СИНТЕЗ ТА АНАЛІЗ БІОЛОГІЧНО АКТИВНИХ РЕЧОВИН

Recommended by Doctor of Pharmacy, professor O.A.Yevtifeyeva

УДК 547.732:547.853.3:66.095.112

SYNTHESIS AND THE ANTIMICROBIAL ACTIVITY OF 3,4-DIHYDROTHIENO[2,3-*d*]PYRIMIDINE-2,4-DIONE-1-ACETIC ACID AMIDES

O.V.Tkachenko, S.V.Vlasov, S.M.Kovalenko, I.O.Zhuravel', V.P.Chernykh

National University of Pharmacy

Key words: thiophene; pyrimidine; alkylation; amide; acetic acid

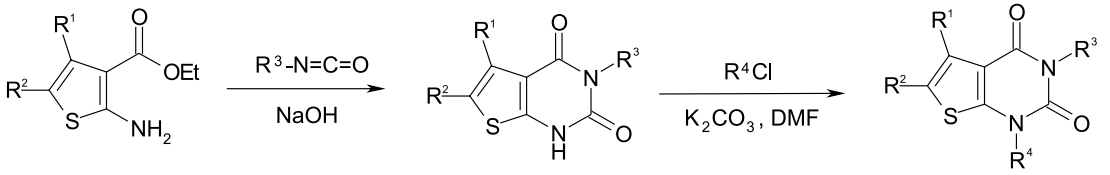
Alkylation of 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-diones, which has been carried out by their treatment with chloroacetamides in DMF with the presence of K_2CO_3 at 120-130°C, resulted in the previously unknown 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-dione-1-acetic acid amides. For all of 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-dione-1-acetic acid amides with the primary acetamide fragment ^{1}H NMR spectra contain the signals of NH in the range of 7.97-10.39 ppm. IR-spectra of all compounds obtained contain the intensive bands of stretching vibrations of v N-H (3288-3306 cm^{-1}) and the band of v C=O (1724-1655 cm^{-1}). The screening of the antimicrobial activity for 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-dione-1-acetic acid amides has been performed by the agar diffusion method. The antimicrobial activity has been estimated by the diameter of the growth inhibition zone for each microorganism. The results of the antimicrobial screening assay show that most of 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-dione-1-acetic acid amides with aliphatic substituents in position 5 and 6 do not display any antimicrobial activity, except for some compounds, which appeared to be active against the strains of Staphylococcus aureus and Bacillis subtilis. For the compounds with the electron-withdrawing acetyl group in position 6 the growth of the spectra and efficacy of the antimicrobial activity have been observed. However, even the activity of this group of compounds was considered to be moderate. The results of the antimicrobial activity investigation for the novel organic compounds – 3,4-dihydrothieno[2,3-d] pyrimidine-2,4-dione-1-acetic acid amides have shown that introduction of the electron-withdrawing acetyl group in position 6 of the heterocyclic system improves their antimicrobial activity.

Among the derivatives of 3,4-dihydrothieno[2,3-d] pyrimidine-2,4-diones substituted in positions 1 and 3 the compounds that are non-peptide antagonist for the human luteinizing hormone [11, 18] have been found. Some of them are proposed as antagonists of A_{2A} adenosine receptors [4], which may be useful to treat the central nervous system disorders, Alzheimer's disease, and drug abuse. Many of those compounds contain aromatic substituents in position 3 [18] and an alkyl or benzyl radical in position 1 [4]. There are some works where the authors presented the biological activity studies for 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-diones modified in position 1 [5, 13, 15] or 3 [6, 8] with the residues of acetic acid or its esters; aldose reductase inhibitors that may be used to treat diabetic complications, namely retinopathy, neuropathy, and cataract [5, 13] are among them. Derivatives of 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-dion-1-acetic acid are also known as endothelin receptor antagonists, which are useful to treat heart insufficiency, myocardial infraction, heart failure, pulmonary hypertension, etc. However, any information about the synthesis of 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-diones with the acetamide fragment in position 1, as well as about the study of their biological activity has not been published.

