Antifungal and antimicrobial activity of some newly synthesized Quinoxaline derivatives.

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Abstract

Heterocycles have a wide range of application in medicinal chemistry. compound contain quinoxalins nucleus have been reported for biological activity like, Antibacterial, Antifungal, Anticancer, antitumor, antiHIV, Hence it was planned to synthesis some novel Quinoxaline derivatives. Orthophenylene diamine was reacted with oxalic acid to form quinoxaling – 2,3 dione was chlorinated by using $POCl_3$ in DMF to form 2,3 dichloro quinoxaline. This dichloro compound reacted with 4 – amino acetophenone gives 1-(4-(3- Chloroquinoxaline – 2 ylamino) ethanone all above compounds were synthesized in Micro oven at 100 watt. 1-(4-(3- Chloroquinoxaline – 2 ylamino) ethanone reacted with substituted aldehyde gives corresponding derivatives. All compound are characterized by IR and ^{1}HNMR and further screened for biological activity like Antifungal and antimicrobial.

Key Words - Quinoxaline, Micro oven, $POCl_3$, DMF.

Introduction:-

History of heterocyclic chemistry began in 1800's in step with the development of organic chemistry. After Second World War there was an enormous explosion research in the field of Heterocycles. About one half of over six million compounds recorded in chemical abstract are heterocyclic. Heterocyclic chemistry is one of the most complex and interesting branch of organic chemistry and heterocyclic compound constitute the largest and most varied family of organic compound. Many broader aspect of heterocyclic chemistry are recognized as disciplines of general significance that impinge on most of all aspects of modern organic chemistry, medicinal chemistry and biochemistry.

Quinoxaline are well known and important nitrogen containing six membered heterocyclic compounds, Various methods have been worked out for their synthesis [1-2] and characterization. Quinoxaline derivative has been a developing field within the realm of heterocyclic chemistry for the past several decades because of their ready associability through synthesis. These derivatives show wide range of chemical reactivity and broad spectrum of biological activity[3-10].

Methods and materials:-

All chemicals and solvents of AR-grade and LR- grade. All compounds were synthesis in Micro Oven Model CE 1030 CAT (SAMSUNG). Melting points were measure in open capillary tube in paraffin liquid. (IR) spectra were recorded as KBr pallets with FTIR: IRAffinity-1 (SHIMADZU). Spectrophotometer. 1H NMR spectra were recorded in DMSO and CDCL3 in BRUKER ADVANCE II 400 NMR Spectrophotometer. Thin layer Chromatography (TLC) was perform on pre-coated aluminum plates (silica gel 60 F254, Merck). Plates were visualized by UV light.

STEP (I).

Synthesis of 1, 4- Dihydro Quinoxaline-2, 3- Dione.

A solution of oxalic acid dehydrated (0.283mole) 30 g in H_2O (100 ml) was heated 100 watt & 4.5ml HCI was added, followed by O-phenylenediamine (0.204 mole) 22grm with staring keep the mixture in microwave at 100 watt for 25 minutes. Completion of reaction was confirmed by TLC. The mixture was cooled by addition of ice. The solid thus formed was washed with water and recrystalised by ethanol.

STEP (II)

Synthesis of 2, 3 dichloro quinoxaline.

A mixture quinoxaline 2,3 dione (16.2grm) freshly distilled phosphorus oxy trichloride ($POCI_3$) 60 ml & N,N – Dimethyl formamide (DMF) 5ml was kept in microwave for 26 minutes at 100 watt Completion of reaction was confirm by TLC. The mixture was slowly poured into ice water with stirring & resulting solid was filtered wash with water, dried & recrystalised by chloroform and n- Hexane.

STEP (III).

Synthesis of 1-(4-(3-Chloroquinoxaline-2-yl amino) phenyl) ethanone.

