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Synthesis of cinnamoyl ketoamides as hybrid structures of antioxidants and calpain inhibitors

Yeong Jae Yoo [a,b], Dong Hyuk Nam [a,b], Seo Yun Jung [a], Jae Wan Jang [c], Hyoung Ja Kim [c], Changbae Jin [c], Ae Nim Pae [c], Yong Sup Lee [a,b,*]

[a] Department of Pharmaceutical Science, College of Pharmacy Kyung Hee University, Seoul 130-701, Republic of Korea
[b] Department of Life and Nanopharmaceutical Sciences, Kyung Hee University, Republic of Korea
[c] Life & Health Division, Korea Institute of Science & Technology, PO Box 131 Cheongryang, Seoul 130-650, Republic of Korea

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ABSTRACT

The excessive calpain activation causes serious cellular damage or even cell death in neurological disorders such as stroke and Alzheimer's disease. Oxidative stress has also been implicated in the initiation or progression of neurodegenerative diseases. In the present studies, a series of cinnamoyl ketoamides **4a–4j** were synthesized as hybrid structures of antioxidants and calpain inhibitors. Cinnamoyl ketoamides, possessing an alkyl chain at the α-position, showed potent μ-calpain inhibitory activities indicating that the cinnamoyl skeleton can be regarded as an acyclic variant of calpain inhibitory chromone carboxamide **2**. Among synthesized, compound **4e** was the most potent inhibitor of μ-calpain (IC_{50} = 0.13 μM) and also exhibited strong antioxidant activities in DPPH and superoxide anion radical scavenging and lipid peroxidation inhibition assay systems.

Calpain is a Ca^{2+}-activated cysteine protease typically associated with cellular necrosis.[1] Two isozymes of μ- and m-calpains show similar biochemical features, except for the calcium concentration necessary for activation in vitro: μ- and m-calpains require micromolar and millimolar levels of calcium, respectively.[2] Calpains are involved in numerous physiological processes; signal transduction, cell migration, differentiation, and apoptosis.[3] However, in some pathological conditions in neurological disorders such as in stroke,[4] Parkinson's disease[5] and Alzheimer's disease,[6] calpains are overactivated to cause serious cell death. Thus the inhibition of this enzyme has been considered as one of strategy for treating neurodegenerative diseases.

Oxidative stress has also been implicated in the initiation or progression of neurodegenerative diseases.[7,8] Reactive oxygen species (ROS) are highly reactive and can attack lipids, proteins, enzymes and DNA, and thus cause cell and tissue injuries.[9] Especially, ROS is also known to induce calpain activation.[10] Therefore, antioxidants may provide a means for preventing or treating oxidative stress-related neurodegenerative disorders.

Recently, combinations of compounds, each possessing a different mechanism of action in preventing cell death, have shown synergistic effects in ischemic animal models.[11,12] It was suggested that a neuroprotectant with multiple mechanisms of action may provide significant efficacy for preventing or retarding cell death in neurodegenerative diseases.[13] Accordingly, we considered a combination of calpain inhibitory and antioxidant activities in the design of neuroprotective agents so that they can protect against cell death through dual mechanisms. Although some reports on the linkage of two antioxidants[14,15] or calpain inhibitory moiety with an antioxidant through an amide bond has been reported,[16] synthesis of hybrid structures of calpain inhibitory and antioxidative moieties was scarce. In connection with our efforts

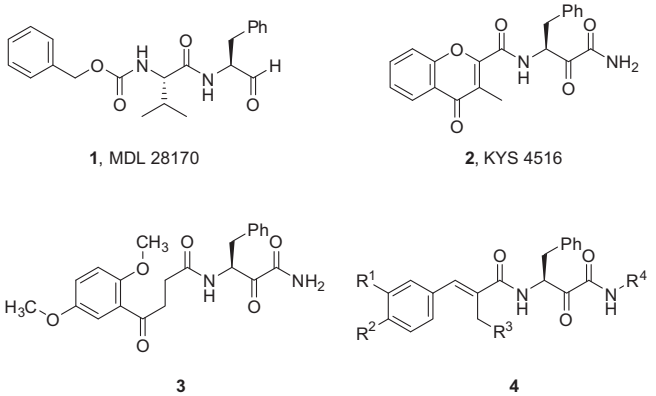

Figure 1. Design of new cinnamoyl ketoamides.

* Corresponding author. Tel.: +82 2 961 0370; fax: +82 2 966 3885.
E-mail address: kyslee@khu.ac.kr (Y.S. Lee).

