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Synthesis of Some Derivatives of the 4H-pyrido[4',3':5,6] pyrano[2,3-d]pyrimidines

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ABSTRACT

An approach is proposed and methods for the synthesis of a series of derivatives of 4*H*-pyrido[4',3':5,6]pyrano[2,3-*d*]pyrimidine, in particular 4-*S*-alkylated products, which containing an alkyl- or arylamide moiety in their structure, for the microbiological screening.

Keywords: synthesis, 4H-pyrido[4',3'5,6]pyrano[2,3-d]pyrimidine, pyridoxal, biologically active compounds, pharmaceutical agents.

INTRODUCTION

The theoretical possibility of the synthesis of thousands substances with methods of combinatorial chemistry leads to an understanding of the need to implement rational pre-synthetic selection of the most promising compounds, depending on each specific aim. One the most successful and effective ways of solving this problem is a computer prediction of diverse properties of chemical compounds, which can be considered a tool for application of experiment planning. Intensive development of computer ADMET-technology helps to significantly reduce the risk of penetration of unwanted substances into the following stages of drug development, which can significantly save resources. Furthermore, the virtual database can be filtered using special QSAR models defining target-specific activity of substances[1,6].

Examples of structures with 4*H*-pyrido [4',3':5,6] pyrano [2,3-*d*] pyrimidine fragment are practically absent in the patent and scientific literature for now. However it should be expected that such compounds will have a high biological activity in analogy with substances containing these cycles or their isosteres in other combinations. For example, among bioisosteric analogues these cyclic systems are known substances with antibacterial, fungicidal, anti-allergic and anti-ulcer properties[7,9].

Taking into account the possible chemical diversity of synthetically available derivatives of 4*H*-pyrido[4',3':5,6]pyrano[2,3-*d*]pyrimidine, we have developed a chemical scheme for the preparation of *S*-alkylation products of 4*H*-pyrido[4',3':5,6] pyrano[2,3-*d*]pyrimidine-4-thiones, namely *N*-aryl/alkyl-2-(6-hydroxymethyl-9-methyl-2-aryl-5*H*-

pyrido[4',3':5,6]pyrimidin-4-ylsulfanyl)acetamides.

Purpose of the study

Development of the method of synthesis of some *S*-alkylation derivatives of 4*H*-pyrido[4',3':5,6] pyrano[2,3-*d*]pyrimidine-4-thiones and confirmation their structure.

MATERIALS AND METHODS

All solvents and reagents were obtained from the commercial sources. Elemental analysis was performed on an Euro EA-3000 apparatus. Melting points were obtained on a Buchi B-520 device. The NMR-spectra were recorded with a Bruker 170 Avance 500 spectrometer at 500 ÌHz (DMSO-d6); TMS was used as an internal standard; chemical shifts were reported in ppm. Analytical TLC was performed on silicagel plates Silufol UV_{254} (5 cm´15 cm) in the solvent system ethyl acetate - toluene (1: 1), ethyl acetate - toluene (1:2) ethyl acetate - hexane (1:2).

EXPERIMENTAL

Synthesis of 2-imino-5-hydroxymethyl-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-3-thiocarboxamide 2.

