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ISSN: 0973-4945; CODEN ECJHAO
E-Journal of Chemistry
2011, **8(2),** 931-937

Synthesis and Biological Activity of Some 2-(2'-(Substituted Phenyl-4-thiazolidinone-3-yl)-1'3'-isoxazol-4-yl)aminoquinoline Derivatives

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Received 10 April 2010; Accepted 5 June 2010

Abstract: Quinoline a heterocyclic nucleus, played a pivotal role in the development of different medicinal agents and in the field of agrochemicals. Several 2-(2'-substituted phenyl-4-thiazolidinon-3-yl)-1'3'-isoxazol-4-yl) amino-quinoline **IV(a-k)** have been prepared 2-(substituted arylideneimino-1'3'-isoxazol-4'-yl) aminoquinoline **III(a-k)** and tested for their antimicrobial and antifungal activity against different microorganism. The structure of compound **III(a-k)** and **IV(a-k)** have confirmed on the basis of their elemental and spectral analysis such as IR, ^{1}H NMR and Mass spectrometry.

Keywords: Quinoline, Isoxazoles, Thiazolidinones, Antibacterial, Antifungal, Insecticidal activity

Introduction

The chemistry of quinoline has gained increasing attention due to its various diverse pharmacological activities[1-3]. Numerous quinoline, derivatives have been prepared and their pharmacological properties were evaluated. Many of these compounds have proved to be active anticancer[4-5], anti-inflammatory[6] antiallergic[7] and antimicrobials[8-11] antimaralial[12] agent. Further, the utility of quinoline derivatives in the preparation of some dyes and pigment have been reported[13]. On the other hand isoxazole derivatives controlled *Botrytis cinera* on cucumbers have been found to have antiviral properties against herpes type II virus[14]. Penicilline derivatives containing isoxazole ring are found to be antibacterial activities. Isoxazole derivatives[15] are used as corrosion inhibitors for fuels and lubricants[16]. Moreover thiazolidinones have a broad spectrum of pharmacological properties *i.e.* antibacterial[17], antifungal[18] and antiinflammatory[19].

Experimental

The melting points were determined in open capillaries with an electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a simadz FT-IR-8400 spectrometer and ^{1}H NMR spectra on Bruker spectrometer (300 M_Z) using TMS as an internal standard. All chemical shift values were recorded as δ (ppm).

*Synthesis of 2-(chloroacetyl)aminoquinoline (**I**)*

Chloroacetyl chloride (0.02 mole) was added to a solution of 2-aminoquinoline (0.02 mole) in dry benzene (80 mL) at 0-5 ^{0}C. The reaction mixture was stirred for 4 h at 45 ^{0}C. Excess of benzene was distilled off. The solid thus obtained was washed with petroleum ether and kept in refrigerator overnight and solid obtained was purified by recrystallization from benzene to yield compound **I,** m.p.189 ^{0}C, yield 96%.

*Synthesis of 2-(2'-amino1'3'-isoxazol-4'-yl)aminoquinoline (**II**)*

A mixture of 2-(chloroacetyl)aminoquinoline (**I**) (0.02 mole) and urea (0.01 mole) in acetone (90 mL) was refluxed for 12 h at 65-70 ^{0}C. The excess of solvent was distilled off and the solid obtained was poured into ice cold water, recrystallized from methanol. Now the solid was washed with 2% sodium carbonate and then with water to liberate the base completely, dried and purified by recrystallization from ethanol. M.p. 205 ^{0}C, yield 86%.

*Synthesis of 2-(substitutedarylideneimino-1'3'-isoxazol-4'-yl)aminoquinoline(**IIIa-k**)*

To a solution of compound **II** (0.02 mole) in ethanol (60 mL), substituted aromatic aldehydes (**a-k**), (0.02 mole) and a few drops glacial acetic acid were added and the mixture refluxed for 10 h. It was then cooled, concentrated and poured into crushed ice and filtered. The product thus obtained was purified by recryatallization from methanol to get compound **III(a-k).** The related physical data are given in Table 1.

