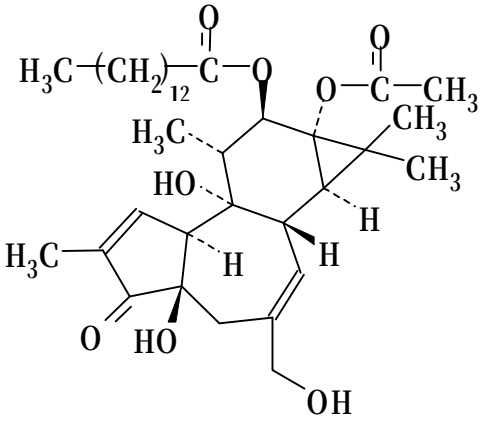
參、抗發炎活性試驗

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 提供抗發炎活性試驗，測試之方法分別採用化合物對於 fMLP **誘導的嗜中性白血球去顆粒作用** (neutrophil degranulation)**抑制試驗、化合物對於** fMLP **誘導的嗜中性白血球超氧自由基生成作用** (neutrophil superoxide formation)**抑制試驗及化合物對於** PMA **誘導的嗜中性白血球超氧自由基生成作用** (neutrophil superoxide formation)**抑制試驗，依其抑制百分率來判定其活性強度，篩選結果分別如：**Table 13 **至** Table 18、Table 19 **至** Table 24 **及** Table 25 **至** Table 30 **所示。**

fMLP **為一種趨化性** (chemotactic peptide) *N*-formyl-methionylleucylphenylalanine (CHO-Met-Leu-Phe-OH) **之簡稱**[87]**。***N*-formyl peptide **類化合物的藥理作用之一是促使嗜中性白血球去顆粒作用，故** fMLP **可作為化合物測定抗發炎的藥理活性試驗時之誘導劑。**fMLP **除可促使嗜中性白血球去顆粒作用外，亦可促使嗜中性白血球超氧自由基生成作用。**

PMA **之全名為** phorbol 12-myristate 13-acetate diester (**亦稱** 12-*o*-tetradecanoylphorbol-13-acetate**；故亦簡稱** TPA)**，其結構如下所示：**

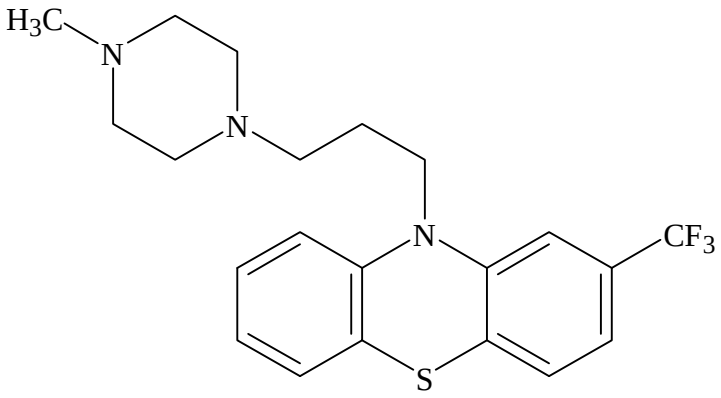


PMA

PMA **與** fMLP **兩者皆能促使嗜中性白血球超氧自由基生成作用，彼此差異在於作用位置不相同，**fMLP **會與嗜中性白血球細胞膜上接受器結合產生超氧自由基之生成**[88]**，而** PMA **則直接進入嗜中性白血球細胞內與細胞內** protein kinase C (PKC)**結合產生超氧自由基生成作用**[89]**，根據彼此的差異點可知，抗發炎化合物其產生藥理活性的**

作用位置。

選用 trifluoperazine[90] (TFP)**當作** positive control **的原因是它可以抑制嗜中性白血球** (neutrophils)**釋放出溶菌酵素** (lysozyme)**，同時減少** $O_2^{\cdot -}$**的形成，而它的作用是** calmodulin antagonist **和** protein kinase C inhibitor**。**



trifluoperazine

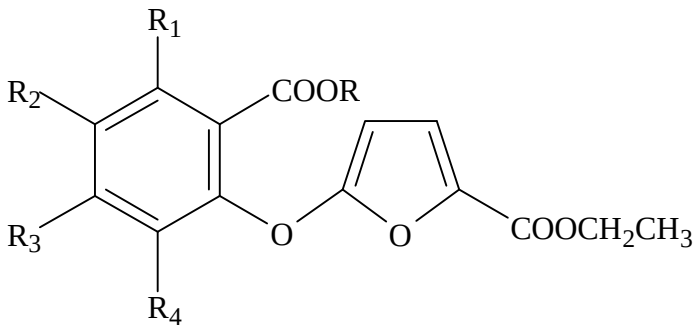
由測試的結果發現：

(一)對於fMLP**誘導的嗜中性白血球去顆粒作用抑制試驗**

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fMLP**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** (**見**Table 13**至**Table 18)**看來，在濃度**30 μM**時，化合物26、27、30、33、41、42、50、53、61-63、65、68、71、81、83-85、87、88、90、92、93及113分別呈現弱的抑制活性** (**具有約**20-42%**的抑制百分率**)**，但是發現化合物25、28及32呈現明顯的抑制活性，其抑制**β-glucuronidase**的**IC_{50}**值分別為**10.5±0.8 μM**、**35.7±3.8 μM**及**12.7±4.4 μM**，而抑制**lysozyme**的**IC_{50}**值分別為**15.5±2.8 μM**、**50.6±4.6 μM**及**18.5±5.3 μM**。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**)**類衍生物中將甲基、甲氧基或溴原子導入苯環時，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} = 12.7±4.4 μM**及抑制**lysozyme**的**IC_{50} = 18.5±5.3 μM)**約為**trifluoperazine**之**IC_{50}**值** (**抑制**β-glucuronidase**的**IC_{50} = 24.4±0.5 μM**及抑制**lysozyme**的**IC_{50} = 22.8±0.5 μM)**的二分之一倍，化合物** ethyl 5-(2'-ethoxycarbonyl-3'-methyl-phenoxy)furan-2-carboxylate (**25**)**的**IC_{50}**值** (**抑制**β-glucuronidase**的**IC_{50} = 10.5±0.8 μM**及抑制**lysozyme**的**IC_{50} = 15.5±2.8 μM)**約與**trifluoperazine**的**IC_{50}**值** (**抑制**β-glucuronidase**的**IC_{50} = 14.2±0.7 μM**及抑制**lysozyme**的**IC_{50} = 16.0±0.9 μM) **相當，化合物** ethyl 5-(2'-methoxy-carbonyl-4'-methoxyphenoxy)furan-2-carboxylate (**28**) **的**IC_{50}**值** (**抑制**β-glucuronidase**的**IC_{50} = 35.7± 3.8 μM**及抑制**lysozyme**的**IC_{50} = 50.6±4.6 μM)**約為**trifluoperazine**之**IC_{50}**值** (**抑制**β-glucuronidase**的**IC_{50} = 24.4± 0.5 μM**及抑制**lysozyme**的**IC_{50} = 22.8±0.5 μM)**的二倍。與甲基、甲氧基或溴原子相較之下，若將碘原子導入苯環，則其活性降低，此外，若將氯原子導入苯環，則其活性降得更低。**

Table 13. The inhibitory effect of ethyl 5-(2'-alkoxycarbonyl substituted phenoxy)-furan-2-carboxylates on rat neutrophil 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

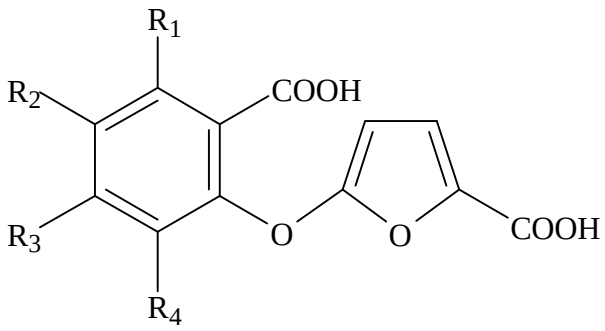
Compound	conc. (μM)	Percent Release β-Glucuronidase	(%inh)	Lysozyme	(%inh)
	Control	15.1±0.9	--	30.4±1.2	--
21	(30)	13.8±0.3	9.0±4.5	22.9±1.0*	28.0±5.1
	(100)	13.5±2.3	7.2±10.7	24.8±3.3	24.7±6.6
22	(30)	12.8±1.8	18.8±9.0	28.0±1.8	11.2±6.3
	(100)	12.7±1.8	14.7±8.3	31.7±2.5	3.0±3.9
23	(30)	13.5±1.5	8.3±8.0	28.1±0.3	17.1±3.9
	(100)	16.4±0.9	-7.7±5.0	32.5±3.3	6.4±8.3
TFP	(3)	13.9±2.0	9.6±4.8	30.5±2.9	8.7±4.1
	(10)	8.1±0.8*	52.1±7.1	15.1±1.2**	52.7±3.7
	(30)	2.2±1.3**	87.8±4.5	3.2±1.7**	89.7±4.8
	IC_{50}	14.3±3.9		12.5±3.7	
	Control	22.6±1.7	--	46.4±2.1	--
24	(30)	22.6±2.5	-0.4±10.0	49.3±6.2	-5.5±9.2
	(100)	21.5±0.7	3.7±8.2	52.5±6.9	-12.5±10.9
	Control	14.8±1.0	--	16.7±1.5	--
TFP	(3)	13.4±1.2	9.6±1.8	14.9±0.9	10.5±2.2
	(10)	8.5±1.3**	43.1±5.3	9.7±0.9*	39.7±9.8
	(30)	5.1±0.4**	64.7±3.1	6.6±0.4**	59.5±5.2

