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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

# Synthesis and antimicrobial activity of new pyridine derivatives-I

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**Abstract** 2-Amino substituted benzothiazoles **2a–l** and 2-chloropyridine-3-carboxylic acid **3** were used to prepare 2-[*N*-(substitutedbenzothiazolyl)amino]pyridine-3-carboxylic acids (**4a–l**) in 2-ethoxy ethanol. Acid chlorides (**5a–l**) were condensed with 2-hydroxyethyl piperazine (**6**) and 2,3-dichloropiperazine (**7**) to prepare amide derivatives 2-[*N*-(substituted benzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl)methanones (**8a–l**) and 2-[*N*-(substituted benzothiazolyl) amino]pyridin-3-yl(2,3-dichloropiperazine-1-yl)methanones (**9a–l**), respectively. The structures of new compounds have been established on the basis of elemental analysis and spectral (IR, $^{1}$H NMR, and Mass spectra) studies. The in vitro antimicrobial activity was screened for all the synthesized compounds. Variable and modest activity were observed against the investigated strains of bacteria and fungi.

**Keywords** 2-Aminobenzothiazoles · 2-Chloropyridine-3-carboxylic acid · Piperazines · Antimicrobial activity

## 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 pose a serious challenge to the scientific community, and the need for an effective therapy has led to a search for novel antibacterial agents. A large number of heterocyclic compounds containing pyridine ring are associated with diverse pharmacological properties such as antimicrobial (Gaonkar *et al.,* 2007; Vijey *et al.,* 2008; Patel and Patel, 2009a, anticonvulsant (Paronikyan *et al.,* 2002), antiviral (Bernardino *et al.,* 2007), anti-HIV (Tucker *et al.,* 2008), antifungal, and antimycobacterial (Mamolo *et al.,* 2004). Several nitrogen containing heterocyclic systems find a wide variety of therapeutic activities that's why the course of recent work on the synthesis of new heterocycles of 2-chloropyridine-3-carboxylic acid with substituted benzothiazoles and piperazines has been undertaken.

2-Aminosubstituted benzothiazoles have been synthesized and used as an intermediate with parent compound 2-chloropyridine-3-carboxylic acid. Benzothiazoles themselves show different activities like antifungal (Lakhan and Rai, 1986), antiproliferative (Al-Soud *et al.,* 2008), and antitumor (Mortimer *et al.,* 2006).

Piperazines are most widely used in treatment of intestinal worms in animals and humans. The most important applications of its derivatives are antibacterial (Letafat *et al.,* 2007), antimicrobial (Patel and Patel, 2009b; Patel and Bhagat, 2006), anti-HIV (Al-Soud *et al.,* 2007), and as cytotoxic agents (Rajabalian *et al.,* 2007).

Prompted by recent literature observations and as a part of our continuous search for biologically active compounds, we have continued our previous work on 2-chloro pyridine-3-carboxylic acid (Patel and Bhagat, 2001, 2002) with substituted benzothiazoles and piperazines. The search for new, effective, and safe nuclei has led to an improvement by increasing their potency. Combination of two active moieties led the significant changes in the biological activities. With these concepts, we have synthesized the new pyridine derivatives of 2-chloropyridine-3-carboxylic acid with 2-aminosubstituted benzothiazoles and

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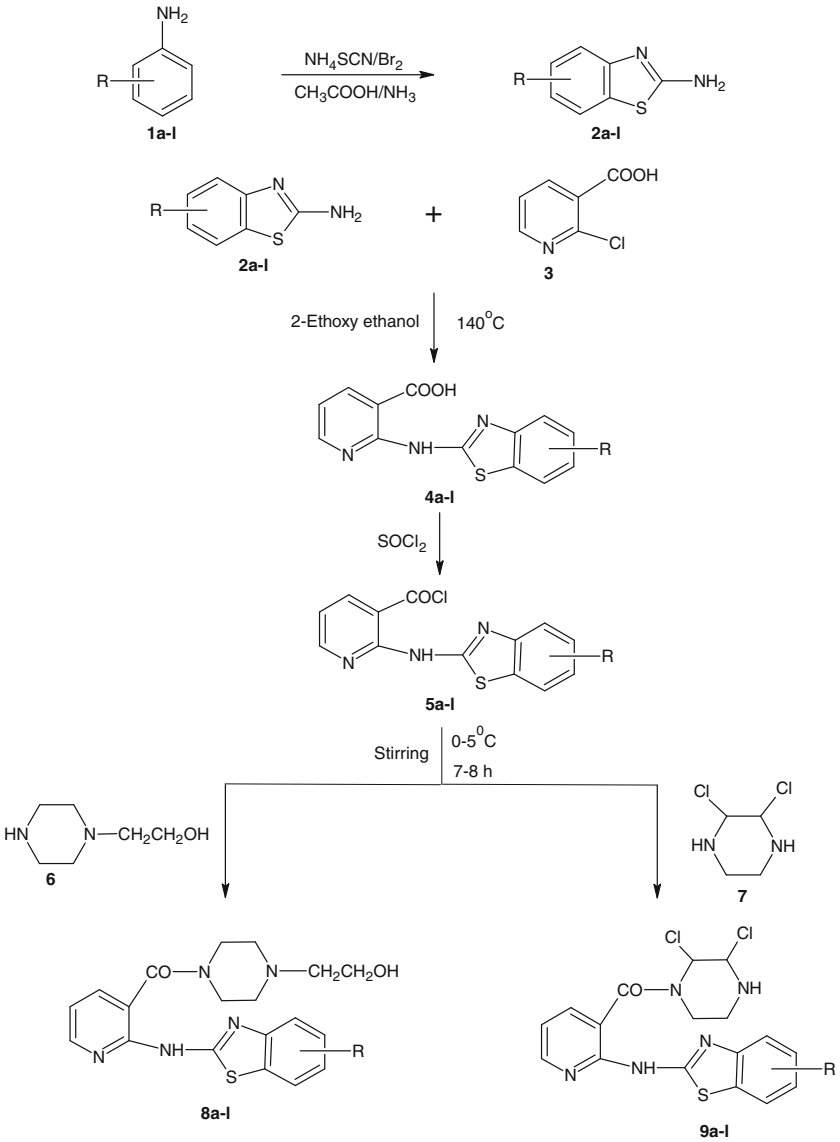
piperazines. This may be achieved by creating new biologically active agents by molecular modifications.

