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SYNTHESIS OF THIOSULPHOESTERS WITH NITROGEN CONTAINING FRAGMENTS

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INTRODUCTION

Modern chemistry of heterocyclic compounds is one of the most promising areas of chemical science. The heterocyclic pyrimidine system is the basic structure of many natural physiologically active substances, in particular, purine alkaloids, nucleic acids, DNA, RNA and others. The quinoline moiety is the basis of the quinine alkaloid, which has been isolated from the bark of quinine and exhibits antibacterial, antipyretic, antimalarial, analgesic and anti-inflammatory activity.

The design and synthesis of new biologically active substances containing pharmacophores of different heterocyclic nature in combination with other pharmacologically active fragments is of a particular interest in organic chemistry. Pyrimidine and quinoline structures are important nitrogen-containing heterocyclic systems used as structural blocks that are part of structures of various pharmaceuticals for the treatment and prevention of infectious diseases (fig. 1).

The cause of many infectious pathologies, in particular nosocomial infections are bacteria, especially gram-negative agents: Escherichia coli, Klebsiella spp., Enterobacter spp.; Pseudomonas aeruginosa and Acinetobacter spp. The pathogens of nosocomial infections are characterized by progressive resistance to antibacterial drugs. The results of studies of new derivatives of nitrogen-containing compounds with the pyrimidine moiety indicate the prospect of studying their properties in order to create effective antimicrobial agents for the prevention and treatment of infectious complications caused by these microorganisms[1].

[1] Shcherbak O.M., Andreieva I.D., Kazmirchuk V.V., Rusak P.S., Menkus O.V. Perspektyvy Zastosuvannia Novykh Pokhidnykh Pirymidynu Pry Nozokomialnykh Infektsiiakh Vyklykanykh Hramnehatyvnymy Mikroorhanizmamy. *Ukrainian journal of surgery.* 2012. № 3 (18). P. 34–37.

Pyrimidine derivatives have also been shown to be active against grams of bacteria and fungi of the genus Candida[2].

Infectious diseases, besides bacteria and fungi, can be the representatives of the protozoa. In particular, agents of African human trypanosomosis (sleep sickness), Chagas disease and leishmaniasis are representatives of the parasitic protozoa *Trypanosoma brucei*, *Trypanosoma cruzi and Leishmania species*. Quinoline derivatives were tested for *T. brucei*, *T. cruzi* and *L. infantum*[3], and their cytotoxic activity were demonstrated to be effective against these pathogens.

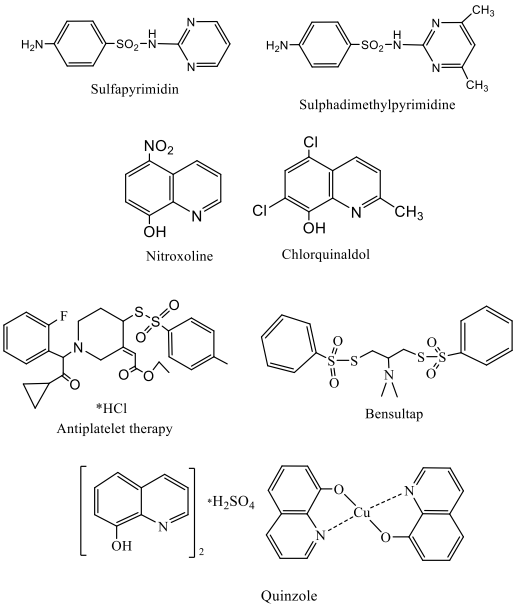


Figure 1

[2] Shcherbak O.M. Perspektyvy Vyvchennia Protymikrobnoi Dii Novykh Pokhidnykh 4N-Pirydo4´3´56pirano-23-Dpirymidynu. *Aktualni Pytannia Farmatsevtychnoi I Medychnoi Nauky Ta Praktyky*. 2011. № 2 (24). P. 116–118.

[3] Pietro O.D., Vicente-García E., Taylor M.C., Berenguer D., Viayna E., Lanzoni A., Sola I., Sayago H., Riera C., Fisa R., Clos M.V., Pérez B., Kelly J.M., Lavilla R., Muñoz-Torrero D. Multicomponent reaction-based synthesis and biological evaluation of tricyclic heterofusedquinolines with multi-trypanosomatid activity. *European Journal of Medicinal Chemistry*. 2015. № 105. P. 120–137. URL: https://doi.org/10.1016/j.ejmech.2015.10.007.

Thiosulphonates ($R_1SO_2SR_2$) is a special class of disulfur-containing compounds in which one sulfur atom is hexavalent in the sulfonyl moiety ($-R_1SO_2$) and divalent sulfur in the sulfide moiety ($-SR_2$).

Interest in thiosulphonic esters has increased significantly over the last two decades, indicating an increase in the number of publications on these compounds[4]. Thiosulfonic acid esters exhibit a wide range of biological effects and are proposed for use as biologically active substances for medicine, agriculture and various industries as antimicrobial agents[5].

1. Synthesis of thiosulphoesters

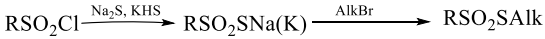
[4] Mampuys P., McElroy C.R., Clark J.H., Orru R.V.A., Maes B.U.W. Thiosulfonates as Emerging Reactants: Synthesis and Applications Adv. *Synth. Catal.* 2020. № 362. P. 3–64. URL: https://doi.org/10.1002/adsc.201901597.

[5] Lubenets V., Stadnytska N., Baranovych D., Vasylyuk S., Karpenko O., Havryliak V., Novikov V. Thiosulfonates: The Prospective Substances against Fungal Infections. *Fungal Infection* / eds. Érico Silva de Loreto and Juliana Simoni Moraes Tondolo. IntechOpen, London, 2019. DOI: 10.5772/intechopen.84436; Pylypets A.Z., Iskra R.Y., Havryliak V.V., Nakonechna A.V., Novikov V.P., Lubenets V.I. Effects of thiosulfonates on the lipid composition of rat tissues. *Український біохімічний журнал.* 2017. № 89. 6. P. 58–64. doi: https://doi.org/10.15407/ubj89.06.056; Oriabinska L.B., Starovoitova S.O., Vasylyuk S.V., Novikov V.P., Lubenets V.I. Ethylthiosulfanilate effect on Candida tropicalis. *Український біохімічний журнал.* 2017. Vol. 89. № 5. P. 70–76. doi: https://doi.org/10.15407/ubj89.05.070; Halenova T.I., Nikolaeva I.V., Nakonechna A.V., Bolibrukh K.B., Monka N.Y., Lubenets V.I., Savchuk O.M., Novikov V.P., Ostapchenko L.I. The search of compounds with antiaggregation activity among S-esters of thiosulfonic acids. *Ukr. Biochem. J.* 2015. № 87. 5. P. 83–92. doi: https://doi.org/10.15407/ubj87.05.083; Lubenets V.I., Stadnitskaya N.Ye., Novikov V.P. Synthesis of thiosulfonates belonging to quinoline derivatives. *Russ. J. Org. Chem.* 2000. № 36. P. 851–853. DOI: https://doi.org/10.1007/BF02757443; Sato, R., Akutsu, Y., Goto, T., Saito, M. Benzopentathiepin as sulfurization reagent. Novel synthesis of thiosulfonates from sulfinates. *Chem. Lett.* 1987. № 16. P. 2161–2162; Baranovich D.B., Lubenets V.I., Novikov V.P. Synthesis of thiosulfonates with functional groups in the aliphatic chain. *Russ. J. Org. Chem.* 2001. № 37. P. 1046–1047; Baranovich D.B., Lubenets V.I., Novikov V.P. Synthesis of S-[2-(4-Aminobenzenesulfonyl)ethyl] and S-[2-(3-Amino-4-methoxybenzenesulfonyl)ethyl] Thiosulfonates. *Russ. J. Gen. Chem.* 2001. № 71. P. 1827–1827. DOI: https://doi.org/10.1023/A:1013987618313; Zhao Q., Lu L., Direct Q. Monofluoromethylthiolation with S-(Fluoromethyl) Benzenesulfonothioate. *Shen, Angew. Chem.* 2017. № 129. P. 11733–11736; *Angew. Chem. Int. Ed.* 2017. № 56. P. 11575–11578. DOI: 10.1002/anie.201705633; Lubenets V.I., Vasylyuk S.V., Novikov V.P. Synthesis of S-(3-chloroquinoxalin-2-yl) esters of aliphatic and aromatic thiosulfonic acids. *Chem. Heterocycl. Compd.* 2005. № 41. P. 1547–1548. DOI: https://doi.org/10.1007/s10593-006-0039-9; Chura B., Lubenets V.I., Goi O.V., Novikov V.P. The Reaction of Sodium 4-Acetylaminobenzenethiosulfonate with 2,3-Dichloroquinoxaline. *Chem. Heterocycl. Compd.* 2002. № 38. P. 1432–1433. DOI: 10.1023/A:1022163417299; Lubenets V.I., Vasylyuk S.V., Goi O.V., Novikov V.P. Reaction of 6,7-dichloroquinoline-5,8-quinone with thiosulfonic acid salts. *Chem. Heterocycl. Compd.* 2006. № 42. P. 961–962. DOI: https://doi.org/10.1007/s10593-006-0189-9.

