СИНТЕЗ ТА АНАЛІЗ БІОЛОГІЧНО АКТИВНИХ РЕЧОВИН

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SYNTHESIS OF THE NEW BIOLOGICAL ACTIVE COMPOUNDS AMONG DERIVATIVES OF 3-MERCAPTO-4-BENZYL-5-METHOXYPHENYL-1,2,4(4*H*)-TRIAZOLE

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The synthesis of new potential biological active substances among derivatives of 3-mercapto-4-benzyl-5-methoxyphenyl-1,2,4(*1H*)-triazole has been carried out. The finished products have been obtained by interaction of 3-mercapto-4-benzyl-5-phenoxymethyl-1,2,4-triazole (4H) with the corresponding chloroacetanilides or chloroacetophenones under the standard alkylation conditions. The structure of the substances synthesized have been proven by elemental analysis and NMR spectra. The prognosis of the pharmacological activity with the PASS-program has shown a high possibility of the hypotensive activity for acetanilides derivatives and the antiulcer activity for acetophenones. The data of the primary pharmacological screening have proven the computer prognosis data.

In recent years, great attention in many pharmaceutical scientific laboratories around the world is paid to the derivatives of 1,2,4-triazole. This is due to several factors – wide opportunities of introducing radicals into the heterocyclic ring, which allows you to vary widely series of compounds, as well as the high potential of the derivatives as potential pharmacological agents. In particular, it has been found derivatives of 1,2,4-triazole with a insecticidal [5], antimicrobial [4, 10], fungicidal [6, 8], anticonvulsant [12] properties, have potential as ligands of serotonin receptors [11] and antihaemostatics [7].

Mercapto- and thioderivatives occupied a special place among the derivatives of 1,2,4-triazole. The presence of sulfur in their structure, appears to increase the lipophylicity of the molecule, a set which improves the ability to penetrate the blood-brain barrier and to show influence on the central nervous system, and also creates conditions for the toxicity to microorganisms.

We have previously observed that the presence benzyl substituents in the molecules of different heterocyclic compounds, creates the serious preconditions for a manifestation of anticonvulsant properties of substances [9], an additional pharmacophores were also phenoxygroups [1]. A number of prospective anticonvulsants was discovered among the thiosubstituted 1,2,3-triazoles [2]. Therefore we have planned the synthesis of 1,2,4-triazole mercaptoderivatives which contain both benzyl radical and phenoxygroup.

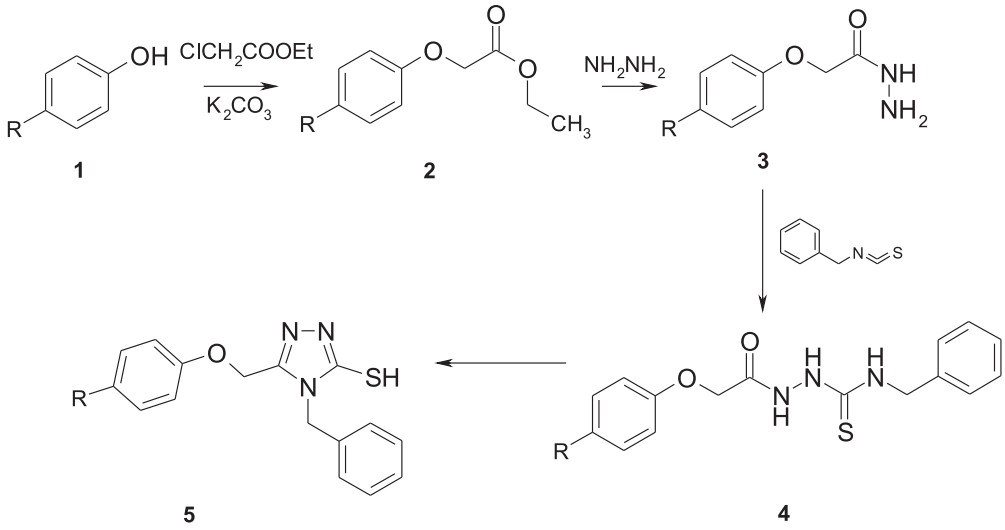
It is known that one of the most successful precursors in the synthesis of 1,2,4-triazoles, allowing to enter various substituents into the 3 (5) position of the ring are the acylhydrazides [13], whose interaction with benzylisothiotcyanate should lead to the planned compounds. Such synthesis of the triazoles from acylated thiosemicarbazide in alkaline medium is the most common and well understood. The synthesis of started mercaptotriazoles 5 was carried out from the corresponding phenols due to Scheme 1. To enhance the possible effects on the CNS except the unsubstituted phenol, we chose the 4-bromsubstituted one (1a, b):

