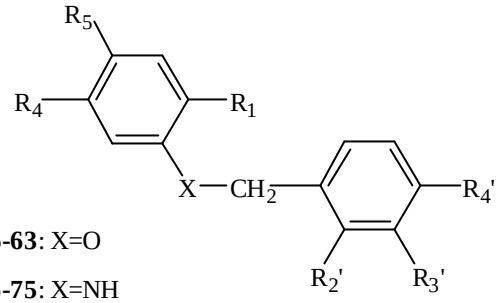
貳、嗜中性白血球脫顆粒反應之抑制活性

如 Table 2 所示，從化合物 17-44, 56-63 及 66-75 對 fMLP 所誘導的嗜中性白血球去顆粒作用之體外試驗中，由 β-Glucuronidase 或 lysozyme 的抑制百分率看來，可知化合物 17-44, 56-63 及 66-75 在嗜中性白血球去顆粒作用之體外試驗中，對 β-glucuronidase 或 lysozyme 並無明顯的抑制效果，其 IC_{50} 皆大於 30 μM。

Table 2. The inhibitory effects of compound 17-44, 56-63, 66-75 on neutrophil degranulation (*in vitro*)



17-44, 56-63: X=O

66-75: X=NH

Animal: Rat Inducer: fMLP 1 μM/5μg/ml cytochalasin B

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	Percent Release			
								β -Glucuronidase	% inh.	Lysozyme	% inh
Control								32.1±1.5		69.9±4.6	
17	CN	H	H	H	H	H	10	26.8±0.6	13.1±5.0	70.1±5.6	1.3±2.1
							30	23.5±2.1	23.6±8.9	65.1±7.6	8.7±5.3
18	CN	H	H	Cl	H	H	10	26.0±0.9	15.9±4.5	66.8±7.1	6.2±4.5
							30	21.3±0.3	30.7±6.6*	60.3±6.5	15.3±4.2
19	CN	H	H	H	Cl	H	10	27.4±2.1	11.8±3.1	70.5±5.0	0.6±1.7
							30	19.9±0.6	35.3±4.9**	60.5±6.1	15.1±3.5
20	CN	H	H	H	H	Cl	10	30.3±1.4	1.9±6.8	71.1±5.2	-0.1±3.2
							30	21.8±1.0	28.6±8.9*	60.5±6.0	14.9±4.4
21	CN	H	H	F	H	H	10	28.8±2.3	7.4±5.1	69.6±6.7	2.1±3.6
							30	23.0±1.4	25.9±3.6	60.5±6.6	14.6±7.4
22	CN	H	H	H	F	H	10	28.2±2.9	9.9±1.8	70.3±6.7	1.2±3.8
							30	22.3±2.0	28.6±1.2*	60.8±8.1	14.7±7.2
23	CN	H	H	H	H	F	10	29.7±3.0	5.2±1.7	64.5±6.4	9.3±3.7
							30	22.1±1.8	28.9±0.6*	58.5±7.0	17.9±5.1
24	CN	H	H	H	OCH_3	H	10	26.9±2.4	13.6±3.2	65.9±5.2	7.1±2.7
							30	23.4±2.5	25.1±1.7	57.4±5.3	19.2±3.0
25	CN	H	H	H	H	OCH_3	10	26.1±1.7	16.1±2.7	65.1±6.9	8.6±4.6
							30	23.1±2.3	26.1±2.3	58.3±6.0	17.9±4.5
26	CH_3	H	H	H	H	H	10	31.3±1.2	-1.5±8.4	72.1±6.2	-1.3±2.9
							30	30.9±0.8	0.01±5.9	72.6±6.2	-2.0±3.0
27	CH_3	H	H	Cl	H	H	10	34.9±3.1	-14.2±16.3	72.9±7.5	-2.3±4.4
							30	16.5±1.3	46.0±7.5**	46.1±5.0	35.3±3.4*
28	CH_3	H	H	H	Cl	H	10	30.9±0.6	0.06±6.2	69.5±6.5	2.2±3.5
							30	19.3±1.7	37.0±8.4**	60.9±3.1	13.8±2.2

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	Percent Release			
								β -Glucuronidase	% inh.	Lysozyme	% inh
29	CH_3	H	H	H	H	Cl	10	33.2±2.0	-6.7±3.4	73.5±5.3	-3.5±1.2
							30	16.5±1.3	46.2±6.9**	54.1±4.3	23.8±2.0
30	CH_2OH	H	H	H	H	H	10	30.8±2.6	4.2±3.6	68.3±4.0	2.0±4.4
							30	27.7±1.0	13.5±2.0	65.7±5.7	6.0±5.4
31	CH_2OH	H	H	Cl	H	H	10	26.2±1.7	15.6±4.1	63.4±5.6	10.9±2.6
							30	19.5±0.7	36.7±4.1**	54.4±6.3	23.7±4.3
32	CH_2OH	H	H	H	Cl	H	10	23.0±3.2	28.9±6.8*	67.1±4.0	3.9±2.0
							30	16.6±2.8	48.7±6.4**	52.6±7.3	25.2±7.9
33	CH_2OH	H	H	H	H	Cl	10	29.8±1.5	3.7±6.9	69.7±5.6	1.9±1.9
							30	24.5±2.0	21.4±3.0	60.4±5.2	15.0±2.5
34	$COOCH_3$	H	H	H	H	H	10	32.8±2.4	-5.6±5.3	66.7±5.2	6.0±1.7
							30	27.8±1.9	10.2±6.8	61.9±5.7	12.9±2.8
35	$COOCH_3$	H	H	Cl	H	H	10	27.5±1.2	14.2±0.3	63.0±6.4	10.1±4.1
							30	25.5±2.5	20.7±4.9	61.7±3.6	11.6±0.8
36	$COOCH_3$	H	H	H	Cl	H	10	29.5±0.8	7.8±2.3	59.6±4.7	14.8±3.2
							30	26.1±1.6	18.6±1.5	56.8±7.2	19.3±5.3
37	$COOCH_3$	H	H	H	H	Cl	10	20.9±1.9	35.0±3.8**	58.3±5.9	16.8±5.1
							30	17.8±1.8	44.7±3.2**	51.2±5.7	27.0±4.8
38	$COOC_2H_5$	H	H	H	H	H	10	22.7±3.6	29.9±8.0**	63.6±8.2	8.9±11.7
							30	21.0±3.2	35.1±7.1**	57.2±7.9	18.0±10.9
39	$COOC_2H_5$	H	H	Cl	H	H	10	22.1±2.9	31.6±6.0**	59.5±3.6	14.8±0.5
							30	24.4±2.6	24.3±4.6*	66.5±5.4	5.1±1.4
40	$COOC_2H_5$	H	H	H	Cl	H	10	24.0±2.2	25.4±3.5*	60.0±3.4	13.9±4.2
							30	22.9±2.7	28.9±5.3*	60.0±1.8	13.6±4.4
41	$COOC_2H_5$	H	H	H	H	Cl	10	18.9±2.6	41.7±5.6**	51.1±4.1	26.3±7.1
							30	21.4±2.5	33.7±4.8**	57.7±3.9	17.3±4.0
42	$CONH_2$	H	H	Cl	H	H	10	24.1±1.7	22.7±1.0	51.3±4.1	27.8±1.4
							30	18.4±1.2	40.8±1.0**	44.8±3.2	36.7±1.9*
43	$CONH_2$	H	H	H	Cl	H	10	27.1±1.5	12.7±2.3	59.8±4.2	15.7±0.8
							30	22.1±1.5	28.7±2.2*	47.2±1.8	33.1±1.6*
44	$CONH_2$	H	H	H	H	Cl	10	30.5±2.8	2.1±4.2	59.4±2.9	16.0±1.0
							30	24.8±2.1	20.4±3.2	44.2±3.3	37.6±2.6*
56	COOH	H	H	H	H	H	10	21.6±2.6	33.0±4.9**	61.0±6.2	12.8±6.8
							30	23.3±1.3	27.5±1.4*	63.6±5.5	8.7±8.2

