



Synthesis and Antimicrobial Activity of Some New Thioether Derivatives of Quinoxaline

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Abstract: 2-Chloro-3-methylquinoxaline was selected as nucleus around which the molecular manipulations were carried out to get new compounds expected to possess better anti microbial activity. Various quinoxaline derivatives have been synthesized by replacing the chlorine at C-2 with a thioether linkage, which in turn attached to 2-(*N*-(substituted phenyl)acetamides. The synthesized compounds (**5**) were tested for their antimicrobial activity. Compounds **5b**, **5c**, **5d** and **5i** were found most active (comparable to the standard antibacterial Ciprofloxacin) amongst them. The structure of the compounds was confirmed on the basis of their spectral data.

Keywords: Quinoxalines, 2-Chloro-*N*-(substituted phenyl)acetamides, 2-(2-Methylquinoxalin-3-ylthio)-*N*-(substituted phenyl)acetamides, Antimicrobial activity.

Introduction

Compounds containing the quinoxaline nucleus exhibit a broad spectrum of biological activity such as antibacterial¹⁻³, antifungal^{4,5}, antiviral⁶, anticancer⁷, antituberculosis⁸, antimalarial⁹ and anti-inflammatory¹⁰. Thioethers have also been reported for their bactericidal, fungicidal, anti-inflammatory anticholesteremic, hypolipidemic and neurotropic activities^{11,12}, therefore in continuation of our previous work¹³ on 2-chloro-3-methylquinoxaline therefore it was thought worthwhile to synthesize thioether derivatives of quinoxaline in search of better antimicrobial agents. We have synthesized twelve new compounds containing thioether linkage.

Experimental

The chemical synthesis (Scheme 1) was initiated with the reaction of *o*-phenylenediamine (**1**) with ethyl pyruvate in *n*-butanol to yield 2-hydroxy-3-methyl quinoxaline (**2**), which on treatment with POCl_3 , yielded 2-chloro-3-methylquinoxaline (**3**). A mixture of the compound (**3**) and sodium sulphide in DMF was refluxed to yield 3-methylquinoxalin-2-thiosodium (**4**), which on treatment with different *N*-substituted chloroacetamides afforded the one-pot synthesis of 2-(2-methylquinoxalin-3-ylthio)-*N*-substituted phenylacetamides (**5a-k**). 2-Chloro-*N*-substituted acetamides (Table 1) were prepared by treating substituted anilines in glacial acetic acid with chloroacetylchloride, warming on the water bath for half an hour and then precipitating, 2-chloro-*N*-substituted acetamides by addition of saturated aqueous solution of anhydrous sodium acetate. A compound 2-(benzylthio)-3-methylquinoxaline (**5l**) was also prepared. All these compounds (**5a-l**) are depicted in Table 2.

