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The synthesis, study of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridyn-3-yl)-(alkyl, heteryl)methanimines and their derivatives

In the pharmaceutical practice directly related to the search of biological active substances and their introduction into medicine or veterinary it is generally recognized that a successful choice of the research object is a prerequisite for a positive final outcome to create original effective and low-toxic drugs. At present, derivatives of 1,2,4-triazoles containing pyridine deserve special attention. That is why the synthesis and study of physicochemical properties of new compounds, which contain 1,2,4-triazole and pyridine rings, are important tasks of modern synthetic and pharmaceutical chemistry.

Aim. To study the reactions associated with formation and transformation of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines and their recovery, study physicochemical properties of new compounds synthesized.

Materials and methods. 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heter-yl)methanimines were obtained by the mixture from 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-amine and aldehydes. The synthesis was carried out in the acetic acid medium. The mixture was kept at room temperature for 6 h. 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines were reduced in the 1,4-dioxane medium. As a reducing agent sodium borohydride was used.

Results and discussion. As a result of synthetic transformations 17 new compounds have been obtained, the structure of the compounds synthesized has been confirmed by modern complex of physicochemical methods of analysis (IR-spectrophotometry, elemental analysis), and their individuality has been proven on an Agilent 1260 Infinity HPLC high-performance liquid chromatograph equipped with an Agilent 6120 mass spectrometer.

Conclusions. The preparative method for the synthesis of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines and 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)-N-(alkyl-, heteryl)pyridine-3-amines has been developed.

Key words: 1,2,4-triazole; pyridine; synthesis; physicochemical properties

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Синтез, дослідження 6-((5-фенетил-4-R-1,2,4-триазол-3-ілтіо)піридин-3-іл)-(алкіл, гетерил)метанімінів та їх похідних

У фармацевтичній практиці, яка безпосередньо пов’язана з пошуком біологічно активних речовин та їх введенням у медицину або ветеринарію, загальним є те, що успішний вибір об’єкта дослідження є необхідною умовою для позитивного кінцевого результату та для створення оригінальних ефективних та малотоксичних препаратів. На цьому етапі на особливу увагу заслуговують похідні 1,2,4-триазолів, що містять піридин. Саме тому синтез та вивчення фізико-хімічних властивостей нових сполук, що містять 1,2,4-триазольний та піридиновий фрагмент, є важливими завданнями сучасної синтетичної та фармацевтичної хімії.

Мета. Вивчити реакцію утворення 6-((5-фенетил-4-R-1,2,4-триазол-3-ілтіо)піридин-3-іл)-(алкіл, гетерил)метанімінів та їх селективного відновлення, дослідити фізичні та хімічні властивості нових синтезованих сполук.

Матеріали та методи. Для отримання 6-((5-фенетил-4-R-1,2,4-триазол-3-ілтіо)піридин-3-іл)-(алкіл-, гетерил)метанімінів використано 6-(5-фенетил-4R-1,2,4-триазол-3-ілтіо)піридин-3-аміни та альдегіди. Синтез проводився в середовищі кислоти оцтової. Суміш залишали при кімнатній температурі на 6 годин. 6-((5-Фенетил-4-R-1,2,4-триазол-3-ілтіо)піридин-3-іл)-(алкіл-, гетерил)метаніміни були відновлені в середовищі 1,4-діоксану. В якості відновника використано натрію боргідрид.

Результати та їх обговорення. В результаті синтетичних перетворень отримано 17 нових сполук, структуру синтезованих сполук підтверджено завдяки сучасному комплексу фізико-хімічних методів аналізу (ІЧ-спектрофотометрії, елементного аналізу), а їх індивідуальність підтверджена дослідженням на високопродуктивному рідинному хроматографі Agilent 1260 Infinity HPLC, обладнаному мас-спектрометром Agilent 6120.

