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POTENTIAL ANTIMICROBIAL ACTIVITY OF SOME NEW 3,5-DIMETHYL PYRAZOLE DERIVATIVES

Anca Mihaela MOCANU* and Constantin LUCA

"Gheorghe Asachi" Technical University of Iasi, Faculty of Chemical Engineering and Environmental Protection, 71 A D. Mangeron Ave, 700050, Iasi, Romania

Abstract

The study presents original contributions to the researches developed in the class of heterocyclic derivatives with potential biological activity. The objective of this study is to evaluate antibacterial activity of new derivatives sinthetized. Synthesis was done by obtaining new molecules with pyralozone structure which combine two pharmacore entities: the amidosulfonyl-R1,R2 phenoxyacetil with the 3,5-dimethyl pyrazole which can have potential biological properties. The microbial properties were confirmed by the microbiological tests. The synthetized compounds were evaluated by measuring zone diameters of bacterial growth inhibition on different types of strains microorganisms: Staphylococcus aureus, Escherichia coli and Candida Albicans.

Keywords: *derivates of pyrazole, microorganisms, difusimetric method, antimicrobial activity.*

Introduction

Among the non-steroid anti-inflammatory compounds the pyrazol derivatives are known as a particularly important class recommended in treating the muscle pains, fever states and arthritis. These compounds are mentioned in recent literature to show not only analgesic and anti-inflammatory effects but also anti-tumor, anti-microbial, anti-oxidative, hypoglycemic and anti-convulsive proprieties bringing thus new potential therapeutic indications into discussion [1-5].

The anti-microbial properties are due to the ability of some constituents of destroying the infectious agents and preventing from their proliferation inside the organisms and environment. Thus, a multitude of such compounds are investigated for their potential applications as therapeutic agents in treating infectious diseases especially those caused by the multi-resistant bacteria [4-6].

The discovery of new therapeutic representatives showing improved pharmacologic profile and therapeutic safety is a major concern of many researchers. The researches reported in the present study are directed to this field being aimed to obtain new heterocyclic derivatives with potential biological activity [5-7].

The novelty and originality of the studies achieved in the present paper consist in the antimicrobial activities of new products which are not mentioned in literature showing potential pharmaceutical [8-10].

The antimicrobial activities of the newly obtained compounds were estimated against a Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) bacteria and on yeasts (Candida albicans).

The comparative inhibiting action was estimated by the difusimetric method in the overlay agar (for bacteria) and Sabouraud (for yeasts). The measured critical diameters afford the germs under study to be classified as "sensitive" and "resistant". The obtained results were expressed by the direct transcription of the inhibition area diameter [11].

Corresponding author: ancamocanu2004@yahoo.com

Experimental

Testing of antimicrobial activity

The technical conditions referring to the culture medium (composition, pH), inoculum, type of the cylinders, test performing, inoculation require an exact standardization [11]. The nutrient value of the media promote the optimum development of a large variety of germs and apart from this they do not contain inhibitors of bacterial substances.

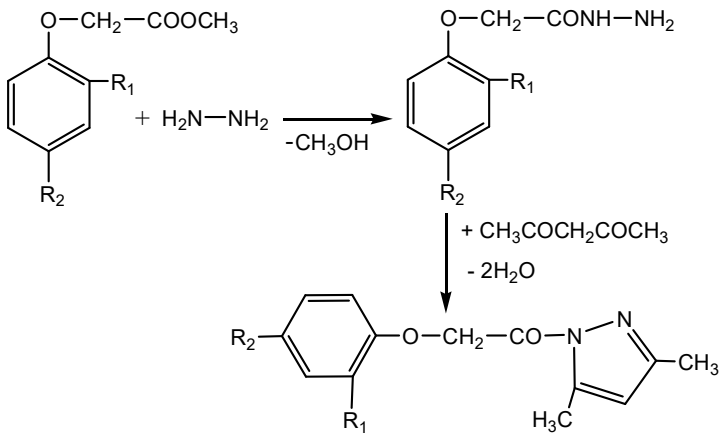
The comparative inhibiting action was estimated by the diffusimetric method in the agar (for bacteria) and Sabouraud (for yeasts) were taken as culture media and placed in Petri dishes as uniform layers of 4 mm thickness, the pH values of 7.2–7.4 (for bacteria) and 6.5 (for yeasts) being previously measured.

From the young cultures of micro-organisms (18 h – bacteria, 72 h – yeasts) microbial suspensions of 1/100 for the micro-organisms to be tested, namely Candida albicans, Escherichia coli and Staphylococcus aureus have been prepared. Every plate was inoculated with 3 mL of the obtained suspensions and let to stay for 3-5 minutes for the inoculum absorption. After removing the inoculum the plates were maintained for 30 min. at the room temperature. Then stainless steel cylinders were applied on the medium surface by means of sterile nippers and 200 µL of every tested sample placed into them. The plates were incubated with the cover down, at 37 ^{o}C for 24 h with bacteria and at 28 ^{o}C for 72 h with yeasts. The microorganism cultures were used for the impregnation of both samples and standard samples (represented by DMSO) since in every experimental model the three compounds were tested with the samples under study and also in comparison with impregnated standard samples under identical cultivation conditions [12,13].

Only the plates with cultures corresponding in purity and density were read. The reading was made to the naked eye by measuring 2-3 times the diameter of the inhibition area (mm) in different directions by means of a rule.

Results and Discussions

Synthesis of derivates was performed in order to obtain new molecules with 3,5-dimethyl-pyrazoles structures by attaching to nucleus sulfonyl-phenoxyacetic a that of dimethyl-pyrazole ring (fig.1).



