ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 11, Issue 4, 2018

Online - 2455-3891
Print - 0974-2441

Research Article

DESIGN, SYNTHESIS, AND PHARMACOLOGICAL EVALUATION OF SOME NOVEL BIS-THIAZOLE DERIVATIVES

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Received: 02 November 2017, Revised and Accepted: 30 December 2017

ABSTRACT

Objective: A series of substituted 5,2-bis-thiazoles derivatives were synthesized by Hantzsch reaction and evaluated *in vitro* for antimicrobial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis,* and *Staphylococcus aureus.*

Methods: 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carbothioamide were synthesized and allowed to react with various α-haloketones to give 5,2-bis-thiazoles, i.e., 2-(4-(benzyloxy)phenyl)-4-methyl-5-(4-substituted thiazol-2-yl)thiazole derivatives in excellent yield. The synthesized compounds were characterized by spectroscopic methods as well as elemental analyses. They were screened for their antimicrobial activity using the agar diffusion method.

Result: Literature survey reveals that the synthesis of 2-(4-(benzyloxy)phenyl)-4-methyl-5-(4-substituted thiazol-2-yl)thiazole, i.e., (5,2-Bis-thiazoles) derivatives (10a-e) was not reported. The entire compound exhibited mild to moderate antimicrobial activity.

Conclusion: The antimicrobial results revealed that the synthesized derivatives have significant antimicrobial properties, and further, structure–activity relationship studies may develop more potent and less toxic molecule.

Keywords: Bis-thiazoles, Thiazolyl-carbothioamide, α-Haloketones, Antimicrobial activity.

 DOI: http://dx.doi.org/10.22159/ajpcr.2018.v11i4.23413

INTRODUCTION

Heterocyclic chemistry is now fast-growing research field in chemistry. Thiazoles are five-membered heterocycles with N and S as a heteroatom. They are ubiquitous in natural product [1] and pharmaceuticals [2]. Substituted 1,3-thiazoles, especially tethered with aryl or heteroaryl groups (in the 2,4,5 positions or disubstituted such as 2,4-diaryl,2,5-diaryl or 4,5-diaryl) are considered privileged structural motifs and have application in various fields, such as materials science, for the preparation of liquid crystals [3], etc. In addition, they are also having numerous applications in medicinal chemistry for access of bioactive lead molecules and drugs candidates. Some di- and tri-substituted 1,3-thiazole derivatives with various pharmacological properties. Febuxostat is a urate-lowering drugs and inhibitor of xanthine oxidase used for the treatment of hyperuricemia and chronic gout [4] and fatostatin is a SREBP inhibitor [5]. Similarly, nizatidine is a useful drug used for the treatment of peptic ulcers and gastroesophageal reflux disease [6]. The thiazole moiety is also found in Vitamin B_1 as well as various other bioactive molecules.

Thiazole ring system is possessing diversified types of pharmacological activities such as antifungal [7], anti-inflammatory [8], antidiabetic [9], antiepileptic [10], antimalarial [11], and antiparasitics [12]. In the recent reviews, many examples of enhanced bioactivity of multivalent drug molecules have been cited [13]. Compounds bearing more than one thiazole ring unit also exhibit good biological activities, the bleomycin containing 2,4'-*bis*-thiazole system acts as an anticancerous, antibiotic, and biological reports also existing on the 5,5'-*bis*-thiazoles [14] and 2,2'-*bis*-thiazoles [15]; it is also present in many bioactive compounds including thrombotic [16], and bacterial DNA-gyrase [17] inhibitors that are pot antifungal, anti-inflammatory and also useful in cardiac and cancer treatment [18], skin whitening properties [19] and have some interesting agricultural application [20].

