REVIEW ARTICLE

An Overview on Nitrogen-containing Heterocyclic Compounds as Anticancer Agents

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ABSTRACT

Cancer accounts for nearly 10 million losses each year. Among the most prevalent cancer types are breast, lung, colon, rectum, and prostate cancers. Astonishingly, around one-third of cancer-related deaths can be attributed to factors such as tobacco usage, a high body mass index (BMI), alcohol consumption, restricted ingestion of fruits and vegetables, and inadequate bodily bustle. In the field of pharmaceuticals, heteroatoms and heterocyclic compounds frequently assume crucial roles and serve as common structural components in numerous active natural products. Statistically, the majority of biologically active compounds is either heterocycles themselves or incorporate a heterocyclic element, with nitrogen-containing heterocycles being the most prevalent structural framework in these intricate molecules. These findings underscore the significant and ever-evolving role of heterocycles in contemporary drug blueprints and drug sighting practice. The chief hub of the review was to explore the documented anti-cancer properties of nitrogen-containing heterocyclic compounds, as reported in current scientific literature.

Keywords: Cancer, Anticancer activity, Nitrogen-containing heterocyclic, Drug discovery, Pharmaceutical research.

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INTRODUCTION

Cancer results from abnormal cell division and has latent to spread throughout the body. A key attribute is swift expansion of anomalous cells inflates afar their usual restrictions, potentially invading neighboring tissues and spreading to other organs, a process known as metastasis. Metastases are the leading cause of death in cancer cases.[1]

Heterocyclic compounds consist of elements other than carbon at their core, with oxygen, nitrogen, and sulfur being the most common substituents. These compounds play a significant role in various medical applications, acting as effective agents against bacteria, viruses, fungi, inflammation, and tumors. The versatility of heterocycles is reflected in their wide range of applications.[1]

Pyrimidine Derivatives as Anticancer Agents

Researchers led by Aleksandra Sochacka-Cwikła synthesized derivatives of 7-aminooxazolo [5,4-d] pyrimidines and conducted evaluations for immunological, antiviral, and anticancer activities. Notably, two of these newly synthesized derivatives, referred as compound 1 and 2, exhibited noteworthy anticancer properties.[2]

Valentina Noemi Madia and her team introduced a novel series of aminopyrimidine derivatives in their investigation, targeting diverse cell lines, with triple-negative breast cancer MDA-MB2313. Among these derivatives, the most potent anticancer compound identified was the N-benzyl pyrimidine derivative, denoted as Compound.[3]

Farag F. Sherbiny and colleagues designed hybrid pyrazolo[3,4-d]pyrimidines and assessed their potential antiproliferative effects on MCF-7, HepG-2, HCT-116, and Hela. Within this series, a synthesized derivative known as Compound 4 demonstrated significant and promising anticancer activity.[4] The details of compound 4 is depicted in Table 1.

Shahin Boumi and colleagues introduced a fresh series of pyrimidine derivatives in their research and tested them against three distinct malignancy cell lines along with a customary cell line (NIH3T3). Among the synthesized compounds, one particular derivative exhibited the chief cytotoxic action

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besides all the tested cell lines. Molecular modeling studies provided further confirmation that synthesized derivatives, specifically compounds 5 and 6, displayed strong binding affinity.[5] The details of compound 4 are depicted in Table 2.

2-Anilinopyrimidine derivatives were synthesized by Omaima M. Aboul Wafa and anticancer commotion was executed.[6] Among Synthesized derivatives, three compounds (Compound 7, 8 and 9) exhibited potent anticancer activity. The synthesized derivative kill cancer cell in G2/M phase. Docking studies also revealed good binding affinities with target enzymes epidermal expansion issue receptor (EGFR) and ARO.

Hanaa M. Al-Tuwaijri and colleagues introduced a novel series of indazol-linked pyrimidine derivatives in their research.[7] Among the synthesized compounds, one specific derivative, referred to as compound 10, exhibited extraordinary anticancer bustle against the A549 cell line, surpassing the efficacy of a usual drug.

