Novel 2-oxoquinoline-6-sulfonamides as thiazide-like diuretics

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A series of novel *N*-aryl-7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonamides were obtained. The structure—activity relationship (SAR) approach was used to study their diuretic effect on rats. Diuretic activity was exhibited by all the test compounds, with 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonanilide being most active. A SAR analysis revealed that the substituted (especially *ortho*-substituted in the benzene ring) arylamides diminish diuresis compared to the most active compound. For the most and least active compounds, their effects on the electrolyte excretion (Na^+, K^+, and Cl^-) and creatinine level were also studied.

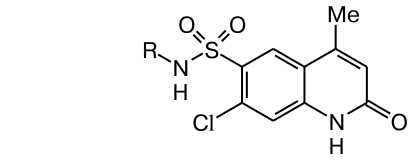
Key words: quinolin-2-ones, sulfonamides, thiazide-like diuretics, structure—activity relationship.

Currently available diuretic drugs that are widely used to treat various diseases include loop, thiazide, and potassium-sparing diuretics and carbonic anhydrase inhibitors.[1] Specifically, diuretics are mostly indispensable for the treatment of cardiovascular (including hypertension and strokes), kidney, and liver diseases as well as glaucoma.[2—5] In the last few decades, thiazides and thiazide-like diuretics have taken a key role in treating hypertension because they are drugs of choice for elderly people. This is due to their antihypertensive effect produced even in low doses, which minimizes the unwanted metabolic effect.[6] However, some side effects (notably, hypokalemia, hypomagnesemia, hyponatremia, hypercalcemia, and hypochloremic alkalosis[3,4,7—9]) have been reported for this group of drugs. Thus, a search for novel efficient thiazide-like diuretics with as few side effects on the human organism as possible is still a challenge.

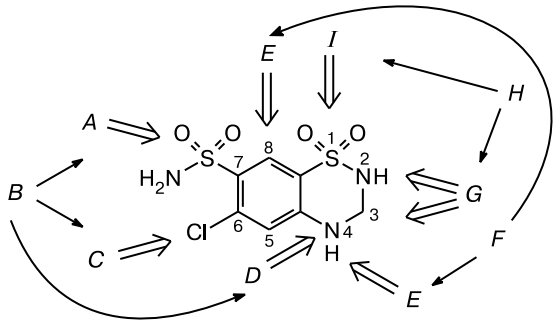
Earlier,[10] we have proposed quinolone scaffold **I** as a basis for searching for novel thiazide-like diuretics (Scheme 1), in compliance with the main concepts of the quantitative structure—activity relationship (QSAR) theory for thiazide diuretics.[11]

It becomes evident from comparison of structure **I** with thiazide drugs (see Scheme 1) that most of the indispensable pharmacophores are already present in basic structure **I**. This structural similarity suggests a possible diuretic effect of sulfonamides **I**, which has been confirmed previously.[10] It should be noted that hydrochlorothiazide (**II**) and thiazide-like diuretics contain an unsubstituted sulfonamide group. However, the closest analog to hydrochlorothiazide **II** among the test compounds, namely, 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonamide (**I**, R = H), unexpectedly showed moderate activity (62%), while 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonanilide (**I**, R = Ph) was most active. The goal of the present work was to obtain a series of novel *N*-aryl-7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonamides and examine their diuretic effect.

Scheme 1



I



II

R = H, Alk, Ar, Het

A is the sulfonamide group, *B* denotes absolutely indispensable groups, *C* is a halogen-containing group, *D* is a heterocyclic or aromatic amino group, *E* is a substituent, *F* denotes promoting groups, *G* denotes lipophilic groups, *H* denotes inhibiting groups, and *I* is an electron-withdrawing group.

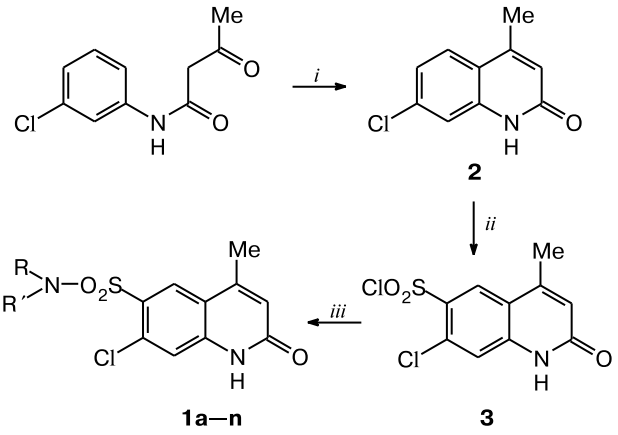
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 10, pp. 1953—1958, October, 2012.

