ISSN: 2249 –4820

Chemistry & Biology Interface, 2011, 1, 2, 228-241

Chemistry & Biology Interface

An official Journal of ISCB, Journal homepage; www.cbijournal.com

Research Article

Synthesis & Biological Evaluation of 2-Amino-3-chloroquinoxaline based Azetidinones & Thiazolidinones as Antibacterial & Antifungal Agents

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Received 26August 2011; Accepted 9 September 2011

Keywords: Quinoxaline, Azetidinone, Thiazolidinone, Antibacterial, Antifungal Agents

Abstract: Twenty compounds belonging to compound series 3-chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(substituted)phenylazetidin-2-one V(a-j) & 3-(3-chloroquinoxalin-2-ylamino)-2-(substituted)phenylthiazolidin-4-one VI (a-j) were synthesized and evaluated for their *in-vitro* antibacterial activity against *E. coli*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae* and *in-vitro* antifungal activity against *C. albicans* & *A. niger*. Structures of all the newly synthesized compounds were confirmed by elemental analysis, ^{1}H-NMR & FT-IR spectral data interpretation. Compounds with electron-withdrawing groups *viz.* Cl, F, CF_3, NO_2, at *ortho*- & *para*-positions on the phenyl ring attached to C-4 & C-2 positions of azetidinone & thiazolinone rings respectively were found to be more active antibacterial & antifungal agents than 2-amino-3-chloroquinoxaline based azetidinones & thiazolidinones with electron-donating groups and unsubstituted phenyl ring at above discussed positions in azetidinone & thiazolinone rings respectively. Against fungal strains under investigation, 2-amino-3-chloroquinoxaline based thiazolidinones were found to be more active as compared to their azetidinone counterparts.

Introduction

Nitrogen containing heterocyclic compounds are indispensable structural unit for both the chemists & biochemists. Among the various classes of benzene fused six membered nitrogen containing heterocyclic compounds, quinoxaline derivatives form an important class of pharmacologically active compounds. Quinoxaline ring is a part of various antibiotics such as hinomycin, levomycin, and actinoleutin that are known to inhibit growth of Gram positive bacteria and are active against various transplantable tumors [1-7]. Quinoxaline derivatives have also been found to be associated with a wide variety of biological activities including antifungal [8-10], antibacterial [10-14], antitubercular [8,9,15-18], anti-

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ISSN: 2249 –4820
Chemistry & Biology Interface, 2011, 1, 2, 228-241

inflammatory agents [19]. Further hydrazinoquinoxalines & their cyclic analogues have been reported as antimicrobial agents [20]. Five member nitrogen & sulphur containing thiazolidinone ring attached with other heterocyclic system have also been found to be associated with wide spectrum of pharmacological activities *viz.* antibacterial [21,22,25,26], antifungal [22], anti-inflammatory [23], antitumor [24], anti-HIV [25], etc. Similarly, four-member nitrogen containing heterocyclic ring azetidinone has also been associated with compounds possessing various pharmacological activities *viz.* antibacterial [27,29,30], anti-inflammatory [27], antifungal [28,29,30], antitubercular [28] etc.

Keeping the above facts in view, it was thought worthwhile to design the synthesis of titled compounds wherein, azetidinone & thiazolidinone rings have been attached to quinoxaline at 2 position with an amino linkage. The present communication reports the multistep synthesis of 3-chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(substituted)phenylazetidin-2-one V(a-j) & 3-(3-chloroquinoxalin-2-ylamino)-2-(substituted)phenylthiazolidin-4-one VI (a-j). All the synthesized have been screened for *in vitro* antibacterial activity against gram positive bacteria *Staphylococcus aureus* (ATCC2913), gram negative bacteria *Klebsella pneumoniae* (ATCC700603), *Pseudomonas aeruginosa* (ATCC27853), *Escherichia coli* (ATCC25922) & antifungal activity against *Candida albicans* (MTCC3017) & *Aspergillus niger* (MTCC281) by using cup-plate method.

Experimental

General

Melting points were determined in open capillary tubes in a Hicon melting point apparatus and are uncorrected. The homogen elemental analyses (C, H, N) of all compounds were performed on the CHNS Elimentar (Analysen systime, GmbH) Germany Vario EL III. All the Fourier-Transform Infra Red (FT-IR) spectra were recorded in KBr pellets on a Jasco FT-IR 410 spectrometer. The ^{1}H- NMR spectra were recorded on Bruker-Spectrospin DCX (300MHz) NMR spectrometer. Chemical shifts (δ) are expressed in ppm relative to tetramethylsilane (TMS) as an internal standard. The purity of the compounds was checked by thin layer chromatography (TLC) on Merck Silica Gel $60F_{254}$ precoated sheets. Iodine chamber and UV lamp were used for the visualization of TLC spots.

Synthesis of Titled Compounds

(1H,4H) Quinoxaline-2,3-dione (I): *o*-Phenylenediamine (0.1 mol) & oxalic acid (0.15 mol) were added to 20% HCl (200 ml) & refluxed for about 3 hours. White crystalline solid was separated by filtration. TLC was monitored by Toluene : Ethylacetate : Formic acid (5:4:1, TEF). Product was washed with methanol & Chloroform & finally recrystallized with dimethylformamide (DMF). White crystalline solid, yield 75%, $R_{f\ (TEF)}$ 0.80, m.p. >320^{0}C; FT-IR (KBr, cm^{-1}) : 854 (aromatic C=C, bend), 1387 (=C-N, str.), 1499 (aromatic C=C, str.), 1535 (-NH, bend), 1688 (>C=O, str.), 3304 (N-H, str.); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 7.042-7.125 (m, 4H, quinoxaline ring protons, J = 1.8-5.7 Hz, *ortho* & *meta*-coupling), 11.902 (s, 2H, N**H**CO)

2,3-Dichloroquinoxaline (II): Compound I (0.12 mol) was added to cold $POCl_3$ (120 ml) in small portions to get a slurry. 5 ml (0.04 mol) of N,N-dimethylaniline (DMA) was added to this slurry. Reaction mixture was refluxed till the appearance of brownish color (it may take nearly 4 hours). Reaction

ISSN: 2249 –4820
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mixture was cooled & poured into 1500 ml of ice-chilled water. White creamy solid was filtered, air dried & recrystallized with DMF. White needle like crystals, yield 70%, $R_{f\,(TEF)}$ 0.85, m.p. 142^{0}C; FT-IR (KBr, cm^{-1}): 769 (*ortho*-disubstituted ring, str.), 964 (aromatic =C-H, bend), 1121 (C-Cl, str.), 1171 (C-N, str.), 1393 (=C-N, str.), 1533 (aromatic C=C, str.), 1688 (C=N, str.); ^{1}H-NMR ($CDCl_3$, 300 MHz, δ / ppm) : 7.782-7.807 (q, 2H, A_2B_2 pattern, quinoxaline ring protons, J = 3.6 Hz, *meta*-coupling), 7.995-8.019 (q, 2H, A_2B_2 pattern, quinoxaline ring protons, J = 3.2 Hz, *meta*- coupling)

