СИНТЕЗ ТА АНАЛІЗ БІОЛОГІЧНО АКТИВНИХ РЕЧОВИН

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SYNTHESIS AND THE ANTIMICROBIAL ACTIVITY OF ETHYL 3-ALKYL-2-(ALKYLTHIO)-5-METHYL-4-OXO-3,4-DIHYDROTHIENO[2,3-*d*]PYRIMIDINE-6-CARBOXYLATE DERIVATIVES

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Key words: thiophene; pyrimidine; mercaptans; alkylation; cyclization

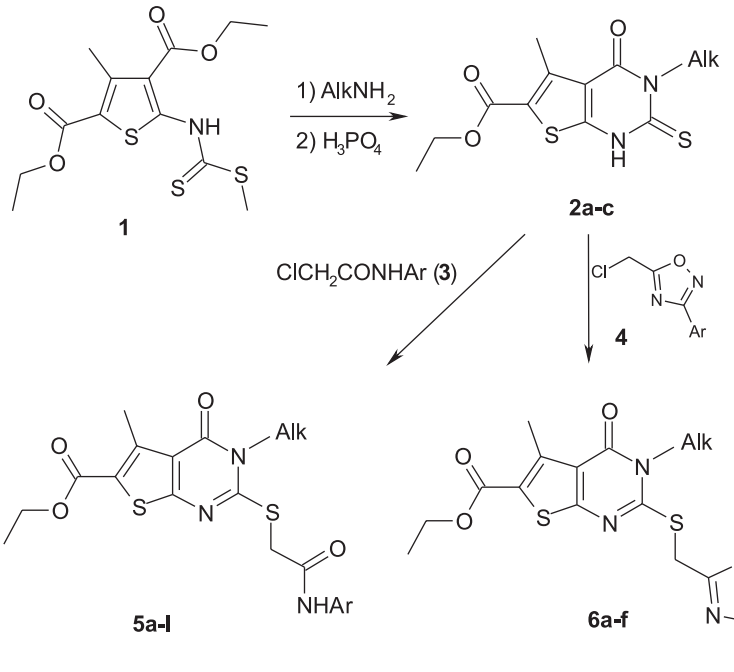
The effective method for the synthesis of ethyl 3-alkyl-5-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-6-carboxylate derivatives by interaction of diethyl 3-methyl-5-{[(methylsulfanyl) carbothioyl]amino}thiophene-2,4-dicarboxylate with low aliphatic amines in the 2-propanol medium has been developed. The conditions proposed facilitate isolation and perceptibly improve the yields of the target thiones. The further modification of ethyl 3-alkyl-5-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-6-carboxylate has been performed by alkylation with chloroacetamides and 3-aryl-5-(chloromethyl)-1,2,4-oxadiazoles (DMF-triethylamine). The structure of the compounds obtained has been confirmed using the NMR spectroscopic methods; the products of alkylation have the signals of the carbethoxy group as two signals in the ranges of 1.27-1.30 ppm (3H, t) and 4.24-4.29 (2H, q), and the signal of SCH_2 protons in the range of 4.22-4.93 ppm. The study of the antimicrobial activity for the functionalized derivatives of thieno[2,3-d]pyrimidine, the corresponding ethyl 3-alkyl-5-methyl-2-({2-[arylamino]-2-oxoethyl}thio)-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylates and ethyl 3-alkyl-5-methyl-4-oxo-2-{[(3-aryl-1,2,4-oxadiazol-5-yl)methyl]thio}-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylate has shown their moderate antimicrobial properties, while for some compounds with the n-butyl substituent at position 3 possess the high inhibitory activity against Candida albicans fungi growth.

