SYNTHESIS AND BIOLOGICAL PROPERTIES OF S-DERIVATIVES OF 5-HETERYL-4(R-AMINO)-1,2,4-TRIAZOLE-3-THIOLS

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Abstract

Novel derivatives of 5-heteryl-4-(R-amino)-1,2,4-triazole-thiols were synthesized in search of new biologically active substances. The structures of the compounds are revealed by the elemental analysis, IR spectroscopy, and ^{1}H NMR spectroscopy. The Quantitative Structure-Activity Relationship of the derived substances was studied.

1. Introduction.

Modern medicine always requires more new drugs with acute pharmacological activity and a small number of side effects. There is a plenty of soporific and analeptic medications, but they all have a whole range of side effects. Drugs regulating CNS functions include psychotropic, narcotic, and soporific medicines, as well as analgesics, anticonvulsants, and analeptic medications, etcetera. The activity of neurotropic drugs is based on their capability to change the process of the excitatory inter-neuron communication. Considering the character of the drug action on the human body, the medications are classified into inhibitory and excitatory ones, which are in their turn conditionally divided into substances with non-selective (for example, narcotics) and selective activity (analgesics, anti-anxiety and antiparkinson drugs, etc.).

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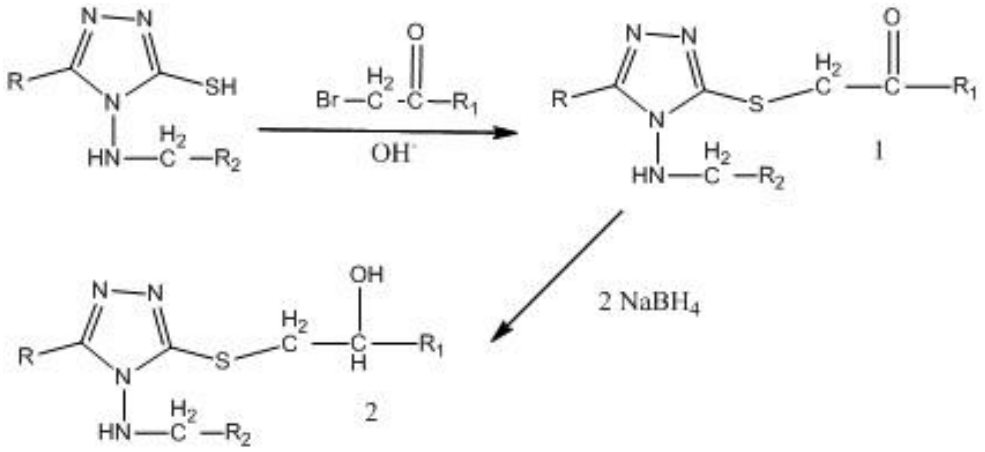
Medications, which have the 1,2,4-triazole nucleus in their structure and show antiseizure, analgesic, antidepressant, antimicrobial, and antifungal activity, proved to be reliable among novel promising low-toxic and highly effective medications [3-11, 13].

2. Chemistry

Such substances as 4-(4-chlorobenzylamino)-5-(heteryl)-4H-1,2,4-triazole-3-thiol and 4-(furan-2-ylmethylamino) were used as precursors, with previously derived [11] fragments of pyridine nucleus (I, II, III, IV, V, VI Tabl. 1) serving as heteryl substituents. The synthesis of 2-(4-(4-chlorobenzylamino)-5-(heteryl)-4H-1,2,4-triazole-3-ylthio)-1-(R)ethanones and 2-(4-(furan-2-ylmethylanimo)-5-(heteryl)-4H-1,2,4-triazole-3-ylthio)-1-(R)ethanones (compounds Ia, IIa, IIIa, IIIb, IVa, Va, Vb, VIa Tabl.1) is performed by the interaction of the corresponding thiols (compounds I, II, III, IV, V, VI Tabl. 1) with α-halogenketones (2-bromine-1-(4-methoxyphenyl)ethanone and 2-bromine-1-(3-methoxypnenyl)ethanone) in methanol base (1). The substances of 2-(4-(4-chlorobenzylamino)-5-(heteryl)-4H-1,2,4-triazole-3-ylthio)-1-(R)ethanols and 2-(4-(furan-2-ylmethylamino)-5-(heteryl)-4H-1,2,4-triazole-3-ylthio)-1-(R)ethanols (2) are synthesized by adding double amount of sodium borohydride to the corresponding ketones in the methyl alcohol and water base in proportion of 30:1. The solution is filtered in 24 hours and neutralized by acetic acid. The sediment of corresponding alcohols is formed (compounds Ib, IIIc, IIId, IVb, Vc, Vd, VIb).

