Novel, Non-acylguanidine-type Na^+/H^+ Exchanger Inhibitors: Synthesis and Pharmacology of 5-Tetrahydroquinolinylidene Aminoguanidine Derivatives

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Received October 2, 2001

In the course of our research into new types of non-acylguanidine Na^+/H^+ exchanger (NHE) inhibitors, we designed and synthesized aryl-fused tetrahydropyranylidene and cyclohexylidene aminoguanidine derivatives **I** (X = O, CH_2), which were tested for their inhibitory effects on rat platelet NHEs. After optimization, we found that the *S* isomer of tetrahydroquinoline derivatives that possess a methyl group in the 4-position and a halogen or methyl group in the *o*-position of Ar^2 exhibited high inhibitory activity. In these compounds, (5*E*,7*S*)-[[7-(5-fluoro-2-methylphenyl)-4-methyl-7,8-dihydro-5(6*H*)-quinolinylidene]amino]guanidine dimethanesulfonate (**18**, T-162559) was found to be a potent inhibitor of both rat and human platelet NHEs, with IC_{50} values of 14 and 13 nM, respectively. Furthermore, in a rat myocardial infarction model in vivo (1 h ischemia−24 h reperfusion), **18** (0.1 mg/kg, intravenously administered 5 min or 2 h before coronary occlusion) showed significant activity (33% or 23% inhibition, respectively). These results suggested that **18** may exhibit a potent and long-lasting protective activity against cardiac injuries induced by ischemia−reperfusion.

Introduction

NHEs are integral plasma membrane proteins that play an important role in the regulation of intracellular pH of the myocardium. NHEs interchange one intracellular H^+ with one extracellular Na^+ when the intracellular pH decreases.[1,2]

In ischemia−reperfusion injuries, the accumulation of intracellular protons leads to the activation of NHEs, and the consequent increase of intracellular Na^+ concentration causes the activation of another ion exchanger, the Na^+/Ca^{2+} exchanger. This results in intracellular Ca^{2+} overload, causing detrimental effects including myocardial contracture, stunning, necrosis, and reperfusion arrhythmia.[3−5]

Inhibition of NHE overactivity would be an effective obstruction of this chain of events and would prevent damage to the myocardium in ischemia−reperfusion. A number of compounds[6−9] with an acylguanidine structure, including amiloride, have been reported as NHE inhibitors (Chart 1). Among these, cariporide[10,11](**23**) and others[12] are currently under clinical evaluations, and it has been demonstrated that NHE inhibitors are therapeutically effective for ischemia−reperfusion injuries in humans. However, only a few examples of non-acylguanidine-type NHE inhibitors such as SL59.1227[13] have been reported.

To find compounds possessing more potent inhibitory activities, we synthesized several non-acylguanidine derivatives and tested their NHE inhibitory activities in rat platelets. We found that [[(2-benzyloxy-3-methoxyphenyl)methylidene]amino]guanidine (**1**) possesses a moderate activity (IC_{50} = 2.3 μM). To increase the NHE inhibitory activity and improve the stability due to the imine structure of **1**, we designed and synthesized

Chart 1

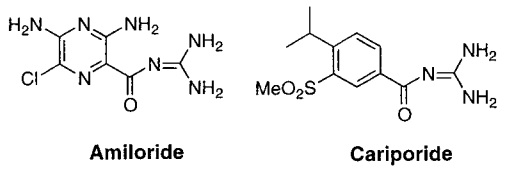
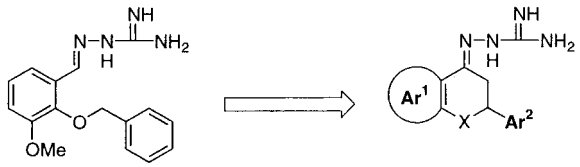


Chart 2. Synthetic Design of Aminoguanidine Derivatives



dihydropyranylidene and cyclohexylidene aminoguanidine derivatives **I** (X = O, CH_2) fused with an aromatic ring (Chart 2). Optimization of the two aromatic rings (Ar^1 and Ar^2), their substituents, and the stereochemistry of the asymmetric carbon atom was carried out. It was found that these compounds were potent NHE inhibitors and a selected compound, (5*E*,7*S*)-[[7-(5-fluoro-2-methylphenyl)-4-methyl-7,8-dihydro-5(6*H*)-quinolinylidene]amino]guanidine dimethanesulfonate (**18**, T-162559), exhibited long-lasting effects (iv, rat).

Herein, we report the design, synthesis, structure−activity relationships, and pharmacological properties of these aminoguanidine derivatives.

Chemistry. The designed aminoguanidine derivatives **I** were prepared by reaction of ketones **II** with aminoguanidine in the presence of hydrochloric acid in good yields (Scheme 1). All the racemic aminoguanidine derivatives except **9b** were isolated and purified as

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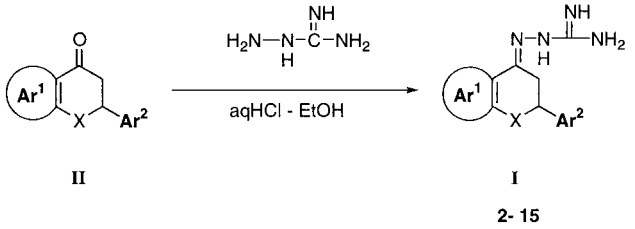
10.1021/jm0104567 CCC: $22.00
Published on Web 05/29/2002

Scheme 1



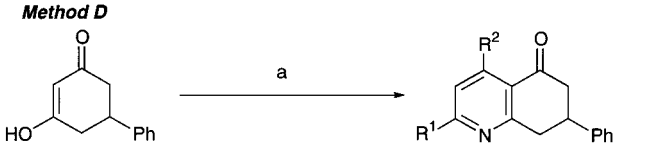
II I

2- 15

hydrochloride salts and their structure and physical data are shown in Tables 1−4. The configuration of the imine bond produced under these reaction conditions was *E*, and no compounds with *Z*-configuration were detected, which may be due to the steric repulsion between the aminoguanidine and the substituent or hydrogen atom in the peri position. This was confirmed by means of X-ray crystallographic analysis of products **16**, **19**, and **21**. All cyclic ketones **II** except flavanone and flavone derivatives were obtained from 5-arylcyclohexane-1,3-diones[14,15] as starting materials, as summarized in Schemes 2−5.

Four methods were used to synthesize the tetrahydroquinolin-5-ones, and these are shown in Schemes 2 and 3. Method A involved condensation of diketones **24** with 1-amino-2-butyne to give enamines **25,** which was followed by cyclization at high temperature to give the desired aromatic compounds **26**.[16] Alternatively tetrahydroquinolin-5-ones could be synthesized under milder conditions according to method B by condensation of 3-aminocyclohexenones **27** with 3-oxobutylaldehyde dimethylacetal, which avoided the requirement for oxidation of the cyclized product.[17] Also, two chlorothiophene derivatives **26s,u** were prepared by chlorination of **26r,t**, respectively.

Scheme 3[a]



24a

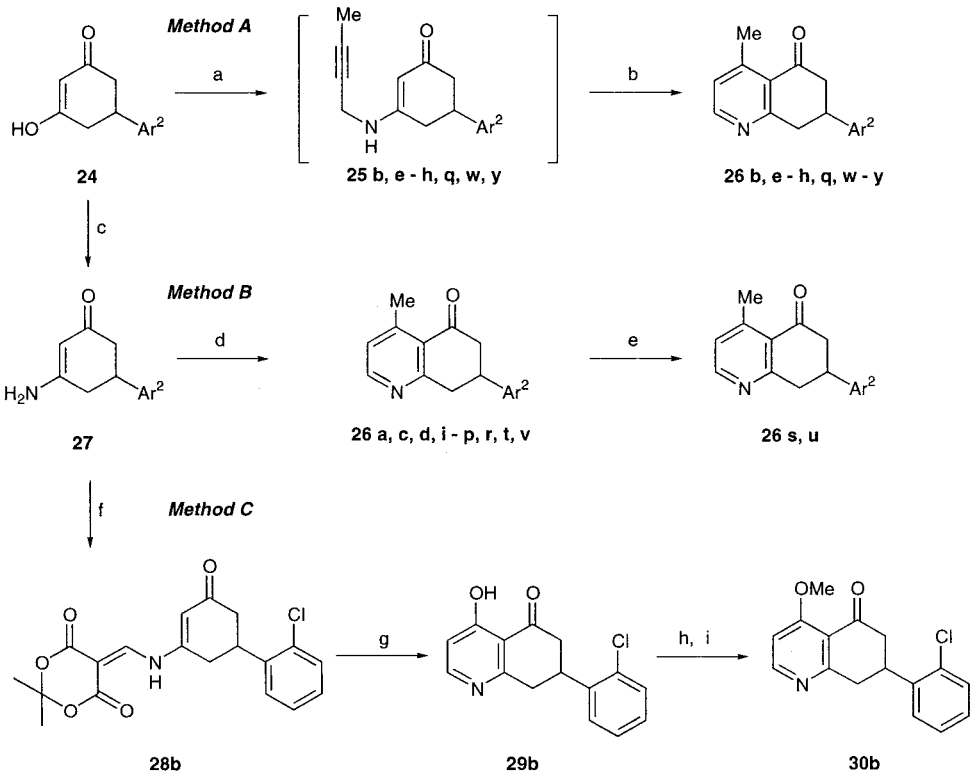
31a R^1 = H, R^2 = H
32a R^1 = Me, R^2 = H
33a R^1 = Me, R^2 = Me

[a] (a) 1,1,3,3-tetramethoxypropane, 1-butyn-3-one or acetylacetone, NH_4OAc, EtOH.

Tetrahydroquinolin-5-one derivatives with a chloro or alkoxy group in the 4-position were synthesized by method C. 3-Aminocyclohexenones **27** were reacted with 5-(methoxymethylene)-2,2-dimethyl-[1,3]-dioxane-4,6-dione[18] followed by heating at 260 °C to yield 4-hydroxytetrahydroquoinolin-5-one (**29b**). Chlorination of **29b** followed by treatment with sodium methoxide in methyl alcohol provided 4-methoxy compound **30b**. Diketone **24a** was reacted with tetramethoxypropane, 1-butyn-3-one, or acetylacetone in the presence of ammonium acetate without isolation of **27a** to afford **31a**−**33a**, respectively (method D). [19,20]

Other cyclohexanones fused with heteroaromatic rings were prepared according to Schemes 4 and 5. Tetrahydroindol-4-ones **35a,e** were obtained by palladium-catalyzed oxidation of enamines **34a,e** followed by cyclization and dehydration.[21] Enamines **34a,e** were obtained by reaction of 5-phenylcyclohexane-1,3-diones **24a,e** and 2-aminoethanol or 2-aminopropanol in THF in the presence of molecular sieves 4A. Condensation of diketone **24b** with acetic acid in the presence of DCC and DMAP gave triketone **36b**,[22] which was reacted

Scheme 2[a]

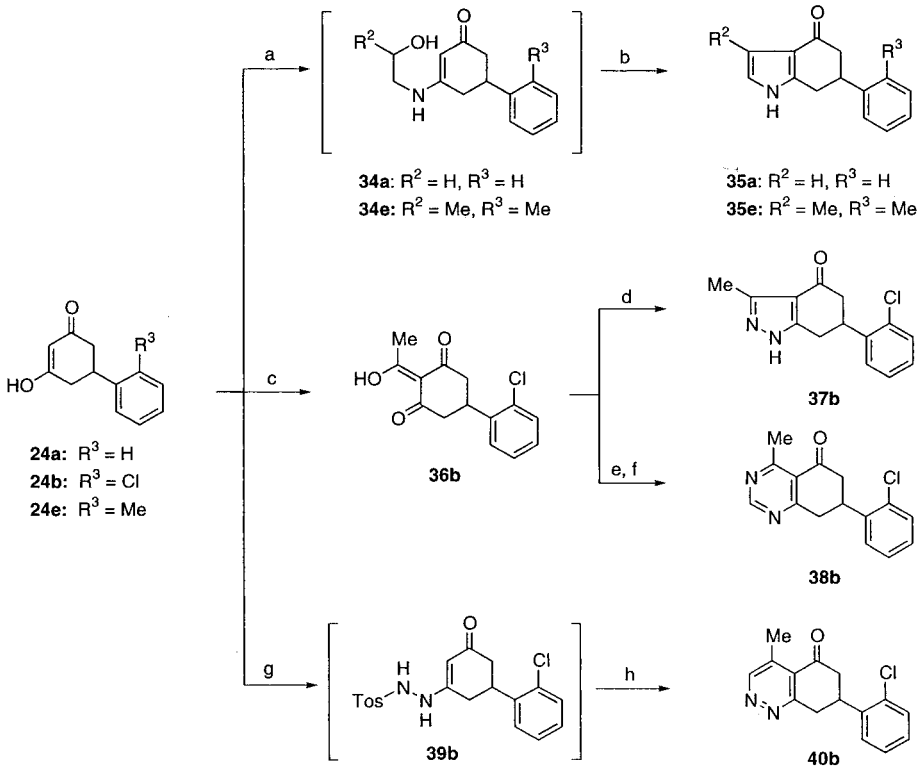


Ar^2 =

a Phenyl
b 2-chlorophenyl
c 3-chlorophenyl
d 4-chlorophenyl
e 2-methylphenyl
f 2-methoxyphenyl
g 2-fluorophenyl
h 2-bromophenyl
i 2,3-dichlorophenyl
j 2,4-dichlorophenyl
k 2,5-dichlorophenyl
l 2,6-dichlorophenyl
m 2-chloro-5-fluorophenyl
n 5-fluoro-2-methylphenyl
o 5-fluoro-2-methoxyphenyl
p 2,5-difluorophenyl
q 2-thienyl
r 3-chloro-2-thienyl
s 3,5-dichloro-2-thienyl
t 3-thienyl
u 2-chloro-3-thienyl
v 2,5-dichloro-3-thienyl
w 2-pyridiyl
x 4-pyridiyl
y 2-furyl