2-Chloro-3-hydrazinylquinoxaline (III): A mixture of compound II (0.05 mol), hydrazine hydrate (0.06 mol) in ethanol (100 ml), was refluxed for 4 hours. Mixture was kept overnight in deep freezer. Product was filtered, air dried & recrystallized with DMF. Red solid, yield 80%, $R_{f\,(Benzene\,:\,Acetone\,=\,7\,:\,3)}$ 0.78, m.p. 220^{0}C; FT-IR (KBr, cm^{-1}) : 971, 1129, 1199, 1374, 1510, 1582 (-NH, bend), 1663, 2942 (-NH of –$NHNH_2$, str.), 3134 (-NH of –$NHNH_2$, str.); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.711-8.742 (q, 2H, A_2B_2 pattern, quinoxaline ring protons, J = 3.6 Hz), 8.018-8.049 (q, 2H, A_2B_2 pattern, quinoxaline ring protons, J = 2.4-3.6 Hz), 7.465-7.582 (br, d, 1H, $NHNH_2$); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm, D_2O Exchange) : 8.645-8.685 (q, 2H, quinoxaline ring protons, J = 2.4-3.6 Hz), 7.894-7.924 (m, 2H, quinoxaline ring protons, J = 2.4-3.3 Hz), 7.32 (br, s, 2H, N**H**N**H**D/ $NDNH_2$)

(E)-2-{2-(substituted)benzylidenehydrazinyl}-3-chloroquinoxaline IV(a-j): Compound III (0.005 mol) & aromatic aldehydes (0.005 mol) in methanol (30 ml) & glacial acetic acid (3 ml) were refluxed for 3-4 hours. Mixtures were kept overnight. Products were filtered & washed with methanol (15 ml), air dried & recrystallized with DMF.

(E)-2-(2-Benzylidenehydrazinyl)-3-chloroquinoxaline (IVa): Light red solid, yield 58%, $R_{f\,(Benzene\,:\,Acetone\,=\,9\,:\,1)}$ 0.82, $R_{f\,(ethylacetate\,:\,hexane\,=\,1\,:\,1)}$ 0.81, m.p. 182^{0}C; FT-IR (KBr, cm^{-1}) : 721 (*mono*-substituted aromatic ring, str.), 971, 1121, 1199, 1402, 1509, 1581, 1650 (CH=N, str.), 3381 (aromatic 2^0 –NH, str.); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.718-8.748 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 3.0-3.3 Hz), 8.012-8.048 (m, 5H, Ar-H, J = 3.3-3.6 Hz), 7.724 (s, 1H, N**H**-N), 7.458-7.481 (d, 1H, -C**H**=N, J = 6.9 Hz, strong *allylic* coupling)

(E)-2-Chloro-3-{2-(2-chlorobenzylidene)hydrazinyl}quinoxaline (IVb): Light orange solid, yield 72%, $R_{f\,(ethylacetate\,:\,hexane\,=\,1\,:\,1)}$ 0.76, m.p. 182^{0}C; FT-IR (KBr, cm^{-1}) : 780 (*ortho*-di-substituted aromatic ring, str.), 971, 1086 (aryl C-Cl, str.), 1124, 1198, 1384, 1537, 1592, 1648, 3388; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 7.538-7.561 (d, 1H, Ar-H, J = 6.9 Hz, *ortho*-coupling), 7.342-7.368 (d, 1H, Ar-H, J = 7.8 Hz, *ortho*-coupling), 7.443-7.457 (t, 2H, Ar-H, J = 3.3-4.2 Hz), 9.738 (s, 1H, -N**H**-N), 7.638 (s, 1H, C**H**=N), 8.731-8.762 (m, 4H, A_2B_2 pattern, quinoxaline ring protons)

(E)-2-Chloro-3-{2-(2-fluorobenzylidene)hydrazinyl}quinoxaline (IVc): Light brown solid, yield 68%, $R_{f\,(ethylacetate\,:\,hexane\,=\,1\,:\,1)}$ 0.84, m.p. 210^{0}C; FT-IR (KBr, cm^{-1}) : 780, 1125, 1198, 1287 (aryl C-F, str.), 1384, 1509, 1581, 1660, 3318; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 7.565-7.595 (d, 1H, Ar-H, J = 9 Hz, *ortho*-coupling), 7.362-7.391 (d, 1H, Ar-H, J = 8.7 Hz, *ortho*-coupling), 7.412-7.442 (t, 2H, Ar-H, J=3.3-4.2 Hz), 9.112 (s, 1H, -N**H**-N), 8.665 (s, 1H, C**H**=N), 8.532-8.563 (q, 4H,

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A_2B_2 pattern, quinoxaline ring protons, J = 3.0-3.3 Hz)

(E)-2-Chloro-3-{2-(2-nitrobenzylidene)hydrazinyl}quinoxaline (IVd): Light brown solid, yield 78%, R_f (ethylacetate : hexane = 1 : 1) 0.85, m.p. 223^{0}C; FT-IR (KBr, cm^{-1}) : 738, 780, 1122, 1198, 1325 (N-O, *sym*. str), 1384, 1480 (N-O, *asym*. str.), 1509, 1581, 1660, 3410

(E)-2-Chloro-3-{2-(4-chlorobenzylidene)hydrazinyl}quinoxaline (IVe): Red solid, yield 83%, R_f (ethylacetate : hexane = 8 : 2) 0.73, m.p. 228^{0}C; FT-IR (KBr, cm^{-1}) : 823 (*para*-disubstituted aromatic ring, str.), 971, 1129 (aryl C-Cl), 1172, 1388, 1500, 1592, 1666, 3240; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.713-8.745 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.6 Hz, *meta*-coupling), 8.012-8.044 (q, 4H, A_2B_2 pattern, Ar-H, J = 3.3 Hz), 8.463 (s, 1H, N**H**-N), 7.534-7.560 (d, 1H, N=C**H**, J = 7.8 Hz, strong allylic coupling)

(E)-2-Chloro-3-{2-(4-fluorobenzylidene)hydrazinyl}quinoxaline (IVf): Red solid, yield 77%, R_f (ethylacetate : hexane = 7 : 3) 0.76, m.p. 243^{0}C; FT-IR (KBr, cm^{-1}) : 867, 1126, 1287 (aryl C-F, str.), 1199, 1384, 1509, 1581, 1660, 3321; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.721-8.753 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.6 Hz, *meta*-coupling), 8.018-8.050 (q, 4H, A_2B_2 pattern, Ar-H, J = 3.3 Hz), 8.428 (1H, s, N**H**-N), 7.640-7.666 (d, 1H, N=C**H**, J = 7.8 Hz, strong *allylic* coupling)

