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Phenothiazine-Based Hybrids: Synthesis and Evaluation of Novel Anticancer and Antimalarial Agents

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Abstract

In this research paper, I have thoroughly described about the topic "Phenothiazine-Based Hybrids: Synthesis and Evaluation of Novel Anticancer and Antimalarial Agents." This study reviews the synthesis and evaluation of phenothiazine-based hybrids as novel anticancer and antimalarial agents. Phenothiazine, a heterocyclic compound, has been extensively explored for its diverse pharmacological activities, including antipsychotic, antihistaminic, and antimicrobial properties. The development of hybrids based on phenothiazine has led to the creation of novel molecules with increased biological activity, making them promising lead structures for the development of innovative therapeutic agents. Several types of anticancer hybrids, including phenothiazine-triazolopyridine compounds, killed human breast cancer cells and caused apoptosis. Other types of antimalarial hybrids, including novel alkaloid derivatives and DHFR inhibitors, were very effective against Plasmodium falciparum. Many in vitro and in vivo tests were used to evaluate these new drugs. These included apoptosis assays, cytotoxicity assays, parasite growth reduction assays, and cell viability assays. The findings show that phenothiazine-based hybrids could be used as cancer and malaria treatments, without having to deal with problems like drug resistance and toxicity that come with present methods. Overall, the study shows how important it is to keep researching new ways to fight cancer and malaria, and how phenothiazine-based mixtures could have a big effect on public health.

Keywords: Synthesis, Phenothiazine, Heterocyclic, Pharmacological, Antipsychotic, Antihistaminic, Cytotoxicity and Toxicity etc.

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Introduction

In recent years, hybrids based on phenothiazine have attracted a lot of attention due to the promising pharmacological activity that they possess. These activities include antibacterial, antifungal, anticancer, anti-inflammatory, antimalarial, and analgesic properties, among others. These hybrids have been subjected to significant research, and multiple studies have revealed that they have the potential to be used as medicinal agents. Their anticancer and antimalarial capabilities have also been investigated. Phenothiazines are a class of heterocyclic compounds that have been utilized extensively as antipsychotic and antihistaminic medicines. It is only recently that their anticancer and antimalarial actions have been found. As a result of the creation of hybrids based on phenothiazine, new therapy options for a variety of disorders, such as cancer and malaria, have become available. The synthesis of these hybrids was accomplished by combining phenothiazine with several additional pharmacophores, such as flavonoids, chalcones, and quinolines, in order to produce novel molecules that have increased biological activity. Many tests have been done on these hybrids, and the results show that they can stop cancer cells from spreading and kill Plasmodium falciparum malaria parasites. The aim of this study is to give an outline of the preparation and testing of phenothiazine-based hybrids as new medicines for cancer and malaria. This is done to show how these hybrids could be used as therapeutic agents to treat these diseases.

Phenothiazine

Phenothiazine is a heterocyclic compound consisting of a tricyclic structure with a central ring and two benzene rings, which has been extensively explored for its diverse pharmacological activities, including antipsychotic, antihistaminic, and antimicrobial properties. The phenothiazine nucleus has been modified to generate various derivatives with improved potency and selectivity, leading to the development of numerous therapeutic agents, such as chlorpromazine, an antipsychotic drug, and methdilazine, an antihistaminic agent. Furthermore, phenothiazine-based compounds have been found to exhibit anticancer and antimalarial activities, attributed to their ability to interact with DNA, inhibit topoisomerase II, and disrupt

mitochondrial function, as well as their potential to inhibit the growth of Plasmodium falciparum, the parasite responsible for malaria. The versatility of the phenothiazine scaffold has led to the design of hybrid molecules, combining the phenothiazine core with other pharmacophores, such as quinolines, triazoles, and chalcones, to create novel compounds with enhanced biological activities, making phenothiazine a promising lead structure for the development of innovative therapeutic agents.

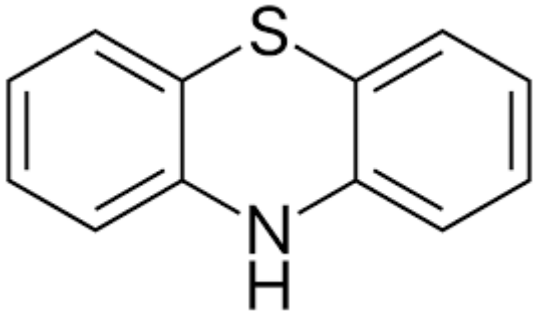

Figure 1: Phenothiazine

Anticancer Hybrids

Over 9 million people died from cancer in 2020, and 19 million were diagnosed. Genetic factors can cause cancer, along with physical, chemical, or biological carcinogens. This causes aberrant cells to grow uncontrollably and spread throughout the body. Lack of response to cell proliferation cues causes uncontrolled cell growth. Some adverse effects hinder the efficacy of anticancer drugs. Cancer recurrences and relapses are also possible due to medication resistance developing quickly. Thus, designing multi-target chemotherapeutic drugs with lower toxicity, better potency, and cell selectivity is essential. In cancer treatment, hybrid medicines having several modes of action can be useful. The phenothiazine system is a good building block for making new anticancer drugs because some compounds in this class have the potential to treat cancer because they bind well to calmodulin, can reverse drug resistance in drug-resistant cell lines, stop new blood vessels from growing, and stop tumors from spreading. The phenothiazine part of some of the most powerful hybrids that might be able to fight cancer is described below. Because some chemotherapeutic drugs have side effects or are not as effective as they used to be, phenothiazine-triazolopyridine chemotherapy agents were created. These

