

Original Article

SYNTHESIS, CHARACTERIZATION AND ANTI INFLAMMATORY ACTIVITY OF NOVEL QUINOXALINE DERIVED CHALCONES

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ABSTRACT

Objective: Quinoxaline derivatives were reported with wide range of biological activities. Hence it was planned to synthesize and screen for their anti-inflammatory (*in vivo*) activity.

Methods: Orthophenylene diamine was reacted with oxalic acid to form quinoxaline 2, 3 dione. Quinoxaline-2, 3 (1H, 4H)-dione was chlorinated by using Phosphorous trichloride (POCl₃) in dimethyl formamide, to form 2, 3- dichloroquinoxaline. This dichloride compound was reacted with 4 amino acetophenone in DMF, refluxed for 5 hours to form 1-(4-(3-chloroquinoxalin-2-ylamino) phenyl) ethanone. Similarly 1-(4-(3-chloroquinoxalin-2-ylamino) phenyl) ethanone was reacted with corresponding aromatic aldehydes to form quinoxaline derived chalcone by Claisen Schmidt reaction. Characterization all the compounds was performed by IR, ¹H NMR and Mass spectroscopic data and screened for anti-inflammatory activity by carrageenan- induced paw edema method.

Results: The anti-inflammatory data suggested that compounds QCAC 2, 6, 8, 9, 10 and 12 showed significant activity and rest of the compounds exhibited moderate activity compared to the standard compound

Conclusion: The compounds bearing nitro, chloro and methoxy groups have shown prominent activity when compared to compounds without these groups.

Keywords: Quinoxaline, dimethylformamide (DMF), Phosphorous trichloride (POCl₃), anti-inflammatory activity (*in-vivo*), diclofenac.

INTRODUCTION

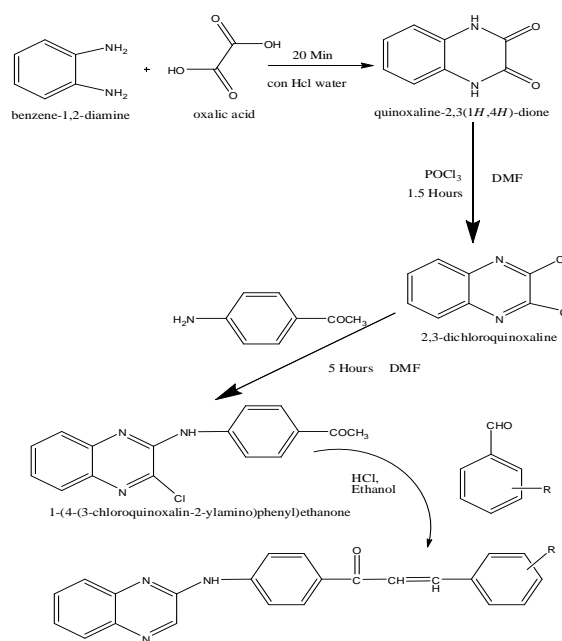
Recently there has been a lot of interest in quinoxalines, nitrogen containing heterocyclic compounds because of their extensive biological activities. Quinoxaline is formed by fusing benzene ring with diazine to form quinoxaline. The synthesis and chemistry of quinoxalines have attracted considerable attention in the past ten years [1]. Some of them exhibited biological activities including anti-inflammatory[2], anti-bacterial[3], anti-tumor[4], anti-HIV[5], AMPA antagonist [6], anti-tubercular[7], and neuro pharmacological agent[8] 5-HT₃ antagonism. They are also used in the agricultural field as fungicides, herbicides, and insecticides [12].

Also, quinoxaline moiety is 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 tumor[13]. In addition, quinoxaline derivatives 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 dehydroannulenes[20]. They also serve as useful rigid subunits in macrocyclic receptors in molecular recognition. Hence in the light of extensive applications, it was planned to synthesize a new series of quinoxaline derivatives and screen for their anti-inflammatory activity.

