

RESEARCH OF THE SYNTHETIC, PHYSICAL AND CHEMICAL PROPERTIES OF 3-ALKYLSULFONYL-5-(CHINOLINE-2-YL, 2-HYDROXYCHINOLINE-4-YL)-4-R₁-2,4-DIHYDRO-3N-1,2,4-TRIAZOLES

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Received: 14 July 2016, Revised and Accepted: 23 September 2016

ABSTRACT

Objective: Fundamental research in pharmacy and medicine have shown that drugs, which are based on nucleus of the 1,2,4-triazole, have a wide range of biological effects. Derivatives of this heterocyclic system have well-known Ukrainian clinicians and the world scientists due to its antifungal, antidepressant, anticancer, cardio- and hepatoprotective properties. The pharmacological activity of most organic compounds depends on several different factors, including bioavailability of the substance. Hence, it is very important to consider the results of the synthetic and biological researches and established dependence of structure on the biological action when scientists model new molecules or improve pharmacological properties of an existing structure. One of the important social and economic problems of the pharmaceutical industry is the implementation in practice of new drugs that could compete with expensive imported drugs. In recent times, 1,2,4-triazole-3-thioderivatives take attention of compatriots and scientists of foreign countries who are working on finding bioactive compounds including heterocyclic systems. The structure, physical and chemical properties, pharmacological activities of 1,2,4-triazoles, and their 3-thioderivatives are understudied. Hence, the study of that will be actually and novelty for modern science. The main purpose of our research is synthesis of 3-alkylsulfonyl-5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R₁-2,4-dihydro-3N-1,2,4-triazoles, studying of its physical and chemical properties.

Methods: The initial compounds have been synthesized previously using known in literature techniques. Oxidation of the sulfur atom of the synthesized compounds to the hexavalent condition was carried out adding solution of hydrogen peroxide.

Results: The structure of the obtained compounds was determined with the modern physical and chemical analysis methods: Element analysis, infrared-spectrophotometry, and their individuality with thin layer chromatography.

Conclusions: Prospect of the further researches is determination of acute toxicity and next studying of pharmacological properties of the synthesized compounds.

Keywords: 1,2,4-triazoles, Synthesis, Chemical properties, Chinoline.

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INTRODUCTION

There is a big variety of antimicrobial medical drugs this time. However, the most of them are effective only against some cultures of bacterium. It is connected with resistance of the most species of pathogenic microorganisms as a result of uncontrolled antibiotics intake. Assortment of the pharmaceutical market counts the considerable number of groups of drugs. Sulfanilamides attract the special attention of doctors. This pharmacological group of drugs is an effective antimicrobial agent because of its structure is like p-aminobenzoic acid. Integration of this pharmacophore into the structure increases water solubility of this compound.

Furthermore, we have found information about antimicrobial properties of some 1,2,4-triazole derivatives. Especially those which are composed of oxidized hexavalent Sulfur atom. Hence, the search of new bio-active compositions among the marches of 5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R₁-3-alkylthio-1,2,4-triazoles actual target for pharmaceutical sphere scientists.

METHODS

We have used 5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R₁-3-alkylthio-1,2,4-triazoles as initial substances (1'-9', Fig. 1). They have

been synthesized previously using known in literature techniques [1-4]. Oxidation of the sulfur atom of the synthesized compounds (1'-9', Fig. 1) to the hexavalent condition was carried out in concentrated acetic acid adding 33% solution of hydrogen peroxide [5-7].

Structure of synthesized of 3-alkylsulfonyl-5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R₁-2,4-dihydro-3N-1,2,4-triazoles (1-9) was determined using element analysis (Table 1) and infrared (IR)-spectrophotometry (Table 2).

EXPERIMENTAL PART

3-alkylsulfonyle-5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R₁-2,4-dihydro-3N-1,2,4-triazoles (1-9)

Method A

10 ml of 33% solution of hydrogen superoxide have been added to the 0.02 mol of consistence solution of 3-alkylsulfonyl-5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R₁-2,4-dihydro-3N-1,2,4-triazoles (1'-9', Fig. 1) in 30 ml of concentrated acetate acid. Reaction mixture has been left at room temperature on the 56 h than solvent has been evaporated. The precipitate has been recrystallized from the mixture of acetic acid: water (2:1) (1-3, 9), mixture of methanol: water 3:1 (4-6), or mixture of propanol-2:water (7, 8). They are white (6-8), yellow (1, 2, 5,