	IC_{50}	19.3±1.3		21.9±2.5	
	Control	42.5±0.8	--	61.5±3.3	--
25	(3)	33.9±2.1**	20.2±3.6	54.4±7.0	12.2±6.8
	(10)	14.8±1.6**	65.1±3.3	29.9±6.3**	51.9±8.0
	(30)	0.7±0.5**	98.1±1.4	14.3±4.5**	77.4±6.3
	IC_{50}	10.5±0.8		15.5±2.8	
TFP	(3)	35.2±0.8	16.8±2.2	55.7±5.3	8.9±1.9
	(10)	22.7±1.6**	44.9±8.6	44.0±6.8	28.0±6.1
	(30)	4.8±0.7**	88.6±2.7	2.0±2.2**	96.9±4.1
	IC_{50}	14.2±0.7		16.0±0.9	
	Control	24.5±0.3	--	46.1±1.1	--
26	(10)	21.5±1.3	12.0±6.4	40.1±1.2	13.1±0.8
	(30)	17.4±0.3**	29.1±1.9	33.7±1.5**	27.0±1.6
	(100)	11.2±2.3**	54.1±9.6	28.0±4.2**	39.5±8.4
	IC_{50}	92.1±12.2			
27	(10)	22.9±0.4	6.4±2.9	43.3±3.1	5.9±7.8
	(30)	18.6±1.4**	23.6±6.8	36.9±1.1	19.6±3.8
	(100)	10.7±2.6**	56.4±10.6	23.2±3.5**	49.6±7.2
	IC_{50}	91.5±12.6			
28	(10)	18.5±1.2**	24.6±5.4	33.5±0.4**	27.1±2.6
	(30)	10.2±1.0**	58.4±4.6	24.5±2.0**	46.9±3.9
	(100)	2.3±0.8**	90.4±3.5	13.1±2.1**	71.7±4.5
	IC_{50}	35.7±3.8		50.6±4.6	
TFP	(10)	27.2±2.8	-10.9±12.5	49.1±2.7	-7.5±4.8
	(20)	13.9±1.8**	43.3±8.2	24.1±5.2**	48.4±4.5
	(30)	9.6±1.5**	60.9±7.0	11.7±4.7**	74.9±8.6
	IC_{50}	24.4±0.5		22.8±0.5	
	Control	31.5±1.5	--	60.5±3.7	--
29	(10)	30.4±1.3	3.5±0.7	62.2±1.5	-3.2±4.2
	(30)	26.0±1.8	17.7±3.0	56.6±3.6	6.4±1.9
TFP	(3)	30.2±0.9	3.4±2.6	58.3±0.8	2.6±5.4
	(10)	20.0±0.5**	35.1±5.1	32.9±1.0**	44.7±4.6
	(30)	4.5±0.4**	85.9±1.2	9.3±1.1**	84.8±3.7
	IC_{50}	11.3±0.8		11.0±0.2	
	Control	24.5±0.3	--	46.1±1.1	--
30	(30)	21.3±0.6	12.9±3.0	33.4±1.9*	27.7±3.4
	(100)	14.2±2.9**	41.9±11.4	23.2±4.4**	49.6±9.5
31	(30)	20.6±1.1	15.7±5.2	39.3±3.1	14.9±6.0
	(100)	20.1±1.5	17.9±7.4	36.2±2.8	21.5±5.8
32	(10)	13.1±1.6**	46.5±7.0	27.9±2.9**	39.7±5.2
	(30)	2.7±1.0**	88.6±4.1	12.7±4.0**	72.3±8.9
	(100)	-0.3±0.5**	101.3±2.3	0.7±1.1**	98.6±2.6
	IC_{50}	12.7±4.4		18.5±5.3	
TFP	(10)	27.2±2.8	-10.9±12.5	49.1±2.7	-7.5±4.8

	(20)	13.9±1.8**	43.3±8.2	24.1±5.2**	48.4±4.5
	(30)	9.6±1.5**	60.9±7.0	11.7±4.7**	74.9±8.6
	IC_{50}	24.4±0.5		22.8±0.5	
	Control	30.4±0.6	--	64.8±1.6	--
33	(10)	24.6±3.1*	19.3±8.6	51.7±3.8*	20.4±4.7
	(30)	24.1±4.5	20.8±13.9	44.9±4.3**	30.8±5.8
TFP	(3)	31.3±0.3	-1.0±2.1	63.9±5.8	2.6±2.1
	(10)	23.7±1.4**	23.2±6.5	54.4±9.7	18.1±10.0
	(20)	5.5±0.7**	82.0±2.6	2.0±1.3**	97.2±1.9
	IC_{50}	14.0±0.5		12.6±0.6	

Neutrophil suspensions were preincubated at 37 ℃ with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Forty-five minutes after the addition of fMLP (1 μM), β-glucuronidase and lysozyme activities in the supernatant were determined. Trifluoperazine (TFP) is a positive control. Values are presented as mean±S.E., N=3-8. *: P<0.05, **: P<0.01.

Table 14. The inhibitory effect of 5-(2'-carboxyl substituted phenoxy)furan-2-carboxylic acids on rat neutrophil 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**: $R_1=R_3=R_4=H$, $R_2=Br$

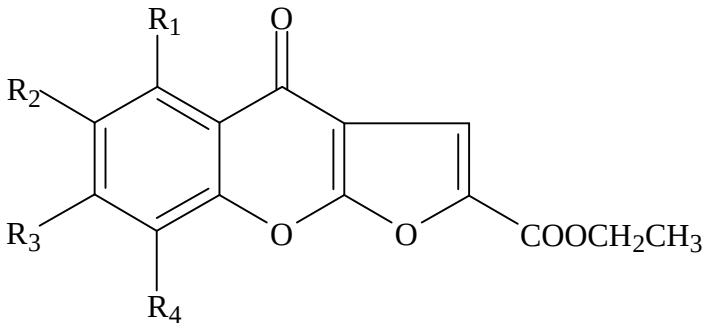
46: $R_1=R_2=R_3=H$, $R_4=OCH_3$ **53**: $R_1=R_3=R_4=H$, $R_2=I$

Compound	conc. (μM)	Percent Release β-Glucuronidase	(%inh)	Lysozyme	(%inh)
	Control	15.1±0.9	--	30.4±1.2	--
41	(30)	10.8±0.3	30.8±5.4	28.3±1.0	9.4±5.9
	(100)	12.5±2.0	14.6±10.1	25.2±0.9*	22.0±4.4
42	(10)	13.7±1.7	12.1±6.2	--	--
	(30)	11.6±0.2*	25.1±3.3	32.8±1.2	-3.0±3.8
	(100)	14.0±0.6	7.0±5.3	35.9±4.0	-11.5±5.3
43	(30)	10.0±0.2**	36.9±4.8	30.7±0.7	-0.3±3.9
	(100)	10.7±0.9*	33.9±4.3	32.4±2.1	-0.5±4.8
TFP	(3)	13.9±2.0	9.6±4.8	30.5±2.9	8.7±4.1
	(10)	8.1±0.8*	52.1±7.1	15.1±1.2**	52.7±3.7
	(30)	2.2±1.3**	87.8±4.5	3.2±1.7**	89.7±4.8
	IC_{50}	14.3±3.9		12.5±3.7	
	Control	22.6±1.7	--	46.4±2.1	--
44	(30)	21.0±0.7	6.1±4.5	47.5±1.6	-3.2±8.0
	(100)	18.6±2.9	18.9±7.3	48.0±6.6	-2.9±10.3
	Control	14.8±1.0	--	16.7±1.5	--
TFP	(3)	13.4±1.2	9.6±1.8	14.9±0.9	10.5±2.2
	(10)	8.5±1.3**	43.1±5.3	9.7±0.9*	39.7±9.8
	(30)	5.1±0.4**	64.7±3.1	6.6±0.4**	59.5±5.2
	IC_{50}	19.3±1.3		21.9±2.5	

	Control	42.5±0.8	--	61.5±3.3	--
45	(10)	35.9±2.5*	15.4±4.5	56.7±5.4	8.1±4.4
	(30)	36.7±2.6*	13.5±4.7	59.1±5.0	4.1±3.6
TFP	(3)	35.2±0.8	16.8±2.2	55.7±5.3	8.9±1.9
	(10)	22.7±1.6**	44.9±8.6	44.0±6.8	28.0±6.1
	(30)	4.8±0.7**	88.6±2.7	2.0±2.2**	96.9±4.1
	IC_{50}	14.2±0.7		16.0±0.9	
	Control	24.5±0.3	--	46.1±1.1	--
46	(30)	22.3±0.5	8.8±3.1	45.3±0.8	1.6±3.5
	(100)	22.9±1.5	6.1±6.9	39.6±1.5	13.7±4.8
47	(30)	24.8±0.5	-1.4±3.2	43.3±2.6	6.1±5.0
	(100)	21.0±0.9	14.5±2.9	41.3±3.2	10.5±6.4
48	(30)	21.8±0.9	10.9±4.5	43.6±3.4	5.6±5.8
	(100)	20.7±1.0	15.5±4.2	41.3±3.3	10.9±5.1
50	(10)	22.1±0.8	9.9±3.0	42.0±2.6	8.9±4.5
	(30)	14.6±1.4**	40.6±5.8	30.3±3.7**	34.3±7.8
	(100)	10.9±1.8**	55.3±8.4	15.8±1.8**	66.0±3.1
	IC_{50}	66.6±4.1		68.0±5.7	
51	(30)	20.4±1.8	17.8±7.9	41.0±1.6	11.1±2.1
	(100)	17.7±1.7**	27.8±7.0	32.3±2.4**	30.0±5.0
52	(30)	21.1±0.7	13.9±3.1	41.2±2.4	10.7±3.8
	(100)	22.3±1.8	9.1±8.1	37.2±2.4	19.3±5.4
TFP	(10)	27.2±2.8	-10.9±12.5	49.1±2.7	-7.5±4.8
	(30)	13.9±1.8**	43.3±8.2	24.1±5.2**	48.4±4.5
	(100)	9.6±1.5**	60.9±7.0	11.7±4.7**	74.9±8.6
	IC_{50}	24.4±0.5		22.8±0.5	
	Control	30.4±0.6	--	64.8±1.6	--
53	(10)	24.2±2.6**	20.6±7.3	54.8±4.3	15.5±5.3
	(30)	22.0±3.3**	27.9±9.7	49.5±5.2*	23.7±6.8
TFP	(3)	31.3±0.3	-1.0±2.1	63.9±5.8	2.6±2.1
	(10)	23.7±1.4**	23.2±6.5	54.4±9.7	18.1±10.0
	(20)	5.5±0.7**	82.0±2.6	2.0±1.3**	97.2±1.9
	IC_{50}	14.0±0.5		12.6±0.6	

Neutrophil suspensions were preincubated at 37 ℃ with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Forty-five minutes after the addition of fMLP (1 μM), β-glucuronidase and lysozyme activities in the supernatant were determined. Trifluoperazine (TFP) is a positive control. Values are presented as mean±S.E., -- not determined. N=3-8. *: P<0.05, **: P<0.01.

