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ORIGINAL ARTICLE

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, ^{1}H NMR and ^{13}C 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 greseofulvin.

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1. Introduction

The number of life threatening infections caused by multidrug-resistant Gram-positive pathogens has reached an alarming level in hospitals and the community. Infections caused by these organisms create a serious challenge to the scientific community and the need for an effective therapy has led to a search for novel antibacterial agents.

Pyridine and its derivatives are widely distributed in nature and are well known to exhibit broad spectrum of biological activities such as antimicrobial (Gaonkar et al., 2007), anti-HIV (Ali et al., 2007), anti-inflammatory (Hosni and Abdulla, 2008; Pavlova et al., 2001), analgesic (Hosni and Abdulla, 2008) and anticonvulsant (Shafiee et al., 2004). Benzothiazole derivatives are also associated with diverse biological activities viz. antiproliferative (Al-Soud et al., 2008), antimalarial (Hout et al., 2004), antitumor (Mortimer et al., 2006; Racane et al., 2006; Akhtar et al., 2008) and antimicrobial (Patel and Agravat, 2007).

Small ring heterocycles containing nitrogen, sulfur and oxygen gained great importance since a long time due to their important medicinal properties. Particularly, 4-thiazolidinones have been shown to have various important biological activities such as anti-inflammatory (Geronikaki et al., 2008), antitubercular (Parekh et al., 2004), antimicrobial (Lokhandwala and Desai, 2008), anticonvulsant (Ulusoy et al., 1998), antiviral (Terzioglu et al., 2006) and anti-HIV (Balzarini et al., 2009; Ravichandran et al., 2008; Rawal et al., 2007a,b).

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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-glass 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 F_{254}, precoated sheets obtained from Merck, Darmstadt (Germany) were used for TLC. Developing solvent system of toluene:ethyl acetate (3:1) was used and the spots were visualised by iodine vapours/ultraviolet light as visualizing agent.

IR spectra (KBr disc) were recorded on Perkin–Elmer-838 FT-IR spectrometer, using KBr pellets in the range of 4000–400 cm^{-1}.

^1H NMR and ^{13}C NMR spectra were scanned on Bruker Avance II 400 spectrometer at 400 MHz and 100 MHz for ^1H NMR and ^{13}C NMR respectively, Chemical shifts are expressed in δ (ppm) relative to TMS as an internal standard using DMSO-d_6 as solvent.

Elemental analyses of the newly synthesized compounds were performed on Carlo Erba 1108 analyzer. Elemental analyses of all the compounds were in agreement with the calculated values.

Antimicrobial activity was performed at Micro Care Laboratory, Suart 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 Agravat, 2007).

2.2.1. Preparation of building block 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-carboxo hydrazide [4]

2-[*N*-(6-methoxybenzothiazolyl)amino] pyridine-3-carboxylic acid **3** (0.01 mol) in $SOCl_2$ (7.0 ml) was refluxed on water bath until the reaction was completed. The mixture was protected from humidity with $CaCl_2$ guard tube. The excess of $SOCl_2$ was removed by vacuum distillation. The solid material 2-[*N*-(6-methoxybenzothiazolyl)amino] pyridine-3-carbonyl chloride was obtained, which was directly used in the next step.

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 triethylamine (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-d_6) 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, $–NH_2$), 3.88 (3H, s, OCH_3).

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) ν 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.), 1038, 1182 (OCH_3, sym., asym.). ^1H NMR (DMSO-d_6) 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, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.1 (C_7), 143.3 (C_8), 112.6–161.5 (C_2–C_6), 104.3–172.5 (C_9–C_{15}), 51.9 (C_{16}), 125.3–136.5 (C_{17}–C_{22}). *Anal*. Calc. for $C_{21}H_{17}O_2N_5S$: C, 62.51; H, 4.25; N, 17.37. Found: C, 62.46; H, 4.15; N, 17.30%.