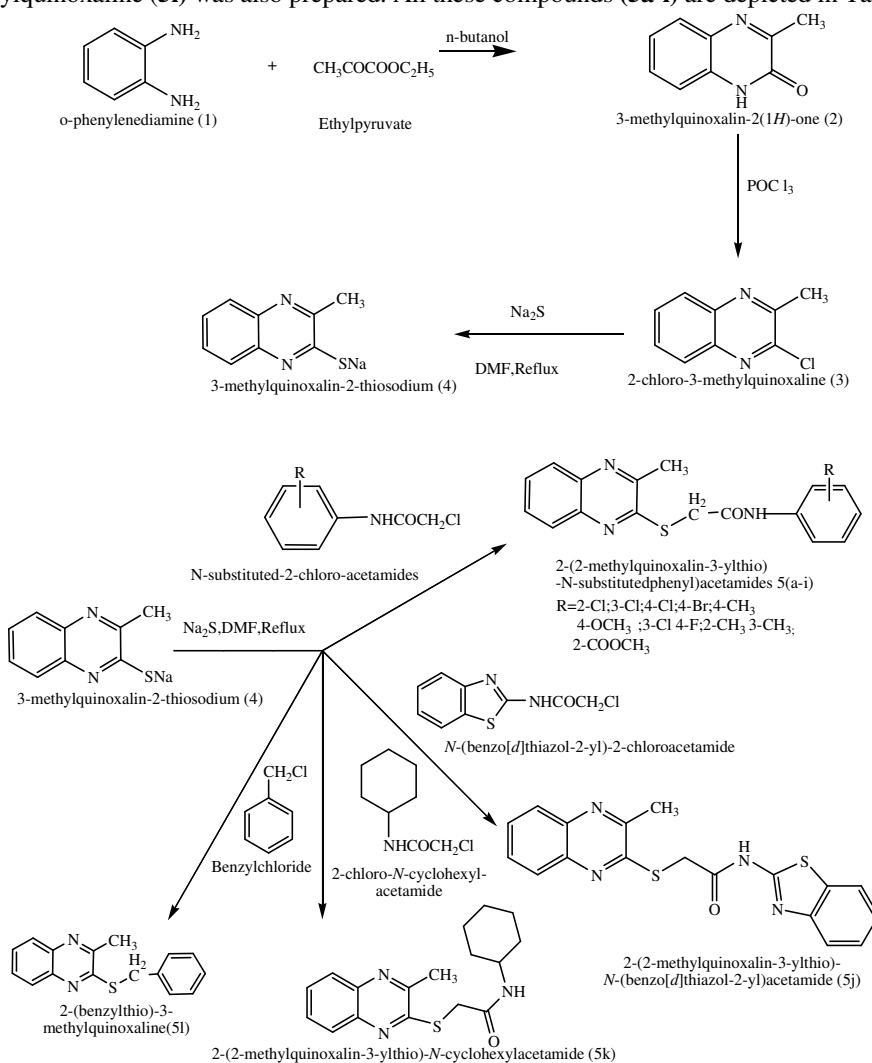
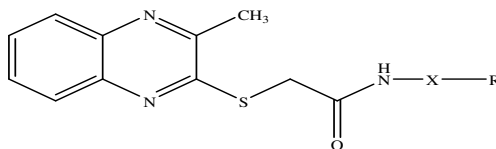




Table 1. Physical data of 2-chloro-*N*-(substituted phenyl)acetamides

S.No	Name	Melting point °C	R _f value
1.	2-Chloro- <i>N</i> -(2-chlorophenyl)acetamide	70-72	0.82
2.	2-Chloro- <i>N</i> -(3-chlorophenyl)acetamide	78	0.80
3.	2-Chloro- <i>N</i> -(4-chlorophenyl)acetamide	164-166	0.75
4.	2-Chloro- <i>N</i> -(4-methoxyphenyl)acetamide	170-172	0.77
5.	2-Chloro- <i>N</i> -(<i>p</i> -tolyl)acetamide	160-162	0.70
6.	2-Chloro- <i>N</i> -(4-methoxyphenyl)acetamide	104	0.86
7.	2-Chloro- <i>N</i> -(3-chloro,4-fluorophenyl)acetamide	75-77	0.64
8.	2-Chloro- <i>N</i> -(2,3dimethylphenyl)acetamide	122-124	0.72
9.	methyl 2-(2-chloroacetamido)benzoate	78	0.90
10.	<i>N</i> -(Benzo[d]thiazol-2-yl)-2-chloroacetamide.	141-142	0.68
11.	2-Chloro- <i>N</i> -cyclohexylacetamide	98	0.88

Mobile phase for TLC, ethyl acetate: *n*-hexane (1:1)

Table 2. Physical data of compounds (5a-l) and its structures

General structure of the synthesized compounds

Compounds	X ; R	Reaction Time	M.P. °C	R _f value
5a.	C ₆ H ₄ ; 2-Cl	6 H	138	0.90
5b.	C ₆ H ₄ ; 3-Cl	6 H	109	0.83
5c.	C ₆ H ₄ ; 4-Cl	6 H	144-145	0.84
5d.	C ₆ H ₄ ; 4-Br	6 H	166-167	0.80
5e.	C ₆ H ₄ ; 4-CH ₃	5 H	176	0.66
5f.	C ₆ H ₄ ; 4-OCH ₃	7 H	160	0.79
5g.	C ₆ H ₃ ; 3-Cl, 4-F	9 H	159-160	0.81
5h.	C ₆ H ₃ ; 2- CH ₃ , 3-CH ₃	6 H	182-183	0.78
5i.	C ₆ H ₄ ; 2-COOCH ₃	6 H	130	0.86
5j.	 ; H	6 H	180	0.57
5k.	 ; H	6 H	168-169	0.60
5l.	R-X-NHCO = C ₆ H ₅	2 H	170-171	0.80