Novel series of pyrimidine derivatives attached with 1,3,4-thiadiazole were synthesized via glycosylation by Hemat S. Khalaf *et al.*[8]

Farhana Islam and her research team uncovered a novel series of pyrimidine derivatives incorporating a thiophene ring.[9] Interestingly, three of the synthesized compounds, namely compounds 12, 13, and 14, demonstrated strong anticancer properties along with the ability to depolymerize microtubules. The details of compound 4 is depicted in Table 3.

Quinoline Derivatives as Anticancer Agents

In their study Yong-Feng Guan and colleagues explored a new series of quinoline derivatives containing a Chalcone moiety.[10] They examined probable anticancer chattels of derivatives. Among the synthesized compounds, one particular derivative emerged as a promising anticancer. Notably, this derivative was established to persuade ROS and influence G2/M phase of the cell. The details of compound 4 is depicted in Table 4.

In a study led by Maria Cristina Al-Matarneh and her team, they delved into a fresh series of quinoline derivatives combined with a Pyrrole moiety.[11] The team assessed these synthesized derivatives beside a variety of leukemia, melanoma, and cancers affecting many organs. Among the synthesized compounds, one specific derivative, known as compound 16, displayed potent anticancer activity. Additionally, molecular docking studies indicated a strong binding interaction between the synthesized compound and Tubulin.

Dina I. A. Othman and her research team explored a new series of quinoline derivatives incorporating a thiophene group.[12] They conducted an evaluation of these synthesized derivatives for their anticancer potential. The standard reference in this study was 5-fluorouracil.

The synthesized derivatives also demonstrated significant inhibitory effects on epidermal EGFR-TK and Topo II enzymes. Notably, compound 17 and 18, among the synthesized derivatives, induced cell death in the G2/M phase, acted as activators for caspase-3 and 9 and apoptosis in cancer cells.
In a study led by Mohamed Hagras and colleagues, new quinoline derivatives were synthesized and assessed, namely HepG-2, HCT-116, and MCF-7, with colchicine used customary indication.

Table 1: Anticancer activity of synthesized derivative

	HePG2	*Hela*	*HCT-116*	*MCF-7*
Compound 4	4.28 ± 0.3	5.18 ± 0.4	3.97 ± 0.3	9.85 ± 0.8
Sorafenib	9.18 ± 0.6	8.16 ± 0.6	5.47 ± 0.3	7.26 ± 0.3

Table 2: Anticancer activity of synthesized derivative

S.NO.	*Anticancer Activity IC_{50}*			
	HT-29	*MCF-7*	*T47D*	*NIH-3T3*
Compound 5	60.0 ± 3.4	1.5 ± 0.2	10.7 ± 1.9	1.9 16 ± 2.5
Compound 6	> 100	45.2 ± 4.45	24.2 ± 3.2	36.3 ± 4.4
PTX	7.1 ± 1.15	0.2 ± 0.03	40.2 ± 2.1	1.5 ± 0.2

Table 3: Compounds with EC50/IC 50 ratio

Compound No	*IC_{50} ± SD (MDA-435 Cells) (nM)*	*EC_{50} Microtubule Depolymerization in A^{-10} Cells (nM)*	*EC_{50}/IC_{50} Ratio*
12	9.0 ± 0.2	19	2.2
13	38.6 ± 5.6	70	1.8
14	36.8 ± 5.2	45	1.2

Table 4: Anticancer activity of synthesized derivative

S.NO.	*IC_{50}*		
	MGC803	*HCT116*	*MCF7*
Compound 15	1.38 ± 0.21	5.34 ± 0.39	5.21 ± 0.51
5-FU	6.22 ± 1.12	10.4 ± 1.23	11.1 ± 1.28

Notably, comp- 19 and 20, among the synthesized derivatives, were found to hinder tubulin polymerization and seize cell cycle in the G2/M phase.[13]

