Aryloxy Acetic Acid Diuretics with Uricosuric Activity. I. Polycyclic Aryloxy Acetic Acids

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In order to obtain lead compounds for uricosuric diuretics, various polycyclic aryloxy acetic acids [isoindole derivative (7), quinazoline derivative (15), benzopyran derivative (20), xanthone derivative (24), benzofuran derivative (30) and indene derivative (36)] were prepared. These compounds were evaluated for diuretic activity in rats, uricosuric activity in rats and antihypertensive activity in 11-deoxycorticosterone acetate (DOCA)/salt hypertensive rats. Among the compounds, 20 showed potent diuretic, uricosuric and moderate antihypertensive activities. Therefore, we selected 20 as a lead compound for development of new uricosuric diuretics.

Keywords aryloxy acetic acid; 2,3-dihydro-1-oxo-1*H*-isoindole; 3,4-dihydro-4-oxo-3*H*-quinazoline; 4-oxo-4*H*-1-benzopyran; xanthone; benzo[*b*]furan; indene; ((5-chloro-4-oxo-3-phenyl-4*H*-1-benzopyran-7-yl)oxy)acetic acid; diuretic; uricosuric; antihypertensive activity

The thiazides have a long history of effective control of a major segment of the hypertensive population. However, long-term administration of the thiazides results in side effects such as hyperuricemia, hypokalemia, and hyperglycemia. In the search for new diuretics which do not cause adverse reactions such as hyperuricemia, many compounds such as tienilic acid,[1] indacrinone,[2] S-8666,[3] and related compounds (IV,[4a] V,[4b] VI[4c]) have been examined, but few drugs have been marketed (Fig. 1).

We undertook research relating to acylphenoxyacetic acids in order to obtain a lead compound for the development of new uricosuric diuretics. In general, the compounds which are represented by formula VII show diuretic activities.[5] Molecular features found to result in potent diuretic and uricosuric activities for this series include the following: (1) Chloro substituents at positions 2 and 3 of the phenoxyacetic acid aromatic ring, a bulky substituent on the acyl group and formation of a bond between the α-position of the carbonyl group and position 5, as exemplified by indacrinone (MK-196),[2] or (2) a halogen substituent at position 2, a bulky substituent on the acyl group and introduction of a bioisoster instead of

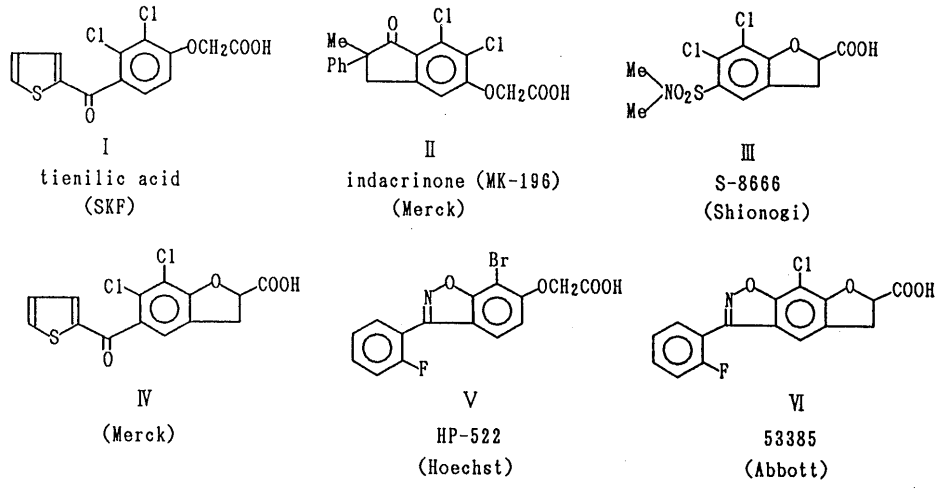

Fig. 1

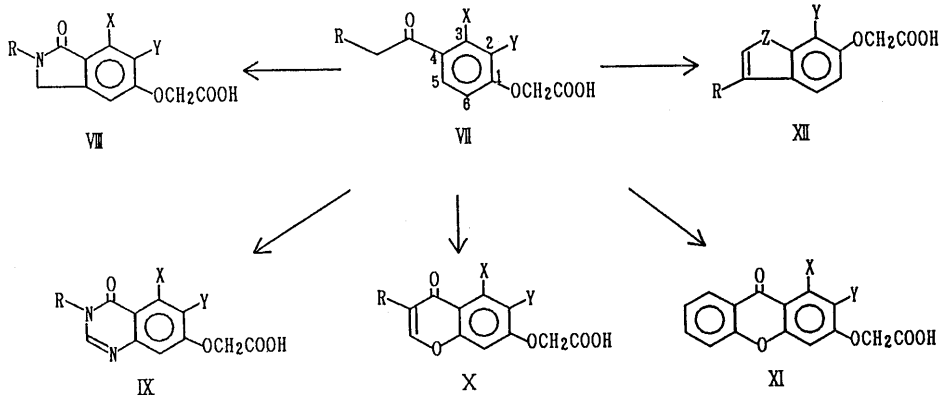

Fig. 2

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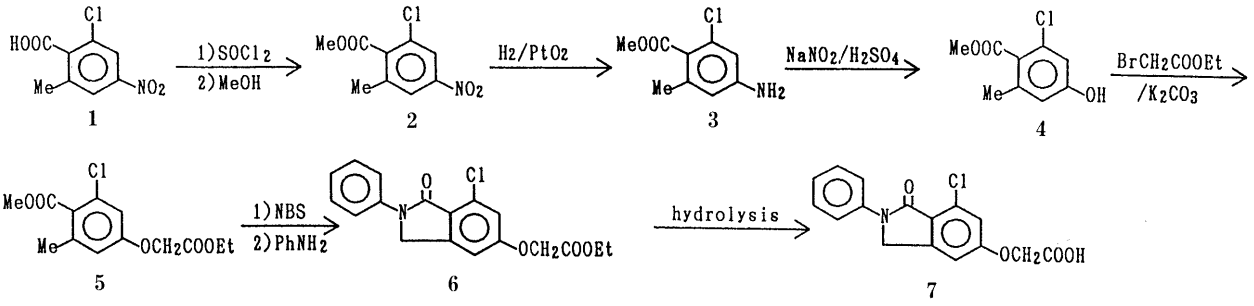

