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SYNTHESIS OF 2,6-SUBSTITUTED 4-(N-ARYLPIPERAZIN-1-YL)PYRIMIDINES AS POTENTIAL ANTICONVULSANTS

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Summary: A series of novel 2,6-substituted 4-(N-arylpiperazin-1-yl)pyrimidines was obtained by interaction of 2,6-R-chloropyrimidines with N-arylsubstituted piperazines. The structure of synthesized compounds was confirmed by ^{1}H NMR and mass spectroscopy. The investigation of pharmacological screening data revealed that the tested compounds show moderate anticonvulsant activity.

Keywords: synthesis, pyrimidine-4(3H)-one, piperazine, anticonvulsant activity.

Introduction. Currently, oxopyrimidines attract a great interest as potent therapeutic agents for treatment of the large number of diseases including neuropsychiatric disorders. It was found that pyrimidine receptors in the brain have an affinity for almost all groups of psychotropic drugs. The data of previous studies of neuropharmacological properties of pyrimidine derivatives allow to consider them as ligands to the intracentral receptors of psychotropic agents[1,6]. Continuing our research on the synthesis of pyrimidine-4(3H)-one derivatives as novel anticonvulsants we analyzed the results of investigations in this field to expand the range of search the substituent's possessing pronounced psychotropic activity. The findings had proved that drugs containing piperazine moiety have affinity to serotonin receptors and exhibit remarkable anxiolytic and antidepressant activity.[7,8] Therefore, the synthesis of new pyrimidine-4(3H)-one derivatives associated with piperazine ring is presently perspective and significant for development of novel psychotropic drugs.

The aim of the research. Synthesis of novel 2,6-substituted 4-(N-arylpiperazin-1-yl)pyrimidine derivatives and investigation of their anticonvulsant activity.

Materials and methods. Melting points were determined in capillaries method. ^{1}H NMR spectra were recorded on Varian Mercury-VX-200 using tetramethylsilane (TMS) as an internal standard and DMSO-*d6* as a solvent. Chemical shifts are given in parts per million (ppm). Mass spectra were recorded on PE SCIEX API 150EX. Elemental analysis of Nitrogen content was performed by Duma's method.

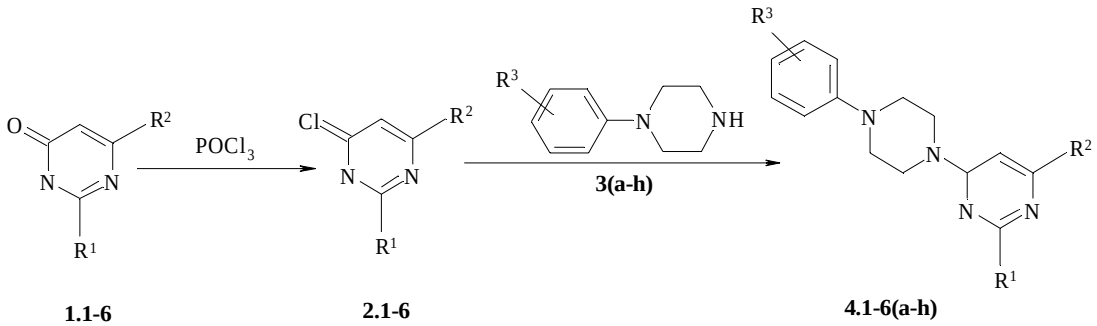
Results of the research and discussion. The initial pyrimidine-4(3H)-ones **1.1-6** were obtained according to the known procedure described previously.[3,4] By halogenation of initial oxopyrimidines 2,6-R-4-chloropyrimidines **2.1-6** were synthesized. For this purpose phosphoryl chloride, phosphorus pentachloride and their mixture are usually used in the presence of tertiary amines.[5] In our study 2,6-substituted 4-chloropyrimidines were synthesized by boiling the corresponding oxopyrimidines with phosphoryl chloride for 5 hours (scheme 1.). The products of reactions were obtained with satisfactory yields of 50–70%.

As outlined in scheme 1 further aminolysis of 2,6-R-4-chloropyrimidines gave a series of target 2,6-substituted derivatives of 4-(N-arylpiperazin-1-yl)pyrimidine.

