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

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We have synthesized 3-(*o*, *m* or *p*-substituted benzylidene)isoindolinone and 3-(2-*o*, *m* or *p*-substituted phenylethylidene)isoindolinone, which possess inhibitory activity for thromboxane A_2 analog (U-46619)-induced vasoconstriction.

Keywords isoindolinone derivative; thromboxane A_2 analog (U-46619); prostacyclin

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 considered to be implicated in circulatory disorders and asthmatic conditions. Therefore, TXA_2 receptor antagonists and PGI_2 derivatives should be clinically useful as therapeutic agents for thrombosis, asthma, ischemia, and myocardial infraction.[4–7]

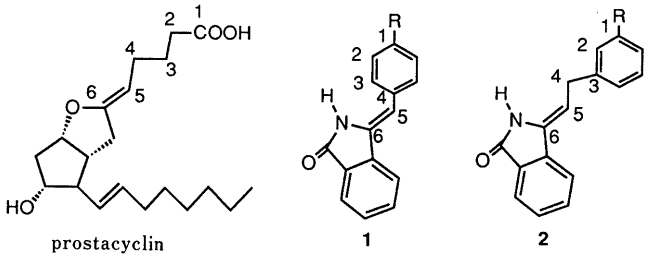
Recently, we have found that some isoindolinone derivatives[8] inhibit TXA_2 analog (U-46619)[9]-induced vascoconstriction. In this paper, we wish to report the synthesis of these isoindolinone derivatives.

Sekiya and Terao[10] have reported the synthesis of 3-benzylideneisoindolinone, which inhibited U-46619-induced vasoconstriction in a screening test.[11] We assumed that the activity of 3-benzylideneisoindolinone is based on the structural similarity between 3-benzylideneisoindolinone and PGI_2. So, in order to obtain thromboxane receptor antagonists, we designed 3-benzylideneisoindolinone derivatives (**1**) and 3-(2-phenylethylidene)isoindolinone derivatives (**2**) by making the following structural modifications of PGI_2 (Chart 1): (1) modification of the 2-oxabicyclo-[3.3.0]octane ring by replacement of the isoindolinone ring; (2) modification of the α side chain of PGI_2 by replacement of the aryl-substituted exocyclic olefin; (3) modification of the 1-COOH group by replacement of the OH group, or of the 1-$COOCH_3$ group by replacement of OCH_3.

In these isoindolinone derivatives (**1** and **2**), it is considered that the exo-olefin of 3-benzylideneisoindolinone derivatives (**1**) or 3-(2-phenylethylidene)isoindolinone derivatives (**2**) is equivalent to the 5,6-double bond of PGI_2 (Chart 1). Therefore, we have introduced a *p*-hydroxy group or *p*-methoxy group in the benzene ring of 3-benzylideneisoindolinone (**1**) and an *m*-hydroxy group or *m*-methoxy group in 3-(2-phenylethylidene) isoindolinone (**2**). Furthermore, to identify the molecular structure responsible for the biological activities of isoindolinone derivatives, we have synthesized 3-benzylideneisoindolinone, 3-(*o*, *m* or *p*-substituted benzylidene)isoindolinone derivatives (**1a—c**, **6a—6c**), 3-(2-phenylethylidene)isoindolinone and 3-(2-*o*, *m* or *p*-substituted phenylethylidene)isoindolinone derivatives (**2a—c**, **10a—c**).

