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Mini review

Hybridization of Thiazole and Pyrazoline heterocycles and the Biological Activities of Their Hybrid Scaffolds

Mariam M. Fakhry [1*], Amr A. Mattar[1*]

[1] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Egyptian Russian University, Badr, Egypt.*

*Corresponding author(s): Mariam M. Fakhry, E-mail: mariam-medhat@eru.edu.eg, Amr A. Matter, E-mail: amr-a-mattar@eru.edu.eg.

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ABSTRACT

Thiazoles and pyrazolines represent a class of heterocyclic compounds with attractive and considerable interest in medicinal chemistry due to their diverse pharmacological activities. Hybridizing thiazole and pyrazoline moieties has emerged as an innovative approach to drug discovery, enabling the synthesis of novel compounds with enhanced therapeutic potential. The hybridization of thiazole and pyrazoline scaffolds allows for incorporating different functional groups and substitution patterns, which can influence the compound's bioactivity, selectivity, and pharmacokinetic profile. The hybridization of these two heterocyclic moieties has resulted in compounds with diverse pharmacological properties, such as antimicrobial, antitumor, anti-inflammatory, and antioxidant. Furthermore, thiazolyl-pyrazolines' ability to interact with specific molecular targets, such as enzymes, receptors, or signalling pathways, makes them attractive candidates for drug development. This abstract provides an overview of the hybridization strategy and highlights the medicinal chemistry aspects and biological activities of thiazolyl-pyrazolines.

Keywords: Thiazole, Pyrazoline, Hybridization, Anti-proliferative.

1 Introduction

Heterocyclic compound plays an essential role in biological activity. Researchers in this discipline have always been attracted to heterocycles that include sulfur or nitrogen due to their diverse biological activities. Pharmacophoric hybridization is a modern but successful method for creating therapeutic anti-cancer, anti-microbial, anti-inflammatory, and anti-diabetic drugs (1, 2). Combines many bioactive groups into a single molecule to obtain more efficacy than single scaffolds. Interestingly, in medicinal chemistry, heterocyclic compounds with oxygen, nitrogen, and sulphur atoms, such as thiazoles and pyrazolines, are viewed as the foundation for creating newer entities (3, 4). The thiazolyl-pyrazoline scaffold offers diverse chemical functionalities, making it an attractive target for medicinal chemistry research. Thiazolyl-pyrazoline hybrids' antitubercular, anti-inflammatory, anti-microbial, anti-mycobacterial, and FabH inhibitor properties have been demonstrated (5). Furthermore, it has been discovered that thiazolyl-pyrazole scaffolds have promise as medicines for combating cancer and as inhibitors of multi-targeting kinases. (6).

2 Pyrazoline chemistry

Pyrazolines have an endocyclic double bond with two neighbouring nitrogen atoms in a five-membered heterocycle. They are mostly formed via Claisen-Schmidt condensation or by synthesising 1,3-dicarbonyl compounds mediated by basic catalysts. The most prevalent of the three tautomeric forms of pyrazolines is 2-pyrazoline. The commonly employed procedure for synthesizing 2-pyrazoline involves the reaction of α, β-unsaturated aldehydes and ketones with hydrazines. This reaction forms a hydrazone intermediate, which can undergo cyclization to yield 2-pyrazoline. The first figure is depicted in the following illustration **(7)**.

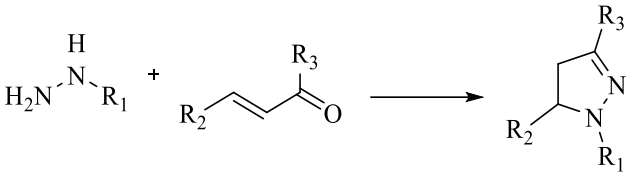


Figure 1: The reaction of α, β-unsaturated aldehydes, and ketones with hydrazines.

Another method involves 1,3 dipolar cycloaddition of nitrile imines **Figure 2** (7).

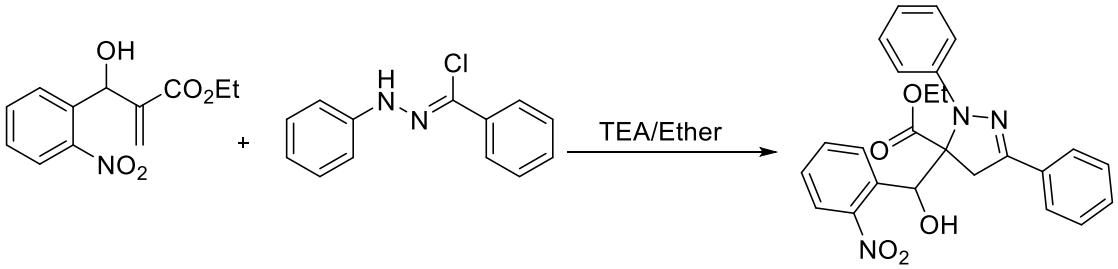


Figure 2: 1,3 dipolar cycloaddition of nitrile imines.

Another method for synthesis of pyrazolone derivatives from ethyl acetoacetate and phenyl hydrazine derivatives **Figure 3** (8).

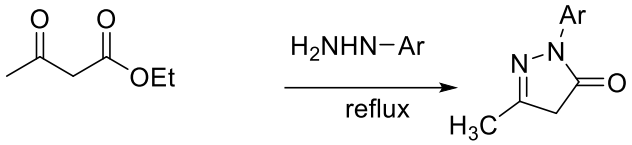


Figure 3: The synthesis of pyrazolone derivatives.

Maleki et al. produced a series of 1, 3, 5-trisubstituted-2-pyrazoline derivatives by thermally cyclizing phenyl hydrazine with unsaturated ketones while utilizing methanoic acid as a catalyst **Figure 4** (9).

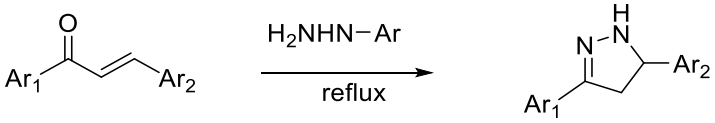


Figure 4: The reaction of unsubstituted ketones with phenylhydrazine

It has been observed that variously substituted pyrazolines exhibit a variety of pharmacological properties, including anticancer activity (10, 11), anti-inflammatory (12), antimicrobial (12, 13), anti-fungal (13, 14), anti-oxidant (14), analgesic (15), antidepressant (16), and anticonvulsant activities (17). Certain cytotoxic medicines derived from pyrazoline compounds also exhibit cancer chemo-preventive characteristics. Following the identification of pyrazofurin, a naturally occurring C-glycoside of pyrazole, which exhibited a broad spectrum of antibacterial activity, pyrazole gained significant interest as a potential antimicrobial agent (18, 19).

3 Thiazole chemistry

The thiazole compound is characterized by a five-membered heterocyclic ring, which possesses an electron-donating group in the form of a sulfur atom (-S-) and an electron-accepting group in the form of a carbon-nitrogen double bond (C=N). According to Huckle's rule, the delocalization of a lone pair of electrons from the sulphur atom to electron-withdrawing nitrogen atoms causes thiazoles to become aromatic. The structural pattern of those compounds can be activated by substituting suitable moieties at positions 2, 4, and 5 of hydrogen atoms in thiazole derivatives. There are different methods for synthesising thiazole and its derivatives (20).

