FIVE MEMBERED RING HYTROCYCLIC COMPOUNDS AS ANTI-CANCER DRUG

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ABSTRACT

The majority of heterocycle compounds and typically common heterocycle fragments present in most pharmaceuticals currently marketed, alongside with their intrinsic versatility and unique physicochemical properties, have poised them as true cornerstones of medicinal chemistry. Apart from the already marketed drugs, there are many other being investigated for their promising activity against several malignancies. In particular, anticancer research has been capitalizing on the intrinsic versatility and dynamic core scaffold of these compounds. Nevertheless, as for any other promising anticancer drugs, heterocyclic compounds do not come without shortcomings. In this review, we provide for a concise overview of heterocyclic active compounds and families and their main applications in medicine. We shall focus on those suitable for cancer therapy while simultaneously addressing main biochemical modes of action, biological targets, structure-activity relationships as well as intrinsic limitation issues in the use of these compounds. Finally, considering the advent of nanotechnology for effective selective targeting of drugs, we shall discuss fundamental aspects and considerations on nanovectorizatiom of such compounds that may improve pharmacokinetic/pharmacodynamic properties of heterocycles. N-heterocyclic compounds are a natural and rich source of pharmacologically active molecules displaying anti-cancer properties through various antiproliferative mechanisms. Some of these N-heterocyclic compounds are already being utilized or evaluated in clinical settings for cancer treatment, highlighting their potential significance in discovering new anti cancer agents. This study aims to gather information from articles published between 2019 and 2021 on the recent advancements in N-heterocyclic derivatives such as indazole, triazolopyrimidine, pyrazolopyrimidine, quinoxaline, benzimidazole, benzodiazepine, indole, and quinoline as promising anticancer agents, including their structure-activity relationships and mechanisms of action.

KEYWORDS*-cancer therapy, heterocyclic compounds, oxygen and nitrogen-based heterocycles, drug delivery, nanomedicine, eterocycles, five-membered heterocycles, antibiotics, antibacterials, nitrogen heterocycles, oxygen heterocycles, sulfur heterocycles, biological activity, drug design, drug discovery.*

INTRODUCTION

Cancer is an extremely challenging and significant public health issue worldwide, posing a serious threat to human life and societal progress. According to the World Health Organization, cancer is the second leading cause of death worldwide, causing the loss of eight million lives. Each year, one out of every six people dies due to cancer, and the burden of this disease continues to rise annually

Given the large number of cells that divide each day, the appearance of abnormal cells can occur either spontaneous or as a result

of a transformation induced by a carcinogen. The cancerization process involves a succession of genetic alterations that can be caused after contact with the carcinogen physical, chemical or microbial . According to various studies, multiple factors can induce the development of abnormal cells in humans such as smoking

Carcinoma is the abnormal growth of normal cells that typically grow beyond their original boundaries, invade surrounding areas, spread to other organs, and result in metastasis, which is one of the main causes of cancer-related death, the second most commoncause of deaths across the globe . Around 10.0 million cancer-related fatalities (9.9 million excluding squamous cell carcinoma) and 19.3 million new cases of cancer (18.1 million excluding squamous cells carcinoma) were estimated globally by 2020. Up to 25% of cancer cases are caused by cancer-causing illnesses such as hepatitis as well as human papillomavirus infections. The most common malignancies in both genders are breast, lung, stomach, colorectal, thyroid, liver, and ovarian. The most fatal cancers are lung

Steroids are natural products that have good capacity to penetrate cells and bind to nuclear and membrane receptors. They are a large group of chemical substances that share a 17 carbon-atom skeleton composed of four fused rings (three six-membered rings and one five membered rings) [5]. They vary from one another in the nature of attached groups, their posi tion, and the configuration of the steroid nucleus. Minor modifications of the chemical structure of steroids can produce significant differences in their biological activities. This diversity in biological action might be due to the presence of various functional groups attached to the tetracyclic core which serve as substrates for different targets. The rationale for employing hydrophobic steroid units lies in their capacity to interact with cell membranes and thus enhance biological efficacy of such hybrid molecules.

