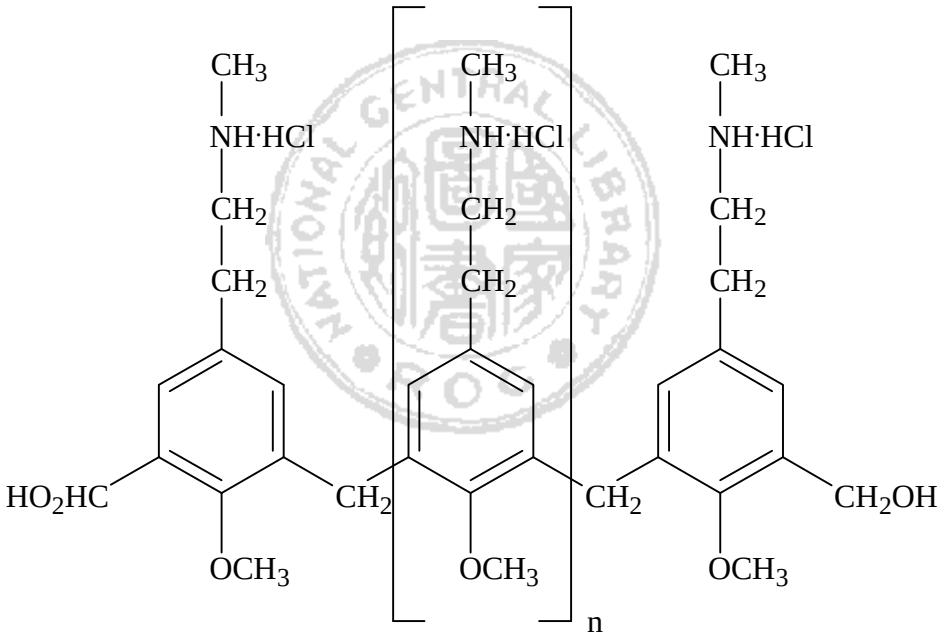
貳、抗過敏活性試驗

將前述合成出及經結構判定正確之化合物21-33、41-48、50-53、61-68、70-73、81-93、101-109、111-114、116-118及120-123提供抗過敏活性試驗，測試之方法採用化合物對於compound 48/80[85]**誘導的肥滿細胞去顆粒作用** (mast cell degranulation)**抑制試驗，依其抑制百分率來判定其活性強度，篩選結果如**Table 7**至**Table 12**所示。**

試　劑　compound 48/80 (compd 48/80) **為** *N*-methyl-*p*-methoxy-phenylethylamine **與甲醛** (formaldehyde)**之縮合物。**



compd 48/80 (e.g. n=11 in tridecamer)

Compound 48/80 **的藥理作用是促使肥滿細胞釋放組織胺** (histamine)**，故可作為化合物測定抗過敏的活性試驗時之誘導劑。**

選用 mepacrine[86] (quinacrine)**當作** positive control **的原因是它可以抑制肥滿細胞釋放組織胺，其作用包括下列三點：**

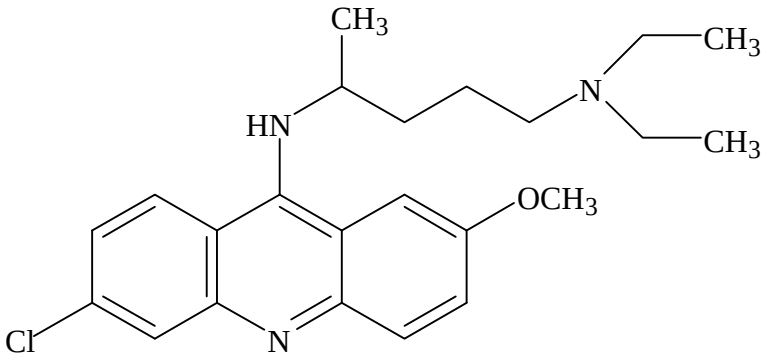
1.**在滑膜的纖維母細胞** (synovial fibroblasts)**上，**mepacrine **可以阻斷緩激**　(bradykinin)**的作用，以達到抑制痛的效果。**

2.**在滑膜的纖維母細胞上，**mepacrine **可以阻斷藉著緩激**　**所誘導的** cAMP **的釋放。另外，**mepacrine **也具有導致** arachidonic acid **和** prostagladin E **釋放的作用。**

3. mepacrine **具有抑制** phospholipase A_2 **的作用而減少組織胺從人類的嗜鹼性白血球** (basophils)**和抗免疫球蛋白** (anti-immuno-

