

Supplementary Materials

Table S1. *In vitro* effect of piplartine and analogues against 49-day-old *S. mansoni*.

Group	Period of incubation (h)	Dead worms (%) ^a		Motor activity reduction (%) ^a				
		M	F	Slight		Significant		
				M	F	M	F	
Control ^b	24	0	0	0	0	0	0	
	48	0	0	0	0	0	0	
	72	0	0	0	0	0	0	
	96	0	0	0	0	0	0	
0.5% DMSO	24	0	0	0	0	0	0	
	48	0	0	0	0	0	0	
	72	0	0	0	0	0	0	
	96	0	0	0	0	0	0	
Praziquantel 2 μ M	24	100	100	0	0	100	100	
	48	100	100	0	0	100	100	
	72	100	100	0	0	100	100	
	96	100	100	0	0	100	100	
Amide piplartine	24	100	100	0	0	100	100	
	10 μ M	48	100	100	0	0	100	100
		72	100	100	0	0	100	100
		96	100	100	0	0	100	100
	5 μ M	24	0	0	100	100	0	0
		48	0	0	100	100	0	0
		72	0	0	100	100	0	0
		96	60	60	0	0	60	60
Amide 1G	24	0	0	0	0	0	0	
	50 μ M	48	0	0	0	0	0	0
		72	0	0	0	0	0	0
		96	0	0	0	0	0	0
	25 μ M	24	0	0	0	0	0	0
		48	0	0	0	0	0	0
		72	0	0	0	0	0	0

	96	0	0	0	0	0	0
10 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
5 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
Amide 1M	24	0	0	0	0	0	0
50 μ M	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
25 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
10 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
5 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
Amide 6B	24	0	0	0	0	0	0
50 μ M	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
25 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0

25 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
10 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
5 μ M	14	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
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Amide 14B	24	0	0	0	0	0	0
50 μ M	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
25 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
10 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
5 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
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Amide 19A	24	0	0	0	0	0	0
50 μ M	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
25 μ M	24	0	0	0	0	0	0
<hr/>							

	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
10 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0
5 μ M	24	0	0	0	0	0	0
	48	0	0	0	0	0	0
	72	0	0	0	0	0	0
	96	0	0	0	0	0	0

^a Percentages relative to the 20 worms investigated.

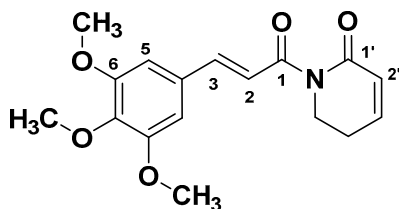
^b RPMI 1640.

The effect of the compounds on motor activity of adult *S. mansoni* was assessed qualitatively.

Figure S1. Description of piplartine and its analogues.

Piplartine, IUPAC name:

1-[(2E)-3-(3,4,5-trimethoxyphenyl)prop-2-enoyl]-1,2,5,6-tetrahydropyridin-2-one



RMN¹ H (300 MHz; CDCl₃): δ 7,68 (d; $J=15,6$ Hz; 1H, H2) ; 7,43 (d; $J=15,6$ Hz; 1H, H3); 6,95 (m, 1H, H2'); 6,81 (s, 2H, H5 e H9); 6,04 (dt; $J=9,9$ e 1,8 Hz; 1H; H3'); 4,05 (t; $J=6,5$ Hz; 2H; H5'); 3,89 (s, 6H; OMe 6 e 8); 3,88 (s; 3H; OMe 7); 2,50 (m; 2H, H4').

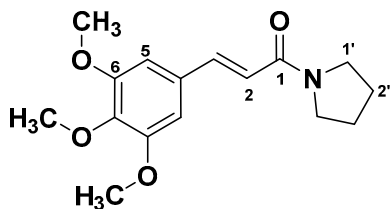
RMN¹³ C (75 MHz; CDCl₃): δ 168,70 (C1); 165,80 (C1'); 153,30 (C6, C8); 145,50 (C3'); 143,70 (C4); 139,90 (C7); 130,60 (C3); 125,70 (C2'); 121,00 (C2); 105,40 (C5, C9); 60,89 (OMe 7); 56,11 (OMe 6 e 8); 41,62 (C5'); 24,70 (C4').

EMBR- m/z (%): 317 (M⁺, 90), 289 (20), 274 (32), 221 (100), 205 (20), 190 (32), 177 (17).

EMAR (IES): calculated to C₁₇H₂₀NO₅⁺[M+H]⁺ = 318,1336; found = 318,1337.

1G, IUPAC name:

(2E)-1-(pyrrolidin-1-yl)-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one



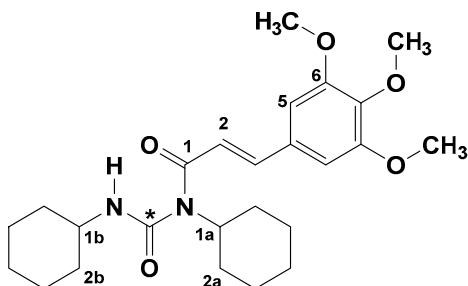
RMN ¹H (300 MHz; CDCl₃): δ 7,62 (d; *J*=15,3 Hz; 1H; H3); 6,75 (s, 2H, H5, H9); 6,62 (d; *J*=15,3 Hz; 1H; H2); 3,89 (s, 6H; OMe 6 e 8); 3,87 (s, 3H, OMe 7); 3,65-3,60 (m, 4H, H1', H4'); 2,01 (m, 2H, H2'); 1,91 (m, 2H, H3').

RMN ¹³C (75 MHz; CDCl₃): δ 164,52 (C1); 153,25 (C6, C8); 141,64 (C3); 139,40 (C7); 130,80 (C4); 117,98 (C2); 104,95 (C5, C9); 60,82 (OMe 7); 56,07 (OMe 6 e 8); 46,51 (C1'); 45,96 (C4'); 26,02 (C2'); 24,23 (C3').

EMAR (IES): calculated to C₁₆H₂₂NO₄⁺[M+H]⁺ = 292,1543; found = 292,1539 .

1M, IUPAC name:

1,3-dicyclohexyl-1-[(2E)-3-(3,4,5-trimethoxyphenyl)prop-2-enoyl]urea



RMN ¹H (500 MHz; CDCl₃): δ 7,57 (d; *J*=15,5 Hz; 1H; H2); 6,70 (s, 2H; H5, H9); 6,62 (d; *J*=15,5 Hz; 1H; H3); 4,16 (m, 1H, H1b); 3,88 (s, 6H; OMe 6 e 8); 3,86 (s, 3H, OMe 7), 3,76 (m, 1H, H1a); 2,02–1,82 (m, 8H, H2a, H2b, H6a, H6b), 1,41–1,15 (m, 12H; H3a, H3b, H4a, H4b, H5a, H5b).

RMN ¹³C (100 MHz; CDCl₃): δ 165,89 (C1); 154,05 (C*); 153,35 (C6, C8); 143,08 (C3); 139,88 (C7); 130,18 (C4); 118,64 (C2); 105,02 (C5, C9); 60,90 (OMe 7); 55,99 (OMe 6 e 8); 55,49 (C1b); 49,98 (C1a); 34,87 (C2b); 33,90 (C6b); 32,77 (C2a); 30,86 (C6a); 26,15 (C3b, C5b); 25,37 (C3a); 25,34 (C5a); 24,67 (C4a, C4b).

