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# Synthesis of New Pyridine Based 4-Thiazolidinones Incorporated Benzothiazoles and Evaluation of Their Antimicrobial Activity

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## Abstract

Substituted Schiff bases (hydrazones) **5a-j** have been prepared from the starting material 2-chloro pyridine-3-carboxylic acid **1** by a sequence of reactions like reaction with 2-amino-6-nitro benzothiazole (Ullamann condensation), thionyl chloride, hydrazine hydrate and different aromatic aldehydes. On cyclocondensation of **5a-j** with thioglycolic acid in dry 1,4-dioxane furnished desired compounds 4-thiazolidinones **6a-j**. The structures of all the synthesized compounds have been assigned on the basis of IR, $^{1}$H NMR, $^{13}$C NMR spectral data and elemental analyses. All the newly synthesized compounds were tested for their *in vitro* antimicrobial activity against several microbes. Some of the compounds showed significant antibacterial as well as antifungal activity.

**Keywords:** 2-Chloro pyridine-3-carboxylic acid; Schiff bases (hydrazones); 4-Thiazolidinones; antimicrobial activity

## Introduction

Pyridine is the parent ring system of a large number of naturally occurring products and important industrial, pharmaceutical, and agricultural chemicals. Pyridine derivatives exhibit various biological activities such as anti-HIV [1], anticancer [2], antimycobacterial [3], antitubercular [4], anticonvulsant [5], anti-inflammatory [6], etc. The growing potent literature of recent years demonstrates that the benzothiazole derivatives exhibit better pharmacological properties such as antitumor [7], anti-inflammatory [8], and many others. Further more, significant biological properties are associated with thiazolidinone derivatives like anticonvulsant [9], anti-inflammatory [10], anti-HIV [11], etc.

In the recent years, we have been involved in the synthesis and chemistry of pyridine [12,13] and thiazolidinone [14,15] derivatives with respect to incorporate diverse bioactive heterocyclic nucleus intact for evaluating their antibacterial and antifungal significance. Led by these considerations, it appeared of interest to synthesize some new 4-thiazolidinone derivatives incorporating with 2-amino-6-nitro benzothiazole and pyridine moieties.

The starting material 2-chloro pyridine-3-carboxylic acid **1** on Ullamann condensation with 2-amino-6-nitro benzothiazole **2** formed the condensed product 2-(6-nitrobenzo[d]thiazol-2-ylamino)nicotinic acid **3** which on subsequent reaction with thionyl chloride and hydrazine hydrate formed 2-(6-nitrobenzo[d]thiazol-2-

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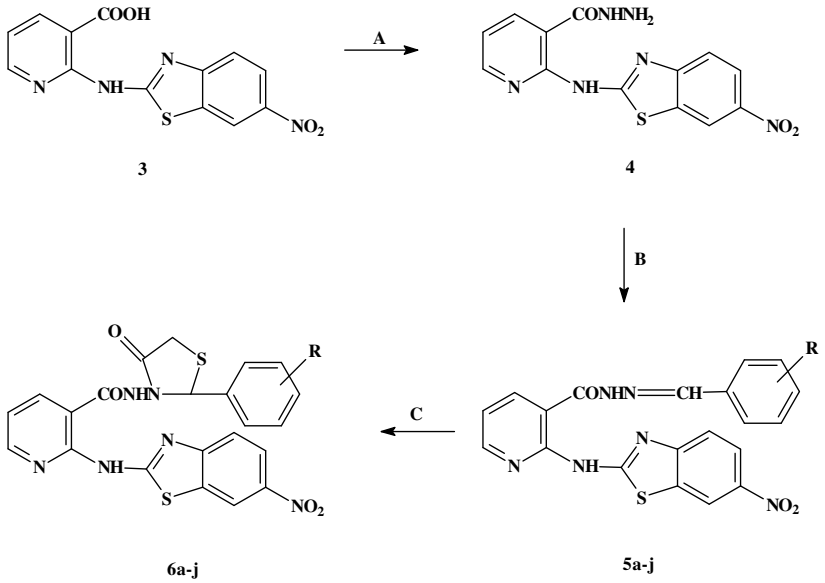



**Scheme 1.** Synthesis of the compounds 4, 5a-j and 6a-j. Reagents and conditions: (A) (i) $SOCl_2$ and (ii) hydrazine hydrate, chloroform, triethylamine; (B) aromatic aldehydes, DMF, 1-2 drop glacial acetic acid, 5-6 h (C) thioglycolic acid, anhydrous $ZnCl_2$, 1,4-dioxane, 12-14 h. a : R = -H, f : R = 4-OH, b : R = 2-Cl, g : R = 4-$OCH_3$, c : R = 4-Cl, h : R = 3-$OCH_3$-4-OH, d : R = 2-$NO_2$, i : R = 3-$OCH_3$-4-OH-5-$NO_2$, e : R = 3-$NO_2$, j : R = $C_4H_3O$ (Furyl).

ylamino)nicotinohydrazide **4**. This hydrazide **4** with different aromatic aldehydes **a-j** yielded *N'*-benzylidene/furan-2-(6-nitrobenzo[d]thiazol-2-ylamino) nicotinohydrazide **5a-j**. The preparation of 4-thiazolidinones **6a-j** has been undertaken by the heterocyclisation of Schiff's bases with thioglycolic acid (Scheme 1).