(E)-2-Chloro-3-{2-(4-(trifluoromethyl)benzylidene}hydrazinyl) quinoxaline (IVg): Red solid, yield 67%, R_f (ethylacetate : hexane = 7 : 3) 0.66, m.p. 253^{0}C; FT-IR (KBr, cm^{-1}) : 780, 869, 1121, 1198, 1288 (C-F, str.),1387, 1509, 1581, 1661, 3401; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm): 8.720-8.752 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.6 Hz, *meta*-coupling), 8.014-8.046 (q, 4H, A_2B_2 pattern, Ar-H, J = 3.3 Hz), 8.421 (s, 1H, s, N**H**-N), 7.430-7.456 (d, 1H, N=C**H**, J = 7.8 Hz, strong *allylic* coupling)

(E)-4-{2-(3-Chloroquinoxalin-2-yl)hydrazono)methyl}phenol (IVh): Deep red solid, yield 73%, m.p. 276^{0}C; FT-IR (KBr, cm^{-1}) : 971, 1123, 1199, 1288 (C-O, str., coupled with H-C-H), 1326, 1510, 1582, 1666, 3682 (phenolic –OH, str.); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.721-8.753 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 3.0-3.3 Hz, *meta*-coupling), 8.013-8.055 (q, 4H, A_2B_2 pattern, Ar-H, J = 3.3 Hz), 8.465 (s, 1H, N**H**-N), 7.583 (s, 1H, N=C**H**, J = 8.1 Hz), 2.482 (s, 1H, -O**H**)

(E)-2-Chloro-3-{2-(4-nitrobenzylidene)hydrazinyl}quinoxaline (IVi): Red orange solid, yield 68%, R_f (ethylacetate : hexane = 7 : 3) 0.77, m.p. 243^{0}C; FT-IR (KBr, cm^{-1}) : 982, 1124, 1197, 1206, 1369 (aromatic –NO_2, *sym*. str.), 1517, 1551 (aromatic –NO_2, *asym*. str.), 1572, 1634, 3271; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.755-8.786 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.3 Hz), 8.043-8.074 (q, 4H, A_2B_2 pattern, Ar-H, J = 2.7-3.6 Hz), 7.453 (s, 1H, N=C**H**), 8.338 (s, 1H, N**H**-N)

(E)-2-Chloro-3-{2-(4-methoxybenzylidene)hydrazinyl}quinoxaline (IVj): Orange solid, yield 80%, R_f (ethylacetate : hexane = 7 : 3) 0.81, m.p. 212^{0}C; FT-IR (KBr, cm^{-1}) : 825 (*para*-disubstituted aromatic ring, str.), 1040 (C-O-C, *sym.* str.), 1121, 1129 (aromatic C-O, str.), 1197, 1240 (C-O-C, *asym*., str.), 1380, 1393, 1631, 3345; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.452-8.486 (m, 4H, quinoxaline ring

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protons), 8.053-8.061 (d, 4H, Ar-H, J = 2.4 Hz), 3.358 (s, 3H, OCH_3), 8.521 (s, 1H, N**H**-N), 7.740-7.767 (d, 1H, C**H**=N, J = 8.1 Hz, strong allylic coupling)

3-Chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(substituted)phenylazetidin-2-one V(a-j) : To a solution of compound (IVa-j) (0.0012 mol), in dry benzene (30 ml) was added to a well stirred mixture of triethylamine (0.0015 mol) & chloroacetylchloride (0.0015 mol), at low temperature (below 5^0C). The resulting solids were filtered & recrystallized with chloroform-methanol mixture (1:1).

3-Chloro-1-(3-chloroquinoxalin-2-ylamino)-4-phenylazetidin-2-one (Va): Brick red crystals, yield 70%, R_f (ethylacetate : hexane = 6 : 4) 0.72, m.p. 178^0C; FT-IR (KBr, cm^{-1}) : 971, 1124, 1198, 1288 (CH-Cl, str.), 1380, 1407, 1581, 1666 (-NCO, str.), 2345; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.721-8.752 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.3 Hz), 8.014-8.045 (m, 5H, Ar-H, J = 3.3 Hz), 3.342 (s, 1H, NH), 3.177 (s, 1H, C**H**-Cl), 3.791 (s, 1H, C**H**-Ar)

3-Chloro-4-(2-chlorophenyl)-1-(3-chloroquinoxalin-2-ylamino)azetidin-2-one (Vb): Red crystals, yield 50%, R_f (benzene : acetone = 9 : 1) 0.78, m.p. 214^0C; FT-IR (KBr, cm^{-1}) : 971, 1037 (aryl C-Cl, str.), 1129, 1198, 1287, 1509, 1581, 1664, 2344; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 7.640-7.664 (d, 2H, quinoxaline ring protons, J = 7.2 Hz, *ortho*-coupling), 7.418-7.469 (t, 2H, quinoxaline ring protons, J = 7.2-8.1 Hz, *ortho*-coupling), 7.201-7.253 (t, 4H, Ar-H, J = 7.2-7.8 Hz), 3.328 (s, 1H, NH), 2.736 (s, 1H, C**H**-Cl), 4.138 (s, 1H, C**H**-Ar)

3-Chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(2-fluorophenyl)azetidin-2-one (Vc): Light red solid, yield 63%, R_f (benzene : acetone = 9 : 1) 0.81, m.p. 217^0C; FT-IR (KBr, cm^{-1}) : 971, 1038 (aryl C-Cl, str.), 1129, 1197, 1286 (aryl C-F, str.), 1502, 1586, 1664, 2346, 3342; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.765-8.793 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.3 Hz), 8.224-8.257 (q, 4H, Ar-H, J = 3.3 Hz), 3.351 (s, 1H, NH), 2.741 (s, 1H, C**H**-Cl), 4.298 (s, 1H, C**H**-Ar)

3-Chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(2-nitrophenyl)azetidin-2-one (Vd): Light red solid, yield 65%; R_f (benzene : acetone = 9:1) 0.79, m.p. 211°C; FT-IR (KBr, cm^{-1}) :969, 1030, 1123, 1189, 1329 (N-O, *sym*. str), 1481 (N-O, *asym*. str.), 1512, 1579, 1668, 2351, 3446

3-Chloro-4-(4-chlorophenyl)-1-(3-chloroquinoxalin-2-ylamino)azetidin-2-one (Ve): Orange crystals, yield 69%, R_f (benzene : acetone = 9 : 1) 0.77, m.p. 267°C; FT-IR (KBr, cm^{-1}) : 973, 1082 (aryl C-Cl, str.), 1123, 1192, 1285, 1399, 1579, 1662, 2333, 3372; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.633-8.664 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.3 Hz), 8.132-8.163 (q, 4H, A_2B_2 pattern, Ar-H, J = 2.7-3.3 Hz), 3.338 (s, 1H, NH), 3.128 (s, 1H, C**H**-Cl), 3.266 (s, 1H, C**H**-Ar)

