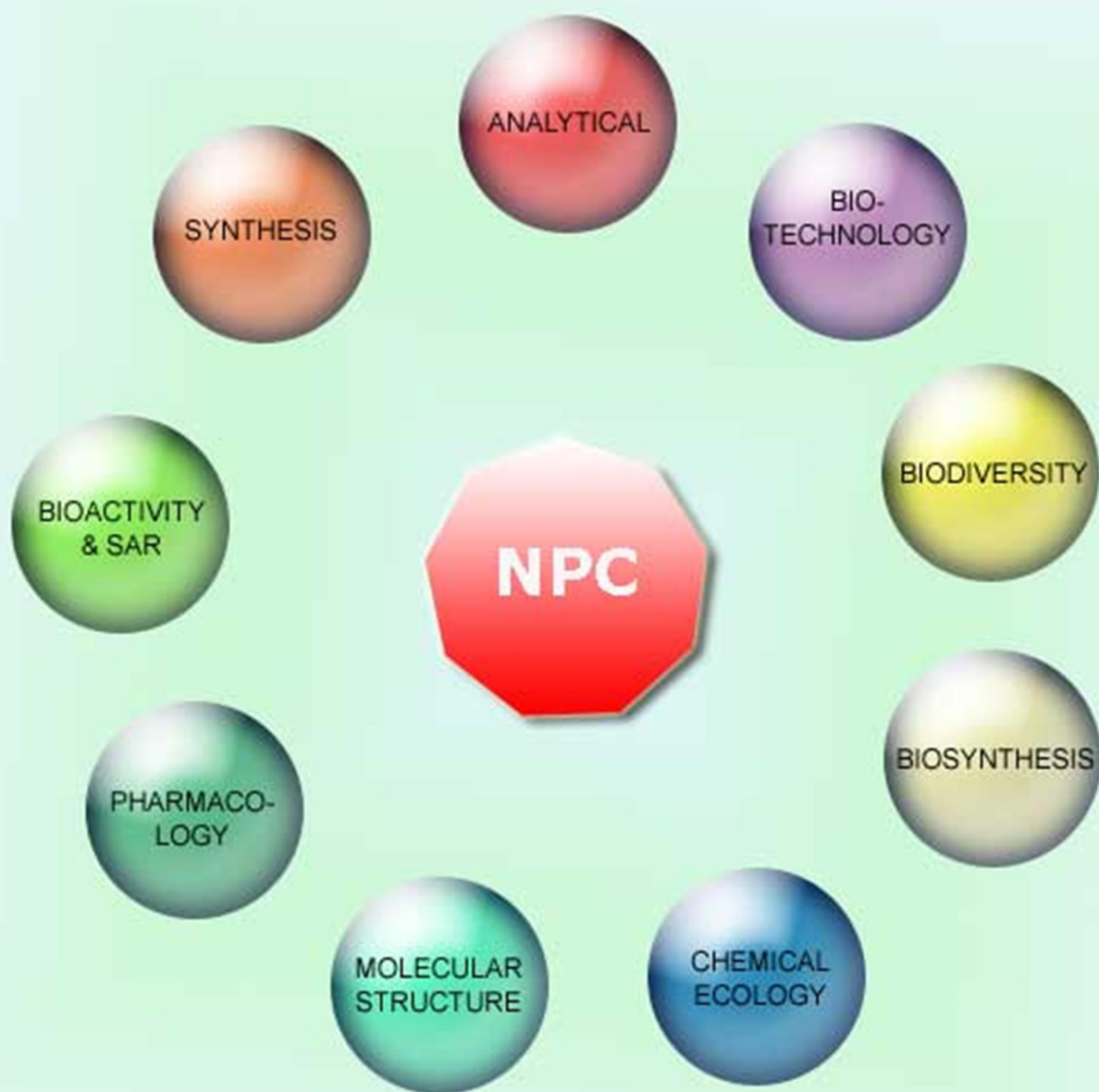


# NATURAL PRODUCT COMMUNICATIONS

An International Journal for Communications and Reviews Covering all  
Aspects of Natural Products Research



Volume 9. Issue 6. Pages 737-888. 2014  
ISSN 1934-578X (printed); ISSN 1555-9475 (online)  
[www.naturalproduct.us](http://www.naturalproduct.us)

## EDITOR-IN-CHIEF

**DR. PAWAN K AGRAWAL**

Natural Product Inc.  
7963, Anderson Park Lane,  
Westerville, Ohio 43081, USA  
agrawal@naturalproduct.us

## EDITORS

**PROFESSOR ALEJANDRO F. BARRERO**

Department of Organic Chemistry,  
University of Granada,  
Campus de Fuente Nueva, s/n, 18071, Granada, Spain  
afbarre@ugr.es

**PROFESSOR ALESSANDRA BRACA**

Dipartimento di Chimica Bioorganica e Biofarmacia,  
Università di Pisa,  
via Bonanno 33, 56126 Pisa, Italy  
braca@farm.unipi.it

**PROFESSOR DEAN GUO**

State Key Laboratory of Natural and Biomimetic Drugs,  
School of Pharmaceutical Sciences,  
Peking University,  
Beijing 100083, China  
gda5958@163.com

**PROFESSOR YOSHIHIRO MIMAKI**

School of Pharmacy,  
Tokyo University of Pharmacy and Life Sciences,  
Horinouchi 1432-1, Hachioji, Tokyo 192-0392, Japan  
mimaki@ps.toyaku.ac.jp

