DOI:10.31557/APJCB.2026.11.3.885

REVIEW

# A Review on Anticancer Heterocyclic Compounds Derivatives

**Ruaa Wassim Adam[1], Hawraa Mohammed Sadiq[1], Zahraa Lateef Razzaq[2], Rana Neama Atiya[3], Alaa Jawad Abdul-Zahra[3]**

[1]Department of Chemistry, Faculty of Science, University of Kufa, Najaf, Iraq. [2]College of Dentistry, University of Kufa, Najaf, Iraq. [3]Pharmaceutical Chemistry Department Faculty of Science, University of Kufa, Najaf, Iraq.

## Abstract

Heterocyclic drugs are an important type of organic chemicals used in medicinal chemistry, particularly in anticancer drug discovery. Many newly authorized anticancer medicines have at least one heterocyclic core, demonstrating their structural variety and extraordinary capacity to interact with a wide range of biological targets. Furthermore, their presence in essential biomolecules such as DNA, RNA, vitamins, and alkaloids underscores their biological significance. This review points out current advances in the design, synthesis, and biological assessment of heterocyclic compounds with anticancer properties. Nitrogen-, oxygen-, and sulfur-containing heterocycles are studied in broad terms, such as benzimidazoles, pyrazoles, triazoles, quinoxalines, coumarins, oxadiazoles, and metal-heterocycle complexes. The topic includes their methods of action, structure-activity relationship (SAR) insights, cytotoxic assessment findings, and selectivity patterns. Overall, the findings highlight the vital significance of heterocyclic structures as platforms for generating safer and more effective anticancer drugs.

**Keywords:** Heterocyclic compounds- Antitumor activity- Drug design and medicinal chemistry

*Asian Pac J Cancer Biol*, **11 (3)**, 885-890

Submission Date: 04/01/2026 Acceptance Date: 05/24/2026

## Introduction

Heterocyclic compounds are cyclic organic compounds that contain at least one heteroatom. The most frequent heteroatoms are nitrogen, oxygen, and sulfur, but heterocyclic rings with additional heteroatoms are also well known. Carbocyclic compound is a cyclic chemical molecule with all carbon atoms arranged in ring configuration. Heterocyclic compounds are considered one of the key types of organic compounds that are used in various biological disciplines, due to their activity in multiple diseases [1]. Biological molecules such as DNA and RNA, chlorophyll, hemoglobin, vitamins and many more contains the heterocyclic ring in major skeleton [2]. There are a lot of heterocyclic compounds which are have application in many common diseases such as; triazine derivatives have been used as antimicrobial herbicides, urinary antiseptics and anti-inflammatory agents [3]. Benzimidazole derivatives have been reports to possess wide range of biological activities such as antibacterial, antifungal, antiviral and anthelmintic, etc [4].

Cancer has been listed as one of the leading causes of patient deaths around the world due to its high prevalence, complexity and dangerous rate of mortality [5]. According to statistical data produced by the International Agency for Research on Cancer, an estimated 18.1 million new cases of cancer were diagnosed in 2018 with 9.5 million cancer deaths around the globe [6] Cancer continues to be a major global health concern and a leading cause of mortality worldwide. Conventional chemotherapeutics often suffer from limited selectivity and severe side effects, prompting the need for novel drug candidates with higher efficacy and lower toxicity [7]. Heterocyclic compounds represent one of the most versatile and promising classes of molecules in medicinal chemistry due to their structural diversity and ability to interact with multiple biological targets. Recent years have witnessed a surge in the design and synthesis of new heterocyclic derivatives aiming at selective anticancer activity [8].

**Corresponding Author:**
Dr. Ruaa Wassim Adam
Department of Chemistry, Faculty of Science, University of Kufa, Najaf, Iraq.
Email: ruaaw.abdulfadhil@uokufa.edu.iq

*1. Nitrogen Containing Heterocycles in Anticancer Drug Design*

*1.1 Pyrazole and Fused Pyrazole Derivatives*

A new series of imidazopyrazole, pyrazoloperidine, and pyrazoloperidone fusion derivatives were synthesized. Five of these new compounds were tested on different human cancer cell lines by the National Cancer Institute in the USA. Compound 1 showed strong anticancer activity (inhibition index, 42.81%). Furthermore, compound 2 showed strong activity against MCF7 breast cancer cells (inhibition index, 49.88%) and moderate activity against T-47D breast cancer cells (inhibition index, 38.15%) [9] (Figure 1).

