Prostanoids and Related Compounds. VII.[1] Synthesis and Inhibitory Activity of 1-Isoindolinone Derivatives Possessing Inhibitory Activity against Thromboxane A_2 Analog (U-46619)-Induced Vasoconstriction

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We have synthesized a series of novel 1-isoindolinone derivatives, which inhibited the contraction of pig coronary artery induced by U-46619, a thromboxane A_2 analog.

Key words 1-isoindolinone derivative; vasorelaxant; thromboxane A_2 analog (U-46619)

Thromboxane A_2 (TXA_2) was discovered by Hamberg *et al*.[2] as a highly unstable and biologically active compound produced from prostaglandin (PG) endoperoxide, which is a potent stimulator of platelet aggregation and mediates vascular and pulmonary smooth muscle contraction.[3] TXA_2 plays an important role in the maintenance of vascular homeostasis together with prostacyclin (PGI_2), which has the opposite pharmacological properties.

However, oversynthesis of TXA_2 has been implicated in circulatory disorders and asthmatic conditions. Therefore, TXA_2 receptor antagonists should be clinically useful as therapeutic agents for thrombosis, asthma, ischemia, and myocardial infarction.[4—7]

Recently, we found that some 1-isoindolinone derivatives[8] inhibit TXA_2 analog (U-46619)[9]-induced vasoconstriction. Sekiya and Terao[10] have also reported the synthesis of a 3-benzylidene-1-isoindolinone [Chart 1, compound A (R=H)], which inhibited U-46619-induced vasoconstriction in a screening test.[11] Thus, in order to obtain 3-benzylidene-1-isoindolinone derivatives posessing higher activities, we earlier prepared 3-[(*o*, *m* or *p*)-hydroxy or methoxybenzylidene]-1-isoindolinones (A) and 3-[2-(*o*, *m* or *p*)-hydroxy or methoxyphenylethylidene]-1-isoindolinones (B),[1] as shown in Chart 1. Amongst these compounds, 3-(2-phenylethylidene)-1-isoindolinone derivatives possess higher activities than the 3-benzylidene-1-isoindolinone analogs. Furthermore, 3-[2-(*o* or *m*)-methoxyphenylethylidene]-1-isoindolinone showed the most potent activity. Therefore, in order to synthesize thromboxane receptor antagonists having more potent activities, we have now synthesized compounds (C), in which a hydroxy group or alkyl group is introduced to the isoindolinone skeleton of 3-(2-phenylethylidene)-1-isoindolinone.

Additionally, Hamanaka *et. al*. reported that compound D shows strong TXA_2 receptor antagonist activity.[12] Thus, we have synthesized *N*-substituted 3-(2-phenylethylidene)-1-isoindolinone derivatives (compound E) as potentially potent analogs.

In this paper, we have synthesized a variety of 5- or 6-hydroxy-3-(2-phenylethylidene)-1-isoindolinone and *N*-substituted-3-(2-phenylethylidene)-1-isoindolinone derivatives from 4-hydroxyphthalic acid or potassium phthalimide in several steps and their inhibitory activities tested. First, we describe the synthesis of 5- or 6-hydroxy-3-(2-phenylethylidene)-1-isoindolinone derivatives (**6**), as shown in Chart 2. 4-Hydroxyphthalic acid (**1**) was treated with 25% ammonia in a sealed tube at 190 °C for 4 h to give **2** in 59% yield. **2** was treated with allyl bromide and K_2CO_3 in acetone at 70 °C for 48 h to afford 4-allyloxyphthalimide (**3a**) (15%) and *N*-allyl-4-allyloxyphthalimide (**3b**) (53%). Subsequently, **3a** was reacted with the Grignard reagent (2 eq) prepared from (2-bromoethyl)benzene with Mg in dry tetrahydrofuran (THF), and successive treatment with 3% ammonia and aqueous NH_4Cl to afford the corresponding alcohol **4a** (69%) and **4b** (25%). Dehydration of each alcohol with HCl in THF give **5a** (99%) and **5b** (97%).

The structures of compounds **5a** and **5b** were confirmed by analyses of their proton nuclear magnetic resonance (^{1}H-NMR), as described in the experimental section. The ^{1}H-NMR spectra of **5a** and **5b** showed a characteristic doublet at

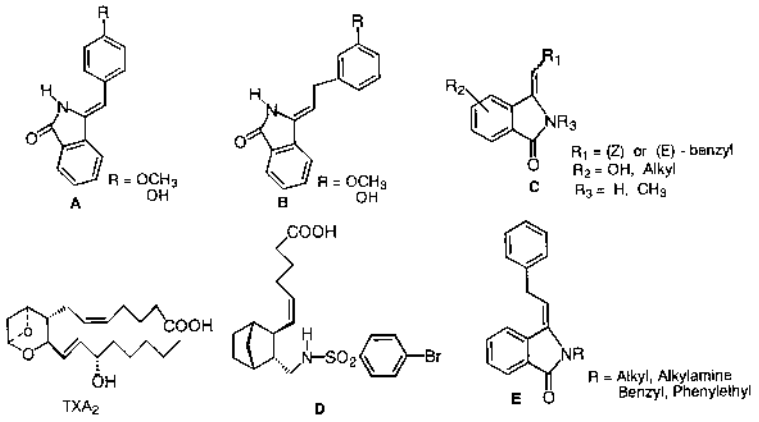

Chart 1

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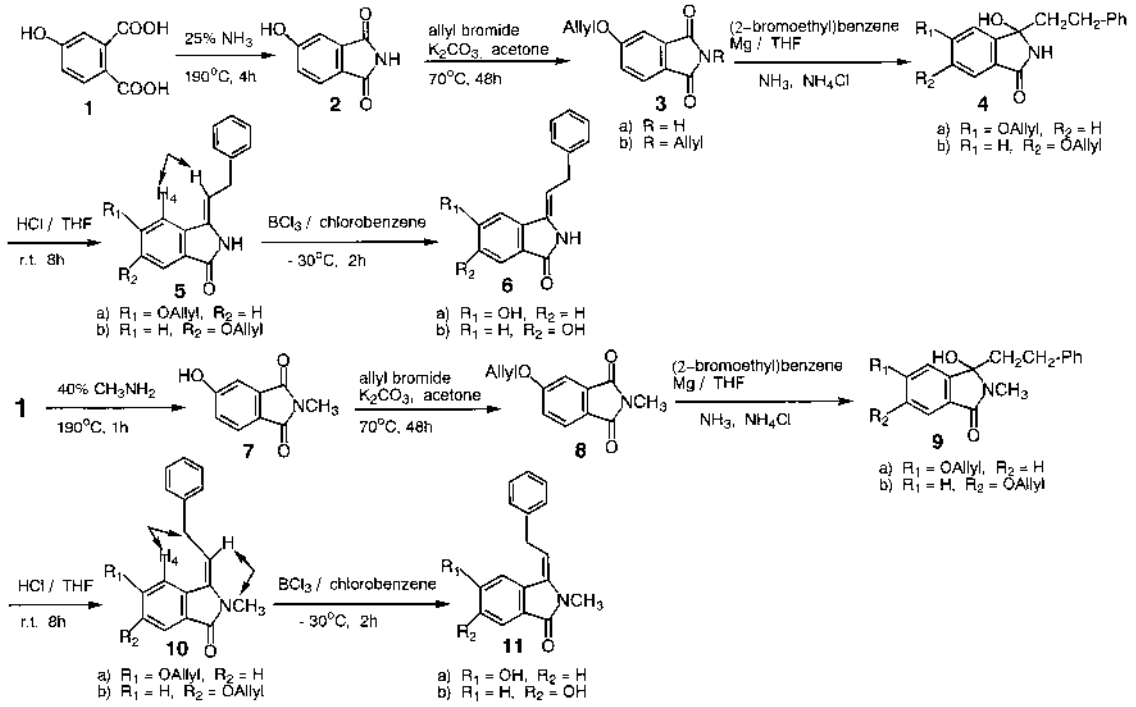


Chart 2

3.70—3.72 ppm due to methylene protons with a coupling constant of 8.0 Hz, and triplet at 5.67—5.73 ppm due to methine protons, with a coupling constant of 8.0 Hz. The configuration of the double bond in both **5a** and **5b** was determined by nuclear Overhauser effect (NOE) experiments. As shown in Chart 2, irradiation of the H-methine of both **5a** and **5b** clearly enhanced the signal intensities of H-4 in both **5a** and **5b**. These findings indicated that both compounds have the *Z* configuration.

