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Synthesis and Biological Evaluation of Some 4-Substituted Quinoxalinones

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A number of quinoxaline-2-ones analogues have been synthesized by condensation of parent compound with different acid chlorides and screened for antibacterial activity against *Escherichia coli*, *Bacillus subtilis*, *Bacillus cereus* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger* and *Candida species* and analgesic activity. The 4-substituted quinoxalinones were characterized using TLC, IR, ^{1}H NMR analysis.

Key Words: Quinoxalinones, Antibacterial, Antifungal, Analgesic.

INTRODUCTION

Quinoxaline is a versatile pharmacophore, which exhibits a wide variety of biological activites including antibacterial and antifungal[1-5], anticonvulsant[6], anxiolytic[7], cytotoxic agent[8]. Quonoxaline can be synthesized from *o*-phenylenediamine[9], by α-amino acid intermediates[10], by catecholl[11], *etc*. One of the quinoxaline derivatives is quinoxaline-2-one which shows different chemical reactions like chlorination, methylation, nitration, ring cleavage, *etc*.

EXPERIMENTAL

Five compounds were synthesized from the parent compound which is 1,2,3,4-tetrahydro-2-oxoquinoxaline (THQ), which in turn were reacted with different benzoyl derivatives to obtain different THQ derivatives.

Preparation of 1,2,3,4-tetrahydro-2-oxoquinoxaline: Chloroacetic acid (9.5 g) neutralized with sodium hydroxide solution (1 N) was added to *o*-phenylenediamine (10.8 g) and the reaction mixture was refluxed at 100ºC for 5-6 h. A brown solid separated out after cooling to room

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temperature. The solid obtained was filtered and dried. It was recrystallized from the water. IR (KBr, cm^{-1}): 3066 ν(aromatic ring), 1673 ν(lactam group), R_f value 0.59 (benzene:methanol::9:1).

4-Benzoyl-1,2,3,4-tetrahydro-2-oxoquinoxaline: 1,2,3,4-tetrahydro-2-oxoquinoxaline (10 g) was suspended in NaOH solution (5 %, 200 mL) in a well corked round-bottomed flask, benzoyl chloride (5.2 mL) was added dropwise and the flask was shaken vigorously for 10-15 min until the odour of benzoyl chloride was not preceived. The solid benzoyl derivative was filtered out and washed with cold water. The product was recrystallized from ethanol IR (KBr, cm^{-1}): 3066 ν(aromatic ring), 1686 ν(lactam ring), 1648 ν(C=O of benzoyl). ^{1}H NMR ($CDCl_3$, δ): 9.65 (s, H broad), 7.3-7.5 (s, 5H), 6.7-6.85 (m, 2H), R_f value 0.68 (benzene:methanol::9:1).

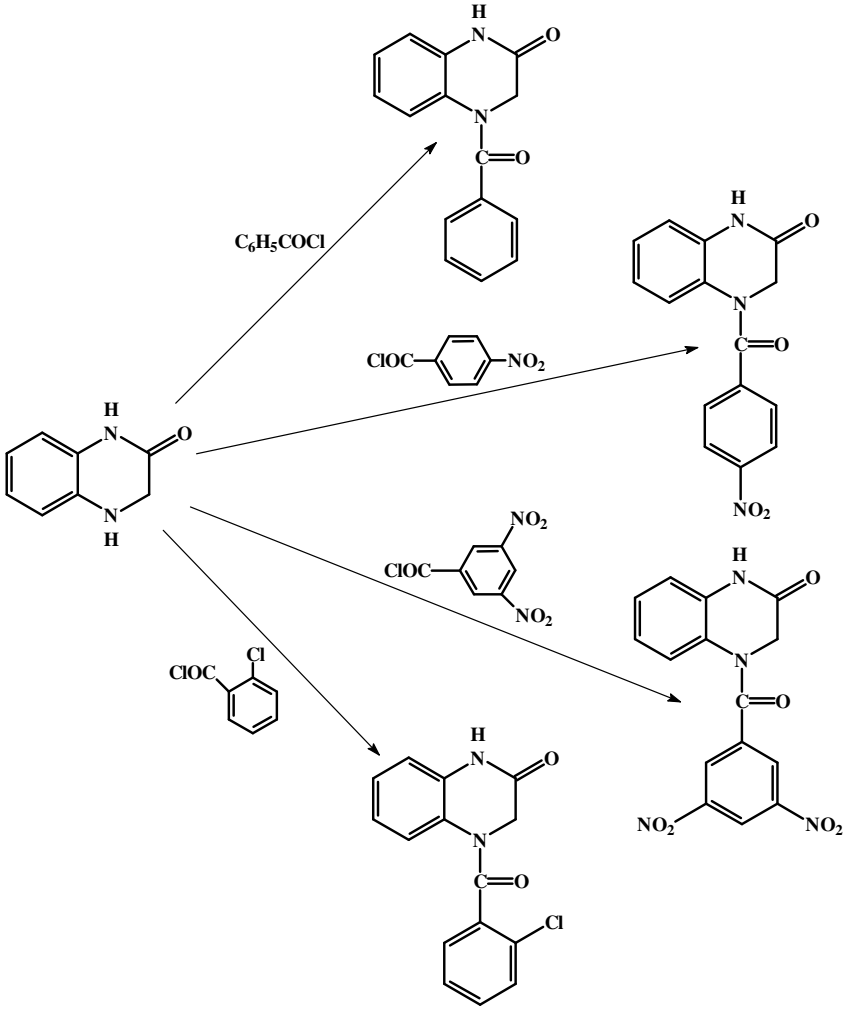
4-(4-Nitro benzoyl)-1,2,3,4-tetrahydro-2-oxoquinoxaline: For preparing this first prepare 4-nitrobenzoyl chloride.