## Results and discussion

All the newly synthesized compounds **8a–l** and **9a–l** (Scheme 1) were screened for antibacterial and antifungal activity. Zone of inhibition for synthesized compounds was determined against two gram-positive bacteria (*Staphylococcus aureus* ATCC 9144 and *Bacillus subtilis* ATCC 6633), two gram-negative bacteria (*Pseudomonas aeruginosa* ATCC 9027 and *Escherichia coli* ATCC 25922) and against fungi (*Candida albicans* ATCC 10231) using cup-plate method (DMF as a solvent) (Barry, 1976). The solution of compounds at 100 μg/ml and 200 μg/ml concentrations, were compared with standard drug Penicillin-G, Ampicillin, Amoxicillin, and Amphotericine-B.

Moderate to modest antimicrobial activity was observed with most of the tested compounds. However, some compounds demonstrated moderate to fair activity compared to reference drugs taken in the study. **8b,i** ($R$ = 4-$NO_2$, 5-$CH_3$), **9b,d,g,i** ($R$ = 4-$NO_2$, 4-$NO_2$, 6-Cl, 5-$CH_3$) against *S. aureus*; **8g,h,k** ($R$ = 6-Cl, 4-$CH_3$, 4-$OCH_3$), **9b,g,k** ($R$ = 4-$NO_2$, 6-Cl, 4-$OCH_3$) against *B. subtilis*; **8g,l** ($R$ = 6-Cl, 6-$OCH_3$), **9b,g,h,l** ($R$ = 4-$NO_2$, 6-Cl, 4-$CH_3$, 6-$OCH_3$) against *E. coli* displayed moderate to fair activity as compared to Penicillin-G and Amoxicillin while with Ampicillin comparable results were found. **8a** ($R$ = H) and **9a** ($R$ = H) displayed fair antibacterial activity against both positive and negative bacteria at both the concentrations. **8b,f** ($R$ = 4-$NO_2$, 5-Cl), **9a,e,l** ($R$ = H, 4-Cl,




**Scheme 1** Protocol for the synthesis of compounds **8a–l** and **9a–l**

6-$OCH_3$), **8j,l** ($R$ = 6-$CH_3$, 6-$OCH_3$), and **9c,j,k** ($R$ = 5-$NO_2$, 6-$CH_3$, 4-$OCH_3$) displayed moderate to fair antifungal activity against *Candida albicans* at higher concentration. It is general observation from above discussion that almost all the synthesized compounds are found to have poor to fair activity against corresponding species.

Table 3 summarized the in vitro activity of the new pyridine derivatives **8a–l** and **9a–l**.

## Conclusion

New pyridine derivatives **8a–l** and **9a–l** were synthesized starting from building blocks 2-amino benzothiazoles **2** and 2-chloro pyridine-3-carboxylic acid (i.e., 2-chloro nicotinic acid) **3** and were studied for their antimicrobial activity.

Overall observation from the results of antimicrobial activity reveals that most of the synthesized compounds are found to have poor to fair activity against corresponding species.

However, the present work provides good outlines on the antimicrobial study of pyridine derivatives encompassing with benzothiazole moiety.

## Experimental

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on Perkin-Elmer-843 spectrometer using KBr pellets. $^1$H NMR spectra were scanned on Bruker DPX-200 FT-NMR (400 MHz) spectrometer using TMS as an internal standard and DMSO-$d_6$ as solvent (chemical shift in $\delta$ ppm) and mass spectra on a Jeol JMS D-300 spectrometer. Elemental analyses of the newly synthesized compounds were carried out on Perkin-Elmer 240C elemental analyzer**.** The compounds gave satisfactory C, H, and N analysis. Samples were routinely purified by crystallization from ethanol: benzene (1:3) and checked by TLC using ethylacetate: toluene (2.5:7.5) as a mobile phase.

### General procedure for the preparation of 2-amino benzothiazoles (**2a–l**)

To glacial acetic acid (20 ml) precooled to 5°C were added (0.08 mol) of ammonium thiocynate and (0.01 mol) of aromatic primary amine. The mixture was placed in freezing mixture of ice and salt, mechanically stirred while 1.6 ml of bromine in 6 ml of glacial acetic acid was added from a dropping funnel at such a rate that the temperature does not rise beyond 0°C. After all the bromine has been added (105 min), the solution was stirred for an additional 2 h at 0°C and at room temperature for 10 h. It was then allowed to stand overnight during which an orange precipitate settled at the bottom, water (6 ml) was added quickly, and slurry was heated at 85°C on a steam bath and filtered while hot. The orange residue was placed in a reaction flask and treated with 10 ml of glacial acetic acid heated again to 85°C and filtered while hot. The combined filtrate was cooled and adjusted to pH-6 with conc. ammonia solution. The dark yellow precipitate formed was collected. Recrystallization from benzene (twice) after treatment with charcoal gave pellets of (**2a–l**).

### General procedure for the preparation of 2-[*N*-(substitutedbenzothiazolyl) amino]pyridine-3-carboxylic acids (**4a–l**)

Mixture of 2-chloropyridine-3-carboxylic acid **3** (0.015 mol), 2-amino benzothiazoles **(2)** (0.015 mol), anhydrous $K_2CO_3$ (0.01 mol), and copper powder (0.01 g) was refluxed in 2-ethoxyethanol (25 ml) under stirring in an oil bath at 140°C for 5 h. The cooled mixture was diluted with water, residue formed was filtered, and the resulted solution was made acidic to pH-5 with dil HCl when pure product precipitated. The product **(4a–l)** was recrystallized from ethanol.

