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RESEARCH OF PHYSICOCHEMICAL, PHARMACOKINETIC AND DRUGLIKENESS PARAMETERS OF A SERIES OF 5-ARYLIDENE DERIVATIVES OF 3-(BENZO[*d*]THIAZOL-2-YLAMINO)-2-THIOXOTHIAZOLIDIN-4-ONE)

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The article presents *in silico* research of physicochemical, pharmacokinetic and druglikeness parameters of a series of 5-arylidene derivatives of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one. The web tool SwissADME was used for prediction of absorption, distribution, methabolism and excretion (ADME) of compounds. Based on the prediction results, it was determined that the introduction of an arylidene moiety into position 5 of the base compound with potentially high peroral availability negatively affects the passive absorption in the gastrointestinal tract. To further characterize the effect of substituents in the arylidene moiety on the manifestation of properties of this type of compounds, a structure of a new derivative of with an unsubstituted benzylidene nucleus was simulated. With the use of another *in silico* tool, SuperPred 3.0, it was established that the introduction of an substituent into the benzylidene moiety promotes the potential affinity of the derivatives to many therapeutic targets to a wide variety of therapeutic targets, as evidenced by their structural similarity to existing broad-spectrum drugs. A common characteristic of all the derivatives is their structural resemblance to the active components of antitumor drugs. Based on the acceptable ADME profile of the studied compounds and their high pharmacological potential, it is advisable to continue thorough studies of parenteral routes of administration or optimize the structure of the molecules to increase oral bioavailability. The obtained predictive information on the possible behavior of the derivatives in the human body can become a theoretical platform for the synthesis of de novo compounds with a polypharmacological profile.

Keywords: rhodanine, benzothiazole, in silico screening, physicochemical analysis, drug development, SwissADME, SuperPred 3.0, structure vs. activity relationships.

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Introduction

Drug discovery was always associated with significant financial costs, involvement of multiple specialists from various scientific fields and the length of the process. Computer technologies, used to simulate the structures of chemical substances and virtually screen them for bio- (BS) and synthetic availability (SA), drug-like properties, toxicity, affinity for therapeutic targets, spectrum of biological activity, etc., have become a potent tool for synthetic chemists, chemoinformaticians, biologists, pharmacologists at the initial stages of drug development. With the emergence of chemoinformatics, a major breakthrough in the development of chemistry from empirical to predictive was made [1]. Computer-aided drug design (CADD) assists chemists in designing bioactive systems, selection of the most promising molecules for synthesis and in-depth biological studies. The quick development of chemoinformatics has led to the emergence of high-accuracy software packages aimed at calculating molecular descriptors, predicting biological action and toxicity of compounds. At the stage of virtual screening,

compounds that are unperspective for medicinal chemistry are weeded out. *In silico* methods allow for the identification of hit compounds and lead compounds with a high probability, which are often proven to be effective in experimental studies [2].

One of the appealing structural fragments for the development of new drugs in modern medicinal and pharmaceutical chemistry is the thiazolidine skeleton. Its derivatives exhibit various types of biological activity, such as anticancer, anti-inflammatory, anti-tuberculosis, antidiabetic, etc. [3]. The significant pharmacological potential of its derivatives is caused by their affinity for various biotargets. In the context of the pharmacophore hybridisation approach, the scaffold hybridisation strategy, it is justified to combine the thiazolidine nucleus with other heterocycles, which often leads to the appearance of a new pharmacological profile, increased therapeutic efficacy, and minimization of side effects [4]. The possibility of introducing substituents at the positions 3 and 5 of 2-thioxothiazolidin-4-one (rhodanine) contributes to the appearance of new hybrid molecules. In our previous studies [5,6], we proved the prospects of combining the «thiazolidine matrix» with a benzothiazole scaffold and 5-arylidene moiety by introducing them at the positions 3 and 5 of the basic heterocycle, respectively. It was proved that the synthesized 5-arylidene derivatives of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one exhibit moderate *in vitro* antitumour (compounds 10 and 11) and antiviral (compounds 7, 13, 15 and 16) activity.

We have put forward the hypothesis that the nature of the 5-arylidene moiety has a significant influence on the expression of these activities. Hence, it was reasonable to predict the behaviour of biologically active molecules in the human body in an *in silico* experiment.

