ISSN 1814-9758. Ukr. Bioorg. Acta, 2021, Vol. 16, N 2
UDC 615.28+547.814+547.83+547.94+004.942
DOI: https://doi.org/10.15407/bioorganica2021.02.023

Ukrainica Bioorganica Acta
www.bioorganica.org.ua

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RESEARCH ARTICLE

Cytisine derivatives as new anti-Escherichia coli agents: *in silico* and *in vitro* studies

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Abstract: QSAR analysis of a 5143 compounds set of previously synthesized compounds tested against multi-drug resistant (MDR) clinical isolate *Escherichia coli* strains was done by using Online Chemical Modeling Environment (OCHEM).The predictive ability of the regression models was tested through cross-validation, giving coefficient of determination q^2 = 0.72-0.8. The validation of the models using an external test set proved that the models can be used to predict the activity of newly designed compounds with reasonable accuracy within the applicability domain (q^2 = 0.74-0.8). The models were applied to screen a virtual chemical library of cytisine derivatives, which was designed to have antibacterial activity. The QSAR modeling results allowed to identify a number of cytisine derivatives as effective antibacterial agents against antibiotic-resistant *E. coli* strains. Seven compounds were selected for synthesis and biological testing. *In vitro* investigation of the selected cytisine derivatives have shown that all studied compounds are potential antibacterial agents against MDR *E. coli* strains.

Keywords: cytisine derivatives, QSAR, *Escherichia coli*, antibacterial activity.

Introduction

In modern conditions, when the therapeutic effectiveness of known antibiotics becomes limited due to the growth of resistance of pathogenic bacteria, research aimed at the search and development of new antibacterial drugs is of particular importance [1, 2]. Modern in silico and in vitro screening methods promise the successful discovery of new biologically active compounds, including the antibacterial type of action, but their further clinical testing can be quite long.

Therefore, one approach to the problem decision of new antibiotics is the so-called repurposing of known chemical compounds, which have already demonstrated, along with the main activity, a wide range of pharmacological effects [3, 4]. Screening of such compounds can be one effective way to detect novel antibacterials.

It is known that natural products as well as their derivatives play a significant role in the discovery of new biologically active compounds in the different areas of the lifetime especially in the pharmacology due to a wide range of their biological properties. They demonstrate the cholinolitic, nootropic, antiviral, anticancer, hemostatic, anti-inflammatory, antiarrhythmic and antioxidant and cytotoxic activity [5, 6]. In the small number of studies carried out to date, such compounds have shown promise in treating bacterial infections.

Cytisine is one of the most promising in terms of possible modification and creation of new biologically active substances [7, 8]. Chemical modifications of cytisine have large potential prospects. Among the various derivatives of cytisine, compounds are constantly found with other types of biological activity that are not characteristic of itself (antispasmodic, antiarrhythmic, hepatoprotective, analgesic, cholinergic, insecticidal, antioxidant, etc.), which attracts attention and encourages the synthesis and study of its new derivatives [9, 10]. Small

Received: 27.08.2021
Revised: 08.09.2021
Accepted: 29.09.2021
Published online: 30.12.2021

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doses of cytisine strongly arouse breathing and increase blood pressure. In the form of a 1.5% aqueous solution (Cityton), the alkaloid is used in medicine in cases of asphyxia and intoxication. Currently, more than 1000 cytisine derivatives of various structures are known, methods of their synthesis are described and pharmacological activity being studied.

The current paper presents the results of the study of cytisine derivatives as antibacterials by QSAR method and experimental testing against antibiotic-resistant E. coli strains.

Results and Discussion

Chemistry

Synthesis of cytisine derivatives (Figure 1) was achieved by linking of the alkaloid with chromone or 2*H*-benzofuran-3-one derivatives using methylene, ethylene or 1,3-propylene linker. Synthesis of desired isoflavone derivative **1a** [11], isoxazole **2** [12] or pyrazole **3** [13] was reported early.

