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4-HYDROXY-2-QUINOLONES. 177*. STUDY OF A STRUCTURE-DIURETIC ACTIVITY RELATIONSHIP IN A SERIES OF 4-HYDROXY-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLIC ACID N-R-AMIDES

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With the aim of deducing a structure-biological dependence we have carried out the synthesis of quinoline-3-carboxylic acid N-R-amides with a p-methoxyphenyl substituent in the amide part of the molecule. The effects of the compounds prepared on the excretory function of the kidney are discussed. Using a system of simplex descriptors and the method of tree type classification a QSAR model has been constructed which is suitable for prediction of the diuretic activity of novel quinolinecarboxylic acid N-R-amides.

Keywords: 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides, tree-type classification, diuretic activity, molecular simplexes, QSAR.

The ability of 4-hydroxy-2-quinolones to show clear diuretic activity was first discovered accidentally amongst 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid arylalkylamides about 20 years ago [2]. In later extended screening studies a similar type of biological activity was revealed in the closely structurally related amide derivatives of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2- and also 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acids ([3-5] and [6-7] respectively). In this way it was possible to show several important structure-biological activity relationships. Firstly, the need was revealed for the presence of an aryl fragment in the amide part of the molecule. Secondly, it was experimentally confirmed that there was a marked increase in diuretic action with approach of the aryl ring to the amide nitrogen atom. Hence in the series 3-arylpropylamide → 2-arylethylamide → benzylamide → anilide with the same substituents in the aromatic ring the most active generally proved to be the anilide. Thirdly, the most powerful positive effect on

* For Communication 176, see [1].

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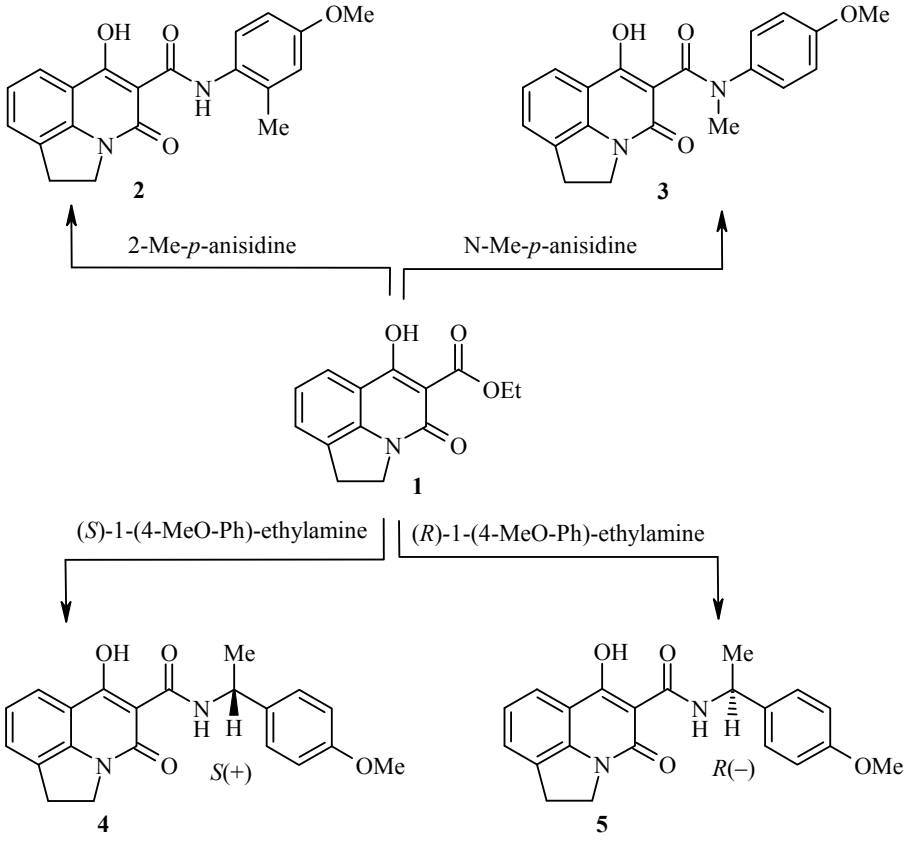
the strength of the diuretic effect proved to be brought about by the presence of a *p*-methoxyphenyl ring. Based on this data, it is logical to propose a search for novel, potential diuretics basiccally through modification of the quinolone part of the molecule.

An additional stimulus for carrying out such an investigation also emerged from the fact that not one new diuretic has appeared in the world pharmaceutical arena for the past few decades. All that are now produced and put on the market are basically the long known furosemide and hypothiazide and their closely structurally related analogs.

Meanwhile for medical practitioners, the clinical value of diuretics is still largely undervalued. Diuretics continue to maintain their established positions in traditional areas of medicine, e.g. in the treatment of arterial hypertension while the list of indications of their use is steadily widening and increasing.

In this connection there is considerable interest in a fundamentally novel class of potential diuretics which are the 4-hydroxy-2-quinolone derivatives. An original confirmation of such a conclusion comes from the PASS program [8] predicting the biological properties of this class of compounds in accordance with which the likelihood of showing diuretic activity amongst 4-hydroxy-2-quinolones is zero. In other words, the experimentally high observed diuretic activity of some 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid N-R- amides indicates that diuretics similar in structure do not yet exist today.

