Recommended by Doctor of Pharmacy, professor S.V.Kolisnyk

UDC 547.398.1:547.461.3

THE SYNTHESIS AND PHYSICOCHEMICAL PROPERTIES OF NEW DERIVATIVES OF 5-R-PHENYLAMINO-2-MERCAPTO-1,3,4-THIADIAZOLE

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Key words: synthesis; 1,3,4-thiadiazole;^{1}H NMR-spectroscopy

With the aim of obtaining new biologically active substances the synthesis of amides of 5-R-phenylamino-1,3,4-thiadiazole-2-yl-thioacetate acid and 5-phenylamino-1,3,4-thiadiazole-2-yl-thio-1-phenon has been conducted. As initial substances 5-R-phenylamino-2-mercapto-1,3,4-thiadiazoles, the corresponding analides of chloracetate acid and chloracetate phenon were used. The reaction of alkylation was conducted in the ethanol medium in the presence of potassium hydroxide. The structure of the compounds synthesized has been confirmed by the method of ^{1}H NMR-spectroscopy. The physicochemical properties and the pharmacological potential of the substances synthesized are discussed. According to the results of calculation methods of prediction of the biological activity (PASSOnline) the probable types of the biological activity of the substances synthesized have been estimated. In compliance with the data of the PASSOnline computer-based prognosis the antineoplastic action (STAT inhibitor of transcription factors) is principally inherent for most compounds of this class.

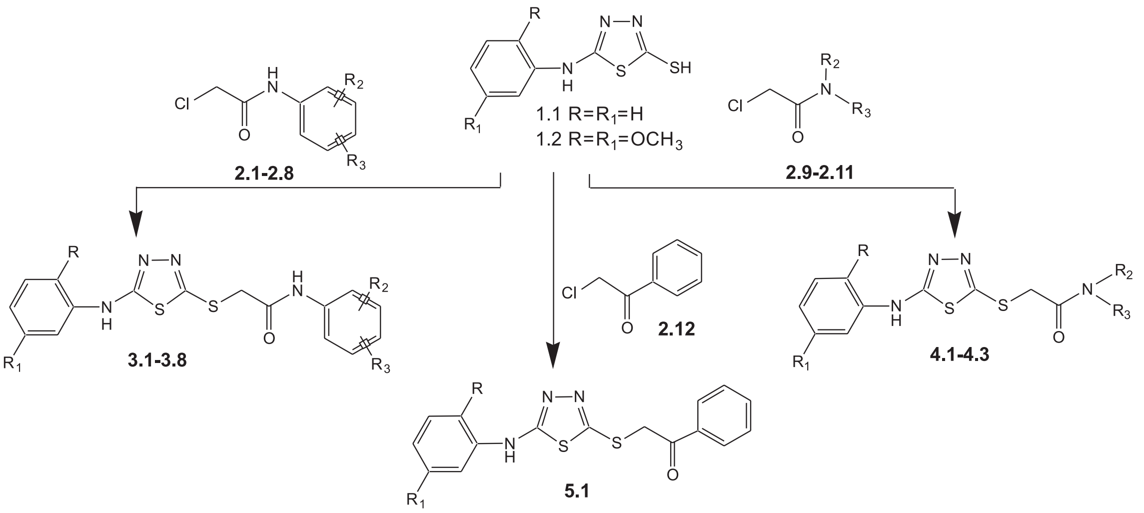
In the current realities the healthcare requires development and introduction of original medicines into production along with manufacture of generic drugs – only this way can raise the pharmaceutical industry of Ukraine to the higher level of quality and to rank it together with the leading European states. In this regard, creation of new effective medicines is a rather topical issue of modern pharmacy. Recently, along with the high pharmacological activity, the simplicity of synthetic methods and availability of the chemical raw material, which provide a relatively law prime cost of finished products, become the most important parameters for the choice of the research objects. With the aim of searching for new biologically active substances we paid attention to the derivatives of 1,3,4-thiadizole, which had already shown themselves as high-efficient bioactive substances exhibiting various types of the pharmacological action [2, 3, 5, 6, 8, 10, 11]. Currently, data on promising applications of derivatives of 1,3,4-thiadiazole for treating cancer appear in scientific literature more often [5, 10-11]. At the moment, the fundamental research of new derivatives are conducted on the basis of this heterocycle as potential antimicrobial agents [3, 6] and anticonvulsants [2, 8]. Thus, the further search of new bioactive substances among the derivatives of 1,3,4-thiadizole is one of the promising directions.