Next, in order to introduce a hydroxy and alkyl group to the isoindolinone skeleton of **5**, we attempted Claisen rearrangement of **5a** and **5b** at 180 °C for 3 h, according to the literature procedure,[13] however this reaction did not proceed. We then attempted Claisen rearrangement by treatment with BCl_3 in chlorobenzene at −30 °C for 2 h, according to the literature procedure.[14] These reactions resulted only in phenol derivatives **6a** (46%) and **6b** (66%). Unexpectedly, **6a** and **6b** showed inhibitory activity against U-46619-induced contraction of pig coronary.

In order to succeed in the Claisen rearrangement process, we protected the NH group of compounds **5a** and **5b**. **10a** and **10b** were synthesized from **1** as the starting material. **7** was synthesized with 40% CH_3NH_2 in a sealed tube at 190 °C for 1 h instead of 25% ammonia. Yields were: **7** (59%), **8** (78%), **9a** (58%), **9b** (14%), **10a** (52%) and **10b** (81%), respectively. The structures of compounds **10a** and **10b** were confirmed by analysis of their ^{1}H-NMR, as described in the experimental section.

The ^{1}H-NMR spectra of **10a** and **10b** showed a characteristic doublet at 3.98 ppm due to methylene protons with a coupling constant of 7.7 Hz and a triplet at 5.50—5.56 ppm due to methine protons with a coupling constant of 7.7 Hz. The configuration at the double bond of **10a** and **10b** was determined by NOE experiments. As shown in Chart 2, irradiation of the H-methine of both **10a** and **10b** clearly enhanced the signal intensities of the N-CH_3 group in both **10a** and **10b**. In the same way, irradiation of H-4 of **10a** and **10b** clearly enhanced the signal intensities of both methylene protons in the side chain of **10a** and **10b**. These findings indicated that both compounds possess the *E* configuration for the double bond.

Next, we attempted Claisen rearrangement of **10a** and **10b** at 180 °C for 3 h, but no reaction occurred. Attempted Claisen rearrangement with BCl_3 in chlorobenzene at −30 °C for 2 h only afford **11a** (46%) and **11b** (85%), which showed biological activity.

We next attempted Claisen rearrangement of **8** as shown in Chart 3. Heating compound **8** at 180 °C for 3 h gave 4-allyl-5-hydroxy-*N*-methylphthalimide (**12a**) (74%) and 3-allyl-4-hydroxy-*N*-methylphthalimide (**12b**) (23%). The structures of these compounds were confirmed by analysis of their ^{1}H-NMR, as described in the experimental section. The ^{1}H-NMR spectrum of **12a** showed two singlets due to H_4 (7.07 ppm) and H_7 (7.38 ppm), respectively. In the case of **12b**, two doublets were present due to H_6 (7.02 ppm) and H_7 (7.47 ppm). **12a** and **12b** were treated with chloromethylmethyl ether in the presence of *N*,*N*-diisopropylethylamine at room temperature for 8 h to afford **13a** (100%) and **13b** (96%), respectively. **13a** reacted with the Grignard reagent (1.5 eq) prepared from (2-bromoethyl)benzene with Mg in dry THF, and successive treatment with 3% NH_3–NH_4Cl solution to afford the corresponding alcohol **14a** (25%) and **15a** (20%). Each alcohol (**14a** or **15a**) reacted with HCl in THF leading to dehydration and removal of the methoxymethyl (MOM) group to give **17a** (50%) and **18a** (74%). The structures of compounds **17a** and **18a** were confirmed by analysis of their ^{1}H-NMR, as described in the experimental section. The ^{1}H-NMR spectra of **17a** and **18a** showed a characteristic doublet at 3.96—3.97 ppm due to methylene protons with a coupling constant of 7.9 Hz and a triplet at 5.50—5.52 ppm due to me-

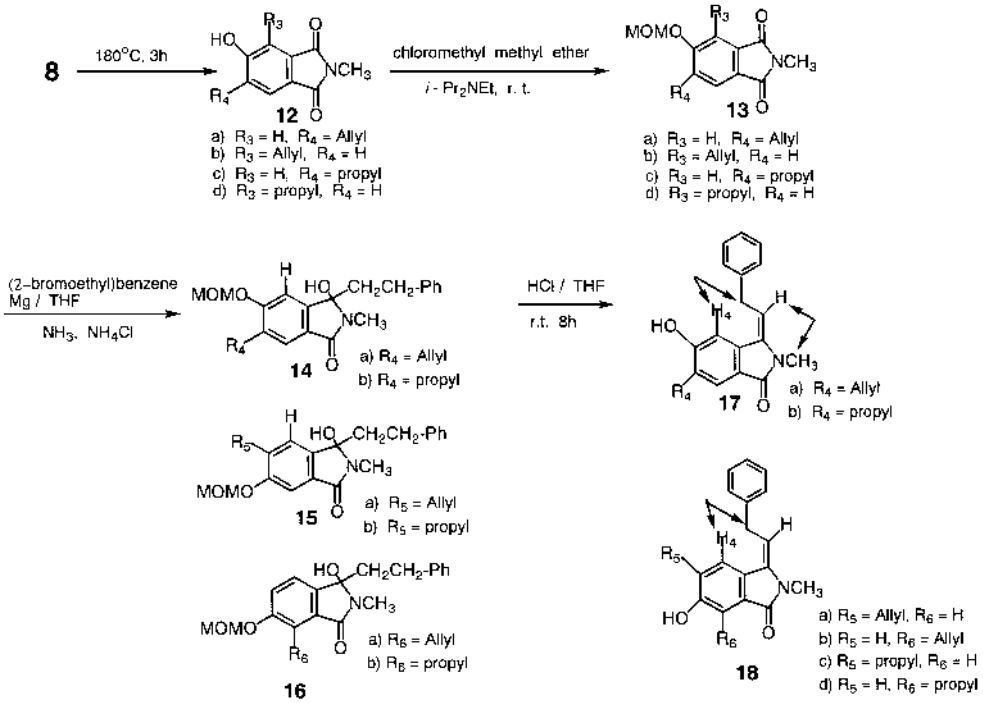


Chart 3

thine protons with a coupling constant of 7.9 Hz. The *E* configuration at the double bond of **17a** and **18a** was determined by nuclear NOE experiments.

In the same way, **13b** reacted with Grignard reagent (1.5 eq) and 3% NH_3–NH_4Cl solution to afford the corresponding alcohol **16a** (65%) as a single product due to the steric influence of the allyl group. **16a** with HCl in THF was dehydrated and the MOM group removed to afford **18b** (61%). The structure of compound **18b** was confirmed by analysis of ^{1}H-NMR, as described in the experimental section. The ^{1}H-NMR spectrum of **18b** showed a characteristic doublet at 3.96 ppm due to methylene protons, with a coupling constant of 7.9 Hz, and a triplet at 5.46 ppm, due to methine protons, with a coupling constant of 7.9 Hz. The *E* configuration at the double bond of **18b** was determined by nuclear NOE experiments.