Table 1. Physical characterization data of synthesized compounds **III(a-k)**

Compd	Mol. Formula	M.W.	Yield %	M.P.	Elements, %					
					C		H		N	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
IIIa	$C_{19}H_{14}N_4O_2$	330.32	69	205	69.08	69.05	4.27	4.21	16.96	16.93
IIIb	$C_{19}H_{14}N_4O_2$	330.32	65	210	69.08	69.06	4.27	4.21	16.96	16.93
IIIc	$C_{19}H_{13}N_4OCl$	348.78	67	126	65.43	65.39	3.75	3.71	16.06	16.01
IIId	$C_{19}H_{13}N_4OCl$	348.78	68	121	65.43	65.39	3.75	3.71	16.06	16.01
IIIe	$C_{19}H_{13}N_4OCl$	348.78	72	136	65.43	65.39	3.75	3.71	16.06	16.01
IIIf	$C_{20}H_{17}N_4O_2$	345.36	59	143	69.55	69.51	4.96	4.91	16.22	16.17
IIIg	$C_{19}H_{13}N_5O_3$	359.31	68	235	63.51	63.48	3.64	3.59	19.49	19.45
IIIh	$C_{19}H_{13}N_5O_3$	359.21	65	205	63.51	63.48	3.64	3.59	19.49	19.45
IIIi	$C_{19}H_{14}N_4O_2$	330.32	71	254	69.08	69.05	4.27	4.21	16.96	16.93
IIIJ	$C_{20}H_{14}N_4O_3$	360.34	73	247	66.66	66.63	4.47	4.42	15.54	15.47
IIIk	$C_{21}H_{19}N_5O$	376.86	59	245	66.92	66.87	5.08	5.02	18.58	18.53

*2-(2'-Substitutedphenyl-4-thiazolidinon-3-yl)-1'3'-isoxazol-4-yl) amino-quinoline **IV(a-k)***

A solution of compound **III** (0.02 mole), thioglycolic acid (0.02 mole) and anhydrous zinc chloride (2 g) in absolute ethanol (60 mL) was refluxed for 8 h, concentrated, cooled and poured into crushed ice and then filtered. The product obtained (Scheme 1) was recrystallized from acetone to get compound **IV(a-k).** The related physical data are given in Table 2.

Spectral Interpretation

*Compound **II***

IR: 3442 cm^{-1}(N-H str.); 3090 cm^{-1}(H-quinoline str.); 2340 cm^{-1}(C-H str. isoxazole); 1680 cm^{-1} (C=N str. isoxazole), 1560 cm^{-1}(C=N str. quinoline), 928 cm^{-1}(quinoline ring-breathing); 896 cm^{-1}(isoxazole ring breathing).