- **Five-Membered Heterocycles Used in the Design of Antibacterial Drugs**

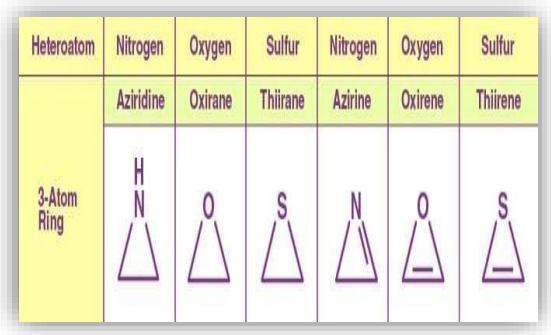
Heterocyclic compounds contain at least two distinct atoms (either as ring atoms or as members of the ring) in the ring. The actual ring is referred to as a heterocycle. The total number of ring atoms and the type is crucial since it determines the ring size. Three-membered rings are the minor shape conceivable. The most significant rings in the antibiotic design are heterocycles, with five and six members [22]. The five-membered heterocycles used in antibacterial drug design contain one to four heteroatoms as follows:

1. One heteroatom (nitrogen, oxygen, or sulfur);
2. Twoheteroatoms (oxygen and nitrogen; sulfur and nitrogen atoms);
3. Three heteroatoms (three nitrogen atoms, e.g., triazoles, and one sulfur and two nitrogen atoms, e.g., thiadiazoles);

The most common heterocycles with five atoms in the molecular structure of approved antibiotics are presented in Table 2 and are individually addressed in the following sections

4.Five-Membered Heterocycles Containing Nitrogen Atoms

Five-membered heterocycles are believed to originate from the cyclopentadienyl compound. They possess properties such as conjugated dienes or acyclic amines, but with a nitrogen atom replacing the "-CH=" group. The characteristics of these compounds are closely linked to the non-participatory electron pair of the heteroatom. They have a planar pentagonal structure, with the six electrons distributed over the five sp2 hybridized atoms. Each carbon atom contributes one electron, and the heteroatom donates two electrons to the aromatic sextet, which confers the aromaticity of the heterocyclic system. The two non-participating electrons of the nitrogen will contribute to the aromatic sextet and are delocalized throughout the heterocycle [1]. These heterocycles are less susceptible to being deprotonated at the nitrogen or carbon atom through the action of nucleophiles. Weak nucleophiles will react with the cation produced by electrophiles, leading to addition or ring-opening reactions. The most reactive compound in this class in terms of compound reactivity is pyrrole. The resonance structures' unevenly distributed energy causes greater reactivity [1]. According to an analysis conducted by Vitaku E. et al. (2014) on FDA-approved small compounds, N-heterocycles form the majority of the structural skeletons of pharmaceutical drugs on the market, accounting for about 84% of all molecules, and 59% of them contain at least one nitrogen heterocycle



Five-Membered Heterocycles Containing Oxygen Atoms

5.1. Furan 5. Five-Membered Heterocycles Containing Oxygen Atoms 5.1. Furan The word furan, which indicates bran, is derived from the Latin furfur [24]. Furan is an aromatic five-membered heterocycle with a centrally positioned sp2 hybridized oxygen atom that is planar and pentagonal (Table 2). Furan's ring atoms all lay in a plane, forming a pentagon with minor distortion. The bond length between C-3 and C-4 is more extended than between C-2 and C-3 and between C-4 and C-5. Therefore, the C-C bond length averages the single and double bond lengths, while the C-O bond is shorter by 0.05 Å. The C-C bond length is approximately the same (1.33 Å). The places next to the heteroatom were previously denoted as and '. Furyl is the name attributed to the monovalent residue [1,22,24]. The word furan, which indicates bran, is derived from the Latin furfur [24]. Furan is an aromatic five-membered heterocycle with a centrally positioned sp2 hybridized oxy gen atom that is planar and pentagonal (Table 2). Furan's ring atoms all lay in a plane, forming a pentagon with minor distortion. The bond length between C-3 and C-4 is more extended than between C-2 and C-3 and between C-4 and C-5.