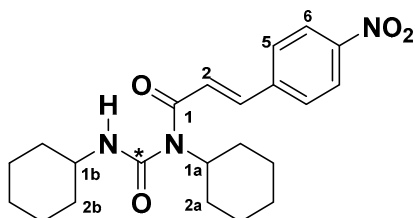
EMBR-*m/z* (%): 319 (40), 236 (100), 222 (55), 221 (50), 207 (32), 194 (25), 190 (30), 180 (27), 163 (20), 133 (21), 121 (20), 98 (45), 77 (20), 68 (20), 55 (25).

EMAR (IES): calculated to C₂₅H₃₇N₂O₅⁺ [M+H]⁺ = 445,2697; found = 445,2725.

IV (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 3291, 2997, 2931, 2854, 2249, 2118, 1761, 1703, 1650, 1583, 1330, 1129, 1006, 973, 892, 822.

6B, IUPAC name:

1,3-dicyclohexyl-1-[(2E)-3-(4-nitrophenyl)prop-2-enoyl]urea



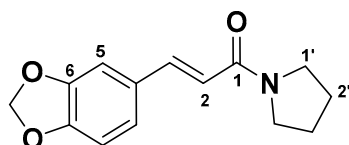
RMN ^1H (300 MHz; CDCl_3): δ 8,24 (d; $J=9,0$ e 2,4 Hz; 2H, H6, H8); 7,69 (d; $J=15,3$ Hz; 1H, H2); 7,62 (d; $J=9,0$ e 2,1 Hz; 2H, H5, H9); 6,84 (d; $J=15,3$ Hz; 1H, H3); 6,55 (sl, NH); 4,19–4,11 (m, 1H, H1b); 3,82–3,74 (m, 1H, H1a); 1,89–1,19 (m, 20H, H2a, H2b, H3a, H3b, H4a, H4b, H5a, H5b, H6a, H6b).

RMN ^{13}C (75 MHz; CDCl_3): δ 165,16 (C1); 153,66 (C*); 148,28 (C7); 140,92 (C4); 140,23 (C3); 128,41 (C5, C9); 124,19 (C6, C8); 123,61 (C2); 55,73 (C1a); 50,05 (C1b); 34,89 (C2a, C6a); 32,78 (C2b); 31,00 (C6b); 26,16 (C3a); 25,42 (C3b); 25,35 (C4a); 25,30 (C4b); 24,66 (C5a, C5b).

EMAR (IES): calculated to $\text{C}_{22}\text{H}_{30}\text{N}_3\text{O}_4^+$: $[\text{M}+\text{H}]^+ = 400,2231$; found = 400,2236.

14B, IUPAC name:

(2E)-3-(2H-1,3-benzodioxol-5-yl)-1-(pyrrolidin-1-yl)prop-2-en-1-one



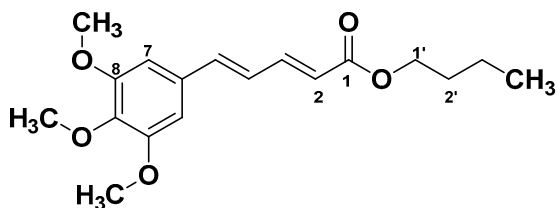
RMN ^1H (300 MHz; CDCl_3): δ 7,61 (d; $J=15,3$ Hz; 1H, H3); 7,04 (d; $J=1,5$ Hz; 1H, H5); 7,02–6,99 (dd; $J=8,4$ e 1,8 Hz; 1H, H9); 6,80 (d; $J=8,1$ Hz; 1H, H8); 6,56 (d; $J=15,3$ Hz; 1H, H2); 5,99 (s, 2H, OCH_2O); 3,63–3,56 (m, 4H, H1', H4') 2,04–1,98 (m; 2H, H2'); 1,94–1,87 (m, 2H, H3').

RMN ^{13}C (75 MHz; CDCl_3): δ 164,76 (C1); 148,84 (C6); 148,10 (C7); 141,30 (C3); 129,68 (C4); 123,75 (C9); 116,82 (C2); 108,41 (C8); 106,32 (C5); 101,32 (OCH_2O); 46,47 (C1'); 45,95 (C4'); 26,07 (C2'); 24,28 (C3').

EMAR (IES): calculated to $\text{C}_{14}\text{H}_{16}\text{NO}_3^+$: $[\text{M}+\text{H}]^+ = 246,1125$; found = 246,1130.

19A IUPAC name:

Butyl (2E,4E)-5-(3,4,5-trimethoxyphenyl)penta-2,4-dienoate



RMN ¹H (300 MHz; CDCl₃): δ 7,42 (qd; *J*=15,5 e 8,9 Hz; 1H, H3); 6,81 (sl, 1H, H5); 6,78 (sl, 1H, H4); 6,69 (s, 2H, H7, H11); 5,99 (d; *J*=15,3 Hz; 1H, H2); 4,18 (*t*, *J*=6,8 Hz; 2H, H1'); 3,90 (s, 6H; OMe 8, 10); 3,87 (s, 3H; OMe 9); 1,72-1,63 (m, 2H, H2'); 1,49–1,39 (m, 2H, H3'); 0,96 (*t*, *J*=7,4 Hz; 3H, H4').

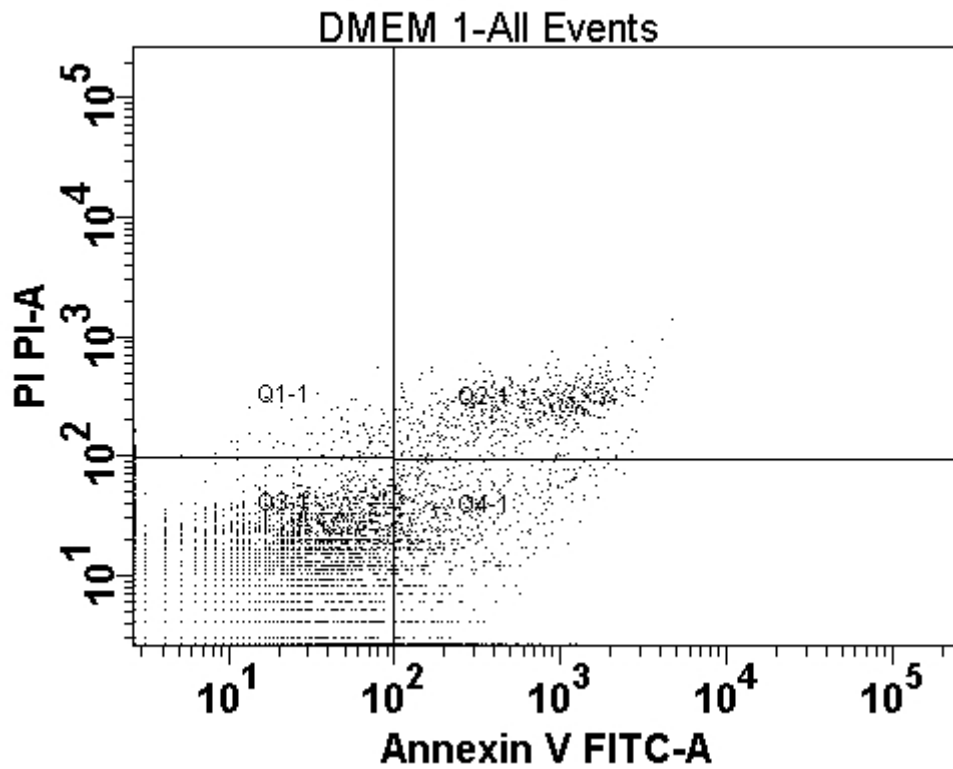
RMN ¹³C (75 MHz; CDCl₃): δ 167,11 (C1); 153,37 (C8, C10); 144,30 (C3); 140,21 (C5); 139,10 (C9); 131,62 (C2); 125,64 (C6); 121,03 (C4); 104,26 (C7, C11); 64,22 (C1'); 60,91 (OMe 9); 56,10 (OMe 8, 10); 30,73 (C2'); 19,15 (C3'); 13,70 (C4').

