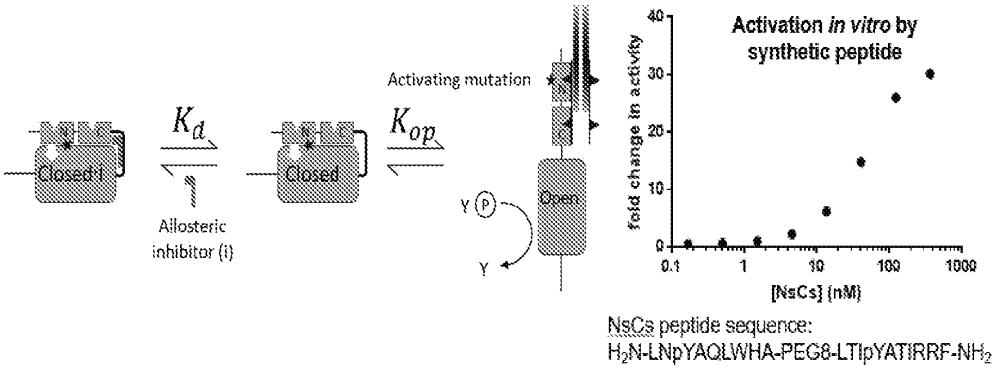


$$Activity \propto Fraction\ Open\ (\theta_{op}):$$

$$\theta_{op} = \frac{K_{op}}{1 + K_{op} + \frac{[i]}{K_d}}$$

Figure 1

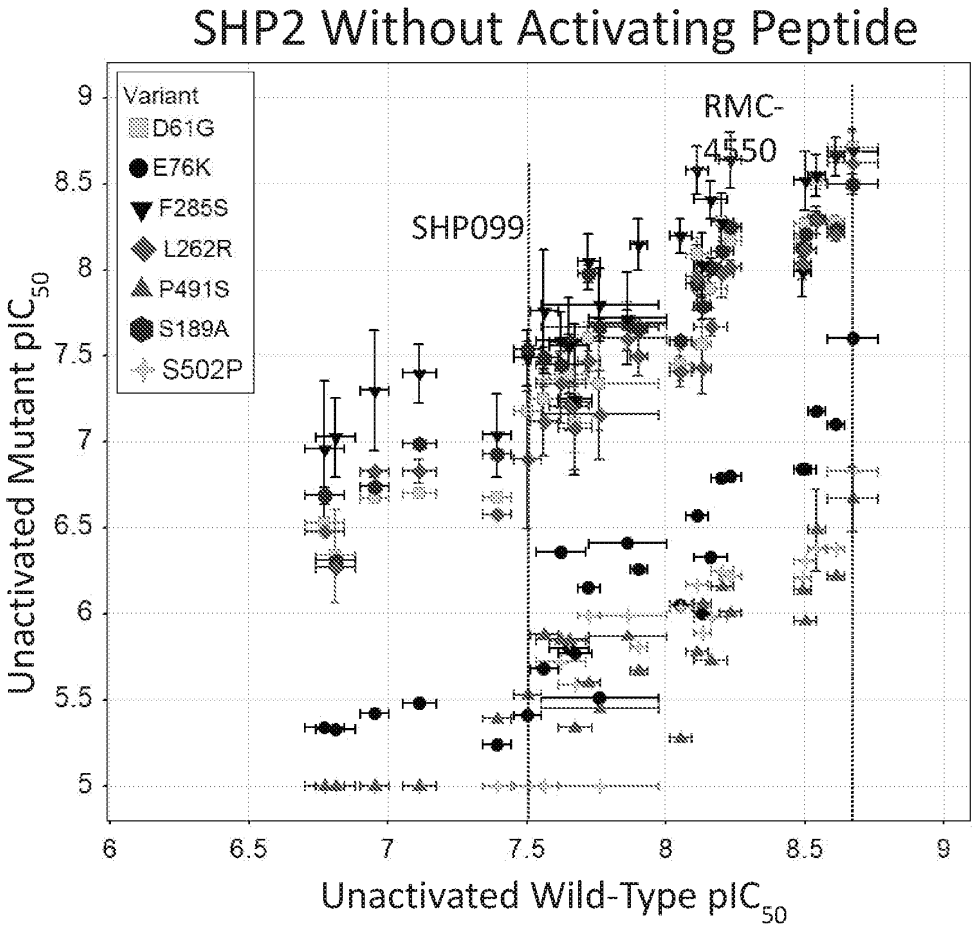

SHP2 Without Activating Peptide
Variant
D61G
E76K
F285S
L262R
P491S
S189A
S502P
SHP099
RMC-4550
Unactivated Mutant pIC50
Unactivated Wild-Type pIC50
9
8.5
8
7.5
7
6.5
6
5.5
5
6
6.5
7
7.5
8
8.5
9