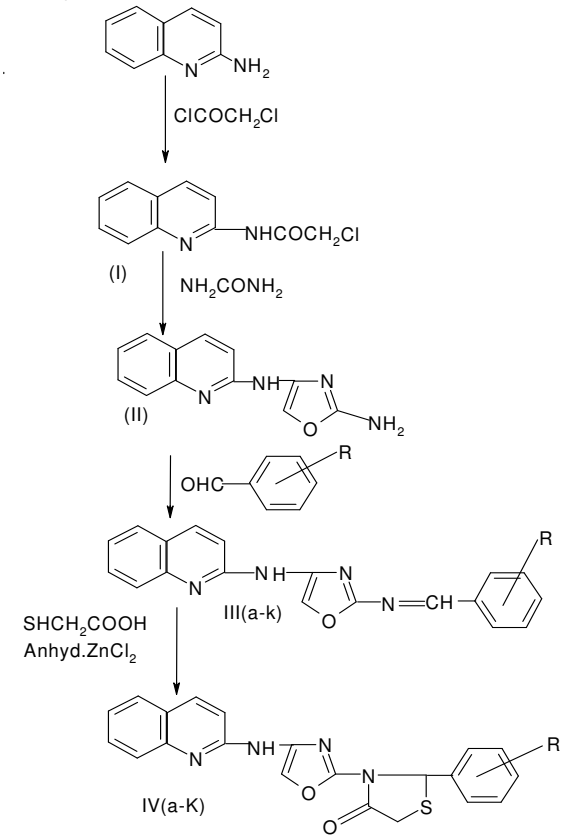
*Compound **IIa***

^{1}H NMR: ($CDCl_3$ in δ ppm): 8.6 δ (s) NH_2; 5.7 δ(s) NH; 4.2 δ (s) (2CH of isoxazole); 6.2δ(Unsy.m.) quinoline ring quinoline.

Table 2. Physical characterization data synthesized compound **IV(a k)**

Compd.	Mol. Formula.	M.W.	Yield %	M.P.	Elements, %					
					C		H		N	
					Calc.	Found	Calc.	Found	Calc.	Found
IVa	$C_{27}H_{20}N_4O_3S$	480.51	67	107	67.48	67.42	4.19	4.15	11.65	11.61
IVb	$C_{27}H_{20}N_4O_3S$	480.51	71	98	67.48	67.43	4.19	4.19	11.65	11.61
IVc	$C_{27}H_{19}N_4O_2SCl$	498.97	68	118	64.99	64.95	3.80	3.75	11.22	11.18
IVd	$C_{27}H_{19}N_4O_2SCl$	498.97	72	121	64.99	64.95	3.80	3.75	11.22	11.18
IVe	$C_{27}H_{19}N_4O_2SCl$	498.97	73	134	64.99	64.95	3.80	3.75	11.22	11.18
IVf	$C_{28}H_{22}N_4O_3S$	494.54	59	148	68.00	67.08	4.48	4.43	11.32	11.28
IVg	$C_{27}H_{19}N_5O_4S$	509.50	68	247	63.64	63.58	3.70	3.67	13.74	13.69
IVh	$C_{27}H_{19}N_5O_4S$	509.50	59	238	63.64	63.58	3.70	3.67	13.74	13.69
IVi	$C_{27}H_{20}N_4O_3S$	480.51	63	189	67.48	67.43	4.19	4.15	11.65	11.61
IVJ	$C_{28}H_{21}N_4O_4S$	509.52	65	122	66.00	65.08	4.15	4.11	10.99	10.96
IVk	$C_{29}H_{25}N_5O_2S$	507.59	76	233	68.62	68.58	4.96	4.92	13.97	13.95

Reaction Sequence:



Scheme 1

R = substitituted group, R = a = 2= OH, A = 4- OH, c = 4- Cl, d = 3-Cl, e = 2-Cl, t = 4-OMe, g = 3-OH_2, h = 2- NO_2 , i = 4- OH, , j = 4-OH, 2-OMe, k = 4-$N(CH_3)_2$

*Compound **IIIa***

IR: 3525 cm^{-1} (O-H str.); 3426 cm^{-1}(N-H str.); 3096 cm^{-1}(C-H str. quinoline); 2460 cm^{-1}(N=C-Hstr.); 2343 cm^{-1}(C-Hstr. Isoxazole); 1820 cm^{-1}(N=CHstr.); 1683 (C=Nstr.isoxazole); 1580 cm^{-1}(C=N str.quinoline); 986 cm^{-1}(quinoline ring breathing);926 cm^{-1}(isoxazole ring breathing).**^{1}H NMR:** ($CDCl_3$ in δ ppm): 8.8 δ (s)OH; 5.8δ(s)-NH-; 3.2δ (s)-N=CH-; 4.1δ (2CH isoxazole); 6.1δ (Unsym.m) quinoline ring; 6.9δ (Unsym.m) orthodisubstitutedphenyl.

