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Studies on 2(1*H*)-Quinolinone Derivatives as Gastric Antiulcer Active Agents. 2-(4-Chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic Acid and Related Compounds

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A series of *N*-acyl amino acid analogues of 2(1*H*)-quinolinone was synthesized and tested for antiulcer activity against acetic acid-induced gastric ulcer in rats. These compounds were synthesized by the acylation of amino acid derivatives of 2(1*H*)-quinolinone, which were obtained from the reaction of ω-bromoalkyl 2(1*H*)-quinolinones and acetamidomalonate in the presence of sodium ethoxide, followed by hydrolysis with diluted hydrochloric acid. Among them, 2-(4-chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic acid (VIIIf) was found to have the most potent activity. The structure–activity relationships are discussed.

Keywords——2-amino-3-[2(1*H*)-quinolinon-4-yl]propionic acid; 2-acylamino-ω-[2(1*H*)-quinolinonyl]alkanoic acid; antiulcer activity; structure–activity relationship; 2-(4-chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic acid; cytoprotective effect

Introduction

Research on therapeutic measures for peptic ulcer has centered mainly on inhibitors of gastric acid secretion such as histamine H_2-antagonists, anticholinoceptor drugs and the other antisecretory drugs. However, since patients with peptic ulcer often show hypoacidity, it seems inappropriate that only gastric acidity reducing drugs are used in treatment. Accordingly, the development of activators of gastric cytoprotection shoud be particularly valuable.

Amino acid derivatives such as glutamine[1] and methionine[2] derivatives are well known as antiulcer drugs that enhance mucosal defence. Recently Benzotript,[3] having an amino acid moiety, was reported as an antagonist of gastrin, though its effect on mucosal defence was not determined. We have been investigating the 2(1*H*)-quinolinone derivatives, and have developed a clinically useful β-adrenergic blocker[4] or stimulant.[5] In studies on Cilostamide, a 2(1*H*)-quinolinone derivative and inhibitor of blood platelet aggregation, we found a relatively high concentration in the stomach as a result of tissue distribution studies, and we found that the drug had antisecretory activity.[6] Therefore, we were interested in synthesizing amino acid analogues of 2(1*H*)-quinolinones for testing of antiulcer activity against acetic acid-induced gastric ulcer in rats, as a model of chronic ulcer.[7]

We describe here the synthesis and antiulcer activity of 2-acylamino-ω-[2(1*H*)-quinolinonyl]alkanoic acids and related compounds.

Synthesis

ω-Bromoalkyl derivatives of 2(1*H*)-quinolinone (Va—e), which are versatile key intermediates in the synthesis of the amino acids (VIIa—f), were synthesized by treatment of ω-hydroxyalkyl derivatives (IVa—e) with excess hydrobromic acid. The starting hydroxyalkyl compounds were synthesized by reduction of carboxaldehydes (Ia, b) with $NaBH_4$ or of

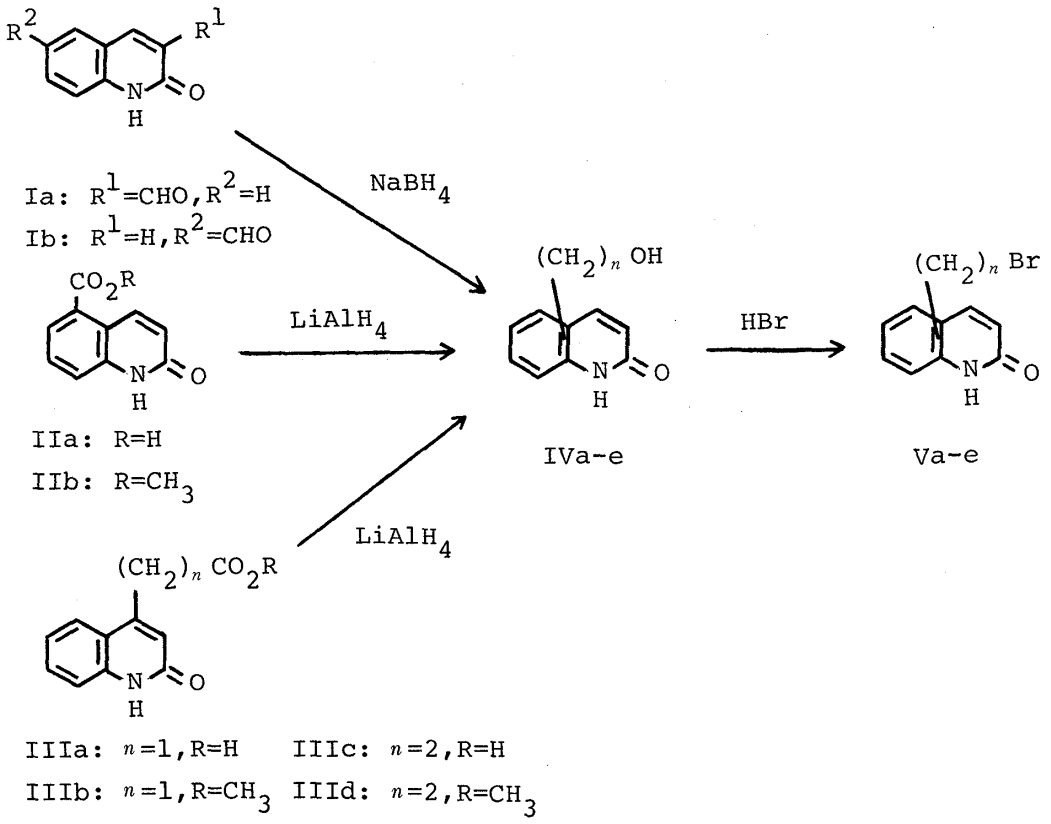
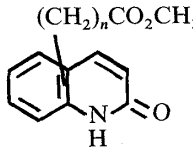


Chart 1

TABLE I. Ester Derivatives of 2(1*H*)-Quinolinonecarboxylic Acid and 2(1*H*)-Quinolinonealkanoic Acid

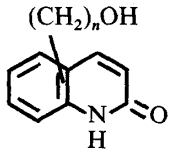


Compd. No.	*n*	Position	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
IIb	0	5	84	Colorless prisms (MeOH)	280—282	$C_{11}H_9NO_3$	65.02 (65.03	4.46 4.47	6.89 6.95)
IIIb	1	4	58	Colorless prisms (MeOH)	207—208.5	$C_{12}H_{11}NO_3$	66.35 (66.23	5.10 5.08	6.45 6.52)
IIId	2	4	72	Pale yellow prisms (MeOH)	166—167	$C_{13}H_{13}NO_3$	67.52 (67.41	5.67 5.66	6.08 5.88)

carboxylic acid esters (IIa, b and IIIa—d) (Table I) with $LiAlH_4$ (Chart 1, Tables II and III).