Chromone-cytisine hybrid **1b** was synthesized by alkylation of 2,3-dimethylchromone (**4a**) [14] with epichlorohydrin in *N*,*N*-dimethylacetamide in presence of K_2CO_3 with subsequent regioselective ring-opening reaction of epoxide **5a** with cytisine. The similar aurone derivative **1c** [15] was synthesized starting from aurone **4c** using described above procedure (Scheme 1).

Mannich reaction of (2*Z*)-6-hydroxy-2-(pyridin-3-ylmethylene)-2,3-dihydro-1-benzofuran-3-one (**4c**) [16] or 4'-chloro-7-hydroxy-5-methoxyisoflavone (**4d**) [17] with cytisine and paraformaldehyde in presence of 4-(dimenthylamino)pyridine (DMAP) led to formation of flavonoid-cytisine hybrids **6a,b** containing methylene group as linker between flavonoid and alkaloid moeties (Scheme 2).

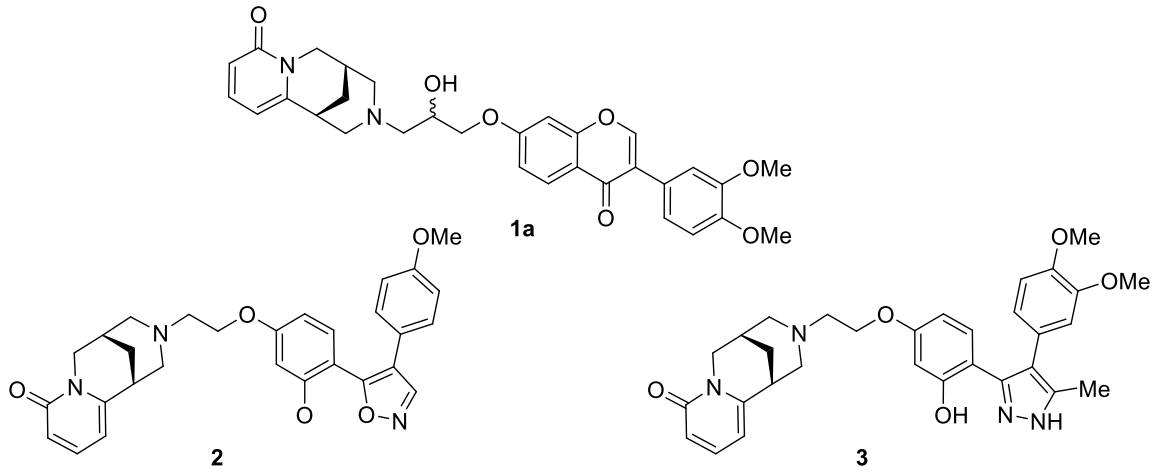
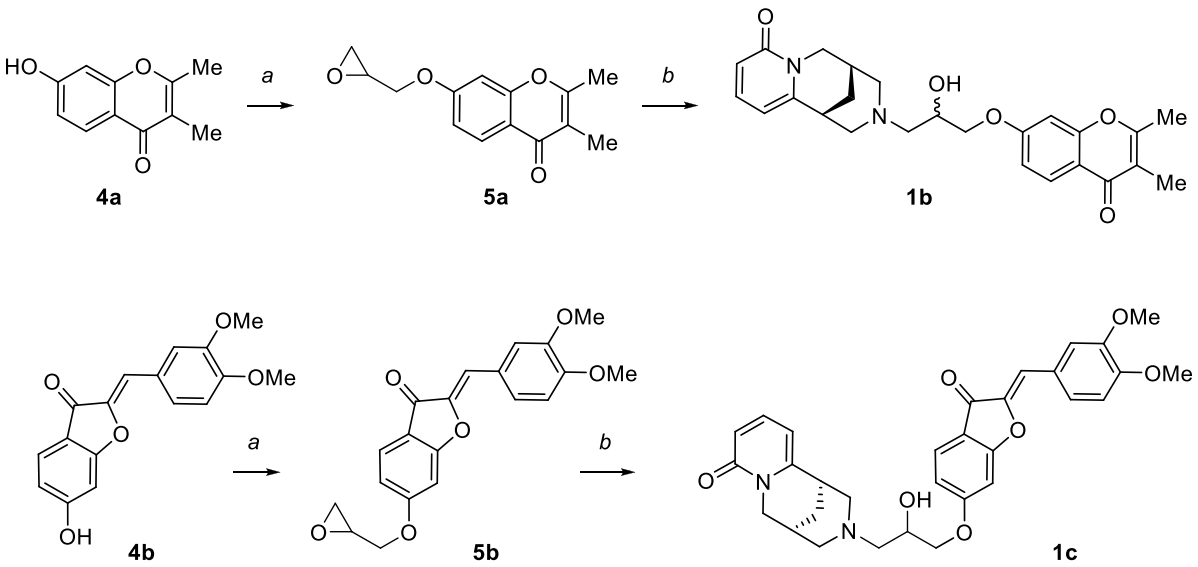
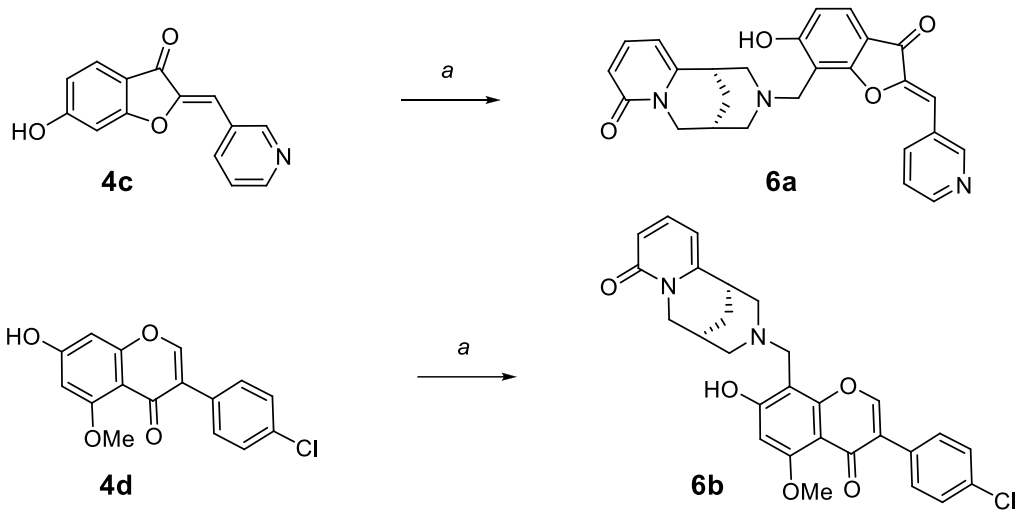


Figure 1. Structures of cytisine derivatives **1a**, **2**, and **3**.



Scheme 1. Reagents and conditions: *a*) epichlorohydrin, K_2CO_3, *N*,*N*-dimethylacetamide, 65-70 °C, 5-10 h; *b*) cytisine, MeCN, $Bu_4N^+I^-$, 80 °C 10-12 h.



Scheme 2. Reagents and conditions: *a*) cytisine, $(CH_2O)_n$, DMAP, *i*-PrOH, 80 °C, 10-12 h.

QSAR modeling

The initial dataset of 5143 compounds with activity against *E. coli* was split by chance into training (3780) and test (1363) sets. The regression models built by the Trans-CNN [18], ASNN [19], and RFR [20] methods (see Table 1) calculated the best performances. For this analysis E-state [21], ALOGPS [22], CDK2 [23], descriptors were included in the best models for all methods. The results are summarized in Table 1 and the performances of individual models are shown in Figure S1 of the *Supplementary materials*.