We have previously found that the alkylation of mercapto derivatives of heterocyclic compounds with chloroacetic acid improves affinity of the central nervous system and promotes the manifestation of biological activity such as a nootropic, anticonvulsant, and others, possibly due to increasing of their lipophilicity. Therefore, to further transformations mercaptotriazoles synthesised (5) were alkylated by chloroacetic acid anilides (amides) or chloroacetophenones in a homogeneous base catalysis conditions, resulting to the compounds 6a-f and 7a-e (Scheme 2).

We have chosen the standard alkylation conditions – the interaction of the initial compounds in alcohol with an aqueous alkali solution and have obtained the end products (7a-f) in high yields and sufficient purity (Table 1).

The structure of the synthesized compounds have been confirmed by ^{1}H NMR spectroscopy data (Table 2).

All spectra of the compounds synthesized are characterized by the presence of signals of three methylene groups. Due to the absence of protons in their surroundings they all look like singlets. The signals of these groups were identified in accordance with the electronegativity of adjacent functional groups: – at 5,22-5,32 ppm – OCH_2; at 5,13-5,19 ppm – SCH_2; at 3,67-4,23 ppm – methylene protons of the benzyl radical. The signals of aromatic



where R=H (a), Br (b)

Scheme 1

protons in most cases overlap each other and are in the form of complex multiplets.

To optimize the pharmacological screening of the substances synthesized previously progosis of their pharmacological activity was carried out using the program PASS [9].

According to computer predictions in the spectrum of pharmacological activity of the compounds synthesized, which contain the fragments of acetanilides 6a-t is antihypertensive effect a main possible (0,528-0,754 Pa), while the second group of compounds 7a-f, except the anti-hypertensive, has a high probability of antiulcer activity, including the action to H. pylori. The mechanism of antiulcer action is most likely inhibition of the H_2-histamine receptor, which is due to the structural similarity of the molecules of histamine and synthesized compounds.

Primary data of pharmacological screening have confirmed the prognosis of activity.

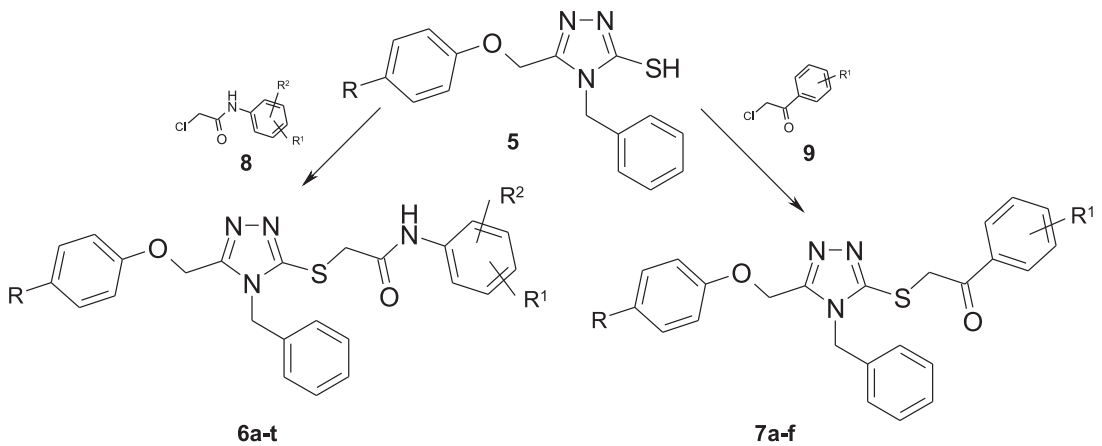
Experimental section

Melting points were determined by open capillary method. NMR ^{1}H spectra were recorded at Bruker WM spectrometer (300 MHz); solvent DMSO-d_6; chemical shifts are in ppm, internal standard was used TMS. The purity of compounds synthesized was monitored by TLC.

