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Original article

# Synthesis and cytotoxicity of 3-aryl acrylic amide derivatives of the simplified saframycin–ecteinascidin skeleton prepared from L-dopa

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ABSTRACT

Twenty four compounds with diversified 3-aryl acrylic amide side chains of the simplified saframycin–ecteinascidin pentacyclic skeleton were synthesized via a 14-step stereospecific route starting from L-dopa. The cytotoxicities of these compounds were tested against eight human tumor cell lines including HCT-8, BEL-7402, BGC-803, A549, A2780, MCF-7, MX-1, and MDA-MB-231. Most of these compounds exhibited potent antitumor activity, and a preliminary structure–activity relationship (SAR) was discussed. Compound **28** with 3-thiophenyl acrylic amide side chain exhibited selective cytotoxicity against MDA-MB-231 cell line with the $IC_{50}$ value of 50 nM.



## 1. Introduction

Bistetrahydroisoquinoline is a large family of natural products that display a range of biological properties such as antitumor and antimicrobial activities [1]. Ecteinascidin 743 (Et-743), which is isolated from the Caribbean tunicate *Ecteinascidia turbinate*, is the most potent one of this family and has been launched in Germany and UK for the treatment of soft tissue sarcoma [2]. The total synthesis of these tetrahydroisoquinoline alkaloids has been studied by us and many other research groups [3–8]. Since the bistetrahydroisoquinoline alkaloids are excellent lead compounds for the search of new antitumor drugs, studies have been reported on their structural modification [9]. As a result, a few promising novel antitumor agents have been discovered, such as phthalascidin (Pt-650) [10–12] and Zalypsis [13–15] (Fig. 1).

In our previous work, we synthesized a series of analogs of a simplified bistetrahydroisoquinoline skeleton prepared from L-dopa [16]. Among those analogs, the compound with the 3-phenyl acrylic acid side chain was found to show promising cytotoxicity. Interestingly, Zalypsis, which is being clinically tested, had a similar (2*E*)-3-(3-thifluoromethyl-phenyl) acrylic amide side chain. Inspired both by our results and the structure of Zalypsis, we decide to further study the structure–activity relationship of this type of simplified compounds with the focus on the investigation of the SAR of the aryl moiety of 3-aryl acrylic amide. All the analogs were evaluated for their *in vitro* cytotoxicity against HCT-8, BEL-7402, BGC-823, A549, A2780, MCF-7 MX-1 and MDA-MB-231 human tumor cell lines.

## 2. Chemistry

The synthetic route basically follows our previous one with the sole difference in the final steps of replacing the *N*-Cbz with *N*-Boc protecting group, which avoided the side reactions in the reductive cyanation step and thus improved the synthetic efficiency. Intermediate **1** was prepared according to the synthetic procedure as we have reported [16c]. Removal of the *N*-Cbz group of **1** by catalytic hydrogenation afforded compound **2**, which was then protected by $(Boc)_2O$ to give **3**. Partial reduction of the lactam ring of **3** to the corresponding cyclic hemiaminal was followed by treatment with KCN to yield compound **4**. Cleavage of the Boc group by $CF_3COOH$ at

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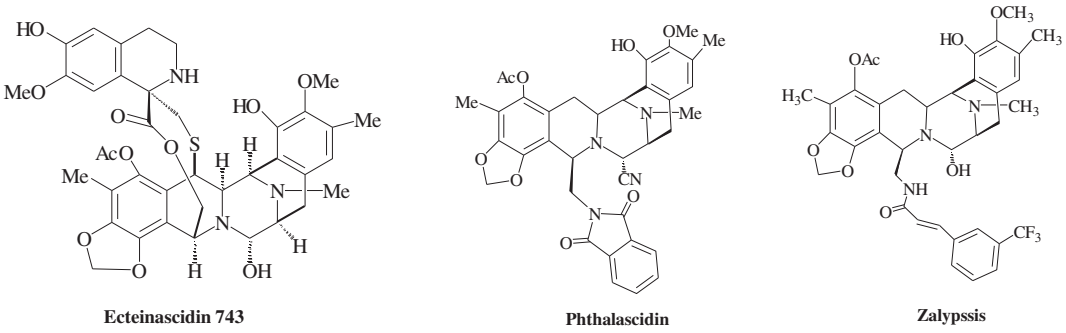



**Fig. 1.** Structures of Et-743, phthalascidin and Zalypsis.

room temperature provided precursor **5**, which was acylated with various 3-aryl acrylic acids to afford the corresponding target amides **6**–**29** (Scheme 1). All the structures of the compounds were confirmed by $^{1}H$, $^{13}C$ NMR, and FAB-MS.

## 3. Cytotoxicity

Cytotoxicity of this series of simplified tetrahydroisoquinoline analogs was evaluated against eight human cell lines: HCT-8 (human colon cancer cell line), BEL-7402 (human hepatic carcinoma cell line), BGC-823 (human gastric adenocarcinoma cell line), A549 (human lung adenocarcinoma epithelial cell line), A2780 (human ovarian cancer cell line), MX-1 (human breast cancer cell line), MDA-MB-231 (human breast cancer cell line), and MCF-7 (human breast cancer cell line) by the standard MTT assay. The results are shown in Table 1.

## 4. Results and discussion

As shown in Table 1, most of the compounds exhibited considerable cytotoxicities to these eight cell lines. Notably, most of these compounds showed selective inhibition against the two breast tumor cell lines of MDA-MB-231 and MX-1 with the $IC_{50}$ values at the level of $10^{-7}$ M regardless of the structural changes of the amide side chain (for example, compounds **8**, **20**, **25**, and **28** with different 3-aromatic rings of the acrylic amide moiety). It is also apparent that this type of bistetrahydroisoquinoline compounds seems to be less sensitive toward the human lung adenocarcinoma epithelial cell line A549. In addition, it is noteworthy that compounds **16**, **18**, **19** and **27** exhibited rather weak cytotoxicity against most of the cell lines in spite of the fact that great differences of the 3-aromatic rings exist among these four compounds. Finally, compound **28**, which had a 3-thiophenyl acrylic amide side chain exhibited broad and potent cytotoxic activity with the strongest selective inhibition activity of 50 nM against MDA-MB-231.

Although a general structure–activity relationship of this type of simplified tetrahydroisoquinoline compounds could not be summarized from these data, it still can be concluded that the structure of the acrylic amide side chain had a certain influence on both the potency and selectivity of their cytotoxicity.

## 5. Conclusions

Twenty-four simplified tetrahydroisoquinoline analogs were prepared from L-dopa through a fourteen-step stereospecific procedure. The cytotoxicities of these compounds were tested against HCT-8, BEL-7402, BGC-823, A549, A2780, MCF-7 MX-1 and MDA-MB-231 human tumor cell lines by standard MTT assay. Most of the compounds showed potent antitumor activity with the $IC_{50}$ values at the level of $10^{-6}$ M or $10^{-7}$ M. Compound **28** showed the most potent cytotoxicity of all these compounds. This study confirmed that the 3-aryl acrylic amide side chain played an important role for the antitumor activity of this type of analogs.

## 6. Experimental protocols

### 6.1. General

Melting points were obtained on Yanaco MP-500D melting point apparatus and were uncorrected. Optical rotations were measured on a PerkinElmer Polarimeter 341LC using 10 cm cells and the sodium D line (589 nm) at 20 °C and concentration indicated. HRMS were carried out by Agilent LC/MSD TOF. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Mercury 400 spectrometer (400 MHz, $^{1}H$; 100 MHz, $^{13}C$) or Varian Mercury 300 spectrometer (300 MHz, $^{1}H$; 75 MHz, $^{13}C$) in $CDCl_3$, using tetramethylsilane (TMS) as an internal standard. Chemical shifts ($\delta$) are expressed in parts per million (ppm), and the following abbreviations are used: singlet (s), doublet (d), triplet (t), doubled doublet (dd), multiplet (m), etc. All common reagents and solvents were purchased from commercial suppliers and purified before use.

