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PRENYLATED ACYLPHLOROGLUCINOLS AND MEROTERPENOIDS FROM *HYPERICUM* PLANTS

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Abstract – *Hypericum* plants {family Clusiaceae (APG: Hypericaceae)} are known to be a rich source of prenylated acylphloroglucinols (PAPs), some of which have attracted attention as new drug leads as well as challenging targets for total synthesis. This review covers the researches of the isolation and structure elucidation of PAPs from *Hypericum* plants from 2006 to 2013. Several meroterpenoids with interesting chemical structures isolated from this genus are also summarized.

INTRODUCTION

The plants of the genus *Hypericum* {family Clusiaceae (APG: Hypericaceae)} are divided into 50 sections including more than 400 species, which are widespred in temperate regions. Several of the botanical species belonging to the genus have been used in traditional remedies.[1] *Hypericum perforatum* (St. John's Wort) counts among the most favorite herbal drugs, and is the only herbal alternative to classic synthetic antidepressants in the therapy of mild to moderate depression.[2] Pharmacological activities of *Hypericum* plants inspired many researchers to investigate the constituents, resulting in the isolation of a variety of natural products such as essential oils, flavonoids, xanthones, naphthodianthrones, terpenoids, and prenylated acylphloroglucinols (PAPs).[1] PAPs are characteristic constituents of the Clusiaceae plant family, and several compounds of this class (e.g. hyperforin from *H. perforatum*) have fascinating chemical structures and intriguing bioactivities, and are paid attention as a new drug lead from plant sources. The biosysnthesis of PAPs is proposed as follows.[3] Condensation of three molecules of malonyl-CoA and one molecule of acyl-CoA gives a tetraketide, which is subsequently cyclized by Dieckmann condensation into an acylphloroglucinol. The alkylations such as prenylation, geranylation, and methylation of the acylphloroglucinol afford PAPs. In 2006, reviews for the occurrence, chemical structure, and biological activity of natural PAPs were summarized by Grossman *et al*.[3] and Singh *et al*.[4]

This paper is dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday.

This review covers the reports on PAPs isolated from *Hypericum* plants that have been published from 2006 to 2013. During this period, 115 PAPs from 21 species (*H. androsaemum, H. ascyron*, *H. beanii*, *H. carinatum*, *H. chinense*, *H. cohaerens, H. elegans*, *H. ellipticum*, *H. empetrifolium*, *H. erectum*, *H. foliosum*, *H. geminiflorum, H. henryi* subsp. *uraloides*, *H. hypericoides*, *H. olympicum, H. prolificum, H. pseudopetiolatum* var. *kiusianum*, *H. sampsonii*, *H. sikokumontanum*, *H. sinaicum,* and *H. yojiroanum*) were reported. In this review, PAPs are classified into sections (**A**) simple PAPs with mono- to tetra-cyclic structures, (**B**) *O*-prenylated acylphloroglucinols, (**C**) PAPs with spiro-structures, (**D**) polycyclic polyprenylated acylphloroglucinols (PPAPs), and (**E**) PPAPs with caged-structures. In addition, meroterpenoids isolated from *Hypericum* plants are also summarized in the section (**F**).

A. SIMPLE PRENYLATED ACYLPHLOROGLUCINOLS

Elliptophenone A (**1**), a simple prenylated benzoylphloroglucinol with two prenyl groups and one methyl group, was isolated from the aerial portions of *Hypericum ellipticum*[5] (Figure 1). This compound showed a weak cytotoxicity against three human colon cancer cell lines (HT-29, HCT-116, and Caco-2) as well as a normal colon cell line (CCD-18Co). An acylphloroglucinol aspidinol C (**2**) (leaves of *H. chinense*)[6] exhibited antimicrobial activity against the NorA efflux protein overexpressing MDR *Staphylococcus aureus* strain SA-1199B with a minimum inhibitory concentration (MIC) of 2 μg/mL. A PAP (**3**) (aerial parts of *H. foliosum*)[7] demonstrated antibacterial activity against a panel of multidrug-resistant strains of *S. aureus* (MRSA) with MICs ranged from 16 to 32 μg/mL. Empetrikathiforin (**4**) was obtained from the aerial parts of *H. empetrifolium*.[8]

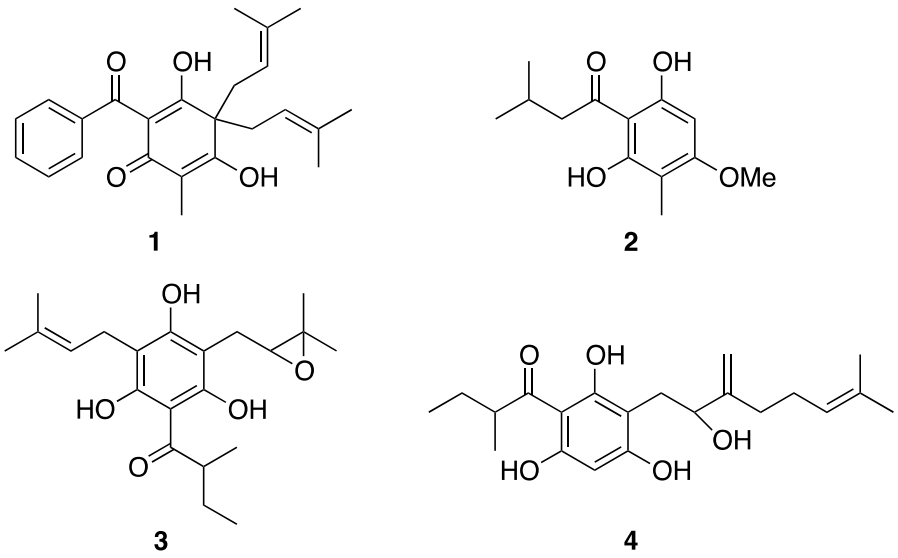


Figure 1. Simple PAPs (**1**–**4**) from *Hypericum* plants

Bicyclic PAPs possessing chromane skeleton such as cariphenones A (**5**) and B (**6**) (leaves of *H. carinatum*),[9] empetrikarinens A (**7**) and B (**8**) and empetrikarinols A (**9**) and B (**10**) (aerial parts of *H.*

empetrifolium),[10] petiolins A (**11**), B (**12**), and J (**13**) (aerial parts of *H. pseudopetiolatum* var. *kiusianum*),[11,12] yojironins D (**14**) and I (**15**) (whole plants of *H. yojiroanum*),[13,14] otogirinins F (**16**) and G (**17**) (aerial parts of *H. erectum*),[15] and prolificin A (**18**) (aerial parts of *H. prolificum*)[16] were reported (Figure 2). Cariphenones A (**5**) and B (**6**) have a benzoyl group as the acyl moiety, and **5** showed a moderate antioxidant activity. Empetrikarinens A (**7**) and B (**8**) and petiolins A (**11**) and B (**12**) are geranylated acylphloroglucinols, and **11** and **12** possess a geminal dimethyl group at the phloroglucinol moiety. Petiolin J (**13**) exhibited antimicrobial activities against *Micrococcus luteus*, *Cryptococcus neoformans*, and *Trichophyton mentagrophytes*. Otogirinin F (**16**) displayed a weak suppressive activity against isovaleric acid generation from L-leucine by *Corynebacterium xerosis*. Prolificin A (**18**) showed a moderate growth inhibition of human tumor cell lines (MCF-7, NCI-H460, SF-268, AGS, and HCT-116).

