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THE SYNTHESIS OF NEW 3-PHENACYLMETYLTHIO-4-ARYL-5-PHENYLAMINOMETHYL-1,2,4-TRIAZOLES(4H) AS POTENTIAL NEUROTROPIC AGENTS

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The series of new substituted 4-phenyl-5-phenylaminomethyl-3-mercapto-1,2,4-triazole (4H) derivatives has been synthesized by alkylation of the correspondent 4-phenyl-5-phenylaminomethyl-3-mercapto-1,2,4-triazoles (4H) with α-chloroacetophenones. The structure of the substances synthesized has been proven by the elemental analysis data and NMR spectra. The high possibility of such types of the pharmacological activity as analgesic, sedative and antineurotic has been determined by the PASS program.

СИНТЕЗ НОВИХ 3-ФЕНАЦИЛМЕТИЛТІО-4-АРИЛ-5-ФЕНІЛАМІНОМЕТИЛ-1,2,4-ТРИАЗОЛІВ (4H) ЯК ПОТЕНЦІЙНИХ НЕЙРОТРОПНИХ АГЕНТІВ
Н.Б.Саїдов, І.М.Кадамов, В.А.Георгіянц
Алкілуванням відповідних 4-феніл-5-феніламінометил-3-меркапто-1,2,4-триазолів(4H) α-хлорацетофенонами синтезовано ряд нових заміщених похідних 4-феніл-5-феніламінометил-3-меркапто-1,2,4-триазолів(4H). Структуру синтезованих сполук підтверджено даними елементного аналізу та спектроскопії ЯМР ^{1}H. За допомогою програми PASS встановлена висока вірогідність прояву таких видів фармакологічної активності, як аналгетична, седативна та антиневротична.

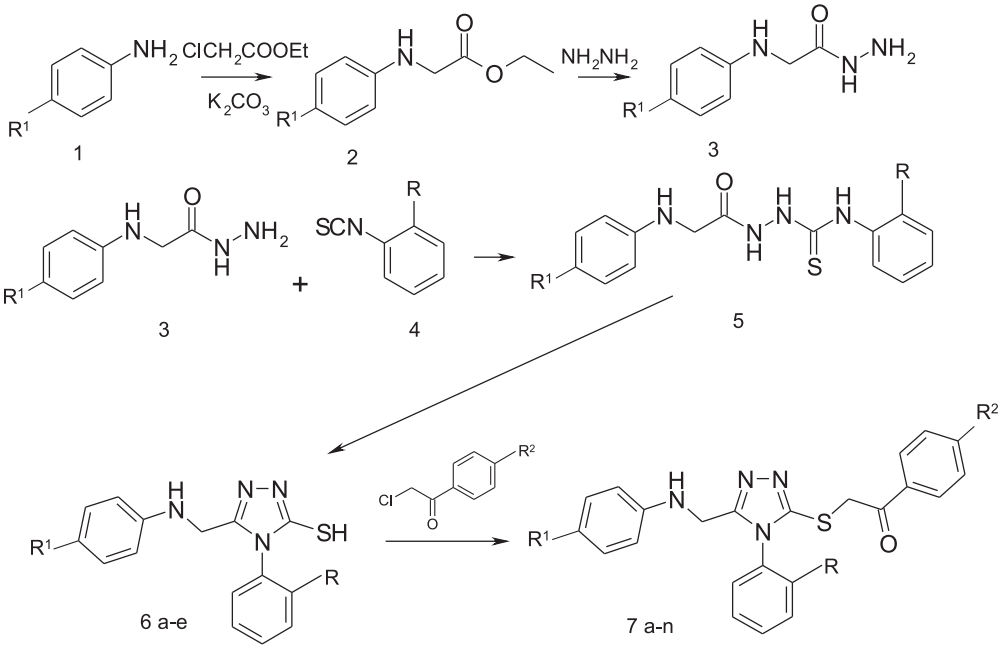
СИНТЕЗ НОВЫХ 3-ФЕНАЦИЛМЕТИЛТИО-4-АРИЛ-5-ФЕНИЛАМИНОМЕТИЛ-1,2,4-ТРИАЗОЛОВ (4H) КАК ПОТЕНЦИАЛЬНЫХ НЕЙРОТРОПНЫХ АГЕНТОВ
Н.Б.Саидов, И.М.Кадамов, В.А.Георгиянц
Алкилированием соответствующих 4-фенил-5-фениламинометил-3-меркапто-1,2,4-триазолов(4H) α-хлорацетофенонами синтезирован ряд новых замещенных производных 4-фенил-5-фениламинометил-3-меркапто-1,2,4-триазолов(4H). Структура синтезированных соединений подтверждена данными элементного анализа и спектроскопии ЯМР ^{1}H. С помощью программы PASS установлена высокая вероятность проявления таких видов фармакологической активности, как анальгетическая, седативная и антиневротическая.