Висновки. Розроблено препаративний метод синтезу 6-((5-фенетил-4-R-1,2,4-триазол-3-ілтіо)піридин-3-іл)-(алкіл-, гетерил)метанімінів і 6-(5-фенетил-4-R-1,2,4-триазол-3-ілтіо)-N-(алкіл-, гетерил)піридин-3-амінів.

Ключові слова: 1,2,4-триазол; піридин; синтез; фізико-хімічні властивості

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Синтез, исследование 6-((5-фенетил-4-R-1,2,4-триазол-3-илтио)пиридин-3-ил)-(алкил, гетерил)метаниминов и их производных

В фармацевтической практике, непосредственно связанной с поиском биологически активных веществ и их введением в медицину или ветеринарию, общепринято, что успешный выбор объекта исследования является предпосылкой для положительного конечного результата, для создания оригинальных эффективных и малотоксичных лекарств. На данный момент особого внимания заслуживают производные 1,2,4-триазолов, которые содержат пиридин. Именно поэтому синтез и изучение физико-химических свойств новых соединений, содержащих 1,2,4-триазольное и пиридиновое кольца, являются важной задачей современной синтетической и фармацевтической химии.

Цель. Изучить реакцию образования 6-((5-фенетил-4-R-1,2,4-триазол-3-илтио)пиридин-3-ил)-(алкил, гетерил)метаниминов и их селективного восстановления, исследовать физические и химические свойства новых синтезированных соединений.

Материалы и методы. Для получения 6-((5-фенетил-4-R-1,2,4-триазол-3-илтио)пиридин-3-ил)-(алкил-, гетерил)метаниминов использовали 6-(5-фенетил-4-R-1,2,4-триазол-3-илтио)пиридин-3-амины и альдегиды. Синтез проводился в среде кислоты уксусной. Смесь оставляли при комнатной температуре на 6 часов. 6-((5-Фенетил-4-R-1,2,4-триазол-3-илтио)пиридин-3-ил)-(алкил-, гетерил)метанимины были восстановлены в среде 1,4-диоксана. В качестве восстановителя был использован натрия боргидрид.

Результаты и их обсуждение. В результате синтетических превращений получено 17 новых соединений, структуру синтезированных соединений подтверждено благодаря современному комплексу физико-химических методов анализа (ИК-спектрофотометрии, элементного анализа), а их индивидуальность подтверждена исследованием на высокопроизводительном жидком хроматографе Agilent 1260 Infinity HPLC, оборудованном масс-спектрометром Agilent 6120.

Выводы. Разработан препаративный метод синтеза 6-((5-фенетил-4-R-1,2,4-триазол-3-илтио)пиридин-3-ил)-(алкил-, гетерил)метаниминов и 6-(5-фенетил-4-R-1,2,4-триазол-3-илтио)-N- (алкил-, гетерил)пиридин-3-аминов.

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

In the pharmaceutical practice directly related to the search of biological active substances and their introduction into medicine or veterinary it is generally recognized that a successful choice of the research object is a prerequisite for a positive final outcome to create original effective and low-toxic drugs. It should be noted that compounds containing 1,2,4-triazole core may be interesting not only for synthetic chemists, but also for pharmacists, physiologists and other scientists [1-4].

During the past decade the literature constantly showed the instance of studying the properties of these heterocyclic compounds [5-7]. At present, derivatives of 1,2,4-triazoles containing pyridine deserve special attention. Such compounds are the subject of attention of various research activities. The systematization of information on the research results for derivatives of 1,2,4-triazoles is absent.

That is why the synthesis and study of physicochemical properties of new compounds, which contain 1,2,4-triazole and pyridine rings, are important tasks of modern synthetic and pharmaceutical chemistry.

The aim of the research was to study the reactions associated with formation and transformation of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines and their recovery, study physicochemical properties of new compounds synthesized.

Materials and methods

6-((5-Phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines. To the solution of 0.02 Mole of 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-amine in 40 ml of acetic acid add 0.02 Mole of aldehydes (formaldehyde, acetaldehyde, benzaldehyde, 4-fluorobenzaldehyde, 4-methoxybenzaldehyde, salicylaldehyde). Keep the mixture at room temperature for 6 h. Then filter compounds **3-14**, wash with ether and dry. New compounds are soluble in organic solvents, but slightly soluble in water. Recrystallize compounds **3-14** from the ethanol-water medium (1 : 1).

