Synthesis and Biological Activity Studies of Some oxadiazole derivatives carrying Quinoline moiety

*Sunil Kumar Chaitanya P and Ishwar Bhat K
Department of Pharmaceutical Chemistry, NGSM Institute of Pharmaceutical Sciences,Mangalore-574160

Abstract:

Oxadiazole derivatives carrying 2-methyl,8-hydroxy quinoline were synthesized by treating 2-[(2-methylquinolin-8-yl)oxy]acetohydrazide with different aromatic acids in presence of phosphorous oxy chloride .The structures of the newly synthesized compounds were confirmed by IR, ^{1}HNMR and Mass spectral analysis. The antibacterial and antifungal activities of the compounds were evaluated by cup and plate method .*Pseudomonas aeruginosa, Bacillus subtilis, Eshcerichia coli, Stapphylococcus aureus* and *Candida albicans* were used as test organisms. The standard drugs used were Ciprofloxacin and Griseofulvin. The compounds were also screened for anti inflammatory activity by paw edema method with indomethacin as standard.

Keywords: Oxadiazoles, antibacterial, antifungal, anti-inflammatory.

Introduction:

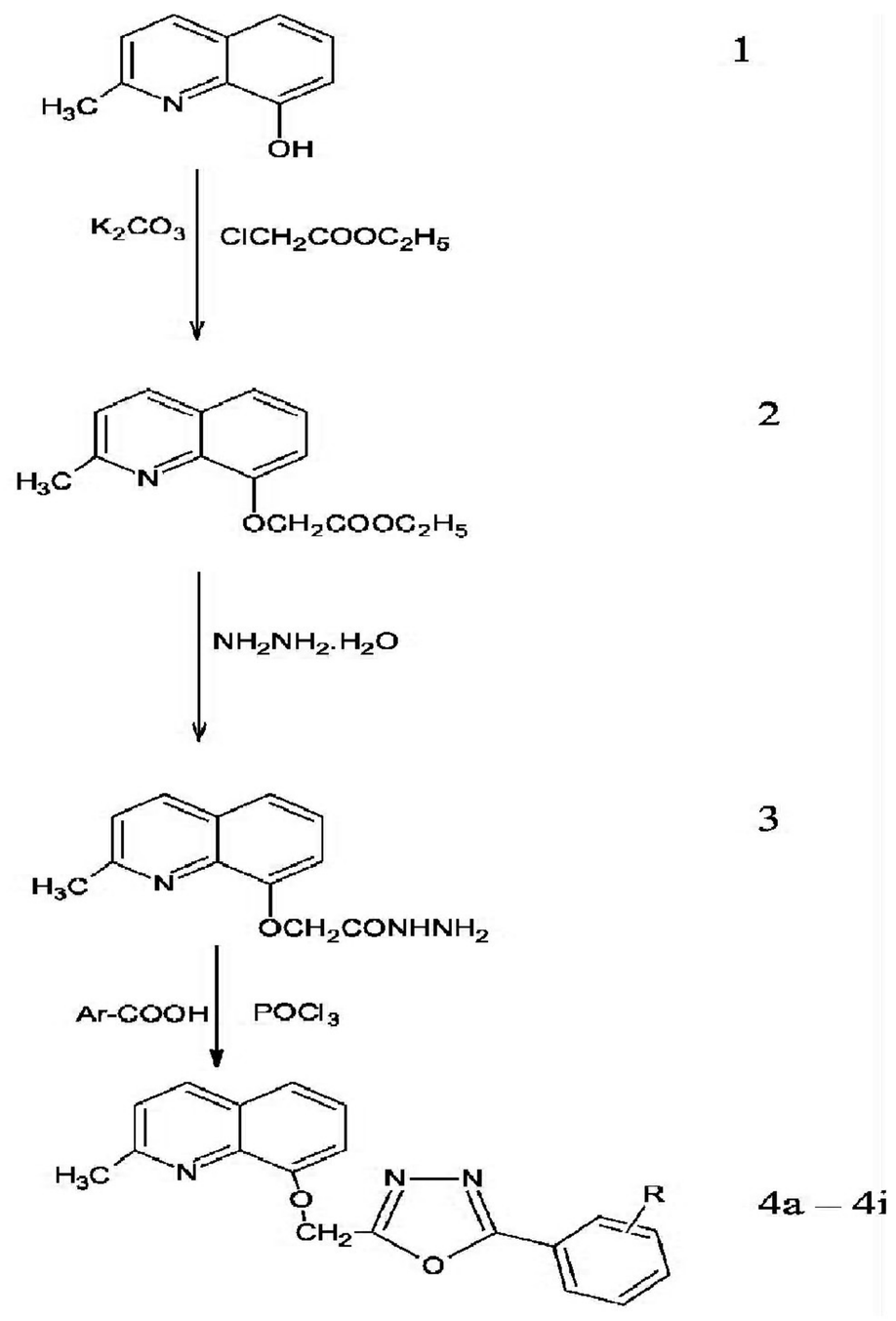
In continuation of our work on synthesis of heterocyclic compounds containing quinoline nucleus ,we report in this paper , synthesis and antimicrobial studies of some 2,5-disubstituted oxadiazoles carrying quinoline moiety.

