Synthesis, Antifungal Activity, and Structure−Activity Relationships of Coruscanone A Analogues

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Coruscanone A, a plant-derived cyclopentenedione derivative, showed potent in vitro antifungal activity against *Candida albicans* and *Cryptococcus neoformans* comparable to amphotericin B and fluconazole. A series of analogues have been synthesized by modification of the cyclopentenedione ring, the enolic methoxy functionality, and the side chain styryl moiety of this natural product lead. A structurally close 1,4-benzoquinone analogue was also prepared. All the compounds were examined for their in vitro activity against major opportunistic fungal pathogens including *C. albicans*, *C. neoformans*, and *Aspergillus fumigatus* and fluconazole-resistant *C. albicans* strains, with several analogues demonstrating potent antifungal activity. Structure−activity relationship studies indicate that the 2-methoxymethylenecyclopent-4-ene-1,3-dione structural moiety is the pharmacophore responsible for the antifungal activity of this class of compounds while the side chain styryl-like moiety plays an important complementary role, presumably contributing to target binding.

Introduction

The limitations of current antifungal drugs, increased incidence of systemic fungal infections, and rapid development of drug resistance have highlighted the need for the discovery of new antifungal agents, preferably with novel mechanisms of action.[1] While synthetic efforts remain the mainstream in antifungal drug discovery, as evidenced by the fact that 18 out of 23 antifungal drugs approved from 1980 to 2002 are synthetic (83% belong to the single azole class), unique antifungal natural products have demonstrated remarkable success in this regard.[2] For example, two major drug classes currently in use, represented by amphotericin B, the "gold standard" in the antifungal armamentarium, and the lipopeptide caspofungin, the most important antifungal drug approved in recent years, are derived from natural products.[1]

In the course of our search for prototype antifungal agents from natural sources, we discovered the antifungal lead coruscanone A (**1**) from the ethanol extract of the piperaceous plant *Piper coruscans*.[3] Coruscanone A possesses a 2-methoxymethylenecyclopent-4-ene-1,3-dione skeleton with a styryl moiety (designated as side chain below) attached to the methylene at C-2. This unique structural property facilitates the coexistence of two geometrical isomers along the C-2 exo double bond in solution, via photoisomerization.[3,4] It must be pointed out that all the compounds of this class described herein have two geometrical isomers in a ratio of almost 1:1 in solution; however, for convenience, the structure of only one isomer is presented. Coruscanone A showed strong antifungal activity against two major opportunistic pathogens *C. albicans* and *C. neoformans* associated with immunocompromised patients (AIDS, cancer, or organ transplant), comparable to the positive controls amphotericin B and fluconazole. The lack of antibacterial activity of **1** against *Staphylococcus aureus* indicated a good selectivity. Coruscanone A represents the most fungicidal plant
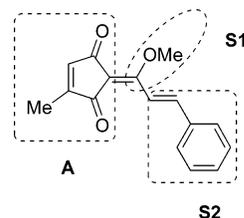

Figure 1. Key structural moieties of coruscanone A (**1**).

metabolite that is active against *C. albicans*.[3] In addition, **1** showed acceptable in vitro cytotoxicity against mammalian Vero cells, comparable to amphotericin B, and is readily accessible by total synthesis.[3] Although the cyclopent-4-ene- and cyclopentane-1,3-dione structural moieties are present in a large number of synthetic compounds with therapeutic applications or potential, the functional groups in these compounds are di- or triketonic in nature,[5] in contrast to the unique diketone enol ether form in **1**. Also, little is known about the mechanisms of action of these compounds. Therefore, this druglike, small-molecule natural product is an ideal structural template for the synthesis of a series of analogues in order to explore their structure−activity relationships (SARs), thus affording the information for further lead optimization of this class of compounds as potential new antimycotics.

Results and Discussion

1. Chemistry. To develop a robust pharmacophoric model and understand the basis for the antifungal activity of coruscanone A (**1**), its structure can be subdivided into three key structural moieties: cyclopentenedione ring (A), enolic methoxy functionality (S1), and the side chain styryl moiety (S2) (Figure 1). Each structural moiety can be modified independently in order to facilitate the systematic refinement of the search for increasingly effective coruscanone A analogues.

The general synthetic methodology for the preparation of coruscanone A analogues is a modified version of a method developed by Clemo et al.,[6] and successful synthesis of coruscanone A has demonstrated its feasibility.[3] As outlined in

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Scheme 1. General Reaction Scheme for Preparation of Coruscanone A (**1**) Analogues
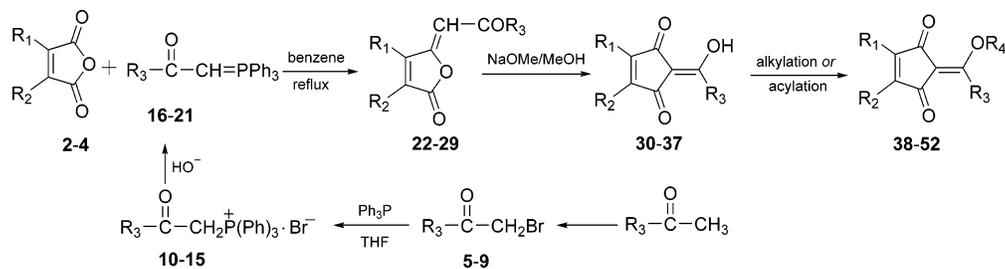
(R_1,R_2: H, CH_3, alkyl, or phenyl; R_3: aromatic, styryl, heteroaromatic, etc.; R_4:CH_3, alkyl, acyl, etc)

Scheme 1, the synthetic sequence starts with Wittig condensation between a maleic anhydride derivative (e.g., 2-methylmaleic anhydride (**2**), 2,3-dimethylmaleic anhydride (**3**), or 2-phenyl-maleic anhydride (**4**)) and a phosphorane (**16**−**21**; refer to Experimental Section for their structures) prepared from the corresponding α-methyl ketone in a three-step sequence, via brominated α-methyl ketone (**5**−**9**) and phosphonium salt (**10**−**15**). The key step is the base-catalyzed rearrangement of the resulting 4-ylidenebutenolide (**22**−**29**), affording the corresponding cyclopent-4-ene-1,3-dione (**30**−**37**). Alkylation or acylation of the cyclopentenediones yields the enolic hydroxy-substituted product (**38**−**52**).

1.1. Structural Modifications of the Cyclopentenedione Ring (Moiety A) of 1. Our first modification of the cyclopentenedione ring of coruscanone A involved the synthesis of 2-(1-methoxy-3-phenylpropenylidene)-4,5-dimethylcyclopent-4-ene-1,3-dione (**38**), since this compound would only have one isomer in solution because of the symmetric nature of the cyclopentenedione ring. It was thus prepared from 2,3-dimethylmaleic anhydride (**3**) and 4-phenyl-1-(triphenylphosphoranylidene)-(3*E*)-buten-2-one (**16**) that was available from styryl methyl ketone as shown in Scheme 1. The second compound, 2-[(*E*)-1-methoxy-3-phenylallylidene]-4-phenylcyclopent-4-ene-1,3-dione (**39**), represented replacement of the methyl substitutent on the cyclopentenedione ring of **1** with a phenyl group, which was prepared from 4-phenylmaleic anhydride (**4**) and phosphorane **16**. It was postulated that introduction of the bulky phenyl group that extends conjugation might have a significant impact on the antifungal activity of the compound.

It is pointed out that Wittig condensation of a monosubstituted maleic anhydride derivative, e.g., **2** or **4**, with a phosphorane always results in a regionally selective and stereoselective formation of an *E*-butenolide as the predominant product, as observed in **22** and **24** (Figure 2). In the case of disubstituted 2,3-dimethylmaleic anhydride (**3**), the intermediate butenolide **23** as the major product possesses *Z*-configuration at the C-4 double bond because of less steric hindrance between the olefinic proton and the cyclic methyl group. However, both types of butenolides can be readily converted to the corresponding cyclopentenediones via a nonstereoselective base-catalyzed rearrangement.[3,6]
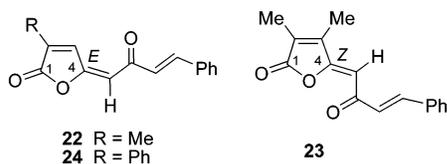

Figure 2. Key butenolide intermediates **22**−**24**.

1.2. Structural Modification of the Enolic Methoxy Functionality of 1 by Alkylation and Acylation (S1). Our previous study has indicated that *O*-methylation of the enolic hydroxy group plays a key role in the antifungal activity of coruscanone A (**1**) when compared to its demethylated precursor coruscanone B (**30**, Figure 3), which shows only marginal antifungal activity.[3] Thus, modification of the enolic methoxy functionality of **1** would have a significant impact on the antifungal activity of synthetic analogues. When **30** was alkylated with Et_2SO_4/K_2CO_3 in acetone and acetylated with acetic anhydride/pyridine, compounds **47** and **49** were obtained, respectively. Similarly, ethylation of cyclopentenedione **31** with Et_2SO_4/K_2CO_3 in acetone yielded **48**. Acylation of **31** with acetic anhydride/pyridine, benzoyl chloride/THF/DMAP, and cinnamoyl chloride/pyridine/DMAP afforded **50**−**52**, respectively.

1.3. Structural Modification of the Styryl Side Chain (Moiety S2) of 1. Selection of α-methyl ketones to construct the side chain of synthetic coruscanone A analogues was based on minor modification of the styryl moiety of **1**, with the aim of achieving improved antifungal potency and better selectivity, thus arriving at meaningful SAR information. With the retention of the structural moieties A and S1 of **1**, six analogues (**40**−**43**, **45**, and **46**) were prepared according to the general synthetic approach illustrated in Scheme 1. While the preparation of **40**−**43** was fairly straightforward, the synthesis of **45** and **46** involved protection/deprotection of a phenolic hydroxy group at appropriate stages (see Experimental section). The side chains in these compounds vary from a phenyl group in **43** to heteroaromatic furanyl and thiophene moieties in **41** and **42**, respectively, and additional substitution at the phenyl group of the styryl moiety in **40**, **45**, and **46**.

The last, simplest synthetic entity in this series is 2-(1-hydroxyethylidene)-4-methylcyclopent-4-ene-1,3-dione (**53**) in which a methyl group replaces the styryl group in **1**. It was prepared by an alternative method via reaction of 2-methyl-maleic anhydride (**2**) and α-methylvinyl acetate in $AlCl_3$/1,2-dichloroethane,[7] followed by methylation with Me_2SO_4/K_2CO_3 in acetone.