Table 15. The inhibitory effect of substituted furo[2,3-*b*]chromone-2-carboxylic acid ethyl esters on rat neutrophil 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**: $R_1=R_3=R_4=H$, $R_2=Br$

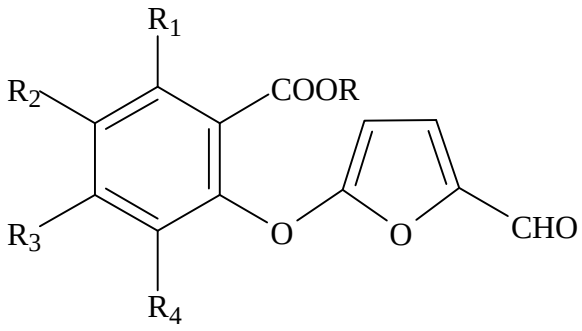
66: $R_1=R_2=R_3=H$, $R_4=OCH_3$ **73**: $R_1=R_3=R_4=H$, $R_2=I$

Compound	conc.	Percent Release			
	(μM)	β-Glucuronidase	(%inh)	Lysozyme	(%inh)
	Control	15.1±0.9	--	30.4±1.2	--
61	(10)	9.8±0.7**	37.5±3.9	--	--
	(30)	11.9±1.4*	24.8±7.1	23.8±2.1*	7.3±7.0
	(100)	7.4±1.1**	56.0±5.0	16.4±1.1**	34.1±5.9
	IC_{50}		70.5±7.8		
62	(10)	13.4±2.1*	12.5±10.2	--	--
	(30)	9.9±0.3**	38.3±2.9	31.2±4.6	10.9±11.5
	(100)	7.7±0.5**	52.1±2.8	24.2±2.7	29.7±5.8
	IC_{50}		77.2±8.1		
TFP	(3)	13.9±2.0	9.6±4.8	30.5±2.9	8.7±4.1
	(10)	8.1±0.8*	52.1±7.1	15.1±1.2**	52.7±3.7
	(30)	2.2±1.3**	87.8±4.5	3.2±1.7**	89.7±4.8
	IC_{50}		14.3±3.9		12.5±3.7
	Control	22.6±1.7	--	46.4±2.1	--
63	(30)	17.9±1.1	20.6±1.1	44.8±1.1	3.2±2.7
	(100)	17.3±1.8	23.7±3.5	49.2±6.0	-5.5±8.3
64	(30)	16.1±2.0	29.0±4.7	50.5±6.0	-8.8±10.8
	(100)	14.9±1.6	34.4±3.0	29.4±3.4	36.3±8.0
	Control	14.8±1.0	--	16.7±1.5	--
TFP	(3)	13.4±1.2	9.6±1.8	14.9±0.9	10.5±2.2

	(10)	8.5±1.3**	43.1±5.3	9.7±0.9*	39.7±9.8
	(30)	5.1±0.4**	64.7±3.1	6.6±0.4**	59.5±5.2
	IC_{50}	19.3±1.3		21.9±2.5	
	Control	21.6±0.6	--	54.7±1.6	--
65	(10)	22.1±0.4	-2.7±4.7	46.0±7.5	16.4±11.8
	(30)	16.7±1.4**	22.1±8.4	40.7±4.3**	25.8±5.8
66	(10)	18.3±0.5**	15.0±5.2	43.9±5.6*	20.0±8.1
	(30)	19.6±0.1*	8.9±3.2	47.9±4.5	12.6±5.9
67	(10)	19.4±0.6*	10.0±2.7	49.3±2.5	9.6±5.3
	(30)	18.1±0.7**	15.9±3.0	48.3±3.3	11.6±5.1
68	(10)	17.9±0.3**	16.9±3.0	45.9±3.7	16.2±4.5
	(30)	17.4±0.2**	17.7±2.1	38.7±6.5**	27.8±10.1
TFP	(3)	24.8±2.0	-14.6±12.7	64.9±6.7	-17.6±11.5
	(10)	17.0±2.0**	21.3±11.4	45.6±3.2	17.5±3.1
	(30)	2.6±0.7**	87.8±3.4	1.3±2.7**	97.3±4.9
	IC_{50}	18.9±2.1		18.3±0.9	
	Control	32.5±0.4	--	48.2±3.0	--
70	(10)	29.2±1.1	10.1±4.7	44.9±3.4	6.7±1.5
	(30)	27.3±1.1	15.9±4.5	45.8±2.8	4.9±3.1
71	(10)	29.2±0.7	10.1±3.1	47.1±3.5	2.4±2.4
	(30)	22.6±1.3**	30.6±3.6	38.3±5.1	20.9±7.0
72	(10)	30.5±0.5	6.1±0.8	51.2±3.0	-6.4±2.0
	(30)	32.3±0.7	0.9±1.2	51.4±4.2	-6.4±3.1
73	(10)	32.7±2.3	-0.7±8.2	53.1±2.0	-10.7±5.1
	(30)	31.3±0.5	3.8±1.4	48.4±3.3	-0.4±2.4
TFP	(3)	37.8±1.3	-14.6±12.7	56.7±4.0	-17.6±11.5
	(10)	24.9±1.3**	21.3±11.4	39.4±1.9	17.5±3.1
	(30)	3.7±0.4**	87.8±3.4	1.1±1.6**	97.3±4.9
	IC_{50}	18.9±2.1		18.3±0.9	

Neutrophil suspensions were preincubated at 37 ℃ with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Forty-five minutes after the addition of fMLP (1 μM), β-glucuronidase and lysozyme activities in the supernatant were determined. Trifluoperazine (TFP) is a positive control. Values are presented as mean±S.E., -- not determined. N=3-8. *: P<0.05, **: P<0.01.

Table 16. The inhibitory effect of 5-(2'-alkoxycarbonyl substituted phenoxy)furfurals on rat neutrophil degranulation (*in vitro*)



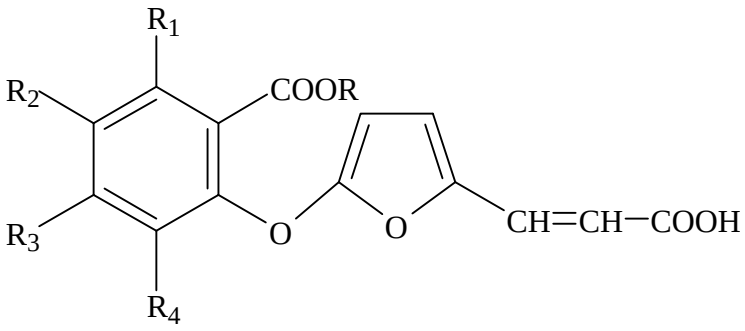
81: R=CH_3, R_1=R_2=R_3=R_4=H
82: R=CH_3, R_1=R_2=R_3=H, R_4=CH_3
83: R=CH_3, R_1=R_2=R_4=H, R_3=CH_3
84: R=CH_3, R_1=R_3=R_4=H, R_2=CH_3
85: R=C_2H_5, R_2=R_3=R_4=H, R_1=CH_3
86: R=CH_3, R_1=R_2=R_3=H, R_4=OCH_3
87: R=CH_3, R_1=R_2=R_4=H, R_3=OCH_3
88: R=CH_3, R_1=R_3=R_4=H, R_2=OCH_3
89: R=CH_3, R_2=R_3=R_4=H, 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. (μM)	Percent Release β-Glucuronidase	(%inh)	Lysozyme	(%inh)
	Control	20.2±0.6	--	25.6±0.7	--
81	(10)	18.3±0.6	9.4±4.1	21.9±0.5	14.3±0.8
	(30)	16.5±0.6**	18.1±4.5	14.8±0.1**	41.9±1.9
82	(10)	19.8±0.6	1.8±2.8	33.7±3.3	-30.8±9.3
	(30)	16.8±0.8**	17.6±4.7	20.8±1.2	18.1±7.7
83	(10)	17.1±0.6*	15.3±3.6	24.5±1.3	4.3±2.4
	(30)	15.9±0.8**	21.2±6.0	16.1±2.2**	37.6±6.9
84	(10)	18.0±0.4	10.7±2.8	37.3±8.6	-43.6±8.0
	(30)	15.1±0.4**	25.3±1.1	17.5±2.3**	32.1±7.0
85	(10)	18.4±1.2	9.0±4.5	32.9±1.3	-28.4±1.2
	(30)	15.8±1.1*	21.6±7.8	20.7±1.4	18.5±8.5
TFP	(3)	20.4±0.6	-0.8±0.2	27.5±0.8	-7.6±5.7
	(10)	15.1±0.6**	25.4±0.8	16.8±0.4**	34.4±0.3
	(30)	2.4±0.4**	87.7±2.1	1.8±0.8**	92.5±3.4
	IC_{50}	12.9±0.2		12.0±0.5	
	Control	31.5±1.5	--	60.5±3.7	--
86	(10)	25.3±1.0	19.6±1.7	60.7±5.1	-0.06±2.2

	(30)	26.4±2.3	16.5±3.3	59.5±7.5	2.4±6.6
87	(10)	27.1±1.2	13.8±0.5	60.5±4.1	0.09±1.0
	(30)	24.2±1.9*	23.2±3.2	54.7±6.5	10.3±5.2
88	(10)	28.6±2.4	9.4±3.4	59.6±4.2	1.6±2.7
	(30)	22.6±0.8*	28.2±2.0	50.8±6.0	16.7±4.5
89	(10)	27.4±3.1	13.3±7.4	60.1±3.0	0.3±3.8
	(30)	25.6±2.5	19.1±4.1	58.2±4.2	3.9±1.8
90	(10)	26.4±3.8	17.0±9.0	56.3±10.0	8.0±12.5
	(30)	23.6±1.3*	25.0±1.1	53.2±5.7	12.4±4.4
91	(10)	31.4±1.9	0.3±2.1	61.1±3.3	-1.0±1.6
	(30)	29.2±2.3	7.5±3.1	56.4±4.4	6.9±2.0
92	(10)	24.5±2.9	22.5±6.5	-1.4±4.9	-1.4±4.9
	(30)	22.8±1.7*	27.6±2.1	54.9±3.4	9.1±1.7
93	(10)	27.3±1.8	13.4±1.5	59.7±2.7	1.1±2.3
	(30)	20.8±1.5**	34.1±2.4	49.5±2.3	18.1±1.3
TFP	(3)	30.2±0.9	3.4±2.6	58.3±0.8	2.6±5.4
	(10)	20.0±0.5**	35.1±5.1	32.9±1.0**	44.7±4.6
	(30)	4.5±0.4**	85.9±1.2	9.3±1.1**	84.8±3.7
	IC_{50}	11.3±0.8		11.0±0.2	

Neutrophil suspensions were preincubated at 37 ℃ with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Forty-five minutes after the addition of fMLP (1 μM), β-glucuronidase and lysozyme activities in the supernatant were determined. Trifluoperazine (TFP) is a positive control. Values are presented as mean±S.E., N=3. *: P<0.05, **: P<0.01.

