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A REVIEW ON DESIGN AND SYNTHESIS OF FUSED HETEROCYCLIC IMIDAZOTHIAZOLE AND BENZOTHIAZOLE ANALOGOUS AS POTENTIAL ANTI CANCER AGENTS

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ABSTRACT

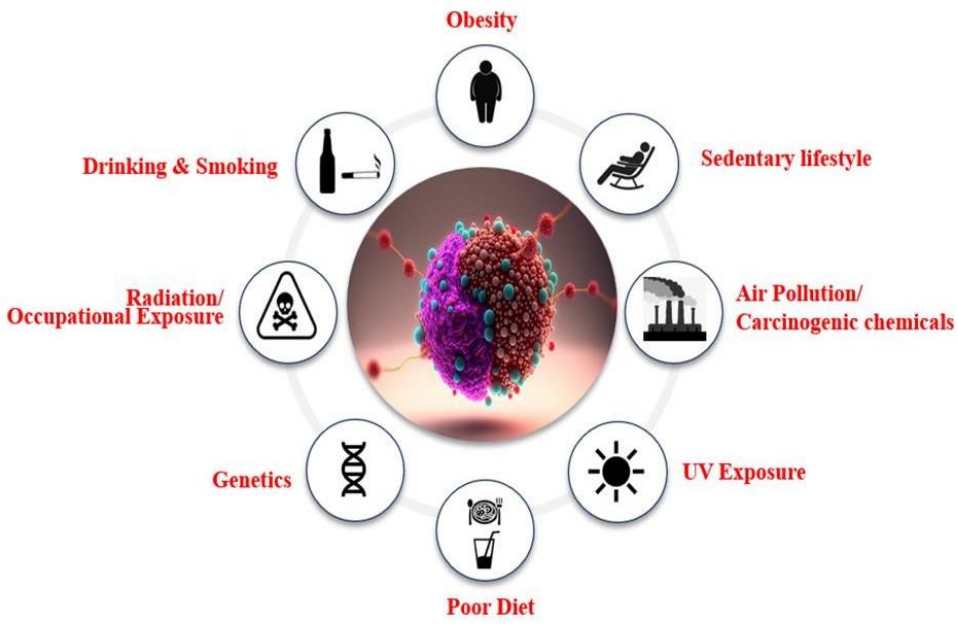
Cancer, a significant global health concern, necessitates innovative treatments. The pivotal role of chronic inflammation in cancer development underscores the urgency for novel therapeutic strategies. Analogues are modified versions of natural or synthetic compounds developed to improve efficacy, enhance solubility and reduce toxicity. Benzothiazole derivatives exhibit promising therapeutic potential due to their distinctive structures and broad spectrum of biological effects. This study aims to explore new anti-tumor small molecule drugs that exhibit simultaneously anti-inflammatory and anticancer based on the advantages of benzothiazole frameworks. Fused heterocyclic compounds, particularly imidazothiazole and benzothiazole derivatives, have gained considerable attention. These molecular framework contain heteroatoms which enhance their ability to interact with biological targets. Various synthetic strategies include one-pot synthesis, microwave assisted methods and green chemistry approaches.

KEYWORDS: Benzothiazole, Imidazothiazole, Fused heterocycles, Anticancer activity, heteroatoms.

INTRODUCTION

Across the world, cancer has become one of the major concerns of public health; it is the most predominant reason for death after cardiovascular disorders. It is considered for

approximately 10 million deaths every year. According to recent data from the World health organization (WHO) on cancer, annually 14 million new cases are reported, which is estimated to become approximately 30 million by 2040. With an expansion in the number of cases, every year, mortality due to cancer is also increasing. As per the WHO report, nearly 10 million deaths were reported out of 18 million cases in 2018 only. With time, cancer becomes a challenge to the healthcare systems. Cancer can occur to any person from any age group, and the major reasons behind are associated to everyday life style unhealthy food habits, sedentary life style, consumption of tobacco and alcohol. In contrast, a variety of studies have shown that there is a solid correlation between increased phosphorylation of the EGF receptor, either by constitutive activation, the overexpression, or the development of mutations in specific domains, and the occurrence of carcinogenic factors such as exposure to ultraviolet radiation, bacterial infections, and smoke inhalation, which may lead to the increased risk of developing malignant tumors in tissues in which the receptor is present. Moreover, it has been proven that EGFR is directly or indirectly associated with the pathogenesis of some of the most common and deadliest cancers in the world, such as lung, breast, colorectal, and head and neck cancer.

