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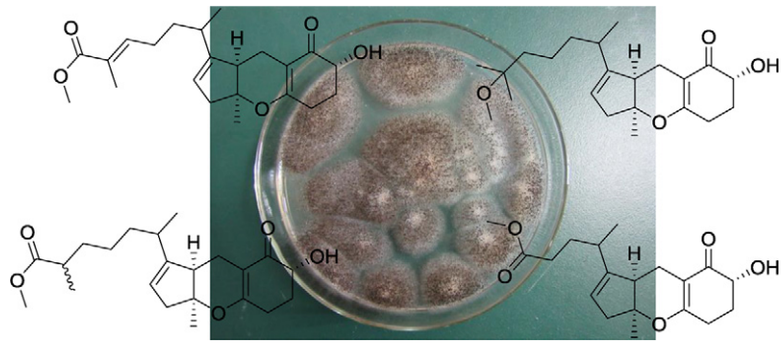
[a]*School of Pharmacy, Anhui University of Chinese Medicine, Anhui Key Laboratory of Modern Chinese Materia Medica, Hefei 230012, China*
[b]*Synergetic Innovation Center of Anhui Authentic Chinese Medicine Quality Improvement, Hefei 230012, China*
[c]*School of Pharmaceutical Sciences, South-Central University for Nationalities, Wuhan 430074, China*
[d]*State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, China*
[e]*University of Chinese Academy of Sciences, Beijing 100049, China*



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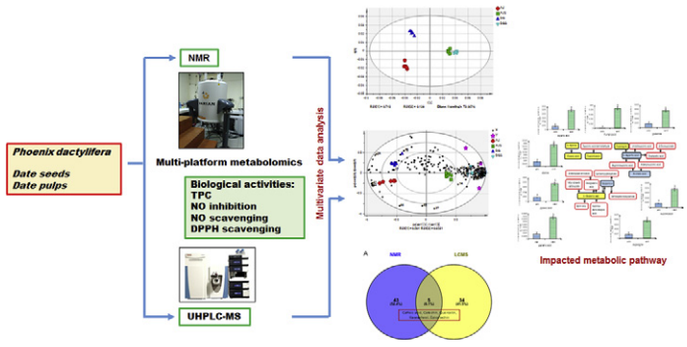
Nur Ashikin Abdul-Hamid[a], Faridah Abas[a,b,*], Intan Safinar Ismail[a,c], Chau Ling Tham[d], M. Maulidiani[e], Ahmed Mediani[f], Sanjay Swarup[g,h], Shivshankar Umashankar[i], Nur Khaleeda Zulaikha Zolkeflee[a]

[a]*Laboratory of Natural Products, Institute of Bioscience, Universiti Putra Malaysia, 43400, Serdang, Malaysia*
[b]*Department of Food Science, Faculty of Food Science and Technology, Universiti Putra Malaysia, 43400, Serdang, Malaysia*
[c]*Department of Chemistry, Faculty of Science, Universiti Putra Malaysia, 43400, Serdang, Selangor, Malaysia*
[d]*Department of Biomedical Science, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400, Serdang, Selangor, Malaysia*
[e]*School of Fundamental Science, Universiti Malaysia Terengganu, 21030, Kuala Nerus, Terengganu, Malaysia*
[f]*Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA, Puncak Alam Campus, 42300, Bandar Puncak Alam, Selangor, Malaysia*
[g]*Department of Biological Science, National University of Singapore, Singapore*
[h]*NUS Environmental Research Institute, National University of Singapore, Singapore*
[i]*Singapore Centre for Environmental Life Science Engineering, National University of Singapore, Singapore*



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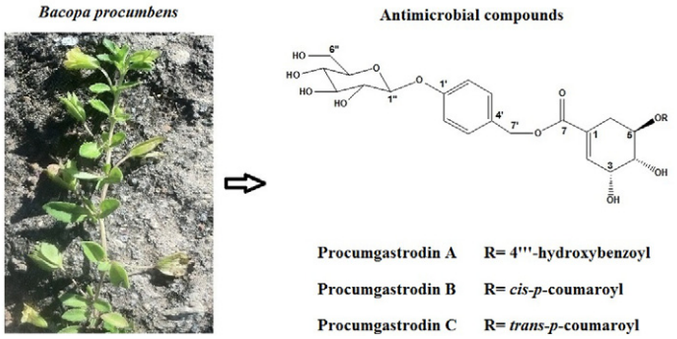
[a]*Centro de Investigación Biomédica del Sur, Instituto Mexicano del Seguro Social, Argentina No. 1, Col. Centro, Xochitepec, Morelos, Mexico*
[b]*Centro de Investigación en Biotecnología Aplicada. Instituto Politécnico Nacional (IPN), Ex-hacienda San Juan Molino Carretera Estatal Tecuexcomac-Tepetitla, Km 1.5, Tlaxcala, Mexico*
[c]*Laboratorio de RMN, Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, Colonia Chamilpa, Cuernavaca, Morelos, Mexico*
[d]*Universidad Juárez Autónoma de Tabasco, Carretera Cunduacán-Jalpa Km. 0.5, 86690 Cunduacán, Tabasco, Mexico*



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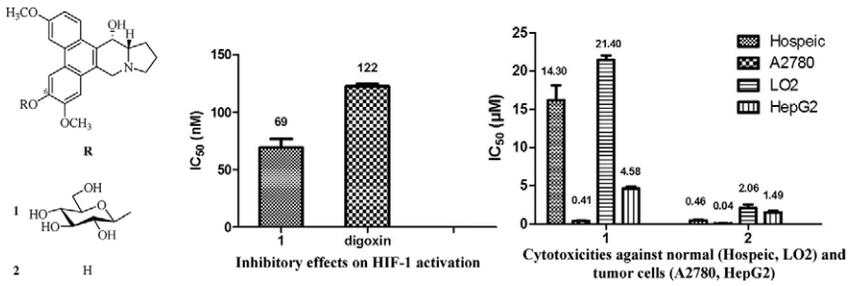
[a]*State Key Laboratory of Quality Research in Chinese Medicine, Macau Institute for Applied Research in Medicine and Health, Macau University of Science and Technology, Taipa, Macau, China*
[b]*Guangxi Key Laboratory of Traditional Chinese Medicine Quality Standards, Guangxi Institute of Chinese Medicine and Pharmaceutical Science, Nanning, 530022, China*



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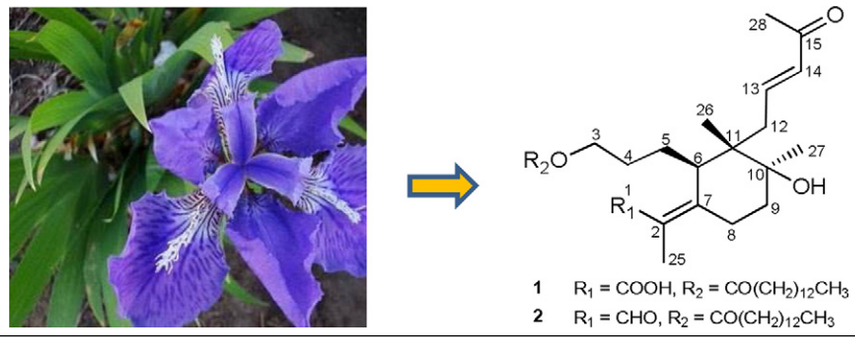
Gang Ni, Jia-Yuan Li, De-Quan Yu*

State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100050, People's Republic of China



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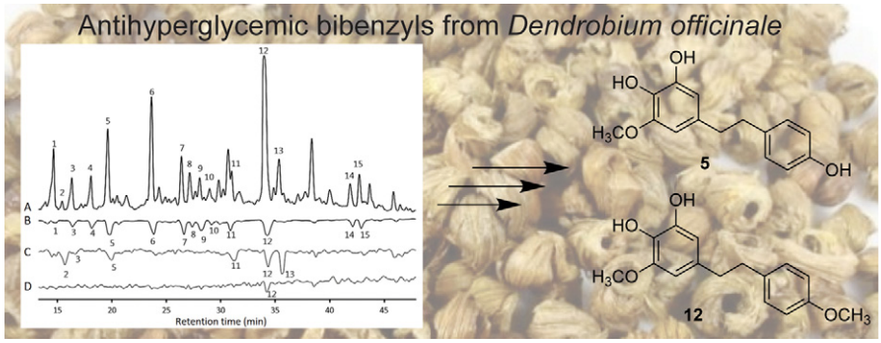
Chu Chu[a,b,1], Tuo Li[b,1], Hans Albert Pedersen[b], Kenneth T. Kongstad[b], Jizhong Yan[a], Dan Staerk[b,*]

[a]*College of Pharmaceutical Science, Zhejiang University of Technology, Hangzhou, PR China*
[b]*Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, 2100 Copenhagen, Denmark*



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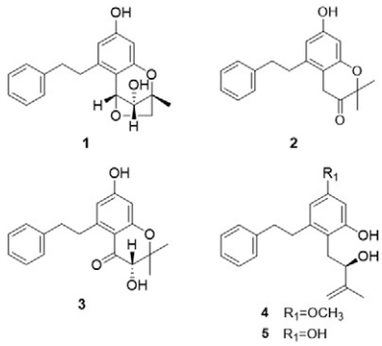
[a]*Department of Natural Products Chemistry, Key Lab of Chemical Biology of the Ministry of Education, Shandong University, Jinan 250012, People's Republic of China*
[b]*School of Chemistry and Chemical Engineering, Shandong University, Jinan 250010, People's Republic of China*
[c]*School of Pharmacy, Linyi University, Linyi 276000, People's Republic of China*
[d]*Vitamin D Research Institute, Shaanxi University of Technology, No. 1 Dongyi Road, Hanzhong, Shanxi 723000, People's Republic of China*

Radula amoena



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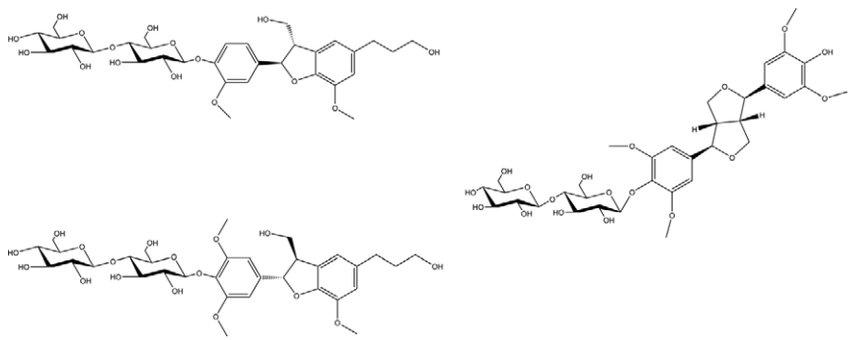
Junyang Ji, Qiwen Wang, Maolin Wang, Jianwei Chen*, Xiang Li*

College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, 210023, China



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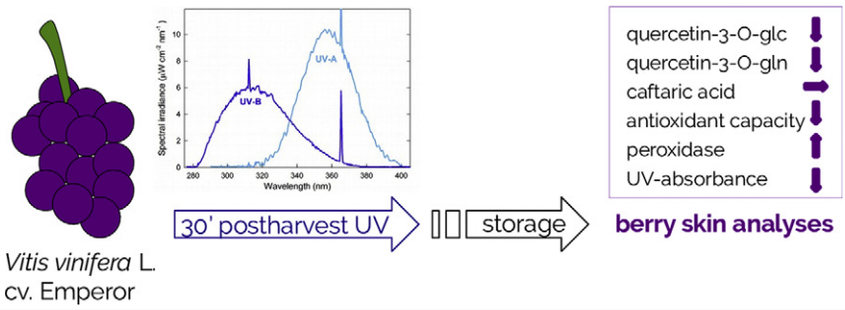
[a]*Department of Plant Biology, Faculty of Sciences, University of Pécs, Hungary*
[b]*Research Institute for Viticulture and Oenology, University of Pécs, Hungary*



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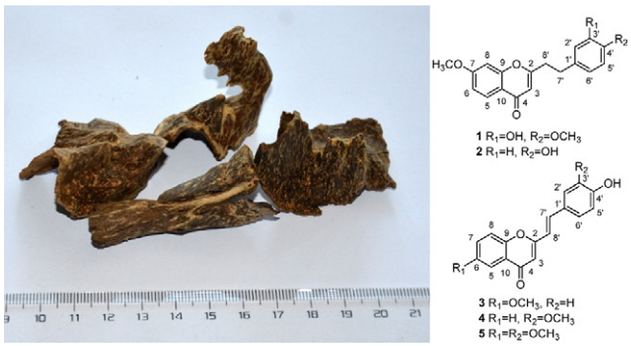
[a]*Key Laboratory of Biology and Genetic Resources of Tropical Crops, Ministry of Agriculture, Institute of Tropical Bioscience and Biotechnology, Hainan Engineering Research Center of Agarwood, Chinese Academy of Tropical Agricultural Sciences, Haikou, 571101, PR China*
[b]*Hainan Key Laboratory for Research and Development of Natural Products from Li Folk Medicine, 571101, Haikou, PR China*
[c]*Institute of Materia Medica, College of Pharmacy and Chemistry, College of Pharmacy and Chemistry, Dali University, Dali, 671003, PR China*



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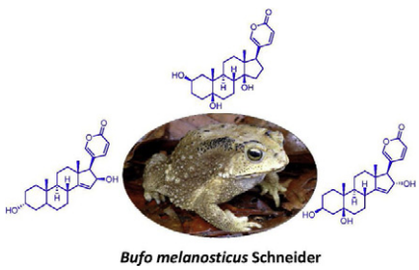
[a]*Guizhou Provincial College-based Key Lab for Tumor Prevention and Treatment with Distinctive Medicines, Zunyi Medical University, Zunyi, Guizhou, 563000, China*
[b]*Research Center for Medicine & Biology, Zunyi Medical University, Zunyi, Guizhou, 563000, China*



