Microwave Assisted Synthesis of p-Methoxycinnamamides and p-Methoxy-β-nitrostyrenes from Ethyl p-methoxycinnamate and Screening their Anti-inflammatory Activity

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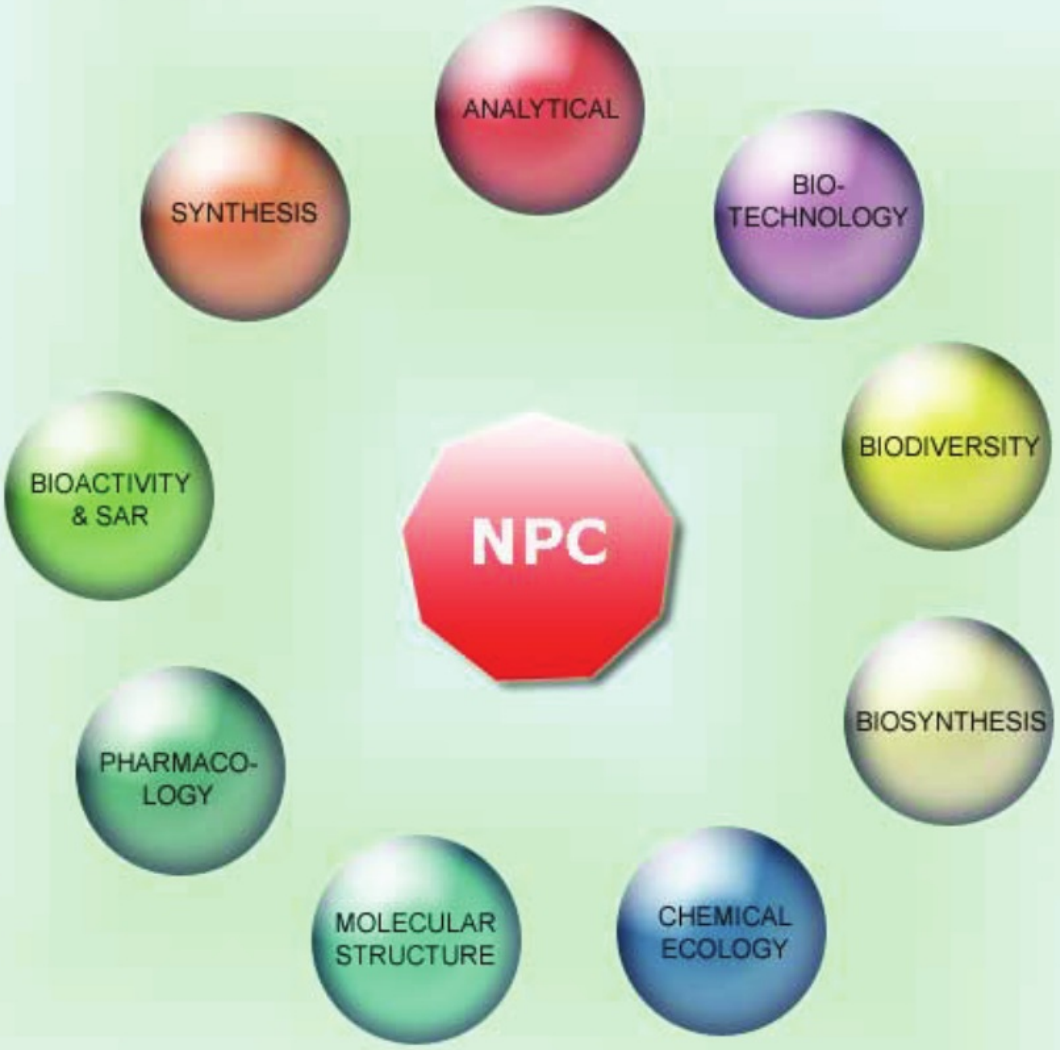

NPC-ISNPF2016: Special Issue

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Prof. Dr. Akira Endo
(Honorable Professor, Tokyo Univerity of Agriculture and Technology, Japan)

