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SEARCH FOR COMPOUNDS WITH ANTITUMOUR ACTIVITY AMONG 5-ISATINYLIDENE-SUBSTITUTED RHODANINE DERIVATIVES WITH BENZOTHIAZOLE MOIETY IN THE MOLECULES

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Introduction. The rhodanine scaffold is a well-known privileged heterocycle in Drug Development. Its derivatives have shown a broad spectrum of biological activity, including anticancer properties.

The aim of the work is assessment of the antitumour potential of 5-isatinylidene derivatives of *N*-(4-oxo-2-thioxothiazolidin-3-yl)-2-(2-oxobenzo[*d*]thiazol-3(2*H*)-yl)acetamide according to the prediction criteria via the online service.

Materials and methods. The series of compounds contains 17 derivatives. *In silico* predictions of the affinity of molecules to the biotargets and determination of their structural similarity to known drugs with establishment of the ATC code was performed using web tool SuperPred 3.0.

Results and discussion. The potential biological activity of derivatives 4–17 was compared with the *in vitro* efficacy of the core heterocycle, previously synthesized compounds 1–3 and the known effect of the drug Sutent (Pfizer Inc., USA). We determined the important role of 5-isatinylidene moiety on the increase of the probable antitumour activity in comparison to the unsubstituted core heterocycle. We established the group structural similarity to antitumour agents. The commonly predicted targets are Cathepsin D, Nuclear factor NF-kappa-B p105 subunit i Cyclin-dependent kinase 5/CDK5 activator 1 with binding probabilities in the range of 85.32–99.76% (Model accuracy >90%).

Conclusions. The highest probability of structural similarity to antineoplastic drugs is predicted for the compound 4 (33.43%), and compound 5 is considered a potential multi-hitter. The most prospective for Drug Development are compounds 4, 6, 11 with potential activity 97.04%, 97.87% and 99.76%, respectively to targets CDK5, NF-kB1 p105, Cath-D (Model accuracy 93.0–98.95%). For hit compounds affinity for common targets is predicted to be higher than for previously studied compounds and Sutent. The prediction results confirmed the viability of further research. The obtained information could be of benefit to the design of new, effective small molecules with anticancer potential.

Keywords: rhodanine, benzothiazole, isatin, Drug Development, relationship ‘chemical structure – biological activity’.

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ПОШУК СПОЛУК З ПРОТИПУХЛИННОЮ АКТИВНІСТЮ СЕРЕД 5-ІЗАТИНІЛІДЕНЗАМІЩЕНИХ ПОХІДНИХ РОДАНІНУ З БЕНЗОТІАЗОЛЬНИМ ФРАГМЕНТОМ У МОЛЕКУЛАХ

Тернопільський національний медичний університет імені І. Я. Горбачевського Міністерства охорони здоров’я України, Тернопіль, Україна

Мета роботи – оцінка протипухлинного потенціалу 5-ізатиніліденпохідних *N*-(4-оксо-2-тіоксотіазолідин-3-іл)-2-(2-оксобензо[*d*]тіазол-3(2*H*)-іл)ацетаміду, згідно з критеріями прогнозування за допомогою онлайн-сервісу SuperPred 3.0. Проведено порівняльний аналіз потенційної біологічної активності сполук 4–17 з *in vitro* встановленою ефективністю базового гетероциклу, раніше синтезованих сполук 1–3 та відомою дією препарату «Сутент» (Pfizer Inc., США). Спільними прогнозованими мішенями є Cathepsin D, Nuclear factor NF-kappa-B p105 subunit i Cyclin-dependent kinase 5/CDK5 activator 1 з високими показниками (ймовірність зв’язування 85,32–99,76% і точність моделей >90%). Сполука 5 є потенційним мультихітером, а похідні 4, 6, 11 можна вважати перспективними «хітами» для подальших досліджень. Для них прогнозується вища, ніж для раніше синтезованих сполук і препарату «Сутент», афінність до спільних мішеней.

Ключові слова: роданін, бензотіазол, ізатин, розробка ліків, взаємозв’язок «хімічна структура – біологічна активність».

