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The Synthesis of Tetrapyrimidines and their Carboxylic Derivatives and the Application of Antimicrobial Properties

Research Article

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Abstract

The article was dedicated to the research directed to the synthesis, transformations and studies of the biologically active substances having multidisciplinary scientific and technical application areas. For the first time, synthesized and functional properties of tetrapyrimidines-derivatives of cyclic thiocarbamides, which are a new generation of multifunctional compounds and their carboxylic-based compounds were examined, the antimicrobial properties of these compounds were studied with the laboratory experiments and was approved that they have active physiologically active compounds compared to their analogues.

Keywords: Cyclic thiocarbamides; Tetrapyrimidines; Carboxylic derivatives; Antimicrobial properties; Gram-positive microorganisms; Bacteria; Meat-and-peptone agar etc.

Introduction

The need for the new researches for raising the efficiency of in the development of the petrochemical and medical industry is noticeable. Especially, there is a specific fundamental and applicable issue in science that the approach on a scientific direction in their solution does not justify itself and is not achieved satisfactory results for many years. The need for a complex scientific approach arises for such issues and the most successful scientific results of recent years are found in the research of the intersection of science with the multidisciplinary approach. From this point of view, as a result of the most recent studies conducted in the Institute of Chemistry of Additives of the Azerbaijan National Academy of Sciences, it was determined that, biocide additives synthesized at the institute shows biological (physiological) activity in other areas too, in addition to protect the oil products from the microbiological damage. For instance, amino ethanol and some derivatives of amino alcohols synthesized by the employees of Institute shows the properties of anesthetic and terminal anesthesia for the mucous membranes of the eye. The studies were conducted at the 1st Moscow State Medical Institute named after I.M.Sechenov. These substances are 7 times greater compared to the widely-used "xycain" , according to its activity. As a result of investigations carried out, in the "Biochemical Pharmacology" Laboratory (Moscow oblast, Kupavna settlement) of Scientific Research Institute for the "Biological Testing" of chemical compounds, their anti-alcohol properties have been also identified,

Bacteriological influence of heteroaryl sulfamides containing

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pyrimidine and pyrazole was investigated in the Microbiology department of Baku State University,and it was determined that, these substances quickly perishes the "stafilococ", "penicillium" and "mold" mushrooms in the concentration of 0,05-0,1%. 3 (beta-hydroxy (oxymethylene)-ethyl-1,3-oxazolidine (was named as "Cyclazole") has a high disinfectant propertiesand its usage was allowed by the Ministry of Health of the Republic of Azerbaijan. In other words, as a results of tests conducted at the Institute for Scientific Research of Virology, Microbiology and Hygiene of the Ministry of Health of the Republic of Azerbaijan, it was determined that the nitrogenous derivatives of alkylphenol and alkylaromatic ketones have the highest disinfectant and antiseptic properties and was advised to apply.

When it comes to the use of these compounds in the oil and chemical industry, it should be noted that, many industrial materials, including the oil products are damaged with microorganisms when they are maintained and their exploitation conditions are violated (the highest humidity and temperature) (Gonik A.A., Kornilov G.G., 1996). Microorganisms affects negatively to the composition, properties and quality of these damaged materials, by adopting the hydrocarbons of petroleum products, as a source of food and energy and as well as affecting them by the metabolic products.

Because of the fact that, the problem of microbiological damage of industrial purpose and other materials is in large scale and the amount of the economic loss is too great, it is in the focus of many scientists currently. [Dormidontova OV, 1-3].

More effective method of fighting against the microbiological loss is the use of antimicrobial properties of the compounds. The experience of foreign and countrywide researchers and users has shown that, especially these substances provide reliable and long-term protection of industrial materials.

"Biobor JF", which is processed by the companies New York Central Reilrood and Standart Oil Co for the protection and preservation of Jet and aircraft fuels [4]. 4-octyl isothiazolone (firm name of biocide Kathon L.P.) and 2-octyl-4-isothiazolin-3-on (CKAH M-8) [5] is used for the preservation of liquid fuels. Vazin [6], Grotan U.K. [7], Florachit [8] biocides are applied for the protection of cutting fluids. These biocides are effective against the bacteria.

It's more than 40 years that the scientific studies are carried out directed to the research of bio-sustainability of oil products and their protection through the biocides, in the Institute of Chemistry of Additives of ANAS. For this purpose, purposeful synthesis of chemical compounds having high biological active properties is carried out [9]. The biological activity of synthesized compounds in oil products (oil, fuel and CF) was studied and the mutual relationship between their chemical structure and antimicrobial activities was determined.

Materials and Methods

The research of antimicrobial properties of the substances synthesized above was studied by the method of thinning out in series.

For this, the substance was carried out with the dilution below in sterile distilled water of 1%, and prepared in ethyl-acetate (1:100, 1:200, 1:400, 1:800), (1,2,3,4).