**PROFESSOR STEPHEN G. PYNE**

Department of Chemistry  
University of Wollongong  
Wollongong, New South Wales, 2522, Australia  
spyne@uow.edu.au

**PROFESSOR MANFRED G. REINECKE**

Department of Chemistry,  
Texas Christian University,  
Forts Worth, TX 76129, USA  
m.reinecke@tcu.edu

**PROFESSOR WILLIAM N. SETZER**

Department of Chemistry  
The University of Alabama in Huntsville  
Huntsville, AL 35809, USA  
wsetzer@chemistry.uah.edu

**PROFESSOR YASUHIRO TEZUKA**

Faculty of Pharmaceutical Sciences  
Hokuriku University  
Ho-3 Kanagawa-machi, Kanazawa 920-1181, Japan  
y-tezuka@hokuriku-u.ac.jp

**PROFESSOR DAVID E. THURSTON**

Department of Pharmaceutical and Biological Chemistry,  
The School of Pharmacy,  
University of London, 29-39 Brunswick Square,  
London WC1N 1AX, UK  
david.thurston@pharmacy.ac.uk

## HONORARY EDITOR

**PROFESSOR GERALD BLUNDEN**

The School of Pharmacy & Biomedical Sciences,  
University of Portsmouth,  
Portsmouth, PO1 2DT U.K.  
axuf64@dsl.pipex.com

## ADVISORY BOARD

Prof. Viqar Uddin Ahmad  
Karachi, Pakistan

Prof. Giovanni Appendino  
Novara, Italy

Prof. Yoshinori Asakawa  
Tokushima, Japan

Prof. Roberto G. S. Berlinck  
São Carlos, Brazil

Prof. Anna R. Bilia  
Florence, Italy

Prof. Maurizio Bruno  
Palermo, Italy

Prof. César A. N. Catalán  
Tucumán, Argentina

Prof. Josep Coll  
Barcelona, Spain

Prof. Geoffrey Cordell  
Chicago, IL, USA

Prof. Fatih Demirci  
Eskişehir, Turkey

Prof. Dominique Guillaume  
Reims, France

Prof. Ana Cristina Figueiredo  
Lisbon, Portugal

Prof. Cristina Gracia-Viguera  
Murcia, Spain

Prof. Duvvuru Gunasekar  
Tirupati, India

Prof. Hisahiro Hagiwara  
Niigata, Japan

Prof. Kurt Hostettmann  
Lausanne, Switzerland

Prof. Martin A. Iglesias Arteaga  
Mexico, D. F., Mexico

Prof. Leopold Jirovetz  
Vienna, Austria

Prof. Vladimir I Kalinin  
Vladivostok, Russia

Prof. Niel A. Koorbanally  
Durban, South Africa

Prof. Chiaki Kuroda  
Tokyo, Japan

Prof. Hartmut Laatsch  
Göttingen, Germany

Prof. Marie Lacaille-Dubois  
Dijon, France

Prof. Shoen-Sheng Lee  
Taipei, Taiwan

Prof. Imre Mathe  
Szeged, Hungary

Prof. Ermino Murano  
Trieste, Italy

Prof. M. Soledade C. Pedras  
Saskatoon, Canada

Prof. Luc Pieters  
Antwerp, Belgium

Prof. Peter Proksch  
Düsseldorf, Germany

Prof. Phila Raharivelomanana  
Tahiti, French Polynesia

Prof. Luca Rastrelli  
Fisciano, Italy

Prof. Stefano Serra  
Milano, Italy

Prof. Monique Simmonds  
Richmond, UK

Dr. Bikram Singh  
Palampur, India

Prof. John L. Sorensen  
Manitoba, Canada

Prof. Johannes van Staden  
Scottsville, South Africa

Prof. Valentin Stonik  
Vladivostok, Russia

Prof. Winston F. Tinto  
Barbados, West Indies

Prof. Sylvia Urban  
Melbourne, Australia

Prof. Karen Valant-Vetschera  
Vienna, Austria

## INFORMATION FOR AUTHORS

Full details of how to submit a manuscript for publication in Natural Product Communications are given in Information for Authors on our Web site <http://www.naturalproduct.us>.

Authors may reproduce/republish portions of their published contribution without seeking permission from NPC, provided that any such republication is accompanied by an acknowledgment (original citation)-Reproduced by permission of Natural Product Communications. Any unauthorized reproduction, transmission or storage may result in either civil or criminal liability.

The publication of each of the articles contained herein is protected by copyright. Except as allowed under national "fair use" laws, copying is not permitted by any means or for any purpose, such as for distribution to any third party (whether by sale, loan, gift, or otherwise); as agent (express or implied) of any third party; for purposes of advertising or promotion; or to create collective or derivative works. Such permission requests, or other inquiries, should be addressed to the Natural Product Inc. (NPI). A photocopy license is available from the NPI for institutional subscribers that need to make multiple copies of single articles for internal study or research purposes.

**To Subscribe:** Natural Product Communications is a journal published monthly. 2014 subscription price: US\$2,395 (Print, ISSN# 1934-578X); US\$2,395 (Web edition, ISSN# 1555-9475); US\$2,795 (Print + single site online); US\$595 (Personal online). Orders should be addressed to Subscription Department, Natural Product Communications, Natural Product Inc., 7963 Anderson Park Lane, Westerville, Ohio 43081, USA. Subscriptions are renewed on an annual basis. Claims for nonreceipt of issues will be honored if made within three months of publication of the issue. All issues are dispatched by airmail throughout the world, excluding the USA and Canada.

