

**Table 1****The list of compounds assayed in this study -Phthalate diesters-**

	Compounds	Molecular Formula	Cas No
<b>Phthalate diesters</b>			
1	Dimethyl phthalate	C <sub>10</sub> H <sub>10</sub> O <sub>4</sub>	131-11-3
2	Diethyl phthalate	C <sub>12</sub> H <sub>14</sub> O <sub>4</sub>	84-66-2
3	Di- <i>n</i> -propyl phthalate	C <sub>14</sub> H <sub>18</sub> O <sub>4</sub>	131-16-8
4	Diisopropyl phthalate	C <sub>14</sub> H <sub>18</sub> O <sub>4</sub>	605-45-8
5	Diallyl phthalate	C <sub>14</sub> H <sub>14</sub> O <sub>4</sub>	131-17-9
6	Dibutyl phthalate	C <sub>16</sub> H <sub>22</sub> O <sub>4</sub>	84-74-2
7	Diisobutyl Phthalate	C <sub>16</sub> H <sub>22</sub> O <sub>4</sub>	84-69-5
8	Benzyl butyl phthalate	C <sub>19</sub> H <sub>20</sub> O <sub>4</sub>	85-68-7
9	Di- <i>n</i> -pentyl phthalate (Diamyl phthalate)	C <sub>18</sub> H <sub>26</sub> O <sub>4</sub>	131-18-0
10	Di- <i>n</i> -hexyl phthalate	C <sub>20</sub> H <sub>30</sub> O <sub>4</sub>	84-75-3
11	Diisohexyl phthalate	C <sub>20</sub> H <sub>30</sub> O <sub>4</sub>	146-50-9
12	Bis(2-ethylhexyl) phthalate	C <sub>24</sub> H <sub>38</sub> O <sub>4</sub>	117-81-7
13	Di- <i>n</i> -heptyl phthalate	C <sub>22</sub> H <sub>34</sub> O <sub>4</sub>	3648-21-3
14	Diisoheptyl phthalate	C <sub>22</sub> H <sub>34</sub> O <sub>4</sub>	41451-28-9
15	Di- <i>n</i> -octyl phthalate	C <sub>24</sub> H <sub>38</sub> O <sub>4</sub>	117-84-0
16	Diisooctyl phthalate	C <sub>24</sub> H <sub>38</sub> O <sub>4</sub>	27554-26-3
17	Diisononyl phthalate	C <sub>26</sub> H <sub>42</sub> O <sub>4</sub>	68515-48-0
18	Diisodecyl phthalate	C <sub>28</sub> H <sub>46</sub> O <sub>4</sub>	26761-40-0

**Table 2****The list of compounds assayed in this study -Phthalate monoesters-**

Compounds	Molecular Formula	Cas No
<b>Phthalate monoesters</b>		
1 Monomethyl phthalate	C <sub>9</sub> H <sub>8</sub> O <sub>4</sub>	4376-18-5
2 Monoethyl phthalate	C <sub>10</sub> H <sub>10</sub> O <sub>4</sub>	2306-33-4
3 Monobutyl phthalate	C <sub>12</sub> H <sub>14</sub> O <sub>4</sub>	131-70-4
4 Mono-iso-butyl phthalate	C <sub>12</sub> H <sub>14</sub> O <sub>4</sub>	30833-53-5
5 Monobenzyl phthalate	C <sub>15</sub> H <sub>12</sub> O <sub>4</sub>	2528-16-7
6 Monohexyl phthalate	C <sub>14</sub> H <sub>18</sub> O <sub>4</sub>	24539-57-9
7 Monoethylhexyl phthalate	C <sub>16</sub> H <sub>22</sub> O <sub>4</sub>	4376-20-9
8 Mono-octyl phthalate	C <sub>16</sub> H <sub>22</sub> O <sub>4</sub>	5393-19-1
9 Mono-2-octyl phthalate	C <sub>16</sub> H <sub>22</sub> O <sub>4</sub>	21395-09-5
<b>Structural analogs</b>		
1 2-Ethylhexyl 4-hydroxybenzoate	C <sub>15</sub> H <sub>22</sub> O <sub>3</sub>	5153-25-3
2 2-Ethylhexyl salicylate	C <sub>15</sub> H <sub>22</sub> O <sub>3</sub>	118-60-5

**Table 3****EC<sub>50</sub> values for the TRPA1 activation by phthalate diesters.**

	TRPA1	
	EC <sub>50</sub> (μM)	Maximum Activation
Dimethyl phthalate	505 (478-532)	0.85 (0.78-0.92)
Diethyl phthalate	142 (112-181)	0.98 (0.85-1.10)
Di- <i>n</i> -propyl phthalate	39 (36-41)	0.97 (0.93-1.00)
Diisopropyl phthalate	48 (43-52)	1.10 (1.05-1.15)
Diallyl phthalate	39 (32-47)	0.98 (0.92-1.05)
Di- <i>n</i> -hexyl phthalate	487 (457-518)	0.86 (0.79-0.94)
Diisohexyl phthalate	27 (23-31)	1.03 (0.98-1.08)
Di- <i>n</i> -octyl phthalate	-	-

Maximum Activation ; Ratio to positive control

**Table 4****EC<sub>50</sub> values for the TRPA1 activation by phthalate monoesters.**

	TRPA1	
	EC <sub>50</sub> (µM)	Maximum Activation
Monobutyl phthalate	315 (289-344)	1.06 (0.99-1.14)
Monoisobutyl phthalate	-	-
Monobenzyl phthalate	419 (361-486)	0.92 (0.83-1.02)
Monoethylhexyl phthalate	6.2 (5.9-6.6)	1.03 (1.00-1.06)
Monoethylhexyl phthalate	0.4 (0.3-0.4)	1.27 (1.22-1.32)
Monooctyl phthalate	0.4 (0.3-0.5)	1.21 (1.15-1.27)
Mono-2-octyl phthalate	2.5 (2.2-2.8)	1.24 (1.18-1.29)

