Three New Tricyclic Guanidine Alkaloids from the Sponge *Batzella* sp.

Ashok D. Patil, Alan J. Freyer,* Priscilla Offen, Mark F. Bean, and Randall K. Johnson

Departments of Biomolecular Discovery, Analytical Sciences, and Physical and Structural Chemistry, SmithKline Beecham Pharmaceuticals, Research and Development, King of Prussia, Pennsylvania 19406-0939

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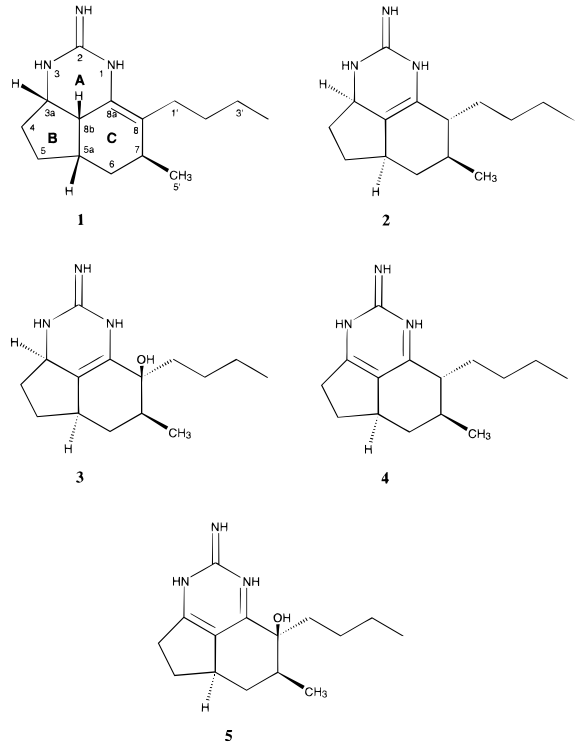
During the large-scale isolation of the batzelladines A and B, which are inhibitors of gp120-CD4 binding, we isolated 19 minor guanidine alkaloids. Three new tricyclic guanidine alkaloids isolated from this group were named 8a,8b-dehydroptilocaulin (**2**), 8a,8b-dehydro-8-hydroxyptilocaulin (**3**), and 1,8a;8b,3a-didehydro-8-hydroxyptilocaulin (**5**). The recently described mirabilin B (**4**) was also isolated. The structures and relative stereochemistry of these compounds were determined by spectral analysis and by comparison with spectral data of ptilocaulin (**1**).

Ptilocaulin (**1**) and isoptilocaulin represent two unique classes of cyclic guanidine alkaloids that were first reported by Rinehart *et al.* from the Caribbean sponge *Ptilocaulis* aff. *P. spiculifer* to display a broad range of activities.[1,2] Thereafter, isolation of ptilomycalin A from the sponges *P. spiculifer* and *Hemimycale* sp.;[3,4] crambescidin 800, crambescidin 816, and isocrambescidin 800 from the sponge *Crambe crambe*;[5−7] and celeromycalin and formiamycalin from the starfish *Celerina hefferenani*[8] and *Formia monolis*[8] were reported. This family of complex pentacyclic guanidine alkaloids, incorporating a ptilocaulin nucleus linked by a linear ω-hydroxy fatty acid to a spermidine or hydroxyspermidine moiety, have been found to act as antifungal, antiviral, and cytotoxic agents. In 1995, we reported the isolation and identification of crambescin A and batzelladines A−E from the MeOH−CH_2Cl_2 extract of the sponge *Batzella* sp. collected in the Bahamas.[9] These compounds were the first low-molecular-weight natural products that inhibited HIV gp120-human CD4 binding. While this work was being carried out, a paper appeared in which Braekman *et al.*[10] reported the isolation of 8b-hydroxyptilocaulin from the sponge *Monanchora arbuscula*, and at the same time Barrow *et al.*[11] reported the isolation of mirabilin B (**4**) and mirabilin E from the sponge *Arenochalina mirabilis*.