- The primary method proposed by Hantzsch in 1889 involves the reaction between α-halocarbonyl compounds and thiourea or thioamides (21).

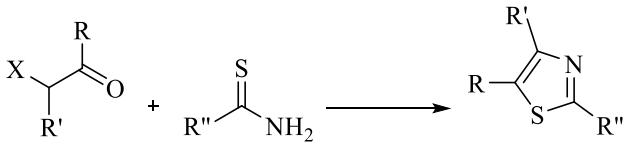


Figure 5: Hantzsch synthesis of thiazoles.

- The cook-Heilbron method is another method to synthesize 2,4-disubstitute5-amino thiazoles, where aminonitrile reacts with carbon disulfide **Figure 6** (22).

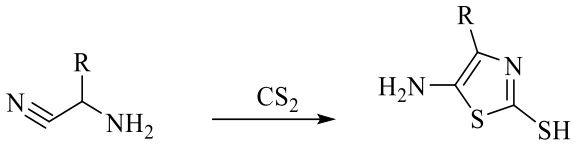


Figure 6: Cook–Heilbron thiazole synthesis.

- Lingaraju et al. synthesized thiazole derivatives *by cyclizing* active methylene isocyanides with methyl arene- and hetarenecarbodithioates in basic conditions **Figure** 7 (23).

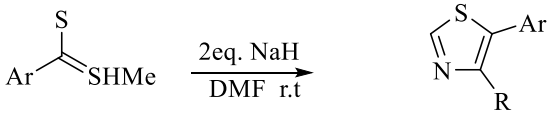


Figure 7: Cyclization of isocyanide with methyl arene- and hetarenecarbodithioatesa.

- Gabriel synthesis is an alternative synthetic process for thiazole derivatives. This method depends on the closure of the thiazole ring by heating acylamino-ketone with phosphorus pentasulfide, producing 2,5- disubstituted thiazole derivatives **Figure 8** (24).

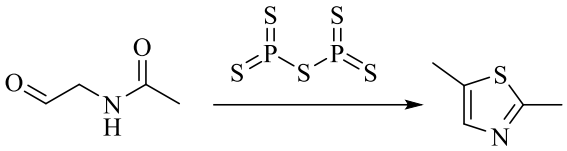


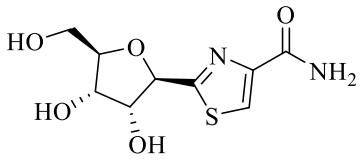
Figure 8: Synthesis of thiazole compound via Gabriel reaction (24)

Thiazole has a wide range of activities, including antioxidant, anticonvulsant, antibacterial, anticancer, cardiovascular, antimalarial, antifungal, antitubercular, antiviral, anthelmintic, antidiabetic, and anti-inflammatory activities (25).

Numerous anticancer medications contain the thiazole ring, including bleomycin, epothilone, vosaroxin, sulfathiazole, thiazofurine, and dasatinib. These medications' excellent pharmacological profiles make the thiazole ring an excellent candidate for developing more potent and secure medications, particularly for cancer.

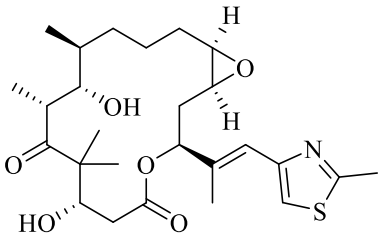
Thiazole-derived compounds exhibit considerable potential as potential candidates in the realm of anticancer drug exploration, offering a diverse array of therapeutic advantages. They have been identified as:

a. Participating in the activity of inosine monophosphate dehydrogenase (IMPDH) and the cytokine known as tumour necrosis factor TNF-α. The enzyme responsible for regulating the rate of de novo synthesis of guanine nucleotides, known as inosine 5' monophosphate dehydrogenase (IMPDH), has exhibited significant upregulation in cells with high proliferation rates. Tiazofurin, a synthetic nucleoside analogue, is a powerful inhibitor of IMPDH. By decreasing GTP and dGTP production, blockage of this enzyme prevents the development of tumour cells. With potential value for treating lung tumours and metastases, tiazofurin is a high-priority candidate for clinical studies (26, 27).



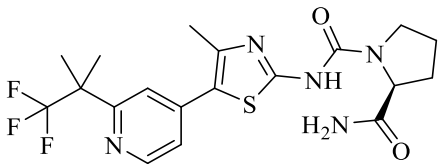
Tiazofurin

b. Apoptosis induction: The epothilones with a thiazole side chain exhibited the highest potency level in inducing apoptosis (28).



Epothilones

c. Selective inhibitors to PIK3 in the PI3K/AKT kinase signaling pathway, such as Alpelisib (FDA approved, 2019), are used in certain types of breast cancer (29).



Alpelisib

4 Thiazoly-pyrazoline scaffold

From the aforementioned data about thiazole and pyrazoline as abroad spectrum scaffolds and their multifarious pharmacological activities that inspire us to review the biological activity of the hybridization of these promising scaffolds. In the last decades, many researchers have focused on synthesising different series of thiazolyl-pyrazoline, and their biological activity has been evaluated. Thiazolyl-pyrazoline hybrids have displayed antitubercular, anti-inflammatory, antimicrobial, antimycobacterial activities, FabH inhibitors, and others (30-32).

4.1 Thiazolyl-pyrazoline as a protein kinase inhibitor

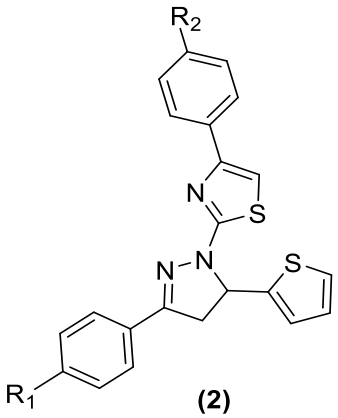
One of the largest and most functionally varied gene families, protein kinases perform crucial regulatory roles in almost every area of cellular function. Protein kinases control the biological activity of proteins by phosphorylating particular amino acids using ATP as the source of phosphate and changing the protein's shape from an inactive to an active state. Their classification is determined based on the side chain of the amino acid that they phosphorylate. In the last decades, many researchers have designed and synthesized different series of thiazolyl-pyrazoline, which were biologically evaluated as kinase inhibitors.

4.1.1 Serine/threonine kinase inhibitors

A class of enzymes known as serine/threonine kinases phosphorylates serine or threonine residues in proteins. They participate in various fundamental cellular signalling pathways that control cellular functions. Examples include the glycogen synthase kinase-3 (GSK-3) pathway, which controls a variety of cellular processes, the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway, which is involved in cell survival and metabolism, and the mitogen-activated protein kinase (MAPK) pathway, which regulates cell growth and differentiation (33, 34).