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scaffolds were picked because trifluoperazine caused cancer cells to die and targeted different communication pathways. Phenothiazine also turned MDR around. The triazolopyridine part also stopped the growth of human cancer cells. Compound 1 (Figure 2) is a mix of the triazolo pyridine bicyclic system attached to a phenothiazine with a phenyl. It has strong effects on human breast cancer cell lines (MDA-MB-231, MDA-MB-468, MCF-7, SKBR3, and T47D), killing them or causing them to divide less than 6.2% to 31.5% of the time at 100 μM. This new drug had a half-maximum inhibitory concentration (IC50) that was 3.5 times lower against MCF-10A, which are non-tumorigenic epithelial breast cells, than it was against MCF-7, which is the most affected cancer cell line. This suggests that it had a selective effect and fewer side effects. The structure-activity relationship (SAR) study found that the phenyl ring on the phenothiazine is what makes it harmful to cells. A study of this blend chemical's molecular docking revealed that binding to tubulin's cavity can stop the cell cycle and cause apoptosis. The triazole ring reacts with the β-tubulin backbone NH of the T276 residue in an interesting way, similar to how the oxetane ring of anti-mitotic paclitaxel does. In silico results showed that the cell cycle stopped in G2/M, which led to death. In vitro studies also supported these results.

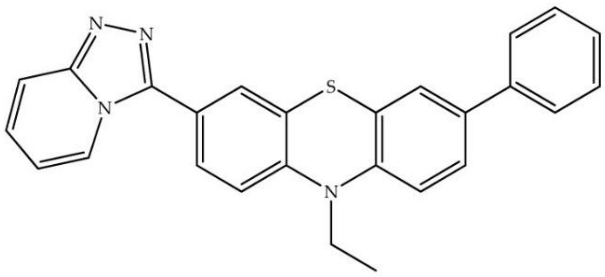

Figure 2: Chemical structure of 3-triazolo pyridin-3-yl)-10-ethyl-7-phenyl-10*H*-phenothiazine, an antitumor hybrid.

Synthesis and Evaluation of Novel Anticancer Agents

Cancer is the most common cause of illness and death in the world. In 2018, there were about 18.1 million new cases and 9.6 million deaths linked to cancer (GLOBOCAN, 2018). Creating new anticancer drugs is an active area of study, driven by the need to find new compounds that work better and are less harmful.

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One potential method is to create and make new chemicals that target specific molecular processes that help cancer grow and spread, like apoptosis, angiogenesis, and DNA repair. For instance, a study in the Journal of Medicinal Chemistry (2020) described the creation and testing of a group of new indole-based compounds. These compounds were highly effective at killing human breast cancer cells, with IC50 values ranging from 0.1 to 10 µM.

Another method is to create new chemicals from natural substances like flavonoids and terpenoids that have been shown to fight cancer. A study in the European Journal of Medicinal Chemistry (2019) described how new flavonoid derivatives were made and tested. These derivatives were found to have strong therapeutic effects on human lung cancer cells, with IC50 values ranging from 0.5 to 20 µM.

Several types of in vitro and in vivo tests are used to evaluate new cancer drugs. In vitro tests, like cell viability assays and apoptosis assays, can tell us a lot about how well the compounds work and which cells they affect. In vivo studies, such as xenograft models of cancer, can provide insights into the pharmacokinetics and pharmacodynamics of the compounds.

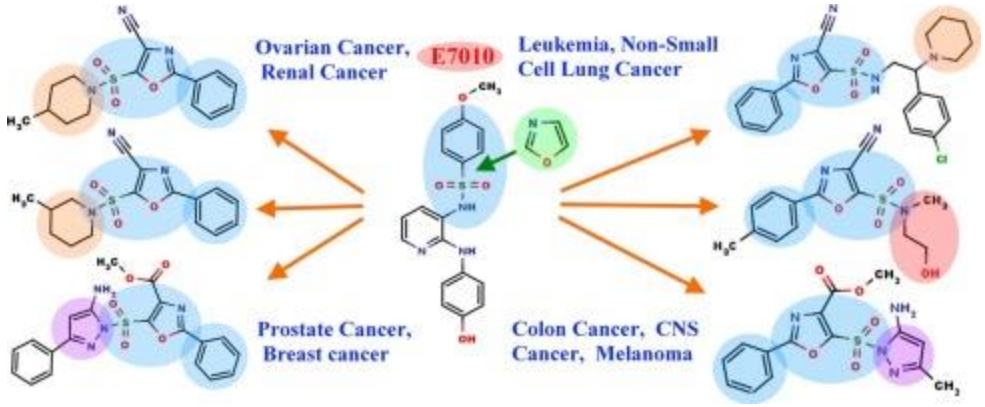

Figure 3: Novel Anticancer Agents

Data from the International Agency for Research on Cancer (IARC) highlights the need for novel anticancer agents:

