

CHEMBIOCHEM

Supporting Information

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Supporting Information

for

Identification of Pharmacological Chaperones for Gaucher Disease and
Characterization of Their Effects on β -Glucocerebrosidase by
Hydrogen/Deuterium Exchange Mass Spectrometry

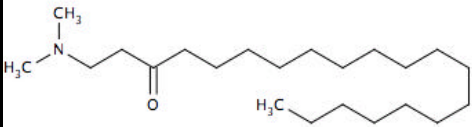
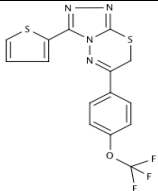
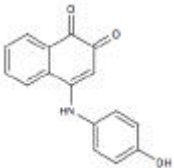
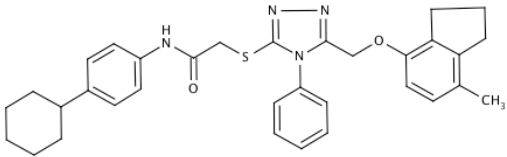
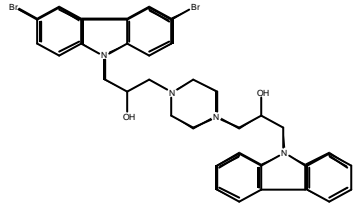
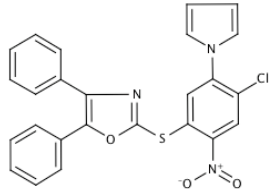
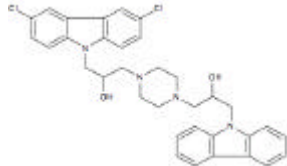
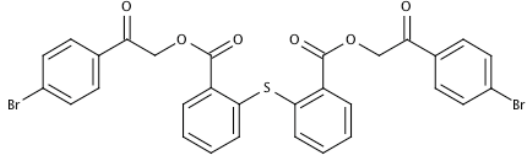
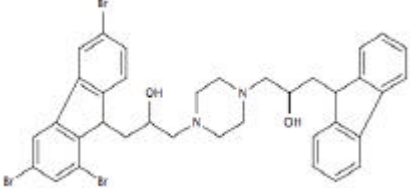
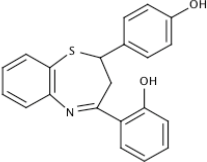
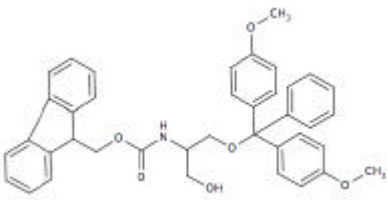
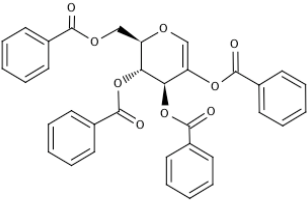
Michael B. Tropak, Gregory J. Kornhaber, Brigitte A. Rigat, Gustavo H. Maegawa,
Justin Buttner, Jan E. Blanchard, Cecilia Murphy, Steven J. Tuske,
Stephen J. Coales, Yoshitomo Hamuro, Eric Brown, and Don J. Mahuran*

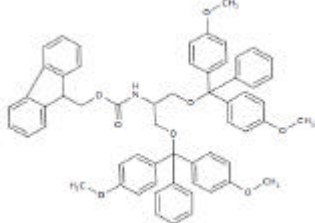
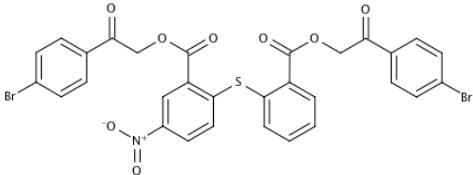
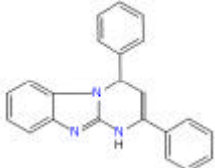
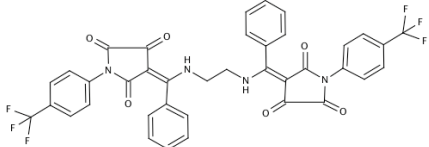
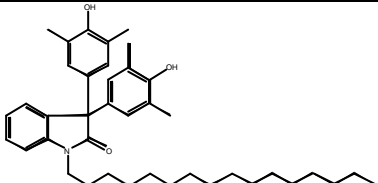
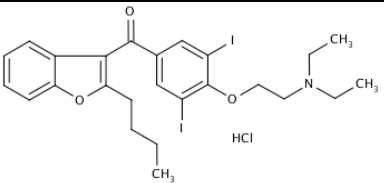
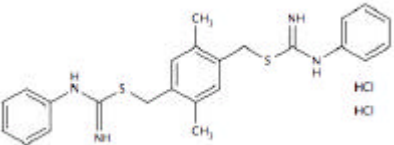
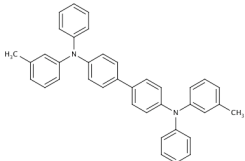
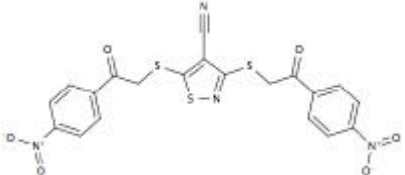
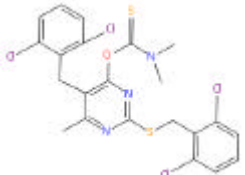
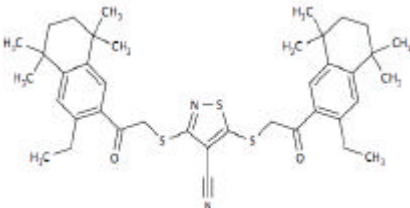
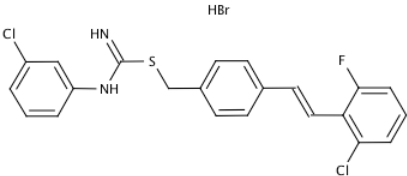
Table S1: List of 108 primary hits that reduced Gcc Residual Activity below 30%. Shown are the Maybridge Identification Code for the compound and directly beneath, the IC₅₀ value (μM) determined in the secondary screen (columns labelled Code) and the 2D structure of the compound (columns labelled Structure).