Therefore, the C-C bond length averages the single and double bond lengths, while the C-O bond is shorter by 0.05 Å. The C-C bond length is approximately the same (1.33 Å). The places next to the het eroatom were previously denoted as α and α'. Furyl is the name attributed to the mono valent residue [1,22,24]. Oneofthetwopairsofnon-participatingelectronsisinansp2hybridizedorbital, while the other pair is in a orbital. These two pairings are in separate orbitals. The ring's bonds are comparable to those in the pyrrolic ring, and the heterocycle displays six delocalized electrons [1]. Furan reacts with electrophilic reagents similarly to benzene, frequently with substitution. However, depending on the reagent and reaction circumstances, it can also react via addition and/or ring-opening [22]. Furan is faster than benzene to participate in electrophilic substitution reactions because it is a heterocycle with excess electrons. Therefore, furan is more reactive than thiophene but less reactive than pyrrole in reactivity [1,22]. Thus, furan is less stable than thiophene due to its lower resonance energy [24]. One of the two pairs of non-participating electrons is in an sp2 hybridized orbital, while the other pair is in a π orbital. These two pairings are in separate orbitals. The ring bonds are comparable to those in the pyrrolic ring, and the heterocycle displays six delo calized electrons [1]. Furan reacts with electrophilic reagents similarly to benzene, fre quently with substitution. However, depending on the reagent and reaction circum stances, it can also react via addition and/or ring-opening [22]. Furan is fast

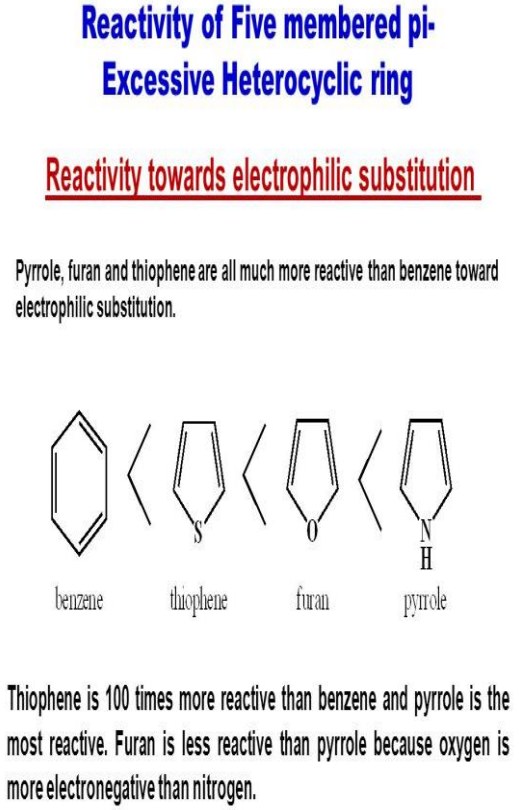
- **Five-Membered Heterocycles Containing One Sulfur Atom**

Tiophene Thiophene is a five-membered unsaturated aromatic heterocycle often referred to as furan's sulfur analog (Table 2) [1]. The sulfur atom's presence has a specific impact on the aromatic nature of the compound as well as its characteristics and reactions. In the electron system, sulfur's "electron pairs" are strongly delocalized and behave as highly reactive, similar to a benzene derivative [160]. Thiophene exhibits an electron cloud, making it similarly reactive to benzene. Due to the weakly electronegative sulfur atom, it is the least reactive to the action of electrophilic agents when compared to furan and pyrrole. However, compared to benzene, its elec trophilic substitutions occur significantly more quickly [1,161]. The bioisosterism link between thiophene and benzene is explained by the discovery of thiophene as an impurity in benzene and the remarkable similarity between the two chemicals' physicochemical features. Therefore, thiophene can be effectively used to replace the benzene nucleus in the structure of molecules of medicinal interest as a bioequivalent [160]. Chemical structures known as structural alerts or toxicophores can be bioactivated to produce reactive metabolites. Le Dang N. et al. (2017) indicated that the thiophene structural alert is unclear. Currently, it is known that thiophenes can be bioactivated by epoxidation. Different oxidative metabolic processes can convert thiophenes into elec trophilic, unstable intermediates such as S-oxides, epoxides, and sulfenic acids. Toxicity can result from the oxidative metabolism of thiophenes, which produces reactive, electrophilic

intermediates [139]. Thiophene is found in various natural compounds, such as biotin (vitamin H) [1]. The biological activity of thiophene and its derivatives include antiviral, antifungal, antibac terial, antileishmanial, antimicrotubule, anti-inflammatory, antioxidant, anticancer, and anti-HIV effects. Because of these effects, thiophene is a critical structural component in several therapeutically relevant drugs

