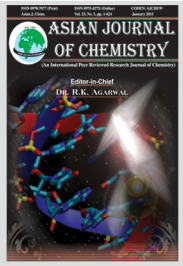
Asian Journal of Chemistry; Vol. 23, No. 9 (2011), 4021-4023

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



# Synthesis and Antimicrobial Activity of Novel Thiazolidinone and Azetidinone Derivatives

S.S. KSHIRSAGAR*, H.M. NIMJE, P.S. CHAUDHARI, J.P. BAYAS, E.K. PATEL, A.H. KARJIKAR, P.D. GIRME and R.J. OSWAL

JSPM's Charak College of Pharmacy and Research, Nagar Road, Wagholi, Pune-412 207, India

*Corresponding author: E-mail: sanpals24@rediffmail.com

(*Received*: 13 November 2010; *Accepted*: 14 May 2011) AJC-9959

Reaction of 2,3-diketoquinoxaline in presence of phosphorus pentachloride and hydrazine hydrate gives 2-hydrazino-3-hydroxyquinoxalin (**4**) which on treatment with various aldehydes in appropriate solvent gives 2-*p*-anisyl-3-(3-hydroxy quinoxalin-2 yl-amino)-4-thiazolidinones (**6**) and 1-N-(3-hydroxy quinoxalin-2'yl-amino)-4-aryl-3-chloro-2-azetidinones (**7**). The structure of compounds **6a-6l** and **7a-7l** has been confirmed by IR and $^1$H NMR data. All these compounds were tested for their antimicrobial and antifungal activity against different microorganisms.

**Key Words: Quinoxaline, NMDA receptor, Thiazolidinones, Azetidinones, Antimicrobial activity.**

## INTRODUCTION

Quinoxaline and its analogs constitute the active class of the compound and possessing wide spectrum of biological activity, antiviral (hepatitis-B), antimicrobial and amoebicidal activity[1-3]. Further thiazolidoes and azetidinones are well known for their antimicrobial 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[4]. All the synthesized compounds were screened for their antibacterial and antifungal activities against some selected microbes.

## EXPERIMENTAL

All melting points are determined in an open capillary tube and are found to be uncorrected. IR spectra (cm$^{-1}$) were recorded on a FTIR-8400s Shimadzu system. Proton magnetic resonance spectra (H NMR) were recorded on Bruker AC-300F NMR spectrometer (300 MHz) using DMSO-$d_6$ as solvent and tetramethyl silane (TMS) as internal standard. All chemical shifts values were recorded as δ (ppm). Success of each step was confirmed by TLC during reaction.

**2,3-Diketoquinoxaline:** *o*-Phenylene diamine (0.25 mol), oxalic acid (0.36 mol) and 4N HCl were refluxed on oil-bath for 1 h and cooled. The solid separated was filtered and washed. m.p. < 300 ºC, yield 82 %; colourless needle shaped crystals. IR (KBr, $\nu_{max}$, cm$^{-1}$) 3350, 2928, 1658, 1593, 1028.

**2-Hydrazino 3-hydroxy quinoxaline (4):** 2,3-Diketo-quinoxaline (0.01 mol) on treatment with phosphorus pentachloride (6 mL) yielded 2-chloro-3-hydroxy quinoxaline. The chloro compound (0.015 mol) and hydrazine hydrate (0.02 mol 99 %) in ethanol (25 mL) refluxed for 3 h to yield 2-hydrazino 3-hydroxy quinoxaline. m.p. 170 ºC, yield 89 %. The product was recrystallized with ethanol to give a pure compound. IR (KBr, $\nu_{max}$, cm$^{-1}$) 3288 and 3186 (for NH of $NH_2$), 1625 (C=N str), 1191 (-C-N str). $^1$H NMR (DMSO-$d_6$): δ 2.52 (s, 3H) 4.23 (br, 2H, $NH_2$ $D_2O$ exchangeable) 6.2 (br, 1H, NH) 7.77 and 7.87 (d, 2H, quinoxaline ring protons) ppm $^{13}$C NMR showed signals at δ 127.98 (d, C-5), 129.68 (d, C-7), 127.69 (d, C-8), 140.98 (s, C-9), 141.18 (s, C-10), 147.07 (s, C-2), 152.00 (s, C-3), 127.98 (d, C-5).