That is why an important part of our work is devoted to the synthesis and the study of the pharmacological activity of 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-dione-1-acetic acid amides. The synthesis of the starting 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-diones has been performed according to the known procedure based on interaction of 2-aminothiophene-3-carboxylates with isocyanates in pyridine. The unsymmetrical urea formed at the first step was cyclized by the action of alkali in water, water-ethanol solution or ethanol [7, 14, 16, 19] (Scheme).

Alkylation of compounds **2** has been carried out by their treatment with 1,1 equivalent of the alkylating agent in DMF in the presence of K_2CO_3 at 120-130°C and intensive stirring. The data concerning compounds **3** obtained is presented in Table 1.

All compounds **3** are white crystalline solids. For all compounds **3** with the primary acetamide fragment ^{1}H NMR spectra contain the signals of NH in the range

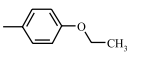
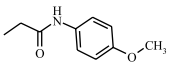
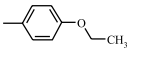
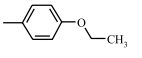
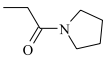
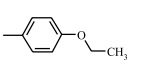
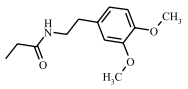
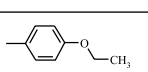
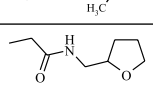
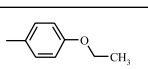
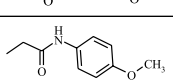
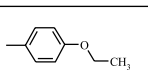
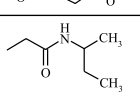
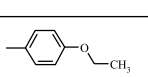
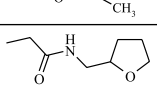
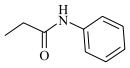
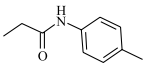
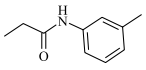
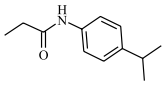
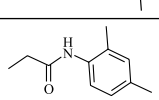
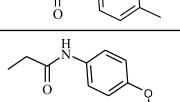
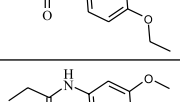
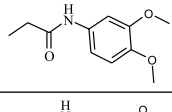


1 **2** **3**

Scheme

Table 1

Physical and chemical proprieties of 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-dione-1-acetic acid 3 amides

Compd.	R^1	R^2	R^3	R^4	Mol. formula M.w.	N, % calc. found	M.p., °C	Yield % *
3a	CH_3	CH_3			$C_{25}H_{25}N_3O_5S$ 479.56	8.76 / 8.77	>300	75
3b	$(CH_2)_3$				$C_{19}H_{19}N_3O_4S$ 385,44	10.90 / 10.91	>300	62
3c	$(CH_2)_3$				$C_{23}H_{25}N_3O_4S$ 439.54	9.56 / 9.57	207-209	68
3d	$(CH_2)_3$				$C_{29}H_{31}N_3O_6S$ 549.65	7.64 / 7.66	215-217	93
3e	$(CH_2)_3$				$C_{24}H_{27}N_3O_5S$ 469.56	8.95 / 8.96	251-252	71
3f	$(CH_2)_3$				$C_{26}H_{25}N_3O_5S$ 491.57	8.55 / 8.55	>300	86
3g	$(CH_2)_4$				$C_{24}H_{29}N_3O_4S$ 455.58	9.22 / 9.23	295-297	61
3h	$(CH_2)_4$				$C_{25}H_{29}N_3O_5S$ 483.59	8.69 / 8.70	263-265	74
3i	CH_3	CH_3CO			$C_{23}H_{19}N_3O_4S$ 433.49	9.69 / 9.73	>300	93
3j	CH_3	CH_3CO			$C_{24}H_{21}N_3O_4S$ 447.52	9.39 / 9.46	>300	84
3k	CH_3	CH_3CO			$C_{24}H_{21}N_3O_4S$ 447.52	9.39 / 9.47	>300	81
3l	CH_3	CH_3CO			$C_{26}H_{25}N_3O_4S$ 475.57	8.84 / 8.92	>300	87
3m	CH_3	CH_3CO			$C_{25}H_{23}N_3O_4S$ 461.54	9.10 / 9.14	>300	90
3n	CH_3	CH_3CO			$C_{25}H_{23}N_3O_5S$ 477.54	8.80 / 8.90	>300	94
3o	CH_3	CH_3CO			$C_{25}H_{23}N_3O_6S$ 493.54	8.51 / 8.53	289-291	83
3p	CH_3	CH_3CO			$C_{25}H_{23}N_3O_6S$ 493.54	8.51 / 8.52	297-299	76

* The yield is given for the alkylation step.

