Two New Insecticidal Amide Dimers from Fruits of *Piper nigrum* LINN.

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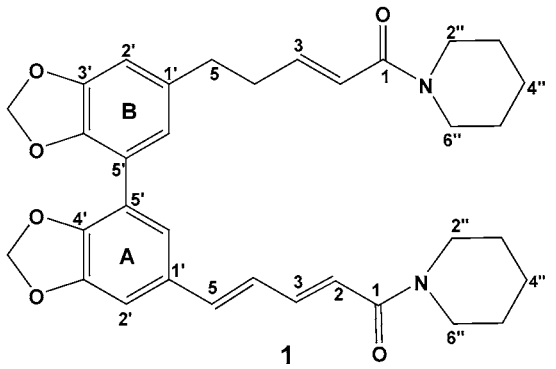
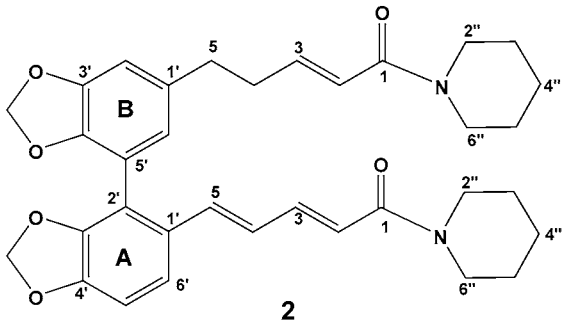
The methanolic extract of dried ground seeds of *Piper nigrum* LINN. afforded fourteen compounds, of which thirteen were amides, including two new isomeric insecticidal amides, pipsaeedine (**1**) and pipbinine (**2**), along with eleven known amides and piptaline; (this is the first report of isolation of these compounds from this plant). The structures of **1** and **2** have been elucidated as (*E*,*E*)-1-[(*E*)-5-(7-{6-[5-(piperidin-1-yl)-5-oxopent-3-enyl]-1,3-benzodioxol-4-yl}-1,3-benzodioxol-5-yl)-1-oxopenta-2,4-dienyl]piperidine and (*E*,*E*)-1-[(*E*)-5-(4-{6-[5(piperidin-1-yl)-5-oxopent-3-enyl]-1,3-benzodioxol-4-yl}-1,3-benzodioxol-5-yl)-1-oxopenta-2,4-dienyl]piperidine, respectively, through extensive 1D- and 2D-NMR spectral studies, while the known constituents have been identified through comparison of their spectral data with those reported in the literature. Compounds **1** and **2** exhibited toxicities of 45.0 and 40.0 ppm, respectively, against fourth instar larvae of *Aedes aegypti* Liston.

Introduction. – The genus *Piper* belongs to the family Piperaceae and has over 700 species distributed in both hemispheres. *Piper nigrum*, commonly known as black pepper, is a climbing perennial shrub. Various *Piper* species have been used as a spice and also as a folk medicine because of their many physiological activities and are, thus of high commercial, economical, and medicinal importance [1–4]. In the course of our investigations towards obtaining plant-based potent insecticides [5–7], studies undertaken on the seeds of *P. nigrum* have resulted in the isolation of two new amides, pipsaeedine (**1**) and pipbinine (**2**), as well as several known compounds from the methanolic extract including seven compounds previously unreported from this species. These include (*E*,*E*)-*N*-(2-methylpropyl)dodeca-2,4-dienamide [8], (*E*,*E*)-*N*-(2-methylpropyl)hexadeca-2,4-dienamide [9], piptaline [8], piperanine [10] [13], $\Delta^{\alpha,\beta}$-dihydrowisanidine [11], $\Delta^{\alpha,\beta}$-dihydrowisanine [12] [13], (*E*,*E*,*E*)-1-{[9-[3,4-(methylenedioxy)phenyl]nona-2,4,8-trienoyl}pyrrolidine [4], (*E*,*E*,*E*)-1-{11-[3,4-(methylenedioxy)phenyl]undeca-2,4,10-trienoyl}piperidine [14], piperine [14] [15], wisanine [16] [17], 1-piperettylpyrrolidine [18] [19], and piperettine [4] [5] by different chromatographic techniques. Five of these compounds, the *tert*-butyldodecadienamide, the *tert*-butylhexadecadienamide, piperanine, the methylenedioxyphenylnonatrienoylpyrrolidine, and the methylenedioxyphenylundecatrienoylpiperidine, exhibited toxicities of 25.0, 27.0, 17.0, 20.0, and 25.0 ppm, respectively, against fourth-instar larvae of *Aedes aegypti* as determined by the WHO method [20]. This is the first report to our knowledge of a dimer-type diamide from this plant – one part consisting of piperine (ring A) and the other of piperanine (ring B) – although dimer-type alkaloids, lignans, and neolignan isolated earlier from this genus have been described [3] [21–23]. Highly substituted, *i.e.*, tetra- or pentasubstituted aromatic compounds have also been reported previously from this genus [3] [24–26].