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	Percent Release			
								β -Glucuronidase	% inh.	Lysozyme	% inh
57	COOH	H	H	Cl	H	H	10	21.3±3.7	34.3±8.9**	59.5±10.5	15.6±12.0
							30	17.6±3.6	45.8±8.7**	52.8±11.3	25.5±12.7
58	COOH	H	H	H	Cl	H	10	22.9±3.7	29.4±8.2**	60.0±7.9	14.7±6.6
							30	21.4±2.2	33.4±3.8**	59.0±9.2	16.1±10.1
59	COOH	H	H	H	H	Cl	10	27.0±1.7	15.9±1.6	65.3±4.9	6.7±2.0
							30	26.5±1.8	17.5±3.2	66.3±3.9	4.9±4.4
60	COOH	H	H	H	H	OCH_3	10	30.2±2.3	3.0±3.2	66.8±5.5	5.8±2.7
							30	28.7±2.3	7.8±0.4	66.0±6.0	7.0±4.1
61	COOH	H	H	H	F	H	10	27.9±2.1	10.4±1.4	67.1±6.2	5.6±3.3
							30	26.4±1.8	15.1±2.7	64.7±6.8	9.1±4.3
62	COOH	H	H	H	H	F	10	29.9±2.4	3.9±4.1	68.7±6.2	3.3±4.3
							30	28.7±2.2	7.9±1.7	67.3±7.1	5.0±5.1
63	COOH	H	H	H	OCH_3	H	10	35.2±3.8	-12.4±3.4	71.7±4.5	-1.2±3.7
							30	31.4±2.9	-0.3±1.0	68.8±5.0	3.0±2.6
66	COOH	H	H	Cl	H	H	10	28.7±2.3	7.0±10.0	62.8±5.0	11.5±1.6
							30	22.0±2.5	28.6±10.1	56.3±4.7	20.6±2.9
67	COOH	H	H	H	Cl	H	10	22.7±1.1	28.3±2.5	57.5±3.9	18.8±2.3
							30	15.7±1.3	49.6±0.4**	49.9±3.8	29.6±1.3
68	COOH	H	H	H	H	Cl	10	26.0±1.5	16.3±2.1	66.0±4.6	6.8±3.4
							30	19.1±2.1	38.9±2.1**	57.7±4.3	18.7±1.6
69	COOH	H	H	F	H	H	10	27.0±1.2	12.6±5.0	64.5±5.9	9.2±4.0
							30	23.6±2.1	24.4±0.8	61.4±6.3	13.8±3.8
70	COOH	H	H	H	F	H	10	29.1±1.1	5.7±7.4	66.7±4.3	5.8±1.9
							30	24.4±0.6	21.1±4.5	59.9±5.0	15.6±3.4
71	COOH	H	H	H	H	F	10	32.4±1.5	-4.6±5.9	69.8±4.6	1.5±1.1
							30	28.7±0.9	7.1±6.6	65.2±4.8	8.1±1.4
72	COOH	H	H	H	OCH_3	H	10	25.9±1.9	16.7±3.1	59.6±5.8	16.2±4.5
							30	20.8±1.2	32.8±4.9*	52.9±3.8	25.3±3.7
73	COOH	H	H	H	H	OCH_3	10	27.3±3.0	12.8±4.5	62.3±6.1	12.4±4.1
							30	23.7±2.4	24.2±1.3	56.7±5.7	20.4±3.7
74	COOH	OCH_3	OCH_3	H	OCH_3	H	10	34.4±3.7	-0.9±14.7	60.7±13.0	16.0±13.9
							30	32.2±6.9	-10.4±8.3	66.7±3.4	5.7±2.1
75	COOH	OCH_3	OCH_3	H	H	OCH_3	10	27.7±2.3	11.1±3.0	68.7±3.9	3.1±0.5
							30	25.3±2.5	19.0±5.0	63.5±3.7	10.3±0.8

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	Percent Release			
								β -Glucuronidase	% inh.	Lysozyme	% inh
TFP							3	33.1±0.6	-3.7±2.9	82.2±0.4	-17.8±2.8
							10	14.3±0.4	55.2±0.2**	45.0±4.3	35.3±6.3**
							30	7.4±1.1	76.7±4.0**	14.4±2.6	79.2±3.8**
IC_{50} (μM)								10.6±0.9		13.2±0.7	

