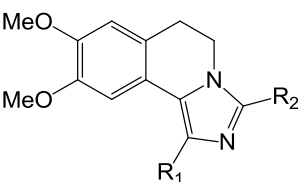
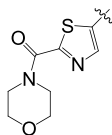
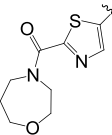
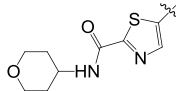
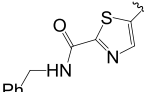
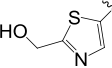
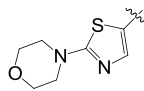
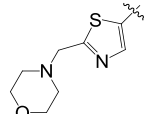
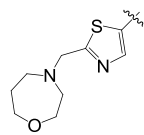


Supporting information

Table S1 Structure and PDE10A inhibitory activities of imidazoisoquinolines

			
No.	R ₁	R ₂	pK _i (nM)
1		H	8.00
2		H	8.82
3 ^s		H	8.37
4		H	7.40
5		H	6.73
6 ^s		H	7.59
7		H	7.59
8		H	8.18
9		H	8.42
10	4-Thiazolyl	H	6.06
11 ^s	5-Oxazolyl	H	7.51
12 ^s	4-Oxazolyl	H	6.29
13	N-Me-5-imidazolyl	H	6.58

To be continued

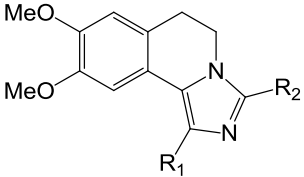
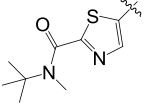
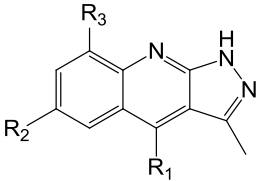
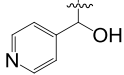
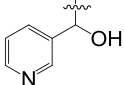
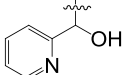
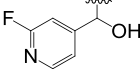
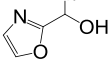
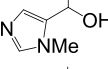
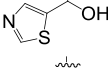
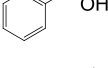
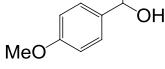
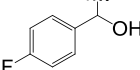
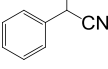
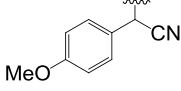
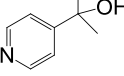
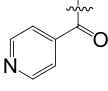
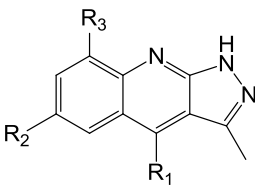
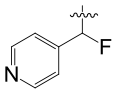
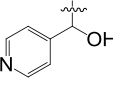
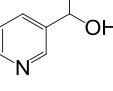
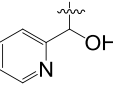
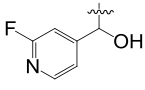
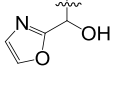
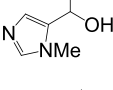
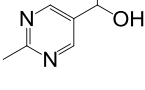
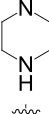
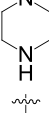
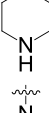
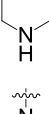
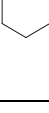
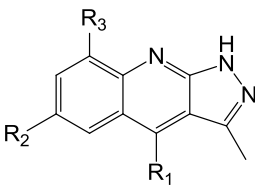
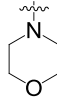
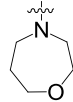
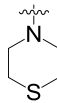
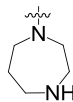
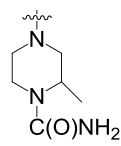
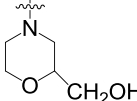
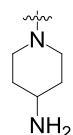
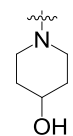
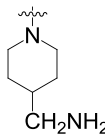
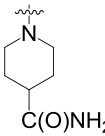
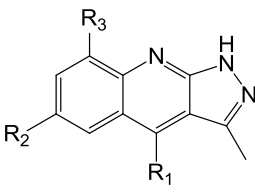
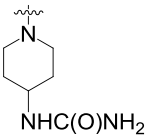
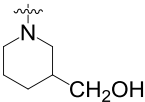
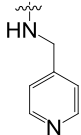
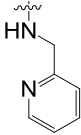
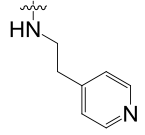
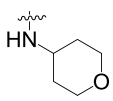
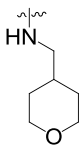
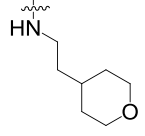
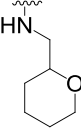
			
