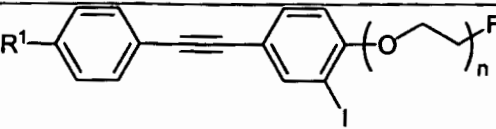
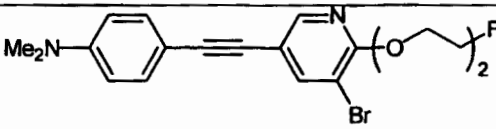


1/11

				
K_i (nM)	R^1	n	K_i (nM)	
6.5 ± 0.9	NMe ₂	2	11 ± 0.8	
6.6 ± 0.8	NHMe	3		

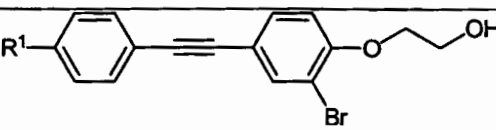
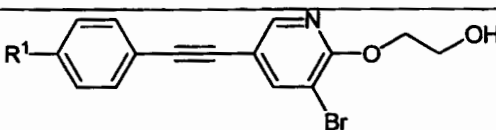
			
K_i (nM)	R^1	K_i (nM)	R^1
3.4 ± 1.1	NMe ₂	6.7 ± 1.3	NMe ₂
6.0 ± 1.1	NHMe	1.6 ± 0.5	NHMe
		6.2 ± 1.2	OH

Figure 1

2/11

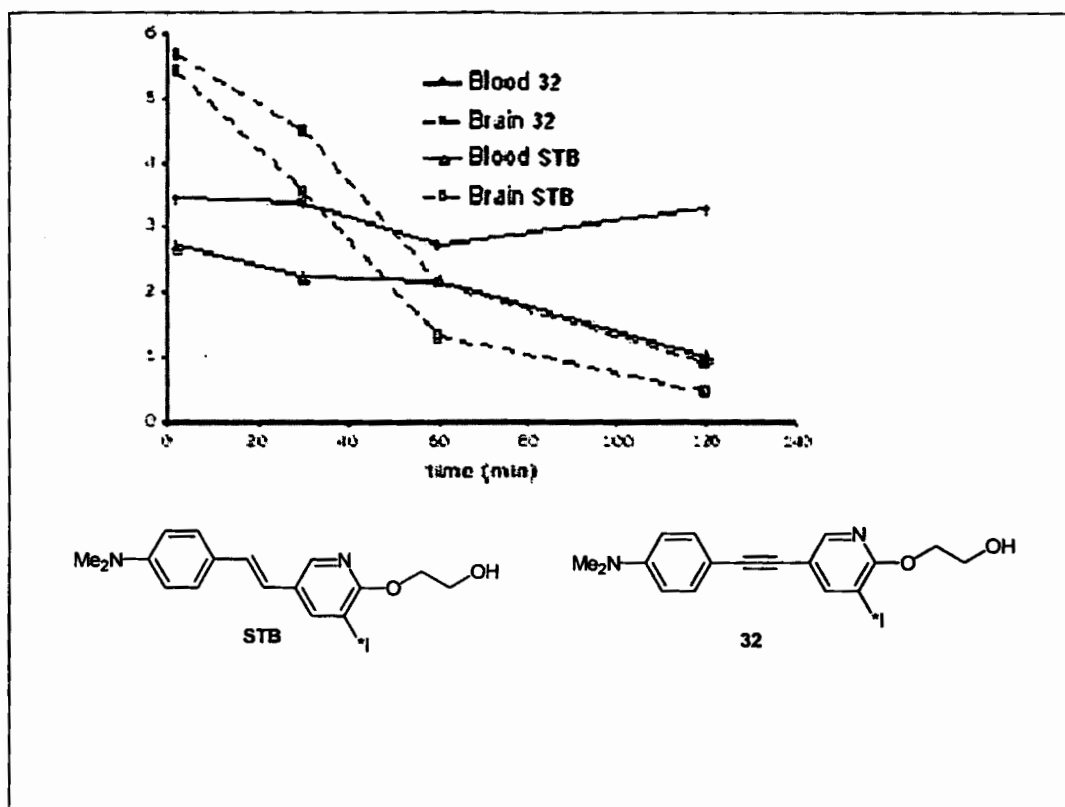
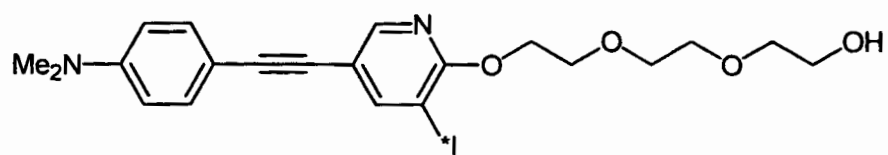