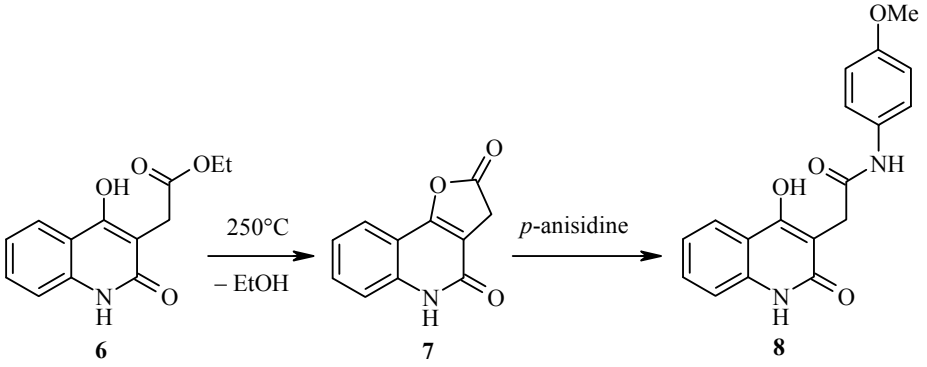
The most active compounds were revealed previously amongst 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2- and 4-hydroxy-(or 4-methyl-)2-oxo-1,2-dihydroquinoline-3-carboxylic acid N-R-amides (*p*Ka 7.20, 7.16, and 7.15 respectively [1]). Hence the subjects of our investigation in this report have been deliberately limited to *p*-methoxyphenyl derivatives of amides of those quinoline-3-carboxylic acids whose acidities are close to or greater [1].



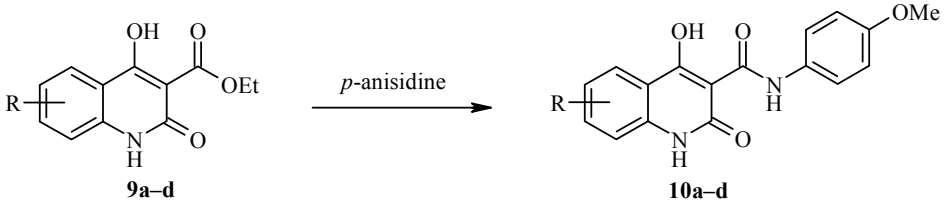
The *p*-methoxy-substituted 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxanilides **2** and **3** with methyl groups respectively in the aromatic amide ring and on the terminal nitrogen atom are of interest for pharmacological investigation. They were prepared by heating equimolar amounts of ester **1** and commercially available *p*-anisidines by a known method [5]. Secondary amines are acylated with somewhat greater complexity hence for the N-methyl derivative the reaction time is increased to 30 min. Despite the steric complication the reaction of the optically active (*S*)- and (*R*)-1-(4-methoxyphenyl)-ethylamines with ester **1** do not need such rigorous conditions, amidation occurring quite readily in refluxing ethanol. The amides **4** and **5** synthesized in this way have exactly the same melting point and identical ^{1}H NMR spectra and optical rotation differing only in signs (see Tables 1 and 2). Because the antipodes **4** and **5** were obtained by an independent route and with the use of different asymmetric reagents there are grounds to consider them as optically pure enantiomers. And observed change of rotation of polarization plane by solution of these materials in an opposite direction to that of the starting amines has to be regarded as an odd fact. As has been repeatedly shown [9, 10] neither racemization nor, especially, inversion of configuration occurs under analogous conditions. Indeed in principle the spatial configuration of the substance is in no way linked to the direction of the plane polarized rotation of its solutions [11].

Study of the biological activities of the amides **2-5** using the standard method [12] shows (Table 1) that methylation of the amide fragments of the 4-methoxyanilide or the 4-methoxybenzylamide of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid presents overall as an undesirable chemical modification. Without exception there is recorded a total loss of diuretic activity when compared with the starting nonmethylated compounds and even the appearance of a strong antidiuretic effect. Hence the (*S*)-1-(4-methoxyphenyl)ethylamide **4** exceeds in specific activity the drug desmopressin which acts as a synthetic analogue of the antidiuretic hormone vasopressin [13].

Suppression of the diuretic function of the kidney was also seen, although less clearly marked, in the 4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl acetic acid 4-methoxyanilide (**8**) which was prepared by the scheme reported below from the corresponding ester **6** *via* the intermediate, more reactive 2,3,4,5-tetrahydrofuro-[3,2-*c*]quinoline-2,4-dione (**7**) [14]:



The appearance of diuretic activity has been noted for halo-substituted 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid 4-methoxyanilides **10**. It was found that both the nature of the halogen and its position in the benzene part of the quinolone ring had an extremely significant effect on the biological activity.