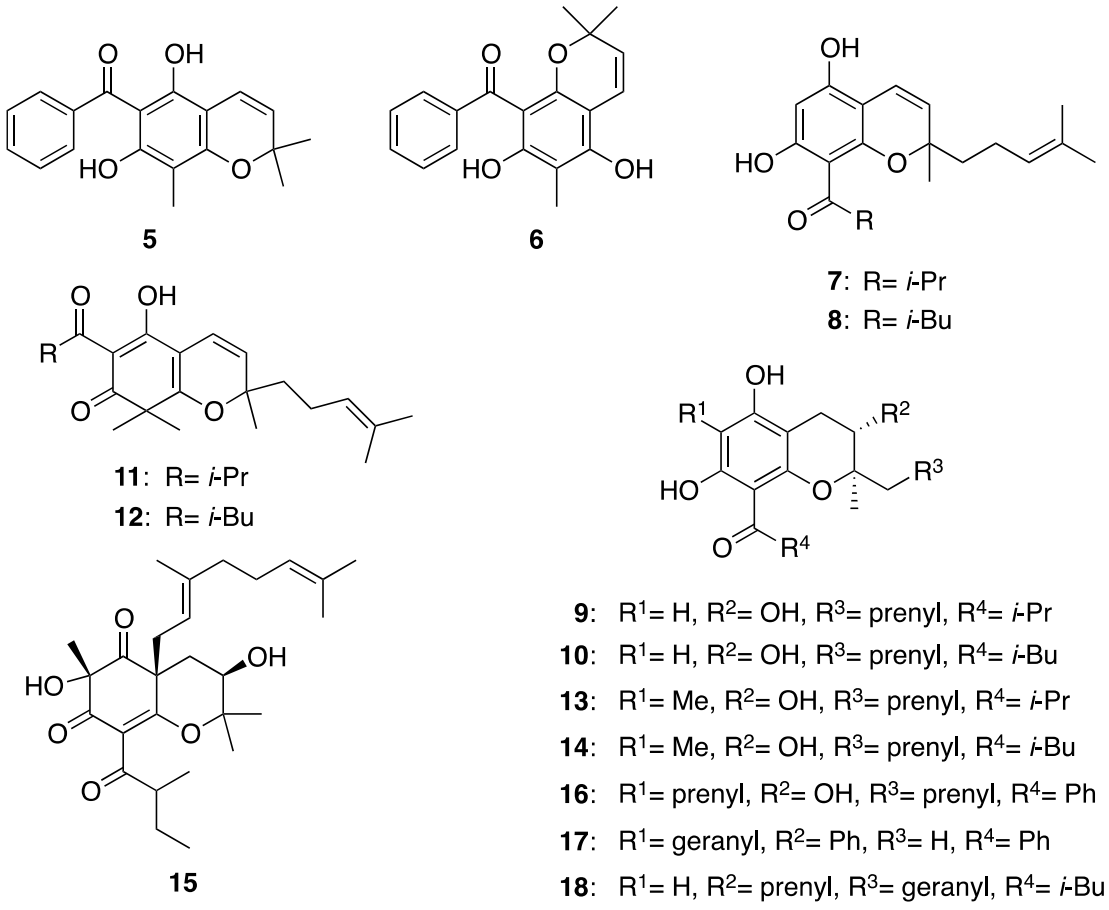


Figure 2. PAPs with bicyclic structures (**5**–**18**) from *Hypericum* plants

The structures of bicyclic PAPs having a dihydrofuran ring, petiolins C (**19**), L (**20**), and M (**22**) (aerial parts of *H. pseudopetiolatum* var. *kiusianum*),[11,12] yojironins C (**21**), E (**23**), F (**24**), G (**25**), and H (**26**) (whole plants of *H. yojiroanum*),[13,14] and takaneols A (**27**) and B (**28**) (aerial parts of *H. sikokumontanum*),[17] are shown in Figure 3. Their structures were assigned on the basis of spectroscopic

analysis. Petiolin C (**19**) and yojironin E (**23**) showed antimicrobial activities, while takaneols A (**27**) and B (**28**) exhibited a moderate cytotoxicity against human cancer cell lines.

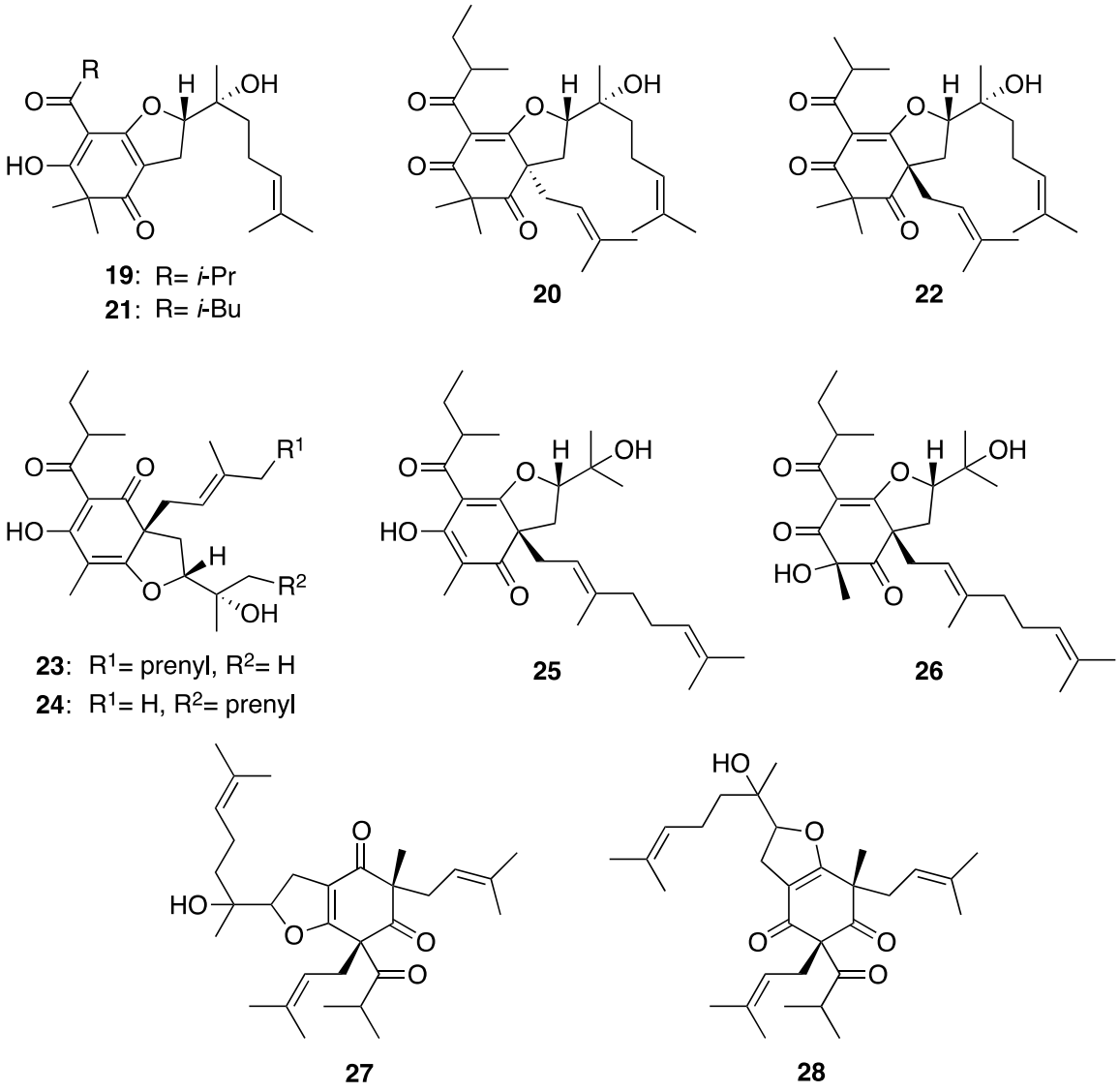
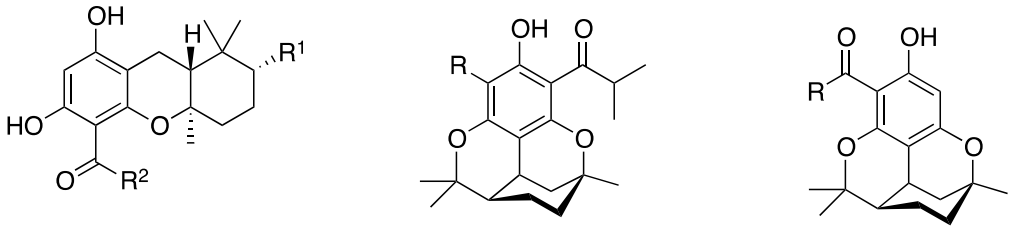


