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Synthesis of Some New Substituted Quinoline-Amino Acids and Dipeptide Derivatives and Studies of Their Antimicrobial Activities

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ABSTRACT. The synthesis of 8-(*N*-phthalyl- or *N*-tosylaminoacyl or free aminoacyl or *N*-tosyldipeptidyl)aminoquinaldines (IV-XIX), 8-(*N*-phthalyl- or *N*-tosylaminoacyl)-aminoquinoline-2-carboxylic acid methyl esters (XX-XXVII) and their corresponding hydrazides (XXVIII-XXX) and some 2-carbonylamino acid methyl ester derivatives (XXXI-XXXIII) are described. 8-Nitroquinoline-2-carbonylamino acid methyl esters (XXXIV-XXXVII) and their corresponding hydrazides (XXXVIII-XLI) and some dipeptide methyl esters (XLII-XLV) have been synthesized by the carbodiimide and azide methods. Fourteen of various 2- and 8-substituted quinoline-amino acid derivatives are found to possess specific antimicrobial activities towards different microorganisms.

In a previous communication (El-Naggar *et al.* 1983a and b), the authors reported the synthesis of some substituted quinolines-amino acids which were found to display antifungal, antimalarial and antimicrobial activities. The effect of substitution in the quinoline nucleus by methyl-, amino-, nitro- and carboxylic acid substituents on the biological properties of quinoline and amino acid derivatives has not yet been studied. In this paper, we report the synthesis of new substituted 8-(aminoacyl)aminoquinaldines and 8-nitroquinoline-2-carbonylamino acids, esters hydrazides and some dipeptide derivatives (IV-XLV) in order to study the effect of different functional variants on biological activity.

Experimental

Methods of Synthesis

For the preparation of 8-(*N*-phthalyl- or *N*-tosylaminoacyl)aminoquinaldines or aminoquinoline-2-carboxylic acid methyl esters (IV-XI and XX-XXVII), the

appropriate *N*-phthalyl- or *N*-tosylamino acid was reacted with 8-aminoquinaldine (I) or 8-aminoquinoline-2-carboxylic acid methyl ester (II) in dioxane-DMF-triethylamine medium using the dicyclohexylcarbodiimide (DCC) procedure.

Hydrazinolysis of 8-(*N*-phthalylaminoacyl)aminoquinaldines (VIII-XI) with 1 M hydrazine hydrate in ethanol under mild reflux afforded 8-(aminoacyl)aminoquinaldines (XII-XV). Chromatographic and electrophoretic studies on (XII-XV) revealed their homogenity (*cf.* Fig. 1), and their structures were convincingly supported by the IR, UV and NMR spectral data.

8-(*N*-Tosyldipeptidyl)aminoquinaldines (XVI-XIX) were prepared by coupling of 8-(aminoacyl)aminoquinaldines (XII-XV) with *N*-tosylamino acids in dioxane-triethylamine medium using the dicyclohexylcarbodiimide (DCC) technique. All dipeptide derivatives (XVI-XIX) were highly purified through repeated recrystallizations and chromatographically homogeneous materials were obtained in 48-69% yields.

Hydrazinolysis of 8-(*N*-tosylaminoacyl)aminoquinoline-2-carboxylic acid methyl esters (XX-XXVII) in methanol afforded the corresponding 8-(*N*-tosylaminoacyl)aminoquinoline-2-carboxylic acid hydrazides (XXVIII-XXX) which gave the positive silver nitrate reactions.

Synthesis of 8-(*N*-tosylaminoacyl)aminoquinoline-2-carbonyl-amino acid methyl esters (XXXI-XXXIII) was carried on from the hydrazides (XXVIII-XXX), which were converted into the corresponding azides. The azides on coupling with the free amino acid methyl esters furnished 8-(*N*-tosylaminoacyl)aminoquinoline-2-carbonylamino acid methyl esters (XXXI-XXXIII), which were isolated and purified in the usual manner (El-Naggar 1971).

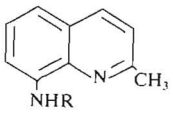
Coupling of 8-nitroquinoline-2-carboxylic acid (III) with the appropriate amino acid methyl ester hydrochlorides in THF-Et_3N medium using the DCC method afforded 8-nitroquinoline-2-carbonylamino acid methyl esters (XXXIV-XXXVII).

Treatment of the methyl esters (XXXIV-XXXVI) with 0.5 M hydrazine hydrate in ethanol at 20° gave 8-nitroquinoline-2-carbonylamino acid hydrazides (XXXVIII-XLI) in 51-73% yields.

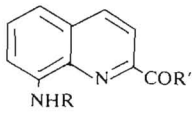
Synthesis of the dipeptide derivatives (XLII-XLV) was carried out by coupling of 8-nitroquinoline-2-carbonylamino acid azides with amino acid methyl ester hydrochlorides in ethyl acetate-triethylamine medium and using the azide method.

The dipeptides XVI-XIX and XLII-XLV gave deep blue complexes with copper (II), λ_{max} 620-680 nm.

Compounds IV-XLV were prepared and characterized for the first time (*cf.* Table 1). All of the compounds which were synthesized (IV-XLV) gave IR, UV and NMR spectra consistent with their assigned structures (*cf.* Fig. 2-4).