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

M.p. 191–192 °C, yield, 58%; IR (KBr) ν cm^{-1}: 3421 (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.), 1036, 1181 (OCH_3, sym., asym.), 760 (C–Cl). ^1H NMR (DMSO-d_6) 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, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.3 (C_7), 143.5 (C_8), 112.1–161.7 (C_2–C_6), 104.7–172.8 (C_9–C_{15}), 51.7 (C_{16}), 126.0–137.1 (C_{17}–C_{22}). *Anal*. Calc. for $C_{21}H_{16}O_2N_5SCl$: 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) ν 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.), 1037, 1180 (OCH_3, sym., asym.), 758

(C–Cl). ^{1}H 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). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.5 (C_7), 143.9 (C_8), 112.2–161.6 (C_2–C_6), 104.7–172.6 (C_9–C_{15}), 52.2 (C_{16}), 128.3–138.9 (C_{17}–C_{22}). *Anal.* Calc. for $C_{21}H_{16}O_2N_5SCl$: C, 57.66; H, 3.69; N, 16.02. Found: C, 57.60; H, 3.61; N, 15.98%.

*2.2.6. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-(2-nitrophenyl) hydrazone [**5d**]*

M.p. 175–176 °C, yield, 49%; IR (KBr) ν cm^{-1}: 3422 (NH str.), 1640 (CONH, amide-I), 1551 (amide-II), 1221 (amide-III), 1611 (C=N str., Schiff base), 1464 (C–N, C–C ring str.), 1339 (C–N str.), 1036, 1180 (OCH_3, sym., asym.), 1370, 1512 (NO_2, sym., asym.). ^{1}H NMR (DMSO-d_6) δ (ppm): 9.37 (s, 1H, NH), 8.82 (s, 1H, CONH), 6.82–8.56 (m, 10H, aromatic and pyridine), 5.81 (s, 1H, N=CH), 3.83 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.0 (C_7), 143.4 (C_8), 112.7–161.8 (C_2–C_6), 104.2–172.3 (C_9–C_{15}), 52.1 (C_{16}), 122.9–148.5 (C_{17}–C_{22}). *Anal.* Calc. for $C_{21}H_{16}O_4N_6S$: C, 56.24; H, 3.60; N, 18.75. Found: C, 56.18; H, 3.50; N, 18.65%.

*2.2.7. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-(3-nitrophenyl) hydrazone [**5e**]*

M.p. 121–123 °C, yield, 54%; IR (KBr) ν cm^{-1}: 3421 (NH str.), 1641 (CONH, amide-I), 1552 (amide-II), 1223 (amide-III), 1611 (C=N str., Schiff base), 1471 (C–N, C–C ring str.), 1338 (C–N str.), 1037, 1178 (OCH_3, sym., asym.), 1369, 1511 (NO_2, sym., asym.). ^{1}H NMR (DMSO-d_6) δ (ppm): 9.37 (s, 1H, NH), 8.89 (s, 1H, CONH), 6.83–8.56 (m, 10H, aromatic and pyridine), 5.87 (s, 1H, N=CH), 3.87 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.8 (C_7), 143.1 (C_8), 112.6–161.7 (C_2–C_6), 104.1–171.9 (C_9–C_{15}), 51.6 (C_{16}), 121.3–149.1 (C_{17}–C_{22}). *Anal.* Calc. for $C_{21}H_{16}O_4N_6S$: C, 56.24; H, 3.60; N, 18.75. Found: C, 56.19; H, 3.52; N, 18.68%.

*2.2.8. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-(4-hydroxyphenyl) hydrazone [**5f**]*

M.p. 173–174 °C, yield, 59%; IR (KBr) ν cm^{-1}: 3422 (O–H), 3202 (NH str.), 1644 (CONH, amide-I), 1548 (amide-II), 1223 (amide-III), 1614 (C=N str., Schiff base), 1466 (C–N, C–C ring str.), 1341 (C–N str.), 1036, 1180 (OCH_3, sym., asym.). ^{1}H NMR (DMSO-d_6) δ (ppm): 9.31 (s, 1H, NH), 8.79 (s, 1H, CONH), 6.82–8.54 (m, 10H, aromatic and pyridine), 5.85 (s, 1H, N=CH), 3.86 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ(ppm): 163.3 (C_7), 143.2 (C_8), 112.4–161.6 (C_2–C_6), 104.5–172.7 (C_9–C_{15}), 51.4 (C_{16}), 115.3–161.5 (C_{17}–C_{22}). *Anal.* Calc. for $C_{21}H_{17}O_3N_5S$: C, 60.13; H, 4.09; N, 16.71. Found: C, 60.05; H, 4.00; N, 16.65%.

