REVIEW ARTICLE

The Emerging Role of Novel Heterocyclic Derivatives in Cancer Therapy

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Abstract

Cancer remains to pose a major worldwide health challenge because of its high incidence, complex pathophysiology, and poor prognosis in advanced stages. Conventional therapies, including chemotherapy, radiotherapy, immunotherapy, and hormonal treatments, have improved survival but are often accompanied by significant systemic toxicity, multidrug resistance, and low target selectivity. Heterocyclic compounds have emerged as pivotal scaffolds in anticancer drug discovery due to their structural diversity, capacity for functional modifications, and favorable pharmacokinetic and pharmacodynamic profiles. This review highlights recent advances in heterocyclic derivatives, including thiazolidine dione, 1,3,4-thiadiazole, and styryl-heterocyclic hybrids, emphasizing their mechanisms of action, structure–activity relationships, and clinical relevance. In addition, the review discusses the pharmacological potential of marketed heterocyclic anticancer drugs and provides insight into future directions for rational design, optimization, and targeted therapy development.

Key words: 1,3,4-Thiadiazole, anticancer therapy, heterocyclic derivatives, styryl-heterocyclic hybrids, thiazolidine dione

INTRODUCTION

This review covers the emerging role of novel heterocyclic derivatives in cancer therapy, with a particular focus on their structural diversity, biological significance, and therapeutic potential. Heterocyclic compounds, containing atoms such as nitrogen, oxygen, or sulfur within their ring systems, have gained considerable importance in anticancer drug development due to their ability to interact with multiple biological targets.[1] The review highlights various classes of heterocyclic scaffolds and their involvement in key mechanisms such as inhibition of cell proliferation, induction of apoptosis, and suppression of tumor progression. It also provides a general overview of structure–activity relationships, emphasizing how chemical modifications influence pharmacological activity and selectivity. In addition, the role of heterocyclic compounds in currently available anticancer drugs is briefly addressed, along with insights into their pharmacokinetic and pharmacodynamic behavior. Overall, this review presents a broad understanding of how heterocyclic derivatives contribute to the development of more effective and targeted cancer therapies, while also indicating future directions for research in this field.

CANCER AND ITS GLOBAL HEALTH BURDEN

Uncontrolled cellular growth is a characteristic of the diverse disease known as cancer, evasion of apoptosis, angiogenesis, and the potential for invasion and metastasis.[1-3] The underlying causes are multifactorial, including genetic mutations, epigenetic alterations, environmental exposures, and lifestyle factors.[4-7] Solid tumors, such as those originating in the breast, lung, colon, or liver, and hematological malignancies, including leukemias and lymphomas, result from the disruption of normal cellular growth control mechanisms.[8-10] The World

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Health Organization estimates that 9.6 million people died from carcinoma and 18.1 million new cases are diagnosed globally in 2018, making it is 2nd leading source of mortality worldwide. The incidence is projected to increase to over 22 million cases annually by 2030, with deaths potentially reaching 21.6 million.[11,12] The increasing prevalence of cancer presents substantial challenges for healthcare systems, necessitating the development of safer, more effective, and more selective therapeutic strategies that can overcome resistance mechanisms and minimize systemic toxicity.[13]

CONVENTIONAL CANCER THERAPIES AND THEIR LIMITATIONS

Current cancer management strategies rely on surgery, chemotherapy, radiotherapy, hormonal therapy, and immunotherapy, either alone or in combination.[14] Chemotherapy remains one of the most widely used systemic treatment modalities, targeting rapidly dividing cells through interference with DNA replication, repair, or mitotic processes.[15] Chemotherapeutic classes include topoisomerase inhibitor (e.g., etoposide), anti-metabolites (e.g., 5-fluorouracil, nelarabine), alkylating agent (e.g., cyclophosphamide), and other compounds such as monoclonal antibodies and molecular-targeted drugs.[16] While these therapies have significantly improved survival in various cancers, they suffer from notable limitations. Low selectivity causes damage to healthy proliferating cells, leading to myelosuppression, cardiotoxicity, gastrointestinal toxicity, and alopecia. High systemic doses required for therapeutic efficacy often compromise immunity, increasing susceptibility to infections.[17] Moreover, tumor cells frequently acquire multidrug resistance via mechanisms such as efflux pump overexpression, target enzyme mutation, or enhanced DNA repair.[16] These challenges highlight the urgent need for the development of novel, targeted, and multi-mechanistic drugs with improved therapeutic indices and reduced adverse effects.

HETEROCYCLIC DERIVATIVES IN DRUG DISCOVERY

Heterocyclic compounds are organic molecules containing at most 1 heteroatom typically oxygen, sulfur, or nitrogen, in a cyclic ring.[18] This structural feature confers unique electronic, steric, and hydrogen-bonding properties, enabling selective interactions with diverse biological targets, including enzymes, receptors, and nucleic acids. Heterocycles are ubiquitous in nature and serve as building blocks for numerous biomolecules essential for life, such as nucleic acids, vitamins, alkaloids, and coenzymes.[19,20] In drug discovery, heterocyclic scaffolds are crucial for imparting biological activity, improving pharmacokinetics (PK), and enhancing target specificity. More than 70% of small-molecule food and drug administration-approved drugs contain at least one heterocyclic ring, including key anticancer agents such as imatinib, dasatinib, erlotinib, and pazopanib.[21] The versatility of heterocycles lies in their capacity for substitution and functionalization, allowing medicinal chemists to fine-tune lipophilicity, solubility, metabolic stability, and binding affinity, which are essential attributes for optimizing therapeutic potential.[22,23]

STRUCTURE-ACTIVITY RELATIONSHIP (SAR) OF HETEROCYCLIC COMPOUNDS

The biological activity of heterocyclic derivatives is closely linked to their chemical structure and the nature of substituents on the core ring. For thiazolidine dione (TZD) derivatives, substitution at the 5-position with aromatic or heteroaromatic moieties enhances π–π interactions with DNA bases and target proteins, facilitating apoptosis induction.[24] Electron-withdrawing groups such as halogens or nitro functionalities increase cellular uptake and cytotoxic potency, while excessive hydrophobicity can reduce selectivity. In 1,3,4-thiadiazole derivatives, electron-donating substituents on the benzamide ring enhance hydrogen-bond interactions with enzymes such as topoisomerase II, improving inhibitory activity.[25] Steric effects from bulky substituents can modulate binding orientation and target selectivity. Styryl-heterocyclic hybrids benefit from planarity and conjugation provided by the styryl moiety, which facilitates DNA intercalation and enhances interactions with transcription factors.[24] Incorporation of indolenine or quinoline scaffolds increases binding affinity to oncogenic targets, demonstrating how precise structural modifications directly impact cytotoxic efficacy and therapeutic selectivity. Rational SAR-based optimization thus forms the cornerstone of modern heterocyclic drug development.[26]