Chart 1

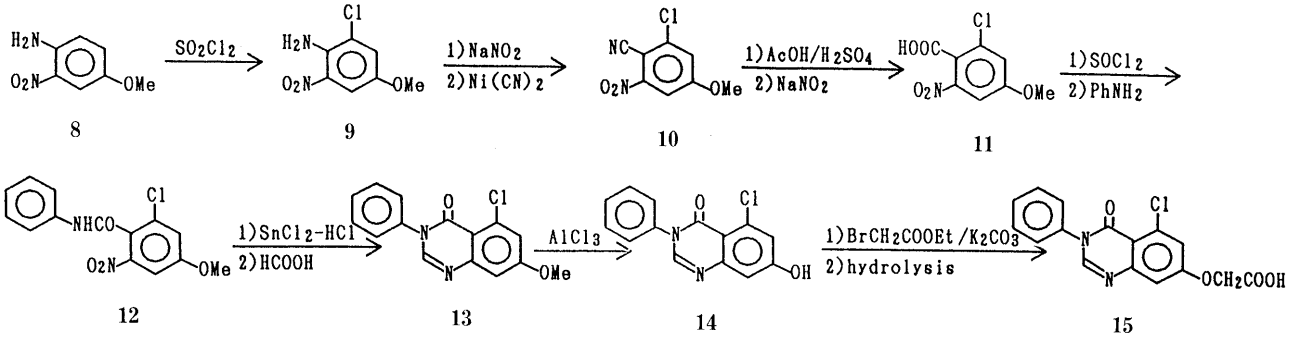

Chart 2

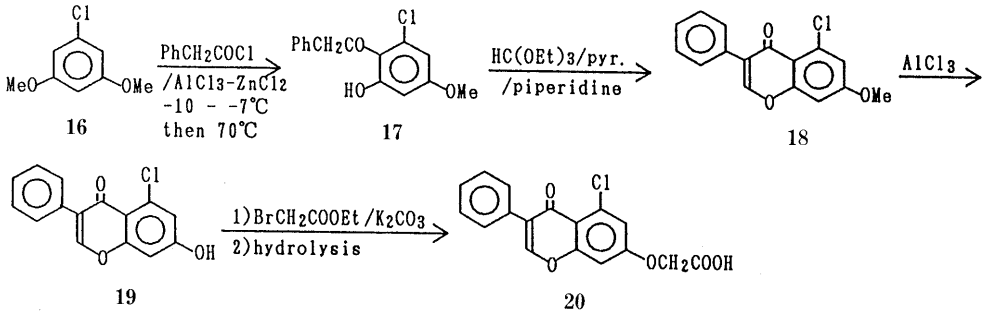

Chart 3

the carbonyl group, with formation of a bond between the bioisoster and position 3, as exemplified by Hp-522.[4b]

We therefore extended this annelation concept to the preparation of new ring-annelated compounds: the 2,3-dihydro-1-oxo-1*H*-isoindole derivative VIII (**7**: R=phenyl, X=Cl, Y=H), the 3,4-dihydro-4-oxo-3*H*-quinazoline derivative IX (**15**: R=phenyl, X=Cl, Y=H), the 4-oxo-4*H*-1-benzopyran derivative X (**20**: R=phenyl, X=Cl, Y=H), the xanthone derivative XI (**24**: X=Cl, Y=H), the benzofuran derivative XII (**30**: R=phenyl, Y=Br, Z=O) and the indene derivative XII (**36**: R=phenyl, Y=Cl, Z=CH_2).

These compounds were synthesized and tested for diuretic, uricosuric and antihypertensive activities. Herein we report the syntheses and biological activities of the newly designed compounds.

Chemistry The compounds prepared for this study are shown in Tables II—VI and their syntheses are outlined in Charts 1—6.

Synthesis of ((7-chloro-2,3-dihydro-1-oxo-2-phenyl-1*H*-isoindol-5-yl)oxy)acetic acid (**7**) was carried out by employing the reaction sequence outlined in Chart 1. Esterification of 2-chloro-6-methyl-4-nitrobenzoic acid (**1**), which was prepared from 2-methyl-4-nitroaniline *via* five reaction steps by the reported method,[6] and successive reduction of the nitro group provided the aniline derivative (**3**) in high yield. Subsequently, the phenol (**4**) obtained by diazotization and hydrolysis from **3** was converted to the ester (**5**) by alkylation with ethyl bromoacetate/K_2CO_3. Bromination of **5** with *N*-bromosuccinimide (NBS) followed by ring closure with aniline gave ethyl ((7-chloro-2,3-dihydro-1-oxo-2-phenyl-1*H*-isoindol-5-yl)oxy)acetate (**6**) in low yield, and this was hydrolyzed to provide the desired compound (**7**).

((5-Chloro-3,4-dihydro-4-oxo-3-phenyl-3*H*-quinazolin-7-yl)oxy)acetic acid (**15**) was prepared as shown in Chart 2. The starting material (**8**) was chlorinated with sulfuryl chloride. The resulting aniline derivative (**9**) was diazotized by the method of Mallory[7] and then treated with $Ni(CN)_2$, which was prepared by the reaction of $NiCl_2$ with NaCN, to give the benzonitrile derivative (**10**). Reaction of **10** with $AcOH/H_2SO_4$, diazotization, and successive degradation reaction led to the benzoic acid derivative (**11**). Chlorination of **11** with thionyl chloride, and reaction with aniline gave the anilide (**12**). Compound **12** was reduced with $SnCl_2$/concentrated HCl and then treated with formic acid

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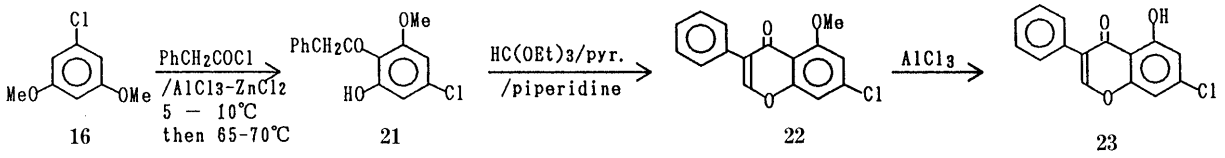

