UDC 547.854.856

S.A. Varenichenko, A.V. Kharchenko, O.K. Farat

SYNTHESIS AND *IN SILICO* ADMET PROFILING OF NOVEL 5-ARYLIDENE-2-(2,3,5,6,7,8-HEXAHYDROACRIDIN-4(1*H*)-YLIDENE)-1,3-THIAZOLIDIN-4-ONES

Ukrainian State University of Chemical Technology, Dnipro, Ukraine

The corresponding thiazolidone derivative was synthesized with a good yield by the reaction of 1,2,3,4,5,6,7,8-octahydroacridine-4-carbonitrile with thioglycolic acid. It was found that this compound is present in DMSO in the form of two isomers, (2E)-2-(2,3,5,6,7,8-hexahydroacridin-4(1H)-ylidene)-1,3-thiazolidin-4-one and (2Z)-2-(2,3,5,6,7,8-hexahydroacridin-4(1H)-ylidene)-1,3-thiazolidin-4-one in a ratio of 9:1, respectively, whereas it is present only in the form of the E-isomer in chloroform. The corresponding 5-arylidene-2-(2,3,5,6,7,8-hexahydroacridin-4(1H)-ylidene)-1,3-thiazolidin-4-ones were obtained with good yields. Isolation of all products is not difficult and is carried out by simple filtration. The physicochemical and pharmacokinetic properties of the obtained compounds were predicted, and a comparative analysis of the obtained indicators with active drugs, pioglitazone and rosiglitazone was carried out by using ADMETlab 2.0 software. All tested compounds comply with the Lipinski rule. Additionally, toxicity, half-life, clearance, intestinal absorption and blood-brain barrier penetration potentials were compared. In most respects, the synthesized compounds are comparable to active drugs. The 1,3-thiazolidin-4-one derivatives characterized in the article are promising as building blocks for the organic synthesis and for further *in vitro* testing.

Keywords: substituted acridine, substituted thiazolidin-4-one, Knoevenagel reaction, isomerism, ADMETlab 2.0.

DOI: 10.32434/0321-4095-2023-151-6-37-43

Introduction

Thiazolidin-4-one is an important structural moiety of a large number of biologically active compounds and represents a preferred scaffold for medicinal chemistry [1]. Substituted thiazolidin-4-one exhibits antituberculosis [2,3], anticancer [4], antiprotozoal [5] and antibacterial [6] activities. Previously, we discovered new methods for the synthesis of acridine [7,8] and xanthene [9] systems. Based on the obtained heterocycles, new dyes [10] and other practically useful compounds were synthesized [11,12]. In this work, based on the product of a previously discovered reaction, hybrid acridine-thiazolidin-4-one compounds were synthesized and their physicochemical and pharmacokinetic parameters were predicted.

Experimental

Unless otherwise stated, all reagents of analytical grade were purchased from commercial suppliers and used without any further purification. The ^{1}H NMR spectra were obtained by using a Varian VXR 200 instrument (200 MHz) in DMSO-d_6 using TMS as a reference and on a Bruker Avance II 400 spectrometer (400 MHz and 100 MHz for ^{1}H and ^{13}C, respectively) in DMSO-d_6 or $CDCl_3$ using residual solvent peak as a reference. The mass spectra were recorded by means of a MX1321 instrument with direct injection of the sample at an ionization chamber temperature of 200^{0}C and with 70 eV ionizing electrons. Elemental analysis was performed by means of a LECO CHN-900 instrument. The reactions and the purity of the obtained compounds were monitored by TLC on Merck Silicagel 60 F-254 plates with 10:1 $CHCl_3$–i-PrOH as eluent. Melting points were carried out using an Electrothermal 9100 Digital Melting Point apparatus

and were uncorrected. Compound 1 was obtained using literature data [7].

Synthesis of 2-(2,3,5,6,7,8-hexahydroacridin-4(1H)-ylidene)-1,3-thiazolidin-4-one 2

0.3 ml (5 mmol) of acetic acid, 0.8 ml (10 mmol) of pyridine and 0.7 ml (10 mmol) of thioglycolic acid were added to a solution of compound 1 (1.06 g, 5 mmol) in 0.4 ml (5 mmol) 1,4-dioxane. The mixture was boiled for 10 h and the precipitated crystals were filtered after cooling. Crystallize from DMF. Yield 1 g (70%), mp 255–256^{0}C. ^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm: 13.02 and 10.61 (1H, br. s, NH), 7.22 and 7.13 (1H, s, CH-10), 3.83 and 3.52 (2H, s), 1.53–2.84 (16H, m). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 13.36 (1H, br. s, NH), 7.05 (1H, s, CH-10), 3.70 (2H, s), 2.83–2.87 (2H, m), 2.64–2.70 (5H, m), 2.37–2.41 (2H, m), 1.70–1.88 (7H, m). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 173.5, 152.7, 149.5, 137.5, 136.5, 127.9, 109.9, 103.5, 32.7, 32.0, 29.3, 28.1, 27.7, 22.9, 22.7, 22.0. MS (EI), *m/z* (I_{rel}, %): 286 $[M]^+$ (73). Calculated $C_{16}H_{18}N_2OS$: C 67.10; H 6.33; N 9.78. Found: C 67.25; H 6.40; N 9.86.

