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SYNTHESIS AND ALKYLATION OF 6-(1*H*-BENZIMIDAZOL-2-YL)-5-METHYLTHIENO[2,3-*d*]PYRIMIDIN-4(3*H*)-ONES

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Key words: thiophene; pyrimidine; imidazole; alkylation

The one-step method for preparation of 6-(1H-benzimidazol-2-yl)-5-methylthieno[2,3-d]pyrimidin-4(3H)-ones by interaction of 5-methyl-4-oxo-3,4-dihydrothieno[2,3-d]pyrimidine-6-carboxylic acid with ortho-pnenylediamines using 1,1'-carbonyldiimidazole as a coupling-reagent has been developed. The procedure proposed allows to obtain easily the target products using common reagents and solvents; and it also requires the simple isolation methods. The selectivity of 6-(1H-benzimidazol-2-yl)-5-methylthieno[2,3-d]pyrimidin-4(3H)-one interaction with benzyl chlorides in DMF – K_2CO_3 conditions has been studied using the NOESY spectroscopic method and alternative synthetic approaches; it has been determined that the reaction occurs at position 3 of the thieno[2,3-d] pyrimidine system. The study of the antimicrobial activity by the agar diffusion method for the compounds obtained has shown that 6-(1H-benzimidazol-2-yl)-3-benzyl-5-methylthieno[2,3-d]pyrimidin-4(3H)-ones reveal the antimicrobial activity against the strains of Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa; while the compound with unsubstituted position 3 appeared to be inactive against these strains of microorganisms. However, this compound exhibited the higher inhibitory activity against the Candida albicans fungi.

СИНТЕЗ ТА АЛКІЛЮВАННЯ 6-(1Н-БЕНЗІМІДАЗОЛ-2-ІЛ)-5-МЕТИЛТІЄНО[2,3-d]ПІРИМІДИН-4(3Н)-ОНІВ
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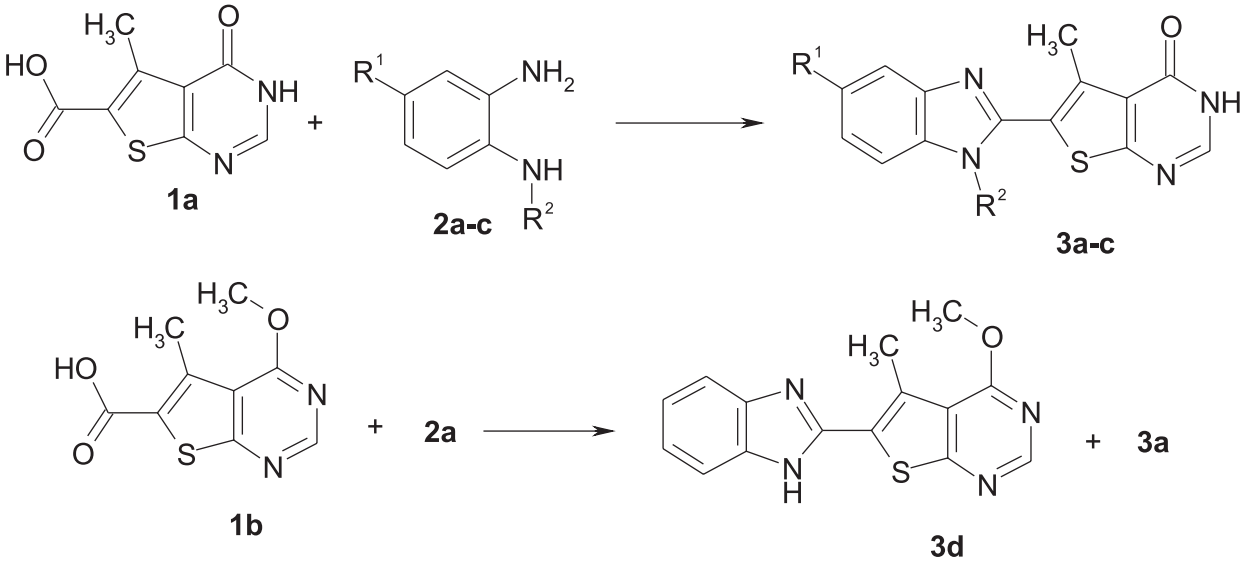
Ключові слова: *тіофен; піримідин; імідазол; алкілювання*
Розроблено ефективний одностадійний метод одержання 6-(1Н-бензімідазол-2-іл)-5-метилтієно[2,3-d] піримідин-4(3Н)-онів шляхом взаємодії 5-метил-4-оксо-3,4-дигідротієно[2,3-d]піримідин-6-карбонової кислоти з орто-фенілендіамінами при використанні 1,1'-карбонілдіімідазолу в якості каплінг-реагента. Запропонована методика дозволяє легко одержувати кінцеві продукти при використанні простих реагентів і розчинників та вимагає стандартних методів виділення продукту. Досліджено напрям реакції 6-(1Н-бензімідазол-2-іл)-5-метилтієно[2,3-d]піримідин-4(3Н)-ону з бензилхлоридами в умовах ДМФа – K_2CO_3, та за допомогою даних спектроскопії NOESY і зустрічного синтезу встановлено, що дана реакція перебігає в положення 3 тієно[2,3-d]піримідинової системи. Дослідження антимікробної активності одержаних сполук методом дифузії в агар дозволило встановити, що 6-(1Н-бензімідазол-2-іл)-3-бензил-5-метилтієно[2,3-d]піримідин-4(3Н)-они виявляють антимікробну активність по відношенню до таких штамів мікроорганізмів як Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, в той же час незаміщена по положенню 3 похідна неактивна по відношенню до цих штамів мікроорганізмів. Проте для незаміщеної похідної характерна дещо більша пригнічуюча активність по відношенню до грибів Candida albicans.