Given the high synthetic and pharmacological potential of thiosulphonic acid derivatives, which are potent electrophilic sulfonylating and nucleophilic thiolating reagents, it is very important to design systems that would contain various combinations of thiosulphonylacetamines. These structures are likely to exhibit new or modified biological activity. The presented study demonstrates the predicted preferential directions of experimental studies of the biological activity of thiosulfonic acid esters with pyrimidine and quinoline fragments in the composition of their molecules and their practical application. To achieve this goal, the design of thiosulfonate structures with nitrogen-containing heterocyclic fragments has been performed, which is presented below.

We have investigated possible ways of obtaining thiosulphoesters with pyrimidine moieties.

One of which can be represented by a number of transformations:



Pyrimidine derivatives with OH- and NH_2- groups are known to be the most sulfonated, but such sulfochlorides are unknown. 2-amino-6-methylpyrimidin-4-ol **1** and dibromohydrate 5-bromomethyl-2-methylpyrimidine-4-amine **7** were selected as the objects of our studies. The intermediate product for the synthesis of thiosulphoesters is the corresponding sulfochloride, so we investigated the chlorosulfonation of 2- amino-6-methylpyrimidin-4-ol **1** five times the excess chlorosulfonic acid at a temperature of 0–5°C, followed by heating the sulfomass to 110–125°C according to fig. 2.

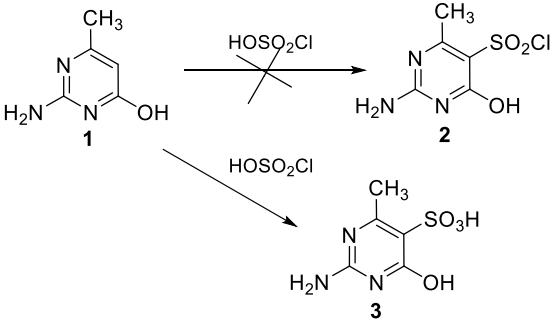


Figure 2

It was not possible to obtain sulfochloride **2** directly under the above conditions. Instead, in 80% yield sulfonic acid **3** was obtained, which was subsequently used to obtain the target sulfochloride **2**. Compound **2** was obtained by boiling salt **4**, which was previously converted to 2-amino-4-hydroxy-6-methylpyrimidine-5-sulfonic acid **3** with excess thionyl chloride.

To obtain the corresponding thiosulfonate **5a,b s**ulfochloride **2** was used without further purification.

Attempts to obtain the sodium and potassium salts of 2-amino-4-hydroxy-6-methyl-pyrimidine-5-thiosulfonic acid **5a, b** were not successful. Because compound **2** is weak and rapidly hydrolyzes, interaction with sodium sulfide or potassium hydrosulfide results in the formation of sodium or potassium sulfonates **6a,b** instead of the target thiosulfonates **5a,b.**

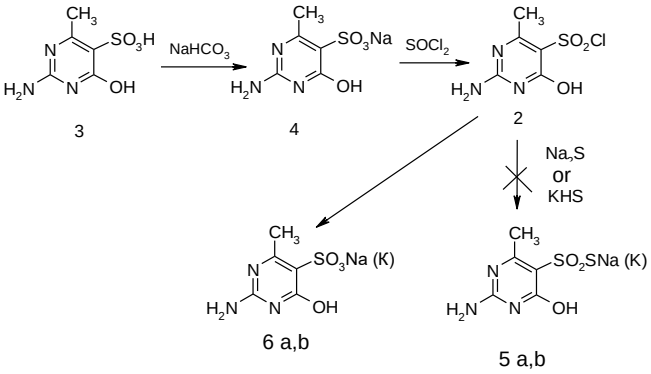


Figure 3

The dibromohydrate of 5-bromomethyl-2-methylpyrimidine-4-amine is an intermediate in the production of vitamin B_1 (thiamine). An additional argument when choosing this feedstock was that its pyrimidine moiety is included in the structure of the anticancer drug Nimustine[6].

The replacement of bromine by the sulfo group in the dibromohydrate of 5-bromomethyl-2-methylpyrimidin-4-amine **7** was carried out with prolonged boiling of compound **7** with saturated sodium sulfite solution.

[6] Mashkovskiy M.D. Lekarstvennyie sredstva. 16-e izdanie, pererab. i dopoln. Moskva : Novaya volna izdatel Umerenkov, 2010. 1216 p.

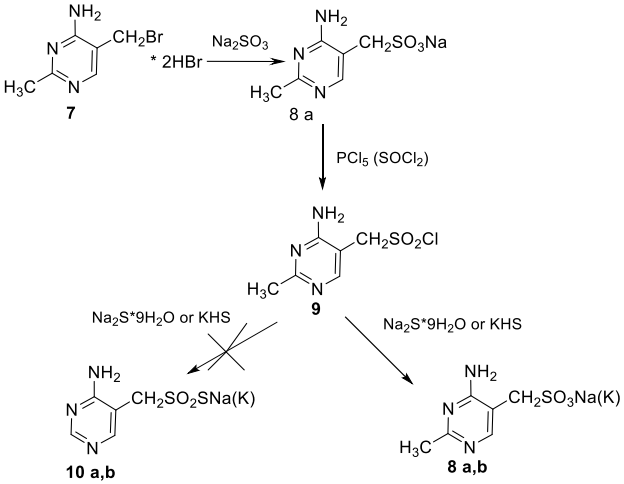


Figure 4

Phosphorus pentachloride or thionyl chloride was used to obtain the corresponding sulfochloride **9** from sodium sulfonate **8a**.

Chlorohydride **9** is an unstable compound that hydrolyzes rapidly. The study of the redox interaction of sulfochloride **9** with potassium hydrosulfide or sodium sulfide found that instead of the predicted thiosulfonates **10 a,b** sodium or potassium sulfonates **8 a,b** were obtained.

Thus, this way of synthesis of thiosulfonic acid esters of pyrimidine derivatives did not produce the expected results, since the investigated sulfochlorides are not heat-resistant at room temperature which makes it difficult to obtain the corresponding salts of thiosulfonic acids from them.

As an alternative method of obtaining thiosulfoesters with a pyrimidine moiety, we investigated the possibility of using 5-bromomethyl-2-methylpyrimidine-4-amine **7** dibromohydrate as an alkylating reagent. The original dibromohydrate was converted to compound **11** and was reacted with potassium or sodium salts of different thiosulfonic acids in acetone-aqueous medium at room temperature for 7–10 days. Solid crystalline thiosulphoesters **12 a-d** were obtained in 29–57% yields, which were soluble in acetone, alcohol and partially in water.

