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# A Review on Anti-Cancer Activity of Benzopyrazole and Thiazolidine-4-One Nucleus

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**ABSTRACT**

**The review covers recent information about antioxidant, anticancer, anti-inflammatory, analgesic, anticonvulsant, antidiabetic, antiparasitic, antimicrobial, antitubercular and antiviral properties of thiazolidin-4-ones. Additionally, the influence of different substituents in molecules on their biological activity was discussed in this paper. Thus, this study may help to optimize the structure of thiazolidin-4-one derivatives as more efficient drug agents. Presented information may be used as a practical hint for rational design of new small molecules with biological activity, especially among thiazolidin-4-ones. The anticancer drug research and development is taking place in the direction where the new entities are developed which are low in toxicity and are with improved activity. Benzoxazole and its derivative represent a very important class of heterocyclic compounds, which have a diverse therapeutic area. Recently, many active compounds synthesized are very effective; natural products isolated with benzoxazole moiety have also shown to be potent towards cancer.**

***Keywords***- Benzoxazole,Thiazolidin-4-ones, Anticancer drug, Isolated Natural Product

## I. INTRODUCTION

Cancer is one of the leading causes of death worldwide, with the current rate of developing cancer listed at 1 in 5 for men and 1 in 6 for women, while cancer mortality is currently 1 in 8 among men and 1 in 10 among women. It was estimated to cause 9.6 million deaths in 2018 and that approximately 18.1 million new cancer cases would occur in 2018. The most common cancers include lung cancer (11.6% of total new cases), breast cancer (11.6% of total new cases), prostate cancer (7.1% of total new cases), colorectal cancer (6.1% of total new cases), stomach cancer (5.7% of total new cases), and liver cancer (4.7% of total new cases) in both sexes combined. Despite the modern technology and multimodal treatments available, intensive research and development of alternative effective anticancer drugs is still ongoing to find a cure for this disease. Steroids are an important group of natural compounds playing a crucial role in many physiological and reproductive functions in the human body. Also, different types of steroids have been developed as drugs and anticancer agents [1]. The ability of hydrophobic steroid core to interact with cell membrane can enable transport of various functional groups or heterocyclic structures through them. As concerns the steroidal ligand-receptor binding mechanism, not only hydrophobic interactions but also hydrogen-bonding in some regions of the bindingpocket is involved. Therefore, semisynthetic modifications involving the apolar sterane skeleton or the polar functional groups at C-3 and C-17 in the natural hormones may exert a significant influence on the binding affinity of the molecule [2].Accordingly, the modifications of steroid molecules, by the addition of new functional groups or heterocyclic rings, resulting in new biological activities of these molecules, have become one of the major goalsof steroid chemistry today. Recently we reported synthesis of new steroidal mono-and bis(thiosemicarbazones) and mono-and bis(1,3,4-thiadiazolines) obtained from several androstene derivatives 1a–f and their cytotoxic activity in vitro[3]. Mono-and bis(thiosemicarbazones) were found to be a mixtures of (E)-and (Z)-isomers differing in configuration on the C(3)=N1 double bond. In all cases the main isomer adopted Econfiguration. The corresponding mono-and bis(1,3,4-thiadiazolines) were formed as single heterocyclic compounds. 3-Thiosemicarbazones and 3,17-bis(thiadiazolines) exhibited the best activity against all cancer cell lines used in this work [3]. The study of the mechanisms of anticancer activity revealed that these compounds induced apoptosis in HeLa cells, through extrinsic and intrinsic signalling pathways [3]. Additionally, these compounds showed a strong anti-angiogenic acitivity.

