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5-ARYLIDENE DERIVATIVES OF 3-(BENZO[*d*]THIAZOL-2-YLAMINO)-2-THIOXOTHIAZOLIDIN-4-ONE AS POTENTIAL ANTINEOPLASTIC AGENTS – *IN SILICO* EVALUATION

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Ключові слова: *роданін, бензотіазол, 5-ариліденпохідні, біологічна активність, розробка ліків, in silico прогноз, антинеопластичні засоби, SAR-аналіз*

Abstract. 5-Arylidene derivatives of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one as potential antineoplastic agents – *in silico* evaluation. Mosula L.M., Zhmura I.O., Mosula V.S. *Computer modeling and in silico prediction of molecular properties are rational approaches in early Drug Development, facilitating the targeted synthesis. One of the promising scaffold for the Drug Design is the rhodanine cycle due to the possibility of introducing substituents in positions 3 and 5. The aim of the work is to study the spectrum of biological activity of a series of 5-arylidene derivatives of 3-(benzo[d]thiazol-2-ylamino)-2-thioxothiazolidin-4-one, predict the affinity for therapeutic targets and establish their possible affiliation to certain codes according to the Anatomical Therapeutic Chemical Classification System of drugs, and predict possible toxicity of hit compounds via the online services. The investigated series of compounds consists of 21 derivatives. In silico prediction was carried out with the use of the web resources SuperPred 3.0, ProTox 3.0. A wide spectrum of biological activity of the derivatives of the series with a predominant antitumour effect is demonstrated. The group structural similarity of compounds to antineoplastic and immunomodulating agents was established. A high probability of group-level efficacy is predicted for the antitumor therapy targets: Krüppel-like factor 5, Nuclear factor erythroid 2-related factor 2, and DNA-(apurinic/apyrimidinic site) lyase. Compounds 3 ((ethyl (E)-4-(2-(2-((3-(benzo[d]thiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)-4-chlorophenoxy)acetamido)benzoate)), 4 ((E)-2-(2-((3-(benzo[d]thiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)-4-chlorophenoxy)-N-(4-sulfamoylphenyl)acetamide) and 9 ((E)-2-(2-((3-(benzo[d]thiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)-4,6-dimethylphenoxy)acetamide) can be considered as hit compounds. With high predictive model accuracy, their potential impact on the specified targets is 99.43%, 95.88%, and 96.92%, respectively. Compound 3 is a potential multi-hitter. The obtained results confirmed the viability of further in vitro, in vivo research.*

Реферат. 5-Ариліденпохідні 3-(бензо[*d*]тіазол-2-іламіно)-2-тіоксотіазолідин-4-ону як потенційні протипухлинні агенти - оцінка *in silico*. Мосула Л.М., Жмура І.О, Мосула В.С. *На початкових етапах створення ліків раціональним є використання комп'ютерного моделювання та in silico прогнозування властивостей молекул, що сприяє цілеспрямованому синтезу. Одним з перспективних структурних «каркасів» для дизайну ліків є роданіновий цикл завдяки можливості введення замісників у 3 і 5 положення. Мета роботи – дослідити спектр біологічної активності ряду 5-ариліденпохідних 3-(бензо[d]тіазол-2-іламіно)-2-тіоксотіазолідин-4-ону, спрогнозувати афінність до терапевтичних мішеней та встановити їх можливу приналежність до певних кодів згідно з анатомо-терапевтичною хімічною класифікацією лікарських засобів, а також передбачити можливу токсичність «сполук-хітів» за допомогою онлайн-сервісів. Досліджуваний ряд сполук містить 21 похідне. In silico прогнозування було проведено за допомогою веб-ресурсів SuperPred 3.0, ProTox 3.0. Продемонстровано потенційно широкий спектр біологічної активності серії похідних з переважаючим протипухлинним ефектом. Установлено групову структурну подібність серії похідних до антинеопластичних та імуномодулюючих лікарських засобів. З високою ймовірністю передбачається групова ефективність стосовно мішеней протухлинної терапії: Krüppel-like factor 5, Nuclear factor erythroid 2-related factor 2 і DNA-(apurinic or apyrimidinic site) lyase. Сполуки 3 (етил (E)-4-(2-(2-((3-(бензо[d]тіазол-2-іламіно)-4-оксо-2-тіоксотіазолідин-5-іліден)метил)-4-хлорофеноксі)ацетамідо)бензоат), 4 ((E)-2-(2-((3-(бензо[d]тіазол-2-іламіно)-4-оксо-2-*

