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Heliotropiumides A and B, new phenolamides with *N*-carbamoyl putrescine moiety from *Heliotropium foertherianum* collected in Hawaii and their biological activities

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ABSTRACT

Two new compounds heliotropiumides A (**1**) and B (**2**), phenolamides each with an uncommon carbamoyl putrescine moiety, were isolated from the seeds of a naturalized Hawaiian higher plant, *Heliotropium foertherianum* Diane & Hilger in the borage family, which is widely used for the treatment of ciguatera fish poisoning. The structures of compounds **1** and **2** were characterized based on MS spectroscopic and NMR analysis, and DP4+ calculations. The absolute configuration (AC) of compound **1** was determined by comparison of its optical rotation with those reported in literature. Compound **2** showed inhibition against NF-κB with an IC_{50} value of 36 μM.

Heliotropium foertherianum (Common name: tree heliotrope and octopus bush) is a flowering plant in the Boraginaceae family. It is native to tropical Asia including southern China, Madagascar, northern Australia, Micronesia and Polynesia. In the Pacific, numerous traditional herbal remedies are preferentially used to treat ciguatera fish poisoning (CFP), but *H. foertherianum* is the most widely used in Pacific islands.[1] Rosmarinic acid was isolated from *H. foertherianum*, which strongly inhibit CFP.[2] Recent studies showed that *H. foertherianum* could also inhibit snake venom-induced hemorrhage, which is due to the presence of rosmarinic acid in the plant.[3] Although not indigenous to Hawaii, *H. foertherianum* is naturalized on almost all the Hawaiian Islands. The plant is found on many sandy Hawaiian beaches. HPLC–UV analysis showed that seeds of *H. foertherianum* contain caffeic acid ((*E*)-3-(3,4-dihydroxyphenyl)prop-2-enoic acid) or ferulic acid ((*E*)-3-(4-hydroxy-3-methoxy-phenyl)prop-2-enoic acid) derivatives, which have the same chromophore as that of rosmarinic acid. Then we decided to study the seeds of this plant. The powdered seeds of heliotrope were extracted with MeOH overnight and the MeOH extract was successively partitioned to yield *n*-hexane and EtOAc sub-extracts. Further separation and purification of the *n*-hexane sub-extract led to the isolation of two new compounds, **1** and **2** (Fig. 1).

Compound **1**[4] was isolated as a colorless solid. Its molecular formula was determined to be $C_{25}H_{31}N_3O_7$ by HR-ESIMS (*m*/*z* 486.2256, calcd for $[M+H]^+$ 486.2240), with twelve degrees of unsaturation. The IR spectrum of **1** showed the existence of carbonyl (1644 and 1600 cm^{-1}) and hydroxyl (3350 cm^{-1}) groups. A detailed analysis of ^1H and ^{13}C NMR spectra (Table 1) demonstrated the presence of two methoxy groups, five methylenes with one being hydroxylated, nine methines including five aromatic and two olefinic, and nine carbons with no hydrogen attached. In the ^1H–^1H COSY spectrum of **1** (Fig. 2), only five spin systems were identified, including a 1,3,4-trisubstituted benzene ring, a 1,3,4,5-tetrasubstituted benzene ring, a *trans* coupled double bond, a CH—CH—CH_2OH and CH_2—CH_2—CH_2—CH_2 spin systems. In the HMBC spectrum of **1** (Fig. 2), H-2 showed correlation to C-3′, C-5′

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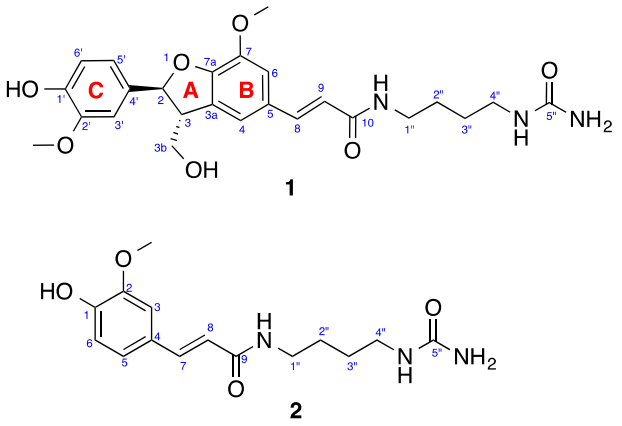

Fig. 1. Structure of compounds **1** and **2**.