The synthesis of 1,2,4-triazole derivatives is carried out today by many scientists in the world. Careful attention to these compounds is primarily due to their high potential as possible pharmaceutical substances [1-7]. This heterocycle has unique properties. On the one hand, it has similarity to some kinds of bioactive molecules such as histamine or cyclic GABA; on the other hand, it has the small size of the molecule. In addition, introduction of different functions at the stage of the triazole ring formation is convenient. These functions can then be pharmacophores or can involve compounds in various biochemical processes.

In Ukraine, the synthesis of biologically active compounds in the series of 1,2,4-triazole derivatives is traditional [8, 9]. The result of this work has been the introduction of the original drug «Thiotriazolin» developed by I.A.Mazur at Zaporozhye State Medical University into clinical practice. Its structural analogues and combined medicines with the improved properties – thiocetam, thiodaron, etc., – have been already registered.

As it is known in medicinal chemistry, any even the smallest modification of the molecule can radically change the effect of a substance on a living organism. Therefore, there is the probability of obtaining new biologically active compounds in the series of 1,2,4-triazole derivatives, in particular, those containing a substituted mercaptogroup, which can increase lipophilicity of a relatively hydrophilic molecule [10].

An additional advantage of this group of substances is the relative simplicity of their synthesis. Previously, we have synthesized derivatives of 3-mercapto-1,2,4-triazole containing 5 position phenoxymethyl residue [11]. A number of them have shown the interesting pharmacological properties. We were interested in observing how the replacement of oxy-



Scheme

gen to nitrogen influences on the pharmacological properties. Therefore, as the starting materials for formation of the 5-substituted triazole nucleus we selected anilines – unsubstituted and 4-substituted ones (1). Resulting from alkylation of ethyl chloroacetate and subsequent hydrazinolysis hydrazides were involved into interaction with phenyl-(2-methyl) isothiocyanates (Scheme).

The thiosemicarbazides synthesized (5) were cyclized in the presence of alkali, the result was the key intermediates – the corresponding 4-aryl-5-phenylaminomethyl-3-mercapto-1,2,4-triazoles (6). Alkylation of them with phenacylchlorides leads to the finished products (7). As with other similar compounds the optimal alkylation conditions were the use of basic catalysis. The reaction was carried out in alcohol in the presence of the alkali solution. Under such conditions we could synthesize the target 3-phenacylmetylthio-4-aryl-5-phenylaminomethyl-1,2,4-triazoles in high yields and sufficient purity (Table 1).

The structure of the compounds synthesized was confirmed by elemental analysis data and ^{1}H NMR spectroscopy [11].

At the ^{1}H NMR spectra of the starting compounds (6a-e) there are signals of the aromatic protons, which

Table 1

Yields, melting points and elemental analysis data for the substances synthesized

