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Research Article

SYNTHESIS OF PYRAZOLINE DERIVATIVES AND EVALUATION OF ITS ANTIMICROBIAL ACTIVITY

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ABSTRACT

The present paper represents the synthesis of pyrazoline compounds. Compounds are synthesized from substituted aniline. Substituted aniline on diazotization gives Ethyl-2-(substituted phenyl hydrazono)-3-oxobutyrates (1a-j). Ethyl-2-(substituted phenyl hydrazono)-3-oxobutyrates (1a-j) reacts with 8-Quinolinoxyacetic acid hydrazide (3) and gives compounds 1-(8'-Quinolinoxyacetyl)-3-methyl-4-substituted phenyl hyazdrzono-2-pyrazolin-5-one (4a-j). Further all derivatives are evaluated for their vitro antimicrobial activity. The antimicrobial activity based on MIC (minimum inhibitory concentration) of tested compounds. The results revealed that most of the newly synthesized pyrazoline derivatives bearing quinoline moiety (4a-j) exhibited promising anti-bacterial activity. Out of the compound tested, compound 4i and 4j having 2 & 4 methyl groups in the phenyl ring exhibited remarkable antibacterial activity (MIC 25 μgmL^{-1}) against *E. coli* (gram negative bacteria) whereas compound 4a having COOH group at 4th position of the phenyl ring showed similar antibacterial potency (MIC 25 μgmL^{-1}) against *S. aureus* (gram positive bacteria) as compared with the broad spectrum antibiotics ofloxacin (MIC 10.0 μgmL^{-1} against *S. aureus* and 12.5 μgmL^{-1} against *E. coli*). The antifungal screening results have shown that the compound 4d and 4g having 4-methoxy and 4-chloro respectively groups in the phenyl ring exhibited good activity (MIC 50 μgmL^{-1}) against *A. niger*, as compared with standard drug ketoconazole (MIC 12.5 μgmL^{-1}).

Keywords: Anti-microbial activity, Ketoconazole, Phenyl hydrazono , Pyrazoline, Minimum inhibitory concentration.

INTRODUCTION

Now a days with ever emergence of bacteria, there is need to develop antimicrobial drugs posing a challenge for the treatment of infections. The treatment of pain continues to be the subject of considerable pharmaceutical and clinical research. Microbial infections often produce pain and inflammation. So there is need to search less toxic drugs than those based on natural sources resulted in the introduction of synthetic substances as drugs in the late 19th century and their widespread use in the 21th century. Initially this development was centered on the natural products isolated from plant and animal materials but as knowledge increased, a wide range of synthetic compounds were evolved as drugs. The pharmacologically active compounds from which these synthetic analogues are developed are now known as lead compound. Once a lead compound has been discovered, extensive and costly efforts are made to prepare a series of analogues in the hope that even better activity can be found. Drug design is an attempt to discover substances effective in a given pathological condition with as favorable a therapeutic index as possible. In other words 'Drug Design' is a process that starts with the identification of a disease and therapeutic target of interest and includes methodology, assay development, leads identification and characterization, animal pharmacological studies, pharmacokinetic and safety studies in animal models.

Resistant bacteria represent a challenge in the treatment of infections, which are well known, necessitated the need to find new chemotherapeutic, analgesic and anti-inflammatory drugs are prescribed simultaneously in normal practice. The compound possessing all three activities is not common. It has been reported that pyrazoline possess analgesic and anti-inflammatory[1], antimicrobial[2], anti-cancer[3], anti-tumor[4], anti-depressant and anti-convulsant[5], antioxidant[6], anti-bacterial[7], anti-HIV[8], insecticides[9], anti-amoebic activities[10], cytotoxic activities[11] and anti-fungal activities[12]. Shamsuzzaman, Alam, Mohd Gulfam synthesized new steriodal pyrazoline[13]. All these make the pyrazoline as heterocyclic lead. So considerable attention has been focused on Pyrazolines and

substituted Pyrazolines due to their interesting biological activities. The purpose of this study was to develop new pyrazoline derivatives as potent anti-microbial agents.

