Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 14 (2006) 7625–7651
Bioorganic & Medicinal Chemistry

# Design, synthesis, and evaluation of cyclic amide/imide-bearing hydroxamic acid derivatives as class-selective histone deacetylase (HDAC) inhibitors

Chihiro Shinji,[a] Satoko Maeda,[b] Keisuke Imai,[c] Minoru Yoshida,[b,d] Yuichi Hashimoto[a] and Hiroyuki Miyachi[a,*]

[a]*Institute of Molecular and Cellular Biosciences, The University of Tokyo, Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan*
[b]*RIKEN, Saitama 351-0198, Japan*
[c]*Lead Discovery Research Labs., Astellas Pharma Inc., 21 Miyukigaoka, Tsukuba-shi, Ibaraki 305-8585, Japan*
[d]*CREST Research Project, Japan Science and Technology Agency, Saitama 332-0012, Japan*

Received 18 May 2006; revised 30 June 2006; accepted 1 July 2006
Available online 31 July 2006

**Abstract**—A series of hydroxamic acid derivatives bearing a cyclic amide/imide group as a linker and/or cap structure, prepared during our structural development studies based on thalidomide, showed class-selective potent histone deacetylase (HDAC)-inhibitory activity. Structure–activity relationship studies indicated that the steric character of the substituent introduced at the cyclic amide/imide nitrogen atom, the presence of the amide/imide carbonyl group, the hydroxamic acid structure, the shape of the linking group, and the distance between the zinc-binding hydroxamic acid group and the cap structure are all important for HDAC-inhibitory activity and class selectivity. A representative compound (**30w**) showed potent p21 promoter activity, comparable with that of trichostatin A (TSA), and its cytostatic activity against cells of the human prostate cell line LNCaP was more potent than that of the well-known HDAC inhibitor, suberoylanilide hydroxamic acid (SAHA).


## 1. Introduction

Reversible acetylation of the side-chain amino groups of specific histone lysine residues plays an important function in modifying chromatin structure and regulating gene expression. The key enzymes that modify histone proteins and regulate gene expression are histone acetyltransferases (HATs) and histone deacetylases (HDACs).[1,2] Both of these acetylating/deacetylating enzymes are included in large protein complexes containing other proteins that are known to function in transcriptional activation and/or repression.[3,4] Such complexes are recruited to specific regions in the DNA and induce expression and/or silencing of the genes. Many recent studies have shown that inhibition of HDAC elicits anticancer effects in several lines of tumor cells by inhibiting cell growth and inducing apoptosis. A well-known target that is upregulated by HDAC is $p21^{WAF1/CIP1}$, which is a cyclin-dependent kinase (CDK) inhibitor that inhibits the kinase activities of a class of CDKs, leading to cell cycle arrest and dephosphorylation of Rb.[5] Much evidence suggests that $p21^{WAF1/CIP1}$ plays an important role in determining the fate of cells during growth and differentiation. Therefore, compounds that inhibit HDAC activity may depress expression of the $p21^{WAF1/CIP1}$ gene, resulting in antiproliferative and antitumor effects.[6] Natural and synthetic HDAC inhibitors have been studied extensively (see Fig. 1).

Numerous biological studies indicated that HDACs are heterogeneous, consisting of 18 isozymes, which can be categorized into four classes (class I, class IIa, class IIb, and class III). Class I and class II HDACs are zinc-containing amidehydrolases, and class III HDAC consists of NAD-dependent amidehydrolase. The biological function and distribution of each class of HDACs have been extensively studied from a molecular-pharmacological viewpoint, but much remains to be learnt. Although some class-selective HDAC inhibitors are known, most of the reported HDAC inhibitors

*Keywords*: HDAC; HDAC inhibitor; Cyclic amide; Class selectivity; Hydroxamic acid.
* Corresponding author. E-mail: miyachi@iam.u-tokyo.ac.jp

0968-0896/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2006.07.008

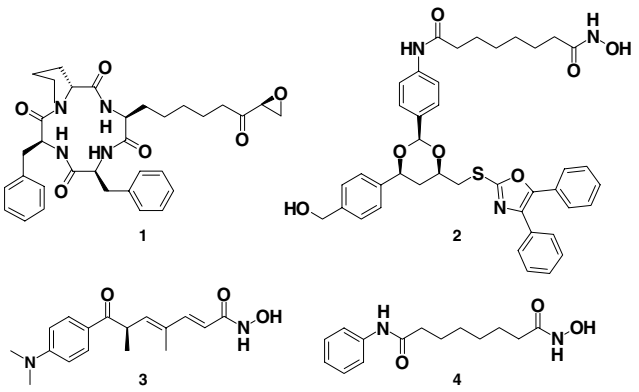


**Figure 1.** Structures of representative natural HDAC inhibitors (**1** (trapoxin A), **3** (TSA)), and synthetic HDAC inhibitors (**2** (tubacin), **4** (SAHA)).

are non-class-selective, pan-inhibitors, and little is known about the structure–activity relationships associated with class selectivity.

We have been engaged in structural development studies of the multi-drug template thalidomide for the creation of structurally novel drug leads[7–12] and have already reported the design and synthesis of potent HDAC inhibitors with phthalimide structure.[13] In this paper, we report the design, synthesis, and structure–activity relationship of novel HDAC inhibitors containing a cyclic amide/imide structure. The in vitro p21 promoter activity and cytostatic effects on the human prostate cancer cell LNCaP of representative compounds are also described.

## 2. Chemistry

Synthetic routes to the present series of cyclic amide derivatives are outlined in Charts 1–7. Selective reduction of one (*para*) carbonyl group of the phthalimide hydroxamic acid derivative (**5**) afforded **6**, then $BH_3$ reduction, followed by PDC oxidation, gave the *N*-benzyl-6-formyl-2,3-dihydroisoindole-1-one derivative (**8**). Compound (**8**) was treated with Horner–Emmons reagent in the presence of base, and subsequent alkaline hydrolysis afforded the cinnamic acid derivative (**10**). Compound (**10**) was condensed with *O*-(tetrahydro-2*H*-pyran-2yl)hydroxylamine via the mixed anhydride to give the protected *N*-hydroxybenzamide derivative (**11**). Deprotection of **11** under acidic conditions afforded the *N*-hydroxybenzamide derivative (**12**) (Chart 1). Regioisomeric isoindolone-hydroxamic acid derivatives were prepared from 4-nitro-2-methylbenzoic acid (**13**). Compound (**13**) was etherified, brominated and treated with benzylamine to afford the cyclic amide derivative (**16**). Compound (**16**) was reduced with 10% Pd on carbon, followed by Meerwein arylation reaction, strong base treatment and alkaline hydrolysis to afford the cinnamic acid derivative (**20**). Compound (**20**) was derivatized to hydroxamic acid (**22**) by means of procedures similar to those employed for the preparation of compound (**12**) (Chart 2).

Our earlier study indicated the importance of the *meta* position carbonyl group of phthalimide hydroxamic acid derivatives. However, the synthetic route depicted in Chart 2 is not convenient for the preparation of various types of amide nitrogen substituents, since the substituents are introduced at the first step of the sequence. Therefore, we tried to develop another route that would be suitable for incorporating diverse amide substituents. This route is outlined in Chart 3. Methyl (or *tert*-butyl) 2-methyl-5-amino benzoate (**23**) was subjected to Meerwein arylation reaction, followed by strong base treatment to afford the methyl (or *tert*-butyl) cinnamate derivatives (**25**). Compound (**25**) was brominated, and treated with various kinds of benzylamines, followed by alkaline hydrolysis to afford various cinnamic acid derivatives (**28**). Compounds (**28**) were condensed with *tert*-butylhydroxylamine or *O*-(tetrahydro-2*H*-pyran-2yl)hydroxylamine by means of the mixed anhydride method to give protected *N*-hydroxybenzamide derivatives (**29**). Deprotection of **29** under acidic conditions

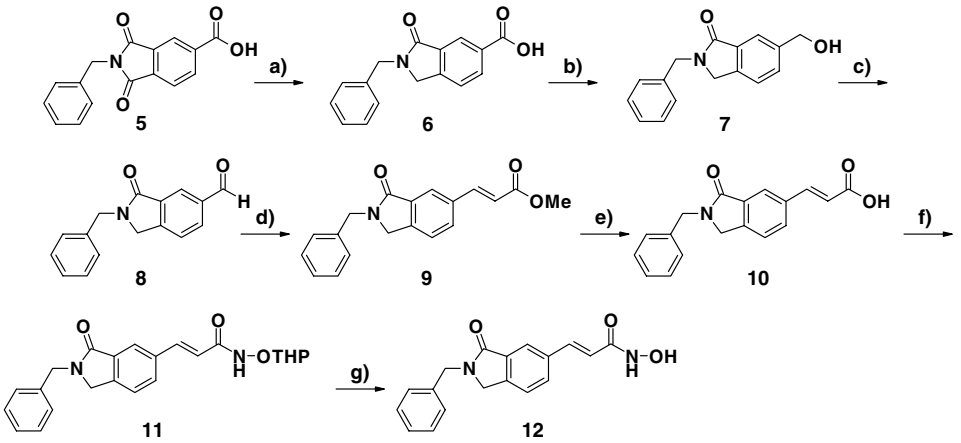


**Chart 1.** Reagents and conditions: (a) Sn, cHCl, AcOH, reflux; (b) $BH_3$, THF, 0 °C; (c) $MnO_2$, $CH_2Cl_2$, rt; (d) $(EtO)_2POCH_2CO_2Me$, *t*-BuOK, THF, rt; (e) 1 mol/L NaOH, MeOH, 50 °C; (f) 1—ethyl chloroformate, triethylamine, THF, 0 °C; 2—*O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine, rt, MeOH; (g) CSA, MeOH, rt.

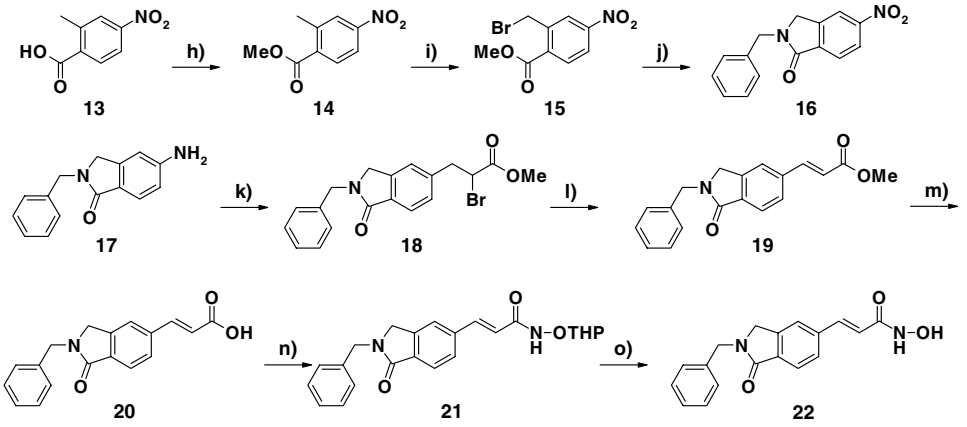



**Chart 2.** Reagents and conditions: (h) MeI, $K_2CO_3$, DMF, rt; (i) NBS, benzoyl peroxide, $CCl_4$, reflux; (j) benzylamine, TEA, MeOH, reflux.; (k) 10% Pd–C, $H_2$, AcOEt, rt.; (k) 1—$NaNO_2$, 47% HBr, acetone, MeOH, <5 °C; 2—methyl acrylate, $Cu_2O$, 35–40 °C; (l) DBU, toluene, reflux; (m) 0.8 mol/L HCl, AcOH, reflux; (n) 1—ethyl chloroformate, TEA, *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine, THF, 0 °C-rt; (o) CSA, MeOH, rt.

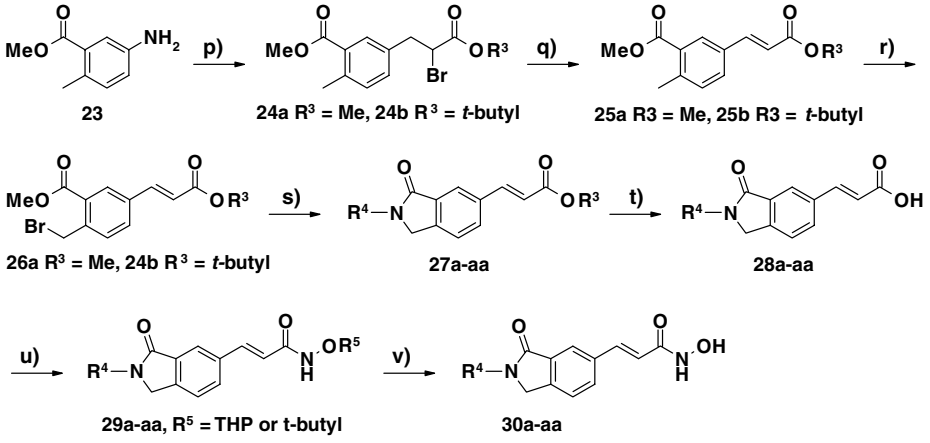



**Chart 3.** Reagents and conditions: (p) 1—$NaNO_2$, 47% HBr, acetone, MeOH, <5 °C; 2—methyl acrylate, $Cu_2O$, 35–40 °C; (q) DBU, toluene, reflux; (r) NBS, benzoyl peroxide, $CCl_4$, reflux; (s) benzylamine, TEA, MeOH, reflux; (t) 0.8 mol/L HCl, AcOH, reflux; (u) 1—ethyl chloroformate, triethylamine, THF, 0 °C; 2—$NH_2OTHP$ (or $NH_2OC(CH_3)_3$), MeOH, rt; (v) CSA, MeOH, rt.

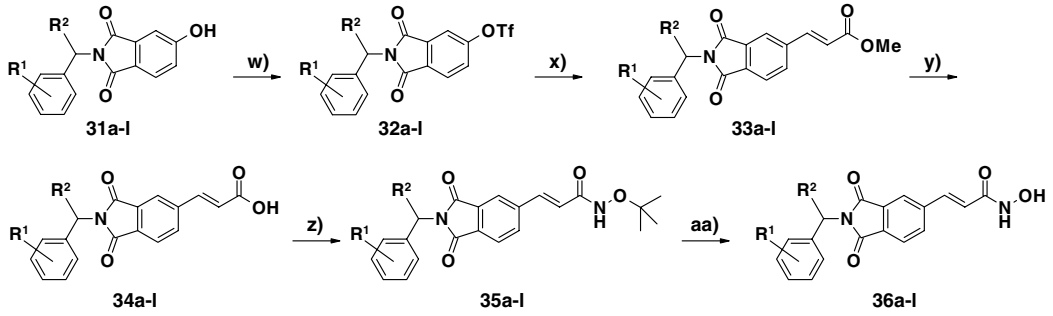



**Chart 4.** Reagents and conditions: (w) trifluoromethanesulfonic anhydride, triethylamine, toluene, rt; (x) methyl acrylate, $(P(Ph)_3)_2PdCl_2$, triethylamine, DMF, reflux; (y) 0.5 mol/L HCl, AcOH, reflux; (z) 1—ethyl chloroformate, triethylamine, THF 0 °C; 2—*tert*-butylhydroxylamine, MeOH, rt; (aa) trifluoroacetic acid, $CH_2Cl_2$, rt.

afforded the desired *N*-hydroxybenzamide derivatives (**30**) (Chart 3).

As previously described,[13] 5-hydroxyphthalimide derivatives (**31**) were treated with trifluoromethanesulfonic anhydride to give the Heck reaction substrates (**32**). Compounds (**32**) were treated with methyl acrylate in the presence of $(P(Ph)_3)_2PdCl_2$ and triethylamine in *N*,*N*-dimethylformamide, and then alkaline hydrolysis afforded the cinnamic acid derivatives (**34**). Compounds (**34**) were condensed with *tert*-butylhydroxylamine by means of the mixed anhydride method to give protected

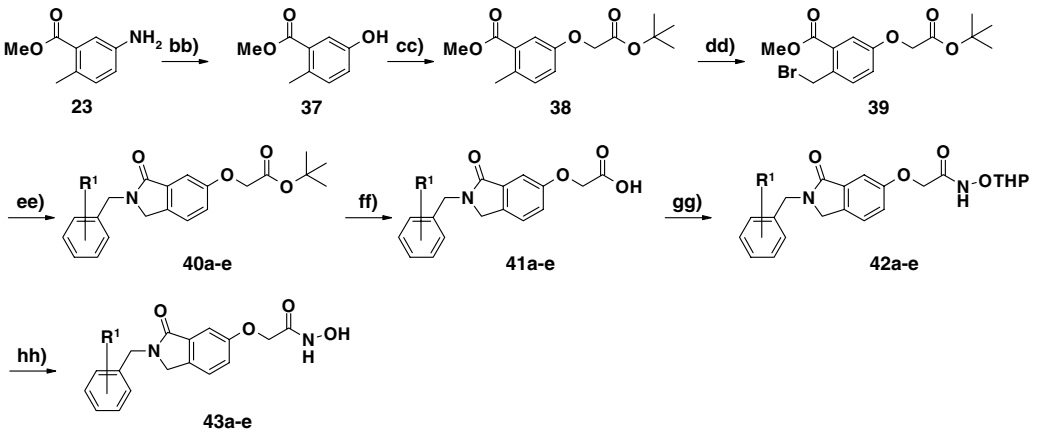



**Chart 5.** Reagents and conditions: (bb) 1—$NaNO_2$, 47% HBr, acetone, MeOH, <5 °C; 2—$Cu_2O$, $H_2O$, reflux; (cc) 1—*tert*-bromoacetoacetate, $K_2CO_3$, acetone, reflux; (dd) NBS, benzoyl peroxide, $CCl_4$, reflux; (ee) substituted benzylamine, TEA, MeOH, reflux; (ff) TFA, rt; (gg) 1—ethyl chloroformate, triethylamine, THF, 0 °C; 2—*O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine, THF, 0 °C-rt. (hh) CSA, MeOH, rt.

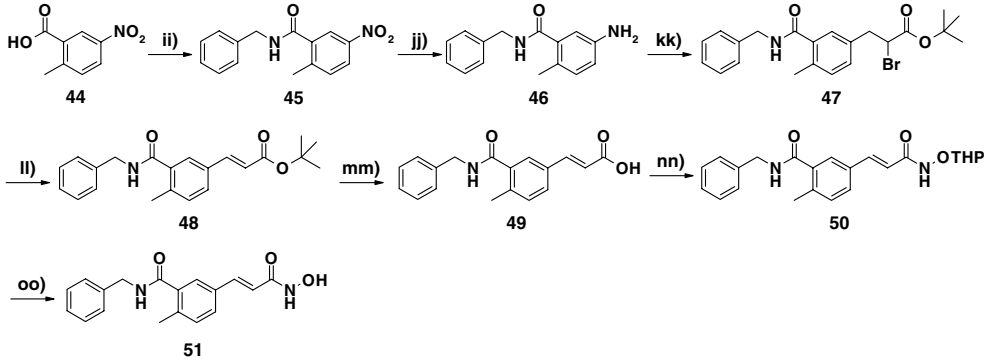



**Chart 6.** Reagents and conditions: (ii) benzylamine, DMC, TEA, THF, 0 °C; (jj) $H_2$, 10% Pd–C, AcOET, rt; (kk) 1—$NaNO_2$, 47% HBr, acetone, MeOH, <5 °C; 2—*tert*-butyl acrylate, $Cu_2O$, 35–40 °C; (ll) DBU, toluene, reflux; (mm) TFA, rt; (nn) 1—ethyl chloroformate, triethylamine, THF 0 °C; 2—*O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine, THF, rt; (oo) CSA, MeOH, rt.

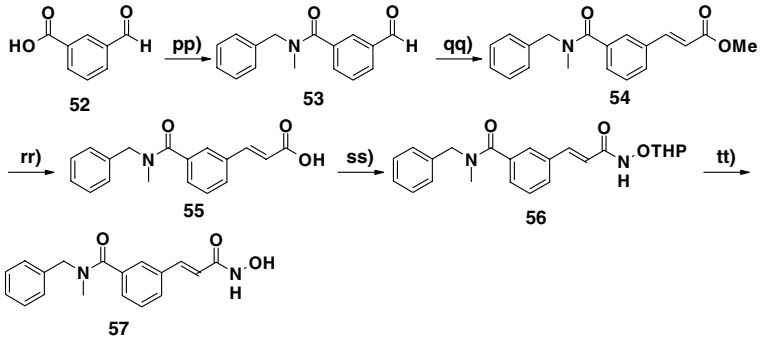



**Chart 7.** Reagents and conditions: (pp) benzylamine, DMC, TEA, THF, 0 °C; (qq) $(EtO)_2POCH_2CO_2Me$, *t*-BuOK, THF, rt; (rr) dil NaOH, MeOH, 60 °C; (ss) 1—ethyl chloroformate, triethylamine, THF, 0 °C; 2—*O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine, THF, rt; (tt) CSA, MeOH, rt.

*N*-hydroxybenzamide derivatives (**35**). Deprotection of the *tert*-butyl group of **35** under acidic conditions afforded the *N*-hydroxybenzamide derivatives (**36**) (Chart 4). Hydroxymethyl-linker derivatives (**43**) were prepared starting from methyl 2-methyl 5-aminobenzoate (**23**). Compound (**23**) was subjected to Sandmeyer reaction and subsequent treatment with *tert*-butyl bromoacetate to afford compound (**38**). This was brominated and treated with substituted benzylamines, then alkaline hydrolysis afforded the phenoxyacetic acid derivatives (**41**). Compounds (**41**) were derivatized to the desired hydroxamic acids (**43**) by means of the procedures similar to those employed for the preparation of compounds (**12**) (Chart 5).

To examine the importance of the cyclic amide (isoindolone) structure, two structural types of acyclic amide derivatives, one with the C–N bond disconnected and

the other with the C–C bond disconnected, were prepared as depicted in Charts 6 and 7. 2-Methyl-5-nitrobenzoic acid (**44**) was amidated with benzylamine, and subsequent reduction afforded *N*-benzyl 5-amino-2-methylbenzamide (**46**). Compound (**46**) was subjected to Meerwein arylation reaction, strong base treatment, and subsequent alkaline hydrolysis to afford the cinnamic acid derivative (**49**). Compound (**49**) was derivatized to the desired C-N bond disconnected-type hydroxamic acid (**51**) by means of the procedures described above (Chart 6). The 3-formylbenzoic acid (**52**) was amidated with *N*-methylbenzylamine, followed by Wittig–Horner–Emmons reaction and subsequent alkaline hydrolysis to afford the cinnamic acid (**55**). Compound (**55**) was derivatized to the desired C–C bond disconnected-type hydroxamic acid (**57**) by means of the procedures described above (Chart 7).

## 3. Pharmacological results and discussion

X-ray crystallographic analysis of histone deacetylase-like protein (HDLP)[14] and HDAC 8,[15] complexed with trichostatin A (TSA, **3**)[16] and/or suberoylanilide hydroxamic acid (SAHA, **4**),[17] has revealed that the HDAC catalytic domain consists of a narrow tube-like pocket spanning a length equivalent to a straight chain of four to six carbons, with the zinc ion buried near the bottom of the active site. Therefore, the structural requirements for potent HDAC-inhibitory activity involve three key regions, that is, (1) a zinc-binding motif, which interacts with the active site zinc, (2) a linking domain, which occupies the channel, and (3) a surface recognition domain, which interacts with residues on the rim of the active site. Previously we have reported novel HDAC inhibitors based on a new structural scaffold.[13] We used a phthalimide structure as a novel linker/cap domain that might be suitable to occupy the narrow channel of the HDAC active site. We expected that the introduction of an aromatic ring might lead to favorable interaction with the side chains of aromatic amino acids located at the active site. Therefore, we prepared compounds of general formula (**I**) and found that the lead compound (**II**) is a potent non-class-selective HDAC inhibitor, as assessed with an HDAC inhibitor assay kit. The potency of compound (**II**) was comparable with that of SAHA, which is under phase III clinical trial (Fig. 2).

We next focused our attention on the phthalimide carbonyl groups of the lead compound (**II**). We considered that reduction of one of the carbonyl groups to methylene might afford a more potent HDAC inhibitor, because most of the amino acids located around the tube-like region of the HDAC active pocket are hydrophobic. At the beginning of our current study, we planned to synthesize the desired compound by selective reduction of the lead compound (**II**) with tin in an acidic medium, but unfortunately, the reduction did not proceed regioselectively, and a 1:1 mixture of regioisomeric decarbonyl products was obtained. Fortunately, however, the regioisomeric mixture exhibited more potent HDAC-inhibitory activity than the imide lead (**II**), as assessed with the HDAC inhibitor assay kit (data not shown). Therefore, we prepared both regioisomers specifically via the synthetic routes depicted in Charts 1 and 2. The assay results indicated that the *meta* position carbonyl group is important, that is, compound (**12**) was about 3 times more potent than the regioisomer (**22**). Furthermore, cyclic amide/imide structure was important for potent HDAC-inhibitory activity, because the acyclic amide derivatives **51** and **57** exhibited decreased HDAC inhibitory activity (Fig. 3). Molecular modeling studies of compounds **12** and **22** complexed with HDAC 8[18] indicated that there might be a weak hydrogen-bonding interaction between the *meta* position carbonyl group of **12** and the α-nitrogen of 151Gly, while there is no apparent interaction between the *para* position carbonyl group of compound **22** and the HDAC8 backbone (Fig. 4). This molecular modeling study also indicated that the benzene ring of **12** and **22**, fused to the cyclic amide skeleton, exhibits a π–π stacking interaction with the side-chain benzyl group of 208Phe of HDAC8. The amino acids 151Gly and 208Phe are both well conserved in HDACs. Therefore, compound **12** was expected to exhibit potent HDAC-inhibitory activity for all classes of HDAC.

