

Secondary Metabolites with Antioxidant and Mushroom Tyrosinase Inhibitory Activities from *Ajuga nipponensis*

Na Sun¹, Tingting Du¹, Yifang Zhang¹, Yiming Luo¹, Xinyu Ma¹,
Ru Zhang¹, Xinru Wu¹, Huanhuan Yang¹, Miao Zhou¹,
Penghua Shu^{1*} and Jihong Huang^{1*}

Food and Pharmacy College, Xuchang University, Xuchang, Henan 461000, P. R. China

(Received January 26, 2022; Revised April 13, 2022; Accepted April 17, 2022)

Abstract: One *neo*-clerodane diterpenoid (**1**), two abietane diterpenoids (**2** and **3**), three flavonoids (**3–6**), one C6-substituted chromone derivative (**7**), one phenylpropanoid (**8**), as well as one chain fatty acid (**9**) were isolated from the whole plants of *Ajuga nipponensis*. Their structures were established by detailed analysis of the HRESIMS, 1D and 2D NMR, UV, and IR. The absolute configuration of compound **1** was firstly determined by ECD calculation and single crystal diffraction. The NMR data of compound **9** are reported for the first time. Compounds **4**, **7–9** were isolated from this medicinal plant for the first time, and **4**, **9** were first discovered from natural products. The isolates **1–7** were tested for their antioxidant and mushroom tyrosinase inhibitory activities. Most of them showed moderate antioxidant activities. Compounds **1**, **4**, **5**, and **7** exhibited obvious antioxidant activities at 50 μ M, with % inhibition values of 32.37 \pm 0.75%, 25.30 \pm 0.66%, 28.76 \pm 0.64%, 31.06 \pm 0.46%, respectively, with L-ascorbic acid used as the positive control (71.29 \pm 0.34%). Compound **7** exhibited significant inhibitory activities against mushroom tyrosinase (%inhibition values of 16.94 \pm 1.28%), with arbutin used as the positive control (29.9 \pm 0.99%).

Keywords: *Ajuga* L.; *Ajuga nipponensis*; diterpenoid; flavonoid; antioxidation; tyrosinase inhibitory activity.
© 2022 ACG Publications. All rights reserved.

1. Introduction

The Labiatae family is one of the bigger families in the world and comprises 220 genera and 3500 species, which widely distributed all over the world. Among them, *Ajuga* L., is about a quarter of Labiatae with 18 species in China, and it is mainly grown in areas south of the Qinling Mountains [1]. Many *Ajuga* plants are used as folk medicines for the treatment of cough, fever, poisoning, swelling, and dysentery [2]. In addition, literature survey revealed that *Ajuga* species are rich for diterpenoids, iridoids, sterones, flavonoids, and lactones [3,4]. In recent years, *neo*-clerodane and abietane diterpenoids, steroids, as well as flavonoids from *Ajuga* have attracted widespread attention due to their novel structures and fascinating bioactivities such as anti-inflammatory, cytotoxic, anti-oxidant, ferroptosis inhibitory, and anti-feedant [5-8].

Ajuga nipponensis Makino, also named “Bai Hua Xia Ku Cao” in China, one or two-year-old herb, is widespread in Eastern, Southern and Southwestern of China. As a traditional Chinese medicine, the whole herb is used to treat pain and inflammation [9]. Previous studies showed that the crude extract of

* Corresponding author: E-Mail: shupenghua@yeah.net; phne:086-374-2968812 Fax: 086-374-2968812;

* Corresponding author: E-Mail: huangjih1216@126.com; Phone: 086-374-2968812 Fax: 086-374-2968812

The article was published by ACG Publications

<http://www.acgpubs.org/journal/records-of-natural-products> Month-Month 202x EISSN:1307-6167

DOI: <http://doi.org/10.25135/mp.321.2201.2330>

Available online: May 06, 2022

this plant exhibits a variety of pharmacological effects of antibacterial, neuroprotection, liver protection, anti-inflammatory, analgesic, etc [10-13]. However, there are few reports on the chemical composition of the plant, especially diterpenoids and flavonoids [14-18], and the chemical composition that exerts pharmacological effects are not clear. In a search for active compounds with novel structure from *Ajuga* plants, the whole plants of *A. nipponensis* were collected and studied, and compounds **1–9** were isolated (Figure 1). The absolute configuration of compound **1** was determined by ECD calculation and single crystal diffraction for the first time. Four of them showed significant antioxidant activity, and only one showed significant tyrosinase inhibitory activity.