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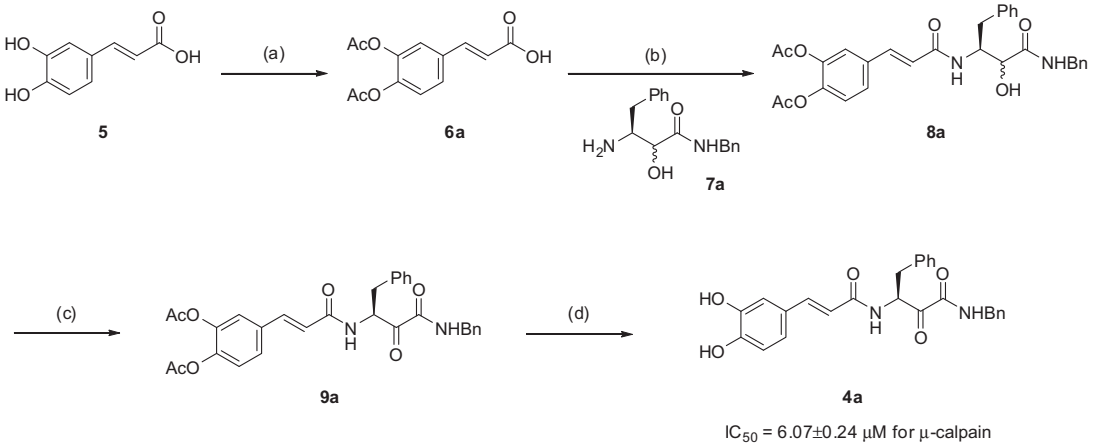


Scheme 1. Reagents and conditions: (a) Ac_2O, pyridine, 82%; (b) EDC, HOBt, DMF, 30%; (c) Dess–Martin periodinane, CH_2Cl_2, 34%; c-HCl, MeOH/H_2O (1:2), 97%.

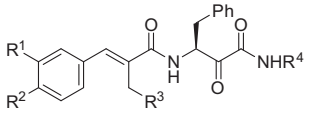
to discover neuroprotectants, we attempted to identify a new scaffold possessing antioxidant activity as well as calpain inhibitory activity. We recently reported calpain inhibitory chromone carboxamide **2**,[17] as a conformationally restricted cyclic analog of MDL 28170 (**1**) and **3**,[18] as an acyclic variants of **2** in order to elucidate the structural requirements for inhibitor binding to the active site of μ-calpain. In this work, we designed a cinnamic acid moiety for the purpose of introducing calpain inhibitory activities since it can be regarded as an acyclic variant of the chromone ring in **2** (Fig. 1). Furthermore, hydroxycinnamic acids such as caffeic acid are already well known for their antioxidant and neuroprotective activities.[19,20]

Before synthesizing a series of cinnamoyl ketoamides **4**, we first examined the importance of an alkyl group at the α-position of the cinnamoyl group on μ-calpain inhibitory activities by the synthesis of **4a**, which possesses no alkyl group (Scheme 1).

The hydroxyl groups in caffeic acid (**5**) were protected as acetyls and the resulting compound **6a** was coupled with hydroxyamide **7a** using EDC and HOBt to afford **8a**. Compound **8a** was oxidized with Dess–Martin periodinane and then deprotected under the acidic condition to provide a caffeoyl ketoamide **4a**. The μ-calpain inhibitory activity of **4a** was moderate (IC_{50} = 6.07 ± 0.24 μM) indicating that the cinnamoyl moiety possesses μ-calpain inhibitory activity, however, its potency was not high enough. Accordingly, it was thought that the substitution of an alkyl chain to this skeleton may be required to further mimic the chromone ring as its acyclic variant and enhance activities (Table 1).

Alkyl-substituted cinnamic acid derivatives **6b–6g** were prepared as illustrated in Scheme 2. (Carbethoxymethylene)-triphenylphosphorane (**8c**) was alkylated with alkyl iodides in refluxing acetonitrile and the resulting alkylated ylides **10** were condensed with benzaldehyde derivatives **11a–11c** through the Wittig olefination reaction to provide alkyl-substituted cinnamic acid ester derivatives **12b–12g**.[21] These consecutive reactions proceeded well with *n*-alkyl iodides (two steps yield, 54–68%), however, when using 1-iodo-2-methylpropane, the reaction afforded **12e** in only 2% yield probably because of bulkiness of alkyl iodide.[22] In the model studies, acetyl was used for the protection of hydroxyl groups in caffeic acid. However, for the synthesis of alkyl-substituted cinnamic acid derivatives **6b–6f**, MOM protection was used since this protecting group is stable in the next basic hydrolysis step. The methyl ester group of compounds **12b–12g** were hydrolyzed with KOH in aqueous ethanol to afford cinnamic acid derivatives **6b–6g**.

