Studies on New Platelet Aggregation Inhibitors 1. Synthesis of 7-Nitro-3,4-dihydroquinoline-2(1*H*)-one Derivatives

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A series of 6-cyclic aliphatic amino-7-nitro-3,4-dihydroquinoline-2(1*H*)-ones were prepared and tested for platelet aggregation inhibitory effect, cardiotonic activity and chronotropic activity. These compounds appeared to show selective inhibitory activity against platelet aggregation. Among them, 6-(4-ethoxycarbonylpiperidino)-7-nitro-3,4-dihydroquinoline-2(1*H*)-one (22f) showed the most potent inhibitory activity and high selectivity. A divergent synthetic route to 6-cyclic aliphatic amino-7-nitro-3,4-dihydroquinoline-2(1*H*)-one derivatives has also been investigated.

Key words antiplatelet agent; *N*-nitroso mimic; 7-nitro-3,4-dihydroquinoline-2(1*H*)-one; divergent synthesis

As platelets play an important role not only in hemostasis and thrombosis but also in atherogenesis and arterial spasm,[1] efforts have been made to synthesize compounds which are significantly more active than acetylsalicylic acid in inhibiting platelet aggregation.[2] In our previous study of the synthesis of 6-(1-piperazinyl)-7-nitro-3,4-dihydroquinoline-2(1*H*)-one derivatives,[3] it was found that the crude sample of 2-(4-methylamino)quinazolinyl derivative (**1**) (Fig. 1) exhibited good antiplatelet activity. However, further investigation revealed that pure **1** has only weak antiplatelet activity; the true active compound is 7-nitro-6-[1-(4-nitrosopiperazinyl)]-3,4-dihydroquinolin-2(1*H*)-one **2**, which was contaminated as an impurity in a screening sample of **1**. Compound **2** had cardiotonic and chronotropic activities (CTA, CRA) in addition to antiplatelet activity (see Table 1).

In the present study, we focused on the structure of **2** and intended to separate its antiplatelet activity from its cardiovascular effects. This paper describes the synthesis of a series of derivatives of **2** and the details of their structure–activity relationship. In addition, a divergent synthetic route to 6-cyclic aliphatic amino-7-nitro-3,4-dihydroquinoline-2(1*H*)-one derivatives has been investigated.

Chemistry

The lead compound **2** and its analogs, having an *N*-acylpiperazine ring (**10**, **12**) or morpholine ring (**7**) at the 6-position of 3,4-dihydroquinoline-2(1*H*)-one, were prepared as shown in Chart 1. The acetal **4** obtained from commercially available 5-chloro-2-nitrobenzaldehyde **3** was converted to the 6-piperazinyl (**6a**) and 6-morpholino (**6b**) derivatives by a series of reactions based on the patent reported by Tominaga *et al.*[4]

As the first step in the preparation of **2**, we examined the *N*-nitrosation of **6a** under conventional reaction conditions ($NaNO_2$ (4.0 eq) in 1 M hydrochloric acid, room temperature, for 4 h). The ^{1}H-NMR spectrum of the sole product from this reaction however showed, the presence of only two aromatic protons (δ 7.10, 7.30 ppm, both as a singlet). The product was identified with **2** by NMR, IR (NO_2: 1523, 1375, 1348 cm^{-1}) and FAB-MS ($M+H^+$: *m/z* 306) spectra. Compound **2** was also identical to the impurity found in the initial screening sample of **1**. The yield of **2** from **6a** was 83%. Simple *N*-nitrosation of **6a** leading to **8** can be performed by the use of isoamyl nitrite in MeOH in 59% yield. Similarly, **6b** underwent nitration at the 7-position by treatment with $NaNO_2$ (1.4 eq, AcOH/trifluoroacetic acid (TFA)=4/1, room temperature, for 0.5 h) to give **7** in 43% yield. Although the actual reaction mechanism of these nitrations is not clear, it has been known that nitrous acid undergoes disproportionation to nitric acid and nitric oxide,[5] and there have been several precedents[6] involving nitration with nitrous acid.

The preparation of the *N*-acetyl analog **10** was carried out by acetylation of **6a** (95% yield, Ac_2O in pyridine) followed by nitration at the 7-position of **9** (61% yield, 1.1 eq of $NaNO_3$) in TFA. The nitration of **9** can also be effected using $NaNO_2$: 64% yield with $NaNO_2$ (1.0 eq) in 1 M hydrochloric acid; 86% yield with $NaNO_2$ (1.0 eq) in AcOH/TFA=4/1. It should be mentioned that, when the above nitration with $NaNO_2$ was carried out in AcOH alone, an inseparable mixture of **10**/the 5-nitro isomer=7.5/1 was formed as evidenced by ^{1}H-NMR spectroscopy.[7] Compound **10** was hydrolyzed to **11** in 73% yield, and the *N*-formyl analog **12** was prepared by formylation of **11** in 45% yield.

At this stage, biological assay results of these compounds suggested that the presence of the 7-nitro group is essential to their inhibitory activity against platelet aggregation (see the next part of the text). As the 7-nitro group in the 3,4-dihydroquinoline-2(1*H*)-one system was expected to allow nucleophilic substitution at the 6-position, a plan was made for a divergent synthetic approach to the analogs, in which a compound having a 7-nitro group as well as a suitable leaving group at the 6-position is to be used as an intermediate.

A synthetic route to the above mentioned intermediate **19** is given in Chart 2. The aldehyde **14**, prepared from commercially available 5-hydroxy-2-nitrobenzaldehyde **13**, was sub-

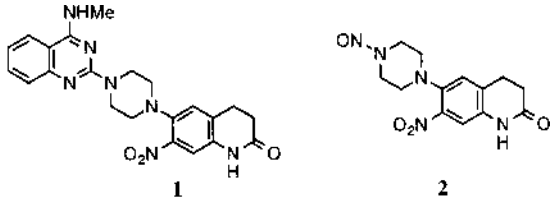

Fig. 1

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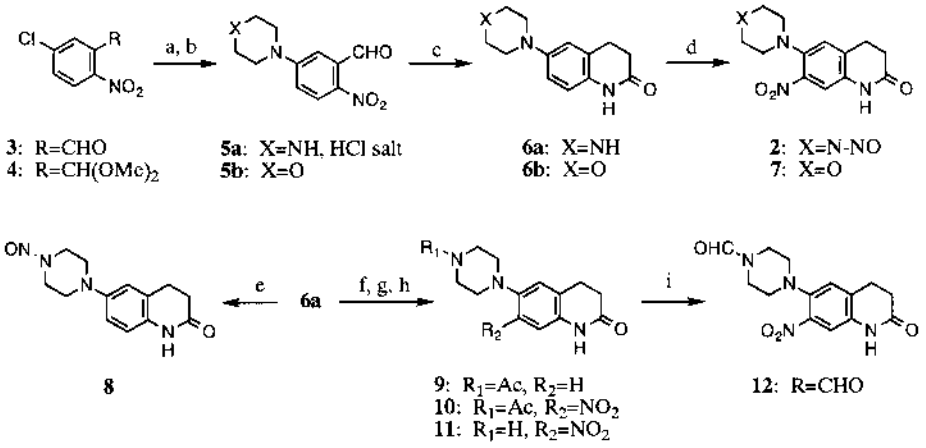
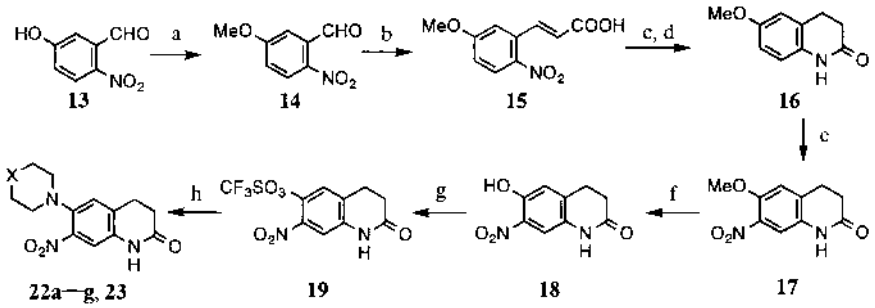


Reagent and conditions: (a) MeOH, *p*-toluenesulfonic acid, reflux; in the case of X=NH: (b) 1) piperazine, *N*,*N*-dimethylformamide, 80 °C; 2) HCl, iso-PrOH–H_2O, reflux; (c) 1) Ac_2O, pyridine; 2) maloic acid, piperidine, reflux; 3) H_2, Pd–C, AcOH; 4) cHCl, reflux; (d) $NaNO_2$, 1 M HCl; in the case of X=O: (b) 1) morpholine, 1,8-diazabicyclo[5,4,0]undec-7-ene, 100 °C; 2) HCl, Acetone–H_2O, 60 °C; (c) 1) malonic acid, pyridine, piperidine, reflux; 2) H_2, Pd–C, AcOH, MeOH, 80 °C; (d) $NaNO_2$, AcOH–TFA; (e) isoamyl-ONO, MeOH; (f) Ac_2O, pyridine; (g) $NaNO_3$, TFA; (h) cHCl, 90 °C; (i) HCOOH, 1,3-dicyclohexylcarbodiimide, $CHCl_3$.

