Pak. j. sci. ind. res., vol. 34, no. 10, October 1991

SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW SUBSTITUTED QUINOLINE AMINO ACID DERIVATIVES

RAGAB A. EL-SAYED, N.S. KHALAF, F. A. KORA AND Y. A. ABBASS*

Chemistry Department, Faculty of Science, Al-Azhar University, Nasr-City, Cairo-Egypt

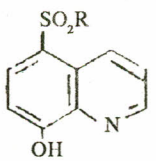
(Received June 29, 1991; revised October 31, 1991)

The synthesis of a series of 8-hydroxyquinoline-5-sulfonamido acids and some of the corresponding methyl esters and hydrazides (II-XIX) is described. Coupling of 8-hydroxyquinoline-5-sulfonamido acids with amino acid methyl ester hydrochloride in THF-ET_3N medium by the N, N'-dicyclohexylcarbodiimide method yield the desired dipeptide methyl esters (XX-XXV). Most of the compounds synthesised (II-XXV) were found to be highly active against a number of microorganisms and fungi.

Key words: Biological activity, Quinoline, Amino acid derivatives.

Introduction

Many substituted quinoline derivatives have been found to exhibit antimalarial, fungistatic, bacteriostatic and antihistaminic activities (1-3). Recently, we reported the synthesis of some quinolines as well as other heterocyclic compounds incorporating amino acid moieties as part of a Programme designed to produce pharmacologically active compounds [4-7]. Moreover, we reported the synthesis of different aromatic and heterocyclic compounds containing sulfur and nitrogen moieties and some compounds showed different biological activities [8-15]. However the effect of various substituents on the quinoline nucleus on the biological properties have not yet been reported in the literature. The present investigation involve the synthesis of a new class of 8-hydroxyquinoline-5-sulfonamido acids, methyl esters, hydrazides, and dipeptide methyl ester derivatives (II-XXV) to study the effect of different functional variants on microbiological activity.

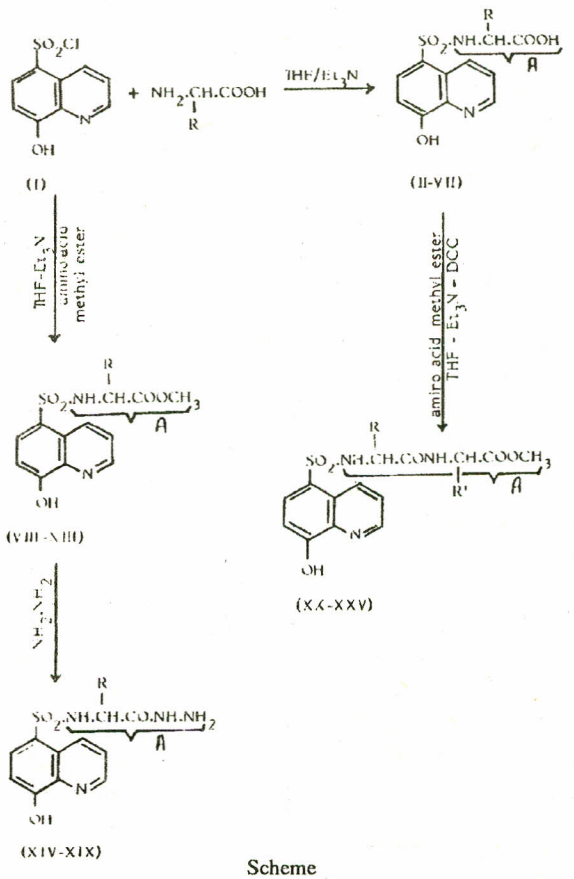


Compounds (II-XXV)

Results and Discussion

In this paper the synthesis and antimicrobial activities of some new derivatives (II-XXV) of 8-hydroxyquinoline-5-sulfonamido acid, methyl esters, hydrazides, and dipeptide derivatives are described. The preparation of 8-hydroxyquinoline-5-sulfonamido acids (II-VII) was carried out by the reaction of 8-hydroxyquinoline-5-sulfonyl chloride (I) with the appropriate amino acid in THF-Et_3N. Most of the products were obtained in crystalline form in 52-71% yield. The compounds (II-VII) were chromatographically homogeneous. Complete acid hydrolysis of (IV) for 24 hrs with 6N HCl at 100° yielded valine.