The development of non-steroidal anti-inflammatory drugs (NSAIDs) is a current topic for medicinal chemistry research, due to the problems that this drugs present. An important number of molecules from this class have been withdrawn from market because of their potentially fatal side effects. Furthermore, most NSAIDs have a high risk of adverse reaction (especially gastrointestinal bleeding) and a low safety profile [21]. C_2 position of thiazole ring requires large hydrophilic, electronegative functional moieties like substituted phenyl ring for enhanced antibacterial activity of thiazole. In our compounds, methyl group is present still most of the compound show good antibacterial activity. C_5 position of the thiazole ring requires small hydrophobic, electronegative functional moieties, for enhanced antibacterial activity of thiazole. It is already known that the thiazole ring could provide a rich spectrum of biological activities [22], being also present in some well-known antibacterial molecules, such as ceftriaxone, ceftazidime, cefixime, and aztreonam. In this context, our aim was to test new derivatives with 5,2-bis-thiazoles scaffold for their antimicrobial activity.

In the present work, some new series of 5,2-bis-thiazole derivatives have been prepared by the Hantzsch. 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carbothioamide were synthesized and allowed to react with various α-haloketones in the presence of isopropyl alcohol to give 5,2-bis-thiazoles, i.e. 2-(4-(benzyloxy)phenyl)-4-methyl-5-(4-substitutedthiazol-2-yl)thiazole derivatives in excellent yield. The structures of newly synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. All the synthesized compounds were evaluated for antibacterial and antifungal activities.

METHODS

Chemistry

Melting points were determined in open capillary and are uncorrected. ^{1}H NMR spectra were recorded on Bruker Avance II 400 spectrometer

in $CDCl_3$ solvent using TMS as internal standard. The ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ solvent, using TMS as an internal standard. Chemical shift values are reported in ppm units, relative to TMS as internal standard. Thin-layer chromatography was performed with E. Merk precoated TLC plates, silica gel 60 F_{254} with thickness of 0.25 mm, and spots were visualized by irradiation with ultraviolet light (254 nm) or by exposing to I_2.

EXPERIMENTAL

Synthesis of 4-(benzyloxy)benzonitrile(3)

Equimolar amount of 4-hydroxybenzonitrile (0.01mol) and benzyl chloride (0.01 mol) was taken in N,N-dimethyl formamide (DMF) (10 ml) as solvent and reaction is carried out in K_2CO_3 (0.005 mol) and reflux for 2 h. The reaction mixture was cooled to room temperature and poured over ice-cold water. The precipitate was filtered, washed with water and dried. The product was recrystallized from ethanol.

Yield 87%. m.p: 94–96°C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.30 (dd, 2H, Ar-H), 7.20 (m, 5H, Ar-H), 7.10 (dd, 2H, Ar-H), 5.25 (S, 2H, -OCH_2Ar). ^{13}C NMR ($CDCl_3$, 100 MHZ): δ 165.4, 141.8, 133.8, 130, 127.9, 127.8, 115.9, 115, 71. Mass (EI): m/z, 209(100%), 210, 211.

Synthesis of 4-(benzyloxy)benzothioamide(4)

To a solution of 4-(benzyloxy)benzonitrile (0.015 mol) (3) in ethanol (50 ml), phosphorous pentasulfide (0.030 mol) was slowly added at room temperature and stirred at RT for 2 h. Reaction mass was poured on ice-cold water. Obtained precipitated was filter, washed with water to yield pure compound.

Yield 80% m.p: 176–182°C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.5 (dd, 2H, Ar-H), 7.21(m, 5H, Ar-H), 6.9 (dd, 2H, Ar-H), 5.18 (S, 2H, -OCH_2), 2.2 (S, 2H, -NH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190, 163, 141.5, 136, 130.9, 130, 127.8, 127.6, 114,70.8. Mass (EI): m/z, 243 (100%), 244, 245.

