Synthesis of some substituted azetidinonyl and thiazolidinonyl-1,3,4-thiadiazino[6,5-b]indoles as prospective antimicrobial agents

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Several 2-[(3-chloro-2-substituted phenyl)-4-azetidinon-3-yl]-1,3,4-thiadiazino[6,5-b]indoles and 2-[(2-substituted phenyl)-4-thiazolidinon-3-yl]-1,3,4-thiadiazino[6,5-b]indoles have been synthesized. The structures of the synthesized compounds are characterized by elemental and spectral analysis. These compounds are also evaluated for their antimicrobial susceptibility test against S.aureus, E.coli, K.pneumoniae, P.vulgaris and A.fumigatus, C.albicans, A. albicans ATCC, C.krusei G03 respectively. Compounds 4c and 5e showed the most potent antibacterial and antifungal activities. These two compounds are devoid of any toxicity.

Keywords: Benzylidenaminoindoles, azetidinon-3-yl-1,3,4-thiadiazino[6,5-b] indoles, antibacterial activity, antifungal activity

IPC Code: Int.Cl.8 C07D

Bacterial resistance to the antibiotics is a big blow to humanity and continual search for newer chemotherapeutic agents is the only way to fortify against this awful threat. Indole and its analogs constitute the active class of the compounds possessing wide spectrum of biological activities1-2. fungicidal3, bactericidal4 and tuberculostatic5. Various indole derivatives exhibited antidepressive3, anti-inflammatory4, fungicidal5, bactericidal6 and tuberculostatic7 activities. Further azetidinones and thiazolidinones are well famed for their antimicrobial8-11 activities. In the light of above reports and also in continuation of our laboratory work on chemoselective reaction of indole derivatives, a drug strategy has been planned to synthesize several indole derivatives possessing azetidinone and thiazolidinone moieties with the hope to possess better antimicrobial activity. All the synthesized compounds were screened for their antibacterial and antifungal activities against some selected microbes.

Result and Discussion

The chemical synthesis initiates with the reaction of indole-2,3-dione with thiosemicarbazide to yield 3-thiosemicarbazidindole-2-one 1. 2-Amino-1,3,4-thiadiazino[6,5-b]indole 2 was prepared by the cyclization of compound 1 with cold, conc. sulphuric acid. Treatment of different aromatic aldehydes in presence of gl. acetic acid with compound 2 yielded 2-substituted arylidenamino-1,3,4-thiadiazino[6,5-b]-indoles 3a-e. 2-[(3-chloro-2-substituted phenyl)-4-azetidinon-3-yl]-1,3,4-thiadiazino[6,5-b]indoles 4a-e were synthesize by reacting compounds 3a-e with chloro acetyl chloride in presence of triethyl amine. Compounds 3a-e were refluxed with thiglycolic acid in presence of anhydrous ZnCl2 to yield 2-[(2-substituted phenyl)-4-thiazolidinon-3-yl]-1,3,4-thiadiazino[6,5-b] indoles 5a-e (Scheme I). The structure of all the newly indole derivatives were confirmed on the basis of spectral and analytical data.

Antimicrobial activity

Preliminary antimicrobial susceptibility tests for all the synthesized indole derivatives were performed by using cup plate method12 at a concentration of 250 μg/mL against some selected pathogenic strains. S. aureus, E.coli., P. vulgaris, K.pneumoniae were used for bactericidal activity and A. fumigatus, C.albicans, C.albicans ATCC, C.krusei G03 for fungicidal activity. Prepared nutrient agar (Qualigen Fine Chem., Mumbai, India) was used to subculture differ-
Scheme I

R=H, p-OCH₃, o-OH, m-OCH₃ & p-OH, p-n(CH₃)₂
ent strains of bacteria while SDA (Sabouraud Dextrose Agar-Himedia Labs., Mumbai) to subculture selected fungal strains. Plates incubated 24 hr for bactericidal and 48 hr for fungicidal activity. The inhibition zone for testing compounds was measured in mm (Table I).

Acute Toxicity

Lethal dose (LD50) of compounds was determined in albino mice. After 24 hr of drug administration, mortality in each group was observed and from the data obtained LD50 was calculated by the method of Carrol13. Data revealed that compound 4a and 5e do not show any toxicity up to dose of 10.25 mg/kg and 12.50 mg/kg body weight in mice.

