Synthesis and Structure−Activity Relationships of a New Series of Retinoid-Related Biphenyl-4-ylacrylic Acids Endowed with Antiproliferative and Proapoptotic Activity

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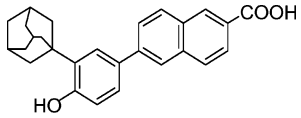
Atypical retinoids (AR) represent a class of proapoptotic agents with promising potential in the treatment of neoplastic diseases. In the present work 4′-hydroxybiphenyl-4-ylacrylic acids were studied as a novel series of AR. The synthesized compounds were evaluated for their antiproliferative activity in a human promyelocytic leukemia cell line (NB4) and in an ovarian carcinoma cell system including IGROV-1, carrying a functional wild-type p53, and a cisplatin-resistant subline, IGROV-1/Pt-1. The presence of a bulky lipophilic group at position 3′ (adamantan-1-yl being the best) and the *E* configuration of the acrylic moiety appear essential for activity below 1 μM. No substitution on the rings or on the double bond improved the activity. A qualitative correlation between the log *P* and molecular volume of the 3′-substituent and the antiproliferative activity was found. From the study of a few selected compounds, it appears that the presence of the carboxylic group is an essential requirement for apoptogenic properties but not for antiproliferative activity, this being maintained in amide derivatives. On the other hand, compounds able to induce apoptosis produced a detectable level of genotoxic damage. This observation supports the hypothesis that the genotoxic stress is a critical event mediating apoptosis induction by compounds of this class. Among the compounds investigated, *E*-3-(3′-adamantan-1-yl-4′-hydroxybiphenyl-4-yl)acrylic acid (**2**) was chosen for further investigation.

Introduction

The treatment of neoplastic diseases with chemotherapeutic agents is still largely unsatisfactory; the development of innovative agents and/or novel combinations is needed to improve the therapeutic effectiveness. Recent advances in molecular biology of tumor cells have identified a number of cellular targets as a basis for the development of novel treatment approaches. Apoptosis or programmed cell death (PCD) is considered the most important process of cell killing activated by cytotoxic agents. Apoptosis is a very complex phenomenon, and the pathways involved depend largely on the cell type and the nature of stress. Defects in apoptosis or alterations in critical pathways have been found in several human malignancies.[1] These defects provide malignant cells with a selective growth advantage by extending the cell life span and allowing survival even under stress conditions. As more information on the apoptotic process becomes available, novel and potentially exploitable molecular targets are discovered and characterized.[1]

In recent years the so-called atypical retinoids (AR) (or retinoid-related molecules (RRMs)[2]) have been developed as a promising class of apoptotic compounds. The best known compound of this series is **1** (AHPN or CD437), which was initially developed as a selective



1 (CD437)

retinoic acid receptor γ (RARγ) agonist.[3,4] However, RARγ itself does not seem to mediate AR apoptotic activity in most neoplastic cell types.[5]

1 is an effective apoptotic agent in vitro,[6] showing activity in preclinical models of leukemia and carcinoma both in vitro and in vivo. The apoptogenic activity of **1** was also found in retinoid-resistant cells and in RARγ-negative cells, thus supporting a receptor-independent mechanism of cell death activated by CD437.[7,8] Other **1** analogues that lack receptor-selective effects were found to be potent inducers of apoptosis.[9] On the other hand, several signaling pathways, including mitogen-activated protein kinases (MAPK), have been found to be implicated in receptor-independent induction of apoptosis.[10] Other studies have implicated the mitochondrion as a critical target of activity of this class of compounds because it controls the intracellular homeostasis of calcium, a cation modulating many aspects of the process of apoptosis.[11,12] Several lines of evidence support the concept that atypical retinoids induce

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genotoxic stress.[13] These DNA lesions could activate apoptotic stimuli which likely integrate other signals involving mitochondrial response. The integration of several proapoptotic stimuli may therefore represent the basis of cell death induction by these agents.[14,15] Although the mechanism of apoptosis induction by the atypical retinoids remains unclear, the therapeutic potential of the novel agents is supported by the wide spectrum of antiproliferative activity, the unique mechanism of action, and the pharmacological profile. The proapoptotic activity of atypical retinoids detected in a wide variety of tumor cells is a promising feature because reduced susceptibility to apoptosis is recognized as a relevant mechanism implicated in the resistance of tumor cells to conventional agents.[1] Synthetic retinoid-related compounds with distinct and more specific features may have additional advantages in terms of improved tolerability because the side effects of classical retinoids is likely to be related to their ability to bind the cognate nuclear receptors.[16]

To identify potent and well-tolerated RAR-independent inducers of apoptosis, we designed and synthesized novel atypical retinoids. An assumption we made at the beginning of this study was to keep the relatively rigid structure of **1** and therefore to maintain the distance between the carbon bearing the adamantyl group and the carboxylic group. This led to compound **2** (ST 1926), endowed with potent antiproliferative and proapoptotic activity, reported in our preliminary communication,[17] which became the lead compound of a new series. The present study was designed to explore the putative key portions of the molecule, i.e., the carboxylic group, the double bond, and the adamantan-1-yl moiety, by introducing substituents or structural modifications in these regions and evaluating the effects of the changes on the activity of the derivatives obtained on appropriate cellular and molecular models. A better definition of the critical requirements for activity and understanding of the cellular determinants of the novel compounds may be useful for improving the pharmacological potential of AR.

Chemistry

The biphenyl scaffold of all compounds was built via a Suzuki−Miyaura reaction,[18] or the commercially available 4′-bromobiphenyl-4-ol (**3**) was used as a starting material. Compound **4** was prepared by alkylation of **3** with adamantan-1-ol in the presence of H_2SO_4/AcOH, 1:9, conditions being accurately chosen to avoid the unwanted formation of small amounts of the 2,6-bis-adamantan-1-yl derivative. Heck reaction with methyl acrylate in the presence of palladium(II) acetate, tri-*o*-tolylphosphine, and Et_3N gave the methyl ester **5**, which was hydrolyzed with LiOH in THF/H_2O, 1:1 (Scheme 1). This sequence afforded compound **2** with a greater than 98% purity without chromatographic separations and could be scaled up to 50 g.

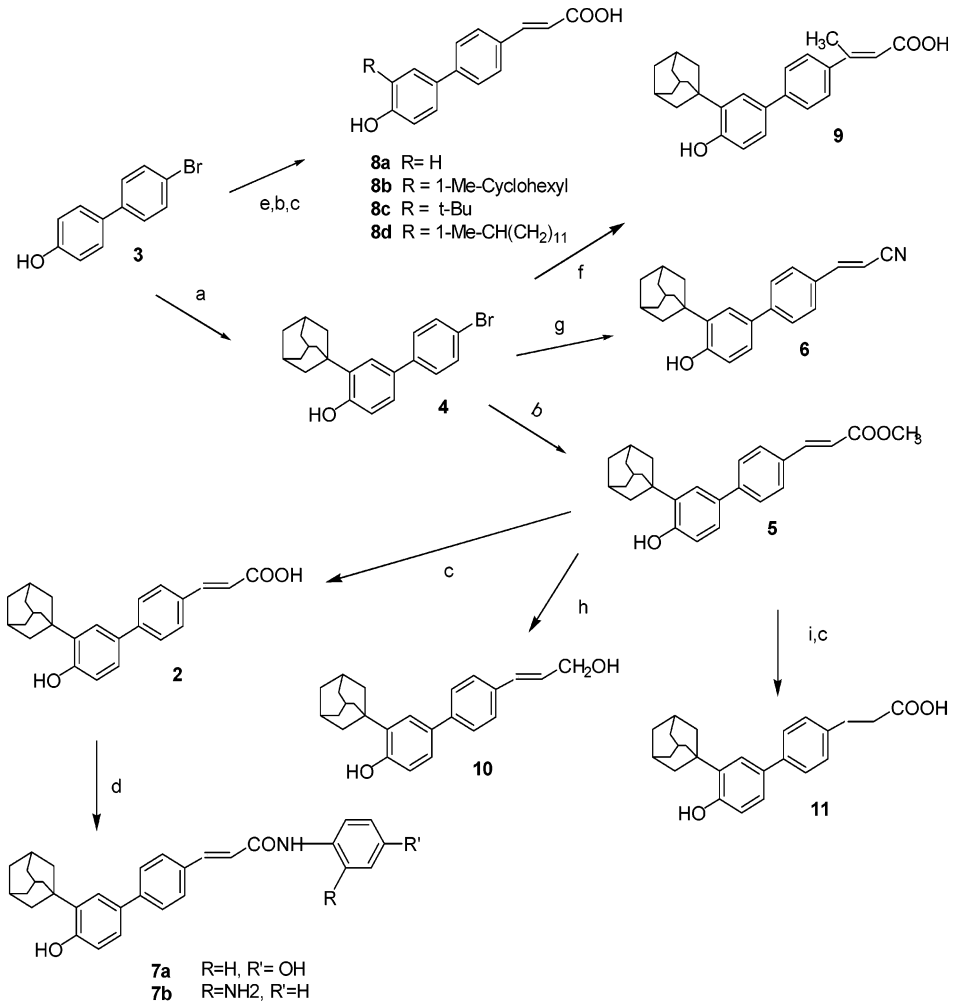
To elucidate the structural requisites for activity, we planned to explore three key portions of the structure of **2**: the carboxylic group, the double bond, and the lipophilic adamantan-1-yl moiety. First, we considered derivatives in which the carboxylic moiety was modified. The methyl ester **5** was reduced with $LiAlH_4$ in THF to afford the alcohol **10**. Nitrile **6** was obtained from **4** via Heck reaction with acrylonitrile. Condensation of **2** with 4-aminophenol and 1,2-phenylenediamine in the presence of WSC and HOBT led to the corresponding amides **7a** and **7b** (Scheme 1). Replacement of the carboxylic group with a phosphonic acid was achieved starting from 2-(adamantan-1-yl)-4-bromophenol **12a**, prepared from 4-bromophenol according to the procedure described by Charpentier.[4] Palladium-catalyzed Suzuki coupling of **12a** with 4-formylbenzeneboronic acid led to the aldehyde **13a**, which was subjected to Horner−Wittig condensation with tetraethylmethylene diphosphonate to afford the phosphonate **14a**, in turn converted into the acid **14b** with trimethylsilyl bromide in dichloromethane (Scheme 2).

To check the importance of the double bond in determining the spatial position of the carboxylic moiety, the ester **5** was hydrogenated to obtain, after hydrolysis, the more flexible saturated acid **11**. Compound **15**, with a triple bond instead of the double bond, was obtained by Wittig condensation of the aldehyde **13b** with ethoxycarbonyliodomethyltriphenylphosphorane and subsequent elimination accompanied by hydrolysis. The double bond was replaced by a cyclopropyl moiety in compound **18**, which was obtained as a mixture of diastereoisomers by palladium-catalyzed condensation of **12b** with *p*-vinylbenzeneboronic acid, followed by cyclopropanation reaction with ethyl diazoacetate and rhodium tetraacetate. The double bond was completely removed in compound **16**, obtained by a $KMnO_4$ oxidation of the aldehyde **13b** (Scheme 2).

Aldehyde **13b** was used as a starting material for the introduction of substituents on the double bond. Compound **17a**, with a methyl group in a position α to the carboxylic group, was prepared by Wittig condensation with the corresponding ylide, whereas the derivative **9** with the methyl group in position β was obtained by Heck condensation of **4** with crotonic acid. The *E* configuration of compound **17a** was established on the basis of the chemical shift of the vinylic proton.[19] In the case of **9**, the *E* configuration is a consequence of the mechanism of the reaction because it has been reported that Heck alkylation with crotonic acid gives exclusively or in a great excess the *E* diastereoisomer.[20] Moreover, the chemical shift of the β-methyl group is consistent with the diagnostic data reported.[21] The two isomeric α-fluoroacrylic acids **17b** and **17c** were obtained by Wittig−Horner reaction with triethyl 2-fluoro-2-phosphonoacetate. The ethyl ester of the *E* acid **17b** was obtained by working at −78 °C,[22] whereas operating at reflux temperature[23] afforded an equilibrium mixture of *E* and *Z* isomers, from which the ester of the *Z* acid **17c** could be separated. The *E* vs *Z* configuration of the two stereoisomers was assigned on the basis of the vicinal H−F coupling constants.[24] Wittig reaction of **13b** with methyl triphenylphosphoranylideneacetate followed by hydrolysis with LiOH constituted an alternative synthesis of ester **5** and acid **2** (Scheme 2).

To elucidate the role of the lipophilic function on the phenolic ring, the bulky adamantan-1-yl group was changed into a 1-methylcyclohexyl (**8b**), *tert*-butyl (**8c**), and 1-methylcyclododecyl (**8d**), all compounds being prepared by alkylation of **3** with the corresponding tertiary alcohols in acid medium, followed by Heck alkylation with methyl acrylate and hydrolysis of the

Scheme 1[a]



[a] (a) Adamantan-1-ol, H_2SO_4/AcOH; (b) methyl acrylate, TOTP, $Pd(OAc)_2$, TEA; (c) LiOH·H_2O, THF/H_2O; (d) WSC, HOBT, 4-aminophenol or 1,2-phenylenediamine, CH_3CN/THF; (e) nothing or 1-methylcyclohexanol or *t*-BuOH or 1-methycyclododecanol, H_2SO_4, CH_2Cl_2; (f) crotonic acid, $Pd(OAc)_2$, Et_3N, TOTP; (g) acrylonitrile, TOTP, $Pd(OAc)_2$, TEA; (h) $LiAlH_4$, THF; (i) H_2/PtO_2, AcOEt.

ester. For the introduction of a phenyl group, 2-phenylphenol (**20**) was used as a starting material, with a sequence of iodination (**21**), Suzuki coupling (**22**), Wittig condensation, and hydrolysis affording the acid **23** (Scheme 3). The chloroderivative **30** was prepared (Scheme 4) via Suzuki reaction of 2-chloro-4-bromophenol with methyl 4-bromocinnamate. Compound **8a**, prepared from **3** by Heck reaction and subsequent hydrolysis of the resulting ester, is devoid of any lipophilic substituent on the phenol ring.