СИНТЕЗ И АЛКИЛИРОВАНИЕ 6-(1Н-БЕНЗИМИДАЗОЛ-2-ИЛ)-5-МЕТИЛТИЕНО[2,3-d]ПИРИМИДИН-4(3Н)-ОНОВ
С.В.Власов, С.Н.Коваленко, В.П.Черных, К.Ю.Кроленко
Ключевые слова: *тиофен; пиримидин; имидазол; алкилирование*
Разработан эффективный одностадийный метод получения 6-(1Н-бензимидазол-2-ил)-5-метилтиено [2,3-d]пиримидин-4(3Н)-онов путем взаимодействия 5-метил-4-оксо-3,4-дигидротиено[2,3-d]пиримидин-6-карбоновой кислоты с орто-фенилендиаминами при использовании 1,1'-карбонилдиимидазола в качестве каплинг-реагента. Данная методика позволяет легко получить конечные продукты при использовании простых реагентов и растворителей и требует стандартных методов выделения продукта. Исследовано направление реакции 6-(1Н-бензимидазол-2-ил)-5-метилтиено[2,3-d]пиримидин-4(3Н)-она с бензилхлоридами в условиях ДМФа – K_2CO_3, и с помощью данных спектроскопии NOESY и встречного синтеза установлено, что реакция протекает в положение 3 тиено[2,3-d]пиримидиновой системы. Изучение противомикробной активности полученных соединений методом диффузии в агар позволило установить, что 6-(1Н-бензимидазол-2-ил)-3-бензил-5-метилтиено[2,3-d]пиримидин-4(3Н)-оны проявляют противомикробную активность по отношению к таким штаммам микроорганизмов как Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa; в то же время незамещенное по положению 3 производное неактивно в отношении этих штаммов микроорганизмов. Однако, для незамещенного производного характерна чуть большая подавляющая активность в отношении грибов Candida albicans.

The derivatives of thieno[2,3-*d*]pyrimidines modified at position 6 with imidazole [1], thiazole [2, 3], oxazole [2, 3], and pyrazole [3] have been considered. Mostly, the key reaction for preparing these compounds is the cross-coupling of 6-bromothieno[2,3-*d*]pyrimidines with metallo-organic compounds derived from the corresponding azoles; in some cases even organic tin compounds are required [2, 3]. These heterocyclic systems were patented as acetyl-CoA-carboxylase inhibitors [2] or A_{2A} adenosine receptor antagonists [3], which may be used to treat obesity [2, 3], blood circulatory dysfunctions in brain and drug ad-



