Synthesis and plant growth inhibitory activity of N-trans-cinnamoyltyramine: its possible inhibition mechanisms and biosynthesis pathway

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Introduction

For more than 70 years, synthetic herbicides have been developed to meet the weed control needs of agronomic and horticultural crops in industrialized nations. Since the late 1990s, many weed biotypes have evolved resistance to one or more herbicide modes of action (Beckie et al. 2000) limiting effective options for growers. In addition, the misuse of some synthetic herbicides has negative implications for human, animal, and environmental health (Vyvyan 2002; Macías et al. 2006; Macías et al. 2007). Development of novel herbicide modes of action has been lacking for more than 16 years; this, combined with more frequent selection of herbicide-resistant weeds, suggests a need to develop weed control technologies based upon natural products (Fürstner 2004).

Allelochemicals are structurally complex and can pose significant challenges for synthesis by organic chemists (Dayan & Duke 2014). Isolation, structural elucidation, and synthesis of natural products are paramount to identification of new molecules with biological activity for controlling weeds. The search for potent, selective bioherbicides has been the focus of numerous studies for several decades. Developing an economically viable total chemical synthesis procedure has been the challenge for commercial-scale application of these nature-derived chemicals. An efficient and low-cost total synthesis of an allelopathic and antitumor N-trans-cinnamoyltyramine (NTCT) first reported in rice (Oryza sativa L.) was successfully achieved by one-step amidation from trans-cinnamic acid and tyramine. The synthesized NTCT inhibited root and hypocotyl growth of cress (Lepidium sativum L.) and barnyardgrass (Echinochloa crus-galli L.) at concentrations as low as 0.24 μM. The means of ED50 (the effective dose required for 50% plant growth inhibition) levels of the compound on cress and barnyardgrass hypocotyl and root elongations were 0.96 and 0.73 μM, respectively. Potential mechanisms underlying NTCT growth inhibition and its biosynthesis pathway were also suggested. The developed synthesis strategy could permit production of this synthesized allelochemical at a commercial scale as a bioherbicide.
Liquid chromatography–mass spectrometry coupling with electrospray ionization (LCMS-ESI) analysis was conducted on a Shimadzu LCMS 2010A using an Acclaim 120 C18 reversed-phase LC column (4.6 × 50 mm) (Thermo Scientific) with a gradient of 10–95% CH3CN/H2O (v/v) (with 0.1% trifluoro acetic acid) at a flow rate 0.8 mL min⁻¹ in 10 min. Compound NTCT was dissolved in DMSO and the UV detector was set to 300 nm.

Synthesis of NTCT

Synthesis was achieved by a one-step amidation procedure revised from that described by Yang et al. (2011) (Scheme 1).

A solution of trans-cinnamic acid (0.98 g, 6.6 mmol) in dry dichloromethane (300 mL) was pre-activated with N,N′-dicyclohexylcarbodiimide (1.50 g, 7.3 mmol) (Scheme 1) in the presence of the base 4-(dimethylamino) pyridine (C7H10N2) (0.033 g, 0.3 mmol) at room temperature for 30 min. The solids resulting from this reaction were dissolved in dichloromethane; tyramine (1.36 g, 9.9 mmol) (Scheme 1) was then added to initiate amidation. The solution was stirred overnight at room temperature and volatiles were removed under reduced pressure. The residue was purified via normal phase flash chromatography with ethyl acetate/CH2Cl2 (1:5) (0.23). Examination of the purified synthesis of NTCT isolated by Thi et al. (2014b) using13C NMR spectroscopy revealed general agreement of 17 carbon positions between synthesized NTCT and natural NTCT isolated from rice as follows: C1 (A = 154.4; B = 154.3); C2 (A = 129.9; B = 129.9); C3 (A = 115.5; B = 115.5); C4 (A = 130.9; B = 130.9); C5 (A = 129.9; B = 129.9). The analysis followed the method described by Thi et al. (2014b). Briefly, all root or hypocotyl length data were transformed to a percentage of control as determined by the following formula: Percentage of control = R/Lcontrol × 100%, where R represents the length ratio, Lcontrol represents the average length of roots or hypocotyls of control plants, and L represents the average length of roots or hypocotyls of treated plants. Three-parameter logistic equation \( F(x) = \frac{d}{1 + \exp\left[b\left(\log(x) - \log(e)\right)\right]} \) from dose–response curve package was used to identify ED50, where \( F \) displays the growth inhibition (%), \( x \) indicates the concentration (µM), and \( e \) represents the ED50 (Knezevic et al. 2007).