Type (A)



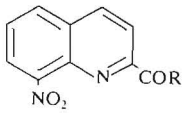
Type (B)

Type – (A)
Compounds IV-XIX

IV, R = Tos–L–Ala
V, R = Tos–L–Ser
VI, R = Tos–L–Val
VII, R = Tos–L–Leu
VIII, R = Pht–L–Ala
IX, R = Pht–L–Ser
X, R = Pht–L–Val
XI, R = Pht–L–Leu
XII, R = L–Ala
XIII, R = L–Ser
XIV, R = L–Val
XV, R = L–Leu
XVI, R = Tos–L–Val–L–Ala
XVII, R = Tos–L–Ser–L–Val
XVIII, R = Tos–L–Leu–L–Ser
XIX, R = Tos–L–Ala–L–Leu

Type – (B)
Compounds XX-XXXIII

XX, R = Tos–L–Ala, R′ = OCH_3
XXI, R = Tos–L–Ser, R′ = OCH_3
XXII, R = Tos–L–Val, R′ = OCH_3
XXIII, R = Tos–L–Leu, R′ = OCH_3
XXIV, R = Pht–L–Ala, R′ = OCH_3
XXV, R = Pht–L–Ser, R′ = OCH_3
XXVI, R = Pht–L–Val, R′ = OCH_3
XXVII, R = Pht–L–Leu, R′ = OCH_3
XXVIII, R = Tos–L–Ser, R′ = $-N_2H_3$
XXIX, R = Tos–L–Val, R′ = $-N_2H_3$
XXX, R = Tos–L–Leu, R′ = $-N_2H_3$
XXXI, R = Tos–L–Ser, R′ = L–Val–OMe
XXXII, R = Tos–L–Val, R′ = L–Leu–OMe
XXXIII, R = Tos–L–Leu, R′ = L–Ala–OMe



Type (C)

Type – (C)
Compounds XXXIV–XLV

XXXIV, R = L–Ala–OMe
XXXV, R = L–Ser–OMe
XXXVI, R = L–Val–OMe
XXXVII, R = L–Leu–OMe
XXXVIII, R = L–Ala–N_2H_3
XXXIX, R = L–Ser–N_2H_3
XL, R = L–Val–N_2H_3
XLI, R = L–Leu–N_2H_3
XLII, R = L–Ala–L–Val–OMe
XLIII, R = L–Ser–L–Leu–OMe
XLIV, R = L–Val–L–Ala–OMe
XLV, R = L–Leu–L–Ser–OMe

Table 1. Physical data of various 8-(*N*-Pht- or *N*-Tos-aminoacyl- or free aminoacyl or *N*-Tos-dipeptidyl)aminoquinaldines (IV-XIX), 8-(*N*-Pht- or *N*-Tos-aminoacyl)aminoquinoline-2-carboxylic acid methyl esters, hydrazides and amino acid derivatives (XX-XXXIII), and 8-nitroquinoline-2-carbonylamino acid methyl esters, hydrazides and dipeptide derivatives (XXXIV-XLV).

Compd. No.	R–	Cryst.* sol.	Yield (%)	m.p. °C	R_f (TLC)	$[\alpha]^{20}_D$ (c = 3, ethanol)	Molecular formula	Elemental analysis, %					
								Calculated			Found		
								C	H	N	C	H	N
	Compounds (IV-XIX) of the Type-(A)												
IV	Tos-L-Ala	(a)	70	210-212	0.71	+220.5	$C_{20}H_{21}N_3O_3S$	62.66	5.48	10.96	62.82	5.60	10.99
V	Tos-L-Ser	(a)	52	243-245	0.54	+119	$C_{20}H_{21}N_3O_4S$	60.15	5.26	10.52	60.23	5.33	10.60
VI	Tos-L-Val	(a)	74	195-197	0.66	+127	$C_{22}H_{25}N_3O_3S$	64.23	6.08	10.21	64.33	6.12	10.23
VII	Tos-L-Leu	(a)	50	233-235	0.81	+ 98.5	$C_{23}H_{27}N_3O_3S$	64.94	6.35	9.88	64.97	6.38	9.92
VIII	Pht-L-Ala	(a)	63	180-182	0.89	+150.3	$C_{21}H_{17}N_3O_3$	70.19	4.73	11.69	70.30	4.81	11.73
IX	Pht-L-Ser	(a)	49	177-179	0.85	+210	$C_{21}H_{17}N_3O_4$	67.23	4.53	11.20	67.35	4.61	11.30
X	Pht-L-Val	(a)	57	167-169	0.66	+157.6	$C_{23}H_{21}N_3O_3$	71.31	5.42	10.85	71.39	5.49	10.90
XI	Pht-L-Leu	(a)	63	190-192	0.69	+180.7	$C_{24}H_{23}N_3O_3$	71.82	5.73	10.47	71.88	5.74	10.50
XII	L-Ala**	(b)	77	260-262	0.51	+175	$C_{13}H_{15}N_3O$	68.12	6.55	18.34	68.22	6.59	18.39
XIII	L-Ser	(b)	70	248-250	0.73	+198.5	$C_{13}H_{15}N_3O_2$	63.67	6.12	17.14	63.81	6.19	17.19
XIV	L-Val	(b)	82	216-218	0.81	+112	$C_{15}H_{19}N_3O$	70.03	7.39	16.34	70.10	7.43	16.31
XV	L-Leu	(b)	69	225-257	0.57	+151	$C_{16}H_{21}N_3O$	70.84	7.74	15.49	70.98	7.75	15.56
XVI	Tos-L-Val-L-Ala	(b)	54	195-197	0.84	+170	$C_{25}H_{30}N_4O_4S$	62.24	6.22	11.61	62.39	6.28	11.66
XVII	Tos-L-Ser-L-Val	(b)	76	188-190	0.95	+221	$C_{25}H_{30}N_4O_5S$	60.24	6.02	11.23	60.23	6.10	11.30
XVIII	Tos-L-Leu-L-Ser	(b)	51	220-222	0.49	+270	$C_{26}H_{32}N_4O_5S$	60.93	6.25	10.93	61.09	6.30	11.01
XIX	Tos-L-Ala-L-Leu	(b)	65	211-213	0.75	+190	$C_{26}H_{32}N_4O_4S$	62.90	6.45	11.29	63.12	6.49	11.37
	Compounds (XX-XXXIII) of the Type-(B); R′ for Compounds (XX-XXVII) = OCH_3, (XXVIII-XXX) = N_2H_3, (XXXI-XXXIII) = See Footenote* **												
XX	Tos-L-Ala	(c)	66	244-246	0.90	+201	$C_{21}H_{21}N_3O_5S$	59.01	4.91	9.83	59.07	4.99	9.89
XXI	Tos-L-Ser	(c)	62	217-219	0.96	+145	$C_{21}H_{21}N_3O_6S$	56.88	4.74	9.48	56.98	4.99	9.50
XXII	Tos-L-Val	(c)	53	190-192	0.84	+169	$C_{23}H_{25}N_3O_5S$	60.65	5.49	9.23	60.77	5.51	9.53