The synthesized molecules in Scheme I were screened for antibacterial and antifungal activity. The results are summarized in Table I. Compound 1 on screening showed poor bioactivity. Cyclization of compound 1 yielded compound 2, exhibited slight increase in bacterial inhibition. The characteristic feature of compounds 3a-e was the presence of azomethine(-N=CH-) linkage. Observation of results cleared that the order of bioactivity was 3c>3b>3e>3d>>3a. As compound 3c and 3b showed equipotent inhibitory effect. Compounds 4a-e were characterized by the presence of substituted azetidinone moiety. The order of biological activity for these compounds 4a-e was found 4c>4e >4d >4b > 4a. Compound 4c was found to possess most inhibitory effect against S.aureus. E.coli respectively. Conversion of compounds 3a-e lead to different thiazolidinones 5a-e. They showed their inhibitory property in order of 5e> 5d> 5c>5b>> 5a. Compound 5a devoid of any biological activity. Compound 5b showed poor while 5c and 5d exhibited moderate activity. It was 5e which demonstrated comparable antifungal activity in comparison to used standard. Considering the potency of these two compounds (4c and 5e), these further revaluated at lower concentration to determine the MIC90 by serial tube dilution method14 against E. coli and C. albicans. The MIC90 levels of the compound 4e were 0.025 μg/mL against E.coli while 1.25 μg/mL for compound 5e against C.albicans.

Discussion

On the basis of structure activity relationship, it is concluded that incorporation of S atom 2 brings an increase in bactericidal inhibition. Azomethine 3a-e linkage enhances antibacterial and antifungal activity. p-Methoxy substituted azetidinone 4c and o-hydroxy substituted thiazolidinone 5e moiety claim most potent antibacterial and antifungal activity. It is interesting to point out that compound 4e showed much potency than the used ampicillin and gatifloxacin standards and compound 5e possessed comparable inhibitory effect to fluconazole.

Experimental Section

The melting points of the compounds were determined in open glass capillaries with the help of themonic melting point apparatus and are uncorrected. The homogeneity of all the newly synthesized compounds was routinely checked by TLC on silica gel G plates and spots were located by using iodine chamber.

Elemental analysis of all the synthesized compounds were determined by a Perkin-Elmer 2400 elemental analyzer, and results were found within the ± 0.4% of theoretical values. IR spectra were recorded in KBr on a Perkin-Elmer-Spectrum RX-I, spectrometer. 1H NMR spectra were recorded by Bruker AC-300 F instrument using DMSO–d6 as solvent and tetramethysilane (TMS) as internal reference standard. All chemical shift values were recorded as δ (ppm). Mass spectra were determined on a VG–70-S instrument.

3-Thiosemicarbazido indole-2-one 1. A mixture of indole-2, 3-dione (2 g), thiosemicarbazide (1.23 g) in methanol (50 mL) was refluxed for 1 hr. The completion of reaction was checked by TLC and excess of methanol distilled out. The cooled, refluxed residual was poured into ice water, filtered, washed with water, dried and recrystallized from methanol to obtain compound 1 (80%), m.p. 200°C; IR (KBr, cm–1): 1200, 1610, 1682, 1710, 3144, 3419; 1H NMR (CDCl3+DMSO–d6): δ 6.75-6.95 (d, 1H d), 7.02-7.10 (t, 1H t), 7.22-7.30 (t, 1H b), 7.5707.62 (d, 1H a), 8.90 (bs, 2H), 9.36 (bs, 1H) ppm. Anal. Calcd for C9H8N4SO: C, 49.09; H, 3.63; N, 25.45. Found: C, 49.38; H, 3.41; N, 25.60%. MS: [M] at m/z 220.

2-Amino-1,3,4-thiadiazino(6,5-b)indole 2. Compound 1 (3 g) was mixed with small quantity of cold and conc. H2SO4 (1.52 mmole). The reaction mixture was left at room temp for 16 hr. After this, reaction mixture was poured into ice-cold water, neutralized with liquid ammonia to obtain solid mass, which was filtered, washed with water, dried and recrystallized from methanol to yield compound 2 (65%), m.p.
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230°C; IR(KBr, Cm-1): 672, 1295, 1611, 1683, 3144, 3420; 1H NMR (CDCl3+DMSO-d6): δ 6.89-6.97 (d, 1H), 7.00-7.05 (t, 1H c), 7.26-7.31 (t, 1H b), 7.56-7.59 (d, 1H a), 8.58 (bs, 2H) ppm. Anal. Calcd for C9H6N4S: C, 53.46; H, 2.97; N, 27.72. Found: C, 53.26; H, 3.15; N, 27.94%. MS: [M]+ at m/z 202.

