DESIGN, SYNTHESIS OF BIOLOGICALLY ACTIVE HETEROCYCLES CONTAINING INDOLE-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-1H-indol-3-yl)methylene]-4,5,6,7-tetrahydro-5,7-dimethylbenzo[d]thiazole-2-amine (4a-c), 2-[(5-Substituted-2-phenyl-1H-indol-3-yl)-3-(4,5,6,7-trimethylbenzo[d]thiazol-2-yl)thiazolidin-4-one (5a-c) and 5-benzylidine-2-(5-Substituted-2-phenyl-1H-indol-3-yl)-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, ¹H, ¹³C 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-1H-indol-3-yl)methylene]-4,5,6,7-tetrahydro-5,7-dimethylbenzo[d]thiazole-2-amine (4a-c), 2-[(5-Substituted-2-phenyl-1H-indol-3-yl)-3-(4,5,6,7-trimethylbenzo[d]thiazol-2-yl)thiazolidin-4-one (5a-c) and 5-benzylidine-2-(5-Substituted-2-phenyl-1H-indol-3-yl)-3-(4,5,6,7-tetrahydro-5,5,7-trimethylbenzo[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.

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], Ca²⁺-channel blocker [18], PAF antagonist [19], cardioprotective [20], anti-ischemic [21], anticancer [22], tumor necrosis factor-α antagonist [23], and nematocidal 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 after 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 1H nuclear magnetic resonance (NMR) and 13C NMR (DMSO-d6) spectra were recorded with a Bruker NMR 500 MHz spectrometer, 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-5,5,7-trimethylbenzo[d]thiazole-2-amine (4a-c)

A mixture of compound 2 (0.01 mol), indol-3-carboxaldehydes 3 (0.01 mol) and sodium acetate (0.02 mol) in glacial acetic acid (10 ml), was refluxed for 3 h using a Dean-stark apparatus, the water formed was removed azeotropically. 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 4a-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) (δv in cm⁻¹): 3111 (NH), 3062 (ArCH), 1698 (C=O), 1612 (C=N), 1125 (C-S-C). 1H NMR (DMSO-d6) (ppm): 1.10 (s, 6H, CH3), 1.17-1.34 (d, J=6.6 Hz, 2H, CH2), 2.33 (s, 3H, CH3), 2.50-2.57 (m, 1H, CH), 3.71 (2H, CH2), 5.88 (s, 1H, CH-S), 7.17-7.27 (m, 8H, Ar-H), 11.09 (s, 1H, indole-NH). 13C NMR (DMSO-d6) (ppm): 17.2, 19.1, 22.0 (2 × CH3), 27.2, 32.8, 46.0, 47.9, 59.1, 111.2, 113.7, 117.8, 119.3, 120.1, 122.3, 124.6, 127.7, 128.4, 129.9, 133.4, 136.5, 149.7, 165.7, 181.9. MS: m/z (%) 507 (M+), 479, 460, 40, 39. Analysis: C, 68.51; H, 5.79; N, 8.88.

3-(4-Chloro-2-phenyl-1H-indol-3-yl)-3-(4,5,6,7-tetrahydro-5,5,7-trimethylbenzo[d]thiazol-2-yl)-thiazolidin-4-one (5b)

Yield 60%; Brown solid m.p. 214-215°C; IR (KBr) (δv in cm⁻¹): 3105 (NH), 3064 (ArCH), 1691 (C=O), 1611 (C=N), 1109 (C-S-C). 1H NMR (DMSO-d6) (ppm): 1.14 (s, 6H, CH3), 1.24-1.36 (d, J=6.6 Hz, 2H, CH2), 2.30 (s, 3H, CH3), 2.51-2.56 (m, 1H, CH), 3.71 (2H, CH2-S), 5.88 (s, 1H, CH-S), 7.10-7.29 (m, 8H, Ar-H), 11.14 (s, 1H, indole-NH). 13C NMR (DMSO-d6) (ppm): 22.1 (2 × CH3), 27.2, 32.1, 46.7, 56.7, 111.1, 113.5, 117.9, 119.4, 120.2, 122.4, 123.8, 129.4, 128.7, 129.7, 131.3, 136.7, 149.6, 166.0, 182.6. MS: m/z (%) 475 (M+), 76. Analysis: C, 62.60; H, 5.16; N, 8.27. Found: C, 62.62; H, 5.21; N, 8.26.