Next, we synthesized **17b**, **18c** and **18d** having a propyl group in the isoindoline moiety. **12c** and **12d** were synthesized quantitatively by hydrogenation of **12a** and **12b** with palladium on carbon in ethanol at room temperature for 1 h. By the same route as for **17a**, **18a** and **18b**, compounds (**17b**, **18c**, **18d**) were synthesized from **12c** and **12d** (**13c**, 93%; **13d**, 87%; **14b**, 40%; **15b**, 16%; **16b**, 46%; **17b**, 43%; **18c**, 74%; **18d**, 50%). The structures of compounds **17b**, **18c** and **18d** were confirmed by analysis of their ^{1}H-NMR, as described in the experimental section. The *E* configuration of the double bond of **17b**, **18c** and **18d** was determined by NOE experiments, in the same way as for **17a**, **18a** and **18b**.

The inhibitory activity for U-46619-induced vasoconstriction of pig coronary artery was measured for compounds **5a**, **b**, **6a**, **b**, **10a**, **b**, **11a**, **b**, **17a**, **b**, **18a**—**d**. As a result, compounds **5a**, **b**, **10a**, **b**, **17a**, **b**, **18a** and **18c** showed no activity. As shown in Table 1, **6a**, **b**, **11a**, **b**, **18b** and **18d** showed biological activity. In the biological activity, it makes little difference whether these isoindolinone derivatives have a *Z* or *E* configuration.

Next, we investigated the synthesis of *N*-substituted-3-(2-phenylethylidene)isoindolinones. Compounds **22a**—**c** were synthesized according to the reaction sequences in Chart 4. Compounds **20a**—**c** were synthesized by *N*-alkylation of potassium phthalimide **19** with butyl iodide, hexyl bromide or heptyl bromide in *N*,*N*-dimethylformamide (DMF) at 120 °C for 2 h according to the literature procedure[15] (**20a**, 90%; **20b**, 31%; **20c**, 96%). Subsequently, **20a**—**c** were reacted with the Grignard reagent (2 eq) prepared from (2-bromoethyl)benzene in dry THF to afford the corresponding alcohol, which was used without further purification. Each crude alcohol was treated with 15% aqueous HCl at room temperature to afford **22a** (33%), **22b** (79%) and **22c** (82%), respectively. In the same way, compounds **20d** and **20e** were synthesized by *N*-alkylation of potassium phthalimide **19** with *N*,*N*-dimethylaminoethyl chloride and γ-dimethylaminopropyl chloride (**20d**, 59%; **20e**, 70%). **20d** and **20e** were reacted with the Grignard reagent, and then with 3% ammonia and NH_4Cl solution to afford the corresponding alcohols **21d** (63%) and **21e** (62%). Each alcohol was treated with 15% aqueous HCl for 8 h at room temperature to afford **22d** (70%) and **22e** (50%), which reacted with methyl iodide in chloroform at room temperature for 8 h to afford **23d** (64%) and **23e** (89%), respectively.

Compounds **22f**—**l** were synthesized by the same synthetic method as **22a**—**c** (**20f**, 77%; **20g**, 78%; **20h**, 82%; **20i**, 89%; **20j**, 82%; **20k**, 86%; **20l**, 58%; **22f**, 45%; **22g**, 67%; **22h**, 46%; **22i**, 53%; **22j**, 27%; **22k**, 48%; **22l**, 34%). **24i**, **25k** and **24l** were synthesized by treatment with $AlBr_3$ or BCl_3 in chlorobenzene to afford **24i** (27%), **25k** (43%) and **24l** (55%).

The inhibitory activity for U-46619-induced vasoconstriction of pig coronary artery was measured for compounds **22a**—**e**, **23d**, **23e**, **22f**—**i**, **24i**, **24l**, **22j**, **22k** and **25k**. Com-

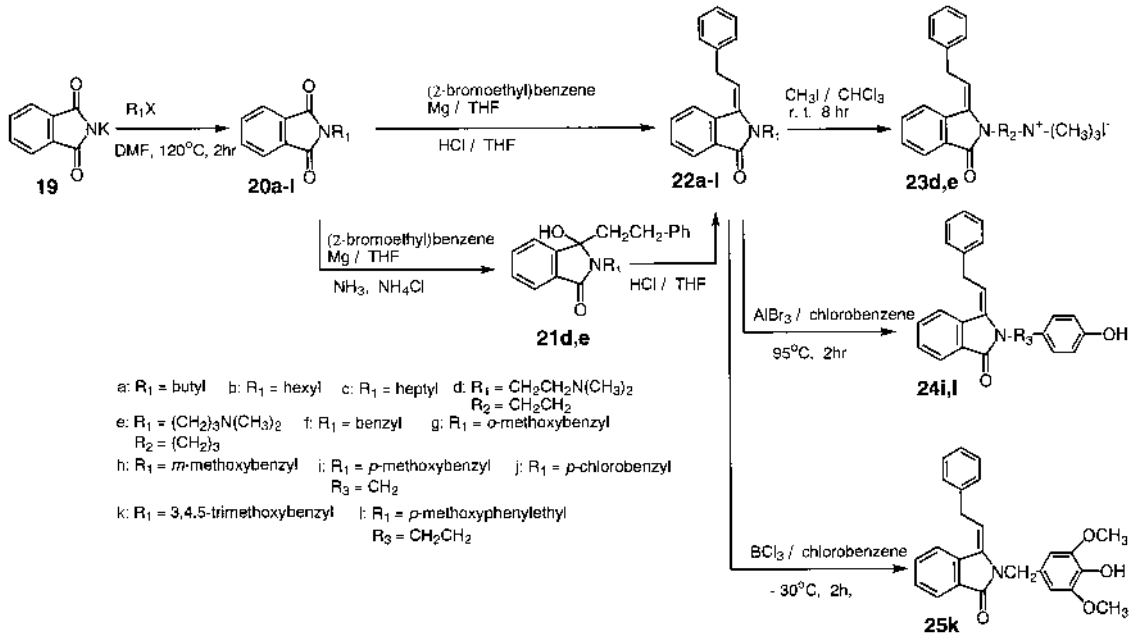


Chart 4

pounds **22a**—**e**, **23d**, **23e**, **22f**—**h** and **22j** showed no activity. As shown in Table 1, **22i**, **24i**, **24l**, **22k** and **25k** showed biological activity. The effect of the substituents at the 2-position on the inhibitory activity was approximately in the following order: benzyl≧phenyl-ethyl>aminoalkyl>alkyl. It is noteworthy that the activities of *p*-hydroxybenzyl-type and *p*-hydroxyphenylethyl-type compounds **24i**, **24l**, and **25k** were inhibitory.

Experimental

Melting points were determined on a micro-melting point apparatus (Yanagimoto) and are uncorrected. IR spectra were taken on JASCO A-202 and JASCO IR-810 infrared spectrophotometers and are given in cm^{-1}. ^{1}H-NMR spectra were recorded on a JEOL JNM-FX90q (90 MHz) spectrophotometer in $CDCl_3$. Chemical shifts are given in δ (ppm) downfield from tetramethylsilane, and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Thin layer chromatography (TLC) was performed on silica gel (Kieselgel 60F_{254} on aluminum sheets, Merck). All compounds were located by spraying the TLC plate with sulfuric acid and heating it on a hot plate. Preparative TLC was performed on a preparative layer chromatography plate (Kieselgel 60F_{254} 2 mm and 0.5 mm, Merck). Column chromatography was performed on silica gel (Kieselgel 60, 70—230 mesh, Merck).

