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Research Article

DESIGN, SYNTHESIS OF BIOLOGICALLY ACTIVE HETEROCYCLES CONTAINING INDOL- THIAZOLYL- THIAZOLIDINONE DERIVATIVES

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ABSTRACT

Objective: The present study envisage a novel series of thiazole, indole and thiazolidine derivatives, namely, *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), 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) and 5-benzylidine-2-(5-substituted-2phenyl-1*H*-indol-3yl)-3-(4,5,6,7-tetrahydro-5,5,7-trimethylbenzo[d]thiazol-2-yl) thiazolidin-4-one (6a-c).

Methods: All the newly synthesized compounds were characterized by infrared, ^{1}H, ^{13}C nuclear magnetic resonance and mass spectral data and elemental analysis and evaluated for *in vitro* antimicrobial activity.

Results: Novel compounds *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), 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) and 5-benzylidine-2-(5-substituted-2phenyl-1*H*-indol-3yl)-3-(4,5,6,7-tetrahydro-5,5,7-trimethyl benzo[d]thiazol-2-yl)thiazolidin-4-one (6a-c) have been made and characterized using spectral and analytical data. The results of antibacterial and antifungal activities showed that some of the synthesized compounds exhibited promising activities.

Conclusion: All the newly synthesized compounds were carried out by the broth microdilution method (NCCLS. 2002) in a DMF concentration of 500, 250, 125, and 62.5 µg/ml. Gentamycin and fluconazole are used as reference standards for antibacterial and antifungal activity, respectively. The final results revealed that compounds 4b, 5b, and 6b exhibited potent antimicrobial activity when compared to the standard drugs.

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

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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 is illnesses caused still remains an important and challenging problem for researchers due to their combination factors increase the number of multidrug-resistant in microbial pathogens developed. In despite a large number of antibiotics and chemotherapeutic drugs available for medicinal use in the market, at the same time, the prominence of old and new antibiotic resistance was developed in the past decades, medicinal properties substances need for new classes of antimicrobial agents. There is a real need for the discovery of new substances which provide with potent antimicrobial activity. However, by the 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 sulfur and nitrogen atoms, occupies an important 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 slightly specific *in vitro* activity against *Mycobacterium tuberculosis* [11]. Thiazolidinone derivatives are also known to exhibit diverse bioactivities such as anticonvulsant [12], antidiarrheal [13], anti-platelet activating factor (PAF) [14], antihistaminic [15], antidiabetic [16], cyclooxygenase inhibitory [17], Ca^{2+}-channel blocker [18], PAF antagonist [19], cardioprotective [20], anti-ischemic [21], anticancer [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 sulfur are of great interest to researchers due to their diverse biological activities. The literature data show that 4-thiazolidinone scaffold is very versatile and has featured in a number of clinically used drugs in the market. They have exhibited as antibacterial, antifungal and antimycobacterial activity [26], antithyroid [27], amoebicidal [28], anticancer [29], and antidiabetic [30] activities. However, based on the wide spectrum of biological profile of indole, thiazole, and thiazolidin-4-one and their derivatives increasing importance in the pharmaceutical and biological field. Hence, linked heterocycles containing indole, thiazole, and thiazolidinone have been synthesized and in continuation of our ongoing research on biologically active heterocycles [31-38], these observations encourage us to design drug strategy to synthesize several indole derivative possessing thiazole and thiazolidin-4-one moieties at 3-position of indole ring in a single molecular framework with potential antimicrobial activity.

MATERIALS AND METHODS

Materials

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 infrared (IR) (KBr pellet) spectra were recorded on a Perkin-Elmer (Spectrum ONE) Fourier-transform infrared spectrometer. The ^{1}H nuclear magnetic resonance (NMR) and ^{13}C NMR (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 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 [39,40]

