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SYNTHESIS AND MICROBIAL ACTIVITY OF NOVEL QUINOXALINE DERIVATIVES

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Abstract :
Quinoxaline-2,3(1H,4H)-dione **1** was chlorinated by using $SOCl_2$/DMF, to form 2,3-dichloroquinoxaline **2**, The dichloro compound **2** was subjected to reaction with Substituted Triazole, 1,10-diaminonaphthalene, 2-aminothiophenol, o-phenylenediamine, 1,2-diaminoethane,Sodim azide, thiocarbohydrazones and thiosemicarbazones to furnish 3'-substituted-(1',2',4') triazolo [5,6-b] [quinoxalo (2,3-e)]-1,3,4-thiadiazine **3a-c**, Quinoxalino [1,4-b]-1,4-dihydronaphto[18-ef][1,4]-diazepine **4,** 7-substituted-1,4-benzothiazino[2,3-b]-quinoxalines **5a-c,** benzopiperazino[2,3-b]-quinoxalines **6 ,** piperazino[2,3-b]-quinoxalines **7,** bis-triazo-[4,5-a/c]-quinoxalines **8,** 2-(benzylidine)-hyrazino-1,3,4-thiadiazino [5,6-b]-quinoxalines **9** and 2-(benzylidine)-imino-1,3,3-thiadiazino [5,6-b]-quinoxalines **10** respectively. Representative samples were screened for their anti-microbial activity against gram-negative bacteria, E coli and Paeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method. The structures of the products were confirmed by IR, ^1H, ^{13}C NMR and elemental analysis.

Key Words: 2,3,-dichloroquinoxaline, Thiocarbohydrazones, Thiosemicarbazones, Sodium Azide, 2-aminothiophenol, and triazole.

Introduction :

The synthesis and chemistry of quinoxalines have attracted considerable attention in the past ten years[1-2] Some of them exhibit biological activities including anti-viral[3], anti-bacterial[4], anti-inflammatory[5] anti-protozoal[6] anti-cancer[7] (colon cancer therapies)[8] anti-depressant[9] anti-HIV[6] and as kinase inhibitors[10-11] They are also used in the agricultural field as fungicides, herbicides, and insecticides[12]. Also, quinoxaline moieties are present in the structure of various antibiotics such as echinomycin, levomycin and actinoleutin, which are known to inhibit the growth of gram positive bacteria and they are active against various transplantable tumors[13]. In addition, quinoxaline derivatives have also found applications in dyes[14], efficient electron luminescent materials[15], organic semiconductors[16], chemically controllable switches[17], building blocks for the synthesis of anion receptors[18], cavitands[19] and dehydoannulenes[2]. They also serve as useful rigid subunits in macrocyclic receptors in molecular recognition[14].

Also, quinoxaline compounds are important components of several pharmacological active moieties[21]. Certain quinoxaline 2, 3-diones and quinoxaline 2-ones were highly potent NMDA receptor antagonists. Hence, due to this commendable biological activity the synthesis of some quinoxalines was reported. Also, quinoxaline based materials were used as ETLs or (Electron transporting layer) or hole blocking layers in OLEDs (organic light emitting diodes) [22-23].

Results and Discussion

The synthesis of 2, 3-dichloroquinoxaline **2** was achieved from Quinoxaline-2,3(1H,4H)-dione[24] **1** using $SOCl_2$/DMF . The titled compounds 3'-substituted-(1',2',4') triazolo [5,6-b] [quinoxalo (2,3-e)]-1,3,4-thiadiazine **3(a-c)**, Quinoxalino [1,4-b]-1,4-dihydronaphto[18-ef][1,4]-diazepine **4**, 7-substituted-1,4-benzothiazino[2,3-b]-quinoxalines **5a-c** , benzopiperazino[2,3-b]-quinoxalines **6** , piperazino[2,3-b]-quinoxalines **7**, bis-triazo-[4,5-a/c]-quinoxalines **8**, 2-(benzylidine)-hyrazino-1,3,4-thiadiazino [5,6-b]-quinoxalines **9 (a-e)** and 2-(benzylidine)-imino-1,3,3-thiadiazino [5,6-b]-quinoxalines **10 (a-e)** were achieved in good yield by reaction of 2,3-dichloroquinoxaline **2** with Substituted Triazole, 1,10-diaminonaphthalene, 2-aminothiophenol, o-phenylenediamine, 1,2-diaminoethane, sodium azide, thiocarbohydrazones and thiosemicarbazone respectively. The structures were elucidated on the basis of their spectral techniques like IR, NMR. Further, representative samples were screened for their anti-microbial activity against gram-negative bacteria, *E coli* and *Paeruginosa* and gram-positive bacteria, *S aureus*, and *C diphtheriae* using disc diffusion method, which shows promising activity against both, gram positive as well as gram-negative bacteria.