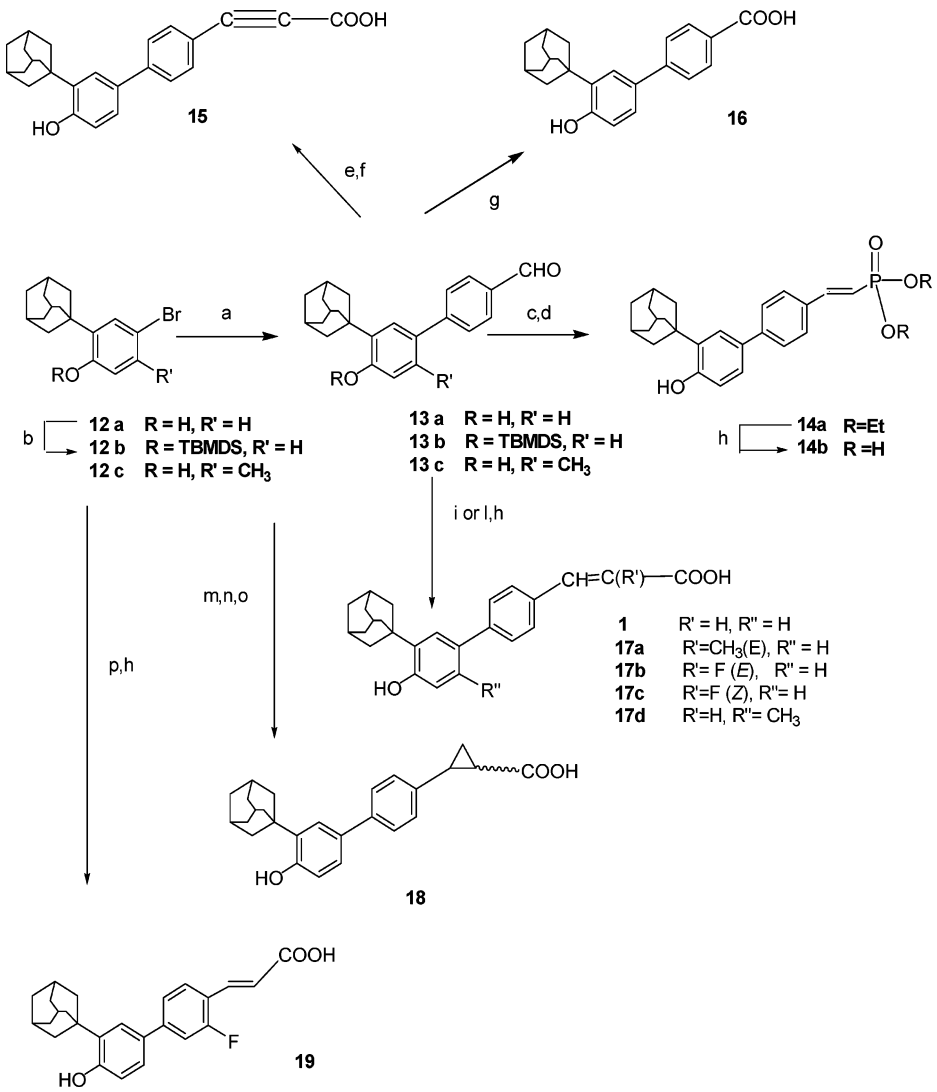
Compounds substituted on one or the other aromatic ring were prepared following similar procedures (Scheme 4). The acids **27a** and **27b** were synthesized from **24a** and **24b** by Heck reaction, followed by Suzuki coupling with **12a** and **12b** and hydrolysis. The synthesis of the chloroderivative **27b** has been recently reported by another group.[25] For the synthesis of the phenanthrene analogue **29** the intermediate aldehyde **26a** was subjected to the Wittig reaction to give the methoxyvinyl-derivative **28**, which after ring closure with methanesulfonic acid[26] and hydrolysis gave **29**. The ester obtained by the ring closure contained only a small amount of the isomer coming from the ring closure ortho to the adamantyl ring. The structure of **29** was established from the absence of an ortho coupling constant for the proton adjacent to the OH, easily assigned on the basis of the high-field chemical shift. From the substituted bromophenol **12c**, compound **17d** was obtained after Suzuki condensation with 4-formylbenzeneboronic acid, Wittig reaction, and hydrolysis, while a Suzuki coupling of **12a** with 4-bromo-2-fluorocinnamate and hydrolysis led to compound **19** (Scheme 2).

Compound **33**, where the adamantyl group and the OH were interchanged, was prepared as described in a patent (Scheme 5).[27] Compound **37** was prepared by a general method of synthesis of 3,5-disubstituted phenols,[28] by addition−elimination of acetylmethylpyridinium bromide onto the chalcone **34** (Scheme 6).[29] However, under the conditions of the literature, i.e., with bases such as triethylamine or sodium acetate, the reaction stopped at a stage of one of the possible intermediates. Only the use of a stronger base, such as DBU, induced the cyclization.

Antiproliferative Activity

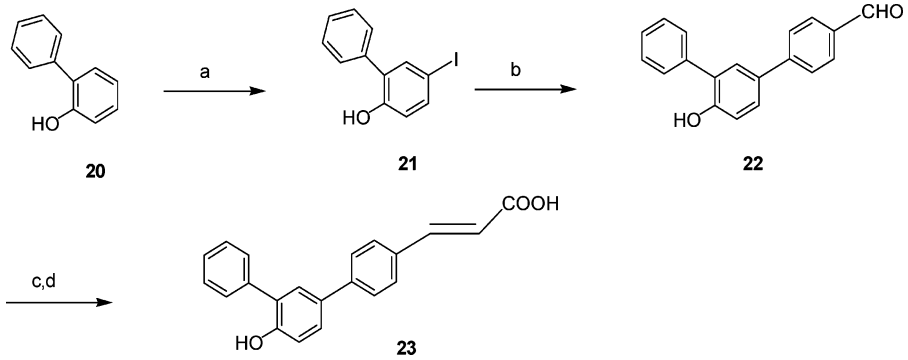
The antiproliferative activity of the synthesized compounds was tested in an ovarian carcinoma cell line, IGROV-1, carrying a functional wild-type p53,[30] in a cisplatin resistant ovarian carcinoma cell line, IGROV-1/Pt-1, and in a human promyelocytic leukemia cell line, NB_4.

Scheme 2[a]



[a] (a) 4-Formylbenzeneboronic acid, Pd tetrakis, Na_2CO_3, toluene; (b) TBDMSCl, Et_3N, DMAP, DMF; (c) tetraethylmethylene diphosphonate, KF/Al_2O_3, THF; (d) $(CH_3)_3SiBr$, CH_2Cl_2; (e) $Ph_3P{=}CH(I)COOEt$, K_2CO_3, MeOH; (f) KOH, MeOH; (g) $KMnO_4$, H_2O/acetone; (h) $LiOH{\cdot}H_2O$, DMF; (i) $Ph_3P{=}C(R'')COOEt/CHCl_3/BuLi/THF$; (l) $EtOCOCHFPO(OEt)_2/BuLi/THF$; (m) *p*-vinylbenzeneboronic acid, $Pd(Ph_3P)_4$, Na_2CO_3, toluene; (n) rhodium tetraacetate bihydrate, ethyl diazoacetate, CH_2Cl_2; (o) KF/Al_2O_3, dimethoxyethane, then $LiOH{\cdot}H_2O$, THF/H_2O; (p) bis(pinacolato)diboron, KOAc, $PdCl_2(dppf)$, methyl 4-Br-2-F-cinnamate, Na_2CO_3.

Scheme 3[a]

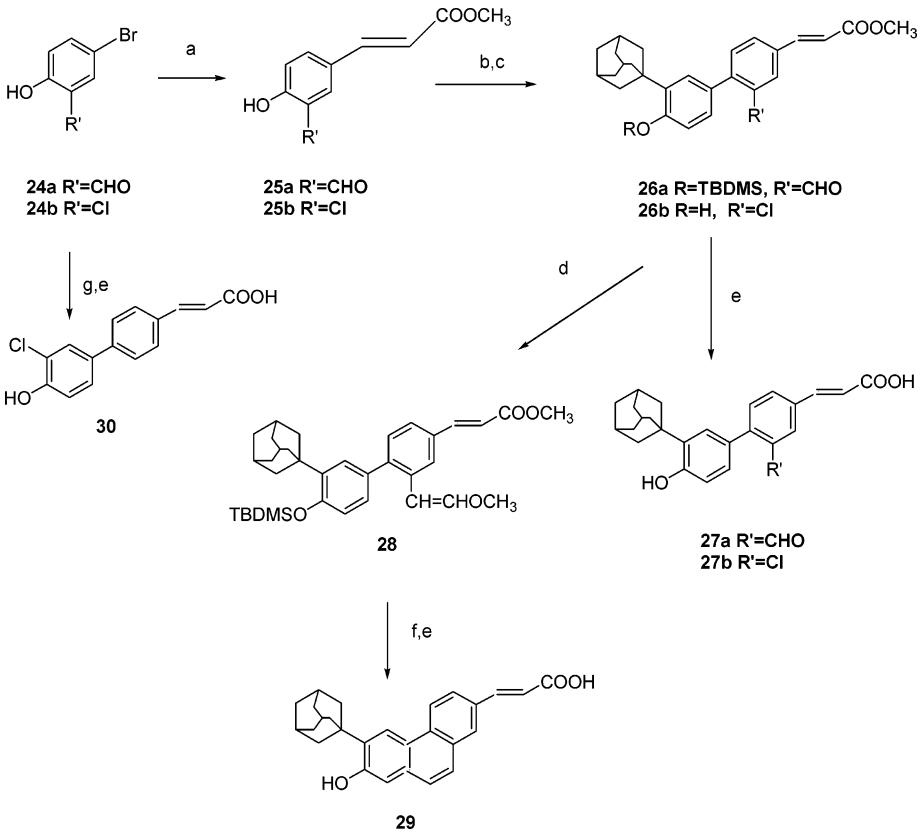


[a] (a) NaI, chloramine T, DMF; (b) *p*-formylbenzeneboronic acid, Pd tetrakis, Na_2CO_3, toluene; (c) $Ph_3P{=}CHCOOCH_3$, $CHCl_3$; (d) $LiOH{\cdot}H_2O$, THF/H_2O.

Results and Discussion

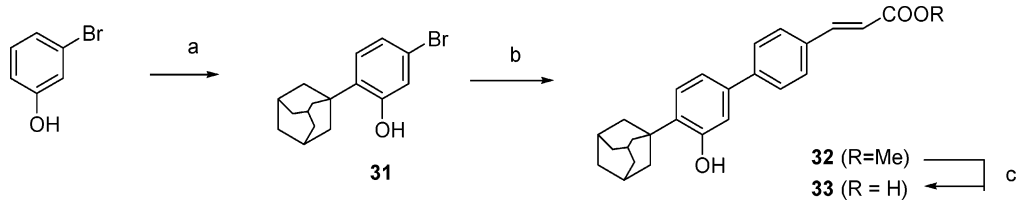
A cell growth inhibition assay was used to determine the antiproliferative activity of the compounds synthesized. The cell systems selected for this study were representative of a solid tumor (ovarian carcinoma) and of a leukemia, i.e., the cell line IGROV-1, the cisplatin-resistant subline IGROV-1/Pt1, and the human promyelocytic leukemia cell line NB_4. In the case of IGROV-1, the parental cell line, characterized by the expression of a wild-type p53, was appreciably more

Scheme 4[a]



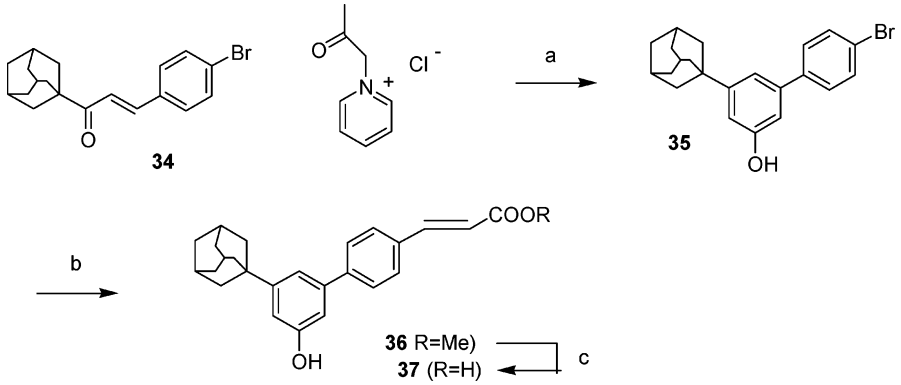
[a] (a) Methyl acrylate, $Pd(OAc)_2$, TOTP, TEA; (b) $C_6H_5N(SO_2CF_3)_2$, TEA, CH_2Cl_2, 0−5 °C; (c) bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), **12a** or **12b**, Na_2CO_3; (d) $CH_3OCH_2PPh_3^+Cl^-$, BuLi, THF, 0 °C; (e) $LiOH \cdot H_2O$, THF/H_2O, 1:1; (f) methanesulfonic acid, CH_2Cl_2, 0 °C; (g) bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), methyl 4-Br-cinnamate, Na_2CO_3.

Scheme 5[a]



[a] (a) Adamantan-1-ol, H_2SO_4/AcOH; (b) bis(pinacolato)di boron, KOAc, $PdCl_2$(dppf), methyl 4-Br-cinnamate, Na_2CO_3; (c) LiOH, THF/H_2O.

Scheme 6[a]



[a] (a) DBU, EtOH, 42%; (b) methyl acrylate, $Pd(OAc)_2$, tri-*o*-tolylphosphine, Et_3N, 50%; (c) LiOH, THF/H_2O, 80%.

responsive to the lead compound **2** than the cisplatin-resistant subline carrying a mutant p53.[30] Since atypical retinoids are able to activate apoptosis through p53-dependent and p53-independent pathways and the relative susceptibility to apoptosis likely reflects a cooperation between these pathways, the reduced apoptotic response in the cisplatin-resistant cells could be the consequence of loss of p53 function.[13] Indeed, the differential sensitivity of the two cell lines to the antiproliferative activity reflected the relative suscep-

Table 1. Antiproliferative Activity of Selected Compounds on IGROV-1, IGROV-1/Pt1, and NB_4 Cellular Lines[a]

	IC_{50} (μM)		
compd	IGROV-1	IGROV-1/Pt1	NB4
1	0.35 ± 0.04	0.62 ± 0.24	0.4 ± 0.05
2	0.23 ± 0.08	0.40 ± 0.08	0.082 ± 0.005
5	0.61 ± 0.2	3.5 ± 1.6	18.2 ± 0.2
6	8.3 ± 1.4	12.7 ± 0.5	14.3 ± 0.2
7a	6.6 ± 0.5	10.50	2 ± 0.02
7b	2.1 ± 0.15	2 ± 0.07	1.8 ± 0.006
8a	89 ± 11	156 ± 2	78.7 ± 7.4
8b	2.58 ± 0.2	2.3 ± 0.1	2.2 ± 0.01
8c	30	30	42.3 ± 3.4
8d	3.57 ± 0.4	nd	nd
9	9.97 ± 1.32	16.65 ± 9.92	6.7 ± 0.02
10	10.8	10.6	9.1 ± 0.08
11	48.42 ± 0.88	44.50 ± 0.28	63.6 ± 11.7
14a	19.7	>20	1.7 ± 0.3
14b	>20	>20	>200
15	1.15	1.52	1.2 ± 0.1
16	>3	>3	35.2 ± 4.5
17a	7.19 ± 1.27	10.04 ± 3.02	2.3 ± 0.3
17b	>3	>3	22.4 ± 0.9
17c,	0.37 ± 0.04	0.63 ± 0.06	0.081 ± 0.002
17d	1.14 ± 0.2	2.92 ± 0.24	1.7 ± 0.05
18	>20	>20	39.4±0.5
19	0.2 ± 0.08	0.43±0.13	0.17 ± 0.02
23	19.0 ± 2	12.5	45.3 ± 3.9
27a	1.28 ± 0.02	2.63 ± 0.24	1.05 ± 0.1
27b	0.58 ± 0.09	0.73 ± 0.38	0.20 ± 0.01
29	2.2 ± 0.3	2.10 ± 0.35	1.5 ± 0.01
30	26 ± 2	nd	nd
33	6.13 ± 0.4	nd	>10
37	1.31 ± 0.22	nd	1.2 ± 0.09

[a] IC_{50} (μM) is the concentration required for 50% inhibition of cell growth (±SD).

tibility to apoptosis.[13] After 72 h of exposure, the level of apoptosis induced by IC_{80} of compound **2** in IGROV-1 was 65%, which is substantially higher than the apoptosis induced in the cisplatin-resistant sublines (30%).