MATERIALS AND METHODS

Experimental

General procedure: Reaction was conducted in oven dried glass wear. Analytical thin layer chromatography (TLC) was performed on per coated silica gel 60 F_{254} plates and column chromatography was accomplished using silica gel, 60 Å (200-400 mesh) and basic alumina. Elemental analyses were recorded using Heraeus Vario EL 111 analyzer and the results were within 0.3% of the theoretical values. Electronic spectra were recorded in methanol on a Shimadzu UV-1601 PC UV Visible spectrophotometer. IR spectra on KBr disks were recorded on a Perkin-Elmer model 1620 FT-IR spectrophotometer. ^{1}H NMR spectra were taken in $CDCl_3$ at ambient temperature using Bruker spectrospin DPX-300 MHZ spectrophotometer with TMS as internal standard. Splitting pattern is designed as follows: s. singlet, d. doublet, t. triplet, m. multiplet. Chemical shift values are given in ppm. The reaction sequences are outlined in scheme-1.

Synthesis of Ethyl-2-(substituted phenyl hydrazono)-3-oxobutyrates (1a-j): To substituted anilines dissolved in a mixture of concentrated hydrochloric acid (15 ml) and water (15 ml), cooled to 0 - 5ºC in an ice bath was added a cold, saturated solution of sodium nitrite (0.15 mole) with stirring. The diazonium salt thus formed was filtered into a cooled solution of ethylacetoacetate (0.1 mole) in ethanol (50 ml) and sodium acetate (2.0 mole) in water (175 ml). The solid was filtered and washed with water and recrystallized from methanol.

Purity of the compound was checked by TLC on silica gel G plates using toluene: ethylacetate: formic acid (5:4:1) as solvent system and the spot was located by exposure to iodine vapours.

IR (KBr): 3418-3386 (N-H), 2993-2982 (C-H), 1705-1686 (C=O), 1583-1571 (C=C).

^{1}HNMR ($CDCl_3$): 1b; 1.20-1.25 (t, 3H, CH_2CH_3), 2.39 (s, 3H, $COCH_3$), 4.22-4.29 (q, 2H, CH_2CH_3), 7.00-7.99 (m, 4H, ArH), 8.28 (s, 1H, NH), 15.25 (s, 1H, COOH).

1d; 1.41-1.43 (t, 3H, CH_2CH_3), 2.60 (s, 3H, $COCH_3$), 3.95 (s, 3H, OCH_3), 4.38-4.41 (q, 2H, CH_2CH_3), 6.92-7.27 (m, 4H, ArH), 11.88 (s, 1H, NH). 1f; 1.25-1.27 (t, 3H, CH_2CH_3), 2.46 (s, 3H, $COCH_3$), 4.25-4.30 (q, 2H, CH_2CH_3), 7.12-7.78 (m, 4H, ArH), 11.75 (s, 1H, NH).

1g; 1.24-1.26 (t, 3H, CH_2CH_3), 2.35 (s, 3H, $COCH_3$), 4.27-4.29 (q, 2H, CH_2CH_3), 7.39-7.40 (m, 4H, ArH), 11.62 (s, 1H, NH). 1h; 1.36-1.41 (t, 3H, CH_2CH_3), 2.53 (s, 3H, $COCH_3$), 4.26-4.35 (q, 2H, CH_2CH_3), 7.19-7.35 (m, 4H, ArH), 11.60 (s, 1H, NH). 1j; 1.31-1.35 (t, 3H, CH_2CH_3), 2.50 (s, 3H, CH_3-ArH), 2.70 (s, 3H, $COCH_3$), 4.20-4.26 (q, 2H, CH_2CH_3), 7.10-7.90 (m, 5H, 4 ArH and 1NH).

