Bioorganic & Medicinal Chemistry

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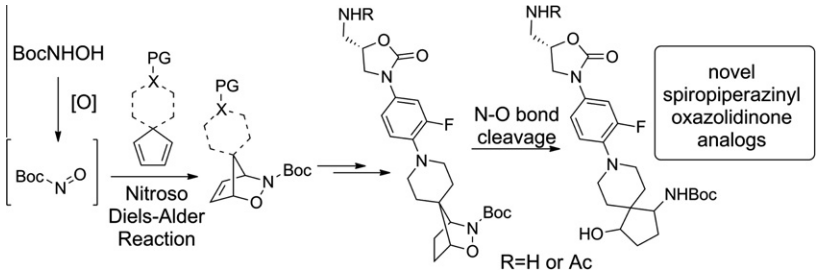
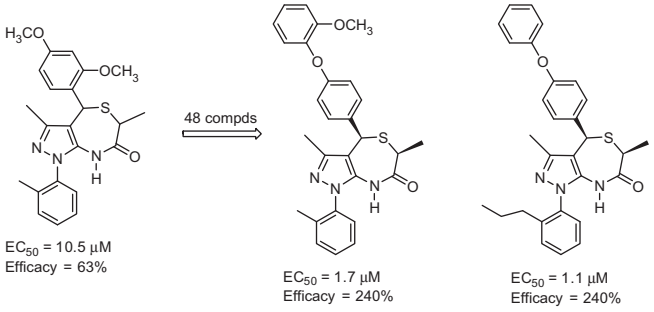
# Bioorganic & Medicinal Chemistry Volume 20, Issue 11, 2012

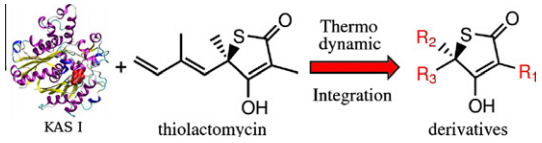
# Contents



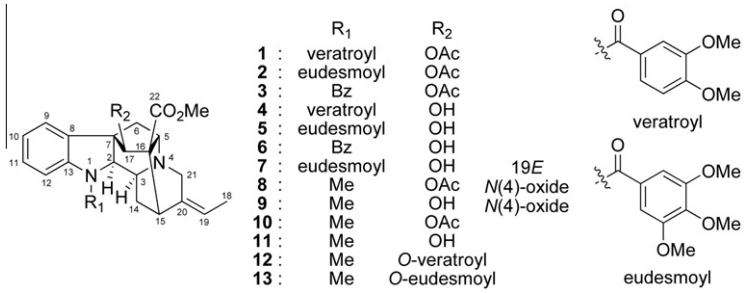


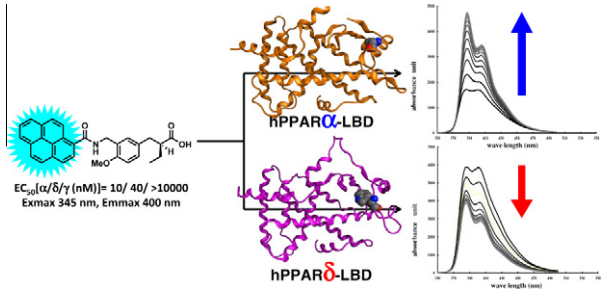





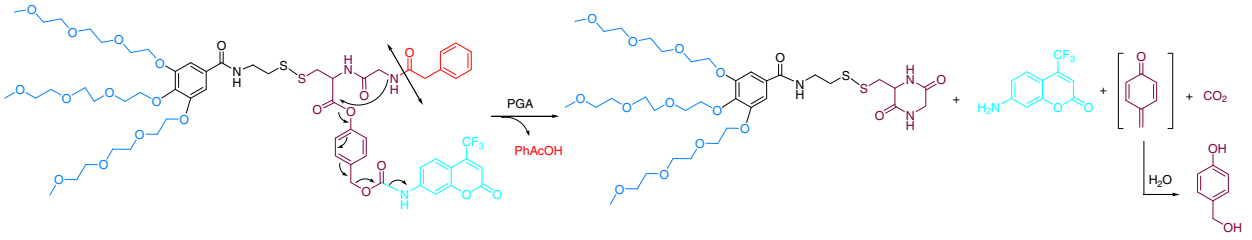





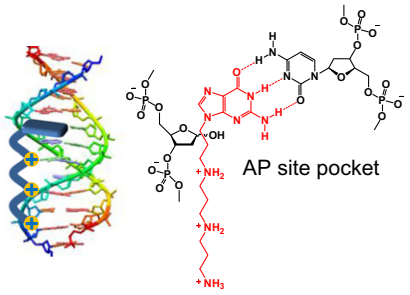





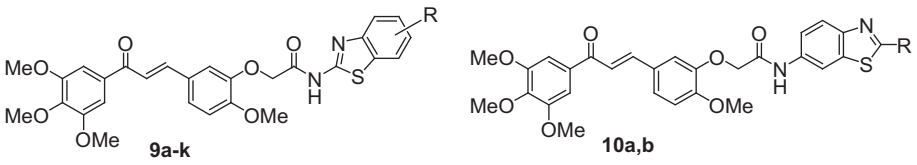


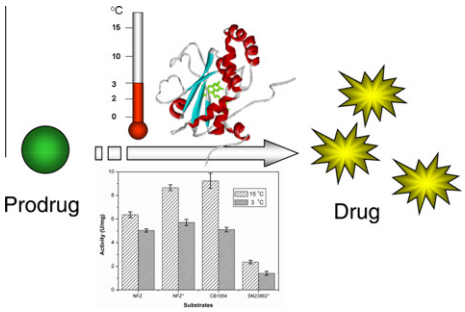





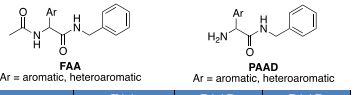







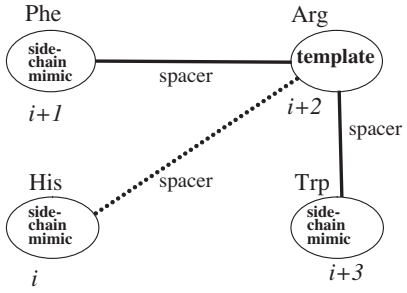



| Ar | FAA MES $ED_{50}$ (mg/kg) | PAAD MES $ED_{50}$ (mg/kg) | PAAD Formalin $ED_{50}$ (mg/kg) |
|---|---|---|---|
|  | 11 | 100 (MAD)[a] | 33 |
|  | 15 | 85 | >160 |
|  | 10 | 85 | 29 |
|  | 12 | 67 | 45 |

