Synthesis, Structure Elucidation and Chemotherapeutic Activity of 6-Substituted 1-Ethyl-1,4-dihydro-7-[(1-imidazolyl)phenylmethyl]-4-oxo-3-quinolinecarboxylic Acids [1]

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The synthesis, structure elucidation and chemotherapeutic activity of novel 3-quinolinecarboxylic acid derivatives are reported. These derivatives are characterized by a group (1-imidazolyl)phenylmethyl attached to the 7-position and chloro **10a**, fluoro **10b** or methoxy **10c** appended to the 6-position.

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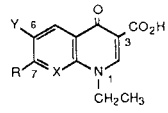
Since the introduction in 1963 of nalidixic acid (**1**) [2] as a systemic Gram-negative antibacterial agent, a large number of related derivatives have been synthesized [3]. Recently, several new analogues containing one fluorine atom at the 6 position and one substituted nitrogen atom at the 7 position have been made. These new derivatives, which include pefloxacin (**2**) [4], norfloxacin (**3**) [5], AT-2266 (**4**) [6] and irloxacin (**5**) [7] are considerably more potent and have a broader spectrum of antimicrobial activity than their predecessors. There are a number of compounds with a carbon atom attached at the 7 position without containing fluorine atoms at the 6 position, such as rosoxacin (**6**) and its derivatives [8], or with fluorine atoms at the 6 position (**7**) [9].



1-7

1 X = N, Y = H, R = CH_3

2 X = CH, Y = F, R = 4-methyl-1-piperazinyl

3 X = CH, Y = F, R = 1-piperazinyl

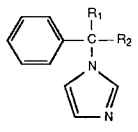
4 X = N, Y = F, R = 1-piperazinyl

5 X = CH, Y = F, R = 1-pyrrolyl

6 X = CH, Y = H, R = 4-pyridinyl

7 X = N, Y = F, R = 4-pyridinyl

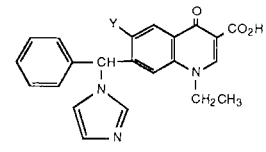
On the other hand, during the past two decades important advances have been made in the antifungal chemotherapy using *N*-substituted imidazoles [10], such as clotrimazole (**8**) [11] or bifonazole (**9**) [12].



8 R_1 = phenyl, R_2 = chlorophenyl

9 R_1 = 4-biphenylyl, R_2 = H

It seemed desirable to synthesize an agent with broad-spectrum antibacterial and antifungal activities. This led us to explore the chemistry of 6-substituted 1-ethyl-1,4-dihydro-7-[(1-imidazolyl)phenylmethyl]-4-oxo-3-quinolinecarboxylic acids **10a-c**.



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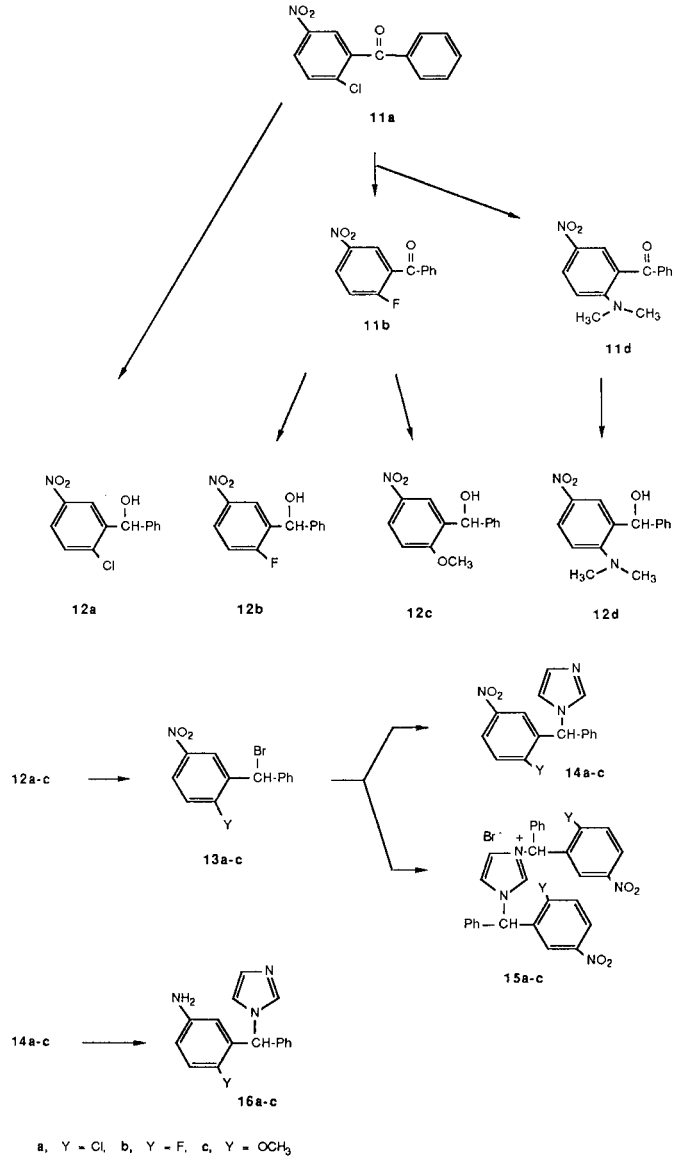
a, Y = Cl, b, Y = F, c, Y = OCH_3

Scheme 1 outlines the synthetic pathway used for the preparation of the required intermediates 1-[(5-amino-2-substituted-phenyl)phenylmethyl]imidazole **16a-c**. 2-Chloro-5-nitrobenzophenone (**11a**) served as the starting material for the synthesis of **12a-d**. The preparation of the benzophenone **11b** was attempted by refluxing **11a** with potassium fluoride in dimethylformamide (Method A), as described by Gilman *et al.* [13]. In our hands, it has resulted in the formation of **11b** along with the substitution product of fluorine by a dimethylamino group **11d**. The structural assignment of **11d** was based on the results of elemental analysis and nmr spectroscopy (Tables 1, 2 and 3). However, the desired fluoro derivative **11b** was obtained in good yield (94%) by refluxing **11a** with potassium fluoride in dimethylsulfoxide (Method B). The carbinols **12a** and **12d** were obtained by reduction of the corresponding benzophenones **11a** and **11d** with sodium borohydride in methanol (Method C). This method was applied to **11b** resulting in the formation of the substitution product of fluorine by a metoxy group **12c** (Tables 1, 2 and 3). The synthesis of the carbinol **12b** was accomplished by reduction of the benzophenone **11b** with lithium aluminium hydride in diethyl ether (Method D).

