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Research Article

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITIES OF SOME 2-PYRAZOLINE DERIVATIVES

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ABSTRACT

After years of misuse or overuse of the antibiotics the bacterias and fungi are becoming antibiotic resistant which has resulted in potential global health crisis. The search of new antimicrobial agents has become a challenging task. The presented study reports the antimicrobial activity of twelve 2-pyrazoline derivatives against *S. aureus* and *A. niger*. Two varieties of acetophenones were condensed with three varieties of substituted benzimidazole derivatives to get six chalcone derivatives which undergo condensation followed by cyclisation with isoniazid and 1-(2-napthyloxy acetate) hydrazine two get the final 2-pyrazoline derivatives. The synthesized compounds were characterized by IR, ^{1}H-NMR and Mass spectral studies. The synthesized compounds were found to have good antimicrobial activity in the range of 20-70 µg/ml.

Keywords: 2-Pyrazoline, antibacterial, antifungal, MIC, zone of inhibition.

INTRODUCTION

During the past few decades many infectious diseases have appeared and the old ones which were previously thought to be controlled have reemerged [1]. Antibiotic resistance bacteria and fungi impose a substantial burden on the human population [2]. As antimicrobial drugs lose their potential and effectiveness due to overuse or misuse, new products should be developed to treat and prevent the transmission of the infections. It has become necessary for the development of new broad spectrum antimicrobial agents to keep pace with the continually evolving resistance pathogens. One of the potential approaches to overcome the problem of drug resistance is to design and develop innovative antimicrobial agents with different mode of action so that no cross resistance with available therapeutics can occur [1].

Staphylococcus aureus is the major cause of bacterial infections which involve the lower respiratory tract, bloodstream, soft tissues and skin in developing as well as developed countries including US. Though penicillin was highly effective against it initially, but emergence of penicillanase producing *S.aureus* in mid 1940s and increased prevalence within a few years had dramatically changed the scenario. The infections caused by *S. aureus* clone known as phase type 80/81was pandemic in the 1950s and early 1960s. The infections due to this clone were controlled by the introduction of methicillin. But again the methicillin resistant *S.aureus* (MRSA) was reported within 2 years. Since then MRSA has spread and is endemic in most hospitals worldwide. The emergence of CAMRSA (community associated MRSA) is one of the most surprising infectious disease in recent time [3].

Though considerable progress has been achieved in past few years, the mortality and morbidity due to invasive fungal infections are still high. *A. niger* is a filamentous fungi which has been accounted for lung infections or ear infections inpatients that have weakened immune system or an impared immune system due to diseases. Aspergillosis or aspergillus infections due to *A. niger* has been reported in HIV positive patients [4]. Itraconazole, voriconazole, amphotericin B, echinocandins are the clinically active compounds for invasive aspergillosis. Although Aspergillus species are susceptible to these compounds, intrinsic and acquired resistance has been documented.

Among the five membered heterocyclics containing two hetero atoms in its ring structure, pyrazole is one of the most important one as large variety of biological activities have been reported for various pyrazole derivatives. Pyrazoline is dihydropyrazole, a five membered heterocyclic compound containing two nitrogen atoms in adjacent positions and possessing only one endocyclic double bond. Among all the pyrazolines, 2-pyrazoline has gained attraction and is frequently studied one [5].

2-Pyrazolines are very much promising when the biological activities of pyrazolines are taken into consideration. The literature survey reveals that 2-pyrazoline derivatives are reported to possess wide range biological activities like antimicrobial [6,7,8,9], antimycobacterial [10,11], antiamoebic [12,13], anti-inflammatory [14], analgesic [15], anticonvulsant [16], antidepressant [17], anticancer [18], acyl-CoA inhibitory [19], neuroprotective [20], antiviral [21], amine oxidase inhibitory [22] etc.

As per literature review the pyridine derivatives and naphthalene derivatives are found to possess antimicrobial [23,24,25,26,27,28] activity. Thus, 2-pyrazolines, naphthalene and pyridine possess worthy and imperative antimicrobial activities, which render them useful substances in antimicrobial drug research.