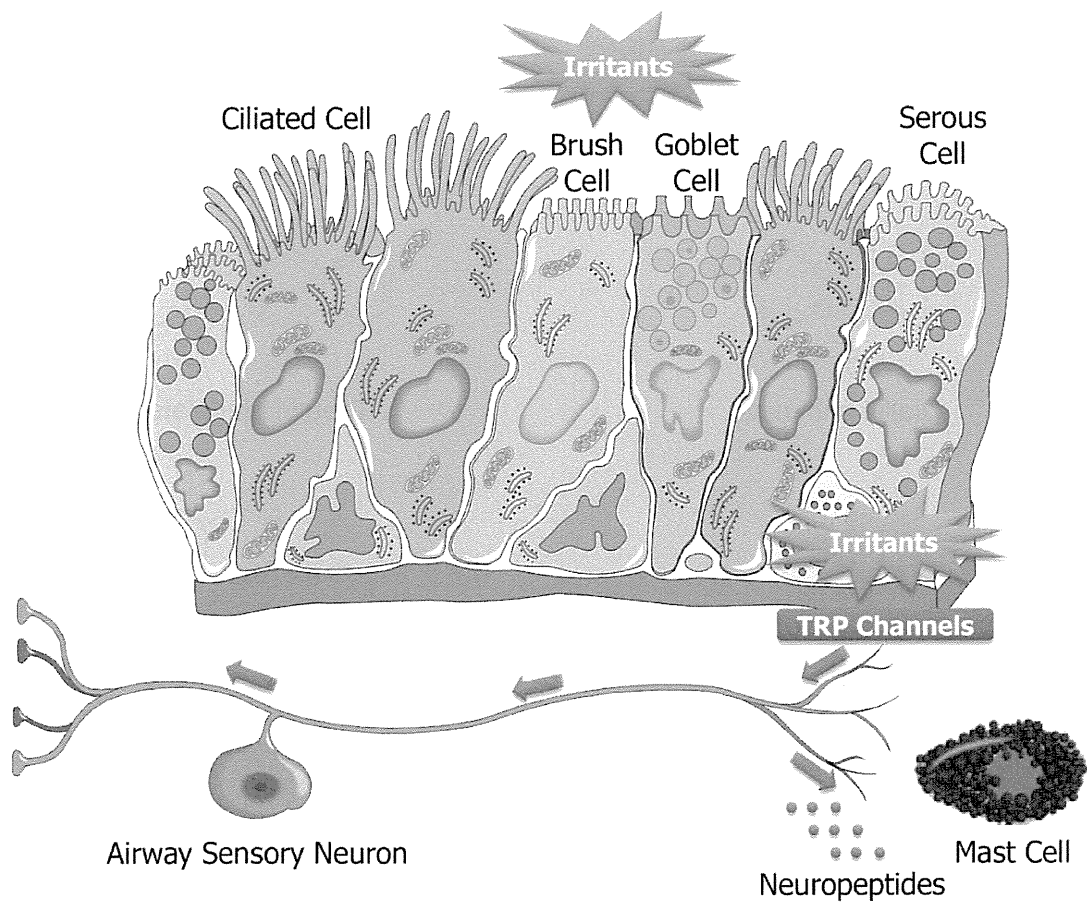
Maximum Activation ; Ratio to positive control

**Table 5****The list of compounds assayed in this study -Isothiazolinones-**

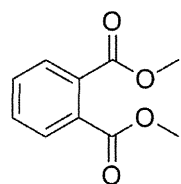
	Compounds	Molecular Formula	Cas No
<b>Isothiazolinones</b>			
1	2-Methyl-4-isothiazolin-3-one (MIT)	C <sub>4</sub> H <sub>5</sub> NOS	2682-20-4
2	5-Chloro-2-methyl-4-isothiazolin-3-one (CI-MIT)	C <sub>4</sub> H <sub>4</sub> ClNOS	26172-55-4
3	2- <i>n</i> -Octyl-4-isothiazolin-3-one (OIT)	C <sub>11</sub> H <sub>19</sub> NOS	26530-20-1
4	4,5-Dichloro-2- <i>n</i> -octyl-4-isothiazolin-3-one (2Cl-OIT)	C <sub>11</sub> H <sub>17</sub> Cl <sub>2</sub> NOS	64359-82-5
5	1,2-Benzisothiazolin-3-one (BIT)	C <sub>7</sub> H <sub>5</sub> NOS	2634-33-5

**Table 6****EC<sub>50</sub> values for the TRPV1 and TRPA1 activation by Isothiazolinones.**

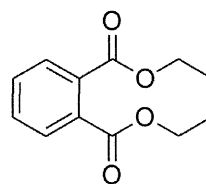
<b>Compounds</b>	<b>EC<sub>50</sub> [<math>\mu</math>M] EC<sub>50</sub> [%]</b>	<b>Maximum Activation</b>
<b>TRPV1</b>		
2-Methyl-4-isothiazolin-3-one (MIT)	-	-
5-Chloro-2-methyl-4-isothiazolin-3-one (CI-MIT)/2-Methyl-4-isothiazolin-3-one (MIT): 3.1	-	-
2- <i>n</i> -Octyl-4-isothiazolin-3-one (OIT)	49(41-57) 1.0E-03	0.88(0.83-0.92)
4,5-Dichloro-2- <i>n</i> -octyl-4-isothiazolin-3-one (2CI-OIT)	-	-
1,2-Benzisothiazolin-3-one (BIT)	433 (404-464) 6.5E-03	0.88 (0.82-0.93)
<b>TRPA1</b>		
2-Methyl-4-isothiazolin-3-one (MIT)	66 (61-72) 7.6E-04	1.04 (0.99-1.09)
5-Chloro-2-methyl-4-isothiazolin-3-one (CI-MIT)/2-Methyl-4-isothiazolin-3-one (MIT): 3.1	- 8.7E-05	0.83 (0.79-0.86)
2- <i>n</i> -Octyl-4-isothiazolin-3-one (OIT)	5.7 (5.2-6.3) 1.2E-04	1.27 (1.23-1.30)
4,5-Dichloro-2- <i>n</i> -octyl-4-isothiazolin-3-one (2CI-OIT)	2.3 (1.9-2.6) 1.3E-04	1.05 (1.01-1.09)
1,2-Benzisothiazolin-3-one (BIT)	3.4 (3.0-3.8) 5.1E-05	1.15 (1.10-1.20)