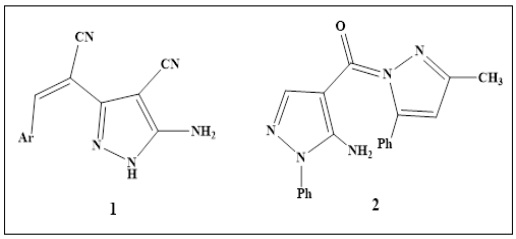


Figure 1. Structures of anticancer compounds 1 and 2

*1.2 Pyrazole contains carbohydrazide*

Acylation of 3-hydrazino-5,6-diphenyl-1,2,4-triazine and hydrazine hydrate with 4-aryl-1,3,7-triphenyl-8-oxa-1,2,6-triazaspiro [4.4] nona-2,6-dien-9-ones gave the corresponding heterocyclic carbohydrazide respectively. A primary in vitro test of compound 7 (concentration 10-4 M) showed activity against leukemia cell lines (CCRFCEM, K-256, MOLT-4, PRMI-8226, SR) [9] (Figure 2).

*1.3 Imidazole derivatives*

Synthesized N-alkyl-2,4-diphenylimidazo [1,2-a] quinoxaline amine derivatives and found that compounds 4,5 & 6 showed the highest activity against three cancer cell lines after 24 and 72 hours, with a median inhibitory concentration $IC_{50}$ value ranging from 9.77 to 15.84 µmol/L against K-562 cells (Figure 3) [10].

*1.4 Benzimidazole Based Derivatives*

Benzimidazole exhibits a unique structure in medicinal chemistry due to its structural similarity to nucleotides. Several benzimidazole derivatives have demonstrated cytotoxic activity against colon cancer cells (HCT-116), liver cancer cells (HepG2), and breast cancer cells (MCF-7). In some studies, synthesized molecules combining benzimidazole with oxadiazole, chalcone, or

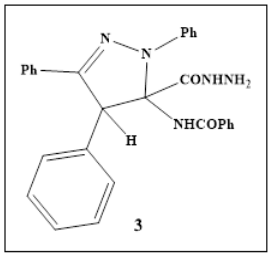


Figure 2. Structure of the Pyrazoline Derivative

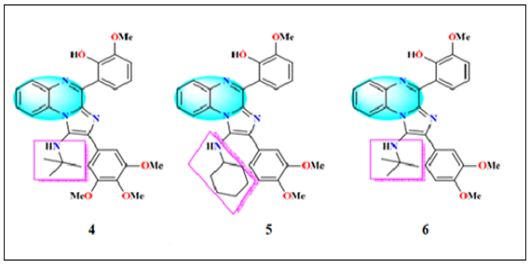


Figure 3. Imidazoquinoxaline Derivatives Highlighting the Diverse Substituted Alkyl and Cyclic Groups

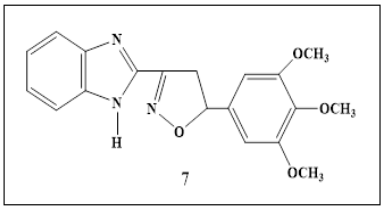


Figure 4. Benzimidazole-oxadiazoline Hybrid

other drug classes have shown enhanced antiproliferative activity compared to reference drugs (Figure 4) [11].

Synthesized a new array of bis-benzimidazole compounds conjugated with aromatic aldehyde and primary amines by microwave irradiation and screened them for their anti-cancer effects in the NCI-60 cell line which represented various human cancer cell lines [12] (Figure 5).

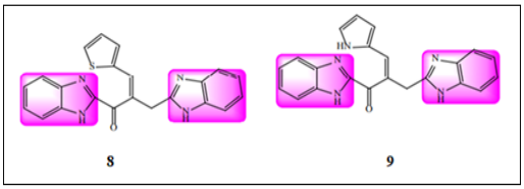


Figure 5. Synthesized bis-benzimidazole Compounds

Evaluated a series of 1H-benzimidazolyl-chalcone for their anti-cancer activity against seven human cancer cell lines. Among the evaluated compounds, compounds 10 ($IC_{50}$ = 0.83µM) and compound ($IC_{50}$ = 0.86µM) exhibited potent inhibition against HCT-116 human colon cancer cell lines [13] (Figure 6).

