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Original Article

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUATION OF SOME NEW BENZOTHIAZOLE DERIVATIVES

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ABSTRACT

Objective: Synthesis, characterization and antimicrobial evaluation of some new 1,3-benzothiazolyl pyrazole derivatives.

Methods: Aseries of novel2-[3-(substituted phenyl)-4-formylpyrazol-1-yl]-6-chloro benzothiazole derivatives (5a-g) have been synthesized by cyclization through Vilsmeier-Haack reaction on hydrazones (4a-g)of substituted aromatic ketones with 6-chloro benzothiazol-2-yl hydrazine under microwave irradiation in fairly good yields. All the newly synthesized compounds were characterized by IR, ^{1}HNMR, Mass spectral studies and elemental analysis and were screened for their *in vitro* antibacterial and antifungal activities also.

Results: The results revealed that all 1,3-benzothiazole pyrazole derivatives(5a-g) were synthesized in satisfactory yields and pharmacologically evaluated for their *in vitro* antimicrobial activity. All the synthesized compounds were in good agreement with elemental and spectral data. Some of the tested compounds showed good to moderate antimicrobial activity against all tested pathogenic bacterial and fungal strains.

Conclusion: For the present investigation we have prepared benzothiazole derivatives that are incorporated with pyrazolyl moiety with the hope of potentiating the activity of two such units in the same compound. Compounds 5b, 5c, and 5a showed excellent antibacterial and antifungal activities as compared to reference drugs norfloxacin and ketoconazole.

Keywords: Benzothiazole, Antibacterial activity, Antifungal activity, Pyrazole.

INTRODUCTION

It is an established fact that benzothiazole derivatives contain extended p-delocalized systems which are capable of binding to DNA molecules via p–p interactions and therefore exhibited various biological properties like antitumor, antimicrobial and anthelmintic activities [1]. Benzothiazoles comprise a novel class of therapeutic compounds found to possess a number of biological activities such as anticancer [2-3], anti-inflammatory [4], antimicrobial [5-6], antidiabetic [7], antiviral [8] and antileishmanial [9]. Therefore from the above facts, we herein report the synthesis of some new formylated pyrazolyl benzothiazole derivatives with the hope of finding of potent antibacterial and antifungal compounds as the need of emergence due to the phenomenon of bacterial resistance of antimicrobial agents.

MATERIALS AND METHODS

All the newly synthesized compounds gave moderate to good yields. The homogeneity of synthesized compounds was ascertained by thin layer chromatography (TLC) on silica gel G (Merck) coated plates by using different solvent systems. The visualization was done by using iodine vaporus and UV light chamber. The chemicals and solvents used for experimental work were commercially procured from CDH,E. Merck, S. D. fine chem. and Qualigens. The silica gel G used for analytical chromatography was obtained from E. Merck. Melting points were determined in open glass capillary tubes in a Hicon melting apparatus and are uncorrected. IR spectra were recorded in KBr pellets on JASCO FT-IR 410 spectrophotometer. The ^{1}HNMR spectra was recorded downfield on VNMRS-500 "Agilent-NMR" using (TMS) tetramethyl silane as an internal standard. The chemical shift are reported in ppm δ scale. LCMS Mass spectra were recorded on MASPEC low resolution mass spectrometer at an ionization potential of 70eV. The elemental analyses (C, H, and N) of all compounds were performed and the measured values agreed within calculated ones.

Experimental

Synthesis of 6-chloro-2-benzothiazolamine (2)

General procedure

A mixture of p-chloroaniline (0.01 mol) and potassium thiocyanate (0.01 mol) in 150 ml glacial acetic acid (10 %) was cooled and stirred mechanically for 30 min at 2-4 ºC. To this solution bromine (0.01 mol, 1.6 ml in 6 ml glacial acetic acid) was added drop wise at such a rate to keep the temperature of the solution below 10ºC throughout the addition. After all the bromine was added (105 min), stirring was continued for an additional 6 h at room temperature. The precipitate of hydrochloric salt of benzothiazole was filtered, washed with acetic acid and dried. Separated hydrochloric salt was dissolved in hot water and neutralized with aqueous ammonia solution (25 %), filtered, washed with water, dried and recrystallized with benzene to obtain 6-chloro-2-benzothiazolamine (2).

