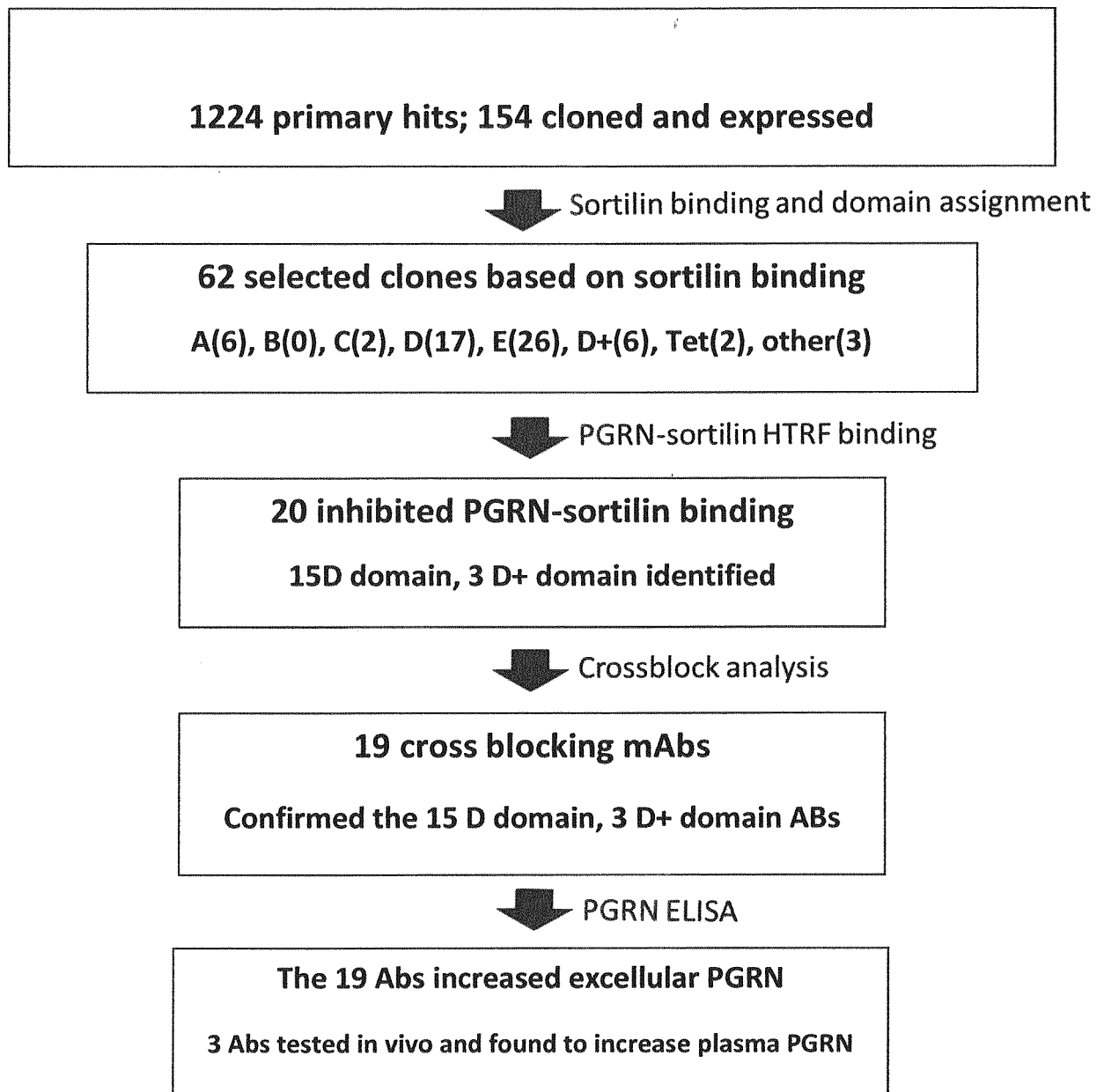


**Fig 1**

|                | A | B | C | D | E | E Ab | D Ab |
|----------------|---|---|---|---|---|------|------|
| Sort-human     |   |   |   |   |   | +    | +    |
| hB01-05        |   |   |   |   |   | -    | -    |
| hB06-10        |   |   |   |   |   | +    | +    |
| hB12390        |   |   |   |   |   | +    | +    |
| hB45678        |   |   |   |   |   | +    | -    |
| Sort-tetraodon |   |   |   |   |   | -    | -    |
| Sort-human     |   |   |   |   |   | +    | +    |

| mAbs | Domain | hSort | hB01-05 | hB06-10 | B12390 | B45678 | Tet |
|------|--------|-------|---------|---------|--------|--------|-----|
| 6    | A      | +     | +       | -       | +      | -      | -   |
| 0    | B      | +     | +       | -       | -      | +      | -   |
| 2    | C      | +     | -       | +       | -      | +      | -   |
| 17   | D      | +     | -       | +       | +      | -      | -   |
| 26   | E      | +     | -       | +       | +      | +      | -   |
| 6    | D+     | +     | -       | -       | +      | -      | -   |
| 2    | Tet    | +     | +       | +       | +      | +      | +   |
| 3    | Other  | +     | +/-     | +/-     | +/-    | +      | -   |

**Fig 2**

| mAb    | Domain | hSort | hB01-05 | hB06-10 | B12390 | B45678 | Tet |
|--------|--------|-------|---------|---------|--------|--------|-----|
| 002    | D      | 2,40  | NB      | 43,30   | 2,44   | NB     | NB  |
| 044    | D      | 1,38  | NB      | 21,20   | 1,03   | NB     | NB  |
| 045    | D      | 1,56  | NB      | 9,60    | 1,10   | NB     | NB  |
| 68     | D+     | 1,80  | NB      | NB      | 1,87   | NB     | NB  |
| 088    | D      | 2,49  | NB      | 9,55    | 1,57   | NB     | NB  |
| 093-01 | D      | 3,47  | NB      | 44,53   | 2,13   | NB     | NB  |
| 093-05 | D      | 2,88  | NB      | 43,24   | 1,78   | NB     | NB  |
| 193    | D      | 2,07  | NB      | 5,57    | 0,83   | NB     | NB  |
| 531    | D+     | 5,50  | NB      | NB      | 2,29   | NB     | NB  |
| 548    | D+     | 4,49  | NB      | NB      | 3,36   | NB     | NB  |
| 562    | D      | 2,23  | NB      | 24,56   | 1,34   | NB     | NB  |
| 566    | D      | 2,93  | NB      | 42,55   | 2,12   | NB     | NB  |
| 811    | D      | 1,81  | NB      | 8,00    | 1,08   | NB     | NB  |
| 849    | D      | 1,01  | NB      | 17,08   | 0,78   | NB     | NB  |
| 924    | D      | 6,76  | NB      | 20,01   | 3,83   | NB     | NB  |
| 1276   | D      | 2,24  | NB      | 8,78    | 0,93   | NB     | NB  |
| 1289   | D      | 1,62  | NB      | 15,23   | 0,96   | NB     | NB  |
| 1320   | D      | 19,14 | NB      | 55,43   | 12,32  | NB     | NB  |

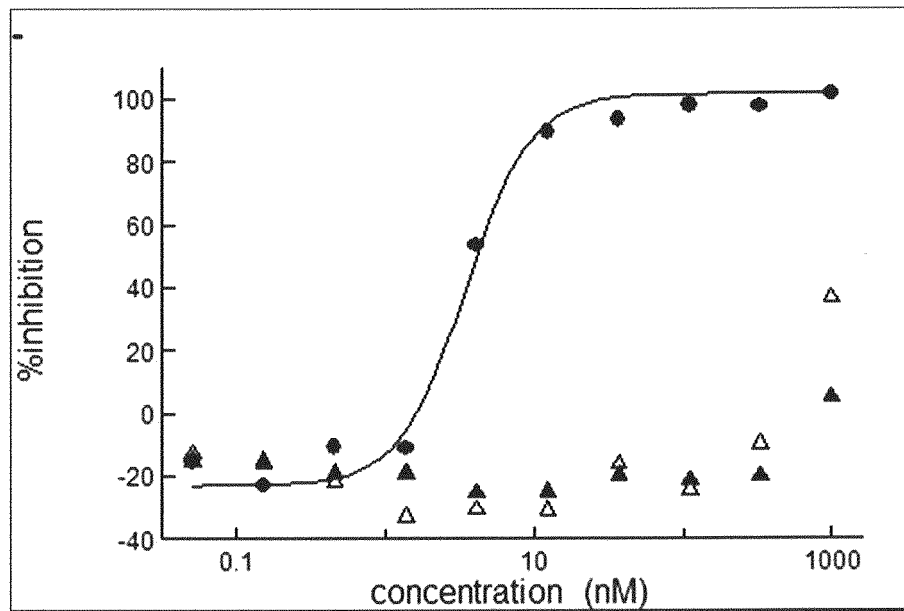
|    |                   |
|----|-------------------|
| +  | EC50 0.1-10 ng/ml |
| +  | EC50 >10 ng/ml    |
| NB | no binding        |

Fig 3

| mAb   | Domain | hSort | hB01-05 | hB06-10 | B12390 | B45678 | Tet |
|-------|--------|-------|---------|---------|--------|--------|-----|
| 1F2F4 | D      | 1,56  | NB      | 9,60    | 1,10   | NB     | NB  |
| 5E1F6 | D      | 1,14  | NB      | 0,72    | 0,59   | NB     | NB  |

|    |            |
|----|------------|
| +  | binding    |
| NB | no binding |

Fig 4



| Antibody        | IC50 (nM) |
|-----------------|-----------|
| IgG1-6003-045   | 3.5 ± 0.6 |
| E-domain Ab     | >1000 *   |
| IgG1-B12 (ctrl) | >1000 **  |

\* antibody too weak to fit a dose-response curve. 6% inhibition at 1μM

\*\* ctrl antibody too weak to fit a dose-response curve. 37% inhibition at 1μM

**Fig 5**

| Ab                | highest conc<br>(nM) | % inh<br>highest<br>conc | IC50<br>(nM) | Domain |
|-------------------|----------------------|--------------------------|--------------|--------|
| IgG1-6003-002     | 500                  | 91                       | 4,3          | D      |
| IgG1-6003-044     | 1000                 | 101                      | 3,4          | D      |
| IgG1-6003-045     | 1000                 | 102                      | 3,9          | D      |
| IgG1-6003-068     | 1000                 | 92                       | 22           | D+     |
| IgG1-6003-088     | 1000                 | 96                       | 2,5          | D      |
| IgG1-6003-093-L01 | 1000                 | 82                       | 13           | D      |
| IgG1-6003-093-L05 | 1000                 | 95                       | 35           | D      |
| IgG1-6003-193     | 1000                 | 93                       | 1,8          | D      |
| IgG1-6003-531     | 1000                 | 102                      | 2,5          | D+     |
| IgG1-6003-548     | 600                  | 87                       | 11           | D+     |
| IgG1-6003-562     | 1000                 | 100                      | 5,8          | D      |
| IgG1-6003-566     | 1000                 | 100                      | 2,6          | D      |
| IgG1-6003-811     | 1000                 | 102                      | 4,4          | D      |
| IgG1-6003-849     | 1000                 | 101                      | 3,8          | D      |
| IgG1-6003-924     | 1000                 | 100                      | 3,3          | D      |
| IgG1-6003-1276    | 1000                 | 108                      | 2,5          | D      |
| IgG1-6003-1289    | 800                  | 98                       | 3,0          | D      |
| IgG1-6003-1320    | 900                  | 75                       | 32           | D      |
| IgG1-B12          | 1000                 | 37                       | -            | -      |

