Journal homepage: www.fia.usv.ro/fiajournal
Journal of Faculty of Food Engineering,
Ştefan cel Mare University of Suceava, Romania
Volume XVIII, Issue 1 - 2019, pag. 13 - 17

(IMIDAZOLE-5-YL)YLIDENTHIAZOLIDONES: A NEW CLASS OF ANTIMICROBIAL AGENTS FOR FOOD INDUSTRY

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Received 23th January, 2019 accepted 28th March 2019

Abstract: *An antimicrobial and antifungal activity of new derivatives of (imidazole-5-yl)ylidenthiazolidinones and its dependence on the substance structure and the type of substitutes in the imidazole and thiazole nucleus have been investigated. It was found that the sulphur of thiazolidone section is the key factor that governs antimicrobial activity of the compounds. High antibacterial and antifungal activity against pathogenic microbes S. aureus ATCC25923, E. coli ATCC25922 and fungi C. albicans ATCC885-653 was determined for some representatives of the compounds series. Since the evaluated acute toxicity of the compounds is quite low, they can be recommended for further systematic investigation as possible prospective disinfection agents for food industry.*

Keywords: *organic synthesis; imidazoles; thiazolidinones; antimicrobial and antifungal activity; foodstuff treatment and production*

1. Introduction

A risk of microbial and/or fungal contamination is one of important problems endangering foodstuff processing, production and storage at every stage of manufacturing. That is why, extensive efforts are made in various directions to safeguard the foodstuff and raw materials from primary and/or secondary bacterial/fungi contamination or to ensure that the pathogenic objects would not be able to grow and develop.

Strict observation of all sanitary and hygienic requirements is considered as one of the most effective actions protecting the food materials from pathogenic germs. Disinfection chemicals are known as inexpensive and very effective solution to reduce or exterminate unwanted microorganisms or yeast-like fungi such as *E. coli*, *S. aureus* and *C. albicans* at every stage of food processing technologies [1].

A number of chemical agents of different nature are used for this purpose: phenolic compounds, chloroorganic compounds, alcohols, aldehydes, oxygen-containing and oxidizing substances, various mixtures of quaternary ammonium salts, guanidine derivatives etc. [2]. However, many of them are either low efficient or toxic, corrosive to the equipment parts or destructive for the foodstuff components. Moreover, it usually takes shorter and shorter time now for the pathogenic germs to develop strong resistance against regular antibiotics or disinfectants [3], which pushes new investiga-

tions directed onto finding of more effective chemical disinfectants.
That is why it is strongly topical problem to investigate and develop new stable disinfection compounds with prolonged activity, low toxicity and other adhere effects.
It is known that 1,2,4-substituted 5-formylimidazoles can be considered as interesting candidates for this category. They have already been used widely to synthesize various biologically active components [4-6] and it has been reported [7] that some derivatives of thiazolidone exhibit distinct antimicrobial and antifungal activity. That is why a deeper investigation of antimicrobial potential of imidazolylmethylenthiazolidones seems topical and promising.

2. Experimental

All target 5-[(1-aryl-1N-imidazole-5-yl)methylen]-1,3-thiazolidine-2-thio-4-ones (Fig. 1, structure 1**)**, 5-[(1-aryl-1N-imidazole-5-yl)methylen]-1,3-thiazolidine-2-thio-4-ones (Fig.1, structure 2) and 5-[(1-aryl-1N-imidazole-5-yl)methyl]-1,3-thiazolidine-2-thio-4-ones (Fig.1, structure 3) were synthesized by the condensation of available 1-arylimidazole-5-carbaldehydes with rhodanine or thiazolidine-2,4-diones under the basic catalysis conditions [8]. General structures of the synthesized compounds are shown in Fig. 1.

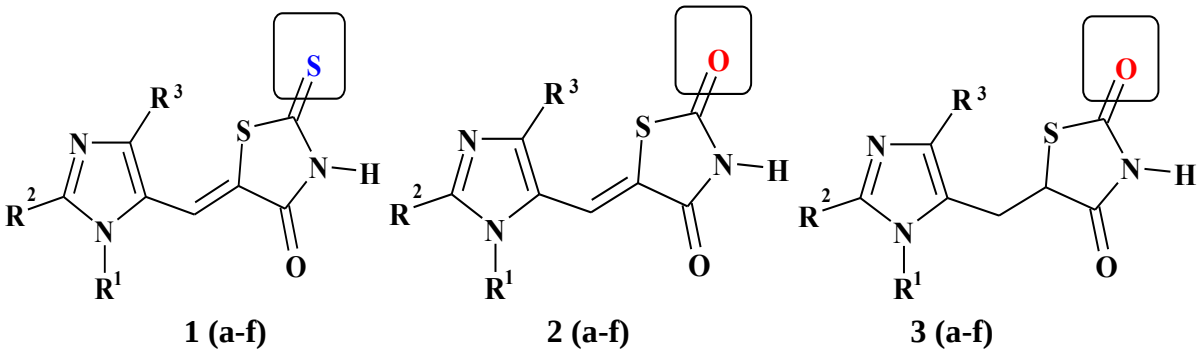

Fig. 1. Structural composition of three classes of antimicrobial/antifungal agents synthesized and investigated in this work. Substitutes R^1, R^2 and R^3 were combined as shown in Table 1.