*1.5 Carbazole derivatives*

Anticancer medicines with diverse mechanisms of activity share the favored structure of the indole, carbazole, and indolocarbazole nuclei ( Figure 7) [14].

*2. Triazole and Tetrazole Derivatives*

*2.1 Triazole based on glucoside derivatives*

Designed and effectively produced were new

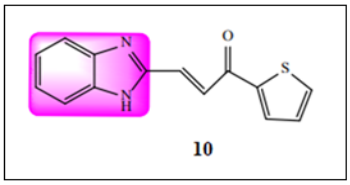


Figure 6. Benzimidazolyl-chalcone Derivative

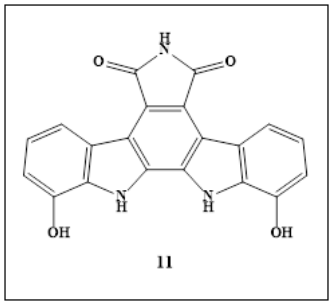


Figure 7. Chemical Structure of the Indolocarbazole Core

derivatives of 1,2,3-triazole-coumarin-glycosyl hybrids and their 1,2,4-triazolethioglycosidic counterparts. The significant potency of the coumarin-triazole-glycoside hybrids 12 against MCF-7 against HOS and MDA human cancer cells was demonstrated by the anticancer activity results against the human HOS, MDA-MB-231, MCF-7, $Caco_2$, and HCT-116 cancer cell lines (Figure 8) [15].

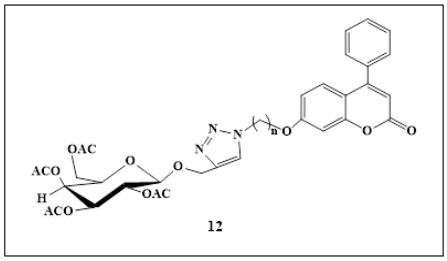


Figure 8. Coumarin-triazole-glycoside Hybrid

*2.2 theophylline contain triazole compounds*

A new series of 1,2,3-triazole theophylline compounds with different amide analogs were synthesized and their biological activity as potential anticancer agents was evaluated. The synthesized compounds underwent anticancer activity tests on four cancer cell lines: lung cancer (A549), colon cancer (HT-29), breast cancer (MCF-7), and melanoma (A375) (Figure 9) [16].

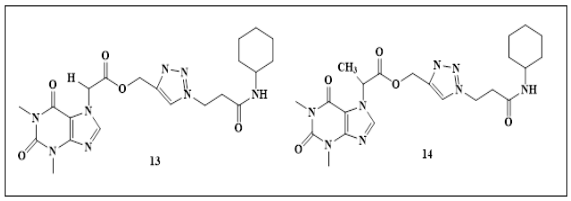


Figure 9. Chemical Structures of Hybrids 13 and 14

*2.3 Tetrazole containing isoxazole*

tetrazole derivatives containing isoxazole 3-(2-chlorophenyl )-1-(5-phenyl-1H-tetrazol-1-yl) prop-2-en-1-one was found to be active with selective influence on ovarian cancer cell lines, especially on SK-OV-3 with a growth % of 34.94 (Figure 10 ) [17].

*3. Indoloquinoline Derivatives*

prepared indole, pyrrole, and benzofuro-quinolin-2 (1H)-ones and 6-anilinoindoloquinoline derivatives. These were tested in vitro using three cell lines:

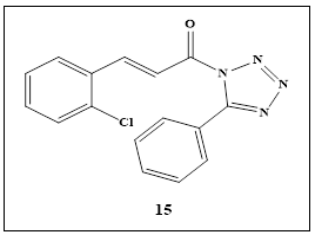


Figure 10. Chemical Structure of Tetrazole Derivative 15

MCF7 (breast), NCI-H460 (lung), and SF-268 (CNS). 1- [3-(11H-Indolo[3,2-c] quinolin-6-ylamino) phenyl] ethenone oxime hydrochloride (25) with $GI_{50}$ = 1.70 M and its 2- chloro derivative17 with $GI_{50}$ = 1.35 M were found to be very potent. Both these compounds 16 and 17 with a $GI_{50}$ value of less than 0.01 M inhibited the growth of SNB-75, which is a CNS cancer cell (Figure 11) [18].