Experimental

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm).
C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Synthesis of *3'-substituted-(1',2',4') triazolo [5,6-b] [quinoxalo (2,3-e)]-1,3,4-thiadiazine*, 3(a-c)

An equimolar mixture of compound **2** (0.01 mol) and Substituted triazole (0.01 mol) in ethanol (20 ml) was refluxed in presence of pyridine (0.02 mol) for about 4-5 hr. The progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was quenched onto crushed ice. The product precipitated out was filtered, washed with water and purified by recrystallization from ethanol to give thiazoles. **3a-c**
The characterization data of the compounds **3a-c** is given in **Table I**.

***3'-methyl-(1',2',4') triazolo [5,6-b] [quinoxalo (2,3-e)]-1,3,4-thiadiazine* (3b)**

IR (KBr) cm^{-1}: 1584 (CN), 3310 (NH), **^{1}H NMR (500 MHz, DMSO-d_6, δ ppm)**: 2.48 (s, 3H, CH_3), 7.6 – 8.2 (m, 8H, ArH), 9.8 (s, 1H, NH), **^{13}C NMR (500 MHz, DMSO-d_6, ppm)**: 23.41(CH_3), 124.24-129.86 (ArC), 149.47 (C=N), 153.67 (C=N), 156.35 (C=N), 159.73 (C=N).
Anal.Calcd for $C_{11}H_8N_6S$: C,51.55;H,3.15;N,32.79%.Found: C,51.48;H,3.11,N,32.68%.

Synthesis of *Quinoxalino [1,4-b]-1,4-dihydronaphto[18-ef][1,4]-diazepine* 4
An equimolar mixture of compound **2** (0.01 mol) and 1, 10-Diaminonapthalene (0.01 mol) in ethanol (20 ml) was refluxed in presence of pyridine (0.02 mol) for about 4-5 hr. The progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was quenched onto crushed ice. The product precipitated out was filtered, washed with water and purified by recrystallization from ethanol to give **4**
The characterization data of the compounds **4** is given in **Table I**.

***Quinoxalino [1,4-b]-1,4-dihydronaphto[18-ef][1,4]-diazepine* (4)**
IR (KBr) cm^{-1}: 1574 (CN), 3302 (NH),**^{1}H NMR (500 MHz, DMSO-d_6, δ ppm)**: 6.86 – 7.67 (m, 10H, ArH), 11.92 (s, 2H, 2×NH), **^{13}C NMR (500 MHz, DMSO-d_6, ppm)**: 119.37-132.84 (ArC), 158.25 (2×C=N). Anal.Calcd for $C_{18}H_{12}N_4$: C,76.04;H,4.25;N,19.71%.Found: C,75.96;H,4.18,N,19.64%.

Synthesis of *7-substituted-1,4-benzothiazino[2,3-b]-quinoxalines* 5a-c
An equimolar mixture of compound **2** (0.01 mol) and Substituted 2- aminothiophenol (0.01 mol) in ethanol (20 ml) was refluxed in presence of pyridine (0.02 mol) for about 4-5 hr. The progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was quenched onto crushed ice. The product precipitated out was filtered, washed with water and purified by recrystallization from ethanol to give **5a-c**
The characterization data of the compounds **5a-c** is given in **Table I**.

***7-methyl-1,4-benzothiazino[2,3-b]-quinoxalines* (5b)**
IR (KBr) cm^{-1}: 1521 (CN), 3324 (NH), **^{1}H NMR (500 MHz, DMSO-d_6, δ ppm)**: 2.39 (s, 3H, CH_3), 7.21 – 8.38 (m, 7H, ArH), 9.73 (s, 1H, NH), **^{13}C NMR (500 MHz, DMSO-d_6, ppm)**: 24.36 (CH_3), 119.34-131.68 (ArC), 155.87 (C=N), 160.24 (C=N), Anal.Calcd for $C_{15}H_{11}N_3S$: C,67.90;H,4.18;N,15.84%.Found: C,67.87;H,4.12,N,15.76%.