4.1.1.1 RAF Inhibitor

The RAF family is serine/threonine protein kinase, which phosphorylates and activates downstream MEK1/2, including A-RAF, B-RAF, and C-RAF. Meng-Yue Zhao et. Al, developed new pyrazole-based compounds as potential BRAF-targeting anticancer agents (32). Compound **2h** displayed potent activity (IC_{50} = 0.05 µM) against $BRAF^{V600E}$ kinases. Furthermore, this compound also displayed significant in vitro antiproliferative activity against MCF-7 with IC_{50} of 0.16 µM, comparable to the standard drug Sorafenib (IC_{50};0.19 µM) (32).

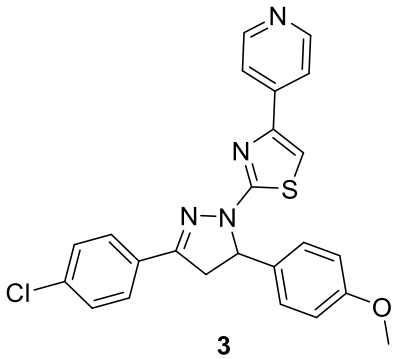


(2)

2	R_1	R_2
a	F	Br
b	F	H
c	F	OCH_3
d	CH_3	Br
e	CH_3	OCH_3
f	Br	OCH_3
g	Cl	H
h	Cl	CF_3

4.1.1.2 mTOR Inhibitor

Cell proliferation, autophagy, and cytoskeletal architecture are regulated by the serine/threonine kinase known as the Mammalian Target of Rapamycin (mTOR). Multiple human diseases, including malignancies like breast and lung cancer, were linked to the dysregulated activity of mTOR. The mTOR pathway has several potential uses in treating different solid tumours and haematological malignancies because of the crucial role that proliferation plays in various malignant cell types (35). Zhao Min Lin et al. developed a series of fluorescent thiazole-pyrazoline derivatives. They biologically assessed them against non-small cell lung cancer (NSCLC) A549 cells in a dose- and time-dependent manner in vitro. Compound **3** of this series displayed inhibition of mTOR via FKBP12, an mTOR activator and autophagy inhibitor. Additionally, it inhibited growth and promoted autophagy of A549 cells. Furthermore, compound **3** showed selectivity without affecting the development of chorioallantoic membrane (CAM) capillaries or normal vascular endothelial cell proliferation in chick embryos (36).



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4.1.1.3 Tyrosine Kinase Inhibitors

Tyrosine kinase (TK) is a class of proteins that controls several physiological and biochemical processes, including cell development, differentiation, and death. The aberrant expression of TK could cause tumorigenesis, metastasis, tumor angiogenesis, and tumor chemotherapy resistance. Therefore, they have become a popular target for anti-tumor drug research. Protein-tyrosine kinases (90 members), and tyrosine kinase-like proteins (44 members). 90 protein-tyrosine kinases are present, 58 of which are receptor tyrosine kinases (RTKs), and 32 of which are non-tyrosine kinases (nRTKs) (37), the former includes the insulin receptor and the receptors for many growth factor families such as epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). Tyrosine kinase inhibitors (TKI) can be classified into many types based on the mode of binding and conformation of kinase in the ATP pocket (38-40).

4.1.1.4 EGFR inhibitors

During the early 1960s, Cohen discovered epidermal growth factor (EGF) as a protein that stimulated the proliferation of epithelial cells. This finding led to the coining the name epidermal growth factor receptor (EGFR). The EGFR family consists of four transmembrane receptor tyrosine kinases, including EGFR (HER1), HER2 (ErbB2, neu), HER3 (ErbB3), and HER4 (ErbB4). Extracellular stimuli are transmitted to intracellular signal transduction pathways, which regulate various cellular responses such as proliferation, survival, and differentiation (41-43). Enhanced EGFR signalling in human malignancies can be attributed to many factors such as the overexpression of the EGFR receptor, gene amplification or rearrangement, and the overproduction of EGFR receptor-specific ligands.

Previous studies have provided evidence indicating a positive association between the upregulation of receptors and ligands and the invasiveness and metastatic potential of tumors. Moreover, this upregulation is associated with an unfavorable prognosis and reduced overall survival time (44-47).

In 2011, Zhu et al (48) targeted a series of thiazolyl pyrazoline derivatives as EGFR inhibitors; the most active compound **4** gave IC_{50} = 60 nm.

In addition, conjugated thiazolyl−pyrazoline derivatives were demonstrated to possess potent EGFR kinase inhibitory activities by introducing the adamantane ring to the thiazole pyrazoline scaffold. They demonstrated the effect of the lead compound on EGFR signalling.

After that, many researchers synthesis series of thiazolyl pyrazoline bulkier group on C5 of pyrazoline, but the activity against EGFR or HER2 decreased (compound **5** gave 180 nM against HER2 while compound **6** gave 3.69 µM against EGFR).

After that, further studies targeted thiazolyl-pyrazoline as EGFR inhibitor by introducing groups able to form H-bond or bulkier groups on thiazole, aiming to increase selectivity.

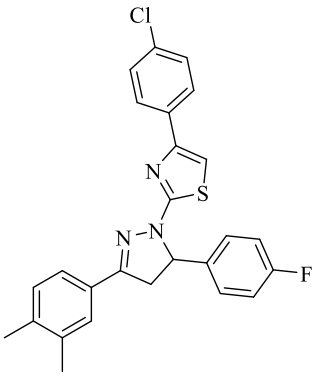
In 2019, 3 series of thiazolyl-pyrazoline quinoline based were designed and synthesized by George et al., (49).

Between these series, compounds 7, 8, and 9 gave promising inhibition activity against EGFR 31.8, 63.08, and 42.52 nM, respectively.

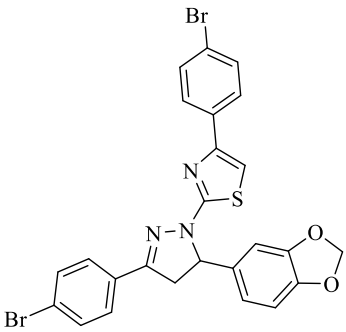
In the same year, a series of thiazolyl-morpholino phenyl-pyrazoline was designed and evaluated as a dual inhibitor EGFR and HER2 compound **10** (50).

In 2022, Fakhry et al. synthesized a new series of dimethoxy aryl thiazolyl-pyrazoline.

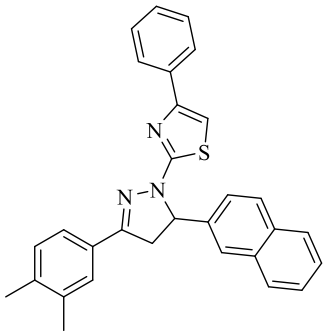
Compounds **12** and **13** demonstrated promising inhibition with IC_{50} values of 0.009 and 0.051 µM, respectively, for EGFR, and 0.013 and 0.027 µM, respectively, for HER2 (51).