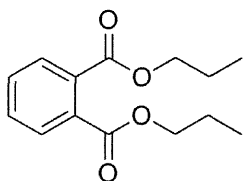
**Fig. 1 Schematic presentation of airway hypersensitivity mediated by TRP ion channels.**



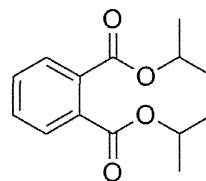
Dimethyl phthalate



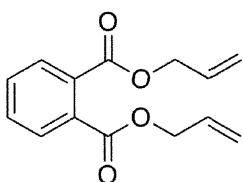
Diethyl phthalate



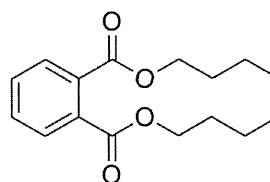
Di-n-propyl phthalate



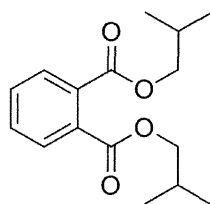
Diisopropyl phthalate



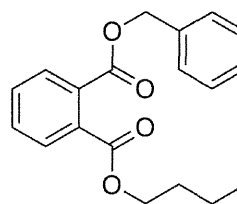
Diallyl phthalate



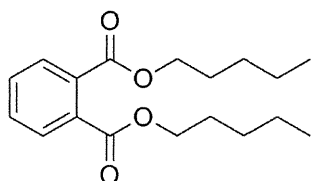
Dibutyl phthalate



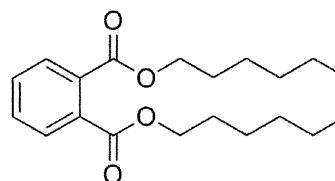
Diisobutyl phthalate



Benzyl butyl phthalate



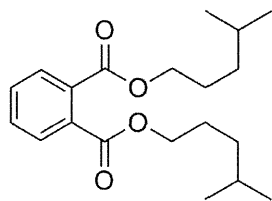
Di-n-pentyl phthalate



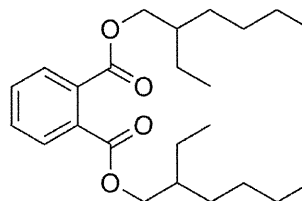
Di-n-hexyl phthalate

**Fig. 2-1 Chemical structures of phthalate diesters.**

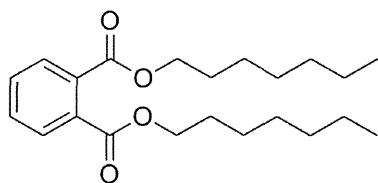




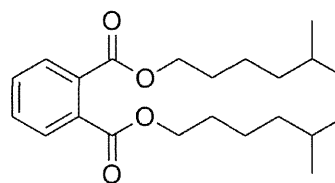
Diisohexyl phthalate



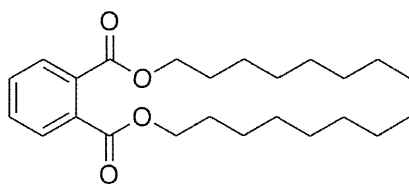
Bis(2-ethylhexyl) phthalate



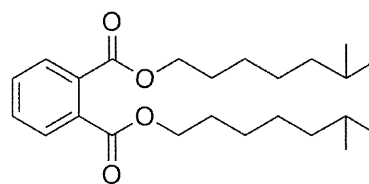
Di-n-heptyl phthalate



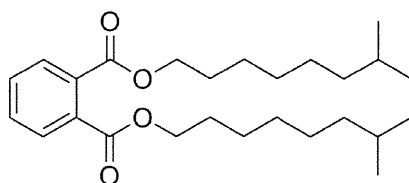
Diisohexyl phthalate



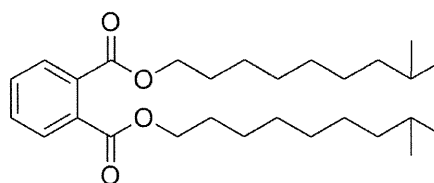
Di-n-octyl phthalate



Diisooctyl phthalate

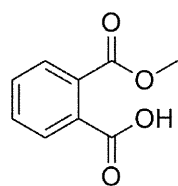


Diisononyl phthalate

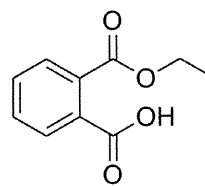


Diisodecyl phthalate

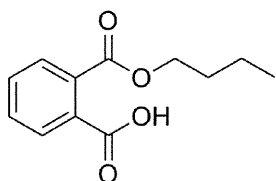
**Fig. 2-2 Chemical structures of phthalate diesters.**