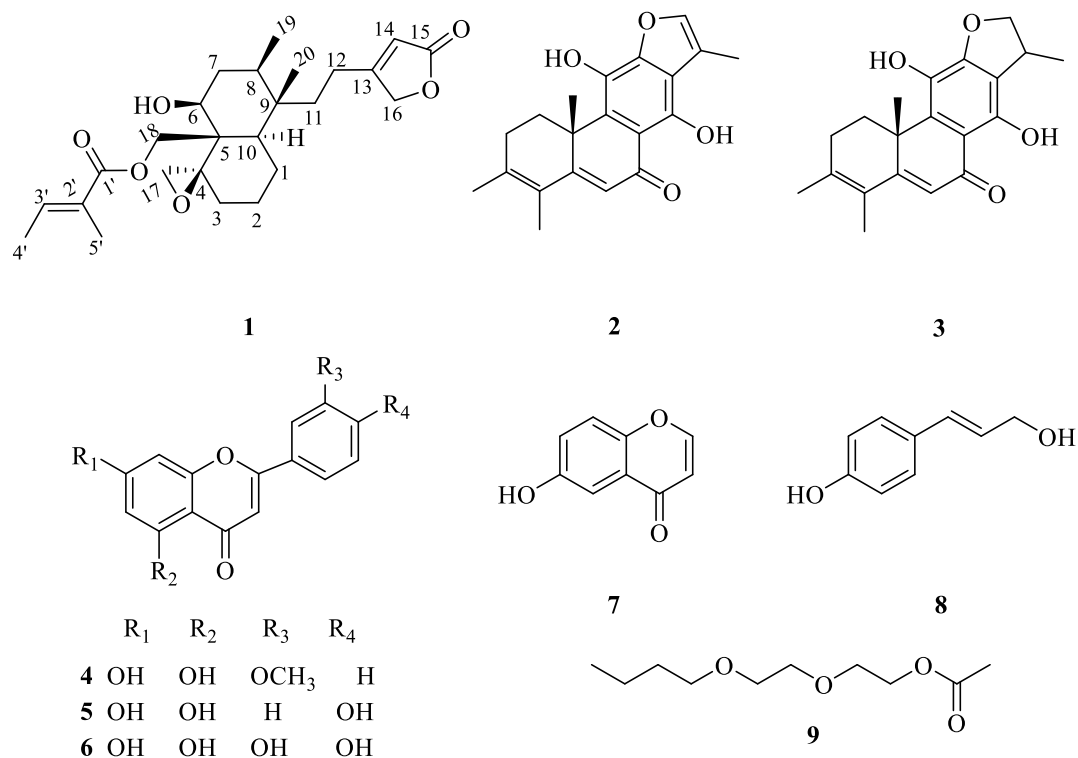


Figure 1. Chemical structures of compounds **1–9**

2. Materials and Methods

2.1. General Experimental Procedures

Melting point was recorded on a SGW X-4A microscopic melting point apparatus (without correction). The crystallographic data were obtained on a Bruker SMART APEX-II CCD diffractometer equipped with graphite-monochromatized Cu K α radiation ($\lambda = 1.54178 \text{ \AA}$). The UV and FT-IR data were obtained on a Puxi Tu-1950 spectrophotometer and a FTIR-650 instruments, respectively. NMR spectra were recorded on a Bruker AM-400 spectrometer referencing to the residuals of chloroform-*d* ($\delta_{\text{H}} 7.27$; $\delta_{\text{C}} 77.23$) and methanol-*d*₄ ($\delta_{\text{H}} 3.31$; $\delta_{\text{C}} 49.15$). HRESIMS were acquired on a Waters Xevo G2-XS QT spectrometer in a positive mode.