PKS AND PHARMACODYNAMICS (PD) OF HETEROCYCLIC DERIVATIVES

The therapeutic success of heterocyclic compounds depends on favorable PK and PD properties. PK characteristics such as absorption, distribution, metabolism, and excretion are influenced by lipophilicity, aromaticity, and heteroatom content.[27] Many heterocyclic derivatives exhibit moderate lipophilicity, which enhances membrane permeability and oral bioavailability. Nitrogen- or sulfur-containing heterocycles often show high plasma protein binding, prolonging systemic circulation, while metabolic stability is achieved by resistance to oxidative degradation via CYP450 enzymes.[28] Active metabolites can contribute to extended therapeutic effects, and hepatic metabolism is generally the primary route of elimination.[29] Pharmacodynamically, heterocyclic derivatives act through multiple mechanisms, including apoptosis induction via mitochondrial pathways, inhibition of DNA replication by topoisomerase inhibition,

cell cycle arrest, and modulation of reactive oxygen species (ROS).[22] TZD derivatives activate peroxisome proliferator-activated receptor gamma (PPARγ)-mediated apoptotic pathways, thiadiazoles inhibit DNA unwinding enzymes, and styryl-heterocyclic hybrids suppress oncogenic transcription factors and oxidative stress, collectively contributing to multi-targeted anticancer efficacy.[23]

MARKETED HETEROCYCLIC ANTICANCER DRUGS

Several clinically approved anticancer agents exemplify the therapeutic relevance of heterocyclic scaffolds. Imatinib, a pyrimidine-based inhibitor of tyrosine kinase, selectively aims BCR-ABL protein fusion within chronic myeloid cancer. Erlotinib and gefitinib, quinazoline derivatives, inhibit epidermal growth factor receptor (EGFR) within non-small lung cell melanoma. Dasatinib, containing a thiazole ring, acts as a multi-kinase inhibitor effective against imatinib-resistant leukemia. Sorafenib and sunitinib, featuring pyridine and indole heterocycles, inhibit multiple tyrosine kinases involved in angiogenesis and tumor growth, while pazopanib, an indazole derivative, exerts antiangiogenic activity through vascular endothelial growth factor receptor (VEGFR) inhibition. These examples illustrate how heterocyclic chemistry contributes to targeted therapy, improved PKs, and enhanced clinical outcomes.[21-23]

ADVANCES IN NOVEL HETEROCYCLIC SCAFFOLDS

TZD derivatives

TZD derivatives are five-membered heterocycles containing both sulfur and nitrogen atoms, known for their multifaceted anticancer properties. Among recently synthesized derivatives, compound 8c demonstrated potent cytotoxic movement opposite MCF-7 cells of breast malignance through IC_{50} by 14.2 μM and showed comparable efficacy against PC-3 prostate cancer cells (IC_{50} 16.5 μM).[30] Compound 10 g, another TZD derivative, exhibited broad-spectrum anticancer activity against A549 lung cancer (IC_{50} 12.7 μM) and malondialdehyde (MDA)-MB-453 breast cancer (IC_{50} 18.3 μM). Machine-like research reveals which these compounds comprise apoptosis through mitochondrial intrinsic path, including instigation of caspase 3 and 9, DNA intercalation, leading to arrest of cell cycle with G2/M stage.[31]

In addition to these examples, TZD analogues such as rosiglitazone derivatives and pioglitazone hybrids have been explored for anticancer activity. These analogues leverage PPARγ activation to modulate cell differentiation and inhibit proliferation.[32] Structural modifications, such as aromatic or heteroaryl substitutions at the 5-position, enhance lipophilicity and DNA-binding affinity, which correlates with increased cytotoxic potency.[30] Preclinical studies suggest that some TZD derivatives may act synergistically with conventional chemotherapeutics, improving efficacy while potentially reducing systemic toxicity.[31] Details of TZD derivatives are presented in Table 1.

1,3,4-Thiadiazole derivatives

1,3,4-Thiadiazole derivatives are stable, nitrogen-sulfur heterocycles with significant lipophilicity, which facilitates cellular uptake and metabolic stability. Novel N-[5-(1,3,4,5-tetrahydroxycyclohexyl)-1,3,4-thiadiazole-2-yl] benzamide derivatives (compounds 5a–5j) demonstrated strong *in vitro* cytotoxicity against MCF7 cells, by IC_{50} value that rangeas10–25 μM.[21] In 7,12-dimethylbenz[a] anthracene-induced murine tumor models, these compounds reduced tumor volume by 40–60% over a 28-day treatment period. Mechanistically, thiadiazoles inhibit topoisomerase II, disrupt microtubule dynamics, and induce

Table 1: Thiazolidinedione derivatives

Compound	Cancer type/ cell line	IC_{50} (μM)	Mechanism of action	SAR insights/structural features
TZD–acridine hybrid	Breast, colon	14–20	DNA intercalation, apoptosis modulation	Dual moiety enhances multi-target activity
TZD–lupeol conjugate	Breast	12–18	Apoptosis induction, cell cycle regulation	Natural triterpene conjugation increases efficacy
TZD–benzimidazole derivative	Various	15–25	Microtubule disruption, PPARγ activation	Hybrid design enhances antiproliferative effect
Rosiglitazone	Preclinical studies	N/A	PPARγ-mediated anti-inflammatory and antiproliferative effects	TZD core structure
Pioglitazone	Preclinical studies	N/A	PPARγ activation, apoptosis modulation	TZD scaffold

SAR: Structure–activity relationship, TZD: Thiazolidinedione, PPARγ: Peroxisome proliferator-activated receptor gamma

apoptosis, as confirmed by annexin V staining and caspase activation assays.[34]

Specific derivatives such as 5b and 5f exhibited remarkable selectivity toward cancer cells, minimizing toxicity to normal fibroblasts *in vitro*. Other notable analogues under investigation include 2-amino-1,3,4-thiadiazole-substituted pyridines and thiadiazole-linked sulfonamides, which are being studied for dual inhibition of topoisomerase and tyrosine kinases.[35] Computational docking studies suggest that hydrogen bonding and π–π stacking interactions with active site residues are critical for inhibitory potency, emphasizing the importance of precise structural modifications for SAR-guided optimization.[34] Details of 1,3,4-thiadiazole derivatives are presented in Table 2.

Styryl-heterocyclic hybrids

Styryl-heterocyclic hybrids represent a class of compounds combining a styryl moiety with nitrogen-containing heterocycles such as indolenine, quinoline, and 1,3,4-oxadiazole. These hybrids are designed to improve DNA intercalation, ROS modulation, and receptor binding. Compound 10d demonstrated the highest cytotoxic activity against HepG2 liver cancer cells (IC_{50} 11.80 μM) and MCF7 cells of breast malignancy (IC_{50} 24.55 μM). Mechanistic studies indicate G0/G1 arrest of cell series, induction of programmed cell death via caspase pathways, and reserve of oncogenic transcription factors such as nuclear factor-κB and STAT3.[36]

Other promising derivatives include indolenine-styryl hybrids 12a–12f, which showed IC_{50} values between 10 and 18 μM across multiple cancer cell lines, including T47D and HeLa. Quinoline-styryl derivatives have also been explored for their dual role as topoisomerase inhibitors and ROS modulators.[37] The hybridization strategy enhances planarity and electronic delocalization, improving DNA binding affinity and cytotoxic selectivity. Preclinical studies indicate favorable PKs, with moderate oral bioavailability and metabolic stability, highlighting the potential for translation into clinical candidates.[36,37] Details of styryl-heterocyclic hybrids are presented in Table 3.

