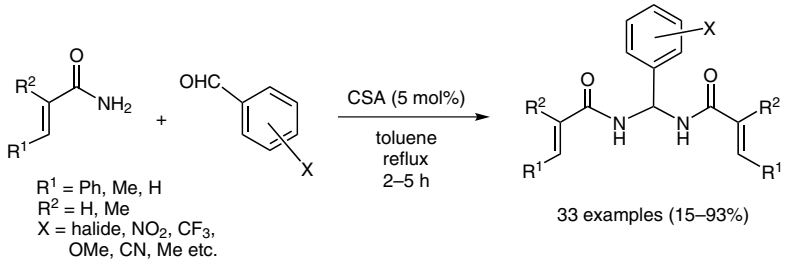
Synthesis J. Uenishi et al. Paper

# Synthesis and Cytotoxic Activity of *N*,*N*′-(Arylmethylene)bisamides

**Jun'ichi Uenishi**[*a]
**Hirokazu Hirano**[a]
**Tsuyoshi Ueda**[a]
**Naoyuki Hoshiya**[a]
**Hiromi Ii**[b]
**Tatsuhiro Yoshiki**[*b]

[a] Department of Pharmaceutical Chemistry, Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan
juenishi@mb.kyoto-phu.ac.jp
[b] Department of Clinical Oncology, Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan
yoshiki@mb.kyoto-phu.ac.jp




Received: 23.04.2015
Accepted after revision: 11.05.2015
Published online: 09.07.2015
DOI: 10.1055/s-0034-1380437; Art ID: ss-20165-f0225-op

**Abstract** *N*,*N*′-(Arylmethylene)bisamides were prepared by an acid-catalyzed reaction of arylaldehydes with cinnamamide or acrylamides. The reaction was carried out in refluxing toluene for a few hours, and simple collection of the precipitate gave the desired products. The bisamides were designed as cytotoxic molecules based on the structure of the potently cytotoxic marine natural product (–)-zampanolide. The activities of the bisamides against two cancer cell lines were evaluated, and several compounds were found to show medium potency with $IC_{50}$ values in the lower micromolar level.

**Key words** amides, medicinal chemistry, cytotoxins, condensation, bisamides

The bisamide group is a unique functional group that consists of two amide moieties connected by a methylene bridge (Figure 1). This group has been used as an important component of retro-inverso peptides,[1] which have attracted the interest of chemists studying the design of biologically active peptides in medicinal chemistry. This structural unit is exceptionally stable in comparison with the other substituted methylene units that contain two heteroatoms (oxygen or nitrogen), such as acetal, diaminomethane, or aminal groups. However, this interesting functional group has rarely been used as a unit of small-molecule drugs other than specific peptides in medicinal chemistry.

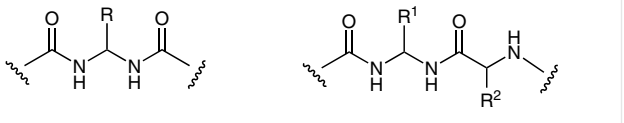



**Figure 1** Structure of the bisamide moiety and partial structure of a retro-inverso peptide (*N*,*N*′-methylenebisamide)

(–)-Zampanolide [(–)-**1**; Figure 2] is a twenty-membered macrolide isolated from a marine sponge.[2] It shows potent cytotoxicity in the nanomolar range of concentrations against many cancer cell lines, including taxol- and doxorubicin (adriamycin)-resistant cells.[3] A recent investigation revealed the crystal structure of the complex of (–)-zampanolide with the α,β-heterodimer of tubulin, and clarified the relationship between the three-dimensional molecular structure of the complex and the cytotoxic action of (–)-**1**.[4] (–)-Zampanolide contains a relatively planar macrocyclic ring with an *N*-dienoylaminal branch unit in a side chain. We surmised that this aminal unit might be a site associated with the activity of the compound.

We have previously reported a total synthesis of (–)-**1**.[5,6] In the construction of the aminal unit of (–)-**1**, the assembly of the (–)-dactylolide as the macrolactone part with the dienoylamide not only gave the desired (–)-**1**, but also gave a proportion of the *N*,*N*′-methylenebis(dienamide) (–)-**2** as a byproduct. The cytotoxicity of (–)-**2** was $10^{-3}$ times weaker than that of (–)-zampanolide, although it still possessed an activity in the low micromolar range.[5]

The specific structure and the potent cytotoxic activity of (–)-**2** led us to design a new *N*,*N*′-bisalkenamide. We hypothesized that simplification of the *N*,*N*′-methylenebisamide segment of (–)-**2** to an *N*,*N*′-arylmethylenebis(cinnamamide) might provide a new and unique functional small molecule with cytotoxic activity.

Here, we report successful syntheses of a series of new *N*,*N*′-(arylmethylene)bisamides by means of simple operations. We also describe the cytotoxic activities of the several products.

*N*,*N*′-Bisamides have been synthesized by an acid-catalyzed reaction in the presence[7a–d] or absence[7e,f] of a solvent; they have also been prepared by an imidazole-promoted reaction.[7g] Recently, the addition of a Grignard reagent to an isocyanate has been reported to give a nonsymmetric bis-

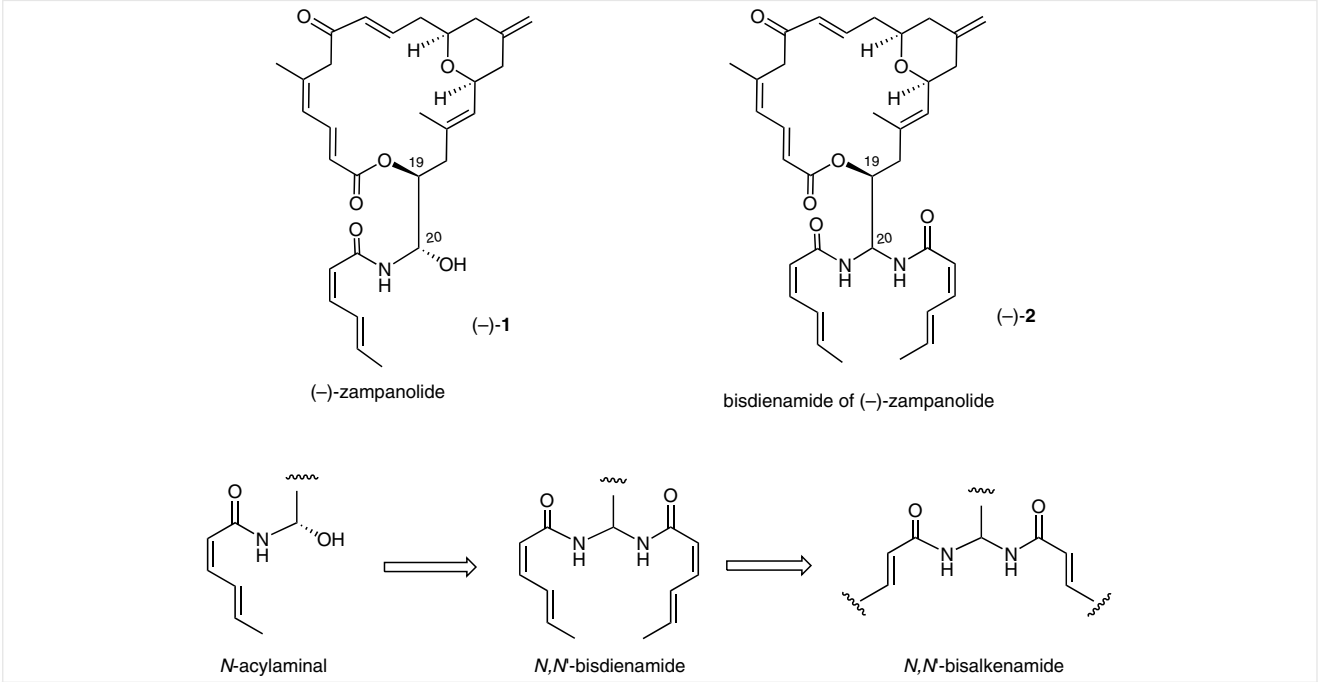
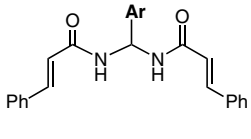



**Figure 2** Structures of (–)-zampanolide, its bisamide derivative, and related functional groups

bisamide.[7h] However, few synthesesof methylenebis(cinnamamide)s have been reported .[7] First, we examined the reaction of benzaldehyde with cinnamamide. When a mixture of *trans*-cinnamamide and benzaldehyde was refluxed in toluene containing *dl*-camphorsulfonic acid (CSA) as a catalyst, *N*,*N*′-benzylidenebis(cinnamamide) [**3**; (2*E*,2′*E*)-*N*,*N*′-(phenylmethylene)bis(3-phenylacrylamide)] was obtained in 93% yield (Scheme 1). Purification of the product was quite simple. When the reaction was complete, the precipitate was collected by filtration and washed successively with benzene and diethyl ether to give a pure solid product that required no further purification. The product was characterized by means of spectroscopic analyses and by microanalysis.