globulin；anti-IgE)的釋放。

綜合上述可知，mepacrine 對於緩激　和組織胺具有拮抗的作用，因此在實驗上選它當作 positive control。



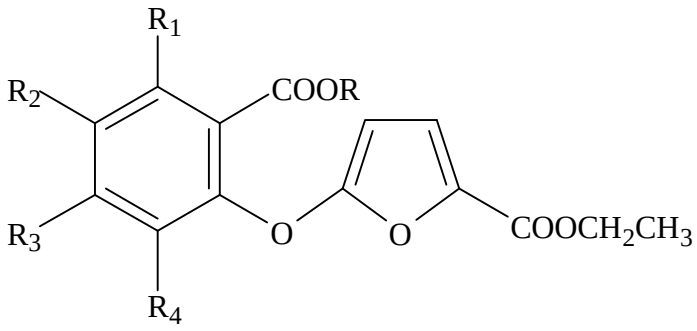
mepacrine

由測試的結果發現：

從化合物 21-33、41-48、50-53、61-68、70-73、81-93、101-109、111-114、116-118 及 120-123 對以 compound 48/80 誘導的肥滿細胞去顆粒作用之體外試驗中，由β-glucuronidase 或 histamine 的抑制百分率(見 Table 7 至 Table 12)看來，在濃度 30 μM 時，化合物 22、25-28、30、33、62、66、83、84、93、101 及 111 分別呈現弱的抑制活性 (具有約 20-35%的抑制百分率)，但是發現化合物 32 呈現明顯的抑制活性，其抑制β-glucuronidase 的 IC_{50} 值為 40.5±1.2 μM 及抑制 histamine 的 IC_{50} 值為 42.7±1.9 μM，而其所接的取代基溴原子為拉電子基，因此減少官能基對於水相的親和力，導致分配係數增加，脂溶性增加[(84)]，所以藥物較容易到達作用位置與接受器結合產生藥效。其他化合物則無明顯的抑制活性。

綜合上述，發現 ethyl 5-(2'-alkoxycarbonyl substituted phenoxy)-furan-2-carboxylates (**21-33**)類衍生物的活性較明顯。在 ethyl 5-(2'-alkoxycarbonyl substituted phenoxy)furan-2-carboxylates (**21-33**)類衍生物中將溴原子導入苯環時，具有較高的活性，而化合物 ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**)的 IC_{50} 值 (抑制β-glucuronidase 的 IC_{50} = 40.5±1.2 μM 及抑制 histamine 的 IC_{50} = 42.7±1.9 μM)約與 mepacrine 的 IC_{50} 值 (抑制β-glucuronidase 的 IC_{50} = 44.0±1.2 μM 及抑制 histamine 的 IC_{50} = 53.6±1.8 μM)相當。與溴原子相較之下，若將甲基、甲氧基或氯原子導入苯環，則其活性降低，此外，若將碘原子導入苯環，則其活性降得更低。

Table 7. The inhibitory effect of ethyl 5-(2'-alkoxycarbonyl substituted phenoxy)-furan-2-carboxylates on rat mast cell degranulation (*in vitro*)



21: R=CH_3, R_1=R_2=R_3=R_4=H
22: R=CH_3, R_1=R_2=R_3=H, R_4=CH_3
23: R=CH_3, R_1=R_2=R_4=H, R_3=CH_3
24: R=CH_3, R_1=R_3=R_4=H, R_2=CH_3
25: R=C_2H_5, R_2=R_3=R_4=H, R_1=CH_3
26: R=CH_3, R_1=R_2=R_3=H, R_4=OCH_3
27: R=CH_3, R_1=R_2=R_4=H, R_3=OCH_3
28: R=CH_3, R_1=R_3=R_4=H, R_2=OCH_3
29: R=CH_3, R_2=R_3=R_4=H, R_1=OCH_3
30: R=CH_3, R_1=R_2=R_4=H, R_3=Cl
31: R=CH_3, R_1=R_3=R_4=H, R_2=Cl
32: R=CH_3, R_1=R_3=R_4=H, R_2=Br
33: R=CH_3, R_1=R_3=R_4=H, R_2=I

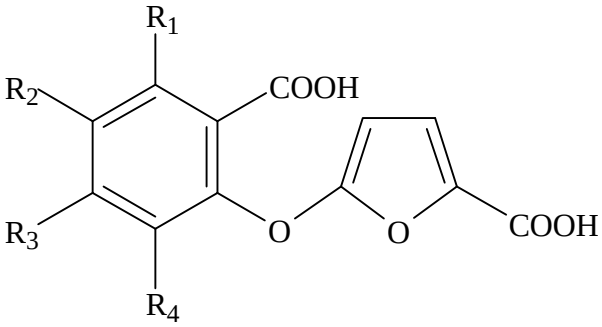
Compound	conc. (μM)	Percent Release β-Glucuronidase	(%inh)	Histamine	(%inh)
	Control	20.2±0.8	--	26.5±1.5	--
21	(30)	20.1±1.4	0.7±3.0	22.6±2.5	14.7±7.2
	(50)	18.0±0.9	10.0±8.3	18.1±1.7	31.4±6.3
	(100)	11.5±0.1**	42.5±2.0	12.4±2.1	53.2±7.6
	IC_{50}			91.1±13.6	
22	(30)	14.8±1.2*	27.0±3.8	18.1±1.3	31.6±3.3
	(50)	10.9±1.5**	45.8±7.1	10.0±2.7	62.8±9.2
	(100)	8.2±1.0**	58.8±6.5	6.3±1.0	76.2±2.5
	IC_{50}	73.2±8.4		52.0±3.6	
23	(30)	17.0±0.9*	15.5±3.3	19.6±0.8	25.8±3.0
	(50)	15.2±1.2**	25.0±3.4	18.1±0.3	31.4±2.5
	(100)	7.1±1.1**	65.2±4.2	5.7±2.3	79.0±8.3
	IC_{50}	80.4±4.5		66.5±3.4	
	Control	18.0±0.9	--	25.0±1.0	--
Mepacrine	(10)	13.4±0.5**	25.2±0.9	16.6±1.7**	33.5±5.4
	(20)	9.0±1.0**	49.6±4.2	12.2±2.1**	73.8±4.2
	(30)	6.8±0.5**	62.1±1.1	4.8±2.4**	93.4±8.8
	IC_{50}	22.3±1.0		14.7±1.7	
	Control	19.8±2.5	--	24.8±1.8	--
24	(30)	17.9±2.5	6.2±4.0	25.2±5.6	6.0±4.4

