International Journal of Recent Advances in Multidisciplinary Research
Vol. 01, Issue 03, pp.045-050, September, 2014

Full Length Research Article

MICROWAVE ASSISTED SYNTHESIS AND ANTIMICROBIAL EVALUATION OF CERTAIN NOVEL THIAZOLES CONTAINING PIPERANOL MOIETY

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ARTICLE INFO

Article History:
Received 22nd June, 2014
Received in revised form
15th July, 2014
Accepted 27th August, 2014
Published online 30th September, 2014

Keywords:
Chalcone,
Thiosemicarbazide,
And various substituted
Phenacyl bromide.

ABSTRACT

A simple method for the synthesis of a pyrasolyl-thiazole derivative containing a piperonal moiety was developed by microwave irradiation. The microwave synthesis route afforded better yields with shorter reaction time. Their chemical structure was confirmed by IR, ^{1}H, ^{13}C NMR, mass and elemental analysis. All the synthesized compounds were also screened for their potent antimicrobial activity.

INTRODUCTION

Modern drug design cannot be imagined without the chemistry of heterocycles (Silverman *et al*., 1992). Heterocycles are commonly regarded an interesting scaffolds (Jungheim *et al*., 1987). Which can be synthesized readily and which are able to incorporate substituents. The cyclic nature of heterocycles provides an inherent constraint arraying the substituents in the desired orientation. For there and other reasons, many pharmaceuticals contain heterocyclic groups. Thiazole exhibit broad spectrum of chemotherapeutic properties such as antibacterial, (Boyd *et al*., 1982) antifungal (Jungheim *et al*., 1988) and antitubercular, (Sangwan *et al*., 1983) anti – HIV (Nasar *et al*., 2003) anticonvulsant, (Turan-Zitouni *et al*., 2000) anticancer, (Gupta *et al*., 1999) anti-inflammatory (Onoe *et al*., 1994) and analgesic. (Ashtekar *et al*., 1987) The thiazole chemistry has been extensively developed because of their unique physiological properties. Thistleis stable, non-carcinogenic aromatic compounds with relatively small size. On the other hand, compounds including pyrazole nucleus are known to possessAnalgesic, anti-inflammatory, antipyretic, antiarrhythmic, muscle relaxant, psychoanalytic, anticonvulsant, hypotensive, monoamineoxidase inhibitor, antidiabetic and antibacterial activities (Ashtekar *et al*., 1987, M. Abid *et al*., 2005). Pyrazole derivative Celebrex is a potential anti-inflammatory drug (Turan-Zitouni *et al*., 2000). In addition, 1, 3-thiazole derivatives have been reported to possess tuberculostatic, antibacterial and antifungal activities (Kumar *et al*., 2005, Chohan *et al*., 2006). It was also reported that fentiazac, 1, 3-thiazole derivative, is potent antinflammatory agent (Ozdemir *et al*., 2007). In the interest of the above suggestion, in our work we synthesis biologically active heterocycles (28-33) we planned to synthesize thiasolyl-pyrasoline derivative for antimicrobial evaluation. The work up procedure is simple and convenient.

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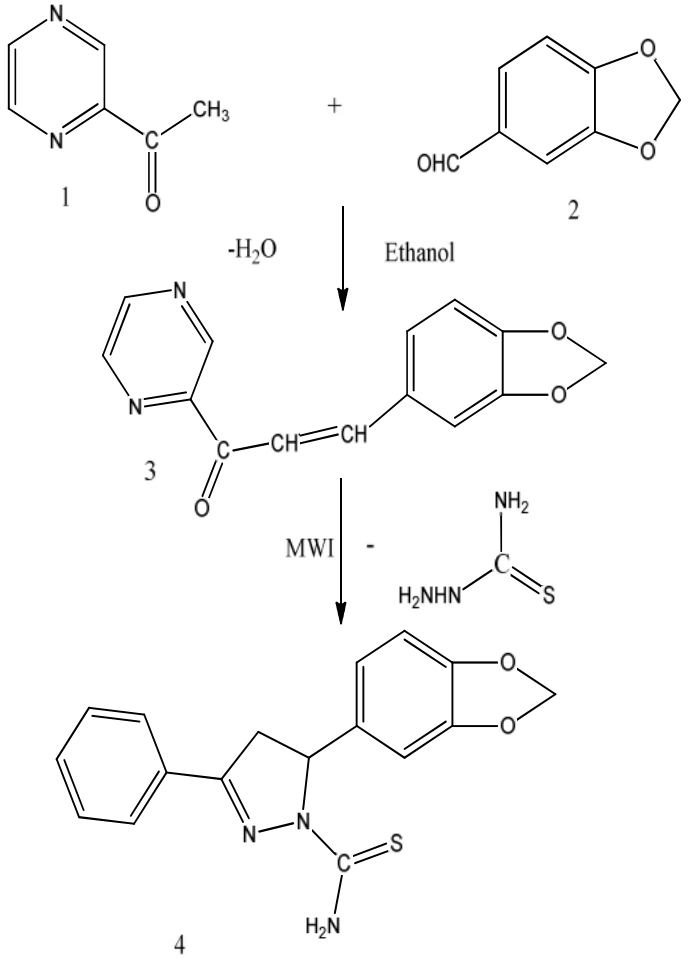
MATERIALS AND METHODS

