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RESEARCH ARTICLE

Syntheses, Characterization and Antimicrobial Activities of 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-2-(((3aR,5R)-3--5- disubstituted -3,3a-dihydro-2*H*-pyrazolo[3,4-d]thiazol-6(5*H*)-yl)amino)ethanone derivatives

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Abstract: A series of novel benzotriazole thiazolo pyrazoline were synthesized. The structures of obtained compounds were identified by elemental as well as by spectroscopic analysis (^{1}H NMR and ^{13}C NMR). The possible antimicrobial and anti-tubercular actions of these compounds were also tested using *S. aureus, E. coli, C. albicans and A. niger*. Compounds containing electron withdrawing group have shown good activity against all bacteria but compounds containing electron donating group have shown promising activity against all fungus.

Keywords: Benzotriazole, Thiazole, Pyrazoline and Antimicrobial activity

Introduction

The number of systemic infections caused by multidrug resistant gram-positive pathogens and increase in the number of immunocompromised hosts has reached an alarming level in hospitals and the community. Patients undergoing anticancer chemotherapy, organ transplant and patients with AIDS, are very sensitive to life threatening microbial infections, due to their immunosuppressed behavior. Microbial infections create a serious challenge to the scientist.

We have been interested from long time in the investigation of the pharmacological potentialities of benzotriazole derivatives conjugated with thiazolidines. Benzotriazole and thiazolidine attract considerable attention because of their significant biological activities and intrsting chemical features. The structure modifications of these compounds were carried out by introduction of new substituents mainly triazole nitrogen. Modification can change potency and type of activities of the basic structures. Benzotriazole and its derivatives

possess broad spectrum of biological activities which include antiviral[1], antimicrobial[2], herbicidal[3], anti-tubercular[4] anti-inflammatory, anticonvulsant[5] and DNA cleavage[6] *etc*.

Molecules with five membered rings, containing two hetero atoms are frequently biologically active. Thiazolidine (A) is an important scaffold well-known to be allied with numerous biological activities[7]. The numerous occurrence of the group-NHCSNH- or its tautomer in thiazolidine derivatives possessing *in vivo* tuberculosis activity has been noted[8].

Thiazolidine moiety is well known for biological[9-12] and pharmacological activities[13-17] such as CNS stimulant anthelmintic[18], antibacterial[19], mosquito repellant[20], analgesic[21-22], diurals, antiinflammatory, antifungal[18,23], hypnotic, amoebicidal[24], anticonvulsant[25] and nematocidal, antitubercular[26] *etc*.

Our strategy for modification of the benzotriazole structure is based on the introduction of thiazolidine fused with pyrazoline ring. Some azitidinones substituted benzotriazoles have been known before introduction of our research strategy[27]. In this work, we discuss their syntheses and structures and evaluate their activities in selected biological assays.

Experimental

TLC was run on Silica Gel 60 F254 precoated aluminum plates (Merck) and Silica Gel (100-200 mesh) was used as a stationary phase for column chromatography. NMR spectra were recorded at 25 ^{0}C on a Bruker Avance III 400 (400 MHz for ^{1}H and 400 MHz for ^{13}C) instrument with DMSO-d6 as solvent. Chemical shifts are given in δ (ppm), multiplicity has given as s (singlet), d (double), t (triplet), q (quartet), m (multiplet) and dd (doublet of doublet). IR spectra were recorded in KBr disks on Shimadzu FTIR-8400S instrument. Elemental analyses were recorded on a Thermoscientific (Flash 2000) element analyzer. Mass spectra were recorded on Shimadzu-LCMS-2010A mass spectrometer. Melting points were measured in open capillary tubes on a Buchi Melting Point B-540 apparatus and were uncorrected.

