



**Trip Report:
American Chemical Society Short Course:
“Drug-Like Properties in Drug Discovery”
San Diego, California
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***Abstract.** The American Chemical Society Short Course: “Drug-like Properties in Drug Discovery” was held in San Diego, California on March 11-12, 2005. The course was designed for scientific professionals whose work involves medicinal, pharmaceutical and analytical chemistry, ADME and Pharmacology (especially those who design, synthesize and test new drug candidates, lead research teams or measure and predict ADME properties of compounds). The course gave a general review of the impact of drug-like properties on drug discovery, in vitro and in vivo biological testing and safety. The course also highlighted the fundamentals of key drug-like properties and the physiological barriers encountered by drugs. This report summarizes some of the highlights of the course.*

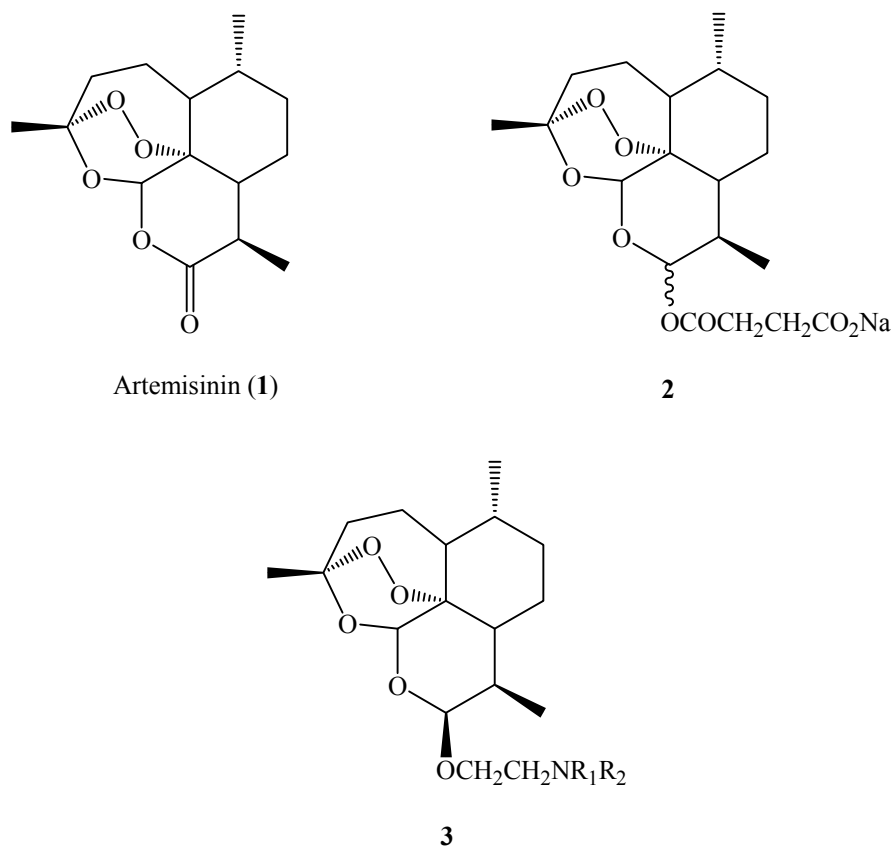
Introduction to Drug Properties:

As medicinal chemists have learned in the past, the hurdle between a compound binding with high affinity to a target and a successful drug on the market can be enormous. In the majority of cases, a successful drug candidate requires not only potency and selectivity, but also a suitable pharmacokinetic profile. Poor drug properties can cause development failure or impose limitations on drug development, such as expensive formulations to overcome insolubility or instability, increase development time, and burden to patients from higher or more frequent doses. It is now widely recognized that physicochemical, pharmacokinetic and biopharmaceutical properties need to be addressed early in drug discovery. Actually, it is necessary to balance optimization of drug activity and drug properties in the process of the discovery of good drug candidates.

Property Profile:

