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Synthesis of novel curcumin mimics with asymmetrical units and their anti-angiogenic activity

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Abstract—Novel curcumin mimics with asymmetrical units phenyl group with alkyl amide, chloro-substituted benzamide, or heteroaromatic amide moieties were synthesized and their anti-angiogenic activity was evaluated with the proliferation and tube formation inhibitory activity on the human umbilical vein endothelial cells. Compounds **5**, **14**, **17**, and **18** showed potent growth inhibitory activity and tube formation inhibitory activity.

Curcumin (Diferuloyl methane, **1**) is a chemopreventive and chemotherapeutic natural product that is isolated from the root of *Curcuma longa* L., which shows suppression, retardation, or inversion of carcinogenesis.[1] Furthermore, it also exhibits anti-inflammatory, antioxidant, antiviral, and anti-infectious activities and wound healing properties.[2]

In particular, there are many reports on the anti-angiogenesis of curcumin (**1**). Arbiser et al.[3], Kwon and co-workers[4], and Bowen and co-workers [5] also reported that curcumin (**1**) and its derivatives have a potent anti-angiogenic activity. Based on our assumption that rigidity of symmetrical aromatic moieties on a curcumin structure plays an important role in enhancing anti-angiogenic activity, we synthesized symmetrical bis-aromatic alkynyl pyridine and thiophene derivatives and bis-aromatic alkyl pyridine and thiophene derivatives, and reported on their biological activity.[6] In 2004, two groups have also reported on the novel curcumin analogs as anticancer and anti-angiogenesis agents.[7] Although structure–anti-angiogenic activity of curcumin (**1**) is not completely understood, curcumin is a promising lead compound for structural modification to discover novel anticancer agents.

But the commonality of reported novel analogs of curcumin is that they have a symmetrical α,β-unsaturated ketone with limited substituents on the aromatic rings.[8]

To search for useful drug candidates in the development of chemotherapeutic agents, it is necessary to bring about substantial chemical modification of the curcumin structure. Therefore, to achieve our objective, we report a novel method for the preparation of asymmetrical curcumin derivatives having a phenyl group with alkyl amide, chloro-substituted benzamide, or heteroaromatic amide moieties (**2**) (Fig. 1).

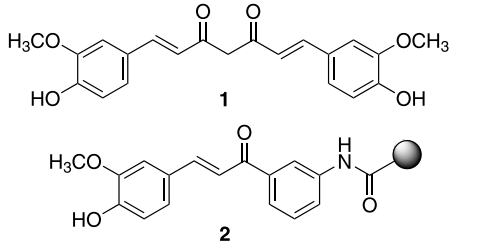

Figure 1.

Keywords: Curcumin; Anti-angiogenic activity; Heteroaromatic amides.
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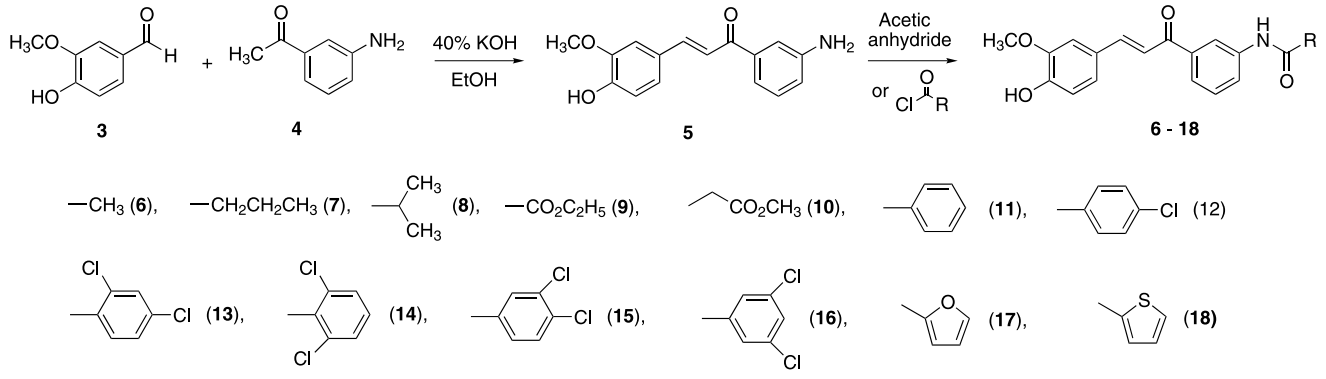
The anti-angiogenic activities of those synthetic compounds were evaluated with the proliferation[9] and tube formation inhibitory activities[10] on the human umbilical vein endothelial cells (HUVEC).

