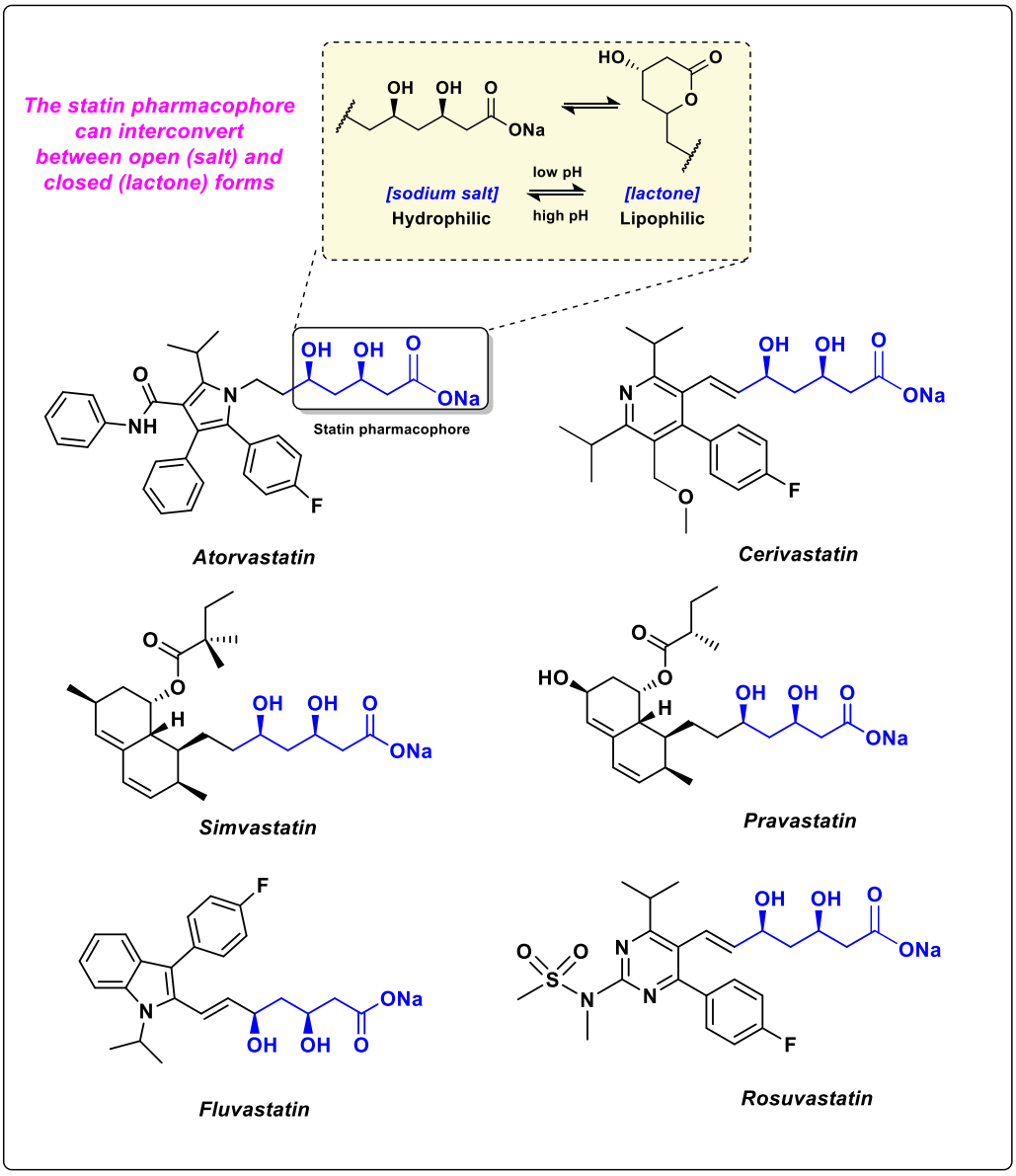
A


The statin pharmacophore can interconvert between open (salt) and closed (lactone) forms
[sodium salt]
Hydrophilic
low pH
high pH
[lactone]
Lipophilic
Statin pharmacophore
Atorvastatin
Cerivastatin
Simvastatin
Pravastatin
Fluvastatin
Rosuvastatin