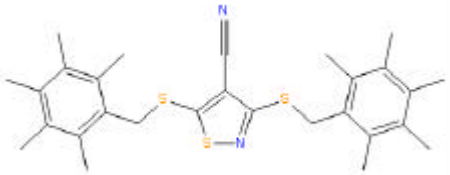
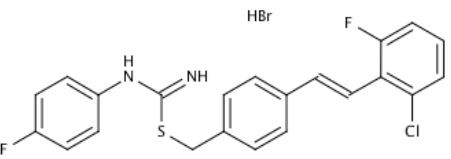
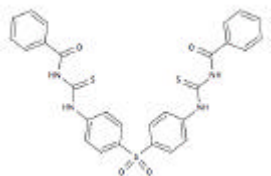
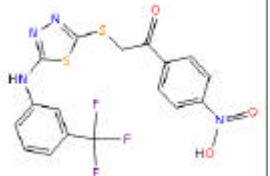
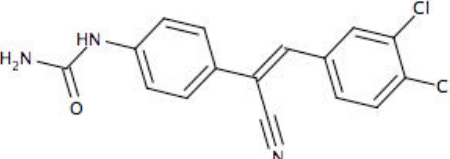
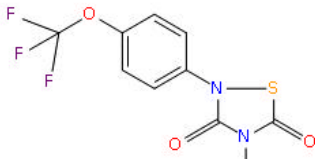
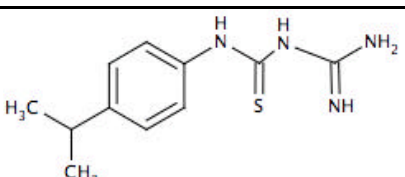
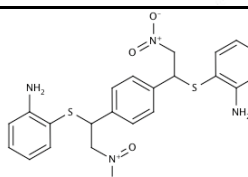
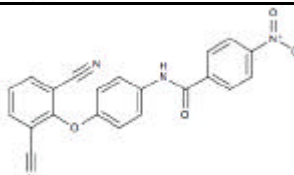
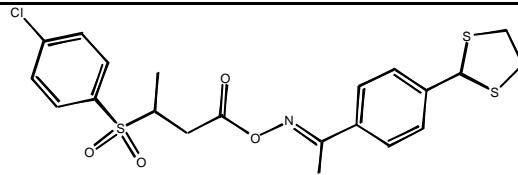
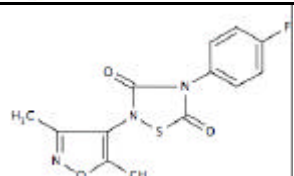
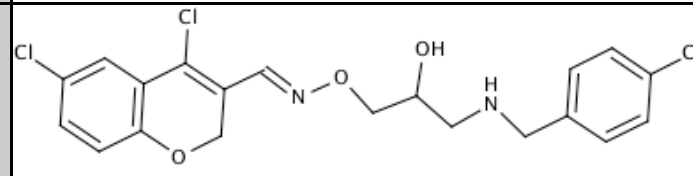
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BLT 00154 50 ± 12		KM 04550 22 ± 5	
BTB 01437 47 ± 16		KM 04984 91 ± 35	
BTB 02328 16 ± 28		KM 07661 31 ± 20	
BTB 02998 32 ± 15		MBE 00142 148 ± 104	
BTB 03346 0.7 ± 0.1		MBE 00145 126 ± 25	

Code	Structure	Code	Structure
BTB 03449 67 ± 17		MBE 00148 2.7 ± 0.5	
BTB 05211 27 ± 6		MBE 00151 14 ± 5	
BTB 05232 41 ± 16		MBE 00152 42 ± 18	
BTB 06478 52 ± 23		ML 00213 42 ± 10	
BTB 07350 33 ± 9		MWP 00649 42 ± 12	
BTB 07496 8.4 ± 1.3		MWP 01127 16 ± 2	

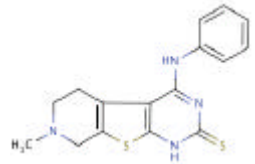
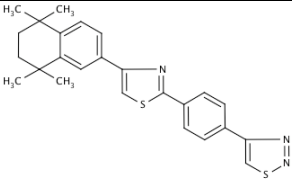
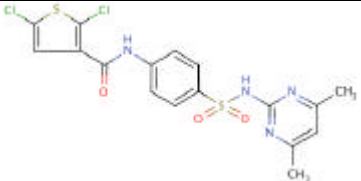
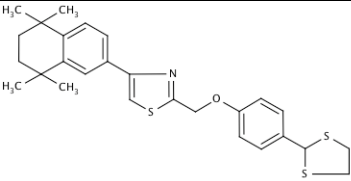
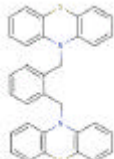
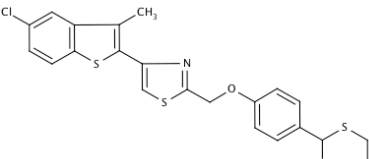
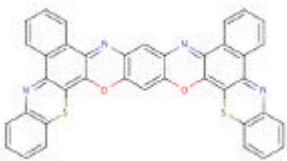
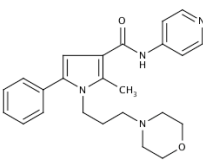
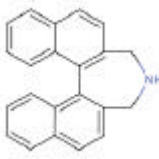
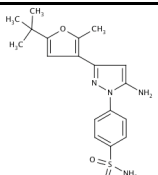
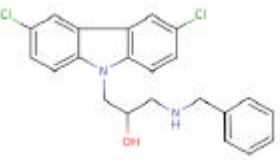
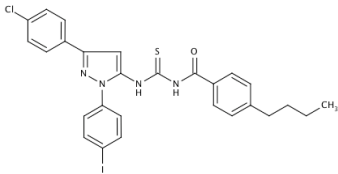
Code	Structure	Code	Structure
BTB 08066 8.2 ± 3.7		MWP 01128 14 ± 8	
BTB 10392 2.1 ± 0.8		NH 00306 64 ± 4	
BTB 11015 200 ± 229		RDR 01439 0.9 ± 0.2	
BTB 11079 104 ± 64		RH 00643 >100	
BTB 11331 >100		RH 00644 7.8 ± 2.7	
BTB 11334 124 ± 117		RH 00783 2.2 ± 0.4	

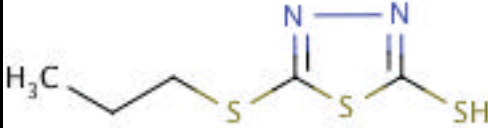
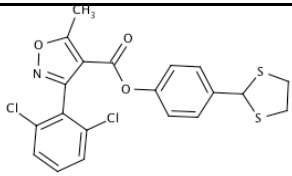
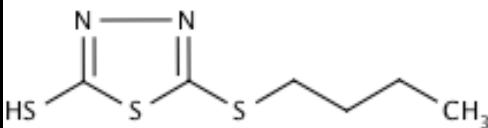
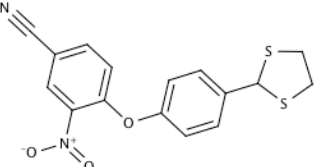
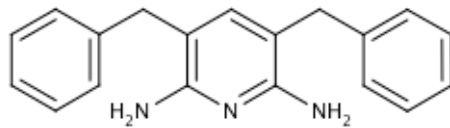
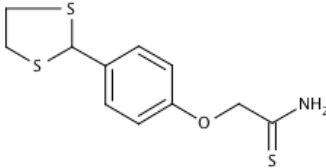
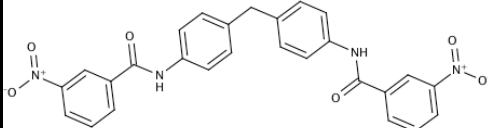
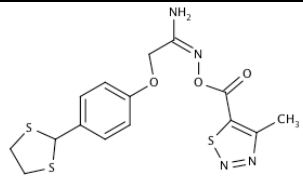
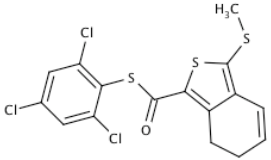
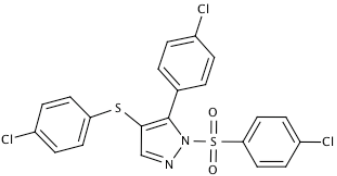
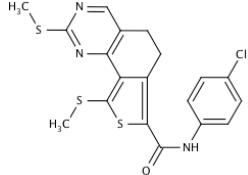
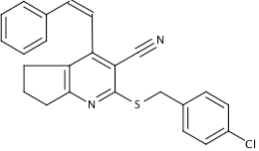
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BTB 12892 >100		RH 01061 2.4 ± 0.9	
BTB 13089 1.3 ± 0.2		RH 01716 34 ± 21	
BTB 13368 18 ± 7		RH 02106 28 ± 16	
BTB 13370 14 ± 6		RJC 00100 28 ± 12	
BTB 13902 147 ± 174		RJC 00357 4.8 ± 1.0	
BTB 14729 20 ± 4		RJC 01351 54 ± 35	