Ethanol was used as the recrystallization solvent Mobile phase for TLC, ethyl acetate: *n*-hexane (1:1)

The melting points were determined in laboratory melting point apparatus using capillary method and are uncorrected. The purity of the compounds was checked by thin layer chromatography using silica gel- G on micro slide glass plates and spots were detected under iodine vapor. IR spectra were recorded in KBr disk on a Simadzu FTIR- 8400 spectrophotometer and ¹H NMR spectra on JEOL FTNMR Spectrometer (300 MHz) using TMS as an internal standard. All chemical shift values were recorded as δ (ppm).

Synthesis of 3-methylquinoxalin-2-(1H)-one (2)

o-Phenylenediamine (10.8 g, 0.10 M) was dissolved in 300 mL of *n*-butanol with warming. ethyl pyruvate [11.6 g (15 mL), 0.10 M] was dissolved in 100 mL of *n*-butanol separately and

it was added to former solution with constant stirring. The solution was set aside for 30 min, and then it was heated for 1 h on water bath. On cooling, the crystals that separated, were collected by filtration, washed with *n*-hexane and were purified by recrystallization from ethanol to yield colorless, needle shaped crystals of 2-hydroxy-3-methyl quinoxaline. Yield 80%, m.p. 246 °C. (Lit. m.p. 245 °C)¹⁴. IR (KBr) 3008 cm⁻¹ for (N-H stretching vibration of 2° amide), 2968 cm⁻¹ for (C-H stretching vibration of methyl group), 1665 cm⁻¹ for (C=O stretching vibration of amide) and 1610 cm⁻¹ for (C=C) multiple bond stretching vibration of aromatic nucleus).

Synthesis of 2-chloro 3-methylquinoxaline (3)

2-Hydroxy-3-methyl quinoxaline (16.0 g, 0.10 M) in 60 mL of POCl₃ was refluxed for 90 min. Then excess of POCl₃ was distilled off and the residue was cooled to room temperature and added to crushed ice taken in a 1L beaker. The mixture was made alkaline by adding 2% NaOH solution to isolate the product. The crude product was recrystallized from petroleum ether (40-60 °C), to yield the crystals of 2-chloro-3-methyl quinoxaline (**3**). Yield : 60%, m.p. 88 °C (Lit. m.p. 86-87 °C)¹⁵. IR (KBr) data clearly showed the disappearance of C=O stretching vibration of amide and appearance of C-Cl stretching vibration of aryl halide at 1038.52 cm⁻¹.

Synthesis of 3-methylquinoxalin-2-thiosodium (4)

A mixture of 2-chloro-3-methylquinoxaline, (0.9 g, 0.005 M) and sodium sulphide, (0.8 g, 0.005 M) in 10 mL of DMF was refluxed for 1.5 h. The completion of reaction was indicated by a change in color of reaction mixture from dirty green to complete yellow color. This compound was prepared separately for each synthesis to follow.

General method of synthesis of 2-chloro-N-(substituted phenyl)-acetamides

Substituted anilines (0.01 M) were dissolved in 10 mL of glacial acetic acid in a clean dry conical flask. Then chloroacetylchloride (0.015 M) was added drop wise and the mixture was warmed on a water bath for 15-30 min with occasional swirling. Saturated solution of anhydrous sodium acetate was added to the warm solution to yield the precipitate on cooling in an ice bath. The product was filtered, washed well with water and purified by recrystallization from ethanol. The purity of compounds was validated by monitoring TLC. *N*-(benzo[d]thiazol-2-yl)-2-chloroacetamide was synthesized separately. A mixture of equimolar amounts of 2-aminobenzothiazole (0.1 mole) and chloroacetyl chloride (0.1 mole) in 30 mL chloroform with anhydrous K₂CO₃ (0.1 mole) were refluxed for 14 h. After completion of the reaction (monitored by TLC), excess of solvent was distilled off. The residue was stirred with water (50 mL) and treated with 5% NaHCO₃ (30 mL) solution. The crude product was filtered washed with water to remove the alkali and recrystallized from methanol to yield the pale yellow product.