Synthesis of 8-Quinolinoxyacetic acid hydrazide (3): In a round bottom flask, a mixture of Ethyl-8-quinolinoxy acetate (2) (0.01 mole), hydrazine hydrate (0.20 mole) and absolute ethanol (50 ml) was added. A condenser with calcium chloride guard tube was attached to the flask and mixture was refluxed for 30 hours on water bath. The mixture was concentrated, cooled and poured in crushed ice. It was kept for 4-5 hours at room temperature and solid mass separated out was filtered, dried and recrystallized from ethanol.

Purity of the compound (3) was checked by TLC on silica gel G plates using methanol: acetone (1:1) as solvent system and the spot was located by exposure to iodine vapours. Physical data of the compound (3) : Yield: 84 %, m.p. 136 ˚C, R_f: 0.57, Molecular formula: $C_{11}H_{11}N_3O_2$, Molecular weight: 217.23. %N: Found: 19.03%; Calcd: 19.34 %.

IR (KBr): 3225 (N-H), 2980 (C-H), 1689 (C=O), 1578 (C=C).

^{1}HNMR ($CDCl_3$): 4.90 (s, 2H, OCH_2), 7.15-8.23 (m, 8H, 6-ArH & 2-NH_2), 8.95 (bs, 1H, NH).

Synthesis of 1-(8′-Quinolinoxyacetyl)-3-methyl-4-substituted phenyl hydrazono-2-pyrazolin-5-one (4a-j): In a 100 ml round bottom flask, a mixture of (1a-j) (0.005 mole) and 3 (0.005 mole) in glacial acetic acid (25 ml) was refluxed for 8-12 hours. The mixture was concentrated, cooled and poured into crushed ice. The solid mass separated out was filtered, dried and recrystallized from methanol. Purity of the compounds (1a-j) was checked by TLC on silica gel G plates using toluene: ethylacetate: formic acid (5:4:1) as solvent system and the spot was located by exposure to iodine vapours.

Physical and Spectral Data of Compounds

1-(8′-Quinolinoxyacetyl)-3-methyl-4-(4″-carboxyphenyl hydrazono)-2-pyrazolin-5-one (4a): Yield 81 %, m.p. 298 ˚C, R_f: 0.62, Molecular formula: $C_{22}H_{17}N_5O_5$, Molecular weight: 431.41. %N: Found: 15.96%; Calcd: 16.23 %.

IR (KBr): 3499(COOH), 2977(C-H), 1690(C=O), 1667(C=N), 1584(C=C).

^{1}HNMR (DMSO-d_6): 2.16 (s, 3H, CH_3), 3.34 (s, 2H, OCH_2), 7.30-8.26 (m, 10H, ArH), 11.52 (s, 1H, NH), 12.40 (s, 1H, COOH).

1-(8′-Quinolinoxyacetyl)-3-methyl-4-(2″-carboxyphenyl hydrazono)-2-pyrazolin-5-one (4b): Yield 68 %, m.p. 286˚C, R_f: 0.63, Molecular formula: $C_{22}H_{17}N_5O_5$, Molecular weight: 431.41, %N Found 16.17%; Calcd: 16.23 %.

IR (KBr): 3502 (COOH), 3004 (C-H), 1690 (C=O), 1664 (C=N), 1580 (C=C).

1-(8′-Quinolinoxyacetyl)-3-methyl-4-(2″-hydroxyphenyl hydrazono)-2-pyrazolin-5-one (4c): Yield: 55 %, m.p. 252 ˚C, R_f: 0.63, Molecular formula: $C_{21}H_{17}N_5O_4$, Molecular weight: 403.40. %N: Found: 17.43%; Calcd: 17.36 %.

IR (KBr): 3542 (-OH), 3000 (C-H), 1691 (C=O), 1660 (C=N), 1599 (C=C).

