Synthesis, physical and chemical properties of 2-((5-(hydroxy(phenyl) methyl)-4R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids and its salts

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Today's a creation of new domestic medicines is very important problem for pharmacy and medicine. Therefore, it is relevant to synthesize new domestic biologically active compounds. It is known that a large number of new 3-thio and 4-amino derivatives on the basis of 1,2,4-triazole have recently been synthesized, among which compounds with high pharmacological activity have been found. Based on the experience of previous studies and with the aim of creating new original drugs, our goal was to synthesize 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids series and to obtain salts on its basis, which have high indicators of pharmacological activity based on the literature data.

The goal of the work is a targeted synthesis of potential low-toxic and highly effective compounds with a wide spectrum of pharmacological activity among 5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-thione derivatives, confirmation of their individuality and structure, as well as the study of physical-chemical properties, for the further pharmacological screening.

Materials and methods. 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids were prepared by heating 5- (hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazol-3-thiones with chloroacetic acid. Subsequently, the synthesized thioacetic acids were subject for modification. Salts of 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids were obtained by reacting thioacetic acids with equivalents of sodium or potassium hydroxides.

To obtain Iron (II), Copper (II) or Zinc (II) salts, half-molar amounts of the appropriate sulfates were added to the obtained solutions. Salts of 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids with organic bases were obtained by the reaction of acids with piperidine or morpholine in ethanol medium.

Results. During the synthetic studies, 13 previously undescribed new compounds were obtained. The individuality of 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids and its salts after recrystallization was confirmed by thin layer chromatography. The structure of synthesized compounds was confirmed by the integrated use of elemental analysis and IR- spectrophotometry.

Conclusions. The results of the work confirm the structure of the synthesized compounds, which shows the possibility of further biological investigation.

Синтез і фізико-хімічні властивості 2-((5-(гідрокси(феніл)метил)-4-R-4*H*-1,2,4-тріазол-3-іл)тіо)ацетатних кислот та їхніх солей

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Ключові слова: 1,2,4-тріазол, синтез, фізико-хімічні властивості.

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Сьогодні в галузі фармації та медицини гостро стоїть питання про створення нових ліків вітчизняного виробництва, які замінили б дорогі закордонні аналоги. Тому актуальним є синтез нових вітчизняних біологічно-активних сполук. Відомо, що на основі 1,2,4-тріазолу останнім часом синтезовано велику кількість нових 3-тіо та 4-амінопохідних, серед них знайдені сполуки, що мають високі показники фармакологічної активності. Спираючись на досвід попередніх досліджень щодо створення нових оригінальних лікарських препаратів, поставлено за мету синтезувати ряд 2-((5-(гідрокси(феніл) метил)-4-R-4*H*-1,2,4-тріазол-3-іл)тіо)ацетатних кислот, на основі яких отримати солі, котрі, за даними наукової літератури, мають високі показники фармакологічної активності.

Мета роботи – цілеспрямований синтез потенційних малотоксичних і високоефективних сполук із широким спектром фармакологічної активності серед похідних 5-(гідрокси(феніл)метил)-4-R-4*H*-1,2,4-тріазол-3-тіонів, підтвердження їхньої індивідуальності й будови, а також вивчення фізико-хімічних властивостей, що надасть перспективи для дальшого фармакологічного скринінгу.

Матеріали та методи. 2-((5-(гідрокси(феніл)метил)-4-R-4*H*-1,2,4-тріазол-3-іл)тіо)ацетатні кислоти отримали нагріванням 5-(гідрокси(феніл)метил)-4-R-4*H*-1,2,4-тріазол-3-тіонів із кислотою монохлорацетатною. Надалі синтезовані тіоацетатні кислоти підлягали модифікації. Солі 2-((5-(гідрокси(феніл)метил)-4-R-4*H*-1,2,4-тріазол-3-іл)тіо)ацетатних кислот отримані взаємодією тіоацетатних кислот з еквівалентами натрій чи калій гідроксидів.