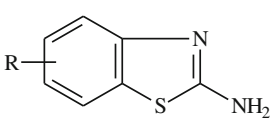
The physical constants of **2a–l** and **4a–l** are given in Table 1.

Spectroscopic characterization data of **2a–l** and **4a–l** are as similar to previous work (Javier *et al.,* 1986)

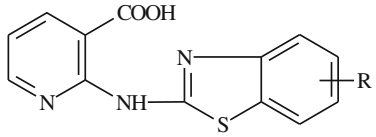
### General procedure for the preparation of 2-[*n*-(substitutedbenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxy ethyl)piperazin-1-yl)methanones (8a–l) and 2-[*n*-(substitutedbenzothiazolyl) amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanones (9a–l)

2-[*N*-(substitutedbenzothiazolyl)amino]pyridine-3-carbonyl chlorides **(5a–l)** prepared by reported method (Vogel, 1998) were dissolved in pyridine (10 ml), and the solution was cooled in an ice bath. To the stirred solution were successively added in small portion, fresh dried pyridine (5 ml) and 2-hydroxyethylpiperazine (0.01) **(6)**. The mixture was warmed for 1.5 h at 70°C. After the completion of reaction; the solvent was removed by vacuum distillation. The crude product 2-[*N*-(substitutedbenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl)methanones **(8a–l)** were obtained, collected, and recrystallized from ethanol: benzene (1:3).

**Table 1** Physical constant of the synthesized compounds **2a–l** and **4a–l**




2a-l




4a-l

| Compound | *R* | Yield (%) | MP (°C) | Molecular formula | Molecular weight |
|---|---|---|---|---|---|
| **2a** | H | 74 | 147 | $C_7H_6N_2S$ | 150.02 |
| **2b** | 4-$NO_2$ | 67 | 140 | $C_7H_5O_2N_3S$ | 195.01 |
| **2c** | 5-$NO_2$ | 72 | 120 | $C_7H_5O_2N_3S$ | 195.01 |
| **2d** | 6-$NO_2$ | 68 | 180 | $C_7H_5O_2N_3S$ | 195.01 |
| **2e** | 4-Cl | 72 | 162 | $C_7H_5O_2N_2SCl$ | 215.97 |
| **2f** | 5-Cl | 74 | 220 | $C_7H_5O_2N_2SCl$ | 215.97 |
| **2g** | 6-Cl | 70 | 198 | $C_7H_5O_2N_2SCl$ | 215.97 |
| **2h** | 4-$CH_3$ | 71 | 119 | $C_8H_8N_2S$ | 164.04 |
| **2i** | 5-$CH_3$ | 74 | 135 | $C_8H_8N_2S$ | 164.04 |
| **2j** | 6-$CH_3$ | 64 | 129 | $C_8H_8N_2S$ | 164.04 |
| **2k** | 4-$OCH_3$ | 68 | 180 | $C_8H_8ON_2S$ | 180.03 |
| **2l** | 6-$OCH_3$ | 72 | 133 | $C_8H_8ON_2S$ | 180.03 |
| **4a** | H | 61 | 216 | $C_{13}H_9O_2N_3S$ | 271.04 |
| **4b** | 4-$NO_2$ | 58 | 208 | $C_{13}H_8O_4N_4S$ | 316.03 |
| **4c** | 5-$NO_2$ | 62 | 224 | $C_{13}H_8O_4N_4S$ | 316.03 |
| **4d** | 6-$NO_2$ | 64 | 241 | $C_{13}H_8O_4N_4S$ | 316.03 |
| **4e** | 4-Cl | 55 | 199 | $C_{13}H_8O_2N_3SCl$ | 305.00 |
| **4f** | 5-Cl | 59 | 191 | $C_{13}H_8O_2N_3SCl$ | 305.00 |
| **4g** | 6-Cl | 61 | 219 | $C_{13}H_8O_2N_3SCl$ | 305.00 |
| **4h** | 4-$CH_3$ | 57 | 228 | $C_{14}H_{11}O_2N_3S$ | 285.06 |
| **4i** | 5-$CH_3$ | 62 | 189 | $C_{14}H_{11}O_2N_3S$ | 285.06 |
| **4j** | 6-$CH_3$ | 59 | 195 | $C_{14}H_{11}O_2N_3S$ | 285.06 |
| **4k** | 4-$OCH_3$ | 54 | 231 | $C_{14}H_{11}O_3N_3S$ | 301.05 |
| **4l** | 6-$OCH_3$ | 56 | 210 | $C_{14}H_{11}O_3N_3S$ | 301.05 |

Similarly, 2-[*N*-(benzothiazolyl)amino]pyridin-3-yl(2,3-dichloropiperazine-1-yl)methanones **(9a–l)** were prepared. Physical constants and antimicrobial activity of compounds **8a–l** and **9a–l** are given in Tables 2 and 3, respectively.

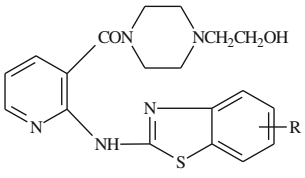
2-[*N*-(benzothiazolyl)amino]pyridin-3-yl(4-(2-hydroxyethyl)piperazin-1-yl)methanone **8a**

IR (KBr) $cm^{-1}$: 3421 (NH), 3375 (OH), 2930, 2855 ($CH_2$), 1675 (C=O), 1612 (C=N aromatic), 1449 (C–S), 1105 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.12 (2H, t, >N–$CH_2$–), 2.84 (4H, m, piperazine), 3.16 (4H, m, piperazine), 3.34 (2H, t, –$CH_2$–O–), 4.58 (1H, s, –OH), 8.43–6.87 (7H, m, pyridine and Ar–H), 10.64 (1H, s, –NH–); MS: m/z: 383 ($M^+$), 353, 339, 312, 298, 284, 257, 229, 150, 137,128, 122, 96, 78, 77, 64, 55, 45, 41, 31, 27; *Anal. Calcd.* for $C_{19}H_{21}O_2N_5S$: C, 59.51; H, 05.52; N, 18.27. Found: C, 59.48; H, 05.50; N, 18.20.

