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A study on Synthesis of Azole Derivatives Optimized for Anticancer Activity

Abstract: Cancer is still the main reason for death volumn in the whole world, this promotes us to create new drugs that are stronger and very specific. This study seeks to construct a highly diversified library of new azole molecules and establish the therapeutic value of these drugs in the treatment of cancer patients. The principal end equally is to synthesize and design the compounds, evaluate their action against some kind of cancer cell lines, find the reliable structure-activity relationships and investigate the mechanisms of bioactivity. The possibility of applying that avenue on the treatment with azoles as base scaffolds to form an entirely new type of highly selective anticancer agents could come strongly from this work. Moreover, these findings will add to existing knowledge that should help with directing a more effective and successful development of next generation azole-like drugs in the future.

Keywords: *Drug, Mortality, Cancer, Derivatives, Agents, Therapeutic*

1. Introduction

Cancer is a disease characterized by the uncontrolled division of abnormal cells that may metastasize (spread to other parts of the body). There is no term more terrifying than cancer, even more so than death itself. The National Cancer Registry Program in India records over 8,00,000 new instances of cancer each year, indicating that it is a major public health concern in the country. Oral and lung cancers are the most prevalent kinds of cancer in males in India, whereas cervical and breast cancers are the most common types of cancer in women. [1] There are an estimated 75,000 to 80,000 new cases in India each year, according to worldwide reports. As the second most common disease in 2010, stomach cancer was responsible for 12.6% of all cancer fatalities. [2] The current annual rate of new instances of breast cancer is around 115,000, and experts predict that this will increase to 250,000 by 2015. Globally, malignancies of the lung (1.8 million cases, or 13% of the total), breast (1.7 million cases, or 11.9% of the total), and colorectum (1.4 million cases, or 9.7% of the total) were the most frequently diagnosed cancers. Lung cancer accounted for 1.6 million deaths, or 19.4% of all malignancies; liver cancer for 0.8 million, or 9.1%; and stomach cancer for 0.7 million, or 8.8%. [3]

Cancers may be broadly categorized into many types, including , One kind of cancer, known as carcinoma, starts in the skin, tissues, or internal organs. Sarcoma is one of several subtypes

of carcinoma; it is a kind of cancer that originates in connective tissues such as cartilage, bone, muscle, blood vessels, fat, or others. [4] Cancers like leukemia start in the bone marrow and other tissues that aid in blood production. A large number of abnormal blood cells are produced and released into the bloodstream. [5,6]

Myeloma and lymphoma begin in cells of the immune system. Cancers of the central nervous system—Early stages of these diseases manifest in the brain and spinal cord. Similar to other chronic illnesses, cancer does not have a single cause but rather a combination of them. [7,8] It is not a hereditary disease per se, but a susceptibility to it is. Mutations in genes that normally exist in cells cause this.[9,10]

The ultimate objective of any cancer therapy should be to eradicate the disease entirely, harm-free. [11,12] Surgery may occasionally do this, although it is typically ineffective due to the cancer's propensity to attack neighboring tissues or move to other places via metastasis. (45, 46) The following are a few examples of cancer control management strategies, and they relate to the many causes of cancer. [13,14]

In the vast array of cancer management strategies A lot of people are using chemotherapy. Because it is readily available and easy to administer. [15] Chemotherapy involves killing cancer cells by delivering anticancer medications. One of the most prevalent cancer therapies, chemotherapy has a long history of use. [16,17] Chemotherapy often kills cancer cells by preventing them from dividing and growing. In the battle against cancer cells, many medication classes have distinct mechanisms of action. Some cancers respond well to chemotherapy alone, while others need additional therapies like radiation or surgery. [18,19]To combat a particular malignancy, a cocktail of chemotherapy medications is often used. The kind of cancer being treated determines the particular sequence in which certain chemotherapy medications are administered. [20]