Experimental

Chemistry

The compounds were synthesized and described earlier in our previous studies [5,6]. Their chemical composition was validated by elemental analysis, and their structure was determined by means of PMR and IR spectroscopy. It became known that for the synthesized derivatives, prototropic hydrazine-hydrazone tautomerism was characteristic, existing in the form of Z- and E-configurations, which are likely to be partially stabilized by the formation of intramolecular hydrogen bonds.

Additionally, to specify the effect of substituents in the benzylidene moiety on the potential oral bioavailability of molecules, we obtained compound 17 by virtual modification. According to its chemical structure, it is a 5-arylidene derivative with an unsubstituted benzylidene moiety. For this molecule, we performed *in silico* predictions of physicochemical, pharmacokinetic, and drug-like parameters using the SwissADME method, and predicted the spectrum of biological activity using the SuperPred 3.0 method.

In silico experiment

For the implementation of the planned experiment, we used the SwissADME chemoinformatics tool, with the help of which we performed the calculation of important molecular descriptors and made a virtual ADME (A, D, M and E stands for absorption, distribution, metabolism and elimination, respectively) prediction of the properties of the researched molecules. This *in silico* method is convenient for interpreting the prediction results for both drug development professionals and non-specialists in the field of CADD. The accuracy of predictions is between 72 and 94% [7].

For compounds 1–16, we have previously predicted and described the potential affinity to therapeutic targets and determined their possible affiliation to certain ATC classes (Anatomical Therapeutic Chemical Classification System of the World Health Organization (WHO)) [8]. An analogues prediction was made for the new virtually simulated derivative (compound 17). Prediction of the biological activity of molecules was realized with the help of the German web server SuperPred 3.0. The accuracy for the ATC prediction increased by almost 5% to 80.5% compared to the previous version, and additionally the scoring function now offers values which are easily assessable at first glance. Additionally, both ATC and target prediction have been reworked and are now based on machine learning models instead of overall structural similarity, stressing the importance of functional groups for the mechanism of action of small molecule substances [9].

The mentioned *in silico* tools are available in open access on the respective Internet platforms [10,11].

Figure 1 shows the general formula of the investigated series of compounds.

The meaning of the physicochemical parameters of a molecule determines its pharmacokinetic properties, on which ADME parameters depend. To determine the value of molecules for medicinal chemistry, it is necessary to predict their drug-like properties, bio- and synthetic availability, assess their similarity to lead compounds, and check for potentially problematic fragments in their structure. For the assessment of the ADME profile of small molecules, the molecular modelling group of the Swiss Institute of Bioinformatics (SIB) has selected a number of fast and reliable methods, a number of which were

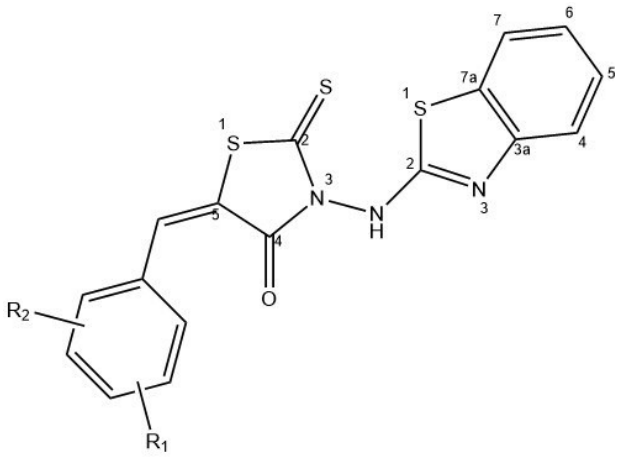


Fig. 1. Differentially substituted 5-arylidene derivatives of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one

developed in-house (e.g. iLOGP or BOILED-Egg). For some physicochemical parameters, several predictions of the same parameter are provided to ensure a consensus assessment of a particular property of a molecule.