Results and Discussion. – Both isomers **1** and **2** were obtained as amorphous powders. Both exhibited molecular-ion peaks at *m/z* 570 by EI-MS and at *m/z* 570.2737 and 570.2735 (calc. 570.2729), respectively, by HR-EI-MS, corresponding to the molecular formula $C_{34}H_{38}N_2O_6$, which requires seventeen degrees of unsaturation. The spectral data suggest that **1** and **2** are adducts of piperine and piperanine that differ only in the position of substituents in one of the aromatic rings. Evidence that supports the proposed substitution patterns includes the presence of four *meta*-coupled H-atoms in the ^{1}H-NMR spectrum of **1** and two *ortho*- and two *meta*-coupled protons in that of **2**. The total structures were easily inferred by ^{1}H- and ^{13}C-NMR, while EI-MS, HR-EI-MS and HMBC connectivities provided conclusive information in favor of the dimer-like compounds.



1



2

The IR spectrum of **1** showed absorptions at 1655, 1635, and 1615–1395 cm^{-1}, indicating the amide C=O, C=C, and aromatic moieties. The UV spectrum of **1** showed the presence of a conjugated benzo[1,3]dioxol moiety [27] with absorptions at 321.3 ($\varepsilon = 35000$) and 313.9 nm ($\varepsilon = 24200$) and a conjugated amide C=O at 264.3 ($\varepsilon = 13000$) and 253.6 nm ($\varepsilon = 11900$). The resonances in the ^{1}H-NMR spectrum of **1** (*Table 1*) revealed the presence of two tetrasubstituted aryl moieties; ring *A* with two *meta*-coupled aromatic H-atoms at δ (ppm) 6.72 (*d*, $J = 1.3$ Hz, H–C(6′)[1]) and 6.66 (*d*, $J = 1.3$ Hz, H–C(2′)). H–C(2′) displayed HMBC connectivities with C-atoms at δ (ppm) 131.7 (C(1′)), 146.9 (C(3′)), 147.8 (C(4′)), 130.1 (C(6′)), and 141.2 (C(5)), while H–C(6′) had correlations to C-atoms resonating at δ 131.7 (C(1′)), 108.8 (C(2′)), 147.8 (C(4′)), 133.3 (C(5′)),

