Journal of University Studies for inclusive Research (USRIJ)
مجلة الدراسات الجامعية للبحوث الشاملة
ISSN: 2707-7675

Journal of University Studies for Inclusive Research

Vol.8, Issue 12 (2022), 8660- 8676

USRIJ Pvt. Ltd.,

Synthesis of Some Benzimidazole and Benzothiazole Derivatives Expected to Have Antitumor Activity

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Abstract

The objective of the study was to clarify how some benzimidazole and benzothiazole compounds, which were predicted to have anticancer activity, were created. The study employed a qualitative method, which seeks to first determine the existing context of an occurrence before attempting to describe it. The results showed that in vitro anticancer experiments reveal that the novel benzimidazoles' 4b and 5b,c analogs are the most effective against all cell lines in the family of CDK2 inhibitors comprised of pyrimidine and benzothiazole hybrids. The three analogs

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(HepG2, HCT 116, and MCF-7) were also demonstrated to be less cytotoxic than 5-FU toward the W138 normal cell line, with 4b having the maximum in vivo activity, as per the data. The strongest DNA-binding affinities were for 4b and 5c. The results showed that every novel benzimidazole meets the prerequisites for effective oral absorption and bioavailability. The study recommended to determine if the benzimidazole series may be utilized effectively as a chemotherapeutic agent to treat carcinoma, in-depth research is required, more research is needed to identify potential anticancer medicines, finally, the creation of new anticancer medications will be made possible by the discovery of a family of potent and highly selective benzimidazole derivatives.

Keywords: *Benzimidazole; Benzothiazole; Antitumor; Cancer*

Introduction

In the world today, cancer is an illness of startling importance. After cardiovascular illnesses, it is the second biggest cause of death (Unger, 1997). According to Bagi, (2002) the leading cause of death globally and a significant global health challenge is cancer. It is actually a sizable collection of more than a hundred distinct diseases, not just one. Uncontrolled cell multiplication and metastasis to various regions of the body are its defining characteristics. Despite the fact that there are medicines, problems such as cytotoxicity have forced researchers to look for more potent forms of treatment. Cytotoxic substances are used in chemotherapy to treat cancer. These are ideally created to selectively kill cancer cells while having little to no cytotoxicity on healthy cells (Simstein et al., 2003).

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The need for new chemotherapeutic drugs to treat cancer is still present due to their toxicity, potential for resistance development, and absence of broad-spectrum therapies. As a result, a wide range of various tactics has been used to create novel therapies or enhance existing ones. A review of the literature found that benzimidazole compounds have a variety of biological functions, most notably anticancer activity (Galal et al., 2010; Gowda et al., 2009).

A new class of anticancer drugs known as pyrrolo [1,2-a] benzimidazoles exhibits cytotoxic action against various cancer cell types. DNA undergoes reductive alkylation, which is followed by the breakage of G and A bases, as part of the cytotoxic mechanism (Schulz et al., 1995; Islam and Skibo, 1990). a cancer-fighting drug [Hoechst-33342], 2'-(4-ethoxyphenyl)-5 (4-methyl 1-piperazinyl) Topoisomerase I has been shown to be inhibited by 2,5'-bis-1H benzimidazole (Chen et al., 1993). Under both in vitro and in vivo experimental circumstances, albendazole, a benzimidazole carbamate (methyl 5-propylthio-1H- benzimidazol-2-yl carbamate) with extensive clinical use as an anthelmintic medication, can also inhibit the growth of hepatocellular carcinoma cells (Pourgholami et al., 2001).

However, a class of medicinal chemicals known as benzothiazole rings has been shown to have a wide spectrum of anticancer activities (Caleta et al., 2009; Youssef et al., 2012). A literature review found that the new class of anticancer drugs 2-(4-aminophenyl) benzothiazoles have inhibitory action against human breast cancer cell lines (Kashiyama et al., 1999; Shi et al., 1996).

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The equilibrium between cellular replication and death is greatly influenced by apoptosis, a selective process of physiological cell deletion. Apoptotic signaling can occur in one of two ways: either through the death receptors that are expressed on cell plasma membranes, or alternatively, through the mitochondria, which have many proteins that control apoptosis. Tumor necrosis factor (TNF) or Fas receptors that are membrane-bound are ligated to start the death receptor pathway, which leads to a caspase-8-dependent cascade and subsequent cell death. Caspase-8 cleaves the BH3 interacting domain (Bid) during this cascade, causing the release of cytochrome c and/or directly activating caspase-3(O'Connor et al., 2000; Burns et al., 2001).

The activation of a series of intracellular cysteine proteases known as caspases is one of the crucial steps in apoptosis. Caspase-3 is able to cleave a wide range of substrates, including poly (ADP-ribose) polymerase, upon proteolytic activation by upstream caspases (PARP). The characteristic morphological and biochemical characteristics of apoptosis are caused by the breakage of a variety of substrates (Datta et al., 1997).