Figure 2

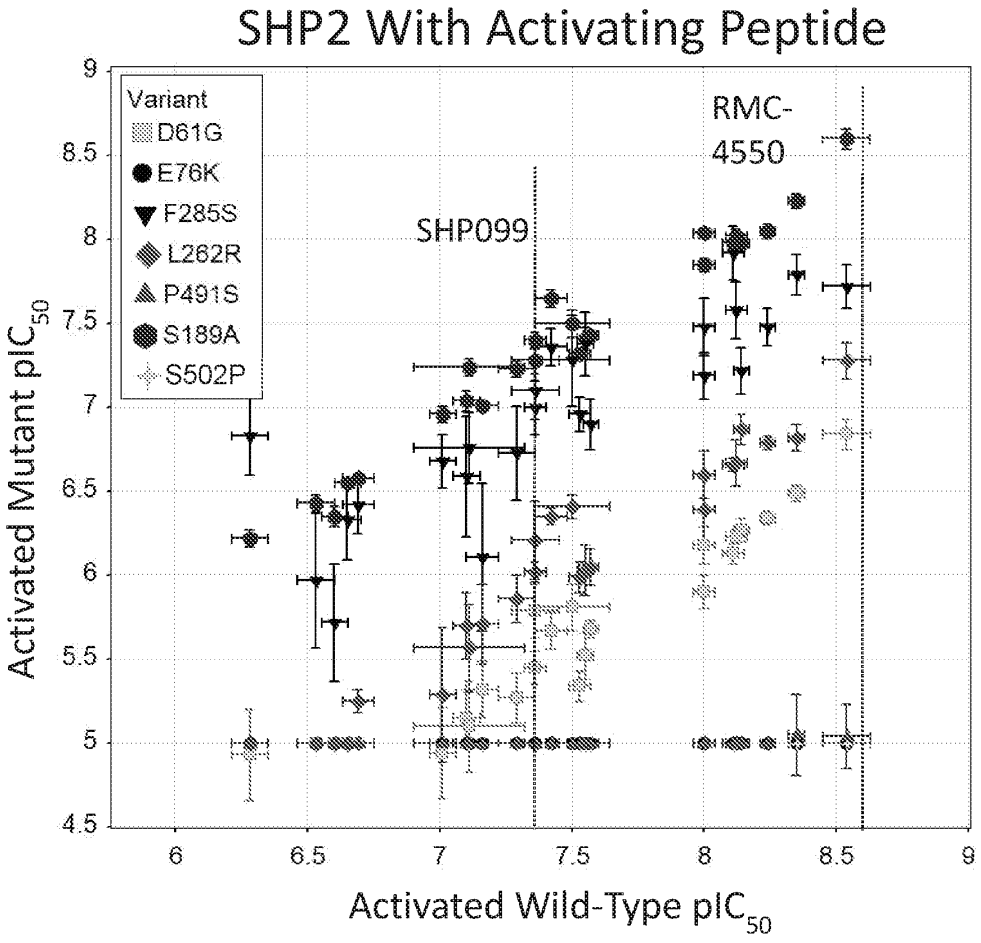

SHP2 With Activating Peptide
Variant
D61G
E76K
F285S
L262R
P491S
S189A
S502P
SHP099
RMC-4550
Activated Mutant pIC50
Activated Wild-Type pIC50
9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
6
6.5
7
7.5
8
8.5
9

