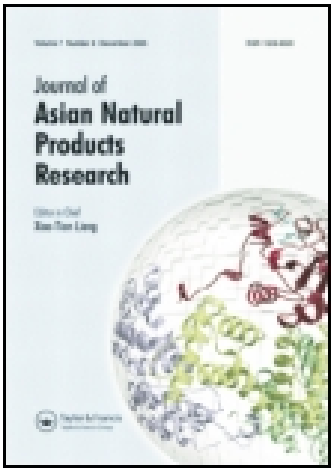

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Three new monomeric indole alkaloids from the roots of Catharanthus roseus

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Three new monomeric indole alkaloids from the roots of *Catharanthus roseus*

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Two new alkaloid glycosides (**1** and **2**) and a new monomeric indole alkaloid (**3**), together with 13 known ones (**4**–**16**), were isolated from the roots of *Catharanthus roseus*. The structures of new compounds were elucidated on the basis of the spectroscopic methods. The absolute configuration of compound **3** was established by the modified Mosher's method.

Keywords: *Catharanthus roseus*; Apocynaceae; indole alkaloid glycoside; Mosher's method

1. Introduction

The plant *Catharanthus roseus* (Apocynaceae) is widely distributed in tropical and semitropical regions. Up to now, over 130 indole alkaloids have been isolated from this plant [1]. Vinblastine and vincristine are the two typical indole alkaloids isolated from this plant in the 1950–1960s [2,3], which were used in clinic for the treatment of various leukemias, Hodgkin's disease, and solid tumors [4]. With the aim of searching for indole alkaloids with high biological activities, we had isolated some new indole alkaloids from the aerial parts of this plant [5,6]. Recently, we have carried out the phytochemical investigations on the roots of this plant. This paper reports the isolation and structural elucidation of three new alkaloids (**1**–**3**) (Figure 1) from the roots of *C. roseus*, together with 13 known ones (**4**–**16**).

2. Results and discussion

Compound **1** was obtained as an amorphous powder. The molecular formula of **1** was determined as $C_{26}H_{34}N_2O_7$ on the basis of its HR-ESI-MS at *m/z* 487.2429 $[M + H]^+$. The IR spectrum of **1** implied the presence of hydroxyl group (3357 cm^{-1}), ester group (1730 cm^{-1}), and double bond (1594 cm^{-1}). The ^1H NMR spectrum showed three aromatic protons at δ_H 6.82 (1H, dd, $J = 8.5, 2.5$ Hz), 6.73 (1H, d, $J = 2.5$ Hz), and 6.56 (1H, d, $J = 8.5$ Hz); an olefinic proton at δ_H 5.48 (1H, q, $J = 7.0$ Hz); three methyl groups at δ_H 3.80 (3H, s), 2.65 (3H, s), and 1.52 (3H, d, $J = 7.0$ Hz); and an anomeric proton at δ_H 4.61 (1H, d, $J = 7.5$ Hz). Accordingly, the ^{13}C NMR spectrum of **1** displayed the signals for an aromatic ring (δ_C 153.2, 150.1, 142.6, 116.9, 112.4, and 111.4), a pair of olefinic carbons (δ_C 138.5 and

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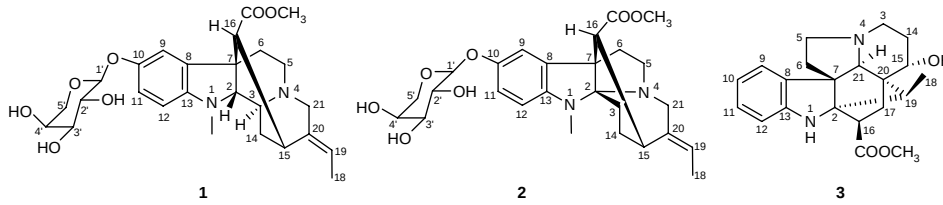

Figure 1. Chemical structures of compounds **1**–**3**.

121.9), an ester carbonyl carbon (δ_C 174.5), three methyls (δ_C 52.4, 35.5, and 13.7), and an arabinopyranose unit (δ_C 104.4, 74.4, 72.5, 69.8, and 67.3).