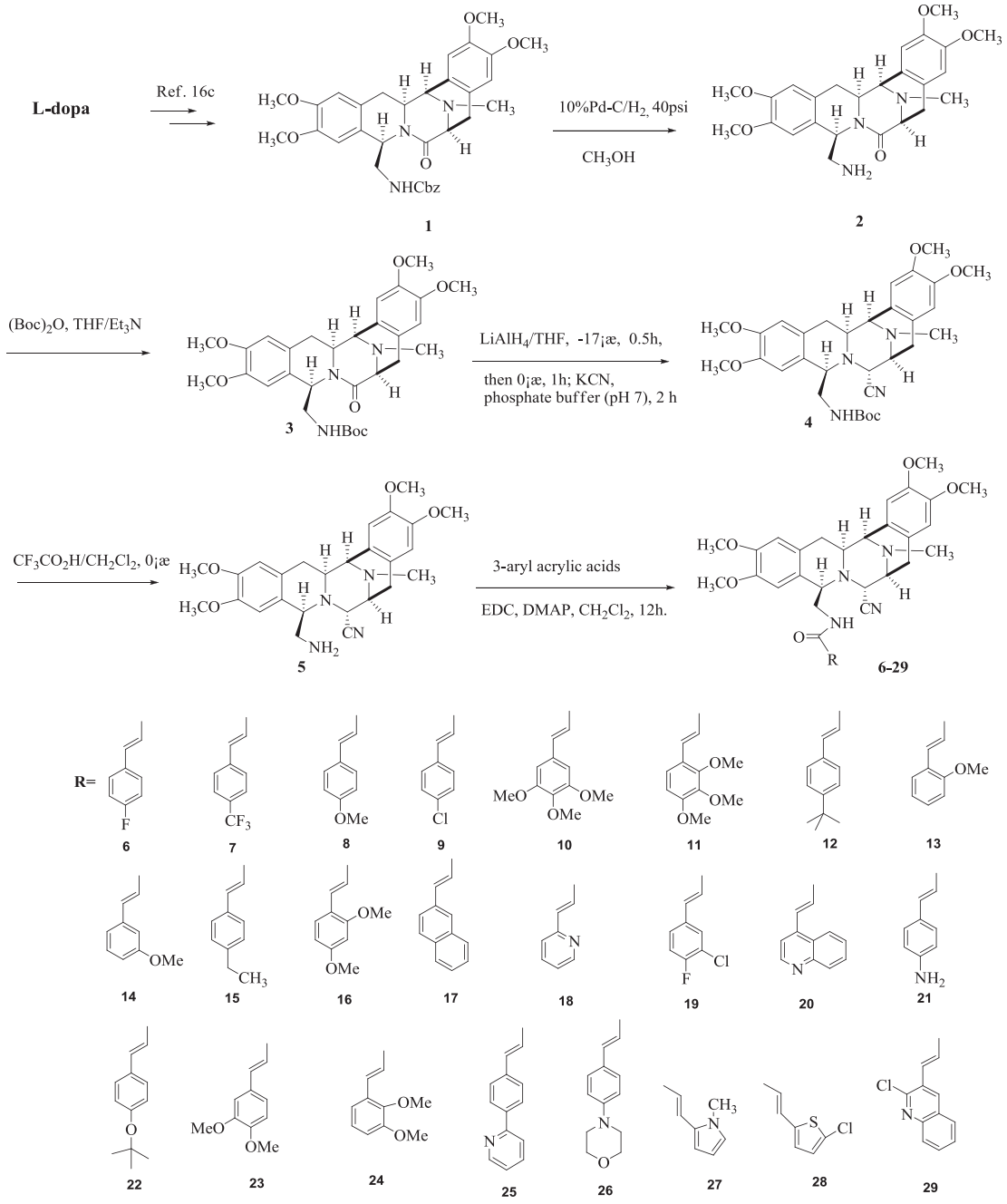
### 6.2. Synthetic procedures for the key intermediate compounds *3* and *4*

Compound **1** was synthesized from L-dopa through a multi-step stereospecific synthetic route we had built previously [16c].

#### 6.2.1. Preparation of intermediate compound *3*

To a solution of compound **1** (60 mg, 0.105 mmol) in $CH_3OH$ (10 mL) were added $Pd(OH)_2$ (moist, Pd content 20%, 20 mg) and acetic acid (2 drops). Then the mixture was hydrogenated in a Parr apparatus (40 psi $H_2$) for 2 h at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give the crude product **2** (39 mg) as a yellow oil (83% yield).

To a solution of compound **2** (31 mg, 0.068 mmol) and $Et_3N$ (0.035 mL, 0.17 mmol) in $CH_2Cl_2$ (10 mL) was added $Boc_2O$ (18 mg in $CH_2Cl_2$, 5 mL) dropwise at 0 °C, and the mixture was stirred at room temperature for 4.5 h. The reaction mixture was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give the crude product. Purification by column chromatography ($CH_2Cl_2$/MeOH = 80:1) afforded the *N*-Boc product **3** (33 mg, 89%) as a yellow solid. Mp: 122–124 °C. $[\alpha]_D^{20}$: −52.6 (*c* 0.10, $CDCl_3$). HRMS calcd. for $C_{30}H_{40}N_3O_7$ $[M + H]^+$ 554.2867, found 554.2861. $^{1}H$ NMR (400 MHz, $CHCl_3$): $\delta$ 6.71 (s, 1H), 6.64 (s, 2H), 6.57




**Scheme 1.** Synthesis of the simplified bistetrahydroisoquinoline compounds.

(s, 1H), 5.16 (t, 1H), 4.38 (d, $J$ = 12 Hz, 1H), 4.03 (d, $J$ = 12 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 6H), 3.84 (s, 3H), 3.76 (d, $J$ = 4 Hz, 1H), 3.71 (d, $J$ = 4 Hz, 1H), 3.27 (dd, $J$ = 4, 12 Hz, 1H), 2.96 (t, 1H), 2.87 (t, 1H), 2.84 (d, $J$ = 12 Hz, 1H), 2.72 (dd, $J$ = 4, 12 Hz, 1H), 2.64 (t, 1H), 2.48 (s, 3H), 1.27 (s, 9H).

### 6.2.2. Preparation of intermediate compound **4**

Compound **3** (31 mg, 0.056 mmol) in dry THF (5 mL) was added to a solution of $LiAlH_4$ (16 mg 0.448 mmol) in THF, and the mixture was stirred for 3 h at 0 °C. Then AcOH (0.06 mL 1.12 mmol) and a solution of 4.8 M KCN in $H_2O$ (0.84 mmol) were added. After stirring at room temperature for 14 h, the reaction mixture was quenched with aqueous 10% $NaHCO_3$ (15 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with $H_2O$ and brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated in vacuo to give 34 mg of a crude product, which was purified by column chromatography ($CH_2Cl_2/CH_3OH$ = 30:1) to afford compound **4** (30 mg) as yellow solid (81% yield). Mp: 152–154 °C. $[\alpha]_D^{20}$: −61.7 ($c$ 0.10, $CHCl_3$). HRMS calcd. for $C_{31}H_{41}N_4O_6$ $[M + H]^+$ 565.3389, found 565.3388. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 6.59 (d, $J$ = 9 Hz, 2H), 6.52 (d, $J$ = 9 Hz, 2H), 4.25 (t, 1H), 4.01(d, $J$ = 6 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.80 (d, $J$ = 6 Hz, 1H), 3.56 (t, 1H), 3.36 (d, $J$ = 6 Hz, 1H), 3.27 (d, $J$ = 12 Hz, 1H), 3.11–3.19 (dd, $J$ = 6, 12 Hz, 1H), 3.03 (t, 1H), 2.82 (t, 1H), 2.59 (d, $J$ = 6 Hz, 1H), 2.53 (d, $J$ = 6 Hz, 1H), 2.38 (s, 3H), 1.34 (s, 9H).