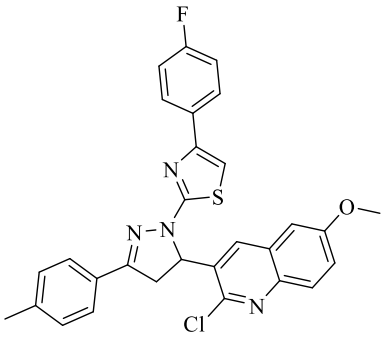
Compound 4



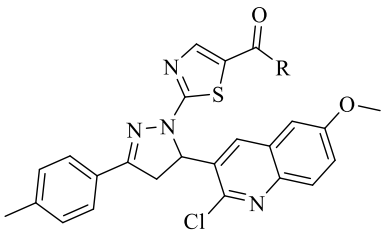
Compound 5



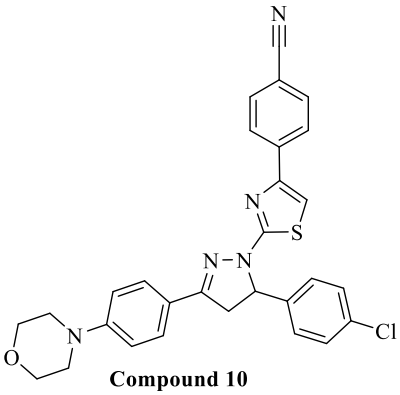
Compound 6



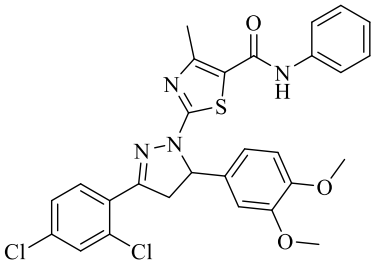
Compound 7



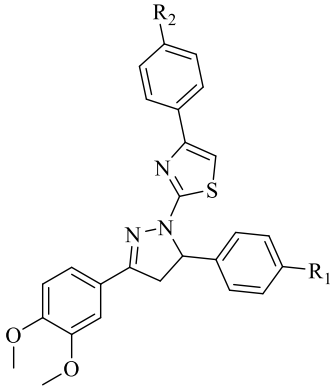
Compound 8; R= OC_2H_5
Compound 9; R= NH-C_6H_5



Compound 10



Compound 11

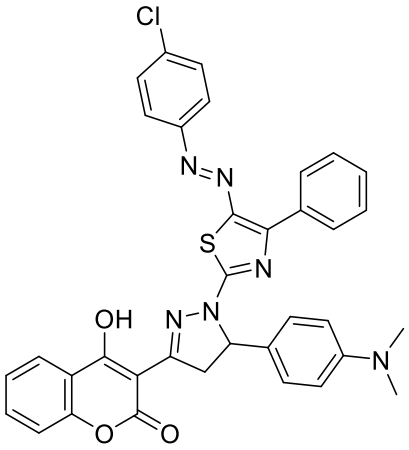


Compound 12; R_1= OCH_3, **R_2**= H
Compound 13; R_1= Cl, **R_2**= F

4.1.1.5 VEGFR inhibitors

It has been demonstrated that the vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are important players in both healthy and pathological angiogenesis, including cancer. VEGF-A controls angiogenesis and vascular permeability by activating the two receptors VEGFR-1 and VEGFR-2. On the other hand, VEGF-C/VEGF-D and their receptor, VEGFR-3, mainly regulate lymphangiogenesis. VEGFR-2, the main signal transducer for angiogenesis, preferentially uses the PLCγ-PKC-MAPK pathway for signalling. The VEGF-VEGFR system is a crucial target for anti-angiogenic therapy in cancer therapy, and it is also a desirable system for pro-angiogenic therapy in the management of ischemic disorders and neuronal degeneration (52).

In 2019, New thiazolyl-pyrazoline coumarin-based derivatives were synthesized and their anti-proliferative effects on five different human cell lines (breast MCF-7, lung A549, prostate PC3, liver HepG2, and normal melanocyte HFB4) were assessed in vitro. Compound **14** of this series displayed higher sensitivity towards MCF7 with IC_{50} = 5.41 μM compared to the reference drug doxorubicin (IC_{50} = 6.73 μM). Moreover, in vitro studies of the VEGFR-2 inhibition showed potent inhibition (IC_{50} = 0.034 μM) compared to sorafenib (IC_{50} = 0.019 μM) as a reference drug (6).



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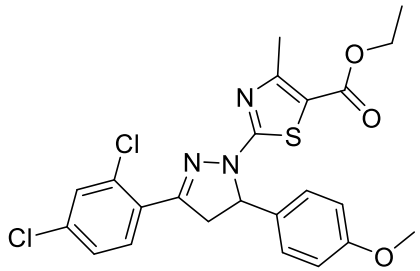
In 2022, thiazolyl-pyrazoline derivatives were synthesised and assessed for their potential as dual EGFR and VEGFR-2 inhibitors. An efficient strategy for overcoming the observed resistance in NSCLC is the concurrent inhibition of both EGFR and VEGFR. In addition, VEGFR-2 inhibition enhances the cytotoxic effect of EGFR inhibitors, whereas VEGFR-2 activation results in accelerated tumour growth independent of EGFR signalling, thereby facilitating the emergence of resistance to EGFR inhibitors. Compounds **15** and **16** of that series exhibited potent and selective inhibitory activity: EGFR (IC_{50} = 40.7 and 32.5 nM, respectively) and VEGFR-2 (IC_{50} = 78.4 and 43.0 nM, respectively) (31).



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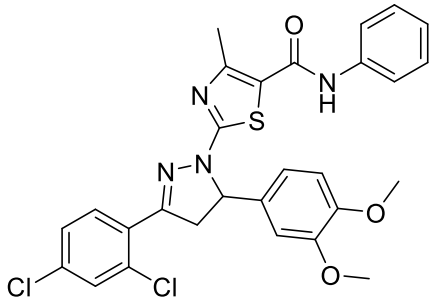

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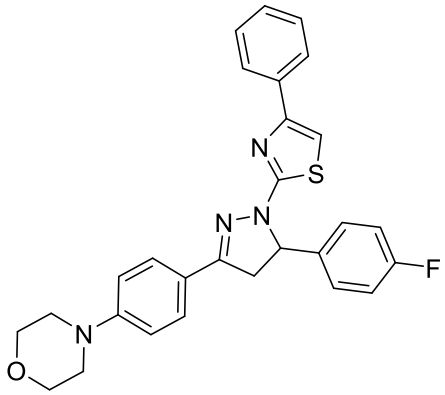
4.2 As acetylcholinesterase and carbonic anhydrase inhibitors

Memory loss and impairment in daily functioning are hallmarks of Alzheimer's disease (AD), a progressive neurodegenerative condition of the brain. Carbonic anhydrase (CA) is an enzyme that plays a crucial role in maintaining the balance of carbon dioxide and pH levels in various tissues and organs, including the brain. Additionally, recent research has shown that human carbonic anhydrases (hCAs) are crucial targets for the therapy of AD (53).

Belgin et. al, in 2020 synthesized a series of morpholino thiazolyl-pyrazoline that exhibit effective inhibition against hCA I with IC_{50} in the range of 11.61 ± 0.66–22.91 ± 0.27 nM. Compound **17,** without any substitution, was defined as the most significant and selective AChE inhibitor. Compound **18** exhibited the most potent and selective inhibition towards hCA II (54).