It is believed that the benzimidazole nucleus is a crucial anchor for the search for novel physiologically active substances. Benzimidazole derivatives are highly interesting anticancer agents (Chu et al., 2015; Mochona et al., 2015; Hegde et al., 2015).

Study Problem

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Several benzimidazole and benzothiazole compounds were created and their anticancer potential was tested in HepG2 cancer cells. Studies in vivo are being conducted to determine the interesting derivatives' mode of action.

Many people can successfully cure their cancer using the most popular therapeutic modalities, such as surgery, radiation therapy, and chemotherapy. One of the most effective and powerful methods for treating malignant tumors is chemotherapy. However, one of the challenges facing the success of cancer chemotherapy is the non-selectivity of chemotherapeutic medicines. The best anticancer medications would eradicate cancer cells without endangering healthy tissues. The design and discovery of new, powerful anticancer medicines with high selectivity and low toxicity are of particular interest to medicinal chemists today since cancer research has become a popular issue.

Questions of The Study

The problem of the current study can be summarized in the following questions**:**

- How to evaluate the activity of benzimidazole and benzothiazole against cancer?
- How to increase anticancer activity through benzothiazole and benzothiazole?

Objective of The Study

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The problem of the current study can be summarized in the following sub-objectives:

- Evaluate the activity of benzimidazole and benzothiazole against cancer.
- Explain the increased anticancer activity through the benzothiazole and benzothiazole

Methodology

The study employs a qualitative approach, which seeks to first determine the existing status of a certain occurrence before attempting to explain it. As a result, it is reliant on the examination of reality or the event as it actually transpires and is concerned with faithfully capturing it (Creswell, 2003).

The qualitative method is important in research since it is viewed as a core tenet of scientific inquiry and is usually regarded as the only way capable of researching many human fields. The qualitative method is concerned with precisely defining and communicating the phenomenon both qualitatively and numerically. According to its definition, this means treating the phenomenon as it actually is (Williams, 2007).

The study followed the qualitative approach to explain the synthesis of some benzimidazole and benzothiazole derivatives expected to have antitumor activity.

Literature Review

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According to docking tests, the novel benzimidazole family of compounds displays cytotoxicity to HepG2 and induces apoptosis via activating aspase-3 activity. Additionally, by causing cells to enter a G1 arrest, which causes cells to undergo apoptosis, they enhanced the expression of p21, a crucial factor in the cell cycle. In certain cancer cell lines, mutations or lack of caspase-3 prevents apoptosis and DNA fragmentation. Since activation of caspase-3 is known to increase the sensitivity of cancer cells to therapy, the caspase-dependent apoptotic effect of the tested compounds may be of therapeutic value in determining the sensitivity versus the resistance of liver cancer cells to such tested compounds. These analogs will make it possible to investigate significant structural factors governing small molecule macromolecular interactions for anticancer activity based on our docking investigations. It will be possible to create new anticancer medications thanks to the identification of a class of potent and highly selective benzimidazole derivatives. Additionally, an in-depth research is necessary to evaluate whether the benzimidazole series may be used as a successful chemotherapy agent to treat hepatocellular cancer (HCC) (Youssef et al., 2012).

A number of novel pyrimidine-based benzothiazole compounds were developed and synthesized in order to create novel CDK2 inhibitors that could be used as anticancer drugs. Some of the target compounds showed strong anticancer activity in vitro against five cancer cell lines, according to the initial biological evaluation. With IC50 values of 0.45, 0.70, 0.92, and 1.80 mM, respectively, the analog 10s in particular showed approximative potency with AZD5438 against four cells, including HeLa,

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HCT116, PC 3, and MDA-MB-231. More intriguingly, molecular docking studies showed that the analogue effectively bonded with the CDK2 binding site and that the most highly active compound in this study, 10s, also possessed promising CDK2/cyclin A2 inhibitory activities with IC50 values of 15.4 nM, which was almost 3-fold potent than the positive control AZD5438. Additional research revealed that compound 10s might cause apoptosis and cell cycle arrest in a concentration-dependent manner. These findings imply that pyrimidine-benzothiazole hybrids constitute a novel class of CDK2 inhibitors and need further study in the search for potential anticancer compounds (Diao et al., 2019).

Escherichia coli ATCC 12435, Bacillus cereus UW 85, Staphylococcus aureus ATCC 29213, Candida albicans, and Aspergillus fumigatus 293 were investigated for antibacterial effectiveness against new benzimidazole analogs. The outcomes showed that compound 10 had strong and versatile antibacterial action. Additionally, the antibacterial activity of 4b and 5c against B. cereus, S. aureus, C. albicans, and A. fumigatus was outstanding. Additionally, C. albicans was interestingly resistant to the antifungal activities of 12 and 14. The novel compounds' antiquorum-sensing effectiveness toward Chromobacterium violacium ATCC 12472 was also investigated. The novel benzimidazoles' in vitro anticancer testing on HepG2, HCT 116, and MCF-7 cancer cell lines revealed that 4b and 5b,c are the most effective analogs against all examined cell lines. The effectiveness of the three powerful in vitro antitumor analogs was further tested for in vivo antitumor activity against EAC in mice and in vitro cytotoxicity against the W138 normal cell line.