The q^2 values were 0.72-0.8 and 0.74-0.8 for training and test sets, respectively. Other statistical parameters of the models are summarized in Table 1 as well as in Figure S1 of the *Supplementary materials*. A consensus model, which is an average of all three models, obtained the best performance. It was used to provide a quantitative evaluation of activity of compounds against *E. coli* as described in the Experimental sections. The variances of individual predictions of the consensus model were used to calibrate the prediction errors and estimate their applicability domain [24].

Evaluation activity of new compounds

A virtual database of drug-like cytisine derivatives was generated based on available synthetic blocks and reactions. It included 26 compounds with different substitution patterns (see *Supplementary materials*, Table S1). These compounds were screened using the consensus model against *E. coli*. The 11 compounds predicted as most active within the applicability domain (i.e., compounds with MIC < 50μM) were selected for further evaluation (see also *Supplementary materials*, Table S1). The next analysis was to examine the toxic effects (mutagenicity, tumorigenicity, irritation and reproductive effectiveness) of the studied compounds using the DataWarrior 5.5 program [25]. As a result of this analysis, only 7 compounds were selected for synthesis and testing. The synthetic feasibility of the compounds was evaluated by organic chemists, and all seven compounds were synthesized and tested for their antibacterial activity against *E. coli*. (see Table 2 and Table S1, in *Supplementary materials*).

Table 1. Statistical coefficients of the regression models.

Method	Training Set[a]			Test Set[a]		
	R^2	q^2	RMSE	R^2	q^2	RMSE
Trans-CNN	0.80 ± 0.01	0.80 ± 0.01	0.48 ± 0.01	0.8 ± 0.02	0.8 ± 0.02	0.48 ± 0.02
ASNN[b]	0.73 ± 0.01	0.72 ± 0.01	0.58 ± 0.01	0.74 ± 0.02	0.74 ± 0.02	0.57 ± 0.03
RFR[b]	0.76 ± 0.01	0.75 ± 0.01	0.55 ± 0.01	0.78 ± 0.02	0.77 ± 0.02	0.53 ± 0.02
Consensus[c]	0.79 ± 0.01	0.79 ± 0.01	0.34 ± 0.01	0.80 ± 0.02	0.79 ± 0.01	0.33 ± 0.01

[a]The training and test sets included 3780 and 1363 molecules, respectively. The cross-validation results are reported for the training set;
[b]ASNN and RFR models developed by using E-state, ALOGPS and CDK2 descriptors;
[c]Consensus model was built by averaging outputs of all three models.
R^2 – square of correlation coefficient; q^2 – coefficient of determination; RMSE – Root Mean Squared Error.

Biology testing

In vitro antimicrobial activity results by measuring the zone diameter of growth inhibition of studied *cytisine derivatives* tested against pathogenic *E. coli* strains are shown in Table 2.

Table 2. *In vitro* activity *of cytisine derivatives* against *E. coli* strains by the diameter of growth inhibition zones.

Compd	Zone diameter of growth inhibition of *E. coli* strains, mm		
	E. coli ATCC[a]	*E. coli* CRBR[b]	*E. coli* MDR[c]
1a	16	14	8
1b	18	16	16
1c	17	17	10
2	15	13	na
3	19	15	10
6a	14	17	na
6b	18	15	9

na - no activity.
[a]American Type Culture Collection (strain 25922).
[b]Carbenicillin resistant clinical isolate of hemolytic *E. coli* strain.
[c]Ampicillin, Ceftazidime, Ofloxacin, Kanamycin, Ceftriaxone resistant *E. coli* clinical isolate.

The results presented in Table 1 show that all studied *cytisine derivatives* exhibited antibacterial activity against *E. coli* ATCC and *E. coli* CRBR strains with diameters of inhibition zones in the range of 13-19 mm. MDR *E. coli* strain has demonstrated the least sensitivity to all compounds (except compound **1b** with inhibition zone of 16 mm).