2.2. Plant Material

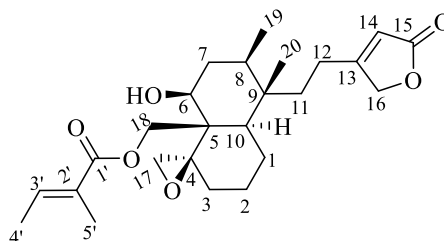
The whole plants of *A. nipponensis* were collected at Nanyang, China, in October 2019. This plant material was authenticated by Prof. Guangmin Yao at Huazhong University of Science and Technology. A voucher specimen (No. 20191001) has been deposited at Food and Pharmacy College, Xuchang University.

2.3. Extraction and Isolation

The air-dried herb of *A. nipponensis* (5.0 kg) were powdered and extracted with 95% EtOH (10.0 L×3) at room temperature. The crude extract (800.0 g) was suspended in H₂O and extracted with petroleum ether to remove the essential oils and then partitioned with chloroform. The chloroform fraction (323.0 g) was fractionated by a silica gel CC (CH₂Cl₂–MeOH, from 30:1 to 5:1) to give five fractions A–E. Fraction A was chromatographed on Sephadex LH-20 CC (100% MeOH) to yield two subfractions, A1 and A2. Fraction A1 was purified by RP C18 HPLC (CH₃OH–H₂O, 70:30) to afford compound **2** (*t*_R = 28.5 min, 8.2 mg) and **9** (*t*_R = 35.5 min, 24.2 mg). Fraction B was fractionated by silica gel CC to give five subfractions, B1–B3, and fraction B2 was separated by Sephadex LH-20 CC to yield two subfractions, B2a–B2c. Compound **1** (55.2 mg) was obtained by precipitation of crystals (CH₂Cl₂–CH₃OH, 60:40) from B2a. Fraction B3 was fractionated by Sephadex LH-20 CC (100% MeOH) to afford compound **3** (5.4 mg). Fraction C was fractionated by RP C18 CC (from 30% MeOH–H₂O to 100%MeOH) to give five subfractions, C1a–C1e. Fraction C1b was purified by a Sephadex LH-20 column (100% MeOH) to afford **5** (7.6 mg). Similarly, compound **4** (5.8 mg) and **6** (4.7 mg) were obtained from C1d and C1c, respectively. Compound **8** (5.2 mg) was obtained from fraction D by Sephadex LH-20 CC. Fraction E was fractionated by silica gel CC (CH₂Cl₂–MeOH, from 15:1 to 3:1) to give fractions E1–E3 and fraction E2 was purified by Sephadex LH-20 CC to yield compound **7** (3.4 mg).

Compound 1: colorless prisms, mp 192–193 °C. $[\alpha]_D^{25} +14.0$ (*c* 1.2, CH₂CN). IR (KBr) ν_{\max} 3473, 2948, 2879, 1747, 1708, 1645, 1249, 1136, 1031 cm⁻¹. UV λ_{\max} (CH₃CN) nm (log ϵ): 211 (5.9). HR-ESI-MS *m/z* 455.2413 [M + Na]⁺ (calcd. for C₂₅H₃₆O₆Na, 455.2410). ¹H-NMR (CDCl₃, 400 MHz) and ¹³C-NMR (CDCl₃, 100MHz) see Table 1.