Chart 4

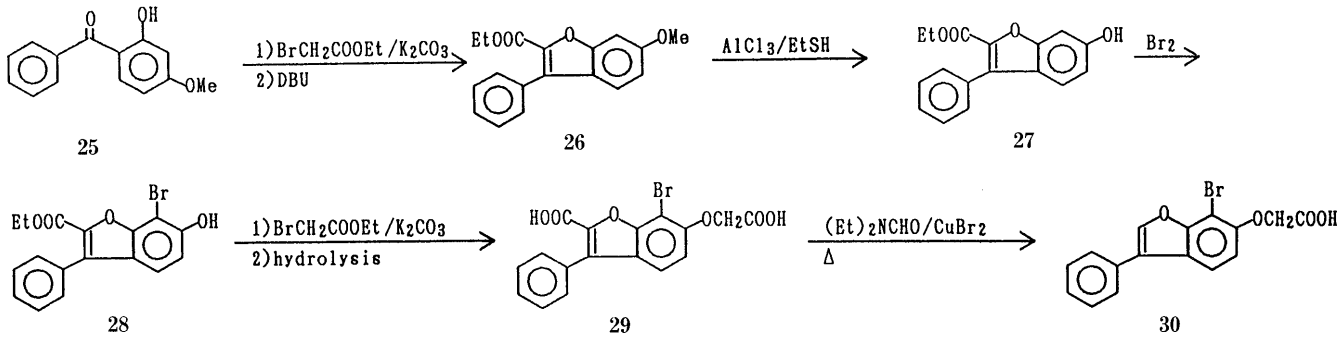

Chart 5

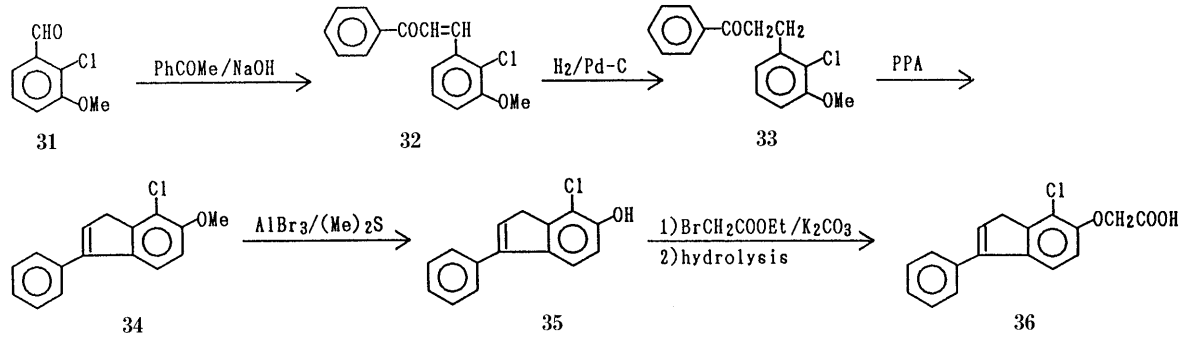

Chart 6

to yield 5-chloro-3,4-dihydro-7-methoxy-4-oxo-3-phenyl-3*H*-quinazoline (**13**). Ether cleavage of **13** with anhydrous $AlCl_3$, alkylation with ethyl bromoacetate/K_2CO_3, and subsequent hydrolysis gave the desired compound (**15**).

((5-Chloro-4-oxo-3-phenyl-4*H*-1-benzopyran-7-yl)oxy)-acetic acid (**20**) was prepared by the route illustrated in Chart 3. Friedel–Crafts reaction at −10——7 °C of 1-chloro-3,5-dimethoxybenzene (**16**) with phenylacetyl chloride and $AlCl_3$–$ZnCl_2$ and subsequent demethylation at 70 °C provided 1-(2-chloro-6-hydroxy-4-methoxyphenyl)-2-phenylethan-1-one (**17**) in moderate yield. Cyclization of **17** to form the benzopyran nucleus was carried out by the general method using ethyl orthoformate/pyridine/piperidine.[8] The resulting compound (**18**) was converted to **20** *via* 5-chloro-7-hydroxy-4-oxo-3-phenyl-4*H*-1-benzopyran (**19**) by a similar route to that described in Chart 2. On the other hand, Friedel–Crafts reaction at 5—10 °C of **16** with phenylacetyl chloride and $AlCl_3$–$ZnCl_2$ and subsequent demethylation at 65—70 °C gave 1-(4-chloro-2-hydroxy-6-methoxyphenyl)-2-phenylethan-1-one (**21**) as the main product, which was led to 7-chloro-5-hydroxy-4-oxo-3-phenyl-4*H*-1-benzopyran (**23**) (Chart 4) by a similar method to that described above. On the basis of the following findings, it is concluded that **19** has a 7-hydroxy group, and **23** has a 5-hydroxy group which can form an intramolecular hydrogen bond to the 4-carbonyl group. The infrared (IR) spectrum (KBr) of **23** showed a hydroxy absorption band at 3090 cm^{-1} attributable to the 5-OH group. On the other hand, the IR spectrum (KBr) of **19** showed a hydroxy absorption band at 3200 cm^{-1} attributable to the free phenolic OH group at position 7. In dilute solutions (0.0011 mmol/ml in $CDCl_3$), where intermolecular association is minimized, the signal of the 5-OH group on the proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **23** was shifted to lower field (12.78 ppm) than that (6.04 ppm) of the 7-OH group of **19**. The comparison of **19** with **23** on thin-layer chromatography (TLC) showed that the *Rf* value of **23** was larger than that of **19** (see Experimental).

((1-Chloroxanthon-3-yl)oxy)acetic acid (**24**) was prepared according to the reported method.[9]

((7-Bromo-3-phenylbenzo[*b*]furan-6-yl)oxy)acetic acid (**30**) was prepared by means of the reaction sequence shown in Chart 5. Alkylation of 2-hydroxy-4-methoxybenzophenone (**25**)[10] with ethyl bromoacetate/K_2CO_3, and subsequent treatment with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) afforded the 6-methoxy-benzofuran (**26**). The ether cleavage of **26** with $AlCl_3$/EtSH[11] gave the 6-hydroxybenzofuran (**27**) in moderate yield. Bromination of **27** with equimolar bromine, and alkylation with ethyl bromoacetate/K_2CO_3, followed by hydrolysis produced the dicarboxylic acid (**29**) in high yield. Compound **29** was selectively decarboxylated by heating with $CuBr_2$ in Et_2NCHO to give the benzofuran derivative (**30**).

((7-Chloro-3-phenylinden-6-yl)oxy)acetic acid (**36**) was prepared according to the synthetic route depicted in

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Chart 6. The benzaldehyde derivative (**31**), which was prepared as suggested by Ginsburg,[12] was treated with acetophenone under basic conditions to give the α,β-unsaturated ketone (**32**). Compound **32** which consisted of a mixture of (*E*) and (*Z*) isomers (the ratio was about 1 : 1) was hydrogenated by catalytic reduction to give the propanone derivative (**33**). A ring annelation to position 6 of **33** by using polyphosphoric acid (PPA) afforded the 6-methoxyindene (**34**), which was dealkylated by $AlBr_3$/$(Me)_2S$[13] to produce the hydroxy product (**35**). This compound was converted to the corresponding oxyacetic acid (**36**).

Biological Activities The compounds bearing an oxyacetic acid side chain prepared in this study were tested for diuretic and uricosuric activities in Wistar rats and for antihypertensive activity in 11-deoxycorticosterone acetate (DOCA)/salt hypertensive rats (see Experimental). The results are shown in Table I. Tienilic acid (TA), indacrinone (MK-196) and **24** were used as reference compounds.

(1) Diuretic Activity The excretion of urine after the administration of the reference compounds and the test compounds paralleled that of Na^+.

The diuretic activity of **20** was more potent than those of TA and **24**, and equipotent to that of MK-196. The diuretic activity of **7** was lower than that of **20**. On the other hand, **15**, **30** and **36** caused no detectable change in the excretion of urine.

(2) Uricosuric Activity Uric acid is the final product of purine metabolism in humans and some primates. However, in nonprimates such as rats and dogs, uric acid is further degraded to allantoin by uricase. It is therefore difficult to detect uricosuric activity in nonprimate animals. However, it was reported that uricosuric activity of TA was evaluated in rats by using the renal clearance method.[14] Similarly, in the present study, we observed that uricosuric agents such as TA and MK-196 produced increases in the fractional excretion rate of uric acid (FEua) without changing the concentration of uric acid in serum and urine.

The uricosuric activity (FEua) of **20** was more potent than those of TA, MK-196 and **24**. In contrast, **7** showed no uricosuric activity. Further investigations on the mechanisms of uricosuric action are in progress.

(3) Antihypertensive Activity In this study, the predrug value of systolic blood pressure (SBP) in DOCA/salt hypertensive rats was approximately 110 mmHg. In control rats, SBP subsequently increased to the level of 191 ± 6 mmHg ($n=8$), 3 weeks later.

The antihypertensive activity of **20** was equivalent to those of MK-196 and **24**, however, **7** was less active than MK-196.

From the biological evaluations described above, it was clear that **20** had the most favorable profile as a uricosuric diuretic. We therefore selected **20** as a lead compound for development of new uricosuric diuretics, and further investigations are in progress.

