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Synthesis, characterization and antimicrobial evaluation of some new 1, 3-benzothiazole derivatives containing pyrazole moiety

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Abstract
A series of 2-[3-(substituted phenyl)-4-formylpyrazol-1-yl]-6-methoxy Benzothiazole derivatives **(5a-g)** were synthesized in satisfactory yield and were evaluated for their antimicrobial activity. All the synthesized compounds were evaluated for their *in vitro* antibacterial activities against four pathogenic bacterial strains, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and two fungal strains *Aspergillus niger* and *Candida albicans* by disc diffusion method. Compounds **5c, 5b, 5a, 5d** were found to be most active. All the synthesized compounds were in good agreement with elemental and spectral data (FT-IR, ^{1}HNMR and mass spectroscopy).

Keywords: 1, 3-benzothiazole pyrazole derivatives, Antibacterial, Antifungal, Antimicrobial

1. Introduction
Benzothiazole is a privileged bicyclic ring system with multiple therapeutic applications. It has great pharmaceutical importance; hence synthesis of compounds with benzothiazole ring scaffold is of considerable interest now a day. Benzothiazole is an important ring system of drugs, possessing several pharmacological functions, rendering this molecule and its derivatives as powerful antimicrobial agents [4, 5, 6], anticancer [7, 12, 13], anthelmintic [11], antidiabetic [9], anticonvulsant [1], anti-inflammatory [8], and amyloid imaging agent in Alzheimer's disease [10].
Benzothiazole derivatives have wide spectrum of biological activities hence the present study was undertaken in order to synthesize new compounds having benzothiazole ring fused with pyrazole ring to enhance the antimicrobial properties of compounds [2, 3].
Therefore, in the view of development of new heterocyclic compounds with potential antimicrobial activities we report to synthesize a new series of 1, 3-benzothiazole pyrazole derivatives **(5a-g)**. All the new compounds were characterized by elemental and spectral analysis and screened for their *in vitro* antibacterial and antifungal activities.

2. 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 were recorded downfield on VNMRS-500 "Agilent-NMR" using (TMS) tetra methyl 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.

3. Experimental Section
Synthesis of 6-methoxy-2-benzothiazolamine 1
A mixture of p-methoxy aniline (0.01 mol) and potassium thiocyanate (0.01 mol) in 150 ml glacial acetic acid (10 %) was cooled and stirred mechanically for 30 minutes at 2-4 ºC. To this bromine solution (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 10 ºC throughout the addition. After all the bromine was added (105 min), stirring was continued for an additional 6h 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 ethanol to obtain 6-methoxy-2-benzothiazolamine **2**.

IR (υ cm^{-1}, KBr): 3330 (NH str), 3015 (CH-Ar), 1580 (C=N), 709 (C-S-C), 1272 (C-N)

^{1}**HNMR** (300 MHz, DMSO-d_6, δ ppm): 3.82 (s, 3H of OCH_3), 6.68 (s, 2H of NH_2), 7.26-7.06 (m, 3H of Ar-H); MS (m/z) 185 [M^+]; Anal. Calcd. for $C_8H_8N_2OS$: C, 53.31; H, 4.47; N, 15.54 Found: C, 53.21; H, 4.28; N, 15.24.

Synthesis of 6-methoxybenzothiazol-2-yl-hydrazine 3: Conc. 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 3hrs. On cooling white solid separate out, which was filtered, washed with water and recrystallized from ethanol **3**.

IR (υ cm^{-1}, KBr): 3330 (NH str), 3015 (CH-Ar), 1462 (C=N), 690 (C-S-C), 1190 (C-N)

^{1}**HNMR** (300 MHz, DMSO-d_6, δ ppm): 2.58 (s, 3H of OCH_3), 7.02 (s, 2H of NH_2), 7.13-7.03 (m, 3H of Ar-H), 9.04 (s, 1H of -NHN, D_2O exchangeable); MS (m/z) 195 [M^+]; Anal. Calcd. for $C_8H_9N_3OS$: C, 49.21; H, 4.65; N, 21.52; Found: C, 49.80; H, 4.46; N, 21.30.