The target compounds were prepared, as shown in Scheme 1. Commercially available 4-hydroxy-3-methoxybenzaldehyde (**3**) was reacted with 3-acetylaniline (**4**) in the presence of basic catalyst (40% KOH) in ethanol at room temperature for 10 h.[11] The crude product was chromatographed ($CHCl_3/CH_3OH$ 97/3) on silica gel to afford 1-(3-aminophenyl)-3-(4-hydroxy-3-methoxyphenyl)propenone (**5**). This amine (**5**) was dissolved in a 1:1 mixture solution of dioxane and H_2O and then cooled to 0 °C (ice bath). Acetic anhydride or one of a variety of acyl chlorides was slowly added to the reaction mixture and then stirred at 0 °C for 5–7 h.[12] The solvent was removed in vacuo. The residues were chromatographed ($CHCl_3$/MeOH 95/5) on silica gel to give amides (**6**–**18**). Synthetic curcumin mimics with an alkyl amide group (**7**–**10**) were of slightly low yield, except for acetamide compound (**6**). Other aromatic amide products (**11**–**18**) gave a quantitative yield. ^1H, ^{13}C NMR spectrum and GC/MS spectrum of synthetic intermediate (**5**) and various curcumin mimics (**6**–**18**) were identified to study the relationship between structural modification and anti-angiogenic activity.[13]

The biological result of synthetic molecules is shown in Table 1. As we had expected, all compounds showed a strong inhibitory activity against HUVEC growth. Compounds with an aromatic amide moiety (**11**–**18**) showed a activity higher than those of alkyl amide groups (**6**–**10**). In particular, benzamide (**11**), furan amide (**17**), and thiophene amide (**18**) exhibited the highest activity. When considering HUVEC growth inhibition activity in our screening set, presence of various amide groups in asymmetric units, especially aromatic amide moieties, was shown to be important for activity. The introduction of mono-chloro or di-chloro substitution in benzamide has no effect of increasing activity.

In the tube formation assay using HUVEC on the Matrigel to conform to the anti-angiogenic activity of



Scheme 1. Synthesis of novel curcumin mimics with asymmetrical units including alkyl amide, chloro-substituted benzamide, or heteroaromatic amide moieties. Yield for **5**, 45%; **6**, 97%; **7**, 21%; **8**, 24%; **9**, 26%; **10**, 25%; **11**, 98%; **12**, 94%; **13**, 85%; **14**, 91%; **15**, 88%; **16**, 70%; **17**, 85%; **18**, 87%.

Table 1. Inhibitory activity of curcumin mimics on HUVEC growth and tube formation

Entry	Cytotoxic activity against cancer cell lines IC_{50} (μg/mL)[a]				[a]HUVEC growth inhibition IC_{50} (μg/mL)	HUVEC tube formation inhibition percentage (%)[b]		
	B16	Vero	U87	SiHa		2.5 μg/mL	5 μg/mL	10 μg/mL
5	11.48	6.02	7.71	12.33	2.87	20	50	90
6	3.62	14.48	>50	15.75	7.06	—	15	32
7	1.43	2.04	5.56	3.94	1.27	40	57	87
8	1.09	3.47	8.31	5.96	1.44	11	51	56
9	7.03	>50	>50	>50	13.3	—	45	66
10	4.41	3.55	12.24	7.71	1.50	—	20	43
11	0.82	3.47	8.82	4.57	0.37	—	48	69
12	0.59	3.82	>50	2.30	0.76	—	42	66
13	12.81	27.22	>50	34.43	0.40	29	51	70
14	1.58	2.48	17.81	3.56	0.46	53	88	99
15	3.88	>50	29.46	25.28	2.97	—	5	45
16	4.83	>50	>50	17.67	0.75	15	51	58
17	5.46	3.11	6.65	0.76	0.38	61	82	100
18	6.93	3.98	14.69	6.57	0.38	71	80	90
Curcumin	—	—	—	—	10.84	—	—	—

[a] IC_{50} was calculated from the nonlinear regression by Graphpad Prism software.

