

Supplementary Materials

To simulate a drug blocking a channel, we used the following equation to scale G_x , based on the IC_{50} and concentration:

$$G_{x,drug} = G_x \left[1 + \left(\frac{C}{IC_{50,x}} \right)^h \right]^{-1}$$

where $G_{x,drug}$ is the maximal conductance of channel x in the presence of the drug; C is the concentration of the drug; $IC_{50,x}$ is the half-maximal inhibitory concentration for that drug; h is the Hill coefficient.

Table S1 A detailed summary of simulated drug-induced APD prolongation, EAD, AP alternans and reported TdP risks of 12 CiPA training compounds¹⁻³.

	CiPA TdP Category	The onset of EAD	AP alternans (onset and magnitude)	ΔAPD% (CL=1000 ms)
Quinidine	High	At all CLs in all cell types	Not applicable	P (91.39%); Epi (EAD); Endo (EAD); M (EAD)
Bepridil	High	CLs>550ms in M cell	At CLs=300~450ms in P cell (6.1817%) At CLs=950~1100ms in M cell (EAD and Alternans)	P (15.01%); Epi (27.02%); Endo (25.64%); M (EAD)
Dofetilide	High	At CLs>850ms in M cell	At CLs=300~450ms in P cell (6.574%)	P (15.15%); Epi (15.75%); Endo (17.73%); M (EAD)
Sotalol	High	At CLs>1550ms in M cell	At CLs=300~450ms in P cell (1.883%)	P (5.53%); Epi (7.75%); Endo (8.09%); M (12.26%)
Chlorpromazine	Intermediate	Not shown	At CLs=300~450ms in P cell (1.834%)	P (2.32%); Epi (3.36%); Endo (3.38%); M (4.69%)
Cisapride	Intermediate	At CLs>900ms in M cell	At CLs=300~450ms in P cell (2.744%)	P (12.64%); Epi (14.30%); Endo (15.71%); M (EAD)
Terfenadine	Intermediate	At CLs>1050ms In M cell	At CLs=300~450ms in P cell (1.949%)	P (9.73%); Epi (13.25%); Endo (13.69%); M (23.65%)
Ondansetron	Intermediate	Not shown	At CLs=300~450ms in P cell (1.852%)	P (3.55%); Epi (5.21%); Endo (5.23%); M (7.63%)
Diltiazem	Low/no risk	Not shown	At CLs=300~450ms in P cell (1.477%)	P (-0.53%); Epi (11.78%); Endo (0.94%); M (8.36%)
Mexiletine	Low/no risk	Not shown	At CLs=300~450ms in P cell (2.014%)	P (-2.29%); Epi (3.78%); Endo (2.63%); M (3.85%)
Ranolazine	Low/no risk	At CLs>1800ms in M cell	At CLs=300~450ms in P cell (1.815%)	P (0.92%); Epi (6.40%); Endo (6.88%); M (9.43%)
Verapamil	Low/no risk	Not shown	At CLs=300~450ms in P cell (0.793%)	P (7.18%); Epi (13.93%); Endo (10.43%); M (17.01%)

Table S2 Model details of Epi, Endo and M cells according to experimental measurements⁴⁻⁶.

Cell Type	Scaling factor (Epi as control)			
Epi	1*G _{NaL}	1*G _{to1}	1*G _{Ks}	1*G _{NaCa}
Endo	1* G _{NaL}	0.18* G _{to1}	0.9* G _{Ks}	0.9* G _{NaCa}
M	1.4* G _{NaL}	0.91* G _{to1}	0.3* G _{Ks}	1.3* G _{NaCa}

Table S3 IC₅₀ and Hill coefficients (h) of 12 CiPA training compounds^{1,7}.

Drug		hERG (I _{Kr})	I _{NaL}	I _{CaL}	I _{Na}	I _{to}	I _{K1}	I _{Ks}	Free Cmax, nmol/L
Quinidine	IC ₅₀ (nmol/L)	992	9417	51592	12329	3487.4	4E+07	4898.9	3237
	h	0.8	1.3	0.6	1.5	1.3	0.4	1.4	
Bepridil	IC ₅₀ (nmol/L)	50	1813.9	2808.1	2929.3	8594	-*	28628.3	33
	h	0.9	1.4	0.6	1.2	3.5	-	0.7	
Dofetilide	IC ₅₀ (nmol/L)	4.9	753160	260.3	380.5	18.8	394.3	-	2
	h	0.9	0.3	1.2	0.9	0.8	0.8	-	
Sotalol	IC ₅₀ (nmol/L)	110600	-	7E+06	1140000000	43143455	3E+06	4221856	14690
	h	0.8	-	0.9	0.5	0.7	1.2	1.2	
Chlorpromazine	IC ₅₀ (nmol/L)	929.2	4559.6	8191.9	4535.6	17616711	9269.9	-	38
	h	0.8	0.9	0.8	2	0.4	0.7	-	
Cisapride	IC ₅₀ (nmol/L)	10.1	-	9E+06	-	219112.4	29498	81192862	2.6
	h	0.7	-	0.4	-	0.2	0.5	0.3	
Terfenadine	IC ₅₀ (nmol/L)	23	20056	700.4	4803.2	239960.8	-	399754	4
	h	0.6	0.6	0.7	1	0.3	-	0.5	
Ondansetron	IC ₅₀ (nmol/L)	1320	19181	22551	57666.4	1023378	-	569807	139
	h	0.9	1	0.8	1	1	-	0.7	
Diltiazem	IC ₅₀ (nmol/L)	13150	21869	112.1	110859	2820000000	-	-	122
	h	0.9	0.7	0.7	0.7	0.2	-	-	
Mexiletine	IC ₅₀ (nmol/L)	28880	8956.8	38244	-	-	-	-	4129
	h	0.9	1.4	1	-	-	-	-	
Ranolazine	IC ₅₀ (nmol/L)	8270	7884.5	-	68774	-	-	36155020	1948.2
	h	0.9	0.9	-	1.4	-	-	0.5	
Verapamil	IC ₅₀ (nmol/L)	288	7028	201.8	-	13429.2	3E+08	-	81
	h	1	1	1.1	-	0.8	0.3	-	

*- indicates no detectable blocking for that channel.

Reference

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