Condensation of 8-hydroxyquinoline sulfonly chloride (1) with the appropriate amino acid methyl ester hydrochloride (1:1.1 mole) in THF-Et_3N medium afforded 8-hydroxyquinoline-5-sulfonamido acid methyl esters (VIII-XIII), the time required for completion of the reaction (3-4 hrs) being monitored by TLC. All the methyl esters (VIII-XIII) were



Scheme

*Chemistry Department, Faculty of Education, Tanta University, Kafr El-Sheick-Egypt.

chromatographically homogeneous. Hydrazinolysis of methyl esters (VIII-XIII) in ethanol gave the corresponding hydrazides (XIV-XIX) as crystalline solids which gave positive benzidine and silver nitrate reactions.

The dipeptide methyl esters (XX-XXV) were prepared by the carbodiimide method. Coupling of 8-hydroxyquinoline-5-sulfonamido acid (II-VII) with amino acid methyl ester hydrochlorides in dioxane-THF mixture containing triethylamine and using the dicyclohexyl carbodiimide (DCC) technique, afforded the dipeptides (XX-XXV). All dipeptide methyl esters (XX-XXV) were highly purified through repeated recrystallization and chromatographically homogeneous materials were obtained in 74-89% yields.

IR and NMR data confirmed the identity of the dipeptide derivatives (XX-XXV), the dipeptide methyl esters (XX-XXV) gave deep blue 1:1 complexes with copper (II) at λ max 650-680 n.m. The methods used for studying the copper (II) complexes are the same as described in the previous papers [16-17].

All the compounds synthesised (II-XXV) gave IR and NMR spectra consistent with their structures.

Experimental

Melting point were determined on an electrothermal melting point apparatus and are uncorrected. This layer chromatography (R_f values) for analytical purposes was taken on silica gel G-1 plastic sheets and developed with (*n*-butanol: acetic acid: water) (4: 1: 1) using iodine, ninhydrine and benzidine as spraying agents. Optical rotation $[\alpha]_D^{20}$ were measured for all compounds in DMF at λmax 589 nm on a Bellingham Stanelly Polarimeter using 5 cm tube at 20°.

The infrared spectra (υmax, cm^{-1}) were taken in KBr disc (pellets) using a Schimadzu IR-408 instrument. NMR spectra chemical shifts δ in ppm, were measured in DMSO-d_6

Table 1. Physical Data of Various 8-Hydroxyquinoline-5-Sulfonamido Acids, Esters, Hydrazides and Dipeptide Derivatives (II-XXV).