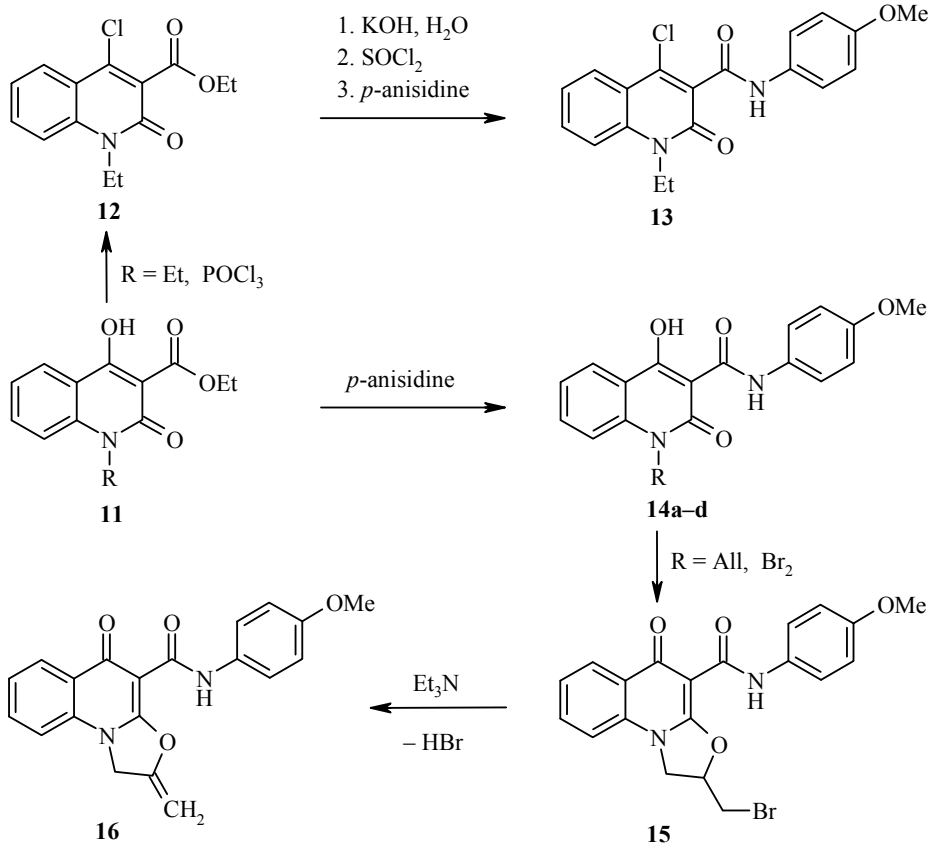


9, 10 a R = 6-Cl, **b** R = 7-Cl, **c** R = 6-Br, **d** R = 6,8-Br_2

In particular, the 6-choro derivative **10a** was significantly more active than the 6- and 6,8-brominated analogs **10c,d** while its 7-chloro-substituted isomer **10b** is a weak antidiuretic.

Exchange of the 4-OH group in the 1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid for chlorine is accompanied by more than one order increase in the acid strength. However, such a change in structure of the starting acid has little effect on the activity of the 4-methoxyanilide **13**.

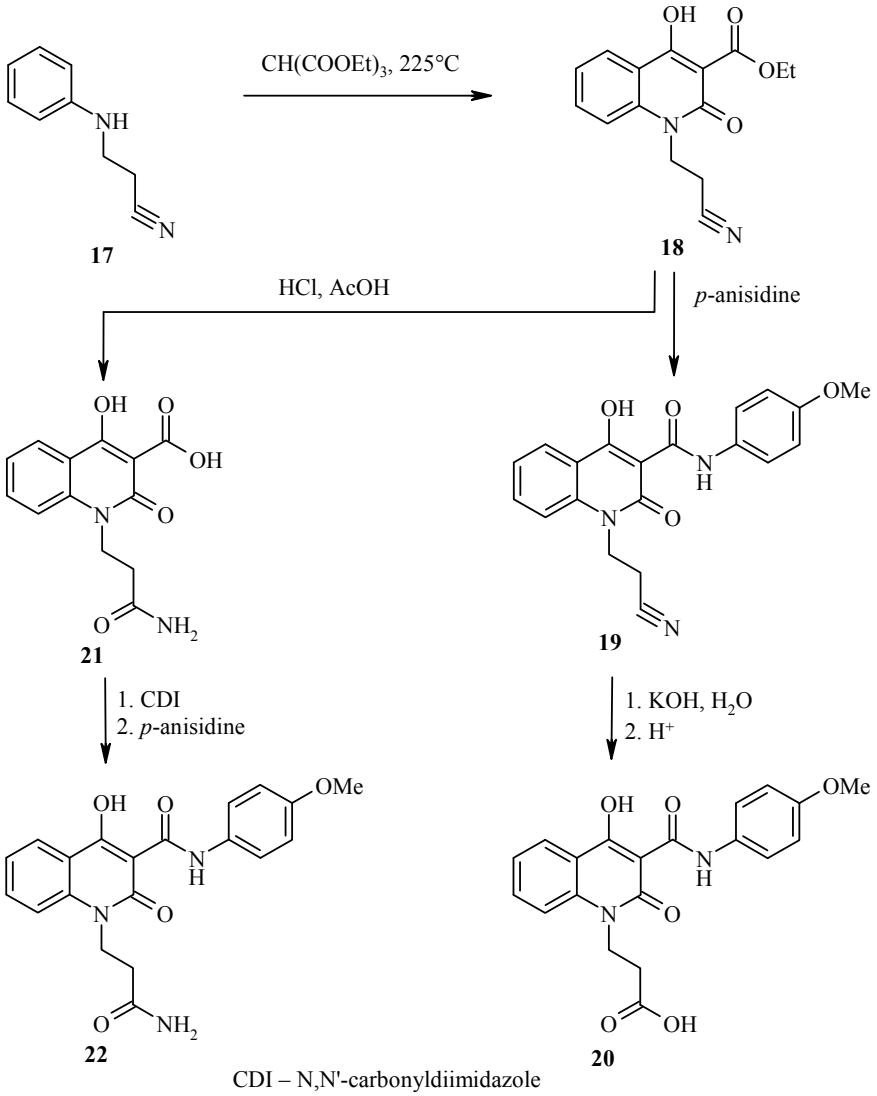
A more successful method of modification of the quinolone structure can occur with the introduction of a substituent at position 1. Hence while the unsubstituted anilide **14a** shows quite a high antidiuretic effect, in its 1-N-benzyl derivative **14c** this effect is markedly lower. With a change to the 1-N-phenyl-substituted product **14d** the product exceeds, although only slightly, the diuretic activity of Hypothiazide. The 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid 4-methoxyanilide (**14b**) is not inferior to this known drug but is used at four times lower dose. In addition, attaching an oxazole ring to the quinolone ring was carried out by bromination of the 1-N-allyl derivatives **14b** with molecular bromine and leads to a fall in diuretic activity. As a result neither the 2-bromomethyloxazoloquinolone **15** nor the product of its dehydrobromination (the methyleneoxazoloquinolone **16**) shows a high activity.



