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Research article

Design, synthesis, anti-infective and anti-cancer potential of thiazole based Pyrazoles bearing benzothiazole moiety

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ABSTRACT

A new series of (*E*)-6-methyl-*N*-((3-phenyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-4-yl)methylene)benzo[*d*]thiazol-2-amine derivatives was developed. Structural investigation of the synthesized derivatives was carried out by several instrumental method of analysis like IR, and ^{1}H-NMR spectroscopy. The titled analogues were examined for *in-vitro* anticancer and antiinfective activities. The biological findings specified that analogues 5a, 5b, 5d, 5e, 5f and 5g showed most potent antibacterial activity (MIC 62.5-250µg/mL) and 5a, 5e, 5f and 5g displayed most potent antifungal action (MIC 62.5-500 µg/mL) than standard drugs. Compounds 5a and 5e were reported to be most active antimalarial analogue having IC_{50} value of 0.24-0.49µg/mL. Compounds 5a, 5e and 5f showed shortest mean paralysis time of (25.6±4.56 min, 26.4±4.97 min and 26.8±4.76 min) and mean death time (47.6±8.01min, 45.6±3.04min and 46.6±7.40min), respectively. Compound 5e showed moderate cytotoxicity with IC_{50} value of 65.4 against MCF-7. The results proved that 1,3-thiazolyl-pyrazole clubbed benzothiazole derivatives showed considerable antiinfective and cytotoxic activity.

Keywords: Anti-infective activity, Cytotoxic activity, Spectroscopic methods, Thiazole, Pyrazole, Benzothiazole.

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INTRODUCTION

It is reported that the tumor is the foremost reason of death with tumor fatality rates from 9.6 million to 16.3 million in 2018 and cases can be increased continuously until 2040. According to WHO (World Health Organization), around 10 million deaths were recorded in 2020, among which lungs and breast cancers are considered to be the major cause for mortality [1-3]. A part from carcinogenic mutagen, infectious diseases like, bacterial and fungal infections have also been reported to rise globally and may also lead to the development of cancer in recent years. The occurrence of malignancy, HIV (Human immunodeficiency virus) infections are considered as plausible cause for getting infections which is further worsened by increased microbial resistance [4]. Although number of therapeutic agents have already been used against cancer cells but associated with potential drawbacks like, toxicity interaction with fewer target response. In order to cope with these serious problems, there is a significant need to develop novel heterocyclic moiety for effective prevention and control. In this regard, among heterocyclic compounds, thiazole has attracted considerable attention of researchers due to its varied spectrum of activity. Thiazole derivatives are reported to possess number of pharmacological actions *viz.* antimicrobial, antioxidant, anti-alzheimer, antihypertensive, anti-inflammatory, antidiabetic and hepatoprotective activities [5-11]. Furthermore, the thiazole core is an important component of several therapeutically utilized anticancer and anti-infective drugs. Based on aforementioned discussion, thiazoles displayed substantial potential as anti-infective and cytotoxic agents. Hence, there is a pressing need to produce thiazole-based heterocyclic congeners depending upon its favorable properties for the expansion of potent agents to solve menace of microbial resistance and should possess anti-infective and cytotoxic potential [12-15].