Results and Discussion

The synthesis of the target compounds **1a**—**n** is sketched in Scheme 2. 7-Chloro-4-methyl-1,2-dihydroquinolin-2-one (**2**) used as a starting material was prepared according to a known procedure.[12] Sulfochlorination of quinolone **2** with a fivefold excess of chlorosulfonic acid gave 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl chloride (**3**) in high yield.[10] Further reactions of sulfonyl chloride **3** with various arylamines in the presence of a hydrogen chloride scavenger produced a number of the corresponding arylamides **1a**—**n**. The compounds obtained were identified from elemental analysis data and ^{1}H NMR and mass spectra (Table 1).

The diuretic effect of compounds **1a**—**n** on rats was estimated by Berkhin´s method. The test compounds and hydrochlorothiazide[13] (**II**) as a reference diuretic were administered orally. To select a proper dose, we tested compound **1a** in doses of 1.0, 5.0, 10.0, and 50.0 mg kg^{-1} (Table 2). The maximum diuresis was observed for a dose of 5 mg kg^{-1}. That is why the whole series of *N*-aryl-7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonamides (**1a**—**n**) was tested for a dose of 5 mg kg^{-1}. The results obtained are given in Table 3.

Scheme 2



i. Conc. H_2SO_4; *ii*. HSO_3Cl, $SOCl_2$; *iii*. NHRR, EtOH.

1	R	R´	**1**	R	R´
a	H	Ph	**h**	H	2-COOH—C_6H_4
b	H	2-MeC_6H_4	**i**	H	3-COOH—C_6H_4
c	H	3-MeC_6H_4	**j**	H	4-COOH—C_6H_4
d	H	4-MeC_6H_4	**k**	H	3-ClC_6H_4
e	H	2-$MeOC_6H_4$	**l**	Et	Ph
f	H	3-$MeOC_6H_4$	**m**	H	2-EtC_6H_4
g	H	4-$MeOC_6H_4$	**n**	H	2,4-$Me_2C_6H_3$

Table 1. Physicochemical characteristics of compounds **1a**—**n**

Compound	Yield (%)	*T*/°C	Found / Calculated (%) C	H	N	Molecular formula	MS (EI), *m/z* (I_{rel} (%))	^{1}H NMR (DMSO-d_6, δ, *J*/Hz)
1a	71	283—285	55.06 55.10	3.72 3.76	8.09 8.03	$C_{16}H_{13}ClN_2O_3S$	350 $[M + 2]^+$ (13), 348 $[M]^+$ (42), 249 $[M - Cl - SO_2]^+$ (45), 210 $[M + 2 - Ph - SO_2]^+$ (23), 208 $[M - Ph - SO_2]^+$ (57), 194 $[M + 2 - PhSO_2NH]^+$ (8), 192 $[M - PhSO_2NH]^+$ (31), 166 $[M + 2 - PhSO_2NH - CO]^+$ (13), 164 $[M - PhSO_2NH - CO]^+$ (36), 157 $[M - PhSO_2NH - Cl]^+$ (28), 92 $[PhNH]^+$ (100), 65 $[C_5H_4]^+$ (58)	2.39 (s, 3 H, C(4)Me); 6.49 (s, 1 H, H(3)); 6.98 (t, 1 H, Ar, *J* = 6.0); 7.05—7.26 (m, 4 H, Ar); 7.38, 8.22 (both s, each 1 H, H(8), H(5)); 10.52, 11.86 (both br.s, each 1 H, SO_2NH, N(1)H)
1b	68	276—277	56.23 56.28	4.15 4.17	7.74 7.72	$C_{17}H_{15}ClN_2O_3S$	364 $[M + 2]^+$ (5), 362 $[M]^+$ (12), 107 $[MeC_6H_4NH + 1]^+$ (20), 106 $[MeC_6H_4NH]^+$ (100), 77 $[Ph]^+$ (27)	2.16, 2.29 (both s, each 3 H, C(2´)Me, C(4)Me); 6.47 (s, 1 H, H(3)); 6.83—7.23 (m, 4 H, Ar); 7.47, 8.02 (both s, each 1 H, H(8), H(5)); 9.74, 11.93 (both br.s, each 1 H, SO_2NH, N(1)H)
1c	64	252—254	56.30 56.28	4.20 4.17	7.79 7.72	$C_{17}H_{15}ClN_2O_3S$	364 $[M + 2]^+$ (1), 362 $[M]^+$ (6), 263 $[M - SO_2 - Cl]^+$ (60), 107 $[CH_3C_6H_4NH + 1]^+$ (48), 106 $[CH_3C_6H_4NH]^+$ (100), 77 $[Ph]^+$ (57)	2.15, 2.40 (both s, each 3 H, C(3´)Me, C(4)Me); 6.50 (s, 1 H, H(3)); 6.77 (d,1 H, Ar, *J* = 7.0); 6.86—6.98 (m, 2 H, Ar); 7.06 (t, 1 H, Ar, *J* = 8.1); 7.37, 8.22 (both s, each 1 H, H(8), H(5)); 10.53, 11.94 (both s, each 1 H, SO_2NH, N(1)H)