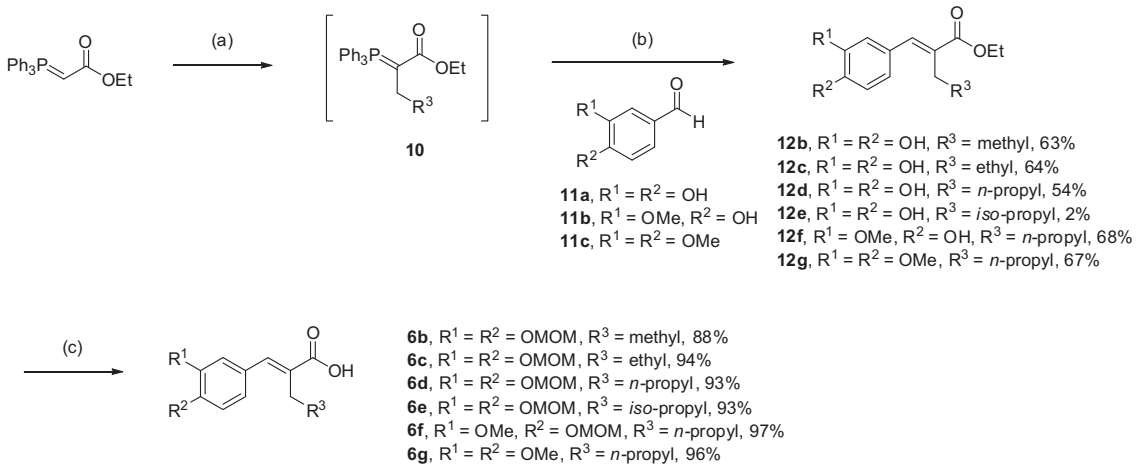
Table 1
The yields of coupling, oxidation, and deprotection steps and the μ-calpain inhibitory activities of **4a**–**4j** and their parent compounds **2** and **3**



4a~4j

Compds	R^1, R^2	R^3	R^4	Yields (%)			Calpain inhibition[a] (IC_{50}, μM)
				EDC coupling	Oxidation	Deprotection	
4a							6.07 ± 0.24
4b	$R^1 = R^2$ = OH	Methyl	Benzyl	72	47	82	0.61 ± 0.06
4c		Methyl	4-Methoxyphenethyl	58	92	83	0.46 ± 0.06
4d		Ethyl	Benzyl	94	89	83	0.36 ± 0.01
4e		Ethyl	4-Methoxyphenethyl	66	97	69	0.13 ± 0.00
4f		*n*-Propyl	Benzyl	81	99	64	0.67 ± 0.01
4g		*n*-Propyl	4-Methoxyphenethyl	22	23	62	0.50 ± 0.04
4h		*iso*-Propyl	Benzyl	56	99	69	0.32 ± 0.02
4i	R^1 = OMe, R^2 = OH	*n*-Propyl	4-Methoxyphenethyl	71	96	69	0.63 ± 0.03
4j	$R^1 = R^2$ = OMe	*n*-Propyl	4-Methoxyphenethyl	64	96	—	1.38 ± 0.05
2							0.07 ± 0.00
3							0.52 ± 0.01

[a] IC_{50} values (defined as concentrations that inhibited activity by 50%) were calculated using GraphPad Prism using data obtained from at least three independent experiments. The IC_{50} values are expressed as the means ± SEM.

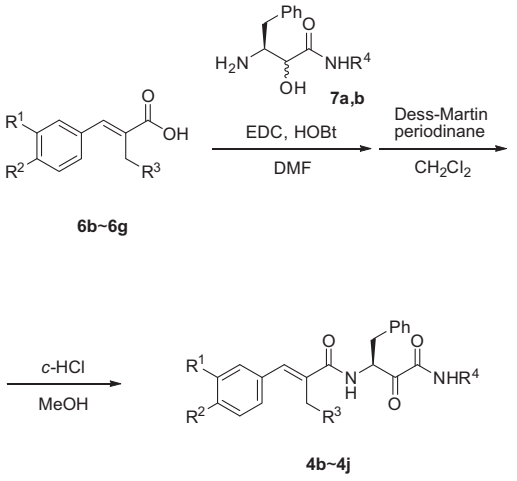


Scheme 2. Reagents and conditions: (a) (i) R^3-CH_2-I, CH_3CN; (ii) NaOH; (b) toluene, reflux; (c) for **12b–12f**; (i) MOM-Cl, NaH, THF; (ii) KOH, EtOH–H_2O; for **12g**, KOH, EtOH–H_2O.