MATERIALS AND METHODS

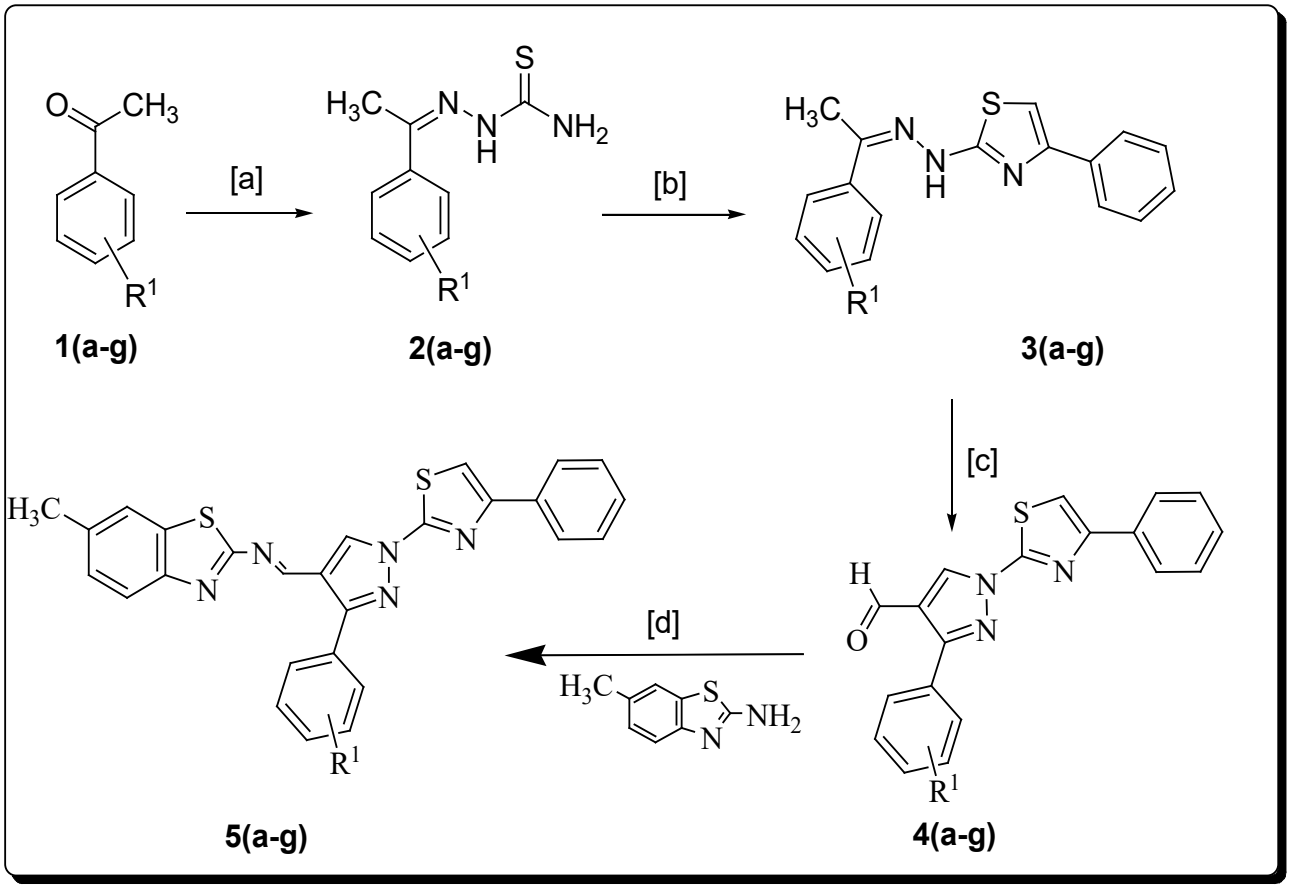
From the commercial firms namely Sigma Aldrich (Darmstadt, Germany), Rankem & Merck New Delhi (India), the chemicals and solvents were acquired and utilized without additional purification. For determining the melting points, Perfit India melting point equipment was used in open glass capillaries and the melting points were not corrected. Thin layer chromatography (TLC) was done with the help of Merck 60G F_{254} (silica gel plates), using ethyl acetate/toluene in the ratio of (10:90) to ascertain the purification of the reaction. Bruker spectrophotometer (Germany) was used for the

recordings of FT-IR spectra (4000-400 cm^{-1}) by using KBr Pellets. Bruker Avance II 400 M*Hz* model (DMSO-d_6) spectrometer using tetramethylsilane as internal standard for ^1H NMR and was performed in Panjab University Chandigarh (SAIF) Sophisticated Analytical Instrumentation Facility.

Synthesis

In the present protocol for the synthesis of thiazole derivatives, freshly produced phenacyl bromide in ethanol yielded the chemical 2-(4-(aryl) thiazol-2-yl)-1-(1-arylethylidene) hydrazine (**3**) via Hantzsch thiazole synthesis. In comparison to other functional groups on phenacyl bromide, a strong electron withdrawing group produced a better yield. Afterwards, a Vilsmeier-Haack cyclization reaction with a corresponding quantity of reagent Dimethylformamide/ Phosphorous oxychloride (DMF/$POCl_3$) at 80-90ºC for 4-5 hours yielded thiazolyl-pyrazole-4-carbaldehydes (**4**). In final step, (*E*)-6-methyl-*N*-((3-phenyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-4-yl)methylene)benzo[*d*]thiazol-2-amine derivatives (**5**) were synthesized on refluxing thiazolyl-pyrazole-4-carbaldehydes (**4**) with suitable benzothiazole amine in ethanol as solvent and fused sodium acetate [16-17]. The synthetic method used in order to develop the expected compounds is briefly described in Figure 1.