Для отримання солей ферум (II), купрум (II) або цинк (II) до розчинів, що одержали, додавали напівмолярні кількості відповідних сульфатів. Солі 2-((5-(гідрокси(феніл)метил)-4-R-4*H*-1,2,4-тріазол-3-іл)тіо)ацетатних кислот з органічними основами отримані за реакцією кислот із піперидином чи морфоліном у середовищі етанолу.

Результати. Під час синтетичних досліджень одержали 13 нових сполук, що не описані раніше. Індивідуальність 2-((5-(гідрокси(феніл)метил)-4-R-4*H*-1,2,4-тріазол-3-іл)тіо)ацетатних кислот та їхніх солей після перекристалізації підтверджено методом тонкошарової хроматографії. Будову синтезованих сполук підтверджено комплексним використанням елементного аналізу та ІЧ-спектрофотометрії.

Висновки. Результати роботи підтверджують структуру синтезованих сполук, що свідчить про можливість надалі застосовувати їх у біологічних дослідженнях.

Ключевые слова: 1,2,4-триазол, синтез, физико-химические свойства.

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Синтез и физико-химические свойства 2-((5-(гидрокси(фенил)метил)-4-R-4*H*-1,2,4-триазол-3-ил)тио)ацетатных кислот, а также их солей

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На сегодняшний день в области фармации и медицины достаточно остро стоит вопрос о создании новых лекарств отечественного производства, которые заменили бы дорогие зарубежные аналоги. Поэтому актуальным является синтез новых отечественных биологически активных соединений. Известно, что на основе 1,2,4-триазола в последнее время синтезировано большое количество новых 3-тио и 4-аминопроизводных, среди которых найдены соединения, имеющие высокие показатели фармакологической активности. Исходя из опыта предыдущих исследований с целью создания новых оригинальных лекарственных препаратов поставлена цель синтезировать ряд 2-((5-(гидрокси (фенил)метил)-4-R-4*H*-1,2,4-триазол-3-ил)тио)ацетатных кислот, на основе которых получить соли, имеющие, по данным научной литературы, высокие показатели фармакологической активности.

Цель работы – целенаправленный синтез потенциальных малотоксичных и высокоэффективных соединений с широким спектром фармакологической активности среди производных 5-(гидрокси(фенил)метил)-4-R-4*H*-1,2,4-триазол-3-тионов, подтверждение их индивидуальности и строения, а также изучение физико-химических свойств, что предоставит возможность проведения дальнейшего фармакологического скрининга.

Материалы и методы. 2-((5-(гидрокси(фенил)метил)-4-R-4*H*-1,2,4-триазол-3-ил)тио)ацетатные кислоты были получены нагреванием 5-(гидрокси(фенил)метил)-4 -R-4*H*-1,2,4-триазол-3-тионов с кислотой хлорацетатной. В дальнейшем синтезированные тиоацетатные кислоты подлежали модификации. Соли 2-((5-(гидрокси(фенил)метил)-4-R-4*H*-1,2,4-триазол-3-ил)тио)ацетатных кислот получены взаимодействием тиоацетатных кислот с эквивалентами натрий или калий гидроксидов. Для получения солей железа (II), меди (II) или цинка (II) к полученным растворам добавляли 0,5 моль соответствующих сульфатов. Соли 2-((5-(гидрокси(фенил)метил)-4-R-4*H*-1,2,4-триазол-3-ил)тио)ацетатных кислот с органическими основами получены реакцией взаимодействия кислот с пиперидином или морфолином в среде этанола.

Результаты. Во время синтетических исследований получено 13 новых соединений, которые не описаны ранее. Индивидуальность 2-((5-(гидрокси(фенил)метил)-4-R-4*H*-1,2,4-триазол-3-ил)тио)ацетатных кислот и их солей после перекристаллизации подтверждена методом тонкослойной хроматографии. Строение синтезированных соединений подтверждено комплексным использованием ИК-спектрофотометрии и элементного анализа.

Выводы. Результаты работы подтверждают структуру синтезированных соединений, что свидетельствует о возможности в дальнейшем применять их в биологических исследованиях.

Introduction

Today a creation of new domestic medicines is very important problem for pharmacy and medicine. Therefore, the synthesis of new domestic biologically active compounds is relevant.