* $P < 0.05$, ** $P < 0.01$; N=3

Trifluoperazine (TFP): positive control

參、嗜中性白血球過氧化物形成之抑制活性

嗜中性白血球在個體防禦病菌感染時扮演重要的角色。在受到適當的刺激時，會產生超氧自由基來殺死病原菌，但細胞過度的活化，會產生過量的超氧自由基，反而對周圍正常的組織細胞有損傷。這些細胞損傷可能與許多疾病的致病原有關，包括肺氣腫、急性呼吸困難、動脈硬化、類風濕性關節炎等疾病的發生與惡化。藥物若能抑制過多的超氧自由基產生，則有助於減少對組織的傷害。

(一) 對於fMLP誘導的嗜中性白血球超氧自由基生成作用抑制試驗

如Table 3所示，從化合物17-44, 56-63及66-75對fMLP所誘導的嗜中性白血球超氧自由基生成作用之體外抑制試驗中，由superoxide formation的抑制百分率看來，可知化合物42-44有抑制活性，效價約為trifluoperazine的二分之一。其他的化合物在fMLP所誘導的嗜中性白血球超氧自由基生成作用之體外抑制試驗中，對superoxide formation並無明顯的抑制效果，其IC_{50}皆大於30 μM。

＊ fMLP為一種趨化性物質(chemotactic peptide)為*N*-formyl-Met-Leu-Phe之簡稱，可以促使嗜中性白血球細胞去顆粒作用及超氧自由基生成作用(superoxide formation)，故fMLP可作為化合物測定抗發炎活性試驗時之誘導劑。

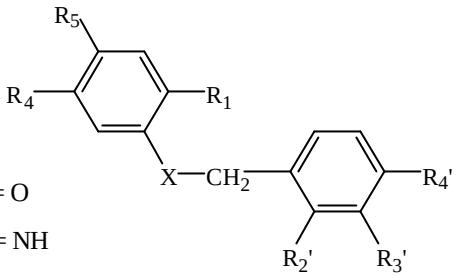
(二) 對於PMA誘導的嗜中性白血球超氧自由基生成作用抑制試驗

如Table 2所示，從化合物17-44, 56-63及66-75對以PMA誘導的嗜中性白血球超氧自由基生成作用之體外抑制試驗的抑制百分率看來，可知此系列化合物並沒有明顯的抑制效果。

＊ PMA(Phorbol 12-myristate l3-acetate diester；又稱

12-*o*-tetradecanoyl-Phorbol-13-acetate,TPA)**其能促使嗜中性白血球超氧自由基生成作用，和**fMLP**不同的是其能直接進入嗜中性白血球細胞內與細胞內接受體結合而產生超氧自由基生成作用，因此，吾人可得知抗發炎化合物產生藥理活性的作用位置。**

Table 3. The inhibitory effects of compound 17-44, 56-63, 66-75 on the neutrophil superoxide formation (*in vitro*)



17-44, 56-63: X= O

66-75: X= NH

Inducer: 0.3 μM fMLP /5μg/ml cytochalasin B

Animal: Rat

Inducer: PMA (3 nM)

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	superoxide formation (nmol/10^6 cells/30 min)			
								fMLP	% inh.	PMA	% inh
Control								2.11±0.02		6.18±0.35	
17	CN	H	H	H	H	H	10	1.89±0.19	22.9±3.2	6.27±0.23	14.3±4.5
							30	1.48±0.19	39.8±4.8**	6.07±0.04	17.1±2.6
18	CN	H	H	Cl	H	H	10	2.45±0.11	-0.7±5.1	7.04±0.20	3.7±5.9
							30	1.76±0.08	27.4±3.8	6.28±0.41	14.5±3.6
19	CN	H	H	H	Cl	H	10	2.09±0.16	14.6±2.5	5.93±0.23	18.8±5.5
							30	1.23±0.07	49.5±1.7**	6.14±0.21	16.0±4.0
20	CN	H	H	H	H	Cl	10	2.00±0.19	18.4±3.2	6.42±0.36	11.9±8.4
							30	1.38±0.10	43.5±2.9**	5.72±0.34	22.0±3.3
21	CN	H	H	F	H	H	10	2.34±0.15	3.7±5.8	6.68±0.16	8.8±2.1
							30	1.60±0.21	35.3±3.2**	7.31±0.49	0.2±7.0
22	CN	H	H	H	F	H	10	2.25±0.19	8.3±1.2	6.60±0.13	9.9±3.3
							30	1.45±0.16	41.0±2.0**	6.12±0.20	16.5±3.4
23	CN	H	H	H	H	F	10	2.17±0.20	11.4±3.7	6.42±0.31	12.0±6.8
							30	1.31±0.19	47.3±3.8**	6.15±0.44	16.0±6.4
24	CN	H	H	H	OCH_3	H	10	1.85±0.17	24.2±3.4	6.63±0.41	9.0±9.2
							30	1.28±0.15	48.0±1.9**	6.18±0.15	15.7±1.2
25	CN	H	H	H	H	OCH_3	10	2.16±0.17	11.7±3.2	6.56±0.16	10.5±1.3
							30	1.79±0.14	26.5±4.9	6.18±0.15	15.5±3.7
26	CH_3	H	H	H	H	H	10	2.22±0.05	8.0±7.8	6.00±0.34	17.6±7.9
							30	2.30±0.15	5.2±8.3	5.98±0.17	18.2±4.0
27	CH_3	H	H	Cl	H	H	10	2.35±0.06	2.7±7.5	6.67±0.26	9.0±1.1
							30	2.02±0.11	16.6±7.0	7.20±0.24	1.8±0.8
28	CH_3	H	H	H	Cl	H	10	2.53±0.16	-3.6±4.6	6.87±0.70	6.6±7.6
							30	2.08±0.10	14.2±5.8	6.07±0.40	17.2±3.5

