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Note

Synthesis and anti microbial activity of quinoxaline based thiazolidinones and azetidinones

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Several 2-aryl-3- (3′methyl quinoxalin-2′-yl-amino) 4-thiazolidinoes **6a-l** and 1-*N*-(3′methylquinoxalin-2′-yl-amino)4-aryl –3-chlodro-2-azetidinones **7a-l** have been synthesized and tested for their antimicrobial and antifungal activity against different microorganism. The structure of compounds **6a-l** and **7a-l** have been conformed on the basis of their elemental and spectral data.

Keywords: Quinoxalines, thiazolodinones, azetidinones, antimicrobial activity.

Quinoxaline and its analogs constitute the active class of the compounds possessing wide spectrum of biological activity[1-8], antiviral[9] (Hepatitis-B), antimicrobial[10], and amoebicidal[11] activity. Further thiazolidinoes and azetidinones are well famed for their antimicrobial[12-22] activities. In the light of above fact we have synthesized some new 4-thiazolidinoes and 2-azedinones derivatives incorporating quinoxaline moiety with the hope to possess better antimicrobial activity. All the synthesized compounds were screened for their antibacterial and antifungal activities against some selected microbes.

Results and Discussion

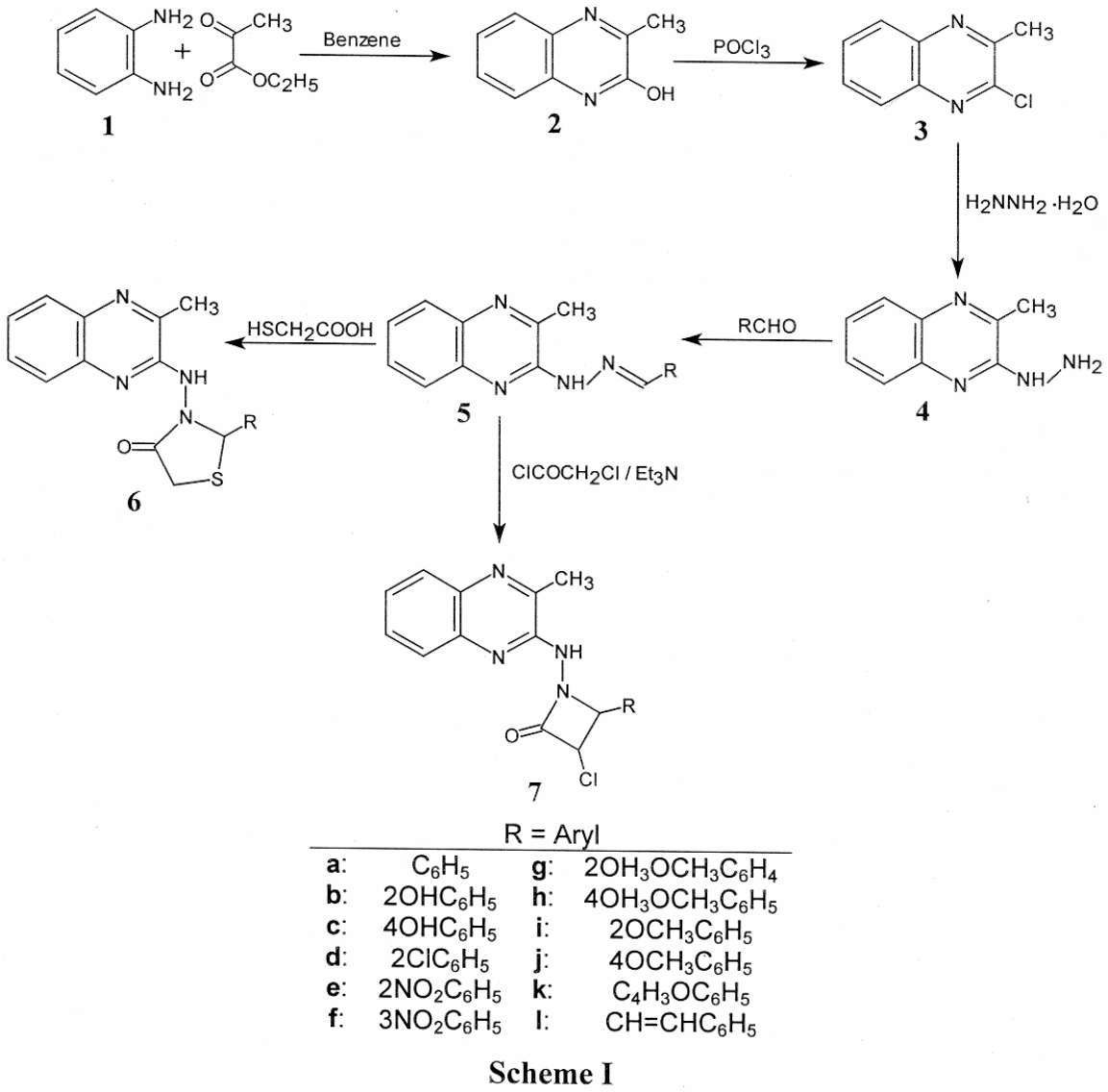
The chemical synthesis initiate with the reaction of *o*-phenylenediamine **1** and ethyl pyruvate were mixed in dry benzene to yield 2-hydroxy-3-methyl quinoxaline **2**, compound **2** on treatment with phosphorus oxychloride yielded 2-chloro-3-methyl quinoxaline **3**. The chloro compound and hydrazine hydrate were refluxed in ethanol for 3 hr. to yield 2-hydrazino 3-methyl quinoxaline **4**. A mixture of compound **4** and different aromatic aldehydes in methanol refluxed to give 3-methyl-2- (arylidene hydrazine) quinoxaline **5a-l.** The compounds **5a-l** was refluxed with thioglycolic acid to yield 2-aryl-3-(3′methyl quinoxalin-2′-yl-amino) 4-thiazolidinones **6a-l**. The compounds **7a-l** were synthesized by reacting compounds **5a-l** with chloro acetyl chloride in presence of triethyl amine (**Scheme I**) .The structure of all the newly quinoxaline derivatives were confirmed on the basis of their spectral and analytical data.