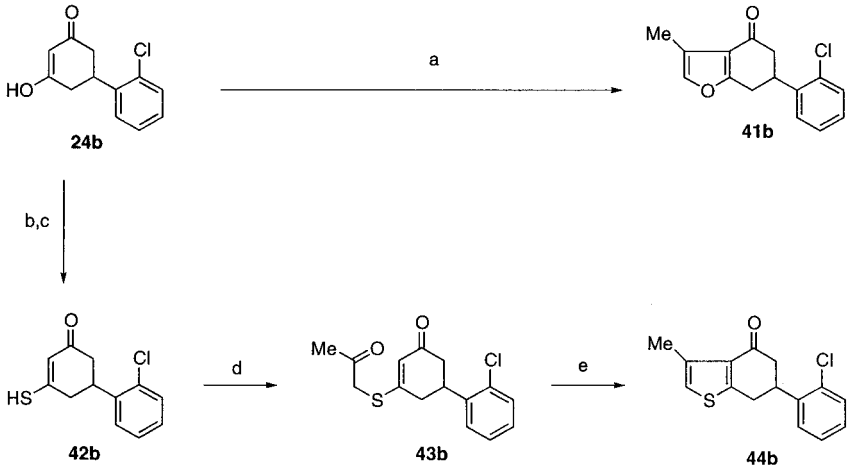
[a] (a) $CH_3C{\equiv}CCH_2NH_2{\cdot}HCl$; (b) 220 °C; (c) NH_4OAc, EtOH; (d) $CH_3COCH_2CH(OMe)_2$, KOH; (e) SO_2Cl_2; (f) 5-(methoxymethylene)-2,2-dimethyl-[1,3]-dioxane-4,6-dione; (g) 260 °C, Ph_2O; (h) $POCl_3$; (i) MeONa.

Scheme 4[a]



[a] (a) $H_2NCH_2CH_2OH$ or $H_2NCH_2CH(OH)CH_3$, MS 4A; (b) bromomesitylene, cat. $Pd(PPh_3)_4$, K_2CO_3; (c) AcOH, DMAP, DCC; (d) $NH_2NH_2 \cdot H_2O$; (e) pyrrolidine; (f) formamidine; (g) $TosNHNH_2$; (h) CH_3COCH_2Cl, K_2CO_3.

Scheme 5[a]



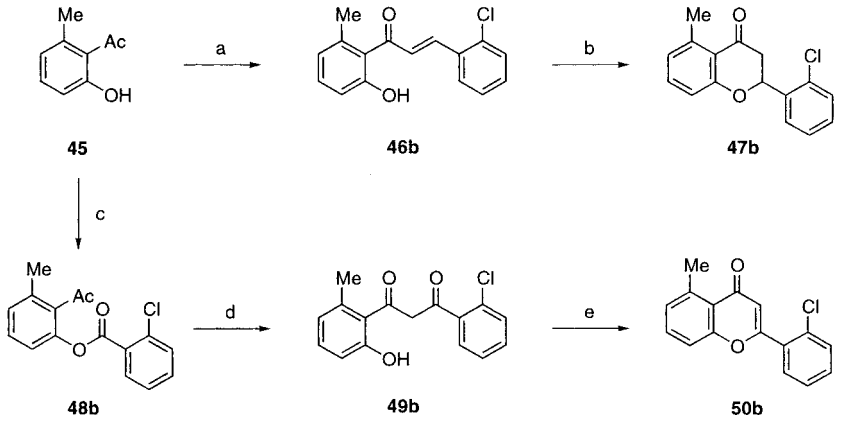
[a] (a) CH_3COCH_2Cl, EtONa, DMF; (b) PCl_3; (c) $Na_2S \cdot 9H_2O$; (d) CH_3COCH_2Cl, NaOEt−EtOH; (e) xylene, reflux.

with hydrazine hydrate in EtOH to provide tetrahydroindazol-4-one **37b** in good yield. In addition, the enamine obtained from **36b** and pyrrolidine was reacted with formamidine to afford tetrahydroquinazolin-5-one **38b**. Tosyl hydrazide **39b** generated from diketone **24b,** and *p*-toluenesulfonyl hydrazide was converted to 4-methyltetrahydrocinnolin-5-one **40b** by reaction with chloroacetone followed by cyclization in 42% yield. This is a new, facile synthetic method for the preparation of tetahydrocinnolin-5-one. Alkylation of diketone **24b** with chloroacetone in the presence of sodium ethoxide in DMF followed by cyclization provided tetrahydrobenzofuran-4-one **41b**. Tetrahydrobenzothiophen-4-one **44b** was synthesized in several steps,[23,24] in which 3-mercapto-2-cyclohexen-1-one **42b** was first obtained from diketone **24b** and then alkylated with chloroacetone to give thioether **43b**. Subsequent cyclization of this compound produced the desired heterocyclic compound **44b**.

The flavanone and flavone derivatives **47b** and **50b** were prepared by standard procedures as shown in Scheme 6.

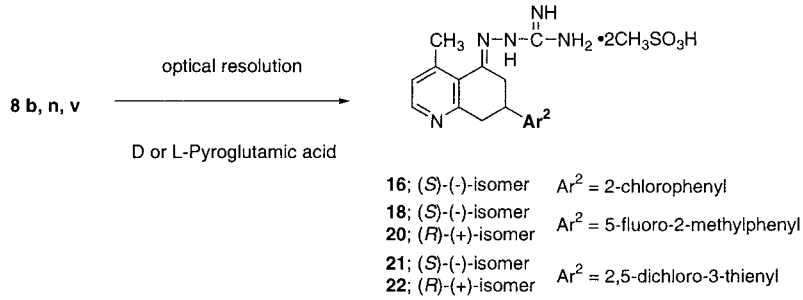
The optical isomers **16** and **18**−**22** were prepared by optical resolution of **8b**, **8n,** and **8v** with D- or L-pyroglutamic acid, respectively (Scheme 7). Compound **17** was synthesized from the (−)-isomer of **26b**, which was obtained by resolution of **26b** by means of Chiralcel OD with *i*-PrOH−hexane as the eluent. The pure enantiomers were converted to the corresponding dimethanesulfonate salts. These salts showed optimal

Scheme 6[a]



[a] (a) 4-chlorobenzaldehyde, aq NaOH, EtOH; (b) AcOH, reflux; (c) 4-chlorobenzoyl chloride; (d) NaH, *t*-BuOH; (e) $MeSO_3H$, AcOH.

Scheme 7



solubilities and physical properties, whereas the corresponding HCl salts or free bases were used for X-ray crystallographic analysis. The absolute configurations of these compounds are listed in Table 5, and the molecular structure of compound **19** (HCl salt) is shown in Figure 1.

Results and Discussion

The synthesized aminoguanidine derivatives were evaluated for their inhibitory effects on acidosis-induced increases in rat platelet cell volume. Namely, the increase in the cell volume caused by the addition of sodium propionate buffer was observed by measurement of the increase in the optical density (OD). The results are displayed in Tables 1−5 as IC_{50} values (i.e., the concentration needed to inhibit the increase in the OD by 50%).

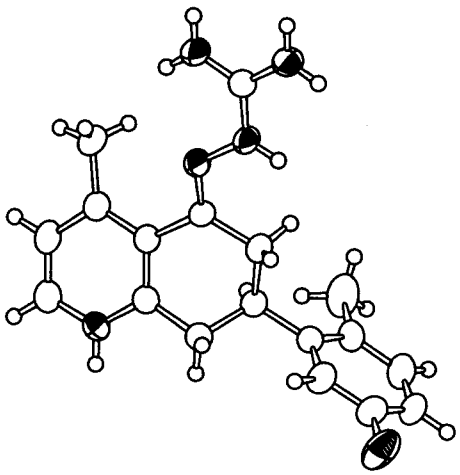


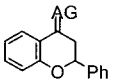
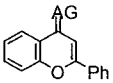
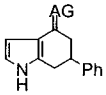
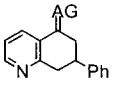
Figure 1. Molecular structure of **19** as determined by X-ray crystallographic analysis.

The initial lead compound **1** was converted into a bicyclic derivative, i.e., flavanone **2a** to improve stability and restrict the conformation. And the related bicyclic compounds, including flavone, tetrahydroindole and tetrahydroquinoline derivatives (**3a**−**5a**) were prepared (see Table 1). Among these compounds, flavanone **2a,** flavone **3a**, and tetrahydroindole **4a** retained similar activity to **1**, whereas tetrahydroquinoline **5a** was about 10 times more potent. These results indicated that bicyclic aminoguanidine derivatives **I** were effective as NHE inhibitors.

Optimization of **5a** was initially investigated by changing the substituents on the pyridine and benzene rings. Tetrahydroquinoline derivatives that possess methyl or methoxy groups on the tetrahydroquinoline ring and/or a chlorine atom on Ar^2 are shown in Table 2. Introduction of a methyl group into the 4-position of the tetrahydroquinoline ring led to an improvement of the in vitro activity. Compound **8a** was about 5 times more potent than **5a**, and **7a** was 15 times more potent than **6a**. On the other hand, the compounds with the methyl group in the 2-position exhibited weaker activities than 2-unsubstituted compounds (**6a** vs **5a**, **7a** vs **8a**).

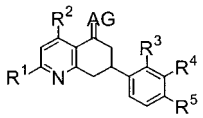
Compound **8b**, having a chlorine atom in the *o*-position of Ar^2, exhibited highly potent activity (IC_{50} value was 0.040 μM) and was twice as potent as **8a** and 10 times more potent than the lead compound **5a**. Also, a chlorine atom in the 3-position of Ar^2 (**8c**) increased the activity (IC_{50} value of **8c** was 0.061 μM), but a chlorine atom in the 4-position (**8d**) reduced the activity (IC_{50} value was 0.55 μM). Substitution of the methoxy group (**9b**) for the methyl group of **8b** retained the activity. These results suggest that substituents, especially a methyl group in the 4-position of Ar^1 and a

Table 1. Physical Properties and in Vitro NHE Inhibitory Activities of Compounds **2a**−**5a**

compound[a]		yield[b] (%)	mp (°C)	recryt. solv.[c]	formula[d]	*in vitro*, IC_{50}[e] (μM)
2a		92	250 dec	E	$C_{16}H_{16}N_4O$•HCl	3.3
3a		56	185 dec	E	$C_{16}H_{14}N_4O$ •HCl	6.4
4a		44	192-194	E	$C_{15}H_{17}N_5$•2HCl	3.5
5a		52	194-197	H_2O-E	$C_{16}H_{17}N_5$•2HCl•H_2O	0.41

[a] AG = N−NH−C(=NH)−NH_2. [b] No attempt was made to optimize yields. Numbers represent the yield for the last step. [c] E = EtOH. [d] Analyses for C, H, and N are within ±0.4% of the expected value for the formula. [e] NHE assay in rat platelets. IC_{50} is the concentration required to inhibit the acid-induced swelling in rat platelets by 50%. All data represent means of triplicate separate experiments.

Table 2. Physical Properties and in Vitro NHE Inhibitory Activities of Tetrahydroquinoline Derivatives **6a**−**9b**



compd[a]	R^1	R^2	R^3	R^4	R^5	yield[b] (%)	mp (°C)	recryst solv[c]	formula[d]	in vitro IC_{50}[e] (μM)
6a	Me	H	H	H	H	71	>300	E	$C_{17}H_{19}N_5$•2HCl•0.1H_2O	2.8
7a	Me	Me	H	H	H	55	270 dec	E	$C_{18}H_{21}N_5$•2HCl	0.18
8a	H	Me	H	H	H	79	184−186	H_2O−E	$C_{17}H_{19}N_5$•2HCl•H_2O	0.091
8b	H	Me	Cl	H	H	71	204 dec	E−EA	$C_{17}H_{18}ClN_5$•2HCl•0.8H_2O	0.040
8c	H	Me	H	Cl	H	90	295 dec	E	$C_{17}H_{18}ClN_5$•2HCl	0.061
8d	H	Me	H	H	Cl	48	197 dec	H_2O	$C_{17}H_{18}ClN_5$•2HCl•0.5H_2O	0.55
9b	H	OMe	Cl	H	H	84	158−159	H_2O−E	$C_{17}H_{18}ClN_5O$•2CH_3SO_3H•H_2O	0.050

[a] AG = N−NH−C(=NH)−NH_2. [b] No attempt was made to optimize yields. Numbers represent the yield for the last step. [c] E = EtOH, EA = ethyl acetate. [d] Analyses for C, H, and N are within ±0.4% of the expected value for the formula. [e] NHE assay in rat platelets. IC_{50} is the concentration required to inhibit the acid-induced swelling in rat platelets by 50%. All data represent means of triplicate separate experiments.

chlorine atom in the *o*-position of Ar^2, were important for potent activity.