*2.2.9. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-(4-methoxyphenyl) hydrazone [**5g**]*

M.p. 165–167 °C, yield, 57%; IR (KBr) ν cm^{-1}: 3421 (NH str.), 1643 (CONH, amide-I), 1545 (amide-II), 1228 (amide-III), 1615 (C=N str., Schiff base), 1469 (C–N, C–C ring str.), 1340 (C–N str.), 1039, 1179 (OCH_3, sym., asym.). ^{1}H NMR (DMSO-d_6) δ (ppm): 9.34 (s, 1H, NH), 8.86 (s, 1H, CONH), 6.86–8.58 (m, 10H, aromatic and pyridine), 5.81 (s, 1H, N=CH), 3.88 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.1 (C_7), 142.9 (C_8), 113.1–160.8 (C_2–C_6), 104.7–172.6 (C_9–C_{15}), 51.3 (C_{16}), 114.1–163.5 (C_{17}–C_{22}). *Anal.* Calc. for $C_{22}H_{19}O_3N_5S$: 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 °C, yield, 63%; IR (KBr) ν cm^{-1}: 3424 (O–H), 3207 (NH str.), 1645 (CONH, amide-I), 1551 (amide-II), 1223 (amide-III), 1616 (C=N str., Schiff base), 1464 (C–N, C–C ring str.), 1342 (C–N str.), 1037, 1181 (OCH_3, sym., asym.). ^{1}H 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). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.5 (C_7), 143.1 (C_8), 112.7–161.2 (C_2–C_6), 104.8–172.9 (C_9–C_{15}), 51.4 (C_{16}), 115.3–151.5 (C_{17}–C_{22}). *Anal.* Calc. for $C_{22}H_{19}O_4N_5S$: 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 °C, yield, 65%; IR (KBr) ν cm^{-1}: 3421 (O–H), 3203 (NH str.), 1647 (CONH, amide-I), 1552 (amide-II), 1225 (amide-III), 1613 (C=N str., Schiff base), 1470 (C–N, C–C ring str.), 1338 (C–N str.), 1037, 1181 (OCH_3, sym., asym.), 1368, 1510 (NO_2, sym., asym.). ^{1}H NMR (DMSO-d_6) δ (ppm): 9.37 (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). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.1 (C_7), 143.3 (C_8), 112.6–161.5 (C_2–C_6), 104.3–172.5 (C_9–C_{15}), 51.9 (C_{16}), 115.3–156.5 (C_{17}–C_{22}). *Anal.* Calc. for $C_{22}H_{18}O_6N_6S$: 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-(furyl) hydrazone [**5j**]*

M.p. 142–144 °C, yield, 55%; IR (KBr) ν cm^{-1}: 3419 (NH str.), 1641 (CONH, amide-I), 1553 (amide-II), 1223 (amide-III), 1614 (C=N str., Schiff base), 1472 (C–N, C–C ring str.), 1339 (C–N str.), 1035, 1181 (OCH_3, sym., asym.). ^{1}H NMR (DMSO-d_6) δ (ppm): 9.38 (s, 1H, NH), 8.86 (s, 1H, CONH), 6.86–8.52 (m, 9H, aromatic and pyridine), 5.81 (s, 1H, N=CH), 3.86 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 162.7 (C_7), 134.3 (C_8), 112.6–161.5 (C_2–C_6), 104.3–172.5 (C_9–C_{15}), 51.9 (C_{16}), 125.3–136.5 (C_{17}–C_{20}). *Anal.* Calc. for $C_{19}H_{15}O_3N_5S$: 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), thioglycolic 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) carboxamido-1,3-thiazolidin-4-one [**6a**]*

M.p. 210–212 °C, yield, 57%; IR (KBr) ν cm^{-1}: 3416 (NH str.), 1712 (amidic lactam), 1646 (amide-I), 1556 (amide-II), 1229 (amide-III), 1469 (C–N, C–C ring str.), 1341 (C–N str.), 1037, 1181 (OCH_3, sym., asym.). ^{1}H NMR (400 MHz,

