Novel Selective Hindlimb Vasodilators: Synthesis and Biological Activity of 1-Acyl-4-aminopiperidine Derivatives

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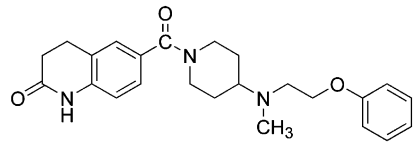
A series of 6-(4-amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinones, and their open form derivatives, were synthesized and evaluated for their ability to stimulate femoral artery blood flow (FBF) in the canine hindlimb. All members of this series stimulated FBF, and subsequent experiments revealed that selected members of this series produced minimal changes in coronary blood flow or systemic blood pressure. Compound **25** was the most promising agent in this respect, and clinical trials are now ongoing to evaluate the effectiveness of this drug as a novel treatment for intermittent claudication and Raynaud's phenomenon.

Introduction

Chronic arterial occlusion (CAO) due to atherosclerosis is characterized by progressive circulation insufficiency that contributes to the major symptoms of this disease, which include feelings of coldness, numbness, intermittent claudication pain, rest pain, and ulceration. In Raynaud's disease, circulatory insufficiency is considered intermittent and induced by exogenous factors (i.e., cold and stress). One objective of drug therapy in CAO or Raynaud's disease is to improve circulation to the extremities and another is to prevent progression of circulation insufficiency. Some effective therapeutics are available for the treatment of CAO. These include the vasoactive antiplatelet drugs cilostazol[1] and beraprost,[2] which produce significant improvements in pain-free walking in patient with intermittent claudication. In the treatment for Raynaud's phenomenon, vasodilators such as the Ca^{2+} antagonists, ketanserin, or iloprost have proven effective treatment for this circulatory insufficiency.[3−5] However, a number of studies have demonstrated that these compounds are ineffective treatment for these circulatory diseases[6−8] and are also associated with problematic side effects.[5,9] A drug discovery program was initiated to identify novel peripheral artery selective vasodilatory compounds that effectively improve circulation to the extremities and have minimal side effects, such as headache or hot flashes.

A large scale systematic screening program to identify drugs with selective vasodilatory activities identified 3,4-dihydro-6-(4-(*N*-methyl-2-phenoxy-1-ethylamino)-1-piperidinyl)carbonyl-2(1*H*)-quinolinone **1** which effectively increased femoral artery blood flow without producing any changes in coronary artery blood flow.



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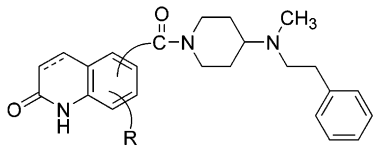
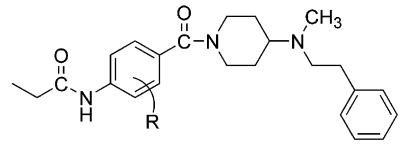


2-17



18-30

Figure 1.

Subsequent investigations revealed that the 2-phenyl-1-ethylamino moiety is a critical component with respect to producing specific effects upon femoral artery blood flow. In this paper, we describe the synthesis and vasodilatory properties of 6-(4-(*N*-methyl-2-phenyl-1-ethylamino)-1-piperidinyl)carbonyl-2(1*H*)-quinolinones **2**−**17** and their quinolinone-opened form derivatives **18**−**30** (Figure 1).

Chemistry

Table 1 shows the 2(1*H*)-quinolinone derivatives that were evaluated for their effects upon coronary and femoral blood flow. These compounds were prepared by condensation of corresponding carboxyquinolinones **I** and 4-(*N*-methyl-2-phenethylamino)piperidine **31** with diethylphosphoryl cyanide (Scheme 1).

Unsubstituted simple 2(1*H*)-quinolinonecarboxylic acid was prepared according to a previous report.[10] The

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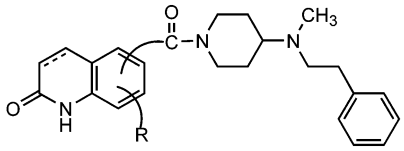
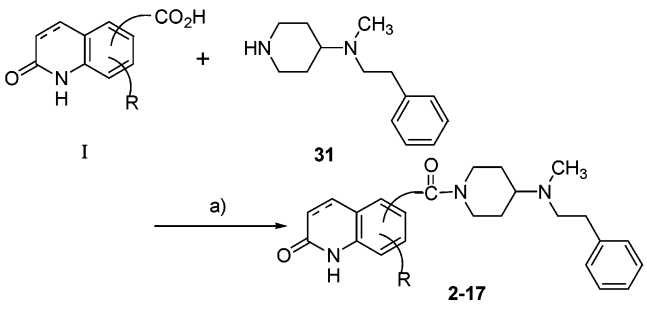
Table 1. Physiological Data and Vasodilatory Activities of Quinolinone Derivatives **2**−**17**



compd	position	3,4-	R	mp, °C	formula[a]	recrystn solvent	FBF ratio[b]	CBF ratio[c]
2	6	S[e]	H	-[d]	$C_{24}H_{29}N_3O_2 \cdot HCl \cdot H_2O$	-[d]	1.64 ± 0.51	0.00
3	6	S	8-Me	-[d]	$C_{25}H_{31}N_3O_2 \cdot HCl \cdot H_2O$	-[d]	0.67 ± 0.08	0.14 ± 0.02
4	6	S	8-Et	200−202	$C_{26}H_{33}N_3O_2 \cdot C_2H_2O_4$	EtOH−H_2O	1.07 ± 0.41	0.18 ± 0.04
5	6	D[f]	8-Et	245−248	$C_{26}H_{31}N_3O_2 \cdot C_2H_2O_4 \cdot 0.25H_2O$	EtOH	0.96 ± 0.24	0.18 ± 0.02
6	6	S	8-i-Pr	235−238	$C_{27}H_{35}N_3O_2 \cdot HCl \cdot 0.75H_2O$	EtOH	1.13 ± 0.12	0.25 ± 0.05
7	6	D	8-Pr	233−235	$C_{27}H_{33}N_3O_2 \cdot HCl \cdot 0.25H_2O$	AcOEt−EtOH	1.61 ± 0.96	0.35 ± 0.01
8	6	D	8-OMe	208−210	$C_{25}H_{29}N_3O_3 \cdot HCl \cdot 1.2H_2O$	AcOEt−EtOH	1.36 ± 0.19	0.04 ± 0.02
9	6	S	8-NO_2	108−110	$C_{24}H_{28}N_4O_4$	AcOEt−Et_2O	0.68 ± 0.07	0.28 ± 0.13
10	6	D	8-NO_2	150−151	$C_{24}H_{26}N_4O_4 \cdot HCl \cdot 1.5H_2O$	EtOH	1.60 ± 1.10	1.15 ± 0.02
11	6	S	7-Me	109−119	$C_{25}H_{31}N_3O_2 \cdot C_2H_2O_4 \cdot 1.2H_2O$	-[d]	3.01 ± 1.62	0.02 ± 0.02
12	6	S	7-OMe	-[d]	$C_{25}H_{31}N_3O_3 \cdot HCl \cdot 2H_2O$	-[d]	1.98 ± 1.02	0.00
13	6	D	7-OMe	147−149	$C_{25}H_{29}N_3O_3 \cdot 0.5 \cdot H_2O$	AcOEt	1.07 ± 0.47	0.04 ± 0.02
14	4	S	H	-[d]	$C_{24}H_{29}N_3O_2 \cdot HCl \cdot 1.5H_2O$	-[d]	0.85 ± 0.57	0.01 ± 0.02
15	5	D	H	-[d]	$C_{24}H_{27}N_3O_2 \cdot HCl \cdot 2.5H_2O$	-[d]	0.32 ± 0.05	0.01 ± 0.01
16	7	S	H	140−142	$C_{24}H_{29}N_3O_2$	EtOH	0.19	0.07
17	8	S	H	-[d]	$C_{24}H_{29}N_3O_2 \cdot HCl \cdot 3H_2O$[g]	-[d]	0.62 ± 0.08	0.09 ± 0.02

[a] Compounds were analyzed for C,H,N; the results agreed to within ±0.4% of theoretical values. [b] FBF means femoral artery blood flow. FBF ratio represents the effect of each test compound (10 nmol) divided by the effect of nifedipine (1 nmol) upon FBF (means ± SE, $n = 3$ or 1). [c] CBF means coronary artery blood flow. CBF ratio represents the effect of each test compound (100 nmol) divided by the effect of nifedipine (10 nmol) upon CBF (means ± SE, $n = 3$ or 1). [d] Amorphous solid. [e] S means single bond. [f] D means double bond. [g] Anal. H; calcd, 7.53; found, 7.00.

Scheme 1[a]



[a] Reagent: (a) Diethyl phosphoryl cyanide (DEPC), Et_3N, DMF.

synthesis of 8-alkyl-2(1*H*)-quinolinones **36**, **37**, **42**−**44**, except the 8-methyl analogues,[11] is summarized in Scheme 2. 8-Ethyl- and 8-propyl-2(1*H*)-quinolinone **36**, **37** were produced by Schotten−Baumann reaction of **32** or **33** with cinnamoyl chloride, followed by $AlCl_3$-catalyzed cyclization. On the other hand, Gassman reaction[12] of 2-isopropylaniline **38** produced the methylthiomethyl derivative **39**. Subsequent acetylation with acetyl chloride, followed by oxidation with $NaIO_4$, provided sulfoxide **40**. Conversion to formyl function from a sulfoxide moiety was accomplished by acid degradation of **40**. Intramolecular aldol reaction of **41** successfully provided 8-isopropyl-2(1*H*)-quinolinone **42**. Palladium-catalyzed hydrogenation of 2(1*H*)-quinolinones **36** or **42** in acetic acid gave the 3,4-dihydro derivatives **43** and **44**, respectively. Introduction of a carboxyl function into the 6-position of alkyl-substituted quinolinones was achieved by Friedel−Crafts reaction with chloroacetyl chloride followed by King's reaction[13] (Scheme 3). The synthesis of 8-methoxy derivatives **64** was accomplished by the same procedure as the 8-isopropyl derivative **42**, as depicted in Scheme 4. 8-Nitro derivative **66** was prepared from **65** by nitration. Subsequent esterification of **66** by thionyl chloride in methanol, followed by oxidation with *N*-bromosuccinimide (NBS) and ester hydrolysis gave the dehydro derivative **69**, as depicted in Scheme 5. The synthesis of 7-methoxy-2(1*H*)quinolines **75** and **76** is summarized in Scheme 6. Methylation of **70** with methyl iodide and Friedel−Crafts reaction with chloroacetyl chloride gave **71**. After King's reaction,[13] stepwise methylation of the carboxylic acid and hydroxy functions of **72** provided **74**. The direct dimethylation of **72** gave a complex mixture which included 1-methylated compounds. Hydrolysis of **74** provided carboxyl derivative **75**. Oxidation of **74** with NBS, followed by hydrolysis and debromination with basic hydrogenolysis, gave **76**.

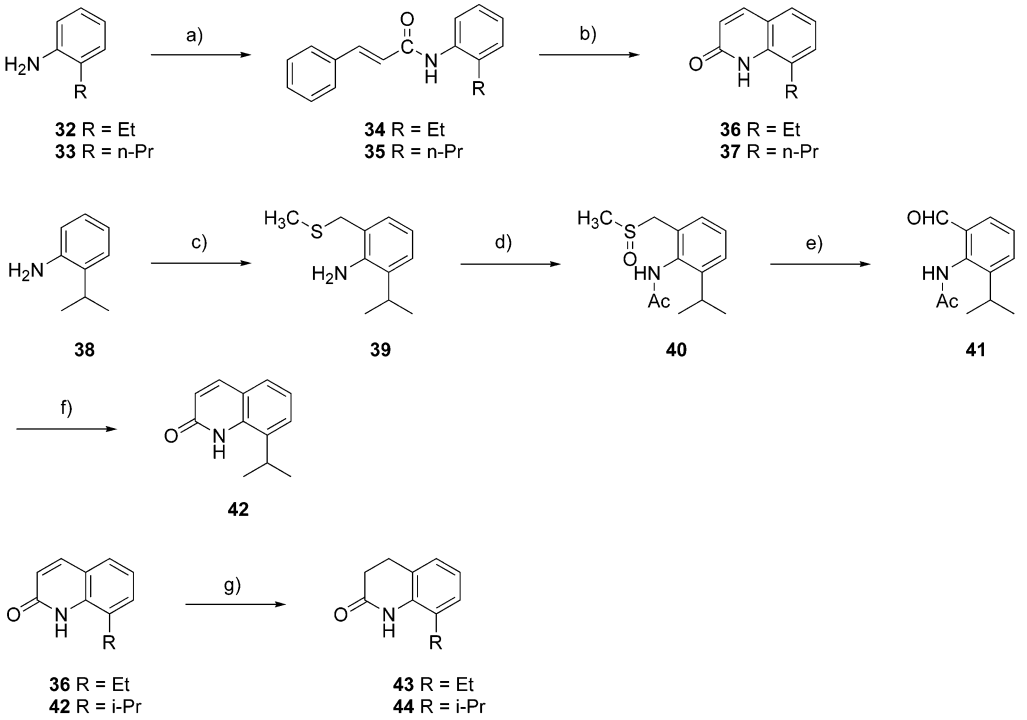
Table 2 shows 2(1*H*)-quinolinone-opened form derivatives which were prepared by Method A or B, as depicted in Scheme 7.

