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Alkaloids from *Toddalia aculeata*

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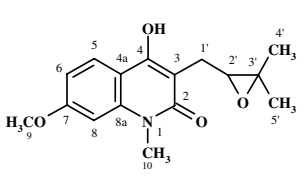
Abstract

Two alkaloids *N*-methyl-4-hydroxy-7-methoxy-3-(2,3-epoxy-3-methylbutyl)-1*H*-quinolin-2-one (**1**) and 3-(2,3-dihydroxy-3-methylbutyl)-4,7-dimethoxy-1-methyl-1*H*-quinolin-2-one (**2a**) have been isolated from CH_2Cl_2:methanol (1:1) and methanol extracts of leaves and stems of *Toddalia aculeata*. Their structures along with that of 15 other compounds, of which three are isolated for the first time from genus *Toddalia*, were established by their detailed spectral studies including 2D NMR viz. ^1H–^1H COSY, ^1H–^{13}C COSY, and HMBC.

Keywords: *Toddalia aculeata*; Alkaloids; *N*-methyl-4-hydroxy-7-methoxy-3-(2,3-epoxy-3-methylbutyl)-1*H*-quinolin-2-one; 3-(2,3-Dihydroxy-3-methylbutyl)-4,7-dimethoxy-1-methyl-1*H*-quinolin-2-one

1. Introduction

Toddalia aculeata (*asiatica*), that belongs to the family Rutaceae, is a well recognized medicinal plant in India and is known to possess various medicinal properties, especially antimalarial and antibacterial. The root bark is used for curing diarrhoea, gonorrhoea, cough, influenza and constitutional debility during convalescence. The fresh leaves are eaten for curing pains in bowels. The unripe fruits and roots are used in rheumatism (Wealth of India). Previous phytochemical studies reported the isolation of few polyphenolics and alkaloids from *T. aculeata* (Combes and Gaignault, 1984; Ishii et al., 1991; Reisch and Strobel, 1982; Sharma et al., 1982).



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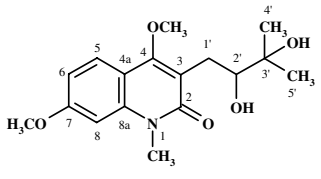
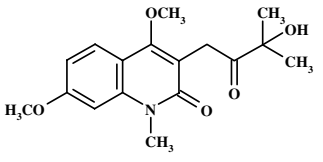
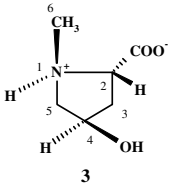


2a



2b



3

As part of our systematic phytochemical investigations on some Indian medicinal plants, we have now examined the leaves and stems of *T. aculeata* and report the isolation and identification of two novel alkaloids **1** and **2a** along with 15 other compounds, of which three are reported here for the Ist time from *Toddalia* genus.

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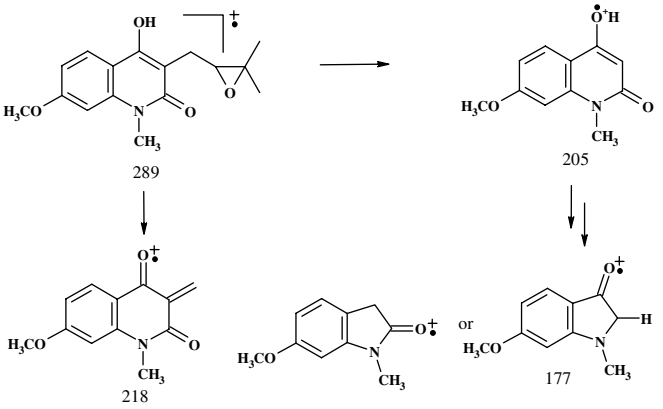
2. Results and discussion

Isolation and purification of the compounds was accomplished by repeated column chromatography followed by crystallization. Compounds **1**, **2a** and **3** were evaluated for antibacterial activity against three bacteria viz. *Escherichia coli*, *Bacillus cereus* and *Lactobacillus lactis*.