### 6.3. General procedure for the synthesis of compounds **6–29**

A mixture of compound **4** (57 mg, 0.101 mmol) in trifluoroacetic acid (1 mL) was stirred at room temperature for 2 h, and then the

**Table 1**
Cytotoxicity of simplified tetrahydroisoquinoline compounds against eight cell lines.

| Compound | $IC_{50}$ (μM)[a] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | HCT-8 | BEL-7402 | BGC-823 | A549 | A2780 | MX-1 | MDA-MB-231 | MCF-7 |
| **6** | 6.82 | 3.10 | 5.83 | >10 | 1.20 | 1.50 | 0.59 | 5.94 |
| **7** | 2.13 | 0.22 | 0.59 | 9.24 | 1.73 | 0.56 | 0.16 | 1.68 |
| **8** | 2.04 | 1.18 | 2.12 | 8.72 | 1.70 | 0.72 | 0.32 | 3.51 |
| **9** | 2.25 | 1.40 | 1.97 | 9.67 | 2.81 | 0.50 | 0.40 | 1.21 |
| **10** | 1.97 | 1.66 | 1.10 | 5.03 | 2.03 | 1.84 | 0.81 | 0.63 |
| **11** | 3.24 | 2.13 | 3.60 | >10 | 3.10 | 1.72 | 0.49 | 3.53 |
| **12** | 0.37 | 1.16 | 1.42 | 9.41 | 1.73 | 0.77 | 0.20 | 1.95 |
| **13** | 4.87 | 3.36 | 5.31 | >10 | 4.90 | 1.69 | 0.42 | 5.13 |
| **14** | 3.06 | 0.87 | 2.60 | 9.45 | 2.24 | 0.34 | 0.12 | 1.73 |
| **15** | 1.74 | 0.68 | 1.71 | 5.49 | 1.64 | 0.58 | 0.16 | 1.72 |
| **16** | >10 | >10 | >10 | >10 | >10 | 3.59 | 0.49 | >10 |
| **17** | 2.12 | 1.14 | 1.79 | 7.68 | 1.70 | 0.46 | 0.24 | 1.91 |
| **18** | >10 | >10 | >10 | >10 | >10 | 3.10 | 1.31 | >10 |
| **19** | >10 | 7.51 | >10 | >10 | >10 | 3.27 | 0.61 | >10 |
| **20** | 1.97 | 2.13 | 2.52 | 8.56 | 1.67 | 0.92 | 0.30 | 5.20 |
| **21** | 4.64 | 4.21 | 5.86 | >10 | 2.89 | 2.04 | 2.93 | 5.47 |
| **22** | 3.42 | 2.56 | 2.06 | 9.76 | 2.97 | 0.99 | 0.31 | 3.73 |
| **23** | 5.18 | 4.93 | 5.17 | >10 | 4.78 | 3.16 | 0.72 | 5.08 |
| **24** | 2.88 | 1.98 | 3.71 | >10 | 1.97 | 0.61 | 0.31 | 5.14 |
| **25** | 1.62 | 1.03 | 1.73 | 5.00 | 1.04 | 0.37 | 0.18 | 1.59 |
| **26** | 3.03 | 2.28 | 3.03 | 6.91 | 2.53 | 0.33 | 0.25 | 2.48 |
| **27** | >10 | >10 | >10 | >10 | >10 | 2.83 | 2.57 | >10 |
| **28** | 0.43 | 0.27 | 0.25 | 0.72 | 0.30 | 0.38 | 0.05 | 0.41 |
| **29** | 3.29 | 2.16 | 3.29 | 9.68 | 2.20 | 0.99 | 0.21 | 3.52 |

[a] The $IC_{50}$ values represent the inhibitory concentration of 50% of cell growth.

mixture was basified with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to give the crude product **5** (39 mg) as a yellow oil (85% yield).

To a solution of compound **5** (1.0 equiv) in $CH_2Cl_2$ was added the corresponding 3-aromatic acrylic acid (1.5 equiv), DMAP (1.0 equiv) and EDC (1.5 equiv), and then the mixture was stirred at room temperature for 7 h. The mixture was diluted with $CH_2Cl_2$, washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $Na_2SO_4$, concentrated under reduced pressure to give the crude product. Purification by column chromatography ($CH_2Cl_2$/$CH_3OH$ = 20:1) afforded compounds **6**–**29**.

*6.3.1. (2E)-N-{[(6S,7R,9R,14aS,15R)-7-Cyano-6,7,9,14,14a,15-hexahydro-2,3,11,12-tetramethoxy-16-methyl-6,15-imino-5H-isoquino[3,2-b][3]benzazocin-9-yl]methyl}-3-(4-fluorophenyl)-2-propenamide (**6**)*

Yellow solid, mp: 113–115 °C. $[\alpha]_D^{20}$: −11.3(*c* 0.0042, $CHCl_3$). HRMS calcd. for $C_{35}H_{38}F_1N_4O_5$ $[M+H]^+$ 613.2821, found 613.2820. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 6 Hz, 2H), 7.32 (d, *J* = 6 Hz, 2H), 7.26 (d, *J* = 12 Hz, 1H), 6.59 (s, 1H), 6.58 (s, 1H), 6.53 (s, 1H), 6.51 (s, 1H), 5.42 (d, *J* = 15 Hz, 1H), 5.13 (s, 1H), 4.07 (s, 1H), 4.01 (s, 1H), 3.91 (s, 3H), 3.82 (s, 6H), 3.79 (m, 1H), 3.73–3.68 (dd, *J* = 8.12 Hz, 1H), 3.62 (s, 3H), 3.43 (m, 2H), 3.18–3.13 (dd, *J* = 10, 15 Hz, 1H), 2.59–2.51 (dd, *J* = 8.12 Hz, 3H), 2.42 (s, 3H), 2.36 (d, *J* = 12 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.73, 148.68, 148.03, 146.75, 146.40, 141.14, 131.94, 128.44 (2C), 128.31 (2C), 127.91, 126.35, 125.96, 125.12, 118.70, 117.48, 112.83, 110.52, 110.32, 109.72, 62.99, 60.07, 59.38, 56.21, 55.94, 55.86, 55.66, 55.58, 44.09, 41.70, 32.38, 28.74, 26.09.

*6.3.2. 3-(4-Trifluorophenyl)-2-propenamide derivative (**7**)*

Yellow solid, mp: 135–137 °C. $[\alpha]_D^{20}$: −18.8 (*c* 0.0038, $CHCl_3$). HRMS calcd. for $C_{36}H_{38}F_3N_4O_5$ $[M+H]^+$ 663.2789, found 663.2790. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.69 (m, 2H), 7.65 (s, 1H), 7.62 (s, 1H), 7.52 (s, 1H), 7.49 (s, 1H), 7.38–7.33 (d, *J* = 15 Hz, 1H), 6.60 (s, 2H), 6.54–6.52 (d, *J* = 6 Hz, 2H), 5.57–5.52 (d, *J* = 15 Hz, 1H), 4.21 (t, 2H), 4.07 (s, 1H), 4.02 (s, 1H), 3.86 (m, 1H), 3.91 (s, 3H), 3.72 (m, 1H), 3.82 (s, 6H), 3.62 (s, 3H), 3.45 (m, 2H), 3.15 (dd, *J* = 6, 12 Hz, 1H), 2.61 (m, 1H), 2.55 (m, 1H), 2.41 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 167.74, 164.76, 148.14 (2C), 139.43, 137.84, 132.45, 130.86 (3C), 128.79 (3C), 128.01 (3C), 125.73, 124.94, 122.18, 113.00, 110.42 (2C), 109.73, 68.15, 63.01, 60.06, 56.26, 55.96, 55.87, 55.62, 55.56, 41.65, 38.72, 30.35, 28.91, 23.73.