Preparation of 4-Hydroxyphthalimide (2) A solution of 4-hydroxyphthalic acid (**1**) (4.0 g, 20 mmol) and 25% ammonia (6.0 g, 88 mmol) was heated at 190 °C for 4 h in a sealed tube. After the solution had cooled, $CHCl_3$ was added, and the whole was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 10 : 1 mixture of $CHCl_3$–MeOH as the eluent to give **2** as a white powder (2.1 g, yield 59 %). 4-hydroxyphthalimide (**2**): IR (KBr): 3227 (OH), 1758, 1687 (C=O). ^{1}H-NMR (CD_3OD): 7.07 (1H, d), 7.15 (1H, s), 7.63 (1H, d).

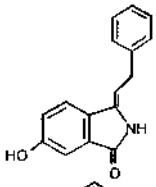
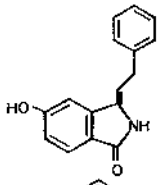
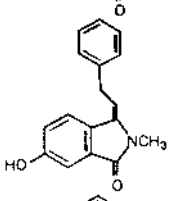
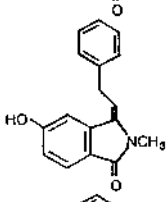
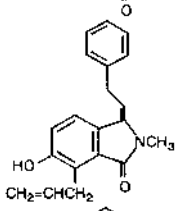
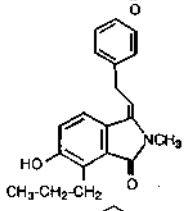
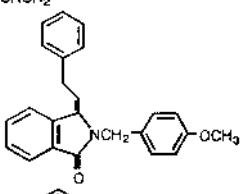
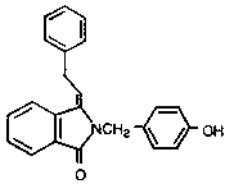
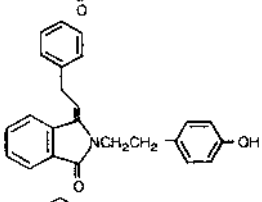
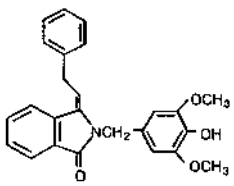
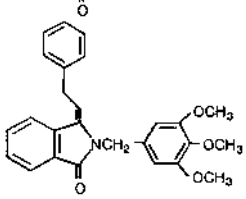
Preparation of 4-Hydroxy-*N*-methylphthalimide (7) A solution of 4-hydroxyphthalic acid (**1**) (20 g, 0.11 mol) and 40% methylamine (34 g, 0.44 mol) was heated at 150 °C for 1 h and 190 °C for 1 h. After the solution had cooled, $CHCl_3$ was added, and the whole was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 10 : 1 mixture of $CHCl_3$–MeOH as the eluent to give **7** (2.1 g, Yield 59%). 4-Hydroxy-*N*-methylphthalimide (**7**): IR (KBr): 3300 (OH), 1755, 1680 (C=O). ^{1}H-NMR (CD_3OD): 3.00 (3H, s), 6.92 (1H, d), 6.97 (1H, s), 7.47 (1H, d).

Preparation of 3a, b, 8 Allyl bromide (1.4 g, 11.8 mmol), K_2CO_3 (1.35 g, 9.8 mmol) and acetone (20 ml) were added to **2** or **7** (9.8 mmol) in a two necked flask, respectively. The mixture was stirred for 48 h at 70 °C. The mixture was extracted with $CHCl_3$ twice and with CH_3COOEt. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 1 : 1 mixture of *n*-hexane-CH_3COOEt as the eluent. In the case of **2**, **3a** (15%) and **3b** (53%) were obtained. In the case of **7**, **8** (78%) was obtained. 4-Allyloxyphthalimide (**3a**): IR (KBr): 1758, 1692 (C=O). ^{1}H-NMR ($CDCl_3$): 4.58 (2H, br d), 5.37 (2H, br d), 5.67—6.25 (1H, m), 7.07 (1H, d, H-6), 7.15 (1H, s, H-4), 7.59 (1H, d, H-7). *N*-Allyl-4-allyloxyphthalimide (**3b**): IR (KBr): 1760, 1685 (C=O). ^{1}H-NMR ($CDCl_3$): 4.18 (2H, br d), 4.58 (2H, br d), 496—6.25 (6H, m), 7.07 (1H, d), 7.19 (1H, s), 7.62 (1H, d). 4-Allyloxy-*N*-methylphthalimide (**8**): IR (KBr): 1760, 1715 (C=O). ^{1}H-NMR ($CDCl_3$): 3.08 (3H, s), 5.13—6.30 (5H, m), 7.13 (1H, d, H-6), 7.21 (1H, s, H-4), 7.64 (1H, d, H-7).

Preparation of 4a, b, 9a, b The Grignard reagent was prepared by the usual method from (2-bromoethyl)benzene (556 mg, 3.0 mmol) and Mg (79 mg, 3.3 mg atom) in dry THF (3 ml). The solution was stirred at 50 °C for 1 h, then allowed to cool. **3a** (1.5 mmol) or **8** (1.5 mmol) in dry THF (10 ml) was gradually added to this Grignard reagent, then the mixture was stirred for 8 h at room temperature and cooled. Aqueous NH_3 (3%, 10 ml) and NH_4Cl (10 ml) were added to the reaction mixture at 0 °C and the whole was stirred for 30 min at room temperature. The reaction mixture was extracted with $CHCl_3$ twice and AcOEt. The organic solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 1 : 2 mixture of *n*-hexane–AcOEt as the eluent. In the case of **3a**, 5-allyloxy-3-hydroxy-3-phenylethyl-1-isoindolinone (**4a**) (69%) and 6-allyloxy-3-hydroxy-3-phenylethyl-1-isoindolinone (**4b**) (25%) were obtained. In the case of **8**, 5-allyloxy-3-hydroxy-2-methyl-3-phenylethyl-1-isoindolinone (**9a**) (58%) and 6-allyloxy-3-hydroxy-2-methyl-3-phenylethyl-1-isoindolinone (**9b**) (14%), were obtained.

Preparation of 5a, b, 10a, b Conc. HCl (3 or 4 drops) was added to a solution of **4a**, **4b**, **9a** or **9b** (0.4 mmol) in THF (15 ml) at 0 °C and the whole was stirred for 8 h at room temperature. The reaction mixture was extracted with $CHCl_3$ twice and AcOEt. The organic solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 1 : 1 mixture of *n*-hexane–AcOEt as the eluent to give **5a** (99%), **5b** (97%), **10a** (52%) and **10b** (81%), respectively. 5-Allyloxy-3-[(*Z*)-2-phenylethylidene]-1-isoindolinone (**5a**): mp 160—161 °C. IR (KBr): 1700 (C=O). MS *m/z*: 291 (M^+). ^{1}H-NMR ($CDCl_3$): 3.70 (2H, d, *J*=8.0 Hz), 4.61 (2H, d) 5.31—5.44 (2H, m) 5.73 (1H, t, *J*=8.0 Hz) 6.02—6.08 (1H, m) 7.01 (1H, d, H-6) 7.09 (1H, s, H-4) 7.29 (5H, s) 7.74 (1H, d, H-7) 8.57 (1H, br s). 6-Allyloxy-3-[(*Z*)-2-phenylethylidene]-1-isoindolinone (**5b**): mp 148—149 °C. IR (KBr): 1703 (C=O). *Anal.* Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.30; H, 5.78; N, 4.68. ^{1}H-NMR ($CDCl_3$): 3.72 (2H, d, *J*=8.0 Hz), 4.60 (2H, d), 5.29—5.44 (2H, m), 5.67 (1H, t, *J*=8.0 Hz), 6.01—6.09 (1H, m), 7.15 (1H, d, H-5),