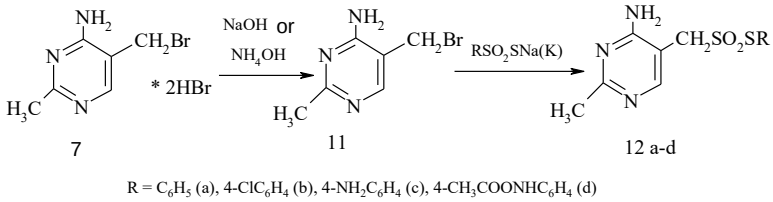


Figure 5

Physicochemical characteristics of the obtained thiosulphoesters **12 a-d:**

Benzenethiosulfonic acid 4-amino-2-methylpyrimidin-5-yl-methyl ester 12a Yield 28%, mp:163–164°C, ^{1}HNMR (300 MHz, $CDCl_3$) δ, pmm: 2,32 (3H, s, CH_3), 4,26 (2H, s , S-CH_2), 6,40 (2H, br.s NH_2), 7,54–8,06 (м. 5H, 5Ar-H), 8,92 (1H, s, CH=N); IR (KBr, cm-1): 3446, 3398 (NH_2), 1600, 1596 (Ar); 1582, 1488, 1464, (pyrimid. cycle); $1326_{\gamma as,}$ $1124_{\gamma s}$, (SO_2); Anal.calcd for $C_{12}H_{13}N_3O_2S_2$: C 48,46 H 4,38 N 14,13 S 21,89; found: C 48,28 H 4,28 N 14,12 S 21,81;

4-Chlorobenzenethiosulfonic acid 4-amino-2-methylpyrimidin-5-yl-methyl ester12 b Yield 52%, mp: 110–112°C, 1HNMR (300 MHz, CDCl3) δ, pmm: 2.36 (3H, s, CH3), 4.34 (2H, s , S-CH2), 6.36 (2H, s, NH2), 7,38–8,0 (4 H, m, 4Ar-H), 8.90 (1H, s, CH=N); IR (KBr, cm-1): 3466, 3380 (NH2), 1606, 1598 (Ar); 1586, 1482, 1460, (pyrimid. cycle); 1332γas, 1144γs, (SO2); Anal.calcd for $C_{12}H_{12}ClN_3O_2S_2$ C 43,08 H 4,23 N 12,64 S 19,39; found: C 43,04 H 4,20 N 12,65 S 19,07;

4-Aminobenziothiosulfonic acid 4-amino-2-methylpyrimidin-5-yl-methyl ester 12 c Yield 56%, mp: 202–203°C, ^{1}HNMR (300 MHz, $CDCl_3$) δ, pmm: 2.48 (3 H, s, CH_3), 4.38 (2 H, s, S-CH_2), 6,46 (2H, s, NH_2), 6,48 (2H, s, 2 NH_2), 7,4–8,1 (4 H, m, 4Ar-H), 8.94 (1H, s, CH=N); IR (KBr, cm-1): 3536, 3502, 3466, 3380 (NH_2), 1600, 1596 (Ar); 1586, 1482, 1460, (pyrimid. cycle); $1332_{\gamma as,}$ $1144_{\gamma s}$, (SO_2); Anal.calcd for $C_{12}H_{14}N_4O_2S_2$. C 46,68 H 4,32 N 18,11 S 20,41 found: C 46,70 H 4,28 N 18,03S 20,09;

4-[(methoxycarbonyl)amino] benzenethiosulfonic acids 4-amino-2-methylpyrimidin-5-yl-methyl ester12 d Yield 30%, mp: 172–173°C, 1HNMR (300 MHz, CDCl3) δ, pmm: 2.32 (3H, s, CH3), 2.64 (3H, s, CH3), 4.24 (2 H, s, S-CH2), 6.62 (2H, s, 2 NH2), 7.76 (2H, д, J=8, CH); 7.92 (2H, д, J=8, CH); 8.11 (1H, s, CH=N) 10.08 (1H, c, NH); IR (KBr, cm-1): 3440, 3400 (NH2), 3326 (NH); 1632, (C=O); 1602 (Ar); 1580, 1540, 1452,

(pyrimid. cycle); 1340γas, 1112γs (SO2); Anal.calcd for $C_{14}H_{16}N_4O_4S_2$ C 45,65 H 4,38 N 15,21 S 17,39; found: C 45,79 H 4,20 N 15,24 S 17,12.

For the synthesis of thiosulphoesters **18 a-g** with heterocyclic nitrogen-containing moiety we have chosen quinoline **14** and 8-quinolinesulfonic acid **13**.

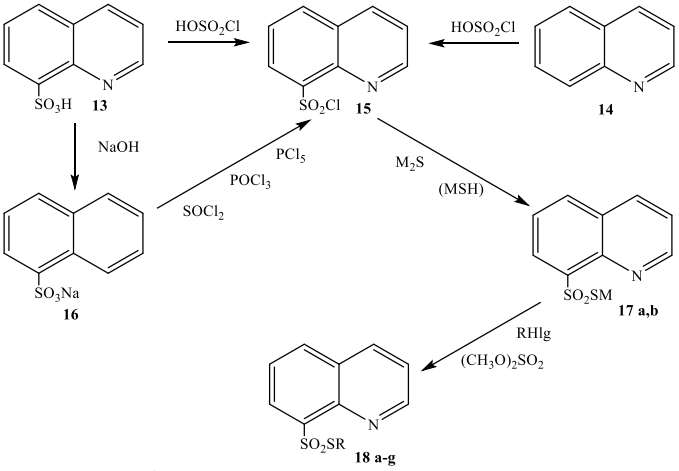


Figure 6

Quinoline and 8-quinolinesulfonic acid were obtained from 8-quinoline sulphochloride **15**, which was subsequently converted to the alkali metal salts of 8-quinolinethiosulfonic acids **17 a,b**.

The redox interaction of the synthesized 8-quinolinesulfochloride **15** with an aqueous solution of sodium sulfide to obtain the sodium salt of 8-quinolintiosulfonic acid **17 a** has been investigated. This process takes place in two stages.

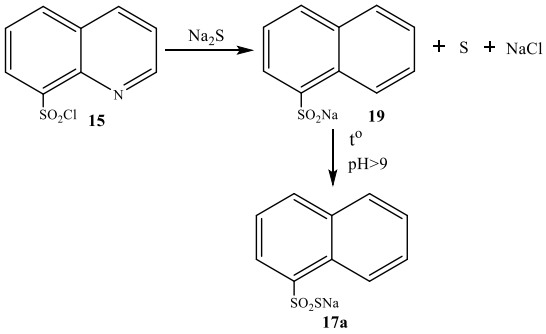


Figure 7

In the first stage, the sulfochloride is reduced to sulfinate with the release of elemental sulfur, which when heated react with each other to form the sodium salt of 8-quinoline thiosulfonic acid (the second stage of interaction). Upon cooling the reaction mass, the final product crystallizes and precipitates. The filtered salt was purified by recrystallization from ethanol. The 8-quinoline thiosulfonic acid potassium salt was prepared analogously to the sodium salt by replacing sodium sulfide with a saturated potassium hydrosulfide solution.

Alkylation of the sodium or potassium salts of 8-quinolinethiosulfonic acids by various alkyl halides or dialkyl sulfates in acetone-water or alcohol media synthesizes the corresponding S-alkyl- (8-quinoline) thiosulfonates.

We also conduct synthesis to produce thiosulphoesters containing an 8-hydroxyquinoline moiety.