1.4. Synthesis of 2-Methoxy-5-methyl-3-styryl-1,4-benzoquinone (60). It is well-known that some 1,4-benzoquinones have good antifungal activity.[8] Since coruscanone A (**1**) shows some similarity to 1,4-benzoquinone derivatives, a structurally close analogue, 2-methoxy-5-methyl-3-styryl-1,4-benzoquinone (**60**), was synthesized for SAR studies. This would also indicate whether any correlation exists between the two classes of compounds regarding their biological activity. Thus, starting from commercially available methoxyhydroquinone (**54**), its methoxymethyl protected ether **55** was treated with pyridinium hydrobromide perbromide in MeOH to give the brominated product **56**, which was subjected to bromine/lithium exchange in MeLi/THF. The lithio derivative was quenched with MeI, and the resultant C-methyl derivative **57** was converted to the lithium salt with BuLi/THF in a directed ortho metalation-type reaction[9] and then coupled with phenylacetaldehyde to give
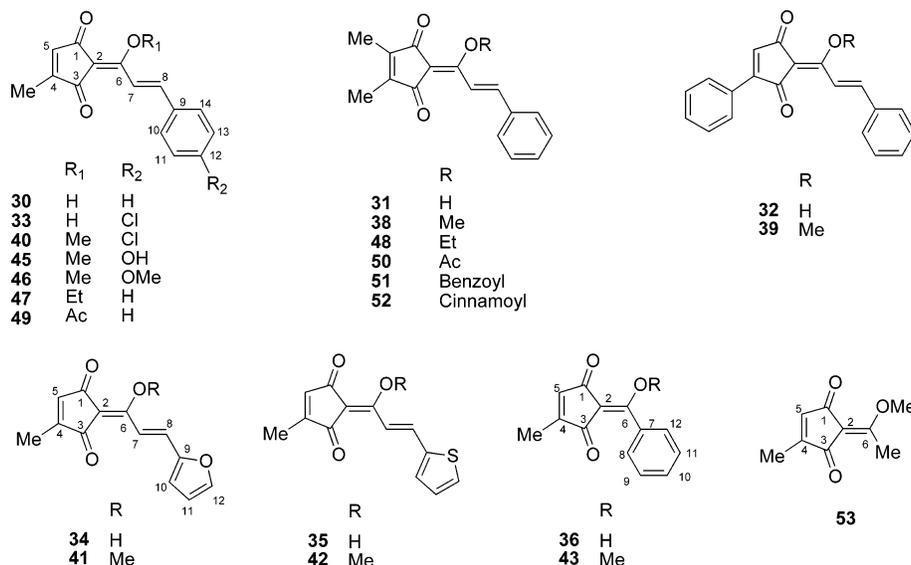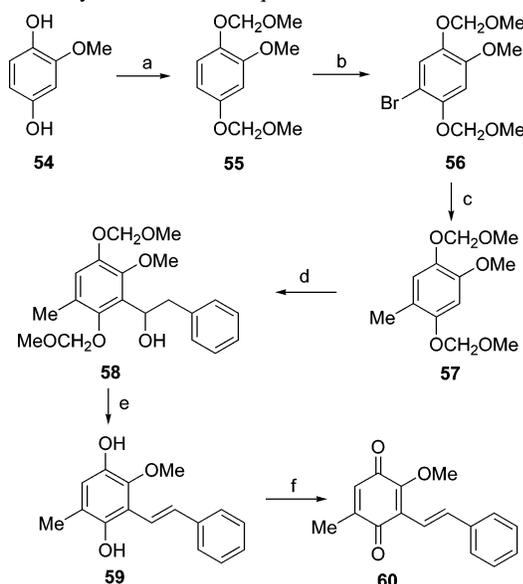
Figure 3. Synthetic coruscanone A analogues.

Scheme 2. Synthesis of Benzoquinone **60**[a]

[a] Reagents and conditions: (a) MeOCH₂Cl/NaH, THF, 0 °C, 24 h, 75%; (b) C₅H₅NHBr₃/MeOH/NaHCO₃, room temp, 25 min, 89%; (c) (i) MeLi/THF, −78 °C, 1 h; (ii) MeI, −78 °C, 1 h, 90%; (d) (i) BuLi/THF, −78 °C, 1 h, then warm to 0 °C, 5 h, room temp, 3 h; (ii) PhCH₂CHO, 0 °C, 0.5 h; 66%. (e) 3 N HCl/dioxane, 50 °C, 3 h, 95%; (f) DDQ/CH₂Cl₂−H₂O, room temp, 12 h, 65%.

benzyl alcohol **58**. Dehydration and deprotection of **58** using mineral acid yielded stilbene **59**, which was oxidized by DDQ to furnish **60** (Scheme 2). In view of the limited number of available methods for the synthesis of styrylbenzoquinones,[10] it is worthwhile mentioning that direct coupling of phenyl-acetaldehyde with diortho-oxygenated benzenes, followed by oxidation, is a facile method for preparation of 2-hydroxy (or methoxy)-3-styrylbenzoquinone derivatives.

2. Biological Activity. Synthetic coruscanone A (**1**) and its analogues (**30−43** and **45−53**) as well as the 1,4-benzoquinone **60** were evaluated for their in vitro antifungal activity against three major opportunistic fungal pathogens *C. albicans*, *C. neoformans*, and *Aspergillus fumigatus* using the drugs amphotercin B and fluconazole as positive controls. Compounds showing 50% growth inhibition (IC₅₀) at a concentration of less than 20 μg/mL were considered to be active and were further

evaluated for their antifungal activity against clinical isolates of fluconazole-susceptible and resistant *C. albicans* (isolates no. 1 and no. 17, respectively) from AIDS patients during flucona-zole therapy.[11] The results indicated that compounds **1**, **33**, **39**, **40−43**, **45−47**, and **49** showed varying degrees of antifungal activity (Table 1) while other compounds were inactive at 20 μg/mL. The in vitro cyctoxicity of the antifungal compounds against mammalian kidney cells (Vero and LLC-PK1) was determined and compared with the anticancer drug doxorubicin. While coruscanone A remains the most potent antifungal compound among the synthetic derivatives, several analogues (**40−42**) demonstrated potent but slightly weaker activity than **1**. In addition, compounds that were active against *C. albicans* retained equivalent activity against fluconazole-resistant *C. albicans* isolate no. 17, which involves several resistance mechanisms, including overexpression of efflux pumps CDR1 (p-glycoprotein) and MDR1 (major facilitator) mRNA, as well as overexpression of fluconazole's target gene ERG11.[11b] Since overexpression of these genes leads to inefficacy of fluconazole via efflux pump activity and/or overproduction of ERG11's product 14α-lanosterol demethylase, a key enzyme in the biosynthesis of egosterol,[11a] coruscanone A and its analogues would target something other than ERG11 and/or are not a substrate for the CDR1 or MDR1 efflux pumps. Meaningful SAR information is summarized below.

2.1. Modifications of the Cyclopentenedione Ring. Compound **38**, with only one additional methyl group on the cyclopentenedione ring when compared to **1**, and its derivatives **31**, **48**, and **50−52** surprisingly lack antifungal activity. This indicates that the antifungal mechanism of coruscanone A regarding its reactive site to the target would be on the cyclo-pentenedione ring, which may be considered as the "warhead" of the molecule. It is thus postulated that **1** may act like maleimide derivatives as a Michael acceptor,[12] reacting at C-5 of the cyclopentenedione ring with a nucleophilic site of the target (enzyme). Additional methyl substitution at C-5 such as in **38** would preclude such a reaction because of steric hindrance. When the methyl group in **1** is replaced by a large phenyl group in **39**, the activity decreases significantly presumably because of decreased affinity to the target.

The lack of antifungal activity of the benzoquinone derivative **60** further indicates that the cyclopentenedione structural moiety of coruscanone A analogues is selective to fungal pathogens,

Table 1. In Vitro Antifungal Activity and Cytotoxicity of Coruscanone A and Its Analogues[a]

| | antifungal activity (IC_{50}[b]/MIC[c]/MFC[d], µg/mL) | | | | | cytotoxicity (IC_{50},[b] µg/mL) | |
	C. albicans ATCC 90028	C. albicans no. 1[e]	C. albicans no. 17[e]	C. neoformans ATCC 90113	A. fumigatus ATCC 90906	Vero[f]	LLC-PK1[g]
1	0.80/2.08/2.08	0.47/1.25/1.25	0.68/2.08/2.08	2.04/8.33/8.33	19/>20/>20	4.9	3.4
33	13/>20/>20	10/>20/>20	13/>20/>20	>20/>20/>20	>20/>20/>20	>10	6.0
39	>20/>20/>20	20/>20/>20	18/>20/>20	>20/>20/>20	>20/>20/>20	>10	5.1
40	1.39/4.17/4.17	0.64/2.08/2.92	0.86/2.92/2.92	2.23/12/12	20/>20/>20	5.5	3.1
41	1.40/4.17/4.17	0.93/2.50/2.50	2.40/4.17/6.67	3.40/10/13	8.98/20/20	3.3	3.3
42	1.21/3.33/3.33	0.74/2.50/2.50	1.39/4.17/4.17	2.49/12/12	9.81/20/>20	3.0	2.8
43	10.6/>20/>20	7.88/>20/>20	6.04/>20/>20	>20/>20/>20	>20/>20/>20	>10	>10
45	3.30/10/10	1.86/5.00/13	5.35/20/20	6.95/>20/>20	>20/>20/>20	3.7	3.4
46	3.03/10/10	1.56/5.00/6.67	4.29/10/13	3.41/15/17	>20/>20/>20	5.0	3.9
47	5.02/20/20	2.49/12/17	4.51/13/20	5.02/20/20	>20/>20/>20	4.8	4.0
49	8.56/>20/>20	3.79/>20/>20	5.84/>20/>20	20/>20/>20	>20/>20/>20	5.5	4.9
AMB[h]	0.15/0.63/1.04	0.12/0.52/1.25	0.17/0.63/0.83	0.41/1.25/1.67	0.73/1.25/2.5	7.0	2.4
FLU[j]	0.22/0.45/>200	0.24/0.45/>200	118/>200/>200	5.65/37/>200	>200/>200/>200	>10	>10
DOX[k]	nt[i]	nt[i]	nt[i]	nt[i]	nt[i]	7.5	0.65

[a] Mean values based on three independent experiments. [b] 50% growth inhibitory concentration. [c] Minimum inhibitory concentration. [d] Minimum fungicidal concentration. [e] Patient isolates during fluconazole therapy:[11] no. 1, first isolate, azole-susceptible; no. 17, last isolate, azole-resistant. [f] African green monkey kidney fibroblast. [g] Pig kidney epithelial cells. [h] Amphotericin B. [i] Not tested. [j] Fluconazole. [k] Doxorubicin.

although a similar Michael addition reaction mechanism may also occur on the benzoquinone skeleton of **60**.

2.2. Modifications to the Enolic Functionality. Different substitutions at the enolic hydroxy group affect the activity. Similar to coruscanone B (**30**), all the synthetic cyclopentenediones with a free enolic hydroxy group (**31, 32, 34−36**) are inactive except for the chlorine-containing compound **33**, which shows moderate activity against *C. albicans* and fluconazole-resistant *C. albicans* strains. Compound **49** with *O*-acetyl substitution is only moderately active against *C. albicans* and marginally active against *C. neoformans*, and **47** with *O*-ethyl substitution is about 10-fold (MIC value) less active against *C. albicans* than **1**. The weak activity of the two compounds, particularly **47**, cannot be simply explained by the reaction mechanism of the Michael addition mentioned above. The binding affinity or selectivity of the structures of the compounds to the reactive site of the target (enzyme) must play an important role. At this point, the enolic *O*-methyl group remains the optimum functional group among all the synthetic analogues.

2.3. Modifications to the Styryl Side Chain. The side chain plays an important role for the activity of coruscanone A analogues. Compounds **40** and **46** that have aromatic chloro and methoxy substituents show a slightly weaker activity than **1**. It is noteworthy that compounds **41** and **42** possessing five-membered heteroaromatic rings instead of a benzene ring display significant activity against *C. albicans* and *C. neoformans* with enhanced activity against *A. fumigatus* compared to **1**. However, when the styryl moiety is replaced by a phenyl group as in **43** or a methyl group as in **53**, the activity is decreased drastically for **43** or completely lost for **53**, implying that the double bond of the styryl moiety or the intact styryl moiety (e.g., in **1**) or styryl-like moiety (e.g., in **41** and **42**) is necessary for the activity. This strongly suggests that the side chain is associated with binding affinity for the target.

2.4. Separation of Antifungal Activity from Cytotoxicity. Although the above antifungal compounds show moderate in vitro cytotoxicity to the mammalian Vero cells (IC_{50} values from 3.3 to >10 µg/mL) and LLC-PK-1 cells (IC_{50} values from 3.1 to >10 µg/mL), their cytotoxicity does not seem to be necessarily correlated to their antifungal activity. For example, compound **47**, which exhibits a cytotoxicity similar to that of **1** (IC_{50} of 4.8 vs 4.9 µg/mL against Vero cells, Table 1), is only moderately active against *C. albicans* (MIC of 20 vs 2.08 µg/mL). Compound **49**, which is even less antifungal than **47**, also shows cytotoxicity similar to that of **1** (IC_{50} of 5.5 vs 4.9

Scheme 3. Proposed Mechanism for Inhibition of Human Chymase by **61**
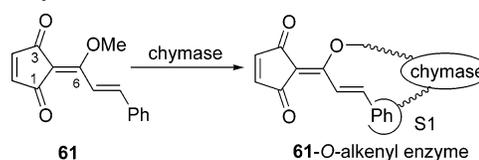
Scheme 4. Possible Interaction Mechanism of **1** with the Target
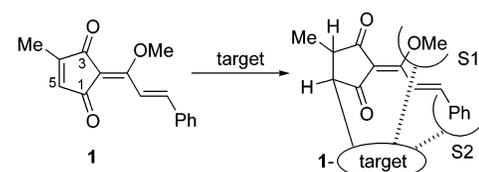
µg/mL against Vero cells, Table 1). In contrast, the most cytotoxic compounds, **41, 42**, and **45**, are not the most potent antifungal compounds. This indicates that these compounds may act via different mechanisms of action for their antifungal activity against *C. albicans* and cytotoxicity against mammalian cells or that minor structural changes afford important alterations in fungal cell permeability/transport, etc. This would render an opportunity to improve the antifungal activity or therapeutic index of the analogues by further chemical modification of the lead structure without effecting cytotoxicity.