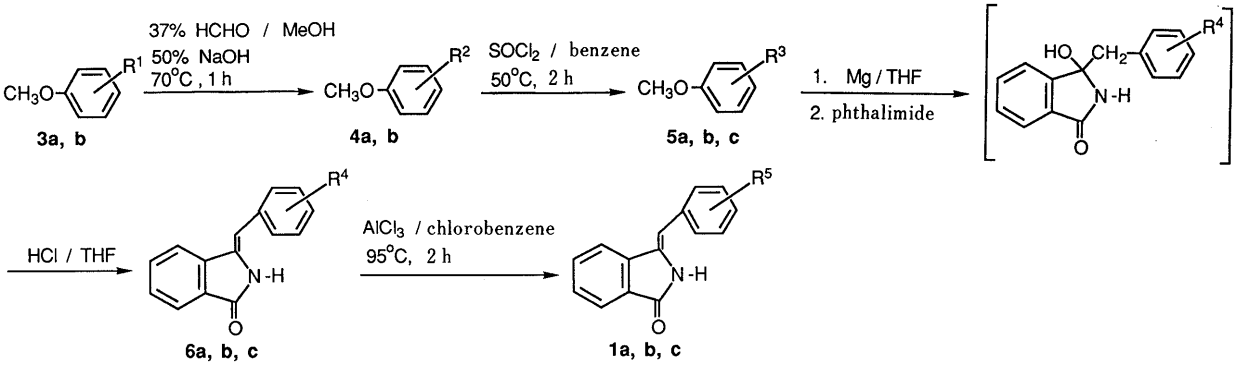
3-Benzylideneisoindolinone and 3-(2-phenylethylidene)-isoindolinone were prepared according to the literature procedure.[10]

Compounds **1a—c** and **6a—c** were synthesized according to the reaction sequence shown in Chart 2. Compounds **1a**, **1b** and **1c** were synthesized from (*o* or *m*)-methoxybenzaldehyde (**3a** and **3b**) except **1c**, which was synthesized from *p*-methoxybenzyl chloride **5c**. Each aldehyde **3** was treated with 37% formalin in methanol to give the alcohol **4** according to the literature procedure[12] (**4a**: 75% yield, **4b**: 87%). Each alcohol **4** was treated with $SOCl_2$ in dry benzene at 50 °C for 2 h to afford the chloride **5** (**5a**: 67% yield, **5b**: 70%). Subsequently, phthalimide (1 eq) was reacted with the Grignard reagent (2 eq) prepared from **5** with Mg in dry tetrahydrofuran (THF) to afford the corresponding alcohol, which was used without further purification. Each crude alcohol was treated with 15% aqueous HCl for 30 min at room temperature to afford **6** (**6a**: 16% yield, **6b**: 12%, **6c**: 18%). The structures of compounds **6a**, **6b** and **6c** were confirmed by analyses of their proton nuclear magnetic resonance (^{1}H-NMR) and infrared (IR) spectra as described in the experimental section. The ^{1}H-NMR spectra of **6a**, **6b** and **6c** showed a singlet at 3.81—3.94 ppm due to the methoxy group, a characteristic singlet at 6.53—6.64 ppm due to the olefinic proton and a broad singlet at 8.28—8.42 ppm due to the amido proton. The IR spectra of **6** showed carbonyl absorption. Compounds **6** were treated with $AlCl_3$ in chlorobenzene under Ar at 95 °C for 2 h to afford **1** (**1a**: 9% yield, **1b**: 8%, **1c**: 13%). The structures of compounds **1a**, **1b** and **1c** were confirmed by analyses of their ^{1}H-NMR and IR spectra as described in the experimental section. The ^{1}H-NMR spectra of **1a**, **1b** and **1c** showed a