Preparation of 4-nitrobenzoyl chloride: A mixture of 4-nitrobenzoic acid (15 g) and phosphorous pentachloride (18.06 g) was placed in a 250 mL round-bottomed flask. The mixture was refluxed on water bath with occasional shaking until the vigorous evolution of hydrogen chloride had almost ceased. A pale yellow homogenous liquid formed phosphorous oxychloride was removed by distillation over a water bath. The flask was cooled to room temperature a small quantity of carbon tetrachloride (15-20 mL) was added and the flask was stoppered and allowed to stand overnight in a refrigerator. The yellow crystalline solid which separated out was filtered and recrystallized from carbon tetrachloride.

1,2,3,4-Tetrahydro-2-oxoquinoxaline (10 g) was taken in a round bottomed flask and dissolved in dry pyridine (10 mL). 4-Nitro benzoyl chloride (10 g) was added and the reaction mixture was refluxed on a water bath for 1 h. The reaction mixture was poured into acidified ice cold water. The crude product that separated out was recrystallized from methanol. IR (KBr, cm^{-1}): 3082 ν(aromatic ring), 1684 ν(lactam ring), 1655 ν(C=O of benzoyl), 1527 ν(due to nitro group). ^{1}H NMR ($CDCl_3$, δ): 7.3-7.5 (s, 5H), 6.7-6.85 (m, 2), 4.65 (m, 3H), TLC R_f value 0.63 (chloroform:methanol:: 9.5:0.5).

4-(3,5-Dinitro benzoyl)-1,2,3,4-tetrahydro-2-oxoquinoxaline: A mixture of 3,5-dinitrobenzoic acid (15 g) and phosphorous pentachloride (18.6 g) was placed in a 250 mL round-bottomed flask. The mixture was refluxed on water bath for 1.25 h. The phosphorous oxychloride formed was removed by distillation over an air water bath. To this a small quantity of carbon tetrachloride (15-20 mL) was added after cooling the reaction mixture. The flask was stoppered and allowed to stand overnight in a refrigerator. A pale yellow solid separated out. It was filtered and recrystallized from carbon tetrachloride.

1,2,3,4-Tetrahydro-2-oxoquinoxaline (10 g) was taken in round bottomed flask and dissolved in dry pyridine (10 mL). 3,5-Dinitro benzoyl chloride (10 g) was added and the reaction mixture was refluxed on water bath for 1 h. The reaction mixture was poured into acidified ice cold water. The crude product that separated out was recrystallized from methanol. IR (KBr, cm^{-1}): 3082 ν(aromatic ring), 1684 and 1655 ν(lactam ring), 1655 ν(C=O of benzoyl), 1544 and 1505 ν(due to nitro group). ^1H NMR ($CDCl_3$, δ): 7.3-7.5 (s, 5H), 6.7-6.85 (m, 2), 4.73 (m, 3H), R_f value 0.65 (chloroform:methanol::9:1).



Scheme-I

TABLE-1
PHYSICAL PARAMETERS OF VARIOUS 4-SUBSTITUTED QUINOXALINONES

Compd.	Substituents (R)	m.w.	Yield (%)	R_f value	m.p. (ºC)
IIIA	C_6H_5COCl	140.5	55	0.68	210-212
IIIB	$4\text{-}NO_2C_6H_4COCl$	183.3	58	0.63	253-255
IIIC	$3,5\text{-}(NO_2)_2C_6H_3COCl$	230.5	54	0.6	250-252
IIID	*o*-ClC_6H_4COCl	175.0	59	0.69	210-212

TABLE-2
ANTIBACTERIAL ACTIVITY OF 4-SUBSTITUTED QUINOXALINONES (BORE CUP METHOD)

Compd.	Zone of inhibition (*diameter in mm)					
	E. coli	*B. subtilis*	*B. cereus*	*S. aureus*	*A. niger*	*Candida*
Control (DMSO)	–	–	–	–	–	–
IIIA	9.5	19	15	11	13	–
IIIB	–	13	19	–	12	–
IIIC	–	20	12	–	–	13
IIID	–	17	10	13	–	10

*Each reading represents an average of three measurements across each zone on inhibition.