Synthesis of compounds 3–7 (general method)

Anhydrous sodium acetate (0.16 g, 2 mmol) and 2 mmol of the corresponding benzaldehyde were added to a solution of compound 2 (0.57 g, 2 mmol) in 10 ml of acetic acid. This mixture was heated at a temperature of 100^{0}C for 8 h, and the precipitated crystals were filtered after cooling. The compounds were crystallized from DMF.

5-Benzylidene-2-(2,3,5,6,7,8-hexahydroacridin-4(1H)-ylidene)-1,3-thiazolidin-4-one 3

Orange powder, mp: 250–252^{0}C, yield 75%. ^{1}H NMR spectrum (200 MHz, DMSO-d_6), δ, ppm: 13.42 (1H, s, NH), 7.43–7.72 (5H, m, Ph), 7.34 (2H, br. s, CH-10 and CH), 1.52–2.83 (14H, m). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 13.45 (1H, br. s, NH), 7.55–7.57 (3H, m, Ar, CH), 7.41–7.46 (2H, m, Ar), 7.30–7.35 (1H, m, Ar), 7.08 (1H, s, CH-10), 2.87–2.94 (2H, m), 2.66–2.75 (4H, m), 2.54–2.58 (2H, m), 1.75–1.92 (6H, m). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 167.9, 153.4, 149.4, 137.6, 134.7, 132.2, 129.5, 128.8, 128.6, 126.2, 123.6, 122.4, 110.0, 105.4, 32.2, 29.3, 28.3, 28.2, 23.0, 22.7, 22.1. MS (EI), *m/z* (I_{rel}, %): 374 $[M]^+$ (65). Calculated $C_{23}H_{23}N_2OS$: C 73.76; H 5.92; N 7.48. Found: C 73.84; H 5.96; N 7.54.

2-(2,3,5,6,7,8-Hexahydroacridin-4(1H)-ylidene)-5-(4-methylbenzylidene)-1,3-thiazolidin-4-one 4

Orange powder, mp: 241–243^{0}C, yield 73%. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 13.43 (1H, br. s, NH), 7.51 (2H, d, ^3J=7.5 Hz, Ar), 7.48 (1H, s, CH), 7.43 (2H, d, ^3J=7.5 Hz, Ar), 7.08 (1H, s, CH-10), 2.86–2.94 (2H, m), 2.65–2.75 (4H, m), 2.54–2.58 (2H, m), 2.32 (3H, s, Me), 1.75–1.93 (6H, m). MS (EI), *m/z* (I_{rel}, %): 388 $[M]^+$ (70). Calculated $C_{24}H_{24}N_2OS$: C 74.19; H 6.23; N 7.21. Found: C 74.28; H 6.28; N 7.27.

2-(2,3,5,6,7,8-Hexahydroacridin-4(1H)-ylidene)-5-(2-methoxybenzylidene)-1,3-thiazolidin-4-one 5

Red powder, mp: 236–238^{0}C, yield 65%. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 13.43 (1H, br. s, NH), 7.73 (1H, s, CH), 7.38 (1H, d, ^3J=7.7 Hz, Ar), 7.26–7.31 (2H, m, Ar), 6.77–6.81 (1H, m, Ar), 7.09 (1H, s, CH-10), 3.62 (3H, s, Me), 2.84–2.94 (2H, m), 2.63–2.73 (4H, m), 2.54–2.58 (2H, m), 1.75–1.93 (6H, m). MS (EI), *m/z* (I_{rel}, %): 404 $[M]^+$ (62). Calculated $C_{24}H_{24}N_2O_2S$: C 71.28; H 5.98; N 6.93. Found: C 71.35; H 6.03; N 7.00.