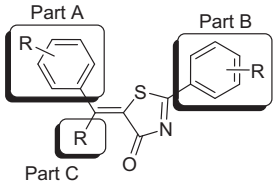
[a] MAD = minimal active dose



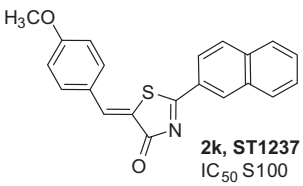




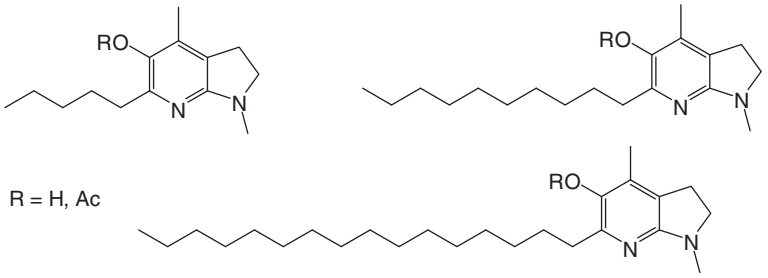

**General structure:**



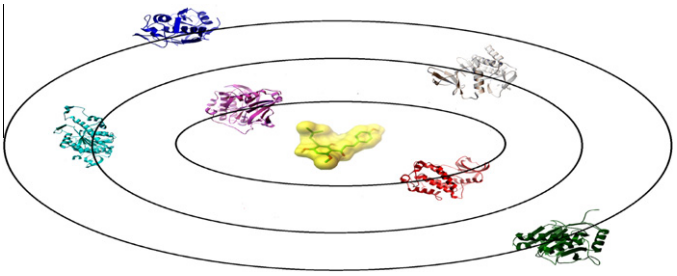

**Most active compound:**



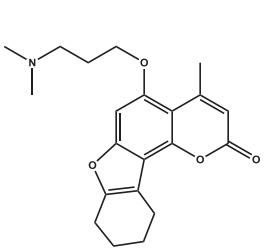

**2k, ST1237**
$IC_{50}$ S100 = 0.08 μM
$IC_{50}$ PMNL = 0.12 μM

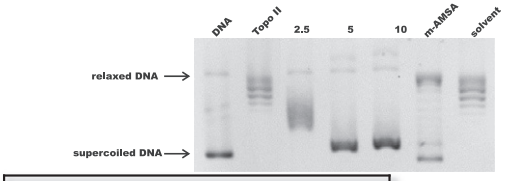




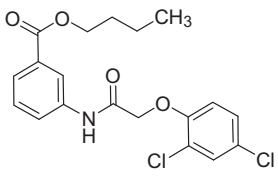




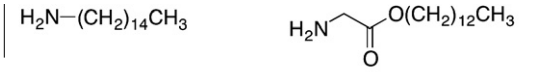




| $IC_{50}$ (μM) | | | |
|---|---|---|---|
| HeLa | | A-431 | |
| UVA | dark | UVA | dark |
| 0.4±0.1 | 7.2±0.3 | 2.0±0.5 | 6.7±1.1 |



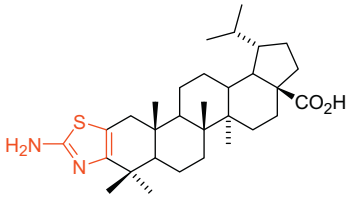



Compound **6**, butyl 3-[2-(2,4-dichlorophenoxy)acetamido]benzoate, binds to DnaJ and inhibits Hsp70/DnaJ protein refolding with an $IC_{50}$ value of 0.13 μM.

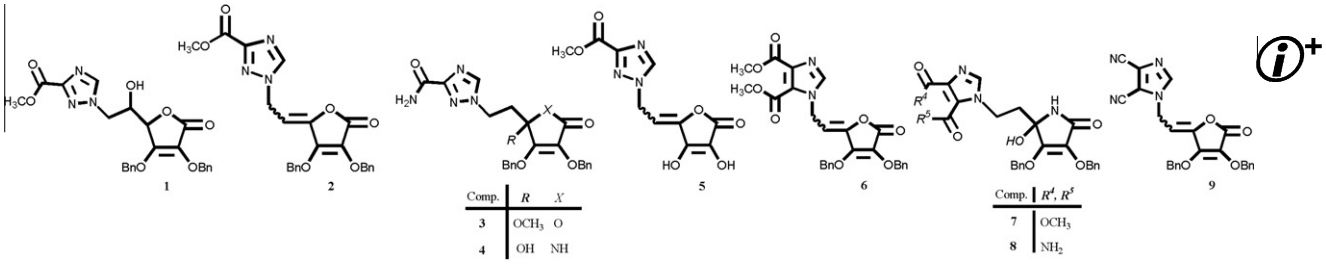



pentadecylamine (**2c**) tridecyl 2-aminoacetate (**11b**)







*Corresponding author
Supplementary data available via SciVerse ScienceDirect

**COVER**

Dipyrone (metamizol) is a common antipyretic drug and the most popular non-opioid analgesic in many countries. In spite of its long and widespread use, molecular details of its fate in the body are not fully known. Two unknown metabolites were now found, viz. arachidonoyl amides, and positively tested for cannabis receptor binding (CB1 and CB2) and cyclooxygenase inhibition. Two more puzzle pieces of the dipyrone story found! (Rogosch, T.; Sinning, C.; Podlewski, A.; Watzer, B.; Schlosburg, J.; Lichtman, A.H.; Cascio, M.G.; Bisogno, T.; Di Marzo, V.; Nüsing, R.; Imming, P. *Bioorg. Med. Chem.* **2012,** *20,* 103–109.]

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# Alstiphyllanines I–O, ajmaline type alkaloids from *Alstonia macrophylla* showing vasorelaxant activity

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ROCs
SAR

ABSTRACT

Seven new ajmaline type alkaloids, alstiphyllanines I–O (**1**–**7**) were isolated from the leaves of *Alstonia macrophylla* together with six related alkaloids (**8**–**13**). Structures and stereochemistry of **1**–**7** were fully elucidated and characterized by 2D NMR analysis. A series of alstiphyllanines I–O (**1**–**7**) as well as the known ajmaline type alkaloids (**8**–**13**) showed that they relaxed phenylephrine (PE)-induced contractions against rat aortic ring. Among them, vincamedine (**10**) showed potent vasorelaxant activity, which may be mediated through inhibition of $Ca^{2+}$ influx through voltage-dependent $Ca^{2+}$ channels (VDCs) and/or receptor-operated $Ca^{2+}$ channels (ROCs) as well as partially mediated the NO release from endothelial cells. The presence of substituents at both N-1 and C-17 may be important to show vasorelaxation activity.



## 1. Introduction

The vasodilators are useful for treatment of cerebral vasospasm and hypertension, and for improvement of peripheral circulation. Several endothelium-dependent vasodilators, such as bradykinin, acetylcholine, and histamine, have been reported to elevate $Ca^{2+}$ levels in endothelial cells and activate NO release, leading to vasorelaxation.[1] On the other hand, contractile response in smooth muscle is caused by $Ca^{2+}$ influx through VDCs and/or ROCs.[2] The endothelium-independent vasodilators, such as nicardipine, niphedipine, dirtiazem, and verapamil, have been reported to inhibit VDCs and led to decrease the intracellular $Ca^{2+}$ concentration in smooth muscle, leading to vasorelaxation.[2] $K^+$ channels play important roles in the regulation of vascular tone.[3–5] Indeed, the $K^+$ channels present in blood vessels indirectly influence vascular tension by changing the resting membrane potential. Many vascularly active agents and drugs induce their vasodilator of vasoconstrictor effects by opening or closing $K^+$ channels.[6]

Our screening study on vasodilators in traditional medicine[7] discovered that the alkaloidal extract of *Alstonia macrophylla* shows remarkably vasodilation activity against rat aorta. The genus Alstonia, which is widely distributed in tropical regions of Africa and Asia, are well-known rich sources of unique monoterpene indole alkaloids with various biological activities such as anticancer, antibacterial, anti-inflammatory, antitussive, and antimalarial properties.[7] Recently, several new indole alkaloids were isolated from extracts of *Alstonia macrophylla* Wall.ex G. Don (Apocynaceae) collected in Indonesia.[8,9] With an aim to isolate additional new alkaloids showing vasorelaxant activity, purification of extracts of *A. macrophylla* led to seven new alkaloids, alstiphyllanines I–O (**1**–**7**) together with six known alkaloids (**8**–**13**). Herein we report the isolation and structure elucidation of alstiphyllanines I–O (**1**–**7**) as well as vasorelaxant activity and structure–activity relationship (SAR) study of these ajmaline type indole alkaloids.