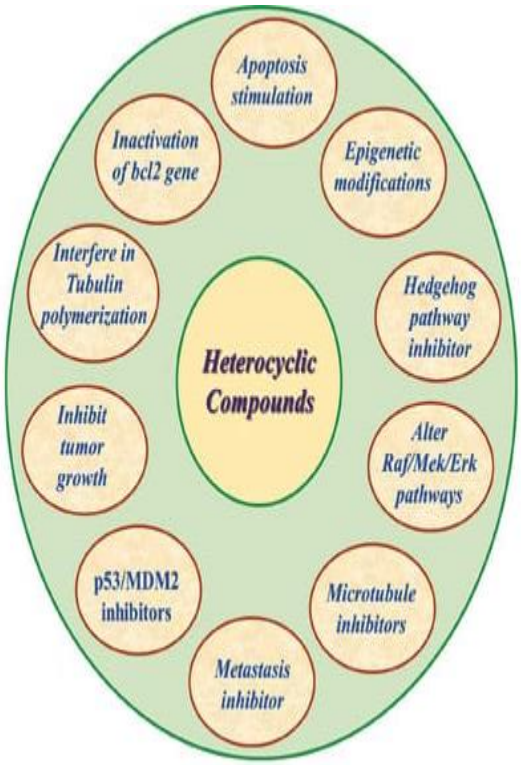
- **five-membered heterocycles containingbsulfur and nitrogen atom**

1,3-Thiazolidine is a saturated five-membered heterocycle with sulfur and nitrogen in positions 1 and 3, respectively (Table 2); it is considered an analog of oxazolidine [161]. When thiazolidines are present in an acidic or basic aqueous solution, they hydrolyze to form aldehyde and amino thiol. The production of an iminium thiolate zwitterion intermediate has led researchers to conclude that the reaction involves breaking the C-S Cefoxitin (2nd generation). Among beta-lactamase–resistant 7-α-methoxy cephalo sporins (cephamycins) is cefoxitin, (6R,7S)-3-(carbamoyloxymethyl)-7-methoxy-8-oxo-7 [(2-thiophen-2-ylacetyl)amino]-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid [29], a compound that contains a thiophene heterocycle in the side chain from the C6 position (Figure 27c). One of the first cephamycins available was cefoxitin (as sodium salt) [123]. The ability of cefoxitin (and in general) to kill resistant bacterial strains is due to the 7-α-methoxyl substituent's protection against hydrolysis by beta-lactamases. Even though cefoxitin is less effective than celothin against Gram-positive.



- **Role of the Heterocycles to Design Anti-Cancer Agents**

Worldwide cancer is regarded as a great threat to mankind. It leads to abnormal growth of the tissues by uncontrolled cell divisions. It was well established that cancer is a disease associated with unsuppressed growth and the spread of anomalistic cells



[1]. It is quite unfortu nate that, till now, there is no specific potent medicine with a 100% success rate for cancer treatments. Though, a large number of drugs have been used for the treatment of various cancers. In some instances, these available drugs are causing side effects

[2]. Efforts have been made to design new drug molecules or modify the existing drugs to reduce the side effects of these drugs

[3]. On the other hand, more than half of the commercially available drugs consist of different heterocyclic skeletons

[4]. Along with other biological activities, various synthetic hetero cyclic scaffolds also showed significant anti-cancer activities

[5]. Interestingly, it has been observed that the majority of the commercially available anti-cancer drugs possess heterocyclic moiety either as the main structural unit or as an important subunit