Results and Discussion

Chemistry

The synthesis of 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-2-(((3aR,5R)-3,5-substituted-3.3a-dihydro-2*H*-pyrazolo[3,4-d] thiazol-6(5H)-yl) amino)ethanone (Compounds **13-18**) is outlined in scheme in six different steps (Scheme 1). The synthesis of compound **2** was previously reported[28]. The compound **2** on reaction with hydrazine hydrate at boiling point yielded of 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-2-hydrazinylethanone (compound **3**). IR spectrum of compound **3** showed absorption for (C-N) and (N-H) while absorption of (C-Cl) has been disappeared. The ^{1}H NMR spectrum of compound **3** displayed a signal for (CH_2-N). The compound **3**, further react with selected *p*-chloro, *m*-nitro and *p*-OH benzaldehyde produced solid schiff bases, that compound showed the characterstic absorption for schiff bases (N=CH) in IR spectra, schiff base furthure on reaction with thioglycolic acid and produced (R)-3-((2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-2- substituted thiazolidin-4-one (**4-6**). In the ^{13}C NMR spectra of compound **4-6** showed signal for carbonyl group of thiazolidinone ring and signal for (N=CH) have been disappeared. Compound **4-6** on further reaction with two different benzaldehydes produced (R,E)-3-((2-(1*H*-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-5-substituted benzylidene)-2-substituted thiazolidin-4-one (**7-12**). In IR compound **7-12** showed absorption for (C=C) bond. The compound **7-12** on treatment with hydrazine hydrate furnished final products compound **13-18**. In IR compound **13-18** showed absorption for (N-N) and absorption for (C=C) bond have been disappeared. Yield and melting point of the compounds were given in Table 1.

Table 1. Characterization of synthesized final compounds

Compd.	R		Molecular formula	MW	M.Pt.(°C)	Yield, %	% Analysis of C,H, and N found (calcualated)		
	R	R'					C, %	H, %	N, %
7	4-ClPh	4-ClPh	$C_{24}H_{17}C_{l2}N_5O_2S$	510.395	124-6	68	56.48 (55.99)	3.36 (3.98)	13.72 (13.11)
8	-NO_2Ph	4-ClPh	$C_{24}H_{17}ClN_6O_4S$	520.948	153-5	70	55.33 (52.32)	3.29 (3.87)	16.13 (16.10)
9	2-OHPh	4-ClPh	$C_{24}H_{18}ClN_5O_3S$	491.949	125-7	72	58.59 (59.01)	3.69 (3.32)	14.24 (14.11)
10	4-ClPh	3-NO_2Ph	$C_{24}H_{17}ClN_6O_4S$	520.948	111-3	80	54.73 (53.98)	3.57 (3.48)	8.87 (8.34)
11	-NO_2Ph	3-NO_2Ph	$C_{24}H_{17}N_7O_6S$	531.500	176-8	73	54.23 (54.21)	3.22 (3.33)	18.45 (18.23)
12	2-OHPh	3-NO_2Ph	$C_{24}H_{18}N_6O_5S$	502.502	201-3	69	57.36 (57.10)	3.61 (3.67)	16.72 (16.12)
13	4-ClPh	4-ClPh	$C_{24}H_{19}C_{l2}N_7OS$	524.425	214-6	72	54.97 (54.74)	3.65 (3.56)	18.70 (18.45)
14	-NO_2Ph	4-ClPh	$C_{24}H_{19}ClN_8O_3S$	534.977	167-9	75	53.88 (53.11)	3.58 (3.34)	20.95 (19.99)
15	2-OHPh	4-ClPh	$C_{24}H_{20}ClN_7O_2S$	505.979	123-5	80	56.97 (56.78)	3.98 (4.00)	19.38 (19.11)
16	4-ClPh	3-NO_2Ph	$C_{24}H_{19}ClN_8O_3S$	534.977	145-7	71	53.88 (52.99)	3.58 (3.24)	20.95 (20.88)
17	-NO_2Ph	3-NO_2Ph	$C_{24}H_{19}N_9O_5S$	545.530	157-9	60	52.84 (52.34)	3.51 (3.21)	23.11 (22.99)
18	2-OHPh	3-NO_2Ph	$C_{24}H_{20}N_8O_4S$	516.532	146-8	80	55.81 (55.26)	3.90 (3.80)	21.69 (20.89)

Biology

All the newly synthesized compounds **7-18** were screened for their *in vitro* antibacterial activity against *S. aureus* (MTCC#6908), *E. coli* (MTCC#46) and antifungal activity against *C. albicans* (MTCC#183) and *A. niger* (MTCC#9652) and their MIC values were determined by serial dilution method. DMSO was used as a control while Streptomycin and Fluconazole were used as standard drugs respectively for bacterial and fungal strains. The antimicrobial activities of MIC values are given in Table 2. Among the compounds reported in this series, compound **10** against *E. coli*, compound **11-12** against *S. aureus* and *E. coli* **18** against *E. coli*, *C. albicans* and *A. niger* against *E. coli* did not show any inhibitory activity even at maximum concentration (100 mg/mL). However compound **7** is showing moderate activity against all four strains and compound **13** is showing best activity against bacterial and fungal strains but compound **15** and **16** are showing good activity against *Aspergillus niger* and *Candida albicans* respectively.