Compound **1** was obtained as a yellow crystalline solid. Its elemental analysis and HREIMS suggested $C_{16}H_{19}O_4N$ to be its molecular formula. It gave orange colour with Dragendorff reagent, characteristic for an alkaloid. Its IR spectrum showed two characteristic bands at 3347 and 1613 cm^{-1} for hydroxyl group and quinolone carbonyl, respectively. The presence of quinolone nucleus was confirmed by its UV spectrum. Its ^1H NMR spectrum showed four singlets at δ 1.27 (3H), 1.36 (3H), 3.89 (3H) and 3.95 (3H) for the presence of four methyls in different environments, probably two β- to electronegative atom and the rest two directly attached to electronegative atoms (OCH_3/N–CH_3). These results were endorsed by its ^{13}C NMR and ^1H–^{13}C COSY spectrum, thereby confirming the presence of gem dimethyl, N–CH_3 and O–CH_3 in **1**. Its ^1H NMR also displayed peaks at δ 3.22 (*m*, 2H) and δ 4.80 (*t*, 1H) which were coupled, indicating the presence of –CH_2–CH–O– moiety in the compound. Chemical shift of methylene protons at δ 3.22, suggested that it could be also allylic. These observations were supported by its ^{13}C NMR values at δ 28.1 and 91.9 for *C*H_2 and –*C*H, respectively. It is rather surprising that –CH– carbon at δ 91.9 has gone downfield than expected. The understanding of this came from HMBC correlation with respect to methyls at δ 1.27 and 1.36. HMBCs C-3 correlation has suggested that the carbon at δ 91.9 was C-3 to these methyls and was attached to oxygen atom. C-2 correlation has suggested that both the methyls were attached to the same quaternary carbon that appeared at δ 71.1, thus confirming the presence of gem dimethyl.

Its ^1H NMR also showed 1,2,4 system in aromatic ring which has also been endorsed by its ^1H–^1H COSY and ^1H–^{13}C COSY spectrum. Therefore, either hydroxyl group or methoxy group could be present in the aromatic ring. HMBC correlation clearly suggested the presence of methoxyl on aromatic ring. We also observed three more quaternary carbons at δ 100.3, 163.5, and 172.8. The HMBC correlation with respect to –N–CH_3 showed correlation at δ 129.8 and 163.5 quaternary carbons suggesting that quinolone carbonyl was at δ 163.5 . The two carbons C-3 and C-4 that appeared at δ 100.3 and δ 172.8 contained butyl chain and hydroxyl group, respectively.

Molecular mass calculation clearly showed that C-2′ and C-3′ must be attached to same electronegative atom (oxygen) thus giving rise to an epoxide ring. This also explained clearly the downfield chemical shift of C-2′ carbon at δ 91.9 and finally suggested compound **1** to be *N*-methyl-4-hydroxy-7-methoxy-3-(2,3-epoxy-3-methylbutyl)-1*H*-quinolin-2-one. The position of methoxyl group, hydroxyl group and butyl chain had been confirmed by HMBC experiments. This is a first report of occurrence of **1** in any natural source, however such a skeleton do exists in the literature (Jacquemond-Collect et al., 2000) (see Fig. 1).



Mass Fragmentation of Compound 1

Compound **2a** was obtained as a yellow crystalline solid. Its IR spectrum showed absorptions at 3409 and 1631 cm^{-1} for hydroxyl group and quinolone carbonyl, respectively. The presence of quinolone nucleus was indicated by its UV spectrum. It also gave orange colour with Dragendorff reagent for an alkaloid. Its ^1H NMR spectrum showed five singlets, for three protons each at δ 1.29, 1.31, 3.91, 3.92 and 3.98. The three downfield singlets were characteristic of methyl groups attached directly to the electronegative atom. The presence of two methoxyl ($2 \cdot OCH_3$), one –N–CH_3 and two methyls was confirmed by its DEPT and ^1H–^{13}C COSY spectrum. Its ^1H NMR displayed two doublets at δ 3.60 (1H) and 3.12 (1H) and a triplet at δ 2.72 (1H). ^1H–^{13}C correlation has suggested that the protons at δ 3.12 and 2.72 were attached to the same carbon atom which appeared at δ 28.0. The proton observed at δ 3.60 was attached to the carbon which appeared at δ 79.0 showing thereby that this carbon was linked to the oxygen atom. ^1H–^1H COSY spectrum suggested that the protons at δ 3.12 and 2.72 were coupled with the proton at δ 3.60 and the presence of these –CH_2– and ≻CH– were confirmed by its DEPT spectrum. The splitting of CH_2 protons at δ 3.12 and 2.72 suggested frozen rotation that is, it could be an allylic methylene.

