Original Article

Synthesis, Characterization and Antibacterial Evaluation of Some Azole Derivatives

Manju Rani[1], Shivani Sharma[2], Rajani Chauhan[2], Swapnil Sharma[2*], and Jaya Dwivedi[1]

[1]Department of Chemistry, Banasthali University, Banasthali Rajasthan, INDIA.
[2]Department of Pharmacy, Banasthali University, Banasthali Rajasthan, INDIA.

ABSTRACT

Purpose: Tremendous rise in development of resistance to the antimicrobials has created alarming situation for researchers and clinicians. **Method:** In this regard, an attempt has been made to develop a series of azole derivatives using Claisen-Schmidt condensation and Micheal addition. All the newly synthesized compounds were authenticated by IR, ^{1}H NMR, ^{13}C NMR and MS spectral analysis. Synthesized compounds 5 (a-e) and 6 (a-e) were screened for their antibacterial activity against three Gram positive bacteria (*S. aureus*, *B. subtilis* and *B. cereus*), two Gram negative bacteria (*E. coli* and *P. fluorescens*) using serial dilution broth method. **Results:** Amongst all, Compound 5-(4-Chlorophenyl)-4-(3, 5-dimethyl-1H-pyrazol-1-yl)-3-phenylisoxazole (5 b) showed significant antibacterial activity against B. subtilis and B. cereus (IC_{50}; 2.6 and 1.2 μg/mL) which was comparable to standard ampicillin (2.5 and 3.1 μg/mL). **Conclusion:** Azole derivatives were prepared using Claisen-Schmidt condensation and Micheal addition exhibits good antibacterial activity and can be further explored to confirm their suitability at clinical level.

Key words: Pyrazole, Synthesis, Claisen-Schmidt condensation, Micheal addition, Antibacterial.

INTRODUCTION

Pyrazole and isoxazole derivatives have received substantial attention in the last two decades as versatile bioactive molecules. Literature is replete with the examples of pyrazole derivatives exhibiting a wide array of pharmacological properties including anticonvulsant,[1] anti-inflammatory,[2] analgesic,[3] antipyretic,[4] antiparasitic,[5] antimalarial,[6] anti-histaminic,[7] antidepressant,[8] antimicrobial,[9] antifungal,[10] enzyme inhibition,[11] and anti-cancer.[12-13] Isoxazole ring system occupies prime position in the design and synthesis of novel therapeutic agents. In addition to this, they are known to possess antiepileptic,[14] anticancer,[15] antimicrobial,[16-17] immunomodulatory,[18] antinociceptive,[19] anti-inflammatory,[20] antiplatelet,[21] antiulcer[22] activities and even more.

During the last decade, most bacterial pathogens have exhibited antimicrobial resistance, and considerable effort has been directed at developing new agents to replace those whose usefulness has been eroded by resistance. Antibacterial and antifungal activities of the azoles are most widely studied and some of them are in clinical practice as antimicrobial agents. In particular, pyrazole derivatives are extensively studied and used as antimicrobial agents.[23] However, the emergence of azalea resistant strains led to the development of new antimicrobial compounds. There are numerous example of hybrid molecules with dual bioactivities that have been incorporated into a single chemical entity.[24] It is with this idea in mind the present study was launched to develop many analogues on the premise to include hybrid features of pyrazole and chalcones having more impressive antibacterial activities.

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Correspondence:
Swapnil Sharma,
Department of Pharmacy,
Banasthali University,
Banasthali,
Rajasthan- 304022, INDIA.
Tel.: 01438228728
E-mail: skspharmacology@gmail.com

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MATERIALS AND METHODS

Experimental

The entire chemicals were purchased from Sigma Aldrich Chemical Company (USA) and solvents were used after purification by distillation. All melting points were measured with a capillary apparatus and are uncorrected. All the compounds were routinely checked by IR, ^{1}H NMR and mass spectrometer. ^{1}H NMR spectra were recorded on a Bruker AVANCE II 400 MHz. ^{13}C NMR spectra were recorded at 100 MHz. The chemical shift were recorded in parts per million (ppm) with TMS as internal reference. IR spectra were recorded in KBr on an Agilent tech, Cary 660 FTIR spectrophotometer. ^{1}H NMR spectra were recorded at ambient temperature using a Brucker spectroscope in $CDCl_3$. The following abbreviations were used to indicate the peak multiplicity s–singlet, d–doublet, t–triplet, m–multiplet. Mass spectra were recorded on waters, QT-OF micromass (LCMS) mass spectrometer using Argon/Xenon (6 kV, 10 mB) gas. Column chromatography was performed on silica gel (Merck). Anhydrous sodium sulfate was used as a drying agent for the organic phase.