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	*T*/°C	Found / Calculated (%) C	H	N	Molecular formula	MS (EI), *m/z* (*I*$_{rel}$ (%))	^{1}H NMR (DMSO-d$_6$, δ, *J*/Hz)
1d	69	294—296	56.32 56.28	4.22 4.17	7.80 7.72	$C_{17}H_{15}ClN_2O_3S$	364 $[M + 2]^+$ (7), 362 $[M]^+$ (23), 106 $[MeC_6H_4NH]^+$ (100), 77 $[Ph]^+$ (27)	2.12, 2.39 (both s, each 3 H, C(4′)Me, C(4)Me); 6.49 (s, 1 H, H(3)); 6.87—7.07 (m, 4 H, Ar); 7.37, 8.19 (both s, each 1 H, H(8), H(5)); 10.43, 11.93 (both br.s, each 1 H, SO_2NH, N(1)H)
1e	62	285—286	53.97 53.90	3.95 3.99	7.45 7.39	$C_{17}H_{15}ClN_2O_4S$	380 $[M + 2]^+$ (16), 378 $[M]^+$ (46), 122 $[MeOC_6H_4NH]^+$ (83), 94 $[PhOH]^+$ (100), 92 $[PhNH]^+$ (47), 65 $[C_5H_4]^+$ (42)	2.30, 3.50 (both s, each 3 H, C(4)Me, OMe); 6.47 (s, 1 H, H(3)); 6.75—6.96 (m, 2 H, Ar); 7.01—7.31 (m, 2 H, Ar); 7.43, 8.01 (both s, each 1 H, H(8), H(5)); 9.50, 11.94 (both s, each 1 H, SO_2NH, N(1)H)
1f	66	234—235	53.93 53.90	3.97 3.99	7.44 7.39	$C_{17}H_{15}ClN_2O_4S$	380 $[M + 2]^+$ (5), 378 $[M]^+$ (16), 299 (25), 279 $[M - SO_2 - Cl]^+$ (100), 278 (53), 166 $[M + 2 - MeOC_6H_4SO_2NH - CO]^+$ (6), 164 $[M - MeOC_6H_4SO_2NH - CO]^+$ (25), 123 (63), 122 $[CH_3OC_6H_4NH]^+$ (58), 95 (70)	2.40, 3.61 (both s, each 3 H, C(4)Me, OMe); 6.42—6.60 (m, 2 H, H(3), Ar); 6.61—6.78 (m, 2 H, Ar); 7.09 (t, 1 H, Ar, J = 8.0); 7.38, 8.24 (both s, each 1 H, H(8), H(5)); 10.62, 11.95 (both s, each 1 H, SO_2NH, N(1)H)