### 1.1. Structures of alstiphyllanines I–O (1–7)

Leaves of *A. macrophylla* were extracted with MeOH, and the extract was partitioned between EtOAc and 3% aqueous tartaric acid. Water-soluble materials, adjusted to pH 9 with satd aq $Na_2CO_3$, were extracted with $CHCl_3$. The $CHCl_3$-soluble materials were subjected to an LH-20 column ($CHCl_3$/MeOH, 1:1) followed by a silica gel column ($CHCl_3$/MeOH, 1:0–0:1). The eluted fractions were further separated by ODS HPLC (MeOH/$H_2O$/TFA) to afford **1** (5.6 mg, 0.0016% dry weight), **2** (12 mg, 0.0039%), **3** (1.5 mg, 0.0004%), **4**

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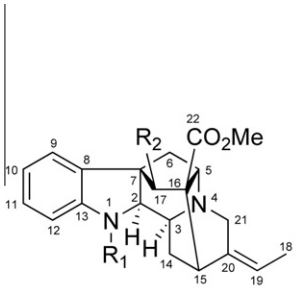
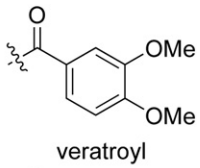
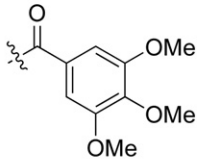


| | $R_1$ | $R_2$ | |
|---|---|---|---|
| **1** : | veratroyl | OAc | |
| **2** : | eudesmoyl | OAc | |
| **3** : | Bz | OAc | |
| **4** : | veratroyl | OH | |
| **5** : | eudesmoyl | OH | |
| **6** : | Bz | OH | |
| **7** : | eudesmoyl | OH | 19*E* |
| **8** : | Me | OAc | *N*(4)-oxide |
| **9** : | Me | OH | *N*(4)-oxide |
| **10** : | Me | OAc | |
| **11** : | Me | OH | |
| **12** : | Me | *O*-veratroyl | |
| **13** : | Me | *O*-eudesmoyl | |




veratroyl




eudesmoyl

(15.2 mg, 0.0029%), **5** (7.2 mg, 0.0021%), **6** (1.5 mg, 0.0004%), and **7** (5.6 mg, 0.0016%), together with six known alkaloids, alstiphyllanine A (**8**),[9] alstiphyllanine H (**9**),[9] vincamedine (**10**),[10] vincamajine (**11**),[11] vincamajine-17-*O*-veratrate (**12**),[12] and vincamajine-17-*O*-3′,4′,5′-trimethoxybenzoate (**13**).[12]

Alstiphyllanine I {**1**, $[\alpha]_D^{26}$ −90 (*c* 1.0, MeOH)} showed the pseudomolecular ion peak at *m/z* 559 $(M+H)^+$ in the ESIMS, and the molecular formula $C_{32}H_{34}N_2O_7$, was established by HRESIMS [*m/z* 559.2455 $(M+H)^+$]. IR absorptions implied the presence of carbonyl (1750 and 1670 $cm^{-1}$) functionalities. The $^1H$ NMR data (Table 1) showed the presence of four aromatic protons, an ethylidene side chain, a methyl ester, and an acetyl group. The $^{13}C$ NMR data (Table 2) revealed thirty-two carbon signals due to six $sp^2$ quaternary carbons, eight $sp^2$ methines, two ester carbonyls, one amide carbonyl, two $sp^3$ quaternary carbons, five $sp^3$ methines, three $sp^3$ methylenes, and five methyl groups. Partial structures C-9 to C-12, C-5 to C-6, C-2 to C-15, and C-18 to C-19 were deduced from detailed analysis of the $^1H$–$^1H$ COSY spectrum of **1**. The HMBC cross-peaks of $H_3$-18 to C-20 and H-19 to C-21 placed the ethylidene side chain at C-20. The presence of veratroyl group ($\delta_C$ 56.5, 56.5, 112.9, 113.3, 124.1, 127.8, 150.7, and 154.6, respectively) and its connection to a nitrogen atom of the indole ring were elucidated by a HMBC correlation for H′-2 to C-23 ($\delta_C$ 170.6). The HMBC correlations for H-17 to C-5 and C-6 and H-2 to C-17 indicated that **1** was an ajmaline-type alkaloid. The presence of an acetyl group was indicated by the HMBC correlations for $H_3$-25 and H-17 to C-24 ($\delta_C$ 169.9). Thus, **1** was an ajmaline-type alkaloid with a 3,4-dimethoxybenzoyl (veratroyl) group in place of a methyl group of vincamedine.[10] The relative stereochemistry of **1** was elucidated by NOESY correlations as shown in computer-generated 3D drawing (Fig. 1). The NOESY correlations of $H_3$-18 to H-21 and H-19 to H-15 indicated that the ethylidene side chain was *Z*. In addition, H-3 correlated with both H-2 and H-14a, and H-14b with H-17 indicating that H-2 was α-oriented and H-17 was β-oriented.

Alstiphyllanine J {**2**, $[\alpha]_D^{26}$ −94 (*c* 1.0, MeOH)} was revealed to have the molecular formula $C_{33}H_{36}N_2O_8$, by HRESITOFMS [*m/z* 589.2548 $(M+H)^+$, Δ −0.2 mmu], which was larger than that of alstiphyllanine I (**1**) by $CH_2O$ unit. Compared with $^1H$ NMR data of **1**, alstiphyllanine J was suggested to be an ajmaline-type backbone with an additional *O*-Me unit at C-5′. The HMBC cross-peak of $H_3$-*O*-Me ($\delta_H$ 3.85) to C-5′ ($\delta_C$ 155.0) revealed the presence of an eudesmoyl moiety.

HRESITOFMS data [*m/z* 499.2220 $(M+H)^+$, Δ −1.3 mmu] of alstiphyllanine K {**3**, $[\alpha]_D^{26}$ −20 (*c* 1.0, MeOH)} established the molecular formula, $C_{30}H_{30}N_2O_5$, which was smaller than that of alstiphylla-