Chemotherapy is a powerful tool in the fight against certain malignancies, but it affects the whole body, not just the cancer cells. [21] This is why a great deal of discomfort during therapy is possible. If we and our caregivers are aware of what to expect from these side effects, we may take steps to mitigate or even avoid them. [22,23]

When it comes to managing cancer and related conditions, chemotherapy is usually at the top of the list. Although several therapeutic treatments have been tested and shown promise in the fight against cancer, they have always been plagued with serious side effects.[24] Furthermore, patients' adherence is impacted as well. In a similar vein, the cost and length of dosages are also important considerations. Accordingly, there is an urgent need to discover

and create new, highly effective therapeutic drugs that may provide more remarkable eyesight with fewer side effects. [25]

2. Objectives

- To study the synthesize variety of azole-based compounds by using highly productive and flexible synthetic strategies;
- To investigate the anticancer activity of the synthesized compounds against a group of cancer cell lines representing diverse tumor types;
- To determine structure-activity relationships which allows optimization of the lead compounds.
- To study the mechanism of action especially including the potential impact.

3. Statement of the problem

Which is still the leading health issue for people though, with high mortality rates and a lot of the needs that remain unmet in a clinical way. Even though modern cancer treatment has a big variety of efficient methods, today`s cancer treatment strategies are typically limited by situations such as drug resistance, secondary effects, and lack of selectivity. Novel and specific agents would be, indeed, much needed for the anticancer immunotherapy to give better outcomes for cancer patients. As hard-won compounds, azole derivatives have shown outstanding promise in pursuit of especially anticancer but this class of compounds requires continued optimization of activity and selectivity to the ongoing research. This research is targeted at dealing with the predicament of the limited inventory of existing azole and therefore, its novel compounds are to be synthesized and the anticancer potential of the same will be assessed. This research finding would help in nurturing more focused and effective azole-based medicines for cancer which may be superior in treating cancer stock compared with the existing ones. In addition, the results of understanding structure-activity relationships as well as mechanisms of action could, in perspective, strengthen the doctor's findings regarding the development of the next generations of drug forms of azoles.

4. Significance of the study

The research on the development and enhancement of azole derivatives made for an anticancer aim is of substantial relevance in the struggle within stand that continues world-wide which is cancer. In spite of the utmost efforts to end this problem made by the researchers and oncologists, cancer still remains the leading cause of death globally and preferred therapy is still restrained by problems, including drug resistance, non-selectivity and undesirable effects. Improving existing anticancer medications, users and targeted ones to

be more effective is a major goal for developing clinically relevant drugs. Azole-based anticancer agents demonstrated promising membrane-targeting activities; however, further optimization with elevated active efficacy and selectivity is a prerequisite for clinical use. It will be explored to use the effect of azole derivatives in cancer therapies' development of new and more effective anticancer programs. The success in isolation and optimization of the lead azole-based compounds in this study could be the seed for more detailed investigations, either at the level of, the main concept of this research can help for the development of new anticancer treatments including azole derivatives that will be able to recover the cancer treatment. One of the arguments can be that it is the one of the method that can involve the improvement of the cancer treatment options.

5. Research methodology

In a 96-well plate, cells were planted at a density of 5×10^{1}cells/ml. The synthesized compounds were added at concentrations ranging from 10-4 to 10-7 molar after an overnight incubation period. Because the drug therapy group also received 1% ethanol. The doxorubicin-treated control group also received 1% ethanol as an additional positive control. Three times each concentration was done. For three days, these cells were placed in a controlled environment with 5% CO2. Following that, 20µl of MTT (3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) was added to every well and left to incubate at 370C for four hours. Adriamycin was dissolved in DMSO after the medium was removed, and the absorbance was measured at 570 nm. The growth inhibition was calculated by subtracting the sample O.D. from the control O.D. divided by the control O.D., and subsequent LC50, TGI, and GI50 values were also computed.