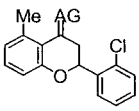
Next, aromatic ring 1 (Ar^1) was modified for a series of compounds with a methyl group in the peri position of the aminoguanidine moiety and a chlorine atom in the *o*-position in Ar^2. The NHE inhibitory activities of these compounds are shown in Table 3. Pyridine, pyridazine, pyrrole, and pyrazole derivatives (**8b**, **10b**, **12e**, and **13b**) showed potent activities, although furan **14b** was slightly less potent. In comparison with these compounds, flavanone **2b**, flavone **3b** (Ar^1 = benzene), and benzothiophene derivatives (**15b**) exhibited much weaker activities. These results suggest that the basicity of the nitrogen atom in the 1-position of compounds (**8b**, **10b**, **12e**, and **13b)** is important for potent activity. Tetrahydroquinazoline **11b** was only weakly active, which may be due to the presence of a nitrogen atom at the 3-position. Among the compounds that exhibited potent NHE inhibitory activity, tetrahydroquinolines were selected for further examination on the basis of their potency, ease of preparation, and physical properties.

Tetrahydroquinoline derivatives (**8e**−**y**) with various aromatic rings (Ar^2) were prepared in order to optimize Ar^2 and the substituents in the *o*-position and are shown in Table 4. Introduction of certain substituents in the 2-position of Ar^2 increased the potency. The IC_{50} values of compound **8e** (2-Me)**, 8g** (2-F), and **8h** (2-Br) were 0.057, 0.032, and 0.056 μM, respectively, whereas compound **8f** with a 2-methoxy group showed weaker activity (IC_{50} = 0.10 μM).

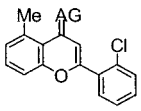
For the disubstituted series of compounds, the presence of two chlorine atoms in the 2- and 5-position (**8k**) maintained potent activities (IC_{50} = 0.058 μM). On the other hand, a 2,3-dichloro compound (**8i**) exhibited relatively weaker activity (IC_{50} = 0.089 μM), and other dichloro derivatives (**8j,l**) were less active. The compounds with a fluorine atom in the 5-position of Ar^2 (**8m**−**p**) exhibited highly potent activities (IC_{50} values were about 0.02−0.04 μM). These results indicated that both the size and lipophilicity of the Ar^2 substituents are important for optimal activity.

Introduction of a thiophene ring as Ar^2 also resulted in compounds with potent NHE inhibitory activities (IC_{50} values of **8q** and **8t** were 0.047 and 0.030 μM, respectively). Furthermore, this activity was increased by the presence of a chlorine atom in the *o*-position of the thiophene ring of **8q** and **8t**, and compounds **8r** and **8v** exhibited the most potent activities (IC_{50} values of both compounds were 0.019 μM). These results agreed

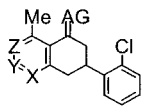
Table 3. Physical Properties and in Vitro NHE Inhibitory Activities of Aminoguanidine Derivatives **2b**−**15b**



2b



3b



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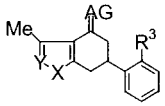

12 - 15

compd[a]	X	Y	Z	R^3	yield[b] (%)	mp (°C)	recryst solv[c]	formula[d]	in vitro IC_{50}[e] (μM)
2b					88	276−277	E	$C_{17}H_{17}ClN_4O{\cdot}HCl$	0.20
3b					35	287−289 dec	EA	$C_{17}H_{15}ClN_4O{\cdot}2HCl{\cdot}0.5H_2O$	0.36
8b	N	CH	CH		71	204 dec	E−EA	$C_{17}H_{18}ClN_5{\cdot}2HCl{\cdot}0.8H_2O$	0.040
10b	N	N	CH		79	241−243	E	$C_{16}H_{17}ClN_6{\cdot}2HCl$	0.026
11b	N	CH	N		63	284 dec	IPE	$C_{16}H_{17}ClN_6{\cdot}2HCl{\cdot}0.5H_2O$	0.24
12e	NH	CH		Me	4	187 dec	E−EA	$C_{17}H_{21}N_5{\cdot}2HCl{\cdot}0.5H_2O$	0.034
13b	NH	N		Cl	79	220 dec	H_2O−E	$C_{15}H_{17}ClN_6{\cdot}2HCl{\cdot}0.5H_2O$	0.055
14b	O	CH		Cl	80	300 dec	IPE	$C_{16}H_{17}ClN_4{\cdot}HCl$	0.082
15b	S	CH		Cl	87	246 dec	E	$C_{16}H_{17}ClN_4S{\cdot}HCl$	0.22

[a] AG = N−NH−C(=NH)−NH_2. [b] No attempt was made to optimize yields. Numbers represent the yield for the last step. [c] E = EtOH, EA = ethyl acetate, IPE = diisopropyl ether. [d] Analyses for C, H and N are within ±0.4% of the expected value for the formula. [e] NHE assay in rat platelets. IC_{50} is the concentration required to inhibit the acid-induced swelling in rat platelets by 50%. All data represent means of triplicate separate experiments.

Table 4. Physical Properties and in Vitro NHE Inhibitory Activities of Tetrahydroquinoline Derivatives

compd	Ar^2	yield[a] (%)	mp (°C)	recryst solv[b]	formula[c]	in vitro IC_{50}[d] (μM)
8e	2-methylphenyl	88	218 dec	E−EA	$C_{18}H_{21}N_5{\cdot}2HCl{\cdot}0.5H_2O$	0.057
8f	2-methoxyphenyl	50	192 dec	E−EA	$C_{18}H_{21}N_5O{\cdot}2HCl{\cdot}0.2H_2O$	0.10
8g	2-fluorophenyl	61	240 dec	E	$C_{17}H_{18}FN_5{\cdot}2HCl{\cdot}0.2H_2O$	0.032
8h	2-bromophenyl	70	233 dec	H_2O−E	$C_{17}H_{18}BrN_5{\cdot}2HCl{\cdot}0.5H_2O$	0.056
8i	2,3-dichlorophenyl	98	270−272	E	$C_{17}H_{17}Cl_2N_5{\cdot}2HCl$	0.089
8j	2,4-dichlorophenyl	90	193−195	H_2O−E	$C_{17}H_{17}Cl_2N_5{\cdot}2HCl{\cdot}0.5H_2O$	0.34
8k	2,5-dichlorophenyl	91	>300	H_2O	$C_{17}H_{17}Cl_2N_5{\cdot}2HCl{\cdot}0.5H_2O$	0.058
8l	2,6-dichlorophenyl	89	>300	E	$C_{17}H_{17}Cl_2N_5{\cdot}2HCl{\cdot}0.25H_2O$	23%(0.3)[e]
8m	2-chloro-5-fluorophenyl	39	268 dec	E−EA	$C_{17}H_{17}ClFN_5{\cdot}2HCl{\cdot}0.5H_2O$	0.019
8n	5-fluoro-2-methylphenyl	86	202−205	E	$C_{18}H_{20}FN_5{\cdot}2HCl{\cdot}0.5H_2O$	0.037
8o	5-fluoro-2-methoxyphenyl	86	>300	E	$C_{18}H_{20}FN_5O{\cdot}2HCl$	0.032
8p	2,5-difluorophenyl	90	290 dec	E	$C_{17}H_{17}F_2N_5{\cdot}2HCl$	0.039
8q	2-thienyl	73	225 dec	H_2O−E	$C_{15}H_{17}N_5S{\cdot}2HCl{\cdot}H_2O$	0.047
8r	3-chloro-2-thienyl	67	204 dec	CH_2Cl_2	$C_{15}H_{16}ClN_5S{\cdot}2HCl$	0.019
8s	3,5-dichloro-2-thienyl	57	184−187	E	$C_{15}H_{15}Cl_2N_5S{\cdot}2HCl{\cdot}0.5H_2O$	0.049
8t	3-thienyl	93	>300	E	$C_{15}H_{17}N_5S{\cdot}2HCl{\cdot}0.3EtOH$	0.030
8u	2-chloro-3-thienyl	69	281 dec	E	$C_{15}H_{16}ClN_5S{\cdot}2HCl$	0.022
8v	2,5-dichloro-3-thienyl	96	>300	E	$C_{15}H_{15}Cl_2N_5S{\cdot}2HCl$	0.019
8w	2-pyridyl	76	260 dec	H_2O−E	$C_{16}H_{18}N_6{\cdot}3HCl{\cdot}0.2H_2O$	23%(0.3)[e]
8x	4-pyridyl	77	267 dec	H_2O−E	$C_{16}H_{18}N_6{\cdot}3HCl{\cdot}0.5H_2O$	25%(1)[e]
8y	2-furyl	86	>300	E	$C_{15}H_{17}N_5O{\cdot}2HCl$	0.11

[a] No attempt was made to optimize yields. Numbers represent the yield for the last step. [b] E = EtOH, EA = ethyl acetate. [c] Analyses for C, H, and N are within ± 0.4% of the expected value for the formula. [d] NHE assay in rat platelets. IC_{50} is the concentration required to inhibit the acid-induced swelling in rat platelets by 50%. All data represent means of triplicate separate experiments. [e] Percent inhibition at the concentration (micromolar) represented in parentheses.

with the structure−activity relationships observed for compounds with a benzene ring as Ar^2. In contrast, compounds with basic heterocycles such as 2- or 4-pyridyl (**8w** or **8x**) in the 7-position of the tetrahydroquinoline showed poor activities, and the activity of 7-(2-furyl)tetrahydroquinoline **8y** was relatively weak.

Optical isomers (**16**−**18**, **20**−**22**) of three tetrahydroquinoline racemates (**8b**, **8n,** and **8v**) that exhibited potent NHE inhibitory activities were also tested and the results are summarized in Table 5. The IC_{50} values of *S* enantiomers (**16, 18,** and **21**) were 20, 14, and 17 nM, respectively. The *S* isomers showed about 2−35 times more potent activity than the *R* isomers. And these activities were 115−150 times more potent than the initial lead compound **1** and about 4−6 times more potent than **23** (IC_{50} = 75 nM).

These three enantiomers (**16**, **18**, **21**) were evaluated for their NHE inhibitory effects on human platelets in vitro. The results showed that these compounds exhibited excellent activities on human platelets, and they were about 16−30 times more potent than **23**, with IC_{50} values of 9.0, 13, 7.0, and 210 nM, respectively. Compound **23** exhibited weak activity in human platelets compared with rat platelets. The compounds were then tested in a rat myocardial infarction model in vivo, in which the left coronary artery was occluded for 1 h and then reperfused for 24 h. Aminoguanidine derivative **16**, **18**, or **21** (0.1 mg/kg) or acylguanidine derivative **23** (0.3

Table 5. Physical Properties and in Vitro NHE Inhibitory Activities of Enantiomers of Tetrahydroquinoline Derivatives **16**−**22**

compd[a]	formula[b]	mp (°C)	recryst solv[c]	IC_{50}[d] (nM)
16	$C_{17}H_{18}ClN_5 \cdot 2CH_3SO_3H$	194−195	E	20
8b				40
17	$C_{17}H_{18}ClN_5 \cdot 2CH_3SO_3H$	194−196	E−A	700
18	$C_{18}H_{20}FN_5 \cdot 2CH_3SO_3H$	202−204	E	14
8n				37
20	$C_{18}H_{20}FN_5 \cdot 2CH_3SO_3H$	202−204	E	220
21	$C_{15}H_{15}Cl_2N_5S \cdot 2CH_3SO_3H$	229−231	E	17
8v				19
22	$C_{15}H_{15}Cl_2N_5S \cdot 2CH_3SO_3H$	225−229	E	33
23	cariporide			75

[a] Structures are given in Tables 2 and 4. [b] Analyses for C, H, and N are within ±0.4% of the expected value for the formula. [c] E = EtOH, A = acetone. [d] NHE assay in rat platelets. IC_{50} is the concentration required to inhibit the acid-induced swelling in rat platelets by 50%. All data represent means of triplicate separate experiments.

Table 6. NHE Inhibitory Activities in Human Platelets in Vitro and Inhibitory Effect on the Myocardial Infarct Size of Ischemia−Reperfusion Injury Model of Rat in Vivo

	human platelet[b]	ischemia−reperfusion injury model[d]	
compd[a]	IC_{50}[c] (nM)	% inhibition	n
16	9.0	44	5
18	13	33	7
21[e]	7.0	43	6
23	210	28[f]	6

[a] Structures are given in Scheme 7. [b] NHE assay in human platelets. [c] IC_{50} is the concentration required to inhibit the acid-induced swelling in human platelets by 50%. All data represent means of triplicate separate experiments. [d] Compounds (0.1 mg/kg) were administered intravenously 5 min before occlusion. [e] The hydrate was used in this experiment. [f] Compound **23** (0.3 mg/kg) was administered intravenously 5 min before occlusion.

mg/kg) was administered intravenously 5 min before occlusion. Potent cardioprotective effects were observed with **16**, **18**, and **21** inhibiting the extension of infarct size by 44%, 33%, and 43%, respectively (Table 6). Compound **23** (0.3 mg/kg) showed weaker activity (28% inhibition) than the aminoguanidine derivatives.