Physicochemical parameters provide a global description of the structure of a molecule. Crucially important is the accuracy of the calculation of such physicochemical parameters as molecular weight (MW), number of heavy atoms (N-HA) and aromatic heavy atoms (N-AHA), number of bonds around which a molecule can rotate (N-RB), the number of acceptors (N-HBA) and hydrogen bond donors (N-HBD), the fraction of carbon in sp^3 hybridisation (F-Csp^3), molar refractivity (MR), and the topological area of the polar surface of the molecule (TPSA). For understanding the permeability of molecules through cell membranes and their distribution in the body, the coefficients of lipophilicity (Log $P_{o/w}$) and water solubility (Log *S*) have an important meaning. An increase in Log $P_{o/w}$ correlates with an increase of biological activity of compounds and the rate of skin penetration, but at the same time, it leads to a decrease in their water solubility [12]. For a complex assessment of a molecule's lipophilicity, the software offers five computational methods and the calculation of the consensus value (Consensus Log $P_{o/w}$) based on them. It is important to calculate Log *S*, especially if the development is aimed at developing a perorally available drug. Water solubility of a compound is also important for parenteral medicines. For this type of prediction, SwissADME offers three methods (ESOL, Ali and SILICOS-IT). All of them show a strong correlation between predicted and experimental data.

For a quick assessment of the potential peroral availability of a compound, a bioavailability radar is used. We take into account six physicochemical properties of the molecule: lipophilicity, size, polarity, solubility, saturation and flexibility. The physicochemical range on each axis is determined with the use of descriptors and outlined by a pink area, which the radar graph of the molecule must completely fall into for it to be considered available for peroral use.

Similarity of the molecule to existing medicines is established based on studies of structural or physicochemical descriptors. SwissADME provides access to five drug similarity filters. They are based on rules with different ranges of properties for perorally active drugs and are derived from the analyses done by major pharmaceutical companies: Lipinski (Pfazer), Ghose (Amgen), Veber (GSK), Egan (Pharmacia), Muegge (Bayer).

The calculation of BS is carried out based on the Abbot scale. This offers an opportunity to predict the probability that a compound will have at least 10% peroral bioavailability in rats or measurable Caco-2 permeability. This semi-quantitative indicator is based on rules and takes into account the total charge, TPSA and the violation of the Lipinski rules. Four classes of compounds with probabilities of 11%, 17%, 56% and 85% are distinguished.

While studying the routes of administration of biologically active compounds (BAC), it is important to predict the potential absorption in the gastrointestinal tract (GI absorption), permeability through the blood-brain barrier (BBB permeant), and skin (Log *K*p). For prediction of the distribution and active elimination of molecules from the body, knowledge of their ability to be a P-glycoprotein (P-gp) substrate is required. Possible metabolism of compounds can be predicted based on the results of prediction of their effect on the five cytochrome P-450 (CYP) isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4).

In the initial stages of drug development, it is useful to predict the value of small molecules for medicinal chemistry. SwissADME provides free access to the PAINS and Brenk structural filters for recognizing fragments that interfere with carrying out the analysis or may be chemically reactive, metabolically unstable or toxic, etc. On this online platform, there is a possibility to determine the similarity of molecules to lead compounds (Leadlikeness) and their synthetic accessibility (SA) [7]. The knowledge of these aspects helps chemists to determine the applicability of molecules for structural optimization.

Results and discussion

Operating a Swiss chemoinformatics tool, we have calculated the values of physicochemical

parameters of the molecules, on which such important criteria as size, lipophilicity, polarity, solubility, saturation and flexibility depend. The obtained results indicate that 5-arylidene derivatives of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one possess acceptable ADME properties. All the compounds in the series have MW≤500 g/mol, which proportionally increases with the elongation of radicals at the 2, 3, and 4 positions of the benzylidene moiety. Each molecule can be an acceptor and a donor of hydrogen bonds, the number of which follows the specified criteria. A common positive trait of the compounds is the optimal flexibility of the molecules (N-RB≤9). An acceptable value of molar refractivity (MR≤130 cm^3/mol) is characteristic to the majority of the derivatives. This has a positive effect on the ease and speed of molecular penetration through the biological membranes.

Physicochemical properties determine the drug-like properties of the molecules and the possibility of their peroral administration. The lowest number of violations of the optimal range of physicochemical parameters that are characteristic of peroral medicines is predicted for derivatives whose radar plots are shown in Fig. 2.

