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POLYFUNCTIONAL THIAZOLE/THIAZOLIDINONE DERIVATIVES AS A NEW CLASS OF HETEROCYCLIC COMPOUNDS WITH NOVEL MECHANISMS OF ANTICANCER ACTIVITY

Thiazole and thiazolidinone derivatives constitute an important class of heterocyclic compounds, widely investigated in modern medicinal chemistry for their diverse biological activities and significant potential for structural modification. Particular attention has focused on their anticancer properties and the design of multifunctional hybrid molecules with improved pharmacological profiles. This review summarizes recent advances in the synthesis and biological evaluation of functionally substituted condensed and non-condensed thiazole/thiazolidinone derivatives with anticancer activity. Available literature demonstrates that many of these compounds exhibit pronounced cytotoxic and pro-apoptotic effects across various tumor models. Their biological activity is associated with interactions with multiple molecular targets, including PPARγ receptors, integrins, PI3K/mTOR signaling pathways, histone deacetylases, matrix metalloproteinases, STAT3, and Pim-kinases. These multitarget mechanisms highlight the potential of these heterocyclic scaffolds for developing innovative anticancer agents. Analysis of structure–activity relationships has revealed promising directions for further optimization of the lead compounds. Overall, thiazole and thiazolidinone derivatives remain attractive platforms for the rational design of new anticancer drugs with improved selectivity and reduced toxicity.

Keywords: thiazole, thiazolidinone, antitumor activity, biotargets, hybrid molecules.

Drug design is an extremely lengthy, labor-intensive, and multi-stage process that takes many years and requires enormous financial investment. One of the key stages in drug development that is closely related to modern pharmaceutical and medical chemistry is the search for and optimization of lead compounds. Identification of specific compounds is the starting point for obtaining molecules with the necessary activity, selectivity, and acceptable ADMET parameters (absorption, distribution, metabolism, elimination, and toxicity).

Sources of lead compounds may include the endogenous ligands, in particular enzyme substrates, transport proteins, or receptor agonists; other ligands, including existing drugs, compounds isolated during drug metabolism, or substances at clinical trial stages; derivatives identified through screening of chemical libraries, including naturally occurring compounds [1].

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The search for lead compounds is based on using two key elements: high-throughput screening and synthetic approaches, which include target-oriented synthesis, synthesis of focused libraries, diversity-oriented synthesis (DOS), etc. [2]. In turn, DOS includes the following strategies: multicomponent reactions, cycloaddition reactions, cyclization and tandem reactions, the concept of combining functional groups, and the strategy of privileged structures [3].

It should be noted that thiazole derivatives and their functional derivatives are a class of compounds that can serve as the basis for obtaining lead compounds, as they possess not only a wide spectrum of biological activity but also significant potential for further chemical modification. The thiazole core forms the basis of numerous naturally occurring compounds, including the glycosidic anticancer antibiotic bleomycin; macrolides latrunculin A, leinamycins, and langbiabelins; cyclic peptides argyrin A, gracyptide, promotiocin, and microcyclamides; linear peptides tubulysins; and diterpenes eretazoles, which are currently registered as anticancer drugs or are at preclinical study stages [4].

Among natural thiazole-based compounds and their functional derivatives with antimicrobial activity, β-lactam antibiotics of the penicillin and monobactam series, thiopeptide antibiotics (nocathiacin, nosiheptide, and thiomuracin A), as well as cystothiazoles A–F with notable antifungal activity have been identified. On the other hand, thiazole derivatives form the basis of numerous synthetic drugs, including pramipexole as a dopamine receptor agonist used for the treatment of Parkinson's disease and Restless Legs Syndrome (RLS); HIV-1 protease inhibitor ritonavir and CYP3A4 inhibitor cobicistat, used in the treatment of HIV infection; H2-histamine receptor antagonists nizatidine and famotidine as anti-ulcer drugs; antihelmintic drugs thiabendazole, levamisole, and tetramisole; riluzole as a therapy for amyotrophic lateral sclerosis; antidiabetic drugs pioglitazone, troglitazone, rosiglitazone, lobeglitazone as PPARγ receptor agonists; non-purine xanthine oxidase inhibitor febuxostat as an antigout agent; non-steroidal anti-inflammatory drug meloxicam; tyrosine kinase inhibitor dasatinib as an anticancer agent; coenzyme vitamin B1 cocarboxylase; sulfonamide drugs sulfathiazole and phthalylsulfothiazole; and radiopharmaceutical for Alzheimer's disease diagnosis flutemetamol (^{18}F) [5].