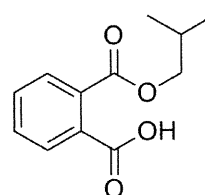
Monomethyl phthalate



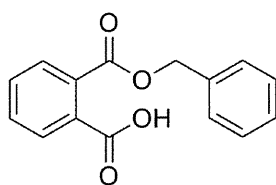
Monoethyl phthalate



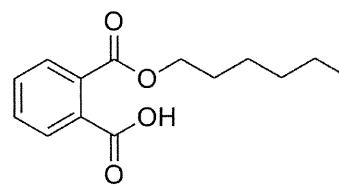
Monobutyl phthalate



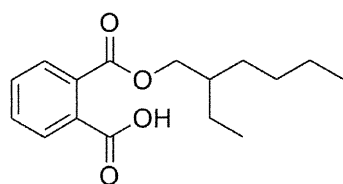
Monoisobutyl phthalate



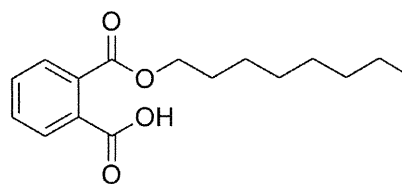
Monobenzyl phthalate



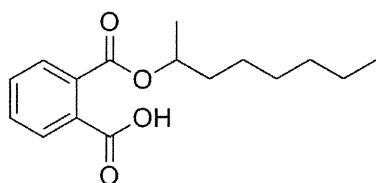
Monohexyl phthalate



Mono(2-ethylhexyl) phthalate

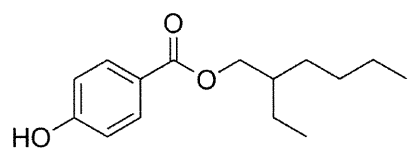


Mono-octyl phthalate

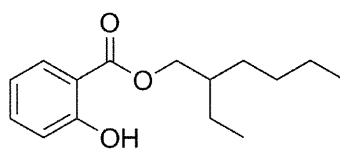


Mono-2-octyl phthalate

**Fig. 3 Chemical structures of phthalate monoesters.**



2-Ethylhexyl 4-hydroxybenzoate



2-Ethylhexyl salicylate

**Fig. 4 Chemical structures of mono(2-ethylhexyl) hydroxybenzoate.**

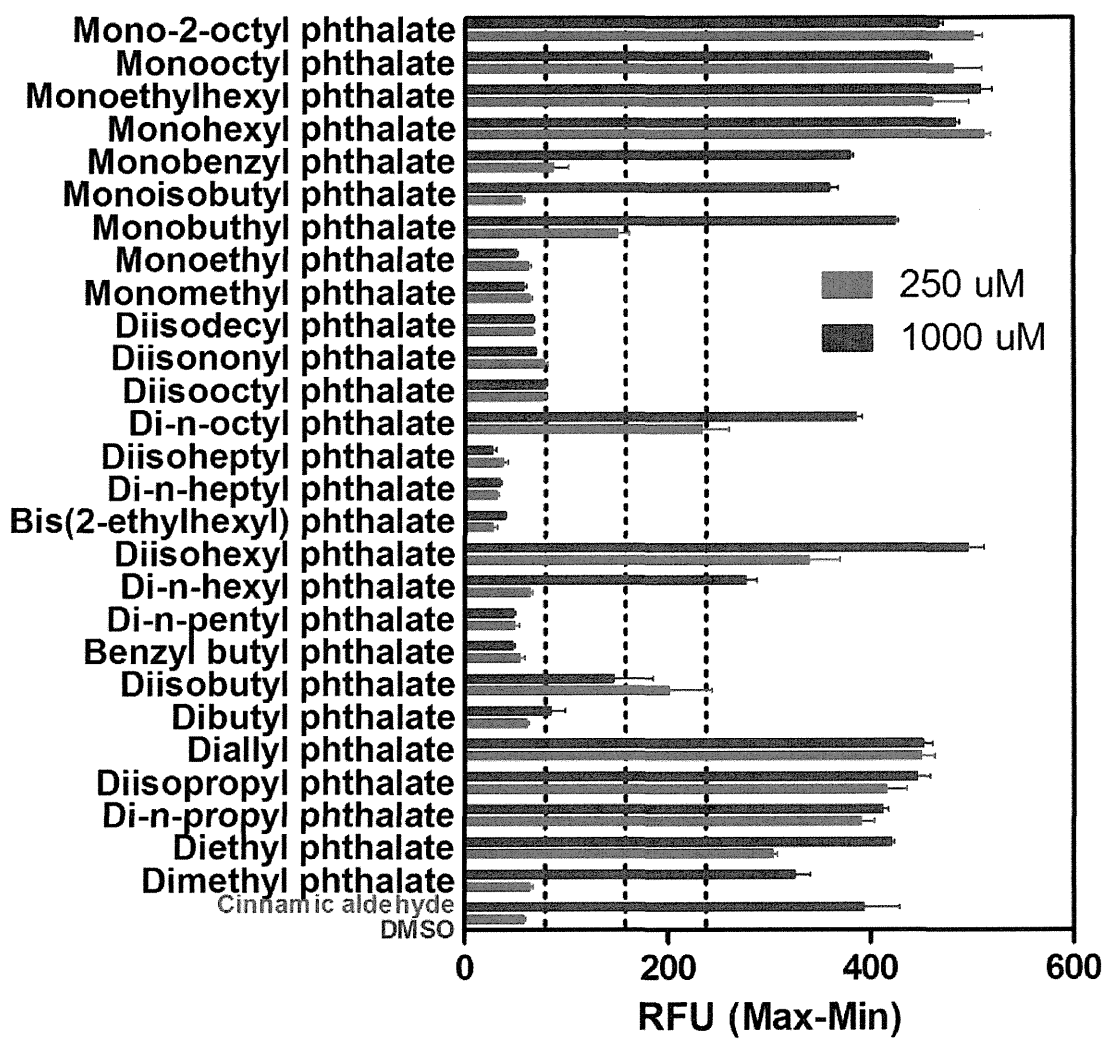


Fig. 5 Activation of TRPA1 by phthalates.