B

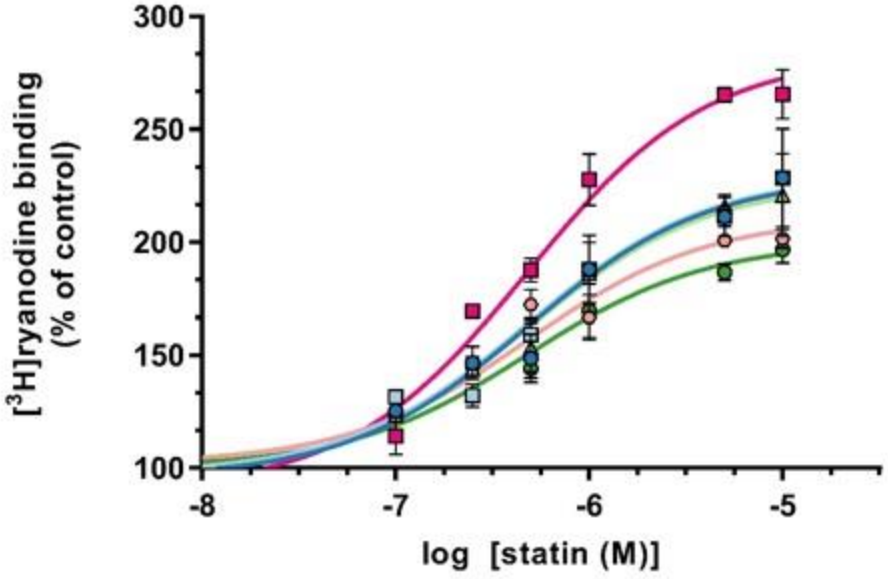

[3H]ryanodine binding (% of control)
300
250
200
150
100
-8
-7
-6
-5
log [statin (M)]