## Possible Role of Fat Tissue in the Pharmacokinetics of Dodeca-2E,4E,8Z,10E/Z-tetraenoic Acid Isobutylamides after Oral Administration of *Echinacea angustifolia* Extract in Rats

Nikoletta Jedlinszki<sup>a,\*</sup>, Dóra Rédei<sup>a</sup>, József Haller<sup>b</sup>, Tamás F. Freund<sup>b</sup>, Judit Hohmann<sup>a</sup> and István Zupkó<sup>c</sup>

<sup>a</sup>Department of Pharmacognosy, University of Szeged, Eötvös u. 6., H-6720 Szeged, Hungary

<sup>b</sup>Institute of Experimental Medicine, Hungarian Academy of Sciences, P.O. Box 67, H-1450 Budapest, Hungary

<sup>c</sup>Department of Pharmacodynamics and Biopharmacy, University of Szeged, Eötvös u. 6., H-6720 Szeged, Hungary

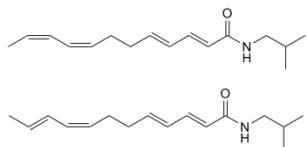
jedlinszki@pharmacognosy.hu

Received: February 20<sup>th</sup>, 2014; Accepted: March 25<sup>th</sup>, 2014

Alkamides are one of the most important constituents of lipophilic extracts of *Echinacea angustifolia* roots. These compounds play an important role in the versatile pharmacological actions of this plant. The present study aimed to compare the concentrations of isomeric dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides (DTAI) in brain and periepididymal fat tissues and blood plasma of rats. Thirty, 60, 240 and 720 min after the oral administration of *E. angustifolia* root extract, tissue and plasma concentrations were determined by reversed-phase HPLC with ESI-MS/MS detection. The calculated terminal  $t_{1/2}$  of the mixture of DTAI was 8.28 h, which indicates a relatively slow elimination. In the 0.5–4 h period the brain/plasma and fat/plasma concentration ratios were continuously above 3 and 18, respectively, followed by equilibrium at 12 h. Our results indicate substantial accumulation of alkamides in lipid-rich tissues, which presumably contributes to a maintained pharmacological action.

**Keywords:** HPLC-MS/MS, Pharmacokinetics, *Echinacea angustifolia*, Alkamide, Dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides.

*Echinacea* species are the most widely used immunomodulatory plants in the treatment of common cold. Pharmacologically active constituents of *Echinacea* species are alkamides, alkylketones, caffeic acid derivatives and polysaccharides [1, 2]. Isomeric dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides (DTAI) (Figure 1) are the main alkamides in the roots of *E. purpurea*, *E. angustifolia* and *E. pallida* and in the herbs of *E. purpurea* and *E. angustifolia* [3].



**Figure 1:** Chemical structures of dodeca-2E,4E,8E,10E/Z-tetraenoic acid isobutylamides.

Alkamides may play an important role in the medicinal benefits of *Echinacea* extracts. Alkamides of *E. purpurea* stimulated, dose-dependently, the phagocytic activity of alveolar macrophages in rats [4]. Two *Echinacea*-derived alkamides suppressed the ability of activated Jurkat T cells to produce IL-2 in a dose-dependent manner [5]. The alkamide mixture purified from *E. angustifolia* decreased significantly the lipopolysaccharide stimulated NF- $\kappa$ B level, TNF- $\alpha$  and NO production in macrophages *in vitro* [6]. Polyunsaturated alkamides isolated from *Achillea* species and *E. angustifolia* roots were shown to possess inhibitory activity in *in vitro* cyclooxygenase and 5-lipoxygenase assays [7]. These data suggest that alkamides may have not only immunostimulatory but also anti-inflammatory activity. DTAI have been found to inhibit both cyclooxygenase and 5-lipoxygenase at micromolar concentrations [8]. Extract of *E. angustifolia* decreased anxiety in the elevated plus-maze, social interaction and social avoidance tests in rodents [9]. The extract of the plant can significantly regulate excitatory, but not inhibitory,

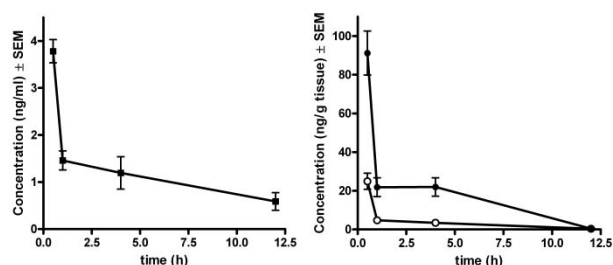
synaptic transmission in the hippocampus, and this action might be involved in its anxiolytic effects observed in behaviour tests [10]. Certain alkamides act as cannabinomimetics at both the cannabinoid CB1 and CB2 receptors [11–13]. Alkamides of *E. angustifolia* extract may contribute to decreased mild anxiety symptoms since CB1 receptors are implicated in anxiety [14]. Data concerning the absorption, metabolism, bioavailability, and bioactivity of natural products and their metabolites are primarily important to link results from *in vitro* assays and clinical studies. Woelkart *et al.* evaluated the pharmacokinetics of DTAI in rat plasma, as well as in liver and brain tissues [15]. Goey *et al.* have described a validated HPLC-MS/MS procedure for quantitative analysis of DTAI in human plasma [16]. Although lipid soluble substances may be deposited in fat tissues which may fundamentally influence the pharmacokinetic behaviour of such compounds, no data are available concerning the concentrations of DTAI in depot fat.