Considering the above mentioned facts twelve 2-pyrazoline derivatives containing pyridine and naphthalene moieties were synthesized and characterized and their antibacterial activity against *S. aureus* and antifungal activity against *A. niger* were evaluated.

MATERIALS AND METHODS

The all reagents used in the present study were of analytical grade. The melting points of the synthesized compounds were determined by open capillary tube method and are uncorrected. The ^{1}H-NMR spectra were recorded at 400 MHz at BRUKER NMR spectrophotometer in DMSO and chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane. The IR spectra were recorded on Shimadzu FTIR 8400S using potassium bromide pellet technique. The completions of the reaction were monitored by Thin Layer Chromatographic technique (TLC) on pre-coated silica gel (HF254-200 mesh) aluminium plates from E-merk using ethyl acetate: n-hexane (4:1) as the mobile phase. Detection of the spots was done under UV chamber.

Synthesis

Scheme 1: Preparation of Chalcones (A_1-A_6) [29]

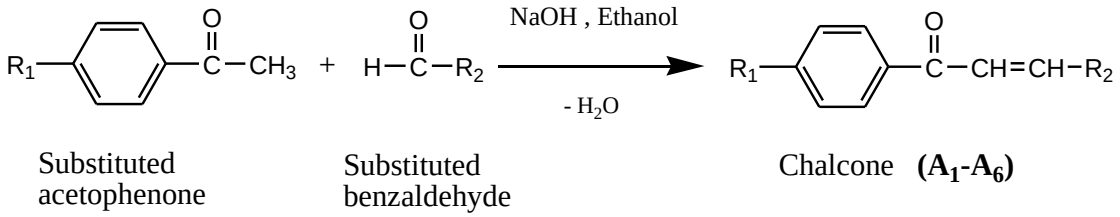
A mixture of acetophenone (0.01mol) and aryl aldehyde (0.01 mol) was stirred in ethanol (30ml) and then an aqueous solution of KOH (40%, 15ml) added to it. The mixture was kept overnight at room temperature and then it was poured into crushed ice and acidified with HCl. The solid separated was filtered and crystallized from ethanol.

Scheme 2: Preparation of 1-(2-napthyloxyacetyl)hydrazine(B)[30]

2-napthol (1.44g, 0.01mol), anhydrous K_2CO_3 and ethyl bromoacetate (1.67g, 0.01mol) in 50 ml anhydrous acetone were

refluxed on an oil bath for 6 hr. After that the reaction mixture was filtered, excess of solvent was removed by distillation under reduced pressure. The residue and 1.00 g hydrazine monohydrate (0.02mol) were dissolved in 50 ml absolute ethanol and refluxed on steam bath for 1 hour. The solid mass obtained was filtered, dried and recrystallised from ethanol.

Scheme 1:



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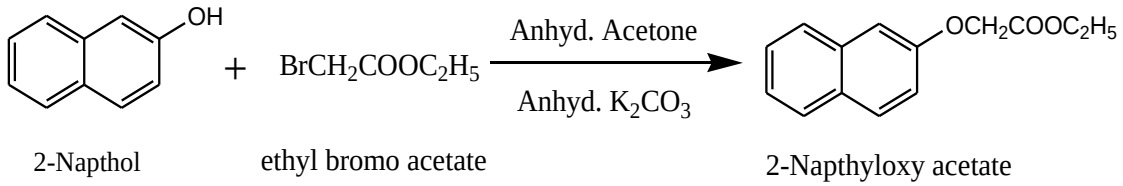
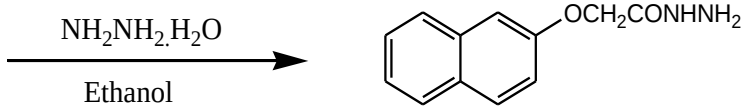
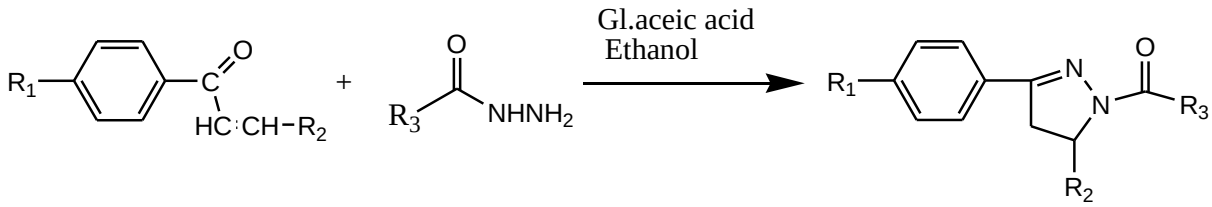
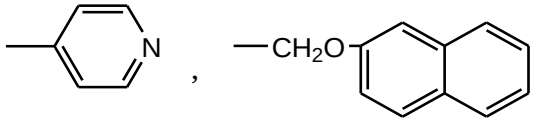