Figure 1

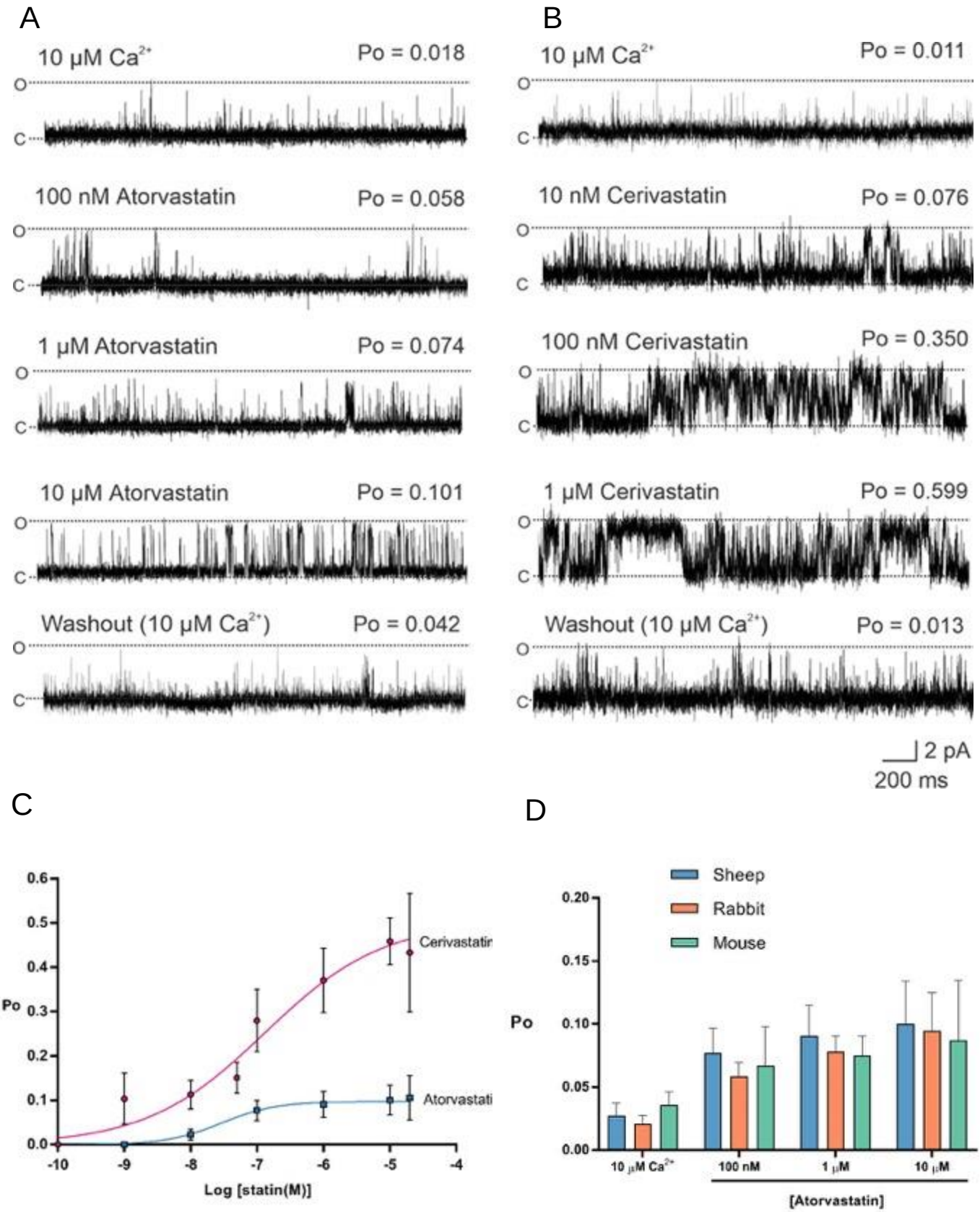

A
10 μM Ca2+
Po = 0.018
O
C
100 nM Atorvastatin
Po = 0.058
1 μM Atorvastatin
Po = 0.074
10 μM Atorvastatin
Po = 0.101
Washout (10 μM Ca2+)
Po = 0.042
B
10 μM Ca2+
Po = 0.011
10 nM Cerivastatin
Po = 0.076
100 nM Cerivastatin
Po = 0.350
1 μM Cerivastatin
Po = 0.599
Washout (10 μM Ca2+)
Po = 0.013
2 pA
200 ms
C
Po
Cerivastatin
Atorvastatin
Log [statin(M)]
D
Sheep
Rabbit
Mouse
Po
10 μM Ca2+
100 nM
1 μM
10 μM
[Atorvastatin]