Preparation of 2-(3, 5-dimethyl-1H-pyrazol-1-yl)-1-phenylethanone (3)

A mixture of 3,5-dimethyl-1H-pyrazole **(1)** (1.92 g, 0.02 mol)**,** 2-bromacetophenone **(2)** (4.26 g, 0.02 mol), and potassium carbonate (2.76 g, 0.02 mol) dissolved in acetonitrile (25 mL) stirred and refluxed at 85 ºC for 5 h. Completion of the reaction was checked by TLC. After completion the reaction, the target compound was obtained by pouring the reaction mixture into ice-cold water. The mixture was filtered and washed with water to obtain compound **(3)** and purified by column chromatography using hexane: Ethyl acetate (8:2) as solvent. Finally, white brown solid were obtained.

Yield 73 %; mp 76-78 °C; IR (KBr) cm-1: 3058 (C-H str Ar), 1691 (C=O), 2934 (Ar-CH_3), 1578 (C=N); ^{1}H NMR, (δ/ppm in $CDCl_3$): 7.51 (t, JH, H = 6.56 Hz, 2 H, Ph), 7.62 (t, JH,H = 6.12 Hz, 1 H, Ph), 7.99 (d, JH,H = 7.2 Hz, 2 H, Ph), 5.45 (s, 1 H, vinylic), 5.91 (s, H, pyrazole -C4), 2.23 (s, 3H,CH_3), 2.16 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 192.75 (1C,C=O), 148.36 (1C, C-3), 140.60 (1C, C-5), 134.58 (1C, C-10), 134.02 (1C, C-13), 128.95 (2 × 1C, C-11,C-15), 128.12 (2 ×1C, C-12,C-14), 105.88 (1C, C-4), 55.27 (1C, C-8), 13.53 (1C, C-6), 11.04 (1C, C-7); MS *m/z*: 216[M$^+$]; Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.76; H, 6.60; N, 13.15.

(Z)-3-(4-bromophenyl)-2-(3, 5-dimethyl-1H-pyrazol-1-yl)-1-phenylprop-2-en-1-one 4 (a)

A mixture of 2-(3,5-dimethyl-1H-pyrazol-1-yl)-1-phenylethanone **(3)** (1.07 g, 0.005 mol) and 4-substituted benzaldehyde (0.005 mol) dissolved in N,N Dimethylformamide (DMF) refluxed at 155 ºC for 10 h in presence of strong base like sodium hydride. Completion of the reaction was checked by TLC, after completion, reaction mixture was poured into ice-cold water. The crude pale yellow color, amorphous solid was filtered off (1.54 g, yield: 81%). Finally, product **(4a)** was recrystallized from ethanol. Similarly, compounds **4 (b-e)** of this series were synthesized.

Yield 81%; mp 155-156°C; IR (KBr) cm^{-1}: 3090(C-H str Ar), 2973(Ar-CH_3), 1679 (C=O),1586 (C=C), 570(C-Br); ^{1}H NMR (δ/ppm in $CDCl_3$): 8.12 -7.76 (m, 5H, ArH), 7.61 (d, 2H, Ar, *J* = 8.7), 7.55 (d, 2H, Ar, *J* = 8.9) 5.99 (s, 1 H, vinylic), 5.34 (s, 1H, pyrazole), 2.53(s, 3H, CH_3), 2.43 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 183.93 (C=O),148.8 (C-5, C-3),136.0 (C-10), 135.59 (C-13), 133.14 (C-17, C-20), 131.48 (C-11, C-15), 130.83 (C-8), 129.02 (C-12,C-14), 128.53 (C-19), 128.28 (C-18), 120.04 (C-16),106.23 (C-4), 13.50 (C-6), 10.87 (C-7) ; MS *m/z*: 381 [M$^+$],383 [M$^+$+2](1:1), 263;Anal. Calcd. for $C_{20}H_{17}BrN_2O$: C, 71.32; H, 5.09; N, 8.32 Found: C, 71.26;H, 5.12; N, 8.38.

