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Multicomponent/Palladium-Catalyzed Cascade Entry to Benzopyrrolizidine Derivatives: Synthesis and Antioxidant Evaluation

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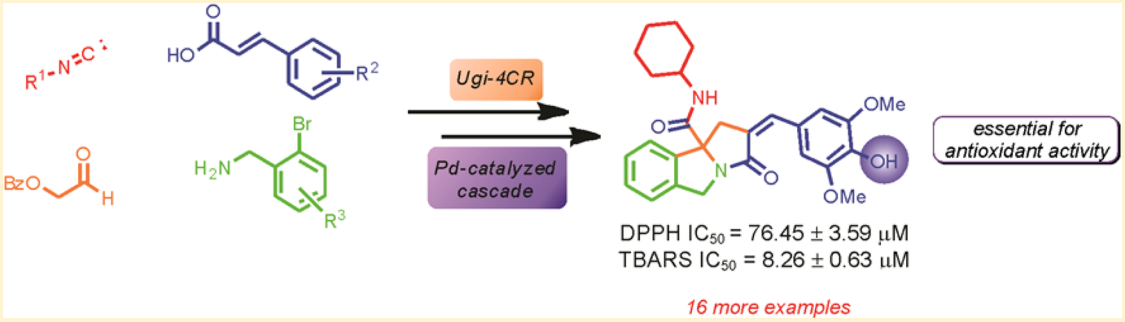
Supporting Information



ABSTRACT: A versatile and efficient protocol for the synthesis of highly substituted benzopyrrolizidines (tetrahydro-3*H*-pyrrolo[2,1-*a*]isoindol-3-ones) is reported. The strategy consisted of an Ugi four-component reaction/elimination methodology to afford dehydroalanines containing *trans*-cinnamic acid derivatives and different substituted 2-bromobenzylamines, followed by a palladium-catalyzed 5-exo-trig/5-exo-trig cascade carbocyclization process. Gratifyingly, benzopyrrolizidines were obtained in moderate to good yields (42−77%) with a *Z* geometry due to the structural requirements for *syn*-*β*-hydride elimination. The prepared heterocyclic scaffolds are decorated with several substituents and incorporate a benzopyrrolizidine-fused system, along with an embedded cinnamic acid derivative, two privileged medicinal chemistry scaffolds. Additionally, since some of the compounds are derived from the well-known antioxidants ferulic and sinapinic acids, they were tested for their in vitro antioxidant capacity. The data suggested that compounds having a *p*-hydroxyl group showed moderate 2,2-diphenyl-1-picrylhydrazyl-radical-scavenging activity and were effective antioxidants in preventing lipoperoxidation in a thiobarbituric acid reactive substances assay.

INTRODUCTION

Alkaloids and aza-heterocycles are considered to be privileged scaffolds in medicinal chemistry, since they can act as either hydrogen acceptors or hydrogen donors during their interaction with biological targets.[1] Pyrrolizidines are widely distributed alkaloids that play a key role in the protection system of several living organisms.[2,3] Despite the well-documented toxicity of pyrrolizidines,[4] a plethora of relevant biological activities of interest in medicine and agriculture have been attributed to these aza-heterocycles.[5] Specifically, the benzo-fused pyrrolizidine core has received special interest because of its presence in numerous biologically important natural products[6] such as the tricyclic antimalarial flinderole C (**1**)[7] and the psychoactive yuremamine[8] (**2**). Additionally, non-natural benzopyrrolizidine derivatives (such as **3**) possess moderate insecticidal, antiproliferative, and antimicrobial activities (Figure 1).[9] Although there is ample evidence to highlight the biological relevance of the benzopyrrolizidine core, there are a limited number of methods to access this aza-heterocycle, and the reported protocols lack of structural diversity or require several synthetic steps.[11] Thus, the establishment of practical and efficient synthetic protocols

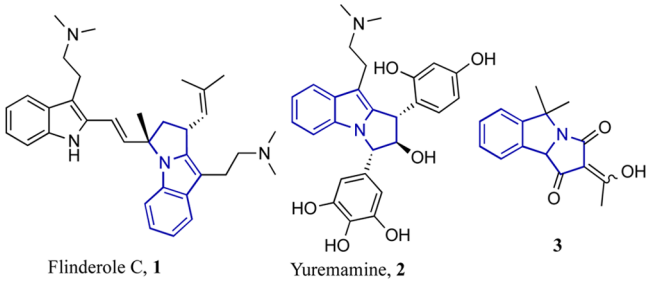


Figure 1. Some relevant natural and synthetic benzopyrrolizidine compounds.

that give access to libraries of benzopyrrolizidine derivatives is a valuable research goal, particularly in the search for new lead compounds for pharmaceutical applications.

In recent decades, the sequence of an Ugi four-component reaction (Ugi 4-CR)[10] with further postcondensations protocols has been extensively used for the combinatorial creation of

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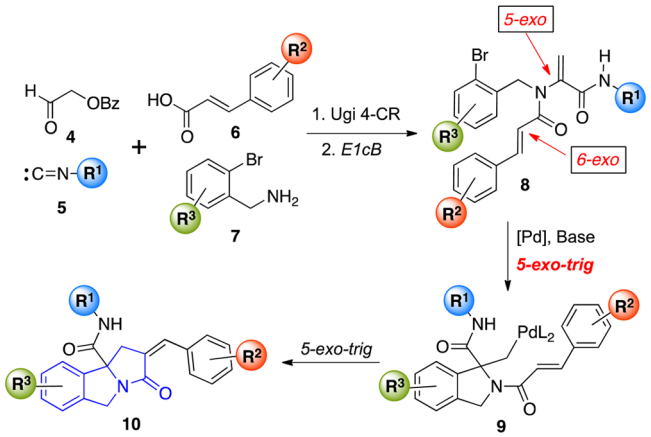
molecular libraries of structurally diverse aza-heterocycles.[12−18] The atom-economic Ugi reaction (only a H_2O molecule is lost) connects a carboxylic acid, an aldehyde, an amine, and an isocyanide in a single product.[19] Van der Eycken and co-workers have elegantly exploited the combination of this multicomponent reaction with palladium-[20] and gold-metal-catalyzed[21] carbocyclizations in the synthesis of several polysubstituted aza-heterocycles. Given these antecedents, we envisioned that a collection of diversely substituted benzo-fused pyrrolizidines **10** (tetrahydro-3*H*-pyrrolo[2,1-*a*]isoindol-3-ones) might be constructed via a Heck 5-exo/5-exo sequential C−C bond forming process[22−25] from the Ugi-derived dehydroalanine **8** (Scheme 1). The captodative double bond

Scheme 1. Synthetic Strategy Proposed To Construct Benzopyrrolizidine Derivatives



in such molecules has been explored[26] in other palladium-catalyzed processes. It is noteworthy that the heterocyclic scaffold **10** incorporates two privileged motifs in medicinal chemistry: a benzopyrrolizidine fused system with an embedded cinnamic acid derivative. Moreover, contrary to the previously reported methodologies,[11] this strategy offers the advantage of being a three-step synthesis that can easily generate a series of highly substituted benzopyrrolizidine derivatives.

In the proposed protocol, the first C−C bond formation would afford the σ-alkyl−palladium(II) halide **9**, through a 5-exo-trig cyclization, which is expected to be kinetically favored over the 6-exo possibility. If the latter assumption were true, then the lack of a β-hydrogen in **9**, indispensable to allow the otherwise fast β-elimination, would be architecturally adjusted to undergo another 5-exo insertion to produce the benzo-fused pyrrolizidines **10**, upon a β-elimination. One of the main advantages of this synthetic protocol is that diversely substituted dehydroalanines **8** might be easily assembled in an Ugi 4-CR/elimination[27] two-step sequence using 2-benzoyloxyacetaldehyde **4**, cinnamic acid derivatives **6**, 2-bromobenzylamines **7**, and various isocyanides **5**, as the Ugi 4-CR input set (Scheme 1).

RESULTS AND DISCUSSION

Chemistry. Our first efforts toward the proposed synthetic route involved establishing the best conditions to carry out the Ugi 4-CR. We employed *tert*-butyl isocyanide **5**, (*E*)-cinnamic acid **6**, benzoyloxyacetaldehyde **4**, and 2-bromobenzylamine **7a** in the model reaction (Table 1, entry 1). The corresponding Ugi adduct **11a** was obtained in an adequate 83% yield by mixing the above components in methanol for 2 days at room temperature. At this point, the elimination reaction, required to secure the diene intermediate **8a**, was investigated. Gratifyingly, the previously reported[27] biphasic protocol (aqueous 50% KOH and PhMe, with 0.3% of TBAI as a phase transfer catalyst) for accessing the dehydroalanines provided the diene **8a** in excellent yield (90%). As the diene **8a** was obtained without further complications, we then prepared several analogues by changing the nature of the isocyanide, the benzylamine, and the cinnamic acid derivative in the four-component input set (Table 1). Benzoyloxyacetaldehyde was used as the aldehyde component in all of the experiments, because it was required to construct the dehydroalanine double bond. All the Ugi adducts (**11b−h**) and dienes (**8b−h**) derived from different cinnamic acid derivatives were obtained in moderate to good yields using *tert*-butyl (entries 5, 6−9, 11−14, 16, and 17), cyclohexyl (entries 5, 10, and 15), and 2,6-dimethylphenyl isocyanides (entry 2). We also conducted the Ugi 4-CR/elimination sequence using benzylamines bearing electron-donating (entry 3, 6, 11−13, and 16) and electron-withdrawing substituents (entries 7 and 8) to produce the expected dienes. The use of electron-rich 3,4-dimethoxycinnamic acid did not affect the efficiency of the Ugi reaction and the subsequent elimination process, and good yields of dienes **8d−h** were obtained (entries 4−8).

Because of these important results, we focused our interest on the incorporation of hydroxycinnamic acid derivatives in the Ugi 4-CR. This not only would extend the scope of the methodology but also could provide attractive molecules with potentially useful pharmacological activity. Specifically, the addition of ferulic and sinapinic acids attracted our attention, because of their importance as antioxidant species that function by scavenging exogenous reactive oxidant species (ROS).[28] Thus, the multicomponent reaction, when carried out using ferulic (entries 9−13) and sinapinic acids (entries 14−16), under the aforementioned conditions, afforded the corresponding adducts **11i−p** in good yields (Table 1, entries 9−16). Not surprisingly, the biphasic conditions (aqueous 50% KOH and PhMe), used previously for the elimination process, were ineffective for these reactions, apparently due to the presence of the acidic phenolic hydrogen in the molecule. Thus, new methodology for the benzoate elimination had to be developed. It was soon determined that DBU and triethylamine in dichloromethane afforded the desired elimination products after a few hours at room temperature. The elimination also took place when DBU was used alone, but the reaction required more time and occurred in lower yield. Both ferulic- (**8i−m**) and sinapinic-containing products (**8n−p**) were satisfactorily obtained using this two-step methodology. Interestingly, the chloroethyl alkylated diene **8q** was formed when dichloroethane was used as the solvent and DBU as the base in the elimination process, starting from the Ugi adduct **11n**. Under these conditions, the elimination of the benzoate group took place along with the in situ alkylation of the phenoxide with the solvent, to afford **8q** in 78% yield.

With the diversely substituted dienes **8a−q** in hand (Table 1), efforts to implement the Pd-mediated 5-exo-trig/5-exo-trig cascade sequence were undertaken. The first experiment was carried out using the Ugi-derived dehydroalanine **8a** and $PdCl_2(PPh_3)_2$, as the palladium source, in refluxing toluene, conditions previously used in other Heck cascade sequences.[25] Under these conditions, however, we observed only trace

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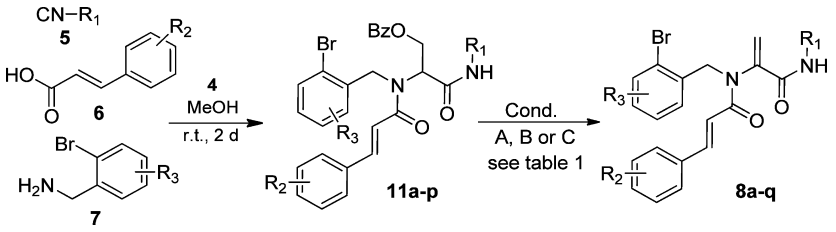
Table 1. Ugi/Elimination Protocol



entry	compd	R^1	R^2	R^3	yield (%) 11	yield (%) 8
1	**11a/8a**	*t*-Bu	H	H	83	90[a]
2	**11b/8b**	2,6-diMePh	H	H	84	70[a]
3	**11c/8c**	*t*-Bu	H	5-OMe	79	81[a]
4	**11d/8d**	*t*-Bu	3,4-diOMe	H	76	70[a]
5	**11e/8e**	Cy	3,4-diOMe	H	82	81[a]
6	**11f/8f**	*t*-Bu	3,4-diOMe	5-OMe	78	77[a]
7	**11g/8g**	*t*-Bu	3,4-diOMe	5-F	76	82[a]
8	**11h/8h**	*t*-Bu	3,4-diOMe	6-F	84	83[a]
9	**11i/8i**	*t*-Bu	4-OH, 3-OMe	H	87	85[a]
10	**11j/8j**	Cy	4-OH, 3-OMe	H	67	78[b]
11	**11k/8k**	*t*-Bu	4-OH, 3-OMe	4-Me	70	82[b]
12	**11l/8l**	*t*-Bu	4-OH, 3-OMe	5-MeO	71	80[b]
13	**11m/8m**	*t*-Bu	4-OH, 3-OMe	4,5-diMeO	72	65[b]
14	**11n/8n**	*t*-Bu	4-OH, 3,5-diMeO	H	79	77[b]
15	**11o/8o**	Cy	4-OH, 3,5-diMeO	H	76	86[b]
16	**11p/8p**	*t*-Bu	4-OH, 3,5-diMeO	4,5-diMeO	78	89[b]
17	**8q**	*t*-Bu	4-O$(CH_2)_2$Cl-3,5-diOMe	H	–	78[c]

