Experimental and clinical pharmacology

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THE STUDY OF PROPERTIES OF 2-[5-R-4-(2-METHOXYPHENYL)-1,2,4-TRIAZOLES 3-YLTHIO]-1-ARYLETANONES

Keywords: 1,2,4-triazole, physical and chemical properties

Introduction. Searching of the biologically active substances among heterocyclic nitrogen containing compounds causes a considerable interest and attention of many researchers. This is not surprising. Because an amount of highly efficient drugs always supplements with derivatives of such heterocyclic systems. Derivatives of 1,2,4-triazoles are characterized by a number of valuable properties, namely low toxicity, reactionary ability, expressed biological activity. Therefore, the combination of this kind of molecule with various sintons is an actual task for modern pharmacy and medicine.

The aim of our research was a purposeful search of new substances among 2-(1,2,4-triazoles-3-ylthio)-1-aryletanone, research of their physical, chemical and biological properties.

Materials and methods. Research of physical and chemical properties of obtained compounds performed, using methods that are listed in the State Pharmacopoeia of Ukraine. The melting point determined by open capillary method on the device PTP (M). The structure of compounds was confirmed by elemental analysis on the Elementar Vario L cube (CHNS) device, IR-spectra (4000 - 400 cm^{-1}) were removed on a module of the ALPHA-T spectrometer Bruker ALPHA FT-IR. ^{1}H NMR spectra of compounds were recorded, using a spectrometer «Mercury 400» (solvent - DMSO-d_6, internal standard - tetramethylsilane). Chromatographic and mass spectral researches performed on the instrument Agilent 1100 Series LC/MSD System, ionization method - chemical ionization at atmospheric pressure (APCI).

Results and discussion. To the alkylation of 1,2,4-triazoles-3-thiones by α-halogen ketone is devoted several works of national and foreign authors.

Established that the reaction of 1,2,4-triazoles-3-thiones with α-halogen ketones proceeds exclusively using sulfur atom with a formation of 2-(1,2,4-triazoles-3-ylthio)-1-aryletanones.

During the alkylation of 4-(2-methoxyphenyl)-5-methyl-1,2,4-triazoles-3-thione and 4-(2-methoxyphenyl)-5-phenyl-1,2,4-triazoles-3-thione by α-halogen ketones in ethanol medium with an addition of equimolecular amount of sodium hydroxide occurs a formation of corresponding 2-[5-R-4-(2-methoxyphenyl)-1,2,4-triazoles 3-ylhtio]-1-aryletanones (Pic. 1).

R= CH_3, C_6H_5; R_1=H, C_6H_5; R_2=C_6H_5, C_6H_5-C_6H_5, $C_6H_4NO_2$-4, C_6H_4Cl-4, $C_6H_4OCH_3$-4

Pic. 1. The scheme of synthesis of 2-[5-R-4-(2-methoxyphenyl)-1,2,4-triazoles-3-ylthio]-1-aryletanones.

Obtained 2-[5-R-4-(2-methoxyphenyl)-1,2,4-triazoles-3-ylthio]-1-aryl-ethanones (1-15) - white (1-3 , 6-11, 14, 15), yellow (4, 5, 12, 13) crystalline substance, practically insoluble in water, soluble in alcohol and dimethyl formamide. For analysis compounds recrystallized from methanol (2, 10), a mixture of acetate acid: water (2:1) (4); ethanol, n-propanol (1: 1) (3) or n-propanol (1, 5-9, 11-15).

Individuality of compounds 1-15 confirmed by the method of thin layer chromatography in different solvent systems.