5-(4-bromo-phenyl)-4-(3, 5-dimethyl-1H-pyrazol-1-yl)-3-phenylisoxazole 5(a)

The mixture of hydroxylamine hydrochloride 2.76 g (0.04 mol), sodium methoxide 0.54 g (0.01 mol) in absolute methanol (30 mL) was stirred for 10 minutes. (Z)-3-(4-substituted phenyl)-2-(3, 5-dimethyl-1H-pyrazol-1-yl)-1-phenylprop-2-en-1-one **4 (a)** (1.52 g, 0.004 mol) was added and the mixture was refluxed at 65 ºC for 5 h. Reaction was monitored by TLC. After completion, most of the methanol was evaporated under reduced pressure and the mixture was poured into ice-cold water. The solid separated was filtered, washed with diethyl ether and dried. Recrystallization from ethanol gave the solid product. Similarly, compounds **5 (b-e)** of this series were synthesized.

Yield 68%; mp 140-142°C; IR (KBr) cm^{-1}: 3059 (C-H str Ar), 2922 (Ar-CH_3), 1671 (C=N-O), 531 (C-Br); ^{1}H NMR, (δ/ppm in $CDCl_3$): 8.12 -7.73 (m, 5H, ArH), 7.58 (d, 2H, Ar, *J* = 8.2), 7.45 (d, 2H, Ar, *J* = 8.1), 5.47 (s, 1H, pyrazole-C-20), 2.21 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.64 (1C, C-5), 153.53 (1C, CH_3-3), 147.51 (2 × 1C, C-19, C-21), 137.29 (1C, C-12), 135.32 (1C, C-6), 132.36 (2 ×1C, C-8, C-10),

129.59 (2 ×1C, C-7, C-11), 128.72 (2 × 1C, C-14, C-16), 127.01 (2 × 1C, C-13, C-17), 123.19 (1C, C-9), 105.99 (1C, C-20), 100.55 (1C, C-4), 13.31 (1C, C-24), 10.32 (1C, C-23); MS *m/z*: 394 [M^+], 396 [M^++2] (1:1); Anal. Calcd. for $C_{20}H_{18}BrN_3O$: C, 60.93; H, 4.09; N, 10.66. Found: C, 60.85; H, 4.11; N, 10.66.

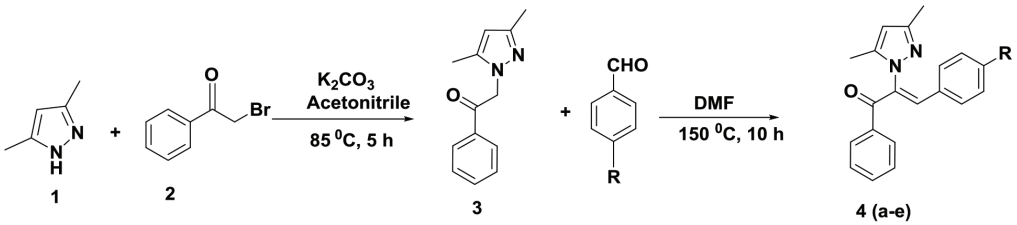
1-(5-(4-bromophenyl)-3-phenyl-1H-pyrazol-4-yl)-3, 5-dimethyl-1H-pyrazole 6(a)

A solution of compound (Z)-3-(4-substituted phenyl)-2-(3,5-dimethyl-1H-pyrazol-1-yl)-1-phenylprop-2-en-1-one **4 (a)** (1.52 g, 0.004 mol), Hydrazine hydrate (5.0 mL, 0.1 mol), sodium ethoxide in (25–30 mL) ethanol was stirred and refluxed at 79°C for 5 h. Reaction was monitored by TLC. After completion, the solvent was removed under reduced pressure and the residue was dissolved in 10mL of chloroform and dried over anhydrous sodium sulphate and filtered. After evaporation of solvent, creamy white solid was obtained **6(a)**. Similarly, compounds **6 (b-e)** of this series were synthesized.