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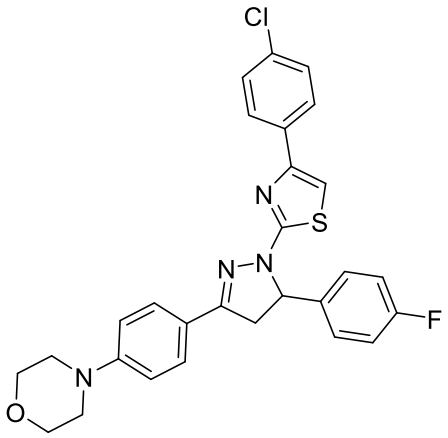

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4.3 As anti-oxidant and anti-inflammatory agents

Antioxidants and anti-inflammatory effects are closely interconnected. Antioxidants help mitigate oxidative stress, a driver of inflammation while modulating key inflammatory pathways and immune responses. Antioxidants help prevent or neutralize the damaging effects of reactive oxygen species (ROS) and free radicals in the body. These highly reactive molecules are produced as natural byproducts of cellular metabolism and can cause oxidative stress, leading to cellular damage and inflammation. Antioxidants donate electrons or hydrogen atoms to stabilize and neutralize these harmful species, reducing oxidative stress.

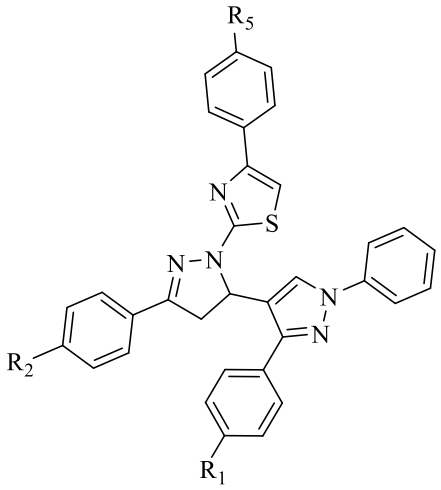
On the other hand, inflammation is a complex biological response triggered by various stimuli, such as infection, tissue injury, or immune system dysregulation. While acute inflammation is a normal protective response, chronic inflammation can lead to tissue damage and the development of various diseases, including cardiovascular diseases, neurodegenerative disorders, and certain cancers. Inflammation involves the release of pro-inflammatory mediators, such as cytokines, chemokines, and prostaglandins, which promote immune cell activation and tissue inflammation (55, 56).

The relationship between antioxidants and anti-inflammatory effects can be understood through several mechanisms. One of them is Scavenging Reactive Oxygen Species (ROS): Antioxidants can directly scavenge and neutralize ROS, thereby reducing oxidative stress and preventing the activation of pro-inflammatory pathways. By reducing oxidative damage, antioxidants indirectly contribute to the suppression of inflammation. Another mechanism is interaction with Anti-Inflammatory Enzymes. Some antioxidants can interact with specific enzymes involved in regulating inflammation, such as cyclooxygenase (COX) and lipoxygenase (LOX), which are responsible for synthesising pro-inflammatory mediators. By inhibiting these enzymes, antioxidants can reduce the production of inflammatory molecules (57).

From this point of view, Dattatraya et al., in 2020, synthesized a series of asymmetric thiazolyl pyrazolines, and their activity as antioxidants and anti-inflammatory was evaluated. Thiazolyl derivatives have the ability to capture radical species and inhibit them from causing injury by donating electrons to unstable free radicals to convert them into more stable species. The final compounds exhibited moderate to good H_2O_2 scavenging activity comparable to ascorbic acid, with excellent SOR scavenging activity (58).

Antioxidant activity result reveals that compound **19 b** (43.21%) showed excellent suppression of H_2O_2 radical inhibiting activity, reveals that compound **19 c** (48.95%) was exhibited excellent inhibition of NO radical compared to standard ascorbic acid (32.32%) according to the NO radical inhibiting activity result. In comparison to ascorbic acid, the compounds **19 a** (76.19 percent), **19 b** (90.41 %), **19 c** (85.71 %), and **19 d** (80.95 %) showed possible suppression of superoxide scavenging radical activity (74.07 %).

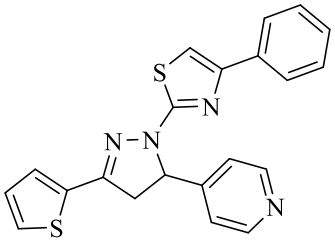
For the anti-inflammatory screening of the final compounds, **19 b** (91.74%) exhibited excellent anti-inflammatory activity compared to Diclofenac sodium (90.21%) as standard.



19	**R_1**	**R_2**	**R_3**
a	**H**	**H**	**H**
b	**CH_3**	**CH_3**	**H**
c	**H**	**CH_3**	**Cl**
d	**H**	**CH_3**	**CH_3**

4.4 As antimicrobial agents

Ozdemir et. al, in 2006 (59) developed 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline series. All of the compounds of this series showed effective antibacterial and antifungal activity when compared with reference drugs. Compounds **20** and **21** especially showed very high activity against *S. faecalis*, while compounds **22** showed strong activity. This series also showed significant activity against *A. hydrophila*, as compounds **20** and **22** showed very high activity.



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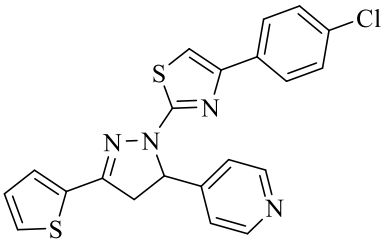

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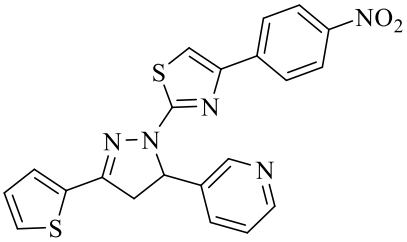
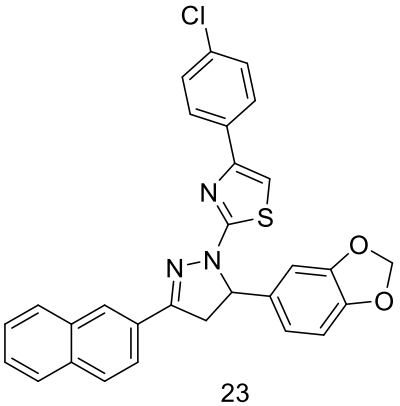


22

Mansour et. al, in 2019, developed a series of thiazolyl pyrazoline derivatives linked to benzo[1,3]dioxole moiety and investigated for biological properties as antimicrobial agents. Between this set, compound **23** showed interesting antimicrobial activity in addition to significant antifungal activity with inhibition zone 2.5 mm against A. funigatus. While compound **24** had a promising activity with MIC value of 0.115 mg/mL against S. aureus (60).