Scheme 3:



R_1 = -Cl , -OH ; R_2 = 4-$NO_2C_6H_5$- , 2-furyl , 2-thienyl

R_3 = 

Scheme 3: Preparation of Pyrazoline derivatives [8,31]

To a solution of compounds A_1-A_6 (0.01mol) in absolute ethanol (30 ml), hydrazine derivatives (0.01mol) and few drops of glacial acetic acid were added. The reaction mixtures were refluxed for 8 hr. The excess of solvent was distilled off and crude products were poured into ice water. The separated solids were filtered and recrystallised from ethanol.

Compound D1: (3-(4-chlorophenyl)-4,5-dihydro-5-(4-nitrophenyl)pyrazol-1-yl) pyridin-4-yl) methanone. Mf- $C_{21}H_{15}ClN_4O_3$, Mp-135^0-137^0 C, R_f- 0.62, yield- 62.15%, I R (KBr) ν_{max} (cm^{-1}) :3087.19 (C-H aromatic str.), 1658.41 (C=O str.), 1616.02 (C=N str. Pyrazoline), 1592.12 (C=C str.), 1528.36 (NO_2 assym. str.), 1345.03 (NO_2 sym. str.), 710.93 (C-Cl str.); ^{1}H NMR (DMSO) δ ppm: 7.57-8.53(m,6H, ArH), 5.19-5.26 (dd,1H,CH Pyrazoline), 3.46-3.52(dd,1H, CH_2 Pyrazoline), 3.05-3.12(dd,1H, CH_2 Pyrazoline)MS(m/e): 406.8 (M$^{+)}$, 408.8(M+2)

Compound D2: (3-(4-hydroxyphenyl)-4,5-dihydro-5-(4-nitrophenyl)pyrazol-1-yl)(pyridin-4-yl) methanone. Mf- $C_{21}H_{16}N_4O_4$, Mp-214-216^{0}C, R_f- 0.45, yield- 54.24%, IR (KBr) ν_{max} (cm^{-1}) :3616.92 (O-H aromatic str.) 3118.89 (C-H aromatic str.), 1645.58 (C=O str.), 1602.41 (C=N str. Pyrazoline), 1593.84 (C=C str.),1526.37 (NO_2 assym. str.), 1345.02 (NO_2 sym.str.); ^{1}H NMR (DMSO) δ ppm: 9.89(s,1H,ArOH), 7.46-8.40(m,6H, ArH), 5.13-5.18(dd,1H,CH Pyrazoline), 3.52-3.58(dd,1H, CH_2 Pyrazoline), 3.10-3.18(dd,1H, CH_2 Pyrazoline); MS(m/e): 388.4(M$^{+)}$

Compound D3: (3-(4-chlorophenyl)-5-(furan-2-yl)-4,5-dihydropyrazol-1-yl)(pyridin-4-yl) methanone, Mf- $C_{19}H_{14}ClN_3O_2$, Mp-102-104^{0}C, R_f- 0.57, yield- 65.5%, IR (KBr) ν_{max} (cm^{-1}) :3141.84 (C-H aromatic str. furan), 3101.30 (C-H aromatic str. substituted benzene), 1651.09 (C=O str.), 1605.93 (C=N str. Pyrazoline), 1587.06 (C=C str.), 702.30 (C-Cl str.); ^{1}H NMR (DMSO) δ ppm: 6.75-8.31(m,6H, ArH), 5.23-5.29(dd,1H,CH Pyrazoline), 3.43-3.49(dd,1H,