2-(2,3,5,6,7,8-Hexahydroacridin-4(1H)-ylidene)-5-(2-hydroxybenzylidene)-1,3-thiazolidin-4-one 6

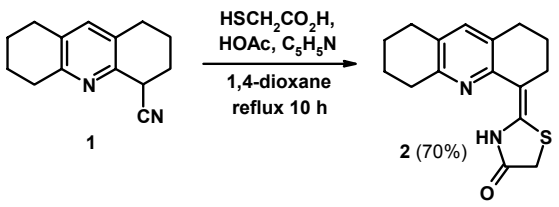
Red powder, mp: 240–241^{0}C, yield 60%. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ ppm: 13.45 (1H, br. s, NH), 8.03 (1H, br. s, OH), 7.81 (1H, s, CH), 7.44–7.48 (1H, m, Ar), 7.23–7.28 (2H, m, Ar), 6.83 (1H, d, ^3J=7.7 Hz, Ar), 7.07 (1H, s, CH-10), 2.82–2.92 (2H, m), 2.65–2.73 (4H, m), 2.54–2.59 (2H, m), 1.75–1.93 (6H, m). MS (EI), *m/z* (I_{rel}, %): 390 $[M]^+$ (67). Calculated $C_{23}H_{22}N_2O_2S$: C 70.74; H 5.68; N 7.17. Found: C 70.81; H 5.73; N 7.21.

5-(4-Bromobenzylidene)-2-(2,3,5,6,7,8-hexahydroacridin-4(1H)-ylidene)-1,3-thiazolidin-4-one 7

Orange powder, mp: 254–256^{0}C, yield 70%. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 13.41 (1H, br. s, NH), 7.88 (2H, d, ^3J=7.8 Hz, Ar), 7.51 (1H, s, CH), 7.70 (2H, d, ^3J=7.8 Hz, Ar), 7.08 (1H, s, CH-10), 2.85–2.93 (2H, m), 2.63–2.74 (4H, m), 2.54–2.58 (2H, m), 1.74–1.93 (6H, m). MS (EI), *m/z* (I_{rel}, %): 454 [M (^{81}Br)]$^+$ (73), 452 [M (^{79}Br)]$^+$ (74). Calculated $C_{24}H_{24}N_2OS$: C 60.93; H 4.67; N 6.18. Found: C 70.13; H 4.78; N 6.27.

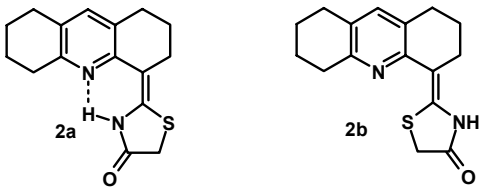
Results and discussion

When acridine 1 reacts with thioglycolic acid at boiling in a mixture of 1,4-dioxane and pyridine in the presence of acetic acid for 10 hours, hybrid acridine-thiazolidin-4-one compound 2 is formed with a good yield (Scheme 1).



Scheme 1

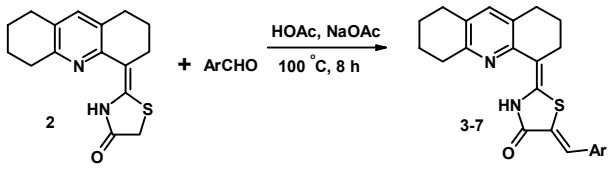
The structure of compound 2 was established using NMR spectroscopy on ^{1}H and ^{13}C nuclei, as well as mass spectrometry. The composition of thiazolidin-4-one 2 was confirmed by elemental analysis. The ^{1}H NMR spectra of this compound, recorded in DMSO and chloroform, differ significantly more than could be expected. Thus, analysis of the ^{1}H NMR spectrum in DMSO showed that this compound is in the form of a mixture of two isomers 2a and 2b with a significant predominance of isomer 2a (Scheme 2).



Scheme 2

The ^{1}H NMR spectrum contains a signal in the form of a broadened singlet at 13 ppm, which belongs to the hydrogen atom of the NH group of the thiazolidone ring, as well as a singlet of the aromatic hydrogen atom with a chemical shift of 7.2 ppm and aliphatic hydrogen atoms as an array of peaks in high field. In addition, for the NH group, the hydrogen atom of the pyridine ring and the methylene group, signals of a minor isomer are observed, constituting no more than 10% of the amount of the main isomer. Assignments of the signals of the major 2a and minor 2b isomers were made based on the chemical shifts of the hydrogen atoms of the NH groups. This signal is 13 ppm and 10.6 ppm for isomer 2a and 2b, respectively. This difference in the chemical shifts of these hydrogen atoms is explained by the ability to form a hydrogen bond with the nitrogen atom of the pyridine ring for isomer 2a. Isomer 2b is thermodynamically less stable than isomer 2a due to the repulsion between lone pairs of electrons of the nitrogen atom of the pyridine ring and the sulfur atom of the thiazolide fragment. This is why the content of isomer 2b in DMSO is much lower. When recording the ^{1}H NMR spectrum for compound 2 in $CDCl_3$, we found that isomer 2b was not observed in solution. This confirms that isomer 2b is thermodynamically less stable and, in a solution containing trace amounts of acid, isomerizes into the more stable isomer 2a. The transformation 2b→2a is possible due to the presence in compound 2 of an enamine fragment conjugated with the pyridine ring, which allows the thiazolidine fragment to rotate relative to the acridine ring.

