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Design, Synthesis, and Anticancer Activity of Amide Derivatives of Structurally Modified Combretastatin-A4[1]

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Abstract—A new series of amide derivatives of structurally modified combretastatin-A4 **10a**–**10j** are synthesized, and their structures are confirmed by ^{1}H and ^{13}C NMR, and mass spectral data. The products are tested for their anticancer activity towards human cancer cell lines, MCF-7 (breast), A-549 (lung), Colo-205 (colon), and A-2780 (ovarian). The compounds **10b**, **10c,** and **10d** demonstrate the most promising activity.

Keywords: combretastatin-A4, cefozopram, 1,2,4-thiadiazoles, anticancer activity

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INTRODUCTION

A vast number of heterocyclic derivatives were employed efficiently in anticancer chemotherapy [1–6]. Combretastatin-A4 (**1**), (see the figure) was isolated from South African tree *Combretum caffrumin* [7, 8]. It demonstrated high antitumor activity [9, 10] and acted as vascular disrupting agent (VDA) [11]. Combretastatin-A4 has poor water solubility, high lipophilicity and was easily converted into inactive trans-isomer which made its activity lower [12, 13]. Because of stability problems, many researcher have developed double bond restricted combretastatin derivatives based on triazoles, pyrazoles, thiazoles, furanones, imidazoles, and oxazolones [14-16]. Similarly, 1,2,4-thiadiazole derivatives act as useful units in medicinal chemistry [17] and demonstrate a broad spectrum of biological activities including human leukemia [18], antidiabetic [19], anti-hypertensive [20], allosteric modulators [21], anti-bacterial [22], and many more. The FDA approved antibiotic cefozopram (**2**) [23] contains the 1,2,4-thiadiazole unit.

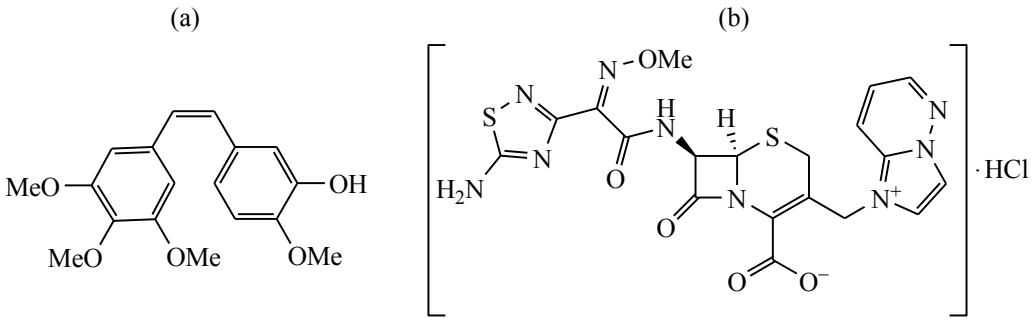
Due to the potent biological activities of combretastin-A4 and 1,2,4-thiadiazole derivatives, we have synthesized a series of structurally modified amide derivatives that combine combretastatin-A4 and 1,2,4-thiadiazole **10a**–**10j**. Their structures were confirmed by ^{1}H and ^{13}C NMR, and mass spectral data. The derivatives were tested for their activity against human cancer cell lines.

RESULTS AND DISCUSSION

The first step of synthesis of new amide derivatives of combretastatin-A4 (Scheme 1) was condensation of commercially available trimethoxyphenyl acetonitrile (**3**) with 4-methoxybenzaldehyde (**4**) in presence of TEA which gave the intermediate **5**. Its following cyclization with 4-nitrobenzothioamide (**6**) in presence of $AlCl_3$ led to compound **7**. The nitro group of the precursor **7** was reduced by zinc dust into the corresponding amine **8**. Coupling reaction of the letter compound **8** with a variety of substituted benzoyl chlorides **9a**–**9j** in presence of TEA resulted in formation of the corresponding target compounds **10a**–**10j.**

***In vitro* cytotoxicity.** All synthesized derivatives **10a**–**10j** were tested for their anticancer activity

[1] The text was submitted by the authors in English.