The preparation of **14a** was attempted by reaction of **12a** with 1,1'-sulfinyldiimidazole as described for triphen-

Scheme 1



ylcarbinol [11]. The reaction was monitored by tlc and by pmr spectra of aliquots, but only compound **12a** was observed and recovered. Another synthetic path was tried in order to obtain **14a** by reaction of (2-chloro-5-nitrophenyl)-phenylchloromethane **(20a)** with imidazole in basic medium or with *N*-trimethylsilylimidazole at 0°. In both cases the starting material was recovered up to 90% and only upon tlc a slight spot of **14a** was observed in the first case. The reaction of (5-amino-2-chlorophenyl)phenyl-chloromethane **(21a)** with imidazole in basic medium also failed.

Table 1

Analytical Data

Compound	Formula	Analysis % Calcd./(Found) C	H	N
11d	$C_{15}H_{14}N_2O_3$	66.66 (67.02)	5.22 (4.95)	10.36 (10.04)
12a	$C_{13}H_{10}ClNO_3$	59.22 (59.33)	3.82 (3.80)	5.31 (5.18)
12c	$C_{14}H_{13}NO_4$	64.86 (64.67)	5.05 (4.85)	5.40 (5.39)
13a	$C_{13}H_9BrClNO_2$	47.81 (47.96)	2.78 (2.96)	4.29 (4.11)
14a	$C_{16}H_{12}ClN_3O_2$	61.25 (61.31)	3.85 (3.76)	13.39 (13.18)
14b	$C_{16}H_{12}FN_3O_2$	64.64 (64.30)	4.07 (4.39)	14.13 (14.05)
14c	$C_{17}H_{15}N_3O_3$	66.01 (65.73)	4.89 (4.53)	15.52 (15.19)
15a	$C_{29}H_{21}BrCl_2N_4O_4$	54.40 (54.22)	3.30 (3.11)	8.75 (8.51)
15c	$C_{31}H_{27}BrN_4O_6$	58.96 (58.90)	4.31 (4.67)	8.87 (8.22)
16a	$C_{16}H_{14}ClN_3$	67.72 (67.98)	4.97 (5.31)	14.81 (14.50)
16b	$C_{16}H_{14}FN_3$	71.89 (71.73)	5.28 (5.48)	15.72 (15.39)
16c	$C_{17}H_{17}N_3O$	73.10 (72.81)	6.13 (5.77)	15.04 (14.64)
18a	$C_{22}H_{16}ClN_3O_3$	64.79 (64.41)	4.45 (4.17)	10.30 (9.92
18b	$C_{22}H_{16}FN_3O_3$	67.51 (67.11)	4.64 (4.86)	10.74 (10.39)
18c	$C_{23}H_{21}N_3O_4$	68.47 (68.10)	5.25 (5.19)	10.42 (10.05)
19a	$C_{24}H_{22}ClN_3O_3$	66.13 (66.16)	5.09 (4.42)	9.64 (9.27)
19b	$C_{24}H_{22}FN_3O_3$	68.72 (69.03)	5.29 (5.57)	10.02 (10.05)
19c	$C_{25}H_{25}N_3O_4$	69.59 (69.39)	5.84 (5.91)	9.74 (9.45)
10a	$C_{22}H_{16}ClN_3O_3$	64.79 (64.53)	4.45 (4.48)	10.30 (10.04)
10b	$C_{22}H_{16}FN_3O_3$	67.51 (67.81)	4.64 (4.88)	10.74 (10.56)
10c	$C_{23}H_{21}N_3O_4$	68.47 (68.52)	5.25 (5.51)	10.42 (10.15)
20a	$C_{13}H_9Cl_2NO_2$	55.34 (55.17)	3.22 (2.95)	4.97 (4.69)
21a	$C_{13}H_{11}Cl_2N$	61.92 (61.85)	4.40 (4.21)	5.56 (5.41)

However, conversion of carbinols **12a-c** to compounds **14a-c** was accomplished by refluxing the appropriate bromo derivatives **13a-c**, freshly prepared by reaction of the corresponding carbinols **12a-c** with thionyl bromide, with an excess of imidazole in acetonitrile. Compounds **14a** and