Table 1
^{1}H and ^{13}C NMR data of **1**.

No.	**1**		No.	**1**	
	δ_H, *J* (Hz)[a]	δ_C[b]		δ_H, *J* (Hz)[a]	δ_C[b]
2	5.49 d 6.9	88.1	1′		147.0
3	*3.50* m	53.2	2′		148.0
3a		130.3	2″-OMe	3.81 s	56.2
3b	3.68 m	63.3	3′	6.92 br s	111.1
4	7.13 br s	117.1	4′		132.3
5		128.9	5′	6.77 br s	119.2
6	7.08 br s	112.3	6′	6.77 br s	115.9
7		144.3	1″	3.15 m	38.9
7-OMe	3.74 s	56.1	2″	1.40 m	28.0
7a		149.2	3″	1.41 m	27.2
8	7.35 d 15.8	139.5	4″	2.97 m	39.4
9	6.49 d 15.5	120.1	5″		160.1
10		165.8			

[a] Spectra recorded at 400 MHz.
[b] Spectra recorded at 100 MHz. Data based on ^{1}H, ^{13}C, HSQC, and HMBC experiments.

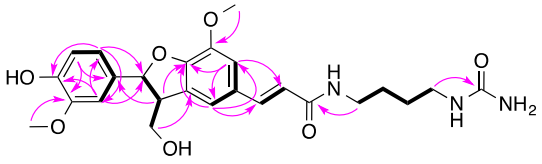

Fig. 2. COSY (Bold) and key HMBC (Single headed) correlations of **1**.

and C-3b, indicating the presence of a C_6–C_3 [Ph-CH(O)-CH(C)-CH_2-OH] fragment. H-9 and H-8 correlated to C-5 and C-10, respectively, indicating the presence of another C_6–C_3 [Ph—CH=CH—CO—] fragment. C-1″ and C-4″ were determined to be nitrogenated on the basis of their chemical shifts (1″: δ_H/δ_C 3.15/38.9; 4″: δ_H/δ_C 2.97/39.4), and they were part of the putrescine fragment (N—CH_2—CH_2—CH_2—CH_2—N). One nitrogen atom in the putrescine fragment must be connected to the carbonyl group in the Ph—CH=CH—CO— fragment to form an amide bond (δ_C 165.8) due to an HMBC correlation from H-1″ to C-10, while another nitrogen atom in the putrescine fragment must be connected to CO—NH_2 to form a mono-substituted urea group (RNH—CO—NH_2, δ_C 160.1). These two carbonyl groups together with one double bond and two benzene rings accounted for eleven unsaturation units, and the remaining unsaturation unit must be due to a ring system. C-2 and C-3 in the one C_6–C_3 [Ph—CH(O)—CH(C)—CH_2OH] fragment must be fused with the benzene ring of another C_6–C_3 [Ph—CH=CH—CO—] fragment to form a 2,3-dihydrofuran with an oxygen bridge between C-2 and C-7a. Like some *meta*-coupled aromatic protons, H-3′, H-4 and H-6 were singlets.[5,6] It was interesting that the *ortho*-coupled H-5′ and H-6′ were overlapped as a broad singlet, which was similar to the two *ortho*-coupled aromatic protons in quinizarin and AQDA.[7,8] The methoxy and hydroxy groups in C ring must be *ortho* to each other because the ^{13}C NMR chemical shifts of the two oxygenated aromatic carbons were at δ_C 147 and 148 ppm for C-1′ and C-2′, respectively. However, if the methoxy and hydroxy groups in C ring were *meta* to each other at C-2′ and C-6′, respectively, the ^{13}C NMR chemical shifts of the two oxygenated aromatic carbons must be at about δ_C 155 or even 160 ppm.[9] Hence, the planar structure of **1** was determined as shown. The coupling constant (*J* = 6.9 Hz) of H-2 with H-3 indicated that the hydroxyl methyl and the *p*-hydroxyl-*m*-methoxy benzene ring had different orientation. Hence the relative configuration of compound **1** was determined as shown.