The commercially available AR and LR grade chemicals were used without further purification. Chemical reagents and solvents were purchased from Sigma Aldrich. Melting points were determined in an open glass capillaries on Gallen camp apparatus and corrected. The percentage composition of the elements (CHNC) for the compounds were determined using an elemental analyzer CHNS model fission EA 1108. The infrared spectra were recorded as potassium bromide disc using a Perkin-elemer spectrophotometer GX. The ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded using JEOL JNM-ECP 400 spectrometer in DMSO-d_6 as the solvent using TMS

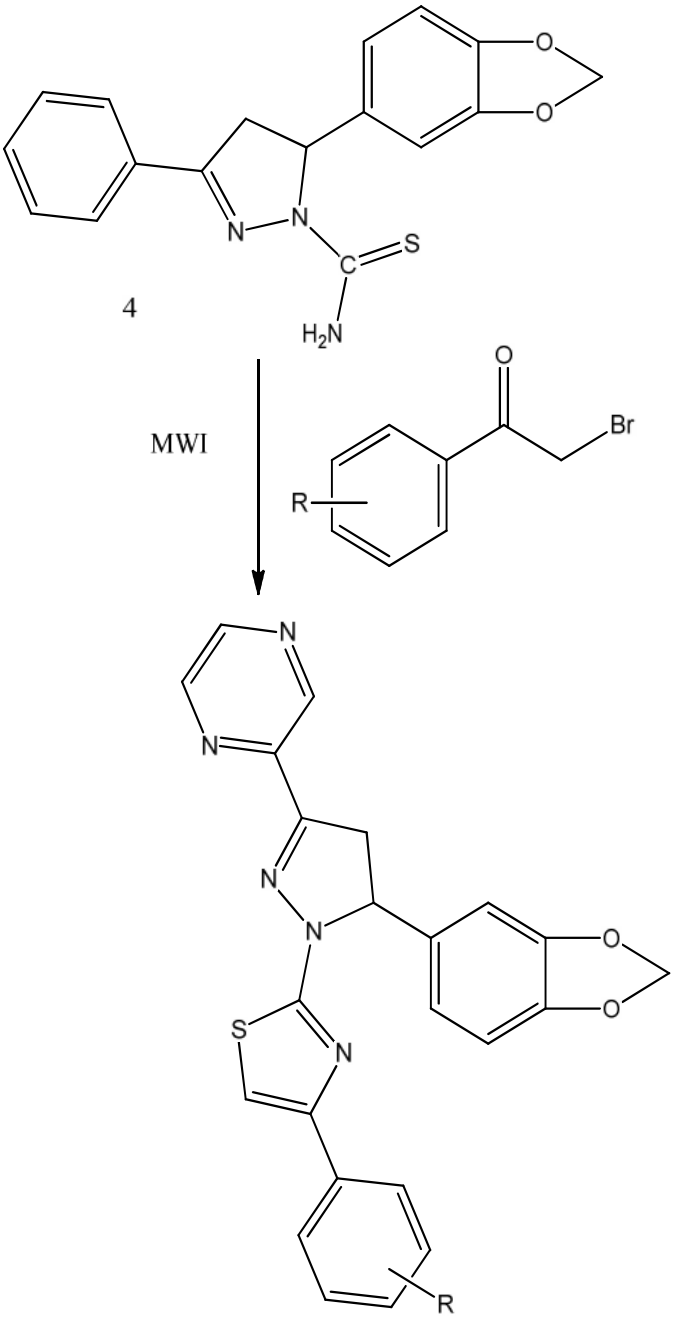
as an internal standard, and chemical shifts are expressed as ppm. Mass spectra were recorded on micro-mass Q-TQF, and shizmadzu LCMS 2010A mass spectrometer and the reactions were followed by TLC (silica gel, aluminium sheets 60 F_{235}, Merck)