Table 2

Physical, Reaction Conditions and Spectral Data

Compound	Mp (°C)	Yield (%)	Method	Reaction time (hours)	Recrystallization solvent [a]	IR (cm^{-1}) [i]	Proton magnetic resonance [k]
11b	46-48 [b]	94	B	15	A	1670, 1530, 1350	8.45 (m, 2H), 7.90-7.45 (m, 6H)
11d	128-130	28	A	12	A	1660, 1520, 1330	8.12 (dd, 1H, J = 1.2 Hz, J = 9.8 Hz), 7.99 (d, 1H, J = 1.2 Hz), 7.82 (m, 2H), 7.58 (m, 3H), 7.05 (d, 1H, J = 9.8 Hz), 2.87 (s, 6H)
12a	74	75	C	3	B	3300, 1530, 1350	8.59 (d, 1H, J = 2.7), 8.12 (dd, 1H), 7.65 (d, 1H, J = 8.7), 7.34 (m, 5H), 6.50 (d, 1H, J = 4.5), 6.04 (d, 1H, J = 5.4)
12b	[c]	86	D	5	[d]	3380, 1535, 1350 [j]	8.52 (m, 1H), 8.16 (m, 1H), 7.32 (m, 6H), 6.38 (b, 1H), 6.05 (s, 1H)
12c	120-122	74	C	5	C	3600, 1520, 1335	8.48 (d, 1H, J = 1.2), 8.14 (dd, 1H, J = 9, J = 1.2), 7.30 (m, 5H), 7.12 (d, 1H, J = 9), 6.09 (s, 2H), 3.91 (s, 3H)
12d	[e]	92	C	4	[d]	3380, 1510, 1320 [j]	8.23 (d, 1H, J = 2), 8.04 (dd, 1H, J = 2, J = 9), 7.32 (m, 5H), 7.17 (d, 1H, J = 9), 6.11 (s, 1H), 4.79 (b, 1H), 2.83 (s, 6H)
13a	80-82	98	E	15	[d]	1520, 1345	8.37 (d, 1H, J = 3 Hz), 8.09 (dd, 1H, J = 3, J = 9), 7.66 (d, 1H, J = 9), 7.32 (m, 5H), 6.79 (s, 1H)
13b	[c]	93	E	37	[d]	1535, 1330 [j]	8.50 (m, 1H), 8.17 (m, 1H), 7.31 (m, 6H), 6.82 (s, 1H)
13c	[c]	97	E	12	[d]	1530, 1335 [j]	8.23 (d, 1H, J = 2), 8.13 (dd, 1H, J = 9), 7.25 (m, 5H), 7.14 (d, 1H, J = 9), 6.62 (s, 1H), 3.92 (s, 3H)
14a	169-171	43	F	24	D	1525, 1355	8.25 (dd, 1H, J = 8.4, J = 2.6), 7.80 (m, 2H), 7.58 (d, 1H, J = 2.6), 7.42 (m, 3H), 7.23 (m, 4H), 7.06 (s, 1H)
14b	142-146	42	F	30 [f]	E-F	1535, 1350	8.34 (m, 1H), 7.67 (m, 3H), 7.40 (m, 3H), 7.23 (m, 4H), 7.05 (s, 1H)
14c	164-168	44	F	24	D	1520, 1350	8.29 (dd, 1H, J = 2.7, J = 9), 7.64 (m, 2H), 7.35 (m, 4H), 7.08 (m, 5H), 3.86 (s, 3H)
15a	257-260	31	F	24	A	1540, 1355	9.79 (s, 0.6H), 9.72 (s, 0.4H), 8.35 (dd, 2H, J = 3, J = 9), 8.07 (m, 2H), 7.94 (d, 2H, J = 9), 7.75 (d, 2H, J = 3), 7.70 (s, 2H), 7.49 (m, 10H)
15c	243-247	37	F	24	A	1520, 1345	9.44 (s, 0.7H), 9.39 (s, 0.3H), 8.37 (dd, 2H, J = 3, J = 9), 7.90 (s, 2H), 7.69 (m, 2H), 7.41 (m, 14H), 3.87 (s, 6H)
16a	163-168	50	G	3	G	3425, 3320	7.10 (m, 8H), 6.72 (m, 2H), 6.47 (dd, 1H, J = 2.5, J = 8.5), 6.03 (d, 1H, J = 2.5), 3.8 (b, 2H), [l]
16b	[c]	48	G	48	[d]	3420, 3320 [j]	7.72-6.70 (m, 10H), 6.58 (m, 1H), 6.22 (m, 1H), 4.25 (b, 2H)
16c	158-162	85	G	1	G	3415, 3315	7.72-6.80 (m, 10H), 6.64 (dd, 1H, J = 2.5), J = 8), 6.24 (d, 1H, J = 2.5), 4.83 (b, 2H), 4.07 (s, 3H)
17a	[c]	66	H	24	[d]	1730, 1705 [j]	[e]
17b	[c]	76	H	48	[d]	1720, 1695 [j]	[e]
17c	148-153	89	H	20	G	1715, 1650	10.59 (d, 1H, J = 14), 8.18 (d, 1H, J = 14), 7.62-6.78 (m, 12H), 4.13 (q, 4H), 3.71 (s, H), 1.22 (t, 6H)

Table 2 (continued)