Figure 2

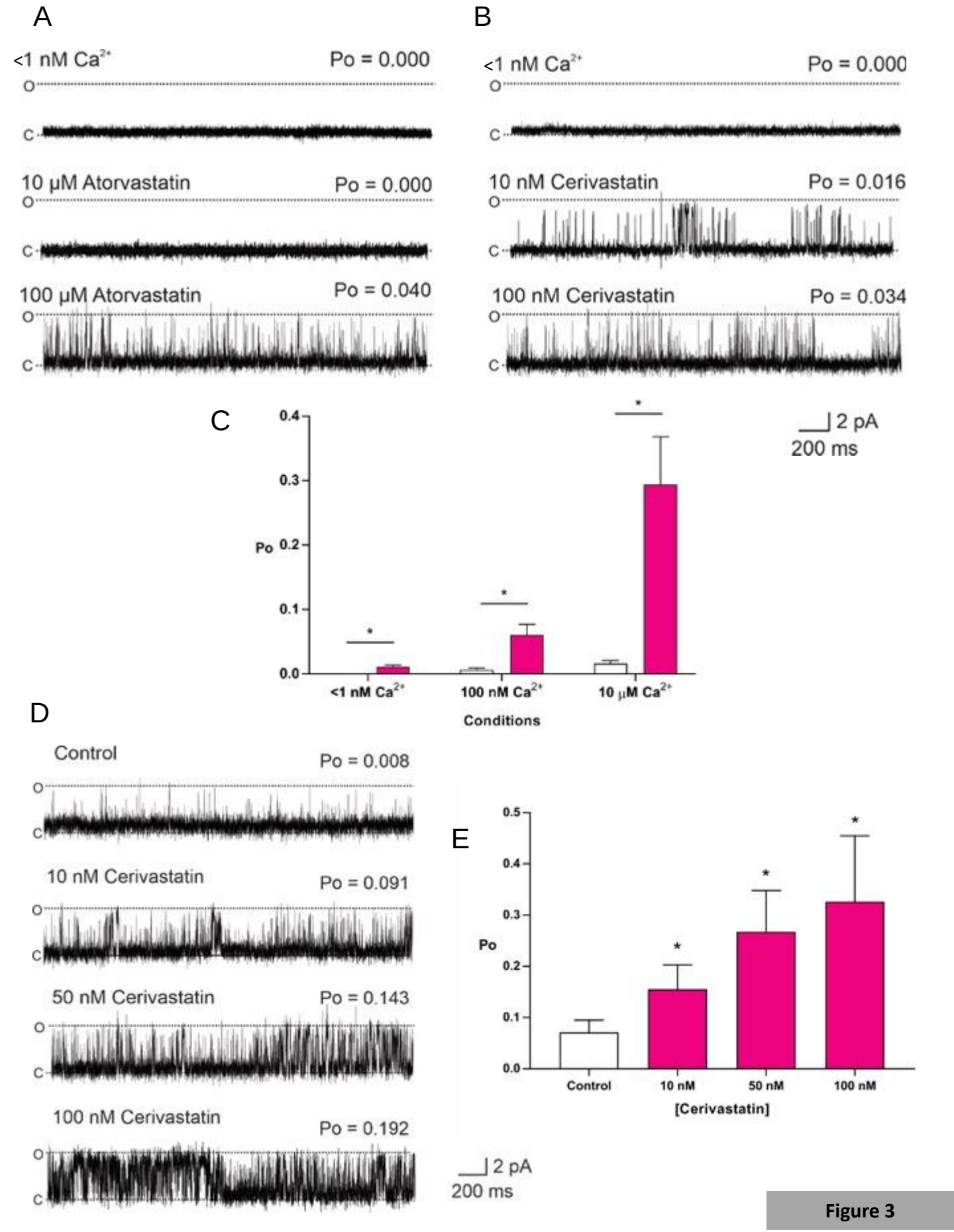

A
<1 nM Ca2+
Po = 0.000
O
C
10 μM Atorvastatin
Po = 0.000
100 μM Atorvastatin
Po = 0.040
B
<1 nM Ca2+
Po = 0.000
10 nM Cerivastatin
Po = 0.016
100 nM Cerivastatin
Po = 0.034
2 pA
200 ms
C
Po
0.4
0.3
0.2
0.1
0.0
*
<1 nM Ca2+
100 nM Ca2+
10 μM Ca2+
Conditions
D
Control
Po = 0.008
10 nM Cerivastatin
Po = 0.091
50 nM Cerivastatin
Po = 0.143
100 nM Cerivastatin
Po = 0.192
2 pA
200 ms
E
Po
0.5
0.4
0.3
0.2
0.1
0.0
Control
10 nM
50 nM
100 nM
[Cerivastatin]