General Procedure for the Synthesis of the Compounds

Several substituted thiazole derivatives were efficiently synthesized by three step process. As depicted in the scheme 3, 4 and 5, the reaction between the commercially available 2-acetyl pyrazine 1, and piperonal 2 with sodium hydroxide in absolute ethanol provided chalcones3in quantitative yield of 90%. The isolated compound 3 was treated with thiosemicarbazide with potassium hydroxide in absolute ethanol at reflux condition for three hours. Then ethanol was evaporated to dryness, filtered the solid washed with water and dried to get the 1-thiocarbamoyl-3, 5-diaryl-2-pyrazoline 4. This intermediate treated with various phenacyl bromide in absolute ethanol was placed in a Pyrex vial and irradiated with 200W for 10 min at 150^0 C (final temperature). The reaction was monitored by TLC, after the completion of the reaction, the reaction mixture was cooled to room temperature and concentrated. The solid obtained was washed with little amount of hexane, filtered and dried under reduced pressure to give the product 5. Analytical and spectral data (^{1}H NMR, ^{13}c NMR, IR, and MS) confirmed the structures of the new compounds. The synthetic route of compounds is outlined in Scheme 1 and Scheme 2.



Scheme 1



Scheme 2

S.No.	R
1	3-Cl
2	4-F
3	4-CH_3
4	4-Cl
5	H
6	4-CN

Spectral Data

1. 2-{5-(1,3-Benzodioxol -5-yl) -1-[4-4(3-chloro) -1,3-thiazol -2-yl]-4,5-dihydro-1H-pyrazol-3-yl} pyrazine.yellow powder, Yield = m.p. =184- 186 °CR_f $_{= 0.62}$ ^{1}H NMR (400 MHz, CDCl3): δ = 9.38 (s, 1H), 8.52–8.50 (m, 2H), 7.64–7.61 (m, 2H), 7.31–7.28 (m, 2H), 6.90 (q, 1H), 6.84 (s, 2H), 6.79–6.77 (d, *J* = 8 Hz, 1H), 5.92 (s, 2H), 5.68 (q, 1H), 3.97 (dd, *J* = 12 Hz, 18 Hz, 1H), 3.49 (dd, *J* = 4 Hz, 16 Hz, 1H). ^{13}C NMR (100 MHz, CDCl3): 164.17, 150.73, 150.49, 148.08, 147.31, 146.66, 143.80, 143.76, 143.23, 135.03, 133.30, 133.19, 128.62,

127.16, 120.36, 108.27, 106.81, 104.43, 101.16, 64.79 and 42.68.MS: m/z (ES), 463 [(M+2)+].

2.2-(5-(benzo[d][1,3]dioxol-5-yl)-3-(pyrazin-2-yl)-4,5-dihydro-1H-pyrazol-1-yl-4-(4-fluorophenyl)thiazole .yellow powder yield=82%m.p.=182 ^{0}C $R_{f\ =0.56}$ ^{1}H NMR (400 MHz, CDCl3): δ = 9.38-9.37 (d, 2H), 8.52–8.50 (m, 2H), 7.64–7.61 (m, 2H), 7.31–7.26 (m, 2H), 6.93-.6.92 (d, 1H), 6.91-6.90 (d, 2H), 6.84 (s, *J* = 8 Hz, 2H), 6.77 (s, 1H), 5.93-5.91 (dd, 2H), 5.68-5.63 (t, *J* = 12 Hz, 18 Hz, 1H), 4.0-3.9 (t, *J* = 4 Hz, 16 Hz, 1H).3.4z^{13}C NMR (100 MHz, CDCl3): 169.45, 135.62, 133.70, 132.06, 131.80, 131.57, 131.32, 130.23129.73, 128.94, 128.11, 127.56, 126.86, 122.06, 120.62, 105.33, 65.54, 62.68, 40.13, 39.92, 39.71, 39.50, 39.30, 39.09, 38.88, 30.70 MS: m/z(ES),463[(M+2)+].

