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Research Article

Synthesis and Antimicrobial Evaluation of 1-(4-Aryl-2-Thiazolyl)-3-(Substituted)-5-Phenyl-2-Pyrazoline Derivatives

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Abstract

Pyrazolines are well known and important five membered heterocyclic compounds and demonstrating a wide range of pharmacological activities. In the current work, 1-(4-aryl-2-thiazolyl)-3-(substituted)-5-phenyl-2-pyrazoline derivatives were synthesized and evaluated for their antimicrobial activity. The final compounds were synthesized by reacting 3-(substituted)-5-aryl-1-thiocarbamoyl-2-pyrazolines with phenacyl bromide in ethanol. The structures of the synthesized compounds were confirmed by IR and 1H NMR spectral data. These compounds were screened for their antibacterial activity against *Staphylococcus aureus* (MTCC 87), *Bacillus subtilis* (MTCC 121), *Pseudomonas aeruginosa* (MTCC 424), *Escherichia coli* (MTCC 40) using Cup and plate agar diffusion method. Preliminary results reveal that the compound 6b exhibited antimicrobial activity against all tested strains but displayed better activity against *E. coli* with zone of inhibition of 17 ± 2 mm. Compound 6e displayed more activity against *P. aeruginosa* (18 ± 2 mm) than standard drug (10 ± 4 mm).

Keywords: *Pyrazoline; Thiazole; Agar Diffusion Method; Antibacterial Activity; Antifungal Activity*

Abbreviations

DMSO: Dimethylsulfoxide; 1H NMR: Proton Nuclear Magnetic Resonance; IR: Infra-red; MTCC: Microbial Type Culture Collection; SDA: Sabouraud Dextrose Agar; TLC: Thin Layer Chromatography; TMS: Tetramethylsilane

Introduction

Despite significant progress made in the treatment of infectious diseases, caused by bacteria and fungi, it remains a major worldwide health problem due to rapid development of resistance against the existing antimicrobial drugs [1]. There is already evidence that antibacterial resistance is associated with an increase in mortality [2]. A potential approach to overcome the problem of antibiotic resistance is to design innovative agents with different modes of action so that no cross resistance with present drugs can occur [3]. So, there is a clear need for new antimicrobial agents with new mechanisms of action or broad-spectrum activity, to face the issues of drug-resistant microorganisms.

Compounds containing five membered heterocyclic ring systems like pyrazolines and thiazoles continue to attract considerable interest due to the wide range of biological activities they possess [4,5]. Pyrazoline shows an integral architectural concept in heterocyclic chemistry. It represents a common motif in many pharmaceutical active compounds and demonstrating a wide range of activities such as antimicrobial [6-8], analgesic and anti-inflammatory [9,10], antidepressant [11], antiviral [12], anti-amoebic [13], antimalarial [14], monoamine oxidase inhibitor [15], anticonvulsant [16], anti-tubercular [17], antifungal [18], antioxidant [19].

Thiazoles are important class of potent biologically active molecules and an interesting building block in variety of natural products. Numerous studies demonstrated that, some thiazole derivatives are used as analgesics, anti-inflammatory [20,21], anticancer [22], anti-HIV [23], antimicrobial [24], antimycobacterial [25] antioxidant [26], antiallergic agents [27], anticonvulsants [28], antifungal [29] and antiprotozoal agents [30].

In view of the above mentioned knowledge of different hetrocyclics and in continuation of our research, we have synthesized a series of pyrazoline derivatives bearing thiazole. Compounds were subjected to evaluation of their antimicrobial potency against Gram positive bacteria *Staphylococcus aureus* (MTCC 87), *Bacillus subtilis* (MTCC 121), two Gram negative bacteria *Pseudomonas aeruginosa* (MTCC 424), *Escherichia coli* (MTCC 40) and *fungal strains Candida albicans* (MTCC 183), *Fusarium solani* (MTCC 2935) and *Fusarium oxysporum* (MTCC 284).