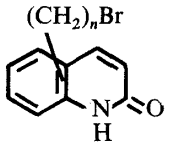
Condensation of the bromoalkyl derivatives (Va—f) with diethyl acetamidomalonate in the presence of sodium ethoxide in EtOH afforded the corresponding ester derivatives (VIa—f) (Table IV), which were hydrolyzed with 20% HCl to give the amino acids (VIIa—f) (Table V). Various amide compounds (VIIIa—t) were easily prepared from VIIa—f and acyl chlorides by the Schotten–Baumann reaction (Chart 2, Table VI). Since the structure–activity relationship of VIII indicated that 2(1*H*)-quinolinones substituted at the 3- and 4-positions

TABLE II. ω-Hydroxyalkyl-2(1*H*)-quinolinone Derivatives



Compd. No.	*n*	Position	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
IVa	1	3	97	Colorless prisms (MeOH)	238—241.5	$C_{10}H_9NO_2$	68.56 (68.50	5.18 5.28	8.00 7.83)
IVb	2	4	91	Pale yellow needles (MeOH)	210—214	$C_{11}H_{11}NO_2$	69.82 (69.74	5.86 6.10	7.40 7.38)
IVc	3	4	64	Pale yellow prisms (EtOH)	172—174.5	$C_{12}H_{13}NO_2$	70.91 (70.71	6.45 6.39	6.89 6.57)
IVd	1	5	78	Colorless prisms (MeOH–Ether)	255—257	$C_{10}H_9NO_2$	68.56 (68.52	5.18 5.10	8.00 8.05)
IVe	1	6	54	Pale yellow needles (EtOH–H_2O)	235—238	$C_{10}H_9NO_2$ 1/4 H_2O	66.84 (66.46	5.33 5.28	7.79 7.73)

TABLE III. ω-Bromoalkyl-2(1*H*)-quinolinones



Compd. No.	*n*	Position	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
							C	H	N
Va	1	3	88	Colorless needles (MeOH)	218.5—219 (dec.)	$C_{10}H_8BrNO$	50.45 (50.81	3.39 3.49	5.88 5.72)
Vb	2	4	83	Pale yellow needles (EtOH)	173—174	$C_{10}H_{10}BrNO \cdot$ 1/4 H_2O	51.49 (51.40	4.12 3.84	5.46 5.42)
Vc	3	4	72	Colorless needles (EtOH)	155—156	$C_{12}H_{12}BrNO$	54.16 (54.03	4.55 4.44	5.26 5.08)
Vd	1	5	44	Colorless needles (MeOH)	247.5—248 (dec.)	$C_{10}H_8BrNO$	50.45 (58.85	3.39 3.37	5.88 5.82)
Ve	1	6	49	White powder (DMF–H_2O)	232—233	$C_{10}H_8BrNO$	50.45 (50.84	3.39 3.30	5.88 5.50)

were most promising (*vide infra*), our synthetic work on 2(1*H*)-quinolinone derivatives was concentrated on 3- and 4-substituted compounds.

Alkylation of VIb with alkyl halides in the presence of NaH gave the N^1-alkyl derivatives (IXa—f) (Table IV), which were hydrolyzed with 20% HCl to give the amino acids (Xa—f) (Table V), which were converted to the amide derivatives (XIa—h) by treatment with substituted benzoyl chlorides in the same manner as for VIII (Chart 3, Table VI).

The sulfonamide (XII) was prepared from VIIb and *p*-chlorobenzenesulfonyl chloride in the usual manner. Compound VIIb was hydrogenated using Pd–C to give the 3,4-dihydro-2(1*H*)-quinolinone analogue (XIII), which was benzoylated to afford the corresponding

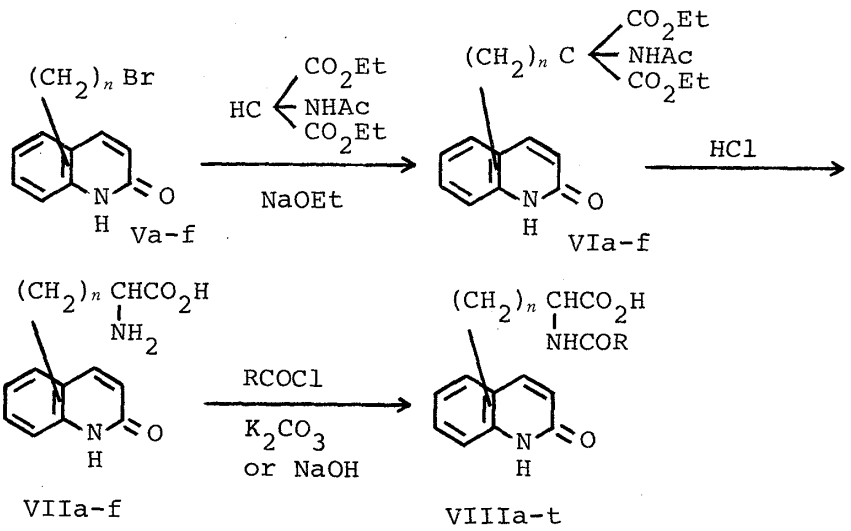
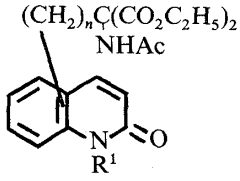


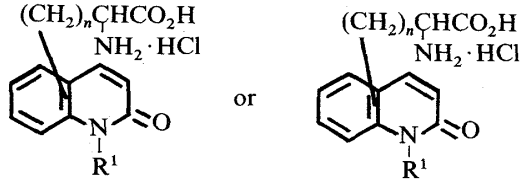
Chart 2

TABLE IV. 2-Acetylamino-2-ethoxycarbonyl-ω-[2(1*H*)-quinolinonyl]alkanoate Derivatives