Antimicrobial activity

The antimicrobial activity was assayed by the cup-plate agar diffusion method [23-24] at the concentration of 40 μg/mL. All the synthesized compounds were tested *in vitro* for their antimicrobial activities against various microbes such as *Escherichia Coli, A. niger*, *Bacillus subtilis*, *Pseudomonas aeruginosa* etc. Plates incubated 24 hr for bactericidal and 48 hr for fungicidal activities the inhibition zone of testing compounds was measured in mm (**Table I**). Under the identical conditions, the standard antibiotics showed zone of inhibition like ampicillin 15-26 mm, chloramphenicol 15-18 mm, penicillin 18-23 mm against bacterial strains. It can be concluded from the **Table I** that compounds **6a, 6b, 6c, 6g, 6h, 6i** and **7d, 7i** and **7l** were highly active against *Bacillus Subtilis*. The compound **6b, 6e, 6f, 6h** and **7b, 7c, 7d,**and **7f** showed significant activity against *Bacillus serus* and **6a, 6g, 6j, 7b, 7d, 7k** and **7l** were found active against pseudomonas. In the case of *Escherichia coli*, all the compounds **6** and **7d, 7i, 7j**,and **7k** showed maximum activity. All the compounds **6** and **7d, 7e** and **7i** showed highest activity against *Aspergillum niger*. The other compounds showed either moderate or less activity against these organism.

Discussion

The IR. spectrum of compound **4** showed a sharp doublet at 3286 and 3188 cm^{-1} due to the NH str of NH_2. Compound **4** on condensation with carbonyl compounds, these bands disappear and a band at 3298 cm^{-1} is observed due to NH str of NH=N- group. The ^1H NMR spectrum of compound **4** showed a broad signal at δ 4.25 due to NH_2 protons and at 6.5 the characteristics of NH proton. The compound on condensation with carbonyl compounds the hydrazone formed shows the disappearance of NH_2 proton signals, while that of NH proton signal is shifted up



R = Aryl

a:	C_6H_5	**g**:	$2OH_3OCH_3C_6H_4$
b:	$2OHC_6H_5$	**h**:	$4OH_3OCH_3C_6H_5$
c:	$4OHC_6H_5$	**i**:	$2OCH_3C_6H_5$
d:	$2ClC_6H_5$	**j**:	$4OCH_3C_6H_5$
e:	$2NO_2C_6H_5$	**k**:	$C_4H_3OC_6H_5$
f:	$3NO_2C_6H_5$	**l**:	$CH{=}CHC_6H_5$