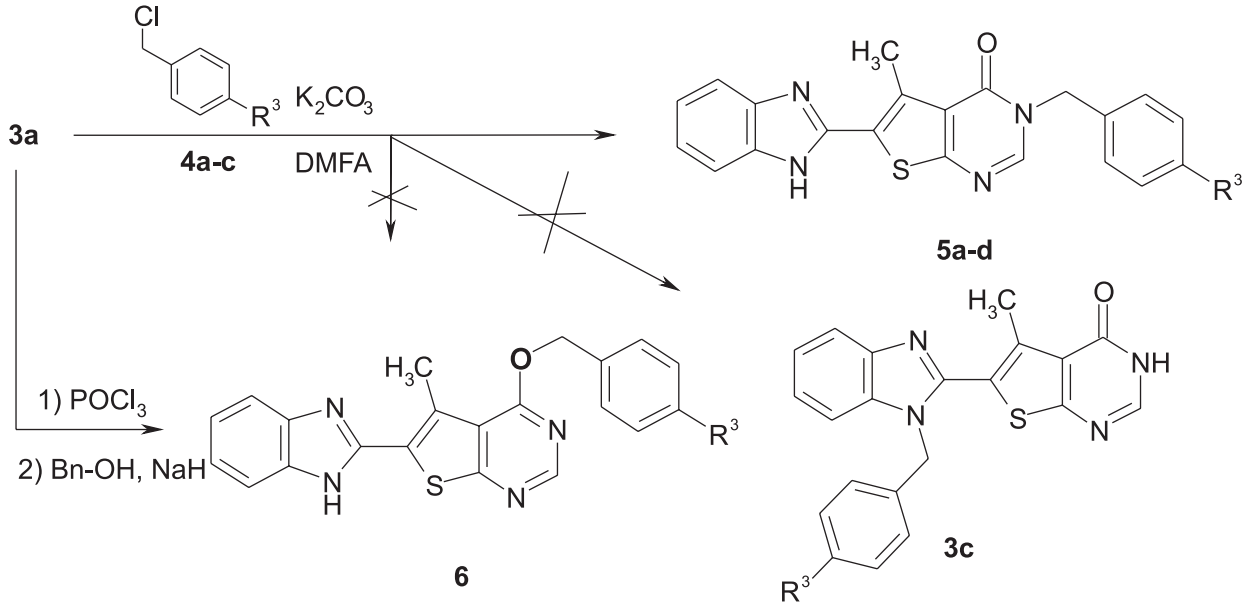
Scheme 1

diction [3]. However, no information about the derivatives of thieno[2,3-*d*]pyrimidine modified at position 6 with the benzimidazole fragment has been reported. Therefore, development of the effective method for synthesis of 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones has been chosen as our research task.

It is known that benzimidazoles are readily prepared by the reaction of carboxylic acids with *ortho*-phenylenediamines [4-8] when heating in the acidic medium like polyphosphoric acid. The reaction of 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid **1a** [9] with *ortho*-pnenylediamine **2a** was carried out in the polyphosphoric acid medium for 5 h at 190°C when heating, but the desired 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one was not isolated after this procedure. To modify the method we have chosen the method with the use of 1,1'-carbonyldiimidazole. The reaction was carried out in the anhydrous DMF, first at 70-80°C for preparation of the soluble imidazolide and then at 130°C after addition of *ortho*-pnenylediamine for 3-4 h. As the result, 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **3a,b** were obtained in a good yield. This reaction also appeared to be suitable for preparation of 6-(1-benzyl-1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one **3c**.

The reaction of 4-methoxy-5-methylthieno[2,3-*d*] pyrimidine-6-carboxylic acid **1b** with *ortho*-pnenylediamine **2a** resulted in the mixture of 4-methoxy product **3d** and compound **3a**. Probably, the molecule of water produced during the benzimidazole ring closure hydrolyses the methoxy group at position 4.

For further modification of compounds **3** we studied their interaction with benzyl chlorides using conditions of the alkylation reaction (K_2CO_3-DMF) and compound **3a** as the model one. Considering the mo-



Scheme 2

lecule of 6-(1*H*-benzimidazol-2-yl)-5-methylthieno [2,3-*d*]pyrimidin-4(3*H*)-ones **3a** containing three centres, which could potently be attacked by benzyl chloride, three possible isomers were expected. The characteristics of the isolated individual product did not match the properties of compound **3c** previously obtained. Moreover, the NOESY spectrum of the compound obtained contained the cross-peak of benzylic CH_2 protons and the proton of CH at position 2 of thieno[2,3-*d*]pyrimidine system, which was the evidence for assumption of structure **5**. To deflate the hypothesis about the possible O-alkylation the synthesis of compound **6** (R^3=H) was carried out by the interaction of the unstable 4-chloro derivative with sodium benzylate prepared *in situ* using the interaction of benzyl alcohol with sodium hydride. In the ^{1}H NMR spectrum of compound **6** the signal of the methylene group protons is located at 5.65 ppm, which is distinctively different from the position of methylene protons signals for product **5a** (5.19 ppm) and compound **3c** (5.49 ppm). All the facts collected confirm that alkylation of 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones with benzyl chlorides proceeds at position 3 of the thieno[2,3-*d*] pyrimidine ring system.