Yield: 73 %; m. p. 209-211 °C; IR (KBr, cm^{-1}): 3410 (N-H), 3080 (CH-Ar), 1580 (C=N), 1280 (C-N),

612 (C-S-C, benzothiazole), 1080 (C-Cl, benzothiazole);^{1}HNMR (300 MHz, DMSO-d_6, δ ppm): 6.78-6.70 (m, 3H, Ar-H), 7.14 (s, 2H, NH_2, D_2O exchangeable); MS (m/z): 183 [M$^+$]; Anal. Calcd. for $C_7H_5ClN_2S$: C, 45.53 %; H, 2.73 %; N, 15.17 %. Found: C, 45.52 %; H, 2.70 %; N, 15.15 %.

Synthesis of 6-chlorobenzothiazol-2-yl-hydrazine (3)

General procedure

In a flat bottomed flaskconc. HCl (6 ml) was added drop wise with stirring to hydrazine hydrate (99 %, 6 ml) at 5-10 ºC. To it ethylene glycol (24 ml) and compound (2) (0.03 mol) were added in portions and refluxed for 3 h. On cooling white solid separate out, which was filtered, washed with water and recrystallized from ethanol (3). Yield: 82 %; m. p. 220-224 °C; IR (KBr, cm^{-1}): 3330 (N-H), 3015 (CH-Ar), 1462 (C=N),1250 (C-N), 690 (C-S-C, benzothiazole), 970 (C-Cl, benzothiazole);^{1}HNMR(300 MHz, DMSO-d_6, δ ppm): 4.93 (s, 2H, NH_2), 9.12 (s, 1H,-NHN, D_2O exchangeable), 7.12-6.92 (m, 3H, Ar-H); MS (m/z): 199 [M$^+$]; Anal. Calcd. for $C_7H_6ClN_3S$: C, 42.11 %; H, 3.03 %; N, 21.05 %. Found: C, 42.13 %; H, 3.05 %; N, 21.07 %.

Synthesis of 6-chlorobenzothiazol-2-yl-hydrazones (4a-g)

General procedure

A mixture of 6-chlorobenzothiazole-2-yl hydrazine (3) (1.5 mmol)

and appropriate aromatic ketones(2.2 mmol) in absolute ethanol (60 ml) containing glacial acetic acid (4-5 drops) was taken and refluxed for 5-13 h on water bath. (Till a different spot on TLC may appear).

On cooling solid separated out, which was filtered, washed with little water and recrystallized from absolute alcohol to get hydrazones (4a-g).

6-chloro-2-(-2-[1-(4-chlorophenyl)ethylidene]hydrazinyl)-1,3-benzothiazole (4a)

Yield: 56 %; m. p. 175-177 °C; IR (KBr, cm^{-1}): 3356 (N-H), 1622 (C=N),1254 (C-N), 680 (C-S-C, benzothiazole), 1004 (C-Cl, benzothiazole); ^{1}HNMR(300 MHz, DMSO-d_6, δ ppm): 4.52 (s, 1H, NH), 2.32 (s, 3H, CH_3-C=N-, D_2O exchangeable), 6.84-7.12 (m, 3H, Ar-H);MS (m/z): 336 [M^+]; Anal. Calcd. for $C_{15}H_{11}Cl_2N_3S$: C, 53.61 %; H, 3.02 %; N, 12.50 %. Found: C, 53.70 %; H, 3.07 %; N, 12.40 %.

2-(-2-[1-(4-bromophenyl) ethylidene]hydrazinyl)-6-chloro-1,3-benzothiazole (4b)

Yield: 58 %; m. p. 148-150 °C; IR (KBr, cm^{-1}): 3256 (N-H), 1592 (C=N),1258 (C-N), 698 (C-S-C), 570 (C-Br); ^{1}HNMR(300 MHz, DMSO-d_6, δ ppm): 4.42 (s, 1H, NH, D_2O exchangeable), 2.30 (s, 3H, CH_3-C=N-), 7.84-7.92 (m, 3H, Ar-H);MS (m/z): 379[M^+]; Anal. Calcd. for $C_{15}H_{11}BrClN_3S$: C, 42.11 %; H, 3.03 %; N, 21.05 %. Found: C, 42.17 %; H, 3.15 %; N, 21.17 %.