Figure 1: Scheme of synthetic steps of targeted derivatives 5(a-g).



Reagents and conditions

[**a**] Thiosemicarbazide, ethanol, H_2SO_4 3-4 drops, reflux 4h,

[**b**] $ArCOCH_2Br$, ethanol, reflux 3 h.

[**c**] DMF, $POCl_3$, heat 70-80°C, 5 h.

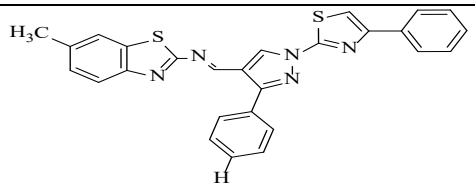
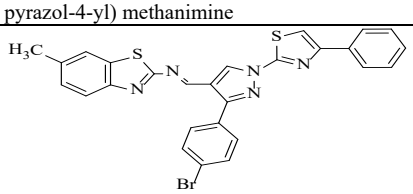
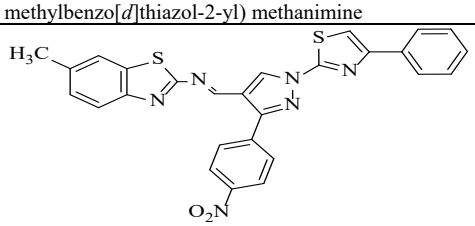
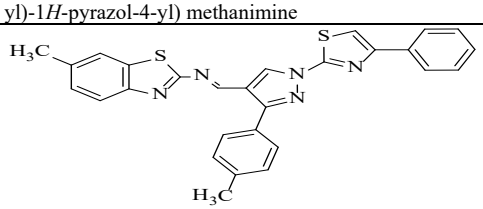
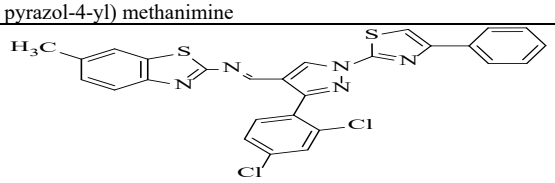
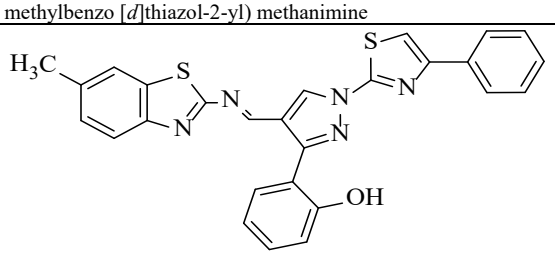
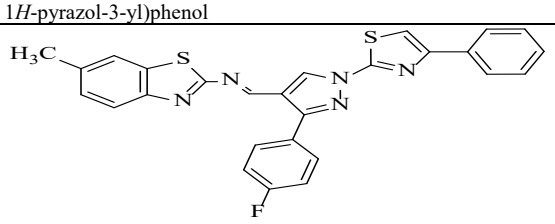
[**d**] Ethanol, fused CH_3COONa, reflux 3-4 h**.**

Table1: Physical properties of analogues (5a-5g)

Compd.	R^1	Molecular formula*	Molecular weight*	Melting point	Yield (%)	R_f Value
5a	H	$C_{27}H_{19}N_5S_2$	477.6	170-172˚C	81.8%	0.76
5b	*p*-Br	$C_{27}H_{18}BrN_5S_2$	556.5	180-182˚C	83.4%	0.75
5c	*p*-NO_2	$C_{27}H_{18}N_6O_2S_2$	522.6	185-187˚C	90.4%	0.67
5d	*p*-CH_3	$C_{28}H_{21}N_5S_2$	491.6	195-198˚C	91.1%	0.81
5e	2,4-*di*Cl_2	$C_{27}H_{17}Cl_2N_5S_2$	546.4	140-142˚C	87.4%	0.78
5f	2-OH	$C_{27}H_{19}N_5OS_2$	493.4	180-182˚C	79.5%	0.70
5g	*p*-F	$C_{27}H_{18}FN_5S_2$	495.4	165-167˚C	78.1%	0.69