2,5-disubstituted-1,3,4-oxadiazole derivatives have been reported to possess diversified activities like antibacterial, antifungal, anticancer, insecticidal, anti-inflammatory, CNS stimulant and antihypertensive activities. Similarly quinoline nucleus is also credited with myriad pharmacological activities . The quinoline nucleus also forms an integral part of a class of natural products i.e cinchona alkaloids. The quinoline nucleus is also found to be present in flouro quinolone group of drugs. In view of the above observations and in continuation of our studies on heterocyclic compounds of biological interest we have synthesized a new series of oxadiazoles carrying quinoline moiety and screened them for antibacterial, antifungal and anti-inflammatory activities .

In the present work 2-methyl,8-hydroxy quinoline (**1**) when teated with ethylchloroacetate in presence of Potassium carbonate in dry acetone yielded ethyl[(2-methylquinolin-8-yl)oxy]acetate (**2**) .Hydrazinolysis of **2** with hydrazine hydrate yielded 2-[(2-methylquinolin-8-yl)oxy]acetohydrazide (**3**) Cyclization of **3** with various aromatic acids in presence of Phosphorous oxy chloride afforded 2-(substituted phenyl)-5-((2-methyl quinolin-8-yloxy)methyl-1,3,4-oxadiazole derivatives (**4a-o).**

The structures of the synthesized compounds were assigned on the basis of IR, ^{1}HNMR and Mass spectral analysis. The compounds were screened for their in vitro antibacterial and antifungal activities. The compounds were also screened for their anti inflammatory activity

2. Experimental :



Author for correspondence:
P. Sunil Kumar Chaitanya.
Department of Pharmaceutical Chemistry,
N.G.S.M. Institute of Pharmaceutical Sciences,
Paneer, Deralakatte- 574 160.
Mangalore. Karnataka. India.
Tel.: +91 824 2203993, +91 824 2203991;
fax: +91 824 2203992.,Mob: +919986570323
E-mail: sunilchaitanya@yahoo.co.in

Procedure:

Synthesis of ethyl{(2-methylquinolin-8-yl)oxy}acetate(2)

A mixture of 2-methyl,8-hydroxyquinoline **1** (0.05mol), ethylchloroacetate (0.05mol) and anhydrous potassium carbonate in dry acetone were refluxed for 24 hours on water bath at 70°C. The resultant reaction mixture was cooled and filtered. The excess solvent was distilled off and the reaction mixture was dissolved in ice cold water. Further extracted with ether and the ethereal layer was washed with cold water and dried over anhydrous sodium sulphate. The ether portion was concentrated to get the corresponding ester.

IR(Cm^{-1}):3053.83(CH),1755.26(C=O, ester),1249.05(C-O-C)
1HNMR(δPPM):7.30-6.87(5H,m,Ar), 4.86 (2H,s,OCH_2), 4.20 (2H,m,CH_2,ethyl),2.67(3H,s,CH_3),1.23(3H,m,CH_3, ethyl).