TABLE-3
APPROXIMATE LD_{50} VALUE OF THE SYNTHETIC COMPOUNDS

Compound	LD50 value (mg/kg)
IIIA	50
IIIB	100
IIIC	200
IIID	215

4-(2-Dinitro benzoyl)-1,2,3,4-tetrahydro-2-oxoquinoxaline: Anhydrous 2-chlorobenzoic acid (15 g) and thionyl chloride (20 mL) was placed in a 250 mL round-bottomed flask. The flask was fitted with a calcium guard tube and later connected a gas absorption device. The flask was heated until reaction commenced and then for a further 2 h. A pale yellowish homogenous mixture formed. The excess of thionyl chloride was removed by vacuum distillation over hot water bath. A pale yellow liquid was obtained.

1,2,3,4-Tetrahydro-2-oxoquinoxaline (10 g) was taken in round bottomed flask and dissolved in dry pyridine (12 mL). 2-Chlorobenzoyl chloride (10 mL) was added and the flask was refluxed on water bath for

TABLE-4

EFFECT OF QUINOXALINONE ON TAIL FLIC RESPONSE IN MICE (UNIT EXPRESSED IN s)

Control	Compound 1		Compound 2		Compound 3		Compound 4		Compound 5	
	Dose (mg/kg)	Effect	Dose (mg/kg)	Effect	Dose (mg/kg)	Effect	Dose (mg/kg)	Effect	Dose (mg/kg)	Effect
1.4 ± 0.22	5	3.2 ± 0.64[a]	10	3.4 ± 0.50[b]	25	2.4 ± 0.24[b]	25	2.8 ± 0.37[b]	30	2.8 ± 0.37[b]
1.4 ± 0.22	10	7.6 ± 0.67[c]	20	7.2 ± 0.86[c]	50	7.0 ± 0.70[c]	50	8.2 ± 0.64[c]	60	6.4 ± 0.50[c]
1.4 ± 0.22	30	12.2 ± 0.70[c]	60	12.2 ± 0.70[c]	150	11.4 ± 0.50[c]	150	12.0 ± 0.63[c]	180	10.8 ± 0.26[c]

Value expressed mean as ± SEM for five animals in each group; p value a < 0.05, b < 0.01; c < 0.001 when compared to control.

TABLE-5

EFFECT OF QUINOXALINONE ON TAIL CLIP RESPONSE IN MICE (UNIT EXPRESSED IN s)

Control	Compound 1		Compound 2		Compound 3		Compound 4		Compound 5	
	Dose (mg/kg)	Effect	Dose (mg/kg)	Effect	Dose (mg/kg)	Effect	Dose (mg/kg)	Effect	Dose (mg/kg)	Effect
1.6 ± 0.07	5	3.2 ± 0.37[c]	10	3.2 ± 0.40[b]	25	3.2 ± 0.40[b]	25	3.0 ± 0.40[b]	30	3.2 ± 0.40[b]
1.6 ± 0.07	10	7.4 ± 0.57[c]	20	6.4 ± 0.57[c]	50	7.0 ± 0.56[c]	50	7.4 ± 0.51[c]	60	6.8 ± 0.51[c]
1.6 ± 0.07	30	12.4 ± 0.47[c]	60	11.4 ± 0.47[c]	150	11.2 ± 0.51[c]	150	12.2 ± 0.49[c]	180	11.6 ± 0.47[c]

Value expressed mean as ± SEM for five animals in each group; p value a < 0.05, b < 0.01; c < 0.001 when compared to control.

2 h. The flask was cooled and contents were poured into acidified ice cold water. The crude product that separated out was washed with a little cold water and recrystallized from methanol. IR (KBr, cm^{-1}): 3082 ν(aromatic ring), 1685 and 1663 ν(lactam ring). ^1H NMR ($CDCl_3$, δ): 7.3-7.5 (s, 5H), 4.73 (m, 3H), TLC R_f value 0.69 (chloroform:methanol:: 9.5:0.5).

Antimicrobial activity: All the compounds were screened *in vitro* for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Bacillus cereus*, *Escherichia coli*, *Aspergillus niger* and *Candida species* by bore cup method, DMSO was chosen as solvent for all synthesized compounds. After 24 h of incubation at 37ºC, the MIC was obtained.

Analgesic activity: LD_{50} value of the synthesized compounds was taken. Tail flick method. Tail clip methods were used for studying analgesic activity[12].

RESULTS AND DISCUSSION

All the synthesized compounds were characterized by IR, ^1H NMR and elemental analysis. The compounds were also evaluated for antibacterial and antiinflammatory activities. In the antimicrobial evaluation, the 4-chloro derivative showed the maximum activity against gram negative *E. coli*, gram positive *Cocci*, *Bacilli*, yeast-*Candida*, mould *Aspergillus niger* whereas other compounds were moderately active (Table-2). The compound **1** is the most toxic and compound **5** is the least toxic among the six synthesized compound. In the analgesic study, all the synthesized compounds showed analgesic activity (Tables 3-5).

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