Benzylidenamino-1,3,4-thiadiazino[6,5-b]indole 3a. The equimolar mixture (.01 mole) of compound 2 and benzaldehyde (.01 mole) in methanol (50 mL) was refluxed for 6 hr in presence of gl. acetic acid. The completion of reaction was checked by TLC and excess of methanol distilled off. After this, refluxed reaction mixture was poured into ice-water, filtered, washed with water and dried. Dried mass was recrystallized from ethanol to yield compound 3a (68%) m.p. 224°C; IR(KBr, cm-1): 672, 1296, 1611, 1682, 31; 1H NMR (CDCl3+DMSO-d6): δ 6.47-6.68 (m, 5H), 6.86-6.96 (d, 1H a), 7.02-7.12 (t, 1H c), 7.23-7.28 (t, 1H b), 7.56-7.60 (d, 1H b), 8.29 (s, 1H) ppm. Anal. Calcd for C16H10N4S: C, 66.20; H, 3.44; N, 19.31. Found: C, 65.96; H, 3.61; N, 19.18%. MS: [M]+ at m/z 290.

Table I — Antibacterial and antifungal activity of the synthesized compounds

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<th>E. coli (diameter in mm)</th>
<th>P. vulgaris (diameter in mm)</th>
<th>K. pneumoniae (diameter in mm)</th>
<th>A. fumigatus (diameter in mm)</th>
<th>C. albicans ATCC (diameter in mm)</th>
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Ampicillin 20 18 18 14 - - - - -
Gatifloxacin 25 22 20 21 - - - - -
Fluconazole - - - - - - - - -

*250 μg/mL - Drug concentration.

2-[4-Hydroxy-3-methoxybenzylidenamino]-1, 3, 4-thiadiazino[6,5-b]indole 3b. m.p. 245°C (methanol-water); IR (KBr, cm-1): 673, 1062, 1297, 1612, 1680, 3145, 3420; 1H NMR (CDCl₃+DMSO-d₆): δ 3.72 (s, 3H), 6.72 (s, 1H c), 6.90-6.92 (d, 1H d), 7.01-7.06 (t, 1H e), 7.27-7.32 (t, 1H f), 7.54-7.56 (d, 1H g), 7.76-7.79 (d, 1H h), 7.87-7.90 (d, 1H i), 8.25 (s, 1H j), 12.78 (s, 1H) ppm. Anal. Calcd for C₁₇H₁₂N₄O₂S: C, 60.71; H, 3.57; N, 16.66. Found: C, 60.50; H, 3.32; N, 16.39%. MS: [M]+ at m/z 336.

2-[4-Methoxybenzylidenamino]-1, 3, 4-thiadiazino[6,5-b]indole 3c. m.p. 232-33°C (ethanol-water); IR (KBr, cm-1): 673, 1062, 1297, 1610, 1681, 31448; 1H NMR (CDCl₃+DMSO-d₆): δ 3.68 (s, 3H), 6.52-6.75 (m, 4H), 6.92-6.93 (d, 1H d), 7.00-7.04 (t, 1H e), 7.26-7.31 (t, 1H f), 7.36-7.37 (d, 1H g), 8.31 (s, 1H i), 12.78 (s, 1H) ppm. Anal. Calcd for C₁₇H₁₂N₄O₂S: C, 63.75; H, 3.75; N, 17.50. Found: C, 63.49; H, 3.50; N, 17.74%. MS: [M]+ at m/z 320.

2-[4-N-Dimethyl benzylidenamino]-1, 3, 4-thiadiazino[6,5-b]indole 3d. m.p. 212-13 °C (DMF-Water); IR (KBr, cm-1): 673, 1297, 1610, 1683,
3144; 1H NMR (CDCl₃+DMSO-d₆): δ 2.15 (s, 6H), 6.63-6.78 (m, 4H), 6.88-6.90 (d, 1H₃), 6.989-7.02 (t, 1H₄), 7.28-7.30 (t, 1H₅), 7.36-7.39 (d, 1H₆), 8.29 (s, 1H) ppm. Anal. Calcd for C₁₃H₁₂N₂S: C, 54.87; H, 4.12; N, 15.17%. MS: [M]+ at m/z 336.