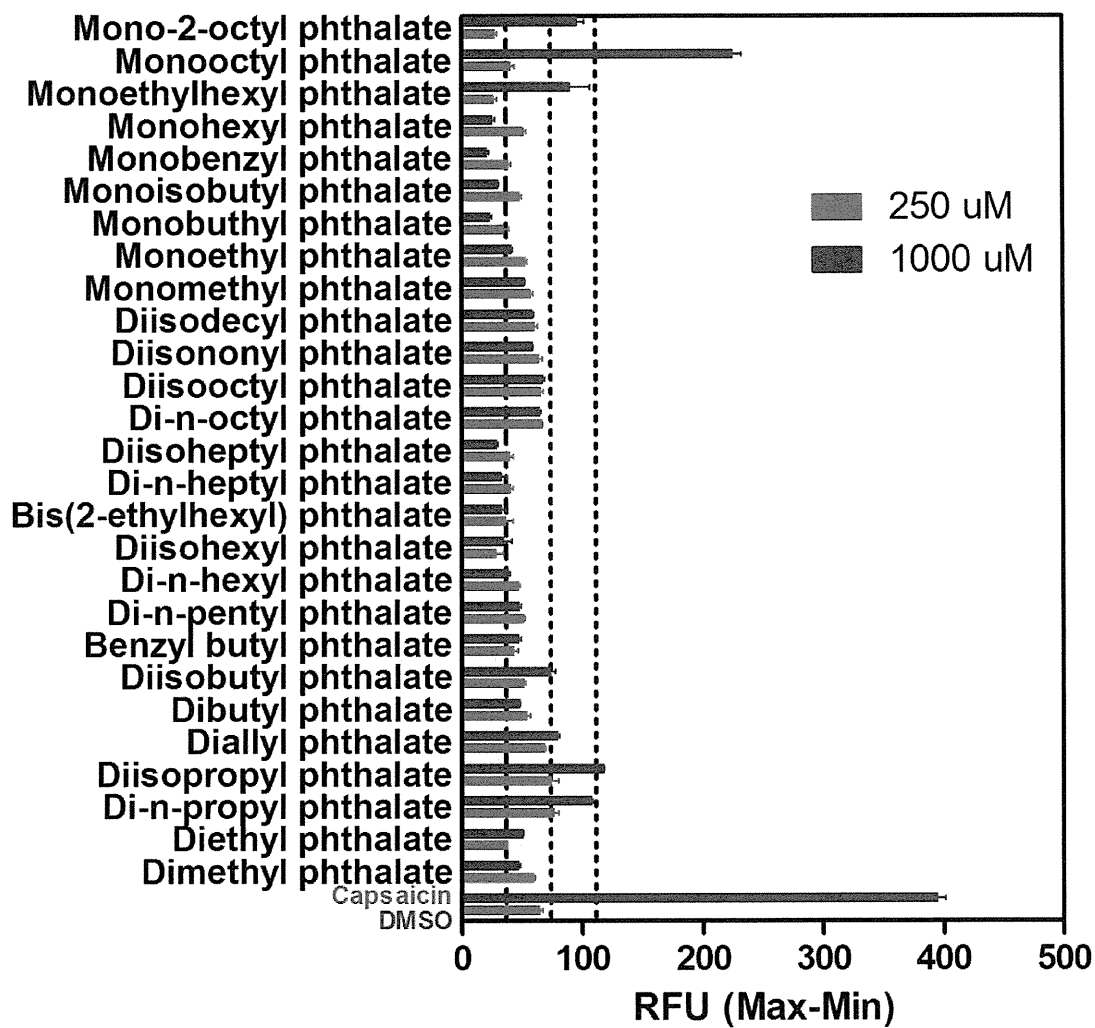


Fig. 6 Activation of TRPV1 by phthalates.