For compounds **5** and the starting 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one **3a** the screening of the antimicrobial activity by the agar well diffusion method was performed. The strains recommended by the WHO for the activity study of antimicrobial drugs were used for the experiment [10, 11]. The results are given in Tab. 2.

It has been determined that the compounds under research exhibit the antimicrobial activity against the strains of *Staphylococcus aureus* and *Bacillus subtilis* less or at the same level as the reference drugs Metronidazole and Streptomycin. The presence of the benzyl substituent at position 3 of 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one promotes the antimicrobial properties against the strains of *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa* compared to compound **3a** although compound **3a** is a little more active against the *Candida albicans* fungi.

Table 1

Data of the 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives **3**, **5**, **6** obtained

Compnd	R^1	R^2	R^3	Mol. formula M.w.	M.p., °C	Yield, %
3a	H	H	-	$C_{14}H_{10}N_4OS$ 282.33	>300	62
3b	Cl	H	-	$C_{14}H_9ClN_4OS$ 316.77	>300	75
3c	H	Bn	-	$C_{21}H_{16}N_4OS$ 372.45	>300	46
5a	H	H	H	$C_{21}H_{16}N_4OS$ 372.45	246-248	64
5b	H	H	CH_3	$C_{22}H_{18}N_4OS$ 386.48	211-213	68
5c	H	H	F	$C_{21}H_{15}FN_4OS$ 390.44	248-250	57
5d	H	H	Cl	$C_{21}H_{15}ClN_4OS$ 406.90	293-295	73
6	H	H	H	$C_{21}H_{16}N_4OS$ 372.45	266-268	35

Experimental Part

All of the solvents and reagents were obtained from the commercial sources. The melting points (°C) were measured with a Kofler melting point apparatus and

Table 2

The results of the antimicrobial activity screening for 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones **3a** and **5a-d**

	Growth inhibition zone diameter, mm Number of experimental trials, 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*
3a	13, 14, 14	growth	growth	growth	14, 14, 14	15, 16, 16
5a	14, 15, 14	14, 14, 15	14, 13, 14	14, 13, 13	14, 14, 14	14, 14, 14
5b	13, 14, 14	14, 14, 14	13, 14, 13	14, 15, 14	14, 14, 14	14, 14, 14
5c	15, 16, 15	14, 14, 13	12, 13, 13	14, 15, 14	14, 14, 14	14, 14, 14
5d	15, 14, 15	13, 14, 14	13, 13, 14	12, 13, 13	14, 14, 14	14, 14, 14
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, the concentration – 30 μg/ml); ** Strept. – Streptomycin (H_2O solution, the concentration – 30 μg/ml).

were not corrected. ^{1}H NMR spectra were recorded on a Varian Mercury (200 MHz) spectrometer in DMSO-d_6 using TMS as an internal standard (chemical shifts are in ppm). ^{13}C NMR and NOESY spectra were recorded on a Varian Gemini (300 MHz) spectrometer in DMSO-d_6 using TMS as an internal standard (chemical shifts are in ppm). LC/MS was recorded with PE SCIEX API 150EX chromatograph equipped with a mass-spectrometer.

5-Methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid (1a) and **4-methoxy-5-methylthieno[2,3-*d*]pyrimidine-6-carboxylic acid (1b)** were obtained by the previously reported methods [9].

6-(1*H*-Benzimidazol-2-yl)-5-methylthieno [2,3-*d*]pyrimidin-4(3*H*)-ones (3). To the suspension of 0.025 mole of 5-methyl-4-oxo-3,4-dihydrothieno [2,3-*d*]pyrimidine-6-carboxylic acid in 30 ml of the anhydrous DMF add 0.026 mole of 1,1'-carbonyldiimidazole, and heat the reaction mixture to the complete liberation of carbon dioxide and then heat additionally for 15 min. After that, add 0.025 mole of *ortho*-phenylediamine **2** to the hot solution. Stir the reaction mixture and heat at 130°C for 3-5 h. After cooling quench the reaction mixture with water, filter the precipitate formed and wash with 50% water solution of 2-propanol. The product can be crystallized from the 2-propanol-DMF mixture.