These substances have been studied with alcohol, nitrofurgin, as well as ethyl-acetate in comparative manner. Gold staphylococci (St. aureus) from gram-positive microorganisms, colon bacillus (E. coli) from gram-negatives, a blue-green pus bacillus those which makes pigment (Ps. aeruginoza), Cand. albicans which is from Candida species were taken from the mushrooms as testing culture.

(MPA) meat-and-peptone agar nutritious environment was used for cultivating bacteria and Saburo nutritious environment is used for cultivating mushrooms.

Plantings were carried out in 10, 20, 40, 60 minutes, and were maintained in the thermostat of 37^0C temperature for bacteria for 24 hours and in the thermostat of 28^0C temperature for mushrooms for 48 hours.

In the experiments 1-2 drops emulsion having 500 million germs in 1 ml was distilled to each of the tubes (any dilution). 1 hour planting was carried out from each test tube in every 10-20 minutes. Antimicrobial effect of new, synthesized substances and controls was given in the table below.

As seen from the table, newly synthesized substances influenced in different kinds of microorganisms in different ways. In general, synthesized substances have antimicrobial affects.

As seen from the table, the newly synthesized substances displayed antimicrobial affect from the solution of ethyl acetate. So, every 3 substances displayed more active antimicrobial affect against gram negative microbes. For ex: ethyl-6-methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate and benzyl-6-methyl-2-thioxo-4-(o-tolyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate has peri-shed E.colin in 1:400 ratio for 10 minutes, and in 1:800 ratio for 40 minutes. It does not perish ethyl-6-methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate in 1:800 ratio even in 1 hour, but benzyl-6-methyl-2-thioxo-4- (o-tolyl) -1,2,3,4-tetrahydropyrimidine -5-carboxylate effects lethally in 60 minutes.

Every 3 substances affects on the mushroom Candida in 1:400 ratio in 10 minutes, and even ethyl-4-(2-hydroxyfenil)-6-methyl-2-thioxo-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate and benzyl-6-methyl-2-thioxo-4-(o-tolyl)-1,2,3,4-tetra-hydropyrimidine-5-carboxylate affects it fungicidally in 1: 800 ratio. But, ethyl acetate also affects on Candida like ethyl-6-methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate. Therefore, newly synthesized substances are more noticeable with bactericidal effect.

As for the impact of staphylococcus, ethyl-4-(2-hydroxy fenil)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate and benzyl-6-methyl-2-thioxo-4-(o-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate is considered more active. So, they perished this microbe in dilution 1:200 ratio in 20 minutes.

Experimental

General methods

The reactions of three-component condensation going at one stage ends at 65-70 °C for 2-4 hours. The process of reaction is regulated by the method of thin-layer chromatography. Eluent is the mixture of isopropyl alcohol and hexane (3:1 ratio). The presence of

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Table 1: Antimicrobial affect of synthesized substances and controls.

Test cultures	Exposure time (minute)	Analysis of the items												Check for											
		1				2				3				Ethyl acetate				Ethyl alcohol				Nitrofungin			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
St. Aureus	10	-	+	+	+	-	-	+	+	-	-	+	+	+	+	+	+	-	+	+	+				
	20	-	+	+	+	-	-	-	+	-	-	-	+	-	-	+	+	-	+	+	+				
	40	-	-	-	-	-	-	-	+	-	-	-	+	-	-	+	+	-	+	+	+				
	60	-	-	-	-		-	-	-	+	-	-	-	+	-	-	-	+	-	+	+	+				
Ps. Aeruginoza	10	-	-	-	+	-	-	-	+	-	-	-	+	-	-	+	+	+	+	+	+				
	20	-	-	-	+	-	-	-	+	-	-	-	+	-	-	+	+	-	+	+	+				
	40	-	-	-	+	-	-	-	-	-	-	-	+	-	-	+	+	-	+	+	+				
	60	-	-	-	+		-	-	-	-	-	-	-	-	-	+	+	-	+	+	+				
E. coli	10	-	-	-	+	-	-	-	+	-	-	+	+	-	-	+	+	+	+	+	+				
	20	-	-	-	+	-	-	-	-	-	-	-	+	-	-	+	+	-	+	+	+				
	40	-	-	-	-	-	-	-	-	-	-	-	+	-	-	+	+	-	+	+	+				
	60	-	-	-	-		-	-	-	-	-	-	+	-	-	+	+	-	+	+	+				
Candida albicans	10	-	-	-	+	-	-	-	+	-	-	-	+	-	-	-	+	+	+	+	+	+	+	+	+
	20	-	-	-	+	-	-	-	+	-	-	-	+	-	-	-	+	+	+	+	+	+	+	+	+
	40	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	+	-	+	+	+	-	+	+	+
	60		-	-	-	+		-	-	-	-	-	-	-	-	-	+	-	+	+	+	-	+	+	+

the blot has explained with iodine smoke.