Chart 1. Synthesis of 6-Piperazinyl and 6-Morpholino Derivatives **2**, **6a**, **7**, **8**, **10**—**12**



Reagent and conditions: (a) MeI, Cs_2CO_3, DMF; (b) malonic acid, pyridine, piperidine, reflux; (c) H_2, Pd–C, AcOH; (d) AcOEt, 70 °C; (e) $NaNO_2$, TFA; (f) $AlCl_3$, dichloroethane, reflux; (g) CF_3SO_2Cl, Et_3N, DMF; (h) X⟨⟩NH, CH_3CN, 80 °C.

Chart 2. Divergent Synthesis of Cyclic Aliphatic Amine Derivatives **22a**—**g**, **23**

jected to Knoevenagel condensation with malonic acid to give **15** in 71% yield. After hydrogenation of the nitro group in **15**, cyclization was effected simply by heating the reaction mixture at 70 °C for 1 h, which gave **16** in 88% yield.

Nitration at the 7-position of **16** was examined under several conditions. When fuming nitric acid (1.0 eq) was used in combination with an acid anhydride (0 °C, for 20—30 min), the desired 7-nitro derivative **17** always accompanied a considerable amount of the 7,8-dinitrated product (Ac_2O with a small amount of conc. H_2SO_4: **17**/7,8-dinitrated product=1/3; $(CF_3CO)_2O$: **17**/7,8-dinitrated product=2/1) together with some of the starting material. Use of $NaNO_3$ (1.0 eq) was also discouraging, either forming a mixture of **17**/8-nitro isomer=9/1 in TFA (room temperature, for 3 h) or giving the 8-nitro isomer in AcOH (100 °C, for 1.5 h, 68% yield).[8] The best result was obtained again when **16** was reacted with a 1.0 eq of $NaNO_2$ in TFA (0 °C, for 20 min, 88% yield of **17**).

Compound **19**, which was a key intermediate in our new synthetic approach, was prepared by demethylation of **17** with $AlCl_3$ (97% yield) followed by treatment of the resulting product (**18**) with CF_3SO_2Cl (79% yield). Nucleophilic substitution of **19** with cyclic aliphatic amines (**20a**—**g**, **21**, see Fig. 2) was carried out in CH_3CN at 80 °C. This gave the desired analogs (**22a**—**g**, **23**) in 4—51% yields.

Some of cyclic aliphatic amines (**20d**, **e**, **g**, **21**), which were

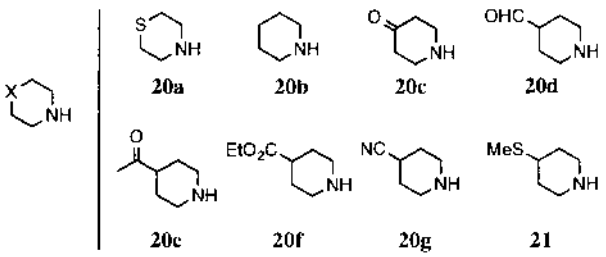


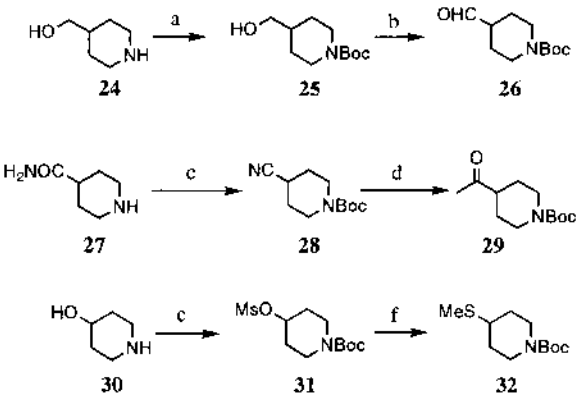
Fig. 2. Chemical Structures of Cyclic Aliphatic Amines Used for the Preparation of **22a**—**g**, **23**

not commercially available, were prepared as shown in Chart 3. The aldehyde **26** was obtained from **24** in an overall yield of 40%: *tert*-butoxycarbonylation followed by the Dess–Martin oxidation. Preparation of the nitrile **28** was carried out by using **27** in an overall yield of 83%: *tert*-butoxycarbonylation and subsequent dehydration with trifluoroacetic anhydride (TFAA). The methyl ketone **29** was prepared from **28** with methyl magnesium iodide in 43% yield. The methyl sulfide **32** was prepared from **30** in an overall yield of 57%: *tert*-butoxycarbonylation, mesylation and finally thiomethylation. These *N*-*tert*-butoxycarbonyl (*N*-Boc) piperidines (**26**, **28**, **29**, **32**) were used for the above-mentioned reaction of **19** after treatment with TFA. Also carried out was further de-

rivatization of **22a** and **23** to the corresponding sulfoxides [**22h** (45% yield), **22j** (79% yield)] and sulfones [**22i** (61% yield), **22k** (77% yield)] by *m*-chloroperoxybenzoic acid (mCPBA) oxidation, as shown in Chart 4.

Pharmacological Activities and Discussions

All 6-cyclic aliphatic amino-7-nitro-3,4-dihydroquinoline-2(1*H*)-ones (**2**, **8**, **6a**, **10**—**12**, **22a**—**k**) synthesized in this study were evaluated for their effect on platelet aggregation inhibitory activity (PIA) in rabbit platelet-rich plasma (PRP),[9] CTA and CRA on isolated guinea pig atria[10] by the procedures described in the Experimental Section. These results are summarized in Tables 1 and 2.



Reagent and conditions: (a) di-*tert*-butyl dicarbonate (Boc_2O), AcOEt, THF; (b) Dess–Martin, CH_2Cl_2; (c) Boc_2O, CH_2Cl_2, pyridine, then TFAA; (d) MeMgI, Et_2O; (e) Boc_2O, CH_2Cl_2, dioxane, then methanesulfonyl chloride (MsCl), Et_3N, CH_2Cl_2; (f) NaSMe, DMF, 80 °C.

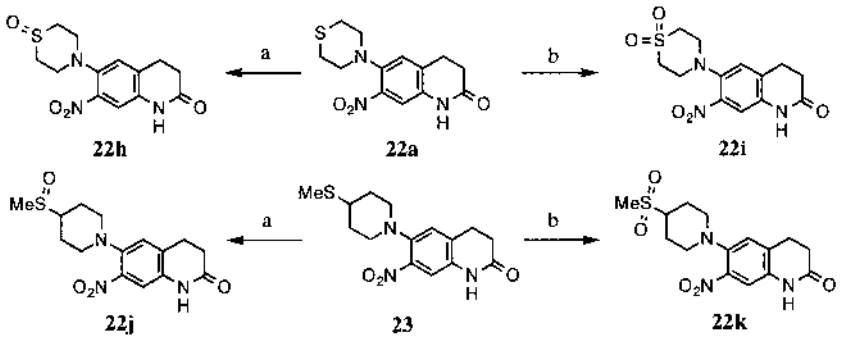
Chart 3. Synthesis of 4-Substituted-piperidine Derivatives **26**, **28**, **29**, **32**

When the 7-nitro group was removed from the lead compound **2**, the PIA decreased significantly, as can be seen from the data of **8** in Table 1. As *N*-nitroso compounds are generally known to be mutagenic or carcinogenic,[11] **2** was considered to be fatal for medicinal application. However, as shown in the cases of **11** and **6a**, removal of the *N*-nitroso group uniformly resulted in the disappearance of the activities, except the CTA of **11**.

One would anticipate that a certain electron-withdrawing group could act as a mimic of the nitroso group. Compounds **10** and **12** were prepared based on this assumption. Although the *N*-acetyl derivative **10** was devoid of PIA, we thought the PIA of the *N*-formyl derivative **12** deserved further investigation along this line. As can be seen from the data of **7**, **22a** and **22b** in Table 2, replacement of one nitrogen atom of the piperazine ring can be done without significant loss of PIA only by an oxygen atom, which is more electronegative than carbon and sulfur atoms. This suggested again that the introduction of an electron-withdrawing functionality to this portion could be promising.

While the sulfur-oxidized analogues (**22h**, **i**) of **22a** gave rather discouraging results, the carbonyl-introduced analog **22c** showed PIA activity comparable to that of **2**. An additional appeal of **22c** is in its improved selectivity: the effects of this compound to CTA and CRA are much weaker than those of **2**.

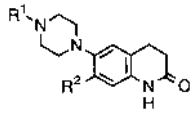
Compounds having an electron-withdrawing functionality at the 4-position of the piperidine ring were also prepared. Among these compounds **22d**—**g**, **j**, **k**, the 4-ethoxycarbonyl derivative **22f** was found to have PIA as high as **2** with a much weaker CTA. It should be mentioned that the PIA of **22f** is higher than that of cilostazol,[12] which has been applied clinically to treat thrombosis.