Table 2: 1,3,4-thiadiazole derivatives

Compound	Cancer type/ cell line	IC_{50} (μM)	Mechanism of action	SAR insights/structural features
Filanesib (SNS-032)	Breast, lung	N/A	KSP inhibition, mitotic arrest, apoptosis	Thiadiazole scaffold critical for spindle protein binding
Indole–thiadiazole schiff base	Multiple	10–20	Apoptosis induction, proliferation inhibition	Indole substitution improves DNA binding
Pyrimidine–thiadiazole hybrid	Various	12–25	DNA synthesis inhibition, cell cycle arrest	Pyrimidine–thiadiazole hybridization enhances dual activity
Hydroxylated benzamide-thiadiazole	MCF-7	10–25	Topoisomerase II inhibition, apoptosis	Hydroxylation and benzamide substitution improve permeability and selectivity
Methazolamide	-	-	-	Thiadiazole core
Acetazolamide	-	-	-	Thiadiazole core

SAR: Structure–activity relationship

Table 3: Styryl-heterocyclic hybrids

Compound	Cancer type/cell line	IC_{50} (μM)	Mechanism of action	SAR insights/structural features
Styryl–indolenine hybrid	HepG2, MCF-7, T47D, HeLa	10–18	Apoptosis induction, proliferation inhibition, ROS modulation	Styryl conjugation enhances planarity and DNA intercalation
Phenylpyrazole–styryl hybrid	Bladder cancer	12–20	Apoptotic and autophagic cell death	Dual functional hybrid strategy enhances multi-pathway cytotoxicity
Styryl–quinoline hybrid	Various	15–25	Topoisomerase inhibition, cell cycle arrest	Quinoline moiety improves enzyme binding and ROS modulation
Tamoxifen	Breast cancer	N/A	Selective estrogen receptor modulation	Styryl-containing core
Raloxifene	Osteoporosis, potential anticancer	N/A	Estrogen receptor modulation	Styryl scaffold

ROS: Reactive oxygen species, SAR: Structure–activity relationship

HETEROCYCLIC SCAFFOLDS IN ANTICANCER DRUG DEVELOPMENT

Benzoxazole derivatives

Benzoxazole derivatives have emerged as potent scaffolds for anticancer drug development due to their versatile chemical modifications and favorable biological activities [Figure 1]. Al-Harthy *et al*. developed a series of benzoxazole derivatives incorporating piperazine and fluorine moieties through a multistep process involving nitration, piperazinylation, and subsequent *in situ* reductive cyclization.[38-40] The synthesized compounds were then assessed for their cytotoxic activity against A549 human lung epithelial cancer cells using the CellTitre-Glo luminescent cell proliferation assay, and certain intermediates displayed promising cytotoxicity, although solubility issues in aryl-piperazine derivatives limited initial activity.[41-45] Murty *et al*. extended this work by coupling benzoxazole derivatives with piperazine rings and evaluating cytotoxic potential across 5 cell lines (HeLa, MCF-7, A431, HepG2, and A549).[46] Composites with amide linkages showed enhanced activity, particularly against A431 cells, while most derivatives displayed IC_{50} values below 100 µM in MCF-7 cells. Researchers reported benzoxazole hydrazone derivatives and observed significant anti-glioma activity, particularly for N'-(1,1'-Biphenyl-4-yl-methylene)-2-[(5-fluorobenzoxazole-2-yl)thio]acetohydrazide, which induced dose-dependent late apoptosis in C6 glioma cells. Collectively, these studies highlight benzoxazole as a versatile scaffold, capable of selective cytotoxicity and kinase inhibition.

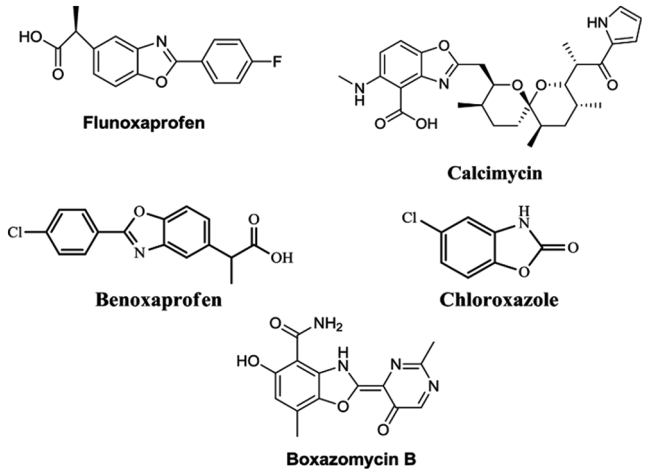

Figure 1: Benzoxazole derivatives

Piperazine-based compounds

Piperazine scaffolds have been widely explored due to their ability to enhance solubility, bioavailability, and cytotoxicity