Table 1. Relaxing Activities of Isoindolinone Derivatives on Pig Coronary Artery Precontracted with 0.1 μM U-46619

Compd. No.	Compound	IC_{50} (10^{-6} M)	Compd. No.	Compound	IC_{50} (10^{-6} M)
6b		3.2	**6a**		1.2
11b		1.0	**11a**		0.8
18b		1.8	**18d**		1.1
22i		2.4	**24i**		0.6
24l		0.7	**25k**		1.0
22k		0.9			

Pig coronary artery was carefully isolated from fresh adult pig heart, and muscle strips approximately 2 mm wide and 10 mm long were prepared. Each strip was mounted in an organ bath filled with 10 ml of Tyrode's solution (158.3 mM NaCl, 4.0 mM KCl, 2.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 10.0 mM $NaHCO_3$, 0.4 mM NaH_2PO_4, and 5.6 mM glucose), maintained under a tension of 1.5 g at 37 °C and bubbled with a 95% O_2–5% CO_2 gas mixture. Isometric tension was measured with a force displacement transducer and pen-writing recorder (TB-612T, WI-641G, Nihon Kohden).

The activity is expressed as the concentration caused 50% inhibition (IC_{50}) of U-46619-induced vascontraction.

7.26 (1H, s, H-7), 7.30 (5H, s), 7.53 (1H, d, H-4), 9.01 (1H, br s). 5-Allyloxy-2-methyl-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**10a**): IR (neat): 1680 (C=O). ^{1}H-NMR ($CDCl_3$): 3.21 (3H, s), 3.98 (2H, d, J=7.7 Hz), 4.57 (2H, d), 5.29—5.47 (2H, m), 5.56 (1H, t, J= 7.7 Hz), 5.96—6.10 (1H, m), 7.00 (1H, d), 7.26 (1H, s), 7.31 (5H, s), 7.75 (1H, d). 6-Allyloxy-2-methyl-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**10b**): mp 84—86 °C. IR (KBr): 1685 (C=O). ^{1}H-NMR ($CDCl_3$): 3.25 (3H, s), 3.98 (2H, d, J=7.7 Hz), 4.62 (2H, d), 5.30—5.40 (2H, m), 5.50 (1H, t, J=7.7 Hz), 6.02—6.10 (1H, m), 7.13 (1H, d), 7.31 (5H, s), 7.37 (1H, s), 7.77 (1H, d).

Preparation of 6a, b,11a, b BCl_3 (0.52 mmol) in chlorobenzene (3 ml) was added to a solution of **5a**, **5b**, **10a** or **10b** (0.52 mmol) in chlorobenzene (3 ml) at −30 °C, and the mixture stirred at −30 °C for 2 h. CH_3OH was added, and the whole was washed with brine. The solution was extracted with $CHCl_3$ twice and CH_3COOEt. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residues were subjected to column chromatography on SiO_2 using a 1 : 2 mixture of *n*-hexane–AcOEt as the eluent to give **6a** (46%), **6b** (66%), **11a** (46%), and **11b** (85%), respectively. 5-Hydroxy-3-[(*Z*)-2-phenylethylidene]-1-isoindolinone (**6a**): mp 216—217 °C. IR (KBr): 3192 (OH), 1654 (C=O). MS *m/z*: 251 (M^+). ^{1}H-NMR ($CDCl_3$): 3.64 (2H, d, J=8.0 Hz), 5.65 (1H, t, J=8.0 Hz), 6.82 (1H, d), 6.94 (1H, s), 7.18 (5H, s) 7.54 (1H, d). 6-Hydroxy-3-[(*Z*)-2-phenylethylidene]-1-isoindolinone (**6b**): mp 211—213 °C. IR (KBr): 3160 (OH), 1662 (C=O). MS *m/z*: 251 (M^+). ^{1}H-NMR ($CDCl_3$): 3.63 (2H, d, J=8.0 Hz), 5.59 (1H, t, J=8.0 Hz), 6.91 (1H, d), 7.06 (1H, s), 7.17 (5H, s), 7.38 (1H, d). 5-Hydroxy-2-methyl-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**11a**): mp 216—218 °C. IR (KBr): 3112 (OH), 1660 (C=O). MS *m/z*: 265 (M^+). ^{1}H-NMR ($CDCl_3$): 3.17 (3H, s), 4.02 (2H, d, J=7.8 Hz), 5.57 (1H, t, J=7.8 Hz), 6.84 (1H, d) 7.13 (1H, s) 7.17 (5H, s) 7.54 (1H, d). 6-Hydroxy-2-methyl-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**11b**): mp 194—197 °C. IR (KBr): 3114 (OH), 1675 (C=O). *Anal*. Calcd for $C_{17}H_{15}NO_2$: C,76.96; H, 5.70; N, 5.28. Found: C, 76.62; H, 5.64; N, 5.15. ^{1}H-NMR ($CDCl_3$): 3.17 (3H, s), 3.98 (2H, d, J=7.8 Hz), 5.53 (1H, t, J=7.8 Hz), 6.95 (1H, d) 7.03 (1H, s) 7.23 (5H, s) 7.78 (1H, d).

Preparation of 12a, b **8** (2.0 g, 9.2 mmol) was stirred under Ar at 180 °C for 3 h. The mixture was cooled at room temperature. The resulting residue was subjected to column chromatography on SiO_2 using $CHCl_3$ as eluent to give **12a** (1.5 g, 74%) and **12b** (0.5 g, 23%), respectively. 4-Allyl-5-hydroxy-*N*-methylphthalimide (**12a**): IR (neat): 3275 (OH), 1750, 1675 (C=O). ^{1}H-NMR ($CDCl_3$): 2.97 (3H, s), 3.40 (2H, br d), 5.01 (2H, br d), 5.57—6.27 (1H, m), 7.07 (1H, s, H-4) 7.38 (1H, s, H-7). 3-Allyl-4-hydroxy-

N-methylphthalimide (**12b**): IR (neat): 3259 (OH), 1756, 1682 (C=O). ^{1}H-NMR ($CDCl_3$): 2.94 (3H, s), 3.70 (2H, br d), 4.93 (2H, br d), 5.57—6.15 (1H, m), 7.02 (1H, d, H-6) 7.47 (1H, d, H-7).

Preparation of 12c, d 5% Pd–C (98 mg) was added to a solution of **12a** or **12b** (4.5 mmol) in ethanol (30 ml). Hydrogen was charged at ordinary pressure and the reaction mixture was vigorously stirred for 1 h at room temperature. Removal of the catalyst by suction filtration and concentration of the filtrate under reduced pressure gave **12c** (98%) or **12d** (91%), respectively. 4-Hydroxy-*N*-methyl-5-propylphthalimide (**12c**): ^{1}H-NMR ($CDCl_3$): 0.95 (3H, t), 1.58 (2H, m), 2.67 (2H, t), 3.11 (3H, s), 7.27 (1H, s), 7.53 (1H, s). 4-Hydroxy-3-propyl-*N*-methylphthalimide (**12d**): ^{1}H-NMR ($CDCl_3$): 0.98 (3H, t), 1.63 (2H, m), 3.07 (2H, t), 3.13 (3H, s), 6.95 (1H, d), 7.52 (1H, d).