14 a R = H, **b** R = $CH_2CH{=}CH_2$, **c** R = CH_2Ph, **d** R = Ph

In the series of 4-methoxylanilides of 1-substituted 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids special mention should be made of 3-(quinolin-1-yl)propionic acids. Synthesis of compounds of this type can conveniently begin with condensation of 3-phenylaminopropionitrile (**17**) with triethylmethane tricarboxylate. The ethyl 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**18**) obtained

can then be amidated by *p*-anisidine to the anilide **19** which, in turn, undergoes base hydrolysis to give the quinolin-1-ylpropionic acid **20**. The 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates can be hydrolyzed by a mixture of hydrochloric and acetic acids with a low water content which is one of the most successful methods for the preparative synthesis of the corresponding quinoline-3-carboxylic acids [15]. In the case of the ester **18** this is accompanied by a parallel hydration of the nitrile group to give the 1-(2-carbamoylethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**21**) in the final step [1]. Subsequent conversion of the acid **21** to the 4-methoxyanilide **22** need not cause a problem if one remembers that the 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids show a very high tendency towards decarboxylation. Hence their synthesis should be carried out immediately after making up solutions and without the use of strong heating. It is of interest that, of all of the 4-methoxyanilides in this series, the highest diuretic activity is shown only by the product with a free carboxyl group in the 1-N-alkyl fragment, i.e. the acid **20** [7]. The presence of such a substituent in the anilide part of the molecule is generally known [7] to bring about a totally opposite effect independently of its position in the aromatic ring.



CDI – N,N'-carbonyldiimidazole

TABLE 1. Characteristics of the Quinolinecarboxylic Acid N-R-Amides

Compound*	Empirical formula	Found, % / Calculated, %			mp, °C*[2]	Yield, %	Diuretic activity, % relative to control*[3]
		C	H	N			
2	$C_{20}H_{18}N_2O_4$	68.69 / 68.56	5.27 / 5.18	7.88 / 8.00	207-209	94	-39
3	$C_{20}H_{18}N_2O_4$	68.66 / 68.56	5.25 / 5.18	7.93 / 8.00	196-198	75	-35
4	$C_{21}H_{20}N_2O_4$	69.30 / 69.22	5.62 / 5.53	7.76 / 7.69	118-120	92	-74
5	$C_{21}H_{20}N_2O_4$	69.34 / 69.22	5.64 / 5.53	7.78 / 7.69	118-120	90	-50
8	$C_{18}H_{16}N_2O_4$	66.53 / 66.66	5.08 / 4.97	8.55 / 8.64	265-267	91	-15
10a	$C_{17}H_{13}ClN_2O_4$	59.35 / 59.23	3.91 / 3.80	8.20 / 8.13	337-339	95	+38
10b	$C_{17}H_{13}ClN_2O_4$	59.32 / 59.23	3.87 / 3.80	8.22 / 8.13	330-332	89	-15
10c	$C_{17}H_{13}BrN_2O_4$	52.58 / 52.46	3.29 / 3.37	7.11 / 7.20	334-336	93	+15
10d	$C_{17}H_{12}Br_2N_2O_4$	43.55 / 43.62	2.47 / 2.58	6.06 / 5.98	221-223	90	+7
13	$C_{19}H_{17}ClN_2O_3$	64.08 / 63.96	4.93 / 4.80	7.74 / 7.85	203-205	88	+15
14a	$C_{17}H_{14}N_2O_4$	65.69 / 65.80	4.47 / 4.55	8.94 / 9.03	273-275	83	- 39
14b	$C_{20}H_{18}N_2O_4$	68.42 / 68.56	5.07 / 5.18	8.12 / 8.00	140-142	86	+ 55
14c	$C_{24}H_{20}N_2O_4$	71.85 / 71.99	4.91 / 5.03	6.92 / 7.00	152-154	88	-15
14d	$C_{23}H_{18}N_2O_4$	71.58 / 71.49	4.84 / 4.70	7.33 / 7.25	224-226	90	+58
15	$C_{20}H_{17}BrN_2O_4$	55.84 / 55.96	4.10 / 3.99	6.46 / 6.53	227-229	91	+11
16	$C_{20}H_{16}N_2O_4$	68.85 / 68.96	4.49 / 4.63	8.12 / 8.04	179-181	96	+27
19	$C_{20}H_{17}N_3O_4$	66.24 / 66.11	4.81 / 4.72	11.68 / 11.56	183-185	87	-8
20	$C_{20}H_{18}N_2O_6$	62.75 / 62.82	4.86 / 4.74	7.44 / 7.33	197-199	83	+ 61
22	$C_{20}H_{19}N_3O_5$	63.10 / 62.99	4.94 / 5.02	10.91 / 11.02	236-238	86	- 39
	Hypothiazide	—	—	—	—	—	+ 52

* Compound **4** $[\alpha]^{20}_D$ = +27.2º (*c* = 5, DMF), compound **5** $[\alpha]^{20}_D$ = -27.2º (*c* = 5, DMF).

*[2] Solvents: DMF (compounds **2, 10a-d, 14a-d, 19, 20, 22**) or ethanol (compounds **3-5, 8, 13, 15, 16**).

*[3] "+" indicates an increase and "-" a decrease in diuresis relative to the control taken as 100%.

With regard to the results of the pharmacological testing carried out it should be recognised that the acidity of the starting quinoline carboxylic acids, which served as one of the main criteria for the selection of candidate substances for this study, is in no way connected with the diuretic properties of the 4-methoxyphenyl-substituted amides prepared from them.