Figure 3. PAPs with bicyclic structures (**19**–**28**) from *Hypericum* plants

Empetriferdinans A (**29**) and B (**30**) and empetriferdinol (**31**) are tricyclic PAPs found in the aerial parts of *H. empetrifolium*[10] (Figure 4). The ECD spectra of **29**–**31** suggested that the absolute stereochemistry of their tricyclic ring system was identical. Tetracyclic PAPs with citran skeleton, petiolins D (**32**) and K (**33**) (aerial parts of *H. pseudopetiolatum* var. *kiusianum*)[18,12] and empetrifranzinans A–C (**34**–**36**) (aerial parts of *H. empetrifolium*)[10] were isolated. X-Ray analysis and optical rotations of **32** and **33** suggested that they were racemates, whereas **36** was optically active. Empetrifranzinans A (**34**) and B (**35**) were afforded as an inseparable mixture.



29: R^1= H, R^2= *i*-Pr
30: R^1= H, R^2= *i*-Bu
31: R^1= OH, R^2= *i*-Bu

32: R= geranyl
33: R= Me
35: R= H

34: R= *i*-Pr
36: R= *i*-Bu

Figure 4. PAPs with tricyclic (**29**–**31**) and tetracyclic (**32**–**36**) structures from *Hypericum* plants

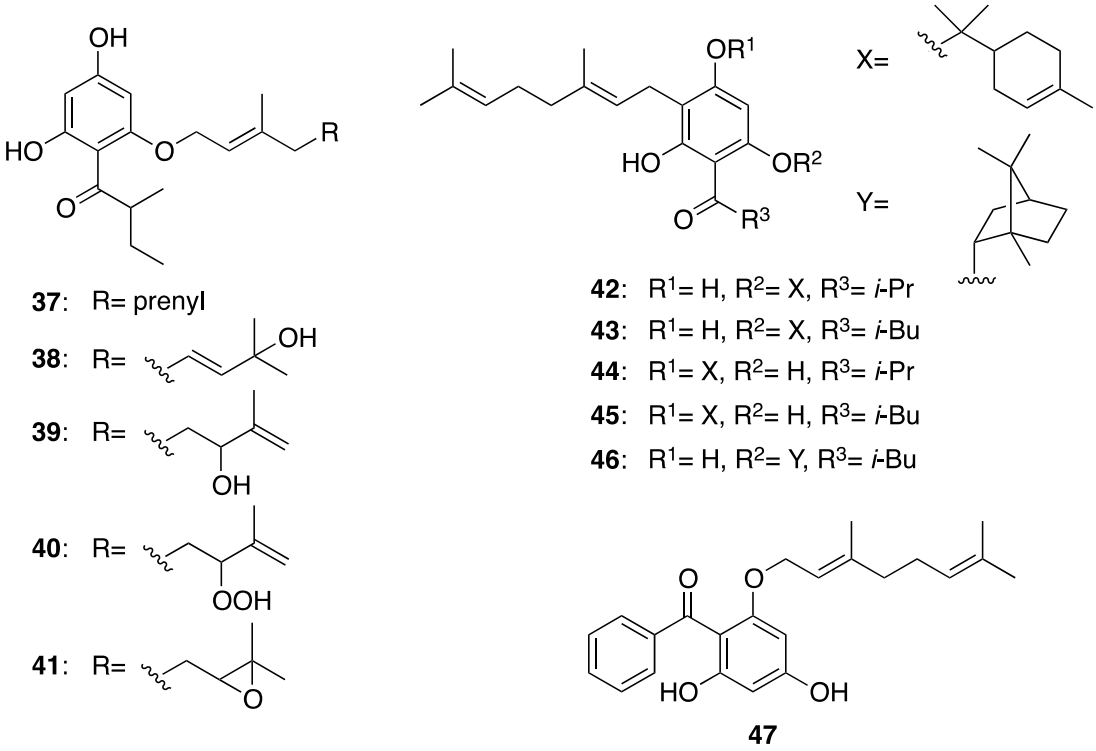


Figure 5. *O*-Prenylated acylphloroglucinols (**37**–**47**) from *Hypericum* plants

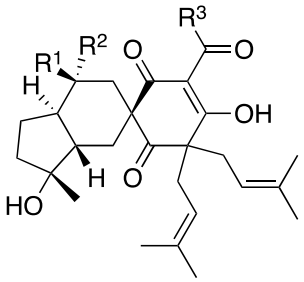
B. *O*-PRENYLATED ACYLPHLOROGLUCINOLS

The isolation of five *O*-prenylated acylphloroglucinols, olympicins A–E (**37**–**41**) (aerial parts of *H. olympicum*)[19] (Figure 5) and the synthesis of **37** using a simple four-step method were reported. Comparison of optical rotations for natural and synthetic olympicin A indicated the *S* configuration for the chiral center of acyl group in **37**. Olympicin A (**37**) showed exceptional activities against methicillin-resistant and multidrug-resistant strains of *S. aureus* with MICs of 0.5–1 μg/mL, while **38**–**41** showed moderate activities (MICs 64–128 μg/mL). Furthermore, **37** exhibited antimicrobial activities against four *Mycobacterium* strains (*M. smegmatis*, *M. fortuitum*, *M. phlei*, and *M. smegmatis*). In contrast,

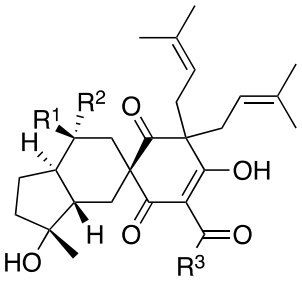
37 was not active against Gram-negative bacteria. Empetrifelixins A–D (**42**–**45**) (aerial parts of *H. empetrifolium*), antiproliferative PAPs possessing a limonene moiety linked via hydroxy groups of the acylphloroglucinol moieties, were isolated, together with a PAP with a bornane moiety, empetrikajaforin (**46**).[8] Elegaphenone (**47**) (aerial parts of *H. elegans*) was assigned as a benzoylphloroglucinol with an *O*-geranyl group, and showed cytotoxicity against HD-MY-Z, K-562, and KE-37 cancer cell lines.[20]

C. PRENYLATED ACYLPHLOROGLUCINOLS WITH SPIRO-STRUCTURES

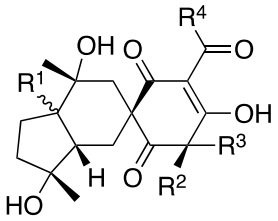
PAPs possessing unique spiro-structures with a geminal diprenyl group and a monoterpene moiety, tomoeones A–H (**48**–**55**) (Figure 6), were isolated from the aerial parts of *H. ascyron*.[21]



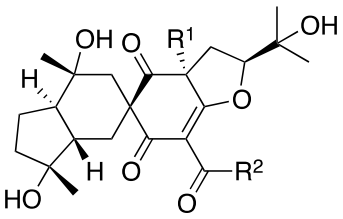
48: R^1= Me, R^2= OH, R^3= *i*-Pr
50: R^1= OH, R^2= Me, R^3= *i*-Pr
52: R^1= Me, R^2= OH, R^3= *i*-Bu
54: R^1= OH, R^2= Me, R^3= *i*-Bu
58: R^1= Me, R^2= OH, R^3= Ph
59: R^1= Me, R^2= OOH, R^3= Ph