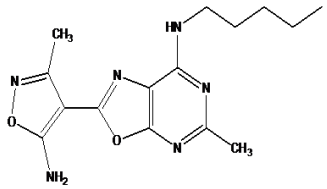
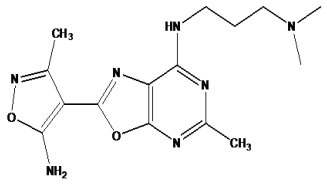
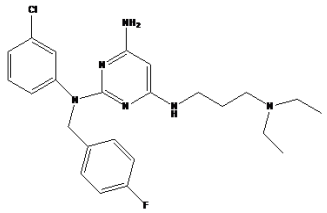
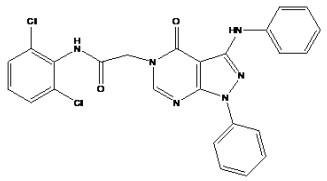
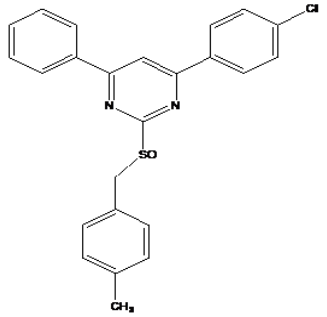
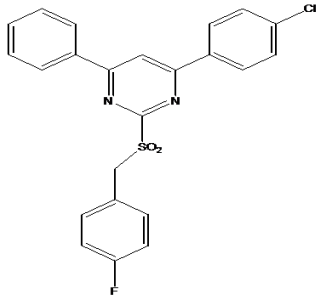
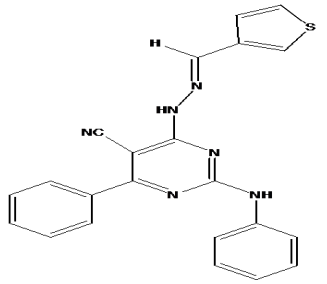
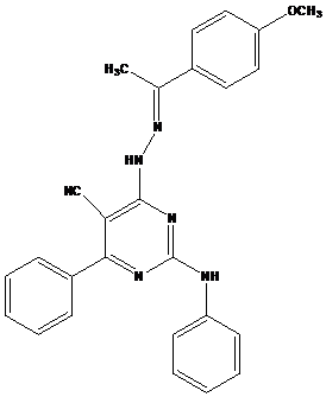
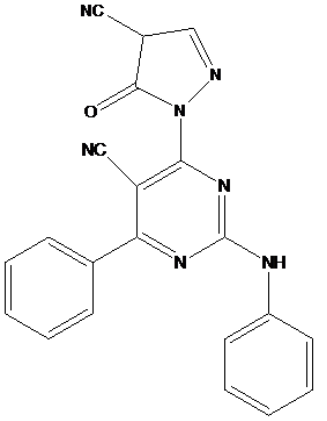
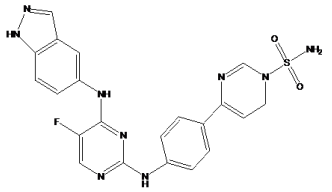
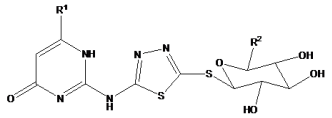
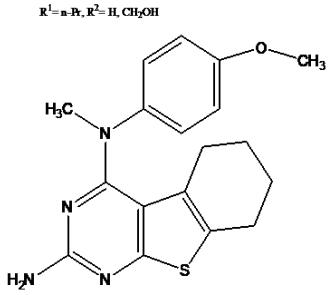
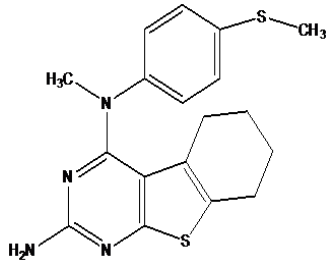
Monika Krawczyk introduced a fresh series of glycoconjugates derivatives in her study.[14] Among synthesized compounds, compound 21 stood out for its ability to impede the proliferation of cancer cells. It's worth noting the anticancer activity of compounds influenced by sugar moiety, the linker component, and the quinoline ring.

Pyridine derivatives

In research conducted by Nazeer Ahmad Khan and collaborators,[15] pyridine and dihydropyridine derivatives were explored, showcasing anticancer action besides HeLa and MCF-7. An assessment was carried out using the MTT assay and human tissue nonspecific h-TNAP enzyme. The synthesized derivatives demonstrated their anticancer potential by stir up apoptosis via various mechanisms, including the generation of ROS, interruption of mitochondrial utility, DNA dent, and cell cycle clutch at G1.