1g	69	274—276	53.94 53.90	3.93 3.99	7.49 7.39	$C_{17}H_{15}ClN_2O_4S$	380 $[M + 2]^+$ (9), 378 $[M]^+$ (20), 122 $[CH_3OC_6H_4NH]^+$ (100)	2.36, 3.61 (both s, each 3 H, C(4)Me, OMe); 6.48 (s, 1 H, H(3)); 6.77 (d, 2 H, Ar, J = 9.2); 7.03 (d, 2 H, Ar, J = 9.2); 7.39, 8.12 (both s, each 1 H, H(8), H(5)); 10.22, 11.93 (both s, each 1 H, SO_2NH, N(1)H)
1h	63	293—295	52.00 51.98	3.38 3.34	7.18 7.13	$C_{17}H_{13}ClN_2O_5S$	394 $[M + 2]^+$ (7), 392 $[M]^+$ (23), 210 $[M + 2 - C_6H_4COOH - SO_2]^+$ (9), 208 $[M - C_6H_4COOH - SO_2]^+$ (37), 120 $[C_6H_4COO]$ (81), 119 $[NHC_6H_4COOH - H_2O]$ (100), 92 $[PhNH]^+$ (26)	2.48 (s, 3 H, C(4)Me); 6.51 (s, 1 H, H(3)); 6.91—7.14 (m, 1 H, Ar); 7.38 (s, 1 H, H(8)); 7.41—7.50 (m, 2 H, Ar); 7.91 (d, 1 H, Ar, J = 7.7); 8.36 (s, 1 H, H(5)); 11.70, 11.97 (both br.s, each 1 H,SO_2NH, N(1)H)
1i	62	300—302	51.94 51.98	3.31 3.34	7.20 7.13	$C_{17}H_{13}ClN_2O_5S$	394 $[M + 2]^+$ (12), 392 $[M]^+$ (36), 293 $[M - SO_2 - Cl]^+$ (38), 292 $[M - SO_2 - Cl - H]^+$ (30), 258 $[M + 2 - C_6H_4COOH]^+$ (9), 256 $[M - C_6H_4COOH]^+$ (27), 210 $[M + 2 - C_6H_4COOH - SO_2]^+$ (29), 208 $[M - C_6H_4COOH - SO_2]^+$ (100), 194 $[M + 2 - COOH—C_6H_4SO_2NH]^+$ (15), 192 $[M - COOH—C_6H_4SO_2NH]^+$ (41), 166 $[M + 2 - COOH—C_6H_4—SO_2NH - CO]^+$ (13), 164 $[M - COOH—C_6H_4SO_2NH - CO]^+$ (34), 157 $[M - COOH—C_6H_4SO_2NH - Cl]^+$ (27), 137 $[NHC_6H_4COOH]$ (28), 119 $[NHC_6H_4COOH - H_2O]$ (82), 65 $[C_5H_4]^+$ (26)	2.42 (s, 3 H, C(4)Me); 6.50 (s, 1 H, H(3)); 7.29—7.36 (m, 2 H, Ar); 7.38 (s, 1 H, H(8)); 7.48—7.55 (m, 1 H, Ar); 7.73 (s, 1 H, Ar); 8.28 (s, 1 H, H(5)); 10.90 (s, 1 H,SO_2NH); 11.95 (br.s, 1 H, NH)