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	superoxide formation (nmol/10^6 cells/30 min) fMLP	% inh.	PMA	% inh
29	CH_3	H	H	H	H	Cl	10	2.56±0.20	-4.8±3.6	6.82±0.31	7.1±1.5
							30	2.63±0.20	-7.3±1.9	6.88±0.27	6.2±2.9
30	CH_2OH	H	H	H	H	H	10	1.90±0.15	10.0±8.3	5.62±0.28	8.7±5.0
							30	1.44±0.12	31.6±6.4**	4.78±0.20	21.9±6.9
31	CH_2OH	H	H	Cl	H	H	10	2.13±0.21	13.5±1.7	7.33±0.70	0.4±6.6
							30	1.63±0.14	33.4±2.2*	7.48±0.14	-2.0±4.0
32	CH_2OH	H	H	H	Cl	H	10	2.09±0.05	0.8±3.1	5.58±0.75	10.3±7.6
							30	1.37±0.01	35.1±0.1**	4.55±0.39	26.6±2.7
33	CH_2OH	H	H	H	H	Cl	10	2.85±0.13	-17.4±7.7	6.59±0.17	9.9±5.1
							30	2.05±0.12	15.8±3.4	6.95±012	5.1±4.0
34	$COOCH_3$	H	H	H	H	H	10	2.07±0.27	16.0±4.5	6.17±0.10	15.7±2.3
							30	1.74±0.19	29.0±2.9*	5.73±0.23	21.4±5.9
35	$COOCH_3$	H	H	Cl	H	H	10	1.60±0.09	23.9±5.4*	5.10±0.23	16.6±7.9
							30	1.36±0.03	35.6±2.4 **	4.65±0.63	23.5±12.7
36	$COOCH_3$	H	H	H	Cl	H	10	1.78±0.04	15.5±2.9	5.78±0.72	7.0±7.3
							30	1.47±0.06	30.2±3.4**	4.96±0.36	19.8±1.3
37	$COOCH_3$	H	H	H	H	Cl	10	1.73±0.14	17.8±8.0	5.19±0.47	15.3±10.0
							30	1.18±0.13	43.9±7.0**	5.20±0.16	14.9±7.4
38	$COOC_2H_5$	H	H	H	H	H	10	1.84±0.12	12.7±6.8	5.03±0.83	19.2±10.9
							30	1.28±0.16	39.1±8.5**	4.54±0.64	26.918.3
39	$COOC_2H_5$	H	H	Cl	H	H	10	1.70±0.06	19.5±2.0	5.95±0.38	8.0±0.8
							30	1.59±0.05	24.8±3.4*	5.59±0.31	9.5±2.2
40	$COOC_2H_5$	H	H	H	Cl	H	10	1.84±0.06	12.8±3.8	5.06±0.96	18.6±14.1
							30	1.78±0.06	15.5±3.6	4.80±0.93	22.7±13.9
41	$COOC_2H_5$	H	H	H	H	Cl	10	1.90±0.07	9.8±4.2	5.47±0.56	11.9±4.6
							30	1.80±0.04	12.6±1.4	5.22±0.35	15.1±6.0
42	$CONH_2$	H	H	Cl	H	H	3	1.66±0.20	32.0±2.8*	--	
							10	1.15±0.23	53.3±5.1**	6.60±0.23	9.9±1.9
							30	1.09±0.22	55.8±3.8**	6.93±0.43	5.7±3.6
IC_{50} (μM)								14.7±2.9			
43	$CONH_2$	H	H	H	Cl	H	3	1.93±0.19	20.4±4.9	--	
							10	1.37±0.16	43.9±1.0**	6.18±0.42	15.7±5.6
							30	0.93±0.18	62.2±4.1**	5.86±0.22	19.8±4.9
IC_{50} (μM)								15.0±2.2			

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	superoxide formation (nmol/10^6 cells/30 min) fMLP	% inh.	PMA	% inh
44	$CONH_2$	H	H	H	H	Cl	3	2.04±0.12	14.6±8.5	--	
							10	1.11±0.11	53.1±6.8**	6.14±0.07	16.1±2.4
							30	0.67±0.08	71.6±4.8**	6.42±0.55	12.5±6.9
IC_{50} (μM)								20.7±9.8			
56	COOH	H	H	H	H	H	10	1.86±0.15	11.4±8.6	5.91±0.52	4.4±6.1
							30	1.57±0.06	25.4±3.8*	5.18±0.38	15.7±7.0
57	COOH	H	H	Cl	H	H	10	1.59±0.10	24.8±5.3*	5.66±0.20	7.9±5.8
							30	1.12±0.16	46.6±8.3**	4.93±0.70	20.9±6.6
58	COOH	H	H	H	Cl	H	10	1.67±0.20	20.7±10.2	5.54±0.70	10.7±7.4
							30	1.16±0.08	45.1+3.5**	4.96±0.55	19.9±6.7
59	COOH	H	H	H	H	Cl	10	1.67±0.27	20.3±13.7	5.39±0.50	12.9±4.1
							30	1.61±0.02	23.6+1.8*	5.44±0.39	11.7±6.2
60	COOH	H	H	H	H	OCH_3	10	2.04±0.22	17.3±2.2	6.21±0.26	15.4±1.1
							30	1.68±0.19	31.6±2.9*	5.90±0.38	19.7±2.4
61	COOH	H	H	H	F	H	10	2.07±0.17	15.4±2.3	6.25±0.28	14.9±1.9
							30	1.76±0.22	28.7±3.2*	5.33±0.20	27.2±3.8
62	COOH	H	H	H	H	F	10	2.17±0.27	12.0±3.6	6.33±0.25	14.1±2.1
							30	2.11±0.25	14.5±4.2	6.05±0.14	17.4±1.4
63	COOH	H	H	H	OCH_3	H	10	2.04±0.24	17.4±2.6	6.40±0.32	12.8±1.7
							30	1.71±0.27	30.9±6.3*	6.22±0.32	15.2±2.5
66	COOH	H	H	Cl	H	H	10	2.38±0.35	4.2±7.3	8.21±0.71	-11.7±7.5
							30	1.83±0.23	25.7±3.5	8.41±0.51	-14.4+3.8
67	COOH	H	H	H	Cl	H	3	2.28±0.23	5.9±3.0	--	
							10	1.89±0.10	21.8±4.8	8.09±0.67	-9.7±5.8
							30	1.15±0.20	53.1±4.4**	8.38±0.56	-13.9±3.6
IC_{50} (μM)								29.1±3.7			
68	COOH	H	H	H	H	Cl	10	2.59±0.35	-4.7±6.5	7.93±0.52	-7.7±3.5
							30	1.89±0.38	23.9±11.1	7.93±0.71	-7.6±6.1
69	COOH	H	H	F	H	H	10	2.36±0.28	4.3±4.7	6.93±0.50	5.8±3.6
							30	2.07±0.33	16.9±7.1	7.67±0.51	-4.4±5.0
70	COOH	H	H	H	F	H	10	2.34±0.27	5.1±4.1	6.63±0.49	9.9±3.7
							30	1.80±0.19	27.0±1.8	7.05±0.05	3.6±4.3
71	COOH	H	H	H	H	F	10	2.50±0.29	-1.4±3.1	6.65±0.23	9.3+0.4
							30	2.18±0.24	10.9±6.0	6.09±0.27	17.0±1.4