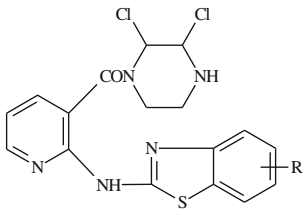
2-[*N*-(4-Nitrobenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl)methanone **8b**

IR (KBr) $cm^{-1}$: 3441 (NH), 3365 (OH), 2921, 2842 ($CH_2$), 1674 (C=O), 1614 (C=N aromatic), 1449 (C–S), 1101 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.15 (2H, t, >N–$CH_2$–), 2.78 (4H, m, piperazine), 3.15 (4H, m, piperazine), 3.34 (2H, t, –$CH_2$–O–), 4.60 (1H, s, –OH), 8.42–6.85 (6H, m, pyridine and Ar–H), 10.75 (1H, s, –NH–); MS: m/z: 428 ($M^+$), 384, 357, 343, 329, 302, 274, 195, 180, 154, 149, 136, 122, 77, 55, 45, 41, 31, 27; *Anal. Calcd.* for $C_{19}H_{20}O_4N_6S$: C, 53.26; H, 04.71; N, 19.62. Found: C, 53.22; H, 04.68; N, 19.56.

**Table 2** Physical constant of the synthesized compounds **8a–l** and **9a–l**




8a-l




9a-l

| Compound | *R* | Yield (%) | MP (°C) | Molecular formula | Molecular weight |
|---|---|---|---|---|---|
| **8a** | H | 70 | 212 | $C_{19}H_{21}O_2N_5S$ | 383.14 |
| **8b** | 4-$NO_2$ | 64 | 199 | $C_{19}H_{20}O_4N_6S$ | 428.13 |
| **8c** | 5-$NO_2$ | 65 | 232 | $C_{19}H_{20}O_4N_6S$ | 428.13 |
| **8d** | 6-$NO_2$ | 69 | 207 | $C_{19}H_{20}O_4N_6S$ | 428.13 |
| **8e** | 4-Cl | 59 | 234 | $C_{19}H_{20}O_2N_5SCl$ | 417.10 |
| **8f** | 5-Cl | 64 | 210 | $C_{19}H_{20}O_2N_5SCl$ | 417.10 |
| **8g** | 6-Cl | 58 | 189 | $C_{19}H_{20}O_2N_5SCl$ | 417.10 |
| **8h** | 4-$CH_3$ | 56 | 242 | $C_{20}H_{23}O_2N_5S$ | 397.16 |
| **8i** | 5-$CH_3$ | 63 | 239 | $C_{20}H_{23}O_2N_5S$ | 397.16 |
| **8j** | 6-$CH_3$ | 63 | 194 | $C_{20}H_{23}O_2N_5S$ | 397.16 |
| **8k** | 4-$OCH_3$ | 58 | 224 | $C_{20}H_{23}O_3N_5S$ | 413.15 |
| **8l** | 6-$OCH_3$ | 63 | 228 | $C_{20}H_{23}O_3N_5S$ | 413.15 |
| **9a** | H | 71 | 222 | $C_{17}H_{15}ON_5SCl_2$ | 407.04 |
| **9b** | 4-$NO_2$ | 65 | 199 | $C_{17}H_{14}O_3N_6SCl_2$ | 452.02 |
| **9c** | 5-$NO_2$ | 68 | 191 | $C_{17}H_{14}O_3N_6SCl_2$ | 452.02 |
| **9d** | 6-$NO_2$ | 67 | 210 | $C_{17}H_{14}O_3N_6SCl_2$ | 452.02 |
| **9e** | 4-Cl | 55 | 226 | $C_{17}H_{14}ON_5SCl_3$ | 441.00 |
| **9f** | 5-Cl | 67 | 214 | $C_{17}H_{14}ON_5SCl_3$ | 441.00 |
| **9g** | 6-Cl | 61 | 235 | $C_{17}H_{14}ON_5SCl_3$ | 441.00 |
| **9h** | 4-$CH_3$ | 58 | 219 | $C_{18}H_{17}ON_5SCl_2$ | 421.05 |
| **9i** | 5-$CH_3$ | 63 | 239 | $C_{18}H_{17}ON_5SCl_2$ | 421.05 |
| **9j** | 6-$CH_3$ | 62 | 229 | $C_{18}H_{17}ON_5SCl_2$ | 421.05 |
| **9k** | 4-$OCH_3$ | 56 | 207 | $C_{18}H_{17}O_2N_5SCl_2$ | 437.05 |
| **9l** | 6-$OCH_3$ | 57 | 195 | $C_{18}H_{17}O_2N_5SCl_2$ | 437.05 |

2-[*N*-(5-Nitrobenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl)methanone **8c**

IR (KBr) $cm^{-1}$: 3445 (NH), 3369 (OH), 2928, 2843 ($CH_2$), 1678 (C=O), 1613 (C=N aromatic), 1448 (C–S), 1104 (C–N aliphatic); $^1$H NMR (DMSO-$d_6$): $\delta$ 2.17 (2H, t, >N–$CH_2$–), 2.82 (4H, m, piperazine), 3.19 (4H, m, piperazine), 3.32 (2H, t, –$CH_2$–O–), 4.62 (1H, s, –OH), 8.41–6.84 (6H, m, pyridine and Ar–H), 10.71 (1H, s, –NH–); MS: m/z: 428 ($M^+$), 384, 357, 343, 329, 302, 274, 195, 180, 154, 149, 136, 122, 77, 55, 45, 41, 31, 27; *Anal. Calcd*. for $C_{19}H_{20}O_4N_6S$: C, 53.26; H, 04.71; N, 19.62. Found: C, 53.20; H, 04.65; N, 19.55.