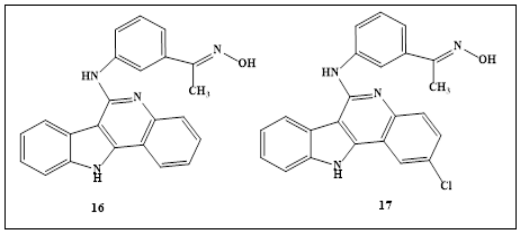


Figure 11. Structures of Bioactive Indoloquinolines

*4. Polymeric and Nanostructured Heterocyclic Systems*

Chitosan-derived Schiff bases, containing five-membered heterocyclic rings, exhibited enhanced cytotoxic activity against HepG-2, HCT-116, and MCF-7 cells. Apoptosis studies revealed caspase-3 activation and a modulation of the Bax/Bcl-2 ratio, indicating apoptotic mechanisms. Furthermore, the nanoparticle formulations improved bioavailability and cellular uptake (Figure 12) [19].

*5. nitrogen- and Sulfur-Containing Heterocycles*

*5.1 Benzo[d]thiazole–Pyrazolidine Dione*

The compound 1-(benzo[d]thiazol-2- yl) pyrazolidine-3,5-dione 18 exhibits good anticancer activity against SKG-4, AMGM5, and REF cell lines in vitro, showing the highest activity against SKJ-T4 and AMGM5 cells at a low concentration of 6 mg./ml, compared to REF

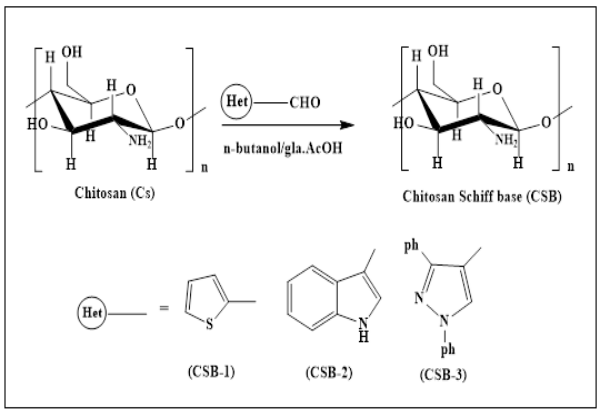


Figure 12. Synthesis Heterocyclic Based on Chitosan

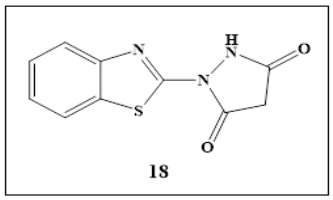


Figure 13. Benzothiazole-pyrazolidine Derivative 18

cells. The presence of a pyrazole ring in compound 11 allows it to bind to multiple sites on the EGFR receptor (Figure 13) [20].

*6.Oxygen- and nitrogen -Containing Heterocycles*

*6.1 Oxadiazole Derivatives*

synthesis of 1,2,4-oxadiazole derivatives conjugated to 1H-benzimidazole were designed and synthesized, and their anticancer efficacy against A549 lung cancer cell lines, MCF-7 breast cancer, and A375 skin cancer was studied, using the MTT assay with doxorubicin as a reference drug [21] (Figure 14).

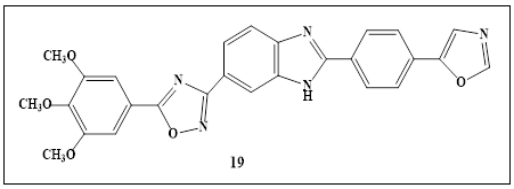


Figure 14. Benzimidazole-oxadiazole Hybrid 19

The synthesized compound 3-(5-(4-amino-2,6-dibromophenyl)-1,3,4-oxadiazol-2-yl)-1-(1H-benzo[d] imidazol-2-yl) proban-1-one (Compound 16) exhibited superior antiproliferative activity, surpassing other tested analogs. The compound demonstrated significant growth inhibition across the NCI-60 family of human cancer cell lines, with $GI_{50}$ values ranging from 0.49 to 48.0 μM. These results highlight Compound 20 as a promising leading structure for further refinement and development as a broad-spectrum anticancer agent (Figure 15) [22].