Synthesis of 2-(2-methylquinoxalin-3-ylthio)-N-substituted phenylacetamides (5a-k)

3-Methylquinoxalin-2-thiosodium was prepared as described earlier and then equimolar quantities of pure 2-chloro-*N*-(substituted phenyl)acetamide were added to the reaction vessel containing DMF and refluxed further for 6-9 h. The reaction mixture was cooled to room temperature and added to ice water in a beaker with stirring. The crude product that separated was filtered, washed well with water, decolorized with activated charcoal and purified by recrystallization from ethanol.

2-(Benzylthio)-3-methyl quinoxaline (5l)

Benzyl chloride (0.6 mL, 0.005 M) was added to reaction vessel containing 3-methylquinoxalin-2-thiosodium in DMF and refluxed for 2 h. The mixture was cooled to room temperature and poured in to ice water in a beaker with stirring to yield the product, which was filtered, washed with water and recrystallized from ethanol to yield crystals of 2-(benzylthio)-3-methylquinoxaline. The purity of compound was validated by m.p. determination and TLC technique. Physical data of compounds (**5a-l**) and structures are shown in the Table 2.

Spectral data of the synthesized compounds (5a-5l)*2-(2-Methylquinoxalin-3-ylthio)-N-(2-chlorophenyl)acetamide (5a)*

IR (KBr cm^{-1}): 3280 (N-H), 3040 (C-H), 2960(- CH_2 -), 1650 (C=O), 1600 (C=N), 1440 and 1250 (-C-S- CH_2), 1050 (C-Cl) aryl chloride and 640 (CH_2 -S). ^1H NMR (CDCl_3): δ 2.745 (s,3H, CH_3) δ 4.224 (s,2H, CH_2), δ 6.987-8.345 (m,8H, Ar-H) and at δ 9.166 (s,1H,N-H).

2-(2-Methylquinoxalin-3-ylthio)-N-(3-chlorophenyl)acetamide (5b)

IR (KBr cm^{-1}): 3260 (N-H), 3040 (C-H), 2880(- CH_2 -), 1660 (C=O), 1600 (C=N), 1420 and 1250 (-C-S- CH_2), 1050 (C-Cl) aryl chloride and 680 (CH_2 -S). ^1H NMR (CDCl_3): δ 2.839 (s, 3H, CH_3), δ 4.065 (s, 2H, CH_2), δ 7.218--8.024 (m, 8H, Ar-H) and δ 8.495 (s, 1H, N-H).

2-(2-Methylquinoxalin-3-ylthio)-N-(4-chlorophenyl)acetamide (5c)

IR (KBr cm^{-1}): 3250 (N-H), 3040 (C-H), 2890(- CH_2 -), 1650 (C=O), 1595 (C=N), 1440 and 1250 (-C-S- CH_2), 1050 (C-Cl) aryl chloride and 660 (CH_2 -S). ^1H NMR (CDCl_3): δ 2.737 (s,3H, CH_3) , δ 4.070 (s,2H, CH_2) , δ 7.188--8.052 (m,8H, Ar-H) and δ 9.748 (s,1H,N-H).

2-(2-Methylquinoxalin-3-ylthio)-N-(4-bromophenyl)acetamide (5d)

IR (KBr cm^{-1}): 3280 (N-H), 3040 (C-H), 2890(- CH_2 -), 1650 (C=O), 1600 (C=N), 1440 and 1250 (-C-S- CH_2), 1045 (C-Br) aryl bromide and 680 (CH_2 -S). ^1H NMR (CDCl_3): δ 2.736 (s,3H, CH_3), δ 4.067 (s,2H, CH_2), δ 7.257-8.056 (m,8H, Ar-H) and δ 9.756 (s,1H,N-H).