Compound	Mp (°C)	Yield (%)	Method	Reaction time (hours)	Recrystallization solvent [a]	IR (cm^{-1}) [i]	Proton magnetic resonance [k]
18a	250-252	78	I	4	A	1720, 1630	10.50 (b, 1H), 9.15 (s, 1H), 8.56 (s, 1H), 8.18 (s, 1H), 7.76 (m, 2H), 7.53-7.12 (m, 7H), 4.22 (q, 2H), 1.23 (t, 3H) [l]
18b	226-229	56	I	4	H	1720, 1630	12.10 (b, 1H), 8.52 (s, 1H), 8.30 (s, 1H), 8.10 (m, 1H), 7.87-6.90 (m, 9H), 4.30 (q, 2H), 1.29 (t, 3H)
18c	246-248	70	I	4	A	1720, 1620	12.25 (b, 1H), 8.43 (s, 1H), 7.69 (m, 2H), 7.39 (m, 3H), 7.14 (m, 6H), 4.22 (q, 2H), 3.78 (s, 3H), 1.28 (t, 3H)
19a	192-195	46	J	15	A-G	1720, 1700, 1640	8.48 (s, 1H), 8.29 (s, 1H), 7.55-6.96 (m, 9H), 6.70 (s, 1H), 4.32 (q, 2H), 4.04 (q, 2H), 1.34 (t, 3H), 1.26 (t, 3H) [m]
19b	172-175	43	J	16	A-G	1730, 1695, 1630	8.70 (s, 1H), 7.85 (m, 2H), 7.50-7.00 (m, 9H), 4.26 (q, 2H), 4.20 (q, 2H), 1.28 (t, 3H), 1.19 (t, 3H)
19c	187-190	52	J	12	D	1725, 1695, 1615	8.62 (s, 1H), 7.72 (m, 2H), 7.27 (m, 7H), 7.00 (b, 2H), 4.22 (m, 4H), 3.80 (s, 3H), 1.29 (t, 3H), 1.14 (t, 3H)
10a	251-253	70	K	0.5	A	1725, 1615	13.30 (b, 1H), 8.96 (s, 1H), 8.37 (s, 1H), 7.67 (s, 1H), 7.48-7.15 (m, 8H), 7.05 (s, 1H), 4.34 (q, 2H), 1.23 (t, 3H)
10b	217-221	69	K	0.5	D	1730, 1625	14.80 (b, 1H), 9.02 (s, 1H), 8.06 (d, 1H, J = 10), 7.79 (s, 1H), 7.35 (m, 8H), 7.06 (s, 1H), 4.42 (q, 2H), 1.24 (t, 3H)
10c	238-241	92	K	0.5	A	1715, 1620	15.05 (b, 1H), 8.91 (s, 1H), 7.85 (s, 1H), 7.50-7.00 (m, 10H), 4.35 (q, 2H), 3.87 (s, 3H), 1.24 (t, 3H)
20a	79-82	98	E [g]	15	I	1515, 1340	8.46 (d, 1H, J = 2.5), 8.20 (dd, 1H, J = 2.5, J = 8.5), 7.76 (d, 1H, J = 8.5), 7.41 (m, 5H), 6.75 (s, 1H)
21a	117-118	91	[h]	48	I	3380, 3295	7.33 (m, 5H), 6.97 (m, 2H), 6.52 (dd, 1H, J = 2.5, J = 8.5), 5.93 (d, 1H, J = 2.5), 5.20 (b, 2H)

[a] A = ethanol, B = carbon tetrachloride, C = diisopropyl ether, D = ethyl acetate, E = benzene, F = petroleum ether, G = diethyl ether, H = acetonitrile, I = dichloromethane. [b] Lit [13] mp 45-57°. [c] Used in next step without further purification. [d] Not recrystallized. [e] Not analyzed. [f] The solution was stirred 30 hours at 45°. [g] Prepared from **2a** using thionyl chloride as reagent. [h] Prepared from **11a** as described in the literature [13] for the fluoro derivative. [i] Potassium bromide if not otherwise indicated. [j] Film. [k] Solvent: hexadeuteriodimethylsulfoxide if not otherwise indicated. [l] Solvent: hexadeuteriodimethylsulfoxide/TFA (1:1). [m] Solvent: deuteriochloroform.

Scheme 2

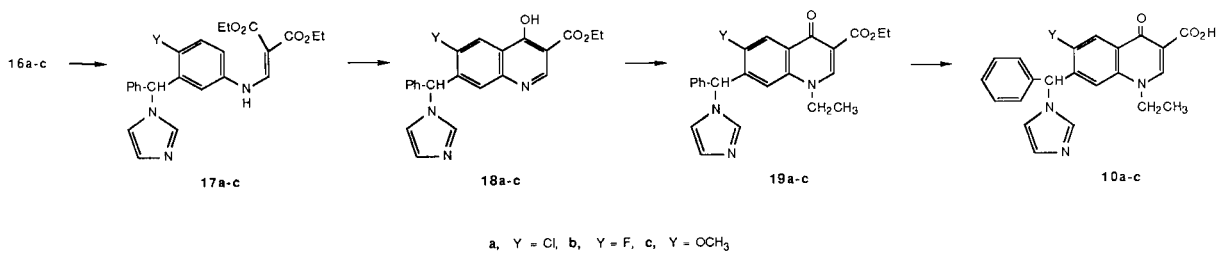
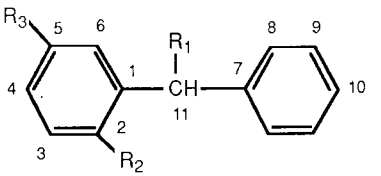


Table 3

Cmr Chemical Shifts for some Substituted Diphenylmethane [a,b]

