A Review on Thiazolidinone Motif as Anticancer Drugs: Structures, SAR & Synthesis

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

The thesis titled "A Review on Thiazolidinone Motif as Anticancer Drugs: Structures, SAR & Synthesis" submitted by Nishat Tanzim Kabir (19146006), of Spring, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy

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Ethics Statement

The entire review was conducted in accordance with ethical principles and norms. There is no utilization of human cell lines or animal models. To uphold academic integrity and prevent plagiarism, all sources used to create the data and conclusions provided in this thesis have been properly cited and acknowledged.

Abstract

Cancer is a global problem which has widespread occurrence and profound effects on people all over the world. With millions of new cases being identified each year, it is one of the major causes of mortality. Anticancer agents are of utmost importance as they play a crucial role in cancer management. Thiazolidinone is a privileged scaffold that has demonstrated antineoplastic potential. However, there have not been many reviews devoted to discussing its chemistry yet. In this thesis, the types, SAR, and synthesis of thiazolidinone derivatives are investigated. It includes a summary of novel thiazolidinone derivatives, such as those with substitutions on the thiazolidinone ring and different heterocycles e.g. benzothiazole. The substituent impacts are highlighted by SAR investigations and their anticancer effects are shown by testing against cell lines in the literature. Lastly, this thesis advances the hunt for more effective therapeutic options by offering insightful information on thiazolidinone-based antineoplastic drugs.

Keywords: Anticancer agents, thiazolidinone, synthesis, SAR, benzothiazole.

Acknowledgement

I would like to express my heartiest gratitude to Almighty Allah for providing me the courage to finish my undergraduate degree including my thesis. I also want to extend my sincere gratitude to Dr. Humair Bin Md. Omer, my academic supervisor at Brac University, for patiently mentoring me through my work. I want to thank Professor Dr. Eva Rahman Kabir, the Dean of School of Pharmacy at Brac University, for the way she has guided and motivated me and my classmates. I would also like to thank Professor Dr. Hasina Yasmin, the deputy chair of the pharmacy school of Brac University, for her unwavering support and advice. Finally, I want to express my gratitude to my parents for their unwavering support during my undergraduate studies and my entire life.

Table of Contents

List of Figures

List of Acronyms

DCC: 1,3-dicyclohexylcarbodiimide

VEGF: Vascular Endothelial Growth Factor

PSA: Prostate Specific Antigen

HDAC: Histone Deacetylase

FDA: Food and Drug Administration

DDS: Drug Delivery System

SAR: Structure Activity Relationship

NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells

Chapter 1

Introduction

1.1 Thiazolidinone motif and its relation to cancer

Millions of individuals around the world are afflicted by the terrible disease of cancer. Due to its complexity and heterogeneity, cancer continues to pose a huge challenge despite extensive research and therapeutic improvements. Cancer can be brought on by a variety of factors, including genetics, the environment, a person's lifestyle, and various conditions. The most prevalent types of cancer worldwide are stomach, lung, breast, colorectal, and colorectal cancers. But the occurrence of some cancers can be influenced by a person's geographic location and demographic traits. Some populations, such as elderly adults, are more susceptible to cancer due to age-related changes in biological processes and cumulative exposure to risk factors. However, cancer can strike anyone at any age, and some illnesses might be more prevalent in certain age groups. Ethnicity can also affect a person's propensity to developing cancer, with some racial and ethnic groups having greater incidences of particular malignancies. Genetic factors, unequal access to healthcare, lifestyle variables, and environmental exposures may all play a role in this difference. A person's ethnicity may also influence their risk of getting cancer, with some racial and ethnic groups having higher rates of specific cancers than others. This discrepancy may be influenced by a variety of reasons, including genetics, differential access to healthcare, lifestyle choices, and environmental exposures. (Hanahan, 2022)

Countless difficulties and issues related to cancer have an effect on patients as well as the healthcare system. Here are some more specifics on the issues brought on by cancer:

1. **Cancer Type Diversity:** A wide range of illnesses with unique traits and behaviors make up cancer. It is difficult to find universal treatments since each type of cancer demands a different strategy to treatment.
2. **Treatment Approaches:** Surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, and hormone therapy are among the cancer treatments that are available. The type of cancer, its stage, and the patient's features all play a role in determining the best course of treatment.
3. **Anticancer medications:** Anticancer medications are essential in the treatment of cancer. Cytotoxic agents, which are chemotherapy medications that target rapidly dividing cells, are effective against different cancer types.
4. **Selectivity and Side Effects:** Anticancer medication selectivity and specificity are extremely difficult to achieve. Drugs should ideally target cancer cells only, leaving healthy cells unharmed. Off-target effects, on the other hand, are possible and can have a negative impact on the patient's quality of life.
5. **Drug Resistance:** Over time, cancer cells may develop a resistance to anticancer medications, making treatments less successful. Genetic mutations, the activation of alternative pathways, and modifications to drug metabolism are all examples of drug resistance mechanisms. It is crucial to conduct research in the area of overcoming medication resistance to enhance treatment outcomes.
6. **Patient compliance:** Complex regimens, including several medications, dose schedules, and supportive therapy, are frequently used in cancer treatment. For the best results, patients must follow all instructions regarding their care, including taking their prescribed medications and attending follow-up appointments. Non-compliance can reduce the efficacy of a treatment and hasten the development of a disease.

7. **Psychosocial Impact:** Patients and their families may have severe psychological, emotional, and social effects as a result of their cancer diagnosis and treatment. To address these psychosocial aspects, supportive care services, such as counseling, mental health assistance, and survival programs, are crucial.

To overcome these challenges, ongoing research and development of novel medicines, tailored treatment plans, enhanced medication delivery methods, and improved ancillary care services are required. Collaboration between medical professionals, researchers, and patients is essential to the development of cancer treatments and the improvement of patient outcomes.

Therefore, the creation of novel and efficient anticancer drugs is urgently needed. Thiazolidinone derivatives are a class of chemicals that have demonstrated promise in the search for new anticancer drugs. (Channar et al., 2021)

Five-membered heterocyclic molecules called thiazolidinones have a nitrogen, sulfur, and carbonyl group as part of their structure which is shown in figure 1(Channar et al., 2021). Numerous biological activities, including antiviral, antibacterial, antifungal, anti-inflammatory, and anticancer effects, have been reported to be exhibited by them. In recent years, there has been a growing interest in the use of thiazolidinone motifs in anticancer drug discovery, as they have shown promise in preclinical studies as potential chemotherapeutics. The general structure of thiazolidinone is as followed:

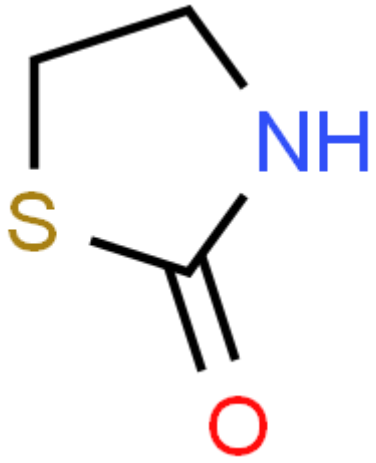


Figure 1: general structure of thiazolidinone. (Channar et al., 2021)

Research teams in the fields of medicinal chemistry and drug development carried out the early studies into the thiazolidinone motif as an anticancer agent. Scientific inquiry frequently involves numerous researchers working separately or together, therefore the precise initial groups or researchers involved may not be explicitly mentioned or documented.

Through the screening and assessment of chemical libraries, it was discovered that thiazolidinone molecules have anticancer properties. Researchers tested different substances for their biological effects on cancer cells, such as cytotoxicity and cell growth inhibition. Tested substances included thiazolidinone derivatives, and potential anticancer activities were seen. Thiazolidinones have been the subject of research on potential anticancer drugs since the late 20th century. (Han et al., 2007b)

Thiazolidinone derivatives' synthesis and design as possible anticancer agents have been shown in a number of investigations. To give one example, Bhat et al. (2020) described the design and synthesis of hybrid compounds carrying 4-thiazolidinone as possible anticancer medicines. In a similar vein, El-Azab et al.'s (2019) review of current developments in the synthesis and biological applications of saturated five-membered thiazolidines and their derivatives examined a similar topic.

Additionally, studies have concentrated on benzothiazole conjugate complexes and their structural alterations as possible chemotherapeutics. (Chopra et al., 2020).

Thiazolidinone derivatives have shown promising results in preclinical studies as potential chemotherapeutics. These substances have been claimed to work through a variety of mechanisms, including the prevention of angiogenesis, the promotion of apoptosis, and, most recently, the inhibition of cell proliferation. In order to effectively treat cancer, it is essential to stop both cell proliferation and apoptosis. Apoptosis functions as a defense mechanism in normal, healthy cells to get rid of damaged or undesired cells. However, this planned cell death pathway is frequently dysregulated in cancer cells, resulting in unchecked cell growth and survival. Anticancer medicines try to enhance apoptosis in cancer cells by focusing on and inhibiting the processes that prevent it. Cancer cell apoptosis induction aids in the removal of these aberrant cells, stopping their development and spread. This may result in the tumor regressing and lessening of the cancer burden. Cancer cells are more likely to divide and multiply quickly, which aids in the growth and spread of tumors. Anticancer treatments try to block the signaling pathways and mechanisms that promote cancer cell growth. The unchecked growth of cancer cells can be inhibited, which will stop the development of tumors, by blocking certain mechanisms. (Anderson & Wright, 2006)

Inhibiting excessive cell proliferation is another crucial method for treating cancer.

Moreover, thiazolidinone derivatives have shown low toxicity, high stability, and good pharmacokinetic properties, making them attractive candidates for anticancer drug development. (Chopra et al., 2020)

We intend to present a thorough overview of thiazolidinone motifs in anticancer drug discovery and development in this study. We will go over the various thiazolidinone motif types and structures, their structure-activity relationship (SAR), and techniques for

synthesizing them. The most recent advancements and encouraging biological activity of thiazolidinone derivatives as prospective anticancer medicines will also be highlighted. We want to give readers a thorough understanding of thiazolidinone derivatives and their potential for use in the creation of fresh, efficient anticancer drugs.

Overall, the development of anticancer drugs using thiazolidinone derivatives is quite promising. The creation of novel and potent anticancer medicines for the treatment of cancer will benefit from a clearer understanding of the kinds, SAR, and synthesis of these molecules.

As the figure 2 represents, Thiazolidinone has shown promising effect in various kinds of cancers including lung, skin, cervical, breast, liver, brain, colorectal cancer. (Chopra et al., 2020)

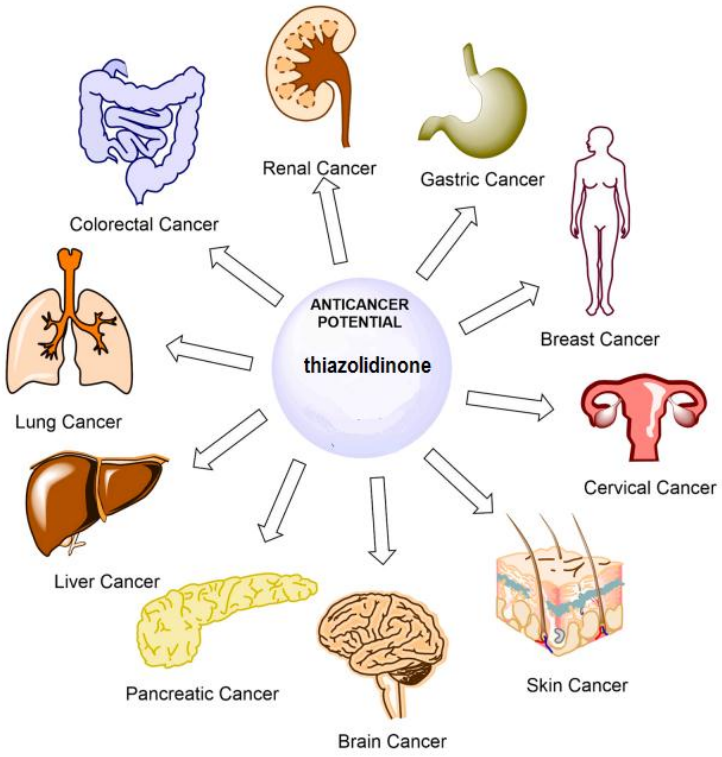


Figure 2: Thiazolidinones that have been studied in the context of anticancer drug discovery. (Chopra et al., 2020)

1.1 Objective

Cancer is still a major global health problem, prompting ongoing research to find new and efficient anticancer drugs. The various chemical structures and possible anticancer activities of thiazolidinone derivatives have made them stand out as interesting candidates. However, the absence of a comprehensive cancer recovery system continues to be a serious problem on a global scale. Therefore, it is imperative that knowledge gaps be filled in order to find a complete cure for cancer. The thesis offers a thorough examination of thiazolidinone derivatives, including information on their kinds, structures, structure-activity relationships (SAR), and synthesis techniques. This thesis consolidates important knowledge about the anticancer potential of thiazolidinone compounds by methodically examining the literature and incorporating research findings from pertinent articles.