Fig 6

7.031

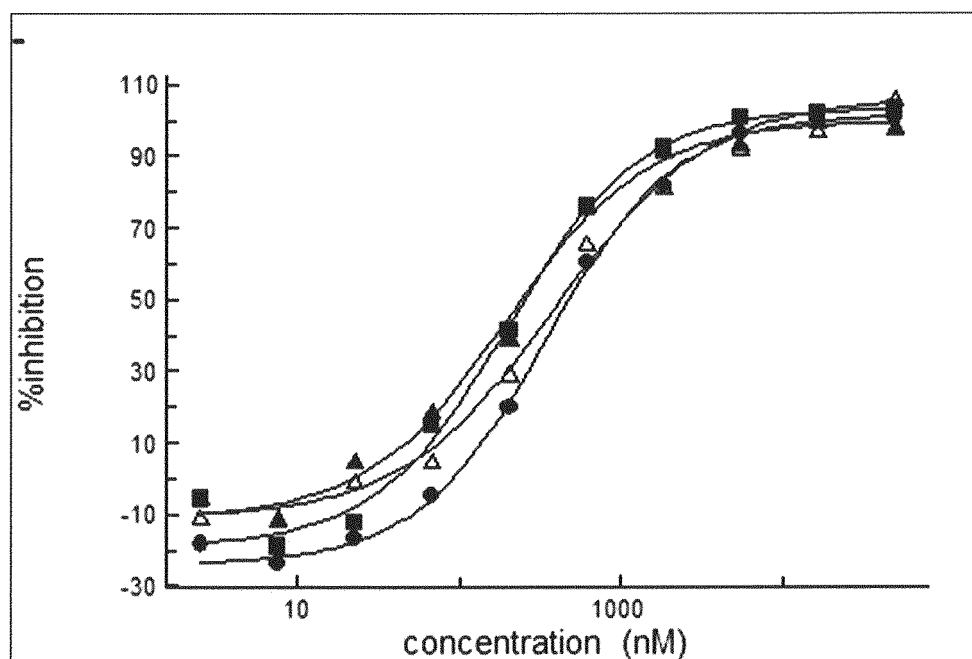
7.031

|        |          | 1276  | 924   | 093-L01 | 093-L05 | 5E1F6 | 1F2F4 | 068   | 1320 | A1   |
|--------|----------|-------|-------|---------|---------|-------|-------|-------|------|------|
|        |          | D     | D     | D       | D       | D     | D     | D+    | D    | A    |
| Domain | antibody | 1276  | 924   | 093-L01 | 093-L05 | 5E1F6 | 1F2F4 | 068   | 1320 | AbA1 |
| D+     | 548      | 0,02  | 0,02  | 0,04    | 0,01    | 0,02  | x     | 0,00  | 0,04 | 0,07 |
| D+     | 531      | 0,01  | 0,01  | 0,01    | 0,02    | 0,02  | x     | 0,00  | 0,04 | 0,69 |
| D      | 002      | 0,02  | 0,03  | 0,00    | 0,01    | 0,07  | x     | -0,02 | 0,02 | 0,57 |
| D      | 044      | 0,01  | 0,01  | 0,00    | 0,03    | 0,02  | x     | -0,01 | 0,01 | 0,49 |
| D      | 045      | 0,01  | 0,01  | 0,01    | 0,03    | 0,01  | x     | 0,00  | 0,01 | 0,52 |
| D      | 088      | 0,01  | 0,02  | 0,01    | 0,02    | 0,01  | x     | -0,02 | 0,03 | 0,77 |
| D      | 193      | 0,03  | 0,02  | 0,03    | 0,02    | 0,03  | x     | 0,01  | 0,04 | 0,42 |
| D      | 562      | 0,00  | 0,00  | 0,00    | 0,01    | 0,01  | x     | -0,01 | 0,01 | 0,23 |
| D      | 566      | -0,03 | -0,01 | 0,01    | 0,00    | -0,02 | -0,01 | -0,04 | 0,01 | 0,58 |
| D      | 811      | 0,00  | 0,01  | 0,00    | 0,01    | 0,01  | x     | -0,02 | 0,01 | 0,77 |
| D      | 1289     | -0,02 | -0,02 | -0,02   | -0,02   | -0,02 | x     | -0,02 | 0,00 | 0,45 |
| D      | 849      | -0,01 | 0,01  | 0,00    | 0,00    | 0,01  | X     | -0,01 | 0,01 | 0,73 |
| D      | 1276     | 0,01  | 0,05  | 0,01    | 0,01    | 0,01  | X     | 0,00  | 0,01 | 0,70 |
| D      | 924      | 0,01  | 0,01  | 0,00    | 0,01    | 0,01  | X     | 0,00  | 0,02 | 0,52 |
| D      | 093-L01  | 0,00  | 0,01  | 0,01    | 0,02    | 0,01  | X     | -0,01 | 0,01 | 0,65 |
| D      | 093-L05  | 0,01  | 0,02  | 0,01    | 0,02    | 0,02  | X     | -0,01 | 0,03 | 0,62 |
| D      | 5E1F6    | 0,02  | 0,02  | 0,02    | 0,02    | 0,01  | 0,02  | 0,00  | 0,03 | 0,39 |
| D      | 1F2F4    | 0,00  | 0,04  | -0,01   | 0,01    | 0,01  | 0,01  | -0,01 | 0,01 | 0,41 |
| D+     | 068      | -0,01 | 0,01  | 0,02    | 0,00    | 0,01  | X     | -0,01 | 0,01 | 0,52 |
| D      | 1320     | -0,01 | 0,00  | 0,04    | 0,00    | -0,01 | 0,00  | -0,01 | 0,00 | 0,19 |

Fig 7 (cont)

|        |          | 530  | 784  | 010  | 471  | 532  | 910  | 550   | 826  | 942  |
|--------|----------|------|------|------|------|------|------|-------|------|------|
|        |          | E    | E    | E    | E    | E    | E    | Tetra | E    | A    |
| Domain | antibody | AbE1 | AbE2 | AbE3 | AbE4 | AbE5 | AbE6 | Abtet | AbE7 | AbA2 |
| D+     | 548      | 0,01 | 0,03 | 0,22 | 0,26 | 0,27 | 0,22 | 0,06  | 0,01 | 0,05 |
| D+     | 531      | 0,28 | 0,60 | 0,83 | 0,92 | 0,93 | 0,87 | 0,69  | 0,51 | 0,22 |
| D      | 002      | 0,25 | 0,52 | 0,74 | 0,70 | 0,79 | 0,78 | 0,67  | 0,42 | 0,19 |
| D      | 044      | 0,18 | 0,42 | 0,64 | 0,73 | 0,68 | 0,68 | 0,56  | 0,32 | 0,20 |
| D      | 045      | 0,23 | 0,47 | 0,67 | 0,72 | 0,72 | 0,70 | 0,60  | 0,36 | 0,19 |
| D      | 088      | 0,42 | 0,79 | 1,00 | 1,19 | 1,13 | 1,09 | 0,96  | 0,64 | 0,24 |
| D      | 193      | 0,19 | 0,38 | 0,54 | 0,57 | 0,52 | 0,53 | 0,43  | 0,27 | 0,19 |
| D      | 562      | b    | 0,23 | 0,39 | 0,36 | 0,33 | 0,33 | 0,24  | 0,13 | 0,13 |
| D      | 566      | 0,25 | 0,55 | 0,77 | 0,88 | 0,87 | 0,79 | 0,60  | 0,35 | 0,24 |
| D      | 811      | 0,42 | 0,79 | 1,02 | 1,17 | 1,13 | 1,09 | 0,97  | 0,65 | 0,24 |
| D      | 1289     | 0,18 | 0,43 | 0,56 | 0,67 | 0,63 | 0,64 | 0,47  | 0,29 | 0,18 |
| D      | 849      | 0,37 | 0,74 | 0,96 | 1,11 | 1,08 | 1,04 | 0,90  | 0,58 | 0,25 |
| D      | 1276     | 0,39 | 0,74 | 0,93 | 1,03 | 1,00 | 0,97 | 0,83  | 0,57 | 0,26 |
| D      | 924      | 0,25 | 0,50 | 0,66 | 0,67 | 0,69 | 0,65 | 0,52  | 0,33 | 0,22 |
| D      | 093-L01  | 0,31 | 0,64 | 0,82 | 0,93 | 0,92 | 0,87 | 0,78  | 0,49 | 0,23 |
| D      | 093-L05  | 0,29 | 0,58 | 0,80 | 0,89 | 0,88 | 0,84 | 0,69  | 0,45 | 0,22 |
| D      | 5E1F6    | 0,19 | 0,39 | 0,62 | 0,57 | 0,59 | 0,54 | 0,40  | 0,27 | 0,18 |
| D      | 1F2F4    | 0,16 | 0,38 | 0,60 | 0,63 | 0,62 | 0,58 | 0,44  | 0,26 | 0,18 |
| D+     | 068      | 0,26 | 0,58 | 0,80 | 0,94 | 0,94 | 0,89 | 0,80  | 0,43 | 0,12 |
| D      | 1320     | b    | b    | 0,22 | 0,28 | 0,28 | 0,29 | 0,17  | b    | b    |

Fig 7 (cont)



| Sortilin + antibody           | IC50 AF38469 (nM) |
|-------------------------------|-------------------|
| Sortilin                      | 371 ± 79          |
| Sortilin + IgG1-6003-045      | 198 ± 32          |
| Sortilin + IgG1-6003-068      | 199 ± 11          |
| Sortilin + hlgG1 isotype ctrl | 385 ± 113         |

Fig 8

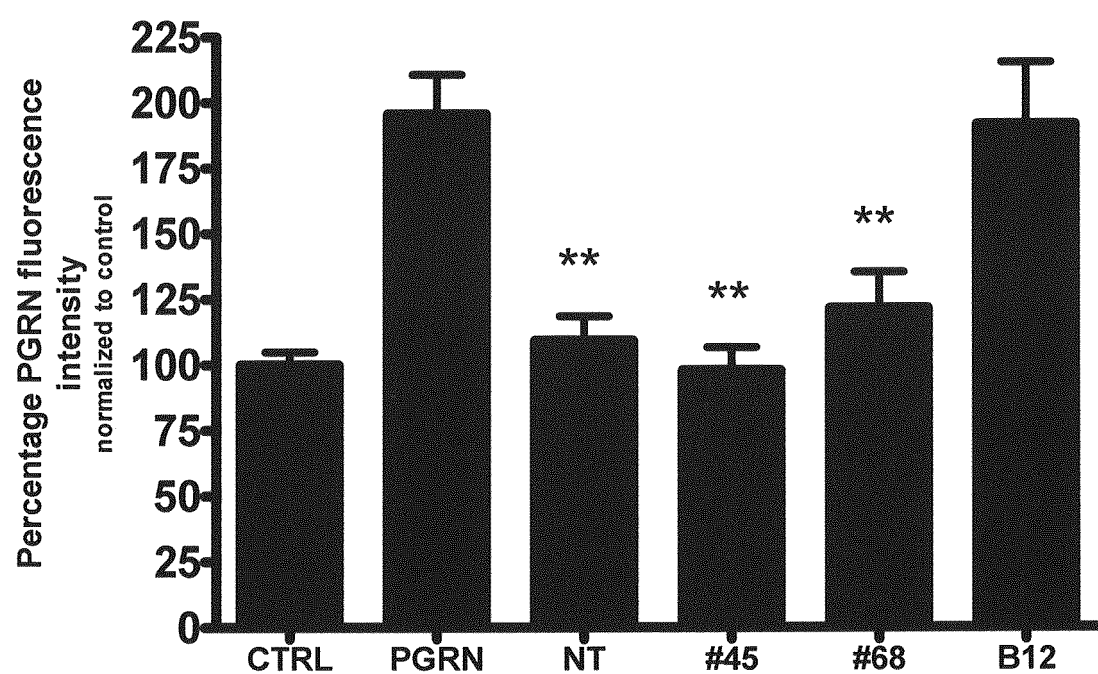


Fig 9

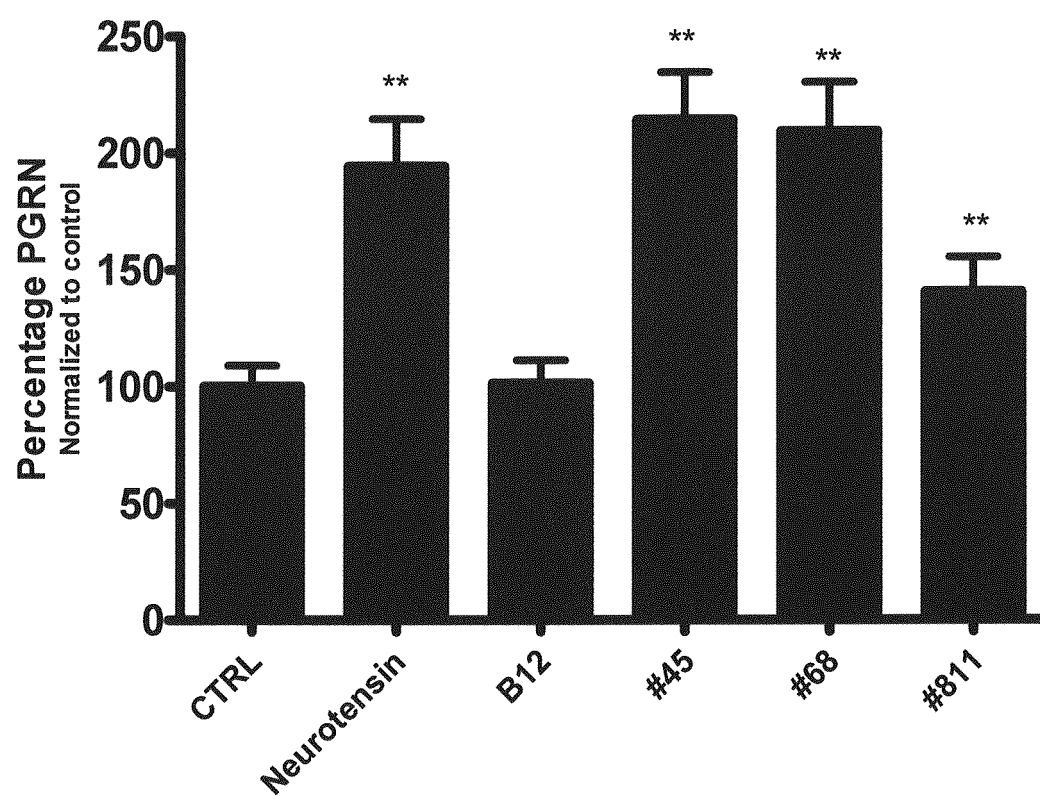


Fig 10

| Ab No | PGRN % | Ab No   | PGRN % |
|-------|--------|---------|--------|
| 002   | 142    | 849     | 149    |
| 044   | 166    | 1276    | 163    |
| 045   | 202    | 924     | 125    |
| 088   | 121    | 093-L01 | 116    |
| 193   | 207    | 093-L05 | 140    |
| 562   | 139    | 1320    | 114    |
| 566   | 139    | 1F2F4   | 282    |
| 811   | 146    | 5E1F6   | 177    |
| 1289  | 117    |         |        |
| 548   | 139    | 68      | 201    |
| 531   | 140    |         |        |