On this basis we have made attempts to reveal the important molecular parameters of the quinolone compounds which decide their diuretic activity *via* the QSAR method. For the construction of the QSAR model we have used a system of simplex descriptors of molecular structure well established as a means of resolving

TABLE 2. ^{1}H NMR Spectra of the Quinolinecarboxylic Acid N-R-Amides

Compound	Chemical shifts, δ, ppm (*J*, Hz)
1	2
2	16.76 (1H, s, 1-OH); 12.33 (1H, s, NH); 7.88 (1H, d, *J* = 8.9, H-6'); 7.71 (1H, d, *J* = 8.1, H-9); 7.59 (1H, d, *J* = 7.0, H-7); 7.26 (1H, t, *J* = 7.7, H-8); 6.88 (1H, s, H-3'); 6.79 (1H, d, *J* = 8.9, H-5'); 4.35 (2H, t, *J* = 7.8, NCH_2); 3.73 (3H, s, OCH_3); 3.39 (2H, t, *J* = 7.8, $NCH_2C\underline{H}_2$); 2.30 (3H, s, 2'-CH_3)
3	11.00 (1H, s, 1-OH); 7.54 (1H, d, *J* = 7.8, H-9); 7.31 (1H, d, *J* = 7.1, H-7); 7.21 (2H, d, *J* = 8.5, H-2',6'); 7.03 (1H, t, *J* = 7.8, H-8); 6.74 (2H, d, *J* = 8.5, H-3',5'); 4.08 (2H, t, *J* = 7.8, NCH_2); 3.61 (3H, s, OCH_3); 3.28 (2H, t, *J* = 7.8, $NCH_2C\underline{H}_2$); 3.20 (3H, s, NCH_3)
4	16.84 (1H, s, 1-OH); 10.77 (1H, d, *J* = 7.6, NH); 7.65 (1H, d, *J* = 8.1, H-9); 7.55 (1H, d, *J* = 7.1, H-7); 7.31 (2H, d, *J* = 8.7, H-2',6'); 7.20 (1H, t, *J* = 7.8, H-8); 6.91 (2H, d, *J* = 8.7, H-3',5'); 5.09 (1H, q, *J* = 7.2, NHC$\underline{H}$); 4.27 (2H, t, *J* = 7.9, NCH_2); 3.72 (3H, s, OCH_3); 3.36 (2H, t, *J* = 7.9, $NCH_2C\underline{H}_2$); 1.49 (3H, d, *J* = 7.2, $CHC\underline{H}_3$)
5	16.84 (1H, s, 1-OH); 10.77 (1H, d, *J* = 7.6, NH); 7.65 (1H, d, *J* = 8.1, H-9); 7.55 (1H, d, *J* = 7.1, H-7); 7.31 (2H, d, *J* = 8.7, H-2',6'); 7.20 (1H, t, *J* = 7.8, H-8); 6.91 (2H, d, *J* = 8.7, H-3',5'); 5.09 (1H, q, *J* = 7.2, NHC$\underline{H}$); 4.27 (2H, t, *J* = 7.9, NCH_2); 3.72 (3H, s, OCH_3); 3.36 (2H, t, *J* = 7.9, $NCH_2C\underline{H}_2$); 1.49 (3H, d, *J* = 7.2, $CHC\underline{H}_3$)
8	11.40 (1H, s, 4-OH); 10.92 (1H, s, NH); 10.08 (1H, s, $CH_2CON\underline{H}$); 7.88 (1H, d, *J* = 8.0, H-5); 7.49 (3H, m, H-7 + H-2',6'); 7.28 (1H, d, *J* = 8.1, H-8); 7.17 (1H, t, *J* = 7.7, H-6); 6.86 (2H, d, *J* = 9.0, H-3',5'); 3.73 (3H, s, OCH_3); 3.71 (2H, s, CH_2)
10a	16.68 (1H, s, 4-OH); 12.34 (1H, s, NH); 12.08 (1H, s, NH); 7.91 (1H, s, H-5); 7.71 (1H, d, *J* = 8.5, H-7); 7.54 (2H, d, *J* = 8.7, H-2',6'); 7.40 (1H, d, *J* = 8.4, H-8); 6.95 (2H, d, *J* = 8.7, H-3',5'); 3.75 (3H, s, OCH_3)
10b	16.60 (1H, s, 4-OH); 12.27 (1H, s, NH); 12.03 (1H, s, NH); 7.97 (1H, d, *J* = 8.4, H-5); 7.55 (2H, d, *J* = 8.8, H-2',6'); 7.40 (1H, s, H-8); 7.32 (1H, d, *J* = 8.4, H-6); 6.94 (2H, d, *J* = 8.8, H-3',5'); 3.75 (3H, s, OCH_3)
10c	16.67 (1H, s, 4-OH); 12.34 (1H, s, NH); 12.12 (1H, s, NH); 8.05 (1H, s, H-5); 7.84 (1H, d, *J* = 8.8, H-7); 7.55 (2H, d, *J* = 8.6, H-2',6'); 7.34 (1H, d, *J* = 8.8, H-8); 6.96 (2H, d, *J* = 8.6, H-3',5'); 3.75 (3H, s, OCH_3)
10d	16.92 (1H, s, 4-OH); 12.19 (1H, s, NH); 10.76 (1H, s, NH); 8.18 (1H, s, H-5); 8.10 (1H, s, H-7); 7.53 (2H, d, *J* = 8.8, H-2',6'); 6.96 (2H, d, *J* = 8.8, H-3',5'); 3.77 (3H, s, OCH_3)
13	10.34 (1H, s, NH); 8.06 (1H, d, *J* = 8.1, H-5); 7.80 (1H, t, *J* = 7.8, H-7); 7.72 (1H, d, *J* = 8.4, H-8); 7.57 (2H, d, *J* = 8.9, H-2',6'); 7.44 (1H, t, *J* = 7.3, H-6); 6.92 (2H, d, *J* = 8.9, H-3',5'); 4.34 (2H, q, *J* = 7.2, NCH_2); 3.74 (3H, s, OCH_3); 1.25 (3H, t, *J* = 7.2, $NCH_2C\underline{H}_3$)
14a	16.30 (1H, s, 4-OH); 12.42 (1H, s, NH); 11.93 (1H, s, NH); 7.96 (1H, d, *J* = 8.0, H-5); 7.69 (1H, t, *J* = 7.8, H-7); 7.57 (2H, d, *J* = 8.8, H-2',6'); 7.40 (1H, d, *J* = 8.1, H-8); 7.26 (1H, t, *J* = 7.6, H-6); 6.93 (2H, d, *J* = 8.8, H-3',5'); 3.75 (3H, s, OCH_3)
14b	16.22 (1H, s, 4-OH); 12.30 (1H, s, NH); 8.09 (1H, d, *J* = 7.9, H-5); 7.83 (1H, t, *J* = 7.8, H-7); 7.67 (2H, d, *J* = 8.9, H-2',6'); 7.54 (1H, d, *J* = 8.2, H-8); 7.39 (1H, t, *J* = 7.5, H-6); 6.96 (2H, d, *J* = 8.9, H-3',5'); 5.95 (1H, m, C$\underline{H}$=CH_2); 5.14 (1H, d, *J* = 10.6, NCH_2CH=C$\underline{H}$-*cis*); 5.02 (1H, d, *J* = 17.8, NCH_2CH=C$\underline{H}$-*trans*); 4.93 (2H, s, NCH_2); 3.74 (3H, s, OCH_3)
14c	16.92 (1H, s, 4-OH); 12.41 (1H, s, NH); 8.12 (1H, d, *J* = 7.9, H-5); 7.70 (1H, t, *J* = 7.7, H-7); 7.58 (2H, d, *J* = 9.0, H-2',6'); 7.47 (1H, d, *J* = 8.5, H-8); 7.34 (1H, t, *J* = 7.6, H-6); 7.27-7.16 (5H, m, C_6H_5); 6.94 (2H, d, *J* = 9.0, H-3',5'); 5.57 (2H, s, CH_2); 3.73 (3H, s, OCH_3)
14d	16.93 (1H, s, 4-OH); 12.24 (1H, s, NH); 8.15 (1H, d, *J* = 8.0, H-5); 7.70-7.32 (9H, m, H-6,7,2',6' + C_6H_5); 6.93 (2H, d, *J* = 8.7, H-3',5'); 6.58 (1H, d, *J* = 8.4, H-8); 3.73 (3H, s, OCH_3)
15	12.33 (1H, s, NH); 8.25 (1H, d, *J* = 7.8, H-6); 7.81 (1H, t, *J* = 7.3, H-8); 7.58 (2H, d, *J* = 8.8, H-2',6'); 7.56 (1H, d, *J* = 8.5, H-9); 7.48 (1H, t, *J* = 7.3, H-7); 6.88 (2H, d, *J* = 8.8, H-3',5'); 5.68 (1H, m, $NCH_2C\underline{H}O$); 4.68 (1H, t, *J* = 9.8, NCH); 4.31 (1H, dd, *J* = 6.6 and *J* = 9.7, NCH); 4.02 (2H, m, CH_2Br); 3.72 (3H, s, OCH_3)
16	12.24 (1H, s, NH); 8.27 (1H, d, *J* = 8.2, H-6); 7.83 (1H, t, *J* = 7.8, H-8); 7.60 (2H, d, *J* = 9.1, H-2',6'); 7.54-7.43 (2H, m, H-7 + H-9); 6.90 (2H, d, *J* = 9.1, H-3',5'); 5.20 (2H, t, *J* = 2.3, NCH_2); 5.14 (1H, m, =CH-*trans*); 4.86 (1H, m, =CH-*cis*); 3.72 (3H, s, OCH_3)