тіоксотіазолідин-5-іліден)метил)-4-хлорофенокси)-N-(4-сульфамоїлфеніл)ацетамід) і 9 ((E)-2-(2-((3-(бензо[d]тіазол-2-іламіно)-4-оксо-2-тіоксотіазолідин-5-іліден)метил)-4,6-диметилфеноксі)ацетамід) можна розглядати як «сполуки-хіти». При високій точності моделей прогнозування їх потенційний вплив на зазначені мішені становить 99,43%, 95,88%, 96,92%, відповідно. Сполука 3 є потенційним мультихітером. Одержані результати підтвердили доцільність подальших in vitro, in vivo досліджень.

Increasing the efficiency of the search for new biologically active compounds (BACs), decreasing the terms of their implementation is only possible if effective pre-experimental studies are carried out. In recent years, researchers have been focused on the use of new approaches to Drug Development, such as exploring the possibilities of the use of targeted synthesis of new substances with potential pharmacological properties on the basis of the modern *in silico* technologies based on the relationship between chemical structure and biological activity. The "structure – activity"relationship (SAR analysis) is a great method for Drug Development, from the evaluation of drug targets to the improvement of the properties of a molecule [1]. Rhodanine derivatives with a benzothiazole moiety in the molecules are convenient objects of study. They are characterised by antitumour, antiviral and anti-tuberculosis activity [2].This leads to the logical conclusion of the viability of their use for the targeted design of highly active substances.

The aim of the work is to study the spectrum of biological activity of a series of 5-arylidene derivatives of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one, predict the affinity for therapeutic targets and establish their possible affiliation to certain codes according to the Anatomical Therapeutic Chemical Classification System (ATC) of drugs, and predict possible toxicity of hit compounds via the online services.

MATERIALS AND METHODS OF RESEARCH

For the *in silico* study we used some earlier synthesized (compounds 1-6) with previously confirmed *in vitro* antitumour activity [2] and virtually modelled (compounds 7-21) derivatives on the basis of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one (Fig. 1).