Compound	A	Yield %	m.p.°C	R_f	Cryst solvent	$[\alpha]_D^{20}$**	Mol.formula	Elemental analysis % Calcd. C	H	N	Found C	H	N
II	Gly	68	290-292	0.80	a	—	$C_{11}H_{11}SO_5N_2$	46.61	3.86	9.91	46.64	3.88	9.89
III	L-Ala	60	300-302	0.78	a	+105	$C_{12}H_{13}SO_5N_2$	48.46	4.40	9.42	48.48	4.37	9.42
IV	L-Val	55	315-317	0.69	a	+117.5	$C_{14}H_{17}SO_5N_2$	51.70	5.21	8.64	51.69	5.23	8.61
V	L-Leu	71	325-327	0.75	a	+80	$C_{15}H_{19}SO_5N_2$	53.11	5.60	8.26	53.09	5.60	8.25
VI	L-Phe	56	341-343	0.70	a	+70	$C_{18}H_{17}SO_5N_2$	57.93	4.55	7.53	57.90	4.55	7.50
VII	L-Tyr	52	345-347	0.62	a	+35	$C_{18}H_{17}SO_6N_2$	55.95	4.42	7.26	55.95	4.40	7.25
VIII	Gly-OMe	60	310-312	0.82	b	—	$C_{12}H_{13}SO_5N_2$	48.49	4.39	9.44	48.48	4.37	9.42
IX	L-Ala-OMe	55	320-322	0.79	b	+88.5	$C_{13}H_{15}SO_5N_2$	50.19	4.82	9.00	50.16	4.82	9.00
X	L-Val-OMe	75	301-303	0.72	b	+130	$C_{15}H_{19}SO_5N_2$	53.11	5.62	8.29	53.09	5.60	8.25
XI	L-Leu-OMe	70	315-316	0.76	b	+15	$C_{16}H_{21}SO_5N_2$	54.40	5.95	7.92	54.39	5.94	7.93
XII	L-Phe-OMe	62	317-319	0.73	b	+18	$C_{19}H_{19}SO_5N_2$	58.88	4.88	7.21	58.91	4.90	7.32
XIII	L-Tyr-OMe	80	330-332	0.65	b	+31	$C_{19}H_{19}SO_6N_2$	56.55	4.70	6.91	56.57	4.71	6.94
XIV	Gly-N_2H_3	78	270-272	0.72	c	—	$C_{11}H_{13}SO_4N_4$	44.41	4.35	18.83	44.44	4.32	18.85
XV	L-Ala-N_2H_3	81	280-282	0.67	c	+80	$C_{12}H_{15}SO_4N_4$	46.29	4.82	18.00	46.30	4.82	18.00
XVI	L-Val-N_2H_3	65	310-312	0.64	c	+58	$C_{14}H_{19}SO_4N_4$	49.55	5.60	16.50	49.55	5.60	16.51
XVII	L-Leu-N_2H_3	63	318-320	0.72	c	+67.5	$C_{15}H_{21}SO_4N_4$	50.98	5.91	15.84	50.99	5.94	15.86
VIII	L-Phe-N_2H_3	58	289-291	0.67	c	+42.5	$C_{18}H_{19}SO_4N_4$	55.81	4.87	14.45	55.81	4.90	14.47
XIX	L-Tyr-N_2H_3	76	300-302	0.58	c	+65	$C_{18}H_{19}SO_5N_4$	53.56	4.70	13.86	53.59	4.71	13.89
XX	L-Leu-L-Phe-OMe	80	156-158	0.70	b	+13	$C_{25}H_{31}SO_6N_3$	59.88	6.13	8.40	59.88	6.18	8.38
XXI	L-Phe-L-Leu-OMe	82	223-225	0.65	b	+30	$C_{25}H_{31}SO_6N_3$	59.84	6.85	8.48	59.88	6.85	8.38
XXII	L-Lleu-L-Ala-OMe	74	213-215	0.72	b	+31	$C_{19}H_{27}SO_6N_3$	53.61	6.33	9.83	53.64	6.35	9.88
XXIII	L-Ala-L-Leu-OMe	89	218-220	0.68	b	+45	$C_{19}H_{22}SO_6N_3$	53.64	6.37	9.91	53.64	6.35	9.88
XXIV	L-Val-L-Try-OMe	83	250-252	0.74	b	+18	$C_{22}H_{25}SO_6N_3$	57.50	5.41	9.19	57.51	5.44	9.15
XXV	L-Ala-L-Phe-OMe	77	270-272	0.80	b	+53	$C_{24}H_{29}SO_7N_3$	57.26	5.79	8.34	57.25	5.76	8.34

*Cryst. solvent: a: Methanol-water, b: Ethanol-water, c: Acetric acid-water. **Optical rotation $[\alpha]_D^{20}$ (were measured in DMFat λmax 589 nm at 20°).

using a Varian EM-360 spectrometer and TMS as internal standard.

8-Hydroxyquinoline-5-sulfonyl chloride (I) was prepared according to the procedure described earlier [18].