	(100)	23.7±1.9	-26.6±8.2	19.6±4.7	23.9±8.2
	Control	20.8±1.5	--	28.5±3.1	--
Mepacrine	(3)	16.1±0.4**	21.7±4.2	26.1±2.5	-4.1±6.9
	(10)	9.9±1.1**	51.1±7.7	13.1±3.0**	48.7±8.2
	(30)	4.1±2.0**	79.6±10.5	3.5±0.7**	84.7±4.4
	IC_{50}	14.2±1.8		16.2±1.0	
	Control	41.8±2.2	--	74.4±0.7	--
25	(10)	38.7±1.2	6.9±4.1	71.7±0.9	3.7±0.3
	(30)	32.5±1.3*	21.8±5.3	62.4±0.2	16.1±1.0
Mepacrine	(10)	26.4±1.7**	36.7±2.4	52.5±3.4**	29.3±3.9
	(30)	21.2±0.9**	48.9±2.2	40.5±2.4**	45.5±2.9
	(100)	4.2±0.4**	89.7±0.9	10.8±1.3**	85.5±1.7
	IC_{50}	32.5±1.7		40.8±4.3	
	Control	47.8±0.7	--	65.2±1.3	--
26	(30)	37.0±2.0*	22.7±3.3	58.7±1.1	9.9±2.5
	(100)	28.1±1.1**	41.1±2.5	43.1±1.6**	33.9±1.7
27	(10)	42.1±2.8	12.0±4.5	63.6±3.1	2.4±4.3
	(30)	34.6±2.5*	27.7±4.3	54.3±1.4	16.6±3.0
	(100)	17.8±0.9**	62.8±1.9	28.1±1.6**	56.7±3.4
	IC_{50}	75.2±2.9		88.5±4.2	
28	(10)	43.5±2.1	9.1±3.3	63.8±1.4	2.0±3.0
	(30)	31.4±1.3**	34.2±1.9	49.2±1.5*	24.6±0.8
	(100)	17.7±5.2**	62.8±11.4	28.7±6.8**	56.2±9.8
	IC_{50}	73.2±7.1		91.0±13.5	
Mepacrine	(10)	36.3±1.8*	24.3±3.7	51.6±3.6	21.1±3.6
	(30)	23.6±0.6**	50.7±1.2	39.6±2.8**	40.7±2.7
	(100)	7.3±0.9**	84.6±2.2	14.6±0.9**	78.1±0.8
	IC_{50}	44.0±1.2		53.6±1.8	
	Control	51.3±3.4	--	68.8±2.2	--
29	(10)	50.1±1.8	1.8±2.9	70.1±1.8	-2.1±1.8
	(30)	45.2±1.4	11.2±4.5	68.9±3.1	-0.1±1.9
Mepacrine	(10)	38.0±0.6*	25.6±0.7	54.9±0.6*	20.1±0.9
	(30)	24.5±0.5**	52.2±0.6	35.7±0.4**	47.5±0.6
	(100)	8.5±0.3**	83.3±0.9	15.8±0.3**	76.6±0.4
	IC_{50}	26.4±0.5		33.2±0.6	
	Control	47.8±0.7	--	65.2±1.3	--
30	(10)	44.2±0.8	7.5±0.6	65.1±0.8	0.1±2.3
	(30)	34.8±0.8*	27.2±2.5	56.0±1.6	14.0±3.2
	(100)	11.6±0.4**	75.7±0.6	19.0±0.4**	70.8±1.0
	IC_{50}	64.4±0.4		73.9±1.1	
31	(30)	41.1±2.4	14.1±3.7	62.7±1.8	3.9±2.0
	(100)	30.2±1.5**	36.8±3.2	47.2±0.9*	27.5±1.4
32	(10)	41.6±0.8	13.0±1.3	60.2±2.6	7.7±3.1
	(30)	13.0±1.5**	72.7±3.5	21.3±2.6**	67.2±4.7

	(100)	7.5±1.9**	84.2±4.1	7.9±2.2**	87.9±3.2
	IC_{50}	40.5±1.2		42.7±1.9	
Mepacrine	(10)	36.3±1.8*	24.3±3.7	51.6±3.6	21.1±3.6
	(30)	23.6±0.6**	50.7±1.2	39.6±2.8**	40.7±2.7
	(100)	7.3±0.9**	84.6±2.2	14.6±0.9**	78.1±0.8
	IC_{50}	44.0±1.2		53.6±1.8	
	Control	33.5±1.3	--	58.4±1.9	--
33	(10)	28.2±1.3	15.7±0.8	50.9±2.8	12.8±3.7
	(30)	30.5±2.8	9.1±7.1	46.2±4.1	21.0±4.8
Mepacrine	(10)	25.4±1.5*	23.7±3.5	48.6±2.4	16.6±2.9
	(30)	19.1±1.1**	42.9±2.9	37.3±3.6**	35.8±6.0
	(100)	2.2±0.7**	93.7±1.9	6.4±1.3**	88.8±2.3
	IC_{50}	42.0±3.5		50.2±4.5	

Mast cell suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds for 3 min. Fifteen minutes after the addition of compound 48/80 (10 μg/ml), β-glucuronidase and histamine activities in the supernatant were determined. Mepacrine is a positive control. Values are presented as mean± S.E., N=3-5. *: P<0.05, **: P<0.01.