The above determination was further validated using quantum chemical calculations of NMR shifts.[10] Hence, the relative configuration at the tetrahydrofuran (*cis* and *trans*) and the nature of the carbonyl group at C-5″ (urea and guanidinium) was challenged. Given the conformational flexibility of the molecule, and considering that the two mentioned units are highly separated, we used the fragment approach to compute the NMR shifts and further correlation with the experimental values found.[11] Two different clusters were considered (Fig. 3), and the NMR shifts of each candidate was computed at the PCM/mPW1PW91/6-31+G**//PCM/B3LYP/6-31G* level of theory, the recommended for DP4+ calculations.[12] When correlating the experimental NMR data for left unit of **1**′ (Fig. 3) with the computed NMR data of **3** and **4** fragment isomers using the DP4+ probability, the best match was observed for the second isomer (DP4+ = 99.7%), suggesting that the most likely stereochemistry at the tetrahydrofuran ring should be *trans*. Regarding the correlation of the experimental NMR data for right unit of **1**′ with the computed NMR data of urea (**5**) and guanidinium (**6**) candidates, the former (**5**) was identified as the most probable candidate (C-DP4+ = 88.5%). This result was consistent with the experimental NMR shifts reported for related compounds, for which it was observed that the carbonyl group of urea derivatives typically resonates at ~160 ppm, about 3 ppm more deshielded than the corresponding guanidinium analogues (~157 ppm).[13] Combining the results obtained for each separated fragment, the most likely structure from theoretical calculations is the same as suggested for compound **1** (Fig. 1).

To determine the absolute configuration, we compared the optical rotation of **1** with those of different 2,3-disubstituted 2,3-dihydrobenzofuran derivatives including compounds **7**–**10**.[14] Compound **1** ($[\alpha]_D^{25}$ +14 (*c* 0.12, MeOH)) had the same sign of optical rotation as that of **7** and **8**, but opposite to that of **9** and **10** (Fig. 4), indicating that **1** had a 2*S*,3*R* configuration.

Compound **2** was isolated as a colorless solid. Its molecular formula was determined to be $C_{15}H_{21}N_3O_4$ by HR-ESIMS (*m*/*z* 308.1592, calcd for $[M+H]^+$ 308.1610). Analysis of NMR data (Table 2) indicated the presence of a *p*-hydroxyl-*m*-methoxy *trans*-cinnamoyl and a carbamoyl putrescine moiety, and these two moieties were connected together through an amide bond. Hence, the structure of compound was readily determined as shown.

Biogenetically, **1** could be derived from *p*-hydroxycinnamoyl-CoA (**11**) and arginine (**13**) (Fig. 5). Oxidation of arginine yields citrulline (**14**), which can be decarboxylated to generate *N*-carbamoylputrescine (**15**). Reaction of the *m*-methoxylated *p*-hydroxycinnamoyl-CoA (**12**) with *N*-carbamoylputrescine (**15**) yields compound **2**. Coupling of compound **2** with *p*-hydroxy-*m*-methoxycinnamic acid (**16**) could produce compound **1** Fig. 6.