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	superoxide formation (nmol/10^6 cells/30 min) fMLP	% inh.	PMA	% inh
72	COOH	H	H	H	OCH_3	H	10	2.14±0.19	12.8±0.7	6.74±0.43	8.2±4.1
							30	1.73±0.15	29.1±1.0*	6.94±0.49	5.6±3.6
73	COOH	H	H	H	H	OCH_3	10	2.50±0.31	-0.9±4.5	7.68±0.27	-4.7±2.0
							30	2.28±0.23	7.1±1.5	7.84±0.53	-6.5±3.9
74	COOH	OCH_3	OCH_3	H	OCH_3	H	10	2.24±0.18	8.4±2.0	6.29±0.32	14.2±3.4
							30	1.74±0.17	29.0±4.2*	6.22±0.54	15.6±4.6
75	COOH	OCH_3	OCH_3	H	H	OCH_3	10	2.28±0.31	7.7±6.5	6.60±0.31	9.9±3.7
							30	1.78±0.20	27.8±2.5	6.21±0.15	15.3±0.9
TFP							1	--		4.46±0.13	27.6±4.2
							3	2.05±0.27	1.7±6.6	2.77±0.13	55.4±9.4**
							5	1.57±0.09	24.2±5.3*	--	
							10	0.40±0.22	79.5±4.2**	1.03±0.16	83.3±5.8**
IC_{50} (μM)								6.6±0.2		2.7±0.6	

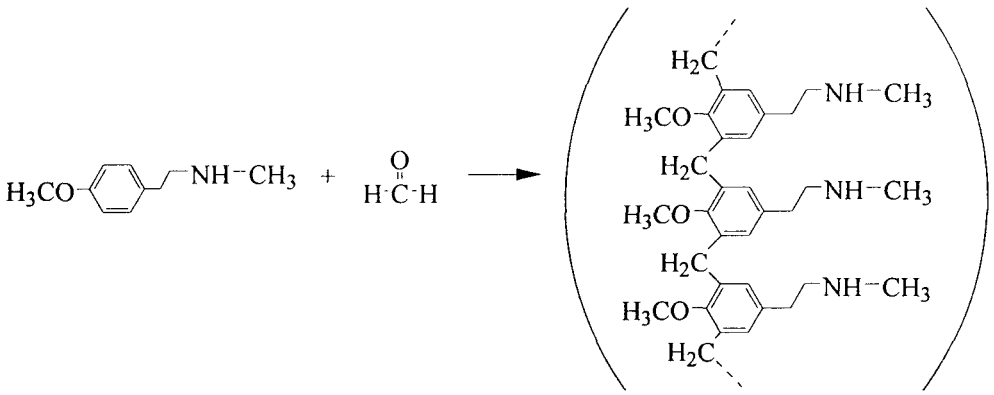
* $P < 0.05$, ** $P < 0.01$; N=3; --: not determined

Trifluoperazine (TFP): positive control

肆、肥胖細胞脫顆粒反應之抑制活性

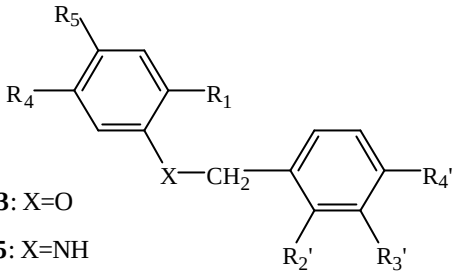
如 Table 4 所示，從化合物 17-44, 56-63 及 66-75 對以 compound 48/80 誘導的肥胖細胞脫顆粒作用之體外試驗中，由 β-Glucuronidase 及 histamine 的抑制百分率看來，可知化合物 17-44, 56-63 及 66-75 在肥胖細胞脫顆粒作用之體外試驗中對 β-Glucuronidase 及 histamine 並無明顯的抑制效果，其 IC_{50} 皆大於 30 μM。

＊ Compound 48/80 為 *N*-methyl-*p*-methoxy-phenethylamine 與甲醛 (formaldehyde)之縮合 polymer，其主要之藥理作用是促使肥胖細胞釋放 histamine，故可作為化合物測定抗過敏活性試驗時之誘導劑。



Compound 48/80

Table 4. The inhibitory effects of compound 17-44, 56-63, 66-75 on the mast cell degranulation (*in vitro*)



17-44, 56-63: X=O

66-75: X=NH

Animal: Rat Inducer: Compound 48/80 (10μg/ml)

