Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2017, 9(22):8-12
(http://www.derpharmachemica.com/archive.html)

Design, Synthesis of Biologically Active Heterocyles Containing Indol-thiazolyl-thiazolidinone Derivatives

Prabhaker Walmik*, Basavaraj S Naraboli, Swathi B, Somashekhar Ghanti

Department of Post-Graduate Studies and Research in Chemistry, Gulbarga University, Kalabuaragi-585106, India

ABSTRACT

The present study conceived a novel series of thiazole, indole and thiazolidine derivatives 4-6 have been developed and characterized by IR, Proton Nuclear Magnetic Resonance (^{1}H-NMR), Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR) and mass spectral data and elemental analysis and evaluated for in vitro antimicrobial activity against bacterial strains such as, Escherichia coli (MTCC-723), Staphylococcus aureus (ATCC-29513), Klebsiella pneumonia (NCTC-13368), Pseudomonas aeruginosa (MTCC-1688) and the fungal strains such as Aspergillus oryzae (MTCC-3567^{T}), Aspergillus niger (MTCC-281), Aspergillus flavus (MTCC-1973), Aspergillus terreus (MTCC-1782). A. niger were carried out by broth micro dilution method (NCCLS., 2002) in DMF concentration at 500, 250, 125 and 62.5 µg/ml. Gentamycin and fluconazole was used as reference standards for antibacterial and antifungal activity, respectively. The newly designed and synthesized compounds were evaluated for their antimicrobial activity. The final results revealed that compounds 4b, 5b and 6b were exhibited potent antimicrobial activity when compared to the standard drugs.

Keywords: Indole, Thiazole, Thiazolidin-4-one, Antibacterial, Antifungal activities

INTRODUCTION

Heterocyclic compounds have occupied a unique place in the chemistry and these compounds displayed a wide range of biological activities, such as antibacterial and antifungal activities [1-6]. Further, the treatment of infectious diseases still remains an important and challenging problem to researcher, because of their combination factors, such as emerging infectious diseases and their increasing number of multi-drug resistant in microbial pathogens. In despite of a large number of antibiotics and chemotherapeutics drugs available for medicinal use in the market, at the same time the emergence of old and new antibiotic resistance developed in the last decades medicinal properties substances need for new classes of antimicrobial agents. There is a real need for the discovery of new compounds provide with good antimicrobial activity. Similarly, in recent year increase incidence of fungal infections has been observed as consequence of the growing number of immune compromised patients and the frequent use of antibacterial and cytotoxic drugs. For many fungal infections, polyenes such as amphotericin B, represent the standard therapy. The polyenes antibiotics represent a class of biologically active fungal metabolites, Leakage and cell death. Amphotericin B is active against most pathogenic fungi in humans, and for over 40 years has been the cornerstone of therapy for critically ill patients with invasive fungal infections. However by high frequency of renal toxicity and several adverse effects [7] though the various synthesized molecules and for the above aim and to reduce the adverse effects [8,9].

It was demonstrated that, thiazoles a unique heterocycle containing sulphur and nitrogen atoms, occupies an importance place in medicinal chemistry in terms of decreased toxicity after oral or intravenous administration and are often utilized in the treatment of fungal infections. Therefore, the derivative of thiazole could be considered as possible antimicrobial agents [9]. Further, the thiazole nucleus frequently appears in various natural products and biologically active compounds. Similarly, there has been a keen interest in the chemistry of thiazolidin-4-one ring system, which is a core structure in various synthetic pharmaceuticals displaying a wide range of biological activities [10]. Thiazolidinone ring also occurs in nature; thus actithiazic acid isolated from *Streptomyces* strains exhibit highly specific *in vitro* activity against *Mycobacterium tuberculosis* [11]. Thiazolidinone derivatives are also known to exhibit diverse bioactivities such as anticonvulsant [12], antidiarrheal [13], antiplatelet activating factor [14], antihistaminic [15], antidiabetic [16], cyclooxygenase (COX) inhibitory [17], Ca^{2+}-channel blocker [18], platelet activating factor (PAF) antagonist [19], cardioprotective [20], anti-ischemic [21], anti-cancer [22], tumor necrosis factor-α antagonist [23] and nematicidal activities [24]. The synthesis of heterocycles containing multi structure in a molecule has received much attention in recent years [25].

It is well known that heterocyclic compounds containing nitrogen and sulphur are of great interest to researchers because of their diverse

biological activities. The review of literature data shows that 4-thiazolidinone scaffold is very versatile and has featured in a number of clinically used drugs. They have found uses as antibacterial, antifungal and antimycobacterial activity [26], antithyroid [27], amoebicidal [28,29], molluscicidal [30], antianticancer [31] and antidiabetic [32] activities. Moreover they have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activity. Hence it was thought interesting to study such type of moieties shown in Scheme 1. However, based on the wide spectrum of biological profile of indole, thiazole and thiazolidin-4-one and their increasing importance in pharmaceutical and biological field. Hence, linked heterocycles containing indole, thiazole and thiazolidinone have been reported and in continuation of our ongoing research on biologically active heterocycles [33-37], these observations encourage us to design drug strategy to synthesize several indole derivative possessing thiazole and thiazolidin-4-one moieties at 3-postion of indole ring in a single molecular frame work with potential antimicrobial activity.