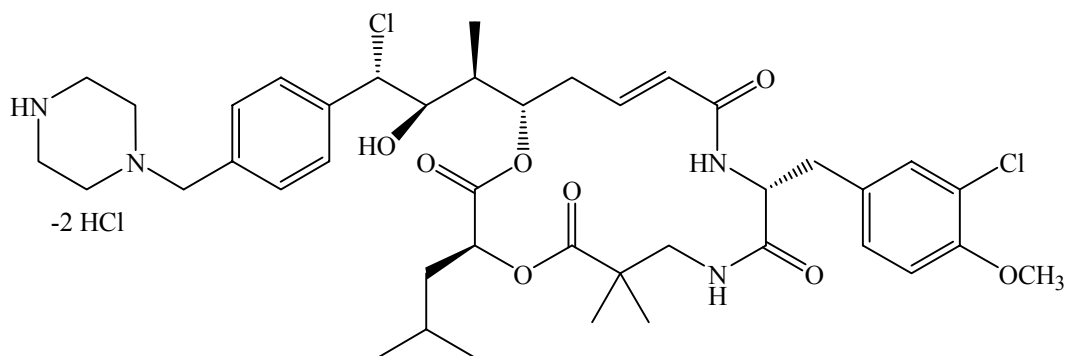
There are many drug properties, such as lipophilicity, permeability, solubility, blood brain barrier, integrity, pKa, stability, metabolism, CYP inhibition, P-glycoprotein, and plasma protein binding, to be evaluated in the process of the discovery of a good lead. Key among these properties are solubility, permeability, absorption, chemical and metabolic stability, and toxicity. For example, solubility is now seen as a property to be addressed at early stages of drug discovery. The first requirement for absorption is dissolution of the active compound. Only compound in the solution is available for permeation across the gastrointestinal membrane. Excessive lipophilicity is a common cause of poor solubility and can lead to erratic and incomplete absorption following oral administration. The incorporation of an ionizable center, such as an amine or similar function group, into a template can bring a number of benefits including aqueous solubility. Artemisinin (**1**) is poorly aqueous soluble compound (Figure 1). Introduction of a sodium salt (compound **2**) into the molecule increases aqueous solubility, but reduces stability of the compound. However, the maleate or oxlate of a basic amine derivative (compound **3**) possesses both improved aqueous solubility and good stability.

Figure 1

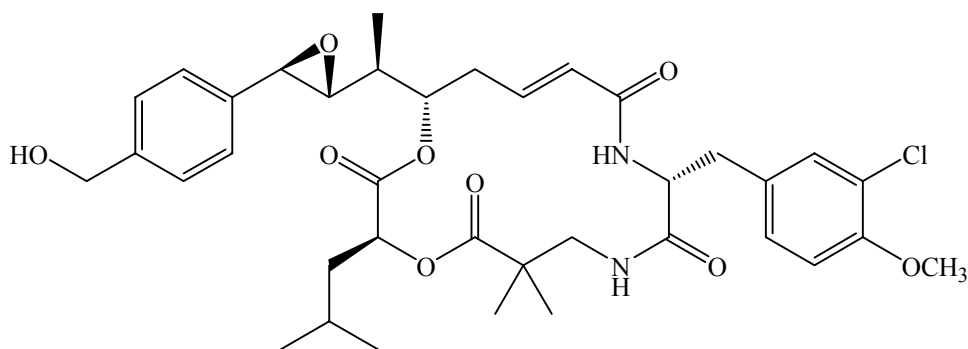


Aqueous solubility could be an issue relating to *in vivo* drug performance. A compound that is the most active *in vitro* is not necessarily the most active compound *in vivo*. Cryptophycin 52 analogue, piperazine dihydrochloride salt **4**, is relatively less active *in vitro* ($\text{IC}_{50} = 0.021 \text{ nM}$) than epoxide **5** ($\text{IC}_{50} = 0.004 \text{ nM}$). By improving the aqueous solubility of the molecule, however, compound **4** has shown high potency *in vivo* (Figure 2).

Figure 2



4

 $IC_{50} = 0.021$ nM, soluble, very active *in vivo*

5

 $IC_{50} = 0.004$ nM, low solubility, weak activity *in vivo*

Strategies for Improving Drug Properties:

In the traditional approach to a lead discovery, drug properties are not evaluated until the activity and selectivity have been optimized for months, or an even longer period of time. In contrast, an emerging approach suggests optimization of activity and properties can be done in parallel. Information from drug property evaluations can provide an early alert to problems, so that a bad series of compounds can be replaced with promising leads earlier to reduce time to find a good lead. Drug design has now come to a stage where an integrated approach including structure-based design and property-based design has become the basic concept in the pharmaceutical industry (Figure 3 and Figure 4).