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 progress of the reaction was checked by thin layer chromatography (TLC) using toluene: ethyl acetate(4:1) as an eluent. After completion of the reaction, the 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) (λ_{max} in cm^{-1}): 3090 (NH), 3052 (ArC-H), 2989 (Aliphatic C-H), 1629 (C=N), 1611 (C=C), 1421 (N=CH), 1102 (C-S-C).^{1}H NMR(DMSO-d6) δ(ppm):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-d6)$^\delta$(ppm): 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). Analysis: 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-1*H*-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) (λ_{max} in cm^{-1}): 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).^{1}H NMR (DMSO-d6) δ(ppm):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, indole-NH).^{13}C NMR (DMSO-d6) δ(ppm): 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). Analysis: 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-1*H*-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) (λ_{max} in cm^{-1}): 3153 (NH), 3029 (ArC-H), 2925 (Aliphatic C-H), 1617 (C=N), 1614 (C=C), 1409 (N=CH), 1108 (C-S-C). ^{1}H NMR (DMSO-d_6) δ(ppm):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, indole-NH); ^{13}C NMR (DMSO-d_6) δ(ppm): 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). Analysis: 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 of2-(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 a catalytic amount of anhydrous $ZnCl_2$, was refluxed for 6 h, the progress of the reaction was checked by TLC using toluene: ether(3:1) as an eluent. The reaction mixture was cooled at room temperature and then poured into crushed 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) (λ_{max} in cm^{-1}): 3111 (NH), 3062 (ArC-H), 1698 (C=O), 1612 (C=N), 1604 (C=C), 1125 (C-S-C).^{1}H NMR (DMSO-d_6) $^\delta$(ppm):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, indole-NH). ^{13}C NMR (DMSO-d_6) $^\delta$(ppm): 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). Analysis: 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-1*H*-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) (λ_{max} in cm^{-1}): 3117 (NH), 3064 (ArC-H), 1691 (C=O), 1611 (C=N), 1601 (C=C), 1109 (C-S-C).^{1}H NMR (DMSO-d_6)$^\delta$ (ppm): 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, indole-NH).^{13}C NMR (DMSO-d_6) $^\delta$ (ppm):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). Analysis: 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-1*H*-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) (λ_{max} in cm^{-1}): 3124 (NH), 3049 (ArC-H), 1693 (C=O), 1611 (C=N), 1608 (C=C), 1111 (C-S-C).^{1}H NMR (DMSO-d_6)$^\delta$ (ppm):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, indole-NH).^{13}C NMR (DMSO-d_6)$^\delta$(ppm):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). Analysis: 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 6h. 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 give 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-1*H*-indol-3yl)thiazolidin-4-one (6a)
Yield 64%, Pale brown solid m.p. 189-190°C; IR (KBr) (λ_{max} in cm^{-1}): 3119 (NH), 3069 (ArC-H), 1694 (C=O), 1614 (C=C), 1541 (C=C), 1477 (C=CH), 1101 (C-S-C). ^{1}H NMR (DMSO-d6) δ(ppm):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, indole-NH). ^{13}C NMR (DMSO-d_6) δ(ppm):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). Analysis: 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-1*H*-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) (λ_{max} in cm^{-1}): 3112 (NH), 3066 (ArC-H), 1697 (C=O), 1611 (C=C), 1539 (C=C), 1479 (C=CH), 1108 (C-S-C). ^{1}H NMR (DMSO-d_6) δ(ppm): 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, indole-NH). ^{13}C NMR (DMSO-d_6) δ(ppm):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). Analysis: 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-1*H*-indol-3-yl)-3-(4,5,6,7-tetrahydro-5,5,7-trimethyl benzo[d]thiazol-2-yl)thiazolidin-4-one (6c)
Yield 66%, brown solid m.p. 127-18°C; IR (KBr) (λ_{max} in cm^{-1}): 3129 (NH), 3074 (ArC-H), 1696 (C=O), 1616 (C=C), 1544 (C=C), 1470 (C=CH), 1102 (C-S-C).1H NMR (DMSO-d_6) δ(ppm):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, indole-NH). ^{13}C NMR (DMSO-d_6) δ(ppm):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). Analysis: 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.

BIOLOGICAL ACTIVITIES

Antimicrobial activity

The *in vitro* antimicrobial activity of all the newly synthesized compounds (4-6) was carried out by the broth microdilution method (NCCLS. 2002) in DMF at concentration 500, 250, 125, and 62.5 µg/ml. The Muller Hinton broth was used as a nutrient medium to growth bacteria and the Sabouraud Dextrose broth used for fungal nutrition. Inoculums sizes for test strain were adjusted to 10^8 colony forming unit per milliliter by comparing the turbidity. The strain used for the activity was procured from the 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 the desired concentration of compounds to test for microbial strains. The minimum concentration which showed no visible growth after spot subculture was considered as minimum inhibitory concentration for each compound. The standard antibiotic gentamycin used for comparison, in the present study was for evaluating for antibacterial activity as well as and fluconazole for antifungal activity, respectively. The protocols were summarized in Table 1.

RESULTS AND DISCUSSION

Chemistry

Compound 2 in a condensation reaction with5-Substituted 2-phenyl-1*H*-indol-3-carboxaldehydes (3a-c) [40] in acetic acid under reflux temperature for 3h, 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 ZnCl2 in dimethylformamide solvent under reflux temperature for 6h. Further, compounds (5a-c) on condensation with various aldehydes in the presence of anhydrous sodium acetate in glacial acetic acid at reflux temperature to afford 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 such as 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.