Table 2. *In vitro* antimicrobial and anti-tubercular activity of (**12a-12n**) compounds (MIC (mg/mL))***

Compd.	1*	2*	3*	4*
7	3.12	6.25	12.5	6.25
8	25	50	25	12.5
9	25	50	25	12.5
10	50	100	50	25
11	100	100	50	25
12	100	100	50	50
13	1.56	3.12	3.12	1.56
14	12.5	12.5	6.24	12.5
15	12.5	12.5	25	1.56
16	25	25	1.56	3.12
17	50	25	25	100
18	50	100	100	100
Reference 1**	0.78	0.39	-	-
Reference 2**	-	-	0.78	0.39

** 1. Staphyllococcus aureus, 2. Eschirichia coli, 3. Candida albicans, 4. Aspergillus niger.*
*** Reference.1-Streptomycin, Reference.2- Fluconazol.*
**** Each compound is tested at 10^{-5} M dose level and all practical done in triplicate*

Chemistry

*Synthesis of 1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-hydrazinylethanone (**3**)*

Compound **2** (14 g, 0.072 mol) was dissolved in acetone (35 mL) and hydrazine hydrate (3.6 g, 0.072 mol) was added. The well stirred (2 h) mixture was refluxed for 7 h. After cooling and filtration the solvent was evaporated under *in vacuo* to obtain a solid crude product. This resulting crude product was purified by passing it through a chromatographic column packed with silica gel using acetone/methanol (6:4 v/v) as eluant to obtain pure derivative. The resulting purified product was recrystallized by ethanol to give compound **3**.

*Synthesis of (R)-3-((2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-2-substituted thiazolidin-4-one (**4-6**)*

A mixture of compound **3** (0.01 mol) and respective aromatic aldehyde (0.01 mol) in methanol (20 mL) in the presence of catalytic amount of glacial acetic acid was refluxed for 5 h. The solvent was removed under reduced pressure to and the resulting crude product was purified by passing it through a chromatographic column packed with silica gel using chloroform/methanol (8:2 v/v) as eluant. Resulting purified product was recrystallized by chloroform to give schiff base and in Schiff bases with DMF, mercaptoacetic acid (0.005 mol) and $ZnCl_2$ (0.5 g) were added and the reaction mixture was refluxed for 8h, cooled and poured in to crushed ice, the separate solid was filtered and washed with 10% $NaHCO_3$. The crude product was dried and recrystallized from DMF to obtain the desired compound **4-6**.

*Synthesis of (R,E)-3-((2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-2,5-di-substituted thiazolidin-4-one (**7-12**)*

A mixture of compound **4-6** (0.005 mol), respective aldehyde (0.005 mol) and anhydrous CH_3COONa (0.005 mol) in anhydrous glacial acetic acid (50 mL) was refluxed for 3 h. The reaction mixture was concentrated and then poured into ice-cold water. The solid thus separated was filtered, washed with water and crystallized from glacial acetic acid to obtain the desired compound.

*(R,E)-3-((2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-5-(4-chlorobenzylidene)-2-(4-chlorophenyl)thiazolidin-4-one (**7**)*

^{1}H NMR: 7.96–7.17 (m, 12H, Ar.), 7.60 (s, 1H, CH), 3.78 (d, 2H, CH_2), 2.0 (t, 1H, NH). ^{13}C NMR: 112.20–140.16 (Ar.), 164.4 (cyclic C=O), 168.3 (C=O), 46.8(CH2), 70.3 (cyclic CH), 133.3 (cyclic C), 125.1 (C=).

*(R,E)-3-((2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-5-(4-chlorobenzylidene)-2-(3-nitrophenyl)thiazolidin-4-one (**8**)*

^{1}H NMR: 8.12–7.17 (m, 12H, Ar.), 7.60 (s, 1H CH), 3.76 (d, 2H, CH_2), 2.0 (t, 1H, NH), 5.92 (s, 1H, cyclic CH). ^{13}C NMR: 112.50–147.9 (Ar.), 164.4 (cyclic C=O), 168.3 (C=O), 46.8(CH2), 69.2 (cyclic CH), 129.3 (cyclic C), 125.2 (C=).