General procedure for the synthesis of 8-hydroxyquinoline-5-sulfonylamino acids (II-VII). To a solution of the apropriate amino acid (0.1 mole) in a water (25 ml) THF (15 ml) mixture, was added triethylamine (5 ml) followed by sulfonyl chloride (I) (0.11 mole) portionwise during 30 mins. The temperature of the reaction mixture during the process of addition was kept at 10° and stirring continued for 45 mins- 2 hrs at 20°. Tetrahydrofuran was removed by concentration of the reaction mixture under reduced pressure and water (30 ml) added. The mixture was cooled to 0° and acidified with 2N HCl until acidic to Congo red (pH 5). The crude product was filtered, washed with water and recrystallized from methanol-water. All the products (II-VII) were chromatographically homogeneous when detected with iodine solution, benzidine and gave negative ninhydrin test [cf. Table 1, compounds (II-VII)].

The IR spectra of the products (II-VII) showed characteristic bands at: 3360, 3120, 3080 (NH, SO_2NH, Ar-H),1450, 1360, 1270 (SO_2NH), 1780, 1720 (>C=O), 1640, 1260 (COOH) cm^{-1}, and other characteristic bands due to quinoline and amino acid residues.

The NMR spectra of compounds (II-VII) had characteristic chemical shifts for the five quinoline ring protons centered around δ: 7.32, 7.45, 7.63, 7.86, and 8.10, 5.89 (s, 1H, NH), 10.81 (s, 1H, COOH), and other protons characteristic of the amino acid residue.

General procedure for the synthesis of 8-hydroxyquinoline-5-sulfonamido acid methyl esters (VIII-XIII). A solution of 8-hydroxyquinoline-5-sulfonyl chloride (1) 0.01 mole) in dioxane (25 ml) was added dropwise under stirring to a solution of the amino acid methyl ester hydrochloride. (0.011 mole) in dioxane (25 ml) containing triethylamine (2 ml). The reaction mixture was kept at 0° during the addition. Stirring was continued at room temperature (50 mins) followed by refluxing (1 hr.) until completion of the reaction as checked by TLC. After cooling, the reaction mixture was filtered to remove $Et_3N.HCl$ and any unreacted materials. The solvent was removed in vacuo and the residual material recrystallized from ethanol-water. All the compounds were chromatographically homogenous when developed with iodine solution, benzidine and hydroxamate reactions and showed negative ninhydrin reaction.

The IR spectra of the methyl esters (VIII-XIII) showed bands at: 3360, 3120, 3060 (NH, SO_2NH, Ar-H), 1760, 1720 (>C=O), 1410, 1360, 1080 ($COOCH_3$), 1450, 1370 1280 (SO_2NH) cm^{-1} and other characteristic bands due to quinoline and amino acid residues. The NMR spectra of (VIII-XIII) 7.61 - 7.68 and8.05 (s, 5H, quinoline protons), 3.28 (s, 3H, $COOCH_3$), 5.96 (s, 1H, NH), and other protons characteristic of the amino acid residues.

General procedure of the synthesis of 8-hydroxyquinoline-5-sulfonamido acid hydrazides (XIV-XIX). The methyl esters (VIII-XIII), (0.01 mole) were dissolved in ethanol (25 ml) and hydrazine hydrate 85% (0.05 mole) added. The reaction mixture was stirred for 3 hrs at 20° and left 24 hrs at room temperature. The crystalline products (XIV-XIX) were filtered washed with cold water and recrystallized form acetic acid-water. The hydrazides (XIV-XIX) were chamatographically homogenous when developed with iodine solution, benzidine and showed a negative hydroxamate reaction.

The IR spectra of hydrazides (XIV-XIX) exhibited bands at: 3430, 3140, 3070 (NH_2, NH, ArH, and SO_2NH), 1450, 1370, 1280 (SO_2NH), 1780, 1720 (>C=O).

General procedure of the synthesis of 8-hydroxyquinoline-5-sulfonamido dipetide methyl esters (XX-XXV). To a solution of amino acid methyl esters hydrochloride (0.0082 mole) in THF (50 ml) was added triethylamine (2 ml). The solution was stirred at 20° for 30 mins and cooled to 0°.