3-Chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(4-fluorophenyl)azetidin-2-one (Vf): Dark brown crystals, yield 68%, R_f (benzene : acetone = 9 : 1) 0.87, m.p. 198°C; FT-IR (KBr, cm^{-1}) : 829, 1131, 1190, 1284 (aryl C-F, str.), 1510, 1584, 1664, 1740, 2345, 3364; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.768-8.799 (m, 4H, quinoxaline ring protons, J = 2.7-3.3 Hz), 8.023-8.054 (q, 4H, A_2B_2 pattern, Ar-H, J = 3.3 Hz), 3.264 (s, 1H, NH), 3.079 (s, 1H, C**H**-Cl), 3.381 (s, 1H, C**H**-Ar)

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3-Chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(4-(trifluoromethyl)phenyl)azetidin-2-one (Vg): Brown solid, yield 77%, R_f (benzene : acetone = 9 : 1) 0.86, m.p. 245°C; FT-IR (KBr, cm^{-1}) : 832, 1124, 1194, 1284, 1514, 1577, 1667, 1739, 2344, 3341; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.745-8.777 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.6 Hz), 8.146-8.177 (q, 4H, A_2B_2 pattern, Ar-H, J = 3.3 Hz), 3.249 (s, 1H, NH), 3.062 (s, 1H, C**H**-Cl), 3.388 (s, 1H, C**H**-Ar)

3-Chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(4-hydroxyphenyl)azetidin-2-one (Vh): Red solid, yield 64%; R_f (benzene : acetone = 8 : 2) 0.74, m.p. 241°C; FT-IR (KBr, cm^{-1}) : 829, 972, 1120, 1199, 1287 (C-O, str.), 1390, 1519, 1581, 1666, 2346, 3354, 3564; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.749-8.781 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.4-3.3 Hz), 8.032-8.063 (q, 4H, A_2B_2 pattern, Ar-H, J = 2.7-3.3 Hz), 3.241 (s, 1H, NH), 3.065 (s, 1H, -OH), 3.087 (s, 1H, C**H**-Ar), 2.956 (s, 1H, C**H**-Cl)

3-Chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(4-nitrophenyl)azetidin-2-one (Vi): Light yellow solid, yield 58%; $R_{f\ (TEF)}$ 0.49, m.p. 258°C; FT-IR (KBr, cm^{-1}) : 828, 969, 1119, 1199, 1286, 1327 (aromatic –NO_2, str.), 1509, 1564 (aromatic –NO_2, str.), 1669, 2328, 3355; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.739-8.784 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.9 Hz), 8.052-8.084 (q, 4H, A_2B_2 pattern, Ar-H, J = 2.7-3.6 Hz), 3.242 (s, 1H, NH), 3.087 (s, 1H, C**H**-Cl), 3.340 (s, 1H, C**H**-Ar)

3-Chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(4-methoxyphenyl)azetidin-2-one (Vj): Grey solid, yield 79%; R_f (benzene : acetone = 6 : 4) 0.70, m.p. 187°C; FT-IR (KBr, cm^{-1}) : 829, 964, 1091 (*sym*. C-O-C, str.), 1120, 1129 (aromatic C-O, str.), 1199, 1225 (*asym*. C-O-C, str.), 1284, 1509, 1584, 1666, 2340, 3383; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.751-8.783 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 3.0-3.3 Hz), 8.021-8.053 (q, 4H, A_2B_2 pattern, Ar-H, J = 3.3-3.6 Hz), 3.258 (s, 1H, NH), 3.087 (s, 1H, C**H**-Cl), 3.188 (s, 1H, C**H**-Ar), 2.548 (s, 3H, OCH_3)

3-(3-Chloroquinoxalin-2-ylamino)-2-(substituted)phenylthiazolidin-4-one VI (a-j) : Compound IV(a-j) (200 mg) was added to 8 ml of thioglycollic acid & refluxed at oil-bath for 30 hours. Then excess thioglycollic acid was removed by vacuum distillation. Then resulting mass was treated with 20 ml of 10% sodium bicarbonate & product was isolated. Products were recrystallized with Chloroform/methanol (1:1) mixture.

3-(3-Chloroquinoxalin-2-ylamino)-2-phenylthiazolidin-4-one (VIa): Brown solid, yield 45%, $R_{f\ (TEF)}$ 0.82, m.p. 188°C; FT-IR (KBr, cm^{-1}): 740 (*mono*-substituted aromatic ring, str.), 799 (C-S, str.), 969, 1119, 1194, 1202, 1399, 1509, 1582, 1649, 1759, 3393; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 7.216-7.270 (t, 5H, Ar-H, J = 7.2-8.1 Hz), 7.652-7.674 (d, 2H, quinoxaline ring protons, J = 6.6 Hz), 7.421-7.472 (t, 2H, quinoxaline ring protons, J = 7.8-8.1 Hz), 2.525 (s, 2H, CH_2), 3.426 (s, 1H, NH), 2.475-2.504 (d, 1H, CH-Ar, J = 8.7 Hz, strong allylic coupling)

2-(2-Chlorophenyl)-3-(3-chloroquinoxalin-2-ylamino)thiazolidin-4-one (VIb): Brown solid, yield 61%, $R_{f\ (TEF)}$ 0.82, m.p. 228°C; FT-IR (KBr, cm^{-1}): 779, 799, 954, 1109 (aryl C-Cl, str.), 1172, 1514, 1574, 1711, 1727, 3394; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 7.255 (t, 4H, Ar-H, J = 7.8 Hz), 7.687-7.713 (d, 2H, quinoxaline ring protons, J = 7.8 Hz), 7.423-7.473 (t, 2H, quinoxaline ring protons, J = 7.8-8.1 Hz),

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3.433 (s, 1H, NH), 2.556 (s, 2H, CH_2), 2.486-2.492 (d, 1H, CH-Ar, J = 1.8 Hz)

3-(3-Chloroquinoxalin-2-ylamino)-2-(2-fluorophenyl)thiazolidin-4-one (VIc): Brown solid, yield 59%, $R_{f\ (TEF)}$ 0.80, m.p. 252°C; FT-IR (KBr, cm^{-1}): 778, 799, 964, 1109, 1168, 1284 (aryl C-F, str.), 1509, 1649, 1727, 3374; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 7.337 (t, 4H, Ar-H, J = 7.8 Hz), 7.685-7.710 (d, 2H, quinoxaline ring protons, J = 7.8 Hz), 7.422-7.473 (t, 2H, quinoxaline ring protons, J = 7.8-8.1 Hz), 3.455 (s, 1H, NH), 2.485 (s, 2H, CH_2), 2.792-2.797 (d, 1H, CH-Ar, J = 1.5 Hz)