Fig 11

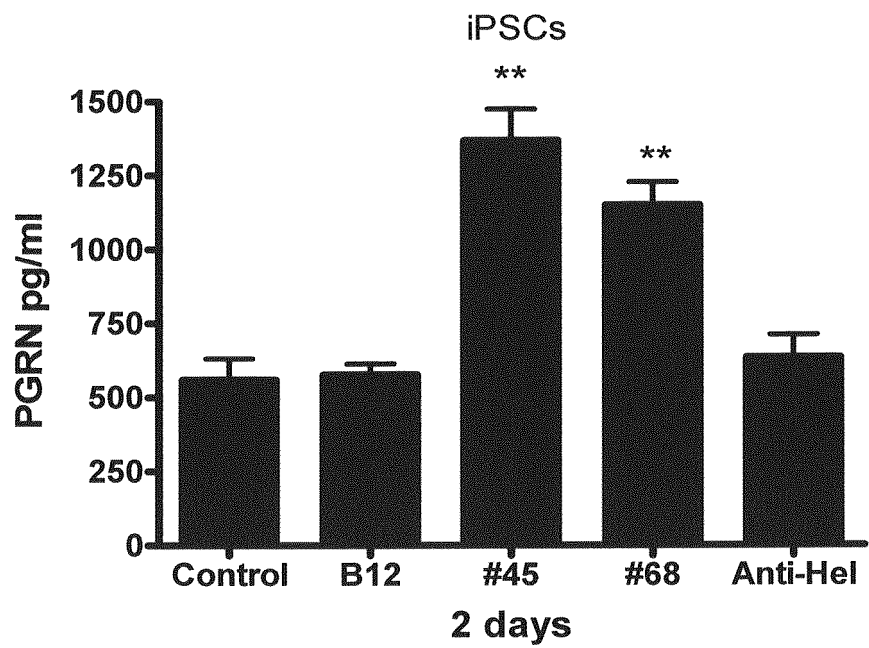
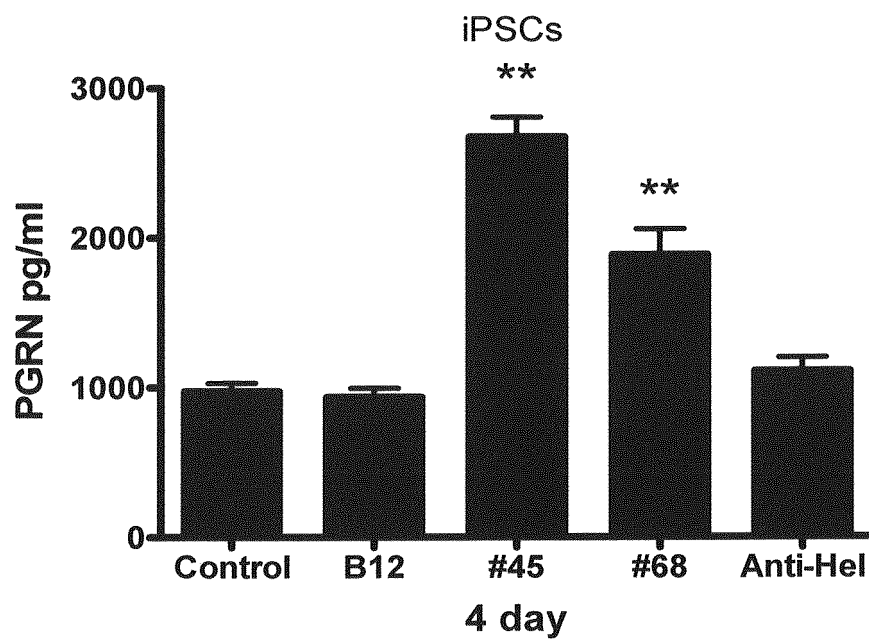