Derivatives of 2-thiothieno[2,3-*d*]pyrimidine-6-carboxylic acid are known as the various biologically active compounds [6, 7, 10], antimicrobials are also found in this range of compounds [12, 13]; therefore, development of their preparation methods is an up-to-date problem of modern organic synthesis. The particular attention is also paid to the molecules containing small substituents, their presence favourably increases their drug-likeness [9]. A convenient approach towards the synthesis of 2-thiothieno[2,3-*d*]pyrimidines is application of xanthogenates as intermediates [2, 3, 6, 11, 12], but according to the conditions proposed, in the cases of using primary amines the reaction requires boiling in dimethylformamide (DMF) with further dilution with water for crystallization of the product. Unfortunately, for the low aliphatic amines, which have lower boiling points than the solvent and also may contain a huge amount of water, such reaction conditions may not be suitable. Though the effectiveness and homogenicity of this reaction, dilution with water does not help to isolate the desired products, it may be caused by the high water solubility of the target thione salts with aliphatic amines. Therefore, the aim of this work was to improve the conditions for the synthesis of ethyl 3-alkyl-5-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-6-carboxylates for their further modification via the alkylation reaction.

Materials and Methods

Chemical Part

All of the solvents and reagents were obtained from the commercial sources. Meting points (˚C) were determined with a Kofler (Hotbench) melting point apparatus. ^{1}H NMR spectra were recorded with a Bruker Avance drx 500 (500 MHz) spectrometer in DMSO-d_6, using TMS as a standard. Chemical shifts (δ) are reported in ppm. LC/MS spectra were recorded using a chromatography/mass spectrometric system consisting of a high-performance liquid chromatograph equipped with a diode-matrix and mass-selective detector. The method of chemical ionization under atmospheric pressure (APCI) was used. Ionization mode with simultaneous scanning of positive ions was in the mass range of 80-



Scheme

1000 m/z. Elemental analysis was performed by Kjeldahl method.

The starting **diethyl 3-methyl-5-{[(methylsulfanyl) carbothioyl]amino}thiophene-2,4-dicarboxylate** (**1**) was obtained using the previously reported methods [1, 8, 11].

The general method for the synthesis of compounds 2. To the suspension of **1** 5 g (0.014 Mole) in 2-propanol (30 ml) add 0.021 Mole of the corresponding amine. Reflux the reaction mixture for 3 h and after cooling dilute with water. Neutralize the solution obtained with H_3PO_4, filter the precipitate formed and wash with plenty of water and 2-propanol.

Ethyl 3,5-dimethyl-4-oxo-2-thioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-6-carboxylate (2a). M.p. – 266-267°C. Yield – 73%. ^{1}H NMR (*DMSO-d_6*) δ: 1.27 (3H, t, $OCH_2C\underline{H}_3$); 2.65 (3H, s, CH_3); 3.52 (3H, s, NCH_3); 4.23 (2H, q, $OC\underline{H}_2CH_3$).

LC/MS: m/z (MH^+) 285.2. Found, %: N 9.97. $C_{11}H_{12}N_2O_3S_2$. Calculated, %: N 9.85. M.w. 284.36.

Ethyl 3-ethyl-5-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydrothieno[2,3-d]pyrimidine-6-carboxylate (2b). M.p. – 253-254°C. Yield – 89%. ^{1}H NMR (*DMSO-d_6*) δ: 1.17 (3H, t, $NCH_2C\underline{H}_3$); 1.27 (3H, t, $OCH_2C\underline{H}_3$); 2.69 (3H, s, CH_3); 4.24 (2H, q, $OC\underline{H}_2CH_3$); 4.33 (2H, q, $NC\underline{H}_2CH_3$); 13.71 (1H, s, NH).

LC/MS: m/z (MH^+) 299.0. Found, %: N 9.46. $C_{12}H_{14}N_2O_3S_2$. Calculated, %: N 9.39. M.w. 298.38.

Ethyl 3-butyl-5-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-6-carboxylate (2c). M.p. – 239-240°C. Yield – 86%. ^{1}H NMR (*DMSO-d_6*): 0.90 (3H, t, CH_3); 1.18-1.40 (5H, m, CH_2+ $OCH_2C\underline{H}_3$); 1.60 (2H, m, CH_2); 2.70 (3H, s, CH_3); 4.17-4.34 (4H, m, $2CH_2$); 13.71 (1H, s, NH). LC/MS: m/z (MH^+) 327.2. Found, %: N 8.79. $C_{14}H_{18}N_2O_3S_2$. Calculated, %: N 8.58. M.w. 326.44.