Preparation of 13a—d *N*,*N*-Diisopropylethylamine (646 mg, 5 mmol) was gradually added to a solution of **12** (3.3 mmol) in dry dichloromethane (15 ml). Chloromethyl methyl ether (317 mg, 4 mmol) was then gradually added. The mixture was stirred for 1 h at 0 °C and for 8 h at room temperature. The reaction mixture was extracted with $CHCl_3$ twice. The organic solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 1 : 1 mixture of *n*-hexane–AcOEt as the eluent to afford **13**. The yields of **13a**—**d** were 100, 96, 93 and 87%, respectively. 4-Allyl-5-(methoxymethyloxy)-*N*-methyl-phthalimide (**13a**): ^{1}H-NMR ($CDCl_3$): 3.03 (3H, s), 3.40 (2H, br d), 3.48 (3H, s), 5.05 (2H, br d), 5.28 (2H, s), 5.65—6.22 (1H, m), 7.29 (1H, s) 7.40 (1H, s). 3-Allyl-4-(methoxymethyloxy)-*N*-methylphthalimide (**13b**): ^{1}H-NMR ($CDCl_3$): 3.11 (3H, s), 3.49 (3H, s), 3.88 (2H, br d), 5.11 (2H, br d), 5.27 (2H, s), 5.65—6.29 (1H, m), 7.26 (1H, d) 7.62 (1H, d). 4-(Methoxymethyloxy)-*N*-methyl-5-propylphthalimide (**13c**): ^{1}H-NMR ($CDCl_3$): 0.95 (3H, t), 1.58 (2H, m), 2.68 (2H, t), 3.08 (3H, s), 3.46 (3H, s), 5.25 (2H, s), 7.41 (1H, s), 7.52 (1H, s). 4-(Methoxymethyloxy)-*N*-methyl-3-propylphthalimide (**13d**): ^{1}H-NMR ($CDCl_3$): 0.96 (3H, t), 1.57 (2H, m), 3.03 (2H, t), 3.06 (3H, s), 3.49 (3H, s), 5.23 (2H, s), 7.17 (1H, d), 7.47 (1H, d).

Reaction of Grignard Reagent with 13a—d **13a**—**d** were reacted with Grignard reagent by the same procedure as for **3a** and **3b**. **13a** gave 6-allyl-3-hydroxy-2-methyl-5-methoxymetholoxy-3-phenylethyl-1-isoindolinone (**14a**) (25%) and 5-allyl-3-hydroxy-2-methyl-6-methoxymethyloxy-3-phenylethyl-1-isoindolinone (**15a**) (20%). **13b** gave 7-allyl-3-hydroxy-2-methyl-6-methoxymethyloxy-3-phenylethyl-1-isoindolinone (**16a**) (65%). **13c** gave 3-hydroxy-2-methyl-5-methoxymethyl-3-phenylethyl-6-propyl-1-isoindolinone (**14b**) (40%) and 3-hydroxy-2-methyl-6-methoxymethyl-3-phenylethyl-5-propyl-1-isoindolinone (**15b**) (16%). **13d** gave 3-hydroxy-2-methyl-6-methoxymethyloxy-3-phenylethyl-7-propyl-1-isoindolinone (**16b**) (46%).

Preparation of 17a, b and 18a—d Conc. HCl (3 or 4 drops) was added to a solution of **14a**, **14b, 15a**, **15b**, **16a** or **16b** (0.8 mmol) in THF (15 ml) at 0 °C and the whole was stirred for 8 h at room temperature. The reaction mixture was extracted with $CHCl_3$ twice and AcOEt. The organic solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residues were subjected to column chromatography on SiO_2 using a 1 : 2 mixture of *n*-hexane–AcOEt as eluent to give **17a** (50%), **17b** (43%), **18a** (74%), **18c** (74%), **18b** (61%), and **18d** (50%), respectively. 6-Allyl-5-hydroxy-2-methyl-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**17a**): mp 259—262 °C. IR (KBr): 3140 (OH), 1664 (C=O). MS *m/z*: 305 (M^+). ^{1}H-NMR ($CDCl_3$): 3.20 (3H, s), 3.45 (2H, d), 3.96 (2H, d, *J*=7.9 Hz), 5.07—5.12 (2H, m), 5.52 (1H, t, *J*=7.9 Hz), 5.99—6.05 (1H, m), 7.33 (1H, s), 7.32 (5H, s), 7.62 (1H, s). 5-Hydroxy-2-methyl-3-[(*E*)-2-phenylethylidene]-6-propyl-1-isoindolinone (**17b**): mp 154—155 °C. IR (KBr): 3187 (OH), 1663 (C=O). MS *m/z*: 307 (M^+). ^{1}H-NMR ($CDCl_3$): 0.97 (3H, t), 1.64—1.70 (2H, m), 2.65 (2H, t), 3.29 (3H, s), 3.95 (2H, d, *J*=7.8 Hz), 5.50 (1H, t, *J*=7.8 Hz), 7.25 (1H, s), 7.29 (5H, s), 7.62 (1H, s). 5-Allyl-6-hydroxy-2-methyl-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**18a**): mp 212—215 °C. IR (KBr): 3104 (OH), 1687 (C=O). MS *m/z*: 305 (M^+). ^{1}H-NMR ($CDCl_3$): 3.23 (3H, s), 3.32 (2H, d), 3.97 (2H, d, *J*=7.9 Hz), 5.07—5.10 (2H, m), 5.50 (1H, t, *J*=7.9 Hz), 5.98—6.03 (1H, m), 7.18 (1H, s), 7.29 (5H, s), 7.61 (1H, s). 7-Allyl-6-hydroxy-2-methyl-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**18b**): mp 184—185 °C. IR (KBr): 3200 (OH), 1677 (C=O). *Anal*. Calcd for $C_{20}H_{19}NO_2 \cdot 1/2H_2O$: C, 76.41; H, 6.41; N, 4.46. Found: C, 76.47; H, 6.27; N, 4.36. ^{1}H-NMR ($CDCl_3$): 3.22 (3H, s), 3.96 (2H, d, *J*=7.9 Hz), 4.16 (2H, d), 5.16—5.22 (2H, m), 5.46 (1H, t, *J*=7.9 Hz), 6.04—6.09 (1H, m), 7.02 (1H, d, *J*=8.5 Hz), 7.26 (5H, s), 7.65 (1H, d, *J*=8.5 Hz). 6-Hydroxy-2-methyl-3-[(*E*)-2-phenylethylidene]-5-propyl-1-isoindolinone (**18c**): mp 188—191 °C. IR (KBr): 3109 (OH), 1683 (C=O). MS *m/z*: 307 (M^+). ^{1}H-NMR ($CDCl_3$): 0.96 (3H, t), 1.63—1.67 (2H, m), 2.67 (2H, t), 3.27 (3H, s), 3.98 (2H, d, *J*=7.8 Hz), 5.46 (1H, t, *J*=7.8 Hz), 7.23 (1H, s), 7.27 (5H, s), 7.60 (1H, s). 6-Hydroxy-2-methyl-3-[(*E*)-2-phenylethylidene]-7-propyl-1-isoindolinone (**18d**): mp 177—179 °C. IR (KBr): 3195 (OH), 1660 (C=O). MS *m/z*: 307 (M^+). ^{1}H-NMR ($CDCl_3$): 1.00 (3H, t), 1.59—1.70 (2H, m), 2.65 (2H, t), 3.21 (3H, s), 3.95 (2H, d, *J*=7.8 Hz), 5.43 (1H, t, *J*=7.8 Hz), 6.97 (1H, d, *J*=8.0 Hz), 7.29 (5H, s), 7.54 (1H, d, *J*=8.0 Hz).