6-chloro-2-(-2-[1-(4-nitrophenyl) ethylidene] hydrazinyl)-1,3-benzothiazole (4c)

Yield: 62 %; m. p. 182-184 °C; IR (KBr, cm^{-1}): 3368 (N-H), 1632 (C=N), 1144 (C-N), 587 (C-S-C), 1320 (C-NO_2); ^{1}HNMR(300 MHz, DMSO-d_6, δ ppm): 4.38 (s, 1H, NH, D_2O exchangeable), 2.33 (s, 3H, CH_3-C=N-), 7.82-8.12 (m, 3H, Ar-H); MS (m/z): 346 [M^+]; Anal. Calcd. for $C_{15}H_{11}ClN_4O_2S$: C, 51.95 %; H, 3.20 %; N, 16.16 %. Found: C, 51.96 %; H, 3.26; % N, 16.26%.

4-(1-[2-(6-chloro-1,3-benzothiazol-2-yl)hydrazinylidene]ethyl phenol (4d)

Yield: 45 %; m. p. 194-196 °C; IR (KBr, cm^{-1}): 3275 (N-H), 1643 (C=N),1056 (C-N), 602 (C-S-C), 3400 (OH); ^{1}HNMR(300 MHz, DMSO-d_6, δ ppm): 4.38 (s, 1H, NH, D_2O exchangeable), 2.33 (s, 3H, CH_3-C=N-), 7.82-8.12 (m, 3H, Ar-H) 10.2 (s, 1H, Ar-OH);MS (m/z): 317 [M^+]; Anal. Calcd. for $C_{15}H_{12}ClN_3OS$: C, 56.69 %; H, 3.81 %; N, 13.22 %. Found: C, 56.75 %; H, 3.85 %; N, 13.34 %.

6-chloro-2-(-2-[1-(4-methoxyphenyl)ethylidene]hydrazinyl)-1,3-benzothiazole (4e)

Yield: 53 %; m. p. 138-140 °C; IR (KBr, cm^{-1}): 3368 (N-H), 1582 (C=N),1214 (C-N), 684 (C-S-C); ^{1}HNMR(300 MHz, DMSO-d_6, δ ppm): 4.48 (s, 1H, NH, D_2O exchangeable), 2.40 (s, 3H, CH_3-C=N-), 7.62-7.72 (m, 3H, Ar-H), 3.85 (s, 3H, OCH_3); MS (m/z): 332 [M^+]; Anal. Calcd. for $C_{16}H_{14}ClN_3OS$: C, 57.93 %; H, 4.25%; N, 12.66% Found: C, 58.05%; H, 4.32 %; N, 12.72 %.

6-chloro-2-(-2-[1-(4-fluorophenyl) ethylidene]hydrazinyl)-1,3-benzothiazole (4f)

Yield: 46 %; m. p. 210-212 °C; IR (KBr, cm^{-1}): 3320 (N-H), 1618 (C=N),1068 (C-N), 670 (C-S-C), 1234 (C-F); ^{1}HNMR(300 MHz, DMSO-d_6, δ ppm): 4.28 (s, 1H, NH, D_2O exchangeable), 2.26 (s, 3H, CH_3-C=N-), 7.78-8.22 (m, 3H, Ar-H); MS (m/z): 320 [M^+]; Anal. Calcd. for $C_{15}H_{11}ClFN_3S$: C, 56.34 %; H, 3.57 %; N, 13.14 %. Found: C, 56.42 %; H, 3.59 %; N, 13.23 %.

4-(1-[2-(6-chloro-1,3-benzothiazol-2-yl)hydrazinylidene] ethyl)aniline (4g)

Yield: 64 %; m. p. 200-202 °C; IR (KBr, cm^{-1}): 3430 (NH_2), 3278 (N-H), 1582 (C=N), 1172(C-N), 658 (C-S-C); ^{1}HNMR (300MHz, DMSO-d_6, δ ppm): 4.32 (s, 1H, NH, D_2O exchangeable), 2.38 (s, 3H, CH_3-C=N-), 7.78-8.20 (m, 3H, Ar-H), 3.20 (s, 2H, NH_2); MS (m/z): 317 [M^+]; Anal. Calcd. for $C_{15}H_{13}ClN_4S$: C, 56.91 %; H, 4.14 %; N, 17.68 %. Found: C, 56.86 %; H, 4.22 %; N, 17.70 %.

