INTRODUCTION

Arene derivatives containing functionally substituted amine fragment in side chain shows the high biological activity. These compounds reveal activity as antiectoparasitic [1], in inactivation of cytochrome P-450 [2-4], pesticide [5], anti-HIV [6], inhibitor of potassium channels [7], having antidepressant activity [8] ligands of calcium receptors [9,10], antihepatit C agent [11], anticancer [12], antihypertensive [13] compounds and at cure of coronary disease [14]. Beside these, this compounds demonstrate high potency for design of new drugs having anti-microbial properties [15-18].

The searching of new antimicrobial agents still remains an important and challenging problem due to rise of mortality and morbidity that caused by different pathogenic bacteria. In addition, the increasing number of multi-drug resistant microbial strain is considered to be one of the major problems in the world nowadays [19]. It is known that 70 % of bacterial infections are resistant to one or more of the antibiotics that generally used to eradicate the infection. Bacteria are able to reduce or eliminate the effectiveness of drugs by different mechanisms such as mutation of their genome, destruction or inactivation and efflux pump system. Therefore, development and synthesis of new effective antimicrobial agents for the treatment of resistant bacterial diseases is an urgent task [20,21].

The design of molecules with antimicrobial properties by means of introduction of amino moiety and methoxy group in the molecule can lead to the purposeful tuning of their chemical properties and hence the biological activity as well. Beside this, aromatic ring is a constituent part of most naturally occurring biologically active compounds and artificially synthesized drugs. The paper reports the synthesis and antimicrobial properties of functionalized substituted amine compounds viz., new derivatives of morpholine and piperidine based on 1-chloro-3-methoxy-propylbenzene.

EXPERIMENTAL

1H, 13C NMR spectra have been taken on the spectrometer Brucker-300 (300 MGz) of system AVANCE, for measure of refract constant used IRF454BM. FTIR spectra were recorded on a Varian 3600 FTIR spectrophotometer. The spectrum was taken in the range of 4000-400 cm⁻¹ at room temperature. The ethylbenzene, morpholine, piperidine reagents were purchased from Sigma Aldrich 99 %, ethanol 95 %, ZnCl₂ 98 % from PEAXIME.

Synthesis of 1-(chloro-3-methoxy-propenyl)benzene: Chlorodimethyl ether (8 g, 0.1 mol) dissolved in 25 g (0.3 mol) of hexane and then 14 g (0.1 mol) of α-chloro-ethyl-benzene added drop-wise to solution. 1 g of ZnCl₂ used as catalyst of reaction. The reaction mixture was stirred for 4 h at 60 °C. At
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the end of reaction the colour of reaction mixture turned black. The hexane was distilled off and residue was dissolved in benzene. Obtained mixture washed with water till neutral reaction achieved several times, then benzene was distilled in vacuo. Yield 75 %; m.p.: 72 °C. 1H NMR (DMSO-d$_6$, δ, m.d.) 2.3 (M, 2H, CH$_2$Cl), 3.25 (C, 3H, OCH$_3$), 3.42 (M, 2H, CH$_2$O), 5.21 (m, 1H, 7.33 (m, 5H, arom.). 13C NMR (DMSO-d$_6$, δ, m.d.) 39.5 (C, CH$_2$), 58.5 (C, OCH$_3$), 60.9 (C, CH), 69.2 (C, CH$_2$O), 127.4 (2C, CH$_{arom}$), 128.7 (2C, CH$_{arom}$), 129.0 (2C, CH$_{arom}$). IR (cm$^{-1}$): 3064-2927 (C-H Ar), 1600-1454 (C-C Ar), 1120-705 (C-H Ar). Anal. Calc. for C$_{15}$H$_{14}$O$_2$: C 75, 205 (methoxy group and amine fragment in side chain we are able to react with 1-chloroethylbenzene, due to the fact that reaction centers are shielded in a great extent in opposite condition. Dimethyl ether leads to obtaining of the product of reaction 1-chloroethylene with chlorodimethyl ether in the presence of zinc chloride catalyst. We studied the molar concentration ratio of reagents on the course of reaction. It was found that carrying out the reaction at 40-60 °C and equimolar amount of zinc chloride and chlorodimethyl ether leads to obtaining of the product of reaction 1-(chloro-3-methoxy-propyl)benzene with 90 % yield. The reaction begins by the attack of zinc chloride on chlorodimethyl ether and then continues as shown in Scheme-I.