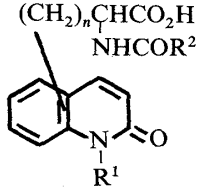
Compd. No.	*n*	Position	R^1	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
								C	H	N
VIa	1	3	H	67	Colorless prisms (EtOH)	228—230 (dec.)	$C_{19}H_{22}N_2O_6$	60.95 (61.09	5.92 5.93	7.48 7.37)
VIb	1	4	H	74	Colorless prisms (EtOH)	224—226 (dec.)	$C_{19}H_{22}N_2O_6$	60.95 (60.88	5.92 5.92	7.48 7.29)
VIc	2	4	H	83	Colorless needles (EtOH–H_2O)	182—183	$C_{20}H_{24}N_2O_6 \cdot 1/2\,H_2O$	60.44 (60.39	6.21 5.95	7.05 7.11)
VId	3	4	H	39	Colorless prisms (EtOH)	156—158	$C_{21}H_{26}N_2O_6 \cdot H_2O$	59.99 (59.76	6.71 6.46	6.66 6.59)
VIe	1	5	H	79	White powder (EtOH)	210—213 (dec.)	$C_{19}H_{22}N_2O_6 \cdot 1/2\,H_2O$	59.52 (59.87	6.05 5.86	7.31 7.27)
VIf	1	6	H	55	White powder (EtOH)	253—256	$C_{19}H_{22}N_2O_6$	60.95 (60.88	5.92 5.96	7.48 7.55)
IXa	1	4	CH_3	39	Colorless prisms (EtOH)	211.5—212.5	$C_{20}H_{24}N_2O_6$	61.85 (61.63	6.23 6.00	7.21 7.18)
IXb	1	4	C_2H_5	31	Colorless needles (EtOH)	204—205	$C_{21}H_{26}N_2O_6$	62.67 (62.36	6.51 6.37	6.96 6.79)
IXc	1	4	*n*-C_4H_9	31	Colorless prisms (EtOH)	110—112.5	$C_{23}H_{30}N_2O_6$	64.17 (64.06	7.02 6.97	6.51 6.60)
IXd	1	4	$CH_2{=}CHCH_2$	39	Colorless prisms (EtOH)	176—178.5	$C_{22}H_{26}N_2O_6$	63.75 (63.58	6.32 6.24	6.76 6.82)
IXe	1	4	$CH{\equiv}CCH_2$	97	White powder (EtOH)	161—163	$C_{22}H_{24}N_2O_6$	64.07 (63.80	5.86 5.71	6.79 6.75)
IXf	1	4	CH_2Ph	54	White powder (EtOH)	155—157	$C_{26}H_{28}N_2O_6$	67.23 (67.12	6.08 6.14	6.03 5.89)

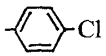
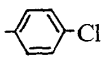
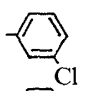
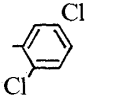
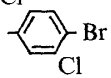
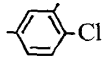
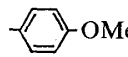
TABLE V. 2-Amino-ω-[2(1*H*)-quinolinonyl]alkanoic Acid Hydrochloride Derivatives

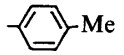
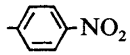
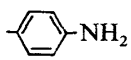
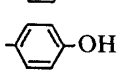
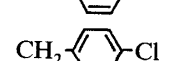
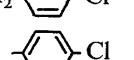
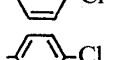
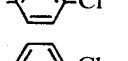
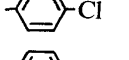
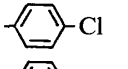
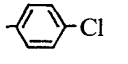
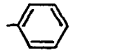
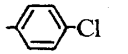
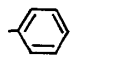
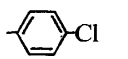
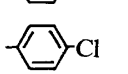
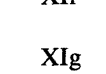
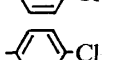


Compd. No.	*n*	Position	R^1	Bond of C(3) and C(4)	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
									C	H	N
VIIa	1	3	H	Double	86	White powder (MeOH–Acetone)	271—272 (dec.)	$C_{12}H_{13}ClN_2O_3$	53.64 (53.99	4.50 4.93	10.43 10.25)
VIIb	1	4	H	Double	89	Colorless prisms (EtOH–H_2O)	220—225 (dec.)	$C_{12}H_{13}ClN_2O_3 \cdot H_2O$	50.27 (50.57	5.27 4.86	9.77 9.79)
VIIc	1	4	H	Single	71	White powder (EtOH–Ether)	237—238 (dec.)	$C_{12}H_{15}ClN_2O_3 \cdot 1/4\,H_2O$	52.37 (52.40	5.68 5.43	10.18 10.31)
VIId	1	6	H	Single	89	White powder (MeOH–Ether)	283—285 (dec.)	$C_{12}H_{15}ClN_2O_3$	53.24 (53.18	5.59 5.39	10.35 10.24)
VIIe	2	4	H	Double	Quant.	White powder (H_2O)	296—298 (dec.)	$C_{13}H_{15}ClN_2O_3 \cdot 1/4\,H_2O$	54.36 (54.27	5.44 5.34	9.75 9.79)
VIIf	1	5	H	Double	Quant.	White powder (DMF–H_2O)	307—309 (dec.)	$C_{12}H_{12}ClN_2O_3 \cdot 1/2\,H_2O$	59.74 (61.06	5.43 5.20	11.61 11.89)
Xa	1	4	CH_3	Double	85	Colorless prisms (EtOH)	175—178 (dec.)	$C_{13}H_{15}ClN_2O_3 \cdot H_2O$	51.92 (51.62	5.70 5.65	9.31 9.46)
Xb	1	4	C_2H_5	Double	94	White powder (MeOH)	255—260 (dec.)	$C_{14}H_{17}ClN_2O_3$	56.66 (56.52	5.43 5.64	9.44 9.53)
Xc	1	4	*n*-C_4H_9	Double	89	White powder (EtOH)	168—170 (dec.)	$C_{16}H_{21}ClN_2O_3 \cdot 2/3\,H_2O$	57.06 (57.06	6.68 6.70	8.32 7.87)
Xd	1	4	$CH_2=CHCH_2$	Double	13	Colorless prisms (EtOH)	166—171 (dec.)	$C_{15}H_{17}ClN_2O_3 \cdot H_2O$	55.13 (54.94	5.86 5.70	8.57 8.70)
Xe	1	4	$CH\equiv CCH_2$	Double	30	White powder (MeOH)	218—221 (dec.)	$C_{15}H_{14}N_2O_3 \cdot H_2O$	62.50 (62.32	5.60 5.57	9.72 9.88)
Xf	1	4	CH_2Ph	Double	94	White powder (EtOH)	166—169 (dec.)	$C_{19}H_{19}ClN_2O_3 \cdot H_2O$	60.56 (60.76	5.62 5.56	7.43 7.40)