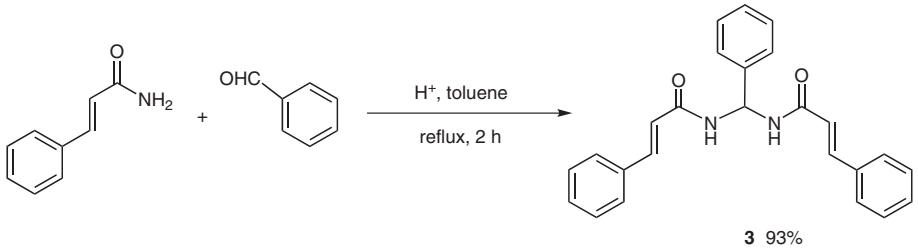
A variety of other aryl aldehydes (Figure 3) similarly reacted with *trans*-cinnamamide to give the corresponding *N*,*N*′-(arylmethylene)bis(cinnamamide)s **4**–**28** in fair to excellent yields (Table 1). The reaction of halobenzaldehydes gave bisamides **4**–**10** in good yields (entries 2–8). The reactions of 2- and 4-nitrobenzaldehydes gave bisamides **11** and **13** in 92 and 84% yield, respectively (entries 9 and 11), whereas 3-nitrobenzaldehyde gave bisamide **12** in only 49% yield (entry 10). Aldehydes in which the nitro group was replaced by a similarly electron-withdrawing trifluoromethyl group were less active (entries 12–14), particularly in the case of 2-(trifluoromethyl)benzaldehyde, which gave a yield of only 15% (entry 12).

Reactions with acetoxybenzaldehydes (entries 15 and 16) and methoxybenzaldehydes (entries 17–20) gave the corresponding bisamides **17**–**22** in good yields. 4-Cyano-,




**3**–**28**

**Figure 3** Structure of *N*,*N*′-(Arylmethylene)bis(cinnamamide)s **3**–**28**




**3** 93%

**Scheme 1** Synthesis of *N*,*N*′-benzylidenebis(cinnamamide) (**3**)

**Table 1** Yields and Melting Points of Bisamides **3**–**28**

| Entry | Product | Ar | Yield (%) | Mp[a] (°C) |
|---|---|---|---|---|
| 1 | **3** | Ph | 93 | 272–273 |
| 2 | **4** | 2-$ClC_6H_4$ | 83 | 233–236 |
| 3 | **5** | 3-$ClC_6H_4$ | 71 | 264–266 |
| 4 | **6** | 4-$ClC_6H_4$ | 73 | 265–269 |
| 5 | **7** | 2-$BrC_6H_4$ | 46 | 258–260 |
| 6 | **8** | 2-$FC_6H_4$ | 61 | 245–249 |
| 7 | **9** | 3-$FC_6H_4$ | 79 | 260–262 |
| 8 | **10** | 4-$FC_6H_4$ | 67 | 274–275 |
| 9 | **11** | 2-$O_2NC_6H_4$ | 92 | 263–265 |
| 10 | **12** | 3-$O_2NC_6H_4$ | 49 | 262–265 |
| 11 | **13** | 4-$O_2NC_6H_4$ | 84 | 281–285 |
| 12 | **14** | 2-$F_3CC_6H_4$ | 15 | 252–254 |
| 13 | **15** | 3,5-$(F_3C)_2C_6H_3$ | 58 | 289–291 |
| 14 | **16** | 4-$F_3CC_6H_4$ | 53 | 282–285 |
| 15 | **17** | 3-$AcOC_6H_4$ | 65 | 246–248 |
| 16 | **18** | 4-$AcOC_6H_4$ | 67 | 260–265 |
| 17 | **19** | 2,5-$(MeO)_2C_6H_3$ | 89 | 264–266 |
| 18 | **20** | 3,4-$(MeO)_2C_6H_3$ | 73 | 255–258 |
| 19 | **21** | 3,5-$(MeO)_2C_6H_3$ | 61 | 261–263 |
| 20 | **22** | 3,4,5-$(MeO)_3C_6H_2$ | 52 | 253–256 |
| 21 | **23** | 4-$NCC_6H_4$ | 68 | 255–259 |
| 22 | **24** | 4-Tol | 89 | 279–281 |
| 23 | **25** | 4-*t*--$BuC_6H_4$ | 83 | 288–290 |
| 24 | **26** | 1-naphthyl | 75 | 266–270 |
| 25 | **27** | 2-naphthyl | 75 | 287–289 |
| 26 | **28** | 3-pyridyl | 40 | 248–249 |

[a] Uncorrected.

4-tolyl, and 4-*tert*-butyl-substituted aryl(methylene)bis(cinnamamide)s (**23**–**24**, respectively) were obtained in 68, 89, and 83% yield (entries 21–23). The reactions of 1- and 2-naphthaldehydes gave the corresponding products **26** and **27** in 75% yield (entries 24 and 25), whereas 3-pyridinecarbaldehyde gave bisamide **28** in only 40% yield (entry 26).

Biscinnamamides are much more stable than other heteroatom-substituted methylene groups. When we examined the acid stability of bisamides under acidic conditions, compound **3** was found to survive heating at 100 °C in pH 2.5 aqueous buffer for 30 minutes without decomposition or hydrolysis.

We have also examined the reactions of crotonamide, acrylamide, and methacrylamide with several aryl aldehydes under the same conditions as those used for cinnamamide. The corresponding *N*,*N*′-(arylmethylene)bisamides **29**–**35** were obtained (Table 2) in yields that were generally lower than those obtained with cinnamamide. For example, the reaction of 4-nitrobenzaldehyde with acrylamide or crotonamide gave the corresponding bisamides **29** and **30** in 70 and 72% yield (Table 2, entries 1 and 2), whereas its reaction with methacrylamide gave **31** in 47% yield (entry 3). Other aldehydes with acrylamides or crotonamide gave bisamides **32**–**35** (entries 4–7).

We examined the cytotoxic activities of bisamides **3**–**35**. Table 3 lists $IC_{50}$ values for nine selected bisamides against HL-60 and U-937 cancer cell lines. Compounds **8** and **20** displayed excellent inhibition of cell growth. However, the effects of the substituent on the aromatic ring could not be readily explained at this stage.

In conclusion, we successfully synthesized a series of *N*,*N*′-arylmethylenebis(cinnamamide)s and *N*,*N*′-(arylmethylene)bis(acrylamide)s in a single step from inexpensive starting materials. The products showed medium cytotoxic activity with $IC_{50}$ values ranging from a few tens to several tens of micromoles per liter. Because (–)-zampanolide has been evaluated as a promising anticancer lead compound,[8] we believe that these small molecules might serve as a good lead molecule for the study of fragment-based design of drugs with an anticancer activity related to that of (–)-zampanolide.

