Tentative Outline

Special Thematic Issue for Current Organic Chemistry

Title of thematic issue: Heterocycles in the management of cancer

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Aims & Scope:

Cancer is one of the most dreadful diseases and a major cause of deaths worldwide, with an estimation of 9.6 million deaths in 2018**.** The existing anti cancer drugs are associated with several demerits that include poor oral bioavailability, non-selectivity and poor pharmacodynamic properties. Therefore, there is an urgent need for the development of more effective and safer anti cancer agents. Heterocyclic compounds are of particular interest in medicinal chemistry and are of highest practical and theoretical importance for lead discovery since they have been found active against different targets with a wide range of biological activities. This can be accomplished through advanced drug designing methodologies such as target template *in-situ* drug synthesis, that assist in a rapid identification of the hit molecules form a diverse pool of leads; and direct biomolecule-drug conjugation, along with bioorthogonal strategies that ensure localization, and a superior target specificity of the directed therapeutic. Further, natural products form a significant portion of medicinal agents that are currently used for the management of cancer. All these natural products have unique structures along with diverse action mechanisms with the capacity to interact with different therapeutic targets of several complex disorders. Although the plants contribute as a major source of natural products with anti-cancer potential, the marine environment and microbes have also bestowed some substantial chemotherapeutic agents. Few examples of anti-cancer agents of natural origin include vincristine, vinblastine, paclitaxel, camptothecin and topotecan obtained from plants, bryostatins, sarcodictyin and cytarabine from marine organisms and bleomycin and doxorubicin from micro-organisms (dactinomycin, bleomycin and doxorubicin). The incredible diversity in the chemical structures and biological properties of compounds obtained from million species of plants, marine organisms and microorganisms present in nature has commenced a new era of potential therapeutic anti-cancer agents.

In this thematic issue, different aspects of heterocyclic compounds of both synthetic and natural origin shall be discussed that shall highlight their interesting therapeutic potential in management of different types of cancer. Further, the role of hetrocycles towards different biotargets and molecular mechanisms like MDM2 (mouse double minute2 homology), CA-IX (carbonic anhydrase-IX), Bcl-2 (B-cell lymphoma-2), VEGFR (vascular endothelial growth factor receptor), MMP2 (matrix metalloproteinases-2), ER (estrogen receptor), HER-2 (human epidermal growth factor receptor-2), SHP-2 (non-membrane protein tyrosine phosphatase), TNF-α (tumor necrosis factor-α) shall also be elaborated.

Keywords:

4-thiazolidinone, cancer, benzimidazole, azole, structure activity relationship, green chemistry, molecular mechanisms, natural products

Subtopics along with Contributing authors and abstract

The subtopics to be covered within this issue are listed below:

Title no. 1: 4-Thiazolidinone Scaffold: Targeting Variable Biomarkers and Pathways Involving Cancer

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- **Abstract:** Cancer can be considered as a genetic as well as a metabolic disorder. Current cancer treatment scenario looks like aggravating tumor cell metabolism, causing the disease to progress even with greater intensity. The cancer therapy is restricted to the limitations of poor patient compliance due to toxicities to normal tissues and multi-drug resistance development. There is an emerging need for cancer therapy to be more focused towards the better understanding of genetic, epigenetic and transcriptional changes resulting in cancer progression and their relationship with treatment sensitivity. The 4-thiazolidinone nucleus possess marked anticancer potential towards different biotargets and mechanisms like MDM2 (mouse double minute2 homology), CA-IX (carbonic anhydrase-IX), Bcl-2 (B-cell lymphoma-2), VEGFR (vascular endothelial growth factor receptor), MMP2 (matrix metalloproteinases-2), ER (estrogen receptor), HER-2 (human epidermal growth factor receptor-2), SHP-2 (non-membrane protein tyrosine phosphatase), TNF-α (tumor necrosis factor-α) and many more, thus targeting multitudinous of cancer types like breast, prostate, lung, colorectal and colon cancers, renal cell adenocarcinomas and gliomas. Therefore, conjugating the 4-thiazolidinone scaffold with other promising moieties like indolin-2-one, pyrazole, benzothiazole, steroids, pyridine or by directing the therapy towards targeted drug delivery systems like use of nanocarriers of 4-thiazolidinones, can provide the gateway for optimizing the anticancer efficiency and minimizing the adverse effects and drug resistance development, thus providing stimulus for personalized pharmacotherapy. This review aims to summarise the work reported on anticancer activity of 4-thiazolidinone derivatives covering the data from the year 2005 till now, which may be beneficial to the researchers for future development of more efficient 4-thiazolidinone derivatives.
- **Keywords:** 4-thiazolidinone, cancer, epigenetic, genetic, transcriptional, nanocarriers

Title no. 2: Green synthesis of heterocycles as anti-cancer agents

- **Author's name:** K.U. Sadek.
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- **Abstract:** Heterocyclic compounds are privileged scaffolds in terms related to biological activities and drug discovery. They possess several activities such as antiinflammatory, antibacterial, antihypertensive, anticancer and so many others. This review article will summarize recent developments in the green synthesis of anticancer relevant heterocycles. These include the utility of water as solvent, glycerol as solvent and/or catalyst, ionic liquids, MW heating, UV irradiation, visible light, asymmetric catalysts, catalyst and solvent free conditions. A diversity of five, six and fused rings are known to have anticancer activity and the review is the first trial to categorize them. Moreover, some docking studies will be cited.
- **Keywords:** Microwave, Green chemistry, anticancer, Fused rings, Molecular docking, Drug discovery