TABLE VI. 2-Acylamino-ω-[2(1*H*)-quinolinonyl]alkanoic Acid Derivatives



Compd. No.	*n*	Position	R^1	R^2	Yield (%)	Activity[a]	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
										C	H	N
VIIIa	1	3	H	CH_3	29	±	Pale yellow powder (H_2O)	228—231 (dec.)	$C_{14}H_{14}N_2O_4$	61.39 (61.18	5.15 5.22	10.21 10.18)
VIIIb	1	3	H		56	+	White powder (MeOH)	261—264 (dec.)	$C_{19}H_{22}N_2O_4$	66.65 (66.15	6.48 6.36	8.18 8.00)
VIIIc	1	3	H		50	+	White powder (EtOH)	255—257.5	$C_{19}H_{16}N_2O_4$	66.96 (67.07	4.88 4.83	8.22 8.20)
VIIId	1	3	H		68	+ +	White powder (EtOH–H_2O)	270—271.5	$C_{19}H_{15}ClN_2O_4$	61.55 (61.49	4.08 4.17	7.56 7.56)
VIIIe	1	4	H		54	+	White powder (EtOH)	283—286 (dec.)	$C_{19}H_{16}N_2O_4 \cdot 2/3\,H_2O$	65.51 (65.47	5.02 4.88	8.04 7.84)
VIIIf	1	4	H		49	+ +	White powder (DMF–H_2O)	288—290 (dec.)	$C_{19}H_{15}ClN_2O_4 \cdot 1/2\,H_2O$	60.09 (59.77	4.25 4.03	7.38 7.35)
VIIIg	1	4	H		54	+	Colorless needles (MeOH–H_2O)	265—267 (dec.)	$C_{19}H_{15}ClN_2O_4$	61.55 (61.34	4.08 4.07	7.55 7.49)
VIIIh	1	4	H		89	±	White powder (MeOH–H_2O)	270.5—271.5 (dec.)	$C_{19}H_{15}ClN_2O_4 \cdot 1/4\,H_2O$	60.81 (60.72	4.16 4.20	7.46 7.48)
VIIIi	1	4	H		58	±	White powder (DMF–H_2O)	287—288.5 (dec.)	$C_{19}H_{15}BrN_2O_4 \cdot 1/2\,H_2O$	53.79 (53.62	3.80 3.57	6.60 6.53)
VIIIj	1	4	H		66	±	White powder (DMF–H_2O)	278—280 (dec.)	$C_{19}H_{14}Cl_2N_2O_4$	56.31 (56.39	3.48 3.53	6.91 7.03)
VIIIk	1	4	H		59	±	White powder (Acetone–H_2O)	259—261 (dec.)	$C_{20}H_{18}N_2O_5$	65.57 (65.37	4.95 4.87	7.65 7.60)

VIIIl	1	4	H		49	+	Colorless needles (EtOH–H_2O)	284—286 (dec.)	$C_{20}H_{18}N_2O_4 \cdot 1/2\,H_2O$	66.84 (66.48	5.33 5.17	7.80 7.82)
VIIIm	1	4	H		52	+	White powder (DMF–H_2O)	290—291 (dec.)	$C_{19}H_{15}N_3O_6 \cdot 1/2\,H_2O$	58.46 (58.23	4.13 4.18	10.76 10.92)
VIIIn	1	4	H		58	+	White powder (DMF–H_2O)	240—242 (dec.)	$C_{19}H_{17}N_3O_4$	64.95 (64.31	4.88 4.87	11.96 11.94)
VIIIo	1	4	H		54	±	White powder (DMF–H_2O)	305.5—306.5 (dec.)	$C_{19}H_{16}N_2O_5 \cdot 2/3\,H_2O$	62.64 (62.62	4.80 4.53	7.69 7.70)
VIIIp	1	4	H		31	+	Colorless needles (MeOH)	252—255 (dec.)	$C_{20}H_{17}ClN_2O_4$	62.42 (62.19	4.45 4.32	7.28 7.21)
VIIIq	2	4	H		62	±	White powder (DMF–H_2O)	295—296 (dec.)	$C_{20}H_{17}ClN_2O_4 \cdot 1/4\,H_2O$	61.70 (61.72	4.53 4.49	7.19 7.34)
VIIIr	3	4	H		22	+ +	White powder (DMF–H_2O)	279.5—280.5 (dec.)	$C_{21}H_{19}ClN_2O_4 \cdot 1/3\,H_2O$	62.30 (62.39	4.90 4.86	6.92 6.90)
VIIs	1	5	H		63	±	Colorless needles (DMF–H_2O)	> 300	$C_{19}H_{15}ClN_2O_4$	61.55 (61.50	4.08 4.06	7.56 7.32)
VIIIt	1	6	H		36	±	Pale yellow powder (DMF–H_2O)	275—280 (dec.)	$C_{19}H_{15}ClN_2O_4$	61.55 (61.53	4.08 3.91	7.56 7.62)
XIa	1	4	CH_3		31	±	Colorless needles (EtOH)	247—249 (dec.)	$C_{20}H_{17}ClN_2O_4$	62.42 (61.99	4.45 4.46	7.28 7.08)
XIb	1	4	CH_3		57	±	White powder (EtOH–H_2O)	227.5—229	$C_{20}H_{18}N_2O_4$	68.56 (68.68	5.18 5.37	8.00 8.13)
XIc	1	4	C_2H_5		59	+ +	White powder (EtOH)	263—264.5 (dec.)	$C_{21}H_{19}ClN_2O_4 \cdot H_2O$	60.51 (59.91	5.08 4.89	6.72 6.71)
XId	1	4	C_2H_5		29	+ +	White powder (EtOH)	226—228 (dec.)	$C_{21}H_{20}N_2O_4$	69.21 (69.02	5.53 5.72	7.69 7.67)
XIe	1	4	n-C_4H_9		61	+	Colorless prisms (EtOH–H_2O)	180.5—182	$C_{23}H_{23}ClN_2O_4$	64.71 (64.38	5.43 5.38	6.56 6.81)
XIf	1	4	$CH_2=CHCH_2$		10	±	Pale yellow powder (AcOEt)	130—135	$C_{22}H_{19}ClN_2O_4$	64.31 (63.91	4.66 4.58	6.82 6.66)
XIg	1	4	$CH\equiv CCH_2$		51	+	Colorless needles (MeOH–H_2O)	271—272 (dec.)	$C_{22}H_{17}ClN_2O_4 \cdot H_2O$	61.91 (61.99	4.49 4.44	6.56 6.65)
XIh	1	4			44	±	White powder (MeOH–H_2O)	230—231 (dec.)	$C_{26}H_{21}ClN_2O_4$	67.75 (67.85	4.59 4.65	6.08 6.15)

a) Statistically significant activity is assessed on the following scale: ±, 10—20% healing ratio at 10 mg/kg/d × 2; +, 20—30% healing ratio at 10 mg/kg/d × 2; + +, > 30% healing ratio at 10 mg/kg/d × 2. For comparison purposes: cimetidine healing ratio at 100 mg/kg/d × 2, +; sucralfate healing ratio at 1 g/kg/d × 2, + +.