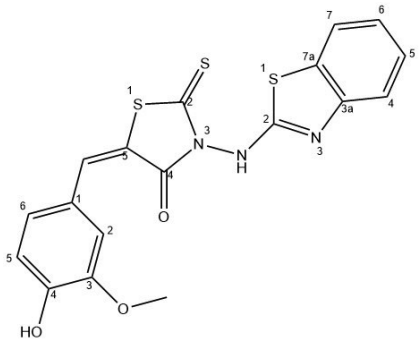
Accounting for the introduction of substituents into the arylidene moiety leads to a potential degradation of the ADME qualities of the compound, we have simulated the structure of (*E*)-3-(benzo[*d*]thiazol-2-ylamino)-5-benzylidene-2-thioxothiazolidin-4-one (compound 17) with an unsubstituted benzylidene nucleus for a comparison. It led to the optimization of all physicochemical properties, except for saturation. The value of F-Csp^3<0.25 is outside the acceptable range of values for perorally available compounds (Fig. 3).

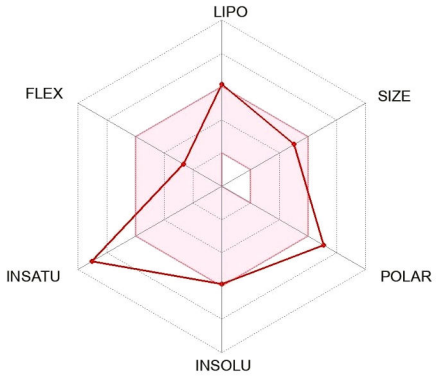
The calculated values of the compounds that are most similar to perorally available drugs by molecular criteria are shown in Table.

According to the *in silico* predictions, all molecules (17 compounds) are characterized by their sufficient biological availability, as shown by the calculated BS value of 0.55. The researched compounds may be considered similar to the existing drugs due to their compliance to the druglikeness rules, among which the most important is Lipinski Rule of Five. All of our molecules pass through Lipinski filter unhindered, and the majority of them also lass through Goshe (compounds 1–9, 11, 12, 14, 16, 16, and 17), Veber and Egan (3–8, 14, 16, and 17) filters. The non-passage of compounds 10 and 13 through the Goshe filter was caused by MR>130 cm^3/mol. The non-compliance with the Veber and Egan rules is caused by the high polarity of the molecules. The upper limit of the TPSA value is different for the filters (140 $Å^2$ and 131.6 $Å^2$, respectively). The predicted obstacle for passing the Muegge filter for all compounds of the series is the value of Log $P_{o/w}$, which according to the XLOGP3 method exceeds 5, and for compounds 11, 15, 16 in addition TPSA>150 $Å^2$. As evidenced by the results of *in silico* prediction of druglikeness, among all the compounds,

Predicted values of compounds 11, 15, 16 and 17

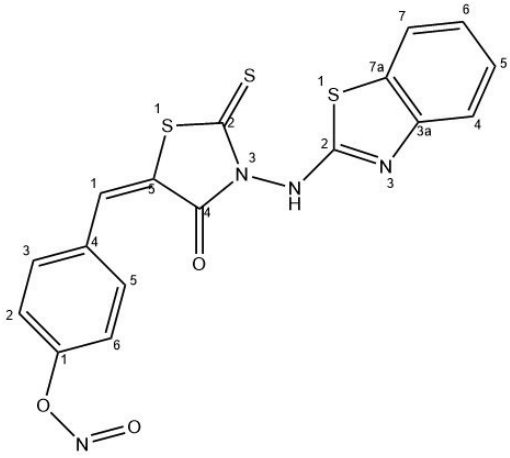
Parameter	Serial number of the compound			
	11	15	16	17
Physical and chemical characteristics				
MW (g/mol)	415.51	414.48	385.48	369.48
N-HA	27	27	25	24
N-AHA	15	15	15	15
F-Csp^3	0.06	0.00	0.00	0.10
N-RB	4	5	3	3
N-HBA	4	5	3	2
N-HBD	2	1	2	1
MR (cm^3/mol)	116.95	114.85	110.45	108.43
TPSA ($Å^2$)	160.32	169.52	151.09	130.86
Lipophilicity and water solubility of molecules				
Log $P_{o/w}$ (Consensus)	3.71	3.24	3.67	4.08
Log *S* (ESOL)	–5.88	–5.84	5.81	–5.95
Indicators of bio- and synthetic availability				
BS	0.55	0.55	0.55	0.55
SA	3.62	3.57	3.49	3.50