Table 2

Data of ^{1}H NMR spectra for 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-dione-1-acetic acid 3 amides

Compd.	Chemical shift, δ, ppm.		
	NH	Aliphatic protons	Aromatic protons
3a	10.20 (1H, t., NH)	2.24 (6H, d., $2CH_3$); 4.10 (2H, m., OCH_2CH_3); 1.30 (3H, t., OCH_2CH_3); 4.70 (2H, c., NCH_2CO); 3.72 (3H, s., OCH_3)	6.87 (2H, d., acetamide 3″H+5″H); 6.96 (2H, d., 3H+5H); 7,10 (2H, d., 2H+6H); 7.47 (2H, d., acetamide 3″H+5″H)
3b	7.26 + 7.64 (2H, s.+s., NH_2)	4.10 (2H, q., OCH_2CH_3); 1.30 (3H, t., OCH_2CH_3); 2.82 (4H, m., 1´+3´CH_2); 2.32 (2H, m., 2´CH_2); 4.48 (2H, s., NCH_2CO)	6.97+7.10 (4H, d.+d., Ar-H)
3c	-	4.0 (2H, q., OCH_2CH_3); 1.4 (3H, t., OCH_2CH_3); 2.8 (4H, m., 1´+3´CH_2); 2.4 (2H, m., 2´CH_2); 4,6 (2H, s., NCH_2CO); 3.6+3.3 (4H, t.+t., 2´+5´CH_2pyrrolidin-1-yl); 1.7-1.9 (4H, m., 3´+4´CH_2pyrrolidin-1-yl)	6.97+7.10 (4H, d.+d., Ar-H)
3d	8.3 (1H, t., NH)	4.1 (2H, q., OCH_2CH_3); 1.4 (3H, t., OCH_2CH_3); 2.8 (4H, m., 1´+3´CH_2); 2.4 (2H, m., 2´CH_2);4.45 (2H, s., NCH_2CO); 3.7 (6H, s., $2OCH_3$); 2.32 (2H, t., NCH_2CH_2 Ar); 3.29 (2H, q., NCH_2CH_2 Ar)	6.64-6.86 (3H, m., acetamide Ar-H)+6.96+7.10 (4H, d.+d., Ar-H)
3e	8.3 (1H, t., NH)	3.6-3.8 (2H, m., $NHCH_2$ tetrahydrofuran); 3.6-3.8 (1H, m., CH tetrahydrofuran); 3.1 (2H, m., 5′CH_2 tetrahydrofuran); 1.2+1.9 (4H, m., 3′CH_2+4′CH_2 tetrahydrofuran); 4.1 (2H, q., OCH_2CH_3); 1.4 (3H, t., OCH_2CH_3); 2.8 (4H, m., 1´+3´CH_2); 2.4 (2H, m., 2´CH_2); 4.5 (2H, s., NCH_2CO)	6.97+7.10 (4H, d.+d., Ar-H)
3f	10.2 (1H, t., NH)	4.0 (2H, q., OCH_2CH_3); 1.3 (3H, t., OCH_2CH_3); 2.8 (4H, m., 1´+3´CH_2); 2.4 (2H, m., 2´CH_2); 4.7 (2H, s., NCH_2CO); 3.7 (3H, s., OCH_3)	6.88 (2H, d., acetamide 3″H+5″H); 6.96 (2H, d., 3H+5H); 7.10 (2H, d., 2H+6H); .45 (2H, d., acetamide 3″H+5″H)
3g	7.97 (1H, d., NH)	4.05 (2H, q., OCH_2CH_3); 1.3 (3H, m., OCH_2CH_3); 0.79 (3H, t., $CH_3CHCH_2CH_3$); 1.02 (3H, d., $CH_3CHCH_2CH_3$); 1.25 (2H, m., $CH_3CHCH_2CH_3$); 3.69 (1H, m., $CH_3CHCH_2CH_3$); 1.62 (4H, m., 6+7 CH_2); 2.69 (4H, m., 5+8 CH_2); 4.48 (2H, s., NCH_2CO)	6.9-7.15 (4H, d.+d., Ar-H)