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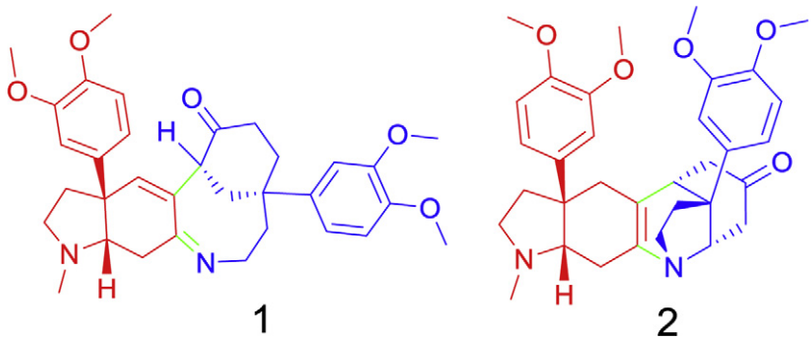
[a]*National Center for Natural Products Research, School of Pharmacy, University of Mississippi, MS, 38677, USA*
[b]*Department of Applied Chemistry and Pharmacy, School of Chemical Engineering and Environment, Beijing Institute of Technology, Beijing, 100081, PR China*
[c]*Division of Pharmacognosy, Department of BioMolecular Sciences, School of Pharmacy, University of Mississippi, MS, 38677, USA*
[d]*TCM and Ethnomedicine Innovation, Development Laboratory, School of Pharmacy, Hunan University of Chinese Medicine, Changsha, Hunan 410208, PR China*
[e]*Department of Pharmaceutical Sciences, Tshwane University of Technology, Private Bag X680, Pretoria, 0001, South Africa*



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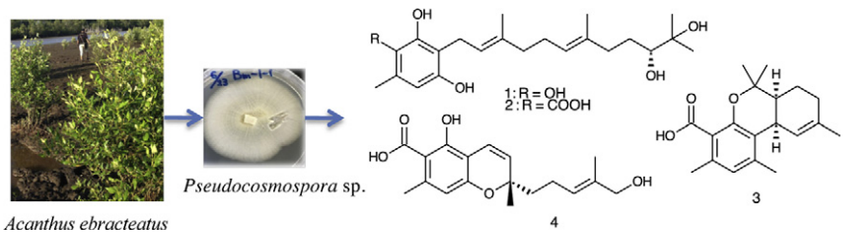
[a]*Department of Food, Life, and Environmental Science, Faculty of Agriculture, Yamagata University, Tsuruoka, Yamagata, 997-8555, Japan*
[b]*The United Graduate School of Agricultural Sciences, Iwate University, Morioka, Iwate, 020-8550, Japan*
[c]*Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Tanjungpura, Pontianak, 78124, Indonesia*
[d]*Department of Geography, Faculty of Mathematics and Natural Sciences Universitas Negeri Makassar, Makassar, 90224, Indonesia*
[e]*Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran, Sumedang 45363, Indonesia*
[f]*Graduate School of Arts and Sciences, Graduate Course in Biological Chemistry and Food Sciences, Iwate University, Morioka, Iwate, 020-8550, Japan*



Secondary metabolites from the Chinese liverwort *Diplophyllum apiculatum*

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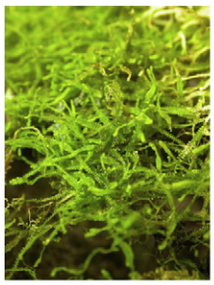
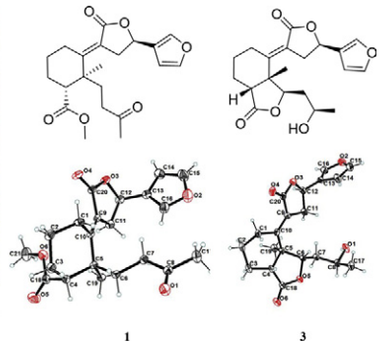
Shenghua Fan[a], Yi Li[a], Jinchuan Zhou[b], Yanan Qiao[a], Chunyang Zhang[a], Yun Gao[a], Xueyang Jin[a], Jiaozhen Zhang[a], Wang Chen[c], Hongxiang Lou[a,*]

[a]Department of Natural Products Chemistry, Key Lab of Chemical Biology of the Ministry of Education, Shandong University, Jinan, 250012, People's Republic of China
[b]School of Pharmacy, Linyi University, Linyi, 276000, People's Republic of China
[c]Vitamin D Research Institute, Shaanxi University of Technology, No. 1 Dongyi Road, Hanzhong, Shaanxi, 723000, People's Republic of China



Diplophyllum apiculatum



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Deoxybenzoin and flavan derivatives from the twigs of *Artocarpus lakoocha*

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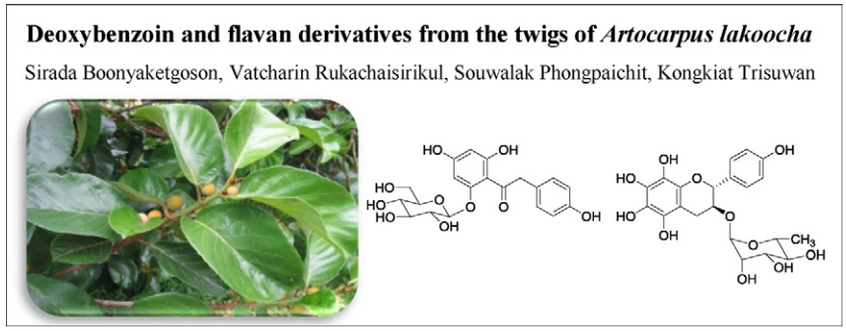
Sirada Boonyaketgoson[a,c], Vatcharin Rukachaisirikul[d], Souwalak Phongpaichit[e], Kongkiat Trisuwan[a,b,*]

[a]Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Chiang Mai University, Chiang Mai, 50200, Thailand
[b]Research Center on Chemistry for Development of Health Promoting Products from Northern Resources, Chiang Mai University, Chiang Mai, 50200, Thailand
[c]Graduate School, Chiang Mai University, Chiang Mai, 50200, Thailand
[d]Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla, 90112, Thailand
[e]Department of Microbiology, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla, 90112, Thailand



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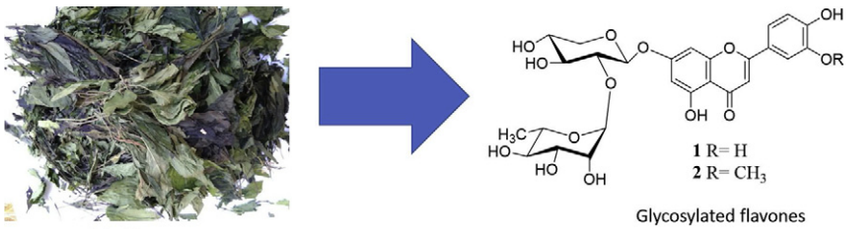
[a]Centre for Natural Products Discovery (CNPD), School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, James Parsons Building, Byrom Street, Liverpool, L3 3AF, UK
[b]Institute of Medical Research and Medicinal Plants Studies, Ministry of Scientific Research and Innovation, PO Box 6163, Yaoundé, Cameroon



Evaluation of the variables altitude, soil composition and development of a predictive model of the antibacterial activity for the genus *Hypericum* by chromatographic fingerprint

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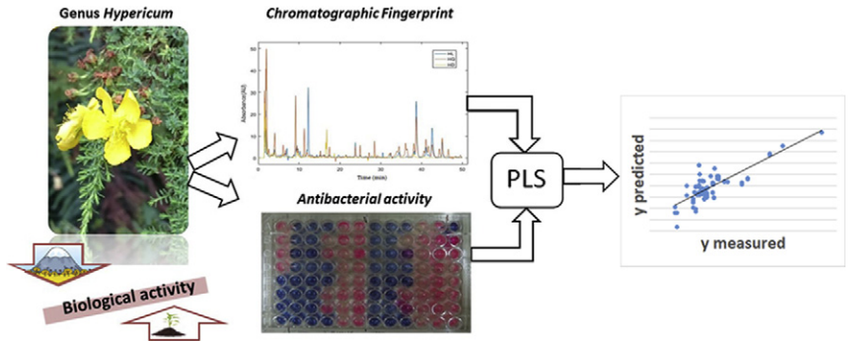
[a]*Department of Biosciences, Faculty of Chemical Sciences, Universidad de Cuenca, Av. 12 de Abril, Cuenca, Ecuador*
[b]*ESPOL Escuela Superior Politécnica del Litoral, ESPOL, Centro de Investigaciones Biotecnológicas del Ecuador, Campus Gustavo Galindo Km. 30.5 Vía Perimetral, P.O. Box 09-01-5863, Guayaquil, Ecuador*
[c]*ESPOL P, Escuela Superior Politécnica del Litoral, ESPOL, Facultad de Ciencias de la Vida, Campus Gustavo Galindo Km. 30.5 Vía Perimetral, P.O. Box 09-01-5863, Guayaquil, Ecuador*



Cyclopalitins A and B, nortriterpenoids from aerial parts of *Cyclocarya paliurus*

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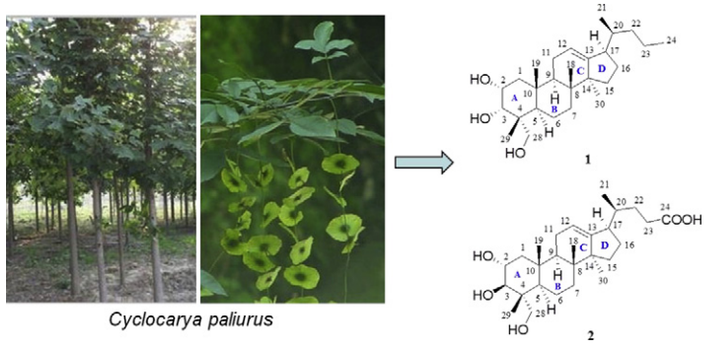
Wenwen Peng[a,c,*], Simeng Zhao[b], Changjiu Ji[d], Guanghua Huo[a], Chunpeng Wan[c], Yuyan Li[c], Yanling Zhang[c]

[a]*Jiangxi Key Laboratory for Conservation and Utilization of Fungal Resources, Jiangxi Agricultural University, Nanchang, 330045, China*
[b]*Ihuman institute, Shanghaitech Universisity, Shanghai, 201210, China*
[c]*College of Agriculture, Jiangxi Agricultural University, Nanchang, 330045, China*
[d]*Jiangxi Yichun University, Yichun, 336000, China*



Two new antiplasmodial flavonolignans from the leaves of *Cecropia obtusifolia*

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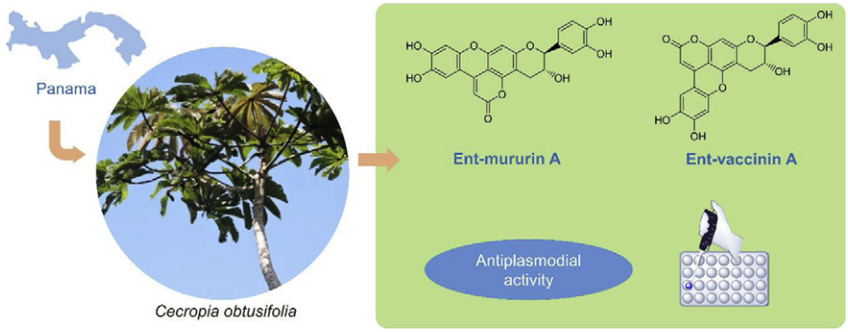
Andrés Rivera-Mondragón[a,*], Emmy Tuenter[a], Sebastiaan Bijttebier[a,b], Paul Cos[c], Sandra Apers[a], Catherina Caballero-George[d], Kenn Foubert[a], Luc Pieters[a]

[a]*Natural Products & Food Research and Analysis (NatuRA), Department of Pharmaceutical Sciences, University of Antwerp, Universiteitsplein 1, 2610, Antwerp, Belgium*
[b]*Flemish Institute for Technological Research (VITO), Business Unit Separation and Conversion Technology (SCT), Mol, Belgium*
[c]*Laboratory of Microbiology, Parasitology and Hygiene (LMPH), Faculty of Pharmaceutical, Biomedical and Veterinary Sciences, University of Antwerp, Universiteitsplein1, B-2610, Antwerp, Belgium*
[d]*Centre of Innovation and Technology Transfer, Institute of Scientific Research and High Technology Services (INDICASAT-AIP), Building 208, City of Knowledge, Panama*



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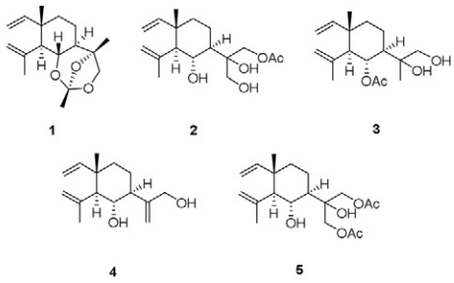
Lin-Fen Ding[a,b], Jiang-Xin Liu[a], Zhang-Qiao Xie[a,b], De-Shen Wang[a,b], Wei Nie[a,b], Liu-Dong Song[b], Xing-De Wu[a,*], Qin-Shi Zhao[a,*]

[a]*State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650201, China*
[b]*School of Pharmaceutical Science & Yunnan Key Laboratory of Pharmacology for Natural Products, Kunming Medical University, Kunming 650500, China*

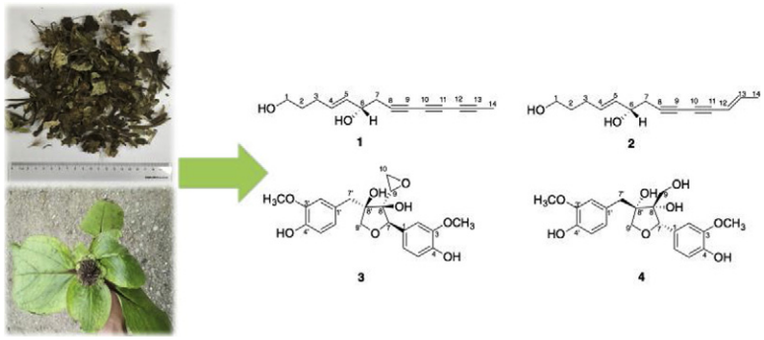


New acetylenic compounds and lignans from *Dolomiaea berardioidea* (Franch.) Shih