Among the functional thiazole derivatives, there is also a large number of synthetic compounds at preclinical research stages, including clomethiazole as an allosteric modulator of type A GABA receptors for the treatment of alcohol withdrawal syndrome; niridazole as an antischistosomal agent; the aldose reductase inhibitor zopolrestat, used in the treatment of diabetic complications; teneligliptin, balaglitazone, mitoglitazone, 2,4-thiazolidinedione, and galicin as agents for the treatment of type 2 diabetes; letosteine as a mucolytic agent in the treatment of bronchopneumopathies; the hypolipidemic agent netoglitazone; pidotimod as an immunomodulatory agent; the A2 adenosine receptor agonist tozadenant as an agent for the treatment of cocaine addiction; efatutazone, quizartinib, pidnarulex, and epalrestat as anticancer agents; talarozole as an agent for the treatment of psoriasis and other skin diseases; piprozoline in the therapy of biliary tract pathology and dyspepsia; the hypouricemic agent dotinurad; ebopiprant as an agent used in preterm labor; and the JNK kinase inhibitor bentamipod for the treatment of endometriosis [6].

Each of the above-mentioned drugs or potential "lead-like compounds" has been designed using completely different approaches; however, what they all have in common is a process that involves chemical modification of thiazole derivatives, followed by obtaining molecules possessing certain biological activity and serving as the basis for the construction of lead compounds [7].

Considering the arguments presented, the search for new biologically active compounds with anticancer activity among multifunctional derivatives based on thiazole/thiazolidinone is a justified and promising direction in modern medical and pharmaceutical chemistry.

A critical review of the literature on the synthesis of thiazole and thiazolidinone derivatives, their structural analogs, and the evaluation of anticancer activity was carried out. Special attention was paid to identifying molecular biotargets, such as PPARγ receptors, integrins, PI3K/mTOR enzymes, HDAC, MMP, STAT3, Pim-kinases, and other signaling targets that determine the mechanisms of cytotoxic, pro-apoptotic, and anticancer action. We attempted to systematize modern approaches to assessing the anticancer potential of many functio-

nally substituted condensed and non-condensed derivatives based on thiazole/4-thiazolidinone, including hybrid molecules containing the fragments of natural compounds in their structure.

While the literature extensively covers the synthesis and anticancer screening of 4-thiazolidinone derivatives, few studies investigate their specific biological mechanisms. Modern medicinal chemistry aims to identify lead compounds for drug development; therefore, simply finding highly active agents is not enough. These compounds must undergo rigorous preclinical and clinical trials, as well as toxicity assessments. Only after these extensive studies can we determine if a compound is truly viable for medical practice. Accordingly, this review is devoted to the analysis of the literature on the mechanisms of biological activity of 4-thiazolidinone derivatives exemplified by the existing drugs or compounds at the preclinical trial stage or other in-depth studies.

Among the 4-thiazolidinone-based derivatives, the most well-known drugs are glitazones, a group of antidiabetic agents with a well-established mechanism of biological activity. The cellular mechanism of the action of glitazones is mediated by binding to and activating the peroxisome proliferator-activated receptor gamma (PPARγ), a nuclear receptor that acts as a transcription factor, regulating the transcription and expression of specific genes [8—10]. Together with other isoforms, such as PPARα and PPARβ, it belongs to the same group as thyroid hormone and steroid receptors. The expression level of PPARγ is the highest in adipocytes, intestinal cells, and macrophages, but very low in most other tissues, including muscle tissue. Endogenous ligands for PPARγ are long-chain unsaturated fatty acids and prostanoids. Upon activation, PPARγ heterodimerizes with the retinoid X receptor, and the activated complex subsequently binds to specific DNA segments to induce transcription of PPAR-responsive elements [11].

