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Synthesis and diuretic activity of 2,3-dihydro-4(1*H*)-quinolinone 4-oxime-*O*-sulfonic acid derivatives

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Abstract – The diuretic activity of 6-chloro-2,3-dihydro-1-propionyl-4(1*H*)-quinolinone 4-oxime **1** (**M12285**) was previously shown to derive from a 6-chloro-2,3-dihydro-1-propionyl-4(1*H*)-quinolinone 4-oxime-*O*-sulfonic acid salt as a rat metabolite. Thus, in the present study, the potassium salt **2** (**M17000**) was synthesized to unambiguously establish the structure as well as the stereochemistry of the oxime. The structural features of compounds **1** and **2** were compared with those of conventional diuretics by electrostatic potential maps. Using compound **2** as a lead compound, various quinolinone oxime sulfonic acid derivatives were synthesized and the diuretic activity for elucidation of the structure–activity relationships examined. Among the compounds synthesized, 7-chloro-2,3-dihydro-1-(2-methylbenzoyl)-4(1*H*)-quinolinone 4-oxime-*O*-sulfonic acid potassium salt **3** (**M17055**) showed a particularly high activity. © Elsevier, Paris

quinolinone oxime-*O*-sulfonic acid / stereochemistry of oxime / electrostatic potential map / diuretic activity / structure–activity relationship

1. Introduction

It has been shown that the diuretic effect of 6-chloro-2,3-dihydro-1-propionyl-4(1*H*)-quinolinone 4-oxime **1** (**M12285**) depends on the species of animal [1]. Briefly, it increases urine volume dose-dependently when administered orally to rats, while its effect is very weak in rabbits and dogs. Investigation of the causes of the species differences indicated that the diuretic activity of **1** apparently derives from a sulfate–metabolite conjugate produced in the rat liver. The metabolite was shown to be a 6-chloro-2,3-dihydro-1-propionyl-4(1*H*)-quinolinone 4-oxime-*O*-sulfonic acid salt [2]. Compound **2** (**M17000**), a potassium salt synthesized in the present study expressed a particularly high diuretic activity in rats, rabbits, and dogs. This salt is a novel diuretic lacking sulfamoyl ($-SO_2NH_2$) or carboxy ($-CO_2H$) which are present in conventional loop diuretics such as furosemide and bumetanide (*figure 1*) [3, 4].

The significance of the sulfonic acid as a trigger of diuretic activity and the roles of the acyl carbonyl were studied here with the aid of computer analysis. Pharmacological investigations [5, 6] indicated com-

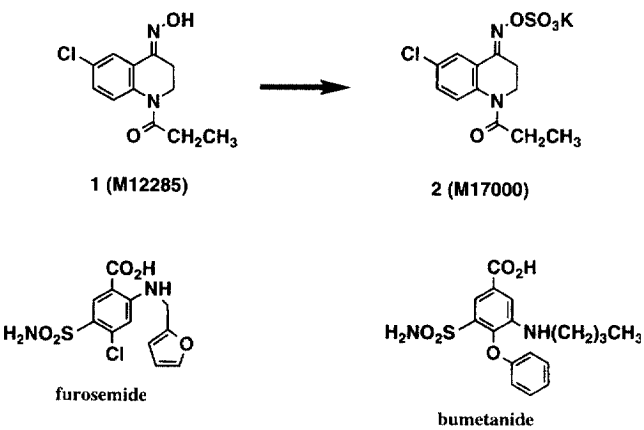

Figure 1. Structures of **1** (**M12285**), **2** (**M17000**) and loop diuretics.

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pound **2** to be fundamentally a loop diuretic. The electrostatic potentials of compounds **1** and **2** and furosemide were thus estimated, and electrostatic potential maps made by computer graphics were compared.

Using compound **2** as a lead compound, various quinolinone oxime sulfonic acid derivatives were synthesized and their diuretic activity was estimated by renal arterial and intravenous administration to dogs.

2. Chemistry

Figure 2 presents the routes of syntheses of oxime-*O*-sulfonic acid compound **2**. 6-Chloro-2,3-dihydro-1-propionyl-4(1*H*)-quinolinone **7** was synthesized by a known method [7] and then reacted with hydroxylamine-*O*-sulfonic acid [8] to obtain oxime-*O*-sulfonic acid derivative **8**. Although this acid **8** readily decomposed to compound **1**, it was isolable as a stable potassium salt **2**. Alternatively, compound **7** was converted to oxime **1** by treatment with hydroxylamine hydrochloride in the presence of pyridine, which was then sulfonated with a pyridine–sulfur trioxide complex to give compound **9** [9]. Eventually, compound **2** was obtained by replacing the counter ion of compound **9** with potassium cation. This route to compound **2** is reminiscent of that in rat metabolism. Although compound **2** is a salt, it has similar features to those of covalently bonded, common organic compounds and can be purified by silica gel chromatography and recrystallization.

NMR spectra are generally used to assign the stereochemistry of the isomers (***E*** or ***Z*** form) of oximes derived from ketones. *Figure 3* shows chemical shifts of the *peri*-position protons of compounds **7**, **1**, and **2** and structurally analogous compounds. Examination of the proton at the 5-position indicated the chemical shifts of compounds **1** (δ 7.90) and **2** (δ 7.95) to be virtually the same as that (δ 7.98) of compound **7**. In the case of oximes of structurally similar 1,8-naphthyridine derivatives [10], the chemical shifts (δ 7.75–8.12) of the *peri*-position protons in ***E*** isomers are essentially the same as those (δ 7.80–8.12) of their parent ketones. On the other hand, chemical shifts of the *peri*-position protons of ***Z*** isomers are substantially influenced by the hydroxy group, the signals appearing in a magnetic field of δ 8.00–8.76. Thus, the stereochemistry of the oxime moiety of compounds **1** and **2** was assigned to be ***E***, which was actually confirmed by the X-ray structural analysis of compound **3** (*figure 4*).