Synthesis of 2-[(2-methylquinolin-8-yl) oxy]acetohydrazide(3)

A mixture of **2** (0.05mol) and hydrazine hydrate99% (0.07mol) in ethanol was refluxed for 6 hours. The excess of solvent is distilled off and the separated product was recrystallized from ethanol.

IR(Cm^{-1}):3369.1(NH),3067.5(CH),1662.6(C=O, amide),1425.7(C-N)

^{1}HNMR(δPPM):10.64(1H,s,NH),8.07-7.12 (5H,m,Ar),4.82(2H,s,OCH_2),3.73(2H,m,NH_2),2.80(3H,s,CH_3)

Synthesis of 2-(4-chlorophenyl)-5-((2-methyl quinolin-8-yloxy)methyl-1,3,4-oxadiazole (4a)

A mixture of 3(0.01mol) and p-chloro benzoic acid(0.01) was heated in the presence of phosphorous oxy chloride (10 ml) at 70ÚC for 6 hours. The reaction mixture was cooled and poured onto crushed ice, stirred well and neutralized with 20% sodium carbonate. The solid thus separated was filtered and recrystallized from DMF.

IR(Cm^{-1}):3063.47(CH),1609.05(C=N),1121.05 (C-O-C),751.82(C-Cl)
^{1}HNMR((δPPM):7.52-7.21(9H,m,Ar), 4.88(2H,s,OCH_2),,2.77(3H,s,CH_3)
Mass(m/z): M+ -351.

Melting points were taken in open capillaries and were uncorrected. IR spectra were recorded on Perkin Elmer FT/IR spectrometer. FAB mass were recorded on Jeol-SX 102/DA-600 mass spectrometer.^{1}HNMR spectra were recorded on Bruker advance II-400 spectrometre using TMS as internal standard.

The physical data of the synthesized compounds (4a-4o) is given in table - I

3.Results and discussion:

Synthesis of oxadiazole derivatives by the described method resulted in products with good yield. All the reactions were carried out under prescribed laboratory conditions. The solvents and reagents used in synthetic work were of laboratory grade and were purified by distillation.

Purity of the newly synthesized compounds were determined by melting point by open capillary method .Progress of the reactions was monitored by TLC.

4.Biological Activity:

Antibacterial activity:

Studies on the antibacterial activity of the synthesized compounds have been carried out against four pathogenic organisms,viz., *Stapphylococcus aureus, Bacillus subtilis, Eshcerichia coli* and *Pseudomonas aureuginosa*. The antibacterial activity of the newly synthesized compounds in the present study was assessed by cup-plate method. The results of the antibacterial studies are shown in table 2.Among the compounds tested 4a,4b,4f,4g and 4l have shown good activity against all the pathogens. Compound 4c showed good activity against *B.subtilis ,E.coli* and no activity against S.aereus.4d and 4i showed moderate activity against S.aereus and E.coli and no activity against *B.subtilis* and *P.aeuriginosa*. Ciprofloxacin (10µg) was used as the standard drug. All the compounds were tested at 50 µg level.

Antifungal activity:

The antifungal activity studies of the synthesized compounds have been carried out against the fungus *Candida albicans* by cup-plate method. Among the compounds tested 4a,4b,4f and 4l have shown good activity and compounds 4k, and 4n have shown moderate activity. Griseofulin was used as standard drug(10 µg).All the compounds were tested at 50 µg level. The results of antibacterial and antifungal activity studies is given in table - II

Anti-inflammatory Activity :

Selected compounds were screened for their anti-inflammatory activity using carageenan – induced paw edema method. Albino rats were divided into control, standard and test groups, each consisting of six rats. A group of rats was treated with tween-80(1%) suspension IP (control). Another group was administered a dose of 100 mg/kg of the suspension of test compounds . After 30 minutes the animals were injected with 0.1 ml of carageenan (1%w/v) in sub plantar region of left hind paw of the rats. The volume of the paw was measured using the mercury displacement technique with the help of a plethesmograph both in control , standard and test

groups of animals at 1/2hr ,1hr, 2hr and 3hr intervals after the injection. The initial volume of the paw was measured within 30 seconds of injection. All the compounds tested have shown significant activity.