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Results showed that the three tested analogs are less cytotoxic than 5-FU toward the W138 normal cell line, with 4b having the maximum in vivo activity. The strongest DNA-binding affinities were found for 4b and 5c when the most potent antibacterial and anticancer analogs were tested. The in vitro experiments showed that every new benzimidazole satisfies the ideal conditions for effective oral absorption and bioavailability. Furthermore, it has been reported that in silico toxicity assessment (Gohary and Shaaban, 2017).

Using two types of scaffolds—benzothiazole/2 aminobenzothiazole and 1,3,4-oxadiazoles—in a single molecule, the study of Subramanyam et al., (2018) created a new series of heterocyclic compounds based on their biological activity in the literature. Spectral analyses verified their molecular structures after their effective synthesis. According to expectations, all of the substances showed anticancer properties against four cancer cell lines. A road map for the design and production of novel therapeutic compounds with antitumor and anticancer action may be provided by this study.

In order to increase its anticancer activity, Abdelgawad and Kamel (2012) study the benzothiazole and benzothiazole isosteres (benzoxazole and benzimidazole) were combined with specific anticancer heterocyclic compounds. This combination's impact on anticancer activity was also studied. This work involved the preparation of substituted pyrazoles IIIa-c by diazotizing amino compounds Ia-c, condensation with acetylacetone, and subsequently hydrazinolysis of intermediates IIa-c (scheme 1). In Scheme 2, the 2-chloromethyl-1Hbenzimidazole (IV) reacts with the

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amino group of Ia-c to produce the new molecules Va-c. The required compounds IXa-c were produced when the amino group of Ia-c reacted with pyrazolopyrimdine VIII (Scheme 3). Compounds IIIa-c, Va-c, and IXa-c were tested against a human breast cancer cell line for cytotoxicity (MCF7).

Twelve 2-substituted benzimidazole, benzothiazole, and indole derivatives were synthesized by Algul et al. (2008) utilizing both microwave irradiation and traditional heating techniques. The microwave approach was shown to be more advantageous since it reduces time by 95 to 98% while increasing yield by 3% to 113%. All substances were examined for hyaluronidase inhibitory activity using the stains-all assay at pH 7 and the Morgan-Elson assay at pH 3.5 at a concentration of 100 M in each. The most effective substance had an IC50 value of 107 M at both pH 7 and 3.5, and its name was 2-(4-hydroxyphenyl)-3 phenylindole (12).

There have been reports of three different reaction pathways that favor intramolecular ring closure over a metal-catalyzed transformation. Without the need for ligands, oxidants, additives, or dangerous solvents, the current co-catalyzed technique offers an environmentally friendly option to synthesize these crucial chemicals. This process is a safe substitute for the current techniques for three fascinating families of compounds, benzoxazoles, benzothiazoles, and benzimidazoles since it uses an environmentally acceptable solvent (ethanol) and a recyclable catalyst. Nine different substances were created and tested for anticancer potential. Utilizing molecular docking studies, the binding mechanisms of

each drug at the estrogen receptor's binding site have been examined. These substances are ranked according to how effective they are as estrogen activity inhibitors (Hajipour et al., 2015).

Conclusion and Recommendation

The main objective of the study is to explain the synthesis of some benzimidazole and benzothiazole derivatives expected to have antitumor activity. The study uses a qualitative method that aims to first ascertain the current situation of an event before making an effort to explain it. Because of this, it depends on examining reality or the event as it truly happens and is concerned with accurately portraying it.

The results show that Hybrids of pyrimidine and benzothiazole are a new family of CDK2 inhibitors, and the 4b and 5b,c are the novel benzimidazoles' most potent analogs against all cell lines, according to in vitro anticancer tests. The three analogs (HepG2, HCT 116, and MCF-7) were also shown to be less cytotoxic than 5-FU toward the W138 normal cell line, with 4b having the highest in vivo activity, according to the results. The DNA-binding affinities for 4b and 5c were the highest. The findings demonstrated that each brand-new benzimidazole satisfies the necessary requirements for efficient oral absorption and bioavailability.

The research produced the following recommendation in light of its findings:

- The discovery of a family of potent and highly selective benzimidazole derivatives will enable the development of novel anticancer drugs.

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- To determine if the benzimidazole series may be utilized effectively as a chemotherapeutic agent to treat carcinoma, in-depth research is required.
- In order to find possible anticancer drugs, more research is required.

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