Figure 5 shows several synthetic outlines to various *O*-sulfonic acid derivatives using compound **2** as the lead compound. More specifically, compounds **11**, **14**, **17**, **20** and **23** were synthesized by the hydroxylamine-*O*-sulfonic acid route presented in *figure 2*

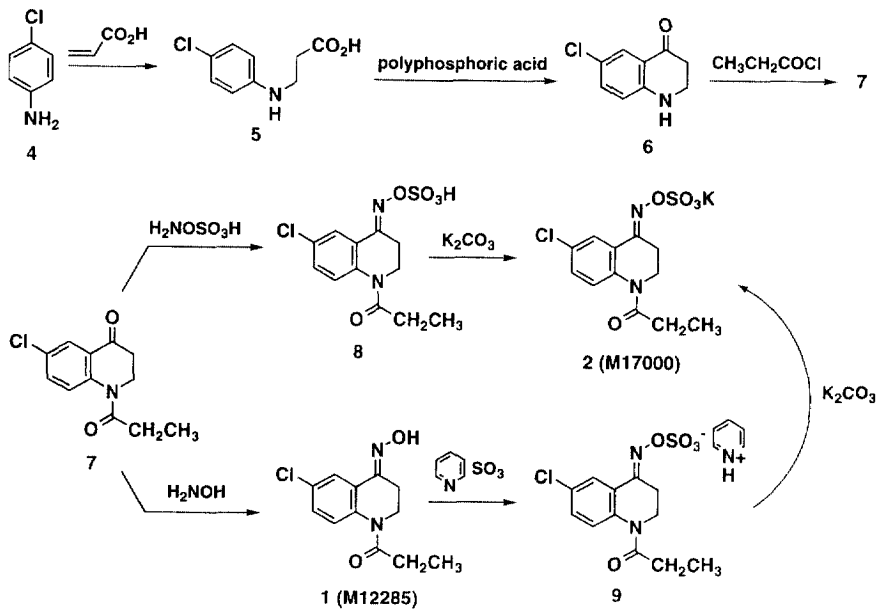

Figure 2. Synthetic pathways to **2** (**M17000**).

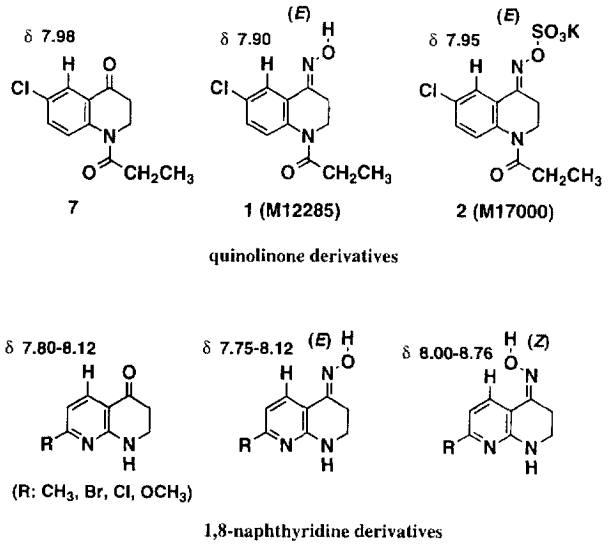

Figure 3. ^{1}H-NMR spectral data of *peri*-protons of quinolinone derivatives and 1,8-naphthyridine derivatives.

after the pertinent quinolinone structure with target substituents had been constructed by starting from quinolinones **6** [7], **12** [7, 11, 12], **15** [13, 14], **18** [11] and **21** [15], respectively (*figure 6*), while the synthesis of compounds **27a,b** with substituents at the 3-position by starting from quinolinone **24**, *via* methylation to **25a,b**, oximation to **26a,b** and then finally *O*-sulfonation (*figure 7*).

3. Diuretic activity and structure–activity relationship

Diuretic activity was determined from the ratio of increase in urine volume after the synthetic compounds administered via the dog renal artery (i.r.a.) or intravenously (i.v.) to that after furosemide administration at the same dose (see Experimental protocols for details). The i.r.a. administration is the most direct method to determine diuretic activity for drugs in vivo. On the other hand, diuretic activity by intravenous injection may reflect pharmacokinetics including metabolism and tissue transport. Diuretic activity after intravenous injection should thus make an accurate measure to select suitable candidates for further development.

The diuretic activity (i.r.a.) of compound **2** was half of that of furosemide. However, since the chemical structure of this compound differs completely from those of the conventional diuretics, we considered it promising as a lead compound to develop a novel diuretic and thus the structure–activity relationships were examined so as to obtain a more active compound.

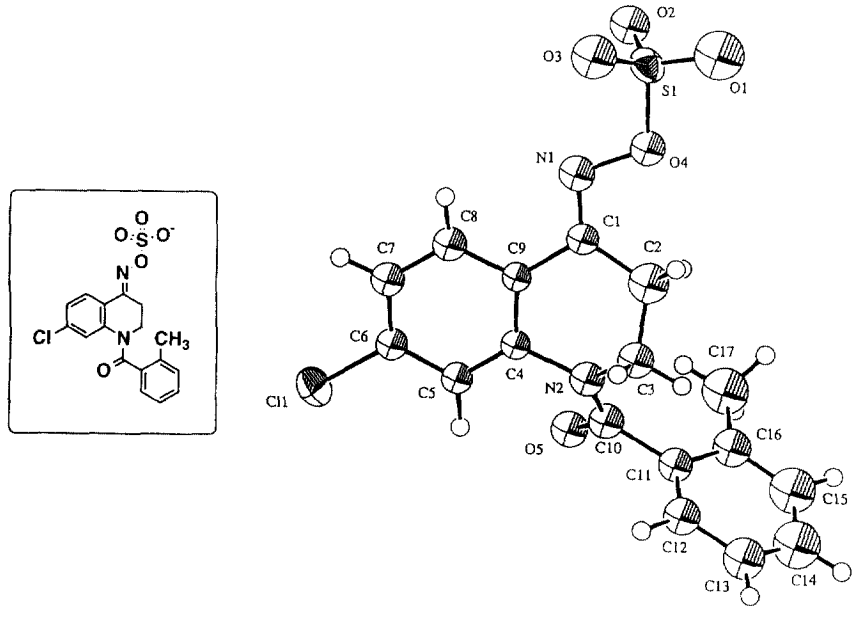

Figure 4. Three-dimensional structure of the crystal conformation of **3** (**M17055**). This drawing was prepared by the computer program ORTEP.