This thesis is significant because it offers a comprehensive understanding of thiazolidinone derivatives as prospective anticancer drugs which is the primary objective of the project.

1.2 Methodology

Searching Google Scholar, PubMed, and Web of Science for pertinent publications served as the technique for this thesis. First, relevant papers were examined to identify any insufficient information about the thiazolidinone motif as treatment option for carcinoma. For further literature research, references were gathered from cross-references within the papers as well as forward citations of highly referenced articles.

From this literature survey, it has been found that thiazolidinone motif and derived compounds has shown to be promising anticancer agent by effectively reducing the cancer proliferating cells. As a result, this methodology has been used in this work for additional

research in order to consolidate the database of knowledge about thiazolidinone for further advancement in the treatment of cancer.

1.3 Types of Thiazolidinone

The oncology literature is currently researching a number of thiazolidinedione-based molecules for the treatment of cancer. The four subclasses of these chemicals that are being studied for their potential antiproliferation activities are listed below:

1. **Thiazolidinedione derivatives:** Due to their capacity to block a number of signaling pathways involved in the development and survival of cancer cells, these substances have been investigated for their potential anticancer action. Rosiglitazone, ciglitazone, and pioglitazone are among examples. (Tripathi et al., 2014)

2. **Natural products that are analogues of thiazolidinone:** Natural substances with anticancer effects include curcumin and resveratrol. These natural compounds' thiazolidinone counterparts have been created and investigated for their enhanced anticancer potential. (Zhang et al., 2010)

3. **Thiazolidinone-peptide conjugates:** To increase the anticancer action of peptide sequences, thiazolidinone motifs have been added. For instance, it has been discovered that thiazolidinone-arginine conjugates can suppress the development of cancer cells and trigger apoptosis. (Tripathi et al., 2014)

4. **Thiazolidinone-metal complexes**: Thiazolidinones have been utilized as ligands to create metal complexes that may have anticancer properties. For instance, the cytotoxicity of copper, nickel, and cobalt thiazolidinone complexes against cancer cells has been investigated. (Tripathi et al., 2014)

1.5 Structure and contribution of Thiazolidinone as anticancer agent

The group of chemical compounds known as thiazolidinone has a distinctive five-membered ring structure that is composed of three carbon atoms, one sulfur atom with one nitrogen atom. This ring is joined to an amide group, which has an exocyclic methylene group (CH_2) linked to one of the ring carbons, a carbonyl group (C=O), and an amino group (NH_2). The kind and position of the substituents attached to the ring and amide group determine the various thiazolidinone structures. Figure 3 shows 3 thiazolidinone derivatives that has different substituent consequently those 3 compounds will have different pharmacology. (Deep et al., 2016)

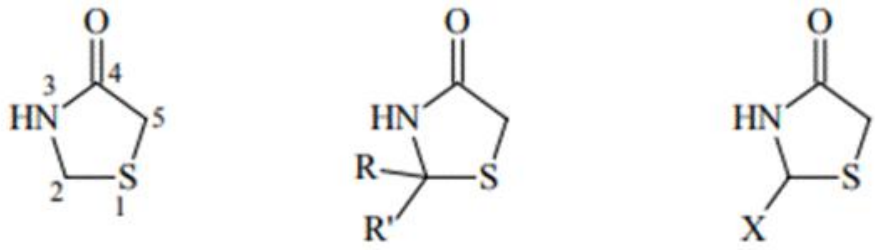


Figure 3: various Thiazolidinone structure based on substituent position. (Deep et al., 2016)

Thiazolidinone has a wide spectrum of biological actions, including anticancer properties. Depending on the specific chemical and cancer type, their complex anticancer methods vary. However, certain general methods have been put out.

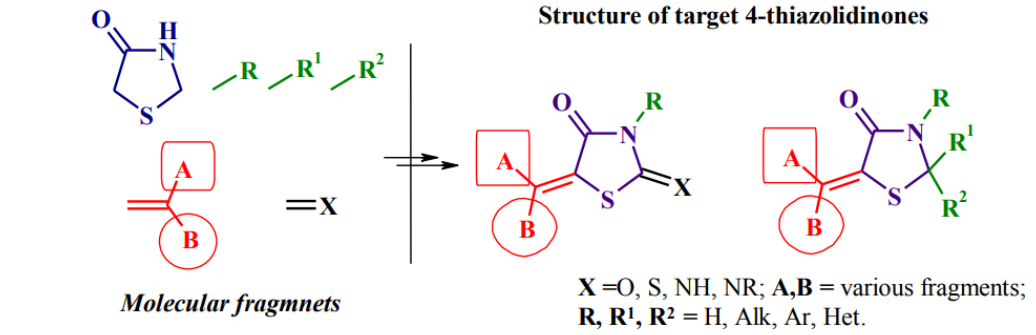


Fig. 1. Structure of the target 5-ene-4-thiazolidinones.

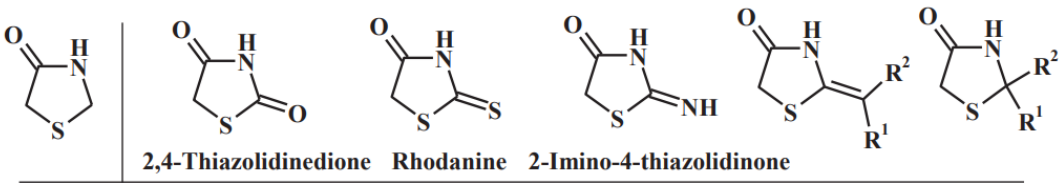


Figure 4: Thiazolidinone derivatives. (Deep et al., 2016)

Here, different compound can be formed based of substituent position as shown in figure 4. For instance, X substituent can be varied to place O, S, and NH. Aditionally, A and B can also be changed. (Deep et al., 2016)

Proposed Mechanism of Action

Thiazolidinones can inhibit histone deacetylases (HDACs), which is one way they work to fight cancer. HDAC inhibitors have been demonstrated to cause differentiation and/or death in cancer cells. HDACs are enzymes that regulate the expression of genes and the growth of cells. For instance, the thiazolidinone-based HDAC inhibitors Belinostat and Vorinostat, which are both used to treat cutaneous T-cell lymphoma, have received FDA approval. (Zhou et al., 2008)

The suppression of particular signaling pathways that are frequently dysregulated in cancer cells is another way that thiazolidinones can exert their anticancer effects. For instance, it has been shown that a number of thiazolidinones inhibit both the PI3K//mTOR pathway, which is

crucial for cell growth and survival, and the NF-B pathway, which is implicated in inflammation and cell proliferation. Thiazolidinones can prevent cancer cells from surviving and proliferating by blocking different mechanisms.

The following are some more processes involving thiazolidinone's anticancer ability:

1. **Apoptosis induction:** Through a variety of methods, including the elevation of pro-apoptotic protein expression and the downregulation of anti-apoptotic protein expression, it has been shown that thiazolidinones can cause cancer cells to undergo apoptosis. By upregulating the expression of Bax and downregulating the expression of Bcl-2, for example, thiazolidinone derivatives have been shown to induce apoptosis in human breast cancer cells. This increases the ratio of pro- to anti-apoptotic proteins and activates the apoptotic pathway.Thiazolidinones can also cause apoptosis, which results in the loss of cellular components and ultimately cell death, by inducing caspases, enzymes that cleave and activate downstream effector proteins. For instance, it has been shown that thiazolidinone derivatives trigger apoptosis in human leukemia cells by activating the crucial effector caspases caspase-3 and caspase-9, which are involved in the apoptotic cascade. (Zhou et al., 2008)

2. **Cell cycle arrest:** Thiazolidinones can also inhibit cancer cells' cell division and proliferation by causing cell cycle arrest. Controlling the synthesis of proteins involved in the cell cycle, such as cyclins and cyclin-dependent kinases (CDKs), which manage the progression of the cell cycle, can be used to do this. For instance, it has been shown that the G1/S transition regulators known as thiazolidinone derivatives can stop the G1 phase of the cell cycle in human breast cancer cells by suppressing the production of cyclin D1 and CDK4.

   Additionally, it arrests the cell cycle by activating checkpoint pathways, which monitor DNA damage and prevent cells from moving forward in the cell cycle until

the damage is repaired. By activating the checkpoint kinase Chk2, for instance, which then inhibits CDK1 and causes the cell cycle to be arrested, it has been shown that thiazolidinone derivatives can cause G2/M phase cell cycle arrest in human colon cancer cells. (Purser et al., 2008)

3. **Inhibition of angiogenesis:** Thiazolidinones can also impede angiogenesis, the process by which new blood vessels are created and which is crucial to the growth and spread of malignancies. Endothelial cells, which are in charge of creating new blood arteries, can be inhibited in their activity, and the expression of pro-angiogenic molecules like vascular endothelial growth factor (VEGF) can be suppressed. For instance, thiazolidinone derivatives were shown to inhibit VEGF-induced angiogenesis in a zebrafish model by downregulating the expression of VEGFR-2 and lowering endothelial cell proliferation in a study published in the journal European Journal of Medicinal Chemistry.

   Furthermore, it has the ability to prevent angiogenesis by regulating the activation of signaling pathways that do so, such as the PI3K/Akt/mTOR pathway. (Purser et al., 2008)

One example of a thiazolidinone with anticancer properties is 5-(4-chlorophenyl)-2-(4-methoxyphenyl)thiazolidin-4-one (CMZ), which is shown in figure 5. It has shown to induce apoptosis in human colon cancer cells via disrupting the PI3K/Akt/mTOR pathway. Another example is the substance 2-[(2-hydroxyphenyl)methylene]-5,5-dimethyl-1,3-thiazolidine-4-one (DMTM), which has been shown to inhibit HDAC activity and induce apoptosis in leukemia cells. (Purser et al., 2008)

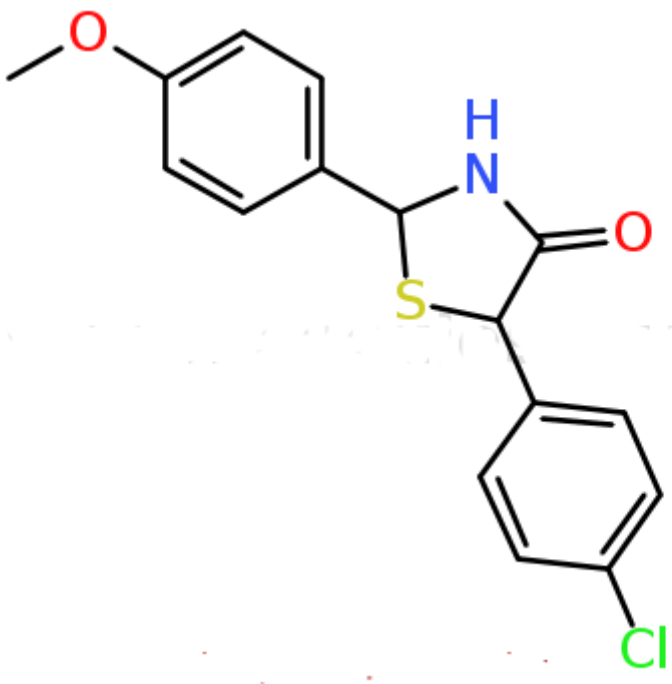


Figure 5: 5-(4-chlorophenyl)-2-(4-methoxyphenyl)thiazolidin-4-one (CMZ), (Purser et al., 2008)

To sum up, thiazolidinones are attractive candidates for the creation of new anticancer medications due to their chemical architectures and capacity to control important cellular processes.