The constitutions of all the above products have been supported by IR, $^1$H NMR and $^{13}$C NMR spectral data and elemental analyses. Biological profiles of all the synthesized products have been screened *in vitro* for their antimicrobial activity against different strain of bacterial and fungal species.

## Materials and Methods

### *Experimental*

Laboratory Chemicals were supplied by Rankem India Ltd. and Fisher Scientific Ltd. Melting points were determined by the open tube capillary method and are uncorrected. The purity of the compounds was determined by thin layer chromatography (TLC) plates (silica gel G) in the solvent system toluene: ethyl acetate (75:25). The spots were observed by exposure to iodine vapors or by UV light. The IR spectra were obtained on a Perkin Elmer-838 FT IR spectrometer (KBr pellets). The $^1$H-NMR & $^{13}$C-NMR spectra were recorded on a Bruker Avance II 400 spectrometer using TMS as an internal standard in DMSO-$d_6$. Elemental analyses of the newly synthesized compounds were carried out on Carlo Erba 1108 analyzer**.** Elemental analyses of all the compounds were in agreement with the calculated values.

Synthesis of 2-amino-6-nitrobenzothiazole **2** and 2-(6-nitrobenzo[d]thiazol-2-ylamino)nicotinic acid **3** was done according to previously reported procedures [13].

### *Synthesis of 2-(6-nitrobenzo[d]thiazol-2-ylamino) nicotinohydrazide 4*

2-(6-nitrobenzo[d]thiazol-2-ylamino) nicotinic acid **3** (0.01 mol) in $SOCl_2$ (7.0 ml) was refluxed on water bath and reaction was monitered by TLC. 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-(6-nitrobenzo[d]thiazol-2-ylamino) nicotinoyl chloride was obtained, which was directly used in forward step.

Hydrazine hydrate (0.02 mole, 80 %) in chloroform (5 mL) was added drop wise in a mixture of above prepared acid chloride (0.01 mole) in chloroform (10 mL) and tri ethyl amine (2-3 drops) under stirring at 0-5°C in half an hour time. Then it was stirred at room

temperature for 3-4 h to complete reaction. The solvent was distilled off and the product hydrazide **4** obtained was collected, dried and recystallised from methanol, yield 63 %, m.p.- 268-270 °C; Calculated for $C_{13}H_{10}N_6O_3S$ requires: C 47.27, H 3.05, N 25.44; Found: C 47.21, H 2.98, N 25.40 %. IR (KBr) $\nu$ $cm^{-1}$: 3365 (NH str.), 1667 (CONH, amide-I), 1547 (amide-II), 1221 (amide-III), 1370,1520 ($NO_2$, sym., asym.). $^1$H NMR (DMSO-$d_6$) δ (ppm): 9.38 (1H, s, -NH-), 8.87 (1H, s, -CONH-), 8.25-6.85 (6H, m, pyridine and aromatic), 4.15 (2H, s, -$NH_2$).

***Synthesis of N′-substituted benzylidene/furan-2-(6-nitrobenzo[d]thiazol-2-ylamino)nicotinohydrazide 5a-j***

To a solution of 2-(6-nitrobenzo[d]thiazol-2-ylamino)nicotinohydrazide (0.01 mole) in 10 ml of DMF; benzaldehyde **(a)** (0.012 mole) and 3-4 drops of glacial acetic acid as a catalyst were added. The reaction mixture was refluxed for 5-6 h. The contents were cooled and poured onto crushed ice and thus the separated solid was isolated, washed with water and recrystallized from ethanol to give the title compound **5a.** The reaction was monitored by TLC on silica gel using toluene: ethyl acetate (75:25).

Similarly, other hydrazone derivatives **5b-j** have been prepared by following the same method.

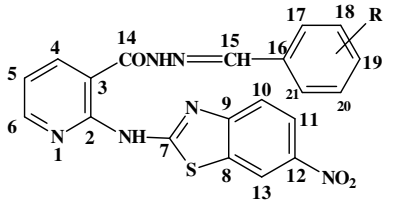
***N′*-benzylidene-2-(6-nitrobenzo[d]thiazol-2-yl amino)nicotinohydrazide 5a :** yield 51 %, m.p. 145-147 °C; Calculated for $C_{20}H_{14}N_6O_3S$ requires: C 57.41, H 3.37, N 20.08; Found: C 57.36, H 3.32, N 20.04 %. IR (KBr) $\nu$ $cm^{-1}$: 3421 (NH str.), 1641 (CONH, amide-I), 1548 (amide-II), 1225 (amide-III), 1611 (C=N str., Schiff base), 1368, 1512 ($NO_2$, sym., asym.). $^1$H NMR (DMSO-$d_6$) δ (ppm): 9.32 (s, 1H, NH), 8.82 (s, 1H, CONH), 8.52-6.79 (m, 11H, aromatic and pyridine), 5.76 (s, 1H, N=CH). $^{13}$C NMR (100MHz, 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 ($C_{17}$-$C_{22}$).