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The results from our research also, suggest that α,β-unsaturated thiosemicarbazone moiety at C-3 as well as the spiro heterocyclic substituent at C-17 position enhanced the activity of investigated compounds [3].Motivated by theresults mentioned aboveand as a continuation of our work on the new heterocyclic steroid derivatives as biologically active molecules [3-5],we decided to prepare new steroidal heterocyclic compounds derived from previously synthesized mono-and bis(thiosemicarbazones) 2a–fand 3a–f(Fig. 1) [3] and to investigate their biological activities.It is well known that thiosemicarbazones have been used as intermediates for agreat variety of heterocyclic products, such as thiazolidinones, thiohydantoines, and thioxopyrimidinediones [6]. Among them 4-thiazolidinone derivatives have attracted continuing atention due to their diverse biological activities [7]. In recent years, the synthesis of 4-thiazolidinone derivatives with anticancer activity against leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate and breast cancers cell lines has become a promising area of research [8,9]. To the best of our knowledge, very few steroidal thiazolidinones have been prepared so far [10-14] and their biological evaluation has been reported only for antibacterial action [15,16]. Here we describe the synthesis and configurational study of novel steroidal mono-and bis(thiazolidin-4-ones), and their in vitro cytotoxic activity.Since one of the goals of this study was to compare the activity of new heterocyclic derivatives with those reported earlier [3], the new compounds weretested against the same human malignant cell lines as the previous ones: cervical adenocarcinoma (HeLa), chronic myelogenous leukemia (K562), breast carcinoma (MDA-MB-453), breast adenocarcinoma (MDA-MB-361) colon adenocarcinoma (LS174) and lung adenocarcinoma (A549) cells. Besides, cytotoxicity of these compounds was tested on normal, human lung fibroblasts (MRC-5). The selectivity in the cytotoxic action of the most active compounds was evaluated against human normal peripheral blood mononuclear cells (PBMC).The specific objective of this studywas to clarifythe mechanisms of the cytotoxic actions of the tested compounds. Therefore, the morphological analysis by fluorescence microscopy andcell cycle analyses by flow cytometry were performed, as well asthe effects on caspase-3, caspase-8 and caspase-9 activities of two selected derivatives. The anti-angiogenic potential of these compounds was also explored. Finally, the effects of two selected steroid derivatives on the gene expression levels of matrix metalloproteinases 2 and 9 (MMP2and MMP9), and vascular endothelial growth factor A (VEGFA) were examined.

Natural products are recognized as an indispensable source for discovery and development of chemopreventive and chemotherapeutic agents. Currently, around 75% of the clinically used anticancer drugs are derived from natural bioresources, including plants, animals, and microorganisms. Ever since ancient times, people have used plants for various medicinal uses, including treatment for injuries, ailments, and general health well-being. The first records of plants used as traditional medicines, written in cuneiform, dates back to 2600 B.C. in Mesopotamia. Plants represent a great source of biologically active natural products, and many of these plant-derived natural products and derivatives have been developed into what is now the standard repertoire of cancer chemotherapy available today, such as paclitaxel, vinblastine, and etoposide.

Up to now, cancer remains a global and serious public health challenge. It is estimated that there are more than 200 different types of cancer, generally named according to the tissue where the cancer was recognized for the first time. Cancer is considered to be one of the significant causes for death in the 21st century and the most critical obstacle for the increase of global life expectancy. According to an analysis by the world health organization (WHO) in 2015, cancer is the second leading cause of death for patients younger than 70 years old in 91 countries and the third or fourth leading cause of death among 22 other countries. Moreover, a global increase of 18.1 million new cancer cases and 9.6 million cancer-related deaths have been reported in a previous study, especially 70% of the death caused by cancer occur in low-income and middle-income countries. The fast growth of the cancer incidence and mortality has turned out to be global health challenges. How to reduce the cancer-related death rate has attracted significant attention from the government, society, medical industry, as well as scientific communities, expecting the rapid development of effective and safe drugs for cancer treatment.

Despite of the impressive progress in biotechnologies and further understandings of the disease biology, the development of new, practical and innovative small molecule drugs remains an arduous, time-consuming, and expensive project, which requires collaborations from many expertise in multidisciplinary fields, including medicinal chemistry, computational chemistry, biology, drug metabolism, clinical research, etc. Furthermore, it has been illustrated that the successful discovery and development of a new drug costs 12 years, and expensive investment. Thus, novel drug development strategies with a reduced cost of time and money, as well as an enhanced efficiency are in high demand, which would contribute to a significant improvement in global health and life expectancy. Since the successful development of HIV protease inhibitor Viracept in the USA in 1997, which was the first drug design fully driven by its target structure, computational methods have served as an essential tool in drug discovery projects and have been a cornerstone for new drug development approaches. This makes the drug developmental process faster and cheaper. Recently, the fast growth in computational power, including massively parallel computing on graphical processing units

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(GPUs), the continuous advances in artificial intelligence (AI) tools, have translated fundamental research into practical applications in the drug discovery field. This attracted considerable attention for their outstanding performance on providing new promising perspectives and solutions to overcome life-threatening diseases.