Reagent and conditions: (a) mCPBA (1 eq), CH_2Cl_2; (b) mCPBA (2 eq), CH_2Cl_2.

Chart 4. Synthesis of Sulfoxide and Sulfone Derivatives **22h**—**k**

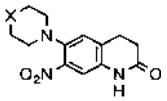
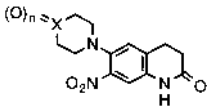
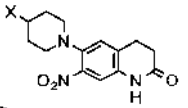
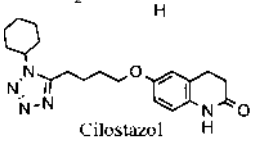
Table 1. Biological Data for 6-Piperazinyl-3,4-dihydroquinolin-2(1*H*)-one Derivatives



Compd.	R^1	R^2	CTA[a] (EC_{30}, μM)	CRA[b] (EC_{10}, μM)	PIA (IC_{50}, μM)
2	NO	NO_2	<1[c]	1.3	3.5
8	NO	H	2.2	32	65
11	H	NO_2	1.6	>100	>100
6a	H	H	>100	>100	>100
10	CH_3CO	NO_2	3.2	>100	>100
12	CHO	NO_2	3.3	6.1	31

a) EC_{30} values were the dose that produced a 30% increase in the epinephrine response. *b*) EC_{10} values were the dose that produced a 10% increase in the basal response. *c*) EC_{30} value was not calculated. Observed CTA 1 μM was a 42% increase of the epinephrine response.

Table 2. Biological Data for 6-Cyclic Aliphatic Amino-7-nitro-3,4-dihydroquinolin-2(1*H*)-one Derivatives

	Compd.	X	*n*	CTA[a] (EC_{30}, μM)	CRA[b] (EC_{10}, μM)	PIA[c] (IC_{50}, μM)
	**7**	O		11	7.3	65
	22a	S		NT	NT	140
	22b	CH_2		NT	NT	>100[c]
	**22c**	C	1	4.4	12	3.6
	22h	S	1	10	29	420
	22i	S	2	NT	NT	200
	**22d**	CHO		18	27	25
	22e	CH_3CO		NT	NT	>100[d]
	22j	CH_3SO		NT	NT	240
	22k	CH_3SO_2		NT	NT	180
	22f	COOEt		>100	10	3.4
	22g	CN		25	>100	32
 Cilostazol				4.4	>100	40

a) EC_{30} values were the dose that produced a 30% increase in the epinephrine response. *b*) EC_{10} values were the dose that produced a 10% increase in the basal response. *c*) IC_{50} values not calculated. Observed PIA inhibition activity was 20% at 100 μM. *d*) IC_{50} values not calculated. Observed PIA was 23% at 100 μM. NT means not tested.

Conclusion

The 7-nitro-3,4-dihydroquinolin-2(1*H*)-one derivatives, possessing various 6-membered heterocyclic rings at the 6-position, were synthesized and evaluated for PIA, CTA and CRA. Functional groups of the 4-position at the piperidine ring in 7-nitro-6-piperidino-3,4-dihydroquinolin-2(1*H*)-one have significant influence on both the potency of antiplatelet activity and the selectivity in antiplatelet, cardiotonic and chronotropic activities. Introduction of an ethoxycarbonyl group at the 4-position of the piperidine ring significantly enhanced the potency and selectivity of platelet aggregation inhibition. Further studies are in progress regarding the mechanism of action of this class of compounds based on their inhibitory activity against phosphodiesterase.

Experimental

Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured at 27 °C (internal standard, Me_4Si) with a Brucker DRX-500 (500 MHz) spectrometer, Brucker AMX-400 (400 MHz) spectrometer or a JEOL GX-270 (270 MHz) spectrometer. Mass spectra (MS) were taken on a JEOL JMS-SX102A (in FAB mode, glycerin, thioglycerin or *m*-nitrobenzyl alchol as a matrix) spectrometer. IR spectra were recorded with a Nicolet 510 FT-IR spectrometer. Column chromatography was carried out on silica gel (Silica gel 60, Merck). Thin layer chromatography (TLC) was performed on silica gel (precoated silica gel plate F_{254}, layer thickness, 0.25 mm, Merck). Preparative TLC was performed on silica gel (precoated silica gel plate F_{254}, layer thickness, 0.5 mm, Merck) or aminopropylated silica gel (precoated silica gel plate F_{254}, layer thickness, 0.25 mm, NH TLC plate, Fuji Silysia Chemical). All organic extracts were dried over anhydrous $MgSO_4$, then filtered. The solvent was removed with a rotary evaporator under reduced pressure.

5-Chloro-2-nitrobenzaldehyde Dimethyl Acetal (4) A solution of 2-nitro-5-chlorobenzaldehyde **3** (3 g, 16.2 mmol) and *p*-toluenesulfonic acid monohydrate (84 mg, 0.488 mmol) in MeOH (30 ml) was heated under reflux for 14 h. The reaction mixture was evaporated *in vacuo*, and the residue was partitioned between Et_2O and saturated aqueous $NaHCO_3$. The organic layer was dried and evaporated to give **4** (3.74 g, 100%) as a light yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 3.42 (s, 6H), 5.92 (s, 1H), 7.55 (dd, J=8.6, 2.2 Hz, 1H), 7.79 (d, J=2.2 Hz, 1H), 7.81 (d, J=8.6 Hz, 1H). IR (neat) cm^{-1}: 1533, 1363, 1196, 1111, 1070, 1060. FAB-MS *m/z*: 200 $(M-OCH_3)^+$. High-resolution (HR)-FAB-MS *m/z*: 230.0236 $(M-H)^+$. Calcd for $C_9H_9ClNO_4$: 230.0220. *Rf* 0.43 (hexane/AcOEt=10/1).

2-Nitro-5-(1-piperazinyl)benzaldehyde Hydrochloride (5a) A solution of **4** (5 g, 21.6 mmol) and anhydrous piperazine (9.3 g, 108 mmol) in *N*,*N*-dimethylformamide (DMF) (30 ml) was stirred at 80 °C for 4 h. The reaction mixture was evaporated *in vacuo*, and the concentrate was partitioned between CH_2Cl_2 and 1 M NaOH. The organic layer was washed with brine and concentrated to give a yellow oil. The residue was dissolved in a mixture of 2-propanol (35 ml) and concentrated HCl (2.6 ml), and the mixture was heated under reflux for 1 h with stirring. The reaction mixture was cooled at 0 °C, and the precipitate was collected by filtration, washed with Et_2O and dried *in vacuo* over P_2O_5 to give **5a** (4.3 g, 73%) as a yellow solid. Recrystallization was achieved from hexane–CH_2Cl_2–MeOH. mp 206—208 °C. ^{1}H-NMR (dimethyl sulfoxide (DMSO)-d_6) δ: 3.18—3.28 (m, 4H), 3.70—3.76 (m, 4H), 7.15 (d, J=2.8 Hz, 1H), 7.27 (dd, J=9.3, 2.8 Hz, 1H), 8.11 (d, J=9.3 Hz, 1H), 9.10—9.35 (br, 2H), 10.33 (s, 1H). IR (KBr) cm^{-1}: 2679—2494, 1693, 1583, 1500, 1325, 1269. FAB-MS *m/z*: 236 $(M+H)^+$. *Rf* 0.30 (CH_2Cl_2/MeOH=5/1). *Anal.* Calcd for $C_{11}H_{13}N_3O_3 \cdot HCl \cdot H_2O$: C, 45.60; H, 5.57; N, 14.50. Found: C, 45.65; H, 5.38; N, 14.80.

6-(1-Piperazinyl)-3,4-dihydroquinolin-2(1*H*)-one (6a) A solution of **5a** (54.0 g, 199 mmol) and acetic anhydride (19.7 ml, 209 mmol) in pyridine (500 ml) was stirred at room temperature for 3.5 h. After the addition of malonic acid (114 g, 1.09 mmol) and piperidine (6.9 ml, 70 mmol), the mixture was heated under reflux for 4 h with stirring. The reaction mixture was evaporated *in vacuo* and the residue was acidified with concentrated HCl. The precipitate was collected by filtration, washed successively with H_2O, EtOH and Et_2O and dried *in vacuo* to leave a yellow solid. The residue was hydrogenated (1 atm) in the presence of 10% Pd–C (6.5 g) in acetic acid (500 ml) at room temperature overnight. The catalyst was removed by filtration, and concentrated HCl (210 ml) was added to the filtrate. The mixture was heated under reflux for 3 h with stirring. After evaporation of the solvent, the precipitate was dissolved in H_2O and washed with $CHCl_3$. The aqueous solution was basified with 2 M NaOH and extracted with $CHCl_3$. The organic extract was dried and evaporated to give **6a** (33.8 g, 73%) as a white solid. Recrystallization was achieved from hexane–CH_2Cl_2–MeOH. mp 71—73 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.57—2.65 (m, 2H), 2.89—2.97 (m, 2H), 3.00—3.11 (m, 8H), 6.67 (d, J=8.9 Hz, 1H), 6.73—6.79 (m, 2H), 7.79 (br s, 1H). IR (KBr) cm^{-1}: 3255, 1670, 1508, 1375. FAB-MS *m/z*: 232 $(M+H)^+$. *Rf* 0.36 (CH_2Cl_2/MeOH/NH_4OH=50/10/1). *Anal.* Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.21; H, 7.45; N, 17.88.