**3-Hydroxy-2-(2'-hydroxy-3-methoxy benzylidene) hydrazino quinoxaline (5):** A mixure of compound **4** (0.01 mol) and *p*-methoxy benzaldehyde (0.01 mol) in methanol was refluxed for 6 h. The product separated was isolated and neutralized with sodium bisulphate to get 3-hydroxy-2-(4'-methoxybenzylidene)hydrazino quinoxaline yield 76 %; m.p. 184 ºC. IR (KBr, $\nu_{max}$, cm$^{-1}$) 3540 (-NH str), 1623 (C=N str), 1498 (-NH def) 1045 (-$COCH_3$). $^1$H NMR (DMSO-$d_6$): 3.89 (s, 3H, -$OCH_3$), 7.0 and 7.22 (d, 2H, quinoxaline ring protons), 8.4 (s, 1H, N=CH-) and 9.11 (s, 1H, -NH-N) ppm.

**2-*p*-Anisyl-3(-3'-hydroxy quinoxaline-2'-yl-amino)-4-thiazolidinones (6a-6l):** A mixture of 3-hydroxy-2(*p*-methoxy benzylidine hydrazino)quinoxaline (0.01 mol) and thioglycolic acid (0.01 mol) was heated on oil bath at 115-120 ºC for 12 h. The resulting mass was treated with 10 % sodium bicarbonate and the product was isolated, yield 40 %, m.p. 145 ºC. IR (KBr, $\nu_{max}$, cm$^{-1}$) 3297 (- NH str), 1709 (C=O str), 1621 (C=N Str), 1546 (-NH def), 1040 (-$CoCH_3$). $^1$H NMR (DMSO-$d_6$): 3.69 (s, 2H, -$CH_2$), 3.89 (s, 3H, -$OCH_3$), 5.41 (s, 1H CH-Ar),

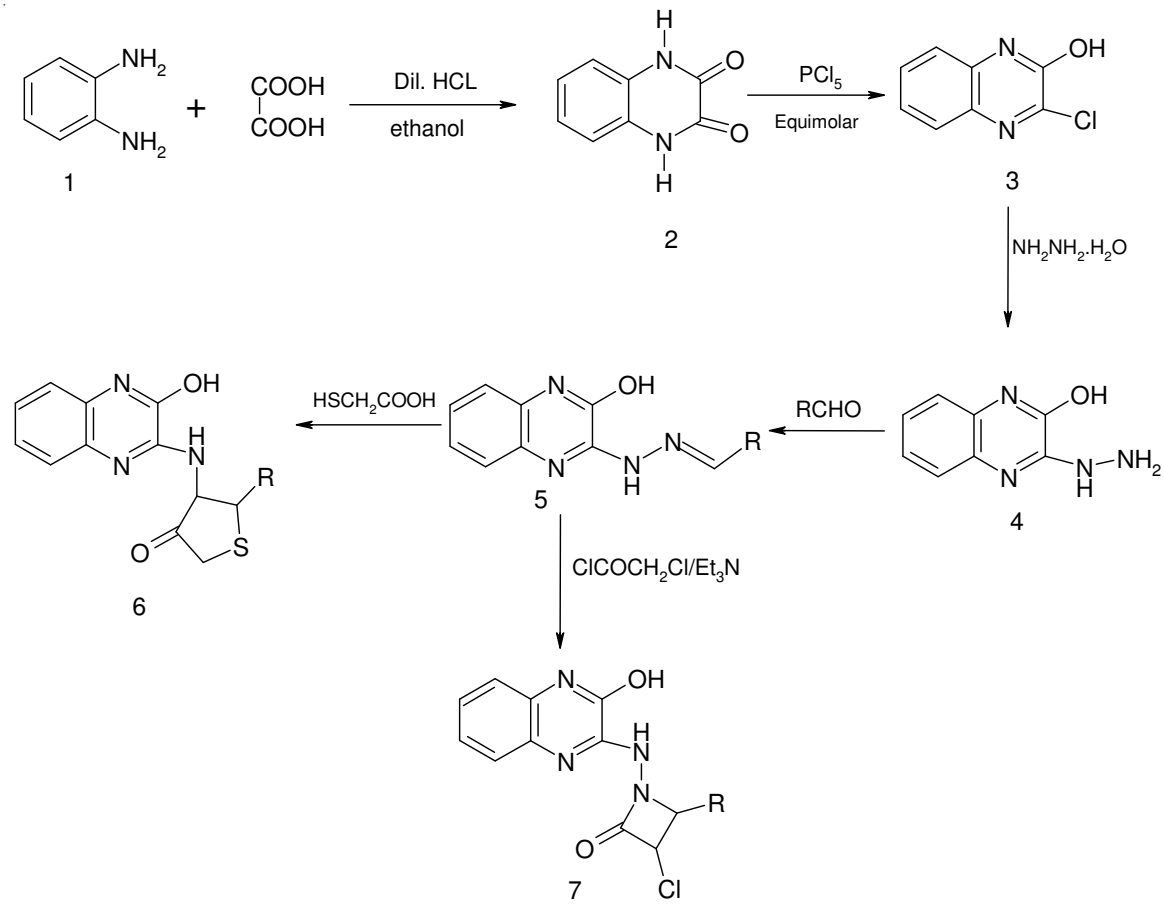
6.89 and 6.95 (d, 2H, Ar-H), 7.0 and 7.32 (d, 2H, quinoxaline ring protons), 7.2 to 7.35 (t, quinoxaline ring protons), 8.1 (br, 1H), 9.11 (s, 1H, -NH-N) ppm.