3h	8.29 (1H, d., NH)	4.07 (2H, q., OCH_2CH_3); 1.33 (3H, m., OCH_2CH_3); 3.5-3.85 (3H, m., CH-O-CH_2); 3.15 (2H, m.,Het-CH_2-NH); 1.4-1.9 (2H, m., $2CH_2$); 1.62 (4H, m., 6+7 CH_2); 2.69 (4H, m., 5+8 CH_2); 4.49 (2H, s., NCH_2CO)	6.9-7.15 (4H, d.+d., Ar-H)
3i	10.39 (1H, s., NH)	2.56 (3H, s., thienyl-CH_3); 2.78 (3H, s., thienyl-$COCH_3$); 4.82 (2H, s., NCH_2CO)	6.9-7.6 (10H, m., Ar-H)
3j	10.31 (1H, s., NH)	2.19 (3H, s., $PhCH_3$); 2.56 (3H, s., thienyl-CH_3); 2.81 (3H, s., thienyl-$COCH_3$); 4.79 (2H, s., NCH_2CO)	6.9-7.6 (9H, m., Ar-H)
3k	10.29 (1H, s., NH)	2.21 (3H, s., $PhCH_3$); 2.56 (3H, s., thienyl-CH_3); 2.81 (3H, s., thienyl-$COCH_3$); 4.79 (2H, s., NCH_2CO)	6.8-7.55 (9H, m., Ar-H)
3l	10.31 (1H, s., NH)	1.12 (6H, d., $PhCH(CH_3)_2$); 2.56 (3H, s., thienyl-CH_3); 2.81 (3H, s., thienyl-$COCH_3$); 4.79 (2H, s., NCH_2CO)	7.0-7.6 (9H, m., Ar-H)
3m	9.69 (1H, s., NH)	2.07 +2.15 (6H, c+c., $Ph(CH_3)_2$); 2.56 (3H, s., thienyl-CH_3); 2.78 (3H, s., thienyl-$COCH_3$); 4.82 (2H, s., NCH_2CO)	6.9-7.6 (8H, m., Ar-H)
3n	10.22 (1H, s., NH)	3.92 (2H, q., OCH_2CH_3); 1.26 (3H, t., OCH_2CH_3); 2.56 (3H, s., thienyl-CH_3); 2.81 (3H, s., thienyl-$COCH_3$); 4.82 (2H, s., NCH_2CO)	6.9-7.6 (9H, m., Ar-H)
3o	10.28 (1H, s., NH)	3.72 (6H, c., $Ph(OCH_3)_2$); 2.56 (3H, s., thienyl-CH_3); 2.79 (3H, s., thienyl-$COCH_3$); 4.78 (2H, s., NCH_2CO)	6.8-7.55 (8H, m., Ar-H)
3p	10.39 (1H, s., NH)	3.67 (6H, c., $Ph(OCH_3)_2$); 2.56 (3H, s., thienyl-CH_3); 2.81 (3H, s., thienyl-$COCH_3$); 4.79 (2H, s., NCH_2CO)	6.21 (1H, t., 4″-H); 6.76 (2H, d., 3″+5″-H); 7.20-7.55 (5H, m., Ar-H)

of 7.97-10.39 ppm. For compound **3a** the signals of two methyl-substituents in positions 5 and 6 are observed near 2.24 ppm.; the spectra of the compounds with the fused five-membered ring (**3b-3f)** show the signals of this fragment as 2.8 ppm. (4H, m., 1´+3´CH_2) and 2.4 ppm (2H, m., 2´CH_2); the signals of the aliphatic six-membered ring (**3g-3h**) are presented by two groups at 1.62 (4H, m., CH_2) and 2.69 (4H, m., CH_2); the compounds with the acetyl group in position 6 (**3i-3p**) show the signal of it at 2.78-2.81 ppm. The signal of acetamide CH_2 fragment is present in the range of 4.45-4.82 ppm.

