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REACTIONS AND BIOLOGICAL ACTIVITY OF SUBSTITUTED QUINOLINE

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Substituted quinoline reacted with halo compounds, amino acids, urea, amides, anilides and hydrazines. All the synthesized derivatives were biologically investigated.

Key words: Biological activity, Quinoline, Chemotherapeutic drugs.

Introduction

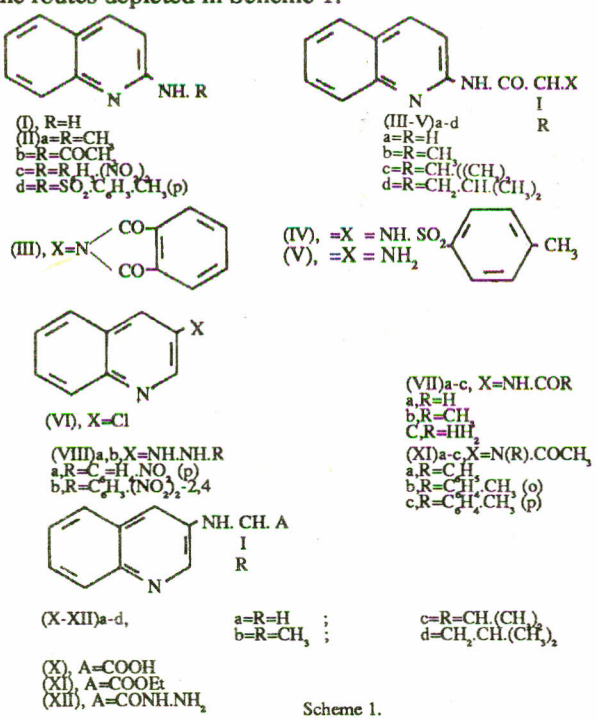
The quinoline chemistry with its diverse biological properties like antihistaminic [1], antihelminthic [2] has got much importance in recent years as chemotherapeutic drugs.

Vioform, 5-chloro-8-hydroxy-7-iodoquinoline is an ameobicide and antiseptic.

Siogen, 5:7-dichloro-8-hydroxy quinaldine is used as a mouth and throat antiseptic. Quinazolone derivatives have also wide applications in medicinal chemistry like CNS depressant [3,4], anticonvulsant [5,6], muscle relaxant [7,8], antivirals [9] and against influenza virus [10].

The present investigation aims to synthesize a number of quinoline derivatives supposed to be potentially active. Thus 2- amino and 3-chloroquinoline (I,VI) [11,12] were synthesized and reacted with halo compounds, amino acids, urea, amides, anilides and hydrazines to synthesize derivatives containing collectively the heterocyclic ring and the latent functional substituents and appear highly promising for biological activity studies.

The synthesis of the designed compounds was achieved by the routes depicted in Scheme 1.



Scheme 1.

Results and Discussion

2-Aminoquinoline (I) reacted with halo compounds namely, methyl iodide, acetyl chloride, 1-chloro-2,4-dinitrobenzene and *p*- toluene sulphonyl chloride to give derivatives (II)a-d respectively. Compound (I) reacted with phthalyl and tosyl derivatives of the amino acids glycine, alanine, valine and leucine to afford products (III & IV) a-d respectively. Hydrazinolysis of compounds (III) a-d gave the corresponding derivatives (V) a-d.

Reaction of 3-chloroquinoline (VI) with amides, urea, hydrazines, anilides and amino acids afforded a number of new products. Thus compound (VI) reacted with amides and urea to afford compounds (VII) a-c. Reaction of compound (VI) with hydrazines gave the corresponding derivatives (VIII) a,b. Also reaction of compound ((VI) with anilides afforded derivatives (IX) a-c. Some free amino acids and their corresponding esters reacted with compound (VI) to afford derivatives (X, XI & XII) a-d.