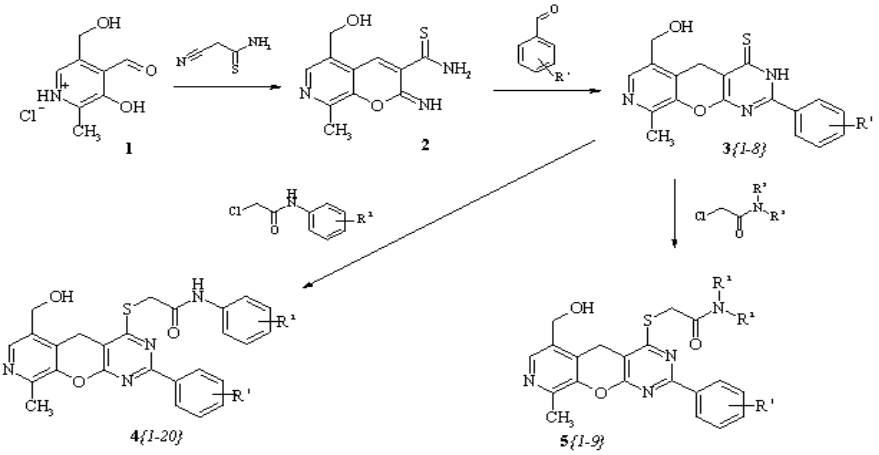
In 75 mL of absolute methanol was dissolved 10 mmol (1.00 g) thiocianoacetamide and to the boiling solution was added 10 mmol (2.04 g) of pyridoxal hydrochloride and 12 mmol (1.2 mL) of freshly distilled piperidine. The reaction mixture was under stirring gradually cooled. The resulting precipitate was filtered, washed with methanol (2 x 25 mL), water (2 x 100 mL) and used without further purification. Yield 80 %. Mp 213-14^{0}C. ^{2}R, cm^{-1}: 3410, 1645, 1608, 1420, 1003. ^{1}H-NMR, δ, ppm: 2.47 (s, 3H, CH_3), 4.67 (d, 2H, J = 7.2 Hz, CH_2), 5.43 (t, 1H, J = 5.7 Hz, OH), 8.22 (s, 1H, H), 8.92 (s, 1H, H-6), 9.41 (s, 1H, =NH), 10.40 (br.s, 1H, NH), 11.42 (br.s, 1H, NH). Anal. for $C_{11}H_{11}N_3O_2S$: calc. N, 16.86; S, 12.86; exp. N, 16.84; S, 12.8.

Synthesis of 2-aryl-6-hydroxymethyl-9-methyl-3,5-dihydro-4*H*-pirido[4',3':5,6] pyrano[2,3-*d*]pyrimidine-4-thiones 3.

To the 25 mL 1-pentanol was added 10 mmol (2.50 g) of 5-hydroxy-2-methyl-imino-8-methyl-2*H*-pyrano[2,3-*c*]pyridine-3-thiocarboxamide, 15 mmol of the corresponding aromatic aldehyde and 1 mmol (0.6 mL) of piperidine. The reaction mixture was refluxed for 10 minutes. The mixture was cooled to 60°C, was added 20 ml of methanol and 20 ml of water, was stirred until complete dissolution of the precipitate, and was added 1 mL of acetic acid. The resulting precipitate was filtered, washed with methanol (10 mL) and water (2x10 mL), crystallized from DMSO.

Synthesis of *N*-aryl-2-(6-hydroxymethyl-9-methyl-2-aryl-5*H*-pyrido[4',3':5,6]pyrano[2,3-*d*] pyrimidin-4-ilsulfanyl)acetamides 4.

A solution 5 mmol (0.28 g) of KOH in 10 mL methanol and 10 mL water was heated on a magnetic stirrer to 50°C and added to 2.5 mmol



Sch. 1: Synthesis of N-aryl/alkyl-2-(6-hydroxymethyl-9-methyl-2-aryl-5H-pyrido[4',3':5,6]pyrimidin-4-ylsulfanyl)acetamides

of the appropriate 6-hydroxymethyl-9-methyl-2-aryl-3,5-dihydro-4*H*-pyrido[4',3':5,6]pirano[2,3-*d*] pyrimidin-4-thione. To this solution was added a solution of 6 mmol of the corresponding 2-chloro-*N*-arylacetamide in 5 mL of methanol and stirring and heating for 30 minutes. The resulting precipitate was filtered, washed with methanol (2 x 5 mL), water (2 x 10 mL) and crystallized from DMF.

