Synthesis and properties of 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid and its salts

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Carboxylic acids and their derivatives are an important component of many biological processes. For example, they can be used to create new medicines that can be useful in the fight against various diseases. Additionally, compounds containing a thiazole moiety may possess beneficial properties in practical pharmacy. The incorporation of this heterocyclic structure in molecules can positively impact several biological characteristics, such as anti-inflammatory, antiviral, and antifungal activities.

Consequently, exploring novel compounds that combine a thiazole fragment with a carboxyl group holds promise for the advancement of new drugs and diagnostic tools that can contribute significantly to the battle against numerous diseases.

The aim of the work was to create a number of organic and inorganic salts of 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid and study of their properties, as well as selective determination of the biological potential of these compounds.

Materials and methods. The synthetic part of the study involved the sequential synthesis of the original compound 4-amino-5-(3-methyl-1*H*-pyrazol-5-yl)-1,2,4-triazole-3-thiol using a well-established method described in previous articles. The next stage involved the reaction of thiol with 2,3-dichlorobenzaldehyde in a medium of glacial acetic acid. The resulting Schiff base was subsequently reacted with 2-chloroethanoic acid in tetrahydrofuran in the presence of an equimolar amount of sodium hydride.

Salts of the corresponding acid were formed during the reaction of 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid with both organic and inorganic bases in an aqueous-alcohol medium. The structures of all synthesized compounds were determined using ^{1}H NMR spectroscopy and elemental analysis. Additionally, the individuality of each compound was confirmed using high-performance liquid chromatography-mass spectrometry.

Results. The study determined the optimal conditions for the formation of both organic and inorganic salts of 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid. The analysis of pharmacokinetic parameters and physicochemical properties using ADME (absorption, distribution, metabolism, and excretion) allowed for the identification of promising synthesized compounds and the selection of more optimal compounds for further investigation.

Conclusions. The structure of 12 compounds was synthesized and confirmed. Physical-chemical and pharmacokinetic analysis of ADME parameters was carried out and promising compounds were selected for more *in-depth* research.

Key words: 1,2,4-triazole, pyrazole, properties, *in silico* research

Current issues in pharmacy and medicine: science and practice, 2023. 16(2), 121-129

Синтез і властивості 6-(2,3-дихлорофеніл)-3-(3-метил-1*H*-піразол-5-іл)-6,7-дигідро-5*H*-[1,2,4]тріазоло[3,4-*b*][1,3,4]тіадіазин-7-карбонової кислоти та її солей

С. О. Федотов, А. С. Гоцуля

Карбонові кислоти та їхні похідні – важлива складова багатьох біологічних процесів. Так, вони можуть бути використані для створення нових лікарських засобів для терапії пацієнтів із різними захворюваннями. Сполуки, що містять тіазоловий фрагмент, також можуть бути корисними в практичній фармації. Наявність цього гетероциклу в структурі може позитивно вплинути на низку біологічних властивостей, включаючи протизапальні, противірусні та протигрибкові.

Отже, дослідження нових молекул, які поєднують фрагмент тіазолу та карбоксильну групу, може сприяти розробленню діагностичних і лікарських засобів, що можна застосовувати під час лікування багатьох захворювань.

ARTICLE INFO

http://pharmed.zsmu.edu.ua/article/view/279460

UDC 547.792'77.03/.04.057.06/.07:004
DOI: 10.14739/2409-2932.2023.2.279460

Current issues in pharmacy and medicine: science and practice, 2023. 16(2), 121-129

Key words: 1,2,4-triazole, pyrazole, properties, *in silico* research.

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Received: 25.04.2023 // Revised: 18.05.2023 // Accepted: 30.05.2023

Мета роботи – створення ряду органічних і неорганічних солей 6-(2,3-дихлорофеніл)-3-(3-метил-1*H*-піразол-5-іл)-6,7-дигідро-5*H*-[1,2,4]тріазол-[3,4-*b*][1,3,4]тіадіазин-7-карбонової кислоти та дослідження їхніх властивостей, а також вибіркове встановлення біологічного потенціалу цих сполук.

Матеріали та методи. Реалізація синтетичної частини передбачала поетапний синтез вихідного 4-аміно-5-(3-метил-1*H*-піразол-5-іл)-1,2,4-тріазол-3-тіолу за відомим методом, що описаний у попередніх статтях. Наступний етап – реакція тіолу з 2,3-дихлорбензальдегідом у середовищі льодяної оцтової кислоти. Одержану основу Шиффа надалі піддавали реакції з 2-хлоретановою кислотою в середовищі тетрагідрофурану за наявності еквімолекулярної кількості натрій гідриду. Солі відповідної кислоти утворювалися в процесі реакції 6-(2,6-дихлорофеніл)-3-(3-метил-1*H*-піразол-5-іл)-6,7-дигідро-5*H*-[1,2,4]тріазолу-[3,4-*b*][1,3,4]тіадіазин-7-карбонової кислоти з органічними та неорганічними основами в водно-спиртовому середовищі. За допомогою ^{1}H ЯМР-спектроскопії та елементного аналізу визначили структуру всіх синтезованих речовин. Метод високоефективної рідинної хромато-мас-спектрометрії підтвердив індивідуальність кожної сполуки.

Результати. Встановили оптимальні умови створення органічних і неорганічних солей 6-(2,3-дихлорофеніл)-3-(3-метил-1*H*-піразол-5-іл)-6,7-дигідро-5*H*-[1,2,4]тріазол[3,4-*b*][1,3,4]тіадіазин-7-карбонової кислоти. Застосування аналізу фармакокінетичних параметрів і фізико-хімічних властивостей ADME дало змогу визначити перспективність синтезованих сполук і обрати оптимальні з них для наступних досліджень.

Висновки. Синтезовано та підтверджено структуру 12 сполук. Здійснили фізико-хімічний і фармакокінетичний аналіз ADME параметрів, обрали перспективні сполуки для детальнішого дослідження.

Ключові слова: 1,2,4-тріазол, піразол, властивості, *in silico* дослідження.

Актуальні питання фармацевтичної і медичної науки та практики. 2023. Т. 16, № 2(42). С. 121-129

Optimizing synthesis conditions and studying the properties of new compounds are always of great importance to the field of chemistry. In this case, 6-(2,3-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid and its salts have significant potential for use in the pharmaceutical industry [2,7,8,12].