EXPERIMENTAL PROCEDURE

Materials and methods

All the reagents/chemicals were purchased commercially and used by further purification using standard procedures. Melting points were determined by an open capillary method and are uncorrected. The purity of all the newly synthesized compounds was checked by thin layer chromatography using silica gel-G coated Al plates (Merck), spots were visualized by exposing the dry plates in iodine vapors. The IR (KBr pellet) spectra were recorded on a Perkin-Elmer (Spectrum ONE) FT-IR Spectrometer. The Proton Nuclear Magnetic Resonance (^{1}H-NMR) and Carbon-13 Nuclear Magnetic Resonance (^{13}C-NMR), Deuterated Dimethyl Sulfoxide (DMSO-d_6) spectra were recorded with a Bruker NMR 500 and 125 MHz spectrometers, and the chemical shift values are expressed in ppm (δ scale) using Tetramethylsilane (TMS) as an internal standard. The mass spectral measurements were carried out by Electron Impact method on JEOL GC mate spectrometer at 70 eV. Elemental analyses were performed on flash EA 1112 series elemental analyzer.

General procedure for the synthesis of 5,5,7-trimethyl-4,5,6,7-tetrahydro-1,3-benzothiazol-2-amine (2) and 5-Substituted 2-phenyl-1H-indol-3-carboxaldehydes (3a-c) were prepared by literature methods [38,39]

General procedure for the synthesis of N-((5-Substituted-2-phenyl-1H-indol-3-yl)methylene)-4,5,6,7-tetrahydro-5,7,-dimethylbenzo [d]thiazole-2-amine (4a-c)

A mixture of compound 2 (0.01 mol), indol-3-carboxaldehydes 3 (0.01 mol) and acetic acid (0.5 ml) were refluxed in toluene for 3 h, using a Dean-stark apparatus, the water formed was removed azeotropically. The progresses of the reaction were checked by Thin Layer Chromatography (TLC) using Toluene: Ethyl acetate (4:1) as an eluent. After completion of the reaction, solvent was removed by distillation, which was filtered, washed with water and dried, recrystallized from ethanol to give pure compounds 4a-c.

4,5,6,7-tetrahydro-5,5,7-trimethyl-N-((2-phenyl-1H-indol-3-yl)methylene)benz[d]thiazole-2-amine (4a): Yield 64%, Dark yellow solid m.p. 136-138°C; IR (KBr): 3090 (NH), 3052 (ArC-H), 2989 (Aliphatic C-H), 1629 (C=N), 1611 (C=C), 1421 (N=CH), 1102 (C-S-C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=0.99 (s, 6H, CH_3), 1.27-1.30 (d, *J*=6.7 Hz, 3H, CH_3), 1.40-1.45 (quasi d, *J*=4.6 Hz, 2H, CH_2), 2.05 (s, 2H, CH_2), 6.19-7.18 (m, 9H, Ar-H), 8.17 (s, 1H, CH=N), 10.81 (s, 1H, Indol-NH); ^{13}C-NMR (DMSO-d_6): δ=21.4, 27.1 × 2CH_3), 27.2, 33.8, 46.0, 47.9, 59.1, 111.2, 113.7, 117.8, 119.3, 120.2, 122.3, 123.4, 129.7, 127.4, 128.9, 129.9, 133.3, 136.8, 149.0, 161.0, 172.2; MS: *m/z* (%) 399 (M+, 77), 219 (19), 193 (100). Anal. Calcd for $C_{25}H_{25}N_2S$: C, 75.15; H, 6.31; N, 10.52. Found: C, 75.19; H, 6.30; N, 10.46.

N-((5-Chloro-2-phenyl-1H-indol-3-yl)methylene)-4,5,6,7-tetrahydro-5,7,-dimethylbenzo[d] thiazole-2-amine (4b): Yield 68%, Yellowish solid m.p. 166-168°C; IR (KBr): 3099 (NH), 3048 (ArC-H), 2999 (Aliphatic C-H), 1619 (C=N), 1621 (C=C), 1400 (N=CH), 1101 (C-S-C), 812 (C-Cl) cm^{-1}; ^{1}H-NMR (DMSO-*d*6): *δ* 1.11 (s, 6H, CH_3), 1.29-1.33 (d, *J*=6.7 Hz, 3H, CH_3), 1.42-1.47 (quasi d, *J*=4.6 Hz, 2H, CH_2), 2.12 (s, 2H, CH_2), 6.29-7.19 (m, 8H, Ar-H), 8.17 (s, 1H, CH=N), 10.81 (s, 1H, indol-NH); ^{13}C-NMR (DMSO-d_6): δ=21.5, 27.0 (2 × CH_3), 27.3, 33.5, 46.1, 47.8, 59.3, 111.2, 113.9, 117.5, 119.5, 120.1, 122.1, 123.4, 129.8, 127.7, 128.9, 129.8, 133.2, 136.5, 149.7, 161.3, 172.6; MS: *m/z* (%) 433 (M+, M^{+2} 77, 26), 225 (19, 7), 193 (80). Anal. Calcd for $C_{25}H_{24}N_2SCl$: C, 69.19; H, 5.57; N, 8 17. Found: C, 69.22; H, 5.64; N, 8.21.