*Compound **IVa***

IR: 3528 cm^{-1} (O-H str.); 3427 cm^{-1}(N-H str.); 3096 cm^{-1} (CH str. quinoline), 3100 cm^{-1}(Ar-H str.) 2346 cm^{-1}(C-H str. isoxazole),1838 cm^{-1}(C=O str.);1690 cm^{-1}(C=N str. isoxazole); 1560 cm^{-1} (C=N str. quinoline); 2985 cm^{-1}(C-H str. thiazoline ring)1120 cm^{-1} (thiazolone ring breathing); 980 cm^{-1} (quinoline ring breathing);938 cm^{-1} (isoxazole ring breathing). **^{1}H NMR:** ($CDCl_3$ in δ ppm) 8.6 δ (s) OH; 5.5δ (s) NH; 4.2δ (s) 2H of thiazolone ring; 3.8δ (s) 1H of thiazolone ring; 4.8δ (s) 2H of isoxazole; 6.0δ (Unsym.m.) quinoline ring 6.2δ (Unsym.m.) ortho-disubstituted phenyl ring.

Results and Discussion

The reaction of chloroacetyl chloride and 2-amino quinoline in dry benzene gave 2-(chloroacetyl) amino quinoline **I**. The structure of **I** was confirmed from its spectral data and analytical studies. The compound **II** was obtained by reaction of **I** with urea in acetone and well characterized using its spectral and analytical data. Its IR spectrum revealed the presence of NH_2 group by exhibiting a strong absorption at 3442 cm-^{1} and the formation of isoxazole ring was confirmed by the absence of C=O str at 1826 cm^{-1}.The NMR spectrum of **II** in $CDCl_3$ show one singlet at 8.6 δ due to NH_2 protons and one singlet at 5.7 δ due to NH proton. The two complex multipletes at 6.2 δ & 4.2 δ was assigned for five aromatic protons. The C, H, N, analysis of the compound **II** was in good agreement with the proposed molecular formula $C_{12}H_9N_3O$ .The reaction of **II** with substituted aromatic aldehyde and few drops of glacial acetic acid gave **III(a-k)** and was well characterized using its spectral and analytical data. Its IR spectra revealed the presence of C=N group by exhibiting a strong absorption at 1683 cm^{-1} the NMR spectrum of **III(a-k)** in $CDCl_3$ show two complex multiplets at δ 6.9 & 6.1 was assigned for seven aromatic protons. Further the reaction of **III(a-k)** with thioglycolic acid in the presence of acetic acid was carried out with an interest that the reaction would proceed as shown in Scheme 1 and at the end, this attempt yield **IV(a-k)**. The IR spectrum of **IV(a-k)** shown strong absorption at 1838 cm^{-1} due to >C=O group. The NMR spectrum exhibited two singlets at 3.8 & 4.2 for C_2-H_2 and C_5-H protons of thiazolidinone ring. Three unsymmetrical multiplets appear in 7.3 δ, 6.0 δ, 6.2 δ with eleven aromatic protons. This was also supported by the mass spectrum of the compound which displayed the molecular ion peak at 480.51. The elemental analysis was also in good agreement with the molecular formula $C_{27}H_{20}N_4O_3S$. All compounds show good to moderate biological activity.

Antimicrobial activity of synthesized quinoline derivatives

Several workers determined antimicrobial activity *in vitro* using:
a). Turbimetric method
b). Serial dilution tube technique.
c). Diffusion methods.