[a]Condition A: Biphasic system of aqueous 50% KOH and PhMe, with 0.3% of TBAI as transfer catalyst. [b]Condition B: DBU (3 equiv) and TEA (2 equiv) in DCM. [c]Condition C: DBU (3 equiv) and TEA (2 equiv) in DCE.

amounts of the desired product **12a**. The catalytic system was then changed to $Pd(AcO)_2$, using triphenylphosphine and potassium carbonate as the ligand and the base, conditions which had been used previously in related Pd-mediated cascade processes.[29] Accordingly, the tricyclic compound **12a** was isolated in reasonable yield (58%). These conditions were then used as optimal, and the remaining dehydroalanines **11b–q** were then submitted to the C–C-bond-forming double-annulation cascade process. The outcome of these experiments is summarized in Table 2, with the expected tricyclic benzopyrrolizidines **12b–q** being obtained in moderate to good yields. It is noteworthy that neither the substituents in the benzylamine moiety nor hydroxylation of the cinnamic acid derivative had any notable effects on the cascade process. The best product yields, however, were observed for those tricyclic compounds (**12b**, **12e**, **12j**, and **12o**) that stemmed from *o*-bromobenzylamine itself. Additionally, variation of the structure of the isocyanide in the initial Ugi 4-CR made no difference in the overall yields of the benzopyrrolizidines.

The structures of the compounds were identified by their NMR, IR and mass spectrometric data (see Experimental Section and Supporting Information), and in the case of compounds **12c** and **12q**, the structures were further corroborated through single-crystal X-ray analyses (Figure 2).[30] With the help of this technique, a *Z* geometry in the exocyclic double bond was established. A plausible explanation for this stereoselectivity is depicted in Scheme 2. After the second 5-exo-trig cyclization, the σ bond of the palladium intermediate **12** rotates to attain the proper conformation in **13** to undergo the *syn*-β-hydride elimination, thus allowing the observed inversion of the geometry of the double bond.

In Vitro Antioxidant Scavenging. It is well-documented that oxidative stress either causes or enhances several chronic diseases, including obesity, cancer, aging, inflammation, neurodegenerative disorders, and cardiovascular illnesses[31] and is a widely accepted participant in the development and progression of diabetes and its complications.[32,33] Accordingly, benzopyrrolizidines **12i–p**, having a hydroxyl at the para position, may serve as scavengers of ROS. As a first approach to measure the in vitro antioxidant activity of this series of compounds, we performed the DPPH (2,2-diphenyl-1-picrylhydrazyl radical) test[34,35] and expressed the results in terms of the percentage of radical scavenging [Table 3 and Table S1 in the Supporting Information (SI)]. As expected, none of the benzopyrrolizidines derived from cinnamic and dimethoxycinnamic acids or the alkylated **12q** scavenged DPPH radical, even at 100 μM (Table S1, SI), while compounds bearing an alcohol group at the para position (compounds **12i–p**), however, showed antioxidant activity ranging from 34 to 67% (Table 3). The effect was dose-dependent and the sinapinic derivatives **12n–p** exhibited higher effects. Interestingly, the other substituents in the tricyclic core had only a minimum effect on the global activity. The IC_{50} values and dose–response curves of the most active compounds (**12n–p**) are shown in Table 3 and Figure S1 (SI), respectively, and ranged from 65.82 to 76.45 μM, which are comparable to the activity of butylhydroxytoluene (BHT), a well-known antioxidant.

In addition, we were interested in evaluating the potential capability of the compounds to inhibit lipid peroxidation, as measured by the thiobarbituric acid reactive substances (TBARS) assay.[36] The percentage of lipid peroxidation inhibition is reported in Table 3. Again, the hydroxylated

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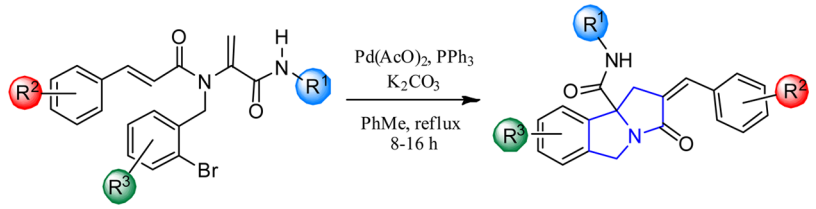
Table 2. Synthesis of Benzopyrrolizidines 12a−q



12a (58%) **12b** (73%) **12c** (58%) **12d** (53%)

12e (64%) **12f** (59%) **12g** (63%) **12h** (42%)

12i (60%) **12j** (77%) **12k** (56%) **12l** (63%)

12m (54%) **12n** (56%) **12o** (74%)

12p (47%) **12q** (45%)

analogues **12i−p** were the most active, with an inhibition ranging from 74 to 96%. The IC_{50} values of the compounds that showed an inhibition higher than 80% are reported in Table 3 and Figure S2 (SI). These compounds are effective in the prevention of lipid peroxidation due to their micromolar IC_{50} values, and the most active compound was **12o** (IC_{50} of 8.26 μM), which has a value similar to that observed for the potent antioxidant α-tocopherol. The data obtained herein suggest that the hydroxylated benzopyrrolizidines **12i−p** are novel antioxidant entities with potential application in the treatment of several chronic diseases in which oxidative stress is involved.

■ CONCLUSIONS

A three-step protocol featuring a cascade palladium-catalyzed 5-exo/5-exo Heck cyclization of Ugi-derived dienes was developed. This process led to the facile preparation of diversely substituted heterocyclic scaffolds that incorporate a benzopyrrolizidine-fused system along with an embedded

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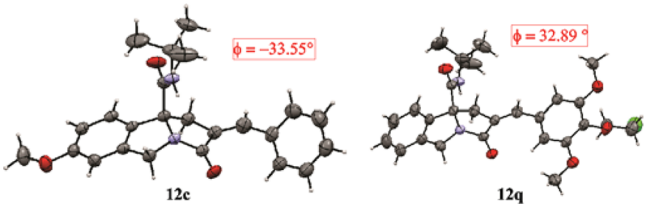
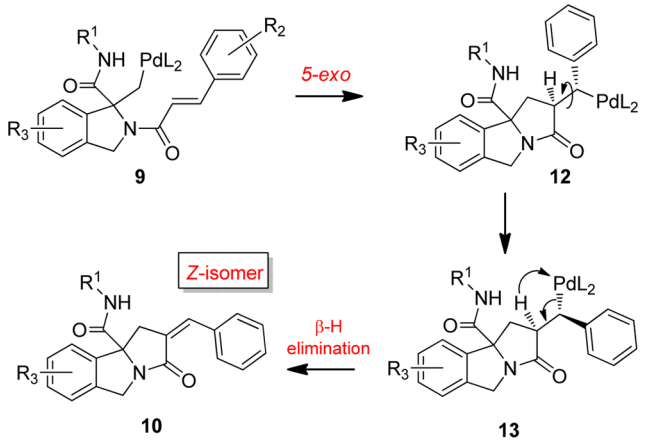


Figure 2. Single-crystal X-ray analysis of **12c** and **12q**. The dihedral angle of the conjugated carbonyl system is shown.

Scheme 2. Plausible Mechanism for *Z*-Isomer Formation



cinnamic acid derivative, two privileged medicinal chemical motifs. Furthermore, the compounds were tested in two in vitro antioxidant models (DPPH and TBARS assays). Those compounds bearing a hydroxyl group showed the most efficient inhibition of lipid peroxidation in the TBARS model. Therefore, benzopyrrolizidines **12i–p** might be considered excellent candidates for further optimization. Although the specific tricyclic core present in these novel heterocyclic scaffolds is not present, as far as we know, in natural products, their synthesis and biological evaluation streamlines the exploration of the molecular diversity in the chemical space.

EXPERIMENTAL SECTION

General Information. The progress of reactions and the purity of final products were monitored by thin layer chromatography (TLC), and UV and sulfuric vanillin were used as revealing agents. For ^{1}H and ^{13}C NMR spectra, $CDCl_3$ was used as solvent, with an internal tetramethylsilane standard (δ = 0.0 for ^{1}H). NMR coupling constants are reported in hertz (Hz), while chemical shifts (δ) are reported in ppm relative to the solvent signal. Signal splitting patterns are described as singlet (s), doublet (d), quartet (q) broad signal (br s), doublet of doublet (dd), multiplet (m), or complex signal (comp). High-resolution mass spectra were recorder with a liquid chromatograph–time of flight mass spectrometer with a DART (direct analysis in real time) ion source. IR spectra were obtained on a universal diamond ATR top-plate (solids) or in $CHCl_3$ solution (oils).

General Procedure for the Ugi 4-CR. In a round-bottom flask, benzoyloxyacetaldehyde (1.8 mmol) and the corresponding benzylamine (1.8 mmol) were dissolved in anhydrous methanol (10 mL); TEA (1.8 mmol) was added when using the hydrochloride. The mixture was stirred for 1 h at room temperature under an argon atmosphere. Then, the corresponding acid (1.5 mmol) was added; after 15 min, the isocyanide (1.5 mmol) was added and the reaction was allowed to stir for 2 d at room temperature. The solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane (20 mL), washed with 10% aqueous $NaHCO_3$ (2 × 10 mL portions), dried with Na_2SO_4, and evaporated. The crude product was purified by flash chromatography.

*2-{(2-Bromobenzyl)-[(2E)-3-phenylprop-2-enoyl]amino}-3-(tert-butylamino)-3-oxopropyl Benzoate (**11a**).* Pale brown solid; yield 841 mg (83%) after purification by flash column chromatography (hexane–AcOEt 85:15); mp 128–130 °C; IR ν (cm^{-1}) 3227, 3063, 2969, 2931, 1724, 1650, 1542, 1452, 1273, 1213, 1114, 1027, 755, 712; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.32 (s, 9H), 4.60–4.52 (m, 1H), 4.79–4.72 (m, 1H), 4.87 (s, 2H), 5.45 (br s, 1H), 6.31 (s, 1H), 6.57 (d, J = 15 Hz, 1H), 7.15–7.09 (comp, 2H), 7.36–7.30 (comp, 5H), 7.44–7.39 (comp, 2H), 7.60–7.53 (comp, 3H), 7.80 (d, J = 15.3 Hz, 1H), 7.95 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.7, 49.5, 51.7, 57.6, 62.1, 116.9, 122.2, 127.1, 127.8, 128.2, 128.5, 128.9, 129.8, 130.3, 133.2, 134.7, 136.1, 145.2, 166.1, 167.5, 169.0; MS (DART+) m/z 563 (M + H); HRMS m/z calcd for $C_{30}H_{32}{}^{79}BrN_2O_4$ [M + H] 563.1545, found 563.1541.

*2-{(2-Bromobenzyl)-[(2E)-3-phenylprop-2-enoylamino}]-3-[(2,6-dimethylphenyl)amino]-3-oxopropyl Benzoate (**11b**).* White solid; yield 924 mg (84%) after purification by flash column chromatography (hexane–AcOEt 80:20); mp 155–157 °C; IR ν (cm^{-1}) 3264, 3062, 3026, 2922, 1723, 1649, 1601, 1449, 1269, 1218, 1112, 1027, 771, 711; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 2.22 (s, 6H), 4.69–4.62(m, 1H), 4.93–4.85 (m, 3H), 5.67 (br s, 1H), 6.62 (d, J = 15.6 Hz, 1H), 7.15–7.08 (m, 6H), 7.46–7.35 (m, 8H), 7.62–7.55 (m, 3H), 7.87 (d, J = 15.3 Hz, 1H), 7.97 (d, J = 8.1 Hz, 2H), 8.16 (br s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 18.6, 50.2, 57.6, 62.0, 116.6, 122.2, 127.5, 127.9, 128.2, 128.3, 128.5, 128.6, 128.9, 129.4, 129.5, 129.6, 129.8, 130.0, 133.1, 133.3, 133.7, 134.5, 135.2, 165.9, 167.1, 169.5; MS (FAB +) m/z 611 (M + H); HRMS m/z calcd for $C_{34}H_{32}{}^{79}BrN_2O_4$ [M + H] 611.1545, found 611.1524.