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	Percent Release			
								β -Glucuronidase	% inh.	Histamine	% inh
Control								50.4±0.5		67.1±1.0	
17	CN	H	H	H	H	H	10	40.4±0.5	19.5±2.4	47.2±1.5	12.2±2.1
							30	38.9±0.6	22.4±2.2*	47.5±4.8	12.0±7.0
18	CN	H	H	Cl	H	H	10	43.1±1.1	14.2±2.7	55.7±4.2	-3.3±5.3
							30	42.6±1.2	15.1±1.6	54.6±4.5	-1.1±5.7
19	CN	H	H	H	Cl	H	10	40.2±0.4	20.0±1.2	50.3±2.8	6.6±3.0
							30	33.9±1.3	32.5±1.6**	47.7±3.0	11.4±3.6
20	CN	H	H	H	H	Cl	10	37.2±1.4	25.7±3.2*	48.8±2.7	9.2±3.5
							30	32.2±0.1	35.9±0.8**	45.2±3.4	16.1±4.3
21	CN	H	H	F	H	H	10	47.6±2.8	5.2±5.8	52.3±2.7	2.8±3.6
							30	43.2±2.9	13.8±7.2	55.3±4.5	-2.7±6.3
22	CN	H	H	H	F	H	10	52.6±3.0	-4.6±5.4	52.5±1.5	2.2±0.9
							30	47.1±2.6	5.9±6.7	54.2±5.3	-0.5±8.3
23	CN	H	H	H	H	F	10	56.5±5.4	-12.3±7.5	54.7±2.3	-1.6±2.0
							30	53.8±2.1	-7.1±4.5	51.2±3.3	4.9±4.1
24	CN	H	H	H	OCH_3	H	10	38.9±0.5	22.5±2.3*	54.3±5.9	-0.5±8.4
							30	35.3±0.2	29.6±1.5**	46.6±3.9	13.5±5.2
25	CN	H	H	H	H	OCH_3	10	41.3±1.3	17.6±3.2	54.5±4.2	-1.0±5.3
							30	42.3±2.7	15.5±6.8	60.0±7.0	-11.0±10.2
26	CH_3	H	H	H	H	H	10	51.0±4.2	-1.5±8.5	52.4±1.9	2.5±1.7
							30	47.1±1.9	6.2±3.9	53.6±2.6	0.5±2.2
27	CH_3	H	H	Cl	H	H	10	54.5±3.0	-8.2±4.4	51.7±1.2	3.7±1.8
							30	53.6±5.8	-6.7±11.5	53.5±3.0	0.7±3.0
28	CH_3	H	H	H	Cl	H	10	43.1±0.8	14.2±2.2	56.6±4.0	-5.0±4.7
							30	44.2±3.4	12.0±7.0	52.7±5.4	2.3±7.7

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	Percent Release			
								β -Glucuronidase	% inh.	Histamine	% inh
29	CH_3	H	H	H	H	Cl	10	42.2±0.9	16.0±1.5	58.2±2.3	-8.2±2.8
							30	42.1±3.2	16.1±6.6	55.0±3.2	-2.0±3.3
30	CH_2OH	H	H	H	H	H	10	44.8±4.7	11.0±8.7	62.8±1.5	6.4±2.2
							30	45.5±0.7	9.7±0.4	59.6±0.5	11.0±1.5
31	CH_2OH	H	H	Cl	H	H	10	45.6±1.8	9.1±4.2	57.3±4.7	-6.3±6.0
							30	43.2±4.2	13.6±9.9	55.4±5.7	-2.8±8.9
32	CH_2OH	H	H	H	Cl	H	10	46.3±1.6	8.1±2.7	65.8±3.9	2.1±4.3
							30	39.3±0.6	22.0±2.1	56.8±1.1	15.2±0.4
33	CH_2OH	H	H	H	H	Cl	10	48.1±2.0	4.2±3.9	54.5±4.1	-1.2±5.9
							30	41.4±1.1	17.5±3.1	52.3±3.9	2.9±4.7
34	$COOCH_3$	H	H	H	H	H	10	60.4±4.2	-20.2±7.9	56.5±3.7	-4.9±4.3
							30	53.1±2.9	-5.7±5.6	53.0±2.7	1.5±2.9
35	$COOCH_3$	H	H	Cl	H	H	10	50.4±2.6	-0.0±4.2	63.1±2.1	5.9±3.1
							30	43.8±1.7	13.0±2.4	60.4±2.6	10.0±3.5
36	$COOCH_3$	H	H	H	Cl	H	10	47.2±2.0	6.3±2.9	60.4±1.1	9.8±2.5
							30	42.3±2.4	15.9±4.0	59.5±1.1	11.3±0.3
37	$COOCH_3$	H	H	H	H	Cl	10	45.7±3.0	9.3±5.0	68.0±2.9	-1.3±2.9
							30	43.6±2.6	13.6±4.3	61.8±2.0	7.9±1.7
38	$COOC_2H_5$	H	H	H	H	H	10	43.8±0.8	13.1±1.6	66.9±2.8	0.3±2.6
							30	44.1±5.4	12.5±10.0	60.0±0.9	10.5±1.5
39	$COOC_2H_5$	H	H	Cl	H	H	10	46.8±2.7	7.0±5.0	67.8±0.1	-1.1±1.7
							30	49.7±4.0	1.4±7.8	64.8±1.7	3.5±1.6
40	$COOC_2H_5$	H	H	H	Cl	H	10	45.2±2.7	10.2±4.9	63.1±1.9	6.0±1.5
							30	40.1±1.8	20.3±4.5	63.7±0.5	5.0±0.8
41	$COOC_2H_5$	H	H	H	H	Cl	10	45.0±3.1	10.7±5.3	60.1±1.2	10.3±2.6
							30	39.7±4.2	21.3±8.1	60.7±2.6	9.7±2.4
42	$CONH_2$	H	H	Cl	H	H	10	41.9±1.4	16.5±3.5	45.5±0.8	15.1±2.7
							30	37.8±0.7	24.6±2.6*	43.9±0.6	18.1±2.6
43	$CONH_2$	H	H	H	Cl	H	10	46.8±0.8	6.7±1.8	52.5±2.7	2.3±4.4
							30	41.2±0.7	17.9±0.3	40.1±0.3	14.0±2.0
44	$CONH_2$	H	H	H	H	Cl	10	40.0±0.2	20.3±1.0	47.9±1.4	10.8±3.3
							30	36.1±0.3	28.1±1.3**	45.5±0.1	15.1±2.3
56	COOH	H	H	H	H	H	10	45.1±1.7	10.3±3.7	66.6±1.8	0.7±1.7
							30	45.5±1.9	9.7±3.0	63.9±3.0	4.8±3.2