The aglycone and sugar unit were obtained by acid hydrolysis of **1**. The spectral and the optical rotation data of the aglycone were the same as those of 10-hydroxycathafoline [7], confirming the aglycone was 10-hydroxycathafoline. The sugar unit was derived and analyzed by GC using authentic samples as references, which suggested the sugar was L-arabinopyranose. The coupling constant ($J = 7.5$ Hz) of the anomeric proton signal indicated the presence of α-L-arabinopyranosyl. The HMBC correlation between H-1′ (δ_H 4.61) and C-10 (δ_C 153.2) (Figure 2) suggested that the arabinopyranose was attached to C-10 position of 10-hydroxycathafoline. Based on the above data, **1** was determined to be 10-hydroxycathafoline 10-*O*-α-L-arabinopyranoside.

Compound **2** was obtained as an amorphous powder. The molecular formula $C_{26}H_{34}N_2O_7$ was established by its HR-ESI-MS at *m/z* 487.2440 $[M + H]^+$. The IR spectrum showed the presence of the absorption bands ascribable to hydroxyl group (3367 cm^{-1}), ester group (1733 cm^{-1}), and double bond (1596 cm^{-1}). The ^1H NMR spectrum gave three protons due to aromatic ring [δ_H 7.04 (1H, d, $J = 2.5$ Hz), 6.81 (1H, dd, $J = 8.0$, 2.5 Hz), and 6.22 (1H, d, $J = 8.0$ Hz)]; one olefinic proton [δ_H 5.50 (1H, q, $J = 7.0$ Hz)]; three methyl signals [δ_H 3.78 (3H, s), 2.57 (3H, s), and 1.60 (3H, d, $J = 7.0$ Hz)]; and an anomeric proton [δ_H 4.59 (1H, d, $J = 7.0$ Hz)]. The ^{13}C NMR spectrum showed the presence of an aromatic ring (δ_C 151.8, 146.6, 139.3, 118.0, 115.6, and 107.0), a pair of olefinic carbons (δ_C 139.9 and 124.5), an ester carbonyl carbon (δ_C 175.3), three methyl groups (δ_C 51.9, 28.8, and 14.0), and an arabinopyranose unit (δ_C 104.9, 74.4, 72.6, 69.8, and 67.2).

Acid hydrolysis of **2** afforded L-arabinopyranose and aglycone, the aglycone was elucidated as 10-hydroxydeformodihydropseudoakuammigine [8,9] by the comparison of its NMR spectral data. The HMBC correlation between H-1′ (δ_H 4.59) and C-10 (δ_C 151.8) (Figure 2) indicated that the L-arabinopyranose unit

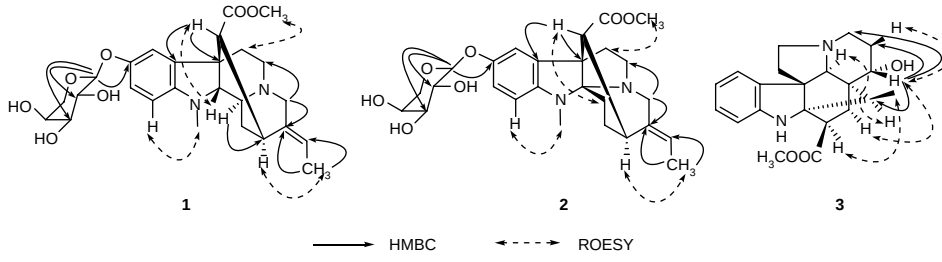

Figure 2. Key HMBC and ROESY correlations of **1**–**3**.

was attached to C-10 position of 10-hydroxydeformodihydropseudoakuammigine. Hence, **2** was characterized as 10-hydroxydeformodihydropseudoakuammigine 10-*O*-α-L-arabinopyranoside.