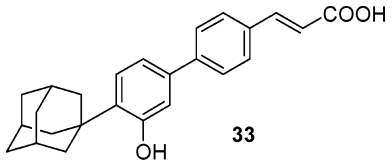
The antiproliferative activities (IC_{50}) of the tested compounds are summarized in Table 1. As said above, the purpose of this study was to explore the putative key portions of the molecule, i.e., the carboxylic group, the double bond, and the adamantan-1-yl moiety, by introducing substituents or structural modifications in these regions and evaluating the effects of the changes on the activity of the derivatives.

Removal (**8a**) or substitution of the lipophilic adamantan-1-yl moiety with a phenyl (**23**) or a *tert*-butyl group (**8c**) resulted in a dramatic reduction of antiproliferative activity. This effect was less marked in compounds **8b** and **8d** containing the methylcyclohexyl and methylcyclododecyl residues, respectively. No direct correlation of the activity of the whole series of compounds prepared with the calculated log *P* could be found because the strongly lipophilic adamantyl group present in almost all the compounds dominates the log *P* value. However, in the restricted series **8a**, **30**, **23**, **8c**, **8b**, **2**, **8d**, where only the substituent on the phenol ring was changed, the trend of activity (e.g., for the IGROV line IC_{50} (μM) is 89, 26, 19, 30, 2.58, 0.23, 3.57, respectively) is similar to that of the lipophilicity of the first six compounds (log *P* is 3.22, 3.78, 4.89, 4.92, 5.68, 5.67, respectively) or of the molecular volume of the first six compounds (188.7, 200.6, 254.0, 255.4, 288, 297.7 cm^3, respectively), to decreasing again for compound **8d**, where log *P* and the molecular volume are 7.78 and 377 cm^3, respectively. This certainly indicates the importance of a bulky lipophilic group ortho to the phenolic OH, with the lipophilicity and/or size of adamantyl being approximately the best.

Replacing the carboxylic group with a phosphonic acid (**14b**) or its diethyl ester (**14a**) again resulted in a substantial reduction of biological effects ($IC_{50} \geq 20$ μM). Similarly, a marked reduction of antiproliferative activity was found following conversion of the carboxylic moiety to the corresponding nitrile **6** or alcohol **10**. In the case of the methyl ester **5**, good activity is maintained only in the IGROV-1 line. This may reflect a different rate of hydrolysis of the ester. Examples of in vivo hydrolysis of esters are well-known.[31] Because the 4-hydroxyphenylamide of retinoic acid (fenretinide) is endowed with antiproliferative and apoptogenic activity,[32] the corresponding amide (**7a**) of compound **2** was prepared, but this modification did not lead to an increase of activity. A similar result was given by amidation with 1,2-phenylenediamine to give **7b**. Modifications involving the double bond, e.g., reduction to the propionic acid **11**, cyclopropanation (**18**), or the introduction of a methyl substituent on each carbon of the double bond (**9** and **17a**, respectively) resulted in a marked reduction of potency. In contrast, the presence of a small-size substituent such as fluorine caused only a marginal effect on activity provided that the *E* configuration of **2** was maintained (**17c**). Conversely, the activity was reduced in the isomer with the *Z* configuration (**17b**). These data emphasize the importance of the optimal geometry of the chain containing the carboxylic group for the activity. In the compound with a triple bond **(15**) only a marginal reduction of antiproliferative activity was observed, in accordance with the small changes in the spatial position of the COOH group (the distance between C-1 of the adamantyl group and the carbon of the carboxyl is 11.69 Å in **15**, whereas it is 11.48 Å in **2**). Contrarily, a substantial decrease of activity was observed when the carboxylic group was directly linked to the ring (**16**). Derivatives with substituents in the rings that could force the biphenyl moiety to assume a more twisted conformation (**17d**, **27a**, **27b**) or where the system was rigidified in a plane as in the phenanthrene derivative **29** were also prepared. The activity of **27b** is still high and comparable with that of **2** and **19**, whereas the methyl derivative **17d** and the aldehyde **27a**, which bear a bulky ortho substituent on one or the other of the aromatic rings, are less active. However, MM2 and AM1 calculations show a value of the dihedral angle between the two rings for all the three compounds **17d**, **27a**, **27b** of around 50−55°, whereas it is 35−40° for **2** and for **19**, where the F atom ortho to the acrylic chain does not influence the twisting of the biphenyl system. Therefore, the twisting of the biphenyl rings does not seem to be an important factor for activity. Similarly, the phenanthrene derivative **29** was not better than **2**. Here, it is difficult to ascribe the decrease in activity to the complete planarity of the compound or to the presence of an additional group within the rings that could interfere with the putative receptor.

From these data we can conclude that the structural requirements for optimal activity are rather strict, in particular that (a) the presence of the carboxylic group is required for activity, (b) the *E* configuration of the

acrylic moiety is necessary, (c) no substitution except a very small one (fluorine) is tolerated on the double bond, (d) substituents on the biphenyl ring that could force twisting of the ring do not increase the activity, (e) a bulky lipophilic substituent in position 3′ is necessary, adamantan-1-yl being so far the best. These results suggest that the interaction of the carboxylic group at the binding pocket is critically dependent on the optimal distance and orientation of the bulky adamantyl group in position 3′. This last statement is supported by the strong decrease of activity (ca. 6 μM on IGROV-1) when the adamantyl and the OH groups in **2** are interchanged (**33**). In this compound the bulky adamantyl group is shifted far away from the COOH and occupies a different region of the space with respect to **2**. To exclude that this effect is due to just the change in the position of the OH group, we prepared compound **37**, which shows a much lesser decrease of activity (1.31 μM on IGROV-1).



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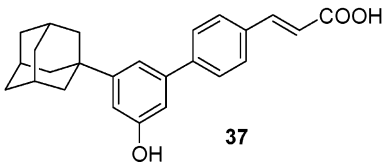

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Among the compounds investigated, *E*-3-(3′-adamantan-1-yl-4′-hydroxybiphenyl-4-yl)-acrylic acid (**2**) appeared the most potent, and was therefore chosen for further investigation.[13,15,17]

Atypical retinoids are known to inhibit proliferation and induce apoptosis in tumor cells in vitro.[2] The extent of growth inhibition and apoptosis induction is likely dependent on the biological context. Using an ovarian carcinoma cell line carrying wild-type p53 and a platinum-resistant p53 mutant subline, we compared the antiproliferative and proapoptotic activities of selected compounds carrying specific modifications in critical positions, i.e., substitution of the adamantan-1-yl moiety (**8a**, **8b**, **23)** or modification of the carboxyl group to give amide derivatives (**7a** and **7b**) **(**Table 2). In contrast to compound **8b**, containing the methylcyclohexyl residue and retaining an appreciable antiproliferative activity and proapoptotic activity in cells with wild-type p53, removal of the adamantan-1-yl moiety (**8a**) or substitution of the adamantan-1-yl moiety with a phenyl ring (**23**) caused a dramatic reduction of antiproliferative activity and an almost complete loss of apoptotic activity. Although it is evident that adamantyl retinoids are able to activate p53-independent pathways of apoptosis,[13] as already observed for compound **2**, a reduced induction of apoptosis in p53 mutant cells was observed with all tested compounds (Table 2). The two amide derivatives (**7a** and **7b**) exhibited no ability to induce significant levels of apoptosis, despite retention of appreciable antiproliferative activity. Thus, the presence of the carboxylic group appears to be an essential requirement for the apoptogenic properties of the adamantyl retinoids but not for antiproliferative activity. An interesting observation of the comparative study of the antiproliferative activities and proapoptotic effects of the compounds tested in Table 2 was a moderate or low induction of apoptosis by compounds characterized by a low antiproliferative potency ($IC_{50} > 5$ μM). Since the study of drug-induced apoptosis was performed at concentrations that strongly inhibited proliferation (IC_{80}), this finding of low proapoptotic ability of these compounds even at concentrations causing a marked growth inhibition indicates that their cytostatic activity was substantially more pronounced than their cytotoxic activity. It is conceivable that the potent antiproliferative activity reflects the drug's ability to induce apoptosis. The involvement of different biological actions and therefore of distinct mechanisms of antiproliferative and apoptotic effects was further supported by the analysis of the cell cycle perturbation of drug-treated cells (Figure 1). The pattern of cell cycle distribution indicated minimal changes induced by the antiproliferative compounds **7a**, **7b**, **8a**, and **23**, in contrast to a G1/S arrest with appearance of sub-G1 cells following treatment with proapoptotic compounds **2** and **8b**. Relevant to this point is the observation that among the tested retinoids only compounds able to induce apoptosis (**2** and **8b**) produced a detectable level of genotoxic damage. Although this observation is limited to few compounds, it supports the hypothesis that the genotoxic stress is a critical event mediating apoptosis induction by adamantyl retinoids.

Table 2. Comparison of Antiproliferative Proapoptotic Activity and Production of DNA Damage by Selected Compounds

	antiproliferative activity[a] IC_{50} (μM)		apoptosis[b] (%)		DNA damage[c] (rad equiv)
compd	IGROV-1	IGROV-1/Pt	IGROV-1	IGROV-1/Pt	
1	0.35 ± 0.04	0.62 ± 0.24	38 ± 4	25 ± 3	180−210
2	0.23 ± 0.08	0.40 ± 0.08	65 ± 6	30 ± 4	350
19	0.20 ± 0.08		47 ± 3		
27b	0.58 ± 0.08		74 ± 4		
15	1.15		52 ± 11		
27a	1.28 ± 0.02		44 ± 9		
7b	2.1 ± 0.15	2 ± 0.07	8 ± 3		0
8b	2.58 ± 0.2	2.3 ± 0.1	25 ± 3	9 ± 1	200
33	6.13 ± 0.4		23 8		
7a	6.6 ± 0.5	10.50	2 ± 2		0
6	8.3 ± 1.4		2 ± 1		
9	9.97 ± 1.32		26 ± 11		
23	19.0 ± 2	12.5 ± 1.5	7 ± 3	1	0
11	48.42 ± 0.88		26		
8a	89 ± 11	156 ± 2	3 ± 2	1	0

[a] IC_{50}, concentration required for 50% inhibition of cell growth (±SD). [b] Apoptosis level (% of apoptotic cells) determined after 72 h exposure to IC_{80}. [c] DNA damage in IGROV-1 cells determined by alkaline elution after 6 h of exposure to IC_{80}.

Retinoids are known to modulate several biological processes including proliferation, differentiation, and metabolism.[33] Some biological effects of these agents could be mediated by common molecular mechanism(s). These synthetic retinoids are relatively selective for RARγ (Table 3), as already reported for compounds **1** and **2**, which show comparable patterns of interaction with receptors.[15,34] However, in these experiments compound **2** did not exhibit clear subtype selectivity. It is noted that the selectivity of compound **1** for RARγ was more evident at low concentrations (<0.1 μM). The less potent compounds **8b**, **7a**, and **7b** were apparently more selective for RARγ than compound **2**. In particular,

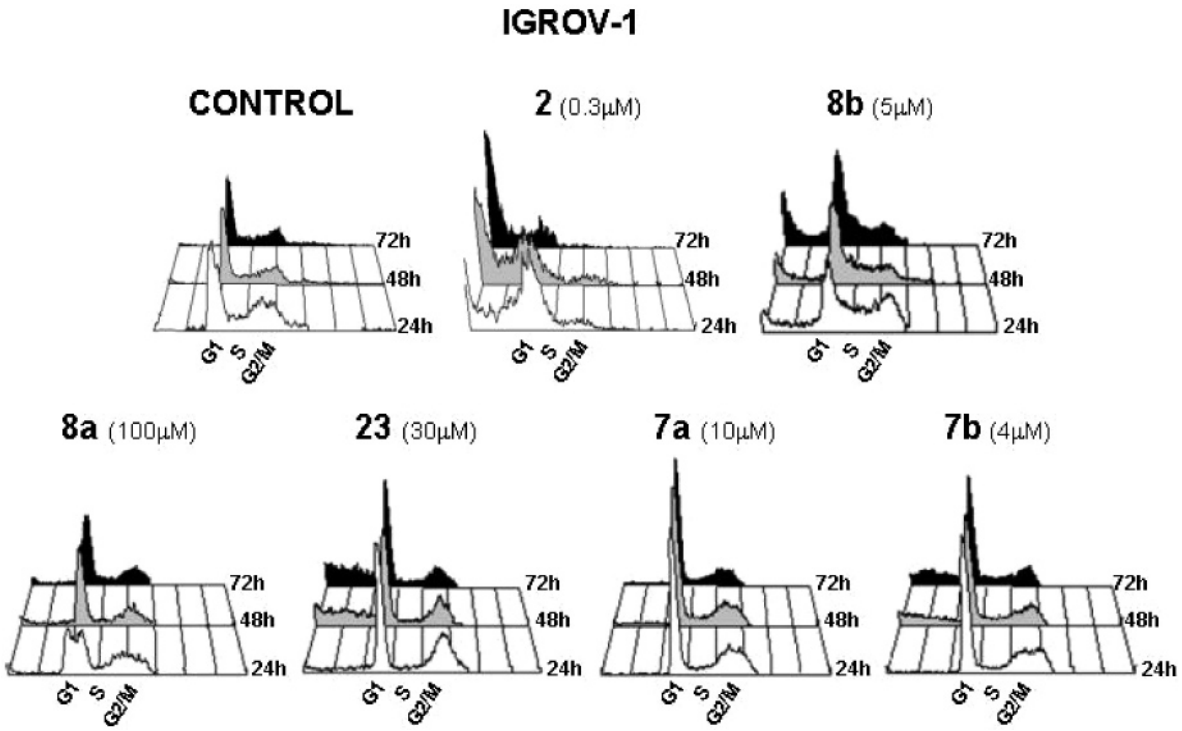

Figure 1. Cell cycle distribution of IGROV-1 ovarian carcinoma cells treated with equitoxic concentrations of atypical retinoids (IC_{80}) for the indicated times.

Table 3. Nuclear Retinoic Acid Receptor Specificity of Some Compounds[a]

compd	RARα EC_{50} (μM)	RARβ EC_{50} (μM)	RARγ EC_{50} (μM)
2	0.2 (0.1−0.4)	0.2 (0.1−0.3)	0.1 (0.1−0.3)
8b	6.4 (4.6−8.9)	5.3 (3.9−7.2)	0.2 (0.1−0.5)
7a	20.3 (13.9−29.7)	7.7 (6.1−9.8)	1.4 (0.8−2.4)
7b	18.2 (5.6−59.1)	17.6 (7.5−41.1)	0.9 (0.6−1.5)
8a	>100	>100	>100
23	>100	>100	>100

[a] COS-7 cells were transfected with the indicated RAR isoform and a DR5-tk-CAT reporter construct. Twenty-four hours following transfection, cells were treated for an additional 24 h with increasing concentrations of the indicated compound. CAT activity was measured in cell extracts and normalized for the level of transfection using a β-galactosidase-based construct. The EC_{50} values for the transactivation of each RAR isoform are expressed as the mean value of three independent replicates (the numbers in parentheses indicate the interval of confidence for each mean value).

compound **8b** exhibited a potency toward RARγ comparable to compound **2**, but it was substantially less potent as an antiproliferative agent and less effective as an apoptosis inducer. Thus, no precise correlation could be found between these biological effects and retinoid receptor binding. This is in agreement with previous studies performed with other synthetic retinoids supporting the finding that the mechanism of action is independent of retinoid receptors.[2] The molecular mechanisms underlying the multiple effects of these agents remain largely undefined. However, it is evident that the antiproliferative activity of compounds tested in this study could not be closely related to their proapoptotic activity, thus supporting the involvement of multiple targets in the biological activity of synthetic retinoids. Consistent with this interpretation is the finding that the activity of compounds characterized by low antiproliferative potency was comparable in cisplatin-sensitive and -resistant IGROV-1 cells, thus indicating a p53-independent cytostatic response. In particular, protein kinases and protein phosphatases have been implicated as cellular targets for apoptosis induction by synthetic retinoids.[35,12] However, we have found that MAP kinases, involved in cellular stress response (e.g., p38 kinase), could be modulated by a compound (**23**) devoid of significant proapoptotic activity (Figure 2). In conclusion, our results support the concept[34,36,37] that distinct molecular mechanisms are responsible for the antiproliferative and apoptotic effects of atypical retinoids.