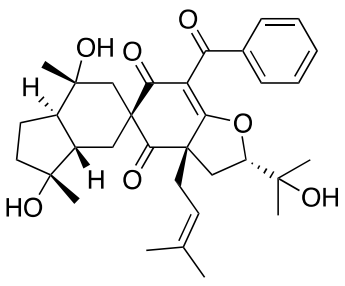
49: R^1= Me, R^2= OH, R^3= *i*-Pr
51: R^1= OH, R^2= Me, R^3= *i*-Pr
53: R^1= Me, R^2= OH, R^3= *i*-Bu
55: R^1= OH, R^2= Me, R^3= *i*-Bu
56: R^1= Me, R^2= OH, R^3= Ph
57: R^1= OH, R^2= Me, R^3= Ph



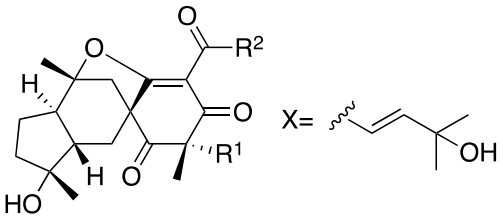
60: R^1= β-H, R^2= prenyl, R^3= Me, R^4= *i*-Bu
61: R^1= α-H, R^2= Me, R^3= prenyl, R^4= *i*-Pr
62: R^1= α-H, R^2= prenyl, R^3= Me, R^4= *i*-Bu



63: R^1= Me, R^2= *i*-Pr
64: R^1= Me, R^2= *i*-Bu
65: R^1= prenyl, R^2= Ph



66



67: R^1= prenyl, R^2= Ph
68: R^1= X, R^2= Ph
69: R^1= prenyl, R^2= *i*-Pr
70: R^1= prenyl, R^2= *i*-Bu

Figure 6. PAPs with spiro-structures (**48**–**70**) from *Hypericum* plants

Tomoeones E (**52**) and F (**53**) demonstrated cytotoxicity against KB cells as well as multi-drug resistant cancer cell lines (KB-C2 and K562/Adr). Recently, benzoyl acylphloroglucinols with the related skeleton, hyperbeanols A–D (**56**–**59**) (aerial parts of *H. beanii*)[22] have been reported. The structure including the relative stereochemistry of **56** was confirmed by a single crystal X-ray diffraction analysis, and **57** and **59** exhibited a modest cytotoxicity against K562 cells. The structures of spiro-PAPs, hyperielliptone HB (**60**) (heartwood of *H. geminiflorum*)[23] and chipericumins C (**61**) and D (**62**) (roots of *H. chinense*),[24] were elucidated. These compounds have a methyl and prenyl groups on the phloroglucinol moiety instead of a geminal diprenyl group in **48**–**59**. Hyperielliptone HB (**60**) exhibited an inhibition of oxidative DNA damage and an inhibitory effect on xanthine oxidase. Chipericumins A (**63**) and B (**64**) (roots of *H. chinense*)[24] are tetracyclic spiro-PAPs related biogenetically to **61** and **62**. The relative configurations of **63** and **64** were deduced by analysis of the NOESY spectra. Phytochemical investigation of the aerial parts of *H. sampsonii* afforded a series of spiro-benzoylphloroglucinols, sampsonols A–F (**65**–**70**).[25] Among them, **67**–**70** have unique tetracyclic structures with an ether linkage between the phloroglucinol and monoterpene moieties. Sampsonols A (**65**) and B (**66**) showed cytotoxicity against human tumor cell lines (MCF-7, HepG2, HT-29, and A549), while sampsonols C (**67**) and F (**70**) exhibited an inhibitory activity against LPS-induced NO production in RAW 264.7 macrophages.

D. POLYCYCLIC POLYPRENYLTED ACYLPHLOROGLUCINOLS

PAPs with highly oxygenated and densely substituted bicyclo[3.3.1]nonane-2,4,9-trione or bicyclo[3.2.1]octane-2,4,8-trione core are called as polycyclic polyprenylated acylphloroglucinols (PPAPs). Their fascinating chemical structures and intriguing biological activities have attracted widespread attention from organic synthesists and pharmacological endeavors.[3,26-30] Hyperforin, a major constituent of *H. perforatum* (St. John's Wort) responsible for its antidepressant effects, belongs to this class. This compound also showed antibacterial activity against Gram-positive bacteria and antitumoral activity in vivo.[26,27] From 2006 to 2013, 23 PPAPs with bicyclo[3.3.1]nonane-2,4,9-trione core including 18-hydroxy-7-epi-clusianone (**71**) and 18-hydroxyclusianone (**72**) (roots of *H. hypericoides*),[31] otogirinins D (**73**) and E (**74**)[15] (aerial parts of *H. erectum*), sampsoniones N–P (**75**–**77**)[32] (roots of *H. sampsonii*), uralodins B (**78**) and C (**79**) (aerial parts of *H. henryi* subsp. *uraloides*),[33] hypercohins B–J (**80**–**88**) (aerial parts of *H. cohaerens*),[34] hypersampsons H (**89**)[35] and K (**90**)[36] (fruits of *H. samposonii*), androforin A (**91**)[37] (aerial parts of *H. androsaemum*), and prolifenones A (**92**) and B (**93**)[16] (aerial parts of *H. prolificum*) were reported (Figures 7 and 8).

18-Hydroxy-7-epi-clusianone (**71**) and 18-hydroxyclusianone (**72**) possess a 3-hydroxybenzoyl group as the acyl moiety (Figure 7). A tetra- or di-hydrofuran ring adjacent to the phloroglucinol moiety is found in **73**–**86** and **88**, while **74** and **80**–**82** have an additional tetrahydrofuran ring on the C_{10} side chains. On the

other hand, **87**, and **89**–**91** have a tetra- or di-hydropyran ring connected to the phloroglucinol moiety (Figure 8). Hypersampsone H (**89**) exhibited cytotoxicity against A549 cells. Prolifenones A (**92**) and B (**93**) are rare PPAPs with a geranyl group at C-16 and absence of an alkyl group at C-7.