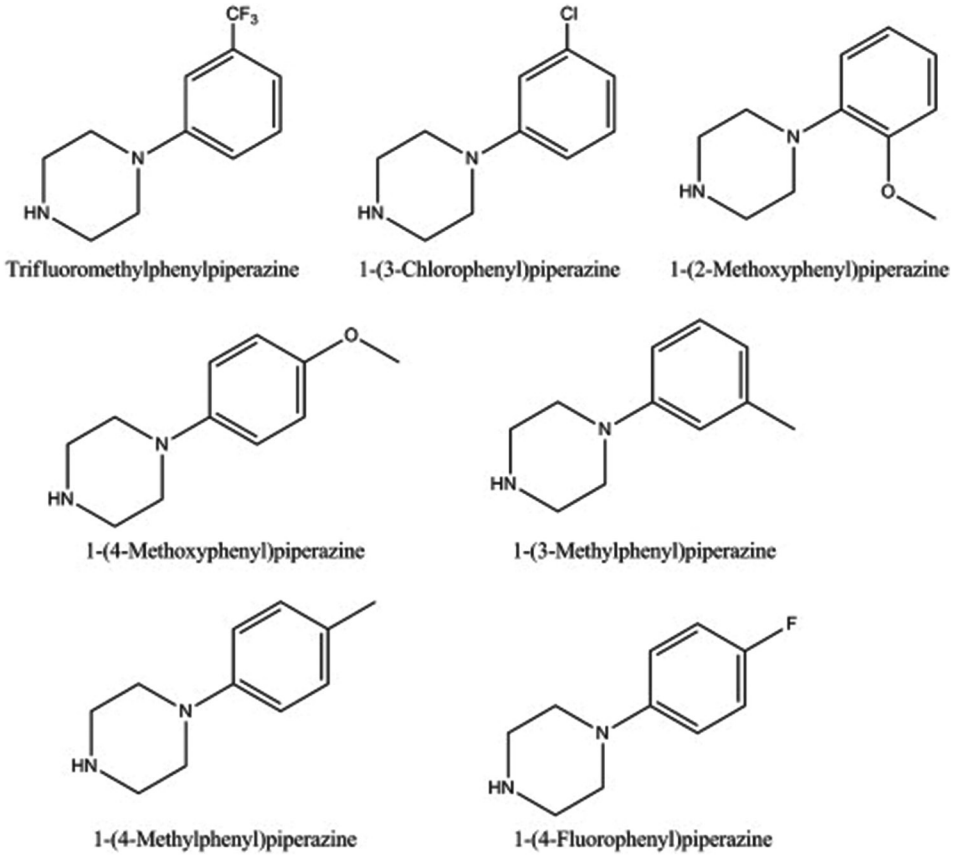

Figure 2: Piperazine-based compounds

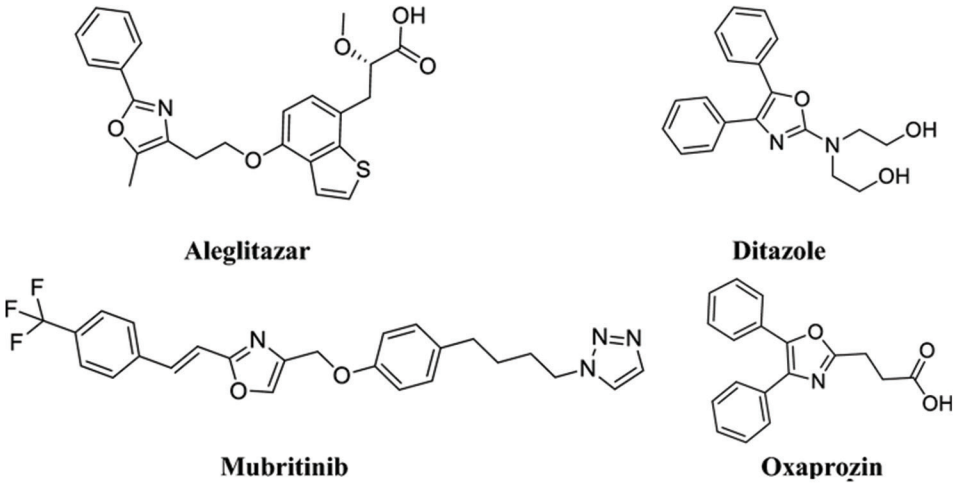

Figure 3: Oxazole derivatives

[Figure 2]. A novel sequence of mono-Mannich base comprising piperazine demonstrated potent inhibition against carbonic anhydrase isozymes hCAI and hCAII, with Ki values in the nanomolar range. 4-fluorophenyl piperazine showed the main tumor selectivity (TS = 59.6), inducing significant cancer cell-based death. Piperazine-acetamide derivatives were synthesized and observed that N-(5-benzyl-4-(tert-butyl)thiazol-2-yl)-2-(piperazin-1-yl)acetamide exerted effective cytotoxicity in contradiction of HeLa cells, inducing G1 phase arrest and apoptosis.[47] Research combined piperazine with ciprofloxacin derivatives, where 7-(4-(2-chloroacetyl)piperazin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid exhibited $IC_{50} \leq 10$ µM across multiple cancer lines. It was demonstrated that benzofuran-piperazine hybrids selectively targeted HeLa cells with higher cytotoxicity than cisplatin. Overall, piperazine derivatives enhance anticancer activity while modulating PK properties.[48-52]

Oxazole derivatives

Oxazole derivatives, known for their planar heterocyclic structures, show significant anticancer activity [Figure 3]. Researchers synthesized 2-methyl-4,5-disubstituted oxazoles and assessed activity in accordance of seven human tumor cell lines. The 11a and 11b showed IC_{50} values as low as 0.35–4.6 nM. SAR studies suggested that trimethoxyphenyl moieties at C-4 enhance activity, while electron-donating groups at meta positions reduce cytotoxicity. Researchers developed propenone and methadone derivatives incorporating oxazole, pyridine, and pyrazoline rings, where 12d with bromo substitution presented highest effectiveness against breast, ovarian, and leukemia cell lines.[53-55]

Indole and spiro-oxindole derivatives

Indole derivatives provide a rich scaffold for anticancer drug discovery [Figure 4]. Researchers synthesized pyrido[3,4-b]indole derivatives, identifying

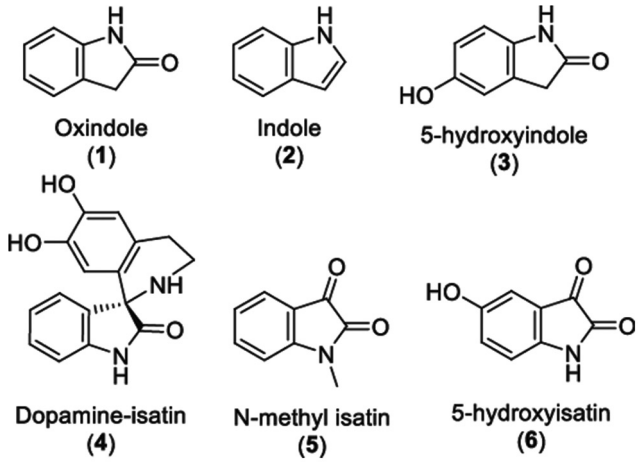

Figure 4: Indole derivatives

1-naphthyl-6-methoxy-9H-pyrido[3,4-b]indole as highly potent against multiple human cancer cell lines, including colon, pancreatic, breast, melanoma, lung, and prostate cancers.[56] Indole-based imidazo[2,1-b][1,3,4] thiadiazole derivatives were active against pancreatic ductal adenocarcinoma cells, while some prepared spiro-oxindole-indole hybrids effective against MCF-7 and K562 leukemia cells [Figure 5].[57,58]

Imidazole derivatives

Imidazole derivatives have been widely reported for their antiproliferative effects [Figure 6]. Research synthesized benzyl-dichloromethyl-nitroimidazoles showing significant activity against cancer cells.[59] It was reported that amino-xantheno-imidazole derivatives targeting MDA-MB-231 breast cancer cells, with SAR indicating increased activity with larger and more basic substituents. Developed imidazole-linked pyrimidine amides as Cyclin-dependent kinase inhibitors, demonstrating enhanced anti-proliferative activity. Other studies included imidazole-benzofuran hybrids and