***N′*-(2-chlorobenzylidene)-2-(6-nitrobenzo[d] thiazol-2-ylamino)nicotino hydrazide 5b :** yield 53 %, m.p. 152-153 °C; Calculated for $C_{20}H_{13}ClN_6O_3S$ requires: C 53.04, H 2.89, N 18.56; Found: C 52.99, H 2.83, N 18.51 %. IR (KBr) $\nu$ $cm^{-1}$: 3419 (NH str.), 1646 (CONH, amide-I), 1550 (amide-II), 1224 (amide-III), 1616 (C=N str., Schiff base), 1369, 1514 ($NO_2$, sym., asym.), 760 (C-Cl). $^1$H NMR (DMSO-$d_6$) δ (ppm): 9.33 (s, 1H, NH), 8.85 (s, 1H, CONH), 8.56-6.81 (m, 10H, aromatic and pyridine), 5.81 (s, 1H, N=CH). $^{13}$C NMR (100MHz, 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 ($C_{17}$-$C_{22}$).

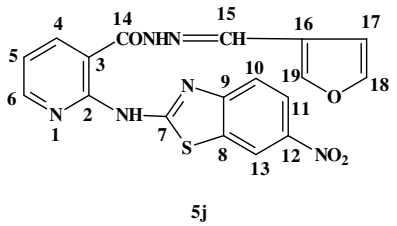
***N′*-(4-chlorobenzylidene)-2-(6-nitrobenzo[d] thiazol-2-ylamino)nicotino hydrazide 5c :** yield 49 %, m.p. 141-143 °C; Calculated for $C_{20}H_{13}ClN_6O_3S$ requires: C 53.04, H 2.89, N 18.56; Found: C 53.04, H 2.87, N 18.49 %. IR (KBr) $\nu$ $cm^{-1}$: 3417 (NH str.), 1642 (CONH, amide-I), 1551 (amide-II), 1226 (amide-III), 1609 (C=N str., Schiff base), 1370, 1510 ($NO_2$, sym., asym.), 758 (C-Cl). $^1$H NMR (DMSO-$d_6$) δ (ppm): 9.38 (s, 1H, NH), 8.86 (s, 1H, CONH), 8.53-6.79 (m, 10H, aromatic and pyridine), 5.82 (s, 1H, N=CH). $^{13}$C NMR (100MHz, 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 ($C_{17}$-$C_{22}$).

***N′*-(2-nitrobenzylidene)-2-(6-nitrobenzo[d]thiazol-2-ylamino)nicotino hydrazide 5d :** yield 58 %, m.p. 137-139 °C; Calculated for $C_{20}H_{13}N_7O_5S$ requires: C 51.83, H 2.83, N 21.16; Found: C 51.74, H 2.77, N 21.09 %. IR (KBr) $\nu$ $cm^{-1}$: 3422 (NH str.), 1640(CONH, amide-I), 1551(amide-II), 1223(amide-III), 1611(C=N str., Schiff base), 1370,1512($NO_2$, sym., asym.). $^1$H NMR(DMSO-$d_6$) δ(ppm): 9.37 (s, 1H, NH), 8.82(s, 1H, CONH), 8.56-6.82 (m, 10H, aromatic and pyridine), 5.81(s, 1H, N=CH). $^{13}$C NMR(100MHz, 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 ($C_{17}$-$C_{22}$).

***N′*-(3-nitrobenzylidene)-2-(6-nitrobenzo[d]thiazol-2-ylamino)nicotino hydrazide 5e :** yield 55 %, m.p. 150-121 °C; Calculated for $C_{20}H_{13}N_7O_5S$ requires: C




**5a-i**




**5j**

**Figure 1.** Hydrazones 5a-j.

51.83, H 2.83, N 21.16; Found: C 51.77, H 2.71, N 21.12 %. IR (KBr) $\nu$ $cm^{-1}$: 3420 (NH str.), 1642 (CONH, amide-I), 1550 (amide-II), 1224 (amide-III), 1611 (C=N str., Schiff base), 1369,1511 ($NO_2$, sym., asym.). $^1$H NMR (DMSO-$d_6$) δ (ppm): 9.37 (s, 1H, NH), 8.89 (s, 1H, CONH), 8.56-6.83 (m, 10H, aromatic and pyridine), 5.87 (s, 1H, N=CH). $^{13}$C NMR (100MHz, 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 ($C_{17}$-$C_{22}$).

***N′*-(4-hydroxybenzylidene)-2-(6-nitrobenzo[d] thiazol-2-ylamino)nicotino hydrazide 5f :** yield 57 %, m.p. 157-158 °C; Calculated for $C_{20}H_{14}N_6O_4S$ requires: C 55.29, H 3.25, N 19.35; Found: C 55.22, H 3.18, N 19.29 %. IR (KBr) $\nu$ $cm^{-1}$: 3422 (NH str.), 1644(CONH, amide-I), 1548(amide-II), 1225(amide-III), 1614(C=N str., Schiff base), 1371, 1515($NO_2$, sym., asym.). $^1$H NMR(DMSO-$d_6$) δ(ppm): 9.31(s, 1H, NH), 8.79(s, 1H, CONH), 8.54-6.82 (m, 10H, aromatic and pyridine), 5.85(s, 1H, N=CH). $^{13}$C NMR(100MHz, 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 ($C_{17}$-$C_{22}$).