Table 1: Cell lines details

Sr. No.	Cell line	Human tissue of Origin	Cells/Well
1	MCF-7	Breast	$5*10^{3}$

- **Parameters Reported:** GI_{50}, LC_{50}, TGI
- **Source of cell line:** NCI, USA
- **Concentrations of drugs used:** 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4} molar
- **Vehicle used:** Dimethyl Sulfoxide (DMSO)
- **Method of Testing:** Sulforhodamine B (SRB) assay

Table 2: Sample details

Sr. No.	Sample Code	Compounds code
1	CI	2.011
2	OP	2.019
3	NNP	2.038
4	NCP	2.037
5	NOI	2.033
6	ADR	-

- **DPPH radical scavenging capacity**

Bios first described the DPPH for measuring free radical scavenging capability, and several other researchers have since made modifications to it. [26] Among the several methods for determining whether plant samples have antioxidant activity, this one sees heavy usage. Very stable, with a maximal UV-vis absorption at 515 nm, the DPPH free organic nitrogen radical interacts with molecules that may donate hydrogen atoms.

Antioxidants scavenge DPPH, which decolorizes the deep purple DPPH methanol solution following a reduction reaction, and this is the basis of the approach. [27] This test uses a UV-vis spectrophotometer to determine how effective antioxidants are in decreasing the DPPH radical. [28, 29] The absorbance of the reaction mixture drops as the DPPH methanol solution becomes more discolored; this indicates that the combination has a high ability to scavenge free radicals. [30]

As a positive control, we use a typical antioxidant such Butylated Hydroxy Toluene (BHT). As a negative control, we utilize a reaction mixture that contains 50% aqueous methanol instead of the sample solution.

The formula is used to compute the free radical scavenging activity, which is measured by the staining of the DPPH solution:

$$\% \text{ inhibition} = 100 \times (A_{\text{control}} - A_{\text{sample}}/A_{\text{control}})$$

6. Results and Discussion

A number of studies have shown that a pyrazole derivative with just minor structural changes might provide an effective antioxidant. It has been suggested that isoxazole derivatives might potentially have antioxidant properties. Hence, the DPPH assay was used to determine the antioxidant activity of the produced isoxazole and pyrazole derivatives. As one of the most used and practical colorimetric methods for gauging the antioxidant capacity of various

substances, the DPPH test is often employed to estimate an antioxidant's capacity to scavenge free radicals. The DPPH assay demonstrated that every single one of the synthetic compounds had very strong antioxidant properties. The CI had the lowest IC50 value at 37.51 µg/ml, while the NCP had the highest at 242.73 µg/ml. The pathophysiology of cancer involves free radicals in several ways. There are several ways in which reactive oxygen species and nitrogen species contribute to cancer development and the malignant evolution of cancer cells, including by increasing their metastatic potential.

Actually, they are now thought to be a hallmark of malignancy. A crucial component in the progression of cancer is the harmful impact on cellular systems caused by free radicals, namely by DNA damage. Among live cells, DNA damage from oxidation is the most common cause of mutations, occurring in human cells at an unpredictable rate of 104 lesions/cell/day Malondialdehyde levels were shown to be increased in breast cancer patients in one study. Once again, the same team of researchers showed that oxidative stress plays a role in how breast cancer develops. Retort to DNA damage in breast cancer cells (MCF7) and fast rise in ROS generation in the mitochondria are both caused by inhibition of JNK (c-Jun, the Terminal of N-kinase).

The inhibition of Bcl-2 phosphorylation, which leads to DNA damage and stimulates the activation of p53, is responsible for this ROS generation. By regulating oncogene expression, activation of the JNK signaling pathway activates an anti-tumorigenic response. The activation of oncogenes regulated by p53 and dependent on oxidative stress is associated with this response. Given the strong antioxidant capacity of the test compounds in this investigation and the well-established function of antioxidants in cancer prevention, we chose to examine the in-vitro anticancer activity of the test samples against the MCF7 human breast cancer cell line. In order to provide a good picture of the spectrum of antioxidant activity, samples were chosen for their potential anticancer effects. Total suppression of cell growth was seen in all test samples. The two most powerful test samples, OP and NOI, respectively, produced 85.8 and 85.9 micromoles of total inhibition. So, it can be concluded from this investigation that the synthetic test materials exhibited strong antioxidant and anticancer properties.