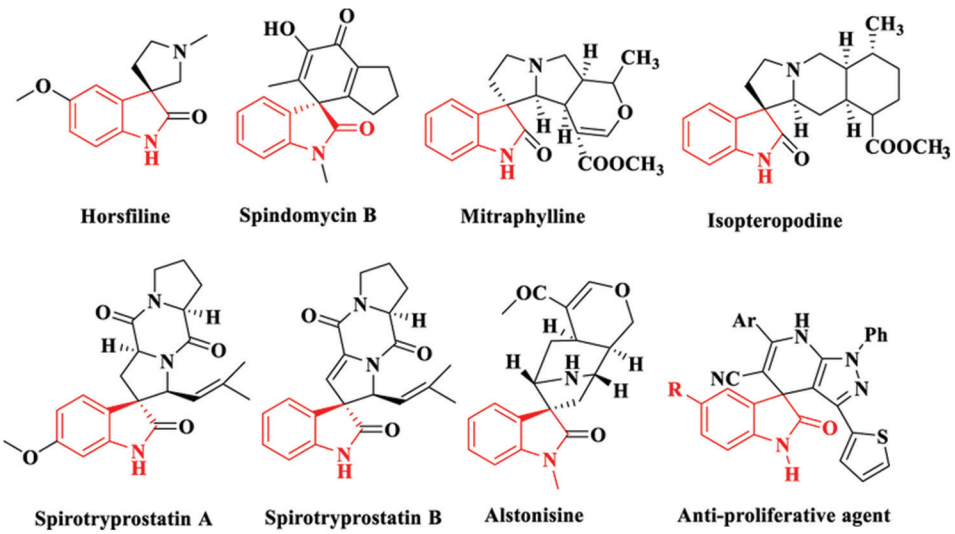

Figure 5: Spiro-oxindole derivatives

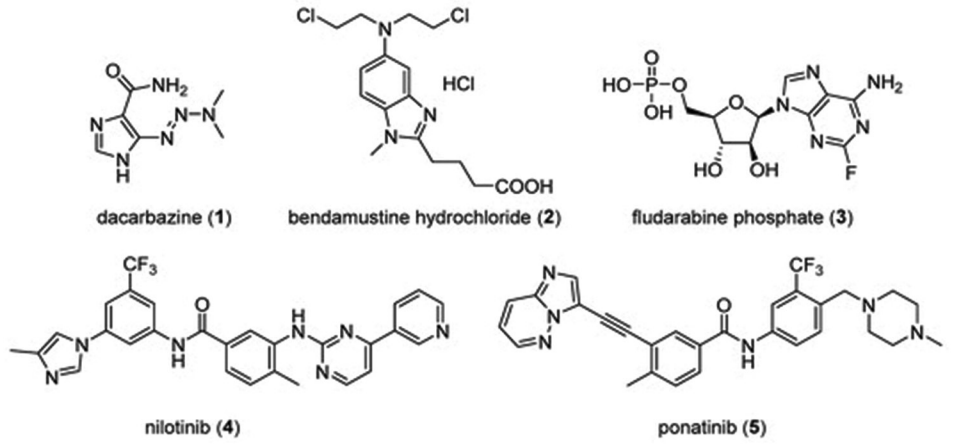

Figure 6: Imidazole derivatives

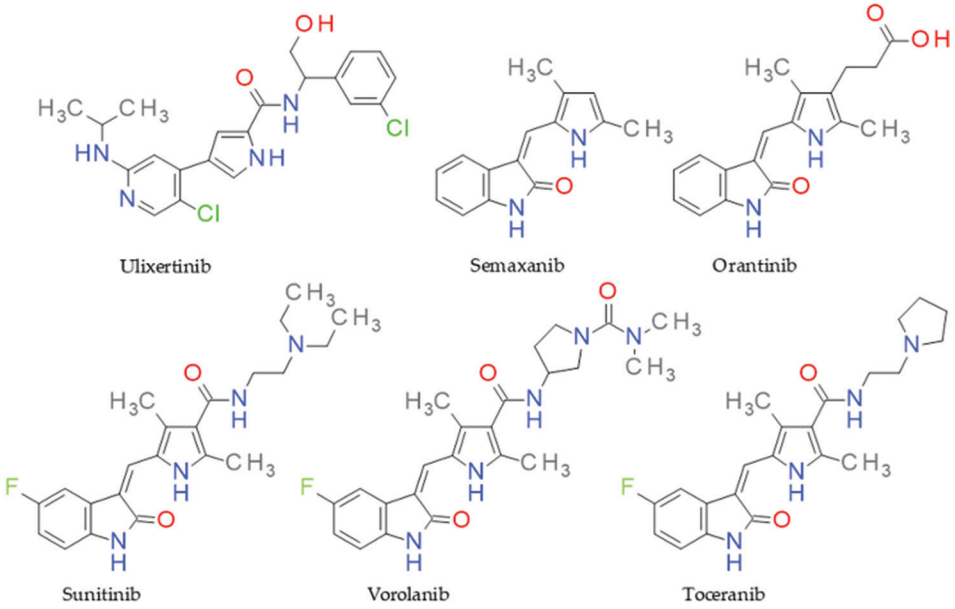

Figure 7: Pyrrole derivatives

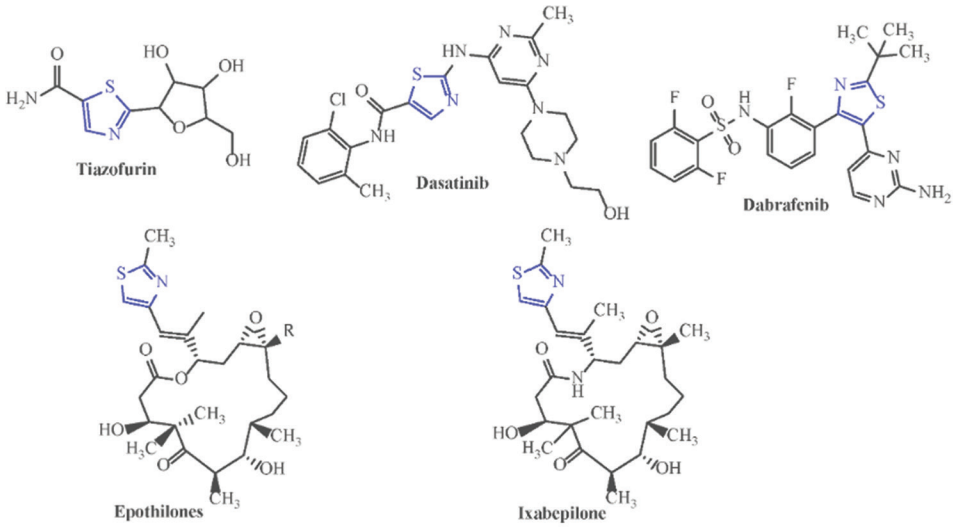

Figure 8: Thiazole derivatives

Schiff base derivatives targeting EGFR and p53-dependent MDM2-amplified cells, with compounds exhibiting strong cytotoxicity and selective kinase inhibition.[60-62]