It should be noted that to search for new biologically active substances, among thiazolidinones, the Knoevenagel reaction is often used to form 5-arylidene derivatives, which exhibit diverse pharmacological activity [13]. We found that the reaction of thiazolidin-4-one 2 with various aromatic aldehydes in acetic acid in the presence of sodium acetate at $100^{0}C$ for 10 h produces derivatives 3–7 with good yields (Scheme 3).



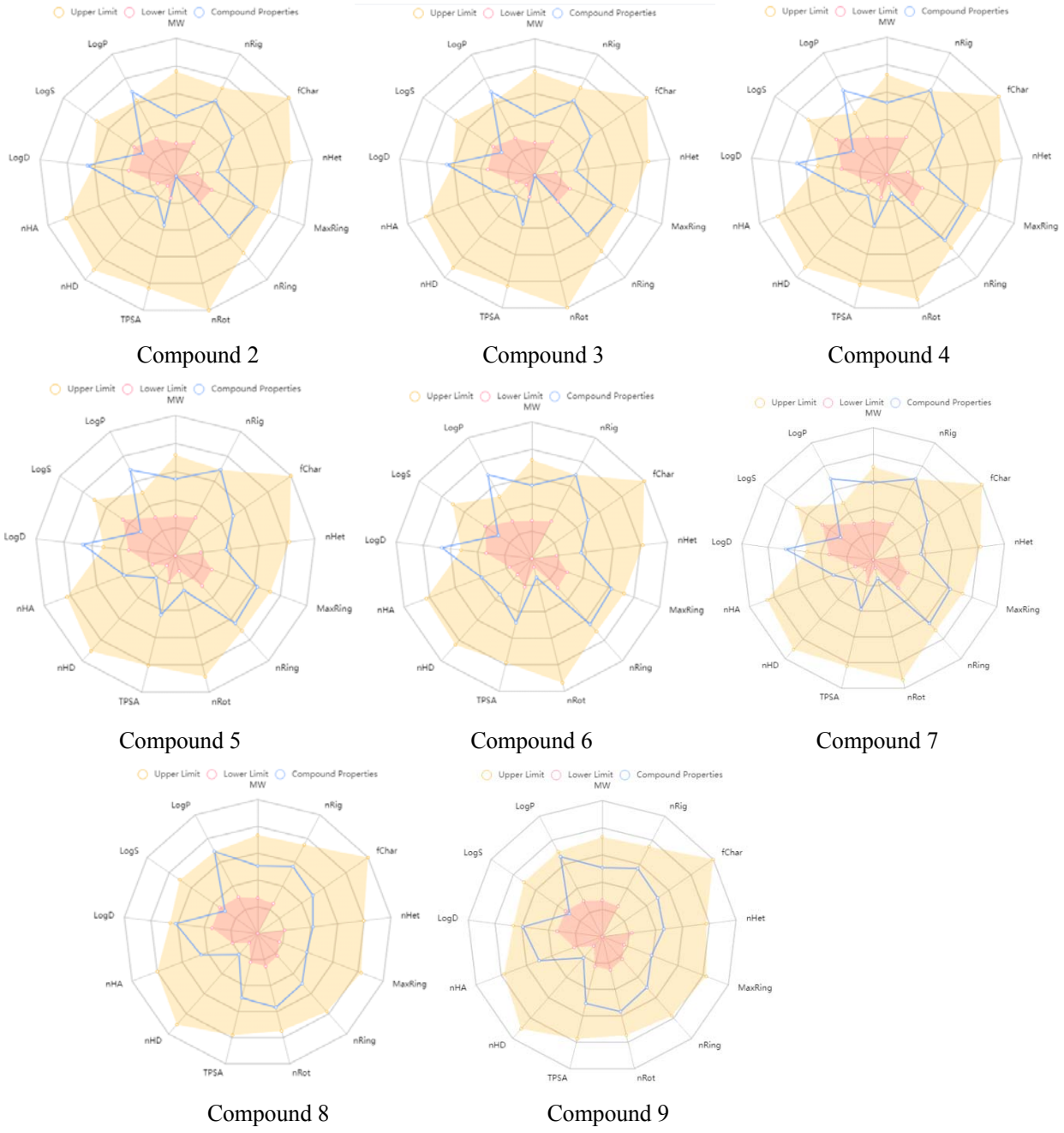
Scheme 3. Ar: 3 – Ph (75%), 4 – 4-MeC_6H_4 (73%), 5 – 2-$MeOC_6H_4$ (65%), 6 – 2-HOC_6H_4 (60%), 7 – 4-BrC_6H_4 (70%)

The structure of compounds 3–7 was established using NMR spectroscopy on ^{1}H and ^{13}C nuclei, as well as mass spectrometry, the composition was confirmed by elemental analysis. The assignment of the configuration of the arylidene fragment was made based on literature data for similar compounds [13]. It should also be noted that compounds 3–7 are present in solutions as a single isomer, which was established using ^{1}H NMR spectroscopy for compound 3 in DMSO and $CDCl_3$.