As part of our search for biologically active natural products, we examined the minor fractions obtained during a scale-up of the batzelladines A−E. One of the non-polar fractions of an extract from the sponge *Batzella* sp., which eluted from a Si gel column using MeOH−CH_2Cl_2, was subjected to extensive Si gel preparative TLC using unusual combinations of solvent systems. This fraction afforded ptilocaulin (**1**), isoptilocaulin, 8b-hydroxyptilocaulin, the novel 8a,8b-dehydroptilocaulin (**2**) and 8a;8b-dehydro-8-hydroxyptilocaulin (**3**), mirabilin B (**4**), and the novel 1,8a;8b,3a-didehydro-8-hydroxyptilocaulin (**5**).

8a,8b-dehydroptilocaulin (**2**), $[\alpha]_D$ +13.3°, was isolated as an oil with a molecular ion at *m/z* 247 in the DCI mass spectrum (three exchangeables). This weight was identical to those of ptilocaulin (**1**) and isoptilocaulin, and it corresponded to a molecular formula of $C_{15}H_{25}N_3$ requiring five degrees of unsaturation. Comparison of the ^{1}H- and ^{13}C-NMR data (see Tables 1 and 2) of **2** with those of ptilocaulin indicated the presence of the same



ring system. The ^{1}H-NMR spectrum (see Table 1) had four methine multiplets appearing between δ 4.25 and 1.68, six methylene pairs and two methyl signals, a doublet at δ 1.04 and a triplet at δ 0.92, while the ^{13}C NMR spectrum (see Table 2) of **2** revealed the presence of 15 carbons, including four methines, six methylenes, two methyls, and three quaternary carbons. These data strongly suggested that **2** was an isomer of **1**.

The COSY NMR spectrum of **2** indicated that H-3a (ddd, δ 4.25) was adjacent to two contiguous methylene groups (H-4 and H-5), which were bracketed on the opposite side by the H-5a methine multiplet at δ 2.44 in ring B as shown in Figure 1. The δ 53.7 carbon chemical shift of C-3a indicated that it was a ring-junction carbon attached to one of the guanidine nitrogens. H-3a shared a 1.0 Hz long-range coupling with H-5a, and a mutual NOE enhancement between them established that they were situated on the same face of the five-membered ring B. The H-6_{ax} signal (ddd, δ 0.88) shared two large axial−axial couplings on the order of 11 Hz, with the transperiplanar H-5a and H-7 signals and a geminal 12.4 Hz coupling. The H-5a multiplet shared mutual NOEs with H-6_{eq} at δ 1.94

* To whom correspondence should be addressed. Phone: (610) 270-6315. FAX: (610) 270-6727. E-mail: Alan_J_Freyer@sbphrd.com.

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Table 1. ^{1}H-NMR Assignments for **1**−**5** in CD_3OD