Table 17. The inhibitory effect of 5-(2'-alkoxycarbonyl substituted phenoxy)-2-furanacrylic acids on rat neutrophil degranulation (*in vitro*)



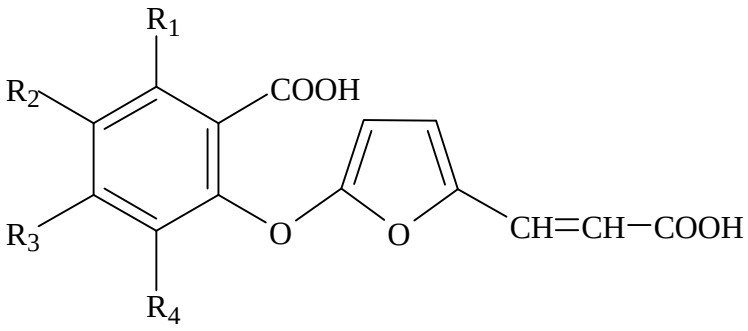
101: R=CH_3, R_1=R_2=R_3=R_4=H
102: R=CH_3, R_1=R_2=R_3=H, R_4=CH_3
103: R=CH_3, R_1=R_2=R_4=H, R_3=CH_3
104: R=CH_3, R_1=R_3=R_4=H, R_2=CH_3
105: R=C_2H_5, R_2=R_3=R_4=H, R_1=CH_3
106: R=CH_3, R_1=R_2=R_3=H, R_4=OCH_3
107: R=CH_3, R_1=R_2=R_4=H, R_3=OCH_3
108: R=CH_3, R_1=R_3=R_4=H, R_2=OCH_3
109: R=CH_3,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

Compound	conc. (μM)	Percent Release β-Glucuronidase	(%inh)	Lysozyme	(%inh)
	Control	20.2±0.6	--	25.6±0.7	--
101	(10)	19.9±0.8	1.5±5.7	47.9±4.8**	-85.9±13.6
	(30)	18.4±0.9	8.8±5.6	41.1±5.1*	-59.1±15.6
102	(10)	19.6±0.5	2.9±1.3	40.1±5.7*	-55.2±12.3
	(30)	21.5±0.8	-5.9±1.6	40.2±8.1	-55.2±17.8
103	(10)	16.5±0.5**	18.4±2.0	41.3±4.2**	-60.4±11.9
	(30)	15.9±0.5**	21.3±0.2	33.9±7.1	-30.6±15.7
104	(10)	18.4±0.5	9.0±1.3	40.8±4.6*	-58.4±13.8
	(30)	18.0±0.4	10.7±2.4	37.6±5.6	-45.5±18.0
105	(10)	19.7±0.2	2.3±1.9	37.3±3.4*	-45.0±8.9
	(30)	21.3±0.7	-5.2±1.1	33.6±0.5	-31.4±6.1
TFP	(3)	20.4±0.6	-0.8±0.2	27.5±0.8	-7.6±5.7
	(10)	15.1±0.6**	25.4±0.8	16.8±0.4**	34.4±0.3
	(30)	2.4±0.4**	87.7±2.1	1.8±0.8**	92.5±3.4
	IC_{50}	12.9±0.2		12.0±0.5	
	Control	31.5±1.5	--	60.5±3.7	--
106	(10)	31.2±2.0	1.1±2.1	63.2±2.5	-4.6±3.1
	(30)	28.4±4.1	10.6±8.9	58.9±6.3	3.0±7.1
107	(10)	32.6±2.7	-3.0±4.1	63.7±2.8	-5.5±3.9

	(30)	29.8±1.9	5.6±1.8	61.5±2.1	-1.9±2.8
108	(10)	33.6±2.6	-6.3±4.0	62.4±2.8	-3.4±2.8
	(30)	31.8±2.0	-0.7±1.8	63.5±2.7	-5.2±2.7
109	(10)	35.8±1.9	-13.6±1.7	64.2±2.4	-6.3±2.4
	(30)	35.3±2.6	-11.8±3.5	63.1±2.8	-4.5±2.3
TFP	(3)	30.2±0.9	3.4±2.6	58.3±0.8	2.6±5.4
	(10)	20.0±0.5**	35.1±5.1	32.9±1.0**	44.7±4.6
	(30)	4.5±0.4**	85.9±1.2	9.3±1.1**	84.8±3.7
	IC_{50}	11.3±0.8		11.0±0.2	

Neutrophil suspensions were preincubated at 37 ℃ with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Forty-five minutes after the addition of fMLP (1 μM), β-glucuronidase and lysozyme activities in the supernatant were determined. Trifluoperazine (TFP) is a positive control. Values are presented as mean±S.E., N=3. *: P<0.05, **: P<0.01.

Table 18. The inhibitory effect of 5-(2'-carboxyl substituted phenoxy)-2-furanacrylic acids on rat neutrophil 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)	Lysozyme	(%inh)
	Control	20.2±0.6	--	25.6±0.7	--
111	(10)	19.7±1.2	2.7±4.0	41.0±6.9*	-58.6±14.8
	(30)	20.4±0.8	-0.6±1.8	37.2±7.8	-43.5±16.8
112	(10)	16.2±1.8	19.2±11.0	45.0±3.7**	-74.8±9.4
	(30)	19.7±0.7	2.5±4.6	43.0±6.5**	-66.5±14.9
113	(10)	21.1±0.6	-4.2±2.7	37.4±4.2	-45.2±12.5
	(30)	15.7±1.9*	21.7±11.1	35.7±4.6	-38.4±14.1
114	(10)	20.0±0.9	0.7±5.8	34.1±1.9	-33.7±11.9
	(30)	20.7±1.7	-3.0±10.9	35.1±0.9	-37.5±8.0
TFP	(3)	20.4±0.6	-0.8±0.2	27.5±0.8	-7.6±5.7
	(10)	15.1±0.6**	25.4±0.8	16.8±0.4**	34.4±0.3
	(30)	2.4±0.4**	87.7±2.1	1.8±0.8**	92.5±3.4
	IC_{50}	12.9±0.2		12.0±0.5	
	Control	31.5±1.5	--	60.5±3.7	--
116	(10)	28.6±2.2	9.3±2.9	65.8±1.7	-9.3±5.0
	(30)	28.3±2.0	10.4±2.8	63.1±1.7	-4.7±3.4
117	(10)	31.3±1.8	0.7±1.7	64.3±0.9	-6.8±5.1
	(30)	29.6±1.6	6.2±0.7	64.6±1.0	-7.4±5.1

118	(10)	30.6±1.3	2.8±1.1	64.4±1.5	-6.9±4.3
	(30)	30.1±2.3	4.8±2.9	62.7±2.5	-3.9±2.5
120	(10)	32.9±2.8	-4.1±3.9	60.3±1.1	-0.1±4.5
	(30)	33.2±3.1	-4.9±5.3	62.9±1.6	-4.3±3.6
121	(10)	35.3±2.3	-11.7±2.5	63.4±2.3	-5.1±2.8
	(30)	32.4±2.6	-2.5±3.6	59.9±2.7	0.8±2.1
122	(10)	37.0±2.4	-17.2±2.4	64.1±2.8	-6.2±3.1
	(30)	35.2±3.4	-11.3±5.9	61.6±2.3	-2.2±4.8
123	(10)	28.7±3.0	9.2±5.8	61.9±0.8	-2.9±4.9
	(30)	28.5±2.1	9.8±2.5	61.4±2.0	-1.7±3.2
TFP	(3)	30.2±0.9	3.4±2.6	58.3±0.8	2.6±5.4
	(10)	20.0±0.5**	35.1±5.1	32.9±1.0**	44.7±4.6
	(30)	4.5±0.4**	85.9±1.2	9.3±1.1**	84.8±3.7
	IC_{50}	11.3±0.8		11.0±0.2	

Neutrophil suspensions were preincubated at 37 ℃ with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Forty-five minutes after the addition of fMLP (1 μM), β-glucuronidase and lysozyme activities in the supernatant were determined. Trifluoperazine (TFP) is a positive control. Values are presented as mean±S.E., N=3. *: P<0.05, **: P<0.01.

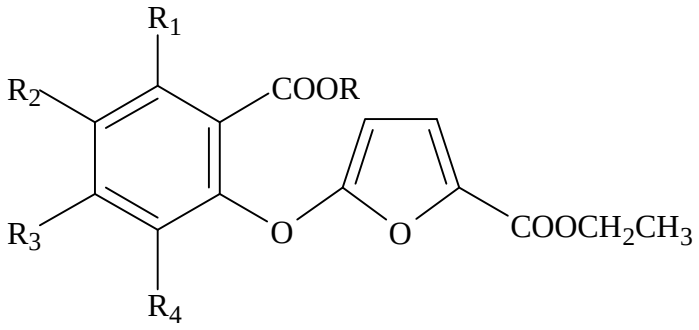
(二)對於fMLP**誘導的嗜中性白血球超氧自由基生成作用抑制試驗**

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fMLP**誘導的嗜中性白血球超氧自由基生成作用之體外試驗中，由**superoxide formation**的抑制百分率** (**見** Table 19**至**Table 24)**看來，在濃度**30 μM**時，化合物23、26、27、30、31、44-46、48、51-53、61、62、65-68、70、72、73、81、83-91、101、108、117、118及120分別呈現弱的抑制活性** (**具有約**20-47%**的抑制百分率**)**，但是發現化合物25、28、32、50、64、71、92及93呈現明顯的抑制活性，其抑制**superoxide formation**的**IC_{50}**值分別為** 15.0±1.9 μM **、** 39.9±2.8 μM**、** 24.3±5.1 μM **、** 35.4±8.0 μM**、** 45.0±3.5 μM**、** 24.4±1.5 μM**、** 13.4±2.9 μM**及**19.6±5.6 μM**。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、** 5-(2'-carboxyl substituted phenoxy)-furan-2-carboxylic acids (**41-48 及 50-53**) **類、** substituted furo[2,3-*b*]-chromone-2-carboxylic acid ethyl esters (**61-68及70-73**)**類及** 5-(2'-alkoxycarbonyl substituted phenoxy)furfurals (**81-93**)**類衍生物的活性較明顯。在** ethyl 5-(2'-alkoxycarbonyl substituted phenoxy)furan-2-carboxylates (**21-33**)**類衍生物中將甲基、甲氧基或溴原子導入苯環時，具有較高的活性，而化合物** ethyl 5-(2'-ethoxycarbonyl-3'-methyl-phenoxy)furan-2-carboxylate (**25**)**的**IC_{50} = 15.0±1.9 μM**約與**trifluoperazine**的**IC_{50} = 14.7± 0.4 μM**相當，化合物** ethyl 5-(2'-methoxy-carbonyl-4'-methoxyphenoxy)furan-2-carboxylate (**28**)**的**IC_{50} = 39.9±2.8 μM**約為**trifluoperazine**之**IC_{50} = 20.1±1.5 μM**的二倍，化合物** ethyl 5-(2'-methoxycarbonyl-4'-bromophenoxy)furan-2-carboxylate (**32**)**的**IC_{50} = 24.3±5.1 μM**約與**trifluoperazine**的**IC_{50} = 20.1±1.5 μM**相當。與甲基、甲氧基或溴原子相較之下，若將氯原子導入苯環，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。在**5-(2'-carboxyl substituted phenoxy)furan-2-carboxylic acids (**41-48及50-53**)**類衍生物中將氯原子導入苯環時，具有較高的活性，而化合物** 5-(2'-carboxyl-5'-chlorophenoxy)furan-2-carboxylic acid (**50**) **的** IC_{50} = 35.4±8.0 μM**約為**trifluoperazine**之**IC_{50} = 20.1±1.5 μM**的二倍。與氯原子相較之下，若將溴原子或碘原子導入苯環，則其活性降低，此外，若將甲基或甲氧基導入苯環，則其活性降得更低。在**substituted furo[2,3-*b*]chromone- 2-carboxylic acid ethyl esters (**61-68及70-73**)**類衍生物中將氯原子導入環上時，具有較高的活性，而化合物**ethyl