ADMETlab 2.0 software [14] was used to evaluate the ability of ligands synthesized by compounds 2–7 to target biological targets, as well as to predict the profile of metabolism, excretion, and toxicity, the so-called ADMET properties of the ligand. To compare properties, 2 active drugs, pioglitazone 8 and rosiglitazone 9, which contain a thiazolidone fragment in their structure, were chosen.

In the course of the comparative analysis, the visualization of the results is presented in the form of «web» graphs (Figure).

Thus, thirteen physicochemical properties that can affect the pharmacokinetic profile are presented. In order for a compound to be considered a good drug candidate, it is desirable that its physicochemical properties fall within the range of the lower and upper



Graphic representation of the analysis of the physical and chemical properties of compounds 2–9

limits of the graphs, that is, within the orange zone and outside the pink zone. When analyzing the obtained results, it can be seen that the active medicinal drugs fully meet this requirement, while the tested compounds demonstrate lipid solubility parameters (LogP) and LogP at physiological pH 7.4 (LogD) slightly outside the defined range.

Among the various parameters calculated by the software, those related to physico-chemical properties are presented in Table 1. In this table, the parameters MW, Log P, nHA and nHD make up the classical «Lipinski Rule» [15]. In addition, TPSA, nRot, Log D and nAR are also considered important in order to more accurately predict the bioavailability of a substance when taken orally.

Pharmacokinetic properties are shown in Table 2. First of all, we highlight the parameters HIA (the potential for gastric absorption of the tested compound in humans), and BBB (the potential for penetration through the blood-brain barrier). The

Table 1

Determined physicochemical parameters of compounds 2–9 using ADMETlab 2.0

Compound	MW	Log P	nHA	nHD	TPSA	nRot	Log D
normative indicators	<500	<5	<10	<5	<140	<11	<3
2	286.11	3.692	3	1	41.990	0	3.345
3	374.15	5.796	3	1	45.750	1	4.719
4	388.16	6.259	3	1	45.750	1	4.897
5	404.16	5.938	4	1	54.980	2	4.761
6	390.14	5.780	4	1	65.980	1	4.604
7	452.06	6.606	3	1	45.750	1	4.941
8	356.12	3.021	5	1	68.290	7	2.725
9	357.11	2.692	6	1	71.530	7	2.560

only compounds 2, 6, 7 and 8 will be well excreted with urine from the body. The T1/2 parameter is the half-life of the drug. Molecules with T1/2>3 were classified as T1/2 «–» (Category 0), and molecules with T1/2J3 were classified as T1/2 «+» (Category 1). The initial value is the probability of being T1/2 «+» within the range from 0 to 1. For the studied compounds, the half-life values are low (T1/2<3 h).

Table 2

Pharmacokinetic parameters of compounds 2–9

Compound	HIA	BBB	CL	$T_{1/2}$
normative indicators		0–1	>5	0–1
2	+(0.003)	+(0.964)	5.403	0.356
3	+(0.003)	+(0.389)	4.119	0.074
4	+(0.003)	+(0.216)	4.178	0.059
5	+(0.003)	+(0.218)	5.675	0.073
6	+(0.004)	+(0.12)	5.339	0.096
7	+(0.003)	+(0.254)	3.021	0.040
8	+(0.004)	+(0.20)	8.271	0.311
9	+(0.009)	+(0.628)	7.799	0.456

Data on predicted toxicity are shown in Table 3. Such parameters as DILI (liver damage potential), AMES (mutagenic potential), and CARC (carcinogenic potential) were considered.

Table 3

Toxicological properties of compounds 2–9

Compound	DILI	AMES	CARC
normative indicators	0–0.7		
2	0.77	0.686	0.688
3	0.979	0.768	0.894
4	0.977	0.802	0.93
5	0.975	0.744	0.95
6	0.977	0.721	0.947
7	0.977	0.158	0.881
8	0.968	0.717	0.268
9	0.977	0.891	0.698

In silico prediction showed that all synthesized compounds exhibit increased toxicity. Therefore, it was shown that the thiazolidone fragment, although it is a privileged group in medicinal chemistry, increases the toxicity of its derivatives.