Synthesis of 2-[3-(4-substitutedphenyl)-4-formyl-pyrazol-1-yl]-6-chloro benzothiazoles (5a-g)

General procedure

To the Vilsmeier-Haack reagent prepared from DMF (10 ml) and $POCl_3$ (1.1 ml, 12 mmol), hydrazone(4 mmol) was added and the reaction mixture was irradiated in microwave oven for 45-120 s. After completion of the reaction each reaction mixture was poured into ice cold water. The solid that separated on neutralization with $NaHCO_3$ was filtered, washed with water and recrystallized from $CHCl_3$-EtOH to get final compound. By following similar procedures compounds (5a-g) were synthesized.

2-[3-(4-chlorophenyl)-4-formyl-pyrazol-1-yl]-6-chloro benzothiazole (5a)

Yield: 45 %; m. p. 180-183 °C; IR (KBr, cm^{-1}): 1720 (C=O), 2780, 2878 (CH-Ar); ^{1}HNMR(300 MHz, DMSO-d_6, δ ppm): 9.05 (s, 1H, pyrazole, D_2O exchangeable), 9.95 (s, 1H, CHO), 7.54-7.52 (m, 3H, Ar-H), 7.94 (s, 2H, Ar-H), 8.06-8.03(m, 2H, Ar-H); MS (m/z): 373 [M^+]; Anal. Calcd. for $C_{17}H_9Cl_2N_3OS$: C, 54.58 %; H, 2.44 %; N, 11.24 % Found: C, 54.86; % H, 2.52 %; N, 11.30 %.

2-[3-(4-bromphenyl)-4-formyl-pyrazol-1-yl]-6-chloro benzothiazole (5b)

Yield: 53 %; m. p. 197-200 °C; IR (KBr, cm^{-1}): 1622 (C=O), 2770, 2885 (CH-Ar); ^{1}HNMR(300 MHz, DMSO-d_6, δ ppm): 9.02 (s, 1H, pyrazole, D_2O exchangeable), 9.94 (s, 1H, CHO), 7.44-7.34(m, 3H, Ar-H), 7.94 (s, 2H, Ar-H), 8.14-8.04(m, 2H, Ar-H); MS (m/z): 416 [M^+]; Anal. Calcd. for $C_{17}H_9ClBrN_3OS$: C, 48.77 %; H, 2.14 %; N, 10.06 %. Found: C, 48.86 %; H, 2.22 %; N, 10.15 %.

2-[3-(4-nitrophenyl)-4-formyl-pyrazol-1-yl]-6-chloro benzothiazole (5c)

Yield: 48 %; m. p. 230-232 °C; IR (KBr, cm^{-1}): 1706 (C=O), 2710, 2875(CH-Ar); ^{1}HNMR(300 MHz,-DMSO-d_6, δ ppm): 9.10 (s, 1H, pyrazole, D_2O exchangeable), 9.84 (s, 1H, CHO), 7.52-7.40 (m, 3H, Ar-H), 7.94 (s, 2H, Ar-H), 8.18-7.96 (m, 2H, Ar-H); MS (m/z): 385 [M^+]; Anal. Calcd. for $C_{17}H_9ClN_4SO_3$: C, 53.07 %; H, 2.38 %; N, 14.58 %. Found: C, 53.16 %; H, 2.32 %; N, 14.70 %.

2-[3-(4-hydroxyphenyl)-4-formyl-pyrazol-1-yl]-6-chloro benzothiazole (5d)

Yield: 55 %; m. p. 178-180 °C; IR (KBr, cm^{-1}): 1690 (C=O), 2768, 2880 (CH-Ar); ^{1}HNMR(300 MHz, DMSO-d_6, δ ppm): 9.16(s, 1H, pyrazole, D_2O exchangeable), 9.98 (s, 1H, CHO), 7.62-7.52 (m, 3H, Ar-H), 7.83 (s, 2H, Ar-H), 8.26-8.10 (m, 2H, Ar-H); MS (m/z): 355 [M^+]; Anal. Calcd. for $C_{17}H_{10}ClN_3SO_2$: C, 57.40 %; H, 2.85 %; N, 11.85 %. Found: C, 57.56 %; H, 2.92 %; N, 11.80 %.