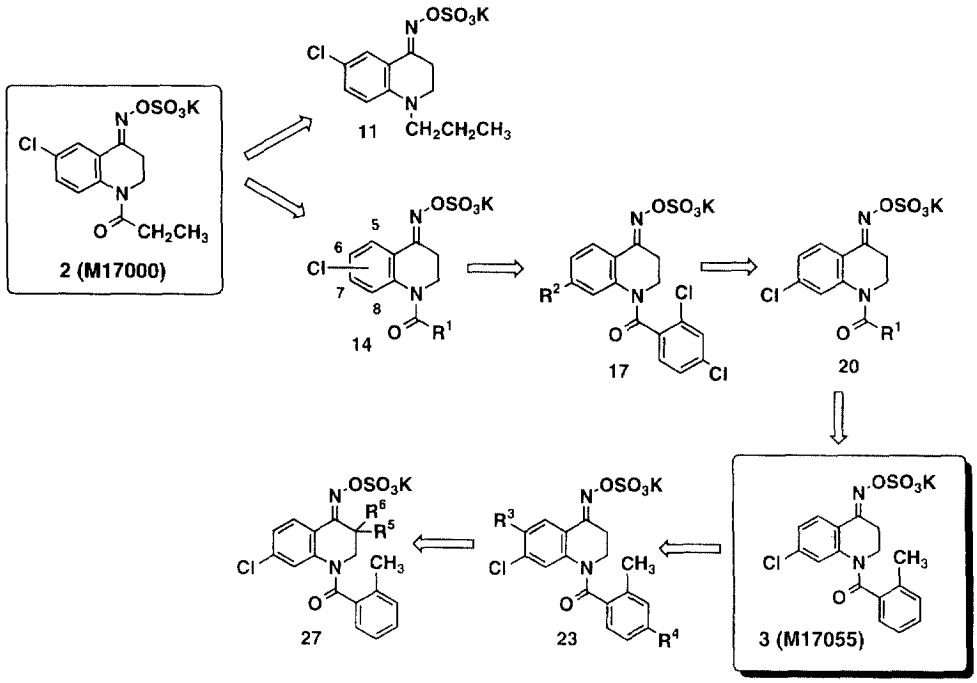

Figure 5. Synthetic outlines for derivatization of **2** (**M17000**).

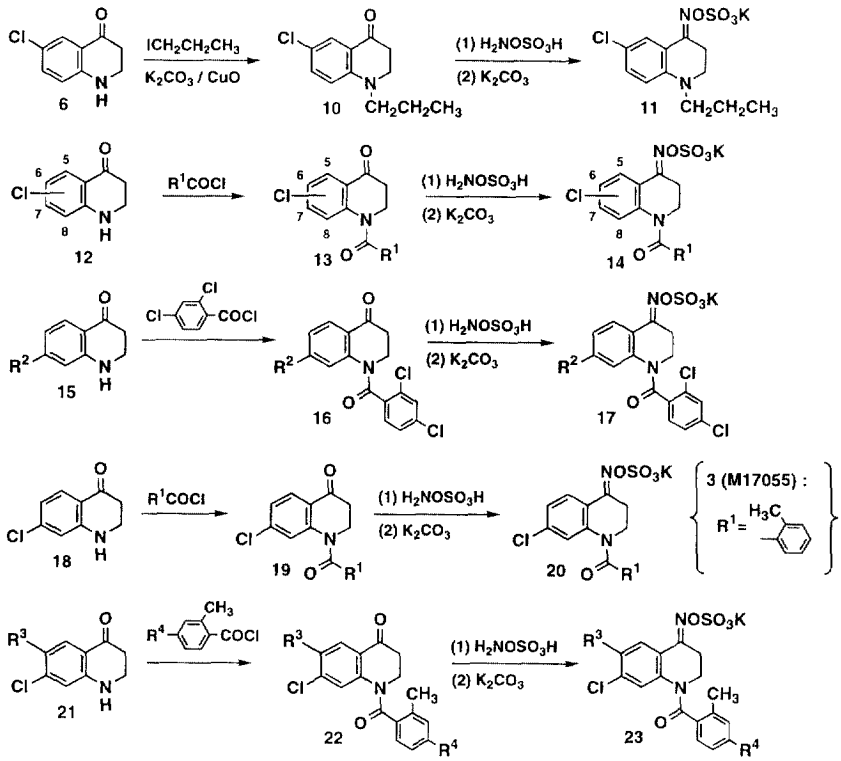

Figure 6. Synthetic pathways to compounds **11**, **14**, **17**, **20** and **23**.

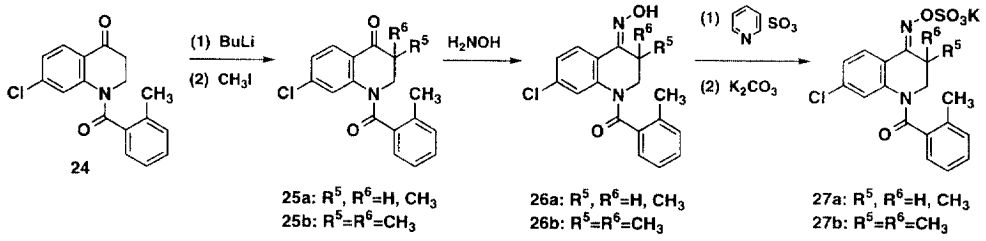

Figure 7. Synthetic pathway to compounds **27a,b**.

Table I shows the diuretic activity of compounds of **11** and general formula **14** having substituent COR^1 at position 1. It has been suggested via in vivo studies that replacement of a bulky group for the Cl of furosemide should enhance the inhibition of the Na^+–K^+–$2Cl^-$ cotransport system. Bumetanide is such a diuretic whose activity is increased by replacing a phenoxy group for the Cl (*figure 1*). The diuretic activity (i.r.a.) of the compounds synthesized in the present study (general formula **14**) increased when ethyl substituent of compound **2** was replaced by a bulky R^1 substituent (**14b–d**). On the other hand, the diuretic activity decreased with a methyl group (**14a**) or by insertion of a methylene (**14e**) or vinylene (**14f**) between the benzene ring and carbonyl group. Cl at position 2 or positions 2 and 4 of the benzene ring (**14g–i**) caused activity to increase to more than that of furosemide. Compound **14i**, with a Cl substituent at

Table I. Diuretic activities of compounds **2** (**M17000**), **11**, **14** and furosemide.

Compound	Position of Cl	R^1	Diuretic activity	
			i.r.a.[a]	i.v.[b]
2 (**17000**)	**6**	CH_2CH_3	0.5	0.3
11	**6**		N[c]	N
14a	**6**	CH_3	0.2	N
14b	**6**	$C(CH_3)_3$	1.1	0.3
14c	**6**	C_6H_{11}	1.0	N
14d	**6**	C_6H_5	1.0	0.3
14e	**6**	$CH_2C_6H_5$	0.4	N
14f	**6**	$CH{=}CHC_6H_5$	0.1	N
14g	**6**	C_6H_4(2-Cl)	1.7	1.1
14h	**6**	C_6H_3(2,4-Cl_2)	2.4	1.5
14i	**7**	C_6H_3(2,4-Cl_2)	5.7	4.0
14j	**8**	C_6H_3(2,4-Cl_2)	0.6	N
furosemide			1.0	1.0

[a]Text compounds were injected into the renal artery of dogs and activity was expressed relative to that of furosemide; [b]text compounds were administered intravenously to dogs and activity was expressed relative to that of furosemide; [c]N: no activity.

the 7-position of the quinolinone ring showed a particularly high diuretic activity by either route of administration. Cl at the 7-position apparently exerts an electronic effect on the oxime moiety at the *p*-position. Compounds with a Cl substituent at the 5-position decomposed readily (data not shown) and compound **14j** with Cl substituent at the 8-position was unstable and showed decreased diuretic activity.