Synthesis of 6-methoxybenzothiazol-2-yl-hydrazones 4a-g: A mixture of 6-methoxybenzothiazole-2-yl hydrazine **3** (1.5 mmole) and appropriate aromatic substituted ketones (2.2 mmole) in absolute ethanol (60 ml) containing glacial acetic acid (4-5 drops) was taken and refluxed for 5-13 hrs on water bath. On cooling solid separated out, which was filtered, washed with little water and recrystallized from absolute alcohol to get hydrazones **4a-g**.

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

IR (υ cm^{-1}, KBr) 4a-g: 3250 (NH str.), 1617 (C=N str.), 685 (C-S-C),
1120 (C-N), 1080 (C-Cl); ^{1}**HNMR** (300 MHz, DMSO-d_6, δ ppm) 2.33 (s, 3H, CH_3-C=N-, D_2O exchangeable), 3.86 (s, 3H, C_6-OCH_3), 4.73 (s, 1H, NH), 6.98-7.12 (m, 3H, Ar-H); MS (m/z) 195 [M^+]; Anal. Calcd. for $C_{16}H_{14}ClN_3SO$: C, 57.91; H, 4.25; N, 12.66. Found: C, 57.85; H, 4.08; N, 12.38

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

IR (KBr, cm^{-1}): 3258 (NH str), 1588 (C=N),1260 (C-N), 685 (C-S-C), 596 (C-Br); ^{1}**HNMR (300 MHz, DMSO-d_6, δ ppm):** 4.32 (s, 1H, NH, D_2O exchangeable), 2.32 (s, 3H, CH_3-C=N-), 7.85-7.92 (m, 3H, Ar-H); MS (m/z) 365 [M^+]; Anal. Calcd. for $C_{16}H_{14}BrN_3SO$: C, 51.05; H, 3.72; N, 11.16. Found: C, 50.94; H, 3.70; N, 11.02

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

IR (KBr, cm^{-1}): 3368 (NH), 1632 (C=N), 1144 (C-N), 590 (C-S-C), 1320 (C-NO_2); ^{1}**HNMR (300 MHz, DMSO-d_6, δ ppm):** 4.35 (s, 1H, NH, D_2O exchangeable), 2.32 (s, 3H, CH_3-C=N), 7.80-8.10 (m, 3H, Ar-H); MS (m/z): 342 [M^+]; Anal. Calcd. for $C_{16}H_{14}N_4O_3S$:
C, 56.12; H, 4.10; N, 16.60. Found: C, 56.03; H, 4.03; N, 16.56

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

IR (KBr, cm^{-1}): 3274 (NH), 1640 (C=N),1058 (C-N), 612 (C-S-C), 3410 (OH); ^{1}**HNMR (300 MHz, DMSO-d_6, δ ppm):** 4.40 (s, 1H, NH, D_2O exchangeable), 2.35 (s, 3H, CH_3-C=N-), 7.82-8.10 (m, 3H, Ar-H) 5.3 (s, 1H, Ar-OH); MS (m/z): 312 [M^+]; Anal. Calcd. for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.40. Found: C, 61.10; H, 4.67; N, 13.22

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

IR (KBr, cm^{-1}): 3268 (NH), 1682 (C=N),1224 (C-N), 694 (C-S-C); ^{1}**HNMR (300 MHz, DMSO-d_6, δ ppm):** 4.46 (s, 1H, NH, D_2O exchangeable), 2.42 (s, 3H, CH_3-C=N-), 7.62-7.72 (m, 3H, Ar-H), 3.84 (s, 3H, Ar-OCH_3), 3.98 (s, 3H, Ar-OCH_3); MS (m/z): 326 [M^+]; Anal. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.35; H, 5.23; N, 12.83. Found: C, 62.02; H, 5.04; N, 12.64