The degree of bioactivity of all the substances has been tested on the museum strains of *S. aureus* ATCC25923, *E. coli* ATCC25922 and pathogenic fungi *C. albicans* ATCC885-653 by the double serial dilution method [9]. According to this method, the disposable 96-hole pads and the 8-channel titrator were used to evaluate an antimicrobial activity of the compounds libraries. The clinical strains mentioned above are known to cause usual invasions in humans and were chosen as the test-cultures to evaluate disinfection potential of the substances synthesized in this project.

The clear bacterial colonies were cultivated in the meat-peptone broth for 24 hours at 37±1 ^{0}C until the number of the cells reached 10^5 CFU/ml. The clear fungi colonies of *C. albicans* were cultivated in Saburo nutritional agar for 7 days at 30±1 ^{0}C until the suspension concentration reached 10 CFU/ml. Then concentration of all solutions was standardized to 0.5 McFarland units by visual comparison. All compounds under investigation were used to prepare a series of solutions with concentrations ranged from 500 μg/ml to 7.8 μg/ml and then the minimum inhibition concentration was found after 24 hours of

cultivation in case of bacteria or after 48-72 hours in case of fungi. The minimum bacteriostatic (MBsC), minimum bactericide (MBcC), minimum fungi static (MFsC) and minimum fungicide concentrations (MFcC) were determined as the lowest solution concentration of a given compound that results in the distinct oppression of the test-cultures growth (static concentrations) or extermination of the colonies (MBcC and MFcC).

3. Results and discussion

It was found that antimicrobial activity of imidazolylmethylenthiazolidones against various types of pathogenic germs depends significantly on the compound structure and composition (see Table 1).

Table 1.

Antimicrobial activity of the 1-3 compound series (μg/ml)

№	R^1	R^2	R^3	*S. aureus* ATCC25923		*E. coli* ATCC25922		*C. albicans* ATCC885-653	
				MBsC	MBcC	MBsC	MBcC	MFsC	MFcC
1 a	CH_3	H	Cl	250	250	250	250	31.3	31.3
1 b	C_6H_5	H	Cl	3.9	3.9	31.3	62.5	7.81	7.81
1 c	4-ClC_6H_4	H	Cl	15.6	31.3	7.81	15.6	31.3	31.3
1 d	CH_3	H	SCH_2CO_2H	31.3	31.3	31.3	125	15.6	31.3
1 e	4-ClC_6H_4	H	SCH_2CO_2H	250	250	250	1000	15.6	125
1 f	4-$CH_3C_6H_4$	Cl	Cl	7.8	7.8	250	250	31.3	62.5
Averaged activity amongst 1 a-f				**-**	**95.7**	**-**	**283.9**	**-**	**48.2**
2 a	C_6H_5	H	Cl	62.5	125	250	500	125	250
2 b	2-$CH_3C_6H_4$	H	Cl	125	250	250	500	62.5	125
2 c	3-$CH_3C_6H_4$	H	Cl	125	250	250	500	125	250
2 d	4-$CH_3C_6H_4$	H	Cl	125	250	250	500	62.5	125
2 e	4-$CH_3OC_6H_4$	H	Cl	500	1000	500	1000	250	500
2 f	1-$C_{10}H_7$	H	Cl	62.5	125	125	500	125	250
Averaged activity amongst 2 a-f				**-**	**333.3**	**-**	**500**	**-**	**250**
3 a	C_6H_5	H	Cl	62.5	125	250	500	125	250
3 b	2-$CH_3C_6H_4$	H	Cl	125	250	250	500	62.5	125
3 c	3-$CH_3C_6H_4$	H	Cl	125	250	250	500	125	250
3 d	4-$CH_3C_6H_4$	H	Cl	125	250	250	500	62.5	125
Averaged activity amongst 3 a-d				**-**	**218.8**	**-**	**500**	**-**	**187.5**
Total averaged activity amongst 1-3 series				**-**	***215.6***	**-**	***450.2***	**-**	***158.7***
**Control*				**7.8*	**15.6*	**7.8*	**15.6*	***3.9*	***1.9*

*Furacilinum (furacin or nitrofurazone) and **Clotrimazole were used in the control experiments as the reference antimicrobial and antifungal compounds correspondingly.

It should be noted that comparatively high antimicrobial and antifungal activities have been registered for all the compounds involved in this work. The total averaged MBcC for the entire series in case of *S. aureus* was 215.6 μg/ml, in case of *E. coli* – 450.2 μg/ml while MFcC was even lower – 158. 7 μg/ml. In our opinion, such a high antifungal efficiency can be caused by imidazole nucleus present in all compounds of the series 1-3. Since bactericide and fungicide indexes are more important than

corresponding 'static' concentrations, we skipped the former parameters in the further analysis.