3-Mercapto-4-benzyl-5-phenoxymethyl-1,2,4-triazole(*4H*) (5a). Into solution of 16,6 g (0,1 mol) of phenoxyacetyl hydrazide **3** in 100 ml ethanol 14,9 g (0,1 mol) benzylisothiocyanate was added dropwise at vigorous stirring. The reaction mixture was refluxed for 1 hour, cooled, the precipitate formed of substituted thiosemicarbazide **4** was filtered and dried. To a suspension of 2,87 g (0,01 mol) of thiosemicarbazide **4** in 80 ml of water 1,12 g (0,02 mol) KOH was added. The reaction mixture was refluxed for 5 hours. After cooling mixture was acidified with hydrochloric acid to pH = 3-4. The resulting precipitate of finished merkaptotriazole **5** was filtered, washed with water and dried.

Anilides of 4-benzyl-5-phenoxymethyl-1,2,4-triazolyl-3ylmerkapto acetic acid (6a-t), 3-phenacylmetylthio4-benzyl-5-phenoxymethyl-1,2,4-triazoles (7a-f) (general procedure).

To a solution of 0,59 g (0,002 mol) mercaptotriazole **5a** in 20 ml ethanol 20 ml of an aqueous solution of 0,002 mole of KOH was added. To the resulting reaction mixture an alcoholic solution of 0.002 mole of the arylchloroacetamide **8** or chloroacetophenone **9** was add-



Scheme 2

Table 1

Yiels, melting points and elemental analysis data for substances synthesized

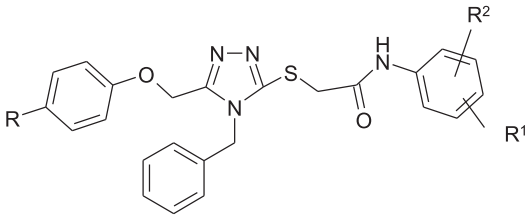
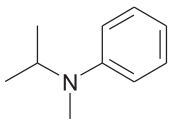
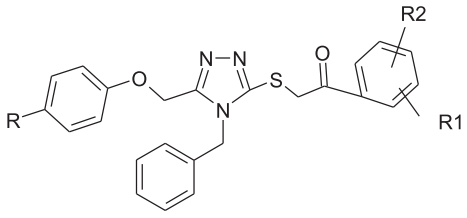
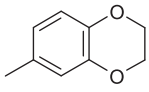
	R	R^1	R^2	Yield, %	M.p., °C	Calculated, %		Formula	Found, %	
						N	S		N	S
										
6a	H	2-CH_3	H	82,21	135-7	12,6	7,21	$C_{25}H_{24}N_4O_2S$	12,7	7,2
6b	H	3-CH_3	H	79,95	128-30	12,6	7,21	$C_{25}H_{24}N_4O_2S$	12,6	7,1
6c	H	4-CH_3	H	82,21	141-3	12,6	7,21	$C_{25}H_{24}N_4O_2S$	12,8	7,1
6d	H	4-C_2H_5	H	80,78	144-6	12,22	6,99	$C_{26}H_{26}N_4O_2S$	12,3	7,1
6e	H	4-$OCHF_2$	H	81,57	135-7	11,28	6,26	$C_{25}H_{22}F_2N_4O_3S$	11,4	6,4
6f	H	2-CH_3	3-CH_3	81,87	118-20	12,22	6,99	$C_{26}H_{26}N_4O_2S$	12,4	6,7
6g	H	NHAr = NHBn		85,59	128-30	12,6	7,21	$C_{25}H_{24}N_4O_2S$	11,2	7,3
6h		NHAr = N(Ph)		90,10	134-6	11,06	6,33	$C_{30}H_{26}N_4O_2S$	11,1	6,4
6i	H	Ar = 1-naphtyl		87,50	145-7	11,66	6,67	$C_{28}H_{24}N_4O_2S$	11,7	6,7
6j	4-Br	4-CH_3	H	87,95	174-6	10,70	6,13	$C_{25}H_{23}BrN_4O_2S$	10,9	6,2
6k	4-Br	4-OC_6H_5	H	81,67	150-2	9,31	5,33	$C_{30}H_{25}BrN_4O_3S$	9,4	5,4
6l	4-Br	2-CH_3	3-CH_3	75,42	148-50	10,42	5,97	$C_{26}H_{25}BrN_4O_2S$	10,5	6,2
6m	4-Br	2-CH_3	4-CH_3	68,90	145-7	10,42	5,97	$C_{26}H_{25}BrN_4O_2S$	10,5	6,1
6n	4-Br	2-CH_3	5-CH_3	78,21	144-6	10,42	5,97	$C_{26}H_{25}BrN_4O_2S$	10,6	6,9
6o	4-Br	2-Cl	4-Cl	82,11	150-2	9,69	5,54	$C_{24}H_{19}BrCl_2N_4O_2S$	9,8	5,5
6p	4-Br	3-Cl	4-Cl	76,99	165-7	9,69	5,54	$C_{24}H_{19}BrCl_2N_4O_2S$	9,8	5,6
6q	4-Br	2-Cl	4-Cl 6-Cl	80,06	180-2	9,69	5,54	$C_{24}H_{19}BrCl_2N_4O_2S$	5,5	5,5
6r	4-Br	2-NO_2	4-OC_2H_5	77,50	136-8	11,70	5,36	$C_{26}H_{24}BrN_5O_5S$	11,8	5,5
6s	4-Br	Ar = 1-naphtyl		86,76	175-7	10,01	5,73	$C_{28}H_{23}BrN_4O_2S$	10,2	5,8
6t	4-Br	NHAr = 		77,13	141-3	10,16	5,81	$C_{27}H_{27}BrN_4O_2S$	10,3	5,8
										