Compound **3** was isolated as colorless needles. The molecular formula was determined as $C_{21}H_{26}N_2O_3$ on the basis of its HR-ESI-MS at *m/z* 355.2019 $[M + H]^+$. The IR spectrum of **3** showed the characteristic absorptions due to hydroxyl group (3374 cm^{-1}) and ester group (1707 cm^{-1}). The ^1H NMR spectrum showed four protons for aromatic ring [δ_H 7.27 (1H, dd, $J = 7.0$, 1.0 Hz), 6.99 (1H, ddd, $J = 7.5$, 7.0, 1.5 Hz), 6.74 (1H, ddd, $J = 8.0$, 7.5, 1.0 Hz), and 6.67 (1H, dd, $J = 8.0$, 1.5 Hz)], and two methyl groups [δ_H 3.69 (3H, s) and 0.96 (3H, d, $J = 7.0$ Hz)]. The ^{13}C NMR spectrum displayed the signals of an aromatic ring (δ_C 151.1, 139.4, 128.6, 124.6, 122.3, and 121.2), one ester carbonyl (δ_C 176.5), two methyls (δ_C 52.5 and 7.4), and five methylenes (δ_C 56.3, 44.9, 37.5, 32.2, and 30.4). The above data indicated that **3** was an analog of vindolinine [10].

Detailed comparison of NMR spectral data of **3** with those of 19(*R*)-vindolinine [10] revealed that the NMR data of two compounds were similar, except the absence of a double bond at C-14 and C-15 in **3**, suggesting that C-14 or C-15 in **3** may be substituted by a hydroxyl group. The HMBC correlations between H-15 (δ_H 3.91) and C-14 (δ_C 32.2)/C-3 (δ_C 56.3)/C-19 (δ_C 49.7) (Figure 2) indicated that the hydroxyl group was attached at C-15 position. The relative configuration of **3** was assigned by the ROESY correlations (Figure 2). The absolute configuration of C-15 could be confirmed by the modified Mosher's method. Differences of proton chemical shift ($\triangle\delta$ values, $\delta_S - \delta_R$) between (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl ester (**3a**) and (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl ester (**3b**) (Figure 3) indicated the presence of *S* configuration at C-15 in **3**.

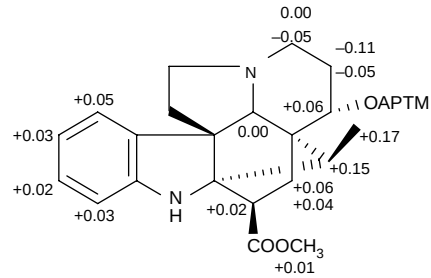

Figure 3. $\triangle\delta$ values ($\delta_S - \delta_R$) of the MTPA esters **3a** and **3b**.

Consequently, **3** was elucidated as 15(*S*)-hydroxy-14,15-dihydrovindolinine.

In addition, 13 known compounds were identified by comparing their spectral data with those of the literatures as tetrahydroalstonine (**4**) [11], ajmalicine (**5**) [12], vindorosine (**6**) [13], vindoline (**7**) [14], 19(*S*)-vindolinine (**8**) [10], 19(*R*)-vindolinine (**9**) [10], (−)-vincapusine (**10**) [15], yohimbine (**11**) [12], serpentine (**12**) [16], 18β-hydroxy-3-epi-α-yohimbine (**13**) [17], sitsirikine (**14**) [18], perivine (**15**) [19], and dihydroantirhine (**16**) [20], respectively.

3. Experimental

3.1 General experimental procedures

Melting points were recorded on an X-5 micro melting point apparatus without correction. Optical rotations were determined on a JASCO P-1020 polarimeter. UV spectra were obtained on a JASCO V-550 UV–vis spectrophotometer. IR spectra were recorded on a JASCO FT/IR-480 plus spectrometer. ^1H, ^{13}C, and 2D NMR spectra were determined on a Bruker AV-500 spectrometer in CD_3OD. ESI-MS were run on a HP-1100 HPLC/EST spectrometer. HR-ESI-MS data were detected on an Agilent 6210 ESI/TOF mass spectrometer. For column chromatography (CC), silica gel (200–300 mesh, Qingdao Marine Chemical Factory, Qingdao, China), Sephadex LH-20 (Pharmacia Biotec AB, Uppsala, Sweden), and Octadecylsilyl (ODS) (YMC, Kyoto, Japan) were

used. TLC analyses were carried out using precoated silica gel GF254 plates (Qingdao Marine Chemical Factory). HPLC separations were carried out on a COSMOSIL C_{18} preparative column (5 μm, 20 × 250 mm, Nacalai Tesque, Kyoto, Japan). L-Arabinopyranose was purchased from Sigma (St Louis, MO, USA).

