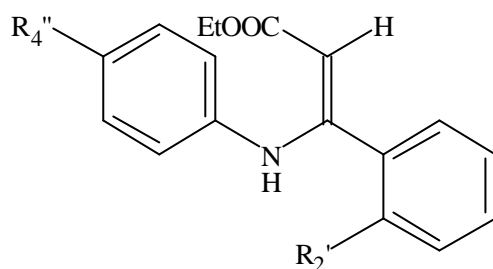


Table 21. The inhibitory effect of compounds (28, 30) on TNF- α formation in medium



Cell line: Raw 264.7 cells

Inducer: LPS (1 μ g/ml)

Cell line: N9 cells

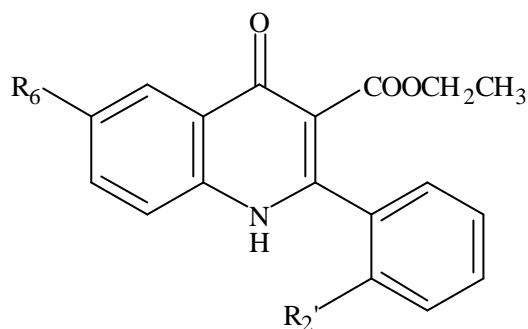
Inducer: LPS (10 ng/ml)+ IFN- γ (10 U/ml)

| No. | Conc. (μ M) | R ₂ ' | R ₄ '' | TNF- α formation (ng/ml) | | | |
|-----------------|------------------------|------------------|-------------------|--|------------------|--|------------------|
| | | | | RAW | % inhibition | N9 | % inhibition |
| | Control | | | 145.4 \pm 6.3 | | 2.12 \pm 0.12 | |
| 28 | 10 | Cl | F | -- | -- | 2.58 \pm 0.08 | -21.9 \pm 3.2 |
| | 30 | | | 131.4 \pm 9.0 | 10.3 \pm 0.4 | | Cytotoxic |
| 30 | 10 | Cl | H | -- | -- | 2.45 \pm 0.18 | -15.2 \pm 2.3 |
| | 30 | | | 112.7 \pm 8.6* | 22.7 \pm 3.7* | | Cytotoxic |
| SB203580 | | | | | | | |
| | 3 | | | 132.8 \pm 3.3 | 8.9 \pm 7.2 | 1.33 \pm 0.04** | 36.4 \pm 3.3** |
| | 10 | | | 107.2 \pm 1.3** | 26.5 \pm 6.0** | 1.02 \pm 0.17** | 51.6 \pm 7.6** |
| | 30 | | | 60.9 \pm 5.3** | 58.2 \pm 2.4** | 0.97 \pm 0.10** | 53.5 \pm 4.3** |
| | IC₅₀ | | | 22.4 \pm 3.4 μM | | 10.2 \pm 1.6 μM | |

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

SB203580: [4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole: positive control

Table 22. The inhibitory effect of compounds (31-33, 35-37, 39, 40) on TNF- α formation in medium



Cell line: Raw 264.7 cells

Inducer: LPS (1 μ g/ml)

Cell line: N9 cells

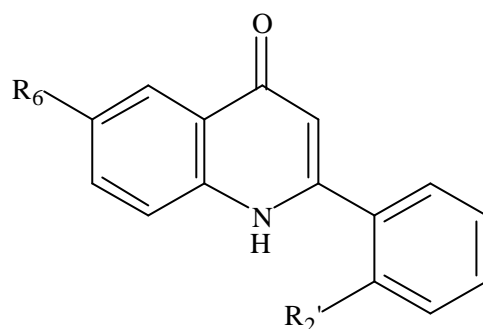
Inducer: LPS (10 ng/ml)+ IFN- γ (10 U/ml)