[1]) Arbitrary numbering; for systematic name and numbering, see *Exper. Part.*

Table 1. *[1]H- and [13]C-NMR Data of* **1**

Position[1]), ring system	$\delta(^{13}C)$ [ppm]	$\delta(^{1}H)$ [ppm]	Multiplicity (J [Hz])
C(1), *A*	164.3	–	–
H–C(2), *A*	120.6	6.45	*d* (16.4)
H–C(3), *A*	144.3	7.57	*dd* (16.4, 10.4)
H–C(4), *A*	124.9	6.81	*dd* (16.8, 10.4)
H–C(5), *A*	141.2	6.88	*dd* (16.8, 1.3)
C(1′), *A*	131.7	–	–
H–C(2’), *A*	108.8	6.66	*d* (1.3)
C(3′), *A*	146.9	–	–
C(4’), *A*	147.8	–	–
H–C(5′), *A*	133.3	–	–
H–C(6′), *A*	130.1	6.72	*d* (1.3)
C(1), *B*	165.5	–	–
H–C(2), *B*	122.1	5.99	*d* (16.3)
H–C(3), *B*	144.6	7.19	*dt* (16.3, 6.7)
H–C(4), *B*	36.5	2.55	*q* (6.7)
H–C(5), *B*	37.2	2.68	*dt* (6.7, 1.7)
C(1′), *B*	132.9	–	–
H–C(2′), *B*	109.4	6.99	*d* (1.7)
C(3′), *B*	150.3	–	–
C(4′), *B*	149.9	–	–
H–C(5′), *B*	132.1	–	–
H–C(6′), *B*	126.1	6.96	*d* (1.7)
$-OCH_2O$, *A*	101.7	5.96	*s*
$-OCH_2O$, *B*	101.1	5.99	*s*
CH_2(2″,6″), *A* and *B*	47.5 – 46.9	3.68 – 3.47	br. *s*
CH_2(3″,4″,5″), *A* and *B*	27.5 – 24.1	1.79 – 1.35	br. *s*

141.2 (C(5)), and 132.1 (C(5′) of ring *B*). Further, in the ^{1}H-NMR spectrum, the other two *meta*-coupled H-atoms of ring *B* resonated at 6.99 (*d*, $J = 1.7$ Hz, H–C(2′)) and 6.96 (*d*, $J = 1.7$ Hz, H–C(6′)). The HMBC cross peaks (*Fig. 1*) were recorded between H–C(2′) and C(1′) (132.9), C(3′) (150.3), C(4′) (149.9), C(6′) (126.1), and C(5) (37.2). The ^{1}H-NMR spectrum of ring *A* showed three *dd* at 7.57 ($J = 16.4$, 10.4 Hz, H–C(3)), 6.81

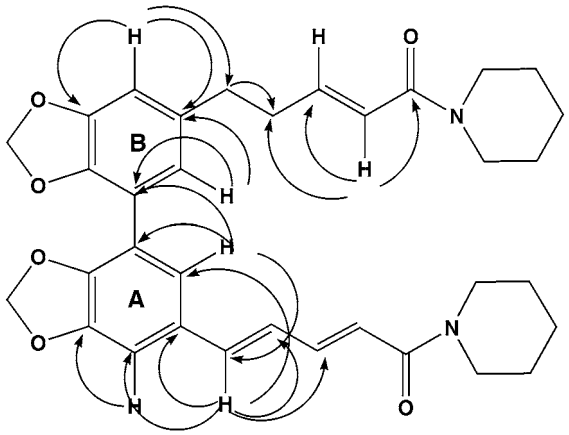


Fig. 1. *Significant HMBC connectivities of* **1**

($J = 16.8$, 10.4 Hz, H–C(4)), and at 6.88 ($J = 16.8$, 1.3 Hz, H–C(5)) while a *d* of 16.4 Hz was observed due to H–C(2) resonating at 6.45 ppm. This spin system was confirmed by ^{1}H-^{1}H-COSY, HMQC, HMBC, and NOESY correlations. Moreover, the resonances in the ^{1}H-NMR spectrum revealed that the chain attached to ring *B* lacks one C=C depicted by the presence of two methylene groups, one upfield in the neighborhood of an α,β unsaturated amide at 2.55 (*q*, $J = 6.7$ Hz, $CH_2(4)$) and the other downfield at 2.68 (*dt*, $J = 6.7$, 1.7 Hz, $CH_2(5)$) attached to the aromatic ring.