In this review, we aim at providing an overview of different subjects of the computational-method-aided new drug discovery processes in general, and anti-cancer therapy discovery in particular. We reviewed some of the most representative examples and clarified fundamental principles by exploring studies on anticancer drug designs with the help of computational methods. A workflow of computational drug discovery is explained in Fig 1.

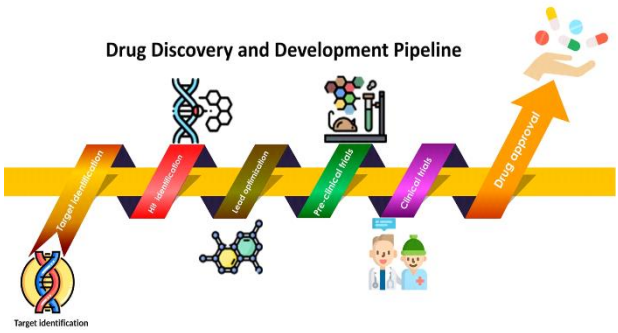



**Fig. 1: Targeted drug discovery to drug development**

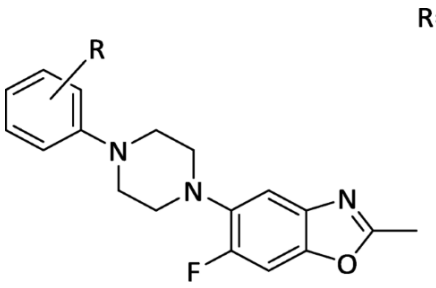
Cancer is a one of the major health problems for human beings with the leading mortality rate [1]. Natural, synthetic, or biological and chemical substances are the cancer-causing agents [2]. Many drugs are used to cure it, but they have their own toxic side effects [3]. Hence, there are lots of research carried out to synthesize new [4,5,6], effective, and affordable anticancer drugs with more selectivity, minimum dosage, and lesser side effects.

Drug discovery over the years have focussed more on the heterocyclic chemistry due to their huge success rate in forming active pharmaceutical intermediate. Among the heterocyclic compounds, benzoxazole is one of the most important heterocyclic compounds which exhibit remarkable pharmacological activities [7,8,9,10,11]. There are many reportation of synthetic compounds and naturally occurring compounds with benzoxazole backbone showing a very active anti-cancer activity. Different research groups have done much progress in designing compounds with benzoxazole, synthesizing them, and collecting anticancer activity data of those against various human cancer cell lines. An attempt has been made to see how various heterocyclic moiety attached with benzoxazole have an effect on the anticancer activity of the various benzoxazole compounds synthesized by different groups. A compiled data of all these recent articles helps in providing a direction towards further research.

## II. BENZOXAZOLE LINKED WITH DIVERSE HETEROCYCLIC MOIETY AND ITS ANTICANCER ACTIVITY

***Moiety of benzoxazole and piperazine***

Benzoxazole attached to piperazine derivatives and tested it over human A-549 lung carcinoma cells. The initial results were not that satisfactory, and the results were low which was due to the low solubility of the aryl piperazine compounds, and these compounds precipitated in the cell culture media. The solubility of the compounds can be improved by using N-methylpiperazine instead of aryl piperazine at position-6 of the benzoxazole, and the methyl group at position-2 can be replaced with a carbamate functional group. The one pot reductive cyclization with indium reduced the number of steps, and compounds were synthesized with high yield. The general compound structure is added below (Fig. 2).