2-[*N*-(6-Nitrobenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl)methanone **8d**

IR (KBr) $cm^{-1}$: 3443 (NH), 3368 (OH), 2925, 2844 ($CH_2$), 1680 (C=O), 1615 (C=N aromatic), 1447 (C–S), 1102 (C–N aliphatic); $^1$H NMR (DMSO-$d_6$): $\delta$ 2.16 (2H, t, >N–$CH_2$–), 2.80 (4H, m, piperazine), 3.18 (4H, m, piperazine), 3.35 (2H, t, –$CH_2$–O–), 4.61 (1H, s, –OH), 8.43–6.87 (6H, m, pyridine and Ar–H), 10.74 (1H, s, –NH–) MS: m/z: 428 ($M^+$), 384, 357, 343, 329, 302, 274, 195, 180, 154, 149, 136, 122, 77, 55, 45, 41, 31, 27; *Anal. Calcd*. for $C_{19}H_{20}O_4N_6S$: C, 53.26; H, 04.71; N, 19.62. Found: C, 53.19; H, 04.67; N, 19.58.

**Table 3** Antimicrobial and antifungal activity data of **8a–l** and **9a–l**

| Zone of inhibition in mm at 100 and 200 μg/ml, respectively | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Compound | Gram-negative | | | | Gram-positive | | | | Fungi | |
| | *P. aeruginosa* | | E. coli | | *S. aureus* | | *B. Subtilis* | | *C. albicans* | |
| **8a** | 8 | 9 | 7 | 8 | 6 | 7 | 6 | 10 | 3 | 5 |
| **8b** | 8 | 11 | 5 | 9 | 8 | 12 | 8 | 9 | 4 | 7 |
| **8c** | 7 | 7 | 4 | 8 | 6 | 11 | 8 | 8 | 2 | 4 |
| **8d** | 6 | 8 | 0 | 5 | 8 | 9 | 0 | 6 | 0 | 2 |
| **8e** | 7 | 9 | 6 | 9 | 7 | 7 | 7 | 8 | 3 | 6 |
| **8f** | 0 | 3 | 5 | 5 | 0 | 0 | 5 | 5 | 3 | 4 |
| **8g** | 7 | 10 | 6 | 10 | 8 | 9 | 7 | 9 | 0 | 1 |
| **8h** | 6 | 7 | 3 | 7 | 4 | 5 | 7 | 10 | 0 | 0 |
| **8i** | 5 | 6 | 6 | 10 | 8 | 10 | 8 | 8 | 1 | 2 |
| **8j** | 0 | 0 | 0 | 6 | 0 | 3 | 0 | 0 | 2 | 5 |
| **8k** | 7 | 9 | 3 | 3 | 6 | 8 | 6 | 10 | 4 | 4 |
| **8l** | 4 | 5 | 8 | 8 | 8 | 9 | 0 | 4 | 0 | 5 |
| **9a** | 4 | 5 | 7 | 8 | 5 | 7 | 6 | 7 | 3 | 5 |
| **9b** | 8 | 9 | 9 | 10 | 8 | 10 | 5 | 10 | 2 | 4 |
| **9c** | 5 | 6 | 4 | 5 | 6 | 9 | 8 | 7 | 1 | 4 |
| **9d** | 6 | 8 | 6 | 6 | 8 | 8 | 7 | 7 | 0 | 3 |
| **9e** | 3 | 3 | 4 | 5 | 3 | 4 | 3 | 6 | 3 | 6 |
| **9f** | 0 | 2 | 2 | 3 | 0 | 0 | 5 | 5 | 1 | 2 |
| **9g** | 8 | 8 | 7 | 9 | 7 | 10 | 5 | 6 | 0 | 1 |
| **9h** | 6 | 7 | 8 | 10 | 4 | 6 | 4 | 4 | 0 | 0 |
| **9i** | 6 | 8 | 5 | 7 | 8 | 10 | 7 | 7 | 2 | 3 |
| **9j** | 0 | 0 | 3 | 3 | 3 | 4 | 0 | 0 | 2 | 5 |
| **9k** | 7 | 8 | 0 | 4 | 6 | 6 | 8 | 9 | 3 | 4 |
| **9l** | 4 | 7 | 8 | 9 | 5 | 6 | - | 2 | 4 | 6 |
| Penicillin-G | 13 | 22 | 14 | 25 | 12 | 21 | 14 | 25 | – | – |
| Ampicillin | 18 | 31 | 18 | 30 | 15 | 28 | 17 | 30 | – | – |
| Amoxicillin | 15 | 27 | 16 | 28 | 13 | 24 | 16 | 29 | – | – |
| Amphotericin-B | – | – | – | – | – | – | – | – | 8 | 18 |

2-[*N*-(4-Chlorobenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl) methanone **8e**

IR (KBr) $cm^{-1}$: 3425 (NH), 3365 (OH), 2939, 2845 ($CH_2$), 1667 (C=O), 1616 (C=N aromatic), 1448 (C–S), 1096 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.15 (2H, t, >N–$CH_2$–), 2.81 (4H, m, piperazine), 3.15 (4H, m, piperazine), 3.31 (2H, t, –$CH_2$–O–), 4.57 (1H, s, –OH), 8.41–6.85 (6H, m, pyridine and Ar–H), 10.68 (1H, s, –NH–); MS: m/z: 417 ($M^+$), 387, 373, 346, 332, 318, 291, 263, 184, 169, 149, 143, 125, 111, 77, 55, 45, 41, 31, 27; *Anal. Calcd*. for $C_{19}H_{20}O_2N_5SCl$: C, 54.66; H, 04.83; N, 16.79. Found: C, 54.55; H, 04.80; N, 16.70.