The triazolothiadiazine framework has demonstrated significant biological activity, including antibacterial, antiviral, antitumor, and antifungal properties [3,9]. Furthermore, the pyrazole component is a well-established bioactive moiety present in drugs such as celecoxib and metformin. Combining these two heterocycles in a single molecule holds the potential for developing new drugs with enhanced pharmacological properties and pronounced activity [4,6,11].

Moreover, the synthesis of new compounds with unique properties is essential for the discovery and development of drugs, and this particular compound can serve as a starting point for further research aimed at optimizing its pharmacological activity [5,10]. Therefore, establishing optimal synthesis conditions and studying the properties of 6-(2,3-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid and its salts represents a relevant and important direction in the field of medicinal chemistry.

Aim

The aim of the work was to create a number of organic and inorganic salts of 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid and study of their properties, as well as selective determination of the biological potential of these compounds.

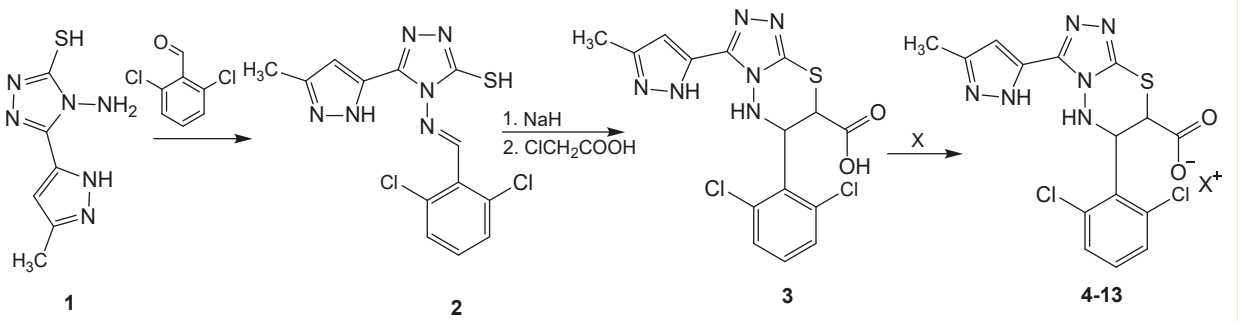
Materials and methods

The synthetic part of the study involved the sequential synthesis of the original compound 4-amino-5-(3-methyl-1*H*-pyrazol-5-yl)-1,2,4-triazole-3-thiol using a well-established method described in previous articles [1].

The first stage of the study focused on optimizing the synthesis conditions for 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid and its corresponding salts.

The synthetic process involved three stages. In the first stage, a nucleophilic addition reaction of 2,6-dichlorobenzaldehyde to the original 4-amino-5-(3-methyl-1*H*-pyrazol-5-yl)-4*H*-1,2,4-triazole-3-thiol was carried out in glacial acetic acid. The second stage involved the reaction of the obtained Schiff's base with 2-chloroethanoic acid in tetrahydrofuran, with the addition of double the amount of sodium hydride. The mixture was stirred for 10 hours, followed by solvent removal, resulting in the formation of 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid. The final stage of the study involved synthesizing salts of the obtained acid by reacting it with inorganic and organic bases in an aqueous-alcohol medium. An ADME analysis was conducted to assess the compounds' compliance with pharmacokinetic parameters and drug-likeness.

Melting points were determined using the "Stanford Research Systems Melting Point Apparatus 100" (SRS, USA) in open capillaries. The percentage content of elements (C, H, N, S) was performed using the "Elementar vario EL cube" analyzer (Elementar Analysensysteme, Germany). IR spectroscopy (spectral range 4000–400 cm^{-1}) was performed using the Bruker ALPHA FT-IR spectrometer with the ALPHA-T module (Bruker optics, Germany). ^{1}H NMR spectra were recorded on a Varian-Mercury 400 spectrometer with tetramethylsilane as an internal standard in DMSO-d6 solution. Chromatograph "Agilent 1260 Infinity HPLC" with spectrometer "Agilent 6120" was used to obtain chromatogram-mass spectra, utilizing the electrospray (ESI) ionization method.



X = Na, K, NH_4, NH_2-CH_3, NH_2-C_2H_5, NH_2-C_2H_5OH, NH_2-$(C_2H_5)_2$, NH_2-$(C_2H_5OH)_2$, piperidine, morpholine

Fig. 1. Scheme of the synthesis of salts 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid.

(*E*)-4-((2,6-dichlorobenzylidene)amino)-5-(3-methyl-1*H*-pyrazol-5-yl)-4*H*-1,2,4-triazole-3-thiol. To 0.01 mol of the original 4-amino-5-(3-methyl-1*H*-pyrazol-5-yl)-4*H*-1,2,4-triazole-3-thiol was added 0.01 mol of 2,6-dichlorobenzaldehyde in 20 ml of glacial ethanoic acid. They heated for two hours. The formed precipitate was filtered, washed with water and used without purification in the next stage.

6-(2,6-Dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid. 2.0 mmol of sodium hydride was added to a solution of compound 2 (1.0 mmol) in dry tetrahydrofuran (20 ml) at room temperature. It was left for salt formation at the temperature for 15 minutes. Then 2-chloroethanoic acid (1.5 mmol) was added and the solution was stirred for 10 hours. The solvent was removed under a vacuum. The residue was crystallized from ethanol to obtain triazolothiadiazines.

General method of synthesis of salts 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid. To 0.01 mol of the original acid was dissolved in 10 ml of a mixture of water : ethanol (1:1), 0.01 mol of the corresponding inorganic base (KOH, NaOH) and organic (NH_4OH, NH_2-CH_3, NH_2-C_2H_5, NH_2-C_2H_4OH, NH_2-$(C_2H_5)_2$, NH_2-$(C_2H_4OH)_2$, piperidine, morpholine). It was heated for two hours. The solvent was removed under a vacuum. The precipitate was crystallized from a water-alcohol mixture of water : ethanol (1:1).

ADME analysis. The evaluation of absorption, distribution, metabolism, and excretion (ADME) is a crucial aspect of drug development. These factors significantly impact the pharmacokinetics, pharmacological activity, and effectiveness of a medicinal product.

In recent years, computer technologies have been employed for the preliminary assessment of pharmacokinetic and pharmacodynamic parameters. This approach offers a cost-effective alternative to in vitro and in vivo experiments. Notably, drug-like criteria are utilized for the optimization and evaluation of virtual combinatorial libraries. The web tool "SwissADME" was used in this study to calculate physicochemical, pharmacokinetic, and drug-likeness parameters for the proposed structures.