N-((5-Methyl-2-phenyl-1H-indol-3-yl)methylene)-4,5,6,7-tetrahydro-5,7,-dimethylbenzo[d] thiazole-2-amine (4c): Yield 63%, Yellow solid m.p. 172°C; IR (KBr): 3153 (NH), 3029 (ArC-H), 2925 (Aliphatic C-H), 1617 (C=N), 1614 (C=C), 1409 (N=CH), 1108 (C-S-C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=1.17 (s, 6H, CH_3), 1.19-1.24 (d, *J*=6.7 Hz, 3H, CH_3), 1.42-1.47 (quasi d, *J*=4.6 Hz, 2H, CH_2), 1.66 (s, 1H, CH_3), 2.12 (s, 2H, CH_2), 6.38-7.26 (m, 8H, Ar-H), 8.22 (s, 1H, CH=N), 10.91 (s, 1H, indol-NH); ^{13}C-NMR (DMSO-d_6): δ=21.1, 27.1 (2 × CH_3), 27.2, 33.6, 46.2, 47.7, 59.1, 111.1, 113.5, 117.7, 119.6, 120.3, 122.3, 123.5, 129.7, 127.6, 128.7, 129.8, 133.1, 136.4, 149.9, 161.5, 172.9; MS: *m/z* (%) 413 (M+ 43), 210 (58), 193 (79). Anal. Calcd for $C_{26}H_{27}N_2$: C, 75.51; H, 6.58; N, 10. 16. Found: C, 75.57; H, 6.60; N, 10. 18.

General procedure for the synthesis of 2-(5-substituted-2-phenyl-1H-indol-3-yl)-3-(4,5,6,7-trimethylbenzo[d]thiazol-2-yl)-thiazolidin-4-one (5a-c)

A mixture of compound 4 (0.01 mol), thioglycolic acid (0.022 mol) in *N*, *N*-dimethylformamide (20 ml) with catalytic amount of anhydrous $ZnCl_2$, were refluxed for 6 h, the progress of the reaction were checked by TLC using Toluene: Ether (3:1) as an eluent. The reaction mixture was cooled at room temperature and then poured into crussed ice. The reaction mixture was kept at room temperature overnight. Thus, the solid separated was filtered, washed with water and purified by column chromatography on silica-gel with hexane-ethyl acetate as eluent to give pure compounds 5a-c.

3-(4,5,6,7-tetrahydro-5,5,7-trimethylbenzo[d]thiazol-2-yl)-2-(2-phenyl-1H-indol-3-yl) thiazolidin-4-one(5a): Yield 62%; Brown solid; m.p. 197-199°C; IR (KBr): 3111 (NH), 3062 (ArC-H), 1698 (C=O), 1612 (C=N), 1604 (C=C), 1125 (C-S-C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=1.10 (s, 6H, CH_3), 1.22-1.32 (d, *J*=6.6 Hz, 3H, CH_3), 1.34-1.35 (quasi d, *J*=4.6 Hz, 2H, CH_2), 2.29 (s, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.50-2.57 (m, 1H, CH), 3.71 (s, 2H, CH_2-S), 5.88 (s, 1H, CH-S), 7.11-7.27 (m, 8H, Ar-H), 11.09 (s, 1H, indol-NH); ^{13}C-NMR (DMSO-d_6): δ=17.2, 19.1, 22.0 (2 × CH_3), 27.2, 33.5, 46.7, 56.9, 111.0, 113.7, 117.5, 119.2, 120.1, 122.1, 123.4, 129.8, 127.7, 128.4, 129.9, 133.4, 136.5, 149.7, 165.7, 181.9. MS: *m/z* (%) 507 (M+, M^{+2} 90, 30). Anal. Calcd for $C_{27}H_{27}N_3OS_2$: C, 68.47; H, 5.75; N, 8.87. Found: C, 68.51, H, 5.79; N, 8.88.