The general method for the synthesis of compounds 5 and 6. To 0.5 mmole of thione **2** in 3.5 ml of DMF add 0.5 mmole of the corresponding alkylating agent **3** or **4** and 0.55 mmole of triethylamine. Stir the reaction mixture at 50-60°C for 3-4 h. Then after cooling dilute the reaction mixture with water, filter the precipitate formed and crystallize from ethanol.

The study of the antimicrobial activity

The study of the antimicrobial activity of the compounds synthesized was performed at the premises of the Laboratory of Biochemistry of Microorganisms and Culture Media at the State Institution "Institute of Microbiology and Immunology named after I.I.Mechnikov of the National Academy of Medical Sciences of Ukraine". According to the WHO recommendations [4, 5] to estimate the activity of the compounds tested the following strains of microorganisms were used: *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Proteus vulgaris* ATCC 4636, *Bacillus subtilis* ATCC 6633, *Candida albicans* ATCC653/885. The inoculum suspension was prepared using a Densi-La-Meter apparatus (made by PLIVA-Lachema, Czech Republic; with the wavelength of 540 nm). The cultures were synchronized using low temperature conditions (4°C). The inoculum density was 10^7 cells per 1 ml of the medium and was determined by comparing with McFarland standard. The 18 to 24-hour old culture of the microorganism was used for the test. Mueller-Hinton agar was used ("HIMedia Laboratories Pvt. Ltd., India") for bacteria. The strain of *Candida albicans* was cultivated using Sabouraud agar ("HIMedia Laboratories Pvt. Ltd., India"). The compounds studied were introduced as DMSO solution in the concentration of 100 μg/ml with the volume of 0.3 ml.

Results and Discussion

To simplify the reaction conditions in order to improve the method the solvent with a low boiling point – 2-propanol was chosen. With the aim to control the concentration of volatile aliphatic amines the excess of

Table 1

Physico-chemical properties of ethyl 3-alkyl-2-(alkylthio)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylates **5** and **6**

Comp.	Alk	Ar	Mol. formula M.w.	Yield, %, alkylation step	M.p., °C	N% calc. / found
5a	$-CH_3$	$-C_6H_5$	$C_{19}H_{19}N_3O_4S_2$ 417.51	82	235-236	10.06 / 10.15
5b	$-CH_3$	$-C_6H_4-CH_3$	$C_{20}H_{21}N_3O_4S_2$ 431.54	84	205-206	9.74 / 9.91
5c	$-CH_3$	$-C_6H_4-CH(CH_3)_2$	$C_{22}H_{25}N_3O_4S_2$ 459.59	76	208-209	9.14 / 9.27
5d	$-CH_3$	$-2-CH_3-5-Cl-C_6H_3$	$C_{20}H_{20}ClN_3O_4S_2$ 465.98	85	236	9.02 / 9.08
5e	$-C_2H_5$	$-C_6H_5$	$C_{20}H_{21}N_3O_4S_2$ 431.54	89	202	9.74 / 9.83
5f	$-C_2H_5$	$-C_6H_4-CH_3$	$C_{21}H_{23}N_3O_4S_2$ 445.56	93	202-203	9.43 / 9.58
5g	$-C_2H_5$	$-C_6H_4-CH(CH_3)_2$	$C_{23}H_{27}N_3O_4S_2$ 473.62	81	199-201	8.87 / 9.02
5h	$-C_2H_5$	$-2-CH_3-5-Cl-C_6H_3$	$C_{21}H_{22}ClN_3O_4S_2$ 480.01	73	240-242	8.75 / 8.80
5i	$-n-C_4H_9$	$-C_6H_5$	$C_{22}H_{25}N_3O_4S_2$ 459.59	91	209-210	9.14 / 9.37
5g	$-n-C_4H_9$	$-C_6H_4-CH_3$	$C_{23}H_{27}N_3O_4S_2$ 473.62	82	207-208	8.87 / 8.92
5k	$-n-C_4H_9$	$-C_6H_4-CH(CH_3)_2$	$C_{25}H_{31}N_3O_4S_2$ 501.67	78	202-203	8.38 / 8.46
5l	$-n-C_4H_9$	$-2-CH_3-5-Cl-C_6H_3$	$C_{23}H_{26}ClN_3O_4S_2$ 508.06	86	229-230	8.27 / 8.38
6a	$-CH_3$	$-C_6H_4-CH_3$	$C_{21}H_{20}N_4O_4S_2$ 456.55	71	159-160	12.27 / 12.32
6b	$-CH_3$	$-C_6H_4-Cl$	$C_{20}H_{17}ClN_4O_4S_2$ 476.96	77	184-185	11.75 / 11.90
6c	$-C_2H_5$	$-C_6H_4-CH_3$	$C_{22}H_{22}N_4O_4S_2$ 470.57	63	154-155	11.91 / 12.05
6d	$-C_2H_5$	$-C_6H_4-Cl$	$C_{21}H_{19}ClN_4O_4S_2$ 490.99	76	161-162	11.41 / 11.56
6e	$-n-C_4H_9$	$-C_6H_4-CH_3$	$C_{24}H_{26}N_4O_4S_2$ 498.63	89	157-159	11.24 / 11.43
6f	$-n-C_4H_9$	$-C_6H_4-Cl$	$C_{23}H_{23}ClN_4O_4S_2$ 519.05	79	145-147	10.79 / 10.80