R= 7a= H
7b= p-$CH_3$
7c= p-OH
7d= p-F
7e= p-$OCH_3$
7f= o-OH
7g= o-F
7h= m-OH
7i= m-$OCH_3$
7j= 3,4-Cl

**Fig. 2: Benzoxazole-piperizine derivatives**

***Synthesis and biological activity of4¢-oxathiazolidinylbenzopyrazoles***

In Pharmacological Studies of Benzo Pyrazole and their derivatives they have been shown to possess a variety of activities including antimicrobial and anti in flam matory[1].4-Oxathizolidinesandtheir5- arylmethylene derivatives also possess a variety of therapeutic activities[2-4]. Therefore, it was thought to combine benzo pyrazole and oxathiazolidine rings together in a molecular framework to see the additive effects of the rings towards the biological activities.

In this paper we report the synthesis of 3-methyl-1-[(2′-substitutedphenyl-4′-oxothiazolidinyl)-3′-amido-methyl]-5,6-substituted-benzopyrazoles**3**and3-methyl-1-[(2′-substituted-phenyl-5′-methyl-4′-oxothia-zolidinyl)-3′-amidomethyl]-5,6-substitutedbenzo-pyrazoles **4** (**Scheme I**). These new compounds are evaluated for their antimicrobial and antitubercular activity. 5,6-Substituted-3-methylbenzopyrazole-1-aceticacidhydrazides**1**werepreparedfrom5,6-substituted-3-methylbenzopyrazoles. There action of compound 1 and substituted benzaldehydes me thanolassolventanda

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fewdrops of aceticacidasacatalystunder reflux,afforded5,6-substituted-3-methyl-1-(substi-tutedbenzalhydrazinocarbonylmethyl)benzopyrazoles**2**in goodyields.Thereactionof**2**withthioglycolicacidandthiola cticacidindrybenzeneandafteraconvenient work-up, gave the corresponding compounds 3-methyl-1-[(2′-substituted-phenyl-4′-oxothiazolidinyl)-3′-amidomethyl]-5,6-substituted-benzopyrazoles**3**and3-methyl-1-[(2′-substituted-phenyl-5′-methyl-4′-oxothiazolidinyl)-3′-amidomethyl]-5,6-substituted-benzopyrazoles **4**, respectively.

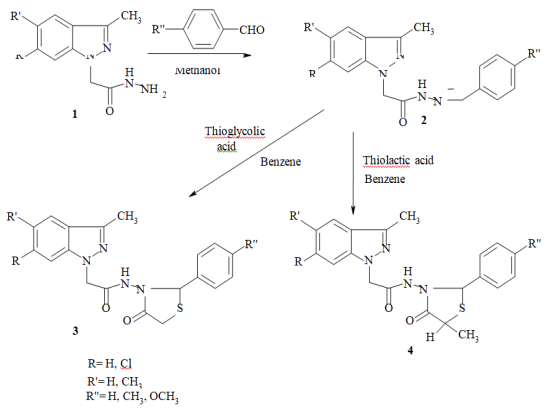


**Fig. 3: Synthesis of 3-methyl-1-[(2′-substituted-phenyl-4′-oxothiazolidinyl)-3′-amidomethyl]**

***Benzoxazole-pyrazolinone derivative***

New derivatives of benzoxazole, benzothiazole, and benzimidazole derivatives [19] (Fig. 4) were prepared. It was observed that without substitution at N-2, the compounds show very poor anti-proliferative activity as compared to substitution at N-2 of pyrazolinone. Phenyl and acetyl substitution was done on the N-2 of pyrazolinone, and it increases the antiproliferative activity of the compounds. The acetylated compound (Fig. 5) was arranged as per their activity 12a > 12b > 12c according to their $IC_{50}$ value. Now if the substitution was changed from acetyl to phenyl, then 13b > 13a > 13c according to their $IC_{50}$ value.

