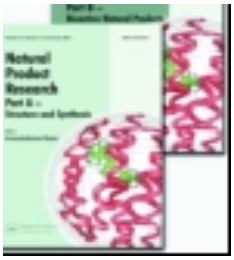

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Polycyclic polyprenylated acylphloroglucinols from *Hypericum choisianum*

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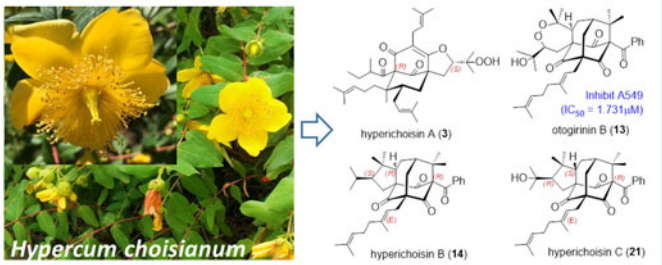
ABSTRACT

Twenty-one polycyclic polyprenylated acylphloroglucinols, including three new compounds named as hyperichoisins A (**3**), B (**14**) and C (**21**), were isolated from the aerial parts of *Hypericum choisianum*. The structures of those new compounds were elucidated by analysis of mass, NMR data, and chiroptical properties. A bioassay showed that otogirinin B had significant inhibitory effect on cell proliferation of A549.



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1. Introduction

Hypericum is a genus comprising of 490 species in the family Hypericaceae (formerly considered a subfamily of Clusiaceae or Guttiferae) (Li et al. 2007; Robson 2012). The widespread interest in the use of *H. perforatum* (St. John's Wort) in mild to moderate depression has attracted much attention in investigating the bioactive metabolites from its related species (Shiu and Gibbons 2009). Polycyclic polyprenylated acylphloroglucinols (PPAPs), possessing highly oxygenated acylphloroglucinol-derived cores decorated with side chains of prenyl and/or geranyl, are a group of structurally

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fascinating natural products exhibiting a broad range of biological activities (Yang et al. 2018).

Hypericum choisianum Wall. ex N. Robson (alternative name *H. choisyanum*), is a shrub distributed in grassy or rocky slopes, cliffs, thickets of Yunnan and Tibet provinces of China, as well as South Asia countries (Bhutan, India, Nepal, and Pakistan), which subjected to little attention except for sparse studies (Demirci et al. 2005; Shiu and Gibbons 2009). As a continuing research for bioactive and diverse ingredients from medicinal plants (Caprioli et al. 2016; Esposito et al. 2013; Keser et al. 2018; Mandrone et al. 2015; Nguyen Viet et al. 2019; Ornano et al. 2018; Simonetti et al. 2016; Venditti and Bianco 2018; Wang et al. 2018a; Wang et al. 2018b; Wang et al. 2019), we investigated the aerial parts of the title plant and led to the isolation of 21 PPAPs including bicyclic PPAPs (bPPAPs, **1**–**10**), adamantine- (**11**–**12**) and *homo*-adamantane-type (**13**–**21**) caged PPAPs (cPPAPs) (Figure 1). Among them, three new PPAPs were identified and named as hyperichoisins A (**3**), B (**14**) and C (**21**), respectively. The anti-tumor activity of those isolated PPAPs against human lung cancer cell line A549 was evaluated, and the result showed that only otogirinin B (**13**) had significant inhibitory effect on cell proliferation of A549 with IC_{50} value of $1.731 \pm 0.149\,\mu M$.

2. Results and discussion

PPAPs are a class of hybrid natural products with diverse structures, the numbering for the carbon atoms have been chaotic. Based on the consideration of bPPAPs and cPPAPs sharing the bicyclo[3.3.1]nonane core, we number the core structure as carbon atoms 1-12 and take those side chains, including prenyls, geranyls, and the alkyl or aryl of acyl, as affiliated substituents whatever they take part in forming new rings with the core or not.

