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Synthesis and Antimicrobial Activity of Some Substituted Cyclopentyl Phenols

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Abstract

Some substituted cyclopentyl phenols were synthesized and screened for possible antibacterial and antifungal activities against *Staphylococcus aureus, Streptococcus viridans, Escherichia coli, Shigella flexneri, Salmonella typhi, Salmonella typhimurium, B.proteus vulgaris, Pseudomonas aeruginosa, Bacterium antracoides, Bacterium subtilis, Klebsiella rhinoscleuromatis and Candida albicans* using the microdilution method. Antimicrobial tests results indicated that all compounds have reasonable activity. They displayed the highest antimicrobial activity against *Streptococcus aureus* and *Streptococcus viridans*. The cyclopentyl phenols containing aryl substituted cyclopentyl radicals were the most active in the series against all tested bacteria and fungi strains.

Keywords

Substituted Cyclopentyl Phenols, Synthesis, Antibacterial Activity, Antifungal Activity

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1. Introduction

The short age of new antibacterial drugs and increasing resistance of bacteria to antimicrobial agents are important issues in drug development studies. It is known that phenolic compounds both synthetic [1, 2] and plant origin [3-7] are of interest for both low-toxicity bactericide Pharmacology and biological antioxidants[8]. Biological effects of phenols associated with their ability to affect microbial cell wall to form complexes with polysaccharides and proteins coagylating [9]. The introduction into the structure of phenols halogen atoms and cyclic radicals may affect the ability of cell wall permeability and, correspondingly, on the biological properties of phenols [10]. Previously, we synthesized some cycloalkyl phenols and evaluated them to their antimicrobial activities [11]. The results showed that cyclic radicals attached to the phenol structure cause a significant change in the antimicrobial effect. The research for the study of these properties in a number of phenols with cyclopentyl substituents demonstrated the possibility of using some of them as insecticides [12] and disinfectants [13].

In this connection it is of interest to further study the effect of the structure of cyclopentyl phenols on their antimicrobial properties [14]. To do this in the present work has been synthesized several known substituted cyclopentyl phenols 1-10 by the most reasonable published methods. Phenols 1-10 were prepared to investigate the effects of the structural modifications on the anticipated antimicrobial activity. It was studied for their antimicrobial activity against Gram positive, Gram-negative, spore, bacteria capsular and yeasts.

2. Experimental

General

^{1}H-NMR spectra were recorded on a JEOL spectrometer (90MHz) in DNSO-d_6 or $CDCl_3$ with TMS as internal

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reference, chemical shifts were measured in the δ scale. IR spectra of compounds were recorded as potassium bromide pellets on a Specord 75-IR instrument. GLC-analysis was performed on a Biokhrom device (5% Apieson L on Inerton N-AW-HMDSW, carrier gas He).

Procedure for Synthesis of Substituted Cyclopentyl Phenols 1-10

Mixture of phenols 1-2 was obtained in a yield of 70% by the alkylation of phenol with cyclopentanol in the presence of phosphoric acid. Following rectification individual phenols 1 and 2 were isolated under the control of the purity by gas-liquid chromatography [15]. Chlorinated cyclopentyl phenols 3-4 were synthesized by demethylation corresponding chlorinated cyclopentyl anisoles in a mixture of 48% HBr and acetic anhydride [16]. The chromatographically pure isomers 5-7 are obtained by distillation of the reaction products of 4-fluoro-, 2-bromo- and chloroanisole with cyclopentene in the presence of $BF_3 \cdot H_3PO_4$ [17]. Phenol 8 was isolated from the reaction products of phenol with 3-phenylcyclopentene in the presence of catalyst $BF_3 \cdot H_3PO_4$ [18]. Phenols 9-10 were prepared by hydrogenation over Ni-Raney corresponding 1,4-diaryl-1,3-cyclopentadienes, produced by reacting 3-(4-alkoxyphenyl)-cyclopentene with phenol in the presence of the same catalyst [19].

Individuality of phenols 1-10 was examined by GLC, the structures were determined by spectral analyses and spectroscopic properties were in accord with data reported previously.

Antimicrobial Activity

The minimal inhibitory concentration (MIC) was determined by microdilution method [20]. *In vitro* antimicrobial activity of the compounds 1-10 was evaluated against standard strains; *Staphylococcus aureus 209-P, Streptococcus viridans 171, Escherichia coli 675, Shigella Flexneri 2a-516, Salmonella typhi 495, Salmonella typhimurium 5710, B.proteus vulgaris 296, Pseudomonas aeruginosa 128, Bacterium antracoides 297, Bacterium subtilis ATCC, Klebsiella rhinoscleuromatis 348 and Candida albicans 688.* All the synthesized phenols were weighed, dissolved in DMSO and diluted with water to prepare the stock solutions. A bacterial suspension, obtained from a 24h culture was added to each probe with a final DMSO concentration. Each experiment was carried out in duplicate.

3. Results and Discussion

The substituted cyclopentyl phenols 1-10 were prepared according to the reported procedures as shown in Scheme 1. These procedures were based on the simply methods with using accessible reagents. The purity of the synthesized compounds was examined by GLC and the structures were determined by spectral analyses.