Compd. No.	R–	Cryst.* sol.	Yield (%)	m.p. °C	R_f (TLC)	$[\alpha]^{20}_D$ (c = 3, ethanol)	Molecular formula	Elemental analysis, %					
								Calculated			Found		
								C	H	N	C	H	N
XXIII	Tos–L–Leu	(c)	55	215-217	0.85	+230	$C_{24}H_{27}N_3O_5S$	61.40	5.75	8.95	61.50	5.85	9.10
XXIV	Pht–L–Ala	(b)	64	223-225	0.91	+117.5	$C_{22}H_{17}N_3O_5$	65.50	4.21	10.42	65.66	4.24	10.40
XXV	Pht–L–Ser	(b)	54	240-242	0.69	+183	$C_{22}H_{17}N_3O_6$	63.01	4.05	10.02	63.09	4.11	10.12
XXVI	Pht–L–Val	(b)	50	253-255	0.58	+115	$C_{24}H_{21}N_3O_5$	66.82	4.87	9.74	66.89	4.98	9.88
XXVII	Pht–L–Leu	(b)	67	249-251	0.74	+188	$C_{25}H_{23}N_3O_5$	67.41	5.16	9.43	67.54	5.23	9.76
XXVIII	Tos–L–Ser	(a)	63	187-189	0.83	+207	$C_{20}H_{21}N_5O_5S$	54.17	4.74	15.80	54.23	4.89	15.90
XXIX	Tos–L–Val	(a)	70	166-168	0.72	+230	$C_{22}H_{25}N_5O_4S$	58.02	5.49	15.38	58.10	5.55	15.54
XXX	Tos–L–Leu	(a)	65	178-180	0.94	+192	$C_{23}H_{27}N_5O_4S$	58.84	5.75	14.92	58.99	5.87	14.98
XXXI	Tos–L–Ser***	(a)	65	198-200	0.76	+154	$C_{26}H_{30}N_4O_7S$	57.56	5.53	10.33	57.60	5.59	10.53
XXXII	Tos–L–Val***	(a)	49	217-219	0.78	+176	$C_{29}H_{36}N_4O_6S$	61.26	6.33	9.85	61.33	6.39	9.89
XXXIII	Tos–L–Leu***	(a)	60	193-195	0.68	+133	$C_{27}H_{32}N_4O_6S$	60.00	5.92	10.37	60.06	6.02	10.44
	Compounds (XXXIV-XLV), of the Type-(C)												
XXXIV	L–Ala–OMe	(d)	77	218-220	0.49	+210	$C_{14}H_{13}N_3O_5$	55.44	4.29	13.86	55.49	4.31	13.91
XXXV	L–Ser–OMe	(d)	63	244-246	0.68	+270	$C_{14}H_{13}N_3O_6$	52.66	4.07	13.16	52.69	4.10	13.20
XXXVI	L–Val–OMe	(d)	60	189-191	0.73	+206	$C_{16}H_{17}N_3O_5$	58.01	5.13	12.68	58.07	5.17	12.70
XXXVII	L–Leu-OMe	(d)	67	202-204	0.57	+279	$C_{17}H_{19}N_3O_5$	59.13	5.50	12.17	59.19	5.56	12.22
XXXVIII	L–Ala–N_2H_3	(a)	51	250-252	0.81	+167.5	$C_{13}H_{13}N_5O_4$	51.48	4.29	23.10	51.54	4.32	13.29
XXXIX	L–Ser–N_2H_3	(a)	53	240-242	0.59	+140.5	$C_{13}H_{13}N_5O_5$	48.90	4.07	21.94	48.98	4.03	22.12
XL	L–Val–N_2H_3	(b)	73	233-235	0.89	+131	$C_{15}H_{17}N_5O_4$	54.38	5.13	21.14	54.47	5.27	21.38
XLI	L–Leu–N_2H_3	(a)	67	212-214	0.69	+195	$C_{16}H_{19}N_5O_4$	55.65	5.50	20.28	55.78	5.67	20.31
XLII	L–Ala–L–Val–OMe	(b)	74	183-185	0.95	+177	$C_{19}H_{22}N_4O_6$	56.71	5.47	13.93	56.77	5.58	13.99
XLIII	L–Ser–L–Leu–OMe	(b)	53	205-207	0.67	+215	$C_{20}H_{24}N_4O_7$	55.55	5.56	12.96	55.67	5.76	12.97
XLIV	L–Val–L–Ala–OMe	(a)	70	170-172	0.83	+244	$C_{19}H_{22}N_4O_6$	56.71	5.47	13.93	56.79	5.68	13.95
XLV	L–Leu–L–Ser–OMe	(b)	57	193-195	0.77	+265	$C_{20}H_{24}N_4O_7$	55.55	5.56	12.96	55.59	5.87	13.07

* Crystallization solvents: (a) = ethanol, (b) = methanol, (c) = methanol-water and (d) = methanol-ether.