Pyrrole derivatives

Pyrrole scaffolds are notable for their incorporation of sulfonamide and morpholine groups [Figure 7]. Researchers synthesized pyrrole derivatives effective against MCF-7, MOLT-4, and HL-60 cell lines, with docking studies indicating multiple hydrogen bond interactions. Researchers designed pyrrole derivatives targeting EGFR and VEGFR kinases, showing stable electrostatic interactions and promising cytotoxicity.[63,64]

Thiazole derivatives

Thiazole derivatives have shown diverse anticancer potential. 2-((1R,2R,4S,5R)-4-(hydroxymethyl)-3,6-dioxabicyclo[3.1.0]hexan-2-yl)thiazole-4-carboxamide, exhibiting potent cytotoxicity against K562 cells was synthesized [Figure 8]. Thiazole-based derivatives were developed and screened against 60 human cancer cell lines, identifying compounds 69 and 70 as potent cytostatic agents across leukemia, central nervous system, melanoma, and renal cancers. Nanosized fluorinated thiazoles and azole-chromene hybrids further demonstrated improved antiproliferative activity compared to cisplatin.[65-67]

Furan and thiophene derivatives

Furan derivatives, such as 1,2-dihydronaphtho[2,1-b]furan-2-yl(p-tolyl)methanone, exhibited selective cytotoxicity against MCF-7 and MDA-MB-468.[68-70] Thiophene derivatives have been explored as anthraquinone hybrids, showing potent antiproliferative activity. It was reported that 5-(thiophen-2-yl)-1,3,4-thiadiazoles active against A549 and HepG2.[71,72]

Triazole derivatives

1,2,3-Triazole derivatives have been widely investigated as tubulin polymerization inhibitors and cytotoxic agents. Researchers synthesized Schiff-linked triazoles active against A549, prepared coumarin-based triazoles with IC_{50} values in the low micromolar range against HeLa and MCF-7. And developed piperazine-triazole derivatives that inhibited tubulin polymerization and arrested the G2/M phase in A549 and taxol-resistant cells.[73-75]

CONCLUSION

Heterocyclic scaffolds, particularly TZD derivatives, 1,3,4-thiadiazoles, and styryl-heterocyclic hybrids, represent a highly promising class of compounds in anticancer drug development. Advances in rational SAR design, PK optimization, and mechanistic elucidation continue to enhance their therapeutic potential. With ongoing preclinical and clinical evaluation, these derivatives hold the promise of improving cancer therapy through targeted, multi-mechanistic approaches that minimize toxicity and overcome drug resistance.

REFERENCES

1. Schwartz SM. Epidemiology of cancer. Clin Chem 2024;70:140-9.
2. Koo MM, Swann R, McPhail S, Abel GA, Elliss-Brookes L, Rubin GP, *et al*. Presenting symptoms of cancer and stage at diagnosis: Evidence from a cross-sectional, population-based study. Lancet Oncol

2020;21:73-9.
3. Tewes M, Baumann F, Teufel M, Ostgathe C. Symptoms during outpatient cancer treatment and options for their management. Dtsch Arztebl Int 2021;118:291-7.
4. Al Bashir S, AlBarakat MM, Alabedalhalim KK, Al-Khalaileh A, Alassaf A, Saleh O, *et al*. Knowledge of cancer symptoms and risk factors: A cross-sectional study from a developing country. Medicine (Baltimore) 2024;103:e37823.
5. Shahbaz A, Mahmood T, Javed MU, Abbasi BH. Current advances in microbial-based cancer therapies. Med Oncol 2023;40:207.
6. Hughes T, Harper A, Gupta S, Frazier AL, Van Der Graaf WT, Moreno F, *et al*. The current and future global burden of cancer among adolescents and young adults: A population-based study. Lancet Oncol 2024;25:1614-24.
7. Chu X, Tian W, Ning J, Xiao G, Zhou Y, Wang Z, *et al*. Cancer stem cells: Advances in knowledge and implications for cancer therapy. Signal Transduct Target Ther 2024;9:170.
8. Kumbhakar DV, Thakkar L, Akhand C, Sharaf S, Vemuganti GK. Nanomaterials targeting cancer stem cells to overcome drug resistance and tumor recurrence. Front Oncol 2025;15:1499283.
9. Garg P, Malhotra J, Kulkarni P, Horne D, Salgia R, Singhal SS. Emerging therapeutic strategies to overcome drug resistance in cancer cells. Cancers (Basel) 2024;16:2478.
10. Evans ST, Jani Y, Jansen CS, Yildirim A, Kalemoglu E, Bilen MA. Understanding and overcoming resistance to immunotherapy in genitourinary cancers. Cancer Biol Ther 2024;25:2342599.
11. Wu Z, Xia F, Lin R. Global burden of cancer and associated risk factors in 204 countries and territories, 1980-2021: A systematic analysis for the GBD 2021. J Hematol Oncol 2024;17:119.
12. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.
13. Mullard A. Addressing cancer's grand challenges. Nat Rev Drug Discov 2020;19:825-6.
14. Anand U, Dey A, Chandel AK, Sanyal R, Mishra A, Pandey DK, *et al*. Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. Genes Dis 2022;10:1367-401.
15. Zafar A, Khatoon S, Khan MJ, Abu J, Naeem A. Advancements and limitations in traditional anti-cancer therapies: A comprehensive review of surgery, chemotherapy, radiation therapy, and hormonal therapy. Discov Oncol 2025;16:607.
16. Yu X, Yang Y, Chen T, Wang Y, Guo T, Liu Y, *et al*. Cell death regulation in myocardial toxicity induced by antineoplastic drugs. Front Cell Dev Biol 2023;11:1075917.
17. Emran TB, Shahriar A, Mahmud AR, Rahman T, Abir MH, Siddiquee MF, *et al*. Multidrug resistance in cancer: Understanding molecular mechanisms, immunoprevention and therapeutic approaches. Front Oncol 2022;12:891652.
18. Maji S, Debnath B, Panda S, Manna T, Maity A, Dayaramani R, *et al*. Anticancer potential of the S-heterocyclic ring containing drugs and its bioactivation to reactive metabolites. Chem Biodivers 2024;21:e202400473.
19. Pathak N, Rathi E, Kumar N, Kini SG, Rao CM. A review on anticancer potentials of benzothiazole derivatives. Mini Rev Med Chem 2020;20:12-23.
20. Al-Sanea MM, Hamdi A, Mohamed AA, El-Shafey HW, Moustafa M, Elgazar AA, *et al*. New benzothiazole hybrids as potential VEGFR-2 inhibitors: Design, synthesis, anticancer evaluation, and *in silico* study. J Enzyme Inhib Med Chem 2023;38:2166036.
21. Jampilek J. Heterocycles in medicinal chemistry II. Molecules 2024;29:4810.
22. Jampilek J. Heterocycles in medicinal chemistry. Molecules 2019;24:3839.
23. Hossain M, Habib I, Singha K, Kumar A. FDA-approved heterocyclic molecules for cancer treatment: Synthesis, dosage, mechanism of action and their adverse effect. Heliyon 2024;10:e23172.
24. Surekha G, Jayeprakash MR, Tahlan S, Verma PK. Biological potential of thiazolidinedione derivatives of synthetic origin. Chem Cent J 2017;11:130.
25. Khalili Ghomi M, Noori M, Nazari Montazer M, Zomorodian K, Dastyafteh N, Yazdanpanah S, *et al*. [1,2,4]Triazolo[3,4-b][1,3,4]thiadiazole derivatives as new therapeutic candidates against urease positive microorganisms: Design, synthesis, pharmacological evaluations, and *in silico* studies. Sci Rep 2023;13:10136.
26. Elebiju OF, Ajani OO, Oduselu GO, Ogunnupebi TA, Adebiyi E. Recent advances in functionalized quinoline scaffolds and hybrids-exceptional pharmacophore in therapeutic medicine. Front Chem 2023;10:1074331.
27. Glassman PM, Muzykantov VR. Pharmacokinetic and pharmacodynamic properties of drug delivery systems. J Pharmacol Exp Ther 2019;370:570-80.
28. Rusu A, Moga IM, Uncu L, Hancu G. The role of five-membered heterocycles in the molecular structure of antibacterial drugs used in therapy. Pharmaceutics 2023;15:2554.
29. Vaja R, Rana M. Drugs and the liver. Anaesth Intensive Care Med 2020;21:517-23.
30. Ranjan G, Ranjan S, Sunita P, Pattanayak SP. Thiazolidinedione derivatives in cancer therapy: Exploring novel mechanisms, therapeutic potentials, and future horizons in oncology. Naunyn Schmiedebergs Arch Pharmacol 2025;398:4705-25.
31. Latambale G, Juvale K. Thiazolidinedione derivatives: Emerging role in cancer therapy. Mol Divers 2025;29:5185-217.