TABLE I. Biological Activities of Aryloxyacetic Acids

Compound No.	Diuretic[a]	Uricosuric[b]	Antihypertensive[c]
7	+	−	+
15	−	NT	NT
20	+++	+++	+++
24	++	+	+++
30	−	NT	NT
36	−	NT	NT
TA	±	+	−
MK-196	+++	+	+++

a) Urine volume (ml/kg/5 h, 100 mg/kg, *p.o.* in rats): $-\leqq 0$, $0 < \pm \leqq 10$, $10 < + \leqq 20$, $20 < ++ \leqq 30$, $30 < +++$. *b*) Excretion of uric acid (%, FE_{ua}, 200 mg/kg, *p.o.* in rats): $-\leqq 0$, $0 < + \leqq 50$, $50 < ++ \leqq 150$, $150 < +++$, NT; not tested. *c*) Systolic blood pressure (Δ mmHg, 100 mg/kg/d, *p.o.* in DOCA/salt hypertensive rats): $-\leqq 10$, $10 < + \leqq 20$, $20 < ++ \leqq 40$, $40 < +++$, NT; not tested.

Experimental

Melting points are uncorrected. IR spectra were taken on a Hitachi 285 spectrometer. ^{1}H-NMR spectra were taken on Hitachi R40 and JNM-FX90Q spectrometers with tetramethylsilane (TMS) as an internal standard. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet). Chemical shifts are expressed in δ values and coupling constants are given in hertz. For column chromatography, Silica gel 60 (E. Merck, 0.063—0.200 mm) was used.

2-Chloro-6-methyl-4-nitrobenzoic Acid (1) The material (**1**) was prepared according to the reported method.[6b]

Methyl 2-Chloro-6-methyl-4-nitrobenzoate (2) A solution of **1** (19.5 g, 90.4 mmol) in $SOCl_2$ (180 ml) was refluxed for 2 h and then excess $SOCl_2$ was evaporated off *in vacuo*. The resulting oily product was taken up in MeOH (200 ml), and the solution was refluxed for 4.5 h, then concentrated to precipitate crystals, which were collected by filtration to give **2** (17.8 g, 86%) (Table II).

Methyl 4-Amino-2-chloro-6-methylbenzoate (3) Compound **2** (31.4 g, 0.137 mol) in AcOEt (500 ml) was catalytically hydrogenated with PtO_2 (800 mg) under atmospheric pressure with absorption of 9.2 l of H_2 gas. After removal of the catalyst by filtration, the solvent was evaporated off *in vacuo*. The resulting residue was dissolved in a small amount of Et_2O and the insoluble product was filtered off. The filtrate was evaporated *in vacuo* to yield **3** (26.6 g, 97.4%) as pale yellow crystals (Table II).

Methyl 2-Chloro-4-hydroxy-6-methylbenzoate (4) Compound **3** (98 g, 0.49 mol) was dissolved in 10% H_2SO_4 (2.5 l) with heating at 70—80 °C and then a solution of (300 ml) of $NaNO_2$ (37.3 g, 0.53 mol) was added in small portions with stirring at the same temperature. After heating for an additional 1.5 h, the reaction mixture was cooled to room temperature and extracted with C_6H_6. The organic layer was dried (Na_2SO_4) and evaporated *in vacuo* to give a residue. The resulting crude product was purified by column chromatography on silica gel with C_6H_6 as the eluent to provide **4** (77 g, 78%) as a brownish solid. ^{1}H-NMR ($CDCl_3$): 6.64 (1H, d, $J=2$), 6.50 (1H, d, $J=2$), 3.91 (3H, s), 2.23 (3H, s).

Ethyl ((3-Chloro-5-methyl-4-methoxycarbonylphenyl)oxy)acetate (5) A mixture of **4** (16.3 g, 81 mmol), ethyl bromoacetate (20.3 g, 0.122 mol) and K_2CO_3 (20.3 g, 0.122 mol) in *N*,*N*-dimethylformamide (DMF) (340 ml) was heated with stirring at 60—70 °C for 5 h. The solvent was evaporated off *in vacuo*, and the resulting oily residue was poured into ice-cooled H_2O, and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. The resulting residue was purified by column chromatography on silica gel with C_6H_6 as the eluent to give **5** (19.9 g, 85.7%) as a brownish solid. ^{1}H-NMR ($CDCl_3$): 6.70 (1H, d, $J=2$), 6.60 (1H, d, $J=2$), 4.52 (2H, s), 4.22 (2H, q, $J=7$), 3.87 (3H, s), 2.30 (3H, s), 1.27 (3H, t, $J=7$). Compound **5** was used for the next reaction step without further purification.

Ethyl ((7-Chloro-2,3-dihydro-1-oxo-2-phenyl-1*H*-isoindol-5-yl)oxy)-acetate (6) A mixture of **5** (19.8 g, 69.1 mmol), NBS (14.8 g, 82.9 mmol) and benzoic peroxide (100 mg) in CCl_4 (500 ml) was refluxed for 6 h. After filtration to remove an insoluble product, a solution of aniline (64.3 g, 0.69 mol) in CCl_4 (200 ml) was added to the filtrate. The mixture was stirred for 1 h at room temperature, and then heated for an additional 1 h at 90—100 °C. After cooling, the reaction mixture was successively washed with 4 N HCl (520 ml) and H_2O, dried (Na_2SO_4), and then evaporated *in vacuo*. The resulting oily residue (18.8 g) was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give **6** (4.3 g, 18%) from **4** as white needles (Table II).

((7-Chloro-2,3-dihydro-1-oxo-2-phenyl-1*H*-isoindol-5-yl)oxy)acetic Acid (7) To a solution of **6** (4.2 g, 12.1 mmol) in DMF (40 ml), 10% NaOH (15 ml) was added in portions with stirring at room temperature. Stirring

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TABLE II. ((7-Chloro-2,3-dihydro-1-oxo-2-phenyl-1*H*-isoindol-5-yl)oxy)acetic Acid (**7**) and Related Compounds

Compound No.	mp (°C) (Solv.)	Yield (%)	Analysis (%) Calcd (Found)			IR (KBr) (cm^{-1})	Solv.[b]	^{1}H-NMR Chemical shift (δ)
			C	H	N			
	90—92	86.0	$C_9H_8ClNO_4$			1730	C	8.00 (1H, d, J=3), 7.90 (1H, d, J=3), 3.95 (3H, s),
2	(MeOH)		47.07	3.51	6.10			2.40 (3H, s)
			(46.63	3.47	6.11)			
3	74—77	97.4	$C_9H_{10}ClNO_2$			1700	C	6.44 (1H, d, J=3), 6.30 (1H, d, J=3), 3.87 (3H, s),
			54.14	5.05	7.02			3.78 (2H, s), 2.23 (3H, s)
			(54.43	5.00	7.10)			
	150—152	18.0[a]	$C_{18}H_{16}ClNO_4$			1735, 1695	C	7.82—7.64 (2H, m), 7.46—7.01 (3H, m), 6.91—6.71
6	(EtOH)		62.52	4.66	4.05			(2H, m), 4.65 (4H, s), 4.26 (2H, q, J=8), 1.31 (3H,
			(62.15	4.75	3.98)			t, J=8)
	207—209	83.0	$C_{16}H_{12}ClNO_3$			1700	D	7.82—7.72 (2H, m), 7.50—7.15 (3H, m), 7.15—7.00
7	(DMF–MeCN)		60.10	3.78	4.38			(2H, m), 4.87 (2H, s), 4.82 (2H, s)
			(60.05	3.89	4.51)			

a) Yield from **5**. *b*) C=$CDCl_3$, D=DMSO-d_6.

was continued for 1 h, then the reaction mixture was poured into H_2O (300 ml), and acidified with concentrated HCl. The precipitated crystals were collected by filtration to give **7** (3.2 g, 82.7%) as white needles (Table II).