[b] Values expressed in percentage of HUVEC total tube length/field as compared to untreated control. Total tube length was measured using Image-pro plus version 3.0 (Media Cybernetics, MD, USA).

synthetic curcumin mimics, all compounds strongly inhibited the tube of HUVEC at a concentration of 10 μg/mL. Interestingly, compound **5** with a free amine group, synthetic intermediate for target molecules, shows 90% inhibition activity. Among the alkyl amide groups (**6**–**10**), only propyl amide compound **7** showed a good activity as 87% at the same concentration. Except **15**, the promising molecules (**11**–**14**, **16**–**18**) possessing aromatic amide groups exhibited a generally strong inhibitory activity against the tube formation. Especially, compounds (**14**, **17**, and **18**) showed the strongest activity at a concentration of 5.0 μg/mL. Even at a concentration of 2.5 μg/mL, compound **18** inhibited about 71%.

To compare the selectivity between HUVEC and tumor cell lines, four types of tumor cells, such as B16, Vero, U87, and SiHa, were used for the MTT assay. All tested molecules have a specific inhibition activity against HUVEC growth, as shown in Table 1. Three compounds (**14**, **17**, and **18**) with higher growth inhibition and tube-forming inhibition activity show a good selectivity on HUVEC. Interestingly, compound **13** inhibits moderately tube formation, but shows the highest selectivity among the tested molecules.

In conclusion, we have readily synthesized various curcumin mimics with asymmetric units possessing alkyl amide, chloro-substituted benzamide, or heteroaromatic amide moieties. Those synthetic molecules showed a stronger anti-angiogenic activity than the mother molecule, curcumin, without exhibiting any cytotoxic activity against HUVEC. In particular, compounds (**14**, **17**, and **18**) need to be studied further in the screening of other cancer cell lines, in vivo study, and toxicology. Substantial structural modifications of curcumin have an important potential for further drug development as antitumor and anti-angiogenesis agents.

Acknowledgment