Duncan’s multiple range tests at \( P \leq 0.001 \) were conducted to separate treatment and ED50 for the biological activity of compound NTCT.

Results and discussion

Synthesized and natural NTCT

The synthesized NTCT was characterized relative to the natural NTCT isolated by Thi et al. (2014b) using 13C NMR spectroscopy (Figures S1 and S2, Supporting Information) and LCMS-ESI analysis. LCMS-ESI analysis confirmed that the retention time of the synthesized NTCT is 3.595 min (the same as the natural one) with m/z 268 [M+H]+ (C17H17NO3, 267.3) (Figures S3 and S4, Supporting Information). Characterization by 13C NMR spectroscopy revealed general agreement of 17 carbon positions between synthesized NTCT (A) and natural NTCT (B) isolated from rice as follows: C1 (A = 154.4; B = 154.3); C2 (A = 115.5; B = 115.5); C3 (A = 129.9; B = 129.9); C4 (A = 130.9; B = 130.9); C5

Scheme 1. Synthesis of N-trans-cinnamoyltyramine (1) from trans-cinnamic acid (2) and tyramine (3).
Compound NTCT (Figure 1) was chemically synthesized by one-step amidation from trans-cinnamic acid and tyramine (Scheme 1). However, biosynthesis of NTCT in rice seedlings as proposed in Scheme 2 is more complex; several steps to synthesize trans-cinnamic acid and tyramine from phenylalanine and tyrosine are required, followed by activation by cinnamoyl CoA, and finally conjugation by tyramine N-(hydroxycinnamoyl)-transferase (THT). Compound NTCT is likely derived from metabolites of the aromatic amino acid phenylalanine and tyrosine, which are produced in the shikimate pathway (Herrmann 1995). As illustrated in Scheme 2, phenylalanine ammonia-lyase converts phenylalanine into cinnamic acid by deamination (MacDonald & D’Cunha 2007). Cinnamoyl CoA is then generated by CoA ligases (Klempien et al. 2012). Tyrosine decarboxylase catalyzes the decarboxylation of tyrosine, which results in tyramine (Hosoi et al. 1970). The final step in the proposed scheme is the conjugation of cinnamoyl CoA and tyramine catalyzed by the enzyme THT, but THT activity is not specific to cinnamoyl CoA and tyramine. Previously, plant defense compounds, such as coumaroyltiramine and feruloyltiramine (Figure 2), have been shown to be synthesized in response to pathogen infection and plant wounding. These compounds are conjugated by THT from hydroxycinnamoyl-CoA and tyramine (Back 2001), which could be similar to the reactions that generate NTCT.

Table 1. The $^{13}$C NMR spectroscopic data for the natural N-trans-cinnamoyltiramine and the synthesized N-trans-cinnamoyltiramine.

| Position | $\delta^{13}$C Natural | $\delta^{13}$C Synthetic |
|----------|------------------------|-------------------------|
| 1        | 154.4                  | 154.3                   |
| 2        | 115.5                  | 115.5                   |
| 3        | 129.9                  | 129.9                   |
| 4        | 130.9                  | 130.9                   |
| 5        | Same as 3              | Same as 3               |
| 6        | Same as 2              | Same as 2               |
| 7        | 34.7                   | 34.8                    |
| 8        | 40.9                   | 41.0                    |
| 9        | 165.6                  | 165.8                   |
| 10       | 120.6                  | 120.5                   |
| 11       | 141.0                  | 141.1                   |
| 12       | 134.8                  | 134.8                   |
| 13       | 127.8                  | 127.8                   |
| 14       | 128.8                  | 128.8                   |
| 15       | 129.6                  | 129.7                   |
| 16       | Same as 14             | Same as 14              |
| 17       | Same as 13             | Same as 13              |

Note: $^{13}$C NMR spectra of both natural and synthesized NTCT were recorded at 500 MHz on a Bruker Avance DRX500 and AV800 spectrometers equipped with HCN (hydrocyanic acid) triple-resonance cryogenic probe and Z-gradient coil with CDCl$_3$ (deuterated chloroform) as the solvent. $\delta$ values are reported in ppm using solvent as internal standard. For numbering, see Figure 1.
Allelopathic activity of synthetic NTCT