In this research, we studied the concentration changes of DTAI in brain and periepididymal adipose tissues of rats using an HPLC-MS/MS method, and compared them with those in plasma of the animals. Terminal  $t_{1/2}$  of DTAI was also calculated.

Oral treatment of rats with 50 mg/kg *E. angustifolia* root extract was performed in order to obtain data concerning the pharmacokinetics of the active constituents both in plasma and lipid-rich brain and fat tissues. DTAI concentration was maximal in all samples collected 30 min after treatment indicating fast absorption and distribution (Figure 2). The plasma curve of DTAI revealed a typical two-compartment pharmacokinetic behaviour with a distribution completed within 1 hour, followed by an elimination phase. The calculated half-life ( $t_{1/2}$ ) of DTAI was 8.27 h and the elimination constant ( $k_e$ ) was 0.084 1/h.

The highest concentration of DTAI was detected in the periepididymal fat. The level in the periepididymal fat tissue was

18–24 times higher than in the plasma in the period 0.5–4 h and reached equilibrium by 12 h (Table 1). High concentrations were found in the brain too but the tissue/plasma ratios were lower (2–6-fold) and also decreased substantially by 12 h.

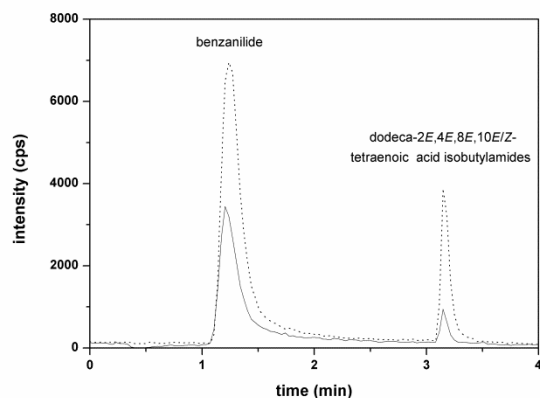


**Figure 2:** DTAI concentrations in the plasma (■), brain (○) and fat tissue (●) samples of rats treated with 50 mg/kg *Echinacea* extract (N: 6).

**Table 1:** Concentration ratios of DTAI.

Time (h)	Brain/plasma ratio	Fat/plasma ratio
0.5	7.10	30.23
1	3.03	20.61
4	4.60	35.22
12	0.51	0.96

DTAI concentrations in plasma, brain and fat tissue samples obtained from rats were determined by means of HPLC-MS/MS 0.5–12 h after oral treatment with *Echinacea* extract (Figure 3). Since the main purpose of our study was the comparison of concentrations in relevant tissues (brain and fat) with those in plasma the timing of the sample collection is not optimal for a complete pharmacokinetic analysis. However, the calculated terminal  $t_{1/2}$  of the analyte was 8.27 h, which indicates a substantially slower elimination than reported previously after the administration of the pure compounds [15]. Therefore, it is suggested that some directly ineffective constituents may exert profound action on the pharmacokinetic profile and therefore the overall effect of the *Echinacea* preparation [17].



**Figure 3:** MRM chromatogram of periepididymal adipose tissue 4 hours after *Echinacea* extract administration (solid line) and the 0.8 ng/20  $\mu$ L concentration calibration standard (dotted line).

Highly lipid-soluble substances tend to accumulate in fat tissue and this may basically influence the disposition of the drug. However, none of the previously published studies were extended to the determination of DTAI in adipose tissue. This is the first report presenting direct comparison of DTAI concentrations in plasma, brain and fat. Our data indicate that DTAI reaches considerably high concentration, presumably maximal in the body in adipose

tissue. DTAI deposited in the fat may contribute to a sustained brain concentration. If such redistribution is operative in humans it may implicate that the relative fat weight may exert a profound action on the disposition of the agents and hence on the duration of their action too.

## Experimental

**Chemicals and reagents:** DTAI was isolated from *E. angustifolia* by Hohmann *et al.* [12] and its identity and purity (95%) was investigated by  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ). Benzanilide (purity 99.9%) and methylcellulose were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA), acetonitrile (LiChrosolv HPLC grade) from Merck KGaA (Darmstadt, Germany), and formic acid and methanol (analytical grade) from Reanal Zrt. (Budapest, Hungary). Millipore Direct-Q UV3 (Millipore, Bedford, MA, USA) clarifier was used to produce purified water for HPLC-MS measurements. The *E. angustifolia* root extract (extraction: ethanol 85%, v/v; ratio of herbal drug - native extract: 6.5–8:1; excipient: maltodextrin 30%; marker: echinacoside 4%) was purchased from Euromed SA (Millet del Valles, Spain; Batch No. 419061).

**Calibration standards and quality control samples:** Standard stock solution was prepared by dissolving solid DTAI in water-acetonitrile (6:4) in a concentration of 1  $\mu\text{g}/20$   $\mu\text{L}$ . Working standard solutions were prepared by serial dilutions using water-acetonitrile (6:4) from the stock solution to final concentrations that covered the concentration range of the assay. The benzanilide internal standard (IS) stock solution, 4.12 ng/20  $\mu\text{L}$ , was prepared using water-acetonitrile (6:4). Its concentration was 1 ng/20  $\mu\text{L}$  in the calibration standards and in the samples. Quality control samples (QC) were prepared using the procedure of sample preparation at the concentrations of 0.023 ng/20  $\mu\text{L}$  (LC) and 0.920 ng/20  $\mu\text{L}$  (HC). The IS concentration was 1 ng/20  $\mu\text{L}$ .

