Synthesis and antimicrobial activity of new 4-thiazolidinone derivatives containing 2-amino-6-methoxybenzothiazole

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ABSTRACT
A novel series of Schiff bases 5a–j and 4-thiazolidinones 6a–j have been prepared from the building blocks 2-chloro pyridine-3-carboxylic acid [1] and 2-amino-6-methoxy-benzothiazole [2]. All of the synthesized compounds have been confirmed by elemental analyses, IR, 1H NMR and 13C NMR spectral data. These newly synthesized compounds were screened for their antimicrobial activity. Variable and modest activity was observed against the investigated strains of bacteria and fungi, however, compound 6h revealed significant antibacterial activity against Escherichia coli. Compounds 1, 2, 3, 5c, 5g and 5h, on the other hand, revealed potent antifungal activity against Candida albicans compared to the reference drug griseofulvin.

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Therefore, it was envisaged that chemical entities with pyridine, benzothiazole and Schiff bases/4-thiazolidinone moieties would result in compounds of interesting biological activities. In view of these findings, we have attempted to incorporate all these three biologically active components together to give a confined structure like the titled compounds for evaluating its antimicrobial activity.

We have already reported some of our work on the synthesis, transformations and biological properties of various 4-thiazolidinones (Patel and Patel, 2007; Patel and Rathod, 2007). These compounds were screened for their antibacterial and antifungal activities and it was found that some of them have moderate to good biological properties. The biological significance of this class of compounds impelled us to continue working on the synthesis of new 4-thiazolidinone derivatives. In this study, we have reported the synthesis of some new 4-thiazolidinone derivatives derived from Schiff bases of pyridine derivatives.

2. Materials and methods

2.1. General

Laboratory chemicals were supplied by Rankem India Ltd., and Fischer Scientific Ltd. Melting points of the synthesized compounds were determined in open-class capillaries on Stuart-SMP10 melting point apparatus and were uncorrected. The purity of the compounds was checked by thin layer chromatography (TLC). Silica gel plates kiesel gel 0.25 mm, 60G and Fischer Scientific Ltd. Melting points of the synthesized compounds were determined in open-glass capillaries on Stuart-SMP10 melting point apparatus and were uncorrected.

Antimicrobial activity was performed at Micro Care Laboratory, Suat according to the protocol mentioned in the Section 2.3 antimicrobial screening using broth dilution method (Rattan, 2005).

2.2. Chemistry

The building blocks 2-amino-6-methoxybenzothiazole [2] and 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-carboxylic acid [3] were prepared according to the reported procedures (Patel and Agrawat, 2007).


Hydrazine hydrate (0.02 mol, 80%) in chloroform (5 mL) was added dropwise in a mixture of acid chloride (0.01 mol) in chloroform (10 mL) and triethyamine (2–3 drops) while stirring at 0–5 °C for half an hour and the stirring was continued at room temperature for 3–4 h. The solvent was evaporated and the product obtained was collected, dried and recrystallized from methanol. m.p. – 245–247 °C, yield, 68%; IR (KBr) cm⁻¹: 3339 (–NH str.), 1648 (CONH, amide-I), 1542 (amide-II), 1224 (amide-III), 1469 (C–N, C–C ring str.), 1337 (C–N str.), 1025, 1205 (C–O–C sym., asym.). ¹H NMR (DMSO-d₆) δ (ppm): 8.30–6.90 (6H, m, pyridine and aromatic), 9.35 (1H, s, –NH–), 8.95 (1H, s, –CONH–), 4.10 (2H, s, –NH₂), 3.88 (3H, s, OCH₃).

2.2.2. General method for preparation of hydrazones [5a-j]

To a solution of 4 (0.01 mol) in 10 mL of DMF; appropriate aldehydes a-j (0.012 mol) and 3–4 drops of glacial acetic acid were added. The reaction mixture was refluxed for 5–6 h. The reaction mixture was cooled and poured onto crushed ice. The reaction was monitored by TLC on silica gel using toluene:ethyl acetate (3:1). The separated solid was isolated, washed with water and recrystallized from ethanol to give 5a-j.