Fig 12

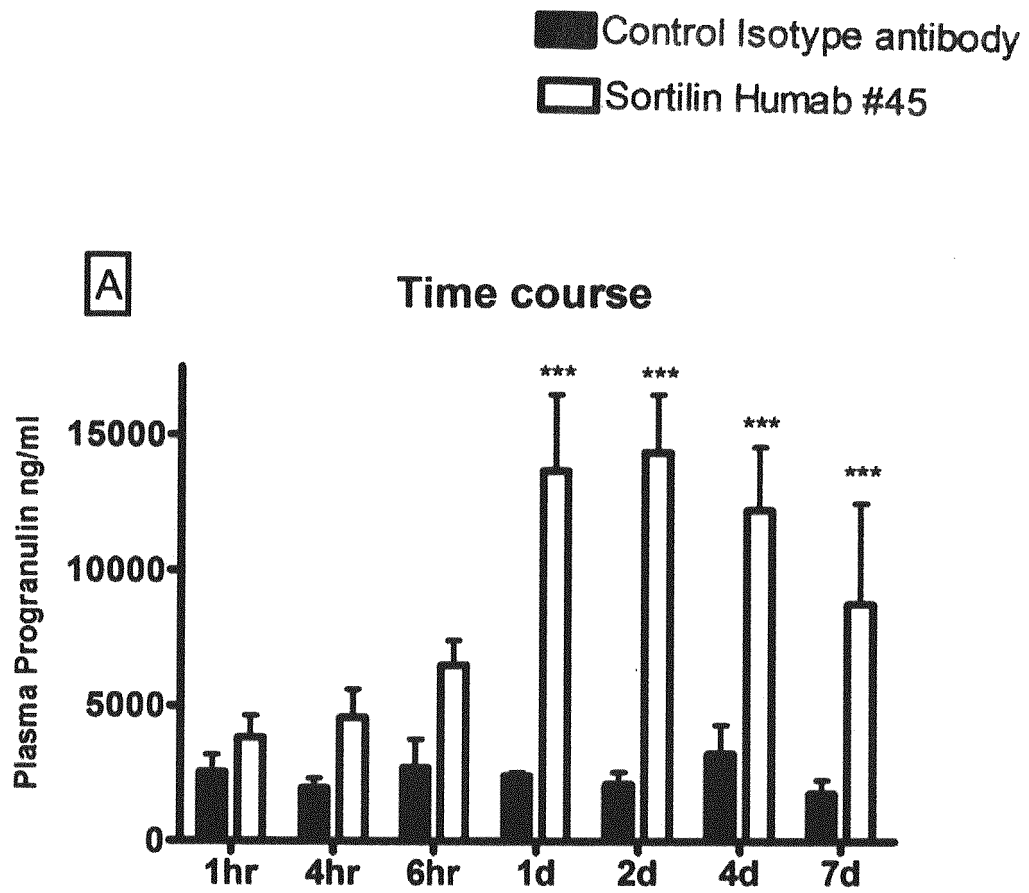


Fig 13 a

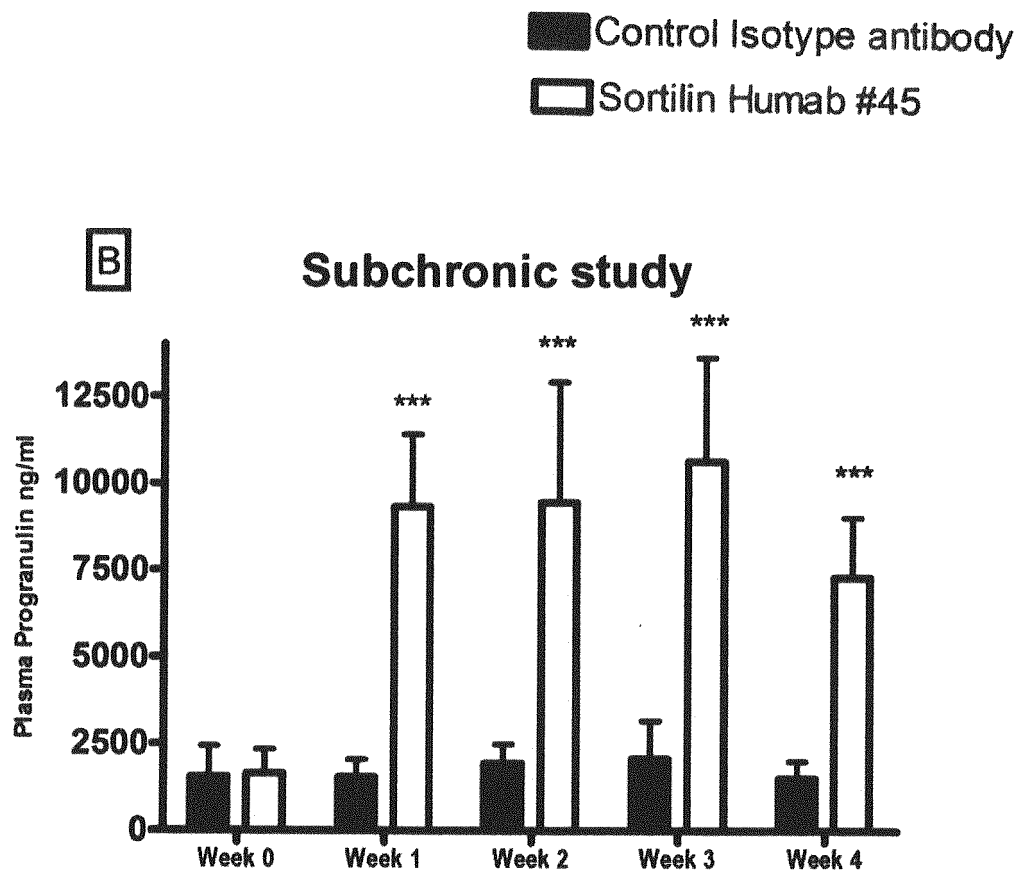


Fig 13 b

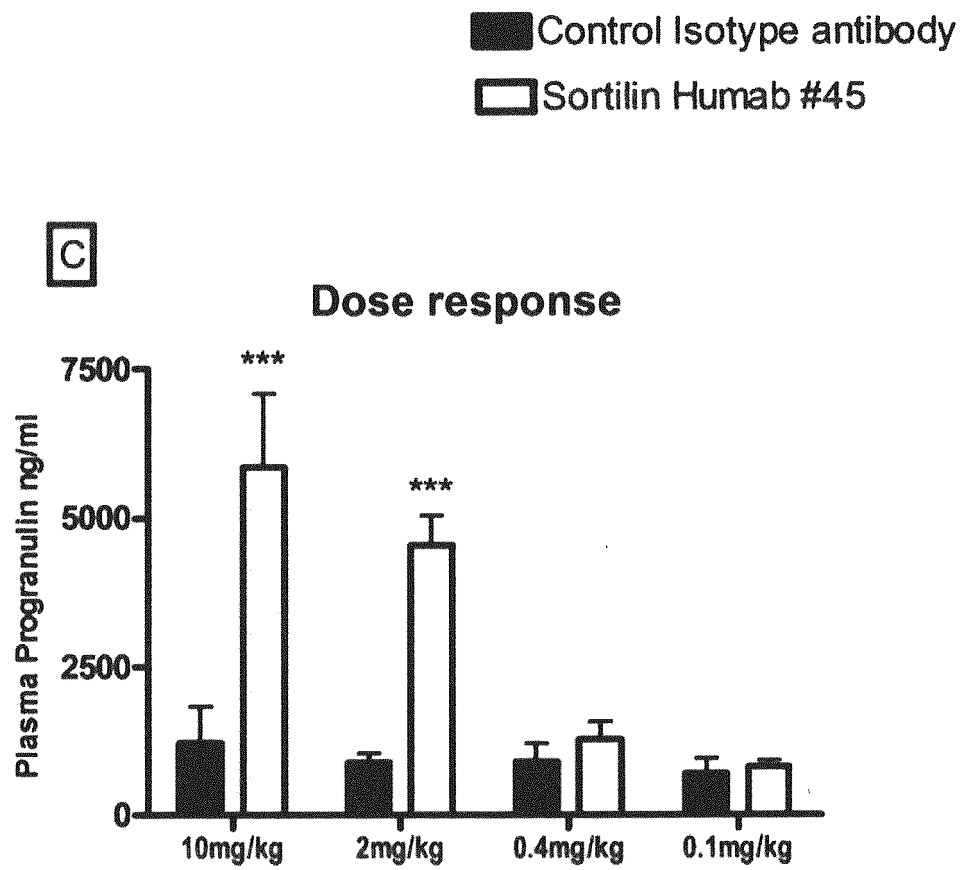


Fig 13 c

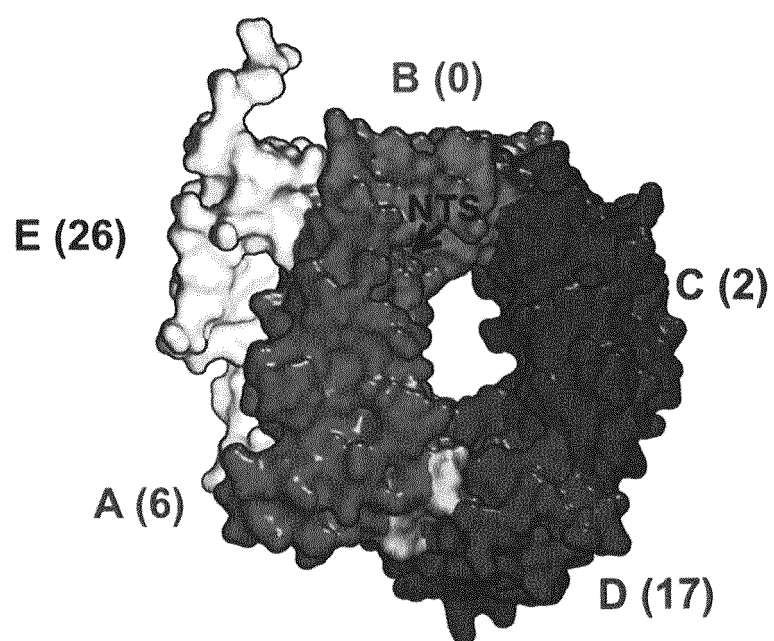
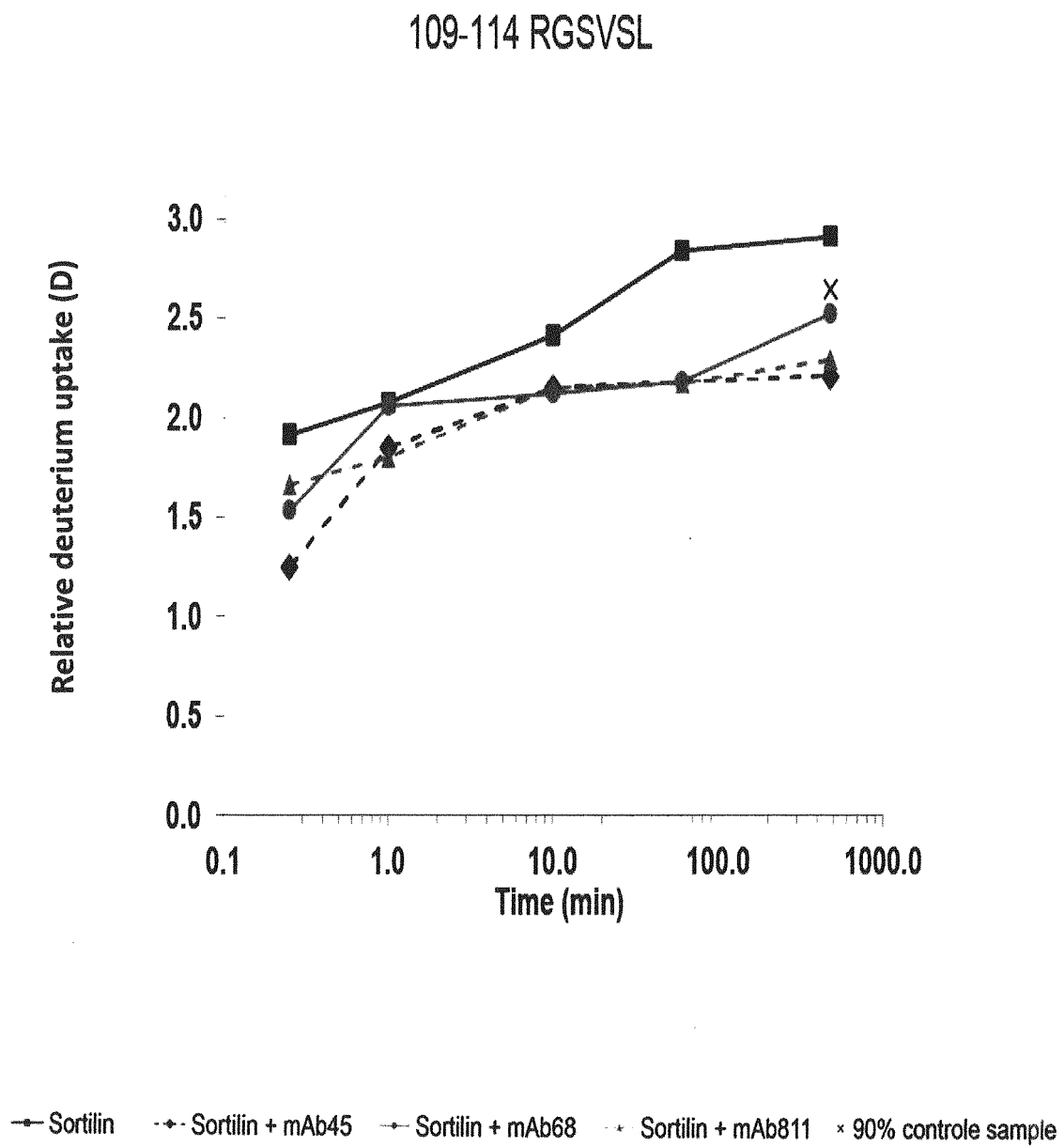
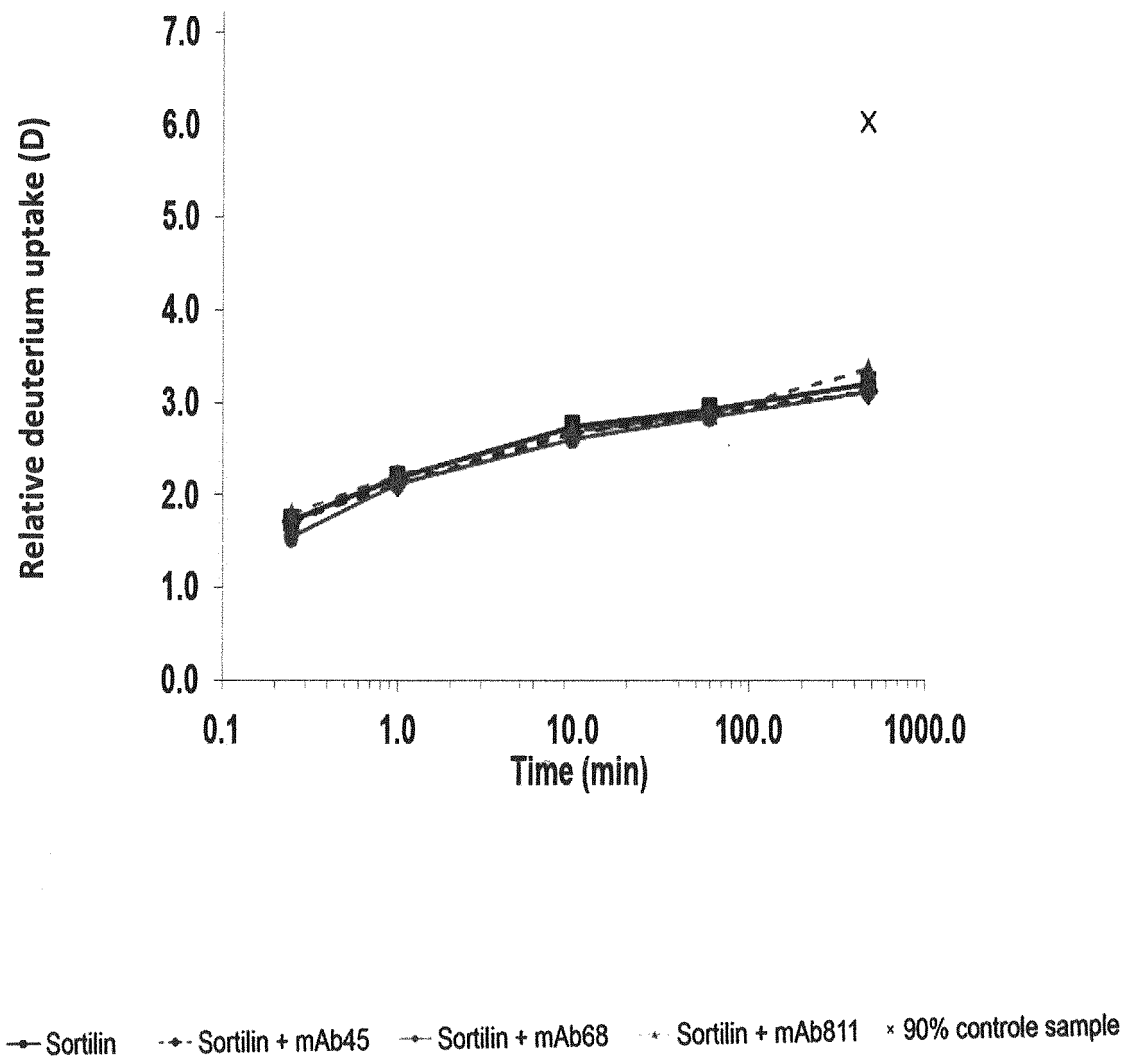