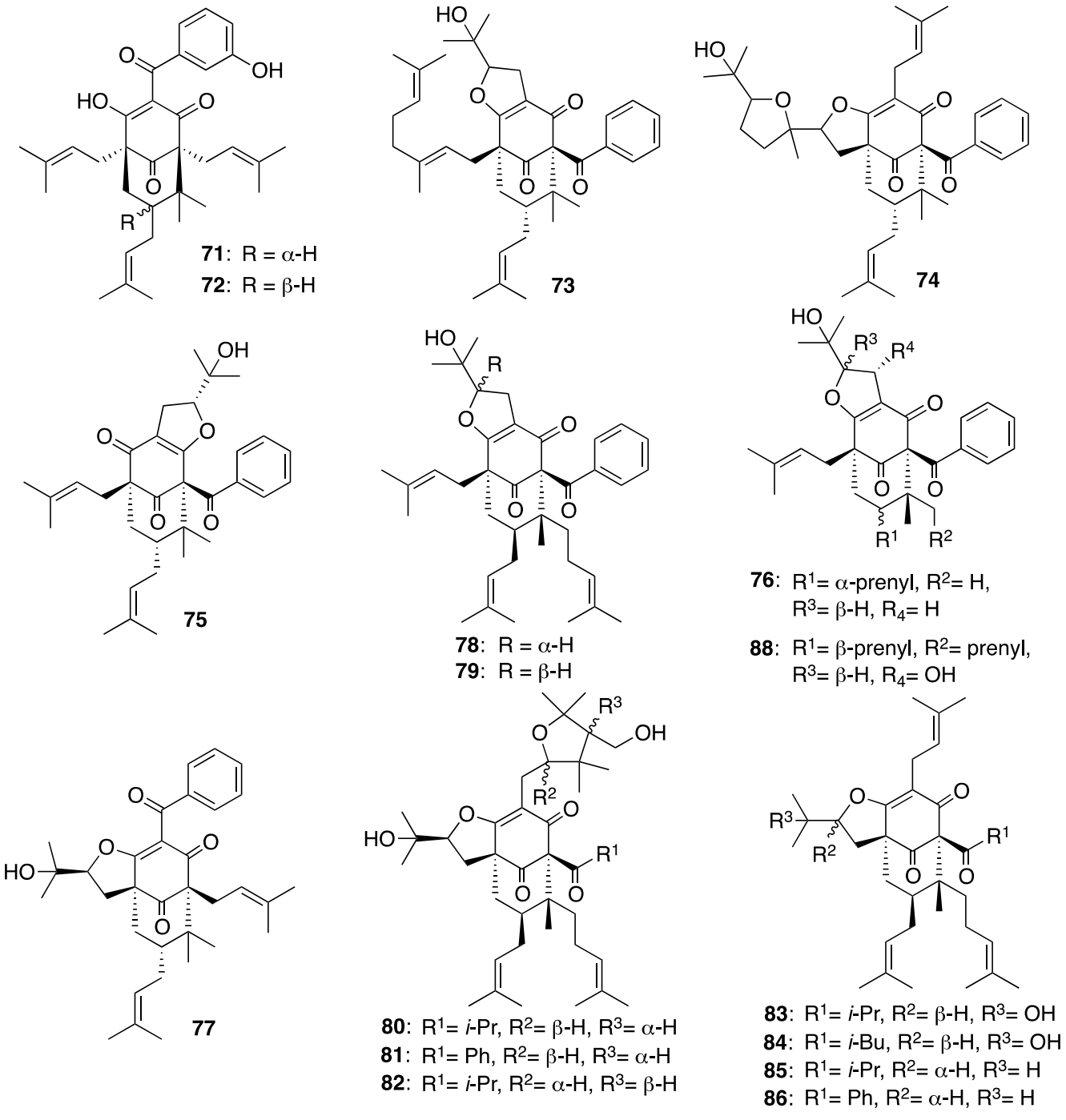


Figure 7. PPAPs with bicyclo[3.3.1]nonane-2,4,9-trione core (**71**–**86**) from *Hypericum* plants

Takaneones A–C (**96**–**98**)[17] (aerial parts of *H. sikokumontanum*) (Figure 9) are tricyclic PPAPs with bicyclo[3.2.1]octane-2,4,8-trione core and C_4 alkyl chain, and showed cytotoxicity against K562/Adr

multi-drug resistant cancer cells. Recently, the isolation of an unusual PPAP possessing a bicyclo[5.3.1]hendecane-8,10,11-trione core accompanied by a six-membered ether ring, hypercohin A (**99**)[38] (aerial parts *H. cohaerens*), was reported. The structure of **99** including the absolute configuration was elucidated by a single crystal X-ray diffractions analysis of its *p*-bromobenzoate ester. Hypercohin A (**99**) showed moderate inhibitory activity on acetylcholinesterase (AChE) and exhibited cytotoxicity against human cancer cell (HL-60, SMMC-7721, A549, MCF-7, and SW-80) and normal cell (Beas-2B) lines.

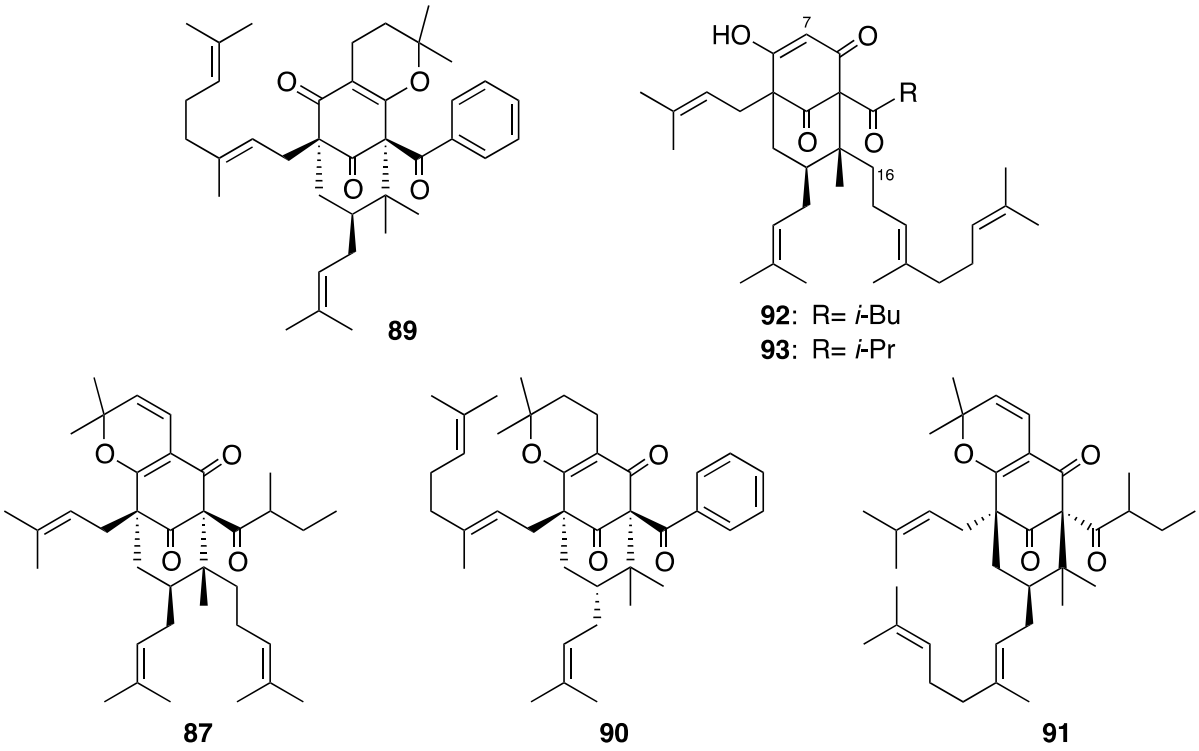


Figure 8. PPAPs with bicyclo[3.3.1]nonane-2,4,9-trione core (**89**–**93**) from *Hypericum* plants

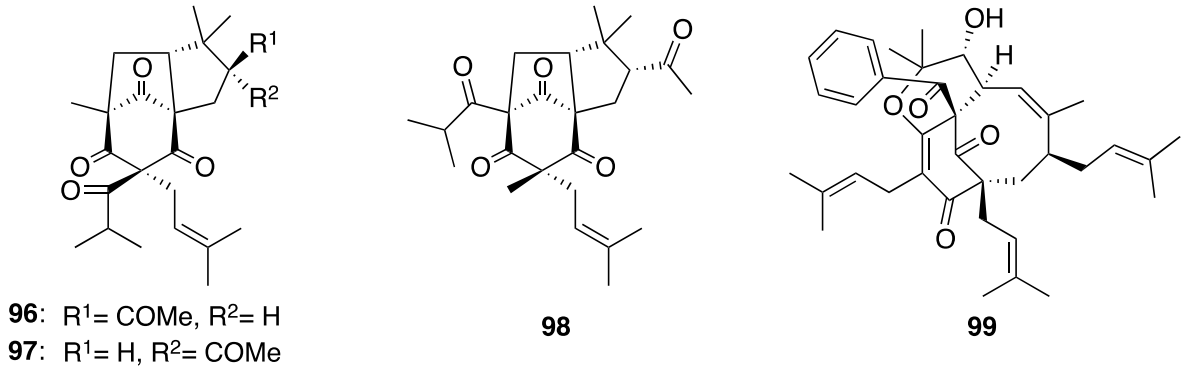


Figure 9. PPAPs with bicyclo[3.2.1]octane-2,4,8-trione core (**96**–**98**) and bicyclo[5.3.1]hendecane-8,10,11-trione core (**99**) from *Hypericum* plants