2-[2-Hydroxy benzylidenamino]-1, 3, 4-thiadiazino[6,5-b]indole 3e. m.p. 239-40°C (DMF-water); IR (KBr, cm⁻¹): 672, 1294, 1611, 1683, 3142; 1H NMR (CDCl₃+DMSO-d₆): δ 6.60-6.76 (m, 4H), 6.92-6.94 (d, 1H₃), 7.02-7.07 (t, 1H₄), 7.28-7.33 (t, 1H₅), 7.37-7.39 (d, 1H₆), 8.30 (s, 1H) ppm. Anal. Calcd for C₁₆H₁₀N₄SO: C, 62.74; H, 3.26; N, 18.30. Found: C, 63.02, H, 3.12; N, 18.47%.

3-[Chloro-2-phenyl]-4-azetidinon-3-yl]-1, 3, 4-thiadiazino[6,5-b]indole 4a. To the ethanolic solution of the synthesized compound 3a (0.01 mole), chloro acetyl chloride (0.01 mole) was added dropwise with constant stirring in presence of triethyl amine (0.01 mole) at 0-5°C. The reaction mixture was refluxed for 8 hr. The completion of the reaction was checked by TLC and excess of ethanol distilled off. The resulting residual mass was cooled, poured into ice water, filtered, washed with water, dried and recrystallized from methanol to yield compound 4a (65%), m.p. 249-50°C; IR (KBr, cm⁻¹): 672, 1295, 1610, 1632, 1675, 1712, 3153; 1H NMR (CDCl₃+DMSO-d₆): δ 4.87-4.91 (d, 1H), 6.56-6.68 (d, 1H), 6.69-6.82 (m, 5H), 6.91-6.92 (d, 1H), 7.08-7.11 (t, 1H₃), 7.27-7.30 (t, 1H₄), 7.36-7.39 (d, 1H₅) ppm. Anal. Calcd for C₁₈H₁₀N₄SOCl: C, 57.57; H, 3.28; N, 14.14. Found: C, 57.64; H, 3.38; N, 14.29%. MS: [M]+ at m/z 382.

2-[3-Chloro-2-(4-Methoxyphenyl)-4-thiazolidinon-3-yl]-1, 3, 4-thiadiazino[6,5-b]indole 5a. To a solution of compound 3a (62%), m.p. 214-15°C; IR (KBr, cm⁻¹): 672, 1293, 1525, 1611, 1685, 1690, 3145; 1H NMR (CDCl₃+DMSO-d₆): δ 3.57 (s, 3H), 3.89 (s, 2H), 6.51 (s, 1H), 6.68-6.77 (m, 5H), 6.90-6.93 (d, 1H₃), 7.11-7.15 (t, 1H₄), 7.28-7.31 (t, 1H₅), 7.57-7.62 (d, 1H₆) ppm. Anal. Calcd for C₁₈H₁₂N₂SO₂Cl: C, 59.34; H, 3.29; N, 115.33. Found: C, 59.56; H, 3.20; N, 15.17%. MS: [M]+ at m/z 382.

2-[2-Hydroxy-3-methoxyphenyl]-4-thiazolidinon-3-yl]-1, 3, 4-thiadiazino[6,5-b]indole 5b. m.p. 231-32°C (methanol-water); IR (KBr, cm⁻¹): 672.2, 1060.4, 1293, 1525, 1611, 1684, 1690, 3145, 3418; 1H NMR (CDCl₃+DMSO-d₆): δ 3.57 (s, 3H), 3.89 (s, 2H), 6.51 (s, 1H), 6.86-6.92 (d, 1H₃), 7.11-7.17 (t, 1H₄), 7.28-7.31 (t, 1H₅), 7.57-7.62 (d, 1H₆) ppm. Anal. Calcd for C₁₈H₁₂N₂SO₂Cl: C, 59.34; H, 3.29; N, 115.33. Found: C, 59.56; H, 3.20; N, 15.17%. MS: [M]+ at m/z 382.

2-[3-Chloro-2-(4-Hydroxy-3-methoxy phenyl)-4-thiazolidinon-3-yl]-1, 3, 4-thiadiazino[6,5-b]indole 5c. m.p. 226-27°C (DMF-water); IR (KBr, cm⁻¹): 633, 673, 1206, 1294, 1617, 1675, 1710, 3154; 1H NMR (CDCl₃+DMSO-d₆): δ 3.78 (s, 3H), 4.86-4.88 (d, 1H), 6.48-6.55 (d, 1H), 6.58-6.78 (m, 4H), 6.93-6.95 (d, 1H), 7.07-7.10 (t, 1H₃), 7.25-7.30 (t, 1H₄), 7.35-7.39 (d, 1H₅) ppm. Anal. Calcd for C₁₅H₁₃N₄SO₂Cl: C, 57.57; H, 3.28; N, 14.14. Found: C, 57.64; H, 3.38; N, 13.92%. MS: [M]+ at m/z 396.