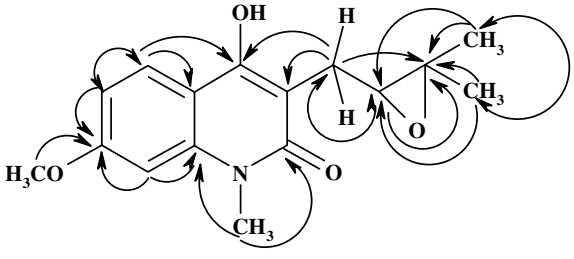


Fig. 1. HMBC correlation of compound **1**.

^{1}H NMR of **2a** also displayed a doublet at δ 7.44, a multiplet at δ 7.22 (*m*, 1H) and another doublet at 7.07 indicating the presence of 1,2,4 system which has been confirmed by its coupling constants, ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY spectrum. This suggested that one of the group (OCH_3) must be present on aromatic nucleus. Rest of the spectroscopic values were very similar to that observed for compound **1**.

Its HMBC correlation studies confirmed that the methyls at δ 1.29 and 1.31 were gem dimethyls and attached to carbon at δ 73.1 as shown by ^{1}H–^{13}C correlation spectrum. This particular carbon at δ 73.1 was also attached to electronegative atom and showed correlation with the carbon that appeared at δ 79.0, suggesting that both these units were linked together.

The HMBC correlation with –N–CH_3 group clearly showed C-3 correlation with carbon at δ 130.4 (*q*) and 167.0 (*q*) further confirming the presence of quinolone nucleus. Its ^{1}H NMR also showed two broad singlets at δ 1.62 and 2.64, both integrating for one proton each, and were D_2O exchangeable. This suggested the presence of vicinal dihydroxy system in the molecule, of which one –OH is secondary and the other is tertiary. This has been confirmed by its oxidation with PCC/CH_2Cl_2 to keto compound **2b**. Thus far, we have accounted for two methyls, one N–CH_3, two gem dimethyls, three aromatic protons, one –CH_2– linked to ≻CH– and downfield quanternary carbons for quinolone carbonyl and gem dimethyl. The position of the other methoxyl group and butyl chain has been fixed on the basis of chemical shift of two remaining quaternary carbons at δ 161.7 and 120.2 for *O*-methyl group and 2′,3′-dihydroxy butyl chain. Thus on the basis of the above discussion, **2a** was assigned the constitution as 3-(2,3-dihydroxy-3-methylbutyl)-4,7-dimethoxy-1-methyl-1*H*-quinolin-2-one, which is a new natural product (see Fig. 2).

Compound **3** was obtained as a colourless crystalline solid. It gave orange colour with Dragendorff reagent for an alkaloid. It gave $[M]^+$ ion at *m*/*z* 145 in EIMS and its elemental analysis suggested $C_6H_{11}O_3N$ to be its molecular formula. ^{1}H NMR spectrum of **3** showed two multiplets each at δ 2.13 (1H) and 2.41 (1H) with geminal coupling. These were attached to the carbon atom at δ 41.5 as indicated by correlation studies of its ^{13}C NMR, ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY spectrums. These two protons were also coupled with a proton at δ 4.11, indicating their nearby position in the molecule. The protons observed at δ 3.13 (*d*, 1H, $J = 13.0$ Hz) and δ 3.88 (*dd*, 1H, $J = 12.9$ and 12.8 Hz) were also attached to the same carbon which appeared at δ 65.9, as shown again by correlation studies of their spectrums. Its ^{1}H NMR also showed a singlet at δ 2.96 integrating for three protons for N^+–CH_3. This was also suggested by its ^{13}C NMR value at δ 46.5 and by ^{1}H–^{13}C COSY spectrum. Besides these, ^{1}H NMR also showed two peaks at δ 4.11 (1H, *t*, $J = 7.5$ and 9.0 Hz) and at δ 4.55 (1H, *brs*) for protons attached to carbons at δ 74.4 and 73.4, respectively, indicated by its ^{13}C NMR, ^{1}H–^{1}H COSY and ^{1}H–^{13}C COSY spectrum. Its IR spectrum displayed two broad bands at 3402 and 1626 cm^{-1} corresponding to the hydroxyl group and carboxylate ion, respectively. The position of –COO^-, –OH and –N^+–CH_3 have been assigned by its HMBC correlation spectrum which clearly showed compound **3** to be 4-hydroxy-1-methyl-pyrrolidin-2-carboxylic acid, commonly known as 4-hydroxy-*N*-methyl proline. Its structure has also been confirmed by single crystal X-ray diffraction studies (see Fig. 3).