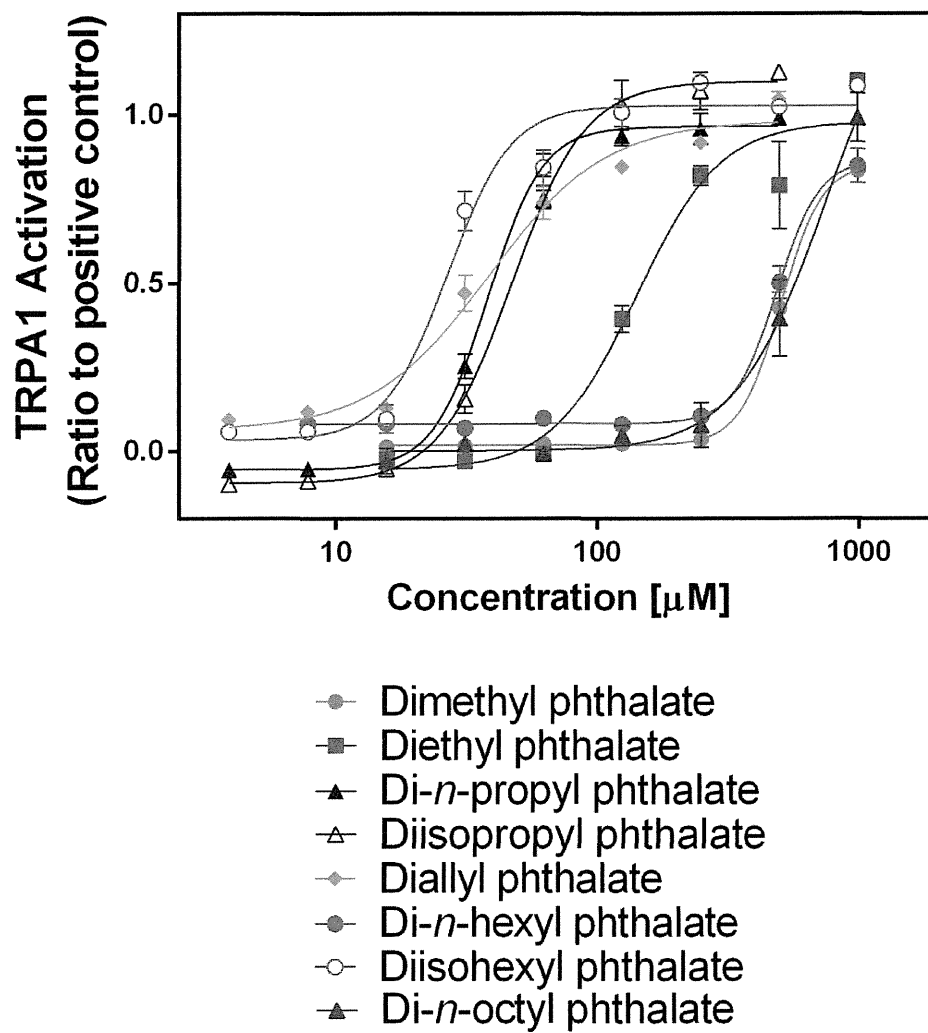


Fig. 7 Dose-dependent activation of TRPA1 by phthalate diesters.

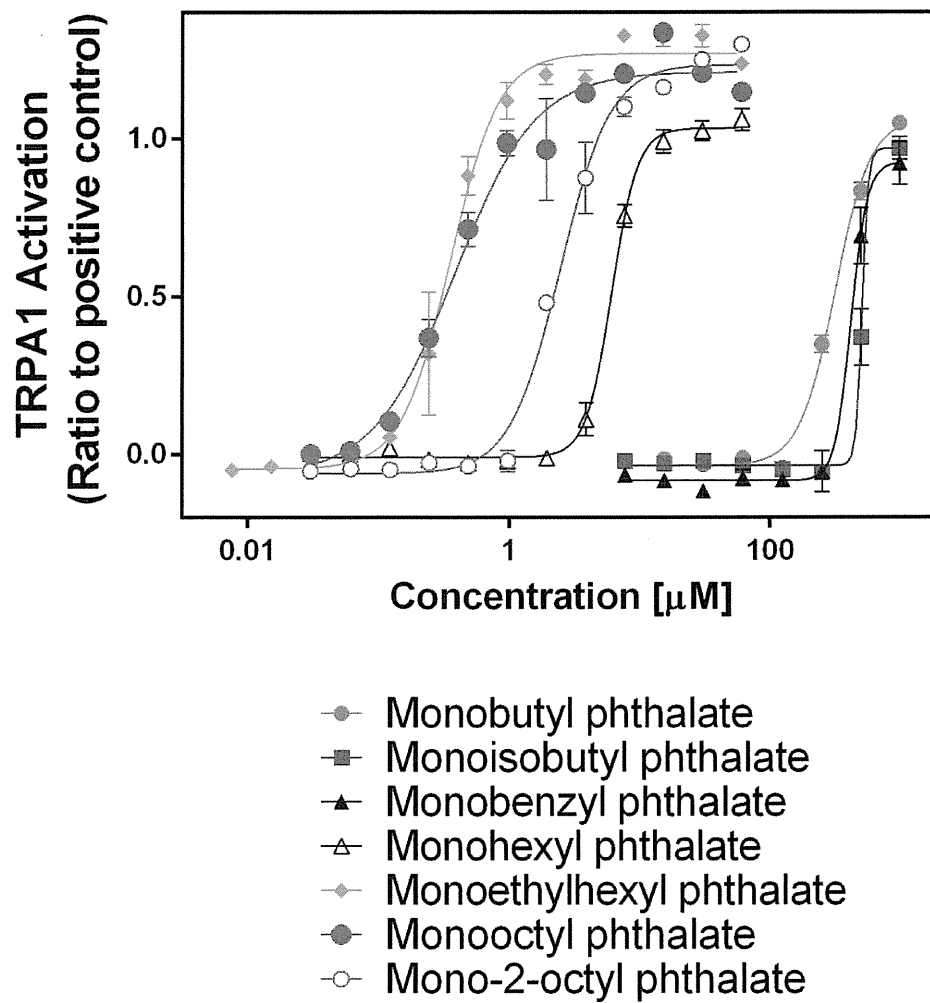
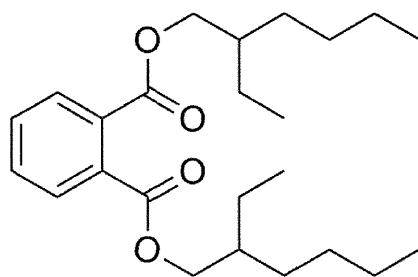
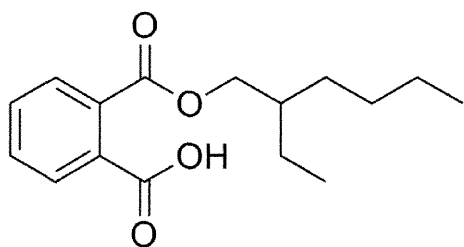
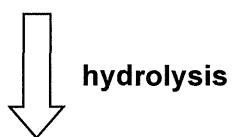


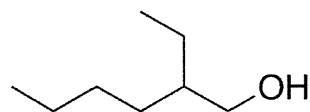
Fig. 8 Dose-dependent activation of TRPA1 by phthalate monoesters.



