Design, Synthesis, And In Vitro Cytotoxic Investigations Of Several New Arylidene-Hydrazinyl-Thiazoles As Anticancer And Apoptosis-Inducing Substances

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Abstract- *One of the biggest challenges facing modern healthcare is cancer, a complex and pervasive group of diseases characterised by unchecked cell proliferation and the potential for metastasis. Cancer is the second most common cause of death worldwide, with a wide range of malignancies displaying distinct biological characteristics and a significant impact on people, families, and societies.1, 2 Even though traditional therapies like radiation, chemotherapy, and surgery have frequently increased survival and brought about remission, their effectiveness is frequently undermined by serious side effects, requiring a careful balancing act between the advantages of treatment and the welfare of the patient. With the advent of precision medicine, immunotherapies, and targeted medicines, the field of cancer treatment has changed dramatically in recent years.*

I. INTRODUCTION

The therapeutic arsenal has been broadened by biological therapies, hormonal medicines, and immunomodulatory drugs, opening up new possibilities for individualised and focused cancer care.3, 4 The overarching objective is still clear as scientists and medical professionals continue to investigate new chemotherapeutic approaches: creating efficient and well-tolerated chemotherapeutic medications that not only fight cancer at its source but also improve the lives of those who are faced with this difficult diagnosis.

Medicinal chemists concentrate on compounds with nitrogen-containing heterocycles; aza-heterocycles represent more than 60% of new pharmaceuticals and are vital in cancer research due to their versatile and dynamic core structure.5−7 Among these, thiazole derivatives stand out as the most common and important heterocyclic compounds, characterized by a high level of structural variability and exhibiting key functions in various pharmacological agents such as alpelisib and dasatinib (anticancer), abafungin and ravuconazole (antifungal), cefdinir (antibiotic), fanetizole (anti-inflammatory) Figure 1, and essential natural compounds (thiamine; vitamin B1).8−13 Many thiazole components found in a large number of marketed drugs, coupled with their inherent adaptability and distinct physicochemical characteristics, have established them as fundamental pillars of medicinal chemistry

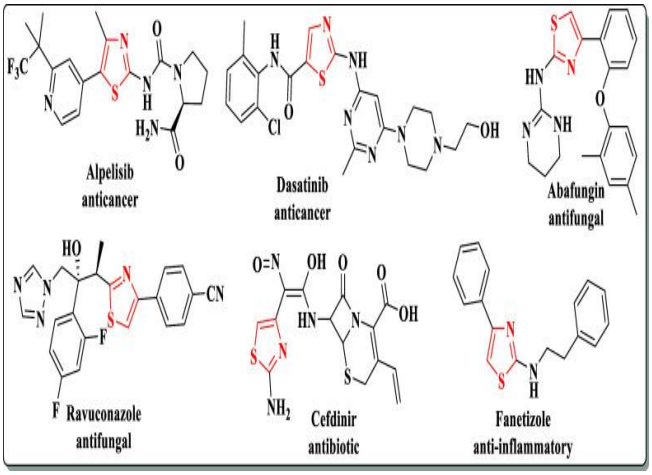


Fig :Marketed drugs containing a thiazole scaffold.

Thiosemicarbazones and similar bioisosteres are commonly present in numerous biologically active compounds, including thioacetazone (an oral antibiotic for tuberculosis) and methisazone (an antiviral medication utilized against smallpox). Triapine, a derivative of thiosemicarbazone, has demonstrated significant antitumor effectiveness by inhibiting ribonucleotide reductase. It has been utilized alongside cytarabine for the treatment of myelodysplastic syndrome and leukemia.17−19 Their capacity to induce oxidative stress and ROS-driven cellular injury has rendered them among the most captivating antitumor agents. Biological and molecular research on anticancer thiosemicarbazones has shown that these compounds affect multiple pathways in cancer cells and provide an excellent foundation for identifying potential candidates in metastatic cancer