2-[3-(4-methoxyphenyl)-4-formyl-pyrazol-1-yl]-6-chloro benzothiazole (5e)

Yield: 56 %; m. p. 280-283 °C; IR (KBr, cm^{-1}): 1712 (C=O), 2775, 2876(C-H); ^{1}HNMR (300 MHz, DMSO-d_6, δ ppm): 9.08 (s, 1H, pyrazole, D_2O exchangeable), 9.95 (s, 1H, CHO), 7.72-7.68 (m, 3H, Ar-H), 7.98 (s, 2H, Ar-H), 7.98-7.86 (m, 2H, Ar-H); MS (m/z): 369 [M^+]; Anal. Calcd. for $C_{18}H_{12}ClN_3SO_2$: C, 58.46 %; H, 3.28 %; N, 11.38 %. Found: C, 58.56 %; H, 3.26 %; N, 11.56 %.

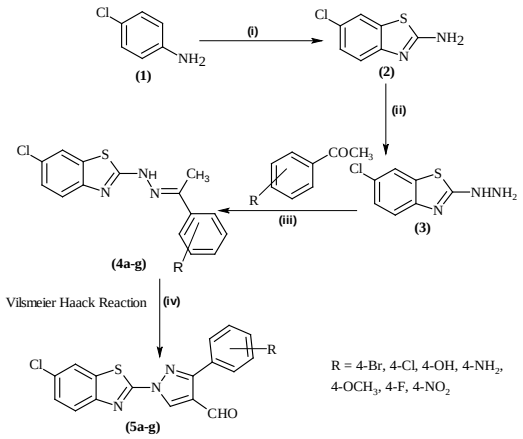
2-[3-(4-fluorophenyl)-4-formyl-pyrazol-1-yl]-6-chloro benzothiazole (5f)

Yield: 49 %; m. p. 267-270 °C; IR (KBr, cm^{-1}): 1708 (C=O), 2769, 2803 (C-H); ^{1}HNMR(300 MHz, DMSO-d_6, δ ppm): 9.04 (s, 1H, pyrazole, D_2O exchangeable), 9.80 (s, 1H, CHO), 7.77-7.66 (m, 3H, Ar-H), 7.94 (s, 2H, Ar-H), 7.84-7.71 (m, 2H, Ar-H); MS (m/z): 357 [M^+]; Anal. Calcd. for $C_{17}H_9ClFN_3OS$: C, 57.08 %; H, 2.56 %; N, 11.78 %. Found: C, 57.16 %; H, 2.59 %; N, 11.85 %.

2-[3-(4-aminophenyl)-4-formyl-pyrazol-1-yl]-6-chloro benzothiazole (5g)

Yield: 52 %; m. p. 146-150 °C; IR (KBr, cm^{-1}): 1682 (C=O), 2786, 2890(C-H); ^{1}HNMR(DMSO-d_6, δ ppm): 9.12 (s, 1H, pyrazole, D_2O exchangeable), 9.95 (s, 1H, CHO), 7.79-7.68 (m, 3H, Ar-H), 7.94 (s, 2H, Ar-H), 7.78-7.66 (m, 2H, Ar-H); MS (m/z): 355 [M^+]; Anal. Calcd.

for $C_{17}H_{11}ClN_4OS$: C, 57.56 %; H, 3.14 %; N, 15.80 %. Found: C, 57.62 %; H, 3.22 %; N, 15.75 %.



Scheme 1: Reagents and Conditions (i) Glacial acetic acid, KSCN, Br_2, Stirring 10 h (ii) $NH_2.NH_2.H_2O$, ethylene glycol, reflux for 3 h (iii) ethanol, reflux 5 h. (iv) DMF/$POCl_3$, MWI

Antibacterial activity

In vitro antibacterial activity of the synthesized compounds (5a-g) was examined against Gram positive bacteria [*Staphylococcus aureus* (ATCC-25923)] and Gram-negative bacteria [*Escherichia coli* (ATCC-25922), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae* (MTCC-432)] by measuring zone of inhibition.

The antibacterial activity was performed by disc diffusion method at the concentration level of 100 µg/ml. Norfloxacin was used as the standard drug at a concentration of 100 µg/ml. Nutrient agar was used as culture media and DMSO was used as the solvent control. The results of antibacterial activity of synthesized compounds are shown in table 1.

Antifungal activity

In vitro antifungal activity of the synthesized compounds (5a-g) was examined against *Aspergillus niger* (MTCC-281) and *Candida albicans* (ATCC 2099)by measuring the zone of inhibition. The antifungal activity was performed by disc diffusion method at the concentration level of 100 µg/ml. Ketoconazole was used as the reference drug for antifungal activity at the concentration level of 100 µg/ml. Sabouraud dextrose agar was used as culture media and DMSO was used as the solvent control. The results of antifungal activity of synthesized compounds are shown in table 2.