MATERIALS AND METHODS

Orthophenylenediamine, phosphorous trichloride, oxalic acid dimethylsulfoxide(DMSO), 4 amino acetophenone, dimethylformamide(DMF), hydrochloric acid, chloroform, hexane, ethanol were used for the synthesis of quinoxalines. The following experimental methods were used for the characterization of the synthesized compounds. Melting points of the synthesized compounds were determined in open capillary tubes and are uncorrected. The IR spectrum was recorded on ELICIO FTIR

spectrometer using potassium bromide pellets. ¹H-NMR spectra of the compounds in deuteriated dimethylsulfoxide was recorded on BRUKER Av 400 MHz spectrometer. Mass spectrum was recorded on GCMS QP 5000 shimadzu. Thin layer chromatography was performed using precoated aluminium plates coated with silica gel GF₂₅₄ [E. Merck]. N-hexane: ethyl acetate was used as the eluent. The spots were visualized in the ultraviolet light chamber.



Scheme

Synthesis of quinoxaline derivatives

Synthesis of 1, 4-dihydro quinoxaline-2, 3-dione

A solution of oxalic acid dihydrate (0.238 mole, 30g) in H₂O (100 ml) was heated to 100°C and 4.5 ml of concentrated hydrochloric acid was added, followed by O-phenylenediamine (0.204 mole, 22g) with stirring, temperature was maintained at 100 °C for 20 min. Completion of the reaction was confirmed by TLC. The mixture was cooled by addition of ice. The precipitate formed was washed with water and recrystallized from ethanol.

Synthesis of 2, 3 dichloro quinoxaline

A mixture of quinoxaline-2,3-dione (16.2 g, 0.1 mole), freshly distilled phosphorous oxy trichloride (POCl₃, 60 mL) and N,N-Dimethyl formamide (DMF, 5 mL) was refluxed with stirring for 1.5 hrs. Completion of the reaction was confirmed by TLC. The cooled reaction mixture was slowly poured into ice-water with stirring and the resulting solid was filtered, washed with water, dried and recrystallized from a mixture of chloroform and n-Hexane.

Synthesis of 1-(4-(3-chloroquinoxalin-2-ylamino)phenyl) ethanone

4-Aminoacetophenone (8.2 g 0.01 mole) and 2, 3 dichloro quinoxaline were dissolved in N, N- Dimethylformamide (40 ml). The reaction mixture was refluxed for 5 hours, cooled and poured into crushed ice. Periodically, sodium carbonate solution (0.005, 0.53g in 10 ml water) was added to neutralize HCl evolved during the reaction. The progress of the reaction was monitored on TLC plate. After completion, the solid separated out was filtered, washed with water, dried and recrystallized from alcohol to give 1-(4-(3-Chloroquinoxalin-2-ylamino)phenyl)ethanone.

Synthesis of quinoxalines derived chalcones

Equimolar quantities of 1-(4-(3-Chloroquinoxalin-2-yl amino) phenyl) ethanone and substituted aldehydes were dissolved in alcoholic solution, and then solution of KOH or NaOH (5 ml of 40%) was added to the reaction mixture with constant stirring at room temperature. After 24 hrs the reaction mixture was neutralized with HCl. The product separated out was filtered, washed with water, dried and recrystallized from ethanol to give quinoxalines derived chalcones.

Characterization

Quinoxaline 2,3 (1H,4H) Dione (Q): % yield: 90%; Melting point: 360-362°C; R_f=0.76 (n-hexane: ethyl acetate) (7:3); IR (KBr) V_{max} (cm⁻¹): CH 3042.3001; ¹HNMR (400 MHz,DMSO D₆) (δppm): 11.8-12.0(s,2H,NH), 7.0-7.1(d,4H, aromatic, j=3.0) mass (m/z)=160(100%), 162(M⁺).