Table 3: Controlled growth of synthetic substances at varying doses as a percentage

	Human Breast Cancer Cell Line MCF-7
	% Control Growth

	Molar Drug Concentrations															
	Experiment 1				Experiment 2				Experiment 3				Average Values			
	10-7 M	10-6 M	10-5 M	10-4 M	10-7 M	10-6 M	10-5 M	10-4 M	10-7 M	10-6 M	10-5 M	10-4 M	10-7 M	10-6 M	10-5 M	10-4 M
CI	86.5	82.3	63.5	-29.1	100.0	84.9	83.8	-2.0	85.6	71.8	65.7	3.6	90.7	79.7	71.0	-9.2
OP	82.3	69.7	40.7	-37.4	85.7	85.5	79.8	-5.1	88.5	68.0	68.8	2.3	85.5	74.4	63.1	-13.4
NNP	73.0	69.3	53.4	-3.4	85.1	80.8	79.6	73.4	92.0	82.8	78.0	56.9	83.4	77.6	70.3	42.3
NCP	87.7	85.5	57.9	-2.7	82.6	80.2	58.3	48.1	91.6	73.9	64.4	46.5	87.3	79.9	60.2	30.6
NOI	83.4	83.1	64.4	-26.3	100.0	99.4	84.3	-21.2	89.5	73.2	70.9	2.1	91.0	85.2	73.2	-15.1
ADR	47.1	10.1	-26.8	-37.4	48.3	7.1	-3.2	-15.2	45.8	7.6	-22.0	-29.9	47.1	8.3	-17.3	-27.5

Table 4: μGraph used to determine molar drug concentrations

MCF7	LC_{50}	TGI	GI_{50}*
CI	>100	90.8	37.4
OP	>100	85.8	31.4
NNP	>100	>100	78.8
NCP	>100	>100	58.6
NOI	>100	85.9	37.1
ADR	>100	34.5	<0.1

1

LC_{50} = Concentration of drug causing 50% cell kill

GI_{50} = Concentration of drug causing 50% inhibition of cell growth

TGI = Concentration of drug causing total inhibition of cell growth

ADR = Adriamycin, Positive control compound

The residual compound with ACTREC will be retained for one month from the date of this report. Enquiries regarding report will not be entertained after this date.

GI_{50} value of $\leq 10^{\wedge-6}$ molar (i.e. 1 µmolar) or ≤ 10µg/ml is considered to demonstrate activity in case of pure compounds. For extracts, GI_{50} value ≤20μg/ml is considered to demonstrate activity
Yellow highlighted test values under GI50 column indicate activity.

This test can accurately measure materials containing antioxidants that are either hydrophilic or lipophilic.

Table 5: Formulas for compounds together with their half-life values (μg/ml)

Comp	Ascorbic acid	2.011	2.012	2.017	2.018	2.019	2.032	2.033	2.037	2.038	2.039
IC50 values (µg/ml)	43.91	37.51	232.28	209.64	174.24	35.82	257.73	36.41	242.73	142.91	147.80

Table 6: Substances together with the percentage of inhibition at various concentrations (μg/ml)

Compounds	**Concentrations (μg/ml)**					
	50	**100**	**150**	**200**	**250**	**SEM**
Ascorbic acid	43.56	70.42	85.01	92.78	98.31	9.807276
2.011	51.85	61.50	70.05	76.10	87.81	6.142613
2.012	18.46	29.24	36.05	44.87	52.49	5.931704
2.017	19.32	26.78	38.82	46.71	59.04	7.049678
2.018	21.07	38.24	47.42	58.12	60.94	7.246696
2.019	48.85	65.5	74.05	82.1	87.81	6.83289
2.032	17.54	25.67	35.83	47.34	54.55	6.782457
2.033	50.85	63.5	70.05	76.1	87.81	6.175799