these reagents was used. It has been found that in such conditions the reaction begins homogeneously and in 1.5-2 h a white precipitate is formed. For complete isolation of the product the cool reaction mixture was diluted with water, and the neutral pH value was adjusted by acidification. The crystals of the products **2** were filtered and washed with 2-propanol (Scheme).

In order to enlarge the chemical diversity compounds **2a-c** were alkylated with chloroacetamides (**3**) and 3-aryl-5-(chloromethyl)-1,2,4-oxadiazoles (**4**) (DMF-triethylamine). As the result of modification the series of S-alkyl derivatives **5** and **6** were obtained (Tab. 1).

In the ^{1}H NMR spectra of the given derivatives **5** and **6** two signals of the carbethoxy group are observed in the range of 1.27-1.30 ppm (3H, t) and 4.24-4.29 (2H, q); in some cases the signal of CH_3 ($COOC_2H_5$) overlaps with the signal of the ethyl radical at position 3 of the thieno[2,3-d]pyrimidine system, while the signal of OCH_2 may be together with SCH_2 protons peak. The spectra of all compounds **5** and **6** also contain the signal of the thiophene ring methyl group at 2.72-2.80 ppm, for compounds **5** the signal of acetamide NH protons in the range of 9.79-10.40 ppm, which position much depends upon the character of the benzene ring substituents, is typical. The signals of SCH_2 are observed in the region of 4.22-4.29 ppm for compounds **5** and strongly shifted downfield for compounds **6** to 4.89-4.93 ppm (Tab. 2).

The results of the antimicrobial activity screening for the series of compounds **5** and **6** allowed determining their wide range, but the moderate antibacterial activity

Table 2

^{1}H NMR spectral data for ethyl 3-alkyl-2-(alkylthio)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylates **5** and **6**