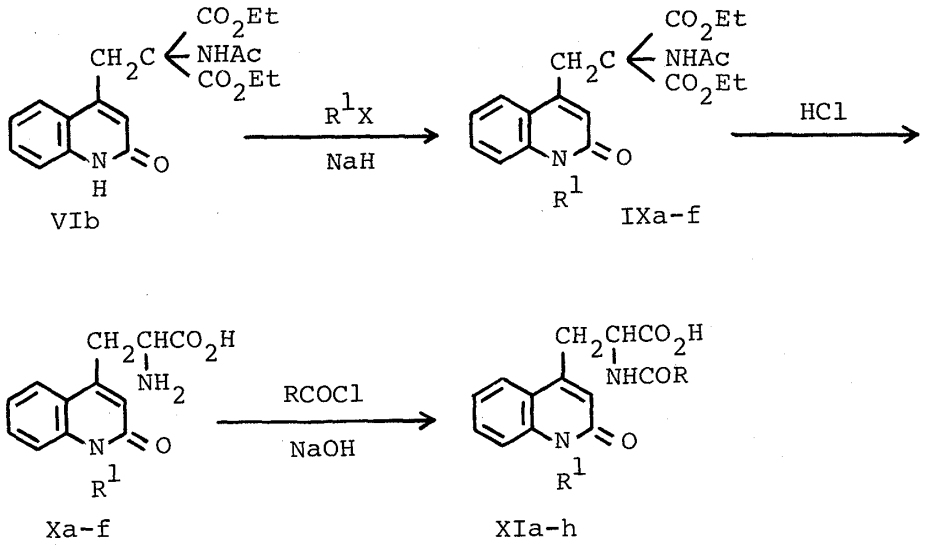


Chart 3

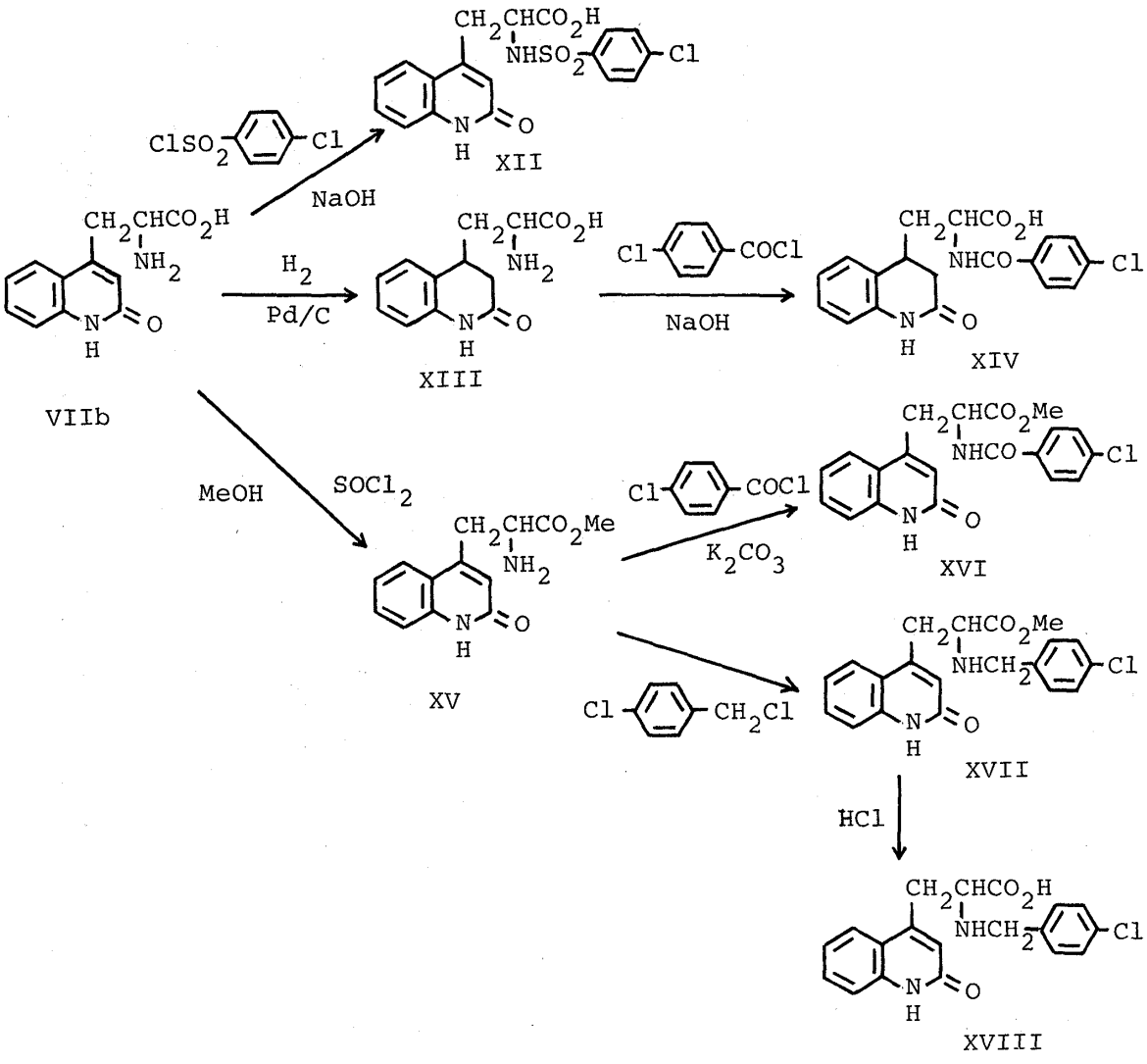
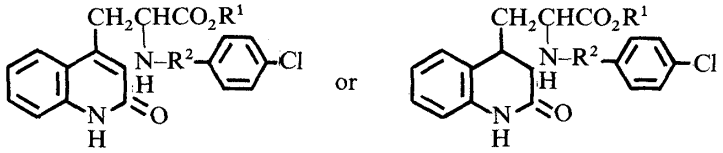


Chart 4

TABLE VII. 2-Amino-[2(1*H*)-quinolinon-4-yl]propionic Acid Derivatives



Compd. No.	R^1	R^2	Bond of C(3) and C(4)	Yield (%)	Activity[a]	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
XII	H	SO_2	Double	59	±	White powder ($DMF-H_2O$)	299—300	$C_{18}H_{15}ClN_2O_5S \cdot 1/2H_2O$	51.99 (51.40)	3.88 (3.64)	6.74 (6.53)
XIV	H	CO	Single	65	±	White powder ($MeOH-H_2O$)	256—257	$C_{19}H_{17}ClN_2O_4$	61.21 (61.05)	4.60 (4.63)	7.51 (7.31)
XV	CH_3	CO	Double	36	±	Colorless needles ($MeOH-CHCl_3$)	275—276.5	$C_{20}H_{17}ClN_2O_4 \cdot 1/2H_2O$	61.00 (61.28)	4.61 (4.56)	7.11 (7.55)
XVIII	H	CH_2	Double	39	±	White powder ($DMF-H_2O$)	272—274	$C_{19}H_{17}ClN_2O_3 \cdot 1/4H_2O$	63.16 (63.05)	4.88 (4.87)	7.75 (7.70)

a) Statistically significant activity is assessed on the following scale: ±, 10—20% healing ratio at 10 mg/kg/d × 2; +, 20—30% healing ratio at 10 mg/kg/d × 2; ++, >30% healing ratio at 10 mg/kg/d × 2. For comparison purposes: cimetidine healing ratio at 100 mg/kg/d × 2, +; sucralfate healing ratio at 1 g/kg/d × 2, ++.

amide (XIV). Treatment of VIIb with thionyl chloride in MeOH gave the corresponding ester derivative (XV), which was benzoylated to give the amide (XVI). Alkylation of XV with *p*-chlorobenzyl chloride gave the *N*-(*p*-chlorobenzyl)amino acid derivative (XVII), which was hydrolyzed with HCl to give the *N*-(*p*-chlorobenzyl) derivative (XVIII) (Chart 4).