The aim of this work was to extend the range of potential bioactive substances on the basis of 5-R-phenylamino-2-mercapto-1,3,4-thiadiazoles. The synthesis of derivatives of 5-R-phenylamino-2-mercapto-1,3,4-thiadiazoles ***1.1-1.2*** was carried out by the interaction of carbonic disulphide and R-phenylthiosemicarbazide in the dimethylformamide medium at the temperature of 75°C with satisfactory yields (78-80%) by the known method [8]. The structure of the compounds obtained was confirmed by modern physical and chemical methods. Formation of the thiadiazole cycle was proven by the absence of NH-NH signal in the ^{1}H NMR-spectra of the compounds synthesized at δ 10.60-10.64 ppm and the presence of a singlet of the mercapto group at approximately 3.40 ppm [1, 9].

The target compounds – anilides of 5-(2,5-dimethoxy) phenylamino-1,3,4-thiadiazole-2-yl-thioacetate acid ***3.1-3.8*** and amides of 5-phenylamino-1,3,4- thiadiazole-2-yl-thioacetate acid ***4.1-4.3*** were obtained by S-alkylation with anilidies ***2.1-2.8*** and alkylamides ***2.9-2.11*** of chloracetate acid.

5-R-phenylamino-2-mercapto-1,3,4-thiadiazoles ***1.1-1.2*** were obtained in ethanol in the presence of the equimolar quantity of potassium hydroxide according to the Scheme given below.

The research results have proven that application of the method allows obtaining the target products with satisfactory yields and sufficient purity (Tab. 1). All compounds obtained after crystallization from ethanol are white crystalline substances with distinct melting points, soluble in most organic solvents (Tab. 1). To study the course of the alkylation reaction when using various alkali reagents the amides of chloracetate acid ***2.1-2.11*** were substituted by chloracetophenon ***2.12.*** (Scheme). The change of the alkylating agent did not affect substantially the yield of the finish product (5-phenylamino-1,3,4-thiadiazole-2-yl-thio-1-phenon ***5.1*** was obtained with the yield of 78%). The structure of the compounds obtained was confirmed by physical and spectral methods. The ^{1}H NMR-spectroscopy was performed, and the melting points of the compounds synthesized were determined. The composition of elements experimentally found corresponds exactly to the structures proposed.



Scheme

Table 1

Physical and chemical properties of the compounds synthesized

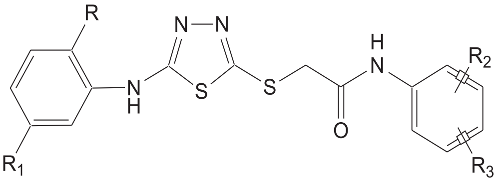
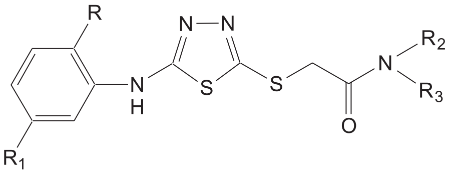
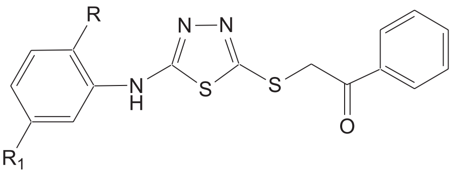
Compound	R	R_1	R_2	R_3	Yield, %	M. p., °C	Chemical formula	N, %	
								counted	founded
									
3.1	OCH_3	OCH_3	$3 – CH_3$	$6 – CH_3$	72	112-116	$C_{22}H_{22}N_4O_3S_2$	13,01	13,03
3.2	OCH_3	OCH_3	$4 – COOCH_3$	H	70	128-130	$C_{20}H_{20}N_4O_5S_2$	12,17	12,18
3.3	OCH_3	OCH_3	3 – Cl	4 – Cl	69	136-138	$C_{18}H_{16}Cl_2N_4O_3S_2$	11,89	11,91
3.4	OCH_3	OCH_3	$2 – COOCH_2\text{-}CH_3$	H	73	128-132	$C_{21}H_{22}N_4O_5S_2$	11,81	11,82
3.5	OCH_3	OCH_3	NHR = naphthyl		69	138-140	$C_{22}H_{20}N_4O_3S_2$	12,38	12,39
3.6	OCH_3	OCH_3	Bn	H	73	130-132	$C_{17}H_{16}N_4O_3S_2$	14,42	14,43
3.7	OCH_3	OCH_3	$2 – CH_3$	$4 – CH_3$	73	116-122	$C_{20}H_{22}N_4O_3S_2$	13,01	13,03
3.8	OCH_3	OCH_3	2 – Cl	3 – Cl	74	120-122	$C_{18}H_{16}Cl_2N_4O_3S_2$	11,89	11,90
									