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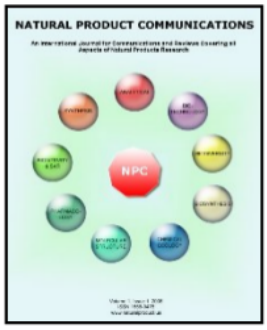
Editorial

NPC-ISNPF2016: Special Issue

To celebrate the 75th birthday of a very distinguished natural products researcher, Prof. Dr. DHC Yoshinori Asakawa, Tokushima Bunri University, Tokushima, Japan, the Phytochemical Society of Asia (PSA) and Natural Product Communications organized an International symposium on Natural Products for the future 2016 (ISNPF2016).

INTERNATIONAL SYMPOSIUM ON NATURAL PRODUCTS FOR THE FUTURE 2016 (ISNPF2016)

(September 1-4, 2016: Tokushima Bunri University, Tokushima, Japan)



Since morphine was isolated by Friedrich Sertürner in 1804, a number of natural compounds possessing a broad and expanding range of biological, pharmacological, and medicinal properties have found clinical, agricultural, and commercial uses. This year, the importance of the development of natural products in health care was recognized through the awarding of the Nobel Prize in Physiology or Medicine to Dr. Satoshi Ōmura and Dr. William C. Campbell for their discovery of a novel therapy against infections caused by roundworm parasites and to Dr. Youyou Tu for her discovery of artemisinin against malaria. The isolation and structure elucidation, total synthesis, and biosynthesis, as well as the metabolomics and pharmacogenomic implications of natural products are endless, and continued essential research is necessary for enhancing the health and the social and economic welfare of the global population. At the same time, reducing the environmental impact of our lives has become a global mantra. Consequently, the role of organic chemistry, including natural products, in the evolving practices of green chemistry are now strongly recommended to reduce the consumption of energy and of organic solvents as resources are being depleted. Meanwhile, a number of flora and fauna are either definitively disappearing or nearing extinction on the planet each year, as the rainforests in Southeast Asia, Central Africa, and the Amazon are burned and cleared for planting and grazing, without their potential being assessed.

The International Symposium on Natural Products for the Future 2016 (ISNPF2016) was about future thinking regarding natural products; it was NOT about past research. During this Symposium, we brought together our novel chemical, biological, pharmaceutical, medical and agricultural ideas for the future application and development of natural products against a number of social and environmental problems of our aging society and considered what is needed to potentiate the sciences and technologies that comprise and impact natural products for the next ten to twenty years. Succinctly, the question was being asked "Where are we going and for whose benefit?"

The Symposium included opening, plenary, and invited lectures, oral presentations, poster sessions, and social activities. The papers presented at ISNPF2016 are now published here in Natural Product Communications as a special issue after review and editing by the organizers and reviewers. The speakers and presenters provided impactful and stimulating inspiration to young (and old !) natural product researchers as to the future evolution in science and technology, and the relevance of contemporary, sustainable natural product research, and encouraged consideration of the essential role of natural products in society for the future. At the same time, young scientists were strongly encouraged through oral presentations and posters, to present their ideas and concerns for the future development of natural products.

Chairpersons
Prof. Dr. DHC Yoshinori Asakawa
President: *Phytochemical Society of Asia* (PSA)
and
Dr. Pawan K. Agrawal
Editor-in-Chief:*Natural Product Communications*

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With some memorable moments from ISNPF2016, Tokushima, Japan

It is worthwhile to mention that ISNPF2016 was able to attract leading world scientists, and their contributions highlight some significant aspects of secondary metabolites. NPC considers all members of the community of natural product researchers as family members and we would like to thank them for making this joint event successful. Many of NPC's editorial board members participated and we are grateful for their enormous support and contributions.

I am very grateful to Professor Yoshinori Asakawa, Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima 770-8514, Japan, for organizing this issue. The editors join me in thanking Professor Asakawa, the authors and the reviewers for their efforts that have made this issue possible, and to the production department for putting it into print.