For the purposeful synthesis of benzene derivative, that contain methoxy group and amine fragment in side chain we carried out the reaction of halogen ethers of aromatic compounds with morpholine and piperidine. Compounds with amine functional group can be obtained by three main ways: alkylation of amines, hydrogenolysis of amides and reductive amination of carbonyl compounds. It is known that the presence of methoxy group in the molecules allow to obtain the biologically active compounds which being insensitive to esterases are resistant to the hydrolysis that in turn increase their retention time in the cell [24].

The synthesis of 1-(3-methoxy-1-phenylpropyl)piperidine and 1-(3-methoxy-1-phenyl-propyl) morpholine have been taken from initial 1-(chloro-3-methoxy-propenyl)benzene, which was obtained by reaction of 1-chloroethylene with chlorodimethyl ether in the presence of zinc chloride catalyst. We studied the molar concentration ratio of reagents on the course of reaction. It was found that carrying out the reaction at 40-60 °C and equimolar amount of zinc chloride and chlorodimethyl ether leads to obtaining of the product of reaction 1-(chloro-3-methoxy-propyl)benzene with 90 % yield. The reaction begins by the attack of zinc chloride on chlorodimethyl ether and then continues as shown in Scheme-I.

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as nucleophiles in the alkylation of preliminarily synthesized 1-(chloro-3-methoxy-propenyl)benzene. It was also interesting to find out the effectiveness of 1-(chloro-3-methoxy-propyl)benzene in synthesis of (3-methoxy-prop-1-en-1-yl)benzene by dehydrochlorination in the presence of sodium ethylate. This reactions are presented in Scheme-II.

\[
\text{Scheme-II: Reactions of 1-(chloro-3-methoxy-propenyl)benzene}
\]

Physico-chemical data of the synthesized compounds presented in Table-1. Have been reported about the bioconversion of tetrahydropyridines with some strains of the mycelial fungi [25]. Antimicrobial properties of morpholine and piperidine derivatives obtained from the substitution reaction of \(\alpha\)-chloro-ethers of propylbenzene are not reported in literature. For finding out the correlation structure-activity, we introduce the morpholine and piperidine moieties by substitution of the chlorine atom in 1-chloro-(3-methoxy-propyl)benzene. The presence of piperidine and morpholine groups provide effective antimicrobial properties of synthesized compounds.

**Antibacterial studies of the synthesized compounds:**

*In vitro* antibacterial study was carried out for all new synthesized arene derivatives compounds. It revealed that all chemical compounds possessed antibacterial activity against tested Gram-positive and Gram-negative bacteria. All compounds exhibited potential inhibition activity and the clear zones around wells inhibited the bacterial growth were determined as shown in Table-2. The antimicrobial effect of molecules was different not only depending on the species of bacteria but also concentration of tested compounds.

Compound 1 [1-(3-methoxy-1-phenyl-propyl)morpholine] at the concentration of 0.1% showed better result when tested with the *A. baumannii* BDU32 and *P. aeruginosa* BDU49, while at the concentration of 0.05% inhibition zones were similar for all studied pathogens except *K. pneumoniae* BDU44. The bacterial activity results revealed that compound 2 [1-(3-methoxy-1-phenyl-propyl)piperidine] at two concentrations, showed potential activity against all tested pathogenic bacteria except *S. aureus* BDU23. Compare with other two chemicals, compound 2 showed high activity against *P. aeruginosa* BDU49, while any inhibition was not detected against *E. coli* BDU12 when the effect of the compound was tested at concentration of 0.05%.

The high inhibition zones were detected against *E. coli* BDU12 and *A. baumannii* BDU32 at the concentration of 0.1% of compound III (3-methoxy-propenyl)benzene, whereas chemical exhibited the lowest activity when tested with *S. aureus* BDU23 and *P. aeruginosa* BDU49 at the concentration of 0.05%. From the results, it is clear that all the new synthesized compounds have sufficiently activity against all tested Gram-negative bacteria, only Gram-positive bacterium *S. aureus* BDU23 are less sensitive.

**TABLE-1**

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<th>Number</th>
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<th><em>Klebsiella pneumoniae</em></th>
<th><em>Pseudomonas aeruginosa</em></th>
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## Conclusion

We reported synthesis of morpholine and piperidine derivatives of aromatic compounds containing β-methoxy group in side chain with good yield. The structures of the synthesized compounds were identified by NMR and IR spectroscopy methods. It was found that introduction of morpholine and piperidine fragments in the structures of molecules influence on their antimicrobial activities. All compounds exhibited potential inhibition activity against Gram-positive and Gram-negative bacteria.

## References