*6.3.3. 3-(4-Methoxyphenyl)-2-propenamide derivative (**8**)*

White solid, mp: 107–109 °C. $[\alpha]_D^{20}$: −10.7 (*c* 0.0028, $CHCl_3$). HRMS calcd. for $C_{33}H_{41}N_4O_6$ $[M+H]^+$ 625.3021, found 625.3022. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.40 (s, 1H), 7.36 (s, 1H), 6.94 (s, 1H), 6.96 (s, 1H), 6.65 (s, 1H), 6.63 (s, 1H), 6.59 (s, 1H), 6.57 (s, 1H), 5.49 (d, *J* = 12 Hz, 1H), 5.12 (s, 1H), 4.12 (s, 1H), 4.01 (s, 1H), 3.92 (s, 3H), 3.90 (d, *J* = 4 Hz, 1H), 3.86 (d, *J* = 4 Hz, 1H), 3.83 (s, 6H), 3.82 (s, 3H), 3.66 (s, 3H), 3.44 (s, 1H), 3.42 (s, 1H), 3.14–3.18 (dd, *J* = 6.12 Hz, 1H), 2.59 (m, 1H), 2.57 (d, *J* = 12 Hz, 2H), 2.42 (s, 3H), 2.39 (d, *J* = 8 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.84, 160.96, 148.53, 148.00, 146.66, 140.81, 129.44 (3C), 127.17, 126.53, 125.99, 125.15, 117.20, 114.18, 112.93, 110.49, 110.32, 109.70, 62.982, 60.04, 59.52, 56.23, 56.21, 55.92, 55.86, 55.66, 55.51, 55.37, 44.03, 41.80, 32.42, 26.00, 22.68.

*6.3.4. 3-(4-Chlorophenyl)-2-propenamide derivative (**9**)*

Yellow solid, mp: 109–111 °C. $[\alpha]_D^{20}$: −14 (*c* 0.0045, $CHCl_3$). HRMS calcd. for $C_{35}H_{38}ClN_4O_5$ $[M+H]^+$ 629.2525, found 629.2524. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 6 Hz, 2H), 7.52 (d, *J* = 6 Hz, 2H), 7.36 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 6 Hz, 2H), 6.54 (s, 1H), 6.52 (s, 1H), 5.55 (d, *J* = 12 Hz, 1H), 5.16 (s, 1H), 4.08 (s, 1H), 4.03 (s, 1H), 3.94 (m, 1H), 3.91 (s, 3H), 3.82 (s, 6H), 3.73–3.77 (dd. *J* = 6, 12 Hz, 1H), 3.62 (s, 3H), 3.45 (m, 2H), 3.43 (m, 1H), 3.19–3.15 (dd, *J* = 6, 12 Hz, 1H), 2.58–2.60 (dd, *J* = 6.12 Hz, 2H), 2.42 (s, 3H), 2.38 (d, *J* = 12 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 164.70, 148.51, 148.10 (2C), 146.70, 139.47, 137.80, 128.01 (4C), 126.65, 125.89, 125.73, 124.93, 122.06, 117.59, 113.14, 110.42, 110.37, 109.69, 62.93, 59.99, 59.48, 56.25, 55.92, 55.85, 55.58, 55.51, 44.02, 41.82, 32.40, 31.92, 25.98.

*6.3.5. 3-(3,4,5-Trimethoxyphenyl)-2-propenamide derivative (**10**)*

White solid, mp: 128–130 °C. $[\alpha]_D^{20}$: −27.8 (*c* 0.0027, $CHCl_3$). HRMS calcd. for $C_{38}H_{45}N_4O_8$ $[M + H]^+$ 685.3232, found 685.3237. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 12 Hz, 1H), 6.65 (s, 2H), 6.55 (s, 2H), 6.53 (s, 2H), 5.50 (d, *J* = 12 Hz, 1H), 4.96 (s, 1H), 4.11 (s, 1H), 4.01 (s, 1H), 3.93 (s, 6H), 3.90 (d, *J* = 6 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.59 (s, 3H), 3.46 (t, 1H), 3.44 (d, *J* = 6 Hz, 2H), 3.40 (s, 1H), 3.15 (dd, *J* = 6, 12 Hz, 1H), 2.60–2.57 (dd, *J* = 6, 12 Hz, 1H), 2.56 (d, *J* = 12 Hz, 1H), 2.43 (s, 3H), 2.37 (dd, *J* = 6, 12 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.11, 148.57, 148.07, 146.71, 139.78, 135.58, 132.90, 129.05 (3C), 129.00 (3C), 126.55, 125.88, 124.99, 120.20, 117.54, 113.06, 110.45, 110.37, 109.68, 62.95, 60.00, 59.41, 56.24, 55.92, 55.86, 55.59, 55.52 (2C), 55.39, 44.03, 41.76, 32.37, 31.91, 26.04, 22.67.

*6.3.6. 3-(2,3,4-Trimethoxyphenyl)-2-propenamide derivative (**11**)*

White solid, mp: 123–125 °C. °C. $[\alpha]_D^{20}$: −28.1 (*c* 0.0028, $CHCl_3$). HRMS calcd. for $C_{38}H_{45}N_4O_8$ $[M + H]^+$ 685.3232, found 685.3233. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 16 Hz, 1H), 7.16 (d, *J* = 8 Hz, 1H), 6.71 (d, *J* = 8 Hz, 1H), 6.60 (s, 2H), 6.56 (s, 1H), 6.55 (s, 1H), 5.65 (d, *J* = 16 Hz, 1H), 5.10 (s, 1H), 4.12 (s, 1H), 4.00 (s, 1H), 3.93 (s, 3H), 3.91 (d, *J* = 6 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.67 (s, 3H), 3.56 (s, 3H), 3.48 (d, *J* = 6 Hz, 2H), 3.42 (s, 1H), 3.40 (t, 1H), 3.17–3.11 (dd, *J* = 6.12 Hz, 1H), 2.60 (m, 1H), 2.56 (m, 1H), 2.40 (s, 3H), 2.33 (d, *J* = 12 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.72, 153.39 (2C), 148.46, 148.04, 147.99, 146.50, 141.66, 139.64, 130.08 (2C), 126.70, 126.04, 125.02, 118.69, 117.62, 113.05, 110.49, 110.18, 109.72, 105.17 (2C), 62.93, 60.92, 59.90, 59.49, 56.19, 56.07, 55.95, 55.86, 55.57, 55.44, 55.30, 44.12, 41.79, 32.41, 25.95, 22.67.

*6.3.7. 3-(4-tert-Butylphenyl)-2-propenamide derivative (**12**)*

Yellow solid, mp: 119–121 °C. $[\alpha]_D^{20}$: −33.7 (*c* 0.0029, $CHCl_3$). HRMS calcd. for $C_{39}H_{47}N_4O_5$ $[M + H]^+$ 651.3541, found 651.3541. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.39 (m, 2H), 7.37 (m, 2H), 7.34 (m, 1H), 6.61 (s, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 6.51 (s, 1H), 5.58–5.54 (d, *J* = 12 Hz, 1H), 5.12 (s, 1H), 4.13 (s, 1H), 4.01 (s, 1H), 3.91 (s, 3H), 3.82 (s, 6H), 3.65 (s, 3H), 3.87–3.85 (d, *J* = 6 Hz, 1H), 3.61 (s, 1H), 3.48 (d, *J* = 6 Hz, 1H), 3.41 (m, 2H), 3.18–3.12 (dd, *J* = 6, 12 Hz, 1H), 2.57 (m, 1H), 2.54 (d, *J* = 12 Hz, 1H), 2.40 (s, 3H), 2.34–2.32 (d, *J* = 12 Hz, 1H), 1.32 (s, 12H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.71, 153.26, 148.58, 148.01, 146.69 (2C), 141.09, 131.69, 129.73 (2C), 127.68, 126.01 (2C), 125.75, 125.10, 118.72, 117.56, 112.85, 110.49 (2C), 110.29, 109.70, 62.97, 60.09, 59.45, 56.21, 55.93, 55.85, 55.71, 55.57, 44.05, 41.75, 34.83, 32.40, 31.91, 31.19, 27.10, 26.01, 22.68.