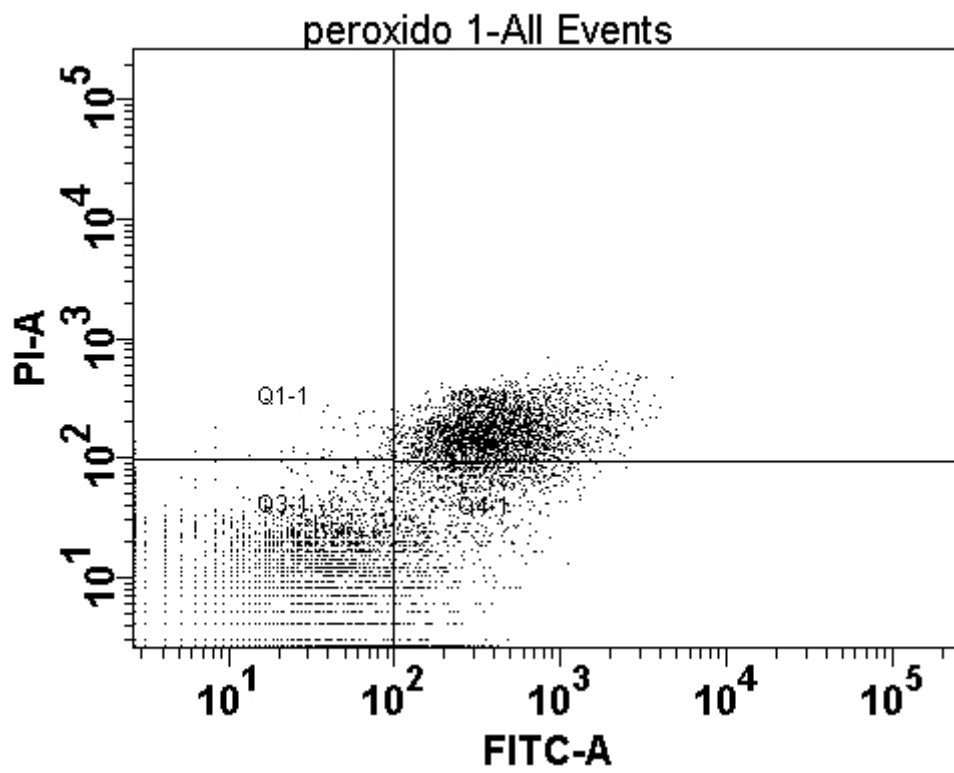
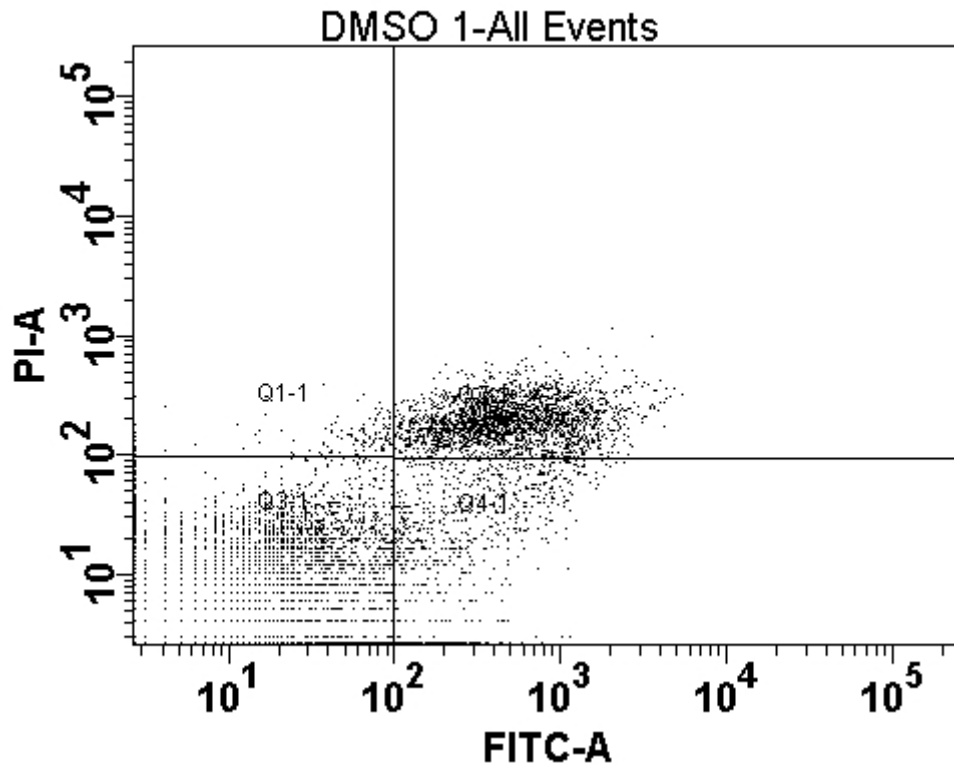
EMBR-*m/z* (%): 320 (25), 219 (100), 204 (30), 188 (55).

EMAR (IES): calculated to C₁₈H₂₄NaO⁺[M+Na]⁺ = 343,1516; found = 343,1513.

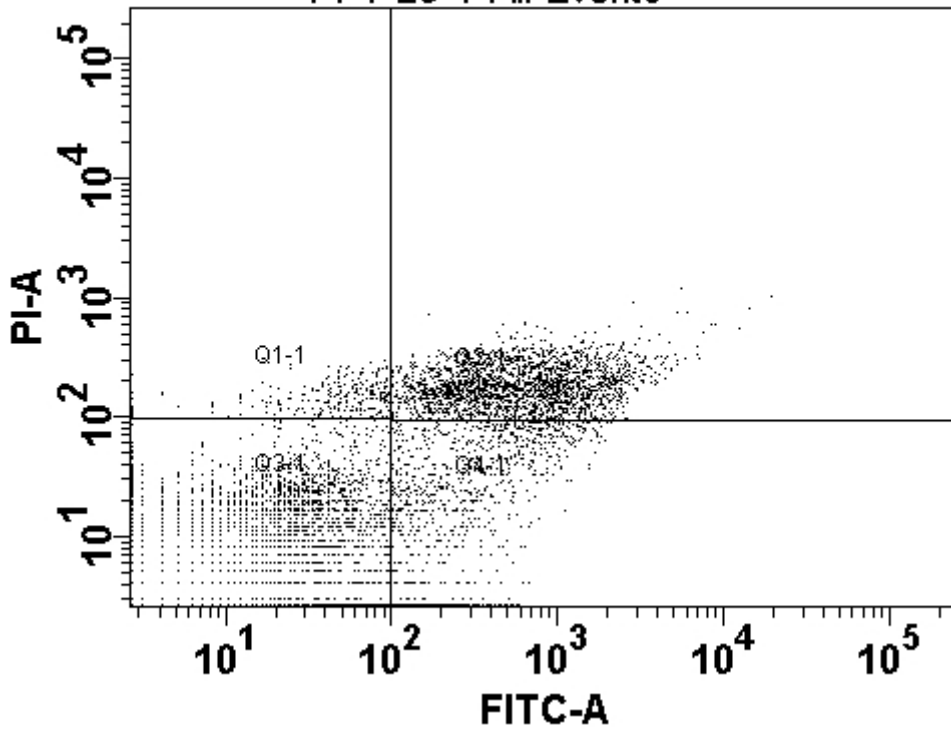
IV (KBr, *v*_{max}/cm⁻¹): 3445, 3005, 2960, 2897, 2838, 1703, 1624, 1579, 1506, 1467, 1419, 1357, 1253, 1244, 1142, 998, 850, 744, 724.

