



**Trip Report for**  
**ACS Short Course**  
**“Essentials of Medicinal Chemistry and Pharmacology”**  
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**Abstract:** *The American Chemical Society Short Course “Essentials of Medicinal Chemistry and Pharmacology” is a program designed to be an introduction of medicinal chemistry principles to the organic synthesis chemist. Topics included a review of the fundamental concepts, pharmacodynamics (PD), pharmacophore development, ADMET, QSAR, practical drug studies relevant to the peripheral nervous system, enzyme inhibitors and CADD basics. The text that follows summarizes some of the highlights of the course.*

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## Fundamental Concepts

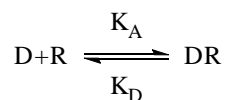
The course started off with a review of the many fundamental concepts of medicinal chemistry, and the biology behind them. The majority of the time spent on this topic was reviewing the association/dissociation of drugs to receptors and how one determines the  $K_d$  or dissociation constant. We then went on to talk about the cell as a whole, and much more in-depth look at the cell membrane covering the various methods of how things can enter into the cell. The lecture then went on to talk about how specific drugs entered into cells, and introduced the concept of a prodrug. Functional groups and their relationship to structure design and receptor sites were discussed in detail. The first lecture then concluded with a discussion on the idea of a therapeutic window and the drug approval process.

### Pharmacodynamics

Pharmacodynamics is the study of the interaction of the drug with its receptor and the effects it has on the body. A couple examples were looked at in detail. The first one was the ion channel receptors. Here we examined how the binding of a drug to the receptor opened up the ion channel to allow ions in/out of the cell.

The second one we looked at was a G-protein coupled receptor (GPCR). Here we looked at how the binding of a drug to the transmembrane protein set off a chain of events inside the cell. In one example, it was the production of cAMP. In another example, it was the inhibition of the production of cAMP. A third example of this was the activation of a phospholipase enzyme.

It was also during this lecture that we looked in detail at what agonists and antagonists are, and examples of both. This then led into the concepts of receptor occupation, and the dose-response curve.



$K_A$  is the association constant,  $K_D$  is the dissociation constant. Using the Henderson-Hasselbach equation:

$$K_D = \frac{[D][R]}{[DR]}$$

If we assume that the proportion of occupied receptors is  $v$ , then the portion of free receptors is  $1-v$ , so  $[R]=(1-v)$ , and  $[DR]=v$ :

$$K_D = \frac{[D](1-v)}{v}$$
$$v = \frac{[D]}{[D] + K_D}$$

Response is proportional to  $v$ , so when you have the highest biological effect,  $E_{\max}$ :

$$Response = \frac{E_{\max} [D]}{[D] + K_D}$$

This then leads to the concept of the  $[EC]_{50}$  which is where  $v$  would be  $1/2$ , so the  $[EC]_{50} = K_D$  when you work the math out. We can then plot the  $\text{Log}[\text{Drug}]$ -Response curve, and find experimentally what the  $[EC]_{50}$  is by taking the concentration at 50% activity. Another way is to find the slope of the plot of  $1/v$  vs  $1/[D]$  which is equal to  $K_D$ .

The discussion then went on to talk about how we can get partial agonists, and see that based on the  $[\text{Dose}]$ -Response curves. We also discussed how these curves can be used to determine whether a drug is more potent or if it is more effective by comparing curves. Antagonists were then talked about, and how one can determine from these curves whether it was a competitive or non-competitive antagonist.

### **Pharmacophore Development**

A pharmacophore is the three-dimensional arrangement of essential functional groups which are necessary to induce biological activity. When one looks for a pharmacophore, one has to look at the active form of the drug, and determine what is and what isn't important. In general this can include areas of hydrophobicity, hydrophilicity, steric bulk, specific functional groups, and many other possibilities.