Phytochemistry Letters 31 (2019) pp. 125–130

Ying-Ying Huang[1], Xin Qiu[1], Yang-Guo Xie, Guo-Jing Wu, Sheng-Lan Zhu, Wei-Dong Zhang, Yan Zhang[*], Chen Dai-Jie[*], Hui-Zi Jin[*]

School of Pharmacy, Shanghai Jiao Tong University, Shanghai, 200240, PR China

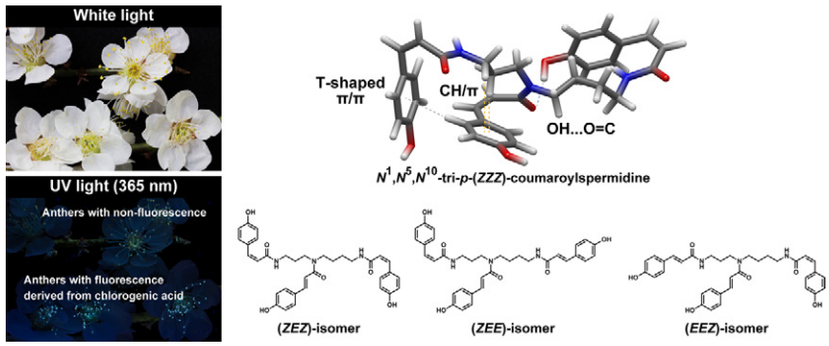


The unusual conformational preference of N^1,N^5,N^{10}-tri-*p*-coumaroylspermidine *E-Z* isomers from the Japanese apricot tree, *Prunus mume*, for the (*ZZZ*)-form

Phytochemistry Letters 31 (2019) pp. 131–139

Shinnosuke Mori[a,*], Miki Akamatsu[a], Hiroshi Fukui[b,1], Junko Tsukioka[c], Katsumi Goto[c,1], Nobuhiro Hirai[a]

[a]*Graduate School of Agriculture, Kyoto University, Kitashirakawa Oiwake-cho, Sakyo-ku, Kyoto, 606-8502, Japan*
[b]*Faculty of Agriculture, Kagawa University, 2393 Ikenobe, Miki, Kagawa, 761-0795, Japan*
[c]*The Garden of Medicinal Plants, Kyoto Pharmaceutical University, 39 Hinohayashi, Fushimi-ku, Kyoto, 601-1405, Japan*

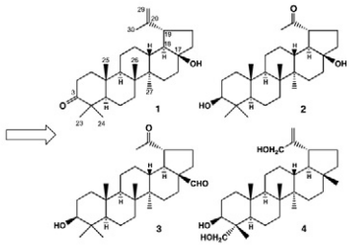


Four new triterpenoids from the bark of *Euonymus alatus* forma *ciliato-dentatus*

Phytochemistry Letters 31 (2019) pp. 140–146

Hiroshi Yamashita[a,*], Madoka Matsuzaki[a], Yuria Kurokawa[a], Takahisa Nakane[b], Masuo Goto[c], Kuo-Hsiung Lee[c,d], Toshiro Shibata[e], Hideo Bando[a], Koji Wada[a]

[a]*Hokkaido University of Science, Faculty of Pharmaceutical Sciences, 4-1, 7-jo 15-choume, Maeda, Teine-ku, Sapporo, 006-8590, Japan*
[b]*Showa Pharmaceutical University, 3-3165, Higashi Tamagawa Gakuen, Machida, Tokyo, 194-8543, Japan*
[c]*Natural Products Research Laboratories, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, NC, 27599-7568, USA*
[d]*Chinese Medicine Research and Development Center, China Medical University and Hospital, Taichung, 40402, Taiwan*
[e]*Tsukuba Division, Research Center for Medicinal Plant Resources, National Institute of Biomedical Innovation, Health and Nutrition, 1-2, Hachimandai, Tsukuba, Ibaraki, 305-0843, Japan*

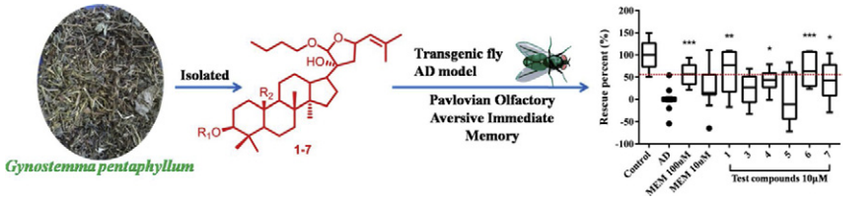


Dammarane-type saponins from *Gynostemma pentaphyllum* and their potential anti-AD activity

Phytochemistry Letters 31 (2019) pp. 147–154

Jun Wang[a,b], Cai-Hong Li[a,b], Mahdi Moridi Farimani[c], Jun-Li Yang[a,*]

[a]*CAS Key Laboratory of Chemistry of Northwestern Plant Resources and Key Laboratory for Natural Medicine of Gansu Province, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences (CAS), Lanzhou, 730000, PR China*
[b]*University of Chinese Academy of Sciences, Chinese Academy of Sciences, Beijing, 100049, PR China*
[c]*Department of Phytochemistry, Medicinal Plants and Drugs Research Institute, Shahid Beheshti University, Evin, Tehran, Iran*



Isolation and structure elucidation of secondary metabolites of two Greek endemic *Inula* species. Biological activities

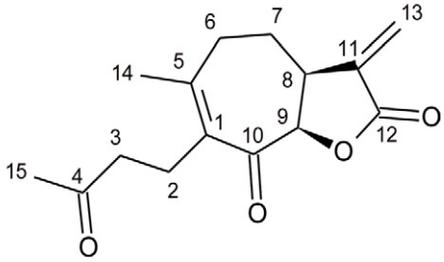
Phytochemistry Letters 31 (2019) pp. 155–160

Eleftheria Michalakea[a], Konstantia Graikou[a], Nektarios Aligiannis[a], George Panoutsopoulos[a], Eleftherios Kalpoutzakis[a], Christos Roussakis[b], Ioanna Chinou[a,*]

[a]*Division of Pharmacognosy & Chemistry of Natural Products, Department of Pharmacy, School of Health Sciences, National and Kapodistrian University of Athens, Panepistimiopolis-Zografou, Athens GR-15771, Greece*
[b]*IICiMED/EA 1155 - Département Cancer du Poumon et Cibles Moléculaires, UFR Sciences Pharmaceutiques - 9 rue Bias, Nantes cedex 1, France*

Inula candida subsp. *decalvans*

Inula candida subsp. *candida*

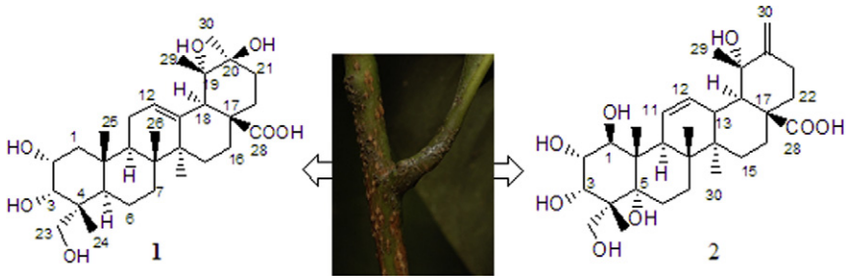


Two new polyhydroxylated pentacyclic triterpenes with cytotoxic activities from *Manilkara pellegriniana* (Sapotaceae)

Phytochemistry Letters 31 (2019) pp. 161–165

Linda D.K. Mogue[a], Patrick Y. Ango[a], Ghislain W. Fotso[a,*], Renameditswe Mapitse[c], Deccaux W.F.G. Kapche[b], Oğuzhan Karaosmanoğlu[e], Victor Kuete[d,e], Ibrahim Demirtas[f], Samuel O. Yeboah[c], Hülya Sivas[e], Ngadjui T. Bonaventure[a,**]

[a]*Faculty of Science, Department of Organic Chemistry, University of Yaoundé I, Cameroon*
[b]*Faculty of Science, Department of Chemistry, University of Botswana, Botswana*
[c]*Higher Teacher Training College, Department of Chemistry, University of Yaoundé I, Cameroon*
[d]*Faculty of Science, Department of Biochemistry, University of Dschang, Cameroon*
[e]*Faculty of Science, Department of Biology, Anadolu, University, Eskişehir, Turkey*
[f]*Faculty of Science, Department of Chemistry, Çankırı Karatekin University, Çankırı, Turkey*

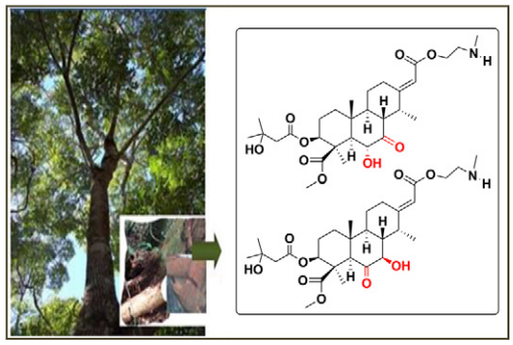


New cassane diterpenoids from the root bark of *Erythrophleum suaveolens*

Phytochemistry Letters 31 (2019) pp. 166–169

Jacques Dibi Konan[a,d], Barthélemy Koffi Attioua[a,*], Claude Landry Ahmont Kablan[a,b,c,d], Faustin Aka Kabran[a,d], Paul Armand Koffi[c], Sandrine Aka Any-Grah[c], Sissouma Drissa[a], Blandine Seon-Meniel[d], Karine LeBlanc[d], Jean-Christophe Jullian[d], Mehdi A. Beniddir[d]

[a]*Laboratoire de Chimie Organique et de Substances Naturelles, UFR Sciences des Structures de la Matière et Technologie, Université Félix Houphouët-Boigny, 22 BP 582 Abidjan 22, Cote d'Ivoire*
[b]*UFR des Sciences Biologiques, Université Peleforo Gon Coulibaly, BP 1328, Korhogo, Cote d'Ivoire*
[c]*Laboratoire de Pharmacie Galénique, Cosmétologie et Législation, UFR des Sciences Pharmaceutiques et Biologiques, Université Félix Houphouët-Boigny, 22 BP 714 Abidjan 22, Cote d'Ivoire*
[d]*Laboratoire de Pharmacognosie, BioCIS, Univ. Paris-Sud, CNRS, Université Paris-Saclay, Faculté de Pharmacie, 5 rue J.-B. Clément, 92290, Châtenay-Malabry, France*

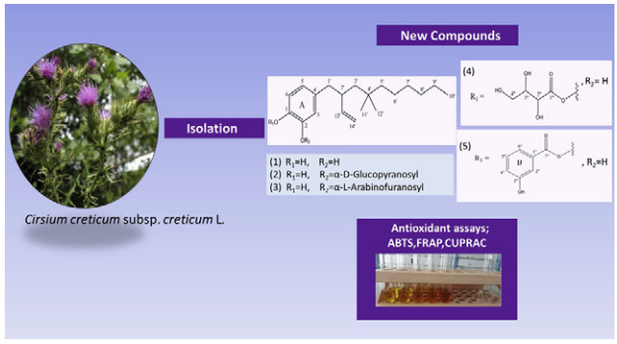


Antioxidant activity of five new phenolic compounds from *Cirsium creticum* subsp. *creticum*

Phytochemistry Letters 31 (2019) pp. 181–186

Temine Sabudak[a,*], Merve Ozer[a], H. Hulya Orak[b], Hilmican Caliskan[a]

[a]*Department of Chemistry, Faculty of Science and Arts, Namik Kemal University, 59030 Tekirdag, Turkey*
[b]*Department of Food Technology, Vocational School of Technical Sciences, Namik Kemal University, 59030 Tekirdag, Turkey*

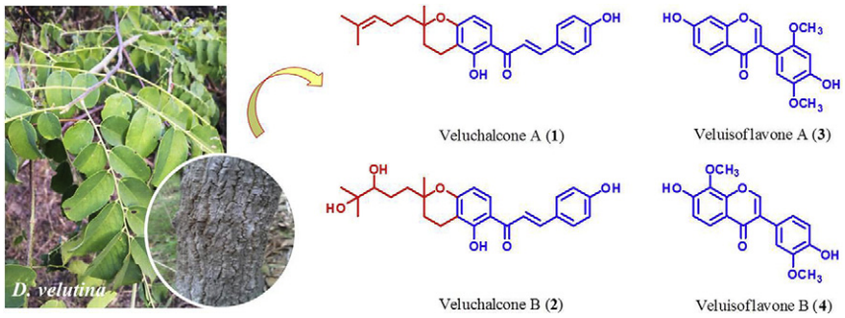


Cytotoxic chalcones and isoflavones from the stems of *Dalbergia velutina*

Phytochemistry Letters 31 (2019) pp. 187–191

Sutin Kaennakam[a,*], Edwin Risky Sukandar[a], Kitiya Rassamee[b], Pongpun Siripong[b], Santi Tip-pyang[a,*]

[a]*Center of Excellence in Natural Products Chemistry, Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok, 10330, Thailand*
[b]*Natural Products Research Section, Research Division, National Cancer Institute, Bangkok, 10400, Thailand*

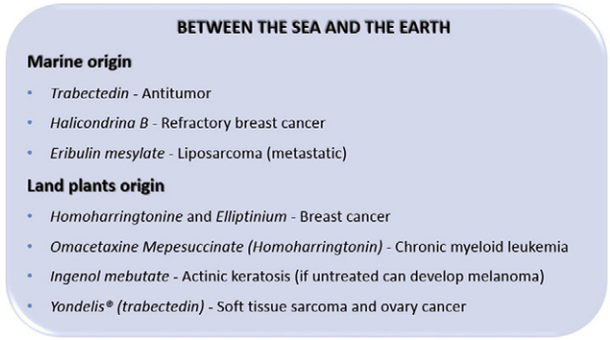


Medicinal plants and bioactive natural compounds for cancer treatment: Important advances for drug discovery