Figure 3

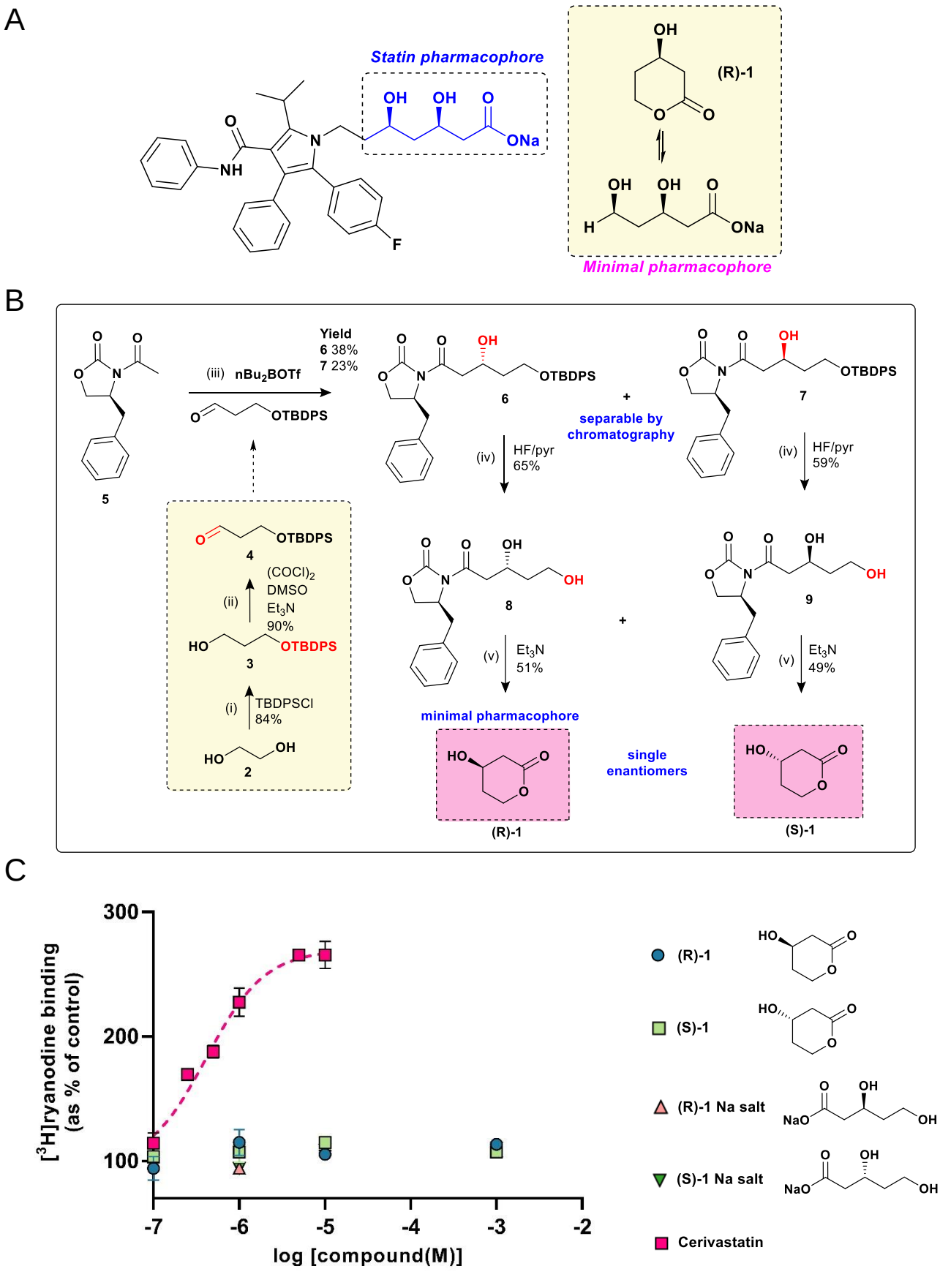
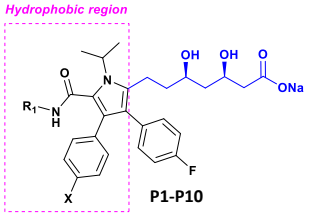
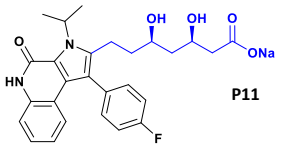
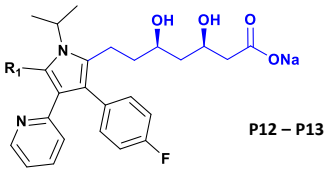

A
Statin pharmacophore
OH
OH
O
ONa
NH
N
O
F
(R)-1
H
Minimal pharmacophore
B
Yield
6 38%
7 23%
(iii) nBu2BOTf
OTBDPS
5
6
7
separable by chromatography
(iv) HF/pyr 65%
(iv) HF/pyr 59%
4
(ii) (COCl)2 DMSO Et3N 90%
3
(i) TBDPSCl 84%
2
8
9
(v) Et3N 51%
(v) Et3N 49%
minimal pharmacophore
single enantiomers
(R)-1
(S)-1
C
[3H]ryanodine binding (as % of control)
300
200
100
-7
-6
-5
-4
-3
-2
log [compound(M)]
(R)-1
(S)-1
(R)-1 Na salt
(S)-1 Na salt
Cerivastatin
NaO

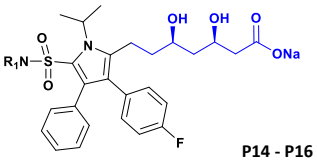
Figure 4

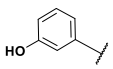
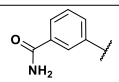
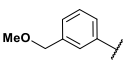
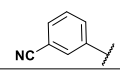
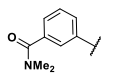
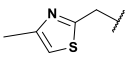
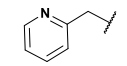
A



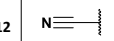


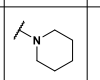
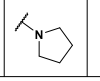