**Animals and treatment:** Animals were treated in accordance with the European Communities Council Directives (86/609/ECC) and the Hungarian Act for the Protection of Animals in Research (XXVIII. section 243/1998). All experiments involving animal subjects were carried out with the approval of the Hungarian Ethical Committee for Animal Research (registration number: IV./01758-2/2008). Male Wistar rats of 200–240 g body weight (Toxi-Coop, Budapest, Hungary) were housed in temperature (20–23°C), humidity (40–60%) and light (12 h of light, 12 h of dark) regulated rooms, with water and standard rodent food (Bioplan, Isaszeg, Hungary) intake available *ad libitum*. Animals were fasted for 16 h before oral treatment with 50 mg/kg *E. angustifolia* extract suspended in 0.25% methylcellulose in a dosing volume of 5 mL/kg. Six animals were randomized into each group.

**Sample collection and preparation:** After 30, 60, 240 and 720 min rats were anesthetized with isoflurane inhalation and blood samples were collected by cardiac puncture. Blood coagulation was prevented and plasma was prepared by centrifugation (4000 RPM, 10 min, 4°C). Plasma samples of 200  $\mu\text{L}$  were extracted 2 times with 1200  $\mu\text{L}$  methanol and 15  $\mu\text{L}$  IS solution was added. The sample was homogenized by vortexing for 90 sec. After both extractions the samples were centrifuged (6200 RPM, 15 min, 4°C) and the collected supernatants were evaporated under nitrogen at room temperature. Whole brains were removed and periepididymal adipose tissues from both sides were collected and wet weights were recorded. Tissues were homogenized in a double volume of methanol, vortexed for 90 sec and centrifuged (6200 RPM, 15 min, 4°C). Fifteen  $\mu\text{L}$  IS solution was added to 500  $\mu\text{L}$  supernatant and evaporated as mentioned before. Samples were dissolved in 200  $\mu\text{L}$  water-acetonitrile (6:4) in an ultrasonic bath and then filtered using

a 0.45 µm pore size syringe filter into chromatographic sample bottles. Pharmacokinetic parameters were calculated by means of PKSolver in noncompartmental analyses [18].

**HPLC-MS/MS conditions:** LC analyses were performed using a Shimadzu HPLC system (Shimadzu, Tokyo, Japan), equipped with 2 LC-20AD pumps, CBM-20A controller, SPD-20A UV-Vis detector, SIL-20A autosampler, DGU-20A3 degasser and CTO-20AC column thermostat, coupled to an API 2000 triple quadrupole mass spectrometer, equipped with an electrospray (ESI) interface (AB SCIEX, Framingham, MA, USA). Chromatographic separation was achieved with a Phenomenex Kinetex XB-C18 column (2.1 × 50 mm; 2.6 µm) and a C18 guard column (both supplied by Gen-Lab Kft., Budapest, Hungary). Eluent A was 0.1% formic acid in acetonitrile and eluent B was 0.1% formic acid in water at a flow rate of 500 µL/min. The elution gradient started with 40% of eluent A, keeping isocratic conditions for 0.5 min. Then, eluent A increased to 90% in 1.0 min and was held for 1.0 min. Finally, initial conditions were reached again in 1.2 min, with a re-equilibration time of 1.7 min in order to restore the column. The sample injection volume was set at 20 µL. The ion source

temperature was 325°C. Measurements were carried out in positive ionization mode and the quantification was accomplished by using multiple reaction monitoring (MRM) with transitions of m/z 248→152 for DTAI and m/z 198→105 for benzanilide. Data acquisition and evaluation were performed using Analyst 1.5.1 software.

**Method validation:** The applied HPLC-MS method, described above, was used and validated by Woelkart *et al.* [15] to quantitate DTAI in rat plasma and other tissues, except periepididymal fat. In this assay, validation was carried out only for periepididymal fat samples. The R<sup>2</sup> value for the standard curve was 0.9992 and the linear range was determined between 0.021–1.050 ng/20 µL. Limit of detection and limit of quantification were 0.0043 and 0.0214 ng/20 µL, respectively. Relative standard deviations of the replicate measurements were 19.8% for LC and 0.87% for HC samples. Extraction recovery was 75% for LC and 58% for HC samples.

**Acknowledgments** - The publication is supported by the European Union and co-funded by the European Social Fund (TÁMOP-4.2.2.A-11/1/KONV-2012-0035).