*6.3.8. 3-(2-Methoxyphenyl)-2-propenamide derivative (**13**)*

White solid, mp: 110–112 °C. $[\alpha]_D^{20}$: −10.9 (*c* 0.0028, $CHCl_3$). HRMS calcd. for $C_{36}H_{41}N_4O_6$ $[M + H]^+$ 625.3021, found 625.3022. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.37–7.33 (d, *J* = 16 Hz, 1H), 7.31–7.29 (d, *J* = 8 Hz, 1H), 7.27 (s, 1H), 7.03–7.01 (d, *J* = 8 Hz, 1H), 6.92 (s, 1H), 6.90–6.88 (d, *J* = 8 Hz, 1H), 6.57–6.50 (m, 3H), 5.63–5.59 (d, *J* = 16 Hz, 1H), 5.09 (s, 1H), 4.10 (s, 1H), 4.01 (s, 1H), 3.92 (s, 3H), 3.87 (d, *J* = 8 Hz, 1H), 3.82 (m, 9H), 3.79 (t, 1H), 3.66 (s, 3H), 3.61 (d, *J* = 4 Hz, 1H), 3.43 (m, 1H), 3.38 (m, 1H), 3.16–3.10 (dd, *J* = 8.16 Hz, 1H), 2.68–2.59 (dd, *J* = 8, 16 Hz, 1H), 2.54 (d, *J* = 16 Hz, 1H), 2.39 (s, 3H), 2.34 (m, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.55, 159.87, 148.55, 148.06, 148.01, 146.63, 145.24, 135.86, 127.76, 126.57, 126.12, 125.08, 120.14, 119.97, 117.64, 115.59, 115.27, 113.22, 112.96, 110.54, 110.27, 109.71, 62.94, 60.12, 59.55, 56.17, 55.94, 55.87, 55.76, 55.57, 55.31, 44.10, 41.77, 32.45, 25.95, 23.67.

*6.3.9. 3-(3-Methoxyphenyl)-2-propenamide derivative (**14**)*

White solid, mp: 121–123 °C. $[\alpha]_D^{20}$: −16.2 (*c* 0.0028, $CHCl_3$). HRMS calcd. for $C_{36}H_{41}N_4O_6$ $[M + H]^+$ 625.3021, found 625.3023. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 12 Hz, 1H), 7.30 (d, *J* = 8 Hz, 1H), 7.02 (d, *J* = 8 Hz, 1H), 6.92 (s, 1H), 6.89 (d, *J* = 8 Hz, 1H), 6.54 (d, *J* = 8 Hz, 2H), 6.53 (d, *J* = 8 Hz, 2H), 5.56 (d, *J* = 12 Hz, 1H), 5.11 (s, 1H), 4.10 (s, 1H), 4.01 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.85 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.79 (t, 1H), 3.66 (s, 3H), 3.61 (s, 1H), 3.43 (d, *J* = 3 Hz, 1H), 3.39 (m, 1H), 3.14 (dd, *J* = 3, 9 Hz, 1H), 2.59–2.55 (dd, *J* = 3, 6 Hz, 1H), 2.58–2.52 (dd, *J* = 3, 6 Hz, 1H), 2.40 (s, 3H), 2.37–2.34 (dd, *J* = 6, 12 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.55, 159.87, 148.55, 148.06, 148.01, 146.63, 141.24, 135.86, 129.76, 126.57, 126.12, 125.08, 120.14, 119.97, 117.64, 115.59, 115.27, 113.22, 112.96, 110.54, 110.27, 109.71, 62.94, 60.02, 59.55, 56.17, 55.94, 55.87, 55.76, 55.57, 55.30, 44.10, 41.77, 32.45, 25.95, 22.67.

*6.3.10. 3-(4-Ethylphenyl)-2-propenamide derivative (**15**)*

White solid, mp: 120–122 °C. $[\alpha]_D^{20}$: −32.8 (*c* 0.0022, $CHCl_3$). HRMS calcd. for $C_{37}H_{43}N_4O_5$ $[M + H]^+$ 623.3228, found 623.3224. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 16 Hz, 1H), 7.33 (d, *J* = 8 Hz, 2H), 7.21 (d, *J* = 8 Hz, 2H), 6.59 (d, *J* = 8 Hz, 2H), 6.53 (d, *J* = 8 Hz, 2H), 5.54 (d, *J* = 16 Hz, 1H), 5.12 (s, 1H), 4.09 (s, 1H), 4.01 (s, 1H), 3.92 (s, 3H), 3.83 (s, 6H), 3.79 (s, 1H), 3.69 (d, *J* = 8 Hz, 1H), 3.62 (s, 3H), 3.60 (d, *J* = 8 Hz, 1H), 3.43 (d, *J* = 8 Hz, 1H), 3.11–3.17 (dd, *J* = 8, 16 Hz, 1H), 2.66 (dd, *J* = 8, 16 Hz, 2H), 2.58 (d, *J* = 8 Hz, 1H), 2.53 (d, *J* = 16 Hz, 1H), 2.49 (s, 1H), 2.39 (s, 3H), 2.34 (s, 1H), 1.25 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 168.00, 148.74, 148.30, 146.90, 140.16, 132.69, 131.12, 130.91, 130.00, 129.93, 129.04 (2C), 126.91, 126.22, 125.30, 119.61, 116.16, 115.99, 113.34, 110.69, 110.61, 109.94, 68.40, 63.20, 60.25, 59.76, 56.48, 56.16, 55.83, 55.77, 44.24, 42.07, 38.97, 32.68, 30.60, 29.16, 23.98.

*6.3.11. 3-(2,4-Dimethoxyphenyl)-2-propenamide derivative (**16**)*

Yellow film. $[\alpha]_D^{20}$: −8.95 (*c* 0.0016, $CHCl_3$). HRMS calcd. for $C_{37}H_{43}N_4O_7$ $[M + H]^+$ 655.3126, found 655.3125. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 12 Hz, 1H), 7.35 (d, *J* = 4 Hz, 1H), 6.60 (d, *J* = 4 Hz, 1H), 6.56 (s, 1H), 6.55 (s, 1H), 6.53 (dd, *J* = 4, 8 Hz, 1H), 6.50 (d, *J* = 4 Hz, 1H), 6.41 (d, *J* = 4 Hz, 1H), 5.69 (d, *J* = 12 Hz, 1H), 5.12 (s, 1H), 4.13 (s, 1H), 3.99 (s, 1H), 3.90 (s, 3H), 3.85 (d, *J* = 4 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.78 (d, *J* = 4 Hz, 1H), 3.65 (s, 3H), 3.75 (m, 1H), 3.48 (d, *J* = 8 Hz, 1H), 3.38 (d, *J* = 4 Hz, 1H), 3.10–3.15 (dd, *J* = 4, 12 Hz, 1H), 2.57 (d, *J* = 8 Hz, 1H), 2.45 (d, *J* = 12 Hz, 1H), 2.39 (s, 3H), 2.36 (d, *J* = 4 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 166.55, 162.28, 159.40, 148.38, 147.97, 146.51, 136.03, 129.50, 126.66, 126.31, 125.46, 123.56, 117.80, 117.68, 116.59, 112.76, 112.22, 110.60, 110.32, 109.81, 105.04, 98.36, 62.97, 60.11, 59.77, 56.14, 56.01, 55.93, 55.88, 55.61, 55.46, 55.38, 44.30, 41.78, 32.52, 25.85, 22.67.