IR:cm^{-1} 3606, 3429, 3185, 3053, 2940,2783, 2480, 1601, 1613, 1553, 1458, 1441, 1322, 1302, 1083, 1052, 985, 940, 842, 769, 755, 701, 711, 654, 588, 506.

3. 2-(5-(benzo[d][1,3]dioxol-5-yl)-3-(pyrazin-2-yl)-4,5-dihydro-1H-pyrazol-1-yl)-4-(p-tolyl)thiazoleYellow solid; Yield: 85 %; m.p. -189- 191 °C.R_f =0.76Infraredspectraldata: (KBr,vincm^{-1}) 3429, 3194, 3033, 2959, 2916, 2753, 2916, 2753, 2673, 2421, 1817, 1609, 1528, 1454, 1419, 1370, 1314, 1228, 1160, 1047, 986, 938, 841, 772, 749, 710, 692, 551, 486, 462. ^{1}H NMR spectra: (400 MHz, $CDCl_3$); δ-value in ppm δ = 9.29-9.2 (d, 1H, Ar), 8.59–8.56 (m, 2H,Ar), 7.49-7.43 (d, 1H, Ar)7.27-7.26 (t, *J* =2.4Hz, 2H, Ar)7. (s, *J* = 24Hz, 1H, Ar)6.82 (s, *J* = 2.4Hz, 1H, Ar)6.77-6.75 (d, *J* = 2Hz, 1H, Ar)6.72-6.66 (d, *J* = 2Hz, 1H, Ar)6.22 (s, *J* = 24Hz, 1H, Ar)6.01-5.96(q, *J* = 6.8Hz, 1H, Ar)5.93 (q, *J* = 7.2Hz, 2H, -O-CH_2-O)3.91-3.83(dd, *J* = 24Hz, 1H, -CH, Ar)3.39-3.33 (dd, *J* = 16Hz, 16Hz, 1H, -CH_2)2.41 (s, *J* = 8.8Hz, 8.8Hz, 1H, -CH_2)s^{13}C NMR spectra: (100 MHz, $CDCl_3$); δ – value in ppm43.27, 64.02, 101.17, 105.87, 108.57, 119.00, 127.51, 135.43, 143.12, 144.16, 145.05, 145.92, 147.12,148.14, 154.89,177.59. LC-MS: m/z 446 (M+1).

4.2-(5-(benzo[d][1,3]dioxol-5-yl)-3-(pyrazin-2-yl)-4, 5 dihydro-1H-pyrazol-1-yl)-4-(4-chlorophenyl)thiazole. Yellow solid; Yield: 90 %; m.p. 219 °C.$R_{f\ =0.62}$Infrared spectral data: (KBr, ν in cm^{-1}) 3398, 3306, 3060, 3030, 2967, 2926, 2225, 1816, 1605, 1557, 1454, 1409, 1337, 1270, 1142, 1044, 915, 846, 741, 702, 657,547, 506. ^{1}H NMR spectra: (400 MHz, $CDCl_3$); δ-value in ppm 9.21 (s, 1H), 8.69–8.65 (m, 2H),8.3(s,1H)7.65-7.63(d, *J* = 18Hz, 1H, Ar)7.32 (d, *J* = 12Hz, 2H, Ar)7.18-7.16 (d,1H Ar)6.98(s, *J* = 10Hz, 1H, Ar)6.95-6.93 (d, 1H, Ar)6.89-6.8 (d, *J* = 20Hz, 3H, Ar)5.97-5.9(d, *J* = 5.6Hz, 2H, -O-CH_2-O)5.68-5.65(t, *J* = 12Hz, 1H, -CH)4.09-4.01 (dd,2H,Ar)3.49-3.36 (dd, *J* = 8Hz, 8Hz, 1H, -CH_2)3.2 (s, *J* = 8Hz, 1H, -CH_2)2.66 (s, 3H, -CH_3)2.32-2.29 (s,1H Ar)^{13}C NMR spectra: (100 MHz, $CDCl_3$); δ – value in ppm30.70, 38.88, 39.50, 39.92, 40.13, 62.68, 65.54, 105.33, 120.62, 125.83, 129.12, 135.25, 137.33,142.5,144.1,143.0,150.3,156.2 144.41, 146.96, 147.18, 148.01, 164.60LC-MS: m/z 442 (M+1).