Preparation of *N*-Alkylphthalimide 20a—l To a solution of potassium phthalimide (11 mmol) in DMF (10 ml), *n*-butyl iodide (16 mmol), *n*-hexyl bromide (16 mmol), *n*-heptyl bromide (16 mmol), *N*,*N*-dimethylaminoethyl chloride (5.5 mmol), γ-dimethylaminopropyl chloride (5.5 mmol), benzyl bromide (16 mmol), *o*-methoxybenzyl chloride (16 mmol), *m*-methoxybenzyl chloride (16 mmol), *p*-methoxybenzyl chloride (16 mmol), *p*-chlorobenzyl chloride (16 mmol), 3,4,5-trimethoxybenzyl chloride (11 mmol), or *p*-methoxyphenylethyl chloride (11 mmol) were added and the mixtures stirred at 120 °C for 2 h. After cooling, DMF was removed *in vacuo*, $CHCl_3$ was added and the whole was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo* to afford **20a** (90%), **20b** (31%), **20c** (96%), **20d** (59%), **20e** (70%), **20f** (77%), **20g** (78%), **20h** (82%), **20i** (89%), **20j** (82%), **20k** (86%), and **20l** (58%), respectively. *N*-Butyl phthalimide (**20a**): IR (neat): 1763, 1702 (C=O). ^{1}H-NMR ($CDCl_3$): 1.03 (3H, t), 1.49 (4H, m), 3.59 (2H, t), 7.55—7.72 (4H, m). *N*-Hexyl phthalimide (**20b**): IR (neat): 1760, 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 0.86 (3H, t), 1.32 (8H, m), 3.61 (2H, t), 7.46—7.78 (4H, m). *N*-Heptyl phthalimide (**20c**): IR (neat): 1762, 1702 (C=O). ^{1}H-NMR ($CDCl_3$): 0.86 (3H, t), 1.30 (10H, m), 3.63 (2H, t), 7.60—7.83 (4H, m). *N*-[2-(Dimethylamino)ethyl]phthalimide (**20d**): IR (KBr): 1760, 1702 (C=O). ^{1}H-NMR ($CDCl_3$): 2.28 (6H, s), 2.58 (2H, t, *J*=6.5 Hz), 3.79 (2H, t, *J*=6.5 Hz), 7.73—7.77 (4H, m). *N*-[3-(Dimethylamino)propyl]phthalimide (**20e**): IR (KBr): 1759, 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 1.77 (2H, m), 2.17 (6H, s), 2.30 (2H, t), 3.68 (2H, t), 7.48—7.80 (4H, m). *N*-Benzyl phthalimide (**20f**): IR (KBr): 1758, 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 4.81 (2H, s), 7.22—7.77 (9H, m). *N*-(2-Methoxybenzyl)phthalimide (**20g**): IR (KBr): 1759, 1702 (C=O). ^{1}H-NMR ($CDCl_3$): 3.85 (3H, s), 4.91 (2H, s), 6.86—7.87 (8H, m). *N*-(3-Methoxybenzyl)phthalimide (**20h**): IR (KBr): 1764, 1702 (C=O). ^{1}H-NMR ($CDCl_3$): 3.78 (3H, s), 4.82 (2H, s), 6.79—7.85 (8H, m). *N*-(4-Methoxybenzyl)phthalimide (**20i**): IR (KBr): 1760, 1702 (C=O). ^{1}H-NMR ($CDCl_3$): 3.78 (3H, s), 4.80 (2H, s), 6.83 (2H, d, *J*=8.5 Hz), 7.38 (2H, d, *J*=8.5 Hz), 7.68—7.83 (4H, m). *N*-(4-Chlorobenzyl)Phthalimide (**20j**): IR (KBr): 1763, 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 4.69 (2H, s), 7.15 (4H, m), 7.52—7.68 (4H, m). *N*-(3,4,5-Trimethoxybenzyl)phthalimide (**20k**): IR (KBr): 1759, 1702 (C=O). ^{1}H-NMR ($CDCl_3$): 3.73 (3H, s), 3.77 (6H, s), 4.67 (2H, s), 6.58 (2H, s), 7.58—7.74 (4H, m). *N*-(4-Methoxyphenylethyl)-phthalimide (**20l**): IR (KBr): 1759, 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 2.93 (2H, t, *J*=6.4 Hz), 3.77 (3H, s), 3.89 (2H, t, *J*=6.4 Hz), 6.82 (2H, d, *J*=8.5 Hz), 7.16 (2H, d, *J*=8.5 Hz), 7.69—7.83 (4H, m).

Preparation of 21d, e **20d**, **e** were reacted with Grignard reagent by the same procedure as for reaction of **3a** and **3b**. **20d** gave 2-[2-(dimethylamino)ethyl]-3-hydroxy-3-phenylethyl-1-isoindolinone (**21d**) (63%). **20e** gave 2-[3-(dimethylamino)propyl]-3-hydroxy-3-phenylethyl-1-isoindolinone (**21e**) (62%).

Preparation of 22a—c, f—l The Grignard reagent was prepared by the usual method from (2-bromoethyl) benzene (1.8 g, 9.8 mmol) and Mg (260 mg, 10.8 mg atom) in dry THF (5 ml). The solution was stirred at 50 °C for 1 h, then allowed to cool. **22a**—**c**, **f**—**l** (4.9 mmol, respectively) in dry THF (20 ml) was gradually added to this Grignard reagent and the mixture stirred for 8 h at room temperature and cooled. Aqueous HCl (15%, 20 ml) was added to the reaction mixture at 0 °C and the whole was stirred for 30 min at room temperature. The reaction mixture was extracted with $CHCl_3$ twice and AcOEt. The organic solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 using a 1 : 1 mixture of *n*-hexane–AcOEt as the eluent to afford **22a** (33%), **22b** (79%), **22c** (82%), **22f** (45%), **22g** (67%), **22h** (46%), **22i** (53%), **22j** (27%), **22k** (48%), and **22l** (34%), respectively. 2-Butyl-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22a**): IR (neat): 1700 (C=O). Positive FAB-MS *m/z*: 292 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$): 0.92 (3H, t), 1.17—1.72 (4H, m), 3.72 (2H, t), 4.02 (2H, d, *J*=8.0 Hz), 5.54 (1H, t, *J*=8.0 Hz), 7.19—7.83 (9H, m). 2-Hexyl-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22b**): IR (neat): 1700 (C=O). Positive FAB-MS *m/z*: 320 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$): 0.84 (3H, t), 1.05—1.72 (8H, m), 3.68 (2H, t), 3.98 (2H, d, *J*=7.8 Hz), 5.54 (1H, t, *J*=7.8 Hz), 7.03—7.78 (9H, m). 2-Heptyl-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22c**): IR (neat): 1695 (C=O). Positive FAB-MS *m/z*: 334 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$): 0.85 (3H, t), 1.04—1.82 (10H, m), 3.71 (2H, t), 4.01 (2H, d, *J*=7.8 Hz), 5.51 (1H, t, *J*=7.8 Hz), 7.04—7.78 (9H, m). 2-Benzyl-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22f**): mp 87—90 °C. IR (KBr): 1690 (C=O). MS *m/z*: 325 (M^+). ^{1}H-NMR ($CDCl_3$): 4.05 (2H, d, *J*=7.9 Hz), 5.03 (2H, s), 5.57 (1H, t, *J*=7.9 Hz),