According to data of previous reports aminolysis is usually performed on boiling with excess of piperazine derivatives using suitable solvents in the presence of organic and inorganic bases.[2,9-10] Taking into account the conditions of performing of reaction in present research we obtained the final products **4.1-6(a-h)** by treating of 2,6-substituted 4-chloropyrimidines with corresponding N-arylsubstituted piperazine derivatives **3(a-h)**.

As outlined in scheme 1 further aminolysis of 2,6-R-4-chloropyrimidines gave a series of target 2,6-substituted derivatives of 4-(N-arylpiperazin-1-yl)pyrimidine.

Scheme 1.



1.1-6 **2.1-6** **4.1-6(a-h)**

1.1, 2.1, 4.1: R^1=Ph; 1.2, 2.2, 4.2: R^1=4-MePh; 1.3, 2.3, 4.3: R^1=4-ClPh; 1.4, 2.4, 4.4 R^1=3-FPh; 1.5, 2.5, 4.5: R^1=4-FPh; 1.6, 2.6, 4.6: R^1=Me. 1.1-5, 2.1-5: R^2=Me; 1.6, 2.6: R^2=pyridine. R^3: a=3-Me; b=4-F; c=4-OMe; d=3-Cl; e=2,5-diMe; f=H; g=4-Cl; h=4-$COCH_3$.

According to data of previous reports aminolysis is usually performed on boiling with excess of piperazine derivatives using suitable solvents in the presence of organic and inorganic bases.[2,9-10] Taking into account the conditions of performing of reaction in present research we obtained the final products **4.1-6(a-h)** by treating of 2,6-substituted 4-chloropyrimidines with corresponding N-arylsubstituted piperazine derivatives **3(a-h)**.

Reaction was carried out on boiling in dioxane for 3–5 hours with addition of sodium bicarbonate. The yields of reaction products were 60–80%.

Table 1. **Characterizations of synthesized compounds**

Compound	Yeald, %	M.p., C°	Calcul. N, %	Found N, %	Formula	[MH+]
2.1	61	75-77	13,69	13,72	$C_{11}H_9ClN_2$	–
2.2	50	84-86	12,81	12,86	$C_{12}H_{11}ClN_2$	–
2.3	57	70-72	11,72	11,75	$C_{11}H_8Cl_2N_2$	–
2.4	70	84-86	12,58	12,63	$C_{11}H_8ClFN_2$	224
2.5	63	70-72	10,27	10,32	$C_{12}H_8ClF_3N_2$	–
2.6	60	77-79	20,43	20,49	$C_{10}H_8ClN_3$	207
4.1.a	62	95-97	16,27	16,31	$C_{22}H_{24}N_4$	–
4.1.b	69	106-108	16,08	16,15	$C_{21}H_{21}FN_4$	349
4.2.c	73	140-142	14,96	14,99	$C_{23}H_{26}N_4O$	–
4.3.c	60	151-153	14,71	14,76	$C_{22}H_{23}ClN_4O$	–
4.3.d	76	128-130	14,54	14,57	$C_{21}H_{20}Cl_2N_4$	400
4.4.a	75	82-84	15,46	15,52	$C_{22}H_{23}FN_4$	–
4.4.b	66	100-102	15,29	15,33	$C_{21}H_{20}F_2N_4$	–
4.4.d	77	109-111	14,63	14,66	$C_{21}H_{20}ClFN_4$	384
4.4.e	71	107-109	15,46	15,51	$C_{23}H_{25}FN_4$	–
4.5.b	70	136-138	13,45	13,49	$C_{22}H_{20}F_3N_4$	–
4.5.c	67	153-155	13,08	13,13	$C_{23}H_{23}F_3N_4O$	–
4.5.d	69	109-111	12,94	12,98	$C_{22}H_{20}ClF_3N_4$	–
4.5.f	72	122-124	14,06	14,11	$C_{22}H_{21}F_3N_4$	399
4.5.g	79	176-178	12,94	12,97	$C_{22}H_{20}ClF_3N_4$	–
4.5.h	74	174-176	12,72	12,77	$C_{24}H_{23}F_3N_4O$	–
4.6.a	79	102-104	20,27	20,33	$C_{21}H_{23}N_5$	346
4.6.c	73	134-136	19,38	19,42	$C_{21}H_{23}N_5O$	–
4.6.d	75	170-172	19,14	19,18	$C_{20}H_{20}ClN_5$	–
4.6.f	80	149-151	21,13	21,19	$C_{20}H_{21}N_5$	–