5.2-(5-(benzo[d][1,3]dioxol-5-yl)-3-(pyrazin-2-yl)-4, 5-dihydro-1H-pyrazol-1-yl)-4-phenylthiazollightyellowsolid. Yield:84%;m.p=.156-158°C.R_f=0.84Infraredspectraldata: (KBr,vincm^{-1}) 434, 3063, 2926, 2806, 1598, 1555, 1528, 1456, 1379, 1344, 1064, 1048, 845, 855, 761, 713, 701, 669, 591, 515, 493. ^{1}H NMR spectra: (400 MHz, $CDCl_3$); δ-value in ppm9.39 (S,1H,Ar)8.55(m,2H)7.82-7.79 (d, *J* = 8Hz, 2H, Ar)7.65-7.62(d, 2H, Ar)7.27 (s, 1H,Ar) 7.03 (s, *J* = 12Hz, 2H, Ar)6.85-6.79 (m, 3H, Ar)6.07(q, *J* = 5.2Hz, 1H, Ar)5.94 (q, *J* = 6Hz, 2H, -O-CH_2-O)5.68 (t, *J* = 10Hz, 1H, -CH)3.90(dd, *J* = 12Hz, 12Hz, 1H, -CH_2)3.31(dd, *J* = 6.4Hz, 6.4Hz, 1H, -CH_2)^{13}C NMR spectra: (100 MHz, $CDCl_3$); δ – value in ppm 21.74,41.87, 63.01, 101.86,107.33, 109.79, 110.17,111.68, 111.73, 112.90, 114.15,120.48, 128.86, 134.14,138.98,139.05, 143.51, 143.95, 147.92, 148.03,148.22.LC-MS: m/z 453 (M+1).

6.2-(5-(benzo[d][1,3]dioxol-5-yl)-3-(pyrazin-2-yl)-4, 5-dihydro-1H-pyrazol-1-yl)-4-Benzonitrile.Brown solid; Yield: 85 %; m.p=197-199 °C. R_f =0.76.

Infrared spectral data: (KBr, ν in cm^{-1})
3312, 3109, 3059, 3028, 2928, 2969, 2868, 2807, 1890, 1816, 1601, 1557, 1483, 14541443, 1335, 1299, 1276, 1141, 1069, 1049, 1026, 948, 915, 839, 771, 753, 701, 669, 620, 587, 520, 504.^{1}H NMR spectra: (400 MHz, $CDCl_3$); δ-value in ppm9.39(S,1H,Ar)8.53(m,2H)7.70-7.66 (t, *J* = 8Hz, 2H, Ar)7.27(t, *J* = 1.6Hz, 1H, Ar)7.06(t, *J* = 14Hz, 2H, Ar)7.00(q, *J* = 16Hz, 1H, Ar)6.95(q, *J* = 9Hz, 1H, Ar)6.91(t, *J* = 16Hz, 3H, Ar)6.86 (q, *J* = 28Hz, 1H, Ar)6.81(q, *J* = 5.2Hz, 1H, Ar)6.78(q, *J* = 6.8Hz, 2H, -O-CH_2-O)5.9(q, *J* = 17.6Hz, 1H, -CH)3.96(dd, *J* =12Hz,12Hz,1H,-CH_2)3.48(dd, *J* =6.4Hz, 6.4Hz, 1H,-CH_2)^{13}CNMR spectra: (100 MHz, $CDCl_3$); δ – value in ppm
21.87,30.70,38.87,39.08,39.50,39.92,40.12,62.66,65.53,105.34, 120.61,122.0,126.87,127.56,128.12,128.38,128.94,129.73,130. 99.131.32,131.57,131.80,132.06,133.69,135.62,150.33,169.44. LC-MS: m/z 429 (M+2).