No.	R ₁	R ₂	pK _i (nM)
14 ^s	Cyclohexyl	H	6.70
15	Phenyl	H	6.92
16	2-Cl-Ph	H	6.20
17	3-Cl-Ph	H	7.48
18	4-Cl-Ph	H	6.74
19	2-OMe-Ph	H	6.67
20	3-OMe-Ph	H	7.52
21 ^s	4-OMe-Ph	H	6.94
22	3-Br-Ph	H	7.49
23	3-OEt-Ph	H	8.10
24	3-(4-Mopholiny)-Ph	H	8.19
25	2-Pyridyl	H	6.62
26	3-Pyridyl	H	7.54
27	4-Pyridyl	H	6.99
28 ^s	5-Pyrimidyl	H	7.40
29		Me	7.60
113		H	7.45
114		Me	7.70
115 ^s		H	8.06
^s Test set			

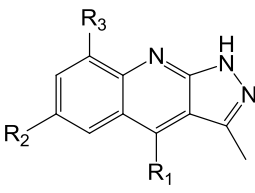
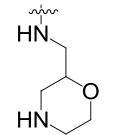
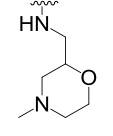
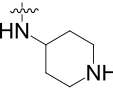
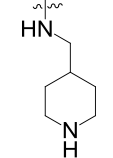
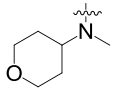
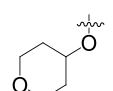
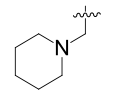
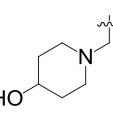
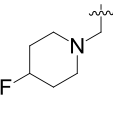
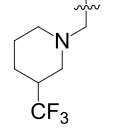
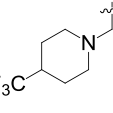
Table S2 Structure and PDE10A inhibitory activities of pyzoloquinolines

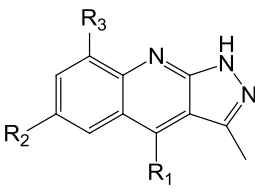
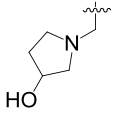
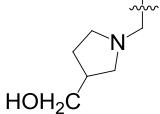
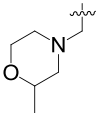
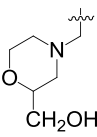
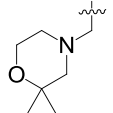
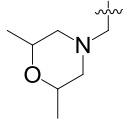
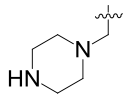
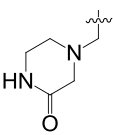
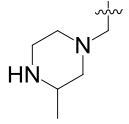
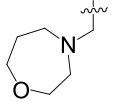
				
No.	R ₁	R ₂	R ₃	p <i>K</i> _i (nM)
30		OMe	Me	10.22
31 ^s		OMe	Me	8.00
32		OMe	Me	7.27
33		OMe	Me	10.15
34		OMe	Me	9.22
35 ^s		OMe	Me	7.68
36		OMe	Me	8.70
37		OMe	Me	7.30
38		OMe	Me	8.70
39		OMe	Me	7.08
40		OMe	Me	7.92
41		OMe	Me	8.70
42		OMe	Me	8.40
43		OMe	Me	9.00