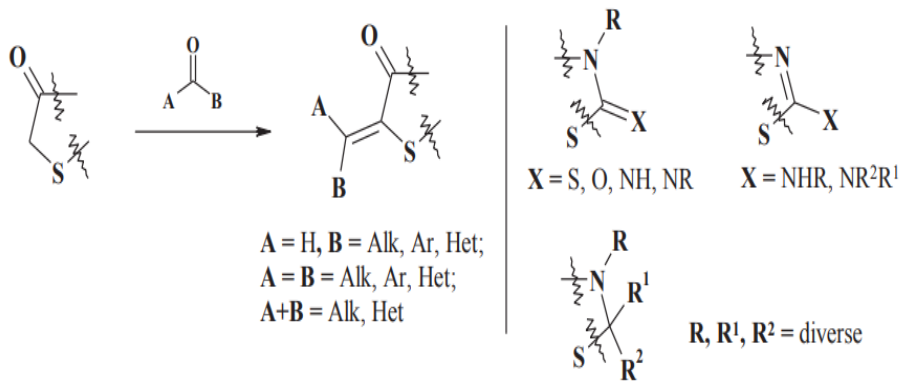
Chapter 2

Introduction to the synthesis of thiazolidinone derivatives

Thiazolidinone compounds have received a lot of attention in recent years due to their prospective anticancer properties. A thiol or amine is often condensed with an appropriate carbonyl molecule to create a thiazolidinone derivative, which is then cycled to create the thiazolidinone ring. The thiazolidinone scaffold can be altered and substituted in various ways to boost its pharmacological qualities and anticancer potential.

2.1 Synthesis of 4-thiazolidinone analogues

A number of 4-thiazolidinone analogues were created and tested for their anticancer activities. The synthesis entails the base-catalyzed reaction of various thiols with various aldehydes or ketones, followed by cyclization to generate the thiazolidinone ring. The created substances significantly inhibit the growth of a variety of cancer cell lines including MCF 7, HeLa and A549. This process is called the Knoevenagel condensation reaction which is demonstrate in figure 6. (Mushtaque et al., 2019).

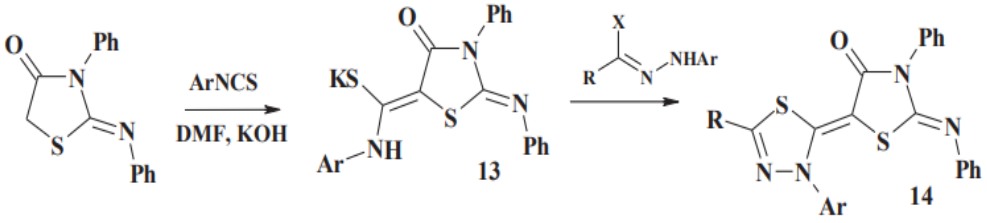


General scheme of Knoevenagel condensation of 4-thiazolidinones.

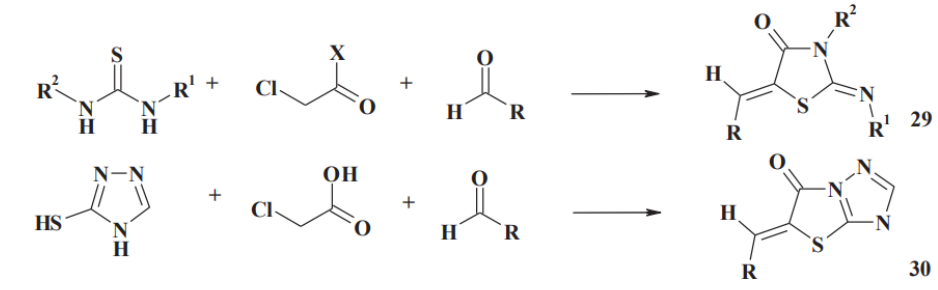
Figure 6: 4-Thiazolidinone Knoevenagel condensation process. (Mushtaque et al., 2019)

2.2 Synthesis of derivatives of 5-enamine-4-thiazolidinone

The process of creating the thiazolidinone ring involves reacting 5-nitro-2-furfural with different thiols in the presence of a base catalyst. The synthetic scheme follows the route that is shown in figure 7 below. Strong trypanocidal and anticancer activity is displayed by the synthesized compounds against a variety of cancer cell lines including MCF 7, HCT 116 and A549. (Holota et al., 2019)



Isothiocynate based synthesis of 5-ene-4-thiazolidinones.



R^2 = H, NHAr; R^1 = H X = OH, OEt, Cl R = Ar

One-pot three component synthesis of 5-ene-4-thiazolidinones.

Figure 7: Synthesis of 5-ene-4-thiazolidinone compounds. (Holota et al., 2019)

2.3 Synthesis of indolyl-pyridine compounds that include azetidinone and thiazolidinone analogues

Synthesis of a number of indolylpyridine analogues contains thiazolidinone and azetidinone a s well as their evaluation for their anticancer activity. Indole-3-carboxaldehyde is synthesized by reacting with different substituted pyridines in the presence of a base catalyst, which is then followed by cyclization to produce the thiazolidinone or azet idinone ring. Figure 8 represents the final product of the reaction which is the desired antineoplastic motif.

The created substances demonstrate strong anticancer action against many cancer cell types. (Verma et al., 2020)

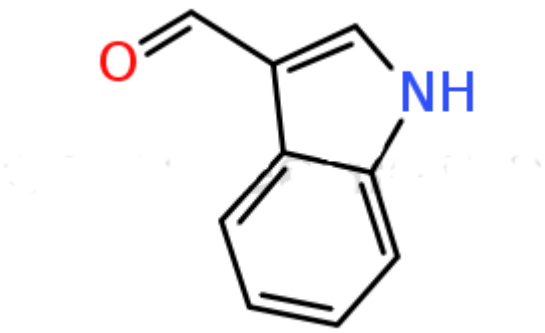


Figure 8: Indole-3-carboxaldehyde. (Verma et al., 2020)

2.4 Synthesis of indolin 2 derivatives

A bicyclic heteroaromatic substance called indolin-2-one has been shown to have anticancer properties. Indolin 2 derivatives are created by changing the substituent position as shown in figure 8 which contains different derivatives of indolin 2. The goal of this work was to create derivatives that contained the 4-thiazolidinone moiety in order to increase the anticancer activity of indolin-2-one. Five-membered heterocyclic ring thiazolidinone has undergone extensive research for its anticancer effects. (Patil et al., 2016)

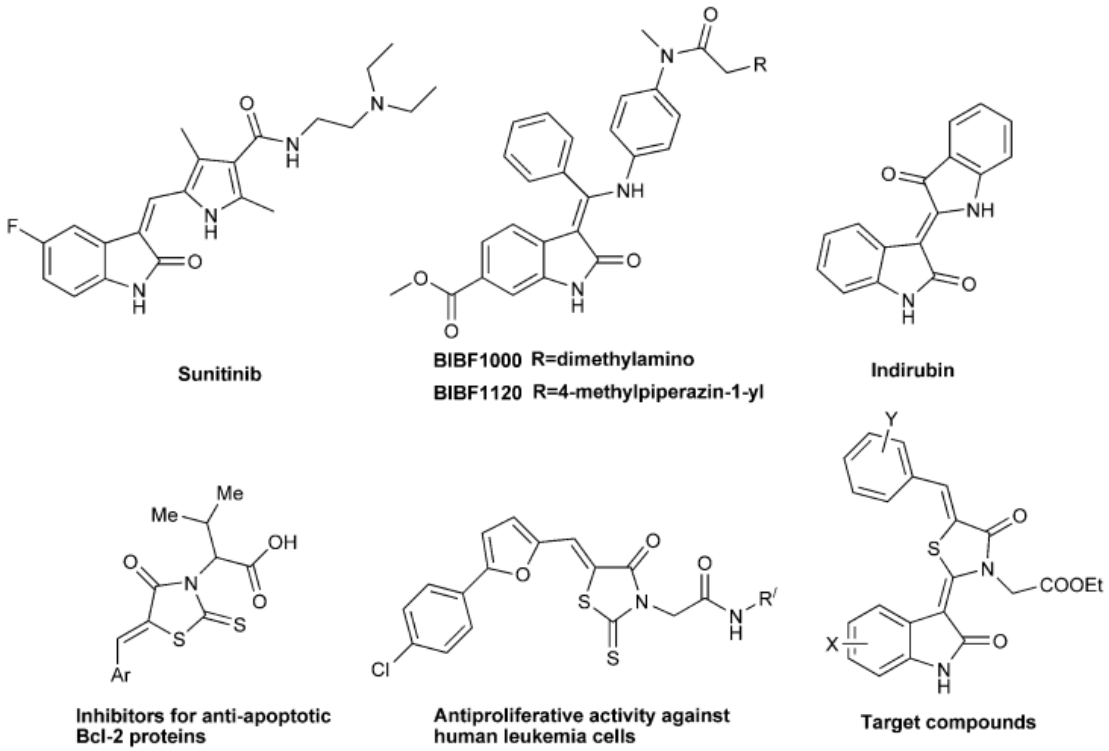


Figure 8: Indolin 2 derivatives, (Patil et al., 2016)

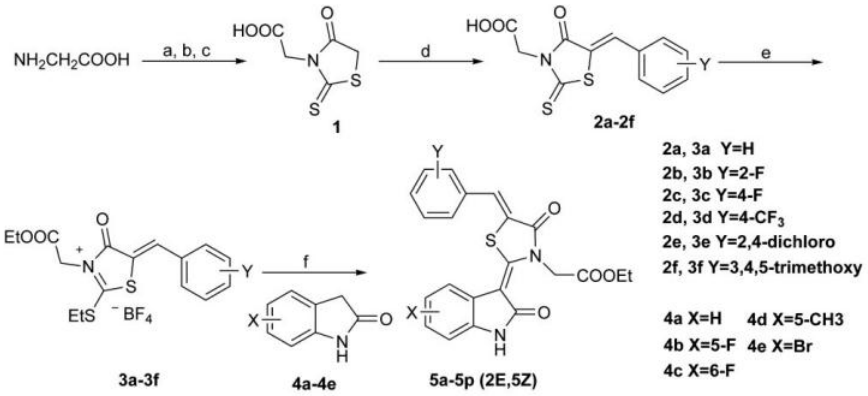


Figure 9: Synthesis of target compounds, (Patil et al., 2016)

The synthesized compounds demonstrated higher potency than the reference chemical, doxorubicin, in their anticancer activities against the evaluated cancer cell lines. A molecular docking analysis was also conducted in a study to look at the ways that the produced chemicals bind to the target proteins. Figure 9 represents an ideal way of synthesizing target compounds from which the desired product can be made of.

2.5 **Synthesis of indolin-2-one derivatives bearing the 4-thiazolidinone moiety with a pyridine nucleus**

In this synthesis, 2-aminopyridine serves as the starting material. It is then combined with ethyl acetoacetate and glacial acetic acid to form the pyridine-containing chalcone derivative. In the presence of ethanol and KOH, the chalcone derivative is subsequently combined with thioglycolic acid to create the equivalent 4-thiazolidinone intermediate.