** Electrophoretic mobilities (E) for compounds (XII) = 7.5 cm, (XIII) = 5.3 cm, (XIV) = 8.5 cm and (XV) = 13 cm and for the remaining compounds (E) = zero.

*** All compounds (XX-XXXIII) are of the type-(B) and R′ for (XX-XXVII) = $-OCH_3$; (XXVIII-XXX) R′ = $-N_2H_3$; (XXXI) R′ = L–Val–OMe; (XXXII) R′ = L–Leu–OMe and for (XXXIII) R′ = L–Ala–OMe, and Pht– = phthalyl group, Tos– = tosyl group.

Experimental Procedures

Melting points were determined by a Kofler hot-stage apparatus and are uncorrected. The IR spectra (ν_{max} in cm^{-1}) were measured with a Unicam SP 1200 in KBr pellets, UV spectra (λ_{max} in nm) were measured in ethanol with a Unicam SP 8000, and NMR data were determined on Varian T-60 A spectrophotometer in DMSO-d_6 and shifts were recorded in ppm (δ) relative to internal TMS. Optical rotations $[\alpha]_D^{20}$ were taken in a Bellingham-Stanely polarimeter 1 dm tube, c = 3 in ethanol. Thin layer chromatography (TLC, R_f values) was made on Silica Gel-G (BDH) using benzene-ethyl acetate (1 : 1) as the solvent system and iodine-potassium iodide (20%) as the detection reagent. Benzidine, ninhydrin, silver nitrate and hydroxamate reactions were used for detection of the amino acid derivatives on Whatman No. 1 paper chromatograms (spot reactions). The electrophoretic mobilities (E) were measured on Whatman No. 1 paper chromatograms with vertical high voltage electrophoresis, (1000 V, 2 hr, in pyridine-acetate buffer, pH 5.6) (*cf.* Fig. 1).

Procedure for synthesis of 8-aminoquinaldine (I), 8-aminoquinoline-2-carboxylic acid methyl ester (II) and 8-nitroquinoline-2-carboxylic acid (III)

The titled compounds prepared according to the procedures described earlier (Roth & Erlenmeyer 1954, Iones 1977, Manske and Kukla 1953).

1. Procedure for the synthesis of 8-(N-phthalyl- or N-tosylaminoacyl)aminoquinaldines (IV-XI) and 8-(N-phthalyl- or N-tosylaminoacyl)aminoquinoline-2-carboxylic acid methyl esters (XX-XXVII)

To a stirred suspension of 8-aminoquinaldine (I, 0.014 mole) or 8-aminoquinoline-2-carboxylic acid methyl ester (II, 0.014 mole) in a mixture of dioxane (25 ml) and DMF (25 ml) containing triethylamine (1.5 ml) at 0° was added *N*-phthalyl- or *N*-tosylamino acid (0.014 mole) in dioxane (30 ml) followed by dicyclohexyl-carbodiimide (2.7 g, 0.014 mole). The reaction mixture was stirred for 2-3 hr at 0° and left for 24 hr at room temperature. Dicyclohexylurea was filtered off and the filtrate was evaporated *in vacuo*. The residual solid was recrystallized from ethanol, methanol, ether or their mixtures (*cf.* Table 1). The products (IV-XI and XX-XXVII) were easily soluble in dioxane, DMF, THF, alcohols, nitromethane and chloroform and insoluble in water and ether. The products were chromatographically homogeneous when detected with benzidine and iodine solution.

2. Procedure for the synthesis of 8-(aminoacyl)aminoquinaldines (XII-XV)

The appropriate 8-(*N*-phthalylaminoacyl)aminoquinaldine (VIII-XI, 0.002 mole) was dissolved in ethanol (25 ml) and the mixture was treated with 1 M hydrazine hydrate in ethanol (1.5 ml). The reaction mixture was refluxed for 2 hr and then left for 24 hr at 20°. The residue obtained after evaporation of the solvent

was treated with 2 N HCl (10 ml) for 15 min at 50°. The reaction mixture was cooled to 5° and the insoluble phthalyl-hydrazide was filtered off. The filtrate was evaporated *in vacuo* and the residual material was dissolved in ethyl acetate (35