32. Laxmi SV, Anil P, Rajitha G, Rao AJ, Crooks PA, Rajitha B. Synthesis of thiazolidine-2,4-dione derivatives: Anticancer, antimicrobial and DNA cleavage studies. J Chem Biol 2016;9:97-106.
33. Janowska S, Khylyuk D, Bielawska A, Szymanowska A, Gornowicz A, Bielawski K, *et al*. New 1,3,4-thiadiazole derivatives with anticancer activity. Molecules 2022;27:1814.
34. Stecoza CE, Nitulescu GM, Draghici C, Caproiu MT, Hanganu A, Olaru OT, *et al*. Synthesis of 1,3,4-thiadiazole derivatives and their anticancer evaluation. Int J Mol Sci 2023;24:17476.
35. Gawande P, Matore BW, Murmu A, Kumar A, Jana S, Roy PP, *et al*. 1,3,4-Thiadiazole derivatives as VEGFR-2 inhibitors and its molecular insight for cancer therapy. Chem Biodivers 2025;22:e01361.
36. Abdelshaheed MM, El Subbagh HI, Tantawy MA, Attia RT, Youssef KM, Fawzy IM. Discovery of new pyridine heterocyclic hybrids; design, synthesis, dynamic simulations, and *in vitro* and *in vivo* breast cancer biological assays. RSC Adv 2023;13:15689-703.
37. Gangwar A, Das A, Jaitak V. Progress in heterocyclic hybrids for breast cancer therapy: Emerging trends, hybridization techniques, mechanistic pathways and SAR insights. Mini Rev Med Chem 2025. doi: 10.2174/0113895575386481250811052953. Epub ahead of print.
38. Al-Harthy T, Zoghaib WM, Pflüger M, Schöpel M, Önder K, Reitsammer M, *et al*. Design, synthesis, and cytotoxicity of 5-fluoro-2-methyl-6-(4-aryl-piperazin-1-yl) benzoxazoles. Molecules 2016;21:1290.
39. Osmaniye D, Korkut Çelikateş B, Sağlık BN, Levent S, Acar Çevik U, Kaya Çavuşoğlu B, *et al*. Synthesis of some new benzoxazole derivatives and investigation of their anticancer activities. Eur J Med Chem 2021;210:112979.
40. Alanazi MM, Mahdy HA, Alsaif NA, Obaidullah AJ, Alkahtani HM, Al-Mehizia AA, *et al*. New bis([1,2,4] triazolo)[4,3-a:3',4'-c]quinoxaline derivatives as VEGFR-2 inhibitors and apoptosis inducers: Design, synthesis, *in silico* studies, and anticancer evaluation. Bioorg Chem 2021;112:104949.
41. Alsaif NA, Taghour MS, Alanazi MM, Obaidullah AJ, Alanazi WA, Alasmari A, *et al*. Identification of new [1,2,4]triazolo[4,3-a]quinoxalines as potent VEGFR-2 tyrosine kinase inhibitors: Design, synthesis, anticancer evaluation, and in silico studies. Bioorg Med Chem 2021;46:116384.
42. Alsaif NA, Dahab MA, Alanazi MM, Obaidullah AJ, Al-Mehizia AA, Aldawas S, *et al*. New quinoxaline derivatives as VEGFR-2 inhibitors with anticancer and apoptotic activity: Design, molecular modeling, and synthesis. Bioorg Chem 2021;110:104807.
43. Abd El-Meguid EA, Naglah AM, Moustafa GO, Awad HM, El Kerdawy AM. Novel benzothiazole-based dual VEGFR-2/EGFR inhibitors targeting breast and liver cancers: Synthesis, cytotoxic activity, QSAR and molecular docking studies. Bioorg Med Chem Lett 2022;58:128529.
44. Omar AM, AboulWafa OM, El-Shoukrofy MS, Amr ME. Benzoxazole derivatives as new generation of anti-breast cancer agents. Bioorg Chem 2020;96:103593.
45. Elkady H, Elwan A, El-Mahdy HA, Doghish AS, Ismail A, Taghour MS, *et al*. New benzoxazole derivatives as potential VEGFR-2 inhibitors and apoptosis inducers: Design, synthesis, anti-proliferative evaluation, flowcytometric analysis, and *in silico* studies. J Enzyme Inhib Med Chem 2022;37:397-410.
46. Murty MS, Rao BR, Katiki MR, Nath LR, Anto RJ. Synthesis of piperazinyl benzothiazole/benzoxazole derivatives coupled with 1,3,4-oxadiazole-2-thiol: Novel hybrid heterocycles as anticancer agents. Med Chem Res 2013;22:4980-91.
47. Chopra A, Anderson A, Giardina C. Novel piperazine-based compounds inhibit microtubule dynamics and sensitize colon cancer cells to tumor necrosis factor-induced apoptosis. J Biol Chem 2014;289:2978-91.
48. Zhang RH, Guo HY, Deng H, Li J, Quan ZS. Piperazine skeleton in the structural modification of natural products: A review. J Enzyme Inhib Med Chem 2021;36:1165-97.
49. Faizan M, Kumar R, Mazumder A, Salahuddin, Kukreti N, Kumar A, *et al*. Synthetic protocols, structural activity relationship, and biological activity of piperazine and its derivatives. Med Chem 2024;20:753-80.
50. Faizan M, Kumar R, Mazumder A, Salahuddin, Kukreti N, Kumar A, *et al*. The medicinal chemistry of piperazines: A review. Chem Biol Drug Des 2024;103:e14537.
51. Rasheed AM, Shetty KK, Roy LD, Kumar J. Novel piperazine derivatives as potent antihistamine, anti-inflammatory, and anticancer agents, their synthesis and characterization. Anticancer Agents Med Chem 2024;24:1063-73.
52. Pediconi N, Ghirga F, Del Plato C, Peruzzi G, Athanassopoulos CM, Mori M, *et al*. Design and synthesis of piperazine-based compounds conjugated to humanized ferritin as delivery system of siRNA in cancer cells. Bioconjug Chem 2021;32:1105-16.
53. Ghodgaonkar S, Jadhav P, Jadhav T, Jain B, Jogi A, Sanap M, *et al*. Exploring novel oxazole derivatives for cancer therapy: Design, synthesis, and mechanistic insights. Curr Drug Discov Technol 2026;23:e15701638370100.
54. Kulkarni S, Kaur K, Jaitak V. Recent developments in oxazole derivatives as anticancer agents: Review on synthetic strategies, mechanism of action and SAR studies. Anticancer Agents Med Chem 2022;22:1859-82.
55. Yan X, Wen J, Zhou L, Fan L, Wang X, Xu Z. Current scenario of 1,3-oxazole derivatives for anticancer activity. Curr Top Med Chem 2020;20:1916-37.
56. Li X, Liu Y, Huang W, Xie X, Zhu H, Peng C, *et al*. Advancements in small molecule PROTACs containing indole/spiro-fused oxindole scaffolds: An emerging degrader targeting cancers. Anticancer Agents Med Chem 2023;23:1164-73.
57. Panda SS, Girgis AS, Aziz MN, Bekheit MS. Spirooxindole: A versatile biologically active heterocyclic scaffold. Molecules 2023;28:618.