All reagents were purchased from Sigma-Aldrich, TCI or Wako Co. Ltd. and used directly. Toluene was distilled from calcium hydride. Melting points were measured on a Yanaco MP-J3 and were uncorrected. IR spectra were recorded on a JASCO FT/IR-410 using a thin film in $CHCl_3$. $^1H$ and $^{13}C$ NMR spectra were recorded on a JEOL JNM-ECX 400 (400 MHz). Chemical shifts were internally referenced to the residual proton resonance in $CDCl_3$ (δ 7.26) for $^1H$ NMR and the solvent signals in $CDCl_3$ (δ 77.00) for $^{13}C$ NMR. Mass spectra were recorded on a JEOL JMS-SX 102A mass spectrometer operated in the fast atom bombardment (FAB) mode with double focusing magnetic sector. Elemental analyses were recorded on a Perkin-Elmer 2400 (N241-03) CHN analyzer.

### Methylenebisamides 3–35; General Procedure

The appropriate amide (2 mmol) was refluxed in dry toluene (25 mL) until it dissolved completely. To this solution was added dropwise a mixture of the appropriate aldehyde (1 mmol) and CSA (0.05 mmol) in toluene (3–5 mL) at r.t., and the resulting mixture was refluxed for 2–5 h then cooled. The precipitate that formed was collected by filtration with suction. The solid product was washed successively with benzene (2–3 mL) and $Et_2O$ (2 × 5 mL) to give an analytically pure product.

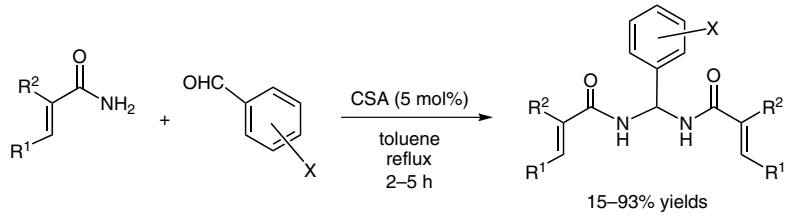
### (2*E*,2′*E*)-*N*,*N*′-(Phenylmethylene)bis(3-phenylacrylamide) (3)

White solid; yield: 711 mg (93%); mp 272–273 °C; $R_f$ = 0.35 (40% EtOAc–hexane).

IR ($CHCl_3$): 3249, 1657, 1626, 1561, 1520 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.84 (d, *J* = 7.7 Hz, 2 H), 7.56 (d, *J* = 7.3 Hz, 4 H), 7.50 (d, *J* = 15.8 Hz, 2 H), 7.32–7.14 (m, 11 H), 6.80 (m, 1 H), 6.80 (d, *J* = 15.8 Hz, 2 H).

**Table 2** Chemical Yields and Melting Points of Bisamides **29**–**35**




| Entry | Product | X | $R^1$ | $R^2$ | Yield (%) | Mp[a] ( °C) |
|---|---|---|---|---|---|---|
| 1 | **29** | 4-$NO_2$ | H | H | 70 | 248–250 |
| 2 | **30** | 4-$NO_2$ | Me | H | 72 | 267–269 |
| 3 | **31** | 4-$NO_2$ | H | Me | 47 | 201–205 |
| 4 | **32** | 4-CN | H | H | 66 | 297–300 |
| 5 | **33** | 4-CN | Me | H | 47 | 260–265 |
| 6 | **34** | 4-$CF_3$ | H | H | 44 | 225–228 |
| 7 | **35** | 3,5-$(OMe)_2$ | Me | H | 60 | 242–247 |

[a] Uncorrected.

**Table 3** Cytotoxic Activity of Nine Selected Compounds against HL-60 and U-937 Cancer Cells[a]

| Entry | Compound | $IC_{50}$ for HL-60 (μM) | $IC_{50}$ for U-937 (μM) |
|---|---|---|---|
| 1 | **8** | 21.0 | 31.8 |
| 2 | **13** | 33.3 | 28.5 |
| 3 | **18** | 34.7 | 31.6 |
| 4 | **20** | 11.2 | 30.2 |
| 5 | **21** | 35.1 | 80.5 |
| 6 | **23** | 59.4 | 47.8 |
| 7 | **32** | 28.3 | 43.1 |
| 8 | **33** | 50.5 | 54.7 |
| 9 | **34** | 45.2 | 48.6 |

[a] Other compounds prepared in this study showed weaker cytotoxic activities, with $IC_{50}$ values in excess of 100 μM.

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 164.1, 140.0, 139.5, 134.7, 129.4, 128.8, 128.3, 127.6, 127.4, 126.3, 121.7, 57.7.

MS (FAB): *m/z* = 383 $[M + H]^+$.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{25}H_{23}N_2O_2$: 383.1759; found: 383.1767.

Anal. Calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.48; H, 5.79; N, 7.28.

**(2*E*,2′*E*)-*N*,*N*′-[(2-Chlorophenyl)methylene]bis(3-phenylacrylamide) (4)**

White solid; yield: 692 mg (83%); mp 233–236 °C; $R_f$ = 0.46 (40% EtOAc–hexane).

IR ($CHCl_3$): 3272, 1658, 1629, 1577, 1557, 1516 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.96 (d, *J* = 7.3 Hz, 2 H), 7.67–7.57 (m, 5 H), 7.54 (d, *J* = 15.5 Hz, 2 H), 7.53 (m, 1 H), 7.48–7.40 (m, 8 H), 7.01 (t, *J* = 7.3 Hz, 1 H), 6.81 (d, *J* = 15.5 Hz, 2 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 164.7, 140.2, 138.0, 135.3, 132.9, 130.3, 130.2, 130.1, 129.5, 128.4, 128.1, 127.8, 122.0, 56.6.

MS (FAB): *m/z* = 417 $[M + H]^+$.

HRMS (FAB): *m/z* $[M + H]^+$ calcd for $C_{25}H_{22}ClN_2O_2$: 417.1370; found: 417.1366.

Anal. Calcd for $C_{25}H_{21}ClN_2O_2$: C, 72.02; H, 5.08; N, 6.72. Found: C, 72.01; H, 4.84; N, 6.59.

**(2*E*,2′*E*)-*N*,*N*′-[(3-Chlorophenyl)methylene]bis(3-phenylacrylamide) (5)**

White solid; yield: 591 mg (71%); mp 264–266 °C; $R_f$ = 0.58 (50% EtOAc–hexane).

IR ($CHCl_3$): 3251, 1661, 1631, 1557, 1518, 689 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.02 (d, *J* = 7.8 Hz, 2 H), 7.62–7.61 (m, 4 H), 7.55 (d, *J* = 16.0 Hz, 2 H), 7.52–7.40 (m, 10 H), 6.82 (d, *J* = 16.0 Hz, 2 H), 6.81 (m, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 165.2, 143.5, 140.8, 135.7, 134.0, 131.3, 130.6, 129.9, 128.7, 128.5, 127.2, 126.3, 122.4, 58.3.

MS (FAB): *m/z* = 417 $[M + H]^+$.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{25}H_{22}ClN_2O_2$: 417.1370; found: 417.1374.

Anal. Calcd for $C_{25}H_{21}ClN_2O_4$: C, 72.02; H, 5.08; N, 6.72. Found: C, 72.07; H, 4.91; N, 6.67.

**(2*E*,2′*E*)-*N*,*N*′-[(4-Chlorophenyl)methylene]bis(3-phenylacrylamide) (6)**

White solid; yield: 608 mg (73%); mp 265–269 °C; $R_f$ = 0.60 (50% EtOAc–hexane).

IR ($CHCl_3$): 3262, 1657, 1631, 1560, 1519, 1494, 692 $cm^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.99 (d, $J$ = 7.8 Hz, 2 H), 7.62–7.60 (m, 4 H), 7.54 (d, $J$ = 16.0 Hz, 2 H), 7.51–7.40 (m, 10 H), 6.83 (d, $J$ = 16.0 Hz, 2 H), 6.81 (m, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 165.2, 140.7, 140.0, 135.7, 133.3, 130.6, 129.9, 129.4, 129.3, 128.5, 122.5, 58.3.

MS (FAB): $m/z$ = 417 [M + H]$^+$.