2.2.3. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-(phenyl) hydrazone [5a]

M.p. 119–121 °C, yield, 55%; IR (KBr) cm⁻¹: 3418 (NH str.), 1645 (CONH, amide-I), 1550 (amide-II), 1224 (amide-III), 1610 (C≡N str., Schiff base), 1463 (C–N, C–C ring str.), 1342 (C–N str.). ¹H NMR (DMSO-d₆) δ (ppm): 9.35 (s, 1H, NH), 8.85 (s, 1H, CONH), 6.84–8.57 (m, 11H, aromatic and pyridine), 5.83 (s, 1H, N=CH), 3.85 (s, 3H, OCH₃). ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 162.1 (C₇), 143.3 (C₈), 112.6–161.5 (C₂–C₅), 104.3–172.5 (C₆–C₁₀), 51.9 (C₁₁), 125.3–136.5 (C₁₇–C₂º). Anal. Calc. for C₂₁H₁₆O₂N₅SCl: C, 57.66; H, 3.69; N, 16.02. Found: C, 57.58; H, 3.60; N, 15.95%.

2.2.4. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-(2-chlorophenyl) hydrazone [5b]

M.p. 191–192 °C, yield, 58%; IR (KBr) cm⁻¹: 3418 (NH str.), 1648 (CONH, amide-I), 1550 (amide-II), 1222 (amide-III), 1614 (C≡N str., Schiff base), 1469 (C–N, C–C ring str.), 1340 (C–N str.). ¹H NMR (DMSO-d₆) δ (ppm): 9.36 (s, 1H, NH), 8.87 (s, 1H, CONH), 6.81–8.56 (m, 10H, aromatic and pyridine), 5.81 (s, 1H, N=CH), 3.86 (s, 3H, OCH₃). ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm): 162.3 (C₇), 143.5 (C₈), 112.1–161.7 (C₂–C₉), 104.7–172.8 (C₆–C₁₀), 51.9 (C₁₁), 125.3–136.5 (C₁₇–C₂º). Anal. Calc. for C₂₂H₁₆O₂N₅SCl: C, 57.66; H, 3.69; N, 16.02. Found: C, 57.58; H, 3.60; N, 15.95%.

2.2.5. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-(4-chlorophenyl) hydrazone [5c]

M.p. 101–104 °C, yield, 48%; IR (KBr) cm⁻¹: 3419 (NH str.), 1642 (CONH, amide-I), 1552 (amide-II), 1223 (amide-III), 1609 (C≡N str., Schiff base), 1461 (C–N, C–C ring str.), 1339 (C–N str.). ¹H NMR (DMSO-d₆) δ (ppm): 8.30–6.90 (6H, m, pyridine and aromatic), 9.35 (1H, s, –NH–), 8.95 (1H, s, –CONH–), 4.10 (2H, s, –NH₂), 3.88 (3H, s, OCH₃).
(C–Cl). 1H NMR (DMSO-d$_6$) δ (ppm): 9.38 (s, 1H, NH), 8.86 (s, 1H, CONH), 6.79–8.53 (m, 10H, aromatic and pyridine), 5.82 (s, 1H, N=CH), 3.84 (s, 3H, OCH$_3$). 13C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 162.5 (C$_7$), 143.9 (C$_5$), 112.2–161.6 (C$_2$–C$_6$), 104.7–172.6 (C$_7$–C$_{13}$), 52.2 (C$_{16}$), 128.3–138.9 (C$_{17}$–C$_{22}$). Anal. Calc. for C$_{25}$H$_{19}$O$_3$N$_5$S: C, 60.95; H, 4.42; N, 16.17. Found: C, 60.85; H, 4.35; N, 16.10%.