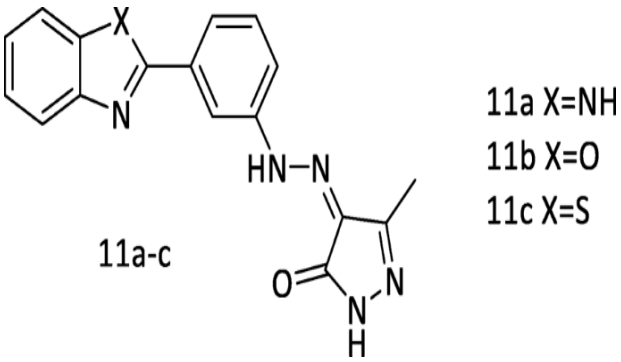


**Fig. 4: Benzoxazole-pyrazolinone derivatives**

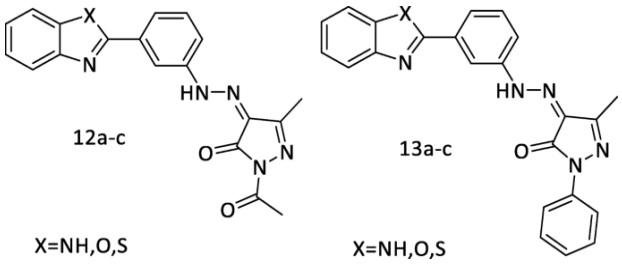


**Fig. 5: Benzoxazole-pyrazolinone derivatives**

Heterocyclic compounds play an important role in many kinds of therapy, where thiazolidin-4-one have been reported to be a potential scaffold to construct new molecules for medicinal chemistry. Thiazolidin-4-one ring is susceptible for modification in Positions 2, 3 and 5. Such modifications capacitate the search for new compounds with desired activity. Literature reported that thiazolidin-4-one is one of the important scaffolds that has therapeutic importance. In case of its modification with other substituents, it shows wide range of biological activities, such as: antidiabetic [1], antioxidant [2], antitubercular [3], antimicrobial [4,5,6,7], anticonvulsant [8] anticancer [9,10,11], antiprotozoal [12,13] and anti-inflammatory activities [14,15]. Additionally, thiazolidine-2,4-diones are well-known group of antidiabetic drugs (Pioglitazone, Rosiglitazone etc.) that reveal affinity to PPARγ [16,17]. The appearance of new information about the activity of thiazolidin-4-ones requires regular systematization and analysis the thiazolidine heterocyclic ring may be responsible for its adaptation to the human peroxiredoxin 5 enzymes [19]. This enzyme plays an important role in the process of fighting free radicals and protecting against oxidative stress. The antioxidant activity of Compounds 1a–1i, 2, 3a–3r, 4a and 4b on lipid peroxidation were evaluated by TBARS assay Fig 6. The studies showed that the substitution of cyclohexyl moiety at Position 4 by the 4-hydroxyphenyl substituent (Compounds 3i and 3r) significantly increased the antioxidant activity in the structures. The Compounds 3i and 3r showed the best inhibitory activity of lipid peroxidation with EC50 0.565 ± 0.051 and 0.708 ± 0.074 mM, respectively. It has been shown that the lack of substitution at the R1 position increases the activity to a maximum (Compound 3i). The precursor of thiazolidine-4-one derivatives (3a–3r) Compounds 1a–1i showed antioxidant activity with EC50 in the range of 1.128–2.489 mM. Compounds containing a cyclopentyl moiety, Compounds 2 (EC50 = 4.156 ± 0.178 mM), 4a (EC50 = 3.30 ± 0.271 mM) and 4b (EC50 = 9.388 ± 0.911 mM), showed the lowest inhibitory capacity against lipid peroxidation among all tested derivatives.

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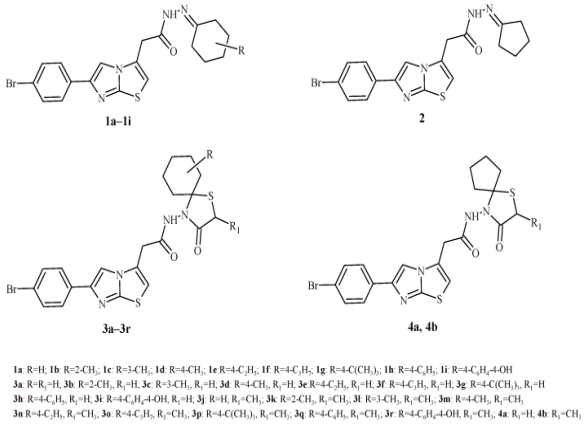
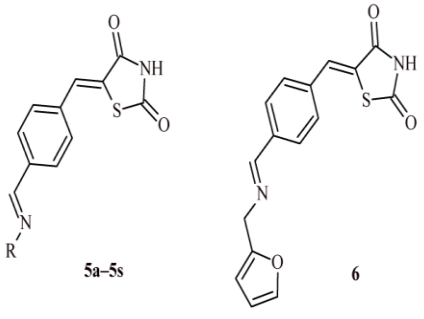