**Calculated*

Table 2: Spectral data of synthesized analogues (5a-5g)

Compd.	Structures	IR (KBR, λ_{max} cm^{-1})	^{1}H-NMR (DMSO-d_6) δ, ppm (Parts per millions)
5a	 (*E*)-*N*-(6-methylbenzo[*d*]thiazol-2-yl)-1-(3-phenyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-4-yl) methanimine	3031 (C-H aromatic), 2351 (C-N), 1634 (C=C), 1372 (C=N), 3222(N-H).	8.19 (s, 1H, N=CH), 8.14 (s, 1H, thiazole), 7.85-8.02 (m, 13H, Ar-CH), 7.26 (s, 1H, pyrazole), 3.52 (s, 3H, CH_3)
5b	 (*E*)-1-(3-(4-bromophenyl)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-4-yl)-*N*-(6-methylbenzo[*d*]thiazol-2-yl) methanimine	3041 (C-H aromatic), 2359 (C-N), 1616 (C=C), 1362 (C=N), 673 (C-Br).	8.34 (s, 1H, N=CH), 8.21 (s, 1H, thiazole), 7.66-7.94 (m, 12H, Ar-CH), 7.35 (s, 1H, pyrazole), 3.51 (s, 3H, CH_3)
5c	 (*E*)-*N*-(6-methylbenzo[*d*]thiazol-2-yl)-1-(3-(4-nitrophenyl)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-4-yl) methanimine	3004 (C-H aromatic), 2376 (C-N), 1683 (C=C), 1396 (C=N), 1338(NO_2).	8.28 (s, 1H, N=CH), 8.02 (s, 1H, thiazole), 7.29-7.44 (m, 12H, Ar-CH), 7.89 (s, 1H, pyrazole), 3.43 (s, 3H, CH_3)
5d	 (*E*)-*N*-(6-methylbenzo[*d*]thiazol-2-yl)-1-(1-(4-phenylthiazol-2-yl)-3-(*p*-tolyl)-1*H*-pyrazol-4-yl) methanimine	3036 (C-H aromatic), 2365 (C-N), 1682 (C=C), 1397 (C=N), 2916 (CH_3).	7.95 (s, 1H, N=CH), 7.49 (s, 1H, thiazole), 7.50-7.87 (m, 12H, Ar-CH), 7.30 (s, 1H, pyrazole), 3.33(s, 6H, CH_3)
5e	 (*E*)-1-(3-(2,4-dichlorophenyl)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-4-yl)-N-(6-methylbenzo [*d*]thiazol-2-yl) methanimine	3066 (C-H aromatic), 2350 (C-N), 1683 (C=C), 1396 (C=N), 663 (C-Cl).	7.98 (s, 1H, N=CH), 7.66 (s, 1H, thiazole), 7.51-7.62 (m, 11H, Ar-CH), 7.29 (s, 1H, pyrazole), 3.63 (s, 3H, CH_3)
5f	 (*E*)-2-(4-(((6-methylbenzo[*d*]thiazol-2-yl) imino)methyl)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-3-yl)phenol	3053 (C-H aromatic), 2360 (C-N), 1683 (C=C), 1362 (C=N), 3228 (OH).	8.33 (s, 1H, N=CH), 7.77 (s, 1H, thiazole), 7.88-8.08 (m, 12H, Ar-CH), 7.22 (s, 1H, pyrazole), 3.33 (s, 3H, CH_3), 8.58(s, 1H, OH)
5g	 (*E*)-1-(3-(4-fluorophenyl)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazol-4-yl)-N-(6-methylbenzo [*d*]thiazol-2-yl) methanimine	3068 (C-H aromatic), 2357 (C-N), 1652 (C=C), 1362 (C=N), 1155 (C-F).	8.32 (s, 1H, N=CH), 8.12 (s, 1H, thiazole), 7.79-7.96 (m, 12H, Ar-CH), 7.46 (s, 1H, pyrazole), 3.61 (s, 3H, CH_3)