Figure 3

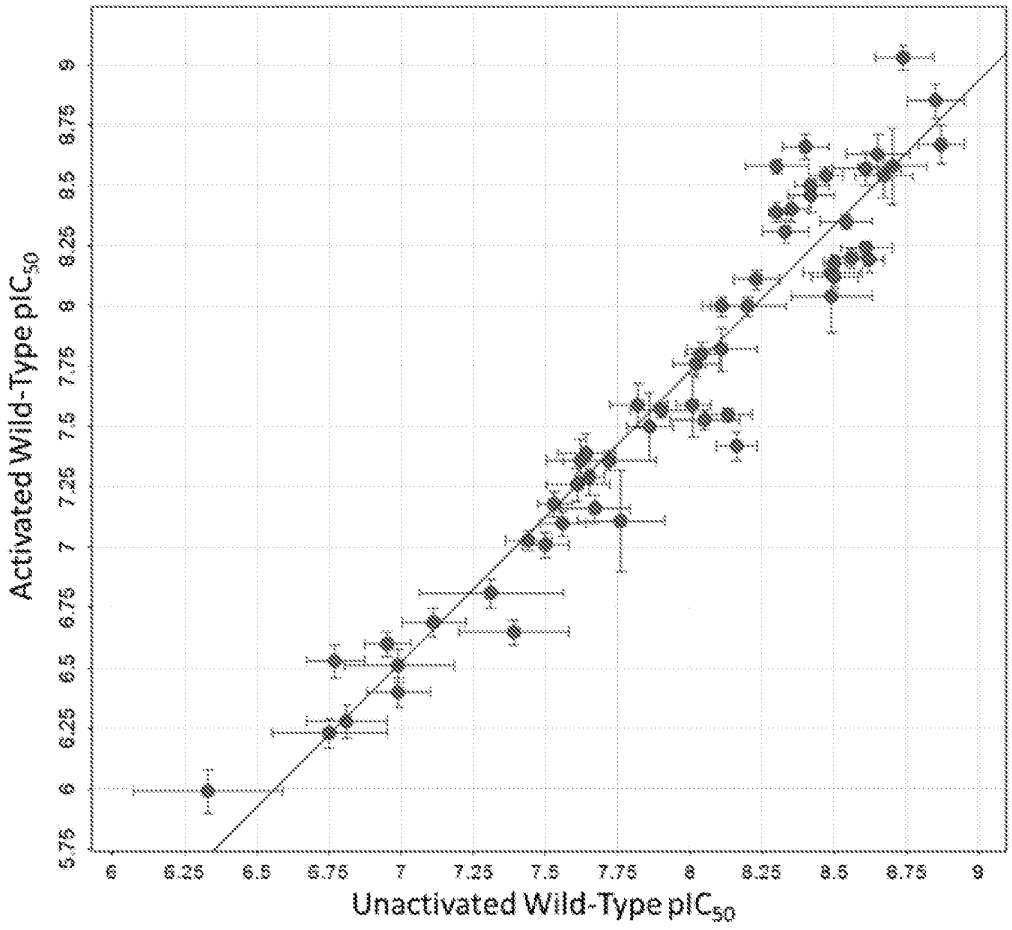

Activated Wild-Type pIC50
Unactivated Wild-Type pIC50
5.75
6
6.25
6.5
6.75
7
7.25
7.5
7.75
8
8.25
8.5
8.75
9