Inhibition of hypocotyl and root growth of cress and barnyardgrass seedlings was detected with the synthesized NTCT at concentrations as low as 0.24 μM (Figures 3 and 4). At 4.8 μM, inhibition of hypocotyl and root growth reached 92.4% and 95.3% for cress (Figure 3) and 90.6% and 95.6% for barnyardgrass seedlings (Figure 4), respectively. In comparing activities of the natural versus NTCT on the same test plant species (Thi et al. 2014b), the synthesized NTCT was 7.6% and 4.7% less active on cress hypocotyl and root growth than the natural NTCT. One possible explanation for differences in activity is a detected trace impurity in the synthesized NTCT (Materials and methods). For barnyardgrass, the activity of synthesized versus NTCT on hypocotyl growth was 4.8% lower, but inhibitory activity was similar for root growth. The ED₅₀ values of the compound for cress hypocotyls and roots were 0.56 and 0.36 μM (Figures 3 and 5), respectively. The ED₅₀ values of the compound for barnyardgrass hypocotyls and roots were 1.35 and 1.11 μM, respectively (Figures 4 and 5). Root elongation was more sensitive to the synthesized NTCT than shoot elongation and cress was more sensitive to the compound than barnyardgrass (Figures 5 and 6).

The response of plant species to an allelochemical under laboratory conditions principally depends upon the physiological and biochemical properties of each species. It was reported that the sensitivity of a receiver plant to phytotoxic extracts from a donor plant (allelochemical) is a function of plant organs and growth stage (Wolf et al. 1984; Hasegawa et al. 1992; Suzuki et al. 2001; Iqbal et al. 2002). The allelopathic activity of NTCT on cress and barnyardgrass appears similar based upon symptomology and ED₅₀ values. Root growth is more sensitive to NTCT than shoot growth, and cress is more sensitive to NTCT than barnyardgrass.

![Figure 3. Effects of N-trans-cinnamoyltirammine on hypocotyl (shoot) and root growth of cress seedlings. ED₅₀ values represent the effective dose to reduce the representative parameter (shoot or root growth) by 50%. Means followed by the same letter are not significantly different using Duncan’s multiple range test at P ≤ .001.](image)

![Figure 4. Effects of N-trans-cinnamoyltirammine on hypocotyl (shoot) and root growth of barnyardgrass seedlings. ED₅₀ values represent the effective dose to reduce the representative parameter (shoot or root growth) by 50%. Means followed by the same letter are not significantly different using Duncan’s multiple range test at P ≤ .001.](image)
(Figure 5). This might be because roots initially absorb allelochemicals from the environment and the permeability of allelochemicals into root tissue is higher than that in shoot tissue (Nishida et al. 2005). Other explanations could include differences between enzyme profiles in shoots versus roots (Dam et al. 2008).

**Possible inhibition mechanisms and a biosynthesis pathway**

In the presence of NTCT, inhibition of cress and barnyardgrass may result from reduced cell division and/or expansion, the two principle components controlling growth (Tefera 2002). Although details of the biochemical mechanism underlying inhibition are lacking, inhibition of enzymes contributing to plant growth by allelochemicals has been reported (Sato et al. 1982; Santos et al. 2004). Interspecific differences may result from many reasons, including from variable responses in membrane potential, auxin dynamics or tyrosine phosphorylation. Plant symptomology in response to NTCT provides clues concerning the mechanisms of action. However, to date, the mechanism of activity for NTCT has not been established. Nonetheless, precursors to NTCT (Figure 2), such as cinnamic acid and benzoic acid derivatives, alter membrane potential, mineral uptake, chlorophyll content, photosynthesis, carbon flow, and phytohormone activity (Einhellig 1994; Blum et al. 1999). Phenolic acids, such as cinnamic acid, could play a key role because different phenolic acids strongly inhibit seed germination (Blum et al. 1999). Einhellig (1994) and Blum et al. (1999) proposed that phenolic acids depolarized the cell membrane, affecting membrane ATPase activity and ion flux. However, substituted cinnamic acid amide analogues (Figure 2), which lose their negative charge on the hydroxyl groups, result in greater inhibition of radish (Raphanus sativus) germination than substituted cinnamic acid alone (Vishnoi et al. 2009). Inhibition of substituted cinnamic acids (3-hydroxy, 4-hydroxy, 2-nitro, 3-nitro, 4-nitro, 3-chloro, and 4-methoxy) and four different types of substituted anilines (H, 2-chloro, 4-methyl, 4-nitro) on radish germination is similar (Vishnoi et al. 2009). Therefore, it appears likely that NTCT does not act by depolarizing the cell membrane; rather, other mechanisms underlying root and hypocotyl elongation are impacted.