TABLE 2 (continued)

1	2
19	16.84 (1H, s, 4-OH); 12.29 (1H, s, NH); 8.13 (1H, d, *J* = 8.0, H-5); 7.82 (2H, m, H-7 + H-8); 7.57 (2H, d, *J* = 9.1, H-2',6'); 7.40 (1H, t, *J* = 7.6, H-6); 6.95 (2H, d, *J* = 9.1, H-3',5'); 4.59 (2H, t, *J* = 6.8, NCH_2); 3.74 (3H, s, OCH_3); 2.97 (2H, t, *J* = 6.8, $CH_2C{\equiv}N$)
20	16.73 (1H, s, 4-OH); 12.47 (1H, br. s, COOH); 12.37 (1H, s, NH); 8.08 (1H, d, *J* = 8.0, H-5); 7.79 (1H, t, *J* = 7.7, H-7); 7.68 (1H, d, *J* = 8.5, H-8); 7.55 (2H, d, *J* = 9.0, H-2',6'); 7.35 (1H, t, *J* = 7.6, H-6); 6.93 (2H, d, *J* = 9.0, H-3',5'); 4.48 (2H, t, *J* = 7.8, NCH_2); 3.73 (3H, s, OCH_3); 2.60 (2H, t, *J* = 7.8, $CH_2C{\equiv}N$)
22	16.75 (1H, s, 4-OH); 12.44 (1H, s, NH); 8.12 (1H, d, *J* = 8.0, H-5); 7.82 (1H, t, *J* = 7.7, H-7); 7.70 (1H, d, *J* = 8.5, H-8); 7.58 (2H, d, *J* = 9.2, H-2',6'); 7.46 (1H, s, CH_2CONH); 7.38 (1H, t, *J* = 7.6, H-6); 6.98 (1H, s, CH_2CONH); 6.90 (2H, d, *J* = 9.2, H-3',5'); 4.47 (2H, t, *J* = 7.7, NCH_2); 3.74 (3H, s, OCH_3); 2.43 (2H, t, *J* = 7.6, $CH_2C{\equiv}N$)

different "structure-activity" problems [16-18]. We initially used a method of partial least squares (PLS) [19] relating to the linear method of statistical analysis. However, adequate models which included all of the compounds of the training group could not unfortunately be obtained

As a statistical tool the nonlinear method of tree like classification [20] was more attractive to us. This allowed a clear, graphical picture of the effect of the structure of the compound studied on its diuretic activity (see Figure 1). In this model two classes of diuretic are considered: 1) Those in which the activity was negative with respect to the control (inactive compounds designated by class "-") and 2) Those in which the corresponding activity was positive (designated by class "+"). In this way all of the compounds considered were separated into two approximately equal groups (see Table 1). In addition, within the class of active substances there were added those studied before which had clear diuretic properties and served as the basis for our investigation of the *p*-methoxyanilides of the 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2- and 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [5] and [7] respectively.

