Isolation and structure elucidation of biological active compounds from *Euphorbia deightonii* and *Centrapalus pauciflorus*

Summary of PhD Thesis

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Doctoral School of Pharmaceutical Sciences
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Szeged
2023

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Szeged, Hungary

2023

Introduction

All through human history, natural products (from plants and animals) have been recognized and used as a source of remedies and treatments for various diseases. It was natural products that provided the source and raw materials for the first conventional drugs. Despite great scientific and technological advances in chemistry, drugs derived from natural product still make an enormous contribution to drug discovery today. Natural products of plant origin will continue to play significant roles in discovery and development of drugs for the foreseeable future.

Africa is home to earth's 'second lungs'. It houses over 45,000 plant species with many of them having medicinal and cultural uses. Given that some conventional drugs such as vincristine, vinblastine, physostigmine, diosgenin were isolated from African plants. This research focuses on evaluating, scientifically, the medicinal properties of two African plants: *Euphorbia deightonii* and *Centrapalus pauciflorus*.

Genus *Euphorbia* is the largest genus in Euphorbiaceae family with about 2000 species. *Euphorbia* spp. are rich in diterpenoids, which have become chemotaxonomic markers of Euphorbiaceae plant family due to their limited distribution and structural variability. *Euphorbia* diterpenoids are classified based on their biosynthetic pathway as higher and lower diterpenes. The distribution of lower diterpenes are restricted to Euphorbiaceae and Thymeleaceae families while the higher terpenes occur in many plant families. Diterpenoids of *Euphorbia* species have attracted significant interest because of their remarkable chemical diversity and promising pharmacological activities, such as anti-inflammatory, antitumor, antiviral, multidrug resistance (MDR) reversal effects and cocarcinogenic effects.

Genus *Centrapalus* belongs to Asteraceae family. It has nine species. In ethnomedicine, it is used in the treatment of malaria, diabetics, chest pain, external injury, cough and gastrointestinal diseases. 5-methylcoumarins derived merotepenoids and their isomers, 5-methylchromones derived meroterpenoids are rare in nature and have a restricted occurrence in the plant kingdom. They are mainly found from the members of tribes Vernonieae, Nassauvieae, Onoserideae and Mutisieae of the Asteraceae family, and occasionally from a few other taxa. Unlike most coumarins that are synthesized through phenylpropanoid pathway, 5-methylcoumarins have been suggested to be derived through the acetate-malonate pathway *via* pentaketide intermediate.

Meroterpenoids are group of secondary metabolites derived from mixed biosynthetic pathways from hybrid polyketide or non-polyketide and terpenoid biosynthesis. The modification of the monoterpene component of coumarin/chromone derived meroterpenoids is the major source of variation in most compounds. Due to their restricted occurrence and few information on 5-methylcoumarins and 5-methylchromones, there are little knowledge of their pharmacological activities. However, plants rich in meroterpenoids have shown cytotoxic, antiproliferative, antifungal, antiprotozoal, antimicrobial, antioxidant, anti-inflammatory and antidiabetic activities.

Aims of the study

The objectives of my research were the isolation and structure determination of new natural compounds from *E. deightonii* and *C. pauciflorus*, and investigation of their biological activities. To achieve these objectives, the following steps were taken:

- Screening of *E. deightonii* for diterpenoids and *C. pauciflorus* for antiproliferative constituents.
- Preparing extracts from aerial parts of *E. deightonii* and leaves of *C. pauciflorus*
- Purification and isolation of compounds from *E. deightonii* and *C. pauciflorus* using a series and combination of chromatographic techniques such as OCC, VLC, FLC, HPLC, PLC and recrystallization methods.
- Structure elucidation of isolated compounds by use of data from advanced spectroscopic analysis of 1D and 2D NMR as well as HRMS.
- Evaluation of pharmacological activiities of isolated compounds (anti-HSV, anti-proliferative and cytotoxic effects).

Materials and Methods

Compounds were isolated through a series of chromatographic techniques that involved open column chromatography (OCC), vacuum liquid chromatography (VLC), flash liquid chromatography (FLC), high performance liquid chromatography (HPLC), preparative thin layer chromatography (PLC) and recrystallization methods. Structural elucidation were done by use of advanced spectroscopic methods: 1D (^{1}H, JMOD) and 2D (HSQC, HMBC, ^{1}H-^{1}H COSY, NOESY) NMR, and HRESIMS. In addition, the absolute configuration of compound **59** was determined by single-crystal X-ray diffraction. The MDR modulating, cytotoxic and antiviral activities of compounds from *E. deightonii* were measured in Department of Medical Microbiology Educational and Research Center, University of Szeged. The antiproliferative activities of compounds from *C. pauciflorus* were measured in Department of Pharmacodynamics and Biopharmacy, University of Szeged.