Synthesis of ethyl 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carboxylate(6)

To a solution of 4-(benzyloxy)benzothioamide (0.012 mol) (4) in 20 ml of isopropyl alcohol, an equimolar quantity of ethyl-2-chloro-acetoacetate (0.012 mol) was added and reflux for 3 h. Completion of reaction was monitored by TLC. The mixture was cooled to room temperature. Obtained solid compound was filtered and dried.

Yield 82% m.p: 106–108°C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (dd, 2H, Ar-H), 7.20 (m, 5H, Ar-H), 6.83 (dd, 2H, Ar-H), 5.20 (S, 2H, -OCH_2Ar), 4.30 (dd, 2H, -CH_2), 2.49 (S, 3H, thiazole-CH_3), 1.30 (m, 3H, -CH_2-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.5, 167, 162,161, 141.4, 129.2, 128.7, 127.8, 127.5, 126, 115, 71, 61, 14.5, 11.3. Mass (EI): m/z, 353 (100%), 354, 355, 356.

Synthesis of 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carboxylic acid(7)

To a solution of ethyl 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carboxylate(0.02 mol) (6) in 4 mL ethanol was refluxed with 5 mL of NaOH (2N) for 2 h. The solution was then cooled, neutralized with H_2SO_4 (10%) and filtered. The solid obtained was washed with water and recrystallized from ethanol.

Yield 70%, m.p: 218–223°C. ^1H NMR ($CDCl_3$, 400 MHz) δ 11.5 (S, 1H, -COOH), 7.37 (dd, 2H, Ar-H), 7.21 (m, 5H, Ar-H), 6.84 (dd, 2H, Ar-H), 5.21 (S, 2H, -OCH_2Ar), 2.48 (S, 3H, thiazole-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ1 69.5, 169, 162, 161, 141.3, 129.4, 128.7, 128, 127.3, 126, 114.9, 70.9, 11.5. Mass (EI): m/z, 325 (100%), 326, 327, 328.

Synthesis of 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carbonitrile(8)

A mixture of the 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carboxylic acid (0.01 mol)(7), hydroxylamine hydrochloride (0.02 mol), and zinc dust (0.02 mol) was taken in 50 ml of polyethylene glycol and stirred at 85°C for 3 h. The reaction mass was extracted with ethyl acetate and separated PEG. The ethyl acetate layers were evaporated, the crude product was purified by column chromatography using silica gel (60–120 mesh).

Yield 74%. m.p: 150–155°C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 (dd, 2H, Ar-H), 7.18 (m, 5H, Ar-H), 6.80 (dd, 2H, Ar-H), 5.19 (S,2H, -OCH_2Ar), 2.40 (S, 3H, thiazole-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9, 160.2, 153.8, 141.3, 129, 128, 127.4, 125,114.6, 114, 113.8, 70.6, 10.3. Mass (EI): m/z, 306 (100%), 307, 308, 309.

Synthesis of 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carbothioamide(9)

To a solution of 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carbonitrile (0.015 mol) in ethanol (50 ml) and then phosphorous pentasulfide (0.030 mol) was slowly added at room temperature and stirred at RT for 2 h. Reaction mass was poured into ice-cold water, precipitated solid was filter, washed with water to yield pure compound.

Synthesis of 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carbothioamide(9)

Yield 78% m.p: 160–165°C. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36 (dd, 2H, Ar-H), 7.19 (m, 5H, Ar-H), 6.83 (dd, 2H, Ar-H), 5.19 (S, 2H, -OCH_2Ar), 2.43 (S, 3H, thiazole-CH_3), 1.9 (S, 2H, C-NH_2). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 204, 169.3, 161.9, 161, 141, 129, 128.6, 127.5, 127, 126, 115, 114, 70.7, 11.3. Mass (EI): m/z, 340 (100%), 341, 342, 343.