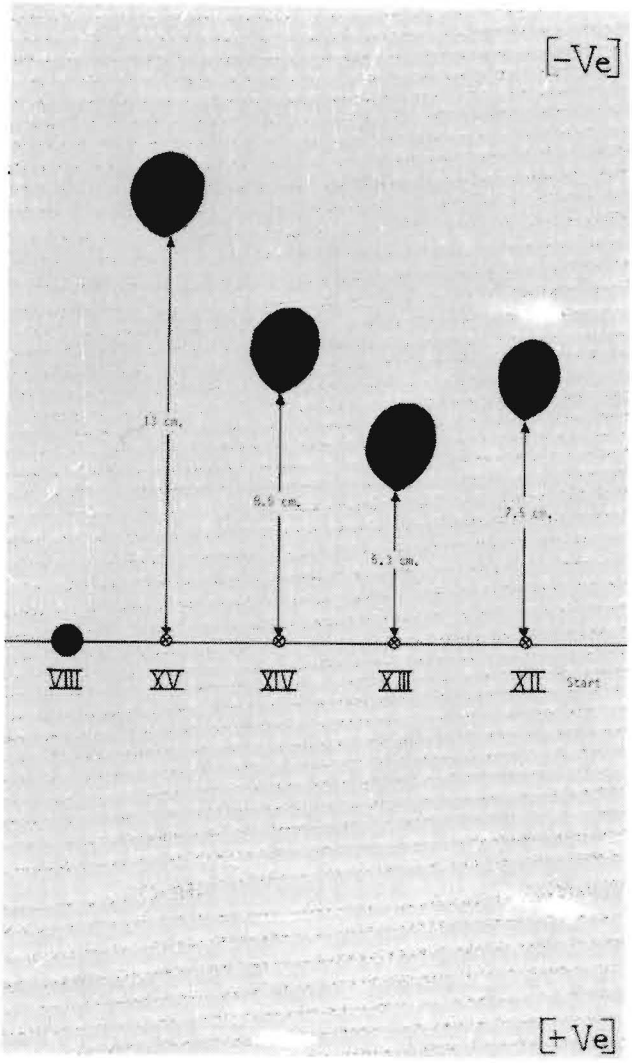


Fig. 1. Electrophoretic pattern of compounds VIII and XII-XV, 1000 V, 2 hr, Pyridine-acetate buffer (pH 5.6). Whatman No. 1 paper detected with ninhydrin.

ml) and treated with triethylamine (9 ml) for 20 minutes at 25°. The reaction mixture was washed with water, sodium bicarbonate (3%), water and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residual material was recrystallized from methanol. The products (XII-XV) were chromatographically homogeneous when developed with benzidine, ninhydrin and iodine solution.

The NMR spectra of compounds (XII-XV) had characteristic chemical shifts for the five quinoline ring protons centered around δ: 7.33, 7.58, 7.69, 7.88 and 8.10; the NH_2 and NH protons at 5.99, 6.12; and the $-CH_3$ protons at 3.26 and other protons characteristic of the amino acid residues (*cf.* Fig. 2).

3. Procedure for the synthesis of 8-(N-tosyldipeptidyl)aminoquinaldines (XVI-XIX)

8-(Aminoacyl)aminoquinaldine (XII-XV, 0.01 mole) and the appropriate *N*-tosylamino acid (0.01 mole) were dissolved in dioxane (35 ml) containing triethylamine (1.5 ml). The mixture was cooled to −5°, dicyclohexylcarbodiimide (0.01 mole) was added and the mixture was stirred for 4-5 hr at 0° and left for 24 hr at room temperature. The reaction mixture was worked up as described for the preparation of (IV-XI). Compounds XVI-XIX were recrystallized from methanol. The dipeptides XVI-XIX were chromatographically homogeneous when detected with benzidine and iodine solution.

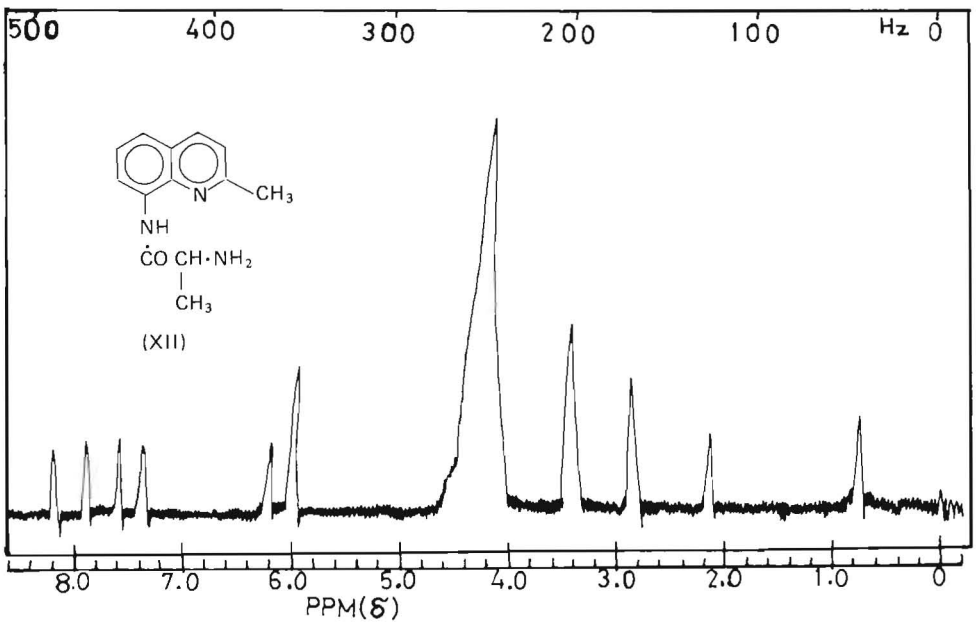


Fig. 2. NMR spectrum of compound (XII).

The IR spectra of compounds (IV-XIX) showed bands at: 3360, 3160, 3080 (NH, CONH, N); 1650, 1560, 1260 (amide I, II and III); 1780, 1720 ($\succ$C=O); 2960, 2820 ($-CH_3$) and other characteristic bands due to quinoline and amino acid or dipeptide residues. UV spectra of (IV-XIX) showed λ_{max} nm (log ε): 228 (4.39); 278 (3.39); and 317 (3.88) characteristic of the quinoline moiety. The NMR spectra of compounds (IV-XIX) had characteristic chemical shifts for the five quinoline ring protons centered around δ: 7.32, 7.55, 7.68, 7.88 and 8.10; the NH amide protons at 5.98 and the $-CH_3$ protons at 3.26 and other protons characteristic of the amino acid or dipeptide residues.

4. Procedure for the synthesis of 8-(N-tosylaminoacyl)aminoquinoline-2-carboxylic acid hydrazides (XXVIII-XXX)

The methyl ester (XXI-XXIII, 0.01 mole) was dissolved in methanol (50 ml) and hydrazine hydrate (85%, 2.5 ml, 0.05 mole) added. The reaction mixture was stirred for 4 hr at 20° and left for 24 hr at room temperature. The crystalline hydrazides (XXVIII-XXX) were filtered, washed with water and recrystallized from ethanol. The hydrazides XXVIII-XXX were chromatographically homogeneous when detected with iodine solution, benzidine and silver nitrate reactions and showed negative hydroxamate reactions.