It was recently demonstrated that a synthetic cyclopentenedione derivative **61** showed potent inhibition of human chymase, a potential drug target associated with cardiovascular diseases and chronic inflammation following fibrosis.[13] A possible mechanism for inhibition of the enzyme by **61** was proposed as shown in Scheme 3; i.e., the enzyme interacts with the inhibitor at C-6 because of its strong electrophilicity, while the phenyl group of the inhibitor is enclosed by the residue of the S1 pocket.[13] However, the reactive site of coruscanone A and its analogues to the target enzyme is apparently different from that of **61**. Coruscanone A may act as a Michael acceptor reacting at C-5 of the cyclopentenedione ring with a nucleophile of the active site residue of the target (enzyme) to form an irreversible covalent adduct,[14] while its styryl and methoxy groups are enclosed by other residues of the target (Scheme 4). The irreversible covalent nature of the adduct may also explain the fungicidal activity of coruscanone A. There is no doubt that Michael acceptors are associated with certain levels of toxicity toward mammalian cells, as observed in coruscanone A

analogues (Table 1). However, numerous reports/patents have described the therapeutic potential of Michael acceptors from the perspective of drug discovery. For example, it is suggested that Michael acceptors can be structurally modified so that they can react selectively with target nucleophiles or can be converted into selective Michael acceptors during metabolism for anti-cancer drug discovery. Representative natural cytotoxic compounds containing Michael acceptors include menadione and shikonin analogues, while the anticancer drug mitomycin is transformed by reductive activation into a conjugated dienone Michael acceptor.[15] Another anticancer drug mitoxantrone acts via oxidative activation involving a Michael acceptor intermediate.[16] Recent work has demonstrated that Michael acceptors are a new class of inhibitors specific for caspases and other Clan cysteine proteases. A large number of aza-peptides composed of a 2-pyridone-containing peptidomimetic binding determinant and an α,β-unsaturated Michael acceptor "warhead" have been synthesized for the development of orally bioavailable inhibitors for the 3C protease, which were tested against rhinoviruses.[17] Moreover, extensive studies have demonstrated that Michael acceptors are an important class of compounds that can induce phase 2 detoxification enzymes (e.g., glutathione transferases, NAD(P)H/quinone reductase, glucoronosyl transferases, epoxide hydrolase) and thus possess anticarcinogenic properties.[18] Moderately reactive Michael acceptors are receiving growing interest for the design of chemoprotective drugs.[19] Therefore, there is great potential for the development of coruscanone A analogues carrying a Michael acceptor "warhead" as therapeutic agents.

Conclusions

This study has demonstrated that the 2-methoxymethylenecy-clopent-4-ene-1,3-dione structural moiety is responsible for the antifungal activity of coruscanone A analogues, with the styryl-like moiety being an ideal supplemental group, presumably contributing to enzyme binding. The putative pharmacophore may act like maleimides as a Michael acceptor[12] reacting with the target to form an irreversible covalent adduct, while additional experimental evidence is needed to support this hypothesis. Although compounds with improved antifungal activity have not yet been found, a meaningful SAR for coruscanone A analogues has been established on the basis of the limited number of compounds synthesized by a rationally designed classical medicinal chemistry approach. This has laid a solid foundation for further lead optimization of this class of compounds by a systematic chemical modification including the synthesis of water-soluble compounds to improve their overall pharmaceutical properties. An effort aimed at elucidating the antifungal mechanism of action of coruscanone A analogues using genomic profiling and biochemical approaches is also underway in our group.

Experimental Section

Melting points were measured with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on Bruker DPX-300, Bruker DRX-400, or Varian Mercury 400BB instruments. Chemical shifts are expressed in ppm relative to the solvent residue signals. ESI-FTMS data were measured on a Bruker-Magnex BioAPEX 30es ion cyclotron high-resolution FT-HPLC spectrometer by direct injection into an electroscopy interface. High-resolution TOF-MS data were measured on an Agilent series 1100 SL equipped with an ESI source. Flash column chromatography was done on silica gel (40 μm, J. T. Baker) and reversed-phase silica gel (RP-18, 40 μm, J. T. Baker). TLC was performed on silica gel sheets (silica gel 60 F$_{254}$, Merck, Germany)

and reversed-phase plates (RP-18 F$_{254S}$, Merck, Germany). Analytical HPLC used to determine the purity of target compounds was conducted on an ODS (Discovery) column (250 mm × 4.6 mm, 10 μm) using two solvent systems, (a) 70% CH$_3$CN in H$_2$O and (b) 80% MeOH in H$_2$O, and UV detection at 254 nm for a 20 min run. The results are expressed as retention times in minutes, and the relative content is expressed as a percentage. All the reagents were obtained from commercial vendors in appropriate grades and were used without further purification.

General Procedure for Preparation of Bromomethyl Ketones 5−8. To a solution of the α-methyl ketone (2 mmol) in dry THF (20 mL) at room temperature under nitrogen was slowly added a solution of the pyrrolidone hydrotribromide (2.4 mmol) in dry THF (40 mL) in 1 h. The mixture was stirred at room temperature for 24 h. After completion of the reaction, excess pyrrolidone hydro-tribromide was removed by filtration. The filtrate was concentrated to dryness. The resulting residue was dissolved in Et$_2$O, washed with brine, and dried (Na$_2$SO$_4$). Removal of the solvents afforded crude product, which was chromatographed on silica gel, eluting with Et$_2$O−hexanes (1:6) to give the bromomethyl ketone.

Bromomethyl Styryl Ketone (5). Yield, 77% from styryl methyl ketone; see ref 3 for spectroscopic data.

(*E*)-1-Bromo-4-(4-chlorophenyl)but-3-en-2-one (6). Yield, 70% from 4-(4-chlorophenyl)but-3-en-2-one, pale-yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 (1H, d, $J = 16$ Hz, β-CH=), 7.51 (2H, d, $J = 8$ Hz, H-3, 5), 7.38 (2H, d, $J = 8$ Hz, H-2, 6), 6.92 (1H, d, $J = 16$ Hz, α-CH=), 4.06 (2H, s, CH$_2$−Br).

(*E*)-1-Bromo-4-(furan-2-yl)but-3-en-2-one (7). Yield, 59% from 4-(furan-2-yl)but-3-en-2-one, colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 (1H, br s, H-5), 7.48 (1H, d, $J = 16$ Hz, β-CH=), 6.87 (1H, d, $J = 16$ Hz, α-CH=), 6.75 (1H, d, $J = 3.2$ Hz, H-3), 6.53 (1H, m, H-4), 4.05 (2H, s, CH$_2$−Br).

(*E*)-1-Bromo-4-(thiophen-2-yl)but-3-en-2-one (8). Yield, 59% from 4-(thiophen-2-yl)but-3-en-2-one, colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78 (1H, dd, $J = 16$, 3.2 Hz, β-CH=), 7.43 (1H, br s, H-5), 7.32 (1H, br s, H-3), 7.06 (1H, br d, H-4), 6.71 (1H, dd, $J = 16$, 3.2 Hz, α-CH=), 4.02 (2H, s, CH$_2$−Br).

(*E*)-1-Bromo-4-[4-*O*-(*tert*-butyldimethylsilyl)phenyl]but-3-en-2-one (9). Yield, 65% from TBS-protected (*E*)-4-hydoxyphenylbut-3-en-2-one that was prepared by a standard procedure,[20] color-less oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.64 (1H, d, $J = 16$ Hz, β-CH=), 7.47 (2H, d, $J = 8$ Hz, H-3, 5), 6.84 (2H, d, $J = 8$ Hz, H-2, 6), 6.80 (1H, d, $J = 16$ Hz, α-CH=), 4.05 (2H, s, CH$_2$Br), 0.97 (9H, s, 3× Me), 0.21 (6H, s, 2× Me).

General Procedure for Preparation of Phosphonium Salts 10−15. To a refluxed solution of the triphenylphosphine (1 mmol) in dry THF (25 mL) under nitrogen was slowly added bromomethyl ketone derivative (1 mmol). The reaction mixture was refluxed for 2−4 h. After completion, the mixture was cooled to room temperature. The white precipitate was collected by the filtration and washed with Et$_2$O.

[2-Oxo-4-phenyl-(3*E*)-butenyl]triphenylphosphonium Bromide (10). Yield, 86% from 5; see ref 3 for spectroscopic data.

[2-Oxo-4-(4-chlorophenyl)-(3*E*)-butenyl]triphenylphosphonium Bromide (11). Yield, 90% from 6, white powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.46 (1H, d, $J = 16$ Hz, β-CH=), 7.90−7.64 (15H, m, Ph), 7.71(2H, d, $J = 8$ Hz, H-3, 5), 7.31 (2H, d, $J = 8$ Hz, H-2, 6), 7.04 (1H, d, $J = 16$ Hz, α-CH=), 5.91 (2H, d, $J = 12$ Hz, CH$_2$−P).

[2-Oxo-4-(furan-2-yl)-(3*E*)-butenyl]triphenylphosphonium Bromide (12). Yield, 56% from 7, white powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.31 (1H, d, $J = 16$ Hz, β-CH=), 7.89−7.58 (15H, m, Ph), 7.48 (1H, br s, H-5), 7.03 (1H, d, $J = 3.6$ Hz, H-3), 6.70 (1H, dd, $J = 16$, 2.4 Hz, α-CH=), 6.45 (1H, m, H-4), 5.82 (2H, d, $J = 12$ Hz, CH$_2$−P).

[2-Oxo-4-(thiophen-2-yl)-(3*E*)-butenyl]triphenylphosphonium Bromide (13). Yield, 56% from 8, white powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.75 (1H, d, $J = 16$ Hz, β-CH=), 7.89−7.63 (17H, m), 7.42 (1H, br d, $J = 4$ Hz, H-3), 7.03 (1H, br s, H-4), 6.64 (1H, d, $J = 16$ Hz, α-CH=), 5.82 (2H, d, $J = 12$ Hz, CH$_2$−P).

(2-Oxo-2-phenylethyl)triphenylphosphonium Bromide (14). Yield, 62% from commercially available 2-bromo-1-phenylethanone, white powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.35 (2H, d, J = 7 Hz, H-2, 6), 7.89−7.95, 7.72, 7.56, 7.48 (18H, m), 6.34 (2H, d, J = 12 Hz, CH$_2$−P).

[2-Oxo-4-(4-*tert*-butyldimethylsilyloxyphenyl)-(3*E*)-butenyl]-triphenylphosphonium Bromide (15). Yield, 75% from **9**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.28 (1H, d, J = 16 Hz, β-CH=), 7.90−7.63, (17H, m), 6.96 (1H, d, J = 16 Hz, α-CH=), 6.81 (2H, d, J = 8 Hz, H-2, 6), 5.83 (2H, d, J = 12 Hz, CH$_2$−P), 0.95 (9H, s, Me × 3), 0.19 (6H, s, Me × 2).

General Procedure for Preparation of Phosphoranes 16−21. To a suspension of the above phosphonium salt **6** (1 mmol) in H$_2$O and MeOH (1:1) was added a solution of 2 N NaOH (10 mL). The mixture was stirred at room temperature overnight. After evaporation of the MeOH, the suspension was extracted with CHCl$_3$. The organic layer was washed with brine, dried (Na$_2$SO$_4$), and concentrated to dryness to give corresponding phosphorane.

4-Phenyl-1-(triphenylphosphoranylidene)-(3*E*)-buten-2-one (16). Yield, 91% from **10**, yellow crystal; see ref 3 for spectroscopic data.

4-(4-Chlorophenyl)-1-(triphenylphosphoranylidene)-(3*E*)-buten-2-one (17). Yield, 80% from **11**, colorless oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71−7.40 (17H, m), 7.34 (1H, d, J = 16 Hz, β-CH=), 7.26 (2H, d, J = 8 Hz, H-2, 6), 6.85 (1H, d, J = 16 Hz, α-CH=), 4.06 (1H, br d, J = 23 Hz, CH=P).