Table 1: 2-Aryl-6-hydroxymethyl-9-methyl-3,5-dihydro-4H-pyrido [4',3':5,6]pyrano[2,3-d]pyrimidine-4-thiones

Compound	R1	Mol. formula M.w.	Yield, %	M.p ., ˚C	N, % Calc.	N, % Exp.	S, % Calc.	S, % Exp.	1H-NMR-data, δ, ppm (DMSO, 200 MHz)
1	2	3	4	5	6		7		8
3*{1}*	H	$C_{18}H_{15}N_3O_2S$ 337.40	69	282-84	12.45	12.45	9.49	9.53	2.49 (s, 3H, CH_3), 3.82 (s, 2H, CH_2), 4.51 (d, 2H, CH_2), 5.28 (t, 1H, OH), 7.50–7.65 (m, 3H, Ar-H), 8.10 (dd, 2H, Ar-H), 8.14 (s, 1H, H-7), 14.10 (s, 1H, NH).
3*{2}*	4-F	$C_{18}H_{14}FN_3O_2S$ 335.39	69	291-93	11.82	11.82	9.01	9.00	2.48 (s, 3H, CH_3), 3.70 (s, 2H, CH_2), 4.45 (d, 2H, CH_2), 5.24 (t, 1H, OH), 7.36 (m, 3H, Ar-H), 8.11 (s, 1H, Ar-H) 8.16 (s, 1H, H-7), 12.40 (s, 1H, NH).
3*{3}*	2-Cl	$C_{18}H_{14}ClN_3O_2S$ 371.84	62	259	11.30	11.32	8.61	8.60	2.49 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 4.49 (d, 2H, CH_2), 5.30 (t, 1H, OH), 7.48-7.68 (m, 4H, Ar-H), 8.18 (s, 1H, H-7), 14.41 (s, 1H, NH).
3*{4}*	3-Cl	$C_{18}H_{14}ClN_3O_2S$ 371.84	80	265	11.30	11.33	8.61	8.64	2.49 (s, 3H, CH_3), 3.86 (s, 2H, CH_2), 4.50 (d, 2H, CH_2), 5.28 (t, 1H, OH), 7.57 (t, 1H, Ar-H), 7.70 (d, 1H, Ar-H), 8.04 (d, 1H, Ar-H), 8.16 (s, 1H, H-7), 8.19 (s, 1H, Ar-H), 14.25 (s, 1H, NH).
3*{5}*	4-Cl	$C_{18}H_{14}ClN_3O_2S$ 371.84	57	270	11.30	11.31	8.61	8.61	2.49 (s, 3H, CH_3), 3.92 (s, 2H, CH_2), 4.49 (d, 2H, CH2), 5.31 (t, 1H, OH), 7.48 (d, 2H, Ar-H), 7.78 (d, 2H, Ar-H), 8.18 (s, 1H, H-7), 13.21 (s, 1H, NH).
3*{6}*	4-Me	$C_{19}H_{17}N_3O_2S$ 351.42	78	268-69	11.96	11.99	9.11	9.10	2.37 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.61 (s, 2H, CH_2), 4.50 (d, 2H, CH_2), 5.25 (t, 1H, OH), 7.33 (d, 2H, Ar-H), 8.02 (d, 2H, Ar-H), 8.13 (s, 1H, H-7), 12.80 (s, 1H, NH).
3*{7}*	2-OMe	$C_{19}H_{17}N_3O_3S$ 367.42	79	266	11.44	11.45	8.71	8.71	2.43 (s, 3H, CH_3), 3.85 (s, 2H, CH_2), 3.92 (s, 3H, OCH_3), 4.52 (d, 2H, CH_2), 5.28 (t, 1H, OH), 7.12 (t, 1H, Ar-H), 7.22 (d, 1H, Ar-H), 7.58 (t, 1H, Ar-H), 7.76 (d, 1H, Ar-H), 8.16 (s, 1H, H-7), 13.53 (s, 1H, NH).
3*{8}*	4-OMe	$C_{19}H_{17}N_3O_3S$ 367.42	82	249 (dec)	11.44	1.42	8.71	8.72	2.40 (s, 3H, CH_3), 3.63 (s, 2H, CH_2), 3.83 (s, 3H, OCH_3), 4.48 (d, 2H, CH_2), 5.24 (t, 1H, OH), 7.03 (d, 2H, Ar-H), 8.08 (d, 2H, Ar-H), 8.11 (s, 1H, H-7), 12.61 (s, 1H, NH).