## References

- [1] Bauer R, Khan IA, Wagner H. (1988) TLC and HPLC analysis of *Echinacea pallida* and *E. angustifolia* roots. *Planta Medica*, **54**, 426-430.
- [2] Barnes J, Anderson LA, Gibbons S, Phillipson JD. (2005) *Echinacea* species (*Echinacea angustifolia* (DC.) Hell., *Echinacea pallida* (Nutt.) Nutt., *Echinacea purpurea* (L.) Moench): a review of their chemistry, pharmacology and clinical properties. *Journal of Pharmacy and Pharmacology*, **57**, 929-954.
- [3] Bauer R, Remiger P. (1989) TLC and HPLC analysis of alkamides in *Echinacea* drugs. *Planta Medica*, **55**, 367-371.
- [4] Goel V, Chang C, Slama JV, Barton R, Bauer R, Gahler R, Basu TK. (2002) Alkylamides of *Echinacea purpurea* stimulate alveolar macrophage function in normal rats. *International Immunopharmacology*, **2**, 381-387.
- [5] Sasagawa M, Cech NB, Gray DE, Elmer GW, Wenner CA. (2006) *Echinacea* alkylamides inhibit interleukin-2 production by Jurkat T cells. *International Immunopharmacology*, **6**, 1214-1221.
- [6] Stevenson L, Matthias A, Banbury L, Penman K, Bone K, Leach D, Lehmann R. (2005) Modulation of macrophage immune responses by *Echinacea*. *Molecules*, **10**, 1279-1285.
- [7] Muller-Jakic B, Breu W, Probstle A, Redl K, Greger H, Bauer R. (1994) *In vitro* inhibition of cyclooxygenase and 5-lipoxygenase by alkamides from *Echinacea* and *Achillea* species. *Planta Medica*, **60**, 37-40.
- [8] Hinz B, Woelkart K, Bauer R. (2007) Alkamides from *Echinacea* inhibit cyclooxygenase-2 activity in human neuroglioma cells. *Biochemical and Biophysical Research Communications*, **360**, 441-446.
- [9] Haller J, Hohmann J, Freund TF. (2010) The effect of *Echinacea* preparations in three laboratory tests of anxiety: comparison with chlordiazepoxide. *Phytotherapy Research*, **24**, 1605-1613.
- [10] Hájos N, Holderith N, Németh B, Papp OI, Szabó GG, Zemankovics R, Freund TF, Haller J. (2012) The effects of an *Echinacea* preparation on synaptic transmission and the firing properties of CA1 pyramidal cells in the hippocampus. *Phytotherapy Research*, **26**, 354-362.
- [11] Woelkart K, Xu W, Pei Y, Makriyannis A, Picone R, Bauer R. (2005) The endocannabinoid system as a target for alkamides from *Echinacea angustifolia* roots. *Planta Medica*, **71**, 701-705.
- [12] Raduner S, Majewska A, Chen J, Xie X, Hamon J, Faller B, Altmann K, Gertsch J. (2006) Alkylamides from *Echinacea* are a new class of cannabinomimetics – Cannabinoid type 2 receptor-dependent and -independent immunomodulatory effects. *The Journal of Biological Chemistry*, **281**, 14192-14206.
- [13] Hohmann J, Rédei D, Forgo P, Szabó P, Freund TF, Haller J, Bojnik E, Benyhe S. (2011) Alkamides and a neolignan from *Echinacea purpurea* roots and the interaction of alkamides with G-protein-coupled cannabinoid receptors. *Phytochemistry*, **72**, 1848-1853.
- [14] Haller J, Freund TF, Pelczar KG, Füredi J, Krecsak L, Zámboi J. (2013) The anxiolytic potential and psychotropic side effects of an *Echinacea* preparation in laboratory animals and healthy volunteers. *Phytotherapy Research*, **27**, 54-61.
- [15] Woelkart K, Frye RF, Derendorf H, Bauer R, Butterweck V. (2009) Pharmacokinetics and tissue distribution of dodeca-2E,4E,8E,10E/Z-tetraenoic acid isobutylamides after oral administration in rats. *Planta Medica*, **75**, 1306-1313.
- [16] Goey AKL, Rosing H, Meijerman I, Sparidans RW, Schellens JHM, Beijnen JH. (2012) The bioanalysis of the major *Echinacea purpurea* constituents dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides in human plasma using LC-MS/MS. *Journal of Chromatography B*, **902**, 151-156.
- [17] Ardjomand-Woelkart K, Kollroser M, Magnes C, Sinner F, Frye RF, Derendorf H, Bauer R, Butterweck V. (2011) Absolute/relative bioavailability and metabolism of dodeca-2E,4E,8Z,10E/Z-tetraenoic acid isobutylamides (tetraenes) after intravenous and oral single doses to rats. *Planta Medica*, **77**, 1794-1799.
- [18] Zhang Y, Huo M, Zhou J, Xie S. (2010) PKSolver: an add-in program for pharmacokinetic and pharmacodynamic data analysis in Microsoft Excel. *Computer Methods and Programs in Biomedicine*, **99**, 306-314.