Pawan K. Agrawal
Editor-in-Chief

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Preface

Natural Product Communications Special Issue for ISNPF2016

It was my great honor and privilege that, along with Dr Pawan K. Agrawal, Editor-in-Chief of *Natural Product Communications* and on behalf of the Phytochemical Society of Asia (PSA), I could organize the *International Symposium on Natural Products for the Future 2016* (ISNPF2016) that was held in Tokushima, Japan between 1st and 4th September 2016. I would like to thank all of our guests, especially Prof. Dr Akira Endo, who has received the Gairdner International and Albert Lasker-DeBakey Awards, the Massry, Alpert, Heinrich Wieland, Japan, and Toray Science-Technology Prizes, along with many others, and the plenary and invited lecturers for their commitment to participate in this symposium and for sharing their experiences and expertize in their respective fields with all the participants, especially the young researchers and post-doctoral fellows and students. For this symposium we attracted natural product chemists from 32 countries, 150 foreign and 250 national participants. Prof. Dr Akira Endo graced this occasion as the guest speaker, and 18 plenary and 18 invited speakers, 37 oral presenters, and 81 poster presentations offered contemporary assessments of natural product research. *Natural Product Communications* and *PSA* each gave three poster awards, "Gold, Silver and Bronze, respectively, in the closing ceremony.

The ISNPF2016 aimed at promoting the international exchange of contemporary ideas on natural product chemistry among researchers in academia, government and industry. This symposium also provided a platform for post-doctoral fellows and graduate students in the region to create a professional network to continue their careers studying the diverse aspect of natural products and their discussion for the next ten to twenty years.

Tokushima is one of the most important cities from the perspective of natural products chemistry in Japan. Prof. Nagayoshi Nagai, who was the founder of the Pharmaceutical Society of Japan, was born in Tokushima and discovered an antitussive agent, ephedrine, from *Ephedra* herb and Prof. Tsunematsu Takemoto isolated a number of pharmacologically important phytochemicals, including kainic acid, which is used as a vermicide drug, from a red alga, insect molting hormones from some ferns and *Achyranthis* radix, and the mogrosides, which are 300 times sweeter than sugar from *Siraitia grosvenorii*. Tokushima was the 10th biggest town in Japan in the 19th century because of the production of highly valued indigo dyes from *Polygonum tinctorum*, and that practice continues here today.

I believe that this symposium provided a good opportunity for the effective exchange of many recent natural product results from around the world, and for the generation and cross-fertilization of new ideas, as well as contributing to a better understanding of the role of natural products in drug discovery and in the protection of our environment.

Dr Pawan K. Agrawal kindly offered to publish the accepted papers from ISNPF2016 in a special edition of *Natural Product Communications*, for which he made me the guest-editor. This special issue was open to both the original work and reviews presented by all the participants. Fifty-eight manuscripts were submitted to the guest editor between 16th December last year to the middle of February this year, of which 49 were accepted for publication in the NPC special issue after review and editing by the organizers and reviewers. As the guest editor of this journal and the organizer of this symposium, I would like to express my sincere thanks to Dr P. K. Agrawal for his kind hospitality and the authors who submitted their papers to this special issue and all the referees who kindly reviewed the papers.

I also wish to express our deepest and sincere gratitude to the Malaysian Natural Products Society, the Natural Products Society of Philippines, the Pharmaceutical Society of Japan, the Japan Society of Bioscience, Biotechnology, and Agrochemistry, the Bryological Society of Japan, the Japan Oil Chemists' Society, the Japanese Society of Phytotherapy, the Japanese Society of Pharmacognosy, the Japan Perfumery & Flavoring Association, the Tokushima Biological Society, Tokushima Prefecture, Tokushima Newspapers and Tokushima Bunri University, as well as all of the private companies and individuals who provided financial support that made this symposium a reality. I would like to congratulate all of the members of the Organizing Committee for such a superb effort to bring to fruition this successful and meaningful international symposium. Without this cooperation and collaborative teamwork, this symposium would not have been possible.