7a	H	H	H	82,21	200-2	10,11	7,72	$C_{24}H_{21}N_3O_2S$	10,4	7,7
7b	H	4-Br	H	74,90	150-2	8,50	6,49	$C_{24}H_{20}BrN_3O_2S$	8,6	6,4
7c	H	4-Cl	H	79,06	120-2	9,34	7,13	$C_{24}H_{20}ClN_3O_2S$	9,4	7,3
7d	H	4-OC_2H_5	H	80,52	138-40	9,14	6,98	$C_{26}H_{25}N_3O_3S$	9,3	6,7
7e	H	4-$OCHF_2$	H	70,61	156-8	8,73	6,66	$C_{25}H_{21}F_2N_3O_3S$	8,4	6,5
7f	H		H	68,64	160-2	8,87	6,67	$C_{26}H_{23}N_3O_4S$	9,1	6,9

Table 2

Chemical shifts (δ, ppm) at NMR ^{1}H spectra of the substances

	CONH, 1H, с	Ar-H,м	OCH_2, 2H, с	SCH_2, 2H, с	CH_2Ph, 2H, с	
6a	9,61	6,87-7,64, 14H	5,27	5,18	4,06	2,24, 3H, с, $C\underline{H}_3$
6b	10,10	6,80-7,43, 14 H	5,29	5,16	4,08	2,33, 3H, с, $C\underline{H}_3$
6c	10,19	6,82-8,20, 14H	5,28	5,17	4,07	2,14, 3H, с, $C\underline{H}_3$
6d	10,09	6,91-7,48, 14H	5,28	5,14	4,08	2,62, к, 2H, $C\underline{H}_2CH_3$; 1,21, т, 3H, $CH_2C\underline{H}_3$
6e	10,31	6,72-7,59, 14 H	5,31	5,17	4,08	-
6f	9,61	6,85-7,35, 13H	5,30	5,18	4,09	2,29, с, 3H, 2,05, s, 3H (2x CH_3)
6g	8,52, т	6,91-7,27, 15 H	5,27	5,14	3,93	4,27, 2H, д, $NHC\underline{H}_2Ph$
6i	10,22	6,91-8,12, 17H	5,32	5,18	4,23	
6j	10,05	6,76-7,48, 13H	5,26	5,14	4,08	2,27, 3H, с, $C\underline{H}_3$
6k	10,18	6,85-7,58, 14H	5,27	5,13	4,08	-
6l	9,62	6,80-7,36, 12H	5,26	5,17	4,12	2,09, с, 3H, 2,26, с, 3H (2x CH_3)
6m	9,58	6,78-7,47, 12H	5,27	5,13	4,05	2,29, с, 3H, 2,17, с, 3H (2x CH_3)
6n	9,49	6,78-7,46, 12H	5,26	5,18	4,07	2,18, с, 3H, 2,29, с, 3H (2x CH_3)
6o	10,08	6,82-8,19, 12H	5,26	5,18	4,15	-
6p	10,24	6,78-7,81, 12H	5,27	5,16	4,11	-
6q	10,04	6,78-7,43, 11H	5,31	5,18	4,15	-
6r	10,42	6,74-7,95, 12 H	5,27	5,18	4,09, 4H, м (+ $OC\underline{H}_2C\underline{H}_3$)	1,38, 3H,т, $OCH_2C\underline{H}_3$
6s	10,26	6,82-8,18, 16 H	5,29	5,18	4,21	-
6t	-	77,25-7,45, м, 10H, 6,83-7,08, дд, 4H	5,22	5,19	3,67	1,01, 6H, с, 2xCH_3
7a	-	6,81-7,98, 15H	5,29	5,18	4,81	-
7b	-	7,31-7,85, дд, 4H, 6,75-7,64, м, 10H	5,29	5,15	4,82	-
7c	-	6,90-8,08, 14 H	5,28	5,16	4,80	-
7d	-	7,16,d + 7,94, д; 4H 6,94-7,30, м, 10H,	5,29	5,17	4,78	4,12,к, 2H, $C\underline{H}_2CH_3$; 1,40,т, 3H, $CH_2C\underline{H}_3$
7e	-	7,33-8,08, , дд, 4H 6,88-7,30, м, 11H, (2xPh + $C\underline{H}F_2$)	5,29	5,18	4,82	-
7f	-	6,88-7,51, 13H	5,29	5,15	4,75	4,29, 2H, т, 4,34, 2H, т (OCH_2CH_2O)