Code	Structure	Code	Structure
BTB 14731 61 ± 15		RJC 01843 24 ± 3	
BTB 14755 28 ± 13		RJC 02132 46 ± 14	
BTB13814 45 ± 146		RJC 02270 73 ± 60	
CD 00240 12 ± 3		RJC 02479 4.0 ± 0.9	
CD 00466 8.9 ± 7.3		RJF 00257 >100	
CD 00469 4.2 ± 6.3		RJF 01158 15 ± 9	

Code	Structure	Code	Structure
CD 00502 17 ± 10		RJF 01159 20 ± 4	
CD 01259 52 ± 9		S 05133 21 ± 8	
CD 02284 >100		S 13592 15 ± 2	
CD 03798 12 ± 2		S 15348 123 ± 28	
CD 11038 3.6 ± 1.0		SEW 00556 22 ± 7	
HTS 01243 32 ± 22		SEW 02957 19 ± 5	

Code	Structure	Code	Structure
HTS 02324 4.2 ± 0.6		SEW 04707 2.1 ± 0.7	
HTS 04241 6.4 ± 2.8		SEW 04852 81 ± 24	
HTS 04578 10 ± 3		SEW 05565 22 ± 11	
HTS 06789 9.8 ± 4.2		SEW 06186 94 ± 27	
HTS 06793 3.9 ± 0.8		SP 00526 8.9 ± 7.7	
HTS 07133 8.3 ± 5.2		SP 00531 66 ± 26	

Code	Structure	Code	Structure
HTS 07424 47 ± 29		SP 00752 136 ± 162	
HTS 07780 31 ± 30		SP 00756 24 ± 2	
HTS 09832 16 ± 3		SP 00859 29 ± 7	
JFD 00243 7.7 ± 0.8		SP 00867 47 ± 8	
JFD 02816 21 ± 4		SP 00991 52 ± 17	
JFD 02972 86 ± 16		SP 01065 8.2 ± 3.3	

Code	Structure	Code	Structure
JFD 03132 >100		SPB 00915 14 ± 3	
JFD 03146 >100		SPB 00968 19 ± 4	
JFD 03571 15 ± 3		SPB 01940 102 ± 62	
JP 00639 7.5 ± 5.3		SPB 02638 127 ± 42	
KM 03455 25 ± 21		SPB 04204 44 ± 15	
KM 04397 16 ± 2		SPB 07453 51 ± 7	

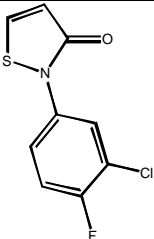
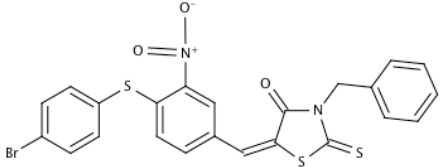
Code	Structure	Code	Structure
KM 04549 56 ± 23	 <chem>O=C1CN(S1)c2ccc(Cl)c(F)c2</chem>	XAX 00155 9.9 ± 2.9	 <chem>O=C1CN(Cc2ccccc2)C(=S1)/C=C/c3ccc(cc3[N+](=O)[O-])Sc4ccc(Br)cc4</chem>