6-(5-Phenethyl-4-R-1,2,4-triazole-3-ylthio)-N-(alkyl-, heteryl)pyridine-3-amines. To the solution of 0.02 Mole of sodium hydroxide in 60 ml of 1,4-dioxane add 0.02 Mole of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl) methanimine. Then add the solution of 0.04 Mole of sodium borohydride in 15 ml of water dropwise for 1 h. Keep the mixture at room temperature for approximately 24 h. Neutralize the compounds synthesized with acetic acid. 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)-N-(alkyl-, heteryl)pyridine-3-amines are soluble in organic solvents and slightly soluble in water. Recrystallize compounds from the ethanol-water medium (1 : 1).

The structure of new compounds synthesized was confirmed by modern complex of physicochemical methods. Melting points were measured by the capillary method. The elemental composition of new compounds was determined by an "ELEMENTAR vario EL cube" analyser (CHNS) (standard – Sulfonamide).

IR-spectra were registered for pellets of potassium bromide using a SPECORD 200 spectrophotometer in the range of frequencies of 4000-500 cm^{-1} (scanning conditions: the target program 3.0, the time constant τ was 3 sec, the scanning time was 33 min). Pellets were prepared using combined grinding of 200 mg of potassium bromide and 2 mg of the compound studied with further pressing [8-10].

The purity and molecular weight of the new compounds synthesized were determined using the method of high performance liquid chromatography. The chromatography-mass spectrometry studies were conducted on an Agilent 1260 Infinity HPLC liquid chromatograph equipped with an Agilent 6120 mass spectrometer (in electrospray ionization (ESI)) [10].

Results and discussion

New 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio) pyridine-3-yl)-(alkyl-, heter-yl)methanimines (com-

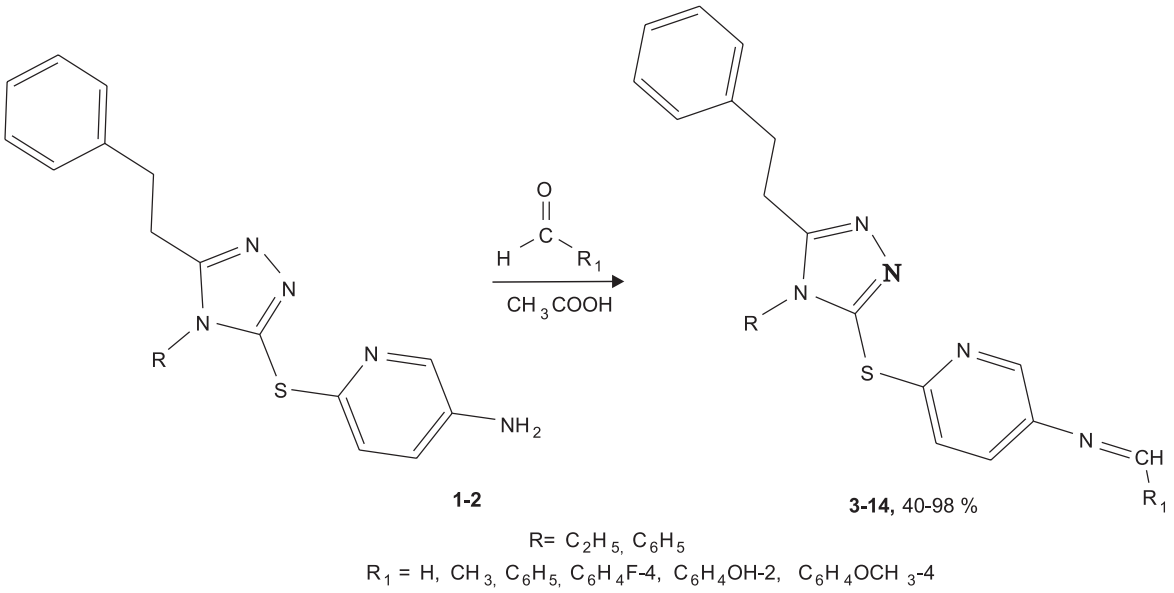


Fig. 1. The scheme of the synthesis of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines

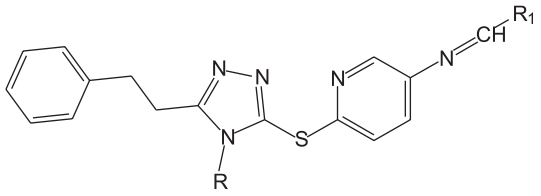
pounds **3-14**) were obtained by the mixture from 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-amine (compounds **1-2**, Fig. 1) and aldehydes (formaldehyde, acetaldehyde, benzaldehyde, 4-fluorobenzaldehyde, 4-methoxybenzaldehyde, salicylaldehyde). The synthesis was carried out in the acetic acid medium. The mixture was kept at room temperature for 6 h. Then compounds **3-14** were filtered, washed with ether and dried (Fig. 1).

The yields of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heter-yl)methanimines were 40-98 %. The highest yields were observed for 6-((5-phenethyl-4-phenyl-1,2,4-triazole-3-ylthio) pyridine-3-yl)methanimine (compound **5**) (98 %) and 6-((5-phenethyl-4-ethyl-1,2,4-triazole-3-ylthio)pyridine-3-yl)ethanimine (compound **8**) (90 %).

The 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio) pyridine-3-yl)-(alkyl-, heteryl)methanimines synthesized (compounds **3-14**, Tab. 1) are gray (compounds **5, 11**), orange (compounds **3, 7, 8, 12**) or brown (compounds **4, 6, 9, 10, 13, 14**) amorphous substances, soluble in organic solvents and slightly soluble

Table 1

Physical and chemical characteristics of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines



Compound	R	R_1	Melting point, °C	Gross formula	Yield, %
3	ethyl	H	78-79	$C_{18}H_{19}N_5S$	69
4	ethyl	CH_3	112-113	$C_{19}H_{21}N_5S$	84
5	phenyl	H	94-96	$C_{22}H_{19}N_5S$	98
6	phenyl	CH_3	114-115	$C_{23}H_{21}N_5S$	79
7	ethyl	C_6H_4F-4	116-117	$C_{24}H_{22}FN_5S$	65
8	ethyl	C_6H_5	203-205	$C_{24}H_{23}N_5S$	90
9	ethyl	C_6H_3OH-2	111-112	$C_{24}H_{23}N_5OS$	75
10	ethyl	$C_6H_4OCH_3$-3	128-129	$C_{25}H_{25}N_5OS$	75
11	phenyl	C_6H_4F-4	109-110	$C_{28}H_{22}FN_5S$	70
12	phenyl	C_6H_3OH-2	193-194	$C_{28}H_{23}N_5OS$	81
13	phenyl	C_6H_5	112-113	$C_{28}H_{23}N_5S$	40
14	phenyl	$C_6H_4OCH_3$-3	126-127	$C_{29}H_{25}N_5OS$	61