Figure 2

3/11



B4b-1

Figure 3

4/11

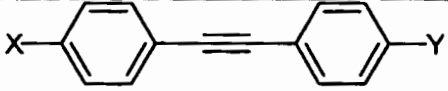
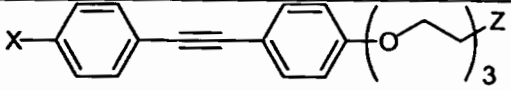
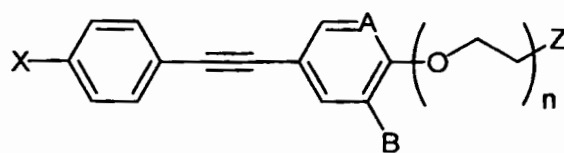
					
K_i (nM)	X	Y	K_i (nM)	X	Z
2.9 ± 0.4	NO_2	OMe	21 ± 6.5	NH_2	F
106 ± 6	NH_2	OH	1.9 ± 0.3	NHMe	F
1.5 ± 0.1	NHMe	OH	2.9 ± 0.1	NMe_2	F
1.6 ± 0.4	NMe_2	OH	67.5 ± 7.5	NH_2	OH
2.9 ± 0.3	OMe	OH	4.5 ± 0.9	NHMe	OH
175 ± 35	H	H	3.4 ± 0.1	NMe_2	OH
76 ± 35	NH_2	NH_2	1.5 ± 0.4	NMe_2	$\text{OCH}_2\text{C}\equiv\text{CH}$

Figure 4A

5/11



<u>Ki (nM)</u>	<u>X</u>	<u>A</u>	<u>B</u>	<u>n</u>	<u>Z</u>
2.9	NMe ₂	C	H	3	F
1.9	NHMe	C	H	3	F
5.0	NMe ₂	N	H	3	F
4.5	NHMe	N	H	3	F
3.2	NMe ₂	N	H	2	F
1.2	NHMe	N	H	2	F
6.6	NHMe	N	I	3	F
9.2	NHMe ₂	N	I	1	OH
17.2	NHMe	N	I	1	OH
2.8	NHMe	N	I	2	OH

Figure 4B

6/11

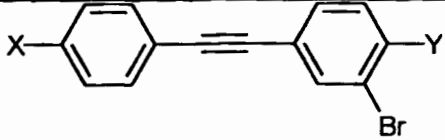
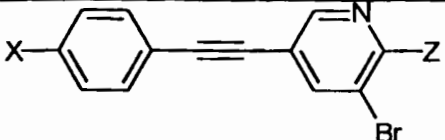
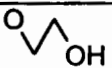
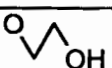
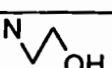
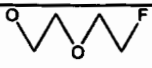
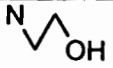
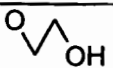
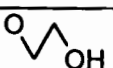
					