Method A: Subsequent acylation of 4-(*N*-methyl-2-phenethylamino)piperidine **31** with 4-nitrobenzoic acid **II**, which is activated by thionyl chloride or diethylphosphoryl cyanide (DEPC), followed by palladium-catalyzed reduction provided **V**. Alternatively, direct acylation with 4-aminobenzoic acid, which is activated by DEPC or bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPC), also gave **V**. Finally, acylation of **V** with propionyl chloride yielded the desired compounds **VI**.

Method B: An alternative method that was used is the early propionation procedure shown in Scheme 7. Subsequent acylation of **VII** with propionyl chloride, followed by basic hydrolysis, gave propionated-benzoic acid **VIII**. Then, condensation of the corresponding benzoic acid with **31** provided the desired compounds **VI**.

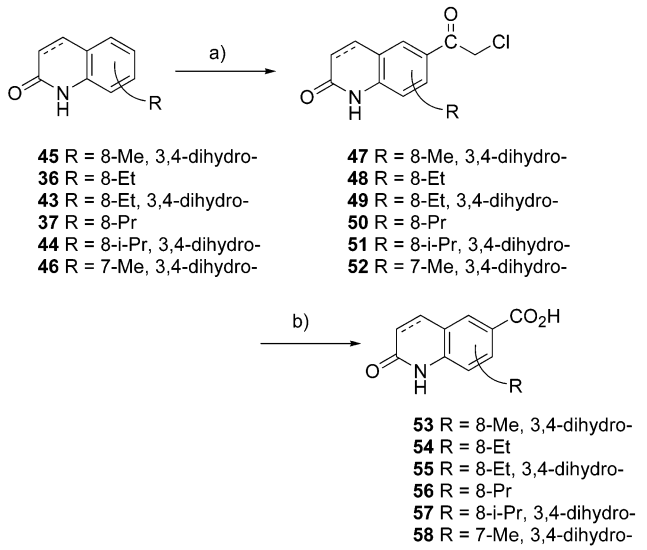
The trisubstituted benzoic acids, including methyl functions, were synthesized using Gassman's method,[12] as depicted in Schemes 8 and 9. In the case of 2-methyl derivatives **84**, Gassman's reaction followed by propionylation gave two isomers **85** and **86**. The nitro derivative can be easily prepared by nitration of methyl 3-methyl-4-propionylaminobenzoate.

Scheme 2[a]



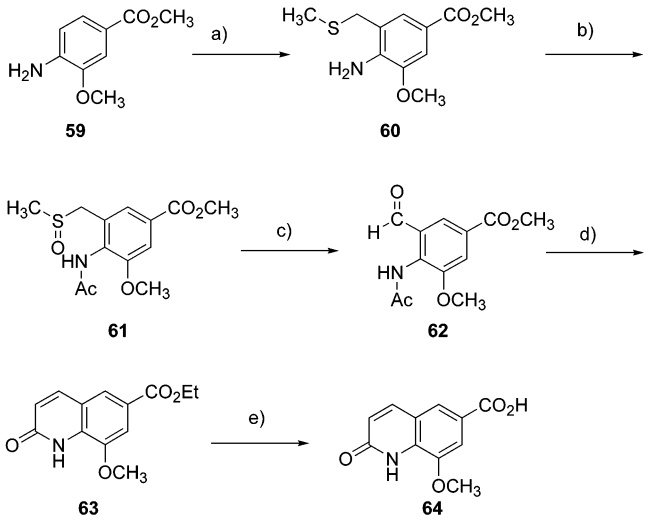
[a] Reagents: (a) cinnamoyl chloride, K_2CO_3, H_2O, acetone; (b) $AlCl_3$, chlorobenzene; (c) *N*-chlorosuccinimide, Me_2S, Et_3N, CH_2Cl_2; (d) (i) AcCl, Et_3N, CH_2Cl_2, (ii) $NaIO_4$, H_2O, MeOH; (e) HCl gas, toluene; (f) Na, EtOH; (g) H_2, 10% Pd−C, AcOH.

Scheme 3[a]



[a] Reagents: chloroacetyl chloride, $AlCl_3$, CS_2; (b) (i) pyridine, (ii) NaOH, H_2O.

Scheme 4[a]



[a] Reagents: (a) *N*-chlorosuccinimide, Me_2S, Et_3N, CH_2Cl_2; (b) (i) AcCl, Et_3N, CH_2Cl_2, (ii) mCPBA, CH_2Cl_2; (c) HCl gas, toluene; (d) NaH, EtOH; (e) NaOH aq, MeOH.

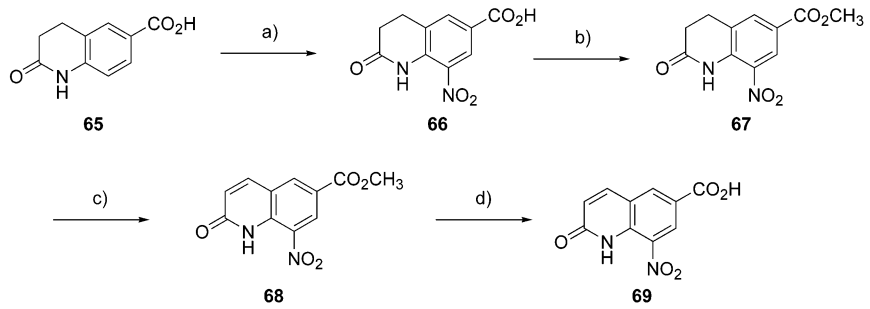
4-(*N*-Methyl-2-phenylethylamino)piperidine **31** was synthesized from 1-benzyl-4-piperidone **89** using a reductive amination method,[14] as depicted in Scheme 10.

Results and Discussion

The vasodilatory activities of all compounds tested were compared with the effects of nifedipine (Nif.) upon femoral artery blood flow (FBF), in autoperfused canine femoral artery preparations, and upon coronary artery blood flow (CBF), in isolated blood perfused canine heart preparations. The activities of quinolinone derivatives are shown in Table 1. The FBF ratio represents the effect of each test compound (10 nmol) divided by the effect of nifedipine (1 nmol) upon FBF. Likewise, the CBF ratio represents the effect of each test compound (100 nmol) divided by the effect of nifedipine (10 nmol) upon CBF. In this screening system, nifedipine increased FBF by 14.5 ± 0.9 mL (mean ± SE) and CBF by 10.1 ± 0.4 mL (mean ± se) at 1 and 10 nmol, respectively.

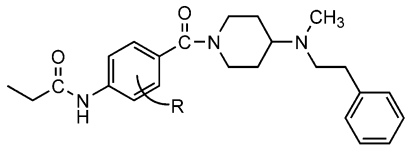
As for the relationship between FBF and the position of the piperidinocarbonyl side chain, the 6-substituted isomer exhibited the most potent activity (**2**, **14**−**17**). In contrast, for the CBF, 7- and 8-substituted isomer exhibited potent activity. Therefore, the 6-substituted isomer possesses the most desirable and highest FBF

Scheme 5[a]



[a] Reagents: (a) HNO_3 (d = 1.52), H_2SO_4; (b) $SOCl_2$, MeOH; (c) NBS, BPO, $CHCl_3$; (d) NaOH aq, MeOH.

Table 2. Physiologocial Data and Vasocilatory Activities of Open Form Derivatives **18**−**30**



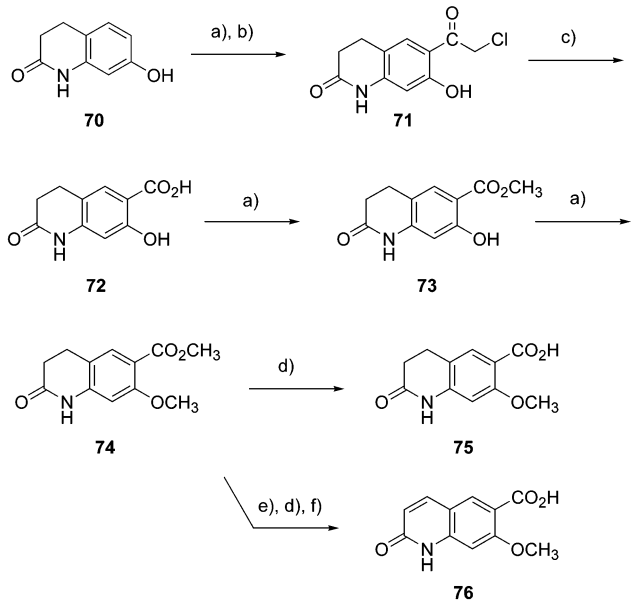
compd	R	method	mp, °C	formula[a]	recrystn solvent	FBF ratio[b]	CBF ratio[c]
18	H	A	150−160	$C_{24}H_{31}N_3O_2{\cdot}0.5C_4H_4O_4{\cdot}H_2O$	EtOH	1.23 ± 0.95	0.02 ± 0.01
19	2-Me	A	231.5−232.5	$C_{25}H_{33}N_3O_2{\cdot}HCl{\cdot}0.25H_2O$	AcOEt−EtOH	1.06	0.05
20	3-Me	A	139−151	$C_{25}H_{33}N_3O_2{\cdot}HCl{\cdot}1.5H_2O$	AcOEt−EtOH	0.27 ± 0.08	0.01 ± 0.01
21	2-OMe	A	-[d]	$C_{25}H_{33}N_3O_3{\cdot}HCl{\cdot}0.25H_2O$[e]	-[d]	0.86	0.00
22	3-OMe	A	-[d]	$C_{25}H_{33}N_3O_3{\cdot}HCl{\cdot}0.75H_2O$	-[d]	0.19	0.11
23	3-Cl	B	-[d]	$C_{24}H_{30}ClN_3O_2{\cdot}HCl{\cdot}H_2O$	-[d]	1.71	0.16
24	3-NO_2	A	-[d]	$C_{24}H_{30}N_4O_4{\cdot}HCl{\cdot}0.5H_2O$	-[d]	0.29	0.26
25	3,5-diMe	B	261.5	$C_{26}H_{35}N_3O_2{\cdot}HCl{\cdot}H_2O$	EtOH−H_2O	1.15 ± 0.81	0.03 ± 0.02
26	2,3-diMe	B	-[d]	$C_{26}H_{35}N_3O_2{\cdot}HCl{\cdot}2.75H_2O$	-[d]	0.43 ± 0.21	0.00
27	2,5-diMe	B	209−211	$C_{26}H_{35}N_3O_2{\cdot}HCl{\cdot}0.5H_2O$	AcOEt-EtOH	0.49 ± 0.08	0.00
28	3-Me,5-OMe	A	214−218	$C_{26}H_{35}N_3O_3{\cdot}HCl$[f]	AcOEt−EtOH	0.70 ± 0.40	0.00
29	3-Me,5-Cl	B	243−246	$C_{25}H_{32}ClN_3O_2{\cdot}HCl{\cdot}H_2O$	EtOH−H_2O	0.10	0.08
30	3-Me,5-NO_2	B	126−128	$C_{25}H_{32}N_4O_4{\cdot}0.25H_2O$	AcOEt−hexane	0.24	0.09

[a] Compounds were analyzed for C, H, N; the results agreed to within ±0.4% of theoretical values. [b] FBF means femoral artery blood flow. FBF ratio represents the effect of each test compound (10 nmol) divided by the effect of nifedipine (1 nmol) upon FBF (means ± SE, n = 3 or 1). [c] CBF means coronary artery blood flow. CBF ratio represents the effect of each test compound (100 nmol) divided by the effect of nifedipine (10 nmol) upon CBF (means ± SE, n = 3 or 1). [d] Amorphous solid. [e] Anal. H: calcd, 7.49; found, 7.92. [f] Anal. H: calcd, 7.78; found, 8.28.

to CBF ratio. The introduction of a single or double bond on the 3,4-position of the quinolinone did not show a clear tendency toward affecting the FBF to CBF ratio. The introduction of an alkyl moiety at position 8 of the quinolinone decreased FBF, compared with nonsubstituted compounds (**2**, **3**−**7**). This is a remarkable tendency of the small alkyl moiety (**3**−**7**). Furthermore, CBF increases due to the introduction of an alkyl group are dependent on bulkiness. As a consequence, the introduction of an alkyl group at position 8 did not affect the FBF to CBF selectivity ratio. In contrast, the introduction of a nitro group suppressed FBF and elevated CBF (**9**). On the other hand, the incorporation of a methyl moiety at the 7-position dramatically elevated FBF while producing minimal effects upon CBF (**11**). No notable effects upon FBF or CBF were produced by the introduction of a methoxy group at positions 7 or 8 (**8**, **12**, **13**).