Several of the cinnamic acid amines exhibit both cytotoxic and phytotoxic properties. In one study, compound NTCT was identified as one of the major cytotoxic agents induced in UV-treated rice leaves (Park et al. 2013). Induction of ‘free’ cinnamic acid amines in response to stress factors (antimicrobial, allelopathic) has been reported in different species,
including pepper (Capsicum annumum L. cv. Early Calwonder) (Newman et al. 2001), tomato (Solanum lycopersicum L.) (López-Gresa et al. 2011) and canola (Brassica napus L.) (Jahangir et al. 2009). Since synthesis of various phenolic acids and NTCT can be induced by certain stresses (Pitts et al. 1998; Bibikova & Gilroy 2003), it may also be possible that NTCT accumulates in response to stresses resulting from competition (biological, chemical, or physical).

Auxin is a potent hormone that impacts root hair development (Bibikova & Gilroy 2003), and aberrations in auxin availability or signaling can cause defects in root hair growth and morphology (Liu et al. 1993; Ni et al. 1999). Compound cinnamic acid is also proposed to inhibit polar auxin transport by blocking the transport at the efflux carrier (Ni et al. 1999). In turn, reduced availability of auxin decreases root hair growth.

The tyramine moiety in NTCT (Scheme 2) may mimic the activity of tyrosine. Hydroxycinnamic acid amides, including coumaroyltyramine and feruloyltyramine (Figure 2), which contain tyramine moieties, inhibit tyrosinase (enzyme present in plant and animal tissues that catalyzes synthesis of melanin) (Feng et al. 1993; Tregnear et al. 1996; Rudrabhatla et al. 2006; Wu et al. 2012). As a tyrosine mimic, NTCT may have both a beneficial and detrimental effect on tyrosine kinase. Dual-specific kinases (act as both tyrosine kinase and serine/threonine kinase) have been reported in many plants, including Arabidopsis thaliana ATN1 and soybean GmPK6 (Feng et al. 1993; Tregnear et al. 1996; Rudrabhatla et al. 2006; Wu et al. 2012). Therefore, it is possible that the tyramine moiety of NTCT could block phosphorylation by dual-specific kinases, ultimately suppressing weed seedling growth.

Differential responses between cress and barnyardgrass as well as among specific tissues (shoot and root) were observed. The specific mechanism(s) of growth inhibition by NTCT are not known to date. However, based upon available literature, NTCT may affect membrane potentials, auxin dynamics and/or could inhibit phosphorylation. Differences in membrane potentials, auxin dynamics or tyrosine phosphorylation may explain variable responses by different species and among tissues within species. The concentration necessary to effectively inhibit plant growth with NTCT approaches the herbicidal activity of dinitroanilines, a family of herbicides that arrest cell division at pro-metaphase (Smeda & Vaughn 1994). Further research is necessary to elucidate if there is a specific mechanism of action of NTCT on plant growth processes.

In conclusion, an efficient one-step synthesis of the naturally occurring allelopathic NTCT was successfully achieved using two commercial precursors. Synthesized NTCT inhibited root and hypocotyl growth of cress and barnyardgrass at micromolar concentrations. Potential modes of action of this compound including effects on membrane potentials, auxin dynamics and/or phosphorylation were proposed. Further research is needed to determine the molecular mechanisms of action and to study selectivity and suitability of bioherbicide.

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Disclosure statement

No potential conflict of interest was reported by the authors.