Structures of (a) Combretastatin-A4 (**1**) and Cefozopram (**2**).

against four types of human cancer cell lines, MCF-7 (breast), A-549 (lung), Colo-205 (colon), and A-2780 (ovarian) by the MTT assay method (see the table). Combretatstatin-A4 was used as a positive control. Most of the derivatives demonstrated moderate activity, among those the compounds **10b, 10c, 10d, 10h, 10i,** and **10j** exhibited very high activity. The preliminary analysis of structure-activity relationships (SARs) showed that compound **10b** containing three electro-donating methoxy substituents in positions 3, 4 and 5 on the phenyl ring demonstrated more potent activity than the positive control. The 3,5-dimethoxyphenyl containing analogue **10c** exhibited lower activity than the product **10b.** Along the same line, the product **10d** containing only one methoxy group on the phenyl ring exhibited even lower activity than compounds **10b** and **10c**. The compound **10i** with 4-methyl group demonstrated moderate activity. Interestingly, compound **10j** with the electron-withdrawing 4-cyano group on the phenyl ring exhibited very good activity. The corresponding 3,5-dinitro analogue was characterized by moderate activity.

EXPERIMENTAL

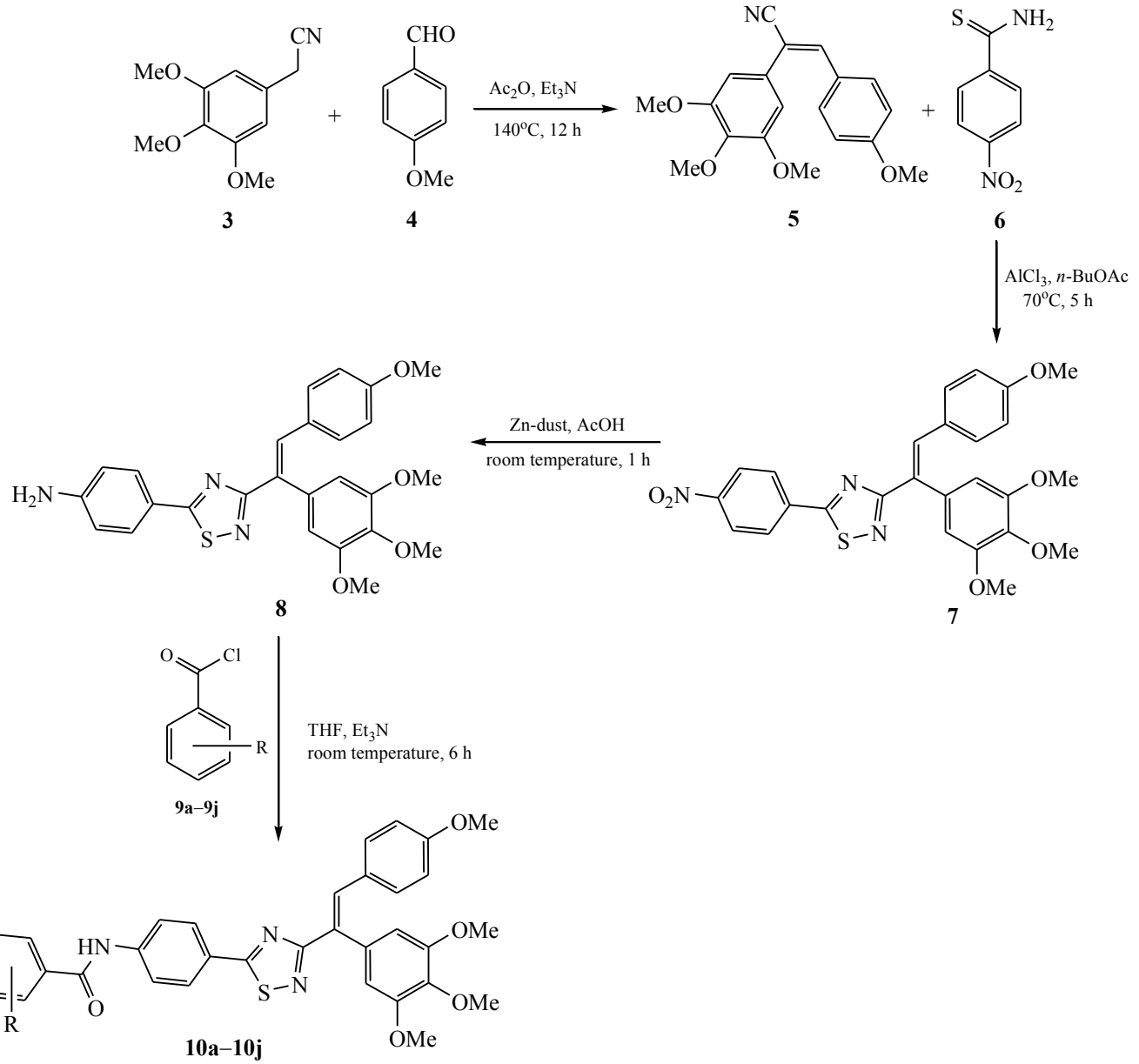
All chemicals were obtained from Aldrich (Sigma–Aldrich, St. Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Company, Ward Hill, MA, USA) and used without further purification. Reactions progress was monitored by TLC, performed on silica gel glass plates containing 60 F-254, and visualized by UV light or iodine indicator. ^{1}H and ^{13}C NMR spectra were measured on a Gemini Varian-VXR-unity (300 MHz) spectrometer using DMSO as a solvent and