The sulfonamido acid (0.008 mole) in THF (25 ml) and dicyclohexylcarbodiimide (DCC 1.62 gm) were added to the above mixture. The reaction mixture was stirred for 2 hrs at 0° and for another 2 hrs at room temperature. Dicyclohexylurea was filtered off, acetic acid (1 ml) added, the solution was filtered and the filtrate was evaporated in vacuo. The residue was recrystallized from methanol-water. The dipeptide methyl ester products were easily soluble in alcohols, DMF, nitromethane, and dioxane and insoluble in water and ether.

The dipeptides were chromatographically homogeneous when detected with iodine solution, benzidine and hydroxamate reactions.

The IR spectra of the dipeptide (XX-XXV) showed bands at: 3340, 3160, 3080 (NH, CONH, SO_2NH, Ar-H), 1760, 1720 (>C=O), 1760,1720, 1430, 1320 (-$COOCH_3$), 1360, 1280, 1090 (SO_2NH) and other bands characteristic to the quinoline and dipeptide residues.

The NMR spectra of compounds (XX-XXV) had characteristic chemical shifts at: 3.34 (s, 3H, $COOCH_3$) 5.98 (s, 2H, NH) and other protons characteristic of the amino acid residues.

Biological screening results. The antimicrobial activities of the synthesized compounds (II-XXV) were determined using the hole plate method and filter paper disc method (19-22). All the synthesized compounds were tested against grampositive and gram-negative bacteria: *Bacillus cereus* (NRRL-B-569); *Bacillus sphaericus* (159); *Staphellococcus*

aureus (ATCC-6538P); *Sareino* species; and *Escherichia coli* (NRRL-B-210). A qualitative screen was performed on all compounds, while quantitative assays were done on active compounds only.

Antimicrobial activity studies of the synthesized compounds (II-XXV) proved that: 8-hydroxyquinoline-5-sulfonyl-Gly (II), and the corresponding L-Ala (III), L-Val (IV), L-Leu (V), L-Phe (VI), L-Tyr (VII), possessed high antimicrobial activities against: *S. aureus*, *Sarc.* species, *B. cereus*, *B. Sphaericus*, and *E. Coli* with minimal inhibitory concentration (MIC) ranging from 25-100 µg/ml (cf. Table2).

Esterification of the terminal carboxyl group of the amino acid moieties enhanced and verified the antimicrobial activities of some of the synthesis amino acid derivatives. Gly-OMe(VII), and the corresponding L-Ala-OMe (IX), L-Val-OMe (X), L-eu-OMe (XI) were found to have marked growth inhibitory effect against the different micro-organisms with MIC 5-100 µg/ml (cf. Table 2).

On the other hand, hydrazinolysis the terminal methyl ester group gave the corresponding hydrazides (XIV-XIX) of verified biological properties (cf. Table 2).

Elongation of the dipeptide chain, as in (XX-XXV), produced compounds which possessed high and specific antimicrobial activity against the tested micro-organisms (cf. Table 2).

Other pharmacological studies are currently in progress.

TABLE 2. MINIMAL INHIBITORY CONCENTRATION (MIC) IN µg/ml OF THE BIOLOGICALLY ACTIVE COMPOUNDS.

	S. aureus		*S. species*		*B. cereus*		*B. sphaeric*		*E. coli*	
	A*	MIC	A*	MIC	A*	MIC	A*	MIC	A*	MIC
II	–	–	++	50	+	100	–	–	++++	5
III	+	100	+	100	+	100	+	100	–	–
IV	+++	25	+++	25	+++	25	+++	25	+++	25
V	++	50	++	50	++	20	–	–	–	–
VI	–	–	++	50	+++	25	–	–	–	–
VII	++	50	++	50	++	50	+	100	–	–
VIII	++++	5	+	100	+	100	+	100	+	100
IX	++	50	–	–	+	100	–	–	++	50
X	+	100	+	100	+	100	+	100	+	100
XI	++	50	++	50	++	50	++	50	++	50
XV	–	–	++	50	+	100	–	–	++	50
XVII	+++	25	+++	25	+++	25	+++	25	+++	25
XX	++	100	++	100	++	50	++	50	+	100
XXII	–	–	–	–	–	–	–	–	+	100

(*) Antimicrobial activity (A) +++ = highly active; ++ = moderately active, + = slightly active, – = inactive.