The known compounds were identified to be furohyperforin (**1**) (Verotta et al. 1999), furoadhyperforin (**2**) (Lee et al. 2006), uralodins A (**4**) and C (**5**) (Chen et al. 2010), otogirinins D (**6**) and B (**13**) (Ishida et al. 2010), hyphenrones T (**7**) and V (**8**) (Liao et al. 2016), oxepahyperforin (**9**) (Verotta et al. 2000), hyphenrone E (**10**) (Yang et al. 2014), sampsonione J (**11**) (Hu and Sim 1999a; Zhu et al. 2014), hyperisampsin G (**12**) (Zhu et al. 2014), hookerione K (**15**) (Ye et al. 2019), sampsoniones D (**16**) and C (**18**) (Hu and Sim 1999b), hypercohone C (**17**, $[\alpha]_D^{20}$−32.9, $c = 0.12$, $CHCl_3$) (Liu et al. 2013), attenuatumione D (**19**) (Zhou et al. 2014), hypersampsonone G (**20**) (Zhang et al. 2016), respectively, by comparison of $[\alpha]_D$, ^1H, ^{13}C NMR and MS data with cited literature data.

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Hyperichoisin A (**3**) was isolated as colourless oil and had the molecular formula of $C_{36}H_{54}O_6$ as judged from the HR-ESI-MS $[M+H]^+$ *m/z* at 583.4003, corresponding to the addition of one oxygen atom of furoadhyperforin (**2**). The ^1H and ^{13}C NMR spectra (Table S1) showed resonance signals for three prenyls (three olefinic protons at δ_H 5.07, 5.04 and 4.95, six tertiary methyls at δ_H 1.70, 1.70, 1.64, 1.63, 1.60 and 1.58), an oxygenated isopentane (a ABM coupling system at δ_H 1.84, 2.56 and 4.89, each 1H,

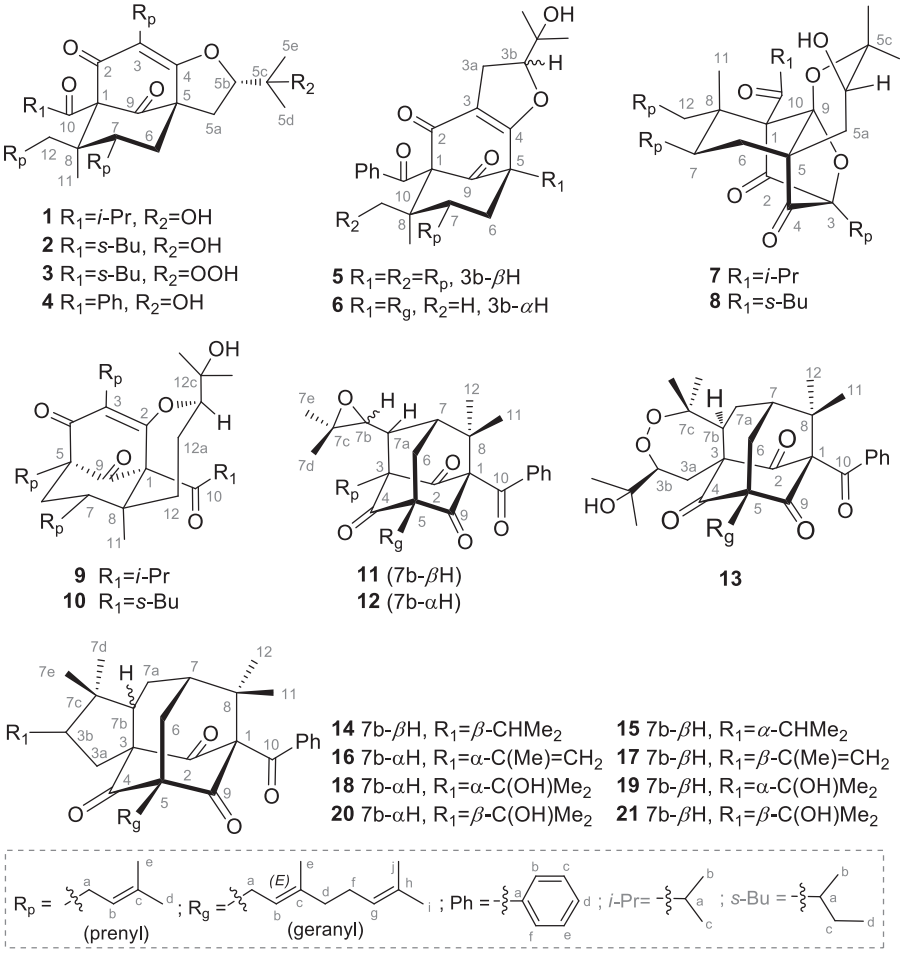

Figure 1. Structures of PPAPs **1 – 21** from *H. choisianum*.