Phenolamide derivatives with putrescine (H_2N—CH_2—CH_2—CH_2—CH_2—NH_2) or agmatine (H_2N—CH_2—CH_2—CH_2—CH_2-

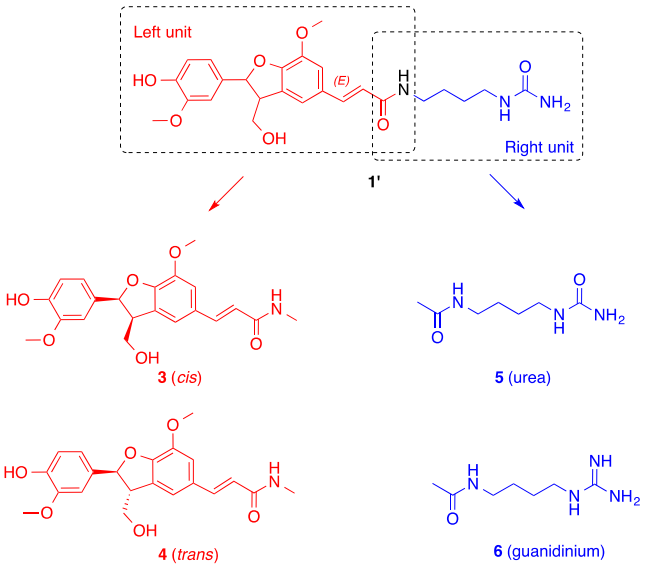

Fig. 3. Structures used for NMR DP4+ calculation.

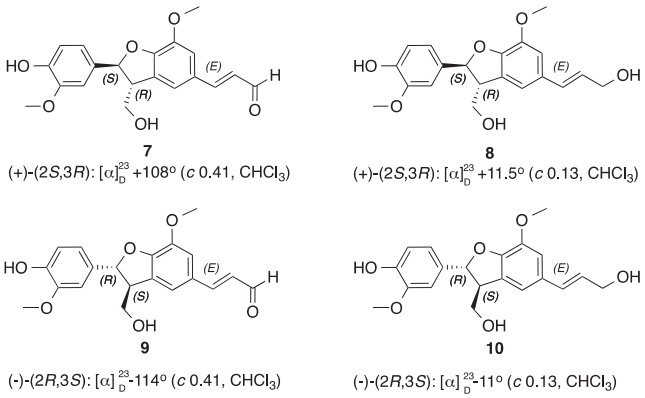

Fig. 4. Structures of **7**–**10** and their optical rotations.[5]

Table 2
^{1}H and ^{13}C NMR data of **2**.

No.	**2**		No.	**2**	
	δ_H, *J* (Hz)[a]	δ_C[b]		δ_H, *J* (Hz)[a]	δ_C[b]
1		88.1	9		165.8
2		53.2	2-OMe	3.86 s	56.0
3	7.12 d 1.9	130.3	1″	2.97 m	39.38
4		63.3	2″	1.39 m	28.07
5	6.98 dd, 8.3 1.9	117.1	3″	1.43 m	27.17
6	6.80 d 8.3	128.9	4″	3.16 m	38.91
7	7.31 d 15.7	112.3	5″		159.23
8	6.44 d 15.7				

[a] Spectra recorded at 400 MHz.
[b] Spectra recorded at 100 MHz. Data based on ^{1}H, ^{13}C, HSQC, and HMBC experiments.

—NH—C(=NH)NH_2 have been isolated from natural sources before. For examples, *N*-feruloylputrescine (**17**) [HO—^{p}Ph(^{m}—OMe)—CH=CH^{E}—CO—NH—CH_2—CH_2—CH_2—CH_2—NH_2] was isolated from the blue fluorescent stress zone of potato tubers (cv. Bintje) infected by *Phoma exigua* var. *foveata*;[15] feruloylagmatine (**18**), an antifungal compound was isolated from crowns of winter wheat;[16] caracasanamide (**19**), a hypotensive agents was isolated from *Verbesiana caracasana*, which could yield *p*-O-methylated feruloyl