***N′*-(4-methoxybenzylidene)-2-(6-nitrobenzo[d] thiazol-2-ylamino)nicotino hydrazide 5g :** yield 56 %, m.p. 131-134 °C; Calculated for $C_{21}H_{16}N_6O_4S$ requires: C 56.24, H 3.60, N 18.74; Found: C 56.17, H 3.52, N 18.68 %. IR (KBr) $\nu$ $cm^{-1}$: 3421 (NH str.), 1643 (CONH, amide-I), 1545 (amide-II), 1228 (amide-III), 1615 (C=N str., Schiff base), 1368, 1510 ($NO_2$, sym., asym.). $^1$H NMR (DMSO-$d_6$) δ (ppm): 9.34 (s, 1H, NH), 8.86 (s, 1H, CONH), 8.58-6.86 (m, 10H, aromatic and pyridine), 5.81 (s, 1H, N=CH), 3.88 (s, 3H, $OCH_3$). $^{13}$C NMR (100MHz, 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 ($C_{17}$-$C_{22}$).

***N′*-(4-hydroxy-3-methoxybenzylidene)-2-(6-nitro benzo[d]thiazol-2-ylamino) nicotinohydrazide 5h :** yield 49 %, m.p. 125-128 °C; Calculated for $C_{21}H_{16}N_6O_5S$ requires: C 54.31, H 3.47, N 18.09; Found: C 54.22, H 3.40, N 18.24 %. IR (KBr) $\nu$ $cm^{-1}$: 3424 (NH str.), 1645 (CONH, amide-I), 1551 (amide-II), 1224 (amide-III), 1616 (C=N str., Schiff base), 1365, 1512 ($NO_2$, sym., asym.). $^1$H NMR (DMSO-$d_6$) δ (ppm): 9.36 (s, 1H, NH), 8.87 (s, 1H, CONH), 8.58-6.83 (m, 9H, aromatic and pyridine), 5.80 (s, 1H, N=CH), 3.86 (s, 3H, $OCH_3$). $^{13}$C NMR (100MHz, 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 ($C_{17}$-$C_{22}$).

***N′*-(4-hydroxy-3-methoxy-5-nitrobenzylidene)-2-(6-nitrobenzo[d]thiazol-2-ylamino)nicotinohydrazide 5i :** yield 52 %, m.p. 161-163 °C; Calculated for $C_{21}H_{15}N_7O_7S$ requires: C 49.51, H 2.97, N 19.25; Found: C 49.43, H 2.90, N 19.17 %. IR (KBr) $\nu$ $cm^{-1}$: 3421 (NH str.), 1645 (CONH, amide-I), 1550 (amide-II), 1225 (amide-III), 1613 (C=N str., Schiff base), 1367, 1511 ($NO_2$, 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), 8.56-6.82 (m, 8H, aromatic and pyridine), 5.84(s, 1H, N=CH), 3.85(s, 3H, $OCH_3$). $^{13}$C NMR(100MHz, 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 ($C_{17}$-$C_{22}$).

***N′*-(furan-3-ylmethylene)-2-(6-nitrobenzo[d] thiazol-2-ylamino)nicotino hydrazide 5j :** yield 59 %, m.p. 149-150 °C; Calculated for $C_{18}H_{12}N_6O_4S$ requires: C 52.94, H 2.96, N 20.58; Found: C 52.85, H 2.86, N 20.50 %. IR (KBr) $\nu$ $cm^{-1}$: 3419 (NH str.), 1641 (CONH, amide-I), 1551 (amide-II), 1224 (amide-III), 1614 (C=N str., Schiff base), 1366, 1510 ($NO_2$, sym., asym.). $^1$H NMR (DMSO-$d_6$) δ (ppm): 9.38 (s, 1H, NH), 8.86 (s, 1H, CONH), 8.52-6.86 (m, 9H, aromatic and pyridine), 5.81 (s, 1H, N=CH). $^{13}$C NMR (100MHz, 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 ($C_{17}$-$C_{20}$).

### *Synthesis of 2-(6-nitrobenzo[d]thiazol-2-ylamino)-N-(4-oxo-2-(substituted phenyl/furan-3-yl)thiazolidin-3-yl)nicotinamides 6a-j*

A mixture of **5a** (0.01 mole), thioglycolic acid (0.015 mole) and a pinch of anhydrous $ZnCl_2$ in dry 1,4-dioxane was refluxed for 12-14 h. The reaction mixture was cooled and neutralized with 10 % sodium bicarbonate solution. The product thus separated was filtered, washed with water and recrystallized from ethanol to give **6a**. The reaction was monitored by TLC on silica gel using toluene: ethyl acetate (75:25).

Similarly, other **2-(6-nitrobenzo[d]thiazol-2-yl amino)-*N*-(4-oxo-2-(substituted phenyl/furan-3-yl) thiazolidin-3-yl)nicotinamides 6b-j** were prepared according to this method.

**2-(6-nitrobenzo[d]thiazol-2-ylamino)-*N*-(4-oxo-2-phenylthiazolidin-3-yl) nicotinamide 6a :** yield 51 %, m.p. 165-167 °C; Calculated for $C_{22}H_{16}N_6O_4S_2$ requires: C 53.65, H 3.27, N 17.06; Found: C 53.59, H 3.20, N 17.00 %. IR (KBr) $\nu$ $cm^{-1}$: 3416 (NH str.), 1712 (C=O of 4-thiazolidinone ring), 1646 (Amide-I), 1556 (Amide-II), 1229 (Amide-III), 1365, 1511 ($NO_2$, sym., asym.). $^1$H NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.32

(s, 1H, NH), 8.91 (s, 1H, CONH), 8.72-6.74 (m, 11H, aromatic and pyridine), 6.11 (s, 1H, CH of 4-thiazolidinone ring), 3.64 (s, 2H, $SCH_2CO$ of 4-thiazolidinone ring). $^{13}C$ NMR (100MHz, 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 ($C_{19}$-$C_{24}$).