The final molecular structure reveals the product to be a five membered (C2–C3–C4–C5–N6) ring in an envelope conformation. The carboxylate group is deprotonated and this proton shifts to nitrogen N6. The ring thus is a zwitterion as shown in Fig. 4. Both C4–C5–C6–N1 and C3–C2–C6–N1 are *anti*, which indicates that the methyl group is projected away from the ring. Each molecule is H-bonded to its neighboring symmetry related molecule through three interactions (Fig. 5). The most important is

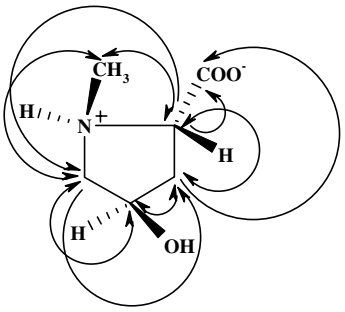


Fig. 3. HMBC correlation of compound **3**.

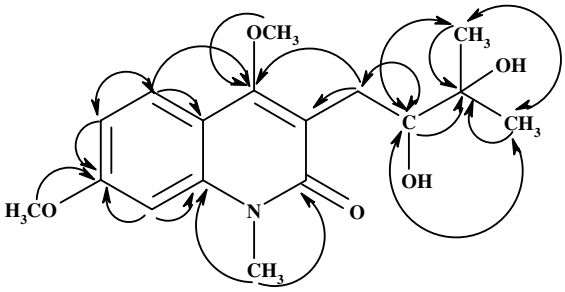


Fig. 2. HMBC correlation of compound **2a**.

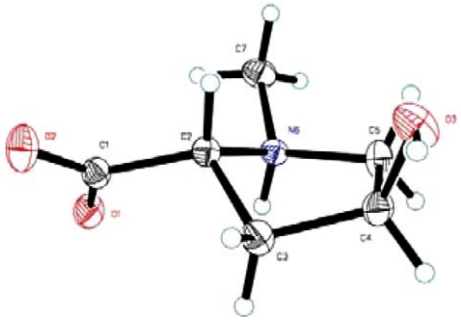


Fig. 4. X-ray of compound **3**.

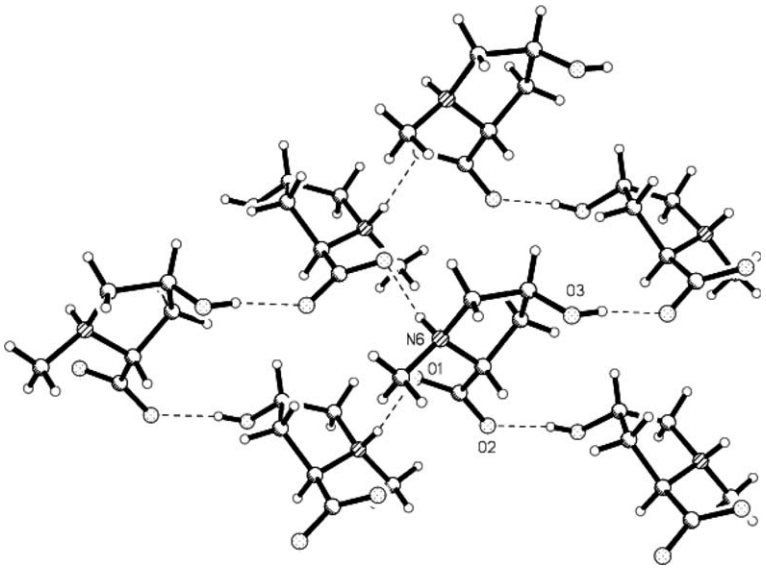


Fig. 5. Showing intramolecular hydrogen bonding in compound **3**.