DMSO-d_6) δ (ppm): 9.32 (s, 1H, NH), 8.91 (s, 1H, CONH), 6.74–8.72 (m, 11H, aromatic and pyridine), 6.11 (s, 1H, CH of 4-thiazolidinone ring), 3.64 (s, 2H, SCH_2CO of 4-thiazolidinone ring), 3.88 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.1 (C_7), 169.3 (C_8), 35.9 (C_9), 57.7 (C_{10}), 111.6–163.5 (C_2–C_6), 104.3–173.9 (C_{11}–C_{17}), 54.9 (C_{18}), 125.3–139.5 (C_{19}–C_{24}). *Anal*. Calc. for $C_{23}H_{19}O_3N_5S_2$: C, 57.85; H, 4.01; N, 14.68. Found: C, 57.80; H, 3.96; N, 14.60%.

*2.2.15. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-[2-(2-chlorophenyl)] carboxamido-1,3-thiazolidin-4-one [**6b**]*

M.p. 216–217 °C, yield, 49%; IR (KBr) ν cm^{-1}: 3417 (NH str.), 1710 (amidic lactam), 1644 (amide-I), 1556 (amide-II), 1227 (amide-III), 1466 (C–N, C–C ring str.), 1340 (C–N str.), 758 (C–Cl), 1037, 1181 (OCH_3, sym., asym.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.34 (s, 1H, NH), 8.89 (s, 1H, CONH), 6.76–8.71 (m, 10H, aromatic and pyridine), 6.10 (s, 1H, CH of 4-thiazolidinone ring), 3.62 (s, 2H, SCH_2CO of 4-thiazolidinone ring), 3.85 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.4 (C_7), 169.2 (C_8), 35.7 (C_9), 57.8 (C_{10}), 111.2–163.7 (C_2–C_6), 104.1–173.6 (C_{11}–C_{17}), 54.7 (C_{18}), 101.3–136.5 (C_{19}–C_{24}). *Anal*. Calc. for $C_{23}H_{18}O_3N_5S_2Cl$: C, 54.01; H, 3.55; N, 13.70. Found: C, 53.95; H, 3.48; N, 13.62%.

*2.2.16. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-[2-(4-chlorophenyl)] carboxamido-1,3-thiazolidin-4-one [**6c**]*

M.p. 198–200 °C, yield, 48%; IR (KBr) ν cm^{-1}: 3416 (NH str.), 1712 (amidic lactam), 1646 (amide-I), 1562 (amide-II), 1229 (amide-III), 1464 (C–N, C–C ring str.), 1340 (C–N str.), 757 (C–Cl), 1036, 1178 (OCH_3, sym., asym.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.31 (s, 1H, NH), 8.93 (s, 1H, CONH), 6.71–8.76 (m, 10H, aromatic and pyridine), 6.15 (s, 1H, CH of 4-thiazolidinone ring), 3.59 (s, 2H, SCH_2CO of 4-thiazolidinone ring), 3.83 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.2 (C_7), 169.7 (C_8), 35.4 (C_9), 57.6 (C_{10}), 111.4–163.8 (C_2–C_6), 104.7–173.5 (C_{11}–C_{17}), 54.4 (C_{18}), 127.3–139.3 (C_{19}–C_{24}). *Anal*. Calc. for $C_{23}H_{18}O_3N_5S_2Cl$: C, 54.01; H, 3.55; N, 13.70. Found: C, 53.96; H, 3.49; N, 13.65%.