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

IR (KBr, cm^{-1}): 3325 (NH), 1610 (C=N),1065 (C-N), 675 (C-S-C), 1230 (C-F); ^{1}**HNMR (300 MHz, DMSO-d_6, δ ppm):** 4.26 (s, 1H, NH, D_2O exchangeable), 2.25 (s, 3H, CH_3-C=N-), 7.77-8.20 (m, 3H, Ar-H), 3.98 (s, 3H, -OCH_3); MS (m/z): 315 [M^+]; Anal. Calcd. for $C_{16}H_{14}FN_3SO$: C, 60.94; H, 4.47; N, 13.32. Found: C, 60.67; H, 4.20; N, 13.15

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

IR (KBr, cm^{-1}): 3420 (NH_2), 3268 (NH str), 1572 (C=N), 1162 (C-N), 657 (C-S-C); ^{1}**HNMR (300 MHz, DMSO-d_6, δ ppm):** 4.32 (s, 1H, NH, D_2O exchangeable), 2.36 (s, 3H, CH_3-C=N-), 7.68-7.80 (m, 3H, Ar-H), 5.24 (s, 2H, NH_2), 3.78 (s, 3H, Ar-OCH_3); MS (m/z): 312 [M^+]; Anal. Calcd. for $C_{16}H_{16}N_4SO$: C, 61.52; H, 5.16; N, 17.92. Found: C, 61.40; H, 5.00; N, 17.68

Synthesis of 2-[3-(4-substitutedphenyl)-4-formyl-pyrazol-1-yl]-6-methoxy benzothiazoles 5a-g: To the Vilsmeier-Haack reagent prepared from DMF (10 ml) and $POCl_3$ (1.2 ml, 12 mmol), hydrazones **4a-g** (4 mmol) were added separately and the reaction mixtures were 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 compounds **5a-g**.

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

IR (KBr, cm^{-1}): 1725 (C=O), 2783, 2868 (CH-Ar); ^{1}**HNMR (300 MHz, DMSO-d_6, δ ppm):** 9.04 (s, 1H, pyrazole, D_2O exchangeable), 9.94 (s, 1H, CHO), 7.54-7.50 (m, 3H, ArH), 7.92 (s, 2H, ArH), 8.16 -8.13(m, 2H, ArH); MS (m/z): 368 [M^+]; Anal. Calcd. for $C_{18}H_{12}ClN_3O_2S$: C, 58.46; H, 3.27; N, 11.36 Found: C, 58.40; H, 3.24; N, 11.28

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

IR (KBr, cm^{-1}): 1628 (C=O), 2775, 2875 (CH-Ar); ^{1}**HNMR (300 MHz, DMSO-d_6, δ ppm):** 9.04 (s, 1H, pyrazole, D_2O exchangeable), 9.96 (s, 1H, CHO), 7.44 -7.34(m, 3H, ArH), 7.94 (s, 2H, ArH), 8.14-8.04(m, 2H, ArH); MS (m/z): 412 [M^+]; Anal. Calcd. for $C_{18}H_{12}BrN_3O_2S$: C, 52.19; H, 2.91; N, 10.14. Found: C, 52.04; H, 2.78; N, 10.08

2-[3-(4-nitrophenyl)-4-formyl-pyrazol-1-yl]-6-methoxy benzothiazole 5c:
IR (KBr, cm^{-1}): 1716 (C=O), 2712, 2874 (CH-Ar); **^{1}HNMR (300 MHz, DMSO-*d*$_6$, δ ppm):** 9.12 (s, 1H, pyrazole, D_2O exchangeable), 9.86 (s, 1H, CHO), 7.52-7.40 (m, 3H, ArH), 7.96 (s, 2H, ArH), 8.20-7.98 (m, 2H, ArH); MS (m/z): 380 [M$^+$]; Anal. Calcd. for $C_{18}H_{12}N_4SO_4$: C, 56.84; H, 3.18; N, 14.70. Found: C, 56.73; H, 2.15; N, 14.57