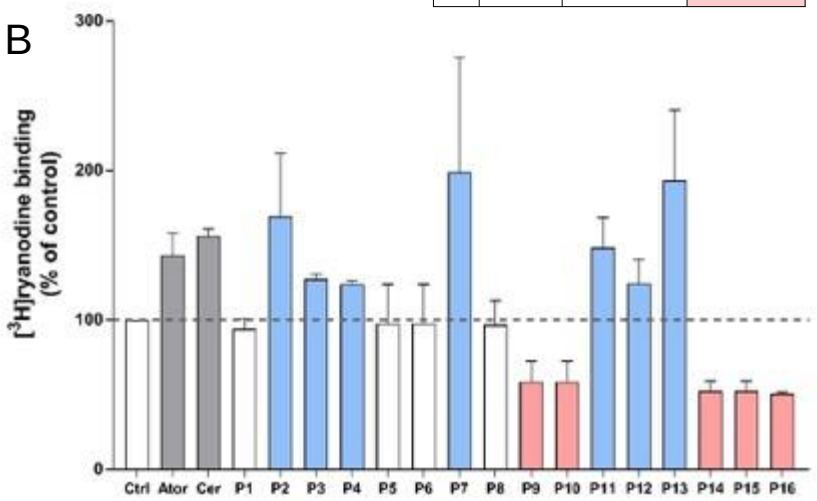
	R_1	X	HMG-CoA IC_{50} (nM)	Max or min binding (% of control)
P1		F	1.8	ND
P2		H	0.4	169
P3		H	0.3	126
P4		H	0.7	125
P5		H	0.2	ND
P6		H	1.2	ND
P7		H	1.5	173
P8		H	0.8	ND
P9		H	12.0	78
P10		H	3.8	59

	HMG-CoA IC_{50} (nM)	Max binding (% of control)
P11	11.7	178

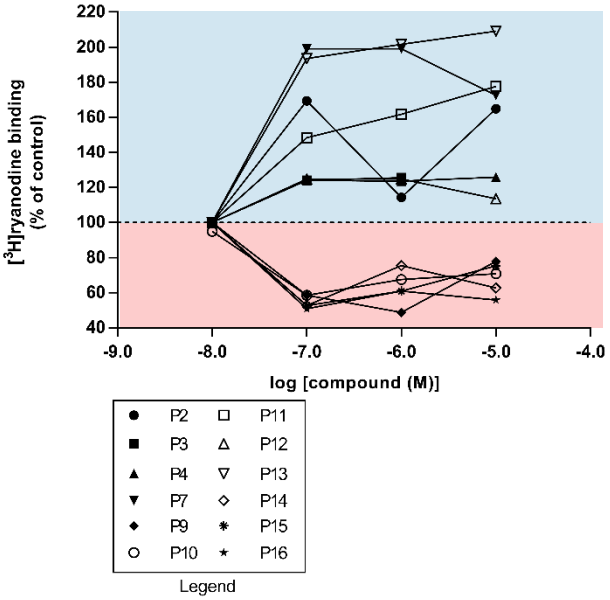
	R_1	HMG-CoA IC_{50} (nM)	Max binding (% of control)
P12		4.8	124
P13		5.3	209

	R_1	HMG-CoA IC_{50} (nM)	Min binding (% of control)
P14		4.5	53
P15		2.9	53
P16		2.6	51