The intended product, an indolin-2-one derivative containing a 4-thiazolidinone moiety and a pyridine nucleus, is then created by reacting the intermediate with isatin in the presence of acetic acid. (Roszczenko et al., 2022)

The reaction scheme for this synthesis is as follows:

*2-aminopyridine + Ethyl acetoacetate + Glacial acetic acid → Pyridine-containing chalcone derivative

*Pyridine-containing chalcone derivative + Thioglycolic acid + KOH in ethanol → 4-thiazolidinone intermediate

*4-thiazolidinone intermediate + Isatin + Acetic acid → Compound bearing indolin-2-one derivative that has 4 thiazolidinone moieties with a pyridine nucleus.

In a nutshell, In order to create the desired product, this synthesis pathway combines a number of chemical processes, including condensation, cyclization, and nucleophilic addition. The resulting 4-thiazolidinone moiety and pyridine nucleus indolin-2-one derivative could be further investigated for its biological activity and potential as an anticancer drug.

2.6 The synthesis of indolin-2-one derivatives having a quinoline nucleus and a 4 Thiazolidinone moiety

The starting substance for this synthesis is 3-(4-chlorobenzyl)indolin-2-one. A thiazolidine intermediate is created when this chemical reacts with thiourea and formaldehyde in ethanol. The final product is created by reacting the intermediate with the proper quinoline carboxylic acid in the presence of triethylamine and 1,3-dicyclohexylcarbodiimide (DCC). (Roszczenko et al., 2022)

The thiazolidine intermediate is produced by a condensation reaction between indolin-2-one and thiourea, which is catalyzed by formaldehyde, in the reaction process. The ultimate product, which has both a thiazolidinone and quinoline nucleus, is created when this intermediate combines with the quinoline carboxylic acid in the presence of triethylamine and DCC. (Roszczenko et al., 2022)

The discovery of a new family of compounds with potential anticancer properties is what makes the synthesis significant. The presence of the quinoline nucleus in the chemical may also improve its bioactivity because quinoline derivatives have been shown to exhibit a variety of biological activities, including anticancer properties.

Overall, this synthesis presents a novel approach for the synthesis of thiazolidinone-based anticancer medicines; however, additional studies are needed to evaluate the efficacy and safety of these compounds in preclinical and clinical settings.

2.7 Synthesis of indolin-2-one derivatives bearing the 4-thiazolidinone moiety with a pyrazole nucleus

It is possible to synthesize indolin-2-one derivatives with the 4-thiazolidinone moiety and pyrazole nucleus using a one-pot, three-component method. In the presence of acetic acid and p-toluenesulfonic acid, indolin-2-one, substituted benzaldehyde, and substituted pyrazole-4-carbaldehyde condense with thioglycolic acid. TLC monitors the reaction's progress while the reaction's mixture is refluxed for four to six hours. The incomplete mixture is cooled when the reaction is complete, and the solid that develops is filtered through cold water and purified to create the finished product. **.** (Roszczenko et al., 2022)

The three main spectroscopic techniques utilized to describe the generated molecules are IR, NMR, and mass spectrometry. According to the biological evaluation of the compounds, some of the generated compounds exhibit noteworthy anticancer activity against a panel of cancer cell lines. According to study, these chemicals mostly cause apoptosis and cell cycle arrest as their mode of action.

The synthesis of indolin-2-one derivatives with a pyrazole nucleus and a 4-thiazolidinone moiety is a novel approach for the development of new anticancer medicines. Making these compounds using the three-component, one-pot method used in this synthesis is efficient and feasible. The use of the catalysts acetic acid and p-toluenesulfonic acid in this reaction also provides a sustainable and environmentally friendly method. (Roszczenko et al., 2022)

2.8 synthesis of 4-thiazolidinone derivatives containing a benzothiazole moiety

The 4-thiazolidinone derivatives are created by reacting the relevant Schiff bases with mercaptoacetic acid after they have been formed by condensation of the o-aminothiophenol with different substituted benzaldehydes. Several spectroscopic techniques can be used to confirm the structures of these substances. One of the technics is shown is figure 10. (Roszczenko et al., 2022)

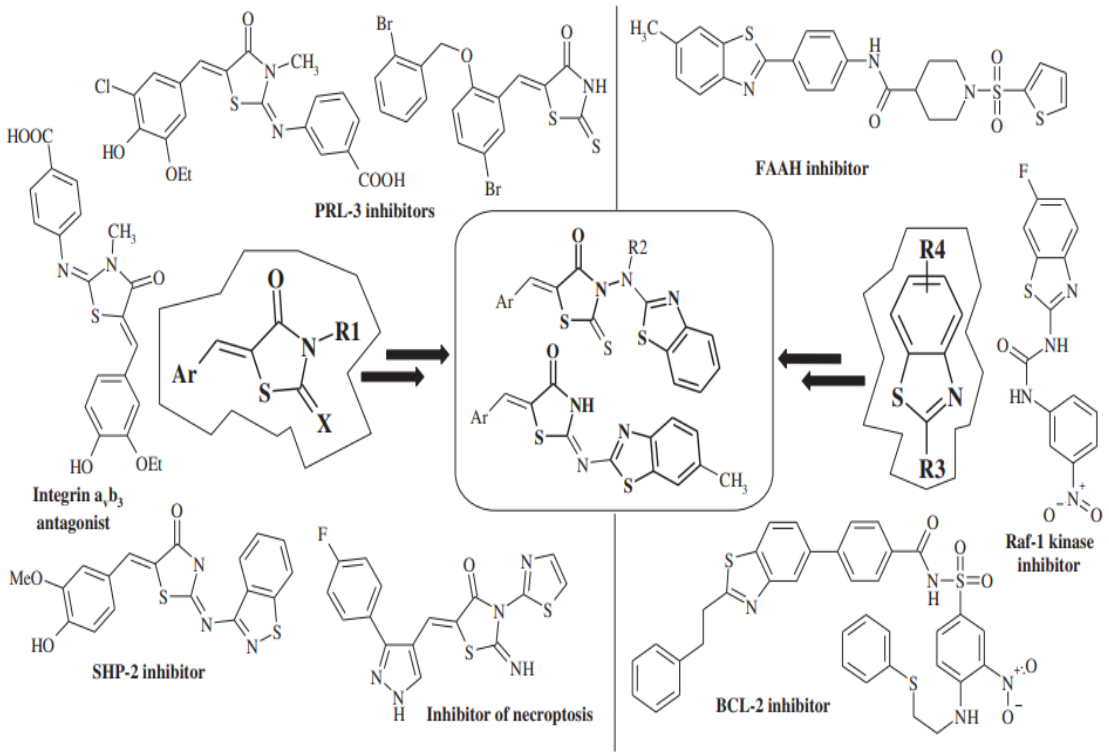


Figure 10: Structures of anticancer agents containing 4-thiazolidinones and benzothiazoles and background for target compounds synthesis, (Roszczenko et al., 2022)

2.8.1 Synthesis of 2-(benzo[d]thiazol-2-yl)acetonitrile:

In this reaction, the 2-aminobenzothiazole and acetonitrile are condensed using the catalysts triethylamine (TEA) and phosphorous oxychloride (POCl3). The reaction mixture is heated in

a reflux atmosphere for a number of hours. The resulting liquid is refrigerated before being neutralized with sodium bicarbonate and extracted with chloroform. The organic layer is dried over anhydrous sodium sulfate while the solvent evaporates under reduced pressure to create the chemical. The chemical structure of the final compound is shown in figure 11. (Roszczenko et al., 2022)

In conclusion, it is found that the cytotoxic activity of against a number of cancer cell lines is significantly increased by the addition of electron-withdrawing groups at the para position of the phenyl ring. The most notable cytotoxic agent is 2-(benzo[d]thiazol-2-yl)acetonitrile, which possesses a nitro group at the para position of the phenyl ring and an IC50 value which is of less than 1M against all tested cell lines. It should be noted that when the benzo[d]thiazole moiety is substituted with other heterocyclic rings, such as benzimidazole or benzothiazole, the cytotoxic effect is reduced. (Roszczenko et al., 2022)

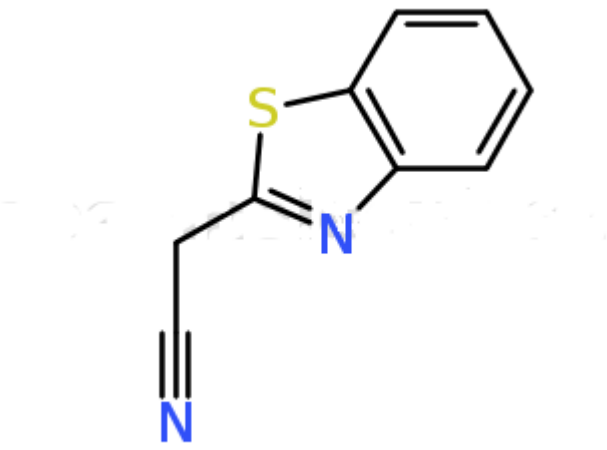


Figure 11: 2-(benzo[d]thiazol-2-yl) acetonitrile, (Roszczenko et al., 2022)

2.8.2 Synthesis of 2-(benzo[d]thiazol-2-yl)acetohydrazide

Compound 1 reacts with hydrazine hydrate in ethanol as a solvent to form compound 2. For several hours, the reaction mixture is heated in a reflux environment. To obtain the desired compound 2, the resultant mixture is cooled, filtered, and the solid is washed with water and dried. The addition of different substituents to compound 2's phenyl ring significantly changed how poisonous it was. In general, cytotoxic activity rose when electron-withdrawing groups, like nitro or chloro, were present in para position mainly of phenyl ring, but cytotoxic activity reduced when electron-donating groups, like methoxy or methyl, were present. It was discovered that 2-(benzo [d] thiazol-2-yl)-N'-(4-nitrophenyl) acetohydrazide was the most potent substance in this series which has the chemical structure as shown in figure 12. (Roszczenko et al., 2022)

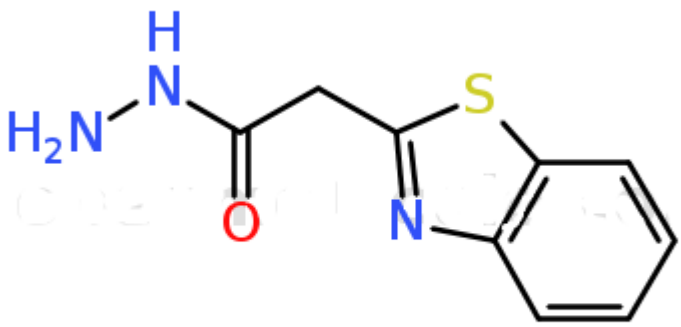


Figure 12: 2-(benzo[d]thiazol-2-yl)acetohydrazide, (Roszczenko et al., 2022)

2.8.3 SAR Studies of some compounds

It becomes clear that the cytotoxic activity of the compounds in this series is greatly influenced by the type of substituent at the 5th position of the thiazolidinone ring. In general, cytotoxic activity is raised when electron-withdrawing groups, like nitro or chloro, are present at the 5-position, but cytotoxic activity is diminished when electron-donating groups, like methoxy or methyl, are present. Additionally, it should be noted that the type of

substituent at the benzo[d]thiazole ring's 2-position only slightly affects the cytotoxic activity. (Deep et al., 2016b)

5-(4-fluorophenyl)-2-(benzo[d]thiazol-2-yl)thiazolidin-4-one: from the figure 13, It has been observed that the 5-methyl substitution on the thiazolidinone ring is the most advantageous for anticancer activities. Smaller modifications (such as H or F) result in decreased activity, but bigger alterations (such as ethyl or isopropyl) do not significantly improve the activity of the chemical