The synthesis of cinnamoyl ketoamides **4b–4j** is shown in Scheme 3. The cinnamic acid derivatives **6g** were coupled with hydroxyamide **7a** or **7b** using general coupling reagents EDC and HOBt at room temperature followed by oxidation of the resulting hydroxylamides with Dess–Martin periodinane to afford cinnamoyl α-ketoamide **4j**. Cinnamoyl ketoamides **4b–4i**, which contain hydroxyl-substituents on its aromatic ring, were obtained by the same procedures as for **4j** with additional deprotection of the MOM group at the final stage by treating with HCl/MeOH (1%) at reflux temperature. The chemical yields at each step are summarized in Table 1.

The μ-calpain inhibitory activities of the cinnamoyl ketoamides **4a–4j** were evaluated using human calpain I isolated from erythrocytes. Suc-Leu-Tyr-AMC was used as the fluorogenic substrate.[23] Parent chromone carboxamide **2** and its acyclic variant **3** were also tested for comparison and assay results are summarized in Table 1. The introduction of alkyl chains to the α-position of the cinnamoyl group increased μ-calpain inhibitory activities in every compound when compared to that of **4a**. The degree of μ-calpain inhibitory activities was increased in the order of propyl ≅ *iso*-butyl > ethyl ≅ butyl as alkyl substituents. Compounds **4b–4h** possessing hydroxyl groups at both C-6 and C-7 positions of the aromatic ring showed more potent activities than methoxy-substituted compounds (**4i**, **4j**). Among synthesized, compound **4e** showed the most potent inhibitory activity (IC_{50} = 0.13 μM) against μ-calpain and its potency was ca. 4-fold higher than that of acyclic variant **3** (IC_{50} = 0.52 μM) and ca. 2-fold lower than that of parent compound **2** (IC_{50} = 0.07 μM).

The docking studies of **4a** and **4e** into the active site of μ-calpain were performed to understand the structural basis of the difference in the inhibitory activities of the cinnamoyl ketoamides. A covalent constraint implemented in GOLD v4.0 was used for docking simulation and the crystal structure of μ-calpain (PDB code: 2G8J) was obtained from the protein data bank.[24,25] The docking study showed that both compounds **4a** and **4e** are stabilized within the active site located near Cys83 residue, called the S1 subsite through hydrogen bond interactions with the residues and the water molecules (Fig. 2).[24] The compound **4e** showed higher docking score (GOLD fitness score = 8.1000) than that of compound **4a** (GOLD fitness score = 3.1271). The hydrogen bond interaction scored by Gold of **4e** was slightly higher than that of **4a**, implying that the angle and distance required for hydrogen bond is more favorable in the compound **4e** (Goldscore.External.Hbond of **4e** = 11.2312 and Goldscore.External.Hbond of **4a** = 9.7694). However, comparison between two docking poses suggested that a major improvement of the inhibitory activity of compound **4e** was caused by additional van der Waals interactions of the propyl and 4-methoxyphenylethyl groups of the inhibitor **4e** with the residues, Ala241 and Trp266, located in the S2 and S1′ subsites, respectively, (Goldscore.External.Vdw of **4e** = 43.5779 and Goldscore.External.Vdw of **4a** = 25.2249).[26] The interaction between Ala241 and an alkyl group of the co-crystallized ligand in the S2 subsite has also been observed in several μ-calpain crystal structures including the 2G8J. The π–π stacking between the 4-methoxyphenylethyl and Trp266 in the S1′ subsite might increase potency similarly to the interaction between the adenine group of the co-crystallized ligand and Trp266 in the crystal structure of 2R9C, which was important for the increased activity of the inhibitors.[27] Thus, the substitutions in the cinnamoyl ketoamides that can occupy the S2 hydrophobic pocket and extend into the S1′ subsite in the cinnamoyl ketoamides of μ-calpain inhibitor might enhance μ-calpain inhibitory activities.