The configuration of each C=C bond was *trans*, as confirmed by the coupling constants. Two two-proton *s* at 5.96 and 5.99 were due to two methylenedioxy moieties attached to aromatic rings *A* and *B*, respectively. These had cross-peaks at 101.7 and 101.1, respectively, in the HMQC. The ^{1}H- and ^{13}C-NMR shifts (rings *A* and *B*) also displayed signals for piperidine rings; integration of all piperidine ring H-atom was double that of other compounds possessing only single piperidine rings. Eight H-atoms ($CH_2(2'',6'')$, *A* and *B*) resonated at 3.68–3.47 ppm as a br. *s*, while the rest of twelve H-atoms ($CH_2(3'',4'',5'')$, *A* and *B*) appeared as a br. *s* at 1.79–1.35 ppm in the ^{1}H-NMR spectrum of **1**. The presence of fragment ions at *m/z* 120 and 134, and the absence of one at 121 suggested the tetra-substituted aromatic ring in the molecule of these dimers.

The spectral data of **2** were very similar to those of **1** except for the coupling of aromatic protons. The new natural product **2** differs from **1** in its more-polar chromatographic mobility. Thus, in the ^{1}H-NMR spectrum of **2**, one pair of *meta*-coupled and one pair of *ortho*-coupled H-atoms were present instead of the two pairs of *meta*-coupled H-atoms of **1**. These spectral data (*Tables 1* and *2*) as well as MS data (*Fig. 2*) indicated that **1** and **2** are isomeric adducts of piperine and piperanine. Both **1** and **2** showed zero optical rotation, which suggests that they are not atropisomeric, a conclusion that is supported by *Dreiding* models. These data led to the assignment of the structure of **1** as 5′-(5′-piperanine)piperine, and in light of the above discussion, the structure of **2** was elucidated as 2′-(5′-piperanine)piperine.