CH_2 Pyrazoline), 3.17-3.22(dd,1H, CH_2 Pyrazoline); MS(m/e): 351.8(M^+), 353.8(M+2)

Compound D4: (5-(furan-2-yl)-4,5-dihydro-3-(4-hydroxyphenyl)pyrazol-1-yl)(pyridin-4-yl) methanone. Mf- $C_{19}H_{15}N_3O_3$, Mp-128-130^{0}C, R_f- 0.52, yield- 47.74%, IR (KBr) ν_{max} (cm^{-1}) :3611.37 (O-H aromatic str.), 3141.82 (C-H aromatic str. furan), 3101.65 (C-H aromatic str. substituted benzene), 1659.58 (C=O str.), 1612.05 (C=N str. Pyrazoline), 1594.06 (C=C str.); ^{1}H NMR (DMSO) δ ppm: 9.88(s,1H,ArOH), 6.93-8.30(m,6H, ArH), 5.20-5.25(dd,1H,CH Pyrazoline), 3.49-3.55(dd,1H, CH_2 Pyrazoline), 3.16-3.21(dd,1H, CH_2 Pyrazoline); MS(m/e): 333.3(M^+)

Compound D5: (3-(4-chlorophenyl)-4,5-dihydro-5-(thiophen-2-yl)pyrazol-1-yl)(pyridin-4-yl) methanone. Mf- $C_{19}H_{14}ClN_3OS$, Mp-124-126^{0}C, R_f- 0.60, yield- 57.85%, IR (KBr) ν_{max} (cm^{-1}) :3128.91 (C-H aromatic str. thiophene), 3091.68(C-H aromatic str. substituted benzene), 1657.70 (C=O str.), 1610.17 (C=N str. Pyrazoline), 1599.12 (C=C str.), 705.03 (C-Cl str.); ^{1}H NMR (DMSO) δ ppm: 6.94-8.38(m,6H, ArH), 5.42-5.47(dd,1H,CH Pyrazoline), 3.33-3.39(dd,1H, CH_2 Pyrazoline), 3.09-3.16(dd,1H, CH_2 Pyrazoline); MS(m/e): 367.8(M^+), 369.8(M+2)

Compound D6: (4,5-dihydro-3-(4-hydroxyphenyl)-5-(thiophen-2-yl)pyrazol-1-yl)(pyridin4-yl)methanone. Mf- $C_{19}H_{15}N_3O_2S$, Mp-163-165^{0}C, R_f- 0.48, yield- 66.33; IR (KBr) ν_{max} (cm^{-1}) :3621.43 (O-H aromatic str.), 3127.14 (C-H aromatic str. thiophene), 3089.12 (C-H aromatic str. substituted benzene), 1640.57 (C=O str.), 1604.57 (C=N str. Pyrazoline), 1600.47 (C=C str.)^{1}H NMR (DMSO) δ ppm: 9.98(s,1H,ArOH), 7.12-8.28(m,6H,ArH), 5.38-5.43(dd,1H,CHPyrazoline), 3.58-3.63(dd,1H, CH_2 Pyrazoline), 3.17-3.22(dd,1H,CH_2 Pyrazoline); MS(m/e): 349.4(M^+)

Compound D7: 1-(3-(4-chlorophenyl)-4,5-dihydro-5-(4-nitrophenyl)pyrazol-1-yl)-2-(naphthae n-2-yloxy)ethanone. Mf- $C_{27}H_{20}ClN_3O_4$, Mp-140-142^{0}C, R_f- 0.90, yield- 48.80%, IR (KBr) ν_{max} (cm^{-1}) : 3109.57 (C-H aromatic str.), 3026.16 (C-H aliphatic str.) 1650.93 (C=O str.), 1616.19 (C=N str. Pyrazoline), 1592.30 (C=C str.), 1528.36 (NO_2 assym. str.), 1345.31 (NO_2 sym. str.), 710.93 (C-Cl str.); ^{1}H NMR (DMSO) δ ppm: 6.82-8.42(m,10H, ArH), 5.30-5.35(dd,1H,CH Pyrazoline), 4.76 (s,2H, $COCH_2$), 3.33-3.38(1H, CH_2 Pyrazoline), 3.13-.19(dd,1H, CH_2 Pyrazoline); MS(m/e): 485.9(M^+), 487.9(M+2)