Result and discussion

Extraction, isolation, and purification of compounds from *E. deightonii*

Research conducted on *E. deightonii* was chemistry guided with emphasis on isolation of diterpenoids. Preliminary studies indicated polyamide OCC 60% MeOH-H_2O fraction was diterpenoid rich. Comprehensive chromatographic analysis led to the isolation of 38 compounds (**1**–**38**) (**Figure 1** and **2**).

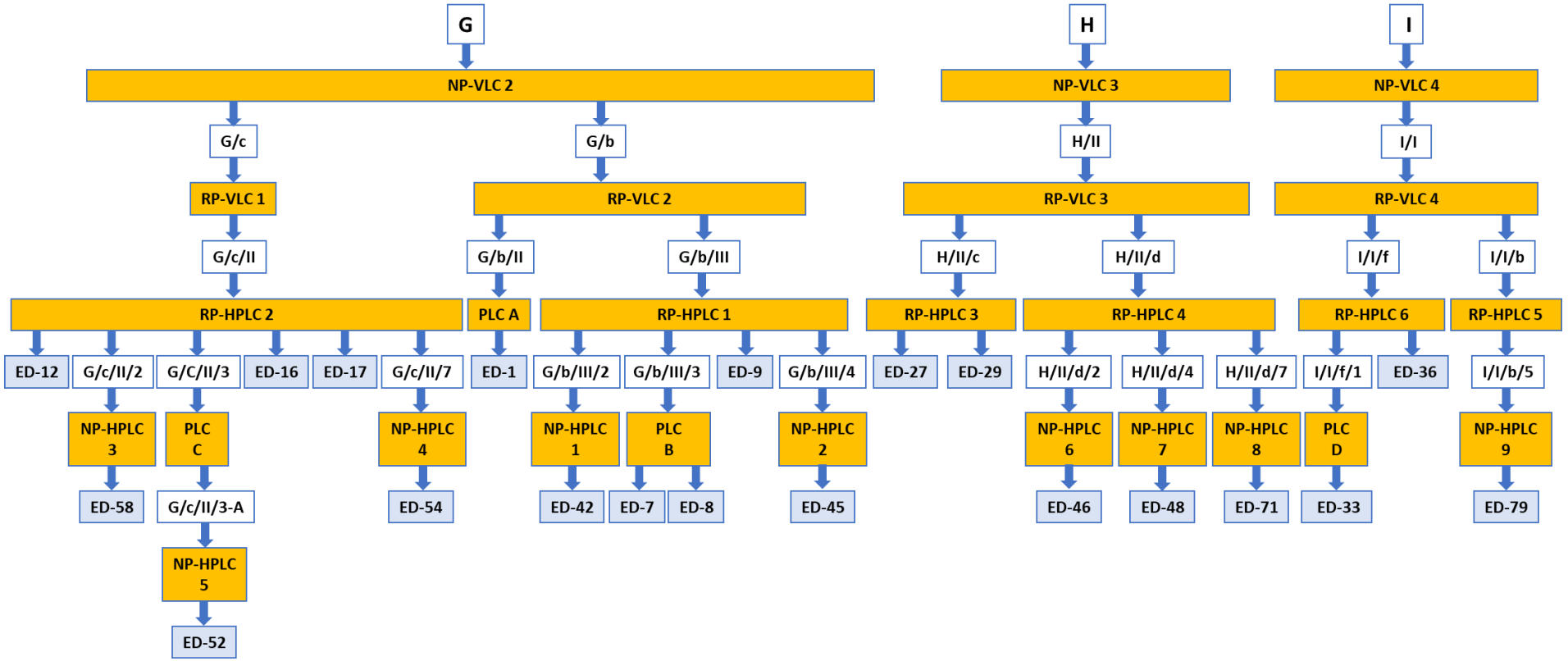


Figure 1. Isolation of compounds from bulk fractions G–I of *E. deightonii*.