[6]. Under this purview, during the last three decades, the screening of anti-cancer efficacy of various heterocyclic scaffolds has increased rapidly. Several naturally occurring, semi-synthetic and synthetic heterocyclic compounds have passed in clinical or preclinical anticancer trials

[7]. Few of them showed significant anti-tumor activities and thus they are available in the market as promising drugs

[8]. This thematic issue titled 'Role of the heterocycles to design anti-cancer agents' has covered a large number of literature related to the potent anti-cancer activities of structurally diverse heterocyclic scaffolds. This thematic issue highlights an up-to-date literature on the follow ing selected seven topics contributed by the eminent research groups. The first contribution titled 'Heterocyclic compounds: Importance in anticancer drug discovery' by Kumar and Goel deals with the role of various heterocyclic skeletons in the design and developments of anti-cancer drugs

[9]. O-heterocycles are very common in natural products and in drug molecules. In the second contribution titled 'Naturally occurring O heterocycles as anticancer agents' Prof. Biswanath Das and his research group nicely presented a wide range of naturally occurring O heterocycles with potential anti-cancer activities

[10]. Dr. Sasadhar Majhi, in the third contribution titled 'Discovery, development, and design of anthocyanins-inspired anticancer agents-a comprehensive review' describes the latest developments in the synthesis and chemical derivatization of various anthocyanin motifs having promising anti-cancer activities

[11]. Pyrans and pyran annulated heterocycles have been found to possess significant anticancer activities

[12]. The fourth contribution titled 'Current developments in the pyran-based analogues as anticancer agents' by Prof. Chawla and her group summarizes the anti-cancer effica cies of various pyran based scaffolds reported in recent times [13]. Various triazole derivatives have been found to possess significant pharmacological efficacies. On many occasions, it was found that the triazole moiety acts as the main building block for the synthesis of novel anticancer drugs. The fifth contribution titled 'Design and develop ment of triazole derivatives as prospective anticancer agents: A review' by Dr. Harshita Sachdeva and her research group describes the latest developments in the synthesis of various triazole derivatives with promising anticancer efficacies [14]. The sixth contribution titled 'Synthesis and anti-cancer applications of benzimidazole derivatives – Recent Studies' by Dr. Ram Singh and his research group highlights the latest developments on the synthesis of structurally diverse benzimidazole derivatives having promising anticancer activities

[15]. The last contribution of this thematic issue titled 'A comprehensive review on journey of pyrrole scaffold against multiple therapeutic targets' by Mir et al. describes the role of various pyrrole derivatives as anticancer, antibacterial, antiviral, antitubercular and anti inflammatory agents

[16]. I am very much thankful to all the contributors for their valuable efforts to build up this special thematic issue for Anti-Cancer Agents in Medicinal Chemistry (ACAMC). I am grateful to the senior journal manager and the entire editorial team of 'Anti-Cancer Agents in Medici nal Chemistry', especially Ms. Sumaiya Azhar, Ms. Sahar Iftakhar and Ms. Ambreen Irshad for their continued support. No words are suffi cient to express my gratitude to Prof. (Dr.) Simone Carradori (Editor-in-Chief) for continued support and guidance. I am also thankful to the respective reviewers for their efforts and suggestions to improve the quality of this special issue.

Classification of Heterocyclic Compounds

Based on the electronic arrangement, we can classify Heterocyclic compounds into two types:

1. Aliphatic Heterocyclic Compounds
2. Aromatic Heterocyclic Compounds.

Aliphatic Heterocyclic Compounds

Aliphatic heterocyclic compounds are those cyclic heterocycles that do not contain any double bond.

The properties of aliphatic heterocyclic compounds are mainly affected due to ring strain.

Examples of aliphatic heterocyclic compounds are Aziridine, Ethylene Oxide, Thiirane, Oxetane, Azetidine, Thietane, Tetrahydrofuran (THF), Dioxane, Pyrrolidine, Piperidine, etc.

Aromatic Heterocyclic Compound

Aromatic heterocyclic compounds, as the name suggests, are cyclic aromatic compounds.

Aromatic Heterocyclic compounds obey Huckels Rule, i.e.

It should be cyclic.

It should be planar.

It should not contain any sp3 hybridised atoms.