3-(3-Chloroquinoxalin-2-ylamino)-2-(2-nitrophenyl)thiazolidin-4-one (VId): Brown solid, yield 63%, $R_{f\ (TEF)}$ 0.85, m.p. 261°C; FT-IR (KBr, cm^{-1}): 779, 796, 966, 1121, 1170, 1326, 1499**,** 1510, 1652, 1714, 3408; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 7.249 (t, 4H, Ar-H, J = 7.8 Hz), 7.680-7.706 (d, 2H, quinoxaline ring protons, J = 7.8 Hz), 7.435-7.486 (t, 2H, quinoxaline ring protons, J = 7.8-8.1 Hz), 3.448 (s, 1H, NH), 2.458 (s, 2H, CH_2), 2.690-2.694 (d, 1H, CH-Ar, J = 1.2 Hz)

2-(4-Chlorophenyl)-3-(3-chloroquinoxalin-2-ylamino)thiazolidin-4-one (VIe): Brown solid, yield 74%, $R_{f\ (TEF)}$ 0.85, m.p. 213°C; FT-IR (KBr, cm^{-1}): 795 (C-S, str.), 837, 963, 1041 (aryl C-Cl, str.), 1192, 1512, 1586, 1664, 1729, 3345; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.759-8.791 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.6 Hz), 8.130-8.161 (q, 4H, A_2B_2 pattern, Ar-H, J = 2.7-3.3 Hz), 3.352 (s, 1H, NH), 2.487 (s, 2H, CH_2), 2.610 (s, 1H, CH-Ar)

3-(3-Chloroquinoxalin-2-ylamino)-2-(4-fluorophenyl)thiazolidin-4-one (VIf): Brown solid, yield 66%, $R_{f\ (TEF)}$ 0.79, m.p. 232°C; FT-IR (KBr, cm^{-1}): 799 (C-S, str.), 839, 969, 1284 (aryl C-F, str.), 1515, 1588, 1665, 1730, 3354; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.750-8.782 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.6 Hz), 8.143-8.174 (q, 4H, A_2B_2 pattern, Ar-H, J = 2.7-3.3 Hz), 3.356 (s, 1H, NH), 2.481 (s, 2H, CH_2), 2.589 (s, 1H, CH-Ar)

3-(3-Chloroquinoxalin-2-ylamino)-2-(4-(trifluoromethyl)phenyl)thiazolidin-4-one (VIg): Brown solid, yield 56%, $R_{f\ (TEF)}$ 0.84, m.p. 231°C; FT-IR (KBr, cm^{-1}) : 794 (C-S, str.), 836, 968, 1109, 1199, 1287 (aryl C-F, str.), 1519, 1587, 1652, 1739, 3321; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.740-8.762 (q, 4H, A_2B_2 pattern, quinoxaline ring protons, J = 2.7-3.6 Hz), 8.130-8.161 (q, 4H, A_2B_2 pattern, Ar-H, J = 2.7-3.3 Hz), 3.358 (s, 1H, NH), 2.495 (s, 2H, CH_2), 2.622 (s, 1H, CH-Ar)

3-(3-Chloroquinoxalin-2-ylamino)-2-(4-hydroxyphenyl)thiazolidin-4-one (VIh): Light brown solid, yield 58%, $R_{f\ (TEF)}$ 0.82, m.p. 210°C; FT-IR (KBr, cm^{-1}): 794, 819, 1097, 1178, 1259 (C-O, str.), 1515, 1572, 1675, 1714, 3339, 3358 (phenolic –OH, str.); ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.650-8.688 (m, 4H, quinoxaline ring protons), 8.057-8.094 (m, 4H, Ar-H), 3.335 (s, 1H, NH), 3.240 (s, 1H, OH), 2.348 (s, 2H, CH_2), 3.285 (s, 1H, CH-Ar)

3-(3-Chloroquinoxalin-2-ylamino)-2-(4-nitrophenyl)thiazolidin-4-one (VIi): Brown solid, yield 75%, $R_{f\ (TEF)}$ 0.86, m.p. 235°C; FT-IR (KBr, cm^{-1}): 793, 823, 934, 1173, 1340 (*sym*. aromatic $–NO_2$, str.), 1522, 1532 (*asym*. aromatic $–NO_2$, str.), 1669, 1730, 3255 ; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 8.670-8.710 (m, 4H, quinoxaline ring protons), 7.960-7.994 (m, 4H, Ar-H), 3.385 (s, 1H, NH), 3.265 (s, 1H, CH-Ar), 2.548 (s, 2H, CH_2)

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3-(3-Chloroquinoxalin-2-ylamino)-2-(4-methoxyphenyl)thiazolidin-4-one (VIj): Brown solid, yield 77%, $R_{f\ (TEF)}$ 0.78, m.p. 214°C; FT-IR (KBr, cm^{-1}): 799, 841, 1094 (*sym*. C-O-C, str.), 1149 (aromatic C-O, str.), 1240 (*asym*. C-O-C, str.), 1499, 1584, 1681, 1729, 3359; ^{1}H-NMR (DMSO-d_6, 300 MHz, δ / ppm) : 7.683-7.708 (d, 2H, quinoxaline ring protons, J = 7.5 Hz), 7.455 (t, 2H, quinoxaline ring protons), 7.360-7.386 (d, 4H, Ar-H, J = 7.8 Hz), 3.154 (s, 1H, NH), 2.864 (s, 1H, CH-Ar), 2.286 (s, 2H, CH_2), 2.364 (s, 3H, OCH_3)

Antibacterial and Antifungal Activities

All the synthesized have been screened for antibacterial activity against gram positive bacteria *S. aureus* (ATCC2913), gram negative bacteria *K. pneumonia* (ATCC700603), *P. aeruginosa* (ATCC27853), *E. coli* (ATCC25922) & antifungal activity against *C. albicans* (ATCC2091) & *A. niger* (MTCC281) by using cup-plate method.

The growth media (Nutrient Agar media for bacterial growth & Sabouraud Dextrose Agar media for fungal growth) were prepared & sterilized in autoclave at 15 psig for 15 minutes. These media were poured into petri-plates under standard conditions & allowed to solidify. On the surface of media, test microorganisms were inoculated with sterilized nickel loop wire. Cups were made by boring on the surface of growth media with previously sterilized borer. Four cups were made on each petri-plate. These cups were filled with different concentrations (50 µg/ml & 100 µg/ml in DMSO) of the test compounds, third with control (DMSO) & fourth one with standard drug. The plates were kept in cold for 1 hour to allow the diffusion of test compounds & then incubated at 35^0C for 48 hours (for antifungal activity) & at 37^0C for 24 hours (for antibacterial activity). The zones of inhibition formed around the cups after respective incubation were measured.