**Fig. 6: Imidazo[2,1-*b*]thiazole-thiazolidin-4-one hybrids (**3a–3r**, **4a **and** 4b**) and their precursors (**1a–1i **and** 2**) with antioxidant activity.**

Another study contemplating on antioxidant activity of thiazolidine-2,4-dione (TZD) derivatives was published in 2020. The antioxidant activity of the 5-(-4-((substituted aryl/alkyl)methyl)benzylidene)thiazolidine-2,4-dione was assessed by applying DPPH radical scavenging method. Ascorbic acid was used as standard drug.

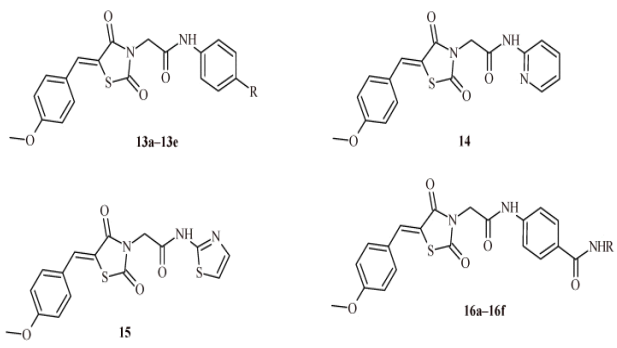
The antioxidant test showed that all twenty synthesized compounds (**5a**–**5s** and **6**)—were more active than the reference drug—ascorbic acid (Figure 7). Their $IC_{50}$ was in the range of 9.18–32.43 µg/mL. The most active derivative among all tested compounds was Derivative **6**. The Compound **6** with (furan-2-ylmethyl)imino substituent showed prominent antioxidant activity results ($IC_{50}$ = 9.18 µg/mL) compared to the reference drug ($IC_{50}$ = 40 µg/mL). Additionally, Compounds **5c**, **5d**, **5i**, **5r** and **5s** were 2-fold more active than ascorbic acid with $IC_{50}$ values in the range of 12.67–18.02 µg/mL. Whereas Compound **5m** with two electron-withdrawing groups ($NO_2$ and Cl) in the benzene ring exhibited the lowest antioxidant activity with $IC_{50}$ = 32.43 µg/mL.




**5a**: R=$C_6H_5$; **5b**: R=$NH_2$; **5c**: R=$C_6H_5NH$; **5d**: R=2-Cl-$C_6H_4$; **5e**: R=3-Cl-$C_6H_4$; **5f**: R=3-$CH_3$-$C_6H_4$
**5g**: R=4-$CH_3$-$C_6H_4$; **5h**: R=2,4-di$CH_3$-$C_6H_3$; **5i**: R=2,6-di$CH_3$-$C_6H_3$; **5j**: R=2-F-$C_6H_4$; **5k**: R=4-Br-$C_6H_4$
**5l**: R=3-$NO_2$-$C_6H_4$; **5m**: R=2-$NO_2$-4-Cl-$C_6H_3$; **5n**: R=2-$CH_3O$-$C_6H_4$; **5o**: R=3-$CH_3O$-$C_6H_4$
**5p**: R=4-$CH_3O$-$C_6H_4$; **5q**: R=4-F-$C_6H_4$; **5r**: R=4-$NO_2$-$C_6H_4$; **5s**: R=$C_{12}H_{25}$

**Fig. 7: The 5-Arylidenethiazolidine-2,4-dione derivatives (**5a–5s**) and** 6 **with antioxidant and antimicrobial activity.**