6-chlorofuro[2,3-*b*]chromone- 2-carboxylate (**71**)**的**IC_{50} = 24.4±1.5 μM **約為**trifluoperazine**之**IC_{50} = 12.9 ±1.0 μM**的二倍。與氯原子相較之下，若將甲基、甲氧基或碘原子導入環上，則其活性降低，此外，若將溴原子導入環上，則其活性降得更低。另外，在**5-(2'-alkoxycarbonyl substituted phenoxy)furfurals (**81-93**)**類衍生物中將溴原子或碘原子導入苯環時，具有較高的活性，而化合物** 5-(2'-methoxycarbonyl-4'-bromophenoxy)furfural (**92**)**的**IC_{50} = 13.4±2.9 μM **約為** trifluoperazine **之** IC_{50} = 6.2±0.3 μM **的二倍，化合物** 5-(2'-methoxycarbonyl-4'-iodophenoxy)furfural (**93**) **的** IC_{50} = 19.6±5.6 μM**約為**trifluoperazine**之**IC_{50} = 6.2±0.3 μM**的三倍。與溴原子或碘原子相較之下，若將甲氧基或氯原子導入苯環，則其活性降低，此外，若將甲基導入苯環，則其活性降得更低。**

Table 19. The inhibitory effect of ethyl 5-(2'-alkoxycarbonyl substituted phenoxy)-furan-2-carboxylates on rat neutrophil superoxide formation (*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

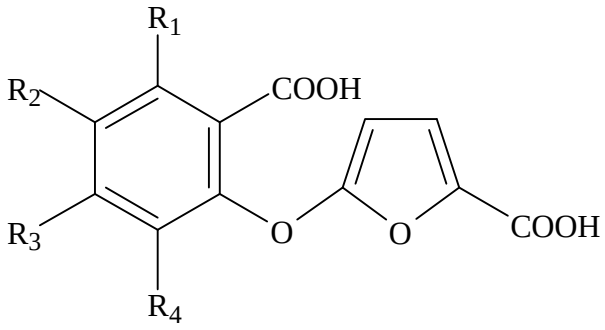
Compound	conc. (μM)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	0.9±0.1	--
21	(30)	0.9±0.0	-1.2±2.3
	(100)	0.6±0.0	6.6±6.6
22	(30)	0.8±0.1	14.9±2.4
	(100)	0.7±0.0*	23.3±6.3
23	(30)	0.8±0.1	20.0±2.1
	(100)	0.6±0.1*	36.4±1.4
TFP	(3)	0.5±0.1**	35.7±2.2
	(5)	0.2±0.0**	71.4±3.4
	(10)	0.1±0.0**	85.7±1.0
	IC_{50}	4.3±0.3	
	Control	1.25±0.21	--
24	(30)	1.02±0.21	19.8±3.9
	(100)	0.80±0.11	34.7±4.7
	Control	1.30±0.17	--
TFP	(3)	1.10±0.27	17.8±1.2
	(10)	0.20±0.03**	84.5±1.2
	(30)	0.05±0.04**	96.1±3.2

	IC_{50}		9.4±2.2	
	Control	2.15±0.23		--
25	(3)	1.61±0.26		24.8±7.9
	(10)	1.31±0.24**		40.5±8.1
	(30)	0.52±0.09**		76.5±1.8
	IC_{50}		15.0±1.9	
TFP	(1)	2.59±0.15		29.4±12.0
	(10)	0.47±0.08**		77.1±7.2
	(30)	0.12±0.03**		93.0±3.0
	IC_{50}		14.7±0.4	
	Control	1.68±0.20		--
26	(30)	1.31±0.25		23.3±6.7
	(100)	1.13±0.22*		33.2±7.5
27	(30)	1.04±0.15*		38.4±2.9
	(100)	0.94±0.25**		47.7±10.1
28	(3)	1.26±0.08		14.6±8.5
	(10)	0.88±0.03**		48.8±2.8
	(30)	0.85±0.08**		49.7±2.5
	(100)	0.53±0.16**		71.2±9.7
	IC_{50}		39.9±2.8	
TFP	(3)	1.52±0.04		3.1±5.3
	(10)	1.05±0.04*		33.0±5.2
	(30)	0.52±0.04**		69.5±10.4
	IC_{50}		20.1±1.5	
	Control	5.47±0.57		--
29	(10)	4.93±0.67		9.7±7.6
	(30)	5.12±0.96		15.6±12.2
TFP	(3)	4.12±0.04		24.3±1.9
	(10)	1.16±0.08**		78.1±5.4
	(30)	0.02±0.05**		99.1±3.3
	IC_{50}		6.2±0.3	
	Control	1.68±0.20		--
30	(30)	1.26±0.22		25.3±7.6
	(100)	1.38±0.24		18.9±7.7
31	(30)	1.05±0.20**		39.0±5.6
	(100)	1.13±0.21*		33.9±7.8
32	(1)	1.23±0.14		15.5±7.3
	(3)	0.89±0.12**		44.0±5.8
	(10)	0.80±0.12**		54.1±5.0
	(30)	0.64±0.09**		61.2±5.8
	IC_{50}		24.3±5.1	
TFP	(3)	1.52±0.04		3.1±5.3
	(10)	1.05±0.04*		33.0±5.2
	(30)	0.52±0.04**		69.5±10.4

	IC_{50}	20.1±1.5	
	Control	1.59±0.05	--
33	(10)	1.23±0.18*	22.5±13.1
	(30)	2.08±0.03**	-30.7±3.5
TFP	(3)	1.27±0.22	20.5±5.3
	(10)	0.91±0.16**	42.9±2.8
	(30)	0.03±0.02**	98.2±0.9
	IC_{50}	13.0±0.3	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of fMLP (0.3 μM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-7. *: P<0.05, **: P<0.01.

Table 20. The inhibitory effect of 5-(2'-carboxyl substituted phenoxy)furan-2-carboxylic acids on rat neutrophil superoxide formation (*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**: $R_1=R_3=R_4=H$, $R_2=Br$

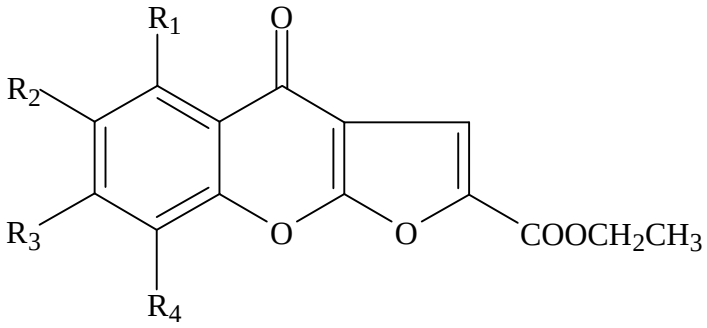
46: $R_1=R_2=R_3=H$, $R_4=OCH_3$ **53**: $R_1=R_3=R_4=H$, $R_2=I$

Compound	conc. (μM)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	0.9±0.1	--
41	(30)	0.9±0.0	-4.8±2.3
	(100)	1.0±0.1	-9.1±8.3
42	(30)	0.9±0.1	5.9±2.9
	(100)	0.7±0.0	21.9±2.5
43	(30)	1.0±0.2	0.0±6.3
	(100)	0.7±0.0	23.1±7.1
TFP	(3)	0.5±0.1**	35.7±2.2
	(5)	0.2±0.0**	71.4±3.4
	(10)	0.1±0.0**	85.7±1.0
	IC_{50}	4.3±0.3	
	Control	1.29±0.22	--
44	(30)	0.83±0.06	31.5±8.4
	(100)	0.72±0.12	44.0±1.7
	Control	1.30±0.17	--
TFP	(3)	1.10±0.27	17.8±1.2
	(10)	0.20±0.03**	84.5±1.2
	(30)	0.05±0.04**	96.1±3.2
	IC_{50}	9.4±2.2	

	Control	2.15±0.23		--
45	(10)	1.36±0.17**		36.6±3.7
	(30)	1.40±0.20**		35.2±3.8
TFP	(1)	2.59±0.15		29.4±12.0
	(10)	0.47±0.08**		77.1±7.2
	(30)	0.12±0.03**		93.0±3.0
	IC_{50}		14.7±0.4	
	Control	1.68±0.20		--
46	(30)	1.14±0.24*		28.2±6.0
	(100)	1.11±0.25*		36.8±9.8
47	(30)	1.31±0.04		11.6±7.5
	(100)	1.05±0.19*		38.4±5.0
48	(30)	1.20±0.09		26.3±8.0
	(100)	1.00±0.12*		37.9±9.1
50	(10)	1.19±0.03		26.7±9.7
	(30)	0.81±0.04**		49.9±4.3
	(100)	0.46±0.09**		75.2±5.0
	IC_{50}		35.4±8.0	
51	(10)	1.18±0.05		20.3±8.2
	(30)	0.96±0.10**		41.3±6.5
	(100)	0.77±0.06**		57.4±6.3
	IC_{50}		72.6±8.9	
52	(30)	1.11±0.04*		38.6±6.4
	(100)	0.98±0.09**		40.1±6.1
TFP	(3)	1.52±0.04		3.1±5.3
	(10)	1.05±0.04*		33.0±5.2
	(30)	0.52±0.04**		69.5±10.4
	IC_{50}		20.1±1.5	
	Control	1.59±0.05		--
53	(10)	1.27±0.10*		19.7±8.6
	(30)	1.06±0.07**		33.6±5.1
TFP	(3)	1.27±0.22		20.5±5.3
	(10)	0.91±0.16**		42.9±2.8
	(30)	0.03±0.02**		98.2±0.9
	IC_{50}		13.0±0.3	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of fMLP (0.3 μM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-7. *: P<0.05, **: P<0.01.