*2.2.17. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine -3-[2-(2-nitrophenyl)] carboxamido-1,3-thiazolidin-4-one [**6d**]*

M.p. 227–229 °C, yield, 59%; IR (KBr) ν cm^{-1}: 3414 (NH str.), 1708 (amidic lactam), 1641 (amide-I), 1558 (amide-II), 1225 (amide-III), 1467 (C–N, C–C ring str.), 1338 (C–N str.), 1371, 1514 (NO_2, sym., asym.), 1036, 1180 (OCH_3, sym., asym.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.35 (s, 1H, NH), 8.92 (s, 1H, CONH), 6.69–8.70 (m, 10H, aromatic and pyridine), 6.14 (s, 1H, CH of 4-thiazolidinone ring), 3.58 (s, 2H, SCH_2CO of 4-thiazolidinone ring), 3.84 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.3 (C_7), 169.4 (C_8), 35.6 (C_9), 57.1 (C_{10}), 111.3–163.4 (C_2–C_6), 104.5–173.7 (C_{11}–C_{17}), 54.6 (C_{18}), 124.3–149.9 (C_{19}–C_{24}). *Anal*. Calc. for $C_{23}H_{18}O_5N_6S_2$: C, 52.87; H, 3.47; N, 16.09. Found: C, 52.80; H, 3.40; N, 16.00%.

*2.2.18. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-[2-(3-nitrophenyl)] carboxamido-1,3-thiazolidin-4-one [**6e**]*

M.p. 236–238 °C, yield, 62%; IR (KBr) ν cm^{-1}: 3416 (NH str.), 1711 (amidic lactam), 1648 (amide-I), 1560 (amide-II), 1227 (amide-III), 1466 (C–N, C–C ring str.), 1343 (C–N str.), 1365, 1510 (NO_2, sym., asym.), 1038, 1182 (OCH_3, sym., asym.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.35 (s, 1H, NH), 8.92 (s, 1H, CONH), 6.72–8.76 (m, 10H, aromatic and pyridine), 6.15 (s, 1H, CH of 4-thiazolidinone ring), 3.59 (s, 2H, SCH_2CO of 4-thiazolidinone ring), 3.84 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.1 (C_7), 169.2 (C_8), 35.7 (C_9), 57.1 (C_{10}), 111.1–163.2 (C_2–C_6), 104.3–173.7 (C_{11}–C_{17}), 54.4 (C_{18}), 123.1–149.1 (C_{19}–C_{24}). *Anal*. Calc. for $C_{23}H_{18}O_5N_6S_2$: C, 52.87; H, 3.47; N, 16.09. Found: C, 52.82; H, 3.41; N, 16.03%.

*2.2.19. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-[2-(4-hydroxyphenyl)] carboxamido-1,3-thiazolidin-4-one [**6f**]*

M.p. 186–189 °C, yield, 67%; IR (KBr) ν cm^{-1}: 3414 (O–H str.), 3206 (NH str.), 1714 (amidic lactam), 1646 (amide-I), 1559 (amide-II), 1228 (amide-III), 1462 (C–N, C–C ring str.), 1341 (C–N str.), 1037, 1181 (OCH_3, sym., asym.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.32 (s, 1H, NH), 8.91 (s, 1H, CONH), 6.74–8.72 (m, 10H, aromatic and pyridine), 6.11 (s, 1H, CH of 4-thiazolidinone ring), 3.64 (s, 2H, SCH_2CO of 4-thiazolidinone ring), 3.85 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.7 (C_7), 169.4 (C_8), 35.5 (C_9), 57.3 (C_{10}), 111.4–163.1 (C_2–C_6), 104.8–173.1 (C_{11}–C_{17}), 54.2 (C_{18}), 115.3–158.7 (C_{19}–C_{24}). *Anal*. Calc. for $C_{23}H_{19}O_4N_5S_2$: C, 55.97; H, 3.88; N, 14.20. Found: C, 55.90; H, 3.80; N, 14.14%.

*2.2.20. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-[2-(4-methoxyphenyl)] carboxamido-1,3-thiazolidin-4-one [**6g**]*

M.p. 256–257 °C, yield, 54%; IR (KBr) ν cm^{-1}: 3416 (NH str.), 1709 (amidic lactam), 1649 (amide-I), 1554 (amide-II), 1229 (amide-III), 1468 (C–N, C–C ring str.), 1346 (C–N str.), 1039, 1186 (OCH_3 str., sym., asym.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.34 (s, 1H, NH), 8.91 (s, 1H, CONH), 6.73–8.74 (m, 10H, aromatic and pyridine), 6.11 (s, 1H, CH of 4-thiazolidinone ring), 3.58 (s, 2H, SCH_2CO of 4-thiazolidinone ring), 3.83 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.6 (C_7), 169.4 (C_8), 35.5 (C_9), 57.6 (C_{10}), 111.9–163.3 (C_2–C_6), 104.1–173.8 (C_{11}–C_{17}), 54.1 (C_{18}), 114.3–159.5 (C_{19}–C_{24}). *Anal*. Calc. for $C_{24}H_{21}O_4N_5S_2$: C, 56.79; H, 4.17; N, 13.81. Found: C, 56.70; H, 4.10; N, 13.76%.