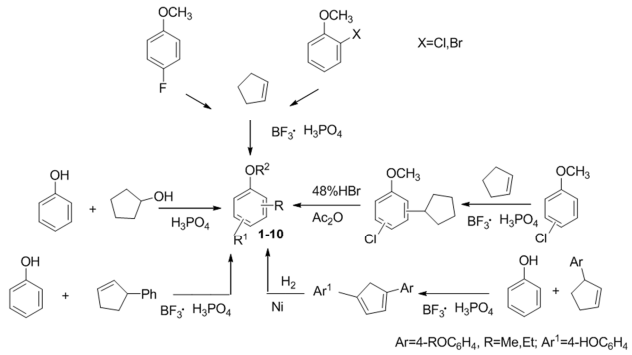

Figure 1. Synthesis of the Substituted Cyclopentyl Phenols 1-10.

1-7 R=cyclo-C_5H_9; 1 2-R, R^1=H, R^2=H; 2 4-R, R^1=H, R^2=H; 3 2-R, R^1=4-Cl, R^2=H; 4 4-R, R^1=2-Cl, R^2=H; 5 2-R, R^1=4-F, R^2=Me; 6 4-R, R^1=2-Cl, R^2=Me; 7 4-R, R^1=2-Br, R^2=Me; 8 R=4-(3-C_6H_5-cyclo-C_5H_8, R^1=H, R^2=H; 9 R=4-[3-(4- $MeOC_6H_4$-cyclo-C_5H_8)], R^1=H, R^2=H; 10 R=4-[3-(4-$EtOC_6H_4$-cyclo-C_5H_8)]

The series of substituted cyclopentyl phenols were evaluated for antimicrobial activity toward the Gram positive and Gram negative bacteria and fungus. To compare the effects of phenol structure on the antimicrobial propertie studied relation to 2-chlorophenol (11). Their antibacterial activities were assessed by measuring minimum inhibitory concentration (MIC) with standard broth dilution assay (Table 1.)

As can be seen from Table 1, all studied cyclopentyl substituted phenols 2, 4, 8-10 have sufficiently strong antimicrobial activity against all tested bacteria and fungi. According to the antimicrobial activity results, all compounds were found to possess high antimicrobial activity against *Snaphylococcus aureus* and *Streptococcus viridans* and low antimicrobial activity against *Pseudomonas aeruginosa.* Among the tested compounds 2, 4, 8, 9 were found to be the most active derivatives against *Staphylococcus aureus* and 2, 3, 4 against *Streptococcus viridans.* Introduction of a chlorine atom in their structure and increasing of the total volume of cyclopentyl radical enhances their antibacterial activity, and transfer of the hydroxyl groups in the alkoxy reduces it (5-7). Introduction the cyclopentyl radical in the phenol structure 4 increases its activity against Gram-positive and Gram-negative bacteria compared with unsubstituted 2-chlorophenol (11). According to the bactericidal properties of the compounds we were found that in order to achieve the death of the test bacteria under the influence of substances necessary to increase minimum inhibitory concentrations (MIC) only 1.5-2 times. Our study revealed that all the compounds had stronger antibacterial activity against Gram positive bacteria when compared to Gram negative bacteria. The findings suggest that the substituted cyclopentyl phenols act on the cell

membranes and surface activity of these compounds may be chiefly responsible for the antibacterial properties of the compounds. However, all the tested compounds exhibited low antifungal activity against *Candida albicans*. The reason for the weaker antifungal activity according to antibacterial effect might be postulated as different action in the mechanism of the compounds such as inhibition effect on respiratory systems of fungus cells, rather than cell wall destrucrion.

Table 1. Antimicrobial Activity of Substituted Cyclopentyl Phenols (MIC) 1-10 in µg/mL.

Phenol No	S. aureus	S. viridans	E. coli	Sh. flexneri	Sal. typhi	Sal. typhimurium	B. proteus vulgaris	Ps. aeruginosa	Bac. antracoides	Bac. subtilis	Kl.rhinos-leuromatis	Candida albicans
1	15,6	7,8	31,25	-	31,25	31,25	62,5	-	-	-	31,25	15,6
2	0,5	1,0	15,6	-	31,25	31,25	31,25	-	-	-	31,25	15,6
3	3,9	1,98	62,5	31,25	31,25	62,5	62,5	62,5	125,0	125,0	62,5	7,8
4	1,0	1,0	7,8	7,8	7,8	7,8	31,25	31,25	15,6	7,8	7,8	1,0
5	62,5	62,5	250,0	62,5	62,5	62,5	62,5	125,0	31,25	62,5	62,5	250,0
6	7,8	15,6	31,25	15,6	15,6	31,25	125,0	125,0	31,25	15,6	7,8	31,25
7	125,0	31,25	250,0	125,0	125,0	125,0	62,5	125,0	62,5	62,5	62,5	125,0
8	1,98	3,9	3,9	7,8	15,6	7,8	31,25	31,25	3,9	-	62,5	15,6
9	1,98	3,9	3,9	7,8	15,6	15,6	62,5	15,6	1,98	-	31,25	7,8
10	3,9	3,9	15,6	7,8	31,25	15,6	62,5	15,6	3,9	-	31,25	15,6
11	15,6	7,8	31,25	31,25	31,25	31,25	31,25	31,25	31,25	62,5	31,25	7,8

4. Conclusions

In summary we have synthesized some substituted cyclopentyl phenols by means of simply methods with using accessible reagents. The purity of the synthesized compounds was examined by GLC and the structures were determined by spectral analyses. The compounds 2, 4, 8, 9 were found to have high activity against *Staphylococcus aureus* and *Streptococcus viridans*. A remarkable activity against all tested bacteria and fungi were found in compounds having substituted cyclopentyl radicals (8-10). Our study also covered the relationship between antimicrobial activity and structure of cyclopentyl phenols.

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