Structure–Activity Relationship

The antiulcer activities of the synthesized compounds against acetic acid-induced gastric ulcer are summarized in Tables VI and VII. The structure–activity relationships are discussed below.

First, the study of these compounds as antiulcer agents involved an evaluation of the positional isomers in the 2(1*H*)-quinolinone series. The results showed that the 4-substituted isomer (VIIIf) exhibited the highest potency when the side chain substitution was maintained as *N*-(*p*-chlorobenzoyl)alanin-3-yl, and the 3-substituted isomer (VIIId) was a little less active, while the 5- and 6-substituted isomers (VIIIs and VIIIt) were much less active. Therefore, further comparison of the substituent effects was done within the series of 4-substituted derivatives.

Next, the N^1-substitution effect was examined; it was found that N^1-alkyl derivatives (XIc and XId) showed high potency and the order was C_2H_5 (XIc) > C_4H_9 (XIe) > CH_3 (XIa). The effect of the number of methylene groups was also examined, and the order of potency was found to be $n=1$ (VIIIf) > $n=3$ (VIIIr) > $n=2$ (VIIIq).

Next, the order as regards amide groups was benzoyl (VIIIc) > cyclohexanecarbonyl (VIIIb) > acetyl (VIIIa). Examination of substitution on the benzoyl group also showed that the 4-chlorobenzoyl compound (VIIIf) was more active than the nonsubstituted compound (VIIIe), whereas the other derivatives showed decreased activity. The sulfonamide derivative (XII) was less active than the amide derivative (VIIIf).

Finally, the ester derivative (XVI) showed a substantial loss of activity, so the carboxy group of the side chain is presumably essential. As regards the quinoline skelton, 3,4-dihydro-2(1*H*)-quinolinone (XIII) was much less active than 2(1*H*)-quinolinone (VIIIf).

Among the compounds synthesized, 2-(4-chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic acid (OPC-12759) was found to have the most potent activity. OPC-12759 showed a cytoprotective effect against gastric necrosis in rats induced by absolute EtOH, 0.2 N NaOH solution or 0.6 N HCl solution.[8]

Experimental

Melting points were determined with a Yamato MP-21 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a JASCO IRA-2 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded in DMSO-d_6 on a Varian EM-390 NMR spectrometer with 3-(trimethylsilyl)propanesulfonic acid sodium salt (DSS) as an internal standard. Mass spectra were obtained on a Varian MAT-312 instrument.

Ia[9] and IIIa[10] were prepared according to the reported methods.

Preparation of 2(1*H*)-Quinolinone-6-carboxaldehyde (Ib)——A solution of sodium metaperiodate (0.20 g, 0.93 mmol) in H_2O (2 ml) was added to a suspension of 6-(1-hydroxy-2-isopropylaminopropyl)-2-(1*H*)-quinolinone[11] in DMF (1 ml) at 60—70 °C. The reaction mixture was heated for 2.5 h, and then poured into ice-water. The precipitates were filtered off and recrystallized from DMF–MeOH to give Ib (0.12 g, 90%) as pale yellow needles, mp 284—285.5 °C; NMR δ: 6.64 (1H, d, J=9.5 Hz), 7.46 (1H, d, J=8.5 Hz), 8.02 (1H, dd, J=8.5, 2.0 Hz), 8.09 (1H, d, J=9.5 Hz), 8.30 (1H, d, J=2.0 Hz), 9.99 (1H, s), 12.17 (1H, br s); IR ν(KBr): 1713, 1681 cm^{-1}; MS *m/e*: 173 (M^+, 100%), 172 (99), 144 (28), 116 (51), 89 (48); *Anal.* Calcd for $C_{10}H_7NO_2$: C, 69.36; H, 4.07; N, 8.09. Found: C, 68.93; H, 3.86; N, 8.05.

Preparation of 2(1*H*)-Quinolinone-5-carboxylic Acid (IIa)——This compound was prepared following the procedure of Tominaga *et al.*[12] A solution of 3-(3-ethoxyacryloylamino)benzoic acid (59.5 g, 253 mmol)[12] in conc. H_2SO_4 (600 ml) was stirred at 40—50 °C for 3 h, and then poured into ice-water. The precipitates were collected by filtration and washed with MeOH. Recrystallization from DMF gave IIa (39 g, 51%) as a white powder, mp 277.5—279 °C; NMR δ: 6.64 (1H, d, J=10 Hz), 7.54 (1H, dd, J=7, 1 Hz), 7.60 (1H, dd, J=7, 7 Hz), 7.75 (1H, dd, J=7, 1 Hz), 8.77 (1H, d, J=10 Hz), 11.97 (1H, br s), 13.10 (1H, br s); IR ν(KBr): 1710, 1675 cm^{-1}; *Anal.* Calcd for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.45; H, 4.00; N, 7.65.

Preparation of 2(1*H*)-Quinolinon-4-ylpropionic Acid (IIIc)——4-Bromomethyl-2(1*H*)-quinolinone[13] (11.9 g, 50 mmol) was added to a stirred boiling solution of diethyl malonate (8.8 g, 55 mmol) and sodium metal (1.4 g, 61 mmol) in absolute EtOH (50 ml). The reaction mixture was refluxed for 3 h and the solution was concentrated *in vacuo*. The residue was poured into water, and the precipitates were collected by filtration. Recrystallization from EtOH–H_2O gave diethyl 2(1*H*)-quinolinon-4-ylmethylmalonate (5.4 g, 34%) as colorless prisms, mp 139—142 °C. A suspension of diethyl 2(1*H*)-quinolinon-4-ylmethylmalonate (5.0 g, 16 mmol) in 20% HCl (50 ml) was refluxed for 10 h, then the reaction mixture was cooled, and the precipitates were collected by filtration. Recrystallization from dil. HCl gave IIIc (3.3 g, 97%) as colorless needles, mp 260—262 °C; NMR δ: 2.67 (2H, t, J=7 Hz), 3.08 (2H, t, J=7 Hz), 6.39 (1H, s), 7.00—7.80 (4H, m), 11.72 (1H, br s); IR ν(KBr): 1730, 1655 cm^{-1}; *Anal.* Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 65.81; H, 5.02; N, 6.37.

Preparation of IIb and IIIb, d. Methyl 2(1*H*)-Quinolinon-4-ylacetate (IIIb)——Thiony chloride (7.1 g, 60 mmol) was added dropwise with stirring to a suspension of IIIa (4.0 g, 21 mmol) in MeOH (100 ml) at 0—10 °C. After being stirred under cooling with ice-water for 2 h, the reaction mixture was evaporated to dryness *in vacuo*. The residue was recrystallized from MeOH to give IIIb (2.5 g, 58%) as colorless prisms, mp 207—208.5 °C; NMR δ: 3.54 (3H, s), 3.88 (2H, s), 6.40 (1H, s), 6.90—7.60 (4H, m), 11.60 (1H, br s); IR ν(KBr): 1730, 1660 cm^{-1}. The elemental analysis data are shown in Table I.