1-(8′-Quinolinoxyacetyl)-3-methyl-4-(4″-methoxyphenyl hydrazono)-2-pyrazolin-5-one (4d): Yield: 62 %, m.p. 200 ˚C, R_f: 0.60, Molecular formula: $C_{22}H_{19}N_5O_4$, Molecular weight: 417.42. %N: Found: 16.54%; Calcd: 16.78 %.

IR (KBr): 2974 (C-H), 1689 (C=O), 1657 (C=N), 1568 (C=C).

^{1}HNMR ($CDCl_3$): 2.27 (s, 3H, CH_3), 3.50 (s, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 6.95-7.39 (m, 10H, ArH), 8.53 (s, 1H, NH).

Mass (m/z): 417 (M^+), 232, 186, 125, 97.

1-(8′-Quinolinoxyacetyl)-3-methyl-4-(4″-bromophenyl hydrazono)-2-pyrazolin-5-one (4e): Yield: 58 %, m.p. 218 ˚C, R_f: 0.81, Molecular formula: $C_{21}H_{16}N_5O_3Br$, Molecular weight: 466.29, %N: Found: 15.41%; Calcd: 15.02 %.

IR (KBr): 3012 (C-H), 1682 (C=O), 1669 (C=N), 1571(C=C), 591(C-Br).
^{1}HNMR ($CDCl_3$): 2.24 (s, 3H, CH_3), 3.47 (s, 2H, OCH_2), 7.24-7.52 (m, 10H, ArH), 8.54 (s, 1H, NH).
Mass (m/z): 466 (M^+), 281, 186, 125, 97.

1-(8′-Quinolinoxyacetyl)-3-methyl-4-(4″-fluorophenyl hydrazono)-2-pyrazolin-5-one (4f)
Yield: 70 %, m.p. 196˚C, R_f: 0.82, Molecular formula: $C_{21}H_{16}N_5O_3F$, Molecular weight: 405.39. %N: Found: 17.38%; Calcd: 17.28%.
IR (KBr): 2969 (C-H), 1686 (C=O), 1668 (C=N), 1574 (C=C), 1065(C-F).

1-(8′-Quinolinoxyacetyl)-3-methyl-4-(4″-chlorophenyl hydrazono)-2-pyrazolin-5-one (4g):
Yield: 73 %, m.p. 216 ˚C, R_f: 0.82, Molecular formula: $C_{21}H_{16}N_5O_3Cl$, Molecular weight: 421.48. %N: Found: 16.84; Calcd: 16.60%.IR (KBr): 3012 (C-H), 1690 (C=O), 1661 (C=N), 1595 (C=C), 776 (C-Cl).
^{1}HNMR ($CDCl_3$): 2.46 (s, 3H, CH_3), 3.79 (s, 2H, OCH_2), 7.44-7.69 (m, 10H, ArH), 8.87 (s, 1H, NH).

1-(8′-Quinolinoxyacetyl)-3-methyl-4-(2″-chlorophenyl hydrazono)-2-pyrazolin-5-one (4h): Yield: 66%, m.p. 214 ˚C, R_f: 0.80, Molecular formula: $C_{21}H_{16}N_5O_3Cl$, Molecular weight: 421.48. %N: Found: 16.42; Calcd: 16.60%.
IR (KBr): 2996 (C-H), 1688 (C=O), 1665 (C=N), 1580 (C=C), 756 (C-Cl).

1-(8′-Quinolinoxyacetyl)-3-methyl-4-(4″-methylphenyl hydrazono)-2-pyrazolin-5-one (4i): Yield: 74%, m.p. 190 ˚C, R_f: 0.77, Molecular formula: $C_{22}H_{19}N_5O_3$, Molecular weight: 401.42. %N: Found: 17.33%; Calcd: 17.45%.
IR (KBr): 2974 (C-H), 1698 (C=O), 1667 (C=N), 1584 (C=C).