Results

The synthetic part of the study was conducted using two approaches and involved the reaction of the initial thiol with 2,6-dichlorobenzaldehyde, resulting in the formation of a Schiff base.

The formation of the acid took place with the participation of a previously obtained Schiff base and 2-chloroethane acid in a tetrahydrofuran environment. Salts of the corresponding acid were synthesized as a result of the reaction of organic and organic salts with acid in a water-alcohol medium (*Fig. 1*).

The synthesized substances are white crystalline powders, soluble in water.

The structure of all synthesized substances was confirmed by physicochemical methods: ^{1}H NMR spectroscopy and elemental analysis. The purity of the chemical reaction products and their identity were confirmed by chromato-mass spectra.

6-(2,6-Dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid. White residue; yield 80 %; m. p. 183–185 °C. ^{1}H NMR, δ (ppm): 11.45 (d, *J* = 6.7 Hz, 2H, COO*H*, N*H*-pyrazole), 7.63 (d, *J* = 6.7 Hz, 1H, H-4 pyrazole), 7.43–7.30 (m, 3H, H-3,4,5 2,6-Cl-C_6H_3), 6.63 (d, *J* = 6.7 Hz, 1H, N-N*H*-), 5.89–5.84 (m, 1H, C^6H, thiadiazine), 5.15 (d, *J* = 5.4 Hz, 1H, C^7H, thiadiazine), 2.53 (s, 3H, CH_3-pyrazole). $C_{15}H_{12}Cl_2N_6O_2S$. ESI-MS: m/z = 411 $[M+H]^+$. Elemental Analysis: C, 43.81; H, 2.94; N, 20.44; S, 7.80. Found: C, 43.70; H, 2.95; N, 20.38; S, 7.82. Crystallized from propan-2-ole.

The structure of inorganic salts was proved by data of elemental analysis.

Sodium 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylate. White residue; yield 75 %; m. p. 243–245 °C. $C_{15}H_{11}Cl_2N_6NaO_2S$. ESI-MS: m/z = 434 $[M+H]^+$. Elemental Analysis: C, 41.59; H, 2.56; N, 19.40; S, 7.40. Found: C, 41.45; H, 2.55; N, 19.45; S, 7.42. Crystallized from propan-2-ole.

Potassium 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylate. White residue; yield 77 %; m. p. 252–254 °C. $C_{15}H_{11}Cl_2N_6KO_2S$. ESI-MS: m/z = 450 $[M+H]^+$. Elemental Analysis: C, 40.09; H, 2.47; N, 18.70; S, 7.13. Found: C, 40.19; H, 2.46; N, 18.74; S, 7.11. Crystallized from propan-2-ole.

Ammonium (6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylate. White residue; yield 78 %; m. p. 221–223 °C. ^{1}H NMR, δ (ppm): 11.46 (s, 1H, N*H*-pyrazole), 10.23 (s, 3H, NH_3^+), 7.64 (d, *J* = 7.1 Hz, 1H, H-4 pyrazole), 7.43–7.30 (m, 3H, H-3,4,5 2,6-Cl-C_6H_3), 6.45 (d, *J* = 7.3 Hz, 1H, N-N*H*-), 5.92–5.86 (m, 1H, C^6*H*, thiadiazine), 5.45 (d, *J* = 5.6 Hz, 1H, C^7*H*, thiadiazine), 2.55 (s, 3H, CH_3-pyrazole). $C_{15}H_{14}Cl_2N_7O_2S$. ESI-MS: m/z = 428 $[M+H]^+$. Elemental Analysis: 42.17; H, 3.30; N, 22.95; S, 7.50. Found: C, 42.28; H, 3.29; N, 22.90; S, 7.52. Crystallized from propan-2-ole.

Methylammonium (6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylate. White residue; yield 71 %; m. p. 216–218 °C. ^{1}H NMR, δ (ppm): 11.44 (s, 1H, N*H*-pyrazole), 9.30 (s, 2H, NH_2-CH_3), 7.65 (d, *J* = 7.0 Hz, 1H, H-4 pyrazole), 7.43–7.30 (m, 3H, H-3,4,5 2,6-Cl-C_6H_3), 6.45 (d, *J* = 7.0 Hz, 1H, N-N*H*-), 5.94–5.87 (m, 1H, C^6*H*, thiadiazine), 5.35 (d, *J* = 5.4 Hz, 1H, C^7*H*, thiadiazine), 2.62 (t, *J* = 3.9 Hz, 3H, NH_2-CH_3), 2.53 (s, 3H, CH_3-pyrazole). $C_{16}H_{16}Cl_2N_7O_2S$. ESI-MS: m/z = 442 $[M+H]^+$. Elemental Analysis: C, 43.55; H, 3.65; N, 22.22; S, 7.26. Found: C, 43.66; H, 3.66; N, 22.16; S, 7.24. Crystallized from propan-2-ole.

Ethylammonium (6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylate. White residue; yield 80 %; m. p. 204–206 °C. ^{1}H NMR, δ (ppm): 11.46 (s, 1H, N*H*-pyrazole), 9.25 (s, 2H, NH_2-CH_2-CH_3), 7.67 (d, *J* = 7.0 Hz, 1H, H-4 pyrazole), 7.43–7.30 (m, 3H, H-3,4,5 2,6-Cl-C_6H_3), 6.43 (d, *J* = 7.0 Hz, 1H, N-N*H*-), 5.91–5.85 (m, 1H, C^6*H*, thiadiazine), 5.33 (d, *J* = 5.4 Hz, 1H, C^7*H*, thiadiazine), 3.03–2.89 (m, 2H, NH_2-CH_2-CH_3), 2.53 (s, 3H, CH_3-pyrazole), 1.38 (t, *J* = 6.6 Hz, 3H, NH_2-CH_2-CH_3). $C_{17}H_{18}Cl_2N_7O_2S$. ESI-MS: m/z = 456 $[M+H]^+$. Elemental Analysis: C, 44.84; H, 3.98; N, 21.53; S, 7.04. Found: C, 44.72; H, 3.99; N, 21.58; S, 7.02. Crystallized from propan-2-ole.