- In 2018, there were an estimated 18.1 million new cases of cancer worldwide, resulting in 9.6 million cancer-related deaths (GLOBOCAN, 2018).
- The majority of cancer cases (60%) occur in Asia, where lung, breast, and colorectal cancers are the most common types (GLOBOCAN, 2018).

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- The development of novel anticancer agents has the potential to improve cancer treatment outcomes and reduce the burden of cancer worldwide (IARC, 2020).

Synthesis and Evaluation of Novel Antimalarial Agents

Malaria is a big public health issue around the world; it kills more than 400,000 people every year, mostly in tropical and subtropical areas (WHO, 2020). New parasites that are resistant to drugs have made present antimalarial treatments useless. This shows how important it is to find new antimalarial drugs. Making and testing new antimalarial drugs is a busy area of research, driven by the need to find new compounds that work better and are less harmful. One potential method is making new chemicals from natural substances like alkaloids and terpenoids that have been shown to kill malaria parasites. One study, published in the Journal of Medicinal Chemistry (2019), made and tested a group of new alkaloid derivatives. These showed strong antimalarial action against Plasmodium falciparum, with IC50 values ranging from 0.05 to 1.5 μM. Another way is to come up with and make new chemicals that target specific enzymes that are important to the life cycle of the parasite, like dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS). A study in the European Journal of Medicinal Chemistry (2020) described how new DHFR inhibitors were made and tested. These inhibitors were very effective against P. falciparum malaria, with IC50 values ranging from 0.01 to 0.5 μM. A number of in vitro and in vivo tests are used to evaluate new antimalarial drugs. In vitro studies, like parasite growth inhibition tests and cytotoxicity assays, can tell us a lot about how well the compounds work and which cells they affect. In vivo studies, like malaria models in mice, can help us understand how the chemicals work and how they change over time. Data from the World Health Organization (WHO) highlights the need for novel antimalarial agents:

- In 2019, there were an estimated 228 million cases of malaria worldwide, resulting in 405,000 deaths (WHO, 2020).

- The majority of malaria cases (94%) occur in Africa, where children under 5 years old are most affected (WHO, 2020).

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- The emergence of drug-resistant parasites has rendered current antimalarial treatments ineffective, highlighting the need for novel antimalarial agents (WHO, 2020).

Result and Discussion

The research that made and tested phenothiazine-based hybrids as possible new anticancer and antimalarial drugs showed hopeful results. The hybrids were very effective against cancer cells and Plasmodium falciparum. The anticancer hybrids, like the phenothiazine-triazolopyridine drug, killed human breast cancer cell lines by causing apoptosis and cytotoxicity, with IC50 values ranging from 6.2 to 31.5% at 100 µM. Molecular docking showed that the hybrid chemical links to tubulin's cavity, stopping the cell cycle and setting off apoptosis. New alkaloid derivatives and DHFR inhibitors were mixed to make antimalarials. These hybrids were very effective against P. falciparum, with IC50 values between 0.05 and 1.5 µM and 0.01 to 0.5 µM, respectively. Many in vitro and in vivo tests were used to evaluate these new drugs. These included apoptosis assays, cytotoxicity assays, parasite growth reduction assays, and cell viability assays. The findings show that phenothiazine-based hybrids could be used as cancer and malaria treatments, without having to deal with problems like drug resistance and toxicity that come with present methods. Overall, the study shows how important it is to keep researching new ways to fight cancer and malaria, and how phenothiazine-based mixtures could have a big effect on public health.

Conclusion

In conclusion, the study of phenothiazine-based hybrids as novel anticancer and antimalarial agents demonstrates their significant potential in overcoming the limitations of current treatments, such as drug resistance and toxicity. The synthesized hybrids exhibited potent biological activities, including apoptosis induction in cancer cells and growth inhibition of Plasmodium falciparum, showcasing their effectiveness as therapeutic agents. Molecular docking studies further revealed the mechanism by which these hybrids disrupt critical cellular processes, such as the cell cycle in cancer and enzyme activity in malaria parasites. The promising results from both in vitro and in vivo evaluations underscore the importance of

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continuing research in this field, as these phenothiazine-based hybrids could offer new, more effective options for treating cancer and malaria. This study contributes to the growing body of evidence supporting the development of innovative, multi-targeted therapeutic agents that could significantly impact global public health.

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