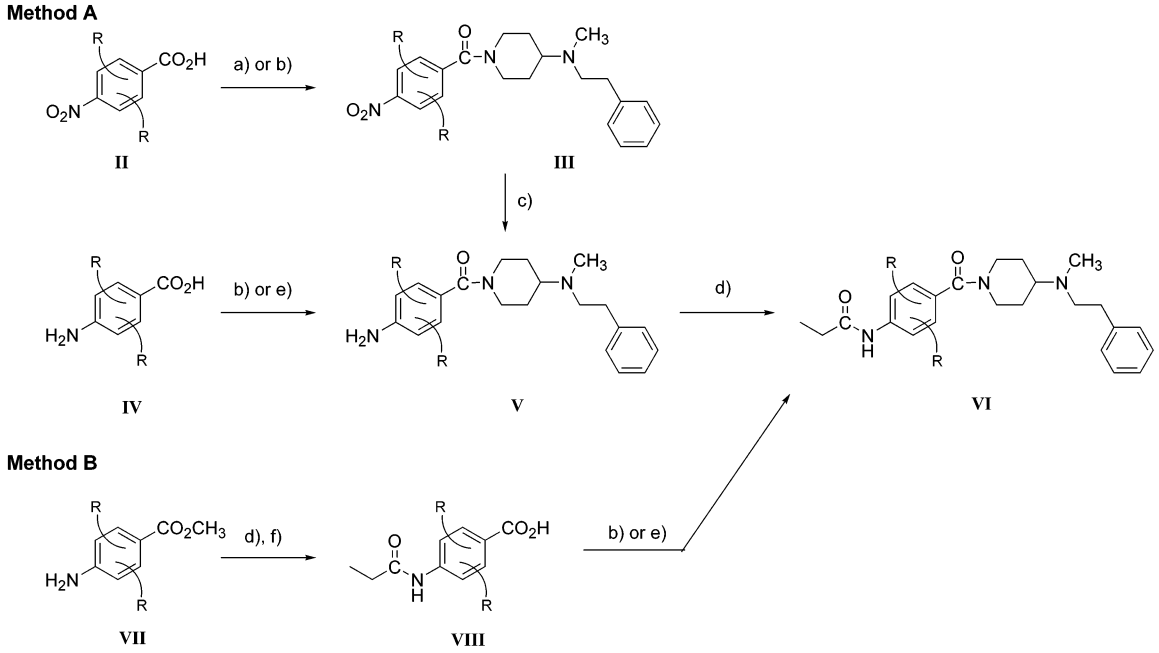
The activities of quinolinone-opened form derivatives are shown in Table 2. Compound **18** produced weaker stimulatory effects upon FBF than those of the original quinolinone **2**. The introduction of an electron-donating substituent decreased FBF, and this characteristic was particularly prominent at position 3 (**19**−**22**). On the other hand, the introduction of an electron-withdrawing moiety stimulated CBF (**18**, **23**−**24**; **20**, **29**−**30**), without producing any effects upon FBF, except for compound **23**. Interestingly, the additional introduction of an electron-donating group to the 3-methyl derivative **20**

Scheme 6[a]



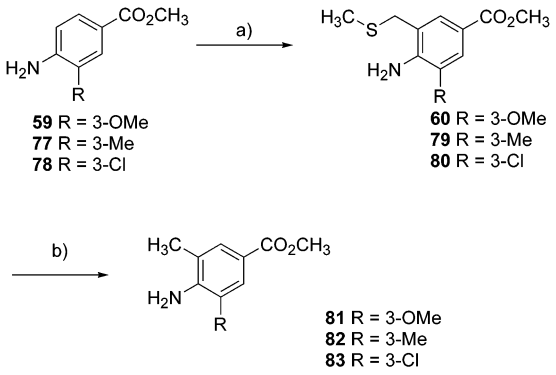
[a] Reagents: (a) MeI, K_2CO_3, DMF; (b) chloroacetyl chloride, $AlCl_3$, dichloroethane; (c) (i) pyridine, (ii) NaOH, H_2O; (d) NaOH, H_2O; (e) NBS, BPO, $CHCl_3$; (f) NaOH, H_2, 10% Pd−C.

Scheme 7[a]



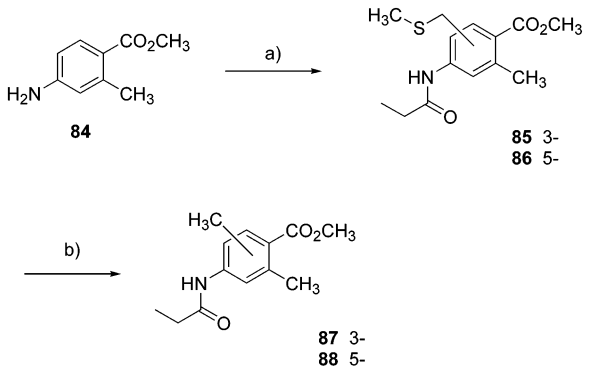
[a] Reagents; (a) (i) $SOCl_2$, CH_2Cl_2, (ii) **31**, Et_3N, DMF; (b) **31**, DEPC, Et_3N, DMF; (c) H_2, Pd−C, EtOH; (d) propionyl chloride, Et_3N, DMF or K_2CO_3, acetone−H_2O; (e) **31**, BOPC, Et_3N, CH_2Cl_2; (f) NaOHaq, MeOH.

Scheme 8[a]



[a] Reagents: (a) *N*-chlorosuccinimide, Me_2S, Et_3N, CH_2Cl_2; (b) Raney Ni, EtOH.

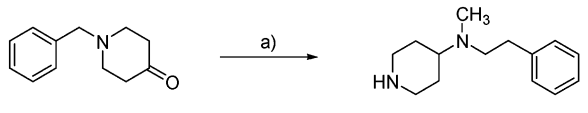
Scheme 9[a]



[a] Reagents: (a) (i) *N*-chlorosuccinimide, Me_2S, Et_3N, CH_2Cl_2, (ii) propionyl chloride, Et_3N, CH_2Cl_2, (b) Raney Ni, EtOH.

elevated FBF and also displayed a desirable inhibition of CBF (**25**−**28**). In particular, **25** and **28**, which have substituents at two of the 3-positons, demonstrated a potent increase in FBF when compared with substitutions at positions 2- and 3 (**26**, **27**). However, their

Scheme 10[a]



[a] Reagents: (a) (i) phenethylamine, AcOH, H_2, 5%Pt−C, EtOH, (ii) formaldehyde, HCO_2H, (iii) H_2, 10% Pd−C, HCl, H_2O, EtOH.

Table 3. Cardiovascular Effect in Anesthetized Open-Chest Dogs

compd	FBF (%)[a]	CBF (%)[a]	DBP (mmHg)[b]
2	38 ± 12	11 ± 1	−9 ± 2
3	32 ± 13	13 ± 5	−26 ± 3
4	54 ± 12	15 ± 4	−26 ± 9
5	78 ± 2	26 ± 11	−22 ± 2
6	73 ± 14	15 ± 4	−19 ± 5
7	67 ± 35	8 ± 7	−22 ± 6
8	55 ± 7	10 ± 4	−10 ± 2
10	32 ± 11	9 ± 2	−21 ± 6
11	41 ± 12	11 ± 2	−13 ± 6
12	26 ± 2	8 ± 2	−8 ± 1
13	26 ± 3	7 ± 1	−9 ± 2
14	101 ± 35	13 ± 7	−15 ± 2
18	38 ± 3	5 ± 3	−7 ± 2
19	51 ± 12	13 ± 3	−15 ± 3
21	48 ± 8	8 ± 1	−12 ± 5
25	67 ± 19	7 ± 3	−11 ± 5
28	48 ± 15	11 ± 2	−14 ± 6
Nif.	−28 ± 1	104 ± 38	−37 ± 8

[a] FBF and CBF activity was shown by change % of prevalue at 10 μg/kg iv dosage (means ± SE, $n = 3$). [b] BP means blood pressure. ΔBP was shown by change value from prevalue at 10 μg/kg iv dosage (means ± SE, $n = 3$).

inhibitory effects upon FBF were caused by the introduction of an electron-donating group at position 3.

Further cardiovascular effects of these aminopiperidine derivatives, that displayed desirable effects in the autoperfused canine femoral artery preparations, were evaluated in anesthetized open-chest dogs (Table 3). The undesirable side effects of compound **23**, which produced substantial changes in FBF, was not investigated. FBF,

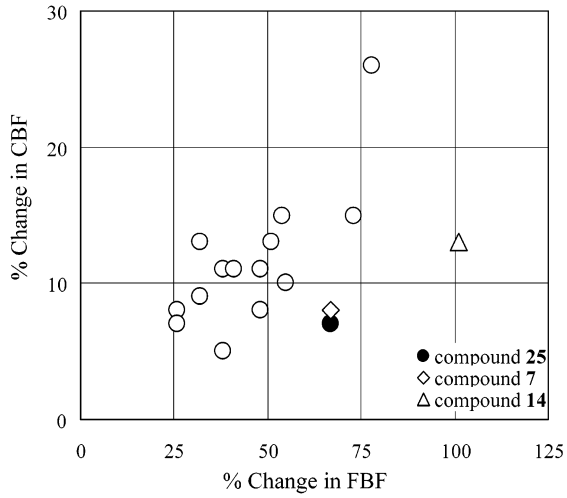


Figure 2. Relationship between femoral blood flow and coronary blood flow.

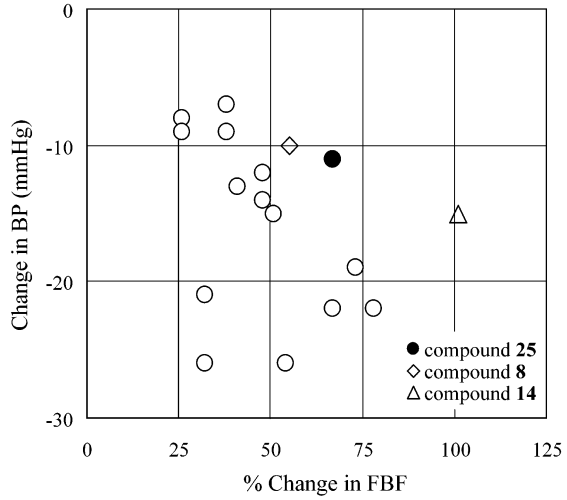


Figure 3. Relationship between femoral blood flow and blood pressure.

CBF, and ΔBP indicate percentage changes from predose values following iv administration of a 10 μg/kg dose. There is no relationship between drug effects upon FBF in the anesthetized open-chest dog paradigm and the autoperfused canine femoral artery preparations. The relationship between FBF and CBF, and ΔBP, are depicted in Figures 2 and 3. Compounds **7**, **14**, and **25**, located in the lower right region of Figure 2, demonstrated high FBF to CBF selectivities. Compounds **8**, **14,** and **25**, located in the upper right region of Figure 3, displayed selective effects on FBF on versus ΔBP. Subsequent pharmacokinetic evaluations of these compounds resulted in the selection of compound **25** as the most promising candidate for producing selective effects upon FBF.

Conclusion

The present study attempted to identify compounds which selectively stimulated femoral arterial blood flow (FBF) for future development as novel safe and effective peripheral vasodilators. A series of compounds were isolated which resulted in the selection of compound **25** This compound stimulated FBF without producing any effects upon coronary artery blood flow (CBF) in both a canine autoperfused femoral artery preparation and anesthetized open-chest dog paradigm. Compound **25** also did not influence changes in blood pressure in the anesthetized dog study. A detailed analysis of the biological characteristics of compound **25** have been reported previously,[15] and this drug candidate is currently in clinical trials in the U.S. as a novel safe and effective treatment for intermittent claudication and Raynaud's phenomenon.

Experimental Section

All melting points were determined using a Yamato melting apparatus (Model MP-21) and are uncorrected. ^{1}H NMR spectra were measured on a Bruker AC-200 (200 MHz), Bruker AC-250 (250 MHz), or Bruker DPX-300 (300 MHz) spectrometer, using tetramethylsilane (TMS) as the internal standard. All elemental analyses were determined using a Yanako MT-5 CHN recorder and were within 0.4% of their respective theoretical values, unless otherwise stated. The purity of all compounds were routinely checked by TLC on Merck silica gel 60 F254 precoated plates. Chromatography refers to flash chromatography using an E. Merck Kieselgel 60, 230−400 mesh silica gel. All materials were commercially available unless otherwise stated.

General Method. **3,4-Dihydro-8-isopropyl-6-(4-(*N*-methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone Hydrochloride (6)**. Diethylphosphoryl cyanide (0.73 mL, 4.3 mmol) and triethylamine (0.60 mL, 4.3 mmol) were added to a solution of 8-isopropyl-3,4-dihydro-6-carboxy-2(1*H*)-quinolinone (**57**; 0.83 g, 3.6 mmol) which was then mixed with 4-(*N*-methyl-2-phenylethyl)aminopiperidine (**31**; 0.78 g, 3.6 mmol) in DMF (10 mL) at 0 °C. After being stirred for 30 min at 0 °C, the reaction mixture was poured into ice−water and extracted with EtOAc. The organic layer was washed with water and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. The residue was acidified with aqueous HCl in EtOH, and recrystallization from EtOH−AcOEt gave **6** as a white powder (1.08 g, 64%): mp 235−238 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.80−10.98 (1H, m), 9.66 (1H, s), 7.20−7.41 (5H, m), 7.15 (1H, s), 7.12 (1H, s), 3.70−4.80 (2H, m), 3.48−3.68 (1H, m), 2.80−3.48 (9H, m), 2.77 (3H, d, J = 4.4 Hz), 2.37−2.56 (2H, m), 1.94−2.25 (2H, m), 1.52−1.87 (2H, m), 1.13 (6H, d, J = 6.6 Hz). Anal. ($C_{27}H_{36}N_3O_2Cl\cdot0.75H_2O$) C, H, N.