Over the last ten years, the number of publications about various aspects of chemistry and use of triazole has been doubled and continues to increase. Publications of recent years [1–6] show that the heterocycle with the 1,2,4-triazole nucleus was proven to be well-established as a broad spectrum of biologically active compounds. This fact points to the interest in these compounds as potential objects of the modern pharmaceutical market, namely, compounds that contain both heterocycles.

The aim and objectives of the study

The main aim of the work is the purposeful synthesis of potential low-toxic and highly effective compounds with a wide spectrum of pharmacological activity among derivatives of 5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-thione, confirmation of their individuality and structure, as well as the study of physical-chemical properties, which will provide prospects for further pharmacological screening.

Materials and methods of research

It is known that a large number of new 3-thio and 4-amino derivatives [7] were recently synthesized on the basis of 1,2,4-triazole, and compounds with high pharmacological activity are found among them. In planning the experiment, a generalization was made regarding the dependence of toxicity and pharmacological activity of substances, which have been synthesized recently on their structure [8,9]. Relying on the experience of previous studies [10] with the aim of creating new original drugs, the goal was to synthesize a series of 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids on the basis of which salt is obtained, which, according to literature [11], has high pharmacological activity.

2-((5-(Hydroxy(phenyl)methyl)-4-R-4H-1,2,4-triazole-3-yl)thio)acetic acids (3, 4, *Table 1*) were obtained by heating 5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-thiones (1, 2; *Fig. 1*) with monochloroacetic acid. The reaction was carried out in equimolecular amount of alkali medium (*Fig. 1*).

The adoption into the medical and veterinary practice of the salts of 2- (5-R-4-R_1-1,2,4-triazole-3-thio)acetic acids with organic bases [12] leaves nothing other than further modification of synthesized thioacetic acids.

Sodium and potassium 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetates (5, 6, 9, 10; *Fig. 1*) were obtained by the reaction of 2-((5-(hydroxy(phenyl) methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids (3, 4) with sodium or potassium hydroxide equivalents. Iron (II), Copper (II), and Zinc (II) 2-((5-(hydroxy(phenyl)methyl)-4-phenyl-4H-1,2,4-triazole-3-yl)thio acetate (11–13; *Fig. 1*) were obtained in two steps. Initially, equivalent amounts of 2-((5 (hydroxy(phenyl)methyl)-4-phenyl-4H-1,2,4-triazole-3-yl)thio)acetic acid (4) and sodium hydroxide were mixed in water, after half-molar amounts of aqueous solutions of Iron (II), Copper (II) or Zinc (II) sulfates were added to the formed solution.