7-Nitro-6-[1-(4-nitrosopiperazinyl)]-3,4-dihydroquinolin-2(1*H*)-one (2) To a solution of **6a** (50 mg, 0.216 mmol) in 1 M HCl (0.65 ml), $NaNO_2$ (60 mg, 0.869 mmol) was added at 0 °C, and the mixture was stirred for 4 h at room temperature. The precipitate was collected by filtration and dried *in vacuo* over P_2O_5 to give **2** (55 mg, 83%) as a yellow solid. Recrystallization was achieved from CH_2Cl_2–Et_2O. mp 238—239 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.64—2.70 (m, 2H), 2.97—3.05 (m, 4H), 3.24 (t, J=5.0 Hz, 2H), 3.98—4.03 (m, 2H), 4.43 (t, J=5.0 Hz, 2H), 7.10 (s, 1H), 7.30 (s, 1H), 8.14 (br, 1H). IR (KBr) cm^{-1}: 1689, 1523, 1375, 1348. FAB-MS *m/z*: 306 $(M+H)^+$.

Rf 0.47 (CH_2Cl_2/MeOH=10/1). *Anal.* Calcd for $C_{13}H_{15}N_5O_4 \cdot 0.2H_2O$: C, 50.55; H, 5.02; N, 22.67. Found: C, 50.79; H, 5.03; N, 22.37.

6-[1-(4-Nitrosopiperazinyl)]-3,4-dihydroquinolin-2(1*H*)-one (8) A mixture of **6a** (21 mg, 0.091 mmol) and isoamyl nitrite (0.12 ml, 0.91 mmol) in MeOH (0.12 ml) was stirred for 2 d at room temperature. After evaporation of the solvent, AcOEt was added to the concentrate. The resulting suspension was filtered, and the filtrate was concentrated *in vacou* and purified by preparative TLC (aminopropylated silica gel, CH_2Cl_2/MeOH=20/1) to give **8** (14 mg, 59%) as a white solid. Recrystallization was achieved from hexane–CH_2Cl_2. mp 207—208 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.59—2.65 (m, 2H), 2.92—2.97 (m, 2H), 3.07—3.11 (m, 2H), 3.33 (t, *J*=5.2 Hz, 2H), 3.98 (t, *J*=5.4 Hz, 2H), 4.42 (t, *J*=5.2 Hz, 2H), 6.69 (d, *J*=8.3 Hz), 6.76—6.80 (m, 2H), 7.73 (br s, 1H). IR (KBr) cm^{-1}: 1674, 1508, 1425, 1383, 1238. FAB-MS *m/z*: 260 M^+. *Rf* 0.27 (CH_2Cl_2/MeOH=20/1). *Anal.* Calcd for $C_{13}H_{16}N_4O_2$: C, 59.99; H, 6.20; N, 21.52. Found: C, 59.96; H, 6.23; N, 21.36.

6-[1-(4-Acetylpiperazinyl)]-3,4-dihydroquinolin-2(1*H*)-one (9) A solution of **6a** (6.0 g, 25.9 mmol) and acetic anhydride (2.58 ml, 27.3 mmol) in pyridine (30 ml) was stirred at room temperature overnight. After evaporation of the solvent, the residue was partitioned between $CHCl_3$ and saturated aqueous $NaHCO_3$. The organic layer was washed with saturated aqueous NH_4Cl, dried, evaporated and crystallized from AcOEt to give **9** (6.70 g, 95%) as a white solid. Recrystallization was achieved from hexane–CH_2Cl_2. mp 208—210 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.03 (s, 3H), 2.35—2.43 (m, 2H), 2.76—2.85 (m, 2H), 2.94—3.00 (m, 2H), 3.00—3.06 (m, 2H), 3.51—3.60 (m, 4H), 6.72 (d, *J*=11 Hz, 1H), 6.77 (d, *J*=11 Hz, 1H), 6.81 (s, 1H), 9.86 (s, 1H). IR (KBr) cm^{-1}: 1672, 1651, 1508, 1421, 1392, 1234. FAB-MS *m/z*: 273 M^+. *Rf* 0.48 (CH_2Cl_2/MeOH=10/1). *Anal.* Calcd for $C_{15}H_{19}N_3O_2 \cdot 0.1H_2O$: C, 65.48; H, 7.03; N, 15.27. Found: C, 65.45; H, 6.94; N, 15.31.

6-[1-(4-Acetylpiperazinyl)]-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (10) To a solution of **9** (2.02 g, 7.39 mmol) in TFA (20 ml), $NaNO_3$ (0.69 g, 8.12 mmol) was added at 0 °C, and the mixture was stirred at room temperature overnight. The reaction mixture was basified with 40% aqueous KOH and extracted with $CHCl_3$. The organic layer was washed with brine, dried and evaporated to give **10** (1.44 g, 61%) as a pale orange solid. Recrystallization was achieved from hexane–CH_2Cl_2. mp 228—230 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.03 (s, 3H), 2.45—2.53 (m, 2H), 2.87—2.91 (m, 2H), 2.91—2.98 (m, 4H), 3.51—3.57 (m, 4H), 7.29 (s, 1H), 7.34 (s, 1H), 10.25 (s, 1H). IR (KBr) cm^{-1}: 1690, 1649, 1517, 1500, 1425, 1342. FAB-MS *m/z*: 319 $(M+H)^+$. *Rf* 0.48 (CH_2Cl_2/MeOH=10/1). *Anal*. Calcd for $C_{15}H_{18}N_4O_4 \cdot 0.3H_2O$: C, 55.65; H, 5.79; N, 17.31. Found: C, 55.54; H, 5.61; N, 17.25.

7-Nitro-6-(1-piperazinyl)-3,4-dihydroquinolin-2(1*H*)-one (11) A solution of **10** (2.70 g, 8.48 mmol) in concentrated HCl (25 ml) was stirred at 90 °C for 3 h. The reaction mixture was basified with 40% aqueous KOH at 0 °C, and extracted with $CHCl_3$. The organic layer was dried and evaporated to give **11** (1.67 g, 73%) as an orange solid. Recrystallization was achieved from CH_3CN–MeOH. mp 280—281 °C (dec.). ^{1}H-NMR (DMSO-d_6) δ: 2.44—2.53 (m, 2H), 2.75—2.88 (m, 6H), 2.91—2.98 (m, 4H), 7.21 (s, 1H), 7.29 (s, 1H), 8.32 (s, 1H), 10.19 (s, 1H). IR (KBr) cm^{-1}: 3360, 1724, 1647, 1529, 1321, 1284. FAB-MS *m/z*: 277 $(M+H)^+$. HR-FAB-MS *m/z* 277.1307 $(M+H)^+$. Calcd for $C_{13}H_{17}N_4O_3$: 277.1301. *Rf*: 0.16 (CH_2Cl_2/MeOH=5/1).

6-[1-(4-Formylpiperazinyl)]-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (12) To a stirred solution of 1,3-dicyclohexylcarbodiimide (DCC) (66 mg, 0.32 mmol) in $CHCl_3$ (0.5 ml), formic acid (0.024 ml, 0.64 mmol) in $CHCl_3$ (0.3 ml) was added at 0 °C. After the mixture was stirred for 5 min, a solution of **11** (43 mg, 0.16 mmol) in pyridine (0.5 ml) was added to the mixture, and the stirring was continued for another 1 h. The reaction mixture was evaporated, and AcOEt was added to the concentrate. After filtration of the resulting suspension, silica gel column chromatography ($CHCl_3$/MeOH=50/1) of the filtrate gave **12** (22 mg, 45%) as an orange solid. Recrystallization was achieved from hexane–AcOEt–CH_2Cl_2. mp 200—202 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.40—2.53 (m, 2H), 2.80—3.00 (m, 6H), 3.44—3.54 (m, 4H), 7.30 (s, 1H), 7.34 (s, 1H), 8.06 (s, 1H), 10.25 (s, 1H). IR (KBr) cm^{-1}: 1685, 1653, 1516, 1317, 1284, 1228. FAB-MS *m/z*: 305 $(M+H)^+$. *Rf*: 0.58 (CH_2Cl_2/MeOH=10/1). *Anal.* Calcd for $C_{14}H_{16}N_4O_4 \cdot 0.3H_2O$: C, 54.29; H, 5.40; N, 18.09. Found: C, 54.59; H, 5.28; N, 17.80.