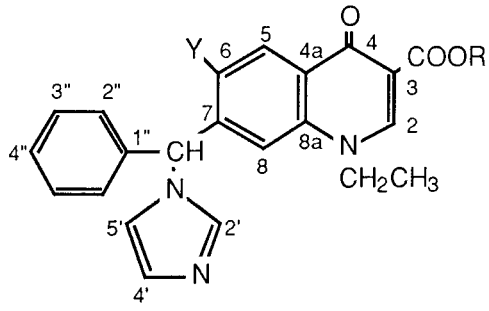


Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	Other C
11b	127.4 (18.5)	162.5 (260)	118.1 (25)	128.6 (11)	126.1 (2.5)	126.1 (5)	135.9	128.9	129.5	134.3	190.4	-
11d	123.1	154.5	114.7	127.3	136.4	126.7	135.6	128.8	129.7	133.5	194.1	42.7[c]
12a	144.6	138.1	130.8	123.5	146.8	122.8	142.4	127.3	128.4	127.7	71.0	
12b	134.5 (16)	163.2 (254)	116.8 (25)	124.8 (10)	144.2 (2)	123.4 (7)	143.1	126.5	128.4	127.5	58.1 (2)	-
12c	135.1	160.8	111.3	124.4	144.0	122.0	141.0	126.6	128.1	127.0	68.1	56.4 [c]
12d	138.2	157.4	118.9	124.7	141.3	123.3	144.5	126.4	128.1	126.9	69.2	44.1 [e]
13a	138.6 (d)	139.7 (d)	131.5	124.8	146.8	123.6	138.5 (d)	123.4	128.9	126.7	50.2	-
13c	129.9	160.7	112.1	125.8	140.6	125.0	139.4	128.1	128.6	128.2	48.2	56.9 [c]
14a	139.47 (d)	139.54 (d)	131.5	124.8	146.8	123.5	137.1	128.3	129.2	128.8	60.8	[g]
14b	129.0 (8.5)	163.1 (258)	117.5 (24)	126.5 (10.5)	144.3 (3)	124.6 (5.5)	137.3	127.8	129.1	128.7	57.7 (2.5)	[h]
14c	129.2	161.6	112.0	126.0	140.8	123.5	138.2	127.6	128.8	128.2	58.2	56.8 [c,i]
15a	136.2	139.9	132.0	125.7	146.6	124.4	134.1	128.6	129.4	129.7	63.4	[f,j]
	136.1	139.8	132.0	125.7	146.6	124.1	134.0	128.4	129.4	129.7	63.4	
15c	125.8	162.0	112.7	127.1	140.7	124.9	135.1	127.7	129.2	129.2	61.3	57.1 [c,f,k]
	125.7	162.0	112.7	127.1	140.7	124.6	135.1	127.9	129.2	129.2	61.3	57.1
16a	138.7	118.4	130.0	115.1	148.2	114.2	137.1	127.8	128.7	128.0	61.1	[l]
16b	126.7 (14.5)	151.6 (234)	115.8 (22)	114.7 (7)	145.4 (2)	113.5 (2)	139.0	127.4	128.7	128.0	57.9 (3.5)	[m]
16c	128.3	147.9	114.7	114.5	142.6	113.4	140.2	127.4	128.6	127.7	58.3	56.4 [c,n]
20a	138.6 (d)	139.4 (d)	131.4	124.6	146.6	124.7	138.2 (d)	127.7	128.7	128.6	59.6	-
21a	144.3 (d)	117.5	129.1	114.2	147.8	113.6	142.7 (d)	126.7	128.0	126.8	70.8	-

[a] Spectra were obtained in hexadeuteriodimethylsulfide as solvent, unless otherwise indicated; chemical shifts obtained by adding 39.7 ppm to values relative to middle signal of headeuteriodimethylsulfoxide. [b] J (C-F) data in hertz given in parentheses. [c] Methoxy group. [d] Assignment may be interchaned. [e] Dimethylamino group. [f] *Meso* and *dl* stereoisomers (see text).

Imidazole chemical shifts values: [g] C-2,137.8; C-4,128.7; C-5,119.6; C-4,129.2; C-5119.6. [h] C-2,137.6; C-4,129.2; C-5,119.3. [i] C-2,137.5; C-4, 128.4; C-5,119.4. [j] C-2,138.4; C-4 and C-5,123.4. [k] C-2,137.5; C-4 and C-5,123.0. [l] C-2,137.3; C-4,127.4; C-5,119.5. [m] C-2,137.3; C-4,128.5; C-5,119.3. [n] C-2,137.3; C-4,128.3; C-5,119.6.

Table 4
CMR Chemical Shifts for some 4-quinolone systems and Associated Substituents [a,b]



Carbon	Compound								
	19a [d]	**19b**	**19c**	**10a**	**10b**	**10c**	**22** [d]	**23**	**5**
C-2	148.4	149.0	147.8	149.3	149.2	147.6	148.2	148.7	148.7
C-3	110.9	109.9	109.5	108.5	107.9	107.4	111.0	108.3	148.7
C4	171.9	171.4	171.9	176.0	176.5 (2.8)	176.5	172.7	176.2	175.9 (2.5)
C-4a	129.2	129.8 (6.7)	129.5	128.7	127.1 (8)	126.7	128.1	126.7	123.7 (7)
C-5	128.2	111.8 (23)	106.5	126.4	111.3 (23)	105.4	126.9	124.5	112.3 (23)
C-6	129.4	156.5 (248)	153.8	130.1	157.1 (250)	154.6	131.0	130.8	151.5 (251)
C-7	141.8	133.0 (17)	132.6	143.2	134.9 (17)	133.2	132.5	133.6	133.3 (12.5)
C-8	116.1	118.3 (3.2)	117.3	118.4	119.2 (4)	117.9	117.8	119.9	112.7
C-8a	135.6	135.1 (1.5)	134.4	136.6	135.8 (2)	136.4	136.8	137.6	136.2 (1.4)
CO_2-	164.2	164.3	164.7	164.8	164.4	165.8	164.9	165.0	164.8
NCH_2-	48.7	48.3	48.1	48.8	49.3	49.1	48.9	48.9	48.7
NCH_2-CH_3	13.6	13.8	13.9	13.4	13.9	14.0	14.3	14.0	13.8
OCH_2-	60.2	59.8	59.7	-	-	-	60.8	-	-
OCH_2-CH_3	13.9	14.3	14.3	-	-	-	14.3	-	-
CH	61.8	58.4	58.8	61.2	58.6	59.0	-	-	-
C-2'	137.2	137.4	137.7	137.4	137.4	137.4	-	-	-
C-4'	129.3	128.5	128.4	126.2	128.4	128.3	-	-	-
C-5'	119.1	119.3	119.6	119.2	119.4	119.4	-	-	-
C-1"	136.8	137.5	138.4	137.6	137.1	137.9	-	-	-
C-2"	128.0	127.8	127.8	128.0	127.8	127.8	-	-	-
C-3"	128.7	128.9	128.7	128.6	128.9	128.6	-	-	-
C-4"	128.6	128.5	128.2	128.3	128.6	128.2	-	-	-
Other C	-	-	56.1 [c]	-	-	56.3[c]	-	-	[e]

[a], [b] and [c], See footnotes in Table 3. [d] Spectra were obtained in deuteriochloroform as solvent; chemical shifts obtained by adding 77.0 ppm to values relative to middle signal of deuteriochloroform. [e] Pyrrole chemical shifts values and J (C-F) in hertz (in parentheses): C-2, 121.4(5.0); C-3, 110.6(3.2).

