

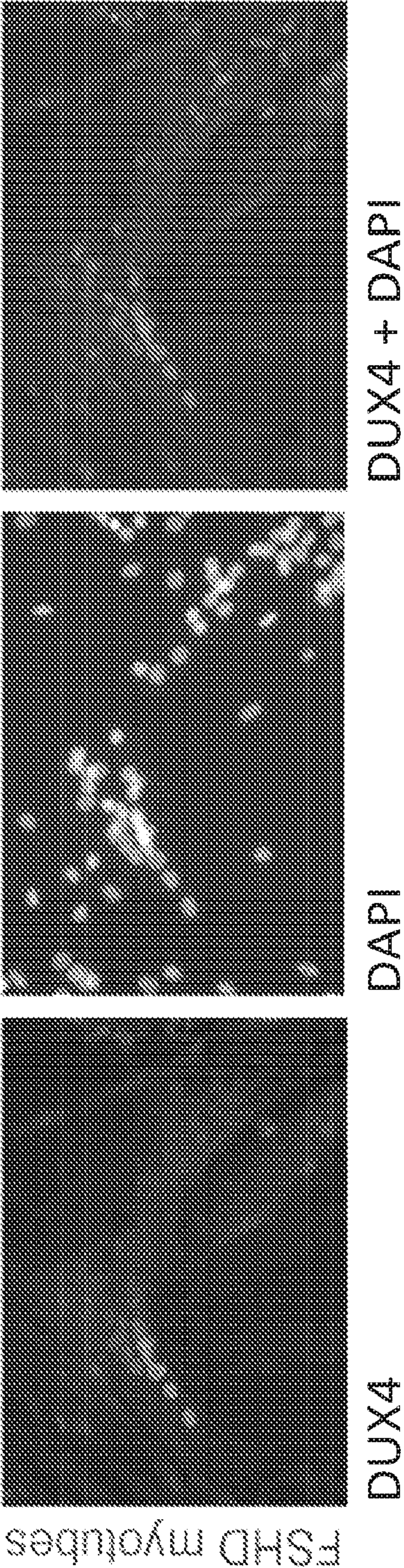


FIG. 1A

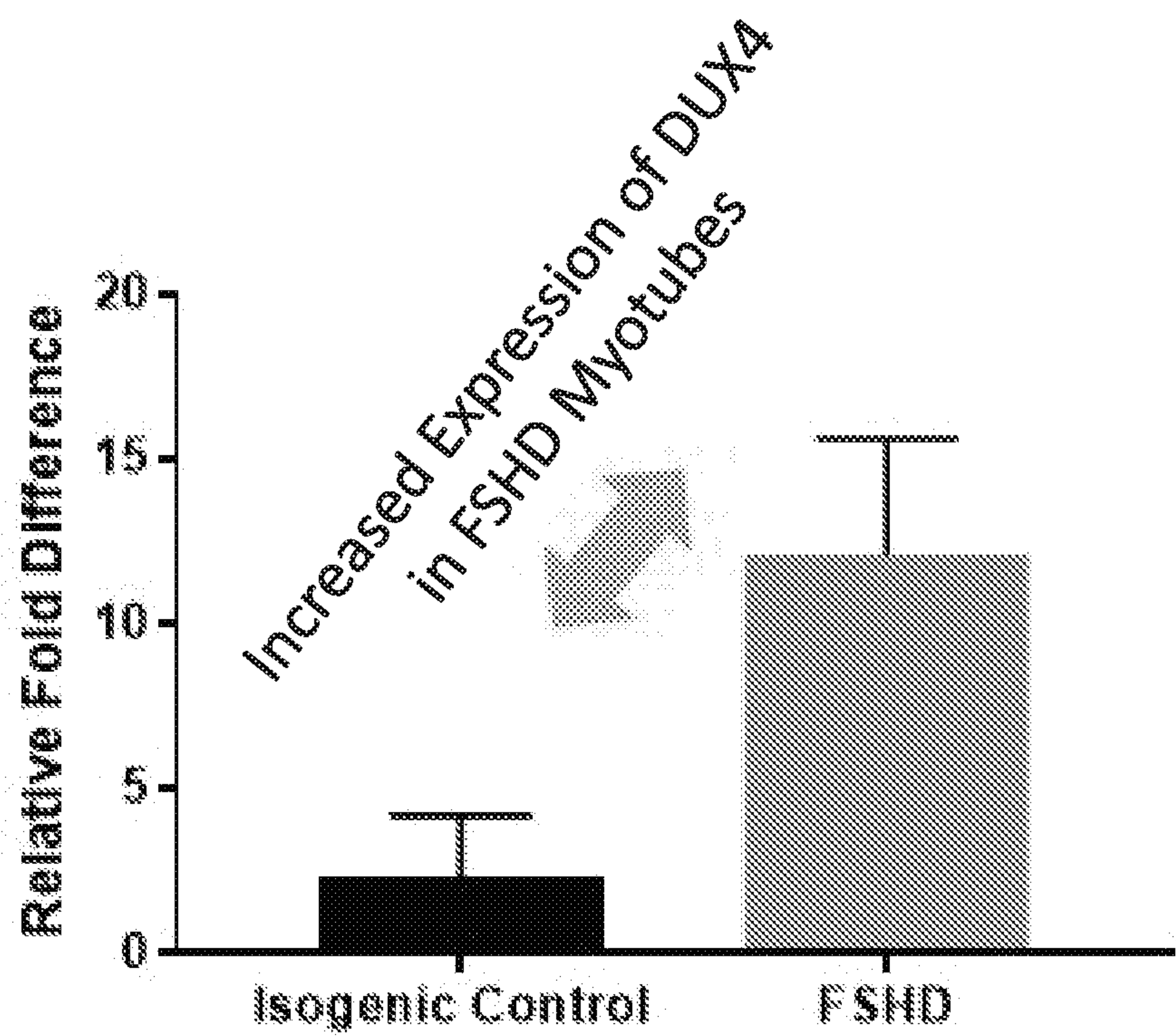


FIG. 1B

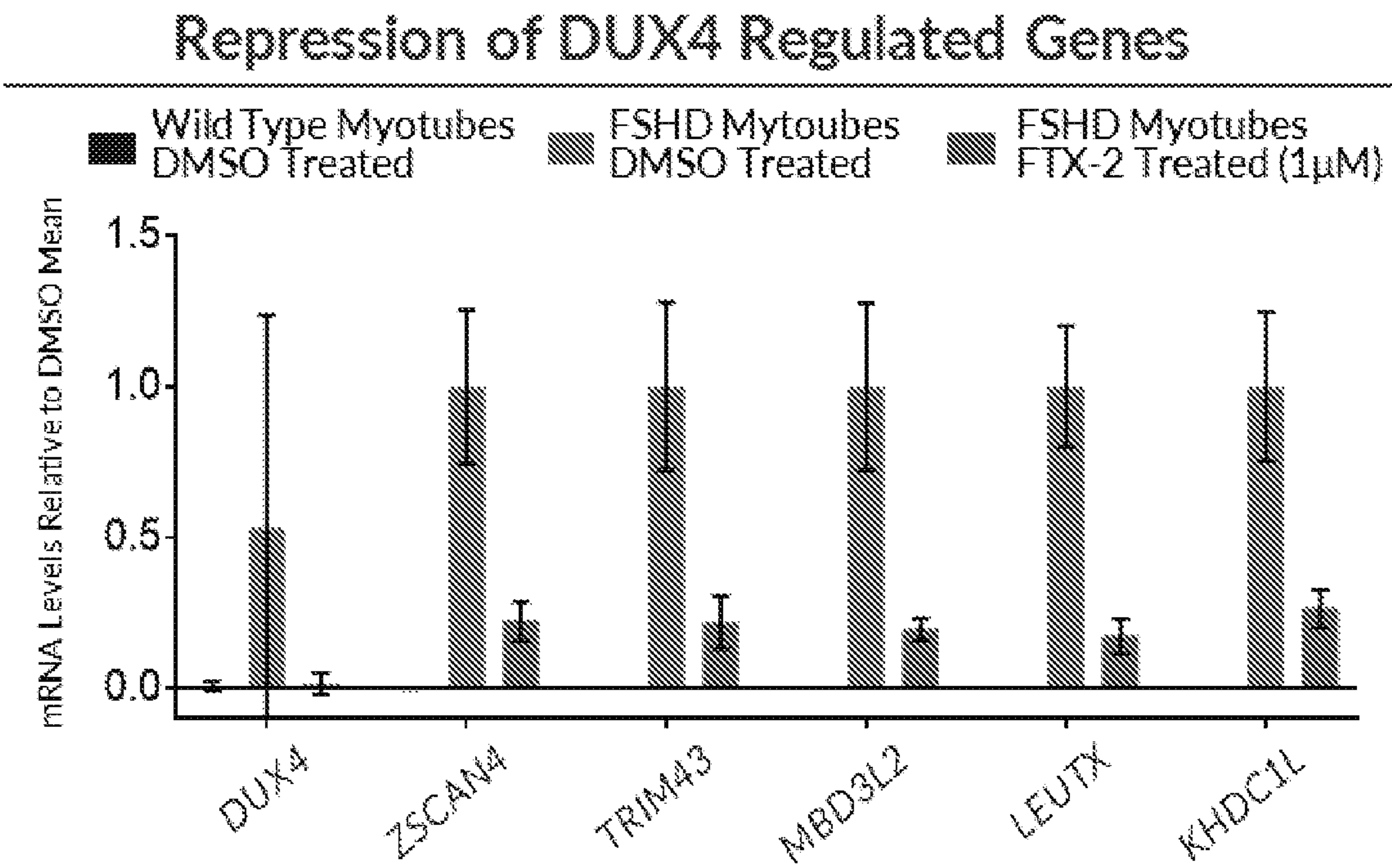


FIG. 2

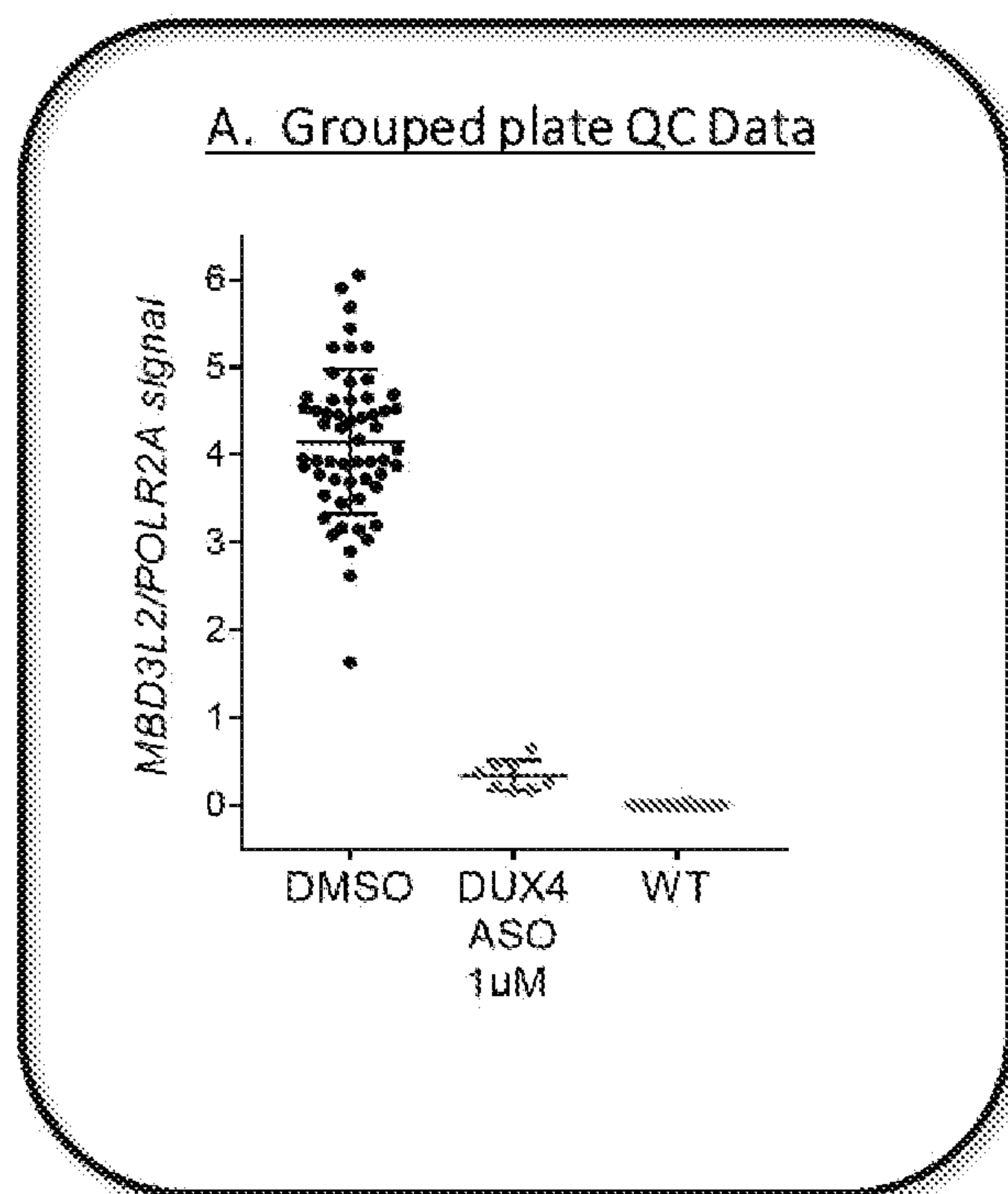


FIG. 3A

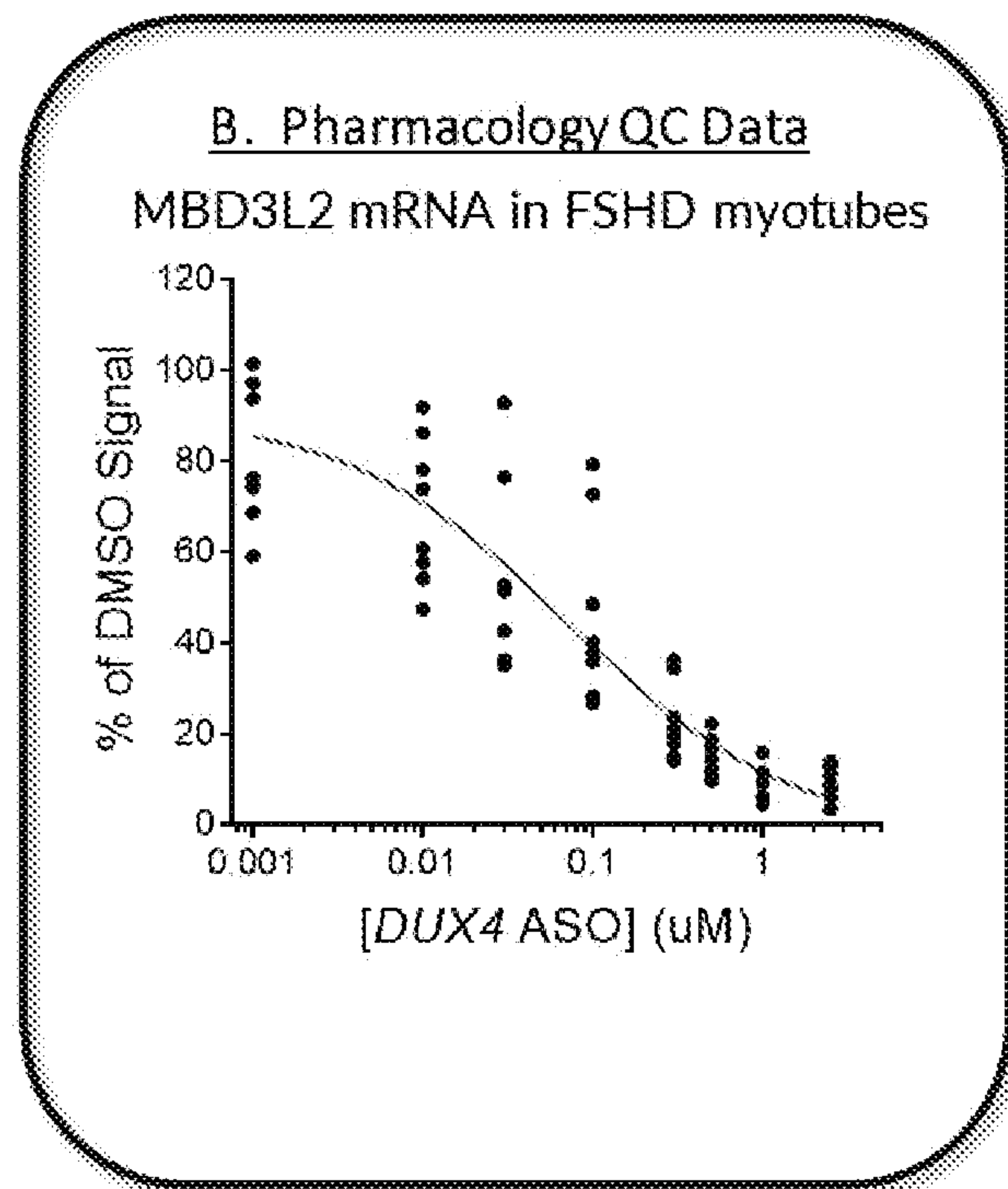