dd, $J = 13.2$, 11.2 and 5.9, two tertiary methyls at δ_H 1.30 and 1.28, and two oxygenated carbons at δ_C 86.5 and 83.1), a *sec*-butyryl at δ_H 1.09 (d, $J = 6.5$ Hz) and 0.78 (t, $J = 7.3$ Hz) and δ_C 209.0 (s), 48.7 (d), 27.4 (t), 16.5 (q) and 11.5 (q), a methylene at δ_C 38.0, a methine at δ_C 43.4, three saturated quaternary carbons at δ_C 83.2, 59.0 and 48.3, an α,β-conjugated enol at δ_C 192.8, 172.8 and 116.8, and a remaining carbonyl at δ_C 204.6. The above evidences indicated a furan-type bPPAP. The characteristic five quaternary carbons at δ_C 83.2, 192.8, 116.8, 172.8 and 59.0 for C-1 – C-5 revealed a tetrahydrofuran ring formed through C_{5b}-*O*-C_4, just like furoadhyperforin (**2**) and 33-deoxy-33-hydroperoxyfurohyperforin (**1a**, R_2 = OOH of **1**). Compared the NMR data of **1a** and **2** (Table 1S), **3** had the almost superposed NMR signals for the furan moiety and the remaining with those of **1a** and **2**, respectively, demonstrating a hydroperoxide of **2** with the same configuration. Therefore, the structure of hyperichoisin A (**3**) was elucidated as shown.

Hyperichoisins B (**14**) and C (**21**) possessed the molecular formulae of $C_{38}H_{50}O_4$ and $C_{38}H_{50}O_5$, respectively, as deduced from their HR-ESI-MS spectra. The ^{1}H and ^{13}C

NMR data of **14** and **21** showed typical resonances for *homo*-adamantane-type cPPAPs in contrast with those of **15** – **20** (Tables S2-S3). The most important NMR difference between **14** and **21** was a quaternary carbon signal at δ_C 73.4 in **21** instead of the methine at δ_C 29.1 in **14**, indicated **21** to be a 3 b-hydroxylated derivative of **14**, which rationalised their NMR differences of the five-number ring formed through the linkage of C_3–C_{7b} and C_{3b}–C_{7c}. According to the summarization by Ye *et al* (Ye et al. 2019), the chemical shifts of C-6 at δ 35.2 and 35.3 in **14** and **21** indicated the β-orientation of H-7b of both, and the small ^{13}C shift differences between Me-7d and Me-7e of **14** (0.4 ppm) and **21** (0.6 ppm) demonstrated the opposite oriented relation between H-3b with H-7b. Hence, the relative configurations of **14** and **21** were elucidated as shown in Figure 1. Both **14** and **21** had the identical NMR data and the opposite optical rotations ($[\alpha]_D^{25}$ −17.4 for **14**; $[\alpha]_D^{31}$ −21.9 for **21**) with those of hypersampsone E (**14a**, $[\alpha]_D^{25}$ +39) (Lin and Wu 2003) and sampsonione F (**21a**, $[\alpha]_D^{31}$ +14.5) (Hu and Sim 1999b), respectively, indicating the enantiomers of **14a** and **21a**. The absolute configuration of **14** and **21** were determined as 1 *R* based on the negative CD absorption around 330 nm as deduction by Zhu *et al* (Zhu et al. 2014).

These isolated PPAPs were evaluated for anti-tumor activity against human lung cancer cell line A549. The results (Table S4) showed that only otogirinin B (**13**), a bPPAP containing peroxy bond, had significant inhibitory effect on cell proliferation of A549 with IC_{50} value of 1.731 ± 0.149 μM.