14c were obtained along with the corresponding quaternized imidazole **15a** and **15c** which were unequivocally characterized by nuclear magnetic resonance spectroscopy (see later).

1-[(5-Nitro-2-substitutedphenyl)phenylmethyl]imidazoles **(14)** were converted (Method G) into the 5-amino analogs **16**, which would become the key intermediates in our synthesis.

With the amino compounds **16** in hand, construction of the 4-oxoquinoline ring was achieved following the general method [3] shown in Scheme 2. The condensation of **16** with diethyl ethoxymethylenemalonate gave the enamine derivatives **17**, which were cyclized in the presence of polyphosphoric acid and phosphoryl chloride to afford ethyl 4-oxo-3-quinolinecarboxylates **(18)**. *N*-Ethylation of **18** with ethyl bromide/potassium carbonate/dimethylforma-

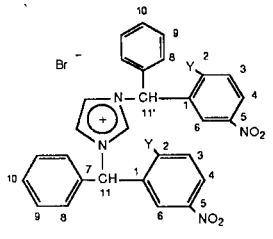
mide in a sealed tube at 40° gave **19a-c**. Alkaline hydrolysis of the ethyl carboxylates **19** (sodium hydroxide/water/ethanol/75°) followed by acidification with acetic acid to a *p*H between 4.5 and 5.5 afforded the desired compounds **10a-c**.

The products described in this work have been studied by pmr and cmr spectroscopy to confirm the proposed structures. As far as we know, very little work have been published [14-16] about cmr of 4-quinoline systems. The nmr spectra are collected in Tables 2 (proton), 3 and 4 (carbon-13). We recorded the broadband-decoupled spectrum and the SEFT (Spin Echo Fourier Transform) pulse sequence of all compounds, as well as the proton undecoupled spectra of some of them.

To assign the cmr signals of compounds **10** and **19** we prepared, by known literature procedures [17], ethyl 1-ethyl-1,4-dihydro-6-chloro-4-oxo-3-quinolinecarboxylate (**22**) and 1-ethyl-1,4-dihydro-6-chloro-4-oxo-3-quinolinecarboxylic acid (**23**), whose chemical shifts are also reported in Table 4.

We made use of the recently described [18] technique of two-bond selective heteronuclear NOE difference spectroscopy for the assignment of quaternary carbons 4a and 6 of compounds **10a**, **19a**, **22** and **23** (see Table 4). On weak irradiation of the double doublet at δ_H = 7.88 (H-7) of compound **23**, a selective two-bond heteronuclear NOE difference experiment resulted in a one-peak cmr spectrum, at δ_C = 130.8, which was therefore assigned to C-6. On the other hand, weak irradiation of the doublet appearing at δ_H = 8.09 (H-5) resulted in an NOE difference spectrum showing signals at δ_C = 130.8 (C-6) and 126.7 (C-4a).

The same experiment was performed with the compound **12d** in order to distinguish between C-5 and C-7 (see Table 3 for numbering). On weak irradiation of the doublet at δ_H = 8.23 (H-6) NOE enhancements can be seen in two peaks of the cmr spectrum, at δ_C = 138.2 (C-1) and δ_C = 141.3 (C-5).



15a,c

a, Y = Cl, c, Y = OCH3

The reaction of **13** with imidazole yielded the desired compound **14** together with **15** which pmr and cmr spectra are given in Tables 2 and 3. It is noteworthy that compounds **15** have two chiral centers (C-11 and C-11') which are identically substituted; the stereoisomers are the *dl* pair of enantiomers and the diastereomeric *meso* form. The nmr spectra have been performed with the stereoisomeric mixture, whose pmr spectra displayed two singlets for the H-2 of the imidazole ring (**15a**, δ = 9.79 and 9.72; **15c**, δ = 9.44 and 9.39) corresponding to the *meso* and *dl* isomers. Further information on this point may be obtained because of the duplicity of some signals showed by cmr spectra (table 3). To confirm the constitution of **15a**, selective heteronuclear NOE difference experiments were performed. On weak irradiation of the doublet at δ_H = 7.94 (H-3) NOE enhancements can be seen in two very close peaks of the cmr spectrum, at δ_C = 139.9 and δ_C = 139.8 (C-2 of both stereoisomers). On the other hand, weak irradiation of the multiplet corresponding to phenyl protons (H-8, H-9, H-10) at δ_H = 7.49 resulted in an NOE difference spectrum showing signals at δ_C = 134.1 and 134.0 (C-7 of both stereoisomers). Final confirmation of structures **15a** was achieved by coherent selective decoupling of protons H-3 (δ_H = 7.94), H-4 (δ_H = 8.35), H-6 (δ_H = 7.75), H-2 of imidazole (δ_H = 9.75) and H-4 and H-5 of imidazole (δ_H = 8.07), as a moderate (DP = 45H) decoupler power setting. Under these conditions, the selectively decoupled cmr spectra showed the following C-H decoupled carbons upon irradiation at the frequencies indicated in parentheses: δ_C = 132.0 (C-3, δ_H = 7.94), δ_C = 125.7 (C-4, δ_H = 8.35), δ_C = 124.4 and δ_C = 124.1 (C-6 of both stereoisomers, δ_H = 7.75), δ_C = 138.4 (C-2 imidazole, δ_H = 9.75) and δ_C = 123.4 (C-4 and C-5 imidazole, δ_H = 8.07).