HRMS (FAB): $m/z$ [M + H]$^+$ calcd for $C_{25}H_{22}ClN_2O_2$: 417.1370; found: 417.1373.

Anal. Calcd for $C_{25}H_{21}ClN_2O_2$: C, 72.02; H, 5.08; N, 6.72. Found: C, 72.29; H, 4.79; N, 6.68.

**(2*E*,2′*E*)-*N*,*N*′-[(2-Bromophenyl)methylene]bis(3-phenylacrylamide) (7)**

White solid; yield: 424 mg (46%); mp 258–260 °C; $R_f$ = 0.10 (30% EtOAc–hexane).

IR ($CHCl_3$): 3213, 1655, 1621, 1558, 1496 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.95 (d, $J$ = 7.5 Hz, 2 H), 7.71 (m, 1 H), 7.64–7.59 (m, 5 H), 7.53 (d, $J$ = 16.0 Hz, 2 H), 7.49–7.40 (m, 7 H), 7.34 (m, 1 H), 6.92 (t, $J$ = 7.5 Hz, 1 H), 6.81 (d, $J$ = 16.0 Hz, 2 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 165.1, 140.5, 140.0, 135.7, 133.8, 130.9, 130.6, 129.9, 129.0, 128.7, 128.5, 123.7, 122.4, 59.3.

MS (FAB): $m/z$ = 461 [M + H]$^+$.

HRMS-FAB: $m/z$ [M + H]$^+$ calcd for $C_{25}H_{22}{}^{79}BrN_2O_2$: 461.0864; found: 461.0861.

Anal. Calcd for $C_{25}H_{21}BrN_2O_2$: C, 65.08; H, 4.59; N, 6.07. Found: C, 65.20; H, 4.39; N, 5.99.

**(2*E*,2′*E*)-*N*,*N*′-[(2-Fluorophenyl)methylene]bis(3-phenylacrylamide) (8)**

White solid; yield: 488 mg (61%); mp 245–249 °C; $R_f$ = 0.50 (50% EtOAc–hexane).

IR ($CHCl_3$): 3262, 1653, 1626, 1558, 1507, 1065 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.00 (d, $J$ = 7.3 Hz, 2 H), 7.59–7.58 (m, 5 H), 7.54 (d, $J$ = 15.8 Hz, 2 H), 7.48–7.39 (m, 7 H), 7.31–7.26 (m, 2 H), 7.05 (t, $J$ = 7.3 Hz, 1 H), 6.81 (d, $J$ = 15.8 Hz, 2 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 165.0, 160.6 ($J_{C-F}$ = 245.0 Hz), 140.6, 135.7, 131.0 ($J_{C-F}$ = 8.6 Hz), 130.6, 129.9, 129.0 ($J_{C-F}$ = 2.9 Hz), 128.5, 128.2 ($J_{C-F}$ = 15.5 Hz), 125.3 ($J_{C-F}$ = 2.9 Hz), 122.4, 116.4 ($J_{C-F}$ = 20.9 Hz), 53.9 ($J_{C-F}$ = 3.8 Hz).

MS (FAB): $m/z$ = 401 [M + H]$^+$.

HRMS-FAB: $m/z$ [M + H]$^+$ calcd for $C_{25}H_{22}FN_2O_2$: 401.1666; found: 401.1660.

Anal. Calcd for $C_{25}H_{21}FN_2O_2$: C, 74.98; H, 5.29; N, 7.00; Found: C, 75.02; H, 5.06; N, 6.97.

**(2*E*,2′*E*)-*N*,*N*′-[(3-Fluorophenyl)methylene]bis(3-phenylacrylamide) (9)**

White solid; yield: 632 mg (79%); mp 260–262 °C; $R_f$ = 0.45 (50% EtOAc–hexane).

IR ($CHCl_3$): 3258, 1659, 1631, 1596, 1559, 1541, 1508, 1075 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.00 (d, $J$ = 7.8 Hz, 2 H), 7.63–7.60 (m, 4 H), 7.55 (d, $J$ = 16.0 Hz, 2 H), 7.52–7.40 (m, 7 H), 7.32–7.27 (m, 2 H), 7.22 (m, 1 H), 6.83 (d, $J$ = 16.0 Hz, 2 H), 6.82 (m, 1 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 165.2, 163.1 ($J_{C-F}$ = 242.2 Hz), 144.0 ($J_{C-F}$ = 6.6 Hz), 140.7, 135.7, 131.1 ($J_{C-F}$ = 7.6 Hz), 130.6, 129.9, 128.5, 123.6, 122.5, 115.5 ($J_{C-F}$ = 20.9 Hz), 114.2 ($J_{C-F}$ = 21.9 Hz), 58.3.

MS (FAB): $m/z$ = 401 [M + H]$^+$.

HRMS-FAB: $m/z$ [M + H]$^+$ calcd for $C_{25}H_{22}FN_2O_2$: 401.1666; found: 401.1658.

Anal. Calcd for $C_{25}H_{21}FN_2O_2$: C, 74.98; H, 5.29; N, 7.00. Found: C, 75.12; H, 4.99; N, 6.89.

**(2*E*,2′*E*)-*N*,*N*′-[(4-Fluorophenyl)methylene]bis(3-phenylacrylamide) (10)**

White solid; yield: 536 mg (67%); mp 274–275 °C; $R_f$ = 0.27 (40% EtOAc–hexane).

IR ($CHCl_3$): 3243, 1658, 1628, 1509, 1159 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.97 (d, $J$ = 7.7 Hz, 2 H), 7.61 (d, $J$ = 6.4 Hz, 4 H), 7.54 (d, $J$ = 15.4 Hz, 2 H), 7.51–7.40 (m, 8 H), 7.28 (t, $J$ = 8.7 Hz, 2 H), 6.85–6.81 (m, 3 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 165.2, 162.6 ($J_{C-F}$ = 242.1 Hz), 140.6, 137.3 ($J_{C-F}$ = 2.8 Hz), 135.7, 130.6, 129.9, 129.5 ($J_{C-F}$ = 30.5 Hz), 128.5, 122.6, 116.1 ($J_{C-F}$ = 87.7 Hz), 58.3.

MS (FAB): $m/z$ = 401 [M + H]$^+$.

HRMS-FAB: $m/z$ [M + H]$^+$ calcd for $C_{25}H_{22}FN_2O_2$: 401.1666; found: 401.1661.

Anal. Calcd for $C_{25}H_{21}FN_2O_2$: C, 74.98; H, 5.29; N, 7.00. Found: C, 75.05; H, 5.16; N, 6.79.

**(2*E*,2′*E*)-*N*,*N*′-[(2-Nitrophenyl)methylene]bis(3-phenylacrylamide) (11)**

White solid; yield: 786 mg (92%); mp 263–265 °C; $R_f$ = 0.50 (50% EtOAc–hexane).

IR ($CHCl_3$): 3270, 1657, 1630, 1556, 1527, 1507, 1346 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.08 (d, $J$ = 7.3 Hz, 2 H), 8.03 (m, 1 H), 7.86–7.78 (m, 2 H), 7.66 (m, 1 H), 7.62–7.61 (m, 4 H), 7.55 (d, $J$ = 16.0 Hz, 2 H), 7.48–7.40 (m, 6 H), 7.23 (t, $J$ = 7.5 Hz, 1 H), 6.77 (d, $J$ = 16.0 Hz, 2 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 165.3, 149.2, 140.8, 135.6, 134.8, 134.2, 130.6, 130.4, 129.9, 129.4, 128.5, 125.4, 122.1, 55.8.

MS (FAB): $m/z$ = 428 [M + H]$^+$.

HRMS-FAB: $m/z$ [M + H]$^+$ calcd for $C_{25}H_{22}N_3O_4$: 428.1610; found: 428.1603.

Anal. Calcd for $C_{25}H_{21}N_3O_4$: C, 70.25; H, 4.95; N, 9.83. Found: C, 70.46; H, 5.07; N, 10.06.