We selected the new HDAC lead **12** for further study, and performed chemical modifications, focusing on the cyclic amide nitrogen substituents, in order to examine the relationship of structure to HDAC class-selective inhibition. The results are summarized in Tables 1 and 2. We selected HDAC 1, HDAC4, and HDAC6 as representatives of class I, class IIa, and class IIb, respectively, because sufficient amounts of these isozymes were

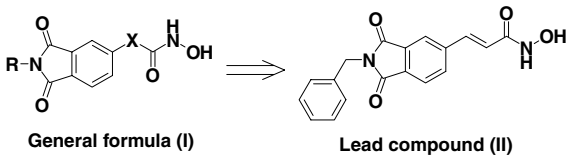



**Figure 2.** Chemical structures of our HDAC inhibitors.

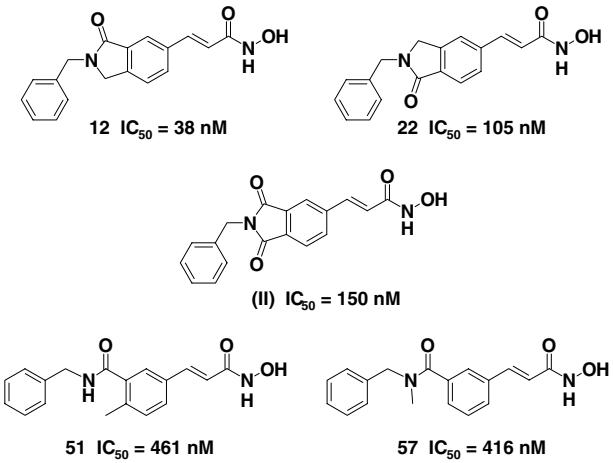



**Figure 3.** Chemical structures of our HDAC inhibitors with cyclic and/or acyclic amide.

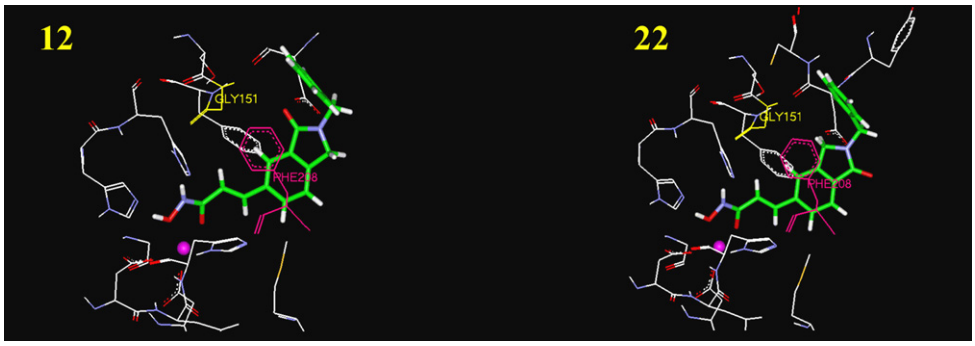
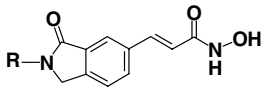



**Figure 4.** Docking model structures of **12** and **22** into the HDAC8 binding pocket (see text).

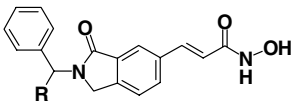
**Table 1.** HDAC-inhibitory activity of the prepared compounds



| Compound | R | Inhibitory activity ($EC_{50}$ (nM)) | | |
|---|---|---|---|---|
| | | HDAC 1[a] | HDAC 4[b] | HDAC 6[c] |
| **12** | Benzyl | 250 ± 30 | 300 ± 30 | 180 ± 30 |
| **30a** | 2-Phenylethyl | 520 ± 20 | 610 ± 20 | 420 ± 30 |
| **30b** | 3-Phenylpropyl | 240 ± 10 | 260 ± 8 | 340 ± 10 |
| **30c** | Cyclohexylmethyl | 520 ± 20 | 610 ± 20 | 420 ± 30 |
| **30d** | 1-Naphthylmethyl | 200 ± 6 | 230 ± 7 | 410 ± 30 |
| **30e** | (2-Cl)Benzyl | 640 ± 70 | 500 ± 9 | 450 ± 40 |
| **30f** | (3-Cl)Benzyl | 240 ± 40 | 190 ± 50 | 360 ± 60 |
| **30g** | (4-Cl)Benzyl | 890 ± 90 | 570 ± 40 | 1480 ± 590 |
| **30h** | (2-$CF_3$)Benzyl | 400 ± 20 | 390 ± 4 | 280 ± 30 |
| **30i** | (3-$CF_3$)Benzyl | 170 ± 7 | 230 ± 20 | 250 ± 20 |
| **30j** | (4-$CF_3$)Benzyl | 320 ± 30 | 230 ± 30 | 640 ± 20 |
| **30k** | (2-MeO)Benzyl | 440 ± 30 | 590 ± 20 | 350 ± 30 |
| **30l** | (3-MeO)Benzyl | 150 ± 10 | 160 ± 70 | 250 ± 40 |
| **30m** | (4-MeO)Benzyl | 160 ± 10 | 99 ± 11 | 300 ± 80 |
| **30n** | (2-Me)Benzyl | 430 ± 30 | 480 ± 50 | 350 ± 40 |
| **30o** | (3-Me)Benzyl | 250 ± 30 | 300 ± 30 | 290 ± 30 |
| **30p** | (4-Me)Benzyl | 200 ± 20 | 240 ± 20 | 500 ± 10 |
| **30q** | (2-Ph)Benzyl | 1310 ± 220 | 630 ± 50 | 420 ± 50 |
| **30r** | (3-Ph)Benzyl | 330 ± 50 | 180 ± 20 | 590 ± 70 |
| **30s** | (4-Ph)Benzyl | 220 ± 30 | 98 ± 6 | 750 ± 110 |
| **30t** | (2-*t*Bu)Benzyl | 480 ± 60 | 500 ± 80 | 490 ± 20 |
| **30u** | (4-*t*Bu)Benzyl | 230 ± 20 | 180 ± 4 | 990 ± 20 |

[a–c]Assays for inhibitory activities toward partially purified HDAC1, 4, and 6 were perfomed according to the reported methods.[19,21]

**Table 2.** HDAC-inhibitory activity of the prepared compounds



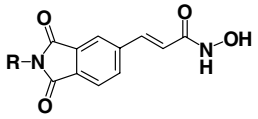
| Compound | R | Inhibitory activity ($EC_{50}$ (nM)) | | |
|---|---|---|---|---|
| | | HDAC 1[a] | HDAC 4[b] | HDAC 6[c] |
| **30v** | Phenyl | 630 ± 40 | 560 ± 20 | 350 ± 90 |
| **30w** | Benzyl | 190 ± 30 | 150 ± 20 | 250 ± 30 |
| **30x** | 2-Phenylethyl | 270 ± 40 | 230 ± 10 | 370 ± 50 |
| **30y** | 3-Phenylpropyl | 420 ± 60 | 240 ± 20 | 370 ± 20 |
| **30z** | (*S*)-Benzyloxymethyl | 250 ± 30 | 220 ± 20 | 460 ± 90 |
| **30aa** | (*R*)-Benzyloxymethyl | 250 ± 5 | 230 ± 30 | 230 ± 30 |

[a–c]See footnotes a–c in Table 1.

available for our purpose. We first examined the effect of the distance between the distal benzene ring and amide nitrogen atom (**12**, **30a**, **30b**, and **30d**) and the importance of the aromatic ring (**30c**). Neither the methylene chain length nor the presence of the aromatic ring was critical, because all the compounds exhibited similar inhibitory activity to each of the HDACs. Therefore, we focused our attention on the effects of substituents introduced on the distal benzene ring (Table 1). Broadly speaking, a substituent at the *meta* position is preferable for HDAC-inhibitory activity, whether it is electron-withdrawing (**30e–j**) or electron-donating (**30k–p**). This might mean that steric factors are more important than electronic factors for the activity. In the cases of HDAC1 and HDAC4, there seemed to be a tendency for the introduction of an electron-donating group to enhance the inhibitory activity. For HDAC6, the introduction of a substituent at the *ortho* position tended to increase the inhibitory activity, while the introduction of a substituent at the *para* position tended to decrease the activity. These results again suggested that steric factor(s) are important. We anticipated that the introduction of a bulky substituent at the *ortho* position might afford HDAC6 selectivity, while the introduction of a bulky substituents at the *para* position might afford HDAC1/4 selectivity. In order to test this hypothesis, we prepared phenyl-substituted and *tert*-butyl-substituted derivatives, and found that the 4-phenyl derivative and the 4-*tert*-butyl derivative (**30s**, **30u**) exhibited apparent HDAC1/4 selectivity. However, the contribution of the bulkiness of the *ortho*-substituent was unclear (**30q**, **30t**).

In order to examine further the SAR for the *para* substituent, we prepared cyclic amide derivatives with branched substituents at the amide nitrogen (Table 2), but these compounds all exhibited non-class-selective pan-HDAC inhibitory activity. This might indicate that highly specific steric features are needed for HDAC class selectivity. Among these compounds, however, the *N*-(1,2-diphenylethyl) derivative (**30w**) was found to exhibit potent pan-HDAC inhibitory activity, and was used for further biological studies. Although our earlier study indicated that the isoindolone skeleton is better than the phthalimide skeleton for potent HDAC inhibitors, there was little information on the HDAC class selectivity of the phthalimide derivatives, and it is also of interest to compare the class selectivity in these two structural series, so we re-investigated the HDAC-inhibitory activity of the phthalimide derivatives (Table 3). As a whole, these phthalimide derivatives tended to show some preference for HDAC4. Compound **30h**, with an optically active, (*S*) form branched substituent, exhibited the most HDAC4-selective inhibitory activity. When we compared compounds in the isoindolone series bearing the same substituents, the isoindolone and phthalimide derivatives exhibited equipotent HDAC4-inhibitory activity, while the phthalimide derivatives exhibited somewhat lower inhibitory activities toward HDAC1 and HDAC6, implying that the phthalimide skeleton might impart a degree of HDAC4 selectivity. Possibly the distal carbonyl group of phthalimide derivatives, which could be positioned outside of the surface recognition domain, has an unfavorable steric or electronic interaction with HDAC1 and HDAC6. Although we have proposed that the cap structure is the primary determinant for HDAC class selectivity, the above results suggest that the linker structure, which connects the cap structure and the zinc binding motif, is also important for class selectivity. Therefore, we prepared hydroxymethyl derivatives as another type of linker (phenoxyacetamides), which was considered to be a bioisoster of a double bond (cinnamamides) (Table 4). It is very interesting to note that although our lead compound, the cinnamamide derivative **12**, exhibited non-class-selective pan-HDAC-inhibitory activity, the phenoxyacetamide derivative **43a** exhibited HDAC6-selective inhibitory activity, that is, **43a** exhibited equipotent HDAC6-inhibitory activity with **12**, while its HDAC1- and HDAC4-inhibitory activity was about 10-fold less. We speculated that the linker structure of **12** might interact more favorably with the narrow tube-like pocket of both HDAC1 and HDAC4, as compared with **43a**. Although the HDAC class-inhibitory

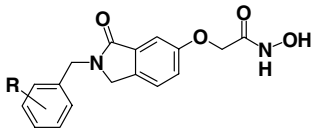
**Table 3.** HDAC-inhibitory activity of the prepared compounds




| Compound | R | Inhibitory activity ($EC_{50}$ (nM)) | | |
|---|---|---|---|---|
| | | HDAC 1[a] | HDAC 4[b] | HDAC 6[c] |
| **36a** | Phenyl | 2310 ± 280 | 900 ± 60 | 1010 ± 190 |
| **36b** | Benzyl | 530 ± 20 | 360 ± 20 | 710 ± 30 |
| **36c** | 2-Phenylethyl | 1130 ± 220 | 440 ± 30 | 610 ± 40 |
| **36d** | Diphenylmethyl | N.T.[d] | N.T.[d] | N.T.[d] |
| **36e** | 2,2-Diphenylethyl | 2640 ± 160 | 910 ± 2 | 1370 ± 250 |
| **36f** | (*S*)-α-Methylbenzyl | 1760 ± 290 | 640 ± 90 | 1080 ± 100 |
| **36g** | (*R*)-α-Methylbenzyl | 4040 ± 580 | 1300 ± 100 | 2070 ± 330 |
| **36h** | (*S*)-α-(Benzyloxymethyl)benzyl | 1160 ± 210 | 270 ± 30 | 1230 ± 250 |
| **36i** | (*R*)-α-(Benzyloxymethyl)benzyl | 1510 ± 90 | 530 ± 80 | 1460 ± 150 |

[a–c]See footnotes a–c in Table 1.
[d] N.T. means not tested.

**Table 4.** HDAC-inhibitory activity of the prepared compounds



| Compound | R | Inhibitory activity ($EC_{50}$ (nM)) | | |
|---|---|---|---|---|
| | | HDAC 1[a] | HDAC 4[b] | HDAC 6[c] |
| **36f** | Phenyl | N.T. | N.T. | N.T. |
| **36g** | (*S*)-Methyl | 1760 ± 290 | 640 ± 90 | 1080 ± 100 |
| **36h** | (*R*)-Methyl | 4040 ± 580 | 1300 ± 10 | 2070 ± 330 |
| **36i** | (*S*)-Benzyloxymethyl | 1160 ± 210 | 270 ± 30 | 1230 ± 250 |
| **36j** | (*R*)-Benzyloxymethyl | 1510 ± 90 | 530 ± 80 | 1460 ± 150 |

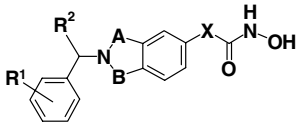
[a–c]See footnotes a–c in Table 1.

profiles of **12** and **43a** are quite different, it is interesting that the influence of a substituent introduced on the benzene ring of *N*-benzyl group appears to be the same. That is, the introduction of a bulky phenyl group or *tert*-butyl group at the *ortho* position (**43b**, **43d**) increased HDAC6-inhibitory activity. However, the introduction of a phenyl group or *tert*-butyl group at the *para* position (**43c**, **43e**) specifically increased HDAC1- and HDAC4-inhibitory activity, causing these compounds to become pan-inhibitors of HDAC.

Our SAR study clearly indicated that the structural features of not only the cap part, but also the linker part of HDAC inhibitors are critical for HDAC class-selective inhibitory activity. Further chemical modification studies combined with X-ray crystallographic and/or molecular modeling studies should make it possible to discover novel low-molecular-weight, class-selective HDAC inhibitors.

As mentioned above, HDAC inhibitors have been reported to upregulate the expression of $p21^{WAF1/CIP1}$ and to downregulate cyclin D1 in many types of tumor cells, in parallel with cell cycle arrest in the G1 phase. Activation of the $p21^{WAF1/CIP1}$ gene is associated with the inhibition of proliferation and induction of differentiation and/or apoptosis of tumor cells, in vitro and in vivo.[5,6] Therefore, we examined the ability of representative compounds of the present series to upregulate the expression of $p21^{WAF1/CIP1}$, by means of reporter gene assay (Table 5).[19] Among the basic structures (lead (**II**), **12**, **22**, and **43a**), compound **12** was found to exhibit the most potent activity. Although the rank order of the activity was **12** > **22** > lead

**Table 5.** p21 promoter-activating activity and LNCaP cell growth-inhibitory activity of representative compounds



| Compound | $R^1$ | $R^2$ | A | B | X | p21 promoter assay LNCaP growth inhibition | |
|---|---|---|---|---|---|---|---|
| | | | | | | $EC_{1000}$ (nM)[a] | $IC_{50}$ (nM)[b] |
| Lead (II) | H | H | CO | CO | CH=CH | 3290 ± 640 | 40% (@10 μM) |
| **12** | H | H | CO | $CH_2$ | CH=CH | 230 ± 80 | 100 |
| **22** | H | H | $CH_2$ | CO | CH=CH | 1460 ± 310 | 690 |
| **30q** | 2-Phenyl | H | CO | $CH_2$ | CH=CH | 870 ± 260 | 886 |
| **30s** | 4-Phenyl | H | CO | $CH_2$ | CH=CH | 180 ± 110 | 101 |
| **30l** | 3-MeO | H | CO | $CH_2$ | CH=CH | 140 ± 50 | 108 |
| **30m** | 4-MeO | H | CO | $CH_2$ | CH=CH | 130 ± 60 | 131 |
| **30i** | 3-$CF_3$ | H | CO | $CH_2$ | CH=CH | 130 ± 10 | 202 |
| **30w** | H | Benzyl | CO | $CH_2$ | CH=CH | 96 ± 21 | 75 |
| **36k** | H | (*S*)-Benzyloxymethyl | CO | CO | CH=CH | 1730 ± 920 | 570 |
| **43a** | H | H | CO | $CH_2$ | O–$CH_2$ | 8160 ± 880 | 7000 |
| SAHA | | | | | | N.T.[c] | 161 |
| TSA | | | | | | 12 ± 5 | 17 |

[a] Assay for P21 promoter activation was performed according to the reported methods.[19,21]

[b] Exponentially growing cells in RPMI1640 medium supplemented with 10% fetal bovine serum were adjusted to $2 \times 10^4$ cells/mL and 100 μL aliquots were plated in 96-well plates and incubated for 24 h at 37 °C under an atmosphere of 5% $CO_2$ in air. After incubation, various concentrations of test compounds were added and incubation was continued for a further 4 days. Viable cells were counted with a cell counting kit (Dojindo). $n = 3$.

[c] N.T. means not tested.

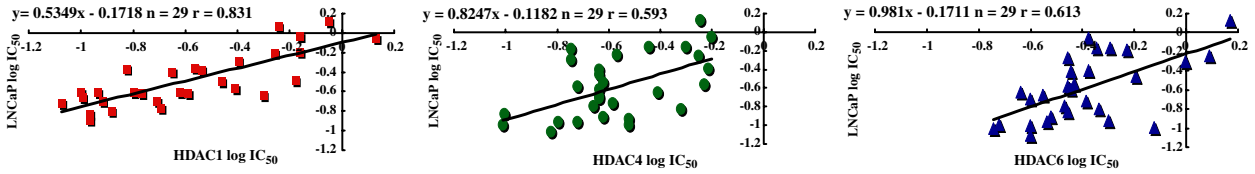



**Figure 5.** Correlation between LNCaP cell growth-inhibitory activity and HDAC-inhibitory activity (left, HDAC1; middle, HDAC4; right, HDAC6). Horizontal bars indicate the $IC_{50}$ values (log(μM)) for LNCaP cell growth inhibition. Vertical bars indicate the $IC_{50}$ values (log(μM)) for inhibition of representatives of each HDAC class.

(**II**) > **43a**, all the compounds exhibited micromolar to sub-micromolar values of $EC_{1000}$ for p21 expression upregulation activity. The reason for this is not known at present, but differences in the ability of the compounds to penetrate the cell membrane might be involved, at least to some extent. Among the compounds tested, we found that **30w** exhibited the most potent activity, being comparable in potency to the natural product TSA. These results indicated that compounds of the present series exhibit significant HDAC-inhibitory activity not only in vitro, but also at the cellular level. Therefore, we further examined their inhibitory activity on the growth of the human prostate cancer cell line LNCaP. These results are also summarized in Table 5. The rank order of effect was similar to that noted above, and compound **12** was the most potent among the lead (**II**), **12**, **22**, and **43a**. Compound **30w** was the most potent in the present series of compounds. Its LNCaP growth-inhibitory activity was more potent than that of SAHA, which is currently under phase III clinical evaluation, and comparable with that of TSA. As can be seen in Table 5, compound **30s**, which exhibited HDAC1/4-selective inhibitory activity, showed potent LNCaP cell growth-inhibitory activity, while compounds **36k** (HDAC4-selective), **30q**, and **43a** (both HDAC6-selective) showed weak LNCaP cell growth-inhibitory activity. Since inhibitory activity toward LNCaP cell growth might be associated with inhibition of a certain class of HDAC, possibly class I, we investigated the correlation between the LNCaP cell growth-inhibitory activity and the HDAC class selectivity of our compounds by means of multivariate analysis.

The values of the correlation coefficients between the LNCaP cell growth-inhibitory activity and the inhibitory activities toward HDAC1, HDAC4, and HDAC6 were $r = 0.831$, $r = 0.593$, and $r = 0.613$, respectively (Fig. 5). That is, the LNCaP cell growth inhibition was most highly correlated with HDAC1 inhibition. Furthermore, we found a strong correlation between LNCaP cell growth inhibition and p21 promoter activity (correlation coefficient $r = 0.752$). We therefore speculated that the mechanism of LNCaP cell growth inhibition by our compounds may involve HDAC1 class-selective inhibition, and subsequent transcriptional augmentation of p21 expression, at least in part. To seek support for this idea, we examined the dose dependency and the time courses of both the LNCaP cell growth inhibition and the degree of expression increase of p21, using **30w** (Figs. 6 and 7). The p21 gene expression

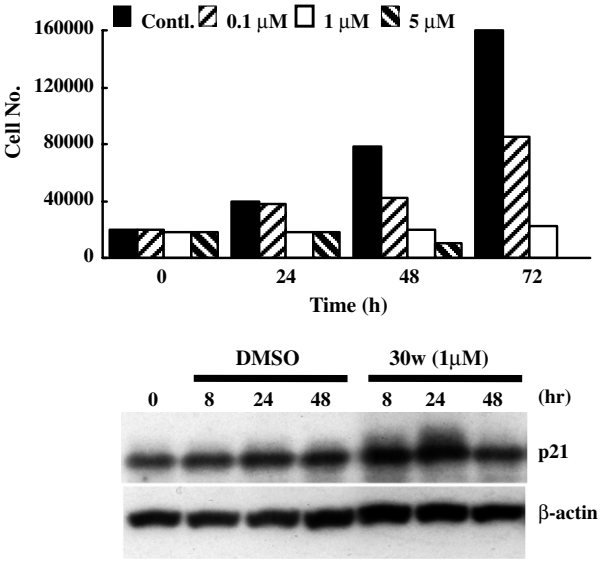



**Figure 7.** Time courses of LNCaP cell growth inhibition and augmentation of p21 message expression by **30w**.

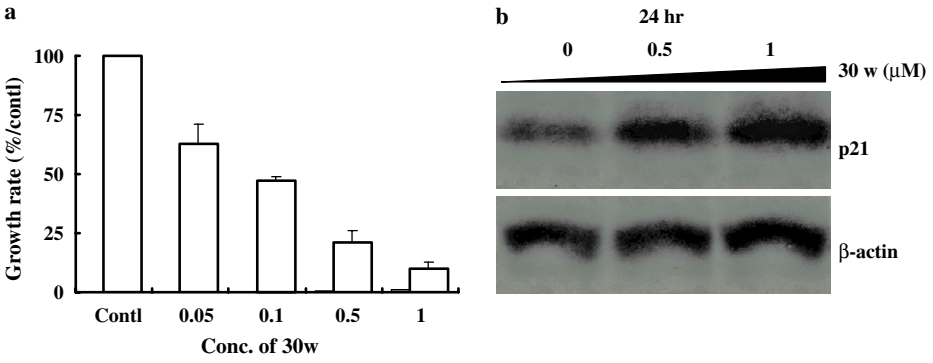



**Figure 6.** Dose dependency of LNCaP cell growth inhibition (a) and augmentation of p21 message expression (b) by **30w**.

of LNCaP cells was augmented after exposure of the cells to compound **30w** for 8 h, and reached the maximum after 24 h. Inhibition of LNCaP cell growth was also observed after treatment with **30w** for 24 h. This evidence strongly suggests that the enhancement of p21 expression is involved in the initial inhibition of LNCaP cell growth by **30w**.

## 4. Conclusion

We have designed and synthesized various structural types of cyclic amide/imide HDAC inhibitors, which show characteristic HDAC class-selective inhibition. SAR study indicated that both the cap structure and the linker structure of the present series of compounds are critical for HDAC class-selective inhibition. Further chemical modification studies based on our present SAR should provide even more potent and more class-selective HDAC inhibitors. Representative compounds of the present series are potent HDAC inhibitors, effective at the cellular level, so these compounds should be useful not only as selective tools to investigate the function(s) of each HDAC class, but also as lead (or candidate) compounds for the treatment of HDAC-related diseases, which include cancer, cranial nerve disease, immune disorders, and so on.

## 5. Experimental

### 5.1. General

Melting points were determined by using a Yanagimoto hot-stage melting point apparatus and are uncorrected. NMR spectra were recorded on a JEOL JNM-GX500 (500 MHz) spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane. Mass spectra were recorded on a JEOL JMS-DX303 spectrometer.

**5.1.1. 2-Benzyl-3-oxoisoindoline-5-carboxylic acid (6).** Compound **5** (461 mg) and Sn (523 mg, 4.41 mmol) were suspended in a mixture of 5 mL of concentrated (concd) HCl and 5 mL of glacial acetic acid and stirred for 9 h at room temperature. The reaction mixture was filtered through Celite and extracted with AcOEt. The extract was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant $CHCl_3$) to afford 282 mg (66%) of the title compound as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.68 (d, 1H, $J$ = 1.5 Hz), 8.28 (dd, 1H, $J$ = 1.5, 8.0 Hz,), 7.50 (d, 1H, $J$ = 8.0 Hz), 7.33 (m, 5H), 4.84 (s, 2H), 4.35 (s, 2H); FAB MS $m/z$ 268 $(M+H)^+$.