Yield 69%; mp 110-112°C; IR (KBr) cm^{-1}: 3432 (N-H str), 3025 (C-H str Ar), 2930 (Ar-CH_3), 1587 (C=N), 547 (C-Br); ^{1}H NMR, (δ/ppm in $CDCl_3$): 8.59 (s, 1H, N-H), 8.17 -7.78 (m, 5H, ArH), 7.64 (d, 2H, Ar, *J* = 8.5), 7.43 (d, 2H, Ar, *J* = 8.4), 5.84 (s, 1H, pyrazole-C-20), 2.27 (s, 3H, CH_3), 2.19 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.49 (2 ×1C, C-3, C-5), 148.29 (2 × 1C, C-19, C-21), 132.21 (1C, C-12), 131.43 (2 ×1C, C-8, C-10), 129.58 (1C, C-6), 129.36 (2 ×1C, C-7, C-11), 129.11 (2 × 1C, C-14, C-16), 128.88 (1C, C-15), 127.62 (2 × 1C, C-13, C-17), 120.11 (1C, C-9), 106.49 (1C, C-20), 103.35 (1C, C-4), 13.15 (1C, C-24), 11.20 (1C, C-23); MS *m/z*: 393 [M^+], 395 [M^++2] (1:1); Anal. Calcd. for $C_{20}H_{19}BrN_4$: C, 61.08; H, 4.36; N, 14.25. Found: C, 61.15; H, 4.39; N, 14.31.

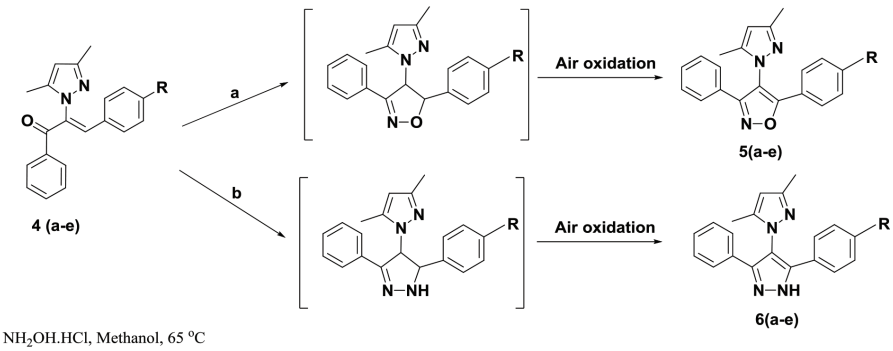
Antibacterial activity

Some novel pyrazolo derivatives 5a, 5b, 5c, 5d, 5e, 6a, 6b, 6c, 6d and 6e were screened for *in- vitro* antibacterial property against both Gram positive and Gram negative bacteria, namely *Bacillus subtilis* (MTCC-7419), *Bacillus cereus* (MTCC-1306), *Staphylococcus aureus* (MTCC-9886) and *Escherichia coli* (MTCC -119), *Pseudomonas flourocence* (MTCC-669) bacterial strains using micro dilution broth method, further, their IC_{50} were also estimated. The bacterial strains were procured from Department of Bioscience and Biotechnology, Banasthali University, Banasthali. Broth was used as blank and control was containing broth and bacterial strain (2µl). Ampicillin was used as standard drug. The various concentrations of 5a, 5b, 5c, 5d, 5e, 6a, 6b, 6c, 6d and 6e were prepared and nutrient broth and bacterial strains were added. All the tubes were then incubated at 37±1°C for 20-24 h. After incubation, OD (optical density) of each culture



R = Br (a), Cl (b), NO_2 (c), OMe (d), Me (e)

Scheme 1: Synthesis of chalcone derivatives.