2.2.10. 2-[N-(6-methoxybenzothiazolyl) amino] pyridine-3-(3-methoxy-4-hydroxyphenyl) hydrazone [5h]

M.p. 127–128 ºC, yield, 63%; IR (KBr) v cm$^{-1}$: 3424 (O–H), 3207 (NH str.), 1645 (CONH, amide-I), 1551 (amide-II), 1223 (amide-III), 1616 (C=C str., Schiff base), 1454 (C=C str., C=C ring str.), 1342 (C=C str.), 1037, 1181 (OCH$_3$, sym., asym.). 1H NMR (DMSO-d$_6$) δ (ppm): 9.36 (s, 1H, NH), 8.87 (s, 1H, CONH), 6.83–8.58 (m, 9H, aromatic and pyridine), 5.80 (s, 1H, N=CH), 3.86 (s, 3H, OCH$_3$). 13C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 163.5 (C$_7$), 143.1 (C$_5$), 112.7–161.2 (C$_7$–C$_{13}$), 104.8–172.9 (C$_7$–C$_{13}$), 51.4 (C$_{16}$), 115.3–151.5 (C$_{17}$–C$_{22}$). Anal. Calc. for C$_{27}$H$_{20}$O$_4$N$_5$S: C, 58.78; H, 4.26; N, 15.59. Found: C, 58.70; H, 4.18; N, 15.50.

2.2.11. 2-[N-(6-methoxybenzothiazolyl) amino] pyridine-3-(3-methoxy-4-hydroxy-5nitrophenyl) hydrazone [5i]

M.p. 156–158 ºC, yield, 65%; IR (KBr) v cm$^{-1}$: 3421 (O–H), 3203 (NH str.), 1647 (CONH, amide-I), 1552 (amide-II), 1225 (amide-III), 1613 (C=C str., Schiff base), 1470 (C=C str., C=C ring str.), 1338 (C=C str.), 1037, 1181 (OCH$_3$, sym., asym.), 1368, 1510 (NO$_2$, sym., asym.). 1H NMR (DMSO-d$_6$) δ (ppm): 9.47 (s, 1H, NH), 8.87 (s, 1H, CONH), 6.82–8.56 (m, 8H, aromatic and pyridine), 5.84 (s, 1H, N=CH), 3.85 (s, 3H, OCH$_3$). 13C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 163.1 (C$_7$), 143.3 (C$_5$), 112.6–161.5 (C$_7$–C$_{13}$), 104.3–172.5 (C$_7$–C$_{13}$), 51.9 (C$_{16}$), 115.3–156.5 (C$_{17}$–C$_{22}$). Anal. Calc. for C$_{28}$H$_{21}$O$_4$N$_5$S: C, 53.43; H, 3.67; N, 17.00. Found: C, 53.35; H, 3.60; N, 16.95%.

2.2.12. 2-[N-(6-methoxybenzothiazolyl) amino] pyridine-3-(4-furyl) hydrazone [5j]

M.p. 142–144 ºC, yield, 55%; IR (KBr) v cm$^{-1}$: 3419 (NH str.), 1641 (CONH, amide-I), 1553 (amide-II), 1223 (amide-III), 1614 (C=C str., Schiff base), 1472 (C=C str., C=C ring str.), 1339 (C=C str.), 1035, 1181 (OCH$_3$, sym., asym.). 1H NMR (DMSO-d$_6$) δ (ppm): 9.85 (s, 1H, NH), 8.84 (s, 1H, CONH), 6.82–8.52 (m, 9H, aromatic and pyridine), 5.81 (s, 1H, N=CH), 3.86 (s, 3H, OCH$_3$). 13C NMR (100 MHz, DMSO-d$_6$) δ (ppm): 162.7 (C$_7$), 134.3 (C$_5$), 112.6–161.5 (C$_7$–C$_{13}$), 104.3–172.5 (C$_7$–C$_{13}$), 51.9 (C$_{16}$), 125.3–136.5 (C$_{17}$–C$_{22}$). Anal. Calc. for C$_{27}$H$_{20}$O$_4$N$_5$S: C, 58.00; H, 3.85; N, 17.81. Found: C, 57.92; H, 3.75; N, 17.75%.