A dependence of antimicrobial activity on the structure of thiazolidone section can easily be understood from comparison between subseries 1 (containing the exocyclic atom of sulphur) and subseries 2 (containing the exocyclic atom of oxygen). An influence of reduction of the methylene fragment to methyl on antimicrobial activity can also be understood from comparison between subseries 2 and 3.

For instance, it can be noted that the series 1 and 2 have same structural composition while antimicrobial and antifungal activities of the sulphur-containing series 1 are higher than those of the oxygen-containing series 2. An average MBcC and MFcC for the set 1 are (μg/ml): 95.7 (*S. aureus*), 283.9 (*E. coli*) and 48.2 (*C. albicans*) correspondingly. Similar values for the set 2 are sufficiently higher that proves lower activity of these compounds: 333.3 (*S. aureus*), 500 (*E. coli*) and 250 μg/ml (*C. albicans*).

Transformation of the methylene structural bridge in the set 2 to the methyl one (set 3) results in some increase of averaged antimicrobial and antifungal activity of the compounds and the corresponding values of MBcC and MFcC decrease down to 218.8, 500 and 187.5 μg/ml (see Table 1).

Therefore, it is obvious that the compounds 1a-f reveal the highest germ-suppressing activity and should be analyzed further to find the most effective representative.

As seen from the data of Table 1, the structure of the imidazole part of a compound is the key factor influencing germ-suppressing activity. For instance, both antimicrobial and antifungal activities are increasing after exchange of a substitute in the first position from methyl (1a) to phenolic (1b) or 5-chlorophenolic (1c).

On the other hand, a substitute in the second position of imidazole cycle also seems influential. When the polar atom of chlorine is inserted in the R^2 position, the value of MBcC improves to 7.8 μg/ml in case of *S. aureus* while MFcS reaches 62.5 μg/ml. In contrary, this substitute makes no effect on the value of MBcC in case of *E. coli* (see comparison between 1a and 1f).

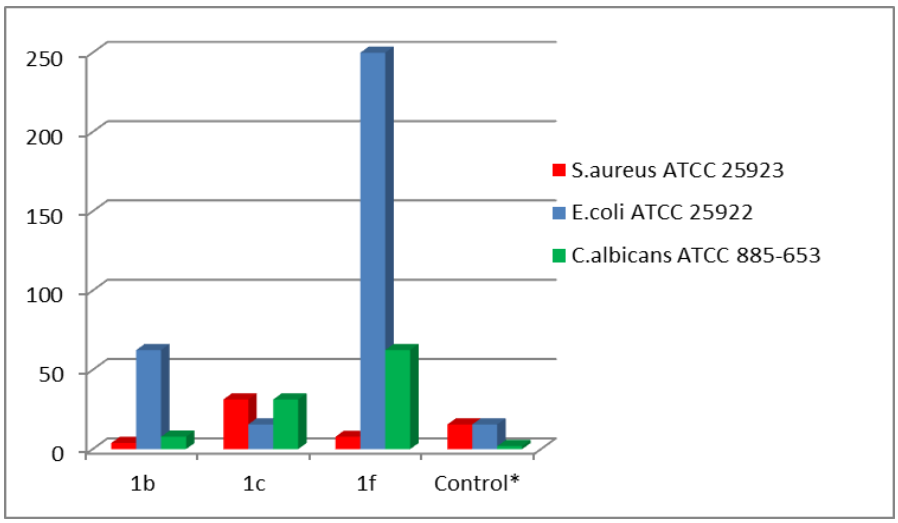

Fig. 2. Comparison of minimal bactericide (MBcC) and fungicide (MFcC) concentrations (mg/ml) for some representatives of the subseries 1 and the control compounds.

It is also interesting to analyze an influence of a substitute to the fourth position of imidazole cycle (R^3). As seen from the comparison between the compounds 1a and 1d, both MBcC and MFsC values get improved for all three types of the germs when chlorine is substituted with the hydrophilic fragment of thioglycolic acid. When there is the aryl fragment in the first position of imidazole fragment (1c and 1e), substitution of chlorine in the fourth position with the thioglycolic acid fragment results in a serious decrease of antigerm activity especially against *S. aureus* and *C. albicans* (compare corresponding values of MBsC, MBcC and MFcC for 1c and 1e). It is interesting to note that the change of MFsC in this case is opposite and it is improving because of the above-mentioned substitution.

The above discussion is visualized graphically in Fig. 2 for better comprehension of comparative bactericide and fungicide activities of some representatives of the subseries 1 and the corresponding control compounds.

Finally, toxicity of all the synthesized compounds has been evaluated using the computer simulation software GUSAR Online [10]. The toxicity of the entire class of the synthesized compounds has been found low: Rat oral LD_{50} = 1027 mg/kg; Rat SC LD_{50} = 1366 mg/kg.

4. Conclusion

A wide spectrum of bactericide and fungicide or static activities has been found for some representatives of the investigated compounds. MBcC and MFcC values were close or sometimes better than those of the control agents. Since predicted toxicity was appropriately low, (imidazole-5-yl) ylidenthiazolidones can be used in further search for the low toxic bacterio- and fungicide agents for food industry.

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