Introduction

In recent years, there has been a general decrease in the registration of new medications for treating pathologies, notably oncology. There is an urgent need for the development of new effective drugs capable of targeted destruction of tumour cells, as traditional cancer treatments (chemotherapy or radiotherapy) have a number of significant drawbacks [1]. This contrasts with the development of technology and science that are aimed to improve the quality of human life. These challenging conditions require continuous efforts in the developing new strategies for drug discovery. One of these strategies in the use of a hybrid pharmacophore approach in the design of new drugs. Despite some difficulties caused by hybrid techniques is a practical approach to expanding the chemotherapeutic

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space of drugs [2]. During the recent decades, scientists have been paying special attention to differently substituted derivatives of 2-thioxothiazolidin-4-one (rhodanine). The structural diversity of rhodanine derivatives has made them attractive candidates for the development of multitargeted agents [3; 4]. The antiviral [5], anti-inflammatory [6] and antitumour [3; 7] effects of rhodanine derivatives were investigated. New hybrid molecules have been developed thanks to the ability to introduce substituents at positions 3 and 5 of the rhodanine scaffold. In our previous work [8], we have proven the prospects of combining the pharmacophores rhodanine and benzothiazole in one molecule and the viability of introducing an isatinylidene moiety at position 5 of the rhodanine scaffold. In the process of searching for the biologically active compounds and the subsequent drug development on their basis, an urgent need to test the properties of a large number of compounds arises. Experimental assessment of the pharmacological potential of such a sample is extremely resourse- and time-consuming, which is why, on the initial stages of drug development, scientists prefer computer methods for the prediction of biological activity of the drug candidates [9]. The use of modern chemoinformatics tools in drug development significantly speeds up this process and cheapens it by screening out non-perspective molecules before the start of their synthesis.

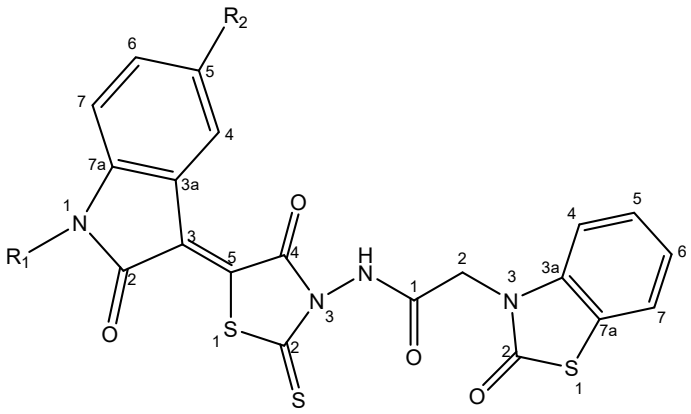
On this basis, we decided to predict the possibility of binding the derivatives of the series to various therapeutic targets on the basis of their structural similarity with known drugs. This allows us to open up new possibilities for already synthesized compounds and to thoroughly study previously unknown derivatives.

The aim of the work is assessment of the antitumour potential of 5-isatinylidene derivatives of *N*-(4-oxo-2-thioxothiazolidin-3-yl)-2-(2-oxobenzo[*d*]thiazol-3(2*H*)-yl) acetamide according to the prediction criteria via the online service.

Materials and methods

The studied series of compounds contains 17 derivatives (Figure 1).

The core heterocycle, according to the SwissADME criteria (http://www.swissadme.ch/), is a lead compound suitable for structural optimization, since its molecular weight is less than 350 g/mol, the number rotatable bonds is less than 7, and Log $P_{o/w}$ according to the XLOGP3 method is less than 3.5 [10]. The chemical composition and structure of the core heterocycle and some of its 5-isatinylidene derivatives (compounds 1–3) were determined by means of elemental analysis and ^{1}H NMR spectroscopy. The synthesized compounds demonstrated *in vitro* moderate antitumour activity. The activity of compounds at a single concentration of 10^{-5} M against 57 cancer cell lines was evaluated. It is noteworthy that there was observed selective influence of compounds on some cancer cell lines. Among them, the most active were the core heterocycle and compound 2. The core heterocycle was highly active on the following cell lines: Renal Cancer RXF 393 (-3.57%), Melanoma SK-MEL-2 (5.64%) and UACC-257 (-0.04%). Compound 2 was active on Renal Cancer cell line ACHN (91.91%) [8]. When selecting compounds for virtual biological activity studies, we were guided by the SwissADME prediction of their ADME properties, as described in our previous work [10]. In the modelling of new derivatives of core heterocycle, by analogy with the previously synthesized active compounds 1–3, we introduced halogens or alkyl substituents into the isatinylidene moiety of the molecules. Position 1 of the isatinylidene moiety was left unsubstituted or linear and branched alkyl radicals were introduced into it (R_1), and