3,4-Dihydro-6-(4-(*N*-methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone Hydrochloride (2): ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.90−11.10 (1H, m), 10.25 (1H, s), 7.18−7.40(7H, m), 6.89 (1H, d, J = 8.1 Hz), 3.65−4.90 (2H, m), 3.00−3.65 (5H, m), 2.80−3.00 (4H, m), 2.75 (3H, d, J = 4.9 Hz), 2.37−2.50 (2H, m), 1.95−2.20 (2H, m), 1.55−1.80 (2H, m). Anal. ($C_{24}H_{30}N_3O_2Cl\cdot H_2O$) C, H, N.

3,4-Dihydro-8-methyl-6-(4-(*N*-methyl-2-phenylethyl)-amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone Hydrochloride (3): ^{1}H NMR (250 MHz, DMSO-d_6) δ 10.60−10.70 (1H, m), 9.60 (1H, s), 7.20−7.40 (5H, m), 7.11 (1H, s), 7.09 (1H, s), 3.40−4.90 (3H, m), 2.80−3.40 (8H, m), 2.78 (3H, d, J = 4.4 Hz), 2.40−2.50 (2H, m), 2.23 (3H, s), 1.90−2.20 (2H, m), 1.50−1.80 (2H, m). Anal. ($C_{25}H_{32}N_3O_2Cl\cdot H_2O$) C, H, N.

3,4-Dihydro-8-ethyl-6-(4-(*N*-methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone Oxalate (4): mp 200−202 °C, ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.63 (1H, s), 7.20−7.40 (5H, m), 7.11 (1H, s), 7.08 (1H, s), 6.50 (2H, brs), 3.35−4.90 (3H, m), 2.78−3.35 (8H, m), 2.72 (3H, s), 2.65 (2H, q, J = 7.4 Hz), 2.40−2.50 (2H, m), 1.85−2.07 (2H, m), 1.50−1.75 (2H, m), 1.10 (3H, t, J = 7.4 Hz). Anal. ($C_{28}H_{35}N_3O_6$) C, H, N.

8-Ethyl-6-(4-(*N*-methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone Oxalate (5): mp 245−248 °C, ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.14 (1H, s), 10.78−11.00 (1H, m), 7.95 (1H, d, J = 9.6 Hz), 7.62 (1H, s), 7.42 (1H, s), 7.20−7.40 (5H, m), 6.57 (1H, d, J = 9.6 Hz), 3.70−4.90 (2H, m), 3.50−3.70 (1H, m), 3.00−3.70 (6H, m), 2.90 (2H, q, J = 7.2 Hz), 2.78 (3H, d, J = 4.8 Hz), 1.93−2.26 (2H, m),

1.55−1.90 (2H, m), 1.18 (3H, t, J = 7.2 Hz). Anal. ($C_{26}H_{32}N_3O_2Cl\cdot0.25H_2O$) C, H, N.

6-(4-(*N*-Methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-8-propyl-2(1*H*)-quinolinone Hydrochloride (7): mp 233−235 °C, ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.20 (1H, s), 10.87−11.10 (1H, m), 7.94 (1H, d, J = 9.6 Hz), 7.62 (1H, d, J = 1.6 Hz), 7.39 (1H, d, J = 1.6 Hz), 7.20−7.40 (5H, m), 6.56 (1H, d, J = 9.6 Hz), 3.70−4.90 (2H, m), 3.50−3.70 (1H, m), 2.90−3.50 (6H, m), 2.87 (2H, t, J = 7.2 Hz), 2.78 (3H, d, J = 4.6 Hz), 1.90−2.30 (2H, m), 1.43−1.90 (4H, m), 0.93 (3H, t, J = 7.2 Hz). Anal. ($C_{27}H_{34}N_3O_2Cl\cdot0.25H_2O$) C, H, N.

8-Methoxy-6-(4-(*N*-methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone Hydrochloride (8): mp 208−210 °C, ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.15−11.40 (1H, m), 11.08 (1H, s), 7.95 (1H, d, J = 9.8 Hz), 7.20−7.45 (6H, m), 7.19 (1H, d, J = 1.2 Hz), 6.60 (1H, d, J = 9.8 Hz), 3.80−4.90 (2H, m), 3.95 (3H, s), 3.55−3.78 (1H, m), 2.85−3.55 (6H, m), 2.80 (3H, d, J = 4.2 Hz), 1.95−2.35 (2H, m), 1.60−1.95 (2H, m). Anal. ($C_{25}H_{30}N_3O_3Cl\cdot1.2H_2O$) C, H, N.

3,4-Dihydro-6-(4-(*N*-methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-8-nitro-2(1*H*)-quinolinone (9): mp 108−110 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.11 (1H, s), 8.16 (1H, s), 7.59 (1H, s), 7.10−7.50 (5H, m), 4.40−4.95 (1H, m), 3.60−4.20 (1H, m), 2.60−3.30 (11H, m), 2.39 (3H, s), 1.72−2.20 (2H, m), 1.40−1.72 (2H, m). Anal. ($C_{24}H_{28}N_4O_4$) C, H, N.

6-(4-(*N*-Methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-8-nitro-2(1*H*)-quinolinone Hydrochloride (10): mp 150−151 °C, ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.13 (1H, s), 10.38−11.00 (1H, m), 8.43 (1H, s), 8.26 (1H, s), 8.15 (1H, d, J = 9.8 Hz), 7.22−7.42 (5H, m), 6.79 (1H, d, J = 9.8 Hz), 4.40−4.85 (1H, m), 3.55−4.05 (2H, m), 2.90−3.50 (6H, m), 2.78 (3H, d, J = 4.6 Hz), 1.92−2.30 (2H, m), 1.65−1.92 (2H, m). Anal. ($C_{24}H_{27}N_4O_4Cl\cdot1.5H_2O$) C, H, N.

3,4-Dihydro-7-methyl-6-(4-(*N*-methyl-2-phenylethyl)-amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone Oxalate (11): mp 109−119 °C, ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.15 (1H, s), 7.18−7.40 (5H, m), 7.02 (1H, brs), 6.70 (1H, s), 5.70 (2H, brs), 4.55−4.75 (1H, m), 3.25−3.57 (2H, m), 2.73−3.25 (8H, m), 2.68 (3H, s), 2.38−2.50 (2H, m), 2.11 (3H, s), 1.74−2.25 (2H, m), 1.25−1.74 (2H, m). Anal. ($C_{27}H_{33}N_3O_6\cdot1.2H_2O$) C, H, N.

3,4-Dihydro-7-methoxy-6-(4-(*N*-methyl-2-phenylethyl)-amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone Hydrochloride (12): ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.80−11.25 (1H, m), 10.14 (1H, s), 7.18−7.40 (5H, m), 6.90−7.13 (1H, m), 6.57 (1H, s), 4.50−4.80 (1H, m), 3.72 (3H, brs), 2.88−3.70 (7H, m), 2.57−3.88 (6H, m), 2.33−2.45 (2H, m), 1.85−2.33 (2H, m), 1.35−1.85 (2H, m). Anal. ($C_{25}H_{32}N_3O_3Cl\cdot2H_2O$) C, H, N.

7-Methoxy-6-(4-(*N*-methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone (13): mp 147−149 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 12.61 (1H, s), 7.73, 7.75 (total 1H, d, J = 9.6 Hz), 7.48, 7.43 (total 1H, s), 7.15−7.40 (5H, m), 6.86 (1H, s), 6.59 (1H, d, J = 9.6 Hz), 4.74−4.92 (1H, m), 3.94 (3H, s), 3.43−3.61 (1H, m), 2.55−3.15 (7H, m), 2.36, 2.38 (total 3H, s), 1.20−2.10 (4H, m). Anal. ($C_{25}H_{29}N_3O_3\cdot0.5H_2O$) C, H, N.

3,4-Dihydro-4-(4-(*N*-methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone Hydrochloride (14): ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.50−10.80 (1H, m), 10.06 (1H, s), 6.80−7.40 (9H, m), 4.20−4.70 (3H, m), 2.90−3.70 (7H, m), 2.77 (3H, d, J = 4.6 Hz), 2.40−2.70 (2H, m), 1.90−2.30 (2H, m), 1.40−1.90 (2H, m). Anal. ($C_{24}H_{30}N_3O_2Cl\cdot1.5H_2O$) C, H, N.

5-(4-(*N*-Methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone Hydrochloride (15): ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.95 (1H, s), 10.50−10.80 (1H, m), 7.00−7.90 (9H, m), 6.54 (1H, d, J = 9.8 Hz), 4.65−4.85 (1H, m), 2.60−3.90 (11H, m), 1.60−2.30 (4H, m). Anal. ($C_{24}H_{28}N_3O_2Cl\cdot2.5H_2O$) C, H, N.

3,4-Dihydro-7-(4-(*N*-methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone (16): mp 140−142 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.91 (1H, s), 7.10−7.38 (6H, m), 6.97 (1H, dd, J = 1.4, 7.6 Hz), 6.90 (1H, d, J = 1.4 Hz), 3.65−4.00 (1H, m), 2.88−3.10 (3H, m), 2.52−2.88 (8H, m), 2.37 (3H, s), 1.65−2.00 (2H, m), 1.30−1.65 (2H, m). Anal. ($C_{24}H_{29}N_3O_2$) C, H, N.

8-(4-(*N*-Methyl-2-phenylethyl)amino-1-piperidinyl)carbonyl-2(1*H*)-quinolinone Hydrochloride (17): ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.90−10.20 (1H, m), 9.37 (1H, s), 7.20−7.43 (6H, m), 7.15 (1H, d, J = 7.4 Hz), 6.99 (1H, t, J = 7.4 Hz), 4.40−4.80 (1H, m), 3.50−3.90 (2H, m), 2.70−3.50 (13H, m), 1.50−2.30 (4H, m). Anal. ($C_{24}H_{30}N_3O_2Cl\cdot3H_2O$) C, H, N.

General Method. Method A. 4-(*N*-Methyl-2-phenylethyl)amino-1-(4-propionylamino) benzoylpiperidine Fumarate (18). 4-Nitrobenzoyl chloride (4.9.g, 26.4 mmol) was added to a solution of 4-(*N*-methyl-2-phenylethyl)aminopiperidine (**31**; 5.0 g, 22.9 mmol) and K_2CO_3 (4.7 g, 34.0 mmol) in acetone (50 mL) and water (50 mL) at 0 °C. After being stirred for 30 min, the reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl and dried (Na_2SO_4). Concentration in vacuo gave 4-(*N*-methyl-2-phenylethyl)amino-1-(4-nitrobenzoyl)piperidine (8.8 g). A solution of the resulting compound (8.2 g, 22.3 mmol) in EtOH (150 mL) and CH_2Cl_2 (100 mL) was hydrogenated over 10% Pd−C (1.0 g) under an atmosphere of H_2 (1 atm) at 25 °C for 3 h. The reaction mixture was filtered through a Celite pad and washed with EtOH. Concentration in vacuo provided anilinic compound (7.5 g). Propionyl chloride (0.45 mL, 5.3 mmol) was added to a solution of the resulting compound (1.5 g, 4.4 mmol) and K_2CO_3 (1.0 g, 7.2 mmol) in acetone (30 mL) and water (15 mL) at 0 °C. The reaction mixture was stirred for 1 h and poured into water. The resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in EtOH and treated with fumaric acid (0.48 g, 4.1 mmol) and then concentrated in vacuo. Recrystallization from EtOH gave **18** as a white powder (0.95 g, 47.9%): mp 158−160 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.04 (1H, s), 7.64 (2H, d, J = 8.6 Hz), 7.32 (2H, d, J = 8.6 Hz), 7.10−7.30 (5H, m), 6.57 (1H, s), 3.40−4.65 (2H, m), 2.55−3.20 (7H, m), 2.33 (2H, q, J = 7.6 Hz), 2.32 (3H, s), 1.60−1.85 (2H, m), 1.25−1.60 (2H, m), 1.08 (3H, t, J = 7.6 Hz). Anal. ($C_{26}H_{33}N_3O_4\cdot H_2O$) C, H, N.

4-(*N*-Methyl-2-phenylethyl)amino-1-(2-methyl-4-propionylamino)benzoylpiperidine Hydrochloride (19): mp 231.5−232.5 °C, ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.75−11.00 (1H, m), 10.00 (1H, s), 7.40−7.55 (2H, m), 7.20−7.40 (5H, m), 7.13 (1H, brs), 4.50−4.75 (1H, m), 3.47−4.65 (1H, m), 2.65−3.47 (7H, m), 2.75 (3H, d, J = 3.6 Hz), 2.31 (2H, q, J = 7.5 Hz), 1.85−2.25 (2H, m), 2.16 (3H, brs), 1.40−1.80 (2H, m), 1.06 (3H, t, J = 7.5 Hz). Anal. ($C_{25}H_{34}N_3O_2Cl\cdot0.25H_2O$) C, H, N.