Table II presents the diuretic activity of compounds of general formula **17** with a substituent at position 7 in the presence of 2,4-dichlorobenzoyl at position 1. Compounds with halogens (**14i**, **17b–d**), especially Cl (**14i**) expressed very high diuretic activity, possibly due to the electronic effect of the 7-halogens.

Table III gives the diuretic activity of compounds of general formula **20** with an acyl substituent. Compound **20a** with a phenyl ring in the acyl group showed a higher diuretic activity than compounds **20b–f** with a heterocyclic ring, including pyridine, thiophene and furan. Halogen, alkyl, and methoxy groups were introduced as the substituent into the phenyl ring and their effects on diuretic activity were investigated (**3**, **14i**, **20g–n**). Following administration via the renal artery, compounds **20g**, **20i**, and **14i** with Cl at the 2- or 4-position of the phenyl and compound **3** with methyl at the 2-position exhibited a high diuretic activity, and after intravenous injection, compounds **20g**, **14i**, and **3** with Cl or methyl at the 2-position of the phenyl gave rise to a high diuretic activity. The intravenous injection of compounds **20h–k** with a phenyl group not substituted at the 2-position showed less diuretic activity than that noted following the renal arterial administration. Some compounds with a high diuretic activity after intravenous injection were then administered orally, among which compound **3** was found to have the greatest diuretic activity, showing its excellent pharmacokinetics.

Table II. Diuretic activities of compounds **14i**, **17** and furosemide.

Compound	R^2	Diuretic activity	
		i.r.a.[a]	i.v.[b]
17a	H	1.4	0.6
17b	F	4.3	2.4
14i	Cl	5.7	4.0
17c	Br	4.4	3.1
17d	I	4.6	2.9
17e	CH_3	1.9	0.4
17f	OH	3.1	2.5
17g	OCH_3	1.3	0.6
17h	$N(CH_3)_2$	N[c]	N
furosemide		1.0	1.0

[a,b,c]See footnotes to *table I*.

Table III. Diuretic activities of compounds **3** (**M17055**), **14i**, **20** and furosemide.

Compound	R^1	Diuretic activity	
		i.r.a.[a]	i.v.[b]
20a	C_6H_5	2.2	3.1
20b		0.5	0.5
20c		1.3	1.8
20d		1.0	1.1
20e		1.1	1.3
20f		1.4	0.8
20g	C_6H_4(2-Cl)	4.4	4.0
20h	C_6H_4(3-Cl)	3.6	1.5
20i	C_6H_4(4-Cl)	6.2	2.8
14i	C_6H_3(2,4-Cl_2)	5.7	4.0
3 (**M17055**)	C_6H_4(2-CH_3)	4.2	4.2
20j	C_6H_4(3-CH_3)	3.0	2.0
20k	C_6H_4(4-CH_3)	2.5	1.6
20l	C_6H_4(2-OCH_3)	2.5	3.4
20m	C_6H_4(2-CH_2CH_3)	3.6	3.2
20n	C_6H_4(2-$CH(CH_3)_2$)	2.4	2.3
furosemide		1.0	1.0

[a,b]See footnotes to *table I*.

Therefore, compound **3** was further modified to those of general formula **23** and **27**, and *table IV* presents their diuretic activity values. The diuretic activity of compounds **23a–b** with a substituent at the 4-position of the toluyl ring (substituent R^4) or compound **23c** with a substituent at the 6-position of quinolinone moiety (substituent R^3) was less than that of compound **3**, since liposolubility may have increased beyond the optimal limit due to greater substituents in the aromatic rings. Compounds **27a–b** substituted at the 3-position decomposed gradually into compounds **26a–b** or compounds **25a–b** at room temperature and diuretic activity was low.

4. Discussion

The significance of introducing sulfonic acid functionality as a trigger of diuretic activity in compound **2** and roles of the acyl group were investigated by computer analysis. Pharmacologically, quinolinone oxime-*O*-sulfonic acid compounds synthesized in the present study have been suggested to act on the same cotransporters of conventional loop diuretics [5, 6]. The mechanism for the action of these loop diuretics including furosemide has been ascribed to the inhibition of the Na^+–K^+–$2Cl^-$ cotransport mechanism in the thick ascending limb of Henle's loop [16, 17]. Conventional diuretics of furosemide class have carboxy $-CO_2^-$ group as a common moiety, which, according to the above mechanism, binds to the Cl^- binding site of the cotransporter to inhibit the cotransport system. Drugs that interact with the same cotransporter should have a similar geometric shape and electrostatic potential. Since it seems that a negatively charged group should play an important role in diuretics [18–20], attention was directed towards the electrostatic potentials in this study. Electrostatic potentials of compounds **1** and **2** and furosemide were calculated by various methods described in the Experimental section, and the electrostatic potential maps prepared by computer graphics were compared. *Figure 8* includes the electrostatic potential of compound **2** to clarify the difference of that of compound **1** by introducing a sulfonic acid group. It can be seen that the electrostatic potential of compound **2** is quite similar to that of furosemide. Sulfonic function ($-SO_3^-$) introduced by the metabolism of compound **1** thus appears to act as a functional group corresponding to $-CO_2^-$ of the conventional diuretics and to bind to the Cl^- binding site of the Na^+–K^+–$2Cl^-$ cotransporter. Carbonyl in the acyl moiety of the present quinolinone oxime derivatives may correspond to the sulfamoyl group of the conventional diuretics and participate in interactions with the cotransporter active site by hydrogen bonding. The high diuretic activity of compound **3** may thus be ascribed to interactions with the cotransporter active sites, as shown in *figure 9*.

5. Conclusions

Quinolinone oxime sulfonic acid compounds are novel diuretics clearly different from conventional diuretics in chemical structure but possessing functio-

Table IV. Diuretic activities of compounds **3** (**17055**), **23**, **27** and furosemide.

Compound	R^3	R^4	R^5	R^6	Diuretic activity	
					i.r.a.[a]	i.v.[b]
3 (M17055)	H	H	H	H	4.2	4.2
23a	H	Cl	H	H	3.2	3.9
23b	H	CH_3	H	H	1.3	3.1
23c	Cl	H	H	H	1.9	3.9
27a	H	H	CH_3	H	1.5	1.0
27b	H	H	CH_3	CH_3	0.5	0.8
furosemide					1.0	1.0

[a,b]See footnotes to *table I*.