| No. | Conc. (μ M) | R ₆ | R ₂ ' | TNF- α formation (ng/ml) | | | |
|------------------------|---------------------|------------------|------------------|--|------------------|--|------------------|
| | | | | RAW | % inhibition | N9 | % inhibition |
| Control | | | | 145.4 \pm 6.3 | | 2.12 \pm 0.12 | |
| 31 | 30 | Cl | F | 156.8 \pm 2.6 | -7.4 \pm 3.9 | 1.29 \pm 0.16** | 39.4 \pm 4.0** |
| 32 | 3 | Cl | Cl | -- | -- | 1.33 \pm 0.07** | 36.6 \pm 3.5** |
| | 10 | | | -- | -- | 0.96 \pm 0.08** | 54.2 \pm 5.8** |
| | 30 | | | 134.9 \pm 2.2 | 7.5 \pm 4.3 | 0.58 \pm 0.09** | 72.4 \pm 5.7** |
| IC₅₀ | | | | 8.4 \pm 2.8 μM | | | |
| 33 | 30 | Cl | OCH ₃ | 140.1 \pm 3.4 | 4.0 \pm 5.0 | 1.50 \pm 0.17* | 29.5 \pm 4.2* |
| 35 | 30 | F | F | 141.8 \pm 3.3 | 2.3 \pm 1.9 | 1.69 \pm 0.03 | 19.9 \pm 3.3 |
| 36 | 30 | F | Cl | 132.7 \pm 1.4 | 8.5 \pm 3.0 | 1.13 \pm 0.01** | 46.3 \pm 2.4** |
| 37 | 30 | F | OCH ₃ | 175.6 \pm 2.8 | -21.0 \pm 3.3 | 1.92 \pm 0.08 | 8.9 \pm 3.1 |
| 39 | 30 | OCH ₃ | F | 128.3 \pm 3.9 | 11.7 \pm 2.1 | 1.79 \pm 0.11 | 15.7 \pm 1.7 |
| 40 | 3 | OCH ₃ | Cl | -- | -- | 1.54 \pm 0.04* | 26.7 \pm 3.4* |
| | 10 | | | -- | -- | 1.37 \pm 0.08* | 35.1 \pm 5.4* |
| | 30 | | | 90.6 \pm 1.3** | 38.1 \pm 4.9** | 0.88 \pm 0.09** | 57.3 \pm 5.3** |
| IC₅₀ | | | | 22.3 \pm 6.4 μM | | | |
| SB203580 | | | | | | | |
| | 3 | | | 132.8 \pm 3.3 | 8.9 \pm 7.2 | 1.33 \pm 0.04** | 36.4 \pm 1.3** |
| | 10 | | | 107.2 \pm 1.3** | 26.5 \pm 6.0** | 1.02 \pm 0.17** | 51.6 \pm 7.6** |
| | 30 | | | 60.9 \pm 5.3** | 58.2 \pm 2.4** | 0.97 \pm 0.10** | 53.5 \pm 4.3** |
| IC₅₀ | | | | 22.4 \pm 3.4 μM | | 10.2 \pm 1.6 μM | |

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

SB203580: [4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole: positive control

Table 23. The inhibitory effect of compounds (43, 44) on TNF- α formation in medium



Cell line: Raw 264.7 cells

Inducer: LPS (1 μ g/ml)

Cell line: N9 cells

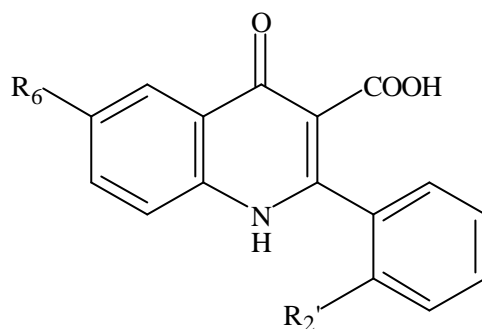
Inducer: LPS (10 ng/ml)+ IFN- γ (10 U/ml)