RESULTS AND DISCUSSION

The IR spectra of all the compounds showed disappearance of absorption band at1640 due to >C=O of chalcones. The IR spectra of all the compounds showed (C=N) stretching at 1500-1600 cm-1 because of the ring closure. The absorption bands at 1110-1270 cm-1 were attributed to the (C-N) stretch vibrations, which also confirmed the formation of the desired pyrazoline ring in all the compounds and 1001-1113 cm-1 due to (C=S) stretch of the thiocarbamoyl group.. In the 400 MHz ^{1}H NMR spectrum of the compounds, the CH_2 protons of the pyrazoline ring resonated as a pair of doublets of doublets at δ 3.23-3.58 ppm (Ha), 3.80-3.96 ppm (Hb). The CH (Hx) proton appeared as doublets of doublets at δ 5.57-5.74 ppm due to vicinal coupling with the two magnetically non-equivalent protons of the methylene group at position 4 of the pyrazoline ring. The screening of compounds is an alternative approach to high-throughput screening for identification of leads for therapeutic targets. A series of novel thiazole derivatives were synthesized and evaluated for their antibacterial and antifungal activity. All the derivatives were efficiently synthesized. In this study, all thiazole derivatives are more active. The structure of the newly synthesized compounds was elucidated by their ^{1}H NMR, ^{13}C NMR, elemental analysis, LC-MS/MS, IR spectral data and melting point analysis. According to structure–activity relationships (SAR), it can be concluded that piperanol, pyrazoline, and thiazole moieties are essential for the antimicrobial activity.

Table 1. Antibacterial activities of the newly synthesized compounds (Zone of Inhibition in mm, MIC in mg/meal given in parenthesis)

Compounds (10 µg/ml)	Streptococcus aureus	Escherichia coli	Pseudomonas aeruginosa	Klebsilla Pneumonia
5a	23(6.25)	20.5(6.25)	21.5(6.25)	20.5(6.25)
5b	23.5(6.25)	6.5(50)	18(6.25)	22(6.25)
5c	22.5(6.25)	25.5(6.25)	19.5(6.25)	21.5(6.25)
5d	19.5(6.25)	22(6.25)	18(6.25)	15.5(6.25)
5e	17(6.25)	14.5(6.25)	12(6.25)	23(6.25)
5f	14.5(6.25)	19(6.25)	13(6.25)	16(6.25)
Ciproflaxocin	24.5(6.25)	25(6.25)	24(6.25)	25.5(6.25)

Antibacterial activity of pyrazolylthiazole bearing piperonal and pyrazine

We have investigated newly synthesized pyrazolylthiazoles for their antibacterial activity against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATTC-27853) and *Klebsiella pneumonia* (recultured) bacterial strains by the disc diffusion method. [Bauer RW*et al*.,]. Solvent and growth controls were kept, the zones of inhibition and minimum inhibitory concentrations (MIC) noted. The results of these studies are given in Table-1 and compared with the standard ciprofloxin. Interestingly, most of them showed the good antibacterial activity. Among the compounds, 5a and 5cwere showing good inhibition towards all the four bacteria tested. Compounds 5b and 5d wereshowing good activity in *Staphylococcus aureus*. Compound 5d shows good activity against *Escherichia coli.* Compounds 5b shows good activity in *Pseudomonas aeruginosa*. Compounds 5e and 5f shows moderate to lowactive against all the strains tested. The structure activity relationship studies revealed that the compounds with Fluoro and cyano substituent at N-1 (5a and 5c) are very much active. By the same time vinyl, cholera and 2-Fluoro phenyl substitution decreases the activity. Since almost all these compounds are effective against these organisms.