References

1. S. Mehorta, J. P. Bathwal, B. R. Pandy, K. P. Bhargava, and S. S. Parmar, J. Heterocyclic Chem.,**17,** 1213 (1980).
2. A. Albert, *Heterocyclic Chemistry, Quinoline and Isoquinoline Derivatives* (University of London, 1968), pp. 159.
3. R. H. Manske and M. Kukla, *The Synthesis of Quinolines, Organic Reactions* (John Wiley, New York, 1953), Vol. 7, pp. 59-215.
4. A. M. El-Naggar, M. H. El-Gamal, B. A. El-Tawil and F. S. Ahmed, Acta Chim. Hung., **89,** 279 (1976).
5. A. M. El-Naggar, F. S. Ahmed, A. M. Abd. El-Salam and T. M. Ibrahim, Egypt J. Chem., **23,** 209 (1980).
6. A. M. El-Naggar, M. N. Abou El-Enein and A. A. Makhlouf, Bull. Soc. Chim., **10,** 545 (1981).
7. A. M. El-Naggar, F. S. Ahmed, A. M. Abd. El-Salam and M. S. El-Shami, Egypt. J. Chem., **26,** 441 (1983).
8. A. M. El-Naggar, A. H. Abd. El-Salam, I. M. Ismail, B. M. Haroum and A. H. Gomma, Indian J. Chem., **19B,** 1088 (1980).
9. A. M. El-Naggar, F. S. Ahmed, A. M. Abd. El-Salam, M. A. Radi and M. S. Latif, J. Heterocylic Chem., **18,** 1203 (1981).
10. A. M. El-Naggar, F. S. Ahmed, A. M. Abd. El-Salam and M. A. El-Gazzar, Ibid., **19,** 1025 (1982).
11. A. M. El-Naggar, A. M. Abd. El-Salam, F. S. Ahmed, M. S. Latif and F. A. El-Cady, II-Farmaco **38,** 391 (1983).
12. A. M. El-Naggar, A. M. Abd. El-Salam, F. S. Ahmed and T. M. Ibrahim, Acta Pharm. Jugosl, **35,** 15 (1985).
13. M. R. Zaher, F. A. Kora, M. E. Hussein, R. A. El-Sayed and A. M. El-Naggar, II-Farmaco **41,** 729 (1986).
14. A. M. El-Naggar, F. A. Kora and R. A. El-Sayed, J. Serb. Chem. Soc., **51,** 441 (1986).
15. F: A. Kora, M. E. Hussein, R. A. El-Sayed and A. M. El-Naggar, Polish. J. Chem., **62,** 749 (1988).
16. A. M. El-Naggar, Egypt. J. Chem., **16,** 229 (1973).
17. A. M. El-Naggar, Y. A. Shehata and M. R. Zaher, Roczniki Chemi., **51,** 233 (1977).
18. A. Yu. Bankovskii, M. Circule, P. I. Brusilovskii and I. A. Tasilinskaya, Khim. Geterosikl. Soed (Russ), **11,** 1501 (1976).
19. J. G. Carlson, H. G. Douglas and H. D. Bissel, J. Bacterial., **55,** 607 (1948).
20. G. W. Irving, T. D. Fontaine and S. P. Doolittle, J. Bacterial., **52,** 10 (1964).
21. J. G. Vincent and H. W. Vincent, Proc. Soc. Exptl. Biol. Med., **55,** 162 (1944).
22. J. A. Epstein, E. J. Foley, I. Perrine and S. W. Lee, J. Lab. Clin. Med., **29,** 319 (1944).