2-Chloro-4-methoxy-6-nitroaniline (9) Sulfuryl chloride (0.96 ml, 12 mmol) was added to a solution of **8** (2.0 g, 12 mmol) in acetic acid (200 ml) at room temperature. After being stirred for 30 min, the solution was poured into ice-cold H_2O, and the whole was evaporated *in vacuo* to yield a brownish solid, which was purified by column chromatography on silica gel with C_6H_6 as the eluent to give **9** (0.6 g, 25%) as pale yellow needles (Table III).

2-Chloro-4-methoxy-6-nitrobenzonitrile (10) A solution of $NiCl_2 \cdot 6H_2O$ (4.5 g, 18.9 mmol) in H_2O (15 ml) was added to a solution of NaCN (10.3 g, 0.21 mol) in H_2O (40 ml), followed by an Na_2CO_3 solution (40 g, 0.377 mol) in H_2O (75 ml), and then the reaction mixture was cooled at 5 °C with stirring. A solution of $NaNO_2$ (2.2 g, 31.9 mmol) in concentrated H_2SO_4 (16 ml) was added to a solution of **9** (5.43 g, 26.8 mmol) in acetic acid (50 ml) in portions with stirring at room temperature. The obtained diazonium salt was added to the previously prepared solution which contained $Ni(CN)_2$ over 1 h at the same temperature. The reaction mixture was stirred for 3 h, then a solution of Na_2CO_3 (40 g, 0.377 mol) in H_2O (100 ml) was added. The resulting product was collected by filtration, and purified by column chromatography on silica gel with C_6H_6 as the eluent to give **10** (3.54 g, 62%) (Table III).

2-Chloro-4-methoxy-6-nitrobenzoic Acid (11) A mixture of **10** (2.82 g, 13.3 mmol), acetic acid (100 ml), concentrated H_2SO_4 (100 ml) and H_2O (40 ml) was heated at 140 °C with vigorous stirring. The reaction temperature was lowered to 100 °C, then a solution of $NaNO_2$ (1.54 g, 22.3 mmol) in H_2O (15 ml) was added, and the mixture was stirred at the same temperature for an additional 30 min. After cooling, the reaction mixture was poured into ice-cold H_2O, and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated *in vacuo* to give **11** (2.39 g, 78%) (Table III).

2-Chloro-4-methoxy-6-nitrobenzanilide (12) A mixture of benzoic acid **11** (2.37 g, 10.2 mmol) and $SOCl_2$ (50 ml) was refluxed for 1 h. The excess $SOCl_2$ was evaporated off *in vacuo* to give the acid chloride, to which aniline (3.72 g, 40 mmol) in C_6H_6 (20 ml) was added, and the mixture was stirred at room temperature for 2 h. The precipitated crystals were collected by filtration to give the anilide **12** (2.99 g, 96%) (Table III).

5-Chloro-3,4-dihydro-7-methoxy-4-oxo-3-phenyl-3*H*-quinazoline (13) A solution of $SnCl_2 \cdot 2H_2O$ (67 g, 0.297 mol) in EtOH (90 ml) was added dropwise to a mixture of the anilide **12** (29 g, 94.6 mmol), EtOH (45 ml) and concentrated HCl (90 ml), and then the mixture was stirred at room temperature for 3 h. The precipitated crystals were collected by filtration, successively washed with H_2O, saturated Na_2CO_3 and H_2O, and dried to give 2-chloro-4-methoxy-6-aminobenzanilide. The filtrate was collected, made basic by adding 20% NaOH and extracted with AcOEt. The AcOEt layer was washed with H_2O, dried (Na_2SO_4) and evaporated *in vacuo* to give the aniline derivative as pale brown crystals. The combined yield of the aniline derivative was 22 g (84%). mp 159—160 °C (C_6H_6). IR (KBr) cm^{-1}: 1660 (–CONH–). ^{1}H-NMR (DMSO-d_6): 10.20 (1H, br s), 7.73—7.53 (2H, m), 7.40—6.90 (3H, m), 6.24 (2H, br s), 5.33 (2H, br s), 3.69 (3H, s).

A mixture of the aniline derivative (21 g, 75.9 mmol) and formic acid (500 ml) was refluxed for 2 h. Excess formic acid was evaporated off *in vacuo* to yield a residue which was purified by column chromatography on silica gel. The resulting residue was recrystallized from EtOH to give **13** (12.4 g, 57%) (Table III).

5-Chloro-3,4-dihydro-7-hydroxy-4-oxo-3-phenyl-3*H*-quinazoline (14) A mixture of **13** (12.4 g, 43.2 mmol) and anhydrous $AlCl_3$ (17.3 g, 0.13 mol) in C_6H_6 (400 ml) was refluxed with vigorous stirring for 2 h. After cooling, the organic layer was removed by decantation, and ice-cold H_2O was added to the resulting insoluble residue. The mixture was vigorously agitated. The resulting solid was collected by filtration, washed with hot H_2O, and then recrystallized from EtOH to give **14** (7.2 g, 61%) (Table III).

((5-Chloro-3,4-dihydro-4-oxo-3-phenyl-3*H*-quinazolin-7-yl)oxy)acetic Acid (15) A mixture of **14** (7.0 g, 25.7 mmol), ethyl bromoacetate (4.5 g, 26.9 mmol) and K_2CO_3 (4.2 g, 30.4 mmol) in DMF (150 ml) was heated at 60 °C with stirring for 2 h. Then 10% NaOH (20 ml) was added, and the mixture was stirred at the same temperature for an additional 1 h. After cooling, the reaction mixture was acidified with 10% HCl, and the precipitated crystals were collected by filtration to give **15** (6.5 g, 77%) (Table III).

1-(2-Chloro-6-hydroxy-4-methoxyphenyl)-2-phenylethan-1-one (17) A solution of **16** (60.4 g, 0.35 mol) in dry $ClCH_2CH_2Cl$ (140 ml) was added dropwise to a mixture of anhydrous $AlCl_3$ (56 g, 0.42 mol) and $ZnCl_2$ (5.72 g, 42 mmol) in dry $ClCH_2CH_2Cl$ (510 ml) with stirring at 0 °C. The mixture was cooled with stirring at −10 °C, then a solution of phenyl acetylchloride (59 g, 0.38 mol) in $ClCH_2CH_2Cl$ (120 ml) was added dropwise while maintaining the temperature at −10—−7 °C. After the addition, the reaction mixture was stirred at room temperature for 1 h, then heated at 70 °C for 1 h, poured into ice-cooled 20% HCl (1 l), and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. The resulting residue was recrystallized from C_6H_6 to give **17** (45.2 g, 46.7%) as white prisms (Table IV).

5-Chloro-7-methoxy-4-oxo-3-phenyl-4*H*-1-benzopyran (18) A mixture of **17** (1.11 g, 4 mmol), ethyl orthoformate (7.6 ml), dry pyridine (10 ml) and dry piperidine (0.4 ml) was refluxed for 4 h. The reaction mixture was poured into ice-cooled 20% HCl (100 ml), and the insoluble material was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and then concentrated to dryness *in vacuo*. The resulting residue was purified by silica gel (50 g) column chromatography with C_6H_6 as the eluent to give **18** (0.53 g, 64%) (Table IV).