The structure of received compounds was approved by the İQ and 1H, 13C NMR spectroscopy.

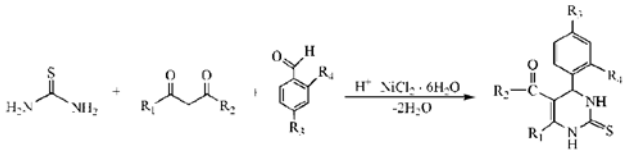
Chemical Synthesis

The synthesis of thioxo 6-methyl-2-ethyl-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate 11.4 g. (0.15 mol) thiourea, 20 ml ethyl acetate and 21.2 gr (0.2 mol) 4-metyl benzaldehyde added to the three – neck flash which equipped with mechanical stirrer, thermometer and drop funnel and dynamically mixed. Mixed in 4 hours in 65°C temperature. Reaction process have observed with thin - layer chromatography. When the reaction completed the mixture persisted during 24 hours at room temperature and white crystals precipitated. Crystals of 6-methyl-2-ethyl-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate filtrated and separated, then washed in dichloromethane and crystallized in ethyl alcohol. Obtained 7.41 g. of 6-methyl-2-ethyl-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate. Yield 65%. M.P.= 232 °C. R_f=0.54.

Discussion and Results

We must say that, by taking into consideration the interest in this field in world literature [10-11], the continuation of research works is actual directed to the synthesis, transformations and research of biological active substances having multidisciplinary scientific and technical application areas. Therefore, the expansion of scientific research aimed at the synthesis of tetrapyrimidines-the derivatives of cyclic thiocarbamides which are the new class of multifunctional compounds, the research and application of functional properties was considered appropriate by us. From this point of view, in the submitted project it is intended to expand the investigations of scientific researches directed to the synthesis of new heterocyclic compounds containing of multifunctional nitrogen and sulfur and the application as antimicrobial and antioxidant.

New cyclical thiocarbamides have been received by continuing conducted researches in the field of synthesis and transformation of various classes of organic sulfur compounds. So, methyl 4-(2-hydroxy (-H)-4-methyl fenil - (- H)) - 6-methyl-2-thioxo-1,2,3,4-tetrahydropyri-midine -5-carboxilates was received based on nickel (II) chloride hexahydrate for the first time by us (Figure 1).



1. R_1=CH_3; R_2=OCH_3; R_3=H; R_4=H
2. R_1=CH_3; R_2=OCH_3; R_3=H; R_4=OH
3. R_1=CH_3; R_2=OCH_3; R_3=H; R_4=CH_3

At the same time, the reactions of three-component condensation of thiocarbamide, ethyl acetate and 4-metyl benzaldehyde was conducted and consequently thioxo 6-methyl-2-ethyl-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate has been synthesized (Figure 2):

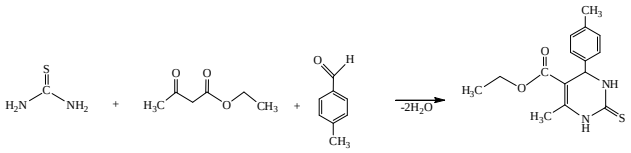


Figure 2:

The reaction of the transformation of combination was carried out at the next stage.

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So, ethyl 3-(2-hidroksibutil)-6-methyl-2-thiokso-4-(p-tolyl)-1,2,3,4-tetrahydropyrimi-dine-5-carboxylate was received by impacting on the ethyl 6-methyl-2- thioxo-4- (p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate with epoxibutan (Figure 3).

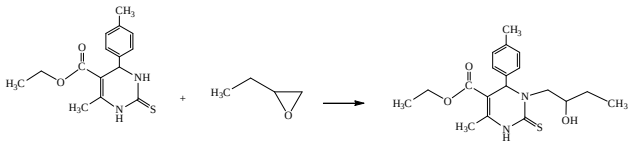

Figure 3:

Laboratory tests of antimicrobial properties of newly synthesized substances (ethyl-6-methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahyropyrimidine-5-carboxylate (1), ethyl-4-(2-hydroxyfenil)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbo-xylate (2) and benzyl-6-methyl-2-thioxo-4-(o-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate) (3) were carried out, their antimicrobial properties were studied and the act was drawn up.

Conclusion

The derivatives having high bactericidal properties of Tetra-pyrimidine-carboxilate have been synthesized. Tested ethyl-6-methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5- car-boxylate, ethyl-4-(2-hydroxyfenil)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimi-dine-5-carboxylate and benzyl-6-methyl-2-thioxo-4-(o-tolyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylate displays high antimicrobial activity against colon bacillus and blue-green pus bacillus.

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