Synthesis of *benzopiperazino[2,3-b]-quinoxalines* (6)
An equimolar mixture of compound **2** (0.01 mol) and o-phenylenediamine (0.01 mol) in ethanol (20 ml) was refluxed in presence of pyridine (0.02 mol) for about 4-5 hr. The progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was quenched onto crushed ice. The product precipitated out was filtered, washed with water and purified by recrystallization from ethanol to give **6**
The characterization data of the compounds **6** is given in **Table I**.

***benzopiperazino[2,3-b]-quinoxalines* (6)**
IR (KBr) cm^{-1}: 1516 (CN), 3285 (NH), **^{1}H NMR (500 MHz, DMSO-d_6, δ ppm)**: 7.08 – 8.13 (m, 8H, ArH), 10.54 (s, 2H, 2×NH), **^{13}C NMR (500 MHz, DMSO-d_6, ppm)**: 123.21-129.34 (ArC), 157.68 (2×C=N), Anal.Calcd for $C_{14}H_{10}N_4$: C,71.78;H,4.30;N,23.92%.Found: C,71.72;H,4.22,N,23.84%.

Synthesis of *piperazino[2,3-b]-quinoxalines* (7)
An equimolar mixture of compound **2** (0.01 mol) and 1, 2-diaminoethane (0.01 mol) in ethanol (20 ml) was refluxed in presence of pyridine (0.02 mol) for about 4-5 hr. The progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was

quenched onto crushed ice. The product precipitated out was filtered, washed with water and purified by recrystallization from ethanol to give **7**
The characterization data of the compounds **7** is given in **Table I**.

piperazino[2,3-b]-quinoxalines **(7)**
IR (KBr) cm^{-1}: 1521 (CN), 3214 (NH), **^{1}H NMR (500 MHz, DMSO-d$_6$, δ ppm)**: 3.34 (t,4H, 2×CH_3), 6.54 – 7.28 (m, 4H, ArH), 8.96 (s, 2H, 2×NH), **^{13}C NMR (500 MHz, DMSO-d$_6$, ppm)**: 41.28 (2×CH_2), 124.54-128.51 (ArC), 162.34 (2×C=N), Anal.Calcd for $C_{10}H_{10}N_4$: C,64.50;H,5.41;N,30.09%.Found: C,64.42;H,5.38,N,30.01%.

Synthesis of *bis-triazo-[4,5-a/c]-quinoxalines* **(8)**
An equimolar mixture of compound **2** (0.01 mol) and sodium-azide (0.04 mol) in glacial acetic acid (20 ml) was refluxed for about 4-5 hr. The progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was quenched onto crushed ice. The product precipitated out was filtered, washed with water and purified by recrystallization from ethanol to give **8**
The characterization data of the compounds **8** is given in **Table I**.

bis-triazo-[4,5-a/c]-quinoxalines **(8)**
IR (KBr) cm^{-1}: 1523 (CN), 3335 (NH), **^{1}H NMR (500 MHz, DMSO-d$_6$, δ ppm)**: 8.06 – 8.76 (m, 4H, ArH), **^{13}C NMR (500 MHz, DMSO-d$_6$, ppm)**: 126.14-132.16 (ArC), 159.26 (2×C=N).
Anal.Calcd for $C_8H_4N_8$: C,45.29;H,1.90;N,52.81%.Found: C,45.21;H,1.82,N,52.78%.

Synthesis of *2-(benzylidine)-hyrazino-1,3,4-thiadiazino [5,6-b]-quinoxalines* **(9a-e)**
An equimolar mixture of compound **2** (0.01 mol) and thiocarbohydrazones (0.01 mol) in ethanol (20 ml) was refluxed in presence of potassium hydroxide (0.02 mol) for about 4-5 hr. The progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was quenched onto crushed ice. The product precipitated out was filtered, washed with water and purified by recrystallization from ethanol to give **9a-e**
The characterization data of the compounds **9a-e** is given in **Table I**.