Phytochemistry Letters 31 (2019) pp. 196–207

Fernanda Majolo[a,b,1], Luciana Knabben de Oliveira Becker Delwing[a,1], Diorge Jônatas Marmitt[a], Ivan Cunha Bustamante-Filho[c], Márcia Inês Goettert[a,*]

[a]*Laboratório de Cultura de Células, Centro de Ciências Biológicas e da Saúde, Universidade do Vale do Taquari - Univates, Lajeado, RS, Brazil*
[b]*Instituto do Cérebro do Rio Grande do Sul (InsCer), Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil*
[c]*Laboratório de Biotecnologia, Universidade do Vale do Taquari - UNIVATES, Lajeado, RS, Brazil*

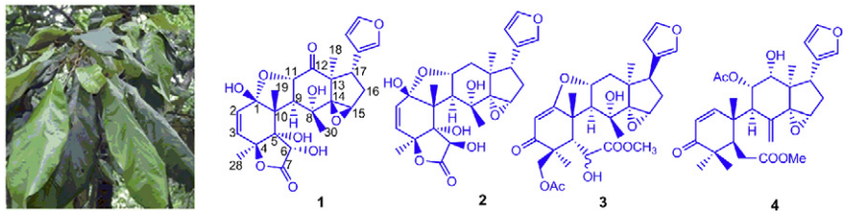


Toonamicronoids A–D, four new B-*seco*-limonoids from *Toona microcarpa*

Phytochemistry Letters 31 (2019) pp. 225–228

Ling Zhang[a,b,1], Jianjun Xia[a,1], Jianyun Yang[a], Long Zhu[a], Danyu Tang[a], Ji Ma[b], Yingliang Zhao[a], Xiaoying Zeng[a], Minghua Qiu[b,*]

[a]*R&D Center of China Tabacco Yunnan Industrial Co., Ltd. Kunming, 650202, China*
[b]*Kunming Institute of Botany, Chinese Academy of Sciences, Kunming, 650201, China*

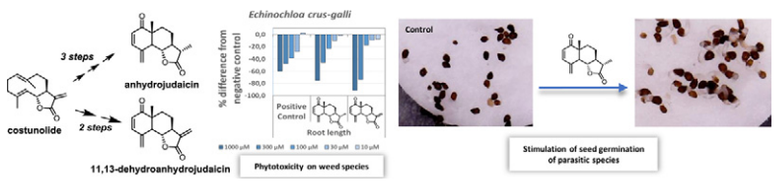


Facile synthesis of anhydrojudaicin and 11,13-dehydroanhydrojudaicin, two eudesmanolide-skeleton lactones with potential allelopathic activity

Phytochemistry Letters 31 (2019) pp. 229–236

Jesús G. Zorrilla, Carlos Rial, Rosa M. Varela, José M.G. Molinillo, Francisco A. Macías[*]

Allelopathy Group, Department of Organic Chemistry, Institute of Biomolecules (INBIO), Campus CEIA3, School of Science, University of Cadiz, C/ Republica Saharaui, 7, 11510, Puerto Real, Cádiz, Spain

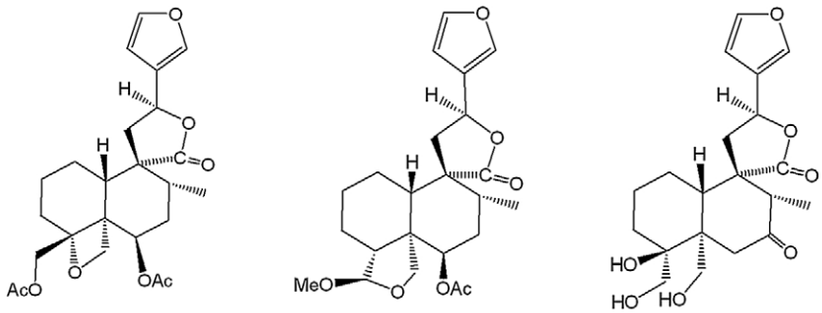


Neo-clerodane diterpenoids from *Teucrium polium* subsp. *vincentinum* (rouy) D. Wood

Phytochemistry Letters 31 (2019) pp. 237–241

Petko I. Bozov[a,*], Plamen N. Penchev[b]

[a]Department of Biochemistry and Microbiology, Plovdiv University, 24 Tsar Asen Str., 4000, Plovdiv, Bulgaria
[b]Department of Analytical Chemistry, Plovdiv University, 24 Tsar Asen Str., 4000, Plovdiv, Bulgaria



Three new constituents from the fungus of *Monascus purpureus* and their anti-inflammatory activity

Phytochemistry Letters 31 (2019) pp. 242–248

Ho-Cheng Wu[a], Ming-Jen Cheng[b,*], Ming-Der Wu[b], Jih-Jung Chen[c,d], Yen-Lin Chen[b], Hsun-Shuo Chang[a,e,**]

[a]Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, 807, Taiwan
[b]Bioresource Collection and Research Center (BCRC), Food Industry Research and Development Institute (FIRDI), Hsinchu, 300, Taiwan
[c]Faculty of Pharmacy, School of Pharmaceutical Sciences, National Yang-Ming University, Taipei, 112, Taiwan
[d]Department of Medical Research, China Medical University Hospital, China Medical University, Taichung, 40447, Taiwan
[e]School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, 807, Kaohsiung, Taiwan

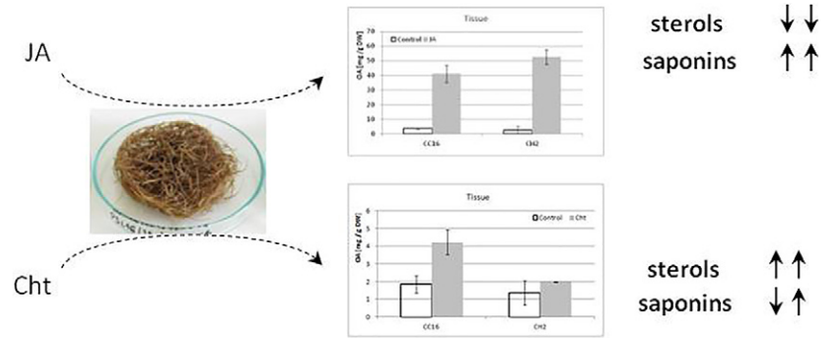
SPECIAL SECTION: INTERNATIONAL SYMPOSIUM ON CHROMATOGRAPHY OF NATURAL PRODUCTS (ISCNP 2018)

Effect of jasmonic acid and chitosan on triterpenoid production in *Calendula officinalis* hairy root cultures

Phytochemistry Letters 31 (2019) pp. 5–11

Abdulwadood Shakir Mahmood Alsoufi[a,b], Cezary Pączkowski[b], Anna Szakiel[b], Marek Długosz[b,*]

[a]Department of Biology, College of Science, University of Tikrit, P.O. Box 42, Iraq
[b]Department of Plant Biochemistry, Faculty of Biology, University of Warsaw, ul. Miecznikowa 1, 02-096, Warszawa, Poland

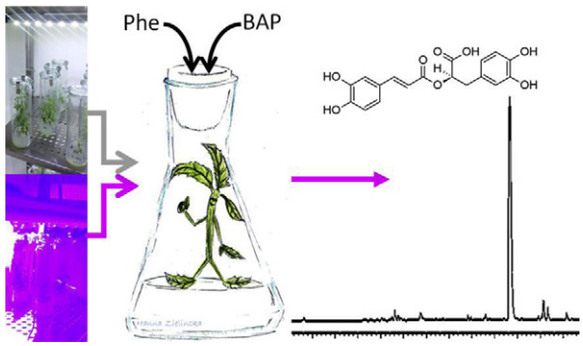


Effect of LED illumination and amino acid supplementation on phenolic compounds profile in *Agastache rugosa in vitro* cultures

Phytochemistry Letters 31 (2019) pp. 12–19

Sylwia Zielińska[a], Andrzej Dryś[b], Ewelina Piątczak[c], Joanna Kolniak-Ostek[d], Marta Podgórska[e], Jan Oszmiański[d], Adam Matkowski[a,f,*]

[a]Department of Pharmaceutical Biology, Wroclaw Medical University, Borowska 211, 50-556, Wroclaw, Poland
[b]Department of Physical Chemistry, Wroclaw Medical University, Borowska 211A, 50-556, Wroclaw, Poland
[c]Department of Biology and Pharmaceutical Botany, Medical University of Łodz, Muszynskiego 1, 90-151, Łodz, Poland
[d]Department of Fruit and Vegetable Technology, Wrocław University of Environmental and Life Sciences, J. Chelmonskiego 37/41, 51-630, Wroclaw, Poland
[e]Student Scientific Club no K76, Department of Pharmaceutical Biology, Wroclaw Medical University, Wroclaw, Poland
[f]Laboratory for Experimental Cultivation of Medicinal Herbs, Botanical Garden of Medicinal Plants, Wroclaw Medical University, Al. Jana Kochanowskiego 10/12/14, Poland

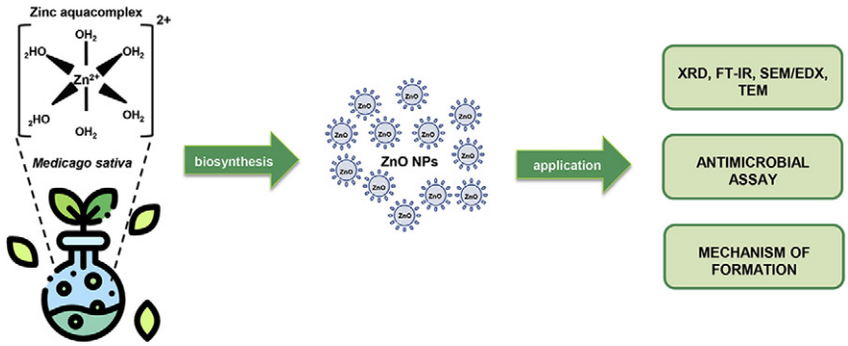


Phytochemical investigation of *Medicago sativa* L. extract and its potential as a safe source for the synthesis of ZnO nanoparticles: The proposed mechanism of formation and antimicrobial activity

Phytochemistry Letters 31 (2019) pp. 170–180

A. Król[a,b], V. Railean-Plugaru[a,b], P. Pomastowski[b], B. Buszewski[a,b,*]

[a]Chair of Environmental Chemistry and Bioanalytics, Faculty of Chemistry, Nicolaus Copernicus University in Torun, 7 Gagarina Str., 87-100, Torun, Poland
[b]Centre for Modern Interdisciplinary Technologies, Nicolaus Copernicus University in Torun, 7 Gagarina Str., 87-100, Torun, Poland

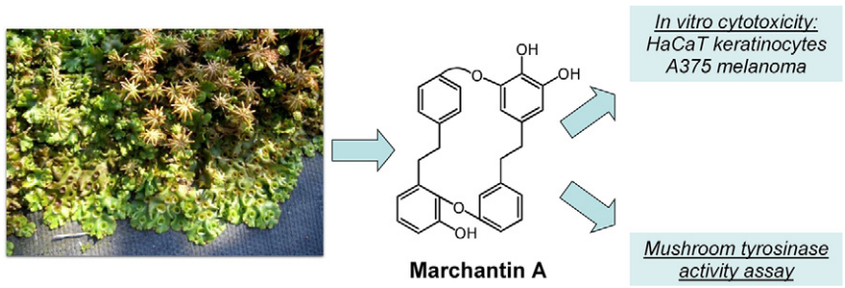


Evaluation of anti-melanoma and tyrosinase inhibitory properties of marchantin A, a natural macrocyclic bisbibenzyl isolated from *Marchantia* species

Phytochemistry Letters 31 (2019) pp. 192–195

Katarzyna Gaweł-Bęben[a,*], Paweł Osika[a], Yoshinori Asakawa[b], Beata Antosiewicz[a], Kazimierz Głowniak[a], Agnieszka Ludwiczuk[c]

[a]Department of Cosmetology, The University of Information Technology and Management in Rzeszow, Sucharskiego 2, 35-225, Rzeszów, Poland
[b]Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho 180, 770-8514, Tokushima, Japan
[c]Department of Pharmacognosy with Medicinal Plant Unit, Medical University of Lublin, Chodźki 1, Lublin, 20-093, Poland

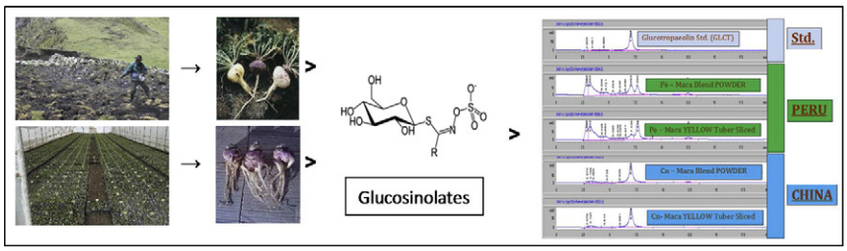


Glucosinolates profiles in Maca phenotypes cultivated in Peru and China (*Lepidium peruvianum* syn. *L. meyenii*)

Phytochemistry Letters 31 (2019) pp. 208–216

Henry O. Meissner[a,*], Lijia Xu[b], Wenting Wan[b], Fan Yi[b]

[a]Faculty of Health Studies, Charles Sturt University & Therapeutic Research, TTD International Pty Ltd, 39 Leopard Ave., Elanora, QLD, 4221, Australia
[b]Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences, Peking Union Medical College, 151 Malianwa N, Haidian District, Beijing, 100193, China

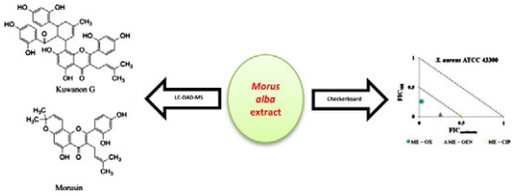


Morus alba leaf extract: Metabolite profiling and interactions with antibiotics against *Staphylococcus* spp. including MRSA