**5.1.2. 2-Benzyl-6-hydroxymethyl-isoindoline-1-one (7).** To a mixture of **6** (282 mg, 1.06 mmol) and 5 mL of anhydrous THF was added dropwise 2.35 mL of 1 mol/L $BH_3$–THF complex, and the whole was stirred for 1 day at room temperature. To the mixture were added 3 mL of water and 870 mg of $K_2CO_3$, and the mixture was washed with saturated (satd) $NaHCO_3$ solution, dilute (dil) HCl, and brine, then dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant $CHCl_3$) to afford 145 mg (54%) of the title compound as an oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.83 (s, 1H), 7.48 (d, 1H, $J$ = 7.7 Hz), 7.27 (m, 6H), 4.74 (s, 4H), 4.18 (s, 2H); FAB MS $m/z$ 254 $(M+H)^+$.

**5.1.3. 2-Benzyl-3-oxoisoindoline-5-carbaldehyde (8).** A mixture of **7** (191 mg, 0.75 mmol), PCC (230 mg, 1.07 mmol), and 10 mL of $CH_2Cl_2$ was stirred for 1 h at room temperature under Ar. The reaction mixture was filtered through Celite, and the filtrate was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt 1:1 v/v) to afford 142 mg (76%) of the title compound as an oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.05 (s, 1H), 8.31 (s, 1H), 8.02 (d, 1H, $J$ = 7.9 Hz), 7.49 (d, 1H, $J$ = 7.9 Hz), 7.27 (m, 5H), 4.77 (s, 2H), 4.31 (s, 2H); FAB MS $m/z$ 252 $(M+H)^+$.

**5.1.4. (*E*)-Methyl 3-(2-benzyl-1-oxoisoindolin-6-yl)acrylate (9).** A mixture of methyl diethylphosphonoacetate (0.11 mL, 0.61 mmol), *t*-BuOK (68 mg, 0.61 mmol), and 10 mL of anhydrous THF was stirred for 10 min at room temperature, then **8** (140 mg, 0.56 mmol) in 3 mL of anhydrous THF was added, and stirring was continued for a further 4 h at room temperature. The reaction mixture was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt 1:1 v/v) to afford 54 mg (31%) of the title compound as an oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.05 (d, 1H, $J$ = 1.2 Hz), 7.74 (d, 1H, $J$ = 6.1 Hz), 7.64 (dd, 1H, $J$ = 1.2, 7.9 Hz), 7.39 (d, 1H, $J$ = 7.9 Hz), 7.30 (m, 5H), 6.52 (d, 1H, $J$ = 6.1 Hz), 4.80 (s, 2H), 4.28 (s, 2H), 3.81 (s, 3H); FAB MS $m/z$ 308 $(M+H)^+$.

**5.1.5. (*E*)-3-(2-Benzyl-1-oxoisoindolin-6-yl)acrylic acid (10).** A mixture of **9** (160 mg, 0.52 mmol), 8 mL of glacial acetic acid, and 8 mL of 0.5 mol/L of HCl was stirred overnight at 85 °C. The mixture was extracted with AcOEt, and the extract was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated to afford 149 mg (98%) of the title compound as a colorless solid. $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 7.99 (d, 1H, $J$ = 1.5 Hz), 7.80 (dd, 1H, $J$ = 1.5, 7.9 Hz), 7.75 (d, 1H, $J$ = 6.1 Hz), 7.53 (d, 1H, $J$ = 7.9 Hz,), 7.31 (m, 5H), 6.58 (d, 1H, $J$ = 6.1 Hz), 4.80 (s, 2H), 4.38 (s, 2H); FAB MS $m/z$ 294 $(M+H)^+$.

**5.1.6. (*E*)-3-(2-Benzyl-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (11).** To a mixture of **10** (60 mg, 0.27 mmol), triethylamine (0.086 mL, 0.819 mmol) and 5 mL of anhydrous THF was added ethyl chloroformate (0.029 mL, 0.41 mmol) at 0 °C, and the whole was stirred for 1 h. Then, *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine (53 mg, 0.45 mmol) was added and stirring was continued for 4 h at room temperature. The reaction mixture was washed with satd $NaHCO_3$, dil HCl, and brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/

AcOEt 1:3 v/v) to afford 52 mg (49%) of the title compound as an oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.98 (s, 1H), 7.72 (d, 1H, $J$ = 5.5 Hz), 7.71 (d, 1H, $J$ = 7.9 Hz), 7.53 (d, 1H, $J$ = 7.9 Hz), 7.28 (m, 5H), 6.52 (d, 1H, $J$ = 5.5 Hz), 5.05 (m, 1H), 4.77 (s, 2H), 4.24 (s, 2H), 3.99 (m, 1H), 3.61 (m, 1H), 1.81 (m, 3H), 1.55 (m, 3H); FAB MS $m/z$ 393 $(M+H)^+$.

**5.1.7. (*E*)-3-(2-Benzyl-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (12).** A mixture of **11** (26 mg, 0.066 mmol), *d*-10-camphorsulfonic acid (18 mg, 0.073 mmol), and 5 mL of methanol was stirred for 1 h at room temperature under Ar. After evaporation of the solvent, the residue was redissolved in AcOEt, then the solution was washed with satd $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was recrystallized from a mixed solvent of acetone, ethanol, and AcOEt to afford 1.6 mg (7.9%) of the title compound. Mp 172–174 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.77 (s, 1H), 9.09 (s, 1H), 7.86 (s, 1H), 7.76 (d, 1H, $J$ = 7.3 Hz), 7.57 (d, 1H, $J$ = 7.3 Hz), 7.53 (d, 1H, $J$ = 5.8 Hz), 7.35 (m, 2H), 7.28 (m, 3H), 6.56 (d, 1H, $J$ = 5.8 Hz), 4.72 (s, 2H), 4.38 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{18}H_{17}N_2O_3$, 309.1239. Found: 309.1259.

**5.1.8. Methyl 2-methyl-4-nitrobenzoate (14).** A mixture of 2-methyl-4-nitrobenzoic acid (1.00 g, 5.5 mmol), iodomethane (863 mg, 6.08 mmol), $K_2CO_3$ (1.14 g, 8.28 mmol), and 10 mL of DMF was stirred for 2 h at room temperature, then poured into water and extracted with AcOEt. The extract was washed with water and brine, dried over anhydrous $MgSO_4$, and evaporated to afford 1.05 g (98%) of the title compound as an oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.11 (s, 1H), 8.07 (d, 1H, $J$ = 8.6 Hz), 8.03 (d, 1H, $J$ = 8.6 Hz), 3.95 (s, 3H), 2.69 (s, 3H); FAB MS $m/z$ 196 $(M+H)^+$.

**5.1.9. Methyl 2-bromomethyl-4-nitrobenzoate (15).** A mixture of **14** (985 mg, 5.05 mmol), NBS (989 mg, 5.56 mmol), benzoyl peroxide (15 mg, 0.06 mmol), and 20 mL of carbon tetrachloride was heated at 85 °C for 8 h. Further NBS (92 mg, 0.52 mmol) was added and the whole was refluxed for 1 h. The mixture was washed with satd $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt 3:1 v/v) to afford 1.35 g (98%) of the title compound as an oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.30 (d, 1H, $J$ = 2.1 Hz), 8.20 (dd, 1H, $J$ = 2.1, 6.2 Hz), 8.10 (d, 1H, $J$ = 6.2 Hz), 4.96 (s, 2H), 4.00 (s, 3H); FAB MS $m/z$ 273, 275 $(M+H)^+$.

**5.1.10. 2-Benzyl-5-nitroisoindolin-1-one (16).** A mixture of **15** (300 mg, 1.10 mmol), benzylamine (0.13 mL, 1.21 mmol), triethylamine (0.17 mL, 1.21 mmol), and 10 mL of methanol was refluxed for 24 h. The mixture was diluted with AcOEt, washed with dil HCl and brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt 3:1 to 1:1 v/v) to afford 255 mg (86%) of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.35 (d, 1H, $J$ = 8.2 Hz), 8.25 (s, 1H), 8.04 (d, 1H, $J$ = 8.2 Hz), 7.32 (m, 5H), 4.83 (s, 2H), 4.38 (s, 2H); FAB MS $m/z$ 269 $(M+H)^+$.

**5.1.11. 5-Amino-2-benzylisoindolin-1-one (17).** A mixture of **16** (180 mg, 0.67 mmol), 10% Pd–C (18 mg), and 10 mL AcOEt was hydrogenated at room temperature for 6 h. The catalyst was removed by filtration through Celite and the filtrate was evaporated to afford 131 mg (82%) of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.63 (d, 1H, $J$ = 8.0 Hz), 7.26 (m, 5H), 6.67 (dd, 1H, $J$ = 1.5, 8.0 Hz), 6.56 (d, 1H, $J$ = 1.5 Hz), 4.72 (s, 2H), 4.11 (s, 2H), 3.73 (s, 2H); FAB MS $m/z$ 239 $(M+H)^+$.

**5.1.12. Methyl 3-(2-benzyl-1-oxoisoindolin-5-yl)-2-bromopropanoate (18).** A mixture of **17** (270 mg, 1.13 mmol), 3 mL of 47% HBr, 6 mL of methanol, and 15 mL of acetone was cooled to below 5 °C, and sodium nitrite solution (94 mg/3 mL) was added dropwise. After 30 min, methyl acrylate (1.01 ml, 11.3 mmol) was added and the whole was heated rapidly to 40 °C. $Cu_2O$ (10 mg, 0.068 mmol) was added portionwise and the whole was stirred for 7 h at 35–40 °C. The reaction mixture was evaporated and the residue was redissolved in AcOEt, washed with dil NaOH, dil HCl and brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt 6:1 to 4:1 v/v) to afford 90 mg (21%) of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.79 (d, 1H, $J$ = 7.9 Hz), 7.28 (m, 6H), 7.20 (s, 1H), 4.74 (s, 2H), 4.37 (dd, 1H, $J$ = 7.3 Hz, 8.0 Hz), 4.20 (s, 2H), 3.68 (s, 3H), 3.49 (dd, 1H, $J$ = 7.3 Hz, 4.3 Hz), 3.27 (dd, 1H, $J$ = 7.3 Hz, 4.3 Hz); FAB MS $m/z$ 432, 434 $(M+H)^+$.

**5.1.13. (*E*)-Methyl 3-(2-benzyl-1-oxoisoindolin-5-yl) acrylate (19).** A mixture of **18** (90 mg, 0.23 mmol), DBU (0.042 mL, 0.28 mmol), and 10 mL of toluene was refluxed for 5 h. The reaction mixture was evaporated and the residue was redissolved in AcOEt. This solution was washed with dil HCl and brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt 1.5:1 v/v) to afford 68 mg (96%) of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.82 (d, 1H, $J$ = 7.5 Hz), 7.68 (d, 1H, $J$ = 6.0 Hz), 7.58 (d, 1H, $J$ = 7.5 Hz), 7.46 (s, 1H), 7.26 (m, 5H), 6.45 (d, 1H, $J$ = 6.0 Hz), 4.76 (s, 2H), 4.24 (s, 2H), 3.77 (s, 3H); FAB MS $m/z$ 308 $(M+H)^+$.

**5.1.14. (*E*)-3-(2-Benzyl-1-oxoisoindolin-5-yl)acrylic acid (20).** This compound was prepared from **19** by means of a procedure similar to that used for **10** (97%). $^1$H NMR (500 MHz, $CD_3OD$) $\delta\delta$ 7.82 (d, 1H, $J$ = 8.0 Hz), 7.75 (s, 1H), 7.74 (d, 1H, $J$ = 8.0 Hz), 7.73 (d, 1H, $J$ = 6.5 Hz), 7.31 (m, 5H), 6.58 (d, 1H, $J$ = 6.5 Hz), 4.81 (s, 2H), 4.40 (s, 2H); FAB MS $m/z$ 294 $(M+H)^+$.

**5.1.15. (*E*)-3-(2-Benzyl-1-oxoisoindolin-5-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (21).** This compound was prepared from **20** by means of a procedure similar to that used for **11** (52%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.18 (s, 1H), 7.81 (d, 1H, $J$ = 7.9 Hz), 7.72 (d, 1H,

$J$ = 5.5 Hz), 7.55 (d, 1H, $J$ = 7.9 Hz), 7.41 (s, 1H), 7.26 (m, 5H), 6.46 (d, 1H, $J$ = 5.5 Hz), 5.00 (m, 1H), 4.76 (s, 2H), 4.22 (s, 2H), 3.95 (m, 1H), 3.61 (m, 1H), 1.80 (m, 3H), 1.56 (m, 3H); FAB MS $m/z$ 393 $(M+H)^+$.

**5.1.16. (*E*)-3-(2-Benzyl-1-oxoisoindolin-5-yl)-*N*-hydroxyacrylamide (22).** This compound was prepared from **21** by means of a procedure similar to that used for **12** (68%). Mp 186–188 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 11.33 (s, 1H), 9.08 (s, 1H), 7.73 (d, 1H, $J$ = 8.0 Hz), 7.72 (s, 1H), 7.67 (d, 1H, $J$ = 8.0 Hz), 7.52 (d, 1H, $J$ = 5.8 Hz), 7.35 (m, 2H), 7.28 (m, 3H), 6.54 (d, 1H, $J$ = 5.8 Hz), 4.72 (s, 2H), 4.38 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{18}H_{17}N_2O_3$, 309.1239. Found: 309.1259.

**5.1.17. Methyl 5-(2-(methoxycarbonyl)-2-bromoethyl)-2-methylbenzoate (24a; R$^3$ = Me).** This compound was prepared from **23** by means of a procedure similar to that used for **18** (40%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.76 (s, 1H), 7.25 (d, 1H, $J$ = 8.0 Hz), 7.19 (d, 1H, $J$ = 8.0 Hz), 4.39 (dd, 1H, $J$ = 7.3, 8.0 Hz), 3.89 (s, 3H), 3.74 (s, 3 H), 3.45 (dd, 1H, $J$ = 8.0, 14.0 Hz), 3.23 (dd, 1H, $J$ = 7.3, 14.0 Hz), 2.57 (s, 3H); FAB MS $m/z$ 315, 317 $(M+H)^+$.

**5.1.18. Methyl 5-(2-(*tert*-butoxycarbonyl)-2-bromoethyl)-2-methylbenzoate (24b; R$^3$ = *tert*-butyl).** This compound was prepared from **23** and *tert*-butyl acrylate by means of a procedure similar to that used for **18** (35%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.84 (d, 1H, $J$ = 1.5 Hz), 7.33 (dd, 1H, $J$ = 1.5, 7.6 Hz), 7.25 (d, 1H, $J$ = 7.6 Hz), 4.35 (dd, 1H, $J$ = 7.0, 8.2 Hz), 3.48 (dd, 1H, $J$ = 8.2, 14.3 Hz), 3.25 (dd, 1H, $J$ = 7.0, 14.3 Hz), 3.95 (s, 3H), 2.64 (s, 3H), 1.49 (s, 9H); FAB MS $m/z$ 357, 359 $(M+H)^+$.

**5.1.19. (*E*)-Methyl 5-(2-(methoxycarbonyl)vinyl)-2-methylbenzoate (25a; R$^3$ = Me).** This compound was prepared from **24a** by means of a procedure similar to that used for **19** (quant.). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.06 (d, 1H, $J$ = 1.8 Hz), 7.67 (d, 1H, $J$ = 5.9 Hz), 7.53 (dd, 1H, $J$ = 1.8, 8.0 Hz), 7.26 (d, 1H, $J$ = 8.0 Hz), 6.45 (d, 1H, $J$ = 5.9 Hz), 3.91 (s, 3H), 3.80 (s, 3H), 2.61 (s, 3H); FAB MS $m/z$ 235 $(M+H)^+$.

**5.1.20. Methyl 5-(2-(*tert*-butoxycarbonyl)vinyl)-2-methylbenzoate (25b; R$^3$ = *tert*-butyl).** This compound was prepared from **24b** by means of a procedure similar to that used for **19** (50%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.84 (d, 1H, $J$ = 1.5 Hz), 7.33 (dd, 1H, $J$ = 1.5, 7.6 Hz), 7.25 (d, 1H, $J$ = 7.6 Hz), 4.35 (dd, 1H, $J$ = 7.0, 8.2 Hz), 3.48 (dd, 1H, $J$ = 8.2, 14.3 Hz), 3.25 (dd, 1H, $J$ = 7.0, 14.3 Hz), 3.95 (s, 3H), 2.64 (s, 3H), 1.49 (s, 9H); FAB MS $m/z$ 357, 359 $(M+H)^+$.

**5.1.21. (*E*)-Methyl 5-(2-(methoxycarbonyl)vinyl)-2-bromomethylbenzoate (26a; R$^3$ = Me).** This compound was prepared from **25a** by means of a procedure similar to that used for **15** (49%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.08 (d, 1H, $J$ = 1.8 Hz), 7.63 (d, 1H, $J$ = 5.9 Hz), 7.59 (dd, 1H, $J$ = 1.8, 8.0 Hz), 7.45 (d, 1H, $J$ = 8.0 Hz), 6.47 (d, 1H, $J$ = 5.9 Hz), 4.92 (s, 2H), 3.94 (s, 3H), 3.79 (s, 3H); FAB MS $m/z$ 313, 315 $(M+H)^+$.

**5.1.22. (*E*)-Methyl 5-(2-(*tert*-butoxycarbonyl)vinyl)-2-bromomethylbenzoate (26b; R$^3$ = *tert*-butyl).** This compound was prepared from **25b** by means of a procedure similar to that used for **15** (36%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.10 (d, 1H, $J$ = 1.8 Hz), 7.60 (dd, 1H, $J$ = 1.8, 8.3 Hz), 7.56 (d, 1H, $J$ = 6.2 Hz), 7.47 (d, 1H, $J$ = 8.3 Hz), 6.42 (d, 1H, $J$ = 6.2 Hz), 4.95 (s, 2H), 3.96 (s, 3H), 1.54 (s, 9H); FAB MS $m/z$ 355, 357 $(M+H)^+$.

**5.1.23. (*E*)-Methyl 3-(1-oxo-2-phenethylisoindolin-6-yl)acrylate (27a).** This compound was prepared from **26a** by means of a procedure similar to that used for **16** (11%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.03 (d, 1H, $J$ = 1.2 Hz), 7.76 (d, 1H, $J$ = 5.8 Hz), 7.65 (dd, 1H, $J$ = 1.2, 7.6 Hz), 7.40 (d, 1H, $J$ = 7.6 Hz), 7.27 (m, 5H), 6.53 (d, 1H, $J$ = 5.8 Hz), 4.23 (s, 2H), 3.90 (t, 1H, $J$ = 7.3 Hz), 3.84 (s, 3H), 3.03 (t, 2H, $J$ = 7.3 Hz); FAB MS $m/z$ 322 $(M+H)^+$.

**5.1.24. (*E*)-Methyl 3-(1-oxo-2-(3-phenylpropyl)isoindolin-6-yl)acrylate (27b).** This compound was prepared from **26a** by means of a procedure similar to that used for **16** (85%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.00 (d, 1H, $J$ = 1.5 Hz), 7.74 (d, 1H, $J$ = 5.9 Hz), 7.64 (dd, 1H, $J$ = 1.5, 7.9 Hz), 7.43 (d, 1H, $J$ = 7.9 Hz), 7.26 (m, 2H), 7.18 (m, 3 H), 6.52 (d, 1H, $J$ = 5.9 Hz), 4.36 (s, 2H), 3.81 (s, 3H), 3.67 (t, 2H, $J$ = 7.3 Hz), 2.69 (t, 2H, $J$ = 7.8 Hz), 1.99 (m, 2H); FAB MS $m/z$ 336 $(M+H)^+$.

**5.1.25. (*E*)-*tert*-Butyl 3-(2-(cyclohexylmethyl)-1-oxoisoindolin-6-yl)acrylate (27c).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (66%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.98 (d, 1H, $J$ = 1.5 Hz), 7.65 (d, 1H, $J$ = 6.2), 7.64 (dd, 1H, $J$ = 1.5, 7.9 Hz), 7.43 (d, 1H, $J$ = 7.9 Hz), 6.45 (d, 1H, $J$ = 6.2), 4.39 (s, 2H), 3.45 (d, $J$ = 7.4 Hz, 2H), 1.71 (m, 5H), 1.54 (s, 9H), 1.20 (m, 6H); FAB MS $m/z$ 356 $(M+H)^+$.

**5.1.26. (*E*)-*tert*-butyl 3-(2-((naphthalene-1-yl)methyl)-1-oxoisoindolin-6-yl)acrylate (27d).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (66%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.22 (d, 1H, $J$ = 7.7 Hz), 8.05 (s, 1H), 7.87 (d, 1H, $J$ = 9.2 Hz), 7.85 (d, 1H, $J$ = 8.8 Hz), 7.61 (d, 1H, $J$ = 5.8 Hz), 7.59 (d, 1H, $J$ = 7.9 Hz), 7.50 (m, 4H), 7.29 (d, 1H, $J$ = 7.9 Hz), 6.45 (d, 1H, $J$ = 5.8 Hz), 5.26 (s, 2H), 4.15 (s, 2H), 1.54 (s, 9H); FAB MS $m/z$ 400 $(M+H)^+$.

**5.1.27. (*E*)-Methyl 3-(2-(2-chlorobenzyl)-1-oxoisoindolin-6-yl)acrylate (27e).** This compound was prepared from **26a** by means of a procedure similar to that used for **16** (70%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.05 (s, 1H), 7.75 (d, 1H, $J$ = 5.9 Hz), 7.66 (d, 1H, $J$ = 7.6 Hz), 7.42 (d, 1H, $J$ = 7.6 Hz), 7.40 (m, 1H), 7.34 (m, 1H), 7.24 (m, 2H), 6.52 (d, 1H, $J$ = 5.9 Hz), 4.96 (s, 2H), 4.36 (s, 2H), 3.82 (s, 3H); FAB MS $m/z$ 342 $(M+H)^+$.

**5.1.28. (*E*)-Methyl 3-(2-(3-chlorobenzyl)-1-oxoisoindolin-6-yl)acrylate (27f).** This compound was prepared from **26a** by means of a procedure similar to that used for **16** (71%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.05 (d, 1H,

$J$ = 1.5 Hz), 7.75 (d, 1H, $J$ = 6.1 Hz), 7.65 (dd, 1H, $J$ = 1.5, 7.9 Hz), 7.42 (d, 1H, $J$ = 7.9 Hz), 7.27 (m, 3H), 7.19 (m, 1H), 6.53 (d, 1H, $J$ = 6.1 Hz), 4.77 (s, 2H), 4.30 (s, 2H), 3.82 (s, 3H); FAB MS $m/z$ 342 $(M+H)^+$.

**5.1.29. (*E*)-Methyl 3-(2-(4-chlorobenzyl)-1-oxoisoindolin-6-yl)acrylate (27g).** This compound was prepared from **26a** by means of a procedure similar to that used for **16** (87%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.05 (d, 1H, $J$ = 1.2 Hz), 7.75 (d, 1H, $J$ = 5.9 Hz), 7.66 (dd, 1H, $J$ = 1.2, 8.0 Hz), 7.41 (d, 1H, $J$ = 8.0 Hz), 7.31 (d, 2H, $J$ = 8.3 Hz), 7.24 (d, 2H, $J$ = 8.3 Hz), 6.53 (d, 1H, $J$ = 5.9 Hz), 4.78 (s, 2H), 4.28 (s, 2H), 3.82 (s, 3H); FAB MS $m/z$ 342 $(M+H)^+$.

**5.1.30. (*E*)-*tert*-Butyl 3-(2-(2-(trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl)acrylate (27h).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (69%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.04 (s, 1H), 7.67 (d, 1H, $J$ = 7.6 Hz), 7.65 (d, 1H, $J$ = 7.9 Hz), 7.64 (d, 1H, $J$ = 6.2 Hz), 7.49 (dd, 1H, $J$ = 7.6, 7.6 Hz), 7.42 (d, 1H, $J$ = 7.9 Hz), 7.40 (d, 1H, $J$ = 7.6 Hz), 7.37 (dd, 1H, $J$ = 7.6, 7.6 Hz), 6.46 (d, 1H, $J$ = 6.2 Hz), 5.00 (s, 2H), 4.29 (s, 2H), 1.54 (s, 9H); FAB MS $m/z$ 418 $(M+H)^+$.

**5.1.31. (*E*)-*tert*-Butyl 3-(2-(3-(trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl)acrylate (27i).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (71%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.04 (s, 1H), 7.65 (d, 1H, $J$ = 7.9 Hz), 7.65 (d, 1H, $J$ = 6.2 Hz), 7.56 (s, 1H), 7.55 (d, 1H, $J$ = 7.7 Hz), 7.50 (d, 1H, $J$ = 7.7 Hz), 7.46 (dd, 1H, $J$ = 7.7, 7.7 Hz), 7.40 (d, 1H, $J$ = 7.9 Hz), 6.46 (d, 1H, $J$ = 6.2 Hz), 4.86 (s, 2H), 4.30 (s, 2H), 1.54 (s, 9H); FAB MS $m/z$ 418 $(M+H)^+$.

**5.1.32. (*E*)-*tert*-Butyl 3-(2-(4-(trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl)acrylate (27j).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (52%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.04 (s, 1H), 7.65 (d, 1H, $J$ = 7.6 Hz), 7.65 (d, 1H, $J$ = 6.2 Hz), 7.60 (d, 1H, $J$ = 8.3 Hz), 7.42 (d, 1H, $J$ = 8.3 Hz), 7.40 (d, 1H, $J$ = 7.6 Hz), 6.46 (d, 1H, $J$ = 6.2 Hz), 4.86 (s, 2H), 4.30 (s, 2H), 1.54 (s, 9H); FAB MS $m/z$ 418 $(M+H)^+$.