Scheme 3.

The cinnamoyl ketoamides **4a–4j** were evaluated for antioxidant activities using DPPH and superoxide anion radical scavenging, and lipid peroxidation inhibition assays (Table 2).[28] For comparison purpose, the antioxidant activities of ascorbic acid and trolox were included as positive controls. Every compound exhibited a similar level of antioxidant activities each other in three assay systems, while the parent chromone carboxamide **2**

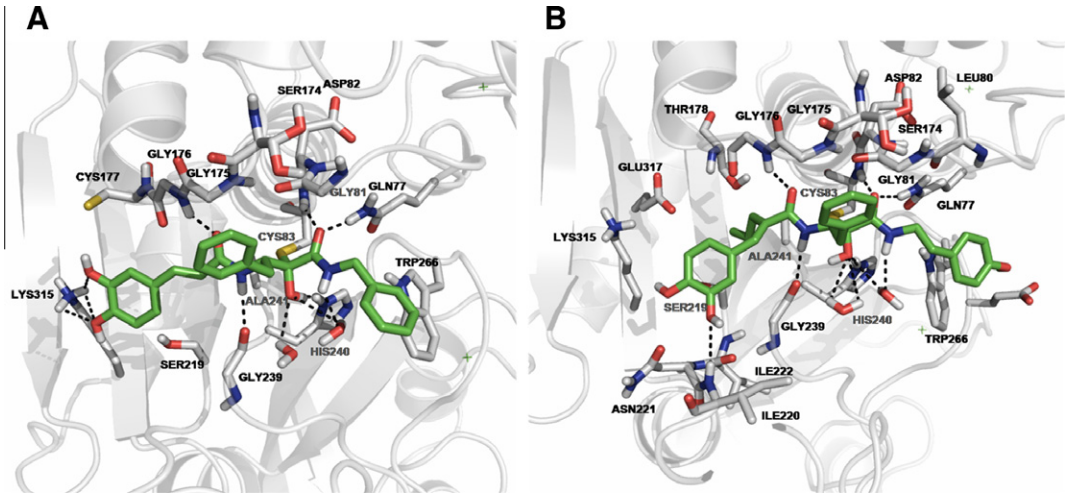


Figure 2. The cinnamoyl ketoamides **4a** (A) and **4e** (B) docked into the active site of μ-calpain crystal structure (PDB ID: 2G8J). The inhibitor is colored as green, and residues involved in the hydrogen bonding and van der Waals contact are shown and represented as a white stick form. The hydrogen bond interactions are represented as black dashed lines. Note that the propyl and 4-methoxyphenethyl substituents in **4e**, whereas **4a** does not have, show a good contact with Ala241 and Trp266, respectively. The image was generated using PyMol (http://www.pymol.org).

Table 2
The antioxidant activities of **4a**–**4j** and their parent compound **2** and **3**

Compds	DPPH scavenging[a]	Superoxide anion scavenging[b]	Lipid peroxidation inhibition[c]
	IC_{50}[d] (μM)		
4a	40.43 ± 1.61	31.19 ± 1.01	7.53 ± 0.24
4b	45.48 ± 0.72	15.48 ± 0.82	6.09 ± 0.24
4c	46.05 ± 0.72	29.22 ± 3.92	6.40 ± 0.33
4d	42.18 ± 1.59	27.12 ± 2.08	6.15 ± 0.12
4e	48.64 ± 0.17	37.99 ± 1.10	5.71 ± 0.20
4f	36.72 ± 2.14	3093 ± 1.50	7.34 ± 1.06
4g	38.87 ± 2.42	41.44 ± 1.41	5.88 ± 0.28
4h	44.65 ± 1.92	41.68 ± 1.91	6.06 ± 1.07
4i	>100	>100	36.11 ± 3.71
4j	>100	>100	>100
2	>100	>100	>100
3	>100	>100	>100
Ascorbic acid	30.81 ± 0.60	>100	>100
Trolox	—	—	71.44 ± 5.54

[a] DPPH radical scavenging activity.
[b] Scavenging activity of superoxide anion radicals generated in the xanthine/xanthine oxidase system.
[c] Iron-dependent lipid peroxidation inhibition activity using rat liver homogenate.
[d] IC_{50} values (defined as concentrations that inhibited activity by 50%) were calculated using GraphPad Prism using data obtained from at least three independent experiments. The IC_{50} values are expressed as the means ± SD.