Compounds IIb and IIId were obtained by the same procedure as described for IIIb; the yields, mp and elemental analysis data are listed in Table I.

Preparation of IVa and IVe. 3-Hydroxymethyl-2(1*H*)-quinolinone (IVa)——$NaBH_4$ (7.4 g, 0.20 mol) was added to a solution of Ia (34.0 g, 0.20 mol) in MeOH (800 ml) with stirring under cooling in ice-water. The reaction mixture was stirred for 3 h, and the precipitated crystals were collected by filtration. Recrystallization from MeOH gave IVa (33.2 g, 96.5%) as colorless prisms, mp 238—239.5 °C; NMR δ: 4.39 (2H, ABq, J=6, 1.5 Hz), 5.18 (1H, t, J=6 Hz), 7.00—7.90 (5H, m), 11.70 (1H, br s); IR ν(KBr): 3300, 1660 cm^{-1}. The elemental analysis data are shown in Table II.

Compound IVe was obtained by the same procedure as described for IVa; the yield, mp and elemental analysis data are shown in Table II.

Preparation of IVb—d. 4-(2-Hydroxyethyl)-2(1*H*)-quinolinone (IVb)——A suspension of IIIb (2.4 g, 12 mmol) in dry THF (50 ml) was treated with $LiAlH_4$ (2.1 g, 55 mmol) under cooling in ice-water. The reaction mixture was stirred at room temperatute overnight. Water was carefully added to destroy the excess $LiAlH_4$. The mixture was poured into ice-dil. H_2SO_4. After removal of the THF, the precipitated crystals were collected by filtration. Recrystallization from MeOH gave IVb (1.9 g, 91%) as pale yellow needles, mp 210—214 °C; NMR δ: 2.89 (2H, t, J=6 Hz), 3.63 (2H, t, J=6 Hz), 5.40 (1H, br s), 6.31 (1H, s), 6.90—7.70 (4H, m), 11.40 (1H, br s); IR ν(KBr): 3380, 1670 cm^{-1}. The elemental analysis data are shown in Table II.

Compounds IVc—d were obtained by the same procedure as described for IVb; the yields, mp and elemental analysis data are listed in Table II.

Preparation of Va—e. 3-Bromomethyl-2(1*H*)-quinolinone (Va)——A suspension of IVa (5.0 g, 29 mmol) in 47% HBr (50 ml) was heated at 70—80 °C for 3 h with stirring, then allowed to cool. The precipitated crystals were collected by filtration. Recrystallization from MeOH gave Va (6.0 g, 88%) as colorless needles, mp 218.5—219 °C (dec.); NMR δ: 4.57 (2H, s), 7.00—7.80 (4H, m), 8.11 (1H, s), 11.90 (1H, br s); IR ν(KBr): 1670 cm^{-1}. The elemental analysis data are shown in Table III.

Compounds Vb—e were obtained by the same procedure as described for Va; the yields, mp and elemental analysis data are listed in Table III.

Preparation of VIa—f. Ethyl 2-Acetylamino-2-ethoxycarbonyl-3-[2(1*H*)-quinolinon-4-yl]propionate (VIb)——4-Bromomethyl-2(1*H*)-quinolinone[13] (12.0 g, 50 mmol) was added to a stirred, boiling solution of diethyl acetamidomalonate (12.0 g, 55 mmol) and sodium metal (1.5 g, 65 mmol) in absolute EtOH (150 ml). The reaction mixture was refluxed for 2 h and concentrated *in vacuo*. The residue was poured into water. The precipitated crystals were collected by filtration. Recrystallization from EtOH gave VIb (13.0 g, 69%) as colorless prisms, mp 224—226 °C (dec.); NMR δ: 1.17 (6H, t, J=7 Hz), 1.80 (3H, s), 3.64 (2H, s), 4.10 (4H, q, J=7 Hz), 6.09 (1H, s), 6.90—7.50 (4H, m), 8.22 (1H, br s), 11.63 (1H, br s); IR ν(KBr): 1750, 1730, 1680, 1660 cm^{-1}. The elemental analysis data are shown in Tale IV.

Compounds VIa and VIc—f were obtained by the same procedure as described for VIb; the yields, mp and elemental analysis data are shown in Table IV.

Preparation of VIIa—f and Xa—f. 2-Amino-3-[2-(1*H*)-quinolinon-4-yl]propionic Acid Hydrochloride (VIIb)——A suspension of VIb (5.0 g, 13 mmol) in 20% HCl (150 ml) was refluxed for 9 h and then evaporated to dryness *in vacuo*. The residue was recrystallized from EtOH–H_2O to give VIIb (3.2 g, 89%) as colorless prisms, mp 220—225 °C (dec.); NMR (DMSO-d_6–D_2O) δ: 3.20—3.50 (2H, m), 4.30—4.50 (1H, m), 6.37 (1H, s), 6.70—7.80 (4H, m); IR ν(KBr): 1740, 1660 cm^{-1}. The elemental analysis data are shown in Table V.

Compounds VIIa, VIIc—f and Xa—f were obtained by the same procedure as described for VIIb; the yields, mp and elemental analysis data are shown in Table V.

Preparation of VIIIa—t, XIa—h, XIV and XVI. 2-(4-Chlorobenzoylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic Acid (VIIIf)——*p*-Chlorobenzoyl chloride (2.1 g, 12 mmol) was added dropwise to a solution of VIIb (2.7 g 10 mmol) and K_2CO_3 (4.2 g, 30 mmol) in acetone (100 ml) and water (20 ml) with stirring under cooling in ice-water, and the reaction mixture was stirred for 2 h. After the removal of acetone under reduced pressure, the residue was acidified with dil. HCl. The resulting precipitates were collected by filtration. Recrystallization from MeOH–H_2O gave VIIIf (1.8 g, 49%) as a white powder, mp 288—290 °C (dec.); NMR δ: 3.00—3.70 (2H, m), 4.50—4.90 (1H, m), 6.43 (1H, s), 7.10—8.00 (8H, m), 8.85 (1H, d, J=9 Hz), 11.60 (1H, br s); IR ν(KBr): 1730, 1660, 1640 cm^{-1}. The elemental analysis data are shown in Table VI.

Compounds VIIIa—e, VIIIg—t, XIa—h, XIV and XVI were obtained by the same procedure as described for VIIIf, and the yields, mp and elemental analysis data are shown in Tables VI and VII.