58. Miankooshki FR, Bayat M, Nasri S, Samet NH. 1,3-Dipolar cycloaddition reactions of isatin-derived azomethine ylides for the synthesis of spirooxindole and indole-derived scaffolds: Recent developments. Mol Divers 2023;27:2365-97.
59. Tolomeu HV, Fraga CA. Imidazole: Synthesis, functionalization and physicochemical properties of a privileged structure in medicinal chemistry. Molecules 2023;28:838.
60. Aboulhoda BE, Omar AM, Elfarrash S, Alghamdi MA, Emam AA, El-Gamal R, *et al*. Novel anticancer effect of substituted imidazole derivatives against urothelial carcinoma: Integrating *in vitro* screening and molecular docking for target kinases. BMC Cancer 2025;25:1524.
61. Dziduch K, Janowska S, Andrzejczuk S, Strzyga-Łach P, Struga M, Feldo M, *et al*. Synthesis and biological evaluation of new compounds with nitroimidazole moiety. Molecules 2024;29:3023.
62. Alsirhani AM, Aali I, Hussein MF, Elkanzi NA, Ali AM, Aboelez MO. Rational design, green synthesis, and biological evaluation of novel imidazole derivatives as potent EGFR inhibitors via one-pot four-component reaction. Arch Pharm (Weinheim) 2025;358:e70044.
63. Kuznietsova H, Dziubenko N, Byelinska I, Hurmach V, Bychko A, Lynchak O, *et al*. Pyrrole derivatives as potential anti-cancer therapeutics: Synthesis, mechanisms of action, safety. J Drug Target 2020;28:547-63.
64. Noti V, Pontiki E, Hadjipavlou-Litina D. Development of novel pyrrole derivatives and their cinnamic hybrids as dual COX-2/LOX inhibitors. Molecules 2023;28:7958.
65. Saini H, Mehra A, Mittal A. Thiazole derivatives in cancer therapy: Mechanistic insights, bioactivity, and future perspective. Future Med Chem 2025;17:2021-42.
66. Maghraby MT, Abou-Ghadir OM, Abdel-Moty SG, Ali AY, Salem OI. Novel class of benzimidazole-thiazole hybrids: The privileged scaffolds of potent anti-inflammatory activity with dual inhibition of cyclooxygenase and 15-lipoxygenase enzymes. Bioorg Med Chem 2020;28:115403.
67. Osmaniye D, Karaca Ş, Kurban B, Baysal M, Ahmad I, Patel H, *et al*. Design, synthesis, molecular docking and molecular dynamics studies of novel triazolothiadiazine derivatives containing furan or thiophene rings as anticancer agents. Bioorg Chem 2022;122:105709.
68. Bukhari SN, Ejaz H, Elsherif MA, Junaid K, Zaki I, Masoud RE. Design and synthesis of some new furan-based derivatives and evaluation of *in vitro* cytotoxic activity. Molecules 2022;27:2606.
69. Lu D, Zhou Y, Li Q, Luo J, Jiang Q, He B, *et al*. Synthesis, *in vitro* antitumor activity and molecular mechanism of novel furan derivatives and their precursors. Anticancer Agents Med Chem 2020;20:1475-86.
70. Acar Çevik U, Sağlık BN, Osmaniye D, Levent S, Kaya Çavuşoğlu B, Karaduman AB, *et al*. Synthesis and docking study of benzimidazole-triazolothiadiazine hybrids as aromatase inhibitors. Arch Pharm (Weinheim) 2020;353:e2000008.
71. Fayed EA, El-Sebaey SA, Ebrahim MA, Abu-Elfotuh K, El-Sayed Mansour R, Mohamed EK, *et al*. Discovery of novel bicyclic and tricyclic cyclohepta[b] thiophene derivatives as multipotent AChE and BChE inhibitors, *in-vivo* and *in-vitro* assays, ADMET and molecular docking simulation. Eur J Med Chem 2025; 284:117201.
72. Thakur S, Kumar D, Jaiswal S, Goel KK, Rawat P, Srivastava V, *et al*. Medicinal chemistry-based perspectives on thiophene and its derivatives: Exploring structural insights to discover plausible druggable leads. RSC Med Chem 2024;16:481-510.
73. Matin MM, Matin P, Rahman MR, Ben Hadda T, Almalki FA, Mahmud S, *et al*. Triazoles and their derivatives: Chemistry, synthesis, and therapeutic applications. Front Mol Biosci 2022;9:864286.
74. Zhang J, Lin F, Xiao Y, Cen SY, Wan BW, Li X, *et al*. Discovery and optimization of 1,2,4-triazole derivatives as novel ferroptosis inhibitors. Eur J Med Chem 2025;284:117192.
75. Carlucci R, Di Gresia G, Mediavilla MG, Cricco JA, Tekwani BL, Khan SI, *et al*. Expanding the scope of novel 1,2,3-triazole derivatives as new antiparasitic drug candidates. RSC Med Chem 2022;14:122-34.

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