*6.3.12. 3-(Naphthalen-2-yl)-2-propenamide derivative (**17**)*

Yellow film. $[\alpha]_D^{20}$: −17.1 (*c* 0.0043, $CHCl_3$). HRMS calcd. for $C_{39}H_{41}N_4O_5$ $[M + H]^+$ 645.3071, found 645.3070. $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.26–8.22 (d, *J* = 12 Hz, 1H), 8.14–8.12 (d, *J* = 12 Hz, 1H), 7.88–7.85 (dd, *J* = 8, 12 Hz, 2H), 7.60–7.58 (d, *J* = 8 Hz, 1H), 7.55 (s, 1H), 7.53 (s, 1H), 7.51 (s, 1H), 7.50 (s, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 5.70–5.66 (d, *J* = 12 Hz, 1H), 5.24 (s, 1H), 4.19 (s, 1H), 4.05 (s, 1H), 3.83–3.81 (m, 9H), 3.69–3.64 (dd, *J* = 8, 12 Hz, 1H), 3.61 (s, 1H), 3.54–3.51 (q, 1H), 3.45 (s, 3H), 3.45–3.40 (m, 2H), 3.17–3.11 (dd, *J* = 8, 16 Hz, 1H), 2.61–2.54 (m, 2H), 2.49–2.45 (d, *J* = 16 Hz, 1H), 2.38 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.41, 148.53, 148.05, 146.68, 137.99, 133.59, 131.64, 131.39, 129.99, 128.62, 126.57, 126.51, 126.15, 126.03, 125.66, 125.18, 124.58, 123.51, 123.36, 122.39, 117.71, 112.94, 110.52, 110.28, 109.73, 62.95, 60.03, 59.58, 56.13, 55.95, 55.87, 55.56, 55.42, 44.09, 41.80, 32.49, 25.92, 22.67.

*6.3.13. 3-(Pyridin-2-yl)-2-propenamide derivative (**18**)*

Yellow solid. Mp: 163–165 °C. $[\alpha]_D^{20}$: −24.8 (*c* 0.0035, $CHCl_3$). HRMS calcd. for $C_{34}H_{38}N_5O_5$ $[M + H]^+$ 596.2867, found 597.2826. $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.59 (d, *J* = 8 Hz, 1H), 7.69 (d, *J* = 8 Hz, 1H),

7.38 (d, $J$ = 12 Hz, 1H), 7.32 (d, $J$ = 8 Hz, 1H), 7.22 (d, $J$ = 12 Hz, 1H), 6.63 (s, 1H), 6.56 (s, 2H), 6.52 (s, 1H), 6.36 (d, $J$ = 12 Hz, 1H), 5.29 (s, 1H), 4.14 (s, 1H), 4.09 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.82 (s, 3H), 3.74 (m, 1H), 3.65 (s, 3H), 3.58 (s, 1H), 3.39 (d, $J$ = 8 Hz, 1H), 3.34 (d, $J$ = 12 Hz, 1H), 3.28 (m, 1H), 3.14–3.08 (dd, $J$ = 8, 12 Hz, 1H), 2.60 (d, $J$ = 8 Hz, 1H), 2.56 (m, 2H), 2.36 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 165.20, 152.89, 149.61, 148.48, 148.06, 147.99, 146.62, 139.37, 136.97, 126.59, 126.51, 125.13, 124.51, 124.11, 123.91, 117.75, 112.74, 110.82, 110.47, 109.66, 62.94, 60.23, 59.87, 56.17, 55.99, 55.92, 55.62 (2C), 55.60, 44.35, 41.71, 32.57, 25.89.

*6.3.14. 3-(3-Chloro-4-fluorophenyl)-2-propenamide derivative (**19**)*

White solid. Mp: 125–127 °C. $[\alpha]_D^{20}$: −21.1 ($c$ 0.0032, $CHCl_3$). HRMS calcd. for $C_{35}H_{37}ClFN_4O_5$ $[M + H]^+$ 647.2431, found 647.2427. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.62 (d, $J$ = 15 Hz, 1H), 7.46 (dd, $J$ = 8, 12 Hz, 1H), 7.12 (dd, $J$ = 8, 12 Hz, 1H), 7.05 (dd, $J$ = 8, 12 Hz, 1H), 6.57 (d, $J$ = 8 Hz, 2H), 6.53 (d, $J$ = 8 Hz, 2H), 5.46 (d, $J$ = 15 Hz, 1H), 5.12 (s, 1H), 4.08 (d, $J$ = 16 Hz, 1H), 4.01 (m, 1H), 3.92 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.77 (d, $J$ = 8 Hz, 1H), 3.62 (m, 1H), 3.60 (s, 3H), 3.43 (m, 2H), 3.15 (dd, $J$ = 6, 12 Hz, 1H), 2.57 (d, $J$ = 6 Hz, 1H), 2.50 (dd, $J$ = 6, 12 Hz, 1H), 2.43 (s, 3H), 2.35 (d, $J$ = 6 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 164.91, 163.97, 148.54, 148.14, 146.65, 135.51, 135.38, 128.79 (3C), 125.90, 124.95, 122.29, 117.25, 117.06, 114.80, 114.63, 112.85, 110.52, 110.42, 109.67, 96.10, 62.95, 60.09, 59.31, 56.14, 55.96, 55.90, 55.56, 55.33, 43.99, 41.70, 32.40, 31.92, 22.68.

*6.3.15. 3-(Quinolin-4-yl)-2-propenamide derivative (**20**)*

Yellow film. $[\alpha]_D^{20}$: −27.1 ($c$ 0.0037, $CHCl_3$). HRMS calcd. for $C_{38}H_{40}N_5O_5$ $[M + H]^+$ 646.3024, found 646.3020. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.98 (d, $J$ = 4 Hz, 1H), 8.15 (s, 1H), 8.12 (d, $J$ = 4 Hz, 1H), 8.08 (s, 1H), 7.71–7.75 (dd, $J$ = 8, 16 Hz, 1H), 7.55–7.59 (dd, $J$ = 8, 16 Hz, 1H), 7.43 (d, $J$ = 4 Hz, 1H), 6.58 (t, 3H), 6.52 (d, $J$ = 8 Hz, 1H), 5.70 (d, $J$ = 16 Hz, 1H), 5.26 (dd, $J$ = 8, 16 Hz, 1H), 4.09 (s, 1H), 4.04 (s, 1H), 3.85 (s, 6H), 3.82 (s, 3H), 3.80 (s, 1H), 3.74 (d, $J$ = 8 Hz, 1H), 3.62 (s, 1H), 3.53 (s, 3H), 3.44 (d, $J$ = 8 Hz, 1H), 3.14–3.20 (dd, $J$ = 8, 16 Hz, 1H), 2.58–2.61 (dd, $J$ = 8, 12 Hz, 1H), 2.53 (d, $J$ = 12 Hz, 1H), 2.50 (d, $J$ = 4 Hz, 1H), 2.40 (s, 3H), 2.34 (d, $J$ = 4 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 164.15, 149.87, 148.53, 148.13 (2C), 146.73 (2C), 135.26, 129.84, 127.38, 127.22, 126.68, 126.14, 125.94, 124.93, 123.72 (2C), 123.27, 117.90 (2C), 117.80, 117.61, 113.27, 110.44, 109.71, 62.90, 60.02, 59.54, 56.23, 55.95, 55.86, 55.56, 55.50, 55.44, 44.19, 41.80, 32.39, 25.98.

*6.3.16. 3-(4-Aminophenyl)-2-propenamide derivative (**21**)*

Yellow film. $[\alpha]_D^{20}$: −50.8 ($c$ 0.0025, $CHCl_3$). HRMS calcd. for $C_{35}H_{40}N_5O_5$ $[M + H]^+$ 610.3024, found 610.3012. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.32 (d, $J$ = 8 Hz, 1H), 7.22 (d, $J$ = 12 Hz, 1H), 6.65 (d, $J$ = 8 Hz, 2H), 6.59 (d, $J$ = 8 Hz, 2H), 6.53 (d, $J$ = 8 Hz, 2H), 6.49 (m, 1H), 5.37 (d, $J$ = 12 Hz, 1H), 5.06 (s, 1H), 4.09 (s, 1H), 3.99 (s, 1H), 3.92 (s, 3H), 3.87 (d, $J$ = 12 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.65 (s, 3H), 3.61 (d, $J$ = 4 Hz, 1H), 3.43 (m, 2H), 3.11–3.18 (dd, $J$ = 8, 12 Hz, 1H), 2.56 (d, $J$ = 4 Hz, 1H), 2.46 (d, $J$ = 12 Hz, 1H), 2.44 (d, $J$ = 4 Hz, 1H), 2.39 (s, 3H), 2.34 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 166.43, 148.73, 148.37, 148.21, 146.87, 141.49, 131.28, 129.78, 126.83, 126.32, 125.52, 125.09, 123.80, 117.99, 115.74, 115.05, 114.58, 113.13, 112.49, 110.73, 110.57, 109.96, 63.24, 60.28, 59.82, 57.06, 56.33, 56.10, 55.91, 55.85, 55.81, 44.25, 42.07, 33.27, 26.16.