Experimental Section

General Methods. All reagents and solvents were reagent grade or were purified by standard methods before use. Melting points were determined in open capillaries on a Büchi melting point apparatus and are uncorrected. Column chromatography was carried out on flash silica gel (Merck 230−400 mesh). TLC analysis was conducted on silica gel plates (Merck $60F_{254}$). NMR spectra were recorded at 300 MHz with a Bruker instrument. Chemical shifts (δ values) and coupling constants (J values) are given in ppm and Hz, respectively. Mass spectra were recorded at an ionizing voltage of 70 eV on a Finnigan TQ70 spectrometer. The relative intensities of mass spectrum peaks are listed in parentheses. HPLC analysis of the mixture of diastereoisomers was performed on an HP 1050 quaternary pump fitted with a Rheodyne injector (20 μL loop) and a HP-1050 diode-array detector. Chromatograms were recorded at 360 and 400 nm. The column was a Rainin C18, 25 cm × 0.4 cm, flow 1 mL/min, with a gradient of CH_3CN/H_2O from 30:70 to 100:0 in 20 min.

Solvents were routinely distilled prior to use. Anhydrous tetrahydrofuran (THF) and ether (Et_2O) were obtained by distillation from sodium benzophenone ketyl. Dry methylene chloride was obtained by distillation from phosphorus pen-

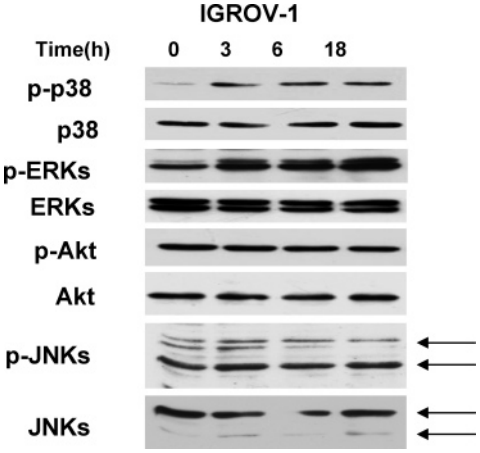

Figure 2. Modulation of MAPKs by compound **23** in ovarian carcinoma IGROV-1 cells. MAPK activation and expression were analyzed in whole-cell lysates by Western blotting. Activated kinases were detected by the use of phosphospecific antibodies recognizing phospho-p44/42 ERKs (p-ERK1/2), phospho-JNK (p-JNKs), and phospho p38 (p-p38). Filters were then stripped and reprobed with antibodies recognizing the respective proteins (ERK1/2, JNKs, and p38).

toxide. All reactions requiring anhydrous conditions were performed under a positive nitrogen flow, and all glassware was oven-dried and/or flame-dried. Purity of the products to be tested was checked by elemental analysis and HPLC.

MM2, AM1, and log *P* calculations were performed using ChemOffice ChemBats3D, and molecular volume data were obtained from the ChemSketch program.

2-(Adamantan-1-yl)-4-(4-bromophenyl)phenol (4). A finely pulverized mixture of 4-(4-bromophenyl)phenol (**3**, 200 mg, 0.8 mmol) and adamantan-1-ol (122 mg, 0.8 mmol) was added in portions and with stirring to 0.8 mL of a mixture of 9:1 $AcOH/H_2SO_4$. After 4 days at room temperature addition of ice/water and filtration gave 100% of **4**, mp 140−143 °C, lit.[4] 148−149 °C. ^1H NMR ($CDCl_3$) δ: 1.75 (6H, s, 6Ad), 2.03 (3H, s, 3Ad), 2.12 (6H, s, 6Ad), 6.70 (2H, d, 1Ar, J = 8.56 Hz), 7.85 (1H, d, 1Ar, J = 8.56 Hz), 7.25 (1H, m, 1Ar), 7.30−7.42 (3H, m, 3Ar), 7.45 (2H, m, 2Ar).

Methyl *E*-3-(3′-Adamantan-1-yl-4′-hydroxybiphenyl-4-yl)acrylate (5). A flask containing a mixture of 3.34 g (8.71 mmol) of **4**, 1.2 g (13.94 mmol) of methyl acrylate, 19.5 mg (0.087 mmol) of palladium acetate, and 104 mg (0.34 mmol) of tri-*o*-tolylphosphine in 4 mL of triethylamine was immersed in an oil bath preheated at 50 °C and kept at 100−110 °C for 4 h. Ice was added, and the mixture was taken up with 1 N HCl to pH 2−3 and extracted repeatedly with ethyl acetate. The organic phases were washed with water and dried over Na_2SO_4 and the solvent was evaporated to give 3.3 g (98%) of **5**, mp >240 °C. ^1H NMR (DMSO-d_6) δ: 1.75 (6H, s, 6Ad), 2.03 (3H, s, 3Ad), 2.12 (6H, s, 6Ad), 3.70 (3H, s, −OCH3), 6.60 (1H, d, CH═, J = 16.18 Hz), 6.85 (1H, d, 1Ar, J = 8 Hz), 7.30−7.40 (2H, m, 2Ar), 7.55−7.80 (5H, m, 4Ar + CH═), 9.5 (1H, s, −OH). Anal. ($C_{26}H_{28}O_3$) C, H.

(*E*/*Z*)-3-(3′-(Adamantan-1-yl-4′-hydroxy-biphenyl-4-yl)-acrylonitrile (6). Compound **4** (300 mg, 0.782 mmol), 66.4 mg (1.25 mmol) of acrylonitrile, 8.78 mg (0.0391 mmol) of $Pd(OAc)_2$, and 23.80 mg (0.00782 mmol) of tri-*o*-tolylphosphine in 0.600 mL of Et_3N were mixed in a round flask and heated at 100 °C for 8 h. Water and ice were added, 2 N HCl was added, and the aqueous phase was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 80:20) to give 124 mg of the product.(*E*/*Z* isomers, 2:1). Yield 45%. ^1H NMR ($CDCl_3$), *E*, δ: 1.78 (6H, s), 2.13 (3H, s), 2.17 (3H, s), 4.9 (1H, bs, OH), 5.87 (1H, d, J = 16.5 Hz), 6.72 (1H, d, J = 8.50 Hz), 7.30 (1H, dd, J = 8.50 Hz, J = 2.30 Hz), 7.41 (1H, d, J = 16.50 Hz), 7.45 (1H, d, J = 2.30 Hz), 7.47 (2H, d, J = 8.60 Hz), 7.58 (2H, d, J = 8.60 Hz). MS (EI) *m*/*z*: 355 (56, M^+), 97 (100). ^1H NMR ($CDCl_3$), *Z*, δ: 1.78 (6H, s), 2.13 (3H, s), 2.17 (6H, s), 4.9 (1H, bs, OH), 5.40 (1H, d, J = 11.3 Hz), 6.72 (1H, d, J = 8.50 Hz), 7.13 (1H, d, J = 11.3 Hz), 7.33 (1H, dd, J = 8.50 Hz, J = 2.30 Hz), 7.48 (1H, d, J = 2.30 Hz), 7.62 (2H, d, J = 8.50 Hz), 7.85 (2H, d, 8.50 Hz). Anal. ($C_{25}H_{25}NO$) C, H, N.

***E*-3-(3′-Adamantan-1-yl-4′-hydroxybiphenyl-4-yl)acrylic Acid (2).** Compound **5** (3.28 g, 8.45 mmol) was added to a solution of $LiOH·H_2O$ (1.77 g, 42.25 mmol) in 340 mL of THF/H_2O, 1:1, and the mixture was kept under stirring at room temperature overnight. The THF was evaporated and the mixture was extracted with hexane, acidified with 2 N HCl, and filtered to give 2.82 g (94%) of **2**, mp >240 °C. ^1H NMR (DMSO-d_6) δ: 1.74 (6H, s, 6Ad), 2.04 (3H, s, 3Ad), 2.12 (6H, s, 6Ad.), 6.51 (1H, d, −CH═, J = 16.18 Hz), 6.85 (1H, d, 1Ar, J = 8.82 Hz), 7.30−7.40 (2H, m, 2Ar), 7.55−7.63 (3H, m, 2Ar + CH═), 7.70 (2H, d, 2Ar, J = 8.09 Hz), 9.54 (1H, s, −OH), 12.34 (1H, brs, −COOH). MS (*m*/*z*): 374 (M^+, 100). Anal. ($C_{25}H_{26}O_3$) C, H.

4-Hydroxyphenylamide of *E*-3-(3′-Adamantan-1-yl-4′-hydroxybiphenyl-4-yl)acrylic Acid. (7a). Compound **2** (348 mg, 0.93 mmol) was dissolved under N_2 in 27 mL of a solution of THF/CH_3CN, 5:4. After addition of 178 mg (0.93 mmol) of WSC and 126 mg (0.93 mmol) of HOBT the solution was warmed for 4 h at 60 °C. 4-Aminophenol (112 mg, 1.02 mmol) in 5 mL of THF was then added, and the mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure, and the residual slurry was washed twice with water, filtered, and dried. Purification by flash chromatography (hexane ethyl acetate, 1:1) afforded 200 mg of the pure product. Yield 46%, mp 291−293 °C. ^1H NMR (DMSO-d_6) δ: 1.7 (6H, s, 6Ad), 2.03 (3H, s, 3Ad), 2.12 (6H, s, 6Ad), 6.70 (2H, d, 2Ar, J = 8.56 Hz), 6.75 (1H, d, CH═, J = 15.63 Hz), 7.35 (2H, m, 2Ar), 7.48 (2H, d, 2Ar, J = 8.56 Hz), 7.50 (1H, d, CH═, J = 15.63 Hz), 7.55−7.65 (4H, m, 4Ar), 7.85 (1H, d, 1Ar, J = 8.56 Hz), 9.30 (1H, s, NHCO), 9.51 (1H, s, OH). MS *m*/*z*: 465 (M^+, 10), 357 (80), 135 (100), 109 (40), 79 (40). Anal. ($C_{31}H_{31}NO_3$) C, H, N.

2-Aminophenylamide of *E*-3-(3′-Adamantan-1-yl)-4′-hydroxybiphenyl-4-yl)acrylic Acid (7b). Compound **2** (200 mg, 0.53 mmol) was dissolved under N_2 in 15.5 mL of a solution of THF/CH_3CN, 5:4. After addition of 101 mg (0.53 mmol) of WSC and 71 mg (0.53 mmol) of HOBT, the solution was heated for 4 h at 60−70 °C. Then an amount of 65 mg (0.6 mmol) of 1,2-phenylenediamine was added, and the mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure, and the residue was washed twice with water, filtered, and dried. Purification by flash chromatography (hexane/ethyl acetate, 55:45) afforded 60 mg of the title compound. Yield 25%, mp 210−212 °C. ^1H NMR (DMSO-d_6) δ: 1.75 (6H, s, 6Ad), 2.05 (3H, s, 3Ad), 2.15 (6H, s, 6Ad), 4.95 (2H, s, NH_2), 6.55 (1H, dd, 1Ar, J = 7.82, 7.82 Hz), 6.72 (1H, dd, 1Ar, J = 7.82, 1.86 Hz), 6.80−6.95 (3H, m, 2Ar + CH═), 7.30−7.45 (3H, m, 3Ar), 7.55 (1H, d, CH═, J = 15.26 Hz), 7.58−7.70 (4H, m, 4Ar), 9.38 (1H, s, NHCO), 9.40 (1H, s, OH). MS *m*/*z*: 464 (M^+, 30), 445(90), 357 (100). Anal. ($C_{31}H_{32}N_2O_2$) C, H, N.

***E*-3-(4′-Hydroxybiphenyl-4-yl)acrylic Acid (8a).** Compound **3** (500 mg, 2 mmol), 276 mg (3.2 mmol) of methyl acrylate, 4.5 mg (0.02 mmol) of $Pd(AcO)_2$, and 24 mg (0.08 mmol) of TOTP in 0.95 mL of TEA were mixed in a round flask, which was then put in an oil bath preheated at 60 °C. The mixture was refluxed for 8 h, ice/water was added, and the solution was acidified with 2 N HCl. The aqueous phase was extracted with ethyl acetate (4 × 10 mL), dried, filtered, and evaporated. The product was crystallized from diethyl ether to obtain 352 mg (70%) of methyl *E*-3-(4′-hydroxybiphenyl-4-yl)acrylate, mp 227 °C. The above ester (350 mg, 1.38 mmol) was suspended in a solution of 289 mg (6.88 mmol) of $LiOH·H_2O$ in 44 mL of THF/H_2O, 1:1, and stirred for 23 h at room temperature in the dark. THF was evaporated, and the remaining aqueous phase was washed with hexane and acidified with 0.5 mL of 2 N HCl. The light-yellow precipitate was filtered, dried, and crystallized from diisopropyl ether to afford 213 mg (65%) of the title compound, mp 265 °C. ^1H NMR

(DMSO-d_6) δ 6.50 (1H, d, CH=, J = 16.1 Hz), 6.82 (2H, d, 2 Ar, J = 8.3 Hz), 7.55 (2H, d, 2 Ar, J = 8.8 Hz), 7.60 (2H, d, 2 Ar, J = 8.1 Hz), 7.65 (1H, d, CH=, J = 16.1 Hz), 7.71 (2H, d, 2 Ar, J = 8.1 Hz). MS (EI) *m/z*: 240 (M^+, 100), 165 (50). Anal. ($C_{15}H_{12}O_3$) C, H.