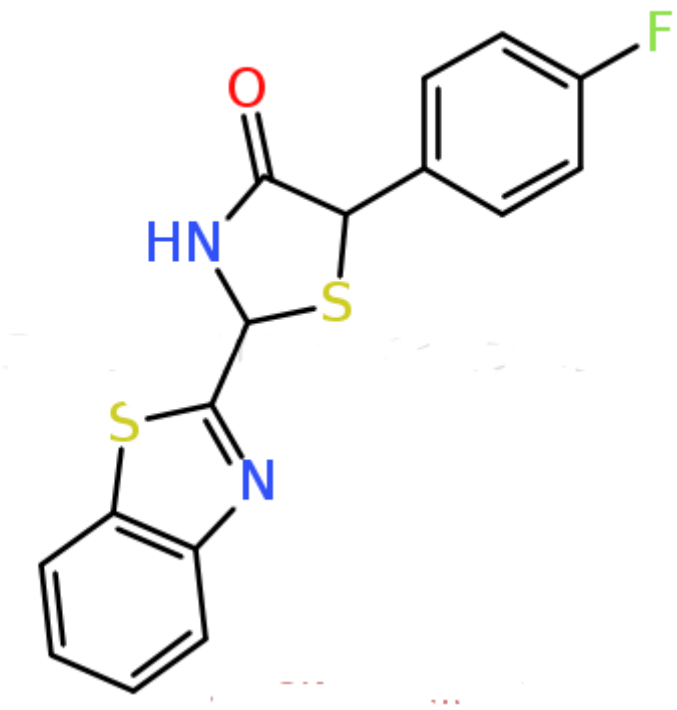


Figure 13: 5-(4-fluorophenyl)-2-(benzo[d]thiazol-2-yl)thiazolidin-4-one. (Deep et al., 2016b)

5-(4-chlorophenyl)-2-(benzo[d]thiazol-2-yl)thiazolidin-4-one: Similar to previous compound, the chemical structure of figure 14 has been reported that the 5-methyl substitution on the thiazolidinone ring is best for anticancer action. Other changes, such ethyl or isopropyl, have a negative impact on activity.

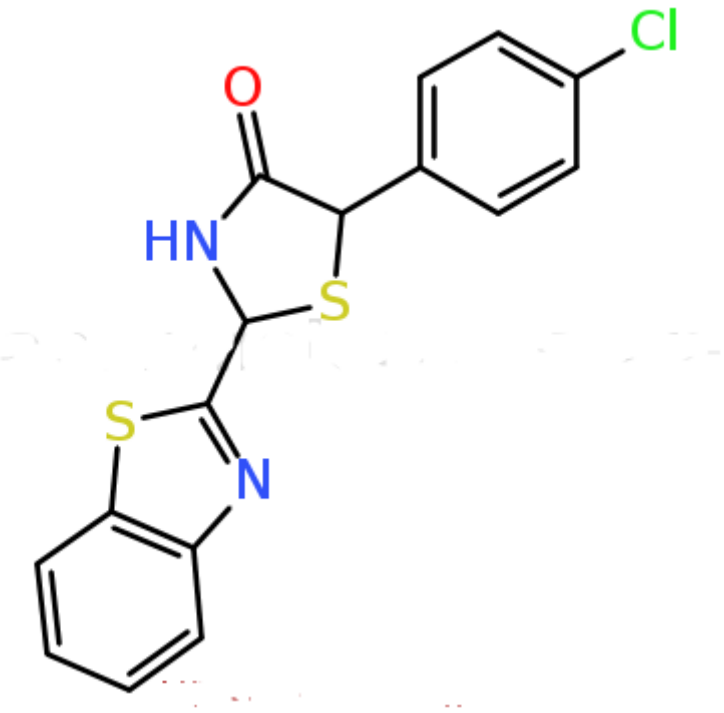


Figure 14: 5-(4-chlorophenyl)-2-(benzo[d]thiazol-2-yl)thiazolidin-4-one. (Deep et al., 2016b)

5-(4-methylphenyl)-2-(benzo[d]thiazol-2-yl)thiazolidin-4-one: Among the substances examined, the 5-methyl substitution on the thiazolidinone ring which is drawn in figure 15 exhibits the greatest activity. Reduced activity is the result of substitutions with bigger groups, such as ethyl or tert-butyl.

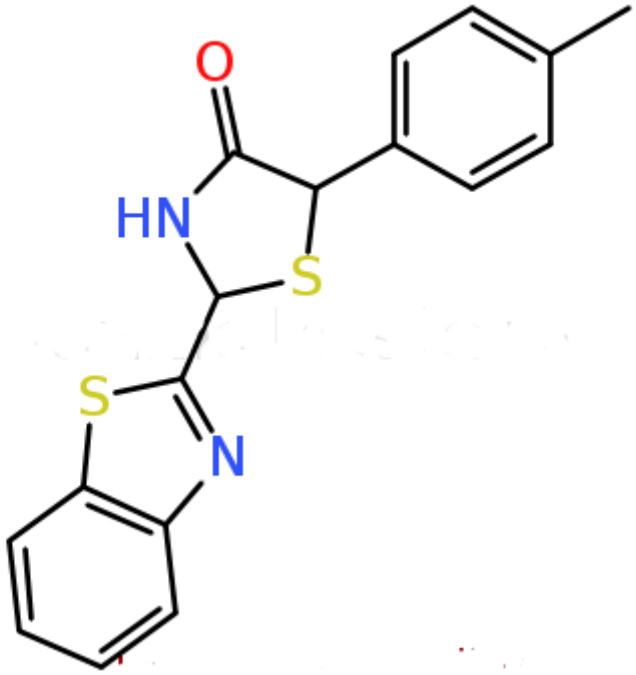


Figure15: 5-(4-methylphenyl)-2-(benzo[d]thiazol-2-yl)thiazolidin-4-one. (Deep et al., 2016b)

2.8.4 Synthesis of 5-substituted-2-(benzo[d]thiazol-2-yl)-N-(substituted phenyl)thiazolidin-4-amine derivatives

5-(4-chlorophenyl)-2-(benzo[d]thiazol-2-yl)thiazolidin-4-one is reacted with different substituted anilines in the presence glacial acetic acid along with ethanol as a catalyst to form 5-(4-chlorophenyl)-2-(benzo[d]thiazol-2-yl)-N-(4-methoxyphenyl)thiazolidin-4-amine. For several hours, the reaction mixture is heated in a reflux environment to obtain the desired compound. The resultant mixture is kept to put off the heat and then filtered which is finally rinsed with water for purification

SAR studies for compound 5-(4-chlorophenyl)-2-(benzo[d]thiazol-2-yl)-N-(4-methoxyphenyl)thiazolidin-4-amine

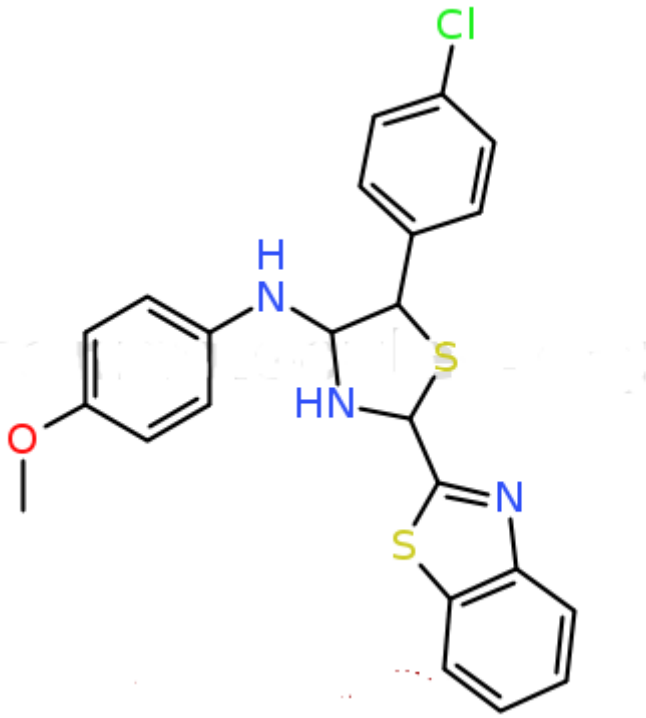


Figure 16: 5-(4-chlorophenyl)-2-(benzo[d]thiazol-2-yl)-N-(4-methoxyphenyl)thiazolidin-4-amine, (Deep et al., 2016b)

The cytotoxic activity of the compounds in this series is significantly influenced. for example, the compound in figure 16 shows variation for the nature of the substituent at the fifth position of the thiazolidinone ring. The most potent compound in this series is found to be 5-(4-chlorophenyl)-2-(benzo[d]thiazol-2-yl).The substance is -N-(4-nitrophenyl)thiazolidin-4-amine, and it has an IC50 value of less than 1 M against a number of cancer cell lines.

1. Effects of substitutes on the thiazolidin-4-amine moiety's phenyl ring:

•The cytotoxicity of compounds with electron-donating substituents is often higher than that of compounds with electron-withdrawing substituents.

•Compounds with 4-methyl and 4-methoxy groups have the maximum cytotoxicity among the electron-donating substituents.

•The molecule with a nitro group has the lowest cytotoxicity among the electron-withdrawing substituents.

2. Effects of substitutes on the benzothiazole moiety's phenyl ring:

•The cytotoxicity of compounds with electron-donating substituents is higher than that of compounds with electron-withdrawing substituents. The most cytotoxic compounds among the electron-donating substituents are those with 4-methoxy and 4-methyl groups.

• The chemical with a nitro group exhibits the lowest cytotoxicity among the electron-withdrawing substituents.

3. Effects of substitutes on the thiazolidin-4-amine moiety's amine group:

• Compounds having aromatic substituents on the amine group typically exhibit higher cytotoxicity than those with aliphatic substituents.

• The 4-nitrophenyl group-containing molecule exhibits the greatest cytotoxicity among the aromatic substituents.

• The cyclohexyl group-containing compound exhibits the greatest cytotoxicity among the aliphatic substituents.

4. The impacts of substituents on the location of the thiazolidin-4-amine moiety:

• Higher cytotoxicity is often shown in compounds containing the thiazolidin-4-amine moiety at position 4 of the benzothiazole ring than at position 5.

5. Effects of substitutes on the propenamide moiety's double bond

•In general, compounds containing a cis double bond exhibit more cytotoxicity than those with a trans double bond. (Deep et al., 2016b)

2.8.5 Synthesis of 5-substituted-2-(benzo[d]thiazol-2-yl)-N-(substituted phenyl)-3-(4-substituted phenyl)-2E-propenamide derivatives

In a reaction involving and different substituted cinnamic acids, ethanol and glacial acetic acid act as catalysts. For several hours, the reaction mixture is heated in a reflux environment. To achieve the desired compound 5, the resultant mixture is cooled, filtered, and the solid is then washed with water and dried. (Deep et al., 2016b)

SAR:

1. **The effect of substituents on the aryl and cinnamic acid moieties:**

   It has been found that the inclusion of electron withdrawing substituents on the aryl and cinnamic acid moieties increases the anticancer activity of the compounds. One compound, for instance, has nitro groups on both the aryl and cinnamic acid moieties and has the most action against the cancer cell types under investigation. This is because it's possible that electron withdrawing groups could enhance the electron density on the thiazolidinone ring's nitrogen atom, leading to higher DNA reactivity.

2. **Effect of the length of the linker between the aryl and cinnamic acid moieties:**

   The length of the linker between the aryl and cinnamic acid moieties has been found to have an impact on the compounds' anticancer activity. The activity of longer linker compounds is greater than that of shorter linker compounds. This is so that, due to the enhanced flexibility of the longer linker, the molecule can adopt a favorable shape for binding to DNA.

3. **Effects of substitution pattern on the cinnamic acid moiety's phenyl ring:**

   The compounds' action is also influenced by the way in which the phenyl ring of the cinnamic acid moiety is substituted. When compared to compounds with a meta-substituted phenyl ring, compounds with a para-substituted phenyl ring have higher activity. This is so

that the functional groups can be arranged more effectively for interacting with DNA in the para-substituted phenyl ring.