1-(8′-Quinolinoxyacetyl)-3-methyl-4-(2″-methylphenyl hydrazono)-2-pyrazolin-5-one (4j): Yield: 68%, m.p. 220 ˚C, R_f: 0.70, Molecular formula: $C_{22}H_{19}N_5O_3$, Molecular weight: 401.42. %N: Found: 17.28%; Calcd: 17.45%.
IR (KBr): 3008 (C-H), 1691 (C=O), 1673 (C=N), 1575 (C=C).
^{1}HNMR ($CDCl_3$): 2.32 (s, 3H, CH_3), 2.50 (s, 3H, CH_3-Ar), 3.76 (s, 2H, OCH_2), 7.03-7.37 (m, 10H, ArH), 8.39 (s, 1H, NH).

BIOLOGICAL ACTIVITY

Compounds (4a-j) have been evaluated for their *in-vitro* anti-microbial activity against *Staphylococcus aureus* (*S. aureus*, ATCC-29737), as an example of gram positive bacteria, *Escherchia coli* (*E. coli*, ATCC-8739) as an example of gram negative bacteria and *Aspergilus niger* (*A. niger*) as a representative of fungi. The microdilution susceptibility test in nutrient agar media (Hi-Media), Sabroaud's dextrose agar media were used for determination of antibacterial and antifungal activities respectively. The minimal inhibitory concentration (MICs, μgmL^{-1}) of the tested compounds were recorded.

The results revealed that most of the newly synthesized pyrazoline derivatives bearing quinoline moiety (4a-j) exhibited promising anti-bacterial activity. Out of the compound tested, compound 4i and 4j having 2 & 4 methyl groups in the phenyl ring exhibited remarkable antibacterial activity (MIC 25 μgmL^{-1}) against *E. coli* (gram negative bacteria) whereas compound 4a having COOH group at 4th position of the phenyl ring showed the similar antibacterial potency (MIC 25 μgmL^{-1}) against *S. aureus* (gram positive bacteria) as compared with the broad spectrum antibiotics ofloxacin (MIC 10.0 μgmL^{-1} against *S. aureus* and 12.5 μgmL^{-1} against *E. coli*).

The antifungal screening results in table-1 have shown that the compound 4d and 4g having 4-methoxy and 4-chloro respectively groups in the phenyl ring exhibited good activity (MIC 50 μgmL^{-1}) against *A.niger* as compared with the standard drug ketoconazole (MIC 12.5 μgmL^{-1}).

RESULT AND DISCUSSION

Ethyl-2-(substituted phenylhydrazono)-3-oxobutyrate(1a-j): The purity of the compounds (1a-j) was checked by TLC and its characterization on the basis of IR and NMR spectral data.

The IR spectrum of the compounds (1a-j) showed peaks at 3418-3386 cm^{-1}, NH stretching; 2993-2982 cm^{-1}, CH stretching; 1705-1686 cm^{-1}, C=O stretching and 1583-1571 cm^{-1}, C=C stretching vibrations of aromatic rings.

The NMR spectrum of the compounds 1b, 1d, 1g, 1j showed a triplet respectively at δ 1.20-1.25,1.41-1.43, δ 1.24-1.26, δ 1.31-1.35. A quartet respectively at δ 4.22-4.29, δ 4.38-4.41, δ 4.27-4.29, δ 4.20-4.26 for CH_3 and OCH_2 protons of ethoxy group**.** A singlet respectively at δ 2.39, δ 2.60, δ 2.35, δ 2.70 for $COCH_3$ proton. 1b, 1g showed a singlet respectively at δ 2.39, δ 2.35 was observed indicating the presence of $COCH_3$ protons. 1b showed a signal of NH proton was observed as a singlet at δ 8.28 whereas, the singlet of COOH proton observed down field at δ 15.25.1d showed a singlet at δ 3.95 for OCH_3 protons.