In the present study the filter paper disc diffusion plate method was employed to evaluate the antimicrobial activity *in vitro*. Filter paper disc diffusion plate method[16] was used. The medium was first inoculated with a loopful of broth culture of the organism and shaken for uniform distribution. It was poured into Petri dish. Discs soaked in test sample solution were placed over the seeded

medium and pressed so that all parts of disc come in contact with the medium. The seeded plates were incubated at 28 ^{0}C for 32 h in case of bacteria and 37 ^{0}C for 72 h in case of fungi. Same procedure was adopted for standard drugs. The activity was determined by using 4% and 2% solution of synthesized isoxazole, thiazolidinone derivatives. 4% and 2% solutions of the standard drugs, streptomycine and tetracycline (for bacteria) and nastytine, amphotericine-B (For fungi) were also prepared. Related data have been given in Table 3 - 6.

Insecticidal activity of synthesized quinoline derivatives

Cockroaches were selected for the study. 4% (w/v) solution of synthesized compounds of isoxazole, thiazolidinone was prepared in acetone. 4% (w/v) of solution of synthesized compounds was injected into the abdominal region of the cockroach with the help of micro syringe. The time of death, the antennae becomes motionless, the appendages shrunk and folded towards the ventral side and cockroach lay dorsally. For each sample, four replications were performed and average KD value noted. Cypermethrin 25% EC was used as standard. Its 4% (w/v) solution was prepared in acetone. It belongs to pyrethroid group. Related graphs are given in Figure 1 & 2.

Table 3. Antibacterial activity of the synthesized **III(a-k)** against various bacteria at two different concentrations (ppm)

Comp	*E. coli*		*B. Subtillis*		*S. aureus*		*B. fragilis*		*K.pneumonie*	
	50	100	50	100	50	100	50	100	50	100
IIIa	++++	+++	++	+++	++	++	++++	+++	-	+
IIIb	++	+	+++	++	+++	++	++	+++	++	++
IIIc	+++	++	+++	++	++	+++	+	++	+++	++
IIId	++	++	++++	++	-	+	+++	++	++	+++
IIIe	-	+	++	+++	+++	++	+++	++	+	++
IIIf	+++	++	+++	++	++	+	++	+	-	++
IIIg	++	+	-	+	+++	++	++	++	-	+
IIIh	++	+++	+	++	-	+	++++	++	++	+
IIIi	+	++	++	+++	++	+++	++	+++	+	++
IIIj	++++	+++	+	++	+	++	-	+	+++	++
IIIk	++	++	+++	++	++	+++	+	++	++	+++

++++ = *Strongly active, +++ = Moderately active, ++ = Weakly active, +, - = Inactive,*

Table 4. Antifungal activity of the synthesized **III(a-k)**against various fungi at two different concentrations (ppm).

Comp	*A. flavus*		*A. niger*		*T. viridae*		*F.oxisporum*		*C.albicans*	
	50	100	50	100	50	100	50	100	50	100
IIIa	+++	+++	+++	++++	++	++++	++	+	++	+++
IIIb	+++	++	++	+	+++	++	+++	+++	+++	++
IIIc	++	+	+++	++	++	+	++	++++	+++	++
IIId	+++	++	++++	+++	+++	++	+++	+++	++	+++
IIIe	+++	++	+++	++	++++	+++	+++	++	-	+
IIIf	++	+++	-	+	++	+	-	+	++	++
IIIg	+	++	++	+++	-	+	+	++	++	+++
IIIh	++	++	++	+++	+	+++	++	+++	+	++
IIIi	++	+++	+++	++	++	++	+++	++	++	+
IIIj	+++	++	+	++	+++	++	++	+++	-	++
IIIk	++	+	++	+++	++	+++	+++	++	+	++

++++ = *Strongly active, +++ = Moderately active, ++ = Weakly active, +, - = Inactive*

Table 5. Antibacterial activity of the synthesized **IV(a-k)** against various bacteria at two different concentrations (ppm)

