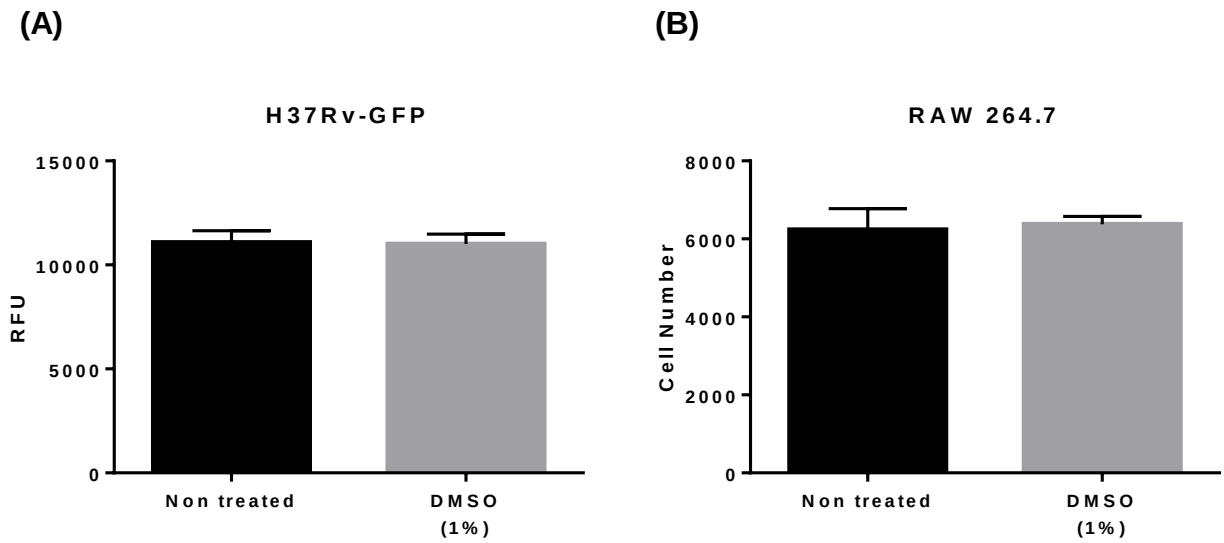


Figure S1. Effect of DMSO (1%) on **A**. Bacterial viability and **B**. RAW 264.7 macrophages survival (n=15). Experiments were conducted over a period of 5 days using the conditions described in the manuscript (medium and cell number).