3. Experimental

3.1. General experimental procedures

The IR spectra were recorded on a Nicolet-Magna-712-FTIR spectrometer (ThermoFisher, Madison, WI, USA) by using KBr disks. 1 D and 2 D NMR spectra were obtained at 500 MHz for ^1H and 125 MHz for ^{13}C, respectively, on a Bruker Advance III 500 spectrometer (Bruker, Ettlingen, Germany) with TMS as reference. HR-ESI-MS and HR-EI-MS were obtained on a Bruker Esquire 3000plus (Bruker) and a Waters/Micromass Q-TOF-Ultima (Waters, Milford, MA, USA) mass spectrometers, respectively. MCI Gel Chp20p (Mitsubishi Chemical, Tokyo, Japan), Silica gel (300-400 mesh, Qingdao Haiyang Chemical Co. Ltd, Qingdao, China), and ODS-A-HG reversed-phase silica gel (12 nm S-50μm, YMC Co., Ltd., Japan) were used for column chromatography (CC). Silica gel HSGF254 (Yantai Jiangyou Guijiao Kaifa Co., Yantai, China) was used for TLC. Semi-preparative HPLC separations were performed on a Waters HPLC system (Waters) with Waters-2545 pump, Waters-2489 detector, and Xbridge-C_{18} column (5 μm, i.d. 10 mm × 250 mm).

3.2. Plant material

The aerial parts of *H. choisianum* were collected from Gongshan county, Yunnan province of China, in Oct 2016, and authenticated by Prof. C.-H. Tan, one of authors. A voucher specimen (No. 20161028) was deposited with the Herbarium of Shanghai Institution of Materia Medica, Chinese Academy of Sciences, China.

3.3. Extraction and isolation

The powdered air-dried aerial parts of *H. choisianum* (9.0 kg) were extracted in EtOH (3 × 60 L) at room temperature to provide crude extract (998 g). The crude extract was suspended with distilled H_2O (3 L) and extracted with petroleum ether (PE, 3 × 3 L), chloroform ($CHCl_3$, 3 × 3 L), ethyl acetate (EA, 3 × 3 L) and n-butanol (BuOH, 3 × 3 L), respectively. The combined PE and $CHCl_3$-soluble fraction (270 g) was subjected to a column chromatography (CC) of MCI (50, 80 and 100% CH_3OH in H_2O) to obtain fractions C1–C3. Silica gel CC of C3 (110 g) with $CHCl_3$–CH_3OH (1: 0, 50: 1, 19: 1, 9: 1, and 1: 1, v/v) yielded five fractions (C3.1–C3.5). Fr. C3.1 (16.95 g) was further chromatographed on a silica gel column (PE–acetone, 50: 1 to 10: 1) to afford four fractions (C3.1A–C3.1D). Fr. C3.1C was separated by sequential CCs of silica gel (PE–acetone, 50:1 to 10: 1; PE–$CHCl_3$–acetone, 35: 15: 1 to 35: 15: 5), ODS (acetone in H_2O, 60–100%) and semipreparative HPLC (MeOH in H_2O, 4 mL/min) to obtain **1** (93 mg), **2** (4 mg) and **3** (6 mg). Fr. C3.1D furnished **4** (78 mg), **5** (13 mg) and **13** (2 mg) after purification of silica gel CC (PE–EA, 10: 1 to 2: 1; CH_2Cl_2–EA, 200: 1 to 50: 1). Fr. C3.2 was isolated by CC of silica gel (PE–acetone, 50: 1 to 5: 1) to obtain five fractions (C3.2A–C3.2E). Fr. C3.2B (7.6 g) was subjected to CCs of silica gel (PE–$CHCl_3$–acetone, 40: 10: 1 to 40: 10: 5) and semipreparative HPLC (MeOH in H_2O, 4 mL/min) to yield **6** (35 mg), **18** (24 mg), **19** (22 mg), **20** (5 mg) and **21** (6 mg). Fr. C3.2A was separated by CC of silica gel (PE–acetone, 50: 1 to 5: 1) to obtain four fractions (C3.2A1–C3.2A4). Fr. C3.2A1 was separated by sequential CCs of ODS (acetone in H_2O, 60-100%) and semipreparative HPLC (MeOH in H_2O, 4 mL/min) to gain **14** (17 mg), **15** (10 mg), **16** (22 mg) and **17** (12 mg). By the similar process, **7** (21 mg), **8** (52 mg), **9** (18 mg) and **10** (12 mg), as well as **11** (11 mg) and **12** (5 mg) were obtained from fr. C3.2A2 (2.57 g) and fr. C3.2A3 (5.04 g), respectively.