Antimicrobial Assay

All the newly developed derivatives were assessed against two bacteria (Gram+ve) namely, *Staphylococcus aureus* (MicrobialType Culture Collection) (MTCC 96) and *Streptococcus pyogenus* (MTCC 442) as well as two strains (Gram-ve) *viz*. *Pseudomonas aeruginosa* (MTCC 1688) and *Escherichia coli* (MTCC 443) for their antibacterial action and antifungal potential

against *Aspergillus niger* (MTCC 282), *Aspergillus clavatus* (MTCC 1323) and *Candida albicans* (MTCC 227) through serial dilution method. By using Mueller-Hinton Broth (Hi-Media), nutritional broth, stock solutions and cultures were prepared according to normal protocol. The antibacterial evaluation was performed with dimethyl sulfoxide (DMSO) as the diluent at concentrations of 500, 250, 200, 125, 100, 62.5, 50 and 25µg/mL in order to obtain anticipated analogue concentrations for testing on standard bacterial strains. Minimum inhibitory concentration (MIC) *i.e.* the smallest concentration required to stop bacterial growth was measured in µg/mL for all newly synthesized analogues and also compared with reference drugs. While determining the antimicrobial potential, reference drugs (nystatin, ciprofloxacin, chloramphenicol, ampicillin and griseofulvin) were used for Gram+ve and Gram-ve bacteria which displayed MIC value 0.05-250 µg/mL for the same. All the evaluations were executed in duplicate and repeated three times [18-19].

Cytotoxic Assay

The MCF-7 (Breast cancer) and Hop-62 (Lung cancer) cells were obtained from ATCC (American Type Culture Collection) U.S.A and cultured in RPMI 1640 media using fetal bovine serum (10%) +2 mM L-glutamine and incubated at 37 ºC using 5% carbon dioxide and 95% air below the moistened environment for *in vitro* cytotoxicity testing. Before use, a new stock solution (0.1-100 mM) was produced and diluted in culture medium. In the experiment of SRB (Sulforhodamine-B) based cytotoxicity, the final concentration of 0.1% (DMSO) must have no effect on the cytotoxicity. A negative control of a comparable DMSO concentration in the culture media has been employed in all of the assays. Cultivated cell lines were pipetted into microtiter plate wells and allowed for incubation at 37°C (in a humidified incubator). After 24h, each cell containing two plates were incubated again (for 60 min at 4ºC) with a moderate dose of 10% w/v TCA (Tricarboxylic acid) 50 ml to get cell population reading earlier than test compounds/drugs were added (T*z*). Various doses of test analogues using lowest amount of DMSO (10, 20, 40, and 80 µg/mL) were produced, and aliquots of 10ml each were seeded into microtiter plates. After 48-hour incubation period and using the (SRB) protein assay, cell viability was determined. Following staining, an unbound dye on plates has been alienated by washing five times using acetic acid (1%) and air drying. The absorbance (A) was measured by (Enzyme linked immunosorbent assay) ELISA plate reader at max 540 nm using a reference at max 690nm after solubilizing the bound dye with 10 mM trizma base [20-21].

Antimalarial Assay

The *in-vitro* anti-malarial action has been performed on microtiter plates (96 well) accordant to the micro assay procedure of rieckmann and co-workers with significant adjustment. *P. falciparum* colonies have been kept in RPMI 1640 medium supplemented with 25Mm HEPES (4(2-hydroxyethyl)-1-piperazineethane sulphonic acid) which contain 1% (D-glucose), 0.23% ($NaHCO_3$), and 10% (heat deactivated human serum). Followed by D-sorbitol (5%) treatment, the asynchronous *P. falciparum* parasites were synchronized, resulting in only ring stage parasitized cells. In an entire quantity of 200 µl of medium RPMI-1640, an initial ring stage parasitemia of 0.8-1.5 percent at 3 percent hematocrit was resolved by J. S. Bhattacharya (JSB) staining, to examine the percentage of parasitemia (rings) and equitably preserved with fifty percent red blood cells (O^+). In DMSO, a 5mg/mL standard solution of every test illustrations was produced and culture medium is utilized for the preparation of successive dilutions. In order to get final concentration (at 5 time dilutions) range among 0.4 µg/mL in replicate well comprising parasite cell formulation, the test wells were loaded with diluted sample in the volume of 20 µl. Then cultured plates were kept in a candle jar and allowed for incubation at 37°C (36-40h). After which, from each well, a thin blood smears were produced and stained with (JSB) stain. Then monitoring of the slides was done with the help of microscope to assess the maturation of ring stage parasites into trophozoites and schizonts in existence of test agents in various concentrations. The test concentration that prevented the full progression into schizonts was verified in terms of MIC. For the reference drug, chloroquine was used [22-23].