B



C



D

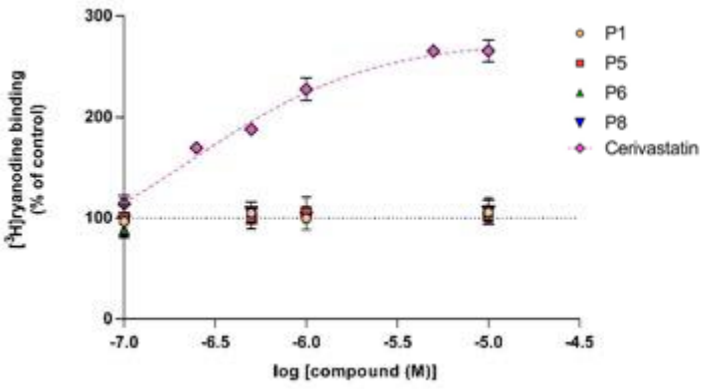
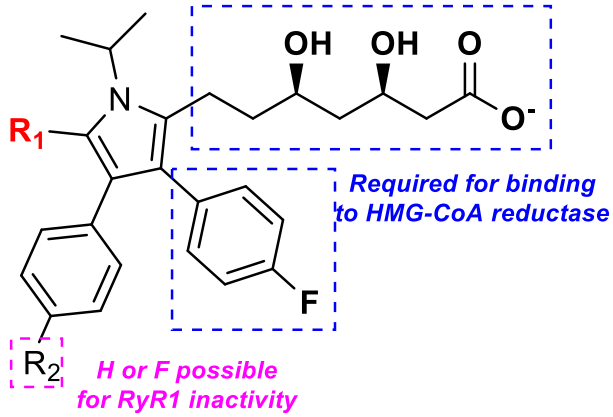
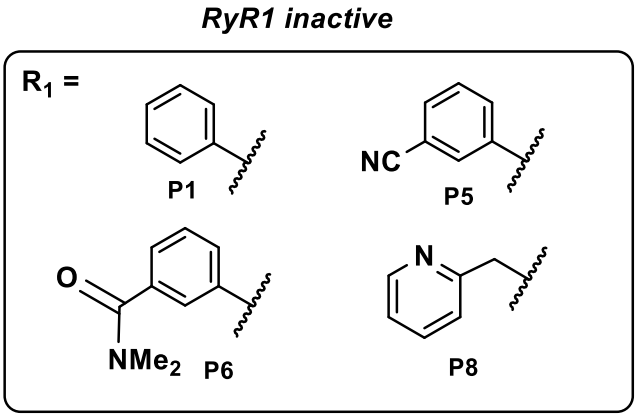
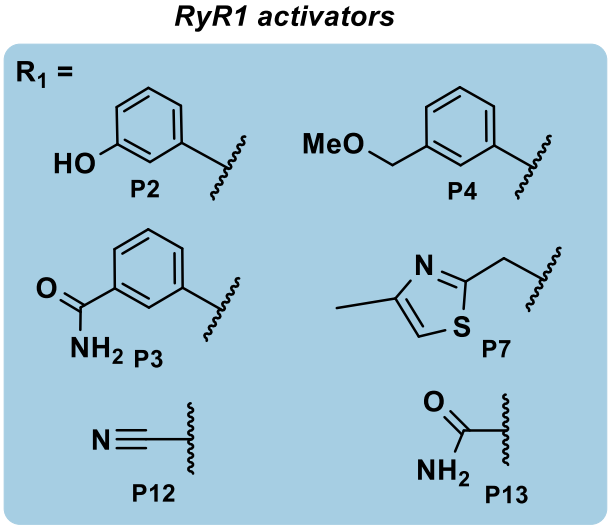


Figure 5


OH
OH
O
O-
N
R1
F
R2
Required for binding
to HMG-CoA reductase
H or F possible
for RyR1 inactivity


RyR1 inactive
R1 =
P1
NC
P5
O
NMe2
P6
N
P8


RyR1 activators
R1 =
HO
P2
MeO
P4
O
NH2
P3
N
S
P7
N
P12
O
NH2
P13

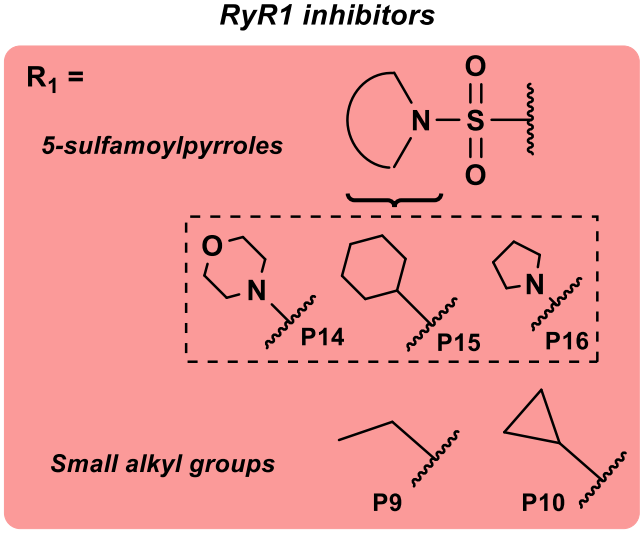

RyR1 inhibitors
R1 =
5-sulfamoylpyrroles
N
S
O
O
O
N
P14
P15
N
P16
Small alkyl groups
P9
P10

Figure 6