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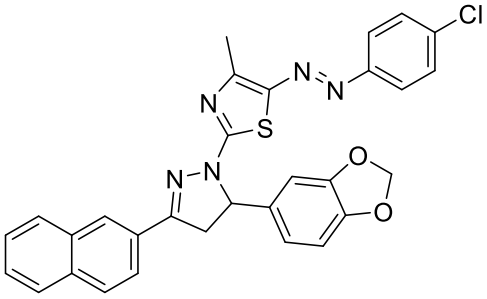
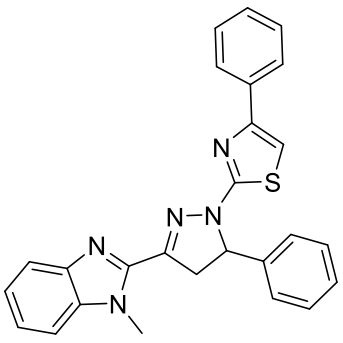


24

Nofal et al., in 2021 developed a new set of pyrazole fragments coupled with (N-substituted) benzimidazole or phenyl moieties in a pyrazol-thiazole-p-substituted phenyl scaffold. This series was designed based on the biological importance of thiazole as anti-microbial, pyrazole derivatives heavily researched heterocycles in anti-microbial treatment as Lonazolac, Fipronil, and Tolpiprazole drugs bearing pyrazole nucleus, and using benzimidazole as significant core in many anti-microbial commercial drugs (61-64). The resulting compounds were tested for their antibacterial abilities against Gram-positive bacteria (Staphylococcus aureus ATCC29213) and Gram-negative bacterium Escherichia coli (65). Compounds **25** and **26** showed no promising activity. Optimization and structural improvement are required for more effective antimicrobial analogues.



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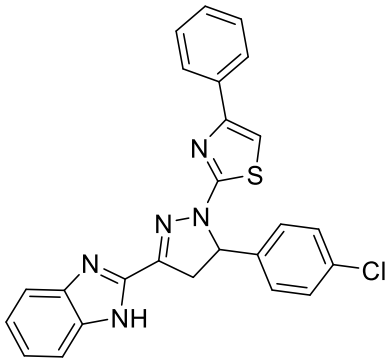

26

5.Conclusion

In conclusion, the hybridization of thiazole and pyrazoline heterocycles has emerged as a promising strategy in medicinal chemistry, leading to the development of novel hybrid scaffolds with diverse biological activities. The combination of these two heterocyclic frameworks has proven to be highly successful in creating compounds with enhanced potency, selectivity, and therapeutic potential. The synthesis of thiazole-pyrazoline hybrids has been achieved through various synthetic methodologies, including conventional approaches and modern techniques, allowing researchers to efficiently generate a wide range of hybrid molecules, enabling researchers to explore their biological properties. One of the key advantages of thiazole-pyrazoline hybrids is their ability to exhibit multitargeted activities. These compounds have demonstrated promising results in various biological assays, including anti-proliferative, antioxidant, antimicrobial, antiviral and anti-inflammatory activities.

Furthermore, the exploration of the mechanism of action of thiazole-pyrazoline hybrids has shed light on their mode of interaction with biological targets. These compounds have been found to modulate various signalling pathways and enzymatic activities, thereby affecting key cellular processes. The elucidation of their molecular targets has paved the way for further optimization and rational design of hybrid molecules with improved activity and reduced toxicity. Thiazole-pyrazoline hybrids have also demonstrated potential in overcoming drug resistance, a significant issue in the field of chemotherapy. The hybrids have exhibited synergistic effects when combined with existing drugs, leading to enhanced efficacy against drug-resistant strains. This highlights the potential of these hybrid scaffolds as adjuvants in combination therapy approaches. Further investigation regarding particular pharmacophoric features covering more chemical spaces around the thiazolyl-pyrazoline core and their effect on certain phenotypic, biological abnormalities was needed. Utilizing thiazolyl-pyrazoline moiety potentiates fruitfully the pharmacological activities, particularly regarding developing cancer-targeted therapeutics, which encourages researchers to design new compounds containing hybrid thiazolyl-pyrazoline scaffold. In conclusion, the hybridization of thiazole and pyrazoline heterocycles represents a promising approach in medicinal chemistry, leading to the discovery of novel hybrid scaffolds with diverse biological activities. The development of these hybrid molecules has demonstrated their potential as multitargeted agents against various diseases. Continued research in this area holds great promise for the future development of hybrid compounds with improved therapeutic outcomes.

- **Conflict of Interest**

  The authors declare no conflict of interest.

6. Reference

1. Chen T-C, Wu C-L, Lee C-C, Chen C-L, Yu D-S, Huang H-S. Structure-based hybridization, synthesis and biological evaluation of novel tetracyclic heterocyclic azathioxanthone analogues as potential antitumor agents. European journal of medicinal chemistry. 2015;103:615-27.
2. Teli G, Chawla PA. Hybridization of imidazole with various heterocycles in targeting cancer: a decade's work. ChemistrySelect. 2021;6(19):4803-36.
3. Gümüş M, Yakan M, Koca İ. Recent advances of thiazole hybrids in biological applications. Future Medicinal Chemistry. 2019;11(16):1979-98.
4. Sashidhara KV, Rao KB, Kushwaha P, Modukuri RK, Singh P, Soni I, et al. Novel chalcone–thiazole hybrids as potent inhibitors of drug resistant Staphylococcus aureus. ACS medicinal chemistry letters. 2015;6(7):809-13.
5. Gondru R, Sirisha K, Raj S, Gunda SK, Kumar CG, Pasupuleti M, et al. Design, Synthesis, In Vitro Evaluation and Docking Studies of Pyrazole-Thiazole Hybrids as Antimicrobial and Antibiofilm Agents. ChemistrySelect. 2018;3(28):8270-6.
6. Mohamed TK, Batran RZ, Elseginy SA, Ali MM, Mahmoud AE. Synthesis, anticancer effect and molecular modeling of new thiazolylpyrazolyl coumarin derivatives targeting VEGFR-2 kinase and inducing cell cycle arrest and apoptosis. Bioorganic chemistry. 2019;85:253-73.
7. Lévai A. Synthesis of pyrazolines by the reactions of α, β-enones with diazomethane and hydrazines. Chemistry of Heterocyclic Compounds. 1997;33(6):647-59.
8. Orrego-Hernández J, Cobo J, Portilla J. Chemoselective Synthesis of 5-Alkylamino-1H-pyrazole-4-carbaldehydes by Cesium-and Copper-Mediated Amination. European Journal of Organic Chemistry. 2015;2015(23):5064-9.
9. Maleki B, Azarifar D, Moghaddam KM, Hojati FS, Gholizadeh M, Salehabadi H. Synthesis and characterization of a series of 1, 3, 5-trisubstituted-2-pyrazolines derivatives using methanoic acid under thermal condition. Journal of the Serbian Chemical Society. 2009;74(12):1371-6.
10. Karabacak M, Altıntop MD, İbrahim Çiftçi H, Koga R, Otsuka M, Fujita M, et al. Synthesis and Evaluation of New Pyrazoline Derivatives as Potential Anticancer Agents. Molecules [Internet]. 2015; 20(10):[19066-84 pp.].
11. Nitulescu GM, Draghici C, Missir AV. Synthesis of new pyrazole derivatives and their anticancer evaluation. European Journal of Medicinal Chemistry. 2010;45(11):4914-9.
12. Thach T-D, Nguyen TM-T, Nguyen TA-T, Dang C-H, Luong T-B, Dang V-S, et al. Synthesis and antimicrobial, antiproliferative and anti-inflammatory activities of novel 1,3,5-substituted pyrazoline sulphonamides. Arabian Journal of Chemistry. 2021;14(11):103408.
13. Kini S, Gandhi AM. Novel 2-pyrazoline derivatives as potential antibacterial and antifungal agents. Indian journal of pharmaceutical sciences. 2008;70(1):105-8.
14. Dhonnar SL, Jagdale BS, Adole VA, Sadgir NV. PEG-mediated synthesis, antibacterial, antifungal and antioxidant studies of some new 1,3,5-trisubstituted 2-pyrazolines. Molecular Diversity. 2022.