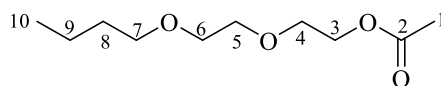
Table 1. ¹H and ¹³C NMR data of **1** [a]



Position	δ_C	δ_H (mult, J, Hz)	Position	δ_C	δ_H (mult, J, Hz)
1	25.0	1.36 m, 1.91 m	14	115.1	5.75 s
2	20.7	1.38 m, 1.54 m	15	173.7	
3	31.9	2.02 m, 1.03 d (13.5)	16	73.0	4.68 s
4	66.9		17	48.7	2.38 d (2.4), 3.17 d (2.4)
5	45.2		18	62.0	4.49 s
6 α	73.2	3.51 dd (10.0, 4.0)	19	17.5	0.69 s
7	33.9	1.44 m, 1.55 m	20	15.4	0.78 d (5.4)
8	34.5	1.51 m	1'	168.0	
9	38.6		2'	128.4	
10	47.1	1.30 m	3'	137.8	6.91 q (6.7)
11	34.6	1.46 m, 1.56 m	4'	14.5	1.71 d (7.0)
12	22.1	2.21 m, 2.06 m	5'	12.0	1.78 s
13	170.2				

[a] 400 MHz for ¹H and 100 MHz for ¹³C, recorded in CDCl₃.

Compound 9: yellow oil, HR-ESI-MS *m/z* 227.1261 [M + Na]⁺ (calcd. for C₁₀H₂₀O₄Na, 227.1259). ¹H-NMR (CD₃OD, 400 MHz) and ¹³C-NMR (CD₃OD, 100MHz) see Table 2. The NMR data of **9** are reported for the first time.

Table 2. ^1H and ^{13}C NMR data of **9** ^[a]

Position	δ_{C}	δ_{H} (mult, J, Hz)	Position	δ_{C}	δ_{H} (mult, J, Hz)
1	20.9	2.05 s	6	71.7	3.57 m
2	172.9		7	71.3	3.47 m
3	64.9	4.20 m	8	33.0	1.56 m
4	70.2	3.69 m	9	29.5	1.38 m
5	72.2	3.63 m	10	14.4	0.94 t (4.0)

^[a] 400 MHz for ^1H and 100 MHz for ^{13}C , recorded in CD_3OD .

2.4. Antioxidant and Mushroom Tyrosinase Inhibition Assay

Antioxidant and mushroom tyrosinase inhibition assay were assayed according to the literature procedures [19]. The results were analyzed by program GraphPad Prism 5.0. Data are expressed as means \pm SEMs of triplicate.

3. Results and Discussion

3.1. Isolation and Structure Elucidation

A phytochemical study on the chloroform fraction of the whole plants of *A. nipponensis* led to the isolation of 9 compounds with one *neo*-clerodane diterpenoid ajugacumbin B (**1**) [20], two abietane diterpenoids ajuforrestins A (**2**) and B (**3**) [21], three flavonoids 5,7-dihydroxy-2-(3'-methoxyphenyl)chromone (**4**) [22], apigenin (**5**), and luteolin (**6**) [12], one C6-substituted chromone derivative 6-hydroxy-4-oxo-4H-1-benzopyran (**7**) [23] and one phenylpropanoid 1-(3-hydroxyphenyl)but-1-ene (**8**) [24], as well as one chain fatty acid diethylene glycol monobutyl ether acetate (**9**) [25]. This is the first time to report the absolute configuration of **1** by ECD calculation and X-ray single crystal diffraction. Except for **1–3**, all of the compounds were isolated from this plant for the first time.