In a study led by Mohamed El-Naggar, a fresh series of Pyridine derivatives was identified and subjected to screening for anticancer prospective beside breast cancer MCF-7 cell

Table 5: Compounds and their structures

Compound	*Structure*
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	

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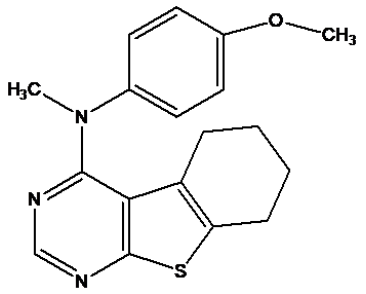

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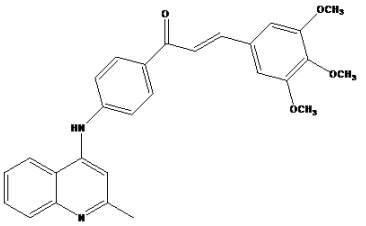

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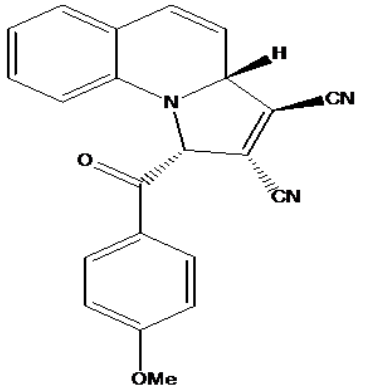

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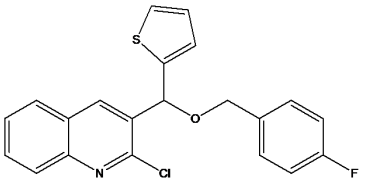

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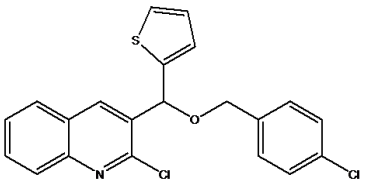

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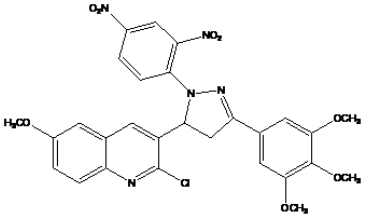

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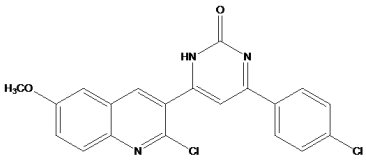

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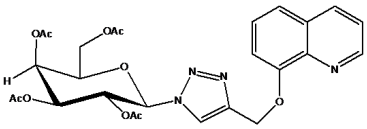

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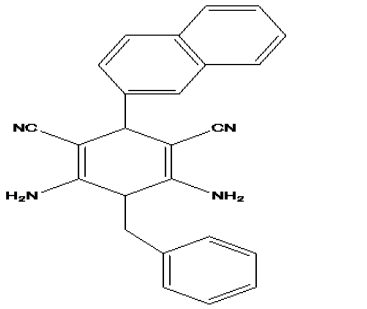

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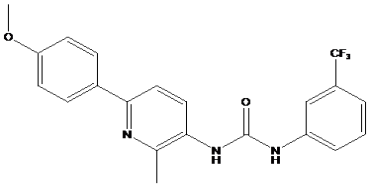

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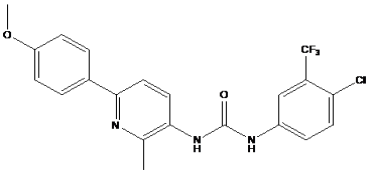

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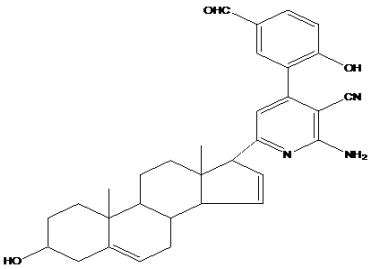