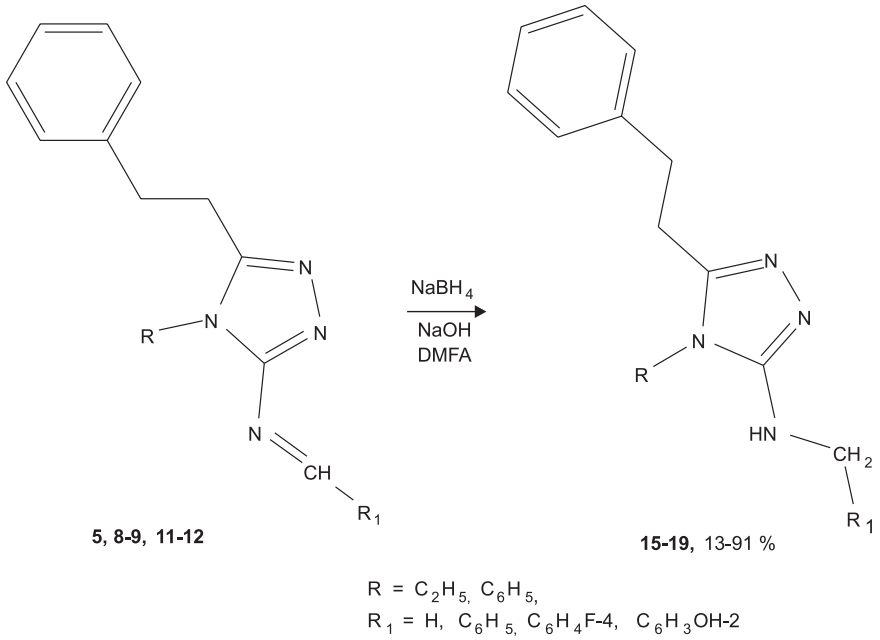


Fig. 2. The scheme of the synthesis of 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)-N-(alkyl-, heteryl)pyridine-3-amines

in water. Compounds **3 – 14** were recrystallized from the ethanol-water medium (1 : 1).

Then 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio) pyridine-3-yl)-(alkyl-, heter-yl)methanimines were reduced. The reduction of compounds **3-14** was in the 1,4-dioxane medium, and it led to formation of 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)-N-(alkyl-, heteryl)pyridine-3-amines (compounds **15-19**, Fig. 2). As a reducing agent sodium borohydride was used. Due to this substance the double aliphatic bond was restored (Fig. 2).

The yields of 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)-N-(alkyl-, heteryl)pyridine-3-amines were 13-91 %. The highest yields were observed for 2-(((5-phenethyl-4-phenyl-1,2,4-triazol-3-yl)amino)methyl)phenol (91 %).

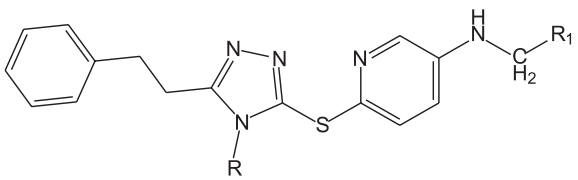
The 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)-N-(alkyl-, heteryl)pyridine-3-amines synthesized (compounds **15-19**, Tab. 2) are brown (compounds **15, 17**), orange (compounds **16, 19**) or white (compound **18**) amorphous substances, soluble in organic solvents and slightly soluble in water. Compounds were recrystallized from the ethanol-water medium (1 : 1).

The structure of new compounds obtained was confirmed by the complex application of the elemental analysis and IR-spectrophotometry. Individuality of these substances was proven by the method of HPLC/DAD-MS. Some of the physicochemical properties are shown in Tab. 1, 2 and 3. The results of the elemental composition determination indicate that the experimental data do not differ from the theoretical ones by more than 0.25 %.

The results of IR-spectra of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl) methanimines and 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)-N-(alkyl-, heteryl)pyridine-3-amines are presented in Tab. 4. There are bands detected due to C=N-groups (in the cycle) in the range of 1610-1535 cm^{-1},

Table 2

Physical and chemical characteristics of 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)-N-(alkyl-, heteryl)pyridine-3-amines



Compound	R	R_1	Melting point, °C	Gross formula	Yield, %
15	phenyl	H	78-79	$C_{22}H_{21}N_5S$	58
16	ethyl	C_6H_3OH-2	112-113	$C_{24}H_{25}N_5OS$	52
17	ethyl	C_6H_5	137-138	$C_{24}H_{25}N_5S$	13
18	phenyl	C_6H_4F-4	123-124	$C_{28}H_{24}FN_5S$	72
19	phenyl	C_6H_3OH-2	164-165	$C_{28}H_{25}N_5OS$	91