2-[3-(4-hydroxyphenyl)-4-formyl-pyrazol-1-yl]-6-methoxy benzothiazole 5d:
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, ArH), 7.83 (s, 2H, ArH), 8.26-8.10 (m, 2H, ArH), 5.2 (Ar-OH); MS (m/z): 350 [M$^+$]; Anal. Calcd. for $C_{18}H_{13}N_3SO_3$: C, 61.53; H, 3.73; N, 11.96. Found: C, 61.44; H, 3.65; N, 11.78

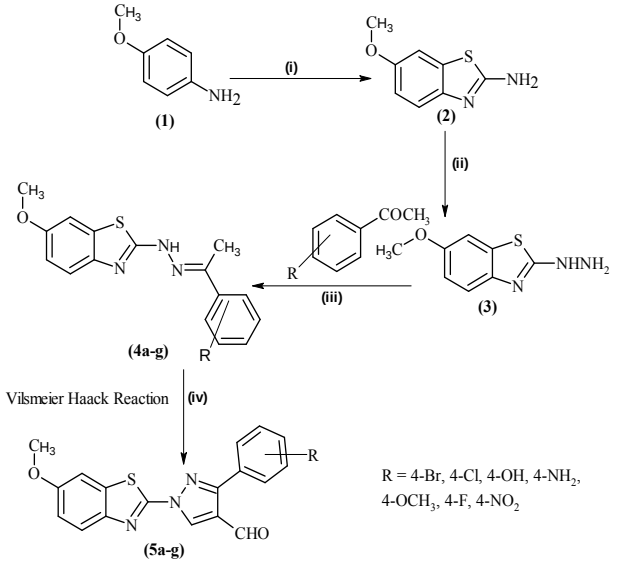
2-[3-(4-methoxyphenyl)-4-formyl-pyrazol-1-yl]-6-methoxy benzothiazole 5e:
IR (KBr, cm^{-1}): 1712 (C=O), 2775, 2876 (C-H); **^{1}HNMR (300 MHz, DMSO-*d*$_6$, δ ppm):** 9.08 (s, 1H, pyrazole, D_2O exchangeable), 9.95 (s, 1H, CHO), 7.72-7.68 (m, 3H, ArH), 7.98 (s, 2H, ArH), 7.98-7.86 (m, 2H, ArH); MS (m/z): 365 [M$^+$]; Anal. Calcd. for $C_{19}H_{15}N_3SO_3$: C, 62.45; H, 4.14; N, 11.50 Found: C, 62.32; H, 4.10; N, 11.44

2-[3-(4-fluorophenyl)-4-formyl-pyrazol-1-yl]-6-methoxy benzothiazole 5f:
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, ArH), 7.94 (s, 2H, ArH), 7.84-7.71 (m, 2H, ArH); MS (m/z): 353 [M$^+$]; Anal. Calcd. for $C_{18}H_{12}FN_3O_2S$: C, 61.18; H, 3.42; N, 11.89. Found: C, 61.02; H, 3.30; N, 11.67

2-[3-(4-aminophenyl)-4-formyl-pyrazol-1-yl]-6-methoxy benzothiazole 5g:
IR (KBr, cm^{-1}): 1688 (C=O), 2785, 2892 (C-H); **^{1}HNMR (300 MHz, DMSO-*d*$_6$, δ ppm):** 9.10 (s, 1H, pyrazole, D_2O exchangeable), 9.93 (s, 1H, CHO), 7.77-7.68 (m, 3H, ArH), 7.91 (s, 2H, ArH), 7.76-7.66 (m, 2H, ArH); MS (m/z): 350 [M$^+$]; Anal. Calcd. for $C_{18}H_{14}N_4O_2S$: C, 61.70; H, 4.03; N, 15.99. Found: C, 61.60; H, 3.96; N, 15.82
Physical data of all the synthesized compounds are shown in **Table 1.**