Phytochemistry Letters 31 (2019) pp. 217–224

Petruta Aelenei[a,b], Simon Vlad Luca[a,*], Cristina Elena Horhogea[c], Cristina Mihaela Rimbu[c], Gabriel Dimitriu[d], Irina Macovei[a,e], Mihaela Silion[f], Ana Clara Aprotosoaie[a], Anca Miron[a]

[a]Department of Pharmacognosy, Faculty of Pharmacy, Grigore T. Popa University of Medicine and Pharmacy Iasi, Universitatii Str. 16, Iasi 700115, Romania
[b]Regulatory Affairs Department, Fiterman Pharma LLC, Pacurari Road 127, Iasi 700544, Romania
[c]Department of Public Health, Faculty of Veterinary Medicine, Ion Ionescu de la Brad University of Agricultural Sciences and Veterinary Medicine of Iasi, Mihail Sadoveanu Al. 8, Iasi 700489, Romania
[d]Department of Medical Informatics and Biostatistics, Faculty of Medicine, Grigore T. Popa University of Medicine and Pharmacy Iasi, Universitatii Str. 16, Iasi 700115, Romania
[e]Department of Drug Analysis, Faculty of Pharmacy, Grigore T. Popa University of Medicine and Pharmacy Iasi, Universitatii Str. 16, Iasi 700115, Romania
[f]Laboratory of Polymer Materials Physics, Petru Poni Institute of Macromolecular Chemistry, Grigore Ghica Voda Al. 41A, Iasi 700487, Romania

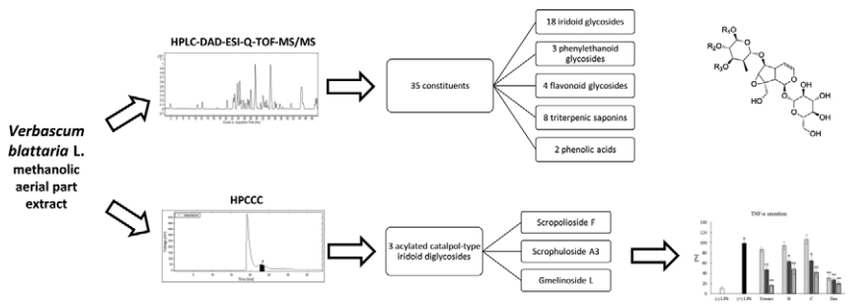


Inhibition of cytokine secretion by scrophuloside A_3 and gmelinoside L isolated from *Verbascum blattaria* L. by high-performance countercurrent chromatography

Phytochemistry Letters 31 (2019) pp. 249–255

Simon-Vlad Luca[a,b,*], Monika Ewa Czerwińska[c], Laurent Marcourt[e], Anca Miron[a], Ana Clara Aprotosoaie[a], Nina Ciocarlan[d], Jean-Luc Wolfender[e], Sebastian Granica[c], Krystyna Skalicka-Woźniak[b]

[a]Department of Pharmacognosy, Grigore T. Popa University of Medicine and Pharmacy Iasi, Universitatii 16, 700115, Iasi, Romania
[b]Department of Pharmacognosy with Medicinal Plant Unit, Medical University of Lublin, Chodźki 1, 20-093, Lublin, Poland
[c]Department of Pharmacognosy and Molecular Basis of Phytotherapy, Medical University of Warsaw, Banacha 1, 02-097, Warsaw, Poland
[d]Botanical Garden, Academy of Sciences of Moldova, Padurii 18, MD-2002, Chisinau, Republic of Moldova
[e]School of Pharmaceutical Sciences, EPGL, University of Geneva, University of Lausanne, CMU, Michel Servet 1, 1211, Geneva 4, Switzerland

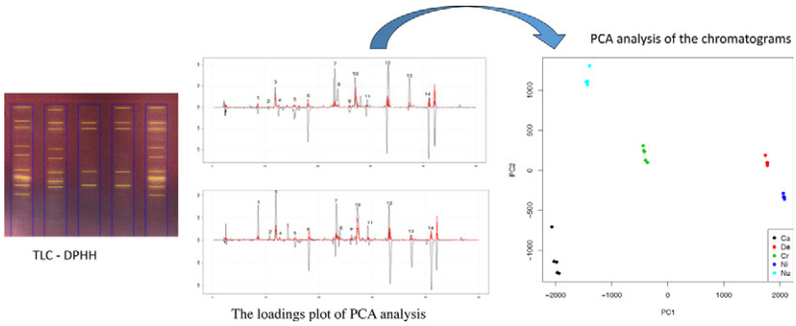


Analysis of phenolic compounds and antioxidant activity of methanolic extracts from inflorescences of *Carduus* sp

Phytochemistry Letters 31 (2019) pp. 256–262

Małgorzata Kozyra[a,*], Łukasz Komsta[b], Krzysztof Wojtanowski[a]

[a]*Chair and Department of Pharmacognosy with Medicinal Plant Unit, Medical University of Lublin, 1 Chodźki St., 20-093, Lublin, Poland*
[b]*Department of Medicinal Chemistry, Medical University of Lublin, Jaczewskiego 4, 20-090, Lublin, Poland*



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Meroterpenoids produced by *Pseudocosmospora* sp. Bm-1-1 isolated from *Acanthus ebracteatus* Vahl

Tomoki Nakamura[a], Takuma Suzuki[a], Nanang Rudianto Ariefta[b], Takuya Koseki[a], Takako Aboshi[a], Tetsuya Murayama[a], Ari Widiyantoro[c], Rikhsan Kurniatuhadi[c], Abdul Malik[d], Suwardi Annas[d], Desi Harneti[e], Rani Maharani[e], Unang Supratman[e], Junpei Abe[f], Naoaki Kurisawa[f], Ken-ich Kimura[b,f], Yoshihito Shiono[a,b,*]

[a] Department of Food, Life, and Environmental Science, Faculty of Agriculture, Yamagata University, Tsuruoka, Yamagata, 997-8555, Japan
[b] The United Graduate School of Agricultural Sciences, Iwate University, Morioka, Iwate, 020-8550, Japan
[c] Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Tanjungpura, Pontianak, 78124, Indonesia
[d] Department of Geography, Faculty of Mathematics and Natural Sciences Universitas Negeri Makassar, Makassar, 90224, Indonesia
[e] Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran, Sumedang 45363, Indonesia
[f] Graduate School of Arts and Sciences, Graduate Course in Biological Chemistry and Food Sciences, Iwate University, Morioka, Iwate, 020-8550, Japan

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ABSTRACT

Fractionation of ethyl acetate extract obtained by culturing the endophytic fungus *Pseudocosmospora* sp. Bm-1-1 resulted in the isolation of four new meroterpenoids, cosmosporin A (**1**), 6-carboxy-cosmosporin A (**2**), *rel*-(6a*S*,10a*R*)-Δ^9-tetrahydrocannabiorcolic acid B (**3**) and 8′-hydroxy-cannabiorcichromenic acid (**4**), in addition to four known compounds **5–8**. Structures were elucidated by spectral analysis, as well as by directly comparing the spectral data of new compounds with those of known compounds. Cannabiorcichromenic acid (**5**), decarboxy-cannabiorcichromenic acid (6), and *rel*-(6a*S*,10a*R*)-decarboxy-Δ^9-tetrahydrocannabiorcolic acid B (**8**) restored growth of a *Saccharomyces cerevisiae* mutant strain involving Ca^{2+} signal transduction. Furthermore, compounds **3** and **8** had cytotoxic activity against HL60 cells (**3**: IC_{50} = 24.1 μM and **8**: IC_{50} 1.6 μM).

1. Introduction

Endophyte fungi are known to produce many different types of secondary metabolites with a wide variety of biological activities such as antimicrobial, antimalarial, cytotoxic and antioxidant activities. Our previous work on the mangrove endophytic fungus *Cosmospora vilior* IM2-155 resulted in the isolation of the dichroloresorcinol derivatives cosmochlorins A, B, and C. Cosmochlorins A and B inhibit glycogen synthase kinase (GSK)-3β activity (Shiono et al., 2016). These unique halogenated compounds, cosmochlorins, accumulated only in culture media containing 3% NaCl. This indicated that in *C. vilior* IM2-155, metabolite production was significantly influenced by the presence of NaCl in the culture media (Shiono et al., 2016). In this regard, it is not surprising that the metabolite profiles of chemically prolific endophytes from marine origins are modulated by environmental NaCl, and also that these species tolerate high concentrations of salt (Gogoi et al., 2008; Orfali et al., 2015). Because fungal endophytes are most often isolated from terrestrial plants, rather than from those of marine origin, we have chosen to focus on marine-derived fungi in order to yield a wide variety of novel metabolites that may possess differential biological effects than those produced by terrestrial species.

In continuing study of bioactive compounds from microorganisms isolated from mangrove plants, the fungal strain *Pseudocosmospora* sp. Bm-1-1 was isolated from *Acanthus ebracteatus* Vahl collected in Pontianak, Indonesia. This mangrove plant belongs to the *Acanthaceae* family (Tomlinson, 1986). This plant is a shrub with ranging from 50 to 120 cm tall and naturally reproduces vegetatively and also by seeds, thus generation length is difficult to determine for this plant (Robertson and Alongi, 1992). They are often sympatric with *Acanthus ilicifolius* L. and inhabit in all soil type, especially muddy areas along the mid to high intertidal regions of South and Southeast Asia (India, Brunei Darussalam, China, South Taiwan, India, Malaysia, Philippines, Singapore, Thailand, Viet Nam, Cambodia, and Indonesia) and Australasia (northeast and northwest Australia, Papua New Guinea, and the

* Corresponding author at: Department of Food, Life, and Environmental Science, Faculty of Agriculture, Yamagata University, Tsuruoka, Yamagata, 997-8555, Japan.
E-mail address: yshiono@tds1.tr.yamagata-u.ac.jp (Y. Shiono).

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Solomon Island) (Ellison et al., 2010).

Chemical investigation undertaken on the fermented extract of this fungus led to the isolation of four new compounds, cosmosporin A (**1**), 6-carboxy-cosmosporin A (**2**), an analogue of tetrahydrocannabiorcolic acid B (**3**), and 8′-hydroxy-cannabiorcichromenic acid (**4**). The extract also contained four known compounds, cannabiorcichromenic acid (**5**), decarboxy-cannabiorcichromenic acid (**6**), 6-carboxyl-4-dechloro-ascochlorin (**7**), and *rel*-(6a*S*,10a*R*)-decarboxy-Δ^9-tetrahydro cannabiorcolic acid B (**8**). The present report concerns the isolation and structural determination of the new compounds, including spectral data for **7**, which has not been previously reported in the primary literature, and the compounds' activities against Ca^{2+} signal transduction in mutant yeast and HL60 cells.

2. Results and discussion

A large fermentation of *Pseudocosmospora* sp. Bm-1-1 was conducted in unpolished rice medium. A crude MeOH extract was prepared from the fermented media, and was separated by column chromatography, followed by flash column chromatography or HPLC purification to yield compounds **1**-**8**. Based on the NMR and HRESITOFMS data and comparison to the reported data, three known compounds were identified as cannabiorcichromenic acid (**5**), decarboxy-cannabiorcichromenic acid (**6**) (Quaghebeur et al., 1994; Liu et al., 2013), *rel*-(6a*S*,10a*R*)-decarboxy-Δ^9-tetrahydrocannabiorcolic acid B (**8**) (Zhou et al., 2007) (Fig. 1). The detailed structural elucidations of the new compounds and **7** are described below.

Cosmosporin A (**1**) was obtained as a white amorphous powder. Its molecular formula was determined by HRESITOFMS to be $C_{22}H_{34}O_4$, with six degrees of unsaturation. The UV spectrum of **1** showed absorption maxima bands at 274 and 282 nm, indicating the presence of an aromatic moiety. The IR spectrum showed absorption at 3310 cm^{-1}, indicating the presence of hydroxyl group. The ^{13}C NMR spectral data (Table 1) of **1** displayed 22 carbons, including five methyls, five methylenes, four methines, and eight quaternary carbons identified using a DEPT experiment. The ^1H NMR spectral data (Table 2) of **1** displayed characteristic signals for a singlet aromatic methine [δ_H 6.21 (2H, s, H-4 and H-6)], suggesting the presence of a symmetrical 1,2,3,5-tetra-substituted benzene ring, as well as resonances for three tertiary olefinic methyls at δ_H 1.57 (s, H-14′), 2.16 (s, Me-7) and 1.75 (s, H-15′); two tertiary methyls at δ_H 1.14 (s, H-12′) and 1.19 (s, H-13′); two olefinic methine protons at δ_H 5.18 (t, J = 6.0 Hz, H-2′) and 5.10 (t, J = 6.0 Hz, H-6′); an oxymethine proton at δ_H 3.37 (dd, J = 10.2, 1.2 Hz, H-10′) and five methylenes at δ_H 1.37–1.41 (*m*, H-9′), 2.04–2.07 (m, H-4′ and H-8′), 2.09–2.14 (m H-5′), 2.17–2.20 (m, H-8′), 3.35 (d, J = 6.6 Hz, H-1′) and 1.37–1.41 (*m*, H-9′). The HMBC correlations (Fig. 2) from Me-7 to C-4, C-5 and C-6, and from H-4 to C-2 and C-6, and from H-1′ to C-1 and C-3 indicated the presence of a 1,3-dihydroxy-5-methyl-benzene ring moiety. The COSY spectrum indicated three partial structures including H-1′/H-2′, H-4′/H-5′/H-6′, and H-8′/H-9′/H-10′ units. The HMBC correlations from H-15′ to C-2′, C-3′ and C-4′, from H-14′ to C-6′, C-7′ and C-8′, and from H-12′ and H-13′ to C-10′ and C-11′, revealed a sesquiterpene moiety from C-1′ to C-15′ (Fig. 2). The *E* stereochemistry of trisubstituted Δ2′ and Δ6′ double bonds was determined based on the relative upfield shift of the vinylic methyl groups (C-14′ and C-15′) (Blunt et al., 1985). Finally, the absolute configuration at C-10′ in **1** was determined using the modified Mosher's method (Ohtani et al., 1991). The ^1H chemical-shift differences between the (*S*)-2-methoxy-2-phenyl-2-(trifluoromethyl) acetic acid (MTPA) esters (**1a**) of **1** and (*R*)-(**1b**) of **1** are shown in Fig. 3, and suggested the *R* configuration for C-10′, establishing the absolute structure of **1**.