FIG. 3B

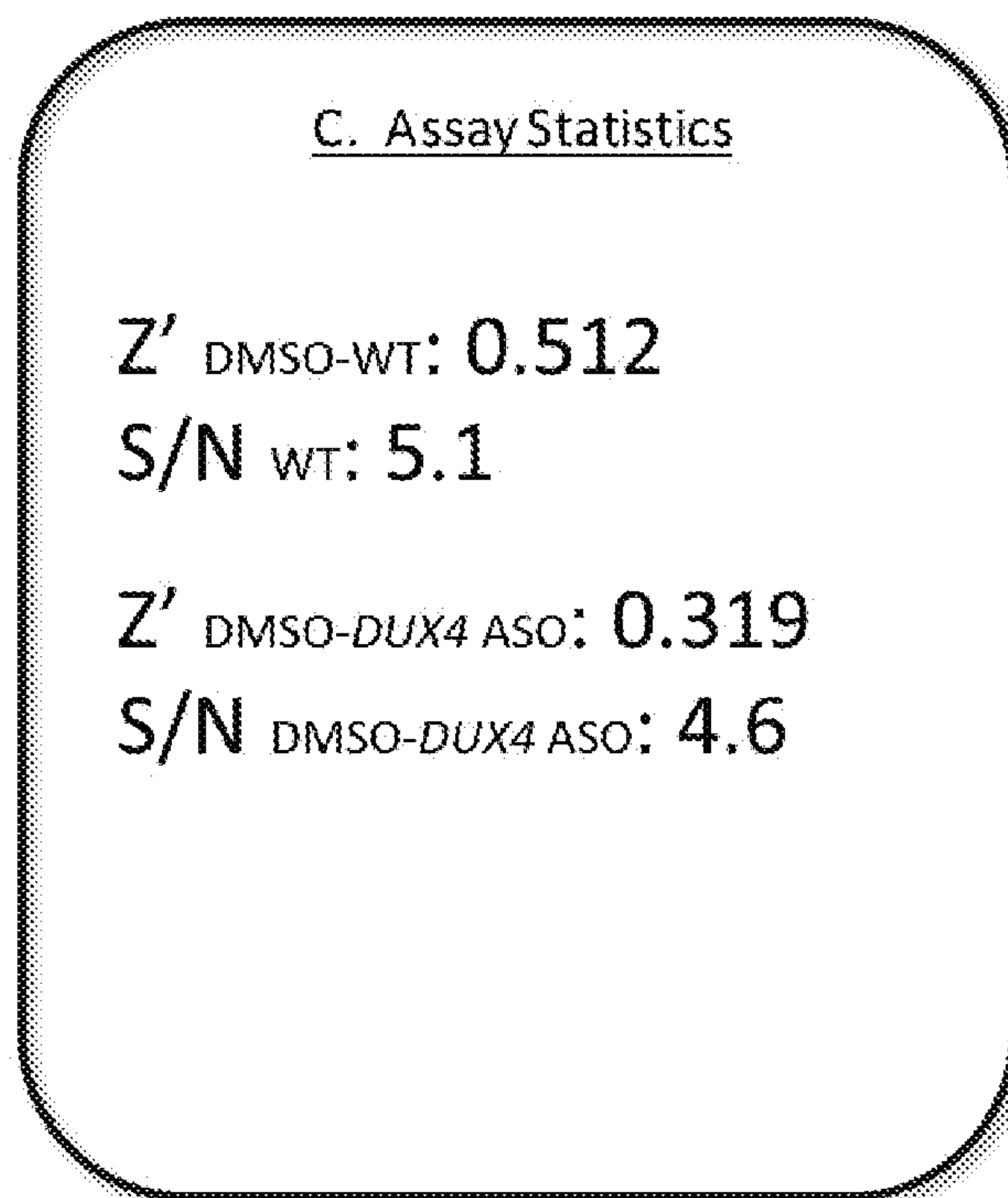


FIG. 3C

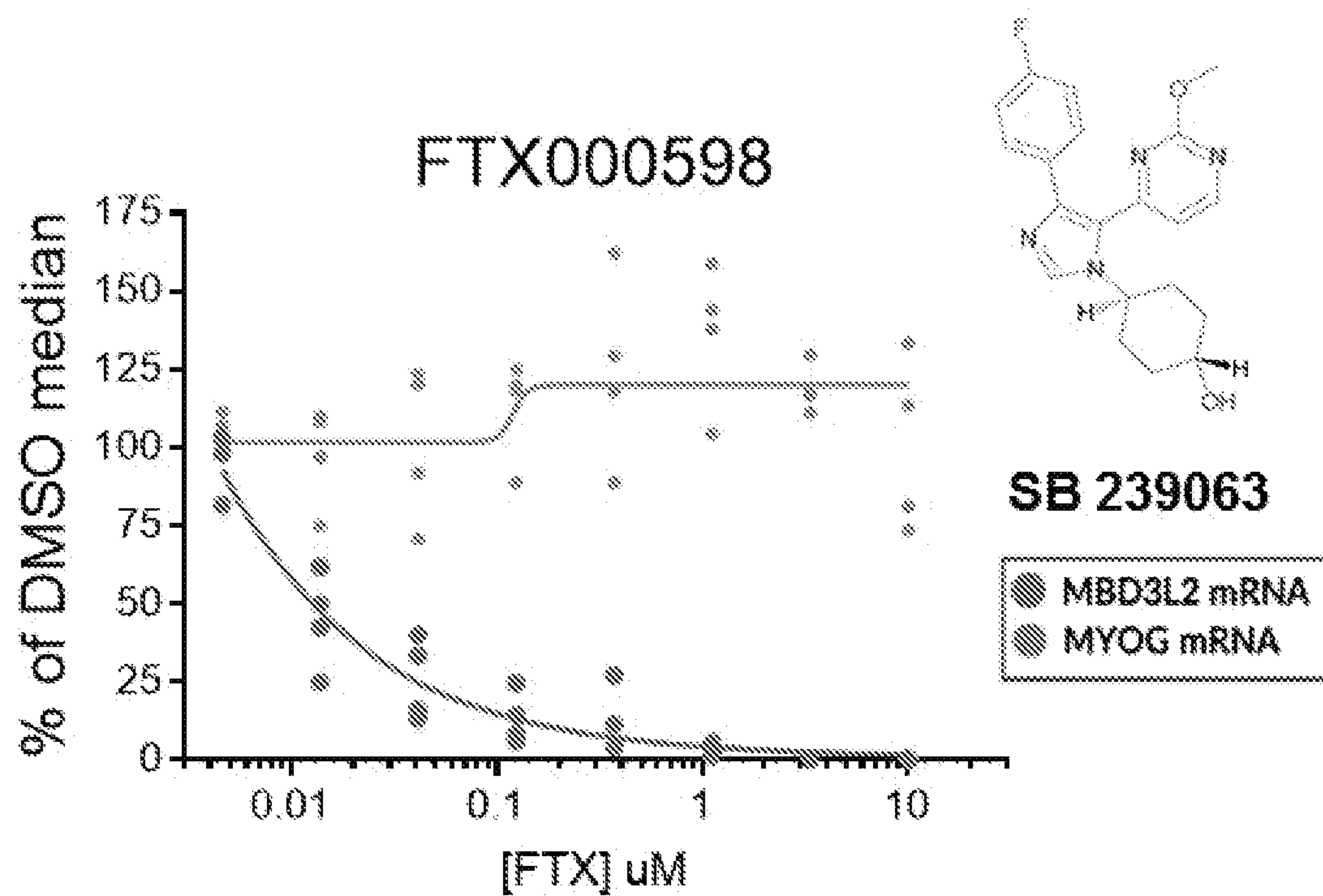


FIG. 4A

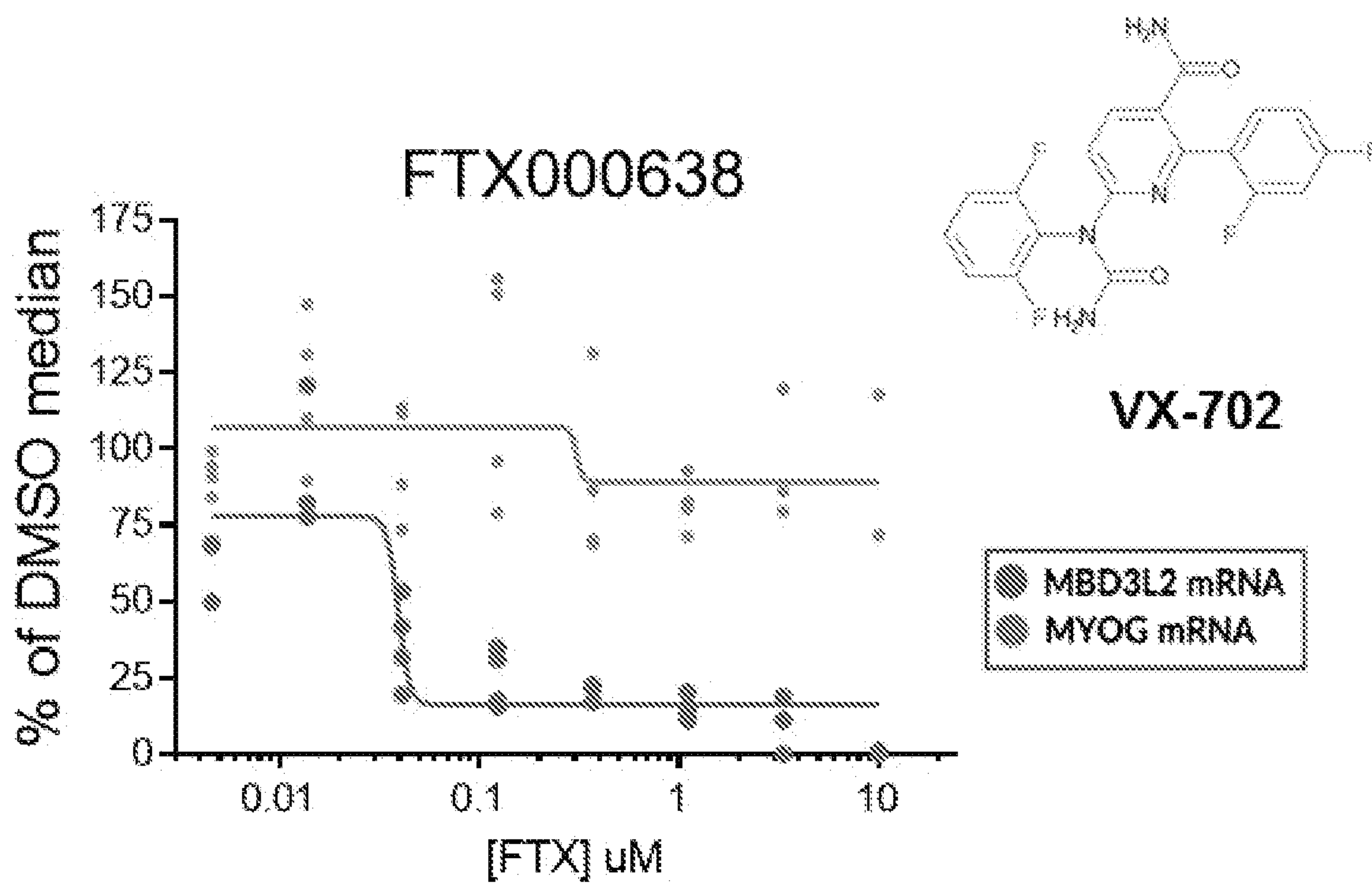


FIG. 4B

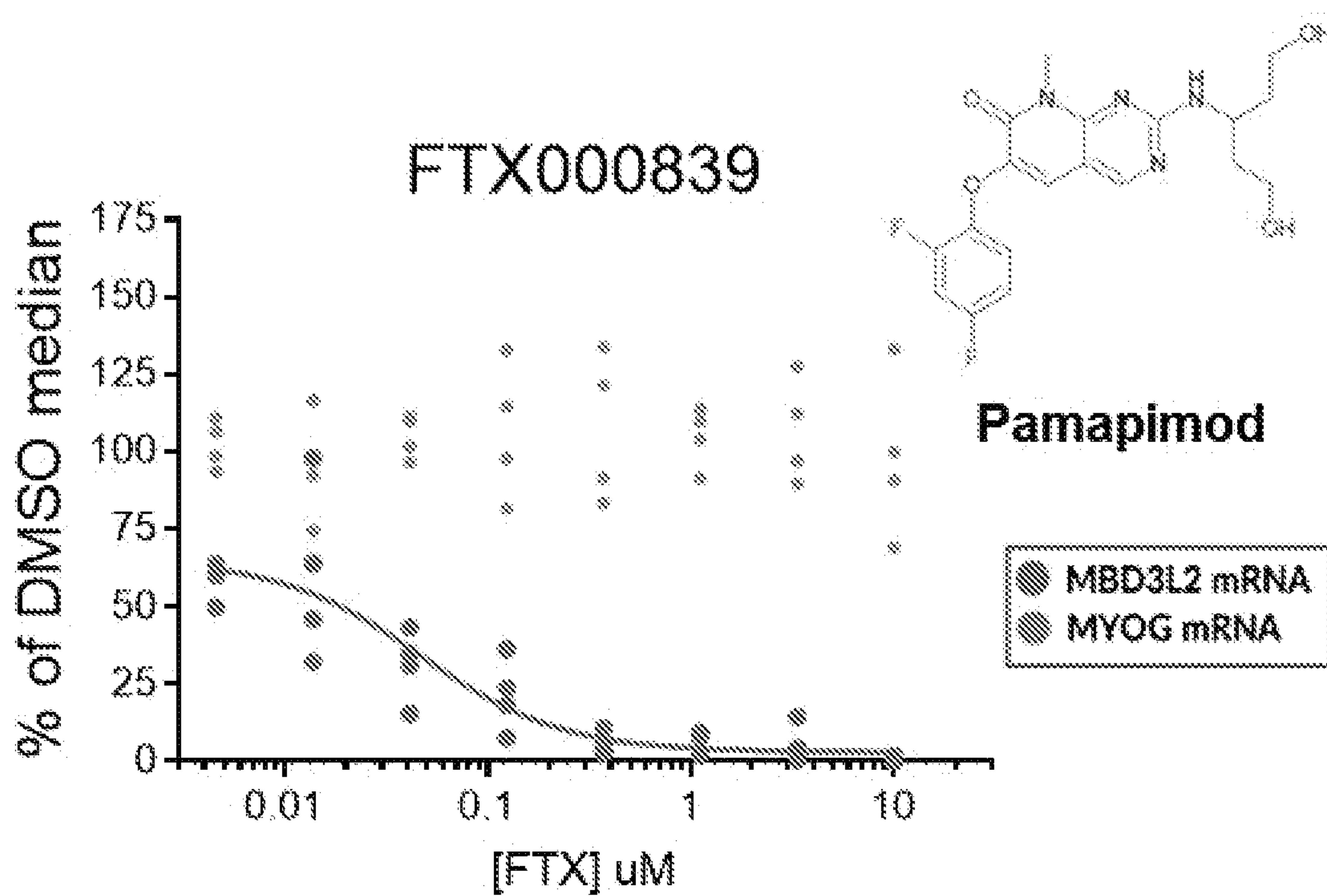
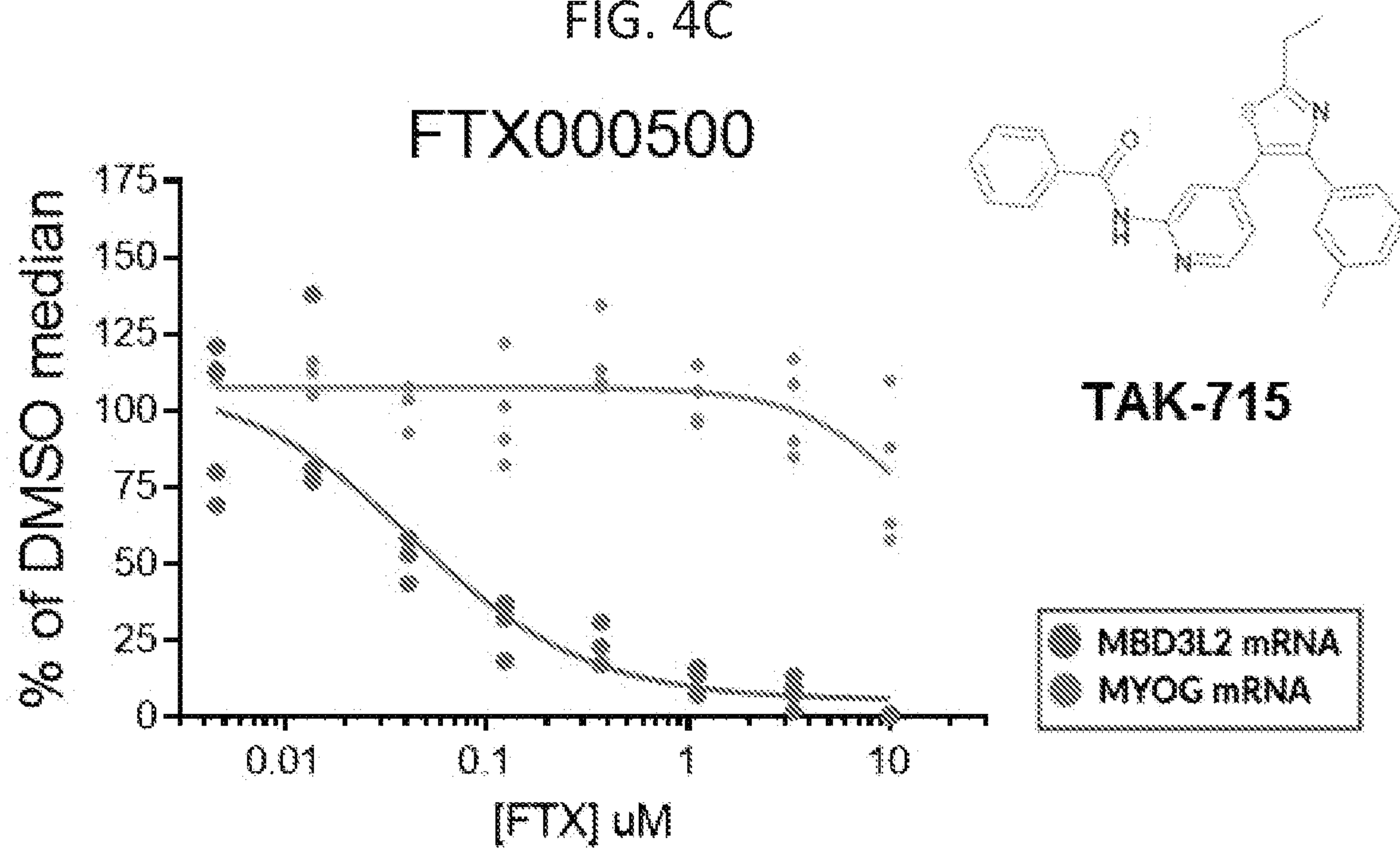