Scheme I

Table I — Antimicrobial data (inhibition zones 16 mm- 25 mm) of some selected synthesized compounds

Standard Antibiotics	*B.subtilis*	*B.serus*	*E.coli*	*Pseudomonas*	*A.niger*
Ampicillin 15-25mm	**6a,6b,6c 6g,6h,6i**	**6b,6e, 6f,6h,**	**6a-6l 7d,7i**	**6a,6g,6j 7b,7d,7k**	**6c,6h,6i 6j,6k,6l**
Chloramphenicol 15-28 mm	**7d,7i,7l**	**7b,7c, 7d,7f**	**7j,7k**	**7l**	**7d,7e,7i**
Penicillin 18-23 mm					
Greseofulvin 15-20 mm					

a,C_6H_5-; **b,**2-OH-C_6H_5-; **c,**4-OH-C_6H_5-; **d,**2-Cl-C_6H_5; **e,**2-NO_2-C_6H_5-; **f,**3-NO_2-C_6H_5; **g,2**-OH-3-OCH_3- C_6H_4; **h,**4-OH-3-OCH_3- C_6H_4-; **I,2**-OCH_3- C_6H_4-; **j,**4-OCH_3- C_6H_4; **k,**C_4H_3O C_6H_5-; **l,**-CH=CH- C_6H_5-

field at δ 9.12 as a result of de shielding effect of CH=N- group .The proton of azomethine (-N=CH-) group lead to a sharp singlet at 8.4. The multiplet signals at 6.9-8.4 are the characteristics of the aromatic ring protons. A sharp signal appears at δ 3.93, the characteristics of the protons of -OCH_3, similarly a sharp signal at δ 2.27 is characteristics of the protons of -CH_3. In all the compounds a sharp singlet at δ 2.6 is due to the protons of –CH_3 attached to the heteryl nucleus (quinoxaline ring). In case of 2-*p*-anisyl-3- (3′-methylquinoxalin-2′yl-amino) 4-thiazolidinone gave a sharp signal at δ 3.69 the characteristics of the protons of –CH_2 group of 4-thiazolidinone ring. The ^{1}H NMR spectrum of 1-*N*-(3′methylqunoxalin-2′yl-amino) 4-2′methoxy benylidene –3-chloro-2-azetidinone gave two doublets at δ 4.67 and 3.75 due to the two hydrogen atoms on C_3 and C_4 carbon atom respectively**.**

Experimental Section

All the recorded melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a simadzu FT-IR -8400 spectrophotometer and ^{1}H NMR spectra on Bruker Spectrometer (300 Mz) using TMS as an internal standard. All chemical shift values were recorded as δ (ppm).

2-Hydrazino-3-methyl quinoxaline 4. *o*-Phenylenediamine (0.01 mole) and ethyl pyruvate (0.01 mole) were mixed in dry benzene to yield 2-hydroxy-3-methyl quinoxaline which (0.01 mole) on treatment with phosphorus oxychloride (6 mL) yielded 2-chloro-3-methyl quinoxaline. The chloro compound (0.015 mole) and hydrazine hydrate (0.02 mole 99%) in ethanol (25 mL) refluxed for 3 hr. to yield 2-hydrazino 3-methyl quinoxaline **4** yield 92.5%; m.p. 172 °C. The product was recrystallised with ethanol to give the pure compound. IR (KBr) 3288 and 3186 (doublet for NH of NH_2), 1625 (C=N Str), 1573 (-NH def) 1191 cm^{-1} (-C-N Str).). ^{1}H NMR (DMSO-d_6): δ 2.52 (s, 3H) 4.25 (br, 2H, NH_2 D_2O exchangeable) 6.2 (br, 1H, NH) 7.74 & 7.86 (d, 2H, quinoxaline ring protons), 7.43 and 7.56 (t, 2H, quinoxaline ring protons) ppm. ^{13}C NMR showed signals at δ 127.98 (d, C-5), 127.52 (d, C-6), 129.62 (d, C-7), 129.69 (d, C-8), 140.36 (s, C-9), 141.18 (s, C-10), 147.02 (s, C-2), 152.00 (s, C-3) carbon atoms of quinoxaline moiety and δ 22,83 (quartet) ppm of methyl carbon on C-2. Anal. Calcd for $C_9H_{10}N_4$ C, 62.05; H, 5.78; N, 31.17. Found: C, 62.25; H, 5.92; N, 32.01%.