Table 8. The inhibitory effect of 5-(2'-carboxyl substituted phenoxy)furan-2-carboxylic acids on rat mast cell degranulation (*in vitro*)



41: $R_1=R_2=R_3=R_4=H$ **47**: $R_1=R_2=R_4=H$, $R_3=OCH_3$

42: $R_1=R_2=R_3=H$, $R_4=CH_3$ **48**: $R_1=R_3=R_4=H$, $R_2=OCH_3$

43: $R_1=R_2=R_4=H$, $R_3=CH_3$ **50**: $R_1=R_2=R_4=H$, $R_3=Cl$

44: $R_1=R_3=R_4=H$, $R_2=CH_3$ **51**: $R_1=R_3=R_4=H$, $R_2=Cl$

45: $R_2=R_3=R_4=H$, $R_1=CH_3$ **52**: $R_1=R_3=R_4=H$, $R_2=Br$

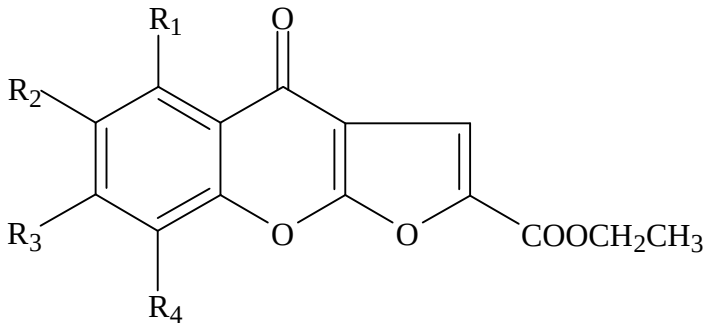
46: $R_1=R_2=R_3=H$, $R_4=OCH_3$ **53**: $R_1=R_3=R_4=H$, $R_2=I$

Compound	conc.	Percent Release			
	(μM)	β-Glucuronidase	(%inh)	Histamine	(%inh)
	Control	27.4±5.3	--	41.9±2.2	--
41	(30)	29.4±6.9	-6.2±9.4	46.0±4.3	-9.0±4.5
	(100)	25.9±6.1	6.6±4.1	42.2±2.6	-0.6±0.9
42	(30)	22.9±1.9	13.0±9.8	37.3±4.3	10.2±11.2
	(100)	21.4±2.4	19.1±8.1	41.0±2.1	1.4±5.7
43	(30)	24.6±4.4	8.9±9.7	47.0±4.6	-11.4±6.5
	(100)	20.2±4.2	26.4±5.2	38.0±3.1	9.5±2.6
	Control	18.0±0.9	--	25.0±1.0	--
Mepacrine	(10)	13.4±0.5**	25.2±0.9	16.6±1.7**	33.5±5.4
	(20)	9.0±1.0**	49.6±4.2	12.2±2.1**	73.8±4.2
	(30)	6.8±0.5**	62.1±1.1	4.8±2.4**	93.4±8.8
	IC_{50}	22.3±1.0		14.7±1.7	
	Control	20.8±1.5	--	28.5±3.1	--
44	(30)	20.3±1.1	-2.9±10.2	27.1±5.0	12.4±6.2
	(100)	20.6±1.4	-4.9±12.6	25.8±5.4	18.6±8.0
Mepacrine	(3)	16.1±0.4**	21.7±4.2	26.1±2.5	-4.1±6.9
	(10)	9.9±1.1**	51.1±7.7	13.1±3.0**	48.7±8.2
	(30)	4.1±2.0**	79.6±10.5	3.5±0.7**	84.7±4.4
	IC_{50}	14.2±1.8		16.2±1.0	
	Control	41.8±2.2	--	74.4±0.7	--
45	(10)	40.6±1.7	2.7±1.6	72.1±1.3	3.1±0.8

	(30)	39.7±1.2	4.5±3.8	72.9±0.5	2.0±0.5
Mepacrine	(10)	26.4±1.7**	36.7±2.4	52.5±3.4**	29.3±3.9
	(30)	21.2±0.9**	48.9±2.2	40.5±2.4**	45.5±2.9
	(100)	4.2±0.4**	89.7±0.9	10.8±1.3**	85.5±1.7
	IC_{50}	32.5±1.7		40.8±4.3	
	Control	47.8±0.7	--	65.2±1.3	--
46	(30)	43.9±2.5	8.2±5.1	64.5±0.6	1.0±2.0
	(100)	48.1±1.9	-0.6±4.0	69.4±2.1	-6.4±1.3
47	(30)	43.4±1.9	9.1±4.5	65.4±0.8	-0.5±2.4
	(100)	44.0±2.2	7.9±3.7	67.0±1.5	-2.8±1.1
48	(30)	41.1±1.6	14.0±2.3	62.6±2.0	4.1±1.5
	(100)	43.2±3.9	9.4±7.3	66.1±4.2	-1.4±5.6
50	(30)	42.6±2.4	10.8±4.8	66.3±2.4	-1.9±6.0
	(100)	45.3±1.6	5.1±4.3	66.3±2.0	-1.8±2.7
51	(30)	42.8±1.9	10.5±3.8	65.1±0.2	0.04±1.6
	(100)	45.9±2.7	3.9±6.1	66.0±1.2	-1.3±2.4
52	(30)	41.6±2.9	3.0±5.3	63.9±0.5	1.9±1.6
	(100)	43.9±0.9	8.2±0.6	64.0±1.0	1.8±0.5
Mepacrine	(10)	36.3±1.8*	24.3±3.7	51.6±3.6	21.1±3.6
	(30)	23.6±0.6**	50.7±1.2	39.6±2.8**	40.7±2.7
	(100)	7.3±0.9**	84.6±2.2	14.6±0.9**	78.1±0.8
	IC_{50}	44.0±1.2		53.6±1.8	
	Control	33.5±1.3	--	58.4±1.9	--
53	(10)	29.7±1.8	11.4±1.8	57.6±2.6	1.3±2.9
	(30)	29.2±1.6	13.0±2.0	53.1±3.0	8.9±4.6
Mepacrine	(10)	25.4±1.5*	23.7±3.5	48.6±2.4	16.6±2.9
	(30)	19.1±1.1**	42.9±2.9	37.3±3.6**	35.8±6.0
	(100)	2.2±0.7**	93.7±1.9	6.4±1.3**	88.8±2.3
	IC_{50}	42.0±3.5		50.2±4.5	