Thus it is worth to note the activity of compound **1b** which showed high antibacterial properties against all *E. coli* strains. Moreover compounds **1c, 3,** and **6b** possessed the high antibacterial effect against *E. coli* ATCC and *E. coli* CRBR strains.

Conclusions

A number of predictive regression models based on different machine learning techniques were built using the OCHEM platform. The created models demonstrated good stability, robustness, and predictive power. Our results demonstrated that designed and synthesized seven compounds were found to be active against the *E. coli* ATCC and *E. coli* CRBR strains. These compounds can be perspective antibacterial against MDR *E. coli* clinical isolate due to future structural optimization.

Experimental section

Data

The data for our analysis were obtained from multiple publications and uploaded into the On-line Chemical Database and Modeling Environment (OCHEM) [26].The structure of compounds, their antibacterial activity and the literary source of all data are freely available on the OCHEM website. The initial dataset of 5143 consisted of diverse chemical series with minimum inhibitory concentration (MIC) values of the molecules ranging from 1.94 nM to 260 mM against the *E. coli* ATCC 25922 strain. MICs were converted into log(1/MIC) values and were used as the target variable to develop regression models.

Machine-learning methods

Well-known machine-learning methods such as Transformer Convolutional Neural Network (Trans-CNN) [18], Associative Neural Networks (ASNNs) [19] and Random Forest (RFR) [20] were used to build QSAR models.

Transformer Convolutional Neural Network (Trans-CNN). The Trans-CNN method uses the internal representation of molecules based on their SMILES notation for extracting information-rich real-value embedding during the encoding process and uses them for further QSAR-oriented blocks to model biological activity [18]. The Transformer-CNN architecture usually requires a few tens iterations to converge for new tasks. The method developed predicts the endpoint based on an average of individual prognosis for a batch of augmented SMILES belonging to the same molecule. The deviation within the batch can serve as a measure of a confidence interval of the prognosis, whereas the possibility to canonize SMILES can be used for deriving applicability domains of models.

Associative Neural Network (ASNN). ASNN represents a combination of an ensemble of the Feed-Forward Backpropagation Neural Networks and the *k*-Nearest Neighbors (*k*NN) method [19]. While neural networks build an ensemble of global models, *k*NN provides a local correction of the global model set. This combination corrects the bias of the neural network ensemble and increases its accuracy. The ASNN was trained by SuperSAB [27]. The number of input neurons corresponded to the amount of analyzed descriptors. The neural network weight coefficients were initialized with random values within [-0.5; +0.5] for each network in the ensemble. The bias neuron was also presented in both the input and hidden layer of nodes. The ensemble includes 100 neural networks, which were developed using the default parameters provided by OCHEM.

Random Forest (RFR). The random forest is a recursive partition ensemble method consisting of a set of decision trees, each of which is built using a bootstrap replica of the training set and randomly selected subsets of descriptors. The random forest makes predictions by majority votes of the individual trees. Random Forest calculates predictions by using a majority vote of the individual trees. This is a

high-dimensional non-parametric method that operates quickly on large datasets [20].

*Descriprors.*The OCHEM supports multiple software packages for calculation of diverse molecular descriptors. In this study, we used E-state indices [21], AlogPS [22] and CDK2 [16] packages, which were frequently top-performing descriptors according to our previous studies. The electro-topological state indices are 2D descriptors that combine both electronic and topological characteristics of the analyzed compounds [21]. AlogPS estimates lipophilicity and solubility of chemical compounds while electrotopological descriptors describe their electronic and topological characteristics [22]. CDK descriptors (3D) are calculated by the CDK Descriptors Engine and include 204 molecular descriptors such as topological, geometrical, constitutional, electronic, and hybrid descriptors [23].