2-(5-Chloro-2-phenyl-1H-indol-3-yl)-3-(4,5,6,7-trimethylbenzo[d]thiazol-2-yl)-thiazolidin-4-one (5b): Yield 69%; Brown solid; m.p. 214-15°C; IR (KBr): 3117 (NH), 3064 (ArC-H), 1691 (C=O), 1611 (C=N), 1601 (C=C), 1109 (C-S-C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=1.14 (s, 6H, CH_3), 1.24-1.34 (d, *J*=6.6 Hz, 3H, CH_3), 1.35-1.36 (quasi d, *J*=4.6 Hz, 2H, CH_2), 2.30 (s, 2H, CH_2), 2.32 (s, 3H, CH_3), 2.51-2.56 (m, 1H, CH), 3.71 (s, 2H, CH_2-S), 5.88 (s, 1H, CH-S), 7.10-7.29 (m, 8H, ArH), 11.14 (s, 1H, indol-NH); ^{13}C-NMR (DMSO-d_6): δ=22.1 (2 × CH_3), 27.2,

33.1, 46.7, 56.8, 111.1, 113.5, 117.9, 119.4, 120.2, 122.4, 123.8, 129.4, 127.8, 128.9, 129.7, 133.1, 136.7, 149.6, 166.0, 182.6. MS: *m/z* (%) 473 (M+, 76). Anal. Calcd for $C_{27}H_{26}N_3OS_2Cl$: C, 63.82; H, 5.16; N, 8.27. Found: C, 63.84; H, 5.21; N, 8.28.

2-(5-Methyl-2-phenyl-1H-indol-3-yl)-3-(4,5,6,7-trimethylbenzo[d]thiazol-2-yl)-thiazolidin-4-one (5c): Yield 67%; pale brown solid; m.p. 239-40°C; IR (KBr): 3124 (NH), 3049 (ArC-H), 1693 (C=O), 1611 (C=N), 1608 (C=C), 1111 (C-S-C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=1.19 (s, 6H, CH_3), 1.25-1.35 (d, *J*=6.6 Hz, 3H, CH_3), 1.36-1.37 (quasi d, *J*=4.6 Hz, 2H, CH_2), 1.78.(s, 1H, CH_3), 2.33 (s, 2H, CH_2), 2.38 (s, 3H, CH_3), 2.51-2.55 (m, 1H, CH), 3.75 (s, 2H, CH_2-S), 5.91 (s, 1H, CH-S), 7.18-7.25 (m, 8H, ArH), 11.15 (s, 1H, indol-NH); ^{13}C-NMR (DMSO-d_6): δ=19.2, 22.2 (2 × CH_3), 27.3, 33.2, 46.8, 56.8, 111.2, 113.1, 117.8, 119.3, 120.1, 122.1, 123.9, 129.2, 127.1, 128.5, 129.2, 133.2, 136.9, 149.4, 166.1, 181.9. MS: *m/z* (%) 487 (M+, 87). Anal. Calcd for $C_{28}H_{29}N_3OS_2$: C, 68.96; H, 5.99; N, 8.62. Found: C, 69.00; H, 6.09; N, 8.71.

General procedure for the 5-benzylidine-2-(5-substituted-2phenyl-1H-indol-3yl)-3-(4,5,6,7-tetrahydro-5,5,7-trimethylbenzo[d]thiazol-2-yl)thiazolidin-4-one (6a-c)

A mixture of compound 5 (0.01 mol), corresponding aldehydes (0.01 mol) and sodium acetate (0.02 mol) in a glacial acetic acid (10 ml), was refluxed for 6 h. The reaction mixture was concentrated and then poured into ice-cold water, the solid thus separated, was filtered, washed with cold water, the crude product obtained was purified by column chromatography on silica gel with hexane-ethyl acetate (4:1) as eluent to gave pure compounds 6a-c.

5-Bynzylidene-3-(4,5,6,7-tetrahydro-5,5,7-trimethylbenzo[d]thiazol-2-yl)-2-(5-methyl-2-phenyl-1H-indol-3yl)thiazolidin-4-one (6a): Yield 64%, Pale brown solid; m.p. 189-190°C; IR (KBr): 3119 (NH), 3069 (ArC-H), 1694 (C=O), 1614 (C=C), 1541 (C=C), 1477 (C=CH), 1101 (C-S-C) cm-1; 1H NMR (DMSO-*d*6): *δ* 0.96 (s, 6H, CH_3), 1.21-1.26 (d, *J*=6.7 Hz, 3H, CH_3), 1.54-1.56 (quasi d, *J*=4.6 Hz, 2H, CH_2), 2.11 (s, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.61-2.66 (m, 1H, -CH-S), 5.19 (s, 1H, C=CH), 6.52 (s, 1H, CH-S), 7.07-7.30 (m, 14H, Ar-H), 11.0 (s, 1H, indol-NH); ^{13}C-NMR (DMSO-d_6): δ=21.6, 26.2, 27.3 (2 × CH_3), 46.6, 47.0, 55.5, 113.4, 111.3, 117.6, 119.2, 120.2, 122.1, 123.5, 125.3, 126.4, 127.6, 128.2, 128.7, 128.9, 129.3, 133.8, 135.4, 136.1, 138.3, 148.8, 158.2, 172.3. MS: *m/z* (%) 561 (M+, 98). Anal. Calcd for $C_{34}H_{31}N_3OS_2$: C, 72.69.; H, 5.56; N, 7.48. Found: C, 72.74.; H, 5.60; N, 7.55.