Anticancer activity of newly synthesized compounds **10a**–**10j**[a]

Compound	IC_{50}, μM			
	A-549[b]	MCF-7[c]	A-375[d]	HT-29[e]
10a	2.870±1.7700	3.450±2.5500	Not active	6.23±3.440
10b	0.011±0.0030	0.023±0.0070	0.120±0.0120	1.78±0.380
10c	0.020±0.0054	0.041±0.0031	0.670±0.0300	1.90±0.440
10d	0.054±0.0043	0.077±0.0090	1.330±0.8200	Not active
10e	2.090±1.8800	2.650±1.5500	7.230±4.7600	10.40±5.790
10f	2.110±1.9300	2.170±1.3400	4.500±3.2200	No active
10g	3.450±2.0900	3.000±1.9900	5.120±3.6800	9.34±5.290
10h	1.440±0.6600	1.200±0.0560	0.330±0.0480	5.13±3.730
10i	0.540±0.0410	1.650±0.990	1.100±0.0320	2.99±1.560
10j	0.060±0.0012	0.013±0.0088	0.098±0.0078	Not active
Combretastatin-A4	0.110±0.0200	0.180±0.0210	0.210±0.0290	0.93±0.034

[a] Each data represents as mean ±S.D values. From three different experiments performed in triplicates.[b] (A-549) human lung cancer cell line. [c] (MCF-7) human breast cancer cell line. [d] (A-375) human melanoma cancer cell line. [e] (HT-29) human colon cancer cell line.

Scheme 1. Synthesis of amide derivatives of structurally modified combretastatin-A4.



R = H (**9a**, **10a**), 3,4,5-trimethoxy (**9b**, **10b**), 3,5-dimethoxy (**9c**, **10c**), 4-methoxy (**9d**, **10d**), 4-chloro (**9e**, **10e**), 4-bromo (**9f**, **10f**), 4-nitro (**9g**, **10g**), 3,5-dinitro (**9h**, **10h**), 4-methyl (**9i**, **10i**), 4-cyano (**9j**, **10j**).

TMS as an internal standard. ESI spectra were measured on Micro mass, Quattro LC using ESI+ software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined on an electrothermal melting point apparatus, and are uncorrected.