Synthesis of the 5,2-bis-thiazoles (10a-f)

A mixture of 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carbothioamide (0.010 mol) in 20 ml of isopropyl alcohol, an equimolar quantity of the corresponding α-chloroketone (0.010 mol) was added and it was reflux for 3–4 h. On completion of the reaction, monitored by TLC, the mixture was cooled to room temperature. Solid compound obtained, filtered dried and recrystallized from ethanol. Analytical and physical data are given in Table 1.

Synthesis of ethyl-2-(2-(4-(benzyloxy)phenyl)-4-methylthiazol-5-yl)-4-methylthiazole-5-carboxylate(10a)

^1H NMR ($CDCl_3$, 400 MHz): δ 7.50–8.0 (m, 5H, Ar-H), 7.20 (dd, 2H, Ar-H), 6.80 (dd, 2H, Ar-H), 5.30(S, 2H, -OCH_2Ar), 4.29 (dd, 2H, -CH_2), 2.72 (S, 3H, thiazole-CH_3), 2.64 (S, 3H, thiazole-CH_3), 1.34 (m, 3H, -CH_2-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.20, 167, 164.20, 161.30, 159.8, 155, 141.10, 128.60, 128, 127.80, 127.6, 127.5, 124.9, 115.8, 114.20, 70.80, 60.66, 13.9, 11.8, 11.50. Mass (EI): m/z, 450 (100%), 451, 452, 453.

2-(4-(benzyloxy)phenyl)-5-(4-(4-chlorophenyl)thiazol-2-yl)-4-methylthiazole (10b)

^1H NMR ($CDCl_3$, 400 MHz): δ 8.48 (S, 1H, thiazole-C_5-H), 7.54 (dd, 2H, Ar-H), 7.44 (dd, 2H, PhCl), 7.38 (dd, 2H, PhCl), 7.21 (m, 5H, Ar-H), 6.85 (dd, 2H, Ar-H), 5.21 (S, 2H, -OCH_2Ar), 2.74 (S, 3H, thiazole-CH_3). ^{13}C NMR ($CDCl_3$, 100MHz): δ 170, 164.8, 161, 154.8, 152.9, 141.8, 134.8, 131.4, 129.4, 129, 128.9, 128, 127.6, 127.4, 126, 115, 110.7, 70.8, 11.8. Mass (EI): m/z, 474 (100%), 475, 476, 477.

2-(4-(benzyloxy)phenyl)-4-methyl-5-(4-(4-nitrophenyl)thiazol-2-yl)thiazole (10c)

^1H NMR ($CDCl_3$, 400 MHz): δ 8.55(S, 1H, thiazole-C_5H), 8.34 (dd, 2H, $PhNO_2$), 8.26 (dd, 2H, $PhNO_2$), 7.60 (dd, 2H, Ar-H), 7.23 (m, 5H, Ar-H), 6.84 (dd, 2H, Ar-H), 5.21 (S, 2H, -OCH_2Ar), 2.80 (S, 3H, thiazole-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.8, 164.8, 160.6, 154, 153, 148.7, 141.6, 139.5, 129, 128.6, 128.6, 127.8, 127.6, 121.7, 115, 114.5, 110.7, 71.1, 11.8. Mass (EI): m/z, 485 (100%), 486, 487, 488.

2-(4-(benzyloxy)phenyl)-4-methyl-5-(5-methyl-4-phenylthiazol-2-yl)thiazole (10d)

^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (dd, 2H, Ar-H), 7.28 (dd, 2H, Ar-H), 7.30 (dd, 2H, Ar-H), 7.18 (m, 5H, Ar-H), 7.10 (m, 1H, Ar-H), 6.80 (dd, 2H, Ar-H), 5.10 (S, 2H, -OCH_2Ar), 2.40 (S, 3H, thiazole-CH_3), 2.34 (S, 3H,

thiazole-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 163.1, 160.5, 153.9, 153, 141, 132.9, 129, 128.7, 128.3, 128, 127.6, 127.1, 115, 70.2, 11.1, 8.2. m/z, 454 (100%), 455, 456, 457.