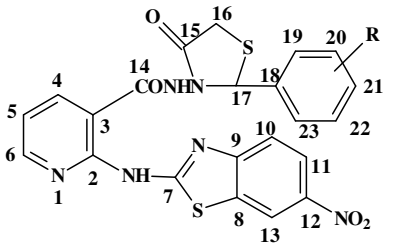
***N*-(2-(2-chlorophenyl)-4-oxothiazolidin-3-yl)-2-(6-nitrobenzo[d]thiazol-2-yl amino)nicotinamide 6b :** yield 60 %, m.p. 174-176 °C; Calculated for $C_{22}H_{15}ClN_6O_4S_2$ requires: C 50.14, H 2.87, N 15.95; Found: C 50.11, H 2.79, N 15.91 %. IR (KBr) $\nu$ $cm^{-1}$: 3417 (NH str.), 1710 (C=O of 4-thiazolidinone ring), 1644 (Amide-I), 1556 (Amide-II), 1227 (Amide-III), 758 (C-Cl), 1367, 1514 ($NO_2$, sym., asym.). $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.34 (s, 1H, NH), 8.89 (s, 1H, CONH), 8.71-6.76 (m, 10H, aromatic and pyridine), 6.10 (s, 1H, CH of 4-thiazolidinone ring), 3.62 (s, 2H, $SCH_2CO$ of 4-thiazolidinone ring). $^{13}C$ NMR (100MHz, 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 ($C_{19}$-$C_{24}$).

***N*-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl)-2-(6-nitrobenzo[d]thiazol-2-yl amino)nicotinamide 6c :** yield 47 %, m.p. 179-180 °C; Calculated for $C_{22}H_{15}ClN_6O_4S_2$ requires: C 50.14, H 2.87, N 15.95; Found: C 50.09, H 2.76, N 15.90 %. IR (KBr) $\nu$ $cm^{-1}$: 3416 (NH str.), 1712 (C=O of 4-thiazolidinone ring), 1646 (Amide-I), 1562 (Amide-II), 1229 (Amide-III), 757 (C-Cl), 1366, 1510 ($NO_2$, sym., asym.). $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.31 (s, 1H, NH), 8.93 (s, 1H, CONH), 8.76-6.71 (m, 10H, aromatic and pyridine), 6.15 (s, 1H, CH of 4-thiazolidinone ring), 3.59 (s, 2H, $SCH_2CO$ of 4-thiazolidinone ring). $^{13}C$ NMR (100MHz, 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 ($C_{19}$-$C_{24}$).

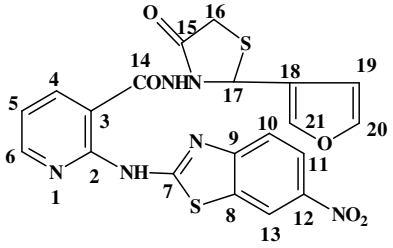
**2-(6-nitrobenzo[d]thiazol-2-ylamino)-*N*-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)nicotinamide 6d :** yield 53 %, m.p. 163-165 °C; Calculated for $C_{22}H_{15}N_7O_6S_2$ requires: C 49.16, H 2.81, N 18.24; Found: C 49.10, H 2.74, N 18.19 %. IR (KBr) $\nu$ $cm^{-1}$: 3414 (NH str.), 1708 (C=O of 4-thiazolidinone ring), 1641 (Amide-I), 1558 (Amide-II), 1225 (Amide-III), 1369, 1509 ($NO_2$, sym., asym.). $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.35 (s, 1H, NH), 8.92(s, 1H, CONH), 8.70-6.69 (m, 10H, aromatic and pyridine), 6.14(s, 1H, CH of 4-thiazolidinone ring), 3.58(s, 2H, $SCH_2CO$ 4-thiazolidinone ring). $^{13}C$ NMR(100MHz, 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 ($C_{19}$-$C_{24}$).

**2-(6-nitrobenzo[d]thiazol-2-ylamino)-*N*-(2-(2-nitrophenyl)-4-oxothiazolidin-3-yl)nicotinamide 6e :** yield 58 %, m.p. 187-188 °C; Calculated for $C_{22}H_{15}N_7O_6S_2$ requires: C 49.16, H 2.81, N 18.24; Found: C 49.08, H 2.76, N 18.17 %. IR (KBr) $\nu$ $cm^{-1}$: 3416 (NH str.), 1711 (C=O of 4-thiazolidinone ring), 1648 (Amide-I), 1560 (Amide-II), 1227 (Amide-III), 1365, 1510 ($NO_2$, sym., asym.). $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.35 (s, 1H, NH), 8.92 (s, 1H, CONH), 8.76-6.72 (m, 10H, aromatic and pyridine), 6.15 (s, 1H, CH 4-thiazolidinone ring), 3.59 (s, 2H, $SCH_2CO$ 4-thiazolidinone ring). $^{13}C$ NMR (100MHz, 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 ($C_{19}$-$C_{24}$).