4.1	H	H	$CH(CH_3)_2$	C_6H_5	79	160-162	$C_{19}H_{20}N_4OS_2$	14,57	14,58
4.2	H	H	H	$3,6 – OCH_3C_6H_4$	80	140-144	$C_{18}H_{18}N_4O_3S_2$	13,92	13,94
4.3	H	H	H	Bn	79	148-152	$C_{17}H_{16}N_4OS_2$	15,72	15,73
									
5.1	H	H	H	H	78	148-150	$C_{16}H_{13}N_3OS_2$	12,83	12,84

Table 2

Chemical shift (δ, ppm) of protons in 1H NMR spectra of the compounds synthesized

Compound	CONH (1H, s)	NH-R (1H, s)	2×OCH_3 (6H, s)	H-Ar	SCH_2 (2H, s)	Signals of protons of other functional groups
3.1	9,55	9,35	3,75	6,45, s, 1H; 6,80, d, 2H; 7,00, s, 1H; 7,40, s, 1H; 8,05, s, 1H.	4,05	2,30 (6H, s, 2×CH_3)
3.2	10,40	9,55	3,75	6,45-6,70, dd, 2H; 7,70, s, 1H; 7,90, s, 3H; 8,05, s, 1H.	4,45	2,50 (3H, s, CH_3)
3.3	10,40	9,55	3,75	6,45, s, 1H; 6,80, s, 1H; 7,35-7,50, dd, 2H; 7,90-8,05, dd, 2H.	4,05	–
3.4	9,55	9,35	3,75	6,45, s, 1H; 6,80-7,00, m, 4H; 8,05, s, 1H; 8,15, s, 1H.	4,10	4,05 (2H, s, CH_2) 1,40 (3H, s, CH_3)
3.5	10,10	9,60	3,75	6,45, s, 1H; 6,85, s, 1H; 7,40-7,50, m, 3H; 7,85, s, 2H 8,15, s, 2H.	4,20	–
3.6	9,05	8,45	3,75	6,45-6,85, dd, 2H; 7,15-7,30, m, 5H; 8,00, s, 1H.	4,30	3,80 (2H, s, CH_2)
3.7	9,55	9,35	3,75	6,45, d, 1H; 6,90-7,00, m, 4H; 7,30-7,40, m, 1H.	4,05	2,90 (6H, s, 2×CH_3)
3.8	9,58	9,45	3,75	6,45-6,80, dd, 2H; 7,60, s, 1H; 7,90, s, 3H; 8,10, s, 1H.	4,10	–
4.1	–	10,15	–	4,80, d, 1H; 6,90, d, 1H; 7,20-7,35, d, 4H; 7,40-7,55, d, 5H.	3,70	4,80 (1H, s, CH) 1,50 (6H, s, 2×CH_3)
4.2	10,39	9,49	3,7	6,55, d, 1H; 6,90-7,00, d, 2H; 7,30, d, 2H; 7,55, d, 2H; 7,75, s, 1H.	4,14	–
4.3	10,29	8,65	–	6,90, d, 1H; 7,19-7,35, m, 5H; 7,55, d, 2H.	4,30	3,92 (2H, s, CH_2)
5.1	10,23	–	–	6,90, d, 1H; 7,30, m, 2H; 7,50-7,70, m, 5H; 8,05, d, 2H.	4,88	–

Compounds **3.1-3.8, 4.2-4.3, 5.1** that contain the amide group in ^{1}H NMR-spectra have a general appropriate singlet signal of the NH-amide proton in the weak field in the interval of δ 9.05-10.39 ppm. The methylene group is located near a strong acceptor represented on the ^{1}H NMR-spectra by the shift of the singlet of the methylene group protons to the weak field (3.70-4.88 ppm). The spectra of compounds **3.1-3.8** have general signals of the aromatic protons of the 2,5-dimethoxyaminophenylic fragment registered in the range of δ 6.45-8.15 ppm.