Comp	*E. coli*		*B. fragilis*		*S. aureus*		*B. subtilis*		*K.pneumonie*	
	50	100	50	100	50	100	50	100	50	100
IVa	++	++	+++	++	++	++	+++	++	++	++
IVb	++	++	++	+++	++	++	++	+++	++	+++
IVc	+++	++	+++	++	+++	+++	+++	++	+++	+++
IVd	+++	+++	++	+++	++++	+++	++	++	+++	++
IVe	++	+++	+	++	++	+++	-	+	++	++
IVf	+	++	++	+++	++	+++	++	+++	-	+
IVg	++	+++	+	++	+++	++	+++	++	++	++
IVh	+++	++	+++	+++	+	++	++++	+++	++	+++
IVi	+++	++	++	++	-	++	+++	++	+++	++
IVj	++	++	++	++	+	+	++	+++	+++	++
IVk	+	+	+	++	++	+++	+	++	++	+

++++ = *Strongly activee, +++ = Moderately active, ++ = Weakly active, +, - = Inactive*

Table 6. Antifungal activity of the synthesized **IV(a-k)** against various fungi at two different concentrations (ppm)

Comp	*A. flavus*		*A. niger*		*T. viridae*		*F.oxisporum*		*C.albicans*	
	50	100	50	100	50	100	50	100	50	100
IVa	++	+++	++	+++	++	+++	++	+++	++	+
IVb	+++	++	++	++	+++	++	++	+++	++	+++
IVc	++	+++	++++ -	+++	++	+	+++	++	+++	++
IVd	++	++	++	+++	++	+	++	++	++	+++
IVe	+	++	+++	++	+++	++	++++	++	-	+
IVf	+++	++	++	+++	+	++	++	+++	++	+++
IVg	++++	++	+++	++	++	+++	+++	+++	+	++
IVh	+	++	+++	++	-	+	++	++	++	++
IVi	++	+++	++	+++	+	++	+	++	++	+++
IVj	-	+	-	+	++	+++	-	+	+++	++
IVk	++	+++	++	+++	+++	++	++	+++	++	+++

++++ = *Strongly activee, +++ = Moderately active, ++ = Weakly active, +, - = Inactive*

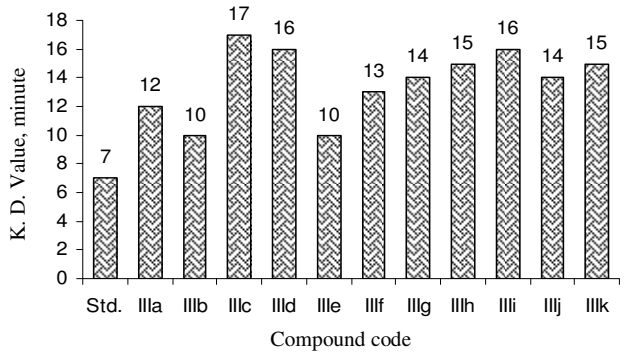


Figure 1. Insecticidal activity of **III(a-k)**

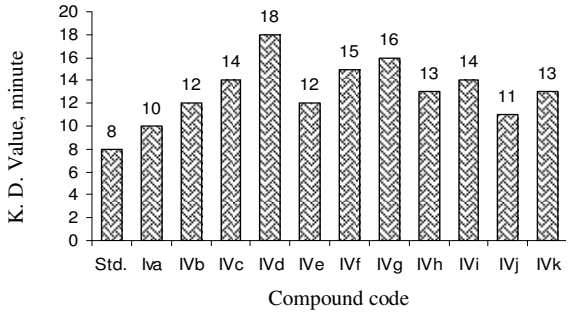


Figure 2. Insecticidal activity of **IV(a-k)**

Acknowledgment

The authors are thankful to SAIF, CDRI Lucknow for providing NMR spectral and mass spectral data of synthesized heterocyclic derivatives. We are also thankful to Prof. Mehta Department of Botany for his kind assistance in performing antimicrobial activity in Botany Department and Prof. O. P. Shrivastava, Head Department of Chemistry, Dr. H.S. Gour University, Sagar providing IR spectral data and laboratory facilities.

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