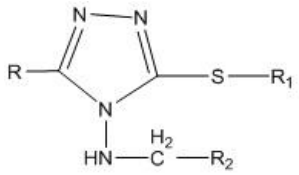


Scheme 1. Synthesis of 2-(4-(R_2-amino)-5-R-4H-1,2,4-triazole-3-ylthio)-1-(R_1) ethanones and 2-(4-(R_2-amino)-5-R-4H-1,2,4-triazole-3-ylthio)-1-(R_1)ethanols.

3. Results and discussion

The structures of the synthesized compounds were confirmed by analytical (Table 1) and spectral data (IR, ^{1}H NMR) (Table 3, Table 4) [2]. The IR-spectra of Ia, IIa, IIIa, IIIb, IVa, Va, Vb, VIa exhibited C=O bands in the 1697-1657 cm^{-1}. The absorption bands at 705-570 cm^{-1} are due to the presence of –C–S–. The evident fluctuation bands are characteristic to the groups of 1,2,4-triazole nucleus: NH- within 3400-3100 cm^{-1}, –C=N–1681-1606 cm^{-1}. The ^{1}H NMR spectra of compounds Ia, IIa, IIIa, IIIb, IVa, Va, Vb, VIa reveals OCH_3 within the interval of 3,63 – 3,84, as well as N-CH_2 within the interval of 3,90 – 4,31 and CO-CH_2 within the interval of 4,93 – 5,03.

Table 1.Physical and chemical constants of 4-(4-chlorobenzylamino)-5-R-4H-1,2,4-triazole-3-thiols and N-(4-chlorobenzyl)-3-R_1-5-R-4H-1,2,4-triazoles-4-amines.



Compd	R	R_1	R_2	M.p. ^{0}C	Formula	Yield (%)
I	pyridin-2-yl	H	4-chlorobenzyl	193-195	$C_{14}H_{12}ClN_5S$	59,79
Ia	pyridin-2-yl	$CH_2COC_6H_4OCH_3$-п	4-chlorobenzyl	146-148	$C_{23}H_{20}ClN_5O_2S$	83,69
Ib	pyridin-2-yl	$CH_2CHOHC_6H_4OCH_3$-п	4-chlorobenzyl	40-42	$C_{23}H_{22}ClN_5O_2S$	52,63
II	pyridin-2-yl	H	furan-2-ylmethyl	148-150	$C_{12}H_{11}N_5OS$	63,09
IIa	pyridin-2-yl	$CH_2COC_6H_4OCH_3$-м	furan-2-ylmethyl	113-115	$C_{21}H_{19}N_5O_3S$	68,88
III	pyridin-3-yl	H	4-chlorobenzyl	217-219	$C_{14}H_{12}ClN_5S$	75,84
IIIa	pyridin-3-yl	$CH_2COC_6H_4OCH_3$-м	4-chlorobenzyl	137-139	$C_{23}H_{20}ClN_5O_2S$	62,23
IIIb	pyridin-3-yl	$CH_2COC_6H_4OCH_3$-п	4-chlorobenzyl	118-120	$C_{23}H_{20}ClN_5O_2S$	73,18
IIIc	pyridin-3-yl	$CH_2CHOHC_6H_4OCH_3$-м	4-chlorobenzyl	52-55	$C_{23}H_{22}ClN_5O_2S$	40,66
IIId	pyridin-	CH_2CHOHC_6H	4-	42-44	$C_{23}H_{22}ClN_5$	39,47