Conclusions

Thus, it was established that the reaction of 1,2,3,4,5,6,7,8-octahydroacridine-4-carbonitrile with thioglycolic acid yields the corresponding hybrid acridine-thiazolylated derivative. This derivative exists in DMSO as two isomers: (2E)-2-(2,3,5,6,7,8-hexahydroacridin-4(1H)-ylidene)-1,3-thiazolidin-4-one and (2Z)-2-(2,3,5,6,7,8-hexahydroacridin-4(1H)-ylidene)-1,3-thiazolidin-4-one in a ratio of 9:1, and only in the form E-isomer in chloroform. Based on their physicochemical and pharmacokinetic parameters, which were predicted using ADMETlab 2.0 program, the synthesized compounds are of interest for medicinal chemistry and further *in vitro* testing.

Acknowledgments and funding

Authors are thankful to the Ministry of Education and Science of Ukraine (project № 0123U101168) for the financial support.

REFERENCES

1. *Mech D., Kurowska A., Trotsko N.* The bioactivity of thiazolidin-4-ones: a short review of the most recent studies // Int. J. Mol. Sci. – 2021. – Vol.22. – No. 21. – Art. No. 11533.

2. *Trotsko N.* Antitubercular properties of thiazolidin-4-ones – a review // Eur. J. Med. Chem. – 2021. – Vol.215. – Art. No. 113266.

3. *Facile* synthesis of 1,3-thiazolidin-4-ones as antitubercular agents / Subhedar D.D., Shaikh M.H., Arkile M.A., Yeware A., Sarkar D., Shingate B.B. // Bioorg. Med. Chem. Lett. – 2016. – Vol.26. – No. 7. – P.1704-1708.

4. *Synthesis*, characterization, anticancer, and antioxidant activity of some new thiazolidin-4-ones in MCF-7 cells /

Isloor A.M., Sunil D., Shetty P., Malladi Sh., Pai K.S.R., Maliyakkl N. // Med. Chem. Res. – 2013. – Vol.22. – P.758-767.

5. *Thiazolidin-4-one-based* derivatives – efficient tools for designing antiprotozoal agents. A review of the last decade / Tuszewska H., Szczepanski J., Mandziuk S., Trotsko N. // Bioorg. Chem. – 2023. – Vol.133. – Art.No. 106398.

6. *Thiazolidin-4-ones* as potential antimicrobial agents: experimental and in silico evaluation / Tratrat Ch., Petrou A., Geronikaki A., Ivanov M., Kostic M., Sokovic M., Vizirianakis I.S., Theodoroula N.F., Haroun M. // Molecules. – 2022. – Vol.27. – No. 6. – Art. No. 1930.

7. *Rearrangement* of 5',6',7',8'-tetrahydro-1'H-spiro(cyclohexane-1,2'-quinazolin)-4'(3'H)-one during Vilsmeier reaction / Markov V.I., Farat O.K., Varenichenko S.A., Velikaya E.V. // Mendeleev Commun. – 2012. – Vol.22. – P.101-102.

8. *Varenichenko S.A., Farat O.K., Markov V.I.* Reactivity of substituted 2-spiropyrimidin-4-ones under Vilsmeier-Haack conditions // Chem. Heterocycl. Compd. – 2015. – Vol.50. – P.1602-1607.

9. *Novel* rearrangement of 1,3-benzo(naphtho)dioxin-4(1)-ones under Vilsmeier-Haack reagent / Farat O.K., Kovtun A.V., Varenichenko S.A., Mazepa A.V., Markov V.I. // Monatsh. Chem. – 2021. – Vol.152. – P.95-101.

10. *Novel* xanthene push-pull chromophores and luminophores: Synthesis and study of their spectral properties / Farat O.K., Farat S.A., Ananyev I.V., Okovytyy S.I., Tatarets A.L., Markov V.I. // Tetrahedron. – 2017. – Vol.73. – No. 51. – P.7159-7168.

11. *Reactions* of octahydroacridine-4-carbonitrile (carboxamide) with electrophilic reagents / Zaliznaya E.V., Farat O.K., Gorobets N.Yu., Markov V.I., Zubatyuk R.I., Mazepa A.V., Vashchenko E.V. // Chem. Heterocycl. Compd. – 2015. – Vol.51. – No. 4. – P.327-333.

12. *Functionalization* of tetra- and octahydroacridine derivatives through Michael addition / Zaliznaya E.V., Farat O.K., Varenichenko S.A., Mazepa A.V., Markov V.I. // Tetrahedron Lett. – 2016. – Vol.57. – P.3485-3487.

13. *Recent* approaches in the synthesis of 5-arylidene-2,4-thiazolidinedione derivatives using Knoevenagel condensation / Paul A., Maji A., Sarkar A., Saha S., Janah P., Maity T.K. // Mini-Rev. Org. Chem. – 2023. – Vol.20. – No. 1. – P.5-34.