***N*-(2-(4-hydroxyphenyl)-4-oxothiazolidin-3-yl)-2-(6-nitrobenzo[d]thiazol-2-ylamino)nicotinamide 6f :** yield 50 %, m.p. 182-184 °C; Calculated for $C_{22}H_{16}N_6O_5S_2$ requires: C 51.96, H 3.17, N 16.53; Found: C 51.89, H 3.10, N 16.48 %. IR (KBr) $\nu$ $cm^{-1}$: 3414 (NH str.), 1714 (C=O of 4-thiazolidinone ring), 1646 (Amide-I), 1559 (Amide-II), 1228 (Amide-III), 1368, 1512 ($NO_2$, sym., asym.). $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.32 (s, 1H, NH), 8.91 (s, 1H,




**6a-i**




**6j**

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

CONH), 8.72-6.74 (m, 10H, aromatic and pyridine), 6.11 (s, 1H, CH 4-thiazolidinone ring), 3.64 (s, 2H, $SCH_2CO$ 4-thiazolidinone ring). $^{13}C$ NMR (100MHz, 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 ($C_{19}$-$C_{24}$).

***N*-(2-(4-methoxyphenyl)-4-oxothiazolidin-3-yl)-2-(6-nitrobenzo[d]thiazol-2-ylamino)nicotinamide 6g :** yield 63 %, m.p. 197-199 °C; Calculated for $C_{23}H_{18}N_6O_5S_2$ requires: C 52.86, H 3.47, N 16.08; Found: C 52.81, H 3.39, N 15.99 %. IR (KBr) $\nu$ $cm^{-1}$: 3416 (NH str.), 1709 (C=O of 4-thiazolidinone ring), 1649 (Amide-I), 1554 (Amide-II), 1229 (Amide-III), 1039,1186 ($OCH_3$ str., sym., asym.), 1369, 1511 ($NO_2$, sym., asym.). $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.34 (s, 1H, NH), 8.91 (s, 1H, CONH), 8.74-6.73 (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 (100MHz, 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 ($C_{19}$-$C_{24}$).

***N*-(2-(4-hydroxy-3-methoxyphenyl)-4-oxo thiazolidin-3-yl)-2-(6-nitrobenzo [d]thiazol-2-yl amino)nicotinamide 6h :** yield 49 %, m.p. 156-158 °C; Calculated for $C_{23}H_{18}N_6O_6S_2$ requires: C 51.29, H 3.37, N 15.60; Found: C 51.22, H 3.29, N 15.53 %. IR (KBr) $\nu$ $cm^{-1}$: 3410 (NH str.), 1711 (C=O of 4-thiazolidinone ring), 1647 (Amide-I), 1558 (Amide-II), 1225 (Amide-III), 1036,1195 ($OCH_3$ str., sym., asym.), 1366,1510 ($NO_2$, sym., asym.). $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.34 (s, 1H, NH), 8.95 (s, 1H, CONH), 8.73-6.69 (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 (100MHz, 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($C_{19}$-$C_{24}$).

***N*-(2-(4-hydroxy-3-methoxy-5-nitrophenyl)-4-oxo thiazolidin - 3 - yl) - 2 - (6-nitro benzo [d] thiazol - 2 - yl amino) nicotinamide 6i :** yield 55 %, m.p. 207-208 °C; Calculated for $C_{23}H_{17}N_7O_8S_2$ requires: C 47.34, H 2.94, N 16.80; Found: C 47.26, H 2.87, N 16.73 %. IR (KBr) $\nu$ $cm^{-1}$: 3416 (NH str.), 1711 (C=O of 4-thiazolidinone ring), 1646 (Amide-I), 1561 (Amide-II), 1225 (Amide-III), 1035,1196 ($OCH_3$ str., sym., asym.), 1369, 1516 ($NO_2$, sym., asym.). $^1H$ NMR (400 MHz, DMSO-$d_6$) δ (ppm): 9.37 (s, 1H, NH), 8.94 (s, 1H, CONH), 8.75-6.71 (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 (100MHz, 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 ($C_{19}$-$C_{24}$).

***N*-(2-(furan-3-yl)-4-oxothiazolidin-3-yl)-2-(6-nitro benzo[d]thiazol-2-yl amino)nicotinamide 6j :** yield 58 %, m.p. 195-197 °C; Calculated for $C_{20}H_{14}N_6O_5S_2$ requires: C 49.79, H 2.92, N 17.42; Found: C 49.71, H 2.84, N 17.36 %. IR(KBr) $\nu$ $cm^{-1}$: 3412 (NH str.), 1710(C=O 4-thiazolidinone ring), 1649(Amide-I), 1558(Amide-II),1225(Amide-III), 1368,1512($NO_2$,sym., asym.). $^1H$ NMR(400 MHz, DMSO-$d_6$) δ(ppm): 9.34(s, 1H, NH), 8.94(s, 1H, CONH), 8.71-6.72 (m, 9H, aromatic and pyridine), 6.13(s, 1H, CH 4-thiazolidinone ring), 3.63(s, 2H, $SCH_2CO$ 4-thiazolidinone ring), 3.85(s, 3H, $OCH_3$). $^{13}C$ NMR (100MHz, 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 ($C_{19}$-$C_{24}$).