Mast cell suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds for 3 min. Fifteen minutes after the addition of compound 48/80 (10 μg/ml), β-glucuronidase and histamine activities in the supernatant were determined. Mepacrine is a positive control. Values are presented as mean± S.E., N=3-5. *: P<0.05, **: P<0.01.

Table 9. The inhibitory effect of substituted furo[2,3-*b*]chromone-2-carboxylic acid ethyl esters on rat mast cell degranulation (*in vitro*)



61: $R_1=R_2=R_3=R_4=H$ **67**: $R_1=R_2=R_4=H$, $R_3=OCH_3$

62: $R_1=R_2=R_3=H$, $R_4=CH_3$ **68**: $R_1=R_3=R_4=H$, $R_2=OCH_3$

63: $R_1=R_2=R_4=H$, $R_3=CH_3$ **70**: $R_1=R_2=R_4=H$, $R_3=Cl$

64: $R_1=R_3=R_4=H$, $R_2=CH_3$ **71**: $R_1=R_3=R_4=H$, $R_2=Cl$

65: $R_2=R_3=R_4=H$, $R_1=CH_3$ **72**: $R_1=R_3=R_4=H$, $R_2=Br$

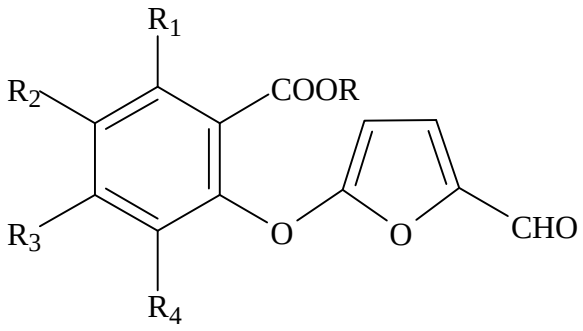
66: $R_1=R_2=R_3=H$, $R_4=OCH_3$ **73**: $R_1=R_3=R_4=H$, $R_2=I$

Compound	conc.	Percent Release			
	(μM)	β-Glucuronidase	(%inh)	Histamine	(%inh)
	Control	27.4±5.3	--	41.9±2.2	--
61	(30)	23.4±5.8	15.7±6.9	36.5±5.4	14.0±9.2
	(100)	22.8±3.3	14.8±6.4	38.8±3.6	6.7±8.6
62	(30)	20.1±3.3	25.1±9.5	29.8±3.5	28.9±6.1
	(100)	18.0±4.1	34.8±6.5	36.5±5.5	14.1±8.1
	Control	18.0±0.9	--	25.0±1.0	--
Mepacrine	(10)	13.4±0.5**	25.2±0.9	16.6±1.7**	33.5±5.4
	(20)	9.0±1.0**	49.6±4.2	12.2±2.1**	73.8±4.2
	(30)	6.8±0.5**	62.1±1.1	4.8±2.4**	93.4±8.8
	IC_{50}	22.3±1.0		14.7±1.7	
	Control	19.8±2.5	--	24.8±1.8	--
63	(30)	18.6±2.0	-1.2±15.9	22.2±5.8	13.0±4.0
	(100)	12.2±2.5**	35.8±9.2	14.3±4.3*	45.2±9.3
	Control	20.8±1.5	--	28.5±3.1	--
64	(30)	17.9±1.2	9.5±7.7	29.3±4.9	2.3±13.3
	(100)	15.2±2.0**	24.9±7.8	25.2±5.3	20.5±7.8
Mepacrine	(3)	16.1±0.4**	21.7±4.2	26.1±2.5	-4.1±6.9
	(10)	9.9±1.1**	51.1±7.7	13.1±3.0**	48.7±8.2
	(30)	4.1±2.0**	79.6±10.5	3.5±0.7**	84.7±4.4
	IC_{50}	14.2±1.8		16.2±1.0	