A big typhoon approached near to Tokushima just before the symposium, but, fortunately, it was long gone by the time of the meeting and the weather was fantastic during the symposium!

I hope that all the participants in this symposium enjoyed it, as well as the planned social events, especially the "Awa dance", the banquet and excursion (dying tissue and T-shirts with indigo and visit to the orchid farm), as well as the Japanese traditional culture and wonderful cuisine.

(Arigatou gozaimashita, Thank you very much)
21st July 2017

浅川義範
Prof. Dr DHC Yoshinori Asakawa
Chairperson, ISNPF2016
(President, Phytochemical Society of Asia)

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Microwave Assisted Synthesis of *p*-Methoxycinnamamides and *p*-Methoxy-β-nitrostyrenes from Ethyl *p*-methoxycinnamate and Screening their Anti-inflammatory Activity

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A new modification reaction of ethyl *p*-methoxycinnamate (**1**) to afford a series of *p*-methoxycinnamamide and *p*-methoxy-β-nitrostyrene has been developed by using the assistance of the unmodified microwave oven. The synthesized compounds were characterized by using various spectroscopic techniques and furthermore screened for their anti-inflammatory activity by using anti-denaturation of heat bovine serum albumin (BSA) method. The result of bioassay indicated that *p*-methoxycinnamamide derivatives and *p*-methoxy-β-nitrostyrenes showed interesting anti-inflammatory activity.

Keywords: Ethyl *p*-methoxycinnamate, *p*-Methoxycinnamamide, *p*-Methoxy-β-nitrostyrene, Microwave oven synthesis, Anti-denaturation, Anti-inflammatory.

Previous research has reported that ethyl *p*-methoxycinnamate (**1**) is the major isolated compound from the rhizome of *Kampferia galanga* (Zingiberaceae), in which this compound was also reported to have a potential property as an anti-inflammatory agent [1,2]. In order to develop and study structure activity relationship of compounds derived from **1**, here we are reporting new method on synthesizing of series *p*-methoxycinnamamide and *p*-methoxy-β–nitrostyrene from **1**. In recent years, the microwave-assisted reaction has a great attention due to it has proven to be often lead a reduces the reaction time, increase yield and easily reaction with green chemistry method [3,4]. Therefore, in this study, we attempt to do the synthetic reaction by using the assistance of unmodified microwave oven. Furthermore, the product of synthesis was evaluated for its anti-inflammatory activity by using bovine serum albumin (BSA) anti-denaturation assay which was designed as preliminary stages in the screening of the selecting compounds for anti-inflammatory development [5]. In this research, compound **1** was obtained from the purification of *n*-hexane and ethyl acetate extracts of the rhizome of *K. galanga* to give 70.7 and 18.4 % yield, respectively. The structure of the isolated and synthetic compound was characterized by using spectroscopic data IR, ^{1}H & ^{13}C-NMR, GCMS and a comparison to those of previously reported.

Cinnamamide or 3-phenylacrylamide is a compound with a simple structure that has phenyl ring and amide which are linked by olefin. Modification in three regions of cinnamamide (phenyl, linker, and amide) resulting in a broad spectrum of biological activities such as anti-malarial, anti-atherosclerotic, antidepressant, neuroprotective, tyrosinase inhibitor, analgesic, anti-inflammatory, muscle relaxant and sedative/hypnotic [6]. β-Nitrostyrene is a class of compound that has phenyl ring and nitroalkane. Similar to cinnamamide, modification in the phenyl and nitroalkane of β-nitrostyrene cause it exhibits various biological activities such as anti-proliferative agents, selective human telomerase inhibitors, antiplatelet, inhibitor NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasone activation, antifungal and antibacterial [7–9].