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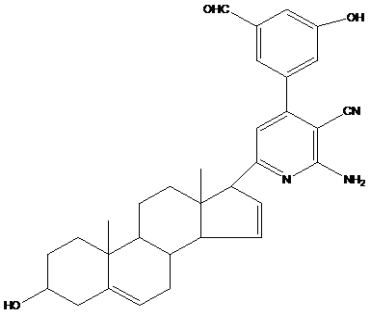

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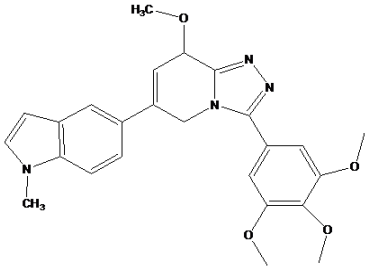
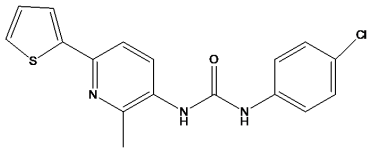
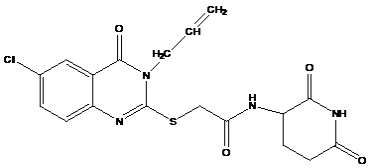
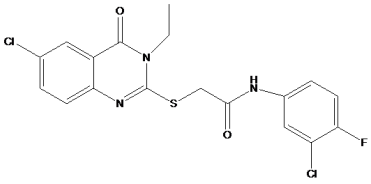


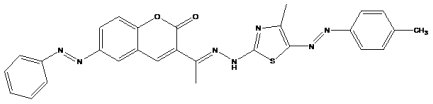
line, by doxorubicin used as reference.[16] Notably, two of the synthesized pyridine derivatives, namely Compound 23 and 24, were identified as budding agents.

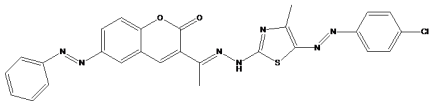
In a study conducted by Ya-Ling Song and colleagues[17] pyridine

28 

29 

30 

31 

32 

derivatives incorporating a steroidal ring were examined for their budding anticancer properties against MCF-7 and Hela cell lines. Here two derivatives, denoted as Compound 25 and 26, established noteworthy latent.

Cheng-Jun Wu and his team[18] introduced a fresh series of Pyrimidine derivatives that integrated indole and a 1,2,4-triazole ring. They conducted evaluations to assess the anticancer perspective on different cancer cell lines. Notably, among synthesized derivatives, one pyrimidine derivative is referred to as compound 27.

Wagdy M. Eldehna and collaborators[19] developed a narrative series of pyridine derivatives featuring a phenyl urea ring and subjected them to evaluation against various cancer cell lines, including the A549 lung cancer cell line and the HCT-116 colon cancer. Within this series, one synthesized derivative, known as compound 28, emerged as a potent and broad-spectrum anticancer agent.

Miscellaneous Heterocyclic Compound with Anticancer Activity

Anas Ramadan Kotb[20] introduced a novel derivative of thalidomide and assessed its potential for anticancer activity against three cancer cell lines. Among the synthesized compounds, two derivatives, labeled as compound 29 and 30, displayed remarkable anticancer activity.

In the research conducted by Tariq Z. Abolibda and colleagues,[21] a new derivative of 3-Thiazolyl-Coumarin was investigated for its potential in treating breast cancer by targeting the VEGFR-2 signaling system. Among the synthesized compounds, two derivatives, known as compound 31 and 32, exhibited greater anticancer activity as judged against Sorafenib. All the structures are depicted in Table 5.

CONCLUSION

Due to their intrinsic ingenuity and usefulness as well as excellent physicochemical potencies, heterocyclic systems have dignified themselves as factual keystones of medicinal chemistry. nitrogen-containing heterocyclics has established an imperative compound in a meadow of medicinal chemistry. The prominence was given to the latest literature about the anticancer activity of nitrogen-containing heterocyclics. As a whole, the assemblage and presentation of the summary in this review article will assuredly help the new researchers and intend to work in this area of nitrogen heterocyclics.

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