Fig S1A - IC₅₀ - page 1/2

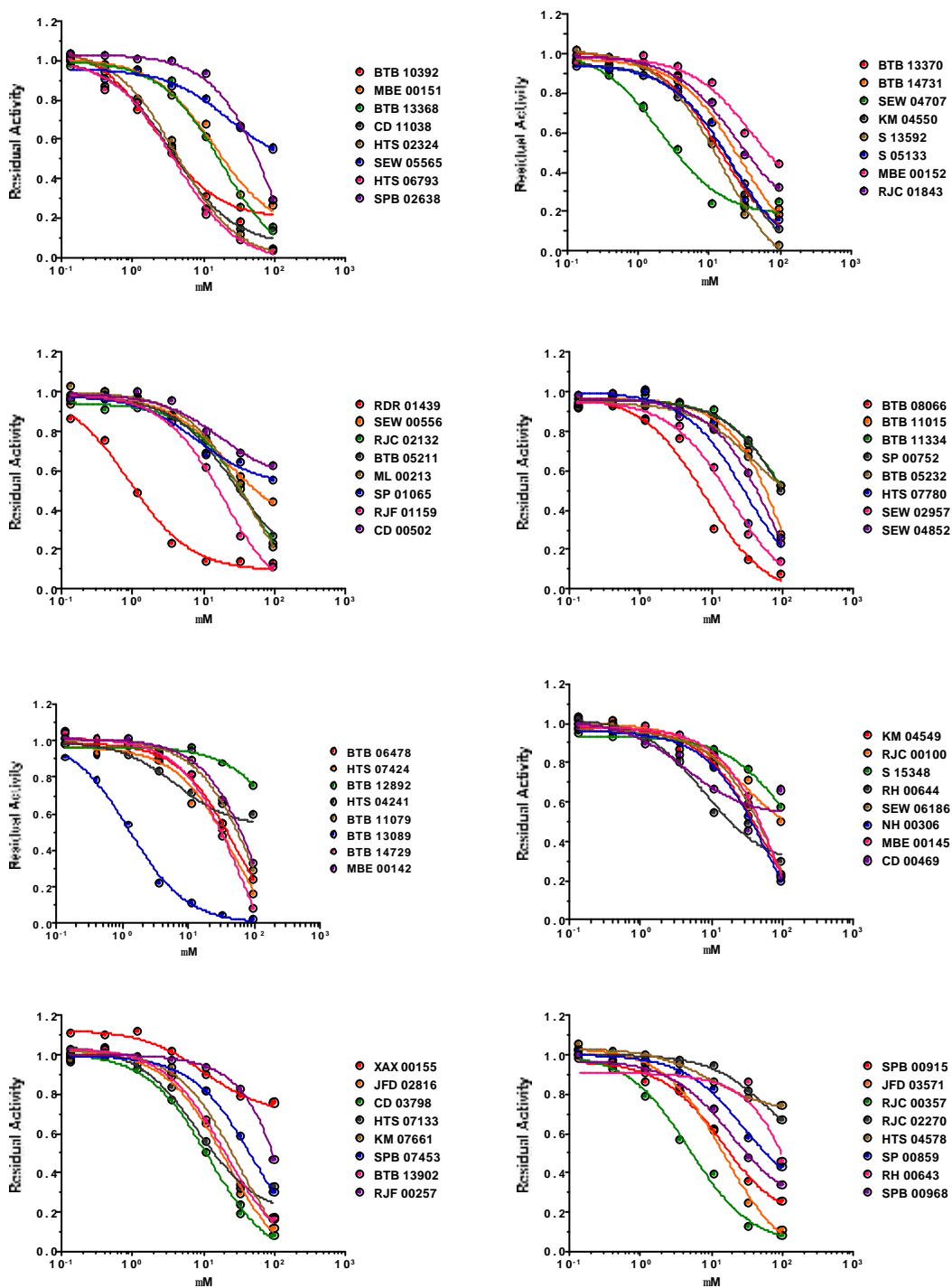


Figure S1. All 108 hits from the primary screen were evaluated for 3 characteristics using 4 assays: A) inhibition assay, to confirm and determine the IC₅₀ value in the presence of 0.8 mM MUGlc; B) heat denaturation attenuation assay, i.e. remaining Gcc activity in the pre-sence of the compound following heating to 50^oC for 20 min.; changes in intracellular levels C) Gcc and D) Hex activity in GD patient fibroblasts (N370S/N370S) after cells were treated for five days with the indicated concentration of test compound.

Fig S1A - IC₅₀ - page 2/2

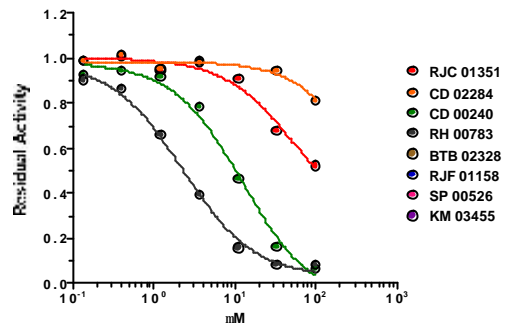
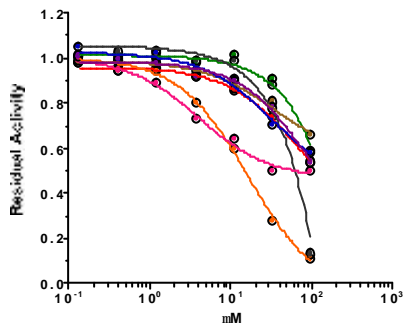
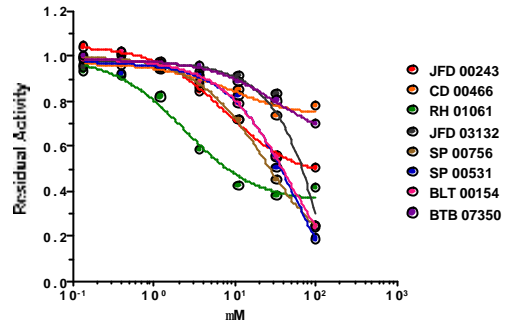
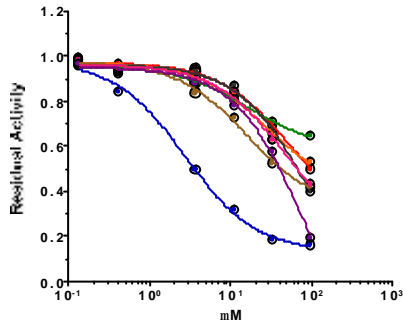
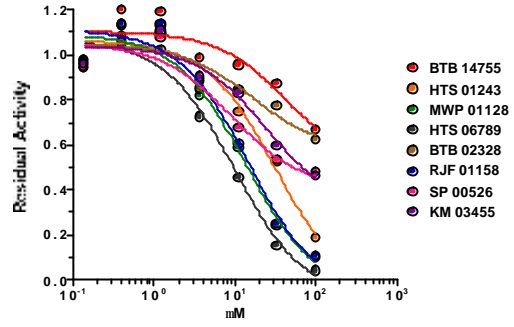
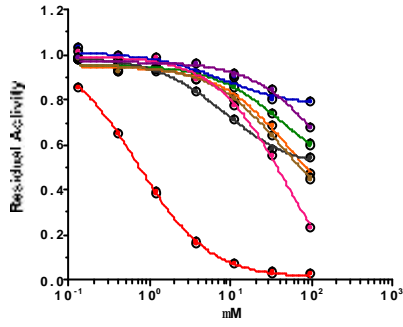


Fig S1B -Attenuation Heat Denaturation- page 1/2

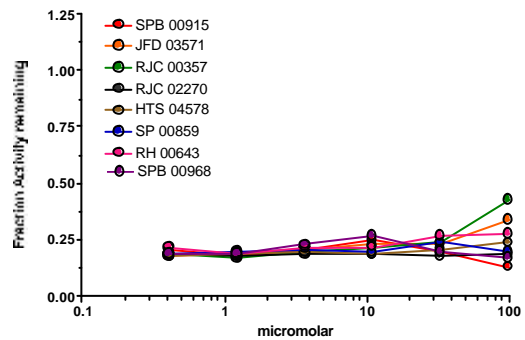
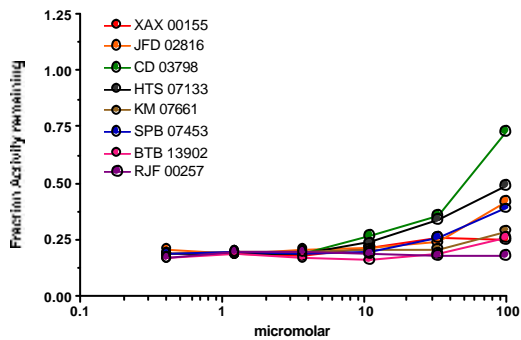
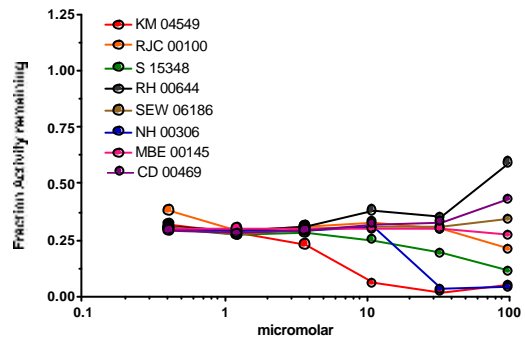
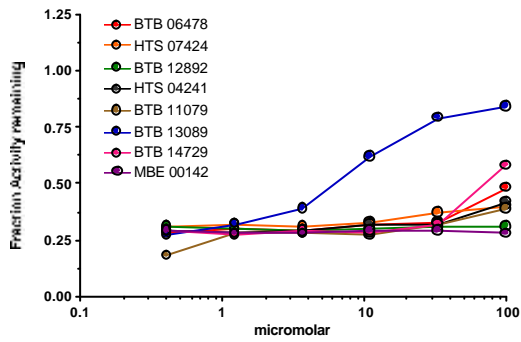
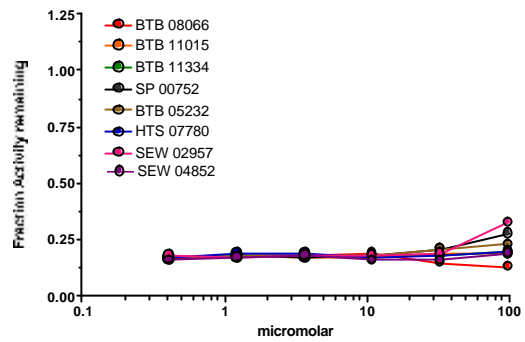
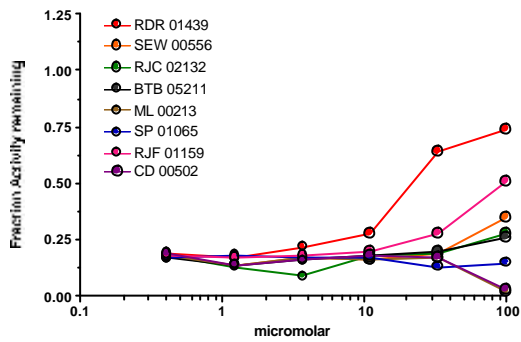
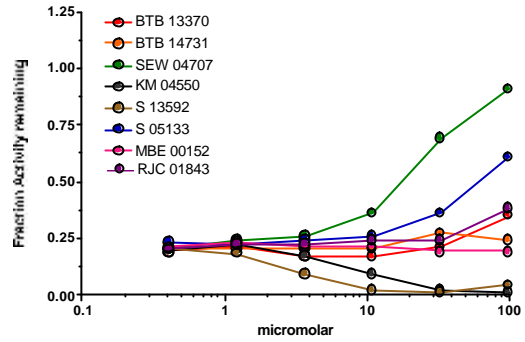
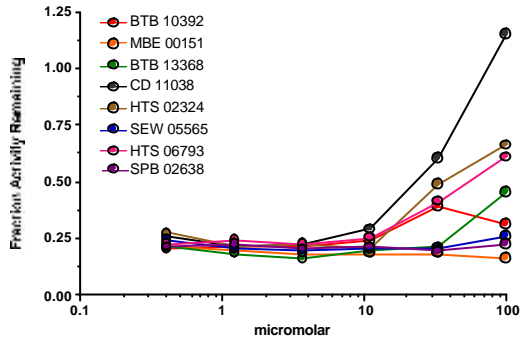