	3-yl	$_4OCH_3$-п	chlorobenzyl		O_2S	
IV	pyridin-3-yl	H	furan-2-ylmethyl	105-107	$C_{12}H_{11}N_5OS$	71,83
IVa	pyridin-3-yl	$CH_2COC_6H_4OCH_3$-п	furan-2-ylmethyl	178-180	$C_{21}H_{19}N_5O_3S$	54,98
IVb	pyridin-3-yl	$CH_2CHOHC_6H_4OCH_3$-п	furan-2-ylmethyl	38-40	$C_{21}H_{21}N_5O_3S$	42,76
V	pyridin-4-yl	H	4-chlorobenzyl	270-272	$C_{14}H_{12}ClN_5S$	75,00
Va	pyridin-4-yl	$CH_2COC_6H_4OCH_3$-м	4-chlorobenzyl	120-122	$C_{23}H_{20}ClN_5O_2S$	66,67
Vb	pyridin-4-yl	$CH_2COC_6H_4OCH_3$-п	4-chlorobenzyl	80-82	$C_{23}H_{20}ClN_5O_2S$	70,38
Vc	pyridin-4-yl	$CH_2CHOHC_6H_4OCH_3$-м	4-chlorobenzyl	52-54	$C_{23}H_{22}ClN_5O_2S$	22,66
Vd	pyridin-4-yl	$CH_2CHOHC_6H_4OCH_3$-п	4-chlorobenzyl	50-52	$C_{23}H_{22}ClN_5O_2S$	39,47
VI	pyridin-4-yl	H	furan-2-ylmethyl	226-228	$C_{12}H_{11}N_5OS$	66,66
VIa	pyridin-4-yl	$CH_2COC_6H_4OCH_3$-п	furan-2-ylmethyl	119-121	$C_{21}H_{19}N_5O_3S$	60,80
VIb	pyridin-4-yl	$CH_2CHOHC_6H_4OCH_3$-п	furan-2-ylmethyl	53-55	$C_{21}H_{21}N_5O_3S$	46,05

Compd.	**Required, %**				**Found, %**			
	C	**H**	**N**	**S**	**C**	**H**	**N**	**S**
I	52,91	3,81	22,04	10,09	52,75	3,79	22,04	10,04
Ia	59,29	4,33	15,03	6,88	59,58	4,34	15,10	6,87
Ib	59,03	4,74	14,97	6,85	59,26	4,73	15,02	6,88
II	52,73	4,06	25,62	11,73	52,88	4,04	25,54	11,76
IIa	59,84	4,54	16,62	7,61	60,01	4,55	16,57	7,63
III	52,91	3,81	22,04	10,09	52,91	3,79	21,90	10,12
IIIa	59,29	4,33	15,03	6,88	59,17	4,34	14,95	6,89
IIIb	59,29	4,33	15,03	6,88	59,05	4,31	15,06	6,85
IIIc	59,03	4,74	14,97	6,85	58,85	4,76	14,89	6,87
IIId	59,03	4,74	14,97	6,85	58,85	4,75	15,01	6,87
IV	52,91	3,81	22,04	10,09	53,06	3,83	22,15	10,05
IVa	59,84	4,54	16,62	7,61	59,54	4,55	16,53	7,58
IVb	59,56	5,00	16,54	7,57	59,32	4,98	16,49	7,60
V	52,91	3,81	22,04	10,09	53,06	3,83	22,15	10,05
Va	59,29	4,33	15,03	6,88	59,09	4,31	15,10	6,91
Vb	59,29	4,33	15,03	6,88	59,52	4,31	15,07	6,92
Vc	59,03	4,74	14,97	6,85	58,73	4,74	14,94	6,83
Vd	59,03	4,74	14,97	6,85	59,32	4,76	15,04	6,83