5-Benzylidine-2-(5-chloro-2-phenyl-1H-indol-3yl)-3-(4,5,6,7-tetrahydro-5,5,7-trimethyl benzo[d]thiazol-2-yl)thiazolidin-4-one (6b): Yield 63%, Pale brown solid; m.p. 203-04°C; IR (KBr): 3112 (NH), 3066 (ArC-H), 1697 (C=O), 1611 (C=C), 1539 (C=C), 1479 (C=CH), 1108 (C-S-C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=1.05 (s, 6H, CH_3), 1.20-1.25 (d, *J*=6.7 Hz, 3H, CH_3), 1.55-1.58 (quasi d, *J*=4.6 Hz, 2H, CH_2), 2.12 (s, 2H, CH_2), 2.40 (s, 3H, CH_3), 2.61-2.66 (m, 1H, -CH-S), 5.21 (s, 1H, C=CH), 6.50 (s, 1H, CH-S), 7.09-7.34 (m, 13H, Ar-H), 10.99 (s, 1H, indol-NH); ^{13}C-NMR (DMSO-d_6): δ=20.9, 26.3, 27.5 (2 × CH_3), 46.8, 47.0, 55.4, 113.7, 111.7, 117.5, 119.3, 120.1, 122.5, 123.4, 125.3, 126.5, 127.4, 128.7, 128.8, 128.9, 129.4, 133.7, 135.4, 136.4, 138.4, 148.9, 158.3, 172.6. MS: *m/z* (%) 596 (M^{+2}, 98, 33). Anal. Calcd for $C_{34}H_{30}N_3OS_2Cl$: C, 68.49; H, 5.07; N, 7.05. Found: C, 68.52; H, 5.09; N, 7.09.

5-Benzylidine-2-(5-methyl-2-phenyl-1H-indol-3-yl)-3-(4,5,6,7-tetrahydro-5,5,7-trimethylbenzo [d]thiazol-2-yl)thiazolidin-4-one (6c): Yield 66%, brown solid; m.p. 127-18°C; IR (KBr): 3129 (NH), 3074 (ArC-H), 1696 (C=O), 1616 (C=C), 1544 (C=C), 1470 (C=CH), 1102 (C-S-C) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ=1.07 (s, 6H, CH_3), 1.21-1.26 (d, *J*=6.7 Hz, 3H, CH_3), 1.55-1.57 (quasi d, *J*=4.6 Hz, 2H, CH_2), 1.69 s, 1H, CH_3), 2.09 (s, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.61-2.66 (m, 1H, -CH-S), 5.17 (s, 1H, C=CH), 6.50 (s, 1H, CH-S), 7.07-7.30 (m, 13H, Ar-H), 11.01 (s, 1H, indol-NH); ^{13}C-NMR (DMSO-d_6): δ=21.5, 26.2, 27.4 (2 × CH_3), 46.7, 47.5, 55.6, 113.4, 111.4, 117.8, 119.3, 120.3, 122.2, 123.7, 125.4, 126.5, 127.7, 128.3, 128.9, 128.8, 129.3, 133.9, 135.5, 136.2, 138.4, 148.7, 158.5, 172.5. MS: *m/z* (%) 575 (M+, 75). Anal. Calcd for $C_{35}H_{33}N_3OS_2$: C, 73.01. H, 5.78; N, 7.30. Found: C, 73.04.; H, 5.69; N, 7.35.