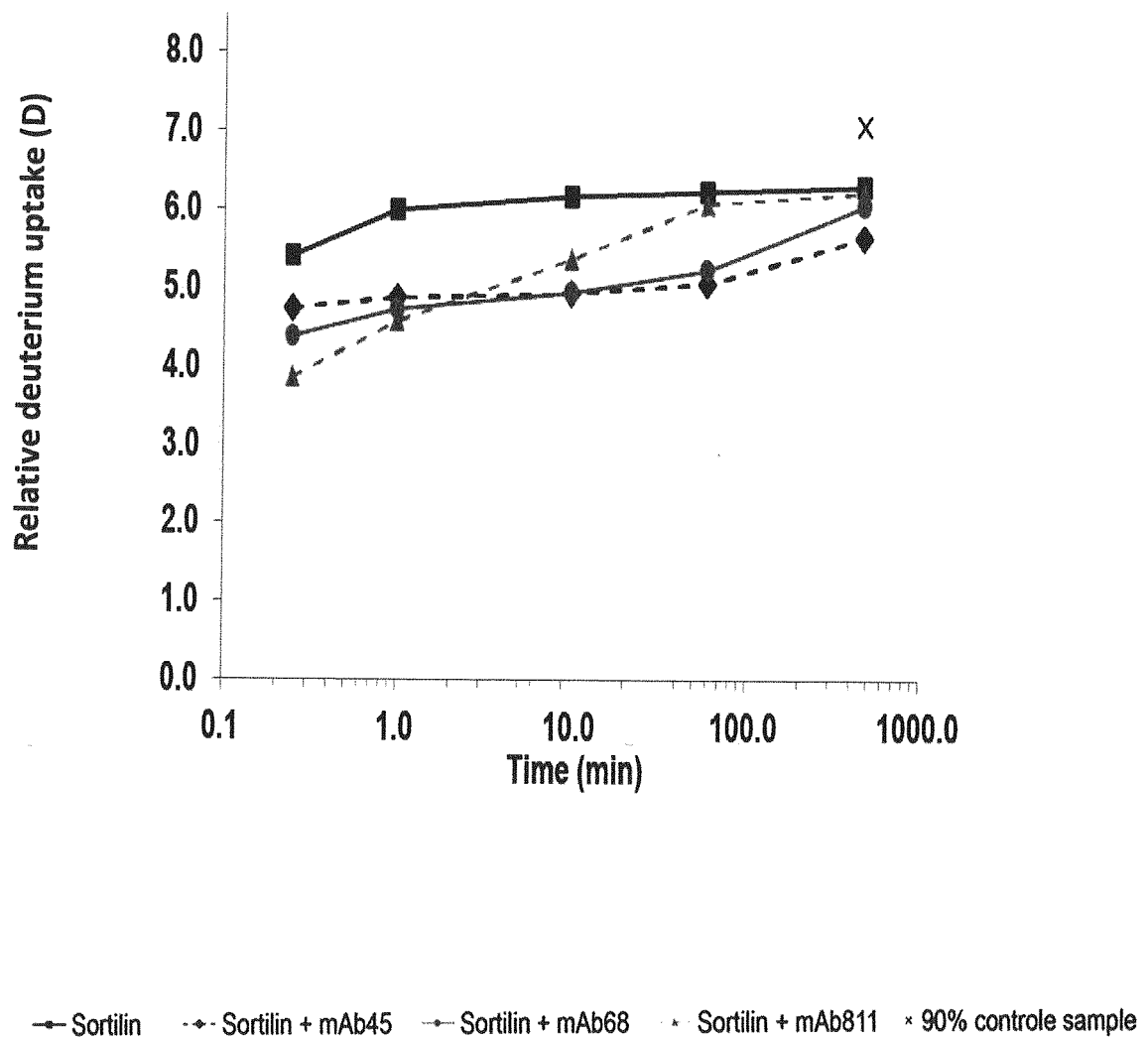
Fig 14

**Fig 15 a (1)**

115-125 SWVGDSTGVIL

**Fig 15 a (2)**

126-138 VLTTFHVPLVIMT

**Fig 15 a (3)**

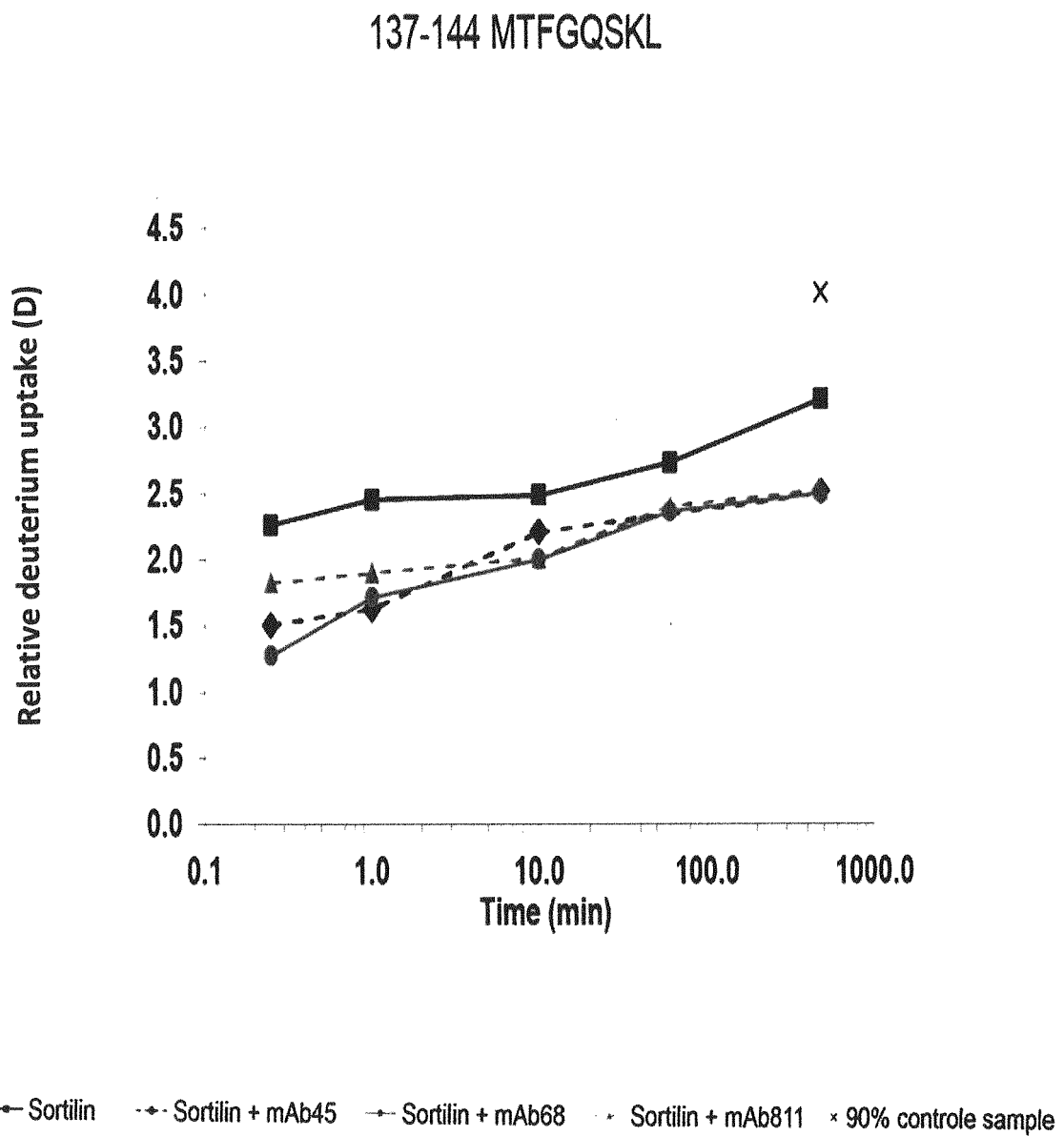


Fig 15 a (4)

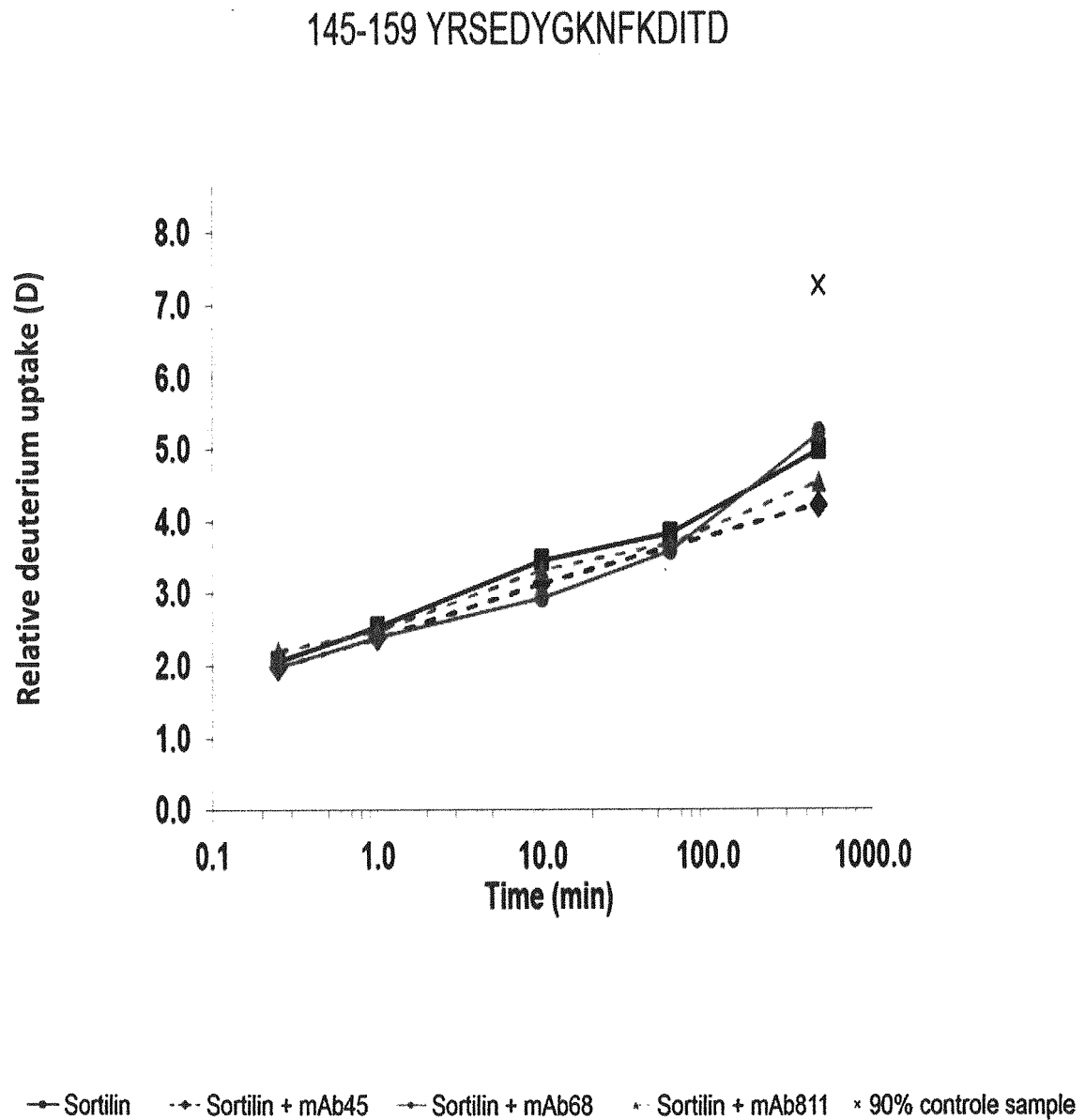
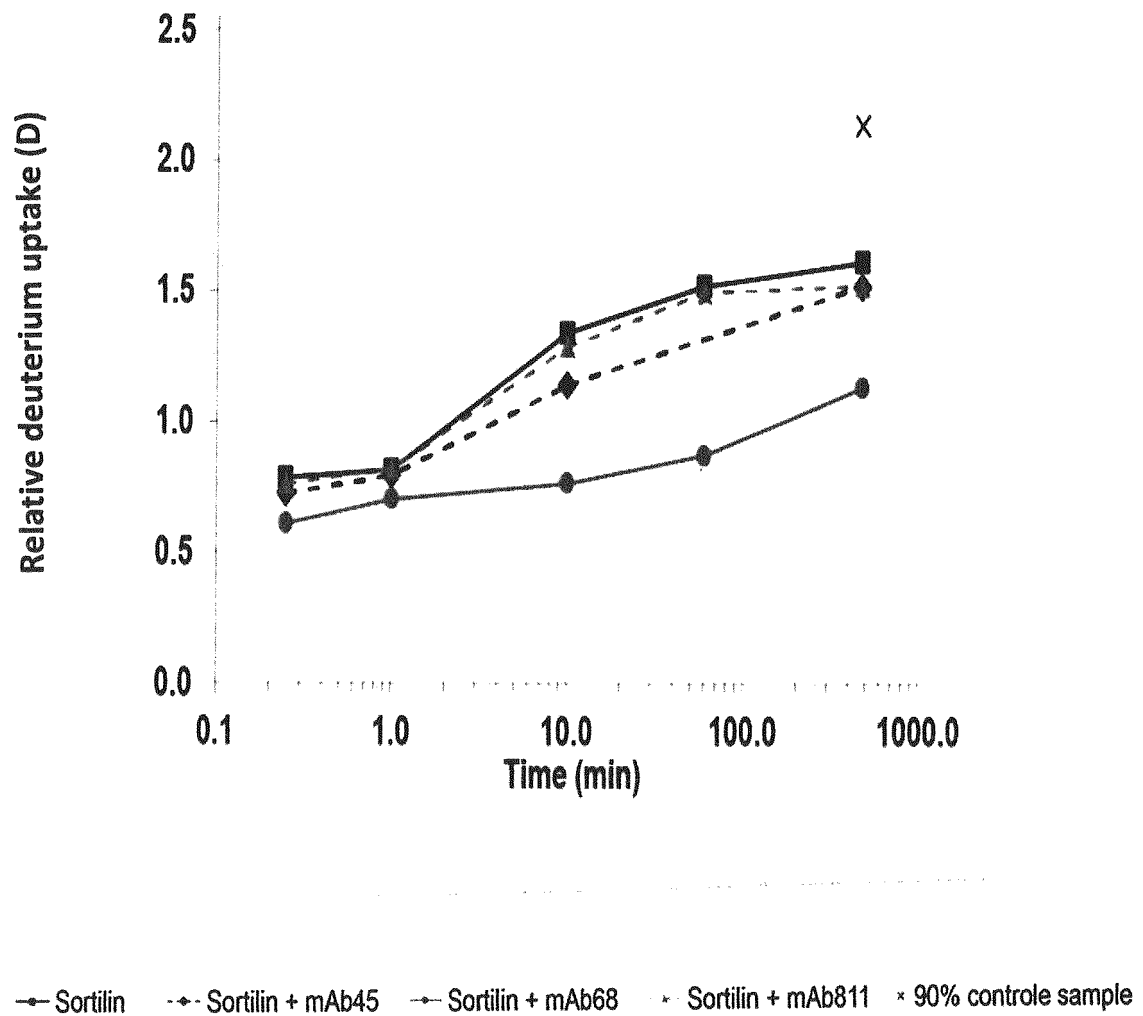
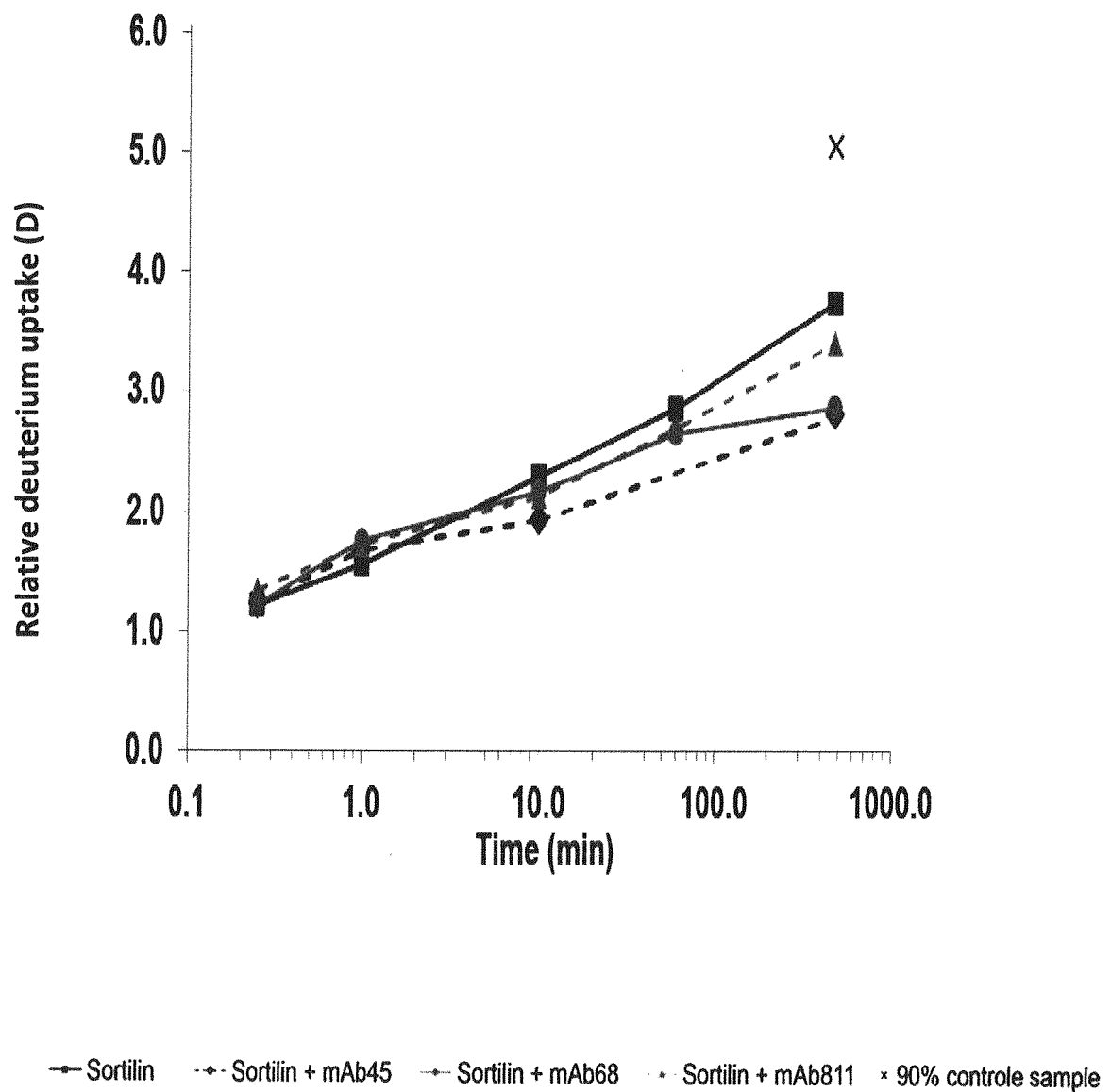


