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SYNTHESIS, PHYSICO-CHEMICAL PROPERTIES AND PROGNOSIS OF THE PHARMACOLOGICAL ACTIVITY OF 4-PHENYL-5-(1,2,3-BENZOTRIAZOLYL-1)-3-MERCAPTO-1,2,4-TRIAZOLE(4*H*) DERIVATIVES

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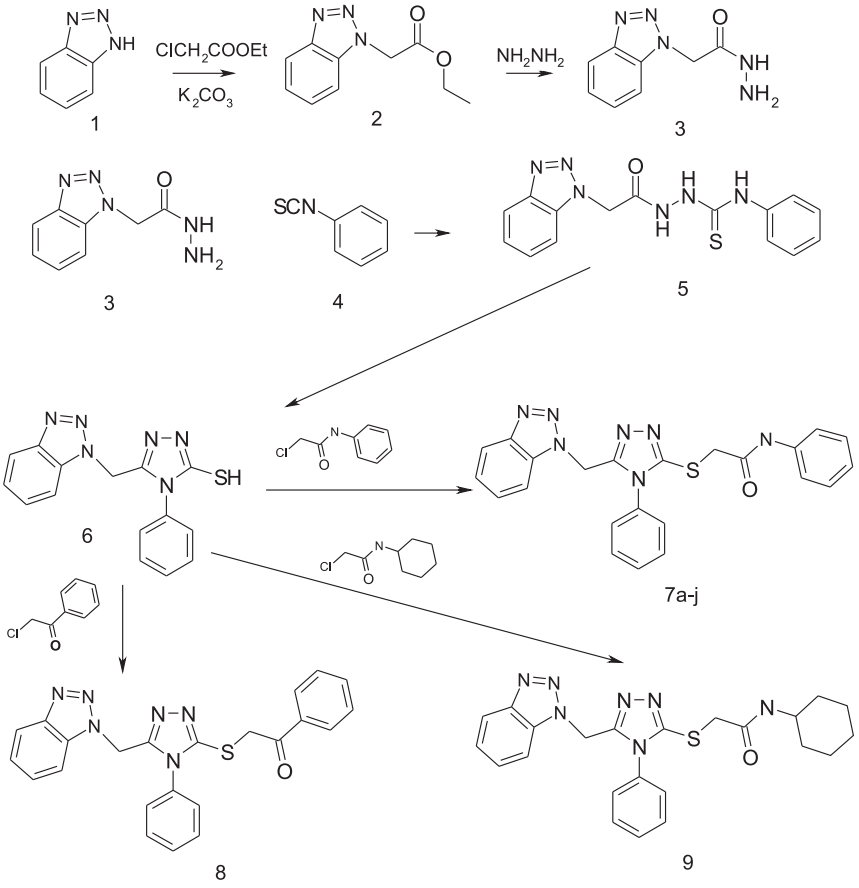
The series of new substituted 4-phenyl-5-(1,2,3-benzotriazolyl-1)-3-mercapto-1,2,4-triazole (4H) derivatives has been synthesized by alkylation of 4-phenyl-5-(1,2,3-benzotriazolyl-1)-3-mercapto-1,2,4-triazole (4H) by the corresponding chloroacetamides (anilides) or by phenacylchlorides. The structure of the substances synthesized has been proven by elemental analysis data and NMR spectra. The pharmacological screening has been planed in accordance with PASS-prognosis.

СИНТЕЗ, ФІЗИКО-ХІМІЧНІ ВЛАСТИВОСТІ ТА ПРОГНОЗ ФАРМАКОЛОГІЧНОЇ АКТИВНОСТІ ПОХІДНИХ 4-ФЕНІЛ-5-(1,2,3-БЕНЗОТРИАЗОЛІЛ-1)-3-МЕРКАПТО-1,2,4-ТРИАЗОЛУ(4H)
Н.Б.Саїдов, І.М.Кадамов, В.А.Георгіянц
Ряд нових похідних 4-феніл-5-(1,2,3-бензотриазоліл-1)-3-меркапто-1,2,4-триазолу (4H) синтезовано алкілуванням вихідного 4-феніл-5-(1,2,3-бензотриазоліл-1)-3-меркапто-1,2,4-триазолу (4H) відповідними амідами (анілідами) хлорацетатної кислоти або фенацилхлоридами. Структуру синтезованих речовин доведено даними елементного аналізу та ЯМР1Н-спектрів. Фармакологічний скринінг спланований у відповідності до PASS-прогнозу.