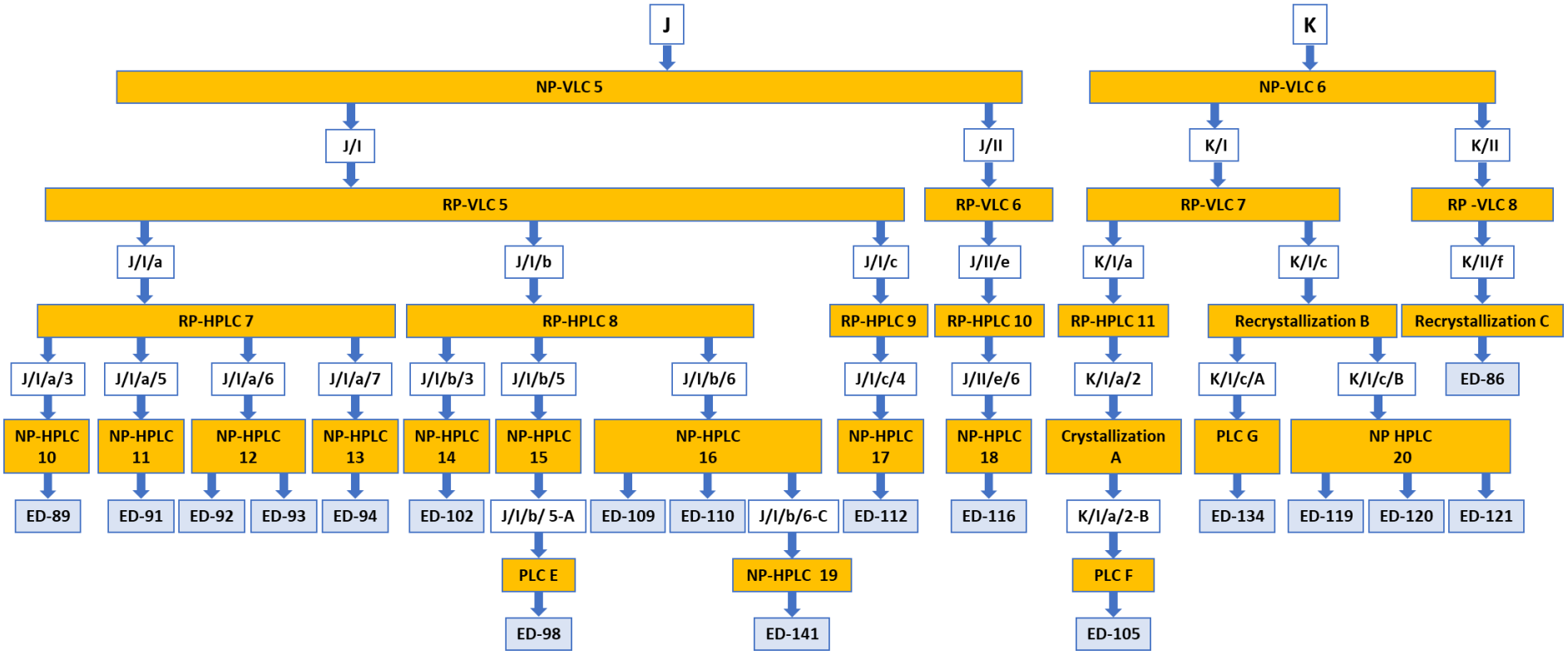
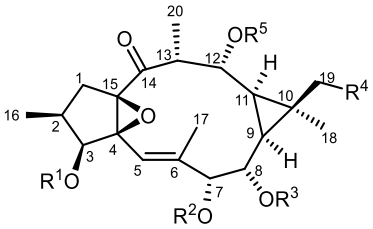
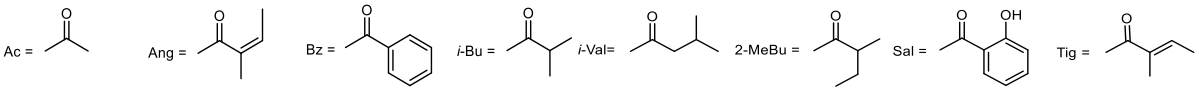


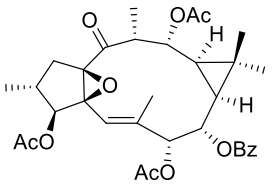
Figure 2. Isolation of compounds from bulk fractions J and K of *E. deightonii*.

Compounds isolated from *E. deightonii* can be grouped into; diterpenoids (**1**–**30**; **1**–**9** are novel), triterpenoids (**31**–**33**; **31** is novel), lignans or neolignans (**34**–**36; 34** is novel), coumarin (**37**) and ellagic acid derivative (**38**). Compounds **1**–**27** are lathyrane type diterpenoids. Compound **28** and **29** are *ent*-atisane diterpenoids while **30** belongs to the rare stachane diterpenoid group.