The purity and individuality of the samples with quinoline fragments **18 a-g** and **25 a-c** are attested by the TLC method. The structure and composition of the synthesized thiosulphoesters were confirmed by IR, ^{1}H NMR spectroscopy, elemental analysis which is provided below:

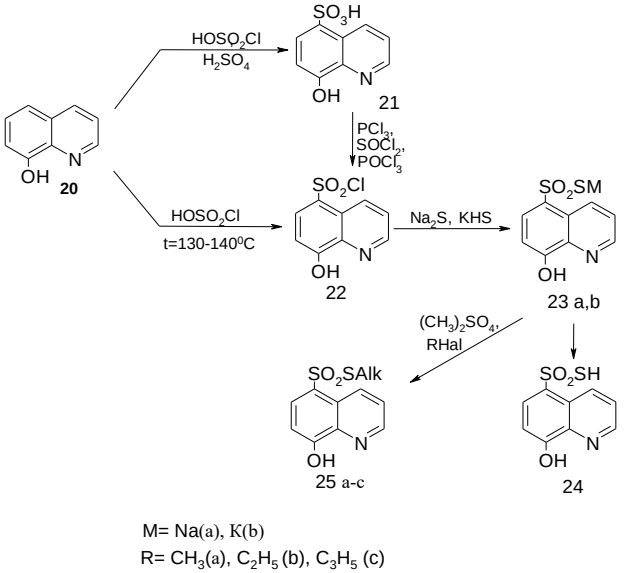


Figure 8

S-Methyl-8-quinoline thiosulphonate 18 a Yield 50%, mp: 120°C, 1HNMR (300 MHz, CDCl3) δ, pmm: 1.74 с (3H,SCH3), 7.68–7.82 м (3H, Ar-H), 7.68–9.15 м (6H, Ar-H); IR (KBr, cm-1): 1306, 1132 (SO2); 832, 788, 764 (quinoline nucleus); Anal.calcd for $C_{10}H_9NO_2S_2$ C 50.19 H 3.79 N 5.85 S 26.79; found: C 50.00 H 4.03 N 5.77 S 26.61;

S-Ethyl-8-quinoline thiosulphonate 18 b Yield 42%, mp: 77 °C, ^{1}HNMR (300 MHz, $CDCl_3$) δ, pmm: 1.23 т (3H,CH_3), 3.30 к (2H, SCH_2), 7.76–7.88 м (3H, Ar-H), 7.76–9.16 м (6H, Ar-H); IR (KBr, cm^{-1}): 1308, 1136, 1124 (SO_2); 828, 784, 760 (quinoline nucleus); Anal.calcd for $C_{11}H_{11}NO_2S_2$ C 52.15 H 4.38 N 5.53 S 25.31; found: C 52.41 H 4.63 N 5.57 S 25.51;

S-Allyl-8-quinoline thiosulphonate 18 c Yield 42%, mp: 58–60°C, ^{1}HNMR (300 MHz, $CDCl_3$) δ, pmm: 4.02 д(2H,SCH_2), 4.98–5.88 м (2H,=CH_2), 5.52–5.86 м (H,-CH=), 7.70–9.20 м (6H, Ar-H),7.70–7.90 м (3H, Ar-H); IR (KBr, cm^{-1}): 1640 (CH=CH_2), 1320, 1160, 1124 (SO_2); 832, 792, 772 (quinoline nucleus); Anal.calcd for $C1_2H_{11}NO_2S_2$ C 54.32 H 4.18 N 5.28 S 24.16; found: C 54.43 H 4.37 N 5.36 S 24.24;

S-Propyl-8-quinoline thiosulphonate 18 d Yield 60%, mp: 55°C, ^{1}HNMR (300 MHz, $CDCl_3$) δ, pmm: 0.99 т (3H,CH_3), 1.75 м (2H, CH_2), 2.85 м (2H, SCH_2), 7.69–8.14 м (3H, Ar-H), 7.69–9.17 м (6H, Ar-H); IR (KBr, cm^{-1}): 1326, 1116, (SO_2); 830, 786, 764 (quinoline nucleus); Anal.calcd for $C_{12}H_{13}NO_2S_2$ C 53.91 H 4.90 N 5.24 S 23.98; found: C 53.90 H 5.18 N 5.19 S 24.18;

S-Iso-propyl-8-quinoline thiosulphonate 18 e Yield 17%, mp: 150°C, 1HNMR (300 MHz, CDCl3) δ, pmm: 1.48 д (3H,CH3), 2.96 м (6H, SCH(CH3)2, 6.95–7.73 м (3H, Ar-H), 6.95–9.16 м (6H, Ar-H); IR (KBr, cm^{-1}): 1332, 1112 (SO2); 836, 790, 758 (quinoline nucleus); Anal.calcd for $C_{12}H_{13}NO_2S_2$ C 53.91 H 4.90 N 5.24 S 23.98; found: C 53.73 H 5.12 N 5.20 S 23.96;

S-Butyl-8-quinoline thiosulphonate 18 f Yield 70%, mp: 65°C, 1HNMR (300 MHz, CDCl3) δ, pmm: 0.94 т (3H,CH3), 1.58 м (2H, CH2), 1.62 м (2H, CH2), 2.95 м (2H, SCH2), 7.75–8.81 м (3H, Ar-H), 7.75–9.17 м (6H, Ar-H); IR (KBr, cm-1): 1340, 1116 (SO2); 886, 830, 762 (quinoline nucleus); Anal.calcd for $C_{13}H_{15}NO_2S_2$ C 55.49 H 5.37 N 4.98 S 22.79; found: C 55.62 H 5.65 N 4.94 S 22.63;

S-Iso-butyl-8-quinoline thiosulphonate 18 g Yield 24%, mp: 160°C, ^{1}HNMR (300 MHz, $CDCl_3$) δ, pmm: 0.96 с (3H,CH_3), 0.98 с (3H,CH_3), 2.00 м (H, CH), 2 78 д (2H, SCH_2), 7.73–8.24 м (3H, Ar-H), 7.73–9.16 м (6H, Ar-H); IR (KBr, cm^{-1}): 1308, 1126 (SO_2); 832, 790, 766 (quinoline nucleus); Anal.calcd for $C_{13}H_{15}NO_2S_2$ C 55.49 H 5.37 N 4.98 S 22.79; found: C 55.72 H 5.50 N 4.90 S 22.70;

S-Methyl-8-hydroxyquinoline thiosulphonate 25 a Yield 62%, mp: 72–73°C; IR (KBr, cm^{-1}): 3600 (OH); 1340, 1136 (SO_2); Anal.calcd for $C_{10}H_9NO_3S_2$ C 47.05 H 3.55 N 5.49 S 3.94; found: C 46.82 H 3.83 N 5.31 S 24.93;

S-Ethyl-8-hydroxyquinoline thiosulphonate 25 b Yield 41%, mp: 121°C; IR (KBr, cm^{-1}): 3605 (OH); 1330, 1124 (SO_2); Anal.calcd for $C_{11}H_{11}NO_3S_2$ C 49.06 H 4.12 N 5.20 S 33.80; found: C 48.85 H 4.35 N 5.06 S 23.62;

S-Allyl-8- hydroxyquinoline thiosulphonate 25 c Yield 56%, mp: 37°C; IR (KBr, cm^{-1}): 3600 (OH); 1620 ($CH=CH_2$), 1320, 1112 (SO_2); Anal.calcd for $C_{12}H_{11}NO_3S_2$ C 51.23 H 3.94 N 4.98 S 22.79; found: C 51.06 H 4.23 N 4.76 S 22.63ю

2. Predicted activity

Computer-aided biological screening for Prediction of Activity Spectra for Substances (PASS) was performed for the above compounds. The principle of operation of this program is based on the analysis of the dependence “structure-activity” for substances in the training sample, which contains more than 80,000 different biologically active substances (substances of known drugs and physiologically active compounds), the data of which are constantly updated with new results of biological activity of compounds published in the scientific and technical literature and numerous databases, as well as with information from unpublished documents[7].

A particularly promising trend in studies of the biological activity of substances is to increase the physiological effect of drugs. Therefore, data on the full spectrum of biological action of known and first synthesized potential biologically active compounds, the identification of certain types of biological activity of substances and the correlation between structure and biological action can be the basis for their practical use, in particular as medicinal substances. Advanced screening of biological activity can determine the direction of further experimental studies of synthesis compounds without significant time and cost.

The average forecast accuracy of the PASS program is about 85%, which is sufficient to use the data obtained to predict the spectrum of biological activity of new substances (the expected average prediction accuracy of one of the 500 types of activity is only about 0.2%)[8]. The results of the forecast provide information on the list of likely activities and the estimated probability of (Ra) presence and (Ri) absence of each activity. The numerical estimates of the probabilities of Ra and Ri are in the range from 0 to 1, and their sum is usually not equal to one, since the probabilities of the presence and absence of a certain type of physiological activity are calculated independently. The results of the screening are shown in Tables 1–3.