Dichloro Quinoxalines (QC): % yield: 70%; Melting point: 150-152°C R_f=0.34 (n-hexane: ethyl acetate)(7:3); IR (KBr) V_{max} (cm⁻¹): CH 2938; ¹HNMR (400 MHz,DMSO D₆) (δppm): 7.0-7.1(m,4H, aromatic, j=3.0) mass(m/z)=190(100%),198(M⁺).

1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)Ethanone (QCAC): % yield: 75%; Melting point: 294-296°C R_f=0.34 (n-hexane: ethyl acetate)(7:3); IR (KBr) V_{max} (cm⁻¹): 1594 (C=C),1165(C-NH), 1674(CH=CH); ¹HNMR (400 MHz,DMSO D₆) (δppm): 6.8(d,2H, CH=CH, j=3.0).

1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)-3-Phenylprop-2-En-1-One(1): % yield: 60%; Melting point: 294-296°C R_f=0.34 (n-hexane: ethyl acetate)(7:3); IR KBr cm⁻¹: 1594 (C=C),1169(C-NH), 1673(CH=CH); ¹HNMR (400 MHz,DMSO D₆) (δppm):3.8(d,3H,CH₃ J=4.0), 6.8(d,2H, CH=CH, j=3.0), 7.0-8.4(m,10H,aromatic), 9.8(s,1H,NH) mass (m/z)=375(100%), 385(M⁺).

1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)-3-(4-Methoxyphenyl)Prop-2-En-1-One(2): % yield: 50%; Melting point: 284-286°C R_f=0.19(n-hexane: ethyl acetate)(8:2); IR (KBr) V_{max} (cm⁻¹): 1598 (C=C),1177(C-NH), 1670(CH=CH); ¹HNMR (400 MHz,DMSO D₆) (δppm):3.8(d,3H,CH₃ J=4.0),6.7(d,2H,CH=CH,j=3.0), 7.2-8.4(m,12H,aromatic),9.8(s,1H,NH) mass(m/z)=175,254,415 (100%)(M⁺).

1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)-3-(4-Hydroxy-3-Methoxy Phenyl)Prop-2-En-1-One(3): % yield: 58%; Reaction time: 18 hours; Melting point: 274-276°C R_f=0.12 (n-hexane: ethyl acetate)(6:4); IR (KBr) V_{max} (cm⁻¹): 1603 (C=C), 1179 (C-NH), 1670(CH=CH), (OCH₃) 2835; ¹HNMR (400 MHz,DMSO D₆) (δppm):3.8(d,3H, CH₃ J=4.0), 6.7(d,2H, CH=CH, j=3.0), 7.2-8.4(m,12H,aromatic),9.8(s,1H,NH) mass (m/z)=431(100%)(M⁺).

1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)-3-(Furan-2yl)Prop-2-En-1-One(4): % yield: 56.9; m. p(°c):224-226; R_f Vale: 0.76(n-hexane: ethyl acetate); IR (KBr) V_{max} (cm⁻¹):1596.35(C=C), 3339.26(C-NH), 1667.16(CH=CH); ¹HNMR (400Mz,DMSO d₆) (δppm):3.2-3.3(d,3H,CH₃) J=2.4,6.7-6.73(d,2H,CH=CH)J=2.6,7.1-8.3(m,9H,aromatic),9.9(s,1H,NH);mass (m/z):380(100%)1, 385,386.

1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)-3-(2-Nitro Phenyl)Prop-2-En-1-One(5): % yield: 52. m. p(°c):208-210°C; R_f Value: 0.97(n-hexane: ethyl acetate); IR (KBr) V_{max} (cm⁻¹): 1466.85(C=C),1177.54(C-NH),1618.59(CH=CH); ¹HNMR (400Mz, DMSO d₆) (δppm): 3.43.43 (s, 3H,CH₃), 4.4-4.5(s,1H,NO₂) 7.28.4(m,11H,aromatic). 9.8(s,1H,NH), 4-12.5(s, 1H,CH₂).13.7 (s, 1H, CH₂).mass m/z: 174.190,194(100%),430(M⁺).