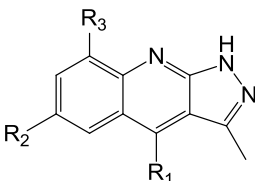
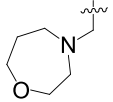
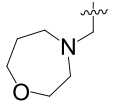
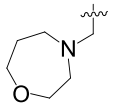
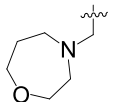
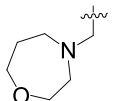
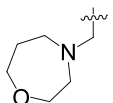
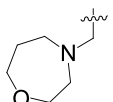
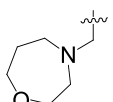
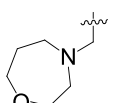
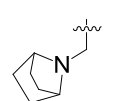
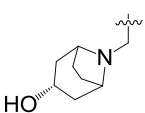
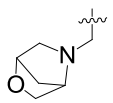
				
No.	R ₁	R ₂	R ₃	p <i>K</i> _i (nM)
To be continued				
44		OMe	Me	9.52
45		Cl	Me	9.70
46 ^s		Cl	Me	7.96
47		Cl	Me	7.41
48		Cl	Me	9.00
49		Cl	Me	9.40
50		Cl	Me	7.68
51		Cl	Me	8.52
52 ^s		OMe	H	6.23
53		H	H	6.26
54 ^s		Cl	Me	7.45
55		Cl	H	6.38
56		OMe	Me	6.44
To be continued				

				
No.	R ₁	R ₂	R ₃	p <i>K</i> _i (nM)
57		OMe	Me	7.64
58		OMe	Me	8.44
59 ^s		OMe	Me	6.71
60		OMe	Me	7.82
61		OMe	Me	8.48
62		OMe	Me	8.02
63		OMe	Me	9.00
64		OMe	Me	7.85
65		OMe	Me	9.30
66 ^s		OMe	Me	8.52
To be continued				

				
No.	R ₁	R ₂	R ₃	p <i>K</i> _i (nM)
67		OMe	Me	7.57
68 ^s		OMe	Me	7.54
69 ^s		OMe	Me	9.22
70		OMe	Me	8.22
71 ^s		OMe	Me	7.15
72 ^s		OMe	Me	7.92
73		OMe	Me	7.28
74 ^s		OMe	Me	6.39
75		OMe	Me	6.89
To be continued				

				
No.	R ₁	R ₂	R ₃	p <i>K</i> _i (nM)
76		OMe	Me	8.30
77 ^s		OMe	Me	6.55
78		OMe	Me	7.26
79 ^s		OMe	Me	7.82
80		OMe	Me	7.39
81		OMe	Me	8.51
82 ^s		OMe	Me	6.09
83		OMe	Me	7.24
84		OMe	Me	6.69
85 ^s		OMe	Me	6.45
86		OMe	Me	6.06
To be continued				

				
No.	R ₁	R ₂	R ₃	pK _i (nM)
87		OMe	Me	7.62
88		OMe	Me	8.52
89		OMe	Me	7.49
90		OMe	Me	9.00
91		OMe	Me	8.52
92		OMe	Me	9.22
93		OMe	Me	6.77
94		OMe	Me	7.59
95		OMe	Me	7.31
96		OMe	Me	8.05
97		OMe	Me	7.52
98		OMe	H	6.82
To be continued				

				
No.	R ₁	R ₂	R ₃	p <i>K</i> _i (nM)
99		CF ₃	H	6.98
100		OMe	Me	8.30
101		OH	Me	8.70
102		O(CH ₂) ₂ OMe	Me	9.00
103		OiPr	Me	8.10
104		OCF ₃	Me	7.72
105 ^s		OMe	OMe	7.85
106		Cl	Me	7.39
107		Br	OCF ₃	7.43
108		OMe	Me	5.92
109 ^s		OMe	Me	6.58
110 ^s		OMe	Me	7.34
To be continued				