2.2.13. General method for preparation of 4-thiazolidinones [6a–j]

A mixture of appropriate hydrazones 5a–j (0.01 mol), thiglycolic acid (0.015 mol) and a pinch of anhydrous ZnCl$_2$ in dry 1,4-dioxane was refluxed for 12–14 h. The reaction was monitored by TLC on silica gel using toluene:ethyl acetate (3:1). The reaction mixture was cooled and neutralized with 10% sodium bicarbonate solution. The separated solid was filtered, washed with water and recrystallized from ethanol to give 6a–j.

2.2.14. 2-[N-(6-methoxybenzothiazolyl) amino] pyridine-3-(2-phenyl) carboxamide-1,3-thiazolidin-4-one [6a]

M.p. 210–212 ºC, yield, 57%; IR (KBr) v cm$^{-1}$: 3416 (NH str.), 1712 (amide lactam), 1646 (amide-I), 1556 (amide-II), 1229 (amide-III), 1469 (C=N–C ring str.), 1341 (C=N str.), 1037, 1181 (OCH$_3$, sym., asym.). 1H NMR (400 MHz,
2.2.15. 1.3C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.7 (C$_2$–C$_6$), 115.4–151.7 (C$_{19}$–C$_{24}$). Anal. Calc. for C$_{23}$H$_{19}$O$_4$N$_5$S$_2$: C, 55.97; H, 3.55; N, 13.70. Found: C, 53.95; H, 3.48; N, 13.62%.

2.2.16. 1.3C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.2 (C$_7$), 169.3 (C$_8$), 35.4 (C$_9$), 57.6 (C$_{10}$), 114.4–163.8 (C$_{2}$–C$_6$), 104.7–173.5 (C$_{17}$–C$_{1}$), 54.4 (C$_{18}$), 127.3–139.3 (C$_{19}$–C$_{24}$). Anal. Calc. for C$_{24}$H$_{21}$O$_5$N$_5$S$_2$: C, 55.06; H, 4.05; N, 13.38. Found: C, 55.90; H, 3.80; N, 14.14%.

2.2.17. 1.3C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.2 (C$_7$), 169.4 (C$_8$), 35.6 (C$_9$), 57.6 (C$_{10}$), 111.4–163.8 (C$_{2}$–C$_6$), 104.5–173.7 (C$_{17}$–C$_{1}$), 54.6 (C$_{18}$), 124.3–149.9 (C$_{19}$–C$_{24}$).

2.2.18. 1.3C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.2 (C$_7$), 169.3 (C$_8$), 35.4 (C$_9$), 57.1 (C$_{10}$), 111.3–163.4 (C$_2$–C$_6$), 104.5–173.7 (C$_{17}$–C$_{1}$), 54.6 (C$_{18}$), 124.3–149.9 (C$_{19}$–C$_{24}$). Anal. Calc. for C$_{23}$H$_{19}$O$_4$N$_5$S$_2$: C, 52.87; H, 3.47; N, 16.09. Found: C, 52.80; H, 3.40; N, 16.00%.

2.2.19. 1.3C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.2 (C$_7$), 169.4 (C$_8$), 35.4 (C$_9$), 57.6 (C$_{10}$), 111.9–163.3 (C$_2$–C$_6$), 104.1–173.8 (C$_{17}$–C$_{1}$), 54.1 (C$_{18}$), 114.3–159.5 (C$_{19}$–C$_{24}$). Anal. Calc. for C$_{24}$H$_{21}$O$_5$N$_5$S$_2$: C, 56.79; H, 4.17; N, 13.81. Found: C, 56.70; H, 4.10; N, 13.76%.