5-Morpholino-2-nitrobenzaldehyde (5b) A mixture of **4** (1.0 g, 4.3 mmol), morpholine (0.38 ml, 4.3 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) (0.64 ml, 4.3 mmol) was stirred at 100 °C for 4 h. The reaction mixture was partitioned between AcOEt and H_2O. Silica gel column chromatography ($CHCl_3$) of the organic layer gave 5-morpholino-2-nitrobenzaldehyde dimethyl acetal (1.06 g, 87%, *Rf*: 0.21, hexane/AcOEt=3/1) as a yellow oil. A solution of the dimethyl acetal (1.0 g, 3.54 mmol) in a mixture of acetone (40 ml) and 2 M HCl (10 ml) was stirred at 60 °C for 1 h. After evaporation of the reaction mixture, the concentrate was partitioned between AcOEt and 2 M NaOH. The organic layer was dried and evaporated to give **5b** (740 mg, 88%) as yellow needles. Recrystallization was achieved from hexane–AcOEt. mp 149—150 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.41—3.47 (m, 4H), 3.84—3.90 (m, 4H), 6.97 (dd, *J*=9.3, 3.0 Hz, 1H), 7.17 (d, *J*=3.0 Hz, 1H), 8.14 (d, *J*=9.3 Hz, 1H), 10.53 (s, 1H). IR (KBr) cm^{-1}: 1682, 1593, 1574, 1493, 1317, 1234, 1120, 1036. FAB-MS *m/z*: 237 $(M+H)^+$. *Rf*: 0.58 (hexane/AcOEt=1/2). *Anal.* Calcd for $C_{11}H_{12}N_2O_4$: C, 55.93; H, 5.12; N, 11.86. Found: C, 56.02; H, 5.08; N, 12.06.

6-Morpholino-3,4-dihydroquinolin-2(1*H*)-one (6b) To a refluxing solution of **5b** (330 mg, 1.40 mmol) and piperidine (0.17 ml, 1.72 mmol) in pyridine (9 ml), malonic acid (204 mg, 1.96 mmol) was added, and the mixture was heated under reflux for 1 h. After evaporation of the solvent, the concentrate was acidified with 1 M HCl. The precipitate was collected by filtration, washed successively with H_2O and with AcOEt and dried *in vacuo* to give a yellow solid. The solid was hydrogenated in the presence of 10% Pd–C (30 mg) in AcOH (3 ml) and MeOH (30 ml) for 8 h at room temperature. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo.* Silica gel column chromatography (CH_2Cl_2/MeOH=50/1) of the filtrate gave **6b** (144 mg, 44%) as a white solid. Recrystallization was achieved from hexane–CH_2Cl_2. mp 179—180 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.35—2.42 (m, 2H), 2.77—2.84 (m, 2H), 2.96—3.02 (m, 4H), 3.68—3.74 (m, 4H), 6.73 (s, 2H), 3.79 (s, 1H), 9.85 (s, 1H). IR (KBr) cm^{-1}: 1662, 1514, 1387, 1238, 1119. FAB-MS *m/z*: 232 $(M)^+$. *Rf*: 0.29 (CH_2Cl_2/MeOH=20/1). *Anal.* Calcd for $C_{13}H_{16}N_2O_2 \cdot 0.1H_2O$: C, 66.70; H, 6.98; N, 11.97. Found: C, 66.73; H, 6.95; N, 11.93.

6-Morpholino-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (7) To a solution of **6b** (76 mg, 0.327 mmol) in a mixture of AcOH (4 ml) and TFA (1 ml), $NaNO_2$ (31 mg, 0.449 mmol) was added, and the mixture was stirred for 0.5 h at room temperature. After evaporation of the solvent, silica gel column chromatography (AcOEt) of the concentrate gave **7** (39 mg, 43%) as an orange solid. Recrystallization was achieved from hexane–AcOEt. mp 61—62 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.63—2.70 (m, 2H), 2.98—3.06 (m, 6H), 3.81—3.87 (m, 4H), 7.02 (s, 1H), 7.26 (s, 1H), 7.80 (s, 1H). IR (KBr) cm^{-1}: 1697, 1522, 1329, 1113. FAB-MS *m/z*: 278 $(M+H)^+$. *Rf*: 0.46 (AcOEt). *Anal.* Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.15. Found: C, 56.29; H, 5.50; N, 15.07.

5-Methoxy-2-nitrobenzaldehyde (14) To a stirred suspension of 5-hydroxy-2-nitrobenzaldehyde **13** (3 g, 18.0 mmol) and Cs_2CO_3 (5.86 g, 18.0 mmol) in DMF (20 ml), MeI (1.12 ml, 18.0 mmol) was added dropwise at 0 °C. The stirring was continued for 3 d at room temperature. The reaction mixture was partitioned between AcOEt and H_2O. Silica gel column chromatography (hexane/AcOEt=3/1) of the organic layer gave **14** (3.07 g, 94%) as colorless needles. Recrystallization was achieved from hexane–AcOEt. mp 80—81 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.91 (s, 3H), 7.16 (dd, *J*=9.1, 2.9 Hz, 1H), 7.34 (d, *J*=2.9 Hz, 1H), 8.17 (d, *J*=9.1 Hz, 1H), 10.49 (s, 1H). IR (KBr) cm^{-1}: 2850, 1691, 1583, 1504, 1329. FAB-MS *m/z*: 182 $(M+H)^+$. *Rf*: 0.41 (hexane/AcOEt=3/1). *Anal.* Calcd for $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 53.05; H, 3.90; N, 7.80.

5-Methoxy-2-nitrocinnamic Acid (15) A stirred solution of **14** (10 g, 55.2 mmol), malonic acid (28.7 g, 276 mmol) and piperidine (1.36 ml, 13.8 mmol) in pyridine (100 ml) was heated under reflux for 4 h. After evaporation of the solvent, the residue was acidified with 1 M HCl. The precipitate was collected by filtration, washed successively with 2-propanol and then with Et_2O and dried *in vacuo* over P_2O_5 to give **15** (8.8 g, 71%) as a white solid. Recrystallization was achieved from hexane–MeOH. mp 183—184 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.94 (s, 3H), 6.55 (d, *J*=15.7 Hz, 1H), 7.17 (dd, *J*=9.1, 2.7 Hz, 1H), 7.32 (d, *J*=2.7 Hz, 1H), 7.96 (d, *J*=15.7 Hz, 1H), 8.12 (d, *J*=9.1 Hz, 1H), 12.71 (s, 1H). IR (KBr) cm^{-1}: 3000—2500, 2833, 1695, 1577, 1506, 1344. FAB-MS *m/z*: 224 $(M+H)^+$. *Rf*: 0.18 (CH_2Cl_2/MeOH/NH_4OH=50/10/1). *Anal.* Calcd for $C_{10}H_9NO_5$: C, 53.82; H, 4.06; N, 6.28. Found: C, 53.70; H, 4.04; N, 6.39.

6-Methoxy-3,4-dihydroquinolin-2(1*H*)-one (16) A solution of **15** (2.58 g, 11.6 mmol) in AcOH (25 ml) was hydrogenated in the presence of 10% Pd–C (260 mg) for 14 h at room temperature. After the mixture was heated at 70 °C for 1 h, the catalyst was removed by filtration and the filtrate was evaporated. The residue was partitioned between AcOEt and 1 M NaOH. The organic layer was evaporated to give **16** (1.82 g, 88%) as colorless needles. Recrystallization was achieved from hexane–AcOEt. mp 144—146 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.59—2.64 (m, 2H), 2.92—2.97 (m, 2H), 3.82 (s, 3H), 6.67 (d, *J*=8.3 Hz, 1H), 6.70—6.75 (m, 2H), 7.69 (br, 1H). IR (KBr) cm^{-1}: 1662, 1500, 1387, 1242, 1039. FAB-MS *m/z*: 178 $(M+H)^+$. *Rf*: 0.54 (AcOEt). *Anal.* Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C,

67.65; H, 6.23; N, 7.96.

6-Methoxy-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (17) To a stirred solution of **16** (1.0 g, 5.64 mmol) in TFA (20 ml), $NaNO_2$ (0.389 g, 5.64 mmol) was added portionwise at 0 °C, and the stirring was continued for 0.5 h at room temperature. The reaction mixture was poured into ice water. The precipitate was collected by filtration, washed with Et_2O and dried *in vacuo* over P_2O_5 to give **17** (1.11 g, 88%) as a light yellow solid. Recrystallization was achieved from Et_2O–AcOEt–MeOH. mp 238—241 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.44—2.51 (m, 2H), 2.94—3.01 (m, 2H), 3.88 (s, 3H), 7.28 (s, 1H), 7.38 (s, 1H), 10.17 (s, 1H). IR (KBr) cm^{-1}: 1676, 1522, 1346, 1263. FAB-MS *m/z*: 223 $(M+H)^+$. *Rf*: 0.46 (CH_2Cl_2/MeOH=10/1). *Anal.* Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.84; H, 4.54; N, 12.50.