The structure of all the synthesized derivatives was confirmed by: (i) correct elemental analysis (ii) IR (iii) NMR compounds IVa, Va, VIIa,b and IXa showed bands at 1720, 1665, 1688, 1730, 1740 cm^{-1} characteristic to (γ C=O); bands at 3100, 3200, 3080, 3220, 3140 cm^{-1} characteristic to (γNH) for compounds IIa, IIIc, Vd, XIa and XIIb, bands at 3400, 3240 cm^{-1} characteristic to (γOH) for compounds Xa,d and bands at 1720, 1320 cm^{-1} characteristic to ($COOC_2H_5$).

NMR spectra showed bands attributable to quinoline protons at δ6.7-7.2 for compound (II), at δ6.8-7.4 for compound IXa and at δ 7.0- 8.0 for compound VIIIb.

Biological screening. The biological screening for the synthesized derivatives was carried out using the hole plate and filter paper disc methods [13,14]. Introduction of the functional substituents at quinoline moiety have shown high antimicrobial activity for some derivatives and inactivity for the others. Esterification for example of the terminal carboxyl group for compounds Xa,b has led to inactive derivatives XIa-d while hydrazinolysis of products (IIIa-d led to active derivatives Va,b,d. Results are summarised in Table 1.

Experimental

All melting points are uncorrected. The IR spectra were recorded with a Unicam SP 1200 spectrophotometer using the

TABLE 1. ACTIVITY (A) AND MINIMUM INHIBITORY CONCENTRATION (MIC) CALCULATED AS Na/ML FOR THE SYNTHESIZED DERIVATIVES.

Comp. No.	*Bacillus subtilis* ICC Strain		*Bacillus mycoids* USSR		*Bacillus cereus* NRRL-B569		*Escherichia coli* NRRL-B-210		*Salmonella typhosa* NRRL-B-573		*Phenicillium chryspgenum*	
	A	MIC	A	MIC	A	MIC	A	MIC	A	MIC	A	MIC
Va	+++	60	+++	30	++++	30	++++	15	++++	30	+++	30
b	++	125	+++	60	++	125	++++	30	+++	60	+++	60
d	+++	30	++	125	+++	60	+++	30	++++	30	+++	30
Xa	++	125	++++	30	++++	30	++	115	+++	15	+++	60
b	++++	30	+++	60	+++	30	++	125	++++	30	++	125

KBr technique. NMR spectra were recorded in DMSO-d_6 on a Varian A-60 spectrophotometer [chemical shift (δ), ppm] using TMS as internal standard. Thin layer chromatography (TLC, R_f) values was carried out on silica gel-G(BDH) using benzene-ethyl acetate (1:1) as a solvent system and an iodine-potassium iodide solution (20%) as the detection reagent. Ninhydrin, benzidine and silver nitrate reactions were used for detection of the amino acid derivatives on Watmann No.1 paper chromatograms (spot reactions).

Reaction of 2-aminoquinoline (I) with halo compounds: Formation of Compounds (II)a-d. A mixture of 2-aminoquinoline (I, 0.01 mole) and halo compounds, namely methyl iodide, acetyl chloride, 1-chloro-2,4-dinitrobenzene and *p*-toluene sulphonyl chloride (0.15 mole) was dissolved in (20 ml) pyridine. The reaction mixture was refluxed for 3 hr. then poured into ice cold water and the product yielded was crystallized from benzene to give compounds (III)a-d respectively Table 2.

Reaction of (I) with phthalyl and tosyl amino acids:. Formation of compounds (III & IV) a-d. N-Phthalyl or N-tosylamino acid namely glycine, alanine, valine and leucine (0.002 mole) and 2-aminoquinoline (I, 0.002 mole) were dissolved in tetrahydrofuran (120 ml). The reaction mixture was cooled to 0°, then dicyclocarbodiimide (0.0042 g) was added and the mixture stirred for 2 hr. at 0°, left for 24 hr. at 0° and for another 24 hr. at room temperature. The dicyclohexylurea was filtered off and the filterate was evaporated in *vacuo* and the residual was recrystallized from ethanol or methanol-water to give products (IV&V) a-d (Table 2).