Table 3

The PASS-prognosis of the biological activity for 5-substituted derivatives of 2-mercapto-1,3,4-thiadiazole

Compound	STAT3 inhibitor of transcription factor	STAT inhibitor of transcription factor	Inhibitor of cytidine-desaminase	Anta-gonist Mcl-1	Inhibitor of transcription factor	Inhibitor of calpain	Inhibitor of Cl-transporting of ATphase	Inhibitor of acro-cylindro-pepsin	Inhibitor of sugar-pepsin
3.1	0,725	0,705	0,673	0,579	0,547	0,541	–	–	–
3.2	0,734	0,713	0,687	0,588	0,559	–	–	–	–
3.3	0,669	0,635	0,605	0,582	–	0,542	–	–	–
3.4	0,677	0,648	0,649	0,529	0,584	0,552	–	–	–
3.5	0,581	0,563	0,569	0,587	–	0,523	–	–	–
3.6	0,604	0,580	–	–	–	0,546	–	–	–
3.7	0,713	0,689	0,658	0,564	0,536	0,531	–	–	–
3.8	0,608	0,577	0,567	0,582	–	0,506	–	–	–
4.1	–	–	–	0,545	–	–	0,586	0,525	0,525
4.2	0,732	0,780	0,598	0,643	0,597	0,517	–	–	–
4.3	0,539	0,581	–	0,571	–	0,533	0,541	–	–
5.1	0,568	0,607	–	0,698	0,521	–	0,724	–	–

The difference of ^1H NMR-spectra of the structures obtained from spectra of the initial compounds is in disappearance of a one-proton singlet of the mercapto group at δ 3.40 ppm and appearance of compounds of the CONH-group singlet on the spectra (Tab. 2).

According to the results of calculation methods of prediction of the biological activity (PASS) the probable types of the biological activity of the substances synthesized have been estimated. In compliance with the data of the PASS computer-based prognosis the antineoplastic action (STAT inhibitor of transcription factors) is principally inherent for most compounds of this class. In this series of the compounds synthesized the index of probability of STAT inhibition of transcription factors is in the range from 0.568 to 0.725, and it indicates the prospects of research for the antitumor activity (Tab. 3) [4, 7].

Experimental Part

Melting points were determined by the capillary method on the Kofler unit. The elemental analysis of the nitrogen content was conducted by the Dumas method.

^1H NMR-spectra were registered on a Varian Mercury device at the frequency of 200 MHz, the solvent – DMSO-d_6, the internal standard – tetramethylsilane (TMS). The chemical shifts are presented in the scale δ (ppm).

5-Phenylamino-2-mercapto-1,3,4-thiadiazole 1.1. Dissolve 104.65 g of 5-phenylthiosemicarbazide in dimethylformamide in the presence of methyl(methoxy) ammonium salt of 2,5-dimercaptothiadiazole at the temperature of 75°C. Then add 45 of carbon disulphide. Recrystallize from ethanol.Yield – 83.72 g (80%); M. p. – 180-182°C. Chemical formula: $C_8H_7N_3S_2$; ^1H NMR, DMSO-d_6, d, ppm: 3.40, 1H, s, (SH); 7.05-7.64, 5H, m (Ar-H); found N % 20.09;calculated N % 20.08.

Compound ***1.2*** was obtained by the similar method.

3,6-Dimethylanilide of 5-(2',5'-dimethoxy)phenylamino-1,3,4-thiadiazole-2-yl-thioacetate acid 3.1. To solution of 2.7 g (0.01 Mole) 5-(2',5'-dimethoxyphenilamino)-2-mercapto-1,3,4-thiadiazole in 50 ml of ethanol add 0.015 Mole (0.84 g) of potassium hydroxide while stirring. Then add 2.3 g (0.01 Mole) of 3,6-dimethylanilide of chloracetate acid to 30 ml of ethanol. Boil under reflux the reaction mixture for an hour, after that evaporate to dryness. Triturate a dry extract in 150 ml of water, filter the precipitate, and dry. Recrystallize from ethanol.

Anilides ***3.2-3.8***, amides ***4.1-4.3***, *5*-phenylamino-1,3,4-thiadiazole-2-yl-thio-1-phenon ***5.1*** were obtained by the similar method.

CONCLUSIONS

The synthesis of 5-R-phenylamino-2-mercapto-1,3,4-thiadiazoles, amides of 5-R-phenylamino-1,3,4-thiadiazole-2-yl-thioacetate acid and 5-phenylamino-1,3,4-thiadiazole-2-yl-thio-1-phenon has been carried out. The chemical structure of the compounds synthesized has been proven by ^1H NMR-spectroscopy.