2.2.21. 1.3C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.2 (C$_7$), 169.3 (C$_8$), 35.4 (C$_9$), 57.6 (C$_{10}$), 111.9–163.3 (C$_2$–C$_6$), 104.1–173.8 (C$_{17}$–C$_{1}$), 54.1 (C$_{18}$), 114.3–159.5 (C$_{19}$–C$_{24}$). Anal. Calc. for C$_{24}$H$_{21}$O$_5$N$_5$S$_2$: C, 56.79; H, 4.17; N, 13.81. Found: C, 56.70; H, 4.10; N, 13.76%.

2.2.22. 1.3C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.2 (C$_7$), 169.3 (C$_8$), 35.4 (C$_9$), 57.6 (C$_{10}$), 111.9–163.3 (C$_2$–C$_6$), 104.1–173.8 (C$_{17}$–C$_{1}$), 54.1 (C$_{18}$), 114.3–159.5 (C$_{19}$–C$_{24}$). Anal. Calc. for C$_{24}$H$_{21}$O$_5$N$_5$S$_2$: C, 56.79; H, 4.17; N, 13.81. Found: C, 56.70; H, 4.10; N, 13.76%.

2.2.23. 1.3C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.2 (C$_7$), 169.3 (C$_8$), 35.4 (C$_9$), 57.6 (C$_{10}$), 111.9–163.3 (C$_2$–C$_6$), 104.1–173.8 (C$_{17}$–C$_{1}$), 54.1 (C$_{18}$), 114.3–159.5 (C$_{19}$–C$_{24}$). Anal. Calc. for C$_{24}$H$_{21}$O$_5$N$_5$S$_2$: C, 56.79; H, 4.17; N, 13.81. Found: C, 56.70; H, 4.10; N, 13.76%.

2.2.24. 1.3C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.2 (C$_7$), 169.3 (C$_8$), 35.4 (C$_9$), 57.6 (C$_{10}$), 111.9–163.3 (C$_2$–C$_6$), 104.1–173.8 (C$_{17}$–C$_{1}$), 54.1 (C$_{18}$), 114.3–159.5 (C$_{19}$–C$_{24}$). Anal. Calc. for C$_{24}$H$_{21}$O$_5$N$_5$S$_2$: C, 56.79; H, 4.17; N, 13.81. Found: C, 56.70; H, 4.10; N, 13.76%.

2.2.25. 1.3C NMR (100 MHz, DMSO-d$_6$) $\delta$ (ppm): 163.2 (C$_7$), 169.3 (C$_8$), 35.4 (C$_9$), 57.6 (C$_{10}$), 111.9–163.3 (C$_2$–C$_6$), 104.1–173.8 (C$_{17}$–C$_{1}$), 54.1 (C$_{18}$), 114.3–159.5 (C$_{19}$–C$_{24}$). Anal. Calc. for C$_{24}$H$_{21}$O$_5$N$_5$S$_2$: C, 56.79; H, 4.17; N, 13.81. Found: C, 56.70; H, 4.10; N, 13.76%.
1561 (amide-II), 1225 (amide-III), 1465 (C–N, C–C ring str.), 1342 (C–N str.), 1369, 1516 (NO2, sym., asym.), 6.72–8.71 (m, 9H, aromatic and pyridine), 6.13 (s, 1H, CH of 4-thiazolidinone ring), 3.63 (s, 2H, SCH2CO of 4-thiazolidinone ring), 8.94 (s, 1H, CONH), 6.71–8.75 (m, 8H, aromatic and pyridine), 6.10 (s, 1H, CH of 4-thiazolidinone ring), 3.63 (s, 2H, SCH2CO of 4-thiazolidinone ring), 3.82 (s, 3H, OCH3). 13C NMR (100 MHz, DMSO-d6) δ (ppm): 9.37 (s, 1H, NH), 8.94 (s, 1H, CONH), 6.71–8.75 (m, 8H, aromatic and pyridine), 6.10 (s, 1H, CH of 4-thiazolidinone ring), 3.63 (s, 2H, SCH2CO of 4-thiazolidinone ring), 3.82 (s, 3H, OCH3). 13C NMR (100 MHz, DMSO-d6) δ (ppm): 163.5 (C7), 169.7 (C8), 35.7 (C9), 57.3 (C10), 111.7–113.8 (C2–C6), 104.1–173.5 (C11–C17), 54.4 (C18), 118.1–153.1 (C19–C24). Anal. Calc. for C24H20O7N6S2: C, 50.70; H, 3.55; N, 14.79. Found: C, 51%; IR (KBr) v/cm−1: 3412 (NH str., sym.), 2922, 2851 (OCH3 str., sym., asym.), 1H NMR (400 MHz, DMSO-d6) δ (ppm): 9.34 (s, 1H, NH), 8.94 (s, 1H, CONH), 6.72–8.71 (m, 9H, aromatic and pyridine), 6.13 (s, 1H, CH of 4-thiazolidinone ring), 3.63 (s, 2H, SCH2CO of 4-thiazolidinone ring), 3.85 (s, 3H, OCH3). 13C NMR (100 MHz, DMSO-d6) δ (ppm): 163.5 (C7), 169.1 (C8), 35.0 (C9), 57.1 (C10), 111.2–113.8 (C2–C6), 104.4–173.1 (C11–C17), 54.8 (C18), 104.7–151.5 (C19–C24). Anal. Calc. for C21H17O4N5S2: C, 53.95; H, 3.67; N, 14.99. Found: C, 53.88; H, 3.60; N, 14.90% (Figs. 1 and 2).