Figure 4

FIG. 5A

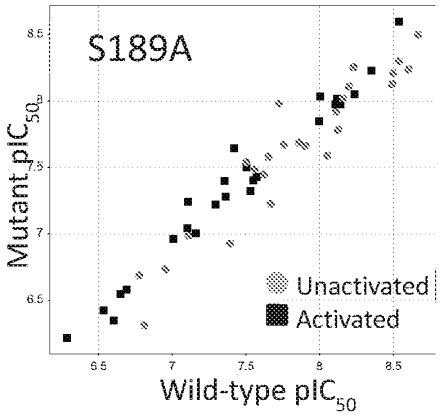


FIG. 5B

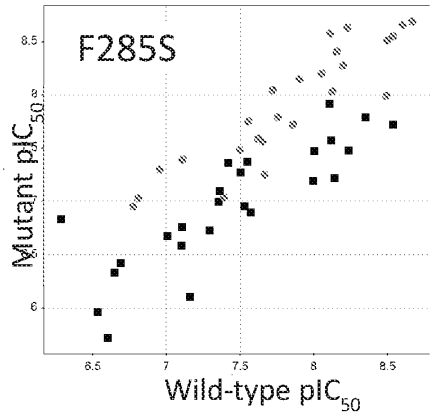


FIG. 5C

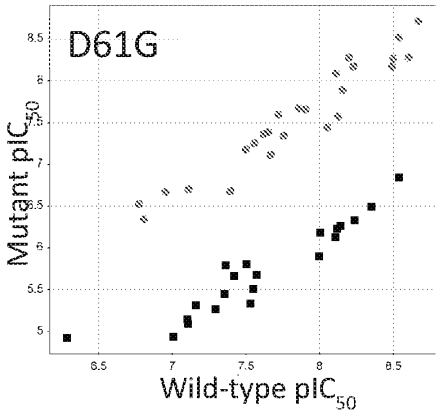


FIG. 5D

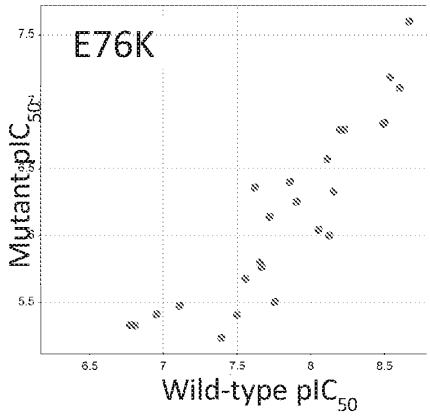


Figure 5

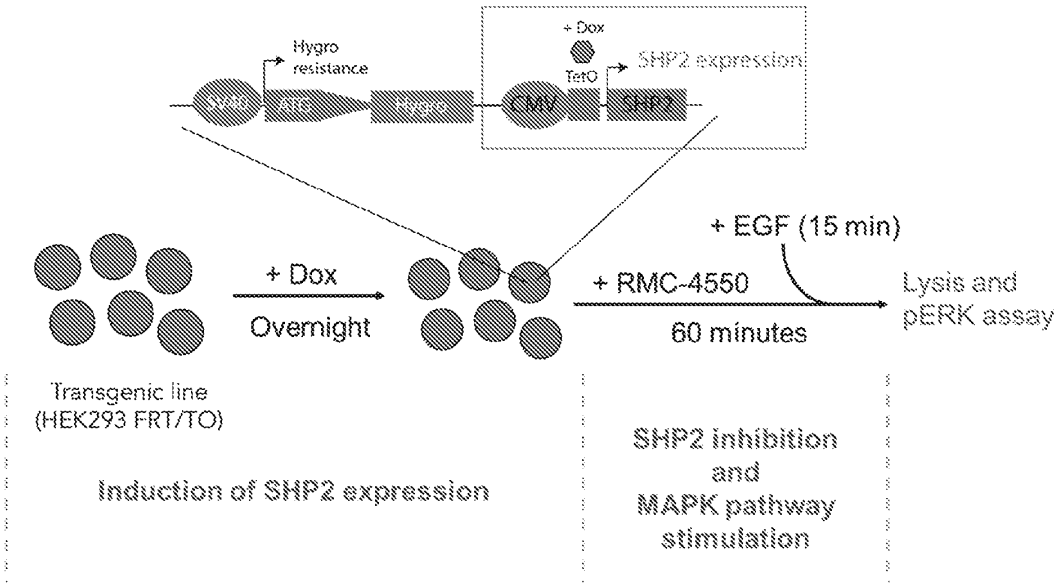

+ Dox
Hygro resistance
TetO
SHP2 expression
SV40
ATG
Hygro
CMV
SHP2
+ EGF (15 min)
+ Dox
Overnight
+ RMC-4550
60 minutes
Lysis and pERK assay
Transgenic line (HEK293 FRT/TO)
Induction of SHP2 expression
SHP2 inhibition and MAPK pathway stimulation