Compound **1**, was obtained as colorless prisms (MeOH), mp 192–193 °C. A molecular formula of $\text{C}_{25}\text{H}_{36}\text{O}_6$ was assigned to **1** based on the HRESIMS ion at m/z 455.2413 $[\text{M} + \text{Na}]^+$ (calcd. for $\text{C}_{25}\text{H}_{36}\text{O}_6\text{Na}$, 455.2410) and the ^{13}C NMR data, indicating eight unsaturation degrees. The IR spectrum displayed the characteristic absorptions attributable to hydroxyl groups (3373 cm^{-1}), a carbonyl group ($1747, 1708\text{ cm}^{-1}$), and a double bond (1645 cm^{-1}). The NMR data explained that the structure of **1** is consistent with the known compound ajugacumbin B. However, the absolute configuration of **1** has not been determined. To determine the absolute configuration, the electronic circular dichroism (ECD) of (4*R*,5*R*,6*S*,8*R*,9*S*,10*R*)-**1** and its enantiomer were calculated by a time-dependent density functional theory (TD-DFT) methodology at the B3LYP/6-311++G (d,p)//B3LYP/6-31G(d) level with CH_3CN as solvent by the IEFPCM solvation model implemented in Gaussian 09 program, according to the previous method [26]. As shown in Figure 2, the measured ECD spectrum of **1** fits well with the calculated ECD spectrum of (4*R*,5*R*,6*S*,8*R*,9*S*,10*R*)-**1** and is opposite to that of its enantiomer. Therefore, the absolute configuration of **1** was established as (4*R*,5*R*,6*S*,8*R*,9*S*,10*R*). Finally, single-crystal X-ray diffraction analysis confirmed the absolute configuration of **1** as (4*R*,5*R*,6*S*,8*R*,9*S*,10*R*) 4,17-epoxy-18-tigloyl-*neo*-clerod-13-en-15,16-olide (Figure 3) with the calculated Flack parameter of $-0.01(7)$. The crystallographic data for compound **1** (CCDC 2164862) has been deposited in the Cambridge Crystallographic Data Centre.

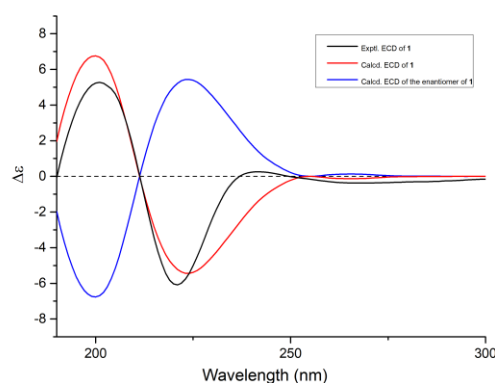
Secondary metabolites from *Ajuga nipponensis*

Figure 2. Experimental and calculated ECD spectra of **1** and its enantiomer in CH₃CN

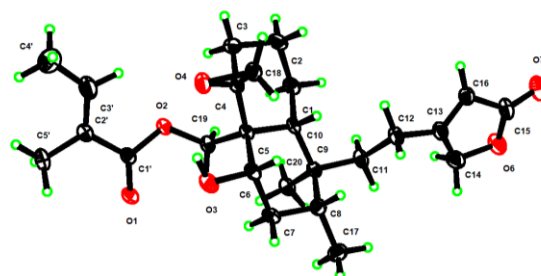


Figure 3. ORTEP drawing of Ajugacumbin B

3.2. Antioxidant and Tyrosinase Inhibitory Activities

Compounds **1–7** were evaluated for their antioxidant activities with DPPH radical scavenging assay, using L-ascorbic acid as the positive control. As shown in Table 3, compounds **1**, **4**, **5**, and **7** exhibited obvious DPPH radical scavenging activities. In particular, compound **1** exhibited the strongest antioxidant activities at 50 μ M, with %inhibition values of $32.37 \pm 0.75\%$, indicating the importance of *neo*-clerodane diterpenoid to the antioxidant activity. This is the first report of the antioxidant activity of 4,18-epoxy-*neo*-clerodanes, although the antioxidant activity of *neo*-clerodane diterpenoids have been reported [27]. Analysis of the structures and antioxidant activity of **4–6** revealed that 5,7-dihydroxy-flavonoid with 3'-OCH₃ (**4**) or 3'-H (**5**) showed more antioxidant activity than 5,7-dihydroxy-flavonoid with 3'-OH (**6**). This suggested that the substituents at C-3' position is essential for activity in the 5,7-dihydroxy-flavonoids. Compound **7**, as a C6-substituted chromone derivative, exhibited significant antioxidant activity, which further verified the good antioxidant activity of chromone derivatives [28].