1 g showed a singlet at δ 2.50 for CH_3 protons attached to the phenyl ring. A multiplate respectively at δ 7.00-7.99, δ 6.92-7.27, δ 7.39-7.40 four protons in the aromatic region was observed indicating the presence of phenyl protons, (1j) showed a multiplet of five protons at δ 7.10-7.90 indicating the presence of four phenyl protons and one NH proton.

8-Quinolinoxyacetic acid hydrazide (3): The IR spectrum of the compound showed peaks at 3225 cm^{-1}, NH stretching; 2980 cm^{-1}, CH stretching; 1689 cm^{-1}, C=O stretching and 1578 cm^{-1}, C=C stretching vibrations of aromatic ring.

The structure of the compound was further supported by its NMR spectrum which showed a singlet at δ 4.90 OCH_2 protons. In the aromatic region a multiplet of eight protons at δ 7.15-6.23 was observed indicating the presence of six aromatic and two NH_2 protons. The broad singlet of CONH proton was observed at δ 8.95.

1-(8-Quinolinoxyacetyl)-3-methyl-4-substituted phenyl hydrazono-2-pyrazoline-5-ones (4a-j): The IR spectrum of the compounds (4a-j) showed peaks at 3012-2969 cm^{-1}, CH stretching; 1691-1682 cm^{-1}, C=O stretching of pyrazoline ring; 1673-1657 cm^{-1}, C=N stretching and 1599-1568 cm^{-1}, C=C stretching vibrations of aromatic rings.The NMR spectrum of the compounds 4a, 4d, 4e, 4g, 4j showed a singlet respectively at δ 2.16, δ 2.27, δ 2.24, δ 2.46, δ 2.32 indicating the presence of methyl protons. Singlet respectively at δ 3.34, δ 3.50, δ 3.47, δ 3.79, δ 3.76 of OCH_2 protons attached to the quinoline

ring. Singlet respectively at δ 11.52, δ 8.53, δ 8.54, δ 8.87, δ 8.39 indicating the presence of NH proton.

Compounds (4a) showed a singlet at δ 12.40 of COOH proton and (4d) showed a singlet at δ 3.85 of methoxy protons attached to the phenyl ring. Multiplet respectively at δ 7.30-8.26, δ 6.95-7.39, δ 7.24-7.52, δ 7.44-7.69, δ 7.03-7.37 indicating the presence of 10 aromatic protons.

Mass spectral of (4d) showed molecular ion peak M^+ at m/z 417, corresponding with the molecular formula $C_{22}H_{19}N_5O_4$. Further peaks were obtained at m/z 232, 186, 125 and 97.

Mass spectral of (4e) showed molecular ion peak M^+ at m/z 466, corresponding with the molecular formula $C_{21}H_{16}N_5O_3Br$. Further peaks were obtained at m/z 281, 186, 125 and 97.

CONCLUSION

In this paper, we disclose the synthesis of 1-(8'-Quinolinoxyacetyl)-3-methyl-4-substituted phenyl hyazdrzono-2-pyrazolin-5-one (4a-j) and evaluated for in-vitro antimicrobial activity against *E. coli* and *S. aureus* and compared with ofloxacin and standard drug ketoconazole. Compound 4i and 4j having 2 & 4 methyl groups in the phenyl ring exhibited remarkable antibacterial activity having MIC 25 μgmL^{-1} against *E. coli*. as compared with the broad spectrum antibiotics ofloxacin having MIC 10.0 μgmL^{-1} against *S. aureus* and 12.5 μgmL^{-1} against *E. coli*. Compound 4d and 4g having 4-methoxy and 4-chloro respectively groups in the phenyl ring exhibited good antifungal activity having MIC 50 μgmL^{-1} against *A. niger* as compared with standard drug ketoconazole with MIC 12.5 μgmL^{-1}.