Materials and Methods

The commercial chemicals employed in the synthetic work were purchased from Sigma-Aldrich, Loba chemie, Spectrochem, Merck India and S.D. fine-chemical Ltd. The solvents employed were also of LR grade and obtained from Loba chemie, Spectrochem and S.D. fine-chemical Ltd. Precoated E Merck silica gel $60F_{254}$ plates with 0.2 mm layer thickness were used for thin layer chromatography. Various solvent system used for developing the chromatogram were Benzene: petroleum ether: methanol (9:0.9:0.1), chloroform: methanol (7:3). The identification of spots was done with UV light and iodine vapours. Melting points were determined by capillary method using

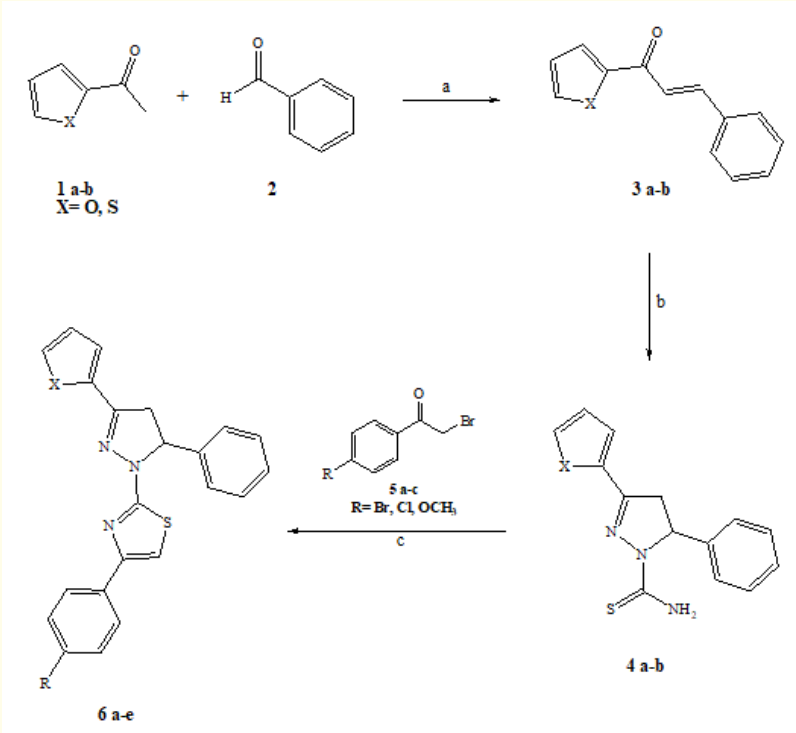

Figure 1: *: Scheme 1. The synthetic route for the preparation of pyrazoline derivatives (6 a-e).*

Reagents and conditions: (a) 10% aqueous sodium hydroxide solution, ethanol, stirring, 6h.

(b) thiosemicarbazide, NaOH, ethanol, reflux, 24h. (c) substituted phenacylbromide, ethanol, reflux, 12h.

melting point apparatus (Perfit India) and are uncorrected. The identification and characterization of the compounds were carried out by determining melting point, IR, ^{1}H NMR and TLC. All the infra-red (IR) spectra were recorded by KBr pellet technique using solid pellet method on Perkin-Elmer IR spectrometer (4000-400 cm^{-1}) ^{1}H NMR spectra were recorded on Bruker Model Advance 11 400 spectrometer. Chemical shifts were recorded in parts per million using tetramethylsilane (TMS) as standard.

Synthesis of 1-(substituted)-3-aryl-2-propan-1-ones (3 a-b)

A mixture of 2-acetylthiphene or 2-acetylfuran (0.04 mol) (1 a-b), benzaldehyde (0.04 mol) (2) and 10% aqueous sodium hydroxide (10 ml) in ethanol (30 ml) was stirred at low temperature for 5-6 hours. The resulting solid was filtered, washed, dried and recrystallized from ethanol [2].

Synthesis of 3-(substituted)-5-aryl-1-thiocarbamoyl-2-pyrazoline (4 a-b)

A mixture of sodium hydroxide (1g, 0.025 mol) was dissolved in ethanol (50 ml) and the solution was added to the chalcone (3a-b) to form a suspension. Thiosemicarbazide (0.012 mol) was added to the above mixture and refluxed for 24 hours, the solution was then poured onto crushed ice and the solid separated was filtered, dried and crystallized from ethanol to get the compound (4a-b).