## Results and Discussion

### *Chemistry*

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), 1610 (-N=CH-), 1550 (amide-II), 1225 (amide-III), 1368, 1512 ($NO_2$, sym., asym.). In $^1H$-NMR spectra common signals that appear are: $\delta_H$ (ppm): a singlet at δ 8.82 corresponds to >CONH, a singlet at δ 5.85 for -N=CH-, a multiplet at δ 6.86-8.58 corresponds to aromatic proton.

The structures of compounds **6a–j** were supported by elemental analyses and IR spectra as observed in **5a–j** with disappearance of 1610 $cm^{-1}$ for -N=CH- band with appearance of 1712 $cm^{-1}$ for >C=O of thiazolidinone. The $^1H$-NMR singlet signals of cyclilized thiazolidinones were 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**. $^{13}C$ NMR spectral data also supports the formation of compounds **5a-j** and **6a-j**.

### *Antimicrobial Activity*

The Minimum inhibitory concentrations (MICs) of synthesized compounds were carried out by broth micro dilution method as described by Rattan [16]. Minimum inhibitory concentrations (MICs) of the tested compounds for antibacterial and antifungal activities are shown in Table **1** and Table **2**, respectively. The

**Table 1.** Antibacterial activity of intermediates and compounds 5a-j & 6a-j

| Compound | R | Minimal Bactericidal Concentration (MBC) (µg/ml) | | | |
|---|---|---|---|---|---|
| | | Gram positive bacteria | | Gram negative bacteria | |
| | | *S. aureus* MTCC- 96 | *S. pyogenes* MTCC-442 | *E. coli* MTCC-443 | *P. aeruginosa* MTCC- 741 |
| **1** | --- | 200 | 250 | 150 | 150 |
| **2** | --- | 500 | 500 | 250 | 1000 |
| **3** | --- | 250 | 500 | 100 | 250 |
| **4** | --- | 250 | 250 | 500 | 1000 |
| **5a** | -H | 500 | 500 | 62.5 | 200 |
| **5b** | 2-Cl- | 250 | 200 | 100 | 50 |
| **5c** | 4-Cl- | 150 | 250 | 50 | 125 |
| **5d** | 2-$NO_2$- | 250 | 500 | 125 | 500 |
| **5e** | 3-$NO_2$- | 500 | 500 | 100 | 250 |
| **5f** | 4-OH- | 500 | 500 | 200 | 500 |
| **5g** | 4-$OCH_3$- | 250 | 250 | 250 | 1000 |
| **5h** | 3-$OCH_3$-4-OH- | 200 | 250 | 500 | 500 |
| **5i** | 3-$OCH_3$-4-OH-5-$NO_2$- | 200 | 250 | 200 | 200 |
| **5j** | $C_4H_3O$(Furyl) | 100 | 62.5 | 200 | 100 |
| **6a** | -H | 500 | 500 | 500 | 250 |
| **6b** | 2-Cl- | 250 | 500 | 125 | 500 |
| **6c** | 4-Cl- | 200 | 500 | 500 | 1000 |
| **6d** | 2-$NO_2$- | 100 | 250 | 250 | 250 |
| **6e** | 3-$NO_2$- | 500 | 100 | 500 | 500 |
| **6f** | 4-OH- | 250 | 500 | 500 | 250 |
| **6g** | 4-$OCH_3$- | 150 | 500 | 125 | 500 |
| **6h** | 3-$OCH_3$-4-OH- | 200 | 250 | 100 | 250 |
| **6i** | 3-$OCH_3$-4-OH-5-$NO_2$- | 250 | 250 | 500 | 200 |
| **6j** | $C_4H_3O$(Furyl) | 62.5 | 200 | 100 | 100 |
| **Ampicillin** | --- | 250 | 100 | 100 | 100 |

different compounds **5a-j** and **6a-j** were tested *in vitro* against two Gram positive (*S. aureus* MTCC 96, *S. pyogenus* MTCC 442) and two Gram negative (*E. coli* MTCC 443, *P. aeruginosa* MTCC 741) bacteria for antibacterial and three fungal species (*C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323) for antifungal activity. Ampicillin was used as a standard antibacterial agent whereas greseofulvin was used as a standard antifungal agent.

*Antibacterial Activity*

The starting compound 2-chloro pyridine-3-carboxylic acid **1**, **3** and **4** showed good activity against *S. aureus* compared to ampicillin.

In the Schiff base series, some of compounds showed comparable activity against gram positive and gram negative bacteria. Compounds **5b** (R= 2-Cl), **5c** (R= 4-Cl), **5d** (R= 2-$NO_2$), **5g** (R= 4-$OCH_3$), **5h** (R= 3-$OCH_3$-4-OH), **5i** (R= 3-$OCH_3$-4-OH-5-$NO_2$) and **5j** (furyl nucleus) showed good activity against *S. aureus*. Compound **5j** (furyl nucleus) exhibited very good activity against *S. pyogenes*. Compounds **5a** (R= -H), **5b** (R= 2-Cl), **5c** (R= 4-Cl) and **5e** (R= 3-$NO_2$) demonstrated good to moderate activity against *E. coli*., **5b** (R= 2-Cl) and **5j** (furyl nucleus) showed good activity against *P. aeruginosa.* All other compounds from Schiff base series showed moderate activity.