IR-spectrum of 1-15 compounds characterized by vibrational bands of the NH-groups within the ranges 3500-3300 cm^{-1}; C = N-groups within the ranges 1660-1470 cm^{-1}; O_2N groups within 1650-1620 cm^{-1} (ν_{as}) and 1345-1310 cm^{-1} (ν_s) (compounds 5, 13). CO-groups within the ranges 1725-1700 cm^{-1}, also available vibrational bands between 1600-1460 cm^{-1} and below 1050 cm^{-1}, which is typical for an aromatic ring. Planar deformational C-H vibrations in areas 1025-1005 cm^{-1} and 775-744 cm^{-1}, also an additional band among 2845-2865 cm^{-1} demonstrate the presence of 2-methoxyphenyle fragment. The aromatic protons in ^1H NMR spectra of compounds 1-15 observed as two single-proton doublets (at 7,38-7,34 ppm and at 7,17-7,13 ppm)

and two single–proton triplets (at 7, 13- ppm and 7.06 ppm at 7,56-7,51). CH_3O-group resonates in area 3,77-3,62 ppm, CH_3 signal appears as singlets at 2,22-2,09 ppm.

In ^1H NMR spectrum of compounds available signals of single-proton aromatic doublets at 7.34 ppm (1H, H-6, J = 7,8 Hz) and at 7.29 ppm (1H, H-2, J = 8,3 Hz) and signals of aromatic single-proton triplets at 7.56 ppm (H-4, J = 8,1 Hz) and at 7.13 ppm (1H, H-5, J = 7,6 Hz). Registered also a singlet of methoxy group at 3.77 ppm (2-CH_3O) and the methyl group at 2.09 ppm (5-CH_3). In a strong part of magnetic area present resonating protons of methoxy group at 3.83 ppm. 2-methoxyphenyle balance has two proton doublets (H-6 at 7.34 ppm, H-3 at 7.24 ppm) and two proton triplets: H-5 at 7.51 ppm, H-4 resonates at 7.14 ppm.

Table 1

2-[5-R-4-(2-methoxyphenyle)-1,2,4-triazole-3-ylthio]-1-arylethanones (1–15)

Compound	R	R_1	R_2	T m., °C	Formula	Yield, %
1	CH_3	H	C_6H_5	102 - 104	$C_{18}H_{17}N_3O_2S$	79
2	CH_3	H	$C_6H_4CH_3$-4	67 - 69	$C_{19}H_{19}N_3O_2S$	83
3	CH_3	H	$C_6H_4OCH_3$-3	182 - 184	$C_{19}H_{19}N_3O_3S$	65
4	CH_3	H	$C_6H_4OCH_3$-4	177 - 179	$C_{19}H_{19}N_3O_3S$	69
5	CH_3	H	$C_6H_4NO_2$-4	201 - 202	$C_{18}H_{16}N_4O_4S$	73
6	CH_3	H	$C_6H_3CH_3$-2-CH_3-4	124-125	$C_{20}H_{21}N_3O_2S$	86
7	CH_3	H	$C_6H_3OCH_3$-2-OCH_3-5	121	$C_{20}H_{21}N_3O_4S$	76
8	CH_3	H	C_6H_5-C_6H_4	112 - 114	$C_{24}H_{21}N_3O_2S$	88
9	CH_3	C_6H_5	C_6H_5	162 - 163	$C_{24}H_{21}N_3O_2S$	71
10	C_6H_5	H	C_6H_5	123 - 125	$C_{23}H_{19}N_3O_2S$	59
11	C_6H_5	H	$C_6H_4OCH_3$-3	208	$C_{24}H_{21}N_3O_3S$	66
12	C_6H_5	H	$C_6H_4OCH_3$-4	188 - 191	$C_{24}H_{21}N_3O_3S$	60
13	C_6H_5	H	$C_6H_4NO_2$-4	230	$C_{23}H_{18}N_4O_4S$	76
14	C_6H_5	H	C_6H_5-C_6H_4	164 - 166	$C_{29}H_{23}N_3O_2S$	85
15	C_6H_5	C_6H_5	C_6H_5	229 - 231	$C_{29}H_{23}N_3O_2S$	82