Bis(2-ethylhexyl) phthalate



Mono(2-ethylhexyl) phthalate



2-Ethyl-1-hexanol

**Fig. 9 Hydrolysis of Bis(2-ethylhexyl) phthalate**



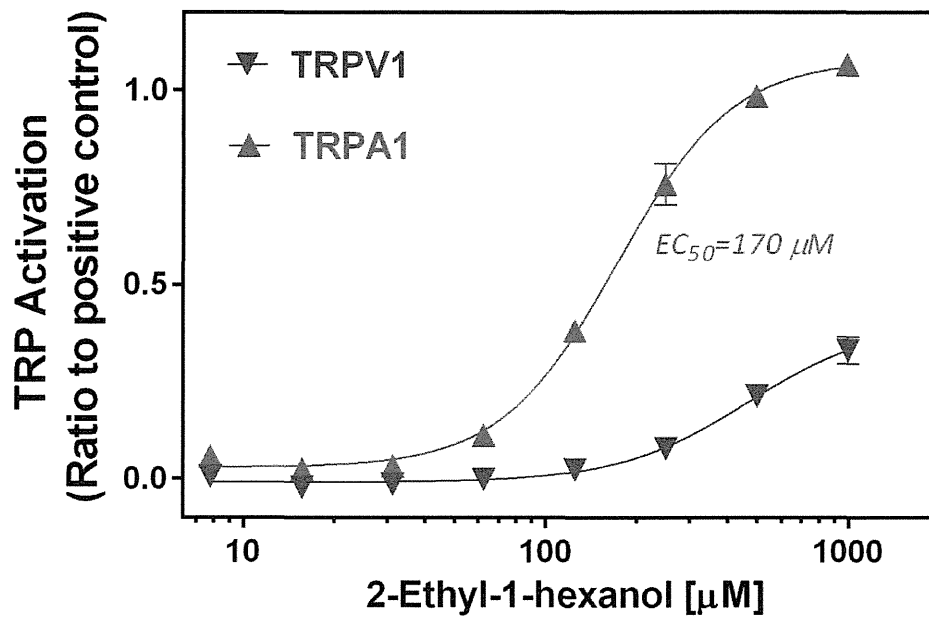
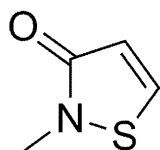
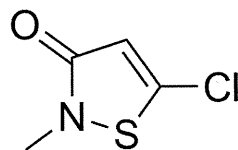


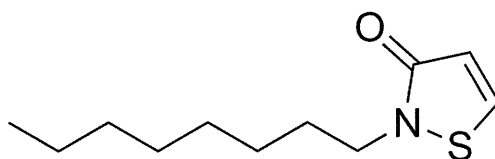
Fig. 10 Dose-dependent activation of TRPV1 and TRPA1 by 2-ethyl-1-hexanol.



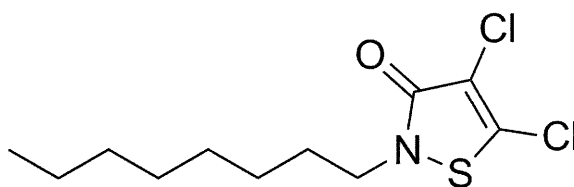
2-Methyl-4-isothiazolin-3-one  
(MIT)



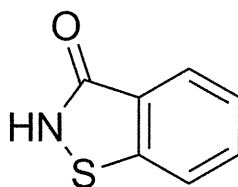
5-Chloro-2-methyl-4-isothiazolin-3-one  
(Cl-MIT)



2-*n*-Octyl-4-isothiazolin-3-one (OIT)



4,5-Dichloro-2-*n*-octyl-4-isothiazolin-3-one (2Cl-OIT)



1,2-Benzisothiazolin-3-one (BIT)

**Fig. 11 Chemical structures of isothiazolinone derivatives.**

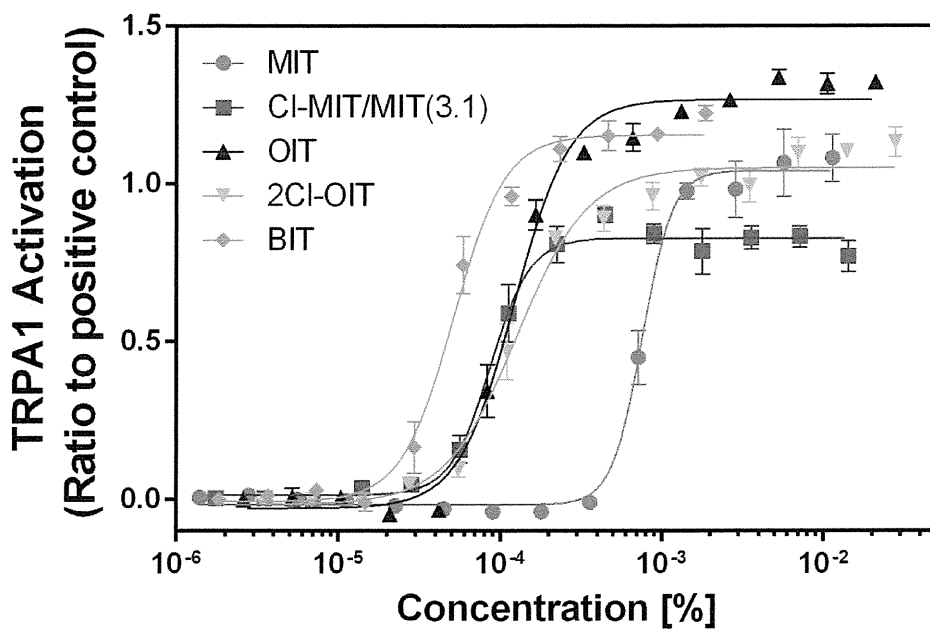
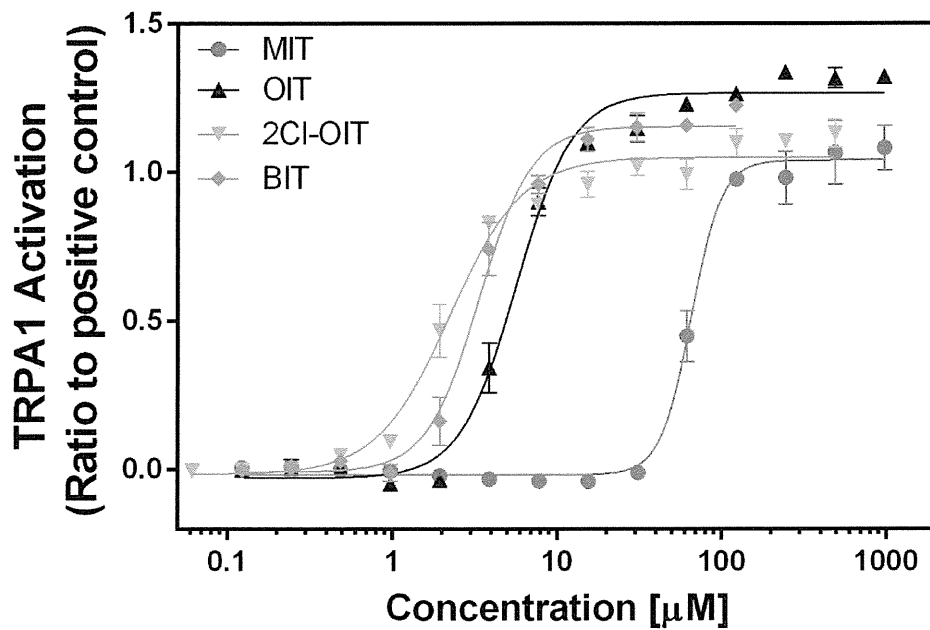