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13. Analytical data for **5**: yield 45%; mp 154–155 °C; TLC (methylene chloride/methanol 94/6) $R_f = 0.39$; ^{1}H NMR ($CDCl_3$): δ 3.82 (2H, s, NH_2), 3.97 (3H, s, OCH_3), 5.89 (1H, s, OH), 6.88–6.90 (1H, m, $NH_2C_6H_4$), 6.96 (1H, d, $J = 8.21$ Hz, $CH_3OC_6H_3$), 7.13 (1H, d, $J = 1.76$ Hz, $CH_3OC_6H_3$), 7.21 (1H, dd, $J = 8.21$ and 1.80 Hz, $CH_3OC_6H_3$), 7.28–7.39 (3H, m, $NH_2C_6H_4$), 7.33 (1H, d, $J = 15.63$ Hz, CH=C*H*Ar), 7.73 (1H, d, $J = 15.63$ Hz, C*H*=CHAr) ppm. ^{13}C NMR ($CDCl_3$): δ 56.0, 110.2, 114.4, 115.1, 118.7, 119.2, 119.9, 123.4, 127.3, 129.4, 139.6, 145.0, 146.9, 147.1, 148.6, 190.9. GC/MSD (*m*/*z*) 269 (M^+); for **6**: yield 97%; mp 119–120 °C; TLC (methylene chloride/methanol 94/6) $R_f = 0.33$; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.20 (3H, s, CH_3), 3.97 (3H, s, OCH_3), 6.64 (1H, s, OH), 6.96 (1H, d, $J = 8.18$ Hz, $CH_3OC_6H_3$), 7.15 (1H, d, $J = 1.58$ Hz, $CH_3OC_6H_3$), 7.21 (1H, dd, $J = 8.19$ and 1.65 Hz, $CH_3OC_6H_3$), 7.36 (1H, d, $J = 15.67$ Hz, CH=C*H*Ar), 7.41–7.47 (1H, m, NHC_6H_4), 7.72 (1H, m, NHC_6H_4), 7.75 (1H, d, $J = 15.67$ Hz, C*H*=CHAr), 7.96 (1H, d, $J = 7.52$ Hz, NHC_6H_4), 8.04 (1H, s, NHC_6H_4), 8.31 (1H, br s, NH) ppm.^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 24.5, 56.1, 110.3, 115.1, 119.5, 119.6, 123.5, 123.9, 124.0, 127.3, 129.2, 138.8, 139.1, 145.5, 147.1, 148.7, 168.9, 190.3. GC/MSD (*m*/*z*) 311 (M^+); for **7**: yield 21%; TLC (ethyl acetate/*n*-hexane 1/1) $R_f = 0.20$; ^{1}H NMR ($CDCl_3$): δ 1.01 (3H, t, $J = 14.76$ Hz, $CH_2CH_2CH_3$), 1.75–1.80 (2H, m, $CH_2CH_2CH_3$), 2.38 (2H, t, $J = 14.87$ Hz, $CH_2CH_2CH_3$), 3.94 (3H, s, OCH_3), 6.10 (1H, s, OH), 6.94 (1H, d, $J = 8.17$ Hz, $CH_3OC_6H_3$), 7.11 (1H, d, $J = 1.68$ Hz, $CH_3OC_6H_3$), 7.20 (1H, dd, $J = 8.22$ and 1.70 Hz, $CH_3OC_6H_3$), 7.34 (1H, d, $J = 15.59$ Hz, CH=C*H*Ar), 7.44 (1H, t, $J = 15.8$ Hz, NHC_6H_4), 7.71 (1H, br s, NH), 7.71–7.72 (1H, m, NHC_6H_4), 7.74 (1H, d, $J = 15.59$ Hz, C*H*=CHAr), 7.96 (1H, d, $J = 7.7$ Hz, NHC_6H_4), 8.03 (1H, s, NHC_6H_4) ppm. ^{13}C NMR ($CDCl_3$): δ 13.8, 19.0, 29.8, 39.6, 56.1, 110.2, 114.9, 119.5, 119.6, 123.5, 124.1, 127.3, 129.3, 138.6, 139.1, 145.7, 146.9, 148.5, 171.8, 190.4. GC/MSD (*m*/*z*) 339 (M^+); for **8**: yield 24%; TLC (ethyl acetate/*n*-hexane 1/1) $R_f = 0.23$; ^{1}H NMR ($CDCl_3$): δ 1.28 (6H, d, $J = 6.87$ Hz, CH_3), 2.55–2.58 (1H, m, CH), 3.96 (3H, s, OCH_3), 5.99 (1H, br s, OH), 6.95 (1H, d, $J = 8.23$ Hz, $CH_3OC_6H_3$),