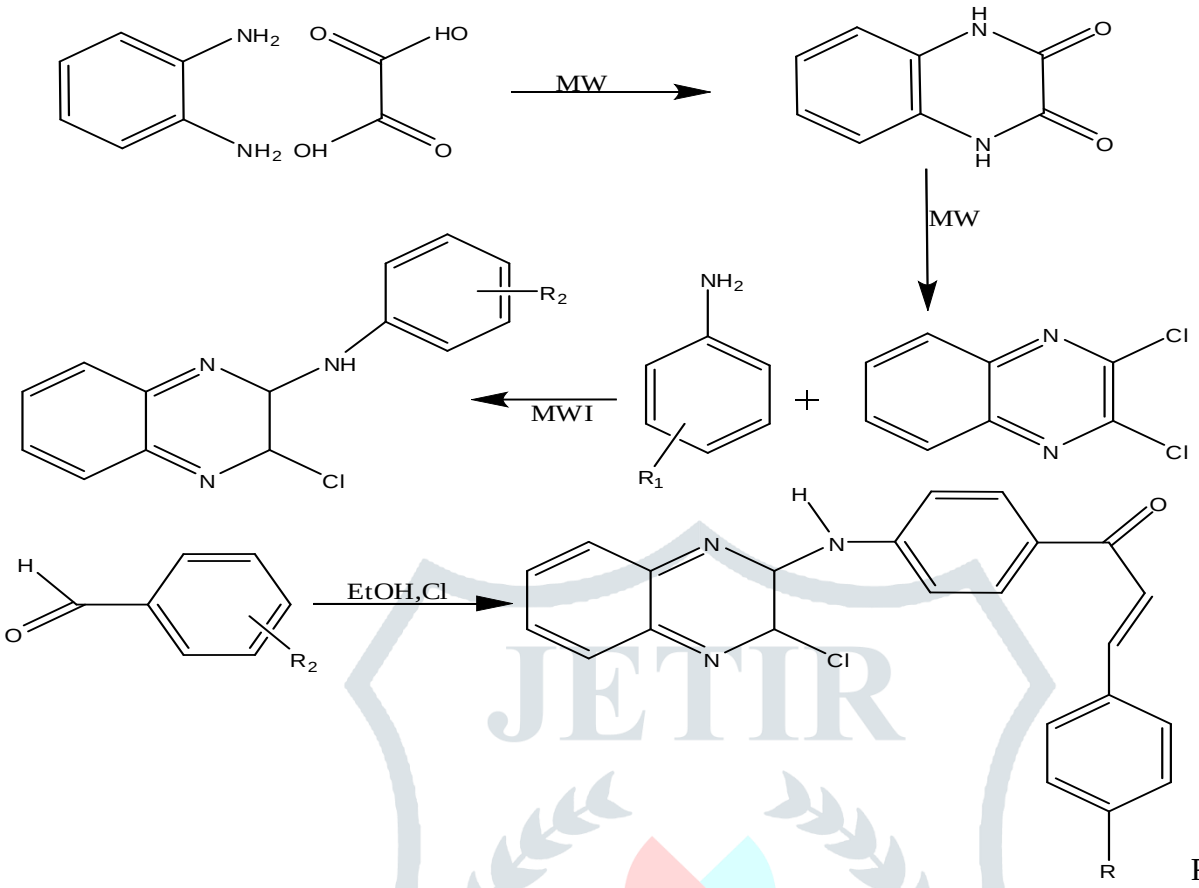
4-Aminoacetophenone (8.2g 0.01 mole) and 2,3 dichloro quinoxaline were dissolved in N, N-Dimethyl formamide (40 ml). Kept this reaction mixture in microwave for 22 min. at 100 watt Cool and poured into crushed ice. Periodically, a sodium carbonate solution (0.005, 0.53g in10 ml water) was added to neutralize HCI evolved during the reaction. The progress of the reaction monitored on TLC plate. The solid separate out was filtered, washed with water, dried and recrystalised from alcohol.

STEP (IV).

Preparation of Quinoxaline derivatives.

Equimolar quantities of 1-(4-(3-Chloroquinoxaline-2-yl amino) phenyl) ethanone with different substituted benzaldehyde was dissolve in alcoholic solution and then the solution of NaOH (5 ml of 40%) was added to reaction mixture with constant stirring at room temperature. After 24 h a reaction mixture was neutralized with HCI. The product separated out was filtered , wash with water, dried and recrystalised from ethanol.