2.037	30.46	38.23	44.53	41.82	51.89	3.53373
2.038	52.83	69.06	74.33	79.93	83.77	5.398972
2.039	25.93	39.22	57.35	66.57	63.15	7.733361

7. Conclusion

The research on the development and enhancement of azole derivatives made for an anticancer aim is of substantial relevance in the struggle within stand that continues world-wide which is cancer. In spite of the utmost efforts to end this problem made by the researchers and oncologists, cancer still remains the leading cause of death globally and preferred therapy is still restrained by problems, including drug resistance, non-selectivity and undesirable effects. Improving existing anticancer medications, users and targeted ones to be more effective is a major goal for developing clinically relevant drugs. Azole-based anticancer agents demonstrated promising membrane-targeting activities; however, further optimization with elevated active efficacy and selectivity is a prerequisite for clinical use. It will be explored to use the effect of azole derivatives in cancer therapies' development of new and more effective anticancer programs. Through the synthesis of azole library that could be used and evaluated for their anticancer activity, the approach of the study would give a good perspective about the structure-activity relationship of this subset of molecules as well guide the optimal way in which the molecules could be further designed. Additionally, probing into the mode of action, in particular, the study of the possible interactions between the compounds and the cancer-related protein targets, will widen the knowledge on the anti-cancer process, inspiring future development of more targeted and active therapy. Finally, the success in isolation and optimization of the lead azole-based compounds in this study could be the seed for more detailed investigations, either at the level of Generally speaking, the main concept of this research can help for the development of new anticancer treatments including azole derivatives that will be able to recover the cancer treatment. One of the arguments can be that it is the one of the method that can involve the improvement of the cancer treatment options.

7.1 Findings of the study

The key findings of the study can be summarized as follows:The key findings of the study can be summarized as follows:

1. DPPH test showed remarkable antioxidant activity for all sample test compounds with the lowest IC50 value of 37.51 μg/ml which was recorded for CI (2.011) and NCP (2.037) having the highest value of 242.73 μg/ml.
2. Through the in vitro or anticancer activity evaluation which was carried against the MCF-7 human breast cancer cell line, all test samples had a full complete inhibition of the cell growth.
3. OP (2.019) and NOI (2.033), demonstrated excellent toxicity scores, where they happened to be the most active compound in preventing cell proliferation at the lowest doses: 85.8 and 85.9 microgram/mL respectively.
4. Adriamycin (ADR) was shown as positive check compound, with GI50 value. It was less than 0.1 μM; this means that it is highly effective against MCF-7 cancer cells.
5. Study raised hope concerning their applicability as lead compounds to generate new anticancer therapeutics.

7.2 Scope for further research

The concerned study on finding a better way for azole derivatives for anticancer purpose could draw out so many lines of the future work that could benefit the humanity and patients. One important zone of the research would be the synthesized array of diverse azole compounds which can indeed constitute a base for the finding of new lead compounds with a higher potency better selectivity as well as better drug-like characteristics. As well as investigating the particular active mechanism which is functioning, the latest azole derivative may include their interactions with a cellular target that has a key function. The molecular mechanisms studies, e.g. target validation, pathway analysis, and investigating resistance mechanisms, can uncover more of the basis how these compounds inhibit cancer growth. This info could contribute to the emergence of more directed approach and effective tactics towards the therapy. The azole derivative-based anticancer compounds from this work may then be evaluated in combination with existing cancer treatments or other promising medicines. Seeking synergistic effects or complementary strategies may result in the evolution of more efficient multi-therapy options that will improve therapy outcomes better. The directions for the further exploration of the azyls derivate synthesis and their optimization for anticancer action are quite numerous. They at the moment offer the chance to deepen the existing knowledge on the topic and to come up with the new drugs.

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