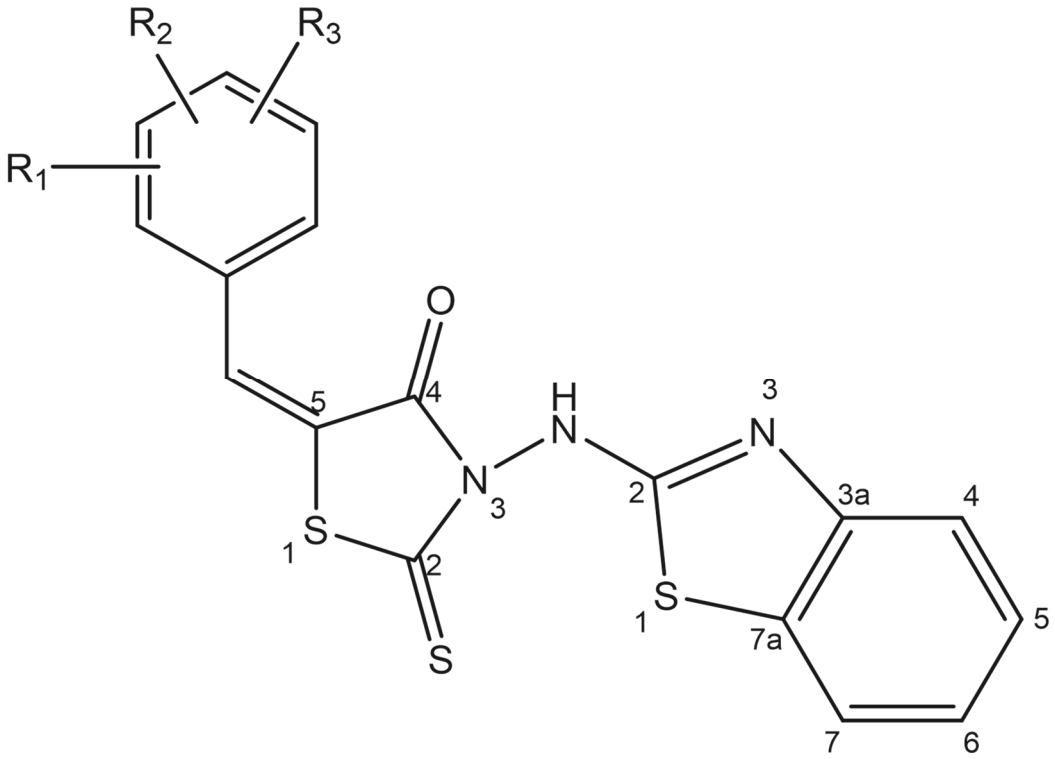


Fig. 1. General structural formula of differentially substituted 5-arylidene derivatives of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one

Previous *in silico* studies of the physicochemical and pharmacokinetic properties of the molecules confirmed the prospects of searching for BACs among rhodanine derivatives with a benzothiazole fragment in the molecules. Prediction of ADME properties of compounds in a series, performed on the

Swiss ADME online platform, described by us earlier [3]. In this study, we describe the impact of variously substituted arylidene fragments introduced at position 5 of the rhodanine ring on the biological activity of the compounds, and present the results of *in silico* toxicity prediction, which represents an important component of the Drug Development process. The antitumour activity of some derivatives (compounds 1-6) has been proven *in vitro* and described earlier. These derivatives exhibited moderate antitumour activity with high selectivity of action against certain lines of cancer cells. Among them, a highly active compound 2((*E*)-2-(2-((3-(benzo[*d*]thiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)-4-chlorophenoxy)-*N*-(4-methoxyphenyl)acetamide), was identified which was found to be non-toxic (LD_{50}>1000 mg/kg) *in vivo* [2].

Chemistry

The chemical composition and structure of the core heterocycle and compounds 1-6 were determined with the use of elemental analysis and ^{1}H NMR-spectroscopy [2]. This paper discusses the potential of the new hybrid structures (compounds 7-21), that were virtually modeled on the basis of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one, and the earlier synthesized compounds 1-6.

***In silico* experiment**

For our set goal we used the capabilities of the updated version of the web tool SuperPred 3.0 [4], that allows us with high reliability to compare the inputted molecule to all available targets at once and to predict their possible ATC codes with accuracy of up to 80.5%. According to the definition provided by SuperPred 3.0, a compound is considered a potential multi-hitter if it shows a high probability (>1%) of belonging to specific ATC classes and a very high possibility of binding to a biotarget (>80%). These thresholds may appear simple, yet they are underpinned by complex logic involving machine learning, statistical validity, and practical interpretation within the pharmaceutical context. They are designed to identify compounds capable of interacting with multiple targets and exhibiting therapeutic activity across various pharmacological classes. Small parts of the molecule are enough to detect structural similarity to finished pharmaceutical products (FPPs) [5].Using this web-platform it is possible to calculate quantitative parameters of the probable binding of ligands to targets (in %) and the overall accuracy of the prediction model (in %) with a high accuracy [6].

Additionally, to reduce the number of animal experiments in future research, we performed computational toxicity estimations for the main hit compounds using the online software ProTox 3.0 [7].

The prediction results were obtained with the use of *in silico* tools SuperPred 3.0 and ProTox 3.0, therefore they do not entail the use of statistical methods and research involving humans or animals. Independent bioethics committee approval and written consent were not obtained.

RESULTS AND DISCUSSION

We studied the structural similarity of 5-arylidene derivatives to the known FPPs and their ability to bind with biomolecular targets and their probable affiliation to certain ATC classes. According to the prognosis of SuperPred 3.0, all the derivatives of the series have more than one indication, so they belong to several ATC codes. There is a group structural similarity of the compounds to antineoplastic and immunomodulating agents, which are assigned code (L01XE – *protein kinase inhibitors*). The highest possibility of a structural similarity is predicted for compound 5 which is 35.80%. Additionally, for compounds 8, 12, 14, 16–21 a similarity to drugs with a code L04AA *(selective immunosuppressants)* is predicted. Compound 20 is the most structurally similar to them (28.60%).