a strong intermolecular H-bonding between the carboxylate oxygen O2 and the hydroxyl oxygen O3 in the compound. Hydroxyl oxygen O3 is donating a H-bond to the carboxylate oxygen O2, forming a O3–H3A···O2^{i} bond with O3···O2^{i} 2.691(3) Å, H3A···O2^{i} 1.9 Å and O3–H3A···O2^{i} 170°, where (i) $= -x + 1, y - 0.5, -z$. The second carboxylate oxygen O1 forms a H-bond with NH group of the neighboring molecule. This is the second report of isolation of compound **3** from *Toddalia* genus (Nakayama et al., 2003).

3. Experimental

3.1. General

Melting points were determined in a Fischer Johns apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin–Elmer Spectrophotometer. ^{1}H, ^{13}C NMR and 2D NMR spectra were recorded on Bruker 300 Spectrometer in $CDCl_3$/CD_3OD/DMSO-d_6 as required, with TMS as internal standard. The mass spectra were taken on Jeol Spectrophotometer and with Bruker Esquire LC-00141 and elemental analysis by GmbH Vario EL V3.00. Silica gel used were of 60–120 mesh from Merck.

3.2. Plant material

The leaves and stems of *T. aculeata* were collected from Botanical Survey of India (BSI), Experimental garden, Barapani, Shillong, and were identified by Mr. J. Singh.

3.3. Extraction and isolation

Dried and finely powdered plant material (2.0 kg) was extracted separately for several hours with cold CH_2Cl_2:MeOH and hot MeOH in succession using a Soxhlet apparatus. Organic solvent was removed from both the extracts separately, under reduced pressure and the residue (25 and 30 g) left was subjected to column chromatography on silica gel. Elutions were accomplished with a gradient of petroleum ether/$CHCl_3$/MeOH. A total of 300 fractions (400 ml each) were collected and pooled on the basis of their TLC behaviour to make 18 major fractions (F1–F18) from cold CH_2Cl_2:MeOH extract. Similarly, 320 fractions (400 ml each) were collected from hot MeOH extract, and compound **1** (10 mg) and **2a** (12 mg) were isolated from fractions F6 and F9, respectively, as yellow crystalline solids. F11 gave compound **3** as colourless crystalline solid (12 mg). Besides these, we have also isolated fourteen other known compounds viz., β-sitosterol, stigmasterol, 7-methoxy-2*H*-1-benzopyran-2-one, 5,7-dimethoxy-2*H*-1-benzopyran-2-one, 2,3-dimethoxy-12-methyl[1,3]benzodioxolo[5,6-c]phenanthridinium chloride, 1,2-dimethoxy-12-methyl[1,3]benzodioxolo[5,6-c]phenanthridinium chloride, 5,7-dimethoxy-6-(2-hydroxy-3-methyl-but-3-enyl)-2*H*-1-benzopyran-2-one, 7-(3,7-dimethyl-octa-2,6-dienyloxy)-2*H*-1-benzopyran-2-one, 5,7-dimethoxy-6-(2,3-dihydroxy-3-methylbutyl)-2*H*-1-benzopyran-2-one, hexacosanoic acid, heptacosanoic acid, dotriacontanol, D-mannitol, benzoic acid and an unidentified alkaloidglycoside from cold and hot extracts of leaves and stems of *T. aculeata.* Stigmasterol, dotriacontanol and D-mannitol are reported here for the first time from this genus.