[7] Gloriozova A., Filimonov D.A., Lagunin A.A., Poroykov V.V. Testirovanie kompyuternoy sistemyi dlya predskazaniya biologicheskoy aktivnosti PASS na vyibor kenovyih himicheskih soedineniy. *Him.-farm. zhurnal.* 1998. № 32. 12. P. 32–39.

[8] Lagunin A., Stepanchikova A., Filimonov D., Poroikov V. PASS: prediction of activity spectra for biologically active substances. *Bioinformatics.* 2000. № 16.8. P. 747–748.

Table 1

The predicted effect of the biological action of 4-amino-2-methylpyrimidin-5-yl-methyl thiosulfonic acid esters 12 a-d according to PASS program

Activity	Number of the compound			
	C_6H_5	4-ClC_6H_4	4-$NH_2C_6H_4$	4- $CH_3COONHC_6H_4$
4-Hydroxybenzoate-CoA ligase inhibitor	0.512	0.441	0.477	-
Alcohol O-acetyltransferase inhibitor	0.693	0.655	0.675	0.868
Antineoplastic (solid tumors)	0.482	0.462	0.467	0.792
Antiprotozoal (Coccidial)	-	0.397	0.409	-
Benzoate-CoA ligase inhibitor	0.927	0.908	0.918	0.594
Butyrate-CoA ligase inhibitor	0.641	0.387	0.487	-
Cathepsin T inhibitor	0.451	-	-	-
Cathepsin T inhibitor	0.451	-	-	-
CDP-glycerol glycerophosphotransferase inhibitor	-	-	-	0,492
Chemoprotective	0.84	0.821	0,825	0,469
Glycine-tRNA ligase inhibitor	0.573	0.528	0.552	0.45
Glycosylphosphatidylino sitol phospholipase D inhibitor	-	0.437	-	-
Imidazoline I1 receptor agonist	-	-	-	0.335
Kinase inhibitor	0,462	0,434	0,446	-
Phosphodiesterase inhibitor	0,712	0,588	0,638	0.403
Thiamine pyridinylase inhibitor	-	-	0.447	-
Thioredoxin inhibitor	0.475	-	-	-
Venombin AB inhibitor	0.477	-	-	-

According to the data obtained, the title compound is benzene thiosulfonic acid 4-amino-2-methylpyrimidin-5-yl-methyl ester. Alcohol O-acetyltransferase, Benzoate-CoA ligase, Chemoprotective Glycine-tRNA ligase, Phosphodiesterase, and Antineoplastic (solid tumors) activity have been found to inhibit the activity of all esters.

Table 2

The predicted effect of the biological action of S-alkyl esters of 8-quinoline thiosulfonic acid *18 a-g* according to PASS program

Activity	Number of the compound						
	-CH_3	-C_2H_5	-C_3H_5	-C_3H_7	-C_3H_7 i30	-C_4H_9	-C_4H_9 i30
1	2	3	4	5	6	7	8
(R)-6-hydroxynicotine oxidase inhibitor	0.83	0.729	0.774	0.673	0.752	0.645	0.65
(S)-3-hydroxyacid ester dehydrogenase inhibitor	0.717	-	0.63	-	-	-	-
(S)-6-hydroxynicotine oxidase inhibitor	0.853	0.749	0.796	0.683	0.774	0.65	0.661
2-Hydroxyquinoline 8-monooxygenase inhibitor	0.758	-	0.643	0.572	-	-	-
4-Hydroxyproline epimerase inhibitor	0.728	-	0.566	-	-	-	-
4-Methoxybenzoate monooxygenase (O-demethylating) inhibitor	-	-	0.668	-	-	-	-
Aldehyde dehydro-genase (pyrroloquinoline-quinone) inhibitor	0.813	-	0.827	-	0.724	-	-
Alkane 1-monooxygenase inhibitor	0.745	-	0.634	-	0.703	-	0.521
Antiseborrheic	-	-	-	0.689	-	0.626	0.729
Antihypertensive	-	-	-	-	-	-	0.499
Amine dehydrogenase inhibitor	-	-	0.544	-	-	-	-
Arylacetonitrilase inhibitor	0.818	0.828	0.594	0.626	0.71	0.525	0.626
Arylalkyl acylamidase inhibitor	0.843	0.753	0.75	0.628	0.79	0.519	0.522
Aspulvinone dimethylallyltransferase inhibitor	-	-	0.696	-	-	-	-
Benzoate-CoA ligase inhibitor	-	-	-	-	-	0.563	-
Biotinidase inhibitor	-	-	-	-	-	-	0.613
Bothrolysin inhibitor	0.829	-	0.754	0.562	0.723	0.514	0.562
Carbon-monoxide dehydrogenase inhibitor	-	-	0.572	-	-	-	0.5
Carboxypeptidase Taq inhibitor	0.847	0.79	0.779	0.819	0.814	0.837	0.699
Carnitinamidase inhibitor	0.802	0.761	0.714	0.732	-	0.696	0.652
Cathepsin T inhibitor	-	-	-	-	-	-	0.512
Chemoprotective	0.717	-	0.6	-	-	0.545	0.515
Chenodeoxycholoyltaurine hydrolase inhibitor	-	-	0.543	-	-	-	-
Chloride peroxidase inhibitor	-	-	0.623	-	-	-	-
Cis-1,2-dihydro-1,2-dihydroxynaphthalene dehydrogenase inhibitor	-	-	0.531	-	-	-	-
Corticosteroid side-chain-isomerase inhibitor	0.719	-	0.557	-	-	-	-
Creatininase inhibitor	0.805	-	0.667	-	0.736	-	-
Cyanoalanine nitrilase inhibitor	-	-	0.613	-	-	-	0.526
Cysteamine dioxygenase inhibitor	-	-	-	0.557	-	0.524	0.533
Dehydro-L-gulonate decarboxylase inhibitor	0.82	0.764	0.74	0.655	0.791	0.607	0.655
2,4-Dichlor-ophenol 6-monooxygenase inhibitor	-	-	-	0.57	-	0.589	0.598

Continuation of Table 2

1	2	3	4	5	6	7	8
Electron-transferring-flavoprotein dehydrogenase inhibitor	-	-	0.555	0.717	-	0.69	-
Endopeptidase So inhibitor	0.774	0.76	0.699	0.776	0.742	0.792	0.682
Ferredoxin hydrogenase inhibitor	-	-	0.548	-	-	-	-
Ferredoxin-NAD+ reductase inhibitor	0.756	-	0.653	-	0.716	-	0.553
Fibrolase inhibitor	-	-	0.547	-	-	-	0.58
Formaldehyde dehydrogenase inhibitor	-	-	-	-	-	0.511	-
Fragilysin inhibitor	0.788	0.826	0.673	0.779	0.747	0.745	0.848
Fructose 5-dehydrogenase inhibitor	-	-	0.547	-	0.785	-	-
Gamma-guanidinobutyraldehyde dehydrogenase inhibitor	0.817	0.752	0.72	0.622	-	0.572	0.622
Gluconate 2-dehydrogenase (acceptor) inhibitor	-	-	0.644	-	-	-	-
Glutathione thiolesterase inhibitor	0.786	0.716	0.689	0.588	0.749	-	0.588
Glycosylphosphatidylinositol phospholipase D inhibitor	0.914	0.843	0.876	0.821	0.861	0.798	0.777
Glyceryl-ether monooxygenase inhibitor	-	-	0.561	0.642	-	0.663	0.581
Gly-X carboxypeptidase inhibitor	-	-	0.596	0.552	-	0.508	0.552
Guanidinoacetase inhibitor	-	-	0.541	0.587	-	0.628	-
Histidinol-phosphatase inhibitor	-	-	0.542	-	-	-	-
Horrilysin inhibitor	-	-	0.558	-	-	-	0.499
Hydroxylamine oxidase inhibitor	0.71	-	0.617	0.647	-	0.67	0.536
IgA-specific metalloendopeptidase inhibitor	0.869	0.849	0.786	0.861	0.832	0.877	0.755
3-Isopropyl-malate dehydratase inhibitor	-	-	-	-	-	-	0.53
Linoleate diol synthase inhibitor	-	-	-	-	-	-	0.56
Linoleoyl-CoA desaturase inhibitor	-	-	-	-	-	-	0.554
Leucolysin inhibitor	0.732	0.752	0.601	0.63	0.727	0.577	0.63
Lysostaphin inhibitor	0.763	-	0.657	-	-	-	0.554
Manganese peroxidase inhibitor	-	-	0.529	-	-	-	-
Meprin B inhibitor	-	-	0.502	-	-	-	-
Methanol dehydrogenase inhibitor	-	-	0.562	-	-	-	-
4-Metho-xybenzoate monooxygenase (O-demethylating) inhibitor	-	-	-	-	-	-	0.521
Monodehydroascorbate reductase (NADH) inhibitor	-	-	0.561	0.585	-	-	-