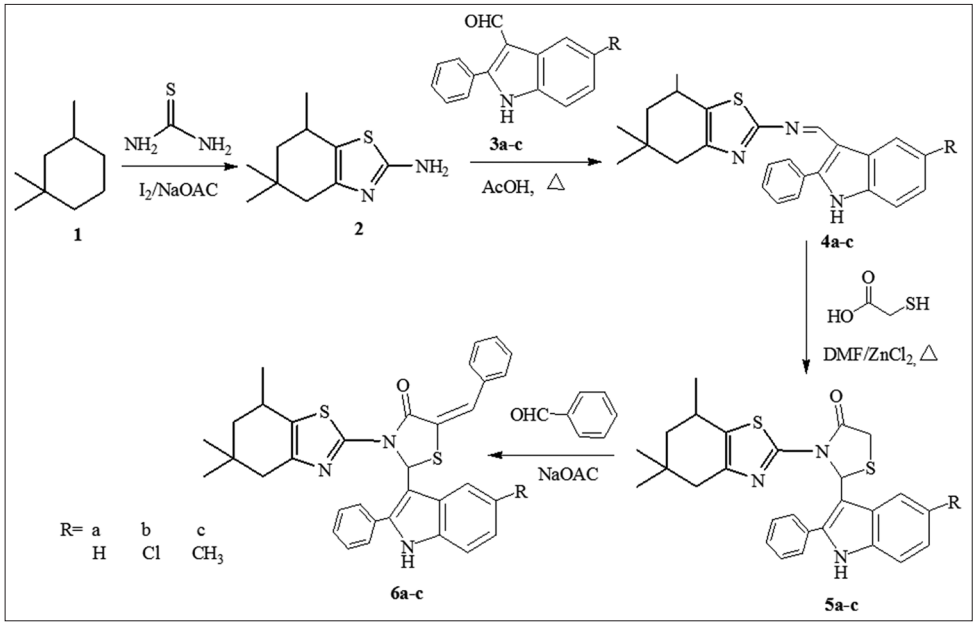
Antimicrobial activity

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 gentamicin and fluconazole. Antibacterial activity of screened samples, compound 4a showed potent activity (62.5 µg/ml) against *E. coli* (MTCC-723), 5b showed potent activity (62.5 µg/ml) against *P. aeruginosa* (MTCC-1688), and 6b showed potent activity (62.5 µg/ml)

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

Comp. code	Antibacterial activity (MIC µg/ml)				Antifungal activity (MIC µg/ml)			
	EC[a]	SA[b]	KP[c]	PA[d]	AO[e]	AN[f]	AF[g]	AT[h]
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

Values are expressed in mean (n=3). [a]EC: *Escherichia coli* (MTCC-723), [b]SA: *Staphylococcus aureus* (ATCC-29513), [c]KP: *Klebsiella pneumonia* (NCTC-13368), [d]PA: *Pseudomonas aeruginosa* (MTCC-1688), [e]AO: *Aspergillus oryzae* (MTCC-3567^T), [f]AN: *Aspergillus niger* (MTCC-281), [g]AF:*Aspergillusflavus* (MTCC-1973), [h]AT: *Aspergillus terreus* (MTCC-1782). MIC: minimum inhibitory concentration



Scheme 1: Synthetic pathway of the compounds 4-6

against *S. aureus* (ATCC-29513) and *P. aeruginosa* (MTCC-1688), this potent activity may be due to the presence of electron withdrawing chlorine atom at the 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 the compounds are in the series exhibited moderate to less activity.

Antifungal activity screening results revealed that the compounds 4b and 5b showed potent activity (62.5 µg/ml) against *A. niger* (MTCC-281), 6b showed potent activity (62.5 µg/ml) against *A. oryzae* (MTCC-3567^{T}), *A. flavus (*MTCC-1973), and *A. terreus* (MTCC-1782), this potent activity may be due to the presence of chlorine atom at the 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.

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), and *P. aeruginosa* (MTCC-1688) and the fungal strains such as *A. oryzae* (MTCC-3567^{T}), *A. niger* (MTCC-281), *A. flavus* (MTCC-1973), and *A. terreus* (MTCC-1782). *A. niger* carried out by the broth microdilution 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.

AUTHORS CONTRIBUTION

Dr. Prabhaker walmik is the advisor involved in crafting and in the generation of new heterocyles containing indol-thiazolyl-thiazolidinone derivatives, he is the supervisor of the overall work. Mr. Basavaraj S. Naraboli was mainly involved in synthesis/ characterization of entitled molecules, Dr. Swati B. and Dr. Somashekar Ghanti were involved in carrying out *in vitro* antimicrobial activities.

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CONFLICT OF INTEREST

Declared none.

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