Descriptor preprocessing. The unsupervised filtering of descriptors was used. Descriptors with fewer than two unique variables or with a coefficient of variance, less than 0.01 were excluded. Moreover, descriptors with a pairwise non-parametric Pearson's correlation coefficient R > 0.95 were grouped. Additionally, the Unsupervised Forward Selection (UFS) method [28] was used to select a representative non-redundant set for model development.

Model validation. Two validation protocols were used. First of all, the initial data were split by chance into training and test sets. For the training set five-fold cross-validation with variable selection in each step of the analysis was used to estimate accuracy of models for the training set [29]. To avoid incorrect estimation of the models due to over-fitting by the variable selection, the OCHEM repeats the cross-validation step for all steps of model development.

Estimation of prediction accuracy. The OCHEM estimates the applicability domain and the accuracy for each prediction [24]. We used two criteria to access the goodness of fitting: the squared correlation coefficient R^2 and the coefficient of determination q^2. In addition, we used root mean square error (RMSE) and the Mean Absolute Error (MAE) statistics to estimate the errors in predictions [26]. A detailed description of used machine-learning methods, all selected descriptors, and validation procedures can be found in the OCHEM manual [30].

Chemistry

^{1}H spectra were recorded on Varian 400 (400 MHz) spectrometers in $CDCl_3$ [residual $CHCl_3$ (δ_H = 7.26 ppm) as internal standard] Melting points were determined in open capillary tubes using Buchi B-535 apparatus and were uncorrected. Mass spectra were obtained using an Agilent 1100 spectrometer using APCI (atmospheric-pressure chemical ionization).

2,3-Dimethyl-7-(oxiran-2-ylmethoxy)-4H-chromen-4-one ***(5a)*** synthesized as previously was described procedure [31].

Yield 73%; mp 112-114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* 8.9 Hz, 1H), 6.95 (dd, *J* 8.9, 2.4 Hz, 1H), 6.80 (d, *J* 2.4 Hz, 1H), 4.34 (dd, *J* 11.1, 2.9 Hz, 1H), 4.00 (dd, *J* 11.1, 5.9 Hz, 1H), 3.44-3.34 (m, 1H), 2.95 (dd, *J* 4.9, 4.1 Hz, 1H), 2.80 (dd, *J* 4.9, 2.6 Hz, 1H), 2.39 (s, 3H), 2.04 (s, 3H). LC/MS (APCI) *m/z* 247.0 $[M+H]^+$. Anal. calcld. for $C_{14}H_{14}O_4$: C, 68.28; H. 5.73. Found: C, 68.53; H, 5.99.

(2Z)-2-(3,4-Dimethoxybenzylidene)-6-(oxiran-2-ylmethoxy)-1-benzofuran-3(2H)-one ***(5b)*** synthesized as previously was described procedure [31].

Yield 81%; mp 165-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* 8.9 Hz, 1H), 7.50-7.43 (m, 2H), 6.93 (d, *J* 8.3 Hz, 1H), 6.79 (s, 1H), 6.77-6.75 (m, 2H), 4.39 (dd, *J* 11.1, 2.8 Hz, 1H), 4.03 (dd, *J* 11.1, 5.9 Hz, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.44-3.38 (m, 1H), 2.98-2.92 (m, 1H), 2.80 (dd, *J* 4.8, 2.6 Hz, 1H). LC/MS (APCI) *m/z* 335.2 $[M+H]^+$. Anal. calcld. for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.53; H, 5.40.

(1S,5R)-3-{3-[(2,3-Dimethyl-4-oxo-4H-chromen-7-yl)-oxy]-2-hydroxypropyl}-1,2,3,4,5,6-hexahydro-8H-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one ***(1b)*** synthesized as previously was described procedure [31].