1 R_1 = H, R_2 = H
2 R_1 = H, R_2 = CH_3
3 R_1 = H, R_2 = Br
4 R_1 = H, R_2 = I
5 R_1 = H, R_2 = Cl
6 R_1 = H, R_2 = C_2H_5
7 R_1 = H, R_2 = *n*-C_3H_7
8 R_1 = H, R_2 = *i*-C_3H_7
9 R_1 = H, R_2 = *n*-C_4H_9
10 R_1 = H, R_2 = *i*-C_4H_9
11 R_1 = H, R_2 = *n*-C_5H_{11}
12 R_1 = H, R_2 = *i*-C_5H_{11}
13 R_1 = CH_3, R_2 = *n*-C_3H_7
14 R_1 = C_2H_5, R_2 = *n*-C_3H_7
15 R_1 = *n*-C_3H_7, R_2 = *n*-C_3H_7
16 R_1 = *i*-C_3H_7, R_2 = *i*-C_3H_7
17 R_1 = *n*-C_4H_9, R_2 = *n*-C_4H_9

Fig. 1. 5-Isatinylidene derivatives of N-(4-oxo-2-thioxothiazolidin-3-yl)-2-(2-oxobenzo[d] thiazol-3(2H)-yl)acetamide

the same radicals were introduced into position 5 or they were replaced with a halogen (Br^-, I^-, Cl^-) (R_2).

For a comprehensive assessment of the potential biological activity of compounds, we used the capabilities of the web resource SuperPred 3.0 (http://www.swissadme.ch/). This method of prediction has been refined and redesigned compared to SuperPred 1.0 and SuperPred 2.0 and is now based on machine learning models using logistic regressions and 2028 Morgan fingerprints rather than on the overall structural similarity. For the identification of a target the ChEMBL database version 29 is used [11]. The probability of the ligands binding to targets of 'Homo sapiens' is predicted with high reliability [9]. Furthermore, it is possible to predict ATC codes according to the World Health Organization (WHO) classification for the inputted molecules that is based on the structural similarity of some parts of new molecule with the finished medicinal product (FMP) with up to 80.5% accuracy, unlike previous versions [12]. A compound is considered to be a potential multi-hitter if it is predicted to have a high probability of binding to a biotarget (>80%). The web tool calculates with high precision all quantitative indicators. The criteria for predicting biological activity are: Structure similarity *(not general, but the presence of small parts of structure)* of input molecule with a FMP belonging to a certain ATC code, which is determined using a linear logistic regression model, Therapeutic targets *(predicted for compound)*, Probability *(percentage of possibility that the input molecule binds with the specific target)* and Model accuracy *(total accuracy of the corresponding model in %, which displays a 10-fold cross-validation score of the respective logistic regression model)* [11]. This help in the selection of the most promising compounds for the further study of their biological activity *in vitro*, *in vivo*.

In this work, we discuss the potential of new hybrid structures (compounds 4–17) and predict the possible biological actions of previously synthesized compounds.