It must have (4n+2) **π** electrons.

Aromatic Heterocyclic compounds are analogous to Benzene.

Examples: Furan, Pyrrole, Thiophene, Indole, Benzofuran, Carbazole, Quinoline, Isoquinoline, Imidazole, Oxazole, Pyrazole, Pyridazine, Pyrimidine, Purine, etc.

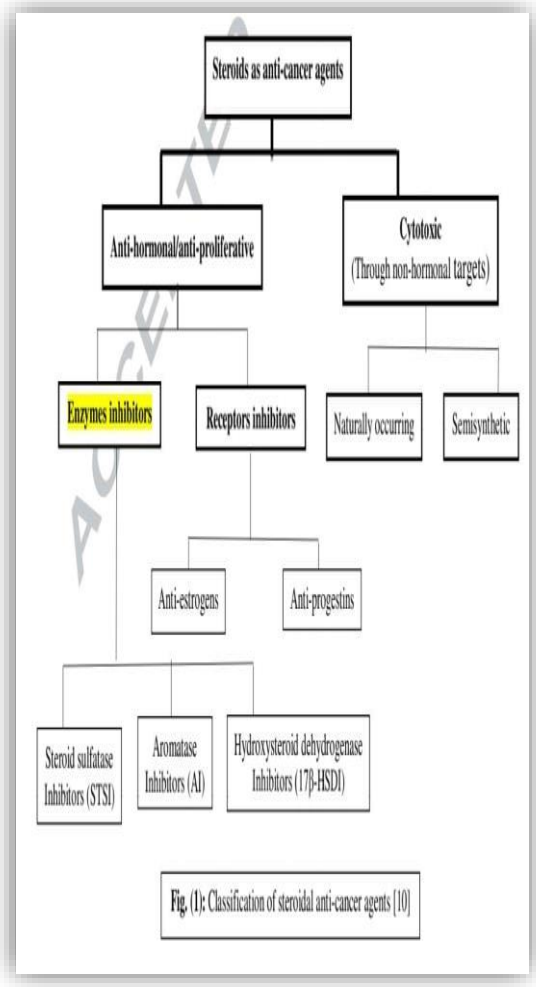


Fig. (1): Classification of steroidal anti-cancer agents [10]

Conclusion

In this study, a new series of indazolylthiazole moieties was effectively generated and described in a new range of novel pyridine, pyran, furan, thiophene, and pyrazole-carrying compounds. The newly synthesized compounds showed great potency as selective anticancer drugs against both HepG-2 and Caco-2 cell lines, with high SI values and low IC50 values. The antitumor activity of the synthesized derivatives included obvious tumor cell damage and stimulated a clear alteration of the cell morphology in a dose-dependent manner. Among the tested compounds, derivatives 6 and 4 revealed potent antitumor activity, where derivative 8

showed the highest antitumor activity toward both tested tumor cells with SI values of approximately 26 and IC50 values of 5.9 µg/mL, attributed to the presence of a thiazolylpyrazole moiety, with acetonitrile, in the pyrazole ring. The gene expression level study confirmed apoptosis induction through upregulation of the p53 gene (2–eightfold) in both treated HepG-2 and Caco-2 cells. On the other hand, compound 3 revealed significant broad-spectrum antibacterial activity against Streptococcus mutans (MIC of 11.2 µg/mL) and Pseudomonas aeruginosa (MIC of 18.29 µg/mL), comparable to that of ampicillin MIC (13.5 µg/mL) and ciprofloxacin (18.7 µg/mL), which could be attributed to the incorpo rated thiazolopyridine ring. The newly prepared compounds revealed low to medium antifungal activity against Candida albicans with a maximum antifungal activity through compound 3 (36% clotrimazole activity). Many synthesized compounds revealed antibiofilm formation activities (58.5–79% inhibition) against the three applied pathogens. Collectively, the results confirmed the effectiveness of newly synthesized compounds as promising antitumor drugs with antimicrobial activity. The current study results encourage our research team to go deeper into the exact antitumor/antimicrobial mechanisms of the newly prepared potent derivatives and explore the structural–functional relationship.

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