1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)-3-(4-Nitrophenyl)Prop-2-En-1-One(6): % yield: 52.7; m. p(°c):208-210°C; R_f Value: 0.97(n-hexane: ethyl acetate); IR (KBr) V_{max} (cm⁻¹):1466.85(C=C),1177.54 (C-NH),1618.59(CH=CH); ¹HNMR (400Mz, DMSO d₆) (δppm):3.4-3.43(s,3H,CH₃),4.4-4.5(s,1H,NO₂). 7.28.4 (m,11H, aromatic). 9.8(s,1H,NH),4-12.5(s,1H,CH₂).13.7 (s,1H,CH₂); mass m/z: 174.190,194(100%),430(M⁺).

3-(2-Chlorophenyl)-1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)Prop-2-En-1-One(7): % yield: 53.7;m. p(°c):274-276; R_f Value: 0.114(n-hexane: ethyl acetate); IR (KBr) V_{max} (cm⁻¹): 1482.08(C=C), 1131.13(C-NH), 1621.19(CH=CH); ¹HNMR (400MHz DMSO d₆) (δ ppm): 3.8(singlet 3H,CH₃),5.1(d,2H,CH=CH)J=3.6 7.21 8.3(m, 10H,aromatic),9.7(s,1H,C-NH),10.3-10.4(t,1H,CH₂); mass (m/z):135,190,247,421(M⁺).

3-(4-Chlorophenyl)-1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)Prop-2-En-1-One(8): % yield: 53.7; m. p(°c):274-276; R_f Value: 0.114(n-hexane: ethyl acetate); IR (KBr) V_{max} (cm⁻¹): 1482.08(C=C), 1131.13(C-NH), 1621.19(CH=CH); ¹HNMR (400MHz DMSO d₆) (δ ppm): 3.8(singlet 3H,CH₃),5.1(d,2H,CH=CH)J=3.6,7.21-8.3(m,10H,aromatic),9.7(s,1H,C-NH),10.3-10.4(t,1H,CH₂); mass(m/z):135,190,247,421(M⁺).

1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)-3-(2-Hydroxyphenyl)Prop-2-En-1-One(9): % yield: 58.7; brown crystals; m. p(°c):198-200; R_f Value: 0.27(n-hexane: ethyl acetate); IR (KBr) V_{max} (cm⁻¹): 1457.85(C=C), 1177.56 (C-NH),1680.91(CH=CH); ¹HNMR (400Mz DMSO d₆) (δppm):2.9(S,2H,CH₂),3.6(S,3H,CH₃),6.8-6.9(d,2H,CH=CH)J=0.35,7.21-8.3(m,6H,aromatic),9.8(s,1H,NH),10.3-10.4(s,1H,OH)); Mass (m/z):280,376, 384(100%), 400(M⁺).

1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)-3-(4-Hydroxyphenyl)Prop-2-En-1-One(10): % yield: 57.7; m. p(°c):198-200°C; R_f Value: 0.27, (n-hexane: ethyl acetate); IR (KBr) V_{max} (cm⁻¹): 1457.85(C=C), 1177.56 (C-NH),1680.91(CH=CH); ¹HNMR(400MHz DMSO d₆) (δppm)=2.9(S,2H,CH₂),3.6(S,3H,CH₃),6.8-6.9(d,2H,CH=CH)J=0.35,7.21-8.3(m,6H aromatic),9.8(s,1H,NH),10.3-10.4(s,1H,OH));mass (m/z)280,376,384(100%),400(M⁺).

1-(4)-1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl)-5-Phenylpenta-2,4-Dien-1-One(11): % yield: 53.7. m. p(°c):298-300;R_f Value: 0.75, (n-hexane: ethyl acetate);IR IR (KBr) V_{max} (cm⁻¹):1616.17(C=N),1180.57(C-NH),1616.17(CH=CH); ¹HNMR (400MHzDMSO d₆) (δppm)=3.4(S,3H,CH₃), 5.6(dd,4H,CH=CH), J=4.07.1-8.4(m, a10H, aromatic), 9.3(s,1H,NH)MS (m/z):190, 222, 411(100%)(M⁺).