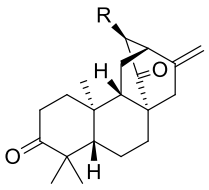


		R^1	R^2	R^3	R^4	R^5			R^1	R^2	R^3	R^4	R^5
1	(ED-29)	Ac	Tig	Ac	H	H	**14**	(ED-16)	Ac	Ac	Tig	H	Ac
2	(ED-58)	Ac	*i*-Bu	Ac	H	Ac	**15**	(ED-17)	Ac	2-MeBu	Ac	H	Ac
3	(ED-71)	Ac	Ac	Sal	H	Ac	**16**	(ED-27)	Ac	Ac	Ac	H	Ac
4	(ED-79)	Ac	Ang	Ac	Ac	Ac	**17**	(ED-42)	Ac	Tig	Ac	H	Ac
5	(ED-91)	H	Tig	Ac	H	Ac	**18**	(ED-46)	Ac	Bz	Me	H	Ac
6	(ED-93)	Ac	Bz	H	H	Ac	**19**	(ED-48)	Ac	Bz	Ac	H	Ac
7	(ED-98)	Ac	Ac	Bz	Ac	Ac	**20**	(ED-52)	Ac	Ang	Me	H	Ac
8	(ED-109)	Ac	Tig	Tig	Ac	H	**21**	(ED-54)	Ac	*i*-Val	Ac	H	Ac
9	(ED-112)	Ac	Ang	Bz	OH	Ac	**22**	(ED-89)	H	Tig	Me	H	Ac
10	(ED-7)	Ac	Ac	2-MeBu	H	Ac	**23**	(ED-92)	Ac	Tig	H	H	Ac
11	(ED-8)	Ac	Ac	Bz	H	Ac	**24**	(ED-94)	Ac	Ang	H	H	Ac
12	(ED-9)	Ac	Ang	Ac	H	Ac	**25**	(ED-102)	Ac	H	Tig	H	Ac
13	(ED-12)	Ac	Ang	Me	H	Ac	**26**	(ED-110)	Ac	Tig	Tig	OH	Ac



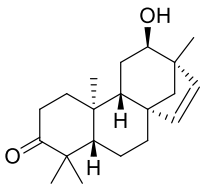


27 (ED-45)

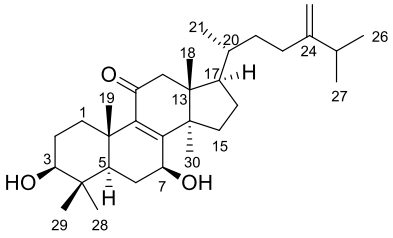


28 (ED-1) R= H

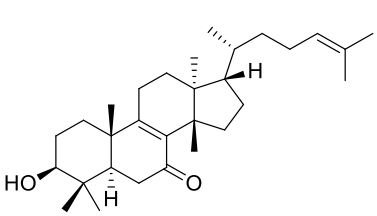
29 (ED-134) R = OH



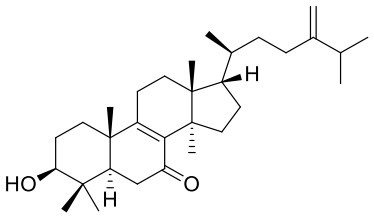
30 (ED-141)



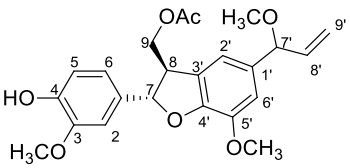
31 (ED-116)



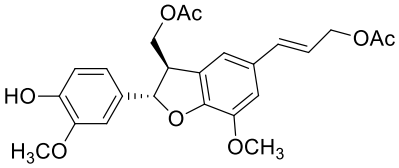
32 (ED-33)



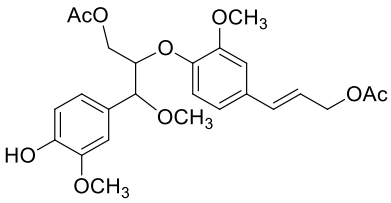
33 (ED-36)



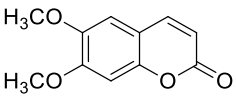
34 (ED-119)



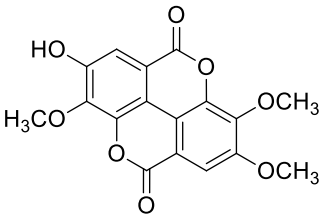
35 (ED-120)



36 (ED-121)



37 (ED-105)



38 (ED-85)

Extraction, isolation, and purification of compounds from *C. pauciflorus*

Study conducted on *C. pauciflorus* followed partly bioassay guided. Fractions obtained from polyamide column chromatography were evaluated for their antiproliferative effect on cervical, ovarian and breast cancer cell lines. 60% methanol fraction displayed significant cytotoxic effect on all cancer cell lines evaluated. Extensive chromatographic studies led to the isolation of 25 compounds (**39–63**), which belonged to the rare 5-methylcoumarin (**39–58; 39**, **41**, **42**, **46**, **47**, **50–56**, **58** are novel) and 5-methylchromone (**59–63**; all are novel) derived meroterpenoids (**Figure 3** and **4**).