Fig 15 a (5)

154-159 FKDITD

**Fig 15 a (6)**

562-572 FTRDPIYFTGL

**Fig 15 b (1)**

## 588-592 FTESF

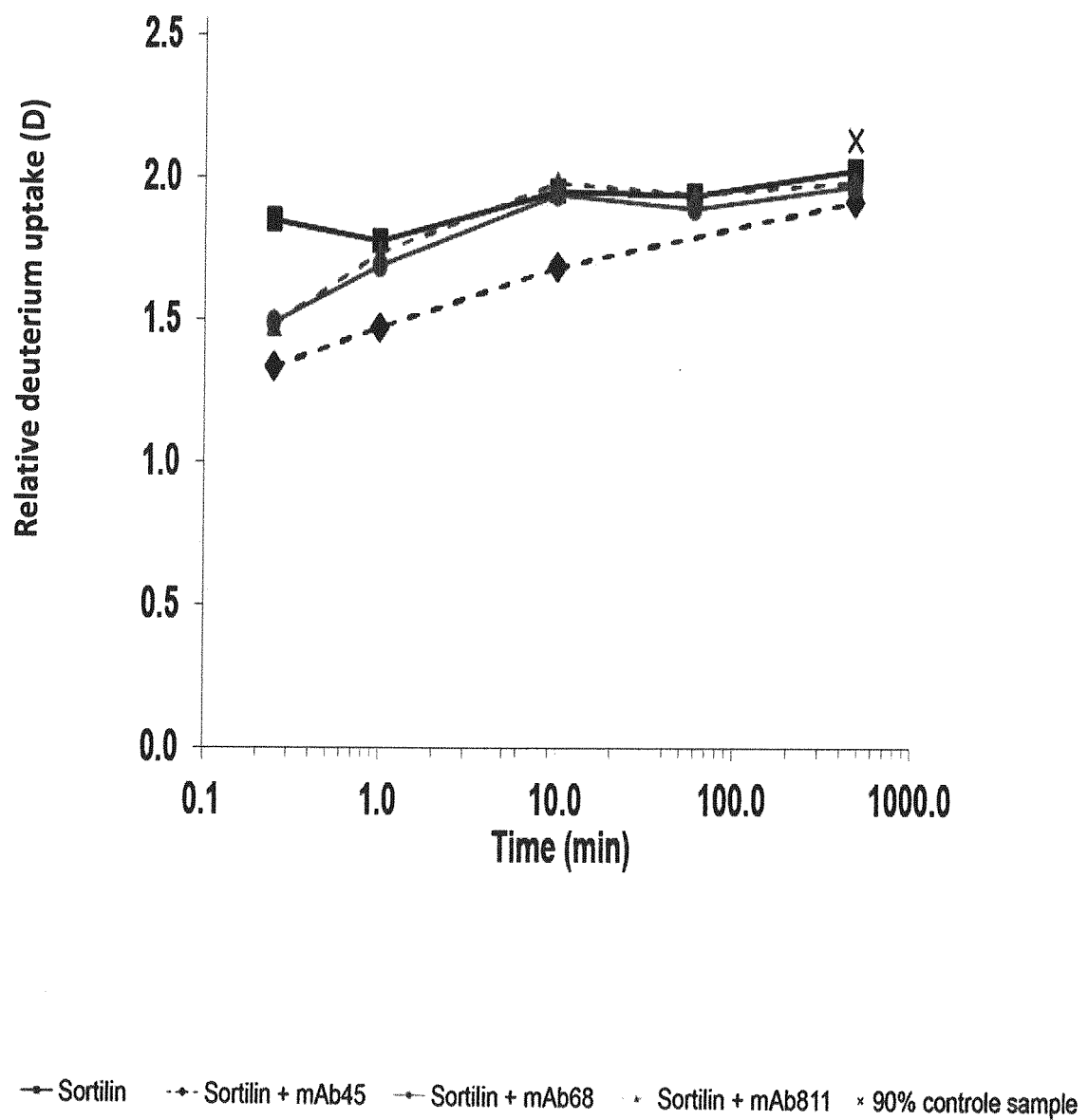
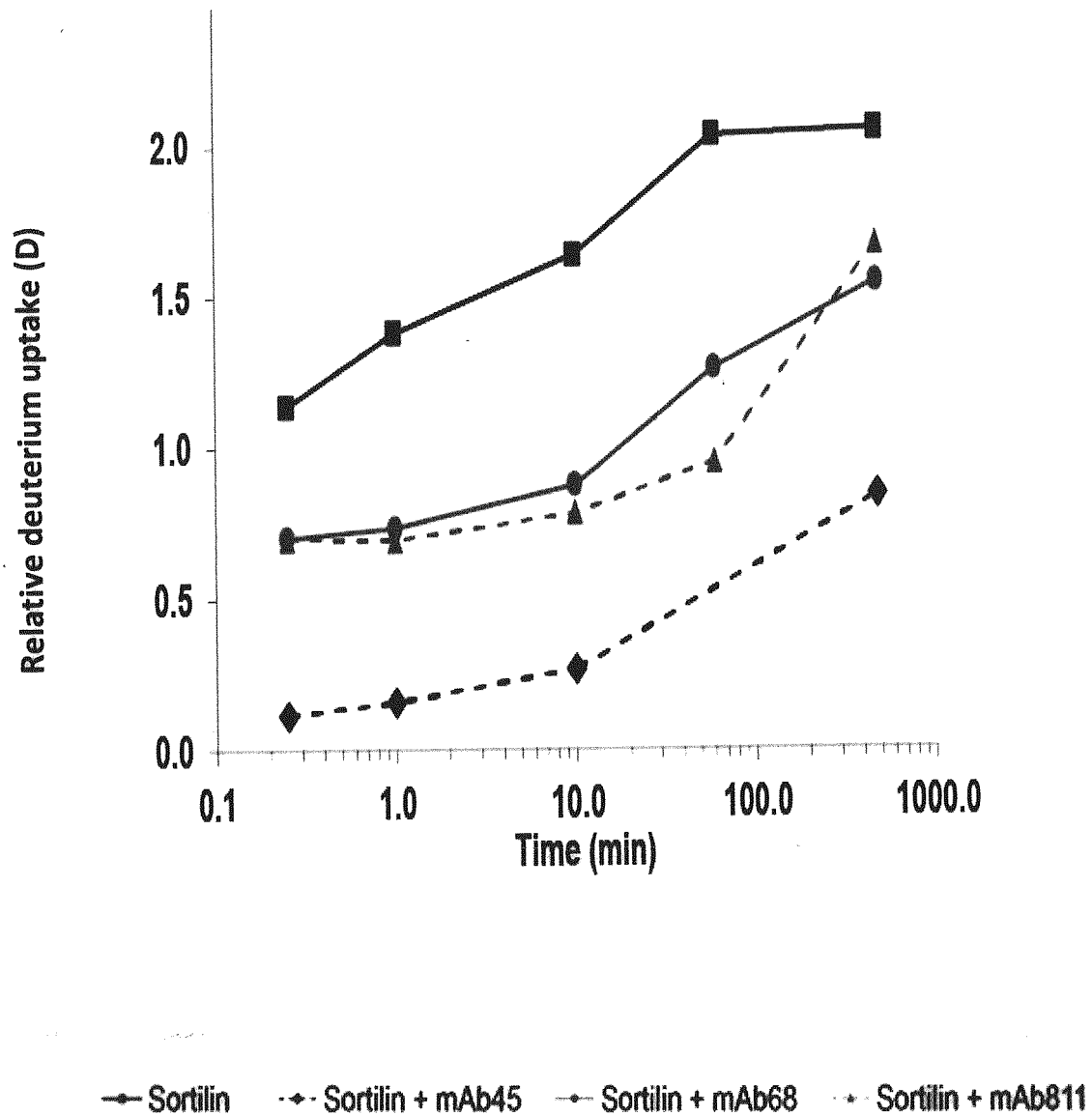
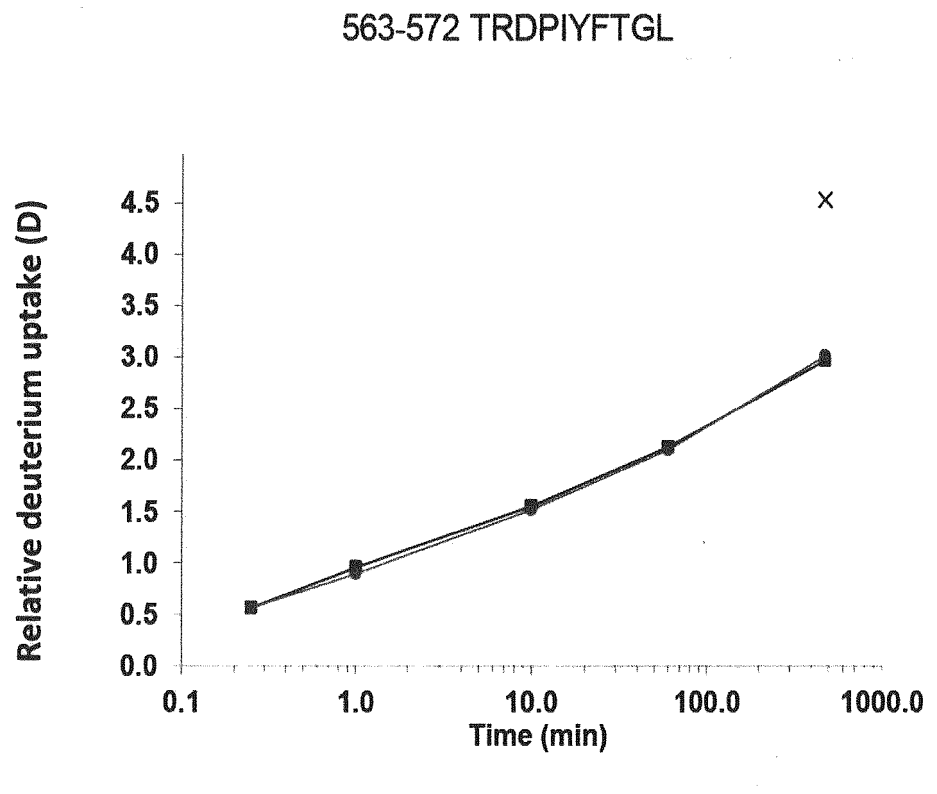


Fig 15 b (2)

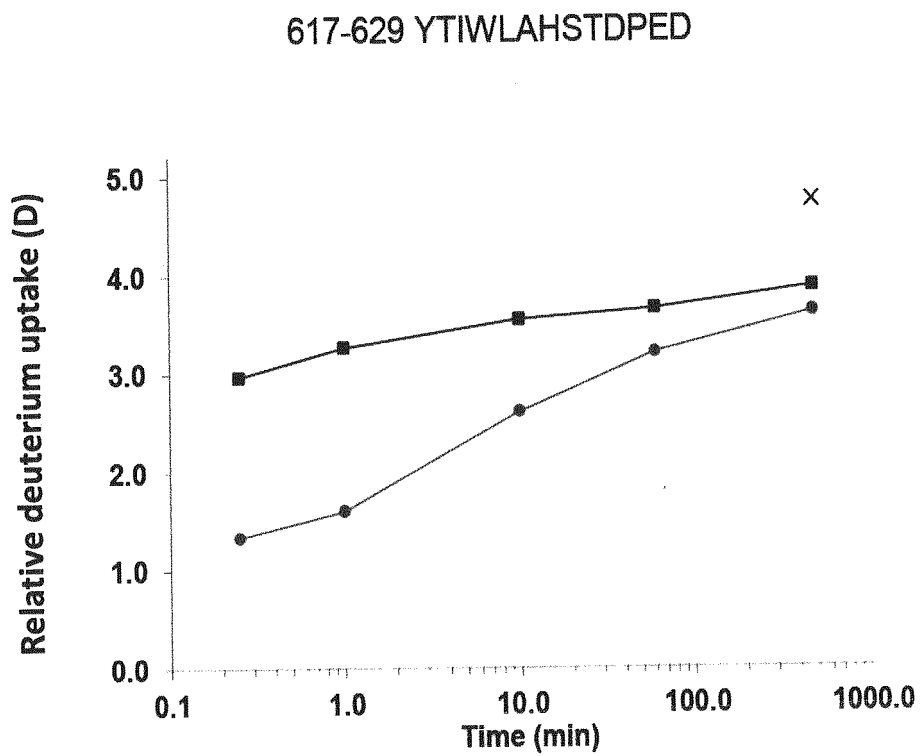
593-597 LTSQW

**Fig 15 b (3)**



—■— Sortilin    —●— Sortilin + mAb30

Fig 16 a (1)



—■— Sortilin    —●— Sortilin + mAb30

Fig 16 a (2)

