Table S1. Potentiating activities of the 13 CFTR primary hits, related to Figure 1.

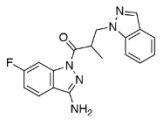
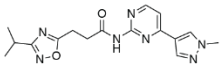
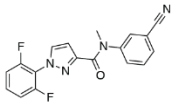
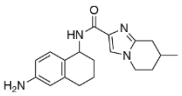
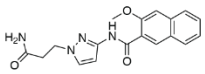
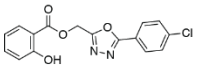
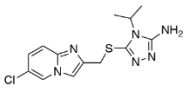
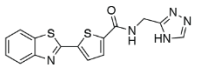
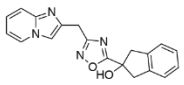
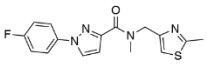
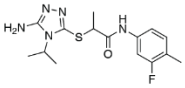
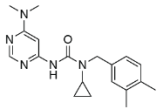
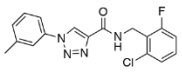
ID	2D structure by NMR	Purity (%)	Fold of stimulation (mean ± SEM)
Z2075279358		99.6	2.38 ± 0.24 (n=3)
Z2194302854		98.8	1.39 ± 0.08 (n=3)
Z1343848401		99.7	1.37 ± 0.08 (n=6)
Z2776419998		99.1	1.36 ± 0.08 (n=3)
Z1224795288		97.7	1.34 ± 0.08 (n=3)
Z19702639		91.2	1.32 ± 0.04 (n=4)
Z1096199008		97	1.30 ± 0.04 (n=4)
Z873519648		>99	1.27 ± 0.11 (n=3)
Z1783799713		97.8	1.25 ± 0.04 (n=4)
Z899051432		>99	1.24 ± 0.04 (n=6)
Z1262422554		>99	1.17 ± 0.03 (n=5)
Z2171315755		95	1.17 ± 0.09 (n=3)
Z995908944		>99	1.15 ± 0.03 (n=4)

Table S2. Summary of EM data and structure refinement statistics for CFTR in complex with ‘853, related to Figure 3 and Figure S2.

Data collection	
Microscope	Titan Krios (FEI)
Voltage (kV)	300
Detector	K2 Summit (Gatan)
Pixel size (Å)	1.03
Defocus range (μm)	1 to 2.5
Movies	6,967
Frames/movie	50
Dose rate (electrons/pixel/s)	8
Total dose (electrons/Å^2)	75
Number of particles	1,948,497
Model composition	
Non-hydrogen atoms	9,682
Protein residues	1,035
Lipids	5
ATP	2
Mg	2
Refinement	
Resolution (Å)	3.8
Sharpening B-factor (Å^2)	-117
RMS deviations	
Bond lengths (Å)	0.005
Bond angles (°)	0.863
Validation	
Molprobity score	2.09
Clashscore, all atoms	16
Favored rotamers (%)	99.9
Ramachandran plot (%)	
Favored	94.87
Allowed	5.13
Outliers	0.0