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	Percent Release			
								β -Glucuronidase	% inh.	Histamine	% inh
57	COOH	H	H	Cl	H	H	10	46.4±3.0	7.9±4.8	65.2±4.2	2.9±4.8
							30	45.2±1.1	10.2±1.5	63.4±1.0	5.4±1.4
58	COOH	H	H	H	Cl	H	10	46.7±1.9	7.4±2.8	65.5±1.8	2.4±1.4
							30	45.1±2.5	10.5±4.0	63.0±1.7	6.1±1.2
59	COOH	H	H	H	H	Cl	10	48.0±2.9	4.7±4.7	65.1±2.3	3.1±1.9
							30	45.8±2.4	9.2±3.9	61.1±3.5	8.9±3.7
60	COOH	H	H	H	H	OCH_3	10	45.8±2.6	8.7±5.0	54.0±3.3	-0.2±3.5
							30	43.2±1.3	13.9±3.1	56.0±7.5	-3.6±11.5
61	COOH	H	H	H	F	H	10	44.5±1.2	11.2±3.1	54.3±3.4	-0.8±3.8
							30	42.7±0.8	14.9±1.8	54.0±4.3	-0.1±5.4
62	COOH	H	H	H	H	F	10	51.1±2.9	-1.8±6.2	55.4±4.6	-2.6±6.0
							30	43.3±0.9	13.7±2.6	51.9±4.2	3.7±5.3
63	COOH	H	H	H	OCH_3	H	10	70.2±4.0	-39.6±6.4	50.9±1.8	5.3±1.7
							30	63.1±1.9	-25.6±2.0	56.0±3.8	-3.9±4.5
66	COOH	H	H	Cl	H	H	10	48.4±0.9	3.6±0.5	63.3±1.3	-17.9±1.5
							30	43.5±1.5	13.2±3.0	67.2±0.7	-25.1±3.2
67	COOH	H	H	H	Cl	H	10	43.8±0.5	12.7±2.6	57.9±1.1	-7.6±1.7
							30	45.6±0.5	9.2±1.6	63.0±2.0	-17.2±1.6
68	COOH	H	H	H	H	Cl	10	46.0±1.2	8.4±3.2	57.5±0.4	-7.0±2.1
							30	42.9±1.1	14.5±1.4	60.3±2.5	-12.0±1.7
69	COOH	H	H	F	H	H	10	68.5±3.0	-36.1±4.3	64.6±3.1	-20.0±2.6
							30	62.8±2.9	-24.8±3.7	74.3±5.0	-38.8±13.0
70	COOH	H	H	H	F	H	10	46.2±1.3	7.8±3.4	61.6±0.8	-14.6±2.1
							30	46.3±3.5	7.7±7.6	62.9±1.0	-17.2±3.9
71	COOH	H	H	H	H	F	10	48.9±1.0	2.5±3.3	59.6±1.1	-11.0±2.0
							30	46.2±0.7	8.0±0.8	61.4±0.8	-14.4±2.1
72	COOH	H	H	H	OCH_3	H	10	54.8±3.0	-9.0±5.6	77.7±5.9	-44.2±7.3*
							30	48.5±0.1	3.4±1.6	66.2±6.2	-23.5±12.7
73	COOH	H	H	H	H	OCH_3	10	63.5±3.5	-26.2±6.1	71.1±6.8	-31.8±9.8
							30	57.7±1.7	-14.9±2.7	68.7±2.4	-27.8±3.2
74	COOH	OCH_3	OCH_3	H	OCH_3	H	10	46.6±0.4	7.2±0.6	54.8±0.4	-2.0±2.0
							30	47.6±1.7	5.2±2.2	54.7±1.3	-1.8±2.3
75	COOH	OCH_3	OCH_3	H	H	OCH_3	10	47.8±0.7	4.8±2.7	51.0±2.0	5.0±4.0
							30	46.2±0.6	7.9±1.6	51.1±1.0	4.7±2.5

Compound	R_1	R_4	R_5	R_2'	R_3'	R_4'	Conc. (μM)	Percent Release			
								β -Glucuronidase	% inh.	Histamine	% inh
mepacrine							3	35.4±1.0	29.5±1.9*	50.8±2.8	24.2±3.1
							10	24.5±2.4	51.0±5.1**	43.0±2.6	35.5±3.2*
							30	20.0±1.4	59.8±3.3**	30.3±1.9	54.5±2.2**
IC_{50} (μM)								13.7±3.2		23.3±3.0	

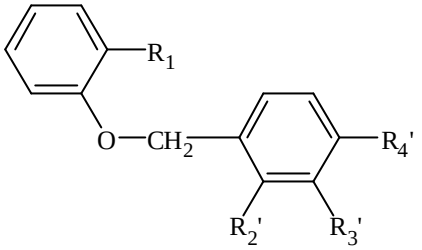
* $P < 0.05$, ** $P < 0.01$; N=3

mepacrine: positive control

伍、一氧化氮蓄積之抑制活性

如 Table 5 所示，從化合物 30, 32, 35-41 及 56-59 對以 LPS 刺激細胞培養液(cell line: RAW 264.7 cells)，亞硝酸鹽蓄積作用之體外試驗中，以及對 LPS 10 + IFN-? 刺激細胞培養液(cell line: N9 cells)，亞硝酸鹽蓄積作用之體外試驗中，由 nitrite accumulation 的抑制百分率看來，可知化合物 30, 32, 35-41 及 56-59 在亞硝酸鹽蓄積作用之體外試驗中，對 nitrite accumulation 並無明顯的抑制效果，其 IC_{50} 皆大於 30 μM。

Table 5. The inhibitory effects of compound 30, 32, 35-41, 56-59 on accumulation of nitrite in medium