Table 2: N-Aryl-2-(6-hydroxymethyl-9-methyl-2-aryl-5H-pyrido[4',3':5,6] pyrano[2,3-d]pyrimidin-4-ylsulfanyl)acetamides

Compound	R1	R2	Mol. formula M.w.	Yield, %	M.p., ˚C	1H-NMR-data, δ, ppm (DMSO, 200 MHz)
1	2	3	4	5	6	7
4*{1}*	H	H	$C_{26}H_{22}N_4O_3S$ 470.55	83	298-99	2.49 (s, 3H, CH_3), 3.95 (s, 2H, CH_2),4.30 (s, 2H, CH_2), 4.57 (d, 2H, CH_2), 5.34 (t, 1H, OH), 7.03 (m, 1H, Ar-H), 7.31 (m, 4H, Ar-H),7.44 (m, 1H, Ar-H), 7.63 (d, 2H, Ar-H), 8.18 (s, 1H, H-7), 8.33 (d, 2H, Ar-H), 10.50 (s, 1H, NH).
4*{2}*	H	2-F	$C_{26}H_{21}FN_4O_3S$ 488.54	49	306-07	2.50 (s, 3H, CH_3), 3.97 (s, 2H, CH_2), 4.42 (s, 2H, CH_2), 4.58 (d, 2H, CH_2),5.35 (t, 1H, OH), 7.12 (m, 2H, Ar-H), 7.30 (m, 1H, Ar-H), 7.44 (m, 3H, Ar-H), 7.92 (m, 1H, Ar-H), 8.17 (s, 1H, H-7), 8.38 (m, 2H, Ar-H), 10.50 (s, 1H, NH).
4*{3}*	H	3-Cl	$C_{26}H_{21}ClN_4O_3S$ 505.00	61	291-93	2.51 (s, 3H, CH_3), 3.97 (s, 2H, CH_2) ,4.30 (s, 2H, CH_2), 4.58 (d, 2H, CH_2), 5.34 (t, 1H, OH), 7.11 (m, 1H, Ar-H), 7.34 (m, 2H, Ar-H), 7.46 (m, 3H, Ar-H), 7.82 (m, 1H, Ar-H), 8.18 (s, 1H, H-7) , 8.32 (d, 2H, Ar-H), 10.70 (s, 1H, NH).
4*{4}*	H	4-Cl	$C_{26}H_{21}ClN_4O_3S$ 505.00	59	>300	2.50 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 4.58 (d, 2H, CH_2), 5.34 (t, 1H, OH), 7.35 (d, 4H, Ar-H), 7.46 (m, 1H, Ar-H), 7.66 (d, 2H, Ar-H), 8.18 (s, 1H, H-7), 8.32 (d, 2H, Ar-H), 10.65 (s, 1H, NH).
4*{5}*	4-F	3-Me	$C_{27}H_{23}FN_4O_3S$ 502.57	59	318-19	2.26 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 4.58 (d, 2H, CH_2), 5.35 (t, 1H, OH), 6.86 (d, 1H, Ar-H), 7.12 (t, 1H, Ar-H), 7.18 (t, 2H, Ar-H), 7.40 (d, 1H, Ar-H), 7.45 (s, 1H, Ar-H), 8.17 (s, 1H, H-7), 8.37 (dd, 2H, Ar-H), 10.91 (s, 1H, NH).
4*{6}*	4-F	4-Me	$C_{27}H_{23}FN_4O_3S$ 502.57	70	325	2.24 (s, 3H, CH_3), 2.51 (s, 3H, CH_3) ,3.99 (s, 2H, CH_2), 4.31 (s, 2H, CH_2), 4.60 (d, 2H, CH_2), 5.35 (t, 1H, OH), 7.11 (dd, 2H, Ar-H), 7.16 (m, 2H, Ar-H), 7.50 (d, 2H, Ar-H), 8.16 (s, 1H, H-7), 8.40 (dd, 2H, Ar-H), 10.38 (s, 1H, NH).
4*{7}*	4-F	2,6-diMe	$C_{28}H_{25}FN_4O_3S$ 516.60	63	306	2.00 (s, 6H, $2CH_3$), 2.49 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 4.40 (s, 2H, CH_2), 4.56 (d, 2H, CH_2), 5.35 (t, 1H, OH), 7.01 (m, 3H, Ar-H), 7.31 (t, 2H, Ar-H), 8.16 (s, 1H, H-7), 8.48 (dd, 2H, Ar-H),