FIG. 4C



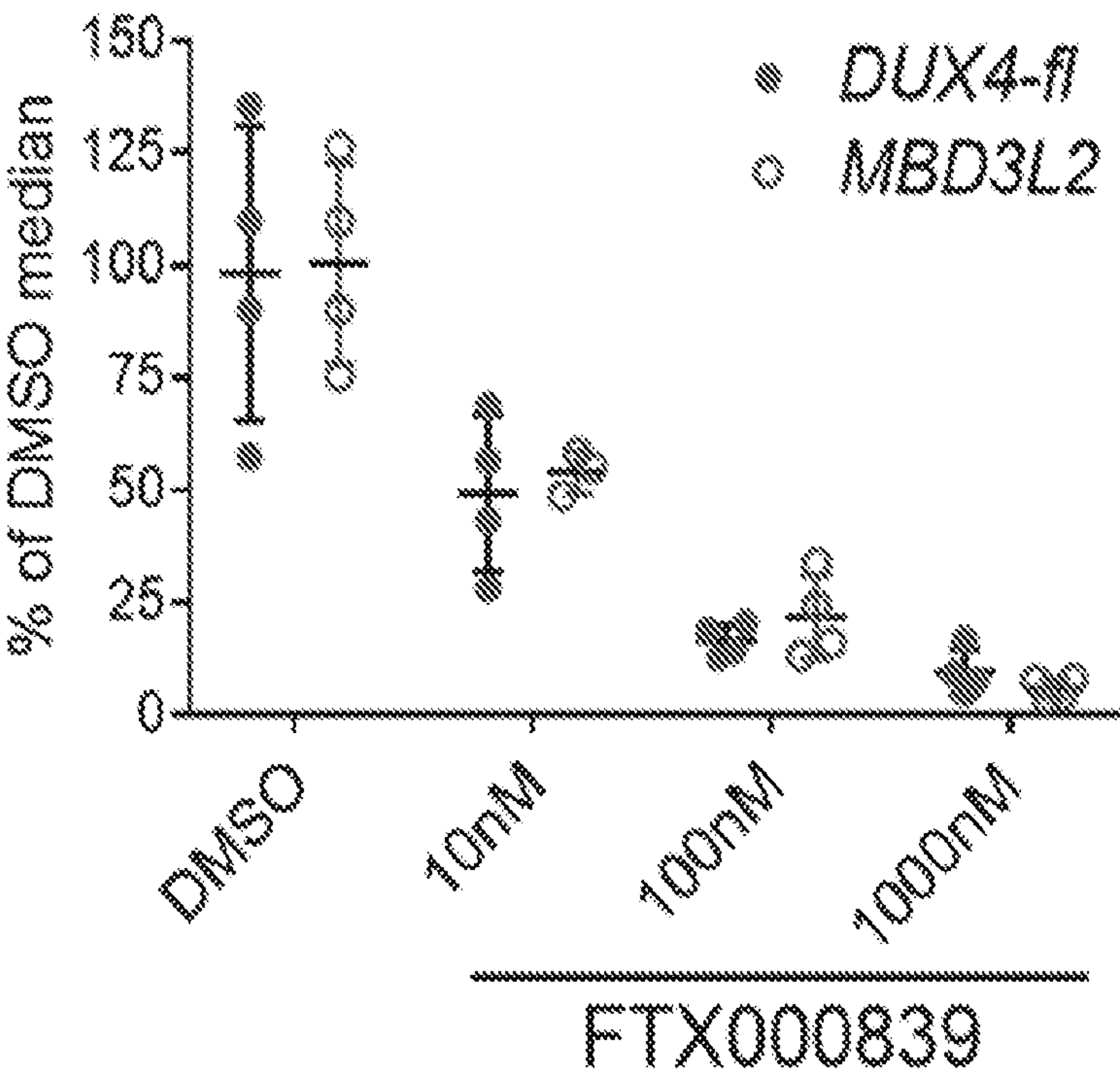


FIG. 5A

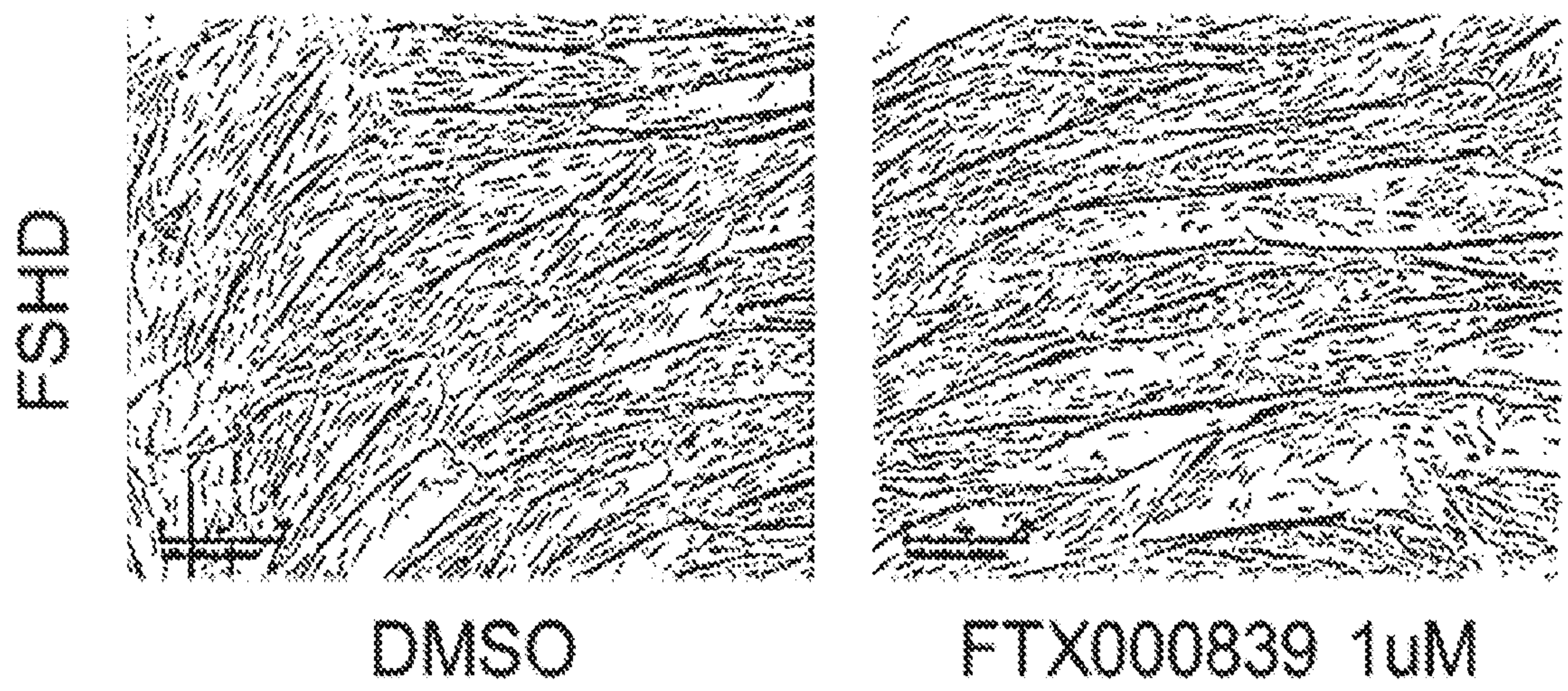


FIG. 5B

FIG. 6A

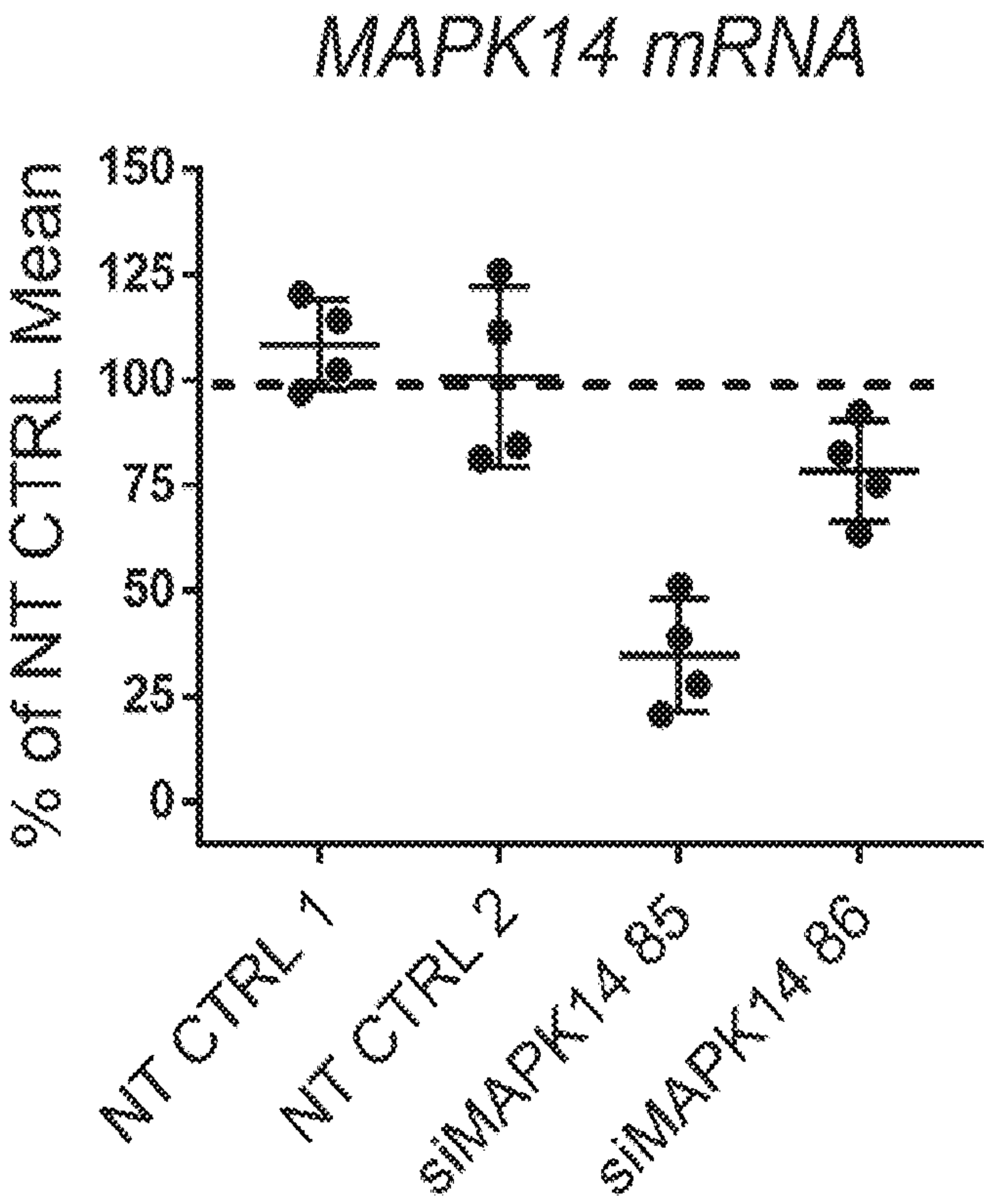


FIG. 6B

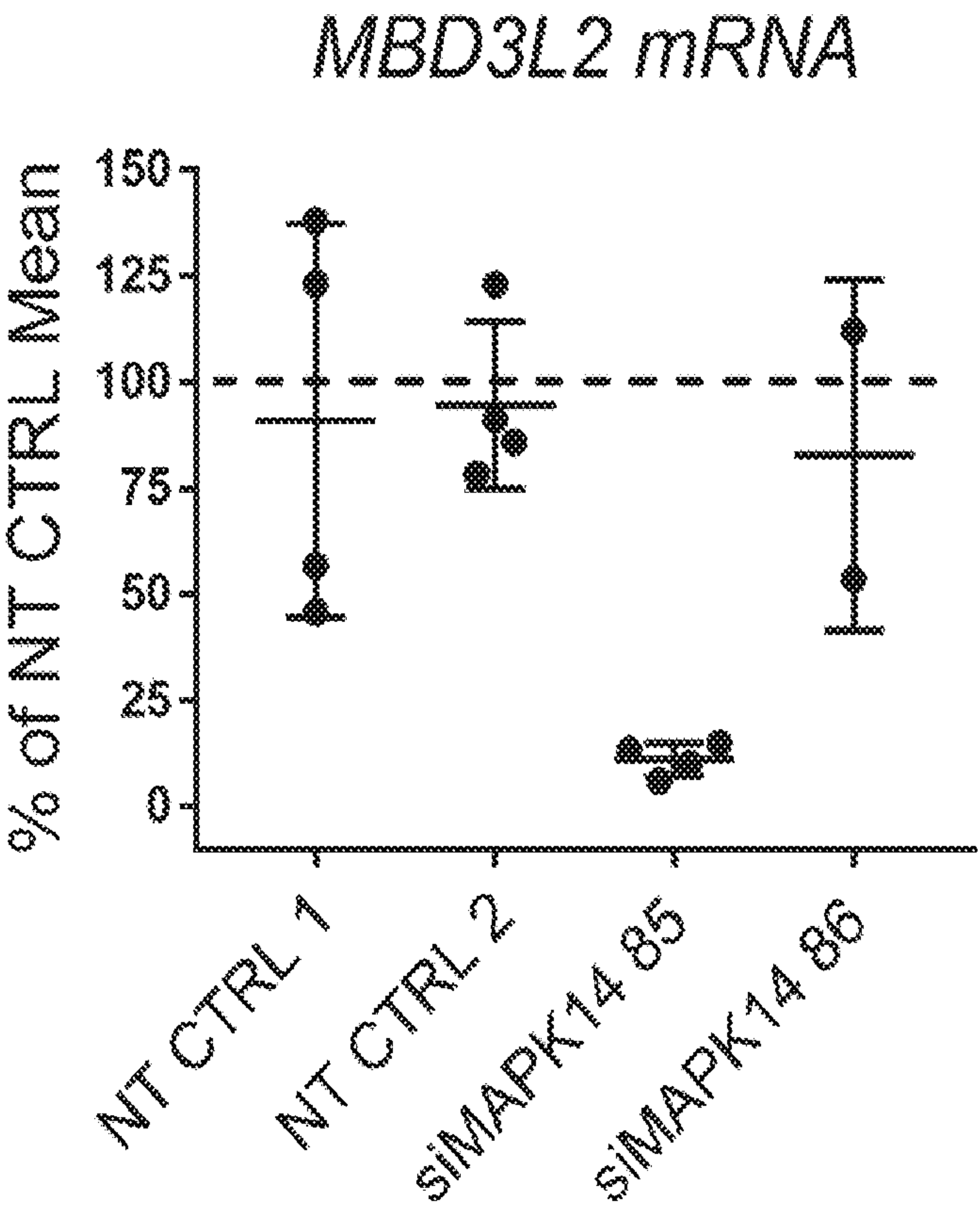
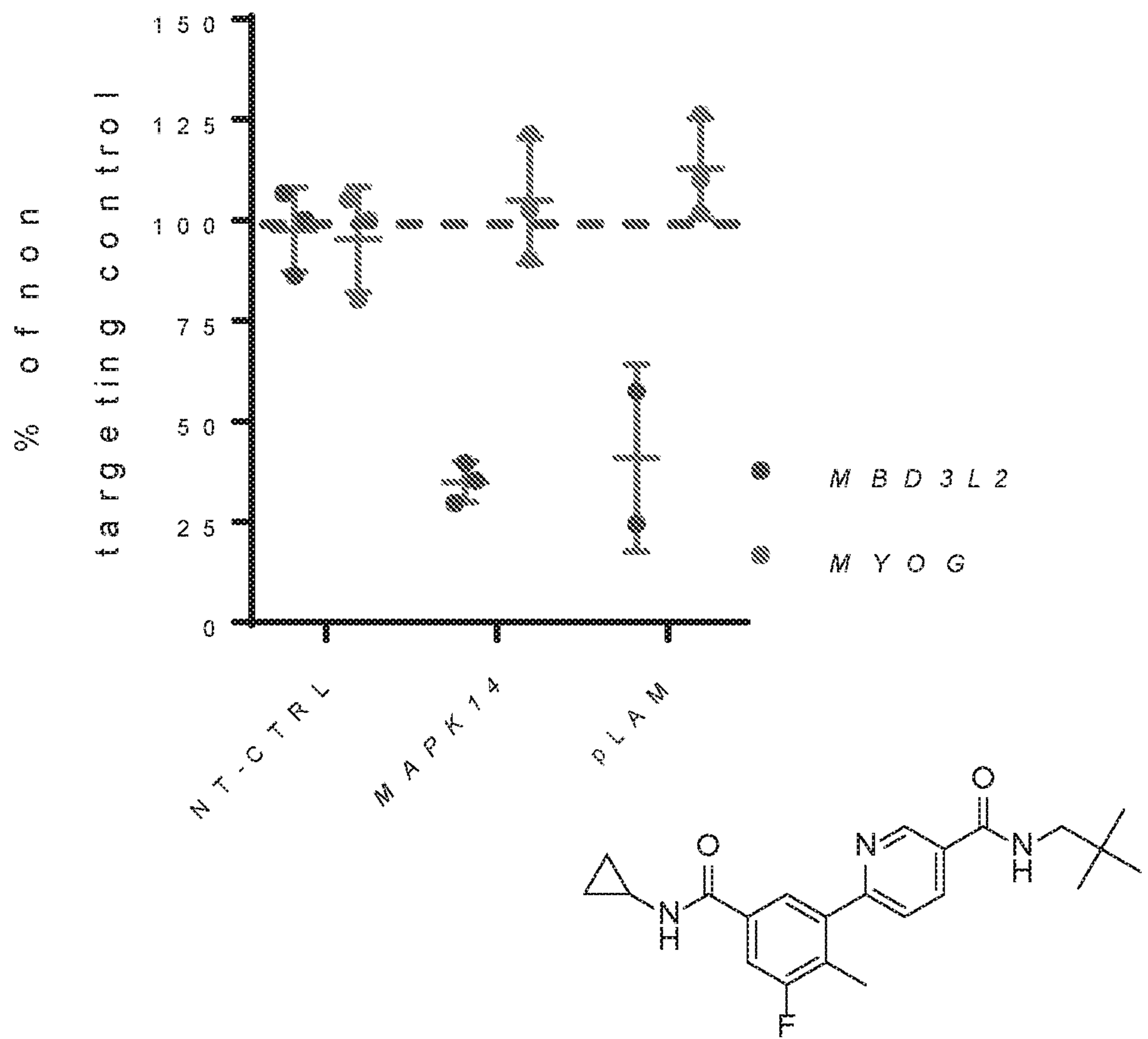
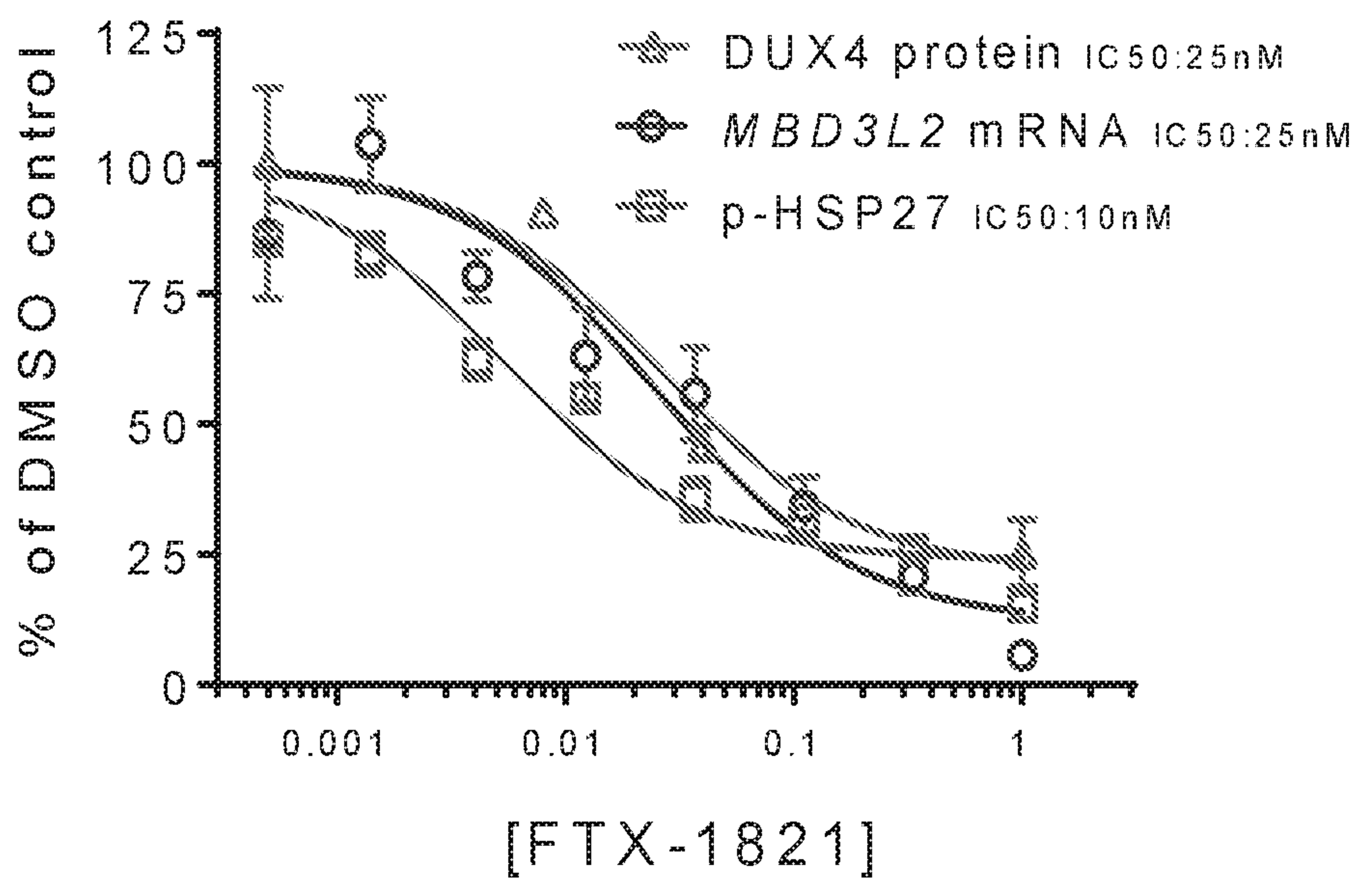


FIG. 6C



FTX-1821

FIG. 7



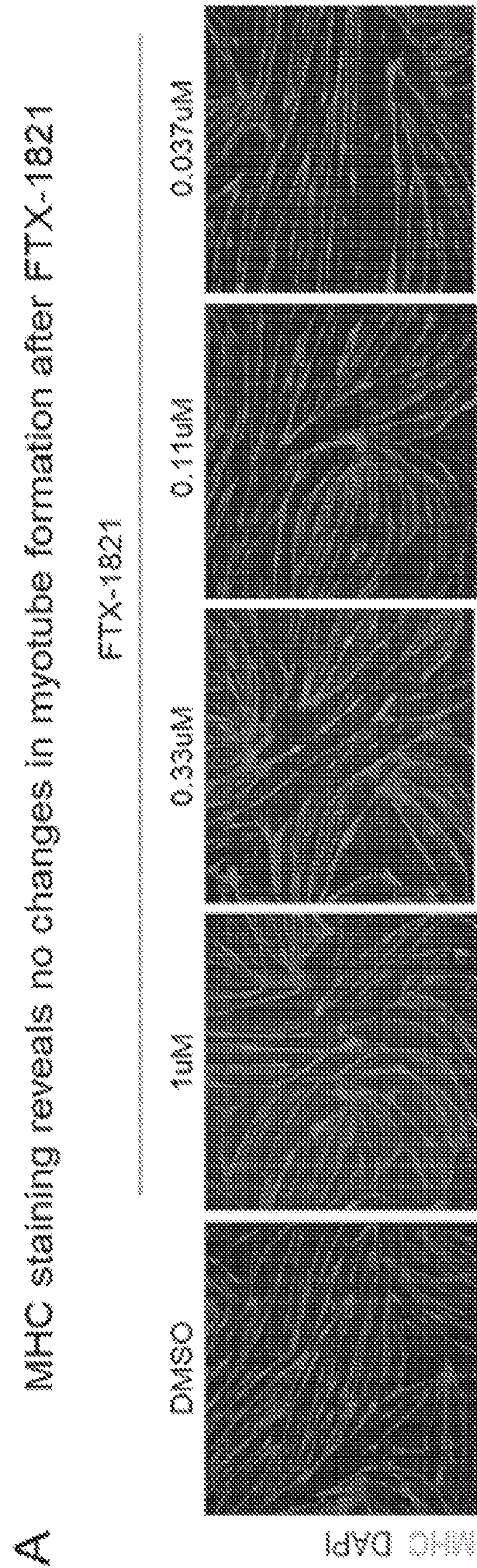
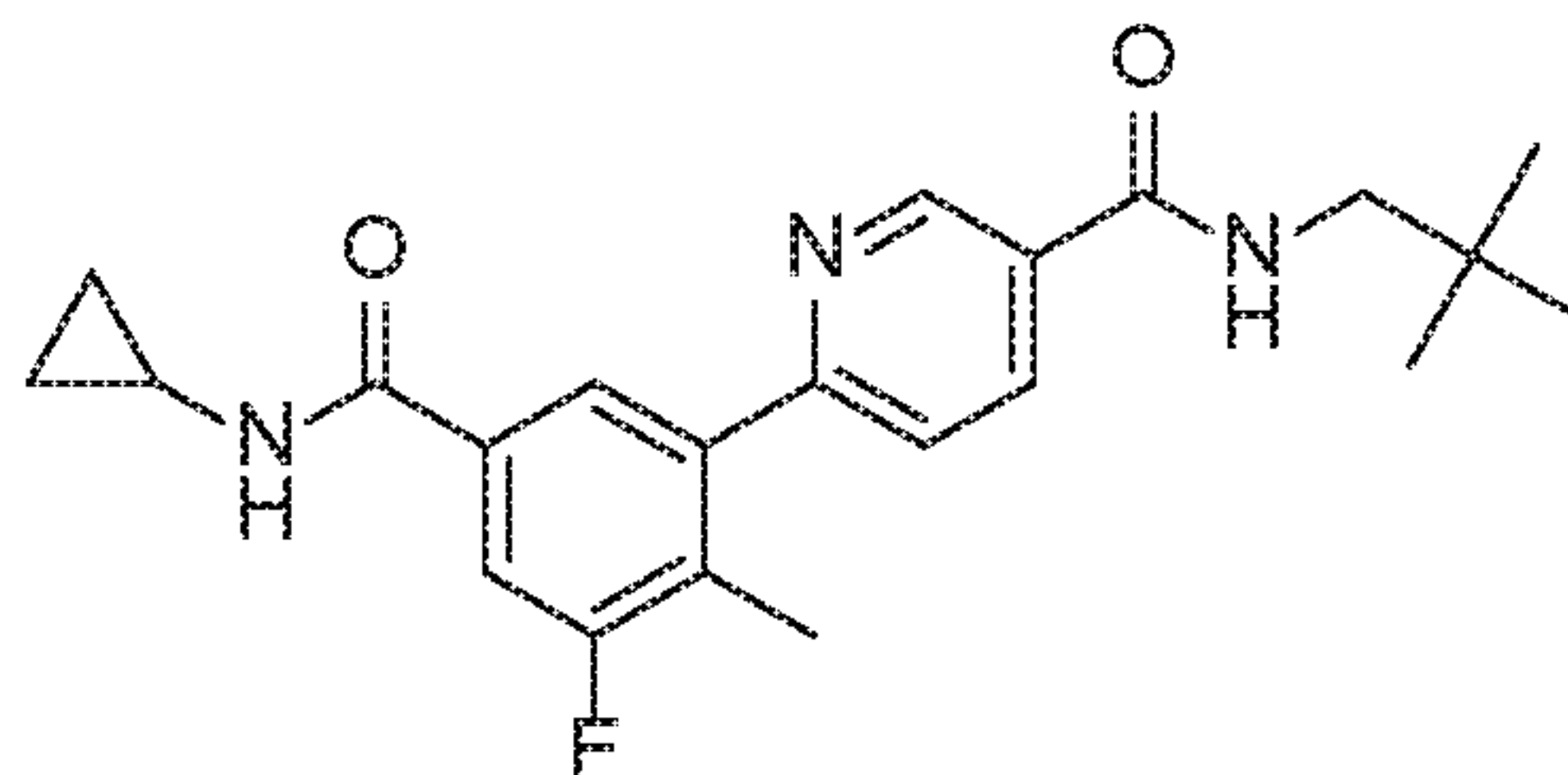