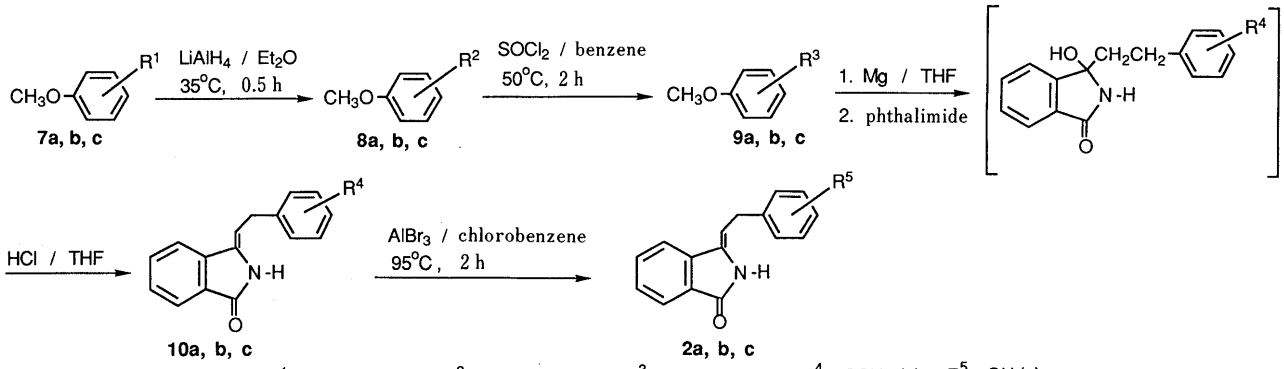
prostacyclin **1** **2**

Chart 1



a : R^1 = CHO (*o*) R^2 = CH_2OH (*o*) R^3 = CH_2Cl (*o*) R^4 = OCH_3 (*o*) R^5 = OH (*o*)
b : R^1 = CHO (*m*) R^2 = CH_2OH (*m*) R^3 = CH_2Cl (*m*) R^4 = OCH_3 (*m*) R^5 = OH (*m*)
c : R^3 = CH_2Cl (*p*) R^4 = OCH_3 (*p*) R^5 = OH (*p*)

Chart 2



a : R^1 = CH_2COOH (*o*) R^2 = CH_2CH_2OH (*o*) R^3 = CH_2CH_2Cl (*o*) R^4 = OCH_3 (*o*) R^5 = OH (*o*)
b : R^1 = CH_2COOH (*m*) R^2 = CH_2CH_2OH (*m*) R^3 = CH_2CH_2Cl (*m*) R^4 = OCH_3 (*m*) R^5 = OH (*m*)
c : R^1 = CH_2COOH (*p*) R^2 = CH_2CH_2OH (*p*) R^3 = CH_2CH_2Cl (*p*) R^4 = OCH_3 (*p*) R^5 = OH (*p*)

Chart 3

characteristic singlet at 6.62—6.65 ppm due to the olefinic proton and the IR spectra showed carbonyl and hydroxyl absorptions.

Compounds **2a**—**c** and **10a**—**c** were synthesized according to the reaction sequences in Chart 3. Compounds **2a**, **2b** and **2c** were synthesized from (*o*, *m* or *p*)-methoxyphenylacetic acid, **7a**, **7b** and **7c**. Treatment of **7** with lithium aluminum hydride in dry ether afforded the corresponding alcohol **8** (**8a**: 87% yield, **8b**: 97%, **8c**: 85%). Each alcohol **8** was treated with $SOCl_2$ in dry benzene at 50 °C for 2 h to afford the chloride **9** (**9a**: 75% yield, **9b**: 81%, **9c**: 74%). Subsequently, phthalimide (1 eq) was reacted with the Grignard reagent (2 eq) prepared from **9** with Mg in THF to afford the corresponding alcohol, which, without further purification, was treated with 15% HCl aqueous for 30 min at room temperature to afford **10** (**10a**: 43% yield, **10b**: 51%, **10c**: 14%). The structures of compounds **10a**, **10b** and **10c** were confirmed by analyses of their ^{1}H-NMR and IR spectra as described in the experimental section. The ^{1}H-NMR spectra of **10a**, **10b** and **10c** showed a characteristic doublet at 3.60—3.75 ppm due to methylene protons with a coupling constant of 7.7—8.4 Hz, a singlet at 3.79—3.90 due to methoxy protons, a triplet at 5.78—5.81 ppm due to the olefinic proton with a coupling constant of 7.7—8.4 Hz and a broad singlet at 8.12—9.32 ppm due to the amido proton. The IR spectra of **10** showed carbonyl absorption. Compounds **10** were treated with $AlBr_3$ in chlorobenzene under Ar at 95 °C for 2 h to afford **2** (**2a**: 31% yield, **2b**: 29%, **2c**: 32%). The structures of compounds **2a**, **2b** and **2c** were confirmed by analyses of the ^{1}H-NMR and IR spectra as described in the experimental section. The ^{1}H-NMR spectra of **2a**, **2b** and **2c** showed a characteristic doublet at 3.72—3.73 ppm due to methylene protons with a coupling constant of 8.0—8.3 Hz and a triplet at 5.86—5.87 ppm due to the olefinic proton with a coupling constant of 8.0—8.3 Hz. The IR spectra of **2** showed carbonyl and hydroxyl absorptions.