4-(Furan-2-yl)-1-(triphenylphosphoranylidene)-(3*E*)-buten-2-one (18). Yield, 93% from **12**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70−7.31 (17H, m), 7.18 (1H, d, J = 16 Hz, β-CH=), 6.81 (1H, d, J = 16 Hz, α-CH=), 6.36 (1H, m, H-4), 3.98 (1H, br d, J = 24 Hz, CH=P).

4-(Thiophen-2-yl)-1-(triphenylphosphoranylidene)-(3*E*)-buten-2-one (19). Yield, 93% from **13**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71−7.47 (16H, m), 7.16 (1H, br d, H-5), 7.06 (1H, br d, H-3), 6.95 (1H, m, H-4), 6.71 (1H, d, J = 16 Hz, α-CH=), 3.97 (1H, br d, J = 24 Hz, CH=P).

2-Phenyl(triphenylphosphoranylidene)ethan-2-one (20). Yield, 90% from **14**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 (2H, br d, H-2, 6), 7.75−7.35 (18H, m, Ph, H-3, 4, 5), 4.43 (1H, d, J = 24 Hz, CH=P).

4-(4-*tert*-Butyldimethylsilyloxyphenyl)-1-(triphenylphosphoranylidene)-(3*E*)-buten-2-one (21). Yield, 80% from **15**, yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68−7.37 (19H, m, Ph, H-3, 5, α-CH=, β-CH=), 6.77 (2H, br d, H-2, 6), 3.97 (1H, br d, CH=P), 0.97 (9H, s, Me × 3), 0.18 (6H, s, Me × 2).

General Procedure for Preparation of Butenolides 22−29. A solution of maleic anhydride derivative (1.2 mmol) in benzene (10 mL) was added to a refluxed solution of a phosphorane (1 mmol) in benzene (50 mL) under nitrogen. After completion of the reaction (monitored by TLC), the reaction mixture was evaporated to dryness and the residue was chromatographed on silica gel, eluting with hexane−acetone (4:1) to yield the desired product.

(5*E*)-3-Methyl-5-[(*E*)-2-oxo-4-phenylbut-3-enylidene]furan-2(5*H*)-one (22). Yield, 73% from 2-methylmaleic anhydride (**2**) and **16**; see ref 3 for spectroscopic data.

(5*Z*)-3,4-Dimethyl-5-[(*E*)-2-oxo-4-phenylbut-3-enylidene]furan-2(5*H*)-one (23). Yield, 96% from 2,3-dimethylmaleic anhydride (**3**) and **16**, yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (1H, d, J = 16 Hz, H-4′), 7.65 (2H, m, H-6′, 10′), 7.56 (1H, d, J = 16 Hz, H-3′), 7.42 (3H, m, H-7′, 8′, 9′), 5.78 (1H, s, H-1′), 2.13 (3H, s, Me), 2.03 (3H, s, Me); ^{13}C NMR (100 MHz, CDCl$_3$) δ 187.5, 168.9, 155.8, 148.4, 144.0, 134.7, 130.7, 129.0 (2C), 128.4, 128.7 (2C), 125.2, 106.2.

(5*E*)-5-[(*E*)-2-Oxo-4-phenylbut-3-enylidene]-3-phenylfuran-2(5*H*)-one (24). Yield, 56% from 2-phenylmaleic anhydride (**4**) and **16**, yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.57 (1H, s, H-3), 8.01 (2H, br d), 7.68 (1H, d, J = 16 Hz, H-4′), 7.61 (2H), 7.47−7.43 (6H), 6.92 (1H, d, J = 16 Hz, H-3′), 6.56 (1H, s, H-1′).

(5*E*)-5-[(*E*)-4-(4-Chlorophenyl)-2-oxobut-3-enylidene]-3-methylfuran-2(5*H*)-one (25). Yield, 56% from **2** and **17**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.09 (1H, s, H-3),

7.58 (1H, d, J = 16 Hz, H-4′), 7.51 (2H, d, J = 8 Hz, H-7′,9′), 7.38 (2H, d, J = 8 Hz, H-6′,10′), 6.83 (1H, d, J = 16 Hz, H-3′), 6.43 (1H, s, H-1′), 2.10 (3H, s, Me).

(5*E*)-5-[(*E*)-4-(Furan-2-yl)-2-oxobut-3-enylidene]-3-methylfuran-2(5*H*)-one (26). Yield, 50% from **2** and **18**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.10 (1H, s, H-3), 7.53 (1H, br d, H-8′), 7.41 (1H, d, J = 16 Hz, H-4′), 6.76 (1H, d, J = 16 Hz, H-3′), 6.74 (1H, br d, H-7′), 6.51 (1H, br d, H-6′), 6.37 (1H, s, H-1′), 2.09 (3H, s, Me); HRESIMS m/z [M + H]+ 231.0652 (calcd for C$_{13}$H$_{11}$O$_4$, 231.0652).

(5*E*)-3-Methyl-5-[(*E*)-2-oxo-4-(thiophen-2-yl)but-3-enylidene]-furan-2(5*H*)-one (27). Yield, 50% from **2** and **19**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.10 (1H, s, H-3), 7.76 (1H, d, J = 15.6 Hz, H-4′), 7.44 (1H, br d, H-8′), 7.35 (1H, br d, H-7′), 7.08 (1H, brd, H-6′), 6.67 (1H, d, J = 15.6 Hz, H-3′), 6.39 (1H, s, H-1′), 2.10 (3H, s, Me); HRESIMS m/z [M + H]+ 247.0424 (calcd for C$_{13}$H$_{11}$O$_3$S, 247.0423).

(5*E*)-3-Methyl-5-(2-oxo-2-phenylethylidene)furan-2(5*H*)-one (28). Yield, 56% from **2** and **20**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.10 (1H, s, H-3), 7.95 (2H, d, J = 7 Hz), 7.59 (1H, m), 7.51 (2H, d, J = 7 Hz), 6.90 (1H, s, H-1′), 2.11 (3H, s, Me); HRESIMS m/z [M + H]+ 215.0703 (calcd for C$_{13}$H$_{11}$O$_3$, 215.0703).

(5*E*)-5-[(*E*)-4-(*tert*-Butyldimethylsilyloxyphenyl)-2-oxobut-3-enylidene]-3-methylfuran-2(5*H*)-one (29). Yield, 40% from **2** and **21**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.10 (1H, s, H-3), 7.59 (1H, d, J = 15 Hz, H-4′), 7.48 (2H, br d), 6.86 (2H, d, J = 8 Hz), 6.75 (1H, d, J = 15 Hz, H-3′), 6.45 (1H, s, H-1′), 2.10 (3H, s, Me), 0.98 (9H, s, Me × 3), 0.22 (6H, s, Me × 2).

General Procedure for Preparation of Cyclopentenediones 30−37. A solution of the butenolide (1 mmol) in dry MeOH (20 mL) was added to a solution of NaOMe (10 mmol) in MeOH (5 mL), and the resulting orange solution was stirred at room temperature for 3−6 h and then poured into ice−water (100 mL) and acidified to pH 1.0 with 2 M HCl. The MeOH was removed by evaporation, and the suspension was extracted with Et$_2$O. Evaporation of the dried extracts gave the crude products, which were generally crystallized from MeOH.

2-[(*E*)-1-Hydroxy-3-phenylallylidene]-4-methylcyclopent-4-ene-1,3-dione (30). Yield, 62% from **22**; see ref 3 for physical and spectroscopic data including NMR signal assignments.

2-[(*E*)-1-Hydroxy-3-phenylallylidene]-4,5-dimethylcyclopent-4-ene-1,3-dione (31). Yield, 82% from **23**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.05 (1H, br s, OH), 7.73 (2H, br s), 7.58 (2H, br d), 7.37 (3H, br s), 1.96 (6H, br s, 2 × Me); ^{13}C NMR (100 MHz, CDCl$_3$) δ 200.9, 192.1, 166.2, 151.4, 147.4, 142.3, 134.9, 130.5, 128.9 (2C), 128.5 (2C), 117.7 and 102.8 [for C-1, 3, 6, 4, 5, 8, 9, 12, 11 (13), 10 (14), 7, 2], 9.0 (Me), 8.4 (Me); HRESIMS m/z [M + H]+ 255.1014 (calcd for C$_{16}$H$_{15}$O$_3$, 255.1016).

2-[(*E*)-1-Hydroxy-3-phenylallylidene]-4-phenylcyclopent-4-ene-1,3-dione (32). Yield, 47% from **24**, yellow powder; ^{1}H NMR (400 MHz, benzene-d$_6$, Z/E-isomers) δ 12.65 (br s), 8.13/8.06 (1H each, d, J = 16 Hz, H-7), 7.82 (1H × 2, d, J = 16 Hz, H-8), 7.76 (2H × 2, m, H-10, 14), 7.34 (2H × 2, m), 7.07 (3H × 2, m), 6.98 (3H × 2, m), 6.54 (1H × 2, s, H-5); ^{13}C NMR (100 MHz, CDCl$_3$, Z/E-isomers) δ 200.6, 199.8, 191.2, 191.1, 169.0, 168.9, 153.7, 150.8, 143.5, 143.4, 137.7, 134.9, 134.8, 134.5, 131.1 (2C), 131.0 (2C), 130.4, 130.0 (2C), 129.4, 129.2 (2C), 129.0 (2C), 128.9 (2C), 130.4, 128.8 (4C), 128.7 (4C), 117.7, 117.5, 104.4, 104.2; HRESIMS m/z [M + H]+ 303.1001 (calcd for C$_{20}$H$_{15}$O$_3$, 303.1016).

2-[(*E*)-3-(4-Chlorophenyl)-1-hydroxyallylidene]-4-methylcyclopent-4-ene-1,3-dione (33). Yield, 55% from **25**, yellow powder; ^{1}H NMR (400 MHz, benzene-d$_6$, Z/E-isomers) δ 12.70/12.40 (1H each, br s, OH), 7.91/7.84 (1H each, d, J = 16 Hz, H-7), 7.58 (1H × 2, d, J = 16 Hz, H-8), 6.94 (2H × 2, br d), 6.90 (2H × 2, br d), δ 5.98 (1H × 2, s, H-5), 1.53 and 1.47 (3H each, s, Me-4); ^{13}C NMR (100 MHz, CDCl$_3$, Z/E-isomers) δ 201.1, 200.5, 192.1, 191.6, 167.4, 167.1, 158.2, 154.3, 141.5, 141.4 (2C), 140.9, 137.1 (2C), 136.6, 133.3, 129.7 (4C), 129.2 (4C), 118.1, 118.0, 103.5, 103.3, 10.5, 10.3; HRESIMS m/z [M + H]+ 275.0470 (calcd for C$_{15}$H$_{12}$O$_3$Cl, 275.0470).

2-[(*E*)-3-(Furan-2-yl)-1-hydroxyallylidene]-4-methylcyclopent-4-ene-1,3-dione (34). Yield, 50% from **26**, yellow powder; ^{1}H NMR (400 MHz, benzene-d_6, *Z/E*-isomers) δ 12.64/12.35 (1H each, br s, OH), 8.03/7.98 (1H each, d, *J* = 16 Hz, H-7), 7.48 (1H $\times$ 2, d, *J* = 16 Hz, H-8), 6.82 (1H $\times$ 2, br d, H-12), 6.05 (1H $\times$ 2, br d, H-10), 5.95 (1H $\times$ 2, br d, H-11), 5.85 (1H $\times$ 2, s, H-5), 1.52 and 1.45 (3H each, s, Me); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 201.1, 200.6, 192. 0, 191.5, 167.5, 167.3, 157.9, 153.9, 151.7 (2C), 145.7, 145.6, 140.6, 136.7, 129.0, 128.9, 116.03, 115.99, 115.4, 115.3, 112.8 (2C), 103.2, 103.0, 11.3, 10.5; HRESIMS *m/z* [M + H]$^+$ 231.0641(calcd for C$_{13}$H$_{11}$O$_4$, 231.0652).