The compounds **14a-c** and **10a-c** were evaluated *in vitro* as possible antibacterials and antifungals. The antibacterial activity was tested *vs.* three Gram-positive bacteria (*Bacillus subtilis, Staphylococcus aureus* and *Streptococcus faecalis*) and six Gram-negative organisms (*Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa, Salmonella tiphymurium* and *Serratia marcescens*). The antifungal activity was tested *vs.* eitht strains (*Candida albicans, Candida, krusei, Torula herbarum, Saccharomyces cerevisiae, Hansela anomala, Aspergillus niger, Fusarium moniliformis* and *Cladosporium herbarum*). No substantial activity was detected in our compounds. Only the microorganisms *Bacilus subtilis* and *Escherichia coli* were inhibited by the compounds **10a** and **10b** at 8 μg/ml.

EXPERIMENTAL

Proton magnetic resonance (pmr) spectra were obtained with a Bruker AM-100 spectrometer operating at 100 MHz and cmr spectra were obtained with a Bruker AM-100 Fourier transform spectrometer operating at 25.1 MHz (solution in hexadeuteriodimethylsulfoxide) with chemical-shift values reported in δ (parts per million) relative to an internal standard. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Infrared spectra of solid samples were run as KBr

pellets on a Perkin-Elmer 177 spectrophotometer. Elemental analyses were obtained for all new compounds reported that could be purified. Mass spectra were determined with a Hewlett-Packard 5895 spectrometer, using the direct-insertion method and electron-impact at an ionizing voltage of 70 eV.

2-Fluoro-5-nitrobenzophenone (**11b**) and 2-Dimethylamino-5-nitrobenzophenone (**11d**). Method A.

A mixture of 2-chloro-5-nitrobenzophenone (**11a**) [19] (5.23 g, 20 mmoles), anhydrous potassium fluoride (5.48 g, 94 mmoles) and anhydrous dimethylformamide (40 ml) was refluxed overnight. After cooling, the mixture was poured over ice and extracted with ethyl acetate. The organic material was combined, washed well with sodium chloride solution, dried and concentrated to dryness. The residue was purified by column chromatography on silica gel using diethyl ether-petroleum ether (1:1) as an eluent. The first fraction gave 3.1 g (63%) of **11b**, mp 46-48° (recrystallized from ethanol) (lit [13] mp 45-47°); see Tables 2 and 3. The second fraction afforded 1.5 g (28%) of **11d**, mp 128-130° (recrystallized from ethanol); see Tables 1, 2 and 3.

2-Fluoro-5-nitrobenzophenone (**11b**). Method B.

A mixture of 2-chloro-5-nitrobenzophenone (**11a**) (26.2 g, 0.1 mole), spray-dried potassium fluoride (Fluka Co.) (26 g, 0.45 mole) and anhydrous dimethylsulfoxide (250 ml) was stirred and refluxed overnight. After cooling, the mixture was poured over ice and extracted with ethyl acetate-petroleum ether (9:1). The organic material was combined, washed successively with sodium chloride solution and water, dried over sodium sulfate, and the solvent was evaporated. The residue recrystallized from ethanol gave 23.1 g (94%) of **11b**, which was identical in all respects to that obtained on method A.

(2-Chloro-5-nitrophenyl)phenylcarbinol (**12a**). Method C.

To a suspension of **11a** (26.16 g, 0.1 mole) in methanol (500 ml), cooled at 15°, was added for half an hour a solution of sodium borohydride (4.9 g, 0.13 mole) in 10% sodium hydroxide (100 ml). After the addition was concluded, the solution was stirred for three hours at room temperature. The methanol was evaporated *in vacuo*. The residue was taken up in a mixture of 10% hydrochloric acid and chloroform. The organic phase was separated, washed with water and dried over sodium sulfate. Activated charcoal was then added and the mixture was filtered. The solvent was evaporated and the residue recrystallized from carbon tetrachloride gave 19.85 g (75%) of **12a**, mp 74°; see Tables 1, 2 and 3.

(2-Methoxy-5-nitrophenyl)phenylcarbinol (**12c**). Method C.

To a suspension of **11b** (5.5 g, 22.5 mmoles) in methanol (100 ml), cooled at 15°, was slowly added a solution of sodium borohydride (1.1 g, 29 mmoles) in 10% sodium hydroxide (25 ml). After the addition was concluded, the solution was stirred for five hours at room temperature. The methanol was evaporated *in vacuo*. The residue was taken up in a mixture of 10% hydrochloric acid and chloroform. The organic phase was separated, washed with water, dried over sodium sulfate, and the solvent was evaporated. The residue recrystallized from diisopropyl ether afforded 4.3 g (74%) of **12c**, mp 120-122°; see Tables 1, 2 and 3.

(2-Fluoro-5-nitrophenyl)phenylcarbinol (**12b**). Method D.

To a suspension of lithium aluminium hydride (4.2 g, 0.11 mole) in anhydrous diethyl ether (250 ml), cooled at 5°, was added for half an hour a solution of **11b** (24.5 g, 0.1 mole) in anhydrous diethyl ether (200 ml). After the addition was concluded, the solution was stirred for five hours at 5-10°. The excess of lithium aluminium hydride was destroyed with 5% sodium hydroxide while the reaction temperature was kept at 5-10°. The organic phase was separated and the aqueous solution was extracted three times with diethyl ether. The organics were combined, washed with water, dried over sodium sulfate, and the solvent was evaporated. The residue, **12b**, 21.25 g (86%), gave a single spot on tlc, and was used without further purification; see Tables 2 and 3.

(2-Chloro-5-nitrophenyl)phenylbromomethane (**13a**). Method E.

A solution of **12a** (26.35 g, 0.1 mole) and thionyl bromide (11.7 ml, 0.15 mole) in 200 ml anhydrous diethyl ether was refluxed for 15 hours. After cooling, the solution was poured over ice. The organic phase was separated, washed successively with water, 5% sodium carbonate solution and water, dried over sodium sulfate, and the solvent was evaporated. The residue, **13a**, 32.2 g (98%), mp 80-82°, gave a single spot on tlc, and was kept in the refrigerator under nitrogen atmosphere without further purification; see Tables 1, 2 and 3.