SuperPred 3.0 found structural similarity of the studied compounds to not just antitumour MPs, but also other drugs, however a group similarity to other FPPs with a different pharmacological activity is not predicted. Compounds 1, 3, 7 and 9, as well as the core heterocycle, are most structurally similar to antifungals for topical use (D01AE). For those derivatives the predicted values range from 92.52% to 15.17%, notably the highest value is predicted for compound 3. For other derivatives (compounds 13-19 and 21) structural similarity to antithrombotic agents (platelet aggregation inhibitors, except for heparin B01AC) is predicted with a probability in the range of 39.12-8.74%, and compound 2 is most similar to FPPs from the group of direct factors Xa inhibitors (B01AF). With a probability of 16.19% and 17.38% compounds 10 and 11 are predicted to belong to the group of hypnotics and sedatives (N05CM). The highest value of structural similarity to antiglaucoma preparations and miotics (S01EC) is predicted for compound 4 (21.15%), and for compound 12, the predicted similarity to cardiovascular system drugs (simple angiotensin II receptor blockers plain C09CA) is 18.69%.

Among the predicted targets, those associated with antitumor therapy predominated. We considered targets common to all compounds in the series that demonstrated the highest binding probabilities and high predictive model accuracy (>85%) (Fig. 2).

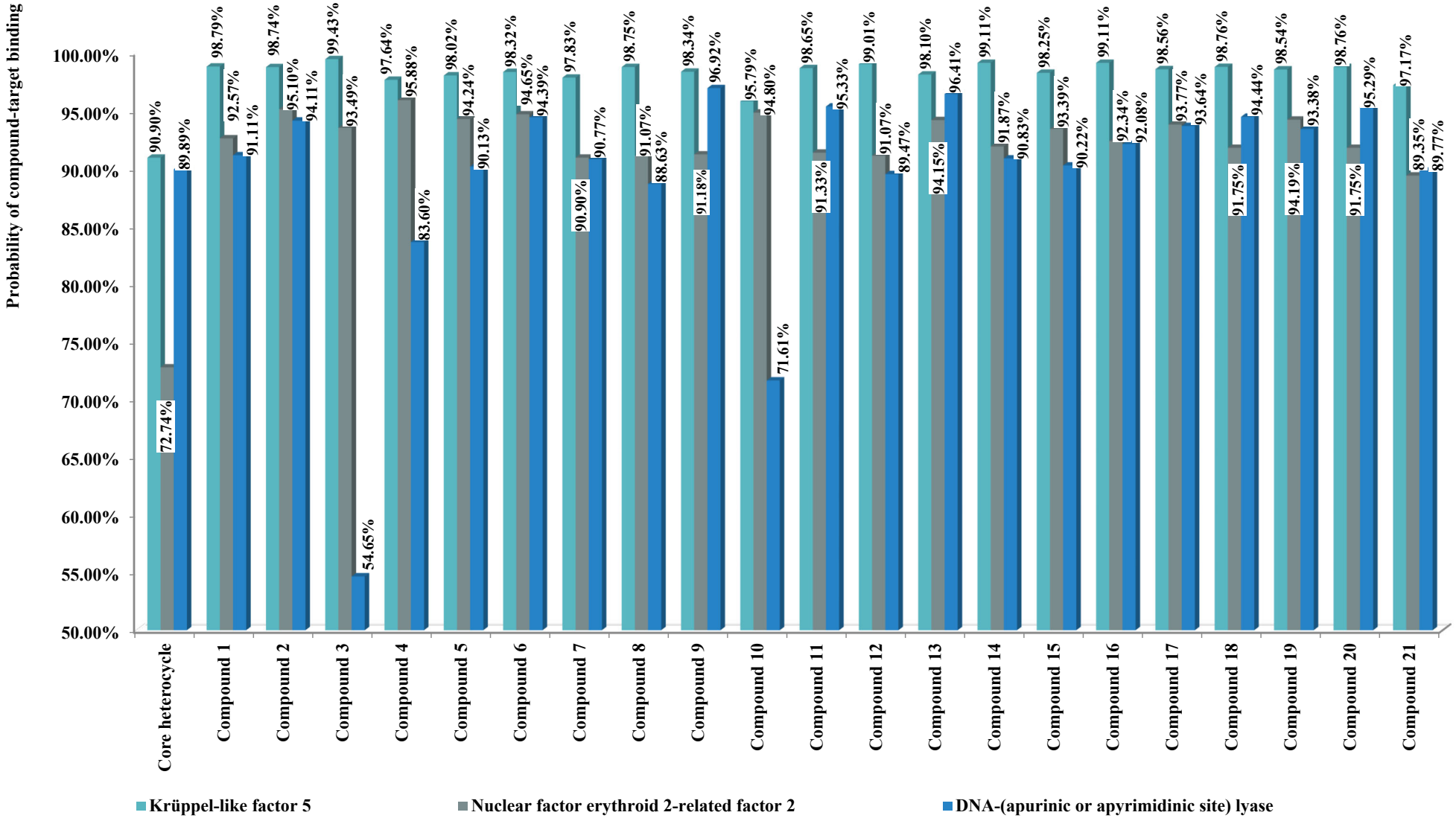


Fig. 2. The highest probability of binding of the core heterocycle and compounds 1–21 with targets for cancer therapy (in %)

The highest level of binding of the compounds was determined for three targets: Krüppel-like factor 5 (KLF5), Nuclear factor erythroid 2-related factor 2 (NRF2) and DNA-(apurinic or apyrimidinic site) lyase (DNA AP lyase). Compound 3 exhibited the highest predicted interaction probability with KLF5, compound 4 – with NRF2, and compound 9 – with DNA AP lyase, which supports their classification as hit compounds, i.e., promising candidates for further lead optimization. For these compounds, we performed *in silico* oral toxicity prediction using the ProTox 3.0 web server. The prediction results are presented in Table 1.

Table 1

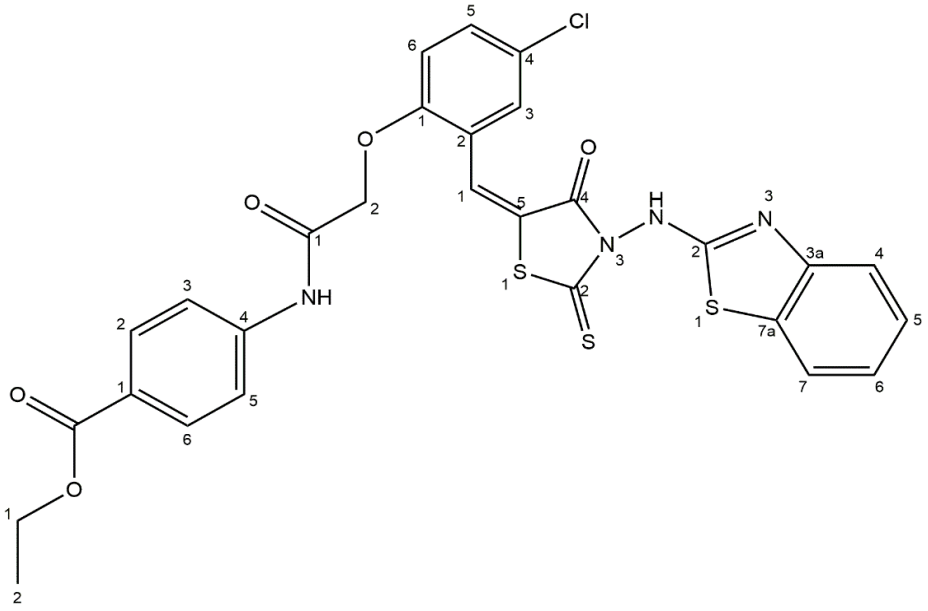
Predicted oral toxicity of hit compounds

	Compound 3	Compound 4	Compound 9
Hepatotoxicity	**+ (62%)**	**+ (54%)**	**-**
Carcinogenicity	**-**	**-**	**+ (51%)**
Immunotoxicity	**-**	**-**	**-**
Mutagenicity	**-**	**-**	**-**
Cytotoxicity	**-**	**-**	**-**
LD_{50} (mg/kg)	**1400**	**2000**	**1400**
Class	**IV**	**IV**	**IV**

Compounds classified under toxicity class IV (harmful if swallowed; $300<LD_{50}\leq2000$ mg/kg) are not considered critically toxic, yet they require careful attention during Drug Development.