4-(*N*-Methyl-2-phenylethyl)amino-1-(3-methyl-4-propionylamino)benzoylpiperidine Hydrochoride (20): mp 139−141 °C, ^{1}H NMR (250 MHz, DMSO-d_6) δ 10.70−10.90 (1H, m), 9.33 (1H, s), 7.53 (1H, d, J = 8.3 Hz), 7.15−7.40 (7H, m), 4.20−5.00 (1H, m), 3.50−4.10 (2H, m), 2.55−3.50 (6H, m), 2.78 (3H, d, J = 4.8 Hz), 2.34 (2H, q, J = 7.5 Hz), 1.85−2.25 (2H, m), 2.23 (3H, s), 1.55−1.85 (2H, m), 1.10 (3H, t, J = 7.5 Hz). Anal. ($C_{25}H_{34}N_3O_2Cl\cdot1.5H_2O$) C, H, N.

1-(2-Methoxy-4-propionylamino)benzoyl-4-(*N*-methyl-2-phenylethyl)aminopiperidine Hydrochloride (21): ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.84−11.18 (1H, m), 10.15 (1H, s), 7.49 (1H, s), 7.01−7.44 (7H, m), 4.52−4.76 (1H, m), 3.75 (3H, brs), 2.51−3.70 (11H, m), 2.34 (2H, q, J = 7.6 Hz), 1.81−2.30 (2H, m), 1.40−1.81 (2H, m), 1.08 (3H, t, J = 7.6 Hz). Anal. ($C_{25}H_{34}N_3O_3Cl$) C, H, N.

1-(3-Methoxy-4-propionylamino)benzoyl-4-(*N*-methyl-2-phenylethyl)aminopiperidine Hydrochloride (22): ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.81−11.10 (1H, m), 9.18 (1H, s), 8.06 (1H, d, J = 8.2 Hz), 7.16−7.44 (5H, m), 7.06 (1H, d, J = 1.6 Hz), 6.97 (1H, dd, J = 1.6, 8.2 Hz), 3.74−4.30 (2H, m), 3.86 (3H, s), 2.70−3.74 (7H, m), 2.77 (3H, d, J = 4.4 Hz), 2.42 (2H, q, J = 7.4 Hz), 1.90−2.32 (2H, m), 1.55−1.90 (2H, m), 1.06 (3H, t, J = 7.4 Hz). Anal. ($C_{25}H_{34}N_3O_3Cl$) C, H, N.

4-(*N*-Methyl-2-phenylethyl)amino-1-(3-nitro-4-propionylamino)benzoylpiperidine Hydrochloride (24): ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.80−11.10 (1H, m), 10.51 (1H, s), 7.97 (1H, s), 7.66−7.80 (2H, m), 7.20−7.46 (5H, m), 4.25−4.75

(1H, m), 2.60−3.90 (8H, m), 2.76 (3H, d, J = 4.2 Hz), 2.38 (2H, q, J = 7.6 Hz), 1.93−2.27 (2H, m), 1.60−1.93 (2H, m), 1.06 (3H, t, J = 7.6 Hz). Anal. ($C_{24}H_{31}N_4O_4Cl\cdot0.5H_2O$) C, H, N.

1-(5-Methoxy-3-methyl-4-propionylamino)benzoyl-4-(*N*-methyl-2-phenylethyl)aminopiperidine Hydrochloride (28): mp 214−218 °C, ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.10−11.37 (1H, m), 9.17 (1H, s), 7.20−7.45 (5H, m), 6.90 (1H, s), 6.89 (1H, s), 4.30−4.90 (1H, m), 3.52−4.00 (2H, m), 3.78 (3H, s), 2.60−3.50 (6H, m), 2.79 (3H, d, J = 4.0 Hz), 2.33 (2H, q, J = 7.4 Hz), 1.95−2.26 (2H, m), 2.14 (3H, s), 1.55−1.95 (2H, m), 1.11 (3H, t, J = 7.4 Hz). Anal. ($C_{26}H_{36}N_3O_3Cl$) C, H, N.

General Method. Method B. 1-(3-Chloro-4-propionylamino)benzoyl-4-(*N*-methyl-2- phenylethyl)aminopiperidine Hydrochloride (23). Propionyl chloride (1.07 g, 11.6 mmol) was added to a solution of methyl 4-amino-3-chlorobenzoate (1.65 g, 8.9 mmol) and Et_3N (1.6 mL, 11.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After the mixture was stirred for 1.5 h at room temperature, Et_3N (0.8 mL, 5.8 mmol) and propionyl chloride (0.5 mL, 5.8 mmol) were added again. The mixture was stirred for 1 h at room temperature and poured into water. After extraction with CH_2Cl_2, the organic layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Recrystallization from isopropyl ether gave methyl 3-chloro-4-propionylaminobenzoate as colorless needles (1.32 g). 5 N aqueous NaOH (3 mL) was added to a solution of the resulting compound (1.27 g, 5.3 mmol) in MeOH (30 mL) and stirred for 4.5 h. The reaction mixture was concentrated in vacuo. The residue was dissolved in water (20 mL) and acidified with AcOH. Filtration provided the desired benzoic acid as a white powder (0.41 g). A suspension of the resulting acid (0.4 g, 1.75 mmol), 4-(*N*-methyl-2-phenylethyl)aminopiperidine (**31**; 0.38 g, 1.75 mmol), and Et_3N (0.6 mL, 4.19 mmol) in CH_2Cl_2 (10 mL) was treated with bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOPC; 0.53 g, 2.10 mmol) and stirred for 1 h at room temperature. After addition of CH_2Cl_2 (20 mL), the reaction mixture was washed with water, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (5% CH_2Cl_2-MeOH) gave a yellow oil. The resulting compound was dissolved in EtOH, treated with equimolar aqueous HCl, and concentrated in vacuo. The residue was dried under reduce pressure to obtain **23** as a white amorphous solid (0.54 g, 67%): ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.10−11.40 (1H, m), 9.56 (1H, s), 7.82 (1H, d, J = 8.2 Hz), 7.54 (1H, d, J = 1.8 Hz), 7.16−7.45 (6H, m), 4.20−4.90 (1H, m), 3.50−4.20 (2H, m), 2.55−3.50 (6H, m), 2.75 (3H, d, J = 3.4 Hz), 2.42 (2H, q, J = 7.6 Hz), 1.92−2.30 (2H, m), 1.50−1.92 (2H, m), 1.08 (3H, t, J = 7.6 Hz). Anal. ($C_{24}H_{31}N_3O_2Cl_2\cdot H_2O$) C, H, N.

1-(3,5-Dimethyl-4-propionylamino)benzoyl-4-(*N*-methyl-2-phenylethyl)aminopiperidine Hydrochloride (25): mp 261.5 °C, ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.75−11.10 (1H, m), 9.32 (1H, s), 7.18−7.44 (5H, m), 7.11 (2H, s), 4.20−4.90 (1H, m), 3.50−4.20 (2H, m), 2.60−3.50 (6H, m), 2.77 (3H, d, J = 4.4 Hz), 2.35 (2H, q, J = 7.6 Hz), 1.86−2.25 (2H, m), 2.15 (6H, s), 1.50−1.85 (2H, m), 1.13 (3H, t, J = 7.6 Hz). Anal. ($C_{26}H_{36}N_3O_2Cl\cdot H_2O$) C, H, N.

1-(2,3-Dimethyl-4-propionylamino)benzoyl-4-(*N*-methyl-2-phenylethyl)aminopiperidine Hydrochloride (26): ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.70−11.00 (1H, m), 9.41 (1H, s), 6.83−7.45 (7H, m), 4.58−4.83 (1H, m), 2.60−3.74 (11H, m), 2.35 (2H, q, J = 7.6 Hz), 1.37−2.28 (10H, m), 1.10 (3H, t, J = 7.6 Hz). Anal. ($C_{26}H_{36}N_3O_2Cl\cdot2.75H_2O$) C, H, N.

1-(2,5-Dimethyl-4-propionylamino)benzoyl-4-(*N*-methyl-2-phenylethyl)aminopiperidine Hydrochloride (27): mp 209−211 °C, ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.90−11.25-(1H, m), 9.30 (1H, s), 6.60−7.55 (7H, m), 4.58−4.87 (1H, m), 2.65−3.75 (11H, m), 2.37 (2H, q, J = 7.6 Hz), 1.40−2.30 (10H, m), 1.11 (3H, t, J = 7.6 Hz). Anal. ($C_{26}H_{36}N_3O_2Cl\cdot0.5H_2O$) C, H, N.

1-(5-Chloro-3-methyl-4-propionylamino)benzoyl-4-(*N*-methyl-2-phenylethyl)aminopiperidine Hydrochloride (29): mp 243−246 °C, ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.70−11.00 (1H, m), 9.50 (1H, s), 7.15−7.50 (7H, m), 3.50−4.90 (3H, m), 2.75−3.50 (6H, m), 2.77 (3H, d, J = 4.3 Hz), 2.35 (2H, q, J = 7.5 Hz), 2.20 (3H, s), 1.96−2.20 (2H, m), 1.57−1.96 (2H, m), 1.13 (3H, t, J = 7.5 Hz). Anal. ($C_{25}H_{33}N_3O_2Cl_2\cdot H_2O$) C, H, N.

1-(3-Methyl-5-nitro-4-propionylamino)benzoyl-4-(*N*-methyl-2-phenylethyl)aminopiperidine (30): mp 126−128 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.60 (1H, s), 7.81 (1H, d, J = 1.6 Hz), 7.49 (1H, d, J = 1.6 Hz), 7.15−7.40 (5H, m), 4.45−4.90 (1H, m), 3.50−4.55 (1H, m), 2.60−3.23 (7H, m), 2.48 (2H, q, J = 7.6 Hz), 2.37 (3H, s), 2.29 (3H, s), 1.34−2.05 (4H, m), 1.27 (3H, t, J = 7.6 Hz). Anal. ($C_{25}H_{32}N_4O_4\cdot0.25H_2O$) C, H, N.

2′-Ethylcinnamanilide 34. A solution of cinnamoyl chloride (191 g, 1.14 mol) in acetone (200 mL) was added to a solution of 2-ethylaniline (132 g, 1.09 mol) and K_2CO_3 (166 g, 1.20 mol) in acetone−ice (1.2 L-1.2 kg) and stirred for 1 h. The reaction mixture was poured into an ice−water. Filtration gave **34** as a white powder (266 g, 97%): mp 168−169 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93 (1H, brs), 7.77 (1H, d, J = 15.5 Hz), 7.05−7.65 (10H, m), 6.57 (1H, d, J = 15.5 Hz), 2.67 (2H, q, J = 7.5 Hz), 1.27 (3H, t, J = 7.5 Hz).

2′-Propylcinnamanilide 35. Using the same procedure as **34**, **35** (8.2 g, 83.6%) was obtained as colorless needles from **33** (5.0 g, 37 mmol): mp 139−142 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.90 (1H, brs), 7.76 (1H, d, J = 15.5 Hz), 7.05−7.65 (10H, m), 6.58 (1H, d, J = 15.5 Hz), 2.61 (2H, t, J = 7.4 Hz), 2.67 (2H, tq, J = 7.3, 7.4 Hz), 1.27 (3H, t, J = 7.3 Hz).

8-Ethyl-2(1*H*)-quinolinone 36. $AlCl_3$ (706 g, 5.3 mol) was added to a suspension of **34** (266, 1.06 mol) in chlorobenzene (800 mL) at 0 °C, portionwise. The reaction mixture was stirred for 1 h at 80 °C and poured into an ice−water (10L). After addition of MeOH (1 L), insoluble material was collected by filtration. The filtrate was extracted with CH_2Cl_2 (2 × 2 L), and the resulting organic layer was washed with water. After concentrated in vacuo, the residue was combined with above insoluble material and treated with active charcoal in AcOEt. Recrystallization from AcOEt gave **36** as colorless needles (145 g, 79%): mp 136−137 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.80 (1H, brs), 7.77 (1H, d, J = 9.5 Hz), 7.32−7.50 (2H, m), 7.16 (1H, dd, J = 7.6, 7.6 Hz), 6.67 (1H, d, J = 9.5 Hz), 2.88 (2H, q, J = 7.5 Hz), 1.34 (3H, t, J = 7.5 Hz).

8-Propyl-2(1*H*)-quinolinone 37. Using the same procedure as **36**, **37** (4.5 g, 80.4%) was obtained as colorless needles from **35** (8.0 g, 30 mmol): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.99 (1H, brs), 7.77 (1H, d, J = 9.5 Hz), 7.42 (1H, dd, J = 1.4, 7.7 Hz), 7.34 (1H, dd, J = 1.4, 7.4 Hz), 7.14 (1H, dd, J = 7.4, 7.7 Hz), 6.66 (1H, d, J = 9.5 Hz), 2.84 (2H, t, J = 7.5 Hz), 1.76 (2H, tq, J = 7.2, 7.5 Hz), 1.04 (3H, t, J = 7.2 Hz).