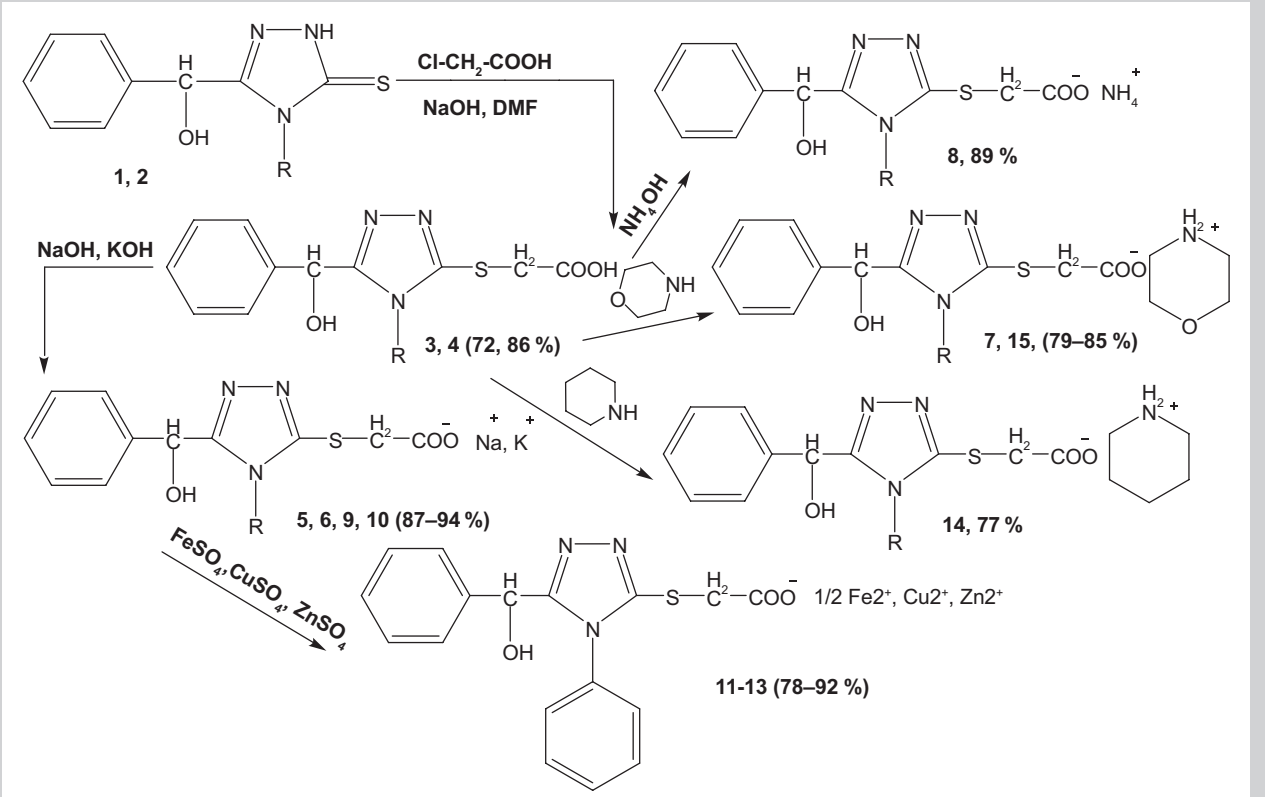


Fig. 1. Scheme of synthesis of 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids and their salts.

Ammonium 2-((5-(hydroxy(phenyl)methyl)-4-phenyl-4*H*-1,2,4-triazole-3-yl)thio)acetate (8; *Fig. 1*) was obtained by evaporation of the solution 2-((5-(hydroxy(phenyl) methyl)-4-phenyl-4*H*-1,2,4-triazole-3-yl)thio)acetic acid in 25 % ammonia solution.

Salts of 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids with organic bases (7, 14, 15; *Fig. 1*) were obtained by reaction of acids (3, 4) with piperidine or morpholine. In this case, the reaction medium was ethanol.

Results and discussion

The individuality of 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids and their salts was confirmed by thin layer chromatography in a system of solvents dioxane:ethylacetate:methanol:acetone 1:1:1:1 after recrystallization. The structure of synthesized compounds (3–15) was confirmed by the complex using of elemental analysis (*Table 2*) and IR-spectrophotometry (*Table 3*). The elemental composition of the compounds corresponds within the limits of the calculated data error (*Table 2*). There are absorption bands -C=N groups at 1610–1573 cm^{-1}, -OH groups at 3530–3488 cm^{-1}, -C-S groups at 707–620 cm^{-1}, and also absorption of aromatic ring bands at 1501–1470 cm^{-1} in the IR-spectra of all synthesized compounds. IR-spectra of acids (3, 4) additionally contain absorption bands of -CH_2-COOH groups at 1710–1700 cm^{-1}, and spectra of salts (5–15) contain bands that are inherent to COO-groups in the range of 1407–1300 cm^{-1} and at 1595–1536 cm^{-1}, respectively [13].

The chemical names of the compounds are given in accordance with the IUPAC nomenclature (1979) and the IUPAC (1993) recommendations.

The study of some physical and chemical properties of the synthesized compounds was carried out in accordance with the methods presented in the State Pharmacopoeia of Ukraine (SPU, version 1). The melting temperature was determined by the capillary method (2.2.14) with the PTP (M) device.

Elemental composition of new compounds was established with elemental analyzer ELEMENTAR vario EL cube (sulfanilamide was a standard).