3-Methyl-2-(2′-hydroxy-3′-methoxy benzylidene) hydrazine quinoxaline 5g. A mixture of compound **4** (0.01 mole) and *p*-methoxybenzaldehyde (0.01 mole) in methanol was refluxed for 6 hr. The product separated was isolated and neutralized with sodium bisulphite to get 3-methyl–2-(4′-methoxy benzylidene) hydrazino quinoxline yield 85%; m.p. 185 °C. IR (KBr): 3540 (-NH Str), 1600 (C=N Str), 1541 (NH def) 1166 (C-N Str) and 1040 cm^{-1} (-C-OCH_3). ^{1}H NMR (DMSO-d_6): δ 2.62 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.85 and 6.95 (d, 2H, *J*=10Hz part of A_2B_2system of protons from methoxy containing aryl ring) 7.0 and 7.25 (d, 2H, quinoxaline ring protons) 7.2 and 7.35 (t, 2H, quinoxaline ring protons), 7.75 and 7.85 (d, 2H, *J*=10Hz part of A_2B_2system of protons from methoxy containing aryl ring) 8.4 (s, 1H, N=CH-), and 9.12(s, 1H, –NH-N). Anal. Found C, 65.99; H, 5.15; N, 18.10 $C_{17}H_{16}N_4O_2$ requires C, 66.23; H, 5.19 and N, 18.18%. Similarly other member of compound **5** was prepared.

2-*p*-Anisyl-3 (-3′ methyl quinoxalin-2′ yl-amino) 4-thiazolidinones 6. A mixture of 3-methyl-2-(*p*-methoxy benzylidene hydrazino)quinoxaline (0.01 mole) and thioglycolic acid (0.94 g 0.01 mole) was heated on the oil-bath at 115-20 °C for 12 hr. The resulting mass was treated with 10% sodium bicarbonate and the product was isolated, yield 50%; m.p. 145 °C. IR (KBr) 3361 (-NH Str), 1708 (C=O Str), 1660 (C=N Str), 1577 (NH def) 1184 (C-N Str), 1040 (-C-OCH_3) and 659 cm^{-1} (C-S-C Str). ^{1}H NMR (DMSO-d_6):δ 2.62 (s, 3H, CH_3), 3.69 (s, 2H, –CH2), 3.93 (s, 3H, OCH3) 5.39 (s, 1H, CH-Ar) 6.85 and 6.95 (d, 2H, Ar-H), 7.75 & 7.85 (d, 2H) 7.0 and 7.25 (d,2H, quinoxaline ring protons), 7.2 and 7.35 (t, 2H, quinoxaline ring protons) 8.80 (br, 1H). Anal. Found C, 61.80; H, 4.60; N, 11.40. $C_{19}H_{17}N_3O_3S$ requires C, 62.12; H, 4.63 and N, 11.44%. Similarly other members of compounds **6** were prepared.

Preparation of 1-*N*-(-3′ methyl quinoxalin-2′yl-amino) 4-aryl-3-chloro-2-azetidinones 7. To a solution of 3-methyl-2-(2′-methoxy benzylidene hydrazino) quinoxaline (0.01 mole) in dry dioxane (35 mL) was added to well-stirred mix of triethyl amine (0.012 Mole) and chloroacetyl chloride (0.012 mole) at low temperature. The resulting solid was crystallized from chloroform-methanol mixture to give pure 1-*N* (-3'methyl quinoxalin-2′-yl-amino) 4-

aryl-3-chloro-2-azetidinone yield 58%; m.p. 148 °C. IR (KBr): 3256(-NH Str), 1762 (β-lactam ring C=O Str), 1604 (C=N Str), 1542 (NH def) 1184 (C-N Str), 1040 (-C-OCH_3) and 752 cm^{-1} (C-Cl Str). ^1H NMR (DMSO-d_6): δ 2.69 (s, 3H), 4.97 (d, 1H), 3.74 (d, 1H), 3.97 (s, 3H) 6.92-7.8 (m, 4H) 7.43 & 7.56 (t, 2H, quinoxaline ring protons), 7.74 and 7.86 (d, 2H, quinoxaline ring protons) 11.6 (br, 1H). Anal. Found C, 62.0; H, 4.85; N, 15.20. $C_{19}H_{18}N_4O_2Cl$ requires C, 62.12; H, 4.90 and N, 15.25%.

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