2-[(*E*)-1-Hydroxy-3-(thiophen-2-yl)allylidene]-4-methylcyclopent-4-ene-1,3-dione (35). Yield, 50% from **27**, yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$, *Z/E*-isomers) δ 12.08/11.98 (1H each, br s, OH), 7.90 (1H $\times$ 2, d, *J* = 16 Hz, H-7), 7.51/7.49 (1H each, brd, *J* = 16 Hz, H-8), 7.50 (1H $\times$ 2, br s, H-12), 7.37 (1H $\times$ 2, br d, H-10), 7.11 (1H $\times$ 2, m, H-11), 6.68/6.60 (1H each, s, H-5), 2.11/2.12 (3H each, s, Me); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 201.1, 200.5, 192.1, 191.6, 167.5, 167.3, 157.9, 154.0, 140.6 (2C), 136.8 (2C), 135.6, 135.5, 131.6, 131.5, 130.0, 129.9, 128.4 (2C), 116.4, 116.3, 103.0, 102.8, 11.3, 10.5; HRESIMS *m/z* [M + H]$^+$ 247.0411 (calcd for C$_{13}$H$_{11}$O$_3$S, 247.0423).

2-[Hydroxy(phenyl)methylene]-4-methylcyclopent-4-ene-1,3-dione (36). Yield, 52% from **28**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$, *Z/E*-isomers) δ 8.06 (2H $\times$ 2, d, *J* = 8 Hz, H-8, 12), 7.59 (1H $\times$ 2, t, *J* = 8 Hz, H-10), 7.50 (2H $\times$ 2, t, *J* = 8 Hz, H-9, 11), 11), 6.74/6.59 (1H each, q, *J* = 1.2 Hz, H-5), 2.12/ 2.09 (3H each, s, *J* = 1.2 Hz, Me); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 202.7, 202.1, 190.3, 189.8, 173.8, 173.5, 157.5, 153.0, 140.4, 136.2, 133.0, 131.2, 129.9 (2C), 129.7 (4C),128.0 (4C), 103.2, 102.9, 11.4, 10.4; HRESIMS *m/z* [M + H]$^+$ 215.0681 (calcd for C$_{13}$H$_{11}$O$_3$, 215.0703).

2-[(*E*)-3-[4-*O*-(*tert*-Butyldimethylsilyl)]phenyl-1-methoxyallylidene]-4-methylcyclopent-4-ene-1,3-dione (37). Yield, 50% from **29**, pale-yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$, *Z/E*-isomers) δ 12.1/12.0 (1H each, br s, OH), 7.76 (1H $\times$ 2, d, *J* = 16 Hz, H-7), 7.61/7.58 (1H each, d, *J* = 16 Hz, H-8), 7.56 (2H $\times$ 2, dd, *J* = 8, 2 Hz, H-10, 14), 6.89 (2H $\times$ 2, d, *J* = 8 Hz, H-11, 13), 6.67/6.68 (1H each, q, *J* = 1.6 Hz, H-5), 2.12/2.11 (3H each, d, *J* = 1.6 Hz, Me), 1.02 (6H $\times$ 2, s, Me), 0.25 (6H $\times$ 2, s, 2 $\times$ Me).

General Procedure for Alkylation of Cyclopentenediones 30−37. To a solution of the cyclopentenedione (1 mmol) in dry acetone (20 mL) under argon was added K$_2$CO$_3$ (1.5 mmol). After the mixture was refluxed for 5 min, Me$_2$SO$_4$ or Et$_2$SO$_4$ (1.2 mmol) was added to the deep-yellow solution, and reflux was continued for 1−3 h. After completion of the reaction, K$_2$CO$_3$ was removed by filtration. The filtrate was concentrated to dryness, and the residue was subjected to reversed-phase RP-18 column chromatography using aqueous MeOH (60−80%) to give the desired product.

2-[(*E*)-1-Methoxy-3-phenylallylidene]-4-methylcyclopent-4-ene-1,3-dione (1, Coruscanone A). Yield, 93% from methylation of **30**; see ref 3 for physical and spectroscopic data including NMR signal assignments. Anal. HPLC [t_R (min) (content)]: 5.65 (97.7%) from solvent a or 5.72 (99.0%) from solvent b.

2-[(*E*)-1-Methoxy-3-phenylallylidene]-4,5-dimethylcyclopent-4-ene-1,3-dione (38). Yield, 60% from methylation of **31**, yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.04 (1H, d, *J* = 16 Hz, H-7), 7.61 (2H, br d), 7.55 (1H), 7.33 (3H, m), 4.18 (3H, s, OMe), 1.99 (6H, br s, Me); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194. 6, 192.2, 167.3, 150.8, 150.3, 141.9, 135.6, 130.1, 128.9 (2C), 128.4 (2C), 121.3, 108.6, 64.5, 9.02 (2C); HRESIMS *m/z* [M + H]$^+$ 269.1171 (calcd for C$_{17}$H$_{17}$O$_3$, 269.1172). Anal. HPLC [t_R (min) (content)]: 6.56 (99.5%) from solvent a or 5.72 (99.6%) from solvent b.

2-[(*E*)-1-Methoxy-3-phenylallylidene]-4-phenylcyclopent-4-ene-1, 3-dione (39). Yield, 92% from methylation of **32**, yellow powder; ^{1}H NMR (400 MHz, benzene-d_6, *Z/E*-isomers) δ 8.48/ 8.35 (1H each, d, *J* = 16 Hz, H-7), 7.84 (2H $\times$ 2, m, H-2′, 6′), 7.62 (1H $\times$ 2, d, *J* = 16 Hz, H-8), 7.45 (3H $\times$ 2, m), 7.11 (3H $\times$ 2, m), 7.02 (3H $\times$ 2, m), 6.78/6.76 (1H each, s, H-5), 4.0/3.92 (3H each, s, OMe); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 194.0, 193.4, 191.3, 191.1, 170.0, 169.9, 153.0, 152.8, 143.2, 143.0, 138.4,

138.1, 135.5 (2C), 130.8, 130.7, 130.4 (2C), 130.0, 129.1 (4C), 129.0 (3C), 128.9 (4C), 128.8 (2C), 128.6 (4C), 121.4, 121.2, 110.0, 109.8, 64.8, 64.7; HRESIMS *m/z* [M + H]$^+$ 317.1160 (calcd for C$_{21}$H$_{17}$O$_3$, 317.1172). Anal. HPLC [t_R (min) (content)]: 9.56 (99.5%) from solvent a or 11.70 (99.7%) from solvent b.

2-[(*E*)-3-(4-Chlorophenyl)-1-methoxyallylidene]-4-methylcyclopent-4-ene-1,3-dione (40). Yield, 95% from methylation of **33**, yellow powder; ^{1}H NMR (400 MHz, benzene-d_6, *Z/E*-isomers) δ 8.30/8.23 (1H each, d, *J* = 16 Hz, H-7), 7.39 (1H $\times$ 2, d, *J* = 16 Hz, H-8), 7.08 (2H $\times$ 2, d, *J* = 7.6 Hz, H-11, 13), 6.94 (2H $\times$ 2, d, *J* = 7.2 Hz, H-10, 14), 6.22/6.19 (1H each, s, H-5), 3.98/3.93 (3H each, s, OMe), 1.60 (6H, br s, H-6); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 195.2, 194.0, 192.4, 191.6, 168.4, 168.2, 157.0, 156.5, 141.0 (2C), 140.7, 140.4, 136.1 (2C), 134.0 (2C), 129.6 (2C), 129.5 (2C), 129.2 (4C), 121.9, 121.7, 108.9, 108.8, 64.8, 64.7, 11.2, 11.1; HRESIMS *m/z* [M + H]$^+$ 289.0611 (calcd for C$_{16}$H$_{14}$O$_3$Cl, 289.0626). Anal. HPLC [t_R (min) (content)]: 7.68 (96.7%) from solvent a or 7.46 (99.4%) from solvent b.

2-[(*E*)-3-(Furan-2-yl)-1-methoxyallylidene]-4-methylcyclopent-4-ene-1,3-dione (41). Yield, 90% from methylation of **34**, yellow powder; ^{1}H NMR (400 MHz, benzene-d_6, *Z/E*-isomers) δ 8.42/ 8.35 (1H each, d, *J* = 16 Hz, H-7), 7.33 (1H $\times$ 2, d, *J* = 16 Hz, H-8), 6.89 (1H $\times$ 2, brd, H-12), 6.20 (1H $\times$ 2, br d), 6.15 (1H $\times$ 2, br d), 5.91 (1H $\times$ 2, br s, H-5), 3.94/3. 89 (3H each, s, OMe), 1.59/1.58 (3H each, s, Me); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 195.0, 193.9, 192.5, 191.7, 168.6, 168.4, 156.6, 156.4, 152.2 (2C), 145.3 (2C), 140.4, 140.2, 128.8 (2C), 119.2, 119.0, 115.2 (2C), 112.7 (2C), 108.7, 108.6, 64.6, 64.5, 11.1, 11.0; HRESIMS *m/z* [M + H]$^+$ 245.0793 (calcd for C$_{14}$H$_{13}$O$_4$, 245.0809). Anal. HPLC [t_R (min) (content)]: 4.22 (98.7%) from solvent a or 3.88 (98.0%) from solvent b.

2-[(*E*)-1-Methoxy-3-(thiophen-2-yl)allylidene]-4-methylcyclopent-4-ene-1,3-dione (42). Yield, 90% from methylation of **35**, yellow powder; ^{1}H NMR (400 MHz, benzene-d_6, *Z/E*-isomers) δ 8.29/8.23 (1H each, d, *J* = 16 Hz, H-7), 7.66 (1H, d, *J* = 16 Hz, H-8), 6.85 (1H $\times$ 2, br d), 6.71 (1H $\times$ 2, br d), 6.54 (1H $\times$ 2, br d), 6.19/6.16 (1H each, s, H-5), 3.94/3.89 (3H each, s, OMe), 1.60/ 1.59 (3H each, s, Me); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 195.2, 194.0, 192.5, 191.7, 168.6, 168.4, 156.7, 156.3, 141.3 (2C), 140.5, 140.2, 135.3, 135.2, 130.9, 130.8, 129.3 (2C), 128.3 (2C), 120.4, 120.2, 108.4 (2C), 64.7, 64.6, 11.15, 11.1; HRESIMS *m/z* [M + H]$^+$ 231.0564 (calcd for C$_{14}$H$_{13}$O$_3$S, 261.0580). Anal. HPLC [t_R (min) (content)]: 4.77 (95.8%) from solvent a or 4.64 (96.0%) from solvent b.

2-[Methoxy(phenyl)methylene]-4-methylcyclopent-4-ene-1, 3-dione (43). Yield, 88% from methylation of **36**, pale-yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$, *Z/E*-isomers) δ 7.50 (3H $\times$ 2, m), 7.29 (2H $\times$ 2, m), 6.70/6.57 (1H each $\times$ 2, s, H-5), 3.77/3.76 (3H each $\times$ 2, s, OMe), 2.06/1.95 (3H each $\times$ 2, s, Me); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 193.7, 193.5, 193.0, 192.3, 171.7, 171.5, 156.6, 156.4, 140.4, 140.3, 131.1, 131.0, 130.8 ,130.7, 128.9 (4C), 128.7 (4C), 107.8(2C), 59.4, 59.2, 11.22, 11.17; HRESIMS *m/z* [M + H]$^+$ 229.0839 (calcd for C$_{14}$H$_{13}$O$_3$, 229.0859). Anal. HPLC [t_R (min) (content)]: 2.98 (97.7%) from solvent a or 2.95 (98.1%) from solvent b.

2-[(*E*)-3-[4-*O*-(*tert*-Butyldimethylsilyl)phenyl]-1-methoxyallylidene]-4-methylcyclopent-4-ene-1,3-dione (44). Yield, 85% from methylation of **37**, yellow oil; ^{1}H NMR (400 MHz, CDCl$_3$, *Z/E*-isomers) δ 7.83/7.81 (1H each, d, *J* = 16 Hz, H-7), 7.58 (1H $\times$ 2, d, *J* = 16 Hz, H-8), 7.52 (2H $\times$ 2, d, *J* = 8 Hz, H-11, 13), 6.84 (2H $\times$ 2, d, *J* = 8 Hz, H-10, 14), 6.68/6.66 (1H each, s, H-5), 4.18 (3H $\times$ 2, s, OMe), 2.08 (3H $\times$ 2, s, Me), 0.98 (9H $\times$ 2, s, 3 $\times$ Me), 0.22 (6H $\times$ 2, s, 2 $\times$ Me).