1-(4-(3-Chloroquinoxalin-2-Ylamino)Phenyl) (4(Dimethyl amino) Phenyl) Prop-2-En-1-One (12): % yield: 45.4; m. p(°c): 300-302; R_f Value: 0.54; IR (KBr) V_{max} (cm⁻¹):1595. 45(C=C),1174.74(CNH), 1658.09(CH=CH); ¹HNMR (400MHz, DMSO,d₆) (δppm): 3.51,3.8(doublet,6H,CH₃)J=3.4,6.(d,2H,CH=CH) J=2.4,7.2-8.7(m,12H,aromatic),9.2(s,1H,NH); MS (m/z): 428 (100%) (M⁺).

Evaluation of acute oral toxicity

The protocol of the work was approved by Institutional Animal Ethics Committee (IAEC) (1725/GO/a/13/CPCSEA). The acute oral toxicity of the synthesized compounds was performed according to OECD guidelines 423. In this method the toxicity of the synthesized compounds was tested using a step wise procedure, each step using 3 mice of a single sex. The mice were fasted to dosing (food but not water should be withheld for 3-4 hrs). Following the period of fasting the animals should be weighed and the synthesized compounds were administered orally at a dose of 2000 mg/kg body weight. Animals were observed individually after dosing at least once for the duration of first 30 min; sporadically during the first 24 hrs with special attention given during the first four hours and daily thereafter, for a sum of 14 days

Anti inflammatory activity (*in vivo*)

Carrageenan induced rat hind paw edema method [21].

The initial paw volume of each rat was noted by mercury displacement method by plethysmometer. Animals in group-1 were administered with aqueous solution of DMSO (1 ml), the group-2 received diclofenac at a dose 25mg/kg body weight. 3-9 groups received the test samples after the drug treatment. 1% w/w Carrageenan solution (0.1 ml/ paw) was injected subcutaneously into planter surface of the left hind paw of the rat. The paw volume of rats in control, standard and test groups was measured with the help of the plethysmometer during the interval of 30, 60,120,180,240 minutes after Carrageenan administration.

Percentage protection (or inhibition) was calculated by using the formula

$$1. \quad \% \text{ protection} = (1 - V_t/V_c) * 100$$

V_t = increase the paw volume in the test animal

V_c = increase the paw volume in the control group

Statistical analysis

The results were expressed as MEAN±SEM and were analyzed

using one way analysis of variance (ANOVA) followed by dunnett's t-test. The probability of 0.05 or less was considered statistically significant

RESULTS AND DISCUSSION

Acute toxicity studies

The synthesized compounds were administered at a dose of 2000mg/kg in 1% DMSO and observed 14 days for the mortality due to acute toxicity. Careful observation was made at least twice a day for the effect on CNS, ANS, motor activity, salivation, skin coloration and other general signs of toxicity were also observed and recorded. Since no sign of toxicity observed at 2000mg/kg to the group animals, the LD₅₀ value of the synthesized compounds expected 2000mg/kg and represented as class 5 (2000mg/kg < LD₅₀<2500mg/kg).

From the toxicity studies the data revealed that all synthesized compounds proved to be the non toxic at the tested dose levels and well tolerated by the experimental animals as their LD₅₀ wt of values 2000mg/kg between therefore, the 1/10th of the above dose was selected and fixed for the further pharmacological evaluation.

The anti-inflammatory activity (*in vivo*) of the compounds (QCAC 1-12) was evaluated by Carrageenan induced rat paw edema method. The compounds were tested at 200mg/kg dose and the results were compared with that of diclofenac as reference drug. The results were summarized in the table-1; suggested that the anti-inflammatory activity of the compounds was in the range of 0.66 to 99.0 % inhibition, where as the standard drug diclofenac showed activity of 38.59% inhibition after four hours.