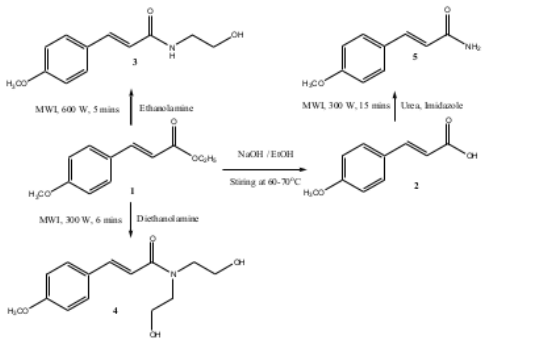

Figure 1: Synthesis of *p*-methoxycinnamamide derivatives.

Amidation reaction of **1** with ethanolamine and diethanolamine result in the production of N-(2-hydroxyethyl)-*p*-methoxy-cinnamamide (**3**) [10,11] and N,N-bis-(2-hydroxyethyl)-*p*-methoxy-cinnamamide (**4**) [10,12], respectively (Figure 1). Previously, a conventional synthetic reaction of *p*-methoxycinnamic chloride with ethanolamine and diethanolamine for 4-24 hours has given **3** and **4**, respectively [10,12]. In the other reported, Deng *et al* [11] also performed a conventional synthesized of **3** by using *p*-methoxy-cinnamic acid as starting material. It took about **4** hours to finish the reaction in 52.7 % yield. In this report, we used ethyl *p*-methoxy-cinnamate (**1**) as starting material and reaction was performed by using irradiation of unmodified microwave oven in 5-6 minutes to give 61.3 and 92.2 % of **3** and **4**, respectively. NMR data of **3** and **4** were corresponding to those of previous reported [11,12].

In adopting of the previous work of Khalafi *et al* [3], in this study we synthesized *p*-methoxycinnamamide (**5**) through reaction of hydrolysis of **1**, *p*-methoxycinnamic acid (**2**) with urea by using imidazole as a catalyst (Figure 1). A literature search indicated that there are no reports of previously synthesized and spectroscopic data of **5**.

According to literature, various methods and reagents have reportedly been used for the synthesis of *p*-methoxy-β-nitrostyrene **7** [13–17]. Recently, the nitro decarboxylation reaction of **2** by using $(COCl)_2$ + DMF in the presence of KNO_3 or $NaNO_2$ under conventional and non-conventional conditions has successfully afforded **7** in the range of 74-80% yields [13]. The reaction of methoxycinnamaldehyde and nitromethane by using Henry condensation condition has successfully obtained **7** in the 59-96 % yield. In this report, we performed the new method to obtain **7**, which was adopted from the previous cold nitration method [4]. The reaction was initiated by performing irradiation of the mixture of pre-cooled reagents, **1** and HNO_3. Unfortunately, this reaction was not successful in giving β-nitrostyrene derivative. Subsequently, the reaction was performed by reacting pre-cooled reagents, **2** and HNO_3. As shown in Figure 2, variation in the method, gave a different product of *p*-methoxy-β-nitrostyrene (**7**) and 2-nitro *p*-methoxy-β-nitrostyrene (**8**). A literature search indicated that there have been no reports of the previously synthesized and spectroscopic data of **8**.

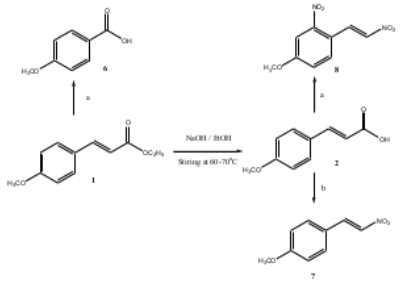

Figure 2: Synthesize of *p*-methoxy-β-nitrostyrene derivatives.
a. Both pre-cooled reagents were mixed and then the mixture immediately irradiated by using the microwave, 450 W, 2 mins
b. Both pre-cooled reagents were mixed and then the mixture was continued cooling for 30 minutes and irradiated by using microwave, 300 W, 1 min

Table 1: Anti-denaturation activity of product synthesis.

