

Cloe Screen

Log D_{7.4}

Shake Flask

Background Information



'A compound with moderate lipophilicity (Log D 0–3) has a good balance between solubility and permeability and is optimal for oral absorption, cell membrane permeation in cell-based assays, is generally good for BBB penetration (optimal Log D ~2) and has low metabolic liability.'

¹Di L and Kerns EH. (2003) *Current Opinion in Chemical Biology* 7; 402-408.

- Lipophilicity is a key determinant of the pharmacokinetic behaviour of drugs. It can influence distribution into tissues, absorption and the binding characteristics of a drug, as well as being an important factor in determining the solubility of a compound.
- Log D (distribution co-efficient) is used as a measure of lipophilicity. Determining the partition of a compound between an organic solvent (typically octanol) and aqueous buffer is one of the most common methods for determining this parameter.
- Cloe Screen Log D_{7.4} uses the octanol / buffer miniaturised shake flask method for determining lipophilicity. The method evaluates three different ratios of octanol with the compound saturated in buffer. LC-MS/MS is used to quantify the samples.

Protocol

Method
Miniaturised shake flask method

Partition Solvent
n-Octanol

Ratio of Buffer:Octanol
50:1, 5:1, 1:2 (v/v)

Positive Control Compounds
Acebutolol, Ketoconazole

Compound Requirements
1 mg solid compound in >10 mL vial

Analysis Method
LC-MS/MS quantification

Data Delivery
Log D_{7.4}

Increasing lipophilicity of a compound series generally increases permeability, protein binding and volume of distribution, and decreases solubility and renal extraction².

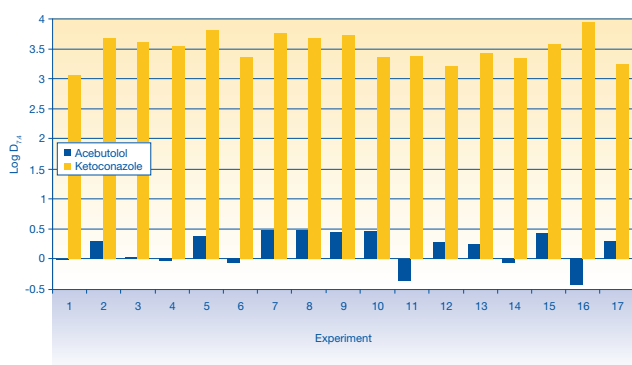


Cloe Screen Log $D_{7,4}$ Shake Flask

The log $D_{7,4}$ values generated by the Cloe Screen shake flask method are consistent with data generated from the GLpKa (calculated from log P and pK_a), which is considered to be the gold standard for these measurements.

Figure 1

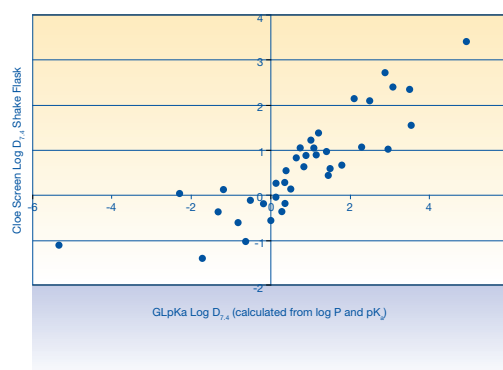
Data generated for acebutolol and ketoconazole in the Cloe Screen Log $D_{7,4}$ Shake Flask assay.



The graph illustrates reproducibility of the Cloe Screen. Log $D_{7,4}$ Shake Flask assay over 17 consecutive experiments for the two control compounds, acebutolol and ketoconazole.

Figure 2

Comparison of Cloe Screen Log $D_{7,4}$ Shake Flask data with Log $D_{7,4}$ calculated from the GLpKa.



References

- Di L. and Kerns EH. (2003) *Current Opinion in Chemical Biology* 7; 402-408.
- Kerns EH and Di L. (2003) *Drug Discovery Today* 8 (7); 316-323.