IR-spectra of all of compounds **3** contain the intensive bands of stretching vibrations of ν N-H (3288-3306 cm^{-1}) and the band of ν C=O (1724-1655 cm^{-1}).

The screening of the antimicrobial activity for compounds **3** has been performed by the agar diffusion me-

Table 3

Data of IR-spectra for 3,4-dihydrothieno[2,3-d] pyrimidine-2,4-dione-1-acetic acid 3 amides

Compd.	Wavenumber, ν, cm^{-1}			
	ν N-H	ν C-H	ν C=O	ν C=N ν C=C
3a	3294	3139 3067 2970 2934 2838	1713 1665	1609 1575 1541 1513 1471 1414
3b	3427 3323 3206	3067 2973 2940 2917 2864	1713 1687 1655	1611 1591 1565 1533 1515 1477
3c	3358	3067 3051 2964 2932 2882 2861	1712 1655	1607 1565 1532 1512 1484
3d	3316	3083 2982 2960 2926 2872 2858	1718 1668	1608 1591 1559 1537 1520 1476
3e	3298	3029 2967 2941 2864	1710 1657	1610 1591 1562 1531 1514
3f	3265	3138 3067 3004 2969 2934 2857	1713 1658	1610 1566 1535 1510 1481 1406
3g	3296	3090 2973 2936 2880 2834	1714 1663	1611 1594 1573 1543 1518 1469
3h	3306	3078 2978 2935 2871	1710 1663	1610 1592 1543 1515 1473
3i	3296	3142 3059	1720 1675	1600 1545 1498 1468 1420 1361
3j	3295	3130 3059 2990 2937	1720 1680	1636 1600 1543 1499 1469 1420
3k	3292	3058 2835	1722 1672	1637 1594 1547 1499 1420 1368
3l	3310	3123 3058 2964 2871	1724 1671	1598 1539 1500 1416 1362 1334
3m	3288	3059	1720 1669	1636 1595 1538 1499 1470 1417
3n	3293	3139 3061 2980 2939	1721 1671	1546 1508 1418 1367 1334
3o	3296	3142 3068 2993 2937 2836	1723 1671	1634 154 1500 1468 1419 1366
3p	3306	3065 2996 2942 2907 2837	1720 1672	1635 1605 1544 1499 1468 1432

thod. The antimicrobial effect was measured by the diameter of the growth inhibition zone based on the known data about active antibiotics researched by the diffusion method against susceptible microorganism strains [1-3].

Table 4

Antimicrobial properties of 3,4-dihydrothieno [2,3-d]pyrimidine-2,4-dione-1-acetic acid 3 amides in the concentration of 100 μg per mL*

Compd.	Staphylococcus aureus ATCC 25923	Escherichia coli ATCC 25922	Pseudomonas aeruginosa ATCC 27853	Proteus vulgaris ATCC 4636	Bacillis subtilis ATCC 6633	Candida albicans ATCC 653/885
3a	–	–	–	–	–	–
3b	–	–	–	–	–	–
3c	–	–	–	–	–	–
3d	–	–	–	–	–	–
3e	–	–	–	–	–	–
3f	++	–	–	–	++	–
3g	++	–	–	–	++	–
3h	++	–	–	–	++	–
3i	++	++	++	++	++	++
3j	++	+	+	++	++	+
3k	++	+	+	++	++	++
3l	++	+	+	++	++	++
3m	++	++	++	++	++	++
3n	++	++	++	++	++	++
3o	++	+	++	++	++	+
3p	++	++	++	++	++	++

* – diameter of the growth inhibition zone less than 10 mm;
+ – diameter of the growth inhibition zone of 10-15 mm;
++ – diameter of the growth inhibition zone of 15-25 mm;
+++ – diameter of the growth inhibition zone more than 25 mm.