As seen in Figure 1 the tree obtained allows a correct classification of 21 of the studied compounds on the basis of only three structural parameters (var2, var29, and var84) *via* the chosen QSAR model from more than 200 simplex descriptors. In fact, in association with one another, these parameters allow a correct classification to be carried out.

Each rectangle (terminal tree – Node) showed how many compounds of the "-" and "+" classes remained after the preceding step. In the final rectangle (Nodes 1, 4, 5, and 6) compounds from only one class are found. Each branch of the tree corresponds to a specific condition. For example, on exiting from Node 3 there exist 8 molecules divided into two groups according to the value of parameter var29: If less than or equal to 69 crossing to Node 5 otherwise in the opposite case to Node 6.

Node 0 corresponds to the starting situation, 10 being inactive molecules and 11 active. There is then a subsequent classification depending on the values of the simplex descriptors var2, var29, and var84. For each molecule the classification (movement along the tree) ends in some kind of terminal point (Nodes 1, 4, 5, or 6).

From the analysis of the obtained tree it can be concluded that the active molecules in the group studied are those in which the structural parameter var2 = 0 or those in which var2 = 0 but with var84 $\leq$ 40 and var29 $\leq$ 69.

The structural parameters var2, var29, and var84 characterizing the number of specific molecular fragments are presented in Table 3. As is apparent from this table the parameter var2 corresponds to the bound aromatic fragment which contains atoms of two types with characteristic lipophilicity $-0.5 < \log P \leq 0$ or $0 < \log P \leq 0.5$. Parameter var29 corresponds to a molecular fragment consisting of atoms with the same lipophilicity parameters but not bonded. Parameter var84 corresponds to a nonbonded molecular fragment in which there emerge atoms of four types relating to the distribution of partial charges on them: $q_A \leq -0.1$, $0.05 < q_E \leq 0.1$, $0.1 < q_F$ and $0 < q_D \leq 0.05$.

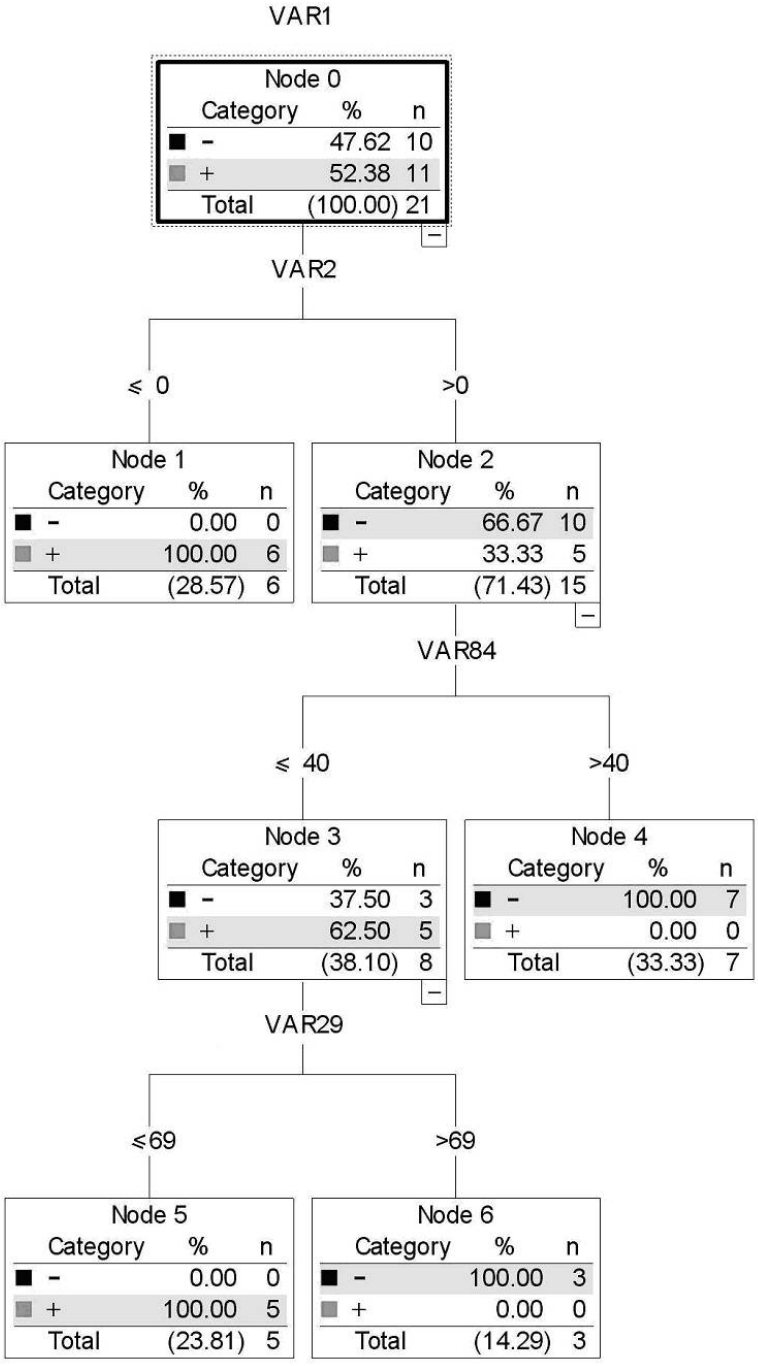
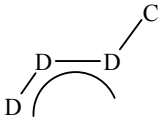
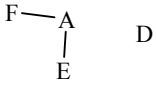
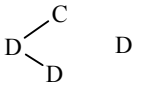


Fig. 1. 2D-QSAR model describing the effect of the structure of the quinolinecarboxylic acid N-R-amides on their diuretic activity.