Table 3. DPPH radical scavenging activity of compounds **1**, **3**, **4**, **5**, **7**, and L-ascorbic acid^[a]

Compound	DPPH radical scavenging activity (%)	Compound	DPPH radical scavenging activity (%)
1	32.37 ± 0.75	5	28.76 ± 0.64
2	14.67 ± 0.72	6	9.95 ± 0.77
3	6.49 ± 1.36	7	31.06 ± 0.46
4	25.30 ± 0.66	L-ascorbic acid (positive control)	71.29 ± 0.34

^[a]Measured at a concentration of 50 μ M. Three independent experiments were performed and results were expressed as means \pm SEMs.

Compounds **1–7** were evaluated for their tyrosinase inhibitory activities at a concentration of 25 μ M. However, only **7** exhibited obvious inhibitory activities, with %inhibition values of $16.94 \pm 1.28\%$, with arbutin used as the positive control ($29.9 \pm 0.99\%$). According to literature reports, C6-substituted

chromone derivatives have strong inhibitory activities against Alzheimer-related enzymes such as: human acetylcholinesterase ($IC_{50} = 5.58 \mu M$) and human monoamine oxidase B ($IC_{50} = 7.20 \mu M$) [29]. Structure-activity analysis indicated that the substitution at the C-6 may be a potential reactive group. Therefore, we speculate that the inhibitory effect of **7** on tyrosinase may be related to its C6-hydroxyl group.

Acknowledgments

We thank Zhaoxue Sun and Lixiang Li for the plant collection and Prof. Guangmin Yao for the material identification. This work was financially supported by National Natural Science Foundation of China (21702178), Project of Science and Technology Department of Henan Province (212102311031), Zhongyuan Scholars in Henan (192101510004), Training Plan of Young Backbone Teachers in Universities of Henan Province (2021GGJS144), Key Scientific Research Program in Universities of Henan Province (22A350010), Undergraduate Training Program for Innovation and Entrepreneurship of Henan Province (S202110480020), School-land Cooperation Project (96333) and Distinguished Young Scholars Fund of Xuchang University (2019).

Supporting Information

Supporting information accompanies this paper on <http://www.acgpubs.org/journal/records-of-natural-products>

ORCID

Na Sun: [0000-0002-9540-8206](https://orcid.org/0000-0002-9540-8206)

Tingting Du: [0000-0002-9432-2021](https://orcid.org/0000-0002-9432-2021)

Yifang Zhang: [0000-0002-8732-1821](https://orcid.org/0000-0002-8732-1821)

Yiming Luo: [0000-0002-8707-4875](https://orcid.org/0000-0002-8707-4875)

Xinyu Ma: [0000-0002-8052-2399](https://orcid.org/0000-0002-8052-2399)

Ru Zhang: [0000-0002-9245-1954](https://orcid.org/0000-0002-9245-1954)

Xinru Wu: [0000-0001-9356-438X](https://orcid.org/0000-0001-9356-438X)

Huanhuan Yang: [0000-0002-3430-2707](https://orcid.org/0000-0002-3430-2707)

Miao Zhou: [0000-0001-8165-3908](https://orcid.org/0000-0001-8165-3908)

Penghua Shu: [0000-0001-6018-8429](https://orcid.org/0000-0001-6018-8429)

Jihong Huang: [0000-0002-0754-409X](https://orcid.org/0000-0002-0754-409X)