*2-{(2-Bromo-5-methoxybenzyl)-[(2E)-3-phenylprop-2-enoyl]-amino}-3-(tert-butylamino)-3-oxopropyl Benzoate (**11c**).* Yellow solid; yield 843 mg (79%) after purification by flash column chromatography (hexane–AcOEt 85:15); mp 41–43 °C; IR ν (cm^{-1}) 3326, 3063, 2966, 2931, 1723, 1681, 1650, 1602, 1453, 1274, 1114, 712; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.32 (s, 9H), 3.57 (s, 3H), 4.61–4.49 (m, 1H), 4.80–4.74 (m, 1H), 4.83 (s, 2H),

Table 3. DPPH Scavenging and Lipid Peroxidation Inhibition of the Most Active Compounds 12i–p

	% DPPH scavenging				TBARS test	
compd	100 μM	10 μM	1 μM	IC_{50}	inhibn at 50 μM (%)	IC_{50} (μM)[a]
12i	40.74	3.88	−4.86	ND	74.49	45.48 ± 1.78
12j	48.52	9.67	1.20	ND	95.44	24.60 ± 0.81
12k	34.43	3.69	−0.77	ND	93.44	35.49 ± 2.35
12l	41.34	9.72	−0.31	ND	74.55	ND
12m	40.87	7.85	1.72	ND	78.22	ND
12n	60.40	7.15	−6.06	67.06 ± 7.11	97.15	12.71 ± 0.86
12o	63.55	11.70	2.03	76.45 ± 3.59	96.23	8.26 ± 0.63
12p	66.50	9.80	0.67	65.82 ± 4.88	92.46	31.89 ± 2.46

[a]IC_{50} are reported as mean ± standard error (SEM) of n observations (n = 3). ND: not determined.

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5.47−5.37 (m, 1H), 6.27 (s, 1H), 6.60 (d, J = 15.6 Hz, 1H), 6.79−6.64 (m, 1H), 6.92 (br s, 1H), 7.43−7.34 (comp, 7H), 7.47 (d, J = 8.7 Hz, 1H), 7.57−7.52 (comp, 2H), 7.80 (d, J = 15.3 Hz, 1H), 7.97 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.7, 29.9, 49.6, 51.7, 55.5, 57.7, 62.2, 112.3, 113.9, 115.2, 116.9, 128.3, 128.5, 128.6, 129.0, 129.7, 130.3, 133.3, 133.5, 133.8, 134.8, 137.2, 145.2, 159.4, 166.2, 167.5, 168.9; MS (DART+) m/z 593 (M + H); HRMS m/z calcd for $C_{31}H_{34}{}^{79}BrN_2O_5$ [M + H] 593.1651, found 593.1629.

*2-{(2-Bromobenzyl)-[(2E)-3-(3,4-dimethoxyphenyl)prop-2-enoyl]-amino}-3-(tert-butylamino)-3-oxopropyl Benzoate (**11d**).* White solid; yield 852 mg (76%) after purification by flash column chromatography (hexane−AcOEt 80:20); mp 155−157 °C; IR ν (cm^{-1}) 3306, 3062, 2964, 2930, 1716, 1692, 1646, 1583, 1513, 1444, 1272, 1024, 712; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.33 (s, 9H), 3.80 (s, 3H), 3.87 (s, 3H), 4.81−4.54 (m, 2H), 4.88 (s, 2H), 5.48 (m, 1H), 6.41−6.35 (comp, 2H), 6.99−6.79 (comp, 3H), 7.11 (m, 1H), 7.43−7.31 (comp, 4H), 7.58−7.52 (m, 2H), 7.71 (d, J = 15.3 Hz, 1H), 7.96 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.7, 49.4, 51.7, 55.9, 56.0, 57.5, 62.1, 110.0, 111.1, 114.8, 122.1, 122.5, 127.8, 127.9, 128.5, 129.2, 129.8, 130.2, 133.1, 133.3, 133.4, 136.5, 144.9, 149.2, 151.1, 166.1, 167.6, 169.2; MS (FAB+) m/z 623 (M + H); HRMS m/z calcd for $C_{32}H_{36}{}^{79}BrN_2O_6$ [M + H] 623.1757, found 623.1749.

*2-{(2-Bromobenzyl)-[(2E)-3-(3,4-dimethoxyphenyl)prop-2-enoyl]-amino}-3-(cyclohexylamino)-3-oxopropyl Benzoate (**11e**).* Pale yellow solid; yield 958 mg (82%) after purification by flash column chromatography (hexane−AcOEt 75:25); mp 70−72 °C; IR ν (cm^{-1}) 3301, 3063, 2930, 2853, 1721, 1644, 1594, 1512, 1446, 1261, 1023, 729, 711; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.96−1.09 (m, 10H), 3.74 (br s, 1H), 3.81 (s, 3H), 3.88 (s, 3H), 4.66−4.58 (m, 1H), 4.83−4.76 (m, 1H), 4.87 (s, 2H), 5.52 (br s, 1H), 6.47−6.36 (comp, 2H), 6.80 (br s, 2H), 7.0−6.98 (m, 1H), 7.15−7.07 (comp, 2H), 7.44−7.35 (comp, 3H), 7.59−7.53 (comp, 2H), 7.72 (d, J = 15.3 Hz, 1H), 7.96 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 24.8, 25.6, 33.0, 48.4, 49.6, 55.9, 56.1, 57.2, 62.1, 110.0, 111.1, 114.8, 122.1, 122.5, 127.7, 127.9, 128.4, 128.5, 129.3, 129.8, 133.1, 133.3, 136.3, 145.0, 149.2, 152.1, 166.1, 167.5, 169.2; MS (FAB+) m/z 649 (M + H); HRMS m/z calcd for $C_{34}H_{38}{}^{79}BrN_2O_6$ [M + H] 649.1913, found 649.1921.

*2-{(2-Bromo-5-methoxybenzyl)-[(2E)-3-(3,4-dimethoxyphenyl)-prop-2-enoyl]amino}-3-(tert-butylamino)-3-oxopropyl Benzoate (**11f**).* Yellowish solid; yield 917 mg (78%) after purification by flash column chromatography (hexane−AcOEt 80:20); mp 108−110 °C; IR ν (cm^{-1}) 3370, 3082, 2953, 2930, 1712, 1667, 1649, 1592, 1452, 1257, 1141, 1104, 1024, 854, 714; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.34 (s, 9H), 3.57 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 4.61−4.51 (m, 1H), 4.81−4.75 (m, 1H), 4.83 (s, 2H), 5.45 (br s, 1H), 6.30 (s, 1H), 6.42 (d, J = 15.3 Hz, 1H), 6.67−6.64 (m, 1H), 6.86−6.80 (comp, 2H), 7.02−6.96 (comp, 2H), 7.41 (t, J = 7.5 Hz, 2H), 7.46 (d, J = 8.7 Hz, 1H), 7.58−7.53 (m, 1H), 7.72 (d, J = 15 Hz, 1H), 7.98 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.7, 49.5, 51.8, 55.5, 56.0, 56.1, 57.7, 62.2, 110.0, 111.,1 113.9, 114.8, 115.4, 122.5, 123.2, 127.8, 128.5, 129.9, 133.3, 133.7, 137.6, 144.9, 146.8, 149.2, 151.1, 159.5, 166.2, 167.7, 169.1; MS (DART+) m/z 653 (M + H); HRMS m/z calcd for $C_{33}H_{38}{}^{79}BrN_2O_7$ [M + H] 653.1862, found 653.1852.

*2-{(2-Bromo-5-fluorobenzyl)-[(2E)-3-(3,4-dimethoxyphenyl)prop-2-enoyl]amino}-3-(tert-butylamino)-3-oxopropyl Benzoate (**11g**).* White solid; yield 877 mg (76%) after purification by flash column chromatography (hexane−AcOEt 75:25); mp 126−128 °C; IR ν (cm^{-1}) 3344, 3068, 2968, 2936, 1722, 1680, 1648, 1600, 1514, 1454, 1268, 1159, 1112, 1027, 756, 713; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.34 (s, 9H), 3.82 (s, 3H), 3.88 (s, 3H), 4.59−4.52 (m, 1H), 4.82−4.73 (m, 1H), 4.89 (s, 2H), 5.57 (br s, 1H), 6.32 (d, J = 15 Hz, 1H), 6.48 (br s, 1H), 6.92−6.79 (comp, 3H), 6.99 (br s, 1H), 7.15 (dd, J = 9 and 3 Hz, 1H), 7.47−7.41 (comp, 2H), 7.56−7.51 (comp, 2H), 7.71 (d, J = 15 Hz, 1H), 7.98 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.6, 48.9, 51.8, 55.9, 56.0, 57.1, 62.0, 110.0, 111.1, 114.3, 115.85 (d, J = 7.5 Hz), 116.4 (d, J = 22.5 Hz), 122.5, 127.6, 128.5, 129.5, 129.8, 130.2, 133.3, 134.4 (d, J = 7.5 Hz), 139.2 (d, J = 7.5 Hz), 145.3, 149.2, 151.2, 162.4 (d, J = 247.5 Hz), 166.1, 167.5, 169.0; MS (DART+) m/z 641 (M + H); HRMS m/z calcd for $C_{32}H_{35}{}^{79}BrFN_2O_6$ [M + H] 641.1663, found 641.1638.

*2-{(2-Bromo-6-fluorobenzyl)-[(2E)-3-(3,4-dimethoxyphenyl)prop-2-enoyl]amino}-3-(tert-butylamino)-3-oxopropyl Benzoate (**11h**).* White solid; yield 969 mg (84%) after purification by flash column chromatography (hexane−AcOEt 80:20); mp 164−166 °C; IR ν (cm^{-1}) 3290, 3075, 2961, 2868, 1718, 1687. 1646, 1568, 1513, 1449, 1271, 1227, 1025, 803, 712; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.29 (s, 9H), 3.84 (s, 3H), 3.89 (s, 3H), 4.71−4.61 (m, 1H), 4.88−4.71 (m, 3H), 5.35 (br s, 1H), 6.34 (s, 1H), 6.60 (d, J = 15.3 Hz, 1H), 6.90−6.81 (comp, 2H), 7.09−6.97 (comp, 3H), 7.43−7.38 (comp, 2H), 7.57−7.52 (m, 1H), 7.72 (d, J = 15 Hz, 1H), 7.97 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.5, 43.3, 51.5, 55.9, 56.0, 57.9, 62.0, 110.0, 111.1, 114.7, 115.6 (d, J = 23 Hz), 122.3, 124.6, 127.8, 128.4, 129.7, 133.2, 144.7, 149.2, 151.1, 166.1, 167.6, 168.9; MS (DART+) m/z 641 (M + H); HRMS m/z calcd for $C_{32}H_{34}{}^{79}BrFN_2O_6$ [M + H] 641.1657, found 641.1638.

*2-{(2-Bromobenzyl)-[(2E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoyl]amino}-3-(tert-butylamino)-3-oxopropyl Benzoate (**11i**).* White solid; yield 954 mg (87%) after purification by flash column chromatography (hexane−AcOEt 75:25); mp133−135 °C; IR ν (cm^{-1}) 3325, 3066, 2967, 2931, 1722, 1680, 1592, 1515, 1453, 1273, 1209, 1028, 754, 712; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.33 (s, 9H), 3.84 (s, 3H), 4.80−4.51 (m, 2H), 4.87 (s, 2H), 5.47 (m, 1H), 5.85 (s, 1H), 6.38 (comp, 2H), 7.04−6.80 (m, 3H), 7.24−7.13 (m, 1H,), 7.44−7.29 (comp, 4H), 7.59−7.53 (comp, 2H), 7.70 (d, J = 15.3 Hz, 1H), 7.97 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.8, 49.4, 51.7, 56.0, 57.6, 62.1, 109.8, 114.5, 114.8, 122.8, 127.4, 127.7, 127.9, 128.5, 129.0, 129.3, 129.7, 129.8, 133.1, 133.3, 145.1, 146.8, 148.0, 166.1, 167.7, 169.2; MS (DART+) m/z 609 (M + H); HRMS m/z calcd for $C_{31}H_{34}{}^{79}BrN_2O_6$ [M + H] 609.1600, found 609.1568.

*2-{(2-Bromobenzyl)-[(2E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoyl]amino}-3-(cyclohexylamino)-3-oxopropyl Benzoate (**11j**).* White solid; yield 766 mg (67%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 79−81 °C; IR ν (cm^{-1}) 3292, 3065, 2928, 2853, 1719, 1642, 1587, 1268, 1112, 1027, 710; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.35−1.14 (m, 4H), 1.66−1.51 (m, 4H), 1.95−1.77 (m, 2H), 3.71 (br s, 1H), 3.80 (s, 3H), 4.64−4.58 (m, 1H), 4.81−4.74 (m, 1H), 4.91 (s, 2H), 5.51 (br s, 1H), 5.92 (br s, 1H), 6.37 (d, J = 15.3 Hz, 1H), 6.48 (d, J = 8.4 Hz, 1H), 6.93−6.79 (comp, 3H), 7.12 (br s, 1H), 7.44−7.38 (comp, 3H), 7.59−7.53 (comp, 3H), 7.71 (d, J = 15.3 Hz, 1H), 7.96 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 24.8, 25.5, 32.8, 48.5, 55.9, 57.1, 62.2, 109.8, 114.3, 114.9, 122.1, 122.8, 127.2, 127.9, 128.3, 128.5, 129.2, 129.7, 129.8, 130.1, 133.1, 133.3, 136.4, 145.2, 146.9, 148.1, 166.1, 167.5, 169.3; MS (FAB+) m/z 635 (M + H); HRMS m/z calcd for $C_{33}H_{36}{}^{79}BrN_2O_6$ [M + H] 635.1757, found 635.1750.