*7. Metal–Heterocycle Complexes*

Cyclopentane compounds containing heterogeneous ligands have shown promise as alternatives to cisplatin. Some platinum compounds have demonstrated superior antiproliferative activity against MDA-MB-231 and HT-29 cells while maintaining enhanced selectivity against non-cancerous cell lines. These results suggest that ligand modification can significantly influence cytotoxic potency and selectivity (Figure 16) [23].

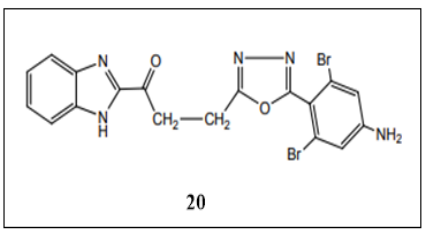


Figure 15. Structure of the Lead Anticancer Compound 20

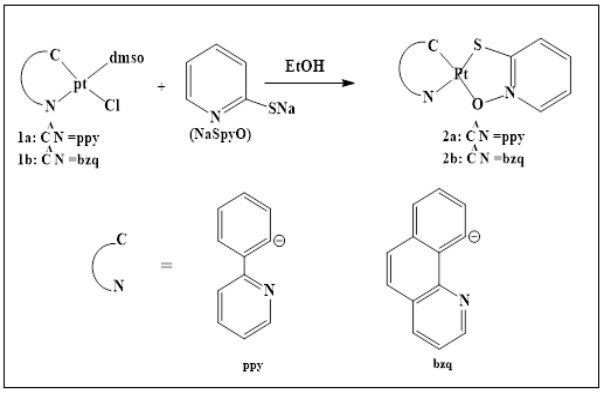


Figure 16. Cyclopentane Compounds Containing Heteroatoms

*8. Pyridinyl Sugar Derivatives*

The anticancer effect of dipyridyl or pyridinyl sugar hydrazones linked to phenyl or methyl furyl rings, as well as pyridine Thio glycosides involving naphthyl and furyl systems, is achieved through a multi-step process (Figure 17) [24].

*9.Heterocyclic contain oxygen*

*9.1 Flavanone derivatives*

preparation of heterocycle-substituted flavanone derivatives which displayed anticancer activity against HT29 (human colon adenocarcinoma), MCF7 (human breast adenocarcinoma), and A498 (human kidney adenocarcinoma) cell lines (Figure 18) [25].

*9.2 Coumarin derivatives*

The inhibitory activity of anticancer of heterocyclic compounds 6-acetyl-7-hydroxy-4-methyl-2H-Coumarine -2-one 21 and 6-(1-((4-aminophenyl)imino)ethyl)-7-hydroxy-4-methyl-2H-chromen-2-one 22 have good results for the study Colorectal Cancer (CaCo-2), this type of Cancer is more common than another type (Figure 19) [26].