Monoethanolammonium (6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylate. White residue; yield 80 %; m. p. 201–202 °C. ^{1}H NMR, δ (ppm): 11.47 (s, 1H, NH-pyrazole), 9.15 (s, 2H, NH_2-CH_2-CH_2-OH), 7.63 (d, *J* = 7.1 Hz, 1H, H-4 pyrazole), 7.41–7.28 (m, 3H, H-3,4,5 2,6-Cl-C_6H_3), 6.46 (d, *J* = 7.0 Hz, 1H, N-N*H*-), 5.93-5.88 (m, 1H, C^{6}H, thiadiazine), 5.35 (d, *J* = 5.4 Hz, 1H, C^7*H*, thiadiazine), 4.65 (t, *J* = 5.6 Hz, 1H, NH_2-CH_2-CH_2-O*H*), 3.96-3.91 (m, 2H, NH_2-CH_2-CH_2-OH), 3.32–3.28 (m, 2H, NH_2-CH_2-CH_2-OH), 2.52 (s, 3H, CH_3-pyrazole). $C_{17}H_{18}Cl_2N_7O_3S$. ESI-MS: m/z = 472 $[M+H]^+$. Elemental Analysis: C, 43.32; H, 3.85; N, 20.80; S, 6.80. Found: C, 43.43; H, 3.86; N, 20.75; S, 6.77. Crystallized from propan-2-ole.

Diethylammonium (6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylate. White residue; yield 80 %; m. p. 196–198 °C. ^{1}H NMR, δ (ppm): 11.46 (s, 1H, NH-pyrazole), 9.88 (s, Hz, 1H, N*H*$(C_2H_5)_2$, 7.59 (d, *J* = 7.1 Hz, 1H, H-4 pyrazole), 7.43–7.30 (m, 3H, H-3,4,5 2,6-Cl-C_6H_3), 6.44 (d, *J* = 7.0 Hz, 1H, N-N*H*), 5.91–5.85 (m, 1H, C^6*H*, thiadiazine), 5.39 (d, *J* = 5.9 Hz, 1H, C^7*H*, thiadiazine), 3.27–3.16 (m, 4H, NH-$(CH_2)_2$-$(CH_3)_2$), 2.55 (s, 3H, CH_3-pyrazole), 1.52 (t, *J* = 7.5 Hz, 6H, NH-$(CH_2)_2$-$(CH_3)_2$). $C_{19}H_{22}Cl_2N_7O_2S$. ESI-MS: m/z = 484 $[M+H]^+$. Elemental Analysis: C, 47.21; H, 4.59; N, 20.28; S, 6.63. Found: C, 47.32; H, 4.60; N, 20.38; S, 7.79. Crystallized from propan-2-ole.

***N*,*N*-Diethylhydroxylammonium (6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylate.** White residue; yield 80 %; m. p. 181–183 °C. ^{1}H NMR, δ (ppm): 11.43 (s, 1H, NH-pyrazole), 9.27 (s, 1H, N*H*-$(CH_2)_2$-$(CH_2)_2$-$(OH)_2$), 7.61 (d, *J* = 7.1 Hz, 1H, H-4 pyrazole), 7.46 – 7.31 (m, 3H, H-3,4,5 2,6-Cl-C_6H_3), 6.46 (d, *J* = 7.0 Hz, 1H, N-N*H*), 5.94-5.87 (m, 1H, C^6*H*, thiadiazine), 5.42 (d, *J* = 5.9 Hz, 1H, C^7*H*, thiadiazine), 4.59 (t, *J* = 6.2 Hz, 2H, NH-$(CH_2)_2$-$(CH_2)_2$-(O*H*)$_2$), 4.05–3.98 (m, 4H, NH-$(CH_2)_2$-$(CH_2)_2$-$(OH)_2$), 3.58–3.49 (m, 4H, NH-$(CH_2)_2$-$(CH_2)_2$-$(OH)_2$), 2.52 (s, 3H, CH_3-pyrazole). $C_{19}H_{22}Cl_2N_7O_4S$. ESI-MS: m/z = 516 $[M+H]^+$. Elemental Analysis: C, 44.28; H, 4.30; N, 19.02; S, 6.22. Found: C, 44.17; H, 4.29; N, 19.07; S, 6.25. Crystallized from propan-2-ole.

Piperidinium (6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylate. White residue; yield 80 %; m. p. 217–219 °C. ^{1}H NMR, δ (ppm): 11.48 (s, 1H, NH-pyrazole), 9.60 (s, 1H, N*H*-piperidine), 7.63 (d, 1H, d, *J* = 7.1 Hz, 1H, H-4 pyrazole), 7.43–7.30 (m, 3H, H-3,4,5 2,6-Cl-C_6H_3), 6.43 (d, *J* = 7.0 Hz, 1H, N-N*H*), 5.93–5.88 (m, 1H, C^6*H*, thiadiazine), 5.39 (d, *J* = 5.9 Hz, 1H, C^7*H*, thiadiazine), 3.40–3.29 (m, 4H, H-2,6 piperidine), 2.51 (s, 3H, CH_3-pyrazole), 2.34–2.15 (m, 4H, *H-3,5* piperidine), 1.55–1.42 (m, 1H, H-4 piperidine). $C_{20}H_{22}Cl_2N_7O_2S$. ESI-MS: m/z = 496 $[M+H]^+$. Elemental Analysis: C, 48.49; H, 4.48; N, 19.79; S, 6.47. Found: C, 48.60; H, 4.49; N, 19.74; S, 6.44. Crystallized from propan-2-ole.

Morpholinium (6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylate. White residue; yield 80 %; m. p. 169–171 °C. ^{1}H NMR, δ (ppm): 11.46 (s, 1H, NH-pyrazole), 8.68 (s, 1H, N*H*- morpholine), 7.61 (d, 1H, d, *J* = 7.1 Hz, 1H, H-4 pyrazole), 7.44 (m, 3H, H-3,4,5 2,6-Cl-C_6H_3), 6.45 (d, *J* = 7.0 Hz, 1H, N-N*H*), 5.95–5.89 (m, 1H, C^6*H*, thiadiazine), 5.40 (d, *J* = 5.9 Hz, 1H, C^7*H*, thiadiazine), 4.18 – 4.05 (m, 4H, H-3,3′,5,5′ morpholine), 3.57–3.44 (m, 4H, H-2,2′,6,6′ morpholine), 2.53 (s, 3H, CH_3-pyrazole). $C_{19}H_{20}Cl_2N_7O_3S$. ESI-MS: m/z = 497 $[M+H]^+$. Elemental Analysis: C, 45.88; H, 4.05; N, 19.71; S, 6.45. Found: C, 45.77; H, 4.06; N, 19.65; S, 6.49. Crystallized from propan-2-ole.