5. Procedure for the synthesis of 8-(N-tosylaminoacyl)aminoquinoline-2-carbonylamino acid methyl esters (XXXI-XXXIII)

8-(*N*-Tosylaminoacyl)aminoquinoline-2-carboxylic acid hydrazide (XXVIII-XXX, 0.01 mole) was dissolved in a mixture of acetic acid (25 ml), 5 N HCl (10 ml) and water (100 ml) and cooled to $-5°$, and a solution of sodium nitrite (2.8 g) in water (15 ml) was added to it; the mixture was stirred for 10 min at $-10°$. The azide was extracted with 200 ml ethyl acetate and the extract washed successively with water, aq. $NaHCO_3$ (3%), and water and dried (Na_2SO_4).

The amino acid methyl ester hydrochloride (0.011 mole) was dissolved in ethyl acetate (60 ml) containing triethylamine (2.5 ml) and the mixture shaken for 20 min at 20° and cooled to $-5°$.

Compounds (XXXI-XXXIII) were prepared by the addition of the above cooled, dried solution of the azide to the cold ethyl acetate solution of the amino acid methyl ester. The reaction mixture was allowed to stand for 24 hr at 0° and 24 hr at 20° and washed with 0.5 N HCl, water, $NaHCO_3$ (3%), water and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the residual material recrystallized from ethanol. The products (XXXI-XXXIII) were chromatographically homogeneous (detection with benzidine, iodine solution and hydroxamate reactions) and gave negative ninhydrin reaction.

The IR spectra of compounds (XX-XXXIII) showed bands at: 3360, 3120, 3080 (NH, CONH, N); 1790, 1720 ($\succ$C=O); 1650, 1560, 1320 (amide I, II and

III) and other characteristic bands due to quinoline and amino acid residues. UV spectra of (XX-XXXIII) showed λ_{max} nm (log ε): 226 (4.21); 275 (3.35) and 315 (3.89) (quinoline moiety). The NMR spectra of compounds (XX-XXXIII) showed δ: 7.26, 7.61, 7.66 and 8.09 (s, 5H, quinoline protons); 5.96 (s, 2H, 2NH) and other protons characteristic of the amino acid and quinoline residues (*cf.* Fig. 3).

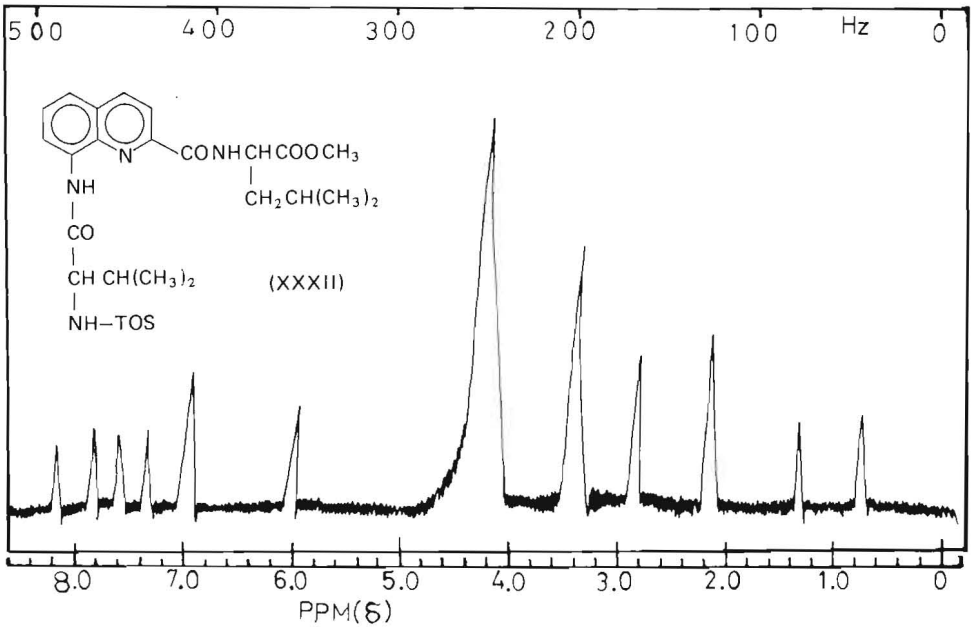


Fig. 3. NMR spectrum of compound (XXXII).

6. Procedure for the synthesis of 8-nitroquinoline-2-carbonylamino acid methyl esters (XXXIV-XXXVII)

8-Nitroquinoline-2-carboxylic acid (III, 0.003 mole) and the appropriate amino acid methyl ester hydrochloride (0.0032 mole) were dissolved in tetrahydrofuran (75 ml) containing triethylamine (1.5 ml). The mixture was cooled to −5°, dicyclohexylcarbodiimide (0.003 mole) was added and the mixture was stirred for 3-4 hr at 0°, and then left for 24 hr at 0° and for another 24 hr at 20°. The reaction mixture was worked up as described for the preparation of IV-XI. The products (XXXIV-XXXVII) were recrystallized from methanol-water (1 : 1) mixture. All the compounds were chromatographically homogeneous when developed with iodine solution, benzidine and hydroxamate reactions and gave negative ninhydrin reaction.

The NMR spectra of compounds (XXXIV-XXXVII) showed chemical shifts δ: 7.35, 7.48, 7.60, 7.77 and 8.10 (s, 5H, quinoline protons); 5.99 (s, 1H, NH) and other protons characteristic of the amino acid residues.