Compound D8: 1-(4,5-dihydro-3-(4-hydroxyphenyl)-5-(4-nitrophenyl) pyrazol-1-yl)-2-(naphtha len -2-yloxy)ethanone . Mf- $C_{27}H_{21}N_3O_5$, Mp-191-192^{0}C, R_f- 0.87, yield- 54.42%, IR(KBr) ν_{max}(cm^{-1}) : 3604.52 (O-H phenolic str.), 3112.09 (C-H aromatic str.), 3026.86 (C-H aliphatic str.) 1654.28 (C=O str.), 1610.26 (C=N str. Pyrazoline), 1597.41 (C=C str.), 1528.36 (NO_2 assym. str.), 1345.19 (NO_2 sym. Str); ^{1}H NMR (DMSO) δ ppm: 9.75(s,1H,ArOH), 6.87-8.30(m,10H, ArH), 5.29-5.34(dd,1H,CH Pyrazoline), 4.82 (s,2H, $COCH_2$), 3.38-3.44(dd,1H, CH_2 Pyrazoline), 3.10-3.15(dd,1H, CH_2 Pyrazoline); MS(m/e): 467.4(M^+)

Compound D9: 1-(3-(4-chlorophenyl)- 4,5-dihydro-5-(furan-2-yl)-pyrazol-1-yl)-2-(naphthalen-2-yloxy)ethanone. Mf- $C_{25}H_{19}ClN_2O_3$,Mp-118-120^{0}C, R_f- 0. 0.72, yield- 45.55%, IR (KBr) ν_{max}(cm^{-1}) : 3158.12 (C-H aromatic str. furan), 3091.30 (C-H aromatic str. Substituted benzene), 3012.34 (C-H aliphatic str.) 1652.79 (C=O str.), 1605.93 (C=N str. Pyrazoline), 1591.31 (C=C str.) ^{1}H NMR (DMSO) δ ppm: 6.87-8.08(m,10H, ArH), 5.39-5.45(dd,1H,CH Pyrazoline), 4.78 (s,2H, $COCH_2$), 3.38-3.44(dd,1H, CH_2 Pyrazoline), 3.05-5.10(dd,1H, CH_2 Pyrazoline); MS(m/e): 430.8(M^+), 432.8(M+2)

Compound D10: 1-(3-(4-hydroxyphenyl)-4,5-dihydro-5-(furan-2-yl)pyrazol-1-yl)-2-(naphthale n-2-yloxy)ethanone. Mf- $C_{25}H_{20}N_2O_4$, Mp-132-134^{0}C, R_f- 0.79, yield- 57.72%, IR(KBr) ν_{max}(cm^{-1}) : 3615.93 (O-H aromatic str.), 3158.65 (C-H aromatic str. furan), 3084.14 (C-H aromatic str. Substituted benzene), 3012.61 (C-H aliphatic str.) 1652.84 (C=O str.), 1604.11 (C=N str. Pyrazoline), 1598.52 (C=C str.) ^{1}H NMR (DMSO) δ ppm: 9.68(s,1H,ArOH), 6.88-8.04(m,10H, ArH), 5.35-5.40(dd,1H,CH Pyrazoline), 4.78 (s,2H, $COCH_2$), 3.38-3.44(dd,1H, CH_2 Pyrazoline), 3.04-3.10(dd,1H, CH_2 Pyrazoline); MS(m/e): 412.4(M^+)