General procedure for the synthesis of compounds (6a-e)

Phenacyl bromide derivatives (0.01 mol) (5 a-c) were added to the suspension of substituted pyrazoline (0.01 mol) (4a-b) in ethanol (15 ml). The mixture was then heated to reflux for 12 hours. After cooling the precipitates formed were collected by suction filtration. The product was dried and crystallized from appropriate solvent.

4-(4-bromophenyl)-2-(3-(furan-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl) thiazole (6a)

Yield: 65%; melting point: 350 - 360°C; IR (KBr, cm^{-1}): 1666 (C=N), 3103 (CH-Ar), 1031 (C-O), 708 (C-Br); ^{1}H NMR ($CDCL_3$, 400 MHz, δ ppm): 3.90, 3.65 (d, 2H, CH_2), 5.20 (t, 1H, CH), 7.28 (s, 1H, S-CH), 6.52 (t, 1H, CH), 7.20 - 7.79 (m, 9H, Ar-H), 6.93 (d, 1H, CH), 7.75 (d, 1H, CH).

4-(3-(furan-2-yl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-4-(4-methoxy phenyl) thiazole (6b)

Yield: 48%; melting point: 270 - 280°C; IR (KBr, cm^{-1}): 1646 (C=N), 3076 (CH-Ar), 1052 (C-O), 2930 (C-H); ^{1}H NMR ($CDCL_3$, 400 MHz, δ ppm): 3.96, 3.50 (d, 2H, CH_2), 5.19 (t, 1H, CH), 7.32 (s, 1H, S-CH), 6.72 (t, 1H, CH), 7.20-7.75 (m, 9H, Ar-H), 6.85 (d, 1H, CH), 7.85 (d, 1H, CH), 3.83 (s, 3H, O-CH_3).

4-(4-methoxyphenyl)-2-(5-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole (6c)

Yield: 65%; melting point: 280 - 290°C; IR (KBr, cm^{-1}); 1654 (C=N), 3082 (CH-Ar), 675 (C-S-C), 2942 (C-H); ^{1}H NMR ($CDCL_3$, 400 MHz, δ ppm): 3.88, 3.45 (d, 2H, CH_2), 5.25 (t, 1H, CH), 7.20 (s, 1H, S-CH), 7.17-7.69 (d, 6H, CH), 7.05 - 7.40 (m, 9H, Ar-H), 3.79 (s, 3H, O-CH_3).

4-(4-chlorophenyl)-2-(5-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole (6d)

Yield: 66%; melting point: 250 - 260°C; IR (KBr, cm^{-1}); 1671 (C=N), 3075 (CH-Ar), 705 (C-S-C), 672 (C-Cl); ^{1}H NMR ($CDCL_3$, 400 MHz,δ ppm): 3.98, 3.70 (d, 2H, CH_2), 5.17 (t, 1H, CH), 7.30 (s, 1H, S-CH), 7.15-7.70 (d, 3H, CH), 7.29 - 7.98 (m, 9H, Ar-H).

4-(4-bromophenyl)-2-(5-phenyl-3-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)thiazole (6e)

Yield: 45%; melting point: 280 - 300°C; IR (KBr, cm^{-1}); 1662 (C=N), 3009 (CH-Ar), 676 (C-S-C), 734 (C-Br); ^{1}H NMR ($CDCL_3$, 400 MHz, δ ppm): 4.05, 3.66 (d, 2H, CH_2), 5.29 (t, 1H, CH), 7.37 (s, 1H, S-CH), 7.15-7.75 (d, 3H, CH), 7.25 - 8.00 (m, 9H, Ar-H).