Figure 3

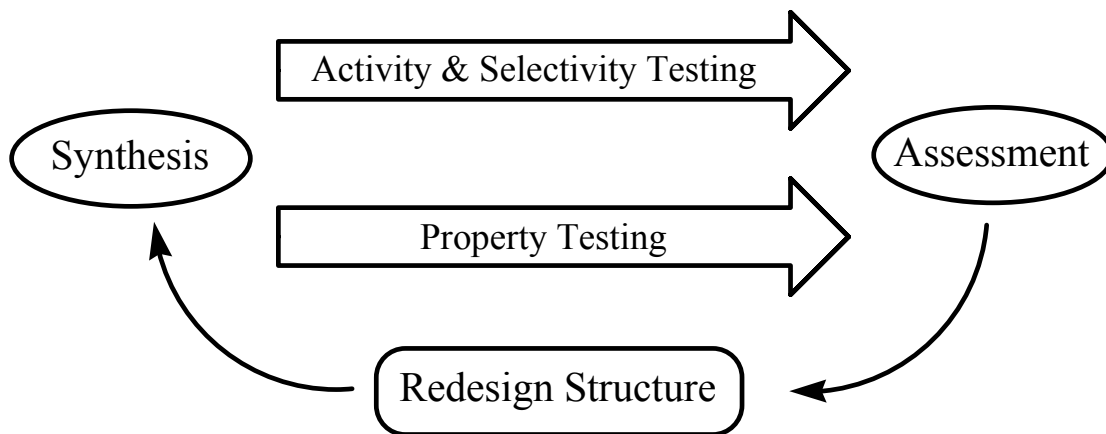
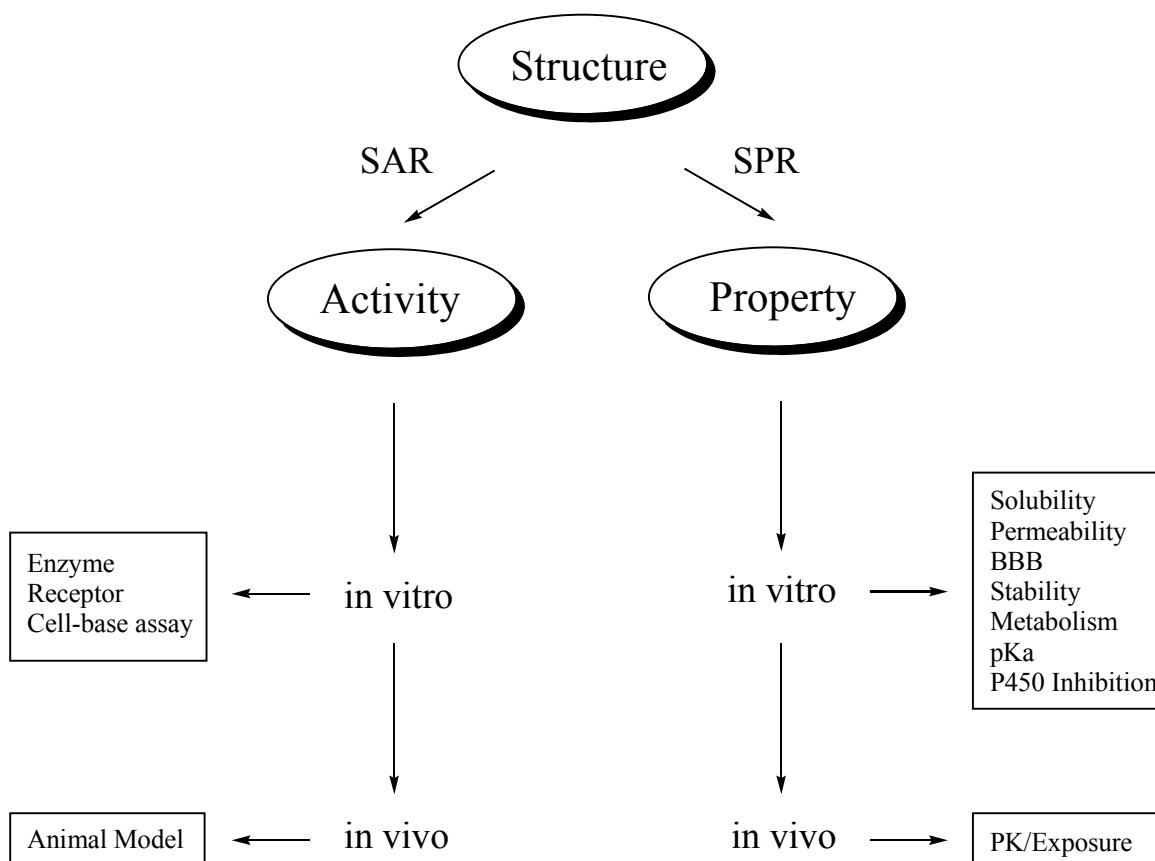


Figure 4



Recommended Reading Material:

Following are some of articles and books recommended by the Short Course:

1. Van de Waterbeemd, H.; Smith, D.A.; Beaumont, K.; Water, D.K. Property-based design: Optimization of drug absorption and pharmacokinetics. *J. Med. Chem.* **2001**, *44*, 1313-1332.
2. Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Delivery Rev.* **1997**, *23*, 3-25.
3. Lipinski, C.A. Avoiding investment in doomed drugs. *Curr. Drug Disc.* **2001**, 17-19.
4. Di, L.; Kerns, E.H. Profiling drug-like properties in discovery research. *Curr. Opin. Chem. Biol.* **2003**, *7*, 402-408.
5. Di, L.; Kerns, E.H. Pharmaceutical profiling in drug discovery. *Drug Discovery Today*, **2003**, *8*, 316-323.
6. Avdeef, A. *Absorption and Drug Development*, **2003**, Wiley-Interscience, Hoboken, NJ.
7. Borchardt *et al.* *Pharmaceutical Profiling in Lead Selection*, **2004**, AAPS Press, Washington, D.C.
8. Testa *et al.* *Pharmacokinetic Optimization in Drug Research*, **2001**, Verlag Helvetica Chim. Acta., Zurich.
9. Van de Waterbeemd *et al.* *Drug Bioavailability*, Wiley-VCH, Weinheim.