

	logEC <sub>50</sub> (M)	E <sub>MAX</sub>
<b>binding</b>		
MAB2814	-9.3 +/- 0.1	85.6 +/- 1.7
TB-001-003	-9.3 +/- 0.3	252.8 +/- 3.7*
TB-222-023	-9.4 +/- 0.3	248.1 +/- 9.2*
TB-222-040	-9.0 +/- 0.2	119.4 +/- 4.4*
TB-222-089	-8.9 +/- 0.2	155.2 +/- 7*

\*significant interaction by one-way ANOVA and p<0.05 compared to MAB2814

#### **G protein agonism**

exendin-4 (1-39)	-8 +/- 0.3	100.9 +/- 3.1
exendin-(9-39)	-7.7 +/- 0.3	1.8 +/- 0.1*
GLP1 (7-37)	-8.8 +/- 0.1	99.4 +/- 2.3
Liraglutide	-8.0 +/- 0.1	99.3 +/- 0.6
GLP1 (1-37)	-5.9 +/- 0.1*	93.5 +/- 2*
GLP1 (7-36) Amide	-8.0 +/- 0.1	80.8 +/- 0.4*
Glucagon	-6.7 +/- 0.1*	100.3 +/- 0.7
TB-001-003	N/A	N/A
TB-222-023	N/A	N/A
TB-222-040	-9.3 +/- 1*	0.7 +/- 0*
TB-222-089	N/A	0.5 +/- 0*

\*significant interaction by one-way ANOVA and p<0.05 compared to exendin-4

#### **β-arrestin 2 agonism**

exendin-4 (1-39)	-6.7 +/- 0.2	117.8 +/- 4.5
exendin-(9-39)	N/A	N/A
TB-001-003	N/A	N/A
TB-222-023	N/A	N/A
TB-222-040	N/A	N/A
TB-222-089	N/A	N/A

#### **β-arrestin 2 antagonism**

exendin-(9-39)	-6.3 +/- 0.1	-35.7 +/- 1.4
TB-001-003	-6.1 +/- 0.1*	-39.3 +/- 1.2*
TB-222-023	-6.7 +/- 0.1*	-33.4 +/- 1.1
TB-222-040	N/A	N/A
TB-222-089	N/A	N/A

\*significant interaction by one-way ANOVA and p<0.05 compared to exendin-(9-39)

#### **G protein antagonism (exendin-4)**

exendin-(9-39)	-6.4 +/- 0.1	-97.8 +/- 2.5
TB-001-003	-6.7 +/- 0.1*	-103.8 +/- 1.8*

TB-222-023	-7.0 +/- 0.1*	-100.7 +/- 1.9
TB-222-040	N/A	N/A
TB-222-089	N/A	N/A

\*significant interaction by one-way ANOVA and  $p < 0.05$  compared to exendin-(9-39)

#### G protein antagonism (GLP-1, 7-37)

exendin-(9-39)	-6.8 +/- 0.2	-87.9 +/- 1
TB-001-003	-7.6 +/- 0.2*	-93.6 +/- 4.6
TB-222-023	-7.8 +/- 0.2*	-88 +/- 3.3

\*significant interaction by one-way ANOVA and  $p < 0.05$  compared to exendin-(9-39)

#### G protein antagonism (liraglutide)

exendin-(9-39)	-6.3 +/- 0.3	-80 +/- 2.9
TB-001-003	-7.4 +/- 0.3*	-69.3 +/- 6.2
TB-222-023	-7.4 +/- 0.3*	-75.6 +/- 7.7

\*significant interaction by one-way ANOVA and  $p < 0.05$  compared to exendin-(9-39)

#### G protein antagonism (GLP-1, 1-37)

exendin-(9-39)	-6.6 +/- 0.1	-90.2 +/- 1.1
TB-001-003	-7.7 +/- 0.2*	-82.8 +/- 3.2
TB-222-023	-7.8 +/- 0.3*	-87.7 +/- 7.3

\*significant interaction by one-way ANOVA and  $p < 0.05$  compared to exendin-(9-39)

#### G protein antagonism (GLP-1, 7-36, amide)

exendin-(9-39)	-6.0 +/- 0.2	-81.9 +/- 3.5
TB-001-003	-6.9 +/- 0.4*	-69.6 +/- 12.4
TB-222-023	-7.5 +/- 0.4*	-70 +/- 10.1

\*significant interaction by one-way ANOVA and  $p < 0.05$  compared to exendin-(9-39)

#### G protein antagonism (glucagon)

exendin-(9-39)	-5.1 +/- 0.1	-92.9 +/- 2.7
TB-001-003	-6.4 +/- 0.1*	-93 +/- 3.9
TB-222-023	-6.4 +/- 0.1*	-107.4 +/- 7.4*

\*significant interaction by one-way ANOVA and  $p < 0.05$  compared to exendin-(9-39)

**Table S1.** Efficacy ( $E_{MAX}$ ) and potency ( $\log EC_{50}$ ) for each molecule in every assay presented. Values are presented as calculated from fitting to curve  $Y = \text{Bottom} + (\text{Top} - \text{Bottom}) / (1 + 10^{-(\log EC_{50} - X)})$  in Graphpad Prism. Where  $EMAX = \text{Top} - \text{Bottom}$ . Error is the standard deviation, as calculated from 95% confidence intervals from curve fits. N/A reported when curves were not able to be accurately fit to the data. For each group, a one-way ANOVA was performed on values and standard deviations for  $EC_{50}$  and  $EMAX$  separately, with a Tukey's posthoc comparison to indicated controls.