FIG. 8A



FTX-1821

## Quantification of nuclei in MHC+ myotubes after FTX-1821

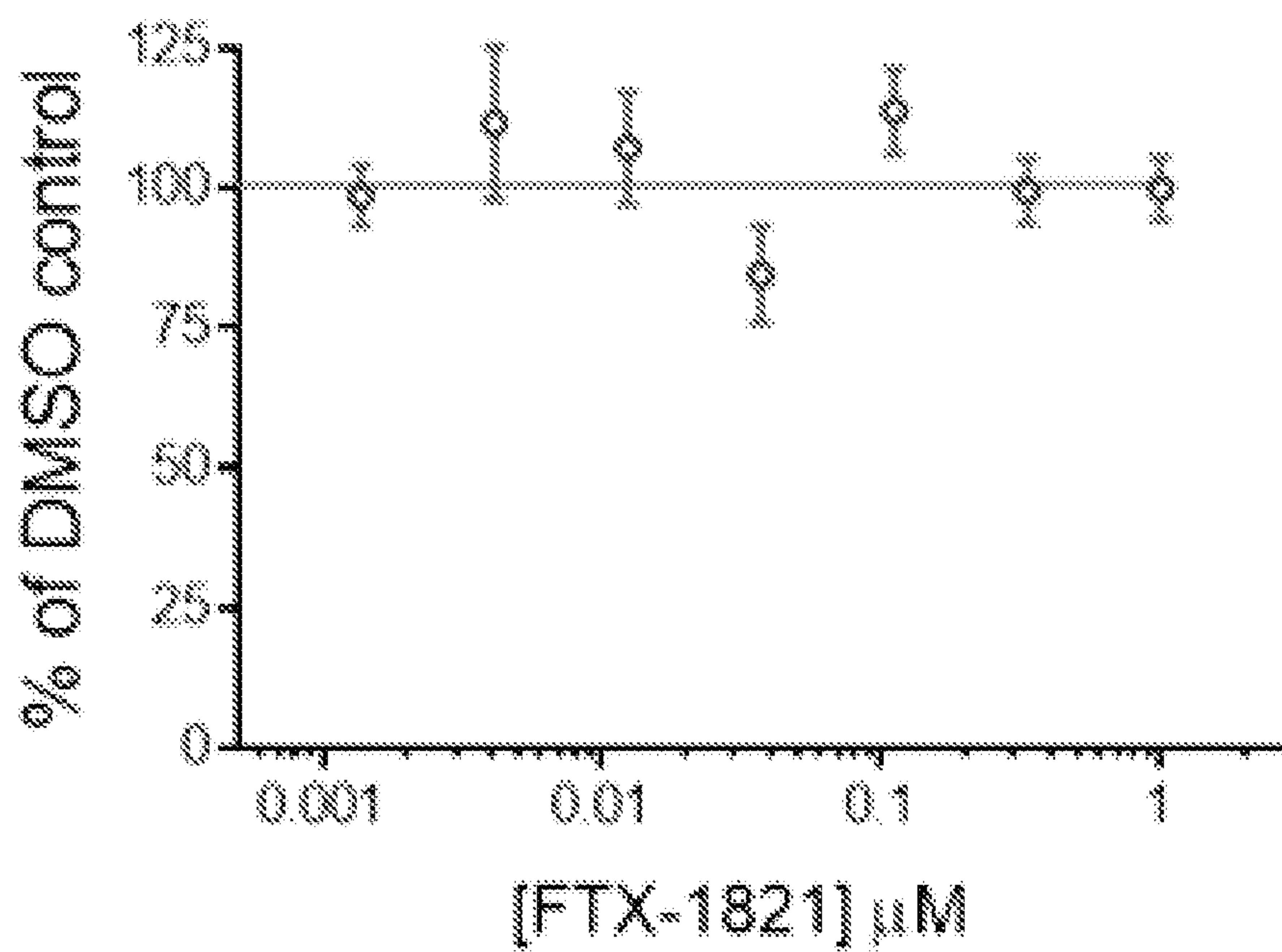


FIG. 8B

Apoptosis detection in FSHD myotubes

A

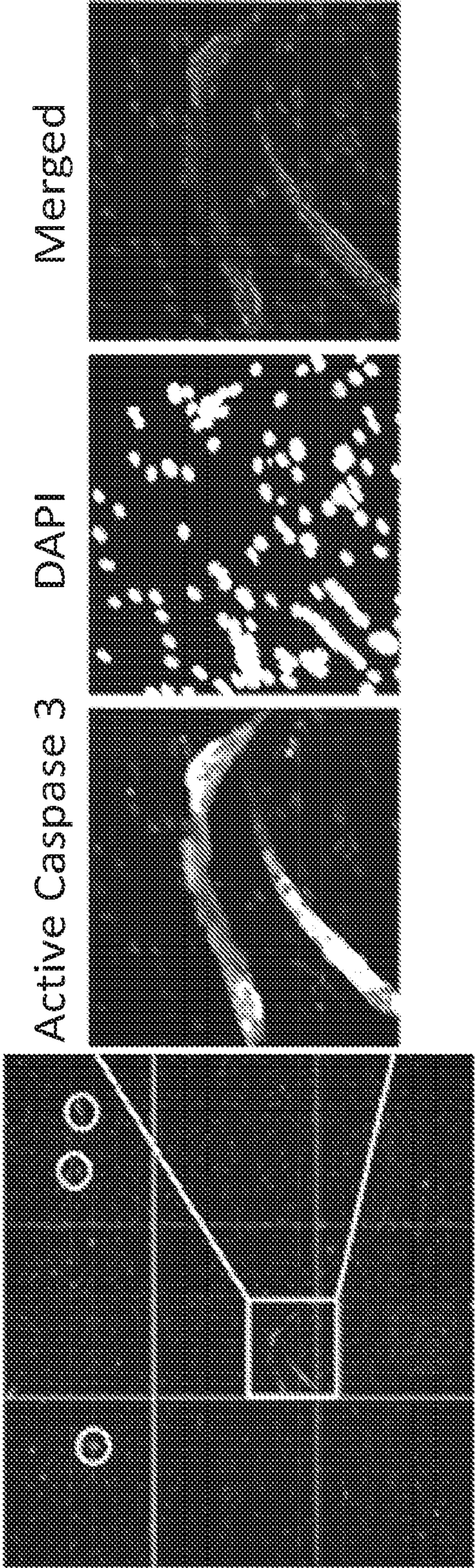


FIG. 9A

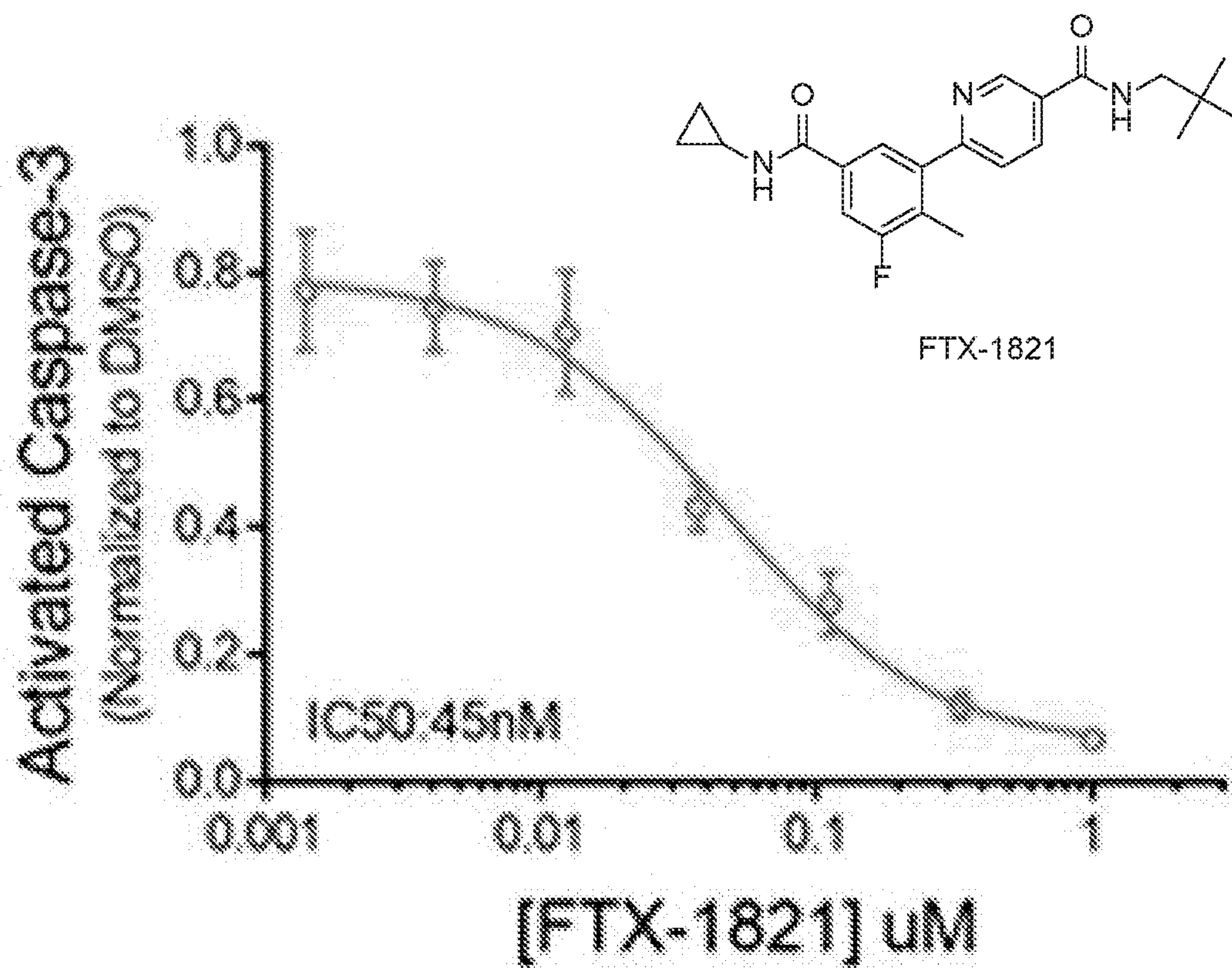
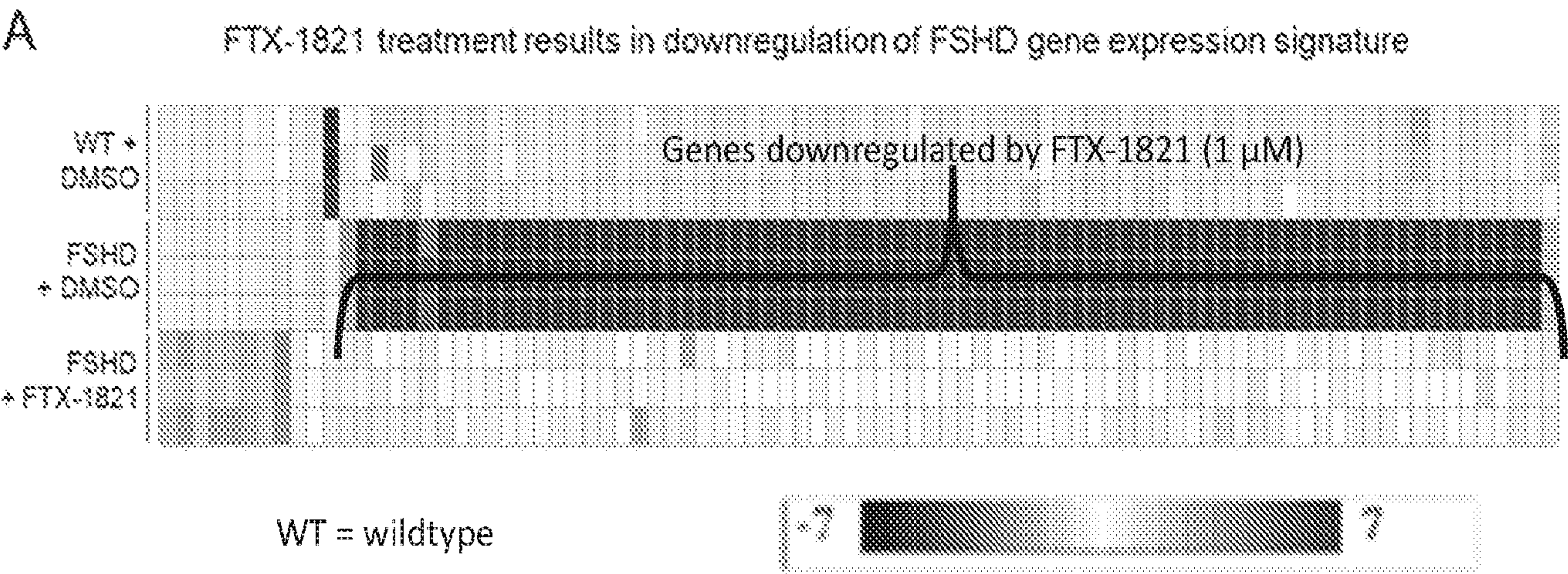


FIG. 9B



Genes downregulated by FTX-1821:

|          |          |          |          |            |           |
|----------|----------|----------|----------|------------|-----------|
| ZSCAN4   | TRIM51BP | MBD3L3   | UBTFL5   | AP001043.1 | ABRA      |
| PRAMEF20 | KHDC1P1  | KDM4F    | HNRNPCL3 | MBD3L5     | WIPF3     |
| PRAMEF6  | RFPL4A   | DUXA     | ZIM3     | TRIM51CP   | UBTFL1    |
| PRAMEF17 | ZSCAN5DP | TPRX1    | TRIM53BP | TRIM53CP   | POU5F1B   |
| PRAMEF1  | PRAMEF9  | PRAMEF13 | TRIM53AP | CILP       | UBTFL2    |
| ZNF705E  | KLF17    | TRIM43   | DPPA3    | SLC2A3     | FAM151A   |
| LEUTX    | RFPL2    | MBD3L2   | MBD3L2B  | TRIM49     | TRIM60    |
| PRAMEF15 | CCNA1    | PRAMEF11 | USP29    | ZNF705G    | PRAMEF28P |
| ZNF705A  | PRAMEF2  | PRAMEF14 | ZNF296   | TRIM43CP   | KLF18     |
| PRAMEF12 | HNRNPCL1 | KHDC1L   | F2RL1    | TRIM48     | SNAI1P1   |
| SLC34A2  | DUXB     | PRAMEF19 | FREM2    | UBTFL6     | HUNK      |
| HNRNPCL2 | HSPA6    | PRAMEF4  | PRAMEF8  | PRAMEF33   | P2RX1     |
| PRAMEF18 | TRIM43B  | KDM4E    | TRIM51   | C1DP2      | TPRX2P    |
| TRIM49C  | TC2N     | TRIM49B  | IGFN1    | DPYSL5     | FAM9C     |
|          |          |          |          |            | GJA5      |
|          |          |          |          |            | IMPG2     |

FIG. 10A

FTX-1821 downregulated  
genes are FSHD specific

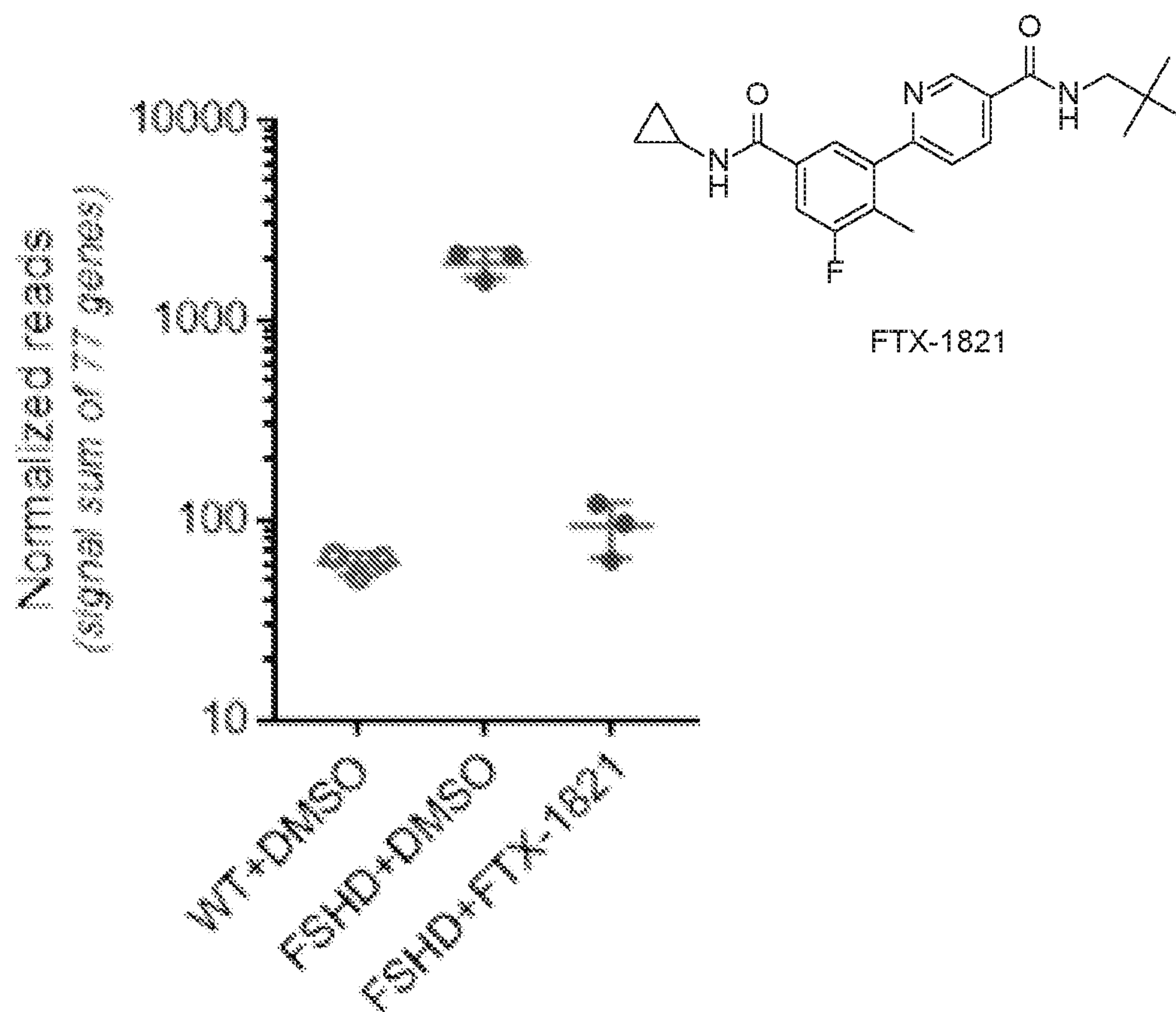


FIG. 10B

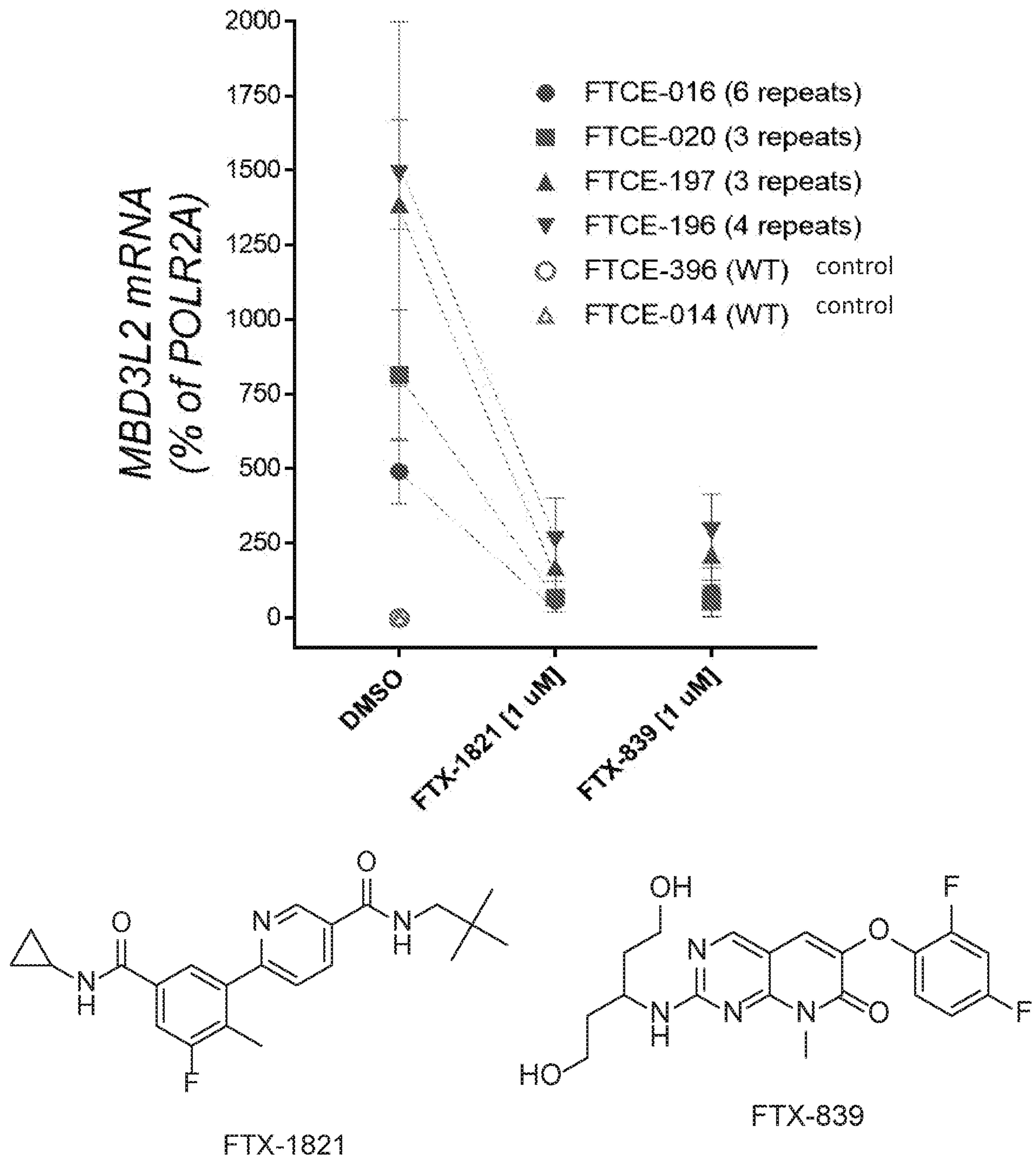


FIG. 11

Table 1.