Fig S1B -Attenuation Heat Denaturation- page 2/2

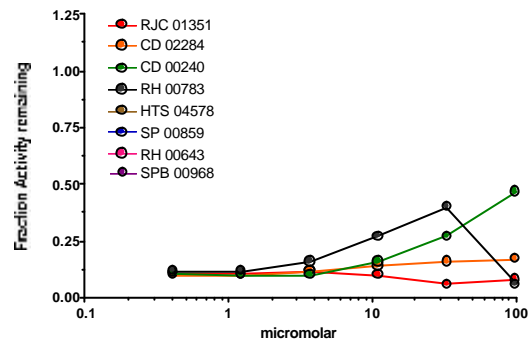
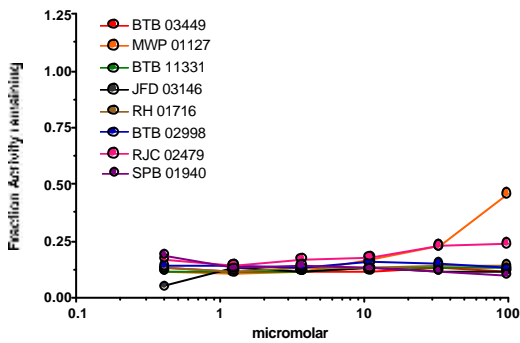
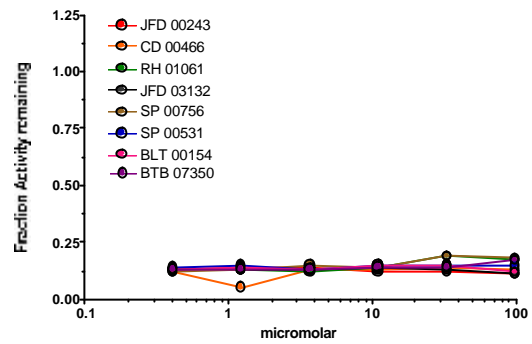
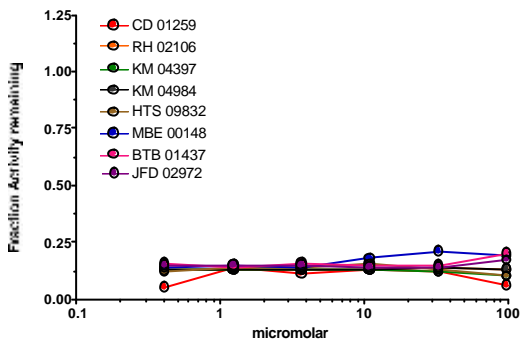
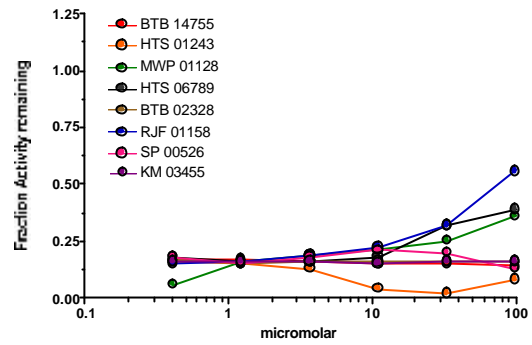
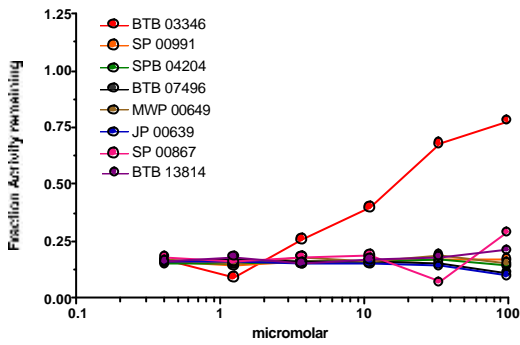