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	*T*/°C	Found / Calculated (%) C	H	N	Molecular formula	MS (EI), *m/z* (I_{rel} (%))	^{1}H NMR (DMSO-d_6, δ, *J*/Hz)
1j	69	292—293	51.91 51.98	3.30 3.34	7.18 7.13	$C_{17}H_{13}ClN_2O_5S$	394 $[M + 2]^+$ (12), 392 $[M]^+$ (34), 293 $[M - SO_2 - Cl]^+$ (30), 292 $[M - SO_2 - Cl - H]^+$ (25), 210 $[M + 2 - C_6H_4COOH - SO_2]^+$ (23), 208 $[M - C_6H_4COOH - SO_2]^+$ (68), 194 $[M + 2 - COOH—C_6H_4SO_2NH]^+$ (10), 192 $[M - COOH—C_6H_4SO_2NH]^+$ (31), 166 $[M + 2 - COOH—C_6H_4SO_2NH - CO]^+$ (11), 164 $[M - COOH—C_6H_4SO_2NH - CO]^+$ (26), 137 $[NHC_6H_4COOH]$ (40), 119 $[NHC_6H_4COOH - H_2O]$ (62), 43 $[NHCO]^+$ (100)	2.46 (s, 3 H, C(4)Me); 6.51 (s, 1 H, H(3)); 7.18 (d, 2 H, Ar, *J* = 8.6); 7.37 (s, 1 H, H(8)); 7.77 (d, 2 H, Ar, *J* = 8.6); 8.32, 11.14 (both s, each 1 H, H(5), SO_2NH); 11.96 (br.s, 1 H, N(1)H)
1k	70	273—275	50.19 50.14	3.20 3.16	7.40 7.31	$C_{16}H_{12}Cl_2N_2O_3S$	386 $[M + 4]^+$ (2), 384 $[M + 2]^+$ (10), 382 $[M]^+$ (14), 285 $[M + 2 - SO_2 - Cl]^+$ (22), 283 $[M - SO_2 - Cl]^+$ (100), 258 $[M + 2 - NHC_6H_4Cl]^+$ (9), 256 $[M - NHC_6H_4Cl]^+$ (25), 210 $[M + 2 - C_6H_4Cl - SO_2]^+$ (25), 208 $[M - C_6H_4Cl - SO_2]^+$ (76), 194 $[M + 2 - Cl—C_6H_4SO_2NH]^+$ (15), 192 $[M - ClC_6H_4SO_2NH]^+$ (66), 166 $[M - ClC_6H_4SO_2NH - CO]^+$ (11), 164 $[M + 2 - ClC_6H_4SO_2NH - CO]^+$(30), 157 $[M - ClC_6H_4SO_2NH - Cl]^+$ (54)	2.43 (s, 3 H, C(4)Me); 6.52 (s, 1 H, H(3)); 6.99—7.15 (m, 3 H, Ar); 7.23 (t, 1 H, Ar, *J* = 8.0); 7.40, 8.26 (both s, each 1 H, H(8), H(5)); 10.92, 11.98 (both s, each 1 H, SO_2NH, N(1)H)
1l	64	244—245	57.40 57.37	4.59 4.55	7.50 7.43	$C_{18}H_{17}ClN_2O_3S$	378 $[M + 2]^+$ (2), 376 $[M]^+$ (3), 277 $[M - SO_2 - Cl]^+$ (100), 120 $[EtNHPh]^+$ (99), 77 $[Ph]^+$ (36)	1.00 (t, 3 H, $C\underline{H}_3CH_2$, *J* = 7.0); 2.28 (s, 3 H, C(4)Me); 3.76 (q, 2 H, $CH_3C\underline{H}_2$, *J* = 7.0); 6.49 (s, 1 H, H(3)); 7.14—7.39 (m, 5 H, Ar); 7.46, 7.92 (both s, each 1 H, H(8), H(5); 12.00 (s, 1 H, N(1)H)
1m	68	239—240	57.43 57.37	4.60 4.55	7.57 7.43	$C_{18}H_{17}ClN_2O_3S$	378 $[M + 2]^+$ (1), 376 $[M]^+$ (3), 120 $[EtC_6H_3NH]^+$ (100)	1.02 (t, 3 H, $C\underline{H}_3CH_2$, *J* = 7.6); 2.30 (s, 3 H, C(4)Me); 2.61, 6.49 (q, 2 H, $CH_3C\underline{H}_2$, *J* = 7.6); (s, 1 H, H(3)); 6.85 (d, 1 H, Ar, *J* = 7.2); 7.03 (td, 1 H, Ar, *J* = 7.2, *J* = 2.0); 7.09—7.25 (m, 2 H, Ar); 7.48, 8.01 (both s, each 1 H, H(8), H(5)); 9.81, 12.00 (both s, each 1 H, SO_2NH, N(1)H)
1n	71	290—291	57.34 57.37	4.53 4.55	7.39 7.43	$C_{18}H_{17}ClN_2O_3S$	378 $[M + 2]^+$ (2), 376 $[M]^+$ (5), 120 $[(Me)_2C_6H_3NH]^+$ (100)	2.11, 2.15, 2.29 (all s, each 3 H, C(4′)Me, C(2′)Me, C(4)Me); 6.49 (s, 1 H, H(3)); 6.74—6.89 (m, 2 H, Ar); 6.95 (s, 1 H, Ar); 7.46, 7.99 (both s, each 1 H, H(8), H(5)); 9.70, 11.99 (both s, each 1 H, SO_2NH, N(1)H)