no.	1	2	3	4	5
3a	3.78 (1H, ddd, *J* = 6.4, 7.2, 10.8 Hz)	4.25 (1H, ddd, *J* = 1.0, 5.2, 8.1 Hz)	4.27 (1H, ddd, *J* = 1.0, 5.2, 8.1 Hz)		
4	1.97 (1H, m)	2.17 (1H, m)	2.20 (1H, m)	2.90 (1H, m)	2.92 (1H, m)
	1.43 (1H, m)	1.68 (1H, m)	1.77 (1H, m)	2.54 (1H, m)	2.56 (1H, m)
5	1.77 (1H, m)	1.97 (1H, m)	2.00 (1H, m)	2.36 (1H, m)	2.36 (1H, m)
	1.62 (1H, m)	1.28 (1H, m)	1.31 (1H, m)	1.51 (1H, m)	1.55 (1H, m)
5a	2.52 (1H, m)	2.44 (1H, m)	2.43 (1H, m)	2.91 (1H, m)	2.89 (1H, m)
6	1.99 (1H, m)	1.94 (1H, m)	1.72 (1H, m)	2.03 (1H, m)	1.78 (1H, ddd, *J* = 2.6, 5.2, 12.4 Hz)
	1.38 (1H, m)	0.88 (1H, ddd, *J* = 11.3, 11.3, 12.4 Hz)	1.17 (1H, ddd, *J* = 11.4, 11.4, 12.7 Hz)	0.90 (1H, ddd, *J* = 11.3, 11.3, 12.4 Hz)	1.24 (1H, ddd, *J* = 11.3, 12.0, 12.4 Hz)
7	2.36 (1H, m)	1.68 (1H, m)	1.83 (1H, m)	1.88 (1H, m)	2.03 (1H, m)
8		1.88 (1H, m)		2.19 (1H, ddt, *J* = 1.7, 9.4, 4.5 Hz)	
8b	2.60 (1H, ddd, *J* = 2.2, 7.2, 7.4 Hz)				
1′	2.16 (2H, m)	1.68 (2H, m)	1.84 (1H, m)	2.08 (1H, m)	2.21 (1H, m)
			1.62 (1H, m)	1.78 (1H, m)	1.87 (1H, m)
2′	1.42 (1H, m)	1.25 (1H, m)	1.17 (1H, m)	1.32 (1H, m)	1.16 (1H, m)
	1.32 (1H, m)	1.14 (1H, m)	1.08 (1H, m)	1.05 (1H, m)	0.89 (1H, m)
3′	1.38 (2H, m)	1.33 (2H, m)	1.35 (2H, m)	1.28 (2H, m)	1.28 (2H, m)
4′	0.94 (3H, t, *J* = 7.0 Hz)	0.92 (3H, t, *J* = 7.2 Hz)	0.92 (3H, t, *J* = 7.2 Hz)	0.87 (3H, t, *J* = 7.2 Hz)	0.86 (3H, t, *J* = 7.2 Hz)
5′	1.18 (3H, d, *J* = 7.3 Hz)	1.04 (3H, d, *J* = 6.6 Hz)	0.97 (3H, d, *J* = 6.9 Hz)	1.09 (3H, d, *J* = 6.7 Hz)	1.05 (3H, d, *J* = 7.0 Hz)

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Table 2. ^{13}C-NMR Assignment for **1**−**5** in CD_3OD

no.	1	2	3	4	5
2	153.1	154.8	155.1	164.6	165.2
3a	55.0	53.7	53.4	176.2	177.4
4	32.9	33.8	33.5	34.3	34.4
5	28.2	30.4	30.6	34.1	34.2
5a	35.5	37.7	38.4	39.0	39.5
6	35.3	40.1	34.8	40.8	35.8
7	31.6	33.6	36.5	35.2	38.2
8	128.1	44.0	72.9	48.2	75.3
8a	122.7	128.8	129.7	167.3	165.8
8b	36.9	119.1	121.6	126.8	126.5
1′	28.5	28.4	35.1	31.1	36.6
2′	31.8	27.3	28.1	28.6	28.3
3′	24.0	24.2	24.1	24.4	24.3
4′	14.5	14.4	14.4	14.4	14.3
5′	21.1	20.4	14.8	21.3	15.4

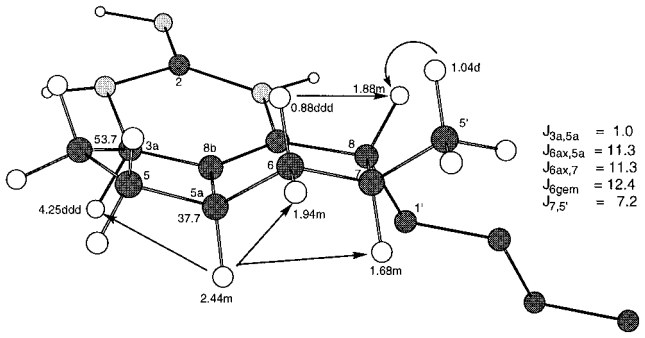

Figure 1. Molecular model of **2** with arrows representing NOE enhancements.

and H-7 at δ 1.68, confirming that H-5a and H-7 were on the opposite face of ring C from H-6_{ax} as shown in Figure 1.

H-7 shared a 6.6 Hz coupling with the CH_3-5′ doublet at δ 1.04 and correlated to H-8 in the HMBC spectrum, which, in turn, showed correlations extending to the *n*-butyl side chain, which was attached at C-8. Mutual NOEs between H-6_{ax}, CH_3-5′, and H-8 indicated that they all resided on the same face of ring C, away from H-5a and H-7. The ^{1}H and ^{13}C correlation data clearly established that the double bond in **2** was situated between C-8a and C-8b rather than between C-8 and C-8a as in **1**. The lack of an 8b methine proton, the presence of an H-8 methine signal and HMBC correlations between C-8b (δ119.1) and H-3a, H-4, H-5, H-5a, and H-6 all supported the proposed location of the ring A/C double bond.