6-Hydroxy-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (18) To a solution of **17** (1.1 g, 4.95 mmol) in 1,2-dichloroethane (20 ml), Aluminum chloride ($AlCl_3$) (0.79 g, 5.92 mmol) was added portionwise, and the mixture was refluxed for 0.5 h. To this mixture, additional $AlCl_3$ (0.79 g, 5.92 mmol) was added portionwise. After further stirring for 1 h at the same temperature, the reaction mixture was evaporated *in vacuo.* The concentrate was quenched by adding H_2O. The precipitate was collected by filtration, washed with Et_2O and dried *in vacuo* over P_2O_5 to give **18** (1.0 g, 97%) as a yellow solid. Recrystallization was achieved from CH_2Cl_2–Et_2O–MeOH. mp 235—238 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.40—2.48 (m, 2H), 2.88—2.95 (m, 2H), 6.99 (s, 1H), 7.41 (s, 1H), 10.15 (s, 1H), 10.55 (s, 1H). IR (KBr) cm^{-1}: 1668, 1537, 1387, 1257. FAB-MS *m/z*: 209 $(M+H)^+$. *Rf*: 0.25 (CH_2Cl_2/MeOH=50/1). *Anal.* Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.71; H, 3.92; N, 13.23.

7-Nitro-6-trifluoromethanesulfonyloxy-3,4-dihydroquinolin-2(1*H*)-one (19) To a solution of **18** (0.40 g, 1.92 mmol) in DMF (4 ml), Et_3N (0.29 ml, 2.09 mmol) was added at 0 °C. After the mixture was stirred at 0 °C for 5 min, CF_3SO_2Cl (0.22 ml, 2.09 mmol) was added, and stirring was continued for 18 h at room temperature. The reaction mixture was partitioned between AcOEt and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried and evaporated. Silica gel column chromatography (hexane/AcOEt=2/1) of the concentrate gave **19** (0.52 g, 79%) as a colorless powder. Recrystallization was achieved from hexane–AcOEt. mp 187—188 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.51—2.58 (m, 2H), 3.04—3.11 (m, 2H), 7.67 (s, 1H), 7.71 (s, 1H), 10.60 (s, 1H). IR (KBr) cm^{-1}: 1685, 1535, 1423, 1346, 1207. FAB-MS *m/z*: 341 $(M+H)^+$. *Rf*: 0.18 (hexane/AcOEt=3/1). *Anal.* Calcd for $C_{10}H_7F_3N_2O_6S$: C, 35.30; H, 2.07; N, 8.23. Found: C, 35.25; H, 2.14; N, 8.29.

7-Nitro-6-thiomorpholino-3,4-dihydroquinolin-2(1*H*)-one (22a) A solution of **19** (357 mg, 1.05 mmol) and thiomorpholine (0.53 ml, 5.25 mmol) in CH_3CN (10 ml) was stirred at 80 °C for 4 h. The reaction mixture was concentrated *in vacuo.* Preparative TLC (silica gel, hexane/AcOEt=2/1) of the residue gave **22a** (156 mg, 51%) as an orange solid. Recrystallization was achieved from hexane–AcOEt. mp 203—204 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.64—2.72 (m, 2H), 2.76—2.82 (m, 4H), 2.98—3.06 (m, 2H), 3.22—3.28 (m, 4H), 7.02 (s, 1H), 7.28 (s, 1H), 9.00 (br s, 1H). IR (KBr) cm^{-1}: 1716, 1522, 1377, 1333, 1281. FAB-MS *m/z*: 294 $(M+H)^+$. *Rf*: 0.25 (hexane/AcOEt=1/2). *Anal.* Calcd for $C_{13}H_{15}N_3O_3S \cdot 0.2H_2O$: C, 52.58; H, 5.23; N, 14.15. Found: C, 52.76; H, 5.05; N, 14.02.

6-(4-Methylthiopiperidino)-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (23) A solution of **32** (300 mg, 1.30 mmol) in TFA (5 ml) was stirred at 0 °C for 0.5 h. The mixture was allowed to stand to come to room temperature, then stirred for 1 h. The reaction mixture was made basic with 2 M NaOH at 0 °C, extracted with a mixture of CH_2Cl_2 and MeOH (5 : 1), dried and evaporated *in vacuo* to give a yellow oil (163 mg). A solution of the oil and **19** (70 mg, 0.308 mmol) in CH_3CN (2 ml) was stirred at 90 °C for 2 h. The reaction mixture was concentrated *in vacuo.* Preparative TLC (silica gel, hexane/AcOEt=1/1) of the residue gave **23** (29 mg, 29%) as orange plates. Recrystallization was achieved from hexane–AcOEt. mp 170—172 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.75—1.87 (m, 2H), 2.02—2.09 (m, 2H), 2.13 (s, 3H), 2.62—2.77 (m, 3H), 2.80—2.89 (m, 2H), 2.96—3.03 (m, 2H), 3.20—3.28 (m, 2H), 6.99 (s, 1H), 7.28 (s, 1H), 8.45 (br s, 1H). IR (KBr) cm^{-1}: 1678, 1522, 1379, 1333, 1284. FAB-MS *m/z*: 322 $(M+H)^+$. *Rf*: 0.08 (hexane/AcOEt=1/1). *Anal.* Calcd for $C_{15}H_{19}N_3O_3S$: C, 56.06; H, 5.96; N, 13.07. Found: C, 55.92; H, 5.93; N, 13.21.

7-Nitro-6-piperidino-3,4-dihydroquinolin-2(1*H*)-one (22b) The title compound was obtained as orange plates (27%), starting from piperidine and following the method as described for **22a**. Recrystallization was achieved from AcOEt. mp 202—203 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.54—1.62 (m, 2H), 1.68—1.76 (m, 4H), 2.61—2.66 (m, 2H), 2.93—3.02 (m, 6H), 6.98 (s, 1H), 7.23 (s, 1H), 7.44 (br, 1H). IR (KBr) cm^{-1}: 1684, 1522, 1379, 1343, 1234. FAB-MS *m/z*: 276 $(M+H)^+$. *Rf*: 0.21 (hexane/AcOEt=1/1). *Anal.* Calcd for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 60.93; H, 6.14; N, 15.15.

7-Nitro-6-(4-oxopiperidino)-3,4-dihydroquinolin-2(1*H*)-one (22c) The title compound was obtained as an orange solid (4%), starting from 4-piperidone monohydrate hydrochloride and following the method as described for **22a**. Recrystallization was achieved from hexane–AcOEt. mp 251—252 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.61—2.69 (m, 6H), 2.98—3.07 (m, 2H), 3.30—3.37 (m, 4H), 7.06 (s, 1H), 7.31 (s, 1H), 8.66 (br, 1H). IR (KBr) cm^{-1}: 1718, 1684, 1533, 1377, 1334, 1281. FAB-MS *m/z*: 290 $(M+H)^+$. *Rf*: 0.31 (AcOEt). *Anal.* Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found: C, 57.97; H, 5.26; N, 14.29.

6-(4-Formylpiperidino)-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (22d) The title compound was obtained as an orange solid (4%), starting from **26** and following the method as described for **23**. Recrystallization was achieved from hexane–AcOEt. mp 211—212 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.83—1.95 (m, 2H), 1.98—2.07 (m, 2H), 2.36—2.46 (m, 1H), 2.63—2.69 (m, 2H), 2.83—2.92 (m, 2H), 2.96—3.03 (m, 2H), 3.17—3.22 (m, 2H), 7.00 (s, 1H), 7.27 (s, 1H), 8.24 (br, 1H), 9.71 (s, 1H). IR (KBr) cm^{-1}: 1720, 1664, 1522, 1377, 1323, 1288. FAB-MS *m/z*: 304 $(M+H)^+$. *Rf*: 0.38 (AcOEt). *Anal.* Calcd for $C_{15}H_{17}N_3O_4 \cdot 0.3H_2O$: C, 58.36; H, 5.75; N, 13.61. Found: C, 58.49; H, 5.62; N, 13.31.

6-(4-Acetylpiperidino)-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (22e) The title compound was obtained as an orange solid (12%), starting from **29** and following the method as described for **23**. Recrystallization was achieved from hexane–AcOEt. mp 182—183 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.80—1.90 (m, 2H), 1.93—2.00 (m, 2H), 2.20 (s, 3H), 2.40—2.48 (m, 1H), 2.62—2.69 (m, 2H), 2.79—2.88 (m, 2H), 2.96—3.03 (m, 2H), 3.22—3.28 (m, 2H), 6.99 (s, 1H), 7.25 (s, 1H), 7.64 (br, 1H). IR (KBr) cm^{-1}: 1701, 1676, 1508, 1381, 1317, 1273. FAB-MS *m/z*: 318 $(M+H)^+$. *Rf*: 0.33 (AcOEt). *Anal.* Calcd for $C_{16}H_{19}N_3O_4 \cdot 0.3H_2O$: C, 59.54; H, 6.12; N, 13.02. Found: C, 59.66; H, 5.82; N, 13.17.

6-(4-Ethoxycarbonylpiperidino)-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (20f) The title compound was obtained as orange plates (46%), starting from ethyl isonipecotate and following the method as described for **22a**. Recrystallization was achieved from hexane–AcOEt. mp 173—175 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (t, *J*=7.1 Hz, 3H), 1.87—2.06 (m, 4H), 2.38—2.48 (m, 1H), 2.61—2.69 (m, 2H), 2.78—2.87 (m, 2H), 2.96—3.03 (m, 2H), 3.17—3.25 (m, 2H), 4.17 (q, *J*=7.1 Hz, 2H), 6.99 (s, 1H), 7.25 (s, 1H), 7.78 (br, 1H). IR (KBr) cm^{-1}: 1736, 1678, 1516, 1375, 1323, 1282. FAB-MS *m/z*: 348 $(M+H)^+$. *Rf*: 0.47 (AcOEt). *Anal.* Calcd for $C_{17}H_{21}N_3O_5$: C, 58.78; H, 6.09; N, 12.10. Found: C, 58.76; H, 6.06; N, 12.09.