Title no. 3: Benzimidazole: A multifaceted nucleus for anticancer agents

- **Author's names:** Yogita Bansal,* Ankit Singhal, Radhey Krishan Arora, Gulshan Bansal
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- **Abstract:** Cancer is characterized by uncontrolled proliferation of cells, dedifferentiation, invasiveness and metastasis. Endothelial growth factor (eGF), Insulin-like growth factor (IGF), Platelet derived growth factor (PDGF), Fibroblast growth factor (FGF), Vascular endothelial growth factor (VEGF), Checkpoint kinase 1 & 2 (CHk1 & CHk2), Aurora kinases, Topoisomerases, Histone deacetylators (HDAC), Poly (ADP-Ribose) polymerase (PARP), Farnesyl transferases, RAS-MAPK pathway and PI3K-Akt-mTOR pathway are some of the prominent mediators implicated in proliferation of tumor cells. A huge artillery of natural and synthetic compounds as anticancer, which act by inhibiting one or more of the enzymes and/or pathways responsible for progression of tumor cells, is reported in literature. One of the major limitations of anticancer agents used in clinics as well as under development in literature is normal cell toxicity and other side effects due to lack of specificity. Hence, medicinal chemists across the globe have been working since decades to develop potent and safe anticancer agents from natural sources as well as from different classes of heterocycles. Benzimidazoles is one of the most important and explored heteronucelus because of its versatility in biological actions as well as synthetic applications in medicinal chemistry. Structural similarity of amino derivatives of benzimidazole with purines makes it a fascinating nucleus for development of especially

anticancer, antimicrobial and anti-HIV agents. This review article is an attempt to critically analyzing various reports on benzimidazoles as anticancer in order to understand the structural requirements around benzimidazole nucleus. The idea is to propose structure–activity relationship for benzimidazole derivatives to enable medicinal chemists in rational development of antitumor agent.

- **Keywords:** Benzimidazole, Endothelial growth factor, Insulin-like growth factor, Platelet derived growth factor, Fibroblast growth factor, Vascular endothelial growth factor, Structure activity relationship,

Title no. 4: Heterocyclic compounds as potential therapeutics in the treatment of Gliomas: A review

- **Author's names:** Faizana Fayaz[1], Anjali Sharma[1], Shaik Khasimbi[1], Sadat Shafi[2], Faheem Hyder Pottoo[3]
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- **Abstract:** Cancer is one of the most alarming disease and a major cause of death worldwide, with an estimation of 9.6 million deaths in 2018**.** Glioma that occurs in glial cells surrounding nerve cells, is a type of tumor that occurs in the brain and spinal cord. Majority of the patients with gliomas have a lethal prognosis, and the ailment has significant sway on patients and their families be it physical, psychological or economic wellbeing. As Gliomas exhibits both intra- and intertumor heterogeneity multidrug resistance and current therapies like hormonal therapy, surgery, radiotherapy and chemotherapy become ineffective. Also, the existing drugs for Gliomas treatment are associated with several drawbacks such as poor oral bioavailability, non-selectivity and poor pharmacodynamics properties. Therefore, there is an urgent need for the development of more effective and safer anti Gliomas agents. Heterocyclic compounds are of particular interest in medicinal chemistry and are of highest practical and theoretical importance for lead discovery since they have been found active against different targets with a wide range of biological activities. In this review we are going to illustrate convenient strategies, different kind of chemical reactions that have been employed to obtain different heterocyclic derivatives, with special emphasis on 5-membered and 6-membered heterocyclic compounds, having interesting therapeutic potential in mitigation of Gliomas.

- **Keywords:** Cancer, Gliomas, Heterocyclic compounds, chemical reactions.

Title no. 5: Synthesis and anticancer properties of *'azole'* based chemotherapeutics as emerging chemical moieties: A comprehensive review

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- **Abstract:** Azole frameworks serve as privileged scaffolds in the contemporary drug design paradigm owing to their unique physicochemical profile that promotes the development of highly selective, physiological benevolent chemotherapeutics. Several azole nuclei function as bioisostere in medicinal chemistry and prompt the development of tailored therapeutics for targeting the desired biological entities. In addition, the azole scaffold forms an integral part in the advanced drug designing methodologies such as target template in-situ drug synthesis, that assist in a rapid identification of the hit molecules form a diverse pool of leads; and direct biomolecule-drug conjugation, along with bioorthogonal strategies that ensure localization, and a superior target specificity of the directed therapeutic. Lastly, the structural diversity of azole framework and high yielding click synthetic methods provide a comprehensive SAR analysis for design optimization of the potential drug molecules. This review provides a comprehensive analysis of the synthesis and anticancer potential of azole based chemotherapeutics.
- **Keywords:** Azole, bioisostere, biomolecule-drug conjugation, bioorthogonal strategies, design optimization, Structure activity relationship studies

Schedule:

- Manuscript submission deadline: 31, May 2020
- Peer Review Due: 30, June 2020
- Revision Due: 31, July 2020
- Announcement of acceptance by the Guest Editors: 15, August 2020
- Final manuscripts due: 31, August 2020

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