Figure S2. Original data from mouse BALB/cN macrophage (J774A.1) cell line analyzed by flow cytometry (10.000 events/sample) to evaluate the cell death mechanism mediated by piplartine and analogues 1G 1M, 6B, 14B and 19A, following treatment for 24 h at 25, 100 and 400 $\mu\text{g}/\text{mL}$ concentrations using Annexin-V FITC (apoptosis marker) and Propidium Iodide (PI, necrosis marker) staining. The controls DMEM, DMSO and H_2O_2 (peroxido) were used as comparisons parameters.

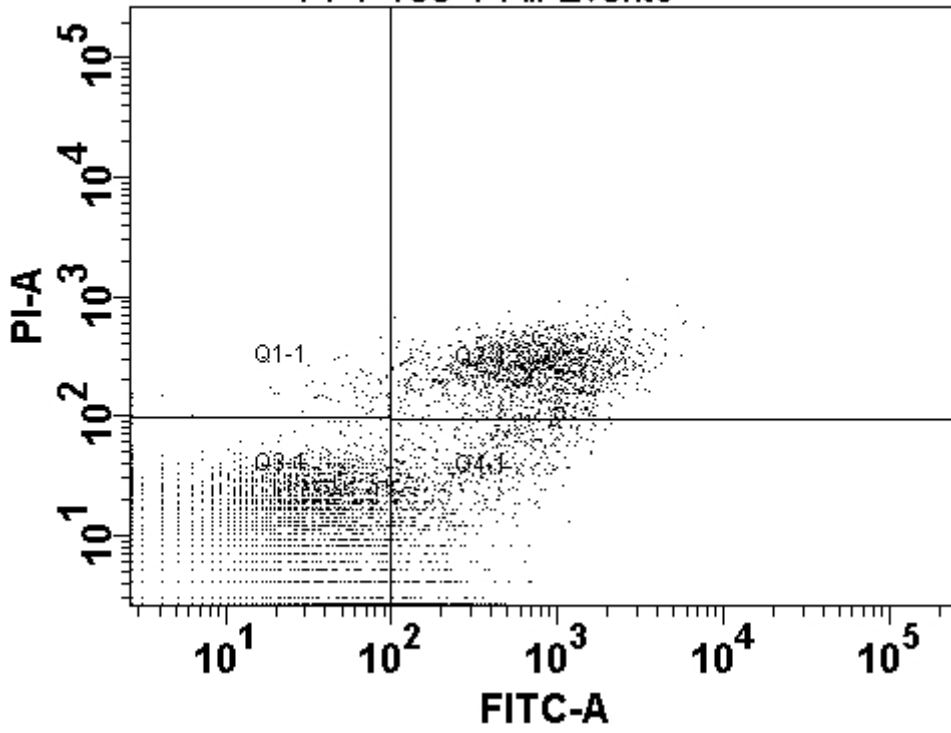




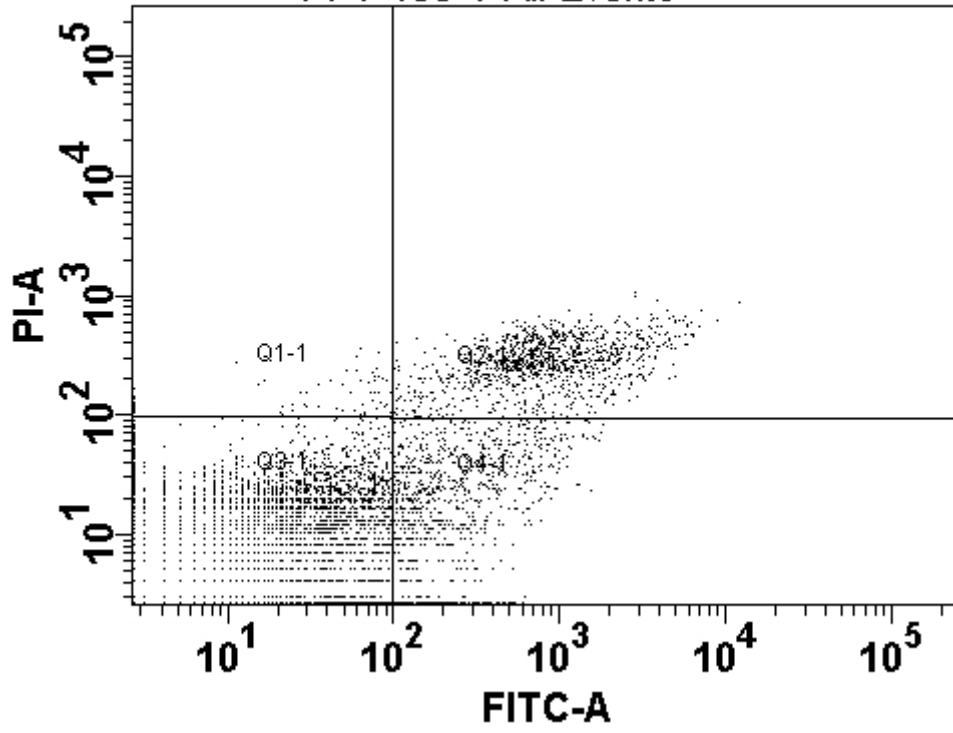
PPT 25-1-All Events



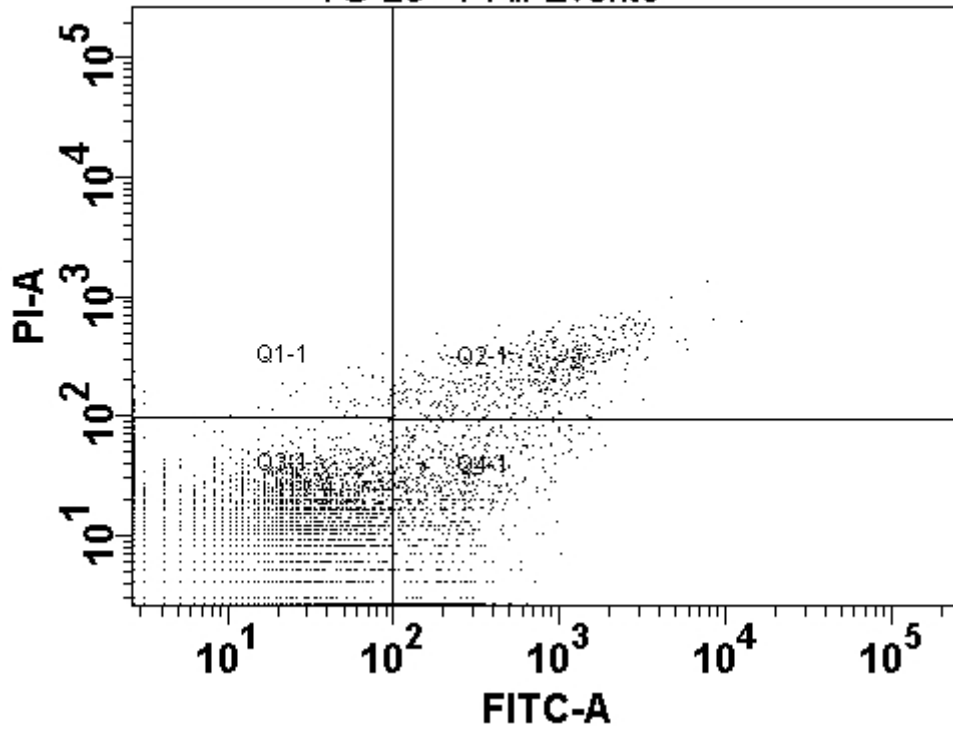
PPT 100-1-All Events

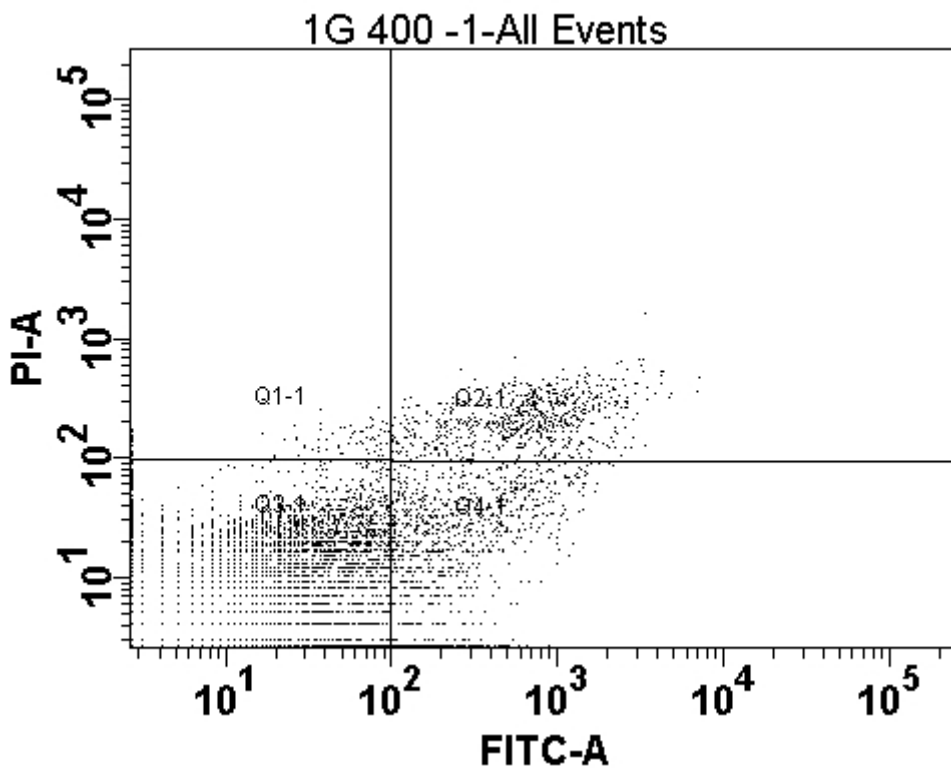
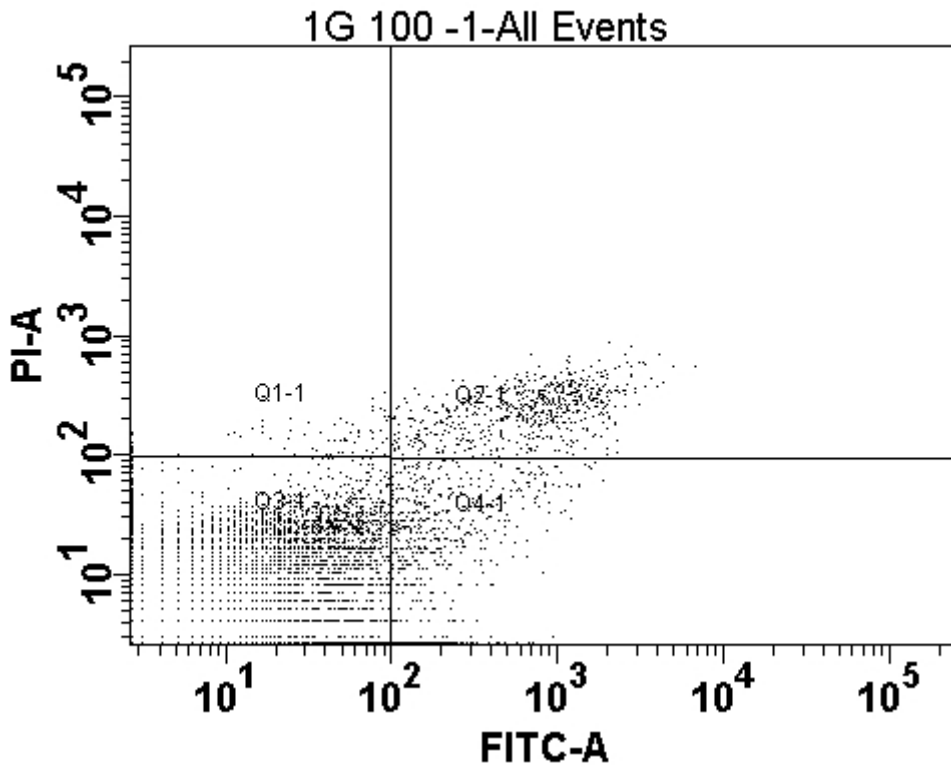


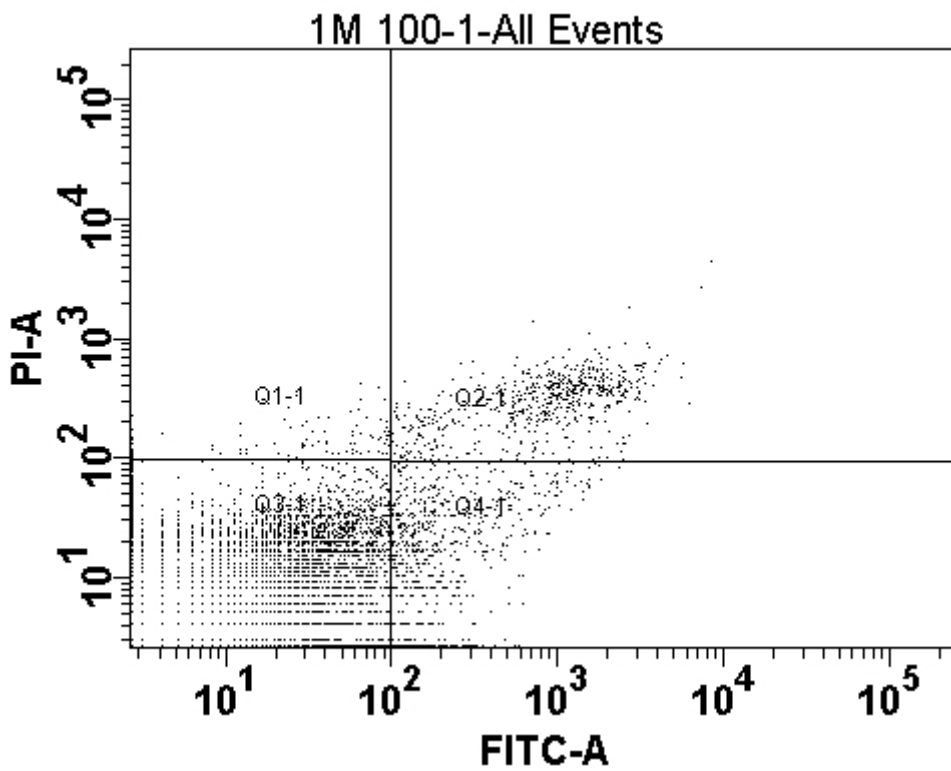
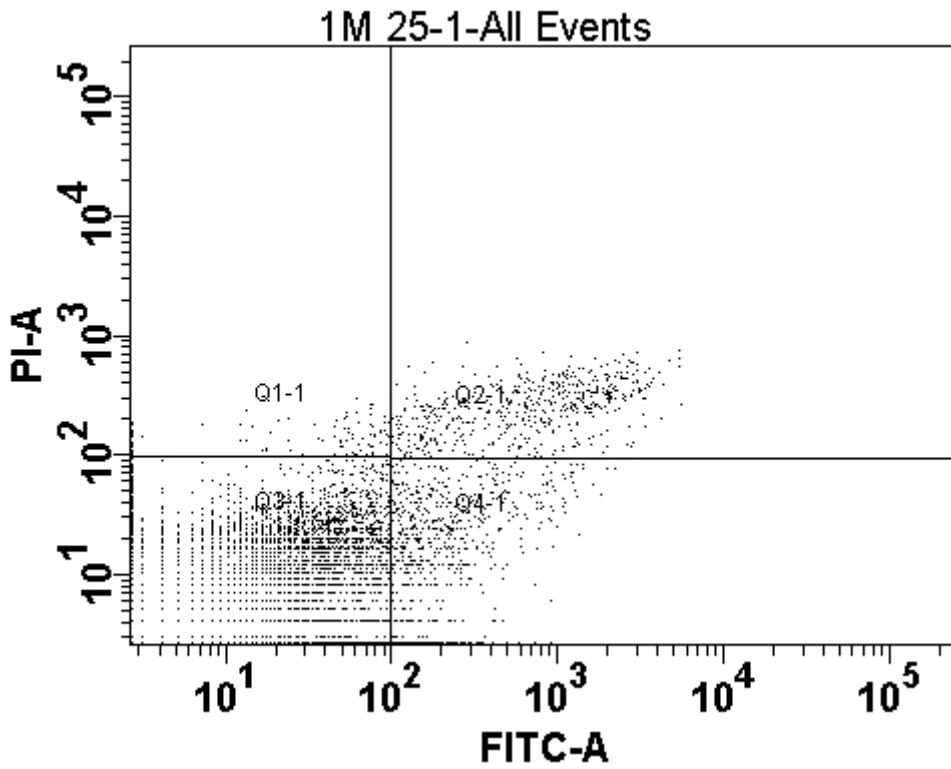
PPT 400-1-All Events