Hence the data obtained suggest that the overall direction of the effect of the N-R-amides **2-22** on the excretory function of the kidney is determined not by the presence of any specific molecular fragment but by a combination of atoms with a fixed distribution of lipophilicity and partial charges. This somewhat hinders the interpretation of the dependence obtained since the conditions indicated above can themselves correspond to a

TABLE 3. Molecular Fragments, the Number of which Determine the Diuretic Activity

var2 bonded simplex, grouped according to lipophilicity	var84 nonbonded simplex, grouped according to charge	var29, nonbonded simplex, grouped according to lipophilicity
		

Groups according to lipophilicity, relating to the lipophilicity of the atoms:
A ≤ –1 < **B** ≤ –0.5 < **C** ≤ 0 < **D** ≤ 0.5 < **E** ≤ 1 < **F**.
Groups according to charge, relating to the charges on the atoms:
A ≤ –0.1 < **B** ≤ –0.05 < **C** ≤ 0 < **D** ≤ 0.05 < **E** ≤ 0.1 < **F**.

variety of structural fragments. Unfortunately the limited choice of compounds studied does not permit an overall conclusion regarding the relationship between structure and diuretic properties. None the less the direction of the effect of each specific molecular fragment on diuresis is clearly tracked hence the QSAR model obtained is fully suited to predict the biological activity of novel quinoline carboxylic acid N-R-amides.

EXPERIMENTAL

^{1}H NMR spectra for the compounds synthesized were recorded on a Varian Mercury-VX-200 instrument (200 MHz) using DMSO-d_6 and with TMS as internal standard. In the syntheses reported in this work the compounds used were commercial 2-methyl- and N-methyl-*p*-anisidines and also 3-phenylamino-propionitrile from the Aldrich. (*S*)- and (*R*)-1-Ethyl(4-methoxyphenyl)amines (with optical purity not less than 99% in both cases), triethylmethane tricarboxylate, anhydrous DMF for peptide synthesis, and N,N'-carbonyl-diimidazole were obtained from the Fluka company.

Substituted Anilides and 1-Ethyl(4-methoxyphenyl)amides of 1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic Acids 2-5 were prepared by amidation of ester **1** by the corresponding anilines or 1-ethyl(4-methoxyphenyl)amines by methods [5] or [4].

4-Hydroxy-2-oxo-1,2-dihydroquinolin-3-ylacetic Acid 4-Methoxyanilide (8) was prepared from ester **6** and *p*-anisidine using a known method [15].

4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid 4-Methoxyanilides 10 and 14 were prepared by reaction of esters **9** and **11** with *p*-anisidine under thermolysis conditions in the presence of a small amount of DMF [5].

4-Chloro-1-ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid 4-Methoxyanilide (13) was synthesized from 4-chloro-1-ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylc acid [21] and *p*-anisidine using the method in [22].

2-Bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylic Acid 4-Methoxy-anilide (15) was prepared by halocyclization of 4-methoxyanilide **14b** as reported in [23].

2-Methylene-5-oxo-1,2-dihydro-5H-oxazolo[3,2-a]quinoline-4-carboxylic Acid 4-Methoxyanilide (16) was synthesized by dehydrobromination of the 2-bromomethyloxazoloquinolone **15** by the method in [24].

Ethyl 1-(2-Cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (18). 3-Phenylamino-propionitrile (**17**) (14.6 g, 0.1 mol) was added in small portions to triethylmethane tricarboxylate (23.2 ml, 0.11 mol) stirred and heated to 215ºC in such a way that the temperature was maintained within ±5ºC of the initial. The ethanol evolved in the reaction process was distilled off through a suitable condenser. After adding all of the 3-phenylaminopropionitrile the reaction mixture was held for 10-15 min at the same temperature and then cooled. A 10% aqueous solution of Na_2CO_3 (300 ml) was added and heated to 70-80ºC. The solution obtained was purified using carbon and filtered. After cooling the filtrate was acidified with dilute HCl (1:1) to pH 4.5-5.0. The precipitated ester **18** was filtered off, washed with water, and dried to give a 24.6 g yield of product (85%); mp 161-163ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.23 (1H, s, OH); 8.08 (1H, dd, *J* = 8.0, and *J* = 1.3, H-5); 7.74 (1H, td, *J* = 7.8, and *J* = 1.5, H-7); 7.67 (1H, d, *J* = 8.3, H-8); 7.31 (1H, td, *J* = 7.2 and 1.6, H-6); 4.45 (2H, t, *J* = 6.9, NCH_2); 4.32 (2H, q, *J* = 7.2, OCH_2); 2.88 (2H, t, *J* = 6.9, $NCH_2C\underline{H}_2$); 1.29 (3H, t, *J* = 7.2, $OCH_2C\underline{H}_3$). Found, %: C 62.81; H 5.06; N 9.88. $C_{15}H_{14}N_2O_4$. Calculated, %: C 62.93; H 4.93; N 9.78.

1-(2-Cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid 4-Methoxyanilide (19) was prepared from ester **18** and *p*-anisidine by heating in the presence of a small amount of DMF [5].

1-(2-Ethoxycarbonyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid 4-Methoxyanilide (20). A mixture of nitrile **19** (3.63 g, 0.01 mol), KOH (5 g), and water (100 ml) was refluxed until evolution of NH_3 had ceased (~ 4 h). The product was cooled and filtered and the filtrate was acidified to pH 3 with HCl. The precipitated acid **20** formed was filtered off, washed with water, and dried.

1-(2-Carbamoylethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid 4-Methoxyanilide (22). N,N'-Carbonyldiimidazole (1.78 g, 0.011 mol) was added to a solution of acid **21** (2.76 g, 0.01 mol) in anhydrous DMF (30 ml) protected from moisture with a $CaCl_2$ drying tube and held at a temperature not above 40ºC for about 2 h until evolution of CO_2 ceased. *p*-Anisidine (1.23 g, 0.01 mol) was added and the reaction mixture was heated to 90ºC and held at this temperature for 2 h. It was then cooled and diluted with HCl and water. The precipitated anilide **22** was filtered off, washed with water, and dried.

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