5-Chloro-7-hydroxy-4-oxo-3-phenyl-4*H*-1-benzopyran (**19**) was prepared from **18** in a similar manner to that used for the preparation of **14** from **13** (Table IV). ^{1}H-NMR (0.0011 mmol/ml in $CDCl_3$): 7.83 (1H, s, 2-H), 7.53—7.37 (5H, m, arom. H), 6.95 (1H, d, J=2.5, 6-H or 8-H), 6.80 (1H, d, J=2.5, 6-H or 8-H), 6.04 (1H, s, 7-OH).

((5-Chloro-4-oxo-3-phenyl-4*H*-1-benzopyran-7-yl)oxy)acetic acid (**20**) was prepared from **19** in a similar manner to that used for the preparation of **15** from **14** (Table IV).

1-(4-Chloro-2-hydroxy-6-methoxyphenyl)-2-phenylethan-1-one (21) A solution of phenyl acetylchloride (16.8 g, 0.109 mol) in dry $ClCH_2CH_2Cl$

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TABLE III. ((5-Chloro-3,4-dihydro-4-oxo-3-phenyl-3*H*-quinazolin-7-yl)oxy)acetic Acid (**15**) and Related Compounds

Compound No.	mp (°C) (Solv.)	Yield (%)	Analysis (%) Calcd (Found)			IR (KBr) (cm^{-1})	Solv.[a]	^{1}H-NMR Chemical shift (δ)
			C	H	N			
9	115—116 (C_6H_6)	25.0	$C_7H_7ClN_2O_3$ 41.50 (41.60)	3.48 (3.44)	13.83 (14.03)	3480, 3370 1500, 1210	D	7.45 (2H, s), 6.90 (2H, br s), 3.75 (3H, s)
10	127—128	62.0	$C_8H_5ClN_2O_3$ 45.20 (45.33)	2.37 (2.50)	13.18 (13.19)	2220	C	7.62 (1H, d, $J=3$), 7.26 (1H, d, $J=3$), 3.95 (3H, s)
11	158—160	78.0	$C_8H_6ClNO_5$ 41.49 (41.59)	2.61 (2.50)	6.05 (6.07)	1710	C–D	7.52 (1H, d, $J=3$), 7.26 (1H, d, $J=3$), 3.92 (3H, s)
12	188—190	96.0	$C_{14}H_{11}ClN_2O_4$ 54.83 (55.20)	3.61 (3.75)	9.13 (9.15)	1650	D	10.55 (1H, br s), 7.80—7.50 (4H, m), 7.45—6.95 (3H, m), 3.93 (3H, s)
13	175—176 (EtOH)	48.0	$C_{15}H_{11}ClN_2O_2$ 62.84 (63.13)	3.87 (3.98)	9.77 (9.81)	1690	D	8.22 (1H, s), 7.47 (5H, s), 7.12 (1H, d, $J=3$), 7.05 (1H, d, $J=3$), 3.90 (3H, s)
14	>280 (EtOH)	61.0	$C_{14}H_9ClN_2O_2$ 61.66 (61.57)	3.33 (3.42)	10.27 (10.13)	1690	D	10.88 (1H, br s), 8.15 (1H, s), 7.46 (5H, s), 6.98 (1H, d, $J=2$), 6.90 (1H, d, $J=2$)
15	258—259 (EtOH)	77.0	$C_{16}H_{11}ClN_2O_4$ 58.11 (58.41)	3.35 (3.44)	8.47 (8.46)	1700	D	8.23 (1H, s), 7.47 (5H, m), 7.17 (1H, d, $J=3$), 7.04 (1H, d, $J=3$), 4.88 (2H, s)

a) D = DMSO-d_6, C = $CDCl_3$.

TABLE IV. ((5-Chloro-4-oxo-3-phenyl-4*H*-1-benzopyran-7-yl)oxy)acetic Acid (**20**) and Related Compounds

Compound No.	mp (°C) (Solv.)	Yield (%)	Analysis (%) Calcd (Found)		IR (KBr) (cm^{-1})	Solv.[b]	^{1}H-NMR Chemical shift (δ)
			C	H			
17	123—125 (C_6H_6)	46.7	$C_{15}H_{13}ClO_3$ 65.10 (65.26)	4.74 (4.80)	1610, 1320, 1210, 1150	C	12.89 (1H, s), 7.40—7.00 (5H, m), 6.50 (1H, d, $J=3$), 6.30 (1H, d, $J=3$), 4.50 (2H, s), 3.78 (3H, s)
18	173—174 (C_6H_6)	64.0	$C_{16}H_{11}ClO_3$ 67.02 (67.39)	3.87 (4.02)	1635	C	7.81 (1H, s), 7.60—7.20 (5H, m), 6.96 (1H, d, $J=2$), 6.75 (1H, d, $J=2$), 3.86 (3H, s)
19	284—286 (MeOH)	96.3	$C_{15}H_9ClO_3$ 67.02 (67.33)	3.87 (4.02)	3200, 1630, 1590, 1270	D	11.05 (1H, s), 8.20 (1H, s), 7.60—7.20 (5H, m), 6.90 (1H, d, $J=2$), 6.80 (1H, d, $J=2$)
20	242—245 (MeCN)	73.0[a]	$C_{17}H_{11}ClO_5$ 61.74 (61.64)	3.35 (3.43)	1735, 1640	D	8.37 (1H, s), 7.60—7.30 (5H, m), 7.16 (2H, s), 4.93 (2H, s)
21	74—75 (C_6H_6)	54.4	$C_{15}H_{13}ClO_3$ 65.10 (65.24)	4.74 (4.80)	3020, 1630, 1590, 1210	C	7.70—7.40 (5H, m), 6.55 (1H, d, $J=2$), 6.32 (1H, d, $J=2$), 4.30 (2H, s), 3.85 (3H, s)
22	91—93 (EtOH)	73.9	$C_{16}H_{11}ClO_3$ 67.02 (67.01)	3.87 (3.96)	1660	C	7.71 (1H, s), 7.48—7.12 (5H, m), 6.93 (1H, d, $J=3$), 6.69 (1H, d, $J=3$), 3.89 (3H, s)
23	142—143 (EtOH)	91.7	$C_{15}H_9ClO_3$ 66.06 (65.80)	3.34 (3.33)	3090, 1650, 1060	D	12.91 (1H, s), 8.62 (1H, s), 7.60—7.42 (5H, m), 6.96 (2H, s)

a) Yield from the corresponding hydroxy compound. *b*) C = $CDCl_3$, D = DMSO-d_6

(40 ml) was added dropwise to a mixture of **16** (17.2 g, 0.1 mol), anhydrous $AlCl_3$ (16 g, 0.12 mol) and $ZnCl_2$ (1.64 g, 12 mmol) in dry $ClCH_2CH_2Cl$ (140 ml) with stirring at 5—10 °C. The reaction mixture was stirred at room temperature for an additional 1 h, and then heated at 65—70 °C for 3 h, poured into ice-cooled 4 N HCl (800 ml) and extracted with Et_2O. The extract was washed with H_2O, dried (Na_2SO_4), and then evaporated to give an oily residue (28.3 g). Petroleum ether (300 ml) was added to a solution of the resulting residue in C_6H_6 (30 ml) to precipitate white prisms. The crystals were collected by filtration to yield **21** (7.41 g). The filtrate was evaporated, and the resulting residue was purified by silica gel (300 g) column chromatography with C_6H_6–petroleum ether (1 : 1, v/v) as the eluent to give **21** (7.64 g). The total yield of **21** was 15.05 g (54.4%) (Table IV).