(***E*)-2-(3,4,5-Trimethoxyphenyl)-3-(4-methoxyphenyl)acrylonitrile (5).** A mixture of 2-(3,4,5-trimethoxyphenyl)acetonitrile (**3**) (15 g, 0.072 mol) with 4-methoxy benzaldehyde (4) (8.8 mL, 0.072 mol) and TEA (10 mL) in Ac_2O (50 mL) was stirred at 140°C for 12 h. After completion of the process (TLC), the reaction mixture was cooled down to room temperature and the solvent was evaporated. The crude product was diluted with aqueous NaOH for saponification, acidified with acetic acid and extracted with dichloromethane. The extract was dried over Na_2SO_4, and the solvent was evaporated. The residue was crystallized from ethyl acetate-hexane mixture to

afford pure compound **5**. Yield 54%. ^{1}H NMR spectrum, δ, ppm: 3.78 s (6H), 3.80 s (3H), 3.89 s (3H), 6.63 s (2H), 6.79 d (2H, *J* = 8.40 Hz), 7.19 d (2H, *J* = 8.40 Hz), 7.24 s (1H). MS (ESI): 326 [*M* + H]$^+$.

3-[(*E*)-1-(3,4,5-Trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-5-(4-nitrophenyl)-1,2,4-thiadiazole (7). A mixture of **5** (12 g, 0.0369 mmol) with $AlCl_3$ (5 g, 0.0369 mmol) and butylacetate (40 mL) was stirred at 70°C, and the 4-nitrobenzothioamide (**6**) (2.4 mL, 0.184 mmol) was added dropwise into the reaction flask and stirred at 70°C for 5 h. After cooling down to room temperature, water (0.3 mL) was added into it. The reaction mixture was stirred at room temperature for 24 h. The organic and aqueous layers were separated, and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 1) as an eluent to afford pure compound **7**. Yield 76%. ^{1}H NMR spectrum, δ, ppm: 3.79 s (6H), 3.81 s (3H), 3.90 s (3H), 6.66 s (2H), 6.82 d (2H, *J* = 8.41 Hz), 7.21 d (2H, *J* = 8.41 Hz), 7.26 s (1H), 7.66 d (2H, *J* = 7.30 Hz), 7.78 d (2H, *J* = 7.30 Hz). MS (ESI): 506 [*M* + H]$^+$.

4-{3-[(*E*)-1-(3,4,5-Trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-1,2,4-thiadiazol-5-yl}benzenamine (8). To a solution of **7** (13 g, 0.0257 mmol) in acetic acid (40 mL) was added zinc powder (2.3 g, 0.077 mmol). The reaction mixture was stirred at room temperature for 1 h. Upon completion of the reaction (TLC), the mixture was filtered over Celite, and the filtrate was evaporated to dryness to give pure compound **8.** Yield 83%. ^{1}H NMR spectrum, δ, ppm: 3.77 s (6H), 3.80 s (3H), 3.89 s (3H), 5.49 br.s (2H), 6.65 s (2H), 6.81 d (2H, *J* = 8.39 Hz), 7.20 d (2H, *J* = 8.39 Hz), 7.24 s (1H), 7.57 d (2H, *J* = 7.27 Hz), 7.69 d (2H, *J* = 7.27 Hz). MS (ESI): 477 [*M* + H]$^+$.

Synthesis of benzamides 10a–10j. To the solution of compound **8** (500 mg, 0.001mmol) in 10 mL of dry THF, were added an appropriate benzoyl chloride **9a–9j** (0.001 mmol) and TEA (0.3 mL, 0.002 mmol). The reaction mixture was stirred at room temperature for ca 12 h till the completion of the process, as monitored by TLC, washed with water, extracted with dichloromethane, and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using ethyl acetate–hexane (7 : 3) as an eluent to obtain the corresponding pure compound **10a–10j**.

***N*-{4-(3-[(*E*)-1-(3,4,5-Trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-1,2,4-thiadiazol-5-yl)phenyl}-benzamide (10a).** Yield 50%, mp 210–212°C. ^{1}H NMR spectrum, δ, ppm: 3.78 s (6H), 3.81 s (3H), 3.90 s (3H), 6.65 s (2H), 6.75 d (2H, *J* = 8.42 Hz), 7.22 d (2H, *J* = 8.42 Hz), 7.23 s (1H), 7.36 t (1H), 7.60 d (2H, *J* = 7.30 Hz), 7.64–7.73 (m, 4H), 7.76 d (2H, *J* = 7.31 Hz), 8.56 s (1H). ^{13}C NMR spectrum, δ, ppm: 56.4, 57.7, 61.2, 115.3, 117.6, 123.4, 128.7, 129.6, 130.3, 131.3, 132.7, 134.7, 135.2, 136.8, 138.4, 139.4, 140.5, 156.4, 160.3, 163.5, 168.4, 170.5. MS (ESI): 581 [*M* + H]$^+$.