Compounds	Concentration (µg/mL)	% Inhibition	Compounds	Concentration (µg/mL)	% Inhibition
3	0.1	28.1 ± 1.7	**7**	0.1	37.0 ± 2.1
	1	37.0 ± 0.4		1	24.2 ± 2.2
	10	53.0 ± 0.8		10	19.6 ± 1.5
	100	75.6 ± 0.4		100	-
4	0.1	50.1 ± 0.4	**8**	0.1	36.0 ± 0.5
	1	56.0 ± 2.1		1	26.7 ± 0.8
	10	73.8 ± 2.0		10	10.3 ± 0.4
	100	78.4 ± 1.2		100	-
5	0.1	30.6 ± 0.2	Na	0.1	1.6 ± 0.4
	1	37.1 ± 0.6	Diclofenac	1	3.0 ± 0.8
	10	41.1 ± 1.2		10	24.9 ± 1.8
	100	81.6 ± 1.7		100	97.4 ± 0.6

(-) : % inhibition ≤ 0
Percentage of inhibition denaturation values are represented as mean±SD (n=3)

Furthermore, the synthesized compounds were screened for their anti-inflammatory activity by using BSA anti-denaturation assay. The result of bio-assay (Table 1) indicated that a series of *p*–methoxycinnamide **3**, **4** and **5** showed interesting anti-denaturation activity in the concentration of 0.1-100 µg/mL (denaturation inhibition > 20 %). Interestingly, these compounds showed higher activity than Na diclofenac at a concentration of 10 µg/mL. It is also found that both **3** and **4** showed higher activity than **5** at a concentration of 10 µg/mL, therefore it is suggested that the presence of hydroxy functional group on the cinnamamide compounds as a result of increasing in its anti-inflammatory activity. The interesting phenomenon was also shown by *p*-methoxy-β-nitrostyrenes **7** and **8**. Results of bio-assay indicated an increase of sample concentrations of both **7** and **8** resulted in decreased anti-inflammatory property as shown in Table 1. These compounds showed interesting activity at a lower concentration of 0.1-1 µg/mL and were found not active at a concentration of 100 µg/mL. However, this phenomenon was coincident with the previous reports which demonstrated some controversial relationship between concentration and activity [5,18].

Experimental

General: The melting point was measured by using DSC-60 SHIMADZU and melting point apparatus Stuart SMP10 without correction. IR spectra were recorded on a Shimadzu FTIR Prestige 21 Shimadzu. The ^{1}H- and ^{13}C-NMR were measured on Jeol-500 MHz (^{1}H; 500 MHz, ^{13}C; 125 MHz) instruments. Chemical shift values were expressed in δ (ppm) downfield from TMS as an internal standard. Reactions were carried out by using microwave assisted (Samsung). Column Chromatography was performed on Silica gel 60 (0.063-0.200 mm) (Merck). Product reaction was analyzed by using GCMS GC/MS-MSD 7890A/5975C (Agilent Technologies) under the following conditions: HP-5MS capillary column (30 m x 0.25 mm ID, 0.25 µm, film thickness) held at 70°C for 2 mins, raised to 285°C, at rate of 20°C /min and held for 20 mins, 285°C for MSD, carrier helium at a flow rate 1.2 mL/min.

Plant materials: The rhizome of *K. galanga* was collected from BALITRO (Balai Penelitian Obat dan Rempah) Bogor, West Java, Indonesia in May 2014. The specimen was identified and stored at Bogoriense Herbarium, Research Center for Biology, Indonesian Institute of Sciences, Indonesia.

Extraction and isolation: The dried and powdered of rhizome *K. galanga* (7685 g) was extracted by using *n*-hexane and ethyl acetate to give 927.9 g (12.1 % yield) and 232.5 g (3.0 % yield) crude extacts, respectively. *n*-Hexane and ethyl acetate extracts were stored in the refrigerator in which 656.0 g (70.7 % yield) and 42.9 g (18.4% yield) of the colorless crystal of **1** obtained respectively, m.p. 50°C (lit. 49°C) [1, 2].