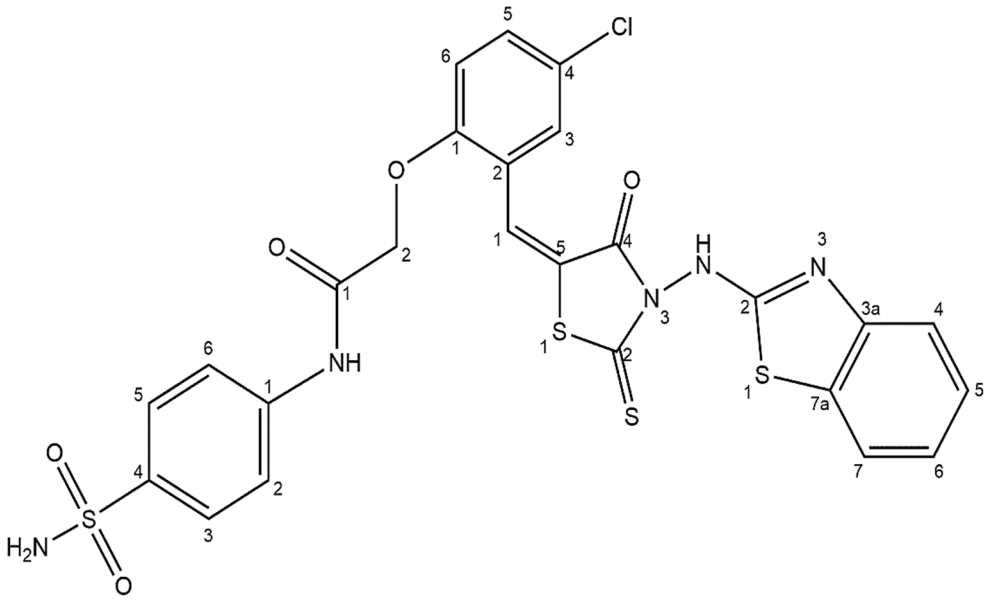
Only the probability of binding compounds to therapeutic targets and model accuracy that exceeded 80% was taken into account. As evident from the results of the virtual prediction, all the studied compounds are likely to exhibit a wide range of biological activity, and a high probability of their interaction with therapeutic targets is predicted with a marked prediction accuracy. Based on the list of predicted targets, 5-arylidene derivatives are similar to the core heterocycle, and compound 3 (R_1 = 1-$OCH_2CONHC_6H_4$-*n*-$COOC_2H_5$; R_2 = 4-Cl) is a potential multi-hitter with a predominant structural similarity to drugs intended to treat dermatological diseases (D01AE). The *in silico* prediction confirmed the *in vitro* antitumor activity of compound 2, with binding probabilities to the specified targets of 98.74%, 95.10%, and 94.11%, respectively. Compounds 3, 4, and 9 were also identified as potential hits (Fig. 3).

Compound 3



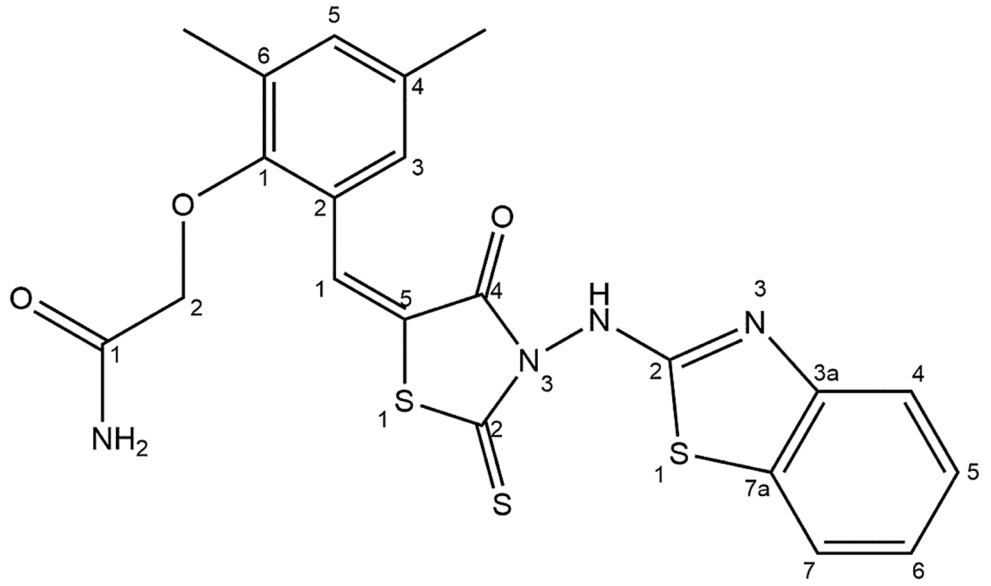
ethyl (*E*)-4-(2-(2-((3-(benzo[*d*]thiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)-4-chloro-phenoxy)acetamido)benzoate (99.43% to KLF5)