*9.3 Furan Derivatives*

synthesized furan derivatives by cyclizing 1-(aryl/

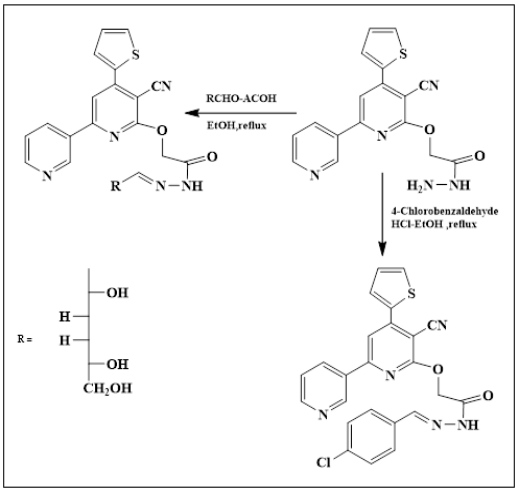


Figure 17. Dipyridyl or Pyridinyl Sugar Hydrazones

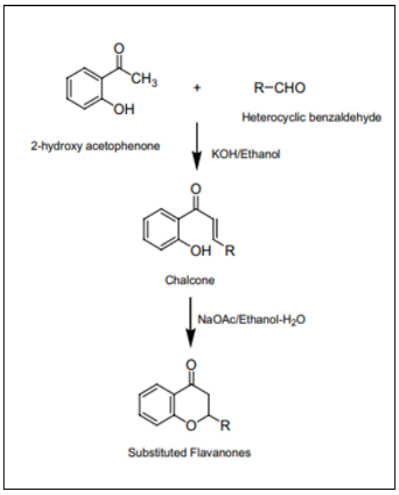


Figure 18. Heterocycle-substituted Flavanone Derivatives

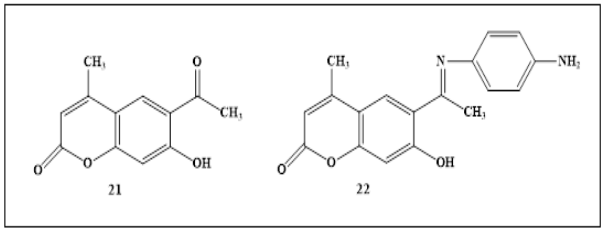


Figure 19. Structures of Bioactive Coumarins 21 and 22

alkyl (arylthiol) methyl)-naphthalen-2-ol and pyridinium bromides in the presence of 1,8- diazabicyclo [5.4.0] undec-7ene (DBU) in good yield. The compound 23 was evaluated against triple negative MCF-7 breast cancer cell line, MDA-MB-468 and non-cancerous lung fibroblast cell line FI-38 cells using MTT assay. The prepared furan derivatives, (1,2-dihydronaphtho [2,1-b] furan-2-yl)(p-tolyl) methanone considered to have best anti-cancer activity from the series of prepared compounds (Figure 20) [27].

*6. Mechanisms of Action*

Heterocyclic chemotherapy drugs work in a variety of ways, such as:

- Topoisomerases I and II inhibition
- Inhibition of polymerizing tubulin
- Targeting the EGFR receptor
- G2/M phase cell cycle arrest
- Apoptosis induction (caspase activation)
- Kinase inhibition and DNA intercalation

Because of their structural flexibility, biological targets implicated in tumor growth can be selectively modulated.

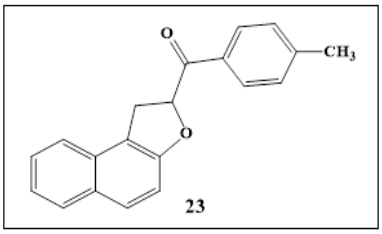


Figure 20. Structure of Dihydronaphthofuran Derivative 23

In conclusion, heterocyclic structures are still important materials in cancer drug discovery because of their chemical diversity, biocompatibility, and compatibility with pragmatic drug development methodologies. The research described in this review show that nitrogen-oxygen-sulfur heterocyclic compounds cause considerable cytotoxicity in a variety of cancer cell lines, frequently via multi-target mechanisms such as kinase inhibition, DNA interaction, apoptosis induction, and cell cycle arrest.

A critical examination of recent studies indicates numerous significant tendencies. First, hybrid heterocyclic systems frequently exhibit higher potency and selectivity than single-core structures, indicating that synergistic pharmacophore integration is a successful method. Second, metal-heterocycle complexes and polymeric/nanostructured formulations are viable options to increasing bioavailability while decreasing systemic toxicity. Third, SAR-guided optimization and computational modeling have become indispensable tools for improving lead compounds and forecasting biological performance.

Despite promising in vitro and in vivo findings, significant translational obstacles remain, such as pharmacokinetic restrictions, off-target toxicity, tumor heterogeneity, and resistance mechanisms. Future research should focus on mechanism-based design, dual- or multi-target techniques, precision oncology approaches, and integration with nanotechnology-driven delivery systems.

To summarize, heterocyclic compounds are both structurally varied chemical entities and dynamic platforms for the discovery of novel anticancer drugs. Continued interdisciplinary studies that combine synthetic chemistry, computational modeling, molecular biology, and translational pharmacology are likely to speed up the development of safer, more selective, and more effective anticancer medicines.