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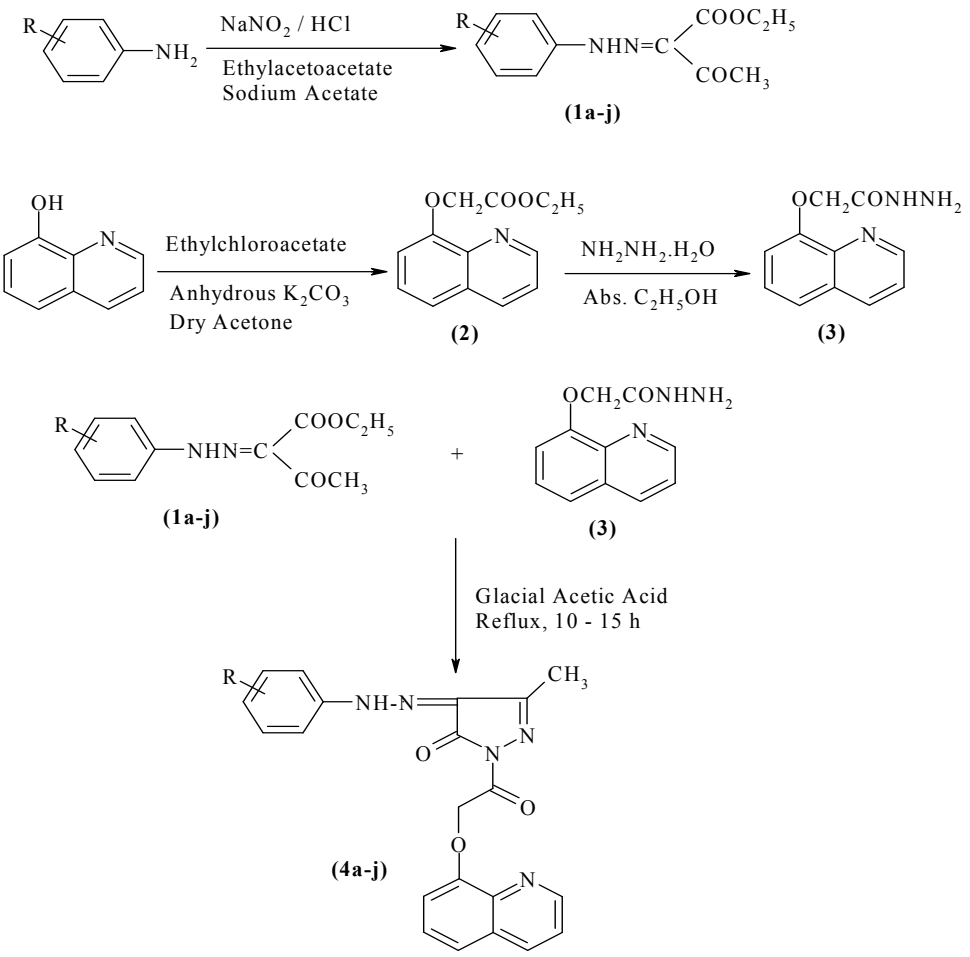
Table 1: Antimicrobial Activities of Quinolinoxyacetyl Pyrazoline Derivatives

Compound No.	MIC (µg/ml)		
	S. aureus	***E. coli***	***A. niger***
Ofloxacin	10.0	12.5	-
Ketoconazole	-	-	12.5
4a	25	100	100
4b	100	200	100
4c	100	200	200
4d	50	100	50
4e	100	100	100
4f	50	100	100
4g	100	200	50
4h	50	50	100
4i	200	25	100
4j	200	25	100



R = 4a: 4-COOH, 4b: 2-COOH, 4c: 2-OH, 4d: 4-OCH_3, 4e: 4-Br, 4f: 4-F, 4g: 4-Cl, 4h: 2-Cl, 4i: 4-CH_3, 4j: 2-CH_3

Scheme - 1

Source of support: Nil, Conflict of interest: None Declared