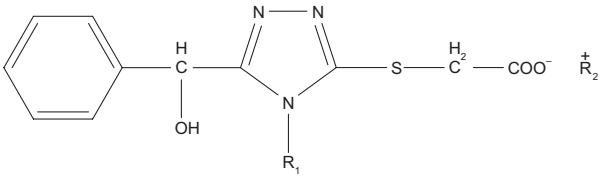
IR-spectra were recorded in tablets of potassium bromide (concentration of 1 %) with a Specord M-80 spectrophotometer in the area of 4000–500 cm^{-1} (scan condition: dense program 3.0, constant time – τ = 3 s, scan time 33 min.). The tablets were prepared by joint grinding 200 mg of potassium bromide and 2 mg of the test compound, followed by compression.

Thin layer chromatography was performed on silica gel 60 ALUGRAMSill G\UV254 (20 x 20 mm aluminum) (Macherei Nagel) or silage gel 60 ALUGRAMSill G\UV254 (10 x 20 aluminum) (Macherei Nagel).

Experimental part

*2-((5-(hydroxy(phenyl)methyl)-4-R-4H-1,2,4-triazole-3-yl)thio)acetatic acids (*3, 4*; Table 1).* 0.1 mole of the corresponding 5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-thione (1, 2) was added to 0.1 mole NaOH solution in 100 ml of DMF, and 0.15 mole of monochloroacetate acid.

Table 1. Physical-chemical constants of 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids and their salts



Compound	R_1	R_2	Melting temperature, °C	Gross formula	Output, %	Rf 100
						1
3	CH_3	H^+	176–178	$C_{12}H_{13}N_3O_3S$	86	73.0
4	C_6H_5	H^+	54–56	$C_{17}H_{15}N_3O_3S$	72	93.0
5	CH_3	Na^+	132–134	$C_{12}H_{12}NaN_3O_3S$	89	80.0
6	CH_3	K^+	160–162	$C_{12}H_{12}KN_3O_3S$	93	94.5
7	CH_3	$C_4H_{10}NO^+$	155–157	$C_{16}H_{22}N_4O_4S$	79	86.9
8	C_6H_5	NH_4^+	51–53	$C_{17}H_{18}N_4O_3S$	89	88.0
9	C_6H_5	Na^+	65–67	$C_{17}H_{14}NaN_3O_3S$	94	81.0
10	C_6H_5	K^+	94–96	$C_{17}H_{14}KN_3O_3S$	87	93.0
11	C_6H_5	$Fe^{2+}/2$	260–262	$C_{17}H_{14}FeN_3O_3S$	87	90.0
12	C_6H_5	$Cu^{2+}/2$	248–250	$C_{17}H_{14}CuN_3O_3S$	78	71.9
13	C_6H_5	$Zn^{2+}/2$	320–322	$C_{17}H_{14}ZnN_3O_3S$	92	73.2
14	C_6H_5	$C_5H_{12}N^+$	119–121	$C_{22}H_{26}N_4O_3S$	77	94.0
15	C_6H_5	$C_4H_{10}NO^+$	118–120	$C_{21}H_{24}N_4O_4S$	85	81.0

Table 2. Results of determination of 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids and their salts

Compound	Found, %				Calculated, %			
	C	H	N	S	C	H	N	S
3	51.78	4.39	15.14	11.64	51.60	4.69	15.04	11.48
4	59.72	4.55	12.53	9.52	59.81	4.43	12.31	9.39
5	–	–	14.08	10.55	–	–	13.95	10.64
6	–	–	13.44	10.19	–	–	13.24	10.10
7	52.19	6.12	15.38	8.91	52.44	6.05	15.29	8.75
8	56.85	5.07	15.53	8.78	56.97	5.06	15.63	8.95
9	–	–	11.42	8.72	–	–	11.56	8.82
10	–	–	11.20	8.44	–	–	11.07	8.45
11	–	–	11.22	8.52	–	–	11.41	8.71
12	–	–	11.52	8.71	–	–	11.54	8.81
13	–	–	11.46	8.70	–	–	11.26	8.59
14	61.75	6.24	13.34	7.43	61.95	6.14	13.14	7.52
15	58.66	5.77	13.27	7.59	58.86	5.65	13.07	7.48

Table 3. The absorption maxima on IR-spectra of 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids and their salts