6-Isopropyl-2-methylthiomethylaniline 39. *N*-Chlorosuccinimide (NCS, 109 g, 816 mmol) was added to a solution of *o*-isopropylaniline **38** (100 g, 740 mmol) and dimethyl sulfide (60 mL, 817 mmol) in CH_2Cl_2 (1 L) at 80 °C, portionwise. Aftrer stirring for 30 min at room temperature, Et_3N (125 mL, 896 mmol) was added to the resulting mixture and refluxed for 5 h. After being cooled to room temperature, the reaction mixture was washed with 10% aqueous NaOH (2 × 1 L), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified with distillation under reduced pressure to obtain **39** as a pale yellow oil (82 g, 57%): bp 155−165 °C (13 mmHg), ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.11 (1H, dd, J = 1.5, 7.7 Hz), 6.89 (1H, dd, J = 1.5, 7.4 Hz), 6.71 (1H, dd, J = 7.4, 7.7 Hz), 4.13 (2H, brs), 3.71 (2H, s), 2.92 (1H, hept, J = 6.8 Hz), 2.00 (3H, s), 1.26 (6H, d, J = 6.8 Hz).

***N*-Acetyl-6-isopropyl-2-methylsulfoniummethylaniline 40.** Acetyl chloride (33 mL, 467 mmol) was added to a solution of **39** (82 g, 421 mmol) and Et_3N (71 mL, 509 mmol) in CH_2Cl_2 (800 mL) at 0 °C, dropwise. After being stirred for 1 h at room temperature, the reaction mixture was washed with water, dried (Na_2SO_4), and concentrated in vacuo. Recrystallization from EtOH−hexane gave colorless needles (92 g). A solution of $NaIO_4$ (74.3 g, 347 mmol) in water (350 mL) was added to a solution of the resulting needles (75 g, 316 mmol) in MeOH (750 mL) at 0 °C, and the reaction mixture was stirred for 2 h at room temperature. MeOH was removed under reduced pressure, and the residue was extracted with in CH_2Cl_2. The organic layer was washed with water, dried

(Na_2SO_4), and concentrated in vacuo. Crystallization from hexane provided **40** as a white powder (72.7 g, 82%): mp 119−122 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.89 (1H, brs), 7.37 (1H, dd, J = 1.7, 7.9 Hz), 7.28 (1H, dd, J = 7.2, 7.9 Hz), 7.02 (1H, dd, J = 1.7, 7.2 Hz), 4.23 (1H, d, J = 14.7 Hz), 3.72 (1H, d, J = 14.7 Hz), 3.06 (1H, hept, J = 7.0 Hz), 2.47 (3H, s), 2.20 (3H, s), 1.24 (3H, d, J = 7.0 Hz), 1.20 (3H, d, J = 7.0 Hz).

***N*-Acetyl-2-formyl-6-isopropylaniline 41.** Gaseous HCl was introduced to a solution of **40** (85.5 g, 337 mmol) in toluene (875 mL) under reflux. The reaction mixture was refluxed for 30 min and concentrated in vacuo. Chromatography (0−2% MeOH−CH_2Cl_2 gradient elution) gave **41** as a white powder (50.5 g, 71%): mp 128−130 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.97 (1H, s), 8.56 (1H, brs), 7.20−7.70 (3H, m), 3.13 (1H, hept, J = 6.9 Hz), 2.23 (3H, s), 1.24 (3H, d, J = 6.9 Hz), 1.23 (3H, d, J = 6.9 Hz).

8-Isopropyl-2(1*H*)-quinolinone 42. 41 (14 g, 68 mmol) was added to a solution of sodium ethoxide in ethanol, which was prepared from sodium (1.7 g, 74 mmol) and dry EtOH (50 mL). The reaction mixture was refluxed for 1 h. After concentration in vacuo, the residue was suspended in water and extracted with CH_2Cl_2. The organic layer was washed with water, saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (2% CH_2Cl_2−MeOH) gave **42** as a pale orange powder (11.7 g, 91%): mp 127−128 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.63 (1H, brs), 7.77 (1H, d, J = 9.5 Hz), 7.36−7.50 (2H, m), 7.19 (1H, dd, J = 7.6, 7.6 Hz), 6.66 (1H, d, J = 9.5 Hz), 3.34 (1H, hept, J = 6.8 Hz), 1.35 (6H, d, J = 6.8 Hz).

3,4-Dihydro-8-ethyl-2(1*H*)-quinolinone 43. A solution of **36** (100 g, 0.58 mol) in AcOH (1 L) was hydrogenated over 10% Pd−C (10 g) under an atmosphere of H_2 (1 atm) at 65 °C for 1.5 h. The reaction mixture was filtered through a Celite pad and concentrated in vacuo. Recrystallization from i-Pr_2O gave **43** as colorless prisms (70.2 g). The filtrate was concentrated in vacuo and purified with chromatography (CH_2Cl_2) to obtain additional **43** (19.6 g, total 88%): mp 99−102 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (1H, brs), 6.87−7.13 (3H, m), 2.90−3.05 (2H, m), 2.55−2.70 (2H, m), 2.58 (2H, q, J = 7.5 Hz), 1.24 (3H, t, J = 7.5 Hz).

3,4-Dihydro-8-isopropyl-2(1*H*)-quinolinone 44. Using the same procedure as **43**, **44** (6.4 g, 90%) was obtained as colorless prisms from **42** (7.0 g, 37.4 mmol): mp 98−100 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.56 (1H, brs), 7.14 (1H, dd, J = 2.2, 6.8 Hz), 6.92−7.07 (2H, m), 2.92−3.05 (2H, m), 2.91 (1H, hept, J = 6.8 Hz), 2.54−2.70 (2H, m), 1.27 (6H, d, J = 6.8 Hz).

6-Chloroacetyl-3,4-dihydro-8-methyl-2(1*H*)-quinolinone 47. $AlCl_3$ (7.0 g, 53 mmol) was added to a solution of chloroacetyl chloride (2.5 mL, 32 mmol) in CS_2 (30 mL), and then **45** (1.7 g, 10.6 mmol) was added to the mixture at room temperature, portionwise. CS_2 was removed by decantation, and the reaction mixture was poured into an ice−water. An insoluble part was collected by filtration, washed with water and MeOH, and dried to obtain **47** as a white powder (2.4 g, 95%): mp 233−236 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.78 (1H, s), 7.68 (1H, s), 7.67 (1H, s), 5.06 (2H, s), 2.86−2.98 (2H, m), 2.42−2.52 (2H, m), 2.26 (3H, s).

6-Chloroacetyl-8-ethyl-2(1*H*)-quinolinone 48. Using the same procedure as **47**, **48** (55 g, 88%) was obtained as a brown powder from **36** (44 g, 0.25 mol): ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.31 (1H, s), 8.24 (1H, d, J = 1.6 Hz), 8.00 (1H, d, J = 9.6 Hz), 7.73 (1H, d, J = 1.6 Hz), 6.60 (1H, d, J = 9.6 Hz), 5.19 (2H, s), 2.92 (2H, q, J = 7.2 Hz), 1.29 (3H, t, J = 7.2 Hz).

6-Chloroacetyl-3,4-dihydro-8-ethyl-2(1*H*)-quinolinone 49. Using the same procedure as **47**, **49** (36 g, 100%) was obtained as a brown powder from **43** (28 g, 0.16 mol): ^{1}H NMR (250 MHz, DMSO-d_6) δ 9.85 (1H, s), 7.70 (1H, s), 7.67 (1H, s), 5.10 (2H, s), 2.88−3.03 (2H, m), 2.70 (2H, q, J = 7.5 Hz), 2.45−2.60 (2H, m), 1.12 (3H, t, J = 7.5 Hz).

6-Chloroacetyl-8-propyl-2(1*H*)-quinolinone 50. Using the same procedure as **47**, **50** (3.0 g, 61%) was obtained as a white powder from **37** (3.5 g, 18.6 mmol): mp 244−247 °C, ^{1}H NMR (250 MHz, DMSO-d_6) δ 11.37 (1H, s), 8.24 (1H, d, J = 1.8 Hz), 8.00 (1H, d, J = 9.5 Hz), 7.90 (1H, d, J = 1.8 Hz), 6.59 (1H, d, J = 9.5 Hz), 5.19 (2H, s), 2.89 (2H, t, J = 7.8 Hz), 1.56 (2H, tq, J = 7.3, 7.8 Hz), 0.95 (3H, t, J = 7.3 Hz).

6-Chloroacetyl-3,4-dihydro-8-isopropyl-2(1*H*)-quinolinone 51. Using the same procedure as **47**, **51** (8.3 g, 99%) was obtained as a white powder from **44** (6.0 g, 31.7 mol): ^{1}H NMR (200 MHz, DMSO-d_6) δ 9.86 (1H, s), 7.72 (1H, s), 7.71 (1H, s), 5.12 (2H, s), 3.35 (1H, hept, J = 6.7 Hz), 2.85−3.05 (2H, m), 2.40−2.60 (2H, m), 1.16 (6H, d, J = 6.7 Hz).

6-Chloroacetyl-3,4-dihydro-7-methyl-2(1*H*)-quinolinone 52. Using the same procedure as **47**, **52** (0.57 g, 65%) was obtained as colorless needles from **46** (0.6 g, 3.7 mmol): mp 201−203 °C, ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.36 (1H, s), 7.77 (1H, s), 6.75 (1H, s), 5.02 (2H, s), 2.85−3.00 (2H, m), 2.43−2.60 (2H, m), 2.39 (3H, s).

6-Carboxy-3,4-dihydro-8-methyl-2(1*H*)-quinolinone 53. A mixture of **47** (7.0 g, 34.6 mmol) and pyridine (50 mL) was stirred for 1 h at 90 °C. After the mixture was cooled to room temperature, the insoluble part was collected by filtration. The insoluble part was suspended in 14% aqueous NaOH (70 mL) and stirred for 1 h at 90 °C. The reaction mixture was poured into an ice−water and acidified with concentrated aqueous HCl. The resuling precipitates were collected by filtration and washed with water to obtain **53** as a white powder (4.2 g, 60%): mp >300 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.53 (1H, brs), 9.66 (1H, s), 7.60 (1H, s), 7.59 (1H, s), 2.85−2.98 (2H, m), 2.40−2.50 (2H, m), 2.24 (3H, s).

6-Carboxy-8-ethyl-2(1*H*)-quinolinone 54. Using the same procedure as **53**, **54** (19 g, 40%) was obtained as pale brown needles from **48** (55 g, 0.22 mol): mp 243−246 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.88 (1H, s), 11.21 (1H, s), 8.15 (1H, d, J = 1.8 Hz), 8.04 (1H, d, J = 9.6 Hz), 7.87 (1H, d, J = 1.8 Hz), 6.57 (1H, d, J = 9.6 Hz), 2.91 (2H, q, J = 7.4 Hz), 1.18 (3H, t, J = 7.4 Hz).

6-Carboxy-3,4-dihydro-8-ethyl-2(1*H*)-quinolinone 55. Using the same procedure as **53**, **55** (32 g, 92%) was obtained as pale brown needles from **49** (41 g, 0.16 mol): mp >300 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.65 (1H, s), 9.76 (1H, s), 7.64 (2H, s), 2.85−3.05 (2H, m), 2.69 (2H, q, J = 7.6 Hz), 2.35−2.55 (2H, m), 1.13 (3H, t, J = 7.6 Hz).

6-Carboxy-8-propyl-2(1*H*)-quinolinone 56. Using the same procedure as **53**, **56** (2.4 g, 89%) was obtained as pale brown needles from **50** (3.0 g, 11.4 mmol): mp >300 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.88 (1H, s), 11.28 (1H, s), 8.15 (1H, d, J = 1.8 Hz), 8.03 (1H, d, J = 9.6 Hz), 7.85 (1H, d, J = 1.8 Hz), 6.56 (1H, d, J = 9.6 Hz), 2.88 (2H, t, J = 8.0 Hz), 1.54 (2H, tq, J = 7.2, 8.0 Hz), 0.93 (3H, t, J = 7.2 Hz).

6-Carboxy-3,4-dihydro-8-isopropyl-2(1*H*)-quinolinone 57. Using the same procedure as **53**, **57** (6.3 g, 87%) was obtained as pale brown needles from **51** (8.3 g, 31.2 mmol): mp 289−291 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 12.67 (1H, s), 9.78 (1H, s), 7.72 (1H, s), 7.65 (H, s), 3.36 (1H, hept, J = 6.5 Hz), 2.87−3.00 (2H, m), 2.45−2.55 (2H, m), 1.17 (3H, d, J = 6.5 Hz).

6-Carboxy-3,4-dihydro-7-methyl-2(1*H*)-quinolinone 58. Using the same procedure as **53**, **58** (1.9 g, 88%) was obtained as a pale yellow powder from **52** (2.5 g, 10.5 mmol): mp >300 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.51 (1H, s), 10.31 (1H, s), 7.74 (1H, s), 6.76 (1H, s), 2.85−3.00 (2H, m), 2.40−2.60 (2H, m), 2.50 (3H, s).

Methyl 4-Amino-3-methoxy-5-methylthiomethylbenzoate 60. Using the same procedure as **39**, **60** (104 g, 61%) was obtained as a white powder from **59** (128 g, 0.71 mol): mp 87−89 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44 (1H, d, J = 1.8 Hz), 7.42 (1H, d, J = 1.8 Hz), 4.64 (2H, brs), 3.91 (3H, s), 3.87 (3H, s), 3.71 (2H, s), 1.97 (3H, s).