Compound	R	R^1	R^2	Yield, %	M.p., °C	Calculated, %		Formula	Found, %	
						N	S		N	S
7a	H	4-Cl	H	77.10	172-4	12.88	7.37	$C_{23}H_{19}ClN_4OS$	12.94	7.27
7b	H	4-Cl	4-Cl	66.10	195-7	11.94	6.83	$C_{23}H_{18}Cl_2N_4OS$	12.11	6.66
7c	H	4-Cl	4-Br	67.25	204-6	10.90	6.24	$C_{23}H_{18}BrClN_4OS$	11.02	6.20
7d	H	4-Cl	4-OCH_3	66.81	151-3	12.05	6.90	$C_{24}H_{21}ClN_4O_2S$	12.24	6.81
7e	H	4-F	H	84.93	157-9	13.39	7.66	$C_{23}H_{18}FN_4OS$	13.40	7.70
7f	H	4-F	4-Cl	75.14	173-4	12.37	7.08	$C_{23}H_{18}ClFN_4OS$	12.51	6.98
7g	H	4-F	4-CH_3	71.68	163-5	12.95	7.41	$C_{24}H_{21}FN_4OS$	13.09	7.35
7h	H	4-CH_3	H	63.58	169-71	13.52	7.74	$C_{24}H_{22}N_4OS$	13.58	7.72
7i	H	4-CH_3	4-Cl	58.04	188-90	12.48	7.14	$C_{24}H_{21}ClN_4OS$	12.63	7.03
7j	H	4-OCH_3	H	74.42	141-3	13.01	7.45	$C_{24}H_{22}N_4O_2S$	13.19	7.42
7k	2-CH_3	4-Cl	H	71.26	152-4	12.48	7.14	$C_{24}H_{21}ClN_4OS$	12.57	7.11
7l	2-CH_3	4-Cl	4-Cl	70.32	155-7	11.59	6.63	$C_{24}H_{20}Cl_2N_4OS$	11.67	6.61
7m	2-CH_3	4-Cl	4-CH_3	69.19	163-4	12.10	6.93	$C_{25}H_{23}ClN_4OS$	12.18	6.74
7n	2-CH_3	4-CH_3	4-Cl	72.51	168-70	12.10	6.93	$C_{25}H_{23}ClN_4OS$	12.22	6.72

Table 2

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

Compound	Ar-H	$N\underline{H}CH_2$, 1H, t	$NHC\underline{H}_2$, 2H, d	$SC\underline{H}_2$, 2H, s	Others
7a	8.00, 2H, t; 7.76, 8H, m; 6.97, 2H; 6.48, 2H, dd	5.81	4.20	4.	1.96, 3H, s, CH_3
7b	7.92, 2H, 7.74, 2H dd; 7.48-7.64, 5H, m; 6.94, 2H, 6.40, 2H, dd	5.64	4.18	4.84	-
7c	7.98, 2H, 7.72, 2H dd; 7.41-7.57, 5H, m; 7.00, 2H; 6.42, 2H, dd	5.92	4.19	4.79	-
7d	8.00, 2H, t; 7.70, 4H, m; 6.98, 3H; d 6.47, 2H, d	5.82	4.18	4.78	3.88, 3H, s, OCH_3
7e	8.03, 2H, d; 7.74, 8H, m; 6.38, 2H; 6.23, 2H, dd	5.14	4.09	4.84	-
7f	8.02, 2H, t; 7.48, 7H, m; 6.76, 2H; 6.49, 2H, dd	5.00	4.19	4.80	-
7g	7.84, 2H, 7.33, 2H, dd; 7.56, s, 5H; 6.82, 2H, 6.51, 2H, dd	5.67	4.17	4.77	2.40, 3H, s, CH_3
7h	7.96, 2H, t; 7.44-7.67, 8H, m; 6.81, 2H; 6.42, 2H, dd	5.45	4.16	4.82	2.12, 3H, s, CH_3
7i	8.00, 2H, m; 7.57, 5H, s; 7.42, 2H, d; 6.81, 2H, 6.38, 2H, dd	5.45	4.16	4.82	2.12, 3H, s, CH_3
7j	7.96, 2H, t; 7.42-7.64, 8H, m; 6.62, 2H; 6.47, 2H, dd	5.49	4.30	4.77	3.63, 3H, s, OCH_3
7k	8.00, 2H, d; 7.26-7.64, 7H, m; 6.91, 2H; 6.50, 2H, dd	5.87	4.15	4.83	1.96, 3H, s, CH_3
7l	8.00, 2H, 7.58, 2H dd; 7.28-7.45, 4H, m; 6.97, 2H; 6.51, 2H, dd	5.85	4.12	4.82	1,97, 3H, s, CH_3
7m	7.87, 2H, t; 7.36-7.45, 6H, m; 6.98, 2H; 6.50, 2H, dd	5.87	4.13	4.83	2.41, 3H, s, CH_3; 1.95, 3H, s, CH_3
7n	8.00, 2H, t; 7.28-7.62, 6H, m; 6.79, 2H; 6.40, 2H, dd	5.33	4.21	4.83	1.96, 3H, s, CH_3