Malignant neoplasms are diseases that occur commonly in our population and have a relatively high mortality rate. It is the second leading cause of death in developed countries, after cardiovascular disease. For many years, both the morbidity and mortality rate from malignant neoplastic diseases have been increasing. Only in recent years this tendency is slowed down [27]. The background to this state of affairs is the change in the demographic structure of societies over the years as well as the exposure to carcinogens, not all recognized to this day. In Poland, there are 155,000 cases and 93,000 deaths annually [28]. Vascular endothelial growth factor (VEGF) is a well-characterized pro-angiogenic factor, necessary for the formation of new blood vessels during both embryonic development and pathological conditions. Research conducted recently has indicated a new role of VEGF as a neurotrophic factor [29]. The 5-(4-Methoxybenzylidene)thiazolidin-2,4-dione derivatives (**13a**–**13e**, **14**, **15** and **16a**–**16f**) were tested for their activity against the HepG2, HCT116 and MCF-7 cell lines [30,31]. Among all tested derivatives Figure 8, Compounds **16f**, **16e**, **16d** and **16c** showed the highest antiproliferative activity in the in vitro studies against HepG2, HCT116 and MCF-7 cell lines. Their $IC_{50}$ values were in the range of 5.1–22.08 µM. Compound **16f** showed most potent activity. It inhibited proliferation of HepG2 ($IC_{50}$ = 6.19 ± 0.50 µM) and MCF-7 ($IC_{50}$ = 5.10 ± 0.40 µM) cells better than reference drugs sorafenib ($IC_{50}$ = 9.18 ± 0.60 µM for HepG2 and $IC_{50}$ = 7.26 ± 0.30 µM for MCF-7) and doxorubicin ($IC_{50}$ = 7.94 ± 0.60 µM and $IC_{50}$ = 6.75 ± 0.40 µM for HepG2 and MCF-7, respectively). Derivative **16f** exhibited also activity against HCT116 comparable to doxorubicin (8.37 ± 0.70 µM vs. 8.07 ± 0.80 µM). All the obtained derivatives were tested for inhibitory activity against the vascular endothelial growth factor receptor-2 (VEGFR-2). Among them Compound **16f** exhibited most potent inhibitory activity with $IC_{50}$ value 0.12 ± 0.02 µM that was comparable with results for reference drug sorafenib ($IC_{50}$ = 0.10 ± 0.02 µM).




**13a**: R=H; **13b**: R=$CH_3$; **13c**: R=COOH; **13d**: R=$COOC_2H_5$; **13e**: R=$NO_2$
**16a**: R=$C_2H_5$; **16b**: R=$C_3H_7$; **16c**: R=$C_4H_9$; **16d**: R=$C_6H_5CH_2$; **16e**: R=4-$CH_3$-$C_6H_4$; **16f**: R=4-$C_2H_5OOC$-$C_6H_4$

**Fig. 8: The 5-(4-Methoxybenzylidene)thiazolidin-2,4-dione Derivatives** 13a–13e**,** 14**,** 15 **and** 16a–16f **with inhibitory effect on VEGFR-2.**

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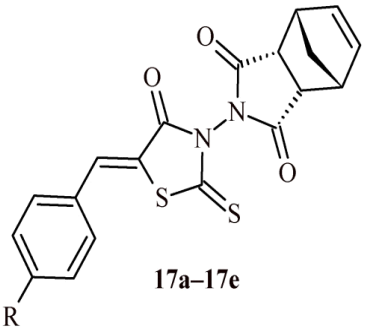
The next step of assay was molecular docking studies that was performed to investigate binding mode and affinities of compounds towards VEGFR-2. The docking studies performed in the Molsoft software showed that all derivatives assume a similar position and orientation at the receptor binding site. The proposed model of connection takes into account the affinity of the Derivative **16f** with a value of −103.50 kcal/mol and the formation of six hydrogen bonds. The carbonyl group at the position of the second thiazolidine-2,4-dione derivative joins forms one of these bonds with Asp1044. In addition, the NH group of the carboxamide linker forms another bond with Glu915. The oxygen atom from the carboxyl group stabilized the hydrogen bonds formed with Arg1025 and Ile1023. The 4-methoxybenzylidene substituent located in the hydrophobic cavity was formed by Arg1025, His1024, Ile1023, Cys1022, Leu1017, Ile890 and Ile886. Furthermore, the thiazolidin-2,4-one moiety itself occupies the hydrophobic cavity formed by Asp1044, Ile890, Leu887, Ile886 and Glu883. The central phenyl group is attached to the cavity provided by Leu1033, Cys917, Phe916, Leu838, and Ala864. The distant ethyl group, on the other hand, combines with the hydrophobic cleft formed by Gly920, Phe919, Lys918, Phe916 and Leu838. The described interactions help to understand the nature of such a strong anti-cancer effect of the **16f** derivative.