2.2.23. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-(2-furyl) carboxamido-1,3-thiazolidin-4-one [6j]

M.p. 204–206 °C, yield, 51%; IR (KBr) v/cm−1: 3412 (NH str.), 1710 (amidic lactam), 1649 (amide-I), 1558 (amide-II), 1225 (amide-III), 1467 (C–N, C–C ring str.), 1345 (C–N str.), 1037, 1186 (OCH3, sym., asym.). 1H NMR (400 MHz, DMSO-d6) δ (ppm): 9.34 (s, 1H, NH), 8.94 (s, 1H, CONH), 6.72–8.71 (m, 9H, aromatic and pyridine), 6.13 (s, 1H, CH of 4-thiazolidinone ring), 3.63 (s, 2H, SCH2CO of 4-thiazolidinone ring), 3.85 (s, 3H, OCH3). 13C NMR (100 MHz, DMSO-d6) δ (ppm): 163.5 (C7), 169.7 (C8), 35.7 (C9), 57.3 (C10), 111.7–163.8 (C2–C6), 104.1–173.5 (C11–C17), 54.4 (C18), 118.1–153.1 (C19–C24). Anal. Calc. for C24H20O7N6S2: C, 50.65; H, 3.45; N, 14.70%.

2.3. Antimicrobial screening

All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against known drugs ampicillin and greseofulvin. Mueller–Hinton broth was used as nutrient medium to grow and dilute the drug suspension. Amplification of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately subcultured (before incubation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was subcultured and incubated overnight at 37 °C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show: similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test included a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted obtaining 2000 μg/ml concentrations, as a stock solution. In primary screening 500, 250 and 125 μg/ml concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, 6.250, 3.125 and 1.5625 μg/ml concentrations. The highest dilution showing at least 99% inhibition is taken as MIC (Scheme 1).

3. Results and discussion

3.1. Chemistry

2-Chloro pyridine-3-carboxylic acid 1 and 2-amino-6-methoxy benzothiazole 2 in presence of anhydrous K2CO3 and catalytic amount of Cu-bronze in DMF solvent were heated (Ullamann Condensation) to form 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-carboxylic acid 3 which on further heating in thionyl chloride and subsequent reaction with hydrazine...
hydrate in chloroform formed acid hydrazide 4. After condens-
ing, 4 with aromatic aldehydes a-j in DMF solvent, Schiff
bases 5a–j were obtained. Finally, 4-thiazolidinones 6a–j were
prepared by refluxing the related hydrazide–hydrazones 5a–j
and thiglycolic acid in dry 1,4-dioxane for 12–14 h using a
Dean–Stark apparatus.