and its acyclic variant **3** showed no antioxidant activities under 100 μM concentrations. The cinnamoyl ketoamides **4a–4h** showed DPPH radical scavenging activities comparable to ascorbic acid and ca. 10-fold higher lipid peroxidation inhibitory activities than trolox. Superoxide radical scavenging activities (IC_{50} = 15.48–41.68 μM) were also observed from every synthesized compound.[29]

In conclusion, cinnamoyl ketoamides were synthesized as hybrid structures of antioxidants and calpain inhibitors. This study demonstrates that the alkylated cinnamoyl skeleton can be regarded as an acyclic variant of the calpain inhibitory chromone ring. The alkyl and 4-methoxyphenylethyl substituents in cinnamoyl ketoamides are likely to increase calpain inhibitory activities through hydrophobic and π–π stacking interaction, respectively, with the residues in the active site of the enzyme from modeling studies. Furthermore, compound **4e** exhibited not only a potent μ-calpain inhibitory activity but also exhibited potent antioxidant activities in DPPH and superoxide anion radical scavenging and lipid peroxidation inhibition assay systems.

Acknowledgment

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29. Spectral data of selected compounds. *Compound* **4d**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (1H, t, J = 6.3 Hz, –*NH*), 9.17 (1H, br s, –*OH*), 9.09 (1H, br s, –*OH*), 8.39 (1H, d, J = 7.1 Hz, –*NH*), 7.32–7.20 (10H, m, aromatic), 6.84 (1H, s, vinyl-*H*), 6.77 (1H, d, J = 1.6 Hz, Ar-*H*2′), 6.76 (1H, d, J = 8.3 Hz, Ar-*H*5′), 6.62 (1H, dd, J = 1.6, 8.3 Hz, Ar-*H*6′), 5.20–5.14 (1H, m, –C*H*–CH_2–Ph), 4.39–4.29 (2H, m, –NH–C*H*$_2$–Ph), 3.17 (1H, dd, J = 4.0, 13.7 Hz, –CH–C*H*$_2$–Ph), 2.94–2.88 (1H, m, –CH–C*H*$_2$–Ph), 2.36 (2H, t, J = 7.5 Hz, –C*H*$_2$–CH_2–CH_3), 1.35–1.26 (2H, m, –CH_2–C*H*$_2$–CH_3), 0.82 (3H, t, J = 7.2 Hz, –CH_2–CH_2–C*H*$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.7, 169.8, 161.1, 145.6, 145.0, 138.5, 138.0, 134.1, 132.9, 129.0 (2C), 128.44, 128.24 (2C), 128.19 (2C), 127.3 (2C), 126.9, 126.87, 126.4, 121.0, 116.1, 115.6, 56.2, 42.0, 34.6, 29.1, 21.4, 13.9. *Compound* **4e**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 (1H, br s, –*OH*), 9.12 (1H, br s, –*OH*), 8.78 (1H, t, J = 6.0 Hz, –*NH*), 8.35 (1H, d, J = 7.2 Hz, –*NH*), 7.33–7.11 (9H, m, aromatic), 6.86 (1H, s, vinyl-*H*), 6.84 (1H, J = 2.0 Hz, Ar-*H*2′), 6.76 (1H, d, J = 8.4 Hz, Ar-*H*5′), 6.67 (1H, dd, J = 2.0, 8.4 Hz, Ar-*H*6′), 5.23–5.18 (1H, m, –C*H*–CH_2–Ph), 3.68 (3H, s, –OCH_3), 3.08 (1H, dd, J = 3.6, 14.0 Hz, –CH–C*H*$_2$–Ph), 2.85–2.79 (1H, m, –CH–C*H*$_2$–Ph), 2.73–2.69 (2H, m, –NH–C*H*$_2$–CH_2–), 2.43–2.40 (2H, m, –CH_2–C*H*$_2$–Ar), 2.38–2.34 (2H, m, –C*H*$_2$–CH_2–CH_3), 1.33–1.28 (1H, m, –CH_2–C*H*$_2$–CH_3), 0.85 (3H, t, J = 7.2 Hz, –CH_2–CH_2–C*H*$_3$); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.8, 169.8, 160.9, 157.7, 145.5, 145.1, 138.1, 134.3, 132.7, 130.9, 129.5 (2C), 129.0 (2C), 128.2 (2C), 126.9, 126.4, 120.9, 116.2, 115.6, 113.7 (2C), 56.1, 54.9, 40.3, 34.5, 33.7, 29.2, 21.4, 13.9..