Molecular docking studies carried out for the remaining derivatives showed that the acetamide linker occupies the same cavity as the urea linker contained in the sorafenib structure. This plays a key role in increasing the affinity for the VEGFR-2 enzyme. The 4-methoxybenzylidene derivative compensates for the *N*-methylpicolinamide substituent effect of sorafenib and increase the chance for hydrogen bond formation as well as increase similarity towards the VEGFR-2 enzyme. The tiazolidine-2,4-dione core enables new compounds to form new hydrogen bonds via the carbonyl group at Position 2 with the basic amino acid Asp1044. Structure elongation plays an important role in the inhibition of VEGFR-2. Hydrophobic distal substituents and their connections give the chance for hydrogen bonds to be formed with the amino acid Glu915, which further increases the similarity to the VEGFR-2 enzyme. Worth noticing that the results of molecular docking studies are correlated very well with biological screening results. The obtained results show the potential usefulness of the considered compounds for the future design, optimization, adaptation and research in order to produce more potent and selective inhibitors of VEGFR-2 with higher anti-cancer analogues. Tyrosinase is a catalyst that regulates the duration of the melanin synthesis process. Melanin is synthesized from l-tyrosine in melanosomes, where this process is controlled by many factors, including tyrosinase [32]. Studies carried out by Isogawa et al. showed that the rhodanine Derivative **17c** (with 4-fluorobenzylidene substituent) strongly inhibited the melanogenesis process in mouse melanoma B16F10 cells in 10 µM concentration (Figure 9) [33]. Compound **17c** reduced the level of tyrosinase activity without modifying its messenger RNA levels or enzymatic activity. This derivative may promote the degradation of tyrosinase proteins; however, this degradation may be associated with simultaneous protein synthesis. Taking this into account, it was found that the Compound **17a** also lowered the activity level of the tyrosinase proteins, while having no effect on tyrosinase related protein 1 (TYRP-1), another protein involved in the melanogenesis process. Compound **17a** (with benzylidene substituent) promotes the breakdown of tyrosinase from TYRP-1 in B16F10 cells. In injured cells, tyrosinase is localized together with TYRP-1 in two regions—the peripheral and the nuclear. The Compound **17a** amplified the peri-nuclear signals while reducing the frequency of the peripheral signals. Other rhodanine Derivatives **17b** (with 4-chlorobenzylidene substituent), **17d** (with 4-methoxybenzylidene substituent) and **17e** (with 4-hydroxybenzylidene substituent) were less effective than Compound **17c**.




**17a–17e**

**17a**: R=H, **17b**: R=Cl, **17c**: R=F, **17d**: R=$OCH_3$, **17e**: R=OH

**Figure 9: Rhodanine compounds that reduced melanogenesis**

## III. CONCLUSION

Cancer possesses a continuous and series threat to the health of every individual in this world. Many researchers across the world are working on this direction to find a better treatment to this problem. Benzoxazole has been a very important moiety in drug discovery due to its diverse pharmacological activity. Present review explores the effect of various functionalization and substitution on benzoxazole and their effect on the anticancer activity. Various target areas like VEGF, VEGFR2, Topo-II, and MEK1 are discussed in the review as well. Further investigation in this direction may lead to development of new derivatives of benzoxazole with better activity, selectivity, and less toxic effect. These compiled data in the article will surely update the scientific community with the recent development in this area and will provide direction for further research in this area. The thiazolidin-4-one system is highly effective in the above-

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mentioned kinds of biological activity. Additionally, some of them showed dual-target or multitarget activity. These properties are desirable in the treatment of complex diseases such as diabetes, cardiovascular diseases, neurodegenerative syndromes or cancer. Therefore, this review may be useful for further development of the thiazolidin-4-one derivatives group as potential bioactive agents.

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