3,4,5-Trimethoxy-*N*-{4-(3-[(*E*)-1-(3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-1,2,4-thiadiazol-5-yl)phenyl}benzamide (10b). Yield 59%, 229–231°C. ^{1}H NMR spectrum, δ, ppm: 3.77 s (6H), 3.81 s (3H), 3.88 s (6H), 3.90 s (3H), 3.93 s (3H), 6.66 s (2H), 6.76 d (2H, *J* = 8.41 Hz), 7.21 d (2H, *J* = 8.41 Hz), 7.23 s (1H), 7.30 s (2H), 7.62 d (2H, *J* = 7.32 Hz), 7.72 d (2H, *J* = 7.32 Hz), 8.56 s (1H). ^{13}C NMR spectrum, δ, ppm: 56.4, 57.4, 58.6, 61.3, 61.9; 107.5, 115.8, 117.5, 123.8, 129.5, 129.9, 130.3, 131.3, 132.7, 134.5, 135.4, 138.6, 139.6, 140.2, 143.3, 156.4, 157.5, 160.4, 161.3, 168.5, 170.4. MS (ESI): 671 [*M* + H]$^+$.

3,5-Dimethoxy-*N*-{4-(3-[(*E*)-1-(3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-1,2,4-thiadiazol-5-yl)pheny})benzamide (10c). Yield 65%, mp 217–219°C. ^{1}H NMR spectrum, δ, ppm: 3.70 s (6H), 3.78 s (6H), 3.81 s (3H), 3.91 s (3H), 6.58 s (1H), 6.65 s (2H), 6.77 d (2H, *J* = 8.41 Hz), 7.10 s (2H), 7.22 d (2H, *J* = 8.41 Hz), 7.23 s (1H), 7.59 d (2H, *J* = 7.31 Hz), 7.69 d (2H, *J* = 7.31 Hz), 8.55 s (1H). ^{13}C NMR spectrum, δ, ppm: 56.3, 57.3, 58.2, 61.6, 106.5, 115.6, 117.6, 118.5, 123.4, 129.5, 130.2, 130.7, 132.4, 134.5, 135.4, 136.2, 138.7, 139.6, 140.5, 156.7, 159.6, 160.6, 163.5, 168.7, 170.5. MS (ESI): 641 [*M* + H]$^+$.

4-Methoxy-*N*-{4-(3-[(*E*)-1-(3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-1,2,4-thiadiazol-5-yl)phenyl}benzamide (10d). Yield 61%, 209–211°C. ^{1}H NMR spectrum, δ, ppm: 3.74 s (3H), 3.78 s (6H), 3.81 s (3H), 3.91 s (3H), 6.66 s (2H), 6.76 d (2H, *J* = 8.42 Hz), 7.22 d (2H, *J* = 8.42 Hz), 7.24 s (1H), 7.36 d (2H, *J* = 7.26 Hz), 7.60 d (2H, *J* = 7.31 Hz), 7.70 d (2H, *J* = 7.31 Hz), 7.75 d (2H, *J* = 7.26 Hz), 8.56 s (1H). ^{13}C NMR spectrum, δ, ppm: 56.4, 57.4, 58.3, 61.6, 115.6, 116.4, 117.6, 123.3, 128.6, 129.6, 130.2, 130.8, 131.5, 132.6, 134.6, 135.7, 138.6, 139.7, 140.6, 156.4, 159.4, 160.4, 163.4, 168.7, 170.6. MS (ESI): 611 [*M* + H]$^+$.