6-(1*H*-Benzimidazol-2-yl)-5-methylthieno [2,3-*d*]pyrimidin-4(3*H*)-one (3a). M.p. >300°C. ^{1}H NMR spectrum: 2.89 (3H, s., CH_3); 7.21 (2H, d., *J = 4.3*); 7.61 (2H, m.); 8.13 (1H, s., CH), 12.59 (2H, br.s., NH). ^{13}C NMR spectrum (75 MHz): 15.49 (CH_3); 123.78; 124.51; 134.27; 146.35; 147.18; 158.73; 164.82. LC/MS, *m/z*: 283 $[M+H]^+$. Found, %: N 19.93. $C_{14}H_{10}N_4OS$. Calculated, %: N 19.84. M.w. 282.33.

6-(5-Chloro-1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (3b). M.p. >300°C. ^{1}H NMR spectrum: 2.89 (3H, s., CH_3); 7.25 (1H, m.); 7.54 (1H, m.); 7.71 (1H, m.); 8.15 (1H, s., CH), 12.59 (1H, br.s., NH); 12.78 (1H, br.s., NH). ^{13}C NMR spectrum (75 MHz): 15.52 (CH_3); 123.13; 124.48; 134.99; 147.35; 158.69; 165.00. LC/MS, *m/z*: 316 $[M]^+$. Found, %: N 11.17. $C_{14}H_9ClN_4OS$. Calculated, %: N 11.19. M.w. 316.77.

6-(1-Benzyl-1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (3c) M.p. > 300°C. ^{1}H NMR spectrum: 2.41 (3H, s., CH_3); 5.49 (2H, s., CH_2); 6.93 (2H, m.); 7.24 (5H, m.); 7.52 (1H, m.); 7.72 (1H, m.); 8.16 (1H, s., CH); 12.45 (1H, br.s., NH). ^{13}C NMR spectrum (75 MHz): 15.09 (CH_3); 47.92 (CH_2); 111.83; 119.97; 120.80; 122.98; 123.76; 126.90; 127.94; 129.10; 135.78; 136.80; 137.01; 143.25; 146.32; 147.48; 158.62; 165.50. LC/MS, *m/z*: 373 $[M+H]^+$. Found, %: N 15.32. $C_{21}H_{16}N_4OS$. Calculated, %: N 15.04. M.w. 372.45.

6-(1*H*-Benzimidazol-2-yl)-3-benzyl-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones (5). To the suspension of 1 mmole of 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one **3a** in DMF add 1 mmole of K_2CO_3, 1 mmole of the corresponding benzyl chloride and 0.1 mmole of potassium iodide. Stir the reaction mixture at the room temperature for 24 h. Then quench the reaction with water, filter the precipitate formed and crystallize from 2-propanol.

6-(1*H*-Benzimidazol-2-yl)-3-benzyl-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (5a). M.p. – 246-248°C. ^{1}H NMR spectrum: 2.88 (1H, s., CH_3); 5.19 (2H, s., CH_2); 7.3 (7H, m.); 7.60 (2H, m.); 8.70 (1H, s., CH); 12.63 (1H, br.s., NH). ^{13}C NMR spectrum (75 MHz): 15.53 (CH_3); 49.20 (CH_2); 123.74; 124.65; 128.18; 129.11; 134.26; 137.09; 146.22; 149.76; 157.88; 163.91. LC/MS, *m/z*: 372 $[M]^+$. Found, %: N 15.12. $C_{21}H_{16}N_4OS$. Calculated, %: N 15.04. M.w. 372.45.

6-(1*H*-Benzimidazol-2-yl)-5-methyl-3-(4-methylbenzyl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (5b). M.p. – 211-213°C. ^{1}H NMR spectrum: 2.26 (3H, s., CH_3); 2.88 (3H, s., CH_3); 5.14 (2H, s., CH_2); 7.01-7.37 (6H, m.); 7.60 (2H, m.); 8.66 (1H, s., CH); 12.63 (1H, br.s., NH). ^{13}C NMR spectrum (75 MHz): 15.53 (CH_3); 21.14 (CH_3); 48.94 (CH_2); 123.72; 124.61; 128.27; 129.63; 134.10; 137.49; 146.23; 149.71; 157.85; 163.88. LC/MS, *m/z*: 387 $[M+H]^+$. Found, %: N 14.69. $C_{22}H_{18}N_4OS$. Calculated, %: N 14.50. M.w. 386.48.