*6.3.17. 3-(4-tert-Butoxyphenyl)-2-propenamide derivative (**22**)*

White solid. Mp: 113–115 °C. $[\alpha]_D^{20}$: −21.7 ($c$ 0.0018, $CHCl_3$). HRMS calcd. for $C_{39}H_{47}N_4O_6$ $[M + H]^+$ 667.3490, found 667.3490. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.34 (d, $J$ = 8 Hz, 1H), 7.32 (d, $J$ = 4Hz, 2H), 6.98 (d, $J$ = 8 Hz, 2H), 6.58 (d, $J$ = 12 Hz, 2H), 6.52 (d, $J$ = 12 Hz, 2H), 5.47 (d, $J$ = 8 Hz, 1H), 5.09 (s, 1H), 4.09 (s, 1H), 4.01 (s, 1H), 3.92 (d, $J$ = 12 Hz, 1H), 3.90 (s, 3H), 3.85 (d, $J$ = 4 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.78 (d, $J$ = 4 Hz, 1H), 3.65 (s, 3H), 3.60 (d, $J$ = 4 Hz, 2H), 3.12 (dd, $J$ = 4 Hz, 1H), 2.56 (d, $J$ = 8 Hz, 1H), 2.54 (d, $J$ = 8 Hz, 1H), 2.39 (s, 3H), 2.34 (d, $J$ = 4 Hz, 1H).

*6.3.18. 3-(3,4-Dimethoxyphenyl)-2-propenamide derivative (**23**)*

White solid. Mp: 114–116 °C. °C. $[\alpha]_D^{20}$: −7.72 ($c$ 0.0025, $CHCl_3$). HRMS calcd. for $C_{37}H_{43}N_4O_7$ $[M + H]^+$ 655.3126, found 655.3125. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.59- 8.58 (dd, $J$ = 8, 16 Hz, 1H), 7.37 (m, 1H), 7.36–7.35 (d, $J$ = 16 Hz, 1H), 7.34 (m, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 6.57 (s, 1H), 6.56 (s, 1H), 5.60–5.57 (d, $J$ = 12 Hz, 1H), 5.13 (s, 1H), 4.09 (s, 1H), 4.03 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.79 (m, 1H), 3.66–3.64 (d, $J$ = 4 Hz, 1H), 3.63 (s, 3H), 3.42 (m, 2H), 3.35 (d, $J$ = 4 Hz, 1H), 3.15–3.19 (dd, $J$ = 4, 12 Hz, 1H), 2.55 (d, $J$ = 8 Hz, 1H), 2.45 (d, $J$ = 12 Hz, 1H), 2.42 (s, 3H), 2.36 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 164.67, 150.51, 149.93, 148.45, 148.09, 146.62, 137.48, 133.71, 130.23, 126.77, 125.99, 124.98, 123.67 (2C), 121.83 (2C), 117.65, 113.14, 110.46, 110.39, 109.71, 62.92, 60.04, 59.57, 56.23, 56.09, 55.93, 55.86, 55.51 (2C), 44.11, 41.80, 32.41, 31.90, 25.93, 22.67.

*6.3.19. 3-(2,3-Dimethoxyphenyl)-2-propenamide derivative (**24**)*

White solid. Mp: 117–119 °C. $[\alpha]_D^{20}$: −17.7 ($c$ 0.0018, $CHCl_3$). HRMS calcd. for $C_{37}H_{43}N_4O_7$ $[M + H]^+$ 655.3126, found 655.3125. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.33 (d, $J$ = 12 Hz, 1H), 7.01 (dd, $J$ = 4 Hz, 1H), 6.97 (d, $J$ = 4 Hz, 1H), 6.87 (d, $J$ = 8 Hz, 1H), 6.58 (d, $J$ = 8 Hz, 2H), 6.54 (d, $J$ = 8 Hz, 2H), 5.45 (d, $J$ = 12 Hz, 1H), 5.00 (s, 1H), 4.09 (s, 1H), 4.01 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (m, 1H), 3.68 (d, $J$ = 4 Hz, 1H), 3.62 (s, 3H), 3.42 (m, 2H), 3.36 (d, $J$ = 4 Hz, 1H), 3.11–3.17 (dd, $J$ = 8, 12 Hz, 1H), 2.56 (d, $J$ = 4 Hz, 1H), 2.46 (d, $J$ = 12 Hz, 1H), 2.40 (s, 3H), 2.33 (d, $J$ = 8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 165.94, 149.122, 148.05 (2C), 146.60, 141.32 (2C), 130.73, 127.48, 125.10, 121.79 (2C), 117.35, 112.92, 112.21, 110.99, 110.63, 110.51, 110.24, 109.97, 109.75, 62.96, 59.99, 59.43, 56.13, 55.97, 55.87 (3C), 55.80 (2C), 55.58, 55.48, 44.13, 41.74, 32.38, 25.89.

*6.3.20. 3-[4-(Pyridin-2-yl)-phenyl]-2-propenamide derivative (**25**)*

Yellow film. $[\alpha]_D^{20}$: −56.6 ($c$ 0.006, $CHCl_3$). HRMS calcd. for $C_{40}H_{42}N_5O_5$ $[M + H]^+$ 672.3180, found 672.3168. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.7 (d, $J$ = 4 Hz, 2H), 8.03 (d, $J$ = 8 Hz, 1H), 7.76 (d, $J$ = 4 Hz, 2H), 7.52 (d, $J$ = 8 Hz, 2H), 7.42 (d, $J$ = 16 Hz, 1H), 6.60 (d, $J$ = 8 Hz, 2H), 6.55 (d, $J$ = 8 Hz, 2H), 5.63 (d, $J$ = 16 Hz, 1H), 5.18 (s, 1H), 4.10 (s, 1H), 4.02 (s, 1H), 3.93 (s, 3H), 3.87 (d, $J$ = 8 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.68 (d, $J$ = 8 Hz, 1H), 3.64 (s, 3H), 3.43 (d, $J$ = 8 Hz, 2H), 3.11–3.20 (dd, $J$ = 12, 16 Hz, 1H), 2.59 (d, $J$ = 12 Hz, 1H), 2.50 (d, $J$ = 12 Hz, 2H), 2.40 (s, 3H), 2.35 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 165.39, 156.50, 149.76, 148.54, 148.53, 148.01, 146.68, 140.63, 136.84, 136.77, 134.97, 128.28, 127.30, 127.22, 126.60, 126.07, 125.08, 123.54, 122.42, 120.57, 120.06, 117.69, 113.02, 110.60, 110.49, 110.30, 109.68, 62.94, 60.00, 59.56, 56.24, 55.91, 55.85, 55.63, 55.53, 55.55, 44.05, 41.80, 32.45, 25.91.