Scheme:-



R=NO_2, Cl, Br, OH, CH_3, OCH_3

Spectral analysis of synthesized compound:

1, 4-Dihydro Quinoxaline-2, 3-dione

% yield = 90%. Melting point = 360 – 362 ºC . Rf = 0.74 (nHexane & ethyl acetate). IR – KBr Cm^{-1} aromatic C – H = 3040, C=C = 1512, N-H = 3100. ^{1}NHMR (400MHz DMSO) ♂ ppm 11.8 – 12.00 (s 2H, NH). 7.00 – 7.1 (d 4H aromatic).

2,3 dichloro quinoxaline.

% yield = 70%. Melting point = 150 – 152 ºC . Rf = 0.30 (nHexane & ethyl acetate). IR – KBr Cm^{-1} aromatic C – H = 3090, C=C = 1544, C=N = 1649,C-CI = 773, C-N = 1269. ^{1}NHMR (400MHz DMSO) ♂ ppm 7.0 – 8.0 (m 4H, aroma

1-(4-(3-Chloroquinoxaline- 2yl amino) phenyl) ethanone.

% yield = 70%. Melting point = 294 – 296 ºC . Rf = 0.34 (nHexane & ethyl acetate). IR – KBr Cm^{-1} aromatic, C=C = 1543, C=N = 1693,C-CI = 771, C-N = 1270, C=O =1710, ^{1}NHMR (400MHz DMSO) ♂ ppm 7.0 – 8.0 (m 8H, aromatic). 9.1-9.5 (1H, NH). 3.5-3.8 (d 3H CH_3)

Ra) (E)-1-(4-((3-chloro-2,3-dihydroquinoxalin-2-yl)amino)phenyl)-3-(4-nitrophenyl) prop-2-en-1-one

% yield = 90%. Melting point = 210 ºC . Rf = 0.67 (nHexane & ethyl acetate). IR – KBr Cm^{-1} C-H = 3066 aromatic, C=N = 1658, C-CI = 763, C-N = 1296, NO_2=1338, N-H= 3288, ^{1}H NMR (400MHz DMSO) δ ppm 7.42 – 8.30 (m 12H, aromatic). 3.92-4.63 (s 1H, NH). 8.35-8.38 (d 2H CH=CH).

Rb) (E)-1-(4-((3-chloro-2,3-dihydroquinoxalin-2-yl)amino)phenyl)-3-(4- chlorophenyl)prop-2-en-1-one.

% yield = 53%. Melting point = 274-276 ^{o}C . Rf = 0.67 (nHexane & ethyl acetate). IR – KBr Cm^{-1} C-H = 3057 aromatic, C=N = 1656, C-CI = 756, C-N = 1232, N-H= 3242, ^{1}H NMR (400MHz DMSO) δ ppm 7.24 – 8.01 (m 12H, aromatic). 2.51-4.62 (s 1H, NH). 8.25-8.30 (d 2H CH=CH).

Rc) (E)-1-(4-((3-chloro-2,3-dihydroquinoxalin-2-yl)amino)phenyl)-3-(4-bromophenyl)prop-2-en-1-one.

% yield = 55%. Melting point = 220-221 ^{o}C . Rf = 0.67 (nHexane & ethyl acetate). IR – KBr Cm^{-1} C-H = 3062 aromatic, C=N = 1666, C-CI = 756, C-N = 1276, N-H= 3282, C- Br =597. ^{1}H NMR (400MHz DMSO) δ ppm 7.16 – 8.11 (m 12H, aromatic). 3.41-4.00 (s 1H, NH). 8.21-8.43 (d 2H CH=CH).