Discussion

The ^{1}H NMR spectra analysis revealed characteristic peaks for the synthesized acid were established in the form of an extended proton signal of the COOH group at 11.45 ppm. The presence of singlet signals at 11.48–11.43 ppm is caused by the presence of a hydrogen atom of the pyrazole fragment and the methyl group associated with it at 2.55–2.51 ppm. The formation of a doublet at 7.67–7.61 ppm corresponds to the hydrogen atom of the C^{4}H-pyrazole fragment. Protons of the 2,6-dichlorophenyl substituent were noted as an extended multiplet in the characteristic "aromatic zone" at 7.46–7.28 ppm. The formation of triazolothiadiazine was characterized by the absence of protons from the amino group of the original thiol, as well as the presence of a multiplet at 5.95–5.85 ppm, which characterizes the C^{6}H-thiadiazine fragment, and a doublet at 5.45–5.33 ppm, which corresponds to the C^{7}H-thiadiazine fragment.

The ^{1}H NMR spectra of the salts were confirmed by the signals of the corresponding protonated amines. Thus, in the spectrum of diethylammonium salt, multiplets are observed in the interval 9.88–9.83 ppm, 3.27–3.16 ppm and a triplet at 1.40–1.33 ppm in accordance. In the spectrum of diethylmonoethanolammonium salt there were three multiplets at 9.27–9.21 ppm, 4.05–3.98 ppm and 3.58–3.49 ppm and the signal of OH groups in the form of a triplet at 4.59 ppm. The spectrum of the morpholine salt had a characteristic set of signals of the protonated morpholine cation in the form of two multiplets at 4.18–4.05 ppm, 3.57–3.44 ppm and singlet at 8.68 ppm The piperidinium salt was characterized by proton signals of organic bases in the form of multiplets of 3.40–3.29 ppm, 2.34–2.15 ppm, and 1.55–1.42 ppm and singlet 9.60 ppm.

Tables 1–5 provide a prediction of the results of the virtual ADME analysis of the obtained series of compounds. Based on the results of the analysis of physical-chemical indicators, we have the following results: most compounds meet the established criteria for molecular weight (from 150 g/mol to 500 g/mol). At the same time, only compounds **4** and **5** meet the established criteria for the topological plane of the polar surface (from 20 to 130 Å^2), the flexibility of the molecule (no more than 9 rotational bonds), and molecular refraction (from 40 to 130) (*Table 1*). The only exceptions are compound **11** exceeds the allowable molecular weight and **12** exceeds the allowable molecular refraction. A significant part of the compounds, including the reference drug, has a low level of molecular saturation since the ratio of sp^3-hybridized carbon atoms for saturation should be at least 0.25 [14].

Using ADME analysis, the consensus value of lipophilicity log Po/w, which is the arithmetic mean of five different predictive values (XLOGP3, WLOGP, MLOGP, SILICOS-IT), is calculated by different methods (*Table 2*). For example, iLOGP takes Gibbs energy into account and is calculated using GB/SA in water and *n*-octanol. According to studies, MLOGP should be less than 4.15, XLOGP3 should be in the range of -0.7 to +5.0 [15,16], and WLOGP should be less than 5.88 [13]. The majority of compounds from the virtual library correspond to these lipophilicity criteria (*Table 2*).

An important factor for parenterally administered drugs is their solubility in water (expressed in log S values), which determines the amount of active substance that can be administered in a small therapeutic dose (*Table 3*). The solubility class is usually evaluated on a log S scale, where "insoluble" < -10 < "poorly soluble" < -6 < "moderately soluble" < -4 < "soluble" < -2 < "well soluble" < 0 < "highly soluble" [13]. According to the ESOL model, the expected values of log S should not exceed -6. Studies have shown that celecoxib and inorganic salts are sparingly soluble in water according to ESOL, while salts of organic origin are highly soluble. Thus, most of the compounds contained in the virtual library can find application in the form of parenteral dosage forms. In addition, an analysis of the pharmacokinetic properties of compounds contained in the library was conducted. The smaller the value of log Kp (expressed in cm/s), the less the molecule penetrates the skin [17,18]. Therefore, the synthesized salts of the virtual library have Log Kp values in the range from -6.40 to -9.86 cm/s, which means that not all of them can be used to create ointments.

Oral administration of medication is the most convenient for the patient, although other methods exist. It is important to know that compounds that are passively absorbed in the gastrointestinal tract, such as celecoxib, are not P-glycoprotein substrates, except as salts. Knowing about this is important for understanding multidrug resistance (MDR), which can become a serious obstacle to the successful treatment of many diseases. The phenomenon of MLS consists of the fact that cells or the body become insensitive to a number of drugs of different chemical structures and with different mechanisms of action. This is particularly important because P-gp protects the central nervous system against xenobiotics. In addition, the five main isoforms of cytochromes P450 (CYP) (CYP1A2, CYP2C19, CYP2C9, etc.) are important for the elimination of drugs from the body. As a result, it turned out that all compounds, except for celecoxib, are not inhibitors of cytochromes (*Table 4*). Medicines that are inhibitors of cytochromes are more slowly removed from the body.

According to the filters used by major pharmaceutical companies (Lipinski (Pfizer), Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer)), the synthesized compounds had small deviations from Lipinski's rule according to two criteria: MW >350, XLOGP3 >3.5, just like celecoxib according to the MW >350 criterion, XLOGP3 >3.5 (*Table 5*).

The SwissADME bioavailability radar is used to assess the drug-likeness of compounds (*Fig. 2*). This radar considers six physicochemical properties such as lipophilicity, size, polarity, solubility, flexibility, and saturation. The range of each property is defined by descriptors and shown as a pink area. The radar plot of a molecule must fall entirely within this region to be considered drug-like. Most of the compounds do not correspond to drug similarity according to the polarity criterion (POLAR). However, celecoxib cannot be considered drug-like either, but according to the criterion of saturation (INSATU), which also applies to the compounds shown in the graph (*Fig. 2*).