	Control	29.3±2.0	--	54.0±2.3	--
65	(10)	26.1±1.3	10.6±1.8	48.2±4.2	11.1±4.1
	(30)	24.6±1.6	16.0±1.8	46.9±3.7	13.3±4.3
66	(10)	24.7±2.4	16.1±3.8	46.1±3.7	14.9±4.3
	(30)	23.9±1.8	18.5±4.0	43.1±2.5	20.2±1.9
67	(10)	25.9±2.5	11.7±4.8	48.2±4.8	11.0±6.8
	(30)	26.5±2.1	9.8±4.2	48.5±3.6	10.4±3.4
68	(10)	27.3±1.3	6.7±2.8	48.9±1.7	9.5±0.6
	(30)	25.9±1.5	11.6±0.8	47.5±3.1	12.3±2.1
Mepacrine	(10)	19.9±0.4**	31.9±2.1	40.6±2.3*	24.6±4.1
	(30)	12.2±0.7**	57.8±2.9	30.4±2.8**	43.5±4.2
	(100)	4.0±0.5**	86.0±2.1	11.7±1.0**	78.2±1.4
	IC_{50}	32.2±3.6		48.5±3.8	
	Control	43.2±1.6	--	56.6±2.0	--
70	(10)	41.9±1.7	2.9±0.4	58.1±1.9	-2.6±2.6
	(30)	39.4±0.9	8.6±3.6	53.7±1.9	4.6±6.3
71	(10)	40.9±1.0	4.9±4.9	57.9±3.0	-2.3±3.2
	(30)	35.3±2.5	18.4±3.6	52.4±2.8	7.6±2.2
72	(10)	43.2±1.2	-0.1±1.0	55.9±2.9	1.3±3.8
	(30)	34.5±1.4*	19.7±5.2	49.4±2.1	12.6±3.9
73	(10)	41.9±1.7	2.9±1.6	54.0±2.8	4.6±2.6
	(30)	37.8±1.8	12.5±0.9	50.0±2.1	11.6±3.4
Mepacrine	(10)	29.9±0.6**	31.9±2.1	42.6±2.7**	24.6±4.1
	(30)	18.2±1.1**	57.8±2.9	31.6±3.4**	43.5±4.2
	(100)	5.9±0.8**	86.0±2.1	12.1±1.2**	78.2±1.4
	IC_{50}	32.2±3.6		48.5±3.8	

Mast cell suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds for 3 min. Fifteen minutes after the addition of compound 48/80 (10 μg/ml), β-glucuronidase and histamine activities in the supernatant were determined. Mepacrine is a positive control. Values are presented as mean± S.E., N=3-5. *: P<0.05, **: P<0.01.

Table 10. The inhibitory effect of 5-(2'-alkoxycarbonyl substituted phenoxy)furfurals on rat mast cell degranulation (*in vitro*)



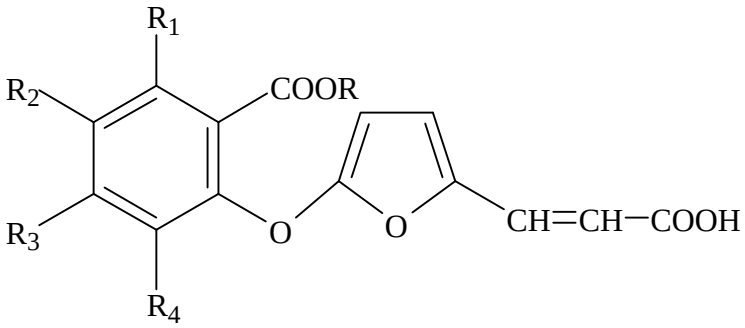
81: R=CH_3, R_1=R_2=R_3=R_4=H
82: R=CH_3, R_1=R_2=R_3=H, R_4=CH_3
83: R=CH_3, R_1=R_2=R_4=H, R_3=CH_3
84: R=CH_3, R_1=R_3=R_4=H, R_2=CH_3
85: R=C_2H_5, R_2=R_3=R_4=H, R_1=CH_3
86: R=CH_3, R_1=R_2=R_3=H, R_4=OCH_3
87: R=CH_3, R_1=R_2=R_4=H, R_3=OCH_3
88: R=CH_3, R_1=R_3=R_4=H, R_2=OCH_3
89: R=CH_3, R_2=R_3=R_4=H, R_1=OCH_3
90: R=CH_3, R_1=R_2=R_4=H, R_3=Cl
91: R=CH_3, R_1=R_3=R_4=H, R_2=Cl
92: R=CH_3, R_1=R_3=R_4=H, R_2=Br
93: R=CH_3, R_1=R_3=R_4=H, R_2=I

Compound	conc.	Percent Release			
	(μM)	β-Glucuronidase	(%inh)	Histamine	(%inh)
	Control	20.5±0.6	--	79.3±1.5	--
81	(10)	17.9±0.4*	12.6±0.7	75.3±1.8	5.0±0.8
	(30)	16.4±0.5**	19.8±0.2	74.6±2.6	6.0±1.6
82	(10)	17.8±0.5**	12.9±0.2	75.2±1.3	5.1±0.5
	(30)	17.2±1.8**	16.4±6.1	75.0±2.0	5.4±1.4
83	(10)	16.4±0.7**	19.9±0.7	74.4±1.4	6.3±0.4
	(30)	16.3±0.3**	20.2±2.3	74.9±1.1	5.6±0.5
84	(10)	17.0±0.3**	16.6±1.4	74.3±2.3	6.3±1.2
	(30)	15.7±0.6**	23.3±0.7	74.3±2.1	6.4±0.8
85	(10)	21.3±0.6	-4.3±6.1	76.2±1.4	3.8±2.3
	(30)	21.6±0.7	-5.5±0.5	78.6±3.2	0.8±3.7
Mepacrine	(10)	15.3±0.1**	25.2±1.8	60.1±1.6**	24.2±0.7
	(30)	8.5±0.1**	58.5±1.1	41.5±0.6**	47.5±1.2
	(100)	2.8±0.1**	86.0±0.5	14.9±0.4**	81.1±0.6
	IC_{50}	23.9±0.7		29.4±0.5	
	Control	51.3±3.4	--	68.8±2.2	--
86	(10)	46.2±2.0	9.6±2.9	68.0±1.0	0.9±1.7