Table 21. The inhibitory effect of substituted furo[2,3-*b*]chromone-2-carboxylic acid ethyl esters on rat neutrophil superoxide formation (*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**: $R_1=R_3=R_4=H$, $R_2=Br$

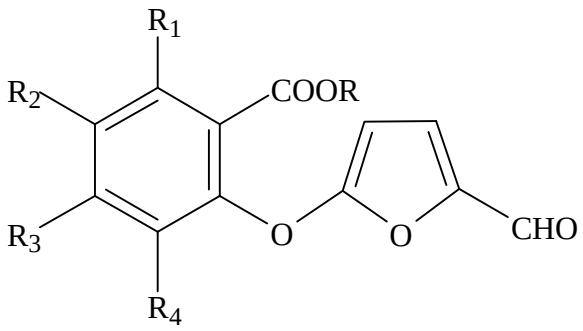
66: $R_1=R_2=R_3=H$, $R_4=OCH_3$ **73**: $R_1=R_3=R_4=H$, $R_2=I$

Compound	conc. (μM)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	0.9±0.1	--
61	(10)	1.0±0.0	-6.1±3.1
	(30)	0.6±0.0**	34.3±3.5
	(100)	0.4±0.1**	54.9±1.9
	IC_{50}	75.9±3.9	
62	(10)	0.8±0.1	2.5±3.1
	(30)	0.5±0.0**	42.2±3.5
	(100)	0.3±0.1**	65.5±7.9
	IC_{50}	57.6±4.1	
TFP	(3)	0.5±0.1**	35.7±2.2
	(5)	0.2±0.0**	71.4±3.4
	(10)	0.1±0.0**	85.7±1.0
	IC_{50}	4.3±0.3	
	Control	1.25±0.21	--
63	(30)	1.29±0.24	-3.2±9.6
	(100)	0.82±0.16	34.8±5.0
	Control	1.63±0.05	--
64	(10)	1.24±0.12*	24.5±5.1
	(30)	0.73±0.06**	54.9±5.9

	(100)	0.42±0.07**		73.7±4.3
	IC_{50}		45.0±3.5	
	Control	1.30±0.17		--
TFP	(3)	1.10±0.27		17.8±1.2
	(10)	0.20±0.03**		84.5±1.2
	(30)	0.05±0.04**		96.1±3.2
	IC_{50}		9.4±2.2	
	Control	2.02±0.34		--
65	(10)	1.54±0.44		24.8±14.1
	(30)	1.50±0.48		28.1±12.3
66	(10)	1.46±0.26		28.1±1.2
	(30)	1.27±0.37*		39.9±8.6
67	(10)	1.32±0.38*		37.5±8.6
	(30)	1.41±0.43		32.5±9.8
68	(10)	1.37±0.30*		33.9±4.9
	(30)	1.07±0.11**		45.9±3.0
TFP	(3)	2.42±0.10		-29.4±12.0
	(10)	0.44±0.05**		77.1±7.2
	(30)	0.10±0.08**		93.0±3.0
	IC_{50}		14.7±0.4	
	Control	1.83±0.05		--
70	(10)	1.55±0.06		15.3±1.7
	(30)	1.16±0.02**		36.7±1.5
71	(10)	1.49±0.05		18.6±0.4
	(20)	1.01±0.08**		44.3±5.8
	(30)	0.73±0.03**		60.1±2.8
	IC_{50}		24.4±1.5	
72	(10)	1.78±0.13		3.0±4.2
	(30)	1.34±0.12*		24.7±7.4
73	(10)	1.42±0.15		21.7±10.4
	(30)	1.08±0.04**		41.2±0.7
TFP	(3)	2.50±0.42		-30.2±11.7
	(10)	1.09±0.28		40.5±11.1
	(30)	0.11±0.06**		93.6±3.3
	IC_{50}		12.9±1.0	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of fMLP (0.3 μM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-6. *: P<0.05, **: P<0.01.

Table 22. The inhibitory effect of 5-(2'-alkoxycarbonyl substituted phenoxy)furfurals on rat neutrophil superoxide formation (*in vitro*)



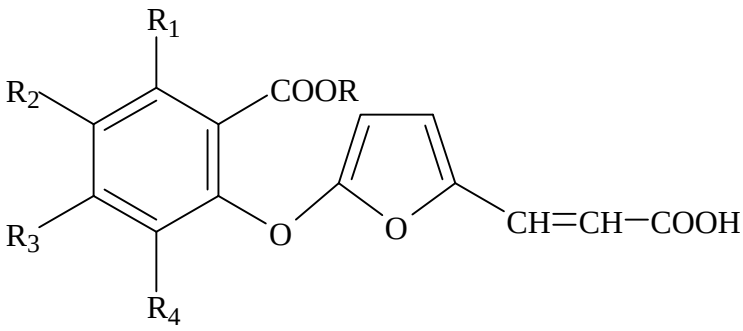
81: R=CH_3, R_1=R_2=R_3=R_4=H
82: R=CH_3, R_1=R_2=R_3=H, R_4=CH_3
83: R=CH_3, R_1=R_2=R_4=H, R_3=CH_3
84: R=CH_3, R_1=R_3=R_4=H, R_2=CH_3
85: R=C_2H_5, R_2=R_3=R_4=H, R_1=CH_3
86: R=CH_3, R_1=R_2=R_3=H, R_4=OCH_3
87: R=CH_3, R_1=R_2=R_4=H, R_3=OCH_3
88: R=CH_3, R_1=R_3=R_4=H, R_2=OCH_3
89: R=CH_3, R_2=R_3=R_4=H, 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. (μM)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	2.40±0.23	--
81	(10)	1.85±1.52	24.29±6.8
	(30)	1.52±0.37*	38.5±8.9
82	(10)	2.18±0.34	9.8±8.5
	(30)	1.97±0.33	17.9±10.0
83	(10)	1.42±0.14*	40.7±0.7
	(30)	1.43±0.12*	38.2±10.3
84	(10)	1.51±0.10*	36.6±2.7
	(30)	1.60±0.10*	32.6±2.6
85	(10)	1.81±0.05	23.2±7.6
	(30)	1.70±0.01	27.9±5.9
TFP	(3)	1.81±0.04*	24.3±1.9
	(10)	0.51±0.08**	78.1±5.4
	(30)	0.01±0.05**	99.1±3.3
	IC_{50}	6.2±0.3	
	Control	5.47±0.57	--

86	(10)	3.93±0.43*		27.6±6.1
	(30)	3.40±0.44**		36.7±9.3
87	(10)	3.61±0.57**		33.8±7.5
	(30)	2.94±0.37**		45.9±5.0
88	(10)	3.72±0.62**		31.6±9.0
	(30)	2.90±0.35**		46.5±7.7
89	(10)	3.80±0.60**		30.4±7.6
	(30)	3.02±0.29**		43.6±8.0
90	(10)	3.80±0.51**		30.1±6.6
	(30)	2.99±0.35**		44.8±6.3
91	(10)	4.33±0.59		20.8±6.5
	(30)	3.83±0.37*		29.3±6.4
92	(3)	3.95±0.29*		27.3±2.4
	(10)	2.96±0.16**		45.2±3.0
	(30)	1.88±0.12**		64.8±4.6
	IC_{50}		13.4±2.9	
93	(3)	3.81±0.27*		29.3±6.0
	(10)	3.28±0.21**		39.1±4.4
	(30)	2.34±0.12**		56.7±2.9
	IC_{50}		19.6±5.6	
TFP	(3)	4.12±0.04		24.3±1.9
	(10)	1.16±0.08**		78.1±5.4
	(30)	0.02±0.05**		99.1±3.3
	IC_{50}		6.2±0.3	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of fMLP (0.3 μM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-5. *: P<0.05, **: P<0.01.

Table 23. The inhibitory effect of 5-(2'-alkoxycarbonyl substituted phenoxy)-2-furanacrylic acids on rat neutrophil superoxide formation (*in vitro*)



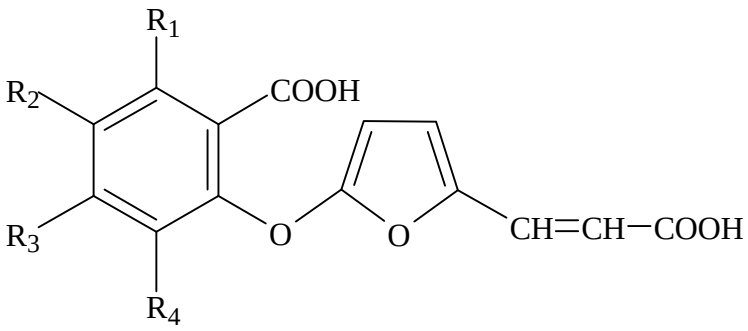
101: R=CH_3, R_1=R_2=R_3=R_4=H
102: R=CH_3, R_1=R_2=R_3=H, R_4=CH_3
103: R=CH_3, R_1=R_2=R_4=H, R_3=CH_3
104: R=CH_3, R_1=R_3=R_4=H, R_2=CH_3
105: R=C_2H_5, R_2=R_3=R_4=H, R_1=CH_3
106: R=CH_3, R_1=R_2=R_3=H, R_4=OCH_3
107: R=CH_3, R_1=R_2=R_4=H, R_3=OCH_3
108: R=CH_3, R_1=R_3=R_4=H, R_2=OCH_3
109: R=CH_3,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

Compound	conc. (μM)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	2.40±0.23	--
101	(10)	2.11±0.22	12.0±1.3
	(30)	1.82±0.14	23.7±2.0
102	(10)	2.12±0.05	9.6±10.3
	(30)	1.93±0.06	17.6±8.4
103	(10)	2.42±0.13	-1.8±4.2
	(30)	2.33±0.18	2.5±2.2
104	(10)	2.53±0.11	-6.5±5.2
	(30)	2.09±0.14	12.1±3.7
105	(10)	2.34±0.41	3.9±7.5
	(30)	2.43±0.09	-2.4±5.6
TFP	(3)	1.81±0.04*	24.3±1.9
	(10)	0.51±0.08**	78.1±5.4
	(30)	0.01±0.05**	99.1±3.3
	IC_{50}	6.2±0.3	
	Control	5.47±0.57	--
106	(10)	4.42±0.42	17.8±9.5
	(30)	4.03±0.36	25.6±4.9

107	(10)	4.40±0.43	18.4±8.8
	(30)	4.69±0.35	12.5±10.5
108	(10)	4.61±0.56	15.4±7.0
	(30)	4.22±0.43	22.2±6.3
109	(10)	4.41±0.62	19.2±7.5
	(30)	4.44±0.59	17.9±10.4
TFP	(3)	4.12±0.04	24.3±1.9
	(10)	1.16±0.08**	78.1±5.4
	(30)	0.02±0.05**	99.1±3.3
	IC_{50}	6.2±0.3	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of fMLP (0.3 μM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-5. *: P<0.05, **: P<0.01.

Table 24. The inhibitory effect of 5-(2'-carboxyl substituted phenoxy)-2-furanacrylic acids on rat neutrophil superoxide formation (*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)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	2.40±0.23	--
111	(10)	2.03±0.15	14.5±6.9
	(30)	2.37±0.14	0.3±4.3
112	(10)	2.28±0.23	5.1±2.4
	(30)	2.16±0.10	7.6±12.6
113	(10)	2.18±0.16	7.7±9.8
	(30)	2.07±0.19	13.2±3.7
114	(10)	2.49±0.13	-4.7±6.1
	(30)	2.35±0.06	0.8±6.6
TFP	(3)	1.81±0.04*	24.3±1.9
	(10)	0.51±0.08**	78.1±5.4
	(30)	0.01±0.05**	99.1±3.3
	IC_{50}	6.2±0.3	
	Control	5.47±0.57	--
116	(10)	4.66±0.75	14.6±10.5
	(30)	4.57±0.63	15.8±8.9
117	(10)	4.69±0.67	13.7±10.0

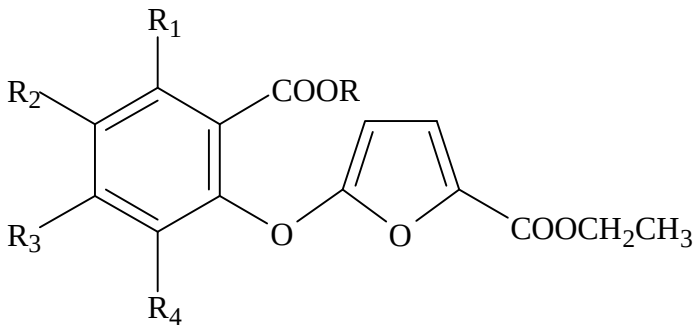
	(30)	3.76±0.03*	29.4±8.7
118	(10)	3.96±0.86*	29.5±8.9
	(30)	3.68±0.75**	34.1±7.3
120	(10)	4.50±0.65	17.2±9.2
	(30)	4.07±0.54	24.5±10.0
121	(10)	5.01±0.48	7.8±4.8
	(30)	4.65±0.50	14.2±7.6
122	(10)	4.89±0.57	9.9±8.3
	(30)	4.52±0.49	16.5±8.5
123	(10)	4.91±0.68	10.0±7.9
	(30)	4.57±0.65	15.9±9.4
TFP	(3)	4.12±0.04	24.3±1.9
	(10)	1.16±0.08**	78.1±5.4
	(30)	0.02±0.05**	99.1±3.3
	IC_{50}	6.2±0.3	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of fMLP (0.3 μM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-5. *: P<0.05, **: P<0.01.