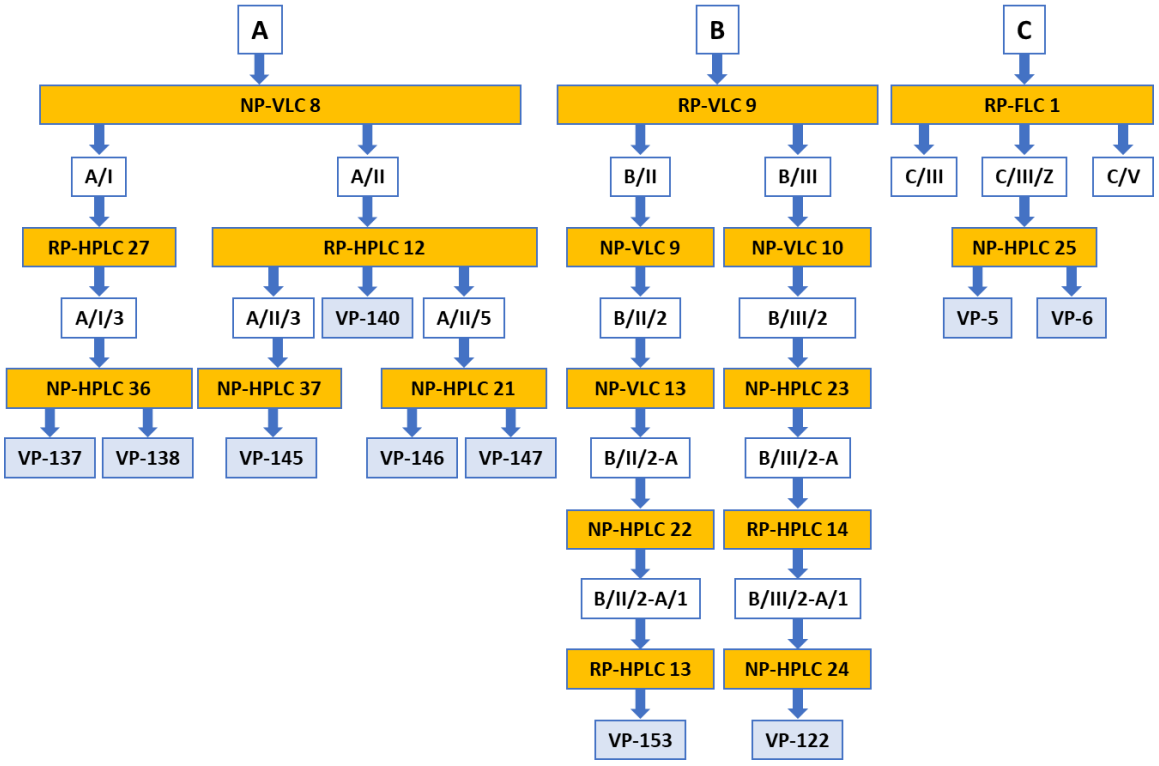
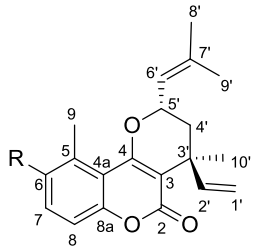
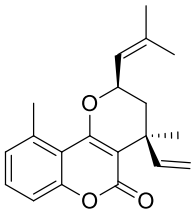


Figure 3. Isolation of compounds from bulk fractions A–C of *C. pauciflorus*.

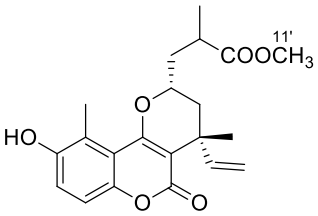
Figure 4. Isolation of compounds from bulk fraction C of *C. paucijlorus*.



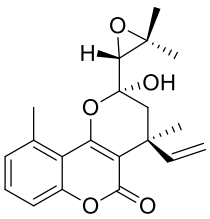
39 (VP-146) R = H
41 (VP-113) R = OH



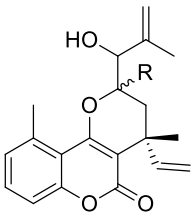
40 (VP-147)



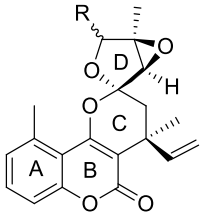
42 (VP-27)



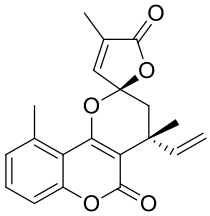
43 (VP-55)



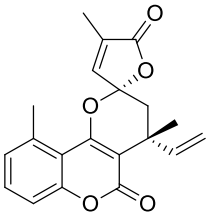
44 (VP-67) R = *β*OH
45 (VP-68) R = *α*OH



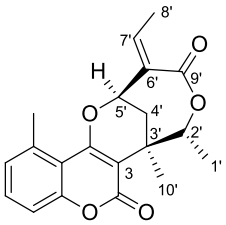
46 (VP-176) R = *β*OH
47 (VP-177) R = *α*OH