Anthelmintic Assay

All the test analogues were analyzed for *in vitro* evaluation of their anthelmintic activity, and the findings of the activity were compared with results of standard drug (albendazole). Earthworms of about comparable size (5-6cm x 0.1-0.2cm). The earthworms were washed in a standard saline solution (0.9 % w/v) to eliminate the fecal matter and soil. The synthesized analogues, as well as the (0.2 % w/v) control, were made by starting with the smallest amount of DMSO and gradually increasing to 20 ml of (0.9 % w/v) standard saline. The synthesized analogues were placed in the petri plates of 2 inches size and in each of the 20 ml of standard and test dilution, six earthworms were placed. The control group consisted of a petri plate having (0.9 percent w/v) standard saline and possessing no test chemical. Each petridish containing six earthworms was evaluated for paralysis (loss of ability to move) and death time of individual worms up to 5 hours into the analysis period. On shaking vigorously when no movement was detected, recorded the mean paralysis time. Following that, each worm's death time was recorded by confirming that the worms were not moveable when shaken or given peripheral stimulation (hot water, 50°C) [24-25]. The findings were affirmed as the mean (Standard deviation) SD and statistical analysis was performed using (Software Version 6.0 in Graph Pad Prism) one-way (Analysis of variance) ANOVA.

RESULTS AND DISCUSSION

Antimicrobial Activity

All the synthesized analogues were examined for their antimicrobial activity. The majority of the derivatives were active against all the tested bacterial strains and the MIC values have been determined to be within the range of 62.5-500µg/mL [Table 3].

Table 3: Antibacterial and antifungal activity (Minimum Inhibition Concentrations) of 5a-5g

Antibacterial Activity Minimum Inhibition Concentration (µg/mL)					Antifungal Activity Minimum Inhibition Concentration (µg/mL)		
Compd.	**A**	**B**	**C**	**D**	**E**	**F**	**G**
5a	125	500	250	500	250	500	>1000
5b	100	125	100	62.5	500	500	>1000
5c	250	100	250	500	500	500	>1000
5d	250	250	100	250	500	500	500
5e	125	100	125	62.5	250	250	250
5f	500	100	62.5	125	250	500	500
5g	125	500	100	250	250	100	100
DMSO	--	--	--	--	--	--	--
Std 1	100	--	250	100	--	-	--
Std 2	50	50	50	50	--	--	--
Std 3	25	25	50	50	--	--	--
Std 4	--	--	--	--	100	100	100
Std 5	--	--	--	--	500	100	100

A; *E. Coli* MTCC 443, **B;** *P. Aeruginosa* MTCC 1688, **C;** *S. Aureus* MTCC 96, **D;** *S. Pyogenus* MTCC 442, **E;** *C. Albicans* MTCC 227, **F;** *A. Niger* MTCC 282, **G;** *A. Clavatus* MTCC 1323. **Std 1;** Ampicillin, **Std 2;** Chloramphenicol, **Std 3;** Ciprofloxacin, **Std 4;** Nystatin **Std 5;** Griseofulvin.