3.3.1. Hyperichoisin A (3)

Colorless oil; $[\alpha]_D^{18}$ +45.78 (*c* 0.075, MeOH); IR (KBr) ν_{max} 3419, 2970, 2855, 1729, 1622, 1455, 1378, 1260, 1233, 1075; ^1H and ^{13}C NMR data see Table S1; HR-ESI-MS *m/z* 583.4003 $[M+H]^+$ (calcd for $C_{36}H_{55}O_6$, 583.3999).

3.3.2. Hyperichoisin B (14)

Yellowish oil; $[\alpha]_D^{20}$ -17.4 (*c* 0.285, $CHCl_3$); IR (KBr) ν_{max} 2920, 2871, 1735, 1701, 1686, 1261, 1237, 1098, 1022, 803; ^1H and ^{13}C NMR data see Tables S2-S3; HR-EI-MS *m/z* 570.3694 $[M]^+$ (calcd for $C_{38}H_{50}O_4$, 570.3704).

3.3.3. Hyperichoisin C (21)

Colorless oil; $[\alpha]_D^{31}$ -21.9 (*c* 0.31, $CHCl_3$); IR (KBr) ν_{max} 3447, 2961, 2852, 1735, 1702, 1448, 1376, 1260, 1235, 1094, 1018, 800; ^1H and ^{13}C NMR data see Tables S2-S3; HR-EI-MS *m/z* 586.3661 $[M]^+$ (calcd for $C_{38}H_{50}O_5$, 586.3653).

3.4. Cell culture

Human lung cancer cells (A549) was provided by the American Type Culture Collection (ATCC, Rockville, MD, USA). The cells were cultured in medium (RPMI1640,

Invitrogen, Carlsbad, CA, USA) supplemented with 10% heat-inactivated fetal bovine serum (FBS, Invitrogen) and antibiotics antimycotics (PSF; 100 units/mL penicillin G sodium, 100 μg/mL streptomycin, and 250 ng/mL amphotericin B). The cells were incubated at 37 °C and 5% CO_2 in a humidified atmosphere.

3.5. In vitro cell proliferation assay

Cell viability was determined by the sulforhodamine B (SRB) protein staining method (Vichai and Kirtikara 2006). In brief, cells were seeded in 96-well plates and incubated for 24 h, and were fixed (for zero day controls) or treated with test compounds for 72 h. After incubation, cells were fixed with 10% trichloroacetic acid (TCA), dried and stained in 4 mg/mL SRB in 1% acetic acid solution. Unbound dye was washed and stained cells were dried and dissolved in 10 mM Tris (pH 10.0). Absorbance was measured by a multiwall spectrophotometer (SpectraMax M5) at 560 nm and cell proliferation was determined as follows: cell proliferation (%) = (average absorbance $_{compound}$ − average absorbance $_{zero\ day}$)/(average absorbance $_{control}$ − average absorbance $_{zero\ day}$) × 100%. IC_{50} values were calculated by non-linear regression analysis using the GraphPad Prism 6 software (GraphPad Software, San Diego, CA, USA).

4. Conclusion

21 PPAPs including three new compounds, hyperichoisins A (**3**), B (**14**) and C (**21**), were isolated from the aerial parts of *Hypericum choisianum*. With the exception of a bPPAP (otogirinin B, **13**) containing peroxy bond, the other PPAPs had not cytotoxic effect on A549. Furthermore, some NMR differences of *homo*-adamantane-type PPAPs showed obvious correlation with the relative configuration changes, which can serve as the benchmark for the determination of the relative configurations of some carbons.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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References

Caprioli G, Alunno A, Beghelli D, Bianco A, Bramucci M, Frezza C, Iannarelli R, Papa F, Quassinti L, Sagratini G, et al. 2016. Polar constituents and biological activity of the berry-like fruits from *Hypericum androsaemum* L. Front Plant Sci. 7: article 232.