*2.2.21. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-[2-(3-methoxy-4-hydroxy-phenyl)] carboxamido-1,3-thiazolidin-4-one [**6h**]*

M.p. 239–241 °C, yield, 56%; IR (KBr) ν cm^{-1}: 3410 (O–H), 3210 (NH str.), 1711 (amidic lactam), 1647 (amide-I), 1558 (amide-II), 1225 (amide-III), 1469 (C–N, C–C ring str.), 1344 (C–N str.), 1032, 1192 (OCH_3 str., sym., asym.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.34 (s, 1H, NH), 8.95 (s, 1H, CONH), 6.69–8.73 (m, 9H, aromatic and pyridine), 6.09 (s, 1H, CH of 4-thiazolidinone ring), 3.61 (s, 2H, SCH_2CO of 4-thiazolidinone ring), 3.87 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.2 (C_7), 169.3 (C_8), 35.4 (C_9), 57.6 (C_{10}), 111.1–163.7 (C_2–C_6), 104.5–173.2 (C_{11}–C_{17}), 54.8 (C_{18}), 115.3–151.7 (C_{19}–C_{24}). *Anal*. Calc. for $C_{24}H_{21}O_5N_5S_2$: C, 55.06; H, 4.05; N, 13.38. Found: C, 55.00; H, 3.95; N, 13.30%.

*2.2.22. 2-[N-(6-methoxybenzothiazolyl)amino] pyridine-3-[2-(3-methoxy-4-hydroxy-5-nitrophenyl)] carboxa-mido-1,3-thiazolidin-4-one [**6i**]*

M.p. 217–220 °C, yield, 62%; IR (KBr) ν cm^{-1}: 3416 (O–H str.), 3212 (NH str.), 1711 (amidic lactam), 1646 (amide-I),

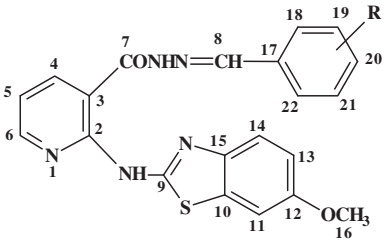
1561 (amide-II), 1225 (amide-III), 1465 (C–N, C–C ring str.), 1342 (C–N str.), 1369, 1516 (NO_2, sym., asym.), 1036, 1194 (OCH_3 str., sym., asym.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.37 (s, 1H, NH), 8.94 (s, 1H, CONH), 6.71–8.75 (m, 8H, aromatic and pyridine), 6.10 (s, 1H, CH of 4-thiazolidinone ring), 3.63 (s, 2H, SCH_2CO of 4-thiazolidinone ring), 3.82 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.5 (C_7), 169.7 (C_8), 35.7 (C_9), 57.3 (C_{10}), 111.7–163.8 (C_2–C_6), 104.1–173.5 (C_{11}–C_{17}), 54.4 (C_{18}), 118.1–153.1 (C_{19}–C_{24}). *Anal.* Calc. for $C_{24}H_{20}O_7N_6S_2$: C, 50.70; H, 3.55; N, 14.79. Found: C, 50.65; H, 3.45; N, 14.70%.