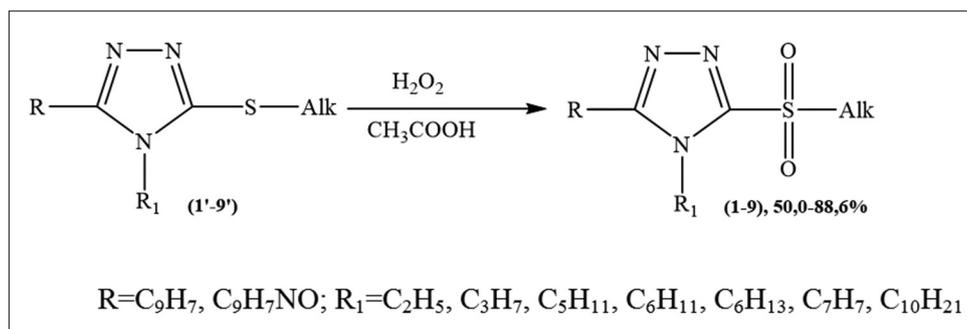


Fig. 1: Synthesis of 3-alkylsulfonyl-5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R1-2,4-dihydro-3N-1,2,4-triazoles

Table 1: Physical and chemical constants of 3-alkylsulfonyl-5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R1-2,4-dihydro-3N-1,2,4-triazoles

No	R	R ₁	R ₂	T _{mel} , °C	Gross formula	Yield, %	Found, %				Calculated, %			
							C	H	C	H	C	H	C	H
1	Chynoline-2-yl	H	C ₃ H ₇	78-80	C ₁₄ H ₁₄ N ₄ O ₂ S	50.0	55.58	4.57	18.65	10.57	55.61	4.67	18.53	10.61
2	Chynoline-2-yl	H	C ₆ H ₁₃	85-87	C ₁₇ H ₂₀ N ₄ O ₂ S	77.3	53.22	5.58	16.98	3.18	53.28	5.85	16.87	3.31
3	2-hydroxychynoline-4-yl	H	C ₂ H ₅	>230	C ₁₃ H ₁₂ N ₄ O ₃ S	50.6	51.28	4.09	18.30	10.55	51.31	3.97	18.41	10.54
4	2-hydroxychynoline-4-yl	H	C ₅ H ₁₁	>230	C ₁₆ H ₁₈ N ₄ O ₃ S	64.0	55.48	5.29	16.19	9.37	55.48	5.24	16.17	9.26
5	2-hydroxychynoline-4-yl	H	C ₁₀ H ₂₁	159-161	C ₂₁ H ₂₆ N ₄ O ₃ S	76.9	60.57	6.88	13.56	7.69	60.55	6.78	13.45	7.70
6	2-hydroxychynoline-4-yl	H	C ₇ H ₇	>230	C ₁₈ H ₁₄ N ₄ O ₃ S	84.0	59.14	3.84	15.24	8.76	59.01	3.85	15.29	8.75
7	2-hydroxychynoline-4-yl	H	C ₆ H ₁₁	>300	C ₁₇ H ₁₈ N ₄ O ₃ S	61.8	57.00	5.14	15.64	9.07	56.97	5.06	15.63	8.95
8	2-hydroxychynoline-4-yl	C ₆ H ₅	C ₃ H ₇	220-222	C ₂₀ H ₁₈ N ₄ O ₃ S	88.6	60.91	4.52	14.28	8.11	60.90	4.60	14.20	8.13
9	2-hydroxychynoline-4-yl	C ₆ H ₅	C ₇ H ₇	>240	C ₂₄ H ₁₈ N ₄ O ₃ S	72.2	65.16	4.08	12.68	7.58	65.14	4.10	12.66	7.25

Table 2: IR-spectra of 3-alkylsulfonyl-5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R1-2,4-dihydro-3N-1,2,4-triazoles

No	Compound	Absorption rate, cm ⁻¹					
		ν _{C=N} in cycle	ν _{Hin}	ν _{C-S}	ν _{CH2}	ν _{CH3}	ν _{R2SO2}
1	3.24	1629	1502	685	2850/2905	2890/2916	1132
2	3.25	1638	1500	764	2846/2909	2877/2924	1140
3	3.26	1650	1581	752	2854/2905	2881/2928	1125
4	3.27	1649	1570	750	2860/2900	2880/2924	1047
5	3.28	1650	1582	613	2849/2918	2895/2925	1059
6	3.29	1676	1584	744	2850/2904	2900/2987	1053
7	3.30	1638	1533	743	2848/2908	2917/2987	1065
8	3.31	1652	1529	699	2860/2925	2880/2900	1140
9	3.32	1643	1520	648	2850/2920	2890/2925	1047

IR: Infrared

9) or light brown (3, 4) crystal substances which are weakly soluble in water, freely soluble in organic solvents.