Figure 6

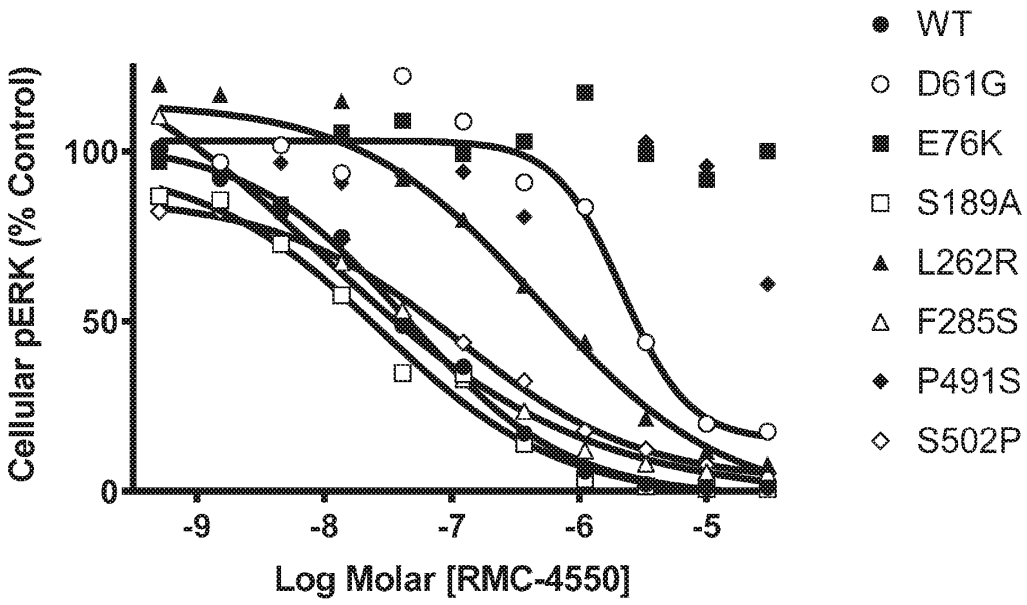

Cellular pERK (% Control)
100
50
0
-9
-8
-7
-6
-5
Log Molar [RMC-4550]
WT
D61G
E76K
S189A
L262R
F285S
P491S
S502P

Figure 7

FIG. 8A

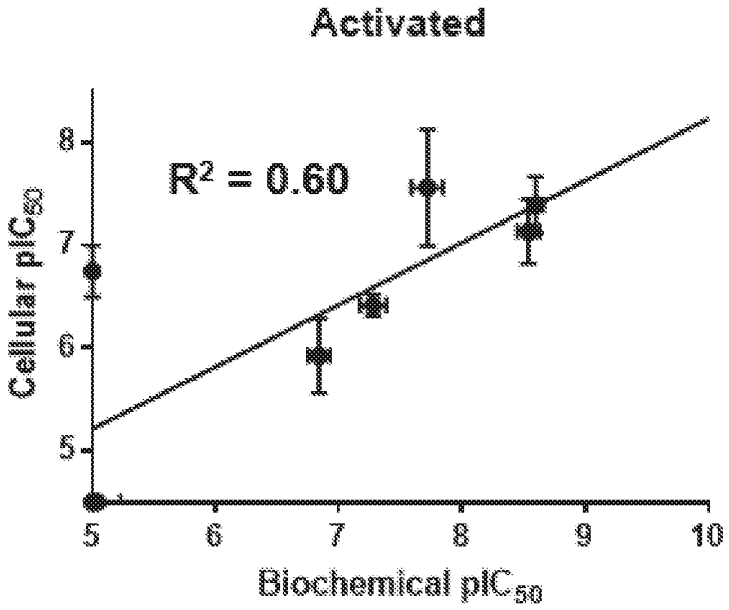


Figure 8

FIG. 8B

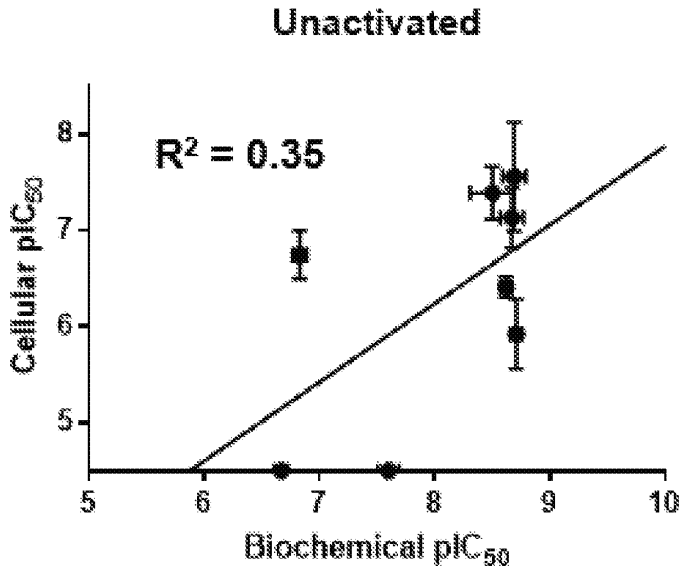


Figure 8 (continued)