4. **The effect of the substitution pattern on the phenyl ring of the aryl moiety:**

   It is discovered that the compounds' activities are affected by the phenyl ring's substitution pattern, with compounds with a meta-substituted phenyl ring demonstrating higher activity than those with a para-substituted phenyl ring. This is due to the fact that the meta-substituted phenyl ring offers a more advantageous configuration of the functional groups for engagement with DNA.

5. **Effect of the double bond's location in the cinnamic acid moiety:**

   The double bond's position in the cinnamic acid moiety also affects the compounds' ability to function. When compared to compounds with the Z configuration, those with the E configuration of the double bond have higher activity. This is due to the fact that the E configuration offers a functional group arrangement that is more ideal for interacting with DNA.

To summarize, the SAR investigations for these compounds show that electron-withdrawing groups on the aryl and cinnamic acid moieties, longer linkers between them, and particular patterns of substitution on the phenyl rings can increase the anticancer activity of these compounds. (Deep et al., 2016b)

2.9 N-(4 chlorophenyl)-2-(benzo[d]thiazol-2-yl)-3-(4 fluorophenyl) 2E propenamide synthesis

1. A solution of 4 fluoroacetophenone and benzothiazole-2-amine in ethanol is added, followed by a few drops of acetic acid, 4-chlorobenzaldehyde and piperidine. The reaction mixture is stirred for six hours at reflux temperature.

2. After the reaction is complete, the mixture is allowed to cool to room temperature, and the solid that is produced is filtered and washed with ethanol. The material is then recrystallized from ethanol to produce 2-(benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-1-phenylpropan-1-one.

3. A mixture of 2-(benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-1-phenylpropan-1-one and substituted aniline is refluxed for 6 hours in the presence of catalytic quantities of piperidine.

4. A solid is created once the mixture has cooled, and it is filtered, ethanol washed, and dried. The resultant solid is treated with glacial acetic acid to yield N-(4-chlorophenyl).-2-(benzo[d]thiazol-2-yl)-2E-propenamide which yields a yellow solid that is 3 (4-fluorophenyl). The resultant compound has the chemical structure that is shown in figure 17. (Deep et al., 2016b)

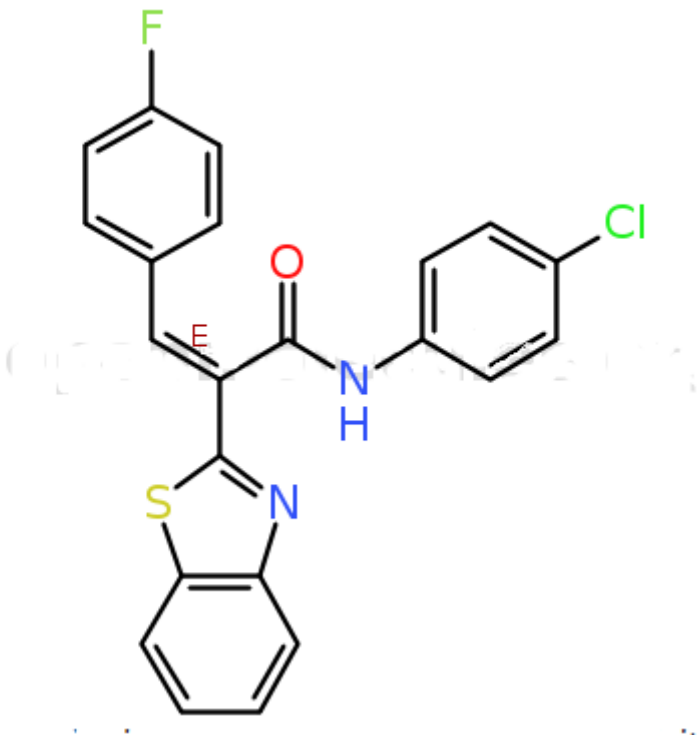


Figure 17: N-(4-chlorophenyl)-2-(benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-2E-propenamide. (Deep et al., 2016b)

2.10 Antineoplastic evaluation and synthesis of 5-[2-Chloro-3-(4-nitrophenyl)-2-propenylidene]-4-thiazolidinones

The 5-[2-Chloro-3-(4-nitrophenyl)-2-propenylidene]-4-thiazolidinone motif has outstandingly exhibited antineoplastic potential. The cytotoxicity of the compound was tested against four cancer cell lines in the study. Figure 18 and 19 explains how the background for the target compound can be deigned. The IC_{50} value for a few of the substances was in the nanomolar range. Under reflux circumstances, 2-chloro-3-(4-nitrophenyl) acrolein was reacted with various substituted thioureas under the catalysis of acetic acid to produce 5-[2-chloro-3-(4-nitrophenyl)-2-propenylidene]-4-thiazolidinone derivatives. The generated compounds' structures can be verified by different analytical means such as carbon NMR, hydrogen NMR, mass spectroscopy and IR technics. The produced compounds are tested for their anticancer activity against the MCF 7, HepG2, HeLa human cancer cell lines, which represent breast, liver and cervical cancer respectively, using the MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide). (Deep et al., 2016b)

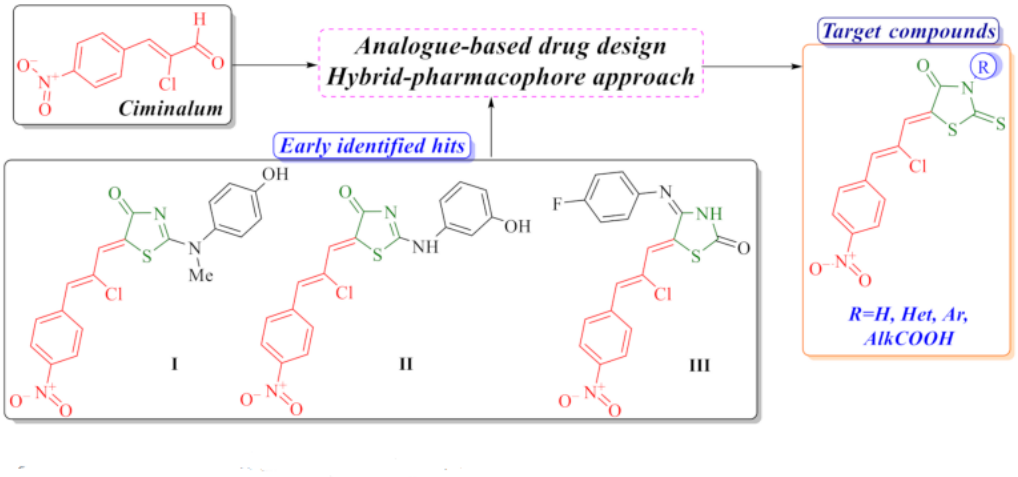


Figure 18: Background of target compound design. (Deep et al., 2016b)

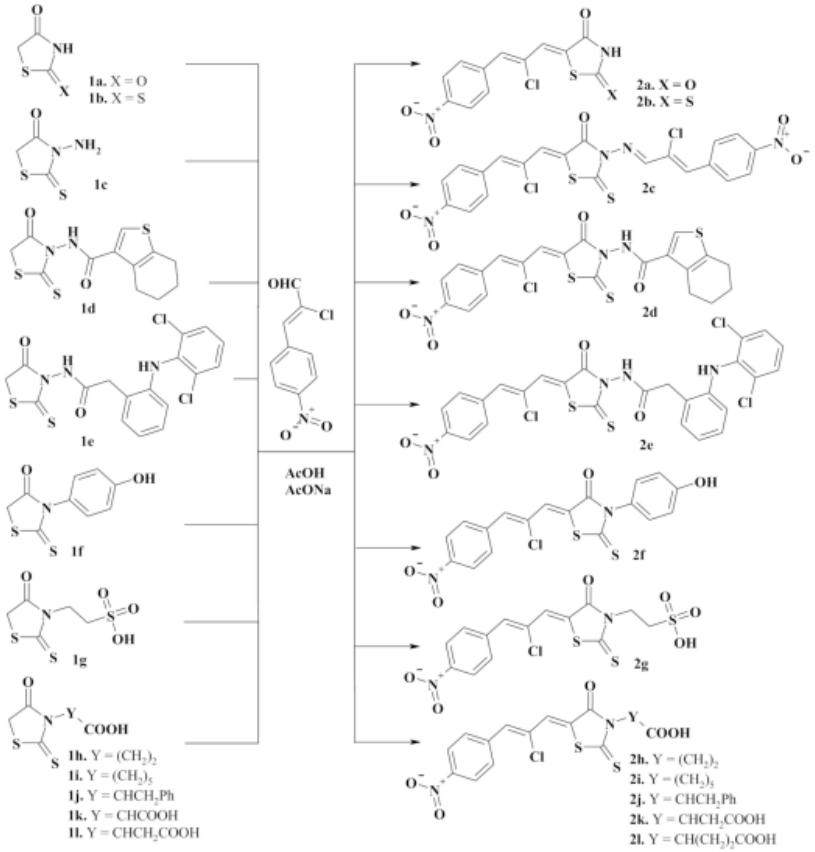


Figure 19: Possible Synthesis routes of 5-[(Z,2Z)-2-chloro-3-(4-nitrophenyl)-2-propenylidene]-4-thiazolidinones. (Deep et al., 2016b)

2.10.1 N-(4-chlorophenyl)-2-(benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-2E-propenamide synthesis

1. A solution of 4-fluoroacetophenone and benzothiazole-2-amine in ethanol is treated with a few drops of acetic acid, followed by the addition of 4-chlorobenzaldehyde and piperidine. The reaction mixture is stirred for six hours at reflux temperature.

2. After the reaction is complete, the mixture is given time to cool to room temperature, and the solid that is produced is filtered and washed with ethanol. The

material is then recrystallized from ethanol to produce 2-(benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-1-phenylpropan-1-one.

3. 2-(benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-1-phenylpropan-1-one and substituted aniline are refluxed for 6 hours in with the addition of catalytic quantities of piperidine.

4. Following the cooling of the mixture, a solid is created, which is filtered, ethanol washed, and dried. The resultant solid is treated with glacial acetic acid to yield N-(4-chlorophenyl).-2-(benzo[d]thiazol-2-yl)A yellow solid called -3-(4 fluorophenyl) -2E-propenamide. The resulting compound has the following chemical structure as shown in figure 20. (Deep et al., 2016b)

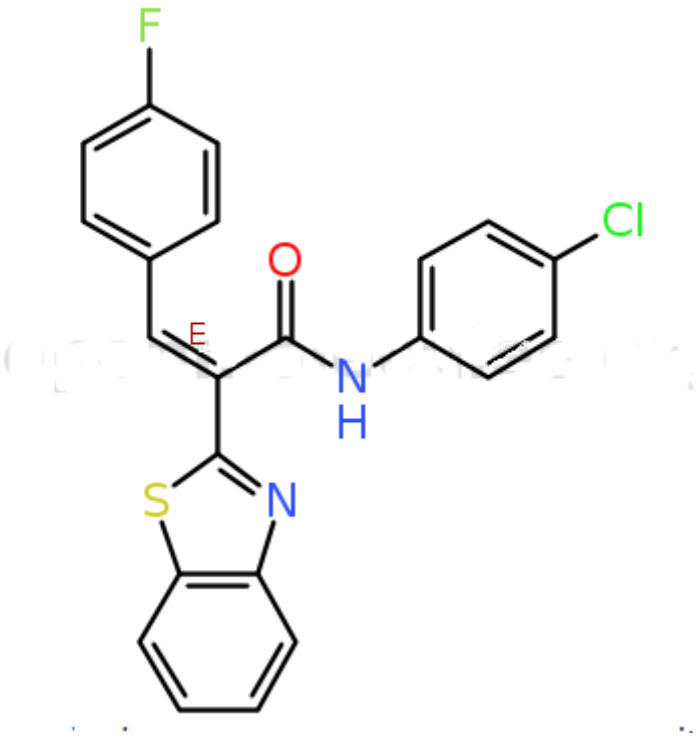


Figure 20: N-(4-chlorophenyl)-2-(benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-2E-propenamide. (Deep et al., 2016b)

SAR:

1. It is found that adding a chloro substituent to the phenyl ring at 4^{th} position of the amide group is beneficial for the anti-proliferative activity against the tested cancer cell lines. Therefore, if the 4-chlorophenyl group at ortho position of the benzothiazole ring were swapped out for a 4-methoxyphenyl or 4-nitrophenyl group, the activity would be decreased.