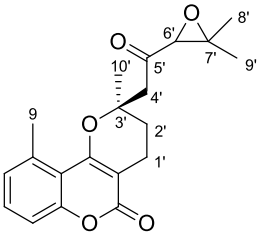
48 (VP-5)



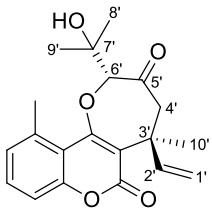
49 (VP-6)



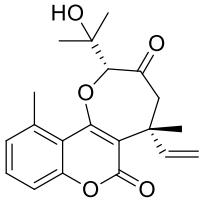
50 (VP-172)
52 (VP-159) H-6′*β*



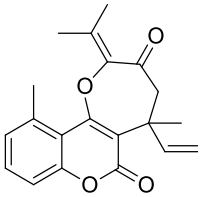
51 (VP-158) H-6′*α*



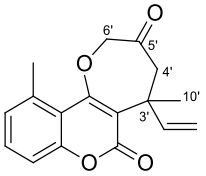
53 (VP-160)



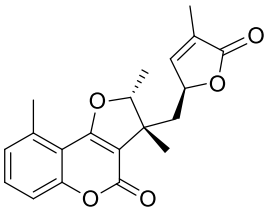
54 (VP-161)



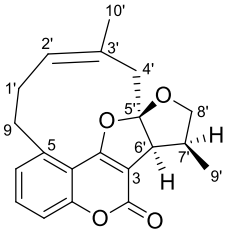
55 (VP-153)



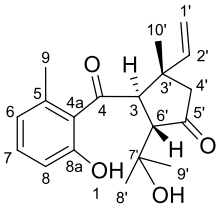
56 (VP-8)



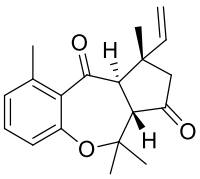
57 (VP-90)



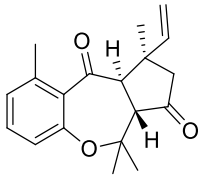
58 (VP-122)



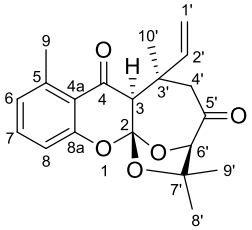
59 (VP-54)



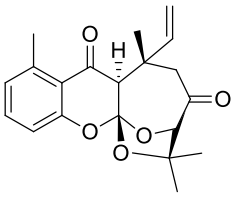
60 (VP-137)



61 (VP-138)



62 (VP-145)



63 (VP-140)

Chemotaxonomy of investigated species

The occurrence of macrocyclic diterpenoids are restricted to Euphorbiaceae and Thymeleaceae families in the plant kingdom and are the major diterpenoid constituents of *Euphorbia* genus. This makes them a significant chemotaxonomic marker in delimiting *Euphorbia* species. This isolated compounds evidenced chemotaxonomically that the *E. deightonii* was rightly placed in the taxonomic order.

5-methylcoumarins and 5-methylchromones derived meroterpeoids have restricted occurrence in few tribes of Asteraceae family namely, Vernonieae, Nassauvieae, Onoserideae and Mutisieae and this makes them a vital chemotaxonomic marker. In Onoserideae and Nassauvieae tribes, mainly sesquiterpenes occur. Mutisieae and Vernonieae tribes have monoterpenes as their terpene components. Furthermore, the presence of the vinyl group in the monoterpene part is common among Vernonieae and Nassauvieae tribes. Since all meroterpenoids isolated have monoterpene component and fifteen of them have a vinyl group, we have thus established that *C. pauciflorus* is well placed in the Vernonieae tribe of Asteraceae family.

Pharmacological activities

MDR-reversing and cytotoxic activities of diterpenoids isolated from *E. deightonii*

Thirteen diterpenes (**5**, **7**, **10**–**15**, **17**, **23**, **24**, **28**, and **29**) were evaluated for their cytotoxicity and anti-MDR effects to establish their structure activity relationship. Inhibition of the efflux pump was evaluated by flow cytometry measurement of the retention of rhodamine 123 in drug-resistant mouse T-lymphoma cells. The cytotoxicity of the thirteen purified diterpenoids were tested on parental and human MDR1-gene transfected mice T-cell lymphoma cells. Ingol esters **11**–**15** demonstrated high P-gp inhibitory effect at concentration of 20 µM, while the *ent*-atisane diterpenoids (**28**, **29**) showed considerably low activity. Regarding the preliminary structure–activity relationships, a decrease in esterification degree of ingol derivatives can lead to a decrease in efflux pump inhibition. The presence of a 19-CH_2OR group instead of a 19-methyl group seemed to decrease the P-gp inhibitory activity. For the ingol esters **14** and **17**, differing in the position of tigloyl and acetyl groups at C-7 and C-8, the FAR values suggested that C-8 tigloyl and C-7 acetyl moieties can lead to a drastic increase in activity, in relation to 8-acetyl and 7-tigloyl. Additionally, the comparison of the P-gp inhibitory activity of compounds **15** and **17** suggested that the presence of a C-7 tigloyl ester was undesirable for the anti-MDR effect of ingol polyesters.