are for *p*-disubstituted benzene rings as doublets of doublets. The same pattern is observed for the alkyl derivatives (7a-n). In addition, the key intermediates have a singlet of mercaptogroup protons at 13,62-13,89 ppm, which disappears after alkylation. Triplets at 5,14-5,87 ppm corresponding to the presence of an amino group that is connected to the methylene are common in the spectrum of all compounds. In turn, the signals of the methylene groups in the spectra appear as doublets at 4.09-4.30 ppm. In addition, at the spectra of the finished compounds signals of S-methylene groups (singlets at 4.77-4.84 ppm) and additional signals of aromatic protons of the phenacyl moiety appear (Table 2).

To determine the biological potential and optimize the pharmacological screening prediction of the possible pharmacological activity for the compounds synthesized was carried out using the program PASS [12, 13] (Table 3).

Comparing the results of the prediction obtained with our earlier data [14], we noted that the replacement of phenoxymethyl moiety with phenylaminomethyl leads to significant changes in the potential pharmacological activity spectrum.

In contrast to their O-analogues the compounds synthesized are promising as agents acting on the central nervous system. In the spectrum of their potential pharmacological activity, such activities as analgesic, sedative and antineurotic ones appear with a high possibility, while a high probability of the antiulcer and antihelicobacter activity due to the presence of 1,2,4-triazole ring remains.

The results of the primary pharmacological screening confirmed the prediction data and allowed to identify leading compounds for in-depth research.

Experimental section

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

3-Mercapto-4-phenyl-5-(4'-chloro)phenylaminomethyl-1,2,4-triazole(*4H*) (6a). Into the solution of 19.96 g (0.1 mol) of 4-chlorophenylaminoacetyl hydrazide **3** in 100 ml ethanol 14.9 g (0.1 mol) of phenylisothiocyanate is added dropwise while vigorously stirring. The reaction mixture is refluxed for 1 hour, then cooled, the precipitate formed of substituted thiosemicarbazide **4** is filtered and dried. To the suspension of 3.35 g (0.01 mol) thiosemicarbazide **4** in 80 ml of water 1.12 g (0.02 mol) KOH is added. The reaction mixture is refluxed for 5 hours. After cooling the mixture is acidified with hydrochloric acid to pH = 3-4. The resulting precipitate of the finished mercaptotriazole **5** is filtered, washed with water and dried.

Yield – 80.13%. M.p. – 206-8°C. Calculated, % N 17.68; S 10.12; $C_{15}H_{13}ClN_4S$. Found, % N 17.82; S

Table 3

Prediction of the pharmacological activity of the substances synthesized (the PASS-program data)

Compound	Analgesic	Antineurotic	Antiulcer	Antihelicobacter	Sedative
7a	0.766	0.702	0.527	0.543	0.504
7b	0.766	0.702	0.527	0.543	0.504
7c	0.741	0.764	-	-	0.514
7d	0.727	0.723	0.510	0.506	-
7e	0.771	0.742	0.51	0.541	-
7f	0.761	0.762	-	-	-
7g	0.750	0.738	0.503	0.531	-
7h	0.754	0.660	0.556	0.566	-
7i	0.744	0.701	0.519	0.533	-
7j	0.736	0.693	0.544	0.545	-
7k	0.686	0.703	0.550	0.501	0.516
7l	0.686	0.703	0.550	0.501	0.516
7m	0.686	0.713	0.546	-	0.514
7n	0.686	0.713	0.546	-	0.514

10.02. NMR ^{1}H-spectrum: 13.79, 1H, s (SH); 6.42, 6.95, dd, 4H; 7.64, m, 5H (Ar-H); 5.74, 1H, t (N<u>H</u>CH_2), 4.03, 2H, d (NHC<u>H</u>$_2$).