***E*-3-(4′-Hydroxy-3′-(1-methylcyclohexyl)biphenyl-4-yl)-acrylic Acid (8b).** 4-(4-Bromophenyl)phenol (**3**, 300 mg, 1.2 mmol) and 211 mg (1.85 mmol) of 1-methylcyclohexan-1-ol were dissolved in 20 mL of dichloromethane. After addition of 92 μL of H_2SO_4, 98%, the mixture was refluxed for 90 h, then washed with water and neutralized with $NaHCO_3$. The organic layer was dried and evaporated. Chromatography (hexane/ethyl acetate, 95:5) afforded 86 mg (21%) of 2-(1-methylcyclohexyl)-4-(4-bromophenyl)phenol as an oil. The above compound (77 mg, 0.23 mmol), 32 mg (0.37 mmol) of methyl acrylate, 0.5 mg (0.0023 mmol) of $Pd(AcO)_2$, and 4 mg (0.011 mmol) of TOTP in 0.1 mL of TEA were mixed in a round flask, which was then put in an oil bath preheated at 60 °C. The mixture was refluxed for 8 h. After addition of ice/water, the solution was acidified with 2 N HCl. The aqueous phase was extracted with ethyl acetate (4 × 10 mL), dried, filtered, and evaporated. The product was crystallized from diethyl ether to obtain 71 mg (88%) of the methyl ester of **8b**, mp 253 °C. The above ester (71 mg, 0.203 mmol) was suspended in a solution of 43 mg (1.01 mmol) of $LiOH·H_2O$ in 8 mL of THF/H_2O, 1:1, and stirred overnight at room temperature in the dark. THF was evaporated, and the remaining aqueous phase was washed with hexane and then acidified with 0.5 mL of 2 N HCl. The light-yellow solid precipitate was filtered and dried to afford 33 mg (48%) of the title compound, mp 215−220 °C. ^{1}H NMR (DMSO-d_6) δ: 1.30 (3H, s, CH3), 1.32−1.5 (8H, m, cyclohex), 2.1−2.3 (2H, m, cyclohex), 6.50 (1H, d, CH=, J = 15.81 Hz), 6.87 (1H, d, 1Ar, J = 8.5 Hz), 7.32 (1H, dd, 1Ar, J = 8.5 Hz, 2.6 Hz), 7.53−7.7 (5H, m, 4 Ar + CH=). MS (EI) *m/z*: 336 (M^+, 100), 253 (35). Anal. ($C_{22}H_{24}O_3$) C, H.

***E*-3-(3′-*tert*-Butyl-4′-hydroxybiphenyl-4-yl)acrylic Acid (8c).** To a solution of CH_3COOH/concentrated H_2SO_4, 9:1 (2 mL), an amount of 500 mg (2.01 mmol) of 4-(4′-bromophenyl)-phenol was added. Then an amount of 0.192 mL (2.01 mmol) of *tert*-butyl alcohol was added dropwise. The mixture was stirred at room temperature for 2 weeks. CH_3COOH was evaporated, and water and ice were added. The white solid was filtered and washed with water. The crude product was purified by flash chromatography (hexane/ethyl acetate, 85:15) to give 163 mg of 2-*tert*-butyl-4-(4′-bromophenyl)phenol. Yield 27%, mp 114−116 °C.

The above compound (160 mg, 0.524 mmol), 72 mg (0.838 mmol) of methyl acrylate, 5 mg (0.0223 mmol) of $Pd(OAc)_2$, and 27 mg (0.0887 mmol) of tri-*o*-tolylphosphine in 0.243 mL of Et_3N were mixed in a round flask and heated at 100 °C for 4 h. Water and ice were added, 2 N HCl was added, and the aqueous phase was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography (dichloromethane/hexane, 95:5), to give 121 mg of methyl *E*-3-(3′-*tert*-butyl-4′-hydroxybiphenyl-4-yl)acrylate. Yield 74%, mp 182 °C.

The above compound (70 mg, 0.226 mmol) was dissolved in a solution of 47.4 mg (1.13 mmol) of $LiOH·H_2O$ in 9.30 mL of THF/H_2O, 1:1, and the solution was stirred overnight at room temperature in the dark. THF was evaporated. The aqueous phase was washed with hexane and Et_2O and then acidified with 2 N HCl (0.6 mL). The white solid was filtered and dried to give 54 mg of pure product. Yield 81%, mp 218 °C. ^{1}H NMR (DMSO-d_6) δ 1.34 (9H, s, $3CH_3$), 6.47 (1H, d, CH=, J = 16.38 Hz), 6.83 (1H, d, 1Ar, J = 8.19 Hz), 7.34 (1H, dd, 1Ar, J = 8.19 Hz, J = 2.23 Hz), 7.40 (1H, d, 1Ar, J = 2.23 Hz), 7.55 (1H, d, CH=, J = 16.38 Hz), 7.58 (2H, d, 2Ar, J = 8.25 Hz), 7.68 (2H, d, 2Ar, J = 8.25 Hz), 9.63 (1H, s, OH). MS (EI) *m/z*: 296 (97, M^+), 281 (100), 253 (64). Anal. ($C_{19}H_{20}O_3$) C, H.

***E*-3-[3′-(1-Methylcyclododecyl)-4′-hydroxybiphenyl-4-yl]acrylic Acid (8d).** 4-Bromophenol (446 mg, 2.58 mmol) and 510 mg (2.58 mmol) of 1-methylcyclododecan-1-ol were dissolved in 1.3 mL of dichloromethane. After slow addition of 137 μL of H_2SO_4, 98%, the mixture was stirred at room temperature for 24 h, then washed with water and neutralized with $NaHCO_3$. The aqueous phase was extracted with ethyl acetate, and the collected organic layers were dried, filtered, and evaporated. Chromatography (hexane/ethyl acetate, 80:20) afforded 2-(1-methylcyclododecyl)phenol as an oil. Yield 10%.

The above compound (86 mg, 0.244 mmol), 75 mg (0.29 mmol) of bis(pinacolato)diboron, 72 mg (0.73 mmol) of KOAc, and 5.36 mg (0.0073 mmol) of $PdCl_2$(dppf) were dissolved in 1.5 mL of dioxane and heated at 80 °C for 2 h under nitrogen. After the solution was cooled to room temperature, methyl 4-bromocinnamate (118 mg, 0.49 mmol), $PdCl_2$(dppf) (5.36 mg, 0.0073 mmol), and 2 N Na_2CO_3 (0.3 mL, 0.61 mmol) were added, and the mixture was heated at 80 °C for 3 h. The solution was cooled to room temperature, diluted with water, and acidified with 2 N HCl (2.6 mL), and the product was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and filtered, and the solvent was evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 75:25) to give 15 mg of methyl *E*-3-[3′-(1-methylcyclododecyl)-4′-hydroxybiphenyl-4-yl]acrylate. Yield 28%, mp 198 °C.

The above ester (15 mg, 0.0345 mmol) was dissolved in a solution of 7.3 mg (0.173 mmol) of $LiOH·H_2O$ in 1.4 mL of THF/H_2O, 1:1, and the solution was stirred overnight at room temperature in the dark. THF was evaporated, and the aqueous phase was washed with hexane and Et_2O and acidified with 2 N HCl (0.19 mL). The solid formed was filtered and dried to give 10 mg of a crude product that was purified by reverse-phase chromatography (MeOH/H_2O, 90:10) to obtain 5 mg of the title compound as a white solid. Yield 34%, mp 173 °C. ^{1}H NMR (acetone-d_6) δ 1.1−2.2 (25H, m, cyclodod), 6.50 (1H, d, CH=, J = 16.0 Hz), 6.90 (1H, d, 1Ar, J = 8.12 Hz), 7.35 (1H, dd, 1Ar, J = 2.20 Hz, J = 8.12 Hz), 7.55 (1H, d, 1Ar, J = 2.20 Hz), 7.60−7.75 (5H, m, 4Ar + CH=), 8.60 (1H, s, OH), 12.0 (1H, bs, COOH).

***E*-3-[3′-(Adamantan-1-yl)-4′-hydroxybiphenyl-4-yl]crotonic Acid (9).** Compound **4** (200 mg, 0.52 mmol), 75 mg (0.87 mmol) of crotonic acid, 1.4 mg (0.006 mmol) of $Pd(OAc)_2$, and 7.3 mg (0.024 mmol) of tri-*o*-tolylphosphine in 0.6 mL of Et_3N were mixed in a round flask and heated at 100−110 °C for 12 h. A 1 M HCl sample was added. The product was extracted with ethyl acetate, the organic phase was dried over Na_2SO_4 and filtered, and the solvent was evaporated. The crude product was purified by reverse-phase flash chromatography (methanol) and crystallized from Et_2O to give 58 mg of pure product. Yield 29%, mp 215−220 °C. ^{1}H NMR (DMSO-d_6) δ 1.75 (6H, s, 6Ad), 2.05 (3H, s, 3Ad), 2.15 (6H, s, 6Ad), 2.50 (3H, s, CH_3), 6.15 (1H, s, CH=), 6.85 (1H, d, 1Ar, J = 8.25 Hz), 7.33 (1H, dd, 1Ar, J = 8.25 Hz, J = 1.50 Hz), 7.35 (1H, d, 1Ar, J = 1.50 Hz), 7.55−7−65 (4H, m, 4Ar). MS (EI) *m/z*: 388 (M^+, 100). Anal. ($C_{26}H_{28}O_3$) C, H.

3-Adamantan-1-yl-4′-(3-hydroxypropenyl)biphenyl-4-ol (10). A solution of 1 M $LiAlH_4$ in THF (386 μL) was diluted in 1 mL of THF and cooled to −5 °C with an ice/salt bath under N_2. To this solution an amount of 150 mg (0.386 mmol) of **4** in 4 mL of anhydrous THF was dropped, and stirring was continued for 2 h at 0 °C. A solution of 10% NH_4Cl was slowly added, cooling with an ice bath. THF was evaporated, and the aqueous phase was extracted with ethyl acetate. The organic layer was dried, filtered, and evaporated. The product was purified by flash chromatography (eluent AcOEt/hexane, 1:2) and crystallized from Et_2O. Yield 10%, mp 196 °C. ^{1}H NMR (acetone-d_6) δ: 1.75 (6H, s, 6Ad), 2.06 (3H, s, 3Ad), 2.25 (6H, s, 6Ad), 4.25 (2H, d, $-CH_2OH$, J = 5.15 Hz), 6.45 (1H, dt, −CH=, J = 15.81 Hz, 5.15 Hz), 6.65 (1H, d, CH=, J = 15.81 Hz), 6.90 (1H, d, 1Ar, J = 8.46 Hz), 7.31 (1H, dd, 1Ar, J = 8.46 Hz, 2.57 Hz), 7.45−7.55 (4H, m, 4Ar), 8.45 (1H, brs, OH). MS (EI) *m/z*: 360 (M^+, 100), 317 (50). Anal. ($C_{25}H_{28}O_2$) C, H.

3-(3′-Adamantan-1-yl-4′-hydroxybiphenyl-4-yl)propionic Acid (11). Compound **5** (80 mg) was dissolved in 40 mL of AcOEt, an amount of 30 mg of PtO_2 was added, and the mixture was hydrogenated for 40 min. After filtration of the

catalyst, the solvent was evaporated to obtain 80 mg (100%) of methyl 3-(3′-adamantan-1-yl-4′-hydroxybiphenyl-4-yl)propionate, mp 150 °C. A solution of 43 mg (1.03 mmol) of $LiOH·H_2O$ and 80 mg (0.205 mmol) of the above ester in 8.4 mL of THF/H_2O, 1:1, was stirred at room temperature for 1.5 h. THF was evaporated, and the remaining aqueous layer was washed with hexane and then acidified with 1 M HCl to pH 2 to obtain, after filtration, 57 mg of a white solid. Yield 74%, mp 197−200 °C. ^{1}H NMR (acetone-d_6) δ: 1.80 (6H, s, 6Ad), 2.10 (3H, s, 3Ad), 2.25 (6H, s, 6Ad), 2.65 (2H, t, $-CH_2-$, J = 7.72 Hz), 2.95 (2H, t, $-CH_2-$, J = 7.72 Hz), 6.90 (1H, d, 1Ar, J = 8.09 Hz), 7.25−7.35 (3H, m, 3Ar), 7.42 (1H, d, 1 Ar, J = 2.21 Hz), 7.50 (2H, d, 2Ar, J = 8.34 Hz), 8.45 (1H, brs, OH). MS (EI) *m/z*: 376 (M^+, 100). Anal. ($C_{25}H_{28}O_3$) C, H.

2-(Adamantan-1-yl)-5-methyl-4-bromophenol (12c). A finely pulverized mixture of 3-methyl-4-bromophenol (500 mg, 2.7 mmol) and 1-adamantanol (409 mg, 2.7 mmol) was added portionwise with stirring to 2.7 mL of CH_3COOH/concentrated H_2SO_4, 9:1. The mixture was stirred at room temperature for 4 days, water and ice were added, and the solid was filtered and washed with water to give 722 mg of the desired product. Yield 84%, mp 155−156 °C.

3′-(Adamantan-1-yl)-4′-hydroxybiphenyl-4-aldehyde (13a). 2-(1-Adamantan-1-yl)-4-bromophenol (**12a**, 2 g, 6.51 mmol) in 13 mL of toluene was added, under a stream of nitrogen, with 6.51 mL of 2 M aqueous Na_2CO_3, 226 mg (0.195 mmol) of $Pd(Ph_3P)_4$, and 1.074 g (7.16 mmol) of 4-formylbenzeneboronic acid (previously suspended in 3.03 mL of EtOH). The resulting solution was refluxed 3 h, then extracted with ethyl acetate. The organic layer was washed with brine and water, dried, and evaporated to give, after chromatography with hexane/ethyl acetate, 7:3, 630 mg of **13a**, yield 30%, mp 252 °C.

3′-(Adamantan-1-yl)-4′-*tert*-butyldimethylsilyloxybiphenyl-4-aldehyde (13b). 3-(Adamantan-1-yl)-4-(*tert*-butyldimethylsilyloxy)bromobenzene **12b**[4] (1.56 g, 3.70 mmol) was dissolved in 7.5 mL of toluene. Then 3.7 mL of a 2 M aqueous solution of Na_2CO_3, 0.128 g (0.11 mmol) of tetrakis-triphenylphosphine-palladium, and a solution of 610 mg (4.07 mmol) of 4-formylbenzeneboronic acid in 1.73 mL of ethanol were added. The mixture was refluxed for 2 h in a stream of nitrogen. It was then cooled, taken up with ethyl acetate, and washed with a NaCl saturated solution. The phases were separated, the organic layer was filtered, dried over Na_2SO_4, and filtered, the solvent was evaporated, and the residue was subjected to flash chromatography (hexane/ethyl acetate, 3:1) to give 1.09 g of the title compound, mp 158 °C.

2′-Methyl-4′-hydroxy-5′-adamantan-1-ylbiphenyl-4-aldehyde (13c). 2-(1-Adamantan-1-yl)-5-methyl-4-bromophenol (**12c**, 393 mg, 1.23 mmol) was dissolved in 2.5 mL of toluene. Then 1.25 mL (2.5 mmol) of 2 N Na_2CO_3, 44 mg (0.038 mmol) of $Pd(PPh_3)_4$, and a suspension of 207 mg (1.38 mmol) of 4-formylbenzeneboronic acid in 0.6 mL of ethanol were added. The mixture was refluxed for 3 h in a current of nitrogen and then diluted with water, and the product was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and filtered. The crude product was purified by flash chromatography (hexane/ethyl acetate, 85:15) to give 231 mg of the pure aldehyde. Yield 55%, mp 84 °C.