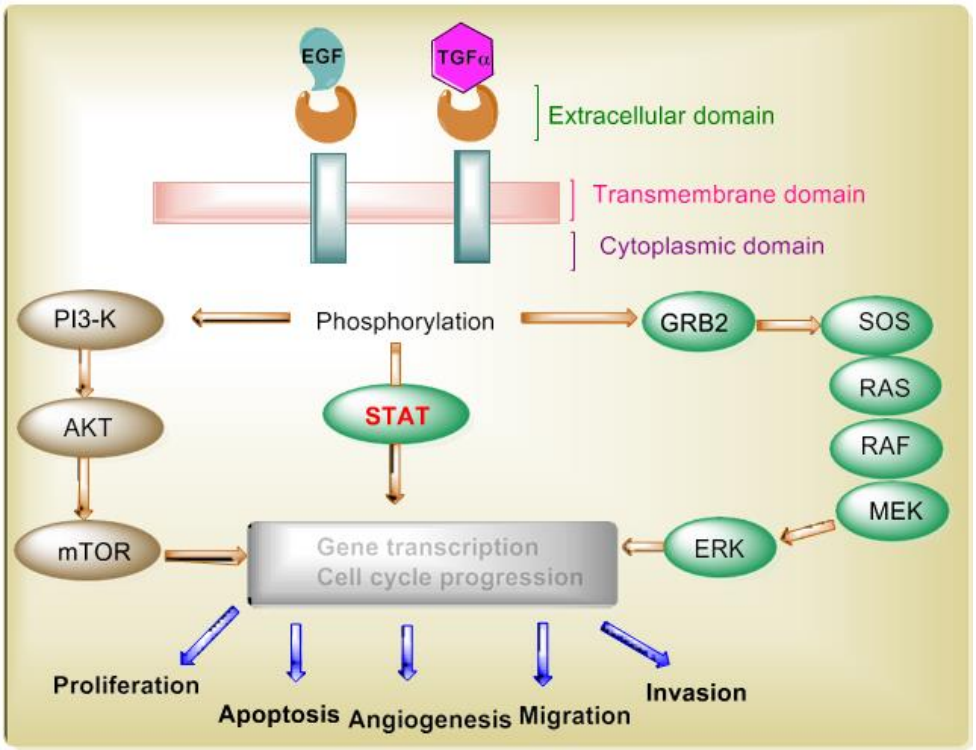


Epidermal growth factor receptor (EGFR) is a component of the ErbB family of proteins. EGFR kinases are of four subtypes named as ErbB-1, ErbB-2, ErbB-3 and ErbB-4. EGFR kinases are involved in various diseases like cardiovascular disease, inflammation, and psoriasis. These kinases are highly expressed in various forms of cancer such as breast cancer, head and neck cancer, lung cancer, non-small cell lung cancer, bladder cancer, *etc.* It

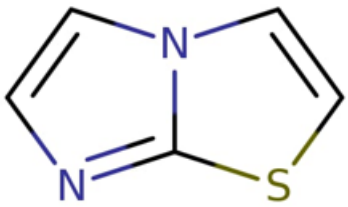
is also reported that in carcinoma pathogenesis, EGFR kinases are involved, which pull a lot of medicinal chemists for the development of potent EGFR kinase inhibitors. EGFR inhibitors are involved in the inhibition of tyrosine kinase phosphorylation which eventually prevented the signalling cascade following the activity of tyrosine kinase

EGFR receptor and the signaling cascade

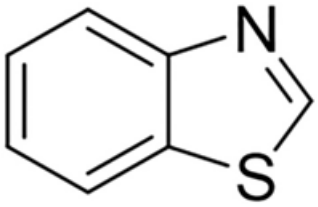
The EGFR includes three subunits. There are three domains: cytoplasmic, transmembrane, and extracellular EGF binding domain (Figure 2). The PTK domain and the C-terminal phosphorylation domain are the two subunits that incorporate the cytoplasmic domain. Numerous cancers have been linked to EGFR overexpression. This reveals that targeting the EGFR with small-molecule inhibitors is a beneficial cancer therapeutic strategy. Researchers have been curious in this subject for the past 20 years, which has resulted in the discovery of various EGFR small-molecule inhibitors. A downstream pathway that happens after transforming growth factor alpha (TGF) or epidermal growth factor (EGF) attaches to EGFR. Signaling network consist of two pathways. The first regulates EGFR's impact on cell cycle progression and proliferation. This comprises the KRAS-RAF-Mitogen-Activated Protein Kinase (MAPK). The second includes anti-apoptosis signals via the phosphatidylinositol 3-kinase (PI3K) pathway. Moreover, STAT proteins have been shown to act as a direct or indirect activation mechanism for intracellular EGFR signalling.



Heterocyclic compounds are organic molecules with at least one carbon atom and at least one additional heteroatom, such as N, O, or S, that play an important part in the metabolism of living cells. It may be either nonaromatic or aromatic. Most of them are five or six membered and some of the rings contain higher than that of three, four, seven or larger rings. Fused heterocyclic compounds, which generally have five or six members, have sparked a lot of interest in medicinal chemistry because of their wide range of pharmacological and therapeutic implications. Among the various fused heterocyclic compounds, Imidazothiazole contains a bridgehead nitrogen atom and a sulphur atom which are biologically active and plays a prominent role in medicinal chemistry. Imidazothiazoles and their derivatives are one of the important scaffolds in pharmaceuticals due to their broad applications and therapeutic properties. It is made up of a five-membered heterocyclic ring thiazole fused to an imidazole ring. The imidazole ring is widely present in natural and synthetic origin and it readily allows binding with receptors and enzymes.