6-Carboxy-cosmosporin A (**2**) was obtained as a white amorphous powder. Its molecular formula was deduced as $C_{23}H_{34}O_6$ from HRESITOFMS and ^{13}C NMR (Table 1) data. The IR spectrum indicated the presence of OH (3310 cm^{-1}) and carboxyl (1620 cm^{-1}) groups. Comparison of the NMR spectra of **2** with those of **1** showed that they were very similar expect for an additional carboxylic group (δ_C 174.3), the absence of signals assigned to symmetrical 1,2,3,5-tetrasubstituted benzene ring (δ_H 6.21, H-4 and H-6) in **1**, and the presence of characteristic signals of penta-substituted benzene rings at δ_H 6.17 (1H, s, H-4), δ_C 163.4 (C-1), 112.6 (C-2), 159.8 (C-3), 110.2 (C-4), 103.7 (C-5), and 140.6 (C-6). These observations indicated that the carboxylic group was at C-6, and this conclusion was supported by the HMBC spectrum (Fig. 2). Therefore, compound **2** was established as 6-carboxy-cosmosporin A. The absolute configuration of C-10′ in **2** was determined to be *R* by comparing the optical rotation value of **2** [$[\alpha]_D$ + 6.3°, (*c* 0.33, MeOH)] to those of **1** [$[\alpha]_D$ + 10.0°, (*c* 0.32, MeOH)]. Further, the similar metabolite, (*S*)-10′,11′-dihydroxyneogrifolic acid ($[\alpha]_D$ − 4.0°, (*c* 0.2, MeOH) differing from **2** in the aromatic substitution pattern and the *β*-hydroxyl group at C-10′ has been found in endophyte *Penicillium* sp. T2-8 (Duan et al., 2016).

Compound **3** was obtained as a white amorphous solid. Its molecular formula was established by HRESITOFMS to be $C_{18}H_{22}O_4$,

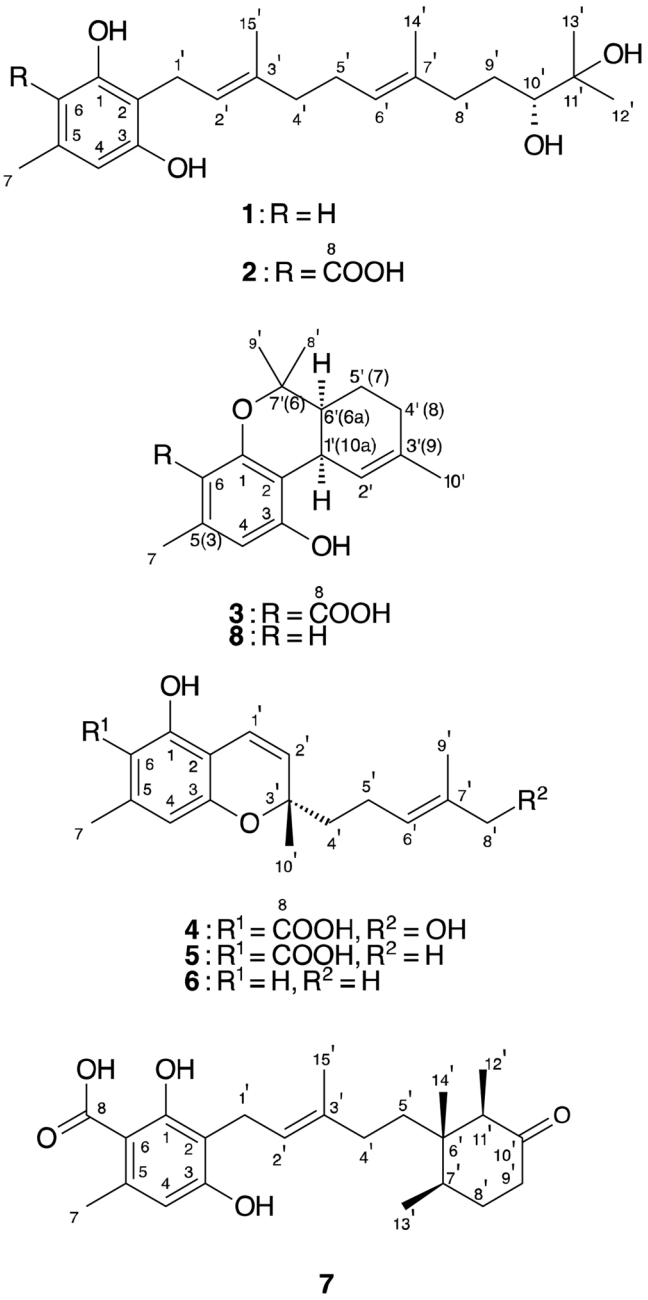

Fig. 1. Structures of compounds **1**-**8**.

Table 1
^{13}C NMR (150 MHz) spectroscopic data for compounds **1**–**4**, and **7**.

No.	**1**[1] δ_C	**2**[2] δ_C	**3**[2] δ_C	**4**[2] δ_C	**7**[2] δ_C
1	155.0 s	163.4 s	151.6 s	160.7 s	163.4 s
2	111.0 s	112.6 s	114.6 s	106.6 s	112.4 s
3	155.0 s	159.8 s	157.9 s	157.6 s	159.8 s
4	110.2 d	110.2 d	108.9 d	110.8 d	110.1 d
5	108.9 s	103.7 s	109.9 s	104.9 s	103.8 s
6	110.2 d	140.6 s	135.2 s	143.4 s	140.6 s
7	21.3 q	23.1 q	18.7 q	23.1 q	23.1 q
8		174.3 s	171.3 s	174.0 s	174.3 s
1’	22.2 t	21.4 t	31.4 d	116.6 d	21.5 t
2’	122.9 d	122.9 d	122.2 d	125.9 d	122.9 d
3’	135.2 s	133.8 s	135.2 s	79.3 s	134.2 s
4’	39.4 t	39.6 t	29.1 t	41.0 t	32.6 t
5’	25.6 t	26.3 t	20.7 t	22.0 t	35.5 t
6’	124.8 d	124.3 d	39.7 d	124.9 d	43.4 s
7’	137.4 s	134.5 s	77.2 s	134.9 s	35.7 d
8’	36.6 t	36.4 t	24.0 q	67.5 t	30.8 t
9’	29.3 t	29.4 t	24.7 q	26.0 q	41.0 t
10’	78.2 d	77.7 d	22.5 q	12.3 q	215.8 s
11’	73.6 s	72.6 s			50.1 d
12’	23.3 q	24.1 q			6.63 q
13’	26.4 q	23.8 q			14.0 q
14’	16.0 q	14.9 q			14.4 q
15’	16.0 q	15.0 q			15.1 q

[1] Recorded in $CDCl_3$.
[2] Recorded in CD_3OD.

suggesting eight degrees of unsaturation. The UV spectra, with absorption maxima at 220 and 261 nm, were indicative of a conjugated chromophore. The IR spectrum, with absorption bands at 3178 and 1700 cm^{-1}, suggested the presence of OH and carbonyl groups. The ^{1}H and ^{13}C NMR spectral data (Tables 1 and 2) revealed similarities to compounds **1**, **4** and **5**. The NMR spectral data of **3** indicated the presence of a penta-substituted benzene ring [δ_H 6.18 (s, H-4), δ_C 151.6 (C-1), 114.6 (C-2), 157.9 (C-3), 108.9 (C-4), 109.9 (C-5), and 135.2 (C-6)] (Fig. 4A). The presence of the 3′-methyl-2′-cyclohexene was supported by COSY and HMBC correlations (Fig. 4B). Substructures A and B were connected using key HMBC correlations, including H-1′ to C-2 and C-3, indicating a bond between C-2 and C-1′. The downfield chemical shift value for C-7′ supported oxygenation at this position. Therefore, the planar structure of **3** was assigned as shown in Fig. **1**. The relative configurations of C-1′ and C-6′ were assigned by analyzing ^{1}H-^{1}H coupling constants in an ^{1}H-^{1}H homonuclear decoupling experiment. Coupling constant (J = 5.0 Hz) was exhibited by H-1′ with H-6′ suggesting a *cis*–juncture of the pyran and cyclohexene rings. In addition, literature searches revealed that **3** is a new *cis* (rel-6a*S*,10a*R*) isomer of (6a*R*,10a*R*)-Δ^9-tetrahydrocannabiorcolic acid B described previously in the patent literature (Cooper and Levy, 2017). However, to our knowledge, the spectral data of (6a*R*,10a*R*)-Δ^9-tetrahydrocannabiorcolic acid B have not been reported in the primary literature.

8′-hydroxy-cannabiorcichromenic acid (**4**) was obtained as a white amorphous powder. Its molecular formula was determined by HRESITOFMS to be $C_{18}H_{22}O_5$. Comprehensive analysis of the ^{1}H and ^{13}C NMR spectroscopic data (Tables 1 and 2), as well as HSQC correlations, indicated the presence of three methyls, three methylenes, nine methines (four olefinic), and eight other carbons with no hydrogen attached (including one conjugated ketone group at δ_C 174.0). Two partial structures, H-1′/H-2′ and H-4′/H-5′/H-6′ were established by the ^{1}H–^{1}H COSY spectrum as shown in Fig. 2. A literature search showed that the NMR data of **4** was very similar to those of **5**, which was previously isolated from *Cylindrocarpon olidum* (Quaghebeur et al., 1994). The only difference between **4** and **5** was the presence of an oxymethylene signal [δ_H 3.85, δ_C 67.5] in **4** instead of a methyl group in **5**. The molecular formula of **4**, which has one more oxygen atom than that of **5**, and the HMBC correlations among the oxymethylene and C-6′and C-9′, suggesting that the hydroxyl group was attached at C-8′. The *E* stereochemistry of the trisubstitute Δ6′ double bond was determined based on the NOE correlations from H-9′ to H-5′ and from H-8′ to H-6′ (Fig. S28 and 29).

Compound **7** was obtained as a white amorphous powder. Its molecular formula was determined to be $C_{23}H_{32}O_5$ by HRESITOFMS. Compound **7** showed IR and UV spectra similar to those of **1**, indicating

Table 2
^{1}H NMR (600 MHz) spectroscopic data for compounds **1**–**4**, and **7**.

No.	**1**[1] δ_H (J in Hz)	**2**[2] δ_H (J in Hz)	**3**[2] δ_H (J in Hz)	**4**[2] δ_H (J in Hz)	**7**[2] δ_H (J in Hz)
4	6.21 s	6.17 s	6.18 s	6.14 s	6.17 s
6	6.21 s				
7	2.16 s	2.43 s	2.19 s	2.47 s	2.48 s
1’	3.35 d (6.6)	3.23 d (7.2)	3.51 m	6.66 d (10.2)	3.25 d (6.6)
2’	5.18 t (6.0)	5.18 t (6.0)	6.23 m	5.50 d (10.2)	5.25 t (6.0)
4’	2.04–2.07 m	1.91–1.94 m	1.85–1.94 m	1.64–1.73 m	1.84 td (12.6, 4.8) 1.97 td (12.6, 4.8)
5’	2.09–2.14 m	2.01–2.06 m	1.42–1.47 m 1.95–1.99 m	2.11 q (7.8)	1.33 ddd (16.2, 12.0, 4.8) 1.40 ddd (16.2, 12.0, 4.8)
6’	5.10 t (6.0)	5.12 t (6.0)	1.74 ddd (9.0, 5.0, 3.0)	5.35 t (7.2)	
7’					1.99–2.04 m
8’	2.04–2.07 m 2.17–2.20 m	1.91–1.94 m 2.16 ddd (14.4, 10.2, 4.8)	1.24 s	3.85 s	1.49–1.57 m 1.79–1.81 m
9’	1.37–1.41 m 1.56–1.61 m	1.28 m 1.63 m	1.35 s	1.58 s	2.16 ddd (13.8, 5.0, 1.2) 2.35 td (13.8, 5.0)
10’	3.37 dd (10.2, 1.2)	3.20 dd (10.2, 1.2)	1.63 s	1.35 s	
11’					2.55 q (6.0)
12’	1.14 s	1.09 s			0.85 d (6.0)
13’	1.19 s	1.16 s			0.83 d (6.0)
14’	1.57 s	1.55 s			0.50 s
15’	1.75 s	1.73 s			1.77 s

[1] Recorded in $CDCl_3$.
[2] Recorded in CD_3OD.