2-(2-Methylquinoxalin-3-ylthio)-N-p-tolyl acetamide (5e)

IR (KBr cm^{-1}): 3290 (N-H), 3040 (C-H), 2890(- CH_2 -), 1650 (C=O), 1610 (C=N), 1400 and 1250 (-C-S- CH_2) and 680 (CH_2 -S). ^1H NMR (CDCl_3) : δ 2.263 and δ 2.319 (d,6H,2 CH_3), δ 3.431 (s,2H, CH_2), δ 6.694-7.691(m,8H, Ar-H) and δ 8.400 (s,1H,N-H).

2-(2-Methylquinoxalin-3-ylthio)-N-(4-methoxyphenyl)acetamide (5f)

IR (KBr cm^{-1}): 3270 (N-H), 3040 (C-H), 2840(- CH_2 -), 1650 (C=O), 1600 (C=N), 1400 and 1250 (-C-S- CH_2), 1250; 1035 (C-O) and 640 (CH_2 -S). ^1H NMR (CDCl_3) : δ 2.738 (s,3H, CH_3), δ 3.743(s,3H, OCH_3), δ 4.073 (s,2H, CH_2), δ 6.774-8.042 (m,8H, Ar-H) and δ 9.487 (s,1H,N-H) .

2-(2-Methylquinoxalin-3-ylthio)-N-(3-chloro-4-fluorophenyl)acetamide (5g)

IR (KBr cm^{-1}): 3280 (N-H), 3020 (C-H), 2880(- CH_2 -), 1670 (C=O), 1600 (C=N), 1440 and 1250 (-C-S- CH_2), 1115 (C-F) aryl chloride 1050 (C-Cl) aryl chloride and 680 (CH_2 -S). ^1H NMR (CDCl_3) : δ 2.737 (s,3H, CH_3) δ 4.062 (s,2H, CH_2) , δ 6.964-8.058 (m,7H, Ar-H) and δ 9.776 (s,1H,N-H).

2-(2-Methylquinoxalin-3-ylthio)-N-(2, 3-dimethylphenyl)acetamide (5h)

IR (KBr cm^{-1}): 3280 (N-H), 3000 (C-H), 2900(- CH_2 -), 1650 (C=O), 1600 (C=N), 1440 and 1250 (-C-S- CH_2), and 680 (CH_2 -S). ^1H NMR (CDCl_3): δ 2.755 (s,3H, CH_3), δ 1.905 and δ 2.198 (d,6H,2 CH_3), δ 4.179 (s,2H, CH_2), δ 6.947-8.005 (m,7H, Ar-H) and δ 8.768 (s,1H, N-H). MS: m/z 338 ($\text{M}^+ + 1$)

Methyl-2-(2-(2-methylquinoxalin-3-ylthio) acetamide)benzoate (5i)

IR (KBr cm^{-1}): 3280 (N-H), 2960 (C-H), 2900(- CH_2 -), 1680 (C=O), 1600 (C=N), 1440 and 1250 (-C-S- CH_2), 1270; 1115 (C-O) and 700 (CH_2 -S). ^1H NMR (CDCl_3): δ 2.794 (s,3H, CH_3), δ 3.760 (s,3H, OCH_3), δ 4.278 (s,2H, CH_2), δ 7.026-8.690 (m,8H, Ar-H) and δ 11.631 (s,1H,N-H).

2-(2-Methylquinoxalin-3-ylthio)-N-(benzo[d]thiazol-2-yl)acetamide (5j)

IR (KBr cm^{-1}): 3260 (N-H), 3040 (C-H), 2900(- CH_2 -), 1700 (C=O), 1600 (C=N), 1440 and 1250 (-C-S- CH_2), 740 (Benzothiazole ring) and 690 (CH_2 -S). ^1H NMR (CDCl_3): δ 2.739 (s,3H, CH_3), δ 4.191 (s,2H, CH_2), δ 7.261-8.143 (m,8H, Ar-H) and δ 11.303 (s,1H,N-H).