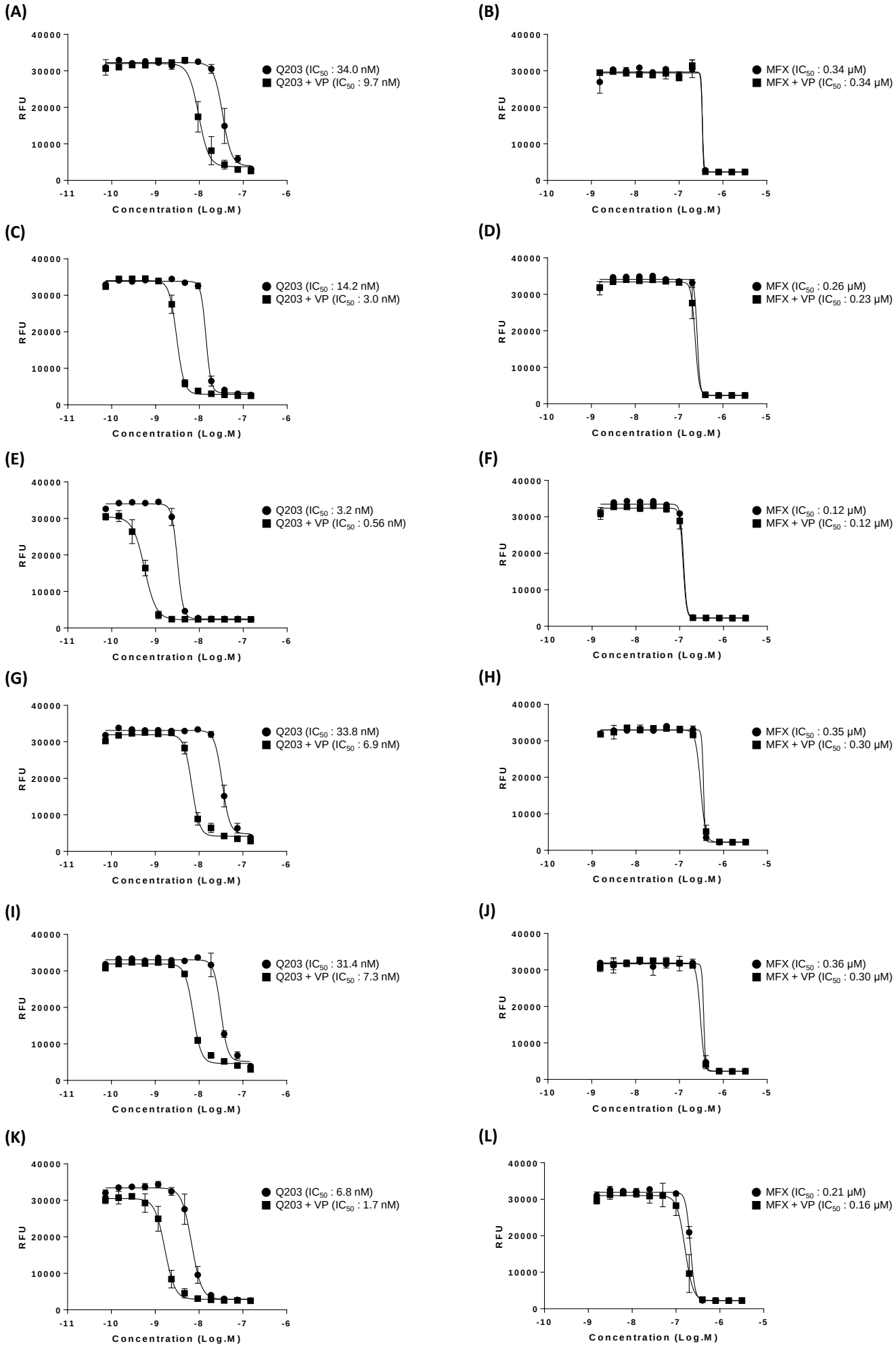
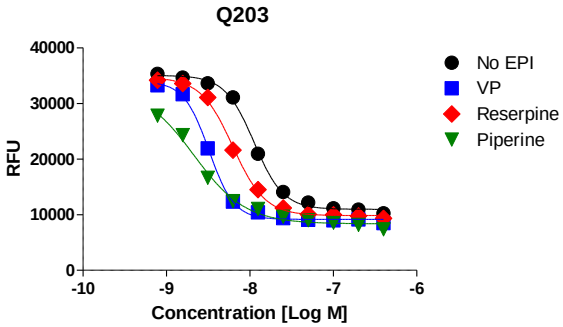
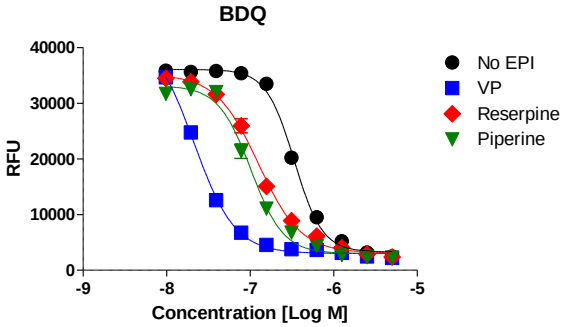