Antifungal Activity of 2-Pyrazoline Bearing Piperonal And Pyrazine

Newly synthesized pyrazolylthiazoles were screened for their antifungal activity against *Aspergillus niger* (MTCC 281), *Candida albicans* (MTCC 227). [Bauer RW*et al*.,] Antifungal activity was determined by measuring the inhibition zone. The results of these studies were given in Table-2 and compared with the standard Keta conazole Most of the compounds synthesized showed good activity against all the fungi tested. Particular compounds 5a and 5b were active against all the above fungi tested. Compounds 5c, 5d, 5e, and 5f have exhibited the moderate to low antifungal activity. The structure activity relationship studies revealed that aliphatic substituent at C-3, aryloxy/ aryl thio at C-4, either substituted or free NH at N-1 may be the cause for their effectiveness against these fungi. In aryl substituents 3- bromo benzyl, 4- methoxy phenyl, 4-cyano phenyl groups linked by the oxygen with the C-4 of the pyrazoline and benzyl group linked by the sulphur with the C-4 of the pyrazoline is very active. Compounds bearing alkyl groups methyl, ethyl, isopropyl, isobutyl, n-pentyl groups at C-3 of the pyrazoline have shown the very good activity. Free NH, methyl or pyridyl substitution at N-1 increases the activity of the compounds by the same time phenyl, trifluoro ethyl and 4-fluorophenyl substitution (in some cases) decreases the activity. On the other hand the methoxy substituent either at aryl ring/ alkyl chains is not found to be effective against these organisms even at the higher concentrations.

Table 2. Antifungal activities of the newly synthesized compounds (Zone of inhibitionin mm, MIC in mg/mL given in parenthesis)

Compound No	Aspergillus Niger	Candida albicans
5a	39.5(6.25)	33.5(6.25)
5b	37.5(6.25)	34(6.25)
5c	26.5(6.25)	31(6.25)
5d	29.5(6.25)	30(6.25)
5e	24(6.25)	27(6.25)
5f	28.5(6.25)	28.5(6.25)
Keta conazole	38.5(6.25)	34.5(6.25)

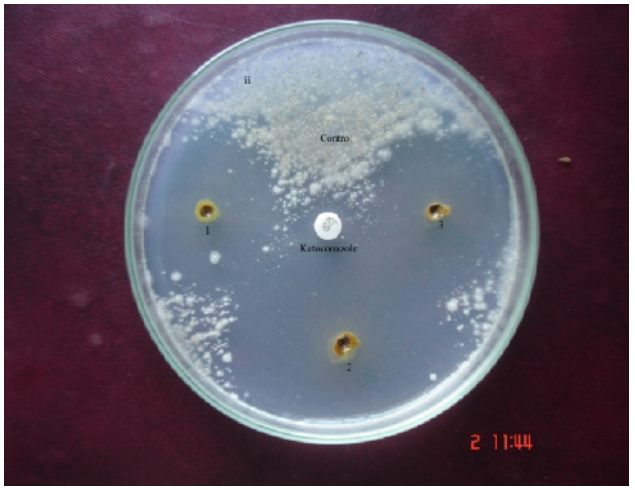
Methods for antibacterial and antifungal activity

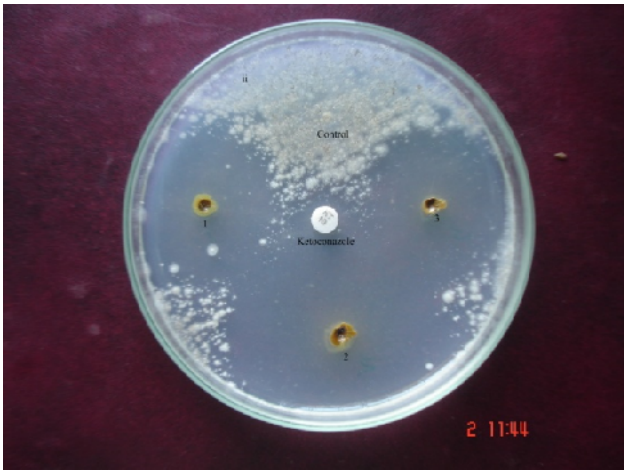
Preparation of inoculums for antibacterial activity