					9.58 (s, 1H, NH).
4*{8}*	4-F3,4-diMe	$C_{28}H_{25}FN_4O_3S$ 516.60	74	316	2.17 (s, 6H, $2CH_3$), 2.49 (s, 3H, CH_3) ,3.95 (s, 2H, CH_2), 4.28 (s, 2H, CH_2), 4.56 (d, 2H, CH_2), 5.31 (t, 1H, OH), 7.04 (d, 1H, Ar-H), 7.15 (t, 2H, Ar-H), 7.31 (d, 1H, Ar-H), 7.36 (s, 1H, Ar-H), 8.16 (s, 1H, H-7), 8.40 (dd, 2H, Ar-H), 10.27 (s, 1H, NH).
4*{9}*	4-F3,5-diMe	$C_{28}H_{25}FN_4O_3S$ 516.60	70	326	2.18 (s, 6H, $2CH_3$), 2.47 (s, 3H, CH_3), 3.94 (s, 2H, CH_2), 4.36 (s, 2H, CH_2), 4.57 (d, 2H, CH_2), 5.31 (t, 1H, OH), 6.68 (s, 1H, Ar-H), 7.12 (t, 2H, Ar-H),

Table 3: N,N-Alkyl-2-(6-hydroxymethyl-9-methyl-2-aryl-5H-pyrido[4',3':5,6] pyrano[2,3-d]pyrimidin-4-ylsulfanyl)acetamides

Compound	R^1	R^2, R^2	Mol. formula M.w.	Yield, %	M.p., ˚C	1H-NMR-data, δ, ppm (DMSO, 200 MHz)
1	**2**	**3**	**4**	**5**	**6**	**7**
5*{1}*	H	Et	$C_{24}H_{26}N_4O_3S$ 450.56	76	203	1.05 (t, 3H, CH_2CH_3), 1.25 (t, 3H, CH_2CH_3), 2.50 (s, 3H, CH_3), 3.32 (q, 2H, CH_2CH_3), 3.54 (q, 2H, CH_2CH_3), 3.95 (s, 2H, CH_2), 4.44 (s, 2H, CH_2), 4.57 (d, 2H, CH_2), 5.35 (t, 1H, OH), 7.52 (m, 3H, Ar-H), 8.16 (s, 1H, H-7), 8.30 (m, 2H, Ar-H).
5*{2}*	H	-(CH2)5-	$C_{26}H_{26}N_4O_3S$ 462.57	65	247-48	1.49 (br.s, 2H, CH_2), 1.64 (br.s, 4H, $2CH_2$), 2.47 (s, 3H, CH_3), 3.44 (t, 2H, CH_2), 3.57 (br.s, 2H, CH_2), 3.87 (s, 2H, CH_2), 4.38 (s, 2H, CH_2),4.54 (d, 2H, CH_2), 5.33 (t, 1H, OH), 7.50 (m, 3H, Ar-H), 8.14 (s, 1H, H-7), 8.30 (m, 2H, Ar-H).
5*{3}*	H	-(CH2)2-O-(CH2)2-	$C_{24}H_{24}N_4O_4S$ 464.55	61	252-53	2.48 (s, 3H, CH_3), 3.46 (d, 2H, CH_2), 3.57 (d, 2H, CH_2), 3.66 (s, 4H, $2CH_2$), 3.92 (s, 2H, CH_2), 4.43 (s, 2H, CH_2), 4.55 (d, 2H, CH_2), 5.32 (t, 1H, OH), 7.53 (m, 3H, Ar-H), 8.16 (s, 1H, H-7), 8.32 (m, 2H, Ar-H).
5*{4}*	4-F	Et	$C_{24}H_{25}FN_4O_3S$ 468.54	63	207	1.00 (t, 3H, CH_2CH_3), 1.21 (t, 3H, CH_2CH_3), 2.49 (s, 3H, CH_3), 3.32 (q,2H, CH_2CH_3), 3.51 (q, 2H, CH_2CH_3), 3.90 (s, 2H, CH_2), 4.37 (s, 2H,