Compound	X	R	Mol. for.	Mol. Wt. (g/ml)	M.p. (°C)	Yield (%)	R_f
6a	O	Br	$C_{22}H_{16}BrN_3O$	450.38	211-213	58	0.61
6b	O	OCH_3	$C_{23}H_{19}N_3O_2S$	401.48	220-222	47	0.69
6c	S	OCH_3	$C_{23}H_{19}N_3OS_2$	417.55	215-217	55	0.62
6d	S	Cl	$C_{22}H_{16}ClN_3S_2$	421.97	228-230	38	0.61
6e	S	Br	$C_{22}H_{16}BrN_3S_2$	466.42	198-200	41	0.68

Table 1: *Physical characterization of synthesized compounds (6 a-e)*

Antimicrobial activity

Test microorganism

All the synthesized compounds were evaluated for their antimicrobial activity by Cup and plate agar diffusion method. All the tested bacterial strains (*Staphylococcus aureus* MTCC 87, *Bacillus subtilis* MTCC 121, *Pseudomonas aeruginosa* MTCC 424, *Escherichia coli* MTCC 40) and fungal strains (*Candida albicans* MTCC 183, *Fusarium solani* MTCC 2935) were obtained from Institute of Microbial Technology (IMTECH), Chandigarh. Nutrient agar medium and Sabouraud dextrose agar (SDA) media were used for bacteria and fungi respectively. The nutrient agar media and SDA were sterilized by autoclaving at 121°C for 15 minutes at 15 psi.

Antibacterial and antifungal screening by Cup and plate agar diffusion method

The synthesized compounds (6a-e) were tested for *in vitro* antimicrobial activity. The synthesized compounds and standard drugs (Ciprofloxacin and fluconazole) were dissolved DMSO to get a concentration of 100 µg/ml. The nutrient media was poured into sterile petri dishes and kept for solidifying. Bores were made on the medium with a sterile borer. 0.1 ml of test solution and standard solution at a concentration of 100 µg/ml were poured into bores. Then the petri plates were incubated at 37°C for 24 hours. The zone of inhibition was then observed and measured.

Results and Discussion

In the present work, five of the pyrazoline derivatives bearing thiazole were synthesized. The intermediate chalcone derivatives (3a-b) were synthesized by reaction of benzaldehyde with 2-acetylthiophene and 2-acetylfuran in the presence of sodium hydroxide in ethanol. The reaction was sensitive to the concentration of sodium hydroxide. The resultant chalcones were reacted with thiosemicarbazide in presence of sodium hydroxide gave pyrazoline derivatives (4a-b). The compounds (6a-e) were obtained by reaction of compound (4a-b) with phenacylbromide derivatives in ethanol. The substitution of the *para* position of phenacyl bromide played an important role in the thiazole formation step.

The synthesized compounds were characterized by IR, ^{1}H NMR, melting point analysis and TLC study. The IR spectrum of compounds (6a-e) showed presence of characteristic strong absorption band at 1666 cm^{-1} of C=N stretch, absorption band at 1093 cm^{-1} of (C-O stretch) of furan ring, absorption band at 2930 cm^{-1} of (C-H) stretch, absorption band at 3103 cm^{-1} of aromatic C-H stretch, absorption at 708 cm^{-1} of C-Br, absorption band at 705 cm^{-1} of (C-S-C) of thiazole ring, absorption band at 672 cm^{-1} of (C-Cl) stretch.

The ^{1}H NMR spectra had multiplet in region of δ 7.05 - 8.00 ppm confirmed the presence of aromatic protons, doublet at δ 3.45 and 3.90 ppm confirmed the presence of two protons of $-CH_2$ group of pyrazoline ring, triplet at δ 5.17 - 5.30 ppm showed one proton of CH of pyrazoline, a singlet at δ 7.20 - 7.37 confirmed the presence of one proton of S-C-H group in thiazole ring and the presence of three protons of methoxy group (O-CH_3) observed as a singlet at δ 3.79 - 3.87. The R_f value of the synthesized compounds was calculated by using the solvent system benzene: petroleum ether: methanol (9: 0.9: 0.1) and ranges between 0.60 - 0.69.