K_i (nM)	X	Y	K_i (nM)	X	Z
61.5 ± 6.5	OH	NMe ₂	1.6 ± 0.5	NHMe	
15.2 ± 3.2	OH	NHMe	6.7 ± 0.3	NMe ₂	
22.5 ± 2.5	OH	OH	90 ± 18	NMe ₂	
38.5 ± 1.2	NH ₂	OH	8.5 ± 0.5	NMe ₂	
5.2 ± 0.8	NMe ₂	NHMe	6.5 ± 0.9	NHMe	
9.1 ± 0.9	NMe ₂				
3.4 ± 1.1	NMe ₂				
6.0 ± 1.1	NHMe				

Figure 5

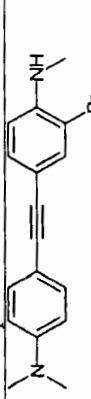
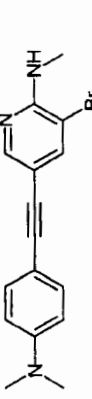
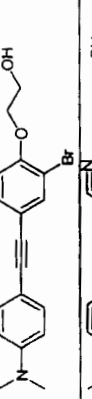
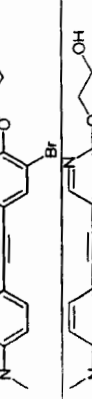
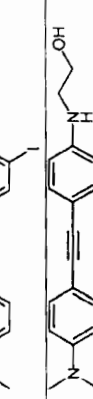
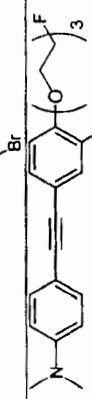
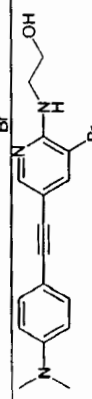
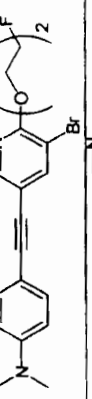
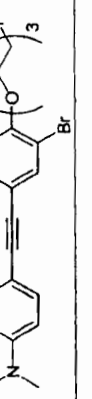
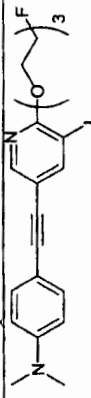
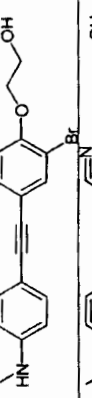
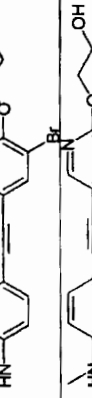
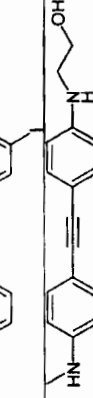
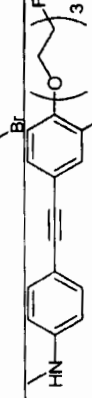
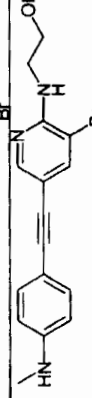
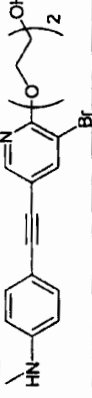
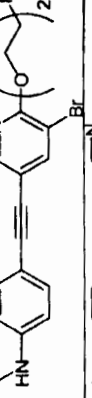
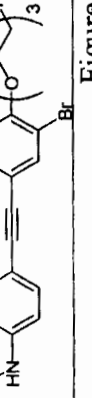
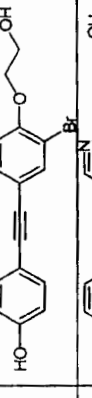
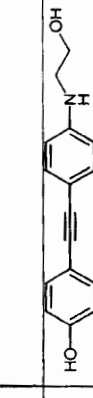
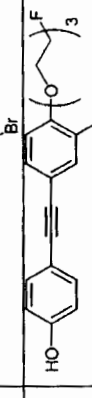
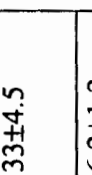
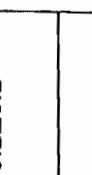
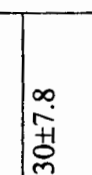
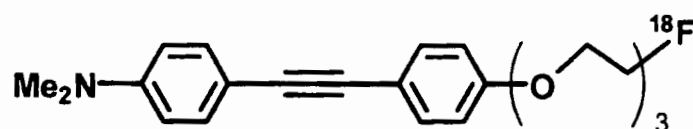
Compound	Ki	Compound	Ki	Compound	Ki
	5.2±0.8		1.2		3.4
	6.7±1.3		9.2±1.7		9.1±0.9
	8.8±1.7		90		6.6±0.9
	8.5		11.2±0.8		
	5.2±0.8		1.2		3.4
	6.7±1.3		9.2±1.7		9.1±0.9
	8.8±1.7		90		6.6±0.9
	8.5		11.2±0.8		
	16.8±1.8				6.0
	1.6±0.5		17±2.0		7.5
	6.6±0.9		200		2.8±0.2
	13.1±1.9				
	15.2±3.2		87.5±16		33±4.5
	6.2±1.2				22.5±2.5
	30±7.8				