(A)
RFU
Concentration (Log.M)
Q203 (IC50 : 34.0 nM)
Q203 + VP (IC50 : 9.7 nM)
(B)
MFX (IC50 : 0.34 μM)
MFX + VP (IC50 : 0.34 μM)
(C)
Q203 (IC50 : 14.2 nM)
Q203 + VP (IC50 : 3.0 nM)
(D)
MFX (IC50 : 0.26 μM)
MFX + VP (IC50 : 0.23 μM)
(E)
Q203 (IC50 : 3.2 nM)
Q203 + VP (IC50 : 0.56 nM)
(F)
MFX (IC50 : 0.12 μM)
MFX + VP (IC50 : 0.12 μM)
(G)
Q203 (IC50 : 33.8 nM)
Q203 + VP (IC50 : 6.9 nM)
(H)
MFX (IC50 : 0.35 μM)
MFX + VP (IC50 : 0.30 μM)
(I)
Q203 (IC50 : 31.4 nM)
Q203 + VP (IC50 : 7.3 nM)
(J)
MFX (IC50 : 0.36 μM)
MFX + VP (IC50 : 0.30 μM)
(K)
Q203 (IC50 : 6.8 nM)
Q203 + VP (IC50 : 1.7 nM)
(L)
MFX (IC50 : 0.21 μM)
MFX + VP (IC50 : 0.16 μM)

Figure S2. Dose-response curves obtained using REMA for the multidrug-resistant (MDR) clinical isolates. MDR1 (**A** and **B**), MDR2 (**C** and **D**), MDR3 (**E** and **F**), MDR4 (**G** and **H**), MDR5 (**I** and **J**), and MDR6 (**K** and **L**) were exposed to Q203, Q203 + verapamil (VP), moxifloxacin (MFX) and MFX + VP, as indicated. IC_{50} values were determined using a sigmoidal dose-response curve fitting performed by Graph Pad Prism 6 software (version 6.05) and are indicated in parenthesis in the legend of each graph.

(A)



(B)



(C)

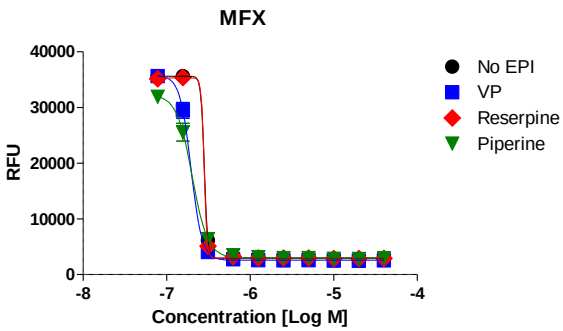
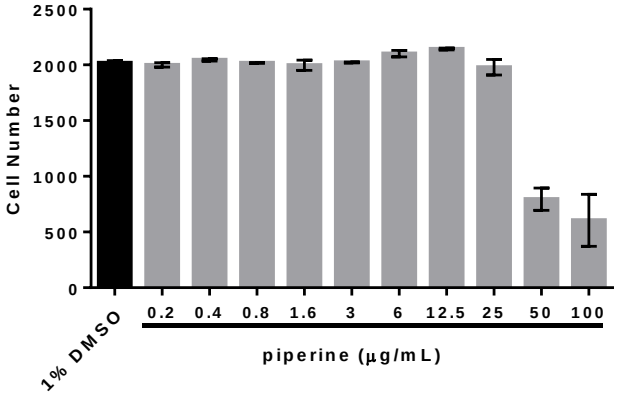
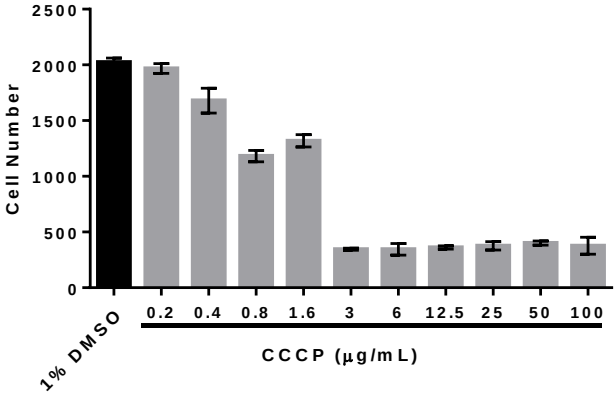
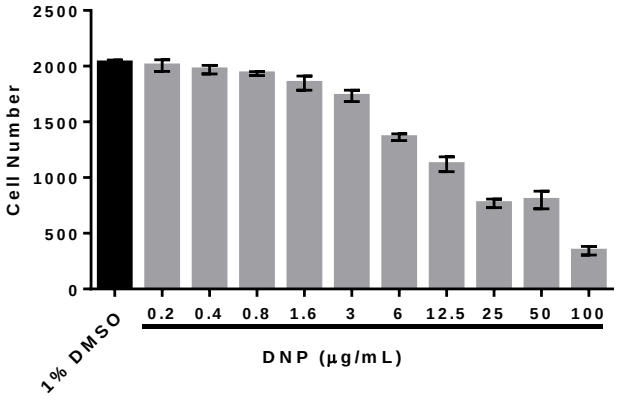