The inhibitory activity for U-46619-induced vasoconstriction of pig coronary artery was measured for **1a**, **1b**, **1c**, **2a**, **2b**, **2c**, **6a**, **6b**, **6c**, **10a**, **10b**, **10c**, 3-benzylidene-isoindolinone and 3-(2-phenylethylidene)isoindolinone. Of the 3-benzylideneisoindolinone derivatives (3-benzylideneisoindolinone, **6a**, **6b**, **6c**, **1a**, **1b**, **1c**), compounds **6a**, **6b** and **1b** exhibited similar activity to 3-benzylideneisoindolinone, whereas **6c**, **1a** and **1c** showed only weak activity. Of the 3-(2-phenylethylidene) isoindolinone derivatives [**10a**, **10b**, **10c**, **2a**, **2b**, **2c**, 3-(2-phenylethylidene)isoindolinone], the activities of **10a** and **10b** were greatly enhanced. Compounds **10c** and **2b** exhibited similar activity to 3-(2-phenylethylidene)isoindolinone, but **2a** and **2b** showed only weak ac-

tivity. Of all the compounds, **10a** and **10b** showed the most potent activity.

These results indicate that 3-(2-phenylethylidene)isoindolinone derivatives have higher activities than 3-benzylideneisoindolinone derivatives.

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 (*o* or *m*)-Methoxybenzyl Alcohol (4a, b) A solution of NaOH (3.5 g, 44.2 mmol) in H_2O (3.5 ml) was added in portions to a stirred solution of (*o* or *m*)-methoxybenzaldehyde (**3**) (4.0 g, 29.4 mmol), 37% formalin (3.1 g, 38.2 mmol) and methanol (40 ml) at 65 °C. The mixture was stirred at 70 °C for 1 h. After the mixture had cooled, H_2O was added, and the whole was extracted with $CHCl_3$ twice. The $CHCl_3$ extract was dried over $MgSO_4$ and concentrated *in vacuo* to give **4** as a colorless oil, which was used without further purification. The yields of *o*-methoxybenzyl alcohol **4a** and *m*-methoxybenzyl alcohol **4b** were 77 and 85%, respectively.

Preparation of (*o* or *m*)-Methoxybenzyl Chloride (5a, b) Thionyl chloride (2.2 g, 18.8 mmol) was added in portions to a stirred solution of (*o* or *m*)-methoxybenzyl alcohol (**4**) (2.0 g, 18.8 mmol) in dry benzene (10 ml) at 0 °C. The mixture was stirred for 2 h at 50 °C, then concentrated *in vacuo*. The resulting residual oily material was distilled *in vacuo* to give **5** as a colorless oil. The yields of *o*-methoxybenzyl chloride **5a** and *m*-methoxybenzyl chloride **5b** were 67 and 70%, respectively.

Preparation of 3-[(*o*, *m* or *p*)-Methoxybenzylidene]isoindolinone (6a—c) A solution of (*o*, *m* or *p*)-methoxybenzyl magnesium chloride was prepared by the usual method from **5** (1.5 g, 9.7 mmol) and Mg (0.26 g, 10.7 mg atom) in dry THF (5 ml). The solution was stirred at 50 °C for 1 h, then allowed to cool. Phthalimide (0.7 g, 4.8 mmol) in dry THF (20 ml) was gradually added to this Grignard reagent, then the mixture was 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 AcOEt 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 give **6**. The yields of **6a**, **6b** and **6c** were 16, 12 and 18%, respectively.

3-(*o*-Methoxybenzylidene)isoindolinone (**6a**): White powder from EtOH. mp 174—175 °C. IR (KBr): 1747 (C=O). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.18; H, 5.25; N, 5.59. ^{1}H-NMR: 3.94 (3H, s), 6.64 (1H, s), 6.94—7.89 (8H, m), 8.30 (1H, br s).