Reaction of IIIa-d with hydrazine hydrate: Formation of compounds Va-d. 2-(N-Pht amino acid)-aminoquinoline (IIIa-d, 0.002 mole) was dissolved in ethanol (30 ml) and treated with hydrazine hydrate in ethanol (15 ml). The reaction mixture was refluxed for 2 hr. and left for 24 hr. at room temperature then the solvent was removed in *vacuo* and (10 ml) of H_2O was added and the solution was acidified to pH 6 with acetic acid. After digestion for 1 hr. on a steam bath, the suspension was diluted with (15 ml) of H_2O, cooled to room

TABLE 2. CHARACTERISATION AND PHYSICAL DATA OF ALL THE SYNTHESIZED DERIVATIVES.

Comp.	M.P. °C	R_f	Molecular formula	Analysis Calc./found		
				C	H	N
II_a	102	0.85	$C_{10}H_{10}N_2$	75.94	6.32	17.72
				75.88	6.17	17.50
b	161	0.51	$C_{11}H_{10}N_2O$	70.96	5.37	15.05
				70.88	5.41	15.02
c	133	0.29	$C_{15}H_{10}N_4O_4$	58.06	3.22	18.06
				58.01	3.17	18.04
d	121	0.72	$C_{16}H_{14}N_2O_2S$	64.42	4.69	9.39
				64.38	4.60	9.39
III_a	202	0.87	$C_{19}H_{13}N_3O_3$	68.88	3.92	12.68
				68.92	3.90	12.71
b	149	0.56	$C_{20}H_{15}N_3O_3$	69.56	4.34	12.17
				69.48	4.30	12.17
c	175	0.62	$C_{22}H_{19}N_3O_3$	70.77	5.09	11.26
				70.53	5.00	11.14
d	154	0.40	$C_{23}H_{21}N_3O_3$	71.31	5.42	10.85
				71.28	5.39	10.92
IV_a	137	0.33	$C_{18}H_{17}N_3O_3S$	60.84	4.78	11.83
				60.77	4.63	11.70
b	152	0.76	$C_{19}H_{20}N_3O_3S$	61.62	5.40	11.35
				61.56	5.30	11.11
c	166	0.81	$C_{21}H_{42}N_3O_3S$	63.31	6.03	10.55
				63.43	6.00	10.62
d	122	0.34	$C_{22}H_{26}N_3O_3S$	64.07	6.31	10.19
				64.01	6.34	10.18
V_a	116	0.91	$C_{11}H_{11}N_3O$	65.67	5.47	20.89
				65.55	5.31	20.97
b	182	0.38	$C_{12}H_{13}N_3O$	66.97	6.04	19.53
				66.85	6.01	19.73
c	145	0.50	$C_{14}H_{17}N_3O$	69.13	6.99	17.28
				69.06	6.94	17.22
d	122	0.67	$C_{15}H_{19}N_3O$	70.03	7.39	16.34
				70.01	7.39	16.26
VII_a	150	0.75	$C_{10}H_8N_2O$	69.76	4.65	16.27
				69.76	4.65	16.42
b	185	0.48	$C_{11}H_{10}N_2O$	70.96	5.37	15.05
				70.82	5.45	15.00
c	160	0.77	$C_{10}H_9N_3O$	64.17	4.81	22.45
				64.06	4.93	22.11

(Table 1 Cont'd...)

(Table 1 Continue)