**5.1.33. (*E*)-*tert*-Butyl 3-(2-(2-methoxybenzyl)-1-oxoisoindolin-6-yl)acrylate (27k).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (62%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.00 (s, 1H), 7.74 (d, 1H, $J$ = 5.9 Hz), 7.61 (d, 1H, $J$ = 7.9 Hz), 7.37 (d, 1H, $J$ = 7.9 Hz), 7.25 (m, 2H), 6.90 (m, 2H), 6.44 (d, 1H, $J$ = 5.9 Hz), 4.83 (s, 2H), 4.31 (s, 2H), 3.86 (s, 3H), 1.54 (s, 9H); FAB MS $m/z$ 380 $(M+H)^+$.

**5.1.34. (*E*)-*tert*-Butyl 3-(2-(3-methoxybenzyl)-1-oxoisoindolin-6-yl)acrylate (27l).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (69%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.03 (s, 1H), 7.74 (d, 1H, $J$ = 5.9 Hz), 7.62 (d, 1H, $J$ = 8.0 Hz), 7.39 (d, 1H, $J$ = 8.0 Hz), 7.26 (s, 1H), 7.25 (d, 1H, $J$ = 7.3 Hz), 6.91 (dd, 1H, $J$ = 7.3, 8.3 Hz), 6.89 (d, 1H, $J$ = 8.3 Hz), 6.50 (d, 1H, $J$ = 5.9 Hz), 4.83 (s, 2H), 4.32 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H); FAB MS $m/z$ 338 $(M+H)^+$.

**5.1.35. (*E*)-Methyl 3-(2-(4-methoxybenzyl)-1-oxoisoindolin-6-yl)acrylate (27m).** This compound was prepared from **26a** by means of a procedure similar to that used for **16** (70%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.05 (d, 1H, $J$ = 1.3 Hz), 7.74 (d, 1H, $J$ = 5.8 Hz), 7.64 (dd, 1H, $J$ = 1.3, 7.9 Hz), 7.40 (d, 1H, $J$ = 7.9 Hz), 7.23 (d, 2H, $J$ = 8.5 Hz), 6.86 (d, 2H, $J$ = 8.5 Hz), 6.53 (d, 1H, $J$ = 5.8 Hz), 4.74 (s, 2H), 4.26 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H); FAB MS $m/z$ 338 $(M+H)^+$.

**5.1.36. (*E*)-*tert*-Butyl 3-(2-(2-methylbenzyl)-1-oxoisoindolin-6-yl)acrylate (27n).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (43%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.03 (d, 1H, $J$ = 1.2 Hz), 7.65 (d, 1H, $J$ = 6.1 Hz), 7.64 (dd, 1H, $J$ = 1.2, 7.8 Hz), 7.37 (d, 1H, $J$ = 7.8 Hz), 7.20 (m, 4H), 6.46 (d, 1H, $J$ = 6.1 Hz), 4.83 (s, 2H), 4.20 (s, 2H), 2.34 (s, 3H), 1.54 (s, 9H); FAB MS $m/z$ 364 $(M+H)^+$.

**5.1.37. (*E*)-*tert*-Butyl 3-(2-(3-methylbenzyl)-1-oxoisoindolin-6-yl)acrylate (27o).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (49%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.04 (d, 1H, $J$ = 1.5 Hz), 7.65 (d, 1H, $J$ = 5.9 Hz), 7.63 (dd, 1H, $J$ = 1.5, 7.9 Hz), 7.38 (d, 1H, $J$ = 7.9 Hz), 7.22 (dd, 1H, $J$ = 7.3, 7.3 Hz), 7.12 (s, 1H), 7.10 (d, 2H, $J$ = 7.3 Hz), 6.45 (d, 1H, $J$ = 5.9 Hz), 4.77 (s, 2H), 4.27 (s, 2H), 2.33 (s, 3H), 1.54 (s, 9H); FAB MS $m/z$ 364 $(M+H)^+$.

**5.1.38. (*E*)-*tert*-Butyl 3-(2-(4-methylbenzyl)-1-oxoisoindolin-6-yl)acrylate (27p).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (69%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.02 (s, 1H, $J$ = 1.4 Hz), 7.63 (d, 1H, $J$ = 7.6 Hz), 7.63 (d, 1H, $J$ = 5.9 Hz), 7.36 (d, 1H, $J$ = 7.6 Hz), 7.19 (d, 2H, $J$ = 7.6 Hz), 7.14 (d, 2H, $J$ = 7.6 Hz), 6.44 (d, 1H, $J$ = 5.9 Hz), 4.76 (s, 2H), 4.25 (s, 2H), 2.33 (s, 3H), 1.54 (s, 9H); FAB MS $m/z$ 364 $(M+H)^+$.

**5.1.39. (*E*)-Methyl 3-(2-(2-phenylbenzyl)-1-oxoisoindolin-6-yl)acrylate (27q).** This compound was prepared from **26a** by means of a procedure similar to that used for **16** (51%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.00 (d, 1H, $J$ = 1.5 Hz), 7.73 (d, 1H, $J$ = 6.2 Hz), 7.62 (dd, 1H, $J$ = 1.5, 7.9 Hz), 7.43 (m, 2H), 7.31 (m, 8H), 6.51 (d, 1H, $J$ = 6.2 Hz), 4.82 (s, 2H), 4.07 (s, 2H), 3.81 (s, 3H); FAB MS $m/z$ 384 $(M+H)^+$.

**5.1.40. (*E*)-Methyl 3-(2-(3-phenylbenzyl)-1-oxoisoindolin-6-yl)acrylate (27r).** This compound was prepared from **26a** by means of a procedure similar to that used for **16** (41%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.06 (s, 1H), 7.76 (d, 1H, $J$ = 5.9 Hz), 7.64 (d, 1H, $J$ = 8.0 Hz), 7.56 (d, 2H, $J$ = 7.4 Hz), 7.52 (s, 1H), 7.51 (d, 1H, $J$ = 8.0 Hz), 7.43 (dd, 2H, $J$ = 7.3, 7.4 Hz), 7.41 (dd, 1H, $J$ = 7.3, 8.0 Hz), 7.40 (d, 1H, $J$ = 8.0 Hz), 7.34 (t, 1H, $J$ = 7.3 Hz), 7.28 (d, 1H, $J$ = 7.3 Hz), 6.53 (d, 1H, $J$ = 5.9 Hz), 4.89 (s, 2H), 4.32 (s, 2H), 3.82 (s, 3H); FAB MS $m/z$ 384 $(M+H)^+$.

**5.1.41. (*E*)-Methyl 3-(2-(4-phenylbenzyl)-1-oxoisoindolin-6-yl)acrylate (27s).** This compound was prepared from **26a** by means of a procedure similar to that used for **16** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.06 (s, 1H), 7.76 (d, 1H, $J$ = 5.9 Hz), 7.65 (d, 1H, $J$ = 7.9 Hz), 7.65 (d, 4H, $J$ = 8.2 Hz), 7.38 (m, 6H), 6.52 (d, 1H, $J$ = 5.9 Hz), 4.84 (s, 2H), 4.33 (s, 2H), 3.82 (s, 3H); FAB MS $m/z$ 384 $(M+H)^+$.

**5.1.42. (*E*)-*tert*-Butyl 3-(2-(2-*tert*-butylbenzyl)-1-oxoisoindolin-6-yl)acrylate (27t).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (49%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.07 (s, 1H), 7.66 (d, 1H, $J$ = 6.2 Hz), 7.64 (d, 1H, $J$ = 8.0 Hz), 7.43 (d, 1H, $J$ = 8.0 Hz), 7.38 (d, 1H, $J$ = 8.0 Hz), 7.21 (dd, 1H, $J$ = 4.6, 8.0 Hz), 7.15 (m, 2H), 6.46 (d, 1H, $J$ = 6.2 Hz), 5.13 (s, 2H), 4.24 (s, 2H), 1.55 (s, 9H), 1.48 (s, 9H); FAB MS $m/z$ 406 $(M+H)^+$.

**5.1.43. (*E*)-*tert*-Butyl 3-(2-(4-tert-butylbenzyl)-1-oxoisoindolin-6-yl)acrylate (27u).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (90%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.03 (s, 1H), 7.65 (d, 1H, $J$ = 5.8 Hz), 7.63 (d, 1H, $J$ = 8.0 Hz), 7.37 (d, 1H, $J$ = 8.0 Hz), 7.35 (d, $J$ = 8.3 Hz), 7.23 (d, 1H, $J$ = 8.3 Hz), 6.46 (d, 1H, $J$ = 5.8 Hz), 4.77 (s, 2H), 4.28 (s, 2H), 1.54 (s, 9H), 1.30 (s, 9H); FAB MS $m/z$ 406 $(M+H)^+$.

**5.1.44. (*E*)-*tert*-Butyl 3-(2-benzhydryl-1-oxoisoindolin-6-yl)acrylate (27v).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (72%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.06 (s, 1H), 7.66 (d, 1H, $J$ = 7.6 Hz), 7.64 (d, 1H, $J$ = 6.7 Hz), 7.26 (m, 11H), 6.46 (d, 1H, $J$ = 7.6 Hz), 5.22 (s, 1H), 4.24 (s, 2H), 1.54 (s, 9H); FAB MS $m/z$ 426 $(M+H)^+$.

**5.1.45. (*E*)-*tert*-Butyl 3-(1-oxo-2-(1,2-diphenylethyl)isoindolin-6-yl)acrylate (27w).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (58%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.93 (s, 1H), 7.60 (d, 1H, $J$ = 5.9 Hz), 7.58 (d, 1H, $J$ = 7.6 Hz), 7.45 (d, 1H, $J$ = 7.6 Hz), 7.35 (m, 3H), 7.26 (m, 6H), 7.15 (m, 1H), 6.40 (d, 1H, $J$ = 5.9 Hz), 5.97 (dd, 1H, $J$ = 6.4, 9.7 Hz), 4.39 (d, 1H, $J$ = 17.1 Hz), 4.10 (d, 1H, $J$ = 17.1 Hz), 3.51 (dd, 1H, $J$ = 6.4, 14.6 Hz), 3.43 (dd, 1H, $J$ = 9.7, 14.6 Hz), 1.53 (s, 9H); FAB MS $m/z$ 440 $(M+H)^+$.

**5.1.46. (*E*)-*tert*-Butyl 3-(1-oxo-2-(1,3-diphenylpropyl)isoindolin-6-yl)acrylate (27x).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (59%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.02 (d, 1H, $J$ = 1.6 Hz), 7.63 (d, 1H, $J$ = 5.8 Hz), 7.61 (dd, 1H, $J$ = 1.6, 8.2 Hz), 7.30 (m, 11H), 6.45 (d, 1H, $J$ = 5.8 Hz), 5.68 (dd, 1H, $J$ = 6.8, 8.6 Hz), 4.30 (d, 1H, $J$ = 17.5 Hz), 4.02 (d, 1H, $J$ = 17.5 Hz), 2.72 (m, 1H), 2.67 (m, 1H), 2.43 (m, 2H), 1.53 (s, 9H); FAB MS $m/z$ 454 $(M+H)^+$.

**5.1.47. (*E*)-*tert*-Butyl 3-(1-oxo-2-(1,4-diphenylbutyl)isoindolin-6-yl)acrylate (27y).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (45%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.00 (s, 1H), 7.63 (d, 1H, $J$ = 6.1 Hz), 7.59 (d, 1H, $J$ = 7.7 Hz), 7.33 (m, 5H), 7.25 (m, 3H), 7.16 (t, 1H, $J$ = 7.0 Hz), 7.14 (d, 2H, $J$ = 8.2 Hz), 6.43 (d, 1H, $J$ = 6.1 Hz), 5.64 (dd, 1H, $J$ = 6.4, 9.5 Hz), 4.18 (d, 1H, $J$ = 17.4 Hz), 3.95 (d, 1H, $J$ = 17.4 Hz), 2.73 (m, 1H), 2.68 (m, 1H), 2.11 (m, 2H), 1.73 (m, 1H), 1.66 (m, 1H), 1.54 (s, 9H); FAB MS $m/z$ 468 $(M+H)^+$.

**5.1.48. (*E*)-(*S*)-*tert*-Butyl 3-(2-(2-(benzyloxy)-1-phenylethyl)-1-oxoisoindolin-6-yl)acrylate (27z).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (35%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.00 (d, 1H, $J$ = 1.6 Hz), 7.63 (d, 1H, $J$ = 5.9 Hz), 7.60 (dd, 1H, $J$ = 1.6, 7.6 Hz), 7.31 (m, 11H), 6.43 (d, 1H, $J$ = 5.9 Hz), 5.78 (dd, 1H, $J$ = 4.9, 7.3 Hz), 4.62 (d, 1H, $J$ = 11.9 Hz), 4.54 (d, 1H, $J$ = 11.9 Hz), 4.43 (d, 1H, $J$ = 17.4 Hz), (2H), 4.14 (d, 1H, $J$ = 17.4 Hz), 4.12 (dd, 1H, $J$ = 7.3, 10.4 Hz), 4.01 (dd, 1H, $J$ = 4.9, 10.4 Hz), 1.52 (s, 9H); $[\alpha]_D^{30.4}$ +31.1° ($c$ 0.165, $CH_3CN$); FAB MS $m/z$ 470 $(M+H)^+$.

**5.1.49. (*E*)-(*R*)-*tert*-Butyl 3-(2-(2-(benzyloxy)-1-phenylethyl)-1-oxoisoindolin-6-yl)acrylate (27aa).** This compound was prepared from **26b** by means of a procedure similar to that used for **16** (37%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.00 (d, 1H, $J$ = 1.6 Hz), 7.63 (d, 1H, $J$ = 5.9 Hz), 7.60 (dd, 1H, $J$ = 1.6, 7.6 Hz), 7.31 (m, 11H), 6.43 (d, 1H, $J$ = 5.9 Hz), 5.78 (dd, 1H, $J$ = 4.9, 7.3 Hz), 4.62 (d, 1H, $J$ = 11.9 Hz), 4.54 (d, 1H, $J$ = 11.9 Hz), 4.43 (d, 1H, $J$ = 17.4 Hz), 4.14 (d, 1H, $J$ = 17.4 Hz), 4.12 (dd, 1H, $J$ = 7.3, 10.4 Hz), 4.01 (dd, 1H, $J$ = 4.9, 10.4 Hz), 1.52 (s, 9H); $[\alpha]_D^{25.5}$ −51.0° ($c$ 0.155, $CH_3CN$); FAB MS $m/z$ 470 $(M+H)^+$.

**5.1.50. (*E*)-3-(1-Oxo-2-phenethylisoindolin-6-yl)acrylic acid (28a).** This compound was prepared from **27a** by means of a procedure similar to that used for **10** (70%). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.39 (s, 1H), 7.91 (d, 1H, $J$ = 1.5 Hz), 7.89 (dd, 1H, $J$ = 1.5, 7.8 Hz), 7.68 (d, 1H, $J$ = 6.1 Hz), 7.58 (d, 1H, $J$ = 7.8 Hz), 7.22 (m, 5H), 6.60 (d, 1H, $J$ = 6.1 Hz), 4.41 (s, 2H), 3.77 (t, 2H, $J$ = 7.3 Hz), 2.92 (t, 2H, $J$ = 7.3 Hz); FAB MS $m/z$ 308 $(M+H)^+$.

**5.1.51. (*E*)-3-(1-Oxo-2-(3-phenylpropyl)isoindolin-6-yl)acrylic acid (28b).** This compound was prepared from **27b** by means of a procedure similar to that used for **10** (76%). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.39 (s, 1H), 7.93 (d, 1H, $J$ = 1.5 Hz), 7.91 (dd, 1H, $J$ = 1.5, 7.8 Hz), 7.68 (d, 1H, $J$ = 5.7 Hz), 7.60 (d, 1H, $J$ = 7.8 Hz), 7.24 (m, 4H), 7.16 (m, 1H), 6.62 (d, 1H, $J$ = 5.7 Hz), 4.51 (s, 2H), 3.54 (t, 2H, $J$ = 7.3 Hz), 2.60 (t, 2H, $J$ = 7.8 Hz), 1.91 (m, 2H); FAB MS $m/z$ 322 $(M+H)^+$.

**5.1.52. (*E*)-3-(2-(Cyclohexylmethyl)-1-oxoisoindolin-6-yl)acrylic acid (28c).** A mixture of **27c** (109 mg, 0.31 mmol), 8 mL of $CH_2Cl_2$, and 8 mL of trifluoroacetic acid was stirred overnight at room temperature. The solvent was evaporated and the residue was recrystallized from *n*-hexane/AcOEt to afford 92 mg (quant.) of the title compound. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 2.40 (s, 1H), 7.92 (s, 1H), 7.90 (d, 1H, $J$ = 7.7 Hz), 7.68 (d, 1H, $J$ = 6.0 Hz), 7.60 (d, 1H, $J$ = 7.7 Hz), 6.60

(d, 1H, $J = 6.0$ Hz), 4.48 (s, 2H), 3.35 (d, 2H, $J = 7.1$ Hz), 1.61 (m, 6H), 1.19 (m, 3H), 0.94 (m, 2H); FAB MS *m/z* 300 $(M+H)^+$.

**5.1.53. (*E*)-3-(2-((Naphthalene-1-yl)methyl)-1-oxoisoindolin-6-yl)acrylic acid (28d).** This compound was prepared from **27d** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.42 (s, 1H), 8.21 (d, 1H, $J = 7.7$ Hz), 8.02 (s, 1H), 7.95 (d, 1H, $J = 7.2$ Hz), 7.90 (m, 2H), 7.68 (d, 1H, $J = 5.9$ Hz), 7.53 (d, 1H, $J = 7.2$ Hz), 7.52 (m, 4H), 6.63 (d, 1H, $J = 5.9$ Hz), 5.18 (s, 2H), 4.28 (s, 2H); FAB MS *m/z* 344 $(M+H)^+$.

**5.1.54. (*E*)-3-(2-(2-Chlorobenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28e).** This compound was prepared from **27e** by means of a procedure similar to that used for **10** (70%). $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 8.00 (d, 1H, $J = 1.5$ Hz), 7.83 (dd, 1H, $J = 1.5$, 7.9 Hz), 7.75 (d, 1H, $J = 6.2$ Hz), 7.66 (m, 1H), 7.56 (d, 1H, $J = 7.9$ Hz), 7.44 (m, 1H), 7.30 (m, 2H), 6.58 (d, 1H, $J = 6.2$ Hz), 4.94 (s, 2H), 4.42 (s, 2H) ; FAB MS *m/z* 328 $(M+H)^+$.

**5.1.55. (*E*)-3-(2-(3-Chlorobenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28f).** This compound was prepared from **27f** by means of a procedure similar to that used for **10** (quant.). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.00 (d, 1H, $J = 1.2$ Hz), 7.83 (dd, 1H, $J = 1.2$, 7.9 Hz), 7.70 (d, 1H, $J = 15.8$ Hz), 7.56 (d, 1H, $J = 7.9$ Hz), 7.33 (m, 3 H), 7.24 (d, 1H, $J = 7.3$ Hz), 6.58 (d, 1H, $J = 15.8$ Hz), 4.85 (s, 2H), 4.43 (s, 2H); FAB MS *m/z* 328.

**5.1.56. (*E*)-3-(2-(4-Chlorobenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28g).** This compound was prepared from **27g** by means of a procedure similar to that used for **10** (71%). $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 8.00 (d, 1H, $J = 1.5$ Hz), 7.83 (dd, 1H, $J = 1.5$, 7.8 Hz), 7.75 (d, 1H, $J = 6.0$ Hz), 7.57 (d, 1H, $J = 7.8$ Hz), 7.35 (d, 2H, $J = 8.7$ Hz), 7.30 (d, 2H, $J = 8.7$ Hz,), 6.58 (d, 1H, $J = 6.0$ Hz), 4.80 (s, 2H), 4.42 (s, 2H); FAB MS *m/z* 328 $(M+H)^+$.

**5.1.57. (*E*)-3-(2-(2-(Trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl) acrylic acid (28h).** This compound was prepared from **27 h** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.43 (s, 1H), 8.03 (s, 1H), 7.95 (d, 1H, $J = 7.8$ Hz), 7.78 (d, 1H, $J = 7.8$ Hz), 7.70 (d, 1H, $J = 6.1$ Hz), 7.65 (d, 1H, $J = 7.3$ Hz), 7.62 (dd, 1H, $J = 7.3$, 7.8 Hz), 7.51 (dd, 1H, $J = 7.3$. 7.3 Hz), 7.35 (d, 1H, $J = 7.8$ Hz), 6.63 (d, 1H, $J = 6.1$ Hz), 4.92 (s, 2H), 4.44 (s, 2H); FAB MS *m/z* 362 $(M+H)^+$.

**5.1.58. (*E*)-3-(2-(3-(Trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl) acrylic acid (28i).** This compound was prepared from **27i** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.42 (s, 1H), 8.01 (s, 1H), 7.93 (d, 1H, $J = 7.8$ Hz), 7.70 (d, 2H, $J = 6.1$ Hz), 7.66 (s, 1H), 7.65 (m, 2H), 7.60 (d, 1H, $J = 7.8$ Hz), 7.59 (m, 1H), 6.63 (d, 1H, $J = 6.1$ Hz), 4.83 (s, 2H), 4.44 (s, 2H); FAB MS *m/z* 362 $(M+H)^+$.

**5.1.59. (*E*)-3-(2-(4-(Trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl) acrylic acid (28j).** This compound was prepared from **27j** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.41 (s, 1H), 8.00 (s, 1H), 7.93 (d, 1H, $J = 7.7$ Hz), 7.71 (d, 2H, $J = 8.3$ Hz), 7.68 (d, 1H, $J = 6.0$ Hz), 7.59 (d, 1H, $J = 7.7$ Hz), 7.49 (d, 2H, $J = 8.3$ Hz), 6.63 (d, 1H, $J = 6.0$ Hz), 4.83 (s, 2H), 4.44 (s, 2H); FAB MS *m/z* 362 $(M+H)^+$.

**5.1.60. (*E*)-3-(2-(2-Methoxybenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28k).** This compound was prepared from **27k** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 12.41 (s, 1H), 7.97 (d, 1H, $J = 1.1$ Hz), 7.91 (dd, 1H, $J = 1.1$, 7.7 Hz), 7.70 (d, 1H, $J = 5.9$ Hz), 7.59 (d, 1H, $J = 7.7$ Hz), 7.27 (dd, 1H, $J = 7.2$, 8.2 Hz), 7.08 (d, 1H, $J = 7.7$ Hz), 7.02 (d, 1H, $J = 8.2$ Hz), 6.90 (dd, 1H, $J = 7.2$, 7.7 Hz), 6.62 (d, 1H, $J = 5.9$ Hz), 4.69 (s, 2H), 4.40 (s, 2H), 3.82 (s, 3H); FAB MS *m/z* 324 $(M+H)^+$.

**5.1.61. (*E*)-3-(2-(3-Methoxybenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28l).** This compound was prepared from **27l** by means of a procedure similar to that used for **28c** (79%). $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 7.99 (d, 1H, $J = 1.5$ Hz), 7.81 (dd, 1H, $J = 1.5$, 7.9 Hz), 7.75 (d, 1H, $J = 6.2$ Hz), 7.55 (d, 1H, $J = 7.9$ Hz), 7.25 (dd, 1H, $J = 7.3$, 7.3 Hz), 6.85 (m, 3H), 6.57 (d, 1H, $J = 6.2$ Hz), 4.77 (s, 2H), 4.40 (s, 2H), 3.75 (s, 3H); FAB MS *m/z* 324 $(M+H)^+$.

**5.1.62. (*E*)-3-(2-(4-Methoxybenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28m).** This compound was prepared from **27m** by means of a procedure similar to that used for **10** (71%). $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 7.99 (d, 1H, $J = 1.5$ Hz), 7.81 (dd, 1H, $J = 1.5$, 7.9 Hz), 7.75 (d, 1H, $J = 6.1$ Hz), 7.55 (d, 1H, $J = 7.9$ Hz), 7.24 (d, 2H, $J = 8.7$ Hz), 6.90 (d, 2H, $J = 8.7$ Hz), 6.58 (d, 1H, $J = 6.1$ Hz), 4.74 (s, 2H), 3.76 (s, 2H), 3.30 (s, 3H); FAB MS *m/z* 324 $(M+H)^+$.

**5.1.63. (*E*)-3-(2-(2-Methylbenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28n).** This compound was prepared from **28n** by means of a procedure similar to that used for **28c** (79%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.03 (d, 1H, $J = 1.2$ Hz), 7.65 (d, 1H, $J = 6.1$ Hz), 7.64 (dd, 1H, $J = 1.2$, 7.8 Hz), 7.37 (d, 1H, $J = 7.8$ Hz), 7.20 (m, 4H), 6.46 (d, 1H, $J = 6.1$ Hz), 4.83 (s, 2H), 4.20 (s, 2H), 2.34 (s, 3H), 1.54 (s, 9H); FAB MS *m/z* 364 $(M+H)^+$.

**5.1.64. (*E*)-3-(2-(3-Methylbenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28o).** This compound was prepared from **28n** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.42 (s, 1H), 7.99 (d, $J = 1.1$ Hz, 1H), 7.91 (dd, $J = 1.1$, 7.7 Hz, 1H), 7.70 (d, $J = 5.9$ Hz, 1H), 7.58 (d, $J = 7.7$ Hz, 1H), 7.23 (dd, $J = 7.2$, 7.5 Hz, 1H), 7.09 (d, $J = 7.5$ Hz, 1H), 7.08 (s, 1H), 7.05 (d, $J = 7.2$ Hz, 1H), 6.63 (d, $J = 5.9$ Hz, 1H), 4.68 (s, 2H), 4.38 (s, 2H), 2.27 (s, 3H); FAB MS *m/z* 308 $(M+H)^+$.