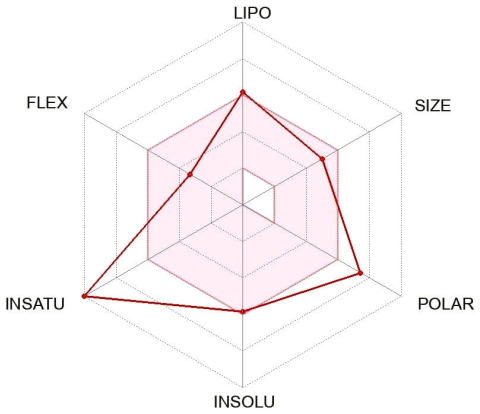




a b

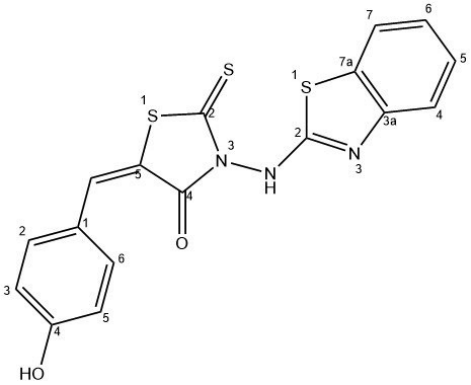
Compound 11, (*E*)-3-(benzo[*d*]thiazol-2-ylamino)-5-(4-hydroxy-3-methoxybenzylidene)-2-thioxothiazolidin-4-one

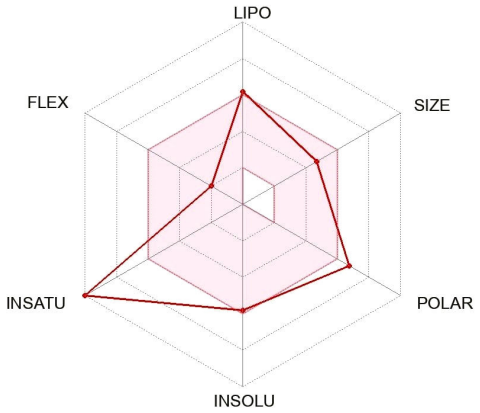




c d

Compound 15, (*E*)-4-((3-benzo[*d*]thiazol-2-ylamino)-4-oxo-2-thioxothiazolidin-5-ylidene)methyl)phenyl nitrate

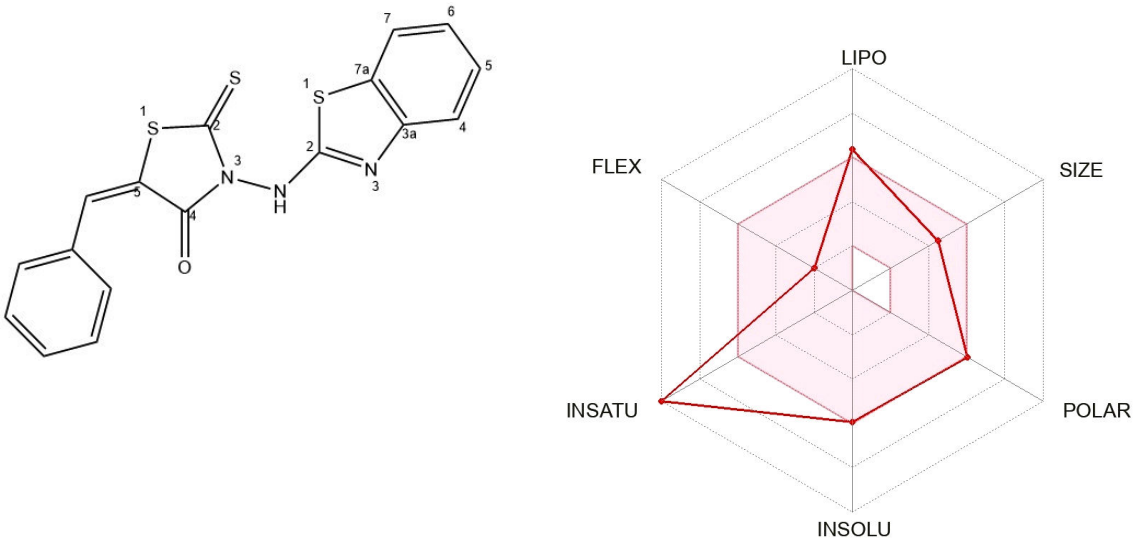




e f

Compound 16, (*E*)-3-(benzo[*d*]thiazol-2-ylamino)-5-(4-hydroxybenzylidene)-2-thioxothiazolidin-4-one