15. Vijesh AM, Isloor AM, Shetty P, Sundershan S, Fun HK. New pyrazole derivatives containing 1, 2, 4-triazoles and benzoxazoles as potent antimicrobial and analgesic agents. European Journal of Medicinal Chemistry. 2013;62:410-5.
16. Kaplancıklı ZA, Özdemir A, Turan-Zitouni G, Altıntop MD, Can ÖD. New pyrazoline derivatives and their antidepressant activity. European journal of medicinal chemistry. 2010;45(9):4383-7.
17. Beyhan N, Kocyigit-Kaymakcioglu B, Gümrü S, Aricioglu F. Synthesis and anticonvulsant activity of some 2-pyrazolines derived from chalcones. Arabian Journal of Chemistry. 2017;10:S2073-S81.
18. Lv P-C, Li H-Q, Sun J, Zhou Y, Zhu H-L. Synthesis and biological evaluation of pyrazole derivatives containing thiourea skeleton as anticancer agents. Bioorganic & medicinal chemistr. 2010;18(13):4606-14.
19. Zhang Y, Wu C, Zhang N, Fan R, Ye Y, Xu J. Recent Advances in the Development of Pyrazole Derivatives as Anticancer Agents. International Journal of Molecular Sciences. 2023;24(16):12724.
20. Siddiqui N, Arshad MF, Ahsan W, Alam MS. Thiazoles: a valuable insight into the recent advances and biological activities. Int J Pharm Sci Drug Res. 2009;1(3):136-43.
21. Ibrahim SA, Rizk HF. Synthesis and biological evaluation of thiazole derivatives. Azoles-Synthesis, Properties, Applications and Perspectives: IntechOpen; 2020.
22. Li JJ, Li JJ. Cook-Heilbron thiazole synthesis. Name Reactions: A Collection of Detailed Reaction Mechanisms. 2003:82-.
23. Lingaraju GS, Swaroop TR, Vinayaka AC, Kumar KSS, Sadashiva MP, Rangappa KS. An easy access to 4, 5-disubstituted thiazoles via base-induced click reaction of active methylene isocyanides with methyl dithiocarboxylates. Synthesis. 2012;44(09):1373-9.
24. Ripain IHA, Ngah N. A brief review on the thiazole derivatives: Synthesis methods and biological activities. Malays J Anal Sci. 2021;25:257-67.
25. Bueno JM, Carda M, Crespo B, Cuñat AC, De Cozar C, León ML, et al. Design, synthesis and antimalarial evaluation of novel thiazole derivatives. Bioorganic & Medicinal Chemistry Letters. 2016;26(16):3938-44.
26. Merino P, Tejero T, Unzurrunzaga FJ, Franco S, Chiacchio U, Saita MG, et al. An efficient approach to enantiomeric isoxazolidinyl analogues of tiazofurin based on nitrone cycloadditions. Tetrahedron: Asymmetry. 2005;16(23):3865-76.
27. Franchetti P, Cappellacci L, Grifantini M, Barzi A, Nocentini G, Yang H, et al. Furanfurin and thiophenfurin: two novel tiazofurin analogs. Synthesis, structure, antitumor activity, and interactions with inosine monophosphate dehydrogenase. Journal of medicinal chemistry. 1995;38(19):3829-37.
28. Matsuya Y, Kawaguchi T, Ishihara K, Ahmed K, Zhao Q-L, Kondo T, et al. Synthesis of macrosphelides with a thiazole side chain: New antitumor candidates having apoptosis-inducing property. Organic Letters. 2006;8(20):4609-12.
29. André F, Ciruelos E, Rubovszky G, Campone M, Loibl S, Rugo HS, et al. Alpelisib for PIK3CA-mutated, hormone receptor–positive advanced breast cancer. New England Journal of Medicine. 2019;380(20):1929-40.
30. Al-Warhi T, Elimam DM, Elsayed ZM, Abdel-Aziz MM, Maklad RM, Al-Karmalawy AA, et al. Development of novel isatin thiazolyl-pyrazoline hybrids as promising antimicrobials in MDR pathogens. RSC advances. 2022;12(48):31466-77.