**5.1.65. (*E*)-3-(2-(4-Methylbenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28p).** This compound was prepared from **27p** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 12.41 (s, 1H), 7.98 (s, 1H, $J$ = 1.4 Hz), 7.91 (dd, 1H $J$ = 1.4, 7.9 Hz), 7.70 (d, 1H $J$ = 6.1 Hz), 7.57 (d, 1H $J$ = 7.9 Hz), 7.16 (s, 4H), 6.62 (d, 1H $J$ = 6.1 Hz), 4.67 (s, 2H), 4.35 (s, 2H), 2.26 (s, 3H); FAB MS $m/z$ 308 $(M+H)^+$.

**5.1.66. (*E*)-3-(2-(2-Phenylbenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28q).** This compound was prepared from **27q** by means of a procedure similar to that used for **10** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.28 (br, 1H), 7.94 (s, 1H), 7.89 (d, 1H, $J$ = 8.0 Hz), 7.68 (d, 1H, $J$ = 5.9 Hz), 7.54 (d, 1H, $J$ = 8.0 Hz), 7.44 (m, 2H), 7.35 (m, 5H), 7.25 (m, 1H), 7.21 (m, 1H), 6.62 (d, 1H, $J$ = 5.9 Hz), 4.69 (s, 2H), 4.24 (s, 2H); FAB MS $m/z$ 370 $(M+H)^+$.

**5.1.67. (*E*)-3-(2-(3-Phenylbenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28r).** This compound was prepared from **27r** by means of a procedure similar to that used for **10** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.41 (s, 1H), 8.00 (s, 1H), 7.91 (d, 1H, $J$ = 7.4 Hz), 7.70 (d, 1H, $J$ = 5.9 Hz), 7.63 (d, 2H, $J$ = 7.3 Hz), 7.59 (d, 1H, $J$ = 7.4 Hz), 7.58 (s, 1H), 7.47 (d, 1H, $J$ = 7.9 Hz), 7.46 (dd, 2H, $J$ = 7.3, 7.3 Hz), 7.44 (dd, 1H, $J$ = 7.9, 7.9 Hz), 7.44 (t, 1H, $J$ = 7.3 Hz), 7.26 (d, 1H, $J$ = 7.9 Hz), 6.63 (d, 1H, $J$ = 5.5 Hz), 4.80 (s, 2H), 4.44 (s, 2H); FAB MS $m/z$ 370 $(M+H)^+$.

**5.1.68. (*E*)-3-(2-(4-Phenylbenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28s).** This compound was prepared from **27s** by means of a procedure similar to that used for **10** (54%). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.41 (s, 1H), 8.01 (d, 1H, $J$ = 1.8 Hz), 7.93 (dd, 1H, $J$ = 1.8, 7.9 Hz), 7.70 (d, 1H, $J$ = 5.8 Hz), 7.63 (m, 5H), 7.44 (m, 2H), 7.36 (m, 3H), 6.64 (d, 1H, $J$ = 5.8 Hz), 4.77 (s, 2H), 4.43 (s, 2H); FAB MS $m/z$ 370 $(M+H)^+$.

**5.1.69. (*E*)-3-(2-(2-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28t).** This compound was prepared from **27t** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.02 (s, 1H), 7.93 (d, 1H, $J$ = 7.7 Hz), 7.70 (d, 1H, $J$ = 6.0 Hz), 7.59 (d, 1H, $J$ = 7.7 Hz), 7.40 (d, 1H, $J$ = 7.7 Hz), 7.20 (dd, 1H, $J$ = 7.7, 7.7 Hz), 7.15 (dd, 1H, $J$ = 7.7, 7.7 Hz), 7.05 (d, 1H, $J$ = 7.7 Hz), 6.64 (d, 1H, $J$ = 6.0 Hz), 4.99 (s, 2H), 4.35 (s, 2H), 1.43 (s, 9H); FAB MS $m/z$ 350 $(M+H)^+$.

**5.1.70. (*E*)-3-(2-(4-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl) acrylic acid (28u).** This compound was prepared from **28u** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.99 (s, 1H), 7.92 (d, 1 H, $J$ = 8.1 Hz), 7.70 (d, 1H, $J$ = 6.2 Hz), 7.57 (d, 1H, $J$ = 8.1 Hz), 7.36 (d, 1H, $J$ = 8.5 Hz), 7.19 (d, 1H, $J$ = 8.5 Hz), 6.63 (d, 1H, $J$ = 6.2 Hz), 4.68 (s, 2H), 4.37 (s, 2H), 1.24 (s, 9H); FAB MS $m/z$ 350 $(M+H)^+$.

**5.1.71. (*E*)-3-(2-Benzhydryl-1-oxoisoindolin-6-yl) acrylic acid (28v).** This compound was prepared from **27v** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.88 (s, 1H), 8.01 (d, 1H, $J$ = 1.5 Hz), 7.94 (dd, 1H, $J$ = 1.5, 8.0 Hz), 7.70 (d, 1H, $J$ = 6.0 Hz), 7.58 (d, 1H, $J$ = 8.0 Hz), 7.26 (m, 8H), 7.19 (d, 2H, $J$ = 7.5 Hz), 6.64 (d, 1H, $J$ = 6.0 Hz), 5.67 (m, 1H), 4.28 (s, 2H); FAB MS $m/z$ 370 $(M+H)^+$.

**5.1.72. (*E*)-3-(1-Oxo-2-(1,2-diphenylethyl)isoindolin-6-yl) acrylic acid (28w).** This compound was prepared from **27w** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.44 (br, 1H), 7.86 (s, 1H), 7.64 (d, 1H, $J$ = 5.8 Hz), 7.54 (d, 2H, $J$ = 8.6 Hz), 7.45 (d, 2H, $J$ = 7.3 Hz), 7.36 (dd, 2H, $J$ = 7.3, 8.0 Hz), 7.28 (t, 1H, $J$ = 8.0 Hz), 7.28 (d, 2H, $J$ = 7.3 Hz), 7.20 (dd, 2H, $J$ = 7.3, 7.3 Hz), 7.11 (t, 1H, $J$ = 7.3 Hz), 6.58 (d, 1H, $J$ = 5.8 Hz), 5.75 (t, 1H, $J$ = 8.3 Hz), 4.58 (d, 1H, $J$ = 18.3 Hz), 4.12 (d, 1H, $J$ = 18.3 Hz), 3.45 (d, 2H, $J$ = 8.3 Hz); FAB MS $m/z$ 384 $(M+H)^+$.

**5.1.73. (*E*)-3-(1-Oxo-2-(1,3-diphenylpropyl)isoindolin-6-yl) acrylic acid (28x).** This compound was prepared from **27x** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 8.10 (s, 1H), 7.83 (d, 1H, $J$ = 6.3 Hz), 7.66 (d, 1H, $J$ = 8.2 Hz), 7.41 (d, 1H, $J$ = 8.2 Hz), 7.40 (dd, 2H, $J$ = 7.3, 8.5 Hz), 7.36 (dd, 2H, $J$ = 7.3, 8.5 Hz), 7.29 (t, 1H, $J$ = 7.3 Hz), 7.25 (d, 2H, $J$ = 8.5 Hz), 7.19 (d, 2H, $J$ = 8.5 Hz), 7.16 (t, 1H, $J$ = 7.3 Hz), 6.54 (d, 1H, $J$ = 6.3 Hz), 5.69 (dd, 1H, $J$ = 6.8, 8.6 Hz), 4.33 (d, 1H, $J$ = 17.5 Hz), 4.06 (d, 1H, $J$ = 17.5 Hz), 2.73 (m, 1H), 2.67 (m, 1H), 2.43 (m, 2H); FAB MS $m/z$ 398 $(M+H)^+$.

**5.1.74. (*E*)-3-(1-Oxo-2-(1,4-diphenylbutyl)isoindolin-6-yl) acrylic acid (28y).** This compound was prepared from **27y** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.95 (s, 1H), 7.90 (d, 1H, $J$ = 8.1 Hz); 7.67 (d, 1H, $J$ = 6.1 Hz), 7.55 (d, 1H, $J$ = 8.1 Hz), 7.34 (m, 4H), 7.25 (m, 3H), 7.14 (m, 3H), 6.60 (d, 1H, $J$ = 6.1 Hz), 5.41 (dd, 1H, $J$ = 6.1, 10.0 Hz), 4.45 (d, 1H, $J$ = 18.5 Hz), 4.04 (d, 1H, $J$ = 18.5 Hz), 2.63 (m, 2H), 2.07 (m, 2H), 1.53 (m, 2H); FAB MS $m/z$ 412 $(M+H)^+$.

**5.1.75. (*E*)-(*S*)-3-(2-(2-(Benzyloxy)-1-phenylethyl)-1-oxoisoindolin-6-yl) acrylic acid (28z).** This compound was prepared from **28z** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.01 (s, 1H), 7.80 (d, 1H, $J$ = 6.1 Hz), 7.64 (d, 1H, $J$ = 7.8 Hz), 7.37 (d, 1H, $J$ = 7.8 Hz), 7.31 (m, 10H), 6.50 (d, 1H, $J$ = 6.1 Hz), 5.80 (dd, 1H, $J$ = 4.9, 7.9 Hz), 4.62 (d, 1H, $J$ = 11.9 Hz), 4.54 (d, 1H, $J$ = 11.9 Hz), 4.47 (d, 1H, $J$ = 17.5 Hz), 4.17 (d, 1H, $J$ = 17.5 Hz), 4.12 (dd, 1H, $J$ = 7.9, 10.3 Hz), 4.01 (dd, 1H, $J$ = 4.9, 10.3 Hz); $[\alpha]_D^{30.1}$ +35.3° ($c$ 0.306, $CH_3CN$); FAB MS $m/z$ 414 $(M+H)^+$.

**5.1.76. (*E*)-(*R*)-3-(2-(2-(Benzyloxy)-1-phenylethyl)-1-oxoisoindolin-6-yl)acrylic acid (28aa).** This compound was prepared from **27aa** by means of a procedure similar

to that used for **28c** (quant.). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.01 (s, 1H), 7.80 (d, 1H, $J$ = 5.9 Hz), 7.64 (d, 1H, $J$ = 7.8 Hz), 7.37 (d, 1H, $J$ = 7.8 Hz), 7.31 (m, 10H), 6.50 (d, 1H, $J$ = 5.9 Hz), 5.80 (dd, 1H, $J$ = 4.9, 7.9 Hz), 4.62 (d, 1H, $J$ = 11.9 Hz), 4.54 (d, 1H, $J$ = 11.9 Hz), 4.47 (d, 1H, $J$ = 17.5 Hz), 4.17 (d, 1H, $J$ = 17.5 Hz), 4.12 (dd, 1H, $J$ = 7.9, 10.3 Hz), 4.01 (dd, 1H, $J$ = 4.9, 10.3 Hz); $[\alpha]_D^{34.5}$ −51.7° (*c* 0.130, $CH_3CN$); FAB MS *m*/*z* 414 $(M+H)^+$.

**5.1.77. (*E*)-*N*-(2-(Trimethylsilyl)ethoxy)-3-(2-benzhydryl-1-oxoisoindolin-6-yl)acrylamide (29v).** To a mixture of **28v** (65 mg, 0.18 mmol) and 5 mL of anhydrous THF were added triethylamine (0.074 mL, 0.53 mmol), and ethyl chloroformate (0.017 mL, 0.18 mmol) at 0 °C, with stirring for 1 h at 0 °C. Then 1 equiv of methanolic *o*-(2-trimethylsilylethyl)hydroxylamine was added and the whole was stirred overnight at room temperature. The reaction mixture was washed with dil NaOH and brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt 2:1 v/v) to afford 25 mg (29%) of the title compound as an oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.21 (br, 1 H), 8.11 (s, 1H), 7.80 (d, 1H, $J$ = 4.5 Hz), 7.59 (d, 1H, $J$ = 7.5 Hz,), 7.33 (m, 9H), 7.19 (d, 2H, $J$ = 7.0 Hz), 6.90 (s, 1H), 6.50 (d, 1H, $J$ = 4.5 Hz), 4.23 (s, 2H), 4.01 (m, 2H), 1.05 (t, 2H, $J$ = 7.8 Hz,), 0.01 (s, 9H); FAB MS *m*/*z* 485 $(M+H)^+$.

**5.1.78. (*E*)-3-(1-Oxo-2-phenethylisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29a).** This compound was prepared from **28a** by means of a procedure similar to that used for **11** (67%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.27 (s, 1H), 8.00 (s, 1H), 7.76 (d, 1H, $J$ = 4.9 Hz), 7.57 (d, 1H, $J$ = 7.6 Hz), 7.35 (d, 1H, $J$ = 7.6 Hz), 7.23 (m, 5H), 6.51 (d, 1H, $J$ = 4.9 Hz), 5.05 (m, 1H), 4.21 (s, 2H), 4.01 (m, 1H), 3.88 (t, 2H, $J$ = 7.1 Hz), 3.65 (m, 1H), 3.00 (t, 2H, $J$ = 7.1 Hz), 1.85 (m, 3H), 1.60 (m, 3H); FAB MS *m*/*z* 407 $(M+H)^+$.

**5.1.79. (*E*)-3-(1-Oxo-2-(3-phenylpropyl)isoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29b).** This compound was prepared from **28b** by means of a procedure similar to that used for **11** (76%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.77 (s, 1H), 8.00 (s, 1H), 7.76 (d, 1H, $J$ = 5.2 Hz,), 7.58 (d, 1H, $J$ = 7.6 Hz), 7.40 (d, 1H, $J$ = 7.6 Hz), 7.24 (m, 5H), 6.57 (d, 1H, $J$ = 5.2 Hz,), 5.08 (m, 1H), 4.37 (s, 2H), 4.04 (m, 1H), 3.68 (t, 2H, $J$ = 7.3 Hz), 3.67 (m, 1H), 2.69 (t, 2H, $J$ = 7.7 Hz), 2.01 (m, 2H), 1.85 (m, 3H), 1.60 (m, 3H); FAB MS *m*/*z* 421 $(M+H)^+$.

**5.1.80. (*E*)-3-(2-(Cyclohexylmethyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29c).** This compound was prepared from **28c** by means of a procedure similar to that used for **11** (52%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.05 (s, 1H), 8.01 (s, 1H), 7.72 (d, 1H, $J$ = 5.6 Hz), 7.60 (d, 1H, $J$ = 7.9 Hz), 7.42 (d, 1H, $J$ = 7.9 Hz), 6.50 (d, 1H, $J$ = 5.6 Hz,), 5.04 (m, 1H), 4.40 (s, 2H), 4.00 (m, 1H), 3.65 (m, 1H), 3.45 (d, 2H, $J$ = 7.3 Hz), 1.74 (m, 12H), 1.20 (m, 3H), 1.05 (m, 2H); FAB MS *m*/*z* 399 $(M+H)^+$.

**5.1.81. (*E*)-3-(2-((Naphthalene-1-yl)methyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29d).** This compound was prepared from **28d** by means of a procedure similar to that used for **11** (49%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.45 (s, 1H), 8.21 (d, 1H, $J$ = 8.0 Hz), 8.06 (s, 1H), 7.84 (m, 2H), 7.76 (d, 1H, $J$ = 5.5 Hz), 7.46 (m, 5H), 7.25 (d, 1H, $J$ = 8.0 Hz,), 6.53 (d, 1H, $J$ = 5.5 Hz), 5.25 (s, 2H), 5.06 (m, 1H), 4.13 (s, 2H), 4.01 (m, 1H), 3.65 (m, 1H), 1.84 (m, 3H), 1.53 (m, 3H); FAB MS *m*/*z* 443 $(M+H)^+$.

**5.1.82. (*E*)-3-(2-(2-Chlorobenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29e).** This compound was prepared from **28e** by means of a procedure similar to that used for **11** (61%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.78 (s, 1H), 8.07 (s, 1H), 7.79 (d, 1H, $J$ = 5.8 Hz), 7.62 (d, 1H, $J$ = 7.9 Hz), 7.41 (d, 1H, $J$ = 7.9 Hz), 7.40 (m, 1H), 7.33 (m, 1H), 7.23 (m, 2H), 6.50 (d, 1H, $J$ = 5.8 Hz), 5.03 (m, 1H), 4.96 (s, 2H), 4.36 (s, 2H), 4.00 (m, 1H), 3.67 (m, 1H), 1.86 (m, 3H), 1.64 (m, 3H); FAB MS *m*/*z* 427 $(M+H)^+$.

**5.1.83. (*E*)-3-(2-(3-Chlorobenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29f).** This compound was prepared from **28f** by means of a procedure similar to that used for **11** (31%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.22 (s, 1H), 8.06 (s, 1H), 7.79 (d, 1H, $J$ = 5.3 Hz), 7.61 (d, 1H, $J$ = 7.9 Hz), 7.40 (d, 1H, $J$ = 7.9 Hz), 7.26 (m, 3H), 7.19 (m, 1H), 6.53 (d, 1H, $J$ = 5.3 Hz), 5.05 (m, 1H), 4.78 (s, 2H), 4.30 (s, 2H), 4.01 (m, 1H), 3.67 (m, 1H), 1.85 (m, 3H), 1.61 (m, 3H); FAB MS *m*/*z* 427 $(M+H)^+$.

**5.1.84. (*E*)-3-(2-(4-Chlorobenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29g).** This compound was prepared from **28g** by means of a procedure similar to that used for **11** (38%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.42 (s, 1H), 8.03 (s, 1H), 7.76 (d, 1H, $J$ = 4.4 Hz), 7.60 (d, 1H, $J$ = 7.5 Hz), 7.37 (d, 1H, $J$ = 7.5 Hz), 7.29 (d, 2H, $J$ = 8.5 Hz), 7.19 (d, 2H, $J$ = 8.5 Hz), 6.53 (d, 1H, $J$ = 4.4 Hz), 5.05 (m, 1H), 4.77 (s, 2H), 4.28 (s, 2H), 4.01 (m, 1H), 3.64 (m, 1H), 1.84 (m, 3H), 1.59, (m, 3H); FAB MS *m*/*z* 427 $(M+H)^+$.

**5.1.85. (*E*)-3-(2-(2-(Trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29h).** This compound was prepared from **28h** by means of a procedure similar to that used for **11** (84%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.65 (s, 1H), 8.06 (s, 1H), 7.77 (d, 1H, $J$ = 5.2 Hz), 7.67 (d, 1H, $J$ = 7.7 Hz), 7.61 (d, 1H, $J$ = 7.3 Hz), 7.48 (dd, 1H, $J$ = 7.3, 7.3 Hz), 7.38 (m, 3H), 6.56 (d, 1H, $J$ = 5.2 Hz), 5.06 (m, 1H), 5.01 (s, 2H), 4.29 (s, 2H), 4.01 (m, 1H), 3.63 (m, 1H), 1.83 (m, 3H), 1.58 (m, 3H); FAB MS *m*/*z* 461 $(M+H)^+$.

**5.1.86. (*E*)-3-(2-(3-(Trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29i).** This compound was prepared from **28i** by means of a procedure similar to that used for **11** (72%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.46 (s, 1H), 8.04 (s, 1H), 7.75 (d, 1H, $J$ = 4.4 Hz,), 7.60 (d, 1H, $J$ = 7.7 Hz), 7.55 (s, 1H), 7.54 (d, 1H, $J$ = 7.6 Hz), 7.49 (d, 1H, $J$ = 7.7 Hz), 7.45 (dd, 1H, $J$ = 7.7, 7.7 Hz), 7.38 (d, 1H,

$J$ = 7.6 Hz), 6.53 (d, 1H, $J$ = 4.4 Hz), 5.06 (m, 1H), 4.86 (s, 2H), 4.30 (s, 2H), 4.00 (m, 1H), 3.64 (m, 1H), 1.85 (m, 3H), 1.59 (m, 3H) ; FAB MS $m/z$ 461 $(M+H)^+$.

**5.1.87. (*E*)-3-(2-(4-(Trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29j).** This compound was prepared from **28j** by means of a procedure similar to that used for **11** (57%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.71 (s, 1H), 8.08 (s, 1H), 7.80 (d, 1H, $J$ = 5.6 Hz), 7.63 (d, 1H, $J$ = 7.7 Hz), 7.59 (d, 2H, $J$ = 8.3 Hz), 7.42 (d, 2H, $J$ = 8.3 Hz), 7.41 (d, 1H, $J$ = 7.7 Hz), 6.51 (d, 1H, $J$ = 5.6 Hz), 5.03 (m, 1H), 4.87 (s, 2H), 4.31 (s, 2H), 3.99 (m, 1H), 3.67 (m, 1H), 1.86 (m, 3H), 1.62 (m, 3H); FAB MS $m/z$ 461 $(M+H)^+$.

**5.1.88. (*E*)-3-(2-(2-Methoxybenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29k).** This compound was prepared from **28k** by means of a procedure similar to that used for **11** (47%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.11 (s, 1H), 8.04 (s, 1H), 7.78 (d, 1H, $J$ = 5.6 Hz), 7.58 (d, 1H, $J$ = 7.6 Hz), 7.37 (d, 1H, $J$ = 7.6 Hz), 7.26 (dd, 1H, $J$ = 7.3, 8.3 Hz), 7.25 (d, 1H, $J$ = 7.6 Hz), 6.90 (dd, 1H, $J$ = 7.3, 7.6 Hz), 6.88 (d, 1H, $J$ = 8.3 Hz), 6.52 (d, 1H, $J$ = 5.6 Hz), 5.04 (m, 1H), 4.84 (s, 2H), 4.32 (s, 2H), 4.00 (m, 1H), 3.86 (s, 3H), 3.65 (m, 1H), 1.84 (m, 3H), 1.60 (m, 3H); FAB MS $m/z$ 423 $(M+H)^+$.

**5.1.89. (*E*)-3-(2-(3-Methoxybenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29l).** This compound was prepared from **28l** by means of a procedure similar to that used for **11** (27%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.25 (s, 1H), 8.05 (s, 1H), 7.78 (d, 1H, $J$ = 5.6 Hz), 7.59 (d, 1H, $J$ = 7.5 Hz), 7.37 (d, 1H, $J$ = 7.5 Hz), 7.24 (dd, 1H, $J$ = 7.6, 7.9 Hz), 6.87 (d, 1H, $J$ = 7.6 Hz,), 6.83 (s, 1H), 6.82 (d, 1H, $J$ = 7.9 Hz), 6.54 (d, 1H, $J$ = 5.6 Hz), 5.05 (m, 1H), 4.77 (s, 2H), 4.29 (s, 2H), 4.01 (m, 1H), 3.77 (s, 3H), 3.65 (m, 1H), 1.86 (m, 3H), 1.64 (m, 3H); FAB MS $m/z$ 423 $(M+H)^+$.

**5.1.90. (*E*)-3-(2-(4-Methoxybenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29m).** This compound was prepared from **28m** by means of a procedure similar to that used for **11** (72%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.37 (s, 1H), 8.03 (s, 1H), 7.76 (d, 1H, $J$ = 5.6 Hz), 7.57 (d, 1H, $J$ = 7.6 Hz), 7.35 (d, 1H, $J$ = 7.6 Hz), 7.23 (d, 2H, $J$ = 8.7 Hz), 6.85 (d, 2H, $J$ = 8.7 Hz), 6.53 (d, 1H, $J$ = 5.6 Hz), 5.06 (m, 1H), 4.74 (s, 2H), 4.25 (s, 2H), 4.01 (m, 1H), 3.78 (s, 3H), 3.67 (m, 1H), 1.84 (m, 3H), 1.60 (m, 3H); FAB MS $m/z$ 423 $(M+H)^+$.

**5.1.91. (*E*)-3-(2-(2-Methylbenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29n).** This compound was prepared from **28n** by means of a procedure similar to that used for **11** (65%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.64 (s, 1H), 8.04 (s, 1 H), 7.76 (d, 1H, $J$ = 5.5 Hz), 7.57 (d, 1H, $J$ = 7.6 Hz), 7.34 (d, 1H, $J$ = 7.6 Hz), 7.18 (m, 4H), 6.55 (d, 1H, $J$ = 5.5 Hz), 5.06 (m, 1H), 4.82 (s, 2H), 4.01 (s, 2H), 4.00 (m, 1H), 3.63 (m, 1H), 2.33 (s, 3H), 1.83 (m, 3H), 1.58 (m, 3H); FAB MS $m/z$ 407 $(M+H)^+$.

**5.1.92. (*E*)-3-(2-(3-Methylbenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29o).** This compound was prepared from **28o** by means of a procedure similar to that used for **11** (76%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.52 (s, 1H), 8.04 (s, 1H), 7.77 (d, 1H, $J$ = 5.6 Hz,), 7.58 (d, 1H, $J$ = 7.7 Hz), 7.35 (d, 1H, $J$ = 7.7 Hz), 7.21 (dd, 1H, $J$ = 7.5, 7.5 Hz), 7.10 (s, 1H), 7.20 (d, 1H, $J$ = 7.5 Hz), 7.20 (d, 1 H, $J$ = 7.5 Hz), 6.55 (d, 1H, $J$ = 5.6 Hz), 5.06 (m, 1H), 4.76 (s, 2H), 4.27 (s, 2H), 4.02 (m, 1H), 3.66 (m, 1H), 2.31 (s, 3H), 1.84 (m, 3H), 1.59 (m, 3H); FAB MS $m/z$ 407 $(M+H)^+$.

**5.1.93. (*E*)-3-(2-(4-Methylbenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29p).** This compound was prepared from **28p** by means of a procedure similar to that used for **11** (71%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.35 (s, 1H), 8.04 (s, 1H), 7.77 (d, 1H, $J$ = 5.6 Hz), 7.58 (d, 1H, $J$ = 7.6 Hz), 7.34 (d, 1H, $J$ = 7.6 Hz), 7.18 (d, 2H, $J$ = 7.9 Hz), 7.12 (d, 2H, $J$ = 7.9 Hz), 6.53 (d, 1H, $J$ = 5.6 Hz), 5.05 (m, 1H), 4.76 (s, 2H), 4.26 (s, 2H), 4.01 (m, 1H), 3.65 (m, 1H), 2.32 (s, 3H), 1.84 (m, 3H), 1.59 (m, 3H); FAB MS $m/z$ 407 $(M+H)^+$.