From these results and other factors including pharmacokinetics, toxicity, and physicochemical properties, **18** was selected for further evaluation. **18** showed long-lasting inhibitory properties. In the rat ischemia−reperfusion injury model described above, compound **18**, administered intravenously 2 h before coronary occlusion, exhibited potent inhibitory effects. The minimum effective dose in this condition was 0.1 mg/kg, due to the desirable pharmacokinetic profile of this compound. The half-life period of **18** was 3.6 h in IGS/SD rat (1 mg/kg iv). In addition, the metabolic velocity in rat (IGS/SD male rat) and human liver microsomes was low (40 and 18 pmol min^{-1} mg^{-1}, respectively).

In the Na^+-dependent pHi recovery assay, **18** inhibited hNHE in a concentration-dependent manner, with IC_{50} values for hNHE1, hNHE2, and hNHE3 of 0.96, 430, and 11000 nM, respectively. The inhibitory activity of **18** was selective for the human NHE-1 isoform.[25]

The potent NHE inhibitory activities of aminoguanidine derivatives are dependent on both the structures and the pK_a values of the compounds. For NHE inhibition by guanidine compounds, it is necessary that the guanidino moiety is protonated and mimics the sodium cation hydrated with three water molecules. The pK_a values of the aminoguanidine derivative **18** and acylguanidine derivative **23** measured in water were 8.4 and 6.2, respectively. Thus, **18** is expected to inhibit NHE at higher pH, that is, at a lower level of acidosis, and to prevent the myocardium damage in the ischemia−reperfusion more effectively.

In summary, in our search for potent and non-acylguanidine-type NHE inhibitors, we investigated aryl-fused tetrahydropyranylidene and cyclohexylidene aminoguanidine derivatives **I** (X = O, CH_2), which were designed on the basis of the structure of an initial lead compound **1**. It was found that *S* isomers of tetrahydroquinoline derivatives that possess a methyl group in the 4-position and a halogen or methyl group in the *o*-position in Ar^2 exhibited potent NHE inhibitory activities. In this series of compounds, (5*E*,7*S*)-[[7-(5-fluoro-2-methylphenyl)-4-methyl-7,8-dihydro-5(6*H*)-quinolinylidene]amino]guanidine dimethanesulfonate (**18**) displayed significant NHE inhibitory activities on the rat and human platelets and showed long-lasting properties in vitro and in vivo. These results suggested that **18** may exhibit significant and long-lasting NHE-1 inhibitory activity and show potent protective effects against cardiac injuries induced by ischemia−reperfusion in clinical application.

Experimental Section

Melting points were obtained with a Yanaco micro melting apparatus and are uncorrected. Proton nuclear magnetic resonance (^1H NMR) spectra not specified were recorded on a Varian Gemini 200 instrument at 200 MHz, with tetramethylsilane as an internal standard. Elemental analyses were carried out by Takeda Analytical Laboratories, Ltd., and are within ±0.4% of the theoretical values unless otherwise noted. Solutions of organic solvents were dried over anhydrous $MgSO_4$. Column chromatography was carried out on silica gel (Wakogel C-300, particle size 45−75 mm) by the flash chromatography technique. Yields were not maximized. All TLC analyses were carried out on Merck silica gel 60 (F254) plates. The enantiomeric excess was measured by HPLC with Ultron ES-OVM.

[[7-(5-Fluoro-2-methylphenyl)-4-methyl-7,8-dihydro-5(6*H*)-quinolinylidene]amino]guanidine Dihydrochloride (8n), Typical Procedure. The mixture of **26n** (1.1 g, 4.1 mmol), aminoguanidine hydrochloride (0.54 g, 4.9 mmol), concentrated HCl (1.0 mL), and water (1.0 mL) in EtOH (30 mL) was refluxed for 6 h. The solvent was evaporated under reduced pressure. The residue was dissolved in water and washed with EtOAc. To the solution was added aqueous $NaHCO_3$, and the mixture was extracted with EtOAc, and the organic layer was washed with water, dried, and evaporated. The residue was dissolved in EtOH, and 1 N HCl (10 mL) was added. The mixture was concentrated, and the residue was recrystallized from EtOH to give **8n** (1.4 g, 86%) as colorless crystals: ^1H NMR(DMSO-d_6) δ 2.31 (3H, s), 2.72−3.03 (1H, m), 2.90 (3H, s), 3.13−3.57 (4H, m), 6.93−7.06 (1H, m), 7.17−7.4 (2H, m), 7.5−8.4 (4H, br s), 7.85 (1H, d, J = 6 Hz), 8.65 (1H, d, J = 6 Hz), 11.39 (1H, s).

The following compounds (**1**−**15b**) were prepared by a manner similar to that used for **8n**.

1: mp 175−176 °C; ^1H NMR (DMSO-d_6) δ 3.89 (3H, s), 5.02 (2H, s), 7.06−7.22 (2H, m), 7.28−7.51 (5H, m), 7.52−8.03 (4H, br s), 7.64−7.75 (1H, m), 8.38 (1H, s), 11.96 (1H, s).

2a: ^1H NMR (DMSO-d_6) δ 7.2−8.0 (4H, br s), 7.37 (1H, dt, J = 2, 8 Hz), 7.50−7.68 (7H, m), 8.09−8.21 (2H, m), 8.45 (1H, dd, J = 1, 8 Hz), 11.93 (1H, s).

2b: ^{1}H NMR (DMSO-d_6) δ 2.65 (3H, s), 2.95 (1H, dd, J = 13, 17 Hz), 3.43 (1H, dd, J = 3, 17 Hz), 5.41 (1H, dd, J = 3, 13 Hz), 6.85−7.01 (2H, m), 7.20−8.32 (1H, m), 7.30−8.05 (4H, br s), 7.40−7.60 (3H, m), 7.70−7.80 (1H, m), 11.18 (1H, s).

3a: ^{1}H NMR (DMSO-d_6) δ 2.92 (1H, dd, J = 12, 17 Hz), 5.30 (1H, dd, J = 3, 12 Hz), 6.95−7.08 (2H, m), 7.20−8.20 (4H, br s), 7.30−7.62 (6H, m), 8.34 (1H, dd, J = 2, 8 Hz), 11.2 (1H, s).

4a: ^{1}H NMR (DMSO-d_6) δ 2.68−3.16 (4H, m), 3.24−3.48 (1H, m), 6.84 (1H, s), 6.95 (1H, s), 7.21−7.50 (5H, m), 7.74 (4H, br s), 10.15 (1H, br s), 11.77 (1H, br s).

5a: ^{1}H NMR (DMSO-d_6) δ 2.74−2.92 (1H, m), 3.16−3.53 (4H, m), 7.24−7.46 (5H, m), 7.81 (1H, dd, J = 4, 8 Hz), 8.04 (4H, br s), 8.78 (1H, d, J = 4 Hz), 9.31 (1H, d, J = 8 Hz), 11.51 (1H, s).

6a: ^{1}H NMR (DMSO-d_6) δ 2.65−2.96 (1H, m), 2.78 (3H, s), 3.15−3.61 (4H, m), 7.25−7.55 (5H, m), 7.6−8.7 (4H, br s), 7.78 (1H, d, J = 8 Hz), 9.72 (1H, d, J = 8 Hz), 11.51 (1H, s).

7a: ^{1}H NMR (DMSO-d_6) δ 2.5−3.8 (5H, m), 2.72 (3H, s), 2.82 (3H, s), 7.23−7.60 (6H, m), 7.6−8.2 (4H, br s), 7.71 (1H, s), 11.33 (1H, s).

8a: ^{1}H NMR (DMSO-d_6) δ 2.76−2.98 (1H, m), 2.87 (3H, s), 3.14−3.46 (4H, m), 7.24−7.48 (5H, m), 7.82 (1H, d, J = 6 Hz), 7.91 (4H, br s), 8.63 (1H, d, J = 6 Hz), 11.45 (1H, s).

8b: ^{1}H NMR (DMSO-d_6) δ 2.65−3.00 (1H, m), 2.88 (3H, s), 3.15−3.78 (4H, m), 7.2−8.2 (4H, br s), 7.28−7.53 (3H, m), 7.58−7.66 (1H, m), 7.83 (1H, d, J = 6 Hz), 8.63 (1H, d, J = 6 Hz), 11.45 (1H, s).

8c: ^{1}H NMR (DMSO-d_6) δ 2.76−3.03 (1H, m), 2.88 (3H, s), 3.16−3.52 (4H, m), 7.32−7.62 (4H, m), 7.86 (1H, d, J = 6 Hz), 7.99 (4H, br s), 8.65 (1H, d, J = 6 Hz), 11.60 (1H, s).

8d: ^{1}H NMR (DMSO-d_6) δ 2.70−2.96 (1H, m), 2.85 (3H, s), 3.14−3.50 (4H, m), 7.47 (4H, s), 7.79 (1H, d, J = 6 Hz), 7.88 (4H, br s), 8.62 (1H, d, J = 6 Hz), 11.46 (1H, s).

8e: ^{1}H NMR (DMSO-d_6) δ 2.35 (3H, s), 2.64−2.96 (1H, m), 2.91 (3H, s), 3.07−3.61 (4H, m), 6.9−8.4 (4H, br s), 7.03−7.30 (3H, m), 7.37−7.48 (1H, m), 7.86 (1H, d, J = 6 Hz), 8.65 (1H, d, J = 6 Hz), 11.36 (1H, s).

8f: ^{1}H NMR (DMSO-d_6) δ 2.70−3.90 (5H, m), 2.87 (3H, s), 3.83 (3H, s), 6.93−7.06 (2H, m), 7.23−7.40 (2H, m), 7.50−8.02 (4H, br s), 7.78 (1H, d, J = 6 Hz), 8.61 (1H, d, J = 6 Hz), 11.20 (1H, s).

8g: ^{1}H NMR (DMSO-d_6) δ 2.80−4.0 (5H, m), 2.83 (3H, s), 7.19−7.44 (3H, m), 7.50−8.02 (4H, br s), 7.51−7.63 (1H, m), 7.77 (1H, d, J = 6 Hz), 8.60 (1H, d, J = 6 Hz), 11.28 (1H, s).

8h: ^{1}H NMR (DMSO-d_6) δ 2.75−3.03 (1H, m), 2.88 (3H, s), 3.16−3.60 (4H, m), 7.22−7.35 (1H, m), 7.41−7.56 (1H, m), 7.69−7.75 (2H, m), 7.4−8.6 (4H, br s), 7.82 (1H, d, J = 6 Hz), 8.63 (1H, d, J = 6 Hz), 11.39 (1H, s).

8i: ^{1}H NMR (DMSO-d_6) δ 2.88 (4H, m), 3.27 (1H, dd, J = 5, 18 Hz), 3.45 (2H, m), 3.74 (1H, m), 7.46 (1H, t, J = 8 Hz), 7.63 (2H, d, J = 8 Hz), 7.82 (1H, d, J = 6 Hz), 7.94 (4H, br s), 8.63 (1H, d, J = 6 Hz), 11.50 (1H, br s).

8j: ^{1}H NMR (DMSO-d_6) δ 2.72−2.96 (1H, m), 2.86 (3H, s), 3.14−3.73 (4H, m), 7.47−7.72 (3H, m), 7.81 (1H, d, J = 6 Hz), 7.93 (4H, br s), 8.62 (1H, d, J = 6 Hz), 11.53 (1H, s).

8k: ^{1}H NMR (DMSO-d_6) δ 2.83−3.03 (1H, m), 2.88 (3H, s), 3.14−3.77 (4H, m), 7.43 (1H, dd, J = 2, 9 Hz), 7.5−8.4 (4H, br s), 7.55 (1H, d, J = 9 Hz), 7.76 (1H, d, J = 2 Hz), 7.83 (1H, d, J = 5 Hz), 8.63 (1H, d, J = 5 Hz), 11.51 (1H, s).

8l: ^{1}H NMR (DMSO-d_6) δ 2.85 (3H, s), 3.07 (1H, dd, J = 4, 16 Hz), 3.28 (1H, d, J = 15 Hz), 3.38 (1H, dd, J = 12, 18 Hz), 4.10 (2H, m), 7.41 (1H, t, J = 8 Hz), 7.57 (2H, d, J = 8 Hz), 7.80 (1H, d, J = 6 Hz), 7.89 (4H, br s), 8.62 (1H, d, J = 6 Hz), 11.46 (1H, br s).

8m: ^{1}H NMR (DMSO-d_6) δ 2.76−3.05 (1H, m), 2.84 (3H, s), 3.13−3.75 (4H, m), 7.0−8.4 (4H, br s), 7.2−7.34 (1H, m), 7.52−7.66 (2H, m), 7.76 (1H, d, J = 6 Hz), 8.6 (1H, d, J = 6 Hz), 11.36 (1H, s).

8o: ^{1}H NMR (DMSO-d_6) δ 2.77−2.92 (4H, m), 3.16 (1H, dd, J = 4, 17 Hz), 3.33−3.61 (3H, m), 3.81 (3H, s), 7.01−7.15 (2H, m), 7.28−7.33 (1H, m), 7.82 (1H, d, J = 6 Hz), 7.91 (4H, br s), 8.62 (1H, d, J = 6 Hz), 11.42 (1H, br s).