Diethyl *E*-[2-(3′-Adamantan-1-yl-4′-hydroxybiphenyl-4-yl)vinyl]phosphonate (14a). The aldehyde **13a** (200 mg, 0.602 mmol) was dissolved in the minimum amount of THF. Then 350 mg (6.02 mmol) of finely crushed KF/Al_2O_3 and 174 mg (0.602 mmol) of tetraethylmethylenediphosponate were added, and the solvent was evaporated. The mixture was left for 3 h at room temperature. THF was then added, and KF/Al_2O_3 was filtered on a Celite pad. The solvent was evaporated, and water was added and acidified with 2 M HCl. The white solid formed was filtered and washed with diisopropyl ether. Flash chromatography (eluent ethyl acetate/hexane, 8:2) afforded the product as a white solid. Yield 38%, mp 229−230 °C. ^{1}H NMR ($CDCl_3$) δ: 1.40 (6H, t, J = 7.3 Hz, CH_3CH_2O-), 1.82 (6H, s, 6 Ad), 2.1 (3H, s, 3 Ad), 2.2 (6H, s, 6 Ad), 4.18 (q, J = 7.3 Hz, CH_3CH_2O-), 5.7 (1H, br s, OH), 6.28 and 7.5 (ABX, J_{AB} = 17.3 Hz, J_{P-HA} = 17.3 Hz, J_{P-HB} = 22 Hz, $PO-CH_A=CH_B$), 6.80 (1H, d, J = 8.5 Hz), 7.43 (1H, dd, J = 8.5 and 2.2 Hz), 7.48 (1H, d, J = 2.2 Hz), 7.5−7.6 (4H, m, Ar). MS (EI) *m/z*: 466 (M^+, 100), 317 (40), 275 (75). Anal. ($C_{28}H_{35}O_4P$) C, H.

***E*-[3-(3′-Adamantan-1-yl)-4′-hydroxybiphenyl-4-yl)vinyl]-phosphonic Acid (14b).** The ester **14a** (90 mg, 0.193 mmol) was dissolved under a stream of nitrogen in 7.5 mL of anhydrous dichloromethane. Trimethylsilyl bromide (259 mg, 1.93 mmol) was then dropped, and the solution was stirred overnight at room temperature protected from light. The solvent and the excess of trimethylsilyl bromide were evaporated, and an amount of 5.4 mL of water was added. After stirring 30 min at room temperature, the solid was evaporated. The mixture was dissolved in 1 N NaOH and stirred 30 min at room temperature, then acidified and stirred for a further 30 min. The solid was filtered to obtain 60 mg of pure product. Yield 76%, mp 200 °C. ^{1}H NMR (DMSO-d_6) δ 1.73 (6H, s, 6 Ad), 2.0 (3H, s, 3 Ad), 2.1 (6H, s, 6 Ad), 6.18 and 6.44 (ABX, J_{AB} = 17.5 Hz, J_{P-HA} = 17.5 Hz, J_{P-HB} = 22 Hz, $PO-CH_A=CH_B$), 6.83 (1H, d, J = 8.6 Hz), 7.30 (1H, dd, J = 8.6 Hz, J = 2.2 Hz), 7.32 (1H, d, J = 2.2 Hz), 7.52−7.65 (4H, m, Ar), 9.5 (1H, s, OH). MS (EI) *m/z*: 411 (M^+, 50), 301 (35), 205 (35), 149 (70), 93 (65), 91 (100). Anal. ($C_{24}H_{27}O_4P$) C, H.

3-[3′-(Adamantan-1-yl)-4′-hydroxybiphenyl-4-yl]-propynoic acid (15). To a vigorously stirred suspension of 367 mg (2.66 mmol) of K_2CO_3 and 800 mg (1.33 mmol) of $Ph_3P^+-CH(I)-COOEt\ I^-$ (in 2 mL of MeOH), an amount of 5.92 mg (1.33 mmol) of the aldehyde **13b** (previously dissolved in 3 mL of $CHCl_3$) was dropped. The resulting suspension was stirred for 11 h. After filtration the solvent was evaporated. Purification by flash chromatography (eluent hexane/dichlorometane, 2:1) led to methyl *Z*-2-iodo-3-(3′-adamantan-1-yl)-4′-*tert*-butyldimethylsilanoxybiphenyl-4-yl)acrylate (where the ester group had exchanged with methanol) as an oil. The above ester (50 mg, 0.080 mmol) was added to a solution of 25% KOH in 4.5 mL of MeOH, and the resulting suspension was refluxed for 1 h. The solvent was evaporated, and water was added. The solid formed after acidification with 2 M HCl was filtered and dried. Purification by reverse-phase chromatography (Merck Lichroprep RP-18, $MeOH/H_2O$, 7:3) afforded 20 mg of pure **15**. Yield 70%, mp 201 °C. ^{1}H NMR (MeOD) δ 1.80 (6H, s, 6Ad.), 2.10 (3H, s, 3Ad.), 2.25 (6H, s, 6Ad.), 6.85 (1H, d, 1Ar, J = 8.0 Hz), 7.35 (1H, dd, 1Ar, J = 8.0 Hz, 1.84 Hz), 7.45 (1H, d, 1Ar, J = 1.84 Hz), 7.5−7.65 (4H, m, 4Ar). MS (FAB glycerol) *m/z*: 373 (M + 1, 100), 301 (50), 207 (40), 115 (40). Anal. ($C_{25}H_{24}O_3$) C, H.

3-[3′-(Adamantan-1-yl)-4′-hydroxybiphenyl-4-yl]-4-carboxylic Acid (16). To a solution of the aldehyde **13b** (50 mg, 0.112 mmol) in 1.6 mL of acetone, an amount of 26 mg (0.168 mmol) of $KMnO_4$ dissolved in 0.5 mL of H_2O was dropped. The solution was heated at 50 °C for 1 h. After filtration of MnO_2, water was added and the aqueous phase was extracted with AcOEt (2 × 5 mL) and CH_2Cl_2 (2 × 5 mL). The organic layers were collected, dried, and evaporated to obtain 40 mg of the *tert*-butyldimethylsilyl derivative of **16** as a white solid. Yield 77%, mp 263 °C. The above compound (32 mg, 0.069 mmol) was dissolved in 0.3 mL of DMF. After addition of 11.6 mg (0.277 mmol) of $LiOH·H_2O$, the solution was stirred at room temperature overnight and then acidified with 2 N HCl. The white solid precipitate was filtered, washed with water, and dried to obtain 11 mg of pure product. Yield 46%, mp 272 °C. ^{1}H NMR ($CDCl_3$) δ 1.73 (6H, s, 6 Ad), 2.05 (3H, s, 3 Ad), 2.1 (6H, s, 6 Ad), 6.85 (1H, d, J = 8.6 Hz), 7.35 (1H, dd, J = 8.6 and 2.2 Hz), 7.37 (1H, s), 7.56 (2H, d, J = 8.6), 7.91 (2H, d, J = 8.6). MS (EI) *m/z*: 348 (M^+, 100), 291 (25), 227(25). Anal. ($C_{23}H_{24}O_3$) C, H.

***E*-2-Methyl-3-[3′-(adamantan-1-yl)-4′-hydroxybiphenyl-4-yl]acrylic Acid (17a).** Under a stream of nitrogen 200 mg (0.448 mmol) of the aldehyde **13b** and 167 mg (0.448 mmol) of $Ph_3P=C(CH_3)-COOEt$ were dissolved in 2.3 mL of $CHCl_3$, and the resulting solution was refluxed for 21 h. The solvent was evaporated, and the crude ester obtained was used without further purification. This compound (390 mg, 0.714 mmol) was

added to 90 mg (2.14 mmol) of LiOH·H_2O dissolved in 30 mL of THF/H_2O, 1:1. The solution was stirred at room temperature for 2 days. After evaporation of THF, the aqueous phase was acidified with 3 mL of 1 M HCl and extracted with AcOEt. Drying, filtration and evaporation of the solvent afforded 312 mg of crude product, which was purified by flash chromatography (hexane/ethyl acetate, 2:1 and then 3:2) to obtain 69 mg of the title compound as a white solid, mp 200 °C. ^{1}H NMR (600 MHz) (DMSO-d_6) δ 1.73−1.76 (6H, s, 6Ad), 2.04−2.06 (3H, m, 3Ad), 2.08 (Me, d, J = 1.59 Hz), 2.12−2.94 (6H, m, Ad), 6.86 (1H, d, H-5′, J = 8.27 Hz), 7.36 (1H, dd, H-6′, J = 2.38 Hz, J = 8.27 Hz), 7.38 (1H, d, H-2′, J = 2.38 Hz), 7.51 (2H, d, H-3 and H-5, J = 8.42 Hz), 7.60 (1H, br s, CH═), 7.63 (2H, d, H-2 and H-6, d, J = 8.42 Hz) 9.50 (1H, s, OH), 12.4 (1H, s, COOH). MS (*m/z*): 388 (M^+, 100), 267 (40), 178 (40), 79 (60). Anal. ($C_{26}H_{28}O_3$) C, H.

***E*-2-Fluoro-3-[3′-(adamantan-1-yl)-4′-hydroxybiphenyl-4-yl]-acrylic Acid (17b).** EtOOC−CH(F)−$PO(OEt)_2$ (124 mg, 0.493 mmol) was dissolved in 1 mL of anhydrous THF, cooled to −78 °C, and treated with a solution of 1.6 M BuLi in hexane (0.364 mL). After stirring for 30 min at −78 °C, an amount of 200 mg (0.448 mmol) of the aldehyde **13b** dissolved in 0.5 mL of THF was dropped, and the solution was slowly brought to room temperature (3 h). After acidification with 6 mL of 2 N HCl the aqueous phase was extracted with AcOEt. The organic layers were washed with brine, dried, filtered, and evaporated to afford 280 mg of a crude product. Purification by flash chromatography (hexane/ethyl acetate, 95:5) gave 180 mg (75%) of the ethyl ester of the tertbutyldimethylsilyl derivative of **17b** as an oil. This compound (97 mg, 0.181 mmol) was suspended in a solution of 38 mg (0.905 mmol) of LiOH·H_2O in 7.4 mL of THF/H_2O, 1:1, and stirred overnight at room temperature in the dark. THF was evaporated and the remaining aqueous phase was washed with hexane, then acidified with 0.5 mL of 2 N HCl. The light-yellow precipitate was filtered and dried to afford 55 mg of the title compound. Yield 77%, mp 202 °C. ^{1}H NMR (acetone-d_6): δ 1.8 (8H, s, 8 Ad), 2.2 (6H, s, 6 Ad), 6.90 (1H, d, J = 8.5 Hz), 7.00 (1H, d, $J_{H,F}$ = 23.9 Hz), 7.36 (1H, dd, J = 8.5 and 2.6 Hz), 7.50 (1H, d, J = 2.6 Hz), 7.60 (2H, d, J = 8.8 Hz), 7.71 (2H, d, J = 8.8 Hz). MS (EI) *m/z*: 392 (M^+, 100). Anal. ($C_{25}H_{25}FO_3$) C, H.

***Z*-2-Fluoro-3-[3′-(adamantan-1-yl)-4′-hydroxybiphenyl-4-yl]acrylic Acid (17c).** EtOOC−CH(F)−$PO(OEt)_2$ (124 mg (0.493 mmol) was dissolved in 1 mL of anhydrous THF, cooled to 0 °C, and treated with 0.364 mL of a solution of 1.6 M BuLi in hexane. After the mixture was stirred for 1 h at 0 °C, the solution was heated to reflux and an amount of 200 mg (0.448 mmol) of the aldehyde **13b** dissolved in 0.5 mL of THF was dropped. Heating was continued for 8 h, then an amount of 6 mL of 2 N HCl was added and the aqueous phase was extracted with AcOEt. The organic layers were washed with brine, dried, filtered, and evaporated to give a crude mixture of the *E* and *Z* isomers. Purification by flash chromatography (hexane/ethyl acetate, 95:5) afforded 38 mg (16%) of the ethyl ester of the *tert*-butyldimethylsilyl derivative of **17c**, mp 125 °C. This ester (30 mg, 0.056 mmol) was suspended in a solution of 12 mg (0.281 mmol) of LiOH·H_2O in 2.3 mL of THF/H_2O, 1:1, and stirred overnight at room temperature in the dark. THF was evaporated, and the remaining aqueous phase was washed with hexane and diethyl ether, then acidified with 0.15 mL of 2 N HCl. The light-yellow solid was filtered and dried to afford 16 mg (73%) of **17c**, mp 282 °C. ^{1}H NMR (acetone-d_6): δ 1.8 (8H, s, 8 Ad), 2.2 (6H, s, 6 Ad), 6.94 (1H, d, J = 8.5 Hz), 7.06 (1H, d, $J_{H,F}$ 36 Hz), 7.40 (1H, dd, J = 8.5 and 2.5 Hz), 7.53 (1H, d, J = 2.5 Hz), 7.70 (2H, d, J = 8.5 Hz), 7.77 (2H, d, J = 8.5 Hz). Anal. ($C_{25}H_{25}FO_3$) C, H.

***E*-3-[5′-(Adamantan-1-yl)-2′-methyl-4′-hydroxy-biphenyl-4-yl]acrylic Acid (17d).** Aldehyde **13c** (210 mg, 0.61 mmol) and 204 mg (0.61 mmol) of methoxycarbonylmethylenetriphenylphosphorane were dissolved in 3.2 mL of chloroform and refluxed for 5 h in a current of nitrogen. The solvent was evaporated, and the residue was purified by flash chromatography (hexane/dichloromethane, 20:80) to give 194 mg of methyl *E*-3-[5′-(1-adamantan-1-yl)-2′-methyl-4′-hydroxybiphenyl-4-yl]acrylate. Yield 80%, mp 236−237 °C.

The above ester (150 mg, 0.37 mmol) was dissolved in a solution of 78 mg (1.86 mmol) of LiOH·H_2O in 12 mL of THF/H_2O, 1:1, and the resulting solution was stirred for 18 h at room temperature in the dark. THF was evaporated, the aqueous phase was washed with hexane and Et_2O and acidified with 2 N HCl. The solid formed was filtered and dried to give 137 mg of pure product. Yield 95%, mp 203 °C. ^{1}H NMR (DMSO-d_6) δ 1.70 (6H, s, 6Ad), 2.00 (3H, s, 3Ad), 2.03 (6H, s, 6Ad), 2.13 (3H, s, CH_3), 6.50 (1H, d, CH═, J = 16.5 Hz), 6.63 (1H, s, 1Ar), 6.85 (1H, s, 1Ar), 7.30 (2H, d, 2Ar, J = 8.25 Hz), 7.58 (1H, d, CH═, J = 16.5 Hz), 7.66 (2H, d, 2Ar, J = 8.25 Hz), 9.28 (1H, s, OH), 12.34 (1H, bs, COOH). MS (EI) *m/z*: 388 (M^+). Anal. ($C_{26}H_{28}O_3$) C, H.

(2-(3-(Adamantan-1-yl)-4-hydroxybiphenyl-4-yl)cyclopropanecarboxylic Acid (Cis and Trans Mixture) (18). To a solution of **12b** (400 mg, 0.949 mmol) in 1 mL of toluene, 0.95 mL of a 2 M solution of Na_2CO_3, 33 mg (0.285 mmol) of Pd tetrakis, and 154 mg (1.04 mmol) of *p*-vinylbenzeneboronic acid (previously dissolved in 0.9 mL of toluene and 0.44 mL of EtOH) were added. The solution was refluxed for 2 h. After addition of AcOEt the organic phase was washed with brine, dried, filtered, and evaporated to obtain 427 mg of crude (3-adamantan-1-yl-4′-vinylbiphenyl-4-oxy)-*tert*-butyldimethylsilane. Purification by flash chromatography using as eluent hexane afforded 277 mg of this compound, mp 137−139 °C. ^{1}H NMR ($CDCl_3$) δ 0.35 (6H, s, $-Si(CH_3)_2$), 1.05 (9H, s, −*t*-Bu), 1.75 (6H, s, 6Ad), 2.05 (3H, s, 3Ad), 2.12 (6H, s, 6Ad), 5.25 (1H, d, CH═, J = 7.5 Hz), 5.75 (1H, d, CH═, J = 14 Hz), 6.75 (1H, dd, CH═, J = 7.5 Hz, 14 Hz), 6.90 (1H, d, 1Ar, J = 7.0 Hz), 7.40−7.65 (6H, m, 6Ar).