*(R,E)-3-((2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-5-(4-chlorobenzylidene)-2-(2-hydroxyphenyl)thiazolidin-4-one (**9**)*

^{1}H NMR: 7.96–6.83(m, 12H, Ar.), 7.60 (s, 1H CH), 3.76 (d, 2H, CH_2), 2.0 (t, 1H, NH), 5.92 (s, 1H, cyclic CH), 5.35 (s, 1H, OH). ^{13}C NMR: 112.50–145.2 (Ar.), 164.4 (cyclic C=O), 168.3 (C=O), 46.8(CH2), 64.0 (cyclic CH), 129.3 (cyclic C), 125.2 (C=).

*(R,E)-3-((2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-2-(4-chlorophenyl)-5-(3-nitrobenzylidene)thiazolidin-4-one (**10**)*

^{1}H NMR: 8.72–7.17 (m, 12H, Ar.), 7.71 (s, 1H CH), 3.76 (d, 2H, CH_2), 2.0 (t, 1H, NH), 5.92 (s, 1H, cyclic CH). ^{13}C NMR: 112.50–145.2 (Ar.), 164.4 168.3 (C=O), 46.8(CH2), 70.2 (cyclic CH), 129.3 (cyclic C), 125.2 (C=).

*(R,E)-3-((2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-5-(3-nitrobenzylidene)-2-(3-nitrophenyl)thiazolidin-4-one (**11**)*

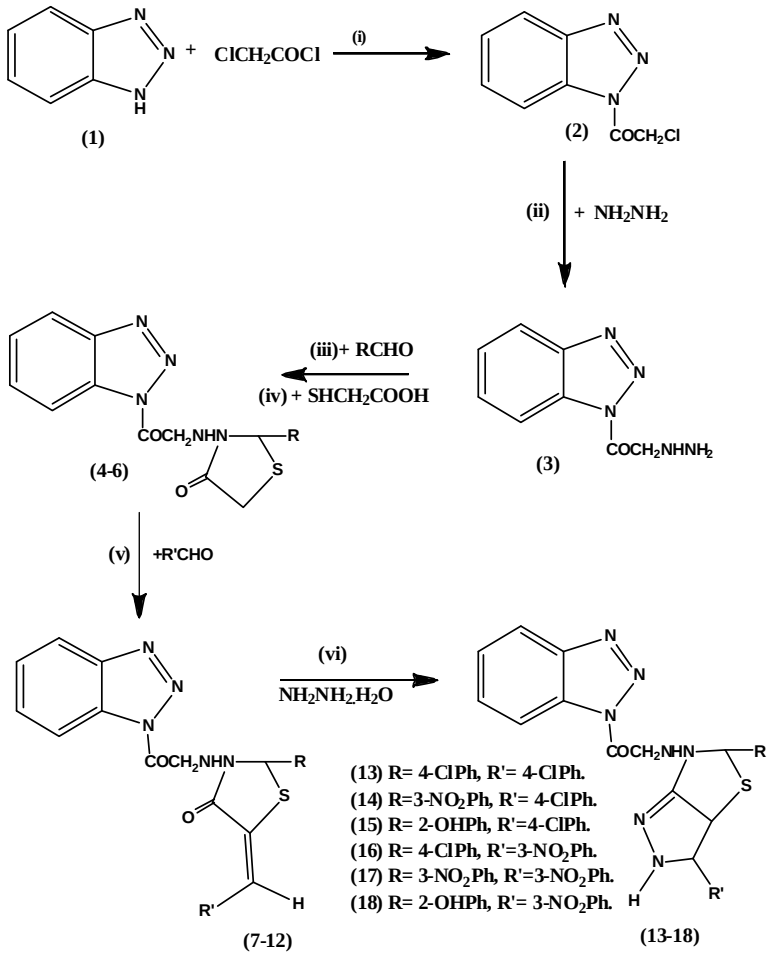
^{1}H NMR: 8.72–7.40 (m, 12H, Ar.), 7.71 (s, 1H CH), 3.76 (d, 2H, CH_2), 2.0 (t, 1H, NH), 5.92 (s, 1H, cyclic CH). ^{13}C NMR: 112.50–147.9 (Ar.), 164.4 (cyclic C=O), 168.3 (C=O), 46.8(CH2), 69.2 (cyclic CH), 129.3 (cyclic C), 125.2 (C=).