Fig S1C -Gcc levels N370S- page 1/2

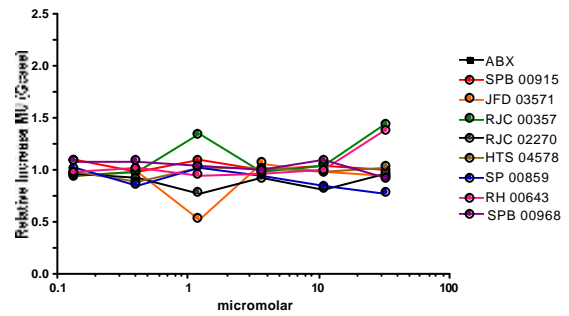
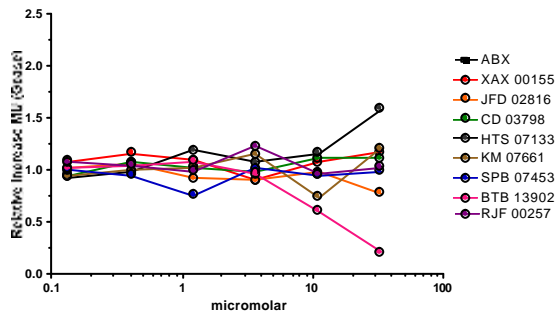
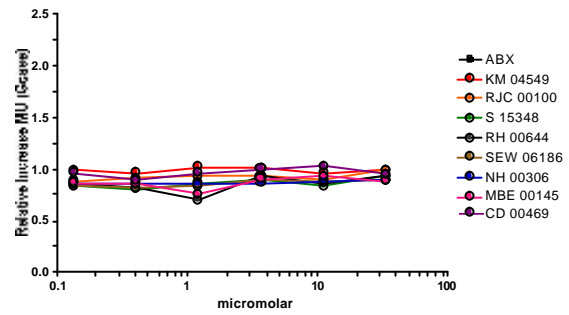
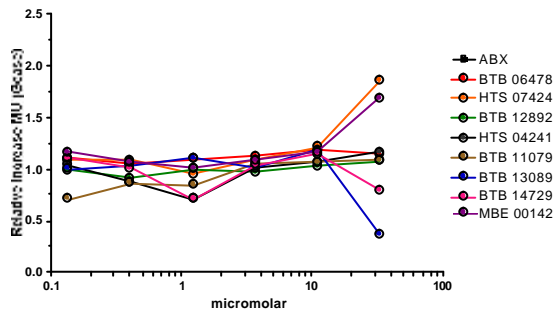
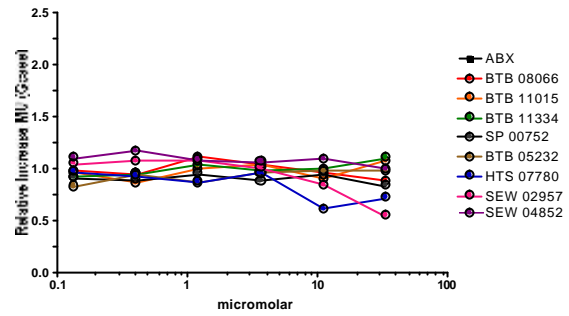
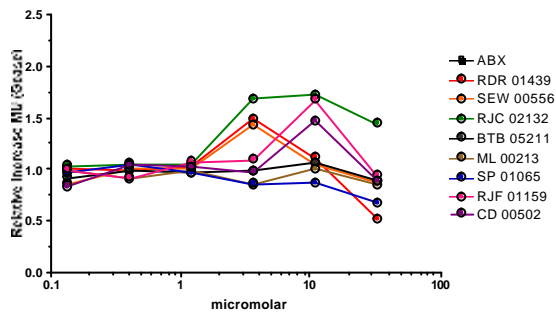
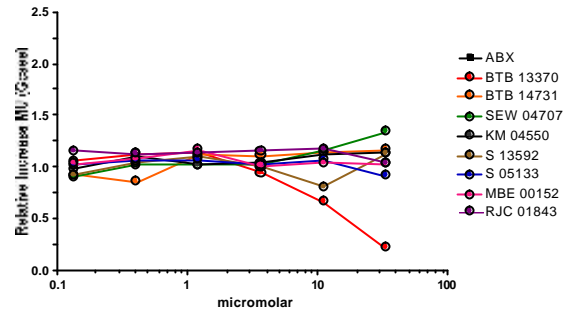
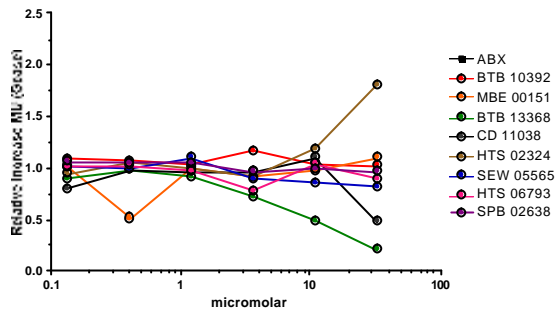


Fig S1C -Gcc levels N370S- page 2/2

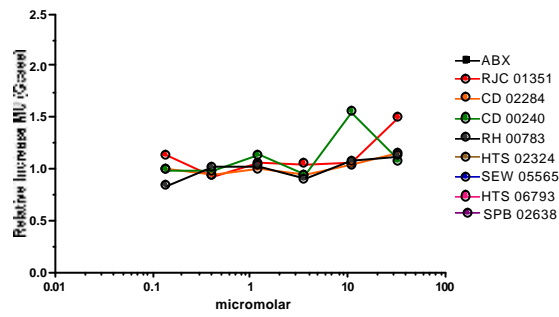
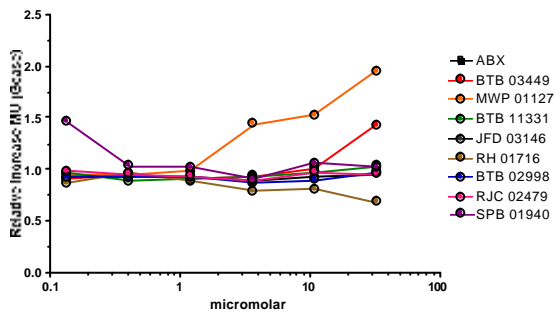
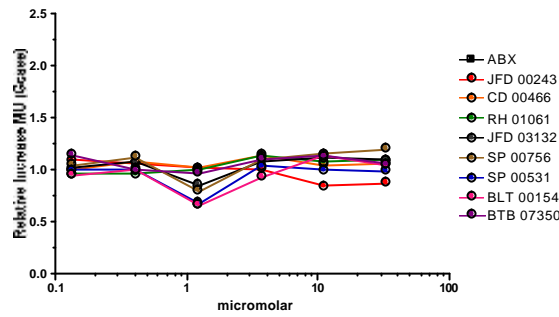
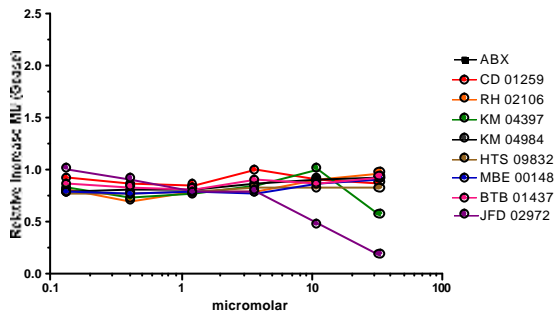
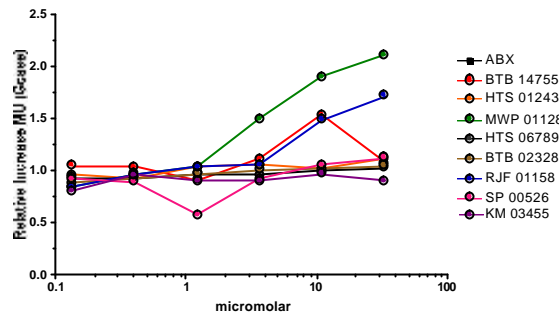
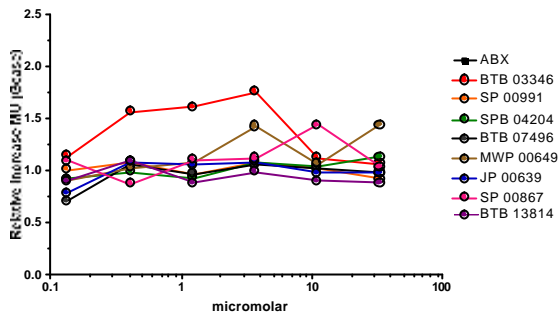