References

- [1] Editorial Board of Flora of China (1997). Chinese Academy of Sciences, Flora of China; Science Press: Beijing, **65**, 55.
- [2] M. Gong, Z. Liu, H. Yang and Y. Li (2015). Research progress on the close relative varieties of *Ajuga* plants including *Jinguciao* (*Ajuga ciliata* Bunge), *Jinchuangxiaocao* (*Ajuga decumbens*) and *Zibeijinpan* (*Ajuga nipponensis*). *Guiding J. Trad. Chin. Med. Pharm.* **21**, 92-94.
- [3] J. Coll and Y. Tandon (2008). *neo*-Clerodane diterpenoids from *Ajuga*: structural elucidation and biological activity. *Phytochem. Rev.* **7**, 25-49.
- [4] X. Qing, H. Yan, Z. Ni, C. Vavricka, M. Zhang, Q. Shi, Y. Gu and H. Kiyota (2017). Chemical and pharmacological research on the plants from genus *Ajuga*, *Heterocyc. Commun.* **23**, 245-268.
- [5] M. Abudukeremu, L. An, B. Dong, Q. Du, Y. Guo, N. Lall, D. Lee, X. Yang and X. Zhang (2020). Anti-inflammatory *neo*-clerodane diterpenoids from *Ajuga pantanthera*, *J. Nat. Prod.* **83**, 894-904.
- [6] Q. Tan, Y. Fang, X. Peng, H. Zhou, J. Xu and Q. Gu (2021). A new ferroptosis inhibitor, isolated from *Ajuga nipponensis*, protects neuronal cells via activating NRF2-antioxidant response elements (AREs) pathway, *Bioorg. Chem.* **115**, 107177.
- [7] Y. Wang, Y. Liu, W. Li, K. Guo and S. Li (2021). Antifeedant, cytotoxic, and anti-inflammatory *neo*-clerodane diterpenoids in the peltate glandular trichomes and fresh leaves of *Ajuga forrestii*, *Phytochemistry* **186**, 112731.