Antimicrobial activity

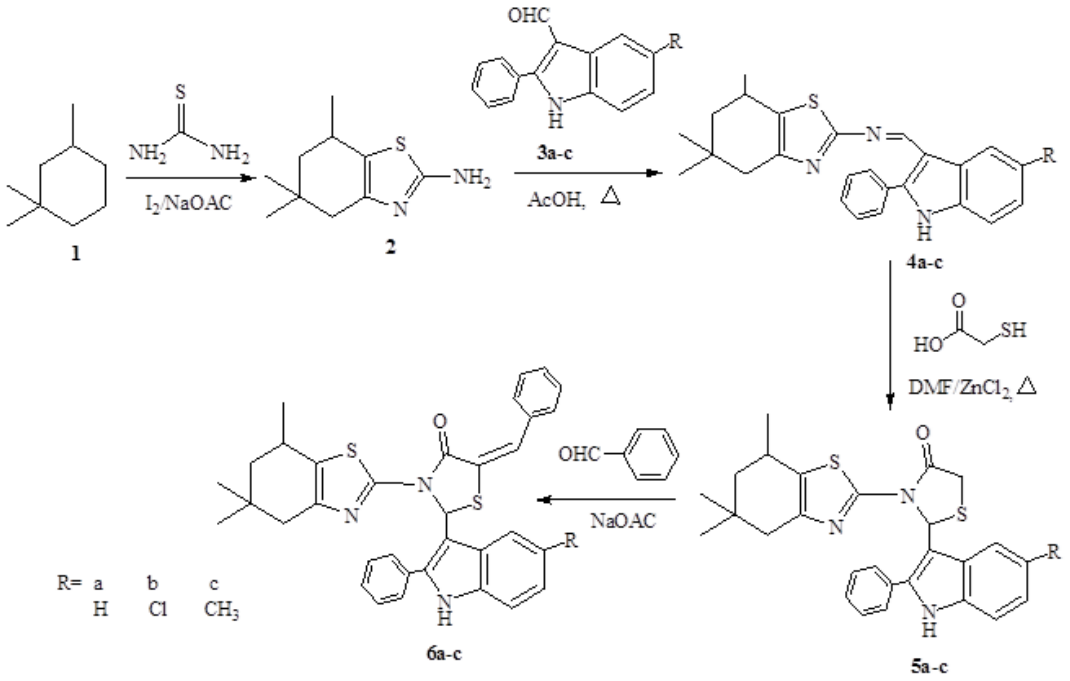
The *in vitro* antimicrobial activity of all the newly synthesized compounds (4-6) were carried out by broth micro dilution method (NCCLS, 2002) in DMF at concentration 500, 250, 125 and 62.5 µg/ml. Muller Hinton broth was used as nutrient medium to growth bacteria and Saboured Dextrose broth used for fungal nutrition. Inoculums sizes for test strain were adjusted to 10^8 CFU (Colony Forming Unit) per milliliter by comparing the turbidity. The strain used for the activity was procured from Department of microbiology, Gulbarga University, Gulbarga.

The compounds (4-6) were screened for their antibacterial and antifungal activity against bacterial strain such as *Escherichia coli* (MTCC-723), *Staphylococcus aureus* (ATCC-29513), *Klebsiella pneumonia* (NCTC-13368) and *Pseudomonas aeruginosa* (MTCC-1688), and fungal strains *Aspergillus oryzae* (MTCC-3567^T), *Aspergillus niger* (MTCC-281), *Aspergillus flavus* (MTCC-1973) and *Aspergillus terreus* (MTCC-1782). DMSO used as a solvent to get desired concentration of compounds to test upon microbial strains. The minimum concentration which was showed no visible growth after spot subculture was considered as MIC for each compound. The standard antibiotics gentamycin used for comparison in present study were for evaluating for antibacterial activity as well as and fluconazole for antifungal activity, respectively. The protocol was summarized in (Table 1).

RESULTS AND DISCUSSION

Chemistry

Compound 2 on condensation reaction with 5-Substituted 2-phenyl-1*H*-indol-3-carboxaldehydes (3a-c) [39] in acetic acid under reflux temperature for 3 h, afforded) *N*-((5-Substituted-2-phenyl-1*H*-indol-3-yl)methylene)-4,5,6,7-tetrahydro-5,7,-dimethylbenzo[d] thiazole-2-amine (4a-c) in good yield. The synthesis of 2-(5-substituted-2-phenyl-1*H*-indol-3-yl)-3-(4,5,6,7-trimethylbenzo[d]thiazol-2-yl)-thiazolidin-4-one (5a-c) was carried out by the cyclocondensation reaction between compounds (4a-c) and mercaptoacetic acid in the presence of $ZnCl_2$ in dimethylformamide solvent under reflux temperature for 6 h. Further, compounds (5a-c) on condensation with various aldehydes in the presence of anhydrous sodium acetate in glacial acetic acid at reflux temperature to afforded 5-benzylidine-2-(5-substituted-2-phenyl-1*H*-indol-3-yl)-3-(4,5,6,7-tetrahydro-5,5,7-trimethylbenzo[d]thiazol-2-yl)thiazolidin-4-one (6a-c) in good yield (Scheme 1). The structure of all the newly synthesized compounds has been accomplished on the basis of elemental analyses and spectral techniques like IR, ^{1}H-NMR, ^{13}C-NMR and Mass spectroscopy. The detailed synthetic strategy is outlined in Scheme 1. Analytical and spectral data of the synthesized compounds are given in the experimental section.



Scheme 1: Synthetic pathway of the compounds 4-6

Antimicrobial activity

The antimicrobial results depicted in (Table 1) revealed that most of the screening compounds exhibited variable inhibitory effects on the growth of tested bacterial and fungal strains in the concentration range of 62.5-250 µg/ml which is comparatively more or equipotent than the standards gentamycin and fluconazole. Antibacterial activity of screened samples, compound 4a showed potent activity (62.5 µg/ml) against *E. coli*, 5b showed potent activity (62.5 µg/ml) against *P. aeruginosa* and 6b showed potent activity (62.5 µg/ml) against *S. aureus* and *P. aeruginosa*, this potent activity may be due to presence of electron withdrawing chlorine atom at C-5 position of indole system. Remaining all the tested compounds exhibited equipotent or less potent activity than the standard. Compounds 4b, 5b and 6b exhibited equipotent activity against all the above four microorganisms when compared with the standard drugs. Whereas, the rest of compounds are in the series exhibited moderate to less activity [40].