Cytotoxicity and anti-HSV-2 activity of the compounds isolated from *E. deightonii*

The anti-herpes simplex virus type-2 activity of the isolated compounds were investigated by qRT-PCR assay on Vero cells after determining cytotoxic concentration 50% (CC_{50}). Triterpenoids **31** and **33** and neolignan **34** showed an antiviral effect. The most pronounced activity was exerted by the coumarin scoparon (**37**); its effect was better in comparison to that of acyclovir. However, selectivity index of **37** was lower than that of acyclovir.

Anti-proliferative effects of compounds isolaed from *C. pauciflorus*

Twenty one compounds (**39–41, 43–54, 57–62**) isolated from *C. pauciflorus* were investigated to describe their antiproliferative properties against a panel of human adherent cell lines of gynecological origin (MCF-7, MDA-MB-231, HeLa, SiHa, A2780) to obtain their structure-activity relationship. Cisplatin was used as the positive control. HeLa was the most sensitive cell line. 5-methylcoumarin derivatives with 2-methyl-1-propenyl group on ring C (**39**–**41**) exhibited similar antiproliferative effects; their activity against HeLa cells was comparable to that of cisplatin. The 5-methylcoumarin derivatives with a seven-membered ring (**50**) proved to be the most potent compound; its action on MCF-7 cells was similar to that of cisplatin, while it was substantially more effective against HeLa cells. The cancer selectivity of this compound was additionally determined using the same assay against intact murine fibroblasts (NIH-3T3). The calculated IC_{50} values against NIH-3T3 cells were 25.42 μM and 5.19 μM for **50** and cisplatin, respectively, indicating an improved cancer selectivity by **50**.

Summary

The main findings of these studies can be summarized as follows:

- A total of sixty-three (63) compounds were isolated from the two plants which includes thirty-eight (38) compounds (**1–38**) from *E. deightonii* and twenty-five (25) compounds (**39–63**) from *C. pauciflorus*. Twenty-nine (29) of the isolated compounds are new natural compounds.
- In specific grouping terms, the isolated compounds from *E. deightonii* comprises of thirty diterpenoids [ingol derivatives (**1**–**27**), *ent*-atisanes (**28**–**29**) and a stachane; (**30**)], three triterpenes (**31**–**33**), two lignans (**34–35**), one neolignane (**36**), one coumarin (**37**), and one ellagic acid derivative (**38**).
- The isolated compounds from *C. pauciflorus* comprises of twenty 5-methylcoumarin derived meroterpenoids (**39**–**58**) and five 5-methylchromone derived meroterpenoids (**59–63**).
- The twenty-nine (29) new natural compounds are ingol-type diterpenoids (**1–9**), triterpenoid (**31**), Lignan (**34**), 5-methylcoumarins (39, 41, 42, 46, 47, 50–56, 58) and five 5-methylchromones (59–63) are novel compounds.
- The MDR reversing effect of **5**, **7**, **10**–**15**, **17**, **23**, **24**, **28**, and **29** on the inhibition of P-gp was investigated. Generally, ingol derivatives demonstrated a high P-gp inhibitory effect while the *ent*-atisane diterpenoids (**28**, **29**) exhibited low activity. Compounds **11**–**15** were the most active. Structure-activity relationship indicated the lesser the esterification, the lower is the activity.
- Anti-HSV2 activity of **31**–**38** was evaluated. Compounds **31**, **33**, **34** and **37** showed different degrees of anti-HSV2 activities. Even though, **37** had a better activity than the positive control, acyclovir, the latter has a greater selectivity index than the **37**.
- Anti-proliferative activities of **39–41, 43–54, 57–62** on MCF-7, MDA-MB-231, HeLa, SiHa, A2780 cell lines revealed HeLa was the most sensitive cell line. Compound **50** demonstrated a higher cytotoxic activity on HeLa than positive control cisplatin. Additionally, **50** exhibited better cancer selectivity than cisplatin by a ratio of 5:1.
- Based on chemotaxonomic evidence of isolated compounds from the investigated species, we thus established that *E. deightonii* is well palced in the right genus of *Euphorbia* (Euphorbiaceae) and that *C. pauciflorus* is also well placed in the Vernonieae tribe of Asteraceae family.

Acknowledgements

I will want to use this medium to express my utmost and profound gratitude to my supervisor *Dr. Dóra Rédei Ph.D.* for providing me with conducive and enabling environment to conduct my research. I will forever remain grateful to her.