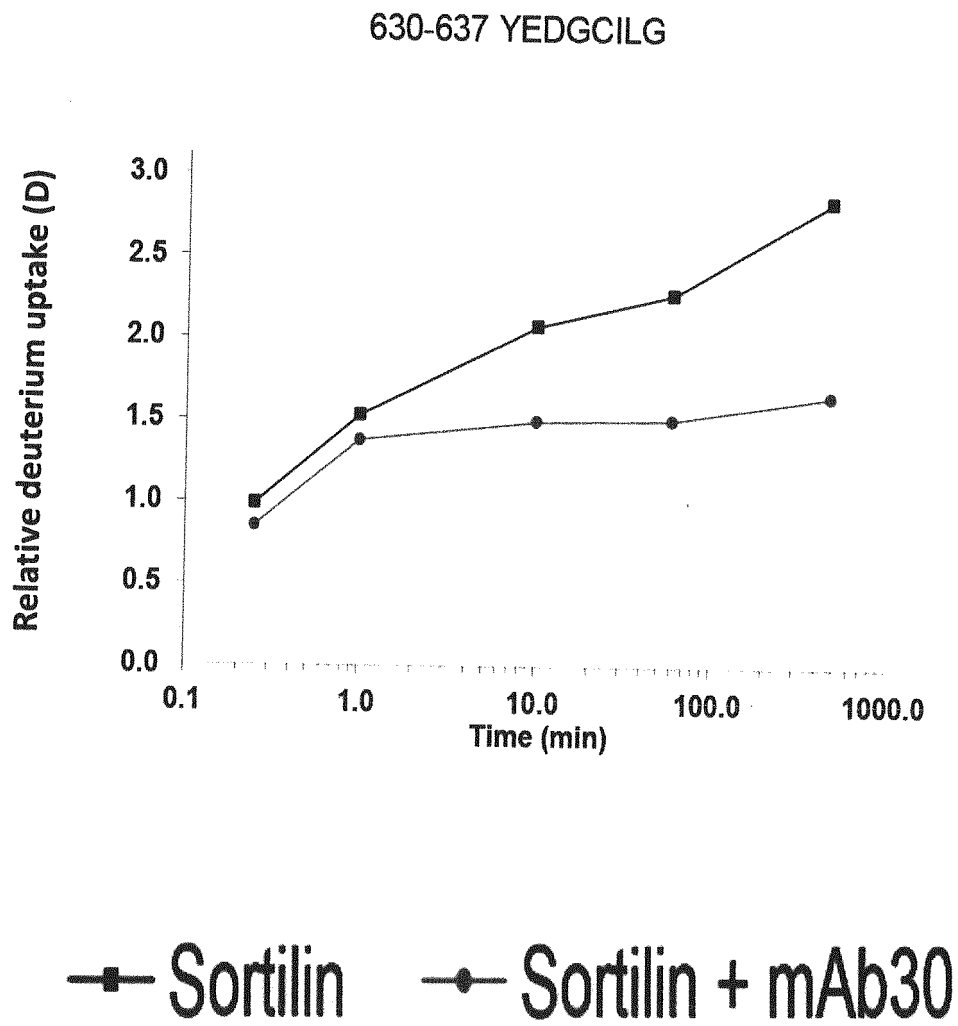


**Fig 16 a (3)**

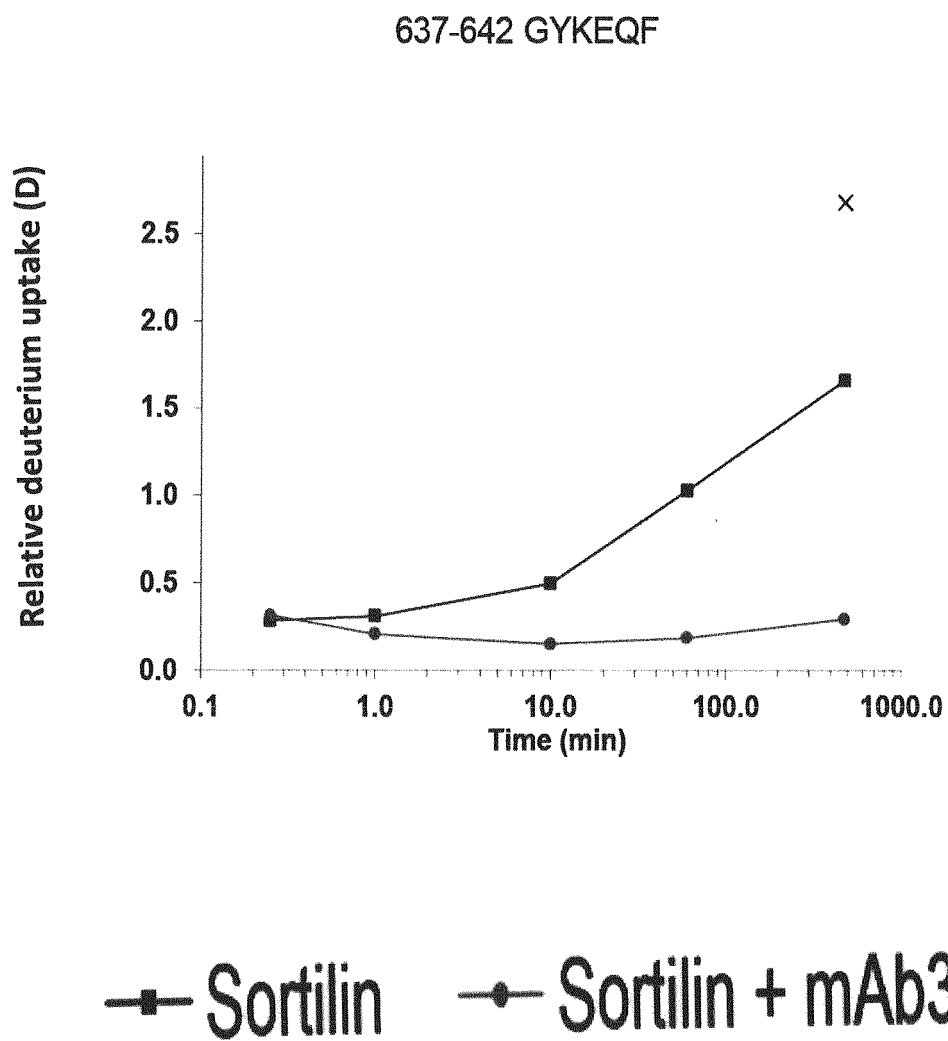
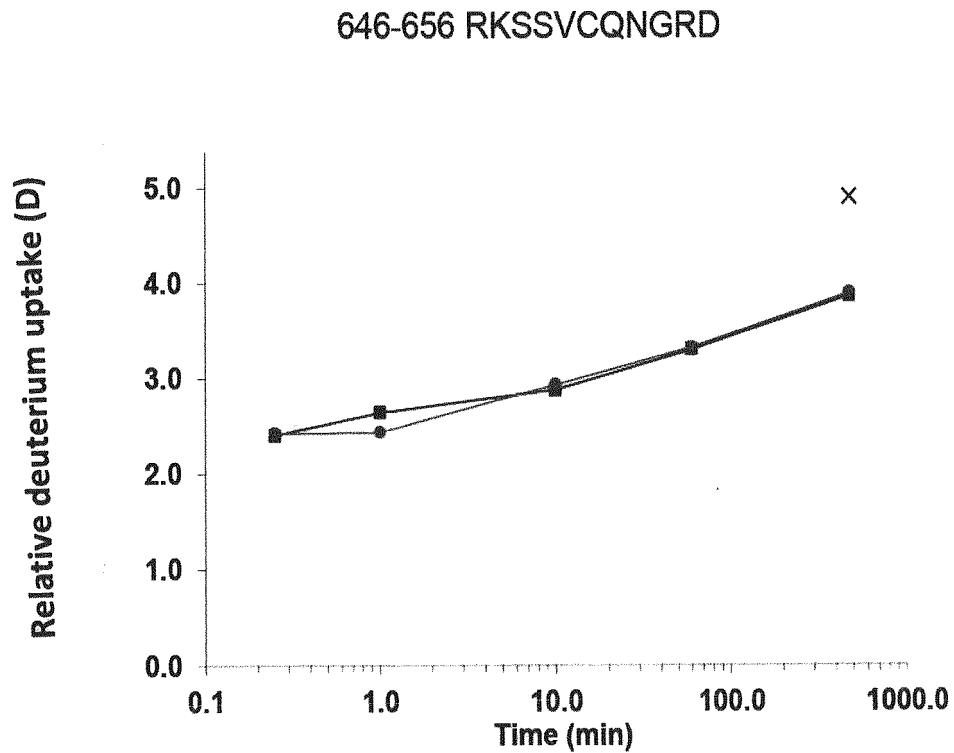
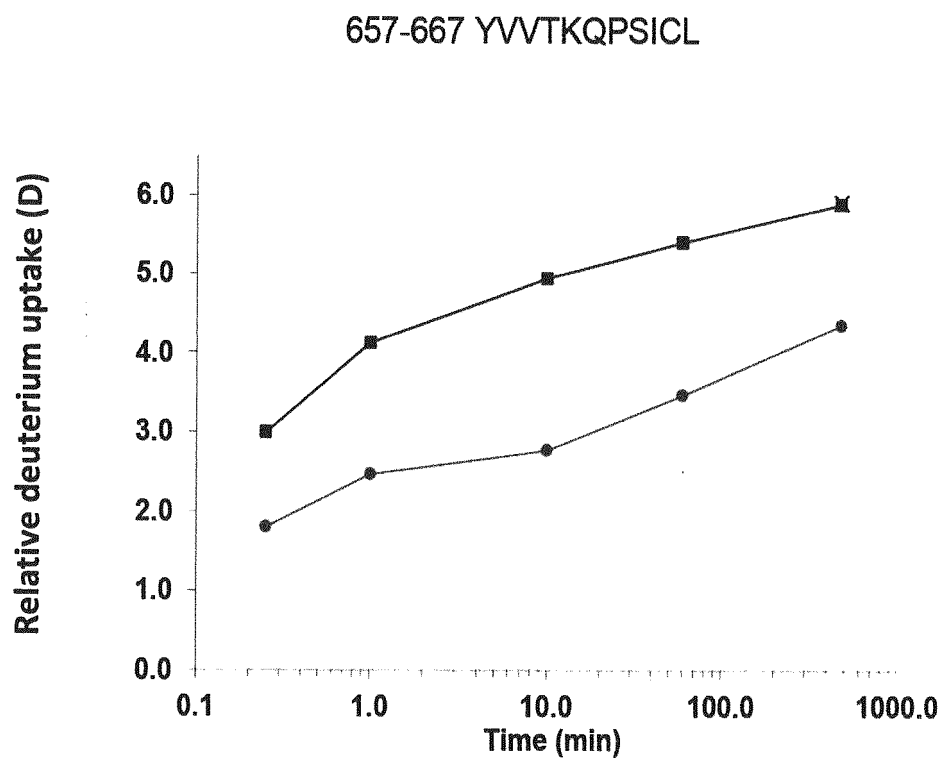


Fig 16 a (4)



—■— Sortilin    —●— Sortilin + mAb30

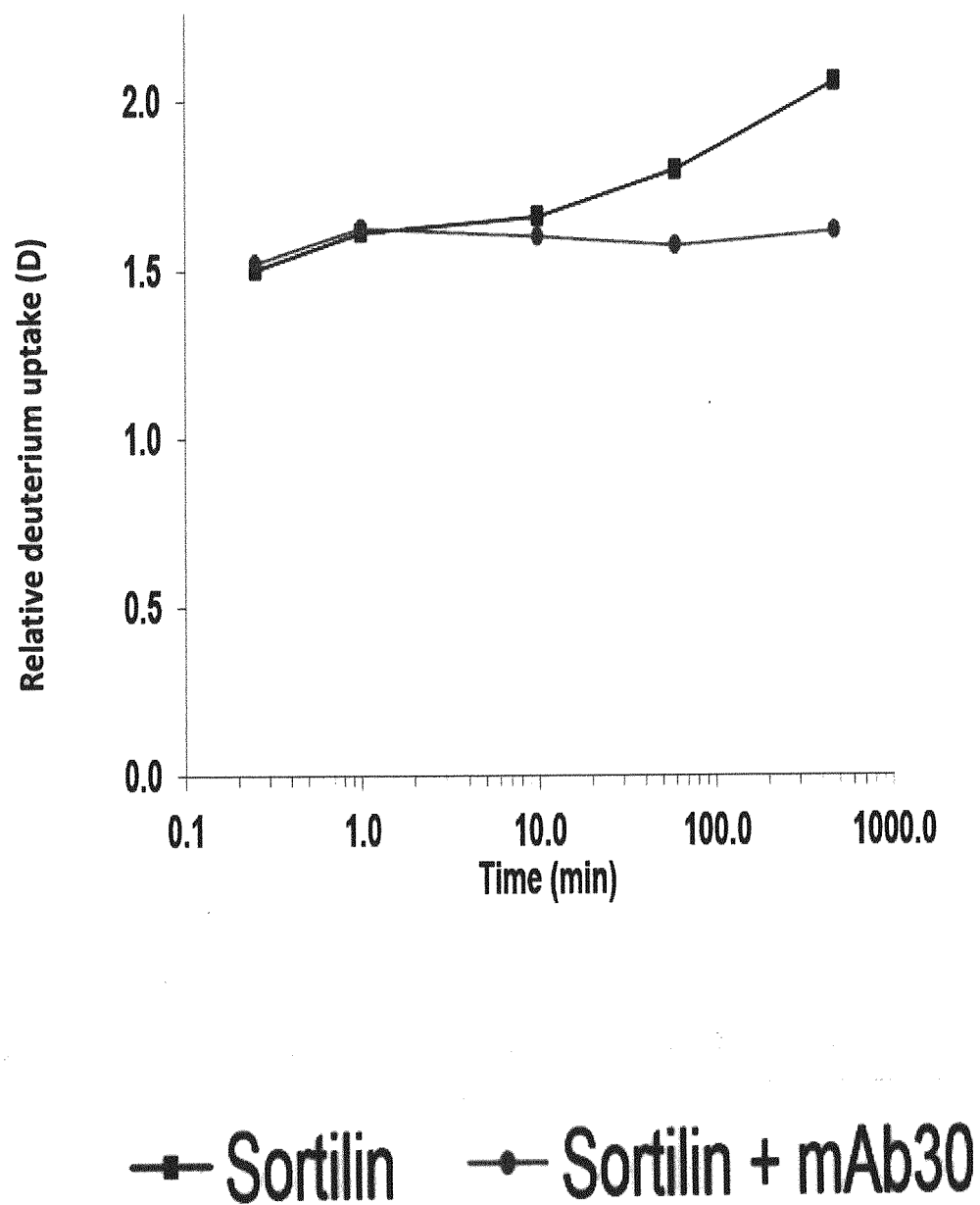
Fig 16 a (5)