6-(4-Cyanopiperidino)-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (22g) The title compound was obtained as orange plates (20%), starting from **28** and following the method as described for **23**. Recrystallization was achieved from hexane–AcOEt. mp 241—242 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.97—2.13 (m, 4H), 2.63—2.70 (m, 2H), 2.83—2.91 (m, 1H), 2.96—3.05 (m, 4H), 3.13—3.22 (m, 2H), 7.05 (s, 1H), 7.28 (s, 1H), 8.38 (s, 1H). IR (KBr) cm^{-1}: 2237, 1678, 1522, 1373, 1336, 1282. FAB-MS *m/z*: 301 $(M+H)^+$. *Rf*: 0.18 (hexane/AcOEt=1/2). *Anal.* Calcd for $C_{15}H_{16}N_4O_3 \cdot 0.3H_2O$: C, 58.93; H, 5.47; N, 18.33. Found: C, 59.23; H, 5.31; N, 18.04.

1-*tert*-Butoxycarbonyl-4-(hydroxymethyl)piperidine (25) To a stirred solution of 4-(hydroxymethyl)piperidine **24** (2.0 g, 19.4 mmol) in a mixture of AcOEt (20 ml) and tetrahydrofuran (THF) (10 ml), di-*tert*-butyl dicarbonate (Boc_2O) (4.23 g, 19.4 mmol) was added at room temperature. The mixture was stirred for 14 h at room temperature. After evaporation of the solvent, the concentrate was partitioned between AcOEt and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried and evaporated *in vacuo* to give **25** (4.17 g, 100%) as a colorless solid. Recrystallization was achieved from hexane–Et_2O. mp 73—74 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 1.10—1.20 (m, 2H), 1.60—1.74 (m, 3H), 2.64—2.77 (m, 2H), 3.47—3.53 (m, 2H), 4.06—4.20 (m, 2H). IR (KBr) cm^{-1}: 3471, 2937, 1674. FAB-MS *m/z*: 216 $(M+H)^+$. *Rf*: 0.18 (hexane/AcOEt=1/1). *Anal.* Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.08; H, 10.09; N, 6.63.

1-*tert*-Butoxycarbonyl-4-formylpiperidine (26) To a solution of **25** (200 mg, 0.929 mmol) in CH_2Cl_2 (2 ml), Dess–Martin reagent[13] (394 mg, 0.929 mmol) was added at room temperature, and the mixture was stirred for 1 h at room temperature. After evaporation of the solvent, the residue was partitioned between AcOEt and 0.1 M NaOH. The organic layer was dried and evaporated. Silica gel column chromatography (hexane/AcOEt=1/1) of the concentrate gave **26** (79 mg, 40%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 1.50—1.60 (m, 2H), 1.86—1.93 (m, 2H), 2.37—2.47 (m, 1H), 2.88—2.97 (m, 2H), 3.94—4.05 (m, 2H), 9.66 (s, 1H). IR (neat) cm^{-1}: 2976, 1728, 1685. FAB(−)-MS *m/z*: 212 $(M-H)^-$. HR-FAB-MS *m/z*

214.1427 $(M+H)^+$. Calcd for $C_{11}H_{20}NO_3$: 214.1443. *Rf*: 0.47 (hexane/AcOEt=1/1).

1-*tert*-Butoxycarbonyl-4-cyanopiperidine (28) To a stirred solution of isonipecotamide **27** (5.0 g, 39.0 mmol) in a mixture of pyridine (24 ml) and CH_2Cl_2 (30 ml), Boc_2O (9.0 g, 41.2 mmol) in CH_2Cl_2 (30 ml) was added at room temperature. The mixture was stirred for 40 min at room temperature. After the addition of TFAA (15 ml), the stirring was continued for 2 h at room temperature. After evaporation of the solvent, the concentrate was partitioned between Et_2O and H_2O. The organic layer was washed successively with 10% aqueous citric acid and with brine, dried and evaporated *in vacuo* over P_2O_5 to give **28** (7.37 g, 83%) as colorless prisms. Recrystallization was achieved from hexane–Et_2O. mp 45—46 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 1.74—1.93 (m, 4H), 2.76—2.84 (m, 1H), 3.29—3.39 (m, 2H), 3.61—3.71 (m, 2H). IR (KBr) cm^{-1}: 2975, 2239, 1697. FAB-MS *m/z*: 211 $(M+H)^+$. *Rf*: 0.55 (hexane/AcOEt=1/1). *Anal.* Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.55; H, 8.72; N, 13.27.

1-*tert*-Butoxycarbonyl-4-acetopiperidine (29) Iodomethane (5.12 ml, 82.2 mmol) was added dropwise to a stirred suspension of Mg (2.0 g, 82.3 mmol) in Et_2O (30 ml) under Ar ambience. A solution of **28** (4.0 g, 19.0 mmol) in THF (50 ml) was added to the prepared MeMgI. After the mixture was stirred for 11 h at room temperature, the reaction mixture was quenched by adding saturated aqueous NH_4Cl, neutralized by adding dilute aqueous HCl and extracted with Et_2O. The organic layer was washed successively with 10% aqueous citric acid and brine, then dried and evaporated. Silica gel column chromatography (CH_2Cl_2/Et_2O=10/1) of the concentrate gave **29** (1.85 g, 43%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 1.47—1.57 (m, 2H), 1.80—1.87 (m, 2H), 2.16 (s, 3H), 2.40—2.50 (m, 1H), 2.73—2.83 (m, 2H), 4.05—4.16 (m, 2H). IR (neat) cm^{-1}: 2976, 1710, 1690. FAB-MS *m/z*: 228 $(M+H)^+$. HR-FAB-MS *m/z* 228.1605 $(M+H)^+$. Calcd for $C_{12}H_{22}NO_3$: 228.1600. *Rf*: 0.40 (CH_2Cl_2/Et_2O=10/1).

1-*tert*-Butoxycarbonyl-4-methanesulfonyloxypiperidine (31) To a stirred solution of 4-hydroxypiperidine **30** (1.0 g, 9.69 mmol) in a mixture of CH_2Cl_2 (10 ml) and 1.4-dioxane (10 ml), Boc_2O (2.11 g, 9.67 mmol) was added at room temperature. The mixture was stirred for 2 h at room temperature. After evaporation of the solvent, the concentrate was partitioned between AcOEt and saturated aqueous NH_4Cl. The organic layer was washed with brine, dried and evaporated to give a yellow oil. To a stirred solution of the oil in CH_2Cl_2 (10 ml), Et_3N (1.41 ml, 10.1 mmol) and methanesulfonyl chloride (0.75 ml, 9.69 mmol) were added at 0 °C, and stirring was continued for 13 h at room temperature. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous NH_4Cl. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and with brine, dried and evaporated to give **31** (2.59 g, 96%) as colorless plates. Recrystallization was achieved from hexane–Et_2O. mp 67—68 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 1.78—1.85 (m, 2H), 1.93—1.99 (m, 2H), 3.04 (s, 3H), 3.26—3.35 (m, 2H), 3.67—3.74 (m, 2H), 4.85—3.92 (m, 1H). IR (KBr) cm^{-1}: 2968, 1689, 1354, 1173. FAB-MS *m/z*: 280 $(M+H)^+$. *Rf*: 0.48 (hexane/AcOEt=1/1). *Anal.* Calcd for $C_{11}H_{21}NO_5S$: C, 47.30; H, 7.58; N, 5.01. Found: C, 47.14; H, 7.77; N, 5.27.

1-*tert*-Butoxycarbonyl-4-methylthiopiperidine (32) To a stirred solution of **31** (700 mg, 2.51 mmol) in DMF (15 ml), sodium methanethiolate (237 mg, 3.38 mmol) was added at room temperature. The stirred mixture was heated at 80 °C for 2 h. The reaction mixture was quenched by adding saturated aqueous NH_4Cl and extracted with AcOEt. The organic layer was washed with H_2O, dried and evaporated. Silica gel column chromatography (CH_2Cl_2) of the concentrate gave **32** (343 mg, 59%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (s, 9H), 1.47—1.56 (m, 2H), 1.87—1.97 (m, 2H), 2.10 (s, 3H), 2.65—2.75 (m, 1H), 2.84—2.96 (m, 2H), 3.90—4.10 (m, 2H). IR (neat) cm^{-1}: 2976, 2920, 1695. FAB-MS *m/z*: 232 $(M+H)^+$. HR-FAB-MS *m/z* 232.1372 $(M+H)^+$. Calcd for $C_{11}H_{22}NO_2S$: 232.1371. *Rf*: 0.20 (hexane/AcOEt=10/1).