| No. | Conc. (μ M) | R ₆ | R ₂ ' | TNF- α formation (ng/ml) | | | |
|------------------------|------------------------|------------------|------------------|--|---|--|------------------|
| | | | | RAW | % inhibition | N9 | % inhibition |
| Control | | | | 145.4 \pm 6.3 | | 2.12 \pm 0.12 | |
| 43 | 0.1 | F | F | -- | -- | 1.21 \pm 0.09** | 42.6 \pm 5.9** |
| | 0.3 | | | -- | -- | 0.99 \pm 0.10** | 53.3 \pm 7.0** |
| | 1 | | | -- | -- | 0.30 \pm 0.06** | 85.5 \pm 4.4** |
| | 3 | | | -- | -- | Cytotoxic | |
| | 10 | | | -- | -- | Cytotoxic | |
| | 30 | | | 154.6 \pm 7.2 | -6.2 \pm 0.3 | Cytotoxic | |
| | IC₅₀ | | | | 0.19 \pm 0.06 μM | | |
| 44 | 0.1 | OCH ₃ | Cl | -- | -- | 1.83 \pm 0.02 | 13.6 \pm 0.7 |
| | 0.3 | | | -- | -- | 1.70 \pm 0.08 | 20.0 \pm 4.8 |
| | 1 | | | -- | -- | 0.83 \pm 0.03** | 60.5 \pm 1.5** |
| | 3 | | | -- | -- | Cytotoxic | |
| | 10 | | | -- | -- | Cytotoxic | |
| | 30 | | | 162.5 \pm 6.8 | -11.8 \pm 2.7 | Cytotoxic | |
| | IC₅₀ | | | | 0.66 \pm 0.02 μM | | |
| SB203580 | | | | | | | |
| | 3 | | | 132.8 \pm 3.3 | 8.9 \pm 7.2 | 1.33 \pm 0.04** | 36.4 \pm 1.3** |
| | 10 | | | 107.2 \pm 1.3** | 26.5 \pm 6.0** | 1.02 \pm 0.17** | 51.6 \pm 7.6** |
| | 30 | | | 60.9 \pm 5.3** | 58.2 \pm 2.4** | 0.97 \pm 0.10** | 53.5 \pm 4.3** |
| IC₅₀ | | | | 22.4 \pm 3.4 μM | | 10.2 \pm 1.6 μM | |

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

SB203580: [4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole: positive control

Table 24. The inhibitory effect of compounds (45-47, 49-51, 53, 54) on TNF- α formation in medium



Cell line: Raw 264.7 cells

Inducer: LPS (1 μ g/ml)

Cell line: N9 cells

Inducer: LPS (10 ng/ml)+ IFN- γ (10 U/ml)

| No. | Conc. (μ M) | R ₆ | R ₂ ' | TNF- α formation (ng/ml) | | | |
|-----------------|------------------------|------------------|------------------|--|------------------|--|------------------|
| | | | | RAW | % inhibition | N9 | % inhibition |
| Control | | | | 145.4 \pm 6.3 | | 2.12 \pm 0.12 | |
| 45 | 30 | Cl | F | 172.7 \pm 5.1 | -18.9 \pm 2.3 | 1.91 \pm 0.21 | 10.4 \pm 5.1 |
| 46 | 30 | Cl | Cl | 148.7 \pm 6.5 | -2.0 \pm 1.3 | 2.14 \pm 0.16 | -0.7 \pm 2.0 |
| 47 | 30 | Cl | OCH ₃ | 137.5 \pm 6.7 | 5.4 \pm 1.6 | 2.05 \pm 0.18 | 3.4 \pm 3.8 |
| 49 | 30 | F | F | 144.7 \pm 6.0 | 0.4 \pm 0.6 | 2.14 \pm 0.12 | -0.7 \pm 1.4 |
| 50 | 30 | F | Cl | 156.7 \pm 0.1 | -7.5 \pm 3.5 | 2.28 \pm 0.09 | -7.8 \pm 2.3 |
| 51 | 30 | F | OCH ₃ | 169.1 \pm 1.5 | -16.0 \pm 3.2 | 2.15 \pm 0.07 | -1.6 \pm 2.7 |
| 53 | 30 | OCH ₃ | F | 134.6 \pm 4.6 | 8.4 \pm 4.0 | 1.67 \pm 0.12 | 21.3 \pm 1.3 |
| 54 | 30 | OCH ₃ | Cl | 127.8 \pm 5.8 | 12.0 \pm 1.8 | 2.15 \pm 0.28 | -0.4 \pm 7.9 |
| SB203580 | | | | | | | |
| | 3 | | | 132.8 \pm 3.3 | 8.9 \pm 7.2 | 1.33 \pm 0.04** | 36.4 \pm 1.3** |
| | 10 | | | 107.2 \pm 1.3** | 26.5 \pm 6.0** | 1.02 \pm 0.17** | 51.6 \pm 7.6** |
| | 30 | | | 60.9 \pm 5.3** | 58.2 \pm 2.4** | 0.97 \pm 0.10** | 53.5 \pm 4.3** |
| | IC₅₀ | | | 22.4 \pm 3.4 μM | | 10.2 \pm 1.6 μM | |

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

SB203580: [4-(4-Fluorophenyl)-2-(4-methylsulfinylphenyl)-5-(4-pyridyl)1H-imidazole: positive control