(三)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**

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 PMA **誘導的嗜中性白血球超氧自由基生成作用之體外試驗中，由** superoxide formation **的抑制百分率(見** Table 25 **至** Table 30)**看來，在濃度** 30 μM **時，化合物 26、28、45、65、66、70、81 及 83 分別呈現弱的抑制活性 (具有約** 20-34%**的抑制百分率)。其他化合物則無明顯的抑制活性。**

Table 25. The inhibitory effect of ethyl 5-(2'-alkoxycarbonyl substituted phenoxy)-furan-2-carboxylates on rat neutrophil superoxide formation (*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

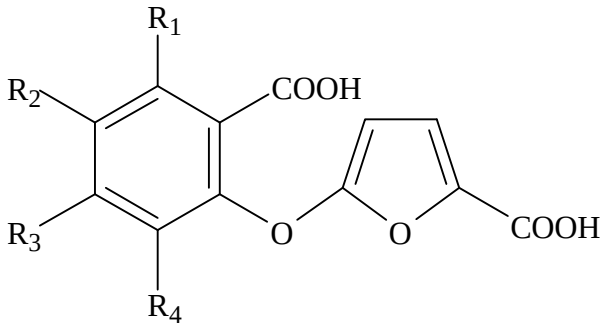
Compound	conc. (μM)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	4.1±0.3	--
21	(30)	3.9±0.1	-11.4±2.2
	(100)	3.6±0.3	-3.0±7.2
22	(30)	3.7±0.2	-3.0±3.8
	(100)	3.7±0.1	-5.2±3.0
23	(30)	3.5±0.2	-1.1±4.0
	(100)	3.4±0.2	2.2±3.8
TFP	(3)	3.5±0.4	19.2±11.2
	(5)	0.8±0.0**	81.4±2.1
	(10)	0.2±0.1**	96.1±2.0
	IC_{50}	4.7±0.5	
	Control	1.75±0.29	--
24	(30)	1.71±0.31	3.1±1.7
	(100)	1.36±0.24	23.1±3.3
	Control	1.92±0.09	--
TFP	(3)	1.34±0.07**	29.8±0.3
	(10)	0.48±0.02**	74.5±0.2
	(30)	0.22±0.01**	88.2±1.3
	IC_{50}	8.8±0.1	

	Control	3.14±0.12		--
25	(10)	2.48±0.26*		21.1±6.7
	(30)	3.10±0.06		1.2±2.2
TFP	(1)	2.55±0.23		16.6±10.1
	(3)	1.59±0.43**		49.5±7.4
	(10)	0.39±0.19**		87.1±4.9
	IC_{50}		4.5±0.3	
	Control	2.16±0.18		--
26	(30)	1.44±0.19**		33.9±5.3
	(100)	1.58±0.13**		32.8±5.1
27	(30)	1.89±0.27		14.1±6.1
	(100)	1.72±0.35*		21.9±7.8
28	(30)	1.56±0.15*		27.1±7.2
	(100)	2.17±0.11		7.3±5.3
TFP	(3)	1.85±0.53*		21.9±7.1
	(5)	1.05±0.08**		53.6±4.0
	(10)	0.53±0.11**		76.4±5.1
	IC_{50}		6.0±0.1	
	Control	6.34±0.25		--
29	(10)	5.99±0.82		5.6±12.1
	(30)	6.23±0.82		1.8±12.2
TFP	(3)	5.63±0.10		8.6±2.0
	(10)	1.18±0.03**		80.2±2.0
	(30)	0.47±0.01**		90.9±0.4
	IC_{50}		7.6±0.3	
	Control	2.16±0.18		--
30	(30)	1.90±0.17		12.2±0.9
	(100)	3.05±0.20*		-29.7±5.7
31	(30)	1.97±0.14		16.1±5.9
	(100)	2.16±0.13		7.3±8.5
32	(30)	2.19±0.35		0.1±11.6
	(100)	2.91±0.38**		-48.8±4.1
TFP	(3)	1.85±0.53*		21.9±7.1
	(5)	1.05±0.08**		53.6±4.0
	(10)	0.53±0.11**		76.4±5.1
	IC_{50}		6.0±0.1	
	Control	3.50±0.03		--
33	(10)	3.24±0.15		7.5±3.7
	(30)	3.14±0.25		10.4±6.7
TFP	(3)	2.33±0.19**		32.5±8.6
	(10)	0.86±0.15**		74.9±5.7
	(30)	0.08±0.03**		97.6±0.7
	IC_{50}		6.8±2.3	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the

presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of PMA (3 nM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-5. *: P<0.05, **: P<0.01.

Table 26. The inhibitory effect of 5-(2'-carboxyl substituted phenoxy)furan-2-carboxylic acids on rat neutrophil superoxide formation (*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**: $R_1=R_3=R_4=H$, $R_2=Br$

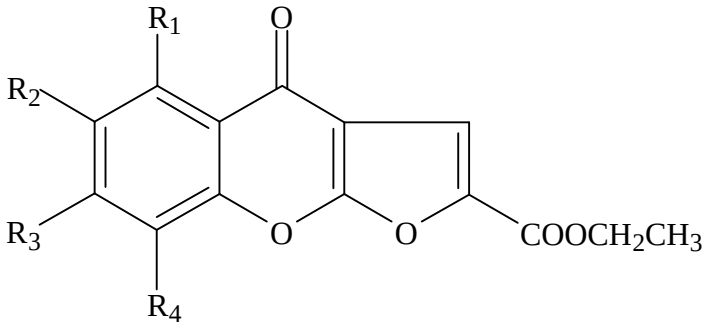
46: $R_1=R_2=R_3=H$, $R_4=OCH_3$ **53**: $R_1=R_3=R_4=H$, $R_2=I$

Compound	conc. (μM)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	4.1±0.3	--
41	(30)	3.9±0.1	-10.4±2.8
	(100)	4.0±0.0	-13.4±0.8
42	(30)	4.1±0.1	-17.0±1.8
	(100)	4.0±0.2	-13.2±4.8
43	(30)	3.9±0.3	
	(100)	3.9±0.1	-14.0±0.5
TFP	(3)	3.5±0.4	19.2±11.2
	(5)	0.8±0.0**	81.4±2.1
	(10)	0.2±0.1**	96.1±2.0
	IC_{50}	4.7±0.5	
	Control	1.75±0.29	--
44	(30)	1.87±0.23	-9.5±6.2
	(100)	1.76±0.35	1.9±8.2
	Control	1.92±0.09	--
TFP	(3)	1.34±0.07**	29.8±0.3
	(10)	0.48±0.02**	74.5±0.2
	(30)	0.22±0.01**	88.2±1.3
	IC_{50}	8.8±0.1	
	Control	3.14±0.12	--

45	(10)	2.61±0.24		17.3±4.6
	(30)	2.48±0.13		20.7±7.4
TFP	(1)	2.55±0.23		16.6±10.1
	(3)	1.59±0.43**		49.5±7.4
	(10)	0.39±0.19**		87.1±4.9
	IC_{50}		4.5±0.3	
	Control	2.16±0.18		--
46	(30)	1.78±0.17		17.4±5.6
	(100)	2.01±0.37		4.8±9.9
47	(30)	2.19±0.07		6.2±7.4
	(100)	1.77±0.14		17.9±2.5
48	(30)	2.00±0.08		6.1±5.2
	(100)	1.65±0.27*		30.0±9.8
50	(30)	1.89±0.25		13.1±7.3
	(100)	1.69±0.24*		28.2±8.8
51	(30)	1.99±0.10		6.2±7.3
	(100)	1.96±0.14		9.0±3.0
52	(30)	2.14±0.16		8.7±7.2
	(100)	1.93±0.31		12.6±9.1
TFP	(3)	1.85±0.53*		21.9±7.1
	(5)	1.05±0.08**		53.6±4.0
	(10)	0.53±0.11**		76.4±5.1
	IC_{50}		6.0±0.1	
	Control	3.50±0.03		--
53	(10)	3.06±0.30		12.9±7.7
	(30)	3.16±0.27		10.0±8.5
TFP	(3)	2.33±0.19**		32.5±8.6
	(10)	0.86±0.15**		74.9±5.7
	(30)	0.08±0.03**		97.6±0.7
	IC_{50}		6.8±2.3	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of PMA (3 nM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-4. *: P<0.05, **: P<0.01.