8p: ^{1}H NMR (DMSO-d_6) δ 2.6−3.03 (1H, m), 2.87 (3H, s), 3.14−3.72 (4H, m), 7.12−7.38 (2H, m), 7.42−7.56 (1H, m), 7.6−8.4 (4H, br s), 7.83 (1H, d, J = 6 Hz), 8.64 (1H, d, J = 6 Hz), 11.58 (1H, s).

8q: ^{1}H NMR (DMSO-d_6) δ 2.60−3.08 (1H, m), 2.86 (3H, s), 3.28−3.80 (4H, m), 6.96−7.08 (1H, m), 7.14 (1H, s), 7.43 (1H, d, J = 5 Hz), 7.6−8.2 (4H, br s), 7.81 (1H, d, J = 6 Hz), 8.63 (1H, d, J = 6 Hz), 11.69 (1H, s).

8r: ^{1}H NMR (DMSO-d_6) δ 2.7−2.97 (1H, m), 2.86 (3H, s), 3.22−4.4 (4H, m), 7.08 (1H, d, J = 5 Hz), 7.4−8.4 (4H, br s), 7.63 (1H, d, J = 5 Hz), 7.8 (1H, d, J = 5 Hz), 8.62 (1H, d, J = 6 Hz), 11.43 (1H, s).

8s: ^{1}H NMR (DMSO-d_6) δ 2.72−2.94 (1H, m), 2.83 (3H, s), 3.20−4.0 (4H, m), 7.24 (1H, s), 7.75 (1H, d, J = 6 Hz), 7.87 (4H, br s), 8.60 (1H, d, J = 6 Hz), 11.47 (1H, s).

8t: ^{1}H NMR (DMSO-d_6) δ 2.86 (3H, s), 2.80−3.02 (1H, m), 3.36 (4H, m), 7.24 (1H, dd, J = 1, 5 Hz), 7.49 (1H, d, J = 2 Hz), 7.56 (1H, m), 7.82 (1H, d, J = 6 Hz), 7.90 (4H, br s), 8.64 (1H, d, J = 6 Hz), 11.65 (1H, br s).

8u: ^{1}H NMR (DMSO-d_6) δ 2.86 (4H, m), 3.04−3.22 (1H, m), 3.39 (3H, m), 7.25 (1H, d, J = 6 Hz), 7.55 (1H, d, J = 6 Hz), 7.82 (1H, d, J = 6 Hz), 7.92 (4H, br s), 8.62 (1H, d, J = 6 Hz), 11.43 (1H, br s).

8v: ^{1}H NMR (DMSO-d_6) δ 2.85 (4H, m), 3.03−3.22 (1H, m), 3.36 (3H, m), 7.42 (1H, s), 7.79 (1H, d, J = 6 Hz), 7.90 (4H, br s), 8.62 (1H, d, J = 6 Hz), 11.44 (1H, br s).

8w: ^{1}H NMR (DMSO-d_6) δ 2.82 (3H, s), 3.03−3.78 (5H, m), 7.4−8.3 (4H, br s), 7.53−7.63 (1H, m), 7.78 (1H, d, J = 8 Hz), 7.84 (1H, d, J = 6 Hz), 8.06−8.17 (1H, m), 8.65 (1H, d, J = 6 Hz), 8.70 (1H, d, J = 5 Hz), 11.57 (1H, s).

8x: ^{1}H NMR (DMSO-d_6) δ 2.70−4.2 (5H, m), 2.85 (3H, s), 7.60−8.4 (4H, br s), 7.76 (1H, d, J = 6 Hz), 8.17 (2H, d, J = 5 Hz), 8.61 (1H, d, J = 6 Hz), 8.97 (2H, d, J = 5 Hz), 11.82 (1H, s).

8y: ^{1}H NMR (DMSO-d_6) δ 2.85 (3H, s), 2.98 (1H, dd, J = 10, 18 Hz), 3.30 (2H, m), 3.56 (2H, m), 6.42 (2H, d, J = 1 Hz), 7.63 (1H, d, J = 1 Hz), 7.82 (1H, d, J = 6 Hz), 7.98 (4H, br s), 8.64 (1H, d, J = 6 Hz), 11.79 (1H, s).

9b: ^{1}H NMR (DMSO-d_6) δ 2.54 (6H, s), 2.72−2.84 (1H, m), 3.06−3.57 (3H, m), 3.63−4.3 (1H, m), 4.21 (3H, s), 7.2−8.0 (4H, br s), 7.36−7.63 (5H, m), 8.61 (1H, d, J = 7 Hz).

10b: ^{1}H NMR (DMSO-d_6) δ 2.78 (3H, s), 2.91 (1H, dd, J = 12, 18 Hz), 3.21−3.34 (1H, m), 3.40−3.56 (2H, m), 3.61−3.78 (1H, m), 7.31−7.70 (4H, m), 8.00 (4H, br s), 9.32 (1H, s).

11b: ^{1}H NMR (DMSO-d_6) δ 2.7−3.0 (2H, m), 2.83 (3H, s), 3.1−3.4 (2H, m), 3.59 (1H, m), 7.32−7.64 (4H, m), 7.76 (4H, br s), 8.89 (1H, s).

12e: ^{1}H NMR (DMSO-d_6) δ 2.33 (3H, s), 2.34 (3H, s), 2.53−3.08 (4H, m), 3.67−3.85 (1H, m), 6.46 (1H, s), 7.05−7.34 (4H, m), 8.30 (1H, br s).

13b: ^{1}H NMR (DMSO-d_6) δ 2.48 (3H, s), 2.68 (1H, dd, J = 12, 17 Hz), 2.94 (2H, d, J = 8 Hz), 3.05 (1H, dd, J = 2, 16 Hz), 3.53−3.72 (1H, m), 6.9−7.9 (4H, br s), 7.24−7.53 (3H, m), 7.56−7.63 (1H, m), 10.86 (1H, s).

14b: ^{1}H NMR (DMSO-d_6) δ 2.21 (3H, s), 2.69 (1H, dd, J = 12.0, 16.2 Hz), 2.99−3.09 (3H, m), 3.71 (1H, m), 7.0−7.8 (4H, br s), 7.27−7.51 (3H, m), 7.42 (1H, s), 7.61 (1H, dd, J = 2.0, 7.4 Hz).

15b: ^{1}H NMR (DMSO-d_6) δ 2.45 (3H, s), 2.73 (1H, dd, J = 12, 17 Hz), 3.0−3.20 (3H, m), 3.56−3.77 (1H, m), 6.9−8.1 (4H, br s), 7.03 (1H, s), 7.25−7.66 (4H, m), 10.77 (1H, s).

(5*E*,7*S*)-[[7-(2-Chlorophenyl)-4-methyl-7,8-dihydro-5(6*H*)-quinolinylidene]amino]guanidine Methanesulfonate (16). To the suspension of **8b** (123.9 g, 0.31 mol) in MeOH (1200 mL) was added dropwise 28% NaOMe in MeOH (119 mL). The mixture was stirred at 50 °C for 30 min and concentrated under reduced pressure. The residue was washed with water and dried to give free base (109.3 g) as colorless crystals. To a solution of this free base in *i*-PrOH (700 mL) was added dropwise a solution of L-pyroglutamic acid (10 g, 77.5 mmol) in *i*-PrOH (700 mL) at 50 °C for 1.5 h, and the mixture was stirred at 50 °C for 1 h and then at room temperature for 2 days. The precipitates formed were filtered and washed with *i*-PrOH to give diastereomeric salt (55.5 g, 46%, 88% ee), which was recrystallized from EtOH to give crystals (44.3 g, 36%, 97% ee). This crystals of salt were

suspended in MeOH (500 mL), and a solution of 28% NaOMe in MeOH (10.9 mL) was added. The mixture was stirred at 50 °C for 30 min and evaporated. The residue was washed with water and dried to give the free base of **16** (38.9 g). To the solution of this free base (38.9 g, 0.11 mol) in EtOH (400 mL) was added methanesulfonic acid (14.3 g, 0.22 mol), and the mixture was evaporated to give crystals, which were recrystallized from EtOH to give **16** (46.8 g) as colorless crystals: 99.2% ee; $[\alpha]_D$ −57.8 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ 2.40 (6H, s), 2.78 (1H, dd, J = 12, 18 Hz), 2.89 (3H, s), 3.08−3.32 (2H, m), 3.44−3.80 (2H, m), 7.2−8.1 (4H, br s), 7.31−7.56 (3H, m), 7.58−7.66 (1H, m), 7.86 (1H, d, J = 6 Hz), 8.66 (1H, d, J = 6 Hz), 10.77 (1H, s).

(5*E*,7*R*)-[[7-(2-Chlorophenyl)-4-methyl-7,8-dihydro-5(6*H*)-quinolinylidene]amino]guanidine Methanesulfonate (17). The mixture of (−)-**8b** (0.33 g, 1.2 mmol), aminoguanidine hydrochloride (0.16 g, 1.5 mmol), concentrated HCl (0.3 mL), and water (0.3 mL) in EtOH (25 mL) was refluxed for 6 h. The solvent was evaporated under reduced pressure. The residue was dissolved in water and washed with Et_2O. Aqueous $NaHCO_3$ was added, and the solution was extracted with EtOAc. The organic layer was washed with water, dried, and evaporated. The residue was dissolved in EtOH, and methanesulfonic acid (0.23 g, 2.4 mmol) was added. The mixture was concentrated, and the residue was recrystallized from EtOH−acetone to afford **17** (0.52 g, 83%) as colorless crystals: >99.9% ee; $[\alpha]_D$ +54.3 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6) was in agreement with that of **16**.

(5*E*,7*S*)-[[7-(5-Fluoro-2-methylphenyl)-4-methyl-7,8-dihydro-5(6*H*)-quinolinylidene]amino]guanidine Dimethanesulfonate (18). To the suspension of **8n** (100.3 g, 0.25 mol) in MeOH (900 mL) was added dropwise 28% NaOMe in MeOH (107.8 g). The solvent was removed under reduced pressure, and the residue was washed with water and dried to give free base (67.5 g) as colorless crystals. To a solution of this free base in EtOH (1000 mL) was added dropwise a solution of D-pyroglutamic acid (27.1 g, 0.21 mol) in EtOH (60 mL) at 80 °C. The mixture was allowed to cool to room temperature slowly and was stirred at the same temperature for 14 h. The precipitate formed was filtered and washed with EtOH to give diastereomeric salt (43.0 g, 45%, 95.7% ee). These crystals of salt were suspended in MeOH (700 mL), and a solution of 28% NaOMe in MeOH (18.3 g) was added. The mixture was evaporated, and the residue was washed with water and dried to give the free base of **18** (30.9 g). To the solution of this free base (3.0 g, 9.2 mmol) in EtOH (20 mL) was added methanesulfonic acid (1.9 g, 19.4 mmol), and the mixture was evaporated and recrystallized from EtOH to afford **18** (3.8 g, 36% from **8n**) as colorless crystals: 99.8% ee; $[\alpha]_D$ −61.4 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ 2.30 (3H, s), 2.35 (6H, s), 2.62−2.95 (1H, m), 2.86 (3H, s), 2.99−3.24 (2H, m), 3.3−3.6 (2H, m), 6.96−7.11 (1H, m), 7.19−7.42 (2H, m), 7.7 (4H, br s), 7.81 (1H, d, J = 5 Hz), 8.65 (1H, d, J = 5 Hz), 10.68 (1H, s).

(5*E*,7*S*)-[[7-(5-Fluoro-2-methylphenyl)-4-methyl-7,8-dihydro-5(6*H*)-quinolinylidene]amino]guanidine Hydrochloride (19). To the solution of the free base of **18** (1.5 g, 4.6 mmol) in EtOH (20 mL) was added concentrated HCl (1.2 mL), and the mixture was concentrated. The residue was recrystallized from EtOH−water to afford **19** (0.96 g, 99.3%) as colorless crystals. This compound was confirmed to be the *S* isomer by X-ray crystal structure analysis: mp 192−198 °C; ^{1}H NMR (DMSO-d_6) δ 2.31 (3H, s), 2.66−3.03 (1H, m), 2.89 (3H, s), 3.12−3.6 (4H, m), 6.94−7.06 (1H, m), 7.16−7.37 (2H, m), 7.4−8.3 (4H, br s), 7.85 (1H, d, J = 6 Hz), 8.64 (1H, d, J = 6 Hz), 11.41 (1H, s).

(5E,7R)-[[7-(5-Fluoro-2-methylphenyl)-4-methyl-7,8-dihydro-5(6H)-quinolinylidene]amino]guanidine Dimethanesulfonate (20). To the combined filtrate obtained in preparation of **18** was added 28% NaOMe in MeOH (25.5 g). The solvent was removed under reduced pressure, and the residue was washed with water and dried to give free base (41.5 g) as colorless crystals. This free base was resolved with L-pyroglutamic acid in the same manner as for the preparation of **18** to give **20** as colorless crystals: 99.4% ee; $[\alpha]_D$ +60.5 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6) was in agreement with that of **18**.

The following compounds (**21, 22**) were prepared by a manner similar to that used for **18** and **20**.