**Table 1**
$^1H$ NMR data [$\delta_H$ (*J*, Hz)] of alstiphyllanines I–O (**1**–**7**)

| | **1**[a] | **2**[a] | **3**[a] | **4**[a] | **5**[a] | **6**[a] | **7**[a] |
|---|---|---|---|---|---|---|---|
| 2 | 4.38 (m) | 4.44 (m) | 4.34 (d, 4.8) | 4.30 (br s) | 4.35 (br s) | 4.29 (m) | 4.35 (br s) |
| 3 | 5.19 (m) | 5.19 (br s) | 4.87 (m) | 4.93 (m) | 5.09 (m) | 4.99 (m) | 5.09 (m) |
| 5 | 4.46 (m) | 4.44 (m) | 4.09 (m) | 4.11 (m) | 4.01 (m) | 4.15 (m) | 4.01 (m) |
| 6a | 2.22 (m) | 2.31 (d, 9.5) | 2.06 (d, 12.3) | 2.01 (d, 13.5) | 2.10 (dd, 12.4, 6.2) | 1.98 (m) | 2.10 (dd, 12.4, 6.2) |
| 6b | 2.87 (d, 11.0) | 2.86 (d, 9.5) | 2.79 (dd, 12.3, 3.6) | 2.86 (d, 13.5) | 2.91 (d, 12.4) | 2.88 (d, 11.0) | 2.91 (d, 12.4) |
| 9 | 7.25 (br s) | 7.23 (br s) | 7.22 (d, 6.6) | 7.29 (m) | 7.32 (m) | 7.32 (d, 6.9) | 7.32 (m) |
| 10 | 7.01 (br s) | 7.01 (m) | 6.98 (dd, 6.6, 7.8) | 7.00 (m) | 7.00 (m) | 7.01 (dd, 6.9, 8.7) | 7.00 (m) |
| 11 | 7.01 (br s) | 7.01 (m) | 6.93 (dd, 7.8, 7.8) | 6.98 (m) | 7.02 (m) | 6.93 (dd, 9.0, 8.7) | 7.02 (m) |
| 12 | 6.23 (br s) | 6.23 (m) | 6.22 (d, 7.8) | 6.27 (m) | 6.27 (m) | 6.11 (d, 9.0) | 6.27 (m) |
| 14a | 2.08 (t, 14.0) | 2.07 (t, 14.0) | 1.91 (m) | 1.85 (t, 13.9) | 1.95 (dd, 14.5, 12.4) | 1.91 (t, 14.3) | 1.95 (dd, 14.5, 12.4) |
| 14b | 2.61 (d, 14.0) | 2.59 (d, 14.0) | 2.53 (dd, 15.0, 6.0) | 2.49 (dt, 13.9, 7.1) | 2.55 (dt, 14.5, 4.9) | 2.49 (dd, 14.3, 5.0) | 2.55 (dt, 14.5, 4.9) |
| 15 | 3.39 (d, 3.6) | 3.37 (br s) | 3.24 (m) | 3.31 (m) | 3.37 (d, 3.6) | 3.33 (m) | 3.85 (m) |
| 17 | 6.02 (s) | 6.02 (s) | 5.96 (s) | 4.49 (s) | 4.52 (s) | 4.50 (s) | 4.56 (s) |
| 18 | 1.61 (d, 6.1) | 1.61 (d, 4.5) | 1.59 (d, 6.6) | 1.59 (d, 6.4) | 1.61 (d, 6.6) | 1.60 (d, 6.8) | 1.67 (d, 6.4) |
| 19 | 5.60 (m) | 5.59 (m) | 5.49 (m) | 5.50 (m) | 5.55 (m) | 5.53 (m) | 5.55 (m) |
| 21a | 4.37 (m) | 4.08 (m) | 3.84 (m) | 3.87 (m) | 4.01 (m) | 3.92 (m) | 4.03 (m) |
| 21b | 4.12 (d, 16.0) | 4.35 (d, 13.8) | 4.09 (m) | 4.11 (m) | 4.26 (m) | 4.18 (m) | 4.03 (m) |
| 25 | 1.91 (s) | 1.88 (s) | 1.90 (s) | | | | |
| $CO_2Me$ | 3.78 (s) | 3.78 (s) | 3.76 (s) | 3.74 (s) | 3.76 (s) | 3.75 (s) | 3.76 (s) |
| 3′-*O*-*Me* | 3.78 (s) | 3.85 (s) | | 3.74 (s) | 3.81 (s) | | 3.81 (s) |
| 4′-*O*-*Me* | 3.92 (s) | 3.78 (s) | | 3.82 (s) | 3.87 (s) | | 3.87 (s) |
| 5′-*O*-*Me* | | 3.85 (s) | | | 3.81 (s) | | 3.81 (s) |
| 2′ | 7.29 (s) | 7.05 (s) | 7.74 (d, 7.5) | 7.28 (m) | 7.01 (s) | 7.70 (m) | 7.01 (s) |
| 3′ | | | 7.52 (dd, 7.6, 7.5) | | | 7.52 (m) | |
| 4′ | | | 7.64 (dd, 7.6, 7.6) | | | 7.65 (t, 6.9) | |
| 5′ | 7.06 (d, 6.9) | | 7.52 (dd, 7.6, 7.5) | 7.02 (d, 6.9) | | 7.52 (m) | |
| 6′ | 7.41 (d, 6.9) | 7.05 (s) | 7.74 (d, 7.5) | 7.34 (d, 6.9) | 7.01 (s) | 7.70 (m) | 7.01 (s) |

[a] TFA salt in $CD_3OD$.

**Table 2**
$^{13}$C NMR data ($\delta_C$) of alstiphyllanines I–O (**1**–**7**)

| | **1**[a] | **2**[a] | **3**[a] | **4**[a] | **5**[a] | **6**[a] | **7**[a] |
|---|---|---|---|---|---|---|---|
| 2 | 68.3 | 68.3 | 69.0 | 69.2 | 69.1 | 69.4 | 69.1 |
| 3 | 57.0 | 57.1 | 55.9 | 56.4 | 57.7 | 56.8 | 57.7 |
| 5 | 64.7 | 64.8 | 63.8 | 63.9 | 64.1 | 64.6 | 64.1 |
| 6 | 34.3 | 34.2 | 35.7 | 34.6 | 34.5 | 34.9 | 34.5 |
| 7 | 56.6 | 57.0 | 57.5 | 57.7 | 57.7 | 57.9 | 57.7 |
| 8 | 129.6 | 129.6 | 130.9 | 130.7 | 131.4 | 131.7 | 131.4 |
| 9 | 125.2 | 125.1 | 125.2 | 127.0 | 127.1 | 127.2 | 127.1 |
| 10 | 124.9 | 125.0 | 124.7 | 124.5 | 124.8 | 124.7 | 124.8 |
| 11 | 129.8 | 129.7 | 129.4 | 128.9 | 129.1 | 129.0 | 129.1 |
| 12 | 117.0 | 117.1 | 116.9 | 116.2 | 116.3 | 116.4 | 116.3 |
| 13 | 145.4 | 145.3 | 145.5 | 145.4 | 145.1 | 145.0 | 145.1 |
| 14 | 22.4 | 22.6 | 25.5 | 22.0 | 21.9 | 22.8 | 21.9 |
| 15 | 36.6 | 36.7 | 35.7 | 36.7 | 36.5 | 36.5 | 30.1 |
| 16 | 60.3 | 61.3 | 60.7 | 61.3 | 61.4 | 61.9 | 61.4 |
| 17 | 74.9 | 74.9 | 76.1 | 75.5 | 75.6 | 75.6 | 75.5 |
| 18 | 12.9 | 12.8 | 12.6 | 12.7 | 12.7 | 12.7 | 13.1 |
| 19 | 123.7 | 123.8 | 121.2 | 121.8 | 122.3 | 121.9 | 122.3 |
| 20 | 128.9 | 128.7 | 129.8 | 131.6 | 129.6 | 131.3 | 129.6 |
| 21 | 52.2 | 52.3 | 52.7 | 52.5 | 52.5 | 52.5 | 55.1 |
| 22 | 169.8 | 170.8 | 171.9 | 172.2 | 172.0 | 172.3 | 172.0 |
| 23 | 170.6 | 170.5 | 171.9 | 171.7 | 171.5 | 172.1 | 171.5 |
| 24 | 169.9 | 169.8 | 170.3 | | | | |
| 25 | 20.5 | 20.4 | 20.6 | | | | |
| $CO_2$*Me* | 53.5 | 53.4 | 52.9 | 52.7 | 52.6 | 52.7 | 52.6 |
| 10-*O*-*Me* | | | | | | | |
| 3′-*O*-*Me* | 56.5 | 61.3 | | 56.9 | 57.1 | | 57.1 |
| 4′-*O*-*Me* | 56.5 | 57.0 | | 56.7 | 61.4 | | 61.4 |
| 5′-*O*-*Me* | | 61.3 | | | 57.1 | | 57.1 |
| *N*(1)-*Me* | | | | | | | |
| 1′ | 127.8 | 130.5 | 136.6 | 128.7 | 131.5 | 136.6 | 131.5 |
| 2′ | 113.3 | 107.8 | 129.8 | 113.7 | 108.0 | 129.6 | 108.0 |
| 3′ | 150.7 | 155.0 | 130.1 | 150.9 | 155.1 | 130.2 | 155.1 |
| 4′ | 154.6 | 143.4 | 133.5 | 154.6 | 143.6 | 133.6 | 143.6 |
| 5′ | 112.9 | 155.0 | 130.1 | 112.7 | 155.1 | 130.2 | 155.1 |
| 6′ | 124.1 | 107.8 | 129.8 | 124.0 | 108.0 | 129.6 | 108.0 |

[a] TFA salt in $CD_3OD$.

nine I (**1**) by $C_2H_4O_2$ unit. The NMR data of **3** were analogous to those of **1** except for the following observation: two methoxy signals ($\delta_H$ 3.78 and 3.92) in **1** were lack in **3**. The presence of a benzoyl group was verified by the HMBC correlations of H-2′ and H-6′ to C-23.