7-Chloro-5-methoxy-4-oxo-3-phenyl-4*H*-1-benzopyran (**22**) was prepared from **21** in a similar manner to that used for the preparation of **18** from **17** (Table IV).

7-Chloro-5-hydroxy-4-oxo-3-phenyl-4*H*-1-benzopyrane (23) A mixture of **22** (1.43 g, 5 mmol) and anhydrous $AlCl_3$ (0.80 g, 6 mmol) in C_6H_6 (20 ml) was heated at 60 °C with stirring for 1 h. After cooling, the reaction mixture was poured into ice-cold H_2O and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4), and then evaporated *in vacuo*. The resulting yellow residue was purified by column chromatography on silica gel with C_6H_6 as the eluent. The obtained product was recrystallized from EtOH to give **23** (1.25 g, 91.7%) (Table IV). ^{1}H-NMR

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TABLE V. ((7-Bromo-3-phenyl-benzo[*b*]furan-6-yl)oxy)acetic Acid (**30**) and Related Compounds

Compound No.	mp (°C) (Solv.)	Yield (%)	Analysis (%) Calcd (Found) C	H	IR (KBr) (cm^{-1})	Solv.[a]	^{1}H-NMR Chemical shift (δ)
27	161—163 (C_6H_6)	65.0	$C_{17}H_{14}O_4$ 72.33 (72.66)	5.00 (5.11)	1690	D	10.16 (1H, s), 7.80—7.30 (6H, m), 7.06 (1H, d, J=2), 6.88 (1H, dd, J=2, 9), 4.23 (2H, q, J=8), 1.20 (3H, t, J=8)
28	153—155 (C_6H_6)	74.0	$C_{17}H_{13}BrO_4$ 56.53 (56.41)	3.63 (3.65)	1710	D	10.93 (1H, s), 7.80—7.30 (5H, m), 7.37 (1H, d, J=9), 7.06 (1H, d, J=9), 4.25 (2H, q, J=8), 1.20 (3H, t, J=8)
30	161—162 (MeCN)	66.0	$C_{16}H_{11}BrO_4$ 55.36 (55.18)	3.19 (3.21)	1700	D	8.32 (1H, s), 7.78 (1H, d, J=9), 7.70—7.20 (5H, m), 7.05 (1H, d, J=9), 4.86 (2H, s)

a) DMSO-d_6.

(0.0011 mmol/ml in $CDCl_3$): 12.78 (1H, s, 5-OH), 7.97 (1H, s, 2-H), 7.53—7.40 (5H, m, arom. H), 6.97 (1H, d, J=1.5, 6-H or 8-H), 6.85 (1H, d, J=1.5, 6-H or 8-H).

Rf value for **19** on TLC (E. Merck, Art 5714, Kieselgel 60 F_{254}) using $CHCl_3$ as the developing solvent was 0.05. On the other hand, that of **23** was 0.50.

Ethyl 6-Methoxy-3-phenylcoumarilate (26) A mixture of **25** (76 g, 0.33 mol), ethyl bromoacetate (58.5 g, 0.35 mol) and K_2CO_3 (92 g, 0.67 mol) in Me_2CO (1 l) was refluxed for 4 d. The precipitated insoluble product was filtered off, and then the filtrate was evaporated *in vacuo* to give a residue. The obtained residue was dissolved in C_6H_6, washed with H_2O, dried (Na_2SO_4) and evaporated *in vacuo* to give the ester (96.0 g, 92%) as an oily product. A solution of the ester (95 g, 0.304 mol) and DBU (22 ml) in C_6H_6 (200 ml) was dehydrated by using a Dean and Stark water separator under reflux for 4 d. The reaction mixture was washed with H_2O, and then the C_6H_6 layer was evaporated *in vacuo*. The resulting product (79.85 g) was recrystallized from C_6H_6–petroleum ether to give **26** (57.5 g, 64%) as pale yellow prisms. mp 87—89 °C. IR (KBr) cm^{-1}: 1710 (–COOEt). ^{1}H-NMR ($CDCl_3$): 7.80—7.25 (6H, m), 7.03 (1H, d, J=2), 6.86 (1H, dd, J=2, 9), 4.25 (2H, q, J=8), 3.75 (3H, s), 1.24 (3H, t, J=8).

Ethyl 6-Hydroxy-3-phenylcoumarilate (27) Ethanethiol (75.6 g, 1.22 mol) was added dropwise to a suspension of anhydrous $AlCl_3$ (54.26 g, 0.41 mol) in $ClCH_2CH_2Cl$ (300 ml) under cooling with ice-cold H_2O. After the anhydrous $AlCl_3$ had dissolved, a solution of **26** (40 g, 0.136 mol) in $ClCH_2CH_2Cl$ (150 ml) was added dropwise at the same temperature. After being stirred for an additional 5 h, the reaction mixture was poured into ice-cold H_2O, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated *in vacuo*. The resulting solid was recrystallized from C_6H_6 to give **27** (25.0 g, 65%) (Table V).

Ethyl 7-Bromo-6-hydroxy-3-phenylcoumarilate (28) A solution of bromine (5.70 g, 35.6 mmol) in acetic acid (200 ml) was added dropwise to a solution of **27** (10 g, 35.6 mmol) in acetic acid (500 ml) with stirring at room temperature. The reaction mixture was poured into H_2O, and then the precipitated product was collected by filtration. The obtained crude **28** (11.7 g) was recrystallized from C_6H_6 to give **28** (9.70 g, 74%) (Table V).

((7-Bromo-2-carboxy-3-phenyl-benzo[*b*]furan-6-yl)oxy)acetic Acid (29) Compound **29** was prepared from **28** in a similar manner to that described for the synthesis of **15**. mp 218—219 °C. IR (KBr) cm^{-1}: 1690 (–COOH). ^{1}H-NMR (DMSO-d_6): 7.70—7.30 (6H, m), 7.08 (1H, d, J=9), 4.90 (2H, s).

((7-Bromo-3-phenylbenzo[*b*]furan-6-yl)oxy)acetic Acid (30) A mixture of **29** (21 g, 41 mmol) and copper(II) bromide (6.0 g, 27 mmol) in $(Et)_2NCHO$ (300 ml) was refluxed for 3 h. After removal of the solvent, the resulting residue was dissolved in AcOEt (100 ml) and the insoluble product was filtered off. The filtrate was acidified with 3 N HCl and evaporated *in vacuo*. The resulting residue was dissolved in Et_2O (300 ml), and the insoluble product was filtered off. To the filtrate was added 10% NaOH (200 ml), and the mixture was shaken vigorously. The separated aqueous layer was adjusted to pH 2 with 4 N HCl and the precipitated crystals were collected by filtration to give **30** (40 g, 66%) as pale yellow prisms (Table V).