Fig. 2. Structural formulae (a, c and e), chemical names and bioavailable radars (b, d and f) of compounds 11 (a and b), 15 (c and d) and 16 (e and f)



a b

Compound 17, (*E*)-3-(benzo[*d*]thiazol-2-ylamino)-5-benzylidene-2-thioxothiazolidin-4-one

Fig. 3. Structural formula (a), chemical name and radar graph (b) of the compound 17

only the derivative with an unsubstituted benzylidene moiety (compound 17) passes the four druglikeness filters (Lipinski, Ghose, Veber, Egan) unhindered. This once again confirms the similarity of compound 17 to perorally available drugs. An important characteristic for all the derivatives is an acceptable consensus value of lipophilicity. The exception is compound 14, its Consensus Log $P_{o/w}$=5.29. The mentioned indicators correlate with the permeability of molecules through the biological membranes: the higher the values of TPSA, MR and MW, the more difficult it is for the compound to pass through cell membranes, and their passive absorption in the gastrointestinal tract is worsened. An increase in Log $P_{o/w}$ entails a decrease in the water solubility of compounds (an increase in the negative value of Log *S*), which also provokes a decrease in peroral bioavailability. According to the SwissADME predictions, the researched derivatives are poorly soluble in water, except for compounds 11 and 15–17, for which moderate water solubility is predicted. Other physicochemical parameters (MW, N-HA, N-AHA, N-RB, N-HBA and N-HBD) of our compounds have acceptable values.

As for the pharmacokinetics of the compounds, the derivatives of the series, as well as the core molecule, are not predicted to pass through the BBB or high skin permeability (Log *K*p values range from −3.71 to −5.10 cm/s). Unlike the core compound, our molecules are predicted to have low passive absorption in the gastrointestinal (GI) tract. The peroral availability of the compounds may be limited due to insufficient saturation of the molecules, since the ability of BAC to interact with enzymes and proteins in the digestive tract is dependent on the F-Csp^3 value. The F-Csp^3 value of all compounds in the series does not exceed 0.25. The predicted low oral bioavailability of the molecules encourages us to investigate potential parenteral routes of administration that bypass the GI tract.

An assessment of the distribution and excretion of molecules in the body is made possible by a predictive assessment of their ability to be a substrate or an inhibitor of P-glycoprotein. On this depends the possibility of active excretion of the compound or its metabolites through biological membranes. Presumably, our compounds are not a substrate of P-gp, and therefore should not be actively excreted from the body.

The results of metabolic prediction are derived from the ability of the molecules to inhibit one of the five isoforms of CYP450. Inhibitory activity of the derivatives of the series towards most of the isoforms presented, except CYP2D6, is probable. It is a positive characteristic of the compounds, since CYP2D6 is responsible for the metabolism and excretion of approximately 25% of drugs [12,13]. Furthermore, compounds 10, 13, and 14 are not expected to inhibit the isoform of CYP1A2, and compound 15 is not expected to inhibit the isoforms of CYP2C9 and

CYP3A4.

Detection of unwanted fragments in the molecules of the compounds under study is allowed by the use of two structural filters PAINS and Brenk, which generate alerts. The PAINS filter generated an alert for the presence of a rhodanine cycle in the structures, and the Brenk filter detected a thiocarbonyl group and Michael acceptors. For compound 15, the Brenk filter additionally alerted to the presence of another unwanted N−O fragment in the nitro group of the 5-arylidene substituent. In the recent years, the view of these fragments being of no prospect for molecular Drug Design has been refuted by the studies of many scientists, since many leading compounds contain these molecular fragments. Based on the polypharmacological approach, Michael acceptors are now being considered as perspective targets for drug development, since their affinity for several therapeutic targets is considered an advantage [14].