Rhodium tetraacetate bihydrate (0.5 mg) and 36 μL of ethyl diazoacetate were added to a solution of 150 mg of the above compound in 2 mL of dichloromethane. The reaction mixture was left for 5 days at room temperature, with the addition of a total of 5 mg of catalyst and 10 μL of ethyl diazoacetate. The catalyst was filtered through Celite, dried over sodium sulfate, evaporated, and chromatographed on silica gel with hexane/ethyl acetate (65:35). A mixture (43 mg) of the two cis and trans diastereoisomers of methyl 2-[(3-(1-adamantan-1-yl)-4-hydroxybiphenyl-4-yl)cyclopropanecarboxylate was obtained.

KF on finely crushed Al_2O_3 (40%) (113 mg) was added to a solution of the above ester (110 mg) in 4.4 mL of dimethoxyethane, and the mixture was stirred at room temperature for 2 days. After filtration, the solvent was evaporated and the crude product was added to a solution of 63 mg of LiOH·H_2O in 12.4 mL of 50% aqueous THF. This was stirred at room temperature for 3 days, and the solvent was evaporated, extracted with ethyl ether, acidified with 2 M HCl, and extracted with ethyl acetate. After evaporation, the product (58 mg) was chromatographed on silica gel (hexane/ethyl acetate, 40:60) to give 6 mg of *trans*-2-(3-(1-adamantan-1-yl)-4-hydroxybiphenyl-4-yl)cyclopropanecarboxylic acid, mp 190 °C, 10 mg of a mixture of diastereoisomers, and 20 mg of *cis*-2-(3-(1-adamantan-1-yl)-4-hydroxybiphenyl-4-yl)cyclopropanecarboxylic acid, mp 204 °C. R_f is 0.23 for cis and 0.44 trans in hexane/ethyl acetate, 4:6. ^{1}H NMR (MeOD), trans, δ: 1.45−1.50 (1H, m, 1-CH_2), 1.60−1−65 (1H, m, 1-CH_2), 1.95−2.0 (7H, m, −CHCOOH + 6Ad), 2.2 (3H, s, 3Ad), 2.35 (6H,s, 6Ad), 2.50−2.58 (1H, m, −CHAr), 6.84 (1H, d, 1Ar, J = 8.46 Hz), 7.24 (2H, dd, 2Ar, J = 7.35 Hz, J = 1.84 Hz), 7.31 (1H, dd, 1Ar, J = 8.46 Hz, 2.57 Hz), 7.42 (1H, d, 1Ar, J = 2.57 Hz), 7.52 (2H, dd, 2Ar, J = 7.35 Hz, J = 1.84 Hz). ^{1}H NMR (MeOD), cis, δ: 1.40−1.50 (1H, m, 1-CH_2), 1.70−1.75 (1H, m, 1-CH_2), 1.95−2.0 (6H, s, 6Ad), 2.10−2.15 (4H, m, 3Ad + −CHCOOH), 2.30 (6H, s, 6Ad), 2.70−2.78 (1H, m, −CHAr), 6.83 (1H, d, 1Ar, J = 8.46 Hz), 7.30 (1H, dd, 1Ar, J = 8.46 Hz, J = 2.57 Hz), 7.38 (2H, dd, 2Ar, J = 7.30 Hz, J = 1.84 Hz), 7.42 (1H, d, 1Ar, J = 2.57 Hz), 7.49 (2H, dd, 2Ar, J = 7.30 Hz, J = 1.84 Hz). MS (*m/z*): 388 (M^+, 100), 135 (50). Anal. ($C_{26}H_{28}O_3$) C, H.

***E*-3-[3′-Adamantan-1-yl)-3-fluoro-4′-hydroxybiphenyl-4-yl]acrylic Acid (19).** 2-(1-Adamantan-1-yl)-4-bromophenol

12a (200 mg, 0.651 mmol), 182 mg (0.716 mmol) of bis(pinacolate)diboron, 191 mg (1.95 mmol) of KOAc, and 14.3 mg (0.0195 mmol) of $PdCl_2$(dppf) were dissolved in 3.9 mL of dioxane and heated at 100 °C for 2 h under nitrogen. After the solution was cooled to room temperature, methyl 4-bromo-2-fluorocinnamate (337 mg, 1.30 mmol), $PdCl_2$(dppf) (14.3 mg, 0.0195 mmol), and 2 N Na_2CO_3 (0.815 mL, 1.63 mmol) were added, and the mixture was heated at 100 °C for 1 h. The solution was cooled to room temperature, diluted with water, and acidified with 2 N HCl (2.6 mL), and the product was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, and filtered, and the solvent was evaporated. The crude product was purified by flash chromatography (dichloromethane/hexane, 80:20) to give 133 mg of methyl *E*-3-[3′-(1-adamantan-1-yl)-3-fluoro-4′-hydroxybiphenyl-4-yl]acrylate. Yield 50%, mp 245 °C.

The above ester (70 mg, 0.172 mmol) was dissolved in a solution of 36.1 mg (0.85 mmol) of $LiOH·H_2O$ in 7 mL of THF/H_2O, 1:1, and the solution was stirred overnight at room temperature in the dark. THF was evaporated, and the aqueous phase was washed with hexane and Et_2O and acidified with 2 N HCl (0.440 mL). The solid formed was filtered and dried to give 60 mg of the pure product. Yield 89%, mp 314 °C. ^{1}H NMR (DMSO-d_6) δ: 1.74 (6H, s, 6Ad), 2.05 (3H, s, 3Ad), 2.13 (6H, s, 6Ad), 6.56 (1H, d, CH=, J = 16.0 Hz), 6.85 (1H, d, 1Ar, J = 8.56 Hz), 7.35 (1H, d, 1Ar, J = 1.49 Hz), 7.38 (1H, dd, 1Ar, J = 8.56 Hz, J = 1.49 Hz), 7.43−7.53 (2H, m, 2Ar), 7.63 (1H, d, CH=, J = 16.0 Hz), 7.80 (1H, dd, 1Ar, J = 8.70 Hz, J = 8.10 Hz), 9.63 (1H, s, OH), 12.5 (1H, bs, COOH). Anal. ($C_{25}H_{25}FO_3$) C, H.

***E*-3-(4′-Hydroxy-[1,1′,3′,1″]terphenyl-4-yl)acrylic Acid (23).** To a solution of 1 g (5.88 mmol) of 2-phenylphenol **20** and 1.058 g (7.06 mmol) of NaI in 39 mL of DMF, an amount of 1.989 g (7.06 mmol) of chloramine T were added in one portion at 22 °C. The solution was stirred 3.5 h at 25 °C, an amount of 40 mL of water was added, and the solution was acidified with 2 N HCl to pH 1 and extracted with AcOEt (2 × 70 mL). After being washed with $Na_2S_2O_3$ (30 mL) and brine (30 mL), the collected organic layers were dried, filtered, and evaporated. Purification by flash chromatography (eluent hexane/dichloromethane, 7:3) gave 1.348 g (77%) of 2-phenyl-4-iodophenol (**21**), mp 35 °C.

Compound **21** (70 mg, 0.172 mmol) was dissolved in 2.5 mL of toluene under a stream of nitrogen. To this solution 1.35 mL of 2 M Na_2CO_3, 94 mg (0.06 mmol) of $Pd(Ph_3P)_4$, and 223 mg (1.49 mmol) of 4-formylbenzeneboronic acid (previously suspended in 0.7 mL of EtOH) were added. The resulting solution was refluxed for 17 h, then extracted with ethyl acetate. The organic layer was washed with water and brine, then dried, filtered, and evaporated. An amount of 15 mg (42%) of pure 4′-hydroxy[1,1′,3′,1″]terphenyl-4-yl)aldehyde (**22**) was obtained as an oil after flash chromatography (hexane/ethyl acetate, 8:2).

The aldehyde **22** (132 mg, 0.48 mmol) was dissolved in 2 mL of $CHCl_3$ under N_2, an amount of 161 mg (0.48 mmol) of Ph_3P=CH−$COOCH_3$ was added, and the resulting solution was refluxed for 5 h. The solvent was evaporated and the crude product was purified by chromatography (hexane/ethyl acetate 8:2) to give 130 mg (82%) of the methyl ester of **23**, mp 145 °C. To a solution of 82 mg (1.95 mmol) of $LiOH·H_2O$ in 6.3 mL of H_2O, a solution of 129 mg (0.39 mmol) of the above ester in 6.3 mL of THF was added. After the mixture was stirred at room temperature for 18 h, THF was evaporated. The aqueous phase was washed with hexane and diethyl ether, then acidified with 2 N HCl. The precipitate was filtered and dried. Purification by flash chromatography on reverse-phase (MeOH/H_2O, 3:1) afforded the title compound as a white solid. Yield 60%, mp 173−174 °C. ^{1}H NMR ($CDCl_3$) δ: 6.50 (1H, d, CH=, J = 16.0 Hz), 7.02 (1H, d, 1Ar, J = 8.10 Hz), 7.23−8.00 (12H, m, 11Ar + CH=), 9.78 (1H, s, OH), 12.33 (1H, brs, COOH). MS (EI) *m/z*: 316 (M^+). Anal. ($C_{21}H_{16}O_3$) C, H.

***E*-3-[3′-(Adamantan-1-yl)-4′-hydroxy-2-formylbiphenyl-4-yl]acrylic Acid (27a).** 2-Hydroxy-5-bromobenzaldehyde (**24a**, 500 mg, 2.5 mmol), 344 mg (4 mmol) of methyl acrylate, 11 mg (0.05 mmol) of $Pd(OAc)_2$, and 60 mg (0.2 mmol) of tri-*o*-tolylphosphine in 1 mL of Et_3N were mixed in a round flask and heated at 100−110 °C for 5 h. Water and ice were added, 2 N HCl was added, and the aqueous phase was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and evaporated to give 500 mg (97%) of methyl 3-(4-hydroxy-3-formylphenyl)acrylate, mp 100−101 °C.

The above product (1.030 g, 5 mmol) was dissolved under nitrogen in 29 mL of dry dichloromethane, Et_3N (2.1 mL, 15 mmol) was added, and the solution was cooled at 0−5 °C. *N*-Phenylbis(trifluoromethanesulfonimide) (2.32 g, 6.5 mmol) was added, and the reaction mixture was allowed to stir at 0−5 °C for 2.5 h. The solvent was evaporated, water was added, and the product was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and evaporated, and the crude product was purified by flash chromatography (hexane/ethyl acetate, 70:30) to give 1.40 g (83%) of methyl 3-(3-formyl-4-trifluoromethanesulfonyloxyphenyl)acrylate, mp 43 °C.

Compound **12b** (810 mg, 1.92 mmol), 533 mg (2.1 mmol) of bis(pinacolate)diboron, 564 mg (5.76 mmol) of KOAc, and 42 mg (0.058 mmol) of $PdCl_2$(dppf) were dissolved in dioxane and heated at 100 °C for 1.5 h under nitrogen. After the solution was cooled to room temperature, methyl 3-(3-formyl-4-trifluoromethanesulfonyloxyphenyl)acrylate (1.30 g, 3.8 mmol), $PdCl_2$(dppf) (42 mg, 0.058 mmol), and 2 N Na_2CO_3 (2.4 mL, 4.8 mmol) were added, and the mixture was heated at 100 °C for 3.5 h. The solution was cooled to room temperature and diluted with water, and the product was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated. After flash chromatography (hexane/ethyl acetate, 85:15), an amount of 447 mg of methyl *E*-3-[3′-(1-adamantan-1-yl)-4′-(*tert*-butyldimethylsilyloxy)-2-formylbiphenyl-4-yl]acrylate **26a** was obtained. Yield 47%, mp 147 °C.

The above ester (100 mg, 0.19 mmol) was dissolved in a solution of 40 mg (0.94 mmol) of $LiOH·H_2O$ in 6.2 mL of THF/H_2O, 1:1, and the solution was stirred overnight at room temperature in the dark. THF was evaporated, and the aqueous phase was washed with hexane and Et_2O and then acidified with 2 N HCl. The solid formed after acidification was filtered and dried to give 65 mg of **27a**. Yield 85%, mp 284 °C. ^{1}H NMR (DMSO-d_6) δ: 1.72 (6H, s, 6Ad), 2.00 (3H, s, 3Ad), 2.05 (6H, s, 6Ad), 6.60 (1H, d, CH=, J = 16.51 Hz), 6.88 (1H, d, 1Ar, J = 8.62 Hz), 7.07 (1H, d, 1Ar, J = 2.23 Hz), 7.11 (1H, dd, 1Ar, J = 8.62 Hz, J = 2.23 Hz), 7.53 (1H, d, 1Ar, J = 8.25 Hz), 7.66 (1H, d, CH=, J = 16.51 Hz), 8.02 (2H, m, 2Ar), 9.73 (1H, s, OH), 9.85 (1H, s, CHO), 12.45 (1H, bs, COOH). MS (EI) *m/z*: 402 (M^+), 327 (30), 135 (29). Anal. ($C_{26}H_{26}O_4$) C, H.

***E*-3-[3′-(1-Adamantyl)-2-chloro-4′-hydroxybiphenyl-4-yl]acrylic Acid (27b).** 4-Bromo-2-chlorophenol (**24b**, 600 mg, 2.89 mmol), 397 mg (4.62 mmol) of methyl acrylate, 6.49 mg (0.0289 mmol) of $Pd(OAc)_2$, and 34.4 mg (0.113 mmol) of tri-*o*-tolylphosphine in 1.14 mL of Et_3N were mixed in a round flask and heated at 100 °C for 4 h. Water and ice were added, 2 N HCl was added, and the aqueous phase was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 70:30) to give 477 mg of (3-chloro-4-hydroxyphenyl)methyl acrylate **(25b)**. Yield 78%, mp 73 °C.

The above ester (440 mg, 2.07 mmol) was dissolved under nitrogen in 12 mL of dry dichloromethane. Et_3N (0.864 mL, 6.21 mmol) was added, and the solution was cooled at 0−5 °C. *N*-Phenylbis(trifluoromethanesulfonimide) (961 mg, 2.69 mmol) was added, and the reaction mixture was allowed to stir at 0−5 °C for 2 h. Dichloromethane was removed, the residue was suspended in water and filtered. After flash chromatography (hexane/ethyl acetate, 90:10) an amount of 656 mg of methyl 3-(3-chloro-4-trifluoromethanesulfonyloxyphenyl)acrylate was obtained. Yield 92%, mp 69−70 °C.

2-(Adamantan-1-yl)-4-bromophenol (**12a**, 200 mg, 0.651 mmol), 184 mg (0.176 mmol) of bis(pinacolate)diboron, 191 mg (1.95 mmol) of KOAc, and 14.3 mg (0.0195 mmol) of $PdCl_2$-

(dppf) were dissolved in 3.98 mL of dioxane and heated at 100 °C for 2 h. After the solution was cooled to room temperature, an amount of 448 mg (1.30 mmol) of methyl 3-(3-chloro-4-trifluoromethanesulfonyloxyphenyl)acrylate, 2 M Na_2CO_3 (0.814 mL, 1.63 mmol), and 14.3 mg (0.0195 mmol) of $PdCl_2$(dppf) were added, and the mixture was heated at 100 °C for 11 h. The solution was cooled to room temperature, diluted with water, and acidified with 2N HCl (2.61 mL), and the product was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 80:20) to give 64 mg of methyl *E*-3-[3′-(adamantan-1-yl)-2-chloro-4′-hydroxybiphenyl-4-yl]acrylate (**26b**). Yield 23%, mp 218 °C.