In addition to metabolic effects, PPARγ plays an important role in the regulation of cell proliferation, differentiation, and apoptosis, which determines its involvement in carcinogenesis. The dysregulation of PPARγ expression or activity is associated with the development and progression of several types of malignant tumors, including colorectal, breast, prostate, and lung cancers. The activation of PPARγ in some models can suppress tumor cell proliferation and induce apoptosis; however, under other conditions, overexpression of this receptor promotes lipid accumulation, remodeling of the tumor microenvironment, and the formation of a pro-tumorigenic phenotype. In particular, PPARγ receptors affect malignant tumor growth by suppressing cancer cell proliferation, promoting apoptosis, and inducing intercellular adhesion and inflammation in the tumor microenvironment [12]. This dual role of PPARγ makes it a promising yet complex target for the development of new anticancer agents among 4-thiazolidinone derivatives.

It should be noted that not only glitazones but also other 4-thiazolidinone derivatives have affinity for PPARγ receptors. For example, in studies by Szychowski et al. [13], functionalized thiazolidinone derivatives were shown to exhibit anticancer activity against the human squamous cell carcinoma line SCC-15 with the involvement of PPARγ receptors.

One of the well-studied biological activities of thiazolidinone derivatives and their structural analogs is their anti-inflammatory effect [14]. The most extensively studied representative is darbofelon, a dual inhibitor of prostaglandin PGF2R and leukotriene LTB4 synthesis. Darbofelon selectively inhibits cyclooxygenase-2 (COX-2) (IC_{50} 0.19 μM) while COX-1 is inhibited significantly less (IC_{50} 20 μM). Preclinical studies have shown no ulcerogenic effect upon its oral administration [15], and the drug is currently in Phase III clinical trials for the treatment of rheumatoid arthritis. Darbofelon's selectivity for COX isoforms significantly exceeds that of meloxicam (COX-1: IC_{50} 36.6 μM; COX-2: IC_{50} 4.7 μM) [15].

Importantly, in addition to its pronounced anti-inflammatory activity, darbofelon is characterized by notable anticancer activity. Ye et al. [16] demonstrated its dose-dependent suppression of cell viability in the human non-small cell lung carcinoma line NCI-H460, disruption of the cell cycle, and induction of apoptosis through the activation of caspases-3 and -8; a similar effect was observed for its structural analog (PD0167570).

Among the thiazolidinone derivatives and structural analogs, a large number of compounds with significant anticancer effects have also been identified [17]. Most studies on thiazolidinone and thiazole derivatives focus on in vitro cytotoxicity rather

than specific anticancer mechanisms. Identifying biological targets remains difficult because tumor development involves complex, poorly understood enzymatic networks. Despite these challenges, researchers have successfully identified probable biotargets for several derivatives in this class. In particular, some thiazolidinone derivatives and structural analogs have been shown to possess antidiabetic and anti-inflammatory activity combined with anticancer activity. In addition, the quinoxaline-thiazolidinone derivative was identified as a highly active inhibitor of gamma phosphoinositide 3-kinase (PI3K), an enzyme that plays a key role in regulating tumor growth [18]. This compound selectively inhibits the enzymatic activity of PI3K gamma, as well as its mediated signaling system and chemotaxis in vitro and in vivo. The compound also showed moderate activity against other PI3K isoforms. The structurally related pyridinylquinoline-thiazolidinone derivative was identified as a dual PI3K/mTOR inhibitor. This compound is currently in Phase I clinical trials in patients with solid tumors or lymphomas [19]. Moreover, recently published clinical study results have demonstrated that the derivative exhibits cytotoxic activity against head and neck squamous cell carcinoma in mouse xenograft models [20].

A large number of biologically active compounds target necroptosis, an alternative form of programmed cell death, contributing to oncogenesis and metastasis [21]. Zheng et al. [22] identified highly active necroptosis inhibitors among thiazolidinone-thiazole-pyrazole hybrid molecules.

Dayam et al. [23] identified a highly active inhibitor of the integrin αVβ3 among the 2-arylimino-5-ylidene-4-thiazolidinone derivatives (IC_{50} 0.03 μM). Integrin αVβ3 is considered a potential target for biologically active compounds, as its abnormal expression is associated with various pathological conditions, including cancer angiogenesis [24].