**(2*E*,2′*E*)-*N*,*N*′-[(3-Nitrophenyl)methylene]bis(3-phenylacrylamide) (12)**

White solid; yield: 418 mg (49%); mp 262–265 °C; $R_f$ = 0.31 (50% EtOAc–hexane).

IR ($CHCl_3$): 3264, 1660, 1631, 1558, 1524, 1349 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 9.16 (d, $J$ = 7.3 Hz, 2 H), 8.32 (s, 1 H), 8.25 (d, $J$ = 8.1 Hz, 1 H), 7.93 (d, $J$ = 8.1 Hz, 1 H), 7.61 (t, $J$ = 8.1 Hz, 1 H), 7.63–7.61 (m, 4 H), 7.56 (d, $J$ = 16.0 Hz, 2 H), 7.50–7.40 (m, 6 H), 6.90 (t, $J$ =7.5 Hz, 1 H), 6.83 (d, $J$ = 16.0 Hz, 2 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ = 165.4, 148.8, 143.3, 141.0, 135.6, 134.5, 131.1, 130.7, 129.9, 128.6, 123.8, 122.3, 121.9, 58.4.

MS (FAB): $m/z$ = 428 [M + H]$^+$.

HRMS-FAB: $m/z$ [M + H]$^+$ calcd for $C_{25}H_{22}N_3O_4$: 428.1610; found: 428.1601.

Anal. Calcd for $C_{25}H_{21}N_3O_4$: C, 70.25; H, 4.95; N, 9.83. Found: C, 70.36; H, 4.70; N, 9.83.

**(2*E*,2′*E*)-*N*,*N*′-[(4-Nitrophenyl)methylene]bis(3-phenylacrylamide) (13)**

White solid; yield: 718 mg (84%); mp 281–285 °C; $R_f$ = 0.43 (50% EtOAc–hexane).

IR ($CHCl_3$): 3266, 1660, 1631, 1558, 1524, 1349 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.14 (d, *J* = 7.7 Hz, 2 H), 8.32 (d, *J* = 8.7 Hz, 2 H), 7.73 (d, *J* = 8.2 Hz, 2 H), 7.62 (d, *J* = 6.8 Hz, 4 H), 7.57 (d, *J* = 16.0 Hz, 2 H), 7.48–7.41 (m, 6 H), 6.90 (t, *J* = 7.7 Hz, 1 H), 6.84 (d, *J* = 16.0 Hz, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 165.5, 148.4, 148.0, 141.0, 135.6, 130.7, 129.9, 128.8, 128.6, 124.6, 122.3, 58.4.

MS (FAB): *m/z* = 428 $[M + H]^+$.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{25}H_{22}N_3O_4$: 428.1610; found: 428.1614.

Anal. Calcd for $C_{25}H_{21}N_3O_4$: C, 70.25; H, 4.95; N, 9.83. Found: C, 70.31; H, 5.02; N, 9.86.

**(2*E*,2′*E*)-*N*,*N*′-{[2-(Trifluoromethyl)phenyl]methylene}bis(3-phenylacrylamide) (14)**

White solid; yield: 135 mg (15%); mp 252–254 °C; $R_f$ = 0.69 (50% EtOAc–hexane).

IR ($CHCl_3$): 3244, 1655, 1626, 1557, 1508, 1123 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.01 (d, *J* = 6.8 Hz, 2 H), 7.89 (m, 1 H), 7.83–7.79 (m, 2 H), 7.63–7.58 (m, 5 H), 7.51 (d, *J* = 15.5 Hz, 2 H), 7.49–7.39 (m, 6 H), 7.11 (t, *J* = 6.8 Hz, 1 H), 6.77 (d, *J* = 15.5 Hz, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 164.8, 140.6, 139.8, 135.7, 133.8, 130.6, 129.9, 129.5, 129.2, 128.5, 127.8 ($J_{C-F}$ = 271.1 Hz), 127.4 ($J_{C-F}$ = 30.5 Hz), 127.0 ($J_{C-F}$ = 10.0 Hz), 122.4, 56.1.

MS (FAB): *m/z* = 451 $[M + H]^+$.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}F_3N_2O_2$: 451.1634; found: 451.1636.

Anal. Calcd for $C_{26}H_{21}F_3N_2O_2$: C, 69.33; H, 4.70; N, 6.22. Found: C, 69.53; H, 4.90; N, 6.02.

**(2*E*,2′*E*)-*N*,*N*′-{[3,5-Bis(trifluoromethyl)phenyl]methylene}bis(3-phenylacrylamide) (15)**

White solid; yield: 601 mg (58%); mp 289–291 °C; $R_f$ = 0.69 (50% EtOAc–hexane).

IR ($CHCl_3$): 3255, 1664, 1635, 1558, 1540, 1507, 1127 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.18 (d, *J* = 7.7 Hz, 2 H), 8.16 (s, 3 H), 7.64–7.63 (m, 4 H), 7.56 (d, *J* = 15.5 Hz, 2 H), 7.50–7.40 (m, 6 H), 6.92 (t, *J* = 7.7 Hz, 1 H), 6.80 (d, *J* = 15.5 Hz, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 165.5, 144.4, 141.1, 135.5, 131.2 ($J_{C-F}$ = 32.4 Hz), 130.7, 129.9, 128.6, 128.5, 124.2 ($J_{C-F}$ = 271.0 Hz), 122.8, 122.1, 58.4.

MS (FAB): *m/z* = 519 $[M + H]^+$.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{27}H_{21}F_6N_2O_2$: 519.1507; found: 519.1510.

Anal. Calcd for $C_{27}H_{20}F_6N_2O_2$: C, 62.55; H, 3.89; N, 5.40. Found: C, 62.85; H, 3.84; N, 5.69.

**(2*E*,2′*E*)-*N*,*N*′-{[4-(Trifluoromethyl)phenyl]methylene}bis(3-phenylacrylamide) (16)**

White solid; yield: 477 mg (53%); mp 282–285 °C; $R_f$ = 0.48 (50% EtOAc–hexane).

IR ($CHCl_3$): 3254, 1660, 1632, 1558, 1520, 1115 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.07 (d, *J* = 7.7 Hz, 2 H), 7.85 (d, *J* = 8.7 Hz, 2 H), 7.68 (d, *J* = 8.7 Hz, 2 H), 7.63–7.61 (m, 4 H), 7.56 (d, *J* = 15.5 Hz, 2 H), 7.48–7.40 (m, 6 H), 6.87 (t, *J* = 7.7 Hz, 1 H), 6.83 (d, *J* = 15.5 Hz, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 165.4, 145.6, 140.8, 135.7, 130.6, 129.9, 129.4 ($J_{C-F}$ = 51.4 Hz), 128.5, 128.3, 126.3 ($J_{C-F}$ = 3.8 Hz), 125.2 ($J_{C-F}$ = 270.7 Hz), 122.4, 58.5.

MS (FAB): *m/z* = 451 $[M + H]^+$.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}F_3N_2O_2$: 451.1634; found: 451.1630.

Anal. Calcd for $C_{26}H_{21}F_3N_2O_2$: C, 69.33; H, 4.70; N, 6.22. Found: C, 69.62; H, 4.62; N, 6.45.

**3-(Bis{[(2*E*)-3-phenylprop-2-enoyl]amino}methyl)phenyl Acetate (17)**

White solid; yield: 551 mg (65%); mp 246–248 °C; $R_f$ = 0.39 (50% EtOAc–hexane).

IR ($CHCl_3$): 3265, 1772, 1657, 1632, 1557, 1508 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.00 (d, *J* = 8.2 Hz, 2 H), 7.62–7.61 (m, 4 H), 7.55 (d, *J* = 16.0 Hz, 2 H), 7.51–7.40 (m, 7 H), 7.35 (m, 1 H), 7.20 (s, 1 H), 7.16–7.14 (m, 1 H), 6.87 (t, *J* = 8.2 Hz, 1 H), 6.85 (dd, *J* = 16.0 Hz, 2 H), 2.30 (s, 3 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 170.1, 165.2, 151.5, 142.8, 140.7, 135.7, 130.6, 130.4, 129.9, 128.5, 124.8, 122.5, 122.3, 120.6, 58.2, 21.8.