Imidazothiazole



Benzothiazole

Benzothiazole represents whole class of sulphur consisting of heterocyclic compounds comprising a benzene ring fused to a thiazole ring. The benzothiazole heterosystem primarily occurs in many natural compounds as it finds immense applications as phytohormones, antioxidants, electroluminescent devices, vulcanization inducers, enzyme inhibitors *etc.*

LITERATURE REVIEW

Rashdan *et al.* 2020 examined the effectiveness of imidazo[2,1-b]thiazole scaffolds coupled thiadiazole derivatives against HepG2 (liver) cancer cell lines. This compound has more antiproliferative activity against HepG2 and normal cell lines, with IC50 values of 12.731.36 and 8.341.81 µg/mL, respectively compared to 3.560.46 and 3.210.32 µg/mL for the reference drug doxorubicin. The *in silico* molecular docking for compound was conducted against GPC protein using the PyRx tool and the binding affinity was found to be -10.30

kcal/mol. The compound forms two pi-cation interactions with the ARG197 at distances of 6.42 and 6.49Å. Therefore, it had a high binding affinity and had superior non-covalent interactions with the target GPC-3.

Bouchet *et al.* (2019) successfully synthesized benzothiazoles with medium to good yields from Thio benzanilides by making use of potassium peroxydisulfate as a sacrificial oxidizing agent and riboflavin as a photosensitizer under visible-light irradiation *via* cyclization reaction. Riboflavin is one of the cheapest natural reagent as a photocatalyst that demonstrates substantial facilities against transition-metal catalysis. Moreover, many functional groups were confirmed by the present technique, and the desired productions were made.

Bhat *et al.* (2019) investigated the microwave irradiated expeditious synthesis of 2-aryl-benzothiazoles from various aryl aldehydes and 2-aminothiophenol in the presence of acacia concinna as a biocatalyst. As compared to the traditional approach, the present protocol possesses distinguishing characteristics such as environmental friendly nature, less reaction time, solvent-free and excellent yields of the products.

Folgueiras *et al.* (2018) found that the supporting electrolyte-free electrochemical and catalyst-free synthesis of benzothiazoles by using a flow electrochemical reactor to produce moderate to good yield and high current performances from arylthioamides. The simple scale-up of the reaction significantly improved the recorded methodologies for the production of benzothiazoles by this process.

Chun *et al.* (2017) developed the reaction of 2-aminobenzenethiols with CO_2 and phenylsilane in the presence of DBU to synthesize benzothiazoles in excellent yields . There was a comprehensive substrate spectrum and functional group resistance for this reaction. Moreover, without any loss of activity, the precatalyst salt could be recovered and utilized several times.

Gao *et al*. (2014) described the DBN catalyzed synthesis of benzothiazoles from 2-aminothiophenols and CO_2 via cyclization reaction in the presence of diethylsilane. Many benzothiazole derivatives were afforded in excellent yields. This work demonstrates that hydrosilane played a important role in the preparation of benzothiazoles and successfully avoided the formation of benzothiazolones as by-products. This method provides an eco-friendly path for synthesizing benzothiazoles and their derivatives.

Bose *et al.* (2006) have established sustainable, effective and expeditious methodology for the synthesis of benzothiazoles from sulfamide substrates *via* cyclization reaction. The reaction was carried out at ambient temperature with DMP as the catalyst and dichloromethane as the reaction solvent. The method discloses that the reaction proceeds in high yields through a thiyl radical to produce the new oxybis benzothiazole compound and is also capable of producing combinatorial libraries.

METHODOLOGY

Various types of sources like research articles, review articles, books, and reports were utilized to gather the different types of data, i.e., Heterocylic compounds, cancer and its latest study, literature survey. A wide range of sources such as Google, Google Scholar, SciFinder, Science Direct, Springer Online, Web of Science, Wiley Online Library, Informa, ResearchGate, Scopus, PubMed was searched for all these data. Different types of information also gathered from the review papers and research papers. Moreover the literature and the articles were searched from the relevant websites and several popular electronic search engines using the various keywords. A variety of books were also studied.

CONCLUSION

Overall, this review article has gone over modern progress in synthesis of benzothiazole, imidazothiazole core structure and its analogues. In precedent years, Benzothiazole have take part in more and further important character in medicinal chemistry. It is proposed that this knowledge would give rise and shows enormous impact for the growth of synthetic pathway for benzothiazoles and also to draw of improved chemical frameworks with higher specificity and superior biological properties, and collectively with development of fresh synthetic approaches.

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