Comp.	Chemical shift, δ, ppm			
	CH_3 thiophene (3H, s)	NH (1H, br.s)	Aliphatic protons	Aromatic protons
5a	2.79	10.38	1.29 (3H, t, $OCH_2C\underline{H}_3$); 3.50 (3H, s, NCH_3); 4.27 (4H, m, SCH_2 + $OC\underline{H}_2CH_3$);	7.07 (1H, t, H-4′); 7.32 (2H, t, H-3′ + H-5′); 7.59 (2H, d, H-2′ + H-6′)
5b	2.79	10.31	1.29 (3H, t, $OCH_2C\underline{H}_3$); 2.25 (3H, s, $ArCH_3$); 3.50 (3H, s, NCH_3); 4.22 (2H, s, SCH_2); 4.28 (2H, q, $OC\underline{H}_2CH_3$);	7.12 (2H, d, H-3′ + H-5′); 7.46 (2H, d, H-2′ + H-6′)
5c	2.78	10.29	1.17 (6H, d, $2CH_3$); 1.29 (3H, t, $OCH_2C\underline{H}_3$); 2.83 (1H, m, $C\underline{H}(CH_3)_2$); 3.50 (3H, s, NCH_3); 4.22 (2H, s, SCH_2); 4.28 (2H, q, $OC\underline{H}_2CH_3$);	7.18 (2H, d, H-3′ + H-5′); 7.48 (2H, d, H-2′ + H-6′)
5d	2.80	9.82	1.30 (3H, t, $OCH_2C\underline{H}_3$); 2.23 (3H, s, $ArCH_3$); 3.51 (3H, s, NCH_3); 4.29 (4H, m, SCH_2 + $OC\underline{H}_2CH_3$);	7.16 (1H, d, H-3′); 7.26 (1H, d, H-4′); 7.50 (1H, s, H-6′);
5e	2.80	10.40	1.29 (6H, m, $OCH_2C\underline{H}_3$ + $NCH_2C\underline{H}_3$); 4.11 (2H, q, $NC\underline{H}_2CH_3$); 4.25 (2H, s, SCH_2); 4.28 (2H, q, $OC\underline{H}_2CH_3$);	7.07 (1H, m, H-4′); 7.32 (2H, t, H-3′ + H-5′); 7.59 (2H, d, H-2′ + H-6′)
5f	2.80	10.25	1.30 (6H, t, $OCH_2C\underline{H}_3$ + $NCH_2C\underline{H}_3$); 2.26 (3H, s, $ArCH_3$); 4.11 (2H, q, $NC\underline{H}_2CH_3$); 4.22 (2H, s, SCH_2); 4.29 (2H, q, $OC\underline{H}_2CH_3$);	7.12 (2H, d, H-3′ + H-5′); 7.46 (2H, d, H-2′ + H-6′)
5g	2.80	10.30	1.18 (6H, d, $2CH_3$); 1.29 (6H, t, $OCH_2C\underline{H}_3$ + $NCH_2C\underline{H}_3$); 2.83 (1H, m, $C\underline{H}(CH_3)_2$); 4.11 (2H, q, $NC\underline{H}_2CH_3$); 4.23 (2H, s, SCH_2); 4.28 (2H, q, $OC\underline{H}_2CH_3$);	7.18 (2H, d, H-3′ + H-5′); 7.48 (2H, d, H-2′ + H-6′)
5h	2.80	9.83	1.30 (6H, t, $OCH_2C\underline{H}_3$ + $NCH_2C\underline{H}_3$); 2.23 (3H, s, $ArCH_3$); 4.11 (2H, q, $NC\underline{H}_2CH_3$); 4.28 (4H, m, SCH_2 + $OC\underline{H}_2CH_3$);	7.16 (1H, d, H-3′); 7.26 (1H, d, H-4′); 7.50 (1H, s, H-6′);
5i	2.79	10.40	0.96 (3H, m, CH_3); 1.29 (3H, m, $OCH_2C\underline{H}_3$); 1.40 (2H, m, CH_2); 1.68 (2H, m, CH_2); 4.04 (2H, m, $NC\underline{H}_2C_3H_7$); 4.24 (4H, m, SCH_2 + $OC\underline{H}_2CH_3$);	7.07 (1H, m, H-4′); 7.32 (2H, m, H-3′ + H-5′); 7.58 (2H, m, H-2′ + H-6′)