*2-{(2-Bromo-4-methylbenzyl)-[(2E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoyl]amino}-3-(tert-butylamino)-3-oxopropyl Benzoate (**11k**).* Pale brown solid; yield 785 mg (70%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 85−87 °C; IR ν (cm^{-1}) 3311, 3066, 3012, 2967, 1719, 1676, 1644, 1587, 1513, 1452, 1268, 1214, 1116, 1031, 769, 710; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.33 (s, 9H), 2.26 (s, 3H), 3.85 (s, 3H), 4.62−4.51 (m, 1H), 4.70−4.76 (m, 1H), 4.83 (s, 2H), 5.43 (br s, 1H), 5.89 (s, 1H), 6.36 (s, 1H), 6.41 (d, J = 15.3 Hz, 1H), 7.06−6.82 (comp, 4H), 7.19 (d, J = 7.5 Hz, 1H), 7.44−7.39 (comp, 3H), 7.58−7.53 (m, 1H), 7.70 (d, J = 15.3 Hz, 1H), 7.96 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 20.7, 28.7, 49.3, 51.7, 56.0, 57.7, 62.2, 110.0, 114.5, 114.9, 121.9, 122.8, 127.4, 128.2, 128.5, 128.7, 129.8, 130.2, 133.3, 133.5, 139.4, 145.0, 146.9, 148.0, 166.1, 167.7, 169.2; MS (FAB+) m/z 623 (M + H); HRMS m/z calcd for $C_{32}H_{36}{}^{79}BrN_2O_6$ [M + H] 623.1757, found 623.1750.

*2-{(2-Bromo-5-methoxybenzyl)-[(2E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoyl]amino}-3-(tert-butylamino)-3-oxopropyl Benzoate (**11l**).* Yellow solid; yield 817 mg (71%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 158−160 °C; IR ν (cm^{-1}) 3325, 3069, 3010, 2968, 2938, 1721, 1678, 1646, 1594, 1274, 1123, 1028, 756, 713; ^{1}H NMR ($CDCl_3$/

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TMS, 300 MHz) δ 1.33 (s, 9H), 3.57 (s, 3H), 3.85 (s, 3H), 4.63−4.50 (m, 1H), 4.70−4.74 (m, 1H), 4.82 (s, 2H), 5.44 (br s, 1H), 5.89 (s, 1H), 6.30 (s, 1H), 6.40 (d, J = 15 Hz, 1H), 6.67−6.64 (m, 1H), 6.98−6.82 (comp, 4H), 7.43−7.38 (comp, 2H), 7.46 (d, J = 8.7 Hz, 1H), 7.57−7.52 (m, 1H), 7.70 (d, J = 15 Hz, 1H), 7.97 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.6, 49.5, 51.7, 55.5, 56.0, 57.6, 62.3, 109.9, 112.2, 114.4, 114.9, 115.3, 122.9, 127.3, 128.5, 129.9, 130.2, 133.2, 133.5, 133.7, 137.6, 145.2, 146.9, 148.1, 159.5, 166.2, 167.6, 169.3; MS (DART+) m/z 639 (M + H); HRMS m/z calcd for $C_{32}H_{36}{}^{79}BrN_2O_7$ [M + H] 639.1706, found 639.1700.

*2-{(2-Bromo-4,5-dimethoxybenzyl)-[(2E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoyl]amino}-3-(tert-butylamino)-3-oxopropyl Benzoate (**11m**).* White solid.Yield: 867 mg (72%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 74−77 °C; IR ν (cm^{-1}) 3223, 3065, 2963, 2923, 2847, 1718, 1675, 1643, 1589, 1507, 1261, 1204, 1116, 1028, 711; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.30 (m, 9H), 3.81 (m, 9H), 4.71−4.56 (m, 1H), 4.89−4.75 (comp, 3H), 5.35 (br s, 1H), 6.47 (br s, 1H), 6.97−6.62 (comp, 3H), 6.99 (s, 2H), 7.44−7.34 (m, 2H), 7.55−7.49 (m, 1H), 7.70 (d, J = 15 Hz, 1H), 7.93 (br s, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.6, 49.6, 51.6, 56.0, 56.2, 56.3, 58.2, 62.6, 109.7, 110.0, 111.6, 112.1, 114.3, 114.9, 115.7, 122.7, 123.4, 127.2, 128.5, 129.7, 130.1, 133.3, 145.2, 146.9, 148.1, 149.2, 166.2, 167.7, 169.3; MS (FAB +) m/z 669 (M + H); HRMS m/z calcd for $C_{33}H_{38}{}^{79}BrN_2O_8$ [M + H] 669.1812, found 669.1801.

*2-{(2-Bromobenzyl)-[(2E)-3-(4-hydroxy-3,5-dimethoxyphenyl)-prop-2-enoyl]amino}-3-(tert-butylamino)-3-oxopropyl Benzoate (**11n**).* White solid; yield 907 mg (79%) after purification by flash column chromatography (hexane−AcOEt 75:25); mp 153−155 °C; IR ν (cm^{-1}) 3521, 3349, 3066, 2968, 2938, 1721, 1680, 1647, 1606, 1515, 1454, 1273, 1219, 1115, 1027, 753, 713; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.34 (s, 9H), 3.83 (s, 6H), 4.64−4.57 (m, 1H), 4.84−4.75 (m, 1H), 4.89 (s, 2H), 5.48 (br s, 1H), 5.73 (s, 1H), 6.39−6.34 (comp, 2H), 6.57 (s, 2H), 7.17−7.09 (comp, 2H), 7.45−7.39 (comp, 3H), 7.59−7.54 (comp, 2H), 7.66 (d, J = 15 Hz, 1H), 7.97 (d, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.8, 49.5, 51.8, 56.4, 57.7, 62.2, 105.2, 115.1, 122.1, 126.4, 128.0, 128.6, 129.3, 129.8, 133.1, 133.3, 136.7, 137.2, 145.1, 147.3, 166.1, 167.6, 169.1; MS (FAB +) m/z 639 (M + H); HRMS m/z calcd for $C_{32}H_{36}{}^{79}BrN_2O_7$ [M + H] 639.1706, found 639.1702.

*2-{(2-Bromobenzyl)-[(2E)-3-(4-hydroxy-3,5-dimethoxyphenyl)-prop-2-enoyl]amino}-3-(cyclohexylamino)-3-oxopropyl Benzoate (**11o**).* Pale brown solid; yield 910 mg (76%) after purification by flash column chromatography (hexane−AcOEt 65:35); mp 84−86 °C; IR ν (cm^{-1}) 3311, 3065, 3006, 2932, 2853, 1720, 1647, 1606, 1514, 1453, 1272, 1115, 753, 713; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.36−1.15 (m, 4H), 1.75−1.50 (m, 3H), 1.96−1.79 (m, 2H), 3.71 (bs, 1H), 3.82 (s, 6H), 4.65 (dd, J = 12 and 8.4 Hz, 1H,), 4.83−4.78 (m, 1H), 4.92 (s, 2H), 5.57 (br s, 1H), 6.36 (d, J = 15 Hz, 1H), 6.75−6.55 (comp, 2H), 7.12 (comp, 2H), 7.47−7.36 (comp, 4H), 7.63−7.57 (comp, 3H), 7.66 (d, J = 15.3 Hz, 1H), 7.98−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 24.8, 25.5, 32.8, 48.5, 49.5, 56.4, 57.1, 62.2, 105.2, 114.9, 122.0, 126.2, 127.9, 128.5, 129.2, 129.8, 130.1, 133.0, 133.3, 136.5, 137.2, 145.2, 147.3, 166.1, 167.4, 169.1; MS (FAB+) m/z 665 (M + H); HRMS m/z calcd for $C_{34}H_{38}{}^{79}BrN_2O_7$ [M + H] 665.1862, found 665.1855.

*2-{(2-Bromo-4,5-dimethoxybenzyl)-[(2E)-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoyl]amino}-3-(tert-butylamino)-3-oxopropyl benzoate (**11p**).* Yellow solid; yield 981 mg (78%) after purification by flash column chromatography (hexane−AcOEt 60:40); mp 88−89 °C; IR ν (cm^{-1}) 3349, 3066, 2964, 2840, 1718, 1677, 1602, 1507, 1454, 1260, 1206, 1111, 1027, 910, 712; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.34 (s, 9H), 3.92−3.85 (comp, 12H), 4.81−4.62 (comp, 2H), 4.85 (br s, 2H), 5.29 (br s, 1H), 5.76 (s, 1H), 6.33 (s, 1H), 6.49 (d, J = 15.6 Hz, 1H), 6.62 (s, 2H), 6.92 (s, 1H), 7.02 (s, 1H), 7.44−7.39 (comp, 2H), 7.58−7.53 (m, 1H), 7.69 (d, J = 15.3 Hz, 1H), 7.95 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.7, 29.7, 49.7, 51.6, 56.4, 58.5, 62.6, 105.3, 115.0, 115.7, 126.3, 128.4, 129.6, 129.7, 130.1, 133.3, 137.3, 145.1, 147.3, 149.2, 166.3, 167.7, 169.0; MS (FAB+) m/z 699 (M + H); HRMS m/z calcd for $C_{34}H_{40}{}^{79}BrN_2O_9$ [M + H] 699.1917, found 699.1920.

General Procedure for the Elimination Reaction A. To a suspension of the corresponding Ugi adduct (0.75 mmol) and TBAI (0.225 mmol of) in toluene (12 mL) was added a 50% aqueous solution of KOH (9 mL). The heterogeneous mixture was vigorously stirred until the completion of the reaction (3−7 h). The organic layer was separated and sequentially washed with 1 N HCl (2 × 10 mL portions) and saturated NaCl solution (10 mL). The solvent was dried with Na_2SO_4 and evaporated. The crude diene was purified by flash chromatography.

General Procedure for the Elimination Reaction B. To a stirred solution of the corresponding Ugi adduct (0.5 mmol) in dichloromethane (10 mL) were added DBU (1.5 mmol) and TEA (1 mmol). The mixture was vigorously stirred until the starting material was consumed. Then, the solution was sequentially washed with 0.1 N HCl (2 × 10 mL portions) and saturated NaCl solution (10 mL). The organic layer was dried with Na_2SO_4 and evaporated. The crude diene was purified by flash chromatography.

General Procedure for the Elimination Reaction C. To a stirred solution of the corresponding Ugi adduct (0.5 mmol) in dichloroethane (10 mL) were added DBU (1.5 mmol) and TEA (1 mmol). The mixture was stirred at 50 °C for 12 h. Then, the solution was sequentially washed with 0.1 N HCl (2 × 10 mL portions) and saturated NaCl solution (10 mL). The organic layer was dried with Na_2SO_4 and evaporated. The crude diene was purified by flash chromatography.

*(2E)-N-(2-Bromobenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-phenylprop-2-enamide (**8a**).* The title compound was prepared according to elimination method A. White solid; yield 198 mg (90%) after purification by flash column chromatography (hexane−AcOEt 85:15); mp 127−128 °C; IR ν (cm^{-1}) 3343, 3086, 2965, 2927, 1661, 1602, 1523, 1365, 1341, 1190, 980, 762; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.17 (s, 9H), 5.06 (s, 2H), 5.51 (s, 1H), 5.74 (s, 1H), 6.44 (s, 1H), 6.60 (d, J = 15.6 Hz, 1H), 7.18 (td, J = 7.5 and 1.8 Hz, 1H), 7.31 (td, J = 7.5 and 1.2 Hz, 1H), 7.38−7.34 (comp, 3H), 7.49−7.44 (comp, 3H), 7.57 (dd, J = 7.95 and 1.5 Hz, 1H), 7.79 (d, J = 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.4, 51.6, 51.9, 117.3, 123.0, 124.7, 128.2, 128.3, 129.0, 129.9, 130.3, 132.0, 133.2, 134.7, 136.1, 142.7, 144.3, 162.5, 166.5; MS (DART+) m/z 441 (M + H); HRMS m/z calcd for $C_{23}H_{26}{}^{79}BrN_2O_2$ [M + H] 441.1178, found 441.1172.

*(2E)-N-(2-Bromobenzyl)-N-[3-(2,6-dimethylphenylamino)-3-oxoprop-1-en-2-yl]-3-phenylprop-2-enamide (**8b**).* The title compound was prepared according to elimination method A. White solid; yield 171 mg (70%) after purification by flash column chromatography (hexane−AcOEt 80:20); mp 197−199 °C; IR ν (cm^{-1}) 3292, 3120, 3025, 2915, 1651, 1605, 1494, 1393, 1232, 1209, 1044, 981, 766, 746; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 2.07 (s, 6H), 5.16 (s, 2H), 5.43 (s, 1H), 6.57 (s, 1H), 6.82 (d, J = 15.3 Hz, 1H), 7.18−7.00 (comp, 4H), 7.36−7.25 (comp, 5H), 7.46−7.43 (comp, 2H), 7.55−7.52 (m, 1H), 7.78 (d, J = 15.6 Hz, 1H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 18.6, 51.2, 117.0, 124.5, 125.8, 127.7, 128.1, 128.3, 128.4, 129.0, 129.7, 130.5, 131.3, 133.16, 133.19, 134.5, 133.5, 135.8, 140.6, 145.1, 161.6, 166.6; MS (DART+) m/z 489 (M + H); HRMS m/z calcd for $C_{27}H_{26}{}^{79}BrN_2O_2$ [M + H] 489.1178, found 489.1176.