Alstiphyllanine L {**4**, $[\alpha]_D^{26}$ −68 (*c* 1.0, MeOH)} was revealed to have the molecular formula $C_{30}H_{32}N_2O_6$, by HRESITOFMS [*m*/*z* 517.2347 $(M+H)^+$, Δ +0.8 mmu], which was smaller than that of alstiphyllanine I (**1**) by an acetyl unit. IR absorption band at 3420 $cm^{-1}$ and $^{13}$C chemical shift at C-17 ($\delta_C$ 75.5) supported the presence of a hydroxyl group at C-17.

HRESITOFMS data [*m*/*z* 547.2429 $(M+H)^+$, Δ −1.5 mmu] of alstiphyllanine M {**5**, $[\alpha]_D^{26}$ −62 (*c* 1.0, MeOH)} established the molecular formula, $C_{31}H_{34}N_2O_7$, which was smaller than that of alstiphyllanine J (**2**) by an acetyl unit. IR absorption band at 3420 $cm^{-1}$ and $^{13}$C chemical shift at C-17 ($\delta_C$ 75.6) supported the presence of a hydroxyl group at C-17.

Alstiphyllanine N {**6**, $[\alpha]_D^{26}$ −62 (*c* 1.0, MeOH)} was revealed to have the molecular formula $C_{28}H_{28}N_2O_4$, by HRESITOFMS [*m*/*z* 457.2132 $(M+H)^+$, Δ +0.5 mmu], which was smaller than that of alstiphyllanine K (**3**) by an acetyl unit. IR absorption band at 3420 $cm^{-1}$ and $^{13}$C chemical shift at C-17 ($\delta_C$ 75.6) supported the presence of a hydroxyl group at C-17.

Alstiphyllanine O {**7**, $[\alpha]_D^{26}$ −53 (*c* 1.0, MeOH)} had a molecular formula $C_{31}H_{34}N_2O_7$ based on the HRESITOFMS [*m*/*z* 547.2429 $(M+H)^+$, Δ −1.5 mmu]. The IR absorption band at 3420 $cm^{-1}$ and $^{13}$C chemical shift at C-17 ($\delta_C$ 75.5) supported the presence of a hydroxyl group at C-17. Analysis of the $^1$H, $^{13}$C, and 2D NMR of **7** gave the same planar structure as **5**, suggesting that **7** should be a stereoisomer of **5**. The NOESY correlation of H-15/$H_3$-18 indicated that the ethylidene side chain was *E*.

A detail 2D NMR analysis of a series of alstiphyllanines J–O (**2**–**7**) suggested their structures were related ajmaline-type indole alkaloids. The relative stereochemistry of a series of alstiphyllanines J–O (**2**–**7**) was elucidated by NOESY correlations. The NOESY correlation of $H_3$-18 to H-21 and H-19 to H-15 indicated that the geometry of ethylidene side chain was *Z* except for that of alstiphyllanine O. The NOESY correlations of H-3/H-2 and H-14a and H-14b/H-17 indicated that H-2 was α-orientated and H-17 was β-oriented.

### 1.2. Vasorelaxant activity in ex-vivo

All isolated compounds except for **3** (it is not enough for evaluation because of the limited amount) were tested for vasorelaxant activity against rat aorta (Fig. 2). When PE (0.3 μM) was applied to thoracic aortic rings with endothelium after achieving a maximal response, a series of alstiphyllanines I, J, L–O (**1**, **2**, **4**–**7**) and their related ajmaline-type alkaloids, alstiphyllanine A (**8**), alstiphyllanine H (**9**), vincamedine (**10**), vincamajine (**11**), vincamajine-17-*O*-veratrate (**12**), and vincamajine-17-*O*-3′,4′,5′-trimethoxybenzoate (**13**), were added and some of them showed potent vasorelaxant effects at 30 μM (Fig. 2). The presence of a hydroxy group at C-17 and an *N*(4)-oxide reduced the potency of vasodilation. On the other hand, the presence of substituents at *N*(1) might affect slightly on vasorelaxation activity. In addition, compared with the geometry at C-19 of **5** and **7**, 19*Z* might increase the potency of vasodilation.

Vincamedine (**10**) showed the excellent activity at early stage within 5–15 min after addition. Furthermore, to investigate the involvement of endothelial cells, vasorelaxant activity was tested using endothelium-denuded aorta (−EC rings) for **10** (Fig. 3).

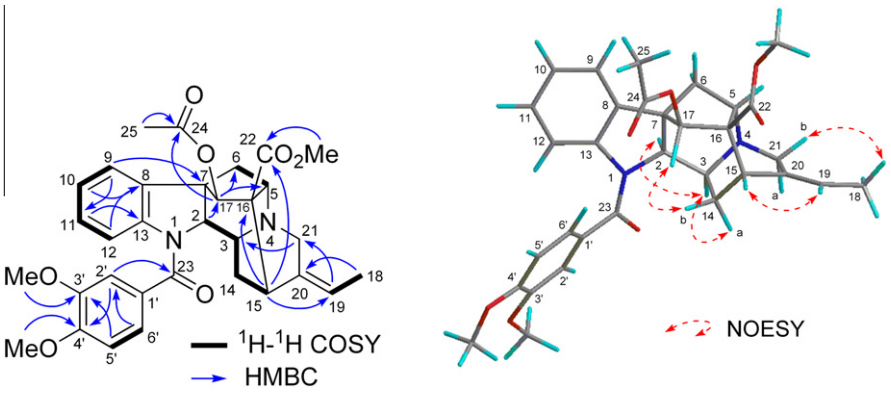



**Figure 1.** Selected 2D NMR correlations for alstiphyllanine I (**1**).

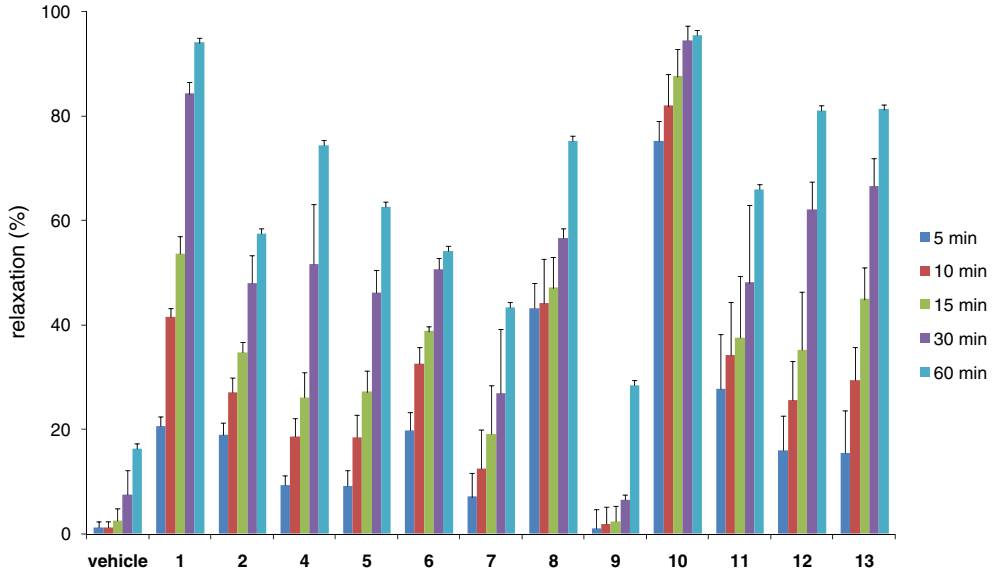



**Figure 2.** Relaxation responses induced by isolated compounds (**1**, **2**, **4**–**13**) at 30 μM on the rat aortic rings precontracted with 0.3 μM phenylephrine. Values are the mean ± S.D. ($n$ = 3).