Chen XQ, Li Y, Cheng X, Wang K, He J, Pan ZH, Li MM, Peng LY, Xu G, Zhao QS. 2010. Polycyclic polyprenylated acylphloroglucinols and chromone *O*-glucosides from *Hypericum henryi* subsp *uraloides*. Chem Biodivers. 7(1):196–204.

Demirci B, Baser KHC, Crockett SL, Khan IA. 2005. Analysis of the volatile constituents of Asian *Hypericum* L. (Clusiaceae, Hyperidoideae) species. J Essent Oil Res. 17(6):659–663.

Esposito F, Sanna C, Del Vecchio C, Cannas V, Venditti A, Corona A, Bianco A, Serrilli AM, Guarcini L, Parolin C, et al. 2013. *Hypericum hircinum* L. components as new single-molecule inhibitors of both HIV-1 reverse transcriptase-associated DNA polymerase and ribonuclease H activities. Pathog Dis. 68(3):116–124.

Hu LH, Sim KY. 1999. Cytotoxic polyprenylated benzoylphloroglucinol derivatives with an unusual adamantyl skeleton from *Hypericum sampsonii* (Guttiferae). Org Lett. 1(6):879–882.

Hu LH, Sim KY. 1999. Sampsoniones C-H, a unique family of polyprenylated benzophenone derivatives with the novel tetracyclo[7.3.1.1^{3,11}.0^{3,7}]tetradecane-2,12,14-trione skeleton, from *Hypericum sampsonii* (Guttiferae). Tetrahedron Lett. 40(4):759–762.

Ishida Y, Shirota O, Sekita S, Someya K, Tokita F, Nakane T, Kuroyanagi M. 2010. Polyprenylated benzoylphloroglucinol-type derivatives including novel cage compounds from *Hypericum erectum*. Chem Pharm Bull. 58(3):336–343.

Keser S, Keser F, Kaygili O, Tekin S, Demir E, Turkoglu I, Turkoglu S, Parlak AE, Yilmaz O, Karatepe M, et al. 2018. Phytochemical compounds and antiradical, antimicrobial, and cytotoxic activities of the extracts from *Hypericum scabrum* L. Flowers. Nat Prod Res. Epub at DOI: 10.1080/14786419.2018.1493735.

Lee JY, Duke RK, Tran VH, Hook JM, Duke CC. 2006. Hyperforin and its analogues inhibit CYP3A4 enzyme activity. Phytochemistry. 67(23):2550–2560.

Li XW, Li J, Norman KBR, Peter FS. 2007. Clusiaceae (Guttiferae). In: Flora of China, Vol 13. Beijing: Scientific Press; p. 11–12.

Liao Y, Yang SY, Li XN, Yang XW, Xu G. 2016. Polyprenylated acylphloroglucinols from the fruits of *Hypericum henryi*. Sci China Chem. 59(9):1216–1223.

Lin YL, Wu YS. 2003. Polyprenylated phloroglucinol derivatives from *Hypericum sampsonii*. HCA. 86(6):2156–2163.

Liu X, Yang XW, Chen CQ, Wu CY, Zhang JJ, Ma JZ, Wang H, Zhao QS, Yang LX, Xu G. 2013. Hypercohones A–C, acylphloroglucinol derivatives with homo-adamantane cores from *Hypericum cohaerens*. Nat Prod Bioprospect. 3(5):233–237.

Mandrone M, Lorenzi B, Venditti A, Guarcini L, Bianco A, Sanna C, Ballero M, Poli F, Antognoni F. 2015. Antioxidant and anti-collagenase activity of *Hypericum hircinum* L. Ind Crop Prod. 76: 402–408.

Nguyen Viet D, Le Ba V, Nguyen Duy T, Pham Thi VA, Tran Thi H, Le Canh VC, Bach Long G, Kim YH, Tuan Anh HL. 2019. Bioactive compounds from the aerial parts of *Hypericum sampsonii*. Nat Prod Res.:1–3. Epub 2019/04/04.