3-(*m*-Methoxybenzylidene)isoindolinone (**6b**): White powder from EtOH. mp 164—166 °C. IR (KBr): 1740 (C=O). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.22; H, 4.94; N, 5.46. ^{1}H-NMR: 3.81 (3H, s), 6.54 (1H, s), 6.86—7.90 (8H, m), 8.42 (1H, br s).

3-(*p*-Methoxybenzylidene)isoindolinone (**6c**): White powder from EtOH. mp 194—196 °C. IR (KBr): 1754 (C=O). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. ^{1}H-NMR: 3.86 (3H, s), 6.53 (1H, s), 6.96—7.90 (8H, m), 8.28 (1H, br s).

Preparation of 3-[(*o*, *m* or *p*)-Hydroxybenzylidene]isoindolinone (1a—c) Aluminum chloride (366 mg, 2.8 mmol) was added to a solution of **6** (300 mg, 1.2 mmol) in chlorobenzene (10 ml) under Ar, then the mixture was stirred at 10 °C for 15 min, and at 95 °C for 2 h. After the mixture had cooled, 2% HCl aqueous (50 ml) was added. The whole was extracted with AcOEt twice, and the extract was washed with 5% aqueous NaOH and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by PTLC with *n*-hexane–AcOEt (1 : 2) to afford **1**. The yields of **1a**, **1b** and **1c** were 9, 8 and 13%, respectively.

3-(*o*-Hydroxybenzylidene)isoindolinone (**1a**): White powder from EtOAc. Decomposition 300 °C. IR (KBr): 1682 (C=O), 3242 (OH). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. ^{1}H-NMR: 6.65 (1H, s), 6.79—7.99 (8H, m).

3-(*m*-Hydroxybenzylidene)isoindolinone (**1b**): White powder from EtOAc. mp 234—237 °C. IR (KBr): 1695 (C=O), 3417 (OH). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. ^{1}H-NMR: 6.62 (1H, s), 6.87—7.98 (8H, m).

3-(*p*-Hydroxybenzylidene)isoindolinone (**1c**): White powder from EtOAc. mp 245—248 °C. IR (KBr): 1678 (C=O), 3331 (OH). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. ^{1}H-NMR: 6.65 (1H, s), 6.80—7.94 (8H, m).

Preparation of (*o*, *m* or *p*)-Methoxyphenylethyl Alcohol (8a—c) A solution of (*o*, *m* or *p*)-methoxyphenylacetic acid (**7**) (8.0 g, 48 mmol) in dry ether (40 ml) was added in portions to a stirred solution of lithium aluminum hydride (2.3 g, 60 mmol) in dry ether (40 ml) at 0 °C. The mixture was refluxed for 30 min. It was cooled, then 10% $NaHCO_3$ aqueous (20 ml) was added at 0 °C, followed by 20% NaOH aqueous (10 ml). The precipitates were removed by suction and washed with a small quantity of ether. The combined filtrate was extracted with ether (30 ml × 2), then the extract and washings were dried over $MgSO_4$ and concentrated *in vacuo* to give **8** as a colorless oil, which was used without further purification. The yields of *o*-methoxyphenylethyl alcohol **8a**, *m*-methoxyphenylethyl alcohol **8b** and *p*-methoxyphenylethyl alcohol **8c** were 87, 87 and 85% respectively.

Preparation of (*o*, *m* or *p*)-Methoxyphenylethyl Chloride (9a—c) Thionyl chloride (6.5 g, 54.2 mmol) was added in portions to a stirred solution of (*o*, *m* or *p*)-methoxyphenylethyl alcohol (**8**) (6.4 g, 41.7 mmol) in dry benzene (10 ml) at 0 °C. The mixture was stirred for 2 h at 50 °C, then cooled, and concentrated *in vacuo*. The residual oily material was distilled *in vacuo* to give **9** as a colorless oil. The yields of *o*-methoxyphenylethyl chloride **9a**, *m*-methoxyphenylethyl chloride **9b** and *p*-methoxyphenylethyl chloride **9c** were 75, 81 and 75%, respectively.