<b>Three New Isoflavonoids from <i>Erythrina caffra</i></b> Zelalem Yibralign Desta and Runner R. T. Majinda	817
<b>Bijayasaline: A New C-Glucosyl-<math>\alpha</math>-hydroxydihydrochalcone from the Heartwood of Bijayasal (<i>Pterocarpus marsupium</i>)</b> Khem Raj Joshi, Hari Prasad Devkota and Shoji Yahara	821
<b>Nelumal A, the Active Principle of <i>Ligularia nelumbifolia</i>, is a Novel Aromatase Inhibitor</b> Francesco Epifano, Salvatore Genovese, Serena Fiorito, Chantal Magne Nde and Colin Clyne	823
<b>Chemical Constituents of <i>Dendrobium venustum</i> and their Antimalarial and Anti-herpetic Properties</b> Prapapun Sukphan, Boonchoo Sritularak, Wanwimon Mekboonsonglarp, Vimolmas Lipipun and Kittisak Likhitwitayawuid	825
<b>HPLC-PDA Simultaneous Determination and Protective Effect of <i>Anemarrhena asphodeloides</i> Against Acute Renal Failure</b> Chang-Seob Seo, Hyekyung Ha, Young-Jung Kim and Ju-Young Jung	829
<b>New Rocaglamide Derivatives from Vietnamese <i>Aglaia</i> species</b> Ngoc Tu Duong, RuAngelie Edrada-Ebel, Rainer Ebel, Wenhan Lin, Anh Tuan Duong, Xuan Quy Dang, Ngoc Hieu Nguyen and Peter Proksch	833
<b>Oxirapentyns A, B and E from the Marine-Derived Strain of <i>Isaria felina</i> KMM 4639 as Stimulators of Initial Stages of Development of Agricultural Plants</b> Mikhail M. Anisimov, Elena L. Chaikina, Olga F. Smetanina and Shamil Sh. Afiyatullov	835
<b>Concerning the Structure of Islandoquinone Isolated from the Lichen <i>Cetraria islandica</i></b> Ksenia L. Borisova, Dmitry N. Pelageev, Tatiana Yu. Kochergina, Nataly D. Pokhilo, Michael A. Pushilin, Vladimir A. Denisenko, Dmitry V. Berdyshev and Victor Ph. Anufriev	837
<b>Methodology for Porphyrin Isolation by High-Performance Countercurrent Chromatography</b> Amaro C. Ramos, Fernanda S. Neves, Maria Raquel G. Vega, Edmilson J. Maria and Rodrigo R. Oliveira	841
<b>Possible Role of Fat Tissue in the Pharmacokinetics of Dodeca-2E,4E,8Z,10E/Z-tetraenoic Acid Isobutylamides after Oral Administration of <i>Echinacea angustifolia</i> Extract in Rats</b> Nikoletta Jedlinszki, Dóra Rédei, József Haller, Tamás F. Freund, Judit Hohmann and István Zupkó	843
<b>Ascidian Tunicate Extracts Attenuate Rheumatoid Arthritis in a Collagen-induced Murine Model</b> Seong-Ho Hong, Jung-Taek Kwon, Jae-Ho Lee, Somin Lee, Ah Young Lee, Won-Young Cho, Munkhjargal Bat-Erdene, Byeong-Dae Choi and Myung-Haing Cho	847
<b>Dialyzable Leukocyte Extracts Activate TLR-2 on Monocytes</b> Uriel García-Hernández, Frank H. Robledo-Ávila, Violeta D. Álvarez-Jiménez, Octavio Rodríguez-Cortés, Isabel Wong-Baeza, Jeanet Serafín-López, Luz M. Aguilar-Anguiano, Sergio Estrada-Parra, Iris Estrada-García, Sonia M Pérez-Tapia and Rommel Chacón-Salinas	853
<b>The Volatile Constituents of <i>Parquetina nigrescens</i> from Southwestern Nigeria</b> Moses S. Owolabi, Oladipupo A. Lawal, Rebecca M. Hauser and William N. Setzer	857
<b>Seasonal Variations in the Composition of the Essential Oils of <i>Lavandula angustifolia</i> (Lamiaceae)</b> Branislava Lakušić, Dmtar Lakušić, Mihailo Ristić, Mirjana Marčetić and Violeta Slavkovska	859
<b>Chemical Composition and Antimicrobial Activity of the Essential Oil from <i>Allium hookeri</i> Consumed in Xishuangbanna, Southwest China</b> Ren Li, Yuan-Fei Wang, Qian Sun and Hua-Bin Hu	863
<b>Chemical Composition, and Cytotoxic, Antioxidant and Antibacterial Activities of the Essential Oil from Ginseng Leaves</b> Rui Jiang, Liwei Sun, Yanbing Wang, Jianzeng Liu, Xiaodan Liu, Hao Feng and Daqing Zhao	865
<b>Essential Oil from Leaves of <i>Liquidambar formosana</i> Ameliorates Inflammatory Response in Lipopolysaccharide-activated Mouse Macrophages</b> Kuo-Feng Hua, Tzu-Jung Yang, Huan-Wen Chiu and Chen-Lung Ho	869
<b>Accumulation of Silicon in Cacti Native to the United States: Characterization of Silica Bodies and Cyclic Oligosiloxanes in <i>Stenocereus thurberi</i>, <i>Opuntia littoralis</i>, <i>Opuntia ficus-indica</i>, and <i>Opuntia stricta</i></b> Cynthia R. Wright, Emanuel A. Waddell and William N. Setzer	873
<b><u>Review/Account</u></b>	
<b>A Phytochemical, Pharmacological and Clinical Profile of <i>Paederia foetida</i> and <i>P. scandens</i></b> Liang Wang, Yiping Jiang, Ting Han, Chengjian Zheng and Luping Qin	879