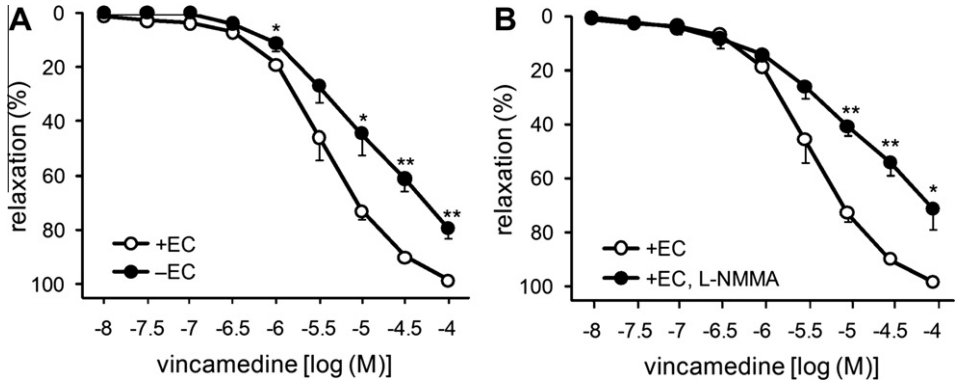



**Figure 3.** Concentration-dependent relaxation by **10** in +EC or −EC rings precontracted with PE (**A**). Vasorelaxant effect of **10** on +EC rings precontracted with PE in the presence or absence of L-NMMA (**B**). Values are the mean ± S.E.M. ($n$ = 3) $^{*}P$ <0.05 and $^{**}P$ <0.01 respectively, versus +EC group.

Compound **10** caused concentration-response relaxation with maximum response at 100 μM in +EC rings (Fig. 3). The relaxation induced by **10** was partly attenuated in –EC rings and in the presence of $N^G$-monomethyl-L-arginine (L-NMMA, 100 μM), an inhibitor of nitric oxide synthase (NOS), suggesting that effects induced by **10** partially mediated the NO release from endothelial cells (Fig. 3). However, vasorelaxant effect of **10** on −EC rings still remained. Hence, subsequent investigations were focused on the direct effect of **10** on vascular smooth muscle cells using −EC rings.

To investigate the involvement of $K^+$ channel, the vasorelaxant effect of **10** in PE-contracted −EC rings was examined by pretreatment of tetraethylammonium chloride [TEA (nonselective large-conductance $Ca^{2+}$-activated $K^+$ channel ($BK_{Ca}$) inhibitor). The concentration-dependent response was not altered by TEA (Fig. 4), which suggested that vasorelaxant effect of **10** did not involved $K^+$ channel.

Cumulative addition of isotonic high-$K^+$ (10–80 mM) elicits a concentration-dependent contraction by $Ca^{2+}$ influx via VDC. High $K^+$-induced contractile response was significantly decrease by pretreatment of **10** (Fig. 5). Therefore, the relaxant effect of **10** was thought to be due to inhibitory effect on VDC-dependent $Ca^{2+}$ influx.

In addition, we investigated the involvement of ROC. After pretreatment with PE and nicardipine in $Ca^{2+}$-free modified Krebs–Henseleit solution (KHS), the contractile response induced by $CaCl_2$ showed dose-dependent manner from 10 μM to 1 mM, presum-

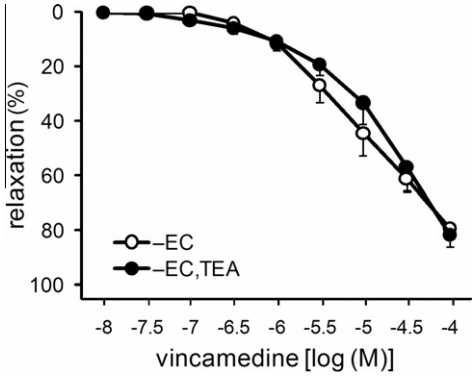



**Figure 4.** Vasorelaxant effect of **10** on PE-precontracted −EC rings in the presence or absence of TEA. Values are the mean ± S.E.M. ($n$ = 3)

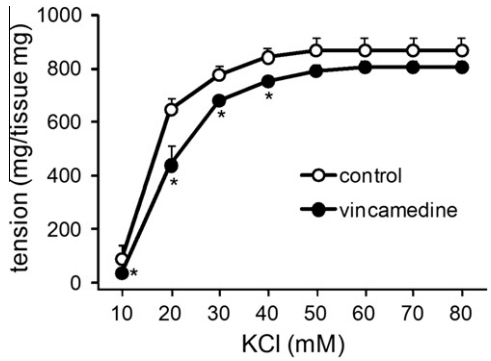



**Figure 5.** Concentration–response curves for isotonic high $K^+$-induced contractions in −EC rings in the presence or absence of **10**. Values are the mean ± S.E.M. ($n = 3$) $^*P < 0.05$ versus control group.

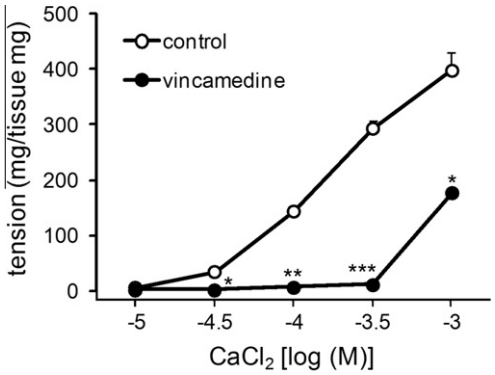



**Figure 6.** Effect of **10** on $CaCl_2$-induced contraction of −EC rings pretreated with PE and nicardipine in $Ca^{2+}$-free medium. Values are the mean ± S.E.M. ($n = 3$) $^*P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ respectively, versus control group.

ably due to the influx of $Ca^{2+}$ via ROC. The addition of **10** significantly inhibited $CaCl_2$-induced contraction dependent on ROC, suggesting that **10** also has inhibitory effect on $Ca^{2+}$ influx via ROC (Fig. 6).

In conclusion, we isolated seven new ajmaline type alkaloids, alstiphyllanines I–O (**1**–**7**) from the leaves of *Alstonia macrophylla* together with six related alkaloids (**8**–**13**). Structures and stereochemistry of **1**–**7** were fully elucidated and characterized by 2D NMR analysis. A series of alstiphyllanines I–O (**1**–**7**) as well as the known ajmaline type alkaloids (**8**–**13**) showed that they relaxed PE-induced contractions against rat aortic ring. The presence of a hydroxy group at C-17 and an *N*(4)-oxide reduced the potency of vasodilation. On the other hand, the presence of substituents at *N*(1) and the geometry at C-19 might affect slightly on vasorelaxation activity. Among them, vincamedine (**10**) showed potent vasorelaxant activity, which may be mediated through inhibition of $Ca^{2+}$ influx through VDCs and/or ROCs as well as partially mediated the NO release from endothelial cells.