Compound	Adsorption frequency, cm^{-1}					
	$\upsilon^{s/as}_{COO^-}$	$\nu_{C=N\ cycle}$	νCH_2-COOH	ν_{Ar}	ν_{C-S}	ν_{OH}
3	–	1607	1710	1487	693	3503
4	–	1590	1700	1495	700	3527
5	1346/1536	1596	–	1497	685	3500
6	1371/1586	1600	–	1490	679	3498
7	1344/1595	1600	–	1494	704	3509
8	1300/1555	1610	–	1487	707	3530
9	1367/1583	1587	–	1471	701	3514
10	1325/1563	1605	–	1477	701	3507
11	1372/1578	1600	–	1477	620	3488
12	1334/1568	1573	–	1498	691	3500
13	1407/1565	1600	–	1501	695	3506
14	1328/1563	1599	–	1500	676	3519
15	1347/1564	1594	–	1470	693	3499

The solution was boiled to acid medium (5 hours), filtered, 50 ml of water was added and left for 24 hours. Precipitates of the reaction products were filtered and dried.

White crystalline substances are slightly soluble in water, soluble in alkaline and alkaline metal carbonate solutions and in organic solvents. 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids (3, 4) were purified by recrystallization from 40 % ethanol for the analysis.

Sodium and potassium 2-((5-(hydroxy(phenyl)methyl)-4-R-4H-1,2,4-triazole-3-yl)thio)acetate (5, 6, 9, 10; Table 1). A mixture of 0.01 mole of 2-((5-(hydroxy(phenyl)methyl)-4-R-4H-1,2,4-triazole-3-yl)thio)acetic acid (3,4) and 0.01 mole of sodium or potassium hydroxide in 30 ml of water was evaporated on a water bath.

Yellow crystalline substances are soluble in water, slightly soluble in organic solvents. Salts (5, 6, 9, 10) were recrystallized from ethanol for analysis.

Iron (II), Copper (II) and Zinc (II) *2-((5-(hydroxy(phenyl)methyl)-4-phenyl-4H-1,2,4-triazole-3-yl)thio)acetates (11–13; Table 1).* Solutions of 0.01 mole Iron (II), Copper (II) or Zinc (II) sulfate in 20 ml of water were added to a solution of 0.02 mole 2-((5-(hydroxy(phenyl)methyl)-4-phenyl-4*H*-1,2,4-triazole-3-yl)thio)acetic acid (4) and 0.02 mole sodium hydroxide in 30 ml of water. The final solution was left for 24 hours, the precipitates were filtered and crystallized from 70 % ethanol.

White (13) or yellow (11, 12) crystalline substances are soluble in hot water, slightly soluble in organic solvents.

Ammonium 2-((5-(hydroxy(phenyl)methyl)-4-phenyl-4H-1,2,4-triazole-3-yl)thio) acetate (8, Table 1). 0.01 mole of 2-((5-(hydroxy(phenyl)methyl)-4-phenyl-4*H*-1,2,4-triazole-3-yl)thio)acetic acid (4) was dissolved in 30 ml of 25 % Ammonia and evaporated.

The yellow crystalline substance is soluble in water and in organic solvents. The compound (4) was recrystallized from a mixture of water:ethanol:acetone (1:1:1) for analysis.

Salts of 2-((5-(hydroxy(phenyl)methyl)-4-R-4H-1,2,4-triazole-3-yl)thio)acetic acids with organic bases (7, 14, 15; Table 1). A solution of 0.01 mole of the corresponding 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl) thio)acetic acid (3, 4), 0.01 mole of organic base (piperidine, morpholine) in 50 ml of ethanol were left for 24 hours at room temperature, the precipitates were filtered, washed with diethyl ether and dried.

Yellow crystalline substances are soluble in water and in organic solvents. Compounds (7, 14, 15) were recrystallized from a mixture of ethanol:acetone (1: 1) for analysis.

Conclusions

1. An effective method of syntethis of 2-((5-(hydroxy(phenyl)methyl)-4-R-4*H*-1,2,4-triazole-3-yl)thio)acetic acids and their salts was developed.

2. The structure of the synthesized substances was confirmed by elemental analysis and IR-spectrophotometry, and their individuality was confirmed by the chromatographic method.

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