The structures of synthesized compounds 5a–j were con-
ﬁrmed by elemental analyses and IR spectra as observed in
Scheme 1. Synthetic protocol of 5a–j and 6a–j. Reagents and condi-
tions: (A) (i) SOCl2 and (ii) hydrazine hydrate, chloroform, triethylamine; (B) aromatic aldehydes,
DMF, 1–2 drop glacial acetic acid, 5–6 h (C) thioglycolic acid, anhydrous ZnCl2, 1,4-dioxane, 12–14 h.

3.2. Antimicrobial activity

Antimicrobial activity of the synthesized compounds 5a–j and
6a–j in form of minimum inhibitory concentrations (MICs)
was evaluated against various pathogenic bacterial strains
(Gram-negative and Gram-positive) viz., Staphylococcus aure-
us MTCC 96, Streptococcus pyogenes MTCC 442, Escherichia
coli MTCC 443, Pseudomonas aeruginosa MTCC 741. Anti-
fungal activity of these compounds 5a–j and 6a–j was evalu-
ated against fungal strains viz. Candida albicans MTCC 227,
Aspergillus niger MTCC 282 and Aspergillus clavatus MTCC
1323. The antimicrobial activities were carried out by broth
micro dilution method as described by Rattan (2005). Min-
imum inhibitory concentrations (MICs) of the tested com-
ounds are shown in Table 1. Ampicillin was used as a
reference drug for antibacterial activity whereas greseofulvin
was used as a reference drug for antifungal activity.

3.3. Antibacterial activity

The results of antibacterial screening of the synthesized com-
pounds are presented in Table 1. Modest antibacterial activity
is observed with most of the tested compounds.

Some of synthesized compounds showed good to moderate
activity with MIC value in the range of 62.5–100 μg/ml. Particu-
larly, compound 5h, 5i, 6b, and 6d showed good activity (MIC
value 100 μg/ml) against E. coli and 6h showed signiﬁcant
activity (MIC value 62.5 and 100 μg/ml, respectively) against
E. coli and P. aeruginosa, respectively. Moreover, 5a, 5b, 5d,
5e, 5g, 5i, 6a, 6b, 6c, 6f, 6g, 6h and 6j displayed comparable
activity (MIC value 100–250 μg/ml) against S. aureus relative
to the reference drug ampicillin.

3.4. Antifungal activity

The results of antifungal screening of the synthesized com-
pounds are presented in Table 1. Starting material 1, 2, 3
and 4 showed better activity against *C. albicans* (MIC value 250–500 μg/ml) compared with standard drug greseofulvin.

Some of the synthesized compounds 5a-j and 6a-j showed good to moderate activity with MIC value in the range of 100–500 μg/ml. Particularly, compounds 5c, 5g and 5h, 5a, 5d, 5e, 5f, 6a, 6b, 6c, 6f, 6g and 6j showed comparable activity against *C. albicans* compared to the reference drug greseofulvin. All compounds from Schiff base and 4-thiazolidinone series showed weak to no activity against *A. niger* and *A. clavatus.*

### 4. Conclusion

Novel Schiff bases and 4-thiazolidinones of pyridine and benzothiazole derivatives were synthesized; starting from building blocks 1 and 2 and were studied for their antimicrobial activity. Overall observation from the results of the antimicrobial activity of the synthesized compounds revealed that compounds containing –Cl, –NO2 group and furan nucleus are more active than the remaining compounds.

### Acknowledgement

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### References


### Table 1 Biological profile of compounds 5a-j and 6a-j.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Minimal inhibitory concentration (MIC) μg/ml</th>
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<td></td>
<td>Gram-negative</td>
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<tr>
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<td>P. aeruginosa</td>
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