2. The presence of a 4-fluorophenyl group at 3rd position of the propenamide moiety is necessary for the propenamide moiety to be active.

3. In addition, compared to the unsubstituted derivative, the inclusion of a fluorine atom at the para position of the phenyl ring resulted in an increase in activity. The electronic properties of the substituents, which affect the electronic distribution and stability of the molecule, are responsible for the observed SAR.

2.10.2 N-(4-methoxyphenyl)-2-(benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-2E-propenamide synthesis system

Step 1: Synthesis of 2-(benzo[d]thiazol-2-yl)-N-(4-fluorophenyl)acetamide

In order to create 2-(4-fluorophenyl)benzo[d]thiazole, 2-aminobenzenethiol is combined with 4-fluorobenzoyl chloride and added with triethylamine. The resultant product is then acylated using acetic anhydride and catalytic quantities of pyridine to create 2-(benzo[d]thiazol-2-yl) acetamide. The chemical structure is shown in figure 21. (Deep et al., 2016b)

• Melting point: 221 °C, yield: 90%

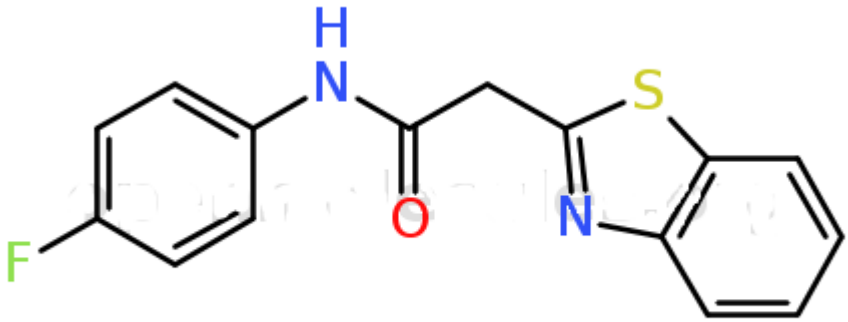


Figure 21: 2-(benzo[d]thiazol-2-yl)-N-(4-fluorophenyl)acetamide. (Deep et al., 2016b)

Step 2: Synthesis of N-(4-methoxyphenyl)-2-(benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-2E-propenamide

• 4-Methoxyphenylacetic acid, triethylamine, and acetonitrile are used to dissolve the end product from step 1 before thionyl chloride is added.

• After stirring the resultant mixture for an hour, the reaction mixture is then mixed with 2-(benzo[d]thiazol-2-yl)acetamide.

• To create N-(4-methoxyphenyl), the resultant product is then combined with 4-fluorobenzaldehyde and triethylamine in ethanol.-2-(benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-2E-propenamide. The chemical structure is shown in figure 22 which is yielded 90% ans has a melting point of 180°C (Deep et al., 2016b)

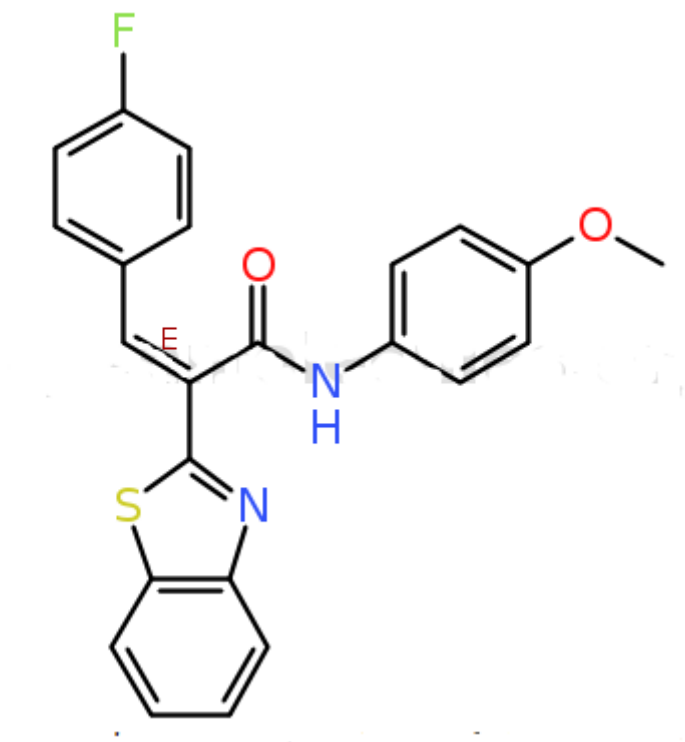


Figure 22: N-(4-methoxyphenyl)-2-(benzo[d]thiazol-2-yl)-3-(4-fluorophenyl)-2E-propenamide. (Deep et al., 2016b)

Chapter 3

Rhodanine: A review on the structure-activity correlations (SAR) and anticancer potentials of rhodanine derivatives

The pharmacological properties of rhodanine which is a five-membered heterocyclic compound, which may have potential anticancer properties, have been extensively studied. The structure of rhodanine derivatives, which combines a thiazolidine-2,4-dione ring with a ketone group to give rise to their biological action, is distinct. The position and nature of substituent can change the pharmacology of the rhodanine derivatives for instance, some of the rhodanine derivatives are shown in figure 23 and 24 where the substituent effect in the anticancer therapy has been reported. (Tomašič & Mašič, 2009)

Preclinical research on rhdonine derivatives as possible anticancer drugs has yielded encouraging findings, and it is believed that its mode of action involves inhibiting a number of targets involved in the growth and survival of cancer cells. (Tomašič & Mašič, 2009)

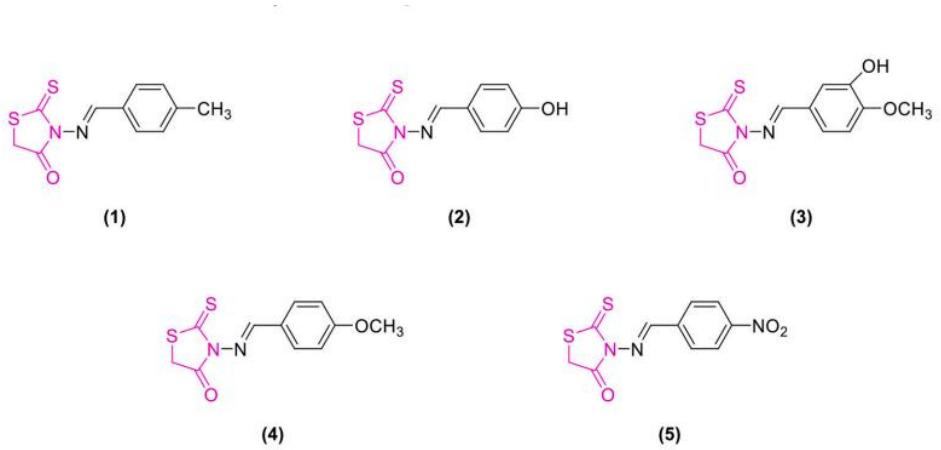


Figure 23: Some rhodanine derived compounds which have great inhibitory activity against pentose phosphate pathway enzymes, (Tomašič & Mašič, 2009)

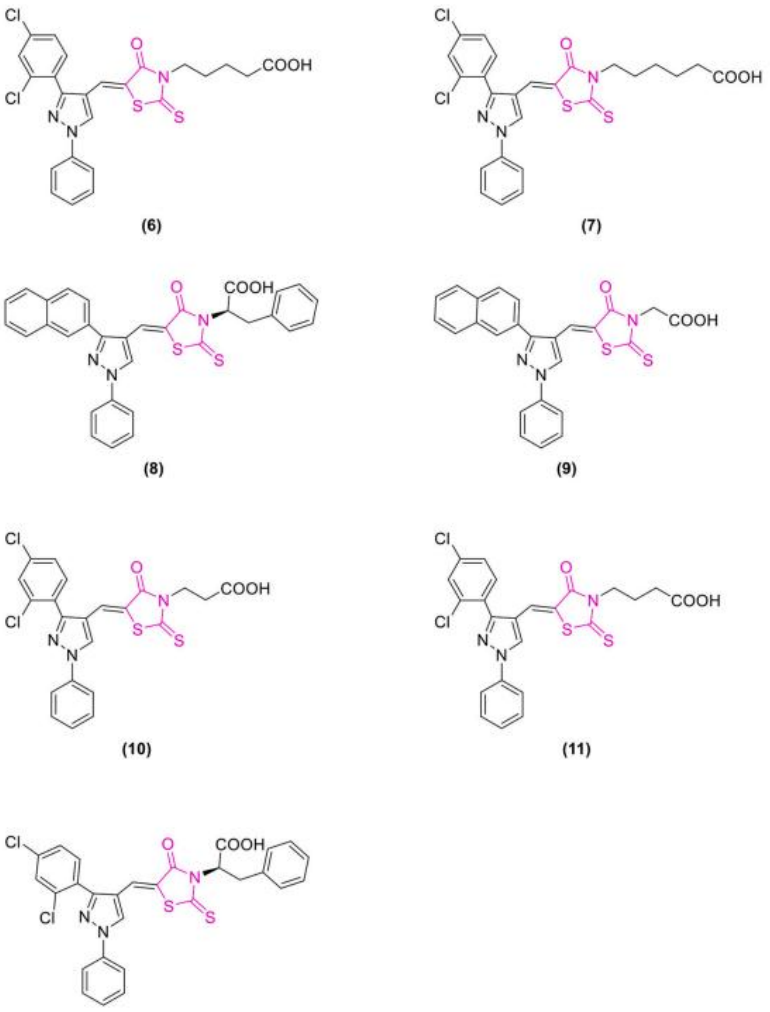


Figure 24: More rhodanine derivative compounds which are potential PTP1B inhibitors.

(Tomašič & Mašič, 2009)

3.1 Mode of Action of Rhodanine

Rhodanine derivatives have been demonstrated to exhibit anticancer activity through a variety of mechanisms of action. The triggering of apoptosis, or the cancer cells' programmed cell death, is one of the main methods. By up-regulating anti-apoptotic proteins and activating the apoptotic pathway enzyme caspases, rhodanine derivatives can cause apoptosis.

Rhodanine derivatives also impede angiogenesis, which is the creation of new blood vessels that tumors require for survival and growth. This is another way that they have anticancer properties. Vascular endothelial growth factor (VEGF) and its receptors, which are involved in the process of angiogenesis, can be targeted by rhodanine derivatives to suppress angiogenesis. (Yin et al., 2022)

By focusing on various pathways involved in cell division and growth, such as the PI3K/Akt/mTOR pathway and the MAPK/ERK pathway, rhodanine derivatives can also reduce the growth of tumor cells. The activity of histone deacetylases (HDACs), which are generally enzymes which are associated with the gene expression regulation and subjected to the emergence of cancer, has also been found to be inhibited by various rhodanine derivatives. (Azizmohammadi et al., 2013)

Overall, the author contends that rhodanine derivatives' varied modes of action contribute to their promise as anticancer drugs, and that additional research is required to completely comprehend their molecular targets and maximize their therapeutic efficacy. (Yin et al., 2022)

3.2 Different kinds of cancers treated by Rhodanine

Rhodanine derivatives have shown anticancer activity against many forms of cancer.Some of the tumors that rhodanine derivatives have been shown to be effective against include:

1. **Breast Cancer:** This is known as a major catagory of carcinoma which is getting more common with the population and rhodanine derivatives have demonstrated strong anti-breast cancer action in this type of carcinoma by inducing apoptosis and preventing the growth of breast cancer cells. Particularly promising efficacy against breast cancer has been seen in compounds containing an arylidene moiety and a modified phenyl group at position 3 of the rhodanine ring.