Compound 4



(*E*)-2-(2-((3-(benzo[*d*]thiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)-4-chlorophenoxy)-*N*-(4-sulfamoylphenyl)acetamide (95.88% to NRF2)

Compound 9



(*E*)-2-(2-((3-(benzo[*d*]thiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)-4,6-dimethylphenoxy)acetamide (96.92% to DNA AP lyase)

Fig. 3. Chemical structures of the compounds with the highest predicted affinity values to anti-tumour targets

KLF5 is a zinc-finger-containing transcription factor that has a significant role in the regulation of the expression of various genes, which impacts diverse cellular functions [8]. KLF5 is highly expressed in various types of cancer. KLF5 knockdown reduces the growth of cancer cells. KLF5 is involved in a variety of cellular functions, such as differentiation, proliferation, migration, apoptosis and regulation of cancer stem cells. The expression and activity of KLF5 is distorted in many types of cancer, including ovarian, cervical, breast, colorectal, lung, pancreatic and thyroid cancers [9].

NRF2, also known as nuclear factor erythroid-derived 2-like 2, is a transcription factor encoded by the NFE2L2 gene in humans. It has a critical role in the regulation of the expression of genes involved in

the oxidative stress response and the maintenance of redox homeostasis [10]. It was found that in the context of cancer, NRF2 plays a dual role. On one hand, it might protect normal cells from oxidative damage and reduce the risk of cancer through the suppression of oxidative stress and inflammation, which contribute to tumour development. On the other hand, many types of cancer show an increased activity of NRF2, which may lead to a poor prognosis and therapeutic resistance [11]. The activation of NRF2 is linked to the upregulation of the genes that facilitate cell survival and proliferation, which makes it a key player in the development of resistance to anticancer therapy. Targeting NRF2 and its pathways downstream has become an area of interest in the development of new therapies for cancer [10].

DNA AP lyase is an enzyme that has a critical role for repairing DNA damage. It is specifically targeted at apurinic/apyrimidinic (AP) sites, which are places in DNA that lack a purine or pyrimidine base. These sites can occur spontaneously or as a result of DNA damage caused by a variety of factors, such as radiation, chemicals or enzymatic activity. Deficiencies in these pathways often lead to mutagenesis and instability of the genome, which is known to be linked to human diseases such as cancer and neurodegenerative disorders [12]. In the context of antitumour therapy, DNA AP lyase is important as it helps maintain genome integrity, repairing DNA damage. A targeted action on DNA repair enzymes, in particular on DNA AP lyase, can increase the effectiveness of antitumour therapy by preventing cancer cells from repairing the damage caused by chemotherapy and radiotherapy [13].

The latest advances in antitumour therapy are focused on various strategies, such as immune checkpoint inhibitors, therapeutic vaccines and adoptive T-cell therapy. These approaches aim to harness the body's immune system to more effectively detect and destroy cancer cells. Using DNA repair inhibitors in combination with these immunotherapies, researchers are hoping for improved treatment outcomes and reduced chances of recurrence of cancer [14, 15, 16].

We performed a comparative analysis of the predicted parameters for the identified hit compounds and known inhibitors of KLF5, NRF2, and DNA AP.

According to SuperPred 3.0, the binding probability of established inhibitors KLF5 (ML264, Tolfenamic acid, Mithramycin A, JQ1, Kenpaullone), NRF2 (ML385, Brusatol, Luteolin, Trigonelline, Halofuginone, Keap1), and DNA AP (CRT0044876, Lucanthone, E3330 (APX3330), Methoxyamine, RN8) ranges from 70% to 95%, depending on the specific compound structure and the predictive model's accuracy.