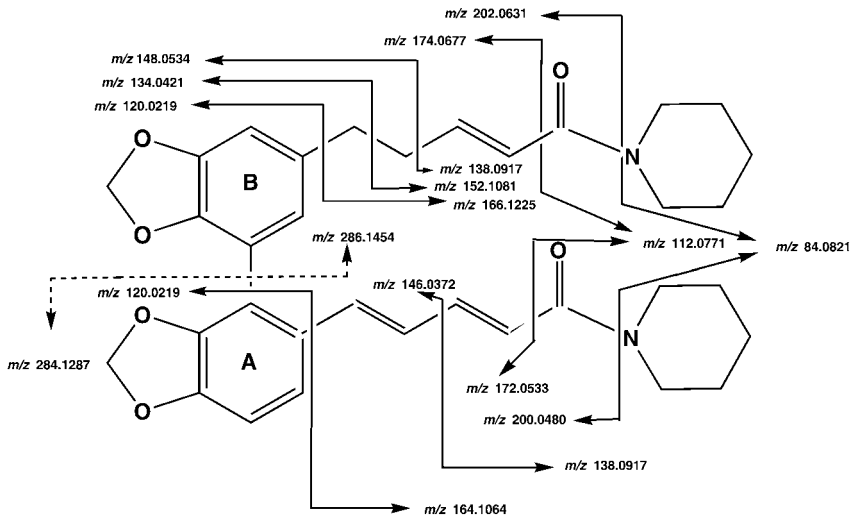


Fig. 2. *Observed HR-EI-MS fragments of* **2**

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

Position[1]), ring system	$\delta(^{13}C)$ [ppm]	$\delta(^1H)$ [ppm]	Multiplicity (J [Hz])
C(1), *A*	164.5	–	–
H–C(2), *A*	120.3	6.49	*d* (15.9)
H–C(3), *A*	143.1	7.59	*ddd* (15.9, 10.1, 1.2)
H–C(4), *A*	125.8	6.85	*dd* (16.3, 10.1)
H–C(5), *A*	140.6	6.91	*dd* (16.3, 1.2)
C(1′), *A*	133.1	–	–
H–C(2′), *A*	131.7	–	–
C(3′), *A*	147.1	–	–
C(4′), *A*	146.6	–	–
H–C(5′), *A*	108.9	6.99	*d* (8.2)
H–C(6′), *A*	121.8	7.03	*d* (8.2)
C(1), *B*	165.7	–	–
H–C(2), *B*	121.9	6.01	*d* (15.5)
H–C(3), *B*	145.5	7.13	*dt* (15.5, 7.0)
H–C(4), *B*	35.4	2.52	*q* (7.0)
H–C(5), *B*	37.1	2.61	*dt* (7.0, 1.5)
C(1′), *B*	136.1	–	–
H–C(2′), *B*	109.7	7.01	*d* (1.5)
C(3′), *B*	152.1	–	–
C(4′), *B*	149.3	–	–
H–C(5′), *B*	130.9	–	–
H–C(6′), *B*	125.9	6.95	*d* (1.5)
$-OCH_2O$, *A*	101.7	6.01	*s*
$-OCH_2O$, *B*	100.9	5.95	*s*
CH_2(2″,6″), *A* and *B*	47.9 – 46.4	3.71 – 3.47	br. *s*
CH_2(3″,4″,5″), *A* and *B*	27.4 – 24.9	1.81 – 1.37	br. *s*

The toxicities of **1** and **2**, determined according to the WHO method [20] are 45.0 and 40.0 ppm, respectively.

Experimental Part

General. Vacuum liquid chromatography (VLC): silica gel *60 PF_{254}* (*Merck*). Flash column chromatography (FC): silica gel *9385* (*Merck*, 0.040 – 0.063 mm). Prep. TLC (PTLC): silica gel *60 PF_{254}* (*Merck*). UV Spectra: *Hitachi U-3200* spectrophotometer; λ_{max} in nm (ε). IR Spectra: *Jasco A-302* spectrophotometer; ν in cm^{-1}. ^{1}H-NMR Spectra (COSY, NOESY, and *J*-resolved): *Bruker*, 500 MHz; in $CDCl_3/CD_3OD$ 1:1; chemical shifts δ in ppm, coupling consants *J* in Hz, referenced to residual solvent signals. ^{13}C-NMR Spectra: *Bruker*, 125 MHz; in $CDCl_3/CD_3OD$ 1:1. The assignments in *Tables 1* and *2* are based on ^{1}H-, COSY-45, *J*-resolved, and ^{13}C-(broad-band and DEPT), HMQC, and HMBC spectra. EI-MS: *Finnigan-Mat-311A*; source at 250° and 70 eV; *m/z* (%). HR-EI-MS: *Jeol JMS-HX-110*, source at 250° and 70 eV; *m/z* (%).

Extraction and Purification. Seeds of *P. nigrum* (5 kg), purchased from the local market in Karachi, were air-dried and ground, then extracted with petroleum ether (3 × 10 l) at r.t. for 72 h. Evaporation of the combined extracts *in vacuo* afforded a dark brown viscous residue (102.1 g). A portion (91.8 g) of this extract was partitioned between petroleum ether and 90% MeOH. The MeOH phase was extracted with AcOEt after saturation with saline soln. The AcOEt layer was dried (anh. Na_2SO_4), and the solvent was evaporated *in vacuo* to give a brownish sirupy concentrate (MEA, 24.8 g). A portion (11.8 g) of this concentrate was subjected to PTLC (petroleum ether/AcOEt 7:3), which yielded eight major bands. All bands were further purified through repeated chromatography on precoated thin-layer cards. Purification of band *2* (408.7 mg) through repeated chromatography on precoated TLC (petroleum ether/AcOEt 8.3:1.7) yielded (*E*,*E*)-*N*-(2-methylpropyl)dodeca-2,4-dienamide (2.1 mg), (*E*,*E*)-*N*-(2-methylpropyl)hexadeca-2,4-dienamide (3.4 mg), and piptaline (2.4 mg); and band *5* (1.74 g) gave six major bands with several sub-bands (petroleum ether/AcOEt 7:3).