Table 3

Results of elemental analysis of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines and their derivatives

Compound	Found, %				Calculated, %			
	C	H	N	S	C	H	N	S
3	64.05	5.70	20.77	9.48	64.07	5.68	20.75	9.50
4	64.95	6.03	19.95	9.07	64.93	6.02	19.93	9.12
5	68.53	4.98	18.15	8.34	68.55	4.97	18.17	8.32
6	69.14	5.31	17.52	8.03	69.15	5.30	17.53	8.02
7	66.82	5.12	16.25	7.42	66.80	5.14	16.23	7.43
8	69.72	5.63	16.92	7.73	69.71	5.61	16.94	7.75
9	67.12	5.41	16.28	7.45	67.11	5.40	16.30	7.46
10	67.72	5.69	15.78	7.24	67.70	5.68	15.79	7.23
11	70.15	4.60	14.58	6.70	70.13	4.62	3.96	14.60
12	70.43	4.84	14.67	6.72	70.42	4.85	14.66	6.71
13	72.84	5.03	15.19	6.94	72.86	5.02	15.17	6.95
14	70.84	5.14	14.27	6.50	70.85	5.13	14.25	6.52
15	68.22	5.44	18.08	8.26	68.19	5.46	18.07	8.27
16	66.81	5.83	16.24	7.42	66.80	5.84	16.23	7.43
17	69.38	6.08	16.86	7.68	69.37	6.06	16.85	7.71
18	69.85	5.04	14.56	6.68	69.83	5.02	14.54	6.66
19	70.10	5.27	14.62	6.66	70.12	5.25	14.60	6.68

there are also symmetric and asymmetric bands, which can be caused by the presence of CH_2-groups at 2870-2820 cm^{-1} and at 3000-2915 cm^{-1}, respectively. In addition, the bands of Amide I and Amide II are present in the infrared spectrum of compounds **3-14** in the range of 1720-1695 cm^{-1} and 1625-1590 cm^{-1},

Table 4

Absorption maxima in IR-spectra of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines and their derivatives

Compound	Absorption frequency, cm^{-1}					
	$V_{C=N\ cycle}$	$\nu^{s/as}_{CH_2}$	V_{C-S}	Amide I	Amide II	ν_{C-N-}
3	1580	2820, 2930	685	1695	1620	–
4	1596	2840, 2915	706	1698	1615	–
5	1598	2840, 2940	698	1705	1620	–
6	1610	2825, 2945	690	1710	1625	–
7	1535	2861, 2910	680	1720	1590	–
8	1605	2865, 2915	700	1710	1620	–
9	1590	2870, 3000	697	1705	1610	–
10	1595	2870, 2970	695	1695	1620	–
11	1589	2870, 2940	708	1705	1610	–
12	1598	2842, 2920	705	1710	1610	–
13	1610	2845, 2950	700	1720	1620	–
14	1586	2845, 2915	705	1705	1605	–
15	1590	2830, 2960	708	–	–	3400
16	1605	2825, 2930	700	–	–	3250
17	1595	2845, 2920	695	–	–	3300
18	1598	2865, 2940	698	–	–	3350
19	1600	2864, 2950	700	–	–	3400

respectively. Moreover, compounds **15-19** have the secondary amide band in the range of 3400-3250 cm^{-1}, which is confirmed by the recovery process.

It was found by the method of HPLC/DAD-MS that the higher was the yield of the compound synthesized the cleaner it was.

Conclusions

1. The preparative method for the synthesis of 6-((5-phenethyl-4-R-1,2,4-triazole-3-ylthio)pyridine-3-yl)-(alkyl-, heteryl)methanimines and 6-(5-phenethyl-4-R-1,2,4-triazole-3-ylthio)-N-(alkyl-, heteryl)pyridine-3-amines has been developed, and 17 new compounds previously unregistered have been obtained.

2. The structure, individuality and physical and chemical constants have been determined for all compounds synthesized using modern methods of physical and chemical analysis.

Conflict of interests: authors have no conflict of interests to declare.

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