The results of anti-inflammatory studies is give in table - III

Spectral data of the compounds:

4b . 2-(4-nitrophenyl)-5-((2-methylquinolin-8-yloxy]methyl)-1,3,4-oxadiazole
IR(Cm^{-1}):3005.58(CH),1604.21(C=N),1183.62(C-O-C),
^{1}HNMR(δ PPM): 8.14-6.85(9H,m,Ar),5.50(2H,s,OCH_2),2.71(3H,s,CH_3)
Mass,m/z – M^+- 364.

4c . 2-(4-methoxyphenyl)-5-((2-methylquinolin-8-yloxy]methyl)-1,3,4-oxadiazole
IR(Cm^{-1}):2987.56(CH),1600.82(C=N),1181.94 (C-O-C),
^{1}HNMR(δ PPM): 8.60-6.85(9H,m,Ar),4.89(2H,s,OCH_2),3.84(3H,s,OCH_3)
2.83(3H,s,CH_3), Mass,m/z – M^+- 347.

4d . 4-(5((2-methylquinolin-8-yloxy)methyl)-1,3,4-oxadiazol-2-yl)phenol
IR(Cm^{-1}):3428.35(OH),2926.15(CH_3)1607.55(C=N),1166.24(C-O-C),
^{1}HNMR(δ PPM): 10.56(1H,s,OH) 8.15-7.28(9H,m,Ar),5.64(2H,s,OCH_2),2.72
(3H,s,CH_3), Mass,m/z – M^+- 333

4e . 8-{[5-(4-bromo phenyl)-1,3,4-oxadiazol-2-yl]methyl}2-methyl quinoline
IR(Cm^{-1}):3004.3(CH),1584.6(C=N),1176.1(C-O-C),
^{1}HNMR(δ PPM): 8.62-6.94(9H,m,Ar),5.21(2H,s,OCH_2), 2.62(3H,s,CH_3)
Mass,m/z – M^+- 395

5. Acknowledgement :

The authors are thankful to Dr. D. Satyanarayana, director (PG-studies and research),Dr.EVS.Subrashmanyam, principal, NGSM Institute of Pharmaceutical Sciences for providing necessary facilities. The authors are also thankful to CDRI-Lucknow, SAIF-Punjab University, IISC-Bangalore for providing spectral data.

TABLE -1

Physical data of the compounds(4a-o)

compound	R	Molecular formula	Molecular weight	Melting point °c	Rf	%yield
4a	4-Cl	$C_{19}H_{14}N_3O_2Cl$	351	196-198	0.72	80
4b	4-NO_2	$C_{19}H_{14}N_4O_4$	362	132-134	0.67	65
4c	4-OCH_3	$C_{20}H_{17}N_3O_3$	347	122-124	0.86	62
4d	4-OH	$C_{19}H_{15}N_3O_3$	333	152-154	0.62	60
4e	2-Br	$C_{19}H_{14}N_3O_2Br$	395	146-148	0.74	52
4f	3,5-NO_2,2-OH	$C_{19}H_{13}N_5O_7$	423	154-156	0.80	79
4g	5-Cl,2-OH	$C_{19}H_{14}N_3O_3Cl$	367	116-118	0.59	54
4h	2,4-Cl	$C_{19}H_{13}N_3O_2Cl_2$	385	124-126	0.60	56
4i	H	$C_{19}H_{15}N_3O_2$	317	170-172	0.54	72
4j	3,4-OCH_3	$C_{19}H_{19}N_3O_4Br$	377	162-164	0.90	62
4k	3-Cl	$C_{19}H_{14}N_3O_2Cl$	351	108-110	0.87	56
4l	2-Cl,4-NO_2	$C_{19}H_{14}N_4O_4Cl$	396	204-206	0.69	65
4m	4-NH_2	$C_{19}H_{16}N_4O_2$	332	186-188	0.70	66
4n	2-Cl	$C_{19}H_{14}N_3O_2Cl$	351	148-150	0.81	54
4o	2-OCH_3	$C_{20}H_{17}N_3O_3$	347	101-103	0.58	66