3.2 Plant material

The roots of *C. roseus* were collected in Haikou City, Hainan Province of China, in April 2009. The plant was authenticated by Prof. Guang-Xiong Zhou of Jinan University. A voucher specimen (No. 0904011) has been deposited in the Institute of Traditional Chinese Medicine and Natural Products, Jinan University, Guangzhou, China.

3.3 Extraction and isolation

The dried roots (12.5 kg) of *C. roseus* were extracted with 95% EtOH. The solution was evaporated *in vacuo* to get residue (890 g). The residue was dissolved in H_2O to form a suspension, and then adjusted to pH 3 with 6% HCl. The acidic suspension was partitioned with $CHCl_3$ to remove the neutral components. The aqueous phase was basified with 2% $NH_3{\cdot}H_2O$ to pH 10 and then extracted with $CHCl_3$ to obtain a total alkaloid part (130 g), 120 g of which was subjected to silica gel CC ($CHCl_3$–CH_3OH, 100:0 → 0:100) to give nine fractions. Fraction 1 (19.0 g) was subjected to silica gel [petroleum ether (PE)–EtOAc, 9:1 → 1:1] and Sephadex LH-20 (MeOH) columns to afford **4** (22 mg), **5** (25 mg), **6** (20 mg), and **7** (36 mg). Fraction 2 (14.0 g) was subjected to silica gel column (PE–EtOAc, 9:1 → 7:3) and purified by preparative HPLC (MeOH–H_2O, 88:12) to yield **8** (25 mg) and **9** (18 mg). Fraction 3 (10.5 g) was subjected to ODS column (MeOH–H_2O, 20:80 → 100:0) and preparative HPLC (MeOH–H_2O, 45:55) to obtain **1** (14 mg), **2** (21 mg), **3** (18 mg), **10** (16 mg), **11** (12 mg), **12** (16 mg), and **13** (10 mg). The same methods were used to isolate **15** (11 mg) and **16** (8 mg) from fraction 4 (11.0 g), as well as **14** (12 mg) from fraction 5 (8.5 g), respectively.

3.3.1 10-Hydroxycathafoline 10-O-α-L-arabinopyranoside (*1*)

An amorphous powder, mp 204–206°C. $[\alpha]_D^{22}$ + 29.3 (c = 0.14, MeOH). UV (MeOH) λ_{max} (log ε): 210 (1.47), 243 (1.97), 302 (1.55) nm. IR (KBr) ν_{max}: 3357, 1730, 1594, 1475, 1072, 762 cm^{-1}. For ^1H and ^{13}C NMR spectral data, see Table 1. HR-ESI-MS *m/z*: 487.2429 $[M + H]^+$ (calcd for $C_{26}H_{35}N_2O_7$, 487.2439).

3.3.2 10-Hydroxydeformodihydro-pseudoakuammigine 10-O-α-L-arabino-pyranoside (*2*)

An amorphous powder, mp 196–198°C. $[\alpha]_D^{22}$ −20.9 (c = 0.11, MeOH). UV (MeOH) λ_{max} (log ε): 214 (2.13), 230 (2.25), 292 (1.96) nm. IR (KBr) ν_{max}: 3367, 1733, 1596, 1085, 794 cm^{-1}. For ^1H and ^{13}C NMR spectral data, see Table 1. HR-ESI-MS *m/z*: 487.2440 $[M + H]^+$ (calcd for $C_{26}H_{35}N_2O_7$, 487.2439).

3.3.3 15(S)-Hydroxy-14,15-dihydrovindolinine (*3*)

Colorless needles, mp 182–184°C. $[\alpha]_D^{22}$ −42.0 (c = 0.15, MeOH). UV (MeOH) λ_{max} (log ε): 211 (0.68), 239 (1.15), 295 (0.69) nm. IR (KBr) ν_{max}: 3374, 1707, 1607, 1466, 1214, 753 cm^{-1}. For ^1H and ^{13}C NMR spectral data see Table 1. HR-ESI-MS *m/z*: 355.2019 $[M + H]^+$ (calcd for $C_{21}H_{27}N_2O_3$, 355.2016).