3-(2-Chloro-2-phenyl-1H-indol-3-yl)-3-(4,5,6,7-tetrahydro-5,5,7-trimethylbenzo[d]thiazol-2-yl)-thiazolidin-4-one (5c)

Yield 67%; pale brown solid m.p. 239-400°C; IR (KBr) (δv in cm⁻¹): 3124 (NH), 3049 (ArCH), 1693 (C=O), 1611 (C=N), 1608 (C=S-C). 1H NMR (DMSO-d6) (ppm): 1.19 (s, 6H, CH3), 1.25-1.35 (d, J=6.6 Hz, 2H, CH2), 1.36-1.37 (quasi d, J=6.4 Hz, 2H, CH2), 1.78 (s, 1H, CH-S), 2.33 (2H, CH2-S), 2.51-2.55 (m, 1H, CH), 3.75 (2H, CH2-S), 5.91 (s, 1H, CH-S), 7.18-7.25 (m, 8H, Ar-H), 11.15 (s, 1H, indole-NH). 13C NMR (DMSO-d6) (ppm): 19.2, 22.2 (2 × CH3), 27.3, 32.3, 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: C, 67.68; H, 5.99; N, 8.62. Found: C, 67.65; H, 5.96; N, 8.71.

General procedure for the synthesis of 5,5-benzylidine-2-(5-substituted-2-phenyl-1H-indol-3-yl)-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 4 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 give pure compounds 6a-c.
The Muller Hinton broth was used as a nutrient medium to growth the screening compounds (4-6) was carried out by the broth microdilution method in vitro. 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), Aspergillus niger (MTCC-281), Aspergillus flavus (MTCC-1973), and Aspergillus terreus (MTCC-1782). DMSO was used as a solvent to get the desired concentration of compounds to test for microbial strains. The minimum concentration which showed no 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 used 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 with 5-Substituted 2-phenyl-1H-indol-3-yl)methylene)-4,5,6,7-tetrahydro-5,7-dimethylbenz[d]thiazole-2-amine (4a-c) in good yield. The synthesis of 2-(5-Substituted-2-phenyl-1H-indol-3-yl)-3-(4,5,6,7-tetrahydro-5,7-dimethylbenz[d]thiazol-2-yl)thiazolidin-4-one (5a-c) was carried out by the cyclodehydration 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 under reflux temperature afforded 5-benzylidene-2-(5-substituted-2-phenyl-1H-indol-3-yl)-3-(4,5,6,7-tetrahydro-5,7-dimethylbenz[d]thiazol-2-yl)thiazolidin-4-one (6a-c) in good yield (Scheme 1).

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

| Comp. code | Antibacterial activity (MIC µg/ml) | Antifungal activity (MIC µg/ml) |
|------------|---------------------------------|--------------------------------|
|            | EC8 | SA8 | KP8 | PA8 | AO8 | AN8 | AP8 | AT8 |
| 4a         | 125 | 500 | 125 | 125 | 500 | 125 | 125 | 125 |
| 4b         | 62.5 | 250 | 125 | 125 | 500 | 125 | 125 | 125 |
| 4c         | 250 | 250 | 250 | 250 | 500 | 125 | 125 | 125 |
| 5a         | 125 | 500 | 250 | 125 | 250 | 500 | 125 | 125 |
| 5c         | 500 | 250 | 250 | 250 | 125 | 125 | 125 | 125 |
| 6a         | 250 | 500 | 250 | 250 | 250 | 250 | 250 | 250 |
| 6b         | 62.5 | 62.5 | 62.5 | 62.5 | 125 | 125 | 125 | 125 |
| 6c         | 500 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |
| Gentamycin | 125 | 500 | 250 | 125 | 500 | 125 | 125 | 125 |
| Fluconazole | -   | -   | -   | -   | 125 | 125 | 125 | 125 |

Values are expressed in mean (n=3). EC8: Escherichia coli (MTCC-723), SA8: Staphylococcus aureus (ATCC-29513), KP8: Klebsiella pneumonia (NCTC-13368), PA8: Pseudomonas aeruginosa (MTCC-1688), AO8: Aspergillus oryzae (MTCC-3567), AN8: Aspergillus niger (MTCC-281), AP8: Aspergillus flavus (MTCC-1973), AT8: Aspergillus terreus (MTCC-1782). MIC: minimum inhibitory concentration.

Antimicrobial activity.

The antimicrobial results depicted in Table 1 revealed that most of the screened 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) against A. niger.
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), *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), *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 exhibited moderate to less activity.

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**CONFLICT OF INTEREST**

Declared none.

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