Cell line: RAW 264.7 cells Inducer: LPS 1 μg/ml

Cell line: N9 cells Inducer: LPS 10 ng/ml + IFN-? 10 U/ml

Compound	R_1	R_2'	R_3'	R_4'	Conc. (μM)	Nitrite accumulation (μ M)			
						RAW	% inh.	N9	% inh.
Control						41.2±0.2		38.2±0.1	
30	CH_2OH	H	H	H	10	42.4±0.4	-2.4±0.5	33.9±0.6	11.2±1.4
					30	40.1±1.1	3.1±2.3	32.2±0.5	15.6±1.2*
32	CH_2OH	H	Cl	H	10	44.2±1.0	-6.7±3.0	33.5±0.7	12.2±2.0
					30	37.8±0.5	8.5±0.8	26.7±0.6	29.9±1.6**
35	$COOCH_3$	Cl	H	H	10	45.4±0.3	-9.6±1.1	29.2±0.9	23.5±2.4**
					30	46.6±0.1	-12.6±0.4	26.6±0.6	30.3±1.7**
36	$COOCH_3$	H	Cl	H	10	43.1±0.4	-4.1±1.5	31.2±0.5	18.2±1.5*
					30	44.7±0.2	-8.1±1.0	29.6±0.4	22.4±1.2**
37	$COOCH_3$	H	H	Cl	10	43.7±0.1	-5.4±1.0	27.1±0.5	29.0±1.5**
					30	43.2±0.7	-4.4±1.4	25.7±0.3	32.7±0.9**
38	$COOC_2H_5$	H	H	H	10	40.2±0.6	2.8±1.0	34.7±0.5	9.2±1.3
					30	44.6±0.7	-7.7±1.7	33.3±0.9	12.9±2.5
39	$COOC_2H_5$	Cl	H	H	10	41.1±0.9	0.7±2.1	30.7±0.3	19.5±0.9**
					30	41.5±0.1	-0.3±0.5	25.7±0.6	32.6±1.5**
40	$COOC_2H_5$	H	Cl	H	10	42.2±0.3	-1.9±1.0	30.3±0.1	20.8±0.1**
					30	43.1±0.7	-4.0±1.4	26.7±0.6	30.1±1.4**
41	$COOC_2H_5$	H	H	Cl	10	45.8±1.1	-10.7±3.3	30.1±2.4	21.1±6.4**
					30	42.5+0.7	-2.6±2.2	28.9±0.6	24.3±1.4**
56	COOH	H	H	H	10	41.2±0.3	0.4±0.9	38.4±1.0	-0.5±2.6
					30	40.7±0.5	1.7±0.8	38.6±0.7	-0.8±1.9
57	COOH	Cl	H	H	10	41.3±0.9	0.2±2.7	36.3±0.7	4.9±1.9
					30	39.1±1.4	5.5±3.9	36.0±0.7	5.7±1.8
58	COOH	H	Cl	H	10	39.4±0.8	4.9±1.6	36.1±0.5	5.5±1.5
					30	34.7±1.5	16.3±3.4**	34.9±1.5	8.6±3.9

Compound	R_1	R_2'	R_3'	R_4'	(μM)	Nitrite accumulation (μ M)			
						RAW	% inh.	N9	% inh.
59	COOH	H	H	Cl	10	40.8±1.2	1.3±2.6	38.8±0.2	-1.5±0.5
					30	37.1±0.2	10.3±0.2	35.7±1.4	6.6±4.0
1400W					3	33.1±2.1	20.0±5.5**	23.7±0.9	37.9±2.3**
					10	19.3±0.5	53.2±1.1**	16.2±0.7	57.6±1.9**
					30	8.1±0.3	80.2±0.8**	12.1±0.3	68.2±0.7**
IC_{50} (μM)						2.9±0.2		2.2±0.1	

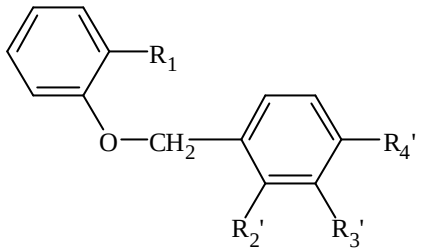
* $P < 0.05$, ** $P < 0.01$; N=3;

N- (3-Aminomethyl) benzylacetamidine (1400W): positive control

陸、TNF-α形成之抑制活性

如 Table 6 所示，從化合物 30, 32, 35-41 及 56-59 對以 LPS 刺激細胞培養液(cell line: RAW 264.7 cells) TNF-α形成作用之體外試驗中，以及對 LPS 10 + IFN-?刺激細胞培養液(cell line: N9 cells) TNF-α形成作用之體外試驗中，由 TNF-a formation 的抑制百分率看來，可知化合物 30, 32, 35-41 及 56-59 在 TNF-α形成作用之體外試驗中，對 TNF-a formation 並無明顯的抑制效果，其 IC_{50} 皆大於 30μM。

Table 6. The inhibitory effects of compound 30, 32, 35-41, 56-59 on TNF-a formation in medium



Cell line: RAW 264.7 cells Inducer: LPS 1 μg/ml

Cell line: N9 cells Inducer: LPS 1 μg/ml + IFN-? 10 U/ml

Compound	R_1	R_2'	R_3'	R_4'	Conc. (μM)	TNF-a formation (ng/ml) RAW	% inh.	N9	% inh.
Control						129.6±6.2		1.90±0.04	
30	CH_2OH	H	H	H	30	150.3±12.0	-15.1±11.2	1.82±0.14	4.4±5.3
32	CH_2OH	H	Cl	H	30	159.9±14.1	-22.8±5.2	1.00±0.04	47.2±0.8**
35	$COOCH_3$	Cl	H	H	30	76.2±3.9	41.2±0.5**	1.24±0.03	34.7±0.2**
36	$COOCH_3$	H	Cl	H	30	108.1±8.5	16.8±3.7	1.20±0.04	36.7±1.5**
37	$COOCH_3$	H	H	Cl	30	92.2±9.0	29.1±3.5**	1.03±0.04	45.6±1.2**
38	$COOC_2H_5$	H	H	H	30	149.8±3.7	-15.8±2.6	1.63±0.06	13.9±1.1
39	$COOC_2H_5$	Cl	H	H	30	91.0±5.8	29.9±1.4**	1.60±0.05	15.5±2.1
40	$COOC_2H_5$	H	Cl	H	30	94.4±0.5	26.7±3.8**	1.78±0.08	6.2±3.0
41	$COOC_2H_5$	H	H	Cl	30	132.0±6.8	-1.8±1.7	1.57±0.05	17.3±1.2
56	COOH	H	H	H	30	148.3±3.5	-14.6±3.4	2.34±0.05	-23.0±2.0
57	COOH	Cl	H	H	30	131.4±15.6	-0.6±7.0	2.68±0.10	-40.8±3.8
58	COOH	H	Cl	H	30	111.1±16.5	15.0±9.2	2.78±0.01	-46.6±2.9*
59	COOH	H	H	Cl	30	114.7±13.9	12.1±6.4	2.36±0.12	-24.4±5.1
SB203580					3	118.7±13.3	8.9±7.2	1.20±0.04	36.4±1.3**
					10	95.8±11.3	26.5±6.0**	0.92±0.17	51.6±7.6**
					30	54.4±5.3	58.2±2.4**	0.88±0.10	53.6±4.3**
IC_{50} (μM)						22.4±3.4		10.2±1.6	

N=3; * *P<0.05*, **P< 0.01

SB203580: [4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)lH-imidazole : positive control