E. POLYCYCLIC POLYPRENYLATED ACYLPHLOROGLUCINOLS WITH CAGED STRUCTURES

Plants of Hypericaceae and Clusiaceae families (APG) produce a series of oxidized and polyprenylated benzophenone derivatives, some of which have complex caged structures with adamantane or homoadamantane skeletons. Several compounds belonging to this class showed a wide range of biological activity such as antimicrobial, antifungal, anticarcinogenic, and anti-HIV inhibitory activities.[39] From 2006, caged PAPs, otogirinins A–C (**100**, **113**, and **115**) (aerial parts of *H. erectum*),[15] sinaicinone (**101**) (aerial parts of *H. sinaicum*),[40] hyperandrone A (**103**) (aerial parts of *H. androsaemum*),[37] 18-hydroxyhyperibone K (**104**) (roots of *H. hypericoides*),[31] sampsonione Q (**102**),[32] and peroxysampsones A (**111**) and B (**112**)[41] (roots of *H. sampsonii*), hypersampsones G (**105**), I (**106**), J (**107**), and L (**114**) (fruits of *H. sampsonii*),[35,36] and hypercohones A–C (**108–110**) (aerial parts of *H. cohaerens*)[42] were reported (Figure 10). **100–104** are adamantane type caged PAPs. Among caged PAPs (**105–115**) with homoadamantae skeleton, **105–110** have an additional cyclopentane ring, whereas **111–113** possess an *endo*-peroxyde moiety. The possible biosynthetic pathway of hypersampson L (**114**), which has the structure with lack of an alkyl group at C-3, was discussed.

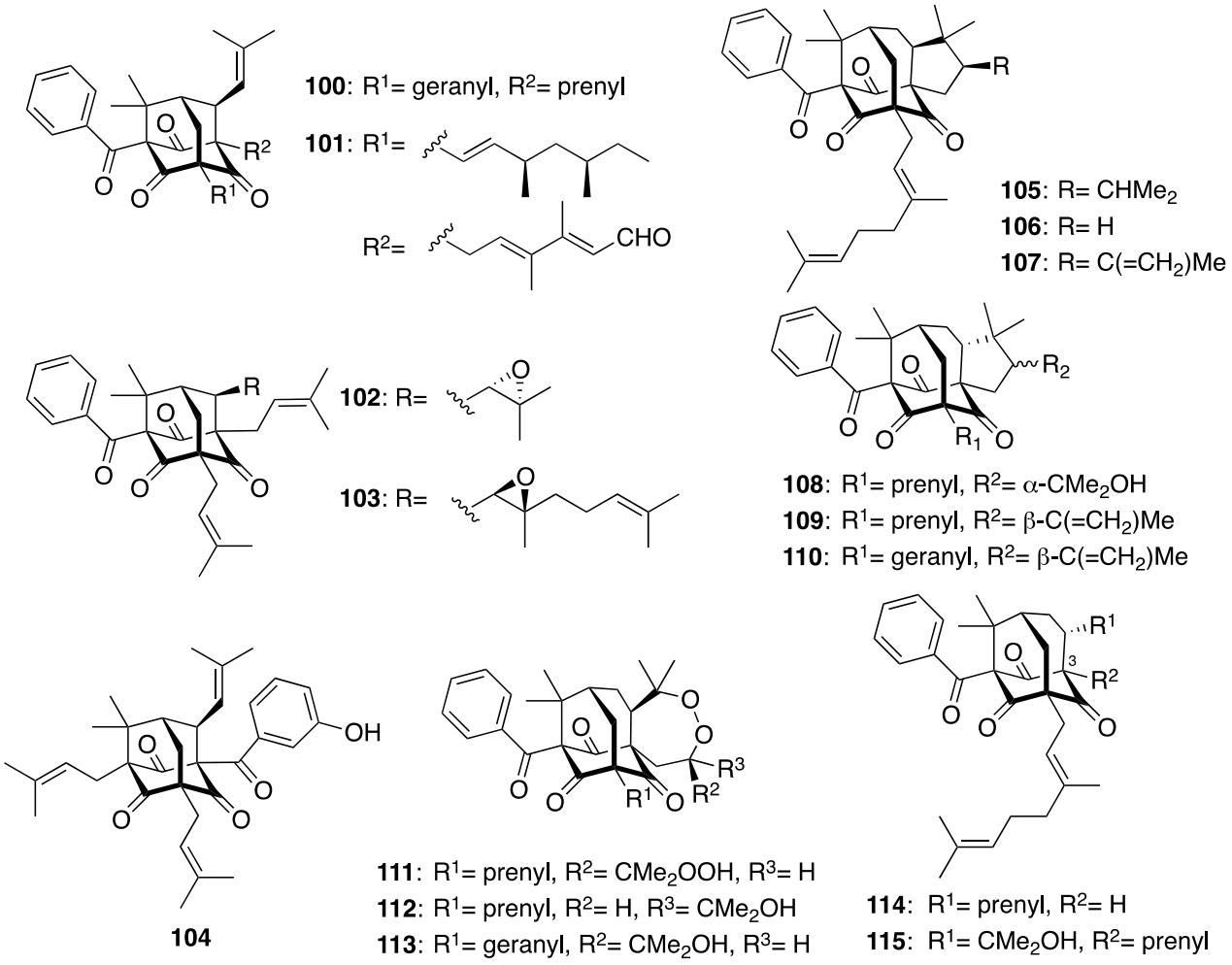


Figure 10. PAPs with caged structures (**100–115**) from *Hypericum* plants

F. MEROTERPENOIDS

Several meroterpenoids have been reported from *Hypericum* plants, some of which have fascinating chemical structures and interesting biological activities. Investigation of the whole plants of *H. yojiroanum* resulted in the isolation of two biogenetically unique meroterpenoids with a γ-butyrolactone moiety, yojironins A (**116**) and B (**117**)[13] (Figure 11), which seem to be composed of three isoprene units, two acetate units, and one 2-methylbutanoyl unit derived from isoleucine (Scheme 1). Yojironin A (**116**) exhibited cytotoxicity against murine lymphoma L1210 and human epidermoid carcinoma KB cells and showed antimicrobial activities against *Aspergillus niger*, *Candida albicans*, *C. neoformans*, *T. mentagrophytes*, *S. aureus*, and *Bacillus subtilis*.

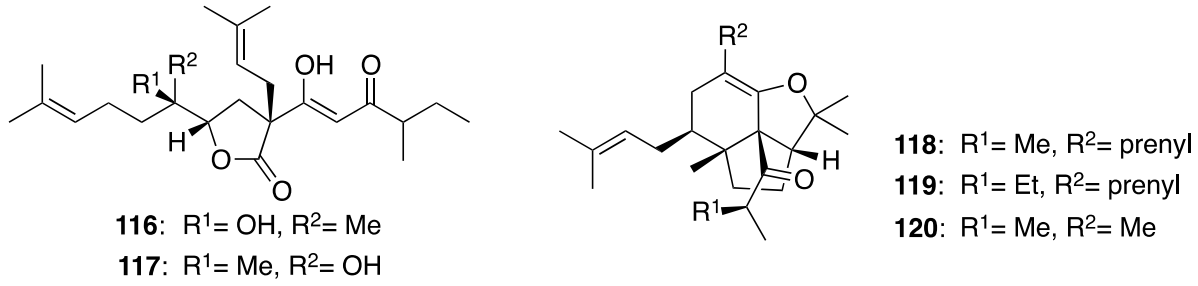
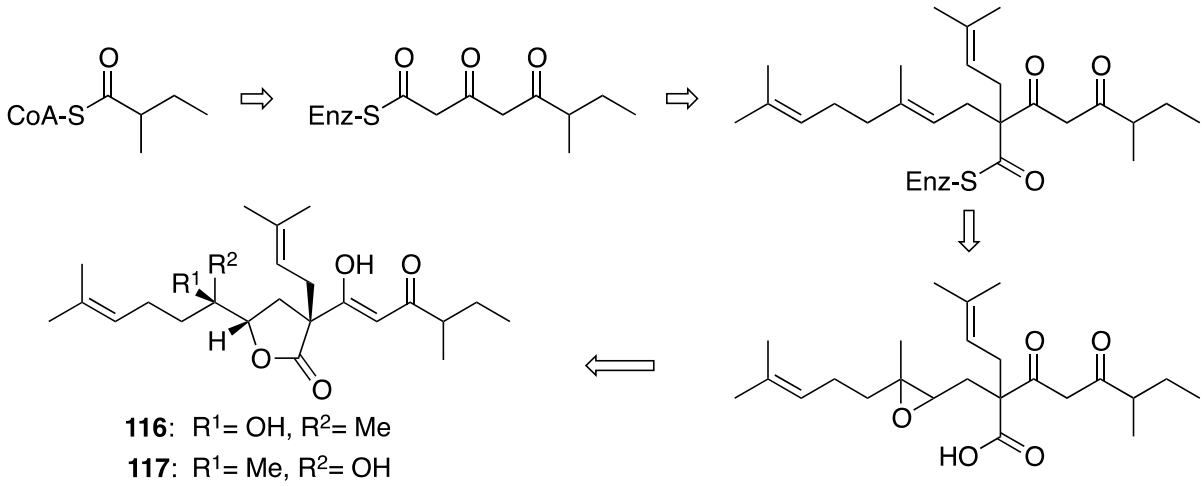