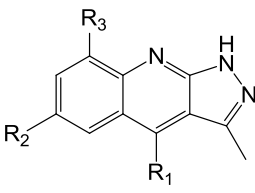
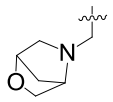
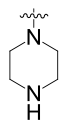
				
No.	R ₁	R ₂	R ₃	p <i>K</i> _i (nM)
111		Cl	Me	6.64
112 ^s		Cl	Me	7.22
116		OMe	Me	7.96
^s Test set				

Table S3 Observed and predicted PDE10A inhibitor activity (pK_i value)

No.	Observed activity	CoMFA		CoMSIA	
		Predicted	Residue	Predicted	Residue
1	8.00	8.013	0.013	7.965	-0.035
2	8.82	8.651	-0.169	8.816	-0.004
3	8.37	8.400	0.030	8.629	0.259
4	7.40	7.306	-0.094	7.476	0.076
5	6.73	6.874	0.144	6.951	0.221
6	7.59	6.934	-0.656	7.794	0.204
7	7.59	7.830	0.240	7.592	0.002
8	8.18	8.254	0.074	8.033	-0.147
9	8.42	8.512	0.092	8.493	0.073
10	6.06	5.978	-0.082	6.148	0.088
11	7.51	6.984	-0.526	7.240	-0.270
12	6.29	6.316	0.026	6.337	0.047
13	6.58	6.366	-0.214	6.564	-0.016
14	6.70	7.158	0.458	6.493	-0.207
15	6.92	6.714	-0.206	6.728	-0.192
16	6.20	6.464	0.264	6.166	-0.034
17	7.48	7.183	-0.297	7.356	-0.124
18	6.74	6.704	-0.036	6.866	0.126
19	6.67	6.767	0.097	6.737	0.067
20	7.52	7.479	-0.041	7.479	-0.041
21	6.94	8.300	1.360	7.038	0.098
22	7.49	7.611	0.121	7.585	0.095
23	8.10	7.999	-0.101	7.903	-0.197
24	8.19	8.214	0.024	8.300	0.110
25	6.62	6.289	-0.331	6.582	-0.038
26	7.54	7.540	0.000	7.488	-0.052
27	6.99	7.256	0.266	7.021	0.031
28	7.40	6.712	-0.688	8.017	0.617
29	7.60	7.689	0.089	7.579	-0.021
30	10.22	9.392	-0.828	10.131	-0.089
31	8.00	7.408	-0.592	8.077	0.077
32	7.27	7.101	-0.169	7.216	-0.054
33	10.15	10.658	0.508	10.149	-0.001
34	9.22	9.373	0.153	9.479	0.259
35	7.68	7.384	-0.296	7.966	0.286
36	8.70	8.643	-0.057	8.415	-0.285
37	7.30	7.489	0.189	7.394	0.094
38	8.70	8.844	0.144	8.816	0.116
39	7.08	7.766	0.686	6.902	-0.178
40	7.92	7.934	0.014	7.893	-0.027