Compound D11: 1-(3-(4-chlorophenyl)-4,5-dihydro-5-(thiophen-2-yl)pyrazol-1-yl)-2-(naphtha en- 2-yloxy)ethanone. Mf- $C_{25}H_{19}ClN_2O_2S$, Mp-144-146^{0}C, R_f- 0.83, yield- 60.28%, IR (KBr) ν_{max} (cm^{-1}): 3154.46 (C-H aromatic str. thiophene), 3135.83 (C-H aromatic str. Substituted benzene), 3009.30 (C-H aliphatic str.) 1657.70 (C=O str.), 1614.95 (C=N str. Pyrazoline), 1589.32 (C=C str.); ^{1}H NMR (DMSO) δ ppm: 6.90-8.05(m,10H, ArH), 5.35-5.41(dd,1H,CH Pyrazoline), 4.77 (s,2H, $COCH_2$), 3.31-3.38(dd,1H, CH_2 Pyrazoline), 3.04-3.10(dd,1H, CH_2 Pyrazoline); MS(m/e): 446.9(M^+), 448.9(M+2)

Compund D12: 1-(3-(4-hydroxyphenyl)-4,5-dihydro-5-(thiophen-2-yl)pyrazol-1-yl)-2-(naphtha en- 2-yloxy)ethanone. Mf- $C_{25}H_{20}N_2O_3S$, Mp-171-173^{0}C, R_f- 0.8, yield- 46.60%, IR (KBr) ν_{max} (cm^{-1}):3087.19 (C-H aromatic str.), 1658.41 (C=O str.), 1616.02 (C=N str. Pyrazoline), 1592.12 (C=C str.), 1528.36 (NO_2 assym. str.), 1345.03 (NO_2 sym. str.), 710.93 (C-Cl str.); ^{1}H NMR (DMSO) δ ppm: 9.75(s,1H,ArOH), 6.87-8.05(m,10H,ArH), 5.37-5.42(dd,1H,CH Pyrazoline), 4.79 (s,2H, $COCH_2$), 3.38-3.42(dd,1H, CH_2 Pyrazoline), 3.07-3.12(dd,1H, CH_2 Pyrazoline); MS(m/e): 428.5(M^+)

Determination of zone of inhibition

Nutrient agar medium was used as the culture medium. Composition includes peptone (5gm), beef extract (3gm), Agar (15gm), Sodium chloride (5gm), Yeast extract (1.5gm). Ph was maintained to7.0. All ingredients were added to the distilled water and were boiled to dissolve them completely. Sterilization of the medium was done by autoclaving at 15 lbs pressure and the temperature was maintained at 121^{0}C for 15 minutes. The test and standard drug solutions were prepared by dissolving the compounds in Dimethyl sulphoxide (DMSO). The stock solutions of the synthesized compounds were prepared at the concentration of 2000 µg/mL in DMSO while the solutions of the standard drugs were prepared at the concentration of 100 µg/mL in DMSO. DMSO was used as the control.

In this study the *in-vitro* antibacterial and antifungal activities of the twelve synthesized 2-pyrazoline derivatives were evaluated with the aid of paper disc agar diffusion method. Effectiveness of the test compounds were compared with the standard compound for antimicrobial activity. Inoculation of the sterilized agar medium (autoclaved at 121°C for 15 min) was done with requisite quantity of suspension of the micro-organism (10^5 cfu mL^{-1}) at a temperature between 40^0-50°C and was immediately poured into the petridishes to obtain a depth of 3 to 4 mm. The dishes were specially selected with flat bottoms and were placed on a level surface so that uniform thickness was ensured. The petridishes were sterilized at 160–170^{o}C for 1 hr, before use. The Whatman filter paper (No.2) was cut down into small discs of 6mm in diameter and sterilized at 180^{o}C for 30 min in hot air oven. Then they were impregnated with the test (50,100 and 200 µg mL^{-1} in dimethyl formamide) and standard drugs (100 µg mL^{-1}) separately. All petridishes were incubated at the required temperatures (37^{o}C for bacteria and 25^{o}C for fungi) for 24 hr. After incubation period was over, the diameters of the circular inhibition zones formed were measured.