Table 2. Dependence of the diuretic activity of compound **1a** and hydrochlorothiazide **II** on their doses*

Compound	Dose /mg kg^{-1}	Urine volume /mL (4 h)	Diuretic activity (%)
1a	1.0	5.83±1.72	208
	5.0	6.08±1.68	221
	10.0	5.58±1.24	195.2
	50.0	4.50±1.30	131.1
Hydrochlorothiazide **II**	1.5	5.30±0.98	189.6
	5.0	5.83±1.47	208
Control	—	1.83±0.53	—

* Here and in Tables 3 and 4, $P < 0.05$.

Table 3. Diuretic activity of sulfonamides **1a—n**

Compound	Urine volume /mL (4 h)	Diuretic activity (%)	Compound	Urine volume /mL (4 h)	Diuretic activity (%)
1a	6.01±0.29	145.3	**1i**	3.70±0.52	51.0
1b	3.50±0.36	42.9	**1j**	4.82±0.55	96.7
1c	3.83±0.60	56.3	**1k**	4.00±0.44	63.3
1d	3.96±0.41	61.6	**1l**	4.16±0.49	69.8
1e	3.38±0.50	38.0	**1m**	3.66±0.48	49.4
1f	4.30±0.28	75.5	**1n**	3.46±0.54	41.2
1g	4.11±0.51	67.8	Hydrochlorothiazide **II**	5.77±0.38	135.0
1h	3.76±0.43	53.5	Control	2.45±0.17	—

Table 4. Effects of compounds **1a**,**b**,**e**,**j** on the electrolyte excretion and creatinine levels

Compound	Fluid studied	Electrolyte excretion /mmol L^{-1}			Na^+/K^+ /mmol L^{-1}	Creatinine level /mL min^{-1}	Creatinine clearance
		K^+	Na^+	Cl^-			
1a	Blood serum	8.99±1.30	155.10±9.16	245.70±26.75	17.25	0.073±0.005	0.383±0.056
	Urine	110.70±11.22	170.00±6.40	505.71±54.30	1.53	1.125±0.085	0.383±0.056
1b	Blood serum	9.25±1.56	170.00±12.60	274.35±22.18	18.38	0.085±0.007	0.206±0.035
	Urine	157.50±15.52	195.40±7.85	609.20±61.55	1.24	1.205±0.035	0.206±0.035
1e	Blood serum	11.12±2.10	169.80±17.22	254.85±15.60	15.30	0.079±0.004	0.170±0.030
	Urine	168.00±12.15	209.20±9.35	587.25±44.25	1.25	1.112±0.217	0.170±0.030
1j	Blood serum	8.26±1.02	162.30±8.16	248.75±18.95	19.65	0.089±0.003	0.280±0.048
	Urine	139.33±17.01	165.90±15.80	530.32±47.35	1.19	1.212±0.189	0.280±0.048
Hydrochlorothiazide **II**	Blood serum	8.40±0.95	166.20±15.78	244.50±31.50	19.79	0.090±0.003	0.362±0.032
	Urine	138.35±10.69	195.90±7.90	548.21±36.95	1.42	1.158±0.156	0.362±0.032
Control	Blood serum	10.11±1.25	171.10±21.70	268.59±15.60	16.92	0.088±0.013	0.145±0.015
	Urine	155.8±10.76	184.60±10.35	521.83±34.95	1.18	1.280±0.093	0.145±0.015

According to the experimental data, the presence of any substituent in the benzene ring of the sulfonamide fragment of structure **I** reduces diuresis. For instance, the diuretic effect of 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonanilide **1a** is comparable with that of hydrochlorothiazide **II** (145.3 and 135.0%, respectively). A high activity (96.7%) was also exhibited by compound **1j**. Most of the test compounds produce moderate diuretic effects: the urine volumes excreted by rats exceed those in the control group by 50—75%. The presence of the *ortho*-substituted benzene ring (**1b**,**e**,**h**,**m**,**n**) reduces diuresis most substantially. It should also be noted that the diuretic effect is virtually insensitive to the electronic nature of the radical (Me, Et, OMe, or COOH).