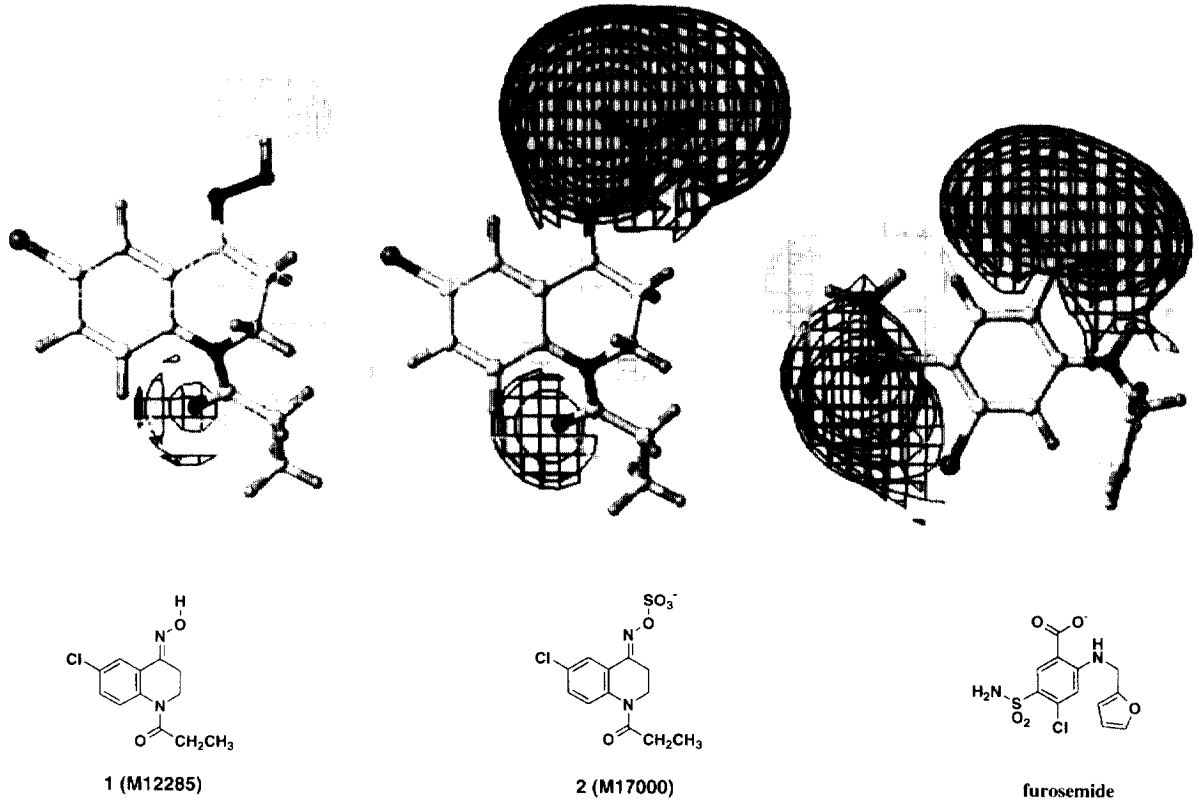

Figure 8. Electrostatic potential energy contour maps of **1 (M12285)**, **2 (M17000)** and furosemide. The thick line is the contour at –30 kcal/mol and the thin line at 10 kcal/mol of the electrostatic potential energy.

nal groups essential to interact with the cotransporter, as shown by computer analysis. Although various derivatives synthesized here showed a high diuretic activity, compound **3 (M17055)** was considered the best for the development of diuretic activity and its pharmacological features were examined in detail [21, 22]. Clinical studies on this compound are presently underway.

6. Experimental protocols

6.1. Chemistry

Melting points were determined on a Mettler FP-800 hot stage melting point apparatus and uncorrected. ^{1}H-NMR spectra were taken on a JEOL FX-90A spectrometer with Me_4Si as internal standard. Signal multiplicities are represented by s (singlet), d (doublet), dd (double doublet), t (triplet), and m (multiplet). Chemical shifts were expressed in ppm and coupling constants (J) in hertz (Hz). Low-mass spectra (EI-MS) and high-resolution mass spectra (HRMS or HR-FAB-MS) were obtained on a JEOL DX-300 and a JEOL SX-102A mass spectrometer. Elemental analysis was carried out with a Carlo Erba model 1106 analyzer and the results were within ± 0.40% of the calculated values. For column chromatography, silica gel (Kieselgel 60, 70–230 mesh, Merck) was used.

Melting points, formula and ^{1}H-NMR data for synthesized 2,3-dihydro-4(1*H*)-quinolinone 4-oxime-*O*-sulfonic acid derivatives were summarized in *table V*.

6.1.1. 6-Chloro-2,3-dihydro-1-propyl-4(1H)-quinolinone 4-oxime-O-sulfonic acid potassium salt ***11***

A mixture of compound **6** (5.5 g, 30 mmol), 1-iodopropane (11.3 g, 67 mmol), K_2CO_3 (4.6 g, 33 mmol) and CuO (0.08 g, 1 mmol) was stirred for 5 h at 110–120 °C and then the solvent was removed by evaporation. The residue was purified by silica

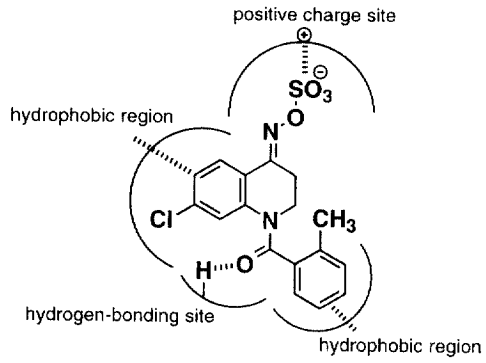

Figure 9. Proposed model of Na^+–K^+–$2Cl^-$ cotransporter active sites bound with **3** (**M17055**) interacting at the positive charge site, hydrogen-bonding site and hydrophobic regions on the binding protein.

gel column chromatography with hexane–CH_2Cl_2 (1:1) as an eluent to give 6-chloro-2,3-dihydro-1-propyl-4(1*H*)-quinolinone **10** (1.1 g, 16%). mp 103–105 °C. MS *m/z*: 223 (M^+). NMR ($CDCl_3$): 0.96 (3H, t, *J* = 7.0), 1.31–1.82 (2H, m), 2.62 (2H, t, *J* = 7.0), 3.27 (2H, t, *J* = 7.0), 3.47 (2H, t, *J* = 7.0), 6.57 (1H, d, *J* = 10.0), 7.20 (1H, dd, *J* = 10.0, *J* = 2.0), 7.72 (1H, d, *J* = 2.0).

To a mixture of compound **10** (1.6 g, 6.8 mmol), MeOH (30 mL) and CH_2Cl_2 (20 mL) was added hydroxylamine-*O*-sulfonic acid (1.2 g, 10.6 mmol) at room temperature. The mixture was stirred at room temperature for 30 min and aqueous K_2CO_3 (1.5 g in 2 mL H_2O, 10.6 mmol) was added. The reaction mixture was stirred at room temperature for 5 h and the solvent was removed by evaporation. The residue was purified by silica gel column chromatography with CH_2Cl_2–MeOH (5:1) as the eluent to give a white solid which was recrystallized from MeOH–CH_2Cl_2 to give **11** (1.4 g, 58%).