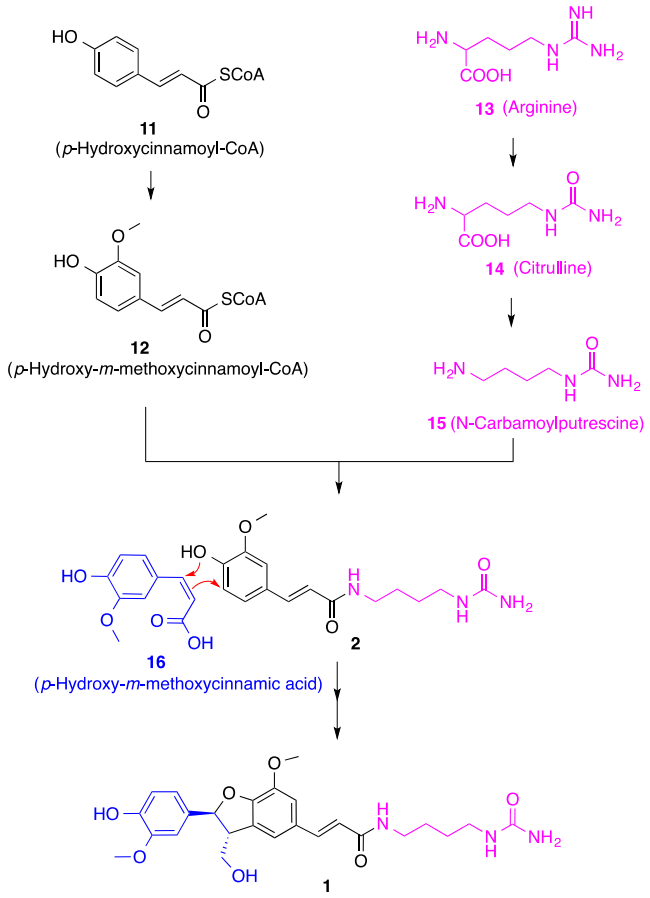

Fig. 5. Proposed biosynthetic pathway for compounds **1** and **2**.

carbamoyl putrescine (**20**) after $Ba(OH)_2$ hydrolysis;[13] hordatines A–C (**21**–**23**) were purified from barley;[17,18] hordatine-like compounds and glycosylated derivatives of hordatines were detected and localized by imaging mass spectrometry of barley seeds.[19–21] However, to the best of our knowledge, **1** and **2** were the first phenolamide derivatives with carbamoylputrescine isolated from a natural source.

Compounds **1** and **2** were tested against cancer cell line A2780,[22] but were inactive. NF-κB signaling is a key factor during inflammation and thus constitutes an attractive target for anti-inflammatory regulation and cancer prevention. The anti-inflammatory effect of new compounds was validated for their ability to inhibit TNF-α induced NF-κB activity.[23] Compound **2** inhibited NF-κB with an IC_{50} value of 36 μM, while compound **1** didn't show inhibition at 40 μM (the highest concentration tested).

Compounds **1** and **2** were further evaluated against four bacterial strains *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus*, and *Bacillus subtilis*, and four fungal strains *Pennicillium chrysogenum*, *Aspergillus niger*, *Paecilomyces lilacinus*, and *Fusarium graminearum* for their antibacterial and anti-fungal activities,[24] but neither was active.

To identify new chemical scaffolds derived from natural products for the interaction with nicotinic acetylcholine receptors (nAChRs), compound **1** and compound **2** were tested in radioligand binding assays for α4β2*, α3β4*, α7*, and $(\alpha1)_2\beta1\gamma\delta$ ('muscle type') subtypes previously described.[25,26] NAChRs are pentameric ligand-gated cation channels and are involved in various diseases.[27] For the assays, crude membrane fractions were prepared from Sprague-Dawley rat forebrains, pig adrenals, and Torpedo californica electroplax, respectively, serving as receptor sources.