Figure S3. Effect of reserpine and piperine against *M. tuberculosis*, as determined using REMA. Curves were fitted using a sigmoidal dose-response curve performed by Graph Pad Prism 6 software (version 6.05).

(A)


Cell Number
2500
2000
1500
1000
500
0
1% DMSO
0.2 0.4 0.8 1.6 3 6 12.5 25 50 100
piperine (µg/mL)


Cell Number
2500
2000
1500
1000
500
0
1% DMSO
0.2 0.4 0.8 1.6 3 6 12.5 25 50 100
CCCP (µg/mL)


Cell Number
2500
2000
1500
1000
500
0
1% DMSO
0.2 0.4 0.8 1.6 3 6 12.5 25 50 100
DNP (µg/mL)

(B)

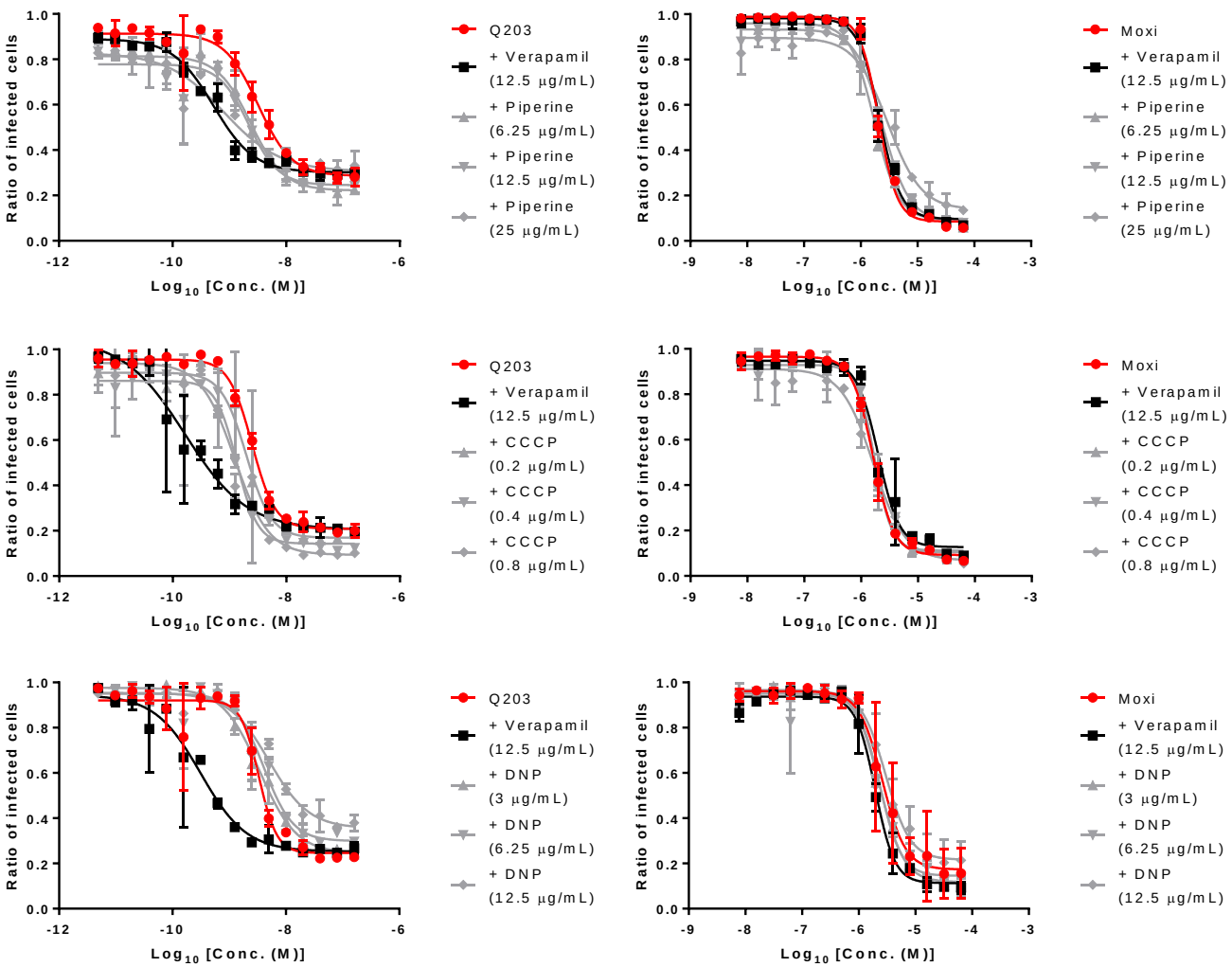

Ratio of infected cells
Log10 [Conc. (M)]
Q203
+ Verapamil (12.5 µg/mL)
+ Piperine (6.25 µg/mL)
+ Piperine (12.5 µg/mL)
+ Piperine (25 µg/mL)
Moxi
+ Verapamil (12.5 µg/mL)
+ Piperine (6.25 µg/mL)
+ Piperine (12.5 µg/mL)
+ Piperine (25 µg/mL)
Q203
+ Verapamil (12.5 µg/mL)
+ CCCP (0.2 µg/mL)
+ CCCP (0.4 µg/mL)
+ CCCP (0.8 µg/mL)
Moxi
+ Verapamil (12.5 µg/mL)
+ CCCP (0.2 µg/mL)
+ CCCP (0.4 µg/mL)
+ CCCP (0.8 µg/mL)
Q203
+ Verapamil (12.5 µg/mL)
+ DNP (3 µg/mL)
+ DNP (6.25 µg/mL)
+ DNP (12.5 µg/mL)
Moxi
+ Verapamil (12.5 µg/mL)
+ DNP (3 µg/mL)
+ DNP (6.25 µg/mL)
+ DNP (12.5 µg/mL)