СИНТЕЗ, ФИЗИКО-ХИМИЧЕСКИЕ СВОЙСТВА И ПРОГНОЗ ФАРМАКОЛОГИЧЕСКОЙ АКТИВНОСТИ ПРОИЗВОДНЫХ 4-ФЕНИЛ-5-(1,2,3-БЕНЗОТРИАЗОЛИЛ-1)-3-МЕРКАПТО-1,2,4-ТРИАЗОЛА(4H)
Н.Б.Саидов, И.М.Кадамов, В.А.Георгиянц
Ряд новых производных 4-фенил-5-(1,2,3-бензотриазолил-1)-3-меркапто-1,2,4-три-азола (4H) синтезированы алкилированием исходного 4-фенил-5-(1,2,3-бензотриазолил-1)-3-меркапто-1,2,4-триазола (4H) соответствующими амидами (анилидами) хлоруксусной кислоты или фенацилхлоридами. Структура синтезированных веществ доказана данными элементного анализа и ЯМР1Н-спектров. Фармакологический скрининг спланирован в соответствии с PASS-прогнозом.

The combination of several pharmacophore in the molecule is one of the modern trends in the pharmaceutical and medicinal chemistry. Such an approach enhances the pharmacological activity, sometimes resulting in synergy. Today, synthetic chemists from different countries, including Ukraine, carry out extensive researches to find potential drugs among the derivatives of 1,2,4-triazole, including anticonvulsants [6-10]. In addition, many reports appeared in the literature about high potential of the derivatives of 1,2,3-benzotriazole as a possible active pharmaceutical ingredients [1-5]. Following the well-known principle of combinig several pharmacophore, we planned the formation of the heterocyclic ring of 1,2,4-triazole with ethyl 1,2,3-benzotriazol-1-ilacetate. We suggested that such combination of heterocyclic systems may lead to the substances with a high level of anticonvulsant activity. To confirm our assumptions, we have carried out a preliminary prediction of pharmacological activity of compounds using the PASS-program [11]. As we had expected, the greatest probability in the spectrum of pharmacological activity for planned to synthesize compounds has an anticonvulsant. We should also note the possibility of antiasthmatic action. Considering the prospects for potential anticonvulsants obtaining, we carried out the synthesis of desired products (Scheme). Key intermediates for synthesis were benzotriazol-1-ylacetohydrazide and arylisothiocyanate.

The synthesis of some 2-benzotriazol-1-ilatsetanilides [1] has been described in the scientific literature. For example Indian scientists carried-out benzotriazole alkylation with chloroacetic acid in chloroform in the presence of pyridine. Synthesized in



Scheme

such a way acid was converted to acylchloride by the action of thionyl chloride in DMF at reflux and then its interaction with suitable anilines was carried out. To simplify the synthetic scheme and due to the high reactivity of hydrazine hydrate, we carried out 1-alkylation of 1,2,3-1H-benzotriazole (1) by ethyl chloroacetate in analogy with the introduction of benzotriazole fragment into such rings as oxadiazole [2], pirazolidine [5] and thiazolidine [3] in the presence of potassium carbonate according to standard procedure of amino compounds alkylation.

Further hydrazinolysis of the ester synthesized (2) with hydrazine hydrate was carried out. Then 1,2,3-benztrazolil-1-ilacetohydrazide (3) was reacted with phenyl isothiocyanate (4) for synthesis of the corresponding thiosemicarbazide (5), which was subjected to an intramolecular condensation to form the initial substance for the synthesis of target products – (6). It should be noted that in the future to study the dependence of activity from the structure it is possible to introduce different substituents at position 4 of 1,2,4-triazole at this stage. The end products (7a-k) were obtained by alkylation of thiol (6) with chloroacetic acid anilides in the presence of basic catalysts. As substituents in the anilide moiety, we chosen the methyl and trifluoromethyl groups as the most prospective for anticonvulsant action. In order to form concepts about the importance of the anilide moiety for this group of compounds we have synthesized substances based on chloroacetic acid cyclohexylamide and phenacylchloride (compounds 8, 9).

Structure of the substances synthesized have been proved by elemental analysis data and NMR spectra. It was noted that after alkylation the chemical shift of mercaptogroup are disappeared and signals of substituents appeared instead them. At all spectra are some general signals. Among them we noted the presence of two singlets due to methylene groups – OCH_2 at 6,01-6,03 ppm, and SCH_2 at 4,09-4,12 ppm (tabl. 2). Assignment of the signals was performed in accordance with the electronegativity of adjacent elements. Signals of aromatic protons of benzotriazole ring and substituents are as multipletes at 6,62-8,01 ppm, Amide groups are as singlets at 9,81-10,22.