## 2. Experimental section

### 2.1. General methods

$^1$H and 2D NMR spectra were recorded on a Bruker AV 400 spectrometer and chemical shifts were reported using residual $CD_3OD$ ($\delta_H$ 3.31 and $\delta_C$ 49.0) as internal standards. Standard pulse sequences were employed for the 2D NMR experiments. $^1$H–$^1$H COSY, HOHAHA, and NOESY spectra were measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1 K data points for each of 256 $t_1$ increments. NOESY spectra in the phase sensitive mode were measured with a mixing time of 800 ms. For HMQC spectra in the phase sensitive mode and HMBC spectra, a total of 256 increments of 1 K data points were collected. For HMBC spectra with Z-axis PFG, a 50 ms delay time was used for long-range C-H coupling. Zero-filling to 1 K for $F_1$ and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation.

### 2.2. Material

The leaves of *Alstonia macrophylla* were collected at Ngliyep, East Java, Indonesia in 2008. The botanical identification was made by Ms. Sri Wuryanti, Purwodadi Botanical Garden, Indonesia. A voucher specimen has been deposited in the herbarium at Purwodadi Botanical Garden, Pasuruan, Indonesia.

### 2.3. Extraction and isolation

The leaves of *A. macrophylla* (900 g) were extracted with MeOH to give the extract (154 g). The MeOH extract (59 g) was treated with 3% tartaric acid (pH 2) and then partitioned with EtOAc. The aqueous layer was treated with satd aq $Na_2CO_3$ aq to pH 9 and extracted with $CHCl_3$ to give alkaloidal fraction (2.0 g). The alkaloidal fraction was purified by LH-20 column ($CHCl_3$/MeOH, 1:0) and $SiO_2$ column ($CHCl_3$/MeOH, 1:0→0:1) and the fractions eluted by $CHCl_3$/MeOH (50:1 to 20:1) were purified by ODS HPLC (59–61% MeOH with 0.1% $CF_3CO_2H$; flow rate, 2 mL/min; UV detection at 254 nm) to afford alstiphyllanines I (**1**, 5.6 mg, 0.0016% dry weight), J (**2**, 12 mg, 0.0039%), K (**3**, 1.5 mg, 0.0004%), L (**4**, 15.2 mg, 0.0029%), M (**5**, 7.2 mg, 0.0021%), N (**6**, 1.5 mg, 0.0004%), and O (**7**, 1.5 mg, 0.0004%), together with six known alkaloids, alstiphyllanine A (**8**),[9] alstiphyllanine H (**9**),[9] vincamedine (**10**),[10] vincamajine (**11**),[11] vincamajine-17-*O*-veratrate (**12**),[12] and vincamajine-17-*O*-3′,4′,5′-trimethoxybenzoate (**13**).[12]

#### 2.3.1. Alstiphyllanine I (1)

Brown amorphous solid; $[\alpha]_D^{26}$ −90 (*c* 1.0, MeOH); IR (film) $\nu_{max}$ 1750 and 1670 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 297 ($\varepsilon$ 9600), 276 (11,300), 217 (24,700) and 202 (30,900) nm; $^1$H and $^{13}$C NMR data (Tables 1 and 2); ESIMS *m*/*z* 559 $(M+H)^+$; HRESITOFMS *m*/*z* 559.2455 [$(M+H)^+$, Δ +1.1 mmu, calcd for $C_{32}H_{35}N_2O_7$, 559.2444].

#### 2.3.2. Alstiphyllanine J (2)

Brown amorphous solid; $[\alpha]_D^{26}$ −94 (*c* 1.0, MeOH); IR (film) $\nu_{max}$ 1750 and 1680 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 293 ($\varepsilon$ 9600), 277 ($\varepsilon$ 35,800), 219 (5000), and 201 (10,600) nm; $^1$H and $^{13}$C NMR data (Tables 1 and 2); ESIMS *m*/*z* 589 $(M+H)^+$; HRESITOFMS *m*/*z* 589.2548 [$(M+H)^+$, Δ −0.2 mmu, calcd for $C_{33}H_{37}N_2O_8$, 589.2550].

#### 2.3.3. Alstiphyllanine K (3)

Brown amorphous solid; $[\alpha]_D^{26}$ −20 (*c* 1.0, MeOH); IR (film) $\nu_{max}$ 1750 and 1680 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 293 ($\varepsilon$ 1900), 268 (2400), 219 (5000) and 201 (10,600) nm; $^1$H and $^{13}$C NMR data (Tables 1 and 2); ESIMS *m*/*z* 499 $(M+H)^+$; HRESITOFMS *m*/*z* 499.2220 [$(M+H)^+$, Δ −1.3 mmu, calcd for $C_{30}H_{31}N_2O_5$, 499.2233].

#### 2.3.4. Alstiphyllanine L (4)

Brown amorphous solid; $[\alpha]_D^{26}$ −68 (*c* 1.0, MeOH); IR (film) $\nu_{max}$ 3420, 1730, and 1670 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 286 ($\varepsilon$ 8400), 273 (9200), 220 (21,700) and 202 (37,300) nm; $^1$H and $^{13}$C NMR data (Tables 1 and 2); ESIMS *m*/*z* 517 $(M+H)^+$; HRESITOFMS *m*/*z* 517.2347 [$(M+H)^+$, Δ +0.8 mmu, calcd for $C_{30}H_{33}N_2O_6$, 517.2339].

### 2.3.5. Alstiphyllanine M (5)

Brown amorphous solid; $[\alpha]_D^{26}$ −62 (*c* 1.0, MeOH); IR (film) $\nu_{max}$ 3420, 1730, and 1670 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 293 ($\varepsilon$ 9200), 273 (15,000), 213 (41,100) and 202 (62,500) nm; $^1H$ and $^{13}C$ NMR data (Tables 1 and 2); ESIMS *m*/*z* 547 $(M+H)^+$; HRESITOFMS *m*/*z* 547.2429 [$(M+H)^+$, Δ −1.5 mmu, calcd for $C_{31}H_{35}N_2O_7$, 547.2444].

### 2.3.6. Alstiphyllanine N (6)

Brown amorphous solid; $[\alpha]_D^{26}$ −62 (*c* 1.0, MeOH); IR (film) $\nu_{max}$ 3420, 1730, and 1670 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 291 ($\varepsilon$ 6300), 271 (8800), 218 (11,100) and 202 (49,100) nm; $^1H$ and $^{13}C$ NMR data (Tables 1 and 2); ESIMS *m*/*z* 457 $(M+H)^+$; HRESITOFMS *m*/*z* 457.2132 [$(M+H)^+$, Δ +0.5 mmu, calcd for $C_{28}H_{29}N_2O_4$, 457.2127].

### 2.3.7. Alstiphyllanine O (7)

Brown amorphous solid; $[\alpha]_D^{26}$ −53 (*c* 1.0, MeOH); IR (film) $\nu_{max}$ 3420, 1730, and 1670 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ 293 ($\varepsilon$ 9200), 271 (15,000), 218 (41,100) and 202 (62,500) nm; $^1H$ and $^{13}C$ NMR data (Tables 1 and 2); ESIMS *m*/*z* 547 $(M+H)^+$; HRESITOFMS *m*/*z* 547.2429 [$(M+H)^+$, Δ −1.5 mmu, calcd for $C_{31}H_{35}N_2O_7$, 547.2444].