Figure S4. **A**. Cytotoxic effects of the efflux pump inhibitors (EPI) piperine, carbonyl cyanide 3-chlorophenylhydrazone (CCCP) and 2,4-dinitrophenol (DNP) on RAW 264.7 cells. Cells were incubated 5 days at 37°C, 5% CO_2 in presence of the EPI before staining for 20 min with 5 µM Syto 60 dye. Images were acquired using fluorescence microscopy and analyzed using in-house scripts to enumerate the number of cells. Three fields were averaged for each well and values shown are the average of 4 replicates. **B**. Dose-response curves of Q203 (left) and moxifloxacin (Moxi, right) showing the evolution of the ratio of infected macrophages as a function of the compound concentration. In red, the effect of the compound alone is shown; in black, the effect of the compound in combination with 12.5 µg/mL verapamil and in grey, the effect of the compound in combination with various doses of EPI. Curves were fitted using a sigmoidal dose-response curve performed by Graph Pad Prism 6 software (version 6.05). IC_{50} values are summarized in **Table S1**.

Supplementary Table

Table S1. IC_{50} values of Q203 and moxifloxacin against H37Rv-GFP replicating in macrophages, in presence or absence of EPIs.

EPI	EPI conc. µg/mL	Q203 (nM)	Moxifloxacin (µM)
No EPI		3.9	2.3
Verapamil	12.5	0.41	2.1
Piperine	6.25	2.5	2.0
Piperine	12.5	2.7	2.8
Piperine	25	0.75	2.9
CCCP	0.2	2.1	1.8
CCCP	0.4	1.5	1.8
CCCP	0.8	1.4	1.9
DNP	3.0	3.5	2.4
DNP	6.25	4.0	2.5
DNP	12.5	3.9	2.8