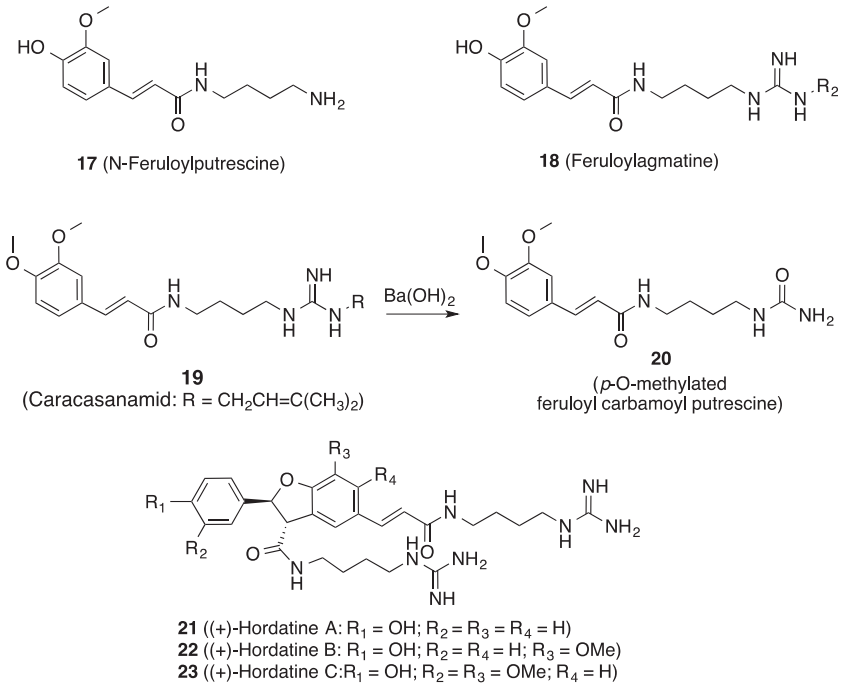

Fig. 6. Some analogs of compounds **1** and **2**.

[^{3}H]Epibatidine ($\alpha4\beta2^*$, $\alpha3\beta4^*$, $(\alpha1)_2\beta1\gamma\delta$) and [^{3}H]MLA ($\alpha7^*$) were used as radioligands. Compounds **1** and **2** did not show any binding inhibition for all four subtypes evaluated. This could be related to the urea motif lacking the cationic center as an important pharmacophoric element for orthosteric interaction. It might be of interest to evaluate some of the amine and guanidine analogs mentioned above in the future.

We calculated important physicochemical properties and parameters for both compounds using ACD/Percepta software.[28] Data are listed in Table S3 (supporting information). Compound **2** does not violate Lipinski's rules, whereas compound **1** has one violation. Both compounds are not in the ideal range for CNS drug-likeness parameters (e.g. logBB, TPSA, number of hydrogen donors). This information can help in further compound profiling activities as soon as biological targets or effects have been identified for both compounds.

Acknowledgments

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A. Supplementary data

Supplementary data (NMR spectra of the new compound) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2017.09.021.