Fig S1D -Hex levels N370S- page 1/2

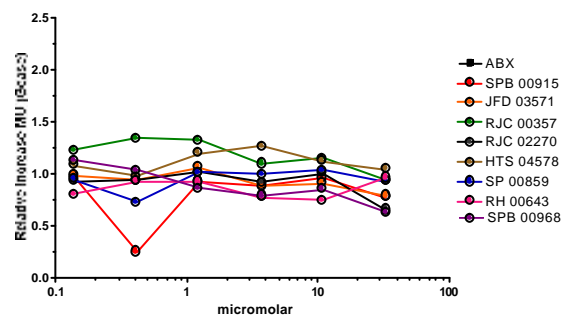
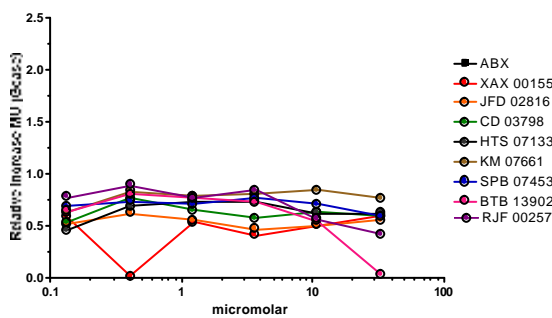
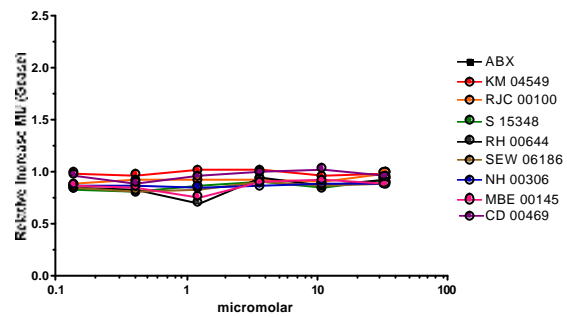
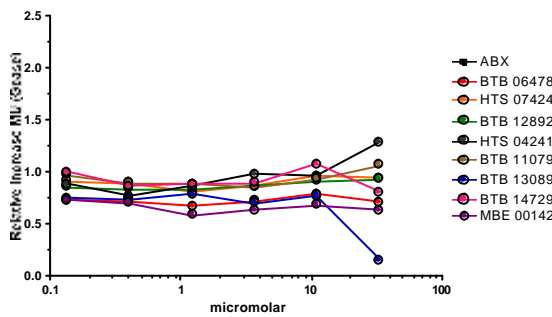
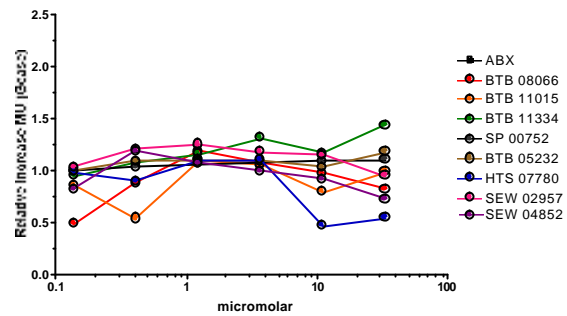
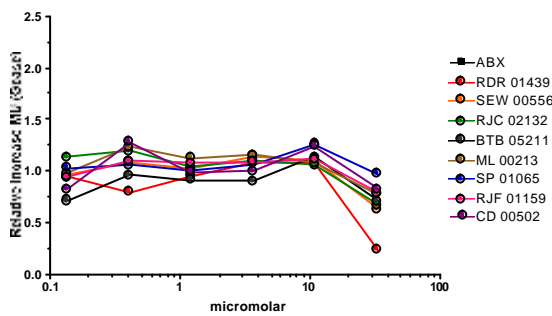
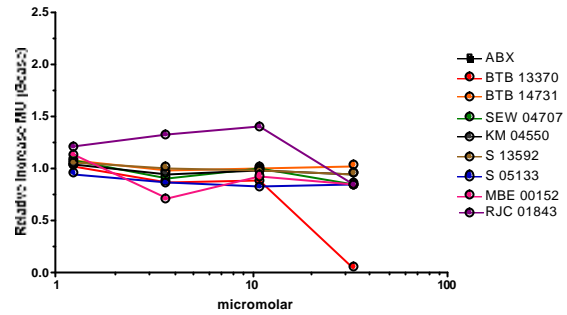
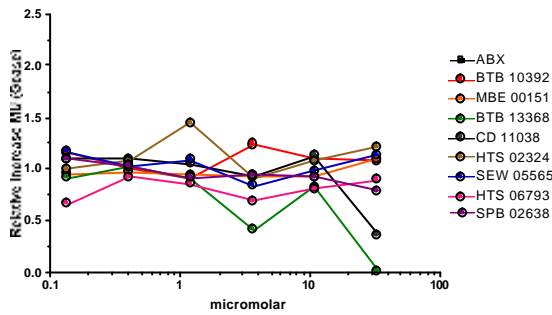
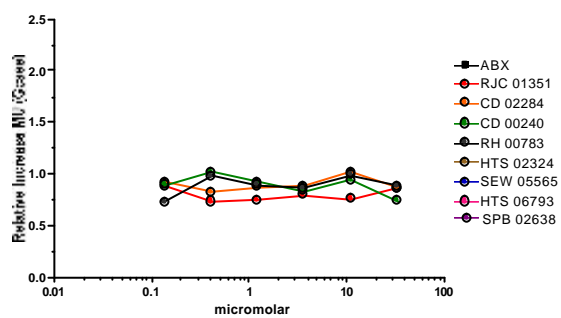
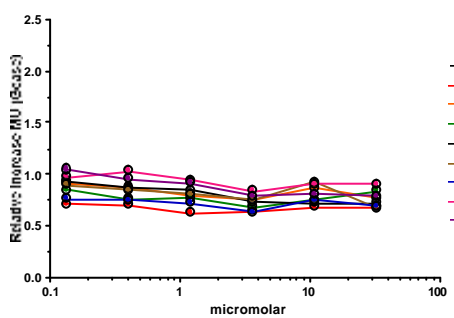
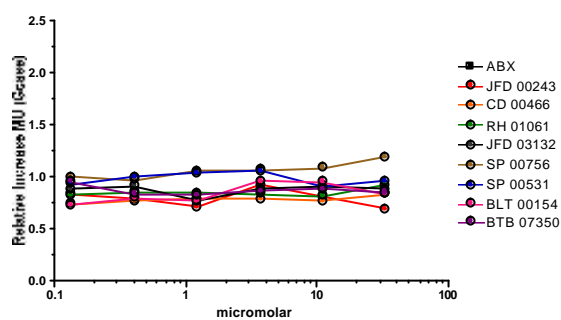
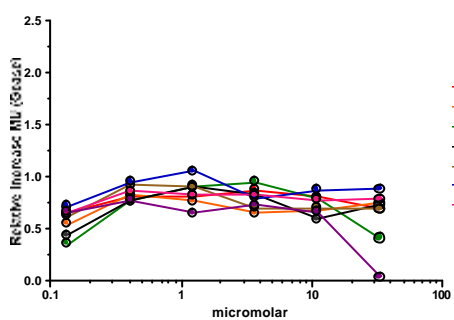
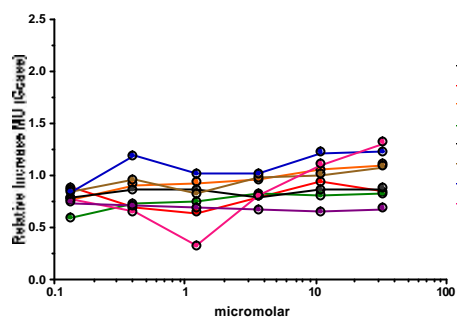
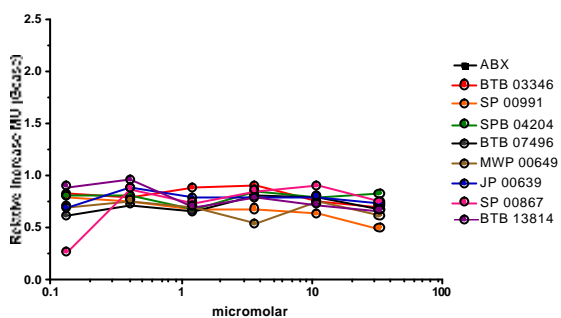