Methyl 4-Acetylamino-3-methoxy-5-methylsulfoniummethylbenzoate 61. Acetyl chloride (35.4 mL, 0.50 mol) was added to a solution of **60** (100 g, 0.41 mol) and Et_3N (69.6 mL, 0.50 mol) in CH_2Cl_2 (1 L) at 0 °C, dropwise. After being stirred for 1 h at room temperature, the reaction mixture was washed with water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (CH_2Cl_2) gave a white powder (64 g). *m*-Chloroperbenzoic acid (mCPBA (80%), 58.5 g (include 46.8 g calculated by 80%), 0.27 mol) was added to a solution of the

resulting powder (64 g, 0.23 mol) in CH_2Cl_2 (1 L) at −10 °C, portionwise. After the mixture was stirred for 30 min at 0 °C, mCPBA (4.9 g (include 3.9 g calculated by 80%), 22.6 mmol) was added to the mixture. The reaction mixture was stirred for 10 h at at 0 °C and washed with 5% aqueous Na_2CO_3 (500 mL). The aqueous layer was extracted with CH_2Cl_2 (7 × 300 mL). The combined organic layer was dried ($MgSO_4$) and concentrated in vacuo. Recrystallization from CH_2Cl_2−Et_2O provided **61** as a white powder (67 g, 54%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.65 (1H, s), 7.62 (1H, d, J = 1.7 Hz), 7.55 (1H, d, J = 1.7 Hz), 4.29 (1H, d, J = 13.6 Hz), 3.93 (3H, s), 3.92 (3H, s), 3.83 (1H, d, J = 13.6 Hz), 2.50 (3H, s), 2.19 (3H, s).

Methyl 4-Acetylamino-5-formyl-3-methoxybenzoate 62. Using the same procedure as **41**, **62** (30 g, 54%) was obtained as a white powder from **61** (67 g, 0.22 mol): ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.90 (1H, s), 8.00−8.25 (1H, brs), 8.12 (1H, d, J = 1.8 Hz), 7.74 (1H, d, J = 1.8 Hz), 3.95 (3H, s), 3.93 (3H, s), 2.28 (3H, s).

6-Ethoxycarbonyl-8-methoxy-2(1*H*)-quinolinone 63. Sodium hydride (ca. 60% in oil, 5.3 g, 0.13 mmol) was added to dry EtOH (400 mL) at room temperature and stirred for 5 min. A solution of **62** (30 g, 0.12 mol) in EtOH (100 mL) was added to the resulting solution and refluxed for 1 h. After concentration in vacuo, the resultant residue was dissolved in CH_2Cl_2, washed with water and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (CH_2Cl_2) gave **63** as a white powder (5.8 g, 25%): mp 188−190 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.37 (1H, s), 7.92 (1H, d, J = 1.5 Hz), 7.78 (1H, d, J = 9.6 Hz), 7.62 (1H, d, J = 1.5 Hz), 6.71 (1H, d, J = 9.6 Hz), 4.42 (2H, q, J = 7.1 Hz), 4.04 (3H, s), 1.43 (3H, t, J = 7.1 Hz).

6-Carboxy-8-methoxy-2(1*H*)-quinolinone 64. 5 N aqueous NaOH (8.1 mL, 40.5 mmol) was added to a suspension of **63** (2.0 g, 8.1 mmol) in MeOH (100 mL) and stirred for 4 days at room temperature. A precipitate was collected by filtration, and the resulting powder was dissolved in water. After acidified with concentrated HCl at 0 °C, the precipitate was collected by filtation to obtain **64** as a white powder (1.6 g, 91%): ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.97 (1H, brs), 11.23 (1H, s), 8.04 (1H, d, J = 8.4 Hz), 7.96 (1H, d, J = 1.6 Hz), 7.57 (1H, d, J = 1.6 Hz), 6.61 (1H, d, J = 8.4 Hz), 3.98 (3H, s).

6-Carboxy-3,4-dihydro-8-nitro-2(1*H*)-quinolinone 66. A mixture of HNO_3 (d=1.52, 12 mL) and concentrated H_2SO_4 (50 mL) was added to a solution of **65** (50 g, 0.26 mol) in H_2SO_4 (750 mL) at 0 °C, dropwise. After being stirred for 3 h at room temperature, the reaction mixture was poured into an ice−water. A precipitate was collected by filtration and washed with water. Recrystallization from MeOH provided **66** as a pale yellow powder (20 g, 32%): mp 256−258 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.38 (1H, brs), 10.00 (1H, s), 8.43 (1H, d, J = 1.9 Hz), 8.12 (1H, d, J = 1.9 Hz), 3.00−3.15 (2H, m), 2.55−2.68 (2H, m).

6-Methoxycarbonyl-3,4-dihydro-8-nitro-2(1*H*)-quinolinone 67. Thionyl chloride (7.0 mL, 96 mmol) was added to a suspension of **66** (15 g, 64 mmol) in MeOH (150 mL) at 0 °C, dropwise. After refluxing for 3 h, the reaction mixture was concentrated in vacuo. Recrystallization from MeOH gave **67** as a pale yellow powder (12.8 g, 80%): mp 144−145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.02 (1H, s), 8.45 (1H, d, J = 1.9 Hz), 8.14 (1H, d, J = 1.9 Hz), 3.88 (3H, s), 3.05−3.18 (2H, m), 2.57−2.68 (2H, m).

6-Methoxycarbonyl-8-nitro-2(1*H*)-quinolinone 68. A catalytic amount of benzoyl peroxide was added to a solution of **67** (12 g, 48 mmol) and *N*-bromosuccinimide (NBS, 10.7 g, 60 mmol) in $CHCl_3$ (200 mL) and refluxed for 3 h. After addition of NBS (5.0 g), the reaction mixture was refluxed for 1 h. The reaction mixture was concentrated in vacuo. Recrystallization from EtOH provided **68** as a pale yellow powder (7.1 g, 60%): mp 189−190 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.40 (1H, s), 9.13 (1H, d, J = 1.8 Hz), 8.50−8.60 (1H, m), 7.87 (1H, d, J = 9.7 Hz), 6.82 (1H, dd, J = 1.9, 9.7 Hz), 4.02 (3H, s).

6-Carboxy-8-nitro-2(1*H*)-quinolinone 69. Using the same procedure as **64**, **69** (6.1 g, 91%) was obtained as a pale yellow powder from **69** (7.1 g, 28.6 mmol): mp 297−298 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 13.68 (1H, s), 11.21 (1H, s), 8.75 (1H, d, J = 1.8 Hz), 8.71 (1H, d, J = 1.8 Hz), 8.27 (1H, d, J = 9.8 Hz), 6.80 (1H, d, J = 9.8 Hz).

6-Chloroacetyl-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone 71. Iodomethane (21 mL, 0.33 mol) was added to a suspension of **70** (50 g, 0.3 mol) and K_2CO_3 (63 g, 0.46 mol) in DMF (250 mL) at 0 °C, dropwise. After being stirred for 15 h at room temperature, the reaction mixture was poured into an ice−water. A precipitate was collected by filtration and recrystallized from MeOH to obtain 7-methoxy derivative as pale yellow needles. Chloroacetyl chloride (22 mL, 0.28 mol) was added to a suspension of $AlCl_3$ (76 g, 0.57 mol) in dichloroethane (200 mL) at 0 °C and stirred for 1 h at room temperature. The 7-methoxy derivative was added to the resulting solution. The mixture was stirred for 3 h at 70 °C and poured into an ice−water. After collection of a precipitate by filtration, recrystallization from DMF−MeOH gave **71** as colorless prisms (20 g, 28%): mp 248−251 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 11.43 (1H, s), 10.44 (1H, s), 7.66 (1H, s), 6.44 (1H, s), 5.01 (2H, s), 2.75−2.95 (2H, m), 2.40−2.60 (2H, m).

6-Carboxy-3,4-dihydro-7-hydroxy-2(1*H*)-quinolinone 72. Using the same procedure as **53**, **72** (30 g, 82%) was obtained as a brown powder from **71** (43 g, 0.18 mol): ^{1}H NMR (200 MHz, DMSO-d_6) δ 13.50 (1H, brs), 11.31 (1H, brs), 10.36 (1H, s), 7.56 (1H, s), 6.41 (1H, s), 2.72−2.93 (2H, m), 2.30−2.45-(2H, m).

3,4-Dihydro-7-hydroxy-6-methoxycarbonyl-2(1*H*)-quinolinone 73. A solution of iodomethane (4.5 mL, 72 mmol) in DMF (50 mL) was added to a suspension of **72** (15 g, 72 mmol) and K_2CO_3 (10 g, 72 mmol) in DMF (250 mL) at 0 °C, dropwise. After being stirred for 40 h at room temperature, the reaction mixture was poured into an ice−water. A precipitate was collected by filtration and recrystallized from DMF-MeOH to obtain **73** as pale yellow needles (8.5 g, 53%): mp 259−263 °C, ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.58 (1H, s), 10.37 (1H, s), 7.58 (1H, s), 6.42 (1H, s), 3.85 (3H, s), 2.75−2.93 (2H, m), 2.37−2.55 (2H, m).

3,4-Dihydro-7-methoxy-6-methoxycarbonyl-2(1*H*)-quinolinone 74. Iodomethane (0.81 mL, 13.0 mmol) was added to a suspension of **73** (2.4 g, 10.8 mmol) and K_2CO_3 (1.8 g, 13.0 mol) in DMF (25 mL) at 0 °C. After the mixture was stirred for 24 h at room temperature, iodomethane (0.34 mL, 5.4 mmol) and K_2CO_3 (0.75 g, 5.4 mmol) were added to the reaction mixture. The reaction mixture was stirred for 5 h at room temperature. The resulting mixture was poured into ice−water and extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. The crude material was purified by chromatography (1% MeOH−CH_2Cl_2). Recrystallization from MeOH gave **74** as pale yellow needles (1.0 g, 39%): mp 185.5−188.0 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.96 (1H, s), 7.70 (1H, s), 6.41 (1H, s), 3.90 (3H, s), 3.87 (3H, s), 2.90−3.03 (2H, m), 2.60−2.73 (2H, m).

6-Carboxy-3,4-dihydro-7-methoxy-2(1*H*)-quinolinone 75. Using the same procedure as **64**, **75** (0.19 g, 96%) was obtained as a white powder from **74** (0.21 g, 0.89 mmol): mp 254−256 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.17 (1H, brs), 10.22 (1H, s), 7.55 (1H, s), 6.57 (1H, s), 3.73 (3H, s), 2.80−2.90 (2H, m), 2.40−2.50 (2H, m).

6-Carboxy-7-methoxy-2(1*H*)-quinolinone 76. A suspension of **74** (2.6 g, 11.1 mmol), NBS (6.9 g, 33 mmol), and catalytic amount of BPO in $CHCl_3$ (50 mL) was refluxed for 2 h. An insoluble part was collected by filtration and treated with 30% aqueous NaOH (50 mL). After being stirred for 2 h at room temperature, the reaction mixture was acidified with concentrated HCl. A precipitated was collected by filtration to obtain a nuclear brominated product as a white powder. A solution of the white powder and 5 N aqueous NaOH (3.4 mL) in H_2O (20 mL) was hydrogenated over 10% Pd−C (0.2 g) under an atmosphere of H_2 (1 atm) at room temperature for 2 h. The reaction mixture was filtered through a Celite pad and acidified with concentrated HCl. A precipitate was collected

by filtration to obtain **76** as a white powder (1.1 g, 45%): ^{1}H NMR (200 MHz, DMSO-d_6) δ 12.53 (1H, brs), 11.76 (1H, brs), 8.07 (1H, s), 7.89 (1H, d, J = 9.4 Hz), 6.88 (1H, s), 6.35 (1H, d, J = 9.4 Hz), 3.84 (3H, s).

Methyl 4-Amino-3-methyl-5-methylthiomethylbenzoate 79. Using the same procedure as **39**, **79** (114 g, 48%) was obtained as a white powder from **77** (174 g, 1.05 mol): mp 81−82 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (1H, s), 7.62 (1H, s), 4.51 (2H, brs), 3.86 (3H, s), 3.72 (2H, s), 2.21 (3H, s), 1.98 (3H, s).

Methyl 4-Amino-3-chloro-5-methylthiomethylbenzoate 80. Using the same procedure as **39**, **80** (3.3 g, 49%) was obtained as a orange powder from **78** (5.0 g, 27.0 mmol): mp 48−50 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93 (1H, d, J = 1.6 Hz), 7.63 (1H, d, J = 1.6 Hz), 5.01 (2H, brs), 3.87 (3H, s), 3.72 (2H, s), 1.97 (3H, s).

Methyl 4-Amino-3-methoxy-5-methylbenzoate 81. A solution of **60** (10 g, 41 mmol) in EtOH (300 mL) was hydrogenated over Raney Ni (wet, 100 g) at room temperature for 1 h. Raney Ni was removed by filtration and washed with EtOH. The filtrate was concentrated in vacuo to obtain **81** as a colorless oil (7.8 g, 97%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48 (1H, d, J = 1.7 Hz), 7.36 (1H, d, J = 1.7 Hz), 4.19 (2H, brs), 3.89 (3H, s), 3.86 (3H, s), 2.18 (3H, s).