MS (FAB): *m/z* = 441 $[M + H]^+$.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{27}H_{25}N_2O_4$: 441.1814; found: 441.1806.

Anal. Calcd for $C_{27}H_{24}N_2O_4$: C, 73.62; H, 5.49; N, 6.36. Found: C, 73.82; H, 5.39; N, 6.34.

**4-(Bis{[(2*E*)-3-phenylprop-2-enoyl]amino}methyl)phenyl Acetate (18)**

White solid; yield: 568 mg (67%); mp 260–265 °C; $R_f$ = 0.50 (50% EtOAc–hexane).

IR ($CHCl_3$): 3265, 1654, 1625, 1559, 1520 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.98 (d, *J* = 7.7 Hz, 2 H), 7.62–7.60 (m, 4 H), 7.55 (d, *J* = 15.5 Hz, 2 H), 7.50 (d, *J* = 8.2 Hz, 2 H), 7.48–7.40 (m, 6 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 6.88 (t, *J* = 7.7 Hz, 1 H), 6.84 (d, *J* = 15.5 Hz, 2 H), 2.31 (s, 3 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 170.0, 165.1, 150.8, 140.5, 138.5, 135.7, 130.4, 129.7, 128.4, 122.6, 122.5, 58.3, 21.6.

MS (FAB): *m/z* = 441 $[M + H]^+$.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{27}H_{25}N_2O_4$: 441.1814; found: 428.1818.

Anal. Calcd for $C_{27}H_{24}N_2O_4$: C, 73.62; H, 5.49; N, 6.36. Found: C, 73.49; H, 5.31; N, 6.12.

**(2*E*,2′*E*)-*N*,*N*′-[(2,5-Dimethoxyphenyl)methylene]bis(3-phenylacrylamide) (19)**

White solid; yield: 787 mg (89%); mp 264–266 °C; $R_f$ = 0.32 (70% EtOAc–hexane).

IR ($CHCl_3$): 3238, 1653, 1618, 1506 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.74 (d, $J$ = 7.3 Hz, 2 H), 7.60–7.58 (m, 4 H), 7.49 (d, $J$ = 15.5 Hz, 2 H), 7.49–7.39 (m, 6 H), 7.08 (d, $J$ = 3.2 Hz, 1 H), 7.01 (d, $J$ = 9.1 Hz, 1 H), 6.99 (t, $J$ = 7.5 Hz, 1 H), 6.93 (dd, $J$ = 9.1, 3.2 Hz, 1 H), 6.80 (d, $J$ = 15.5 Hz, 2 H), 3.80 (s, 3 H), 3.75 (s, 3 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 164.8, 154.0, 151.5, 140.2, 135.8, 130.5, 130.2, 129.9, 128.5, 122.9, 114.9, 113.8, 113.3, 57.1, 56.4, 54.5.

MS (FAB): $m/z$ = 443 $[M + H]^+$.

HRMS-FAB: $m/z$ $[M + H]^+$ calcd for $C_{27}H_{27}N_2O_4$: 443.1971; found: 443.1962.

Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 73.28; H, 5.92; N, 6.33. Found: C, 73.45; H, 5.80; N, 6.57.

**(2*E*,2′*E*)-*N*,*N*′-[(3,4-Dimethoxyphenyl)methylene]bis(3-phenylacrylamide) (20)**

White solid; yield: 646 mg (73%); mp 255–258 °C; $R_f$ = 0.20 (50% EtOAc–hexane).

IR ($CHCl_3$): 3274, 1657, 1628, 1559, 1519 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.86 (d, $J$ = 7.7 Hz, 2 H), 7.61–7.59 (m, 4 H), 7.52 (d, $J$ = 16.0 Hz, 2 H), 7.48–7.39 (m, 6 H), 7.07 (s, 1 H), 7.00 (s, 2 H), 6.82 (d, $J$ = 16.0 Hz, 2 H), 6.77 (t, $J$ = 7.7 Hz, 1 H), 3.81 (s, 3 H), 3.78 (s, 3 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 165.0, 149.6, 149.4, 140.4, 135.8, 133.5, 130.5, 129.9, 128.5, 122.8, 119.5, 112.5, 111.3, 58.6, 56.6, 56.5.

MS (FAB): $m/z$ = 443 $[M + H]^+$.

HRMS-FAB: $m/z$ $[M + H]^+$ calcd for $C_{27}H_{27}N_2O_4$: 443.1971; found: 443.1967.

Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 73.28; H, 5.92; N, 6.33. Found: C, 73.10; H, 5.92; N, 6.36.

**(2*E*,2′*E*)-*N*,*N*′-[(3,5-Dimethoxyphenyl)methylene]bis(3-phenylacrylamide) (21)**

White solid; yield: 539 mg (61%); mp 261–263 °C; $R_f$ = 0.46 (70% EtOAc–hexane).

IR ($CHCl_3$): 3253, 1653, 1620, 1523 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.89 (d, $J$ = 7.7 Hz, 2 H), 7.61–7.59 (m, 4 H), 7.53 (d, $J$ = 16.0 Hz, 2 H), 7.48–7.39 (m, 6 H), 6.82 (d, $J$ = 16.0 Hz, 2 H), 6.75 (t, $J$ = 7.7 Hz, 1 H), 6.63 (d, $J$ = 1.8 Hz, 2 H), 6.52 (t, $J$ = 1.8 Hz, 1 H), 3.79 (s, 6 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 165.1, 161.5, 143.5, 140.5, 135.7, 130.5, 129.9, 128.5, 122.7, 105.7, 100.2, 58.7, 56.2.

MS (FAB): $m/z$ = 443 $[M + H]^+$.

HRMS-FAB: $m/z$ $[M + H]^+$ calcd for $C_{27}H_{27}N_2O_4$: 443.1971; found: 443.1965.

Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 73.28; H, 5.92; N, 6.33. Found: C, 73.54; H, 5.85; N, 6.39.

**(2*E*,2′*E*)-*N*,*N*′-[(3,4,5-Trimethoxyphenyl)methylene]bis(3-phenylacrylamide) (22)**

White solid; yield: 491 mg (52%); mp 253–256 °C; $R_f$ = 0.64 (EtOAc).

IR ($CHCl_3$): 3213, 1655, 1621, 1558, 1496 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.18 (d, $J$ = 7.7 Hz, 2 H), 7.98 (d, $J$ = 6.8 Hz, 4 H), 7.90 (d, $J$ = 16.0 Hz, 2 H), 7.85–7.79 (m, 6 H), 7.21–7.15 (m, 5 H), 4.21 (s, 6 H), 4.08 (s, 3 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 164.1, 152.9, 139.6, 137.4, 136.0, 134.9, 129.6, 129.0, 127.6, 122.0, 104.2, 60.0, 58.1, 56.1, 56.0.

MS (FAB): $m/z$ = 473 $[M + H]^+$.

HRMS-FAB: $m/z$ $[M + H]^+$ calcd for $C_{28}H_{29}N_2O_5$: 473.2076; found: 473.2072.

Anal. Calcd for $C_{28}H_{28}N_2O_5$: C, 71.17; H, 5.97; N, 5.93. Found: C, 71.47; H, 5.97; N, 5.93.

**(2*E*,2′*E*)-*N*,*N*′-[(4-Cyanophenyl)methylene]bis(3-phenylacrylamide) (23)**

White solid; yield: 554 mg (68%); mp 255–259 °C; $R_f$ = 0.29 (50% EtOAc–hexane).

IR ($CHCl_3$): 3215, 2231, 1669, 1624, 1558, 1520 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.09 (d, $J$ = 7.7 Hz, 2 H), 7.93 (d, $J$ = 8.2 Hz, 2 H), 7.65 (d, $J$ = 8.2 Hz, 2 H), 7.62–7.61 (m, 4 H), 7.56 (d, $J$ = 15.5 Hz, 2 H), 7.50–7.40 (m, 6 H), 6.86 (t, $J$ = 7.7 Hz, 1 H), 6.83 (d, $J$ = 15.5 Hz, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 165.4, 146.4, 140.9, 135.6, 133.4, 130.7, 129.9, 128.6, 128.5, 122.3, 119.7, 111.5, 58.6.