2. **Lung cancer:** By preventing tumor cell proliferation and triggering apoptosis, rhodanine derivatives have been shown to have substantial anticancer effect against lung cancer cells. These derivatives can only function if there are electron withdrawing substituents at the rhodanine ring's fourth position.

3. **Prostate cancer:** Rhodanine derivatives have also been shown to be effective against this particular cancer kind. By preventing cell growth low levels of prostate specific antigen (PSA) and apoptosis which a biomarker for prostate cancer, rhonine derivatives has been excellent at prostate cancer inhibition.

4. **Colorectal cancer:** It is described as the development of a precancerous lesion in the normally healthy colon and rectal epithelium that progresses to an invasive carcinoma (adenocarcinoma), which may spread to other distant organs and result in metastatic lesions, with the liver being the organ most frequently affected. Through the induction of apoptosis and the inhibition of cell proliferation, radonine derivatives have been demonstrated to have anticancer efficacy against colon cancer cells. Significant activity against colon cancer has been seen for compounds with an arylidene moiety and a 4-fluorophenyl group at position 3 of the rhodanine ring.

Overall, the ability of rhodanine derivatives to control a variety of signaling pathways involved in cancer genesis and progression is what gives them their anti-cancer efficacy. Depending on the cancer type and the structural characteristics of the rhodanine derivatives, the specific molecular mechanisms of action may change. (Yin et al., 2022)

3.3 Structure-Activity Relationship (SAR)

The presence of electron giving or electron withholding substituents at the fourth position of the phenyl ring can change the activity of rhodanine derivatives. Electron donating substituents, like methyl or methoxy groups, can boost a compound's activity, whereas electron-withdrawing groups, like nitro or chloro groups, can lower it. The compound's activity has also been claimed to be improved by replacing the phenyl ring at the 4-position with a heterocyclic ring like pyridine or furan (Azizmohammadi et al., 2013)

The activity of rhodanine derivatives can also be affected by changes to the thiazolidine ring. For instance, thiohydantoin or thiobarbituric acid rings can substitute the thiazolidine ring to improve activity. In addition, it has been shown that adding a double bond to the rhodanine ring's 2-position increases activity, maybe as a result of better contact with the target protein. The SAR plays a crucial role determining the therapeutic effect some of which is shown in figure 25 and 26.

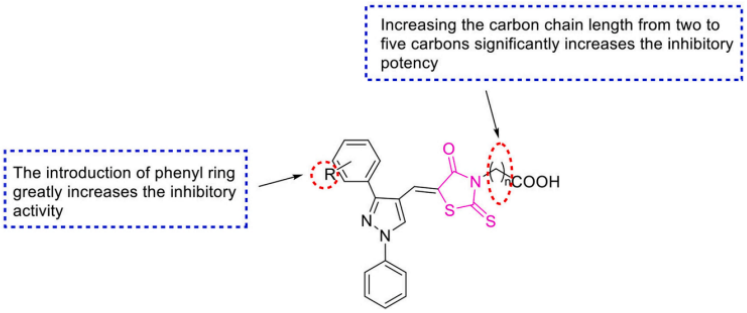


Figure 25: SAR of rhodanine derived compounds as a potent anticancer agent. (Yin et al., 2022)

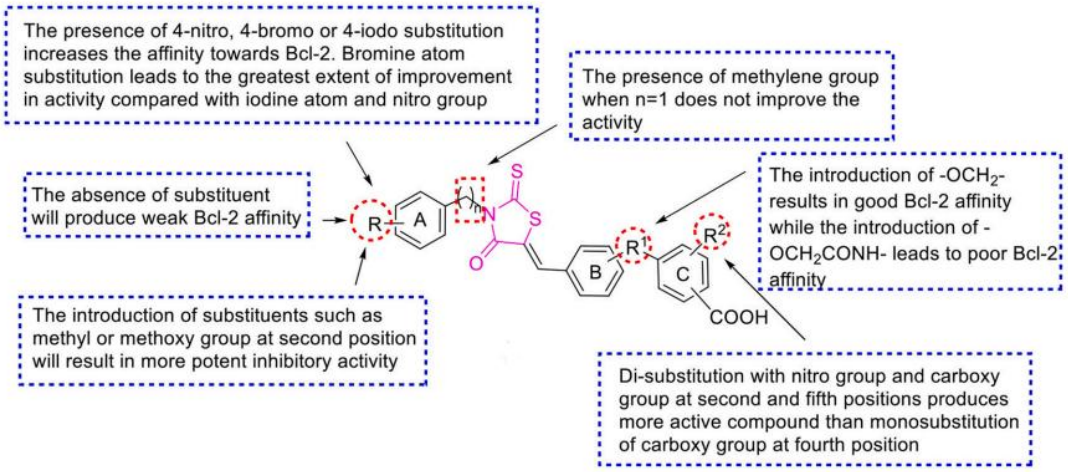


Figure 26: SAR of rhodanine derived compounds as a potent anticancer agent. (Yin et al., 2022)

Chapter 4

4.1 Limitations and drawbacks

Although the review paper sheds light on the positive side of thiazolidinone, however everything comes with its pros and cones. Similarly, this review paper also has some limitations as well as drawbacks which are discussed below:

1. **Limited clinical data:** Despite the numerous mention of the anticancer potential of thiazolidinone derivatives, there may not be enough complete clinical evidence to support their efficacy and safety in human subjects. To demonstrate their efficacy as anticancer medications in a therapeutic context, additional research and clinical trials are required.

2. **Specificity and selectivity:** Although the SAR investigations have shed light on the structural characteristics influencing the anticancer action of thiazolidinone derivatives, additional research into their specificity and selectivity towards cancer cells may be necessary. To prevent unwanted side effects, it is essential to make sure that these substances only affect cancer cells while sparing healthy cells.

3. **Mechanistic understanding:** Understanding of their particular molecular targets and signaling pathways may still be lacking, despite the articles' discussion of the many modes of action of thiazolidinone derivatives. The specific mechanisms by which these substances exert their anticancer effects must be clarified through more study in order to provide a more complete understanding of their mode of action.

4. **Structure-activity relationship diversity:** Diversity in the structure-activity relationship is covered throughout a variety of thiazolidinone derivatives with various structural alterations. There might be further structural alterations and variances, nevertheless, that haven't been thoroughly investigated. The SAR could be better understood by examining a larger range of structural alterations, and this could also result in the identification of brand-new, extremely effective thiazolidinone-based anticancer drugs.

5. **Combination Therapy:** The anticancer activity of thiazolidinone derivatives as single agents is the main topic of the publications. Examining their potential in combination therapy with additional anticancer medications or cancer treatment techniques may be worthwhile. Combination strategies can be synergistic and also could improve therapeutic outcomes overall, overcome medication resistance and increase therapeutic efficacy.

Future studies in the area of thiazolidinone-based anticancer drug discovery can take advantage of these limits and gaps by conducting additional study and experimentation. The thesis can help fill in these gaps so that people have a better knowledge of the thiazolidinone motif and how beneficial it might be in the creation of strong anticancer treatments. (Yin et al., 2022)

4.2 Future Scope and Opportunities

There are a number of potential future applications and opportunities for the development of thiazolidinone-based medications in the treatment of cancer, based on the limits and gaps noted as well as the data from the articles. They are discussed below:

1. **Clinical trials and translational research:** A critical stage in the development of thiazolidinone derivatives as cancer treatments is the conduct of well-planned clinical trials to evaluate the safety, effectiveness, and pharmacokinetics of these compounds in human subjects. These studies can offer insightful information about the drugs' clinical potential, ideal dosage plans, and potential drug-drug interactions.
2. **Targeted therapy and personalized medicine:** The precise molecular targets and pathways impacted by thiazolidinone derivatives need to be further investigated. This information can help with the creation of targeted medicines that are customized to certain people or cancer subtypes, maximizing therapeutic effectiveness while reducing side effects.
3. **Combination therapies:** An intriguing direction is examining the possible synergistic effects of thiazolidinone derivatives in combination with other anticancer medications or treatment regimens. Combination medicines can improve patient response to therapy, combat drug resistance, and offer more thorough and efficient cancer treatment plans.

4. **Drug delivery systems:** It is also plausible to improve the stability, distribution as well as bioavailability of thiazolidinone derivatives by creating efficient drug delivery methods and formulations. Prodrugs, formulation methods, or nanoparticle-based drug delivery systems can improve the therapeutic efficacy of these substances while reducing side effects.
5. **Overcoming drug resistance**: A critical component is looking into how thiazolidinone derivatives might be used to circumvent drug resistance mechanisms including multidrug resistance (MDR).Inhibiting efflux pumps, controlling drug transporters, or focusing on resistant cancer phenotypes are just a few of the ways that these compounds can be used to address drug resistance.
6. **Exploration of the structure-activity connection**: The field of thiazolidinone derivative structure-activity relationship research is still quite young. SAR analyses can be used to guide the investigation of novel structural changes and variations, resulting in the discovery of more powerful and selective molecules with enhanced anticancer potential.
7. **Mechanistic knowledge**: Understanding the specific mechanisms of action of thiazolidinone derivatives can pave the way for the creation of tailored drugs as well as the discovery of possible biomarkers for patient stratification. To maximize these drugs' therapeutic potential, it is important to comprehend how they interact with certain biological targets and influence important signaling cascades.

The field of thiazolidinone-based pharmaceuticals for the treatment of cancer can be furthered by researchers along with pharmaceutical companies by examining these potential future applications and opportunities.These initiatives have the potential to enhance patient outcomes, increase the range of available treatments, and advance the overall progress against cancer. (Yin et al., 2022)

1.2 Conclusion

To summarize, the potential of thiazolidinone derivatives as potent anticancer drugs has been examined in this thesis. A thorough examination of the kinds, structures, structure-activity correlations (SAR), and synthesis techniques of thiazolidinone compounds has yielded important insights into the effectiveness and mechanisms of action of these compounds against cancer cells. (Shawky et al., 2020)

Several thiazolidinone derivatives have been successfully synthesized utilizing diverse synthetic methods and techniques. These substances showed notable anticancer activity against cancer cell lines that had been evaluated, and several of them showed more potency than the reference substances. This demonstrates how effective thiazolidinones may be in the fight against cancer.

Additionally, the impact of structural changes on the anticancer activity of thiazolidinone derivatives has been extensively studied using the structure-activity relationship (SAR) investigations. The prospective use of thiazolidinone derivatives as potent anticancer drugs has been addressed in this thesis in a systematical approach. A thorough examination of the classification, structures, structure-activity correlations (SAR), and lastly synthesis techniques of thiazolidinone compounds has yielded important insights into the effectiveness and mechanisms of action of these compounds against cancer cells. (Shawky et al., 2020)

Several thiazolidinone derivatives have been successfully synthesized utilizing diverse synthetic methods and techniques. These substances showed notable anticancer activity against cancer cell lines that had been evaluated and several of them showed more potency than the reference substances. This demonstrates how effective thiazolidinones may be in the fight against cancer.

Furthermore, the impact of structural changes on the anticancer activity of thiazolidinone derivatives has been extensively reported using the structure-activity relationship (SAR) investigations.

Lastly, this thesis offered a glimpse into the thiazolidinone motif's potential for use in the development of anticancer drugs. In the search for efficient anticancer treatments, it has been brought to light how crucial it is to comprehend the kinds, structures, structure-activity connections, and synthesis techniques of thiazolidinone molecules. The information presented here lays the groundwork for further investigation and the creation of innovative thiazolidinone-based medications with enhanced therapeutic effects in order to give an upper hand in the treatment of cancer. (Azizmohammadi et al., 2013)

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