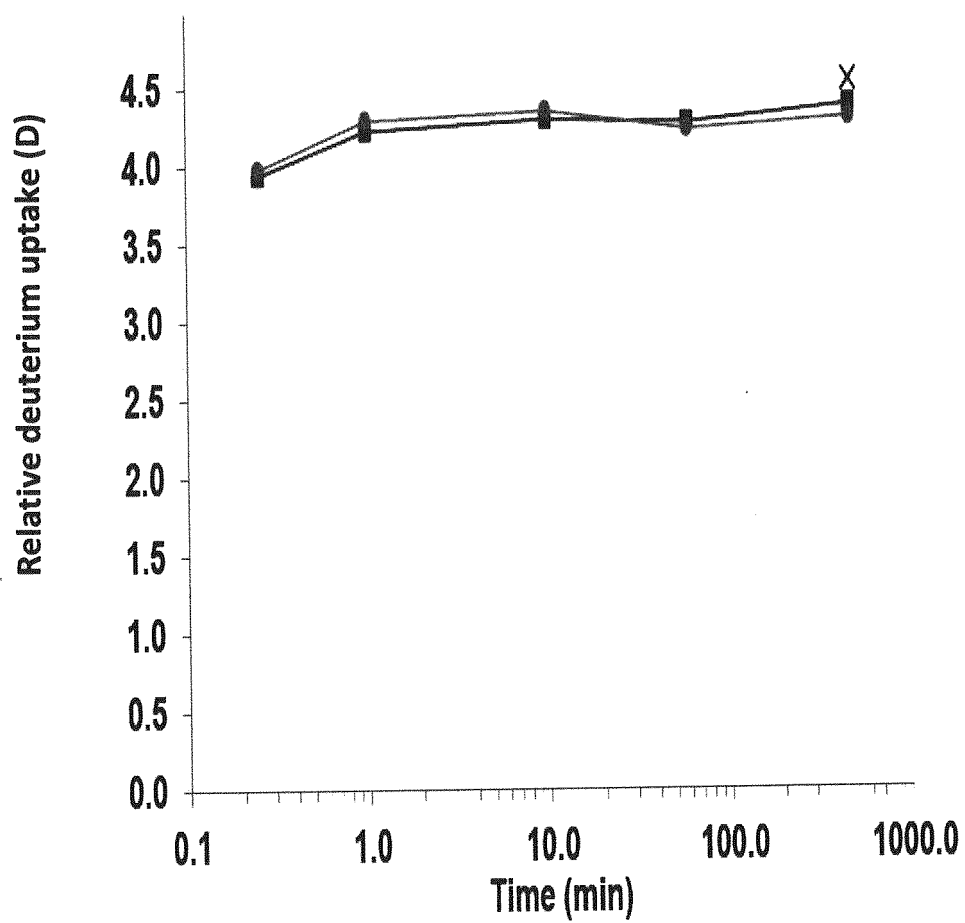
—■— Sortilin    —●— Sortilin + mAb30

Fig 16 a (6)

668-672 CSLED

**Fig 16 b (1)**

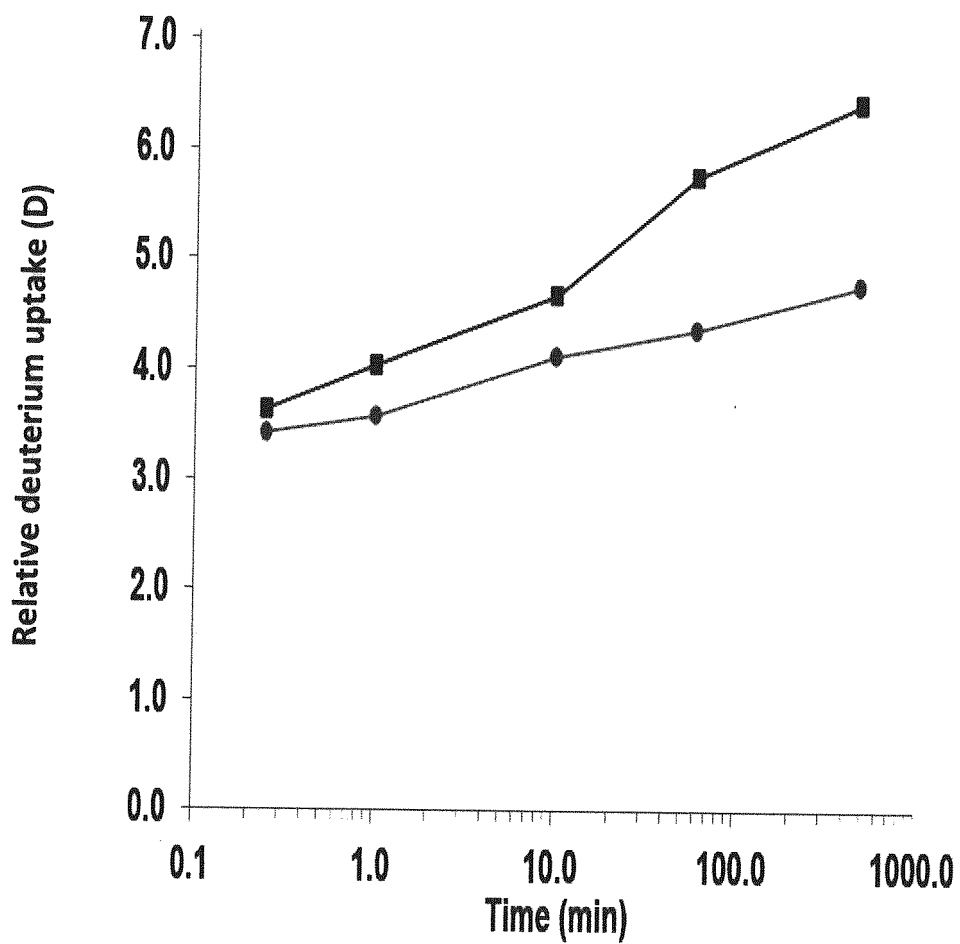
704-714 YGREEHLTTNG



—■— Sortilin    —●— Sortilin + mAb30

Fig 16 b (2)

715-728 YRKIPGDKCQGGVN



—■— Sortilin    —●— Sortilin + mAb30

**Fig 16 b (3)**

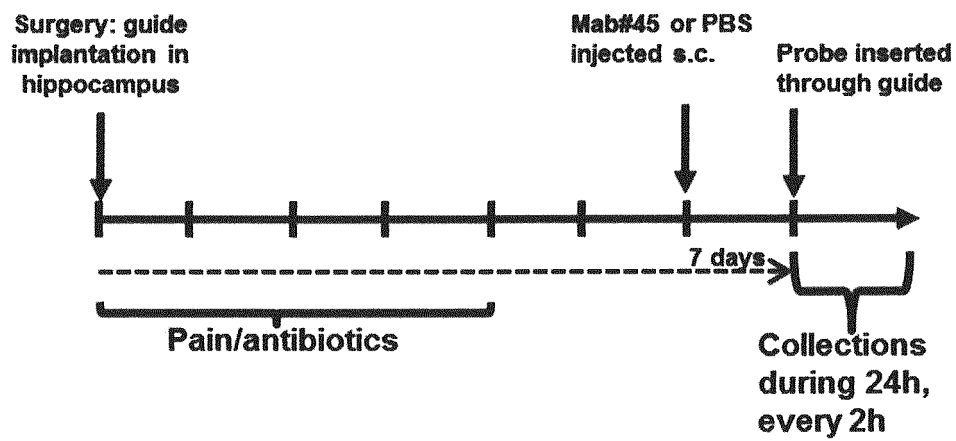
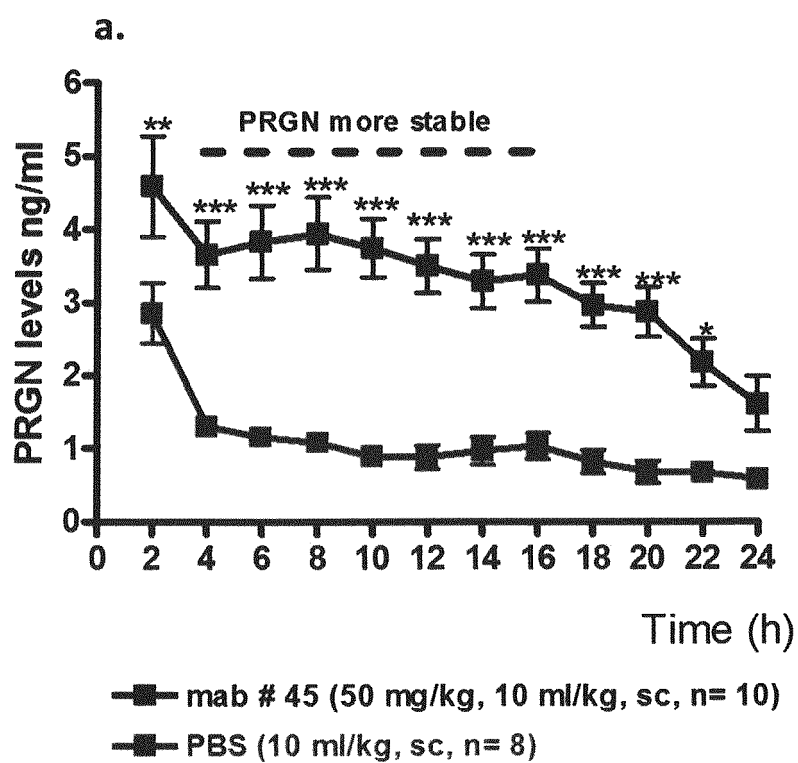
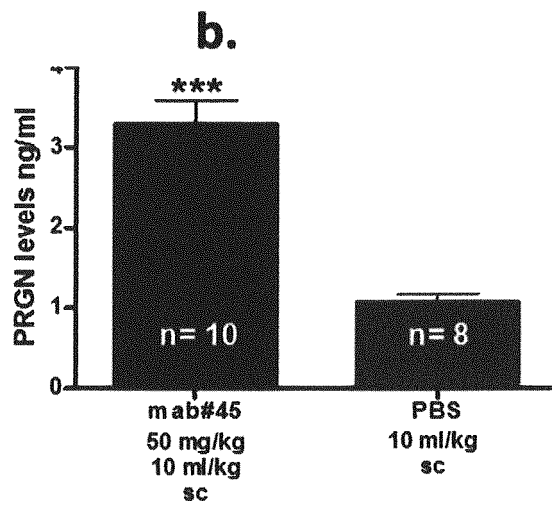


Fig. 17



data: means  $\pm$  SEM; \*,  $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , mab#45 vs PBS, two-way ANOVA followed by Bonferroni post-test

Fig. 18a



24 --> 48 h post-dosing

Data: means  $\pm$  SEM; \*\*\*p<0.001, mab#45 vs PBS, t-test

Fig. 18b

**C.**

| time (h) | mab#45   |          |    | PBS      |          |   |
|----------|----------|----------|----|----------|----------|---|
|          | Y        | SEM      | N  | Y        | SEM      | N |
| 2        | 4.587163 | 0.684416 | 10 | 2.854475 | 0.411770 | 8 |
| 4        | 3.654225 | 0.453960 | 10 | 1.303813 | 0.129774 | 8 |
| 6        | 3.826151 | 0.499164 | 10 | 1.157348 | 0.103958 | 8 |
| 8        | 3.941664 | 0.495235 | 10 | 1.084373 | 0.102409 | 8 |
| 10       | 3.744573 | 0.396738 | 10 | 0.885935 | 0.139000 | 8 |
| 12       | 3.498750 | 0.369875 | 10 | 0.880561 | 0.161299 | 8 |
| 14       | 3.287708 | 0.362766 | 10 | 0.966836 | 0.190743 | 8 |
| 16       | 3.372367 | 0.365127 | 10 | 1.031850 | 0.180413 | 8 |
| 18       | 2.962828 | 0.298671 | 10 | 0.817940 | 0.158949 | 8 |
| 20       | 2.868518 | 0.343551 | 10 | 0.681344 | 0.153457 | 8 |
| 22       | 2.173472 | 0.322407 | 10 | 0.673761 | 0.122029 | 8 |
| 24       | 1.604464 | 0.377046 | 10 | 0.583756 | 0.123556 | 8 |

**BS,**

Fig. 18c