Table 27. The inhibitory effect of substituted furo[2,3-*b*]chromone-2-carboxylic acid ethyl esters on rat neutrophil superoxide formation (*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**: $R_1=R_3=R_4=H$, $R_2=Br$

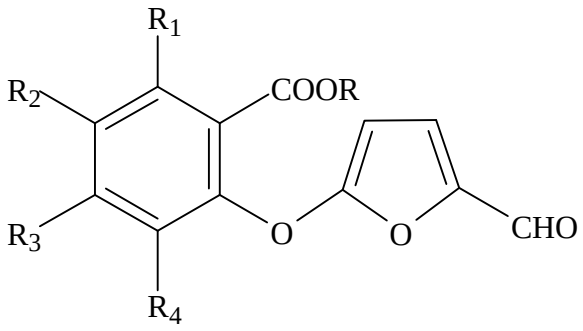
66: $R_1=R_2=R_3=H$, $R_4=OCH_3$ **73**: $R_1=R_3=R_4=H$, $R_2=I$

Compound	conc. (μM)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	4.1±0.3	--
61	(30)	4.0±0.4	0.4±4.4
	(100)	4.3±0.3	-8.8±1.5
62	(30)	3.8±0.2	-7.9±4.8
	(100)	3.6±0.2	-3.0±3.8
TFP	(3)	3.5±0.4	19.2±11.2
	(5)	0.8±0.0**	81.4±2.1
	(10)	0.2±0.1**	96.1±2.0
	IC_{50}	4.7±0.5	
	Control	1.75±0.29	--
63	(30)	1.97±0.28	-14.9±8.0
	(100)	2.17±0.24	-29.1±10.9
64	(30)	1.81±0.34	-1.7±6.6
	(100)	1.71±0.31	3.6±6.3
	Control	1.92±0.09	--
TFP	(3)	1.34±0.07**	29.8±0.3
	(10)	0.48±0.02**	74.5±0.2
	(30)	0.22±0.01**	88.2±1.3
	IC_{50}	8.8±0.1	

	Control	3.47±0.27		--
65	(10)	2.59±0.05*		24.6±5.3
	(30)	2.66±0.08*		22.7±4.6
66	(10)	2.55±0.22**		26.6±1.2
	(30)	2.72±0.26*		22.1±2.6
67	(10)	2.80±0.19		19.2±1.5
	(30)	2.76±0.07*		19.8±5.5
68	(10)	3.05±0.19		11.7±4.3
	(30)	2.99±0.23		14.0±2.7
TFP	(3)	3.24±0.12		5.5±11.3
	(10)	0.67±0.11**		80.6±8.1
	(30)	-0.12±0.08**		103.9±6.1
	IC_{50}		11.0±2.0	
	Control	2.81±0.17		--
70	(10)	2.61±0.23		7.2±5.8
	(30)	2.01±0.32**		28.5±11.1
71	(10)	2.16±0.06		22.4±5.5
	(30)	2.58±0.03		7.7±4.5
72	(10)	2.81±0.63		1.8±15.7
	(30)	2.23±0.15		14.9±6.7
73	(10)	3.11±0.18		-10.9±6.0
	(30)	2.48±0.13		11.1±7.9
TFP	(3)	2.13±0.04		23.7±3.5
	(10)	0.56±0.08**		79.2±4.3
	(30)	0.22±0.09**		91.9±4.3
	IC_{50}		9.7±1.1	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of PMA (3 nM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-4. *: P<0.05, **: P<0.01.

Table 28. The inhibitory effect of 5-(2'-alkoxycarbonyl substituted phenoxy)furfurals on rat neutrophil superoxide formation (*in vitro*)



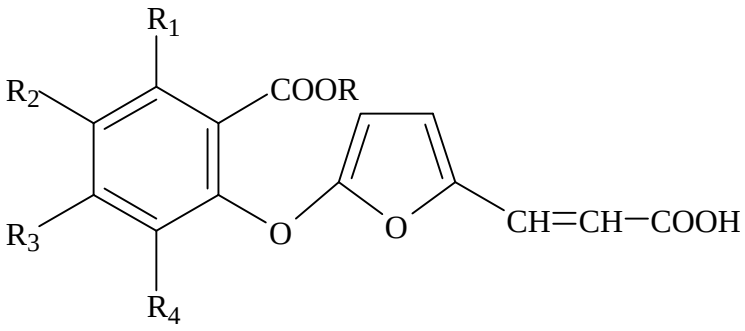
81: R=CH_3, R_1=R_2=R_3=R_4=H
82: R=CH_3, R_1=R_2=R_3=H, R_4=CH_3
83: R=CH_3, R_1=R_2=R_4=H, R_3=CH_3
84: R=CH_3, R_1=R_3=R_4=H, R_2=CH_3
85: R=C_2H_5, R_2=R_3=R_4=H, R_1=CH_3
86: R=CH_3, R_1=R_2=R_3=H, R_4=OCH_3
87: R=CH_3, R_1=R_2=R_4=H, R_3=OCH_3
88: R=CH_3, R_1=R_3=R_4=H, R_2=OCH_3
89: R=CH_3, R_2=R_3=R_4=H, 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. (μM)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	1.61±0.10	--
81	(10)	1.37±0.12	15.6±4.9
	(30)	1.16±0.16*	28.8±8.6
82	(10)	1.63±0.15	-1.3±8.9
	(30)	1.38±0.12	14.5±4.3
83	(10)	1.40±0.12	13.5±3.9
	(30)	1.17±0.13*	27.7±6.3
84	(10)	1.55±0.13	3.6±6.7
	(30)	1.35±0.15	17.5±4.3
85	(10)	1.77±0.09	-11.1±8.9
	(30)	1.49±0.09	7.7±2.1
TFP	(3)	1.43±0.10	8.6±2.0
	(10)	0.30±0.03**	80.2±2.0
	(30)	0.12±0.01**	90.9±0.4
	IC_{50}	7.6±0.3	
	Control	6.34±0.25	--
86	(10)	6.13±0.02	2.9±3.8

	(30)	5.64±0.37	11.2±2.2
87	(10)	5.99±0.53	5.4±7.6
	(30)	5.41±0.51	14.8±5.4
88	(10)	6.39±0.32	-0.7±1.5
	(30)	5.95±0.35	5.9±7.4
89	(10)	5.65±0.10	10.5±5.0
	(30)	5.53±0.23	12.2±7.1
90	(10)	5.71±0.44	10.2±4.1
	(30)	6.02±0.51	5.2±6.2
91	(10)	6.30±0.44	0.7±5.2
	(30)	6.81±0.63	-7.1±6.3
92	(10)	6.11±0.33	3.5±4.5
	(30)	6.86±0.48	-8.0±5.1
93	(10)	5.31±0.65	16.4±9.5
	(30)	6.88±0.18	-9.0±7.3
TFP	(3)	5.63±0.10	8.6±2.0
	(10)	1.18±0.03**	80.2±2.0
	(30)	0.47±0.01**	90.9±0.4
	IC_{50}	7.6±0.3	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of PMA (3 nM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-5. *: P<0.05, **: P<0.01.

Table 29. The inhibitory effect of 5-(2'-alkoxycarbonyl substituted phenoxy)-2-furanacrylic acids on rat neutrophil superoxide formation (*in vitro*)



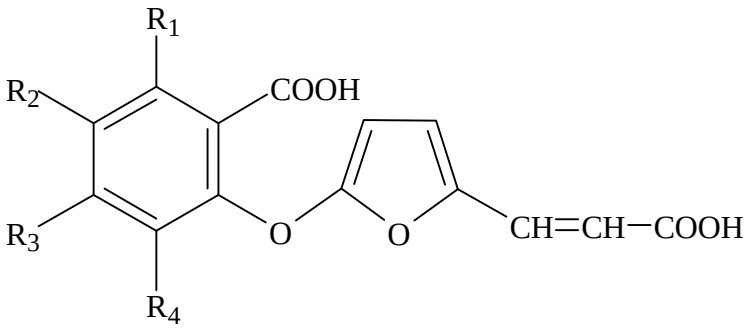
101: R=CH_3, R_1=R_2=R_3=R_4=H
102: R=CH_3, R_1=R_2=R_3=H, R_4=CH_3
103: R=CH_3, R_1=R_2=R_4=H, R_3=CH_3
104: R=CH_3, R_1=R_3=R_4=H, R_2=CH_3
105: R=C_2H_5, R_2=R_3=R_4=H, R_1=CH_3
106: R=CH_3, R_1=R_2=R_3=H, R_4=OCH_3
107: R=CH_3, R_1=R_2=R_4=H, R_3=OCH_3
108: R=CH_3, R_1=R_3=R_4=H, R_2=OCH_3
109: R=CH_3,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

Compound	conc. (μM)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	1.61±0.10	--
101	(10)	1.53±0.13	4.8±7.1
	(30)	1.54±0.13	4.2±7.5
102	(10)	1.63±0.15	-1.0±6.1
	(30)	1.65±0.08	-4.0±8.6
103	(10)	1.53±0.08	4.7±2.5
	(30)	1.32±0.08	17.9±3.9
104	(10)	1.69±0.15	-5.6±11.6
	(30)	1.71±0.15	-6.6±9.8
105	(10)	1.47±0.19	9.3±9.1
	(30)	1.51±0.14	6.2±8.6
TFP	(3)	1.43±0.10	8.6±2.0
	(10)	0.30±0.03**	80.2±2.0
	(30)	0.12±0.01**	90.9±0.4
	IC_{50}	7.6±0.3	
	Control	6.34±0.25	--
106	(10)	5.43±0.14	14.0±3.6
	(30)	5.30±0.34	16.2±6.0
107	(10)	6.18±0.52	2.5±7.8

	(30)	5.31±0.65	15.3±13.3
108	(10)	5.18±0.81	18.8±10.4
	(30)	5.29±0.27	16.3±5.5
109	(10)	6.25±0.40	1.2±6.5
	(30)	5.86±0.21	7.5±0.7
TFP	(3)	5.63±0.10	8.6±2.0
	(10)	1.18±0.03**	80.2±2.0
	(30)	0.47±0.01**	90.9±0.4
	IC_{50}	7.6±0.3	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of PMA (3 nM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-5. *: P<0.05, **: P<0.01.

Table 30. The inhibitory effect of 5-(2'-carboxyl substituted phenoxy)-2-furanacrylic acids on rat neutrophil superoxide formation (*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)	Superoxide Formation nmol/10^6cells/30 min	(%inh)
	Control	1.61±0.10	--
111	(10)	1.77±0.07	-10.7±6.4
	(30)	1.57±0.12	2.3±6.4
112	(10)	1.62±0.09	-0.6±2.4
	(30)	1.61±0.05	-0.6±4.5
113	(10)	1.60±0.14	0.2±10.6
	(30)	1.44±0.11	10.9±4.7
114	(10)	1.53±0.16	5.7±7.3
	(30)	1.65±0.14	-2.1±6.6
TFP	(3)	1.43±0.10	8.6±2.0
	(10)	0.30±0.03**	80.2±2.0
	(30)	0.12±0.01**	90.9±0.4
	IC_{50}	7.6±0.3	
	Control	6.34±0.25	--
116	(10)	5.39±0.08	14.7±2.9
	(30)	5.46±0.95	14.7±11.6
117	(10)	5.51±0.21	13.0±1.7
	(30)	6.03±0.96	4.8±14.9

118	(10)	6.34±0.28	-0.03±1.2
	(30)	6.64±0.62	-4.5±6.8
120	(10)	5.76±0.88	10.0±10.4
	(30)	6.20±0.53	2.4±5.8
121	(10)	6.76±0.24	-6.8±4.5
	(30)	6.36±0.36	-0.2±2.8
122	(10)	5.86±0.47	7.5±7.1
	(30)	5.62±0.90	12.2±10.5
123	(10)	6.86±0.16	-8.6±4.7
	(30)	6.26±0.49	1.2±6.4
TFP	(3)	5.63±0.10	8.6±2.0
	(10)	1.18±0.03**	80.2±2.0
	(30)	0.47±0.01**	90.9±0.4
	IC_{50}	7.6±0.3	

Neutrophil suspensions were preincubated at 37 °C with 0.5 % DMSO or test compounds in the presence of cytochalasin B (5 μg/ml) for 3 min. Fifteen minutes after the addition of PMA (3 nM), the absorbance was determined at 550 nm. Trifluoperazine (TFP) is a positive control. Values are presented as mean± S.E., N=3-5. *: P<0.05, **: P<0.01.