2-(4-(benzyloxy)phenyl)-5-(4-(4-methoxyphenyl)thiazol-2-yl)-4-methylthiazole (10e)

^1H NMR ($CDCl_3$, 400 MHz):δ 7.9 (S, 1H, thiazole-C_5-H), 7.48 (dd, 2H, Ar-OCH_3), 7.38 (dd, 2H, Ar-H), 7.20 (m, 5H, Ar-H), 7.10 (dd, 2H, Ar-OCH_3), 6.83 (dd, 2H, Ar-H), 5.19 (S, 2H, -OCH_2Ar), 3.75 (S, 3H, -OCH_3), 2.50 (S, 3H, thiazole-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.8, 164.9, 160.8, 161, 153, 154, 141.8, 129.8, 128.7, 128, 127.6, 126, 115, 114, 110.8, 71, 56, 11.5. m/z, 470 (100%), 471, 472, 473 (Scheme 1).

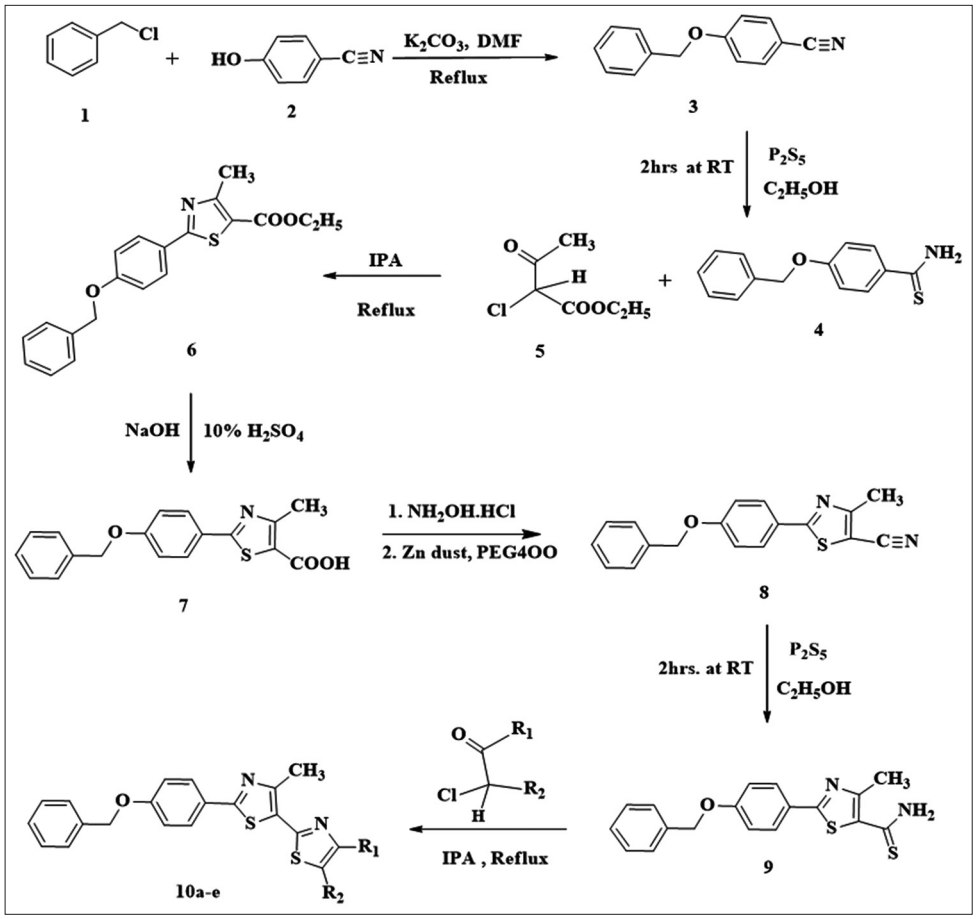
Biological activity

Antibacterial and antifungal studies

The synthesized 5,2-bis-thiazoles derivatives (10a-e) were screened for the antibacterial activity against two Gram-positive bacteria, namely, *Bacillus subtilis* and *Staphylococcus aureus* and two Gram-negative bacteria, namely, *Escherichia coli* and *Pseudomonas aeruginosa* using the disc diffusion method [23]. Ciprofloxacin was used as reference standard for comparing the results and dimethyl sulfoxide (DMSO) as a control solvent. Newly synthesized compounds were screened for their antifungal activity against *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum*, and *Fusarium moniliforme*, by standard agar disc diffusion method [24] using griseofulvin as reference standard and

Table 1: Analytical data and elemental analysis of compounds 10(a-e)

Compound	Molecular formula	M.P. °C	Yield %	Elemental analysis					
				%C		% H		%N	
				Calculated	Found	Calculated	Found	Calculated	Found
10a	$C_{24}H_{22}N_2O3S_2$	145–150	78	63.98	63.95	4.92	4.90	6.22	6.18
10b	$C_{26}H_{19}ClN_2OS_2$	220–222	75	65.74	65.69	4.03	4.01	5.90	5.86
10c	$C_{26}H_{19}N_3O_3S_2$	250–255	82	64.31	64.30	3.94	3.90	8.65	8.62
10d	$C_{27}H_{22}N_2OS_2$	238–244	84	71.33	71.28	4.88	4.85	6.16	6.13
10e	$C_{27}H_{22}N_2O_2S_2$	140–145	80	68.91	68.88	4.71	4.65	5.95	5.91



Scheme 1: Synthesis of 5,2-bis-thiazoles derivatives

Where:	R_1	R_2
10a	-CH_3	-$COOC_2H_5$
10b		H
10c		H
10d		-CH_3
10e		H

DMSO as control solvent. The antibacterial and antifungal activity of the 5,2-bisthiazoles derivatives is shown in Tables 2 and 3, respectively.