3.4 Acid hydrolysis and GC analysis of 1 and 2

Compounds **1** and **2** (each 3.0 mg) were dissolved in 2 mol/l HCl (1.0 ml) and heated at 80°C for 2 h, respectively. The

Table 1. ^{1}H and ^{13}C NMR spectral data of **1**–**3** (measured in 500 MHz for ^{1}H, 125 MHz for ^{13}C, in CD_3OD, δ in ppm, J in Hz).

	1		**2**		**3**	
Position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
2	2.57 br s	80.3	–	99.4	–	81.6
3	3.35 m	50.0	2.57 1.90	41.9	3.41 3.26	56.3
5	3.86 2.71 t (7.0)	51.4	3.36 2.79 t (10.5)	55.8	3.41 2.96 m	44.9
6	3.14 m 1.36 dd (15.5, 5.0)	31.6	2.32 m 1.67	21.5	2.25 dd (15.0, 6.0) 1.79	37.5
7	–	44.2	–	58.7	–	60.8
8	–	142.6	–	139.3	–	139.4
9	6.73 d (2.5)	112.4	7.04 d (2.5)	115.6	7.27 dd (7.0, 1.0)	124.6
10	–	153.2	–	151.8	6.99 ddd (7.5, 7.0, 1.5)	121.2
11	6.82 dd (8.5, 2.5)	116.9	6.81 dd (8.0, 2.5)	118.0	6.74 ddd (8.0, 7.5, 1.0)	128.6
12	6.56 d (8.5)	111.4	6.22 d (8.0)	107.0	6.67 dd (8.0, 1.5)	122.3
13	–	150.1	–	146.6	–	151.1
14	2.38 d (18.0) 1.79 d (18.0)	33.9	1.83 1.77	27.3	2.62 m 1.73	32.2
15	3.64 s	35.3	3.63	36.3	3.91 t (4.5)	69.4
16	3.01 d (3.5)	53.8	2.84 br s	51.9	3.18 t (9.5)	41.5
17	–	–	–	–	2.09 m 1.58 m	30.4
18	1.52 d (7.0)	13.7	1.60 d (7.0)	14.0	0.96 d (7.0)	7.4
19	5.48 q (7.0)	121.9	5.50 q (7.0)	124.5	1.92 q (7.0)	49.7
20	–	138.5	–	139.9	–	50.2
21	3.96 3.06 d (16.0)	55.5	3.82 3.05 d (15.0)	59.1	3.74 s	72.7
$COOCH_3$	–	174.5	–	175.3	–	176.5
$COOCH_3$	3.80 s	52.4	3.78 s	51.9	3.69 s	52.5
N-CH_3	2.65 s	35.5	2.57 s	28.8		

Table 1 – *continued*

Position	**1**		**2**		**3**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1′	4.61 d (7.0)	104.4	4.59 d (7.0)	104.9		
2′	3.73 dd (9.0, 7.0)	72.5	3.74 dd (9.0, 7.0)	72.6		
3′	3.59 dd (9.0, 3.5)	74.4	3.59 dd (9.0, 3.5)	74.4		
4′	3.85 m	69.8	3.85 m	69.8		
5′	3.90 dd (12.5, 2.5)	67.3	3.90 dd (12.5, 2.5)	67.2		
	3.62 dd (12.5, 1.0)		3.61 dd (12.5, 1.0)			

Note: Overlapped signals are reported without designating multiplicity.