**Preparation of 1-N-(3'-hydroxy quinoxaline-2'-yl-amino) 4-aryl-3-chloro-2-azetidinones (7a-7l):** To a solution of 3-hydroxy-2(*p*-methoxy benzylidine hydrazino) quinoxaline (0.01 mol) in dry dioxane was added to well stirred mixture of triethylamine (0.012 mol) and chloroacetyl chloride (0.012 mol) at low temperature. The resulting solid was crystallized from chloroform-methanol mixture to give pure 1-N-(3'-hydroxy quinoxaline-2'-yl-amino)-4-aryl-3-chloro-2-azetidinones. Yield 60 %; m.p. 147 ºC. IR (KBr, $\nu_{max}$, $cm^{-1}$) 3257 (-NH str), 1759 (β-lactam ring C=O str), 1610 (C=N Str), 1496 (-NH def) 1040 (-$CoCH_3$). $^1H$ NMR (DMSO-$d_6$): δ 2.69 (s, 3H, $CH_3$), 4.97 (d, 1H), 3.89 (s, 3H, -$OCH_3$), 6.92-7.8 (m, 4H), 7.0 and 7.22 (d, 2H, quinoxaline ring protons), 8.2 (br, 1H), 8.4(s, 1H, N=CH-) and 9.11 (s, 1H, -NH-N) ppm.

**Antimicrobial activity:** The antimicrobial activity was assayed by the cup plate agar diffusion method at the concentration of 40 mg/mL. All the synthesized compounds were tested *in vitro* for their antimicrobial activities against *Escherichia coli*, *A. niger*, *Bacillus subtilis* and *Pseudomonas aeruginosa.* Plates incubated 24 h for bactericidal and 48 h for fungicidal activities and the inhibition zone of testing compounds was measured in mm (Table-1). Under the identical conditions, standard antibiotics showed zone of inhibition like ampicilline

TABLE-1
ANTIMICROBIAL DATA (INHIBITION ZONES 16-25 MM) OF SOME SELECTED SYNTHESIZED COMPOUNDS

| Std. antibiotics | *B. Subtilis* | *E. coli* | *Pseudomonas* | *A. niger* |
|---|---|---|---|---|
| Ampicillin (15-25 mm) | **6a, 6b, 6h, 6i** | **6a-6l, 7d, 7i** | **6a, 6g, 7b, 7d** | **6c** |
| Chloramphenicol (15-28 mm) | **7d, 7i, 7l** | **7c, 7k** | **7l** | **7d, 7e, 7f** |
| Penicillin (18-23 mm) | – | – | – | – |
| Greseofulvin (15-20 mm) | – | – | – | – |