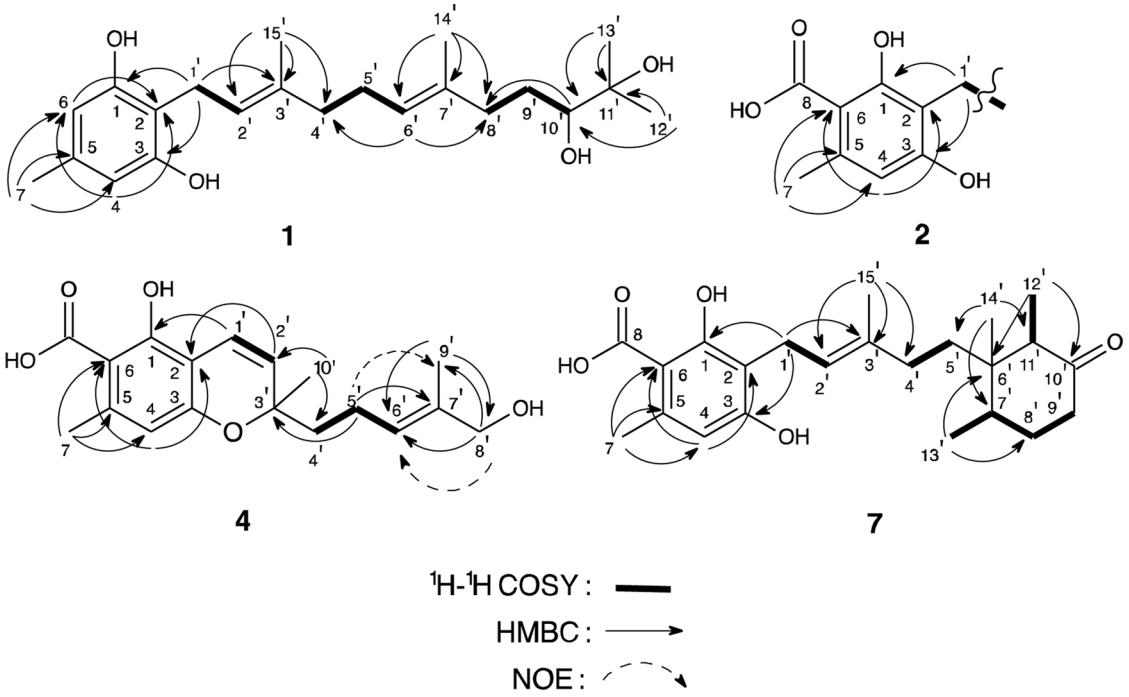

Fig. 2. Selected ^{1}H-^{1}H COSY and HMBC correlations for compounds **1**, **2**, **4** and **7** and NOEs correlations for compound **4**.

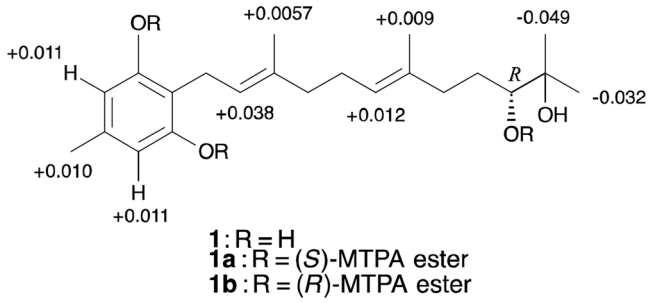

Fig. 3. Chemical shift differences for the (*S*)-(-)-MTPA ester (**1a**) and (*R*)-(+)-MTPA ester (**1b**) in ppm.

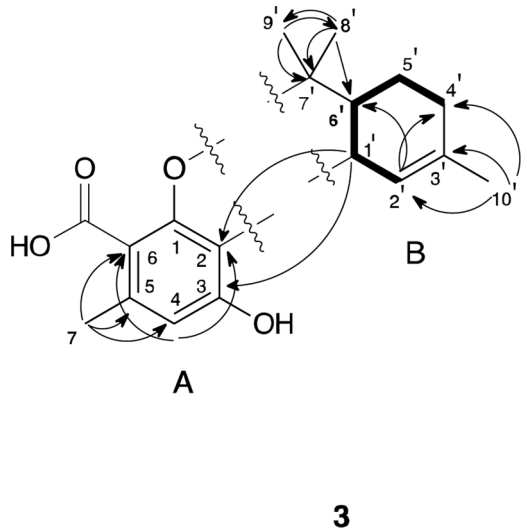

Fig. 4. Selected ^{1}H-^{1}H COSY and HMBC correlations for compound **3**.

that **7** was also a related compound of **1** and **2**. In the ^{1}H NMR spectrum (Table 1), signals of a sesquiterpene group that was present in **1** and **2** was not observed, but signals assigned to 3-methyl-2-pentene (C-1′-C-5′/C-15′) and 2,3,4-trimethyl-cyclohexan-1-one (C-6′-C-11′/C-12′/C-13′/C-14′) moieties were found. The pentene moiety was connected at C-6′ using the HMBC correlations from Me-14′ to C-5′ (Fig. 2). The relative stereochemistry of **7** was the same of that of cylindrol A (Singh et al., 1995) and nectchlorin A (Isaka et al., 2014) at all chiral centers of cyclohexanone, as determined by NOE correlations H-7′/H-11′ and, ^{13}C NMR chemical shifts. Although **7** was reported to be synthesized in a Japanese patent (Tamura et al., 2002), no spectroscopic data was available, and **7** was tentatively named 6-carboxyl-4-dechloro-ascochlorin.

Compounds **1**–**8** were tested for cytotoxicity against human promyelocytic leukemia HL60 cells. Among the compounds tested, **3** and **8** had substantial cytotoxic effects, with IC_{50} of 24.1 μM and 1.6 μM, respectively.

We next examined the biological activities of the isolates using a mutant yeast screening system to search for inhibitors of Ca^{2+} signaling (Shiono et al., 2009). Ca^{2+} signaling affects the progress of the G2/M cell cycle multilaterally in the yeast *Saccharomyces cerevisiae*. The mutant *S. cerevisiae* strain (*zds1Δ erg3Δ pdr1Δ pdr3Δ*: YNS17 strain) used in this study cannot grow at high $CaCl_2$ concentrations, as growth is arrested during the G2 phase by hyperactivation of cellular Ca^{2+} signaling. Inhibition of Ca^{2+} signal transduction can therefore detect the compounds' ability to restore cell growth, as quantified by a growth zone around a paper disc and/or spot containing the active compound (Shitamukai et al., 2000; Ogasawara et al., 2008).

The Ca^{2+} signaling pathways for growth regulation (cell cycle) are comprised of several signaling molecules, including the Ca^{2+} channel (target of anti-hypertension drugs), calcineurin (target of immunosuppressant drugs), Pkc1 protein kinase C (target of anti-cancer drugs), Mpk1 MAPK (target of anti-cancer drugs), and Mck1 GSK-3 (target of anti-diabetes and Alzheimer's disease drugs). In fact, the calcineurin inhibitor FK506 (2.5 ng/spot) had a growth zone of yeast cells in this screening system (Ogasawara et al., 2008). This screening system revealed that **5**, **6**, and **8** had dose-dependent growth-restoring activity in the mutant yeast (from 0.63 μg/spot to 0.01 μg/spot) (Fig. 5),

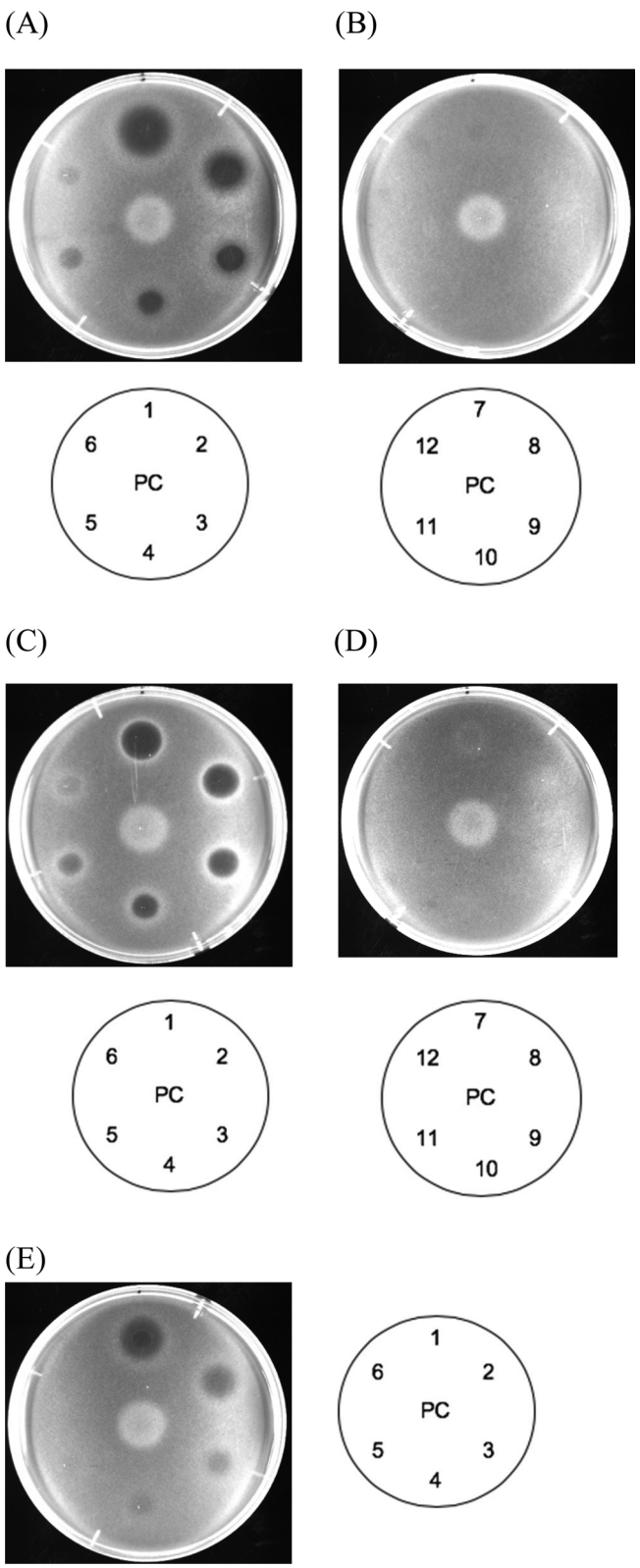

Fig. 5. Growth restored activities of **5** (A and B), **6** (C and D), and **8** (E) against *S. cerevisiae* YNS17 strain (*zds1*Δ *erg3*Δ *pdr1*Δ *pdr3*Δ) in the presence of 0.3 M $CaCl_2$. 1: 5.0 μg/spot, 2: 2.5, 3: 1.25, 4: 0.63, 5: 0.31, 6: 0.16, 7: 0.078, 8: 0.039, 9: 0.020, 10: 0.0098, 11: 0.0048, 12: 0.0024 (μg/spot), PC (FK506): 2.5 ng/spot.

suggesting inhibition of Ca^{2+} signal transduction. However, **1**, **2**, **3**, **4**, and **7** exhibited no activity and/or faint activity even at a dose of 5.0 μg/spot (data not shown).

In the literature, **5** and **6** were originally isolated from the culture of *Cylindrocarpon olidum,* and characterized as fungal antagonists (Quaghebeur et al., 1994; Iwata and Kitanaka, 2011). Although **6** has been reported to inhibit histamine release from mast cells (Iwata and Kitanaka, 2011), to date there has been little research regarding the biological activity of **5**, with exception to preliminary antimicrobial activity and nematodes with mixture of a chloro derivative, 8-chloro-cannabiorcichromenic acid (Quaghebeur et al., 1994). In the present assay system, clear zones were found in **5** and **6,** indicating antifungal activity against the mutant YNS17 strain as well. In addition, **3,** which has a carboxylic acid group, had weaker activity than that of **8**. It is likely that the hydrophobicity is also important for antifungal activity. Furthermore, the cytotoxicity of **3** and **8** against HL60 cells had IC_{50} values at 24.1 μM and 1.6 μM, respectively. Compound **8** was isolated for the first time from a natural origin, and to date very few reports have examined its biological activity. Although further studies of these compounds' mechanisms of action are needed, **5**, **6**, and **8** are newly identified potential Ca^{2+} signal transduction inhibitors.

3. Experimental

3.1. General methods

Column chromatography (CC): SiO_2 (200–300 mesh; *Kanto Chemical Co*., Inc. Tokyo, Japan), ODS (100 μm; *Fuji Silysia*, Aichi, Japan) and flash (25μm, SNAP Ultra, Biotage Japan, Tokyo, Japan). Semi-preparative HPLC was carried out with Shimadzu pump and UV LC-10A detector (210 nm) on Mightysil ODS column (6.0 mm i.d. x 250 mm) at the flow rate of 1.5 ml min^{-1}. Thin-layer chromatography (TLC): SiO_2 GF_{254} plates (20 × 20 cm, *Merck*, Darmstadt, Germany), and spots were detected by spraying with 10% vanillin in H_2SO_4 followed by heating, or by UV irradiation. Optical rotations: *Horiba SEPA-300* polarimeter (*HORIBA*, Kyoto, Japan). UV spectrum: *Shimadzu UV mini-1240* spectrophotometer (*SHIMADZU,* Kyoto, Japan); λ_{max} (log ε) in nm. IR spectra: *Jasco J-20A* spectrophotometer (*JASCO Co.,* Tokyo, Japan); KBr pellets; ν in cm^{-1}. Mass spectra were obtained with a Synapt G2 (*Waters Co*., Meliford, MA, USA). ^{1}H-, ^{13}C-, and 2D-NMR spectra: *Jeol ECZ-600* spectrometer at 600 MHz for ^{1}H and 125 MHz for ^{13}C (*JEOL*, Tokyo, Japan). Chemical shifts are given on a δ (ppm) scale with TMS as an internal standard.

3.2. Biological material

The fungal strains of Bm-1-1 was isolated from a surface sterilized branch of *Acanthus ebracteatus* Vahl, collected at Kapuas River in Pontianak, West Kalimantan, Indonesia (northern latitude: 0°14′22″; east longitude: 109° 9′ 54″). A voucher specimen (No. AM2017091) is deposited at Department of Food, Life, and Environmental Science, Faculty of Agriculture, Yamagata University and Department of Geography, Faculty of Mathematics and Natural Sciences, Universitas Negeri Makassar, Makassar, where Dr. Abdul Malik identified the plant material. Fungal strains Bm-1-1 was identified as *Pseudocosmospora* sp. by using a DNA analysis of the 18S rDNA region and was submitted in GenBank: LC440319 (the sequence data are available on and after 14 June 2019). This strain has been deposited at our laboratory in the Faculty of Agriculture of Yamagata.