Alkaloid **3**, which was isolated as a colorless gum, displayed a molecular ion at *m*/*z* 263 (four exchangeables). The molecular formula was determined to be $C_{15}H_{25}N_3O$, indicating that **3** differed from **2** by one oxygen atom. In addition, the presence of a fragment ion at *m*/*z* 246 ($M^+ - OH$) suggested that the **3** was the hydroxy analog of **2**. The ^{1}H NMR spectrum of **3** was very similar to that of **2**, except that it had only three methine multiplets that resonated between δ 4.27 and 1.83, compared to the four methine multiplets observed for **2**. The absence of a methine multiplet at δ 1.88 in the ^{1}H-NMR spectrum of **3**, which was assigned to H-8 in compound **2**, and the emergence of an aliphatic quaternary carbon signal at δ 72.9 in the ^{13}C NMR spectrum clearly indicated the replacement of H-8 with a hydroxyl group. This supposition was confirmed by the homonuclear and heteronuclear correlation NMR data, and thus **3** was identified as 8a,8b-dehydro-8-hydroxyptilocaulin. Perusal of recent literature indicated that a tricyclic alkaloid named mirabilin E possessed the same basic structure that we proposed for our alkaloid **3**.[11] Comparison of the ^{1}H and ^{13}C chemical shifts observed for the formate salt of **3** in CD_3OD and those of the diacetyl derivative of mirabilin E reported in the literature in $CDCl_3$ indicated that there were substantial differences above and beyond those expected on acetylation, establishing that compound **3** and mirabilin E were different. The $[\alpha]_D$ of **3** was +24.2° (*c* 0.33, MeOH), while that reported in the literature for the acetate of mirabilin E was $[\alpha]_D$ +332 (*c* 0.05, $CHCl_3$). Regrettably, it was not possible to prepare the diacetate of **3** for direct comparison with mirabilin E diacetate because of sample decomposition.

The relative stereochemistry of the CH_3-5′ and OH-8 groups attached to ring C for mirabilin E was not specified. Analysis of the coupling constants and NOE data for our compound **3** suggested that the stereochemistry at C-3a, C-5a, and C-7 was retained from **2** to **3**. Due to extensive overlap of proton resonances,

NOE results were somewhat ambiguous for the determination of stereochemistry at C-8, but it was likely conserved. Consistent with this proposal was the observation that H-6_{ax} in **3** resonated 0.3 ppm further downfield than its counterpart in 8a,8b-dehydroptilocaulin (**2**) presumably because of its proximity to the hydroxyl oxygen on the same face of ring C. The H-6_{eq} signal in **3** experienced a corresponding 0.2 ppm upfield shift from that in **2**. The complete relative stereochemistry of 8a,8b-dehydro-8-hydroxyptilocaulin (**3**) is shown above. The complete relative stereochemistry of mirabilin E diacetate was not assigned in the work previously cited, and it thus seems probable that it and compound **3** are diastereomers.

Compound **4**, also obtained as a gum, showed a molecular ion at *m/z* 245 (two exchangeables) and had the elemental composition of $C_{15}H_{23}N_3$, two mass units lower than that of **2**. A comparison of the ^{1}H and ^{13}C chemical shifts observed for the formate salt of **4** in CD_3OD and those of the monoacetyl derivative of mirabilin B in $CDCl_3$ reported in the literature[11] were in good agreement, indicating that our compound **4** was indeed mirabilin B. Analysis of the coupling constants and NOEs suggested that the relative stereochemistry was also the same.