Table 1. Physical-chemical properties of salts 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazole[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid

No. compounds	MW, g/mol	BA	ABA	Csp^3	OZ	H-BAN	H-BDN	Ref.	TPSA, Å²
Celecoxib	381.37	26	17	0,12	4	7	1	89,96	86,36
3	411.27	26	16	0.20	3	5	3	101.24	134.02
4	433.25	27	16	0.20	4	5	2	99.70	123.02
5	449.36	27	16	0.20	4	5	2	99.70	123.02
6	428.30	27	16	0.20	3	5	3	105.28	136.85
7	442.32	28	16	0.25	3	5	3	110.18	164.49
8	456.35	29	16	0.29	3	5	3	114.99	164.49
9	473.36	30	16	0.29	4	6	5	118.10	181.89
10	484.40	31	16	0.37	5	5	3	124.70	153.46
11	516.40	33	16	0.37	7	7	5	127.02	193.92
12	496.41	32	16	0.40	3	5	3	131.01	153.46
13	498.39	32	16	0.37	3	6	3	127.29	162.69

MW: molecular weight; **BA:** number of heavy atoms; **ABA:** number of aromatic heavy atoms; **Csp^3:** Carbon atoms in sp3-hybridization; **OZ:** number of rotational bonds; **H-BAN:** number of H-bond acceptors; **H-BDN:** number of H-bond donors; **Ref:** molar refractive power; **TPSA:** topological polar surface area.

Table 2. Lipophilicity of salts 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazole[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid

Compounds	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus
Celecoxib	2.56	3.40	5.75	2.65	2.63	3.40
3	1.55	3.27	2.23	2.98	2.13	2.43
4	0.00	3.58	2.15	2.98	1.03	1.95
5	0.00	3.58	2.15	2.98	1.13	1.97
6	0.00	0.26	1.27	-1.49	2.13	0.44
7	2.39	0.27	-0.25	-1.25	2.13	0.66
8	2.73	0.64	0.14	-1.02	2.13	0.93
9	2.54	-0.41	0.45	-1.79	2.13	0.59
10	3.45	1.52	0.49	-0.57	2.13	1.41
11	2.76	-0.58	-1.57	-2.10	2.13	0.13
12	3.41	1.63	0.25	-0.35	2.13	1.41
13	3.06	0.41	-0.90	-1.34	2.13	0.67

Table 3. Solubility in water (Log S) salts 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazole[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid

Com-pounds	ESOL	mg/ml; mol/l	p	Ali	mg/ml; mol/l	p	SILI-COS-IT	mg/ml; mol/l	p
Celecoxib	-4.57	1.04e-02 mg/ml; 2.71e-05 mol/l	MS	-4.89	4.88e-03 mg/ml; 1.28e-05 mol/l	MS	-6.22	2.29e-04 mg/ml; 6.01e-07 mol/l	MS
3	-4.71	8.07e-03 mg/ml; 1.96e-05 mol/l	MS	-5.76	7.17e-04 mg/ml; 1.74e-06 mol/l	MS	-5.07	3.52e-03 mg/ml; 8.57e-06 mol/l	MS
4	-4.96	4.79e-03 mg/ml; 1.11e-05 mol/l	MS	-5.85	6.13e-04 mg/ml; 1.41e-06 mol/l	MS	-5.44	1.58e-03 mg/ml; 3.65e-06 mol/l	MS
5	-5.06	3.95e-03 mg/ml; 8.79e-06 mol/l	MS	-5.85	6.35e-04 mg/ml; 1.41e-06 mol/l	MS	-5.48	1.49e-03 mg/ml; 3.33e-06 mol/l	MS
6	-2.90	5.39e-01 mg/ml; 1.26e-03 mol/l	S	-2.69	8.65e-01 mg/ml; 2.02e-03 mol/l	S	-5.07	3.67e-03 mg/ml; 8.57e-06 mol/l	MS
7	-2.98	4.66e-01 mg/ml; 1.05e-03 mol/l	S	-3.29	2.29e-01 mg/ml; 5.18e-04 mol/l	S	-5.07	3.79e-03 mg/ml; 8.57e-06 mol/l	MS

Cont. of Table 3.

Com-pounds	ESOL	mg/ml; mol/l	p	Ali	mg/ml; mol/l	p	SILI-COS-IT	mg/ml; mol/l	p
8	-3.28	2.38e-01 mg/ml; 5.21e-04 mol/l	S	-3.67	9.77e-02 mg/ml; 2.14e-04 mol/l	S	-5.07	3.91e-03 mg/ml; 8.57e-06 mol/l	MS
9	-2.65	1.07e+00 mg/ml; 2.25e-03 mol/l	S	-2.95	5.37e-01 mg/ml; 1.13e-03 mol/l	S	-5.07	4.06e-03 mg/ml; 8.57e-06 mol/l	MS
10	-3.85	6.80e-02 mg/ml;1.40e-04 mol/l	S	-4.35	2.16e-02 mg/ml; 4.45e-05 mol/l	MS	-5.07	4.15e-03 mg/ml; 8.57e-06 mol/l	MS
11	-2.57	1.38e+00 mg/ml; 2.67e-03 mol/l	S	-3.02	4.91e-01 mg/ml; 9.51e-04 mol/l	S	-5.07	4.43e-03 mg/ml; 8.57e-06 mol/l	MS
12	-4.12	3.79e-02 mg/ml; 7.64e-05 mol/l	MS	-4.47	1.70e-02 mg/ml; 3.43e-05 mol/l	MS	-5.07	4.25e-03 mg/ml; 8.57e-06 mol/l	MS
13	-3.36	2.17e-01 mg/ml; 4.36e-04 mol/l	S	-3.39	2.02e-01 mg/ml; 4.04e-04 mol/l	S	-5.07	4.27e-03 mg/ml; 8.57e-06 mol/l	MS

S: soluble; **MS:** moderately soluble.

Table 4. Pharmacokinetics of salts 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazole[3, 4-*b*][1,3,4]thiadiazine-7-carboxylic acid

Compounds	GI-absorption*	BBB**	P-gp substrate*#	Inhibitor CYP1A2	Inhibitor CYP2C19	Inhibitor CYP2C9	Inhibitor CYP2D6	Inhibitor CYP3A4 i	Log Kp##
Celecoxib	High	–	–	+	–	+	–	–	-6.21
3	High	–	–	–	–	–	–	–	-6.49
4	High	–	+	–	+	–	–	–	-6.40
5	High	–	+	–	+	–	–	–	-6.50
6	High	–	+	–	–	–	–	–	-8.73
7	Low	–	+	–	–	–	–	+	-8.81
8	Low	–	+	–	–	–	–	+	-8.63
9	Low	–	+	–	–	–	–	+	-9.48
10	Low	–	+	–	–	–	–	+	-8.18
11	Low	–	+	–	–	–	–	+	-9.86
12	Low	–	+	–	–	–	–	+	-8.17
13	Low	–	+	–	–	–	–	+	-9.05

*: gastrointestinal absorption; **: blood-brain barrier, *#: P-glycoprotein; ##: penetration through the skin.