7-Nitro-6-thiomorpholino-3,4-dihydroquinolin-2(1*H*)-one *S*-Oxide (22h) To a solution of **22a** (40 mg, 0.136 mmol) in CH_2Cl_2 (6 ml), mCPBA (23 mg, 0.133 mmol) was added at 0 °C, and the mixture was stirred at 0 °C for 2 h. The stirring was continued for 1 d at room temperature. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried and evaporated. Preparative TLC (silica gel, AcOEt then CH_2Cl_2/MeOH=30/1) of the residue gave **22h** (19 mg, 45%) as an orange solid. Recrystallization was achieved from hexane–AcOEt. mp 280—282 °C. ^{1}H-NMR ($CDCl_3$) **δ:** 2.64—2.71 (m, 2H), 2.90—3.07 (m, 6H), 3.09—3.16 (m, 2H), 3.77—3.85 (m, 2H), 7.18 (s, 1H), 7.35 (s, 1H), 8.98 (br, 1H). IR (KBr) cm^{-1}: 1690, 1522, 1327, 1284, 1032. FAB-MS *m/z*: 310 $(M+H)^+$. *Rf*: 0.28 (CH_2Cl_2/MeOH=20/1). *Anal.* Calcd for $C_{13}H_{15}N_3O_4S$: C, 50.48; H, 4.89; N, 13.58. Found: C, 50.60; H, 5.06; N, 13.30.

7-Nitro-6-thiomorpholino-3,4-dihydroquinolin-2(1*H*)-one *S,S*-Dioxide (22i) To a solution of **22a** (40 mg, 0.136 mmol) in CH_2Cl_2 (6 ml), mCPBA (47 mg, 0.272 mmol) was added at 0 °C, and the mixture was stirred for 1 d at room temperature. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried and evaporated. Preparative TLC (silica gel, AcOEt) of the residue gave **22i** (27 mg, 61%) as a light yellow solid. Recrystallization was achieved from hexane–AcOEt. mp 253—254 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.65—2.71 (m, 2H), 3.00—3.07 (m, 2H), 3.20—3.26 (m, 4H), 3.50—3.56 (m, 4H), 7.12 (s, 1H), 7.27 (s, 1H), 7.83 (br, 1H). IR (KBr) cm^{-1}: 1674, 1522, 1302, 1126. FAB-MS *m/z*: 326 $(M+H)^+$. *Rf*: 0.26 (AcOEt). *Anal.* Calcd for $C_{13}H_{15}N_3O_5S\cdot 0.3H_2O$: C, 47.21; H, 4.74; N, 12.70. Found: C, 47.37; H, 4.74; N, 12.95.

6-(4-Methanesulfinylpiperidino)-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (22j) To a solution of **23** (30 mg, 0.093 mmol) in CH_2Cl_2 (5 ml), mCPBA (16 mg, 0.092 mmol) was added at 0 °C, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried and evaporated. Preparative TLC (silica gel, AcOEt then CH_2Cl_2/MeOH=20/1) of the residue gave **22j** (25 mg, 79%) as an orange solid. Recrystallization was achieved from hexane–AcOEt. mp 165—166 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.00 (m, 3H), 2.20—2.28 (m, 1H), 2.59 (s, 3H), 2.61—2.74 (m, 3H), 2.83—2.96 (m, 2H), 2.97—3.05 (m, 2H), 3.31—3.42 (m, 2H), 7.03 (s, 1H), 7.25 (s, 1H), 7.50 (br s, 1H). IR (KBr) cm^{-1}: 1697, 1514, 1317, 1282, 1038. FAB-MS *m/z*: 338 $(M+H)^+$. *Rf*: 0.18 (CH_2Cl_2/MeOH=20/1). *Anal.* Calcd for $C_{15}H_{19}N_3O_4S\cdot 0.1H_2O$: C, 53.12; H, 5.71; N, 12.39. Found: C, 53.02; H, 5.73; N, 12.53.

6-(4-Methanesulfonylpiperidino)-7-nitro-3,4-dihydroquinolin-2(1*H*)-one (22k) To a solution of **23** (20 mg, 0.062 mmol) in CH_2Cl_2 (4 ml), mCPBA (23 mg, 0.133 mmol) was added at 0 °C, and the mixture was stirred for 17 h at room temperature. The reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The organic layer was washed with brine, dried and evaporated. Preparative TLC (silica gel, AcOEt) of the residue gave **22k** (17 mg, 77%) as an orange solid. Recrystallization was achieved from hexane–AcOEt. mp 332—333 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.98—2.08 (m, 2H), 2.22—2.29 (m, 2H), 2.63—2.69 (m, 2H), 2.80—2.90 (m, 5H), 2.91—3.04 (m, 3H), 3.38—3.43 (m, 2H), 7.02 (s, 1H), 7.26 (s, 1H), 7.78 (br, 1H). IR (KBr) cm^{-1}: 1699, 1520, 1296, 1132. FAB-MS *m/z*: 354 $(M+H)^+$. *Rf*: 0.13 (AcOEt). *Anal.* Calcd for $C_{15}H_{19}N_3O_5S\cdot 0.1H_2O$: C, 50.72; H, 5.45; N, 11.83. Found: C, 50.81; H, 5.55; N, 11.56.

CTA on Isolated Guinea Pig Atria Male Hartley guinea pigs (300—450 g) were sacrificed and then the left atria was isolated. CTA was measured in the isolated left atria, according to Horii *et al.*[10b] The left atria was stimulated electrically with a square-wave pulse stimulator at a frequency of 1 Hz and a voltage 20% above the threshold (duration: 5 ms). The atrium was suspended in Krebs–Henselite solution, aerated with 95% O_2 and 5% CO_2 at a temperature of 35 °C, and stretched to a resting tension of 0.5 g. The physiological solution (in mM) consisted of the following: NaCl, 118; KCl, 4.7; $CaCl_2$, 2.55; $MgSO_4$ 1.18; KH_2PO_4, 1.18; $NaHCO_3$, 24.88; glucose, 11.1. Before the construction of dose–response curves for each test compound, the cardiotonic response for epinephrine (10^{-7} M) was established.

The inotropic potency was expressed as the ratio of the response to each compound to the response to epinephrine (10^{-7} M). EC_{30} values (micro mole per liter) represent the dose that produces a 30% increase in the epinephrine response.

CRA on Isolated Guinea Pig Atria Male Hartley guinea pigs (300—450 g) were sacrificed, then the right and left atria were isolated. CRA was measured on these isolated right and left atria. The atrium was suspended in Krebs-Henselite solution in the same condition described above. The chronotropic potency was expressed as the ratio of the response to each compound to the basal response. EC_{10} values (micro mole per liter) represent the dose that produces a 10% increase in the basal response.

Platelet Aggregation in Rabbit PRP Rabbit (Japanese White) blood was obtained from the carotid artery in the presence of a 3.8% trisodium citrate aqueous solution (volume ratio 9 : 1), then centrifuged at 1000 rpm for 10 min at room temperature to give PRP. Platelet counts in PRP were determined using an automated particle counter (model F-800, Toa Medical Electronics Co., Ltd.). Platelet concentration was adjusted to 8—12×10^8 platelets/ml with time-matched platelet-poor plasma (PPP), which was obtained from the precipitate fraction of PRP by centrifugation at 3000 rpm for 10 min at room temperature. The test compound or the control solution (2 μl) was added to the PRP (0.198 ml), then the mixture was incubated at

37 °C with stirring for 1 min before the addition of ADP (20 μl, final conc. 20 μM). Changes in light transmission caused by platelet clotting were measured using an aggregometer (platelet aggregation tracer, Nicho Bioscience Co., Ltd.) until each trace reached a plateau. Platelet aggregation was expressed as the percentage change in light transmittance, with the difference of light transmittance between PRP and PPP as 100%. Antiplatelet activity was expressed as the percent inhibition of the control value.

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7) Data for 5-nitro isomer: ^{1}H-NMR (MeOH-d_4) δ: 2.12 (s, 3H), 2.54—2.62 (m, 2H), 2.80—2.96 (m, 6H), 3.56—3.65 (m, 4H), 7.01 (d, J=9 Hz, 1H), 7.30 (d, J=9 Hz, 1H).
8) Data for 7,8-dinitrated product: ^{1}H-NMR (DMSO-d_6) δ: 2.54—2.61 (m, 2H), 3.27—3.34 (m, 2H), 3.94 (s, 3H), 7.75 (s, 1H), 9.96 (br s, 1H). Regiochemistry of the 7,8-dinitrated product was confirmed based on a nuclear Overhauser effect (NOE) experiment: 18% between 6-OMe and H-5; 14% between H-5 and CH_2-4.; Data for 8-nitro isomer: ^{1}H-NMR (DMSO-d_6) δ: 2.53—2.60 (m, 2H), 2.98—3.05 (m, 2H), 3.81 (s, 3H), 7.35 (d, J=3 Hz, 1H), 7.47 (d, J=3 Hz, 1H), 9.69 (br s, 1H).
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