5j	2.79	10.28	0.95 (3H, t, CH_3); 1.29 (3H, m, $OCH_2C\underline{H}_3$); 1.40 (2H, m, CH_2); 1.69 (2H, m, CH_2); 2.25 (3H, s, $ArCH_3$); 4.04 (2H, m, $NC\underline{H}_2C_3H_7$); 4.22 (2H, s, SCH_2); 4.28 (2H, q, $OC\underline{H}_2CH_3$);	7.12 (2H, d, H-3′ + H-5′); 7.46 (2H, d, H-2′ + H-6′)
5k	2.79	10.32	0.95 (3H, t, CH_3); 1.17 (6H, d, $2CH_3$); 1.29 (3H, m, $OCH_2C\underline{H}_3$); 1.40 (2H, q, CH_2); 1.68 (2H, m, CH_2); 2.83 (1H, m, $C\underline{H}(CH_3)_2$); 4.04 (2H, m, $NC\underline{H}_2C_3H_7$); 4.22 (2H, s, SCH_2); 4.28 (2H, q, $OC\underline{H}_2CH_3$);	7.18 (2H, d, H-3′ + H-5′); 7.48 (2H, d, H-2′ + H-6′)
5l	2.80	9.79	0.95 (3H, t, CH_3); 1.30 (3H, t, $OCH_2C\underline{H}_3$); 1.40 (2H, q, CH_2); 1.69 (2H, m, CH_2); 2.23 (3H, s, $ArCH_3$); 4.05 (2H, m, $NC\underline{H}_2C_3H_7$); 4.29 (4H, m, SCH_2 + $OC\underline{H}_2CH_3$);	7.15 (1H, d, H-3′); 7.25 (1H, d, H-4′); 7.51 (1H, s, H-6′);
6a	2.72	–	1.29 (3H, t, $OCH_2C\underline{H}_3$); 2.35 (3H, s, CH_3); 3.47 (3H, s, NCH_3); 4.25 (2H, q, $OC\underline{H}_2CH_3$); 4.89 (2H, s, SCH_2);	7.33 (2H, d, H-2′ + H-6′); 7.85 (2H, d, H-3′ + H-5′)
6b	2.72	–	1.28 (3H, t, $OCH_2C\underline{H}_3$); 3.48 (3H, s, NCH_3); 4.25 (2H, q, $OC\underline{H}_2CH_3$); 4.91 (2H, s, SCH_2);	7.60 (2H, d, H-2′ + H-6′); 7.97 (2H, d, H-3′ + H-5′)
6c	2.75	–	1.29 (6H, m, $OCH_2C\underline{H}_3$ + $NCH_2C\underline{H}_3$); 2.33 (3H, s, CH_3); 4.08 (2H, q, $NC\underline{H}_2CH_3$); 4.27 (2H, q, $OC\underline{H}_2CH_3$); 4.91 (2H, s, SCH_2);	7.34 (2H, d, H-2′ + H-6′); 7.86 (2H, d, H-3′ + H-5′)
6d	2.76	–	1.29 (6H, m, $OCH_2C\underline{H}_3$ + $NCH_2C\underline{H}_3$); 4.08 (2H, q, $NC\underline{H}_2CH_3$); 4.27 (2H, q, $OC\underline{H}_2CH_3$); 4.93 (2H, s, SCH_2);	7.61 (2H, d, H-2′ + H-6′); 7.98 (2H, d, H-3′ + H-5′)
6e	2.76	–	0.95 (3H, t, CH_3); 1.28 (3H, t, $OCH_2C\underline{H}_3$); 1.39 (2H, q, CH_2); 1.67 (2H, m, CH_2); 2.37 (3H, s, $ArCH_3$); 4.02 (2H, m, $NC\underline{H}_2C_3H_7$); 4.26 (2H, q, $OC\underline{H}_2CH_3$); 4.91 (2H, s, SCH_2);	7.36 (2H, d, H-2′ + H-6′); 7.86 (2H, d, H-3′ + H-5′)
6f	2.74	–	0.95 (3H, t, CH_3); 1.27 (3H, t, $OCH_2C\underline{H}_3$); 1.40 (2H, q, CH_2); 1.67 (2H, m, CH_2); 4.01 (2H, m, $NC\underline{H}_2C_3H_7$); 4.25 (2H, q, $OC\underline{H}_2CH_3$); 4.92 (2H, s, SCH_2);	7.60 (2H, d, H-2′ + H-6′); 7.97 (2H, d, H-3′ + H-5′)