4-Chloro-*N*-{4-(3-[(*E*)-1-(3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-1,2,4-thiadiazol-5-yl)-phenyl}benzamide (10e). Yield 80%, mp 230–232°C. ^{1}H NMR spectrum, δ, ppm: 3.79 s (6H), 3.82 s (3H), 3.91 s (3H), 6.66 s (2H), 6.76 d (2H, *J* = 8.43 Hz), 7.22 d (2H, *J* = 8.43 Hz), 7.24 s (1H), 7.47 d (2H, *J* = 7.29 Hz), 7.61 d (2H, J = 7.33 Hz), 7.71 d (2H, *J* = 7.33 Hz), 7.76 d (2H, *J* = 7.29 Hz), 8.57 s (1H). ^{13}C NMR spectrum, δ, ppm: 56.4, 57.6, 61.7, 115.6, 117.6, 123.6, 127.5, 129.6, 130.3, 130.8, 132.6, 133.6, 134.7, 135.2, 135.8, 138.6, 139.7, 140.6, 141.5, 156.4, 160.6, 163.7, 168.7, 170.7. MS (ESI): 546 [*M* + H]$^+$.

4-Bromo-*N*-{4-(3-[(*E*)-1-(3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-1,2,4-thiadiazol-5-yl)-phenyl}benzamide (10f). Yield 83%, 240–242°C. ^{1}H NMR spectrum, δ, ppm: 3.79 s (6H), 3.82 s (3H), 3.91 s (3H), 6.67 s (2H), 6.77 d (2H, *J* = 8.44 Hz), 7.22 d (2H, *J* = 8.44 Hz), 7.24 s (1H), 7.50 d (2H, *J* = 7.30 Hz), 7.62 d (2H, *J* = 7.34 Hz), 7.71 d (2H, *J* = 7.34 Hz), 7.77 d (2H, *J* = 7.30 Hz), 8.58 s (1H). ^{13}C NMR spectrum, δ, ppm: 56.7, 57.6, 61.8, 115.7, 117.6, 123.6, 124.5, 127.6, 128.7, 129.7, 130.6, 132.4, 133.7, 134.3, 134.9, 135.4, 138.4, 139.6, 140.7, 156.4, 161.7, 165.7, 169.5, 170.8. MS (ESI): 591 [*M* + H]$^+$.

***N*-{4-(3-[(*E*)-1-(3,4,5-Trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-1,2,4-thiadiazol-5-yl)phenyl}-4-nitrobenzamide (10g).** Yield 82%, mp 245–247°C. ^{1}H NMR spectrum, δ, ppm: 3.79 s (6H), 3.82 s (3H), 3.92 s (3H), 6.66 s (2H), 6.76 d (2H, *J* = 8.43 Hz), 7.22 d (2H, *J* = 8.43 Hz), 7.25 s (1H), 7.63 d (2H, *J* = 7.35 Hz), 7.71 d (2H, *J* = 7.35 Hz), 7.77 d (2H, *J* = 7.36 Hz), 7.83 d (2H, *J* = 7.36 Hz), 8.57 s (1H). ^{13}C NMR spectrum, δ, ppm: 56.4, 57.4, 61.5, 115.6, 117.6, 123.6, 125.6, 127.6, 129.7, 130.6, 131.5, 132.5, 134.6, 135.4, 136.7, 138.6, 139.7, 140.7, 151.4, 156.7, 160.3, 163.8, 169.7, 170.8. MS (ESI): 626 [*M* + H]$^+$.

***N*-{4-(3-[(*E*)-1-(3,4,5-Trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-1,2,4-thiadiazol-5-yl)phenyl}-3,5-dinitrobenzamide (10h).** Yield 83%, mp 256–258°C. ^{1}H NMR spectrum, δ, ppm: 3.78 s (6H), 3.82 s (3H), 3.92 s (3H), 6.67 s (2H), 676 d (2H, *J* = 8.44 Hz), 7.23 d (2H, *J* = 8.44 Hz), 7.26 s (1H), 7.64 d (2H, *J* = 7.36 Hz), 7.72 d (2H, *J* = 7.36 Hz), 8.10 s (2H), 8.58 s (1H), 8.64 s (1H). ^{13}C NMR spectrum, δ, ppm: 56.4, 57.8, 61.8, 115.6, 117.8, 123.6, 124.7, 128.6, 129.6, 130.6, 131.3, 132.4, 134.5, 135.9, 136.3, 136.7, 138.5, 139.7, 148.4, 156.2, 159.6, 160.7, 168.9, 170.9. MS (ESI): 671[*M* + H]$^+$.