31. Abdelsalam EA, Abd El-Hafeez AA, Eldehna WM, El Hassab MA, Marzouk HMM, Elaasser MM, et al. Discovery of novel thiazolyl-pyrazolines as dual EGFR and VEGFR-2 inhibitors endowed with in vitro antitumor activity towards non-small lung cancer. Journal of Enzyme Inhibition and Medicinal Chemistry. 2022;37(1):2265-82.
32. Zhao M-Y, Yin Y, Yu X-W, Sangani CB, Wang S-F, Lu A-M, et al. Synthesis, biological evaluation and 3D-QSAR study of novel 4,5-dihydro-1H-pyrazole thiazole derivatives as BRAFV600E inhibitors. Bioorganic & Medicinal Chemistry. 2015;23(1):46-54.
33. Cross TG, Scheel-Toellner D, Henriquez NV, Deacon E, Salmon M, Lord JM. Serine/threonine protein kinases and apoptosis. Experimental cell research. 2000;256(1):34-41.
34. Edelman AM, Blumenthal DK, Krebs EG. Protein serine/threonine kinases. Annual review of biochemistry. 1987;56(1):567-613.
35. Thomson AW, Turnquist HR, Raimondi G. Immunoregulatory functions of mTOR inhibition. Nature Reviews Immunology. 2009;9(5):324-37.
36. Lin Z, Wang Z, Zhou X, Zhang M, Gao D, Zhang L, et al. Discovery of new fluorescent thiazole–pyrazoline derivatives as autophagy inducers by inhibiting mTOR activity in A549 human lung cancer cells. Cell Death & Disease. 2020;11(7):551.
37. Gschwind A, Fischer OM, Ullrich AJNRC. The discovery of receptor tyrosine kinases: targets for cancer therapy. Nature Reviews Cancer. 2004;4(5):361-70.
38. Dar AC, Shokat KM. The evolution of protein kinase inhibitors from antagonists to agonists of cellular signaling. Annual review of biochemistry. 2011;80(1):769-95.
39. Lamba V, Ghosh I. New directions in targeting protein kinases: focusing upon true allosteric and bivalent inhibitors. Current pharmaceutical design. 2012;18(20):2936-45.
40. Bennasroune A, Gardin A, Aunis D, Crémel G, Hubert PJCrioh. Tyrosine kinase receptors as attractive targets of cancer therapy. 2004;50(1):23-38.
41. Klijn J, Berns P, Schmitz P, Foekens J. The clinical significance of epidermal growth factor receptor (EGF-R) in human breast cancer: a review on 5232 patients. Endocrine reviews. 1992;13(1):3-17.
42. Roskoski Jr R. The ErbB/HER family of protein-tyrosine kinases and cancer. Pharmacological Research. 2014;79:34-74.
43. Al-Warhi T, Almahli H, Maklad RM, Elsayed ZM, El Hassab MA, Alotaibi OJ, et al. 1-Benzyl-5-bromo-3-hydrazonoindolin-2-ones as Novel Anticancer Agents: Synthesis, Biological Evaluation and Molecular Modeling Insights. Molecules [Internet]. 2023; 28(7).
44. Witton CJ, Reeves JR, Going JJ, Cooke TG, Bartlett JM. Expression of the HER1–4 family of receptor tyrosine kinases in breast cancer. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland. 2003;200(3):290-7.
45. Waks AG, Winer EP. Breast cancer treatment: a review. Jama. 2019;321(3):288-300.
46. Fox SB, Smith K, Hollyer J, Greenall M, Hastrich D, Harris AL. The epidermal growth factor receptor as a prognostic marker: results of 370 patients and review of 3009 patients. Breast cancer research and treatment. 1994;29:41-9.
47. Fakhry MM, Mattar AA, Alsulaimany M, Al-Olayan EM, Al-Rashood ST, Abdel-Aziz HA. New Thiazolyl-Pyrazoline Derivatives as Potential Dual EGFR/HER2 Inhibitors: Design, Synthesis, Anticancer Activity Evaluation and In Silico Study. Molecules. 2023;28(21):7455.
48. Lv P-C, Li D-D, Li Q-S, Lu X, Xiao Z-P, Zhu H-L. Synthesis, molecular docking and evaluation of thiazolyl-pyrazoline derivatives as EGFR TK inhibitors and potential anticancer agents. Bioorganic & Medicinal Chemistry Letters. 2011;21(18):5374-7.

49. George RF, Samir EM, Abdelhamed MN, Abdel-Aziz HA, Abbas SES. Synthesis and anti-proliferative activity of some new quinoline based 4,5-dihydropyrazoles and their thiazole hybrids as EGFR inhibitors. Bioorganic Chemistry. 2019;83:186-97.
50. Sever B, Altıntop MD, Radwan MO, Özdemir A, Otsuka M, Fujita M, et al. Design, synthesis and biological evaluation of a new series of thiazolyl-pyrazolines as dual EGFR and HER2 inhibitors. European Journal of Medicinal Chemistry. 2019;182:111648.
51. Fakhry MM, Mahmoud K, Nafie MS, Noor AO, Hareeri RH, Salama I, et al. Rational Design, Synthesis and Biological Evaluation of Novel Pyrazoline-Based Antiproliferative Agents in MCF-7 Cancer Cells. Pharmaceuticals. 2022;15(10):1245.
52. Byzova TV, Goldman CK, Pampori N, Thomas KA, Bett A, Shattil SJ, et al. A mechanism for modulation of cellular responses to VEGF: activation of the integrins. Molecular cell. 2000;6(4):851-60.
53. Jang BG, Yun S-M, Ahn K, Song JH, Jo SA, Kim Y-Y, et al. Plasma carbonic anhydrase II protein is elevated in Alzheimer's disease. Journal of Alzheimer's Disease. 2010;21(3):939-45.
54. Sever B, Türkeş C, Altıntop MD, Demir Y, Beydemir Ş. Thiazolyl-pyrazoline derivatives: In vitro and in silico evaluation as potential acetylcholinesterase and carbonic anhydrase inhibitors. International Journal of Biological Macromolecules. 2020;163:1970-88.
55. Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. The molecular targets and therapeutic uses of curcumin in health and disease. 2007:105-25.
56. Wang L, Tu Y-C, Lian T-W, Hung J-T, Yen J-H, Wu M-J. Distinctive antioxidant and antiinflammatory effects of flavonols. Journal of agricultural and food chemistry. 2006;54(26):9798-804.
57. Zhang H, Tsao R. Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. Current Opinion in Food Science. 2016;8:33-42.
58. Raut DG, Lawand AS, Kadu VD, Hublikar MG, Patil SB, Bhosale DG, et al. Synthesis of Asymmetric Thiazolyl Pyrazolines as a Potential Antioxidant and Anti-Inflammatory Agents. Polycyclic Aromatic Compounds. 2022;42(1):70-9.
59. Özdemir A, Turan-Zitouni G, Asım Kaplancıklı Z, Revial G, Güven K. Synthesis and antimicrobial activity of 1-(4-aryl-2-thiazolyl)-3-(2-thienyl)-5-aryl-2-pyrazoline derivatives. European Journal of Medicinal Chemistry. 2007;42(3):403-9.
60. Mansour E, Aboelnaga A, Nassar EM, Elewa SI. A new series of thiazolyl pyrazoline derivatives linked to benzo[1,3]dioxole moiety: Synthesis and evaluation of antimicrobial and anti-proliferative activities. Synthetic Communications. 2020;50(3):368-79.
61. Singh N, Pandurangan A, Rana K, Anand P, Ahamad A, Tiwari AK. Benzimidazole: A short review of their antimicrobial activities. Int Current Pharm J. 2012;1(5):119-27.
62. Bakthavatchala Reddy N, Zyryanov GV, Mallikarjuna Reddy G, Balakrishna A, Padmaja A, Padmavathi V, et al. Design and synthesis of some new benzimidazole containing pyrazoles and pyrazolyl thiazoles as potential antimicrobial agents. Journal of Heterocyclic Chemistry. 2019;56(2):589-96.
63. Sharifzadeh B, Mahmoodi NO, Mamaghani M, Tabatabaeian K, Chirani AS, Nikokar I. Facile regioselective synthesis of novel bioactive thiazolyl-pyrazoline derivatives via a three-component reaction and their antimicrobial activity. Bioorganic & medicinal chemistry letters. 2013;23(2):548-51.
64. Das J, Chen P, Norris D, Padmanabha R, Lin J, Moquin RV, et al. 2-Aminothiazole as a Novel Kinase Inhibitor Template. Structure− Activity Relationship Studies toward the Discovery of N-(2-Chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl)]-2-methyl-4-

pyrimidinyl] amino)]-1, 3-thiazole-5-carboxamide (Dasatinib, BMS-354825) as a Potent pan-Src Kinase Inhibitor. Journal of medicinal chemistry. 2006;49(23):6819-32.
65. Nofal ZM, Srour AM, Mansour NM, El-Karim SSA. Synthesis of Novel Heterocyclic Compounds Containing Thiazolyl-Pyrazoline Moiety from Chalcone Derivatives. Polycyclic Aromatic Compounds. 2022;42(8):5411-21.