Continuation of Table 2

1	2	3	4	5	6	7	8
Mucomembranous protector	-	-	0.64	-	-	-	0.598
Naphthalene 1,2-dioxygenase inhibitor	0.756	-	0.653	-	0.716	0.606	0.553
N-benzyloxycarbonylglycine hydrolase inhibitor	0.83	0.81	0.725	0.747	-	0.697	0.683
N-carbamoyl-L-amino-acid hydrolase inhibitor	0.78	0.746	0.679	0.636	0.724	0.591	0.636
Nicotine dehydrogenase inhibitor	0.729	-	0.654	0.586	-	0.559	0.551
Nicotinic alpha-6beta-3beta-4-alpha-5- receptor antagonist	-	-	0.581	-	-	-	-
Nicotinic alpha4beta4 receptor agonist	-	-	-	-	-	-	0.558
Nitrate reductase (cytochrome) inhibitor	0.781	0.804	0.663	0.797	0.72	0.809	0.696
P-benzoquinone reductase (NADPH) inhibitor	-	-	0.534	-	-	-	-
Peptidyl-dipeptidase Dcp inhibitor	-	-	-	-	-	-	0.6
Phthalate 4,5-dioxygenase inhibitor	0.857	0.753	0.8	0.671	0.778	0.64	0.671
Peroxidase inhibitor	-	-	-	-	-	-	0.584
Polyneuridine-aldehyde esterase inhibitor	0.71	-	0.575	0.559	-	-	0.559
Procollagen N-endopeptidase inhibitor	-	-	-	-	-	0.52	-
Pseudolysin inhibitor	0.725	-	0.637	0.604	-	0.573	0.689
Pullulanase inhibitor	0.797	0.722	0.626	0.756	-	0.786	-
Rhamnulose-1-phosphate aldolase inhibitor	0.79	-	0.647	0.671	0.716	0.709	-
Salicylate 1-monooxygenase inhibitor	-	-	0.546	-	-	-	-
Snapalysin inhibitor	-	-	-	-	-	-	0.532
Sulfur reductase inhibitor	-	0.711	0.6	0.72	-	0.733	0.632
Superoxide dismutase inhibitor	0.753	0.754	0.655	0.738	0.76	0.762	0.579
Quercetin 2,3-dioxygenase inhibitor	-	-	-	-	-	-	0.494
Thioredoxin inhibitor	0.778	0.753	0.695	0.786	0.862	0.761	0.664
tRNA-pseudouridine synthase I inhibitor	0.759	-	0.654	0.558	0.722	-	0.558
Tryptophanamidase inhibitor	0.763	0.728	0.621	-	-		0.549
Urethanase inhibitor	-	-	0.522	0.607	-	0.64	0.586
Venom exonuclease inhibitor	-	-	0.515	-	-	-	0.492
X-methyl-His dipeptidase inhibitor	-	-	-	-	-	-	0.574

For a number of S-alkyl esters of 8-quinoline thiosulfonic acid there is a general pattern of decreasing activity with increasing length of the alkyl chain. Accordingly, the leader among them is the S-methyl ester of 8-quinolinethiosulfonic acids. For all esters inhibitory activity against Thioredoxin, Superoxide dismutase, Phthalate 4,5-dioxygenase, Nitrate reductase (cytochrome), N-carbamoyl-L-amino-acid hydrolase, Leucolysin, IgA-specific metalloendopeptidase, Glycosylphosphatipidipididinase Fragilysin, Carboxypeptidase Taq, Dehydro-L-gulonate decarboxylase, Arylacetonitrilase, Arylalkyl acylamidase, (R) -6-hydroxynicotine oxidase, (S) -6-hydroxynicotine oxidase.

Table 3

The predicted effect of the biological action of S-alkyl esters of 8-hydroxyquinoline thiosulfonic acid *25 a-c* according to PASS program

Activity	Number of the compound		
	-CH_3	**-C_2H_5**	**-C_3H_5**
(R)-6-hydroxynicotine oxidase inhibitor	0.742	-	0.637
(S)-3-hydroxyacid ester dehydrogenase inhibitor	0.817	0.754	0.729
(S)-6-hydroxynicotine oxidase inhibitor	0.746	-	0.622
2-Hydroxyquinoline 8-monooxygenase inhibitor	0.722	-	0.655
2,4-Dichlorophenol 6-monooxygenase inhibitor	-	-	0.513
Alkane 1-monooxygenase inhibitor	0.817	0.811	0.787
Antiseborrheic	0.765	0.851	0.704
Antifungal	-	-	0.529
Apoptosis agonist	-	-	0.595
Arylacetonitrilase inhibitor	0.883	0.916	0.839
Aspulvinone dimethylallyltransferase inhibitor	0.712	-	0.644
Carboxypeptidase Taq inhibitor	-	-	0.632
Cis-1,2-dihydro-1,2-dihydroxynaphthalene dehydrogenase inhibitor	0.765	-	0.633
Corticosteroid side-chain-isomerase inhibitor	0.792	0.72	0.675
Cysteamine dioxygenase inhibitor	0.751	0.791	0.688
Dehydro-L-gulonate decarboxylase inhibitor	0.879	0.875	0.859
Gamma-guanidinobutyraldehyde dehydrogenase inhibitor	0.72	0.714	0.67
Glucose oxidase inhibitor	0.731	-	-
Glutathione thiolesterase inhibitor	0.856	0.85	0.831
Glyceryl-ether monooxygenase inhibitor	0.887	0.884	0.865
Glycosylphosphatidylinositol phospholipase D inhibitor	0.804	0.721	0.687
Guanidinoacetase inhibitor	0.775	0.745	0.708
Histidinol-phosphatase inhibitor	0.776	0.746	0.709
Hydroxylamine oxidase inhibitor	0.767	0.755	0.729
IgA-specific metalloendopeptidase inhibitor	-	-	0.565
Indanol dehydrogenase inhibitor	-	-	0.605
Methylaspartate ammonia-lyase inhibitor	-	-	0.553
4-Methoxybenzoate monooxygenase (O-demethylating) inhibitor	-	-	0.67

Continuation of Table 3

Activity	Number of the compound		
	-CH_3	**-C_2H_5**	**-C_3H_5**
Monodehydroascorbate reductase (NADH) inhibitor	0.825	0.892	0.822
Mucomembranous protector	-	-	-
N-carbamoyl-L-amino-acid hydrolase inhibitor	0.796	0.821	0.743
Nicotinic alpha4beta4 receptor agonist	-	-	-
Nicotine dehydrogenase inhibitor	0.79	0.75	0.726
Nitrate reductase (cytochrome) inhibitor	-	-	-
Nitrilase inhibitor	-	0.745	-
Nucleoside oxidase (H_2O_2-forming) inhibitor	-	-	0.533
Quercetin 2,3-dioxygenase inhibitor	-	0.774	-
P-benzoquinone reductase (NADPH) inhibitor	0.764	-	0.652
Phosphoglycerate mutase inhibitor	-		0.587
Phthalate 4,5-dioxygenase inhibitor	0.729	-	0.611
Rhamnulose-1-phosphate aldolase inhibitor	0.89	0.878	-
Platelet activating factor antagonist	-	-	0.511
Platelet aggregation inhibitor	-	-	0.682
Porphobilinogen synthase inhibitor	-	-	0.587
Quercetin 2,3-dioxygenase inhibitor	-	-	0.6
Rhamnulose-1-phosphate aldolase inhibitor	-	-	0.859
Steroid 9alpha-monooxygenase inhibitor	-	-	0.603
Sulfite reductase inhibitor	-	-	0.589
Sulfur reductase inhibitor	-	-	0.559
Thiol oxidase inhibitor	-	0.711	0.525
Thioredoxin inhibitor	-	0.729	0.643
TRPA1 agonist	-	-	-
UGT2B12 substrate	0.817	0.791	0.779
Venom exonuclease inhibitor	0.734	0.771	0.629