2-(2-Methylquinoxalin-3-ylthio) -N-cyclohexylacetamide (5k)

IR (KBr cm^{-1}): 3280 (N-H), 2960 (C-H), 2900(- CH_2 -), 1640 (C=O), 1550 (C=N), 1440 and 1250 (-C-S- CH_2), and 720 (CH_2 -S). ^1H NMR (CDCl_3): δ 1.005-1.841 (m,10H, C_6H_{10}), δ 2.838 (s,3H, CH_3), δ 3.722-3.748(t,1H, CH), δ 3.927 (s,2H, CH_2) δ 7.144-7.986 (m,4H, Ar-H) and δ 8.011 (s,1H,N-H).

2-(Benzylthio)-3-methylquinoxaline (5l)

IR (KBr cm^{-1}): 2960 (C-H), 2900(- CH_2 -), 1600 (C=N), 1440 and 1250 (-C-S- CH_2) and 720 (CH_2 -S). ^1H NMR (CDCl_3): δ 2.834 (s, 3H, CH_3), δ 4.065 (s, 2H, CH_2) and δ 7.260-8.051 (m, 9H, Ar-H).

Antibacterial activity

The antibacterial activity was assayed by agar plate disc diffusion method¹⁶ at the concentration of 50 μg per disk. All the synthesized compounds were tested *in vitro* for their antibacterial activity against gram positive microorganisms such as *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2439) and gram negative *Escherichia coli* (NCIM 2831), *Pseudomonas aeruginosa* (NCIM 2863) strains. Each test compounds were dissolved in dimethyl sulphoxide (DMSO) to get a concentration of 10 mg/mL. The disc (6 mm in diameter) was impregnated with 5 μL of each test solution to get 50 μg /disc, air dried and placed on the agar medium, previously seeded with 0.2 mL of broth culture of each organism for 18 h. The plates were incubated at 37 $^\circ\text{C}$ for 24 h and the inhibition zones were measured in mm. Discs impregnated with DMSO were used as a control and ciprofloxacin discs as antibacterial reference standard.

Antifungal activity

The antifungal activity¹⁷ was assayed by sabouraud dextrose agar media plate disc diffusion method at the concentration of 50 μg per disk. All the synthesized compounds were tested *in vitro* for their antifungal activity against microorganisms such as *Aspergillus niger* (NCIM 618) and *Candida albicans* (NCIM 3557). Each test compound was dissolved in dimethyl sulphoxide (DMSO) to get a concentration of 10 mg/mL. The disc (6 mm in diameter) was impregnated with 5 μL of each test solution to get 50 μg /disc; air dried and placed on the sabouraud dextrose agar media, previously seeded with 0.2 mL of broth culture of each organism for 18 h. The plates were incubated at 22 $^\circ\text{C}$ for 48 h and the inhibition zones were measured in mm. Discs impregnated with DMSO were used as a control and fluconazole discs as antifungal reference standard.

Results and Discussion

The IR spectra of compounds (**5a-k**) showed bands at 3280 cm^{-1} (N-H) stretching vibration for secondary amides, at 2920 cm^{-1} ($-\text{CH}_2-$) stretching vibration, at 1650-1700 cm^{-1} (C=O) stretching vibration for amides, at 1440-1250 cm^{-1} ($-\text{C-S-CH}_2-$) stretching vibration and at 640 cm^{-1} ($-\text{C-S-}$) stretching vibration. The ^1H NMR spectra also confirmed this synthesis by showing δ values for various hydrogens. The ^1H NMR spectra revealed a singlet at δ 2.838 for CH_3 of quinoxaline ring, a singlet at δ 3.900-4.300 for ($-\text{S-CH}_2-$), a singlet at δ 8.000-9.700 for secondary (N-H) and multiplets at δ 6.900-8.000 for aromatic hydrogens. The attachment of various substituent groups in the synthesized compounds were also validated by their respective IR and ^1H NMR spectra. The mass spectrum of compound (**5h**) has further validated the structure of this compound.