Alkaloid **5** was isolated as an oil, $[\alpha]_D$ +39.3°, and it showed a molecular ion at *m/z* 261 (three exchangeables) corresponding to a molecular formula of $C_{15}H_{23}N_3O$. Comparison of the molecular formula and the number of exchangeable hydrogens with those of **4** suggested that **5** differed from **4** by a hydroxyl group in the same manner that **3** differed from **2**. The ^{1}H-NMR spectrum of **5** revealed the presence of only two methine multiplets resonating at δ 2.89 and δ 2.03, six methylene pairs and two methyl signals, a doublet at δ 1.05, and a triplet at δ 0.86. The H-8 methine signal observed in **4** was absent in **5**, confirming the presence of a C-8 hydroxyl group. The ^{13}C-NMR spectrum of **5** included four downfield quaternary resonances as well as two methines, six methylenes, and two methyl signals in the aliphatic portion of the spectrum, along with a newly observed oxygenated quaternary signal at δ 75.3. The ^{13}C spectrum of **5** closely resembled that of **4**, except for the additional oxygenated quaternary signal and the presence of two rather than three aliphatic methines, strongly suggesting that **5** was the 8-hydroxyl analog of **4**. The homonuclear and heteronuclear correlation NMR data for **5** confirmed that this was indeed the case.

Analysis of the coupling constants and NOEs suggested that the stereochemistry at C-5a, C-7, and C-8 was conserved from **4** to **5**. The H-6_{ax} signal at δ 1.24 shared large transperiplanar couplings with H-5a and H-7 and a geminal coupling, while H-5a shared mutual NOEs with H-6_{eq} and H-7. These observations indicated that H-5a and H-7 were situated on the same face of ring C and that H-6_{ax} was situated on the opposite face. As was the case for **3** compared to **2**, H-6_{ax} appeared 0.3 ppm further downfield in **5** than in **4**, suggesting that the C-8 hydroxy group was again situated on the same face of ring C as H-6_{ax}. At the same time, H-6_{eq} experienced a 0.2 ppm upfield shift from **4** to **5**.

Complete ^{1}H- and ^{13}C-NMR chemical shift data were recently presented for ptilocaulin (**1**, HNO_3 salt) and 8b-hydroxyptilocaulin (HCl salt).[10] In our work, both of these compounds were isolated as formate salts along with the compounds described above. Upon comparing the ^{13}C chemical shift assignments, we arrived at the reverse assignments for the C-8 and C-8a resonances. Instead of assigning C-8 at δ 121.0 and C-8a at δ 127.0 (HNO_3 salt) in ptilocaulin (**1**), we assigned C-8 at δ 128.1 and C-8a at δ 122.7 (formate salt) based on HMBC correlations between C-8 and CH_3-5′ and H-6 protons as well as the HMBC correlation between C-8a and H-3a. A similar reversal of assignments was made for C-8 and C-8a in 8b-hydroxyptilocaulin.[10] Literature assignments placed C-8 at δ 122.2 and C-8a at δ 129.8 (HCl salt) in 8b-hydroxyptilocaulin, while we assigned C-8 at δ 130.3 and C-8a at δ 124.2 (formate salt) based on the same correlations described above.

Experimental Section

General Experimental Section. IR spectra were recorded on a Nicolet Model 20 DXB FTIR spectrometer. All homonuclear and heteronuclear 1D and 2D NMR data were recorded on a Bruker AMX-400 spectrometer in CD_3OD. The LRDCIMS and HRDCIMS were acquired on a VG-70SE using CH_4 and NH_3 gases. Analytical and preparative TLC was carried out on precoated Si gel G (Kiesel gel G_{254}) and reversed-phase (Whatman KC18F) plates. Optical rotations were recorded on a Perkin-Elmer 241 MC polarimeter. UV spectra were recorded on a Beckman DV-7 spectrophotometer. Reagent grade chemicals (Fisher and Baker) were used throughout.