Result & Discussion

Chemistry

(1H,4H) Quinoxaline-2,3-dione **(I)** was synthesized by refluxing *ortho*-phenylenediamine & oxalic acid in 20% HCl. Compound (I) was refluxed with $POCl_3$ to yield 2,3-dichloroquinoxaline **(II)**, which on further refluxing with hydrazine hydrate in ethanol yielded 2-chloro-3-hydrazinylquinoxaline **(III)**. Compound (III) on refluxing with various aromatic aldehydes in methanol furnished respective Schiff's bases *viz.* (E)-2-{2-(substituted)benzylidenehydrazinyl}-3-chloroquinoxaline **IV(a-j)**. These schiff's bases were further cyclized to 3-chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(substituted)phenylazetidin-2-one **V(a-j)** by stirring with equimolar mixture of chloroacetylchloride and triethylamine in dry benzene at 0^0-5^0C. Schiff's bases IV (a-j) were also cyclized to 3-(3-chloroquinoxalin-2-ylamino)-2-(substituted)phenylthiazolidin-4-one **VI (a-j)** by refluxing with thioglycollic acid in oil bath. Structures of all the newly synthesized compounds were confirmed by elemental analysis, FT-IR & ^{1}H-NMR spectral data interpretation.

Formation of (1H,4H) quinoxaline-2,3-dione **I** was confirmed by ^{1}H-NMR & FT-IR spectra interpretation. FT-IR of compound I showed bands at 3304 cm^{-1}, 1688 cm^{-1}, 1535 cm^{-1} & 1387 cm^{-1} corresponding to –NH, >C=O, -NH (bend) & =C-N groups respectively, while its ^{1}H-NMR spectra showed a multiplet peak at δ7.042-7.125 ppm corresponding to quinoxaline ring protons & broad singlet peak at δ11.902

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ppm confirming the two protons of –NHCO group. FT-IR spectra of compound **II** showed bands at 1121 cm^{-1}, 1171 cm^{-1}, & 1688 cm^{-1}confirming C-Cl, C-N, C=N respectively & ^{1}H-NMR of this compound showed two quartlet peaks. One quartlet peak with A_2B_2 pattern was present at δ7.995-8.019 ppm for two quinoxaline ring protons close to nitrogen vicinity & another quartlet peak with A_2B_2 pattern was present at δ7.782-7.807 ppm corresponding to other two protons of quinoxaline ring. FT-IR spectrum of compound **III** showed three extra bands at 1582 cm^{-1}, 2942 cm^{-1} & 3134 cm^{-1} belonging to –NH (bend), -NH (of –$NHNH_2$, str.) & -NH_2 (of –$NHNH_2$, str.) respectively. In this spectrum, band at 1129 cm^{-1} confirmed presence of aryl –Cl group, confirming substitution of one –Cl group of compound II with hydrazinyl group to form compound III. ^{1}H-NMR spectrum of compound III showed a quartlet peak with A_2B_2 pattern in the region δ8.711-8.742 ppm (belonging to two protons of quinoxaline ring closer to nitrogen vicinity) & another quartlet peak also with A_2B_2 pattern in region δ8.018-8.049 ppm (belonging to another two protons of quinoxaline ring). Another broad doublet peak was appeared at δ7.465-7.582 ppm belonging to one proton of –$NHNH_2$. However this proton exhibited the characteristics of exchangeable protons since after D_2O exchange, this peak had been shifted to the region δ7.32 ppm. FT-IR spectrum of compound **IVa** showed bands at 721 cm^{-1}, 1121 cm^{-1}, 1650 cm^{-1} & 3381 cm^{-1} confirming the presence of *mono*-substituted aromatic ring, aromatic C-Cl, CH=N & aromatic 2^0 –NH_2 groups. Last two peaks confirmed the formation of Schiff base **IVa**. In ^{1}H-NMR spectrum of this compound, a quartlet peak with A_2B_2 pattern was appeared in region δ8.718-8.748 ppm (belonging to four protons of quinoxaline ring), a multiplet peak in region δ8.012-8.048 ppm (belonging to five protons of phenyl ring) with J = 3.3-3.6 Hz, suggested *meta* & *para* coupling between the aromatic protons. One singlet peak at δ7.724 ppm confirmed one proton of NH-N, while one doublet peak at δ7.458-7.481 ppm belonging to one proton of imine linkage (CH=N) with J = 6.9 Hz suggested strong allylic coupling between imine proton & phenyl proton.

Cyclization of different Schiff's bases (IVa-j) to their azetidinone derivatives (Va-j) have also been confirmed by FT-IR & ^{1}H-NMR spectral data interpretation. FT-IR spectrum of compound **Va** showed additional bands at 1288 cm^{-1} & 1666 cm^{-1} confirming CH-Cl & -NCO group of azetidinone ring. ^{1}H-NMR spectrum of this compound showed one quartlet peak with A_2B_2 pattern in region δ8.721-8.752 ppm (belonging to four protons of quinoxaline ring), one multiplet peak in region δ8.014-8.045 ppm confirmed five aromatic protons, one singlet at δ3.342 ppm confirmed one proton belonging to –NH linkage between C-2 of quinoxaline ring & N-1 of azetidinone ring, a singlet at δ3.177 ppm confirmed one proton of CH-Cl group (at C-3 of azetidinone ring) and another singlet at δ3.791 ppm confirmed one proton at C-4 of azetidinone ring having phenyl group.

Cyclization of different Schiff's bases (IVa-j) to 2-amino-3-chloroquinoxaline based thiazolidinones (VIa-j) have also been confirmed by FT-IR & ^{1}H-NMR spectral data interpretation. In FT-IR spectrum of compound **VIa**, an additional band at 799 cm^{-1} confirmed cyclic C-S bond, which is part of thiazolidinone nucleus. In, ^{1}H-NMR spectrum of this compound, a triplet peak in region δ7.216-7.270 ppm with J = 7.2-8.1 Hz confirmed five protons of phenyl ring attached to C-2 of thiazolidinone nucleus. J value of 7.2-8.1 Hz indicated towards *ortho*-coupling between these protons. In this ^{1}H-NMR spectrum, a doublet at δ7.652-7.674 ppm belonging to two protons of

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quinoxaline ring also appeared with additional triplet peak at δ7.421-7.472 ppm belonging to another two protons of quinoxaline ring. A singlet peak at δ2.525 ppm confirmed two protons at C-5 of thiazolidinone ring, another singlet peak at δ3.426 ppm confirmed one proton of amine linkage between C-2 of quinoxaline ring & N-3 of thiazoidinone ring. Another doublet at δ2.475-2.504 ppm also confirmed one proton at C-2 of thiazolidine ring. J value of 8.7 Hz suggested a strong allylic coupling between proton at C-2 & one proton of phenyl group attached to C-2 of thiazolidinone ring. Similarly other synthesized compounds were confirmed.

Antibacterial and Antifungal Activities

All the newly synthesized compounds have also been evaluated for their *in-vitro* antibacterial activity against bacterial strains *E. coli*, *S.aureus*, *P. aeruginosa*, *K. pneumonia* and *in-vitro* antifungal activity against *C. albicans* & *A. niger* using cup-plate method. Ciprofloxacin (30 µg/ml) & voriconazole (30 µg/ml) were used as standard drugs for antibacterial & antifungal activities respectively, while Nutrient Agar Medium & Sabouraud Dextrose Agar Medium were selected as growth medium for bacterial & fungal growth respectively. Observations regarding antibacterial and antifungal activities are shown in Table 1.