Computer prognosis of pharmacological action today permit to optimize the pharmacological screening. This approach reduces the cost of the animals and reagents. Post-soviet counties scientists widely used for this PASS program [11] in combination of a logical approach chemist pharmacophore analysis software, which are part of the molecules, produce good results [12]. For this group compound due to literature analysis data and our previous researches for 1,2,3- and 1,2,4-triazole derivatives we estimated probability of anticonvulsant action [6-10]. PASS-prognosis demonstrated some activities which are more likely. So, as we expected compounds synthesized may show anticonvulsant action (Pa = 0,504-

Table 1

Yiels, melting points and elemental analysis data for substances synthesized

Compound	R	R^1	Yield,%	M.p., °C	Calculated, %		Formula	Found, %	
					N	S		N	S
7a	H	3-Me	72,5	148-9	21,52	7,04	$C_{24}H_{21}N_7OS$	21,6	7,0
7b	H	4-Me	80,2	197-9	21,52	7,04	$C_{24}H_{21}N_7OS$	21,5	7,0
7c	H	3-OMe	73,4	155-7	20,79	6,80	$C_{24}H_{21}N_7O_2S$	20,8	6,9
7d	H	4-OPh	85,9	178-80	18,37	6,01	$C_{29}H_{23}N_7O_2S$	18,5	6,0
7e	H	2-CF_3	79,4	134-6	19,24	6,29	$C_{24}H_{18}F_3N_7OS$	19,2	6,2
7f	H	3-CF_3	72,6	130-1	19,24	6,29	$C_{24}H_{18}F_3N_7OS$	19,4	6,3
7g	2-Me	5-Me	79,8	136-8	20,88	6,83	$C_{25}H_{23}N_7OS$	21,1	6,7
7h	2-Me	6-Me	75,5	205-7	20,88	6,83	$C_{25}H_{23}N_7OS$	20,9	6,7
7i	2-Me	3-Cl	77,1	160-2	20,01	6,54	$C_{24}H_{20}ClN_7OS$	20,2	6,6
7j	2-OMe	5-OMe	69,0	122-4	19,55	6,39	$C_{25}H_{23}N_7O_2S$	19,6	6,2

0,787). Moreover some of these substances may act as antiasthmatic agents (Pa = 0,569-0,609). It should be noted that the computer program does not provide a high probability for other types of pharmacological activity, probably due to lack of information on the structural fragments.

Substances synthesized will be examined as possible anticonvulsants.

Experimental section

Melting points were determined by open capillary tube. NMR ^{1}H spectra were recorded on a Bruker WM spectrometer (300 MHz); solvents – $CDCl_3$ or DMSO-d_6; chemical shifts are in ppm, internal srandard was used TMS. The purity of compounds synthesized was monitored by TLC.

Ethyl 1H-benzotriazol-1-yl-acetate (2). To a solution of benzotriazole 0,01 mol in ethanol in the presence of dry K_2CO_3 (0,5 g) ethyl chloroacetate 0,01 mol was added. The mixture was refluxed at stirring for 6 hrs. Filtration was done and the filtrate was evaporated in water bath. The resulting precipitates were recrystallized from chloroform. Brownish needles. Yield – 79%. M.p. – 42-44°C.

Found N 20,6 $C_{10}H_{11}N_3O_2$ Requires N 20,5. NMR ^{1}H ($CDCl_3$, ppm): 1,20 (t, 3H, $CH_2\underline{CH_3}$); 3,60 (s, 2H, N-CH_2); 4,10 (q, 2H, $\underline{CH_2}CH_3$); 7,30-7,80 (m, 4H, Ar-H).

Acetohydrazido benzotriazole (3). A mixture of ethyl 1H-benzotriazol-1-yl-acetate (2) (0,02 mole) and hydrazine hydrate (0,02 mole) in 50 ml of ethanol was refluxed on the waterbath for about 5 hrs, cooled and filtered. White crystals. Yield – 84%. M.p. – 87-88°C.

Found N 36,6 $C_8H_9N_5O$ Requires N 36,6. NMR ^{1}H ($CDCl_3$, ppm): 3,55 (s, 2H, N-CH_2); 4,52 (s, 2H, NH_2); 7,30-7,85 (m, 4H, Ar-H); 7,90 (s 1H, CONH).