## Acknowledgments

*Statement of Transparency and Principles*

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute.
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

## References

1. K. Slman D, A. Satar H, A. Ketan Z, A. Jawad A. Heterocyclic Compounds: A Study of its Biological Activity. Al-Nahrain Journal of Science. 2024 Dec 01;27(5):19-24. https://doi.org/10.22401/ANJS.27.5.03
2. Kabir E, Uzzaman M. A review on biological and medicinal impact of heterocyclic compounds. Results in Chemistry. 2022 01;4:100606. https://doi.org/10.1016/j.rechem.2022.100606
3. Abd El-Salam NM, Mostafa MS, Ahmed GA, Alothman OY. Synthesis and Antimicrobial Activities of Some New Heterocyclic Compounds Based on 6-Chloropyridazine-3(2H)-thione. Journal of Chemistry. 2013 01;2013(1):890617. https://doi.org/10.1155/2013/890617
4. Omar A. Review Article; Anticancer Activities Of Some

Fused Heterocyclic Moieties Containing Nitrogen And/Or Sulfur Heteroatoms. Al-Azhar Journal of Pharmaceutical Sciences. 2020 09 01;62(2):39-54. https://doi.org/10.21608/ajps.2020.118375
5. Amewu RK, Sakyi PO, Osei-Safo D, Addae-Mensah I. Synthetic and Naturally Occurring Heterocyclic Anticancer Compounds with Multiple Biological Targets. Molecules. 2021 Nov 25;26(23):7134. https://doi.org/10.3390/molecules26237134
6. Irfan A, Batool F, Zahra Naqvi SA, Islam A, Osman SM, Nocentini A, Supuran CT. Benzothiazole derivatives as anticancer agents. Journal of Enzyme Inhibition and Medicinal Chemistry. 2020;35(1):265–279. https://doi.org/10.1080/14756366.2019.1698036.
7. Choudhary A. Synthesis and Characterization of New Heterocyclic Compounds with Anticancer Potential. Journal of Pharmaceutical Chemistry and Drug formulation ISSN: 3108-0782 (Online). 2025 Nov 04;7(2).
8. Hasanin M, Hashem AH, El-Rashedy AA, Kamel S. Synthesis of novel heterocyclic compounds based on dialdehyde cellulose: characterization, antimicrobial, antitumor activity, molecular dynamics simulation and target identification. Cellulose. 2021 09;28(13):8355-8374. https://doi.org/10.1007/s10570-021-04063-7
9. Mansour AK, Eid MM, Khalil NSAM. Synthesis and Reactions of Some New Heterocyclic Carbohydrazides and Related Compounds as Potential Anticancer Agents. Molecules. 2003 Oct 31;8(10):744-755. https://doi.org/10.3390/81000744
10. Ettahiri W, Saber M, Ouzrour Z, Sanae L. Recent Advances In The Development Of Nitrogen- Containing Heterocyclic Compounds As Anticancer Agents: A Review. 2023;22(2).
11. Nofal ZM, Soliman Ea, Abd El-Karim Ss, Elzahar Mi, Srour Am, Sethumadhavan S, Maher Tj, Et Al., "Novel Benzimidazole Derivatives As Expected Anticancer Agents". Drug Research. 2011;68(4):519-534.
12. Rashid M. Design, synthesis and ADMET prediction of bis-benzimidazole as anticancer agent. Bioorganic Chemistry. 2020 03;96:103576. https://doi.org/10.1016/j.bioorg.2020.103576
13. Ren Y, Wang Y, Li G, Zhang Z, Ma L, Cheng B, Chen J. Discovery of Novel Benzimidazole and Indazole Analogues as Tubulin Polymerization Inhibitors with Potent Anticancer Activities. Journal of Medicinal Chemistry. 2021 04 22;64(8):4498-4515. https://doi.org/10.1021/acs.jmedchem.0c01837
14. Sherer C, Snape TJ. Heterocyclic scaffolds as promising anticancer agents against tumours of the central nervous system: Exploring the scope of indole and carbazole derivatives. European Journal of Medicinal Chemistry. 2015 06;97:552-560. https://doi.org/10.1016/j.ejmech.2014.11.007