Structure of synthesized compounds can be divided into three different parts *viz.* 3-chloroquinoxaline, amino group attached to C-2 of quinoxaline ring & a heterocyclic ring (five membered thiazolidinone or four membered azetidinone) attached to amino group. In this present communication, we have concentrated on "the effect of various substitutions at the aromatic ring attached to neighbouring carbon of N-atom of azetidinone & thiazolidinone ring of 3-chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(substituted)phenylazetidin-2-one V(a-j) & 3-(3-chloroquinoxalin-2-ylamino)-2-(substituted)phenylthiazolidin-4-one VI (a-j) on antibacterial & antifungal activity".

Against *E. coli*, compound **(VIe)** with *para*-chlorophenyl substitution on C-2 of thiazolidinone ring exhibited maximal activity. Compounds with electron-withdrawing substitutions *viz. ortho*-nitrophenyl **(Vd)**, *para*-chlorophenyl **(Ve)**, *para*-trifluoromethylphenyl **(Vg)** & *para*-hydroxyphenyl **(Vh)** substitutions on C-4 of azetidinone ring have shown better antibacterial activity against *E. coli*, while compound with electrons donating group *para*-methoxy **(Vj)** on phenyl ring & unsubstituted phenyl ring **(Va)** attached to above said position on azetidinone ring has exhibited minimal antibacterial activity against all the bacterial strains under investigation. Same trend was followed by 2-amino-3-chloroquinoxaline based thiazolidinones for antibacterial activity against *E. coli*. Compounds with *ortho*-chloro **(VIb)**, *ortho*-fluoro **(VIc)**, *ortho*-nitro **(VId)**, *para*-chloro **(VIe)**, *para*-fluoro **(VIf)**, *para*-trifluoromethyl **(VIg)** & *para*-nitro **(VIi)** substitutions on phenyl ring attached to C-2 of thiazolidinone nucleus have shown better activity as compared to compound with *para*-methoxy **(VIj)** substitution on earlier discussed position in thiazolidinone ring. Among 2-amino-3-chloroquinoxaline based azetidinone & thiazolidines, compounds with electron withdrawing substitutions viz. *ortho*-chloro **(Vb, VIb)**, *para*-chloro **(Ve, VIe)**, *ortho*-hydroxy **(Vh, VIh)** & *para*-nitro **(VIi)** substitutions on phenyl ring attacehed to C-4 & C-2 of azetidinone & thiazolidinone ring respectively exhibited fantastic activity against *S. aureus*, while compounds with *para*-methoxyphenyl **(Vj, VIj)** group on earlier mentioned positions in azetidinone & thiazolidine rings exhibited minimal activity .

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Against, *P. aeruginosa*, 2-amino-3-chloroquinoxaline based azetidinone & thiazolidines exhibited mild to moderate activity. Among azetidinone derivatives, compounds with *para*-chloro **(Ve)** & *para*-trifluoromethyl **(Vg)** groups on phenyl ring at C-4 position in azetidinone ring were reported as most active compounds, while among thiazolidinone derivatives, compounds with *ortho*-chlorophenyl **(VIb)**, *ortho*-fluorophenyl **(VIc)**, *para*-chlorophenyl **(VIe)** & *para*-nitrophenyl **(VIi)** at C-2 position in thiazolidinone ring were found to be more active. Compound with *ortho*-chlorophenyl **(Vb)**, *ortho*-fluorophenyl **(Vc)**, *para*-chlorophenyl **(Ve, VIe)**, *para*-fluorophenyl **(Vf)**, *para*-hydroxyphenyl **(Vh, VIh)** & *para*-nitrophenyl **(Vi, VIi)** groups on earlier discussed positions on azetidinone & thiazolidinone rings exhibited strong antibacterial activity against *K. pneumoniae*. From the above discussion, it can be concluded that electron withdrawing groups placed at *ortho* & *para*-positions of phenyl ring attached to C-4 & C-2 of azetidinone & thiazolidinone rings of 2-amino-3-chloroquinoxaline based azetidinone & thiazolidines increase antibacterial activity, while unsubstituted phenyl ring & electron donating groups at the earlier mentioned positions in above discussed compound series decrease antibacterial activity against all the bacterial strains under investigation.

Newly synthesized compounds belonging to compound series 3-chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(substituted)phenylazetidin-2-one V(a-j) & 3-(3-chloroquinoxalin-2-ylamino)-2-(substituted)phenylthiazolidin-4-one VI (a-j) were also evaluated for their antifungal activity against *C. albicans* & *A. niger*. Against *C. albicans* & *A. niger*, 2-amino-3-chloroquinoxaline based thiazolidinones were found to be more active as compared to their azetidinone counterparts. 2-Amino-3-chloroquinoxaline based azetidinones with *ortho*-nitrophenyl **(Vd)** & *para*-hydroxyphenyl **(Vh)** on C-4 position exhibited maximal activity against *C. albicans*, while phenyl **(Va)** & *para*-trifluoromethylphenyl **(Vg)** on C-4 position of azetidinone ring exhibited minimal activity. 2-Amino-3-chloroquinoxaline based thiazolidinones with *ortho*-chlorophenyl **(VIb)**, *para*-chlorophenyl **(VIe)**, *para*-hydroxyphenyl **(VIh)** & *para*-nitrophenyl **(VIi)** substitutions on C-2 position were reported as most active antifungal agents against *C. albicans*.

Against *A. niger*, same trend, as in case of *C. albicans*, was followed by 3-chloro-1-(3-chloroquinoxalin-2-ylamino)-4-(substituted)phenylazetidin-2-one V(a-j) & 3-(3-chloroquinoxalin-2-ylamino)-2-(substituted)phenylthiazolidin-4-one VI (a-j). 2-Amino-3-chloroquinoxaline based azetidinones with *ortho*-nitrophenyl **(Vd)**, *para*-trifluoromethylphenyl **(Vg)**, *para*-nitrophenyl **(Vi)** on C-4 position showed fantastic activity against *A. niger*, while among 2-amino-3-chloroquinoxaline based thiazolidinones, compounds with *ortho*-fluorophenyl **(VIc)**, *para*-chlorophenyl **(VIe)**, & *para*-nitrophenyl **(VIi)** substitutions on C-2 position exhibited strong antifungal activity.