2-(4'-methoxybenzylidine)-hyrazino-1,3,4-thiadiazino [5,6-b]-quinoxalines **(9c)**
IR (KBr) cm^{-1}: 1513 (CN), 3295 (NH),**^{1}H NMR (500 MHz, DMSO-d$_6$, δ ppm)**: 3.78 (s, 3H, OCH_3), 6.82-8.24 (m, 8H, ArH), 8.54 (s, 1H, N=CH), 10.29(s, 1H, NH-N), 10.40 (s, 1H, NH),
^{13}C NMR (500 MHz, DMSO-d$_6$, ppm): 55.74 (OCH_3), 119.24-132.81 (ArC), 146.23 (C=N), 151.24 (C=N), 157.25 (C=N), 161.13 (C=N).
Anal.Calcd for $C_{17}H_{14}N_60S$: C,58.27;H,4.03;N,23.98%.Found: C,58.19;H,3.98,N,23.94%.

Synthesis of *2-(benzylidine)-imino-1,3,3-thiadiazino [5,6-b]-quinoxalines* **(10a-e)**
An equimolar mixture of compound **2** (0.01 mol) and thiosemicarbohydrazone (0.01 mol) in ethanol (20 ml) was refluxed in presence of potassium hydroxide (0.02 mol) for about 4-5 hr. The progress of reaction was monitored by TLC. Upon completion of reaction, the reaction mixture was quenched onto crushed ice. The product precipitated out was filtered, washed with water and purified by recrystallization from ethanol to give **10a-e**
The characterization data of the compounds **10a-e** is given in **Table I**.

***2-(4-methoxybenzylidine)-imino-1,3,3-thiadiazino [5,6-b]-quinoxalines* (10c)**
IR (KBr) cm^{-1}: 1535 (CN), 3258 (NH), **^{1}H NMR (500 MHz, DMSO-d_6, δ ppm)**: 3.86 (s, 3H, OCH_3), 6.74-8.48 (m, 8H, ArH), 8.63 (s, 1H, N=CH), 10.40 (s, 1H, NH), **^{13}C NMR (500 MHz, DMSO-d_6, ppm)**: 55.85 (OCH_3), 121.24-131.92 (ArC), 147.84 (C=N), 150.36 (C=N), 156.36 (C=N), 159.29 (C=N), Anal.Calcd for $C_{17}H_{13}N_50S$: C,60.88;H,3.91;N,20.88%.Found: C,60.81;H,3.84,N,20.79%.

Antimicrobial and antifungal activities
All the newly synthesized compounds were evaluated for their antibacterial activity against gram-negative bacteria, E coli and P aeruginosa and gram-positive bacteria, S aureus, and C diphtheriae using disc diffusion method[25-26]. The zone of inhibition was measured in mm and the activity was compared with standard drug. The data is given in **Table II**.