MS (FAB): $m/z$ = 408 $[M + H]^+$.

HRMS-FAB: $m/z$ $[M + H]^+$ calcd for $C_{26}H_{22}N_3O_2$: 408.1712; found: 408.1716.

Anal. Calcd for $C_{26}H_{21}N_3O_2$: C, 76.64; H, 5.19; N, 10.31. Found: C, 76.44; H, 4.92; N, 10.12.

**(2*E*,2′*E*)-*N*,*N*′-[(4-Tolyl)methylene]bis(3-phenylacrylamide) (24)**

White solid; yield: 705 mg (89%); mp 279–281 °C; $R_f$ = 0.33 (40% EtOAc–hexane).

IR ($CHCl_3$): 3265, 1658, 1630, 1562, 1514 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.89 (d, $J$ = 7.7 Hz, 2 H), 7.61–7.59 (m, 4 H), 7.53 (d, $J$ = 16.0 Hz, 2 H), 7.48–7.39 (m, 6 H), 7.34 (d, $J$ = 8.2 Hz, 2 H), 7.24 (d, $J$ = 8.2 Hz, 2 H), 6.84 (d, $J$ = 16.0 Hz, 2 H), 6.80 (t, $J$ = 7.7 Hz, 1 H), 2.34 (s, 3 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 165.1, 140.4, 138.1, 137.9, 135.8, 130.5, 129.9, 129.8, 128.5, 127.3, 122.7, 58.5, 21.6.

MS (FAB): $m/z$ = 397 $[M + H]^+$.

HRMS-FAB: $m/z$ $[M + H]^+$ calcd for $C_{26}H_{25}N_2O_2$: 397.1916; found: 397.1920.

Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.58; H, 6.19; N, 7.04.

**(2*E*,2′*E*)-*N*,*N*′-[(4-*tert*-Butylphenyl)methylene]bis(3-phenylacrylamide) (25)**

White solid; yield: 728 mg (83%); mp 288–290 °C; $R_f$ = 0.63 (50% EtOAc–hexane).

IR ($CHCl_3$): 3220, 1654, 1558, 1540, 1520, 1508 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.73 (d, $J$ = 7.7 Hz, 2 H), 7.55 (d, $J$ = 7.3 Hz, 4 H), 7.47 (d, $J$ = 15.5 Hz, 2 H), 7.42–7.32 (m, 10 H), 6.77 (d, $J$ = 15.5 Hz, 2 H), 6.74 (t, $J$ = 7.7 Hz, 1 H), 1.27 (s, 9 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 164.9, 151.0, 140.2, 138.1, 135.7, 130.3, 129.7, 128.3, 126.9, 125.9, 122.7, 58.5, 35.0, 31.9.

MS (FAB): $m/z$ = 439 $[M + H]^+$.

HRMS-FAB: $m/z$ $[M + H]^+$ calcd for $C_{29}H_{31}N_2O_2$: 439.2385; found: 439.2393.

Anal. Calcd for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.90; N, 6.39. Found: C, 79.67; H, 6.83; N, 6.54.

**(2*E*,2′*E*)-*N*,*N*′-(1-Naphthylmethylene)bis(3-phenylacrylamide) (26)**

White solid; yield: 648 mg (75%); mp 266–270 °C; $R_f$ = 0.47 (50% EtOAc–hexane).

IR ($CHCl_3$): 3264, 1659, 1626, 1558, 1518 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.03 (d, *J* = 7.7 Hz, 2 H), 8.00 (d, *J* = 6.0 Hz, 1 H), 7.95 (t, *J* = 9.1 Hz, 2 H), 7.69 (d, *J* = 6.8 Hz, 1 H), 7.57–7.51 (m, 9 H), 7.42–7.35 (m, 6 H), 6.79 (d, *J* = 16.0 Hz, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 164.3, 139.9, 135.7, 134.9, 133.6, 130.4, 129.8, 129.1, 128.9, 128.7, 127.7, 126.8, 126.1, 125.4, 123.5, 122.9, 121.7, 55.3.

MS (FAB): *m*/*z* = 433 $[M + H]^+$.

HRMS-FAB: *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{25}N_2O_2$: 433.1916; found: 433.1909.

Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.29; H, 5.58; N, 6.35.

**(2*E*,2′*E*)-*N*,*N*′-(2-Naphthylmethylene)bis(3-phenylacrylamide) (27)**

White solid; yield: 648 mg (75%); mp 287–289 °C; $R_f$ = 0.33 (40% EtOAc–hexane).

IR ($CHCl_3$): 3261, 1656, 1625, 1556, 1507 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.92 (d, *J* = 7.7 Hz, 2 H), 7.96–7.90 (m, 4 H), 7.57–7.49 (m, 9 H), 7.43–7.35 (m, 6 H), 6.96 (t, *J* = 7.7 Hz, 1 H), 6.82 (d, *J* = 15.5 Hz, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 164.4, 139.7, 137.7, 134.9, 132.7, 132.6, 129.6, 129.0, 128.1, 127.9, 127.6, 127.5, 126.4, 126.2, 124.9, 124.8, 121.9, 58.1.

MS (FAB): *m*/*z* = 433 $[M + H]^+$.

HRMS-FAB: *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{25}N_2O_2$: 433.1916; found: 433.1925.

Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.62; H, 5.57; N, 6.56.

**(2*E*,2′*E*)-*N*,*N*′-(Pyridin-3-ylmethylene)bis(3-phenylacrylamide) (28)**

White solid; yield: 306 mg (40%); mp 248–249 °C; $R_f$ = 0.45 (70% EtOAc–hexane).

IR ($CHCl_3$): 3210, 3019, 1654, 1615, 1556, 1519 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.07 (d, *J* = 7.3 Hz, 2 H), 8.68 (m, 1 H), 8.59–8.58 (m, 1 H), 7.86 (m, 1 H), 7.63–7.60 (m, 4 H), 7.55 (d, *J* = 16.0 Hz, 2 H), 7.50–7.40 (m, 7 H), 6.84 (t, *J* = 7.3 Hz, 1 H), 6.82 (d, *J* = 16.0 Hz, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 165.3, 149.9, 148.9, 140.8, 136.5, 135.7, 135.3, 130.6, 129.9, 128.5, 124.4, 122.4, 57.4.

MS (FAB): *m*/*z* = 384 $[M + H]^+$.

HRMS-FAB: *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{22}N_3O_2$: 384.1712; found: 384.1706.

Anal. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96. Found: C, 74.89; H, 5.39; N, 10.87.

***N*,*N*′-[(4-Nitrophenyl)methylene]bisacrylamide (29)**

White solid; yield: 336 mg (70%); mp 248–250 °C; $R_f$ = 0.33 (70% EtOAc–hexane).

IR ($CHCl_3$): 3272, 1669, 1625, 1558, 1508, 1354 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.09 (d, *J* = 7.8 Hz, 2 H), 8.30 (d, *J* = 8.7 Hz, 2 H), 7.65 (d, *J* = 8.7 Hz, 2 H), 6.77 (t, *J* = 7.8 Hz, 1 H), 6.39 (dd, *J* = 16.9, 10.0 Hz, 2 H), 6.21, (dd, *J* = 16.9, 1.8 Hz, 2 H), 5.72 (dd, *J* = 10.0, 1.8 Hz, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 165.0, 148.1, 148.0, 131.9, 128.8, 127.7, 124.6, 58.2.

MS (FAB): *m*/*z* = 276 $[M + H]^+$.

HRMS-FAB: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{14}N_3O_4$: 276.0984; found: 276.0991.

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.68; H, 4.48; N, 15.42.

**(2*E*,2′*E*)-*N*,*N*′-[(4-Nitrophenyl)methylene]bis(but-2-enamide) (30)**

White solid; yield: 385 mg (72%); mp 267–269 °C; $R_f$ = 0.41 (70% EtOAc–hexane).