To analyze a possible mechanism of diuretic action, we measured the contents of electrolytes and creatinine in

urine and serum for the most (**1a**,**j**) and least active compounds (**1b**,**e**) (Table 4). According to the results obtained, all of them produce a similar effect on the excretion of Na^+, K^+ and Cl^- by rats as hydrochlorothiazide **II** does. In all the cases, diuresis is mainly due to the excretion of Na^+; the Na^+/K^+ ratio for novel compounds is more favorable than that for hydrochlorothiazide **II**. Compound **1a** is superior to all the other compounds (including **II**) in Na^+ excretion and potassium-sparing effect. The best creatinine clearance was also observed for sulfonamide **1a**.

An acute toxicity test with mice (*per os*)[14] for 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonanilide (**1a**) as the most active compound showed that its LD_{50} is >10 000 mg kg^{-1}. This value makes it more attractive than hydrochlorothiazide **II** (*cf.* LD_{50} = 3000 mg kg^{-1} (*per os*)[15]).

To sum up, our biological tests revealed that novel *N*-aryl-7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonamides **1a**—**n** are similar in diuretic activity to hydrochlorothiazide **II**. The best results among the compounds studied were achieved with 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonanilide (**1a**), which is of interest as a potential antihypertensive drug. Analysis of the structure—activity relationship showed that the sulfonamides containing a substituted benzene ring diminish diuresis compared to unsubstituted analog **1a**.

Experimental

Melting points were determined on a Kofler hot stage. ^1H NMR spectra were recorded on a Varian Mercury VX-200 instrument (200 MHz) in DMSO-d_6 with Me_4Si as the internal standard. Mass spectra (EI, 70 eV) were recorded on a Varian 1200L instrument.

7-Chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonanilide (1a). A mixture of 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl chloride (**3**) (2.92 g, 10 mmol), aniline (11 mmol), triethylamine (11 mmol) and ethanol (50 mL) was refluxed for 1 h. The reaction mixture was cooled, diluted with water, and acidified with HCl to pH 3—4. The precipitate that formed was filtered off, washed with water, and recrystallized from ethanol. The yield of compound **1a** was 2.48 g (71%), colorless crystals, m.p. 283—285 °C.

N-Aryl sulfonamides **1b**—**g**,**k**—**n** were obtained as described for compound **1a**, with appropriate arylamines instead of aniline. The products were recrystallized from ethanol. Their yields are specified in Table 1.

2-(7-Chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonylamino)benzoic acid (1h). A mixture of 7-chloro-4-methyl-2-oxo-1,2-dihydroquinoline-6-sulfonyl chloride (**3**) (2.92 g, 10 mmol) and *o*-aminobenzoic acid (2.74 g, 20 mmol) in ethanol (50 mL) was refluxed for 1 h. The reaction mixture was cooled, diluted with water, and acidified with HCl to pH 3—4. The precipitate that formed was filtered off, washed with water, and recrystallized from ethanol—DMF. The yield of compound **1h** was 2.47 g (63%), colorless crystals, m.p. 293—295 °C.

N-Aryl sulfonamides **1i**,**j** were obtained as described for compound **1h**, with appropriate aromatic amino acids instead of *o*-aminobenzoic acid. The products were recrystallized from ethanol—DMF. Their yields are specified in Table 1.

Diuretic activity was studied according to Berkhin´s method with outbred white male rats (150±30 g in weight). The dose of the test compounds was 5 mg kg^{-1} (for compound **1a**, doses of 1.0, 5.0, 10.0, and 50.0 mg kg^{-1} were used). Each dose was tested in six animals, with hydrochlorothiazide **II** as a reference diuretic. The compounds were intragastrically administered in one portion as aqueous suspensions stabilized by Tween 80 with water burden (3 mL per 100 g of body weight). The results obtained were compared with those of a control group (the animals of this group were given saline and Tween 80 in the same amounts).

The concentrations of K^+ and Na^+ ions in urine and blood serum were measured on a PAZh-3 flame automated photometer. The concentration of chloride ions was determined by titration.[13]

Urinary and serum creatinine concentrations were determined using the Jaffe method.[13] The creatinine clearance was calculated by a known formula.

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Received June 21, 2012