I would like to express my immense and sincere gratitude and appreciation to the Head of our research group, *Univ. Professor Dr. Judit Hohmann D.Sc.* for her unwavering support throughout the scope of this research. Indeed, we have gained a lot from her pool of knowledge and wealth of experience. Her contributions were critical to the achievements attained throughout the research. I will call her 'A living hero of pharmacognosy and science'. *Univ. Professor Dr. Judit Hohmann* and *Dr. Dóra Rédei* are embodiment of goodness and specimens of great scientist.

I also wish to thank *Dr. Norbert Kúsz Ph.D.* and *Dr. Anita Barta Pharm.D.* (Institute of Pharmacognosy, University of Szeged) for the NMR measurements; *Dr. Gordana Krystic Ph.D.* (Faculty of Chemistry, University of Belgrade) and *Dr. Norbert Kúsz Ph.D.* for NMR structure elucidation of compounds; *Dr. Róbert Berkecz Ph.D.* (Institute of Analytical Chemistry, University of Szeged) for the HRESIMS measurements; *Dr. Petra Bombicz Ph.D.* (Chemical Crystallography Research Laboratory, Research Centre for Natural Sciences, Hungarian Academy of Sciences) and *Dr. Pierre Fertey Ph.D.* (Synchrotron SOLEIL L'Orme des Merisiers – Saint Aubin, Gif-sur-Yvette Cedex, France) for the X-ray data; *Univ. Prof. Dr. Katalin Burián Ph.D.*, *Dr. Gabriella Spengler Ph.D.*, *Dr. Annamária Kincses Ph.D.*, and *Dr. Dávid Kókai Ph.D.* (Department of Medical Microbiology Educational and Research Center, University of Szeged) for testing the compounds for their MDR modulating, cytotoxic and antiviral activities; and *Univ. Prof. Dr. István Zupkó D.Sc.* and *Hazhmat Ali* (Department of Pharmacodynamics and Biopharmacy, University of Szeged) for measuring the antiproliferative activity of plant extracts and isolated compounds, *Prof. Abubakar Ahmad* (Ahmadu Bello University, Zaria, Nigeria) for his mntorship.

I would also like to thank Staff members of the Institute of Pharmacognosy, *Dr. Andrea Vasas Ph.D.* for her kindness, generosity and guidance. My appreciation also goes to *Dr. Katalin Veres Ph.D.*, who was always there whenever I needed extra hours for research after the official closing hours. My sincere appreciation also goes to *Attila Horváth*, who was always available to help with the repair of any laboratory equipment including HPLC. My special thanks goes to *Tamara Sápi* and *Kornél Szemerédi* for their help.

I would like to thank my parents; *Mr. S. M. Bello* and *Mrs. Fatima Ahmad*, my great uncle; *Mr. M. K Bello*, for their spiritual and moral support. My gratitude also goes to my siblings, relatives, and entire family members.

Lastly, my appreciation goes to stipendium hungaricum scholarship, the Nigerian government, Nigeria Federal scholarship board and Nigeria embassy in Budapest for their support and coordination.

List of publications

The thesis is based on the following publications

Saidu, M. B., Kúsz, N., Tsai, Y. C., Vágvölgyi, M., Berkecz, R., Kókai, D., Burián, K., Hohmann, J., Rédei, D.

Triterpenes and phenolic compounds from *Euphorbia deightonii* with antiviral activity against herpes simplex virus type-2.

Plants. **11**, 764 (2022). **IF: 4.658**

Saidu, M. B, Kúsz, N., Berkecz, R., Rácz, B., Spengler, G., Hohmann, J., Rédei, D.

Ingol, *ent*-atisane, and stachane-type diterpenoids from *Euphorbia deightonii* with multidrug resistance reversing activity.

Phytochemistry; **204**, 113344 (2022). **IF: 4.004**

Saidu, M. B., Krstić, G., Todorović, N., Berkecz, R., Ali, H., Zupkó, I., Hohmann, J., Rédei, D.

Monoterpenoid 5-methylcoumarins from *Centrapalus pauciflorus* with antiproliferative activity.

Arabian Journal of Chemistry **16**, 104777 (2023). **IF: 6.212**

Krstić, G., **Saidu, M. B.,** Bombicz, P., De, S., Ali, H., Zupkó, I., Berkecz, R., Gallah, U. S., Rédei, D., Hohmann, J.

Pauciflorins A–E, unexpected chromone–monoterpene-derived meroterpenoids from *Centrapalus pauciflorus*.

Journal of Natural Products **86**, 891-896 (2023). **IF: 4.803**

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Ingol and *ent*-atisane diterpenes from the aerial parts of *Euphorbia deightonii*.

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