Method B

10 ml of 33% of hydrogen peroxide have been added to the 0.02 mol of 5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R₁-3-alkylthio-1,2,4-

triazole (1) in 30 ml of concentrated acetate acid during 1 h. Mixture has been heated on the heated bath during 5 h at temperature 75°C, solvent has been evaporated. Synthesized substance has been recrystallized from the mixture of acetate acid: water (2:1).

Mixing test of the substance 1 received using methods A and B has not shown the depression of the melting temperature.

Chemical names of the compounds have been given according to the IUPAC nomenclature (1979 year) and IUPAC recommendations (1993 year).

The ascertainment of some physical and chemical properties of the synthesized compounds was performed by the methods which are described in the State Pharmacopoeia of Ukraine (SPhU, ed.1). The melting point has been determined by capillary method (2.2.14) on PTP (M) apparatus [2].

The elemental composition of new compounds has been set in elemental analyzer ELEMENTAR vario EL cube (standard-sulfonamide).

IR spectra have been recorded in potassium bromide tablets (substance concentration is 1%) with Specord M-80 spectrophotometer in the region of 4000-500/cm (scanning conditions: Program 3.0, the time constant $\tau = 3$ seconds, scan time 33 minutes).

Nuclear magnetic resonance (NMR) spectra have been recorded with spectrophotometer of NMR "Varian VXR-300," the solvent is DMSO-D₆, an internal standard is tetramethylsilane. The data have been deciphered with computer program ADVASP 143.

Calculations of the electronic structures of the molecules have been performed with half-empirical method AM1 (MOPAK 2000) with complete optimization of geometric molecule structure to receive meanings of the molecular orbital energies using program Hyper Chem® 6.0.

The research of synthesized compounds has been set with the use of LC MS device: Agilent 1260 Infinity HPLC System (Degasser, Binary Pump, Autosampler, Thermostat Column Compartment, DAD); Agilent single-quadrupole mass spectrometer 6120 with electrospray ion source (ESI); OpenLAB Software CDS. Conditions for HPLC-MS research. (1) Binary gradient. A: H₂O (HCOOH 0.1%), B: CH₃CN (HCOOH 0.1%); (2) Column Zorbax SB-C18, 30 mm × 4.6 mm, 1.8 μm; (3) the column temperature: 40°C; (4) DAD: 210, 254 nm; (5) Ion Source: API-ES; (6) Scan. Mass range: 160-1000; (7) Fragmentor: 10 V; (8) Positive polarity.

Thin-layer chromatography has been carried out using the silicagel 60 ALUGRAMSill G\UV254 (alumin. 20×20) (Macherei-Nagel) plates or silicagel 60 ALUGRAMSill G\UV254 (alumin. on hook 10×20) (Macherei-Nagel) plates.

RESULTS

Results of the element analysis show in Table 1 that experimental data do not differ from theoretic data more than on 0.29%.

DISCUSSION

Analyzing IR-spectra of 3-alkylsulfonyl-5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R₁-2,4-dihydro-3*N*-1,2,4-triazoles (1-9) we've found absorption strips on interval 2860-2846/cm, 2925-2905/cm, on interval 2917-2877/cm, and 2987-2900/cm which are in congruence with methylene and methyl groups (symmetrical and nonsymmetrical absorption strips) properly. The strips on interval 1140-1047/cm denote R₂SO₂-groups (Fig. 1) [8].

CONCLUSION

1. We have developed the effective methods of 3-alkylsulfonyl-5-(chinoline-2-yl, 2-hydroxychinoline-4-yl)-4-R₁-2,4-dihydro-3*N*-1,2,4-triazoles receiving. Nine new compounds have been synthesized (Table 1).
2. The structure of the synthesized compounds was determined with the modern physical and chemical analysis methods (Table 2).
3. The next stage of the research will be determination of the biological activity of the synthesized compounds.

PROSPECTS OF THE FURTHER SCIENTIFIC INVESTIGATIONS

Prospect of the further researches is determination of acute toxicity and next studying of pharmacological properties of the synthesized compounds.

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