R_1= -CH_3 , -$SO_2N(C_2H_5)_2$, -$SO_2N(C_4H_9)_2$, Cl;
R_2= -$SO_2NHC_4H_9$,-$SO_2N(C_4H_9)_2$, Cl , -$SO_2NHC_2H_5$;

Fig. 1. The synthesis of new 3,5-dimethyl pyrazole derivatives

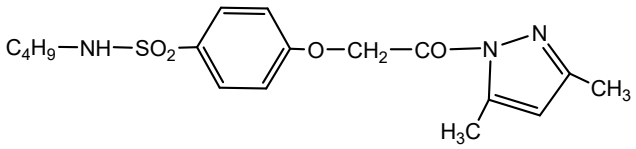
The new derivatives were synthesized according to the method described in our previous paper [14].

The newly analyzed compounds and their denominations data are given in Fig. 2.

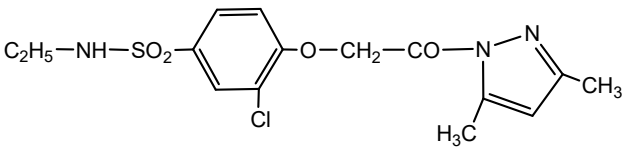
There are different levels of sensitivity to the tested compounds against of the microorganisms (Table 1).

Table 1. The levels of sensitivity to the tested compounds

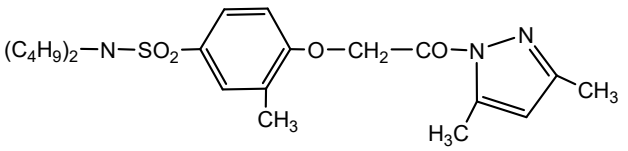
Microorganism tested	1	2	3	Standard (DMSO)
Staphylococcus aureus	6	17	8	0
Escherichia coli	32	45	40	0
Candida albicans	11	16	20	0



1-(2-methyl, 4-buthyl-amidosulfonyl)-phenoxyacetil-3,5-dimethyl pyrazole (**1**)
Chemical formula: $C_{18}H_{25}N_3O_4S$
Molecular weight: 379
Melting point: 141-143 ^oC



1- (2-chloro, 4-ethyl-amidosulfonyl)-phenoxyacetil-3,5-dimethyl pyrazole (**2**)
Chemical formula: $C_{15}H_{18}N_3O_7SCl$
Molecular weight: 371.5
Melting point: 186-188 ^oC



1-(2-methyl, 4-dibutyl-amidosulfonyl)-phenoxyacetil-3,5-dimethyl pyrazole (**3**)
Chemical formula: $C_{22}H_{35}N_3O_4S$
Molecular weight: 437
Melting point: 136-138 ^oC

Fig. 2. Structures of new compounds

The research results prove the antibacterial action of the three compounds tested against microorganisms.

The anti-bacterial activity was made evident for the compounds, with the Staphylococcus aureus species where the inhibition area diameters were of rather close values (6 mm for compound 1 and 8 mm for compound 3) while compound (2) a show pronounced anti-bacterial effect.

In the case of testing the antibacterial action of compounds there was highlighted a greater sensitivity of Gram-negative bacteria (Escherichia coli) compared with Gram-positive bacteria (Staphylococcus aureus), phenomenon given by the presence of substitutes of chlorine and methyl type of compound, which can obviously influence the growth and spreading of this microorganisms.

Also, compunds (2) and (3) influence, differentially the development of the microorganisms, antibacterial activity being obvious in case of Gram-negative bacteria which presents a higher level of sensitivity to chlorine groups from compound (2) and substitutes of methil from compound (3). As revealed by the data obtained with the Escherichia coli species all the tested compounds showed anti-bacterial action decreasing in the following order: 2<3<1 (Table 1).

The inhibition diameter zones vary between 32-45 mm in case of Escherichia coli species and 6-17 mm in case testing the Staphylococcus aureus species (Table 1).

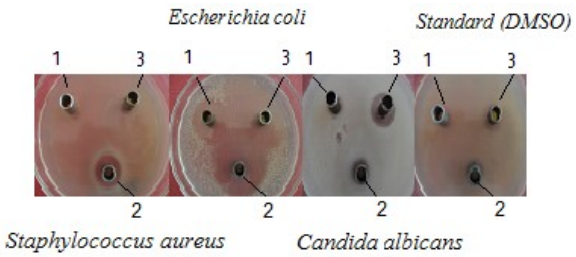


Fig. 3. Testing of the antimicrobial action against Staphylococcus aureus Escherichia coli and Candida albicans

With Candida albicans the inhibition area diameters were different, especially for compound (2) -16 mm and (3) - 20 mm, while a slighter inhibition was noticed with compound (1) with an inhibition area diameter of only 11 mm compared to the standard sample.

As made evident by the data of the anti-microbial tests the sensitivity/resistance of the micro-organisms is different toward the tested compounds due to both the different chemical structures of the compounds and the different types of the micro-organisms under study differing in their cell ultra-structures and response manner to the chemical compounds: Gramm-positive bacteria (Staphylococcus aureus), Gramm-negative bacteria (Escherichia coli) and yeasts (Candida albicans).

The obtained results are indicative of an increased sensitivity of the Escherichia coli bacterium and as and yeasts (Candida albicans) to the tested compounds.

Conclusions

The original results reported herein were obtained by testing the newly obtained compounds which revealed potential anti-microbial action.

According to the results of the study the compounds present antimicrobial effects against Gram-positive, Gram-negative bacteria and on yeasts.

The antimicrobial activity was estimated by measuring the growth inhibition area against types of microorganism strains.

The antibacterial activity was detected in the case of the compounds tested, demonstrating that substituents, can influence this activity.

The antimicrobial activity towards some micro-organisms presented by this compounds, provides useful information for potential therapeutic use.

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