Recently, molecular hybridization has become a crucial method in drug design, especially for creating new anticancer agents. This technique entails merging two or more pharmacophores into one molecule, thereby boosting biological efficacy and enhancing therapeutic properties. As mentioned previously, the thiazole framework, recognized for its various pharmacological characteristics, has been thoroughly investigated in medicinal chemistry. When combined with hydrazone groups, known for their anticancer properties, the resulting compounds frequently show synergistic effects that boost their effectiveness against cancer cells

To achieve improved biological effectiveness, we have developed a novel series of hybrid arylidene-hydrazinyl-thiazoles connecting various heteroaromatic frameworks, aiming to serve as anticancer and apoptotic-inducing agents, utilizing alpelisib (thiazole pharmacophore) and triapine (thiosemicarbazone probe) anticancer drugs as foundational compounds. In addition to these commercial drugs, numerous thiosemicarbazone and thiazole derivatives have demonstrated anticancer effects via different mechanisms

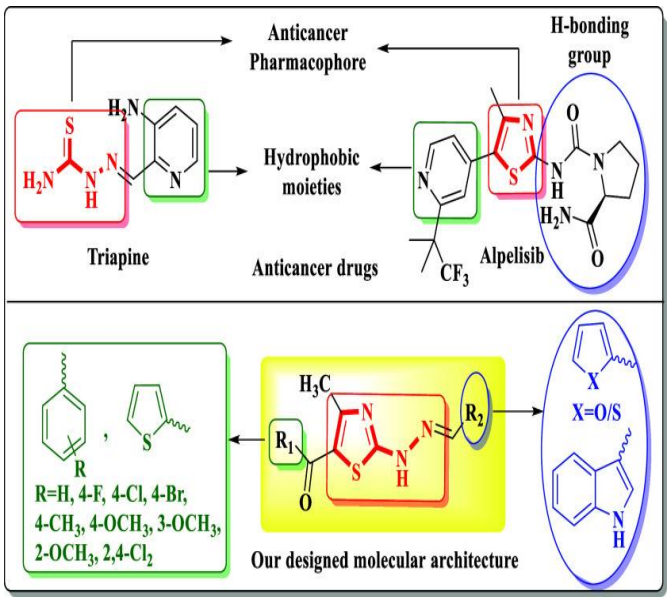


Fig :Rationale of drug design.

Based on the previously stated facts and as part of our ongoing research into the synthesis of biologically active thiazole compounds, we report the synthesis of novel thiazole scaffolds via an NBS-mediated domino reaction involving thiosemicarbazide 1, heteroaryl aldehydes 2, and 1,3-diketones 3, all under environmentally friendly visible-light conditions. The synthesized derivatives were comprehensively assessed for cytotoxicity and apoptosis induction, with systematic tests demonstrating their efficacy against various cancer cell lines. The research offered important information regarding the effects of thiazole compounds on cell survival and their ability to trigger apoptosis. Furthermore, the study explored the molecular processes involved in apoptosis induction, deepening our comprehension of the compounds' therapeutic possibilities in cancer therapy

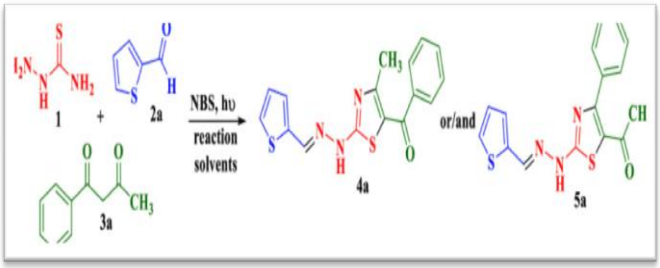
Result

Outcome and Analysis

Chemistry

Drawing from our previous research on visible-light driven organic transformations, we have created a thoughtfully designed library of arylidene-hydrazinyl-thiazole compounds 4(a-s) utilizing white LED as an environmentally friendly energy source. Visible-light photocatalysis enhances reaction conditions by providing high yields, cost-effective and readily accessible energy sources, straightforward workup procedures, environmentally friendly reaction settings, and safe, sustainable synthesis