*(2E)-N-(2-Bromo-5-methoxybenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-phenylprop-2-enamide (**8c**).* The title compound was prepared according to elimination method A. White solid; yield 191 mg (81%) after purification by flash column chromatography (hexane−AcOEt 85:15); mp 122−124 °C; IR ν (cm^{-1}) 3402, 3335, 3001, 2968, 2936, 1662, 1615, 1515, 1476, 1367, 1242, 761; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.18 (s, 9H), 3.77 (s, 3H), 5.02 (s, 2H), 5.51 (s, 1H), 5.75 (s, 1H), 6.43 (s, 1H), 6.60 (d, J = 15.6 Hz, 1H), 6.74 (dd, J = 8.85 and 3.3 Hz, 1H), 7.044 (br s, 1H), 7.37−7.35 (comp, 3H), 7.45 (d, J = 8.7 Hz, 1H), 7.49−7.47 (comp, 2H), 7.79 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.4, 51.6, 51.9, 55.7, 114.8, 115.5, 117.4, 122.8, 128.3, 129.0, 130.3, 133.8, 134.7, 137.1, 142.7, 144.3, 147.2, 159.5, 162.6, 166.5; MS (DART+) m/z 471 (M + H); HRMS m/z calcd for $C_{24}H_{28}{}^{79}BrN_2O_3$ [M + H] 471.1283, found 471.1281.

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*(2E)-N-(2-Bromobenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-(3,4-dimetoxyphenyl)prop-2-enamide (**8d**).* The title compound was prepared according to elimination method A. Colorless oil; yield 175 mg (70%) after purification by flash column chromatography (hexane−AcOEt 85:15); IR ν (cm^{-1}) 3343, 3062, 2965, 2930, 1661, 1600, 1514, 1448, 1263, 1141, 1025, 752, 715; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.16 (s, 9H), 3.83 (s, 3H), 3.89 (s, 3H), 5.05 (s, 2H), 5.50 (s, 1H), 5.73 (s, 1H), 6.41 (s, 1H), 6.42 (d, J = 15 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 1.5 Hz, 1H), 7.07 (dd, J = 8.4 and 1.5 Hz, 1H), 7.17 (td, J = 7.8 and 1.5 Hz, 1H), 7−32−7.27 (m, 1H), 7.47−7.44 (m, 1H), 7.58−7.55 (m, 1H), 7.73 (d, J = 15 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.4, 51.6, 52.0, 56.0, 56.1, 110.0, 111.2, 115.0, 122.7, 124.6, 127.7, 128.0, 128.2, 129.8, 132.0, 133.2, 136.2, 142.8, 144.4, 149.3, 151.2, 162.7, 166.7; MS (FAB+) m/z 501 (M + H); HRMS m/z calcd for $C_{25}H_{30}{}^{79}BrN_2O_4$ [M + H] 501.1389, found 501.1375.

*(2E)-N-(2-Bromobenzyl)-N-[3-(cyclohexylamino)-3-oxoprop-1-en-2-yl]-3-(3,4-dimethoxyphenyl)prop-2-enamide (**8e**).* The title compound was prepared according to elimination method A. Pale yellow solid; yield 213 mg (81%) after purification by flash column chromatography (hexane−AcOEt 80:20); mp 164−166 °C; IR ν (cm^{-1}) 3332, 3042, 2927, 2851, 1659, 1613, 1588, 1264, 1137, 1021, 800, 758; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 0.89−1.12 (m, 2H), 1.34−1.21 (m, 2H), 1.74−1.54 (m, 6H), 3.75−3.64 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 5.05 (s, 2H), 5.50 (s, 1H). 5.97 (d, J = 8.1 Hz, 1H), 6.44 (d, J = 8.1 Hz, 1H), 6.45 (s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 1.8 Hz, 1H), 7.08 (dd, J = 8.1 Hz and 1.8, 1H), 7.16 (td, J = 7.5 Hz and 1.8, 1H), 7.32−7.27 (m, 1H), 7.45−7.42 (m, 1H), 7.55 (dd, J = 7.9 Hz and 1.2, 1H), 7.74 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 24.8, 25.4, 32.6, 48.8, 51.6, 56.0 (2C), 110.1, 111.1, 114.8, 122.5, 123.5, 124.5, 127.7, 128.0, 129.7, 131.7, 133.2, 135.9, 141.7, 144.5, 149.2, 151.1, 162.4, 166.7; MS (DART+) m/z 527 (M + H); HRMS m/z calcd for $C_{27}H_{32}{}^{79}BrN_2O_4$ [M + H] 527.1545, found 527.1547.

*(2E)-N-(2-Bromo-5-methoxybenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-(3,4-dimethoxyphenyl)prop-2-enamide (**8f**).* The title compound was prepared according to elimination method A. Colorless oil; yield 204 mg (77%) after purification by flash column chromatography (hexane−AcOEt 80:20); IR ν (cm^{-1}) 3401, 3339, 3002, 2966, 2937, 1661, 1615, 1599, 1514, 1465, 1264, 1141, 1025, 806, 755; 1H-NMR ($CDCl^3$/TMS, 300 MHz) δ 1.78 (s, 9H), 3.76 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 5.00 (s, 2H), 5.50 (s, 1H) 5.78 (s, 1H), 6.42 (d, J = 15 Hz, 1H), 6.39 (s, 1H), 6.72 (dd, J = 8.85 and 3 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 1.5 Hz, 1H), 7.02 (br s, 1H), 7.07 (dd, J = 8.1 and 1.8 Hz, 1H), 7.43 (d, J = 8.7 Hz, 1H), 7.72 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.4, 51.6, 51.9, 55.7, 56.0, 56.1, 110.0, 111.1, 114.7, 115.0, 115.4, 117.4, 122.5, 122.6, 127.7, 133.7, 137.2, 142.8, 144.3, 149.2, 151.1, 159.4, 162.8, 166.7; MS (DART+) m/z 531 (M + H); HRMS m/z calcd for $C_{26}H_{32}{}^{79}BrN_2O_5$ [M + H] 531.14945, found 531.1511.

*(2E)-N-(2-Bromo-5-fluorobenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-(3,4-dimethoxyphenyl)prop-2-enamide (**8g**).* The title compound was prepared according to elimination method A. Colorless oil; yield 213 mg (82%) after purification by flash column chromatography (hexane−AcOEt 70:30); IR ν (cm^{-1}) 3398, 3338, 3065, 2967, 2936, 1665, 1616, 1514, 1465, 1266, 1141, 1026, 808, 755; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.23 (s, 9H), 3.89 (s, 3H), 3.91 (s, 3H), 5.01 (s, 2H), 5.48 (s, 1H), 5.78 (s, 1H), 6.39 (s, 1H), 6.45 (d, J = 15.3 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 6.95−6.89 (m, 1H), 6.97 (d, J = 1.5 Hz, 1H), 7.10 (d, J = 8.4 and 1.8 Hz, 1H), 7.60−7.43 (comp, 2H), 7.74 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.5, 51.7, 51.8, 56.07, 56.1, 110.1, 111.2, 114.7, 117.0 (d, J = 22.5 Hz), 118.4 (d, J = 22.5 Hz), 122.7, 127.7, 128.7, 130.0, 133.7, 134.4 (d, J = 7.5 Hz), 138.4, 144.7, 149.3, 151.3, 162.3 (d, J = 247.5 Hz), 162.7, 166.9; MS (DART+) m/z 519 (M + H); HRMS m/z calcd for $C_{25}H_{29}{}^{79}BrFN_2O_4$ [M + H] 519.1295, found 519.1295.

*(2E)-N-(2-Bromo-6-fluorobenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-(3,4-dimethoxyphenyl)prop-2-enamide (**8h**).* The title compound was prepared according to elimination method A. Pale yellow solid; yield 215 mg (83%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 154−156 °C; IR ν (cm^{-1}) 3405, 3013, 2964, 2838, 1660, 1615, 1511, 1452, 1259, 1137, 1023, 762, 731; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.20 (s, 9H), 3.87 (s, 3H), 3.90 (s, 3H), 4.98 (s, 1H), 5.21 (s, 1H), 5.48 (s, 1H), 5.65 (s, 1H), 6.07 (s, 1H), 6.38 (d, J = 14.7 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.96 (br s, 1H), 7.21−7.02 (comp, 3H), 7.41−7.31 (br s, 1H), 7.72 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.4, 51.4, 51.6, 55.9, 56.0, 109.8, 110.0, 111.1, 114.9 (d, J = 17 Hz), 115.4, 122.6 (d, J = 11 Hz), 124.8, 127.7, 129.1, 130.1 (d, J = 10 Hz), 130.9 (d, J = 13 Hz), 140.9, 144.3, 149.2, 151.1, 162.5, 164.7 (d, J = 394 Hz), 166.4; MS (DART+) m/z 519 (M + H); HRMS m/z calcd for $C_{25}H_{29}{}^{79}BrFN_2O_4$ [M + H] 519.1295, found 519.1286.

*(2E)-N-(2-Bromobenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-(4-hydroxy-3-methoxyphenyl)prop-2-enamide (**8i**).* The title compound was prepared according to elimination method B. White solid; yield 207 mg (85%) after purification by flash column chromatography (hexane−AcOEt 80:20); mp 58−60 °C; IR ν (cm^{-1}) 3399, 3324, 3064, 3007, 2969, 2935, 1659, 1592, 1515, 1391, 1274, 1213, 1032, 754; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.17 (s, 9H), 3.89 (s, 3H), 5.06, (s, 2H), 5.51 (s, 1H), 5.77 (s, 1H), 6.02 (s, 1H), 6.42 (d, J = 15 Hz, 1H), 6.42 (s, 1H), 6.90 (d, J = 9 Hz, 1H), 6.94 (d, J = 1.8 Hz, 1H), 7.05 (dd, J = 8.25 and 1.8 Hz, 1H), 7.18 (td, J = 7.7 and 1.8 Hz, 1H), 7.33−7.28 (m, 1H), 7.48−7.45 (m, 1H), 7.57 (dd, J = 7.8 and 1.2 Hz, 1H), 7.72 (d, J = 15 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.2, 51.5, 51.8, 56.0, 109.6, 114.5, 114.8, 122.6, 123.1, 127.2, 128.0, 129.1, 129.3, 129.7, 131.8, 133.1, 136.1, 144.4, 146.8, 147.9, 162.6, 166.6; MS (DART+) m/z 487 (M + H); HRMS m/z calcd for $C_{24}H_{28}{}^{79}BrN_2O_4$ [M + H] 487.1232, found 487.1226.

*(2E)-N-(2-Bromobenzyl)-N-[3-(cyclohexylamino)-3-oxoprop-1-en-2-yl]-3-(4-hydroxy-3-methoxyphenyl)prop-2-enamide (**8j**).* The title compound was prepared according to elimination method B. White solid; yield 200 mg (78%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 160−172 °C; IR ν (cm^{-1}) 3307, 3065, 3012, 2932, 2854, 1655, 1590, 1514, 1387, 1273, 1200, 1031, 750; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.10−0.90 (m, 3H), 1.33−1.20 (m, 2H), 1.76−1.52 (m, 5H), 3.76−3.64 (m, 1H), 3.89 (s, 3H), 5.05 (s, 2H), 5.49 (s, 1H), 5.99 (s, 2H), 6.42 (d, J = 15.3 Hz, 2H), 6.89 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 1.8 Hz, 1H), 7.03 (dd J = 8.4 and 1.8 Hz, 1H), 7.16 (td, J = 7.8 and 1.8 Hz, 1H), 7.32−7.27 (m, 1H), 7.45−7.42 (br s, 1H), 7.55 (dd, J = 8.1 and 1.2 Hz, 1H), 7.72 (d, J = 15 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 24.8, 25.4, 32.7, 48.8, 51.6, 56.2, 109.8, 114.5, 114.9, 123.1, 123.5, 124.5, 127.3, 128.1, 129.7, 131.7, 133.2, 136.0, 141.8, 144.7, 146.9, 148.1, 162.5, 166.8; MS (DART+) m/z 513 (M + H); HRMS m/z calcd for $C_{26}H_{30}{}^{79}BrN_2O_4$ [M + H] 513.1389, found 513.1383.