6-(1*H*-Benzimidazol-2-yl)-3-(4-fluorobenzyl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (5c). M.p. – 248-250°C. ^{1}H NMR spectrum: 2.88 (3H, s., CH_3); 5.16 (2H, s., CH_2); 7.17 (4H, m.); 7.44 (2H, m.); 7.60 (2H, m.); 8.69 (1H, s., CH); 12.64 (1H, br.s., NH). ^{13}C NMR spectrum (75 MHz): 15.52 (CH_3); 48.59 (CH_2); 115.74; 116.02; 123.74; 124.68; 130.53; 130.64; 133.27; 134.23; 146.21; 149.68; 157.87; 160.53; 163.911. LC/MS, *m/z*: 390 $[M]^+$. Found, %: N 14.42. $C_{21}H_{15}FN_4OS$. Calculated, %: N 14.35. M.w. 390.44.

6-(1*H*-Benzimidazol-2-yl)-3-(4-chlorobenzyl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one (5d). M.p. – 293-295°C. ^{1}H NMR spectrum: 2.88 (3H, s., CH_3); 5.17 (2H, s., CH_2); 7.22 (2H, m.); 7.41 (4H, m.); 7.59 (2H, m.); 8.69 (1H, s., CH); 12.62 (1H, br.s., NH). ^{13}C NMR spectrum (75 MHz): 15.51 (CH_3); 48.69 (CH_2); 123.74; 124.71; 129.04; 130.20; 132.93; 134.22; 136.06; 146.20; 149.71; 157.85; 163.93. LC/MS, *m/z*: 407 $[M+H]^+$. Found, %: N 13.98. $C_{21}H_{15}ClN_4OS$. Calculated, %: N 13.77. M.w. 406.90.

6-(1*H*-Benzimidazol-2-yl)-4-(benzyloxy)-5-methylthieno[2,3-*d*]pyrimidine 6. To 1 g of 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one **3a** add 12 ml of $POCl_3$, and boil the mixture for 5 h after formation of a clear transparent solution. Then pour the cool reaction mixture into the crashed ice, filter the precipitate formed and dry. To the solution of 1.1 ml of benzyl alcohol in 5 ml of DMF add 0.42 of 60% NaH suspension in mineral oil; stir the mixture until the complete liberation of hydrogen. To the solution of sodium benzylate obtained add the dried

chloro derivative. Stir the reaction mixture for 12 h at 50°C. Then dilute the reaction mixture with water and neutralize; filter the precipitate formed and dry. Boil a dry precipitate in hexane and filter hot. The further isolation of the product was performed by flash chromatography using silica gel (eluting with ethyl acetate). M.p. – 266-268°C. ^{1}H NMR spectrum: 2.90 (3H, s., CH_3); 5.65 (2H, s., CH_2); 7.12-7.80 (9H, m., Ar-H); 8.71 (1H, s., CH); 12.78 (1H, br.s., NH). LC/MS, *m/z*: 373 $[M+H]^+$. Found, %: N 15.27. $C_{21}H_{16}N_4OS$. Calculated, %: N 15.04. M. 372.45.

The study of the antimicrobial activity

According to the WHO recommendations [10,11] the following test-strains were used: *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Proteus vulgaris* ATCC 4636, *Bacillus subtilis* ATCC 6633, *Candida albicans* ATCC 653/885. The bacterial concentration was 10^7 CFU/ml (determined by McFarland standard). Overnight cultures kept for 18-24 h at 36°C±1°C were used. The bacterial suspension was inoculated onto the entire surface of Mueller-Hinton agar (Dagestan Research Institute of Nutrient Media). The compounds were introduced to the wells in the form of DMSO solution in the concentrations of 100 μg/ml; the open wells were filled with 0.3ml of the solution.

Conclusions

An effective one-step method for synthesis of 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones by interaction of 5-methyl-4-oxo-3,4-dihydrothieno[2,3-*d*]pyrimidine-6-carboxylic acid with *ortho*-pnenylediamines, using 1,1'-carbonyldiimidazole as a coupling-reagent has been developed. It has been proven that alkylation of 6-(1*H*-benzimidazol-2-yl)-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-one occurs at position 3 of the thieno[2,3-*d*]pyrimidine system and results in 6-(1*H*-benzimidazol-2-yl)-3-benzyl-5-methylthieno[2,3-*d*]pyrimidin-4(3*H*)-ones. The results of the antimicrobial activity study have shown that the presence of a benzyl substituent at position 3 of 6-(1*H*-benzimidazol-2-yl)-5-methylthieno [2,3-*d*]pyrimidin-4(3*H*)-one promotes the antimicrobial activity against the strains of *Escherichia coli*, *Proteus vulgaris*, *Pseudomonas aeruginosa* compared to 3-unsubstituted derivative.

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