6.1.2. 7-Chloro-2,3-dihydro-1-(2-methylbenzoyl)-4(1H)-quinolinone 4-oxime-O-sulfonic acid potassium salt **3** *(**M17055**)*

To a mixture of 7-chloro-2,3-dihydro-4(1*H*)-quinolinone **18** (20.0 g, 0.110 mol), pyridine (26.0 g, 0.329 mol) and CH_2Cl_2 (200 mL) was added 2-methylbenzoyl chloride (26.0 g, 0.168 mol) at room temperature with stirring. The mixture was heated at reflux for 4 h, poured into H_2O and extracted with CH_2Cl_2. The extract was washed successively with 1 M aqueous HCl and H_2O, dried over Na_2SO_4 and evaporated. Recrystallization from CH_2Cl_2–hexane gave 7-chloro-2,3-dihydro-1-(2-methylbenzoyl)-4(1*H*)-quinolinone (**24**) (28.0 g, 85%). mp 107–108 °C. MS *m/z*: 299 (M^+). NMR (DMSO-d_6): 2.30 (3H, s), 2.82 (2H, t, *J* = 6.3), 4.03 (2H, t, *J* = 6.3), 7.27–7.55 (6H, m), 7.90 (1H, d, *J* = 8.6).

Compound **3** (12.0 g, 83%) was prepared from compound **24** (10.0 g, 33.3 mmol) by the same procedure as for compound **11**. The other compounds **14**, **17**, **20** and **23** were prepared in the same way.

6.1.3. 7-Chloro-2,3-dihydro-3,3-dimethyl-1-(2-methylbenzoyl)-4(1H)-quinolinone 4-oxime-O-sulfonic acid potassium salt **27b**

To a cooled (–75 °C to –70 °C) solution of compound **24** (20.0 g, 67.8 mmol) in dry THF (500 mL) was added *n*-BuLi (ca. 1.6 M in hexane: 50 mL, 80.0 mmol) and the mixture was stirred for 1 h. To the mixture was added a solution of MeI (14.3 g, 0.1 mol) in THF (20 mL) over 30 min. The reaction mixture was warmed to 0 °C over 2 h, acidified with 2 M aqueous HCl under cooling and extracted with Et_2O. The extract was washed successively with H_2O and brine, dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography with CH_2Cl_2–hexane (1.5:1) as the eluent to give 7-chloro-2,3-dihydro-3-methyl-1-(2-methylbenzoyl)-4(1*H*)-quinolinone **25a** (2.0 g, 10%) and 7-chloro-2,3-dihydro-3,3-dimethyl-1-(2-methylbenzoyl)-4(1*H*)-quinolinone (**25b**) (5.1 g, 23%). **25a**, m.p. 117–120 °C. NMR (DMSO-d_6): 1.06 (3H, d, *J* = 7.1), 2.30 (3H, s), 2.60–3.20 (1H, m), 3.70 (1H, dd, *J* = 11.7, *J* = 10.1), 4.11 (1H, dd, *J* = 11.7, *J* = 10.1), 7.20–7.60 (6H, m), 7.91 (1H, d, *J* = 8.4). HRMS Calc. for $C_{18}H_{16}ClNO_2$ (M^+): 313.0869. Found: 313.0889. **25b**, m.p. 110–111 °C. NMR (DMSO-d_6): 1.06 (6H, s), 2.35 (3H, s), 3.80 (2H, s), 7.20–7.70 (6H, m), 7.93 (1H, d, *J* = 8.8). HRMS Calc. for $C_{19}H_{18}ClNO_2$ (M^+): 327.1026. Found: 327.1012.

To a mixture of compound **25b** (14.9 g, 45.5 mmol), pyridine (7.2 g, 91.0 mmol) and EtOH (250 mL) was added hydroxylamine hydrochloride (6.3 g, 91.0 mmol). The mixture was heated at reflux for 2 h and poured into H_2O and the precipitated crystals were separated by filtration. The crude product was washed with H_2O, dried and recrystallized from EtOH to give 7-chloro-2,3-dihydro-3,3-dimethyl-1-(2-methylbenzoyl)-4(1*H*)-quinolinone 4-oxime **26b** (14.0 g, 90%). M.p. 181–183 °C. NMR (DMSO-d_6): 1.35 (6H, s), 2.25 (3H, s), 3.75 (2H, s), 7.10–7.50 (6H, m), 7.88 (1H, d, *J* = 8.6), 11.50 (1H, s). HR-FAB-MS Calc. for $C_{19}H_{20}ClN_2O_2$ $(M + H)^+$: 343.1213. Found: 343.1202.

To a solution of compound **26b** (14.0 g, 40.8 mmol) in CH_2Cl_2 (250 mL) was added a pyridine–sulfur trioxide complex (7.1 g, 44.9 mmol). The reaction mixture was stirred at room temperature for 24 h and the solvent was removed by evaporation. The residue was treated with MeOH (200 mL) and then aqueous K_2CO_3 (6.2 g in 10 mL H_2O, 45.0 mmol). Treatment as in **11** was conducted to obtain compound **27b**.

Compound **27a** was prepared from compound **25a** in the same way.

6.2. Crystallography

This process was conducted using colorless prismatic crystal of **3** (**M17055**), (0.30 x 0.15 x 0.05 mm) grown from methanol solution, Rigaku AFC5R diffractometer and graphite monochromated Cu Kα radiation (λ = 1.54178 Å). Cell constants were obtained from least-squares refinement at setting angles of 18 carefully centered reflections at 19.12° < 2θ < 46.48°. Intensity was determined by the ω–2θ scan technique up to $2\theta_{max}$ = 103.1°. Crystal data: formula $C_{17}H_{14}ClKN_2O_5S$, formula weight 480.98, triclinic system, space group P1, *a* = 13.641 (4), *b* = 11.081 (7), *c* = 7.517 (7) Å, α = 109.71 (6), β = 98.23 (6), γ = 91.27 (4)°, *V* = 1055 (2) Å, *Z* = 2, D_c = 1.513 g/cm^3.

The structure was determined by direct methods and refined by the least-squares method to *R* = 0.098 and R_w = 0.118 for 951 reflections with $I > 3\sigma(I)$. The atoms of K, Cl and S were refined anisotropically, while the other non-hydrogen atoms were refined isotropically because of small number of observed reflections relative to the number of atoms. The comparatively large *R* may thus possibly have been due to poor crystal quality. All calculations were made using the TEXSAN crystallographic software package [23], and ORTEP 2.0 for drawing [24].