Table 3

The antimicrobial activity of ethyl 3-alkyl-2-(alkylthio)-5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylates **5** and **6**

Comp.	Diameter of the growth inhibition zone in mm, number of experiments n=3					
	Staphylococcus aureus ATCC 25923	*Escherichia coli ATCC 25922*	*Proteus vulgaris ATCC 4636*	*Pseudomonas aeruginosa ATCC 27853*	*Bacillus subtilis ATCC 6633*	*Candida albicans ATCC 653/885*
5a	15, 14, 15	15, 15, 15	growth	growth	17, 16, 17	18,18, 19
5b	15, 16, 16	16, 15, 14	growth	13, 14, 15	16, 16, 17	18, 18, 18
5c	17, 18, 17	17, 17, 17	14, 15, 15	15, 14, 15	16, 17, 17	17, 16, 17
5d	16, 16, 17	17, 17, 18	14, 15, 15	15, 15, 15	18, 18, 18	16, 17, 17
5e	12, 13, 13	18, 16, 17	growth	13, 14, 13	17, 16, 17	16, 16, 17
5f	17, 17, 18	16, 17, 17	16, 16, 17	17, 17, 16	17, 18, 17	18, 17, 18
5g	17, 17, 17	16, 17, 15	16, 16, 16	16, 16, 17	19, 19, 18	18, 18, 18
5h	16, 16, 16	16, 16, 17	14, 15. 15	14, 15, 16	17, 16, 17	17, 18, 18
5i	16, 16, 16	15, 16, 16	14, 14, 14	17, 17, 18	18, 17, 18	16, 16, 17
5j	14, 13, 14	14, 14, 14	growth	15, 14, 14	16, 16, 17	20, 21, 21
5k	18, 17, 17	16, 16, 15	15, 15, 16	16, 16, 16	19, 20, 20	23, 22, 23
5l	13, 13, 14	15, 16, 16	16, 15, 16	15, 16, 16	18, 17, 18	22, 23, 23
6a	17, 18, 17	17, 16, 16	15, 15, 15	16, 17, 16	18, 19, 18	18, 17, 18
6b	16, 16, 15	16, 17, 17	16, 15, 15	16, 15, 16	17, 18, 18	16, 17, 17
6c	12, 13, 12	13, 13, 14	growth	14, 15, 15	16, 16, 17	17,17, 16
6d	18, 17, 18	17, 16, 17	15, 14, 15	16, 16, 17	18, 19, 19	13, 13, 14
6e	14, 14, 15	16, 15, 16	growth	14, 15, 15	16, 17, 17	20, 21, 20
6f	14, 14, 14	16, 16, 16	14, 13, 14	14, 15, 15	18, 18, 17	21, 22, 21
Metr.*	14, 15, 14	14, 13, 14	growth	growth	16, 15, 16	14, 14, 14
Strept.**	15, 16, 15	15, 16, 17	growth	growth	17, 16, 17	growth

* Metr. – Metronidazole, DMSO solution, with the concentration of 30 μg/ml;
** Strept. – Streptomycin, H_2O solution, with the concentration of 30 μg/ml;

for the most of the compounds tested, being similar to the reference drugs Streptomycin and Metronidazole. The most active compounds with *n*-butyl substituent in position 3 of the thieno[2,3-d]pyrimidine system **5j-5l** and **6e,f**, were found to inhibit the growth of *Candida albicans* (Tab. 3).

CONCLUSIONS

A novel and effective method for the synthesis of ethyl 3-alkyl-5-methyl-4-oxo-2-thioxo-1,2,3,4-tetrahydrothieno[2,3-*d*]pyrimidine-6-carboxylate derivatives has been developed with further modification of these compounds to obtain 2-alkylthio derivatives. The study of the antimicrobial activity of the final products has allowed to determine their moderate antibacterial activity though some compounds containing the *n*-butyl substituent in position 3 of the thieno[2,3-d]pyrimidine system significantly inhibit the growth of *Candida albicans* fungi.

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СИНТЕЗ ТА АНТИМІКРОБНА АКТИВНІСТЬ НОВИХ ПОХІДНИХ ЕТИЛ 3-АЛКІЛ-2-(АЛКІЛТІО)-5-МЕТИЛ-4-ОКСО-3,4-ДИГІДРОТІЄНО[2,3-*d*]ПІРИМІДИН-6-КАРБОКСИЛАТІВ

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Ключові слова: *тіофен; піримідин; меркаптани; алкілування; циклізація*