Fig. 12 Activation of TRPA1 by isothiazolinone derivatives.

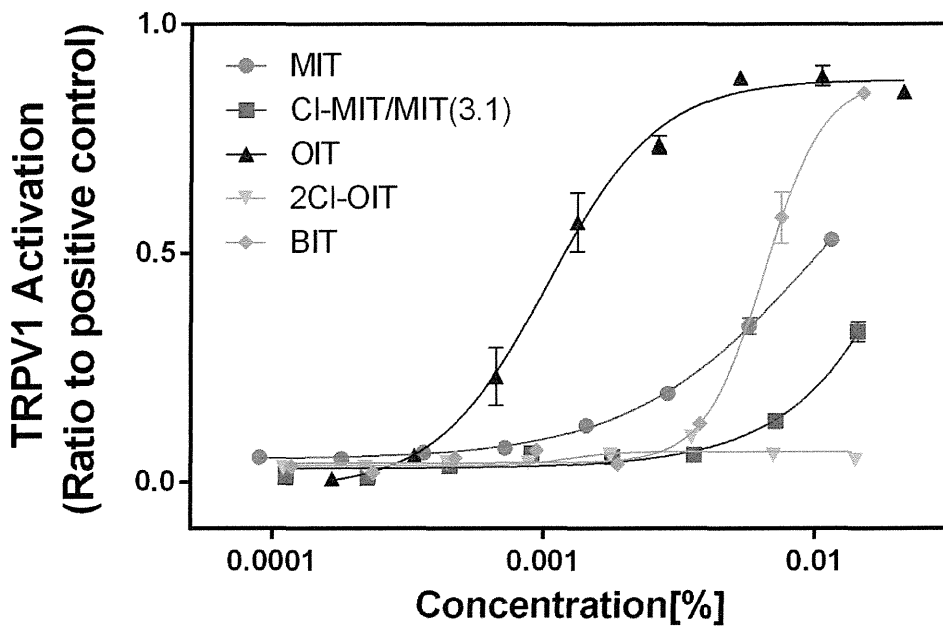
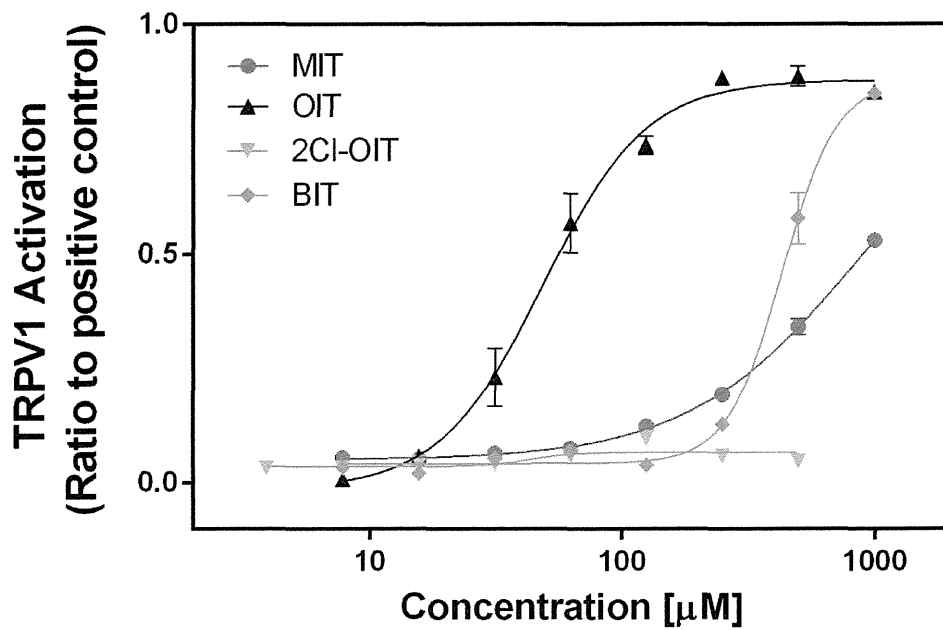


Fig. 13 Activation of TRPV1 by isothiazolinone derivatives.