Among the compounds, screened for anti-inflammatory activity, compounds QCAC 2,6, 8,9,10 and 12 showed maximum anti-inflammatory activity 20.5 to 99% inhibition where as rest of the compounds showed moderate activity 0.66 to 15.3 % inhibition. The inflammation is due to the release of histamine, serotonin and prostaglandin. Therefore the anti-inflammatory activity of the synthesized compounds may be due to the inhibition of histamine, serotonin or prostaglandin synthesis.

Table 1: Anti Inflammatory values for synthesized compounds (*In-Vivo*)

S. No.	Experimental Groups	Mean ±SEM (Paw Volume in ml) followed by % inhibition				
		0 hr	1 hr	2 hr	3 hr	4 hr
01	Control	1.48±0.03	1.82±0.04	2.19±0.12	2.28±0.32	2.26±0.26
02	Standard (Diclofenac Sodium)	1.37±0.14	1.47±0.16	1.51±0.13	1.47±0.13	1.40±0.16
03	QCAC-1	7.43 (13.86*)	19.23 (2.72)	31.05 (0.66)	35.24 (5.04)	38.59 (7.08)
04	QCAC-2	1.18±0.08	1.43±0.14	1.50±0.12	1.39±0.10	1.29±0.10
05	QCAC-3	1.23±0.13 (10.21*)	1.42±0.16	1.82±0.11 (3.40)	1.28±0.24 (20.05*)	1.27±0.14 (12.09*)
06	QCAC-4	1.32±0.10 (3.64)	1.49±0.07 (1.03)	1.68±0.11 (11.02)	1.69±0.18 (14.96*)	1.58±0.09 (12.85*)
07	QCAC-5	1.18±0.09 (13.86*)	1.43±0.11 (2.72)	1.54±0.09 (1.68)	1.52±0.10 (3.40)	1.49±0.06 (6.42)
08	QCAC-6	1.16±0.08 (15.03*)	1.32±0.09 (10.20*)	1.34±0.1 (11.25)	1.26±0.07 (14.28*)	1.24±0.06 (11.40)
09	QCAC-7	1.30±0.013 (5.10*)	1.46±0.11 (0.68)	1.69±0.10 (11.92*)	1.74±0.09 (18.36*)	1.73±0.04 (23.57*)
10	QCAC-8	1.21±0.14 (11.67*)	1.35±0.12 (8.16)	1.62±0.11 (7.28)	1.43±0.20 (2.72)	1.39±0.11 (0.71)
11	QCAC-9	1.40±0.14 (2.18)	1.83±0.11 (24.48*)	1.51±0.12 (99.0*)	1.61±0.12 (9.52)	1.47±0.10 (5.00)
12	QCAC-10	1.32±0.10 (3.64)	1.57±0.19 (6.80)	1.84±0.13 (21.85*)	1.86±0.6 (26.53*)	1.81±0.08 (29.28*)
13	QCAC-11	1.27±0.14 (7.29*)	1.59±0.22 (8.163)	1.73±0.21 (14.56*)	1.78±0.22 (21.08*)	1.61±0.16 (15.07*)
14	QCAC-12	1.17±0.09 (14.05*)	1.35±0.07 (8.16)	1.61±0.13 (6.60)	1.42±0.11 (3.40)	1.25±0.06 (10.71)
		1.27±0.14 (7.29*)	1.75±0.22 (19.04*)	1.73±0.21 (14.5*)	1.78±0.22 (21.08*)	1.56±0.1 (11.04)

Note: % inhibition was denoted in the parenthesis

CONCLUSION

The compounds bearing nitro, chloro, hydroxy and methoxy groups have shown prominent activity when compared to compounds without these groups. It was also confirmed that the groups in para position showed better activity when compared to the groups in ortho position. Further investigation in this area may help to bring more potent drugs.

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CONFLICT OF INTERESTS

Declared None

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