7.07—7.98 (14H, m). 2-(2-Methoxybenzyl)-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22g**): IR (neat): 1681 (C=O). Positive FAB-MS *m/z*: 356 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$): 3.67 (3H, s), 3.93 (2H, d, *J*=7.8 Hz), 4.99 (2H, s), 5.57 (1H, t, *J*=7.8 Hz), 6.64—7.92 (13H, m). 2-(3-Methoxybenzyl)-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22h**): mp 127—130 °C. IR (KBr): 1698 (C=O). Positive FAB-MS *m/z*: 356 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$): 3.71 (3H, s), 4.05 (2H, d, *J*=7.9 Hz), 5.00 (2H, s), 5.58 (1H, t, *J*=7.9 Hz), 6.70—7.97 (13H, m). 2-(4-Methoxybenzyl)-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22i**): mp 124—126 °C. IR (KBr): 1691 (C=O). ^{1}H-NMR ($CDCl_3$): 3.77 (3H, s), 4.07 (2H, d, *J*=7.8 Hz), 4.97 (2H, s), 5.60 (1H, t, *J*=7.8 Hz), 6.79—7.98 (13H, m). 2-(4-Chlorobenzyl)-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22j**): mp 81—83 °C. IR (KBr): 1690 (C=O). *Anal*. Calcd for $C_{23}H_{18}ClNO$: C, 76.77; H, 5.04; N, 3.89. Found: C, 76.35; H, 5.12; N, 3.68. ^{1}H-NMR ($CDCl_3$): 3.95 (2H, d, *J*=8.0 Hz), 4.99 (2H, s), 5.51 (1H, t, *J*=8.0 Hz), 7.09—7.97 (13H, m). 2-(3,4,5-Trimethoxybenzyl)-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22k**): mp 135—136 °C. IR (KBr): 1686 (C=O). *Anal*. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07; N, 3.37. Found: C, 74.25; H, 6.01; N, 3.13. ^{1}H-NMR ($CDCl_3$): 3.74 (6H, s), 3.81 (3H, s), 3.98 (2H, d, *J*=8.0 Hz), 4.95 (2H, s), 5.65 (1H, t, *J*=8.0 Hz), 6.46 (2H, s), 7.15—7.98 (9H, m). 2-(4-Methoxyphenylethyl)-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22l**): mp 105—109 °C. IR (KBr): 1708 (C=O). ^{1}H-NMR ($CDCl_3$): 2.89 (2H, t), 3.76 (3H, s), 4.10 (2H, t), 4.10 (2H, d, *J*=7.8 Hz), 5.58 (1H, t, *J*=7.8 Hz), 6.77—7.92 (13H, m).

Preparation of 22d, e **22d**, **e** were prepared by the same procedure as for the reactions of **4a**, **4b**, **9a**, **9b** with HCl [**22d** (70%), **22e** (50%)]. 2-[2-(dimethylamino)ethyl]-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22d**): IR (neat): 1687 (C=O). Positive FAB-MS *m/z*: 307 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$): 2.27 (6H, s), 2.50 (2H, t, *J*=6.6 Hz), 3.88 (2H, t, *J*=6.6 Hz), 4.06 (2H, d, *J*=8.0 Hz), 5.62 (1H, t, *J*=8.0 Hz), 6.85—7.87 (9H, m). 2-[3-(dimethylamino)propyl]-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**22e**): IR (neat): 1682 (C=O). Positive FAB-MS *m/z*: 321 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$): 2.14 (6H, s), 1.65—2.41 (4H, m), 3.75 (2H, t, *J*=6.5 Hz), 3.97 (2H, d, *J*=7.9 Hz), 5.57 (1H, t, *J*=7.9 Hz), 6.92—7.78 (9H, m).

Preparation of 23d, e Methyl iodide (81 mg, 0.57 mmol) was added to a solution of **22d** or **22e** (0.47 mmol) in $CHCl_3$ (10 ml). The mixture was stirred for 8 h at room temperature to afford **23d** (64%) or **23e** (89%), respectively. 3-[(*E*)-2-Phenylethylidene]-2-[2-(trimethylammonio)ethyl]-1-isoindolinone iodide (**23d**): mp 158—160 °C. IR (KBr): 1690 (C=O). ^{1}H-NMR ($CDCl_3$): 3.43 (2H, t), 3.46 (9H, s), 4.11 (2H, d, *J*=8.0 Hz), 4.30 (2H, t), 5.93 (1H, t, *J*=8.0 Hz), 7.18—7.93 (9H, m). 3-[(*E*)-2-Phenylethylidene]-2-[3-(trimethylammonio)propyl]-1-isoindolinone iodide (**23e**): mp 152—154 °C. IR (KBr): 1685 (C=O). ^{1}H-NMR ($CDCl_3$): 2.23 (2H, m), 3.38 (9H, s), 3.70 (2H, t), 3.94 (2H, t), 4.05 (2H, d, *J*=8.0 Hz), 5.91 (1H, t, *J*=8.0 Hz), 7.21—7.90 (9H, m).

Preparation of 24i, l Aluminium bromide (515 mg, 1.9 mmol) in chlorobenzene (10 ml) was added to a solution of **24i** or **24l** (0.84 mmol) in chlorobenzene (3 ml) under Ar, and the mixture stirred at 10 °C for 15 min and 95 °C for 2 h. After cooling, dilute HCl (50 ml) was added. The solution was extracted with CH_3COOEt. The extract was washed with 5% NaOH solution dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on SiO_2 using a 1 : 2 mixture of *n*-hexane–AcOEt as the eluent to give **24i** (27%) or **24l** (55%), respectively. 2-(4-Hydroxybenzyl)-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**24i**): mp 209—213 °C. IR (KBr): 3111 (OH), 1670 (C=O). *Anal*. Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.79; H, 5.61; N, 4.07. ^{1}H-NMR ($CDCl_3$): 4.05 (2H, d, *J*=8.1 Hz), 4.89 (2H, s), 5.77 (1H, t, *J*=8.1 Hz), 6.63—8.06 (13H, m). 2-(4-Hydroxyphenylethyl)-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**24l**): mp 109—111 °C. IR (KBr): 3200 (OH), 1674 (C=O). *Anal*. Calcd for $C_{24}H_{21}NO_2 \cdot 1/2H_2O$: C, 79.10; H, 6.08; N, 3.84. Found: C, 79.41; H, 5.95; N, 3.79. ^{1}H-NMR ($CDCl_3$): 2.78 (2H, t), 3.91 (2H, t), 4.00 (2H, d, *J*=7.8 Hz), 5.55 (1H, t, *J*=7.8 Hz), 6.69—7.79 (13H, m).

Preparation of 25k BCl_3 (61 mg, 0.52 mmol) in chlorobenzene (5 ml) was added to a solution of **22k** (0.52 mmol) in chlorobenzene (5 ml) at −30 °C, then the mixture was stirred at −30 °C for 2 h and for 8 h at room temperature. CH_3OH was added. The whole was washed with brine. The solution was extracted with $CHCl_3$ twice and CH_3COOEt. The extract was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on SiO_2 using a 1 : 1 mixture of *n*-hexane–AcOEt as the eluent to give **25k** (43%). 2-(4-Hydroxy-3,5-dimethoxybenzyl)-3-[(*E*)-2-phenylethylidene]-1-isoindolinone (**25k**): mp 112—113 °C. IR (KBr): 3356 (OH), 1691 (C=O). ^{1}H-NMR ($CDCl_3$): 3.74 (6H, s), 3.95 (2H, d, *J*=8.0 Hz), 4.93 (2H, s), 5.66 (1H, t, *J*=8.0 Hz), 6.47 (2H, s), 7.14—7.96 (9H, m).

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