Original Research Article

Synthesis, characterization and biological evaluation of some novel quinoxaline derivatives

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Abstract

Heterocycles containing quinoxaline ring in their structure were reported with wide range of biological activity. There for aim of this project was to synthesis some novel quinoxaline derivative. All derivatives were synthesized by microwave irradiation method and resulting compounds was characterized by IR and 1H NMR spectroscopy, and screen for biological activity.

Key Words: Microwave irradiation, Quinoxaline.

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INTRODUCTION

The chemistry of heterocyclic compound have been interesting field of study for long time. Quinoxaline are well known and important nitrogen containing heterocyclic compound containing a ring complex made up of benzene ring and pyrazine ring so called benzopyrazine. Quinoxaline derivatives have different pharmacological activities such as Antimicrobial[1], Antimalerial[2], Antitumer[3], Antifungal[4], Antitubercular[5] and Anticancer[6] activities.

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. 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 and 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 recrystalized by ethanol.

Synthesis of 2, 3 dichloro quinoxaline: A mixture quinoxaline 2,3 dione (16.2grm) freshly distilled phosphorus oxy trichloride ($POCl_3$) 60 ml and 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 and resulting solid was filtered wash with water, dried and recrystalized by chloroform and n-Hexane.

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 recrystalized from alcohol.

Synthesis of Quinoxaline derivatives: Equimolar quantities of 1-(4-(3-Chloroquinoxaline-2-yl amino) phenyl) ethanone with substituted aldehyde 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 recrystalized from ethanol gives quinoxaline derivative

Scheme

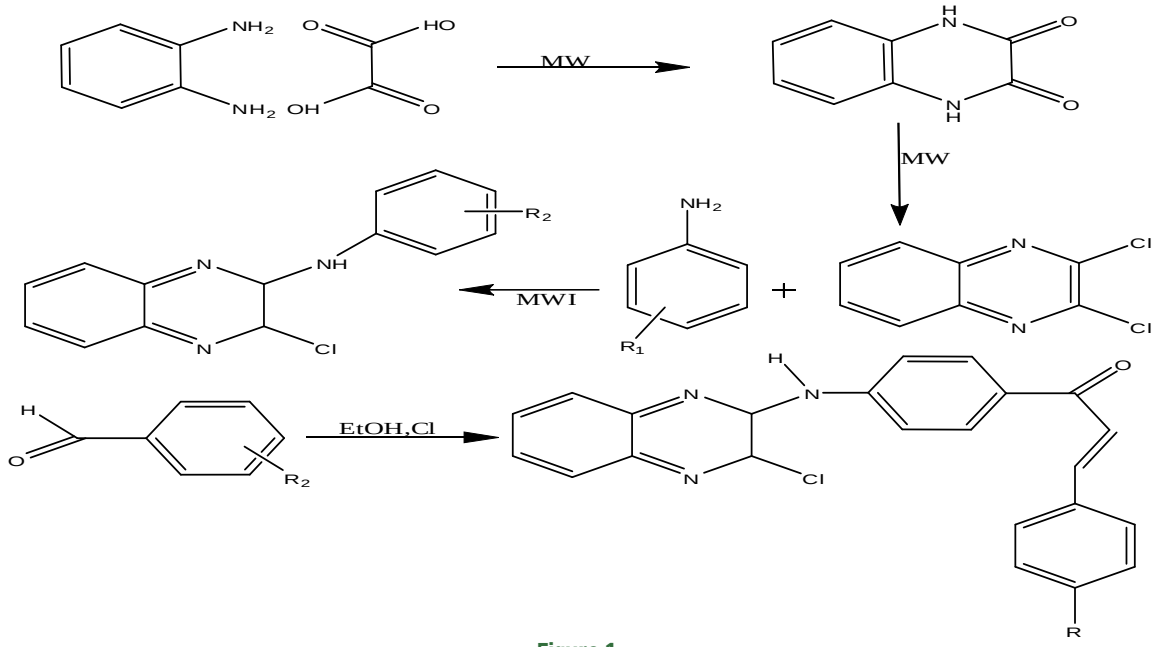

Figure 1:

Spectral analysis of synthesized compound: 1, 4-Dihydro Quinoxaline-2, 3-dione % yield = 80%. Melting point = 360 – 362 ^{o}C. Rf = 0.74 (nHexane and 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 ^{o}C. Rf = 0.30 (nHexane and 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 ^{o}C. Rf = 0.34 (nHexane and ethyl acetate). IR – KBr Cm^{-1} aromatic C – H = 3090, 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 = 207 – 210 ^{o}C. Rf = 0.67 (nHexane and ethyl acetate). IR – KBr Cm^{-1} aromatic C=C = 1597, C=N = 1658,C-CI = 682, C-N = 1296, CH=CH =3066, NO_2=1338, 1NHMR (400MHz DMSO) ∂ ppm 7.0 – 8.4 (m 12H, aromatic). 9.8-9.0 (1H, NH). 6.0-6.7 (d 2H CH=CH). Rb) (E)-1-(4-((3-chloro-2,3-dihydroquinoxalin-2-yl)amino)phenyl)-3-(2nitrophenyl) prop-2-en-1-one % yield = 70%. Melting point = 200 – 205 ^{o}C. Rf = 0.72 (nHexane and ethyl acetate). IR – KBr Cm^{-1} aromatic C=C = 1600, C=N = 1687,C-CI = 663, C-N = 1249, CH=CH =3068, NO_2=1323, 1NHMR (400MHz DMSO) ∂ ppm 7.0 – 8.0 (m 12H, aromatic). 9.7-9.0 (1H, NH). 6.0-6.5 (d 2H CH=CH).Rc)) (E)-1-(4-((3-chloro-2,3-dihydroquinoxalin-2-yl)amino)phenyl)-3-(2-chiorophenyl)prop-2-en-1-one % yield = 55%. Melting point = 275 – 280 ^{o}C. Rf = 0.50 (nHexane and ethyl acetate). IR – KBr Cm^{-1} aromatic C=C = 1598, C=N = 1651,C-CI = 671, C-N = 1271, CH=CH =3062, 1NHMR (400MHz DMSO) ∂ ppm 7.0 – 8.0 (m 12H, aromatic).

9.5-9.0 (1H, NH). 6.0-6.5 (d 2H CH=CH). Rd) (E)-1-(4-((3-chloro-2,3-dihydroquinoxalin-2-yl)amino)phenyl)-3-(4- chiorophenyl)prop-2-en-1-one yield = 53%. Melting point = 274 – 276 ^{o}C. Rf = 0.51 (nHexane and ethyl acetate). IR – KBr Cm^{-1} aromatic C=C = 1597, C=N = 1665, C-CI = 756, C-N = 1232, CH=CH =3057, 1NHMR (400MHz DMSO) ∂ ppm 7.0 – 8.0 (m 12H, aromatic). 9.5-9.0 (1H, NH). 6.0-6.5 (d 2H CH=CH). Re) (E)-1-(4-((3-chloro-2,3-dihydroquinoxalin-2-yl)amino)phenyl)-3-(2- bromophenyl)prop-2-en-1-one
% yield = 62%. Melting point = 220 – 222 ^{o}C. Rf = 0.42 (nHexane and ethyl acetate). IR – KBr Cm^{-1} aromatic C=C = 1516, C=N = 1654, C-CI = 663, C-N = 1230, CH=CH =3059, C-Br= 590. 1NHMR (400MHz DMSO) ∂ ppm 7.0 – 8.1 (m 12H, aromatic). 9.5-9.0 (1H, NH). 6.0-6.6 (d 2H CH=CH). Rf) (E)-1-(4-((3-chloro-2,3 dihydroquinoxalin-2-yl)amino)phenyl)-3-(4bromophenyl) prop-2-en-1-one. % yield = 55%. Melting point = 220 – 221 ^{o}C. Rf = 0.44 (nHexane and ethyl acetate). IR – KBr Cm^{-1} aromatic C=C = 1516, C=N = 1654, C-CI = 663, C-N = 1230, CH=CH =3059, C-Br= 590. 1NHMR (400MHz DMSO) ∂ ppm 7.0 – 8.1 (m 12H, aromatic). 9.5-9.0 (1H, NH). 6.0-6.6 (d 2H CH=CH).

RESULT AND DISCUSSION

Determination of antimicrobial 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.

Table 1:

Bacteria Compound	E. coli	S. aureus	Salmonella typhi	Klebsiella pheunoniae	Bacillus cereus
Ra	ND	9mm	10mm	9mm	9mm
Rb	ND	15mm	ND	8mm	10mm
Rc	ND	8mm	12mm	ND	ND
Rd	ND	11mm	ND	ND	12mm
Re	ND	ND	ND	ND	ND
Rf	ND	ND	6mm	ND	ND

Determination of antifungal activity: Compound Ra to Rf were tested for their antifungal activity by disk diffusion method against different fungal strain.

Table 2:

Fung. strain Comp.	Aspergillus Niger	Tricoderma Viride.	Cryptococcus neoform	Phoma
Ra	13mm	21mm	18mm	20mm
Rb	10mm	16mm	12mm	15mm
Rc	ND	22mm	ND	ND
Rd	ND	18mm	ND	ND
Re	ND	4mm	ND	ND
Rf	8mm	8mm	3mm	ND

Microwave assisted synthesis shows better yield than conventional method. Compound Ra, Rb and Re shows good yield. Compound containing Nitro and Chloro group shows prominent activity when compared to other compound. Para substituent shows better activity than ortho substituent.

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