21: 99.5% ee; $[\alpha]_D$ −38.7 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ 2.41 (6H, s), 2.70−2.94 (1H, m), 2.86 (3H, s), 2.97−3.26 (2H, m), 3.27−3.57 (2H, m), 7.2−8.4 (4H, br s), 7.41 (1H, s), 7,82 (1H, d, J = 6 Hz), 8.65 (1H, d, J = 6 Hz), 10.80 (1H, s).

22: 99.9% ee; $[\alpha]_D$ +39.5 (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6) was in agreement with that of **21**.

7-(2-Chlorophenyl)-4-methyl-5,6,7,8-tetrahydroquinolin-5-one (26b), Typical Procedure. To a mixture of **24b** (1.1 g, 4.7 mmol), 1-amino-2-butyne hydrochloride (0.5 g, 4.7 mmol), and molecular sieves 4A (2 g) in THF (20 mL) was added triethylamine (0.48 g, 4.7 mmol). The mixture was stirred at room temperature for 1 h and then refluxed for 12 h and cooled. Insoluble material was filtered off, and the solvent was removed under reduced pressure. The residue was stirred at 220 °C for 4 h. To the mixture were added EtOAc and aqueous $NaHCO_3$. The organic layer was washed with water, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc−hexane as eluent to afford crystals, which were recrystallized from EtOAc−hexane to give **26b** (0.20 g, 16%) as colorless crystals: mp 97−98 °C; ^{1}H NMR ($CDCl_3$) δ 2.71 (3H, s), 2.84 (1H, dd, J = 13, 16 Hz), 3.02 (1H, ddd, J = 2, 4, 16 Hz), 3.30 (1H, dd, J = 12, 17 Hz), 3.48 (1H, ddd, J = 2, 4, 17 Hz), 3.88−4.07 (1H, m), 7.11 (1H, d, J = 5 Hz), 7.16−7.34 (4H, m), 8.50 (1H, d, J = 5 Hz). Anal. ($C_{16}H_{14}ClNO$) C, H, N.

The following compounds (**26e**−**h,q,w**−**y**) were prepared by a manner similar to that used for **26b**.

26e: mp 104−106 °C; ^{1}H NMR ($CDCl_3$) δ 2.36 (3H, s), 2.70 (3H, s), 2.75−3.03 (2H, m), 3.17−3.48 (2H, m), 3.54−3.77 (1H, m), 7.08 (1H, d, J = 5 Hz), 7.10−7.34 (4H, m) 8.47 (1H, d, J = 5 Hz). Anal. ($C_{17}H_{17}NO$) C, H, N.

26f: colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.70 (3H, s), 2.75−3.05 (2H, m), 3.23−3.48 (2H, m), 3.71−3.93 (1H, m), 3.83 (3H, s), 6.86 (2H, m), 7.07 (1H, d, J = 5 Hz), 7.18−7.32 (2H, m) 8.47 (1H, d, J = 5 Hz).

26g: colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.70 (3H, s), 2.83−3.08 (2H, m), 3.29−3.46 (2H, m), 3.71−3.77 (1H, m), 7.02−7.36 (5H, m), 8.49 (1H, d, J = 4 Hz).

26h: mp 106−107 °C; ^{1}H NMR ($CDCl_3$) δ 2.71 (3H, s), 2.82 (1H, dd, J = 13, 16 Hz), 3.03 (1H, ddd, J = 2, 4, 10 Hz), 3.28 (1H, dd, J = 12, 17 Hz), 3.49 (1H, ddd, J = 2, 4, 11 Hz), 3.86−4.06 (1H, m), 7.08−7.47 (4H, m), 7.57−7.66 (1H, m), 8.50 (1H, d, J = 5 Hz). Anal. ($C_{16}H_{14}BrNO$) C, H, N.

26q: mp 105−107 °C; ^{1}H NMR ($CDCl_3$) δ 2.69 (3H, s), 2.90 (1H, dd, J = 11, 16 Hz), 3.14 (1H, ddd, J = 2, 4, 11 Hz), 3.37 (1H, dd, J = 11, 16 Hz), 3.61 (1H, ddd, J = 2, 4, 11 Hz), 3.69−3.88 (1H, m), 6.86−7.04 (2H, m), 7.09 (1H, d, J = 5 Hz), 7.21 (1H, dd, J = 1, 5 Hz), 8.49 (1H, d, J = 5 Hz). Anal. ($C_{14}H_{13}NOS$) C, H, N.

26w: colorless oil; ^{1}H NMR($CDCl_3$) δ 2.69 (3H, s), 2.98 (1H, ddd, J = 1, 4, 16 Hz), 3.15 (1H, dd, J = 11, 16 Hz), 3.37−3.76 (3H, m), 7.08 (1H, d, J = 5 Hz), 7.18 (1H, ddd, J = 1, 5, 8 Hz), 7.24 (1H, d, J = 8 Hz), 7.66 (1H, dt, J = 2, 8 Hz), 8.47 (1H, d, J = 5 Hz), 8.58 (1H, ddd, J = 1, 2, 5 Hz).

26x: colorless oil; ^{1}H NMR($CDCl_3$) δ 2.69 (3H, s), 2.87 (1H, dd, J = 12, 16 Hz), 2.92−3.08 (1H, m), 3.25−3.62 (3H, m), 7.12 (1H, d, J = 5 Hz), 7.22−7.35 (1H, m), 8.50 (1H, d, J = 5 Hz), 8.57−8.65 (1H, m).

26y: mp 70−71 °C; ^{1}H NMR($CDCl_3$) δ 2.68 (3H, s), 2.92 (1H, dd, J = 10, 17 Hz), 3.08 (1H, ddd, J = 2, 4, 7 Hz), 3.40 (1H, dd, J = 10, 17 Hz), 3.59 (2H, m), 6.08 (1H, d, J = 3 Hz), 6.31 (1H, dd, J = 2, 3 Hz), 7.08 (1H, d, J = 5 Hz), 7.36 (1H, d, J = 2 Hz), 8.49 (1H, d, J = 5 Hz). Anal. ($C_{14}H_{13}NO_2$) C, H, N.

7-(5-Fluoro-2-methylphenyl)-4-methyl-5,6,7,8-tetrahydroquinolin-5-one (26n), Typical Procedure. A mixture of **24n** (3.0 g, 13.6 mmol) and ammonium acetate (3.1 g, 40.9 mmol) in EtOH (50 mL) was refluxed for 14 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc. The mixture was washed with water,

dried, and evaporated under reduced pressure to give **27n** (2.7 g). The mixture of **27n** (2.7 g, 12.3 mmol), 3-oxobutylaldehyde dimethylacetal (4.1 g, 30.8 mmol), and powdery KOH (0.57 g, 10.2 mmol) in EtOH (70 mL) and toluene (120 mL) was refluxed for 3.5 h. In this period powdery KOH (0.12 g, 2.1 mmol) was added three times for 30 min each, and 3-oxobutylaldehyde dimethylacetal (0.33 g, 2.5 mmol) was added 1 h later. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc and washed with water, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc−hexane as eluent to afford crystals, which were recrystallized from EtOAc−hexane to give **26n** (1.5 g, 41%) as colorless crystals: mp 113−114 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (3H, s), 2.71 (3H, s), 2.78−2.98 (2H, m), 3.24 (1H, dd, J = 11, 16 Hz), 3.28−3.44 (1H, m), 3.55−3.74 (1H, m), 6.82−7.04 (2H, m), 7.12 (1H, d, J = 5 Hz), 7.07−7.22 (2H, m), 8.50 (1H, d, J = 5 Hz). Anal. ($C_{17}H_{16}FNO$) C, H, N.

The following compounds (**26a**−**d,i**−**p,r**−**v**) were prepared by a manner similar to that used for **26n**.

26a: mp 73−74 °C; ^{1}H NMR ($CDCl_3$) δ 2.70 (3H, s), 2.80−3.07 (2H, m), 3.23−3.60 (3H, m), 7.10 (1H, d, J = 5 Hz), 7.23−7.46 (5H, m), 8.50 (1H, d, J = 5 Hz). Anal. ($C_{16}H_{15}NO$) C, H, N.

26c: mp 112−113 °C; ^{1}H NMR ($CDCl_3$) δ 2.70 (3H, s), 2.77−3.06 (2H, m), 3.22−3.58 (3H, m), 7.11 (1H, d, J = 5 Hz), 7.13−7.37 (4H, m), 8.50 (1H, d, J = 5 Hz). Anal. ($C_{16}H_{14}ClNO$) C, H, N.

26d: mp 124−125 °C; ^{1}H NMR ($CDCl_3$) δ 2.70 (3H, s), 2.84 (1H, dd, J = 12, 17 Hz), 2.98 (1H,ddd, J = 2, 4, 17 Hz), 3.29 (1H, dd, J = 12, 17 Hz), 3.35−3.6 (2H, m), 7.1 (1H, d, J = 5 Hz), 7.2−7.4 (4H, m), 8.49 (1H, d, J = 5 Hz). Anal. ($C_{16}H_{14}ClNO$) C, H, N.

26i: mp 123−124 °C; ^{1}H NMR ($CDCl_3$) δ 2.72 (3H, s), 2.81 (1H, dd, J = 12, 16 Hz), 3.03 (1H, ddd, J = 2, 4, 8 Hz), 3.29 (1H, dd, J = 11, 17 Hz), 3.49 (1H, ddd, J = 2, 4, 8 Hz), 4.03 (1H, m), 7.13 (1H, d, J = 5 Hz), 7.24 (2H, m), 7.43 (1H, m), 8.51 (1H, d, J = 5 Hz). Anal. ($C_{16}H_{13}Cl_2NO$) C, H, N.

26j: mp 136−137 °C; ^{1}H NMR ($CDCl_3$) δ 2.71 (3H, s), 2.81 (1H, dd, J = 12, 16 Hz), 3.00 (1H, ddd, J = 2, 4, 16 Hz), 3.27 (1H, dd, J = 12, 17 Hz), 3.46 (1H, ddd, J = 2, 4, 17 Hz), 3.83−4.03 (1H, m), 7.12 (1H, d, J = 5 Hz), 7.22−7.33 (2H, m), 7.45 (1H, d, J = 2 Hz), 8.51 (1H, d, J = 5 Hz). Anal. ($C_{16}H_{13}Cl_2NO$) C, H, N.

26k: mp 116−117 °C; ^{1}H NMR ($CDCl_3$) δ 2.72 (3H, s), 2.80 (1H, dd, J = 12, 16 Hz), 3.00 (1H, ddd, J = 2, 4, 17 Hz), 3.26 (1H, dd, J = 12, 17 Hz), 3.46 (1H, ddd, J = 2, 4, 16 Hz), 3.83−4.04 (1H, m), 7.12 (1H, d, J = 5 Hz), 7.21 (1H, dd, J = 2, 8 Hz), 7.31 (1H, d, J = 2 Hz), 7.36 (1H, d, J = 8 Hz), 8.50 (1H, d, J = 5 Hz). Anal. ($C_{16}H_{13}Cl_2NO$) C, H, N.

26l: isolated as HCl salt; mp 184−185 °C; ^{1}H NMR (DMSO-d_6) δ 2.55−2.65 (1H, m), 2.79 (3H, s), 3.35 (1H, ddd, J = 2, 4, 11 Hz), 3.74 (1H, dd, J = 14, 17 Hz), 4.19 (1H, dd, J = 13, 17 Hz), 4.48−4.58 (1H, m), 7.33−7.57 (1H, m), 7.50−7.54 (2H, m), 7.75 (1H, d, J = 6 Hz), 8.77 (1H, d, J = 6 Hz). Anal. ($C_{16}H_{13}ClNO\cdot HCl$) C, H, N.

26m: colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.71 (3H, s), 2.79 (1H, dd, J = 13, 16 Hz), 3.01 (1H, ddd, J = 2, 4, 17 Hz), 3.26 (1H, dd, J = 12, 17 Hz), 3.48 (1H, ddd, J = 2, 4, 17 Hz), 3.83−4.03 (1H, m), 6.87−7.07 (2H, m), 7.13 (1H, d, J = 5 Hz), 7.34−7.43 (1H, m), 8.51 (1H, d, J = 5 Hz). Anal. ($C_{16}H_{13}ClFNO$) C, H, N.

26n: mp 113−114 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (3H, s), 2.71 (3H, s), 2.78−2.98 (2H, m), 3.24 (1H, dd, J = 11, 16 Hz), 3.28−3.44 (1H, m), 3.55−3.74 (1H, m), 6.82−7.04 (2H, m), 7.12 (1H, d, J = 5 Hz), 7.07−7.22 (2H, m), 8.50 (1H, d, J = 5 Hz). Anal. ($C_{17}H_{16}FNO$) C, H, N.

26o: isolated as HCl salt; mp 174−175 °C; ^{1}H NMR (DMSO-d_6) δ 2.71−2.86 (4H, m), 3.10 (1H, dd, J = 13, 17 Hz), 3.5−3.64 (2H, m), 3.68−4.03 (4H, m), 6.99−7.24 (3H, m), 7.76 (1H, d, J = 6 Hz), 8.78 (1H, d, J = 6 Hz). Anal. ($C_{17}H_{15}FNO_2\cdot HCl$) C, H, N.