Yield 83%; mp 173-175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* 8.9 Hz, 1H), 7.51-7.38 (m, 1H), 7.06 (d, *J* 2.2 Hz, 1H), 7.03-6.95 (m, 1H), 6.40 (dd, *J* 8.8, 4.7 Hz, 1H), 6.30 (dd, *J* 7.1, 1.4 Hz, 1H), 3.93-3.85 (m, 4H), 3.18-2.85 (m, 3H), 2.70-2.61 (m, 1H), 2.56-2.41 (m, 5H), 2.38 (s, 3H), 2.05-1.85 (m, 2H), 1.80 (s, 3H). LC/MS (APCI) *m/z* 437.2 $[M+H]^+$. Anal. calcld. for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.47; N, 6.42. Found: C, 69.03; H, 6.22; N, 6.70.

(1S,5R)-3-(3-{[(2Z)-2-(3,4-Dimethoxybenzylidene)-3-oxo-2,3-dihydro-1-benzofuran-6-yl]oxy}-2-hydroxypropyl)-1,2,3,4,5,6-hexahydro-8H-1,5-methanopyrido[1,2-a][1,5]-diazocin-8-one ***(1c)*** synthesized as previously was described procedure [31].

Yield 77%; mp 124-126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, *J* 8.4, 1.2 Hz, 1H), 7.53-7.46 (m, 2H), 7.29-7.20 (m, 1H), 6.95 (d, *J* 8.8 Hz, 1H), 6.80 (s, 1H), 6.72-6.64 (m, 2H), 6.45 (d, *J* 9.0 Hz, 1H), 6.03-5.93 (m, 1H), 3.99 (s, 3H), 3.95 (s, 3H), 3.93-3.85 (m, 4H), 3.18-2.85 (m, 3H), 2.70-2.61 (m, 1H), 2.56-2.41 (m, 5H), 2.01-1.80 (m, 2H). LC/MS (APCI) *m/z* 545.2 $[M+H]^+$. Anal. calcld. for $C_{31}H_{32}N_2O_7$: C, 68.37; H, 5.92; N, 5.14. Found: C, 68.21; H, 5.12; N, 5.02.

(1S,5R)-3-{[(2Z)-6-Hydroxy-3-oxo-2-(pyridin-3-ylmethylene)-2,3-dihydro-1-benzofuran-7-yl]methyl}-1,2,3,4,5,6-hexahydro-8H-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one ***(6a)*** synthesized as previously was described procedure [32].

Yield 63%; mp 219-221 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 9.03 (d, *J* 8.5 Hz, 1H), 8.93 (d, *J* 5.7 Hz, 1H), 8.13 (dd, *J* 8.2, 5.7 Hz, 1H), 7.75 (d, *J* 8.5 Hz, 1H), 7.48 (t, *J* 8.0 Hz, 1H), 7.06 (s, 1H), 6.95 (d, *J* 8.5 Hz, 1H), 6.49 (d, *J* 9.0 Hz, 1H), 6.41 (d, *J* 7.0 Hz, 1H), 4.49 (d, *J* 14.1 Hz, 1H), 4.43 (d, *J* 14.1 Hz, 1H), 4.11 (d, *J* 15.8 Hz, 1H), 3.93-3.82 (m, 1H), 3.77-3.65 (m, 1H), 3.65-3.55 (m, 1H), 3.51-3.30 (m, 3H), 2.79-2.65 (m, 1H), 2.02-1.78 (m, 2H). LC/MS (APCI) *m/z* 442.2 $[M+H]^+$. Anal. calcld. for

$C_{26}H_{23}N_3O_4$: C, 70.74; H, 5.25; N, 9.52. Found: C, 70.93; H, 5.48; N, 9.31.

(1S,5R)-3-{[3-(4-Chlorophenyl)-7-hydroxy-5-methoxy-4-oxo-4H-chromen-8-yl]methyl}-1,2,3,4,5,6-hexahydro-8H-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one ***(6b)*** synthesized as previously was described procedure [32].