Figure 11. Meroterpenoids (**116**–**120**) from *Hypericum* plants



Scheme 1. Possible biogenetic pathway of yojironoins A (**116**) and B (**117**)

Yezo'otogirins A–C (**118**–**120**) (Figure 11) are structurally unique tricyclic meroterpenoids isolated from the aerial parts of *H. yezoense*.[43] The structure of **118**, including octahydroindenofuran core, three tertiary methyl groups, two prenyl groups, and one 2-methylpropanoyl group, were revealed by analysis of the ^{1}H-^{1}H COSY and HMBC spectra, taking the molecular formula elucidated by the HRESIMS into consideration (Figure 12). Interpretation of the NOESY spectrum of **118** suggested the β-orientations for

the substituents at C-2, C-3, and C-4. The absolute stereochemistry of **118** was elucidated based on analysis of the CD spectrum. Similarly, the structures of **119** and **120** were assigned. The bioinspired protective group-free total synthesis of (±)-yezo'otogirin C was achieved from 3-methyl-4-prenylcylohex-2-enone by Lee *et al*.[44]

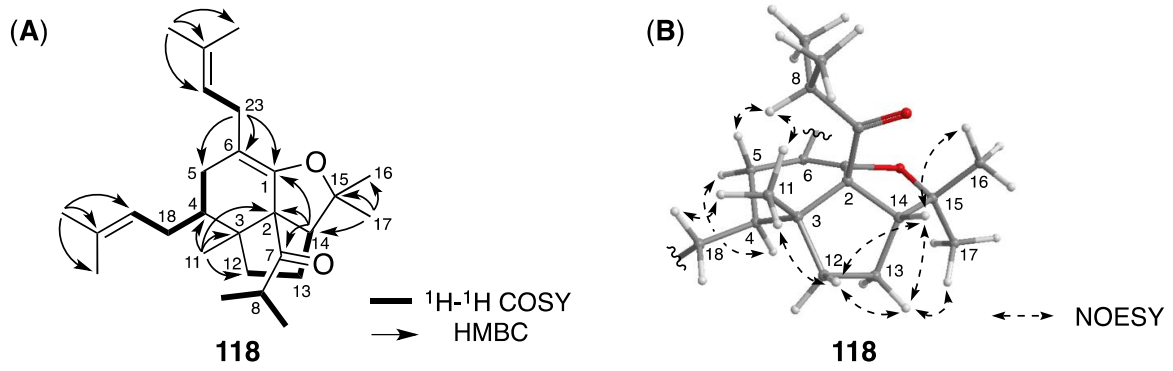


Figure 12. (**A**) Selected 2D NMR correlations and (**B**) relative stereochemistry for yezo'otogirin A (**118**)

Three meroterpenoids with spiro-lactone structures, hyperolactones A–C (**121**–**123**), and one related lactone, hyperolactone D (**124**), were isolated from the leaves of *H. chinense* (Figure 13).[45] Biosynthetic pathway of **121**–**124** was also proposed, where **121**–**124** may be biosynthesized from isopentenyl phosphate and polyketide. Hyperolactone D related meroterpenoids, 4-hydroxyhyperolatone D (**125**) and 5,6-dihydrohyperolactone D (**126**), were reported from the same species.[46] The absolute stereochemistries of hyperolactones A (**121**) and B (**122**) were confirmed by the total syntheses.[47-49] The total syntheses of hyperolactone C (**123**) were also reported by several groups.[48,50-56] Recently, biomimetic syntheses of hyperolactone D (**124**) and 4-hydroxyhyperolactone D (**126**) has been reported.[55]

Together with **125** and **126**, structurally unique meroterpenoids, biyouyanagins A (**127**)[57] and B (**128**)[46] (Figure 13), which have hybrid structures of **123** and a sesquiterpene (*ent*-zingiberene), were isolated from the leaves of *H. chinense*. Biyouyanagin A (**127**) exhibited an anti-HIV activity and showed an inhibitory activity against LPS-induced production of IL-10, IL-12, and TNF-α. The total syntheses of **127** and **128** proceeded by Nicolaou *et al*. through cascade sequences that produced enantiomerically pure building blocks *ent*-zingiberene and **123** and featured a novel [2+2] photoinduced cycloaddition reaction, resulting in the revision of the stereochemistries of **127** and **128**.[51,54,58] Xie *et al*. also achieved the total synthesis of **127**.[53] Recently, the library of synthesized analogues of **127** was subjected to biological screening, aiming to search lead compounds for antiviral and anti-inflammatory agents.[59]

Six meroterpenoids, biyoulactones A–E (**129**–**133**) (roots of *H. chinense*)[60,61] and biyouyanagiol (**134**) (stems of *H. chinense*),[46] were isolated (Figure 14). Biyoulactones A–C (**129**–**131**) are pentacyclic

meroterpenoids with a unique structure containing C–C bonded bi- and tri-cyclic γ-lactone moieties. The gross structures of three partial structures (units A–C) in **129** were elucidated based on analysis of the 2D NMR spectra (Figure 15). A single crystal X-ray diffraction analysis of **129** revealed the connectivities among units A–C as well as the absolute stereochemistry of **129**.