The results of the antimicrobial screening assay show that most of compounds **3** with aliphatic substituents in position 5 and 6 do not display any antimicrobial activity, except of compounds **3f-3h**, which appeared to be active against the strains of *Staphylococcus aureus* and *Bacillis subtilis*. For compounds **3i-3p** with the electron-withdrawing acetyl group (CH_3CO–) in position 6 the growth of the spectra and efficacy of the antimicrobial activity have been observed. However, even the activity of this group of compounds is considered to be moderate.

Experimental Part

Chemical research

The melting points (°C) were measured with the Koeffler melting point apparatus and were not corrected. IR spectra were recorded on the Bruker Tensor 27 spectrometer in KBr. ^{1}H NMR spectra were recorded on the Bruker DRX-500 (500 MHz) and Varian Mercury – 200 (200 MHz) spectrometers in DMSO-d_6 using TMS as an internal standard (chemical shifts are in ppm).

Ethyl 2-aminothiophene-3-carboxylates 1 were obtained by Gewald reaction [9, 10, 12, 17].

General method for synthesis of compounds 3.

To the suspension of 0.065 mole of ethyl 2-aminothiophene-3-carboxylate **1**, in 50 ml of pyridine add

0.065 mole of isocyanate and stir the mixture at 50-80°C for 3-5 hours. After cooling the reaction mixture to the room temperature dilute it with water, filter and dry the precipitate of urea. Add the urea obtained (0.055 mole) into 150 ml of alkaline solution (0.165 mole) in ethanol or water and stir the mixture at 50-100°C for 5-8 hours after dissolution of the precipitate. Then to the solution of 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-dione **2** add concentrated acetic acid (0.165 mole) and filter the precipitate formed, wash with plenty of water and dry. Compounds **2** were used for further transformations without additional purification. To 0.9 mmole of compound **2** in DMF add 1 mmole of K_2CO_3 and 1 mmole of an alkylating agent. Heat the reaction mixture at 120-130°C for 2-3 hours. After cooling dilute the mixture with water, filter product **3** and recrystallize it from 2-propanol.

The antimicrobial activity study

According to the WHO recommendations [2, 3] to test the activity of the compounds under research such test-strains as *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Proteus vulgaris* ATCC 4636, *Bacillis subtilis* ATCC 6633, *Candida albicans* ATCC653/885 were used. The bacterial concentration was 10^7 CFU/mL (determined by McFarland standard). Overnight cultures kept for 18-24 h at 36ºC±1ºC were used. The bacterial suspension was inoculated onto the entire surface of the Mueller-Hinton agar (Dagestan Research Institute of Nutrient Media). The compounds were introduced to the wells in the form of DMSO solution in the concentration of 100 μg/mL; the open wells were filled with 0.3 mL of the solution.

CONCLUSIONS

By alkylation of 3-aryl-3,4-dihydrothieno[2,3-d]pyrimidine-2,4-diones the novel amides of 3,4-dihydrothieno[2,3-d]pyrimidine-2,4-dione-1-acetic acid have been obtained; the study of their antimicrobial activity by the agar diffusion method has shown the growth of the spectra and efficacy of the antimicrobial activity for the compounds with the electron-withdrawing acetyl group (CH_3CO–) in position 6 comparing to the compounds substituted in position 5 and 6 with saturated aliphatic radicals.