Table 1: Physical data of all the synthesized compounds 5a-g

Compound	R	Colour	Melting Point	% Yield	R*f* Value
2		White	163-166	81	0.66 (benzene/acetone 8:2)
3		White	210-214	80	0.65 (benzene/acetone 8:2)
4a	Cl	Yellow	161-163	48	0.64 (benzene/acetone 8:2)
4b	Br	Brown	177-180	50	0.79 (benzene/acetone 8:2)
4c	NO_2	Gray	186-189	40	0.76 (benzene/acetone 9:1)
4d	OCH_3	Yellow	189-192	44	0.71 (benzene/acetone 8:2)
4e	OH	White	166-170	50	0.80 (benzene/acetone 9:1)
4f	F	Gray	216-220	47	0.83($CHCl_3$/CH_3OH 9.5:0.5)
4g	NH_2	White	181-184	55	0.82($CHCl_3$/CH_3OH 9.5:0.5)
5a	Cl	Yellow	191-194	46	0.84 (benzene/acetone 8:2)
5b	Br	Brown	175-179	52	0.74 (benzene/acetone 8:2)
5c	NO_2	Gray	191-195	40	0.68 (benzene/acetone 9:1)
5d	OCH_3	Yellow	197-200	52	0.82 (benzene/acetone 8:2)
5e	OH	White	215-220	50	0.76 (benzene/acetone 9:1)
5f	F	Gray	209-214	42	0.72($CHCl_3$/CH_3OH 9.5:0.5)
5g	NH_2	White	179-182	44	0.83($CHCl_3$/CH_3OH 9.5:0.5)



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

4. Results and Discussion

4.1 Antibacterial activity

All the synthesized compounds **(5a-g)** were screened for their antibacterial potency 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 standard drug at a concentration of 100 µg/ml. Nutrient agar was used as culture media and DMSO was used as solvent control. The results of antibacterial activity are shown in **Table 2**.

4.2 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 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 solvent control. The results of antifungal activity are shown in the **Table 3**.

Table 2: Antibacterial activity of the synthesized compounds (5a-g)

Compound	Zone of Inhibition (mm)			
	S. aureus	***E. coli***	***P. aeruginosa***	***K. pneumoniae***
5a	17	16	16	16
5b	20	16	18	20
5c	21	18	19	20
5d	17	15	16	17
5e	13	13	14	15
5f	11	12	12	13
5g	13	12	13	13
Norfloxacin	22	19	20	21
DMF (Control)	-	-	-	-

Table 3: Antifungal activity of the synthesized compounds (5a-g)

Compound	Mean Zone of Inhibition (mm)	
	Aspergillus niger	***Candida albicans***
5a	14	16
5b	16	15
5c	16	16
5d	14	15
5e	10	11
5f	12	11
5g	11	12
Ketoconazole	19	18
DMF (Control)	-	-

Various 2-[3-(4-substitutedphenyl)-4-formyl-pyrazol-1-yl]-6-nitro benzothiazoles derivatives **(5a-g)** have been prepared in fairly good yields by **Scheme 1**. The structures of synthesized compounds have been confirmed by their elemental analysis, IR and ^{1}HNMR spectra. The FT-IR spectra exhibited a strong characteristic band in the region 1685-1730 cm^{-1} due to C=O (str.), and a weak band in the region 2730-2790 cm-^{1} due to C-H (str.) of the aldehyde group. The ^{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 antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and antifungal activity against *Aspergillus niger* and *Candida albicans.* Compounds **5c**, **5b**, **5a**, **5d** showed excellent antimicrobial activity while the other compounds showed moderate activity. Compounds **5c**, **5b**, **5a**, **5d** were also showed good activity against *Aspergillus niger* and *Candida albicans*.

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