TABLE-II

Anti microbial data of the compounds (4a-o):

Compound	Diameter of zone of inhibition				
	B.subtilis	*S.aureus*	*E.coli*	*P.aeruginosa*	*C.albicans*
4a	17	19	21	17	15
4b	16	20	23	15	13
4c	14	-	18	10	07
4d	-	14	18	-	-
4e	12	13	17	09	06
4f	16	18	19	16	14
4g	16	19	22	15	10
4h	15	16	18	13	08
4i	-	12	14	-	-
4j	14	13	17	-	-
4k	15	15	18	14	10
4l	16	18	20	16	15
4m	15	17	18	-	09
4n	14	17	16	13	10
4o	12	-	15	-	-
Ciprofloxacin	18	20	24	19	-
Griseofulvin	-	-	-	-	17

III . Anti-inflammatory activity data of the compounds (4a-g):

Compound	dose	edema volume in ml				reduction %			
	(Mg/kg)	½ hr	1 hr	2hr	3hr	½ hr	1hr	2hr	3hr
Control (gum acacia)		0.699	0.832	0.727	0.616				
Standard indomethacin)	25	0.245	0.218	0.193	0.133	64.03*	73.40**	73.46**	76.62**
4a	200	0.254	0.226	0.346	0.250	63.13	72.62	52.26**	58.85**
4b	200	0.257	0.223	0.214	0.170	63.22	72.75	70.36**	72.51**
4c	200	0.267	0.307	0.231	0.164	61.70**	62.89**	64.41*	62.48**
4d	200	0.311	0.386	0.267	0.158	55.04**	53.30**	62.98**	74.52**
4e	200	0.270	0.228	0.205	0.181	61.36**	72.35**	71.63*	70.52**
4f	200	0.257	0.231	0.195	0.169	63.73*	72.03**	73.06*	72.57**
4g	200	0.265	0.238	0.200	0.178	62.83*	68.89**	70.34*	73.45**

Significance at P<0.05*, 0.01**

6.References:

Agalwadi KR,.Suresh S, Pattan SR, Pujar GV and .Javali.MCInd.J.Het.Chem,17 (2007),93.

Balakrishna Kalluraya, Ramesh Chimbalkar and Prashanth Gunaga. Ind.J.Het.Chem,6(1996)106.

Dubey AK, Sangwan NK.Ind.J.Chem,33B(1994),1043.

Mogilaiah K, .Srinivas Chowdary D, and Babu Rao.R.Ind.J.Chem,40B(2001),43.

Mohan TP,.Vishalakshi B,Bhat,KS Rao KS and Kendappa GN.Ind.J.Chem,43B (2004),1798.

Mohd.Amir SA, Javed and Harish Kumar.Ind.J.Chem,45B(2006),2506.

Priya V Frank and Balakrishna Kalluraya.Ind.JChem,44B(2005),1456.

Priya V Frank, KS Girish and Balakrishna Kalluraya.J.Chem.Sci(2007),119.

Ponticello GS, Englehardt EL and Baldwin,J.Het.Chem,17(1980),425.

Rajasekhara.H, .Ramesh,D. Chandrasekar.C, .Mahadevan. KM and Vaidhya VP Ind.J.Het.Chem,16(2007),353.

Ravindra KC, Vagdevi HM, Vaidhya VP and Basvaraj Padmashali.Ind.J.Chem, 45B,(2006),2506.

Subrahmanya Bhat K, Karthikeyan MS,Shivarama Holla B and .Sucheta Shetty N.Ind.J.Chem,43B(2004),1765.

Xin-Ping Hui, Chang-Hu Chu & Zi-Zi Zangh.Ind.J.Chem,41B,(2002),2176.