Preparation of IXa—f. Ethyl 2-Acetylamino-2-ethoxycarbonyl-3-[1-methyl-2(1*H*)-quinolinon-4-yl]propionate (IXa)——A suspension of VIb (7.5 g, 20 mmol) in THF (200 ml) was treated with NaH (50% dispersion in mineral oil, 1.1 g, 23 mmol) at room temperature, and the reaction mixture was stirred until the evolution of H_2 gas ceased. Then methyl iodide (5.6 g, 39 mmol) was added dropwise at room temperature and the reaction mixture was refluxed for 2 h. After removal of the solvent, the residue was poured into water. The precipitated crystals were collected by filtration. Recrystallization from EtOH gave IXa (5.2 g, 67%) as colorless needles, mp 191—192.5 °C; NMR δ: 1.16 (6H, t, J=7.5 Hz), 1.78 (3H, s), 3.54 (3H, s), 3.65 (2H, s), 4.08 (4H, q, J=7.5 Hz), 6.18 (1H, s), 7.10—7.70 (4H, m), 8.20 (1H, s); IR ν(KBr): 1755, 1670, 1650 cm^{-1}. The elemental analysis data are shown in Table IV.

Compounds IXb—f were obtained by the same procedure as described for IXa, and the yields, mp and elemental analysis data are shown in Table IV.

Preparation of 2-(4-Chlorobenzenesulfonylamino)-3-[2-(1*H*)-quinolinon-4-yl]propionic Acid (XII)——*p*-Chlorobenzenesulfonyl chloride (1.3 g, 6.2 mmol) was added dropwise to a solution of VIIb (1.8 g, 6.7 mmol) and NaOH (0.8 g, 20 mmol) in acetone (50 ml) and H_2O (50 ml) with stirring at room temperature, and the reaction mixture was stirred for 3 h. The insoluble material was removed by filtration, and the filtrate was acidified with dil. HCl. The resulting precipitates were collected by filtration. Recrystallization from DMF–H_2O gave XII (1.6 g, 59%) as a white powder, mp 299—300 °C (dec.); NMR δ: 2.60—3.50 (2H, m), 4.00 (1H, m), 6.41 (1H, s), 7.00—7.70 (8H, m), 8.65 (1H, d, J=9 Hz), 11.65 (1H, br s); IR ν(KBr): 1700, 1660 cm^{-1}. The elemental analysis data are shown in Table VII.

Preparation of 2-Amino-3-[3,4-dihydro-2(1*H*)-quinolinon-4-yl]propionic Acid Hydrochloride (XIII)——A mixture of VIIb (5.0 g, 19 mmol) and 10% Pd–C (1.0 g) in water (150 ml) was heated at 70 °C under atmospheric pressure of hydrogen with stirring until theoretical amount of H_2 was absorbed. The mixture was cooled to room temperature, the catalyst was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from EtOH–Et_2O to give XIII (3.6 g, 71%) as a white powder, mp 237—238 °C (dec.); NMR δ: 1.80—3.90 (6H, m), 6.80—7.40 (4H, m), 10.13 (1H, br s); IR ν(KBr): 1730, 1660 cm^{-1}; *Anal.* Calcd for

$C_{12}H_{15}ClN_2O_3 \cdot 1/4H_2O$: C, 52.37; H, 5.68; N, 10.18. Found: C, 52.40; H, 5.43; N, 10.31.

Preparation of Methyl 2-Amino-3-[2(1*H*)-quinolinon-4-yl]propionate (XV)——Thionyl chloride (5.3 g, 45 mmol) was added dropwise with stirring to a suspension of VIIb (4.0 g, 15 mmol) in MeOH (50 ml) at 0—10 °C. After being stirred at room temperature overnight, the reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in 0.5 N NaOH aqueous solution (100 ml). The solution was concentrated *in vacuo* and the residue was extracted with $CHCl_3$ (50 ml × 3). The extracts were combined and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from $CHCl_3$–*n*-hexane to give XV (2.5 g, 69%) as colorless needles, mp 182—183 °C (dec.); NMR δ: 3.00 (2H, br s), 2.80—3.40 (2H, m), 3.50—3.80 (1H, m), 3.60 (3H, s), 6.43 (1H, s), 7.10—7.87 (4H, m); IR ν(KBr): 1750, 1660 cm^{-1}; *Anal.* Calcd for $C_{13}H_{14}N_2O_3 \cdot 1/4H_2O$: C, 62.26; H, 5.83; N, 11.17. Found: C, 62.35; H, 5.71; N, 11.32.

Preparation of Methyl 2-(4-Chlorobenzylamino)-3-[2(1*H*)-quinolinon-4-yl]propionate (XVII)——A suspension of XV (5.0 g, 20 mmol) and *p*-chlorobenzyl chloride (1.6 g, 10 mmol) in xylene (100 ml) was refluxed for 9 h. The reaction mixture was cooled, then the insoluble material was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel; eluent, $CHCl_3$: MeOH = 50 : 1) and recrystallized from AcOEt–*n*-hexane to give XVII (1.3 g, 17%) as colorless needles, mp 151—152 °C; NMR δ ($CDCl_3$): 2.90—3.80 (5H, m), 3.61 (3H, s), 6.57 (1H, s), 7.00—7.70 (8H, m), 12.90 (1H, br s); IR ν(KBr): 1740, 1670, 1630 cm^{-1}; *Anal.* Calcd for $C_{20}H_{19}ClN_2O_3$: C, 64.78; H, 5.16; N, 7.55. Found: C, 64.83; H, 5.30; N, 7.57.

Preparation of 2-(4-Chlorobenzylamino)-3-[2(1*H*)-quinolinon-4-yl]propionic Acid (XVIII)——A suspension of XVII (1.2 g, 3.2 mmol) in 20% HCl (40 ml) was refluxed for 3 h then allowed to cool, and the precipitated crystals were collected by filtration. Recrystallization from DMF–H_2O gave XVIII (0.5 g, 39%) as a white powder, mp 272—274 °C (dec.); NMR (DMSO-d_6–D_2O–NaOD) δ: 2.60—3.80 (5H, m), 6.50 (1H, s), 6.90—7.90 (8H, m); IR ν(KBr): 1670, 1660 cm^{-1}. The elemental analysis data are shown in Table VII.

Biological Method[7]——Midline epigastric laparotomy was done in rats under ether anesthesia, and after exteriorizing the stomach, 0.015 ml of 30% acetic acid was injected into the subserosal layer at the junction of the body of the glandular stomach and the antrum in the anterior wall. Subsequently, the abdomen was closed and all rats were maintained normally on Oriental rat chow and water *ad lib.* Animals were sacrificed at 9 d after the operation. Each stomach was removed, filled with 10 ml of 1% formalin, and immersed in 1% formalin to fix it lightly. The stomach was then opened along the greater curvature, and the ulcerated area was examined and measured under a dissecting microscope (10 ×) with a square grid. The area of damage (mm^2) was used as the ulcer index. The results were analyzed using Student's *t*-test, and the percentage healing ratio of gastric ulcers in the drug-treated group was calculated as follows.

$$\text{Healing ratio (\%)} = \frac{\text{ulcer index of control group} - \text{ulcer index of drug-treated group}}{\text{ulcer index of control group}} \times 100$$

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