a = $NH_2OH.HCl$, Methanol, 65 °C
b = $NH_2NH_2.H_2O$, Ethanol,79 °C
R= Br (a), Cl (b), NO_2 (c), OMe (d), Me (e)

Scheme 2: Synthesis of azole derivatives.

tube was measured at 630 nm and compared with standard ampicillin.[25]

RESULT AND DISCUSSION

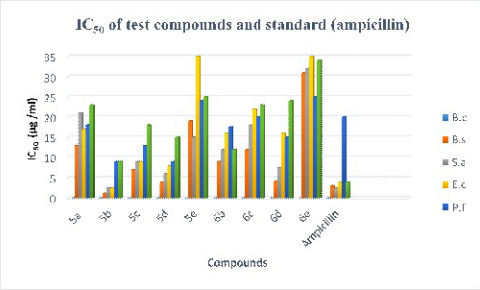
Chemistry

As a part of our endeavor to create novel heterocyclic scaffold of anticipated biological activity from easily accessible starting material here in this paper we report, the preliminary result of our studies on the synthesis of some azole derivatives (**Scheme 1 and 2**). Synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and MS spectral data which were found consistent to the assigned structure.

In the first step 3, 5 dimethylpyrazole was allowed to react with phenacyl bromide to yield 2-(3, 5-dimethyl-1H-pyrazol-1-yl)-1-phenylethanone (3).[26] Its formation was ascertained by IR absorption band at 1691 cm^{-1} assignable to >C=O stretching, a band at 1578 cm^{-1} due to C=N stretching and by disappearance of -NH peak at 3500-3400 cm^{-1}. ^{1}H NMR of the compound (**3)** exhibited sharp upfield singlet at δ 2.23 and δ 2.16 to the six proton of two -CH_3 group attached to pyrazole ring and a upfield singlet which appeared at δ 5.45 due to two proton of CH_2 (methylene group) attached to pyrazole ring. ^{13}C NMR spectrum of compound (**3)** showed three characteristic signals of pyrazole ring at δ 148.29, 105.91, and 140.73 due to C-3, C-4, and C-5 respectively.

The synthesis of pyrazole substituted chalcones **(4)** was achieved via Claisen-Schmidt condensation[27] of 2-(3, 5-dimethyl-1H-pyrazol-1-yl)-1-phenylethanone **(3)** with the corresponding 4 substituted benzaldehyde. Dimethyl formamide (DMF) was used as the solvent as it provides a better medium for reaction and sodium hydride (NaH) used as the strong base. The IR spectrum of compound revealed the presence of new absorption band at 1586 cm^{-1} (C=C stretching) due to C=C of α, β conjugated ketone group which was further confirmed by the presence of a singlet at δ 5.94 of one proton of –C=CH (vinylic) in ^{1}H NMR spectrum of compound **(4).**

Chalcones are versatile reagents that readily undergo Michael addition reaction with bidentate nucleophiles such as hydrazine hydrate and hydroxylamine hydrochloride to yield pyrazole and isoxazole derivatives respectively. Exploring this synthetic strategy the isoxazole derivatives **5 (a-e)** and pyrazole derivatives **6 (a-e)** were prepared. The IR spectrum of compounds displayed at 1671 cm^{-1} due to C=N-O of isoxazole ring **5 (a-e),** a peak at 3432 cm^{-1} due to N-H stretching of pyrazole **6 (a-e)** and the disappearance of peak at 1691 cm^{-1} >C=O of α, β unsaturated ketone at and 1586 cm^{-1} (C=C stretching) clearly indicated the formation of isoxazole ring and pyrazole ring. The presence of singlet at δ 8.69 for proton assignable to -NH of pyrazole ring and disappearance of singlet peak of -C=CH (ethylene) in ^{1}H NMR spectrum of **5 (a-e)** and **6 (a-e**) further corroborated the formation of isoxazole ring and pyrazole ring.