*(2E)-N-(2-Bromo-4-methylbenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-(4-hydroxy-3-methoxyphenyl)prop-2-enamide (**8k**).* The title compound was prepared according to elimination method B. Yellow oil; yield 205 mg (82%) after purification by flash column chromatography (hexane−AcOEt 70:30); IR ν (cm^{-1}) 3305, 3068, 2965, 2930, 1653, 1588, 1512, 1267, 1180, 1123, 1031, 800, 728; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.17 (s, 9H), 2.31 (s, 3H), 3.88 (s, 3H), 5.02 (s, 2H), 5.48 (s, 1H), 5.75 (s, 1H), 5.93 (s, 1H), 6.40 (d, J = 15.3 Hz, 2H), 6.88 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 1.8 Hz, 1H), 7.03 (dd, J = 8.4 and 1.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.39 (br s, 1H), 7.71 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 20.8, 28.4, 51.6, 52.0, 56.1, 109.7, 114.8, 114.9, 122.8, 123.2, 127.4, 128.5, 128.9, 129.8, 131.8, 133.1, 133.6, 140.1, 144.4, 146.9, 148.0, 162.8, 166.7; MS (DART+) m/z 501 (M + H); HRMS m/z calcd for $C_{25}H_{30}{}^{79}BrN_2O_4$ [M + H] 501.1385, found 501.1389.

*(2E)-N-(2-Bromo-5-methoxybenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-(4-hydroxy-3-methoxyphenyl)prop-2-enamide (**8l**).* The title compound was prepared according to elimination method B. Yellow solid; yield 207 mg (80%) after purification by flash column chromatography (hexane−AcOEt 75:25); mp 71−73 °C; IR ν (cm^{-1}) 3395, The title compound was prepared according to elimination method B.3324, 3068, 3004, 2968, 2938, 1657, 1594, 1516, 1428, 1277, 1034, 815, 756; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz)

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δ 1.19 (s, 9H), 3.76 (s, 3H), 3.87 (s, 3H), 5.02 (s, 2H), 5.52 (s, 1H), 5.81 (s, 1H), 6.33 (br s, 1H), 6.41 (s, 1H), 6.42 (d, J = 15.3 Hz, 1H), 6.73 (dd, J = 8.85 and 3 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 1.8 Hz, 1H), 7.05−7.01 (comp, 2H), 7.44 (d, J = 8.7 Hz, 1H), 7.71 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.3, 51.6, 51.9, 55.6, 56.0, 109.8, 114.6, 114.9, 115.4, 117.3, 122.5, 123.1, 127.2, 129.8, 133.7, 137.1, 142.9, 144.5, 147.0, 148.1, 159.4, 162.8, 166.8; MS (DART+) *m*/*z* 517 (M + H); HRMS *m*/*z* calcd for $C_{25}H_{30}{}^{79}BrN_2O_5$ [M + H] 517.1338, found 517.1317.

*(2E)-N-(2-Bromo-4,5-dimethoxybenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-(4-hydroxy-3-methoxyphenyl)prop-2-enamide (**8m**).* The title compound was prepared according to elimination method B. White solid; yield 178 mg (65%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 64−66 °C; IR ν (cm^{-1}) 3393, 3045, 2961, 2851, 1654, 1591, 1507, 1454, 1258, 1208, 1161, 1027, 800, 728; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.20 (s, 9H), 3.85 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 5.01 (s, 2H), 5.45 (s, 1H), 5.68 (s, 1H), 6.41 (d, J = 15.3 Hz, 1H), 6.42 (br s, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 1.8 Hz, 1H), 7.00 (s, 1H), 7.04 (dd, J = 8.4 and 1.8 Hz, 1H), 7.13 (br s, 1H), 7.27 (s, 1H), 7.70 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.4, 29.8, 51.5, 56.2, 56.37, 56.4, 109.7, 114.3, 114.8, 114.9, 115.5, 122.9, 123.2, 127.4, 128.56, 128.6, 142.8, 144.4, 146.9, 148.0, 149.0, 149.6, 162.8, 166.84; MS (DART+) *m*/*z* 547 (M + H); HRMS *m*/*z* calcd for $C_{26}H_{32}{}^{79}BrN_2O_6$ [M + H] 547.1443, found 547.1422.

*(2E)-N-(2-Bromobenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enamide (**8n**).* The title compound was prepared according to elimination method B. Yellow oil; yield 199 mg (77%) after purification by flash column chromatography (hexane−AcOEt 75:25); IR ν (cm^{-1}) 3355, 3065, 3009, 2968, 2936, 1669, 1616,1516, 1457, 1331, 1218, 1116, 1028, 754; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.18 (s, 9H), 3.89 (s, 6H), 5.07 (s, 2H), 5.52 (s, 1H), 5.76 (s, 1H), 6.41 (d, J = 15 Hz, 1H), 6.43 (s, 1H), 6.71 (s, 2H), 7.21−7.16 (m, 1H), 7.35−7.28 (m, 1H), 7.47−7.45 (m, 1H), 7.58 (dd, J = 8.1 and 1.2 Hz, 1H), 7.71 (d, J = 15.3 Hz, 1H). ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.3, 51.6, 51.9, 56.4, 105.2, 115.0, 126.2, 128.1, 128.5, 129.8, 132.0, 133.2, 135.3, 136.1, 137.1, 142.7, 144.7, 147.3, 165.0, 166.6; MS (DART+) *m*/*z* 517 (M + H); HRMS *m*/*z* calcd for $C_{25}H_{30}{}^{79}BrN_2O_5$ [M + H] 517.1338, found 517.1330.

*(2E)-N-(2-Bromobenzyl)-N-[3-(cyclohexylamino)-3-oxoprop-1-en-2-yl]-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enamide (**8o**).* The title compound was prepared according to elimination method B. White solid; yield 233 mg (86%) after purification by flash column chromatography (hexane−AcOEt 65:35); mp 139−141 °C; IR ν (cm^{-1}) 3021, 3095, 2993, 2929, 2853, 1652, 1587, 1513, 1324, 1193, 1156, 1113, 1050, 731; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 11−0.92 (m, 2H), 1.33−1.21 (m, 3H), 1.81−1.53 (m, 5H), 3.77−3.86 (m, 1H), 3.89 (s, 6H), 5.04 (s, 2H), 5.49 (s, 1H), 5.86 (s, 1H), 6.09 (d, J = 8.1 Hz, 1H), 6.43 (d, J = 15.3 Hz, 1H), 6.44 (s, 1H), 6.69 (s, 2H), 7.16 (td, J = 7.5 and 1.5 Hz, 1H), 7.32−7.27 (m, 1H), 7.43−7.41 (m, 1H), 7.55 (dd, J = 7.8 and 0.9 Hz, 1H), 7.67 (d, J = 15 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 24.7, 25.3, 32.5, 48.7, 51.6, 56.4, 105.2, 114.7, 123.4, 124.4, 126.1, 127.9, 129.6, 131.5, 133.1, 135.8, 137.1, 141.6, 144.9, 147.2, 162.4, 166.6; MS (DART+) *m*/*z* 543 (M + H); HRMS *m*/*z* calcd for $C_{27}H_{32}{}^{79}BrN_2O_5$ [M + H] 543.1495, found 543.1481.

*(2E)-N-(2-Bromo-4,5-dimethoxybenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enamide (**8p**).* The title compound was prepared according to elimination method B. Yellow solid; yield 257 mg (89%) after purification by flash column chromatography (hexane−AcOEt 55:45); mp 84−86 °C; IR ν (cm^{-1}) 3391, 3054, 2962, 2842, 1656, 1604, 1507, 1454, 1258, 1209, 1157, 1111, 1026, 801, 727; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.19 (s, 9H), 3.86 (s, 3H), 3.87 (s, 3H), 3.89 (s, 6H), 5.02 (s, 2H), 5.47 (s, 1H), 5.69 (s, 1H), 5.83 (br s, 1H), 6.40 (d, J = 15.3 Hz, 2H), 6.70 (s, 2H), 7.00 (s, 1H), 7.11 (s, 1H), 7.69 (d, J = 15 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.4, 51.4, 51.5, 56.3, 56.4, 56.5, 105.2, 114.2, 115.1, 115.4, 122.9, 126.3, 128.5, 137.2, 142.7, 144.6, 147.3, 149.0, 149.5, 162.8, 166.7; MS (DART+) *m*/*z* 577 (M + H); HRMS *m*/*z* calcd for $C_{27}H_{34}{}^{79}BrN_2O_7$ [M + H] 577.1549, found 577.1537.

*(2E)-N-(2-Bromobenzyl)-N-[3-(tert-butylamino)-3-oxoprop-1-en-2-yl]-3-[(2-chloroethoxy)-3,5-dimethoxyphenyl]prop-2-enamide (**8q**).* The title compound was prepared according to elimination method C. Colorless oil; yield 226 mg (78%) after purification by flash column chromatography (hexane−AcOEt 80:20); IR ν (cm^{-1}) 3403, 3323, 3054, 2964, 2935, 1660, 1612, 1582, 1502, 1281, 1125, 1024, 824, 729; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.19 (s, 9H), 3.76 (t, J = 6.9 Hz, 2H), 3.85 (s, 6H), 4.23 (t, J = 6.9 Hz, 2H), 5.07 (s, 2H), 5.51 (s, 1H), 5.75 (s, 1H), 6.42 (s, 1H), 6.47 (d, J = 15.3 Hz, 1H), 6.68 (s, 2H), 7.18 (td, J = 8.4 and 1.8 Hz, 1H), 7.33−7.28 (m, 1H), 7.49−7.44 (m, 1H), 7.58 (dd, J = 8.55 and 1.5 Hz, 1H), 7.70 (d, J = 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.4, 42.3, 51.6, 51.9, 56.3, 72.9, 105.4, 116.8, 122.7, 124.5, 128.1, 129.8, 130.8, 132.0, 133.2, 136.0, 138.5, 142.7, 144.2, 153.5, 162.6, 166.3; MS (DART+) *m*/*z* 579 (M + H); HRMS *m*/*z* calcd for $C_{27}H_{33}{}^{79}Br^{35}ClN_2O_5$ [M + H] 579.1261, found 579.1267.

General Procedure for the Synthesis of Pyrrolo[2,1-*a*]-isoindol-3-ones (12a−q). In a round-bottom flask, the corresponding diene (0.3 mmol) was dissolved in toluene (5 mL), and $Pd(AcO)_2$ (0.045 mmol), PPh_3 (0.09 mmol), and K_2CO_3 (0.6 mmol) were added. The solution was degasificated by bubbling with argon for 20 min. After that, the mixture was allowed to reflux for 8−12 h under argon atmosphere. Then, the solvent was evaporated and the resulting crude was diluted with dichloromethane (20 mL). The precipitate was filtered and the filtrate was sequentially washed with water (2 × 15 mL portions) and with a saturated NaCl solution (2 × 10 mL portions). The organic layer was evaporated and the product was finally purified by silica gel flash column chromatography.

*(2Z)-2-Benzylidene-N-tert-butyl-3-oxo-2,3-dihydro-1H-pyrrolo-[2,1-a]isoindole-9b(5H)-carboxamide (**12a**).* Pale brown solid; yield 63 mg (58%) after purification by flash column chromatography (hexane−AcOEt 85:15); mp 135−137 °C; IR ν (cm^{-1}) 3383, 3315, 3068, 2964, 2919, 1704, 1663, 1511, 1454, 1356, 1225, 737, 696; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.28 (s, 9H), 3.33 (dd, J = 16.35 and 3 Hz, 1H), 3.70 (dd, J = 16.2 and 1.5 Hz, 1H), 4.44 (d, J = 15.3 Hz, 1H), 5.10 (d, J = 15.3 Hz, 1H), 6.33 (s, 1H), 6.79 (br s, 1H), 7.39−7.23 (comp, 7H), 7.69−7.66 (m, 1H), 7.83−7.79 (m, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.8, 43.8, 50.4, 51.6, 74.4, 122.6, 124.1, 128.2, 128.5, 128.7, 129.1, 130.0, 130.4, 134.3, 136.3, 137.5, 141.3, 171.3, 172.0; MS (DART+) *m*/*z* 361 (M + H); HRMS *m*/*z* calcd for $C_{23}H_{25}N_2O_2$ [M + H] 361.1916, found 361.1907.

*(2Z)-2-Benzylidene-N-(2,6-dimethylphenyl)-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12b**).* White solid; yield 90 mg (73%) after purification by flash column chromatography (hexane−AcOEt 80:20); mp 261−263 °C; IR ν (cm^{-1}) 3287, 3050, 3023, 2954, 2915, 1692, 1671, 1504, 1381, 1349, 1229, 1095, 761, 745; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 2.00 (s, 6H), 3.41 (dd, J = 15.9 and 3 Hz, 1H), 3.87 (dd, J = 15.9 and 1.5 Hz, 1H), 4.59 (d, J = 15.3 Hz, 1H), 5.19 (d, J = 15.3 Hz, 1H), 6.86 (br s, 1H), 7.08−6.98 (comp, 3H), 7.38−7.29 (comp, 6H), 7.73−7.69 (m, 1H), 7.80 (dd, J = 7.65 and 1.8 Hz, 2H), 7.86 (br s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 18.1, 44.5, 50.4, 74.8, 122.8, 124.2, 127.7, 128.2, 128.3, 128.7, 129.1 (2C), 130.2, 130.3, 132.9, 134.2, 135.3, 136.4, 137.4, 140.6, 170.7, 171.6; MS (FAB+) *m*/*z* 409 (M + H); HRMS *m*/*z* calcd for $C_{27}H_{25}N_2O_2$ [M + H] 409.1916, found 409.1904.