Rd) (E)-1-(4-((3-chloro-2,3-dihydroquinoxalin-2-yl)amino)phenyl)-3-(4-hydroxyphenyl)

prop-2-en-1-one

% yield = 64%. Melting point = 200-202 ^{o}C . Rf = 0.67 (nHexane & ethyl acetate). IR – KBr Cm^{-1} C-H = 3053 aromatic, C=N = 1676, C-CI = 758, C-N = 1228, N-H= 3325, C-OH = 3695. ^{1}H NMR (400MHz DMSO) δ ppm 7.32 – 8.01 (m 12H, aromatic). 3.43-2.98 (s 1H, NH). 8.05-8.19 (d 2H CH=CH). 4.48 (s 1H Hydroxy).

Re) (E)-1-(4-((3-chloro-2,3-dihydroquinoxalin-2-yl)amino)phenyl)-3-(4-methyl phenyl) prop-2-en-1-one

% yield = 72%. Melting point = 255-257 ^{o}C . Rf = 0.67 (nHexane & ethyl acetate). IR – KBr Cm^{-1} C-H = 3157 aromatic, C=N = 1647, C-CI = 754, C-N = 1226, N-H= 3344. ^{1}H NMR (400MHz DMSO) δ ppm 7.38 – 8.18 (m 12H, aromatic). 3.38 (s 1H, NH). 8.21-8.29 (d 2H CH=CH). 2.51-2.50 (s 3H methyl).

Rf) (E)-1-(4-((3-chloro-2,3-dihydroquinoxalin-2-yl)amino)phenyl)-3-(4-methoxy phenyl) prop-2-en-1-one

% yield = 53%. Melting point = 284-286 ^{o}C . Rf = 0.67 (nHexane & ethyl acetate). IR – KBr Cm^{-1} C-H = 3057 aromatic, C=N = 1662, C-CI = 756, C-N = 1269, N-H= 3286. ^{1}H NMR (400MHz DMSO) δ ppm 7.26 – 8.04 (m 12H, aromatic). 4.46-3.44 (s 1H, NH). 8.08-8.40 (d 2H CH=CH). 3.27-2.97 (s 3H methoxy).

Determination of antimicrobial and Antifungal activity by disk diffusion method.

The antimicrobial activity of compound was determined by means of disk diffusion method. Each bacteria were inoculated nutrient agar broth and incubated at 37^{0}C for 16 h then adjusted to OD625 ¼ 0.08 – 0.1. The bacterial suspension was placed agar in 60 mm petri dish and spread homogeneously. Solution of compound Ra to Rf in DMSO were placed on agar surface containing bacterium which was incubated at 37^{0}C for h. The inhibition zones were measured with caliper considering total diameter. Compound Ra to Rf were tested for their antifungal activity by disk diffusion method against different fungal strain.

Table- 1- Antimicrobial activity against different bacteria.

Bacteria / Compound	E. coli	S. aureus	Salmonella typhi	Klebsiella pheunoniae	Bacillus cereus
Ra	14mm	16mm	ND	16mm	12mm
Rb	12mm	ND	13mm	14mm	18mm
Rc	11mm	14mm	17mm	18mm	16mm
Rd	16mm	11mm	14mm	12mm	16mm
Re	ND	14mm	14mm	18mm	14mm
Rf	ND	16mm	ND	10mm	16mm

Table- 1- Antifungal activity against different fungal strain.

Fung.strain / Comp.	Aspergillus Niger	Tricoderma Viride.	Cryptococcus neoform	Phoma
Ra	18mm	ND	23mm	ND
Rb	10mm	11mm	19mm	10mm
Rc	22mm	15mm	10mm	16mm
Rd	12mm	16mm	21mm	14mm
Re	ND	13mm	16mm	11mm
Rf	10mm	12mm	14mm	ND

Result and discussion:-

Microwave assisted synthesis is best method it is time saving and eco friendly also shows better yield than conventional method. Compound Ra, Rd and Re shows good yield. From above tables it is clear that these newly synthesized derivatives shows good to moderate activity against different bacterial strain like Escherichia Coli, Staphylococcus aureus, Salmonella typhi, Klebsiella Pheunoniae and Bacillus Cereus and antifungal activity against Aspergillus Niger, Tricoderma Virid, Cryptococcus neoform and Phoma species.

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