E.c.- E. coli, B.c.- B.cereus, B.s. - B. Subtilis, S.a- S.aurues, P.f – P. flourocenece

Figure 1: IC50 of test compounds and standard (ampicillin)

Antibacterial activity

The synthesized derivatives **5** (**a-e**) and **6** (**a-e**) were screened for their antibacterial activities using microdilution method. The IC_{50} values of all tested compound against five bacterial strain, three gram positive *B. subtilis, B. cereus, S. aureus* and two are gram negative, *E. coli, P. flourocence,* are presented in Figure 1. The investigation of antibacterial screening revealed that all the tested compounds except **(5e and 6e)** showed moderate to good bacterial inhibition for gram positive and gram negative bacteria (except *P. flourocenece*). Compound 6 (**a**) was found to be inactive against every strain and hence its data has been excluded from the results of antibacterial studies. Compound 5b was found to be most active with IC_{50} values 1.2µg /mL (*B.c*), 2.6 µg /mL (*B.s*), 2.5 µg /mL (*S.a*), 9 µg /mL (*E.c*) and 9 µg /mL (*P.f*) which was even better to standard ampiciliin which showed with IC_{50} values3.1 µg /mL (*B.c*), 2.5µg /mL (*B.s*), 3.9µg /mL (*S.a*), 20µg /mL (*E.c*) and 4µg /mL (*P.f*) respectively. IC_{50} values of these compound advocated two important certitudes, first the compounds are comparatively more efficacious towards gram positive bacterial strains and secondly that the isoxazole derivatives **5 (b-d)** are found to be more effective than bispyrazole derivatives **6 (b-d).** SAR of the structures of the screened compounds perceived that electron donor group (chloro/methoxy) containing derivatives **5 (b & d) and 6 (b & d)** are more active amongst all, meticulously, the chloro compounds are even better to that of methoxy derivatives against each strain that may be attributed to higher lipophilicity of chlorophenyl groups.

CONCLUSION

In conclusion, this study highlights some synthesized compounds which are worthy of further investigation for their antibacterial activity against gram positive bacteria.

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CONFLICT OF INTEREST

Author declare no conflict of interest.

ABBREVIATIONS USED

SAR: Structure activity relationship; **IC_{50}**: Inhibitory concentration 50, **S.a:** Staphylococcus aureus; **B.s:** Bacillus subtilis and B.c Bacillus cereus; **E.c:** Escherichia coli; **P.f.:** Pseudomonas fluorescensce; **s:** singlet; **d:** doublet; **t:** triplet; **m:** multiplet; **TLC:** thin layer chromatography.

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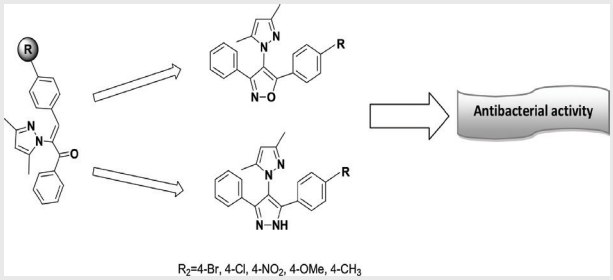
PICTORIAL ABSTRACT



SUMMARY

Emergence of azalea resistant strains led to the development of new antimicrobial compounds. In view of this, a novel series of azole derivatives have been synthesized using Claisen-Schmidt condensation and Micheal addition. Newly synthesized compounds have been characterized by IR, 1H NMR, and 13C NMR and MS spectral analysis. Synthesized compounds 5 (a-e) and 6 (a-e) have been screened for their antibacterial activity against using serial dilution broth method.

About Authors

Dr. Swapnil Sharma: He is Associate Professor (Pharmacology) at Department of Pharmacy, Banasthali University, Banasthali, Rajasthan (India). His research area includes drug development from natural and synthetic sources.

Dr. Jaya Dwivedi: She is Professor & Head at Department of Chemistry, Banasthali University, Banasthali, Rajasthan (India). Her area of research includes synthetic organic chemistry and natural product.

Dr. Rajani Chauhan: She is Associate Professor (Pharmaceutical Chemistry) at Department of Pharmacy, Banasthali University, Banasthali, Rajasthan (India). Her area of research includes synthetic organic chemistry and natural product.

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