2-[(*E*)-3-(4-Hydroxyphenyl)-1-methoxyallylidene]-4-methylcyclopent-4-ene-1,3-dione (45). To a solution of **44** (20 mg) in dry THF (10 mL) tetra-*tert*-butylammonium fluoride (TBAF) was added under N$_2$. After being stirred for 3 h at room temperature, the reaction mixture was extracted with Et$_2$O. The organic layers were separated, dried (Na$_2$SO$_4$), and evaporated to give the crude product, which was purified by column chromatography on silica gel using 30% EtOAc in hexanes to give a pale-orange powder

(11.2 mg in a yield of 80%). ^{1}H NMR (400 MHz, CDCl$_3$, *Z/E*-isomers) δ 7.84/7.83 (1H each, d, *J* = 16 Hz, H-7), 7.61 (1H × 2, d, *J* = 16 Hz, H-8), 7.56 (2H × 2, d, *J* = 8 Hz, H-10, 14), 6.96 (2H × 2, m, H-11, 13), 6.70/6.68 (1H each, s, H-5), 6.63/6.47 (1H each, br s, OH), 4.21 (3H × 2, s, OMe), 2.10/2.09 (3H each, s, Me); HRESIMS *m/z* [M + H]$^+$ 271.0935 (calcd for C$_{16}$H$_{15}$O$_4$, 271.0965). Anal. HPLC [t_R (min) (content)]: 3.21 (96.4%) from solvent a or 3.84 (98.8%) from solvent b.

2-[(*E*)-1-Methoxy-3-(4-methoxyphenyl)allylidene]-4-methyl-cyclopent-4-ene-1,3-dione (46). To a solution of **45** (1 mmol) in dry acetone (20 mL) under argon was added K$_2$CO$_3$ (1.5 mmol). After the mixture was refluxed for 5 min, MeI (1.2 mmol) was added to the deep-yellow solution, and reflux continued for 3 h. After filtration, the filtrate was concentrated to dryness to give a residue, which was purified by flash chromatography using 30% EtOAc in hexanes to give **46** as yellow powder in a yield of 90%. ^{1}H NMR (400 MHz, CDCl$_3$, *Z/E*-isomers) δ 7.87/7.85 (1H each, d, *J* = 16 Hz, H-7), 7.62 (1H × 2, d, *J* = 16 Hz, H-8), 7.59 (2H × 2, d, *J* = 8 Hz, H-10, 14), 6.93 (2H × 2, d, *J* = 8 Hz, H-11, 13), 6.70/6.68 (1H each, q, *J* = 1.6 Hz, H-5), 4.21 (3H × 2, s, OMe), 3.86 (3H × 2, s, Ar−OMe), 2.10/2.09 (3H each, s, Me); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 195.4, 194.3, 192.6, 191.9, 169.6, 169.4, 161.6 (2C), 156.5, 156.1, 142.78, 142.76, 140.2, 140.0, 130.3 (4C), 128.3 (2C), 118.9, 118.8, 114.4 (4C), 108.2, 108.1, 64.6, 64.5, 55.4 (2C), 11.1. 11.0; HRESIMS *m/z* [M + H]$^+$ 285.1088 (calcd for C$_{17}$H$_{17}$O$_4$, 285. 1121. Anal. HPLC [t_R (min) (content)]: 5.31 (97.7%) from solvent a or 5.67 (99.3%) from solvent b.

2-[(*E*)-1-Ethoxy-3-phenylallylidene]-4-methylcyclopent-4-ene-1,3-dione (47). Yield, 92% from ethylation of **30**, yellow needles (MeOH), mp 75−76 °C; ^{1}H NMR (400 MHz, CDCl$_3$, *Z/E*-isomers) δ 8.02/8.00 (1H each, d, *J* = 16 Hz, H-7), 7.61 (3H × 2, m, H-8, 10, 14), 7.36 (3H × 2, m, H-11, 12, 13), 6.67/6.66 (1H each, s, H-5), 4.45 (2H × 2, m, O*CH$_2$*CH$_3$), 2.06 (3H × 2, s, Me), 1.45 (3H × 2, m, OCH$_2$*CH$_3$*); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 195.7, 194.5, 192.9, 192.1, 168.1, 167.9, 156.9, 156.5, 143.0 (2C), 140.7, 140.4, 135.7 (2C), 130.5 (2C), 129.1 (4C), 128.7 (4C), 122.0, 121.9, 109.4, 109.3, 74.0, 73.9, 16.0 (2C), 11.41, 11.36; HRESIMS *m/z* [M + H]$^+$ 269.1155 (calcd for C$_{17}$H$_{17}$O$_3$, 269.1172). Anal. HPLC [t_R (min) (content)]: 5.82 (97.4%) from solvent b.

2-[(*E*)-1-Ethoxy-3-phenylallylidene]-4,5-dimethylcyclopent-4-ene-1,3-dione (48). Yield, 83% from ethylation of **31**, yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.08 (1H, d, *J* = 16 Hz, H-7), 7.68 (1H, d, *J* = 16 Hz, H-8), 7.58 (2H, m, H-10, 14), 7.36 (3H, m, H-11, 12, 13), 4.42 (2H, m, O*CH$_2$*CH$_3$), 1.99 (3H, s, Me), 1.45 (3H, t, OCH$_2$*CH$_3$*); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 194.7, 192.3, 166.2, 150.6, 150.2, 141.9, 135.7, 130.0, 128.8 (2C), 128.4 (2C), 121.9, 109.2, 73.4, 15.7, 8.9. Anal. HPLC [t_R (min) (content)]: 9.11 (96.7%) from solvent a or 9.50 (99.0%) from solvent b.

General Procedure for Acylation of Cyclopentenediones 30 and 31. A solution of the cyclopentenedione (50 mg) in pyridine (2 mL) and Ac$_2$O (2 mL) was kept at room temperature for 24 h. In the case of using the acylating reagents benzoyl chloride and cinnamoyl chloride, the solution of cyclopentenedione and a catalytic amount of DMAP in pyridine was first cooled to 0 °C. After addition of the acylating reagent, the reaction mixture was brought to room temperature and kept for 24 h. The reaction mixture was poured into ice−water and extracted with Et$_2$O. The Et$_2$O layer was washed with brine, dried (Na$_2$SO$_4$), and evaporated to dryness. The residue was chromatographed on silica gel, eluting with hexane−acetone (6:1) to afford the product.

2-[(*E*)-1-Acetoxy-3-phenylallylidene]-4-methylcyclopent-4-ene-1,3-dione (49). Yield, 76% from **30**, yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$, *Z/E*-isomers) δ 8.14/8.13 (1H each, d, *J* = 16 Hz, H-7), 7.61 (2H × 2, m, H-10, 14), 7.45−7.39 (4H × 2, m, H-11, 12, 13, H-8), 6.88/6.82 (1H each, q, *J* = 1.2 Hz, H-5), 2.49/2.48 (3H each, s, OAc), 2.12/2.08 (3H each, d, *J* = 1.2 Hz, Me); ^{13}C NMR (100 MHz, CDCl$_3$, *Z/E*-isomers) δ 193.3, 192.0 (2C), 190.6, 167.52, 167.47, 159.2, 158.9, 155.7, 155.5, 143.2, 143.1, 142.7, 142.3, 134.9 (2C), 130.8 (2C), 129.0 (4C), 128.72 (2C), 128.68 (2C), 119.4, 119.3, 113.4 (2C), 20.91, 20.88, 11.4, 11.3;

HRESIMS *m/z* [M + H]$^+$ 283.0964 (calcd for C$_{17}$H$_{15}$O$_4$, 283.0965). Anal. HPLC [t_R (min) (content)]: 5.06 (97.8%) from solvent a or 4.67 (100%) from solvent b.

2-[(*E*)-1-Acetoxy-3-phenylallylidene]-4,5-dimethylcyclopent-4-ene-1,3-dione (50). Yield, 90% from **31**, yellow powder, mp 214−216 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.18 (1H, d, *J* = 16 Hz, H-7), 7.62 (2H, m, H-10, 14), 7.42−7.39 (4H, m, H-8, 11, 12, 13), 2.50 (3H, s, OAc), 2.06/2.02 (3H each, s, Me); ^{13}C NMR (100 MHz, CDCl$_3$) δ 192.7, 191.5, 167.7, 154.3, 153.4, 153.0, 142.3, 135.1, 130.6, 129.0 (2C), 128.6 (2C), 119.5, 113.0, 20.9, 9.24, 9.15. HRESIMS *m/z* [M + H]$^+$ 297.1125 (calcd for C$_{18}$H$_{17}$O$_4$, 297.1121). Anal. HPLC [t_R (min) (content)]: 5.94 (99.6%) from solvent a or 5.72 (99.6%) from solvent b.

2-[(*E*)-1-Benzoxy-3-phenylallylidene]-4,5-dimethylcyclopent-4-ene-1,3-dione (51). Yield, 77% from **31**, yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.30 (1H, m, d, *J* = 16 Hz, H-7), 8.27 (2H, d, *J* = 7.2 Hz, H-2′, 6′), 7.71 (1H, t, *J* = 7.2 Hz), 7.63−7.56 (4H, m), 7.45 (1H, d, *J* = 16 Hz, H-8), 7.39 (4H, m), 2.09/2.00 (3H each, s, Me); ^{13}C NMR (100 MHz, CDCl$_3$) δ 192.7, 191.2, 163.5, 154.6, 153.5, 153.2, 142.4, 135.1, 133.9, 130.6, 130.5 (2C), 129.0 (2C), 128.8 (3C), 128.6 (2C), 119.6, 113.1, 9.3, 9.2; HRESIMS *m/z* [M + H]$^+$ 359.1263 (calcd for C$_{23}$H$_{19}$O$_4$, 359.1278). Anal. HPLC [t_R (min) (content)]: 10.11 (99.5%) from solvent a or 10.79 (99.5%) from solvent b.

2-[(*E*)-1-Cinnamoyloxy-3-phenylallylidene]-4,5-dimethylcyclo-pent-4-ene-1,3-dione (52). Yield, 78% from **31**, yellow powder; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.23 (1H, d, *J* = 16 Hz, H-7), 7.94 (1H, d, *J* = 16 Hz, β-H of cinnamoyl), 7.63 (3H, m, H-10, 14), 7.44−7.38 (8H, m), 6.74 (1H, d, *J* = 16 Hz, α-H of cinnamoyl), 2.07/2.00 (3H each, s, Me); ^{13}C NMR (100 MHz, CDCl$_3$) δ 193.0, 191.5, 163.7, 154.5, 153.5, 153.3, 148.0, 142.5, 135.4, 134.2, 131.1, 130.8, 129.2 (4C), 128.8 (4C), 119.8, 116.5, 113.4, 9.5, 9.4. Anal. HPLC [t_R (min) (content)]: 12.33 (97.6%) from solvent a or 10.49 (97.9%) from solvent b.