14. *ADMETlab*: a platform for systematic ADMET evaluation based on a comprehensively collected ADMET database / Dong J., Wang N., Yao Z., Zhang L., Cheng Y., Ouyang D., Lu A., Cao D. // J. Cheminform. – 2018. – Vol.10. – Art.No. 29.

15. *Experimental* and computational approaches to estimate solubility and permeability in drug discovery and development settings / Lipinski C.A., Lombardo F., Dominy B.W., Feeney P.J. // Adv. Drug Deliv. Rev. – 2001. – Vol.46. – No. 1-3. – P.3-26.

Received 08.08.2023

СИНТЕЗ ТА IN SILICO ADMET ПРОГНОЗУВАННЯ НОВИХ 5-АРИЛІДЕН-2-(2,3,5,6,7,8-ГЕКСАГІДРОАКРИДИН-4(1*H*)-ІЛІДЕН)-1,3-ТІАЗОЛІДИН-4-ОНІВ

С.А. Вареничeнко, О.В. Харченко, О.К. Фарат

Відповідне похідне тіазолідону було синтезовано з хорошим виходом реакцією 1,2,3,4,5,6,7,8-октагідроакридин-4-карбонітрилу з тіогліколевою кислотою. Встановлено, що ця сполука присутня в ДМСО у формі двох ізомерів: (2E)-2-(2,3,5,6,7,8-гексагідроакридин-4(1H)-іліден)-1,3- тіазолідин-4-он і (2Z)-2-(2,3,5,6,7,8-гексагідроакридин-4(1H)-іліден)-1,3-тіазолідин-4-он у співвідношенні 9:1, відповідно, а у хлороформі – тільки у вигляді E-ізомеру. Відповідні 5-ариліден-2-(2,3,5,6,7,8-гексагідроакридин-4(1H)-іліден)-1,3-тіазолідин-4-они одержано з хорошими виходами. Виділення всіх продуктів не є складним і здійснюється простим фільтруванням. Спрогнозовано фізико-хімічні та фармакокінетичні властивості одержаних сполук та виконано порівняльний аналіз отриманих показників з діючими препаратами піоглітазоном і розиглітазоном за допомогою програмного забезпечення ADMETlab 2.0. Усі перевірені сполуки відповідають правилу Ліпінського. Крім того, порівнювали токсичність, період напіввиведення, кліренс, кишкову абсорбцію та потенціал проникнення через гематоенцефалічний бар'єр. За більшістю показників синтезовані сполуки можна порівняти з діючими препаратами. Охарактеризовані у статті похідні 1,3-тіазолідин-4-ону є перспективними як будівельні блоки для органічного синтезу та для подальшого тестування *in vitro*.

Ключові слова: заміщені акридини, заміщені тіазолідин-4-они, реакція Кньовенагеля, ізомеризація, ADMETlab 2.0.

SYNTHESIS AND *IN SILICO* ADMET PROFILING OF NOVEL 5-ARYLIDENE-2-(2,3,5,6,7,8-HEXAHYDROACRIDIN-4(1*H*)-YLIDENE)-1,3-THIAZOLIDIN-4-ONES

S.A. Varenichenko* *, *A.V. Kharchenko, O.K. Farat

Ukrainian State University of Chemical Technology, Dnipro, Ukraine

* **e-mail: svetlanavarenichenko@gmail.com**

The corresponding thiazolidone derivative was synthesized with a good yield by the reaction of 1,2,3,4,5,6,7,8-octahydroacridine-4-carbonitrile with thioglycolic acid. It was found that this compound is present in DMSO in the form of two isomers, (2E)-2-(2,3,5,6,7,8-hexahydroacridin-4(1H)-ylidene)-1,3-thiazolidin-4-one and (2Z)-2-(2,3,5,6,7,8-hexahydroacridin-4(1H)-ylidene)-1,3-thiazolidin-4-one in a ratio of 9:1, respectively, whereas it is present only in the form of the E-isomer in chloroform. The corresponding 5-arylidene-2-(2,3,5,6,7,8-hexahydroacridin-4(1H)-ylidene)-1,3-thiazolidin-4-ones were obtained with good yields. Isolation of all products is not difficult and is carried out by simple filtration. The physicochemical and pharmacokinetic properties of the obtained compounds were predicted, and a comparative analysis of the obtained indicators with active drugs, pioglitazone and rosiglitazone was carried out by using ADMETlab 2.0 software. All tested compounds comply with the Lipinski rule. Additionally, toxicity, half-life, clearance, intestinal absorption and blood-brain barrier penetration potentials were compared. In most respects, the synthesized compounds are comparable to active drugs. The 1,3-thiazolidin-4-one derivatives characterized in the article are promising as building blocks for the organic synthesis and for further in vitro testing.