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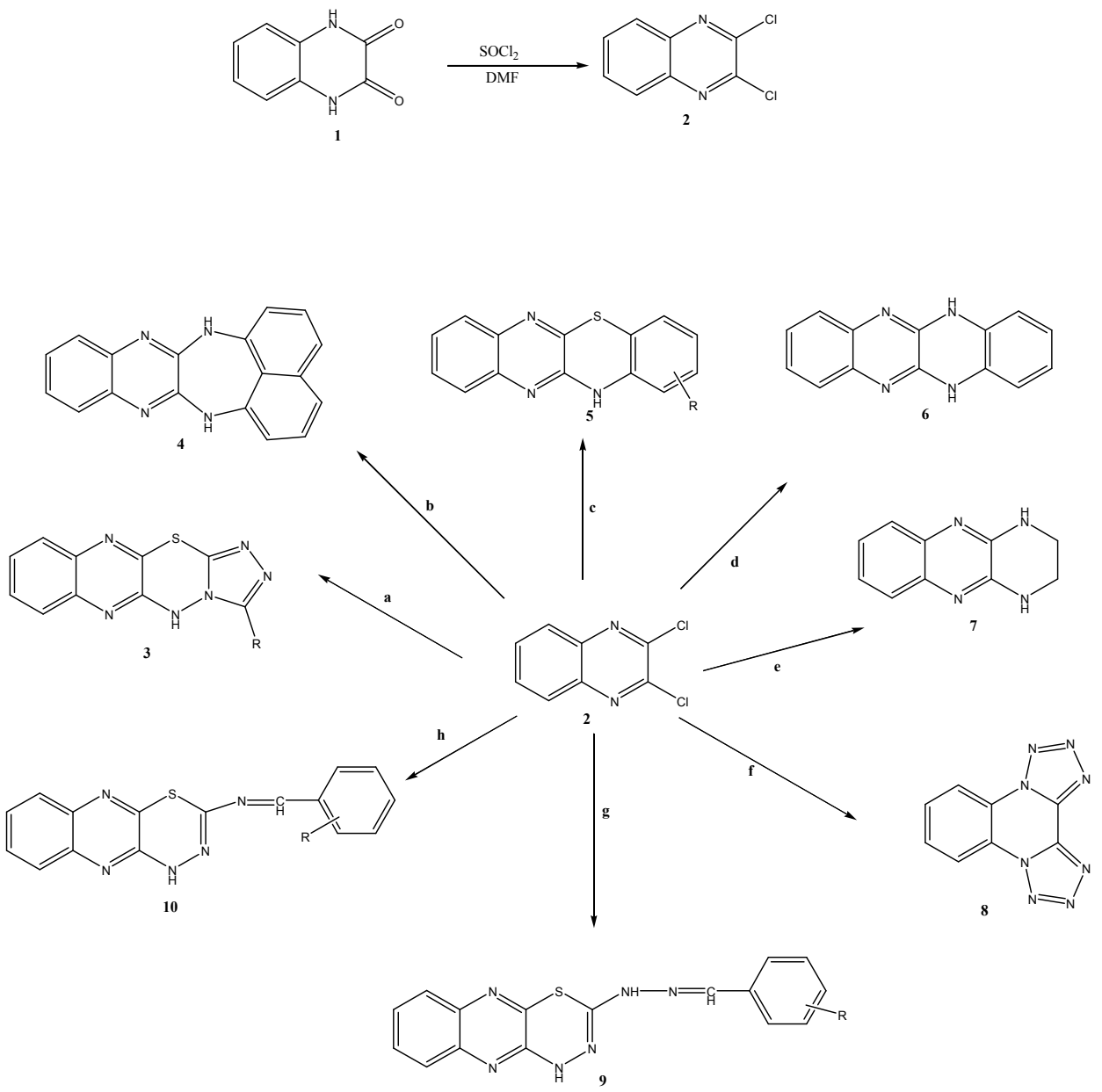
SCHEME I



a = Triazole/Ethanol/Pyridine **b = 1,10-diaminonaphthalene/ Ethanol/Pyridine**

c = Aminothiophenol/Ethanol/Pyridine **d = o-phenylenediamine/Ethanol/Pyridine**

e = 1,2-diaminoethane/Ethanol/Pyridine **f = NaN3/Glacial Acetic Acid**

g = thiocarbohydrazones/ Ethanol/KOH **h = thiosemicarbazones/Ethanol/KOH**

Table I: Physical Characterization of Synthesized Compounds

Compounds	R	m.p. (°C)	Yield (%)
3a	H	185-87	69
3b	CH_3	192-94	78
3c	C_2H_5	225-28	72
4	-----	194-97	63
5a	H	187-89	67
5b	CH_3	172-75	70
5c	Cl	168-70	75
6	-----	169-71	74
7	-----	182-84	66
8	-----	198-201	63
9a	H	185-88	69
9b	4-Cl	168-71	76
9c	4-OCH_3	196-98	82
9d	2-OH	219-21	84
9e	4-OH,3-OCH_3	227-29	79
10a	H	185-87	71
10b	4-Cl	194-97	65
10c	4-OCH_3	198-200	73
10d	2-OH	223-25	66
10e	4-OH,3-OCH_3	245-48	69

Table II. *in vitro* antibacterial activity of representative compounds

Compds	**Zone of inhibition (in mm)***			
	Gram Positive		**Gram Negative**	
	S.aureus	***C. diphtheria***	***E. coli***	***P. aeruginosa***
3b	17	18	17	17
4	24	23	18	16
5c	21	20	20	20
6	18	18	15	17
7	23	20	17	15
8	20	22	20	18
9c	23	21	18	17
9e	18	17	15	16
10c	24	23	21	20
10e	22	20	18	18
Ciprofloxacin	25	24	24	22
DMSO	0	0	0	0

* N.B. Concentration selected was 100 µg/ml and DMSO was used as the solvent