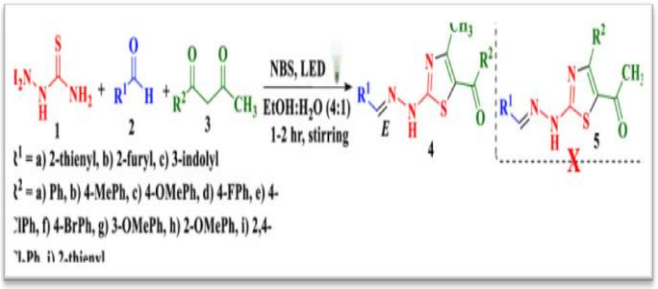
A one-pot multicomponent domino strategy was utilized to investigate the reactivity of thiosemicarbazide 1, thiophene-2-carbaldehyde 2a, and phenylbutane-1,3-dione 3a with N-bromosuccinimide (NBS) in several polar aprotic (dichloromethane (DCM), dichloroethane (DCE), tetrahydrofuran (THF), dimethylformamide (DMF)) and polar protic solvent systems (methanol (MeOH), ethanol (EtOH), and water (H2O)) under visible-light irradiation (Table 1). The most favorable outcomes regarding reaction time and yields were observed with polar protic solvents (MeOH, EtOH, and H2O), especially in a mixture of ethanol and water (EtOH/H2O; 4:1). Throughout the optimization process, thin-layer chromatography (TLC) analysis demonstrated the presence of a single regioisomeric product, distinguishable from the two potential results, 4a or/and 5a. Further characterization of this product was performed using advanced analytical methods such as IR and 1D and 2D NMR spectroscopy



Optimization of Reaction Solvents Under Visible-Light (LED) Conditions[a]

The 1H NMR spectrum of the obtained product 4a/5a showed a distinct singlet at δ 2.28 ppm corresponding to the three protons of the methyl group and a broadened singlet at δ 12.60 ppm attributed to the –NH proton. A singlet around δ 8.32 ppm suggested the –CH of the Schiff base linkage, while the aromatic section displayed the pattern for protons of the thienyl and phenyl rings. In addition to the necessary quantity of aromatic signals, the 13C NMR spectrum displayed the signals at δ 187.7 ppm assigned to the carbonyl carbon and δ 18.6 ppm corresponding to the methyl carbon. The IR spectrum also verified the existence of –NH, –CO, and –C=N- groups, showing three unique absorption bands at 3295, 1642, and 1612 cm–1, respectively. Additionally, the HRMS (ESI) m/z calculated for C16H13N3OS2 is 327.0500 and was recorded at 328.0498 for (M + H)+, confirming the successful condensation of reactants to yield the desired arylidene-hydrazinyl-thiazole 4a/5a.

To guarantee the effective condensation yielding arylidene-hydrazinyl-thiazoles, additional 2D NMR experiments, including 1H–1H NOESY, (1H–13C) HMBC, (1H–13C) HSQC, (1H–15N) HMBC, and (1H–15N) HSQC, have been performed to confirm the accurate regioisomeric composition of the resulting product. The 1H–1H NOESY experiment revealed cross peaks between iminic C–H and N–H protons, suggesting that these two protons are near each other (Figure 3). The outcomes were achieved solely for the E stereochemistry of the compound.



One-Pot Multicomponent Strategy for the Synthesis of **4**.

Biological Activity

In Vitro Toxicity Assessment

Synthesized arylidene-hydrazinyl-thiazoles 4(a-s) underwent in vitro evaluation for their cytotoxic effects against a set of five cancer cell lines: human breast cell lines (BT-474 and MCF-7), human pancreatic cancer cell line (BxPC-3), leukemia cell line (MOLT-4), and lung carcinoma cell line (A-549). All analogues were tested at a concentration of 10 μM against five distinct cancer cell lines, and the findings are presented in Table 2. Upon examining the provided data, it was determined that arylidene-hydrazinyl-thiazoles displayed moderate to significant cytotoxicity. Among these, compounds 4b, 4g, and 4q exhibited a moderate degree of cytotoxic activity. Specifically, the three prominent compounds 4m, 4n, and 4r exhibited exceptional activity, showcasing a significant range of percentage cell survival against the evaluated cancer cell lines

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