| DRUG_NAME   | Formatted ID | IC50 <i>MBD3L2</i> (nM) |
|-------------|--------------|-------------------------|
| TAK-715     | FTX000500    | 48                      |
| VX-702      | FTX000638    | 41                      |
| R1487       | FTX000830    | 6                       |
| Pamapimod   | FTX000839    | 10                      |
| AS1940477   | FTX001341    | 20                      |
| Losmapimod  | FTX001821    | 30                      |
| LY2228820   | FTX002865    | 10                      |
| SCIO-469    | FTX004078    | 25                      |
| Doramapimod | FTX004385    | 42                      |
| BMS-582949  | FTX005041    | 68                      |
| PH-797804   | FTX005042    | 10                      |
| Pexmetinib  | FTX005043    | 5                       |

FIG. 12A

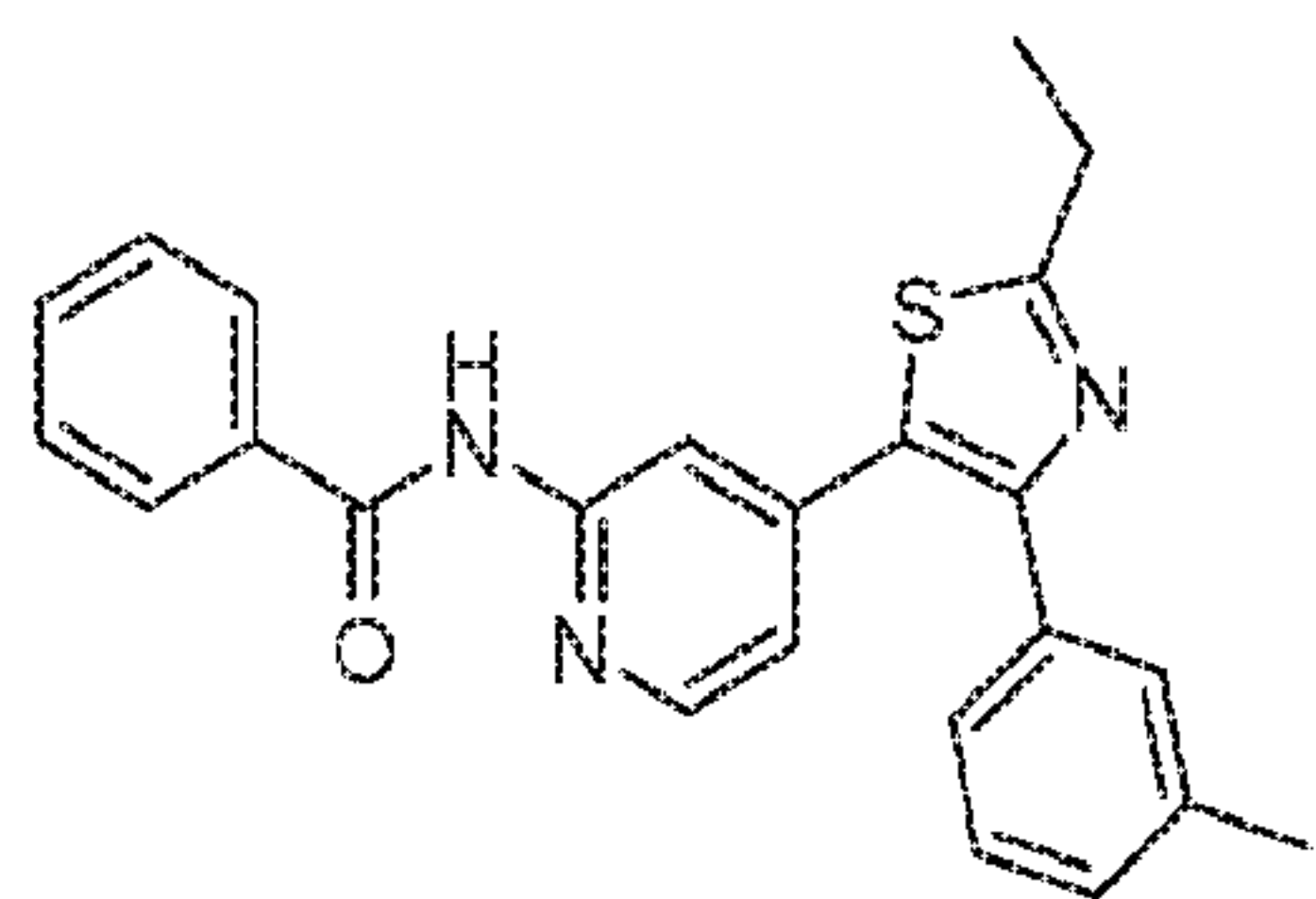
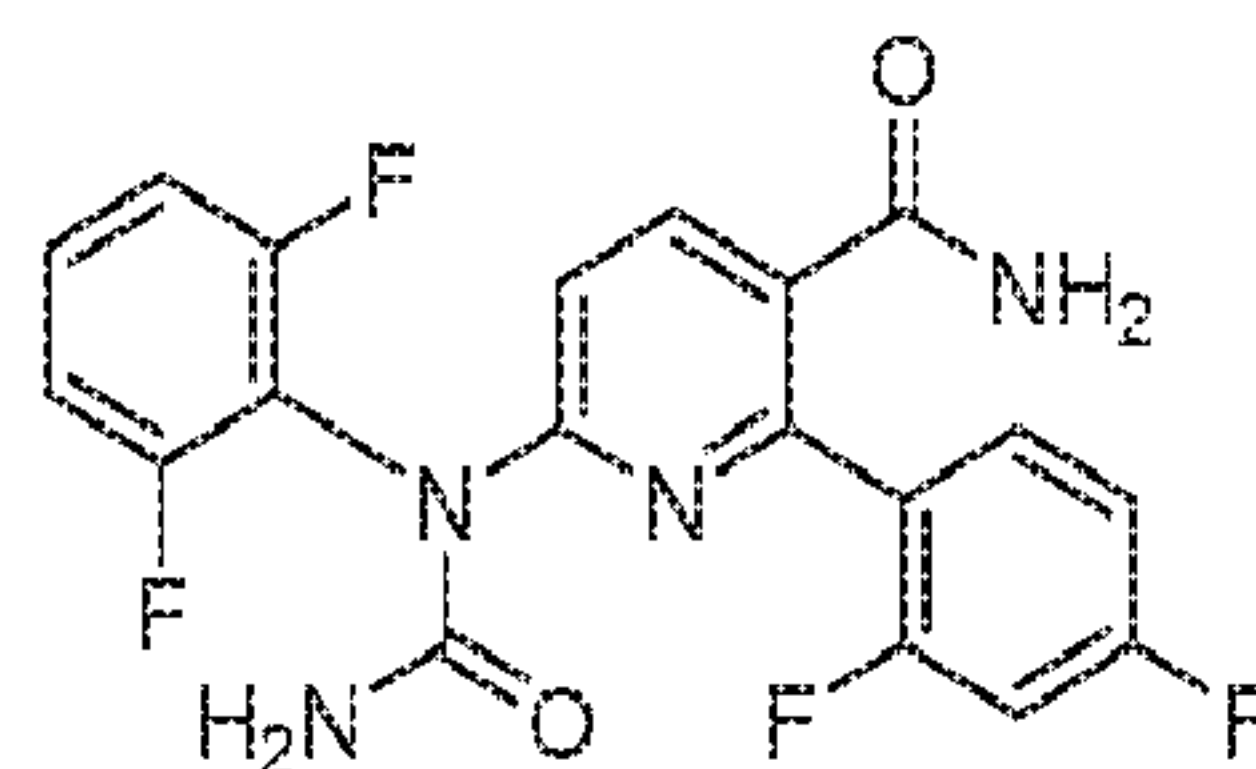
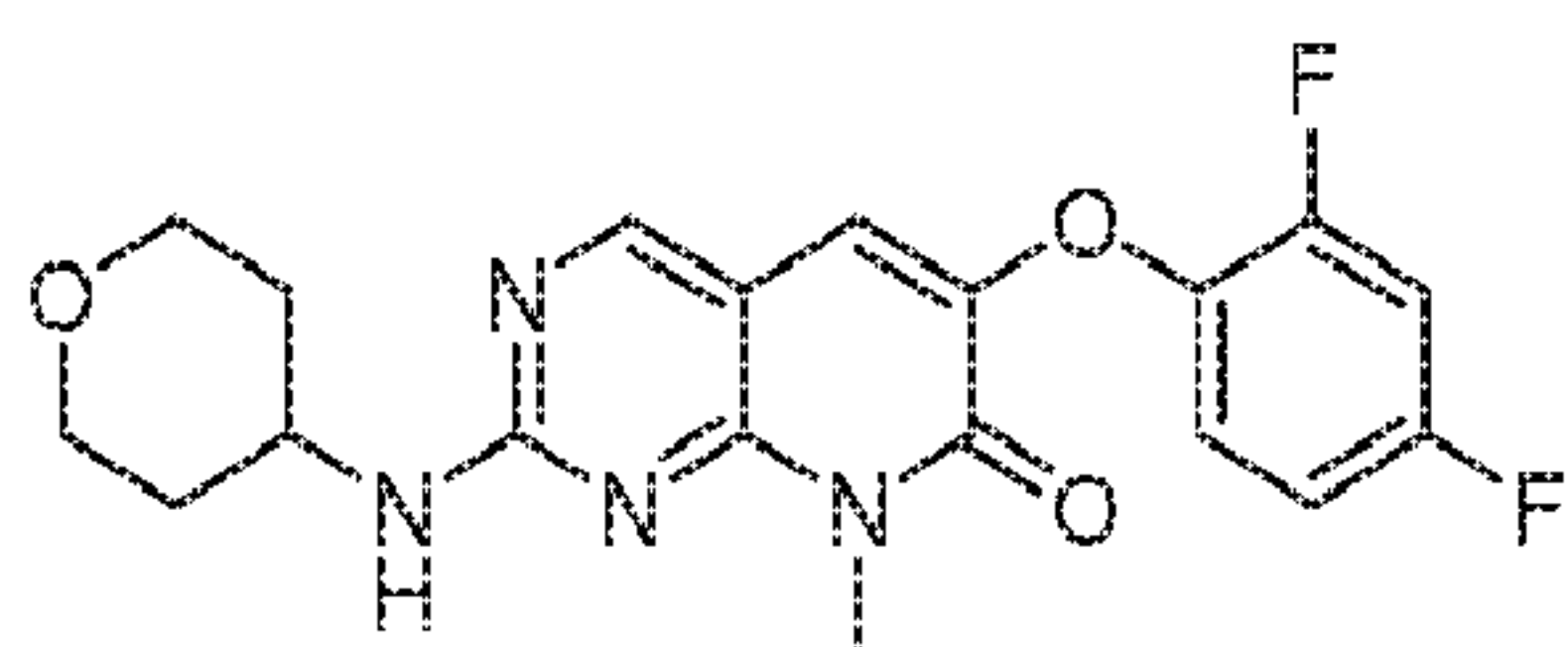
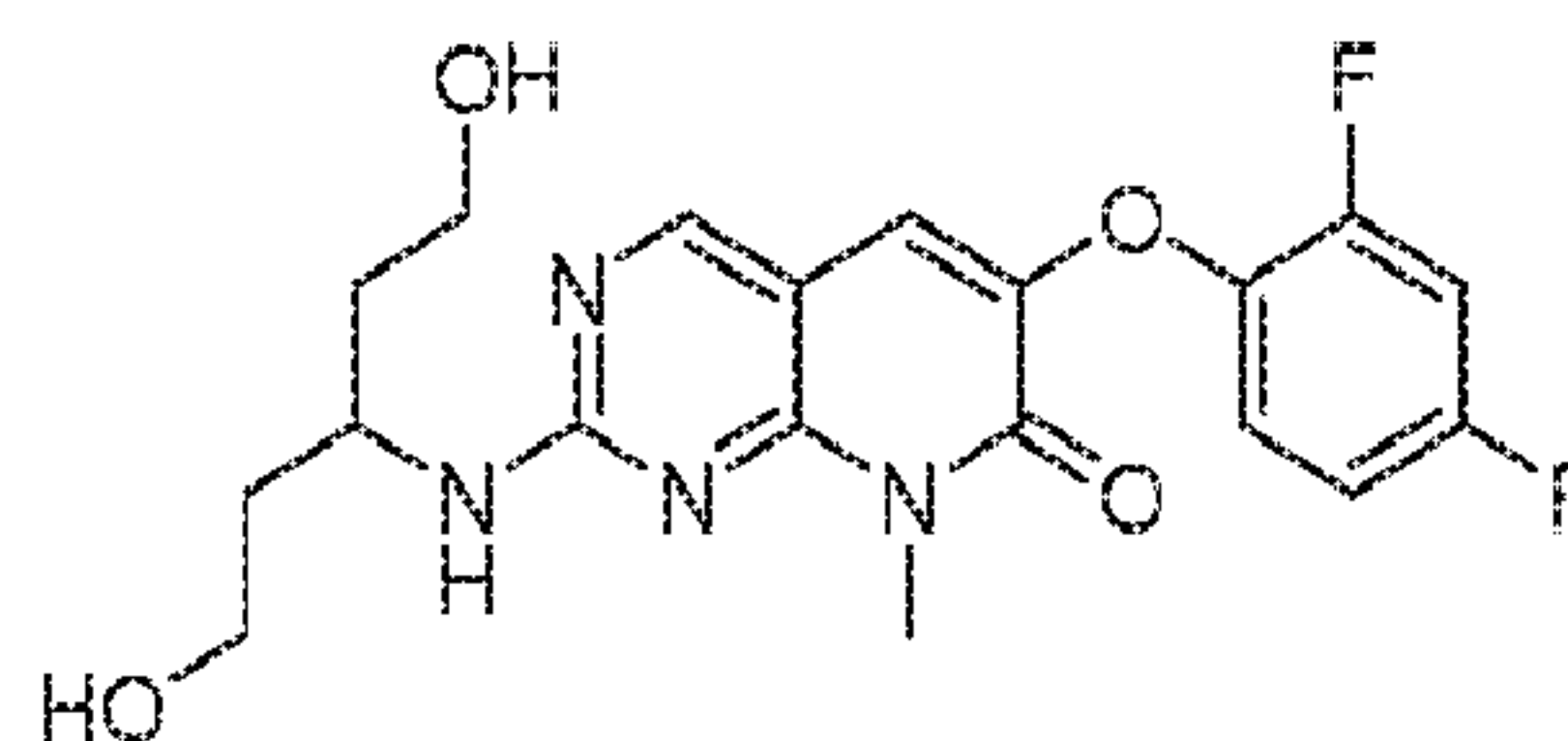
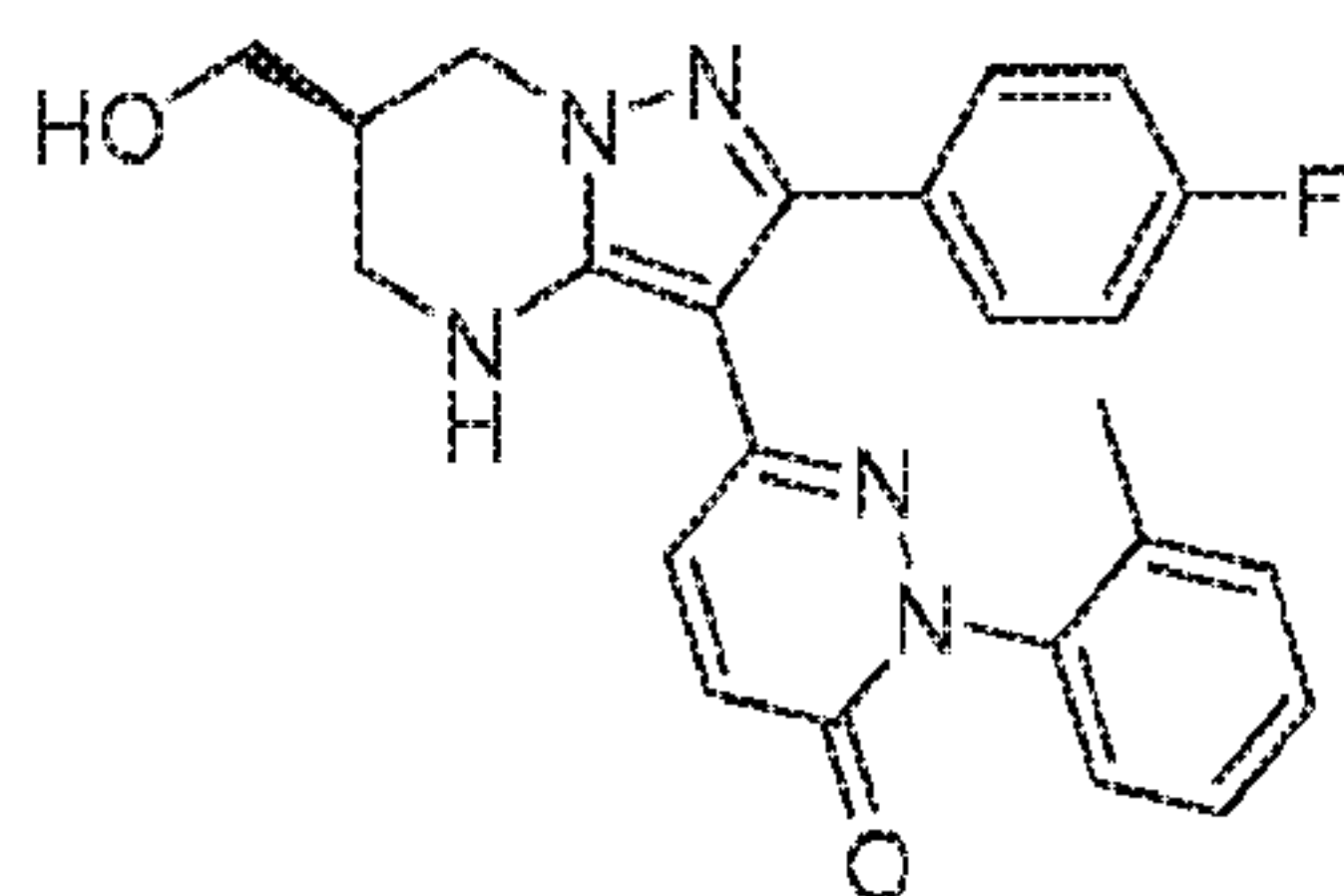
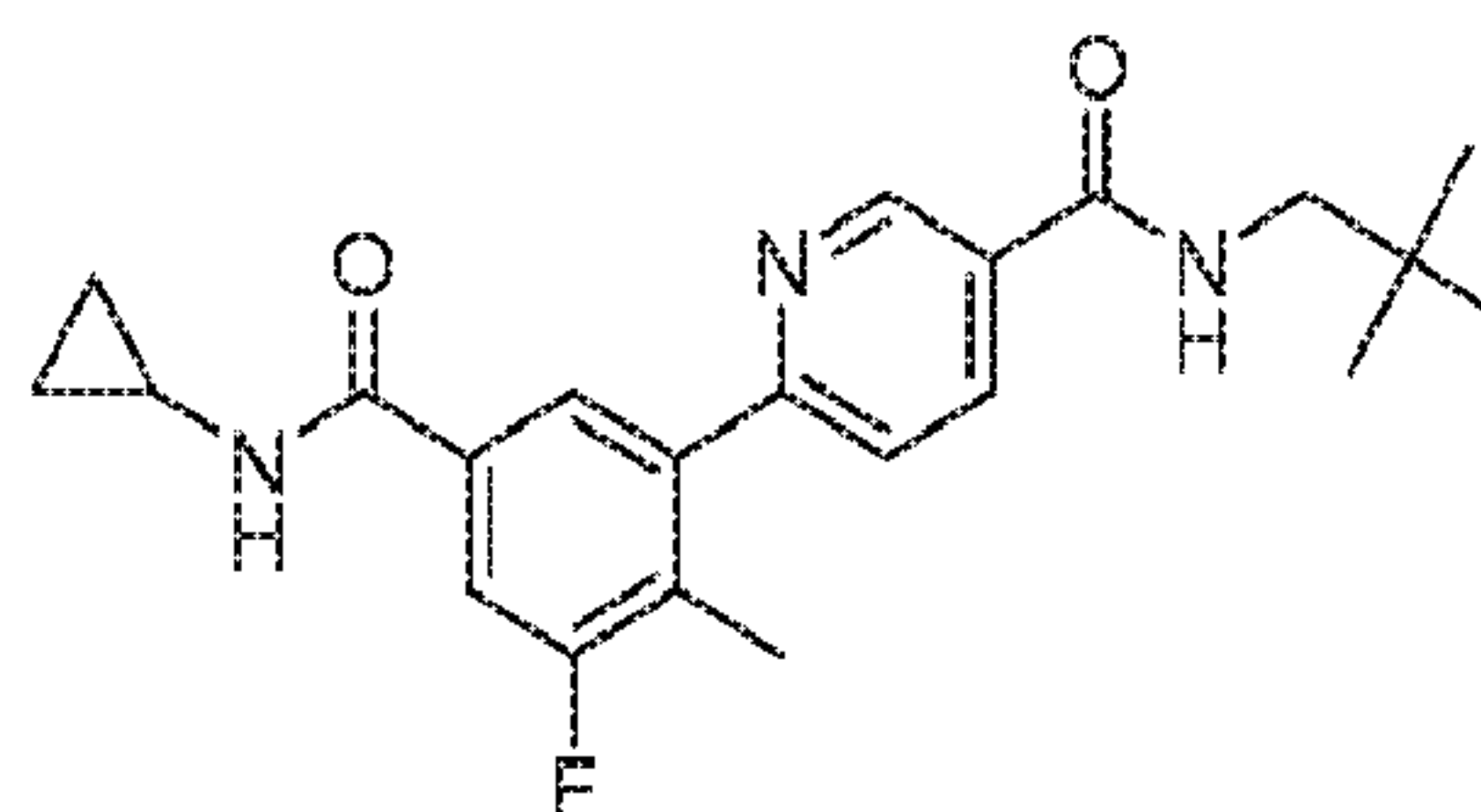
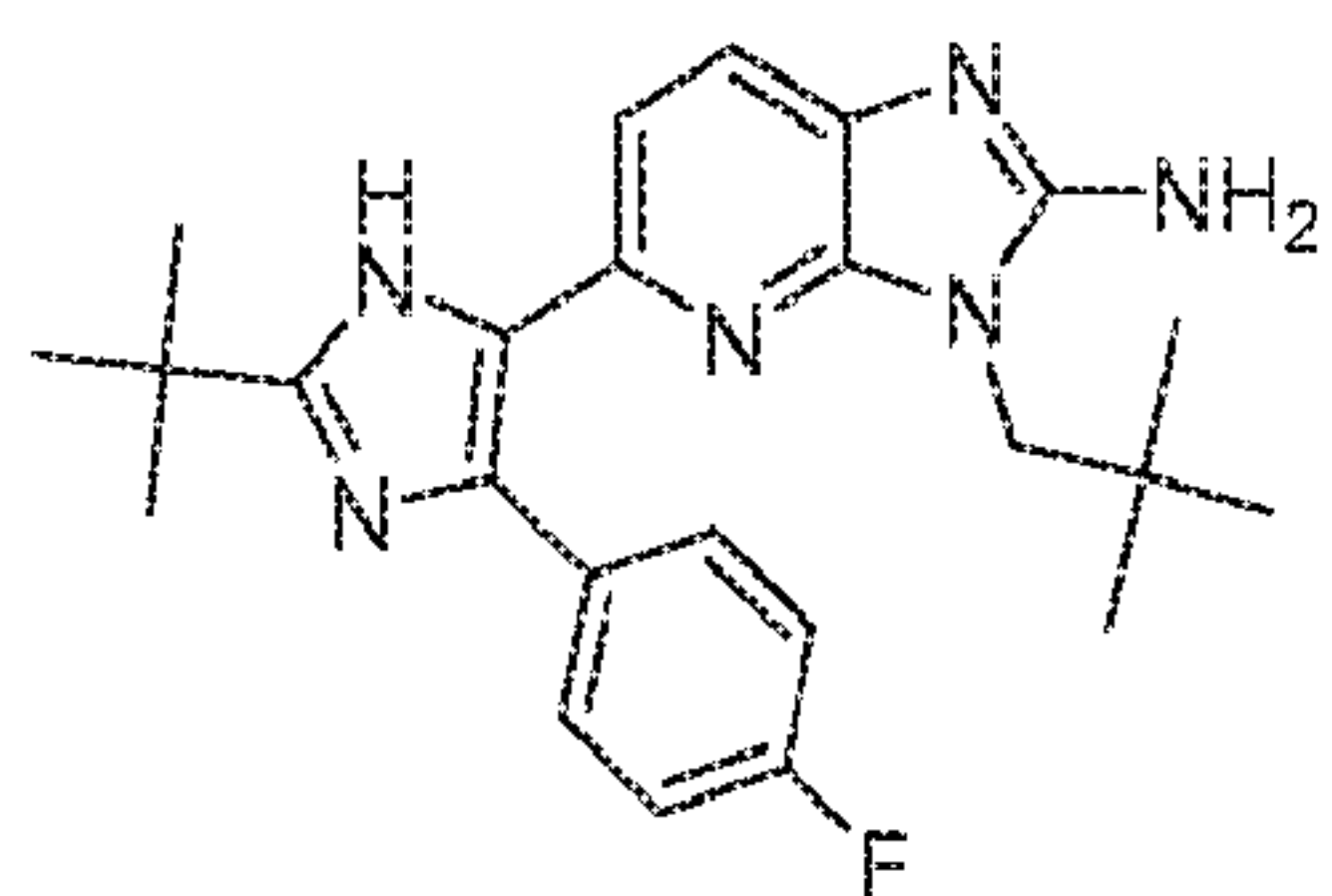
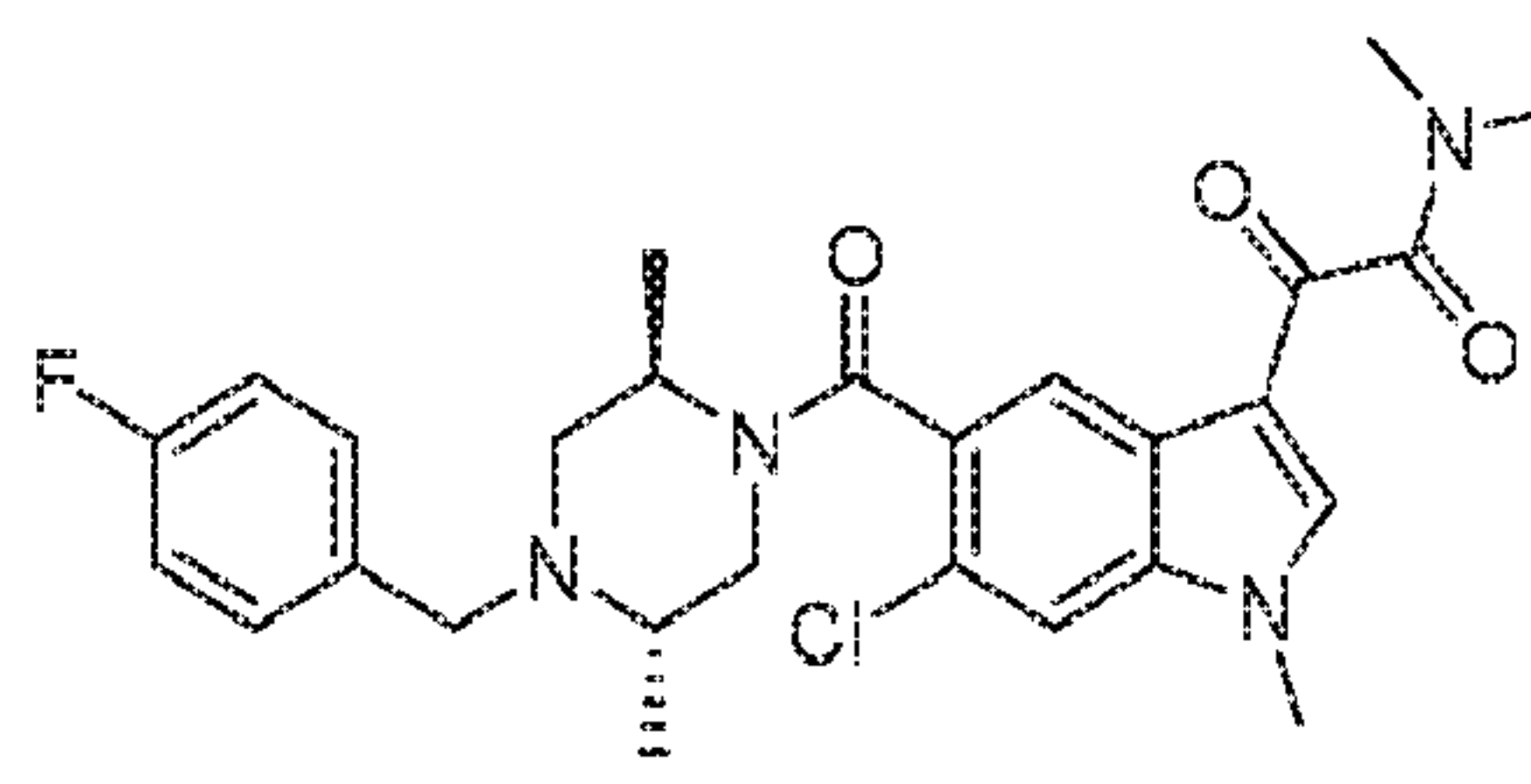
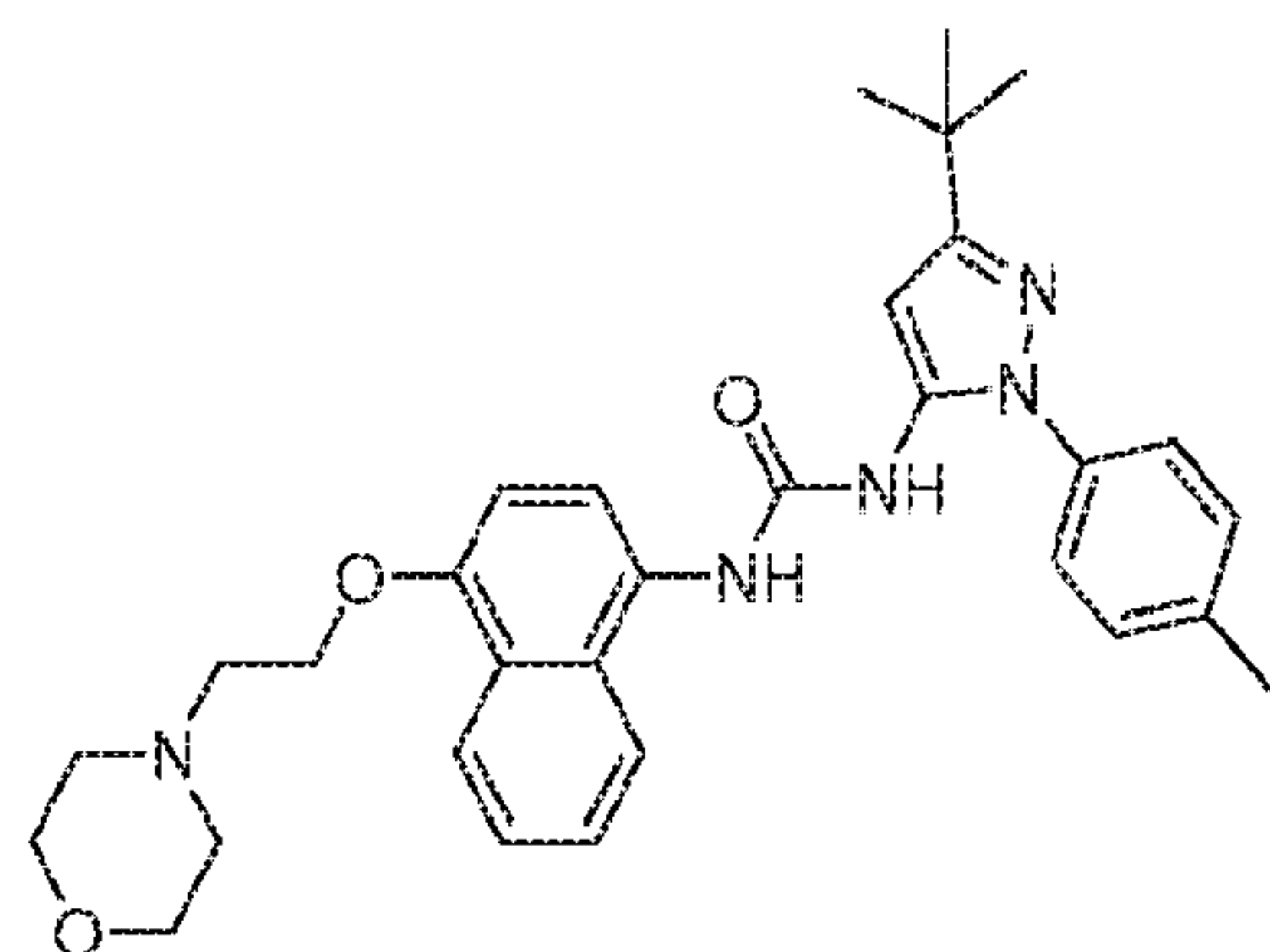
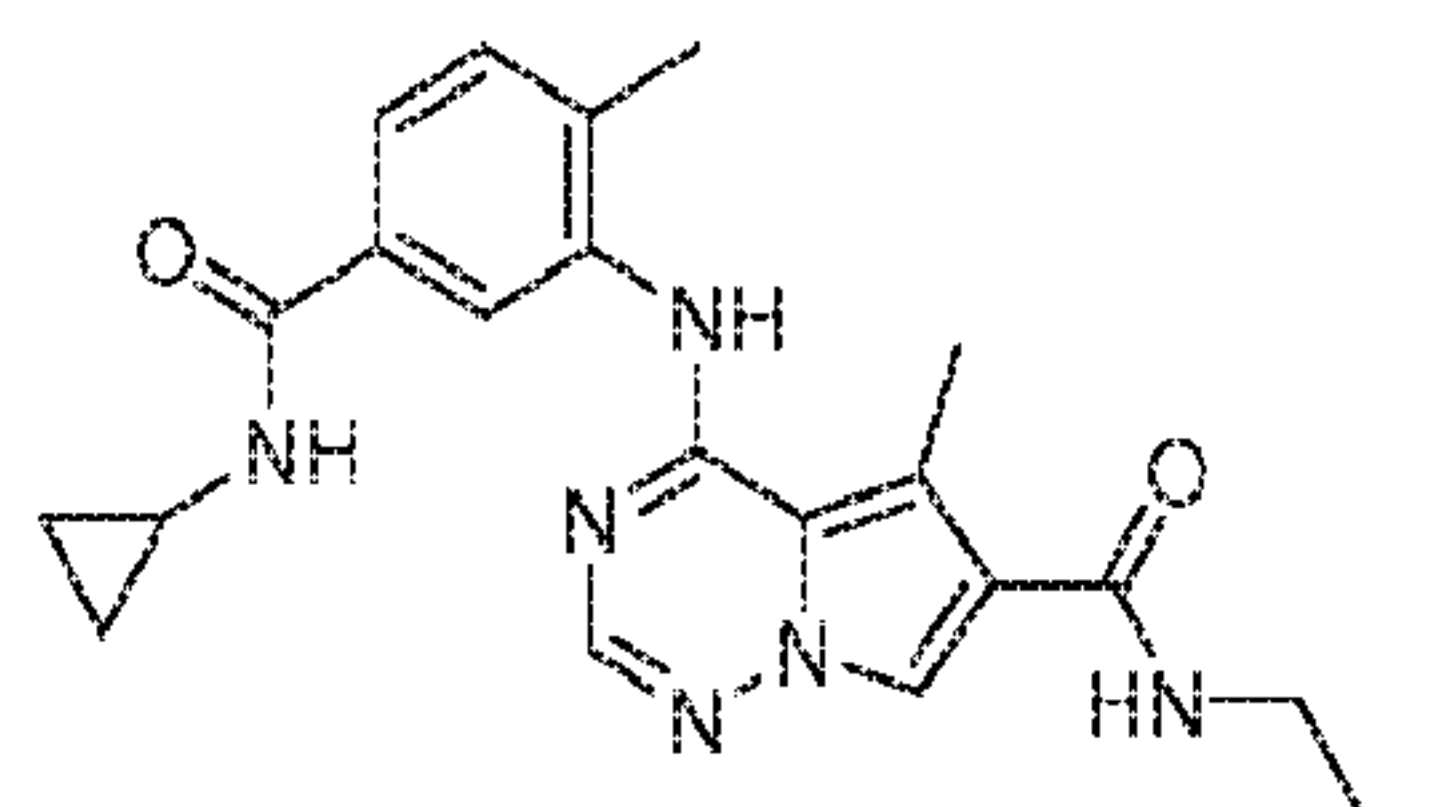
FTX-500  
"TAK-715"FTX-638  
"VX-702"FTX-830  
"R1487"FTX-839  
"Pamapimod"FTX-1341  
"AS1940477"FTX-1821  
"Losmapimod"FTX-2865  
"LY2228820"FTX-4078  
"SCIO-469"