Among derivatives based on 2-thioxo-4-thiazolidinone (rhodanine), several highly active compounds with anticancer activity have also been identified, and for some of them, the mechanisms of biological activity have been thoroughly established. In particular, the 5-ylidene-3-phenylrhodanine derivative containing a cinnamaldehyde fragment in its structure is capable of stabilizing the binding of integrin αMβ2 with its endogenous ligands proMMP-9 and fibrinogen. The compound inhibits αMβ2-dependent in vitro cell migration and inflammation-induced neutrophil migration in vivo [25]. Also, derivative 1.153 suppressed the growth of leukemia and lymphoma xenografts in mice and significantly prolonged their survival. Further studies on the activity of the compound against various types of leukemia, particularly lymphomas, are ongoing [26].

The rhodanine-benzimidazole derivative was identified as a selective inhibitor of Pim-1, -2, and -3 kinases with IC_{50} values of 16, 13, and 6.4 nM, respectively. Moreover, the compound inhibited the proliferation of solid tumor and hematologic cancer cell lines at submicromolar concentrations. In the studied cell lines, the compound inhibited phosphorylation of Pim signaling substrates, disrupted the cell cycle, and induced apoptosis [27].

Vatolin et al. [28] identified the 5-ylidene-3-phenylrhodanine derivative as an inhibitor of protein disulfide isomerase (PDI). It was established that multiple myeloma cells produce much more disulfide-containing proteins compared to other cells. Inhibition of PDI, which is key for protein folding in the endoplasmic reticulum (ER), induces ER stress, subsequently leading to the death of this tumor cell type [29]. The compound was shown to bind PDI A1, A3, and A4 in multiple myeloma cells and demonstrated approximately 100-fold stronger inhibition of this enzyme compared to the known inhibitors PACMA 31 and LOC14 [27].

Huang et al. [30] identified the rhodanine derivative as a c-Myc inhibitor. c-Myc heterodimerizes with the Max-interacting protein, resulting in transactivation of downstream target genes in leukemogenesis [31]. The rhodanine-carboxylic acid derivative was identified as an inhibitor of the interaction between the BH3 domain and Bcl-xL [32], which is important for the induction of apoptosis [33].

Among rhodanine-based derivatives, the compound was also identified as a highly active inhibitor of JNK-stimulating phosphatase-1 (JSP-1) [34]. JSP-1 phosphatase belongs to the class of atypical dual-specificity phosphatases, which regulate various cellular processes, including growth, proliferation, differentiation, metabolism, immune response, cell–cell adhesion, and cell–matrix contacts. In the search for potential anticancer agents, JSP-1 phosphatase is an interesting target, particu-

larly for cancer types associated with the dysfunction of the Jnk1 signaling system [35].

Carter et al. [36] reported the rhodanine derivative as a highly active inhibitor of tumor necrosis factor alpha (TNF-α). TNF-α, a pleiotropic cytokine, plays a central role in inflammation and immune system homeostasis and is involved in a range of pathological states, including chronic inflammation, autoimmune diseases, and cancer [37, 38].

Among the thiazole derivatives, several highly active anticancer agents with established mechanisms of action have also been identified. Anh et al. [39] identified 2-(4-chlorobenzamido)-N-hydroxythiazole-4-carboxamide as a highly effective histone deacetylase (HDAC) inhibitor. The IC_{50} of the compound was 0.033 μM, comparable to that of a typical inhibitor of this enzyme, N-hydroxy-N'-phenyl-octanediamide (vorinostat) (IC_{50} 0.025 μM). It is known that the overexpression of various classes of HDACs increases cell proliferation and blocks apoptosis while simultaneously preventing cell differentiation, and contributes to angiogenesis and cell migration [40].

Ge et al. [41] synthesized a series of thiazole derivatives, among which one compound exhibited the highest inhibitory activity against matrix metalloproteinases (MMP) 2 and 8. These enzymes play a role in the extracellular matrix remodeling, proteolytic degradation of the extracellular matrix, disruption of cell–cell and cell–matrix interactions, cancer cell migration, and angiogenesis [42].

In the work by Hu et al. [43], thiazole derivatives were reported to disrupt the Hec1/Nek2 interaction — critical mitotic regulators that ensure proper chromosome segregation, whose overexpression is often observed in cancers with poor prognosis.