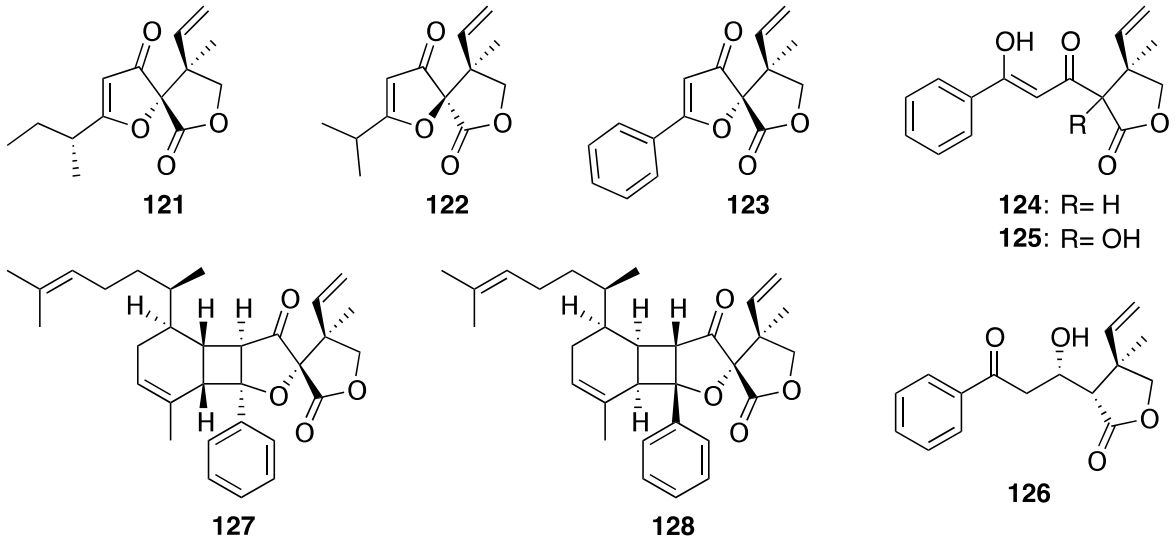


Figure 13. Meroterpenoids (**121**–**128**) from *Hypericum* plants

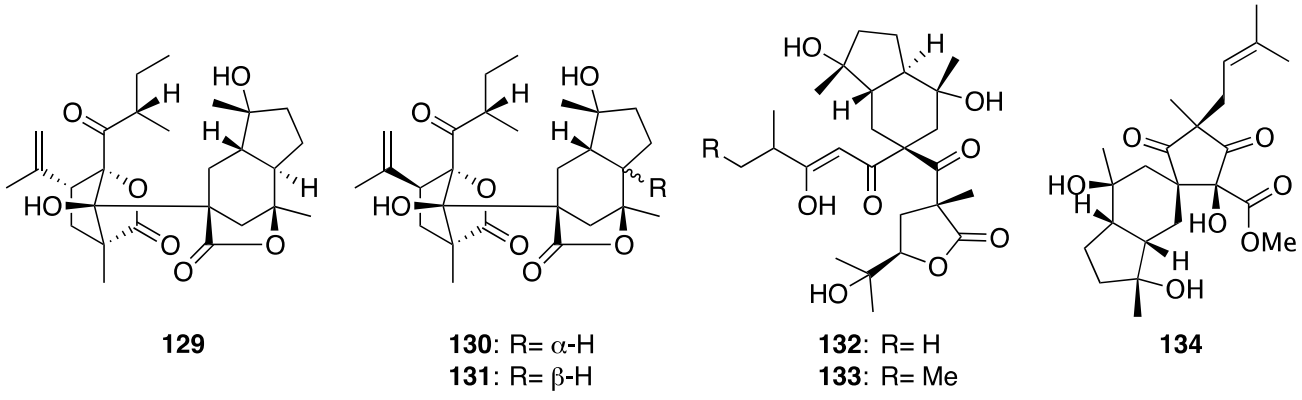


Figure 14. Meroterpenoids (**129**–**134**) from *Hypericum* plants

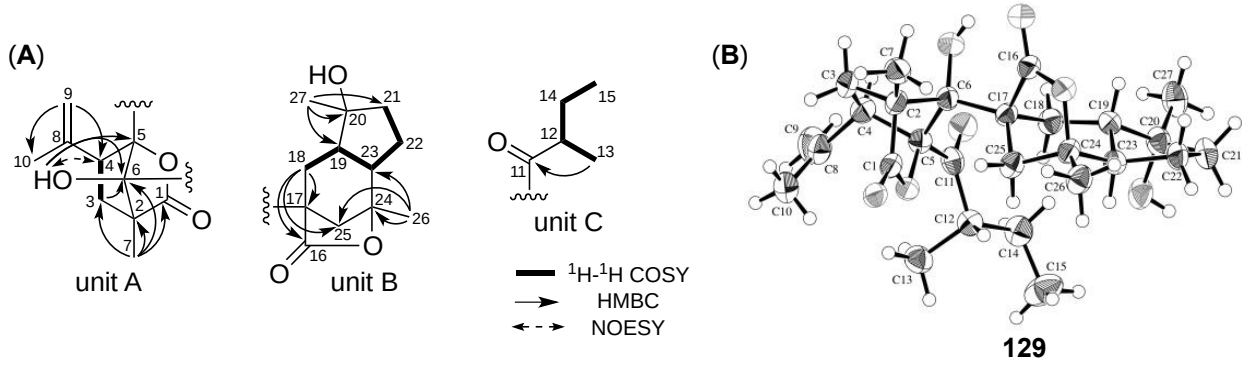


Figure 15. (**A**) Selected 2D NMR correlations and (**B**) ORTEP drawing of biyoulactone A (**129**)

Biyoulactones D (**132**) and E (**133**) are meroterpenoids possessing an octahydroindene ring, a γ-butyrolactone ring, and a β-diketone moiety. The structures of **132** and **133** including the relative configurations were assigned based on spectroscopic data and conformational analysis. The octahydroindene moiety is found in **129**–**134** in common, which is also seen in PAPs **61**–**64** (Figure 6) isolated from the same origin. These meroterpenoids (**129**–**134**) and PAPs (**61**–**64**) are presumed to be biogenetically related to PAPs, chinesins I or II,[62] major constituents for the flowers of *H. chinense*.

A meroterpenoid with a novel skeleton containing an oxepane ring, hypertricone (**135**), was reported from the leaves of *H. geminiflorum*[63] (Figure 16). Examination of the aerial parts of *H. perforatum* yielded a meroterpenoid, preforatumone (**136**).[64] A plausible biosynthetic route of **136** from hyperforin involving a Baeyer-Villiger ring cleavage and pinacol rearrangement was proposed. Meroterpenoids, hyperscabrins A–C (**137**–**139**), were reported as constituents of the aerial parts of *H. scabrum*.[65] The absolute configurations of **137**–**139** were elucidated by study of the CD spectra.

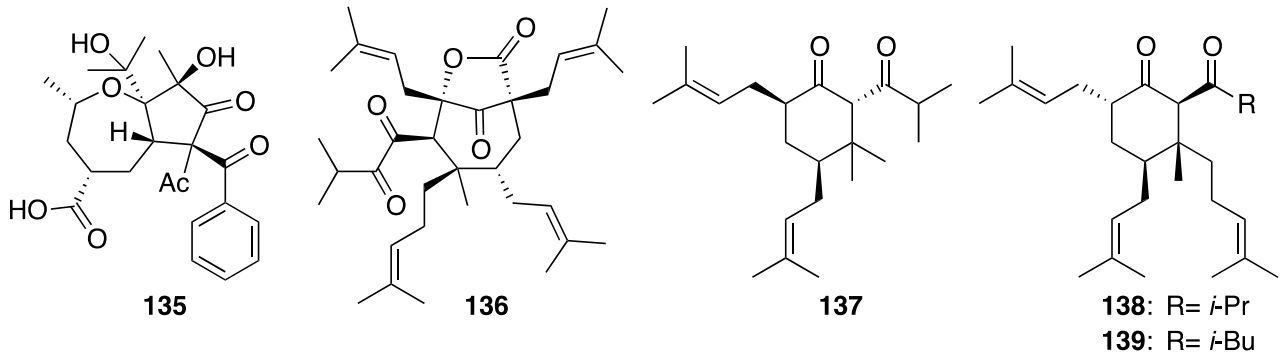


Figure 16. Meroterpenoids (**135**–**134**) from *Hypericum* plants

CONCLUSIONS

Studies for the isolation and structure elucidation of prenylated acylphloroglucinols (PAPs) isolated from *Hypericum* plants from 2006 to 2013 were reviewed. A part of PAPs were found to show interesting biological activity, whereas many of them have not been fully evaluated for their biological activities. Meroterpenoids from *Hypericum* plants were also summarized, whose unique chemical structures and intriguing biological activities will attract attention as new drug leads as well as challenging target of total synthesis. Though meroterpenoids from *Hypericum* plants have a wide variety of chemical structures, their biosynthesis pathway remains largely unsolved. Further efforts at understanding the properties of PAPs and meroterpenoids from *Hypericum* plants as well as phytochemical investigations of this genus are therefore needed.

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