3-Mercapto-4-phenyl-5-(4'-fluoro)phenylaminomethyl-1,2,4-triazole(*4H*) (6a).

Yield – 75.33%. M.p. – 181-3°C. Calculated, % N 18.65; S 10.68. $C_{15}H_{13}FN_4S$. Found, % N 18.81; S 10.54. NMR ^{1}H-spectrum: 13.62, 1H, s (SH); 6.39, 6.78, dd, 4H; 7.39, m, 5H (Ar-H); 5.27, 1H, t (N<u>H</u>CH_2), 4.03, 2H, d (NHC<u>H</u>$_2$).

3-Mercapto-4-phenyl-5-(4'-methyl)phenylaminomethyl-1,2,4-triazole(*4H*) (6b).

Yield – 71.18%. M.p. – 193-5°C. Calculated, % N 18.90; S 10.82. $C_{16}H_{16}N_4S$. Found, % N 18.98; S 10.74. NMR ^{1}H-spectrum: 13.61, 1H, s (SH); 6.42, 6.81, dd, 4H; 7.54, m, 5H (Ar-H); 5.31, 1H, t (N<u>H</u>CH_2), 4.02, 2H, d (NHC<u>H</u>$_2$), 1.93, s, 3H (CH_3).

3-Mercapto-4-phenyl-5-(4'-methoxy)phenylaminomethyl-1,2,4-triazole(*4H*) (6c).

Yield – 68.04%. M.p. – 168-70°C. Calculated, % N 17.93; S 10.26. $C_{16}H_{16}N_4OS$. Found, % N 18.01; S 10.11. NMR ^{1}H-spectrum: 13.72, 1H, s (SH); 6.41, 6.82, dd, 4H; 7.44, m, 5H (Ar-H); 5.24, 1H, t (N<u>H</u>CH_2), 4.03, 2H, d (NHC<u>H</u>$_2$), 3.63, s, 3H (CH_3).

3-Mercapto-4-(2'-methyl)phenyl-5-(4'-chloro) phenylaminomethyl-1,2,4-triazole(*4H*) (6d).

Yield – 71.24%. M.p. – 194-6°C. Calculated, % N 16.93; S 9.69. $C_{16}H_{15}ClN_4S$. Found, % N 9.82; S 9.64. NMR ^{1}H-spectrum: 13.60, 1H, s (SH); 6.44, 6.78, dd, 4H; 7.39-7.81, m, 4H (Ar-H); 5.24, 1H, t (N<u>H</u>CH_2), 4.03, 2H, d (NHC<u>H</u>$_2$); 1.96, s, 3H (CH_3).

3-Mercapto-4-(2'-methyl)phenyl-5-(4'-methyl) phenylaminomethyl-1,2,4-triazole(*4H*) (6e).

Yield – 64.81%. M.p. – 179-81°C. Calculated, % N 18.05; S 10.33. $C_{17}H_{18}N_4S$. Found, % N 18.17; S 10.17. NMR ^{1}H-spectrum: 13.77, 1H, s (SH); 6.34, 6.76, dd, 4H; 7.39-7.82, m, 4H (Ar-H); 5.26, 1H, t (N<u>H</u>CH_2), 4.01, 2H, d (NHC<u>H</u>$_2$); 1.96, s, 6H (2xCH_3).

3-Phenacylmetylthio-4-phenyl-5-phenylaminomethyl-1,2,4-triazoles (7a-e, table 1) (general procedure).

To a solution of 0.002 mol mercaptotriazole **6a-f** 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 chloroacetophenone **9** was added at stirring. The solution obtained was refluxed for 1 hour, cooled, poured into 200 ml water. The precipitate of the finished product **7a-e** was filtered and dried.

Conclusions

1. 3-Phenacylmetylthio-4-aryl-5-phenylaminomethyl-1,2,4-triazoles have been synthesized by alkylation of the initial 3-mercapto-4-benzyl-5-phenylaminomethyl-1,2,4-triazole with cloroacetophenones. The structure of the substances synthesized have been proven by elemental analysis and spectral data.

2. The compounds synthesized have shown promise as agents acting on the central nervous system. In the spectrum of their potential pharmacological activity appears with high possibility, such as analgesic, sedative and antineurotic.

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