2-(1-Methoxyethylidene)-4-methylcyclopent-4-ene-1,3-dione (53). To a solution of 2-methylmaleic anhydride (**2**) (8.0 g, 71.4 mmol) in dry 1,2-dichloroethane (200 mL) at room temperature under N$_2$ was added anhydrous AlCl$_3$ (32.3 g, 133.4 mmol). The suspension was cooled to 0 °C, and α-methylvinyl acetate (10.7 g, 107.1 mmol) was added dropwise over 15 min. The mixture was subsequently refluxed for 1.5 h. After cooling, the mixture was poured into ice−water containing 10% HCl (300 mL). The aqueous layer was extracted with CHCl$_3$ (150 mL × 3). The combined organic layers were washed with brine (150 mL) and H$_2$O (200 mL × 4), dried (Na$_2$SO$_4$), and concentrated to dryness to yield a residue (8.5 g), which was chromatographed on silica gel, eluting with hexane−EtOAc (1:2) to afford 2-(1-hydroxyethylidene)-4-methylcyclopent-4-ene-1,3-dione (5.97 g, 55%) as a pale-yellow powder. ^{1}H NMR (400 MHz, CDCl$_3$, *E/Z*-isomers) δ 11.8 (br s, OH), 6.50/6.42 (br s, H-5), 2.22 (s, Me), 1.91 (s, Me-4); ^{13}C NMR (100 MHz, CDCl$_3$, *E/Z*-isomers) δ 200.4/199.6/192.1/191.7 (CO), 176.9/176.7 (C-6), 157.8/153.4 (C-4), 140.5/136.2 (C-5), 104.2 (2C, C-2), 17.9 (vinylic Me), 11.2/10.2 (Me-4); HRTOFMS *m/z* [M + H]$^+$ 153.0585 (calcd for C$_8$H$_9$O$_3$, 153.0546). With the general procedure for methylation of cyclopentenediones, the title compound was obtained from the above compound in a yield of 46% as a yellow powder. ^{1}H NMR (400 MHz, CDCl$_3$, *E/Z*-isomers) δ 6.61/6.59 (br s, H-5), 4.01 (s, OMe), 2.62 (br s, vinylic Me), 2.03/2.05 (s, Me-4); ^{13}C NMR (100 MHz, CDCl$_3$, *E/Z*-isomers) δ 195.4/194.5/193.0/192.5 (C=O), 173.8/173.5 (C-6), 155.8/155.2 (C-4), 139.7/139.1 (C-5), 107.2 (2C, C-2), 56.0/55.9 (OMe), 14.05/13.99 (vinylic Me), 11.0/10.8 (Me-4); HRTOFMS *m/z* [M + H]$^+$ 167.0682 (calcd for C$_9$H$_{11}$O$_3$, 167.0703). Anal. HPLC [t_R (min) (content)]: 2.51 (97.6%) from solvent a or 2.66 (98.5%) from solvent b.

2-Methoxy-1,4-bismethoxymethoxybenzene (55). A solution of methoxyhydroquinone (**54**) (1 g, 7.14 mmol) in dry THF (30 mL) was added to an ice-cooled, stirred suspension of NaH (0.68 g of 60% dispersion in mineral oil, 17.00 mmol) in dry THF (100 mL). After the mixture was stirred for 10 min at 0 °C, chloromethoxymethyl ether (2.29 g, 28.44 mmol) was added and stirring continued for 24 h. Crushed ice and water (200 mL) were added

to the reaction mixture. The aqueous phase was extracted with Et_2O (200 mL × 3). The organic layers were combined, washed with H_2O (150 mL), dried (Na_2SO_4), and concentrated to dryness. The residue was chromatographed on silica gel using $CHCl_3$ as solvent to give **55** (1.23 g, yield, 75%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (1H, d, $J = 8.7$ Hz), 6.63 (1H, d, $J = 2.6$ Hz), 6.56 (1H, dd, $J = 8.7$, 2.6 Hz), 5.13 (2H, s), 5.11 (2H, s), 3.84 (3H, s), 3.50 (3H, s), 3.47 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5 (s), 151.2 (s), 141.8 (s), 118.2 (d), 107.5 (d), 102.4 (d), 96.6 (t), 95.5 (t), 56.5 (q), 56.3 (q), 56.2 (q).

1-Bromo-4-methoxy-2,5-bismethoxymethoxybenzene (56). To a stirred solution of **55** (1 g, 4.386 mmol) and $NaHCO_3$ (368 mg, 4.386 mmol) in MeOH (100 mL) at room temperature was added slowly a solution of pyridium hydrobromide perbromide ($C_5H_5N^+HBr_3^-$) (1.47 g, 4.596 mmol) in MeOH (50 mL) in 25 min. The reaction was complete immediately after the addition. The reaction mixture was diluted with ice−water (150 mL) and extracted with Et_2O (125 mL × 4). The combined organic layers were washed with brine and H_2O, dried ($MgSO_4$), and concentrated to dryness to give **56** (1.2 g, yield, 89%) as a purple powder. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (1H, s), 6.78 (1H, s), 5.16 (2H, s), 5.12 (2H, s), 3.84 (3H, s), 3.52 (3H, s), 3.49 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.2 (s), 149.6 (s), 142.2 (s), 121.5 (d), 102.7 (d), 102.5 (s), 96.4 (t), 96.3 (t), 56.6 (q), 56.4 (q), 56.3 (q).

1-Methoxy-2,5-bismethoxymethoxy-4-methylbenzene (57). To a solution of **56** (0.88 g, 2.857 mmol) in dry THF (30 mL) at −78 °C was added MeLi (2.45 mL of 1.4 M in Et_2O, 3.43 mmol). After stirring at −78 °C for 1 h, MeI (2.03 g, 14.296 mmol) was added to the resultant white cloudy suspension. The solution was stirred at −78 °C for 1 h and then warmed to room temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl (20 mL) and water (20 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (50 mL × 3). The combined organic layers were washed with brine and H_2O, dried ($MgSO_4$), and concentrated to dryness to yield **57** (0.62 g, yield, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.88 (1H, s), 6.68 (1H, s), 5.08 (4H, s), 3.78 (3H, s), 3.46 (3H, s), 3.44 (3H, s), 2.12 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.1 (s), 148.9 (s), 141.3 (s), 120.3 (d), 119.5 (s), 101.5 (s), 96.6 (t), 95.8 (t), 56.5 (q), 56.4 (q), 56.2 (q), 15.8 (q).

1-(2-Methoxy-3,6-bismethoxymethoxy-5-methylphenyl)-2-phenylethanol (58). To a solution of **57** (0.59 g, 2.438 mmol) in dry THF (5 mL) at −78 °C was added *n*-BuLi (1.46 mL of 2.5 M in hexane, 3.657 mmol). After being stirred at −78 °C for 1 h, the solution was warmed to 0 °C and stirring continued at 0 °C for 5 h. The solution was again warmed to 25 °C and stirred for 3 h. The resultant white cloudy suspension was cooled to 0 °C. Phenylacetaldehyde (0.37 g, 3.657 mmol) was added slowly over 10 min, and stirring continued for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (20 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (30 mL × 3). The combined organic layers were washed with brine and H_2O, dried ($MgSO_4$), and concentrated to dryness. The residue was chromatographed on silica gel using CH_2Cl_2 and then CH_2Cl_2−MeOH (50:1) to yield **58** (0.55 g, yield, 66%) as an off-white oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (5H, m, H-2″-6″), 6.92 (1H, s, H-4′), 5.28 (1H, dd, $J = 8.4$, 5.5 Hz, H-1), 5.16 (1H, s, MeOCH_2O-3′), 4.96/4.89 (1H each, ABq, $J = 5.6$ Hz, MeOCH_2O-6′), 3.90 (3H, s, MeO-2′), 3.60 (3H, s, *Me*OCH$_2$O-6′), 3.52 (3H, s, *Me*OCH$_2$O-4′), 3.29 (1H, dd, $J = 13.6$, 8.4 Hz, H-2a), 3.18 (1H, dd, $J = 13.7$, 5.5 Hz, H-2b); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.2 (s, C-6′), 147.1 (s, C-2′), 146.9 (s, C-3′), 139.8 (s, C-1″), 130.8 (s, C-1′), 129.9 (2C, d, C-3″,5″), 128.6 (2C, d, C-2″,6″), 127.0 (s, C-5′), 126.6 (s, C-4″), 118.6 (d, C-4′), 100.4 (d, MeOCH_2O-6′), 95.9 (d, MeOCH_2O-3′), 70.3 (d, C-1), 61.6 (q, MeO-2′), 57.9 (q, *Me*OCH$_2$O-6′), 56.7 (q, *Me*OCH$_2$O-3′), 44.6 (t, C-2), 17.4 (q, Me-5′). The above NMR signal assignments were facilitated by a 2D HMBC experiment.

2-Methoxy-5-methyl-3-styrylbenzene-1,4-diol (59). A solution of **58** (100 mg, 0.291 mmol) and 3 N HCl (3 mL) in dioxane (10 mL) was stirred under argon at 50 °C for 8 h. The reaction mixture

was diluted with H_2O (20 mL) and then extracted with Et_2O (30 mL × 3). The combined organic layers were washed with brine and H_2O, dried ($MgSO_4$), and concentrated to dryness to give **59** (71 mg, yield, 95%) as an off-white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (2H, br d, $J = 7.2$ Hz, H-2″,6″), 7.39 (2H, br t, $J = 7.1$ Hz, H-3″,5″), 7.32 (1H, d, $J = 7.5$ Hz, H-4″), 7.29 (1H, d, $J = 16.3$ Hz, H-1′), 7.20 (1H, d, $J = 16.9$ Hz, H-1′), 6.71 (1H, s, H-5), 3.76 (3H, s, MeO-2), 2.22 (3H, s, Me-5).

2-Methoxy-5-methyl-3-styryl-1,4-benzoquinone (60). A solution of **59** (70 mg, 0.273 mmol) and DDQ (160 mg, 0.705 mmol) in CH_2Cl_2 (15 mL) and H_2O (2 mL) was stirred under argon at room temperature for 12 h. The reaction mixture was diluted with H_2O (20 mL) and then extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with brine and H_2O, dried ($MgSO_4$), and concentrated to dryness. The residue was chromatographed on silica gel using CH_2Cl_2 as solvent to yield **60** (45 mg, yield, 65%) as a red powder. UV (CH_3CN), λ_{max} (log ϵ) 278 (4.35), 292 (4.35) nm; IR (KBr) ν_{max}, 1652, 1611, 1559, 1448, 1336, 1305, 1230, 1135, 965, 885, 750, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (1H, d, $J = 16.6$ Hz, H-8), 7.60 (2H, d, $J = 7.2$ Hz, H-11,15), 7.43 (2H, t, $J = 7.2$ Hz, H-12,14), 7.35 (1H, t, $J = 7.2$ Hz, H-14), 7.25 (1H, d, $J = 16.6$ Hz, H-9), 6.54 (1H, q, $J = 1.5$ Hz, H-6), 4.19 (3H, s, OMe), 2.13 (3H, d, $J = 1.4$ Hz, H-7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.0 (s, C-1), 183.6 (s, C-4), 154.3 (s, C-2), 146.0 (s, C-5), 138.9 (d, C-9), 138.0 (s, C-10), 132.1 (s, C-6), 128.9 (d, C-12,14), 128.8 (d, C-13), 127.3 (d, C-11,15), 126.2 (C-4), 117.6 (C-8), 61.3 (OMe), 16.2 (C-7); ESIMS m/z [M ($C_{15}H_{11}O_3$) + H]$^+$ 255.

In Vitro Antifungal Susceptibility Testing. A modified version of the CLSI (formerly NCCLS) methods was used for susceptibility testing.[21] Organisms were obtained from either the American Type Culture Collection (Manassas, VA) (*Candida albicans* ATCC 90028, *Cryptococcus neoformans* ATCC 90113, and *Aspergillus fumigatus* ATCC 90906) or provided by Spencer Redding/Ted White (*C. albicans* isolates no. 1 (fluconazole-susceptible) and no. 17 (fluconazole-resistant)).[11] Samples were serially diluted in 20% DMSO/saline and transferred in duplicate to 96-well flat-bottom microplates. Inocula were prepared by correcting the OD_{630} of microbe suspensions in incubation broth (RPMI 1640/2% dextrose/0.03% glutamine/MOPS at pH 6.0 (Cellgro) for *C. albicans*, Sabouraud dextrose for *C. neoformans*, and 5% Alamar Blue/RPMI 1640 broth (2% dextrose, 0.03% glutamine, buffered with 0.165M MOPS at pH 7.0) for *A. fumigatus*) to afford final target inocula of *C. albicans* (1.0×10^4), *C. neoformans* (1.0×10^5), and *A. fumigatus* (3.0×10^4 CFU/mL). Drug controls (amphotericin B (ICN Biomedicals, OH) and fluconazole (Sequoia Research Products Ltd., U.K.) were included in each assay. All organisms were read at 630 nm using the EL-340 biokinetics reader (Bio-Tek Instruments, VT) prior to and after incubation (*C. albicans* at 37 °C for 18−24 h; *C. neoformans* and *A. fumigatus* at 30 °C for 72 h) except *A. fumigatus*, which was read at 544 nm excitation and 590 nm emission using the Polarstar Galaxy plate reader (BMG LabTechnologies, Germany). Percent growth was calculated and plotted versus test concentration to afford the IC_{50} (sample concentration that affords 50% growth of the organism). The minimum inhibitory concentration (MIC) is defined as the lowest test concentration that allows no detectable growth. Minimum fungicidal concentrations (MFCs) were determined by removing 5 μL from each clear (or blue) well, transferring to agar and incubating as previously mentioned. The MFC was defined as the lowest test concentration that allows no growth of the organism on agar.