REFERENCES

1. *Бактеріологічний контроль поживних середовищ. Інформаційний лист МОЗ України №05.4.1/1670. – К., 2001.*
2. *Волянський Ю.Л., Грищенко І.С., Широбоков В.П. та ін. Вивчення специфічної активності антимікробних лікарських засобів: Метод. рекоменд. – К., 2004. – 38 с.*
3. *Некрасова Л.С., Свита В.М., Глушкевич Т.Г. та ін. Визначення чутливості мікроорганізмів до антибактеріальних препаратів: Метод. рекоменд. – К., 2007. – 79 с.*
4. *Пат. US 2007208040 (2007). Заявл.: 02.03.2007. Опубл.: 06.09.2007. Режим доступу: http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=2007208040A1&KC=A1&FT=D&ND=3&date=20070906&DB=EPODOC&locale=en_EP*
5. *Пат. US 4898867 (1990). Заявл.: 16.09.1988. Опубл.: 06.02.1990. Режим доступу: http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=4898867A&KC=A&FT=D&ND=3&date=19900206&DB=EPODOC&locale=en_EP*
6. *Пат. US 6140325 (2000). Заявл.: 30.09.1996. Опубл.: 31.10.2000. Режим доступу: http://worldwide.espacenet.com/publicationDetails/originalDocument?CC=US&NR=6140325A&KC=A&FT=D&ND=3&date=20001031&DB=EPODOC&locale=en_EP*
7. *Briel D., Rybak A., Kronbach C., Unverferth K. // Eur. J. Med. Chem. – 2010. — Vol. 45, №1. – P. 69-77.*
8. *Cho N., Nara Y., Harada M. et al. // Chem. Pharm. Bull. – 1998. – Vol. 46, №11. – P. 1724-1737.*
9. *Gewald K., Schinke E., Boettcher H. // Chem. Ber. – 1966. – Vol. 99. – P. 94-100.*
10. *Ivashchenko A.V., Kovalenko S.M., Tkachenko O.V., Parkhomenko O.O. // J. Comb. Chem. – 2004. – Vol. 6, №4. – P. 573-583.*
11. *Kazuhiro M., Takenori H., Takashi I. et al. // J. Med. Chem. – 2011. – Vol. 54. – P. 4998-5012.*
12. *Kovalenko S.N., Vlasov S.V., Fedosov A.I., Chernykh V.P. // J. of Org. and Pharmac. Chem. – 2007. – Vol. 5, №3. – P. 34-40.*
13. *Ogawva K., Yamawaki I., Matsusital Y.I. et al. // Eur. J. Med. Chem. – 1993. – Vol. 28. – P. 769-781.*
14. *Pathak U.S., Gandhi N.V., Singh S. et al. // Ind. J. Chem. – 1992. – Vol. 31B. – P. 223-229.*
15. *Romeo G., Russo F., Caruso A. et al. // Arzneimit. Forsch. – 1998. – Vol. 48, №2. – P. 167-172.*
16. *Russo F., Romeo G., Santagati N.A. et al. // Eur. J. Med. Chem. – 1994. – Vol. 29, №3. – P. 569-578.*
17. *Sabnis R.W., Rangnekar D.W., Sonawane N.D. // J. Heterocycl. Chem. – 1999. – Vol. 36, №2. – P. 333-345.*

18. Sasaki S., Cho N., Nara Y. et al. // J. Med. Chem. – 2003. – Vol. 46. – P. 113-124.
19. Sauter F. // Monatshefte fuer Chemie. – 1970. – Vol. 101. – P. 535-543.