26p: mp 75−76 °C; ^{1}H NMR ($CDCl_3$) δ 2.71 (3H, s), 2.86 (1H, dd, J = 12, 17 Hz), 2.9−3.07 (1H, m), 3.33 (1H, dd, J = 11, 17 Hz), 3.37−3,53 (1H, m), 3.68−3.87 (1H, m), 6.86−7.15 (4H, m), 8.50 (1H, d, J = 5 Hz). Anal. ($C_{16}H_{13}F_2NO$) C, H, N.

26r: colorless oil; ^{1}H NMR ($CDCl_3$) δ 2.70 (3H, s), 2.82 (1H, dd, J = 12, 17 Hz), 3.08 (1H, ddd, J = 2, 4, 16 Hz), 3.32 (1H, dd, J = 11, 17 Hz), 3.54 (1H, ddd, J = 2, 4, 17 Hz), 3.86−4.06 (1H, m), 6.93 (1H, d, J = 5 Hz), 7.12 (1H, d, J = 5 Hz), 7.2 (1H, d, J = 5 Hz), 8.50 (1H, d, J = 5 Hz).

26t: mp 92−93 °C; ^{1}H NMR ($CDCl_3$) δ 2.69 (3H, s), 2.85 (1H, dd, J = 12, 17 Hz), 3.09 (1H, ddd, J = 2, 4, 16 Hz), 3.28 (1H, dd, J = 11, 17 Hz), 3.61 (2H, m), 7.08 (3H, m), 7.38 (1H, m), 8.49 (1H, d, J = 5 Hz). Anal. ($C_{14}H_{13}NOS$) C, H, N.

26v: mp 138−140 °C; ^{1}H NMR ($CDCl_3$) δ 2.70 (3H, s), 2.75 (1H, dd, J = 12, 17 Hz), 2.93 (1H, ddd, J = 2, 4, 16 Hz), 3.22 (1H, dd, J = 11, 17 Hz), 3.39 (1H, ddd, J = 2, 5, 17 Hz), 3.57−3.76 (1H, m), 6.72 (1H, s), 7.11 (1H, d, J = 5 Hz), 8.50 (1H, d, J = 5 Hz). Anal. ($C_{14}H_{11}Cl_2NOS$) C, H, N.

7-(3,5-Dichlorothiophen-2-yl)-4-methyl-5,6,7,8-tetrahydroquinolin-5-one (26s). To the solution of **26r** (0.74 g, 2,7 mmol) in EtOAc (10 mL) were added pyridine (0.22 mL, 0.21 g, 2.7 mmol) and SO_2Cl_2 (0.22 mL, 0.38 g, 2.8 mmol), and the mixture was stirred for 3 h at room temperature. The solution was diluted with EtOAc and washed successively with aqueous $NaHCO_3$ and water, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc−hexane as eluent to give **26s** (0.56 g, 66%) as colorless crystals: mp 109−111 °C; ^{1}H NMR($CDCl_3$) δ 2.68 (3H,s), 2.76 (1H, dd, J = 12, 16 Hz), 3.04 (1H, ddd, J = 2, 4, 17 Hz), 3,24 (1H, dd, J = 11, 17 Hz), 3,51 (1H, ddd, J = 2, 4, 17 Hz), 3.82−3.99 (1H, m), 6.76 (1H, s), 7.11 (1H, d, J = 5 Hz), 8.49 (1H, d, J = 5 Hz). Anal. ($C_{14}H_{11}Cl_2NOS$) C, H, N.

Compound **26u** was prepared by a manner similar to that used for **26s**.

26u: amorphous; ^{1}H NMR($CDCl_3$) δ 2.70 (3H, s), 2.77 (1H, dd, J = 12, 17 Hz), 2.97 (1H, ddd, J = 2, 5, 17 Hz), 3.29 (1H, dd, J = 11, 17 Hz), 3.32 (1H, ddd, J = 2, 5, 18 Hz), 3.72 (1H, m), 6.89 (1H, d, J = 6 Hz), 7.12 (2H, m), 8.50 (1H, d, J = 6 Hz).

2,2-Dimethyl-5-[([3-oxo-5-(2-chlorophenyl)-1-cyclohexenyl]amino)methylene]-[1,3]-dioxane-4,6-dione (28b). A mixture of 5-(methoxymethylene)-2,2-dimethyl-[1,3]-dioxane-4,6-dione (1.7 g, 9.0 mmol) and **27b** (2.2 g, 9.9 mmol) in CH_3CN (15 mL) was stirred at room temperature for 13 h. Precipitated crystals were filtered and washed with CH_3CN to give **28b** (1.7 g, 50%) as colorless crystals: mp 112 °C dec; ^{1}H NMR ($CDCl_3$) δ 1.75 (6H, s), 2.62−2.84 (3H, m), 2.95 (1H, dd, J = 5, 17 Hz), 3.89−4.09 (1H, m), 6.0 (1H, d, J = 2 Hz), 7.14−7.52 (4H, m), 8.38 (1H, d, J = 14 Hz), 11.03 (1H, d, J = 14 Hz). Anal. ($C_{19}H_{18}ClNO_5$) C, H, N.

7-(2-Chlorophenyl)-4-hydroxy-5,6,7,8-hexahydroquinolin-5-one (29b). A solution of **28b** (1.6 g, 4.3 mmol) in Ph_2O (20 mL) was stirred at 260 °C for 30 min. The solvent was removed under reduced pressure, and the residue was washed with petroleum ether and recrystallized from EtOH to give **29b** (1.1 g, 93%) as colorless crystals: mp 243 °C dec; ^{1}H NMR (DMSO-d_6) d 2.59−2.77 (1H, m), 2.92−3.6 (3H, m), 3.77−4.0 (1H, m), 6.53 (1H, br s), 7.23−7.58 (4H, m), 8.03 (1H, br s). Anal. ($C_{15}H_{12}ClNO_2$) C, H, N.

7-(2-Chlorophenyl)-4-methoxy-5,6,7,8-tetrahydroquinolin-5-one (30b). The mixture of phosphorus oxychloride (5.4 g, 35.1 mmol) and **29b** (0.60 g, 2.2 mmol) was stirred at 100 °C for 2 h. The mixture was cooled and concentrated under reduced pressure. To the residue was added 1 N NaOH. The mixture was extracted with EtOAc, and the organic layer was washed with water, dried, and evaporated to afford the 4-chloro derivative (0.55 g, 86%) as colorless crystals. The mixture of these crystals (0.2 g, 0.68 mmol) and NaOMe (0.074 g, 1.4 mmol) in MeOH (20 mL) was refluxed for 2 h. The solvent was removed, and EtOAc was added. The organic layer was washed with water, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc−hexane as elutent to yield **30b** (0.1 g, 61%) as colorless crystals: mp 116−117 °C; ^{1}H NMR ($CDCl_3$) δ 2.81 (1H, dd, J = 12, 16 Hz), 3.0 (1H, ddd, J = 2, 4, 17 Hz), 3.25 (1H, dd, J = 12, 17 Hz), 3.45 (1H, ddd, J = 2, 4, 17 Hz), 3.80−4.16 (1H, m), 4.00 (3H, s), 6.85 (1H, d, J = 6 Hz), 7.16−7.45 (4H, m), 8.53 (1H, d, J = 6 Hz) Anal. ($C_{16}H_{14}ClNO_2$) C, H, N.

7-Phenyl-5,6,7,8-tetrahydroquinolin-5-one (31a). The mixture of **24a** (5.0 g, 26.6 mmol), 1,1,3,3-tetramethoxypropane (8.7 g, 53.1 mmol), and ammonium acetate (6.1 g, 79.7 mmol) in AcOH (100 mL) was refluxed for 48 h. The solvent was removed under reduced pressure, and the residue was neutralized with aqueous $NaHCO_3$. The mixture was extracted with EtOAc, and the organic layer was washed with water, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc−hexane as eluent to afford crystals, which were recrystallized from EtOAc−hexane to give **31a** (1.1 g, 19%) as colorless crystals: mp 78−79 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.89 (1H, dd, J = 12, 17 Hz), 2.95−3.12 (1H, m), 3.04 (1H, dd, J = 11, 17 Hz), 3.4−3.63 (2H, m), 7.20−7.43 (6H, m), 8.33 (1H, dd, J = 1.8, 7.6 Hz), 8.73 (1H, dd, J = 1.8, 4.7 Hz). Anal. ($C_{15}H_{13}NO$) C, H, N.

2-Methyl-7-phenyl-5,6,7,8-tetrahydroquinolin-5-one (32a). The mixture of **24a** (1.2 g, 6.4 mmol), ammonium acetate (0.49 g, 6.4 mmol), and 3-butyn-2-one (0.44 g, 6.4 mmol) in EtOH (20 mL) was stirred at room temperature for 1.5 h and refluxed for 18 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc. The solution was washed successively with aqueous $NaHCO_3$ and water, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc−hexane as eluent to give **32a** (0.88 g, 58%) as colorless crystals: mp 79−81 °C; ^{1}H NMR ($CDCl_3$) δ 2.61 (3H, s), 2.85 (1H, dd, J = 12, 17 Hz), 3.00 (1H, ddd, J = 1, 4, 17 Hz), 3.23−3.63 (3H, m), 7.18 (1H, d, J = 8 Hz), 7.22−7.43 (5H, m) 8.21 (1H, d, J = 8 Hz). Anal. ($C_{16}H_{15}NO$) C, H, N.

7-Phenyl-2,4-dimethyl-5,6,7,8-tetrahydroquinolin-5-one (33a). A mixture of **24a** (2.0 g, 10.6 mmol), ammonium acetate (0.9 g, 11.7 mmol), and acetylacetone (1.1 g, 10.6 mmol) in EtOH (30 mL) was stirred at room temperature for 1 h and refluxed for 21 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc. The solution was washed successively with aqueous $NaHCO_3$ and water, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc−hexane as eluent to give crystals, which was recrystallized from IPE−hexane to afford **33a** (0.6 g, 23%) as colorless crystals: mp 97−99 °C; ^{1}H NMR ($CDCl_3$) δ 2.54 (3H, s), 2.66 (3H, s), 2.77−3.04 (2H, m), 3.24−3.44 (2H, m), 3.51−3.94 (1H, m), 6.96 (1H, s), 7.00−7.33 (5H, m). Anal. ($C_{17}H_{17}NO$) C, H, N.

3-Methyl-6-(2-methylphenyl)-4,5,6,7-tetrahydroindol-4-one (35e). A mixture of **24e** (2.0 g, 9.9 mmol), 1-amino-2-propanol (0.97 g, 12.9 mol), molecular sieves 4A (12 g), and THF (30 mL) was refluxed for 12 h. Insoluble materials were filtered off. The solvent was removed under reduced pressure, and the residue was dissolved in DMF (40 mL). To the solution were added 2-bromomesitylene (2.0 g, 9.9 mmol), $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol), and K_2CO_3 (2.7 g, 19.8 mmol), and the mixture was stirred at 150 °C for 5 h. The solvent was removed under reduced pressure. The residue was dissolved in EtOAc, and the solution was washed successively with aqueous $NaHCO_3$ and water, dried, and evaporated. The residue was chromatographed on silica gel with EtOAc−hexane as eluent to afford **35e** (1.5 g, 63%) as colorless crystals: mp 190−191 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (3H, s), 2.34 (3H, s), 2.53−3.08 (4H, m), 3.67−3.85 (1H, m), 6.46 (1H, s), 7.05−7.34 (4H, m), 8.30 (1H, br s). Anal. ($C_{16}H_{17}NO\bullet 0.1H_2O$) C, H, N.

The following compound **35a** were prepared by a manner similar to that used for **35e**.

35a: mp 187−189 °C; ^{1}H NMR($CDCl_3$) δ 2.72 (1H, s), 2.76 (1H, dd, J = 16, 20 Hz), 3.02 (1H, dd, J = 16, 26 Hz), 3.06 (1H, dd, J = 16, 20 Hz), 3.43−3.61 (1H, m), 6.56 (1H, t, J = 3 Hz), 6.72 (1H, t, J = 3 Hz), 7.10−7.48 (5H, m) 9.31 (1H, br s). Anal. ($C_{14}H_{13}NO$) C, H, N.

2-(1-Hydroxyethylidene)-5-(2-chlorophenyl)cyclohexane-1,3-dione (36b). To a solution of **24b** (1.5 g, 6.7 mmol), acetic acid (0.73 g, 7.4 mmol), and 4-(dimethylamino)pyridine (0.12 g, 6.7 mmol) in DMF (65 mL) was added dicyclohexylcarbodiimide (1.5 g, 7.4 mmol), and the mixture was stirred at room temperature for 13 h. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc. The solution was washed successively with aqueous $NaHCO_3$ and water, dried, and evaporated. The residue was recrystallized from EtOAc−hexane to afford **36b** (1.4 g, 79%) as colorless crystals: mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 2.66 (3H, s), 2.53−3.04 (4H, m), 3.76−3.95 (1H, m), 7.17−7.45 (5H, m). Anal. ($C_{14}H_{13}ClO_3$) C, H.