The purity of the products was proved by TLC. The structures of compounds listed in the table above were confirmed by ^{1}H NMR and mass spectrometry. ^{1}H NMR spectra of compounds **2.1-6** are characterized by the presence of all characteristic signals of protons: singlet signals of CH_3 protons and signals of aryl protons. A singlet CH-5 proton signal of **2.1-6** compounds shifts to lower field region (7,43–8,40 ppm) in comparison with initial pyrimidinones **1.1-6 (**6,15–6,25 ppm).[4] ^{1}H NMR spectra of compounds **4.1-6(a-h)** showed two triplet signals in the range of δ 3,07 ppm to 3,88 ppm due to the presence of piperazine ring protons.

The preliminary prognosis of pharmacological activity of substances was performed by PASS programme. According to its data substances have a high probability of manifestation of anxiolytic, antidepressant, sedative and anticonvulsant activity (activity index of the synthesized compounds is in the range from 0,528 to 0,884).

Based on preliminary prediction of pharmacological activity investigated compounds were tested for an anticonvulsant activity in pentylenetetrazole test. It was found that compounds exhibit moderate anticonvulsant properties comparable to standart drug lamotrigine.

Experimental section. *General procedure of synthesis of 2,6-substituted 4-chloropyrimidine derivatives* ***2.1-6.*** 0,01 mole of pyrimidine-4(3H)-one derivative **1.1-6** is heated in excess of phosphoryl chloride during 5 hours. The solution is dissolved in water with ice. The precipitate is filtered.

General procedure of synthesis of 2,6-R-4-(N-arylpiperazin-1-yl)pyrimidines ***4.1-6(a-h)***. A mixture of 0,01 mole of respective 2,6-substituted 4-chloropyrimidine **2.1-6** and 0,015 mole of appropriate N-arylpiperazine **3(a-h)** is heated in dioxane during 3–5 hours in the presence of sodium bicarbonate. The reaction mixture is diluted with water and then it is subjected for filtration and recrystallization from ethanol.

^{1}H-NMR DMSO-d_6 (ppm):

4–Chloro–6–methyl–2–phenylpyrimidine (2.1): 2,52 (s, 3H, CH_3), 7,43-7,57 (m, 4H, Ar, CH-5), 8,25-8,38 (m, 2H, Ar).

4-Chloro-2-(4-methylphenyl)-6-methylpyrimidine (2.2): 2,25 (s, 3H, CH_3), 2,34 (s, 3H, CH_3), 7,21 (d, 2H, Ar), 8,10-8,25 (м, 3H, Ar, CH-5).

4-Chloro-2-(4-chlorophenyl)-6-methylpyrimidine (2.3): 2,28 (s, 3H, CH_3), 7,46 (d, 2H, Ar), 8,20-8,40 (мм, 3H, Ar, CH-5).

4-Chloro-2-(3-flurophenyl)-6-methylpyrimidine (2.4): 2,50 (s, 3H, CH_3), 7,20-7,42 (m, 1H, Ar), 7,44-7,63 (m, 2H, Ar, CH-5), 7,85-8,05 (m, 1H, Ar), 8,15 (d, 1H, Ar).

4-Chloro-6-methyl-2-[4-(trifluoromethyl) phenyl]pyrimidine (2.5): 2,52 (s, 3H, CH_3), 7,57 (s, 1H, CH-5), 7,85 (d, 2H, Ar), 8,45 (d, 1H, Ar).

4-Chloro-2-methyl-6-(pyridin-2-yl)pyrimidine (2.6): 2,65 (s, 3H, CH_3), 7,52-7,63 (m, 1H, Ar), 7,93-8,04 (m, 1H, Ar), 8,11 (s, 1H, CH-5), 8,37 (d, 1H, Ar), 8,35 (d, 1H, Ar), 8,71 (d, 1H, Ar).