VI	52,73	4,06	25,62	11,73	52,57	4,08	25,72	11,69
VIa	59,84	4,54	16,62	7,61	59,66	4,56	16,68	7,64
VIb	59,56	5,00	16,54	7,57	59,38	4,99	16,58	7,55

4. Biological activity

We applied the interaction of the researched substances with the narcotic substances to the rats. The phenomenon of potentiating of sodium thiopental narcosis (30 mg/kg) by new 1,2,4-triazole derivatives was studied in the research.

For the goal to be achieved, the researches were conducted on the intact white non-linear rats of different gender weighing from 90 to 210 grams with 7 animals in each group. Polysorbat-80 stabilized (for those insoluble in water) water suspension of 1,2,4-triazole derivatives and water solution (for those soluble in water) of compounds (in dose of 1/10 from LD_{50} with 1 ml of solution\suspension for 100 gram of the animal's weight) were to be taken per os 1 hour before the injection of sodium thiopental. The duration time of the sodium thiopental narcosis action was judged in accordance to the period of time during which the animal was lying on its side, to be more distinct, since the moment of turn-over reflex disappearance. As the comparison etalon, Aminazine and Caffeine and sodium benzoate were used, with them being injected in doses of 10mg/kg and 50mg/kg correspondently [1].

5. Conclusion.

The study of the effect of 5-heteryl-4-(R-amino)-1,2,4-triazole-3-thiols derivatives on the central nervous system demonstrates that these compounds show activity in the interval of -89,40 – 274,17% ($P < 0,05$). The most evident analeptic effect is shown by 2-((4-((4-chlorobenzyl)amino)-5-(pyridin-4-yl)-4H-1,2,4-triazole-3-yl)thio)-1-(4-methoxyphenyl)ethanol (compound Vd), which contains pyridine-4-yl substituent by the C_5 carbon atom of 1,2,4-triazole cycle, 4-chlorobenzyl substituent compounded with the amino group by N_4 atom, and (4-methoxyphenyl)ethanol by the sulphur atom. 2-((4-((4-chlorobenzyl)amino)-5-(pyridin-3-yl)-4H-1,2,4-triazole-3-yl)thio)-1-(3-methoxyphenyl)ethanone demonstrates the inhibitory effect and exceeds the comparison etalon by 59,54 % ($P < 0,05$).

The moderate inhibitory effect is demonstrated by such compounds as I, II, IIIb, V, Va, with their activity increased within the interval of 18,84 – 176,62% ($P < 0,05$). Among them, the most significant inhibitory effect is shown by 2-((4-((4-chlorobenzyl)amino)-5-(pyridin-3-yl)-4H-1,2,4-triazole-3-yl)thio)-1-(4-methoxyphenyl)ethanone, which contains 4-chlorobenzyl radical that is compounded with the amino group by N_4 atom, the substitution of which with furan-2-ylmethyl atom causes the decrease of the effect (compound II, IV).

The substitution of the pyridine-3-yl substituent with the pyridine-4-yl one and the reduction of the ketogroup in the molecule of 2-((4-((4-chlorobenzyl)amino)-5-(pyridin-3-yl)-4H-1,2,4-triazole-3-yl)thio)-1-(4-methoxyphenyl)ethanone cause the analeptic effect.

Table 2. The effect of 5-heteryl-4-(R-amino)-1,2,4-triazole-3-thiols derivatives on the central nervous system.