Ornano L, Feroci M, Guarcini L, Venditti A, Bianco A. 2018. Chapter 6 - Anti-HIV agents from nature: natural compounds from Hypericum hircinum and carbocyclic nucleosides from iridoids. In: Studies in Natural Products Chemistry, Vol 56. Amsterdam: Elsevier. p. 173–228.

Robson NKB. 2012. Studies in the genus *Hypericum* L. (Hypericaceae) 9. Addenda, corrigenda, keys, lists and general discussion. Phytotaxa. 72(1):1–111.

Shiu WKP, Gibbons S. 2009. Dibenzofuran and pyranone metabolites from *Hypericum revolutum* ssp. *revolutum* and *Hypericum choisianum*. Phytochemistry. 70(3):403–406.

Simonetti G, Tocci N, Valletta A, Brasili E, D'Auria FD, Idoux A, Pasqua G. 2016. *In vitro* antifungal activity of extracts obtained from *Hypericum perforatum* adventitious roots cultured in a mist bioreactor against planktonic cells and biofilm of Malassezia furfur. Nat Prod Res. 30(5): 544–550.

Venditti A, Bianco A. 2018. Secondary metabolites of *Hypericum richeri* Vill. collected in Central Italy: chemotaxonomy and ethnomedicinal relevance. Trends Phytochem Res. 2:155–162.

Verotta L, Appendino G, Belloro E, Jakupovic J, Bombardelli E. 1999. Furohyperforin, a prenylated phloroglucinol from St. John's wort (Hypericumperforatum). J Nat Prod. 62(5):770–772.

Verotta L, Appendino G, Jakupovic J, Bombardelli E. 2000. Hyperforin analogues from St. John's wort (*Hypericum perforatum*). J Nat Prod. 63(3):412–415.

Vichai V, Kirtikara K. 2006. Sulforhodamine B colorimetric assay for cytotoxicity screening. Nat Protoc. 1(3):1112.

Wang WP, Jiang K, Zhang P, Shen KK, Qu SJ, Yu XP, Tan CH. 2018a. Highly oxygenated and structurally diverse diterpenoids from *Euphorbia helioscopia*. Phytochemistry. 145:93–102.

Wang XF, Li H, Jiang K, Wang QQ, Zheng YH, Tang W, Tan CH. 2018b. Anti-inflammatory constituents from *Perilla frutescens* on lipopolysaccharide-stimulated RAW264.7 cells. Fitoterapia. 130: 61–65.

Wang XF, Liu FF, Zhu ZD, Fang QQ, Qu SJ, Zhu WL, Yang L, Zuo JP, Tan CH. 2019. Flueggenoids A - E, new dinorditerpenoids from Flueggea virosa. Fitoterapia. 133:96–101.

Yang XW, Ding YQ, Zhang JJ, Liu X, Yang LX, Li XN, Ferreira D, Walker LA, Xu G. 2014. New acylphloroglucinol derivatives with diverse architectures from *Hypericum henryi*. Org Lett. 16(9): 2434–2437.

Yang XW, Grossman RB, Xu G. 2018. Research progress of polycyclic polyprenylated acylphloroglucinols. Chem Rev. 118(7):3508–3558.

Ye Y, Yang XW, Zhou Y, Xu G. 2019. *homo*-Adamantane type polycyclic polyprenylated acylphloroglucinols from *Hypericum hookerianum*. Fitoterapia. 133:43–50.

Zhang JS, Zou YH, Guo YQ, Li ZZ, Tang GH, Yin S. 2016. Polycyclic polyprenylated acylphloroglucinols: natural phosphodiesterase-4 inhibitors from *Hypericum sampsonii*. RSC Adv. 6(58): 53469–53476.

Zhou ZB, Zhang YM, Pan K, Luo JG, Kong LY. 2014. Cytotoxic polycyclic polyprenylated acylphloroglucinols from *Hypericum attenuatum*. Fitoterapia. 95:1–7.

Zhu HC, Chen CM, Yang J, Li XN, Liu JJ, Sun B, Huang SX, Li DY, Yao GM, Luo ZW, et al. 2014. Bioactive acylphloroglucinols with adamantyl skeleton from *Hypericum sampsonii*. Org Lett. 16(24):6322–6325.