2-[*N*-(5-Chlorobenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl)methanone **8f**

IR (KBr) $cm^{-1}$: 3429 (NH), 3364 (OH), 2938, 2846 ($CH_2$), 1665 (C=O), 1618 (C=N aromatic), 1451 (C–S), 1097 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.16 (2H, t, >N–$CH_2$–), 2.82 (4H, m, piperazine), 3.14 (4H, m, piperazine), 3.32 (2H, t, –$CH_2$–O–), 4.56 (1H, s, –OH), 8.42–6.86 (6H, m, pyridine and Ar–H), 10.66 (1H, s, –NH–); MS: m/z: 417 ($M^+$), 387, 373, 346, 332, 318, 291, 263, 184, 169, 149, 143, 125, 111, 77, 55, 45, 41, 31, 27; *Anal. Calcd*. for $C_{19}H_{20}O_2N_5SCl$: C, 54.66; H, 04.83; N, 16.79. Found: C, 54.58; H, 04.78; N, 16.68.

2-[*N*-(6-Chlorobenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl)methanone **8g**

IR (KBr) $cm^{-1}$: 3428 (NH), 3366 (OH), 2940, 2847 ($CH_2$), 1666 (C=O), 1617 (C=N aromatic), 1450 (C–S), 1099 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.14 (2H, t, >N–$CH_2$–), 2.80 (4H, m, piperazine), 3.13 (4H, m, piperazine), 3.30 (2H, t, –$CH_2$–O–), 4.55 (1H, s, –OH), 8.43–6.87 (6H, m, pyridine and Ar–H), 10.65 (1H, s, –NH–); MS: m/z: 417 ($M^+$), 387, 373, 346, 332, 318, 291, 263, 184, 169, 149, 143, 125, 111, 77, 55, 45, 41, 31, 27; *Anal. Calcd*. for $C_{19}H_{20}O_2N_5SCl$: C, 54.66; H, 04.83; N, 16.79. Found: C, 54.56; H, 04.81; N, 16.72.

2-[*N*-(4-Methylbenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl) methanone **8h**

IR (KBr) $cm^{-1}$: 3446 (NH), 3358 (OH), 2927, 2855 ($CH_2$), 1684 (C=O), 1614 (C=N aromatic), 1448 (C–S), 1096 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.10 (2H, t, >N–$CH_2$–), 2.85 (4H, m, piperazine), 3.16 (4H, m, piperazine), 3.36 (2H, t, –$CH_2$–O–), 4.58 (1H, s, –OH), 8.43–6.87 (6H, m, pyridine and Ar–H), 10.64 (1H, s, –NH–); MS: m/z: 397 ($M^+$), 367, 353, 326, 312, 298, 271, 243, 164, 149, 123, 105, 91, 77, 55, 45, 41, 31, 27; *Anal. Calcd*. for $C_{20}H_{23}O_2N_5S$: C, 60.43; H, 05.84; N, 17.63. Found: C, 60.35; H, 05.82; N, 17.58.

2-[*N*-(5-Methylbenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl)methanone **8i**

IR (KBr) $cm^{-1}$: 3445 (NH), 3355 (OH), 2925, 2854 ($CH_2$), 1685 (C=O), 1619 (C=N aromatic), 1446 (C–S), 1097 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.12 (2H, t, >N–$CH_2$–), 2.88 (4H, m, piperazine), 3.15 (4H, m, piperazine), 3.37 (2H, t, –$CH_2$–O–), 4.56 (1H, s, –OH), 8.41–6.89 (6H,

m, pyridine and Ar–H), 10.65 (1H, s, –NH–); MS: m/z: 397 ($M^+$), 367, 353, 326, 312, 298, 271, 243, 164, 149, 123, 105, 91, 77, 55, 45, 41, 31, 27; *Anal. Calcd*. for $C_{20}H_{23}O_2N_5S$: C, 60.43; H, 05.84; N, 17.63. Found: C, 60.38; H, 05.81; N, 17.56.

2-[*N*-(6-Methylbenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl)methanone **8j**

IR (KBr) $cm^{-1}$: 3444 (NH), 3358 (OH), 2926, 2854 ($CH_2$), 1681 (C=O), 1615 (C=N aromatic), 1445 (C–S), 1099 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.09 (2H, t, >N–$CH_2$–), 2.86 (4H, m, piperazine), 3.14 (4H, m, piperazine), 3.35 (2H, t, –$CH_2$–O–), 4.57 (1H, s, –OH), 8.40–6.88 (6H, m, pyridine and Ar–H), 10.69 (1H, s, –NH–); MS: m/z: 397 ($M^+$), 367, 353, 326, 312, 298, 271, 243, 164, 149, 123, 105, 91, 77, 55, 45, 41, 31, 27; *Anal. Calcd*. for $C_{20}H_{23}O_2N_5S$: C, 60.43; H, 05.84; N, 17.63. Found: C, 60.34; H, 05.80; N, 17.57.

2-[*N*-(4-Methoxybenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl) methanone **8k**

IR (KBr) $cm^{-1}$: 3460 (NH), 3370 (OH), 2915, 2850 ($CH_2$), 1665 (C=O), 1616 (C=N aromatic), 1446 (C–S), 1106 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.14 (2H, t, >N–$CH_2$–), 2.86 (4H, m, piperazine), 3.11 (4H, m, piperazine), 3.32 (2H, t, –$CH_2$–O–), 4.56 (1H, s, –OH), 8.45–6.86 (6H, m, pyridine and Ar–H), 10.75 (1H, s, –NH–); MS: m/z: 413 ($M^+$), 383, 369, 342, 328, 314, 287, 259, 180, 165, 149, 138, 128, 120, 106, 77, 55, 45, 41, 31, 27; *Anal. Calcd*. for $C_{20}H_{23}O_3N_5S$: C, 58.09; H, 05.61; N, 16.95. Found: C, 58.01; H, 05.60; N, 16.88.