6-Methyl-4-[4-(3-methylphenyl)piperazin-1-yl]-2-phenylpyrimidine (4.1.a): 2,23 (s, 3H, CH_3), 2,34 (s, 3H, CH_3), 3,26 (t, 4H, $2CH_2$), 3,83 (t, 4H, $2CH_2$), 6,57-6,85 (m, 4H, Ar, CH-5), 7,04-7,16 (t, 1H, Ar), 7,39-7,5 (m, 3H, Ar), 8,28-8,39 (m, 2H, Ar).

4–[4–(Fluorophenyl)piperazin–1–yl]–6-methyl-2-phenylpyrimidine (4.1.b): 2,34 (s, 3H, CH_3), 3,17 (t, 4H, $2CH_2$), 3,84 (t, 4H, $2CH_2$), 6,7 (s, 1H, CH-5), 6,95-7,13 (m, 4H, Ar), 7,39-7,54 (m, 3H, Ar), 8,27-8,41 (m, 2H, Ar).

4–[4–(Methoxyphenyl)piperazin–1–yl]-2-(4-methylphenyl)-6-methylpyrimidine (4.2.c): 2,33 (s, 6H, $2CH_3$), 3,07 (t, 4H, $2CH_2$), 3,67 (s, 3H, OCH_3), 3,83 (t, 4H, $2CH_2$), 6,67 (s, 1H, CH-5), 6,83 (d, 2H, Ar), 6,95 (d, 2H, Ar), 7,24 (d, 2H, Ar), 8,23 (d, 2H, Ar).

2-(4-Chlorophenyl)-4-[4-(4-methoxyphenyl) piperazin-1-yl]-6-methylpyrimidine (4.3.c): 2,35 (s, 3H, CH_3), 3,08 (t, 4H, $2CH_2$), 3,65 (s, 3H, OCH_3), 3,82 (t, 4H, $2CH_2$), 6,71 (s, 1H, CH-5), 6,82 (d, 2H, Ar), 6,95 (d, 2H, Ar), 7,5 (d, 2H, Ar), 8,34 (d, 2H, Ar).

2–(4–Chlorophenyl)–4–[4–(3-chlorophenyl) piperazin-1-yl]-6-methylpyrimidine (4.3.d): 2,34 (s, 3H, CH_3), 3,28 (t, 4H, $2CH_2$), 3,85 (t, 4H, $2CH_2$), 6,68-6,86 (m, 2H, Ar, CH-5), 6,88-7,03 (m, 2H, Ar), 7,16-7,29 (t, 1H, Ar), 7,49 (d, 2H, Ar), 8,33 (d, 2H, Ar).

2–(3–Fluorophenyl)–4–[4-(3-methylphenyl) piperazin-1-yl]-6-methylpyrimidine (4.4.a): 2,23 (s, 3H, CH_3), 2,35 (s, 3H, CH_3), 3,2 (t, 4H, $2CH_2$), 3,83 (t, 4H, $2CH_2$), 6,6 (d, 1H, Ar, CH-5), 6,77 (d, 3H, Ar), 7,05-7,17 (t, 1H, Ar), 7,21-7,35 (m, 1H, Ar), 7,42-7,57 (m, 1H, Ar), 8,02 (m, 1H, Ar), 8,18 (d, 1H, Ar).

2–(3–Fluorophenyl)–4–[4–(4–fluorophenyl) piperazin-1-yl]-6-methylpyrimidine (4.4.b): 2,34 (s, 3H, CH_3), 3,16 (t, 4H, $2CH_2$), 3,83 (t, 4H, $2CH_2$), 6,74 (s, 1H, CH-5), 6,94-7,13 (m, 4H, Ar), 7,21-7,35 (m, 1H, Ar), 7,43-7,6 (m, 1H, Ar), 8,03 (m, 1H, Ar), 8,17 (d, 1H, Ar).

4-[4-(3-Chlorophenyl)piperazin-1-yl]-2-(3-fluorophenyl)-6-methylpyrimidine (4.4.d): 2,35 (s, 3H, CH_3), 3,3 (t, 4H, $2CH_2$), 3,83 (t, 4H, $2CH_2$), 6,68-6,84 (m, 2H, Ar, CH-5), 6,87-7,00 (m, 2H, Ar), 7,16-7,35 (m, 2H, Ar), 7,43-7,57 (m, 1H, Ar), 8,03 (m, 1H, Ar), 8,17 (d, 1H, Ar).