6-(2-Chlorophenyl)-3-methyl-4,5,6,7-tetrahydroindazol-4-one (37b). A solution of **36b** (0.31 g, 1.2 mmol) and hydrazine hydrate (0.065 g, 1.3 mmol) in EtOH (10 mL) was refluxed for 30 min. The solvent was removed under reduced pressure, and the residue was recrystallized from EtOAc−hexane to give **37b** (0.26 g, 83%) as colorless crystals: mp 168−170 °C; ^{1}H NMR ($CDCl_3$) δ 2.59 (3H, s), 2.6−2.8 (2H, m), 2.94 (1H, dd, J = 11, 16 Hz), 3.22 (1H, dd, J = 4, 16 Hz), 3.90−4.06 (1H, m), 7.07−7.43 (4H, m). Anal. ($C_{14}H_{13}ClN_2O$) C, H, N.

7-(2-Chlorophenyl)-4-methyl-5,6,7,8-tetrahydroquinazolin-5-one (38b). A mixture of **36b** (0.48 g, 1.8 mmol), pyrrolidine (0.14 g, 1.9 mmol), anhydrous Na_2SO_4 (1.0 g, 7.0 mmol) and benzene (15 mL) was refluxed under argon atmosphere for 2 h. The solvent was removed under reduced pressure. To the residue were added formamidine acetate (0.19 g, 1.8 mmol), K_2CO_3 (0.25 g, 1.8 mmol), and MeOH (10 mL). The mixture was refluxed under argon atmosphere for 2 h, and the solvent was removed under reduced pressure. The residue was extracted with EtOAc. The organic layer was washed, dried, and chromatographed on silica gel with EtOAc−hexane as eluent to give **38b** (41 mg, 8%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.81−3.11 (2H, m), 2.90 (3H, s), 3.19−3.50 (2H, m), 4.00 (1H, m), 7.21−7.33 (3H, m), 7.44 (1H, dd, J = 1.4, 7.0 Hz), 9.06 (1H, s).

4-Methyl-7-(2-chlorophenyl)-5,6,7,8-tetrahydrocinnolin-5-one (40b). A mixture of **24b** (5.5 g, 25 mmol), *p*-toluene sulfonylhydrazide (4.6 g, 25 mmol), and EtOH (70 mL) was refluxed for 70 min and cooled, and precipitated crystals were filtered and washed with EtOH to afford colorless crystals (7.2 g). A mixture of these crystals (1.2 g, 3 mmol), anhydrous K_2CO_3 (1.1 g, 8 mmol), chloroacetone (0.34 g, 3.6 mmol), NaI (0.4 g, 2.7 mmol), EtOH (7.5 mL), and DME (7.5 mL) was stirred at 80 °C for 4 h. The solvent was removed under reduced pressure, and the residue was extracted with EtOAc. The organic layer was concentrated, and the residue was chromatographed on silica gel to give **40b** (0.34 g, 42%) as pale yellow crystals: mp 108−109 °C; ^{1}H NMR ($CDCl_3$) δ 2.71 (3H, s), 2.88 (1H, dd, J = 13, 17 Hz), 3.09 (1H, ddd, J = 2, 4, 17 Hz), 3.49 (1H, dd, J = 5, 17 Hz), 3.79 (1H, ddd, J = 2, 4, 17 Hz), 3.93−4.1 (1H, m), 7.22−7.35 (3H, m), 7.45 (1H, dd, J = 2, 7 Hz), 9.16 (1H, s). Anal. ($C_{15}H_{13}ClN_2O$) C, H, N.

6-(2-Chlorophenyl)-3-methyl-4,5,6,7-tetrahydrobenzofuran-4-one (41b). To a solution of **24b** (1.11 g, 5.0 mmol) in DMF (20 mL) was added 60% NaH (0.22 g, 5.5 mmol, washed three times with hexane), and the mixture was stirred under argon atmosphere at room temperature for 15 min. To the mixture was added chloroacetone (0.52 g, 5.7 mmol), and the mixture was stirred at 150 °C for 15 h. The solvent was removed under reduced pressure. To the residue was added ice−water, and the mixture was extracted with EtOAc. The organic layer was washed, dried, and evaporated. The residue was chromatograhed on silica gel with EtOAc−hexane as eluent to afford **41b** (0.35 g, 27%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.23 (3H, s), 2.73 (1H, s), 2.77 (1H, d, J = 5.2 Hz), 2.97 (1H, dd, J = 10.6, 17.0 Hz), 3.20 (1H, dd, J = 5.2, 16.8 Hz), 4.05 (1H, m), 7.12 (1H, s), 7.20−7.34 (3H, m), 7.41 (1H, dd, J = 1.2, 7.0 Hz).

5-(2-Chlorophenyl)-3-mercapto-2-cyclohexen-1-one (42b). A mixture of **24b** (3.0 g, 13.5 mmol) and PCl_3 (0.62 g, 4.5 mmol) in chloroform (10 mL) was stirred at 100 °C. After 2.5 h PCl_3 (0.62 g, 4.5 mmol) was added, and the mixture was stirred at 100 °C for 2 h and concentrated under reduced pressure. The mixture was poured onto ice−water and extracted with EtOAc. The organic layer was washed, dried, and evaporated. To the residue were added EtOH (3 mL) and the solution of $Na_2S\bullet 9H_2O$ (2.0 g, 8.3 mmol) in water (3 mL). The mixture was stirred at room temperature for 2 h and evaporated. Water was added to the residue, and the solution was washed with Et_2O. To the aqueous layer was added 4 N HCl to make the

solution acidic, and the solution was extracted with EtOAc. The organic layer was washed, dried, and evaporated to yield **42b** (1.8 g, 91%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.50−2.80 (4H, m), 3.52 (1H, s), 3.83−4.01 (1H, m), 6.20 (1H, s), 7.14−7.43 (4H, m).

5-(2-Chlorophenyl)-3-[(2-oxopropyl)thio]-2-cyclohexen-1-one (43b). To a solution of **42b** (1.8 g, 7.6 mmol) and chloroacetone (0.7 g, 7.6 mmol) in EtOH (20 mL) was added a solution of 20% NaOEt in EtOH (0.48 g, 8.2 mmol), and the mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure, the residue was extracted with EtOAc, and the organic layer was washed, dried, and evaporated to afford **43b** (2.3 g, quant) as colorless crystals: mp 81−82 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (3H, s), 2.52−2.80 (4H, m), 3.76 (2H, s), 3.79−3.99 (1H, m), 5.85 (1H, s), 7.16−7.43 (4H, m). Anal. ($C_{15}H_{15}ClO_2S$) C, H.

6-(2-Chlorophenyl)-3-methyl-4,5,6,7-tetrahydrobenzothiophene-4-one (44b). A solution of **43b** (1.0 g, 3.4 mmol) in xylene (10 mL) was refluxed for 7.5 days. The reaction mixture was chromatographed on silica gel with EtOAc−hexane as eluent to give **44b** (0.07 g, 8%) as an oil: ^{1}H NMR ($CDCl_3$) δ 2.48 (3H, s), 2.64−2.92 (2H, m), 3.09 (1H, dd, J = 11, 17 Hz), 3.35 (1H, dd, J = 4, 17 Hz), 3.96−4.13 (1H, m), 6.70 (1H, s), 7.14−7.50 (4H, m).

2-(2-Chlorophenyl)-5-methylchroman-4-one (47b). To the solution of 2′-hydroxy-6′-methylacetophenone (0.2 g, 1.3 mmol) in EtOH (4 mL) were added 50% NaOH (260 mg) and 2-chlorobenzaldehyde (0.2 g, 1.4 mmol). The solution was stirred at 50 °C for 1.5 h and acidified with 2 N HCl. Water was added and the mixture was extracted with EtOAc, and the organic layer was washed, dried, and evaporated. The residue was washed with MeOH to afford **46b** as yellow crystals. This was dissolved in AcOH (5 mL) and refluxed for 6 h. The mixture was concentrated under reduced pressure and chromatograhed on silica gel with EtOAc−hexane as eluent to afford **47b** (0.24 g, 27%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.69 (3H, s), 2.87 (1H, dd, J = 13, 17 Hz), 3.02 (1H, dd, J = 3, 17 Hz), 5.83 (1H, dd, J = 3, 13 Hz), 6.82−6.97 (2H, m), 7.25−7.44 (4H, m), 7.71−7.77 (1H, m).

2-(2-Chlorophenyl)-5-methyl-4*H*-chromen-4-one (50b). The solution of 2′-hydroxy-6′-methylacetophenone (0.45 g, 3 mmol) and 2-chlorobenzoyl chloride (0.58 g, 3.3 mmol) in pyridine (3 mL) was stirred at room temperature for 30 min. To the solution was added water (0.2 mL), and the mixture was extracted with EtOAc. The organic layer was washed successively with dilute HCl, aqueous $NaHCO_3$, and water, dried, and evaporated to afford **48b** as colorless oil. To the solution of **48b** in *t*-BuOH (8 mL) was added 60% NaH (0.24 g, 6 mmol). The mixture was stirred at room temperature for 30 min and concentrated under reduced pressure. The residue was dissolved in water, washed with Et_2O, and acidified with HCl. The mixture was extracted with *i*-Pr_2O, and the organic layer was washed, dried, and evaporated to afford **49b** as a yellow oil. To the solution of **49b** in AcOH (10 mL) was added $MeSO_3H$ (0.3 mL, 4.5 mmol), and the mixture was stirred at 165 °C for 3 h. The mixture was concentrated and extracted with EtOAc. The organic layer was washed with aqueous $NaHCO_3$ and water, dried, and evaporated. The residue was recrystallized from *i*-Pr_2O to give **50b** (0.66 g, 81%) as pale yellow crystals: mp 99−100 °C; ^{1}H NMR ($CDCl_3$) δ 2.90 (3H, s), 6.58 (1H, s), 7.13−7.66 (7H, m). Anal. ($C_{16}H_{11}ClO_2$) C, H.

NHE Assay in Rat and Human Platelets. Inhibitory effects of compounds on rat and human NHE were determined by a platelet assay.[26]

Blood was obtained from male Wistar rats (13−15 weeks) and was centrifuged at 3000 rpm for 5 s to obtain platelet-rich plasma (PRP). The remainder of the blood sample was then centrifuged at 3000 rpm for 5 min to prepare platelet-poor plasma (PPP). The PRP was diluted with physiological saline to a concentration of 40 × $10^4/\mu$L. A platelet aggregometer (Hematoracer, Niko Bioscience) was used for the measurement of NHE activity. Two hundred microliters of the PRP was poured into a cuvette and 600 μL of sodium propionate solution (135 mM sodium propionate, 10 mM glucose, 20 mM Hepes, 1 mM $CaCl_2$, and 1 mM $MgCl_2$; pH 6.7) was added while the mixture was stirred at 37 °C. The change in the light transmission of PRP at 550 nm, which was induced by the activation of NHE, was observed 1 min after the treatment with sodium propionate. PPP was used to correct for the light transmission of the nonplatelet part of PRP. The test compound dissolved in dimethyl sulfoxide (DMSO) was added to PRP 3 min before the treatment with sodium propionate. At this stage, the compound concentration was 4-fold higher than the final one in the assay and the concentration of DMSO was 4% (final concentration of 1%). The rate of inhibition of the compound on NHE-1 was calculated, designating the difference obtained between the treatments with vehicle and high concentration of HOE-642 (10^{-5}M), as 100%.

In the human platelet assay, blood samples were collected from the forearm vein of normal adult men, and the platelet number was adjusted to 10 × $10^4/\mu$L. In addition, the maximum upstroke velocity of the light transmission was calculated during the first minute after application of sodium propionate solution and used to determine the inhibitory effect of the compound on human platelet NHE-1.

Inhibitory Effects on the Extension of Myocardial Infarction in Rats. The details of the procedure of the experiment were previously reported.[27] Briefly, male Wistar rats (11−12 weeks) were anesthetized, and acute myocardial infarction was induced by occlusion of the left coronary artery (1 h) followed by reperfusion (24 h). The rats were anesthetized again and the heart was removed. The coronary artery was ligated at the same position previously occluded. Area at risk (AAR) was determined by the injection of 1% Evans blue. The left ventricle was cut into six slices and was incubated with 1% 2,3,5-triphenyltetrazolium chloride at 37 °C for 10 min to stain intact tissue. Infarct size was determined as a percentage of AAR based on weight. Compounds were intravenously administered 5 min before coronary occlusion.

X-ray Crystallography. A colorless crystal of approximate dimensions 0.40 × 0.40 × 0.30 mm was mounted on a glass fiber and transferred to a Rigaku AFC5R diffractometer. The intensity data were collected at 295 K by a 2θ/ω scan technique with Cu Kα radiation. The structure was solved by direct methods and refined on F2 by full-matrix least-squares techniques. Data processing and initial phase determination were carried out on the teXsan[28] system. The structure was refined by SHELXL-93.[29] This crystal contains two chlorine ions and disordered water molecules per asymmetric unit. Hydrogen atoms were included by use of a riding model. At convergence, *w*R2 = 0.0925 and GOF = 1.024 for 257 variables refined against all 3518 unique data. The absolute configuration was reliably determined by the refined Flack[30] parameter [−0.004(13)].

Acknowledgment. We thank Drs T. Naka and Z. Terashita for their encouragement and helpful advice. We thank H. Igata for the in vivo assay, A. Abe for the platelet assay, and T. Kawamoto for the hNHE assay, as well as A. Fujishima and K. Higashikawa for their X-ray crystallographic analysis.

Supporting Information Available: Analytical data and crystallographic data and details of refinement are available for compound **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM0104567