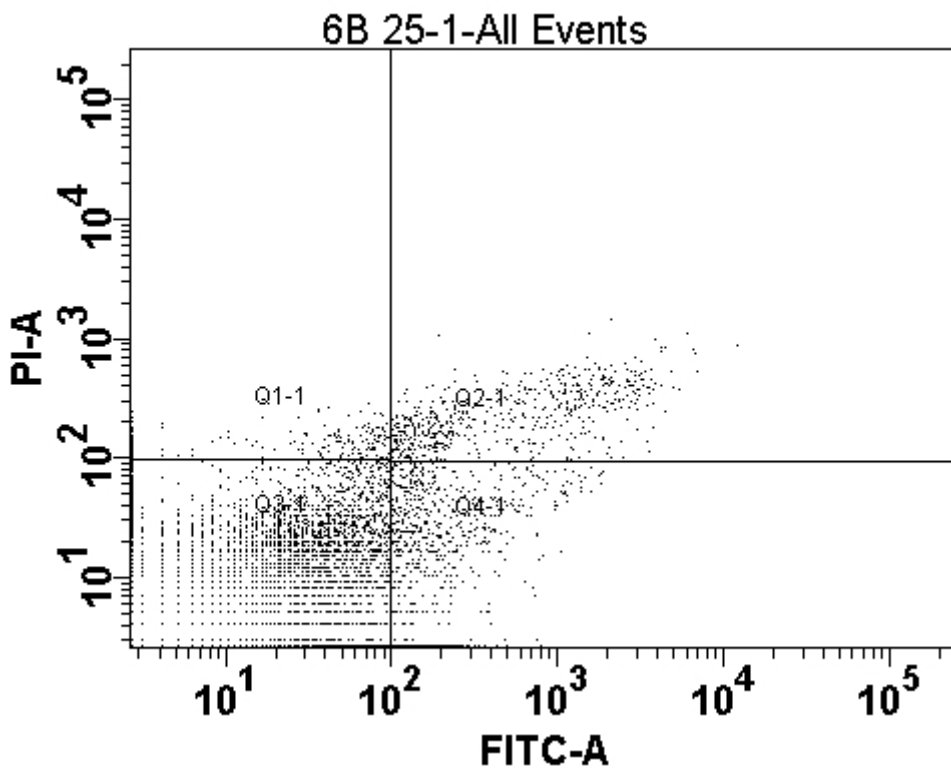
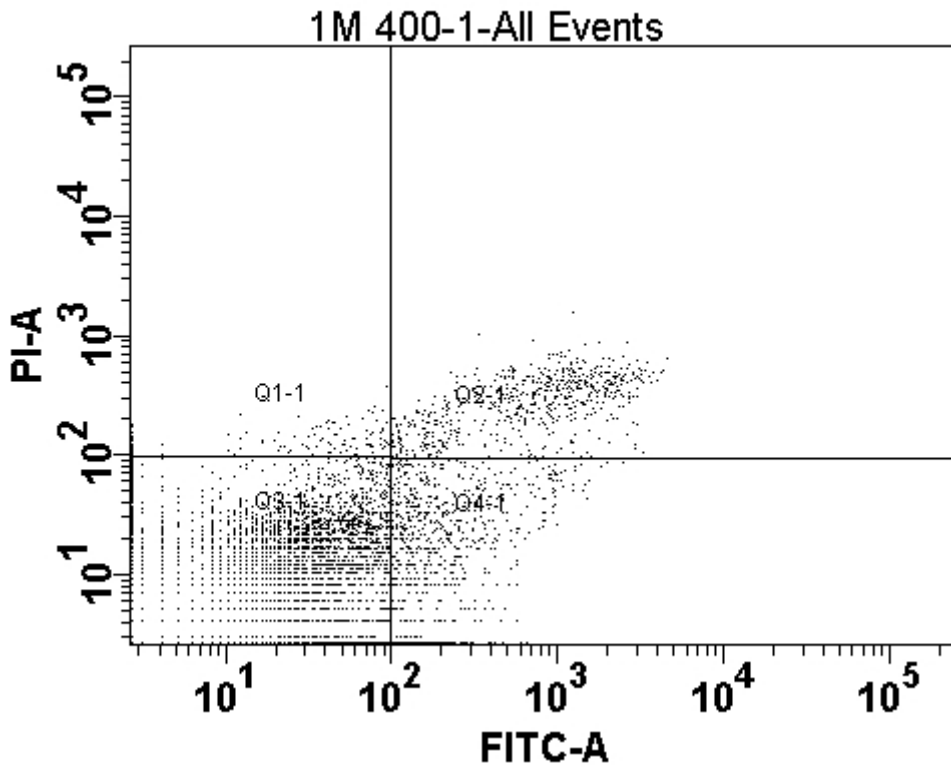