Hydrolysis of 1: Mixture solution of **1** (15.48 g, 75 mmol), NaOH (4.80 g) and ethanol (375 mL) was stirred at a temperature of 60-70°C for 3 hours. The product of the reaction was washed with aquadest (50 mL) and added HCl 15 % until the final pH should be 4. The residue was filtrated and air-dried to give 12.70 g of colorless crystals of *p*-methoxycinnamic acid (**2**) (82.0 % yield), m.p. 175°C (lit. 169°C) [19].

Amidation of 1 with ethanolamine: In 100 mL Erlenmeyer flask with the cup, a solution of **1** (1.06 g, 5.1 mmol) in 10 mL ethanolamine was irradiated by using the unmodified microwave oven at 600 W for 5 minutes. The product of the reaction was extracted by using ethyl acetate and further purified to obtain 0.65 g of N-(2-hydroxyethyl)-*p*-methoxycinnamamide (**3**) (61.3 % yield).

N-(2-Hydroxyethyl)-*p*-methoxycinnamamide (3)
MP: 123-125°C (lit 122-124°C) [10]
NMR data are in agreement with those of previously reported [11].
GCMS (*m/z*): 221, 202, 178, 161 (base peak), 133, 114, 89, 63, 44.

Amidation of 1 with diethanolamine: In 100 mL Erlenmeyer flask with the cup, a solution of **1** (1.03 g, 5.0 mmol) in 10 mL diethanolamine was irradiated by using the unmodified microwave oven at 300 W for 6 minutes. Product reaction was extracted by using ethyl acetate and further purified to obtain 0.95 g of N,N-bis-(2-hydroxyethyl)-*p*-methoxycinnamamide (**4**) (92.2 % yield).

N,N-bis-(2-hydroxyethyl)-*p*-methoxycinnamamide (4)
MP: 84-85°C (lit 85°C) [12]
NMR data are in agreement with those of previously reported [12].
GCMS (*m/z*): 265, 220, 161 (base peak), 133, 89, 63, 44.

Amidation of 2 with urea: This method was adopted and modified from the previous reported [3]. In 100 mL Erlenmeyer flask with the cup, mixture of **2** (1.60 g, 9.0 mmol), urea (2.16 g, 36.0 mmol) and imidazole (0.61 g, 9.0 mmol) was mixed with the mortar and then the mixture was irradiated by using the unmodified microwave oven at 300 W for 15 minutes. The resulting crude product was purified by using column chromatography to obtain 0.34 g of the pale yellow crystal of *p*-methoxycinamamide (**5**) (21.3 % yield).

***p*-Methoxycinamamide (5)**
MP: 194-197°C
FTIR (KBr): 3458, 3361, 3183, 2925, 1598, 1513, 1386, 1304, 1253, 1177, 1112, 1023, 940, 826, cm^{-1}
^{1}H-NMR (500 MHz, $CDCl_3$): 3.83 (3H,s), 5.54 (2H, s), 6.33 (1H, d, J = 15.6 Hz), 6.92 (2H, d, J = 8.4 Hz), 7.47 (2H, d, J = 9.1 Hz), 7.62 (1H, d, J = 15.6 Hz)
^{13}C-NMR (125 MHz, $CDCl_3$): 55.5, 114.9, 117.1, 127.5, 129.7, 142.5, 161.3, 168.2.
GCMS (*m/z*): 177 (basepeak), 161, 133, 118, 103, 89, 77, 63, 44.

The reaction of 1 with HNO_3: Both pre-cooled (-12°C) of **1** (2.50 g, 9.6 mmol) and 65% HNO_3 (10 mL) were mixed and then the mixture was irradiated by using a unmodified microwave oven at 450 W for 2 minutes. Immediately, after irradiation, the reaction product was then poured into ice cold water to give yellow solid then filtrated. The solid product was then crystallized to give 0.50 g of compound *p*-methoxybenzoic acid (**6**) as colorless crystals (20.0 % yield), m.p. 189°C (lit 182-184°C) [20].