The leader among the S-alkyl esters of 8-hydroxyquinoline thiosulfonic acids is also the S-methyl ester of 8-hydroxyquinoline thiosulfonic acids. For all esters inhibitory activity against Venom exonuclease, N-carbamoyl-L-amino-acid hydrolase, Nicotine dehydrogenase, Monodehydroascorbate reductase (NADH), Glycosylphosphatidylinositol phospholipase D, Guanidinoacetase, Histidinol-phosphatase, Hydroxylamine oxidase, Glutathione thiolesterase, Glyceryl-ether monooxygenase, Gamma-guanidinobutyraldehyde dehydrogenase, Corticosteroid side-chain-isomerase, Cysteamine dioxygenase, Dehydro-L-gulonate decarboxylase, Arylacetonitrilase, (S)-3-hydroxyacid ester dehydrogenase, Alkane 1-monooxygenase, and UGT2B12 substrate, Antiseborrheic activities are also predicted.

For the methyl, ethyl and allyl esters of 8-quinoline thiosulfonic acids, experimental studies were conducted on their antibacterial and fungicidal activities on E. coli C-600, Candida albicans test cultures table 3.

Table 4

Sensitivity of test cultures to synthesized thiosulfonates *18 a-g*

Number of the compound	Test –culture	Time of the experiment, hour	Dilution and concentration of the drug						
			1:500 (2mg/ml)	1:1000 (1mg/ml)	1:2000 (0.5 mg/ml)	1:5000 (0.2 mg/ml)	1:10000 (0.1 mg/ml)	1:100000 (0.01 mg/ml)	1:1000000 (0.001 mg/ml)
	Escherihia coli	24	+	+	+	+	+	+	+
		48	+	+	+	+	+	+	+
		120	+	+	+	+	+	-	-
	Candida albicans	24	+	+	+	+	+	+	+
		48	+	+	+	+	+	+	+
		120	+	+	+	+	+	-	-
	Escherihia coli	24	+	+	+	+	+	+	+
		48	+	+	+	+	+	+	+
		120	+	+	+	+	+	-	-
	Candida albicans	24	+	+	+	+	+	+	+
		48	+	+	+	+	+	+	+
		120	+	+	+	+	+	+	-
	Escherihia coli	24	+	+	+	+	+	+	+
		48	+	+	+	+	+	+	-
		120	+	+	+	+	+	-	-
	Candida albicans	24	+	+	+	+	+	+	+
		48	+	+	+	+	+	+	-
		120	+	+	+	+	+	-	-
Quinzole	Escherihia coli	24	+	+	+	+	+	+	-
		48	+	+	+	+	+	-	-
		120	+	+	+	+	+	-	-
	Candida albicans	24	+	+	+	+	+	+	-
		48	+	+	+	+	+	-	-
		120	+	+	+	+	-	-	-
Nitroxolin	Escherihia coli	24	+	+	+	+	+	+	+
		48	+	+	+	+	+	+	+
		120	+	+	+	+	+	+	+
	Candida albicans	24	+	+	+	+	+	+	+
		48	+	+	+	+	+	+	+
		120	+	+	+	+	+	+	+

Note: + complete delay in the development of test cultures (fungicide); + partial delay in the development of test cultures (fungibacteristic; – no influence of the drug, active growth of test culture

3. Cytotoxicity

CLC-Pred (Cell Line Cytotoxicity Predictor) is a web-service for in silico prediction of cytotoxic effect of chemical compounds in non-transformed and cancer cell lines based on structural formula. CLC-Pred provides a prediction of the cytotoxicity of a chemical compound to assess the relevance of the substance's inclusion in experimental screening.

The cytotoxicity of the test compounds was tested for lung cancer, breast, skin, and blood cell lines.

Table 5

Predicted cytotoxicity of 4-amino-2-methylpyrimidin-5-yl-methyl esters of thiosulfonic acids *12 a-d*

Cell line	Full name of the cell line	The value of Pa for the corresponding compound			
		п-C_6H_5	п-ClC_6H_4	п-$NH_2C_6H_4$	п-$CH_3COONHC_6H_4$
SR	Adult immunoblastic lymphoma	0.806	0.791	0.792	0.621
HOP-92	Non-small cell lung carcinoma	0.687	0.702	0.656	-
NCI-H522	Non-small cell lung carcinoma	0.650	0.642	0.630	0.567
MOLT-4	Acute T-lymphoblastic leukemia	0.632	0.612	0.668	-
IGROV-1	Ovarian adenocarcinoma	0.565	0.530	0.533	-
T47D	Breast carcinoma	-	0.505	-	-

As a result of the analysis, the cytotoxicity of 4-amino-2-methylpyrimidin-5-yl-methyl thiosulfonic acid esters revealed that 4-amino-2-methyl-pyrimidin-5-yl-methyl ester of 4-chlorobenzenethiosulfonic acid exhibited the broadest protein activity. However, the highest values of activity indicators are 4-amino-2-methylpyrimidin-5-yl-methyl ester of 4-benzenethiosulfonic acid.

Table 6

The predicted cytotoxicity of S-alkyl esters of 8-quinoline thiosulfonic acid *18 a-g*

Cell line	Full name of the cell line	The value of the Pa for the corresponding compound						
		$-CH_3$	$-C_2H_5$	$-C_3H_5$	$-C_3H_7$	$-C_3H_7$ iso	$-C_4H_9$	$-C_4H_9$ iso
1	2	3	4	5	6	7	8	9
SR	Adult immunoblastic lymphoma	0.988	0.987	0.985	0.980	0.984	0.974	0.977
A549	Lung carcinoma	0.990	0.966	0.969	0.942	0.903	0.938	0.955
NCI-H522	Non-small cell lung carcinoma	0.954	0.951	0.943	0.909	0.918	0.901	0.912
HOP-92	Non-small cell lung carcinoma	0.937	0.936	0.925	0.892	0.896	0.886	0.932
SK-MEL-5	Melanoma	0.935	0.931	0.919	0.889	0.895	0.883	0.891
IGROV-1	Ovarian adenocarcinoma	0.868	0.869	0.839	0.817	0.741	0.830	0.859
MOLT-4	Acute T-lymphoblastic leukemia	0.836	0.847	0.850	0.730	0.800	0.713	0.830
UACC-257	Melanoma	0.809	0.828	0.803	0.709	0.693	0.701	0.705
HCC 2998	Colon adenocarcinoma	0.795	0.831	0.728	0.687	0.637	0.674	0.696
MCF7	Breast carcinoma	0.755	0.694	0.692	0.684	0.886	0.748	0.669
Malme-3M	Melanoma	0.737	0.766	0.738	0.731	0.668	0.687	0.690
786-0	Renal carcinoma	0.735	0.764	0.721	0.719	0.626	0.651	0.672
HL-60	Promyeloblast leukemia	0.512	-	-	-	-	-	-
T47D	Breast carcinoma	-	-	-	-	0.785	-	-
MDA-MB-231	Breast adenocarcinoma	-	-	-	-	0.604	-	-

When analyzing the results of the predicted cytotoxicity of S-alkyl esters of 8-quinoline thiosulphonic acid, it was found that only S-isopropyl ester of 8-quinoline thiosulphonic acids showed activity against the lines Breast carcinoma (T47D) and Breast adenocarcinoma 23 (MDA). However, the width of the spectrum of cytotoxic action and the value of predicted activity (Pa) is the leader of S-methyl ester of 8-quinoline thiosulfonic acids. In general, there is a decrease in Ra indices with increasing length of the hydrocarbon radical.