The analogues **5a** (phenyl), **5b** (4-Br) and **5c** (4-NO_2) demonstrated equipotent activity in contrast to *S. aureus* and *E. coli* in comparison with ampicillin (standard drug) with MIC value 250 µg/mL, 100 µg/mL and 250 µg/mL respectively. Derivatives **5b**, **5d** (4-CH_3), **5e** (2, 4-diCl_2) and **5g** (4-F) demonstrated superior activity towards *S. aureus* within a MIC range of 100-125µg/mL than reference drug ampicillin MIC 250µg/mL. Analogues **5b** and **5e** displayed excellent activity in contrary to *S. pyogenus* MIC values at 62.5µg/mL than ampicillin and **5f** (2-OH) in contrast to bacteria *S. aureus* depicted MIC values at 62.5µg/mL than standard drugs (chloramphenicol and ciprofloxacin) at MIC 50 µg/mL. The aimed compounds were also examined against fungal strains, compounds **5a**, **5e**, **5f** and **5g** showed outstanding activity (MIC 250µg/mL) and **5b**, **5c** and **5d** with MIC values of 500 µg/mL demonstrated comparable action in contrast to *C. albicans* in comparion with griseofulvin (standard drug) at MIC 500µg/mL. Compound **5g** depicted equipotent activity against *A. niger* and *A. clavatus* in comparison with reference drugs (nystatin and griseofulvin) with MIC values of 100µg/mL and compound **5e** depicted MIC values at 250 µg/mL in contrast to *A. niger* and *A. clavatus*, but less potent than reference drugs, nystatin and griseofulvin (MIC 100 µg/mL). The remaining analogues revealed moderate activity.

Anthelmintic Activity

The anthelmintic data of derivatives **5a-5g** and its comparison with standard drug albendazole has been given in [Table 4]. The biological data suggested that all the prepared analogues displayed moderate to excellent anthelmintic activity in contrast to reference compound (albendazole). Compounds **5a** (Phenyl), **5e** (2, 4-diCl_2) and **5f** (OH) demonstrated shortest mean paralysis time of (25.6±4.56 min, 26.4±4.97 min and 26.8±4.76 min) and mean death time (47.6±8.01min, 45.6±3.04min and 46.6±7.40min), respectively. It was noted that strong electron accepting and electron donating groups *i.e.* **5a** (Phenyl), **5e** (2, 4-*di*Cl_2) and **5f** (OH) at terminal benzene of 1st thiazole moiety improves the activity. Rest of the compounds exhibited moderate activity.

Table 4: Result of anthelmintic action of synthesized compounds (5a-5g)

Compd.	Concentration (w/v)	Mean paralysis time (min.) ± SD	Mean death time (min.) ± SD
5a	0.2 %	25.6±4.56	47.6±8.01
5b	0.2 %	33.8±5.11	51.2±6.05
5c	0.2 %	31±11.81	58.2±4.96
5d	0.2 %	31.6±8.41	50.6±6.42
5e	0.2 %	26.4±4.97	45.6±3.04
5f	0.2 %	26.8±4.76	46.6±7.40
5g	0.2 %	33.4±11.21	53.6±5.59
Albendazole	0.2 %	29.0 ± 0.8	49.2 ± 1.9

Antimalarial Activity

The antimalarial action of all newly synthesized analogues was tested. The compounds were tested at the various concentrations to determine their MIC value toward *Plasmodium falciparum* and compared with standard drugs [Table 5].

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

Anti-malarial Activity [*Plasmodium falciparum*]	
Compd.	**Mean IC_{50} values**
5a	0.24
5b	0.78
5c	1.43
5d	2.03
5e	0.49
5f	0.93
5g	1.08
Chloroquine	0.020
Quinine	0.268

Outcomes indicated that compounds **5a** and **5e** demonstrated effective antimalarial activity at IC_{50} value of 0.24 and 0.49 µg/mL than standard drugs chloroquine and quinine having IC_{50} value of 0.020 and 0.268µg/mL. Similarly, compounds **5b** (phenyl) and **5f** (2-OH) displayed moderate antimalarial activity at IC_{50} value of 0.78 and 0.93µg/mL. It was noticed that the presence of an electron-donating group *i.e.* (Phenyl and OH groups) has a great influence on activity.