7.13 (1H, d, J = 1.64 Hz, $CH_3OC_6H_3$), 7.22 (1H, dd, J = 8.22 and 1.71 Hz, $CH_3OC_6H_3$), 7.36 (1H, d, J = 15.59 Hz, CH=C*H*Ar), 7.46 (1H, t, J = 15.85 Hz, NHC_6H_4), 7.49 (1H, br s, NH), 7.72 (1H, s, NHC_6H_4), 7.76 (1H, d, J = 15.59 Hz, C*H*=CHAr), 7.87 (1H, d, J = 7.52 Hz, NHC_6H_4), 8.04 (1H, s, NHC_6H_4) ppm.^{13}C NMR ($CDCl_3$): δ 19.6, 36.7, 56.0, 110.2, 114.9, 119.5, 119.6, 123.5, 124.0, 124.1, 127.3, 129.3, 138.7, 139.1, 145.7, 146.9, 148.5, 175.8, 190.4. GC/MSD (*m*/*z*) 339 (M^+); for **9**: yield 26%; TLC (chloroform/methanol 95/5) R_f = 0.35; ^{1}H NMR ($CDCl_3$): δ 1.07 (3H, t, J = 14.11 Hz, CH_2CH_3), 3.97 (3H, s, OCH_3), 4.45 (2H, q, J = 7.09 Hz, CH_2CH_3), 5.98 (1H, s, OH), 6.96 (1H, d, J = 8.14 Hz, $CH_3OC_6H_3$), 7.14 (1H, s, $CH_3OC_6H_3$), 7.25 (1H, t, J = 15.73 Hz, $CH_3OC_6H_3$), 7.36 (1H, d, J = 15.59 Hz, CH=C*H*Ar), 7.53(1H, t, J = 15.82 Hz, NHC_6H_4), 7.78 (1H, d, J = 15.59 Hz, C*H*=CHAr), 7.84 (1H, d, J = 7.73 Hz, NHC_6H_4), 7.99 (1H, d, J = 7.96 Hz, NHC_6H_4), 8.19 (1H, s, NHC_6H_4), 9.04 (1H, s, NH) ppm. ^{13}C NMR ($CDCl_3$): δ 14.0, 56.1, 64.0, 110.1, 114.9, 119.2, 119.7, 123.6, 123.7, 125.4, 127.3, 129.6, 136.8, 139.4, 145.9, 146.8, 148.5, 154.2, 160.7, 189.7. GC/MSD (*m*/*z*) 369 (M^+); for **10**: yield 25%; TLC (chloroform/methanol 97/3) R_f = 0.11; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 2.23 (3H, s, CH_3), 3.95 (3H, s, OCH_3), 4.72 (2H, s CH_2), 6.94 (1H, d, J = 8.07 Hz, $CH_3OC_6H_3$), 7.16 (1H, d, J = 1.56 Hz, $CH_3OC_6H_3$), 7.18 (1H, dd, J = 8.20 and 1.68 Hz, $CH_3OC_6H_3$), 7.36 (1H, d, J = 15.58 Hz, CH=C*H*Ar), 7.46 (1H, t, J = 15.78 Hz, NHC_6H_4), 7.74 (1H, d, J = 15.58 Hz, C*H*=CHAr), 7.75 (1H, d, J = 7.96 Hz, NHC_6H_4), 8.00 (1H, d, J = 7.96 Hz, NHC_6H_4), 8.12 (1H, s, NHC_6H_4), 8,12 (1H, s, OH), 9.38 (1H, s, NH) ppm.^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 20.8, 56.0, 63.0, 110.7, 115.5, 119.1, 119.8, 123.5, 124.1, 124.2, 126.8, 129.2, 138.2, 139.1, 145.7, 147.7, 149.4, 165.9, 170.1, 190.2. GC/MSD (*m*/*z*) 369 (M^+); for **11**: yield 98%; mp 80–82 °C; TLC (chloroform/methanol 95/5) R_f = 0.33; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.93 (3H, s, OCH_3), 6.93 (1H, d, J = 8.04 Hz, $CH_3OC_6H_3$), 7.15–7.18 (2H, m, $CH_3OC_6H_3$), 7.39 (1H, d, J = 16.00 Hz, CH=C*H*Ar), 7.45–7.49 (3H, m, benzoyl-*H*), 7.52 (1H, t, J = 14.48 Hz, NHC_6H_4), 7.74 (1H, d, J = 16.00 Hz, C*H*=CHAr), 7.75 (1H, m, NHC_6H_4), 8.00 (2H, d, J = 7.26 Hz, benzoyl-*H*), 8.16 (1H, d, J = 8.24 Hz, NHC_6H_4), 8.19 (1H, s, OH), 8.35 (1H, s, NHC_6H_4),9.69 (1H, s, NH) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.0, 110.8, 115.5, 119.3, 120.5, 123.4, 123.9, 124.7, 126.8, 127.7, 128.4, 129.0, 131.7, 135.0, 139.0, 139.3, 145.5, 147.6, 149.3, 166.5, 190.4. GC/MSD (*m*/*z*) 373 (M^+); for **12**: yield 94%; mp 212–215 °C; TLC (chloroform/methanol 95/5) R_f = 0.31; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 4.04 (3H, s, OCH_3), 6.87 (1H, d, J = 7.77 Hz, $CH_3OC_6H_3$), 7.11–7.13 (2H, m, $CH_3OC_6H_3$), 7.31–7.40 (2H, m, 4-chlorobenzoyl-*H*), 7.43 (1H, t, J = 17.2 Hz, NHC_6H_4), 7.39 (1H, d, J = 16.00 Hz, CH=C*H*Ar), 7.68 (1H, d, J = 16.00 Hz, C*H*=CHAr), 7.69 (1H, m, NHC_6H_4), 7.94 (2H, d, J = 8.45 Hz, 4-chlorobenzoyl-*H*), 8.10 (1H, d, J = 7.60 Hz, NHC_6H_4), 8.26 (1H, s, NHC_6H_4), 8.40 (1H, s, OH), 9.89 (1H, s, NH) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.3, 111.2, 116.0, 119.5, 120.9, 123.8, 124.3, 125.1, 127.1, 128.8, 129.3, 129.7, 133.7, 138.0, 139.3, 139.7, 145.9, 148.1, 149.8, 165.7, 190.6. GC/MSD (*m*/*z*) 407 (M^+); for **13**: yield 85%; mp 170–172 °C; TLC (chloroform/methanol 95/5) R_f = 0.34; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.96 (3H, s, OCH_3), 6.94 (1H, d, J = 7.96 Hz, $CH_3OC_6H_3$), 6.95 (1H, s, OH), 7.15 (1H, d, J = 1.66 Hz, $CH_3OC_6H_3$), 7.22 (1H, dd, J = 8.21 and 1.65 Hz, $CH_3OC_6H_3$), 7.36–7.40 (1H, m, 2,4-dichlorobenzoyl-*H*), 7.38 (1H, d, J = 15.00 Hz, CH=C*H*Ar), 7.49 (1H, d, J = 1.67 Hz, 2,4-dichlorobenzoyl-*H*), 7.52 (1H, t, J = 15.88 Hz, NHC_6H_4), 7.67 (1H, d, J = 8.27 Hz, 2,4-dichlorobenzoyl-*H*), 7.76 (1H, d, J = 15.00 Hz, C*H*=CHAr), 7.76–7.80 (1H, m, NHC_6H_4), 8.08 (1H, d, J = 7.25 Hz, NHC_6H_4), 8.22 (1H, s, NHC_6H_4), 9.08 (1H, s, NH) ppm.^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.1, 110.4, 115.2, 119.4, 120.0, 123.5, 124.2, 124.6, 127.2, 127.5, 129.3, 130.0, 131.0, 131.9, 134.2,136.9, 138.4, 139.3, 145.8, 147.2, 148.9, 164.2, 190.2. GC/MSD (*m*/*z*) 442 (M^+); for **14**: yield 91%; mp 157–160 °C; TLC (chloroform/methanol 95/5) R_f = 0.29; ^{1}H NMR ($CDCl_3$ + DMSO-d_6):δ 3.96 (3H, s, OCH_3), 6.87 (1H, s, OH), 6.95 (1H, d, J = 8.17 Hz, $CH_3OC_6H_3$), 7.16 (1H, d, J = 1.48 Hz, $CH_3OC_6H_3$), 7.22 (1H, dd, J = 8.12 and 1.51 Hz, $CH_3OC_6H_3$), 7.29–7.39 (3H, m, 2,6-dichlorobenzoyl-*H*), 7.39 (1H, d, J = 16.00 Hz, CH=C*H*Ar), 7.52 (1H, t, J = 15.74 Hz, NHC_6H_4), 7.76 (1H, d, J = 16.00 Hz, C*H*=CHAr), 7.79 (1H, m, NHC_6H_4), 8.10 (1H, d, J = 7.93 Hz, NHC_6H_4), 8.25 (1H, s, NHC_6H_4), 9.24 (1H, s, NH) ppm.^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.1, 110.4, 115.2, 119.6, 120.0, 123.5, 124.3, 124.6, 127.2, 128.0, 129.3, 130.7, 132.5, 136.3, 138.4, 139.3, 145.6, 147.2, 148.8, 162.9, 190.2. GC/MSD (*m*/*z*) 442 (M^+); for **15**: yield 88%; mp 208–210 °C; TLC (chloroform/methanol 95/5) R_f = 0.32; ^{1}H NMR (DMSO-d_6): δ 3.87 (3H, s, OCH_3), 6.85 (1H, d, J = 8.00 Hz, $CH_3OC_6H_3$), 7.30 (1H, d, J = 7.94 Hz, $CH_3OC_6H_3$), 7.51 (1H, s, $CH_3OC_6H_3$), 7.59 (1H, t, J = 7.55 Hz, NHC_6H_4), 7.71 (2H, s, 3,4-dichlorobenzoyl-*H*), 7.85 (1H, d, J = 8.25 Hz, CH=C*H*Ar), 7.96–8.00 (1H, m, NHC_6H_4), 7.99 (1H, d, J = 8.25 Hz, C*H*=CHAr), 8.11 (1H, d, J = 7.73 Hz, NHC_6H_4), 8.28 (1H, s, 3,4-dichlorobenzoyl-*H*), 8.38 (1H, s, NHC_6H_4), 9.73 (1H, br s, OH), 10.60 (1H, s, NH) ppm. ^{13}C NMR (DMSO-d_6): δ 56.2, 112.2, 116.0, 119.0, 120.3, 124.4, 124.6, 125.0, 126.5, 128.5, 129.5, 130.0, 131.2, 131.7, 134.9, 135.2, 138.9, 139.5, 145.6, 148.3, 150.2, 163.7, 189.2. GC/MSD (*m*/*z*) 442 (M^+); for **16**: yield 70%; mp 202–206 °C; TLC (chloroform/methanol 95/5) R_f = 0.36; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.95 (3H, s, OCH_3), 6.93 (1H, d, J = 8.26 Hz, $CH_3OC_6H_3$), 7.17–7.19 (2H, m, $CH_3OC_6H_3$), 7.40 (1H, d, J = 15.57 Hz, CH=C*H*Ar), 7.50 (1H, t, J = 15.97 Hz, NHC_6H_4), 7.52 (1H, s, 3,5-dichlorobenzoyl-*H*), 7.74 (1H, d, J = 15.57 Hz, C*H*=CHAr), 7.77 (1H, m, NHC_6H_4), 8.02 (2H, d, J = 1.47 Hz, 3,5-dichlorobenzoyl-*H*), 8.18 (1H, d, J = 8.04 Hz, NHC_6H_4), 8.35 (1H, s, NHC_6H_4), 8.88 (1H, s, OH), 10.32 (1H, s, NH) ppm.^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.3, 111.2, 116.0, 119.3, 120.8, 123.7, 124.3, 124.9, 126.9, 129.3, 131.4, 134.2, 135.2, 138.0, 139.2, 139.4, 145.8, 148.2, 150.0, 163.8, 190.3. GC/MSD (*m*/*z*) 442 (M^+); for **17**: yield 85%; mp 82–84 °C; TLC (chloroform/methanol 95/5) R_f = 0.30; ^{1}H NMR ($CDCl_3$): δ 3.96 (3H, s, OCH_3), 6.01 (1H, s, OH), 6.58–6.59 (1H, m, furan-*H*), 6.96 (1H, d, J = 8.15 Hz, furan-*H*), 7.14 (1H, s, $CH_3OC_6H_3$), 7.23 (1H, d, J = 8.32 Hz, $CH_3OC_6H_3$), 7.27 (1H, t, J = 7.13 Hz, $CH_3OC_6H_3$), 7.37 (1H, d, J = 15.67 Hz, CH=C*H*Ar), 7.51 (1H, t, J = 15.91 Hz, NHC_6H_4), 7.54 (1H, d, J = 0.72 Hz, furan-*H*), 7.78 (1H, d, J = 15.67 Hz, C*H*=CHAr), 8.05 (1H, d, J = 7.69 Hz, NHC_6H_4), 8.16 (1H, s, NHC_6H_4), 8.26 (1H, s, NH) ppm.^{13}C NMR ($CDCl_3$): δ 56.1, 110.2, 112.7, 114.9, 115.7, 119.5, 119.7, 123.6, 124.1, 124.4, 127.4, 129.4, 137.9, 139.3, 144.5, 145.7, 146.9, 147.5, 148.5, 156.3, 190.2. GC/MSD (*m*/*z*) 363 (M^+); for **18**: yield 87%; mp 193–195 °C; TLC (chloroform/methanol 95/5) R_f = 0.28; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.97 (3H, s, OCH_3), 6.79 (1H, s, OH), 6.95 (1H, d, J = 8.27 Hz, $CH_3OC_6H_3$), 7.13–7.15 (2H, m, $CH_3OC_6H_3$), 7.21–7.23 (1H, m, thiophene-*H*), 7.39 (1H, d, J = 15.68 Hz, CH=C*H*Ar), 7.48–7.52 (1H, t, J = 7.80 Hz, NHC_6H_4), 7.57 (1H, d, J = 4.97 Hz, thiophene-*H*), 7.75–7.79 (1H, m, NHC_6H_4), 7.77 (1H, d, J = 15.68 Hz, C*H*=CHAr), 7.83 (1H, d, J = 3.71 Hz,

thiophene-*H*), 8.13 (1H, d, J = 7.76 Hz, NHC_6H_4), 8.20 (1H, s, NHC_6H_4), 8.90 (1H, s, NH) ppm. ^{13}C NMR ($CDCl_3$ + DMSO-d_6): δ 56.1, 110.4, 115.1, 119.5, 120.1, 123.5, 124.1, 124.5, 127.2, 127.8, 128.8, 129.3, 131.1, 138.7, 139.1, 139.6, 145.6, 147.1, 148.8, 160.5, 190.3. GC/MSD (m/z) 379 (M^+).