1G 25 -1-All Events

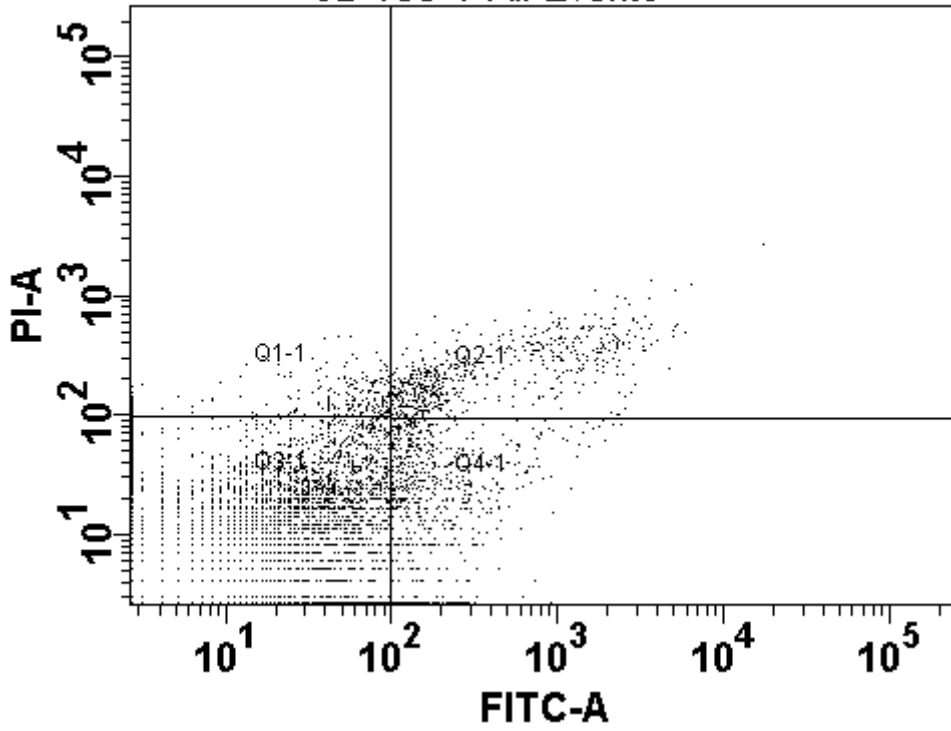




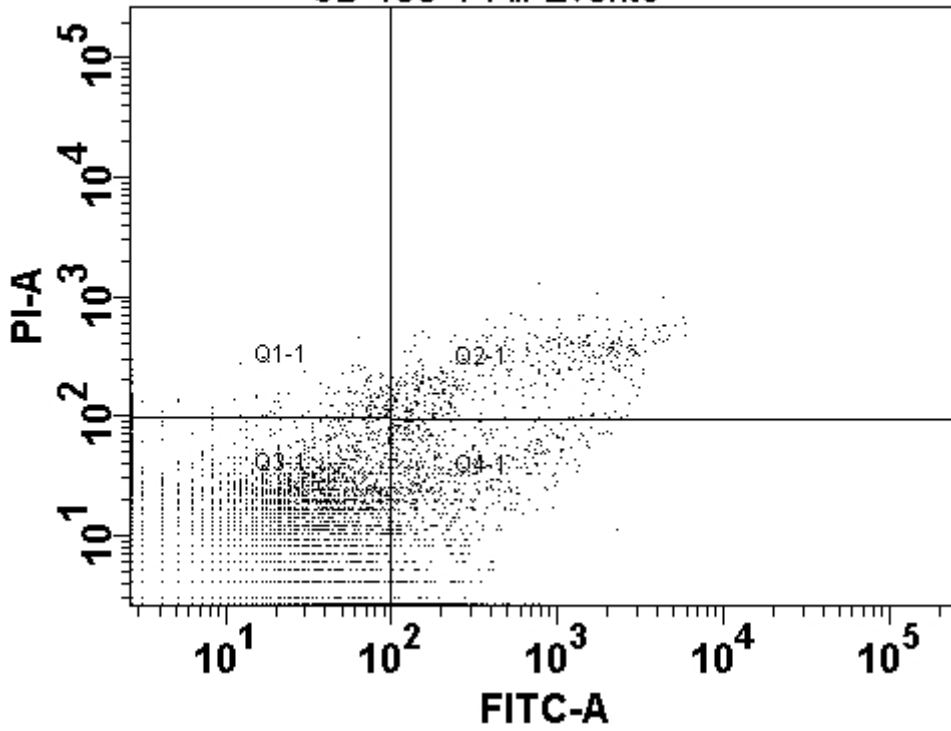




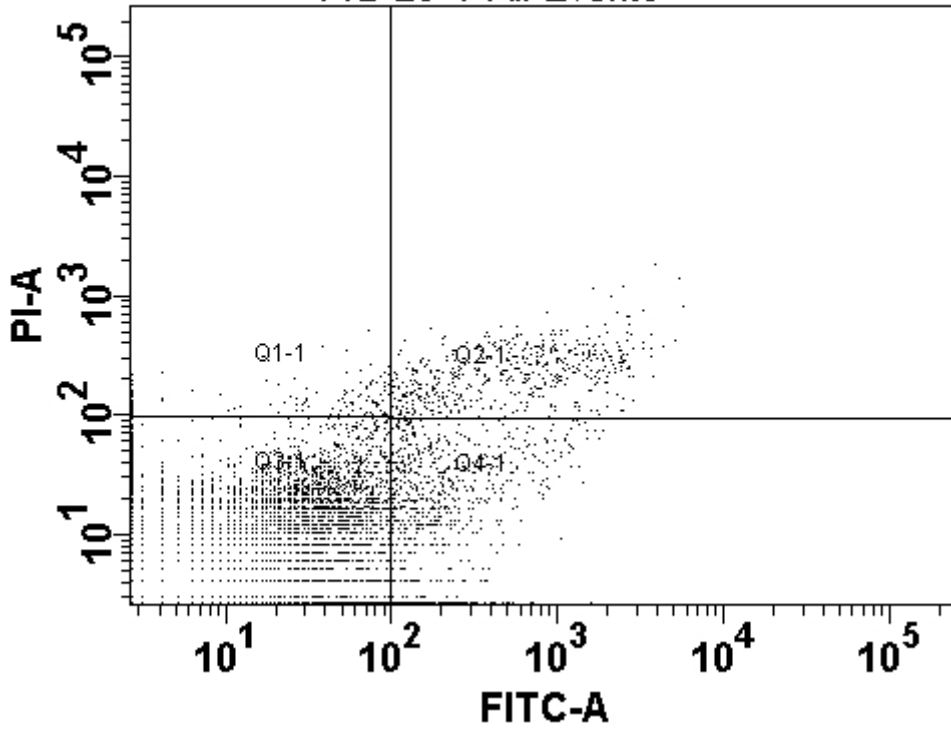
6B 100-1-All Events



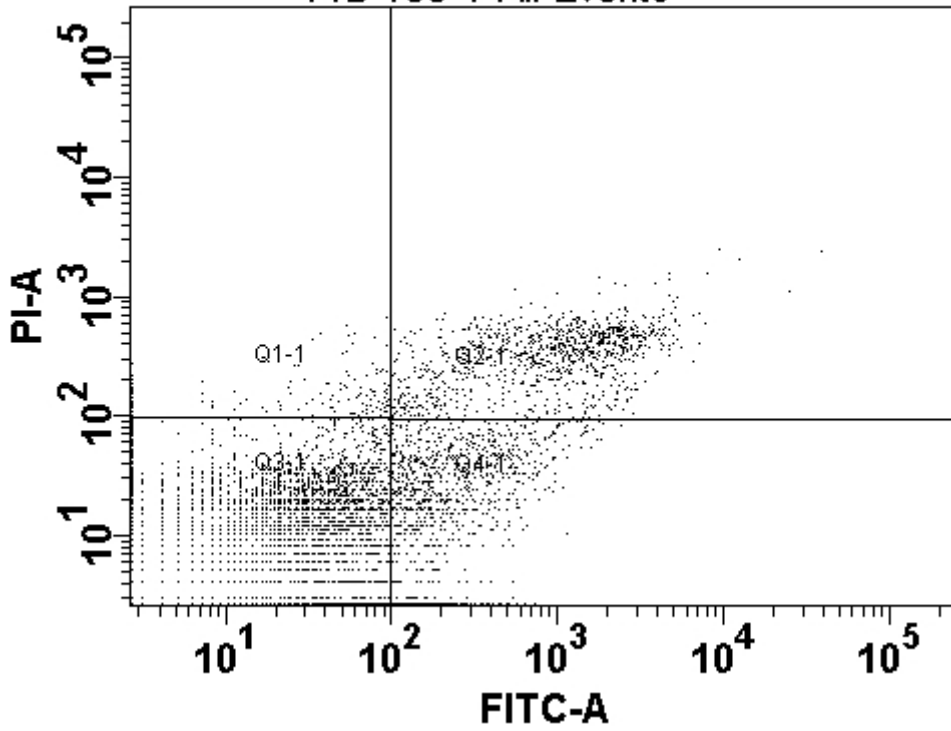
6B 400-1-All Events