**5.1.94. (*E*)-3-(2-(2-Phenylbenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29q).** This compound was prepared from **28q** by means of a procedure similar to that used for **11** (62%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.45 (s, 1H), 7.97 (s, 1H), 7.72 (d, 1H, $J$ = 5.3 Hz), 7.52 (d, 1H, $J$ = 7.3 Hz), 7.27 (m, 10H), 6.49 (d, 1H, $J$ = 5.3 Hz), 5.01 (m, 1H), 4.77 (s, 2H), 4.03 (s, 2H), 3.95 (m, 1H), 3.59 (m, 1H), 1.79 (m, 3H), 1.54 (m, 3H); FAB MS $m/z$ 469 $(M+H)^+$.

**5.1.95. (*E*)-3-(2-(3-Phenylbenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29r).** This compound was prepared from **28r** by means of a procedure similar to that used for **11** (62%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.52 (s, 1H), 8.05 (s, 1H), 7.76 (d, 1H, $J$ = 5.3 Hz), 7.56 (d, 1H, $J$ = 7.6 Hz), 7.54 (d, 2H, $J$ = 7.3 Hz), 7.51 (s, 1H), 7.50 (d, 1H, $J$ = 7.6 Hz), 7.40 (dd, 2 H, $J$ = 7.3, 7.3 Hz), 7.38 (dd, 1H, $J$ = 7.3, 7.6 Hz), 7.33 (d, 1H, $J$ = 7.3 Hz), 7.32 (t, 1H, $J$ = 7.3 Hz), 7.27 (d, 1H, $J$ = 7.6 Hz), 6.54 (d, 1H, $J$ = 5.3 Hz), 5.06 (m, 1H), 4.87 (s, 2H), 4.31 (s, 2H), 4.01 (m, 1H), 3.64 (m, 1H), 1.58 (m, 3H), 1.25 (m, 3H); FAB MS $m/z$ 469 $(M+H)^+$.

**5.1.96. (*E*)-3-(2-(4-Phenylbenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29s).** This compound was prepared from **28s** by means of a procedure similar to that used for **11** (23%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.57 (s, 1H), 8.09 (s, 1H), 7.62 (d, 1H, $J$ = 5.8 Hz), 7.62 (d, 1H, $J$ = 7.6 Hz), 7.56 (d, 4H, $J$ = 8.2 Hz), 7.38 (m, 6H), 6.49 (d, 1H, $J$ = 5.8 Hz), 5.03 (m, 1H), 4.85 (s, 2H), 4.33 (s, 2H), 3.99 (m, 1H), 3.67 (m, 1H), 1.86 (m, 3H), 1.60 (m, 3H); FAB MS $m/z$ 469 $(M+H)^+$.

**5.1.97. (*E*)-3-(2-(2-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29t).** This compound was prepared from **28t** by means of a procedure similar to that used for **11** (95%). $^1$H NMR

(500 MHz, $CDCl_3$) $\delta$ 8.49 (br, 1H), 8.11 (s, 1H), 7.82 (d, 1H, $J$ = 5.2 Hz), 7.62 (d, 1H, $J$ = 7.6 Hz), 7.43 (d, 1H, $J$ = 7.6 Hz), 7.38 (d, 1H, $J$ = 8.0 Hz), 7.22 (dd, 1H, $J$ = 4.0, 8.6 Hz), 7.14 (m, 2H), 6.47 (d, 1H, $J$ = 5.2 Hz), 5.13 (s, 2H), 5.03 (m, 1H), 4.25 (s, 2H), 3.99 (m, 1H), 3.69 (m, 1H), 1.86 (m, 3H), 1.58 (m, 3H), 1.48 (s, 9H); FAB MS $m/z$ 449 $(M+H)^+$.

**5.1.98. (*E*)-3-(2-(4-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29u).** This compound was prepared from **28u** by means of a procedure similar to that used for **11** (95%). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.56 (br, 1H), 8.07 (s, 1H), 7.80 (d, 1H, $J$ = 5.4 Hz), 7.60 (d, 1H, $J$ = 8.0 Hz), 7.38 (d, 1H, $J$ = 8.0 Hz), 7.35 (d, 2H, $J$ = 8.2 Hz), 7.23 (d, 2H, $J$ = 8.2 Hz), 6.46 (d, 1H, $J$ = 5.4 Hz), 5.03 (m, 1H), 4.78 (s, 2H), 4.29 (s, 2H), 3.99 (m, 1H), 3.67 (m, 1H), 1.86 (m, 3H), 1.62 (m, 3H), 1.30 (s, 9H); FAB MS $m/z$ 449 $(M+H)^+$.

**5.1.99. (*E*)-3-(1-Oxo-2-(1,2-diphenylethyl)isoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29w).** This compound was prepared from **28w** by means of a procedure similar to that used for **11** (99%). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 8.79 (s, 1H), 7.92 (s, 1H), 7.72 (d, 1H, $J$ = 5.0 Hz), 7.53 (d, 1H, $J$ = 7.2 Hz), 7.45 (d, 2H, $J$ = 7.3 Hz), 7.26 (m, 8H), 7.14 (t, 1H, $J$ = 7.3 Hz), 6.38 (d, 1H, $J$ = 5.0 Hz), 5.96 (dd, 1H, $J$ = 6.4, 9.8 Hz), 5.02 (m, 1H), 4.38 (d, 1H, $J$ = 17.1 Hz), 4.08 (d, 1H, $J$ = 17.1 Hz), 3.99 (m, 1H), 3.67 (m, 1H), 3.50 (dd, 1H, $J$ = 6.4, 14.5 Hz), 3.42 (dd, 1H, $J$ = 9.8, 14.5 Hz), 1.86 (m, 3H), 1.61 (m, 3H); FAB MS $m/z$ 483 $(M+H)^+$.

**5.1.100. (*E*)-3-(1-Oxo-2-(1,3-diphenylpropyl)isoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29x).** This compound was prepared from **28x** by means of a procedure similar to that used for **11** (61%). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.20 (br, 1H), 8.04 (s, 1H), 7.78 (d, 1H, $J$ = 5.3 Hz), 7.57 (d, 1H, $J$ = 7.7 Hz), 7.40 (m, 2H), 7.34 (m, 3 H), 7.25 (m, 3H), 7.15 (m, 3H), 6.50 (d, 1H, $J$ = 5.3 Hz), 5.67 (dd, 1H, $J$ = 6.9, 8.6 Hz), 5.05 (b. 1H), 4.30 (d, 1H, $J$ = 17.3 Hz), 4.02 (m, 1H, $J$ = 17.3 Hz), 4.01 (m, 1H), 3.67 (m, 1H), 2.72 (m, 1H), 2.66 (m, 1H), 2.42 (m, 2H), 1.85 (m, 3H), 1.60 (m, 3H); FAB MS $m/z$ 497 $(M+H)^+$.

**5.1.101. (*E*)-3-(1-Oxo-2-(1,4-diphenylbutyl)isoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29y).** This compound was prepared from **28y** by means of a procedure similar to that used for **11** (81%). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.55 (br, 1H), 8.02 (s, 1H), 7.77 (d, 1H, $J$ = 5.8 Hz), 7.54 (d, 1H, $J$ = 6.4 Hz), 7.31 (m, 5H), 7.23 (m, 3H), 7.15 (t, 1H, $J$ = 7.3 Hz), 7.14 (d, 2H, $J$ = 7.3 Hz), 6.54 (d, 1H, $J$ = 5.8 Hz), 5.63 (dd, 1H, $J$ = 6.6, 9.2 Hz), 5.07 (m, 1H), 4.18 (d, 1H, $J$ = 17.1 Hz), 4.01 (m, 1H), 3.95 (d, 1H, $J$ = 17.1 Hz), 3.65 (m, 1H), 2.69 (m, 1H), 2.67 (m, 1H), 2.09 (m, 2H), 1.85 (m, 3H), 1.65 (m, 5H); FAB MS $m/z$ 511 $(M+H)^+$.

**5.1.102. (*E*)-(*S*)-3-(2-(2-(Benzyloxy)-1-phenylethyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29z).** This compound was prepared from **28z** by means of a procedure similar to that used for **11** (65%). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.37 (br, 1H), 8.03 (s, 1H), 7.75 (d, 1H, $J$ = 5.0 Hz), 7.56 (d, 1H, $J$ = 7.6 Hz), 7.31 (m, 11H), 6.50 (d, 1H, $J$ = 5.0 Hz), 5.79 (dd, 1H, $J$ = 5.2, 7.3 Hz), 5.05 (m, 1H), 4.62 (d, 1H, $J$ = 12.2 Hz), 4.54 (d, 1H, $J$ = 12.2 Hz), 4.45 (d, 1H, $J$ = 17.7 Hz), 4.17 (d, 1H, $J$ = 17.7 Hz,), 4.12 (dd, 1 H, $J$ = 7.3, 10.4 Hz), 2H, 4.03 (dd, 1H, $J$ = 5.2, 10.4 Hz), 4.00 (m, 1H), 3.64 (m, 1H), 1.83 (m, 3H), 1.59 (m, 3H); $[\alpha]_D^{30.8}$ +50.4° ($c$ 0.163, $CH_3CN$); FAB MS $m/z$ 513 $(M+H)^+$.

**5.1.103. (*E*)-(*R*)-3-(2-(2-(Benzyloxy)-1-phenylethyl)-1-oxoisoindolin-6-yl)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acrylamide (29aa).** This compound was prepared from **28aa** by means of a procedure similar to that used for **11** (77%). $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.37 (br, 1H), 8.03 (s, 1H), 7.75 (d, 1H, $J$ = 5.0 Hz), 7.56 (d, 1H, $J$ = 7.6 Hz), 7.31 (m, 11H), 6.50 (d, 1H, $J$ = 5.0 Hz), 5.79 (dd, 1H, $J$ = 5.2, 7.3 Hz), 5.05 (m, 1H), 4.62 (d, 1H, $J$ = 12.2 Hz), 4.54 (d, 1H, $J$ = 12.2 Hz), 4.45 (d, 1H, $J$ = 17.7 Hz), 4.17 (d, 1H, $J$ = 17.7 Hz), 4.12 (dd, 1H, $J$ = 7.3, 10.4 Hz), 4.03 (dd, 1H, $J$ = 5.2, 10.4 Hz), 4.00 (m, 1H), 3.64 (m, 1H), 1.83 (m, 3H), 1.59 (m, 3H); $[\alpha]_D^{34.5}$ −52.3° ($c$ 0.146, $CH_3CN$); FAB MS $m/z$ 513 $(M+H)^+$.

**5.1.104. (*E*)-3-(1-Oxo-2-phenethylisoindolin-6-yl)-*N*-hydroxyacrylamide (30a).** This compound was prepared from **29a** by means of a procedure similar to that used for **12** (80%). Mp 180–182 °C; $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.70 (s, 1H), 7.69 (d, 1 H, $J$ = 5.9 Hz), 7.52 (d, 1H, $J$ = 7.9 Hz), 7.25 (m, 6H), 6.51 (d, 1H, $J$ = 5.9 Hz), 4.38 (s, 2H), 3.78 (t, 2H, $J$ = 7.3 Hz), 2.92 (t, 2H, $J$ = 7.3 Hz); HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{19}N_2O_3$, 323.1396. Found: 323.1421.

**5.1.105. (*E*)-3-(1-Oxo-2-(3-phenylpropyl)isoindolin-6-yl)-*N*-hydroxyacrylamide (30b).** This compound was prepared from **29b** by means of a procedure similar to that used for **12** (49%). Mp 117–119 °C; $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.81 (s, 1H), 7.76 (d, 1H, $J$ = 7.9 Hz), 7.60 (d, 1H, $J$ = 7.9 Hz), 7.53 (d, 1H, $J$ = 5.9 Hz), 7.21 (m, 5H), 6.55 (d, 1H, $J$ = 5.9 Hz), 4.50 (s, 2H), 3.54 (t, 2H, $J$ = 7.3 Hz), 2.60 (t, 2H, $J$ = 7.9 Hz), 1.91 (m, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{20}H_{21}N_2O_3$, 337.1552. Found: 337.1552.

**5.1.106. (*E*)-3-(2-(Cyclohexylbenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30c).** This compound was prepared from **29c** by means of a procedure similar to that used for **12** (95%). Mp >300 °C; $^1H$ NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.77 (s, 1H), 9.09 (s, 1H), 7.78 (s, 1H), 7.74 (d, 1H, $J$ = 7.3 Hz), 7.58 (d, 1H, $J$ = 7.3 Hz), 7.48 (d, 1H, $J$ = 5.9 Hz), 6.56 (d, 1H, $J$ = 5.9 Hz), 4.47 (s, 2H), 3.35 (d, 2H, $J$ = 7.0 Hz,), 1.61 (m, 6H), 1.17 (m, 3H), 0.95 (m, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{18}H_{23}N_2O_3$, 315.1709. Found: 315.1742.

**5.1.107. (*E*)-3-(2-((Naphthalene-1-yl)methyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30d).** This compound was prepared from **29d** by means of a procedure similar to that used for **12** (29%). Mp >300 °C; $^1H$ NMR

(500 MHz, DMSO-$d_6$) $\delta$ 8.21 (d, 1H, $J$ = 9.1 Hz), 7,95 (d, 1H, $J$ = 7,4 Hz), 7.91 (dd, 1H, $J$ = 4.9, 4.9 Hz), 7.81 (s, 1H), 7.68 (d, 1H, $J$ = 7.4 Hz), 7.52 (m, 5H), 7.29 (d, 1H, $J$ = 7.1 Hz), 6.53 (d, 1H, $J$ = 7.1 Hz), 5.18 (s, 2H), 4.25 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{22}H_{19}N_2O_3$, 359.1396. Found: 359.1370.

**5.1.108. (*E*)-3-(2-(2-Chlorobenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30e).** This compound was prepared from **29e** by means of a procedure similar to that used for **12** (67%). Mp >300 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.74 (s, 1H), 9.07 (s, 1H), 7.87 (s, 1H), 7.78 (d, 1H, $J$ = 7.9 Hz), 7.60 (d, 1H, $J$ = 7.9 Hz), 7.55 (d, 1H, $J$ = 5.9 Hz), 7.49 (m, 1H), 7.33 (m, 2H), 7.26 (m, 1H), 6.57 (d, 1H, $J$ = 5.9 Hz), 4.82 (s, 2H), 4.42 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{18}H_{16}ClN_2O_3$, 3 43.0849. Found: 343.0898.

**5.1.109. (*E*)-3-(2-(3-Chlorobenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30f).** This compound was prepared from **29f** by means of a procedure similar to that used for **12** (35%). Mp 147–149 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.76 (s, 1H), 9.09 (s, 1H), 7.86 (s, 1H), 7.77 (d, 1H, $J$ = 7.3 Hz), 7.58 (d, 2H, $J$ = 7.9 Hz), 7.51 (d, 1H, $J$ = 5.9 Hz), 7.36 (m, 3H), 7.23 (d, 1H, $J$ = 7.3 Hz), 6.58 (d, 1H, $J$ = 5.9 Hz), 4.73 (s, 2H), 4.41 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{18}H_{16}ClN_2O_3$, 343.0849. Found: 343.0865.

**5.1.110. (*E*)-3-(2-(4-Chlorobenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30g).** This compound was prepared from **29g** by means of a procedure similar to that used for **12** (67%). Mp >300 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.82 (s, 1H), 7.74 (d, 1H, $J$ = 7.3 Hz,), 7.56 (d, 1H, $J$ = 7.3 Hz), 7.40 (d, 2H, $J$ = 8.2 Hz), 7.39 (d, 1H, $J$ = 5.9 Hz), 7.29 (d, 2H, $J$ = 8.2 Hz), 6.56 (d, 1H, $J$ = 5.9 Hz), 4.72 (s, 2 H), 4.38 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{18}H_{16}ClN_2O_3$, 343.0849. Found: 343.0889.

**5.1.111. (*E*)-3-(2-(2-(trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30h).** This compound was prepared from **29h** by means of a procedure similar to that used for **12** (61%). Mp 188–190 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.71 (s, 1H), 9.15 (s, 1H), 7.88 (s, 1H), 7.79 (d, 1H, $J$ = 8.0 Hz), 7.77 (d, 1H, $J$ = 7.3 Hz), 7.65 (d, 1H, $J$ = 7.3 Hz), 7.61 (dd, 1H, $J$ = 7.3, 7.3 Hz), 7.51 (dd, 1H, $J$ = 7.3, 7.3 Hz), 7.51 (d, 1H, $J$ = 5.9 Hz), 7.34 (d, 1H, $J$ = 8.0 Hz), 6.56 (d, 1H, $J$ = 5.9 Hz), 4.92 (s, 2H), 4.43 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{16}F_3N_2O_3$, 377.1113. Found: 377.1089.

**5.1.112. (*E*)-3-(2-(3-(Trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30i).** This compound was prepared from **29i** by means of a procedure similar to that used for **12** (73%). Mp 179–181 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.75 (s, 1H), 9.07 (s, 1H), 7.87 (s, 1H), 7.78 (d, 1H, $J$ = 8.0 Hz), 7.65 (m, 2H), 7.58 (m, 3H), 7.51 (d, 1H, $J$ = 5.8 Hz), 6.56 (d, 1H, $J$ = 5.8 Hz), 4.83 (s, 2H), 4.43 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{16}F_3N_2O_3$, 377.1113. Found: 377.1084.

**5.1.113. (*E*)-3-(2-(4-(Trifluoromethyl)benzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30j).** This compound was prepared from **29j** by means of a procedure similar to that used for **12** (35%). Mp >300 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.83 (s, 1H), 9.12 (s, 1H), 7.81 (s, 1H), 7.72 (d, 1H, $J$ = 7.3 Hz, 1H), 7.71 (d, 2H, $J$ = 8.0 Hz), 7.54 (d, 1H, $J$ = 7.3 Hz), 7.48 (d, 2H, $J$ = 8.0 Hz), 7.35 (d, 1H, $J$ = 5.6 Hz), 6.58 (d, 1H, $J$ = 5.6 Hz), 4.82 (s, 2H), 4.41 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{16}F_3N_2O_3$, 377.1113. Found: 377.1094.

**5.1.114. (*E*)-3-(2-(2-Methoxybenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30k).** This compound was prepared from **29k** by means of a procedure similar to that used for **12** (78%). Mp >300 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.95 (s, 1H), 9.03 (s, 1H), 7.86 (s, 1H), 7.70 (d, 1H, $J$ = 7.3 Hz), 7.53 (d, 1H, $J$ = 7.3 Hz), 7.28 (d, 1H, $J$ = 7.7 Hz), 7.27 (dd, 1H, $J$ = 7.3, 7.3 Hz,), 7.07 (d, 1H, $J$ = 7.3 Hz),7.03 (d, 1H, $J$ = 7.9 Hz), 6.89 (dd, 1H, $J$ = 7.3, 7.9 Hz), 6.56 (d, 1H, $J$ = 7.7 Hz), 4.68 (s, 2H), 4.37 (s, 2H), 3.82 (s, 3H) HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{19}F_3N_2O_4$, 339.1345. Found: 339.1367.

**5.1.115. (*E*)-3-(2-(3-Methoxybenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30l).** This compound was prepared from **29l** by means of a procedure similar to that used for **12** (46%). Mp 177–179 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.73 (s, 1H), 9.07 (s, 1H), 7.86 (s, 1H), 7.77 (d, 1H, $J$ = 7.9 Hz), 7.57 (d, 1H, $J$ = 7.9 Hz), 7.54 (d, 1H, $J$ = 5.9 Hz), 7.26 (dd, 1H, $J$ = 7.9, 7.9 Hz), 6.85 (d, 1H, $J$ = 7.9 Hz), 6.84 (s, 1H), 6.83 (d, 1H, $J$ = 7.9 Hz), 6.56 (d, 1H, $J$ = 5.9 Hz), 4.69 (s, 2H), 4.38 (s, 2H), 3.72 (s, 3H); HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{19}F_3N_2O_4$, 339.1345. Found: 339.1312.

**5.1.116. (*E*)-3-(2-(4-Methoxybenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30m).** This compound was prepared from **29m** by means of a procedure similar to that used for **12** (22%). Mp 145–147 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.72 (s, 1H), 9.06 (s, 1H), 7.85 (s, 1H), 7.76 (d, 1H, $J$ = 7.9 Hz), 7.57 (d, 1H, $J$ = 7.9 Hz), 7.54 (d, 1H, $J$ = 5.9 Hz), 7.21 (d, 2H, $J$ = 8.5 Hz), 6.90 (d, 2H, $J$ = 8.5 Hz), 6.56 (d 1H, $J$ = 5.9 Hz), 4.65 (s, 2H), 4.34 (s, 2H), 3.72 (s, 3H); HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{19}F_3N_2O_4$, 339.1345. Found: 339.1368.

**5.1.117. (*E*)-3-(2-(2-Methylbenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30n).** This compound was prepared from **29n** by means of a procedure similar to that used for **12** (80%). Mp >300 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.75 (s, 1H), 7.70 (d, 1H, $J$ = 7.3 Hz), 7.52 (d, 1H, $J$ = 7.3 Hz), 7.18 (d, 1H, $J$ = 5.9 Hz), 7.15 (m, 4H), 6.52 (d, 1H, $J$ = 5.9 Hz), 4.72 (s, 2H), 4.28 (s, 2H), 2.28 (s, 3H); HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{19}N_2O_3$, 323.1396. Found: 323.1386.

**5.1.118. (*E*)-3-(2-(3-Methylbenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30o).** This compound was prepared from **29o** by means of a procedure similar to that used for **12** (80%). Mp >300 °C; $^1$H NMR (500 MHz,

DMSO-$d_6$) $\delta$ 10.88 (s, 1H), 9.08 (s, 1H), 7.78 (s, 1H), 7.71 (d, 1H, $J$ = 6.1 Hz), 7.52 (d, 1H, $J$ = 6.1 Hz), 7.31 (d, 1H, $J$ = 5.7 Hz), 7.22 (dd, 1H, $J$ = 7.9, 7.9 Hz), 7.09 (d, 1H, $J$ = 7.9 Hz), 7.08 (s, 1H), 7.05 (d, 1H, $J$ = 7.9 Hz), 6.57 (d, 1H, $J$ = 5.7 Hz), 4.67 (s, 2H), 4.34 (s, 2H), 2.27 (s, 3H); HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{19}N_2O_3$, 323.1396. Found: 323.1416.

**5.1.119. (*E*)-3-(2-(4-Methylbenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30p).** This compound was prepared from **29p** by means of a procedure similar to that used for **12** (69%). Mp >300 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.77 (s, 1H), 7.71 (d, 1H, $J$ = 6.7 Hz), 7.52 (d, 1H, $J$ = 6.7 Hz), 7.29 (d, 1H, $J$ = 8.3 Hz,), 7.15 (s, 4H), 6.53 (d, 1H, $J$ = 8.3 Hz), 4.67 (s, 2H), 4.32 (s, 2H), 2.26 (s, 3H); HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{19}N_2O_3$, 323.1396. Found: 323.1362.

**5.1.120. (*E*)-3-(2-(2-Phenylbenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30q).** This compound was prepared from **29q** by means of a procedure similar to that used for **12** (88%). Mp 187–189 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.77 (s, 1H), 7.71 (d, 1H, $J$ = 7.4 Hz), 7.50 (d, 1H, $J$ = 7.4 Hz), 7.43 (m, 3H), 7.36 (m, 5H), 7.25 (m, 1H), 7.21 (m, 1H), 6.53 (d, 1H, $J$ = 5.9 Hz), 4.69 (s, 2H), 4.22 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{24}H_{21}N_2O_3$, 385.1552. Found: 385.1528.

**5.1.121. (*E*)-3-(2-(3-Phenylbenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30r).** This compound was prepared from **29r** by means of a procedure similar to that used for **12** (93%). Mp >300 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.79 (s, 1H), 7.71 (d, 1H, $J$ = 7.5 Hz), 7.63 (d, 2H, $J$ = 7.3 Hz), 7.58 (s, 1H), 7.57 (d, 1H, $J$ = 5.5 Hz), 7.53 (d, 1H, $J$ = 7.5 Hz), 7.45 (dd, 2H, $J$ = 7.3, 7.3 Hz), 7.44 (dd, 1H, $J$ = 7.5, 7.9 Hz), 7.44 (d, 1H, $J$ = 7.9 Hz), 7.35 (t, 1H, $J$ = 7.3 Hz), 7.26 (d, 1H, $J$ = 7.5 Hz), 6.53 (d, 1H, $J$ = 5.5 Hz), 4.80 (s, 2H), 4.41 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{24}H_{21}N_2O_3$, 385.1552. Found: 385.1555.

**5.1.122. (*E*)-3-(2-(4-Phenylbenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30s).** This compound was prepared from **29s** by means of a procedure similar to that used for **12** (66%). Mp 176–178 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.84 (s, 1H), 7.75 (d, 1H, $J$ = 7.4 Hz), 7.63 (d, 1H, $J$ = 5.9 Hz), 7.63 (m, 4H), 7.56 (d, 1H, $J$ = 7.4 Hz), 7.44 (m, 2H), 7.36 (m, 3H), 6.57 (d, 1H, $J$ = 5.9 Hz), 4.77 (s, 2H), 4.41 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{24}H_{21}N_2O_3$, 385.1552. Found: 385.1542.