Secondary metabolites from *Ajuga nipponensis*

- [8] Viji, Z. and Paulsamy (2015). In-vitro antioxidant properties and total phenolic, flavonoid and tannin contents of *Pueraria tuberosa* (Roxb. Ex Willd.) DC, *Res. J. Pharmaceut. Biol. Chem. Sci.* **6**, 1202-1209.
- [9] Editorial Board of Flora of China (1997). Chinese Academy of Sciences, Flora of China; Science Press: Beijing, **65**, 76.
- [10] C. Hsieh, W. Ko, W. Ho, C. Chang, G. Chen and J. Tsai (2016). Antioxidant and hepatoprotective effects of *Ajuga nipponensis* extract by ultrasonic-assisted extraction, *Asian Pac. J. Trop. Med.* **9**, 420-425.
- [11] G. Yi, Y. Li, X. Li, G. He, X. Zhu and X. Shen (2011). Study on bacteriostasis of aqueous and ethanol extracts of *Ajugae nipponensis* Makino, *J. TCM Univ. Hunan* **3**, 31-32.
- [12] D. Xu, Z. Huang, Y. Cen, Y. Chen, S. Freed and X. Hu (2009). Antifeedant activities of secondary metabolites from *Ajuga nipponensis* against adult of striped flea beetles, *Phyllotreta striolata*, *J. Pest. Sci.* **82**, 195-202.
- [13] C. Hsieh, J. Cheng, T. Wang, H. Wang and W. Ho (2014). Hypoglycaemic effects of *Ajuga* extract in vitro and in vivo, *J. Funct. Foods.* **6**, 224-230.
- [14] J. Coll, Y. A. Tandrón and X. Zeng (2007). New phytoecdysteroids from cultured plants of *Ajuga nipponensis* Makino, *Steroids* **72**, 270-277.
- [15] J. Coll and Y. A. Tandrón (2006). Isolation and identification of neo-clerodane diterpenes from *Ajuga nipponensis* Makino, *Nat. Prod. Commun.* **37**, 183-189.
- [16] H. Wang, X. Teng, Y. Zhang, Q. Gu and L. He (2021). Diterpenoids from the whole plants of *Ajuga nipponensis* and their inhibition of RANKL-induced osteoclastogenesis, *Chem. Biodivers.* **18**, 200780.
- [17] S. Hiroko, S. Yutaka and O. Kazunori (1989). Neo-clerodane diterpenes from *Ajuga nipponensis*, *Chem. Pharm. Bull.* **37**, 354-357.
- [18] G. He, X. Liang, W. Ouyang, G. Yi, Y. Li, J. Zhao and K. Ikhlas (2013). Chemical constituents from *Ajuga nipponensis*, *J. Chin. Med. Mat.* **36**, 1950-1953.
- [19] P. Shu, L. Zhang, W. Liu, Y. Fei, M. Sun, Y. Lou, A. Liu, M. Yu, J. Li, X. Wei and N. Sun (2021). Chemical constituents from *Typhonium giganteum* rhizome and their antioxidant, tyrosinase inhibitory activities, *Rec. Nat. Prod.* **15**, 53-58.
- [20] S. Hiroko, S. Yutaka and O. Kazunori (1989). Neo-clerodane diterpenes from *Ajuga nipponensis*, *Chem. Pharm. Bull.* **37**, 354-357.
- [21] J. Yi, Y. Luo, B. Li and G. Zhang (2004). Phytoecdysteroids and glycosceramides from *Eriophyton wallchii*, *Steroids* **69**, 809-815.
- [22] U. Jiraporn, W. Chanpen, S. Weerasak, N. Patcharawee and P. Narumol (2011). Synthesis, in vitro evaluation, and docking studies of novel chromone derivatives as HIV-1 protease inhibitor, *J. Mol. Struct.* **1001**, 152-161.
- [23] K. Chand, R. Tiwari, S. Kumar, A. Shirazi, S. Sharma, E. Van der Eycken, V. Parmar, K. Parang and S. Sharma (2015). Synthesis, antiproliferative, and c-Src kinase inhibitory activities of 4-oxo-4H-1-benzopyran derivatives, *J. Heterocyclic Chem.* **52**, 562-572.
- [24] K. Dong, X. Jin, S. Chen, L. Wu and Q. Liu (2020). Controllable synthesis of 2- And 3-aryl-benzomorpholines from 2-aminophenols and 4-vinylphenols. *Chem. Commun.* **56**, 7941-7944.
- [25] Y. Sidorov, A. Kirichek, N. Butko, V. Akselrod, V. Simonenko, M. Dudich and O. Kalashnik (1988). Synthesis of butyl carbitol by dehydration of a mixture of n-butanol and diethylene glycol and its acetate, *J. Appl. Chem. USSR.* **61**, 1635-1640.
- [26] N. Sun, Y. Qiu, Y. Zhu, J. Liu, H. Zhang, Q. Zhang, M. Zhang, G. Zheng, C. Zhang and G. Yao (2019). Rhodomicrosides A-I, analgesic diterpene glucosides with diverse carbon skeletons from *Rhododendron micranthum*, *Phytochemistry* **158**, 1-12.
- [27] V. Nguyen, V. Pham, T. Nguyen, V. Tran and T. Doan (2009). Novel antioxidant neo-clerodane diterpenoids from *Scutellaria barbata*, *Eur. J. Org. Chem.* **33**, 5810-5815.
- [28] N. Phosrithong, W. Samee, P. Nunthanavanit and J. Ungwitayatorn (2012). In vitro antioxidant activity study of novel chromone derivatives, *Chem. Biol. Drug Des.* **79**, 981-989.
- [29] C. Lemke, J. Christmann, J. Yin, J. Alonso, E. Serrano, M. Chioua, L. Ismaili, M. Martínez-Grau, C. Beadle, T. Vetman, F. Dato, U. Bartz, P. Elsinghorst, M. Pietsch, C. Müller, I. Iriepa, T. Wille, J. Marco-Contelles and M. Gütschow (2019). Chromenones as multineurotargeting inhibitors of human enzymes, *ACS Omega* **4**, 22161-22168.

ACG
publications

© 2022 ACG Publications