Yield 66%; mp 186-188 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.45 (d, *J* 8.1 Hz, 2H), 7.38-7.31 (m, 3H), 6.56 (d, *J* 9.1 Hz, 1H), 6.27 (s, 1H), 6.05 (d, *J* 6.8 Hz, 1H), 4.19 (d, *J* 15.6 Hz, 1H), 3.97-3.81 (m, 5H), 3.76 (d, *J* 14.4 Hz, 1H), 3.22-3.03 (m, 3H), 2.65-2.41 (m, 3H), 2.07-1.86 (m, 2H). LC/MS (APCI) *m/z* 505.0 $[M+H]^+$. Anal. calcld. for $C_{28}H_{25}ClN_2O_5$: C, 66.60; H, 4.99; N, 5.55. Found: C, 66.32; H, 5.18; N, 5.79.

Biology

The antimicrobial activity of the cytisine derivatives was evaluated *in vitro* against *E. coli* ATCC 25922 (American Type Culture Collection) strain, *E. coli* CRBR (Carbenicillin resistant clinical isolate of hemolytic *E. coli*) strain and MDR *E. coli* strain (Ampicillin, Ceftazidime, Ofloxacin, Kanamycin, Ceftriaxone resistant) received from the Museum of Microbial Culture Collection of the Shupyk National Healthcare University of Ukraine. Antimicrobial properties were determined by the disc diffusion method in Mueller-Hinton agar [33]. A final inoculum concentration of $1*10^5$ colony-forming unit (CFU) per mL was established using a 0.5 McFarland turbidity standard. The subsequent dilution of 0.02 ml of the tested compounds was applied on standard paper disks (6 mm) which were placed on the agar plate.

The compound content on a disk was 5.0 μM. The activity of tested compounds was identified by measuring the zone diameter of the growth inhibition, which indicates the degree of susceptibility or resistance of bacterial pathogens against the test compounds.

Notes

Supplementary Materials: Supplementary materials can be found at: https://bioorganica.com.ua/index.php/journal/issue/archive

The authors declare no conflict interest.

Author contributions. D. M. H.: conceptualization, investigation of bioactivity, results analysis; supervision, writing most of the manuscript. **V. V. K.**: QSAR investigation, results analysis, writing; **V. M. B.**: investigation; **S. P. B.**: synthesis of compounds; **G. P. M.**: synthesis of compounds, formal analysis; **M. S. F.**: conceptualization, writing, results analysis; **V. S. B.**: conceptualization, supervision; **L. O. M.**: conceptualization, supervision, writing - review & editing.

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Похідні цитизину як нові антибактеріальні агенти проти *Escherichia coli*: *in silico* та *in vitro* дослідження

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Резюме: QSAR аналіз, який базувався на основі набору з 5143 раніше синтезованих сполук з активністю проти культури *Escherichia coli* із множинною лікарською стійкістю (MDR), був проведений за допомогою Онлайн платформи хімічного моделювання (OCHEM). Передбачувана здатність регресійних моделей була перевірена шляхом перехресної перевірки, коефіцієнт детермінації якої становив q^2 = 0,72-0,8. Перевірка моделей з використанням зовнішнього тестового набору підтвердила використання моделей для прогнозування активності нових розроблених сполук із достатньою точністю в межах області застосування (q^2 = 0,74-0,8). QSAR-моделі були використані для скринінгу віртуальної хімічної бібліотеки похідних цитизину, які володіють антибактеріальною активністю. Результати QSAR-моделювання дозволили ідентифікувати ряд похідних цитизину як ефективних антибактеріальних засобів проти антибіотикорезистентних штамів *E. coli*. Для синтезу та біологічного тестування було відібрано сім сполук. *In vitro* дослідження синтезованих похідних цитизину показали, що всі сполуки є потенційними антибактеріальними засобами проти мультирезистентних штамів *E. coli*.

Ключові слова: похідні цитизину, QSAR, *Escherichia coli*, антибактеріальна активність.