	(30)	44.4±1.8	13.1±2.3	64.2±2.0	6.6±0.7
87	(10)	45.5±0.4	10.5±5.0	68.8±0.8	-0.3±4.2
	(30)	43.2±1.7	15.5±2.1	67.5±1.8	1.7±0.5
88	(10)	47.1±1.7	7.8±3.8	68.5±0.8	0.1±3.6
	(30)	42.1±1.2	17.4±3.6	66.8±1.6	2.7±1.3
89	(10)	49.6±2.0	2.8±2.7	69.9±1.6	-1.8±1.2
	(30)	46.6±1.9	8.7±3.9	68.5±1.7	0.2±1.6
90	(10)	48.5±3.2	5.2±2.6	66.2±2.6	3.7±1.6
	(30)	44.8±3.7	12.7±3.9	61.7±4.1	10.4±3.3
91	(10)	51.3±3.2	-0.2±3.4	65.4±4.1	4.9±3.0
	(30)	47.0±2.0	7.9±4.2	62.6±2.4	8.8±1.8
92	(10)	45.4±3.6	11.6±1.1	67.1±0.7	2.3±2.1
	(30)	41.3±1.0	18.8±3.8	62.9±3.3	8.5±2.5
93	(10)	43.8±1.7	14.1±2.5	69.3±0.9	-1.0±3.5
	(30)	39.6±1.2	22.4±2.6	65.1±1.1	5.1±1.6
Mepacrine	(10)	38.0±0.6*	25.6±0.7	54.9±0.6*	20.1±0.9
	(30)	24.5±0.5**	52.2±0.6	35.7±0.4**	47.5±0.6
	(100)	8.5±0.3**	83.3±0.9	15.8±0.3**	76.6±0.4
	IC_{50}	26.4±0.5		33.2±0.6	

Mast cell suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds for 3 min. Fifteen minutes after the addition of compound 48/80 (10 μg/ml), β-glucuronidase and histamine activities in the supernatant were determined. Mepacrine is a positive control. Values are presented as mean± S.E., N=3. *: P<0.05, **: P<0.01.

Table 11. The inhibitory effect of 5-(2'-alkoxycarbonyl substituted phenoxy)-2-furanacrylic acids on rat mast cell degranulation (*in vitro*)



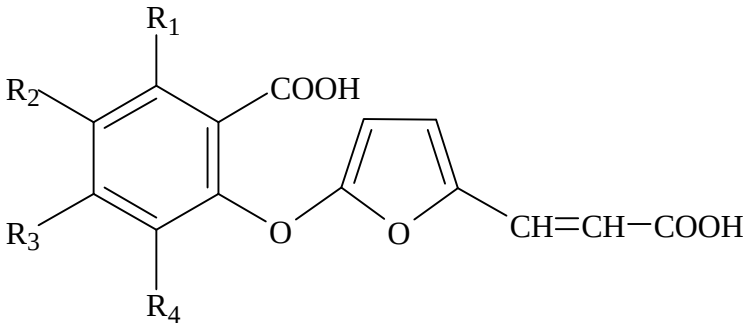
101: R=CH_3, R_1=R_2=R_3=R_4=H
102: R=CH_3, R_1=R_2=R_3=H, R_4=CH_3
103: R=CH_3, R_1=R_2=R_4=H, R_3=CH_3
104: R=CH_3, R_1=R_3=R_4=H, R_2=CH_3
105: R=C_2H_5, R_2=R_3=R_4=H, R_1=CH_3
106: R=CH_3, R_1=R_2=R_3=H, R_4=OCH_3
107: R=CH_3, R_1=R_2=R_4=H, R_3=OCH_3
108: R=CH_3, R_1=R_3=R_4=H, R_2=OCH_3
109: R=CH_3, R_2=R_3=R_4=H, R_1=OCH_3

Compound	conc.	Percent Release			
	(μM)	β-Glucuronidase	(%inh)	Histamine	(%inh)
	Control	20.5±0.6	--	79.3±1.5	--
101	(10)	18.4±0.2	10.1±2.2	76.5±1.5	3.5±1.9
	(30)	15.9±0.3**	21.9±3.7	69.2±1.2**	12.6±1.6
102	(10)	17.4±0.5**	16.4±0.1	77.6±2.6	2.2±2.2
	(30)	19.5±0.1	4.6±2.7	77.4±3.0	2.6±2.0
103	(10)	16.9±0.4**	17.1±1.8	73.8±1.3	6.9±0.5
	(30)	16.7±0.4**	18.3±1.7	71.8±1.3*	9.4±0.6
104	(10)	18.2±0.2	11.3±1.7	76.0±1.4	4.1±0.7
	(30)	17.6±0.1*	13.8±3.1	74.5±1.6	6.0±2.3
105	(10)	18.1±1.3	10.7±9.0	74.1±1.3	6.5±2.6
	(30)	19.7±0.1	3.4±2.8	72.6±1.3	8.3±2.8
Mepacrine	(10)	15.3±0.1**	25.2±1.8	60.1±1.6**	24.2±0.7
	(30)	8.5±0.1**	58.5±1.1	41.5±0.6**	47.5±1.2
	(100)	2.8±0.1**	86.0±0.5	14.9±0.4**	81.1±0.6
	IC_{50}	23.9±0.7		29.4±0.5	
	Control	51.3±3.4	--	68.8±2.2	--
106	(10)	51.4±2.5	-0.5±1.7	68.5±1.4	-0.07±5.4
	(30)	46.8±3.0	8.7±2.1	65.6±1.3	4.4±3.3
107	(10)	55.4±3.4	-8.1±2.1	68.9±1.8	-0.2±0.6
	(30)	51.9±3.6	-1.2±2.2	66.4±1.3	3.2±2.4