СИНТЕЗ ТА АНТИМІКРОБНА АКТИВНІСТЬ АМІДІВ 3,4-ДИГІДРОТІЄНО[2,3-*d*]ПІРИМІДИН-2,4-ДІОН-1-ОЦТОВОЇ КИСЛОТИ

О.В.Ткаченко, С.В.Власов, С.М.Коваленко, І.О.Журавель, В.П.Черних

Ключові слова: *тіофен; піримідин; алкілування; амід; оцтова кислота*

Алкілуванням 3,4-дигідротієно[2,3-d]піримідин-2,4-діонів хлорацетамідами у середовищі ДМФА в присутності K_2CO_3 при температурі 120-130°С були отримані не описані раніше аміди 3,4-дигідротієно[2,3-d]піримідин-2,4-діон-1-оцтової кислоти. У спектрах ^{1}Н ЯМР всіх первинних амідів 3,4-дигідротієно[2,3-d]піримідин-2,4-діон-1-оцтової кислоти спостерігається сигнал протону групи NH в діапазоні 7,97-10,39 м.ч. ІЧ-спектри отриманих сполук містять інтенсивні смуги валентних коливань ν N-H (3288-3306 см$^{-1}$), також у спектрах проявляється смуга ν C=O (1724-1655 см$^{-1}$). Скринінг антимікробної активності амідів 3,4-дигідротієно[2,3-d] піримідин-2,4-діон-1-оцтової кислоти проводили методом дифузії в агар («метод колодязів»). Антибактеріальну активність оцінювали шляхом вимірювання зон затримки росту відповідного мікроорганізму. Результати скринінгу антимікробної активності вказують на те, що більшість тестованих амідів 3,4-дигідротієно[2,3-d]піримідин-2,4-діон-1-оцтової кислоти із аліфатичними замісниками у положеннях 5 та 6 не проявили антимікробної активності. Лише окремі з них виявили помірну активність по відношенню до штамів Staphylococcus aureus та Bacillus subtilis. Проте для сполук, які містили ацетильну групу в положенні 6, спостерігали розширення спектра та підвищення сили антимікробної активності, хоча активність цих сполук по відношенню до більшості штамів мікроорганізмів можна розцінювати як помірну. Результати дослідження антимікробної активності нових органічних сполук – амідів 3,4-дигідротієно[2,3-d]піримідин-2,4-діон-1-оцтової кислоти показали, що введення в положення 6 гетероциклічної системи електроноакцепторної ацетильної групи покращує їх антимікробну активність.

СИНТЕЗ И АНТИМИКРОБНАЯ АКТИВНОСТЬ АМИДОВ 3,4-ДИГИДРОТИЕНО[2,3-*d*] ПИРИМИДИН-2,4-ДИОН-1-УКСУСНОЙ КИСЛОТЫ

Е.В.Ткаченко, С.В.Власов, С.Н.Коваленко, И.А.Журавель, В.П.Черных

Ключевые слова: *тиофен; пиримидин; алкилирование; амид; уксусная кислота*

Алкилированием 3,4-дигидротиено[2,3-d]пиримидин-2,4-дионов хлорацетамидами в среде ДМФА в присутствии K_2CO_3 при температуре 120-130°С были получены не описанные ранее амиды 3,4-дигидротиено[2,3-d]пиримидин-2,4-дион-1-уксусной кислоты. В спектрах ^{1}Н ЯМР всех первичных амидов 3,4-дигидротиено[2,3-d]пиримидин-2,4-дион-1-уксусной кислоты наблюдается сигнал протона группы NH в диапазоне 7,97-10,39 м.д. ИК-спектры полученных соединений содержат интенсивные полосы валентных колебаний ν N-H (3288-3306 см$^{-1}$), также в спектрах проявляется полоса ν C=O (1724-1655 см$^{-1}$). Скрининг противомикробной активности амидов 3,4-дигидротиено[2,3-d]пиримидин-2,4-дион-1-уксусной кислоты проводили методом диффузии в агар («метод колодцев»). Антибактериальную активность оценивали путем измерения зон задержки роста соответствующего микроорганизма. Результаты скрининга противомикробной активности указывают на то, что большинство тестированных амидов 3,4-дигидротиено[2,3-d]пиримидин-2,4-дион-1-уксусной кислоты с алифатическими заместителями в положениях 5 и 6 не проявили противомикробной активности. Только отдельные из них проявили умеренную активность по отношению к штаммам Staphylococcus aureus и Bacillis subtilis. Однако для соединений, которые содержали ацетильную группу в положении 6, наблюдали расширение спектра и повышение силы противомикробной активности, хотя активность этих соединений по отношению к большинству штаммов микроорганизмов можно расценивать как умеренную. Результаты исследования антимикробной активности новых органических соединений – амидов 3,4-дигидротиено[2,3-d]пиримидин-2,4-дион-1-уксусной кислоты показали, что введение в положение 6 гетероциклической системы электроноакцепторной ацетильной группы улучшает их антимикробную активность.

Acknowledgement
The authors are grateful to acknowledge Tatyana P. Osolodchenko, the Head of Microorganisms and Media Biochemistry Laboratory of Research Institute of Microbiology and Immunology named after I.I.Mechnikov at the NAMS of Ukraine for the microbiological experiment.