Determination of Minimum inhibitory concentration (MIC)

Determination of MIC was carried out by Agar streak dilution method. MIC of the synthesized 2-pyrazoline derivatives compounds were determined by Agar streak dilution method. Dimethyl sulphoxide was used to prepare stock solution of test compounds and the standard drugs (1mg/ml). From the stock solution, required quantities of the solutions of the drugs were taken and mixed with the known quantities of molten sterile media in aseptic manner to obtain the following concentrations 100, 90, 80, 75, 70, 65, 60, 55,50, 45, 40, 35, 30, 25, 20, 15,12.5, 10µg/ml.

About 20 ml of the media containing the drug was dispensed to the sterile petridishes and the media were allowed to get solidified. Microorganisms were then streaked one by one on the agar plates in aseptic manner. After the streaking is over all the plates were incubated at 37+1^0 C for 24 hr/48 hr for bacterial and fungal activity respectively. The plates were observed for the growth of the microorganisms. The lowest concentrations that inhibit the growth

of the bacteria and fungus were considered as the MIC for the test compounds against the bacteria and fungus respectively.

Compounds	Zone of inhibition (mm)					
	Bacteria *S. aureus*			Fungi *A. niger*		
	Dose µg/mL					
	50	100	200	50	100	200
D1	12	17	23	11	15	17
D2	10	14	20	9	16	18
D3	11	15	19	8	15	19
D4	9	13	16	-	10	15
D5	-	8	14	-	11	14
D6	8	11	18	9	14	16
D7	12	17	25	10	17	20
D8	11	15	23	11	15	18
D9	9	18	20	8	11	15
D10	10	14	19	-	10	13
D11	-	9	17	10	14	20
D12	9	14	18	11	18	22
Ciprofloxacin		37			-	
Ketaconazole		-			35	

Compounds	Minimum inhibitory concentration (µg /ml)	
	Bacteria *S. aureus*	Fungi *A. niger*
D1	25	20
D2	35	30
D3	20	40
D4	30	70
D5	60	60
D6	45	40
D7	20	35
D8	25	30
D9	30	45
D10	35	60
D11	60	25
D12	50	20
Ciprofloxacin	12.5	-
Ketaconazole	-	10

RESULTS

When compared to the standard drugs (Ciprofloxacin for anti-bacterial and Ketaconazole for anti-fungal activity), the compounds D7,D8,D9,D1,D2 were found to exhibit good anti-bacterial activity and compounds D12,D11,D7,D3 were exhibit good anti-fungal activity at the concentration of 200 µg/ml. Compound D7 exhibited highest antibacterial activity, compound D12 exhibited highest anti-fungal activity as well as comparable to the antibacterial activity and antifungal activity of the standard drugs at 200 µg/ml. The compounds D5 and D11 exhibited no antibacterial activity while compounds D4, D5 and D10 exhibited no antifungal activity against the tested microorganisms at low concentrations (50 µg/ml).

The synthesized compounds were found to have MIC values against *S. epidermidis* and *A. niger* in the range of 20-70 µg/ml. The compounds D7 and D3 were found to have lowest MIC values against *S. epidermidis* (MIC: 20µg/ml). The compounds D12 and D1 exhibited were found to have MIC values against *A. niger* (MIC: 20 µg/ml).

Thus from the antimicrobial activity studies it can be concluded that among the synthesized derivatives compound D7 is the most effective agent against *S. epidermidis* exhibiting zone of inhibition 25 mm at 200 µg/ml and MIC of 20 µg/ml, while compound D12 is the most effective agent against *A. niger* exhibiting zone of inhibition 22 mm µg/ml and MIC of 20 µg/ml

DISCUSSION

The electron withdrawing effect of both –Cl and $-NO_2$ might have resulted in enhancement of antibacterial activity. Moreover when bulkiness of the substituent is considered, presence of bulky group p-nitrophenyl at 5th position of the 2-pyrazoline nucleus along with the presence of napthyloxyacetate/pyridinyl group at 1st position have found to have more antibacterial activity than the presence of less bulky heterocyclic furyl or thiophenyl group at 5th position. While the presence of heterocyclic moiety (furyl) at 5th position and napthyloxyacetate group at 1st position have resulted in better antifungal activity than the presence of electron withdrawing groups.

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