Table V. Physical data of 2,3-dihydro-4(1*H*)-quinolinone 4-oxime-*O*-sulfonic acid derivatives.

Compound	mp (°C) (dec.)[a]	Formula[b]	^{1}H-NMR (DMSO-d_6, ppm)
2 **M17000**	205–206	$C_{12}H_{12}ClKN_2O_5S$	0.97 (3H, t, *J* = 7.3), 2.49 (2H, q, *J* = 7.3), 2.70 (2H, t, *J* = 6.3), 3.74 (2H, t, *J* = 6.3), 7.25–7.81 (2H, m), 7.95 (1H, d, *J* = 2.0)
3 **M17055**	189–191	$C_{17}H_{14}ClKN_2O_5S$	2.23 (3H, s), 2.81 (2H, t, *J* = 6.4), 3.73 (2H, t, *J* = 6.4), 6.90–7.55 (6H, m), 7.95 (1H, d, *J* = 8.9)
11	141–142	$C_{12}H_{14}ClKN_2O_4S$	0.89 (3H, t, *J* = 7.0), 1.25–1.75 (2H, m), 2.68 (2H, t, *J* = 7.0), 3.05–3.40 (4H, m), 6.68 (1H, d, *J* = 9.0), 7.12 (1H, dd, *J* = 9.0, *J* = 2.0), 7.64 (1H, d, *J* = 2.0)
14a	152–153	$C_{11}H_{10}ClKN_2O_5S$	2.21 (3H, s), 2.79 (2H, t, *J* = 6.2), 3.80 (2H, t, *J* = 6.2), 7.40–7.85 (3H, m)
14b	170–171	$C_{14}H_{16}ClKN_2O_5S$	1.29 (9H, s), 2.73 (2H, t, *J* = 6.3), 3.83 (2H, t, *J* = 6.3), 7.25–7.75 (3H, m)
14c	167–168	$C_{16}H_{18}ClKN_2O_5S$	1.09–1.87 (11H, m), 2.70 (2H, t, *J* = 6.4), 3.79 (2H, t, *J* = 6.4), 7.41–7.83 (3H, m)
14d	185–186	$C_{16}H_{12}ClKN_2O_5S$	2.81 (2H, t, *J* = 6.5), 3.82 (2H, t, *J* = 6.5), 6.81–7.81 (8H, m)
14e	155–156	$C_{17}H_{14}ClKN_2O_5S$	2.66 (2H, t, *J* = 6.4), 3.79 (2H, t, *J* = 6.4), 3.88 (2H, s), 7.05–7.79 (8H, m)
14f	170–171	$C_{18}H_{14}ClKN_2O_5S$	2.78 (2H, t, *J* = 6.4), 3.90 (2H, t, *J* = 6.4), 6.98 (1H, d, *J* = 4.0), 7.60 (1H, d, *J* = 14.0), 7.30–7.87 (8H, m)
14g	151–153	$C_{16}H_{11}Cl_2KN_2O_5S$	2.82 (2H, t, *J* = 6.5), 3.62 (2H, t, *J* = 6.5), 7.12–8.00 (7H, m)
14h	154–156	$C_{16}H_{10}Cl_3KN_2O_5S$	2.83 (2H, t, *J* = 6.5), 3.75 (2H, t, *J* = 6.5), 7.13–7.91 (6H, m)
14i	218–221	$C_{16}H_{10}Cl_3KN_2O_5S$	2.80 (2H, t, *J* = 6.4), 3.59 (2H, t, *J* = 6.4), 7.12–7.93 (6H, m)
14j	207–208	$C_{16}H_{10}Cl_3KN_2O_5S$	2.82 (2H, t, *J* = 6.4), 3.55 (2H, t, *J* = 6.4), 7.05–7.95 (6H, m)
17a	192–194	$C_{16}H_{11}Cl_2KN_2O_5S$	2.88 (2H, t, *J* = 6.5), 3.79 (2H, t, *J* = 6.5), 7.01–7.98 (7H, m)
17b	160–163	$C_{16}H_{10}Cl_2FKN_2O_5S$	2.80 (2H, t, *J* = 6.5), 3.59 (2H, t, *J* = 6.5), 6.80–8.00 (6H, m)
17c	206–207	$C_{16}H_{10}BrCl_2KN_2O_5S$	2.86 (2H, t, *J* = 6.5), 3.64 (2H, t, *J* = 6.5), 7.24–7.86 (6H, m)
17d	190–192	$C_{16}H_{10}Cl_2IKN_2O_5S$	2.87 (2H, t, *J* = 6.5), 3.79 (2H, t, *J* = 6.5), 7.30–7.88 (6H, m)
17e	159–160	$C_{17}H_{13}C_2KN_2O_5S$	2.15 (3H, s), 2.82 (2H, t, *J* = 6.5), 3.70 (2H, t, *J* = 6.5), 6.85–7.83 (6H, m)
17f	210–212	$C_{16}H_{11}Cl_2KN_2O_6S$	2.76 (2H, t, *J* = 6.0), 3.72 (2H, t, *J* = 6.0), 6.45–7.69 (6H, m)
17g	150–152	$C_{17}H_{13}Cl_2KN_2O_6S$	2.84 (2H, t, *J* = 6.5), 3.50 (3H, s), 3.75 (2H, t, *J* = 6.5), 6.60–7.81 (6H, m)
17h	189–190	$C_{18}H_{16}Cl_2KN_3O_5S$	2.72 (6H, s), 2.80 (2H, t, *J* = 6.3), 3.89 (2H, t, *J* = 6.3), 6.47–7.79 (6H, m)
20a	167–168	$C_{16}H_{12}ClKN_2O_5S$	2.85 (2H, t, *J* = 6.5), 3.87 (2H, t, *J* = 6.5), 6.99–7.98 (8H, m)
20b	190–192	$C_{15}H_{11}ClKN_3O_5S$	2.89 (2H, t, *J* = 6.5), 3.90 (2H, t, *J* = 6.5), 7.11–7.58 (3H, m), 7.74–8.08 (3H, m), 8.53–8.62 (1H, m)
20c	209–211	$C_{15}H_{11}ClKN_3O_5S$	2.93 (2H, t, *J* = 6.4), 3.90 (2H, t, *J* = 6.4), 7.20–7.62 (3H, m), 7.95–8.06 (2H, m), 8.70–8.77 (2H, m)
20d	242–243	$C_{15}H_{11}ClKN_3O_5S$	2.91 (2H, t, *J* = 6.5), 3.80 (2H, t, *J* = 6.5), 7.24–7.53 (2H, m), 7.90–8.09 (3H, m), 8.88–8.98 (2H, m)
20e	156–158	$C_{14}H_{10}ClKN_2O_5S_2$	2.87 (2H, t, *J* = 6.2), 3.93 (2H, t, *J* = 6.2), 7.09–8.02 (6H, m)
20f	156–158	$C_{14}H_{10}ClKN_2O_6S$	2.84 (2H, t, *J* = 6.2), 3.92 (2H, t, *J* = 6.2), 6.46–7.35 (3H, m), 7.68–8.04 (3H, m)
20g	155–157	$C_{16}H_{11}Cl_2KN_2O_5S$	2.84 (2H, t, *J* = 6.5), 3.68 (2H, t, *J* = 6.5), 7.12–8.00 (7H, m)
20h	171–172	$C_{16}H_{11}Cl_2KN_2O_5S$	2.87 (2H, t, *J* = 6.5), 3.79 (2H, t, *J* = 6.5), 7.05–7.95 (7H, m)
20i	111–112	$C_{16}H_{11}Cl_2KN_2O_5S$	2.83 (2H, t, *J* = 6.5), 3.81 (2H, t, *J* = 6.5), 6.95–7.91 (7H, m)
20j	134–136	$C_{17}H_{14}ClKN_2O_5S$	2.32 (3H, s), 2.85 (2H, t, *J* = 6.4), 3.86 (2H, t, *J* = 6.4), 7.14–8.26 (7H, m)
20k	192–193	$C_{17}H_{14}ClKN_2O_5S$	2.34 (3H, s), 2.85 (2H, t, *J* = 6.4), 3.86 (2H, t, *J* = 6.4), 7.08–8.02 (7H, m)
20l	173–175	$C_{17}H_{14}ClKN_2O_6S$	2.80 (2H, t, *J* = 6.4), 3.46 (3H, s), 4.09 (2H, t, *J* = 6.4), 6.79–7.89 (7H, m)
20m	176–178	$C_{18}H_{16}ClKN_2O_5S$	1.14 (3H, t, *J* = 7.6), 2.59 (2H, q, *J* = 7.6), 2.80 (2H, t, *J* = 6.4), 3.73 (2H, t, *J* = 6.4), 6.91–8.02 (7H, m)
20n	199–201	$C_{19}H_{18}ClKN_2O_5S$	1.20 (6H, d, *J* = 7.0), 2.85 (2H, t, *J* = 6.4), 3.05 (1H, m), 3.75 (2H, t, *J* = 6.4), 7.05–8.00 (7H, m)
23a	184–185	$C_{17}H_{13}Cl_2KN_2O_5S$	2.21 (3H, s), 2.80 (2H, t, *J* = 6.4), 3.69 (2H, t, *J* = 6.4), 7.09–7.91 (6H, m)
23b	138–139	$C_{18}H_{16}ClKN_2O_5S$	2.20 (3H, s), 2.30 (3H, s), 2.82 (2H, t, *J* = 6.4), 3.76 (2H, t, *J* = 6.4), 7.09–8.03 (6H, m)
23c	201–203	$C_{17}H_{13}Cl_2KN_2O_5S$	2.29 (3H, s), 2.81 (2H, t, *J* = 6.4), 3.78 (2H, t, *J* = 6.4), 7.09–8.03 (6H, m)
27a	197–199	$C_{18}H_{16}ClKN_2O_5S$	1.10 (3H, t, *J* = 7.0), 2.30 (3H, s), 3.40 (1H, m), 3.60 (2H, d, *J* = 10.0), 7.20–7.85 (7H, m)
27b	199–202	$C_{19}H_{18}ClKN_2O_5S$	1.31 (6H, s), 2.30 (3H, s), 3.70 (2H, s), 7.00–7.40 (6H, m), 7.89 (1H, d, *J* = 8.4)