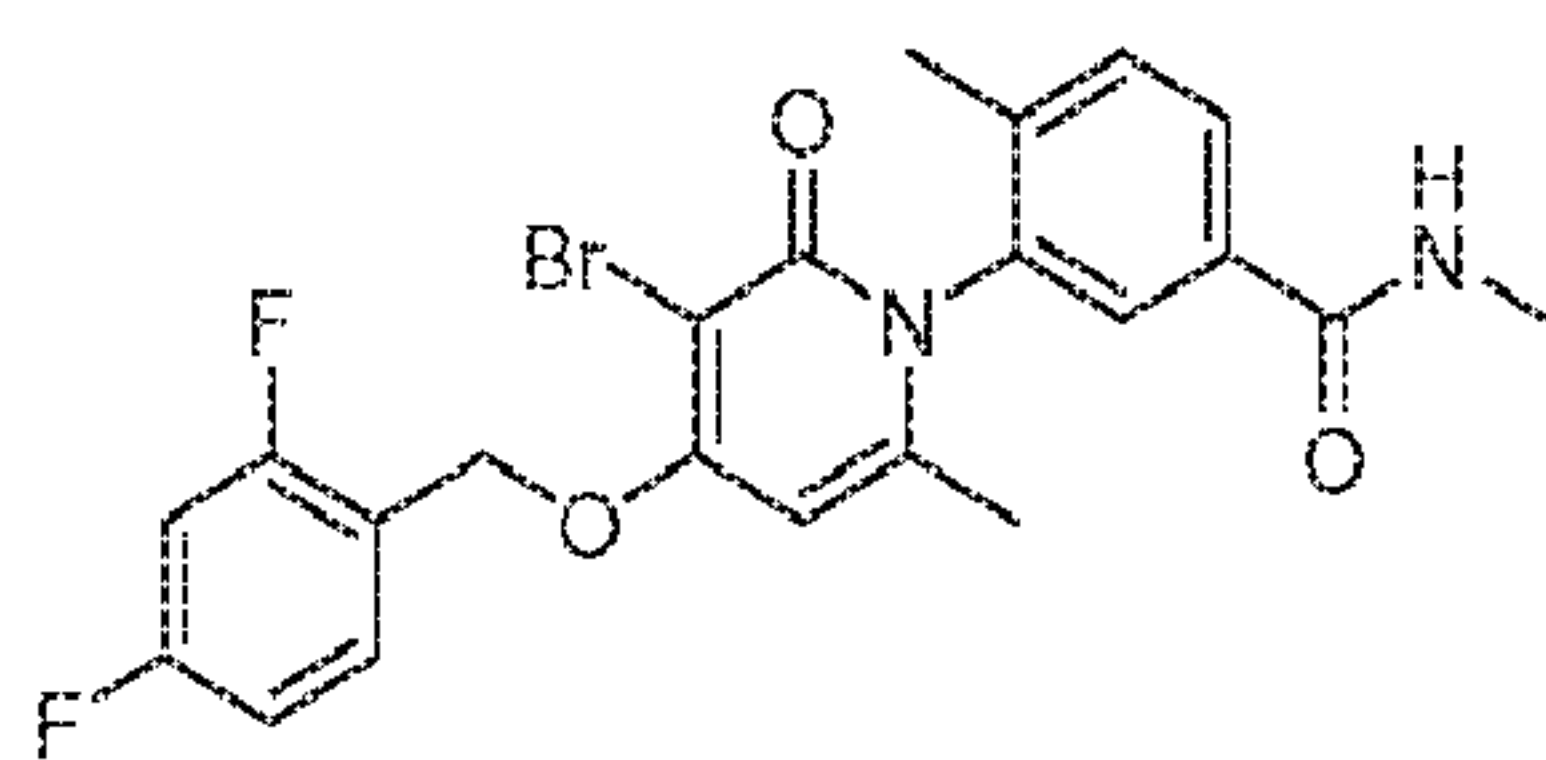
FIG. 12B



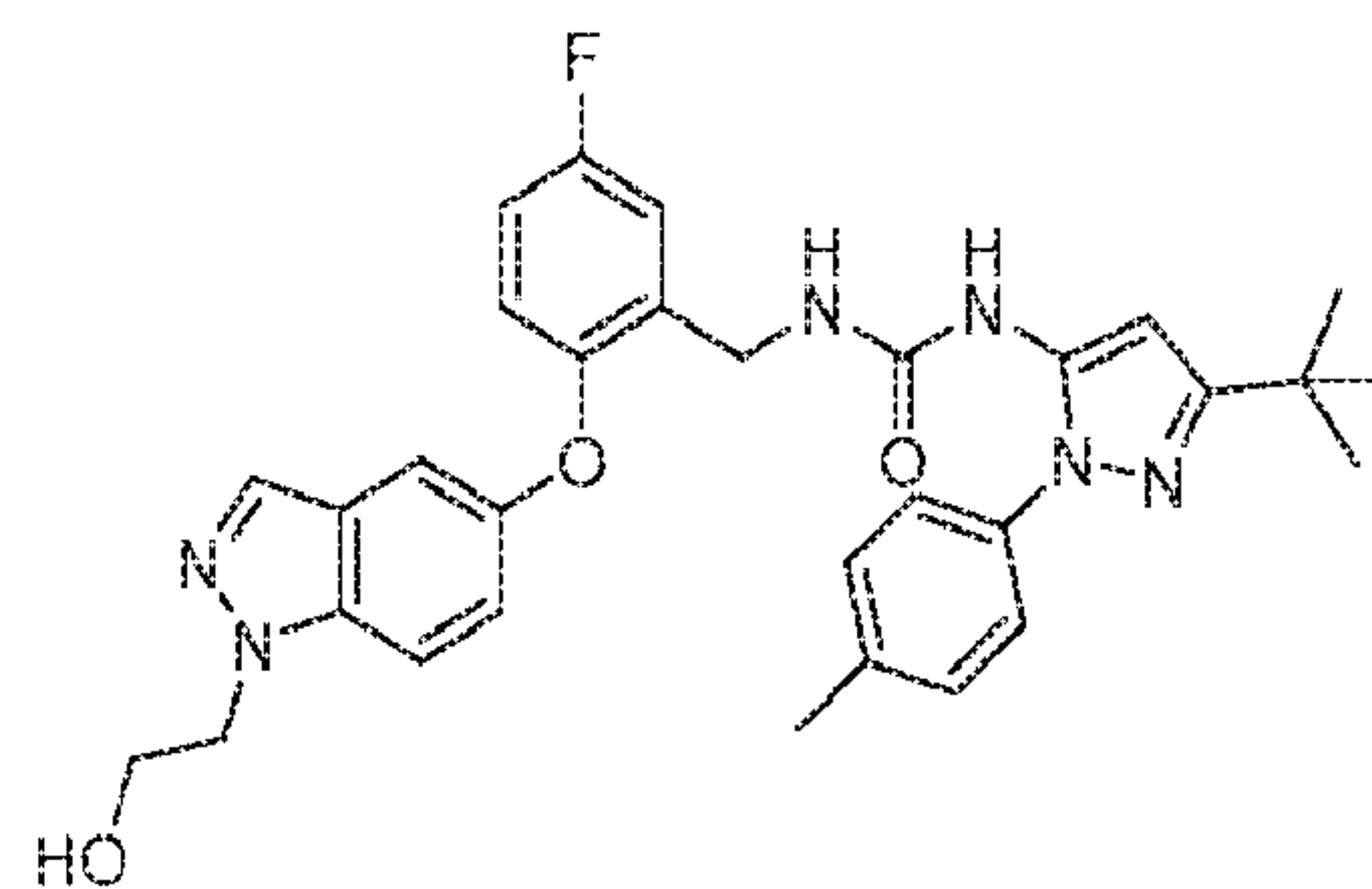
FTX-4385  
"Doramapimod"



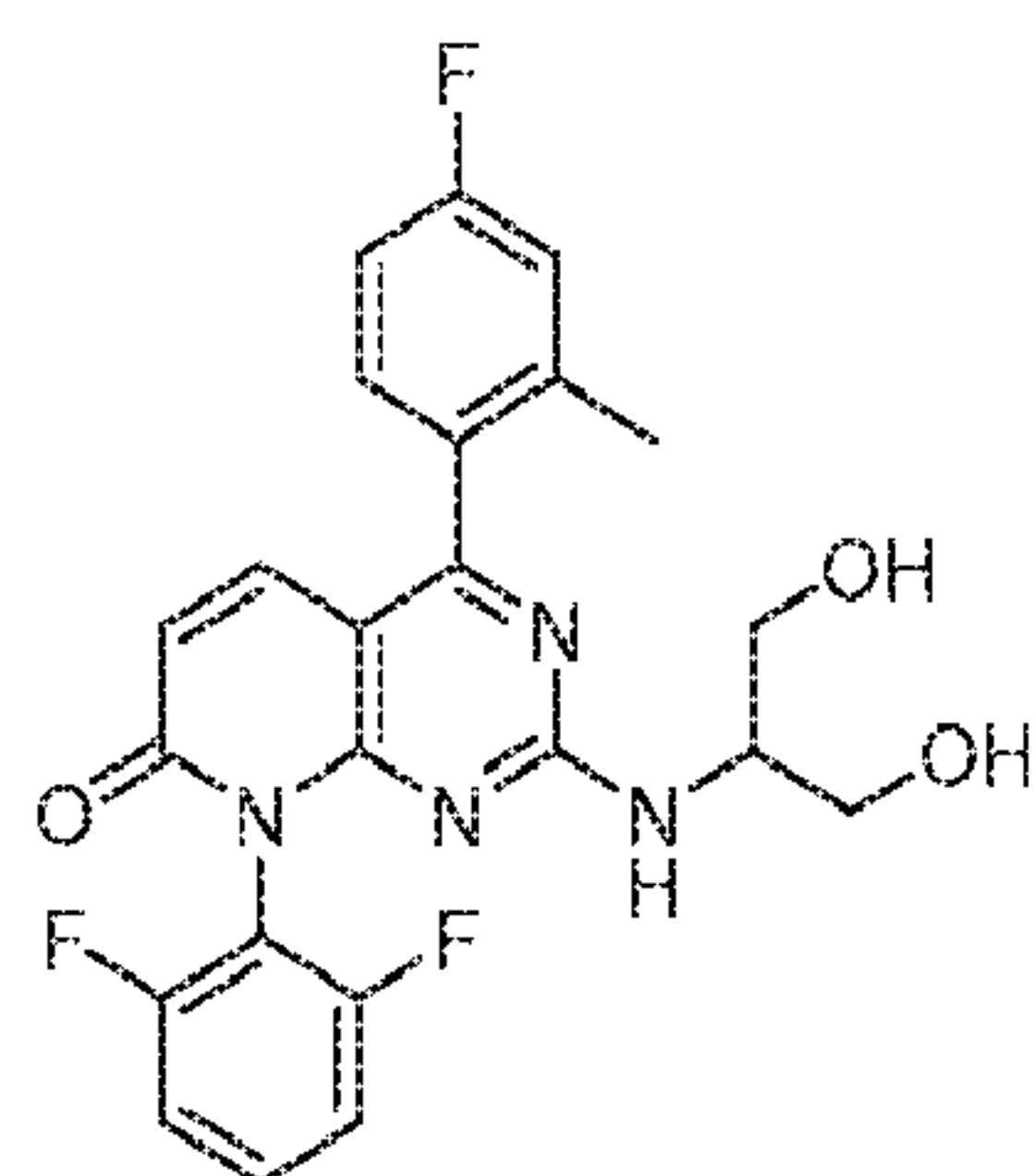
FTX-5041  
"BMS-582949"



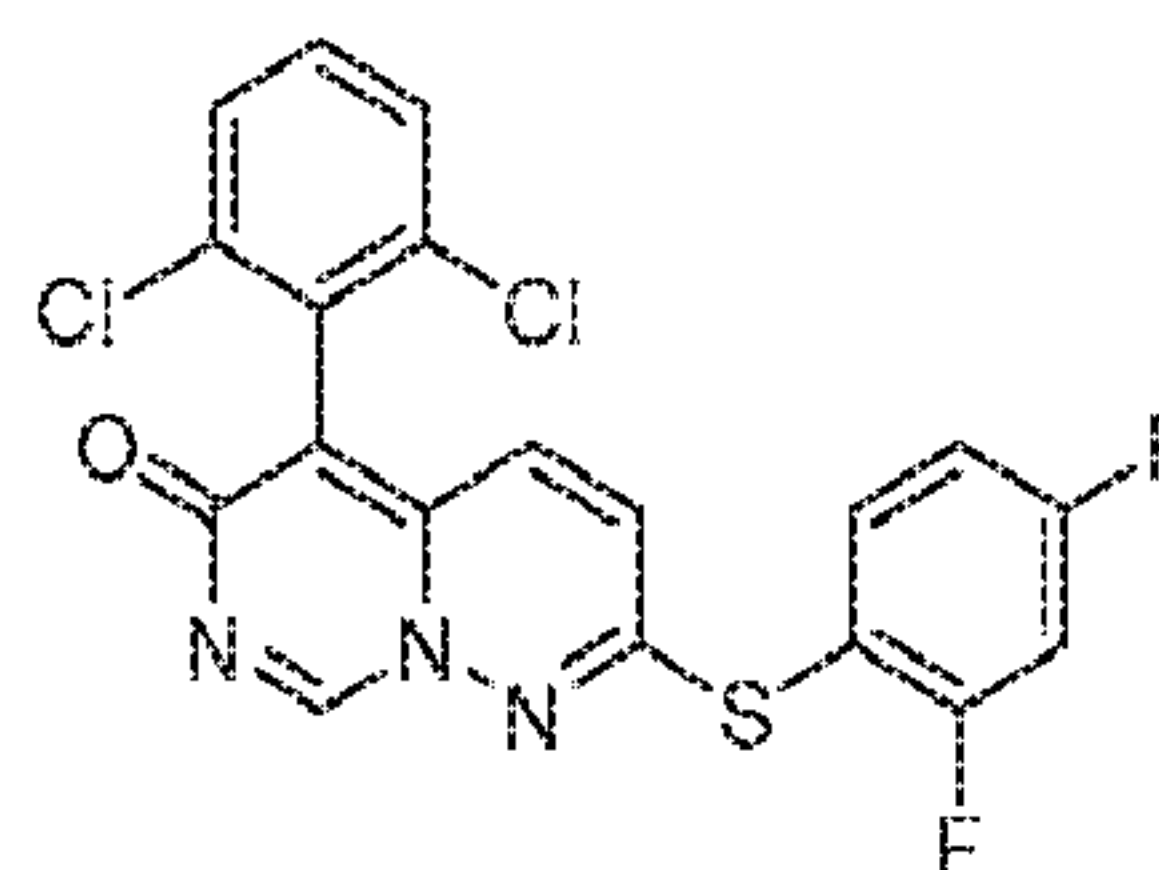
FTX-5042  
"PH-797804"



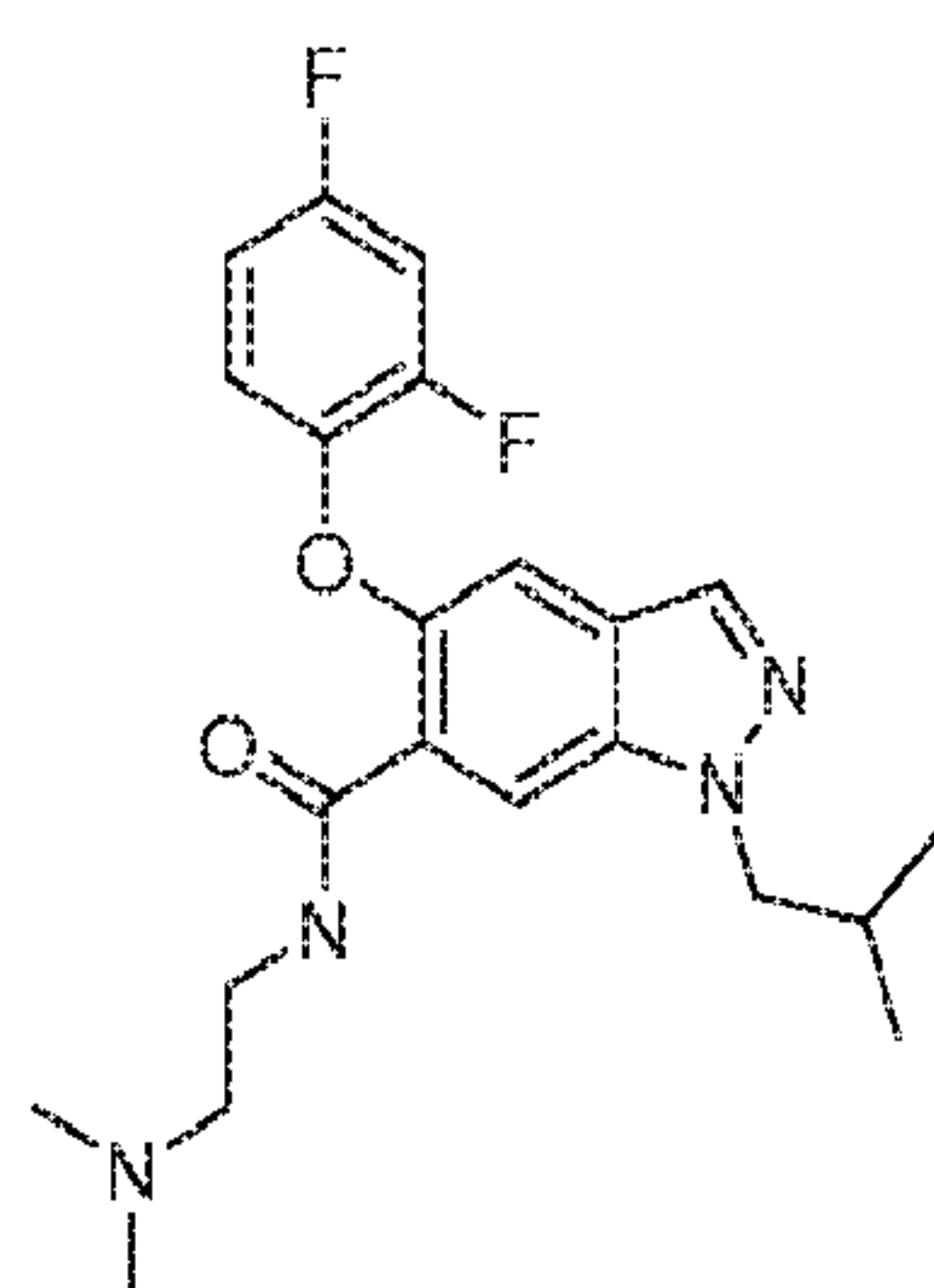
FTX-5043  
"Pexmetinib"



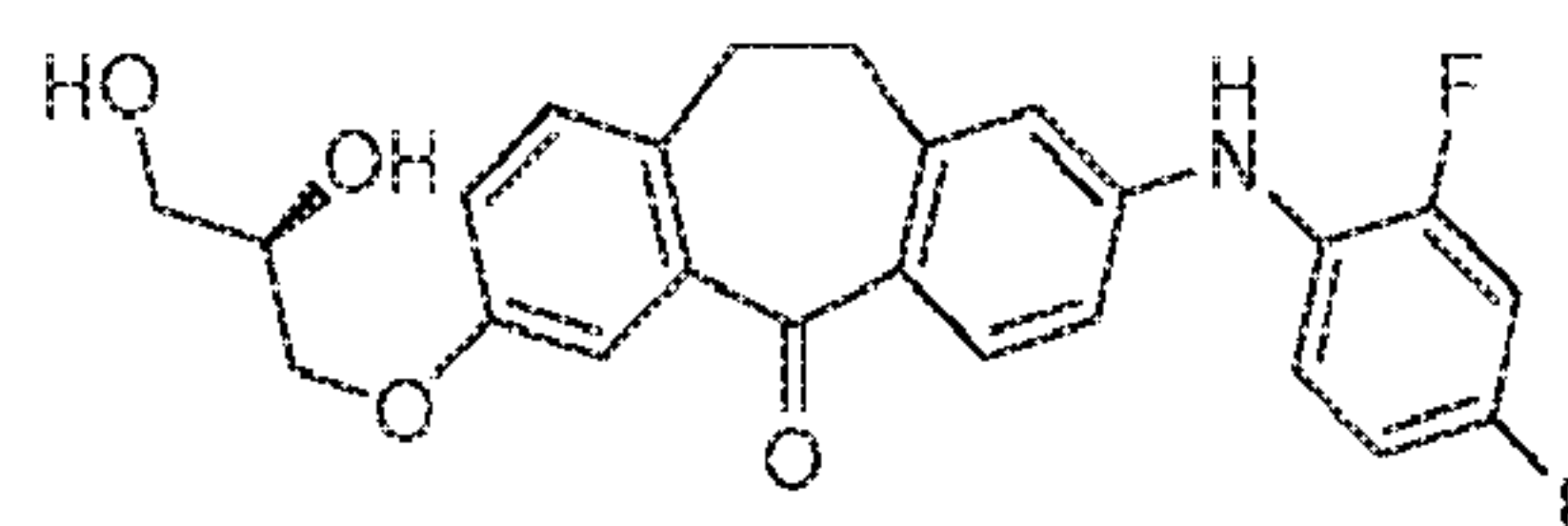
"Dilmapimod"



FTX-4384  
"Neflamapimod"  
"VX-745"



"ARRY-797"



"Skepinone-L"

FIG. 12B (cont.)

Table 2.

| CTID #     | ID       | p/i          | Cell type  | Repeat # | Cntrl/FSHD |
|------------|----------|--------------|------------|----------|------------|
| CTID-001   | FTCE-204 | primary      | Fibroblast | 39       | Control    |
| CTID-002   | FTCE-425 | primary      | Myoblast   | 5.5      | FSHD       |
| CTID-003   | FTCE-423 | primary      | Myoblast   | 3        | FSHD       |
| CTID-004   | FTCE-396 | primary      | Myoblast   | n/a      | Control    |
| CTID-005   | FTCE-422 | primary      | Myoblast   | 2        | FSHD       |
| CTID-006   | FTCE-424 | primary      | Myoblast   | 4.5      | FSHD       |
| CTID-007   | FTCE-426 | primary      | Myoblast   | 4.5      | FSHD       |
| CTID-008   | FTCE-428 | primary      | Myoblast   | SMCHD1   | FSHD2      |
| CTID-009   | FTCE-197 | primary      | Myoblast   | 2        | FSHD       |
| CTID-010   | FTCE-196 | primary      | Myoblast   | 3        | FSHD       |
| CTID-011   | FTCE-429 | primary      | Myoblast   | SMCHD1   | FSHD2      |
| CTID-012   | FTCE-421 | primary      | Myoblast   | 7        | FSHD       |
| CTID-013   | FTCE-205 | primary      | Myoblast   | 12       | Control    |
| CTID-014   | FTCE-427 | primary      | Myoblast   | SMCHD1   | FSHD2      |
| CTID-015   | FTCE-16  | immortalized | Myoblast   | 6.5      | FSHD       |
| C6 Control | FTCE-20  | immortalized | Myoblast   | 3        | FSHD       |
| WT Control | FTCE-14  | immortalized | Myoblast   | n/a      | Control    |
| A4 Control | FTCE-18  | immortalized | Myoblast   | n/a      | Control    |