Table 1: Antibacterial activity of the title compounds (5a-g)

Compound	Inhibition rate [a](%)			
	S. aureus (ATCC-25923)	***E. coli (ATCC-25922)***	***P. aeruginosa (ATCC-27853)***	***K. pneumoniae (MTCC-432)***
5a	72±1.6	80±0.9	75±3.5	71±1.9
5b	89±1.7	80±1.2	88±3.8	94±1.0
5c	94±2.9	93±2.5	94±2.8	94±1.2
5d	44±0.9	53±1.1	50±1.6	53±0.9
5e	50±2.4	60±1.2	63±1.9	59±2.6
5f	39±2.7	53±3.2	50±2.2	53±3.2
5g	50±3.9	53±2.4	56±3.4	53±3.8
Norfloxacin	100±3.7	100±4.9	100±4.2	100±4.8

[a]Average of three replicates, MIC at 100 µg/ml

Table 2: Antifungal activity of the title compounds (5a-g)

Compound	Inhibition rate [a](%)	
	A. niger (MTCC-281)	***C. albicans (ATCC 2099)***
5a	79±2.3	80±1.4
5b	86±3.6	80±1.8
5c	93±4.4	93±2.2
5d	57±1.8	53±2.7
5e	57±2.6	60±3.1
5f	71±3.8	60±4.2
5g	64±5.1	67±3.7
Ketoconazole	100±3.5	100±4.5

[a]Average of three replicates, MIC at 100 µg/ml

RESULTS AND DISCUSSION

The synthesis of various 2-[3-(4-substitutedphenyl)-4-formyl-pyrazol-1-yl]-6-chloro benzothiazole derivatives (5a-g) was accomplished as presented in Scheme 1. It involves the cyclization of p-chloro amine and formation of compound (2), through KSCN then involves the reaction of hydrazine hydrate with compound (2) in the presence of ethylene glycol and formation of compounds (4a-g) through reaction of different methyl phenyl ketones in the presence of ethanol and compound (3) by refluxing for 6 h.

Then Vilsmeier Haack reaction was applied to benzothiazole hydrazones (4a-g) under MWI for 45-120 s to obtain corresponding formylated pyrazolyl benzothiazoles (5a-g)in fairly good yields. The structures of all the new synthesized compounds have been confirmed through their elemental analysis, IR and ^{1}HNMR, and mass spectra. The IR spectra exhibited a strong characteristic band in the region 1690-1720 cm^{-1} due to C=O (str.), and a weak band in the region 2730-2785 cm^{-1} due to C-H (str.) of the aldehyde group present in the pyrazole ring while their ^{1}HNMR spectra showed two sharp singlets at δ 9.05 and δ 9.95 confirmed the presence of C_5-H of the pyrazole ring and C-H of the C_4-aldehyde group respectively. The synthesized compounds were evaluated for their anti-bacterial activity against *S. aureus*, *E. coli*, *P. aeruginosa* and *K. pneumoniae* and anti-fungal activity against *A. niger* and *C. albicans*. TheCompounds 5c, 5b, 5a, showed excellent anti-bacterialand antifungal activity due to substitution of electron withdrawing groups (Cl, Br, NO_2) on 4-position of phenyl ring while the activity is sharply decreased by the substitution of electron donating (OCH_3, NH_2, OH) groups at 4-position of phenyl ring. Compounds 5c, 5b, 5a were also found to have good activity against*A. niger* and *C. albicans*.

CONCLUSION

Herein, we have described an efficient and convenient synthesis of a new series of 2-[3-(substituted phenyl)-4-formylpyrazol-1-yl]-6-chloro benzo thiazole derivatives (5a-g). The structures of these new heterocyclic compounds containing both aminobenzo thiazole and pyrazole ring systems were confirmed by spectral (IR, ^{1}HNMR, Mass) and elemental analysis (C, H, N) analysis and were evaluated for their *in vitro* antibacterial and antifungal activities. The compounds with electron withdrawing groups on 6-position of benzothiazole ring and 4-position of the phenyl ring showed excellent antibacterial and antifungal activities. Thus, the significant antibacterial and antifungal profiles of 6-chloro-1,3-benzothiazolyl-2-yl pyrazole derivatives offer as promising lead molecules for further synthesis of potent compounds of this series.

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CONFLICT OF INTERESTS

Declared None

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