The investigation of antibacterial screening results indicates that compounds 10b, 10c, and 10d showed moderate activity against *E. coli*, *P. aeruginosa, S. aureus,* and *B. subtilis*. Compound 10a showed moderate activity against *E. coli, S. aureus,* and *B. subtilis* but did not exhibit activity against *P. aeruginosa*. Compound 10e showed moderate activity against *E. coli, P. aeruginosa,* and *B. subtilis* but not exhibit activity against *S. aureus*.

The investigation of antifungal activity data revealed that compounds 10a, b, d show inhibitory effect against *A. niger* and compounds 10a, b, c show inhibitory effect against *A. flavus*. Compounds 10b, c, d show inhibitory effect against *P. chrysogenum*. Similarly, most of the compounds are active against *F. moniliforme*. Remaining compounds are inactive against all the fungus.

RESULT AND DISCUSSION

Literature survey reveals that the synthesis of 2-(4-(benzyloxy)phenyl)-4-methyl-5-(4-substitutedthiazol-2-yl)thiazole, i.e., (5,2-Bis-thiazoles) derivatives (10a-e) was not reported. Hence, it was thought worthwhile to synthesize these compounds. Synthesis of 4-(benzyloxy)benzonitrile (3) using para-hydroxybenzonitrile and bezylchloride in the presence of weak base potassium carbonate in DMF solvent under reflux conditions. Synthesis of 4-(benzyloxy) benzothioamide (4) is carried out by using (3) and phosphorous pentasulfide in ethanol as a solvent at room temperature. Synthesis of ethyl 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carboxylate (6) by Hantzsch condensation of benzothioamide(4) with ethyl-2-chloro-acetoacetate. Synthesis of 2-(4-(benzyloxy)phenyl)-4-methylthiazole-5-carboxylic acid (7) is obtained by hydrolysis of ester(6) in a basic condition. Synthesis of 2-(4-(benzyloxy) phenyl)-4-methylthiazole-5-carbonitrile(8) by carboxylic acid(7) to carbonitrile(8) using hydroxylamine hydrochloride and zinc dust in PEG400, it is a one pot conversion of carboxylic acid to nitrile and zinc dust as reductant, PEG400 as a phase transfer catalyst. Synthesis of 2-(4-(benzyloxy) phenyl)-4-methylthiazole-5-carbothioamide (9) is carried out by using phosphorous pentasulfide at room temperature. 5,2-bis-thiazoles (10a-f) is obtained by condensation between thiazolyl-carbothioamide(9) and various α-chloroketones by Hantzsch synthesis.