**5.1.123. (*E*)-3-(2-(2-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30t).** This compound was prepared from **29t** by means of a procedure similar to that used for **12** (60%). Mp 173–174 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.71 (s, 1H), 9.21 (s, 1H), 7.88 (s, 1H), 7.77 (d, 1H, $J$ = 7.9 Hz), 7.57 (d, 1H, $J$ = 7.9 Hz), 7.50 (d, 1H, $J$ = 5.3 Hz), 7.40 (d, 1H, $J$ = 7.0 Hz), 7.20 (dd, 1H, $J$ = 7.0, 7.0 Hz), 7.15 (dd, 1H, $J$ = 7.0, 7.0 Hz), 7.05 (d, 1H, $J$ = 7.0 Hz), 6.57 (d, 1H, $J$ = 5.3 Hz), 4.99 (s, 2H), 4.34 (s, 2H), 1.99 (s, 9H); HR FAB MS: $(M+H)^+$ calcd for $C_{22}H_{25}N_2O_3$, 365.1865. Found: 365.1891.

**5.1.124. (*E*)-3-(2-(4-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30u).** This compound was prepared from **29u** by means of a procedure similar to that used for **12** (51%). Mp 169–170 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.69 (br, 1H), 9.13 (br, 1H), 7.85 (s, 1H), 7.76 (d, 1H, $J$ = 8.0 Hz), 7.56 (d, 1H, $J$ = 8.0 Hz), 7.51 (d, 1H, $J$ = 5.8 Hz), 7.36 (d, 2H, $J$ = 7.9 Hz), 7.19 (d, 2H, $J$ = 7.9 Hz), 6.54 (d, 1H, $J$ = 5.8 Hz), 4.68 (s, 2H), 4.37 (s, 2H), 1.25 (s, 9H); HR FAB MS: $(M+H)^+$ calcd for $C_{22}H_{25}N_2O_3$, 365.1865. Found: 365.1842.

**5.1.125. (*E*)-3-(2-Benzhydryl-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30v).** This compound was prepared from **29v** by means of a procedure similar to that used for **12** (73%). Mp 122–124 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.76 (s, 1H), 9.09 (s, 1H), 7.89 (s, 1H), 7.78 (d, 1H, $J$ = 8.0 Hz), 7.58 (d, 1H, $J$ = 8.0 Hz), 7.56 (d, 1H, $J$ = 5.8 Hz), 7.39 (d, 2H, $J$ = 7.3 Hz), 7.37 (d, 2H, $J$ = 7.3 Hz), 7.33 (t, 2H, $J$ = 7.3 Hz), 7.18 (dd, 4 H, $J$ = 7.3, 7.3 Hz), 6.65 (s, 1H), 6.57 (d, 1H, $J$ = 5.8 Hz), 4.28 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{24}H_{21}N_2O_3$, 385.1552. Found: 385.1528.

**5.1.126. (*E*)-3-(1-Oxo-2-(1,2-diphenylethyl)isoindolin-6-yl)-*N*-hydroxyacrylamide (30w).** This compound was prepared from **29w** by means of a procedure similar to that used for **12** (68%). Mp 136–137 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.73 (s, 1H), 9.07 (s, 1H), 7.73 (s, 1H), 7.72 (d, 1H, $J$ = 7.4 Hz), 7.53 (d, 1H, $J$ = 7.4 Hz), 7.48 (d, 1H, $J$ = 5.8 Hz), 7.45 (d, 2H, $J$ = 7.3 Hz), 7.36 (dd, 2H, $J$ = 7.3, 7.9 Hz), 7.28 (d, 2H, $J$ = 7.3 Hz), 7.27 (t, 1 H, $J$ = 7.9 Hz), 7.20 (dd, 2H, $J$ = 7.3, 7.9 Hz), 7.11 (t, 1 H, $J$ = 7.9 Hz), 6.50 (d, 1H, $J$ = 5.8 Hz), 5.74 (t, 1H, $J$ = 8.2 Hz), 4.58 (d, 1H, $J$ = 18.3 Hz), 4.12 (d, 1H, $J$ = 18.3 Hz), 3.44 (d, 2H, $J$ = 8.2 Hz); HR FAB MS: $(M+H)^+$ calcd for $C_{25}H_{23}N_2O_3$, 399.1709. Found: 399.1744.

**5.1.127. (*E*)-3-(1-Oxo-2-(1,3-diphenylpropyl)isoindolin-6-yl)-*N*-hydroxyacrylamide (30x).** This compound was prepared from **29x** by means of a procedure similar to that used for **12** (69%). Mp 133–134 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.12 (br, 1H), 7.84 (s, 1H), 7.75 (d, 1H, $J$ = 8.0 Hz), 7.56 (d, 2H, $J$ = 8.0 Hz), 7.51 (d, 1H, $J$ = 5.8 Hz), 7.36 (m, 3H), 7.23 (m, 5 H), 7.16 (t, 1H, $J$ = 6.8 Hz), 6.54 (d, 1H, $J$ = 5.8 Hz), 5.40 (dd, 1H, $J$ = 7.7, 9.8 Hz), 4.58 (d, 1H, $J$ = 18.2 Hz), 4.11 (d, 1H, $J$ = 18.2 Hz), 2.57 (m, 2H), 2.38 (m, 2H) ; HR FAB MS: $(M+H)^+$ calcd for $C_{26}H_{25}N_2O_3$, 413.1865. Found: 413.1848.

**5.1.128. (*E*)-3-(1-Oxo-2-(1,4-diphenylbutyl)isoindolin-6-yl)-*N*-hydroxyacrylamide (30y).** This compound was prepared from **29y** by means of a procedure similar to that used for **12** (27%). Mp 153–154 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.68 (s, 1H), 7.67 (d, 1H, $J$ = 7.0 Hz), 7.47 (d, 1H, $J$ = 7.9 Hz), 7.33 (m, 5H), 7.23 (m, 3H), 7.15 (d, 3H), 6.48 (d, 1H, $J$ = 7.0 Hz), 5.41 (dd, 1H, $J$ = 6.1, 9.2 Hz), 4.39 (d, 1H, $J$ = 17.8 Hz), 4.01 (d, 1H, $J$ = 17.8 Hz), 2.63 (m, 2H), 2.06 (m, 2H), 1.53 (m, 2H);

HR FAB MS: $(M+H)^+$ calcd for $C_{27}H_{27}N_2O_3$, 427.2022. Found: 427.2071.

**5.1.129. (*E*)-(*S*)-3-(2-(2-(Benzyloxy)-1-phenylethyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30z).** This compound was prepared from **29z** by means of a procedure similar to that used for **12** (85%). Mp 102–104 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.72 (s, 1H), 9.03 (s, 1H), 7.80 (s, 1H), 7.74 (d, 1H, $J$ = 7.9 Hz), 7.56 (d, 1H, $J$ = 7.9 Hz), 7.41 (d, 1H, $J$ = 6.4 Hz), 7.30 (m, 10H), 6.54 (d, 1H, $J$ = 6.4 Hz), 5.59 (dd, 1H, $J$ = 5.5, 8.5 Hz), 4.59 (d, 1H, $J$ = 12.2 Hz), 4.53 (d, 1H, $J$ = 18.0 Hz), 4.52 (d, 1H, $J$ = 12.2 Hz), 4.30 (d, 1H, $J$ = 18.0 Hz), 4.11 (dd, 1H, $J$ = 8.5, 10.3 Hz), 3.99 (dd, 1H, $J$ = 5.5, 10.3 Hz); $[\alpha]_D^{28.5}$ +63.5° ($c$ 0.158, $CHCl_3$); HR FAB MS: $(M+H)^+$ calcd for $C_{26}H_{25}N_2O_4$, 429.1814. Found: 429.1792.

**5.1.130. (*E*)-(*R*)-3-(2-(2-(Benzyloxy)-1-phenylethyl)-1-oxoisoindolin-6-yl)-*N*-hydroxyacrylamide (30aa).** This compound was prepared from **29aa** by means of a procedure similar to that used for **12** (42%). Mp 102–104 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.72 (s, 1H), 9.03 (s, 1H), 7.80 (s, 1H), 7.74 (d, 1H, $J$ = 7.9 Hz), 7.56 (d, 1H, $J$ = 7.9 Hz), 7.41 (d, 1H, $J$ = 6.4 Hz), 7.30 (m, 10H), 6.54 (d, 1H, $J$ = 6.4 Hz), 5.59 (dd, 1H, $J$ = 5.5, 8.5 Hz), 4.59 (d, 1H, $J$ = 12.2 Hz), 4.53 (d, 1H, $J$ = 18.0 Hz), 4.52 (d, 1H, $J$ = 12.2 Hz), 4.30 (d, 1H, $J$ = 18.0 Hz), 4.11 (dd, 1H, $J$ = 8.5, 10.3 Hz), 3.99 (dd, 1H, $J$ = 5.5, 10.3 Hz); $[\alpha]_D^{28.5}$ −86.3° ($c$ 0.143, $CHCl_3$); HR FAB MS: $(M+H)^+$ calcd for $C_{26}H_{25}N_2O_4$, 429.1814. Found: 429.1822.

**5.1.131. (*E*)-3-(2-Phenyl-1,3-dioxoisoindolin-5-yl)-*N*-hydroxyacrylamide (36a).** Mp 199–201 °C; $^1$HNMR(500 MHz, DMSO-$d_6$) $\delta$ 10.85 (s, 1H), 9.19 (s, 1H), 8.13 (d, 1H, $J$ = 0.6 Hz), 8.06 (dd, 1H, $J$ = 0.6, 7.4 Hz), 7.97 (d, 1H, $J$ = 7.4 Hz), 7.65 (d, 1H, $J$ = 5.9 Hz), 7.52 (m, 2H), 7.44 (m, 3H), 6.74 (d, 1H, $J$ = 5.9 Hz); HR FAB MS: $(M+H)^+$ calcd for $C_{17}H_{13}N_2O_4$, 309.0875. Found: 309.0865.

**5.1.132. (*E*)-3-(2-Benzyl-1,3-dioxoisoindolin-5-yl)-*N*-hydroxyacrylamide (36b).** Mp 163–166 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.84 (s, 1H), 9.17 (s, 1H), 8.05 (s, 1H), 8.00 (d, 1H, $J$ = 8.0 Hz), 7.90 (d, 1H, $J$ = 8.0 Hz), 7.62 (d, 1H, $J$ = 5.9 Hz), 7.30 (m, 5H), 6.70 (d, 1H, $J$ = 5.9 Hz), 4.77 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{18}H_{15}N_2O_4$, 323.1032. Found: 323.1038.

**5.1.133. (*E*)-3-(2-Phenethyl-1,3-dioxoisoindolin-5-yl)-*N*-hydroxyacrylamide (36c).** Mp 187–189 °C; $^1$HNMR (500 MHz, DMSO-$d_6$) $\delta$ 10.78 (s, 1H), 9.28 (s, 1H), 7.99 (s, 1H), 7.96 (d, 1H, $J$ = 7.9 Hz), 7.84 (d, 1H, $J$ = 7.9 Hz), 7.57 (d, 1H, $J$ = 5.9 Hz), 7.24 (m, 2H), 7.18 (m, 3H), 6.68 (d, 1H, $J$ = 5.9 Hz), 3.81 (t, 1H, $J$ = 7.3 Hz), 2.91 (t, 1H, $J$ = 7.3 Hz); HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{17}N_2O_4$, 337.1188. Found: 337.1209.

**5.1.134. (*E*)-3-(2-Benzhydryl-1,3-dioxoisoindolin-5-yl)-*N*-hydroxyacrylamide (36d).** Mp 142–144 °C; $^1$HNMR (500 MHz, $CDCl_3$), $\delta$ 8.48(s, 1H), 7.96 (s, 1H), 7.80 (m, 3H), 7.36 (m, 10H), 6.72 (s, 1H), 6.47 (m, 1H); HR FAB MS: $(M+H)^+$ calcd for $C_{24}H_{19}N_2O_4$, 399.1345. Found: 399.1352.

**5.1.135. (*E*)-3-(2-(2,2-Diphenylethyl)-1,3-dioxoisoindolin-5-yl)-*N*-hydroxyacrylamide (36e).** Mp 199–201 °C; $^1$HNMR (500 MHz, DMSO) $\delta$ 10.81 (s, 1H), 9.16 (s, 1H), 7.95 (s, 1H), 7.93 (d, 1H, $J$ = 7.9 Hz), 7.80 (d, 1H, $J$ = 7.9 Hz), 7.57 (d, 1H, $J$ = 5.9 Hz), 7.33 (d, 4H, $J$ = 7.3 Hz), 7.25 (dd, 4H, $J$ = 7.3 Hz), 7.17 (d, 2H, $J$ = 7.3 Hz), 6.66 (d, 1H, $J$ = 5.9 Hz), 4.57 (t, 1H, $J$ = 8.0 Hz), 4.23 (d, 2H, $J$ = 8.0 Hz); HR FAB MS: $(M+H)^+$ calcd for $C_{25}H_{21}N_2O_4$, 413.1501. Found: 413.1541.

**5.1.136. (*E*)-(*S*)-Hydroxy-3-(1,3-dioxo-2-(1-phenylethyl)isoindolin-5-yl)acrylamide (36f).** Mp 137–138 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.84 (s, 1H), 9.17 (s, 1H), 8.01 (s, 1H), 8.00 (d, 1H, $J$ = 7.9 Hz), 7.86 (d, 1H, $J$ = 7.9 Hz), 7.60 (d, 1H, $J$ = 5.8 Hz), 7.32 (m, 5H), 6.68 (d, 1H, $J$ = 5.8 Hz), 5.45 (q, 1H, $J$ = 7.3 Hz), 1.81 (d, 3H, $J$ = 7.3 Hz): HR FAB MS: $(M+H)^+$ calcd for $C_{19}H_{17}N_2O_4$ 337.1188. Found: 337.1196.

**5.1.137. (*E*)-(*R*)-Hydroxy-3-(1,3-dioxo-2-(1-phenylethyl)isoindolin-5-yl)acrylamide (36g).** Mp 136–138 °C; $^1$HNMR (500 MHz, DMSO-$d_6$) $\delta$ 10.82 (s, 1H), 9.17 (s, 1H), 8.01 (s, 1H), 8.00 (d, 1H, $J$ = 7.9 Hz), 7.86 (d, 1H, $J$ = 7.9 Hz), 7.60 (d, 1H, $J$ = 5.8 Hz), 7.32 (m, 5H), 6.68 (d, 1H, $J$ = 5.8 Hz), 5.45 (q, 1H, $J$ = 7.3 Hz), 1.81 (d, 3H, $J$ = 7.3 Hz): HR FAB MS : $(M+H)^+$ calcd for $C_{19}H_{17}N_2O_4$ 337.1188. Found: 337.1190.

**5.1.138. (*E*)-(*S*)-3-(2-(2-(Benzyloxy)-1-phenylethyl)-1,3-dioxoisoindolin-5-yl)-*N*-hydroxyacrylamide (36h).** Mp 84–86 °C; $^1$HNMR (500 MHz, $CDCl_3$) $\delta$ 9.33 (s, 1H), 7.94 (s, 1H), 7.79 (d, 1H, $J$ = 8.0 Hz), 7.74 (d, 1H, $J$ = 5.5 Hz), 7.72 (d, 1H, $J$ = 8.0 Hz), 7.48 (m, 2H), 7.26 (m, 8H), 6.46 (d, 1H, $J$ = 5.5 Hz), 5.61 (dd, 1H, $J$ = 5.5, 10.3 Hz), 4.65 (dd, 1H, $J$ = 10.3, 10.3 Hz) 4.57 (s, 2H), 4.02 (dd, 1H, $J$ = 5.5, 10.3 Hz); $[\alpha]_D^{25.5}$ +5.47° ($c$ 0.150, $CH_3CN$); HR FAB MS: $(M+H)^+$ calcd for $C_{26}H_{23}N_2O_5$, 443.1607. Found: 443.1643.

**5.1.139. (*E*)-(*R*)-3-(2-(2-(Benzyloxy)-1-phenylethyl)-1,3-dioxoisoindolin-5-yl)-*N*-hydroxyacrylamide (36i).** Mp 84–86 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.33 (s, 1H), 7.94 (s, 1H), 7.79 (d, 1H, $J$ = 8.0 Hz), 7.74 (d, 1H, $J$ = 5.5 Hz), 7.72 (d, 1H, $J$ = 8.0 Hz), 7.48 (m, 2H), 7.26 (m, 8H), 6.46 (d, 1H, $J$ = 5.5 Hz), 5.61 (dd, 1H, $J$ = 5.5, 10.3 Hz), 4.65 (dd, 1H, $J$ = 10.3, 10.3 Hz) 4.57 (s, 2H), 4.02 (dd, 1H, $J$ = 5.5, 10.3 Hz); $[\alpha]_D^{25.5}$ −5.37° ($c$ 0.149, $CH_3CN$); HR FAB MS: $(M+H)^+$ calcd for $C_{26}H_{23}N_2O_5$, 443.1607. Found: 443.1638.

**5.1.140. Methyl 5-hydroxy-2-methylbenzoate (37).** To a mixture of methyl 5-amino-2-methylbenzoate (626 mg, 3.79 mmol), 1 mL of concd $H_2SO_4$, and 16 mL of water, cooled to below 0 °C, was added an aqueous solution of $NaNO_2$ (262 mg, 3.79 mmol in mL of water), and the mixture was stirred for a further 5 min. The solution was added to a refluxing solution of copper (II) sulfate (1.6 g in 28 mL water) and refluxed for 30 min. After

cooling, the reaction mixture was extracted with $CHCl_3$. The product was re-extracted with 1 mol/L NaOH solution, acidified with 2 mol/L HCL, and extracted with $CHCl_3$. The extract was dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt 2:1 v/v) to afford 369 mg (59%) of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.41 (d, 1H, $J$ = 2.8 Hz), 7.11 (d, 1H, $J$ = 8.2 Hz), 6.91 (dd, 1H, $J$ = 2.8, 8.2 Hz), 5.01 (m, 1H), 3.89 (s, 3H), 2.51 (s, 3H); FAB MS *m*/*z* 167 $(M+H)^+$.

**5.1.141. Methyl 5-((*tert*-butoxycarbonyl)methoxy)-2-methylbenzoate (38).** To a mixture of **37** (369 mg, 2.22 mmol) and potassium carbonate (460 mg, 3.33 mmol) in 10 mL of DMF was added *t*-butyl bromoacetate (360 μl, 2.44 mmol). The reaction mixture was stirred for 1 day at 100 °C. After cooling, the reaction mixture was poured into water, extracted with AcOEt, washed with dil HCl, dil NaOH, and brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt 8:1 to 5:1 v/v) to afford 573 mg (92%) of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.43 (d, 1H, $J$ = 2.4 Hz), 7.14 (d, 1H, $J$ = 8.3 Hz), 6.98 (dd, 1H, $J$ = 2.4, 8.3 Hz), 4.51 (s, 2H), 3.87 (s, 3H), 2.51 (s, 3H), 1.48 (s, 9H); FAB MS *m*/*z* 281 $(M+H)^+$.

**5.1.142. Methyl 5-((*tert*-butoxycarbonyl)methoxy)-2-(bromomethyl)benzoate (39).** This compound was prepared from **39** by means of a procedure similar to that used for **15** (57%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.47 (d, 1H, $J$ = 2.7 Hz), 7.37 (d, 1H, $J$ = 8.6 Hz), 7.02 (dd, 1H, $J$ = 2.7, 8.6 Hz), 4.92 (s, 2H), 4.54 (s, 2H), 3.93 (s, 3H), 1.49 (s, 9H); FAB MS *m*/*z* 358, 360 $(M)^+$.

**5.1.143. *tert*-Butyl 2-(2-benzyl-1-oxoisoindolin-6-yloxy)-acetate (40a).** This compound was prepared from **39** by means of a procedure similar to that used for **16** (55%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.26 (m, 7H), 7.11 (dd, 1H, $J$ = 2.4, 8.2 Hz), 4.76 (s, 2H), 4.55 (s, 2H), 4.16 (s, 2H), 1.47 (s, 9H); FAB MS *m*/*z* 354 $(M+H)^+$.

**5.1.144. *tert*-Butyl 2-(2-(2-phenylbenzyl)-1-oxoisoindolin-6-yloxy)acetate (40b).** This compound was prepared from **39** by means of a procedure similar to that used for **16** (80%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.22–7.44 (m, 11H), 7.12 (m, 1H), 4.79 (s, 2H), 4.57 (s, 2H), 4.00 (s, 2H), 1.50 (s, 9H); FAB MS *m*/*z* 430 $(M+H)^+$.

**5.1.145. *tert*-Butyl 2-(2-(4-phenylbenzyl)-1-oxoisoindolin-6-yloxy)acetate (40c).** This compound was prepared from **39** by means of a procedure similar to that used for **16** (22%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.55 (m, 4H), 7.26–7.44 (m, 7H), 7.16 (m, 1H), 4.83 (s, 2H), 4.59 (s, 2H), 4.25 (s, 2H), 1.50 (s, 9H); FAB MS *m*/*z* 430 $(M+H)^+$.

**5.1.146. *tert*-Butyl 2-(2-(2-*tert*-butylbenzyl)-1-oxoisoindolin-6-yloxy)acetate (40d).** This compound was prepared from **39** by means of a procedure similar to that used for **16** (22%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.42 (d, 1H, $J$ = 8.3 Hz), 7.33 (d, 1H, $J$ = 2.4 Hz), 7.27 (d, 1H, $J$ = 8.2 Hz), 7.20 (m, 1H), 7.17 (dd, 1H, $J$ = 2.4, 8.2 Hz), 7.14 (m, 2H), 5.11 (s, 2H), 4.60 (s, 2H), 4.16 (s, 2H), 1.51 (s, 9H), 1.47 (s, 9H); FAB MS *m*/*z* 410 $(M+H)^+$.

**5.1.147. *tert*-Butyl 2-(2-(4-*tert*-butylbenzyl)-1-oxoisoindolin-6-yloxy)acetate (40e).** This compound was prepared from **39** by means of a procedure similar to that used for **16** (43%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.34 (d, 2H, $J$ = 8.3 Hz), 7.29 (d, 1H, $J$ = 2.4 Hz), 7.27 (d, 1H, $J$ = 8.2 Hz), 7.22 (d, 2H, $J$ = 8.3 Hz), 7.15 (dd, 1H, $J$ = 2.4, 8.2 Hz), 4.76 (s, 2H), 4.58 (s, 2H), 4.20 (s, 2H), 1.50 (s, 9H), 1.30 (s, 9H); FAB MS *m*/*z* 410 $(M+H)^+$.

**5.1.148. 2-(2-Benzyl-1-oxoisoindolin-6-yl-oxy)acetic acid (41a).** This compound was prepared from **40a** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 13.01 (s, 1H), 7.44 (d, 1H, $J$ = 8.2 Hz), 7.34 (dd, 2H, $J$ = 7.2, 7.2 Hz), 7.27 (t, 1H, $J$ = 7.2 Hz), 7.25 (d, 2H, $J$ = 7.2 Hz), 7.16 (dd, 1H, $J$ = 2.2, 8.2 Hz), 7.15 (d, 1H, $J$ = 2.2 Hz), 4.77 (s, 2H), 4.71 (s, 2H), 4.28 (s, 2H); FAB MS *m*/*z* 298 $(M+H)^+$.

**5.1.149. 2-(2-(2-Phenylbenzyl)-1-oxoisoindolin-6-yl-oxy)-acetic acid (41b).** This compound was prepared from **40b** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 13.01 (s, 1H), 7.44 (d, 1H, $J$ = 8.2 Hz), 7.34 (dd, 2H, $J$ = 7.2, 7.2 Hz), 7.27 (t, 1H, $J$ = 7.2 Hz), 7.25 (d, 2H, $J$ = 7.2 Hz), 7.16 (dd, 1H, $J$ = 2.2, 8.2 Hz), 7.15 (d, 1H, $J$ = 2.2 Hz), 4.77 (s, 2H), 4.71 (s, 2H), 4.28 (s, 2H); FAB MS *m*/*z* 298 $(M+H)^+$.

**5.1.150. 2-(2-(4-Phenylbenzyl)-1-oxoisoindolin-6-yl-oxy)-acetic acid (41c).** This compound was prepared from **40c** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.55 (d, 2H, $J$ = 7.8 Hz), 7.55 (d, 2H, $J$ = 7.8 Hz), 7.50 (d, 1H, $J$ = 2.0 Hz), 7.43 (dd, 2H, $J$ = 7.8, 7.8 Hz), 7.35 (d, 2H, $J$ = 7.8 Hz), 7.31 (d, 1H, $J$ = 8.3 Hz), 7.23 (dd, 1H, $J$ = 2.0, 8.3 Hz), 7.17 (t, 1H, $J$ = 7.8 Hz), 4.83 (s, 2H), 4.82 (s, 2H), 4.28 (s, 2H); FAB MS *m*/*z* 374 $(M+H)^+$.

**5.1.151. 2-(2-(2-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl-oxy)acetic acid (41d).** This compound was prepared from **40d** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 11.00 (br, 1H), 7.52 (s, 1H), 7.40 (d, 1H, $J$ = 8.0 Hz), 7.27 (d, 1H, $J$ = 8.6 Hz), 7.20 (m, 2H), 7.13 (d, 1H, $J$ = 7.3 Hz), 7.08 (d, 1H, $J$ = 8.0 Hz), 5.10 (s, 2H), 4.80 (s, 2H), 4.18 (s, 2H), 1.45 (s, 9H); FAB MS *m*/*z* 354 $(M+H)^+$.

**5.1.152. 2-(2-(4-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl-oxy)acetic acid (41e).** This compound was prepared from **40e** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 12.02 (br, 1H), 7.56 (d, 1H, $J$ = 1.8 Hz), 7.38 (d, 2H, $J$ = 8.0 Hz), 7.31 (d, 1H, $J$ = 8.6 Hz), 7.25 (m, 3H), 4.86 (s, 2H), 4.80 (s, 2H), 4.26 (s, 2H), 1.34 (s, 9H); FAB MS *m*/*z* 354 $(M+H)^+$.