The reaction of 2 with HNO_3 to give p-methoxy-β-nitrostyrene (7): Both pre-cooled of **2** (1.20 g, 6.7 mmol) and 65% HNO_3 (4 mL) was mixed and stored at freezer (-12°C) for 30 minutes. This cold reaction mixture was irradiated by using an unmodified microwave oven at (300 W, 1 min). Immediately, after irradiation, the reaction product was then poured into ice cold water to give yellow solid and then filtrated. The solid product was then purified by using silica column chromatography to give 0.33 g of a yellow crystal of **7** (27.5 % yield).

***p*-Methoxy-β-nitrostyrene (7)**
MP: 89°C (lit 86-87°C) [17]
FTIR (KBr) 3418, 3105, 2921, 2845, 1441, 1181, 824 cm^{-1}
^{1}H-NMR (500 MHz, $CDCl_3$): 3.87 (3H, s), 6.96 (2H, d, J = 8.5 Hz), 7.51 (2H, d, J = 9.1 Hz), 7.52 (1H, d, J = 13.6 Hz), 7.98 (1H, d, J = 13.6 Hz).
^{13}C-NMR (125 MHz, $CDCl_3$): 55.7, 115.1, 122.7, 131.4, 135.2, 139.2, 163.1
GCMS (*m/z*): 179, 162, 132 (base peak), 118, 89, 63, 50.

The reaction of 2 with HNO_3 to give 2-nitro p-methoxy-β-nitrostyrene (8): Both pre-cooled (-12°C) of **2** (3.0 g, 16.8 mmol) and 65% HNO_3 (12 mL) were mixed and then the mixture was irradiated by using the unmodified microwave oven at 450 W for 2 minutes. After irradiation, the reaction product was then poured into ice cold water to give yellow solid and then filtrated. The solid product was then purified by using silica column chromatography to give 0.41 g of compound **8** as yellow crystal (13.7 % yield).

2-nitro *p*-methoxy-β-nitrostyrene (8)
MP: 158-160°C.
FTIR (KBr): 3098, 2923, 1614, 1526, 1349, 825 cm^{-1}
^{1}H-NMR (500 MHz, $CDCl_3$): 4.0 (3H, s), 7.19 (1H, d, J = 9.1 Hz), 7.56 (1H, d, J =13.6 Hz), 7.74 (1H, dd, J = 9.1, 2.0 Hz), 7.95 (1H, d, J = 13.6 Hz), 8.06 (1H, d, J = 2.0 Hz).
^{13}C-NMR (125 MH, $CDCl_3$): 57.1, 114.6, 122.6, 126.4, 134.7, 136.5 137.5, 155.5.
GCMS (*m/z*): 224 $[M]^+$ 207, 177 (base peak), 162, 147, 129, 117, 102, 89, 76, 63, 44.

Anti-denaturation of heat BSA assay: A Stock solution of 0.2% (w/v) bovine serum albumnin (BSA) fraction V of 96% purity (Sigma Chemical Co) was prepared in a mixture of 0.05 M tris-buffered saline which was adjusted to pH 6.3 with glacial acetic acid. Samples were prepared in methanol at various concentrations. From each of the concentration of samples, 500 µL was added to 5.0 mL of the 0.2% (w/v) stock BSA in the tris-buffered saline to produce concentration 0.1, 1, 10, 100 ppm. Each sample was heated for 5 minutes at 70°C in a test tube placed in a water bath, then cooled for 20 minutes under laboratory conditions and its turbidity measured at 660 nm using Hitachi U-2910 spectrophotometer. Na diclofenac (Sigma-Aldrich) was used as a standard. The degree of inhibition of denaturation or precipitation of the BSA from the solution by each extract was calculated by using following equation [5, 21].

$$I\,(\%) = \frac{(\text{absorbance control} - \text{absorbance sample})}{\text{absorbance control}} \times 100\%$$

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