*(R,E)-3-((2-(1H-benzo[d][1,2,3]triazol-1-yl)-2-oxoethyl)amino)-2-(2-hydroxyphenyl)-5-(3-nitrobenzylidene)thiazolidin-4-one (**12**)*

^{1}H NMR: 8.72–6.83 (m, 12H, Ar.), 7.71 (s, 1H CH), 3.76 (d, 2H, CH_2), 2.0 (t, 1H, NH), 5.92 (s, 1H, cyclic CH), 5.36 (s, 1H, OH). ^{13}C NMR: 112.50–152.7 (Ar.), 164.4 (cyclic C=O), 168.3 (C=O), 46.8(CH2), 64.1 (cyclic CH), 129.3 (cyclic C), 125.2 (C=).

*Synthesis of 1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-(((3aR,5R)-3,5-disubstituted-3,3a-dihydro-2H-pyrazolo[3,4-d]thiazol-6(5H)-yl)amino)ethanone (**13-18**)*

A mixture of compound **7-12** (0.01 mol), hydrazine hydrate (0.01 mol) and anhydrous NaOAc (0.005 mol) in anhydrous glacial AcOH (50 mL), was refluxed for 3 h. The reaction mixture was concentrated and then poured in to ice cold water, the solid thus separated was filtered, washed with water and recrystallised from glacial AcOH to afford pure brown colour solid (**13-18**). Their characteristic analytical data are given in Table 1.



Scheme 1. Reaction Scheme for synthesis of targeting products

1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-(((3aR,5R)-3,5-bis(4-chlorophenyl)-3,3a-dihydro-2H-pyrazolo[3,4-d]thiazol-6(5H)-yl)amino)ethanone ***(13)***

^{1}H NMR: 7.96–7.17 (m, 12H, Ar.), 3.86 (d, 1H, bridging CH), 4.95 (s, 1H, thiazole CH), 4.0 (t, 1H, pyrazoline CH), 7.0 (d, 1H, pyrazoline NH), 2.0 (d, 1H, NH), 3.76 (d, 2H, CH2). ^{13}C NMR: 112.20–145.16 (Ar.), 168.3 (C=O), 47.4(CH_2), 49.5 (bridging CH), 157.0 (bridging C=N), 52.8 (pyrazoline CH), 74.1 (thiazole CH).

1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-(((3aR,5R)-3-(4-chlorophenyl)-5-(3-nitrophenyl)-3,3a-dihydro-2H-pyrazolo[3,4-d]thiazol-6(5H)-yl)amino)ethanone ***(14)***

^{1}H NMR: 8.12–7.40 (m, 12H, Ar.), 3.86 (d, 1H, bridging CH), 4.95 (s, 1H, thiazole CH), 4.2(t, 1H, pyrazoline CH), 7.0 (d, 1H, pyrazoline NH), 2.0 (d, 1H, NH), 3.76 (d, 2H, CH_2). ^{13}C NMR: 112.20–147.8 (Ar.), 168.3 (C=O), 47.4(CH_2), 49.5 (bridging CH), 157.0 (bridging C=N), 52.8 (pyrazoline CH), 73.1 (thiazole CH).

*1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-(((3aR,5R)-3-(4-chlorophenyl)-5-(2-hydroxyphenyl)-3,3a-dihydro-2H-pyrazolo[3,4-d]thiazol-6(5H)-yl) amino)ethanone(**15**)*

^{1}H NMR: 7.96–6.83 (m, 12H, Ar.), 3.86 (d, 1H, bridging CH), 4.95 (s, 1H, thiazole CH), 4.2(t, 1H, pyrazoline CH), 7.0 (d, 1H, pyrazoline NH), 2.0 (d, 1H, NH), 3.76 (d, 2H, CH_2), 5.35 (s, 1H, OH). ^{13}C NMR: 112.20–153.7 (Ar.), 168.3 (C=O), 47.4(CH_2), 49.5 (bridging CH), 157.0 (bridging C=N), 52.8 (pyrazoline CH), 67.9 (thiazole CH).