Further purification by repeated TLC (petroleum ether/AcOEt 7:3 → 6:4) of these sub-bands resulted in the isolation of pure piperanine (5.1 mg), $\Delta^{\alpha,\beta}$-dihydrowisanidine (2.1 mg), $\Delta^{\alpha,\beta}$-dihydrowisanine (3.3 mg), (*E*,*E*,*E*)-1-{9-[3,4-(methylenedioxy)phenyl]nona-2,4,8-trienoyl}pyrrolidine (4.8 mg), (*E*,*E*,*E*)-1-{11-[3,4-(methylenedioxy)phenyl]undeca-2,4,10-trienoyl}pyrrolidine (4.6 mg), and piperine (9.4 mg). Band *8* (2.3 g) also consisted of many bands and sub-bands by TLC (petroleum ether/AcOEt 3:7), further purification of which by repeated PTLC (petroleum ether/AcOEt 6:4 → 1:1) gave wisanine (1.9 mg), 1-piperettylpyrrolidine (2.2 mg), and piperettine (4.3 mg), in order of polarity. Bands *6′–4″* (35.8 mg) gave a single spot by PTLC (petroleum ether/AcOEt 3:7), but could be separated into two spots by repeated (5×) elution (petroleum ether/AcOEt 6:4). The faster-eluting compound was pure pipsaeedine (**1**; 4.8 mg), while the slower-eluting one was pipbinine (**2**; 7.3 mg).

Pipsaeedine (= (E,E)-*1-[(*E*)-5-(7-[6-[5-(Piperidin-1-yl)-5-oxopent-3-enyl]-1,3-benzodioxol-4-yl]-1,3-benzodioxol-5-yl)-1-oxopenta-2,4-dienyl]piperidine*; **1**). Amorphous powder. $[\alpha]_D = 0$ ($c = 0.01$, MeOH). UV (MeOH): 373.5 (45200), 357.2 (41000), 321.3 (35000), 313.9 (24200), 300.8 (25000), 264.3 (13000), 253.6 (11900). IR (KBr): 3053, 2945, 1655, 1635, 1615–1395 (4 peaks), 1250, 1033, 990, 971, 921. ^{1}H- and ^{13}C-NMR data: see *Table 1*. EI-MS 570 (M^+; 44), 486 (25), 458 (13), 402 (29), 374 (32), 346 (20), 286 (25), 284 (50), 240 (41), 224 (21), 202 (42), 200 (51), 174 (19), 172 (15), 166 (33), 168 (25), 164 (28), 152 (21), 148 (22), 146 (24), 138 (44), 135 (9), 134 (38), 120 (70), 112 (35), 103 (11), 84 (40), 69 (100). HR-EI-MS: 570.2737 (M^+, $C_{34}H_{38}N_2O_6^+$; calc. 570.2729), 486.1929 ($[C_{29}H_{28}NO_6]^+$), 458.1971 ($[C_{28}H_{28}NO_5]^+$), 402.1111 ($[C_{24}H_{18}O_6]^+$), 374.1163 ($[C_{23}H_{18}O_5]^+$), 346.1210 ($[C_{22}H_{18}O_4]^+$), 286.1451 ($[C_{17}H_{20}NO_3]^+$), 284.1289 ($[C_{17}H_{18}NO_3]^+$), 240.0439 ($[C_{14}H_8O_4]^+$), 224.1535 ($[C_{10}H_{20}N_2]^+$), 202.0629 ($[C_{12}H_{10}O_3]^+$), 200.0481 ($[C_{12}H_8O_3]^+$), 174.0675 ($[C_{11}H_{10}O_2]^+$), 172.0535 ($[C_{11}H_8O_2]^+$), 166.1221 ($[C_{10}H_{16}NO]^+$), 168.1630 ($[C_{10}H_{20}N_2]^+$), 164.1062 ($[C_{10}H_{14}NO]^+$), 152.1080 ($[C_9H_{14}NO]^+$), 148.0538 ($[C_9H_8O_2]^+$), 146.0370 ($[C_9H_6O_2]^+$), 138.0915 ($[C_8H_{12}NO]^+$), 135.0455 ($[C_8H_7O_2]^+$), 134.0419 ($[C_8H_6O_2]^+$), 120.0212 ($[C_7H_4O_2]^+$), 112.0773 ($[C_6H_{10}NO]^+$), 103.0550 ($[C_8H_7]^+$), 84.0825 ($[C_5H_{10}N]^+$), 69.0710 ($[C_5H_9]^+$).