*6.3.21. 3-[4-(Morpholin-4-yl)-phenyl]-2-propenamide derivative (**26**)*

Yellow solid. Mp: 152–154 °C. $[\alpha]_D^{20}$: −113 ($c$ 0.0042, $CHCl_3$). HRMS calcd. for $C_{39}H_{46}N_5O_6$ $[M + H]^+$ 680.3443, found 680.3450. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.34 (d, $J$ = 8 Hz, 2H), 7.28 (d, $J$ = 12 Hz, 1H), 6.87 (d, $J$ = 8 Hz, 2H), 6.60 (d, $J$ = 8 Hz, 2H), 6.53 (d, $J$ = 8 Hz, 2H), 5.41 (d, $J$ = 12 Hz, 1H), 5.07 (m, 1H), 4.09 (s, 1H), 4.00 (s, 1H), 3.92(s, 3H), 3.90 (d, $J$ = 4 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 1H), 3.82 (s, 3H), 3.80 (d, $J$ = 4 Hz, 1H), 3.68 (s, 1H), 3.66 (s, 3H), 3.57 (d, $J$ = 12 Hz, 1H), 3.42 (m, 4H), 3.23 (d, $J$ = 4 Hz, 4H), 3.11–3.18 (dd, $J$ = 8, 16 Hz, 1H), 2.57 (d, $J$ = 8 Hz, 1H), 2.53 (d, $J$ = 8 Hz, 1H), 2.40 (s, 3H), 2.35 (d, $J$ = 12 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 166.29, 152.38, 148.67, 148.22 (2C), 146.84, 141.20, 129.48 (2C), 126.84, 126.27, 125.88,

125.45, 123.83, 117.97, 116.47, 114.99 (2C), 113.09, 110.70, 110.52, 109.95, 66.94 (2C), 63.21, 60.25, 59.79, 56.44, 56.14, 56.09, 55.95, 55.79 (2C), 48.57 (2C), 44.25, 42.06, 32.70, 26.16.

*6.3.22. 3-(1-Methyl-1H-pyrrol-2-yl)-2-propenamide derivative (**27**)*

White solid. Mp: 101–103 °C. $[\alpha]_D^{20}$: −42.3 (*c* 0.0018, $CHCl_3$). HRMS calcd. for $C_{34}H_{40}N_5O_5$ $[M + H]^+$ 598.3024, found 598.3024. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 16 Hz, 1H), 6.08 (t, 1H), 6.62 (d, *J* = 4 Hz, 1H), 6.56 (d, *J* = 8 Hz, 2H), 6.53 (d, *J* = 8 Hz, 2H), 6.17 (t, 1H), 5.32 (d, *J* = 16 Hz, 1H), 5.01 (d, *J* = 4 Hz, 1H), 4.07 (m, 1H), 3.98 (s, 1H), 3.87 (d, *J* = 4 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.73 (s, 3H), 3.62 (s, 3H), 3.74 (s, 1H), 3.40 (m, 1H), 3.37 (d, *J* = 8 Hz, 1H), 3.10–3.19 (dd, *J* = 8, 16 Hz, 1H), 2.54 (m, 1H), 2.48 (d, *J* = 4 Hz, 1H), 2.44 (d, *J* = 4 Hz, 1H), 2.40 (s, 3H), 2.35 (d, *J* = 8 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 166.20, 148.46, 147.95, 147.91, 146.64, 129.23, 129.09, 126.46, 126.05, 125.74, 123.58, 117.73, 114.45, 112.81, 110.45, 110.39, 110.20, 109.93, 109.70, 109.24, 62.96, 60.05, 59.69, 56.14, 55.88, 55.85, 55.71, 55.68, 55.56, 44.34, 41.81, 34.13, 32.41, 25.98.

*6.3.23. 3-(5-Chlorothiophen-2-yl)-2-propenamide derivative (**28**)*

Yellow solid. Mp: 110–112 °C. $[\alpha]_D^{20}$: −96.8 (*c* 0.0075, $CHCl_3$). HRMS calcd. for $C_{33}H_{36}ClN_4O_5S$ $[M + H]^+$ 635.2089, found 635.2095. $^1H$ NMR (400 MHz, $CDCl_3$): δ 7.33 (d, *J* = 15 Hz, 1H), 6.96 (d, *J* = 4 Hz, 1H), 6.85 (d, *J* = 4 Hz, 1H), 6.60 (s, 1H), 6.54 (d, *J* = 3 Hz, 2H), 6.49 (d, *J* = 3 Hz, 1H), 5.40 (d, *J* = 15 Hz, 1H), 5.07 (m, 1H), 4.08 (s, 1H), 3.98 (s, 1H), 3.92 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.79 (d, *J* = 4 Hz, 1H), 3.73 (s, 3H), 3.71 (d, *J* = 6 Hz, 1H), 3.48 (m, 1H), 3.40 (d, *J* = 6 Hz, 1H), 3.09–3.17 (dd, *J* = 6, 18 Hz, 1H), 2.59 (d, *J* = 6 Hz, 1H), 2.53 (d, *J* = 9 Hz, 1H), 2.45 (d, *J* = 9 Hz, 1H), 2.38 (s, 3H), 2.34 (d, *J* = 8 Hz, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 165.19, 148.70, 148.30, 148.22, 146.84, 138.50, 133.34, 132.50, 129.49, 127.54, 126.82, 126.57, 125.31, 123.80, 118.91, 117.97, 113.13, 110.83, 110.50, 109.93, 63.17, 60.38, 59.97, 56.44, 56.29, 56.12, 56.01, 55.93, 55.81, 44.39, 41.92, 32.75, 26.11.

*6.3.24. 3-(2-Chloroquinolin-3-yl)-2-propenamide derivative (**29**)*

Yellowish film. $[\alpha]_D^{20}$: −35.2 (*c* 0.0042, $CHCl_3$). HRMS calcd. for $C_{38}H_{39}ClN_5O_5$ $[M + H]^+$ 680.2634, found 680.2638. $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 4, 8 Hz, 1H), 7.99 (d, *J* = 4 Hz, 1H), 7.76 (dd, *J* = 4, 12 Hz, 2H), 7.62 (dd, *J* = 4, 12 Hz, 2H), 6.62 (d, *J* = 8 Hz, 2H), 6.54 (d, *J* = 8 Hz, 2H), 5.56 (d, *J* = 12 Hz, 1H), 5.12 (s, 1H), 4.07 (s, 1H), 4.03 (s, 1H), 3.91 (s, 3H), 3.85 (t, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.75 (m, 1H), 3.67 (d, *J* = 4 Hz, 1H), 3.54 (dd, *J* = 4, 8 Hz, 1H), 3.45 (d, *J* = 4 Hz, 1H), 3.15–3.21 (dd, *J* = 8, 12 Hz, 1H), 2.57 (d, *J* = 8 Hz, 1H), 2.50 (d, *J* = 12 Hz, 1H), 2.42 (s, 3H), 2.35 (m, 1H).

### 6.4. Cytotoxicity assay

Each compound was tested *in vitro* against eight different cell lines, including HCT-8 (human colon cancer cell line), BEL-7402 (human hepatic carcinoma cell line), BGC-823 (human gastric adenocarcinoma cell line), A549 (human lung adenocarcinoma epithelial cell line), A2780 (human ovarian cancer cell line), MX-1 (human breast cancer cell line), MDA-MB-231 (human breast cancer cell line), and MCF-7 (human breast cancer cell line). Each sample was prepared as a 20.0 mM stock solution that was dissolved in DMSO and added to the cells with less than 1% DMSO in the final drug dilution with culture medium. Cell lines were cultured in PRMI1640 or DMEM/F12 supplemented with 10% fetal bovine serum, containing penicillin–streptomycin at 37 °C and humidified at 5% $CO_2$. Briefly, cells were placed in the appropriate media on 96-well plates in a 100 μL total volume at a density of 1–2.5 × $10^4$ cells/mL and were allowed to adhere for 24 h before treatment with tested compounds in DMSO solution ($10^{-6}$, $10^{-7}$, $10^{-8}$ mol/L final concentration). The cells were incubated for 72 h after treated with different concentrations of all tested compounds, and cell viability was assayed by MTT assay. The 50% inhibitory concentration ($IC_{50}$) was defined as the concentration that reduced the absorbance of the untreated wells by 50% of vehicle in the MTT assay. Assays were performed in triplicate on three independent experiments.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.ejmech.2013.01.033.

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