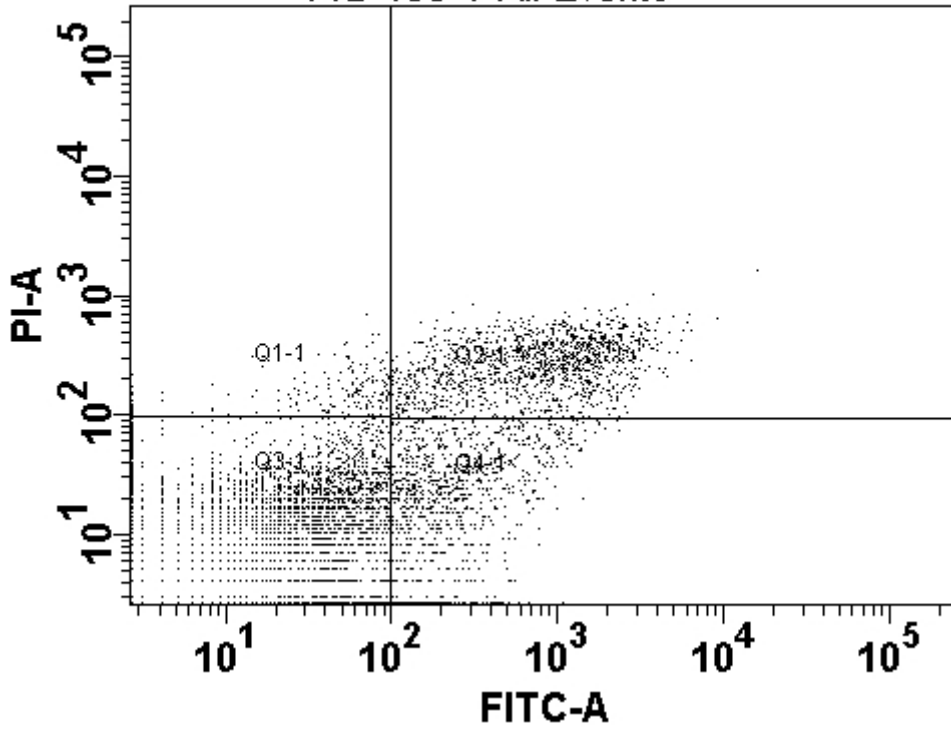
14B 25-1-All Events



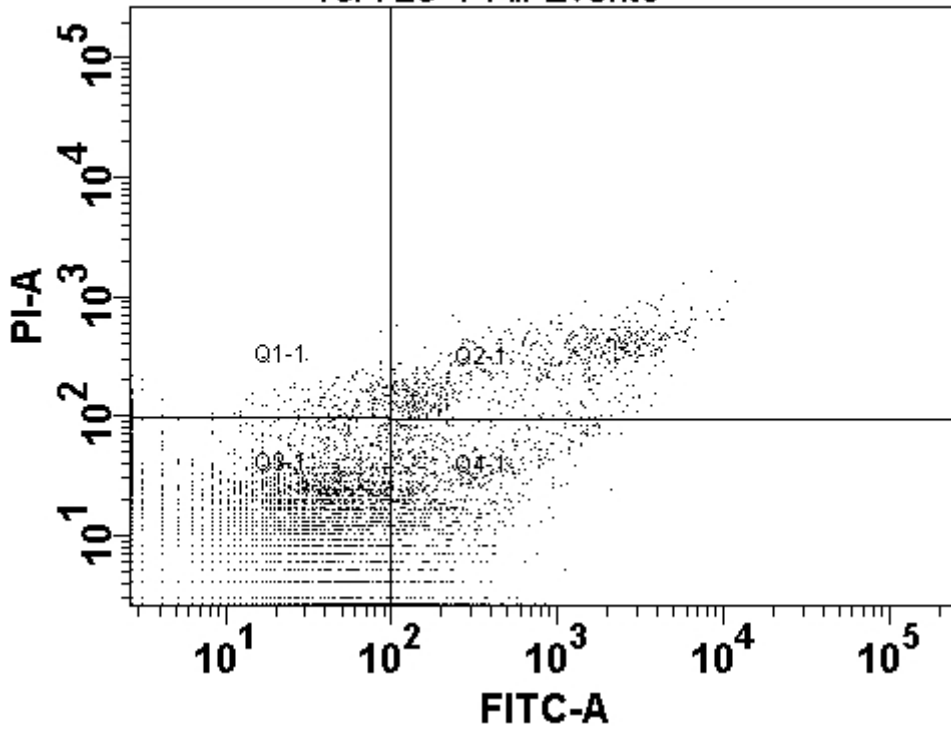
14B 100-1-All Events



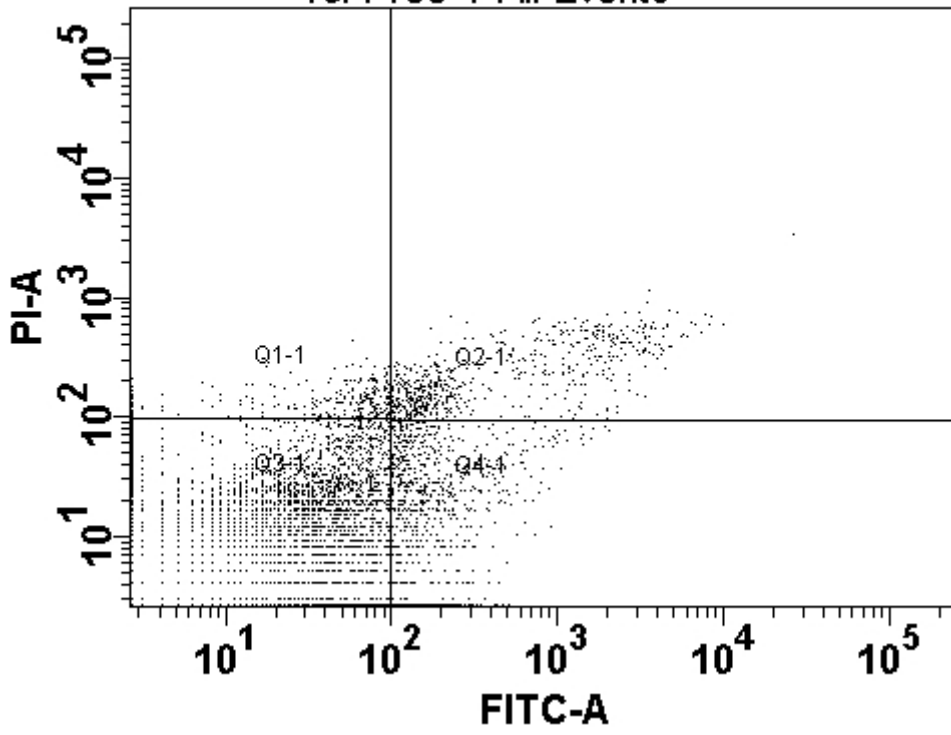
14B 400-1-All Events



19A 25-1-All Events



19A 100-1-All Events



19A 400-1-All Events