Table 5. Similarity and aspects of medicinal chemistry for salts 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazole[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid

Compounds	Bioavailability, Abbot	Synthetic assessment of accessibility	Brenk's warning	Warning PAINS	Leader associations; violation
Celecoxib	0.55	4.26	0	0	No; 2, MW>350, XLOGP3>3.5
3	0.56	4.22	0	0	No; 1 MW>350
4	0.55	4.26	0	0	No; 2: MW>350, XLOGP3>3.5
5	0.55	4.26	0	0	No; 2: MW>350, XLOGP3>3.5
6	0.55	4.36	0	0	No; 1, MW>350
7	0.55	4.47	0	0	No; 1, MW>350
8	0.55	4.58	0	0	No; 1, MW>350
9	0.55	4.65	0	0	No; 1, MW>350
10	0.55	4.79	0	0	No; 1, MW>350
11	0	4.81	0	0	No; 1, MW>350
12	0.55	4.80	0	0	No; 1, MW>350
13	0.55	4.74	0	0	No; 1, MW>350

Drug similarity matching according to Lipinski (Pfizer), Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer) filters – Yes, violations – 0.

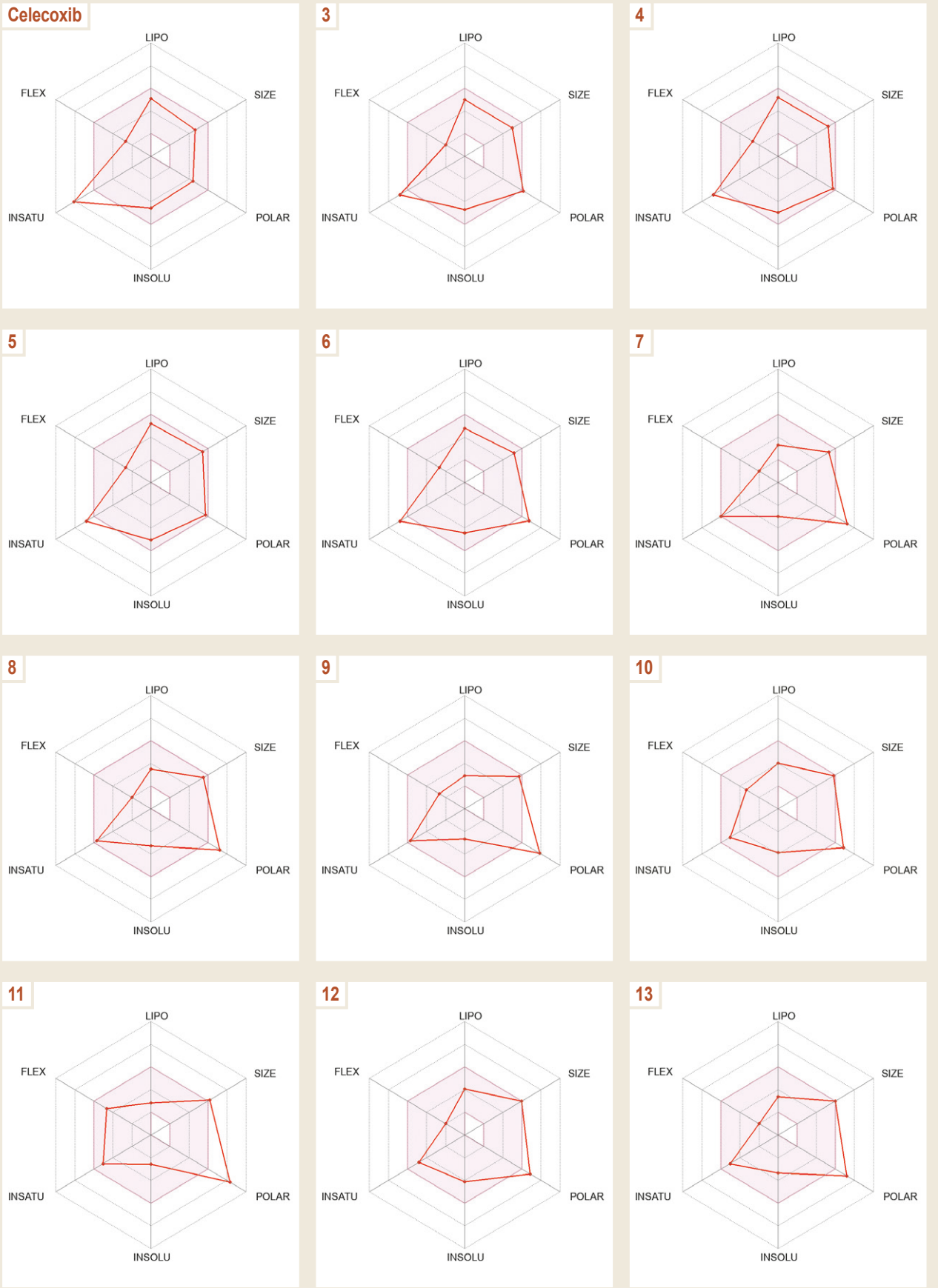


Fig. 2. SwissADME bioavailability radar: lipophilicity (LIPO), size (SIZE), polarity (POLAR), solubility (INSOLU), saturation (INSATU) and flexibility (FLEX).

Conclusions

1. The method of synthesis of 6-(2,6-dichlorophenyl)-3-(3-methyl-1*H*-pyrazol-5-yl)-6,7-dihydro-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-7-carboxylic acid and its salts was investigated.

2. The structure of the synthesized acids and salts was confirmed using modern physical-chemical methods of organic analysis.

3. The physical-chemical properties, lipophilicity criteria, solubility, pharmacokinetics, and drug-likeness were established using the SwissADME service. The parameters of the synthesized compounds were determined and compared with the reference drug celecoxib.