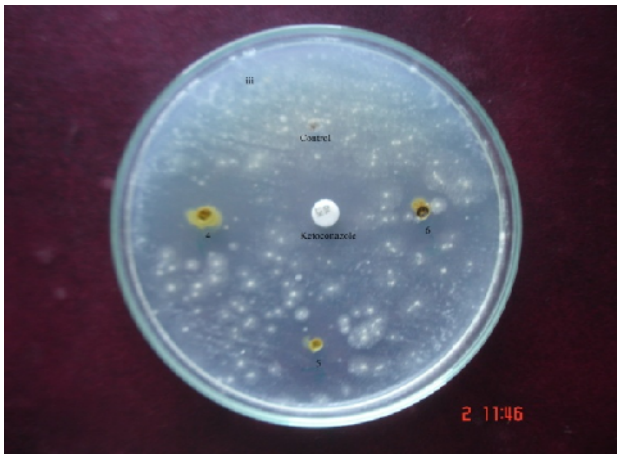
Stock cultures were maintained at 4°C on slopes of nutrient agar. Active cultures for experiments were prepared by transferring a loopful of cells from the stock cultures to test tubes of Mueller-Hinton broth (MHB) for bacteria and Sabouraud dextrose broth (SDB) for fungi that were incubated without agitation for 24 hrs at 37°C and 25°C respectively. The cultures were diluted with fresh Mueller-Hinton and Sabouraud dextrose broth to achieve optical densities corresponding to $2.0x10^6$ colony forming units (CFU/ml) for bacteria.The disc diffusion method was used to screen the antimicrobial activity. In vitro antimicrobial activity was screened by using Mueller Hinton Agar (MHA) obtained from Himedia (Mumbai). The MHA plates were prepared by pouring 15 ml of molten media into sterile petri plates. The plates were allowed to solidify for 5 minutes and 0.1 % inoculum suspension was swabbed uniformly and the inoculum was allowed to dry for 5 minutes. The test compounds at 10 µg/disc (antibacterial activity) were loaded on 6 mm sterile discs. The loaded disc was placed on the surface of the medium and the compound was allowed to diffuse for 5 minutes and the plates were kept in incubation at 37°C for 24 hrs. At the end of incubation, inhibition zones formed around the disc were measured with a transparent ruler in millimeter.

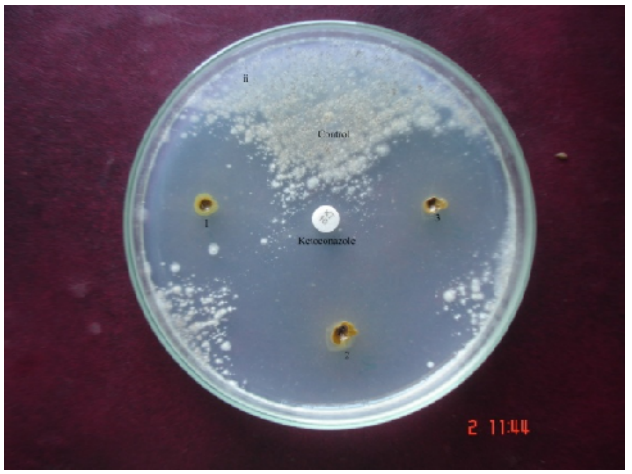
Preparation of inoculums for antifungal activity

Stock cultures were maintained at 4°C on slopes of nutrient agar. Active cultures for experiments were prepared by transferring a loopful of cells from the stock cultures to test tubes of Mueller-Hinton broth (MHB) for bacteria and Sabouraud dextrose broth (SDB) for fungi that were incubated without agitation for 24 hrs at 37°C and 25°C respectively. The cultures were diluted with fresh Mueller-Hinton and Sabouraud dextrose broth to achieve optical densities corresponding to $2.0x10^5$ spores/ml for fungal strains. The disc diffusion method was used to screen the antimicrobial activity. In vitro antimicrobial activity was screened by using Mueller Hinton Agar (MHA) obtained from Himedia (Mumbai). The MHA plates were prepared by pouring 15 ml of molten media into sterile petri plates. The plates were allowed to solidify for 5 minutes and 0.1 % inoculum suspension was swabbed uniformly and the inoculum was allowed to dry for 5 minutes. The test compounds at 1mg/disc (antifungal activity) were loaded on 6 mm sterile discs. The loaded disc was placed on the surface of the medium and the compound was allowed to diffuse for 5 minutes and the plates were kept in incubation at









37°C for 24 hrs. At the end of incubation, inhibition zones formed around the disc were measured with a transparent ruler in millimeter.

Conclusion

In conclusion, we have successfully synthesized a new series of novel thiazole derivatives and moreover most of compounds contain bioactive heterocyclic moiety. The antimicrobial screening suggests that all the newly synthesized compounds showed moderate to good activity against the tested organisms.

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