ed at stirring. The solution obtained was refluxed for 1 hour, cooled, poured into 200 ml water. The precipitate of the finished product **6.7** was filtered and dried.

CONCLUSIONS

1. 4-Benzyl-5-phenoxymethyl-1,2,4-triazolyl-3-ylthioacetic acid anilides were synthesized by alkylation of initial 3-mercapto-4-benzyl-5-phemoxymethyl-1,2,4-triazole with chloroacetic acid anilides. Sructure of substances synthesized was proved by elemental analysis and spectral data.

2. Pharmacological investigatios have been planned due to preliminary computer prognosis (PASS-program). It was directed to discovering of antiulcer and hypotensive activities.

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СИНТЕЗ НОВЫХ БИОЛОГИЧЕСКИ АКТИВНЫХ СОЕДИНЕНИЙ СРЕДИ ПРОИЗВОДНЫХ 3-МЕРКАПТО-4-БЕНЗИЛ-5-МЕТОКСИФЕНИЛ-1,2,4 (4*H*)-ТРИАЗОЛА

Н.Б.Саидов, И.М.Кадамов, В.А.Георгиянц

Осуществлен синтез новых потенциальных биологически активных веществ среди производных 3-меркапто-4-бензил-5-метоксифенил-1,2,4 (*4H*)-триазола. Целевые продукты были получены в результате взаимодействия 3-меркапто-4-бензил-5-феноксиметил-1,2,4-триазола (4Н) с соответствующими хлорацетанилидами или хлорацетофенонами при стандартных условиях алкилирования. Структура синтезированных веществ была доказана с помощью элементного анализа и ЯМР-спектров. Прогноз фармакологической активности с использованием программы PASS показал высокую вероятность гипотензивной активности для производных ацетанилидов и противоязвенной – для ацетофенонов. Данные первичного фармакологического скрининга подтвердили данные компьютерного прогноза.

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СИНТЕЗ НОВИХ БІОЛОГІЧНО АКТИВНИХ СПОЛУК СЕРЕД ПОХІДНИХ 3-МЕРКАПТО-4-БЕНЗИЛ-5-МЕТОКСИФЕНІЛ-1,2,4 (4*H*)-ТРИАЗОЛУ

Н.Б.Саїдов, І.М.Кадамов, В.А.Георгіянц

Здійснено синтез нових потенційних біологічно активних речовин серед похідних 3-меркапто-4-бензил-5-метоксифеніл-1, 2,4 (4Н)-триазолу. Цільові продукти були отримані в результаті взаємодії 3-меркапто-4-бензил-5-феноксиметил-1,2,4-триазолу *(4H)* з відповідними хлорацетанілідами або хлорацетофенонами за стандартних умов алкілування. Структура синтезованих речовин була доведена за допомогою елементного аналізу та ЯМР-спектрів. Прогноз фармакологічної активності з використанням програми PASS показав високу ймовірність гіпотензивної активності для похідних ацетанілідів і противиразкової – для ацетофенонів. Дані первинного фармакологічного скринінгу підтвердили дані комп'ютерного прогнозу.