VIII$_a$	140	0.61	$C_{15}H_{12}N_4O_2$	64.28	4.28	20.00
				64.31	4.14	20.02
b	163	0.44	$C_{15}H_{11}N_5O_4$	55.38	3.38	21.53
				55.44	3.33	21.42
IX$_a$	195	0.85	$C_{17}H_{14}N_2O$	77.86	5.34	10.68
				77.75	5.22	10.54
b	211	0.66	$C_{18}H_{16}N_2O$	78.26	5.79	10.14
				78.11	5.38	10.13
c	188	0.51	$C_{18}H_{16}N_2O$	78.26	5.79	10.14
				78.18	5.58	10.06
X$_a$	175	0.33	$C_{11}H_{10}N_2O_2$	65.34	4.95	13.86
				65.52	4.77	13.94
b	124	0.52	$C_{12}H_{12}N_2O_2$	66.66	5.55	12.96
				66.61	5.23	13.04
c	158	0.61	$C_{14}H_{16}N_2O_2$	68.85	6.55	11.47
				68.74	6.18	11.62
d	103	0.87	$C_{15}H_{18}N_2O_2$	69.76	6.97	10.85
				69.51	6.90	10.49
XI$_a$	132	0.42	$C_{13}H_{14}N_2O_2$	67.82	6.08	12.17
				67.77	6.00	12.12
b	144	0.56	$C_{14}H_{16}N_2O_2$	68.85	6.55	11.47
				68.69	6.17	11.32
c	115	0.28	$C_{16}H_{20}N_2O_2$	70.58	7.35	10.29
				70.61	7.17	10.05
d	162	0.70	$C_{17}H_{22}N_2O_2$	71.32	7.69	9.79
				71.15	7.33	9.28
XII$_a$	171	0.83	$C_{11}H_{12}N_4O$	61.11	5.55	25.92
				61.02	5.61	25.99
b	148	0.65	$C_{12}H_{14}N_4O$	62.60	6.08	24.34
				62.62	6.01	24.11
c	180	0.39	$C_{14}H_{18}N_4O$	65.11	6.97	21.70
				65.04	6.99	21.20
d	130	0.56	$C_{15}H_{20}N_4O$	66.17	7.35	20.58
				66.30	7.12	20.43

temperature, filtered and the solid separated was crystallized from ethanol to give products (V)a-d respectively (Table 2).

Reaction of 3-chloroquinoline (VI) with urea and amides: Formation of compounds (VII)a-c. A mixture of (VI, 0.01 mole) and urea or amide (0.015 mole was refluxed for 1 hr. The solid separated after cooling was crystallized from ethanol to give products (VII)a-c (Table 2).

Reaction of compound (VI) with hydrazines. Formation of compounds (VIII)a,b. A mixture of (VI, 0.01 mole) and hydrazine (0.015 mole) was refluxed in (50 ml) ethanol for 3 hr. After cooling the solid separated was crystallized from benzene to give compounds (VIII)a,b (Table 2).

Reaction of compound (VI) with anilides: Formation of compounds (IX)a-c. A mixture of (VI, 0.01 mole) and anilide (0.01 mole) in (50 ml) benzene was refluxed for 3 hr. The solid separated after cooling was crystallized from benzene to give products (IX)a-c respectively (Table 2).

Reaction of compound (VI) with free amino acids: Formation of compounds (X)$_{a-d}$. A solution of the amino acid (0,0044 mole) in (20 ml) 1N NaOH at 7° was added gradually during 75 min. with stirring to a solution of compound (VI, 0.0044 mole) in benzene. The reaction medium was maintained at 10° till complete addition. Stirring was continued for additional 3 hr. at room temperature. The benzene layer was separated out and the aqueous layer cooled and acidified with 2N HCl to pH 5. The solid separated was filtered and recrystallized from acetone water (1:1) to give products (X)a-d (Table 2).

Reaction of compound (VI) with amino acid ethyl esters: Formation of compounds (XI)a-d. Compound (VI, 0.004 mole) in (20 ml) dioxan was added to the amino acid ethyl ester hydrochloride (0.0053 mole) in (20 ml) dioxan containing (3 ml) triethylamine. The reaction mixture was refluxed for 3 hr. After cooling, triethylamine hydrochloride was filtered off and the oily material separated after evaporation of the solvent was crystallized from ethanol-water to afford products (XI)a–d (Table 2).

Reaction of compound (XI)a-d with hydrazine hydrate: Formation of compounds (XII)a-d. Compounds (XIa-d, 0.0031 mole) were dissolved in 1M alcoholic hydrazine hydrate (prepared from 6.6 ml of hydrazine hydrate in 100 ml of alcohol) and the solution was kept for 24 hr. at room temperature. The solid separated was crystallized from ethanol to give products (XII)a-d respectively (Table 2).

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