7. Procedure for the synthesis of 8-nitroquinoline-2-carbonylamino acid hydrazides (XXXVIII-XLI)

Any of the methyl esters (XXXIV-XXXVII, 0.002 mole) was dissolved in ethanol (35 ml) and 0.5 M hydrazine hydrate in ethanol (2.7 ml) added to it. The reaction mixture was worked up as described for preparation of compounds XXVIII-XXX. The hydrazides XXXVIII-XLI were recrystallized from ethanol. All the products were chromatographically homogeneous when developed with benzidine, iodine solution and silver nitrate reactions and showed negative hydroxamate reaction.

8. Procedure for the synthesis of 8-nitroquinoline-2-carbonyl-dipeptide methyl esters (XLII-XLV)

Any of the hydrazides (XXXVIII-XLI, 0.012 mole) was dissolved in a mixture of acetic acid (25 ml), 5 N HCl (8 ml) and water (100 ml). The mixture was cooled to −5°, and a solution of sodium nitrite (2.7 g) in water (10 ml) was added to it. The azide was extracted with ethyl acetate (125 ml), and washed and dried as described for peparation of XXXI. The azide was coupled with amino acid methyl ester hydrochloride (0.011 mole) in ethyl acetate (60 ml) containing triethylamine (2.5 ml), and the reaction mixture was worked up as described for preparation of

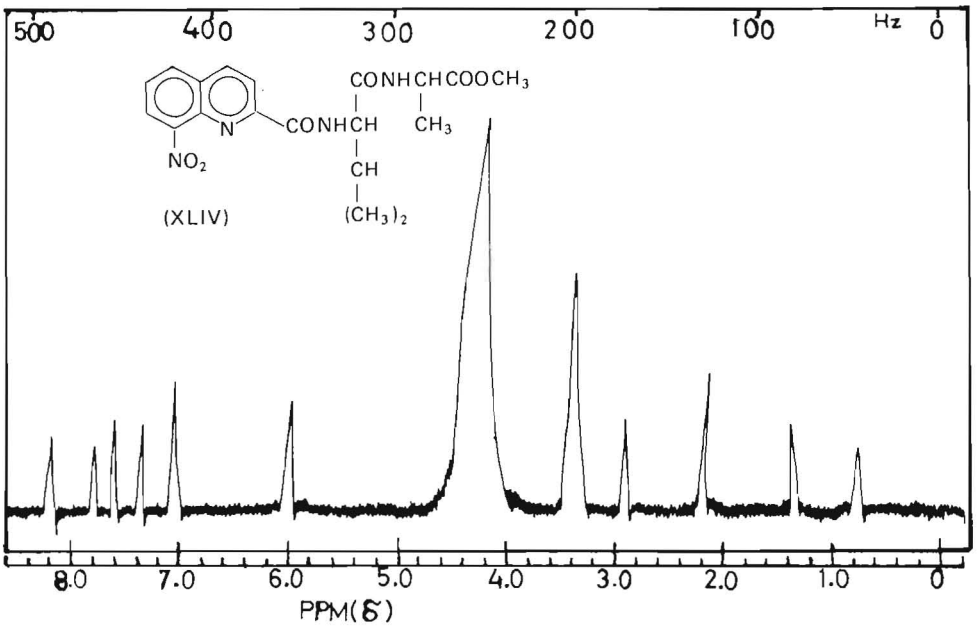


Fig. 4. NMR spectrum of compound (XLIV).

compounds (XXXI-XXXIII). The dipeptides (XLII-XLV) were recrystallized from methanol. All the products (XLII-XLV) were found to be homogeneous and showed negative ninhydrin and silver nitrate reactions.

The IR spectra of compounds (XXXIV-XLV) showed bands at: 3360, 3120, 3080 (NH, CONH, N); 1790, 1720 (>C=O); 1640, 1490, 1380 ($-NO_2$); 1650, 1550, 1320 (amide I, II and III) and other bands due to quinoline and amino acid or dipeptide moieties. UV spectra of compounds (XXXIV-XLV) showed λ_{max} nm (log ε): 228 (4.48), 275 (3.18) and 315 (3.46) characteristic of the quinoline moiety. NMR spectra of compounds (XXXIV-XLV) showed chemical shifts δ: 7.35, 7.49, 7.60, 7.76 and 8.10 (s, 5H, quinoline protons); 5.98 (s, 1H, NH) and other protons characteristic of the amino acid or dipeptide residues (*cf.* Fig. 4).

Results and Discussion

The antimicrobial activity of the compounds that had been synthesized were tested using the hole plate and filter paper disc methods (Carlson 1948, Vincent and Vincent 1944, Epstein 1944, Irving, 1946). Compounds IV-XLV were tested against different gram-positive, gram-negative microorganisms and fungi, *e.g. Bacillus subtilis* (ICC-strain), *Bacillus mycoids* (USSR), *Bacillus cereus* (NRRL-B-569), *Escherichia coli* (NRRL-B-210), *Salmonella typhosa* (NRRL-B-573) and *Penicillium chrysogenum*, and the screening data are given in Table 2. The results were compared with the activity of the parent amino- and nitro-quinoline derivatives (I-III).

All 8-(aminoacyl)aminoquinaldines were found to possess high antimicrobial activities (*cf.* Table 2, compounds XII-XV). However, all 8-(*N*-phthalyl- or *N*-tosylaminoacyl)aminoquinaldines (IV-XI) were biologically inactive.

On the other hand, 8-(*N*-Tos-L-Ser-L-Val or *N*-Tos-L-Leu-L-Ser)aminoquinaldines possess different antimicrobial activities (*cf.* Table 2, compounds XVII-XVIII).