Table 3

The data of synthesized compounds elemental analysis

Compound	Found, %				Calculated, %			
	C	H	N	S	C	H	N	S
1	63,73	5,02	12,41	9,48	63,70	5,05	12,38	9,45
2	64,55	5,45	11,92	9,04	64,57	5,42	11,89	9,07
3	61,79	5,15	11,40	8,65	61,77	5,18	11,37	8,68
4	61,79	5,16	11,40	8,65	61,77	5,18	11,37	8,68
5	56,27	4,16	14,59	8,31	56,24	4,20	14,57	8,34
6	65,39	5,74	11,47	8,71	65,37	5,76	11,44	8,73
7	60,11	5,27	10,49	8,06	60,13	5,30	10,52	8,03
8	69,35	5,12	10,09	7,76	69,37	5,09	10,11	7,72
9	70,12	4,74	10,14	8,73	69,37	5,09	10,11	7,72
10	68,79	4,75	10,49	7,98	68,81	4,77	10,47	7,99
11	66,81	4,87	9,74	7,43	66,80	4,91	9,74	7,43
12	66,77	4,94	9,71	7,45	66,80	4,91	9,74	7,43
13	61,89	4,09	12,51	7,15	61,87	4,06	12,55	7,18
14	72,96	4,83	8,77	6,74	72,93	4,85	8,80	6,71
15	72,96	4,88	8,79	6,67	72,93	4,85	8,80	6,71

Acute toxicity of the synthesized compounds

On the first stage of biological research of synthesized compounds examines mainly an acute toxicity, which significantly allows to reduce the number and intensity of the adverse reactions manifestations in terms of their clinical application.

The aim of toxicological research of compounds, derivatives of 1,2,4-triazoles, was identification of the character and severity of their damaging effects on the organism of experimental animals and evaluation of their safety.

Researches performs, using tabulated express-method of V. B. Prozorovskiy on white rats of the Wistar line.

Were used four groups of animals, 2 observations in each each with an additional application of previous and subsequent dose. Water-soluble compounds dissolved in 1.5 ml of purified water and injected in compliance with the rules of aseptic and antiseptic intraperitoneally. Water-insoluble compounds stabilized with twin-80 and introduced through a metal tube into the stomach. The observations performed after 24 hours.

Table 2

Acute toxicity of 2- [5-R-4-(2-methoxyphenyl)-1,2,4-triazoles 3-iltio]-1-aryletanones (4, 5, 9, 13-15)

Compound	LD_{50}, mg/kg	Compound	LD_{50}, mg/kg
4	421 (415 – 445)	13	490 (475 – 505)
5	474 (455 – 480)	14	564 (540 – 575)
9	740 (720 – 755)	15	790 (760 – 805)

On a quantity of the toxicity of these compounds, affect substituents with phenyl group of the ketone residue. Yes, substituents of 4-methoxy and 4-nitro significantly increase the toxic properties of 2-[5-R-4-(2-methoxyphenyl)-1,2,4-triazoles-3-iltio]-1-aryletanones. It should be noted that the increase in acute toxicity is observed at the recovery of 2-[5-R-4-(2-methoxyphenyl)-1,2,4-triazoles 3-ylthio]-1-aryletanones to 2-[5-R-4-(2-methoxyfenyl)-1,2,4-triazoles-3-ylthio]-1-aryletanoles. Also established that the transition from 2-[5-methyl-4-(2-methoxyphenyl)-1,2,4-triazole-3-ylthio]-1-arylethanones to 2-[5-phenyl-4-(2-methoxyphenyl)-1,2,4-triazole-3-ylthio]-1-arylethanones do not allows to clearly form the correlation dependence between the influence of radicals in fifth position of the nucleus of 1,2,4-triazoles and between a modification of the acute toxicity.

Conclusions

Established the optimal conditions of synthesis of 2-[5-R-4-(2-methoxyphenyl)-1,2,4-triazoles-3-ylthio]-1-aryletanones with 4-(2-methoxyphenyl)-5-R-1,2,4-triazoles-3-thiones. It is proved that the major outputs of the reaction products were observed using ethanol as a solvent. Researched general physical and chemical properties of the compounds.

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