Results and discussion

We have studied the structural similarity of 5-isatinylidene derivatives of core heterocycle to known FMPs and their ability to bind to biomolecular targets. Based on the similarity of individual functional groups or small fragments of molecule to the structure of the known drug, the compounds were assigned to certain ATC classes. SuperPred 3.0 found structural similarities between the input compounds and various drugs (Stepronin, Erdosteine (R05CB – Mucolytics), Parecoxib (M01AH – Coxibs), Meloxicam (M01AC – Oxicams, antiinflammatory and antirheumatic drugs), Dimazole (D01AE – Antifungals for topical use), Glycobiarsol (P01AR – Arsenic compounds, for amoebiasis and other protozoal diseases), etc.), including antineoplastic FMPs (Sutent, Nintedanib, Afatinib, Dacomitinib, Cediranib, Masitinib (L01XE – Protein kinase inhibitors), Teriflunomide, Gusperimus (L04AA – Selective immunosuppressants), etc). Some derivatives of the series are similar to Anxiolytics (benzodiazepine derivatives N05BA), Anticholinergic (tertiary amines N04AA), Hypnotics and sedatives (benzodiazepine derivatives N05CD, other N05CM), Nervous system drugs (Antiepileptics – succinimide derivatives (N03AD) and carboxamide derivatives (N03AF), Opioid analgesics – diphenylpropylamine derivatives (N02AC)). The majority of the derivatives, except for compounds 13–15 and 17, are structurally similar to respiratory system drugs: R05CB (Mucolytics), R03DC (Leukotriene receptor antagonists for obstructive airway diseases). Certain derivatives (compounds 9, 13–15, 17) are structurally similar to Cardiovascular system drugs: C09CA (Angiotensin II receptor blocers (ARBs), plain), C09AA (ACE inhibitors, plain). Other compounds have structural similarity to the FMPs that are assigned ATC codes (A06AB, A04AA, A08AA – Alimentary tract and metabolism drugs; B01AF, B01AC – Blood and blood forming organ drugs; D01AE – Dermatologicals, G04BE – Genito urinary system and sex hormones, H03BA – Systemic hormonal preparations, excl. sex hormones and insulins, M01AB, M01AC, M01AE, M01AH, M02AA, M03BA, M04AB – Musculo-skeletal system drugs). With the introduction of the isatinylidene moiety of the isopropyl radical at position 5, a structural similarity to the FMPs assigned to code S01XA (Other ophthalmologicals) appears with a high probability (predicted similarity compound 8 to such FMP is 38.10%). With the increase in the number of Carbons in the branched alkyl radicals, the percentage of similarity gradually decreases (compound 10 with R_2=5- *i*- C_4H_9 has 1.59%) until its full disappearance (compound 12 with R_2=5-*i*-C_5H_{11} has 0,00%). If at position 1 of isatinylidene moiety an isopropyl radical is additionally introduced, the similarity to Ophthalmic preparations will increase even more – compound 16 is predicted to have 42.93% similarity. Overall, the introduction of an isatinylidene moiety at the position 5 of the core heterocycle had a positive effect on increasing the structural similarity of the compounds to known drugs. The structure of the substituents and their position in the isatinylidene moiety play an important role. The derivatives of the series shown a group structural similarity to the Antineoplastic and immunomodulating agents assigned the code L01XE. In addition, for compounds 9, 11 and 17, similarity to the antineoplastic drugs with the code L04AA is predicted. The highest probability of structural similarity to antineoplastic agents is predicted for compound 4 and is estimated at 33.43%, unlike the core heterocycle with 2.64%. The other derivatives in the series are characterized by different values of predicted similarity ranging from 31.85% (compound 6) to 1.98% (compound 17). An increase in the index of similarity to the drug under the code L01XE was influenced by the introduction of substituents at position 5 of the isatinylidene moiety: -CH_3 (compound 2), -Br (compound 3), -I (compound 4), -C_2H_5 (compound 6), – *n*- C_3H_7 (compound 7), – *i*- C_3H_7 (compound 8), -*n*-C_4H_9 (compound 9), – *i*- C_4H_9 (compound 10), – *n*- C_5H_{11} (compound 11), -*i*-C_5H_{11} (compound 12). In contrast, the replacement of the Iodine atom in position 5 with a Chlorine atom leads to a sharp decrease in the similarity to antineoplastic drugs from 33.43% (compound 4) to 3.75% (compound 5). Negative impact on the structural similarity was caused by an additional introduction of an alkyl radical at position 1 of isatinylidene moiety (compounds 13 (R_1=CH_3), 14 (R_1=C_2H_5), 15 (R_1=*n*-C_3H_7), 16 (R_1=*i*-C_3H_7), 17 (R_1= *n*-C_4H_9): from gradual decrease (7,1–2,85%) to a total loss.

As seen from the results of the virtual prediction, all the studied compounds likely have a wide range of biological activity, a high probability of their interaction with therapeutic targets is predicted with a significant prediction accuracy (near 100%). As per the list of predicted targets, 5-isatinylidene derivatives are similar to the core heterocycle, and compound 5 (R_2=5-Cl) is a potential multi-hitter with a predominant structural similarity (74.15%) to Anxiolytics (N05BA). The most predominant are targets for cancer therapy. With the highest accuracy of the prediction models (93.03–98.59%), the highest level of binding of the compounds in the series was found for three targets: Cathepsin D (Cath-D), Nuclear factor NF-kappa-B p105 subunit (NF-kB1 p105) and Cyclin-dependent kinase 5/CDK5 activator 1 (CDK5) (Figure 2).