Amongst all 8-(*N*-tosyl- or *N*-phthalylaminoacyl)aminoquinoline-2-carboxylic acid methyl esters, only the Tos-L-Ser derivative (XXI) was found to possess high antimicrobial activities. Moreover, replacement of the carboxylic acid methyl ester in position-2 of the quinoline moiety by an L-Val-OMe or L-Leu-OMe or L-Ala-OMe residue, verify and improve the biological action of these derivatives (*cf.* Table 2, compounds XXXI-XXXIII).

All 8-nitroquinoline-2-carbonyldipeptide methyl esters were found to possess high antimicrobial activities (*cf.* Table 2, compounds XLII-XLV). However, replacement of the dipeptidyl residue in the 8-nitroquinoline-2-carbonyldipeptide methyl esters (XLII-XLV) by amino acid methyl ester or amino acid hydrazide moiety abolish the antimicrobial activity of these compounds (*cf.* Table 1, 2; compounds XXXIV-XLI).

Table 2. Results of screening for inhibition of growth of different microorganisms. Activity (A)* and minimum inhibitory concentration (M.I.C.) calculated as μg/ml.

Compd. No.	*Bac. subtilis*		*Bac. mycoids*		*Bac. cereus*		*Esch. coli*		*Salm. typhosa*		*Pen. chryso-genum*	
	A	**M.I.C.**	**A**	**M.I.C.**	**A**	**M.I.C.**	**A**	**M.I.C.**	**A**	**M.I.C.**	**A**	**M.I.C.**
XII	++	50	++	50	+	500	++	50	–	–	–	–
XIII	++	50	+	125	++	50	+++	25	–	–	–	–
XIV	+++	25	++	50	–	–	–	–	–	–	–	–
XV	+	500	+++	30	–	–	–	–	–	–	–	–
XVII	++	50	–	–	+++	25	–	–	–	–	–	–
XVIII	+++	25	–	–	+++	25	–	–	–	–	–	–
XXI	++	50	++	50	–	–	+	500	–	–	–	–
XXXI	++	50	++	50	+++	25	–	–	–	–	–	–
XXXII	+	500	–	–	+++	30	++	50	–	–	–	–
XXXIII	+++	25	+	125	++	50	+++	25	–	–	–	–
XLII	+++	30	+++	30	++	50	++	50	–	–	–	–
XLIII	++	50	+++	25	+++	5	–	–	–	–	–	–
XLIV	+	500	+++	25	–	–	+++	25	–	–	–	–
XLV	+++	25	+++	25	++	50	–	–	–	–	–	–

* Activity (A): +++ = highly active; ++ = moderately active; + = slightly active; – = inactive.

The present investigation concluded that introduction of methyl- or carboxylic acid methyl ester substitutents in the 2-position in the 8-aminoquinoline residue in combination with aminoacyl-, *N*-tosyl-aminoacyl- and *N*-tosyldipeptidyl- moieties gave aminoacyl-aminoquinoline derivatives of highly specific biological properties. Similarly, introduction of nitro substituent in the 8-position of the 2-carbonyl-quinoline residue in combination with dipeptide methyl ester moieties gave 8-nitroquinoline-2-carbonyldipeptide methyl ester derivatives of high antimicrobial properties. The *N*-phthalyl protecting group of all 8-(*N*-phthalylaminoacyl)-aminoquinaldines abolishes the biological action of these compounds, since hydrazinolysis of the *N*-phthalyl protecting group enhances and verifies the biological properties of all unprotected 8-(aminoacyl)aminoquinaldine derivatives (*cf.* Table 2, compounds XII-XV). Other pharmacological studies are currently in progress.

Conclusion

1. Fourty two new substituted quinoline-amino acid and dipeptide derivatives are synthesized, and summerized as follow:

i) 8-(*N*-Phthalyl- or *N*-tosylaminoacyl or free aminoacyl or *N*-tosyldipeptidyl)-aminoquinaldines (Compounds IV-XIX, of the type-(A).

ii) 8-(*N*-Phthalyl- or *N*-tosylaminoacyl)aminoquinoline-2-carboxylic acid methyl esters, hydrazides, and 2-carbonylamino acid methyl esters (Compounds XX-XXXIII, of the type-(B).

iii) 8-Nitroquinoline-2-carbonylamino acid methyl esters, hydrazides and dipeptide methyl esters (Compounds XXXIV-XLV, of the type-(C).

2. The antimicrobial and antifungal properties of all synthesized quinoline-amino acid derivatives are studied, and fourteen compounds were found to possess antimicrobial activities towards different microorganisms.

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تحضير بعض مشتقات كينولين - الأحماض الأمينية والببتيدات الثنائية ودراسة نشاطها المضاد للميكروبات

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تضمن البحث تخليق مجموعة من ٨ - (ن - فثاليل - أو ن - توزيل أمينو آسيل أو أمينو آسيل أو ن - توزيل - ببتيد ثنائى) - أمينوكينالدين، ٨ - (ن - فثاليل - أو ن - توزيل - أمينو آسيل) - أمينوكينولين - ٢ - ميثيل استر للحمض الكربوكسيلى وبعض الهيدرازيدات ومجموعة المشتقات المحتوية على ٢ - كربونيل حمض أمينى ميثيل إستر.

وشمل البحث تخليق مجموعة أخرى من مشتقات ٨ - نيتروكينولين - ٢ - كربونيل - حمض أمينى ميثيل إستر وبعض الهيدرازيدات والببتيدات الثنائية المناظرة.

واستخدمت طرق الكاريودايميد والآزيد لتخليق هذه المركبات.

وبدراسة النشاط البيولوجى للمركبات التى تم تخليقها اتضح أن أربعة عشر مركبا من مركبات ٢ - كربونيل، ٨ - نيترو، ٨ - أمينوكينولين للأحماض الأمينية ذات نشاط بيولوجى عال ومميز تجاه مختلف الكائنات الدقيقة.