To be continued

No.	Observed activity	CoMFA		CoMSIA	
		Predicted	Residue	Predicted	Residue
41	8.70	8.707	0.007	8.592	-0.108
42	8.40	8.502	0.102	8.577	0.177
43	9.00	8.855	-0.145	9.086	0.086
44	9.52	9.281	-0.239	9.780	0.260
45	9.70	9.560	-0.140	9.518	-0.182
46	7.96	8.344	0.384	8.448	0.488
47	7.41	7.296	-0.114	7.489	0.079
48	9.00	9.059	0.059	9.054	0.054
49	9.40	8.959	-0.441	9.152	-0.248
50	7.68	7.715	0.035	7.872	0.192
51	8.52	8.453	-0.067	8.467	-0.053
52	6.23	7.615	1.385	5.820	-0.410
53	6.26	6.478	0.218	6.376	0.116
54	7.45	7.746	0.296	7.081	-0.369
55	6.38	6.714	0.334	6.319	-0.061
56	6.44	6.874	0.434	6.559	0.119
57	7.64	7.540	-0.100	7.656	0.016
58	8.44	8.262	-0.178	8.235	-0.205
59	6.71	6.923	0.213	6.835	0.125
60	7.82	8.038	0.218	7.666	-0.154
61	8.48	8.504	0.024	8.625	0.145
62	8.02	7.898	-0.122	8.041	0.021
63	9.00	8.871	-0.129	8.603	-0.397
64	7.85	7.500	-0.350	7.986	0.136
65	9.30	9.507	0.207	9.478	0.178
66	8.52	8.159	-0.361	8.591	0.071
67	7.57	7.365	-0.205	7.476	-0.094
68	7.54	8.344	0.804	7.135	-0.405
69	9.22	7.183	-2.037	8.492	-0.728
70	8.22	8.659	0.439	8.389	0.169
71	7.15	7.515	0.365	7.445	0.295
72	7.92	8.094	0.174	8.220	0.300
73	7.28	7.371	0.091	7.261	-0.019
74	6.39	6.418	0.028	6.208	-0.182
75	6.89	7.427	0.537	6.796	-0.094
76	8.30	7.647	-0.653	8.074	-0.226
77	6.55	7.951	1.401	6.778	0.228
78	7.26	7.020	-0.240	7.242	-0.018
79	7.82	7.662	-0.158	7.844	0.024
80	7.39	7.410	0.020	7.516	0.126
81	8.51	8.709	0.199	8.672	0.162

To be continued

No.	Observed activity	CoMFA		CoMSIA	
		Predicted	Residue	Predicted	Residue
82	6.09	6.794	0.704	6.555	0.465
83	7.24	6.766	-0.474	7.121	-0.119
84	6.69	6.823	0.133	6.546	-0.144
85	6.45	6.818	0.368	6.174	-0.276
86	6.06	6.354	0.294	6.062	0.002
87	7.62	7.432	-0.188	7.064	-0.556
88	8.52	8.327	-0.193	8.703	0.183
89	7.49	7.561	0.071	7.603	0.113
90	9.00	8.706	-0.294	8.562	-0.438
91	8.52	8.556	0.036	8.366	-0.154
92	9.22	8.839	-0.381	9.181	-0.039
93	6.77	6.848	0.078	6.779	0.009
94	7.59	7.412	-0.178	7.933	0.343
95	7.31	7.830	0.520	7.463	0.153
96	8.05	8.683	0.633	8.181	0.131
97	7.52	7.595	0.075	7.455	-0.065
98	6.82	6.446	-0.374	7.170	0.350
99	6.98	6.729	-0.251	6.785	-0.195
100	8.30	8.492	0.192	7.988	-0.312
101	8.70	8.204	-0.496	8.548	-0.152
102	9.00	8.895	-0.105	8.997	-0.003
103	8.10	7.910	-0.190	7.914	-0.186
104	7.72	7.732	0.012	7.708	-0.012
105	7.85	6.671	-1.179	7.913	0.063
106	7.39	7.865	0.475	7.859	0.469
107	7.43	7.577	0.147	7.536	0.106
108	5.92	6.195	0.275	6.448	0.528
109	6.58	6.984	0.404	6.530	-0.050
110	7.34	7.53	0.190	7.477	0.137
111	6.64	6.64	0.000	6.553	-0.087
112	7.22	8.425	1.205	7.341	0.121
113	7.45	7.536	0.086	7.508	0.058
114	7.70	7.48	-0.220	7.539	-0.161
115	8.06	7.536	-0.524	8.067	0.007
116	7.96	7.962	0.002	8.117	0.157