3.4. Crystal and molecular structure of compound **3**

$C_6H_{11}NO_3$, $M = 145.6$, monoclinic, $a = 6.746(1)$ Å, $b = 5.851(2)$ Å, $c = 8.887(2)$ Å, $\beta = 100.83(1)°$, $V = 344.5(2)$ Å^3, $Z = 2$, $D_c = 1.390$ g cm^{-3}, space group $= P2_1$. Intensity data were collected up to $\theta = 30°$ by using θ–2θ scan mode. Data were corrected for Lorentz and polarization effects. The structure was solved by direct methods using SIR92 (Altomore et al., 1993) and refined to a *R*-fac-

tor of 0.037, $wR_2 = 0.1025$, by full matrix least-squares refinement techniques based on F^2 using SHELXTL (Sheldrick, 1995). All the non-hydrogen atoms were refined anisotropically. The hydrogens were fixed geometrically as riding atoms with a displacement parameter equal to 1.2 (CH, CH_2) or 1.5 (NH_3) times that of the parent atom. The hydroxyl hydrogens were located by difference Fourier map and was not refined.

3.5. Antibacterial activity

The antibacterial activities of **1**, **2a**, and **3** were studied against three bacteria viz., *E. coli* (0157:H7), *B. cereus* (M.1.16) and *L. lactis* (NCC946). For this purpose, the optical density of the growing culture (Luria Broth) was measured after 21 h, using two different concentrations of compounds **1**, **2a** and **3**. The results are tabulated in Table 2 which clearly showed that these compounds possess strong antibacterial activity.

3.6. N-methyl-4-hydroxy-7-methoxy-3-(2,3-epoxy-3-methylbutyl)-1H-quinolin-2-one (*1*)

Yellow crystalline solid (m.p. 110–112 °C); UV (MeOH) λ_{max}: 324, 299, 250, 248, 243, 238, 232 nm; IR ν_{max} (KBr) cm^{-1}: 3347, 1613, 1585, 1430, 826; Elemental analysis: C, 66.0%; H, 7.0%; O, 22.1%; N, 4.8% (required C, 66.4%; H, 6.57%; O, 22.1%; N, 4.8%); ^{1}H NMR ($CDCl_3$): 1.27 (*s*, 3H, CH_3), 1.36 (*s*, 3H, CH_3), 3.22 (*m*, 2H, –CH_2–), 3.89 (*s*, 3H, –OCH_3), 3.95 (*s*, 3H, N–CH_3), 4.80 (*t*, 1H, –CH–), 7.03 (*d*, 1H, $J = 4.5$ Hz), 7.23 (*m*, 1H), 8.04 (*d*, 1H, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$): see Table 1; mass (Esquire-LC 00141) *m/z* (M^++1) = 290 and with high resolution [EI-LC order HR] 289, 246, 218, 205, 177, 147, 135, 121, 107, 91, 77, 57, 43.

3.7. 3-(2,3-Dihydroxy-3-methylbutyl)-4,7-dimethoxy-1-methyl-1H-quinolin-2-one (*2a*)

Yellow crystalline solid (m.p. 89–92 °C); UV (MeOH) λ_{max}: 331, 284, 257, 238, 232 nm; IR ν_{max} (KBr) cm^{-1}: 3409, 1631; ^{1}H NMR ($CDCl_3$): 1.29 (*s*, 3H, CH_3), 1.31 (*s*, 3H, CH_3), 1.62 (*brs*, 1H), 2.64 (*brs*, 1H), 2.72 (*t*, 1H, $J = 13.5$ and 10.2 Hz), 3.12 (*d*, 1H, $J = 10.0$ Hz), 3.60 (*d*, 1H, $J = 10.0$ Hz), 3.91 (*s*, 3H, OCH_3), 3.92 (*s*, 3H, OCH_3), 3.98 (*s*, 3H, N–CH_3), 7.07 (*d*, 1H, $J = 3.8$ Hz), 7.22 (*m*, 1H), 7.44 (*d*, 1H, $J = 7.8$ Hz); ^{13}C NMR ($CDCl_3$): see Table 1; mass, TOFMS ES$^+$ *m/z*: 322 (M^++1), 304 (M^++1−18), 290, 214.