2-[*N*-(6-Methoxybenzothiazolyl)amino]pyridin-3-yl (4-(2-hydroxyethyl)piperazin-1-yl) methanone **8l**

IR (KBr) $cm^{-1}$: 3459 (NH), 3371 (OH), 2914, 2851 ($CH_2$), 1664 (C=O), 1611 (C=N aromatic), 1449 (C–S), 1105 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.10 (2H, t, >N–$CH_2$–), 2.85 (4H, m, piperazine), 3.10 (4H, m, piperazine), 3.31 (2H, t, –$CH_2$–O–), 4.57 (1H, s, –OH), 8.43–6.87 (6H, m, pyridine and Ar–H), 10.78 (1H, s, –NH–); MS: m/z: 413 ($M^+$), 383, 369, 342, 328, 314, 287, 259, 180, 165, 149, 138, 128, 120, 106, 77, 55, 45, 41, 31, 27; *Anal. Calcd*. for $C_{20}H_{23}O_3N_5S$: C, 58.09; H, 05.61; N, 16.95. Found: C, 58.03; H, 05.58; N, 16.90.

2-[*N*-(benzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9a**

IR (KBr) $cm^{-1}$: 3464 (NH), 2931 ($CH_2$), 1675 (C=O), 1612 (C=N aromatic), 1450 (C–S), 1103 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.14 (2H, t, –$CH_2$N–, piperazine), 2.42 (2H, t, –$CH_2$N–, piperazine), 2.70 (1H, d, –CHClN–), 2.96 (1H, d, –CHClN–), 8.43–6.87 (7H, m, pyridine and Ar–H), 10.64 (2H, s,–NH–); MS: m/z: 407 ($M^+$), 346, 332, 284, 257, 229, 152, 150, 135, 125, 109, 91, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{17}H_{15}ON_5SCl_2$: C, 50.12; H, 03.71; N, 17.20. Found: C, 50.05; H, 03.67; N, 17.15.

2-[*N*-(4-Nitrobenzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9b**

IR (KBr) $cm^{-1}$: 3435 (NH), 2915, 2854 ($CH_2$), 1669 (C=O), 1614 (C=N aromatic), 1448 (C–S), 1096 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.13 (2H, t, –$CH_2$N–, piperazine), 2.36 (2H, t, –$CH_2$N–, piperazine), 2.70 (1H, d, –CHClN–), 2.94 (1H, d, –CHClN–), 8.39–6.86 (6H, m, pyridine and Ar–H), 10.71 (2H, s, –NH–); MS: m/z: 452 ($M^+$), 389, 375, 327, 300, 272, 195, 180, 153, 152, 149, 135, 125, 121, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{17}H_{14}O_3N_6SCl_2$: C, 45.13; H, 03.12; N, 18.59. Found: C, 45.09; H, 03.10; N, 18.50.

2-[*N*-(5-Nitrobenzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9c**

IR (KBr) $cm^{-1}$: 3436 (NH), 2918, 2855 ($CH_2$), 1668 (C=O), 1613 (C=N aromatic), 1449 (C–S), 1095 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.12 (2H, t, –$CH_2$N–, piperazine), 2.35 (2H, t, –$CH_2$N–, piperazine), 2.71 (1H, d, –CHClN–), 2.92 (1H, d, –CHClN–), 8.43–6.87 (6H, m, pyridine and Ar–H), 10.69 (2H, s, –NH–); MS: m/z: 452 ($M^+$), 389, 375, 327, 300, 272, 195, 180, 153, 152, 149, 135, 125, 121, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{17}H_{14}O_3N_6SCl_2$: C, 45.13; H, 03.12; N, 18.59. Found: C, 45.08; H, 03.08; N, 18.52.

2-[*N*-(6-Nitrobenzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9d**

IR (KBr) $cm^{-1}$: 3434 (NH), 2921, 2857 ($CH_2$), 1665 (C=O), 1614 (C=N aromatic), 1452 (C–S), 1092 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.15 (2H, t, –$CH_2$N–, piperazine), 2.38 (2H, t, –$CH_2$N–, piperazine), 2.74 (1H, d, –CHClN–), 2.91 (1H, d, –CHClN–), 8.43–6.86 (6H, m, pyridine and Ar–H), 10.66 (2H, s, –NH–); MS: m/z: 452

($M^+$), 389, 375, 327, 300, 272, 195, 180, 153, 152, 149, 135, 125, 121, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{17}H_{14}O_3N_6SCl_2$: C, 45.13; H, 03.12; N, 18.59. Found: C, 45.05; H, 03.09; N, 18.51.

2-[*N*-(4-Chlorobenzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9e**

IR (KBr) $cm^{-1}$: 3465 (NH), 2926, 2852 ($CH_2$), 1685 (C=O), 1612 (C=N aromatic), 1449 (C–S), 1102 (C–N aliphatic); $^1$H NMR (DMSO-$d_6$): $\delta$ 2.19 (2H, t, –$CH_2$N–, piperazine), 2.46 (2H, t, –$CH_2$N–, piperazine), 2.61 (1H, d, –CHClN–), 2.85 (1H, d, –CHClN–), 8.42–6.86 (6H, m, pyridine and Ar–H), 10.75 (2H, s, –NH–); MS: m/z: 441 ($M^+$), 380, 366, 318, 291, 263, 184, 169, 152, 149, 143, 125, 111, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{17}H_{14}ON_5SCl_3$: C, 46.26; H, 03.20; N, 15.88. Found: C, 46.19; H, 03.17; N, 15.82.

2-[*N*-(5-Chlorobenzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9f**

IR (KBr) $cm^{-1}$: 3466 (NH), 2924, 2848 ($CH_2$), 1684 (C=O), 1615 (C=N aromatic), 1446 (C–S), 1099 (C–N aliphatic); $^1$H NMR (DMSO-$d_6$): $\delta$ 2.22 (2H, t, –$CH_2$N–, piperazine), 2.44 (2H, t, –$CH_2$N–, piperazine), 2.65 (1H, d, –CHClN–), 2.85 (1H, d, –CHClN–), 8.38–6.86 (6H, m, pyridine and Ar–H), 10.77 (2H, s, –NH–); MS: m/z: 441 ($M^+$), 380, 366, 318, 291, 263, 184, 169, 152, 149, 143, 125, 111, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{17}H_{14}ON_5SCl_3$: C, 46.26; H, 03.20; N, 15.88. Found: C, 46.15; H, 03.15; N, 15.79.