# Natural Product Communications

## 2014

Volume 9, Number 6

### Contents

<u>Original Paper</u>	<u>Page</u>
<b>A New Source of (R)-Limonene and Rotundifolone from Leaves of <i>Lippia pedunculosa</i> (Verbenaceae) and their Trypanocidal Properties</b> Leociley Rocha Alencar Menezes, Nilmaria Nunes Santos, Cássio Santana Meira, Jamyle Andrade Ferreira dos Santos, Elisalva Teixeira Guimarães, Milena Botelho Pereira Soares, Angelita Nepel, Andersson Barison and Emmanoel Vilaça Costa	737
<b>Improved Synthesis of (±)-Trichodiene – A Volatile Marker for Trichothecene Mycotoxins</b> Julian Gebauer, Martina Werneburg and Matthias Koch	741
<b>Synthesis and Insecticidal Activities of Novel Nitrogenous Derivatives of Celangulin-V</b> Jiwen Zhang, Lihui Cui, Longbo Li, Zhan Hu, Qianliang Zhang, Zhaonong Hu and Wenjun Wu	745
<b>An Easy Way to Pyrimidine Based Nucleoterpene</b> Serena Fiorito, Salvatore Genovese and Francesco Epifano	149
<b>Diastereoselective Addition of Diazomethane to Zaluzanin A</b> Adriana Ortiz-León, J. Martín Torres-Valencia, J. Jesús Manríquez-Torres, José G. Alvarado-Rodríguez, Uvaldo Hernández-Balderas, Carlos M. Cerda-García-Rojas and Pedro Joseph-Nathan	753
<b>Tauroarenarones A and B, New Taurine-containing Meroterpenoids from the Marine Sponge <i>Dysidea</i> sp.</b> Natalia K. Utkina and Vladimir A. Denisenko	757
<b>Stereo and Regioselective Microbial Reduction of the Clerodane Diterpene 3,12-Dioxo-15,16-epoxy-4-hydroxycleroda-13(16),14-diene</b> Jair Mafezoli, Maria C. F. Oliveira, José R. Paiva, Antônio H. Sousa, Mary A. S. Lima, José N. Silva Júnior, Francisco G. Barbosa, E. M. Kithsiri Wijeratne and A. A. Leslie Gunatilaka	759
<b>Scalarane Sesterterpenes from the Paracel Islands Marine Sponge <i>Hyrtios</i> sp.</b> Fan Yang, Jian-Hong Gan, Xiao-Yan Liu and Hou-Wen Lin	763
<b>Novel Cucurbitane Triterpenoids and Anti-cholinesterase Activities of Constituents from <i>Momordica charantia</i> L.</b> Wichuta Kuanhüt, Thammarat Aree, Surachai Pornpakakul and Pattara Sawasdee	765
<b>Immunomodulatory Action of Triterpene Glycosides Isolated from the Sea Cucumber <i>Actinocucumis typica</i>. Structure-Activity Relationships</b> Evgeny A. Pisyagin, Dmitry L. Aminin, Alexandra S. Silchenko, Sergey A. Avilov, Pelageya V. Andryjashchenko, Vladimir I. Kalinin and Krishna Padmakumar	771
<b>Chromatographic Fingerprint Combined with Content of Asperosaponin VI and Antioxidant Activity for Quality Evaluation of Wine-fried <i>Dipsaci Radix</i></b> Li Song, Shaoyun Wang, Xiaoju Duan, Xinhua Liu, Zhaofang Li, Lei Nie and Guangyi Chu	773
<b>Morphological, Chemical and Molecular Characterization of <i>Centella asiatica</i> Germplasms for Commercial Cultivation in the Indo-Gangetic Plains</b> Archana Prasad, Sunita S. Dhawan, Ajay K. Mathur, Om Prakash, Madan M. Gupta, Ram K. Verma, Raj K. Lal and Archana Mathur	779
<b>Ring A Conformation of Aconine and Pseudoaconine in CDCl<sub>3</sub></b> Hong-Ying Deng, Qiao-Hong Chen and Feng-Peng Wang	785
<b>Revised NMR Data for 9-O-Demethylgalanthine: an Alkaloid from <i>Zephyranthes robusta</i> (Amaryllidaceae) and its Biological Activity</b> Marcela Šafratová, Zdeněk Novák, Andrea Kulhánková, Jiří Kuneš, Martina Hrabínová, Daniel Jun, Kateřina Macáková, Lubomír Opletal and Lucie Cahliková	787
<b>Structure Revision of N-Mercapto-4-formylcarbostyryl Produced by <i>Pseudomonas fluorescens</i> G308 to 2-(2-Hydroxyphenyl)thiazole-4-carbaldehyde [aeruginaldehyde]</b> Lumeng Ye, Pierre Cornelis, Karel Guillemin, Steven Ballet, Carsten Christophersen, and Ole Hammerich	789
<b>Accumulation and Function of Trigonelline in Non-leguminous Plants</b> Hiroshi Ashihara and Shin Watanabe	795
<b>Metabolites of the Endophytic Fungus <i>Penicillium</i> sp. FJ-1 of <i>Acanthus ilicifolius</i></b> Jian-Fang Liu, Wei-Jie Chen, Ben-Ru Xin and Jie Lu	799
<b>Overexpression of Cinnamate 4-Hydroxylase and 4-Coumaroyl CoA Ligase Prompted Flavone Accumulation in <i>Scutellaria baicalensis</i> Hairy Roots</b> Young Seon Kim, Yeon Bok Kim, YeJi Kim, Mi Young Lee and Sang Un Park	803
<b>New Isoflavone Glycosides from the Stems of <i>Dalbergia vietnamensis</i></b> Pham Thanh Loan, Hoang Le Tuan Anh, Nguyen Thi Cuc, Duong Thi Hai Yen, Dan Thi Thuy Hang, Tran Minh Ha, Nguyen Xuan Nhiem, Nguyen Van Du, Tran Huy Thai, Chau Van Minh and Phan Van Kiem	809
<b>A Characterization of Content, Composition and Scavenging Capacity of Phenolic Compounds in Parsnip Roots of Various Weight</b> Nada Č. Nikolić, Miodrag M. Lazić, Ivana T. Karabegović, Gordana S. Stojanović and Zoran B. Todorović	811
<b>Variability of Procyanidin type A- and -B Trimers Content in Aerial Parts of Some <i>Vaccinium</i> Species and Cultivars</b> Peeter Toomik, Tõnu Püssa and Ain Raal	815

Continued inside backcover