References

Back K. 2001. Hydroxycinnamic acid amides and their possible utilization for enhancing agronomic traits. Plant Pathol J. 17:123–127.
Beckie HJ, Heap IM, Smeda RJ, Hall LM. 2000. Screening for herbicide resistance in weeds. Weed Technol. 14:428–445.
Blum U, Shafer SR, Lehman ME. 1999. Evidence for inhibitory allelopathic interactions involving phenolic acids in field soils: concepts vs. an experimental model. Crit Rev Plant Sci. 18:673–693.
Cuttito F, D’Abrusco B, DellaGresca M, Di Marino C, Golino A, Previtera L, Zarrelli A. 2003. Cinnamic acid amides from Chenopodium album: effects on seeds germination and plant growth. Phytochemistry, 64:1381–1387.
Dam NM, Tytgat TOG, Kirkegaard JA. 2008. Root and shoot glucosinolate composition of Alyssum species: a comparison of their diversity, function and interactions in natural and managed ecosystems. Phytochem Rev. 8:171–186.
Dayan FE, Duke SO. 2014. Natural compounds as next-generation herbicides. Plant Physiol. 166:1090–1105.
Einhellig FA. 1994. Mechanism of action of allelochemicals in allelopathy. Annu Rev Plant Physiol Mol Biol. 45:97–116.
Feng X-H, Zhao Y, Bottino PJ, Kung S. 1993. Cloning and characterization of a novel member of protein kinase family from soybean. Biochim Biophys Acta BBA – Gene Struct Expr. 1172:200–204.
Fürstner A. 2004. Total syntheses and biological assessment of Macrocylic glycolipids. Eur J Org Chem. 2004:943–958.
Hasegawa K, Mizutani J, Kosumura S, Yamamura S. 1992. Isolation and identification of lepidimide, a new allelopathic compound from mucilage of germinated cress seeds. Plant Physiol. 100:1059–1061.
Herrmann K. 1995. The Shikimate pathway: early steps in the biosynthesis of aromatic compounds. Plant Cell. 7:907–919.
Hosoki K, Yoshida S, Hasegawa M. 1970. L-Tyrosine carboxy-lyase of barley roots. Plant Cell Physiol. 11:389–396.
Iqbal Z, Hiradate S, Noda A, Isojima S-I, Fujii Y. 2002. Allelopathy of buckwheat: assessment of allelopathic potential of extract of aerial parts of buckwheat and identification of fagomine and other related alkaloids as allelochemicals. Weed Biol Manag. 2:110–115.
Jahangir M, Abdel-Farid IB, Kim HK, Choi YH, Verpoorte R. 2009. Healthy and unhealthy plants: the effect of stress on the metabolism of Brassicaceae. Environ Exp Bot. 67:23–33.
Kim B, Byun BY, Mah J-H. 2012. Biogenic amine formation and bacterial contribution in Natto products. Food Chem. 135:2005–2011.
Klemptien A, Kaminaga Y, Quelley A, Nagewodwa DA, Wilhalm JR, Orlova I, Shasany AK, Taguchi G, Kish CM, Cooper BR, et al. 2012. Contribution of CoA Ligases to benzenoid biosynthesis in petunia flowers. Plant Cell. 24:2015–2030.
Knezevic SZ, Streibig JC, Ritz C. 2007. Utilizing R software package for dose-response studies: the concept and data analysis. Weed Technol. 21:840–848.
Lajide L, Escoubas P, Mizutani J. 1995. Termite antifeedant activity in Xylopia aethiopica. Phytochemistry. 40:1105–1112.
Liu C, Xu Z, Chua NH. 1993. Auxin polar transport is essential for the establishment of bilateral symmetry during early plant embryogenesis. Plant Cell. 5:621–630.
López-Gresa MP, Torres C, Campos L, Lisón P, Rodrigo I, Bellés JM, Conejero V. 2011. Identification of defence metabolites in tomato plants infected by the bacterial pathogen Pseudomonas syringae. Environ Exp Bot. 74:216–228.
MacDonald MJ, D’Cunha GB. 2007. A modern view of phenylalanine ammonia lyase. Biochem Cell Biol. 85:273–282.

Macias FA, Marín D, Oliveros-Bastidas A, Chinchilla D, Simonet AM, Molinillo JMG. 2006. Isolation and synthesis of allelochemicals from gramineae: benzoazinones and related compounds. J Agric Food Chem. 54:991–1000.

Macias FA, Molinillo JMG, Varela RM, Galindo JCG. 2007. Allelopathy – a natural alternative for weed control, Pest Manag Sci. 63:327–348.

Negrel J, Javelle F, Paynot M. 1993. Wound-induced tyramine hydroxylase activity relationships and effects of phenylalanine ammonia-lyase by cinnamic acid derivatives and related compounds. J Plant Physiol. 142:518–524.

Newman M-A, von Roepenack-Lahaye E, Parr A, Daniels MJ, Dow JM. 2002. Allelopathic effects of volatile Monoterpenoids produced by Glycine max seedlings. J Chem Ecol. 28:310–322.

Ni DA, Wang LJ, Xu ZH, Xia ZA. 1999. Foliar modifications induced by inhibition of polar transport of auxin. Cell Res. 9:27–33.