2-[3-Chloro-2-(4-N, N-Dimethylphenyl)-4-azetidinon-3-yl]-1,3,4-thiadiazino[6,5-b]indole 4d. m.p. 241-42°C (methanol); IR (KBr, cm⁻¹): 633, 673, 1206, 1294, 1615, 1674, 1710, 3153; 1H NMR (CDCl₃+DMSO-d₆): δ 2.151(s,6H), 4.80-4.84 (d, 1H), 6.50-6.56 (d, 1H), 6.60-6.79 (4H), 6.86-6.90(d, 1H₃), 7.11-7.19 (t, 1H₄), 7.25-7.28 (t, 1H₅), 7.31-7.40 (d, 1H) ppm. Anal. Calcd for C₂₀H₁₆N₅SO₂Cl: C, 58.67; H, 3.91; N, 17.11. Found: C, 58.84; H, 4.12; N, 17.25%. MS: [M]+ at m/z 409.
7.01-7.06 (t, 1H), 7.30-7.32 (t, 1H), 7.57-7.59 (d, 1H), 7.88-7.97 (d, 1H), 8.13-8.16 (d, 1H), 12.72 (ss, 1H) ppm. Anal. Calcd for C₁₉H₁₄N₄S₂O₃: C, 55.60; H, 3.41; N, 13.65. Found: C, 55.37; H, 3.29; N, 13.80%. MS: [M]+ at m/z 410.

2-[2-(4-Methoxyphenyl)-4-thiazolidinon-3-yl]-1,3,4-thiadiazino[b]indole 5c. m.p. 239-40°C (DMF-water); IR (KBr, cm⁻¹) 671, 1061, 1294, 1525, 1611, 1685, 1691, 3146; ¹H NMR (CDCl₃+DMSO-d₆): δ 3.63 (s, 3H), 3.85 (s, 2H), 6.59 (s, 1H), 6.70-6.80 (m, 4H), 6.86-6.90 (d, 1H), 7.07-7.13 (t, 1H), 7.27-7.31 (t, 1H), 7.59-7.63 (d, 1H) ppm. Anal. Calcd for C₁₉H₁₄N₄S₂O₂: C, 57.86; H, 3.55; N, 14.21. Found: C, 57.51; H, 3.29; N, 14.47%. MS: [M]+ at m/z 394.

2-[2-(4-N, N-Dimethylphenyl)-4-thiazolidinon-3-yl]-1,3,4-thiadiazino[6,5-b]indole 5d. m.p. 197-98°C (ethanol); IR (KBr, cm⁻¹): 672, 1293, 1525, 1611, 1684, 1690, 3146; ¹H NMR (CDCl₃+DMSO-d₆): δ 2.14 (s,6H), 3.79 (s, 2H), 6.61 (s, 1H), 6.68-6.79 (m, 4H), 6.85-6.88 (d, 1H), 7.04-7.10 (t, 1H), 7.27-7.29 (t, 1H), 7.57-7.60 (d, 1H) ppm. Anal. Calcd for C₂₀H₁₇N₅S₂O: C, 58.96; H, 4.17; N, 17.19. Found: C, 58.70; H, 4.37; N, 17.40%. MS: [M]+ at m/z 407.

2 - [2-(2-Hydroxyphenyl)-4-thiazolidinon-3-yl] - 1,3,4-thiadiazino[6,5-b]indole 5e. m.p. 227-28°C (DMF-Water); IR (KBr, cm⁻¹): 673, 1294, 1525, 1610, 1684, 1690, 3145; ¹H NMR (CDCl₃+DMSO-d₆): δ 3.85 (s,2H), 6.632 (s,1H), 6.67-6.76 (m, 4H), 6.86-6.89 (d, 1H), 7.06-7.10 (t, 1H), 7.27-7.32 (t, 1H), 7.51-7.58 (d, 1H), 12.71 (ss, 1H) ppm. Anal. Calcd for C₁₉H₁₂N₂S₂O₂: C, 56.84; H, 3.15; N, 14.73. Found: C, 56.60; H, 3.29; N, 14.58%. MS: [M]+ at m/z 380.

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References