15. El-Sayed WA, Alminderej FM, Mounier MM, Nossier ES, Saleh SM, F. Kassem A. New 1,2,3-Triazole-Coumarin-Glycoside Hybrids and Their 1,2,4-Triazolyl Thioglycoside Analogs Targeting Mitochondria Apoptotic Pathway: Synthesis, Anticancer Activity and Docking Simulation. Molecules. 2022 09 03;27(17):5688. https://doi.org/10.3390/molecules27175688
16. Ruddarraju RR, Murugulla AC, Kotla R, Tirumalasetty MCB, Wudayagiri R, Donthabakthuni S, Maroju R. Design, synthesis, anticancer activity and docking studies of theophylline containing 1,2,3-triazoles with variant amide derivatives. MedChemComm. 2017;8(1):176-183. https://doi.org/10.1039/C6MD00479B
17. Bhaskar VH, Mohite PB, "Synthesis, Characterization And Evaluation Of Anticancer Activity Of Some Tetrazole Derivatives"..
18. Negi B, Kwatra A. A Review of Recent Progress on the Anticancer Activity of Heterocyclic Compounds. SynOpen. 2024 08;08(03):185–210. https://doi.org/10.1055/s-0040-1720125.
19. El-Naggar M, Haneen D, Mehany A, Khalil M. New synthetic chitosan hybrids bearing some heterocyclic moieties with potential activity as anticancer and apoptosis inducers. International Journal of Biological Macromolecules. 2020 05;150:1323–1330. https://doi.org/10.1016/j.ijbiomac.2019.10.142.
20. Mohammed AA, Shahad A, Jarallah SA, Abood HM, Fadhil OH, Budoor Sattar Abbas. Anticancer Potential of a Novel Benzothiazole-Derived Heterocyclic Compound: In Vitro, In Vivo, and Molecular Docking Studies: Anticancer Activity of a Novel Benzothiazole Compound. Iraqi j. cancer med. genet. 2024 06;17(1):37–44. https://doi.org/10.29409/ijcmg
21. Satija G. Benzimidazole based derivatives as anticancer agents: Structure activity relationship analysis for various targets. Journal of Heterocyclic Chem. 2022 01;59(1):22–66. https://doi.org/10.1002/jhet.4355.
22. Martins P. Heterocyclic Anticancer Compounds: Recent Advances and the Paradigm Shift towards the Use of Nanomedicine's Tool Box. Molecules. 2015 09;20(9):16852–16891. https://doi.org/10.3390/molecules200916852.
23. Walton I, Cox J, Benson C, Patel D, Chen Y, Benedict J. The role of atropisomers on the photo-reactivity and fatigue of diarylethene-based metal–organic frameworks. New J. Chem. 2016;40(1):101–106. https://doi.org/10.1039/C5NJ01718A.
24. Khalaf H, Tolan H, El-Bayaa M, Radwan M, El-Manawaty M, El-Sayed W. Synthesis and Anticancer Activity of New Pyridine-Thiophene and Pyridine-Furan Hybrid Compounds, Their Sugar Hydrazone, and Glycosyl Derivatives. Russ J Gen Chem. 2020 09;90(9):1706–1715. https://doi.org/10.1134/S1070363220090182.
25. Sachdeva H. Oxygen- and Sulphur-Containing Heterocyclic Compounds as Potential Anticancer Agents. Appl Biochem Biotechnol. 2022 Dec;194(12):6438–6467. https://doi.org/10.1007/s12010-022-04099-w.
26. Al-Fatlawi AAY, Rammahi FAA. Synthesis, Identifications and Study Inhibitory anti-Cancer Activity for Some New Heterocyclic Compounds from Derivatives Coumarine. J. K. Chem. Sci. 2024 Nov;3(3):298–322. https://doi.org/10.36329/jkcm/2024/v3.
27. Kaur A, Shakya A, Singh R, Badhwar R, Sawhney S. Heterocyclic Compounds and their Derivatives with Potential Anticancer Activity. Ind. J. Pharm. Edu. Res. 2024 03;58(1s):26– 39. https://doi.org/10.5530/ijper.58.1s.3.