Cath-D is a high-potential target for the development of anticancer medicines. This lysosomal asparagine protease stimulates the growth of cancer cells in an autocrine manner. The development of Cath-D inhibitors capable of controlling its activity may play a key role in the death of cancer cells, breast cancer in particular [13]. For our compounds, a high probability of binding to this target is predicted in the range 93.35–99.76%, which exceeds the corresponding value for the core heterocycle (92.56%), with a prediction model accuracy of 98.95%.

NF-kB1 p105 is one of the five NF-κB subunits that participates in carcinogenesis, in some cases accelerating the progression of cancer and in others acting as a tumour suppressor [14]. It plays an important role in the development of resistance to cancer therapy. Latest clinical trials prove the effectiveness of using NF-κB inhibitors in the treatment of oncological diseases [15]. Compound 6 is characterized by the highest predicted affinity for this target (97.87%), and compound 5 by the lowest (89.65%), which is still exceeding the value for the base compound (87.95%). Other derivatives of the series also showed a high probability for affinity to this target (≥94.88%). The accuracy of the prediction model is high and amounts to 96.09%.

CDK5 is a member of the cyclin-dependent kinase (CDKs) family. This kinase is a serine/threonine kinase found mainly in nerves. Previously, it was studied as a target for neurological disorders, but recently its importance in the treatment of various types of cancer has been established [16]. Experimentally proven that inhibition or knockdown of CDK5 plays an anti-cancer role through various mechanisms, and can synergize the killing effect of chemotherapeutic drugs [17]. The probability of inhibition on this target by the derivatives of the series fluctuates from 85.32% (compound 13) to 97.04% (compound 4) with a sufficiently high accuracy of the prediction model (93.03%).

With the accuracy of the prediction models over 90%, the compounds with the highest affinity for the common