[a]Recrystallization solvent CH_2Cl_2–MeOH; [b]all compounds were analyzed for C, H and N. Analytical results obtained for these elements were within ± 0.4% of the calculated values for the formulae shown.

6.3. Methods of computation chemistry

6.3.1. Computer programs

The ab initio molecular orbital calculation program GAUSSIAN 92 (GAUSSIAN Inc.), semiempirical molecular orbital calculation program MOPAC 6.0 (JCPE), and molecular modeling package software SYBYL 6.0 (TRIPOS Inc.) were run on a Indigo 2 work station (Silicon Graphics Inc.).

6.3.2. Molecular modeling

The starting geometries of compound **1** (**M12285**) and **2** (**M17000**) were constructed from the X-ray crystal structure of compound **3** (**M17055**) and modified where necessary using the fragment library of SYBYL 6.0. Those geometries were optimized by the semiempirical molecular orbital AM 1 method in MOPAC 6.0. The molecular geometry of furosemide was provided by the Cambridge Structural Databases (CSD).

6.3.3. Electrostatic potential contour map preparation

Electrostatic potential was calculated using the classical Coulomb's equation, which charges were estimated by CHELP method using 3-21G* basis set provided with GAUSSIAN 92. Contour map of electrostatic potential was graphically represented by the isosurface of specific energy (–30 or 10 kcal/mol).

6.4. Pharmacology

6.4.1. i.r.a.: injection via renal artery

Mongrel dogs weighing 7 to 15 kg were used after overnight fasting with free access to H_2O. They were anesthetized with pentobarbital (30 mg/kg, i.v.) and ventilated. Following a left flank incision, the left ureter was cannulated for urine collection and an L-shaped needle connected to polyethylene tubing was inserted into the left renal artery for drug administration. The drug injection route was maintained by infusing 0.9% aqueous NaCl (saline) at 0.05 mL/kg/min. Following the operation, prime 3 mL/kg saline was given initially and saline was continuously infused at 0.1 mL/kg/min from a catheter in the femoral vein. After an equilibration period of 1–2 h, urine was collected every 5 min. All compounds were dissolved in alkaline solution prior to left renal artery injection at 0.01 mg/kg. Administrations were conducted at appropriate intervals.

Increase in urine output in 20 min (ΔUV_{20}) was computed as follows:

ΔUV_{20} = (Urine output in 20 min after the drug injection) – (Urine output in 20 min before the drug injection).

Diuretic activity was expressed as the ratio of ΔUV_{20} to that for furosemide injected in the same dog at the same dose.

6.4.2. i.v.: injection intravenously

Experimental procedures were essentially as for i.r.a. The few exceptions are as follows: (1) no needle was attached to the renal artery; (2) infusion rate of saline into a femoral vein was always 0.15 mL/kg/min; (3) urine was collected every 10 min; (4) compound dosage into femoral vein was 0.1 mg/kg.

Increase in urine output in 90 min (ΔUV_{90}) was determined as follows:

ΔUV_{90} = (Urine output in 90 min after the drug injection) – [(Urine output in 30 min before the drug injection) x 3].

Diuretic activity was expressed as ratio of ΔUV_{90} to that for furosemide administered at the same dose to the same dog.

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