**Hands-on Assignment 5 (two parts)**

1. **Hand-on assignment 5a – Composite Concentration-Response**

Given the following data (observed response vs steady state concentration) that was obtained with a new pharmacological agent under investigation, you assume that a Composite Concentration-Response model is required to fit the data.

1. *Plot the data and decide which* ***composite*** *model to use.*



1. *Obtain initial parameter estimates.*

|  |  |
| --- | --- |
| Parameter | Estimate |
| Imax(pmol/ul) | 100 |
| IC50(uM) | 0.6 |
| n1 | 1 |
| Emax(pmol/ul) | 100 |
| EC50(uM) | 4.6 |
| n2 | 1 |
| E0 | 0 |

1. *Use the Winnonlin ASCII model builder to fit the data.*
2. *Report the parameters*

|  |  |  |
| --- | --- | --- |
| Parameter | Estimate | CV% |
| Imax | 113(pmol/ul) | 9.1 |
| IC50 | 0.61(uM) | 5.0 |
| n1 | 3.48 | 13.9 |
| Emax | 111(pmol/ul) | 8.6 |
| EC50 | 3.47(uM) | 6.2 |
| n2 | 2.99 | 11.8 |
| E0 | 0.98 | 317.3 |

1. **Hands-on Assignment 5b – Enantiomer Interaction (Racemic Drug – Ketamine)**

**Objectives:**

* To model the enantiomeric interaction between S- and R-ketamine
* To implement an agonist/partial agonist model
* To learn how to analyze data simultaneously in WinNonin

**Problem:**

Many drugs are administered as a racemic mixture. Given the differences in stereochemistry, the interaction of each isomer with the pharmacological target is often different. In this exercise, you will need to evaluate the effect of each isomer as well as the racemic mixture.

1. Use WinNonlin-ASCII to evaluate the PD of each isomer as well as for the mixture. Model the data for both isomers and the mixture simultaneously. Report all parameter estimates.



|  |  |  |
| --- | --- | --- |
| Parameter | Estimate | CV% |
| ImaxR(fmol/mg) | 9.31 | 4.26 |
| IC50R(uM) | 0.62 | 6.84 |
| n1 | 1.04 | 6.67 |
| ImaxS(fmol/mg) | 3.99 | 3.41 |
| IC50S(uM) | 1.04 | 3.86 |
| n2 | 3.49 | 7.96 |
| E0R(fmol/mg) | 9.37 | 2.31 |
| E0S(fmol/mg) | 9.34 | 1.32 |
| E0(fmol/mg) | 9.59 | 1.87 |

Code: Use three function statement blocks in the code to represent the Sigmoid functions that should be used for the individual isomers and for the combined R/S data.

Data: Enter the data using three columns. The additional column, “function”, is used to assign each data set to the appropriate code function (1, 2 or 3) block. For example, if the code uses “FUNC 1” for the R-ketamine pharmacodynamic data, then use “1” in the “function” column of the data sheet etc..