3-Mercapto-4-phenyl-5-(1,2,3-benzotriazol-1-yl)-1,2,4-triazole(4*H*) (6). To a solution of acetohydrazido benzotriazol (0,02 mole) **2** in 10 ml ethanol at intense stirring phenylisothiocyanate (0,02 mole) **3** was added dropwise. Reaction mixture was refluxed for 1 hr, cooled and filtered. Thiosemicarbazide **5** obtained was used in the following synthesis without recrystallisation.

Table 2

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

Compound	CONH,1H,c	Ar-H, м	NCH_2, 2H, c	SCH_2, 2H, c	Others
7a	10,09	6,88-7,92, 13H	6,02	4,10	2,29, 3H, s, CH_3
7b	10,12	7,08-7,93, 13H	6,02	4,09	2,28, 3H, s, CH_3
7c	10,19	6,62-7,95, 13 H	6,01	4,10	3,75, 3H, s, OCH_3
7d	10,22	6,97-7,95, 18H	6,02	4,10	-
7e	9,81	7,22-7,93, 13H	6,02	4,12	-
7f	10,54	7,25-8,01, 13 H	6,02	4,11	-
7g	9,50	6,88-7,95 12H	6,02	4,11	2,11, 3H, s, 2,24, 3H, s, 2xCH_3
7h	9,50	7,01-7,95, 12H	6,03	4,11	2,09, 6H, s, 2xCH_3
7i	9,77	7,14-7,92, 12H	6,02	4,11	2,20, 3H, s, CH_3
7j	9,55	6,60-7,92, 12H	6,02	4,11	3,75, 3H, s, OCH_2; 3,69, 3H, s, SCH_2

(0,01 mole) **5** was suspended in 80 ml water, 1,12 g KOH (0,02 mole) was added. Reaction mixture was refluxed for about 5 hrs. After cooling was acidified with HCl to pH=3-4. Precipitate formed was filtered, washrd with water and dried. Yield – 80%. M.p. – 149-50°C.

Found N 27,4 $C_{15}H_{12}N_6O$ Requires N 27,3. NMR ^1H (DMSO-d_6, ppm): 5,90 (s, 2H, N-CH_2); 7,20-7,93 (m, 9H, Ar-H); 13,9 (1H, SH).

4-Phenyl-5-(1,2,3-benzotriazol-1-yl)-1,2,4-triazole(4*H*)-3-yl-thioacetanilides of (7a-j) (general method). To a solution of 0,002 mole 3-mercapto-4-phenyl-5-(1,2,3-benzotriazol-1-yl)-1,2,4-triazole(*4H*) (6) in 20 ml ethanol 20 ml KOH 0,002 M water solution was added. To the solution obtained solution of corresponding cloroacetanilide (0,02 mole) in ethanol was added at stirring. Reaction mixture was refluxed for about 1 hrs, cooled and placed into 200 ml water. Precipitate was collected and dried, recrystalled from ethanol.

4-Phenyl-5-(1,2,3-benzotriazol-1-yl)-1,2,4-triazole(4*H*)3-yl-thioacetic acid cyclohexylamide (8).

Synthesized as general procedure 7a-j.

Yield – 80%. M.p. – 149-50°C.

Found N 22,1 $C_{23}H_{25}N_7O$. Requires N 21,9. NMR ^1H (DMSO-d_6, ppm): 1,20 (6H, m, 3xCH_2), 1,69 (4H, m, 2xCH_2), 3,48 (1H, m, CH), 3,84 (d, 3H, S-CH_2+ CONH), 6,01 (s, 2H, N-CH_2); 7,20-7,96 (m, 9H, Ar-H).

3-Phenacylmethylthio-4-phenyl-5-(1,2,3-benzotriazol-1-yl)methyl-1,2,4-triazole(4*H*) (9).

Synthesized as general procedure 7a-j.

Yield – 76%. M.p. – 149-51°C.

Found N 19,9 $C_{23}H_{18}N_6O$. Requires N 19,7. NMR ^1H (DMSO-d_6, ppm): 4,85 (s, 2H, S-CH_2), 6,01 (s, 2H, N-CH_2); 7,23-7,98 (m, 14H, Ar-H).

Conclusions

1. Series of new 4-phenyl-5-(1,2,3-benzotriazolyl-1)-3-mercapto-1,2,4-triazole (4H) derivatives was synthesized started from benzotriazole and ethyl chloroacetate via intermediate 3-mercapto-4-phenyl-5-(1,2,3-benzotriazol-1-yl)-1,2,4-triazole(4*H*).

2. Due to computer prognosis data the substances synthesized are prospective anticonvulsants and antiasthmatics.

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