*1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-(((3aR,5R)-5-(4-chlorophenyl)-3-(3-nitrophenyl)-3,3a-dihydro-2H-pyrazolo[3,4-d]thiazol-6(5H)-yl)amino)ethanone (**16**)*

^{1}H NMR: 8.18–7.17 (m, 12H, Ar.), 3.86 (d, 1H, bridging CH), 4.95 (s, 1H, thiazole CH), 4.2 (t, 1H, pyrazoline CH), 7.0 (d, 1H, pyrazoline NH), 2.0 (d, 1H, NH), 3.76 (d, 2H, CH_2). ^{13}C NMR: 112.20–147.7 (Ar.), 168.3 (C=O), 47.4(CH_2), 49.5 (bridging CH), 157.0 (bridging C=N), 51.8 (pyrazoline CH), 74.1 (thiazole CH).

*1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-(((3aR,5R)-3,5-bis(3-nitrophenyl)-3,3a-dihydro-2H-pyrazolo[3,4-d]thiazol-6(5H)-yl)amino)ethanone (**17**)*

^{1}H NMR: 8.18–7.40 (m, 12H, Ar.), 3.86 (d, 1H, bridging CH), 4.95 (s, 1H, thiazole CH), 4.2 (t, 1H, pyrazoline CH), 7.0 (d, 1H, pyrazoline NH), 2.0 (d, 1H, NH), 3.76 (d, 2H, CH_2). ^{13}C NMR: 112.20–147.8 (Ar.), 168.3 (C=O), 47.4(CH_2), 49.5 (bridging CH), 157.0 (bridging C=N), 51.8 (pyrazoline CH), 73.1 (thiazole CH).

*1-(1H-benzo[d][1,2,3]triazol-1-yl)-2-(((3aR,5R)-3-(2-hydroxyphenyl)-5-(3-nitrophenyl)-3,3a-dihydro-2H-pyrazolo[3,4-d]thiazol-6(5H)-yl)amino)ethanone (**18**)*

^{1}H NMR: 8.12–6.90 (m, 12H, Ar.), 3.86 (d, 1H, bridging CH), 4.95 (s, 1H, thiazole CH), 4.2 (t, 1H, pyrazoline CH), 7.0 (d, 1H, pyrazoline NH), 2.0 (d, 1H, NH), 3.76 (d, 2H, CH_2), 5.35 (s, 1H, OH). ^{13}C NMR: 112.20–154.0 (Ar.), 168.3 (C=O), 47.4(CH_2), 49.8 (bridging CH), 157.0 (bridging C=N), 46.6 (pyrazoline CH), 73.1 (thiazole CH).

In vitro antibacterial and antifungal activities

In vitro activities of the compounds were tested in Sabourauds dextrose broth (SDB) for fungi and in Nutrient broth (NB) for bacteria by the two-fold serial dilution method[24]. Seeded broth (broth containing microbial spores) was prepared in NB from 24 h old bacterial cultures on nutrient agar (Hi-media, India) at 37±1 ^{0}C while fungal spores from 24 h to 7 days old Sabourauds agar slant cultures were suspended in SDB. The bacterial suspension was adjusted with sterile saline to a concentration of 1 x 10^4-10^5 CFU. The tested compounds and reference drugs were prepared by twofold serial dilution to obtain the required concentrations of 100, 50, 25, 12.5, 6.25, 3.12, 1.56 and 0.78 mg/mL. The tubes were incubated in BOD incubators at 37±1 ^{0}C for bacteria and 28±1 ^{0}C for fungi. The minimum inhibitory concentrations (MICs) were recorded by visual observations after 24 h (for bacteria) and 72-96 h (for fungi except *C. albicans*) of incubation. Streptomycin and Fluconazole were used as standards for bacterial and fungal study, respectively.

Conclusion

It is concluded that the benzotriazole pyrazolo thiazole analogues were synthesized and studied their antimicrobial activities. Some derivatives promising electron withdrawing groups (-Cl, -NO_2) have shown promising activity against all bacteria but compounds containing electron donating groups have shown good antifungal activity. These heterocycles could be considered

as useful templates for future development and further molecular modification of substituents on phenyl ring to obtain more potent and selective antimicrobial agents. This new class of compounds is now being tested in more extensive in vitro studies to determine efficacy against bacterial and fungal strains, used in present study

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