IR ($CHCl_3$): 3262, 1671, 1646, 1541, 1508, 1349 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.82 (d, *J* = 7.8 Hz, 2 H), 8.28 (d, *J* = 8.7 Hz, 2 H), 7.61 (d, *J* = 8.7 Hz, 2 H), 6.74 (t, *J* = 7.8 Hz, 1 H), 6.73 (dd, *J* = 15.5, 6.8 Hz, 2 H), 6.07 (dd, *J* = 15.5, 1.8 Hz, 2 H), 1.84 (dd, *J* = 6.8, 1.8 Hz, 6 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 165.3, 148.7, 147.8, 140.4, 128.7, 126.0, 124.5, 58.0, 18.4.

MS (FAB): *m*/*z* = 304 $[M + H]^+$.

HRMS-FAB: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{18}N_3O_4$: 304.1297; found: 304.1302.

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.35; H, 5.46; N, 13.80.

***N*,*N*′-[(4-Nitrophenyl)methylene]bis(2-methylacrylamide) (31)**

White solid; yield: 382 mg (47%); mp 201–205 °C; $R_f$ = 0.36 (70% EtOAc–hexane).

IR ($CHCl_3$): 3264, 1661, 1626, 1513 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 8.59 (d, *J* = 7.7 Hz, 2 H), 8.27 (d, *J* = 8.7 Hz, 2 H), 7.65 (d, *J* = 8.7 Hz, 2 H), 6.83 (t, *J* = 7.7 Hz, 1 H), 5.82 (s, 2 H), 5.50 (s, 2 H), 1.93 (s, 6 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ =167.6, 148.8, 147.9, 140.0, 128.6, 124.5, 121.6, 58.5, 19.3.

MS (FAB): *m*/*z* = 304 $[M + H]^+$.

HRMS-FAB: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{18}N_3O_4$: 304.1297; found: 304.1302.

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.45; H, 5.67; N, 14.00.

***N*,*N*′-[(4-Cyanophenyl)methylene]bisacrylamide (32)**

White solid; yield: 266 mg (66%); mp 297–300 °C; $R_f$= 0.35 (70% EtOAc–hexane). IR ($CHCl_3$): 3261, 2232, 1668, 1634, 1558, 1541 $cm^{-1}$.

$^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 9.03 (d, *J* = 7.7 Hz, 2 H), 7.91 (d, *J* = 8.2 Hz, 2 H), 7.57 (d, *J* = 8.2 Hz, 2 H), 6.73 (t, *J* = 7.7 Hz, 1 H), 6.38 (dd, *J* = 16.8, 10.0 Hz, 2 H), 6.20 (dd, *J* = 16.8, 1.8 Hz, 2 H), 5.74 (dd, *J* = 10.0, 1.8 Hz, 2 H).

$^{13}C$ NMR (100 MHz, DMSO-$d_6$): δ = 165.0, 146.1, 133.4, 131.9, 128.4, 127.6, 119.6, 111.5, 58.4.

MS (FAB): *m*/*z* = 256 $[M + H]^+$.

HRMS-FAB: *m/z* [M + H]$^+$ calcd for $C_{14}H_{14}N_3O_2$: 256.1086; found: 256.1082.

Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 66.01; H, 4.89; N, 16.49.

**(2*E*,2′*E*)-*N*,*N*′-[(4-Cyanophenyl)methylene]bis(but-2-enamide) (33)**

White solid; yield: 285 mg (47%); mp 260–265 °C; $R_f$ = 0.36 (70% EtOAc–hexane).

IR ($CHCl_3$): 3253, 2230, 1677, 1648, 1558, 1541 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.63 (d, *J* = 7.7 Hz, 2 H), 7.82 (d, *J* = 8.2 Hz, 2 H), 7.48 (d, *J* = 8.2 Hz, 2 H), 6.72–6.63 (m, 1 H), 6.68 (dt, *J* = 15.5, 6.8 Hz, 2 H), 6.03 (t, *J* = 7.7 Hz, 2 H), 1.79 (d, *J* = 6.8 Hz, 6 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ =164.4, 145.9, 139.3, 132.3, 127.4, 125.3, 118.7, 110.4, 57.3, 17.4.

MS (FAB): *m/z* = 284 [M + H]$^+$.

HRMS-FAB: *m/z* [M + H]$^+$ calcd for $C_{16}H_{18}N_3O_2$: 284.1399; found: 284.1392.

Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.77; H, 5.72; N, 15.08.

***N*,*N*′-{[4-(Trifluoromethyl)phenyl]methylene}bisacrylamide (34)**

White solid; yield: 262 mg (44%); mp 225–228 °C; $R_f$ = 0.23 (50% EtOAc–hexane).

IR ($CHCl_3$): 3271, 1668, 1629, 1559 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ =9.02 (d, *J* = 7.3 Hz, 2 H), 7.81 (d, *J* = 8.2 Hz, 2 H), 7.60 (d, *J* = 8.2 Hz, 2 H), 6.75 (t, *J* = 7.3 Hz, 1 H), 6.39 (dd, *J* = 16.9, 10.0 Hz, 2 H), 6.20 (dd, *J* = 16.9, 1.8 Hz, 2 H), 5.71 (dd, *J*= 10.0 1.8 Hz, 2 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ =164.9, 145.4, 132.0, 129.4 ($J_{C-F}$ = 32.4 Hz), 128.3, 127.5, 126.4 ($J_{C-F}$ = 3.8 Hz), 125.1 ($J_{C-F}$ = 270.0 Hz), 58.4.

MS (FAB): *m/z* = 299 [M + H]$^+$.

HRMS-FAB: *m/z* [M + H]$^+$ calcd for $C_{14}H_{14}F_3N_2O_2$: 299.1007; found: 299.1013.

Anal. Calcd for $C_{14}H_{13}F_3N_2O_2$: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.01; H, 4.01; N, 9.27.

**(2*E*,2′*E*)-*N*,*N*′-[(3,5-Dimethoxyphenyl)methylene]bis(but-2-enamide) (35)**

White solid; yield: 436 mg (60%); mp 242–247 °C; $R_f$ = 0.36 (70% EtOAc–hexane).

IR ($CHCl_3$): 3272, 1672, 1644, 1560, 1559, 1522 cm$^{-1}$.

$^1$H NMR (400 MHz, DMSO-$d_6$): δ = 8.41 (d, *J* = 7.7 Hz, 2 H), 6.65 (dq, *J* = 15.1, 6.9 Hz, 2 H), 6.55 (t, *J* = 7.7 Hz, 1 H), 6.47 (d, *J* = 2.3 Hz, 2 H), 6.42 (t, *J* = 2.3 Hz, 1 H), 6.00 (dd, *J* = 15.1, 1.8 Hz, 2 H), 3.72 (s, 6 H), 1.78 (dd, *J* = 6.8, 1.3 Hz, 6 H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ =164.0, 160.5, 142.9, 138.8, 125.6, 104.8, 99.2, 57.4, 55.3, 17.4.

MS (FAB): *m/z* = 319 [M + H]$^+$.

HRMS-FAB: *m/z* [M + H]$^+$ calcd for $C_{17}H_{23}N_2O_4$: 319.1658; found: 319.1655.

Anal. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80. Found: C, 64.34; H, 6.71; N, 8.73.

**Cell Culture and Cytotoxicity Assay**

HL-60 cells and U937 cells were maintained in Roswell Park Memorial Institute (RPMI) medium, supplemented with 10% fetal bovine serum. The cells were initially cultured under humidified 5% $CO_2$/95% air on 96-well plates (5000 cells/well) in an incubator at 37 °C for 24 h. Various concentrations of the relevant sample were added, and the cells were incubated at 37 °C for a further 72 h. Inhibition of cell growth was then measured by means of a WST-8 assay. The cytotoxic effects of the compounds were evaluated in terms of the percentage growth inhibition and are indicated as $IC_{50}$ values.

## Acknowledgements

This work was supported by the Ministry of Education, Science, and Culture of Japan.

## Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380437.

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