Antifungal activity screening results revealed that the compounds 4b and 5b showed potent activity (62.5 µg/ml) against *A. niger*, 6b showed potent activity (62.5 µg/ml) against *A. oryzae, A. flavus* and *A. terreus*, this potent activity may be due to presence of chlorine atom at C-5 position of indole system. Whereas, rest of the compounds are in the series exhibited moderate to less activity. Screening studies have demonstrated that the newly synthesized compounds have promising antibacterial and antifungal properties. Therefore, it was concluded that there exists better scope for further study on this class of compounds.

Table 1: *In vitro* antimicrobial activities of compounds (4-6)

Compound code	Antibacterial activity (MIC µg/ml)				Antifungal activity (MIC µg/ml)			
	Escherichia coli	***Staphylococcus aureus***	***Klebsiella pneumonia***	***Pseudomonas aeruginosa***	***Aspergillus oryzae***	***Aspergillus niger***	***Aspergillus flavus***	***Aspergillus terreus***
4a	125	500	500	500	500	250	125	500
4b	62.5	125	125	125	125	62.5	125	250
4c	250	250	250	250	500	500	250	500
5a	125	500	250	250	250	500	250	500
5b	125	125	250	62.5	125	62.5	250	250
5c	500	250	500	250	250	125	250	500
6a	250	500	500	250	250	125	250	500
6b	62.5	62.5	62.5	62.5	125	125	62.5	125
6c	500	250	500	250	500	250	500	500
Gentamycin	125	125	250	125	--	--	--	--
Fluconazole	--	--	--	--	125	62.5	125	250

CONCLUSIONS

The present study indole derivatives and evaluated for their antimicrobial activity against bacterial strains such as, *E. coli* (MTCC-723), *S. aureus* (ATCC-29513), *K. pneumonia* (NCTC-13368), *P. aeruginosa* (MTCC-1688) and the fungal strains such as *A. oryzae* (MTCC-3567^{T}), *A. niger* (MTCC-281), *A. flavus* (MTCC-1973), *A. terreus* (MTCC-1782). *A. niger* carried out by broth micro dilution method (NCCLS). The antimicrobial results revealed that compounds 4b, 5b and 6b displayed variable inhibitory effects on the growth of tested bacterial and fungal strains in the concentration range of 62.5-250 µg/ml which is comparatively more or equipotent than the standards gentamycin and fluconazole. Most of the compounds showed appreciable antimicrobial activity against the tested bacteria and fungi, and emerged as potential molecules for further development.

ACKNOWLEDGEMENT

The authors are thankful to the Chairman, Department of Chemistry, Gulbarga University, Gulbarga, for providing laboratory facilities, Chairman, Department of Microbiology, Gulbarga University, Gulbarga, for providing facilities to carry out antimicrobial activity and to the Director, Indian Institute of Technology, Chennai for providing ^{1}H-NMR and Mass spectra. One of us (P.W.) is thankful to Council of Scientific and Industrial Research, New Delhi India for providing the financial support as a (CSIR-SRF).