Methyl 4-Amino-3,5-dimethylbenzoate 82. Using the same procedure as **81**, **82** (68 g, 88%) was obtained as colorless needles from **79** (96 g, 0.43 mol): mp 104−107 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66 (2H, s), 3.98 (2H, brs), 3.85 (3H, s), 2.19 (6H, s).

Methyl 4-Amino-3-chloro-5-methylbenzoate 83. Using the same procedure as **81**, **83** (1.4 g, 55%) was obtained as a white powder from **80** (3.2 g, 12.8 mmol): mp 80−81 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.78 (1H, d, J = 1.8 Hz), 7.58 (1H, d, J = 1.8 Hz), 4.60 (2H, brs), 3.83 (3H, s), 2.13 (3H, s).

Methyl 2-Methyl-3-methylthiomethyl-4-propionylaminobenzoate 85, Methyl 2-Methyl-5-methylthiomethyl-4-propionylaminobenzoate 86. Using the same procedure as **39**, a mixture of methylthiomethylated benzoate (12.8 g) was obtained as a colorless oil from **84** (12.8 g, 77.5 mmol). Propionyl chloride (5.4 mL, 62.5 mL) was added to a solution of the resulting oil (12.8 g) and Et_3N (8.8 mL, 62.5 mmol) in CH_2Cl_2 (300 mL) at 0 °C, dropwise. After being stirred for 1 h a at 0 °C, the reaction mixture was washed with water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography (AcOEt:hexane = 1:5) gave **85** as a white powder (3.0 g, 14%) and **86** as a white powder (3.3 g, 15%): for **85**, mp 144−145 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.28 (1H, brs), 8.05 (1H, s), 7.89 (1H, d, J = 8.6 Hz), 7.77 (1H, d, J = 8.6 Hz), 3.88 (3H, s), 3.81 (2H, s), 2.59 (3H, s), 2.48 (2H, q, J = 7.5 Hz), 2.11 (3H, s), 1.29 (3H, t, J = 7.5 Hz), for **86**, mp 141−142 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.46 (1H, brs), 8.05 (1H, s), 7.73 (1H, s), 3.87 (3H, s), 3.72 (2H, s), 2.60 (3H, s), 2.46 (2H, q, J = 7.5 Hz), 1.98 (3H, s), 1.28 (3H, t, J = 7.5 Hz).

Methyl 2,3-Dimethyl-4-propionylaminobezoate 87. Using the same procedure as **81**, **87** (1.8 g, 85%) was obtained as a white powder from **85** (2.5 g, 8.9 mmol): mp 166−167 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.66 (2H, s), 7.13 (1H, brs), 3.87 (3H, s), 2.58 (3H, s), 2.43 (2H, q, J = 7.5 Hz), 2.18 (3H, s), 1.26 (3H, t, J = 7.5 Hz).

Methyl 2,5-Dimethyl-4-propionylaminobezoate 88. Using the same procedure as **81**, **88** (1.7 g, 82%) was obtained as a white powder from **86** (2.5 g, 8.9 mmol): mp 142−143 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (1H, brs), 7.77 (1H, s), 7.01 (1H, brs), 3.87 (3H, s), 2.57 (3H, s), 2.44 (2H, q, J = 7.5 Hz), 2.24 (3H, s), 1.27 (3H, t, J = 7.5 Hz).

4-(*N*-Methyl-2-phenylethylamino)piperidine 31. A solution of **89** (50 g, 0.26 mol), β-phenethylamine (32 g, 0.26 mol) and AcOH (16 g, 0.79 mol) in EtOH (500 mL) was hydrogenated over 5% Pt−C (5.0 g) under an atmosphere of H_2 (1 atm) at 40 °C for 2 h. The reaction mixture was filtered through a Celite pad and concentrated in vacuo. The residue was dissolved in formic acid (80 mL) and treated with 30% aqueous formaldehyde (30 mL). After the mixture was stirred for 1 h at 50 °C for 1 h, EtOH (500 mL) and concentrated HCl (55 mL) was added to the reaction mixture, and it was concentrated in vacuo. Precipitate was collected by filtration from small amount of EtOH. A solution of the resulting powder and concentrated HCl (20 mL) in EtOH (500 mL) and H_2O (200 mL) was hydrogenated over 10% Pd−C (7.0 g) under an atmosphere of H_2 (1 atm) at 40 °C for 3 h. The reaction mixture was filtered through a Celite pad and washed with EtOH. The filtrate was concentrated in vacuo, and the residue was dissolved in H_2O. After basification with 20% aqueous NaOH, the solution was extracted with AcOEt. The organic layer was washed with water and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. The residue was distilled under reduce presser to obtain **31** as a colorless oil (37.6 g, 66%): bp 125−127 °C (0.2 mmHg), ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.12−7.38 (5H, m), 3.07−3.23 (2H, m), 2.43−2.90 (7H, m), 2.36 (3H, s), 1.70−1.90 (2H, m), 1.30−1.70 (3H, m).

Constant-Pressure Auto-Perfused Femoral Artery Preparations. Dogs were anesthetized with pentobarbital sodium (30 mg/kg iv) and intravenously injected with 700 U/kg of heparin sodium. The right femoral artery was perfused at 90 mL/min with the animal's own blood from the carotid artery using a peristaltic pump (Type BP-1, Japan Medical Supply). A Starling pneumatic resistor was placed in parallel with the perfusion circuit to maintain the perfusion pressure at 100 mmHg. The blood flowing through the resistor was returned to the left femoral vein. Throughout the experiments, dogs were artificially ventilated through an endotracheal cannula connected to a respirator (Shinano) with a tidal volume of 20 mL/kg at a rate of 18 breaths/min. Dogs also received intravenous infusion of pentobarbital sodium at 4 mg/kg/h to maintain anesthesia and heparin sodium at 100 U/kg/h to prevent blood coagulation. Femoral artery blood flow was measured using an electromagnetic flow meter (MFV-2100, Nihon-Kohden) placed in the perfusion circuit. Drugs were administered using a microsyringe via a cannula placed in the right femoral artery.

Isolated Blood-Perfused Heart Preparations. Dogs were anesthetized with pentobarbital sodium (30 mg/kg iv), intravenously injected with 500 U/kg of heparin sodium, and exsanguinated. The heart was isolated, immersed in cooled lactate Ringer's solution, and used for various isolated heart preparations. These preparations were kept in glass vessels at 37 °C and perfused with arterial blood from blood donor dogs via a cannula in the carotid artery using a peristaltic pump (Type 1210, Harvard). A Starling pneumatic resistor was placed in parallel with the perfusion circuit to maintain a constant perfusion pressure. The venous blood from the preparations and the blood passing through the resistor were collected in a blood reservoir and returned to the left jugular vein of the donor dogs. The donor dogs were anesthetized with pentobarbital sodium (30 mg/kg iv) and intravenously injected with 500 U/kg of heparin sodium. Throughout the experiments, the dogs were artificially ventilated and received continuous intravenous infusion of pentobarbital sodium at 4 mg/kg/h to maintain anesthesia and heparin sodium at 100 U/kg/h to prevent blood coagulation. Papillary muscle preparations, composed of the ventricular septum and anterior papillary muscle, were prepared according to the method of Endoh and Hashimoto.[16] A cannula was placed in the anterior septal artery for perfusion at a constant pressure of 100 mmHg. Papillary muscle preparations were preloaded with a force of 2 g and stimulated by rectangular pulses (voltage, 1.2 times the threshold voltage; duration, 5 ms; frequency, 120 stimuli/min) generated by an electric stimulator (Type 2907, NEC Sanei) and applied through electrodes placed on the origin of papillary muscle. Anterior septal blood flow was measured using an electromagnetic flow meter (MFV-2100, Nihon-Kohden) as an index of coronary artery blood flow. Drugs were administered using a microsyringe via a catheter connected to the anterior septal artery.

Anesthetized Open-Chest Dogs. Mongrel dogs were anesthetized with 30 mg/kg of pentobarbital sodium. The dogs were artificially ventilated with room air through an endotracheal cannula with a tidal volume of 20 mL/kg at a rate of

18 breaths/min. To maintain constant anesthesia, the dogs received pentobarbital sodium continuously (4 mg/kg/h) throughout the experiments. Thoracotomy was performed at the fifth left intercostal space, and the heart was suspended in a cardiac cradle. Electromagnetic flow meter probes (MFV-2100, Nihon-Kohden) were placed on the origin of the left circumflex coronary and on the right femoral artery to measure coronary and femoral artery blood flow, respectively. A polyethylene tube was placed in the left femoral artery and connected to a pressure transducer (MPU-0.5, NEC San-ei) for the measurement of blood pressure. Drugs were injected via a cannula placed in the femoral vein. When all parameters had stabilized, drug administration was started.

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References

(1) Dawson, D. L.; Cutler, B. S.; Meissner, M. H.; Strandness, D. E., Jr. Cilostazol has beneficial effects in treatment of intermittent claudication. *Circulation* **1998**, *98*, 678−686.

(2) Lievre, M.; Morand, S.; Besse, B.; Fiessinger, J.-N.; Boissel, J.-P. Oral Beraprost sodium, a prostaglandin I2 analogue, for intermittent claudication. *Circulation* **2000**, *102*, 426−431.

(3) Rynaud's Treatment Study Investigators. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud's phenomenon. *Arch. Intern. Med.* **2000**, *160*, 1101−1108.

(4) Coffman, J. D.; Clement, D. L.; Creager, M. A.; Dormandy, J. A.; Janssens, M. M.-L.; McKendry, R. J. R.; Murray, G. D.; Nielsen, S. L. International study of Ketanserin in Raynaud's phenomenon. *Am. J. Med.* **1989**, *87*, 264−268.

(5) Black, C. M.; Halkier-Sørensen, L.; Belch, J. J. F.; Ullman, S.; Madhok, R.; Smit, A. J.; Banga, J.-D.; Watson, H. R. Oral Iloprost in Raynaud's phenomenon secondary to systemic sclerosis: A multicentre, placebo-controlled, dose-comparison study. *Br. J. Rheumatol.* **1998**, *37*, 952−960.

(6) Ettinger, W. H.; Wise, R. A.; Schaffhauser, D.; Wigley, F. M. Controlled double-blind trial of Dazoxiben and Nifedipine in the treatment of Raynaud's phenomenon. *Am. J. Med.* **1984**, *77*, 451−456.

(7) Wigley, F. M.; Wise, R. A.; Malamet, R.; Scott, T. E. Nicardipine in the treatment of Raynaud's phenomenon. *Arthritis Rheum.* **1987**, *30*, 281−286.

(8) Wigley, F. M.; Korn, J. H.; Csuka, M. E.; Medsger, T. A., Jr.; Rothfield, N. F.; Ellman, M.; Martin, R.; Collier, D. H.; Weinstein, A.; Furst, D. E.; Jimenez, S. A.; Mayes, M. D.; Merkel, P. A.; Gruber, B.; Kaufman, L.; Varga, J.; Bell, P.; Kern, J.; Marrott, P.; White, B.; Simms, R.; Phillips, A. C.; Seibold, J. R. Oral Iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis. *Arthritis Rheum.* **1998**, *41*, 670−677.

(9) Wollersheim, H.; Thien, T. Dose−response study of prazosin in Raynaud's phenomenon: Clinical effectiveness versus side effects. *J. Clin. Pharmacol.* **1988**, *28*, 1089−1093.

(10) Tominaga, M.; Yo, E.; Ogawa, H.; Yamashita, S.; Yabuuchi, Y.; Nakagawa, K. Studies on positive inotropic agents. II. Synthesis of (4-substituted 1-piperazinylcarbonyl)-2(1*H*)-quinolinone derivatives. *Chem. Pharm. Bull.* **1986**, *34*, 682−693.

(11) Kametani, T.; Nemoto, H. Chichibabin reaction. II. Chichibabin reaction of 8-methylquinoline and migration of the methyl group in the synthesis of 3,4-dihydro-8-methylcarbostyril by Friedel−Crafts reaction. (Studies on the syntheses of heterocyclic compounds. CCIII). *Chem. Pharm. Bull.* **1967**, *15*, 1910−1915.

(12) Gassman, P. G.; Gruetzmacher, G. D. Azasulfonium salt. Intermediates in a general procedure for the alkylation of aromatic amines. *J. Am. Chem. Soc.* **1974**, *96*, 5487−5495.

(13) King, L. C. The reaction of iodine with some ketones in the presence of pyridine. *J. Am. Chem. Soc.* **1944**, *66*, 894−895.

(14) Adachi, M.; Sasakura, K.; Sugasawa, T. Aminohaloborane in organic synthesis. IX. Exclusive ortho acylation reaction of N-monoaminoalkylanilines. *Chem. Pharm. Bull.* **1985**, *33*, 1826−1835.

(15) Orito, K.; Imaizumi, T.; Yoshida, K.; Fujiki, H.; Kishi, M.; Teramoto, S.; Tanaka, M.; Shimizu, H.; Tominaga, M.; Kimura, Y.; Kambayashi, J.; Mori, T. Mechanisms of action of OPC-28326, a selective hindlimb vasodilator. *J. Pharmacol. Exp. Ther.* **1999**, *291*, 604−611.

(16) Endoh, M.; Hashimoto, K. Pharmaceutical evidence of autonomic nerve activity in canine papillary muscle. *Am. J. Physiol.* **1979**, *218*, 1459−1463.

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