4-[4-(2,5-Dimethylphenyl)piperazin-1-yl]-2-(3-fluorophenyl)-6-methylpyrimidine (4.4.e): 2,22 (s, 6H, $2CH_3$), 2,35 (s, 3H, CH_3), 2,88 (t, 4H, $2CH_2$), 3,82 (t, 4H, $2CH_2$), 6,7-6,87 (m, 3H, Ar, CH-5), 7,05 (d, 1H, Ar), 7,21-7,35 (m, 1H, Ar), 7,41-7,56 (m, 1H, Ar), 8,03 (m, 1H, Ar), 8,18 (d, 1H, Ar).

4-[4-(4-Fluorophenyl)piperazin-1-yl]-6-methyl-2-[4-(trifluoromethyl)phenyl]pyrimidine (4.5.b): 2,37 (s, 3H, CH_3), 3,17 (t, 4H, $2CH_2$), 3,85 (t, 4H, $2CH_2$), 6,78 (s, 1H, CH-5),

6,96-7,15 (m, 4H, Ar), 7,81 (d, 2H, Ar), 8,51 (d, 2H, Ar).

4-[4-(4-Methoxyphenyl)piperazin-1-yl]-6-methyl-2-[4-(trifluoromethyl)phenyl]pyrimidine (4.5.c): 2,36 (s, 3H, CH_3), 3,10 (t, 4H, $2CH_2$), 3,66 (s, 3H, OCH_3), 3,85 (t, 4H, $2CH_2$), 6,75-6,88 (m, 3H, Ar, CH-5), 6,95 (m, 2H, Ar), 7,81 (d, 4H, Ar), 8,52 (d, 2H, Ar).

4-[4-(3-Chlorophenyl)piperazin-1-yl]-6-methyl-2-[4-(trifluoromethyl)phenyl]pyrimidine (4.5.d): 2,37 (s, 3H, CH_3), 3,24 (t, 4H, $2CH_2$), 3,85 (t, 4H, $2CH_2$), 6,74-6,84 (m, 2H, Ar, CH-5), 6,89-7,04 (m, 2H, Ar), 7,18-7,27 (t, 1H, Ar), 7,82 (d, 1H, Ar), 8,52 (d, 2H, Ar).

6-Methyl-4-(4-phenylpiperazin-1-yl)-2-[4-(trifluoromethyl)phenyl]pyrimidine (4.5.f): 2,35 (s, 3H, CH_3), 3,25 (t, 4H, $2CH_2$), 3,87 (t, 4H, $2CH_2$), 6,71-6,86 (m, 2H, Ar, CH-5), 6,98 (d, 2H, Ar), 7,16-7,3 (m, 2H, Ar), 7,83 (d, 2H, Ar), 8,52 (d, 2H, Ar).

4-[4-(4-Chlorophenyl)piperazin-1-yl]-6-methyl-2-[4-(trifluoromethyl)phenyl]pyrimidine (4.5.g): 2,36 (s, 3H, CH_3), 3,27 (t, 4H, $2CH_2$), 3,85 (t, 4H, $2CH_2$), 6,78 (s, 1H, CH-5), 6,99 (d, 2H, Ar), 7,25 (d, 2H, Ar), 7,81 (d, 2H, Ar), 8,52 (d, 2H, Ar).

4-[4-(4-Acetylphenyl)piperazin-1-yl]-6-methyl-2-[4-(trifluoromethyl)phenyl]pyrimidine (4.5.h): 2,37 (s, 3H, CH_3), 2,45 (s, 3H, $COCH_3$), 3,51 (t, 4H, $2CH_2$), 3,87 (t, 4H, $2CH_2$), 6,76 (s, 1H, CH-5), 7,00 (d, 2H, Ar), 7,82 (d, 4H, Ar), 8,52 (d, 2H, Ar).

2-Methyl-4-[4-(3-methylphenyl)piperazin-1-yl]-6-(pyridin-2-yl)pyrimidine (4.6.a): 2,25 (s, 3H, CH_3), 2,45 (s, 3H, CH_3), 3,25 (t, 4H, $2CH_2$), 3,81 (t, 4H, $2CH_2$), 6,61 (m, 1H, Ar), 6,7-6,83 (m, 2H, Ar), 7,04-7,16 (t, 1H, Ar), 7,43-7,57 (m, 2H, Ar, CH-5), 7,87-8,00 (m, 1H, Ar), 8,33 (d, 1H, Ar), 8,68 (m, 1H, Ar).