The above ester (60 mg, 0.142 mmol) was dissolved in a solution of 29.8 mg (0.71 mmol) of LiOH·H_2O in 5.8 mL of THF/H_2O, 1:1, and the mixture was stirred overnight at room temperature in the dark. THF was evaporated, the remaining aqueous phase was washed with hexane and Et_2O and then acidified with 2 N HCl (0.360 mL). The solid obtained was purified by reverse-phase flash chromatography (methanol/water, 85:15) to give 52 mg (90%) of **27b**, mp 259 °C. ^{1}H NMR (DMSO-d_6) δ: 1.68 (6H, s, 6Ad), 1.98 (3H, s, 3Ad), 2.06 (6H, s, 6Ad), 6.57 (1H, d, CH═, J = 16.0 Hz), 6.95 (1H, d, 1Ar, J = 8.20 Hz), 7.10 (1H, dd, 1Ar, J = 8.20 Hz, J = 2.20 Hz), 7.14 (1H, d, 1Ar, J = 2.20 Hz), 7.37 (1H, d, 1Ar, J = 8.60 Hz), 7.54 (1H, d, CH═, J = 16.0 Hz), 7.65 (1H, dd, 1Ar, J = 8.60 Hz, J = 2.20 Hz), 7.82 (1H, d, 1Ar, J = 2.20 Hz), 9.60 (1H, s, OH). MS (EI) *m/z*: 408 (M^+). Anal. ($C_{25}H_{25}ClO_3$) C, H.

***E*-3-(6-Adamantan-1-yl-7-hydroxyphenanthren-2-yl)-acrylic Acid (29).** A suspension of 599 mg (1.75 mmol) of (methoxymethyl)triphenylphosphonium chloride in 4 mL of anhydrous THF was cooled to 0 °C under nitrogen atmosphere and treated dropwise with 1.1 mL (1.75 mmol) of 1.6 N *n*-BuLi in hexane. The resulting red solution was stirred for 20 min at 0 °C and then treated with 370 mg (0.7 mmol) of **26a** previously dissolved in 3 mL of dry THF. The solution was stirred at room temperature for 3 h. After concentration of the solvent in vacuo, the residue was taken up in ethyl acetate, washed sequentially with water and saturated brine, dried over Na_2SO_4, filtered, and evaporated. The crude mixture of *E*/*Z* vinyl ethers **28** was purified by flash chromatography (hexane/ethyl acetate, 95:5) to give 75 mg of the desired product and 58 mg of a product where the ester group had exchanged with butanol from *n*-BuLi.

To a stirred solution of the isomeric mixture of methyl 3-[3′-(1-adamantan-1-yl)-4′-(*tert*-butyldimethylsilyloxy)-2-(2-methoxyvinyl)biphenyl-4-yl]acrylate (70 mg, 0.125 mmol) in 2.4 mL of dry dichloromethane at 0 °C under nitrogen was added methanesulfonic acid (0.5 mL, 6.8 mmol) in 5 min. The reaction mixture was stirred for 2 h at 0 °C, diluted with ice-cold water, and extracted with dichloromethane. The aqueous phase was washed with Et_2O, and the organic phase was dried over Na_2SO_4. Purification of the crude product by flash chromatography (hexane/ethyl acetate, 80.20) afforded 15 mg of a mixture of methyl 3-(8-adamantan-1-yl-7-hydroxyphenanthren-2-yl)acrylate (a) and methyl 3-(6-adamantan-1-yl-7-hydroxyphenanthren-2-yl)acrylate (b). Yield 29%.

The above mixture (15 mg, 0.03 mmol) was suspended in a solution of 7.5 mg (0.18 mmol) of LiOH·H_2O in 1.4 mL of THF/H_2O, 3:2, and the suspension was stirred for 5 days at room temperature in the dark. THF was evaporated, the aqueous phase was washed with hexane and Et_2O and then acidified with 2 N HCl. The solid formed was filtered and dried to give 8 mg of the desired product **29**. Yield 60%, mp 290 °C. ^{1}H NMR (acetone-d_6) δ: 1.85 (6H, s, 6Ad), 2.13 (3H, s, 3Ad), 2.35 (6H, s, 6Ad), 6.68 (1H, d, CH═, J = 16.00 Hz), 7.32 (1H, s, 1Ar), 7.70 (1H, d, 1Ar, J = 8.60 Hz), 7.71 (1H, d, 1Ar, J = 8.60 Hz), 7.85 (1H, d, CH═, J = 16.00 Hz), 7.95 (1H, dd, 1Ar, J = 8.25 Hz, J = 2.23 Hz), 8.15 (1H, d, 1Ar, J = 2.23 Hz), 8.55 (1H, s, 1Ar), 8.75 (1H, d, 1Ar, J = 8.25 Hz), 9.01 (1H, brs, OH). MS (EI) *m/z*: 398 (M^+), 277 (40). Anal. ($C_{27}H_{26}O_3$) C, H.

***E*-3-(3′-Chloro-4′-hydroxybiphenyl-4-yl)acrylic Acid (30).** A mixture of 2-chloro-4-bromophenol (200 mg, 0.96 mmol), 268 mg (1.06 mmol) of bis(pinacolato)diboron, 282 mg (3 mmol) of KOAc, and 21 mg (0.03 mmol) of $PdCl_2$(dppf) was dissolved in dioxane and heated at reflux for 8 h under nitrogen. Then 20 mg of $PdCl_2$(dppf) and 50 mg of bis(pinacolato)diboron were added and the mixture was heated for another 4 h. After the solution was cooled to room temperature, methyl 4-bromocinnamate (463 mg, 1.9 mmol), $PdCl_2$(dppf) (21 mg (0.03 mmol), and 2 N Na_2CO_3 (1.4 mL, 2.78 mmol) were added, and the mixture was heated at reflux for 4 h. The solution was cooled to room temperature and diluted with 6 mL of 2 N HCl, and the product was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated. Flash chromatography with hexane/AcOEt, 8:2, gave 110 mg (40%) of methyl *E*-3-(3′-chloro-4′-hydroxybiphenyl-4-yl)acrylate, mp 153−154 °C. The above ester (110 mg, 0.38 mmol) was dissolved in 8 mL of THF/H_2O, 1:1, containing 80 mg (1.9 mmol) of LiOH·H_2O, and the solution was stirred overnight at room temperature in the dark. THF was evaporated, the aqueous phase was washed with hexane and Et_2O and acidified with 2 N HCl (1 mL). The solid formed was filtered and dried to give 98 mg (94%) of the pure product, mp 233−234 °C. ^{1}H NMR (DMSO-d_6) δ: 6.55 (1H, d, −CH═, J = 16.00 Hz), 7.05 (1H, d, 1Ar, J = 8.56 Hz), 7.53 (1H, dd, 1Ar, J = 8.56 Hz, J = 1.86 Hz), 7.60 (1H, d, −CH═, J = 16.00 Hz), 7.60−7.80 (5H, m, 5Ar), 10.5 (1H, s, −OH), 12.50 (1H, brs, −COOH). Anal. ($C_{15}H_{11}ClO_3$) C, H.

2-(Adamantan-1-yl)-5-bromophenol (31). An amount of 0.44 mL of concentrated H_2SO_4 was added to a mixture of 3-bromophenol (1.42 g, 8.2 mmol) and 1-adamantanol (1.25 g, 8.2 mmol) in 4.1 mL of CH_2Cl_2. The mixture was stirred at room temperature for 24 h. Water and ice were added and then aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O, and the solvent was dried and evaporated. Chromatography with hexane/CH_2Cl_2, 1:1, gave 400 mg of the desired product. Yield 16%, mp 118 °C.

***E*-3-(4′-Adamantan-1-yl-3′-hydroxybiphenyl-4-yl)acrylic Acid (33).** Compound **31** (340 mg, 1.11 mmol), 313 mg (1.22 mmol) of bis(pinacolato)diboron, 326 mg (3.33 mmol) of KOAc, and 25 mg (0.033 mmol) of $PdCl_2$(dppf) were dissolved in dioxane and heated at 100 °C for 1.5 h under nitrogen. After the solution was cooled to room temperature, methyl 4-bromocinnamate (535 mg, 2.2 mmol), $PdCl_2$(dppf) (25 mg (0.033 mmol), and 2 N Na_2CO_3 (1.4 mL, 2.78 mmol) were added, and the mixture was heated at 100 °C for 2 h. The solution was cooled to room temperature and diluted with 4.4 mL of 2 N HCl, and the product was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and evaporated. Crystallization from CH_2Cl_2 gave 180 mg of methyl *E*-3-(4′-adamantan-1-yl-3′-hydroxybiphenyl-4-yl)-acrylate **32**. Yield 42%, mp 273 °C.

The above ester (155 mg, 0.4 mmol) was dissolved in 23 mL of 0.7 N NaOH in MeOH and refluxed for 2 h. Evaporation, taking up with water, acidification with 37% HCl (1.4 mL), and filtration gave 137 mg of **32**, which was purified by chromatography with Lichroprep RP-18 (MeOH/H_2O, 8:2 to 100% MeOH) (93 mg), mp >300 °C. ^{1}H NMR (DMSO-d_6) δ: 1.73 (6H, s, 6Ad), 2.03 (3H, s, 3Ad), 2.09 (6H, s, 6Ad), 6.55 (1H, d, CH═, J = 16.38 Hz), 7.06 (1H, d, 1Ar, J = 2.23 Hz), 7.08 (1H, dd, 1Ar, J = 8.56 Hz, J = 2.23 Hz), 7.16 (1H, d, 1Ar, J = 8.56 Hz), 7.60 (2H, d, 2Ar, J = 7.82 Hz), 7.60 (1H, d, CH═, J = 16.38 Hz), 7.75 (2H, d, 2Ar, J = 7.82 Hz), 9.49 (1H, s, OH), 12.40 (1H, brs, COOH). Anal. ($C_{25}H_{26}O_3$) C, H.

1-(Adamantan-1-yl)-3-(4-bromophenyl)propenone (34). To a solution of 0.09 mL of 21% (w/v) EtONa in 3 mL of EtOH were added 1-adamantylmethyl ketone (0.5 g, 2.8 mmol) and 4-bromobenzaldehyde (0.5 g, 2.8 mmol), and the mixture was stirred for 3 days at room temperature. Cooling at −10 °C, filtration, and washing with cold EtOH gave 320 mg (85%) of the title compound, mp 135 °C.

5-(Adamantan-1-yl)-4′-bromobiphenyl-3-ol (35). To a suspension of 1-acetylmethylpyridinium chloride[38] (224 mg, 1.3 mmol) and **34** (300 mg, 0.9 mmol) in 9 mL of absolute EtOH was added DBU (194 μL). The red solution was stirred under nitrogen for 6 h. Dilution with 10% HCl,

extraction with AcOEt, drying, evaporation, and chromatography with CH_2Cl_2/AcOEt, 9:1 gave 140 mg (42%) of the title compound, mp 156−158 °C.

***E*-3-(5′-Adamantan-1-yl-3′-hydroxybiphenyl-4-yl)acrylic Acid (37).** The above compound (70 mg, 0.18 mmol), 32 μL (0.36 mmol) of methyl acrylate, 1 mg (0.0045 mmol) of $Pd(OAc)_2$, 5.5 mg (0.007 mmol) of tri-*o*-tolylphosphine in 0.163 mL of Et_3N were mixed in a round flask and heated at reflux for 2 days. Water and brine were added, and the aqueous phase was extracted with AcOEt. The organic phase was dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by flash chromatography (hexane/AcOEt, 9:1) to give 35 mg (50%) of methyl 3-(5′-adamantan-1-yl-3′-hydroxybiphenyl-4-yl)acrylate **36**, mp 184−186 °C.

The above ester (40 mg, 0.1 mmol) was dissolved in a solution of 21 mg (0.5 mmol) of $LiOH·H_2O$ in 4 mL of THF/H_2O, 1:1, and the solution was stirred overnight at room temperature in the dark. THF was evaporated, and the aqueous phase was acidified with 2 N HCl (0.2 mL). The white solid was filtered and dried to give 30 mg of pure product. Yield 80%, mp >240 °C. ^{1}H NMR (DMSO-d_6) δ: 1.71 (6H, s, 6Ad), 1.85 (6H, s, 3Ad), 2.02 (3H, s, 6Ad), 6.52 (1H, d, CH═, J = 16.0 Hz), 6.75 (1H, dd, 1Ar, J = 1.86 Hz, J = 1.86 Hz), 6.83 (1H, dd, 1Ar, J = 1.86 Hz, J = 1.86 Hz), 7.04 (1H, dd, 1Ar, J = 1.86 Hz, J = 1.86 Hz), 7.58 (1H, d, CH═, J = 16.0 Hz), 7.60 (2H, d, 2Ar, J = 8.56 Hz), 7.72 (2H, d, 2Ar, J = 8.56 Hz). MS (EI) *m*/*z*:355 (56, M^+), 97 (100). Anal. ($C_{25}H_{26}O_3$) C, H.

Cellular Sensitivity to Drugs. In ovarian carcinoma cells, cellular sensitivity to drugs was evaluated by growth-inhibition assay after 72 h of drug exposure. Cells in the logarithmic phase of growth were seeded in duplicates into six-well plates. Twenty-four hours after seeding, the drug was added to the medium. Cells were harvested 72 h after drug exposure and counted with a cell counter. In leukemia cells, drug exposure was 24 h and the growth inhibition was assessed after 72 h. IC_{50} is defined as the drug concentration causing a 50% reduction of cell number compared with that of untreated control. When standard deviation is reported, the mean value is from three independent experiments.

Determination of Apoptosis. Apoptosis was determined in ovarian carcinoma IGROV-1 cells by TUNEL assay following 72 h of exposure to the drug.[13] Treated cells were fixed in 4% paraformaldehyde for 60 min at room temperature, washed, and resuspended in ice-cold PBS. The in situ cell death detection kit fluorescein (Roche, Mannheim, Germany) was used according to the manufacturers' instructions, and the samples were analyzed by flow cytometry (Becton Dickinson).

Alkaline Elution Assay. DNA single strand breaks were detected by the alkaline elution method. Cells were incubated in the presence of 0.08 μCi/mL [^{14}C]thymidine (Amersham Biosciences, Amersham, U.K.) for 30 h and then for 18 h in the absence of labeled thymidine to chase the DNA-incorporated radioactivity. After treatment with different concentrations of **1** for 6 h, cells were immediately processed for alkaline elution as previously described.[13] A positive control consisting of cells irradiated with 0.4 Gy was used as a reference.

Cell Cycle Analysis. The cell cycle distribution was analyzed in propidium iodide stained cells by FACScan flow cytometry, as previously described.[13]

Western Blot Analysis. Cells were treated for the indicated times with compound **23** at a cytotoxic concentration (20 μM) corresponding to IC_{80}. Analysis of each MAP protein and their activated (i.e., phosphorylated) form was performed as previously reported.[13]

Supporting Information Available: NMR data of intermediates and compounds that were not tested for cytotoxic activity; results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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