In 4-thiazolidinone series, most of the compounds viz **6b** (R= 2-Cl), **6c** (R= 4-Cl), **6d** (R= 2-$NO_2$), **6f** (R= 4-OH), **6g** (R= 4-$OCH_3$), **6h** (R= 3-$OCH_3$-4-OH), **6i**

**Table 2.** Antifungal activity of intermediates and compounds 5a-j & 6a-j

| Compound | R | Minimal Fungicidal Concentration (MFC) (µg/ml) | | |
|---|---|---|---|---|
| | | Fungal species | | |
| | | *C. albicans* MTCC-227 | *A. niger* MTCC-282 | *A. clavatus* MTCC-1323 |
| **1** | --- | 250 | 500 | 500 |
| **2** | --- | 500 | 500 | 500 |
| **3** | --- | 500 | >1000 | >1000 |
| **4** | --- | 250 | 1000 | 1000 |
| **5a** | -H | 500 | 500 | 500 |
| **5b** | 2-Cl- | >1000 | 250 | 250 |
| **5c** | 4-Cl- | 500 | >1000 | >1000 |
| **5d** | 2-$NO_2$- | 500 | >1000 | >1000 |
| **5e** | 3-$NO_2$- | 500 | >1000 | >1000 |
| **5f** | 4-OH- | 500 | 500 | 1000 |
| **5g** | 4-$OCH_3$- | 250 | 500 | 500 |
| **5h** | 3-$OCH_3$-4-OH- | 500 | 500 | 500 |
| **5i** | 3-$OCH_3$-4-OH-5-$NO_2$- | 500 | >1000 | >1000 |
| **5j** | $C_4H_3O$(Furyl) | 500 | >1000 | >1000 |
| **6a** | -H | 500 | >1000 | >1000 |
| **6b** | 2-Cl- | 1000 | 1000 | 1000 |
| **6c** | 4-Cl- | 1000 | 250 | 250 |
| **6d** | 2-$NO_2$- | 250 | 500 | 500 |
| **6e** | 3-$NO_2$- | 500 | 500 | 500 |
| **6f** | 4-OH- | 500 | 500 | 500 |
| **6g** | 4-$OCH_3$- | 1000 | 500 | 500 |
| **6h** | 3-$OCH_3$-4-OH- | 1000 | 1000 | 1000 |
| **6i** | 3-$OCH_3$-4-OH-5-$NO_2$- | 500 | 1000 | 1000 |
| **6j** | $C_4H_3O$(Furyl) | 500 | 500 | 500 |
| **Greseofulvin** | --- | 500 | 100 | 100 |

**5j** and **6j** contains furyl nucleus as illustrated in **Figure 1** and **Figure 2**.

(R= 3-$OCH_3$-4-OH-5-$NO_2$) and **6j** (furyl nucleus) possessed good to very good activity against *S. aureus*. Compound **6e** (R= 3-$NO_2$) showed good activity against *S. pyogenes*. Compounds **6h** (R= 3-$OCH_3$-4-OH) and **6j** (furyl nucleus) exhibited good activity against *E. coli*. Compound **6j** (furyl nucleus) showed good activity against *P. aeruginosa*. Remaining compounds from 4-thiazolidinone series showed moderate activity against all the species.

*Antifungal Activity*

Starting material 2-chloro pyridine-3-carboxylic acid **1**, 2-amino-6-nitro benzothiazole **2**, intermediates **3** and **4** showed comparable activity against *C. albicans.*

In Schiff bases series, all compounds except **5b** (R= 2-Cl) demonstrated comparable activity against *C. albicans* whereas all the compounds are moderate in activity against other two fungal species *A. niger* and *A. clavatus* compared to greseofulvin.

In the 4-thiazolidinone series, compounds **6a** (R= -H), **6d** (R= 2-$NO_2$), **6e** (R= 3-$NO_2$), **6f** (R= 4-OH), **6i** (R= 3-$OCH_3$-4-OH-5-$NO_2$) and **6j** (furyl nucleus) showed good activity against *C. albicans* whereas all the compounds showed moderate activity against other two fungal species *A. niger* and *A. clavatus* compared to greseofulvin.

***Overall Conclusion***

From the above results of antibacterial and antifungal activity, it can be observed that most of the synthesized compounds are comparable with ampicillin; moreover the compounds bearing groups –Cl, $–NO_2$ group and furan nucleus are more active than the remaining compounds. They showed comparatively good antibacterial as well as antifungal activity while compounds containing other functional groups like –OH, $–OCH_3$, –H showed moderate activity. This fact clearly indicates about the effect of various functional groups attached to the aromatic ring on antimicrobial activity.

Modification in a starting material 2-chloro pyridine-3-carboxylic acid **1** via different steps changes the biological activities that are seen from the results.

The structural variation gives the new idea for further investigation on 4-thiazolidinone derivatives. Thus, present work provides good outlines on the study of structure activity relationship of 4-thiazolidinone derivatives, putting special emphasis on incorporation with pyridine and benzothiazole moieties.

Most of synthesized compounds were found to be active against *C. albicans* but they found poorly or less active with other fungal species.

Moreover, activity is increased in many cases for 4-thiazolidinone series compared to starting material 2-chloro pyridine-3-carboxylic acid and 2-amino-6-chloro benzothiazole and intermediates condensed product **3** and hydrazide **4** which clearly indicates about biological importance of 4-thiazolidinones.

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