Collection, Extraction, and Isolation. The sponge, *Batzella* sp., was collected by hand using scuba equipment in December 1990. Specimens were immediately frozen and maintained at −20 °C until extraction. The sponge was identified by Dr. Rob van Soest, and a voucher sample has been deposited in the Zoological Museum of Amsterdam, ZMA, registry no. POR 8788. The freeze-dried sponge (2.5 kg) was extracted with MeOH−CH_2Cl_2 (1:1) to give a dark red solid (270 g) that was triturated with EtOAc, CH_2Cl_2, and MeOH to give 62, 171, and 19 g of extracts, respectively. The CH_2Cl_2 extract (15 g), which showed activity in the gp120-CD4 binding assay, was applied to a column of Sephadex LH-20 and eluted with MeOH−CH_2Cl_2−hexane (1:1:1). The earlier eluting, polar, gp120-CD4 active fractions were monitored by bioassay and combined (11.27 g). Weakly active medium polarity fractions, which eluted later, were combined (2.45 g). Non-polar fractions, which eluted last, were inactive and pooled to afford a residue (0.724 g). This residue, which was a mixture of several compounds, was applied to a column of Si gel (Kieselgel-60, 230−400 mesh) and eluted with a solvent gradient system of MeOH−CH_2Cl_2−H_2O−HCOOH ranging from 9:90:0.5:0.75 to 15:83:1:1.5. Several fractions with almost identical R_f values were collected and monitored by TLC. Fractions with the same TLC profile were combined to yield six (A−F) fractions. Fraction B (93 mg), after RP-18 preparative TLC using H_2O−MeOH−HCOOH (10:90:0.02) followed by Si gel preparative TLC using MeOH−CH_2Cl_2−H_2O−HCOOH (12:86:1:1.5), yielded ptilocaulin (**1**, 46 mg) and isoptilocaulin (23 mg). Fraction C (81 mg) from the Si gel column, which appeared homogeneous by TLC but was clearly a mixture of two compounds by ^{1}H NMR, was resolved by employing first RP-18 preparative TLC (H_2O−MeOH−HCOOH 7.5:92.5:0.02) and then Si gel preparative TLC (MeOH−CH_2Cl_2−H_2O−NH_4OH 8.5:80:8.5:3.0) to afford 8a,8b-dehydro-8-hydroxyptilocaulin (**3**, 34 mg)

and 1,8a;8b,3a-didehydro-8-hydroxyptilocaulin (**5**, 12 mg). Fraction D (75 mg) was subjected to Si gel preparative TLC (MeOH−CH_2Cl_2−H_2O−HCOOH 8.5:80:8.5:3.0) to yield 8b-hydroxyptilocaulin (51 mg). Fraction F (35 mg) was purified by RP-18 preparative TLC (H_2O−MeOH−HCOOH 15:85:0.02) followed by Si gel preparative TLC (MeOH−CH_2Cl_2−H_2O−HCOOH 8.5:80:8.5:3.0) to afford 8a,8b-dehydroptilocaulin (**2**, 19 mg) and mirabilin B (**4**, 9.3 mg) in pure form.

8a,8b-Dehydroptilocaulin (2): colorless oil, $[\alpha]_D$ +13.3° (*c* 1.2, MeOH); UV (MeOH) λ_{max} 228, 242, 306 nm; IR (KBr) ν_{max} 3190, 3000−2800, 1677, 1631, 1590, 1458, 1349 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; LRDCIMS *m/z* 247; HRDCIMS calcd for $C_{15}H_{25}N_3$ 247.2048, found 247.2017.

8a,8b-dehydro-8-hydroxyptilocaulin (3): colorless gum, $[\alpha]_D$ +24.2° (*c* 0.33, MeOH); UV (MeOH) λ_{max} 237, 299 nm; IR (KBr) ν_{max} 3327, 3200, 3100−3000, 1678, 1631, 1587, 1461, 1350 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; LRDCIMS *m/z* 263; HRDCIMS calcd for $C_{15}H_{25}N_3O$ 263.1997, found 263.1985.

Mirabilin B (4): colorless gum, $[\alpha]_D$ +41.6° (*c* 0.48, MeOH); UV (MeOH) λ_{max} 236, 302, 375 nm; IR (KBr) ν_{max} 3321, 3185, 3000−2800, 1630, 1587, 1458, 1385 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; LRDCIMS *m/z* 245; HRDCIMS calcd for $C_{15}H_{23}N_3$ 245.1892, found 245.1879.

1,8a;8b,3a-Didehydro-8-hydroxyptilocaulin (5): colorless oil, $[\alpha]_D$ +39.3° (*c* 0.28, MeOH); UV (MeOH) λ_{max} 239, 246, 309 nm; IR (KBr) ν_{max} 3413, 3221, 3190, 1728 (w), 1608, 1585, 1464, 1384 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; LRDCIMS *m/z* 261; HRDCIMS calcd for $C_{15}H_{23}N_3O$ 261.1841, found 261.1824.

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