№ п/п	Compound code	Average duration of sleep in rats, M±m	Control group comparison proportion,Δ%
1	Control	53,82±2,064	0
2	Aminazine	175,21±23,997	225,57
3	Sodium caffeine-benzoate	16,80±31,193	-68,78
4	I	79,35±12,788	47,44
7	II	71,60±5,888	33,05
9	III	63,96±6,191	18,84
10	IIIb	148,87±20,525	176,62
11	IIIc	39,96±23,196	-25,75
12	IIId	42,83±4,796	-20,41
16	V	85,84±6,740	59,50
17	Vc	40,85±5,303	-24,10
18	VI	56,03±7,857	4,11
21	Control	52,74±4,533	0
22	Aminazine	165,93±22,464	214,63
23	Sodium caffeine-benzoate	19,54±28,773	-62,95
24	IIIa	213,90±36,287	274,17
25	Va	83,04±7,110	37,58
26	Vb	30,78±3,840	-46,16
27	Vd	6,40±12,053	-89,40

6. Experimental protocols.

Researches of physical and chemical properties of the compounds got by us were conducted accordingly to methods which are resulted in State Pharmacopoeia of Ukraine. The temperature of melting was defined by the opened capillary method on the device of PTP (M). The structure of matters is confirmed by the element analysis on the device of Elementar Vario L cube (CHNS), IR-spectra (4000-400 cm^{-1}) were taken off on the module of ALPHA-T (KBr) of Bruker ALPHA FT-IR spectrometer. The ^1H NMR-spectra of compounds were written by the spectrometer of «Mercury-400», with $DMSO_{d6}$ used as a solvent.

6.1 General procedure for the synthesis of 2-((4-((furan-2-ylmethyl)amino)-5-(R)-4H-1,2,4-triazole-3-yl)thio)-1-(R_1)ethanone and 2-((4-((4-chlorobenzyl)amino)-5-(R)-4H-1,2,4-triazole-3-yl)thio)-1-(R_1)ethanone (compounds Ia, IIa, IIIa, IIIb, IVa, Va, Vb, VIa Tabl. 1).

0,01 mol of NaOH is added to 0,01 mol of 4-(4-chlorobenzylamino)-5-R-4H-1,2,4-triazole-3-thiol or 4-(furan-2-ylmethylamino)-5R-4H-1,2,4-triazole-3-thiol, in which R is pyridin-2-yl, pyridin-3-yl or pyridin-4-yl, in methanol base. It is warmed till the sediment dissolves. Then 0,01 mol of α-halogenketone (2-bromine-1-(4-methoxyphenyl)ethanone or 2-bromine-1-(3-methoxyphenyl)ethanone) is added. It is boiled till the neutral pH base is formed. It is vaporized. Then it is over-crystallized from methanol, ethanol or n-propanol.

6.2 General procedure for the synthesis of 2-((4-((4-chlorobenzyl)amino)-5-(heteryl)-4H-1,2,4-triazole-3-yl)thio)-1-(R)ethanol and 2-((4-((furan-2-ylmethyl)amino)-5-(heteryl)-4H-1,2,4-triazole-3-yl)thio)-1-(R)ethanol.

The double amount of sodium borohydride is added to 0.01 mol of 2-(4-(4-chlorobenzylamino)-5-(R)-4H-1,2,4-triazole-3-ylthio)-1-(R_1)ethanone or 2-(4-(furan-2-ylmethylamino)-5-(R)-4H-1,2,4-triazole-3-ylthio)-1-(R_1)ethanone, where R is pyridin-2-yl, pyridin-3-yl or pyridin-4-yl and R_1 is 3-methoxyphenyl or 4-methoxyphenyl, in methyl alcohol and water base in proportion of 30:1. The solution is filtered in 24 hours and neutralized by acetic acid, after that the

sediment of corresponding alcohols appears. The sediment is filtered and over-crystallized from methanol (compounds Ib, IIIc, IIId, IVb, Vc, Vd, VIb).