108	(10)	60.0±2.8	-17.2±2.3	67.2±1.8	2.0±2.9
	(30)	55.6±3.7	-8.3±3.4	62.8±2.4	8.7±0.6
109	(10)	65.1±3.4	-27.1±2.0	67.1±2.4	2.4±1.4
	(30)	59.3±3.2	-15.9±4.8	63.8±2.7	7.2±1.8
Mepacrine	(10)	38.0±0.6*	25.6±0.7	54.9±0.6*	20.1±0.9
	(30)	24.5±0.5**	52.2±0.6	35.7±0.4**	47.5±0.6
	(100)	8.5±0.3**	83.3±0.9	15.8±0.3**	76.6±0.4
	IC_{50}	26.4±0.5		33.2±0.6	

Mast cell suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds for 3 min. Fifteen minutes after the addition of compound 48/80 (10 μg/ml), β-glucuronidase and histamine activities in the supernatant were determined. Mepacrine is a positive control. Values are presented as mean± S.E., N=3. *: P<0.05, **: P<0.01.

Table 12. The inhibitory effect of 5-(2'-carboxyl substituted phenoxy)-2-furanacrylic acids on rat mast cell degranulation (*in vitro*)



111: $R_1=R_2=R_3=R_4=H$
112: $R_1=R_2=R_3=H$, $R_4=CH_3$
113: $R_1=R_2=R_4=H$, $R_3=CH_3$
114: $R_1=R_3=R_4=H$, $R_2=CH_3$
116: $R_1=R_2=R_3=H$, $R_4=OCH_3$
117: $R_1=R_2=R_4=H$, $R_3=OCH_3$
118: $R_1=R_3=R_4=H$, $R_2=OCH_3$
120: $R_1=R_2=R_4=H$, $R_3=Cl$
121: $R_1=R_3=R_4=H$, $R_2=Cl$
122: $R_1=R_3=R_4=H$, $R_2=Br$
123: $R_1=R_3=R_4=H$, $R_2=I$

Compound	conc. (μM)	Percent Release β-Glucuronidase	(%inh)	Histamine	(%inh)
	Control	20.5±0.6	--	79.3±1.5	--
111	(10)	18.4±0.2	10.1±3.5	75.0±1.7	5.4±2.0
	(30)	16.2±0.2**	20.7±3.1	71.8±1.4*	9.5±0.4
112	(10)	17.3±0.3*	15.3±1.0	75.1±1.4	5.4±0.6
	(30)	18.9±0.6	7.7±0.4	74.4±1.2	6.2±0.5
113	(10)	18.2±0.1	11.3±2.1	77.3±1.2	2.6±0.5
	(30)	17.5±0.2*	14.5±2.1	79.1±1.1	0.3±0.6
114	(10)	19.6±0.2	4.2±1.7	77.4±2.5	2.4±3.0
	(30)	19.5±1.3	4.9±3.5	73.2±3.2	7.7±3.7
Mepacrine	(10)	15.3±0.1**	25.2±1.8	60.1±1.6**	24.2±0.7
	(30)	8.5±0.1**	58.5±1.1	41.5±0.6**	47.5±1.2
	(100)	2.8±0.1**	86.0±0.5	14.9±0.4**	81.1±0.6
	IC_{50}	23.9±0.7		29.4±0.5	
	Control	51.3±3.4	--	68.8±2.2	--
116	(10)	46.5±2.0	9.0±3.5	68.4±0.8	0.3±2.5
	(30)	43.8±1.4	13.9±5.6	60.4±3.0	12.2±2.6
117	(10)	48.9±2.3	4.3±2.0	70.9±0.8	-3.4±4.3
	(30)	44.9±1.5	12.0±3.0	67.0±0.7	2.3±3.3
118	(10)	51.7±2.8	-1.0±3.4	67.7±0.9	1.3±3.5
	(30)	48.3±3.0	5.6±3.0	64.5±1.5	6.0±1.9

120	(10)	55.1±4.2	-7.3±2.9	69.2±3.0	-0.5±1.2
	(30)	51.3±3.3	-0.1±3.6	65.3±0.3	4.7±2.6
121	(10)	60.1±3.8	-17.2±3.8	68.1±2.8	1.0±2.4
	(30)	55.4±3.5	-8.3±4.4	64.1±2.9	6.7±2.3
122	(10)	64.7±4.0	-26.3±3.7	65.3±3.1	5.1±1.9
	(30)	60.5±4.4	-18.1±5.6	64.1±3.6	6.9±2.7
123	(10)	46.4±0.3	8.8±5.4	69.3±2.7	-0.8±2.7
	(30)	44.8±1.5	11.9±4.6	62.7±3.5	8.8±2.3
Mepacrine	(10)	38.0±0.6*	25.6±0.7	54.9±0.6*	20.1±0.9
	(30)	24.5±0.5**	52.2±0.6	35.7±0.4**	47.5±0.6
	(100)	8.5±0.3**	83.3±0.9	15.8±0.3**	76.6±0.4
	IC_{50}	26.4±0.5		33.2±0.6	

Mast cell suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds for 3 min. Fifteen minutes after the addition of compound 48/80 (10 μg/ml), β-glucuronidase and histamine activities in the supernatant were determined. Mepacrine is a positive control. Values are presented as mean± S.E., N=3. *: P<0.05, **: P<0.01.