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4. (a) General experimental procedures: See Li CS, Yang B, Turkson J, Cao S. *Phytochemistry*. 2017;140:62–72
(b) Collections and identification of plant: The plant seeds were collected from Kona in 2016. A voucher specimen was deposited at Daniel K. Inouye College of Pharmacy, University of Hawaii at Hilo, USA (accession no. HF2016-1).(c) Isolation of compounds: The dried seeds of HF were grinded to powder, which were extracted with MeOH:CH_2Cl_2/8:2 for three times. After removing solvent, the crude extract was portioned in water, Hexane and EtOAc, respectively, to get hexane and EtOAc extract. Hexane extract was fractionated by preparative HPLC (Phenyl Hexyl column, 100.0 × 21.2 mm; 10 mL/min; with 0.1% formic acid in mobile phases) eluted with 20–80% MeOH–H_2O in 40 min to get 40 sub-fractions (HFH1–HFH40). HFH30 (8 mg) was purified by semi-preparative HPLC (C18 column, 250.0 × 10.0 mm; 3 mL/min; with 0.1% formic acid in 25% MeOH/H_2O) to obtain compound **1** (1.2 mg, t_R 35 min). HFH19 (12 mg) was purified by semi-preparative HPLC (C18 column, 250.0 × 10.0 mm; 3 mL/min; with 0.1% formic acid in 20% MeOH/H_2O) to obtain compound **2** (2.0 mg, t_R 38 min). (**1**) white powder; [α] +14 (c 0.12, MeOH); UV (MeOH) λ_{max} 203, 288, 318 nm; IR (film) ν_{max} 3350, 2929, 2856, 2360, 2359, 2334, 1644, 1600, 1605, 1517, 1492, 1349, 1270, 1213, 1147, 1030 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) and ^{13}C NMR (100 MHz, DMSO): see Table 1; HRESIMS *m/z* 486.2256 [M+H]$^+$ (calcd for $C_{25}H_{32}N_3O_7$, 486.2240). (**2**) white powder; UV (MeOH) λ_{max} 202, 216, 231, 293, 317 nm; IR (film) ν_{max} 3316, 2932, 2860, 2363, 2337, 2334, 1647, 1584, 1552, 1444, 1422, 1334, 1277, 1254, 1210, 1156, 1125, 1023, 982, 821 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) and ^{13}C NMR (100 MHz, DMSO): see Table 1; HRESIMS *m/z* 308.1592 [M+H]$^+$ (calcd for $C_{15}H_{22}N_3O_4$, 308.1610).
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22. (a) Anti-proliferative Assays: Viability of A2780 cells was determined using the CyQuant assay according to the manufacturer's instructions (Life Technologies,

CA, USA). Briefly, cells were cultured in 96-well plates at 1000 cells per well for 24 h and subsequently treated with compounds (20 μg/mL) for 72 h and analyzed. Relative viability of the treated cells was normalized to the DMSO-treated control cells.[17a,b] Delazar A, Byres M, Gibbons S, et al. Iridoid glycosides from Eremostachys glabra. *J Nat Prod*. 2004;67:1584–1587;
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23. NF-κB assay: We employed human embryonic kidney cells 293 Panomic for monitoring changes occurring along the NF-kB pathway. Stable constructed cells were seeded into 96-well plates at 20×10^3 cells per well. Cells were maintained in Dulbecco's modified Eagle's medium (DMEM) (Invitrogen Co.), supplemented with 10% FBS, 100 units/mL penicillin, 100 μg/mL streptomycin, and 2 mM L-glutamine. After 48 h incubation, the medium was replaced and the cells were treated with various concentrations of test compounds. TNF-α (human, recombinant, *E. coli*, Calbiochem) was used as an activator at a concentration of 2 ng/mL (0.14 nM). The plate was incubated for 6 h. Spent medium was discarded, and the cells were washed once with PBS. Cells were lysed using 40 μL (for 96-well plate) of Passive lysis buffer from Promega, by incubating for 5 min on a shaker at room temperature. The luciferase assay was performed using the Luc assay system from Promega. The gene product, luciferase enzyme, reacts with luciferase substrate, emitting light, which was detected using a luminometer (LUMIstar Galaxy BMG, Offenburg, Germany). The samples which showed more than 60% inhibition at 40 μM were tested at different concentrations to find IC_{50}. Data for NF-κB inhibition are expressed as IC_{50} values (i.e., concentration required to inhibit TNF induced NF-κB activity by 50%). As a positive control, two NF-κB inhibitors were used: TPCK or BAY-11. (a) Kondratyuk TP, Park EJ, Yu R, et al. *Mar. Drugs*. 2012;10:451–464.
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28. ACD/Percepta 14.1.0 software (ACD/Labs).