Nishida N, Tamotsu S, Nagata N, Saito C, Sakai A. 2005. Allelopathic effects of volatile Monoterpenoids produced by Salvia leucophylla: inhibition of cell proliferation and DNA synthesis in the root apical meristem of Brassica campestris seedlings. J Chem Ecol. 31:1187–1203.

Park J-H, Fu Y-Y, Chung IS, Hahn T-R, Cho M-H. 2013. Cytotoxic property of ultraviolet-induced rice phytoalexins to human colon carcinoma HCT-116 cells. J Korean Soc Appl Biol Chem. 56:237–241.

Rudrabhatla P, Reddy MM, Rajasekharan R. 2006. Genome-wide analysis and experimentation of plant serine/threonine/tyrosine-specific protein kinases. Plant Mol Biol. 60:293–319.

Santos WDD, Ferrarese MDLL, Finger A, Teixeira ACN, Ferrarese-Filho O. 2004. Lignification and related enzymes in Glycine max root-growth-inhibition by ferulic acid. J Chem Ecol. 30:1203–1212.

Sato T, Kuchi F, Sankawa U. 1982. Inhibition of phenylalanine ammonia-lyase by cinnamic acid derivatives and related compounds. Phytochemistry. 21:845–850.

Schraudner M, Langebartels C, Negrel JHS, Jr. 1993. Plant defense reactions induced in tobacco by the air pollutant ozone. In: Fritig B, Legrand M, editors. Mechanisms of plant defense responses. Volume 2 of the series developments in plant pathology. Springer; p. 286–290.

Smeda RJ, Vaughn KC. 1994. Resistance to dinotroaniline herbicides. In: Powles SB, Holtum JAM, editors. Herbicide resistance in plants: biology and biochemistry. Boca Raton, FL: CRC Press; p. 215–228.

Suzuki T, Usui I, Tomita-Yokotani K, Kono S, Tsubura H, Miki Y, Hasegawa K. 2001. Effects of acid extracts of tomato (Lycopersicon esculentum Mill.) and carrot (Daucus carota L.) wastes from the food industry on the growth of some crops and weeds. Weed Biol Manag. 1:226–230.

Takikawa H. 2006. Synthetic studies on Breviones and structurally related natural products. Biosci Biotechnol Biochem. 70:1082–1088.

Tefeira T. 2002. Allelopathic effects of Parthenium hysterophorus extracts on seed germination and seedling growth of Eragosites tef. J Agron Crop Sci. 188:306–310.

Thi HL, Lin C-H, Smeda RJ, Fritschi FB. 2014a. Isolation and purification of growth-inhibitors from Vietnamese rice cultivars. Weed Biol Manag. 14:221–231.

Thi HL, Lin C-H, Smeda RJ, Leigh ND, Wycoff WG, Fritschi FB. 2014b. Isolation and identification of an allelopathic phenylethylamine in rice. Phytochemistry. 108:109–121.

Tregear JW, Jouannic S, Schwebel-Dugué N, Kreis M. 1996. An unusual protein kinase displaying characteristics of both the serine/threonine and tyrosine families is encoded by the Arabidopsis thaliana gene ATN1. Plant Sci. 117:107–119.

Vishnoi S, Agrawal V, Kasana VK. 2009. Synthesis and structure–activity relationships of substituted cinnamic acids and amide analogues: a new class of herbicides. J Agric Food Chem. 57:3261–3265.

Vyyvan JR. 2002. Allelochemicals as leads for new herbicides and agrochemicals. Tetrahedron. 58:1631–1646.

Wolf RB, Spencer GF, Kwolek WF. 1984. Inhibition of velvetleaf (Abutilon theophrasti) germination and growth by benzyl isothiocyanate, a natural toxicant. Weed Sci. 32:612–615.

Wu Z, Zheng L, Li Y, Su F, Yue X, Tang W, Ma X, Nie J, Li H. 2012. Synthesis and structure–activity relationships and effects of phenylpropanoid amides of octopamine and dopamine on tyrosinase inhibition and antioxidation. Food Chem. 134:1128–1131.

Yang GZ, Zhao S, Li YC. 2002. Studies on the chemical constituents of Lycianthes biflora. Yao Xue Xue Bao. 37:437–439.

Yang Y, Song ZG, Liu ZQ. 2011. Synthesis and antioxidant capacities of hydroxyl derivatives of cinnamoylphenethylamine in protecting DNA and scavenging radicals. Free Radic Res. 45(4):445–453.