REFERENCES

[1] K.F Ansari, C. Lal, J. Chem. Sci., **2009**, 121, 1017.
[2] S. Antus, K. Gulacsi, L. Juhasz, L. Kiss, T. Kurtan, *Pure Appl. Chem*., **2004**, 76, 1025.
[3] T.B. Mostafa, *J. Am. Sci*., **2010**, 6, 512.
[4] A.K. Singh, G. Mishra, K. Jyoti, *J. Appl. Pharm. Sci*., **2011**, 1, 44.
[5] J. Salimon, N. Salih, H. Hussien, E. Yousif, *Eur. J. Sci. Res*., **2009**, 31, 256.
[6] P.F. Xu, Z.H. Zhang, X.P. Hui, Z.Y. Zhang, R.L. Zheng, *J. Chin. Chem. Soc.*, **2004**, 51, 315.
[7] M.S. Chande, V. Suryanarayan, *J. Chem. Res*., **2005**, 345.
[8] C.V. Kavitha, A. Basappa, S.N. Swamy, K. Mantelingu, S. Doreswamy, M.A. Sridhar, J.S. Prasad, K.S. Rangappa, *Bioorg. Med. Chem.*, **2006**, 14, 2290.
[9] B.A. Sobin, *J. Am. Chem. Soc*., **1952**, 2947.
[10] Y. Tanabe, G. Suzukamo, Y. Komuro, N. Imanishi, S. Morooka, M. Enomoto, A. Kojima, Y. Sanemitsu, M. Mizutani, *Tetrahedron Lett*., **1991**, 32, 379.
[11] M.A. Eisenberg, S.C. Hsiung, *Antimicrob. Agents Chemother.*, **1982**, 21, 5.
[12] F.A. Ragab, N.M. Eid, H.A. El-Tawab, *Pharmazie.*, **1997**, 52, 926.
[13] O. Mazzoni, A.M. Bosco, P. Grieco, E. Novellino, A. Bertamino, F. Borelli, R. Capasso, M.V. Diurno, *Chem. Biol. Drug Design.*, **2006**, 67, 432.
[14] Y. Tanabe, H. Okumura, M. Nagaosa, M. Murakami, *Bull. Chem. Soc. Jpn*., **1995**, 8, 1467.
[15] P. Tindara, B. Maria, G.V. Maria, F. Giovanna, O. Francesco, C. Clara, C.P. Rita, *Eur. J. Med. Chem*., **1985**, 22, 67.
[16] V. Prabhakar, K. Vipan, Acta Pharmaceutica Sciencia., **2010**, 52, 411.
[17] A.D. Taranalli, A.R. Bhat, S. Srinivas, E. Saravanan, *Indian J. Pharm. Sci*., **2008**, 70, 159.
[18] A.S.K. Verma, Saraf, *Eur. J. Med. Chem*., **2008**, 43, 897.
[19] S. Rollas, S.G. Kucukguzel, *Molecules.*, **2007**, 12, 1910.
[20] T. Kato, T. Ozaki, K. Tamura, Y. Suzuki, M. Akima, N. Ohi, *J. Med. Chem*., **1999**, 42, 3134.
[21] R. Raghubir, R. Verma, S.S. Samuel, S. Raza, W. Haq, S.B. Katti, *Chem. Biol. Drug. Design*., **2011**, 78, 445.
[22] K. Danylo, K. Dmytro, V. Olexandr, Z. Lucjusz, L. Roman, *Sci. Pharm*., **2011**, 79, 763.
[23] L. Mosula, B. Zimenkovsky, D. Havrylyuk, A.V. Missir, I.C. Chirita, R. Lesyk, *Farmacia*., **2009**, 57, 321.
[24] A. Srinivas, A. Nagaraj, C.S. Reddy, *J. Heterocycl. Chem*., **2008**, 45, 999.
[25] A. Srinivas, A. Nagaraj, C.S. Reddy, *Eur. J. Med. Chem*., **2010**, 45, 2353.
[26] A. Gihsoyl, N. Terzioglul, G. Otuk, *Eur. J. Med. Chem*., **1997**, 17, 181.
[27] K.C. Asati, S.K. Srivastava, S.D. Srivastava, *Indian J. Chem.*, **2006**, 45B, 526.
[28] J.N. Gadre, S. Nair, C. Saurabh, *Indian J. Chem*., **2007**, 46B, 653.
[29] Nizamuddin, A. Singh, *Indian J. Chem*., **2004**, 43B, 90.
[30] A. Mohd, M.S.Y. Khan, M.S. Zaman, *Indian J. Chem*., **2004**, 43B, 2189.
[31] S. Mishra, S.K. Srivastava, S.D. Srivastava, *Indian J. Chem.*, **1997**, 36B, 826.
[32] S. Chandrappa, C.V. Kavitha, M.S. Shahabuddin, K. Vinaya, C.S. Anandakumar, S.R. Ranganatha, S.C. Raghavan, K.S. Rangappa, *Bioorg. Med. Chem*., **2009**, 17, 2576.
[33] A.R. Saundane, W. Prabhaker, *J. Chem*., **2012**, 1-9.
[34] A.R. Saundane, M. Yarlakatti, W. Prabhaker, V. Katkar, *J. Chem. Sci*., **2012**, 124(2), 469.
[35] A.R. Saundane, W. Prabhaker, M. Yarlakatti, V. Katkar, A.V. Vaijeenath, *J. Het. Chem.*, **2014**, 51(2), 301.
[36] A.R. Saundane, W. Prabhaker, *Der Pharma Chemica*, **2015**, 7(6), 131.
[37] A.R. Saundane, W. Prabhaker, *Der Pharma Chemica*., **2014**, 6(4), 70.
[38] A. Nagaraj, G. Ravi, Naseem, Sharath S. Kumar, R.G. Nageswara, *Org. Commun*., **2012**, 5(4), 160.
[39] S.P. Hiremath, J.S. Biradar, M.G. Purohit, *Indian J. Chem*., **1982**, 21B, 249.
[40] National Committee for Clinical Laboratory Standards (NCCLS) 940, West Valley Suite 1400, Wayne, Pennsylvania 19087-1898, USA. Performance standards for antimicrobial susceptibility testing: Twelth Informational Supplement (ISBN 1-56238-454-6) M100-S12, **2002**.