Pipbinine (= (E,E)-*1-[(*E*)-5-(4-[6-[5-(Piperidin-1-yl)-5-oxopent-3-enyl]-1,3-benzodioxol-4-yl}-1,3-benzodioxol-5-yl)-1-oxopenta-2,4-dienyl]piperidine*; **2**). Amorphous powder. $[\alpha]_D = 0$ ($c = 0.07$, MeOH). UV (MeOH): 371.8 (45000), 355.5 (40500), 323.4 (33400), 315.7 (26900), 298.3 (25200), 265.6 (12800), 250.2 (11600). IR (KBr): 3045, 2951, 1657, 1641, 1615, 1600–1403 (4 peaks), 1251, 1035, 990, 970, 921. ^{1}H- and ^{13}C-NMR data: see *Table 2*. EI-MS 570 (M^+; 59), 486 (19), 458 (15), 402 (26), 374 (26), 346 (16), 286 (31), 284 (31), 240 (31), 224 (31), 202 (27), 200 (31), 174 (23), 172 (19), 166 (31), 168 (15), 164 (23), 152 (23), 148 (29), 146 (23), 138 (44.5), 135 (11), 134 (42), 120 (80), 112 (45), 103 (9), 84 (50), 69 (100). HR-EI-MS: 570.2735 (M^+, $C_{34}H_{38}N_2O_6^+$; calc. 570.2729), 486.1925 ($[C_{29}H_{28}NO_6]^+$), 458.1976 ($[C_{28}H_{28}NO_5]^+$), 402.1118 ($[C_{24}H_{18}O_6]^+$), 374.1162 ($[C_{23}H_{18}O_5]^+$), 346.1211 ($[C_{22}H_{18}O_4]^+$), 286.1454 ($[C_{17}H_{20}NO_3]^+$), 284.1287 ($[C_{17}H_{18}NO_3]^+$), 240.0440 ($[C_{14}H_8O_4]^+$), 224.1533 ($[C_{10}H_{20}N_2]^+$), 202.0631 ($[C_{12}H_{10}O_3]^+$), 200.0480 ($[C_{12}H_8O_3]^+$), 174.0677 ($[C_{11}H_{10}O_2]^+$), 172.0533 ($[C_{11}H_8O_2]^+$), 166.1225 ($[C_{10}H_{16}NO]^+$), 168.1633 ($[C_{10}H_{20}N_2]^+$), 164.1064 ($[C_{10}H_{14}NO]^+$), 152.1081 ($[C_9H_{14}NO]^+$), 148.0534 ($[C_9H_8O_2]^+$), 146.0372 ($[C_9H_6O_2]^+$), 138.0917 ($[C_8H_{12}NO]^+$), 135.0450 ($[C_8H_7O_2]^+$), 134.0421 ($[C_8H_6O_2]^+$), 120.0219 ($[C_7H_4O_2]^+$), 112.0771 ($[C_6H_{10}NO]^+$), 103.0551 ($[C_8H_7]^+$), 84.0821 ($[C_5H_{10}N]^+$), 69.0700 ($[C_5H_9]^+$).

Insecticidal Activity. Toxicities were determined against fourth instar larvae of *Aedes aegypti* Liston, as described in [20].

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