**Scheme-I**

15-26 mm, chloramphenicol 15-18 mm, penicillin 18-23 mm against bacterial strains. It can be concluded from the Table-1 that compounds **6a**, **6b**, **6h**, **6i** and **7d**, **7i**, **7l** were highly active against *Bacillus subtilis*. Where, **6a**, **6g**, **7b**, **7d**, **7l** were found active against *Pseudomonas*. In the case of *Escherichia coli*, all the compounds **6a** to **6l** and **7d**, **7i**, **7c**, **7k** showed maximum activity. Compound **6c** and **7d**, **7e** and **7f** showed highest activity against *Aspergillum niger*. The other compounds showed[5-7] either moderate or less activity against these organisms.

## RESULTS AND DISCUSSION

The chemical synthesis initiate with the reaction of *o*-phenylene diamine **1** and oxalic acid were mixed in 4N HCl with ethanol to yield 2,3-diketoquinoxaline **2**, which on treatment with phosphorus pentachloride yielded 2-chloro-3-methyl quinoxaline (**3**). The chloro compound and hydrazine hydrate were refluxed in ethanol for 3 h to yield 2-hydrazino 3-hydroxy quinoxaline (**4**). A mixture of compound **4** and different aromatic aldehydes in methanol refluxed to give 3-hydroxy-2-(arylidene hydrazine) quinoxaline **5a-1**. The compounds **5a-1** was refluxed with thioglycolic acid to yield 2-aryl-3-(3'-hydroxy quinoxalin-2'-yl-amino)-4-thiazolidinone **6a-1**. The compounds **7a-1** was synthesized by reacting compounds **5a-1** with chloro acetyl chloride in presence of triethylamine (**Scheme-I**). The structure of all the newly quinoxaline derivatives were confirmed on the basis of their spectral and analytical data. The IR spectrum of compound **4** showed a sharp doublet at 3286 and 3188 $cm^{-1}$ due to the NH stretch of $NH_2$. On condensation with carbonyl compounds, these bands disappear and a band at 3298 $cm^{-1}$ is observed due to NH stretch 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 δ 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 field at δ 9.12 as a result of de shielding effect of CH=N- group. The proton of azomethane group lead to a sharp singlet at δ 8.4. The multiplet signals at δ 6.9-8.4 are the characteristics of the aromatic protons. A sharp signal appears at δ 3.93, the characteristics of the protons of $-OCH_3$. In case of 2-*p*-anisyl-3-(3'-hydroxyquinoxalin-2'-yl-amino)-4-thiazolidinone gave a sharp signal at δ 3.69 the characteristics of the proton of $-CH_2$ group of 4-thiazolidinone ring. The NMR spectrum of 1-N-(3'-hydroxyquinoxalin-2'-yl-amino)-4-mehoxybenzylidine-3-chloro-2-azetidinone gave two doublets at δ 4.67 and δ 3.75 due to the two hydrogen atoms on $C_3$ and $C_4$ carbon atom, respectively.

## ACKNOWLEDGEMENTS

The authors thanks to the University of Pune for providing the analytical facilities.

## REFERENCES

1. M.B. Deshmukh and A.R. Mali, *Indian J. Chem*., **46B**, 1211 (2007).
2. D.A. Vyas, A.A. Chauhan and A.R. Parikh, *Indian J. Chem*., **46B**, 1699 (2007).
3. G.W.H. Cheeseman and E.S.G. Werstiuk, *Adv. Heterocycl. Chem*., **22**, 367 (1978).
4. V.S. Ingle, A.R. Sawale, R.D. Ingle and R.A. Mane, *Indian J. Chem*., **40B**, 124 (2000).
5. D. Pandya and K.B. Nair, *Pharmazie*, **48**, 414 (1993).
6. R.M. Alington, *J. Med. Chem*., **44**, 1491 (2001).
7. K. Ladva, U. Dave and A. Parekh, *J. Indian Chem. Soc*., **68**, 379 (1991).