Cytotoxic Activity

Newly synthesized derivatives **5a-5e** was examined for their cytotoxic action towards two cell lines *viz.* MCF-7 and Hop-62. The SRB assay indicated that compound **5e** (2, 4-*di*Cl_2, electron withdrawing group) has been identified as the moderate cytotoxic agent in response to MCF-7 cancer cells having GI_{50} 65.4µg/mL than

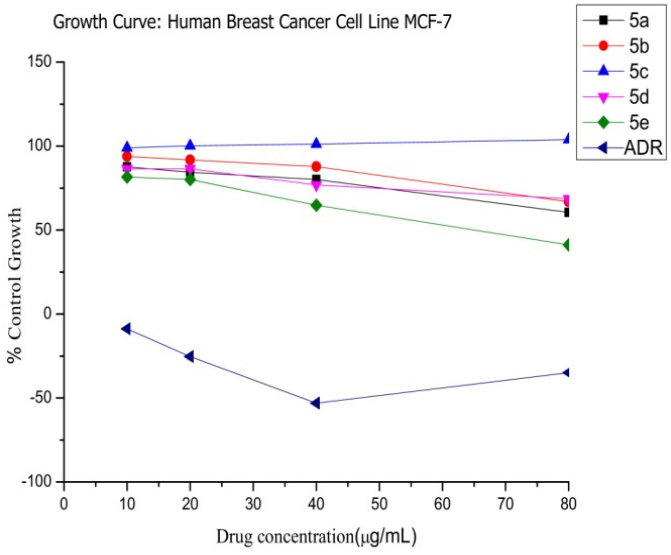
the reference drug adriamycin (GI_{50}<10µg/mL) [Table 6]. Alternatively, all the compounds exhibited the lowest toxicity against Hop-62 with GI_{50}>80µg/mL. The effect of various concentrations on percentage growth inhibition of the HOP-62 and MCF-7 is described in [Figure 2].

GI_{50}= Concentration of the drug that induces 50 per cent cell growth inhibition (Drug concentrations calculated from graph); Positive control compound = Adriamycin (ADR).

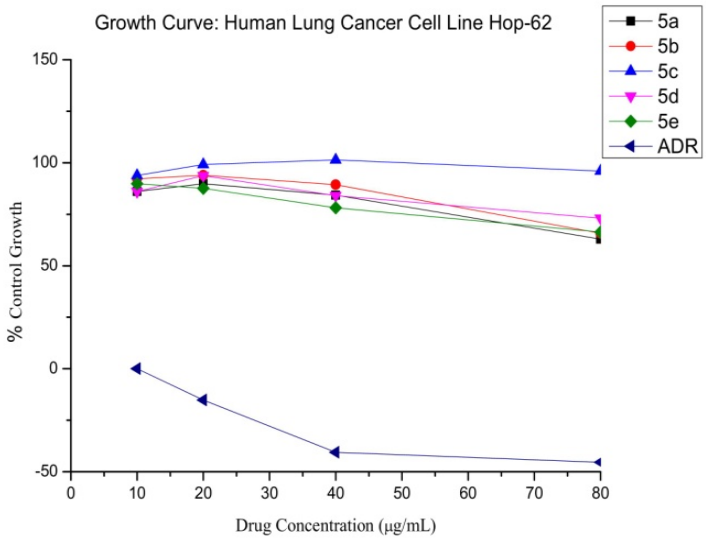
Table 6: Result of cytotoxic activity of synthesized compounds (5a-5e)

Compd.	Human Breast Cancer Cell Line (MCF-7) GI_{50} (µg/mL)	Human lung Cancer Cell Line Hop-62 GI_{50} (µg/mL)
5a	>80	>80
5b	>80	>80
5c	>80	>80
5d	>80	>80
5e	65.4	>80
ADR	<10	<10

Figure 2: Effect of synthesized compounds at different concentrations on percentage growth inhibition of (A) MCF-7 (B) Hop-62 cancer cell lines.



(A)



(B)

CONCLUSION

We have synthesized a novel series of thiazole based pyrazoles bearing benzothiazole moiety and evaluated for antiinfective and anticancer activities. Overall, the results showed that the prepared analogues have promising antimicrobial, antimalarial and anthelmintic propertiesin comparison to their respective reference drugs. Several compounds demonstrated moderate cytotoxic action against the MCF-7 and Hop-62 cell lines. The intriguing findings indicated that further investigation should be done on modification of these analogues for the development in order to generate new effective anti-infective and anticancer drugs. Furthermore, thiazole clubbed pyrazole bearing benzothiazole derivatives might be a promising field for expansion of future research on effective anticancer and anti-infective agents.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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