### 2.4. Vasodilation assay[13]

The thoracic aorta between the aortic arch and the diaphragm was harvested from a male Wistar rat weighting 260 g and placed in oxygenated, modified KHS (118.0 mM NaCl, 4.7 mM KCl, 25.0 mM $NaHCO_3$, 1.8 mM $CaCl_2$, 1.2 mM $NaH_2PO_4$, 1.2 mM $MgSO_4$, and 11.0 mM glucose). After removing loosely adhering fat and connective tissue, the aorta was cut into ring preparations 3 mm in length. The aorta was placed in bath filled well-oxygenated (95% $O_2$, 5% $CO_2$) KHS at 37 °C with connection to a force-displacement transducer (Nihon Kohden, TB-611T, Tokyo, Japan). The aorta ring was equilibrated for 60 min under a resting tension of 1.0 g.

After equilibration, each aorta ring was contracted by treatment with PE (0.3 μM). Aortic rings with 80% relaxation by acetylcholine (ACh, 10 μM) were regarded as endothelium-intact aorta (+EC rings). Following washout, these rings were contracted once again with the same concentration of PE. When the PE-induced contraction reached a plateau, each sample (30 μM) or ACh (1 nM–10 μM) was added cumulatively. $IC_{50}$ of ACh (positive control) was approximately 1 μM in this experimental system.

To test for the involvement of endothelium-dependency in relaxation response, the endothelial cells were removed by rubbing and were confirmed by observing the loss of ACh-induced relaxation (−EC rings). When PE-induced contractions reached a plateau, vincamedine (**10**) was added cumulatively.

To test for the involvement of $K^+$ channel, TEA (1 mM; nonselective large-conductance $Ca^{2+}$-activated $K^+$ channel ($BK_{Ca}$) inhibitor) was applied to the aortic rings 30 min prior to precontraction by PE. Cumulative concentration-response of **10** was compared with or without TEA.

To investigate the involvement of VDC in the vasorelaxant response by **10**, aortic rings were equilibrated in KHS for 60 min. $Ca^{2+}$-free high $K^+$ solution (10–80 mM as KCl) was then added for observation of contractile response (control). When maximum contraction was achieved, the ring was washed and equilibrated for 60 min. After pretreatment of **10** at 30 μM for 30 min, $Ca^{2+}$-free high $K^+$ solution was added once again. A KCl-induced contractile response with or without each sample was compared.

To clarify the involvement of ROC-dependent $Ca^{2+}$ influx, a contractile response induced by $Ca^{2+}$ was recorded twice. Firstly, aortic rings were equilibrated in $Ca^{2+}$-free KHS with 0.01 mM EGTA for 60 min. After pretreatment with nicardipine (1 μM) for 30 min and following PE-prestimulation, aorta ring was contracted by cumulative addition of $CaCl_2$ (10 μM–1 mM). After the confirmation of maximum contraction, the ring was washed and equilibrated for 60 min to carry out second contractile experiment. Vincamedine (**10**) was added before PE-stimulation, and $Ca^{2+}$-induced contractile response was recorded as same as first contractile experiment. These two contractile responses by $Ca^{2+}$ with/without **10** were evaluated.

All tested compounds were dissolved in DMSO and diluted with saline. The final concentration of DMSO in the organ bath was less than 0.1%, and did not show any effects on contraction or relaxation. All other drugs were dissolved in saline.

All results are expressed as means ± S.E.M. Statistical analysis was done by Student's paired or unpaired *t*-test. $P < 0.05$ was considered statistically significant.

These animal experimental studies were conducted in accordance with the Guiding Principles for the Care and Use of Laboratory Animals, Hoshi University and under the supervision of the Committee on Animal Research of Hoshi University, which is accredited by the Ministry of Education, Science, Sports Culture, and Technology of Japan.

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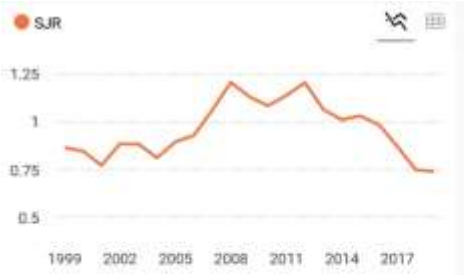
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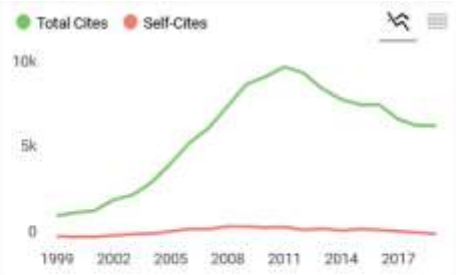
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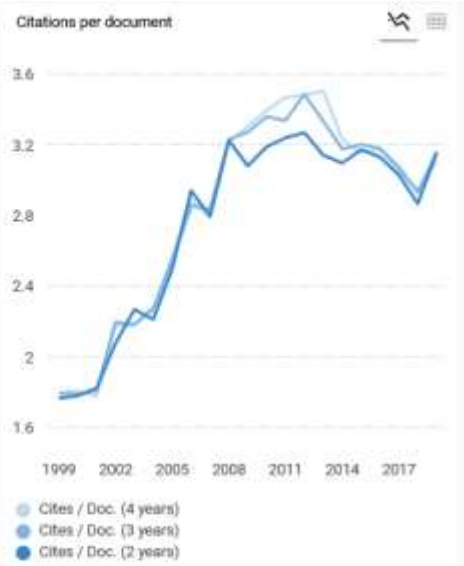
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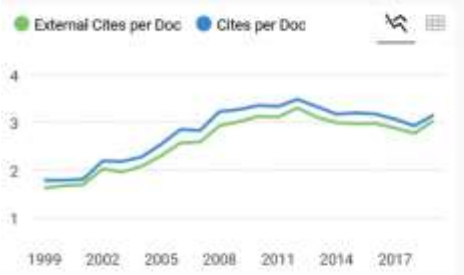
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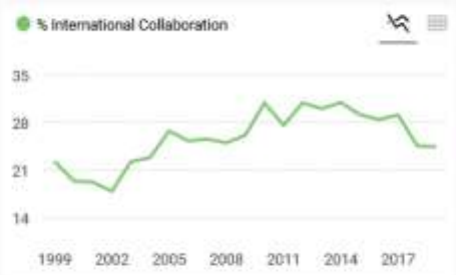
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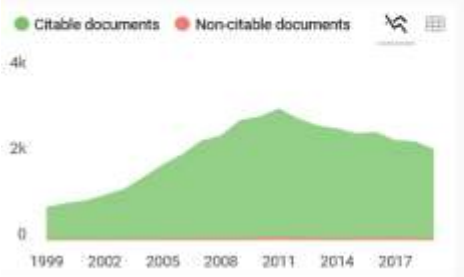
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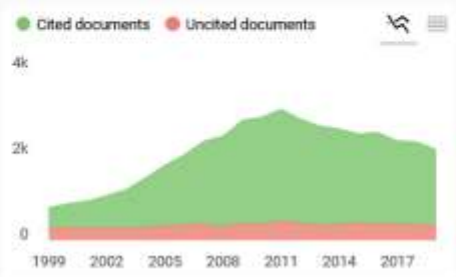
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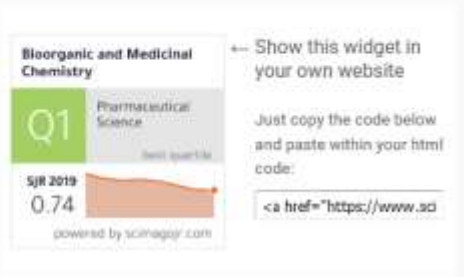
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