4-[4-(4-Methoxyphenyl)piperazin-1-yl]-2-methyl-6-(pyridin-2-yl)pyrimidine (4.6.c): 2,48 (s, 3H, CH_3), 3,17 (t, 4H, $2CH_2$), 3,67 (s, 3H, OCH_3), 3,81 (t, 4H, $2CH_2$), 6,83 (m, 2H, Ar), 6,94 (m, 2H, Ar), 7,44-7,56 (m, 2H, Ar, CH-5), 7,87-7,97 (m, 1H, Ar), 8,33 (d, 1H, Ar), 8,68 (m, 1H, Ar).

4-[4-(3-Chlorophenyl)piperazin-1-yl]-2-methyl-6-(pyridin-2-yl)pyrimidine (4.6.d): 2,49 (s, 3H, CH_3), 3,19 (t, 4H, $2CH_2$), 3,83 (t, 4H, $2CH_2$), 6,79 (m, 1H, Ar), 6,86-7,02 (m, 2H, Ar), 7,17-7,3 (t, 1H, Ar), 7,43-7,60 (m, 2H, Ar, CH-5), 7,87-8,00 (m, 1H, Ar), 8,34 (d, 1H, Ar), 8,68 (d, 1H, Ar).

2-Methyl-4-(4-phenylpiperazin-1-yl)-6-(pyridin-2-yl)pyrimidine (4.6.f): 2,45 (s, 3H, CH_3), 3,25 (t, 4H, $2CH_2$), 3,82 (t, 4H, $2CH_2$), 6,73-6,85 (m, 1H, Ar), 6,96 (d, 2H, Ar), 7,15-7,30 (t, 2H, Ar), 7,43-7,57 (m, 2H, Ar, CH-5), 7,87-8,00 (m, 1H, Ar), 8,32 (d, 1H, Ar), 8,67 (d, 1H, Ar).

Conclusions:

1. A series of novel 2,6-substituted 4-(N-arylpiperazin-1-yl)pyrimidines was synthesized.
2. The structure of obtained compounds was confirmed by ^{1}H NMR and mass spectrometry.
3. The preliminary prediction of pharmacological activity of substances was carried out using PASS programme.
4. The pharmacological screening data showed a moderate anticonvulsant activity of synthesized compounds.

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СИНТЕЗ 2,6-ЗАМЕЩЕННЫХ 4-(N-АРИЛПИПЕРАЗИН-1-ИЛ)ПИРИМИДИНОВ КАК ПОТЕНЦИАЛЬНЫХ АНТИКОНВУЛЬСАНТОВ

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Резюме: Взаимодействием 2,6-R-хлоропиримидинов с N-арилзамещенными пиперазинами получен ряд новых 2,6-замещенных 4-(N-арилпиперазин-1-ил)пиримиинов. Структура полученных веществ подтверждена методами ^{1}H ЯМР и хроматомасс-спектрометрии. По данным фармакологического скрининга синтезированные соединения обладают умеренной противовосудорожной активностью.

Ключевые слова: синтез, пиримидин-4(3H)-он, пиперазин, противосудорожная активность.

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СИНТЕЗ 2,6-ЗАМІЩЕНИХ 4-(N-АРИЛПІПЕРАЗИН-1-ІЛ)ПІРИМІДИНІВ ЯК ПОТЕНЦІЙНИХ АНТИКОНВУЛЬСАНТІВ

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Резюме: Взаємодією 2,6-R-хлоропіримідинів з N-арилзаміщеними піперазинами одержано ряд нових 2,6-заміщених 4-(N-арилпіперазин-1-іл)піримідинів. Структура одержаних речовин підтверджена методами ^{1}H ЯМР та хроматомас-спектрометрії. За даними фармакологічного скринінгу синтезовані сполуки володіють помірною протисудомною активністю.

Ключові слова: синтез, піримідин-4(3H)-он, піперазин, протисудомна активність.

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