***N*-{4-(3-[(*E*)-1-(3,4,5-Trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-1,2,4-thiadiazol-5-yl)phenyl}-4-methylbenzamide (10i).** Yield 54%, mp 229–231°C. ^{1}H NMR spectrum, δ, ppm: 2.43 s (3H), 3.78 s (6H), 3.80 s (3H), 3.90 s (3H), 6.66 s (2H), 6.74 d (2H, *J* = 8.41 Hz), 7.19 d (2H, *J* = 8.41 Hz), 7.23 s (1H), 7.34 d (2H, *J* = 7.28 Hz), 7.48 d (2H, *J* = 7.28 Hz), 7.61 d (2H, *J* = 7.32 Hz), 7.70 d (2H, *J* = 7.32 Hz), 8.55 s (1H). ^{13}C NMR spectrum, δ, ppm: 23.6, 56.5, 57.8, 61.8, 115.8, 117.5, 123.6, 128.6, 129.7, 130.3, 130.8, 132.5, 134.6, 135.3, 135.8, 138.6, 139.7, 140.6, 143.5, 156.7, 160.4, 163.7, 168.7, 170.8. MS (ESI): 595 [*M* + H]$^+$.

4-Cyano-*N*-{4-(3-[(*E*)-1-(3,4,5-trimethoxyphenyl)-2-(4-methoxyphenyl)vinyl]-1,2,4-thiadiazol-5-yl)-phenyl}benzamide (10j). Yield 75%, mp 242–244°C. ^{1}H NMR spectrum, δ, ppm: 3.79 s (6H), 3.81 s (3H), 3.92 s (3H), 6.67 s (2H), 6.75 d (2H, *J* = 8.42 Hz), 7.20 d (2H, *J* = 8.42 Hz), 7.23 s (1H), 7.65 d (2H, *J* = 7.33 Hz), 7.71 d (2H, *J* = 7.33 Hz), 7.80 d (2H, *J* = 7.35 Hz), 7.92 d (2H, *J* = 7.35 Hz), 8.57 s (1H). ^{13}C NMR spectrum, δ, ppm: 56.5, 57.7, 61.8, 114.5, 115.7, 117.8, 119.7, 123.6, 127.6, 129.6, 130.2, 131.4, 132.6, 134.7, 135.7, 136.2, 138.6, 139.7, 140.5, 140.8, 156.4, 160.6, 163.8, 169.2, 170.8. MS (ESI): 606 [*M* + H]$^+$.

MTT assay. Individual wells of a 96-well tissue culture micro titer plates were inoculated with 100 μL of complete medium containing 1×10^4 cells. The plates were incubated at 37°C in a humidified 5% CO_2 incubator for 18 h prior to the experiment. After medium removal, 100 μL of fresh medium containing the test compounds and combretastatn-A4 at different concentrations (0.5, 1, 2 μM) were added to each well and incubated at 37°C for 24 h. Then the medium was discarded and replaced with 10 μL MTT dye. Plates were incubated at 37°C for 2 h. The resulting formazan crystals were solubilized in 100 μL extraction buffer. The optical density was measured at 570 nm with a microplate reader (Multi-mode Varioskan Instrument-Themo Scientific). Percentage of DMSO in the medium never exceeded 0.25%.

CONCLUSIONS

A number of amide derivatives of combretastatin-A4 **10a**–**10j** are synthesized. Their structures are confirmed by ^{1}H and ^{13}C NMR, and mass spectral data. The products are tested for their anticancer activity towards human cancer cell lines, MCF-7 (breast), A-549 (lung), Colo-205 (colon), and A-2780

(ovarian) by the MTT assay. All synthesized compounds are determined to be active. Among those, the compounds **10b, 10c, 10d, 10h, 10i,** and **10j** are characterized by high activity.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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