3.3. Fermentation, extraction, and isolation

The strain was grown under static conditions at 25 °C for 30 days in 1 L Erlenmeyers containing 100 g of the steamed unpolished rice and 150 ml of water. The moldy unpolished rice (1000 g) was extracted with methanol, and the methanol extract was concentrated. The resulting aqueous concentrate was partitioned into *n*-hexane (300 ml) and EtOAc (300 ml × 3) layers. The purification from the EtOAc layer was guided by the intense blue characteristic coloration with vanillin-

sulfuric acid solution on TLC plates. The EtOAc layer (3.6 g) was chromatographed on a silica gel CC using first a stepwise of *n*-hexane/EtOAc (100:0 − 0:100, *v/v*; each 500 ml) and then a mixture of EtOAc/MeOH (50:50) as eluting solvents to give 13 fractions (Frs. 1-1 - 1-13). Frs. 1–3 and 1–4 (300 mg) were subjected to ODS CC by eluting stepwise with H_2O and an increasing ratio of MeOH to afford **5** (380 mg) and crude **6** and **8**, which were finally purified by semi-preparative HPLC eluted with H_2O/MeOH (20:80) to afford **6** (6.0 mg, t_R = 10.1 min) and **8** (10.3 mg, t_R = 9.0 min). Frs. 1–4 and 1–5 (420 mg) were chromatographed on a silica gel CC using a stepwise gradient of $CHCl_3$/EtOAc (100:0 − 0:100, *v/v*; each 300 ml) to give 12 fractions (Frs. 2-1 - 2–12). Fr. 2–4 (300 mg) was subjected to ODS CC by eluting stepwise with H_2O and an increasing ratio of MeOH (100:0 − 0:100, *v/v*; each 100 ml) to afford 12 fractions (Frs. 2–4-1 - 2–4-12). Fr. 2–4-5 (150 mg) was subject to flash silica gel CC (*n*-hexane/EtOAc, 5:1) to afford **1** (4.0 mg), **3** (25 mg) and Fr. 2–4-5-1. Fr. 2–4-5-1 was purified by semi-preparative HPLC eluted with H_2O/MeOH (40:80) to yield **4** (3.7 mg, t_R = 10.5 min). Fr. 1–7 (335 mg) was chromatographed on silica gel CC using a stepwise gradient of $CHCl_3$–EtOAc to give fractions 1–12 (Frs. 3-1 - 3–12). Frs. 3–6 and 3–7 (90 mg) were subjected to ODS CC by eluting stepwise with H_2O and an increasing ratio of MeOH to afford crude compounds **2** and **7**, which were finally purified by flash silica gel CC ($CHCl_3$/MeOH, 50:1) to afford **2** (3.0 mg) and **7** (63.0 mg).

Cosmosporin A (**1**). White amorphous powder; $[\alpha]_D^{25}$ + 10.0 (*c* 0.32, MeOH); UV (MeOH) λ_{max} (log ε) 228 (4.1), 274 (3.1), 282 (3.1); IR (KBr)ν_{max} 3300 (OH), 2930, 1600, 1234, 567 cm^{-1}; ^{13}C NMR (150 MHz, $CDCl_3$) and ^{1}H-NMR (600 MHz, $CDCl_3$) data, see Tables 1 and 2; HRESITOFMS *m/z* 385.2355 ($[M + Na]^+$, calcd for $C_{22}H_{34}NaO_4$, 385.2354)

6-Carboxyl-cosmosporin A (**2**). White amorphous powder; $[\alpha]_D^{25}$ + 6.3 (*c* 0.33, MeOH); UV (MeOH) λ_{max} (log ε) 221 (4.3), 267 (4.0), 302 (3.5); IR (KBr)ν_{max} 3310 (OH), 2929, 1620(CO), 1379, 1423, 1265, 1076, 667 cm^{-1}; see Tables 1 and 2 for ^{1}H ($CDCl_3$, 600 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz); ^{13}C NMR (150 MHz, CD_3OD) and ^{1}H-NMR (600 MHz, CD_3OD) data, see Tables 1 and 2; HRESITOFMS *m/z* 429.2251 ($[M + Na]^+$, calcd for $C_{23}H_{34}NaO_6$, 429.2252).

rel-(6a*S*,10a*R*)-Δ^9-Tetrahydrocannabiorcolic acid B (**3**). White amorphous powder; $[\alpha]_D^{25}$ −18.0 (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε) 220 (4.1), 261 (3.5); IR (KBr)ν_{max} 3178 (OH), 2927, 1700 (CO), 1600, 1450, 1253, 1079, 848 cm^{-1}; ^{13}C NMR (150 MHz, CD_3OD) and ^{1}H NMR (600 MHz, CD_3OD) data, see Tables 1 and 2; HRESITOFMS *m/z* 303.1598 ($[M+H]^+$calcd for $C_{18}H_{23}O_4$, 303.1596).

8′-Hydroxy-cannabiorcichromenic acid (**4**). White amorphous powder; $[\alpha]_D^{25}$ + 10.0 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 252 (4.6), 260 (4.6); IR (KBr)ν_{max} 3317 (OH), 1650 (CO), 1519, 137, 1264, 1176, 671 cm^{-1}; ^{13}C NMR (150 MHz, CD_3OD) and ^{1}H-NMR (600 MHz, CD_3OD) data, see Tables 1 and 2; HRESITOFMS *m/z* 341.1359 ($[M + Na]^+$, calcd for $C_{18}H_{22}NaO_5$, 341.1364).

6-Carboxyl-4-dechloro-ascochlorin (**7**). White amorphous powder; $[\alpha]_D^{25}$ + 5.3 (*c* 0.32, MeOH); UV (MeOH) λ_{max} (log ε) 221 (4.4), 268 (4.0), 308 (3.5); IR (KBr)ν_{max} 3320 (OH), 2969, 1700 (CO), 1620 (CO), 1519, 1434, 1168, 671 cm^{-1}; ^{13}C NMR (150 MHz, CD_3OD) and ^{1}H-NMR (600 MHz, CD_3OD) data, see Tables 1 and 2; HRESITOFMS *m/z* 411.2146 ($[M + Na]^+$, calcd for $C_{23}H_{32}NaO_5$, 411.2147).

Cannabiorcichromenic acid (**5**). Brown amorphous powder; $[\alpha]_D^{25}$ + 10.2 (*c* 0.48, MeOH); UV (MeOH) λ_{max} (log ε): 252 (4.6), 259 (4.6); IR (KBr)ν_{max} cm^{-1}: 3300 (OH), 2970, 1650, 1457, 713; ^{13}C NMR (150 MHz, $CDCl_3$): δ 176.7 (C-8), 160.7 (C-1), 159.3 (C-3), 144.7 (C-6), 132.0 (C-7′), 126.4 (C-2′), 123.9 (C-6′), 116.7 (C-1′), 110.2 (C-4), 107.1 (C-2), 103.7 (C-5), 80.7 s (C-3′), 41.8 (C-4′), 27.3 (C-10′), 25.8 (C-8′), 24.6 (C-7), 22.7 (C-5′), 17.7 (C-9′); ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.72 (1H, d, *J* = 10.2 Hz, H-1′), 6.23 (1H, s, H-4), 5.46 (1H, d, *J* = 10.2 Hz, H-2′), 5.08 (1H, t, *J* = 6.0 Hz, H-6′), 2.53 (3H, s, H-7), 2.08 (m, H-5′), 1.65 (3H, s, H-8′), 1.64–1.76 (2H, m, H-4′), 1.57 (3H, s, H-9′), 1.40 (3H, s, H-10′); HRESITOFMS *m/z* 325.1412 ($[M + Na]^+$, calcd for $C_{18}H_{22}NaO_4$, 325.1416)

2,7-Dimethyl-2-(4-methylpent-3-enyl)-3,4-dihydrochromen-5-ol (**6**). Brown amorphous powder; $[\alpha]_D^{25}$ +28.5 (*c* 0.47, MeOH); UV (MeOH) λ_{max} (log ε): 230 (4.4); IR (KBr)ν_{max} cm^{-1}: 3600 (OH), 2969, 1600, 1542, 671; ^{13}C NMR (150 MHz, $CDCl_3$): δ 154.2 (C-3), 151.1 (C-1), 139.6 (C-1), 131.8 (C-1), 127.3 (C-1), 124.3 (C-1), 116.8 (C-1), 109.9 (C-4), 108.4 (C-1), 106.8 (C-2), 78.3 (C-1), 41.1 (C-1), 26.3 (C-1), 25.8 (C-1), 22.8 (C-1), 21.6 (C-1) 17.7 (C-1); ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.59 (1H, d, *J* = 10.8 Hz, H-1′), 6.23 (1H, s, H-4), 6.10 (1H, s, H-6), 5.47 (1H, d, *J* = 10.8 Hz, H-2′), 5.08 (1H, t, *J* = 6.6 Hz, H-6′), 2.19 (3H, s, H-7), 2.08 (m, H-5′), 1.64 (3H, s, H-8′), 1.60–1.74 (m, H-4′), 1.57 (3H, s, H-9′), 1.36 (3H, s, H-10′); HRESITOFMS *m/z* 281.1598 ($[M + Na]^+$, calcd for $C_{12}H_{22}NaO_2$, 281.1518). 3,6,6,9-Tetramethyl-6,7,8,10-tetrahydrobenzo[c]chromen-1-ol (**8**). Brown amorphous powder; $[\alpha]_D^{25}$ -4.5 (*c* 0.33, MeOH); UV (MeOH) λ_{max} (log ε): 234 (3.9); IR (KBr)ν_{max} cm^{-1}: 3420 (OH), 3270, 1600, 1519, 775; ^{13}C NMR (150 MHz, $CDCl_3$): δ155.0 (C-3), 154.0 (C-1), 137.4 (C-5), 135.1 (C-3′), 122.0 (C-2′), 110.8 (C-6), 109.4 (C-2), 108.8 (C-4), 76.3 (C-7′), 40.1 (C-6′), 31.5 (C-1′), 29.9 (C-4′), 26.1 (C-8′), 25.3 (C-9′), 23.8 (C-10′), 21.0 (C-7), 20.7 (C-5′); ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.23 (1H, s, H-6), 6.20 (1H, d, *J* = 1.2 Hz, H-2′), 6.12 (1H, s, H-4), 3.54 (1H, br.s. H-1′), 2.17 (3H, s, H-7), 1.98 (m, H-5′), 1.93 (m, H-4′), 1.70 (1H, t, *J* = 6.0 Hz, H-6′), 1.69 (3H, s, H-10′), 1.38 (3H, s, H-8′), 1.25 (H, s, H-9′); HRESITOFMS *m/z* 281.1558 ($[M + Na]^+$, calcd for $C_{12}H_{22}NaO_2$, 281.1518).

3.4. Modified Mosher's ester for *1*

To **1** (1.0 mg) in dry pyridine were added (*R*)-(-)-α-methoxy-α-trifluoromethyl phenylacetic chloride (MTPACl, 10 μL), the mixture was stirred at room temperature for 24 h. Purification by column chromatography on silica gel (*n*-hexane: EtOAc) afforded the (*S*)-(-)-MTPA ester (**1a**, 0.7 mg). Compound **1** (1.0 mg) was treated with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetic chloride (MTPACl, 10 μL) in the same procedure to afford the (*R*)-(+)-MTPA ester (**1b**, 0.6 mg).

1a : ^{1}H (600 MHz, $CDCl_3$) δ_H 1.089 (3H, s, Me-13′), 1.134 (3H, s, Me-12′), 1.30 (3H, s, Me-14′), 1.480 (3H, s, Me-15′), 1.62 (2H, m, H-9′), 1.30 (m, H-4′, H-5′, H-8′), 2.919 (2H, m, H-1′), 3.50 (3H, s, MTPA-O*CH*$_3$), 3.53 (6H, s, MTPA- O*CH*$_3$), 4.792 (1H, t, *J* = 6.0 Hz, H-6′), 4.992 (1H, t, *J* = 6.0 Hz, H-2′), 5.082 (1H, m, H-10′), 6.836 (2H, s, H-4 and H-6), 7.44 (6H, m, MTPA-Ar*H*), 7. 64 (9H, m, MTPA-Ar*H*).

1b : ^{1}H (600 MHz, $CDCl_3$) δ_H 1.183 (3H, s, Me-12′), 1.121 (3H, s, Me-13′), 1.292 (3H, s, Me-14′), 1.423 (3H, s, Me-15′), 1.61 (2H, m, H-9′), 1.87 (m, H-4′, H-5′, H-8′), 2.906 (2H, m, H-1′), 3.50 (3H, s, OMe), 3.53 (6H, s, OMe), 4.780 (1H, t, *J* = 6.0 Hz, H-6′), 4.954 (1H, t, *J* = 6.0 Hz, H-2′), 5.10 (1H, m, H-10′), 6.824 (2H, s, H-4 and H-6), 7.53 (6H, m, MTPA-Ar*H*), 7. 74 (9H, m, MTPA-Ar*H*).

3.5. Cell culture and cytotoxicity

HL60 cells (RCB0041, RIKEN BioResource Center, Tsukuba, Japan) were grown in RPMI 1640 medium supplemented with 10% heat-inactivated FBS and penicillin (50 units/ml)-streptomycin (50 μg/ml) in a humidified atmosphere at 37 °C under 5% CO_2 for 48 h. The cytotoxicity of the compounds was examined by MTT assay, as described previously (Arayama et al., 2016).

3.6. Growth restored activity of samples against YNS17 strain

Screening was performed according to previous described method (Ogasawara et al., 2008). Each sample was dissolved in MeOH and two-fold dilutions of them were used. Difco® yeast-peptone-dextrose (YPD) broth and YPD agar were purchased from Becton Dickinson Biosciences (Franklin Lakes, NJ, USA). The mutant yeast, YNS17 (*MAT*a *zds1::TRP1 erg3::HIS3 pdr1::hisG-URA3-hisG pdr3::hisG*) yeast strains was derivatives of strain W303-1A (Ogasawara et al., 2008). A 5 μl aliquot of samples was spotted on a YPD agar medium containing YNS17 strain

and 0.3 M $CaCl_2$. After 3 days of incubation at 28 °C, the intensity of the growth spot was observed as the result of inhibition of Ca^{2+}-signal transduction. FK506 (2.5 ng/spot) was used as a positive control. FK506 was kindly provided by Fujisawa Pharmaceutical Co., Ltd. (the present Astellas Pharma Inc., Tokyo Japan).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phytol.2019.03.014.

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