Figure 6

8/11

Mouse biodistribution and octanol/PBS partition coefficient



(%dose/g, avg of 3 mice $\pm$ SD)

Organ	2 min	30 min	1 hr	2 hr
Blood	5.72 ± 0.51	2.97 ± 0.10	2.51 ± 0.35	2.35 ± 0.39
Heart	9.97 ± 1.51	1.49 ± 0.14	1.04 ± 0.07	0.84 ± 0.10
Muscle	0.79 ± 0.24	0.67 ± 0.10	0.51 ± 0.08	0.42 ± 0.05
Lung	8.38 ± 1.28	2.26 ± 0.25	1.26 ± 0.90	1.47 ± 0.19
Kidney	12.37 ± 2.37	2.68 ± 0.08	2.53 ± 0.21	2.02 ± 0.50
Spleen	4.61 ± 0.76	1.39 ± 0.14	1.13 ± 0.07	1.17 ± 0.17
Liver	23.19 ± 3.53	13.79 ± 0.92	8.13 ± 1.69	6.58 ± 0.43
Skin	0.68 ± 0.17	1.41 ± 0.24	1.28 ± 0.06	0.68 ± 0.18
Brain	6.78 ± 1.16	1.57 ± 0.13	0.77 ± 0.07	0.42 ± 0.03
Bone	1.51 ± 0.34	0.64 ± 0.04	0.56 ± 0.10	0.70 ± 0.11

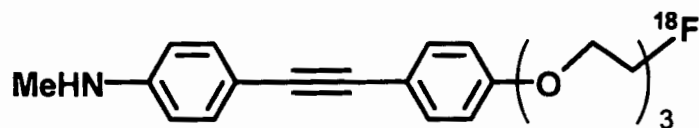
Partition coefficient

1538 (taken from third partition)

Figure 7

9/11

Mouse biodistribution and octanol/PBS partition coefficient



(%dose/g, avg of 3 mice $\pm$ SD)