REFERENCES

1. *Breitmaier E. Structure elucidation by NMR in organic chemistry. – John Wiley @ Sons Ltd, 2002. – 258 p.*
2. *Chhajed M.R., Shrivastava A.K., Tailec V.S. // Macroheterocycles. – 2013. – Vol. 6, №2. – P. 199-209.*
3. *Hussain S., Sharma J., Amir M. // E-Journal of Chem. – 2008. – Vol. 5, №4. – P. 963-968.*
4. *ibmc.msk.ru/PASS/PASSASS.html*
5. *Mullick P., Khan S.A., Verma S., Alam O. // Bul. of the Korean Chem. Soc. – 2011. – Vol. 32, №3. – P. 1011-1016.*
6. *Onkol T., Doruer D.S., Uzun L. et al. // J. of Enzyme Inhibition and Med. Chem. – 2008. – Vol. 23, №2. – P. 277-284.*

7. *Poroikov V., Akimov D., Shabelnikova E. et al. // SAR and QSAR in Environmental Res. – 2001. – Vol. 12, №4. – P. 327-344.*
8. *Rajak H., Aggarwal N., Kashaw S. et al. // J. of the Korean Chem. Soc. − 2010. − Vol. 54, №1. − P. 158-164.*
9. *Silverstein R.M. Spectrometric identification of organic compounds. – 6th ed. – NY: John Wiley & Sons, 2001. – 196 p.*
10. *Sun J, YangY., Li W. et al. // Bioorg. Med. Chem. Lett. − 2011. – Vol. 21, №20. – P. 6116-6121.*
11. *Zhao J., Xuan L., Zhao H. et al. // Chem. Res. in Chinese Universities. − 2014.− Vol. 30, Iss. 5. − P. 764-769.*

СИНТЕЗ ТА ФІЗИКО-ХІМІЧНІ ВЛАСТИВОСТІ НОВИХ ПОХІДНИХ 5-R-ФЕНІЛАМІНО-2-МЕРКАПТО-1,3,4-ТІАДІАЗОЛУ

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Ключові слова: *синтез; 1,3,4-тіадіазол; ^{1}Н ЯМР-спектроскопія*

З метою одержання нових біологічно активних речовин здійснено синтез амідів 5-R-феніламіно-1,3,4-тіадіазол-2-іл-тіоацетатної кислоти та 5-феніламіно-1,3,4-тіадіазол-2-ілтіо-1-фенону. Як вихідні сполуки використовували 5-R-феніламіно-2-меркапто-1,3,4-тіадіазоли, відповідні аніліди хлорацетатної кислоти та хлорацетофенон. Реакція алкілування проведена в середовищі етанолу в присутності калію гідроксиду. Структура синтезованих сполук підтверджена методом ^{1}Н ЯМР-спектроскопії. Обговорені фізико-хімічні властивості та фармакологічний потенціал синтезованих речовин. За результатами розрахункових методів прогнозування біологічної активності (PASSOnline) були оцінені вірогідні види біологічної дії синтезованих речовин. У відповідності з даними комп'ютерного прогнозу PASSOnline більшості сполук цього класу насамперед притаманна протипухлинна дія (інгібітор STAT факторів транскрипції).

СИНТЕЗ И ФИЗИКО-ХИМИЧЕСКИЕ СВОЙСТВА НОВЫХ ПРОИЗВОДНЫХ 5-R-ФЕНИЛАМИНО-2-МЕРКАПТО-1,3,4-ТИАДИАЗОЛА

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Ключевые слова: *синтез; 1,3,4-тиадиазол; ^{1}Н ЯМР-спектроскопия*

С целью получения новых биологически активных веществ осуществлен синтез амидов 5-R-фениламино-1,3,4-тиадиазол-2-ил-тиоуксусной кислоты и 5-фениламино-1,3,4-тиадиазол-2-илтио-1-фенона. В качестве исходных веществ использовали 5-R-фениламино-2-меркапто-1,3,4-тиадиазолы, соответствующие анилиды хлоруксусной кислоты и хлорацетофенон. Реакция алкилирования проведена в среде этанола в присутствии калия гидроксида. Структура синтезированных соединений подтверждена методом ^{1}Н ЯМР-спектроскопии. Обсуждены физико-химические свойства и фармакологический потенциал синтезированных веществ. По результатам расчетных методов прогнозирования биологической активности (PASSOnline) были оценены возможные виды биологического действия синтезированных веществ. В соответствии с данными компьютерного прогнозирования PASSOnline для большинства соединений этого класса прежде всего характерно противоопухолевое действие (ингибитор STAT факторов транскрипции).