aglycone was extracted with CH_2Cl_2, and the aqueous layer was dried by N_2. Dry pyridine (1.0 ml) and L-cysteine methyl ester hydrochloride (3.0 mg) were added to the residue. The mixture was heated at 80°C for 2 h and then dried by N_2. *N*-(Trimethylsilyl)imidazole (0.2 ml) was added, and the mixture was heated at 80°C for 1 h. Finally, H_2O (1.0 ml) was added to stop the reaction and the aqueous layer was extracted with cyclohexane (1.0 ml). The organic layer was analyzed by GC analysis [column, AT-SE-30 (0.32 mm × 30 m, 0.5 μm); detector, FID; column temperature, 220°C; detector temperature, 270°C; injector temperature, 270°C; and carrier gas, N_2]. The standard monosaccharides were subjected to the same reaction and GC analysis under the above conditions [t_R (min): 22.142 (L-Ara) and 23.278 (D-Ara)]. As a result, L-Ara [t_R (min): 22.139 and 22.141] was detected from the hydrolyzates of **1** and **2**, respectively.

3.5 Preparation of α-methoxy-α-(trifluoromethyl)phenylacetyl esters of 3

Compound **3** (4.0 mg) was dissolved in 0.5 ml pyridine, and treated with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl Cl (10 μl) for 24 h in an anhydrous circumstance at room temperature. The reaction mixture was poured into water (5.0 ml) and extracted with EtOAc (5.0 ml). The EtOAc extract was purified by silica gel CC [*n*-hexane–EtOAc (70:30)] to yield (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl ester (**3a**, 1.8 mg). (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl ester (**3b**, 1.6 mg) was obtained using the same method by the treatment of (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl Cl (10 μl).

(*S*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl ester (**3a**): ^{1}H NMR (CD_3OD, 500 MHz) δ_H: 7.48 and 7.23 (phenyl protons of α-methoxy-α-(trifluoromethyl)phenylacetyl), 7.31 (1H, dd,

$J = 7.0$, 1.0 Hz, H-9), 7.09 (1H, ddd, $J = 7.5$, 7.0, 1.5 Hz, H-10), 6.86 (1H, ddd, $J = 8.0$, 7.5, 1.0 Hz, H-11), 6.78 (1H, dd, $J = 8.0$, 1.5 Hz, H-12), 5.48 (1H, t, $J = 4.5$ Hz, H-15), 3.67 (1H, overlapped, H-21), 3.65 (3H, s, H-23), 3.60 (3H, s, OMe of α-methoxy-α-(trifluoromethyl)-phenylacetyl), 3.47 (1H, m, H-3a), 3.35 (1H, m, H-3b), 2.98 (1H, t, $J = 9.0$ Hz, H-16), 2.59 (1H, m, H-14a), 2.32 (1H, overlapped, H-17a), 2.24 (1H, overlapped, H-19), 2.18 (1H, m, H-14b), 1.72 (1H, m, H-17b), 1.12 (3H, d, $J = 7.0$ Hz, H-18); ESI-MS *m/z*: 571 $[M + H]^+$.

(*R*)-α-methoxy-α-(trifluoromethyl)-phenylacetyl ester (**3b**): ^{1}H NMR (CD_3OD, 500 MHz) δ_H: 7.47 and 7.23 (phenyl protons of α-methoxy-α-(trifluoromethyl)phenylacetyl), 7.26 (1H, dd, $J = 7.0$, 1.5 Hz, H-9), 7.06 (1H, ddd, $J = 7.5$, 7.0, 1.5 Hz, H-10), 6.84 (1H, ddd, $J = 8.0$, 7.5, 1.5 Hz, H-11), 6.75 (1H, dd, $J = 8.0$, 1.5 Hz, H-12), 5.42 (1H, t, $J = 4.5$ Hz, H-15), 3.67 (1H, overlapped, H-21), 3.64 (3H, s, H-23), 3.60 (3H, s, OMe of α-methoxy-α-(trifluoromethyl)-phenylacetyl), 3.52 (1H, m, H-3a), 3.35 (1H, m, H-3b), 2.96 (1H, t, $J = 9.0$ Hz, H-16), 2.64 (1H, m, H-14a), 2.29 (1H, overlapped, H-14b), 2.26 (1H, overlapped, H-17a), 2.09 (1H, q, $J = 7.0$ Hz, H-19), 1.68 (1H, m, H-17b), 0.95 (3H, d, $J = 7.0$ Hz, H-18); ESI-MS *m/z*: 571 $[M + H]^+$.

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