Table 3. Infra red (KBr, cm^{-1}) Spectral Data for Compounds

No.	C=O	C=N, C=C	NH	No.	C=O	C=N, C=C	NH	No.	C=O	C=N, C=C	NH
Ia	1674	1596	3310	IIIc	____	1599	3225	Vb	1657	1596	3290
Ib	____	1586	3300	IIId	____	1596	3230	Vc	____	1600	3290
IIa	1678	1581	3260	IVa	1660	1594	3340	Vd	____	1606	3218
IIIa	1697	1596	3330	IVb	____	1595	3330	VIa	1666	1595	3300
IIIb	1683	1597	3259	Va	1697	1597	3360	VIb	____	1605	3245

Table 4. ^{1}H-NMR Spectral Data for Compounds

No.	^{1}H-NMR (DMSO-d^{6} δ ppm
Ia	3,78 (s, 3H, OCH_3), 4,09 (s, 2H, N-CH_2), 5,03 (s, 2H, CO-CH_2), 7,02 (d, 2H, Ar-H), 7,21 (q, 3H, Py-H), 7,49 (m, 7H, Ar-H), 8,62 (d, 2H, Ar-H), 8,85 (s, 1H, Py-H)
IIa	3,71 (s, 3H, OCH_3), 3,90 (s, 2H, N-CH_2), 5,01 (s, 2H, CO-CH_2), 6,05 (d, 2H, Fur-H), 7,01 (d, 2H, Ar-H), 7,21 (q, 3H Ar-H), 7,53 (m, 7H, Ar-H), 7,97 (d, 2H, Ar-H), 8,62 (d, 2H, Py-H), 8,85 (s, 1H, Py-H)
IIIa	3,79 (s, 4H, OCH_3), 4,05 (s, 2H, N-CH_2), 4,97 (s, 2H, CO-CH_2), 7,00 (d, 2H, Ar-H), 7,17 (q, 4H, Ar-H), 7,53 (m, 7H, Ar-H), 8,05 (d, 1H, Py-H), 8,63 (d, 1H, Py-H), 8,86 (s, 1H, Py-H)
IIIb	3,70 (s, 3H, OCH_3), 4,06 (s, 2H, N-CH_2), 4,99 (s, 2H, CO-CH_2), 6,94 (d, 2H, Ar-H), 7,15 (q, 3H, Ar-H), 7,55 (m, 7H, Ar-H), 7,95 (d, 1H, Py-H), 8,60 (d, 1H, Py-H), 9,20 (s, 1H, Py-H)
IVa	3,81 (s, 3H, OCH_3), 4,31 (s, 2H, N-CH_2), 4,93 (s, 2H, CO-CH_2), 6,05 (d, 2H, Fur-H), 7,12 (d, 2H, Ar-H), 7,38 (d, 1H, Ar-H), 7,54 (s, 2H, Py-H), 8,05 (d, 1H, Fur-H), 8,42 (d, 1H, Ar-H), 9,17 (s, 1H, Py-H)
Va	3,63 (s, 4H, OCH_3), 4,06 (s, 2H, N-CH_2), 5.00 (s, 2H, CO-CH_2), 6.99 (d, 2H, Ar-H), 7,19 (q, 3H, Ar-H), 7,57 (m, 7H, Ar-H), 8,03 (d, 1H, Py-H), 8,35 (d, 1H, Ar-H), 8,75 (d, 2H, Py-H)
Vb	3,74 (s, 3H, OCH_3), 4,15 (s, 2H, N-CH_2), 5.01 (s, 2H, CO-CH_2), 7,05 (d, 2H, Ar-H), 7,34 (q, 4H, Ar-H), 7,82 (d, 2H, Ar-H), 8,00 (d, 2H, Py-H), 8,63 (d, 2H, Py-H)
VIa	3,84 (s, 3H, OCH_3), 4,15 (s, 2H, N-CH_2), 4,95 (s, 2H, CO-CH_2), 6,12 (d, 2H, Fur-H), 7,07 (d, 2H, Ar-H), 7,39 (d, 2H, Ar-H), 7,81 (d, 2H, Ar-H), 8,03 (d, 2H, Py-H), 8,61 (d, 2H, Py-H)

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