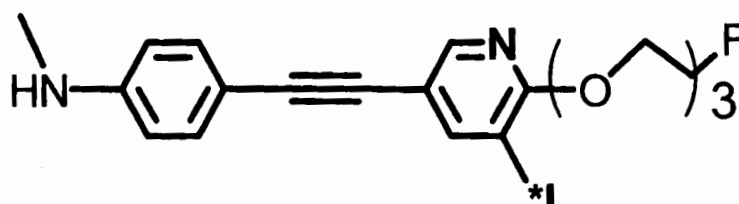
Organ	2 min	30 min	1 hr	2 hr
Blood	3.28 ± 0.63	3.28 ± 0.57	3.22 ± 0.19	3.17 ± 0.62
Heart	4.21 ± 0.79	1.40 ± 0.17	1.24 ± 0.19	0.96 ± 0.19
Muscle	1.97 ± 1.15	0.61 ± 0.10	0.62 ± 0.07	0.39 ± 0.14
Lung	4.64 ± 0.76	2.10 ± 0.30	2.04 ± 0.28	1.72 ± 0.27
Kidney	4.74 ± 1.22	2.90 ± 0.99	2.40 ± 0.22	1.80 ± 0.62
Spleen	2.69 ± 0.60	1.22 ± 0.04	0.95 ± 0.04	1.02 ± 0.15
Liver	25.80 ± 2.80	14.75 ± 4.12	10.16 ± 4.00	9.14 ± 3.24
Skin	1.24 ± 0.29	1.40 ± 0.23	0.95 ± 0.11	0.60 ± 0.17
Brain	4.55 ± 0.82	0.42 ± 0.13	0.37 ± 0.02	0.38 ± 0.07
Bone	1.50 ± 0.16	0.66 ± 0.12	0.65 ± 0.09	0.82 ± 0.15

Partition coefficient

1182 (taken from third partition)

Figure 8

10/11

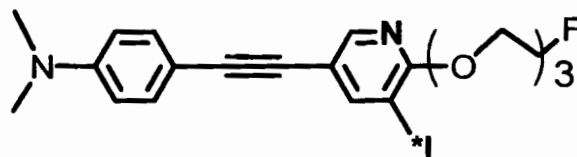
Mouse biodistribution and octanol/PBS partition coefficient

<u>%dose/g</u>				
Organ	2 min	30 min	60 min	120 min
Blood	10.27 ± 2.36	5.11 ± 0.64	3.34 ± 0.94	2.19 ± 0.35
Heart	11.28 ± 4.77	5.08 ± 0.61	4.19 ± 3.53	2.65 ± 0.23
Muscle	1.52 ± 0.50	0.85 ± 0.04	0.68 ± 0.11	0.60 ± 0.18
Lung	6.57 ± 1.24	3.79 ± 0.52	2.77 ± 0.61	2.17 ± 0.19
Kidney	7.73 ± 1.77	5.12 ± 0.83	3.38 ± 0.55	2.73 ± 0.63
Spleen	6.05 ± 1.26	5.72 ± 1.60	4.26 ± 0.21	5.40 ± 0.56
Liver	19.79 ± 6.71	16.09 ± 3.16	10.42 ± 2.20	10.87 ± 0.43
Skin	0.90 ± 0.30	1.07 ± 0.15	0.90 ± 0.07	0.76 ± 0.21
Brain	1.06 ± 0.20	0.53 ± 0.11	0.24 ± 0.07	0.16 ± 0.02
Thyroid	5.70 ± 2.77	7.52 ± 1.75	28.27 ± 11.65	77.20 ± 0.38

P. C. 368 taken from third partition of octanol/0.05 M Na₂HPO₄ - buffer (pH 7.4)

Figure 9

11/11

Mouse biodistribution

Organ	2 min		30 min		1 hr		2 hr	
Blood	3.45	± 0.29	3.38	± 0.51	2.71	± 0.43	3.29	± 0.61
Heart	12.96	± 2.47	2.31	± 0.37	1.41	± 0.33	1.33	± 0.26
Muscle	0.98	± 0.30	1.23	± 0.20	0.71	± 0.09	0.78	± 0.11
Lung	13.03	± 2.32	4.03	± 0.41	2.60	± 0.56	2.77	± 0.86
Kidney	16.63	± 2.48	4.10	± 0.54	2.85	± 0.50	2.40	± 0.47
Spleen	6.33	± 1.03	1.98	± 0.34	1.42	± 0.40	1.73	± 0.45
Liver	17.16	± 2.86	11.25	± 1.59	5.21	± 2.05	2.24	± 0.45
Skin	0.87	± 0.14	2.22	± 0.64	2.46	± 0.27	3.18	± 0.17
Brain	5.67	± 1.49	4.51	± 0.56	2.14	± 0.21	0.91	± 0.17

Figure 10