FIG. 13

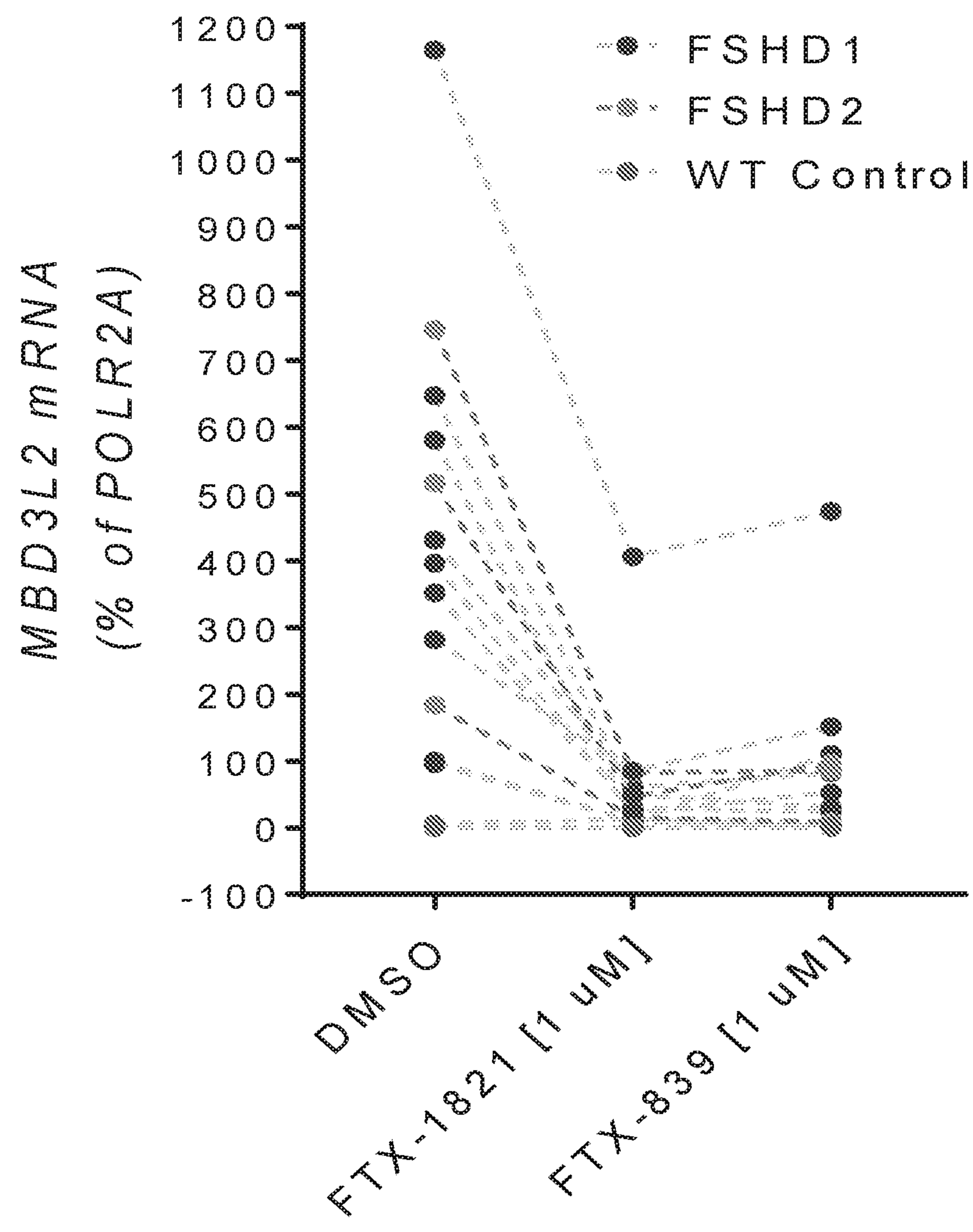


FIG. 14A

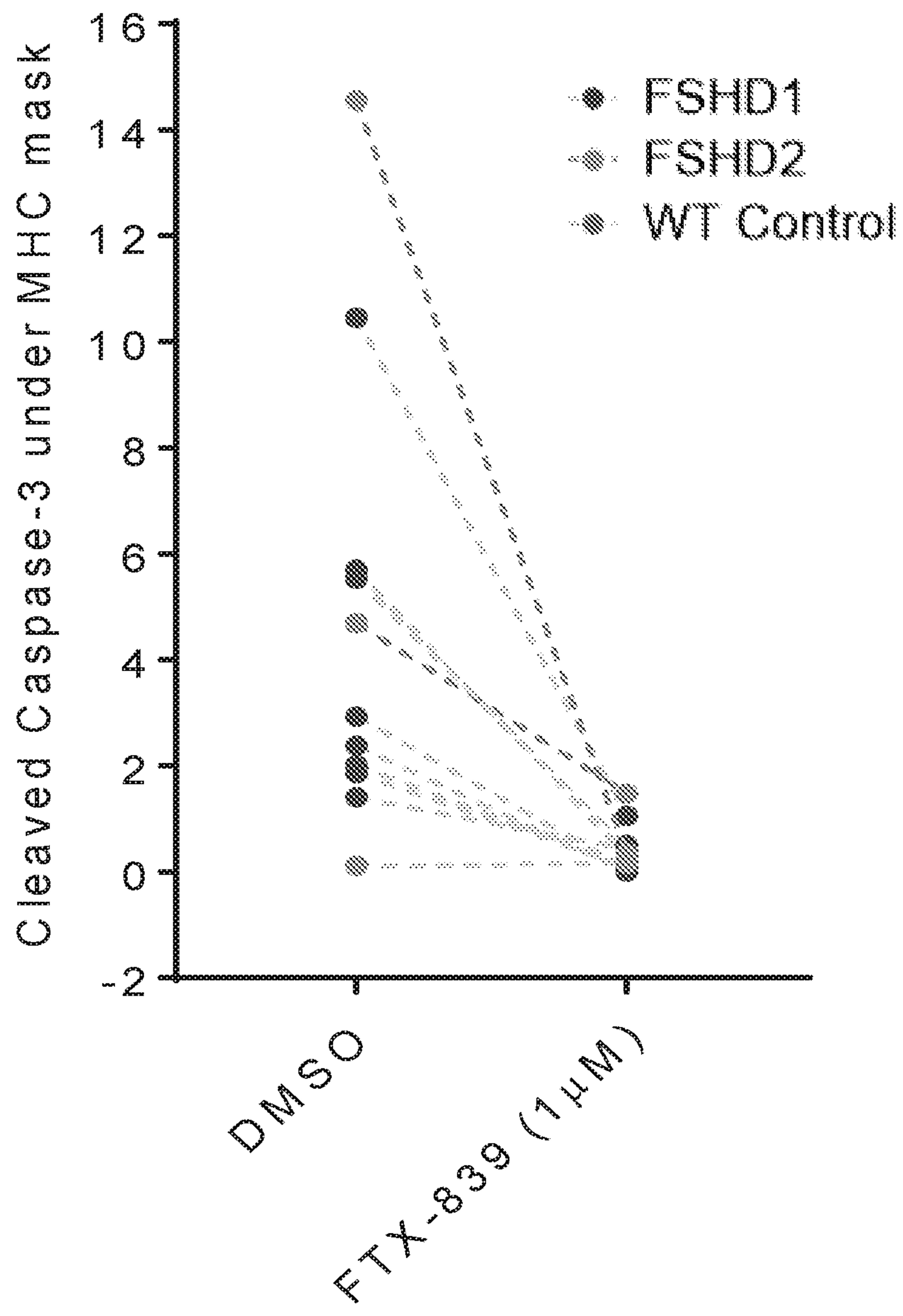


FIG. 14B

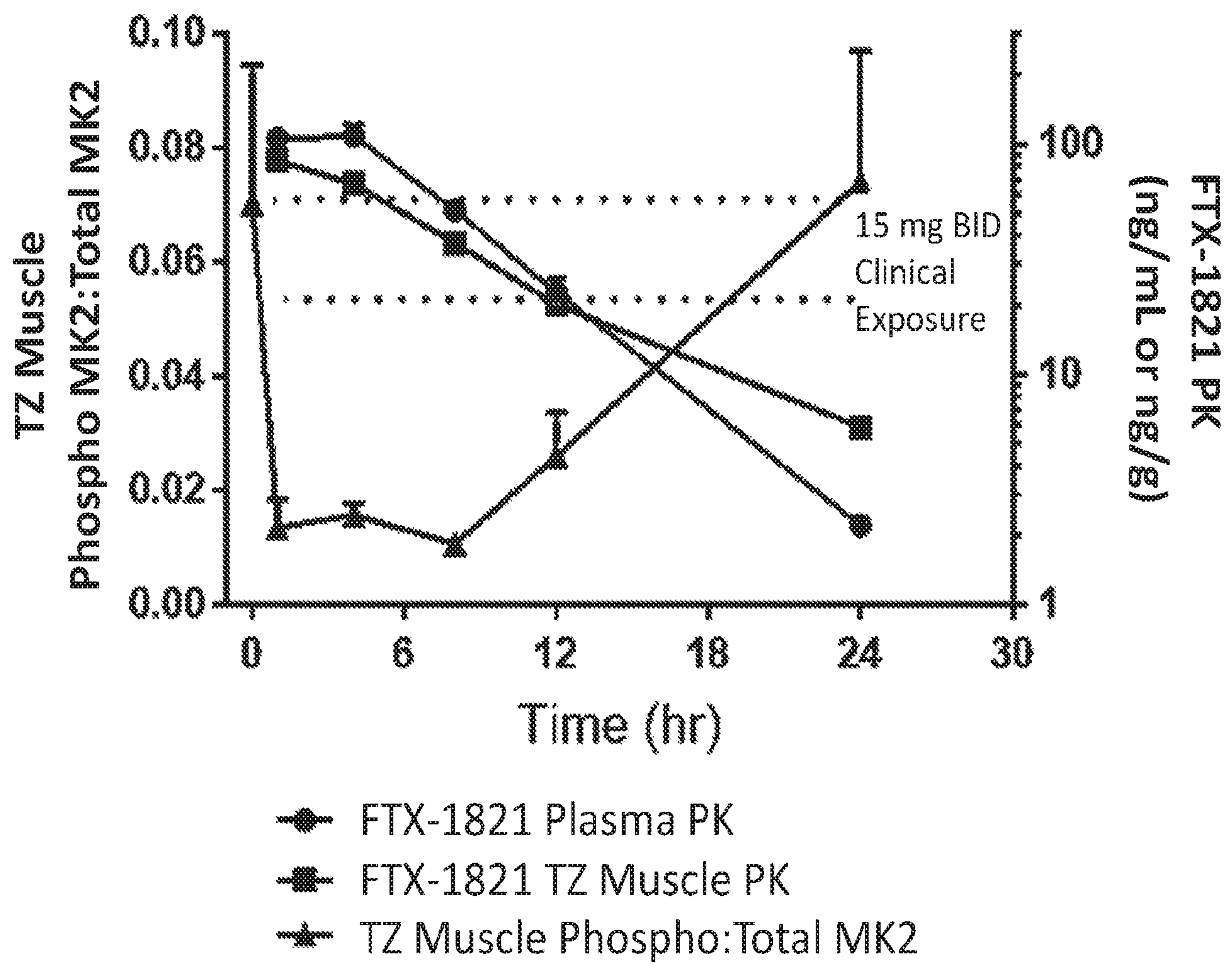


FIG. 15

The Dux4 dependent mRNA program is elevated in muscles of FSHD vs. control xenografted mice

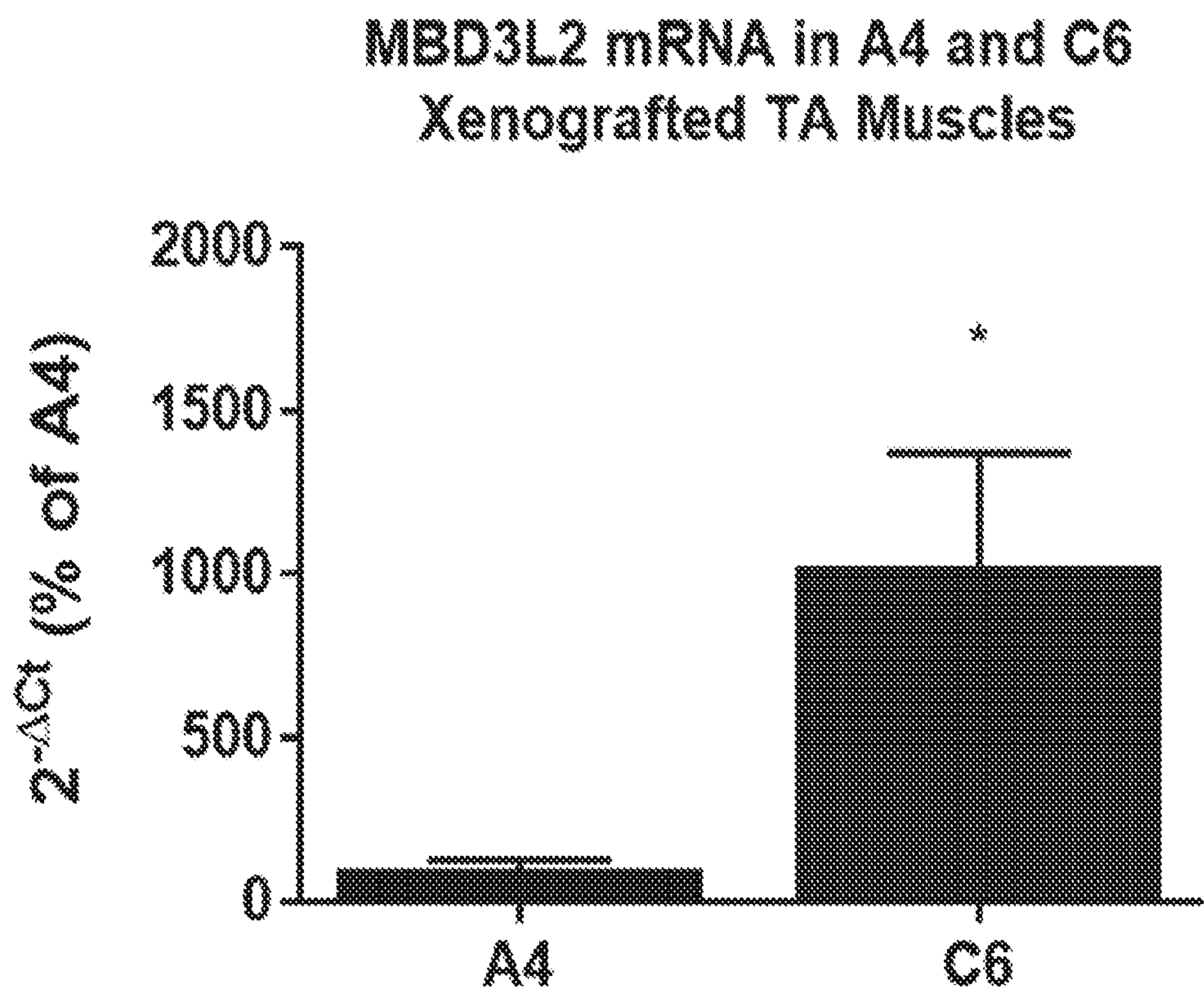


FIG. 16

Treatment of FSHD mice with the potent and selective p38 inhibitor, FTX-2865, produces p38 target engagement in the trapezius muscles

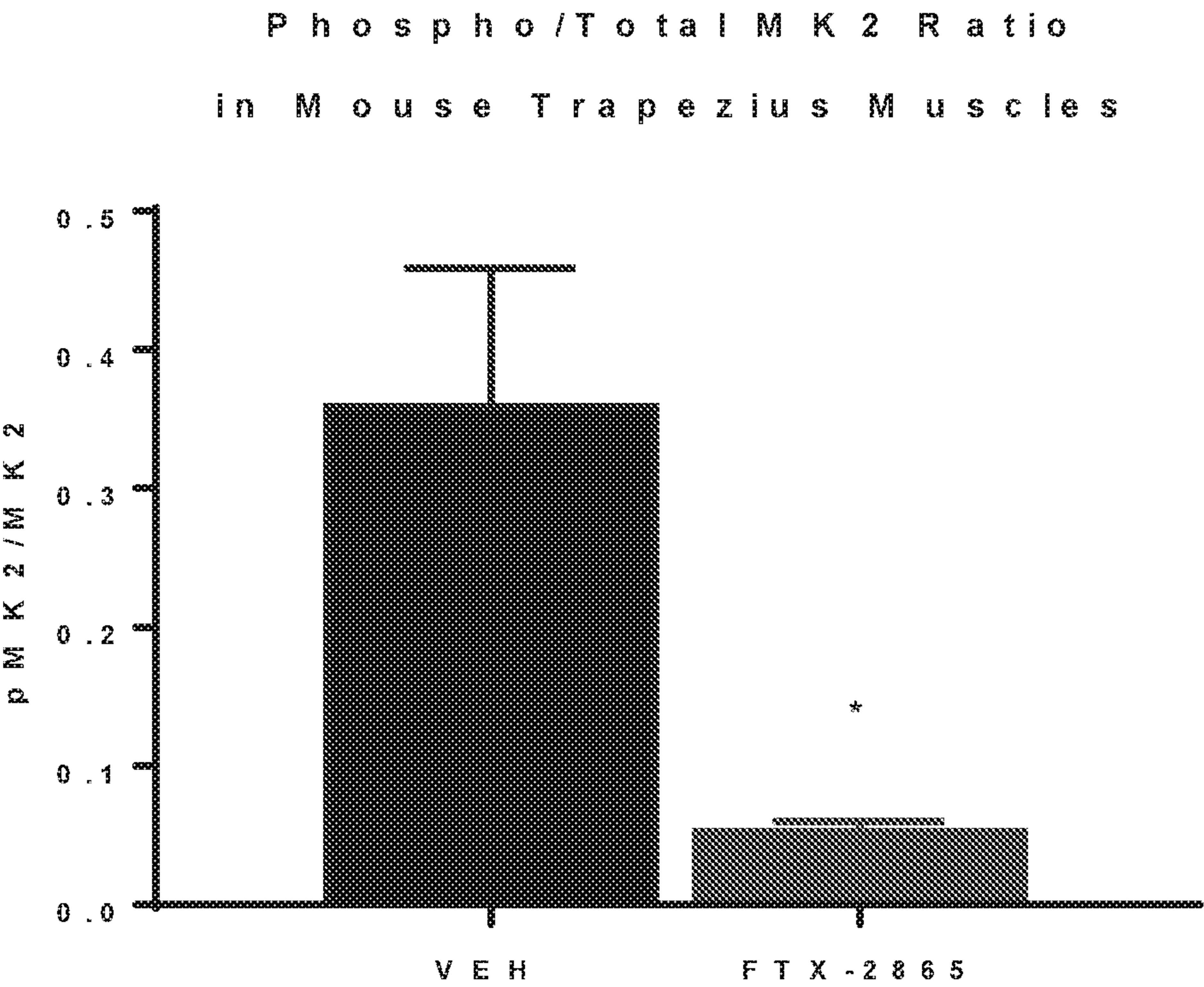


FIG. 17

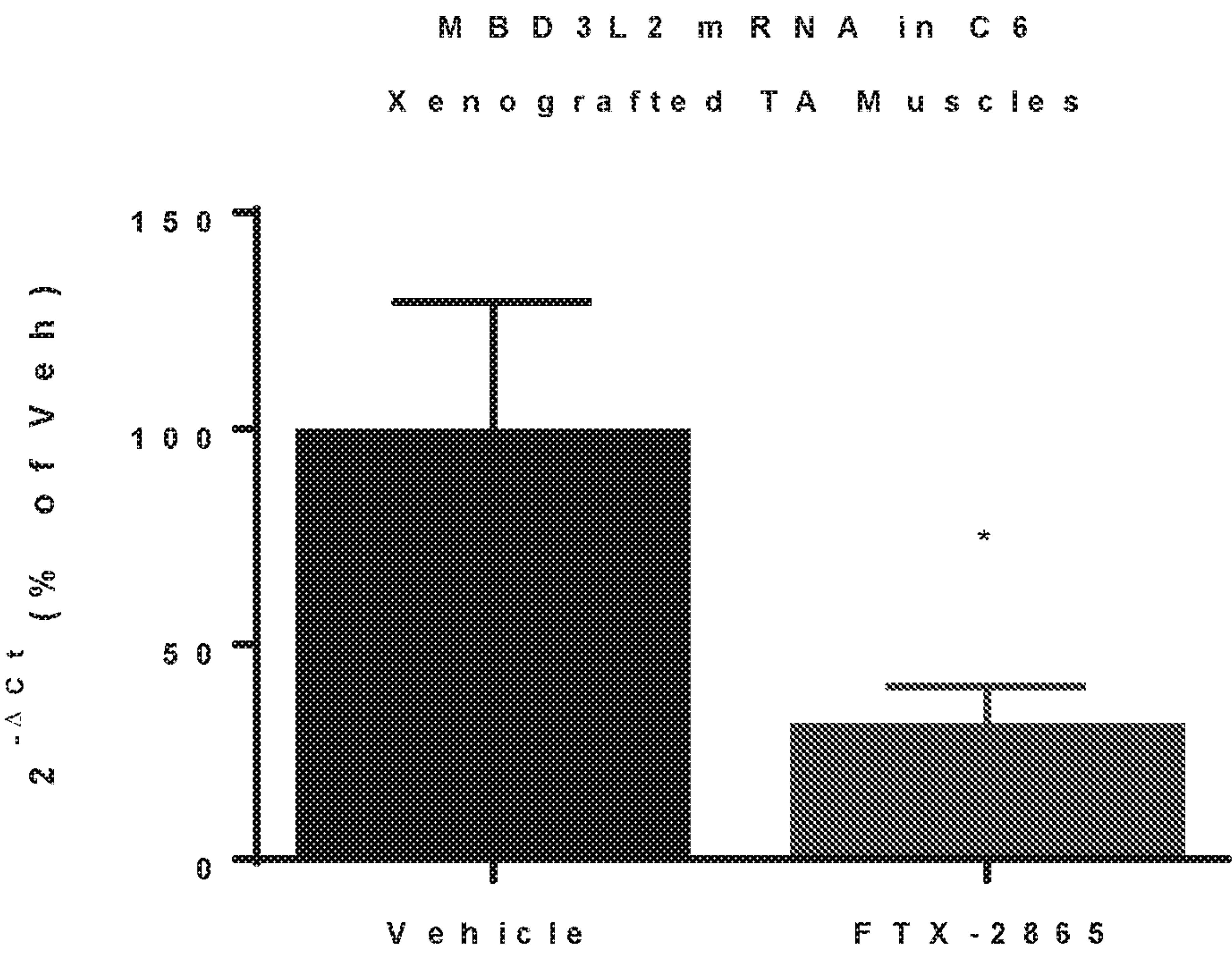


FIG. 18