						CH_2), 4.54 (d, 2H, CH_2), 5.32 (t, 1H, OH), 7.32 (t, 2H, Ar-H), 8.14 (s, 1H, H-7), 8.32 (dt, 2H, Ar-H).
5*{5}*	4-F	-(CH2)5-	$C_{24}H_{25}FN_4O_3S$ 480.56	57	215	1.45 (br.s, 2H, CH_2), 1.60 (br.s, 4H, $2CH_2$), 2.47 (s, 3H, CH_3), 3.44 (t, 2H,CH_2), 3.59 (br.s, 2H, CH_2), 3.90 (s, 2H, CH_2), 4.40 (s, 2H, CH_2), 4.55 (d, 2H, CH_2), 5.31 (t, 1H, OH), 7.32 (t, 2H, Ar-H), 8.14 (s, 1H, H-7), 8.36 (m, 2H, Ar-H).
5*{6}*	4-F	-(CH2)2-O-(CH2)2-	$C_{24}H_{23}FN_4O_4S$ 482.53	56	244	2.46 (s, 3H, CH_3), 3.43 (d, 2H, CH_2), 3.54 (d, 2H, CH_2), 3.64 (s, 4H, $2CH_2$), 3.90 (s, 2H, CH_2), 4.40 (s, 2H, CH_2), 4.53 (d, 2H, CH_2), 5.32 (t, 1H, OH), 7.32 (t, 2H, Ar-H), 8.14 (s, 1H, H-7), 8.35 (dt, 2H, Ar-H).
5*{7}*	4-OMe	Et	$C_{25}H_{28}N_4O_4S$ 480.59	63	258-59	1.02 (t, 3H, CH_2CH_3), 1.24 (t, 3H, CH2CH_3), 2.49 (s, 3H, CH_3), 3.31 (q, 2H, CH_2CH_3), 3.52 (q, 2H, CH_2CH_3), 3.80 (s, 3H, OCH_3), 3.87 (s, 2H, CH_2), 4.37 (s, 2H, CH_2), 4.58 (d, 2H, CH_2), 5.32 (t, 1H, OH), 7.02 (d, 2H, Ar-H), 8.13 (s, 1H, H-7), 8.22 (d, 2H, Ar-H).
5*{8}*	4-OMe	-(CH2)5-	$C_{26}H_{26}N_4O_3S$ 462.57	65	247-48	1.45 (br.s, 2H, CH_2), 1.64 (br.s, 4H, $2CH_2$), 2.49 (s, 3H, CH_3), 3.45 (t, 2H, CH_2), 3.57 (br.s, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.87 (s, 2H, CH_2), 4.37 (s, 2H, CH_2), 4.52 (d, 2H, CH_2), 5.33 (t, 1H, OH), 7.02 (d, 2H, Ar-H),]8.14 (s, 1H, H-7), 8.25 (d, 2H, Ar-H).
5*{9}*	4-OMe	-(CH2)2-O-(CH2)2-	$C_{25}H_{26}N_4O_5S$ 494.57	62	288-90	2.48 (s, 3H, CH_3), 3.47 (m, 2H, CH_2), 3.56 (m, 2H, CH_2), 3.65 (s, 4H, $2CH_2$), 3.82 (s, 3H, OCH_3), 3.85 (s, 2H, CH_2), 4.38 (s, 2H, CH_2), 4.52 (d,2H, CH_2), 5.33 (t, 1H, OH), 7.00 (d, 2H, Ar-H), 8.13 (s, 1H, H-7), 8.24 (d,2H, Ar-H).