1-[(2-Chloro-5-nitrophenyl)phenylmethyl]imidazole (**14a**) and 1,3-bis-[(2-chloro-5-nitrophenyl)phenylmethyl]imidazolium Bromide (**15a**). Method F.

A solution of freshly prepared **13a** (22.9 g, 70 mmoles), imidazole (5.7 g, 84 mmoles) and triethylamine (7.1 g, 70 mmoles) in anhydrous acetonitrile (250 ml) was refluxed for 24 hours under nitrogen. The solution was concentrated to dryness and the residue was taken up in a mixture of water and chloroform. The organic phase was separated, washed with water, dried over sodium sulfate, and the solvent was evaporated. The residue was treated with ethyl acetate and the precipitate was filtered off and washed with ethyl acetate. The dried precipitate afforded 7.0 g (31%) of **15a**, mp 257-260° (recrystallized from ethanol); ms: the cation $C_{29}H_{21}N_4Cl_2O_4^+$(M^+) was not observed. There was signals at m/z 313 (M^+-$C_{13}H_9ClNO_2$) and 246 ($C_{13}H_9ClNO_2$); see Tables 1, 2 and 3.

The combined solutions of ethyl acetate were concentrated, giving crystals of **14a** (9.3 g, 43%) which were collected by filtration, mp 169-171°; ms: m/z 313 (M^+) and 246 (M^+-$C_3H_3N_2$); see Tables 1, 2 and 3.

1-[(5-Amino-2-fluorophenyl)phenylmethyl]imidazole (**16b**). Method G.

A solution of **14b** (5.94 g, 20 mmoles) in methanol (150 ml) was hydrogenated (palladium/charcoal) at 30 psi in a Parr apparatus at room temperature for 48 hours. After hydrogenation was complete the catalyst was filtered and the filtrate concentrated to an oil. The residue was taken up in a mixture of 2*N* hydrochloric acid and chloroform. The aqueous phase was alcalinized with 10% sodium hydroxide, and was extracted with chloroform. This last organic phase was separated, washed with water, dried over sodium sulfate, and the solvent was evaporated. The residue was chromatographed on silica gel. The first fraction eluted with a 99:1 mixture of chloroform-methanol was discarded. The second fraction eluted with a 97:3 mixture of chloroform-methanol afforded 2.8 g (48%) of **16b** as an oil, which showed a single spot in tlc; see Tables 1, 2 and 3.

Diethyl *N*-[4-Chloro-3-[(1-imidazolyl)phenylmethyl]phenyl]aminomethylenemalonate (**17a**). Method H.

A solution of **16a** (1.42 g, 5 mmoles) and diethyl ethoxymethylenemalonate (1.10 g, 5.1 mmoles) in ethanol (25 ml) was refluxed for 24 hours. The solution was concentrated to dryness, the residue was washed with diethyl ether, and the precipitate was filtered off. The precipitate was chromatographed on silica gel. The first fraction eluted with a 99:1 mixture of chloroform-methanol was discarded. The second fraction eluted with a 98:2 mixture of chloroform-methanol afforded 1.5 g (66%) of **17a** as an oil, which showed a single spot in tlc, and was used without further purification; see Table 2.

Ethyl 6-Chloro-7-[(1-imidazolyl)phenylmethyl]-4-hydroxy-3-quinolinecarboxyalte (**18a**). Method I.

A mixture of **17a** (1.5 g, 3.3 mmoles), polyphosphoric acid (9.0 g) and phosphoryl chloride (25 g) was stirred at 70° for 4 hours. To the reaction mixture, with external cooling, successively was added ethanol (20 ml) and water (100 ml). The ethanol was evaporated, the aqueous phase was neutralized with sodium bicarbonate solution, and the precipitate was collected by filtration. The dried precipitate afforded 1.05 g (78%) of **18a**, mp 250-252 (recrystallized from ethanol); see Tables 1 and 2.

Ethyl 1-Ethyl-1,4-dihydro-7-[(1-imidazolyl)phenylmethyl]-6-methoxy-4-oxo-3-quinolinecarboxylate (**19c**). Method J.

A mixture of **18c** (1.0 g, 2.5 mmoles), potassium carbonate (0.44 g, 3.1 mmoles) and bromoethane (0.55, 5 mmoles) in dimethylformamide (50 ml) was stirred, in a sealed tube, at 40° for 12 hours and then at room

temperaure for 15 hours. The solution was poured into cold water and was extracted with chloroform (3 × 25 ml). The combined organic solutions were washed with water, dried over sodium sulfate, and the solvent was evaporated. The residue was chromatographed on silica gel. The first fraction eluted with a 99:1 mixture of chloroform-methanol was discarded. The second fraction eluted with a 98:2 mixture of chloroform-methanol afforded 0.56 g (52%) of **19c**, mp 187-190° (recrystallized from ethyl acetate); see tables 1, 2 and 4.

1-Ethyl-1,4-dihydro-6-chloro-7-[(1-imidazolyl)phenylmethyl]-4-oxo-3-quinolinecarboxylic Acid (**10a**). Method K.

A solution of ethyl ester **19a** (0.35 g, 0.8 mmoles), sodium hydroxide (0.8 g, 20 mmoles), water (3 ml), and ethanol (7 ml) was stirred in a water bath at 75° for 30 minutes. The aqueous layer obtained by removal of the ethanol was diluted with water (10 ml), neutralized with 5% hydrochloric acid, and the *p*H was adjusted to 4.5-5.5 with acetic acid. The pale yellow crystals were collected by filtration, and recrystallized from ethanol to afford 0.23 g (70%) of white crystals of **10a**, mp 251-253°; see Tables 1, 2 and 4.

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