A common positive characteristic of all the derivatives of the series is the predicted SA value, which ranges from 3.47 to 4.01 and testifies to the sufficient ease of synthesis.

With a sufficient structural similarity, biological activity of the molecules is well predictable. With the help of web service SuperPred 3.0, it is possible to make completely accurate predictions about the medical applications of new compounds, as well as to make new conclusions about the already known targets [9]. On the basis of the potentially highest similarity of (*E*)-3-(benzo[*d*]thiazol-2-ylamino)-5-benzylidene-2-thioxothiazolidin-4-one (compound 17) by ADME profile to perorally available drugs, we researched its structural similarity with the known drugs, predicted its possible affiliation with the ATC codes, which maintained by the WHO, and the probability of binding to biotargets. The results obtained for compound 17 were compared with the predictions regarding the possibility of interaction of the other derivatives with proteins, receptors, etc. The SuperPred 3. 0 program found structural similarities of compound 17 with various finished medicinal products (FMPs) intended for the treatment of cardiovascular (angiotensin II receptor blockers (C09CA), hydrazinophthalazine derivatives acting on arteriolar smooth muscle (C02DB)), antifungal for topical use (D01AE), antiviral (for hepatitis C virus (J05AP)), antineoplastic and immunomodulating agents (protein kinase inhibitors (L01XE)) diseases, as well as diseases of the musculoskeletal system (anti-inflammatory and anti-rheumatic drugs (M01AC)), nervous system (benzodiazepine derivatives hypnotics and sedatives (N05CD), other sedative and hypnotic drugs (N05CM), antivertigo drugs (N07CA)), alimentary tract and metabolic disorders (synthetic antispasmodics, amides with tertiary amines (A03AC)).

The correspondence to almost all of these ATC codes is also inherent to compounds 1−16. It is predicted that the compound 17 has the highest structural similarity (5.09%) to drugs used to treat the cardiovascular system (*angiotensin receptor blockers*, which are assigned ATC code C09CA). A common trait of all the derivatives is the structural similarity to the drugs used in the treatment of oncological diseases. Notably, the introduction of benzylidene moiety into position 5 of the core heterocycle generally positively influenced the increase of the structural similarity to the already existing antitumour drugs that are inhibitors of proteinkinase. The index of similarity to drugs for compound 17 (containing an unsubstituted benzylidene moiety) is much lower (1.67%) than predicted for other derivatives of the series (for example, it is 21.18% for compound 7 with R=4-F). According to the predictions, compound 17, like its analogues, possesses a wide spectrum of biological activity. The list of targets with which it can potentially bind is very similar the one that is predicted for the core heterocycle and other compounds of the series. The interaction of benzylidene-substituted derivatives of this series with biological targets and their potential affiliation with certain ATC codes was described earlier. The highest level of binding for the new derivative (compound 17) is predicted with three targets: Aldose reductase (96.93%), Cathepsin D (94.91%) and Transcription intermediary factor 1-alpha (92.68%). The accuracy of the prediction models is rather high and ranges from 92.38 to 98.95%. Inhibition of the mentioned targets can play a decisive role in antitumour therapy [15].

Conclusions

5-Arylidene derivatives of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one are characterised by the satisfactory physicochemical and pharmacokinetic parameters, are sufficiently 'drug-like' and pose interest for the medicinal chemistry. In *in silico* studies, they did not show high absorption in the GI tract, in contrast to the potentially peroral core heterocycle. In terms of lipophilicity, solubility, flexibility and molecular size, the most similar to peroral drugs can be considered the virtually modelled compound 17, which contains an unsubstituted benzylidene moiety at the position 5 of the rhodanine cycle. Its oral availability is limited by the insufficient saturation of the molecule due to non-compliance with the F-Csp^3 criterion. For other molecules, more violations (i2) of the optimal range of such physicochemical descriptors as F-Csp^3, TPSA, MR, Log *S*, Log $P_{o/w}$ are expected. Despite some

unsatisfactory indicators, all the studied derivatives can be considered perspective objects for the rational design of new drugs. Accounting for their sufficient bio- (BS=0.55) and synthetic (SA=3.47−4.01) availability, we consider structural optimisation of the compounds and study of parenteral routes of administration to be promising. The obtained results are the basis for further studies to find new BAC among the specified class of heterocycles.