Antimicrobial activity

All synthesized compounds were evaluated for their *in vitro* antimicrobial activity by the Cup and plate agar diffusion method. Antimicrobial activity was measured against tested microorganisms (*Staphylococcus aureus* MTCC 87, *Bacillus subtilis* MTCC 121, *Pseudomonas aeruginosa* MTCC 424, *Escherichia coli* MTCC 40). Ciprofloxacin was used as standard drugs to compare the antibacterial activity shown by tested compounds. The zone of inhibition was observed in mm and standard deviation was calculated. The synthesized compounds had moderate to good antibacterial activity (Figure 2). The antibacterial screening results are summarized in table 2. Compound 6b showed good activity against all tested bacterial strains. Compound 6a, 6c and 6e were found to be more active against gram positive strains. The compound 6a showed moderate activity against *B. subtilis* and good activity against *E. coli*. Compound 6d had good activity against *P. aeruginosa* and *E. coli* but found to be weak active against gram positive strains. The compound 6e exhibited moderate to good activity against three bacterial strains except *B. subtilis*. The compound with furan ring attached to pyrazoline exhibited most potent antibacterial activity. The 6d compound with chloro substitution was found to be less active. The results of *in vitro* antifungal activity were found to be discouraging. No compound showed the inhibitory activity against fungal strains employed in study.

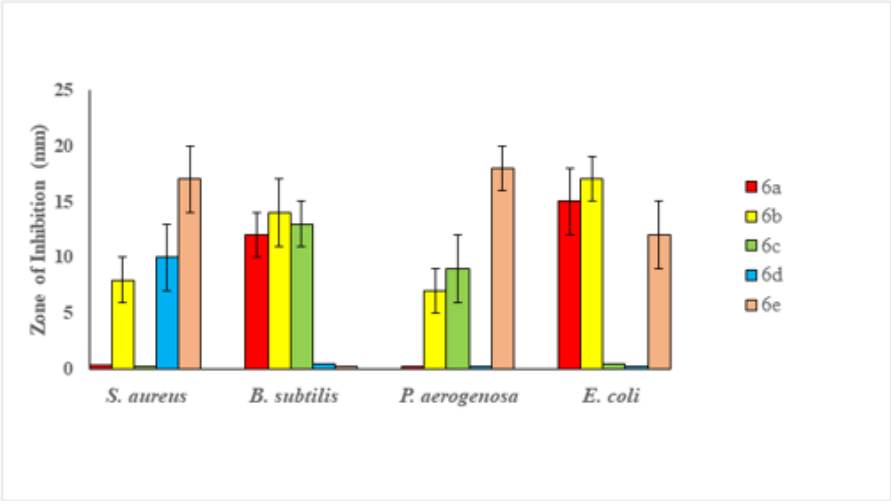

Figure 2: *Antibacterial activity of compounds (6a-e) against gram positive and gram negative bacterial strains.*

Compound	Zone of Inhibition (mm)			
	Gram +ve bacteria		Gram -ve bacteria	
	S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*
6a	NA	12 ± 2	NA	15 ± 3
6b	8 ± 2	14 ± 3	7 ± 2	17 ± 2
6c	NA	13 ± 2	9 ± 3	NA
6d	10 ± 3	NA	NA	NA
6e	17 ± 3	NA	18 ± 2	12 ± 3
Ciprofloxacin	17 ± 4	21 ± 3	10 ± 4	25 ± 2

Table 2: *In vitro antimicrobial activity of the synthesized compounds (6a-e).*

Conclusion

In this study, novel thiazole bearing pyrazoline derivatives were synthesized and investigated for their antimicrobial activity against four bacterial strains. Compounds 6b exhibited promising antibacterial activity against *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli* with zone of inhibition 8 ± 2 mm, 14 ± 3 mm, 7 ± 2 mm and 17 ± 2 mm respectively. Compound 6e also exhibited good antibacterial activity against three bacterial strains except *B. subtilis*. Compound 6e showed zone of inhibition of 17 ± 3 mm against *S. aureus*. The compound displayed more activity as compared to standard drug (10 ± 4 mm) with zone of inhibition of 18 ± 2 mm. Hence, it is concluded that there is ample scope for further study in developing these structures as efficient lead compounds.

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Conflict of Interest

The author declare no conflict of interest, financial or otherwise.

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