Table 2: *In vitro* antibacterial activity for compounds 10(a-e)

Compounds	Zone of Inhibition (mm)			
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*
10a	08	-ve	09	08
10b	15	13	09	14
10c	14	13	11	10
10d	13	15	10	16
10e	09	16	-ve	15
Ciprofloxacin	23	27	21	27
DMSO	-ve	-ve	-ve	-ve

-ve no antibacterial activity, *E. coli: Escherichia coli, P. aeruginosa: Pseudomonas aeruginosa, S. aureus: Staphylococcus aureus, B. subtilis: Bacillus subtilis*

Table 3: Antifungal screening results of the compounds 10(a-e)

Compounds	*A. niger*	*A. flavus*	*P. chrysogenum*	*F. moneliformе*
10a	-ve	-ve	+ve	-ve
10b	-ve	-ve	-ve	-ve
10c	+ve	-ve	-ve	-ve
10d	-ve	+ve	-ve	-ve
10e	+ve	RG	+ve	+ve
Griseofulvin	-ve	-ve	-ve	-ve
DMSO	+ve	+ve	+ve	+ve

-ve no growth antifungal activity present, +ve growth antifungal activity absent, RG, reduced growth, *A. niger: Aspergillus niger, A. flavus: Aspergillus flavus, P. chrysogenum: Penicillium chrysogenum, F. moniliforme: Fusarium moniliforme*

The condensation took place, directly without the formation of the intermediate hydroxyl-thiazoline, all the condensation having yields above 70%. The structures of the synthesized compounds (10a-e) were confirmed on the basis of spectral data. In ^{1}H NMR assignments of the signals are based on the chemical shift and intensity pattern. The ^{1}H NMR spectra of compounds 10a show singlet signals between 2.64 and 2.72 ppm corresponding to 2-CH_3 group in both thiazole ring. In 10b shows singlet signals 8.48 ppm corresponding to thiazole C_5-H, doublet of doublet (dd) signals between 7.38 and 7.44 ppm corresponding to Ph-Cl. In 10e shows singlet signals of 3.75 ppm corresponding –OCH_3 group attached to benzene. It is a confirmatory for the synthesis of 5,2-bis-thiazole derivatives.

CONCLUSION

In summary, it describes the synthesis of 5,2-bis-thiazoles derivatives with their antimicrobial activity. The reaction completion was confirmed by TLC and the synthesized compounds were purified by recrystallization. The structures of the synthesized compounds were assigned on the basis of the spectral data (^{1}H NMR, ^{13}C NMR, and mass). The antimicrobial activity of these compounds was evaluated against various Gram-positive, Gram-negative bacteria. Most of the compounds showed a moderate degree of antimicrobial activity. To improve the design of future bis-thiazoles derivatives active of Gram-negative bacteria, for which the need for new drugs is critical. The data reported in this article may be helpful guide for the medicinal chemist who is working in this area.

ACKNOWLEDGMENT

The author gratefully acknowledges SAIF and CIL Chandigarh, for mass, NMR spectra. The author thanks to Principal Milind College of Science, Aurangabad, for providing research facility.

AUTHOR CONTRIBUTION

All the author's have contributed equally.

CONFLICTS OF INTERESTS

All authors have none to declare.

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