3-(2-Chloro-3-methoxyphenyl)-1-phenyl-2-propen-1-one (32) A 10% NaOH solution (50 ml) was added in portions to a solution of **31** (23.7 g, 0.139 mol) and acetophenone (16.7 g, 0.139 mol) in EtOH (226 ml) with stirring. Vigorous stirring was continued at room temperature for 30 min, then the precipitated crystals were collected by filtration and washed with H_2O to yield a crude product (35.8 g), which was recrystallized from EtOH to give **32** (24.2 g, 63.4%) as white prisms. ^{1}H-NMR ($CDCl_3$) δ: (*E*) isomer: 8.24 (1H, d, J=16), 7.17 (1H, d, J=16). (*Z*) isomer: 6.83 (1H, d, J=9). The product, which consisted of (*E*) and (*Z*) isomers (ratio = 1 : 1), was used for the next step without isolation of the (*E*) and (*Z*) isomers.

3-(2-Chloro-3-methoxyphenyl)-1-phenylpropan-1-one (33) The mixture (13.6 g, 50 mmol) of (*E*) and (*Z*) isomers **32** in AcOEt (150 ml) was catalytically hydrogenated with 10% Pd/C (700 mg) under atmospheric pressure with absorption of 1.12 l of H_2 gas. After removal of the catalyst by filtration, the solvent was evaporated off *in vacuo*. The resulting oily residue (14.5 g) was purified by column chromatography on silica gel to give 33 (8.82 g, 64%) (Table VI).

7-Chloro-6-methoxy-3-phenylindene (34) A mixture of **33** (15 g, 55.6 mmol) and PPA (250 g) was agitated vigorously at 80—90 °C for 50 min. The reaction mixture was poured into ice-cold H_2O, stirred vigorously and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The resulting residue was recrystallized from MeOH to give **34** (10.4 g, 74.5%) (Table VI).

7-Chloro-6-hydroxy-3-phenylindene (35) Compound **34** (0.26 g, 1 mmol) was added to a solution of $AlBr_3$ (0.67 g, 2.5 mmol) in CH_2Cl_2 (5 ml) and $(Me)_2S$ (5 ml), and then stirred at room temperature for 24 h. The reaction mixture was poured into ice-cold H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with H_2O, and then evaporated to dryness *in vacuo*. The resulting oily residue (0.267 g) was purified by column chromatography on silica gel. The obtained crude product was recrystallized from C_6H_6 to give **35** (0.169 g, 88.5%) (Table VI).

((7-Chloro-3-phenylindene-6-yl)oxy)acetic Acid (36) A mixture of **35** (11.0 g, 45.7 mmol), ethyl bromoacetate (22.9 g, 0.137 mol), powdered KOH (7.68 g, 0.137 mol) in dried EtOH (680 ml) was stirred at room temperature for 24 h. The reaction mixture was poured into ice-cooled 4 N HCl (350 ml) and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried (Na_2SO_4), and then evaporated to dryness *in vacuo*. The resulting residue was recrystallized from EtOH to give the ester (8.4 g, 62.9%). mp 100—102 °C.

A solution of KOH (7.01 g, 0.125 mol) in H_2O (250 ml) was added to a solution of the ester (8.2 g, 0.025 mol) in MeOH (800 ml) and the mixture was kept at room temperature for 1 h. After concentration of the reaction mixture to one-fifth, the basic solution was added to ice-cold H_2O (100 ml), then the mixture was acidified with 4 N HCl and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried (Na_2SO_4), and evaporated *in vacuo*. The resulting residue was recrystallized from MeCN to give **36** (7.0 g, 93.8%) (Table VI).

Diuretic and Natriuretic Activities Male Wistar rats weighing 120—180 g were starved for 18 h and deprived of drinking water for 2 h before the test. The animals were orally loaded with 25 ml/kg of physiological saline, immediately followed by oral administration of the test drugs which were suspended in a 0.5% aqueous solution of carboxymethylcellulose sodium (CMC). The rats were housed singly in stainless steel metabolic cages with no access to food or water. Urine was collected during the 5-h period after dosing, and urine volume was measured. Urinary sodium and potassium contents were estimated by using an

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TABLE VI. ((7-Chloro-3-phenylinden-6-yl)oxy)acetic Acid (**36**) and Related Compounds

Compound No.	mp (°C) (Solv.)	Yield (%)	Analysis (%) Calcd (Found)		IR (KBr) (cm^{-1})	Solv.[a]	^{1}H-NMR Chemical shift (δ)
			C	H			
33	58—60 (EtOH)	64.0	$C_{16}H_{15}ClO_2$ 69.94 (70.26)	5.50 5.64)	1690	C	8.10—7.80 (2H, m), 7.60—6.65 (6H, m), 3.85 (3H, s), 3.20 (4H, s)
34	133—134 (MeOH)	74.5	$C_{16}H_{13}ClO$ 74.85 (74.60	5.10 5.05)	3000, 1480, 1280, 1060	C	7.70—7.20 (6H, m), 6.93 (1H, d, J=9), 6.51 (1H, t, J=2), 3.97 (3H, s), 3.55 (2H, d, J=2)
35	138—139 (C_6H_6)	88.5	$C_{15}H_{11}ClO$ 74.23 (74.50	4.57 4.58)	3370	C	7.60—7.20 (6H, m), 6.89 (1H, d, J=8), 6.33 (1H, t, J=3), 5.36 (1H, s), 3.36 (2H, d, J=3)
36	159—160 (MeCN)	58.6	$C_{17}H_{13}ClO_3$ 67.89 (68.16	4.36 4.55)	1720	C	7.65—7.30 (5H, m), 7.28 (1H, d, J=9), 6.86 (1H, br s), 6.84 (1H, d, J=9), 6.50 (1H, t, J=2), 4.74 (2H, s), 3.50 (2H, d, J=2)

a) $C=CDCl_3$.

electrolyte analyzer with ion-selective electrodes (PVA-4, Photovolt, U.S.A.).

Uricosuric Activity Male Wistar rats weighing 180—220 g were starved for 18 h and deprived of drinking water for 2 h before the test. The animals were orally given both 25 ml/kg of saline and the test drugs. Sixty minutes after dosing of the test drugs, the animals were housed singly in the metabolic cages, and urine was collected for 30 min. Immediately after the 30-min collection of urine, blood was taken from the carotid artery under ether anesthesia. At the same time, the remaining urine in the bladder was directly collected by using a syringe, and total urine volume was measured. A blood sample was centrifuged within 30 min after collection, and resultant plasma was used for the measurement of uric acid and creatinine. Plasma and urinary uric acid were estimated by the uricase method (Uric acid β-test, Wako, Osaka, Japan), and creatinine content was determined by Jaffe's method (Creatinin Set, Wako, Osaka, Japan). FEua was calculated by using the following formula: $FEua = C_{ua}/C_{cr}$, where C_{ua} is uric acid clearance and C_{cr} is creatinine clearance.

Antihypertensive Activity Four-week-old male rats (Sprague–Dawley) weighing 150—180 g were used. The left kidney of each rat was removed aseptically under ether anesthesia. From one week after the unilateral nephrectomy, the animals were treated with DOCA (15 mg/kg, s.c., once a week) and received 1% sodium chloride as drinking water.[15] Simultaneously, the test drugs were orally administered to the animals daily for 3 weeks. SBP of the animals in a conscious state was measured weekly prior to the daily dosing, by a tail cuff method.[16]

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