Wilson et al. [44] synthesized a series of thiophene-2-carboxamides containing a 2-aminothiazole fragment and studied their ability to bind urokinase, a key enzyme involved in metastasis. The authors identified several compounds from this class that exhibited inhibitory activity against this enzyme in the submicromolar range.

In several studies, certain condensed thiazole derivatives were also shown to exhibit significant anticancer activity, and their molecular targets were identified. Shen et al. [45] synthesized a triterpenoid orodonin derivative containing a thiazole fragment that demonstrated strong inhibitory activity against signal transducer and activator of transcription 3 (STAT3). Ali et al. [46] synthesized para-cyclophenyl-thiazole-naphthoquinone derivatives with high anticancer activity against SK-MEL-5 melanoma cells, and potent inhibitory activity against certain cyclin-dependent kinase isoforms.

Xie et al. [47] synthesized a benzothiazole derivative with antiproliferative activity against HCT-116 colon carcinoma, MCF-7 breast adenocarcinoma, U87 MG glioma, and A549 epithelial lung carcinoma cell lines, and potent inhibitory activity toward the PI3K/mTOR signaling pathway. Luke et al. [48] reported the synthesis of thiazolopyrimidine derivatives containing a pyrazole fragment, identifying a highly active compound that exhibited strong inhibitory activity against the tyrosine kinase receptor Tie2.

It is noteworthy that Tie2 overexpression is observed in tumor vasculature. Also, Tie2 is expressed outside the vascular system in various cancers, including leukemia, gastric cancer, breast cancer, and glioma [49]. Among thiazolo[3,2-a] pyrimidine derivatives, a highly active compound was identified, showing strong DNA-binding properties that exceeded those of doxorubicin used as a control, as reported by Al-Rashood et al. [50].

In conclusion, many thiazole/thiazolidinone derivatives have been shown to exert anticancer activity both in vitro and in vivo via the inhibition of the key molecules involved in regulating apoptosis, necroptosis, cell adhesion, and metastasis. Many of these derivatives can interact with specific molecular targets, which makes them promising candidates for further optimization and the development of new anticancer therapeutics.

Considering the above, thiazole/thiazolidinone derivatives and their structural analogs possess significant synthetic and pharmacological potential for research aimed at identifying potential "lead-like" molecules as a basis for the development of novel anticancer drugs.

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ПОЛІФУНКЦІОНАЛЬНІ ПОХІДНІ ТІАЗОЛУ/ТІАЗОЛІДИНОНУ ЯК НОВІ КЛАСИ ГЕТЕРОЦИКЛІЧНИХ СПОЛУК З НОВИМИ МЕХАНІЗМАМИ РЕАЛІЗАЦІЇ ПРОТИПУХЛИННОЇ АКТИВНОСТІ

Похідні тіазолу та тіазолідинону є важливим класом гетероциклічних сполук, які активно досліджуються в сучасній медичній та фармацевтичній хімії завдяки широкому спектру біологічної активності та значному потенціалу для структурної модифікації. Особливий інтерес викликають їхні протипухлинні властивості та можливість створення поліфункціональних гібридних молекул з покращеними фармакологічними характеристиками. У даному огляді узагальнено сучасні дані щодо синтезу та біологічного дослідження функціонально заміщених конденсованих і неконденсованих похідних тіазолу та тіазолідинону з протипухлинною активністю. Проаналізовано літературні джерела, що демонструють виражену цитотоксичну та проапоптотичну активність багатьох представників цього класу сполук у різних пухлинних моделях. Показано, що їх біологічна дія пов'язана з взаємодією з низкою молекулярних мішеней, зокрема рецепторами PPARγ, інтегринами, сигнальними шляхами PI3K/mTOR, гістондезацетилазами, матриксними металопротеїназами, STAT3 та Pim-кіназами. Такий мультитаргетний механізм дії підкреслює значний потенціал цих гетероциклічних систем у створенні нових протипухлинних препаратів. Аналіз залежностей «структура–активність» дозволяє визначити перспективні напрямки подальшої оптимізації цих сполук як базових структур. Отже, похідні тіазолу та тіазолідинону залишаються привабливою платформою для раціонального дизайну нових протиракових агентів з підвищеною селективністю та зниженою токсичністю.

Ключові слова: тіазол, тіазолідинон, протипухлинна активність, біологічні мішені, гібридні молекули.