Розроблена ефективна методика одержання похідних етил 3-алкіл-5-метил-4-оксо-2-тіоксо-1,2,3,4-тетрагідротієно[2,3-d]піримідин-6-карбоксилатів шляхом проведення взаємодії діетил 3-метил-5-{[(метилсульфаніл)карботіоїл]аміно}тіофен-2,4-дикарбоксилату з нижчими аліфатичними амінами у середовищі 2-пропанолу. Такі умови реакції дозволяють легко виділяти бажані сполуки та значно покращують виходи цільових тіонів. Подальшу модифікацію етил 3-акліл-5-метил-4-оксо-2-тіоксо-1,2,3,4-тетрагідротієно[2,3-d]піримідин-6-карбоксилатів проводили шляхом взаємодії з хлороацетамідами та 3-арил-5-(хлорометил)-1,2,4-оксадіазолами (ДМФА-триетиламін). Будову отриманих сполук було підтверджено даними ЯМР-спектроскопії; для продуктів алкілування сигнали протонів карбетокси-групи проявляються у вигляді двох сигналів у діапазоні 1.27-1.30 м.ч. (3Н, т) та 4.24-4.29 (2Н, кв), а протони SCH_2 дають сигнал у діапазоні 4.22-4.93 м.ч. Дослідження антимікробної активності продуктів алкілування отриманих фунціоналізованих похідних тієно[2,3-d]піримідину, відповідно етил 3-алкіл-5-метил-2-({2-[ариламіно]-2-оксоетил}тіо)-4-оксо-3,4-дигідротієно[2,3-d]піримідин-6-карбоксилатів та етил 3-алкіл-5-метил-4-оксо-2-{[(3-арил-1,2,4-оксадіазол-5-іл)метил]тіо}-3,4-дигідротієно[2,3-d]піримідин-6-карбоксилатів дозволило встановити, що сполуки чинять помірну антибактеріальну активність, проте похідні з н-бутильним замісником у положенні 3 тієно[2,3-d]піримідинової системи значно пригнічують ріст грибів Candida albicans.

СИНТЕЗ И ПРОТИВОМИКРОБНАЯ АКТИВНОСТЬ НОВЫХ ПРОИЗВОДНЫХ ЭТИЛ 3-АЛКИЛ-2-(АЛКИЛТИО)-5-МЕТИЛ-4-ОКСО-3,4-ДИГИДРОТИЕНО[2,3-*d*]ПИРИМИДИН-6-КАРБОКСИЛАТОВ

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Ключевые слова: *тиофен; пиримидин; меркаптаны; алкилирование; циклизация*

Разработана эффективная методика получения производных этил 3-алкил-5-метил-4-оксо-2-тиоксо-1,2,3,4-тетрагидротиено[2,3-d]пиримидин-6-карбоксилатов путем проведения взаимодействия диэтил 3-метил-5-{[(метилсульфанил)карботиоил]амино}тиофен-2,4-дикарбоксилата с низшими алифатическими аминами в среде 2-пропанола. Такие условия реакции позволяют легко выделять целевые соединения и значительно улучшают выходы целевых тионов. Дальнейшую модификацию этил 3-алкил-5-метил-4-оксо-2-тиоксо-1,2,3,4-тетрагидротиено[2,3-d]пиримидин-6-карбоксилатов проводили путем взаимодействия с хлорацетамидами и 3-арил-5-(хлорометил)-1,2,4-оксадиазолами (ДМФА-триэтиламин). Строение полученных соединений было подтверждено данными ЯМР-спектроскопии; для продуктов алкилирования сигналы протонов карбэтокси-группы проявляются в виде двух сигналов в диапазоне 1.27-1.30 м.д. (3Н, т) и 4.24-4.29 (2Н, кв), а протоны SCH_2 дают сигнал в диапазоне 4.22-4.93 м.д. Исследования противомикробной активности продуктов алкилирования полученных функционализированных производных тиено[2,3-d]пиримидина, соответственно этил 3-алкил-5-метил-2-({2-[ариламино]-2-оксоэтил}тио)-4-оксо-3,4-дигидротиено[2,3-d] пиримидин-6-карбоксилатов и этил 3-алкил-5-метил-4-оксо-2-{[(3-арил-1,2,4-оксадиазол-5-ил) метил]тио}-3,4-дигидротиено[2,3-d]пиримидин-6-карбоксилатов позволило установить, что соединения проявляют умеренную антибактериальную активность, однако производные с н-бутильным заместителем в положении 3 тиено[2,3-d]пиримидиновой системы значительно угнетают рост грибов Candida albicans.