Antibacterial activity

The antibacterial activity was determined by the disc diffusion method at the concentration of 50 μg per disk. All the synthesized compounds were tested *in vitro* for their antibacterial activity against gram positive microorganisms such as *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2439), *Escherichia coli* (NCIM 2831), *Pseudomonas aeruginosa* (NCIM 2863) (gram negative), using ciprofloxacin as standard antibacterial. The results of activity, presented in the Table 3 suggested that the compounds **5a**, **5c**, **5d**, **5h**, **5i**, **5j**, **5k** and **5l** were highly active whereas compounds **5b**, **5e**, **5f** and **5g** were moderately active against microorganism *S. aureus*. The compound **5b** only was found highly active and rest of the compounds was found moderately active against *B. subtilis*. The compounds **5j** and **5k** were found highly active and rest moderately active against microorganism *E. coli*. The activity of the compounds **5b**, **5c**, **5d** and **5i** were found most active, (comparable to standard antibacterial ciprofloxacin), **5j** moderately active whereas compounds **5a**, **5e**, **5f**, **5h** and **5l** were found inactive against microorganism *P. aeruginosa* (Table 3).

Table 3. Results of antimicrobial activity

Compounds	Zone of Inhibition					
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>A. niger</i>	<i>C. albican</i>
5a.	+++	++	++	-	++	-
5b.	++	+++	++	+++	++	-
5c.	+++	++	++	+++	++	-
5d.	+++	++	++	+++	++	-
5e.	++	++	++	-	++	++
5f.	++	++	++	-	++	++
5g.	++	++	++	+++	++	+++
5h.	+++	++	++	-	++	++
5i.	+++	++	++	+++	-	-
5j.	+++	++	+++	++	+++	+++
5k.	+++	++	+++	++	++	+++
5l.	+++	++	++	-	++	++
Ciprofloxacin	+++	+++				
Fluconazole					+++	+++

'-' Inactive (inhibition zone < 6 mm); slightly active = '+' (inhibition zone 7-9 mm); moderately active = '++' (inhibition zone 10-13 mm); highly active = '+++ (inhibition zone > 14 mm).

Antifungal activity

The antibacterial activity was determined by the disc diffusion method at the concentration of 50 µg per disk. All the synthesized compounds were tested *in vitro* for their antifungal activity against microorganisms such as *Aspergellus niger* and *Candida albicans*, using fluconazole as standard antifungal. The compound **5j** was highly active against both microorganisms *Aspergellus niger* (NCIM 618) and *Candida albicans* (NCIM 3557). Compounds **5g** and **5k** were highly active where as compounds **5a**, **5b**, **5c**, **5d** and **5i** were inactive against *Candida albicans* while rest of the compounds showed moderate activity against *Aspergellus niger*.

Conclusion

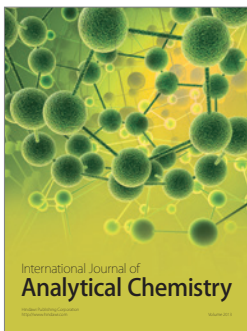
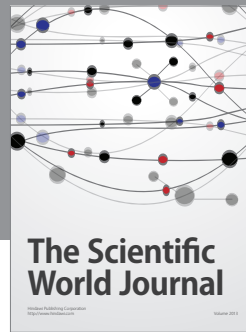
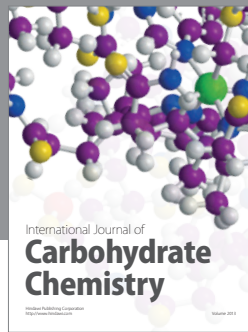
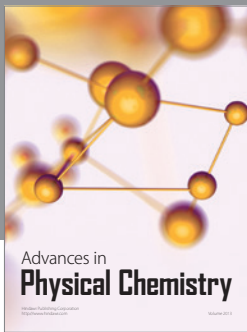
A series of the compounds (**5a-5l**) were synthesized and tested for antimicrobial activity, the compound **5b**, **5c**, **5d** and **5i** were found most active (comparable to standard antibacterial Ciprofloxacin) against *P.aerugenosa*. The compound **5j** was highly active against both microorganisms *Aspergellus niger* and *Candida albicans* when compared to Fluconazole as standard antifungal agent.

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