*(2Z)-2-Benzylidene-N-tert-butyl-7-methoxy-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12c**).* Yellow solid; yield 68 mg (58%) after purification by flash column chromatography (hexane−AcOEt 85:15); mp 171−173 °C; IR ν (cm^{-1}) 3338, 3024, 2962, 2912, 1690, 1663, 1516, 1489, 1330, 1276, 805, 740, 693; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.28 (s, 9H), 3.29 (dd, J = 16.35 and 3 Hz, 1H), 3.67 (d, J = 16.2 Hz, 1H), 3.80 (s, 3H), 4.40 (d, J = 15.3 Hz, 1H), 5.06 (d, J = 15.3 Hz, 1H), 6.30 (s, 1H), 6.78 (br s, 2H), 6.89 (dd, J = 8.4 and 2.1 Hz, 1H), 7.39−7.29 (comp, 3H), 7.56 (d, J = 8.4 Hz,1H), 7.82−7.80 (comp, 2H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.7, 43.8, 50.3, 51.5, 55.5, 73.8, 107.7, 114.5, 124.7, 128.0, 128.9, 130.1, 130.2, 133.3, 134.2, 136.1, 139.0, 160.4, 171.5, 171.8; MS

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(DART+) m/z 391 (M + H); HRMS m/z calcd for $C_{24}H_{27}N_2O_3$ [M + H] 391.2022, found 391.2014.

*(2Z)-N-tert-Butyl-2-(3,4-dimethoxybenzylidene)-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12d**).* Yellowish solid; yield 67 mg (53%) after purification by flash column chromatography (hexane−AcOEt 80:20); mp 200−201 °C; IR ν (cm^{-1}) 3404, 3347, 3090, 3000, 2967, 2934, 1675, 1514, 1460, 1335, 1267, 1144, 1026, 756; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.28 (s, 9H), 3.35 (dd, J = 16.5 and 2.7 Hz, 1H), 3.68 (dd, J = 16.5 and 1.5 Hz, 1H), 3.90 (s, 3H), 3.98 (s, 3H), 4.46 (d, J = 15 Hz, 1H), 5.12 (d, J = 15.3 Hz, 1H), 6.32 (s, 1H), 6.68 (m, 1H), 6.83 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 8.4 and 2.1 Hz, 1H), 7.27−7.25 (m, 1H), 7.35−7.29 (m, 2H), 7.68−7.65 (m, 1H), 8.20 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.8, 43.9, 50.7, 51.6, 55.9, 56.1, 74.3, 110.4, 113.6, 122.5, 124.1, 125.2, 127.1, 127.8, 128.5, 128.7, 136.8, 137.6, 141.5, 148.5, 150.1, 171.4, 172.5; MS (DART+) m/z 421 (M + H); HRMS m/z calcd for $C_{25}H_{29}N_2O_4$ [M + H] 421.2127, found 421.2111.

*(2Z)-N-Cyclohexyl-2-(3,4-dimethoxybenzylidene)-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12e**).* Orange solid; yield 86 mg (64%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 88−90 °C; IR ν (cm^{-1}) 3308, 3024, 2928, 2853, 1660, 1512, 1261, 1025, 744; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.13−1.01 (m, 2H), 1.35−1.21 (m, 2H), 1.91−1.55 (m, 6H), 3.36 (dd, J = 16.2 and 2.7 Hz, 1H), 3.68−3.58 (m, 1H), 3.67 (dd, J = 16.1 and 1.5 Hz, 1H), 3.90 (s, 3H), 3.95 (s, 3H), 4.45 (d, J = 15.3 Hz, 1H), 5.11 (d, J = 15.3 Hz, 1H), 6.37 (d, J = 8.4 Hz, 1H), 6.67 (br s, 1H), 6.82 (d, J = 8.4 Hz, 1H), 7.23−7.16 (comp, 2H), 7.37−7.28 (comp, 2H), 7.70−7.66 (m, 1H), 8.17 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 24.9, 25.5, 33.0, 33.1, 44.1, 48.7, 50.7, 56.0, 56.1, 74.2, 110.3, 113.5, 122.5, 124.1, 125.2, 127.1, 127.7, 128.5, 128.8, 136.8, 137.6, 141.4, 148.5, 150.1, 171.2, 172.5; MS (DART+) m/z 447 (M + H); HRMS m/z calcd for $C_{27}H_{31}N_2O_4$ [M + H] 447.2284, found 447.2268.

*(2Z)-N-tert-Butyl-7-methoxy-2-(3,4-dimethoxybenzylidene)-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12f**).* Yellowish solid; yield 80 mg (59%) after purification by flash column chromatography (hexane−AcOEt 75:25); m.p 183−185 °C; IR ν (cm^{-1}) 3403, 3348, 3089, 2665, 2936, 1675, 1414, 1457, 1330, 1269, 1147, 1027, 806, 759; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.28 (s, 9H), 3.32 (dd, J = 16.5 and 2.7 Hz, 1H), 3.64 (dd, J = 16.5 and 0.9 Hz, 1H), 3.80 (s, 3H), 3.91 (s, 3H), 3.97 (s, 3H), 4.42 (d, J = 15.3 Hz, 1H), 5.08 (d, J = 15.3 Hz, 1H), 6.29 (s, 1H), 6.68 (br s, 1H), 6.77 (d, J = 2.1 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.88 (dd, J = 8.6 and 2.1 Hz, 1H), 7.22 (dd, J = 8.3 and 1.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.7, 43.9, 50.6, 51.4, 55.5, 55.8, 55.9, 73.8, 107.7, 110.2, 113.4, 114.4, 124.7, 125.1, 127.2, 127.7, 133.6, 136.6, 139.1, 148.3, 149.9, 160.3, 171.6, 172.4; MS (DART+) m/z 451 (M + H); HRMS m/z calcd for $C_{26}H_{31}N_2O_5$ [M + H] 451.2233, found 451.2223.

*(2Z)-N-tert-Butyl-7-fluoro-2-(3,4-dimethoxybenzylidene)-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12g**).* Yellow solid; yield 83 mg (63%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 168−170 °C; IR ν (cm^{-1}) 3361, 3087, 2966, 2933, 1665, 1628, 1507, 1259, 1145, 1024, 807, 751; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.28 (s, 9H), 3.33 (dd, J = 16.5 and 2.7 Hz, 1H), 3.64 (dd, J = 16.5 and 1.5 Hz, 1H), 3.91 (s, 3H), 3.96 (s, 3H), 4.42 (d, J = 15.3 Hz, 1H), 5.09 (d, J = 15.3 Hz, 1H), 6.32 (s, 1H), 6.69 (m, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.94 (dd, J = 8.4 and 2.4 Hz, 1H), 7.03 (td, J = 8.8 and 2.4 Hz, 1H), 7.22 (dd, J = 8.4 and 2.1 Hz, 1H), 7.62 (dd, J = 8.4 and 5.1 Hz, 1H), 8.18 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.8, 43.9, 50.6, 51.7, 56.0, 56.1, 73.7, 109.9 (d, J = 22.5 Hz), 110.4, 133.5, 115.9 (d, J = 22.5 Hz), 125.3, 125.6 (d, J = 7.5 Hz), 126.6, 127.7, 137.2, 137.3, 139.9 (d, J = 7.5 Hz), 148.5, 150.2, 163.4 (d, J = 247.5 Hz), 171.3, 172.6; MS (DART+) m/z 439 (M + H); HRMS m/z calcd for $C_{25}H_{28}FN_2O_4$ [M + H] 439.2033, found 439.2016.

*(2Z)-N-tert-Butyl-6-fluoro-2-(3,4-dimethoxybenzylidene)-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12h**).* Orange solid; yield 55 mg (42%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 173−175 °C; IR ν (cm^{-1}) 3368, 3088, 2960, 2923, 1692, 1665, 1507, 1335, 1256, 1231, 1143, 1025, 763; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.29 (s, 9H), 3.31 (dd, J = 16.5 and 2.7 Hz, 1H), 3.66 (dd, J = 16.5 and 1.5 Hz, 1H), 3.91 (s, 3H), 3.97 (s, 3H), 4.45 (d, J = 15.3 Hz, 1H), 5.22 (d, J = 15.6 Hz, 1H), 6.37 (s, 1H), 6.70 (br s, 1H), 6.85 (d, J = 8.4 Hz, 1H), 7.05−6.99 (m, 1H), 7.23 (dd, J = 8.4 and 2.1 Hz, 1H), 7.38−7.33 (m, 1H), 7.46 (d, J = 7.5 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.6, 43.5, 47.8, 51.6, 55.8, 55.9, 74.5, 110.3, 113.4, 115.2 (d, J = 15 Hz), 119.7 (d, J = 3 Hz), 124.3 (d, J = 22.5 Hz), 125.3, 126.2, 127.5, 130.65 (d, J = 7.5 Hz), 137.2, 144.62 (d, J = 4.5 Hz), 148.3, 150.1, 157.3, (d, J = 245 Hz), 170.8, 172.4; MS (DART+) m/z 439 (M + H); HRMS m/z calcd for $C_{25}H_{28}FN_2O_4$ [M + H] 439.2033, found 439.2020.

*(2Z)-N-tert-Butyl-2-(4-hydroxy-3-methoxybenzylidene)-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12i**).* White solid; yield 73 mg (60%) after purification by flash column chromatography (hexane−AcOEt 80:20); mp 208−210 °C; IR ν (cm^{-1}) 3286, 3053, 2959, 2928, 1695, 1649, 1515, 1380, 1277, 1204, 1149, 1034, 734; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.28 (s, 9H), 3.47 (dd, J = 17.7 and 3 Hz, 1H), 3.78 (dd, J = 17.7 and 2.4 Hz, 1H), 3.92 (s, 3H), 4.48 (d, J = 15 Hz, 1H), 5.14 (d, J = 15 Hz, 1H), 6.21 (s, 1H), 6.42 (s, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.96 (s, 1H), 7.08 (dd, J = 8.4 and 2.1 Hz, 1H), 7.38−7.29 (comp, 4H), 7.78−7.73 (m, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.8, 38.9, 51.5, 51.6, 56.1, 75.1, 112.6, 115.1, 122.5, 124.2, 124.3, 126.2, 127.5, 128.4, 128.7, 134.3, 138.2, 141.5, 146.8, 147.4, 171.6, 176.0; MS (DART+) m/z 406 (M + H); HRMS m/z calcd for $C_{24}H_{27}N_2O_4$ [M + H] 407.1971, found 407.1955.

*(2Z)-N-Cyclohexyl-2-(4-hydroxy-3-methoxybenzylidene)-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12j**).* Yellow solid; yield 100 mg (77%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 241−243 °C; IR ν (cm^{-1}) 3287, 3013, 2930, 2855, 1687, 1639, 1513, 1355, 1274, 1147, 1032, 814, 729; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.29−1.05 (m, 5H), 1.73−1.54 (m, 5H), 3.48 (dd, J = 17.7 and 3 Hz, 1H), 3.69−3.58 (m, 1H), 3.82 (dd, J = 17.7 and 2.4 Hz, 1H), 3.92 (s, 3H), 3.97 (d, J = 15.3 Hz, 1H), 5.15 (d, J = 15.0 Hz, 1H), 6.09 (s, 1H), 6.46 (d, J = 8.4 Hz, 1H), 6.96 (br s, 1H), 6.97 (d, J = 8.1 Hz, 1H), 7.07 (dd, J = 8.4 and 1.8 Hz, 1H), 7.38−7.23 (comp, 4H), 7.78−7.75 (m, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 24.9, 25.5, 33.09, 33.1, 39.0, 48.7, 51.5, 56.2, 75.0, 112.6, 115.1, 122.5, 124.30, 124.34, 126.3, 127.5, 128.5, 128.8, 134.3, 138.2, 141.4, 146.8, 147.3, 171.4, 175.9; MS (DART+) m/z 433 (M + H); HRMS m/z calcd for $C_{26}H_{29}N_2O_4$ [M + H] 433.2127, found 433.2123.

*(2Z)-N-tert-Butyl-2-(4-hydroxy-3-methoxybenzylidene)-8-methyl-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12k**).* Yellow solid; yield 71 mg (56%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 237−239 °C; IR ν (cm^{-1}) 3288, 3004, 2959, 2921, 2865, 1694, 1650, 1515, 1380, 1277, 1204, 1034, 805; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.28 (s, 9H), 2.38 (s, 3H), 3.46 (dd, J = 18.5 and 3 Hz, 1H), 3.76 (dd, J = 17.7 and 2.4 Hz, 1H), 3.92 (s, 3H), 4.43 (d, J = 15 Hz, 1H), 5.09 (d, J = 15 Hz, 1H), 6.12 (s, 1H), 6.41 (s, 1H), 6.96 (br s, 1H), 6.97 (d, J = 8.1 Hz, 1H), 7.08 (dd, J = 8.25 and 2.1 Hz, 1H), 7.12 (br s, 2H), 7.36 (t, J = 2.7 Hz, 1H), 7.53 (br s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 21.5, 28.8, 38.9, 51.3, 51.6, 56.1, 75.1, 112.7, 115.1, 122.2, 124.3, 124.7, 126.4, 127.6, 129.6, 134.2, 135.3, 138.3, 141.6, 146.8, 147.4, 171.7, 176.0; MS (DART+) m/z 421 (M + H); HRMS m/z calcd for $C_{25}H_{29}N_2O_4$ [M + H] 421.2127, found 421.2112.