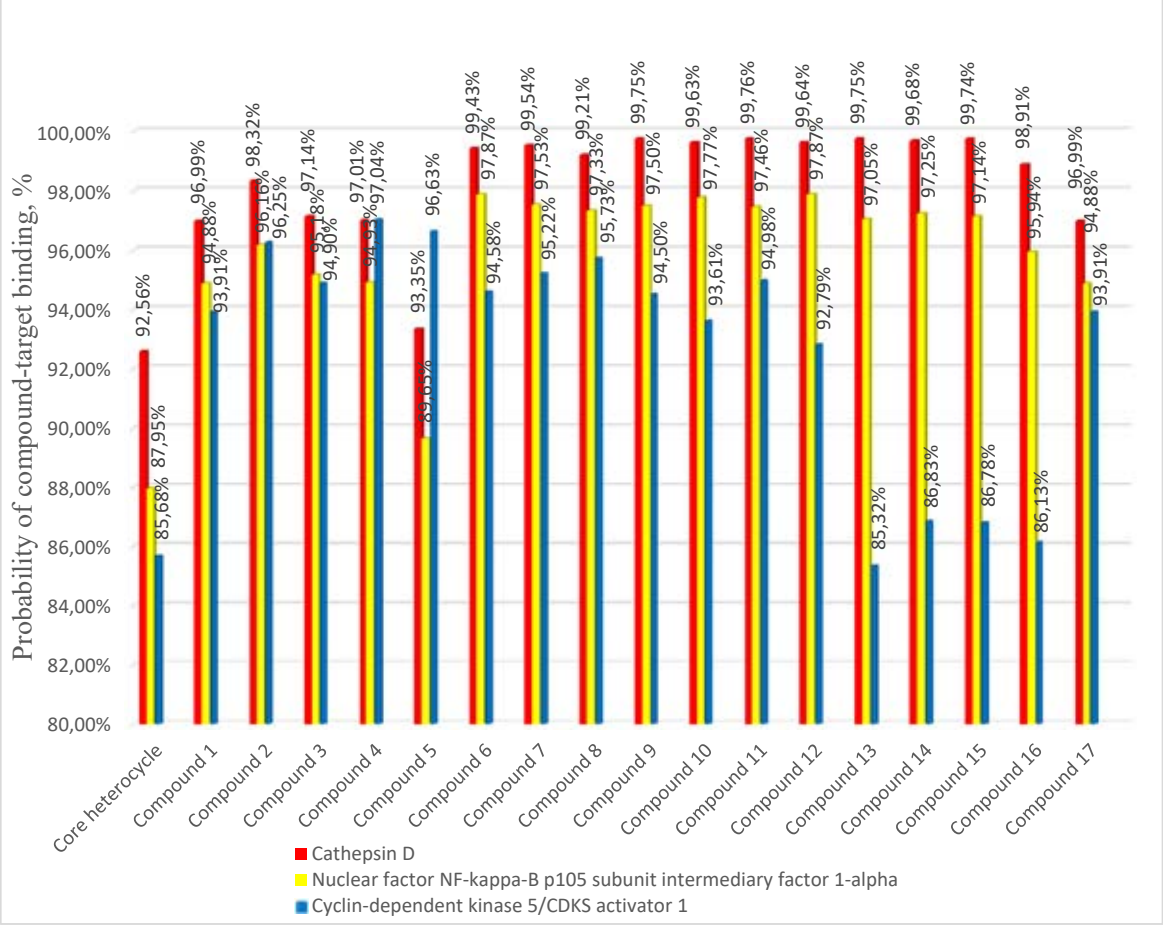


Fig. 2. The highest probability of binding of the core heterocycle and compounds 1–17 with targets for cancer therapy (in %)

predicted targets are 11 (99.76% to Cath-D), 6 (97.87% to NF-kB1 p105), 4 (97.04% to CDK5).

In addition, the selective affinity of derivatives for biotargets of targeted therapy is predicted with high probability (over 90.00%) (Table 1).

Sufficient selective efficacy (probability over 80.00%) of the compounds in this series is also predicted for other targeted therapy targets: Adenosine A3 receptor *(Hepatocellular carcinoma, Solid tumour/cancer)*, Muscarinic acetylcholine receptor M5 *(Solid tumour/cancer),* Platelet-derived growth factor receptor alpha *(Acute myelogenous leukaemia, Acute myeloid leukaemia, Breast cancer, Colon cancer, Colorectal cancer, Gastric adenocarcinoma, Gastrointestinal cancer, Gastrointestinal stromal tumour, Glioblastoma multiforme, Lung cancer, Mast cell leukaemia, Multiple myeloma, Non-small-cell lung cancer, Pancreatic cancer, Prostate cancer, Recurrent glioblastoma, Soft tissue sarcoma, Solid tumour/cancer)*, Sphingosine 1-phosphate receptor Edg-3 *(Brain cancer)*, DNA topoisomerase II alpha *(Solid tumour/cancer)*, DNA topoisomerase I *(Acute lymphoblastic leukaemia, Bladder cancer, Breast cancer, Colorectal cancer, Esophageal cancer, Gastric adenocarcinoma, Glioblastoma multiforme, Lung cancer, Lymphoma, Metastatic colorectal cancer, Ovarian cancer, Renal cell carcinoma, Small-cell lung cancer, Solid tumour/cancer)*, Cyclin-dependent kinase 1/cyclin B1 *(Acute lymphoblastic leukaemia, Breast cancer, Haematological malignancy, Mantle cell lymphoma, Nasopharyngeal carcinoma, Non-small-cell lung cancer, Solid tumour/cancer)*, Casein kinase II alpha/beta *(Cholangiocarcinoma, Solid tumour/cancer)*, Maternal embryonic leucine zipper kinase *(Acute lymphoblastic leukaemia, Acute myeloid leukaemia, Breast cancer, Chronic lymphocytic leukaemia, Myeloproliferative neoplasm)*, Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 *(Nasopharyngeal carcinoma, Non-small-cell lung cancer),* Glutathione S-transferase Pi *(Solid tumour/cancer)*, Cytochrome P450 3A4 *(Solid tumour/cancer)*, Histone deacetylase 4 *(Advanced stage follicular lymphoma, Solid tumour/cancer)*, Protein Mdm4 *(Acute myeloid leukaemia, Haematological malignancy, Solid tumour/cancer)*, P-glycoprotein 1 *(Acute myeloid leukaemia, Non-small-cell lung cancer, Ovarian cancer, Solid tumour/cancer).* Importantly, the *in vitro* data for compounds 1–3 are consistent with their predicted results.