Keywords: substituted acridine; substituted thiazolidin-4-one; Knoevenagel reaction; isomerism; ADMETlab 2.0.

REFERENCES

1. Mech D, Kurowska A, Trotsko N. The bioactivity of thiazolidin-4-ones: a short review of the most recent studies. *Int J Mol Sci*. 2021; 22(21): 11533. doi: 10.3390/ijms222111533.

2. Trotsko N. Antitubercular properties of thiazolidin-4-ones – a review. *Eur J Med Chem*. 2021; 215: 113266. doi: 10.1016/j.ejmech.2021.113266.

3. Subhedar DD, Shaikh MH, Arkile MA, Yeware A, Sarkar D, Shingate BB. Facile synthesis of 1,3-thiazolidin-4-ones as antitubercular agents. *Bioorg Med Chem Lett*. 2016; 26(7): 1704-1708. doi: 10.1016/j.bmcl.2016.02.056.

4. Isloor AM, Sunil D, Shetty P, Malladi S, Pai KSR, Maliyakkl N. Synthesis, characterization, anticancer, and antioxidant activity of some new thiazolidin-4-ones in MCF-7 cells. *Med Chem Res*. 2013; 22: 758-767. doi: 10.1007/s00044-012-0071-5.

5. Tuszewska H, Szczepanski J, Mandziuk S, Trotsko N. Thiazolidin-4-one-based derivatives – efficient tools for designing antiprotozoal agents. A review of the last decade. *Bioorg Chem*. 2023; 133: 106398. doi: 10.1016/j.bioorg.2023.106398.

6. Tratrat C, Petrou A, Geronikaki A, Ivanov M, Kostic M, Sokovic M, et al. Thiazolidin-4-ones as potential antimicrobial agents: experimental and in silico evaluation. *Molecules*. 2022; 27(6): 1930. doi: 10.3390/molecules27061930.

7. Markov VI, Farat OK, Varenichenko SA, Velikaya EV. Rearrangement of 5',6',7',8'-tetrahydro-1'H-spiro(cyclohexane-1,2'-quinazolin)-4'(3'H)-one during Vilsmeier reaction. *Mendeleev Commun*. 2012; 22: 101-102. doi: 10.1016/j.mencom.2012.03.017.

8. Varenichenko SA, Farat OK, Markov VI. Reactivity of substituted 2-spiropyrimidin-4-ones under Vilsmeier-Haack conditions. *Chem Heterocycl Compd*. 2015; 50: 1602-1607. doi: 10.1007/s10593-014-1626-9.

9. Farat OK, Kovtun AV, Varenichenko SA, Mazepa AV, Markov VI. Novel rearrangement of 1,3-benzo(naphtho)dioxin-4(1)-ones under Vilsmeier-Haack reagent. *Monatsh Chem*. 2021; 152: 95-101. doi: 10.1007/s00706-020-02733-z.

10. Farat OK, Farat SA, Ananyev IV, Okovytyy SI, Tatarets AL, Markov VI. Novel xanthene push-pull chromophores and luminophores: synthesis and study of their spectral properties, *Tetrahedron*. 2017; 73: 7159-7168. doi: 10.1016/j.tet.2017.10.027.

11. Zaliznaya EV, Farat OK, Gorobets NYu, Markov VI, Zubatyuk RI, Mazepa AV, et al. Reactions of octahydroacridine-4-carbonitrile (carboxamide) with electrophilic reagents. *Chem Heterocycl Compd*. 2015; 51: 327-332. doi: 10.1007/s10593-015-1703-8.

12. Zaliznaya EV, Farat OK, Varenichenko SA, Mazepa AV, Markov VI. Functionalization of tetra- and octahydroacridine derivatives through Michael addition. *Tetrahedron Lett*. 2016; 57: 3485-3487. doi: 10.1016/j.tetlet.2016.06.096.

13. Paul A, Maji A, Sarkar A, Saha S, Janah P, Maity TK. Recent approaches in the synthesis of 5-arylidene-2,4-thiazolidinedione derivatives using Knoevenagel condensation. *Mini-Rev Org Chem*. 2023; 20(1): 5-34. doi: 10.2174/1570193X19666220331155705.

14. Dong J, Wang NN, Yao ZJ, Zhang L, Cheng Y, Ouyang D, et al. ADMETlab: a platform for systematic ADMET evaluation based on a comprehensively collected ADMET database. *J Cheminform*. 2018; 10: 29. doi: 10.1186/s130321-018-0283-x.

15. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*. 2001; 46: 3-26. doi: 10.1016/s0169-409x(00)00129-0.