

Lipophilic efficiency

Lipophilic efficiency^[1] (**LiPE**), sometimes referred to as **ligand-lipophilicity efficiency** (**LLE**) is a parameter used in drug design and drug discovery to evaluate the quality of research compounds, linking potency and lipophilicity in an attempt to estimate druglikeness.^{[2][3]} For a given compound LiPE is defined as the pIC_{50} (or pEC_{50}) of interest minus the LogP of the compound.

$$\text{LiPE} = pIC_{50} - \log P$$

In practice, calculated values such as $cLogP$ or calculated $LogD$ are often used instead of the measured $LogP$ or $LogD$. LiPE is used to compare compounds of different potencies (pIC_{50} s) and lipophilicities ($LogP$). High potency (high value of pIC_{50}) is a desirable attribute in drug candidates, as it reduces the risk of non-specific, off-target pharmacology at a given concentration. When associated with low clearance, high potency also allows for low total dose, which lowers the risk of idiosyncratic drug reaction.^{[4][5]}

On the other hand, $LogP$ is an estimate of a compound's overall lipophilicity, a value that influence its behavior in a range of biological processes relevant to a drug discovery, such as solubility, permeability through biological membranes, hepatic clearance, lack of selectivity and non-specific toxicity.^[6] For oral drugs, a $LogP$ value comprised between 2 and 3 is often considered optimal to achieve a compromise between permeability and first-pass clearance.

LiPE allows capturing both values in a single parameter, and empirical evidence suggest that quality drug candidates have a high LiPE (>6); this value corresponds to a compound with a pIC_{50} of 8 and a $LogP$ of 2. Plotting $LogP$ against pIC_{50} for a range of compounds allows ranking series and individual compounds.

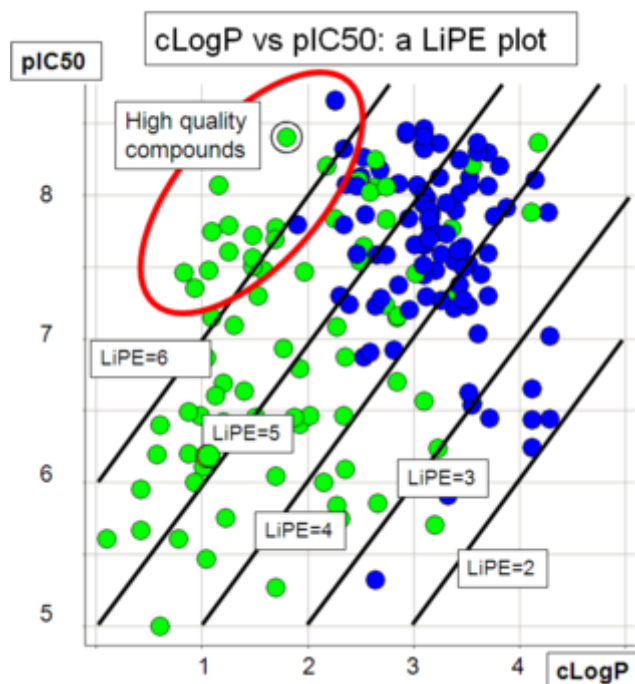
An alternative equation uses the logarithm of the ratio of potency (measured as binding energy) and the partition coefficient to compute a lipophilic ligand efficiency index (LE) with a different scale.^[7]

$$\text{LE}_{\text{lipe}} = \log\left(\frac{-\Delta G}{P}\right)$$

The following review discusses LipE in the context of other compound efficiency metrics.^[8]

References

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A plot of $LogP$ vs pIC_{50} for 2 series of compounds (series 1: green dots, series 2: blue dots). Diagonal lines represents areas of equal LiPE. Analysis of this LiPE plot shows that series 1 includes many compounds with a high LiPE, and thus may represent a better lead series for further optimization.

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