Table 7

The predicted cytotoxicity of S-alkyl esters of 8-hydroxyquinoline thiosulfonic acids *25 a-c*

Cell line	Full name of the cell line	The value of the Pa for the corresponding compound		
		$-CH_3$	**$-C_2H_5$**	**$-C_3H_5$**
SR	Adult immunoblastic lymphoma	0.978	0.976	0.971
A549	Lung carcinoma	0.978	0.937	0.945
NCI-H522	Non-small cell lung carcinoma	0.902	0.899	0.885
SK-MEL-5	Melanoma	0.886	0.885	0.874
HOP-92	Non-small cell lung carcinoma	0.880	0.883	0.867
MCF7	Breast carcinoma	0.823	0.780	0.776
MOLT-4	Acute T-lymphoblastic leukemia	0.787	0.810	0.815
IGROV-1	Ovarian adenocarcinoma	0.773	0.780	0.753
Malme-3M	Melanoma	0.680	0.706	0.685
UACC-257	Melanoma	0.665	0.699	0.669
786-0	Renal carcinoma	0.634	0.680	0.628
HCC 2998	Colon adenocarcinoma	0.627	0.687	0.589
HL-60	Promyeloblast leukemia	0.502	-	-

The spectrum of cytotoxic action and the predicted activity (Ra) of the leader is S-methyl ester of 8-hydroxyquinoline thiosulfonic acid, however, for some lines of colon cancer cells, kidneys, melanoma, ovaries, blood, lungs, S-ethylthioxy ester is more active than S-ethyloxy ester.

4. Acute rat toxicity prediction

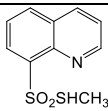
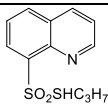
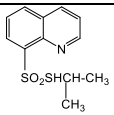
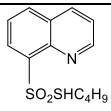
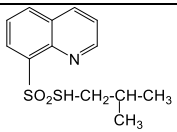
GUSAR software was developed to create QSAR/QSPR models on the basis of the appropriate training sets represented as SDfile contained data about chemical structures and endpoint in quantitative terms.

QSAR was used to model acute toxicity of rats based on a combination of QNA descriptors (Quantitative Neighborhood Atoms). This method allows the prediction of LD_{50} values for compounds by four types of administration (oral, intravenous, intraperitoneal, subcutaneous).

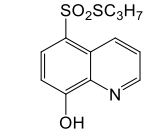
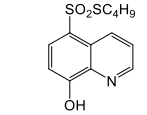
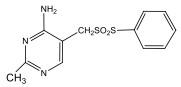
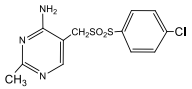
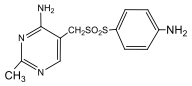
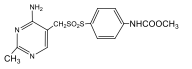
It is common practice to devide chemicals by toxicity into the following classes: extremely toxic, highly toxic, highly toxic, moderately toxic, low toxic, non-toxic.

Table 8

Predicted acute toxicity for rats relative to the type of administration and toxicity class of test esters *12 a-d, 18 a-g, 25 a-c*

Compound		Rat IP LD_{50} Log10	Rat IV LD_{50} log10	Rat Oral LD_{50} log10	Rat SC LD_{50} log10
1		**2**	**3**	**4**	**5**
	mmol/kg	-0.051	0.164	0.268	-0.027
	mg/kg	212.800	348.800	443.700	224.900
	Class	4	5	4	4
	mmol/kg	0.199	0.150	0.310	0.246
	mg/kg	400.300	357.900	517.200	445.900
	Class	4	5	4	4
	mmol/kg	0.261	0.174	0.319	0.198
	mg/kg	483.500	396.000	553.400	418.800
	Class	4	5	4	4
	mmol/kg	0.265	0.172	0.427	0.217
	mg/kg	492.400	397.200	713.900	440.800
	Class	4	5	4	4
	mmol/kg	0.302	0.189	0.399	0.143
	mg/kg	536.500	412.900	670.800	371.900
	Class	5	5	4	4
	mmol/kg	0.234	0.004	0.499	0.323
	mg/kg	482.500	284.300	887.400	591.700
	Class	4	4	4	4
	mmol/kg	0.278	0.044	0.253	0.197
	mg/kg	533.600	311.700	503.900	442.500
	Class	5	5	4	4

Continuation of Table 8

1		2	3	4	5
	mmol/kg	0.045	-0.087	0.180	0.505
	mg/kg	314.300	232.000	429.300	907.400
	Class	4	4	4	4
	mmol/kg	0.038	-0.198	0.405	0.488
	mg/kg	324.300	188.700	756.500	915.400
	Class	4	4	4	4
	mmol/kg	0.100	0.215	0.196	0.745
	mg/kg	372.000	485.100	463.600	1641.000
	Class	4	5	4	5
	mmol/kg	0.070	0.269	0.483	0.906
	mg/kg	387.600	613.200	1004.000	2659.000
	Class	4	5	4	Non Toxic
	mmol/kg	0.031	0.431	0.449	0.803
	mg/kg	333.400	837.300	873.400	1970.000
	Class	4	Non Toxic	4	5
	mmol/kg	-0.263	0.088	0.476	0.814
	mg/kg	201.100	451.600	1102.000	2399.000
	Class	4	5	4	5

Note: IP – Intraperitoneal route of administration; IV – Intravenous route of administration; Oral – Oral route of administration; SC – Subcutaneous route of administration

The results presented in Table 5 indicate that all tested compounds according to the classification of substances by toxicity, according to SOU 85.2–37–736: 2011, belong to the 4th and 5th toxicity classes, ie moderate and low toxic substances, depending on method of administration.

CONCLUSIONS

A new approach to the synthesis of promising nitrogen-containing heterocyclic thiosulphoesters is proposed. Methods of synthesis have been investigated and preparatively convenient methods of obtaining new thiosulfonic acid esters – quinoline, 8-hydroxyquinoline and pyrimidine derivatives have been established. This made it possible to purposely

synthesize thiosulphoesters in which the hetero- or carbocyclic moiety may be located on both thiol and sulfonyl sulfur sides.

The compounds obtained are both valuable reagents in organic synthesis and interesting objects for biological research. The carried out predictive screening of biological activity of the tested compounds accordingg to PASS program indicates the feasibility of conducting experimental studies of antiarrhythmic, antiviral, antiseborrheic, analeptic, anti-inflammatory and antitumor activities, as well as establishing the possibility of their use for the treatment of mucous membrane and inflammation. Given the low toxicity, these substances can be tested on biological sites to further use them as substances for veterinary drugs and medicines.

SUMMARY

The ways of obtaining pyrimidine thiosulfonic acid esters based on 5-bromomethyl-2-methylpyrimidin-4-amine and 2-amino-6-methylpyrimidin-4-ol have been investigated. It has been found that the preparation of thiosulphoesters by chlorosulfonation of basic structures followed by the preparation of the corresponding thiosulphonic acid salts and thiosulphoesters based on them is not suitable for the selected pyrimidines. Thiosulfoesters with a pyrimidine moiety were obtained from the thiol sulfur side by alkylation of 5-bromomethyl-2-methylpyrimidin-4-amine thiosulfonic acid salts.

For the synthesis of 8-quinolinesulfonic, 8-hydroxyquinolinesulfonic acid S-esters, quinoline and 8-quinolinesulfonic acid were selected as the starting material, which were converted to 8-quinolinesulfochloride, which was reduced to the sodium or potassium salts of 8-quinolinesulfonic acids. As a result of alkylation of halogen bromides or dialkyl sulfates in acetone-aqueous or alcohol media, the corresponding S-alkyl-8-quinoline thiosulfonates have been synthesized.

Some regularities of structure – activity dependence have been established, which can be used for directed synthesis of biologically active compounds. Among the synthesized thiosulphonates, substances that exhibit antiarrhythmic, antiviral, antiseborrheic, analeptic, anti-inflammatory and antitumor activity were identified using predictive screening, as well as the possibilities of their use for the treatment of mucous membrane, inflammation of the bowel and ankylosing spondylitis. All test substances

were found to be low toxic according to GUSAR data. The results presented indicate the feasibility of carrying out experimental studies of the biological activity of these substances in order to further use them as substances for veterinary drugs and medicines.

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