Synthesis of *N,N*-alkyl-2-(6-hydroxymethyl-9-methyl-2-aryl-5*H*-pyrido[4',3':5,6]pyrano[2,3-*d*]pyrimidin-4-ilsulfanyl)acetamides 5.

A solution 5 mmol (0.28 g) of KOH in 10 mL methanol and 10 mL water was heated on a magnetic stirrer to 50°C and added to 2.5 mmol of the appropriate 6-hydroxymethyl-9-methyl-2-aryl-3,5-dihydro-4*H*-pyrido[4',3':5,6]pirano[2,3-*d*] pyrimidin-4-thione. To this solution was added a solution of 6 mmol of the corresponding 2-chloro-*N,N*-dialkylacetamide in 5 mL of methanol and stirring and heating for 30 minutes. The resulting precipitate was filtered, washed with methanol (2 x 5 mL), water (2 x 10 mL) and crystallized from DMF.

RESULTS AND DISCUSSION

As starting reagent was choose pyridoxal hydrochloride - heteroanalogue of salycilic

aldehyde. The first stage of proposed scheme is synthesis of 2-imino-5-hydroxymethyl-8-methyl-2H-pyrano[2,3-c]pyridine-3-thiocarboxamide 2 by Knoevenagel reaction - interaction pyridoxal 1 with thiocyanoacetamide. The reaction was conducted in 2-propanol in the presence of catalytic amounts of piperidine10 (Scheme 1).

A systematic series of 2-aryl-6-hydroxymethyl-9-methyl-3,5-dihydro-4H-pyrido[4',3':5,6]pyrano[2,3-d]pyrimidine-4-thiones 3*{1-8}* obtained by condensation of thioamide 2 with aromatic aldehydes in the presence of piperidine. The reaction was proceeded for 5-10 minutes; the yield is 62 - 83 %. 1H NMR spectrum of compounds 3{1-8} are characterized by a singlet signal at the methylene group δ ppm 3.61 ... 3.90 (2H, CH2), NH singlet signal at δ 12.40 ... 14.41 ppm, the resonance signals of methylene fragment (doublet at δ 4.45 ... 4.52 ppm), hydroxyl (triplet at δ 5.24 ... 5.30 ppm) and methyl groups (singlet at δ 2.40 ... 2.50 ppm) (Table 1).

In the 13C-NMR spectrum of the substances 3 there are signals of carbon atom of C = S groups at δ 184 ppm, which confirms the structure dihydropyrimidine for these products.

S-Alkylation compounds 3 were carried out by action of 2-chloro-N-arylacetamides with various substituents in the benzene ring. The reaction was carried out by heating the starting reagents in methanol to obtain the final products 4*{1-20}* (Table 2).

Particular interests from the point of view of medical chemistry are polycyclic structures containing as a substituent alkyl radicals with a tert-amino group. This can increase the lipophilicity of the final products, or obtain water-soluble forms (salt-formation). Therefore, we also carried out the S-alkylation reaction of thiones 3 using 2-chloro-N,N-dialkylacetamides, both linear and cyclic. As a result, the corresponding N,N-alkyl-2-(6-hydroxymethyl-9-methyl-2-aryl-5H-pyrido[4',3':5,6]pyrano[2,3-d] pyrimidin-4-ylsulfanyl)acetamides 5*{1-9}* were obtained (Table 3).

The structures all of obtained compounds were confirmed using 1H and 13C NMR-spectroscopic methods. Further, synthesized compounds will be tested as antifungal agents.

CONCLUSIONS

The method of synthesis of series new derivatives of 2-(6-hydroxymethyl-9-methyl-2-aryl-5H-pyrido[4',3':5,6]pyrano[2,3-d]pyrimidin-4-ylsulfanyl)acetamides has been developed. They are of great interest for further biological screening in order to find substances among them with antifungal properties.

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