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

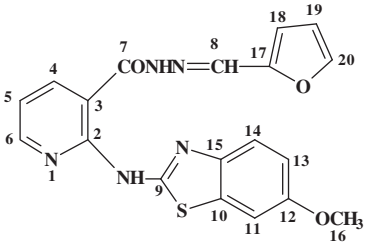
M.p. 204–206 °C, yield, 51%; IR (KBr) ν cm^{-1}: 3412 (NH str.), 1710 (amidic lactam), 1649 (amide-I), 1558 (amide-II), 1225 (amide-III), 1467 (C–N, C–C ring str.), 1345 (C–N str.), 1037, 1186 (OCH_3, sym., asym.). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.34 (s, 1H, NH), 8.94 (s, 1H, CONH), 6.72–8.71 (m, 9H, aromatic and pyridine), 6.13 (s, 1H, CH of 4-thiazolidinone ring), 3.63 (s, 2H, SCH_2CO of 4-thiazolidinone ring), 3.85 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm): 163.8 (C_7), 169.1 (C_8), 35.0 (C_9), 57.1 (C_{10}), 111.2–163.1 (C_2–C_6), 104.4–173.1 (C_{11}–C_{17}), 54.8 (C_{18}), 104.7–151.5 (C_{19}–C_{24}). *Anal.* Calc. for $C_{21}H_{17}O_4N_5S_2$: C, 53.95; H, 3.67; N, 14.99. Found: C, 53.88; H, 3.60; N, 14.90% (Figs. 1 and 2).

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 for the test. Inoculum size for test strain was adjusted to 10^8 CFU (Colony Forming Unit) per milliliter by comparing the turbidity. DMSO was used as diluents to get desired concentration 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

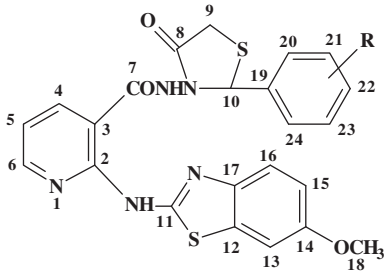


5a-i

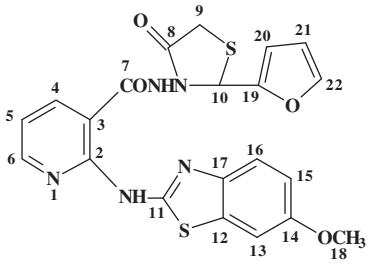


5j

Figure 1 Hydrazones **5a**–**j**.



6a-i



6j

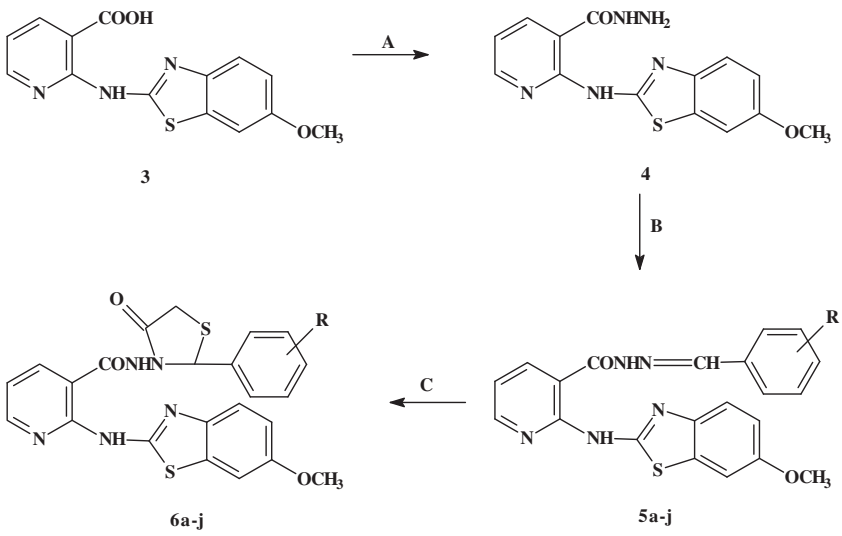
Figure 2 4-Thiazolidinones **6a**–**j**.

subcultured (before inoculation) 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 concentration, 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 K_2CO_3 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



a : R = -H
b : R = 2-Cl
c : R = 4-Cl
d : R = 2-NO_2
e : R = 3-NO_2
f : R = 4-OH
g : R = 4-OCH_3
h : R = 3-OCH_3-4-OH
i : R = 3-OCH_3-4-OH-5-NO_2
j : R = C_4H_3O (Furyl)