Conclusion

From the above discussion, it can be concluded that 2-amino-3-chloroquinoxaline based azetidinones & thiazolidinones with electron-withdrawing groups viz. Cl, F, CF_3, NO_2, at *ortho*- & *para*-positions on the phenyl ring attached to C-4 & C-2 positions of azetidinone & thiazolinone rings respectively are more active antibacterial & antifungal agents than 2-amino-3-chloroquinoxaline based azetidinones & thiazolidinones with electron-donating groups unsubstituted phenyl ring at above

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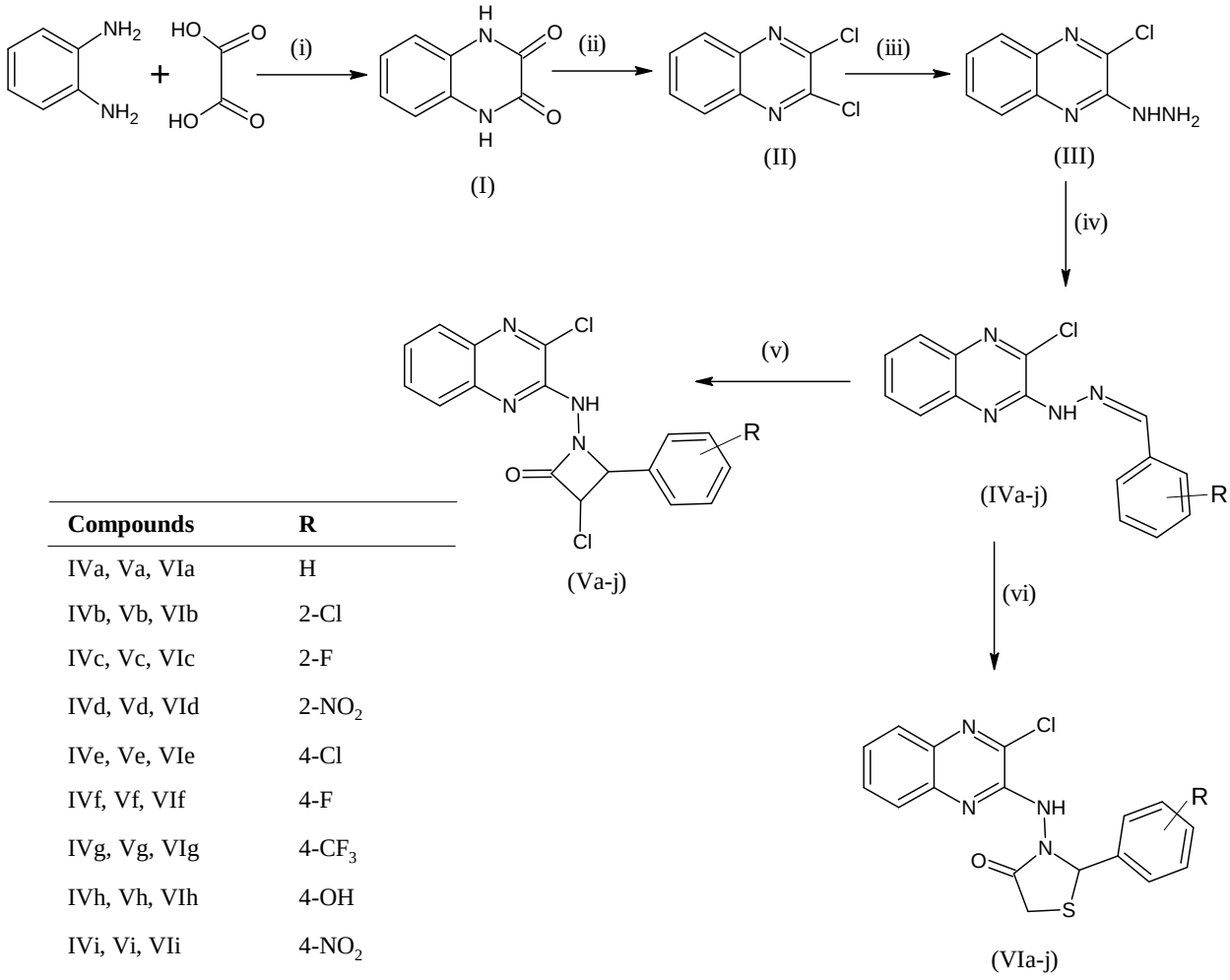
discussed positions in azetidinone & thiazolinone rings respectively. Against fungal strains under investigation, 2-amino-3-chloroquinoxaline based thiazolidinones were found to be more active as compared to their azetidinone counterparts. These compounds may act as leads for further investigations.



Compounds	R
IVa, Va, VIa	H
IVb, Vb, VIb	2-Cl
IVc, Vc, VIc	2-F
IVd, Vd, VId	2-NO_2
IVe, Ve, VIe	4-Cl
IVf, Vf, VIf	4-F
IVg, Vg, VIg	4-CF_3
IVh, Vh, VIh	4-OH
IVi, Vi, VIi	4-NO_2
IVj, Vj, VIj	4-OCH_3

Reagents & Conditions: (i) 20% HCl, Reflux, (ii) $POCl_3$, DMA, Reflux, (iii) $NH_2NH_2.H_2O$, EtOH, Reflux, (iv)R-C_6H_4-CHO, MeOH, Reflux, (v) $ClCH_2COCl$, Et_3N, dry Benzene, 0^0-5^0C, Stirring, (vi) $HSCH_2COOH$, Reflux in oil-bath

Fig 1: Reaction Scheme

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Table 1: Zone of inhibition (mm) of different compounds

Compounds	*a*		*b*		*c*		*d*		*e*		*f*	
	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
Va	9	14	11	16	6	9	7	10	7	10	6	9
Vb	12	17	14	18	7	9	9	12	10	13	9	12
Vc	12	17	10	15	6	9	9	12	9	12	10	13
Vd	13	18	10	15	6	8	7	11	10	14	10	14
Ve	15	19	14	19	7	10	9	13	9	13	7	11
Vf	11	17	11	16	6	9	9	12	8	12	7	10
Vg	12	18	10	14	6	10	7	10	7	10	11	15
Vh	13	18	13	19	6	9	9	12	10	14	9	13
Vi	11	17	12	17	7	9	9	13	10	13	11	15
Vj	9	13	10	14	4	6	6	9	10	13	7	11
VIa	10	14	12	17	5	7	7	10	9	12	7	10
VIb	13	18	14	18	8	10	8	11	11	15	8	13
VIc	12	18	10	14	7	10	6	9	10	13	10	14
VId	13	19	11	16	6	9	8	11	9	11	12	16
VIe	15	20	13	19	8	11	9	12	10	14	12	15
VIf	14	19	12	17	6	8	7	10	10	13	11	16
VIg	12	18	12	17	6	8	7	11	9	12	10	14
VIh	13	17	14	19	5	7	9	12	11	15	9	12
VIi	14	19	14	20	7	10	10	13	11	14	11	15
VIj	9	12	9	13	5	7	6	9	9	12	7	10
Standard	23		23		14		16		17		18	
Control	3		3		2		2		3		4	

a *= E. coli,* ***b*** *= S. aureus,* ***c*** *= P. aeruginosa,* ***d*** *= K. pneumoniae,* ***e*** *= C. albicans ,* ***f*** *= A. niger*

Standards:

For antibacterial activity: Ciprofloxacin 30µg/ml

For antifungal activity: Voriconazole 30µg/ml

Control: DMSO

ISSN: 2249 –4820

Chemistry & Biology Interface, 2011, 1, 2, 228-241

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