Fig 1S -Hex levels N370S- page 2/2



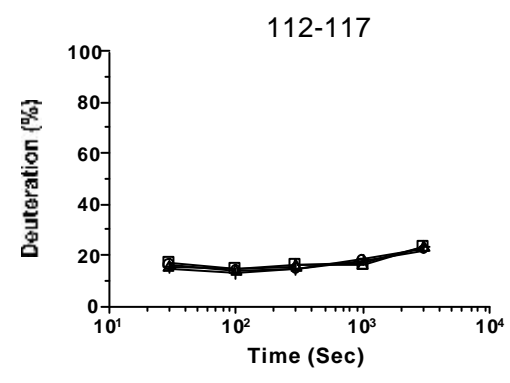
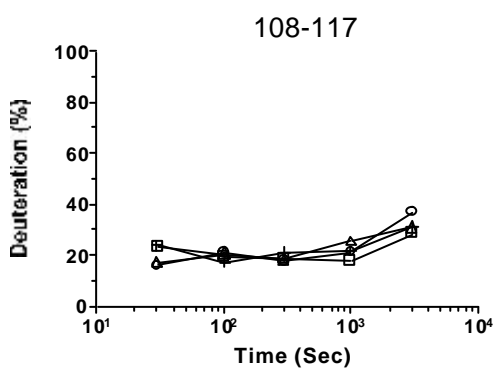
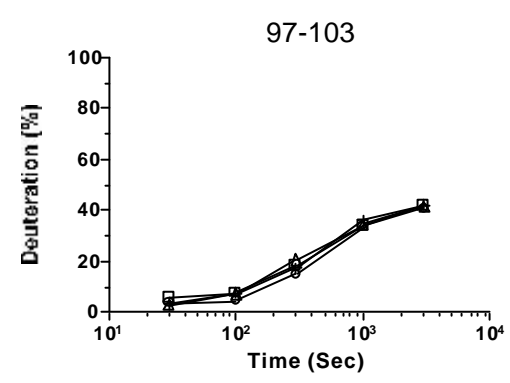
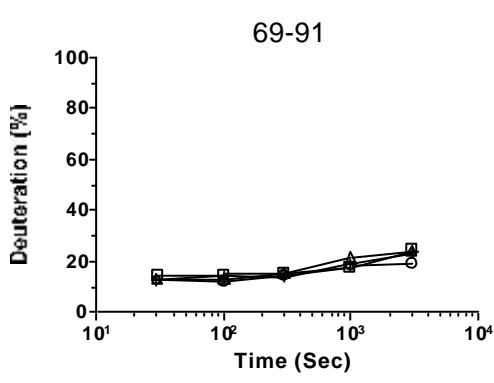
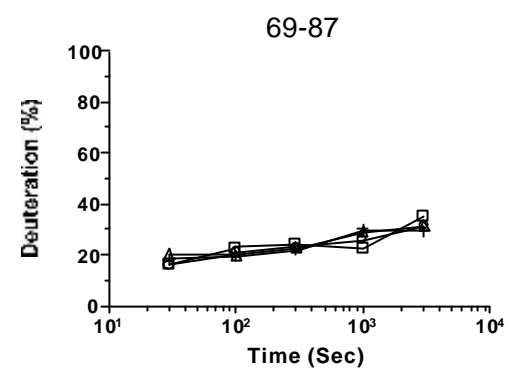
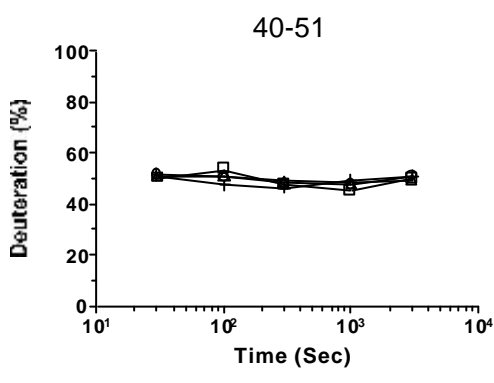
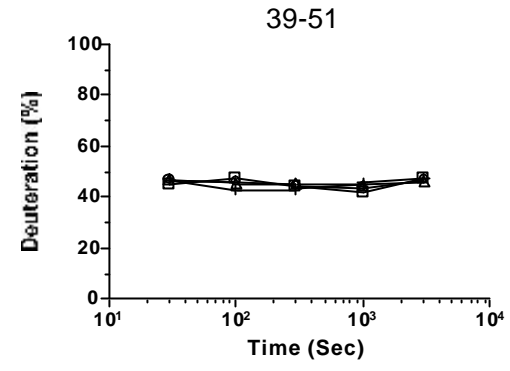
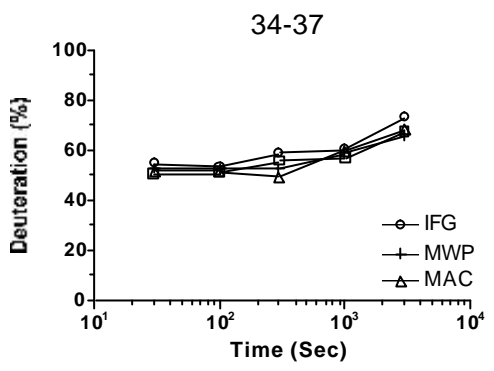


Figure S2. Deuterium build up curves are shown for all segments of Gcc in the absence of ligand (+), or in the presence of excess IFG (Δ), MWP (?) or MAC (o).