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ДОСЛІДЖЕННЯ ФІЗИКО-ХІМІЧНИХ, ФАРМАКОКІНЕТИЧНИХ І «ЛІКОПОДІБНИХ» ПАРАМЕТРІВ 5-АРИЛІДЕНПОХІДНИХ 3-(БЕНЗО[*d*]ТІАЗОЛ-2-ІЛАМІНО)-2-ТІОКСОТІАЗОЛІДИН-4-ОНУ

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У статті описані *in silico* дослідження фізико-хімічних, фармакокінетичних і «лікоподібних» параметрів 5-ариліденпохідних 3-(бензо[*d*]тіазол-2-іламіно)-2-тіоксотіазолідин-4-ону. Для прогнозування абсорбції, розподілу, метаболізму і виведення (ADME) сполук був використаний веб-інструмент SwissADME. За результатами прогнозування встановлено, що введення ариліденового фрагмента у 5 положення базової сполуки із потенційно високою пероральною доступністю негативно впливає на пасивну абсорбцію молекул у шлунково-кишковому тракті. Для конкретизації впливу характеру замісників в ариліденовому фрагменті на прояв властивостей такого роду сполук було змодельовано структуру нового похідного з незаміщеним бензиліденовим ядром. За допомогою іншого *in silico* інструмента SuperPred 3.0 встановлено, що поява замісників в бензиліденовому фрагменті сприяє підвищенню потенційної афінності похідних ряду до багатьох терапевтичних мішеней, про що свідчить структурна подібність їх з існуючими препаратами широкого спектру дії. Спільною характеристикою усіх похідних є схожість структури із діючими речовинами протипухлинних лікарських засобів. Виходячи з прийнятного ADME профілю досліджуваних сполук та їх високого фармакологічного потенціалу, доцільним є продовження ґрунтовних досліджень парентеральних шляхів введення або оптимізація структури молекул для підвищення пероральної біодоступності. Одержані прогностичні відомості про можливу поведінку похідних ряду в організмі людини можуть бути теоретичною платформою для синтезу *de novo* сполук із поліфармакологічним профілем.

Ключові слова: роданін, бензотіазол, *in silico* скринінг, фізико-хімічний аналіз, створення ліків, SwissADME, SuperPred 3.0, взаємозв'язок «структура−активність».

RESEARCH OF PHYSICOCHEMICAL, PHARMACOKINETIC AND DRUGLIKENESS PARAMETERS OF A SERIES OF 5-ARYLIDENE DERIVATIVES OF 3-(BENZO[*d*]THIAZOL-2-YLAMINO)-2-THIOXOTHIAZOLIDIN-4-ONE)

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The article presents *in silico* research of physicochemical, pharmacokinetic and druglikeness parameters of a series of 5-arylidene derivatives of 3-(benzo[*d*]thiazol-2-ylamino)-2-thioxothiazolidin-4-one. The web tool SwissADME was used for prediction of absorption, distribution, methabolism and excretion (ADME) of compounds. Based on the prediction results, it was determined that the introduction of an arylidene moiety into position 5 of the base compound with potentially high peroral availability negatively affects the passive absorption in the gastrointestinal tract. To further characterize the effect of substituents in the arylidene moiety on the manifestation of properties of this type of compounds, a structure of a new derivative of with an unsubstituted benzylidene nucleus was simulated. With the use of another *in silico* tool, SuperPred 3.0, it was established that the introduction of an substituent into the benzylidene moiety promotes the potential affinity of the derivatives to many therapeutic targets to a wide variety of therapeutic targets, as evidenced by their structural similarity to existing broad-spectrum drugs. A common characteristic of all the derivatives is their structural resemblance to the active components of antitumor drugs. Based on the acceptable ADME profile of the studied compounds and their high pharmacological potential, it is advisable to continue thorough studies of parenteral routes of administration or optimize the structure of the molecules to increase oral bioavailability. The obtained predictive information on the possible behavior of the derivatives in the human body can become a theoretical platform for the synthesis of de novo compounds with a polypharmacological profile.

Keywords: rhodanine; benzothiazole; *in silico* screening; physicochemical analysis; drug development; SwissADME; SuperPred 3.0; structure vs. activity relationships.

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