For ML264, one of the most well-known KLF5 inhibitors, the predicted binding probability does not exceed 90%, which is consistent with its experimentally confirmed activity [17]. The predicted binding probability for compound 3 is higher (approximately 100%) at a model accuracy of 86.33%, indicating the reliability of the prediction. This supports the consideration of compound 3 as a potential candidate for further docking analyses and biological testing.

For example, compound 4 demonstrates a higher predicted probability of binding to NRF2 (95.88%) at high model accuracy (96%) compared to ML385 (not exceeding 90%), one of the most well-known selective NRF2 inhibitors that acts through binding to the DLG motif of KEAP1 [18]. This indicates high selectivity and the potential of the novel compound as an NRF2 inhibitor.

The *in silico* predicted interaction probabilities for compound 9 and the known non-specific inhibitor CRT0044876 with DNA AP lyase are comparably high (above 90%). The inhibitory activity of CRT0044876 against DNA AP lyase has been experimentally confirmed and described previously [19]. Subsequent studies demonstrated that CRT0044876 binds to a pocket distant from the active site of APE1 and forms colloidal aggregates, which may lead to non-specific inhibition [20]. The high predicted binding probability of compound 9 to the target, combined with the strong model accuracy (91.11%), indicates its considerable potential.

The obtained results justify further investigation of these compounds as promising candidates for antitumor therapy.

Aside from antitumour activity, the derivatives of the series are predicted to have a high probability of antidiabetic, antifungal, antiarteriosclerotic, antihypertensive and other kinds of activities.

Analysis of the "chemical structure – biological activity" relationship in the series of derivatives allows us to state that arylidene fragment at position 5 has a significant influence on the expression of antitumour activity. The increase in binding probability of the compounds to their respective targets depends on the introduced substituents (R_1, R_2 and R_3). The size of the molecule and branching also play a significant role. The most optimal in this context is the presence of fragments -C_6H_4-*n*-$COOC_2H_5$ (compound 3), -C_6H_4-*n*-SO_2NH_2(compound 4), which are connected to phenoxyacetamide moiety in molecules. Compound 9 is characterized by high branching: R_1=1-OCH_2CONH_2, R_2=4-CH_3, R_3=6-CH_3 (Fig. 3). The introduction of arylidene fragments facilitated the increase in the structural similarity of the derivatives to antineoplastic agents and positively influenced their potential affinity for their aforementioned

targets. This can be clearly traced while analyzing the values obtained for 5-arylidene derivatives and the unsubstituted core heterocycle.

The predicted toxicity class IV of the hit compounds, according to the ProTox 3.0 classification, indicates moderate toxicity and does not warrant their exclusion, particularly in light of their anticipated bioactivity. Thorough optimization of the dosage and administration route is advisable, as the predicted toxicity is associated with oral administration. Several antitumor agents (e.g., Methotrexate, Docetaxel, Vincristine) exhibit similar toxicological profiles yet are successfully used in clinical practice due to their proven efficacy and controlled dosing, which enables safe therapeutic application.

CONCLUSIONS

1. The results of *in silico* prediction indicate a potentially broad therapeutic spectrum and predominantly antitumor activity of the 5-arylidene derivatives of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one. Structural group similarity to known antineoplastic and immunomodulatory agents was observed, and compound 3 is predicted to possess multifunctional properties.
2. Several hit compounds were identified within the series. Compounds 3, 4, and 9 demonstrated higher predicted binding affinities to key targets (Krüppel-like factor 5, Nuclear factor erythroid 2-related factor 2, DNA-(apurinic or apyrimidinic site) lyase) compared to compound 2, whose antitumor activity has been previously confirmed *in vitro*.
3. Despite the predicted toxicity class IV, the identified candidates for further optimization exhibit a favorable balance between potential efficacy and acceptable toxicological profiles (absence of mutagenicity or/and carcinogenicity). The presence of shared pharmacophoric fragments between the hit compounds and known inhibitors of the respective targets supports the rationale for in-depth investigation.
4. The obtained results require further experimental validation.

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Contributors:

Mosula L.M. – conceptualization, data curation, methodology, formal analysis, investigation, writing – original draft, writing – review and editing the manuscript, manuscript translation into English, supervision, project administration;

Zhmura I.O. – formal analysis, investigation, resources search, writing – original draft, visualization.

Mosula V.S. – formal analysis, investigation, resources search, writing – original draft.

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