3.8. 3-(3-Hydroxy-2-oxo-3-methylbutyl)-4,7-dimethoxy-1-methyl-1H-quinolin-2-one (*2b*)

Oxidation of **2a** with PCC in CH_2Cl_2 at room temperature gave brownish solid labeled as **2b**. It gave a single spot on TLC in chloroform/methanol (95:5), $R_f = 0.32$; UV (MeOH) λ_{max}: 324, 299, 250, 248, 243, 238, 232 nm; IR ν_{max} (KBr) cm^{-1}: 3409, 1700, 1631; ^{1}H NMR ($CDCl_3$): 1.29 (*s*, 3H, CH_3), 1.31 (*s*, 3H, CH_3), 1.62 (*brs*, 1H), 3.48 (*d*, 2H,

Table 2
Antibacterial activity of **1**–**3**

Compound	Concentration (μg/ml)	% Inhibition *Escherichia coli*	% Inhibition *Bacillus cerus*	% Inhibition *Lactobacillus lactis*
1	8	28.07	80.74	71.43
	16	72.48	65.93	82.86
2a	8	22.81	69.63	71.43
	16	70.50	80.74	77.14
3	8	23.82	68.89	74.29
	16	70.50	73.34	82.86

Table 1
^{13}C NMR spectral data and HMBC correlations for compounds **1**, **2a** and **3**

	1		**2a**		**3**	
C	C	HMBC	C	HMBC	C	HMBC
1	–		–		–	
2	163.5		167.0		73.4	–N^+CH_3, COO^-, C-5, C-3
3	100.3		120.2		41.5	COO^-, C-2, C-4
4	172.8		161.7		74.4	C-3, C-5
5	118.4	C-4, C-6, C-4a	116.1	C-4a, C-4, C-6	65.9	C-3, –N^+CH_3
6	123.6	C-5, C-7	123.3	C-5, C-7		
7	150.4		149.0			
8	113.5	C-7, C-8a	113.9	C-7, C-8a		
9	128.7		121.3			
10	129.8		130.4			
1′	28.1	C-3, C-4, C-2′, C-3′	28.0	C-4, C-2′, C-3		
2′	91.9	C-1′, C-3′	79.0	C-1′, C-3′, C-4′, C-5′		
3′	71.1		73.1			
4′	26.1	C-2′, C-3′, C-5′	25.6	C-2′, C-3′, C-5′		
5′	24.6	C-2′, C-3′, C-4′	24.7	C-2′, C-3′, C-4′		
6′	56.8	C-7	56.7	C-7		
7′	–		62.4	C-4		
NCH_3/N^+CH_3	36.7	C-8a, C-2	35.9	C-8a, C-2	46.5	C-5, C-2
COO^-					176.2	

$J = 13.5$ Hz), 3.91 (*s*, 3H, OCH_3), 3.92 (*s*, 3H, OCH_3), 3.98 (*s*, 3H, N–CH_3), 7.10 (*d*, 1H, $J = 3.8$ Hz), 7.19 (*m*, 1H), 7.46 (*d*, 1H, $J = 7.8$ Hz), 10.01 (*brs*, 1H).

3.9. 4-Hydroxy-1-methyl-pyrrolidin-2-carboxylic acid (*3*)

Colourless crystalline solid (m.p. 233–234°C); UV (MeOH) λ_{max}: 386, 328, 283, 274, 229 nm; Elemental analysis: C, 49.3%; H, 7.5%; O, 33.8% and N, 9.4 % (required C, 49.6%; H, 7.5%; O, 33.3% and N, 9.6 %); IR ν_{max} (KBr) cm^{-1}: 3402, 1626, 1401, 1351. ^1H NMR (CD_3OD): 2.13 (*m*, 1H, $J = 12.5$ and 12.3 Hz), 2.41 (*m*, 1H, $J = 12.6$ and 12.4 Hz), 2.96 (*s*, 3H, –N^+–CH_3), 3.13 (*d*, 1H, $J = 13.0$ Hz), 3.88 (*dd*, 1H, $J = 12.9$ and 12.8 Hz), 4.11 (*t*, 1H, $J = 9.0$ and 7.5 Hz), 4.55 (*brs*, 1H); ^{13}C NMR (δ, CD_3OD, 75.47 MHz): see Table 1; EIMS *m/z*: (M^+, 145), 143, 129, 125, 110, 100, 85, 83, 71.

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