*(2Z)-N-tert-Butyl-2-(4-hydroxy-3-methoxybenzylidene)-7-methoxy-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12l**).* Yellowish solid; yield 83 mg (63%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 216−218 °C; IR ν (cm^{-1}) 3274, 3001, 2970, 2925, 1694, 1663, 1644, 1514, 1366, 1267, 1171, 1029, 810, 743; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.28 (s, 9H), 3.43 (dd, J = 18 and 3 Hz, 1H), 3.74 (dd, J = 18 and 2.4 Hz, 1H), 3.80 (s, 3H), 3.93 (s, 3H), 4.44 (d, J = 15 Hz, 1H), 5.10 (d, J = 15.3 Hz, 1H), 6.09 (s, 1H), 6.39 (s, 1H), 6.77 (d, J = 2.4 Hz, 1H), 6.89 (dd, J = 8.7 and 2.4 Hz, 1H), 6.96 (s, 1H), 6.97 (d, J = 8.5 Hz,

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1H), 7.09 (dd, J = 8.4 and 1.8 Hz, 1H), 7.37 (m, 1H), 7.62 (s, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.7, 38.8, 51.4, 51.5, 55.6, 56.0, 74.6, 107.7, 112.5, 114.4, 114.9, 124.2, 124.9, 126.3, 127.5, 133.5, 134.2, 139.8, 146.7, 147.2, 160.4, 171.7, 175.9; MS (DART+) m/z 437 (M + H); HRMS m/z calcd for $C_{25}H_{29}N_2O_5$ [M + H] 437.2077, found 437.2064.

(2Z)-N-tert-Butyl-2-(4-hydroxy-3-methoxybenzylidene)-7,8-dimethoxy-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12m**). Yellowish solid; yield 76 mg (54%) after purification by flash column chromatography (hexane−AcOEt 60:40); mp 250−253 °C (dec); IR ν (cm^{-1}) 3400, 3285, 295, 2916, 2854, 1693, 1643, 1592, 1504, 1368, 1256, 1192, 1025, 1006, 818, 700; ^{1}H NMR (DMSO-d_6/TMS, 300 MHz) δ 1.21 (s, 9H), 3.50 (br s, 2H), 3.73 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 4.42 (d, J = 14.7 Hz, 1H), 4.83 (d, J = 14.4 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.95 (s, 1H), 7.03 (s, 1H), 7.18−7.03 (comp, 4H), 7.25 (s, 1H); ^{13}C NMR (DMSO-d_6/TMS, 75 MHz) δ 28.3, 37.6, 50.8, 50.7, 55.6, 55.75 55.8, 74.7, 106.0, 107.3, 114.9, 115.9, 123.1, 126.3, 126.8, 130.7, 132.1, 133.5, 147.7, 148.2, 148.6, 149.2, 171.2, 173.9; MS (DART+) m/z 467 (M + H); HRMS m/z calcd for $C_{26}H_{31}N_2O_6$ [M + H] 467.2182, found 467.2165.

(2Z)-N-tert-Butyl-2-(4-hydroxy-3,5-dimethoxybenzylidene)-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12n**). Yellow solid; yield 73 mg (56%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 237−239 °C (dec); IR ν (cm^{-1}) 3322, 3296, 3096, 2960, 2917, 1692, 1649, 1593, 1516, 1343, 1199, 1109, 821, 742, 649; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.28 (s, 9H), 3.48 (dd, J = 17.9 and 2.7 Hz, 1H), 3.19 (dd, J = 18 and 2.4 Hz, 1H), 3.94 (s, 6H), 4.48 (d, J = 15 Hz, 1H), 5.14 (d, J = 15 Hz, 1H), 5.87 (s, 1H), 6.42 (s, 1H), 6.73 (s, 2H), 7.39−7.24 (comp, 4H), 7.76−7.73 (m, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.7, 38.6, 51.4, 51.5, 56.5, 75.0, 107.3, 122.4, 124.1, 126.3, 126.4, 128.4, 128.6, 134.6, 136.6, 138.1, 141.3, 147.2, 171.4, 175.8; MS (DART+) m/z 437 (M + H); HRMS m/z calcd for $C_{25}H_{29}N_2O_5$ [M + H] 437.2077, found 437.2068.

(2Z)-N-Cyclohexyl-2-(4-hydroxy-3,5-dimethoxybenzylidene)-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12o**). Orange solid; yield 103 mg (74%) after purification by flash column chromatography (hexane−AcOEt 60:40); mp 122−124 °C; IR ν (cm^{-1}) 3299, 3015, 2933, 2855, 1689, 1646, 1594, 1514, 1318, 1212, 1114, 747; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.29−1.05 (m, 6H), 1.75−1.56 (m, 4H) 3.48 (dd, J = 17.8 and 2.7 Hz, 1H), 3.67−3.60 (m, 1H), 3.82 (dd, J = 18 and 2.1 Hz, 1H), 3.94 (s, 6H), 4.48 (d, J = 15.3 Hz, 1H), 5.15 (d, J = 15.3 Hz, 1H), 5.87 (s, 1H), 6.45 (d, J = 8.4 Hz, 1H), 6.73 (s, 2H), 7.35 (br s, 1H), 7.38−7.29 (comp, 3H), 7.78−7.76 (m, 1H); ^{13}C NMR (DMSO-d_6/TMS, 75 MHz) δ 24.8, 25.0, 31.9, 32.0, 37.7, 48.2, 50.5, 56.2, 74.3, 108.0, 122.6, 123.9, 125.1, 127.1, 127.4, 128.1, 132.4, 137.5, 138.9, 141.9, 148.0, 170.5, 173.4; MS (DART+) m/z 463 (M + H); HRMS m/z calcd for $C_{27}H_{31}N_2O_5$ [M + H] 463.2233, found 463.2215.

(2Z)-N-tert-Butyl-2-(4-hydroxy-3,5-dimethoxybenzylidene)-7,8-dimethoxy-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12p**). Yellow solid; yield 70 mg (47%) after purification by flash column chromatography (hexane−AcOEt 30:70); mp 133−135 °C; IR ν (cm^{-1}) 3251, 3064, 2991, 2960, 2872, 1690, 1645, 1596, 1510, 1455, 1324, 1207, 1112, 1019, 821, 746; ^{1}H NMR ($CDCl_3$/TMS, 300 MHz) δ 1.29 (s, 9H), 3.45 (dd, J = 17.7 and 3 Hz, 1H), 3.75 (dd, J = 17.7 and 2.1 Hz, 1H), 3.87 (s, 3H), 3.94 (s, 6H), 3.95 (s, 3H), 4.43 (d, J = 14.4 Hz, 1H), 5.07 (d, J = 14.7 Hz, 1H), 5.95 (s, 1H), 6.40 (s, 1H), 6.74 (s, 3H), 7.24 (s, 1H), 7.36 (br s, 1H); ^{13}C NMR ($CDCl_3$/TMS, 75 MHz) δ 28.8, 38.6, 51.58, 51.64, 56.2, 56.3, 56.6 (2C), 75.3, 105.1, 106.7, 107.4, 126.5, 126.6, 129.8, 133.1, 134.7, 136.7, 147.3, 149.6, 150.0, 171.7, 175.9; MS (DART+) m/z 467 (M + H); HRMS m/z calcd for $C_{27}H_{33}N_2O_7$ [M + H] 497.2288, found 497.2283.

(2Z)-N-tert-Butyl-2-[4-(2-chloroethoxy)-3,5-dimethoxybenzylidene]-3-oxo-2,3-dihydro-1H-pyrrolo[2,1-a]isoindole-9b(5H)-carboxamide (**12q**). Yellow solid; yield 67 mg (45%) after purification by flash column chromatography (hexane−AcOEt 70:30); mp 119−121 °C; IR ν (cm^{-1}) 3333, 3064, 2969, 2934, 1663, 1583, 1504, 1453, 1328, 1228, 1124, 1011, 737; ^{1}H NMR ($CDCl_3$/TMS, 400 MHz) δ 1.28 (s, 9H), 3.36 (dd, J = 16.4 and 3.2 Hz, 1H), 3.69 (dd, J = 16.4 and 1.6 Hz, 1H), 3.77 (t, J = 6.8 Hz, 2H), 3.9 (s, 6H), 4.25 (t, J = 6.8 Hz, 2H), 4.46 (d, J = 15.2 Hz, 1H), 5.12 (d, J = 15.2 Hz, 1H), 6.27 (s, 1H), 6.67 (m, 1H), 7.27−7.25 (m, 1H), 7.37−7.31 (comp, 2H), 7.39 (s, 2H), 7.67−7.65 (m, 1H); ^{13}C NMR ($CDCl_3$/TMS, 100 MHz) δ 28.8, 42.3, 44.1, 50.8, 51.7, 56.4, 72.9, 74.4, 108.6, 122.6, 124.1, 128.6, 128.8, 129.2, 130.5, 136.6, 137.5, 137.6, 141.5, 152.8, 171.3, 172.2; MS (DART+) m/z 499 (M + H); HRMS m/z calcd for $C_{27}H_{32}ClN_2O_5$ [M + H] 499.1999, found 499.1992.

In Vitro Antioxidant Assays. *DPPH-Scavenging Test.* The test was performed on a 96-well plate, with 50 μL of each sample concentration in DMSO. Then, 150 μL of an ethanolic solution of DPPH (133.33 μM) was added (final concentration of 100 μM). The plate was incubated for 30 min with constant stirring at 37 °C in the dark. Finally, the absorbance at 515 nm was measured on an absorbance reader. The activity was expressed as reduction percentage and was calculated using the following formula: % scavenging = $(C - E) \times 100/C$, where C is the absorbance of control (DPPH at 10 μM) and E is the absorbance of the test sample. The samples were measured in triplicate, and the results are represented as mean ± standard error (SEM).

Materials and Method for TBARS. *Animals.* Adult male Wistar rats (200−250 g) were provided by the Instituto de Fisiología Celular, Universidad Nacional Autónoma de México (UNAM). Procedures and care of animals were conducted in conformity with Mexican Official Norm for Animal Care and Handling (NOM-062-ZOO-1999). They were maintained at 23 ± 2 °C on a 12/12 h light−dark cycle with free access to food and water.

Rat Brain Homogenate Preparation. Animal sacrifice was carried out with CO_2 to avoid unnecessary pain. The cerebral tissue (whole brain) was rapidly dissected and homogenized in phosphate-buffered saline (PBS) solution (0.2 g of KCl, 0.2 g of KH_2PO_4, 8 g of NaCl, and 2.16 g of $NaHPO_4{\cdot}7H_2O$/L, pH 7.4) as reported elsewhere[37] to produce a 1/10 (w/v) homogenate. Then, the homogenate was centrifuged for 10 min at 800 rcf (relative centrifugal field) to yield a pellet, which was discarded. The supernatant protein content was measured using Folin and Ciocalteu's phenol reagent[38] and adjusted with PBS at 2.666 mg of protein/mL.

Induction of Lipid Peroxidation and Thiobarbituric Acid Reactive Substances (TBARS) Quantification. As an index of lipid peroxidation, TBARS levels were measured using rat brain homogenates according to the method described by Ng et al.,[39] with some modifications. To supernatant (375 μL) was added 50 μL of 20 μM EDTA and 50 μL of each sample concentration dissolved in DMSO (50 μL of DMSO for control group) and the mixture incubated at 37 °C for 30 min. Lipid peroxidation was started by adding 50 μL of a freshly prepared 100 μM $FeSO_4$ solution (final concentration 10 μM) and the mixture incubated at 37 °C for 1 h. The TBARS content was determined as described by Ohkawa et al.[40] with some modifications. A 500 μL portion of TBA reagent (1% 2-thiobarbituric acid in 0.05 N NaOH and 30% trichloroacetic acid, in 1:1 proportion) was added to each tube, and the final suspension was cooled on ice for 10 min, centrifuged at 13 400 rcf for 5 min, and heated at 80 °C in a water bath for 30 min. After cooling at room temperature, the absorbance of 200 μL of supernatant was measured at λ = 540 nm in a microplate reader. The concentration of TBARS was calculated by interpolation with a standard curve of tetramethoxypropane (TMP) as a precursor of MDA.[41]

Results were expressed as nmol of TBARS/mg of protein. The inhibition ratio [IR (%)] was calculated using following formula IR = $(C - E) \times 100/C$, where C is the absorbance of the control and E is the absorbance of the test sample. Butylated hydroxytoluene (BHT) and α-tocopherol were used as positive standards.

All data are represented as mean ± standard error (SEM). Data were analyzed by one-way ANOVA followed by Dunnett's test for comparison against the control. Values of $p \leq 0.05$ (*) and $p \leq 0.01$ (**) were considered statistically significant. The 50% inhibitory concentration (IC_{50}) was estimated by means of a linear regression.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01742.

^{1}H and ^{13}C NMR data, crystallographic data of **12c** and **12q**, and complementary antioxidant results and discussion (Table S1 and Figures S1 and S2) (PDF)

Crystallographic data for **12c** in CIF format (CIF)

Crystallographic data for **12q** in CIF format (CIF)

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Notes

The authors declare no competing financial interest.

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