**5.1.153. 2-(2-Benzyl-1-oxoisoindolin-6-yloxy)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acetamide (42a).** This compound was prepared from **41a** by means of a procedure similar to that used for **11** (58%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.17 (s, 1H), 7.40 (s, 1H), 7.30 (m, 6H), 7.10 (d, 1H, $J$ = 8.0 Hz), 5.03 (m, 1H), 4.79 (s, 2H), 4.64 (s, 2H), 4.21 (s, 2H), 4.01 (m, 1H), 3.67 (m, 1H), 1.84 (m, 3H), 1.61 (m, 3H); FAB MS $m/z$ 397 $(M+H)^+$.

**5.1.154. 2-(2-(2-Phenylbenzyl)-1-oxoisoindolin-6-yl-oxy)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acetamide (42b).** This compound was prepared from **41b** by means of a procedure similar to that used for **11** (45%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.12 (br, 1H), 7.35 (m, 11H), 7.08 (d, 1H, $J$ = 6.4 Hz), 5.03 (m, 1H), 4.81 (s, 2H), 4.62 (s, 2H), 4.01 (s, 2H), 4.00 (m, 1H), 3.66 (m, 1H), 1.84 (m, 3H), 1.60 (m, 3H); FAB MS $m/z$ 473 $(M+H)^+$.

**5.1.155. 2-(2-(4-Phenylbenzyl)-1-oxoisoindolin-6-yl-oxy)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acetamide (42c).** This compound was prepared from **41c** by means of a procedure similar to that used for **11** (33%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.57 (br, 1H), 7.33-7.57 (m, 11H), 7.11 (m, 1H), 4.84 (s, 2H), 4.65 (s, 2H), 4.27 (s, 2H), 1.29 (s, 9H); FAB MS $m/z$ 445 $(M+H)^+$.

**5.1.156. 2-(2-(2-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl-oxy)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acetamide (42d).** This compound was prepared from **41d** by means of a procedure similar to that used for **11** (31%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.18 (s, 1H), 7.43 (m, 1H), 7.42 (s, 1H), 7.30 (d, 1H, $J$ = 8.2 Hz), 7.20 (m, 1H), 7.13 (m, 2H), 7.11 (d, 1H, $J$ = 8.2 Hz), 5.11 (s, 2H), 5.03 (m, 1H), 4.65 (s, 2H), 4.17 (s, 2H), 4.01 (m, 1H), 3.66 (m, 1H), 1.84 (m, 3H), 1.60 (m, 3H), 1.47 (s, 9H); FAB MS $m/z$ 453 $(M+H)^+$.

**5.1.157. 2-(2-(4-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl-oxy)-*N*-(tetrahydro-2*H*-pyran-2-yloxy)acetamide (42e).** This compound was prepared from **41e** by means of a procedure similar to that used for **11** (25%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.24 (s, 1H), 7.38 (s, 1H), 7.34 (d, 2H, $J$ = 8.3 Hz), 7.28 (d, 1H, $J$ = 8.2 Hz), 7.22 (d, 2H, $J$ = 8.3 Hz), 7.09 (d, 1H, $J$ = 8.2 Hz), 5.03 (m, 1H), 4.75 (s, 2H), 4.63 (s, 2H), 4.21 (s, 2H), 4.01 (m, 1H), 3.65 (m, 1H), 1.83 (m, 3H), 1.60 (m, 3H), 1.29 (s, 9H); FAB MS $m/z$ 453 $(M+H)^+$.

**5.1.158. 2-(2-Benzyl-1-oxoisoindolin-6-yloxy)-*N*-hydroxyacetamide (43a).** This compound was prepared from **42a** by means of a procedure similar to that used for **12** (29%). Mp 126–128 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.83 (s, 1H), 8.96 (s, 1H), 7.45 (d, 1H, $J$ = 8.5 Hz), 7.34 (dd, 2H, $J$ = 7.3, 7.3 Hz), 7.27 (t, 1H, $J$ = 7.3 Hz), 7.25 (d, 2H, $J$ = 7.3 Hz), 7.23 (d, 1H, $J$ = 2.5 Hz), 7.18 (dd, 1H, $J$ = 2.5, 8.5 Hz), 4.71 (s, 2H), 4.54 (s, 2H), 4.28 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{17}H_{17}N_2O_4$, 313.1188. Found: 313.1218.

**5.1.159. 2-(2-(2-Phenylbenzyl)-1-oxoisoindolin-6-yl-oxy)-*N*-hydroxyacetamide (43b).** This compound was prepared from **42b** by means of a procedure similar to that used for **12** (9%). Mp 126–128 °C; $^1$HNMR (500 MHz, DMSO-$d_6$) $\delta$ 10.92 (br, 1H), 8.86 (br, 1H), 7.37 (m, 8H), 7.25 (m, 1H), 7.16 (m, 3H), 4.67 (s, 2H), 4.48 (s, 2H), 4.13 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{23}H_{21}N_2O_4$, 389.1501. Found: 389.1548.

**5.1.160. 2-(2-(4-Phenylbenzyl)-1-oxoisoindolin-6-yl-oxy)-*N*-hydroxyacetamide (43c).** This compound was prepared from **42c** by means of a procedure similar to that used for **12** (9%). Mp 157–158 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.92 (br, 1H), 8.89 (br, 1H), 7.63 (m, 4H), 7.44 (m, 3H), 7.33 (m, 4H), 7.16 (m, 1H), 4.75 (s, 2H), 4.50 (s, 2H), 4.30 (s, 2H); HR FAB MS: $(M+H)^+$ calcd for $C_{23}H_{21}N_2O_4$, 389.1501. Found: 389.1529.

**5.1.161. 2-(2-(2-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl-oxy)-*N*-hydroxyacetamide (43d).** This compound was prepared from **42d** by means of a procedure similar to that used for **12** (41%). Mp 157–158 °C; $^1$H NMR (500 MHz, $CD_3OD$) $\delta$ 7.45 (d, 1H, $J$ = 7.7 Hz), 7.44 (d, 1H, $J$ = 8.4 Hz), 7.38 (d, 1H, $J$ = 2.2 Hz), 7.26 (dd, 1H, $J$ = 2.2, 8.4 Hz), 7.20 (dd, 1H, $J$ = 7.7, 7.7 Hz), 7.14 (dd, 1H, $J$ = 7.7, 7.7 Hz), 7.07 (d, 1H, $J$ = 7.7 Hz), 5.10 (s, 2H), 4.64 (s, 2H), 4.26 (s, 2H), 1.48 (s, 9H); HR FAB MS: $(M+H)^+$ calcd for $C_{21}H_{25}N_2O_4$, 369.1814. Found: 369.1824.

**5.1.162. 2-(2-(4-*tert*-Butylbenzyl)-1-oxoisoindolin-6-yl-oxy)-*N*-hydroxyacetamide (43e).** This compound was prepared from **42e** by means of a procedure similar to that used for **12** (61%). Mp 155–157 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.43 (d, 1H, $J$ = 8.2 Hz), 7.38 (d, 2H, $J$ = 8.3 Hz,), 7.35 (d, 1H, $J$ = 2.6 Hz), 7.24 (dd, 1H, $J$ = 2.6, 8.2 Hz), 7.21 (d, 2H, $J$ = 8.3 Hz), 4.75 (s, 2H), 4.62 (s, 2H), 4.29 (s, 2H), 1.29 (s, 9H); HR FAB MS: $(M+H)^+$ calcd for $C_{21}H_{25}N_2O_4$, 369.1814. Found: 369.1807.

**5.1.163. *N*-Benzyl-2-methyl-5-nitrobenzamide (45).** To a solution of 2-methyl-5-nitrobenzoic acid (500 mg, 2.76 mmol), triethylamine (0.846 mL, 6.07 mmol), and 5 mL of anhydrous THF, cooled to 0 °C, was added ethyl chloroformate (0.264 mL, 2.76 mmol). The mixture was stirred for 1 h, then benzylamine (0.362 mL, 3.31 mmol) was added and the whole was stirred overnight. The reaction mixture was evaporated and the residue was redissolved in AcOEt. This solution was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt 2:1 v/v) to afford 520 mg (70%) of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.24 (d, 1H, $J$ = 2.5 Hz), 8.17 (dd, 1H, $J$ = 2.5, 8.6 Hz), 7.40 (d, 1H, $J$ = 8.6 Hz), 7.38 (m, 5H), 6.12 (m, 1H), 4.65 (d, 2H, $J$ = 5.8 Hz), 2.58 (s, 3H); FAB MS $m/z$ 271 $(M+H)^+$.

**5.1.164. 5-Amino-*N*-benzyl-2-methylbenzamide (46).** A mixture of **45** (520 mg, 1.92 mmol), 48 mg of 10% Pd–C 48 mg (0.846 mL, 6.07 mmol), and 6 mL of AcOEt was hydrogenated at room temperature for 2 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated to afford 420 mg (91%) of the title compound. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.30 (m, 5H), 6.93(d, 1H, $J$ = 7.9 Hz), 6.62 (d, 1H, $J$ = 2.5 Hz),

6.56 (dd, 1H, $J$ = 2.5, 7.9 Hz), 6.17 (m, 1H), 4.54 (d, 2H, $J$ = 5.8 Hz), 3.57 (br, 2H), 2.28 (s, 3H); FAB MS $m/z$ 241 $(M+H)^+$.

**5.1.165. *tert*-Butyl 3-(3-(benzylcarbamoyl)-4-methylphenyl)-2-bromopropanoate (47).** This compound was prepared from **47** by means of a procedure similar to that used for **18** (85%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.36 (m, 5H), 7.23 (s, 1H), 7.16 (m, 2H), 6.00 (m, 1H), 4,62 (d, 2H, $J$ = 5.5 Hz), 4.23 (dd, 1H, $J$ = 7.0, 8.3 Hz), 3.39 (dd, 1H, $J$ = 8.3, 14.1 Hz), 3.14 (dd, 1H, $J$ = 7.0, 14.1 Hz,), 2.44 (s, 3H), 1.42 (s, 9H); FAB MS $m/z$ 432, 434 $(M+H)^+$.

**5.1.166. (*E*)-*tert*-Butyl 3-(3-(benzylcarbamoyl)-4-methylphenyl)acrylate (48).** This compound was prepared from **47** by means of a procedure similar to that used for **19** (quant.). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.50 (d, 1H, $J$ = 5.8 Hz), 7.47 (s, 1H), 7.42 (d, 1H, $J$ = 7.9 Hz), 7.36 (m, 5H), 7.20 (d, 1H, $J$ = 7.9 Hz), 6.30 (d, 1H, $J$ = 5.8 Hz), 6.20 (m, 1H), 4.61 (d, 2H, $J$ = 5.5 Hz), 2.45 (s, 3H), 1.52 (s, 9H); FAB MS $m/z$ 352 $(M+H)^+$.

**5.1.167. (*E*)-3-(3-(Benzylcarbamoyl)-4-methylphenyl)-acrylic acid (49).** This compound was prepared from **47** by means of a procedure similar to that used for **28c** (quant.). $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 12.36 (br, 1H), 8.86 (t, 1H, $J$ = 6.3 Hz), 7.67 (s, 1H), 7.64 (d, 1H, $J$ = 7.8 Hz), 7.58 (d, 1H, $J$ = 5.6 Hz), 7.34 (m, 5H), 7.28 (d, 1H, $J$ = 7.8 Hz), 6.52 (d, 1H, $J$ = 5.6 Hz), 4.44 (d, 2H, $J$ = 6.3 Hz), 2.34 (s, 3H); FAB MS $m/z$ 296 $(M+H)^+$.

**5.1.168. 5-((*E*)-2-(Tetrahydro-2*H*-pyran-2-yloxycarbamoyl)vinyl)-*N*-benzyl-2-methylbenzamide (50).** This compound was prepared from **49** by means of a procedure similar to that used for **11** (52%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 8.96 (br, 1H), 7.58 (d, 1H, $J$ = 5.5 Hz), 7.44 (s, 1H), 7.32 (m, 6H), 7.18 (d, 1H, $J$ = 7.7 Hz), 6.41 (d, 1H, $J$ = 5.5 Hz), 6.28 (br, 1H), 4.97 (m, 1H), 4.59 (d, 2H, $J$ = 5.6 Hz), 3.96 (m, 1H), 3.63 (m, 1H), 2.43 (s, 3H), 1.81 (m, 3H), 1.63 (m, 3H); FAB MS $m/z$ 395 $(M+H)^+$.

**5.1.169. 5-((*E*)-2-(Hydroxycarbamoyl)vinyl)-*N*-benzyl-2-methylbenzamide (51).** This compound was prepared from **49** by means of a procedure similar to that used for **12** (51%). Mp 172–173 °C; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.69 (s, 1H), 9.04 (s, 1H), 8.89 (t, 1H, $J$ = 6.1 Hz), 7.53 (s, 1H), 7.50 (d, 1H, $J$ = 8.1 Hz), 7.42 (d, 1H, $J$ = 6.2 Hz), 7.35 (m, 3H), 7.27 (d, 2H, $J$ = 8.1 Hz), 7.25 (m, 1H), 6.45 (d, 1H, $J$ = 6.2 Hz), 4.43 (d, 2H, $J$ = 6.1 Hz), 2.33 (s, 3H); HR FAB MS: $(M+H)^+$ calcd for $C_{18}H_{19}N_2O_3$, 311.1396. Found: 311.1382.

**5.1.170. *N*-Benzyl-3-formyl-*N*-methylbenzamide (53).** This compound was prepared from **52** by means of a procedure similar to that used for **45** (34%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 10.04 (s, 1H), 9.97 (s, 1H), 7.73 (m, 1H), 7.60 (m, 1H), 7.37 (m, 5H), 7.31(m, 1H), 4.77 (s, 2H), 2.88 (s, 3H), minor; $\delta$ 9.98 (s, 1H), 9.97 (s, 1H), 7.93 (m, 1H), 7.55 (m, 1H), 7.37 (m, 5H), 7.15(m, 1H), 4.50 (s, 2H), 3.07 (s, 3H); FAB MS $m/z$ 254 $(M+H)^+$.

**5.1.171. (*E*)-Methyl 3-(3-(*N*-benzyl-*N*-methylcarbamoyl)phenyl)acrylate (54).** To a mixture of diethylphosphonoacetate (0.176 mL, 0.97 mmol), potassium *tert*-butoxide (109 mg, 0.97 mmol), and 10 mL of anhydrous THF was added a THF solution of **53** ((223 mg, 0.88 mmol)/5 mL) under an Ar atmosphere, and the whole was stirred overnight at room temperature. The reaction mixture was evaporated and the residue was redissolved in AcOEt. This solution was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The residue was purified by silica gel column chromatography (eluant *n*-hexane/AcOEt 1:1 v/v) to afford 214 mg (79%) of the title compound (mixture of regioisomers). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.68 (d, 1H, $J$ = 5.9 Hz), 7.60 (s, 1H), 7.56 (d, 1H, $J$ = 6.7 Hz), 7.37 (m, 6H), 7.16 (d, 1H, $J$ = 6.0 Hz), 6.48 (d, 1H, $J$ = 5.9 Hz), 4.76 (s, 2H), 3.80 (s, 3H), 2.86 (s, 3H), minor; $\delta$ 7.65 (d, 1H, $J$ = 15.5 HzH), 7.60 (s, 1H), 7.52 (d, 1H, $J$ = 6.7 Hz), 7.37 (m, 6H), 7.17 (d, 1H, $J$ = 6.3 Hz), 6.33 (d, 1H, $J$ = 15.5 Hz), 4.50 (s, 2H), 3.80 (s, 3H), 3.06 (s, 3H); FAB MS $m/z$ 310 $(M+H)^+$.

**5.1.172. (*E*)-3-(3-(*N*-Benzyl-*N*-methylcarbamoyl)phenyl)acrylic acid (55).** This compound was prepared from **54** by means of a procedure similar to that used for **10** (75%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ major; $\delta$ 7.77 (d, 1H, $J$ = 5.9 Hz), 7.64 (s, 1H), 7.59 (d, 1H, $J$ = 6.7 Hz), 7.37 (m, 6H), 7.17 (d, 1H, $J$ = 6.3 Hz), 6.48 (d, 1H, $J$ = 5.9 Hz), 4.78 (s, 2H), 2.88 (s, 3H), minor; $\delta$ 7.70 (d, 1H, $J$ = 5.9 Hz), 7.64 (s, 1H), 7.56 (d, 1H, $J$ = 6.7 Hz,), 7.37 (m, 6H), 7.17 (d, 1H, $J$ = 6.3 Hz), 6.33 (d, 1H, $J$ = 5.9 Hz), 4.52 (s, 2H), 3.08 (s, 3H) FAB MS $m/z$ 296 $(M+H)^+$.

**5.1.173. 3-((*E*)-2-(Tetrahydro-2*H*-pyran-2-yloxycarbamoyl)vinyl)-*N*-benzyl-*N*-methylbenzamide (56).** This compound was prepared from **55** by means of a procedure similar to that used for **11** (37%). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ major; $\delta$ 8.99 (br, 1H), 7.38 (m, 8H), 7.16 (d, 1H, $J$ = 6.4 Hz), 6.33 (br, 1H), 5.01 (m, 1H), 4.76 (s, 2H), 3.99 (m, 1H), 3.65 (m, 1H), 2.85 (s, 3H), 1.85 (m, 3H), 1.60 (m, 3H), minor; $\delta$ 9.18 (br, 1H), 7.38 (m, 8H), 7.16 (d, 1H, $J$ = 6.4 Hz), 6.08 (br, 1H), 5.01 (m, 1H), 4.50 (s, 2H), 3.99 (m, 1H), 3.65 (m, 1H), 3.07 (s, 3H), 1.85 (m, 3H), 1.60 (m, 3H); FAB MS $m/z$ 395 $(M+H)^+$.

**5.1.174. 3-((*E*)-2-Hydroxyvinyl)-*N*-benzyl-*N*-methylbenzamide (57).** This compound was prepared from **56** by means of a procedure similar to that used for **12** (78%). $^1$H NMR (500 MHz, DMSO-$d_6$) major; $\delta$ 10.75 (s, 1H), 9.08 (s, 1H), 7.17–7.63 (m, 10H), 6.52 (d, 1H, $J$ = 6.6 Hz), 4.68 (s, 2H), 2.82 (s, 3H), minor; $\delta$ 10.75 (s, 1H), 9.08 (s, 1H), 7.17–7.63 (m, 10H), 6.46 (d, 1H, $J$ = 6.6 Hz), 4.46 (s, 2H), 2.89 (s, 3H); HR FAB MS: $(M+H)^+$ calcd for $C_{18}H_{19}N_2O_3$, 311.1396. Found: 311.1440.

### 5.2. HDAC activity assay kit

The assay of HDAC-inhibitory activity was performed using an HDAC fluorescence activity assay/drug discovery kit (AK-500, BIOMOL Research Laboratories), according to the supplier's protocol. The assay was performed in triplicate and repeated at least two times. The $EC_{50}$ of SAHA (**7**) determined with this assay system was reported to be 280 nM.[20]

### 5.3. Other enzyme assays

Assay of inhibitory activities against partially purified HDAC1, 4, and 6 was done according to the reported methods.[19,21] HDAC1, 4, and 6 were used as representative class I, class IIa, and class IIb enzymes, respectively.

In this study, kit assay was performed as an initial screening method to evaluate the importance of the cyclic amide/imide structure. The individual enzyme assays were performed as a second screen to evaluate the relationship between structure and class-selective HDAC inhibitory activity.

### 5.4. P21 promoter assay

P21 promoter assay was done according to the reported methods.[6,20]

### 5.5. Assay of growth-inhibitory activity toward human prostate cancer cell line LNCap

Exponentially growing cells in RPMI1640 medium supplemented with 10% fetal bovine serum were adjusted to $2 \times 10^4$ cells/mL, then 100 μL aliquots were plated in 96-well plates and incubated for 24 h at 37 °C under an atmosphere of 5% $CO_2$ in air. After incubation, various concentrations of test compounds were added and incubation was continued for a further 4 days. Viable cells were counted with a cell counting kit (Dojindo). Experiments were repeated at least three times.

### 5.6. Western blot analysis

Aliquots of 3 mL each of LNCaP cells ($1 \times 10^5$ cells/mL) in RPMI1640 medium supplemented with 10% fetal bovine serum were plated in 6-well plates and incubated for 24 at 37 °C under an atmosphere of 5% $CO_2$ in air. After incubation, various concentrations of test compounds were added and incubation was continued for the indicated periods. The supernatant was discarded, then the cells were rinsed twice with PBS, and lysed.

Expression of the target genes (p21, β-actin, and androgen receptor) was quantified with appropriate monoclonal antibodies (p21 monoclonal antibody (NeOMarkers), β-actin monoclonal antibody (SIGMA), and androgen receptor monoclonal antibody (NeOMarkers)) by using a chemiluminescence assay system (Amersham Biosciences) according to the supplier's protocol.

### 5.7. Molecular modeling

**5.7.1. Hardware & software.** Molecular modeling studies were carried out using QUANTA97 and CHARMm (ver. 23.2) on a Silicon Graphics octane.

**5.7.2. Reference PDB data.** Construction of protein–ligand complexes was based on an X-ray structure of the HDAC 8 (PDB entry 1W22).

**5.7.3. Molecular modeling of human PPARα-ligand complexes.** Ligands were manually docked into the active site based on the X-ray structure (PDB 1W22). Minimizations were performed with CHARMm (energy minimization condition; gradient convergence condition is 0.01 kcal/mol Å, amino acid residues 5 Å far from the binding site fix, peptide main chain and Zn ion fix, 180His, 178Asp, 267Asp fix).

## Acknowledgment

The work described in this paper was partially supported by a Grant-in-aid for Scientific Research from The Ministry of Education, Culture, Sports, Science and Technology, Japan.

## References and notes

1. Grunstein, M. *Nature* **1997**, *389*, 349.
2. Cheung, W. L.; Briggs, S. D.; Allis, C. D. *Curr. Opin. Cell Biol.* **2000**, *12*, 326.
3. Roth, S.; Denu, J. M.; Allis, C. D. *Annu. Rev. Biochem.* **2001**, *70*, 81.
4. Cress, W. D.; Seto, E. *J. Cell Physiol.* **2000**, *184*, 1.
5. Rosato, R. R.; Wang, Z.; Gopalkrishnan, R. V.; Fisher, P. B.; Grant, S. *Int. J. Oncol.* **2001**, *19*, 181.
6. Weidle, U. H.; Grossmann, A. *Anticancer Res.* **2000**, *20*, 1471.
7. Hashimoto, Y. *Curr. Med. Chem.* **1998**, *5*, 163.
8. Hashimoto, Y. *Bioorg. Med. Chem.* **2002**, *10*, 461.
9. Miyachi, H.; Azuma, A.; Ogasawara, A.; Uchimura, E.; Watanabe, N.; Kobayashi, Y.; Kato, F.; Kato, M.; Hashimoto, Y. *J. Med. Chem.* **1997**, *40*, 2858.
10. Miyachi, H.; Ogasawara, A.; Azuma, A.; Hashimoto, Y. *Bioorg. Med. Chem.* **1997**, *5*, 2095.
11. Miyachi, H.; Azuma, A.; Kitamoto, T.; Hayashi, K.; Kato, S.; Koga, M.; Sato, B.; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1483.
12. Miyachi, H.; Kato, M.; Kato, F.; Hashimoto, Y. *J. Med. Chem.* **1998**, *41*, 263.
13. Shinji, C.; Nakamura, T.; Maeda, S.; Yoshida, M.; Hashimoto, Y.; Miyachi, H. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4427–4431.
14. Finnin, M. S.; Donigian, J. R.; Cohen, A.; Richon, V. M.; Rifkind, R. A.; Marks, P. A.; Breslow, R.; Pavletich, N. P. *Nature* **1999**, *401*, 188.
15. Vannini, A.; Volpari, C.; Filocamo, G.; Casavola, E. C.; Brunetti, M.; Renzoni, D.; Chakravarty, P.; Paolini, C.; Francesco, R.; Gallinari, P.; Steinkuhler, C. D.; Marco, S. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 15064.
16. Yoshida, M.; Kijima, M.; Akita, M.; Beppu, T. *J. Biol. Chem.* **1990**, *265*, 17174.

17. Richon, V. M.; Emiliani, S.; Verdin, E.; Webb, Y.; Breslow, R.; Rifkind, R. A.; Marks, P. A. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 3003.
18. Somoza, J. R.; Skene, R. J.; Katz, B. A.; Joseph, C. M.; Ho, D.; Jennings, A. J.; Andrew, C. L.; Buggy, A. J. J.; Chi, E.; Tang, J.; Sang, B.; Verner, E.; Wynands, R.; Leahy, E. M.; Dougan, D. R.; Snell, G.; Navre, M.; Knuth, M. W.; Swanson, R. V.; E, D.; Leslie, M.; Tari, W. *Structure* **2004**, *12*, 1325.
19. Furumai, R.; Komatsu, Y.; Nishino, N.; Khochbin, S.; Yoshida, M.; Horinouchi, S. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 87.
20. Suzuki, T.; Matsuura, A.; Kouketsu, A.; Nakagawa, H.; Miyata, N. *Bioorg. Med. Chem. Lett.* **2005**, *7*, 331.
21. Furumai, R.; Matsuyama, A.; Kobashi, N.; Lee, K.-H.; Nishiyama, M.; Nakajima, H.; Tanaka, A.; Komatsu, Y.; Nishino, N.; Yoshida, M.; Horinouchi, S. *Cancer Res.* **2002**, *62*, 4916.