In Vitro Cytotoxicity Assay. The mammalian cells, Vero (African green monkey kidney fibroblast) and LLC-PK1 (pig kidney epithelial), used in this study were obtained from ATCC (Manassas, VA). Cytotoxicity was determined by the neutral red method[22] up to the highest concentration of 10 μg/mL. The detailed procedure was described in a previous paper.[23]

References

(1) (a) Georgopapadakou, N. H.; Walsh, T. J. Antifungal agents: chemotherapeutic targets and immunologic strategies. *Antimicrob. Agents Chemother.* **1996**, *40*, 279−291. (b) Kontoyiannis, D. P.; Mantadakis, E.; Samonis, G. Systemic mycoses in the immunocompromised host: an update in antifungal therapy. *J. Hosp. Infect.* **2003**, *53*, 243−258. (c) White, T. C.; Bowden, R. A.; Marr, K. A. Clinical, cellular, and molecular factors that contribute to antifungal drug resistance. *Clin. Microbiol. Rev.* **1998**, *11*, 382−402. (d) Wong-Beringer, A.; Kriengkauykiat, J. Systemic antifungal therapy: new options, new challenges. *Pharmacotherapy* **2003**, *23*, 1441−1462.

(2) Newman, D. J.; Cragg, G. M.; Snader, K. M. Natural products as sources of new drugs over the period 1981−2002. *J. Nat. Prod.* **2003**, *66*, 1022−1037.

(3) Li, X.-C.; Ferreira, D.; Jacob, M. R.; Zang, Q.; Khan, S. I.; Elsohly, H. N.; Nagle, D. G.; Smillie, T. J.; Khan, I. A.; Walker, L. A.; Clark, A. M. Antifungal cyclopentenediones from *Piper coruscans. J. Am. Chem. Soc.* **2004**, *126*, 6872−6873.

(4) (a) Lee, H. H. The structure of lucidone and methyllucidone. *Tetrahedron Lett.* **1968**, 4243−4246. (b) Ng, S.; Lee, H. H.; Bennett, G. ¹³C NMR study on linderones and lucidones. *Magn. Reson. Chem.* **1990**, *28*, 337−342.

(5) (a) Iwataki, I.; Shibuya, M.; Nakada, A.; Mizuno, M. 2-(Aminomethylene)-4-cyclopentene-1,3-diones as Agricultural Fungicides. Patent JP 53101336, 1978. (b) Kataoka, M.; Naruse, N.; Kawabe, N.; Hosoi, K.; Ohno, M.; Okuda, S.; Eguchi, J.; Tosaya, M.; Umezawa, H.; Takeuchi, T. β-Trione Compounds as Fungicides. Patent JP 51001633, 1976. (c) Kawada, H.; Hayashi, S.; Kasugai, A.; Shigematsu, T. Benzylidenecyclopentene Microbicide. Patent JP 52079022, 1977. (d) Lee, D. L.; Michaely, W. J. Herbicidal 2-(2-Substituted benzoyl)-1,3-cyclopentanedione. U.S. Patent 4681621, 1987. (e) Simonov, V. V.; Anishchenkom, A. F.; Popova, E. N.; Dunaeva, T. P.; Gazizov, R. T.; Simonov, V. D. Halogenated Spirans. Patent DE 2804271, 1978.

(6) Clemo, N. G.; Geodge, D. R.; Pattenden, G. Synthesis of calythrone and related cyclopentene-1,3-diones *via* rearrangement of 4-ylidene-butenolides. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1448−1453.

(7) Nilsson, M. Preparation of 2-acetylcyclopent-4-ene-1,3-diones from maleic anhydrides and isopropenyl acetate. *Acta Chem. Scand.* **1964**, *18*, 441−446.

(8) (a) Suzuki, Y.; Kono, Y.; Inoue, T.; Sakurai, A. A potent antifungal benzoquinone in etiolated sorghum seedlings and its metabolites. *Phytochemistry* **1998**, *47*, 997−1001. (b) Haraguchi, H.; Taniguchi, M.; Tanaka, T.; Oi, S.; Hashimoto, K. Citrinin, an electron acceptor having antifungal activity. *Agric. Biol. Chem.* **1989**, *53*, 1741−1742. (c) Wang, H.-J.; Gloer, K. B.; Gloer, J. B.; Scott, J. A.; Malloch, D. Anserinones A and B: new antifungal and antibacterial benzoquinones from the coprophilous fungus *Podospora anserina. J. Nat. Prod.* **1997**, *60*, 629−631. (d) Meazza, G.; Dayan, F. E.; Wedge, D. E. Activity of quinones on Colletotrichum species. *J. Agric. Food Chem.* **2003**, *51*, 3824−3828.

(9) Kalinin, A. V.; Da Silva, A. J. M.; Lopes, C. C.; Lopes, R. S. C.; Snieckus, V. Directed ortho metalation and cross coupling links. Carbamoyl rendition of the Baker−Venkataraman rearrangement. Regiospecific route to substituted 4-hydroxycoumarins. *Tetrahedron Lett.* **1998**, *39*, 4995−4998.

(10) (a) Bruce, J. M.; Creed, D.; Dawes, K. Light-induced and related reactions of quinines. Part VIII. Some (2-hydroxyalkyl)-, phenethyl, (2-ethoxycarbonylethyl)-, and styryl-1,4-benzoquinones. *J. Chem. Soc. C* **1971**, 3749−3756. (b) Irngartinger, H.; Stadler, B. Synthesis, structures and topochemistry of 2-monovinyl-substituted 1,4-benzoquinones. *Eur. J. Org. Chem.* **1998**, 605−626. (c) Brehm, I.; Meier, H. Formation and reactivity of 2-styryl-1,4-benzoquinones. *Eur. J. Org. Chem.* **2001**, 3307−3311. (d) Brehm, I.; Hinneschiedt, S.; Meier, H. 1,4-Benzoquinones with styryl substituents. *Eur. J. Org. Chem.* **2002**, 3162−3170.

(11) (a) Pfaller, M. A.; Rhine-Chalberg, J.; Redding, S. W.; Smith, J.; Farinacci, G.; Fothergill, A. W.; Rinaldi, M. G. Variations in fluconazole susceptibility and electrophoretic karyotype among oral

isolates of *Candida albicans* from patients with AIDS and oral candidiasis. *J. Clin. Microbiol.* **1994**, *32*, 59−64. (b) White, T. C. Increased mRNA levels of ERG16, CDR, and MDR1 correlate with increases in azole resistance in *Candida albicans* isolates from a patient infected with human immunodeficiency virus. *Antimicrob. Agents Chemother.* **1997**, *41*, 1482−1487. (c) White, T. C. The presence of an R467K amino acid substitution and loss of allelic variation correlate with an azole-resistant lanosterol 14α-demethylase in *Candida albicans. Antimicrob. Agents Chemother.* **1997**, *41*, 1488−1494.

(12) (a) Griffiths, D. G.; Partis, M. D.; Sharp, R. N.; Beechey, R. B. N-Polymethylenecarboxy-maleimides. A new class of probes for membrane sulphydryl groups. *FEBS Lett.* **1981**, *134*, 261−263. (b) Partis, M. D.; Griffiths, D. G.; Roberts, G. C.; Beechey, R. B. Cross-linking of protein by ω-maleimido alkanoyl N-hydroxysuccinimido esters. *J. Protein Chem.* **1983**, *2*, 263−277.

(13) Aoyama, Y.; Konoike, T.; Kanda, A.; Naya, N.; Nakajima, M. Total synthesis of human chymase inhibitor methyllinderone and structure−activity relationships of its derivatives. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1695−1697.

(14) McGoverns, S. L.; Caselli, E.; Grigorieff, N.; Shoichet, B. K. A common mechanism underlying promiscuous inhibitors from virtual and high-throughput screening. *J. Med. Chem.* **2002**, *45*, 1712−1722.

(15) Ahn, B. Z.; Sok, S. E. Michael acceptors as a tool for anticancer drug design. *Curr. Pharm. Des.* **1996**, *2*, 247−262.

(16) Zeller, K. P.; Mewes, K.; Ehninger, G.; Blanz, J. Formation of reactive intermediates by cytochrome P-450 mediated oxidation of the anti-cancer drug mitoxantrone. *Pure Appl. Chem.* **1994**, *66*, 2415−2418.

(17) (a) Powers, J. C.; Asgian, J. L.; Ekici, O. D.; James, K. E. Irreversible inhibitors of serine, cysteine, and threonine proteases. *Chem. Rev.* **2002**, *102*, 4639−4750. (b) Ekici, O. D.; Goetz, M. G.; James, K. E.; Li, Z. Z.; Rukamp, B. J.; Asgian, J. L.; Caffrey, C. R.; Hansell, E.; Dvorak, J.; McKerrow, J. H.; Potempa, J.; Travis, J.; Mikolajczyk, J. Salvesen, G. S.; Powers, J. C. Aza-peptide Michael acceptors: A new class of inhibitors specific for caspases and other Clan CD cysteine proteases. *J. Med. Chem.* **2004**, *47*, 1889−1892. (c) Dragovich, P. S.; Prins, T. J.; Zhou, R.; Johnson, T. O.; Hua, Y.; Luu, H. T.; Sakata, S. K.; Brown, E. L.; Maldonado, F. C.; Tuntland, T.; Lee, C. A.; Fuhrman, S. A.; Zalman, L. S.; Patick, A. K.; Matthews, D. A.; Wu, E. Y.; Bennett, M. G.; Borer, C.; Nayyar, N. K.; Moran, T.; Chen, L.; Rejto, P. A.; Rose, P. W.; Guzman, M. C.; Dovalsantos, E. Z.; Lee, S.; McGee, K.; Mohajeri, M.; Liese, A.; Tao, J.; Kosa, M. B.; Liu, B.; Batugo, M. R.; Gleeson, J.-P. R.; Wu, Z. P.; Liu, J.; Meador, J. W.; Ferre, R. N. Structure-based design, synthesis, and biological evaluation of irreversible human rhinovirus 3C protease inhibitors. 8. Pharmacological optimization of orally bioavailable 2-pyridone-containing peptidomimetics. *J. Med. Chem.* **2003**, *46*, 4572−4585. (d) Ekici, O. D.; Li, Z. Z.; Campbell, A. J.; James, K. E.; Asgian, J. L.; Mikolajczyk, J.; Salvesen, G. S.; Ganesan, R.; Jelakovic, S.; Gruetter, M. G.; Powers, J. C. Design, synthesis, and evaluation of aza-peptide Michael acceptors as selective and potent inhibitors of caspases-2, -3, -6, -7, -8, -9, and -10. *J. Med. Chem.* **2006**, *49*, 5728−5749.

(18) (a) Prestera, T.; Holtzclaw, W. D.; Zhang, Y.; Talalay, P. Chemical and molecular regulation of enzymes that detoxify carcinogens. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 2965−2969. (b) Dinkova-Kostova, A. T. Protection against cancer by plant phenylpropenoids: induction of mammalian anticarcinogenic enzymes. *Mini-Rev. Med. Chem.* **2002**, *2*, 595−610. (c) Gao, X.; Talalay, P. Induction of phase 2 genes by sulforaphane protects retinal pigment epithelial cells against photooxidative damage. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 10446−10451.

(19) Rinaldi, R.; Eliasson, E.; Swedmark, S.; Morgenstern, R. Reactive intermediates and the dynamics of glutathione transferases. *Drug Metab. Dispos.* **2002**, *30*, 1053−1058.

(20) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1999; pp 77−80.

(21) (a) *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts*; Approved Standard M27-A2; National Committee on Clinical Laboratory Standards, 2002; Vol. 22, Issue 15. (b) *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi*; Approved Standard, M38-A; National Committee on Clinical Laboratory Standards, 2002; Vol. 22, Issue 16.

(22) Borenfreund, E.; Puerner, J. Toxicity determined in vitro morphological alterations and neutral red absorption. *Toxicol. Lett.* **1985**, *24*, 119−124.

(23) Yang, C.-R.; Zhang, Y.; Jacob, M. R.; Khan, S. I.; Zhang, Y.-J.; Li, X.-C. Antifungal activity of C-27 steroidal saponins. *Antimicrob. Agents Chemother.* **2006**, *50*, 1710−1714.