Scheme 1 Synthetic protocol of **5a–j** and **6a–j**. **5j** and **6j** contains furyl nucleus as illustrated in Figs. 1 and 2. Synthesis of the compounds **4**, **5a–j** and **6a–j**. Reagents and conditions: (A) (i) $SOCl_2$ and (ii) hydrazine hydrate, chloroform, triethylamine; (B) aromatic aldehydes, DMF, 1–2 drop glacial acetic acid, 5–6 h (C) thioglycolic acid, anhydrous $ZnCl_2$, 1,4-dioxane, 12–14 h.

hydrate in chloroform formed acid hydrazide **4**. After condensing, **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 thioglycolic acid in dry 1,4-dioxane for 12–14 h using a Dean–Stark apparatus.

The structures of synthesized compounds **5a–j** were confirmed by elemental analyses and IR spectra (cm^{-1}) absorption bands at 3419 (NH), 1646 (amide-I), 1612 (–N=CH–), 1556 (amide-II), 1340 (C–N), 1225 (amide-III), 1036, 1186 (C–O–C). Some additional peaks appear due to substitution in aromatic ring showing absorption band at 3410 (O–H), 1370, 1512 (–NO_2 sym., asym.), 758 (CCl). In ^{1}H NMR spectra common signals that appear are: δ_H (ppm): a singlet at δ 8.85 corresponds to >CONH, a singlet at δ 5.83 for –N=CH–, a multiplet at δ 6.84–8.57corresponds to aromatic proton. A singlet at δ 3.85 for –OCH_3, and due to the substitution on aromatic ring, a singlet appeared at δ 5.15 corresponding to –OH.

The structure of compounds **6a–j** were supported by elemental analyses and IR spectra as observed in **5a–j** with disappearance of 1612 cm^{-1} for –N=CH– band with 1710 cm^{-1} for >C=O of thiazolidinone. The ^{1}H NMR singlet signals of cyclized thiazolidinone was observed at δ 3.58–3.64, corresponding to –CH_2– in the ring, and δ 6.09–6.15, corresponding to C_2–H. The other signals observed were same as **5a–j**.

3.2. Antimicrobial activity

Antibacterial 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 aureus* MTCC 96, *Streptococcus pyogenes* MTCC 442, *Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 741. Antifungal activity of these compounds **5a–j** and **6a–j** was evaluated 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). Minimum inhibitory concentrations (MICs) of the tested compounds 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 compounds 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. Particularly, compound **5h**, **5j**, **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**, **5j**, **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 compounds are presented in Table 1. Starting material **1**, **2**, **3**

Table 1 Biological profile of compounds **5a–j** and **6a–j**.

Compounds	Minimal inhibitory concentration (MIC) μg/ml						
	Tested bacteria				Tested fungi		
	Gram-negative		Gram-positive				
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*	*A. niger*	*A. clavatus*
1	150	150	200	250	250	500	500
2	150	250	250	500	250	500	500
3	125	500	200	250	250	500	500
4	200	500	500	500	500	500	500
5a	150	200	250	250	500	500	500
5b	500	500	200	200	1000	>1000	>1000
5c	250	250	500	500	100	500	500
5d	200	250	150	200	500	500	1000
5e	250	500	150	150	500	1000	1000
5f	500	500	500	500	500	500	1000
5g	150	200	200	200	100	500	500
5h	100	500	500	500	200	500	500
5i	500	500	250	250	500	>1000	>1000
5j	100	200	150	200	1000	1000	1000
6a	500	1000	250	250	500	1000	1000
6b	100	150	100	150	500	1000	1000
6c	500	250	200	200	1000	>1000	>1000
6d	100	200	250	250	1000	1000	1000
6e	250	250	500	500	500	500	500
6f	200	200	250	500	500	1000	1000
6g	500	500	200	200	500	500	500
6h	62.5	100	250	250	1000	1000	1000
6i	200	500	500	500	1000	1000	1000
6j	200	200	250	250	500	500	500
Ampicillin	100	100	250	100	–	–	–
Greseofulvin	–	–	–	–	500	100	100

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**, **5i**, **6a**, **6b**, **6e**, **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, $–NO_2$ group and furan nucleus are more active than the remaining compounds.

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