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

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References

[1] Fedotov S. O., & Hotsulia A. S. (2022). Synthesis and properties of 3-(ethylthio)-9-methyl-6-(alkylthio) pyrazolo[1,5-d][1,2,4]triazolo[3,4-f][1,2,4]triazines. *Current issues in pharmacy and medicine: science and practice, 15*(3), 227-234. https://doi.org/10.14739/2409-2932.2022.3.263994

[2] Voskoboynik, O. Y., Kolomoets, O. S., Kovalenko, S. I., & Shishkina, S. V. (2017). [1,2,4]Triazino[2,3-c]quinazolines 1. Methods for the preparation and spectral characteristics of substituted 3-R1-6-R3-6,7-dihydro-2H-[1,2,4]triazino[2,3-c]quinazolin-2-ones. *Chemistry of Heterocyclic Compounds*, *53*(8), 892-904. https://doi.org/10.1007/s10593-017-2142-5

[3] Voskoboinik, O. Y., Stavytskyi, V. V., Antypenko, O. M., Kazunin, M. S., Kravtsov, D. V., Shishkina, S. V., & Kovalenko, S. I. (2020). Synthesis and structure of pyrido[1,2-a]quinazoline condensed derivatives. *Synthetic Communications*, *50*(13), 2043-2051. https://doi.org/10.1080/00397911.2020.1762223

[4] Can, N. Ö., Acar Çevik, U., Sağlik, B. N., Levent, S., Korkut, B., Özkay, Y., Kaplancikli Z., & Koparal, A. S. (2017). Synthesis, Molecular Docking Studies, and Antifungal Activity Evaluation of New Benzimidazole-Triazoles as Potential Lanosterol 14α -Demethylase Inhibitors. *Journal of Chemistry*, *2017*. https://doi.org/10.1155/2017/9387102

[5] Shcherbyna, R., Panasenko, O., Polonets, O., Nedorezanıuk, N., & Duchenko, M. (2021). Synthesis, antimicrobial and antifungal activity of ylidenhydrazides of 2-((4-R-5-R$_1$-4*H*-1,2,4-triazol-3-yl)thio)acetaldehydes. *Ankara Universitesi Eczacilik Fakultesi Dergisi, 45*(3), 504-514. https://doi.org/10.33483/jfpau.939418

[6] Chaban, Z., Harkov, S., Chaban, T., Klenina, O., Ogurtsov, V., & Chaban, I. (2017). Recent advances in synthesis and biological activity evaluation of condensed thiazoloquinazolines: A review. *Pharmacia, 64*(3), 52-66.

[7] Aleksandrova, K. V., Levich, S. V., Mykhalchenko, Ye. K., & Sinchenko, D. M. (2016). Synthesis and physical-chemical properties of 3-aryl-(aralkyl)-8-hydrazinemethylxanthines and their N-substituted derivatives. *Current issues in pharmacy and medicine: science and practice*, (2), 26-31. https://doi.org/10.14739/2409-2932.2016.2.70906

[8] Li, Y. S., Tian, H., Zhao, D. S., Hu, D. K., Liu, X. Y., Jin, H. W., Song, G. P., & Cui, Z. N. (2016). Synthesis and bioactivity of pyrazole and triazole derivatives as potential PDE4 inhibitors. *Bioorganic & medicinal chemistry letters*, *26*(15), 3632-3635. https://doi.org/10.1016/j.bmcl.2016.06.002

[9] Suhak, O. A., Panasenko, O. I., Knysh, Ye. G., & Kamyshny, O. M. (2015). Protymikrobna ta protyhrybkova aktyvnist pokhidnykh 3-(alkiltio)-4-R-5-(tiofen-2-ilmetyl)-4H-1,2,4-triazoliv [Antibacterial and antifungal activity of derivatives 3-(alkylthio)-4-R-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazole]. *Current issues in pharmacy and medicine: science and practice*, (3), 67-70. [in Ukrainian]. https://doi.org/10.14739/2409-2932.2015.3.52625

[10] Kaplaushenko, A. G. (2013). Doslidzhennia zi stvorennia novoho orygihinalnoho vitchyznianoho likarskoho zasobu na osnovi 1,2,4-triazolu [The Research of Creating a New Original Domestic Drug Based on 1,2,4-triazole]. *Naukovyi zhurnal MOZ Ukrainy*, (2), 115-121. [in Ukrainian].

[11] Mykhalchenko, Y., Aleksandrova, K., Shkoda, O., & Pruglo, Y. (2019). Prospective biological active compounds among 7-substituted of 3-benzyl-8-propylxanthines for treatment of metabolic syndrome pathologies. *Eureka: Health Sciences*, (5), 52-58. https://doi.org/10.21303/2504-5679.2019.00988

[12] Safonov, A. A. (2020). Method of synthesis novel N'-Substituted-2-((5-(Thiophen-2-Ylmethyl)-4H-1,2,4-Triazol-3-YL)Thio) acetohydrazides. *Ankara Universitesi Eczacilik Fakultesi Dergisi*, *44*(2), 242-252. https://doi.org/10.33483/jfpau.580011

[13] Karpenko, Y., Omelyanchik, L., & Panasenko, T. (2018). Experimental and theoretical spectroscopic study of thione-thiol tautomerism of new hybrides 1,3,4-oxadiazole-2-thion with acridine-9(10h)-one. *Chemistry and Chemical Technology*, *12*(4), 419-428. https://doi.org/10.23939/chcht12.04.419

[14] Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific reports*, *7*, 42717. https://doi.org/10.1038/srep42717

[15] Lovering, F., Bikker, J., & Humblet, C. (2009). Escape from flatland: increasing saturation as an approach to improving clinical success. *Journal of medicinal chemistry*, *52*(21), 6752-6756. https://doi.org/10.1021/jm901241e

[16] Moriguchi, I., Hirono, S., Liu, Q., Nakagome, Izum., & Matsushita, Y. (1992). Simple Method of Calculating Octanol/Water Partition Coefficient. *Chemical and Pharmaceutical Bulletin*, *40*(1), 127-130. https://doi.org/10.1248/cpb.40.127

[17] Cheng, T., Zhao, Y., Li, X., Lin, F., Xu, Y., Zhang, X., Li, Y., Wang, R., & Lai, L. (2007). Computation of octanol-water partition coefficients by guiding an additive model with knowledge. *Journal of chemical information and modeling*, *47*(6), 2140-2148. https://doi.org/10.1021/ci700257y

[18] Potts, R. O., & Guy, R. H. (1992). Predicting skin permeability. *Pharmaceutical research*, *9*(5), 663-669. https://doi.org/10.1023/a:1015810312465