2-[*N*-(6-Chlorobenzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9g**

IR (KBr) $cm^{-1}$: 3467 (NH), 2925, 2849 ($CH_2$), 1683 (C=O), 1613 (C=N aromatic), 1448 (C–S), 1100 (C–N aliphatic); $^1$H NMR (DMSO-$d_6$): $\delta$ 2.20 (2H, t, –$CH_2$N–, piperazine), 2.45 (2H, t, –$CH_2$N–, piperazine), 2.62 (1H, d, –CHClN–), 2.86 (1H, d, –CHClN–), 8.43–6.87 (6H, m, pyridine and Ar–H), 10.74 (2H, s, –NH–); MS: m/z: 441 ($M^+$), 380, 366, 318, 291, 263, 184, 169, 152, 149, 143, 125, 111, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{17}H_{14}ON_5SCl_3$: C, 46.26; H, 03.20; N, 15.88. Found: C, 46.17; H, 03.16; N, 15.83.

2-[*N*-(4-Methylbenzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9h**

IR (KBr) $cm^{-1}$: 3441 (NH), 2936, 2856 ($CH_2$), 1680 (C=O), 1618 (C=N aromatic), 1449 (C–S), 1090 (C–N aliphatic); $^1$H NMR (DMSO-$d_6$): $\delta$ 2.19 (2H, t, –$CH_2$N–, piperazine), 2.33 (2H, t, –$CH_2$N–, piperazine), 2.70 (1H, d, –CHClN–), 2.81 (1H, d, –CHClN–), 8.43–6.87 (6H, m, pyridine and Ar–H), 10.76 (2H, s, –NH–); MS: m/z: 421 ($M^+$), 360, 346, 298, 271, 243, 164, 152, 149, 125, 123, 105, 91, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{18}H_{17}ON_5SCl_2$: C, 51.30; H, 04.07; N, 16.63. Found: C, 51.21; H, 04.04; N, 16.59.

2-[*N*-(5-Methylbenzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9i**

IR (KBr) $cm^{-1}$: 3440 (NH), 2935, 2855 ($CH_2$), 1678 (C=O), 1612 (C=N aromatic), 1448 (C–S), 1091 (C–N aliphatic); $^1$H NMR (DMSO-$d_6$): $\delta$ 2.18 (2H, t, –$CH_2$N–, piperazine), 2.31 (2H, t, –$CH_2$N–, piperazine), 2.68 (1H, d, –CHClN–), 2.88 (1H, d, –CHClN–), 8.45–6.89 (6H, m, pyridine and Ar–H), 10.75 (2H, s, –NH–); MS: m/z: 421 ($M^+$), 360, 346, 298, 271, 243, 164, 152, 149, 125, 123, 105, 91, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{18}H_{17}ON_5SCl_2$: C, 51.30; H, 04.07; N, 16.63. Found: C, 51.23 H, 04.05; N, 16.57.

2-[*N*-(6-Methylbenzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9j**

IR (KBr) $cm^{-1}$: 3442 (NH), 2937, 2854 ($CH_2$), 1680 (C=O), 1611 (C=N aromatic), 1447 (C–S), 1092 (C–N aliphatic); $^1$H NMR (DMSO-$d_6$): $\delta$ 2.21 (2H, t, –$CH_2$N–, piperazine), 2.36 (2H, t, –$CH_2$N–, piperazine), 2.67 (1H, d, –CHClN–), 2.86 (1H, d, –CHClN–), 8.44–6.89 (6H, m, pyridine and Ar–H), 10.69 (2H, s, –NH–); MS: m/z: 421 ($M^+$), 360, 346, 298, 271, 243, 164, 152, 149, 125, 123, 105, 91, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{18}H_{17}ON_5SCl_2$: C, 51.30; H, 04.07; N, 16.63. Found: C, 51.25; H, 04.03; N, 16.56.

2-[*N*-(4-Methoxybenzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9k**

IR (KBr) $cm^{-1}$: 3465 (NH), 2919, 2856 ($CH_2$), 1678 (C=O), 1619 (C=N aromatic), 1450 (C–S), 1090 (C–N aliphatic); $^1$H NMR (DMSO-$d_6$): $\delta$ 2.10 (2H, t, –$CH_2$N–, piperazine), 2.48 (2H, t, –$CH_2$N–, piperazine), 2.66 (1H, d, –CHClN–), 2.90 (1H, d, –CHClN–), 8.43–6.87 (6H, m, pyridine and Ar–H), 10.76 (2H, s, –NH–); MS: m/z: 437 ($M^+$), 376, 362, 314, 287, 259, 180, 165, 152, 149, 139, 125, 121, 107, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{18}H_{17}O_2N_5SCl_2$: C, 49.42; H, 03.92; N, 16.02. Found: C, 49.35; H, 03.90; N, 15.96.

2-[*N*-(6-Methoxybenzothiazolyl)amino]pyridin-3-yl (2,3-dichloropiperazine-1-yl)methanone **9l**

IR (KBr) $cm^{-1}$: 3465 (NH), 2916, 2855 ($CH_2$), 1675 (C=O), 1617 (C=N aromatic), 1451 (C–S), 1092 (C–N aliphatic); $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.13 (2H, t, –$CH_2$N–, piperazine), 2.47 (2H, t, –$CH_2$N–, piperazine), 2.65 (1H, d, –CHClN–), 2.89 (1H, d, –CHClN–), 8.39–6.84 (6H, m, pyridine and Ar–H), 10.75 (2H, s, –NH–); MS: m/z: 437 ($M^+$), 376, 362, 314, 287, 259, 180, 165, 152, 149, 139, 125, 121, 107, 89, 77, 75, 63, 27; *Anal. Calcd*. for $C_{18}H_{17}O_2N_5SCl_2$: C, 49.42; H, 03.92; N, 16.02. Found: C, 49.38; H, 03.88; N, 15.95.

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