We have carried out a comparative analysis of the potential biological activity of new compounds 4–17 with determined *in vitro* types of activity for core heterocycle, previously synthesized compounds 1–3 and the known action of the FMP Sutent (Pfizer Inc., USA). Sutent (sunitinib malate) is primarily used to treat advanced kidney cancer (Renal cell carcinoma, RCC), gastrointestinal stromal tumors (GIST), and pancreatic neuroendocrine tumors (pNET). It works by inhibiting multiple protein kinases involved in tumor growth and blood vessel formation. Our synthesized compounds also showed *in vitro* moderate effects on kidney cancer cell lines. In addition, due a potential affinity of the compounds in this series to the indicated targets, their effectiveness in the treatment of cancer of the gastrointestinal tract, pancreas is also expected. The common anti-tumour targets know for Sutent and predicted for our compounds are: Platelet-derived growth factor receptor alpha, Casein kinase II alpha, Maternal embryonic leucine zipper kinase. For derivatives of the series, the probability of binding to specified targets is predicted over 80.00%. Among the predicted common targets of our compounds and Sutent with a high probability are: Cath-D, NF-kB1 p105, CDK5. The hit compounds are predicted to have higher affinity for these targets than Sutent. Potential probability of Sutent binding to such targets is respectively: 98.39%, 96.07%, 90.81%.

The identified targets may play a key role in the treatment of oncological diseases, which in the future may facilitate molecular modelling and biochemical testing of rhodanine derivatives with a benzothiazole and isatinylidene moieties in the molecules.

The analysis of 'chemical structure – biological activity' relationship in a series of the studied derivatives allows us to state a significant influence of the isatinylidene substituent at the position 5 of the rhodanine cycle on the expression of antitumour activity. The increase in the affinity of these compounds for the corresponding targets depends on the introduction of substituents at the isatinylidene moiety and their position in the cycle. It was found that the modification of the N1 and C5 positions of the isatinylidene cycle has a decisive influence on the expression of antitumour effect of 5-isatinylidene rhodanines with a benzothiazole moiety. In particular, the most optimal in this context is the presence of an iodine atom (compound 4) or ethyl (compound 6) or *n*-pentyl (compound 11) radicals at position 5 of the isatinylidene moiety. The positive effect of the introduced isatinylidene moiety on the expression of antitumour activity of the series derivatives is clearly observed when analyzing the obtained values for 5-isatinylidene derivatives and the unsubstituted core heterocycle. This is reflected in the predicted values of structural similarity to antineoplastic drugs and binding to the corresponding targets. Concretization of conclusions regarding these compounds requires more experimental material.

Conclusions

The obtained results emphasise the broad therapeutic potential of the studied compounds, which goes beyond antitumour activity. Among the 5-isatinylidene derivatives of *N*-(4-oxo-2-thioxothiazolidin-3-yl)-2-(2-oxobenzo[*d*] thiazol-3(2*H*)-yl)acetamide, we found a potential multi-hitter, compound 5. The compounds are characterized by group similarity to antineoplastic and immunomodulating agents (L01XE – *protein kinase inhibitors*). In addition, some derivatives (compounds 9, 11 and 17) are similar in structural fragments to some drugs with the code L04AA *(selective immunosuppressants*). The highest probability of the structural similarity to antineoplastic drugs is predicted for compound 4 and it is 33.43% (ATC code L01XE). The highest probabilities of binding of the series derivatives to targeted therapy targets are predicted for the modelled compounds 4, 6, 11. Their potential activity to CDK5 targets, NF-kB1 p105, Cath-D is 97.04%, 97.87% and 99.76% with high model accuracy (93.0–98.95%), respectively. These values are higher than the probable affinity values of previously synthesized compounds (core

heterocycle and derivatives 1–3) and exceed the predicted values for Sutent. Attempting to establish some regularities of 'chemical structure – biological action', we determined the important role of the 5-isatinylidene moiety on the increase of the probable antitumour activity, compared to the unsubstituted core heterocycle. We determined the negative effect of an additional alkyl radical introduced at the 1 position isatinylidene moiety. The obtained results indicate the viability of the targeted synthesis of the most promising compounds for the subsequent *in vitro* and *in vivo* studies.

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