Preparation of 3-[2-(*o*, *m* or *p*)-Methoxyphenylethylidene]isoindolinone (10a—c) A solution of (*o*, *m* or *p*)-methoxyphenylethyl magnesium chloride was prepared by the usual method from **9** (3.0 g, 17.6 mmol) and Mg (0.46 g, 19.3 mg atoms) in dry THF (10 ml). The Grignard reagent was stirred at 50 °C for 1 h and cooled. To this solution, a solution of phthalimide (1.3 g, 8.8 mmol) in dry THF (20 ml) was gradually added, then the mixture was stirred for 8 h at room temperature. Subsequently, 15% HCl aqueous (20 ml) was added at 0 °C. The reaction mixture was stirred for 30 min at room temperature, and extracted with AcOEt (30 ml × 2). The extract 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 **10**. The yields of **10a**, **10b** and **10c** were 43, 51 and 43%, respectively.

3-(2-*o*-Methoxyphenylethylidene)isoindolinone (**10a**): White powder from EtOH. mp 204—206 °C. IR (KBr): 1700 (C=O). *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.18; H, 5.25; N, 5.59. ^{1}H-NMR: 3.60 (2H, d, J=8.4 Hz), 3.90 (3H, s), 5.78 (1H, t, J=8.4 Hz), 6.89—7.85 (8H, m), 8.12 (1H, br s).

3-(2-*m*-Methoxyphenylethylidene)isoindolinone (**10b**): Pale yellow needles recrystallized from EtOH. mp 162—167 °C. IR (KBr): 1702 (C=O). *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.22; H, 5.61; N, 5.13. ^{1}H-NMR: 3.75 (2H, d, J=7.7 Hz), 3.79 (3H, s), 5.81 (1H, t, J=7.7 Hz), 6.77—7.66 (8H, m), 9.32 (1H, br s).

3-(2-*p*-Methoxyphenylethylidene)isoindolinone (**10c**): Pale yellow needles recrystallized from EtOH. mp 165—168 °C. IR (KBr): 1706 (C=O). *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.18; H, 5.25; N, 5.59. ^{1}H-NMR: 3.67 (2H, d, J=7.9 Hz), 3.80 (3H, s), 5.79 (1H, t, J=7.9 Hz), 6.85—7.89 (8H, m), 8.59 (1H, br s).

Preparation of 3-[2-(*o*, *m* or *p*)-Hydroxyphenylethylidene]isoindolinone (2a—c) Aluminum bromide (694 mg, 2.6 mmol) was added to a solution of **10** (300 mg, 1.1 mmol) in chlorobenzene (10 ml) under Ar, then the mixture was stirred at 10 °C for 15 min and at 95 °C for 2 h. It was cooled, then 2% HCl aqueous (50 ml) was added. The reaction mixture was extracted with AcOEt (40 ml × 2), and the extract was washed with 5% aqueous NaOH (20 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by PTLC with *n*-hexane–AcOEt (1 : 2) to afford **2**. The yields of **2a**, **2b** and **2c** were 31, 29 and 32%, respectively.

3-(2-*o*-Hydroxyphenylethylidene)isoindolinone (**2a**): White powder recrystallized from EtOAc. mp 157—160 °C. IR (KBr): 1690 (C=O), 3239 (OH). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. ^{1}H-NMR: 3.72 (2H, d, J=8.3 Hz), 5.87 (1H, t, J=8.3 Hz), 6.70—7.71 (8H, m).

3-(2-*m*-Hydroxyphenylethylidene)isoindolinone (**2b**): White powder recrystallized from EtOAc. mp 176—178 °C. IR (KBr): 1680 (C=O), 3300 (OH). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. ^{1}H-NMR: 3.73 (2H, d, J=8.1 Hz), 5.86 (1H, t, J=8.1 Hz), 6.59—7.81 (8H, m).

3-(2-*p*-Hydroxyphenylethylidene)isoindolinone (**2c**): White powder recrystallized from EtOAc. mp 184—185 °C. IR (KBr): 1674 (C=O), 3203 (OH). *Anal.* Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.18; N, 5.51. ^{1}H-NMR: 3.72 (2H, d, J=8.0 Hz), 5.86 (1H, t, J=8.0 Hz), 6.59—7.82 (8H, m).

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