumour-selective toxicity when applied to HGF, HPLF, and HPC non-malignant cells, where they were less cytocidal. According to quantitative structure–activity relationship, the amplitude of the Hammett sigma values generally increased along with the cytotoxic potency and selectivity index numbers. Furthermore, 3a–h exhibit cytotoxicity against many leukemic and cells associated with colon cancer. In CEM cells, 4b((3~{E},5~{E})-3,5-bis[(4-fluorophenyl)methylene]-1-[3-(4-hydroximino-1-piperidyl)propanoyl]piperidin-4-one methiodide),4c((3~{E},5~{E})-3,5-bis[(4-chlorophenyl)methylene]-1-[3-(4-hydroximino-1-piperidyl)propanoyl]piperidin-4-one methiodide) decreased the mitochondrial membrane potential, while in Ca9-22 cells, 4d((3~{E},5~{E})-3,5-bis[(3,4-dichlorophenyl)methylene]-1-[3-(4-hydroximino-1-piperidyl)propanoyl]piperidin-4-one methiodide) temporarily increased G2/M accumulation. Five compounds namely 3c((3~{E},5~{E})-3,5-bis[(4-chlorophenyl)methylene]-1-[3-(4-hydroximino-1-piperidyl)propanoyl]piperidin-4-onehydrochloride),3d((3~{E},5~{E})-3,5-bis[(3,4-dichlorophenyl)methylene]-1-[3-(4-hydroximino-1-piperidyl)propanoyl]piperidin-4-onehydrochloride),4c((3~{E},5~{E})-3,5-bis[(4-chloro phenyl)methylene]-1-

[3-(4-hydroximino-1-piperidyl)propanoyl]piperidin-4-onemethiodide), 4d((3~{E},5~{E})-3,5-bis[(3,4-dichlorophenyl)methylene]-1-[3-(4-hydroximino-1-piperidyl)propanoyl]piperidin-4-onemethiodide),4e((3~{E},5~{E})-1-[3-(4-hydroximino-1-piperidyl)propanoyl]-3,5-bis[(4-nitrophenyl)methylene]piperidin-4-one methiodide) were shown to be lead molecules with drug-like characteristics.[22]

CONCLUSION

Piperidones have emerged as a promising class of compounds in the search for effective anticancer agents. Their unique structural features and versatile biological activities make them ideal candidates for anticancer drug development. The comprehensive analysis of their mechanisms of action reveals their ability to induce apoptosis, cause cell cycle arrest, and inhibit critical enzymes and signalling pathways involved in cancer progression. Advances in structure-activity relationship studies have facilitated the optimization of piperidone derivatives, enhancing their potency and selectivity against various cancer cell lines. Despite the significant progress, challenges remain in the development of piperidone-based therapeutics, including issues related to bioavailability, toxicity, and resistance. Addressing these challenges through innovative research and development strategies is crucial for translating the potential of piperidones into clinically effective anticancer therapies. In conclusion, piperidones represent a valuable scaffold for the design of novel anticancer agents. Continued exploration and refinement of these compounds could lead to the discovery of new, more effective treatments for cancer, ultimately improving patient outcomes.

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