This lecture took a detailed look at anti-histamine drugs that block  $H_1$  receptors, and compared them to histamine and each other. From this comparison we got a pharmacophore that would help predict active drugs. The issue of pH now came up too. At biological pH, are our amines protonated or not. Again the Henderson-Hasselbach equation was used to show that amines are mostly the  $NH^+$  species. With this in mind, we also looked at conformational changes and how histamine fits differently in the  $H_1$  and the  $H_2$  receptors.

Different drug development strategies were then discussed and examples of some were given. The different strategies are:

- Variations of substituents
- Extension of structure
- Side chain modifications
- Ring expansion and contractions
- Ring variations
- Isoteres
- Simplification of structures
- Rigidification of structure

## ADMET

ADMET stands for Absorption, Distribution, Metabolism, Elimination, and Toxicity. This in itself is also a discussion of pharmacokinetics which is the study of the body's response to a drug and the effects on the drug. It was here that Lipinski's rules of 5 were introduced as a method of predicting if a compound was drug like. We then looked at the various methods of absorption and distribution of the drug and how different functional groups can play a role in where it is absorbed, and how it is distributed throughout the body. Metabolism was then talked about, and the major kinds of metabolism were examined using examples from the literature:

### Phase 1 – Introduction of polar groups

- Hydrolysis
  - Esters
  - Amides
- Oxidations
  - Aliphatic hydroxylation
  - Aromatic hydroxylation
  - N-Dealkylation
  - O-Dealkylation
  - S-Dealkylation
  - Deamination
  - N-Oxidation
  - S-Oxidation

### Phase 2 – Conjugation reactions

- Glucuronide
- Glutathione
- Sulphate

While talking about metabolism, it was also discussed how this can be both a useful tool for us, or something to work around. For example, some drugs, it's the metabolite that is active and not the administered drug. Prilosec/Nexium and Seldane/Allegra are examples of this in phase 1 metabolism. On the flip side, the metabolites can be toxic and something that has to be worked around. An example of this would be Tylenol being toxic in high doses due to phase 2 metabolism. Toxicity was also discussed at this time.

The last part of this lecture was discussing routes of elimination, and how the common PK descriptors ( $k_{el}$ ,  $t_{1/2}$ , CL,  $V_d$ , AUC, and F) are derived, and how they are all related to each other. I personally found this to be the most useful part of the course.

### Rate of Elimination Derivation:

$c(t)$  is concentration at time  $t$ ,  $c(0)$  is concentration at time = 0,  $c$  is concentration,  $t$  is time and  $k_{el}$  is the elimination constant

$$-\frac{dc}{dt} = k_{el}c, \text{ so } \frac{dc}{c} = -k_{el}dt, \text{ so } \int \frac{dc}{c} = -k_{el} \int dt, \text{ so } \ln c(t) = -k_{el}t + \text{constant}, \text{ so}$$

$$\ln c(0) = \text{constant}, \text{ so } \ln c(t) = -k_{el}t + \ln c_0, \text{ so } c(t) = e^{-k_{el}t} \cdot e^{\ln c_0}, \text{ so } \boxed{c(t) = c_0 e^{-k_{el}t}}$$

$$\ln c(t) = -k_{el}t + \ln c_0, \text{ so } \ln = 2.303 \log, \text{ so } 2.303 \log c(t) = 2.303 \log c_0 - k_{el}t, \text{ so}$$

$$\boxed{\log c(t) = \log c_0 - \frac{k_{el}}{2.303}t}$$

So, when plotting log of drug concentration vs time, the slope is  $-\frac{k_{el}}{2.303}$

### Elimination Half Life ( $t_{1/2}$ ):

$$c(t) = c_0 e^{-k_{el}t_{1/2}}, \text{ so } \frac{c_{p2}}{c_{p1}} = e^{-k_{el}t_{1/2}} = 0.5, \text{ so } \ln 0.5 = -k_{el}t_{1/2}, \text{ so } -0.693 = -k_{el}t_{1/2}, \text{ so}$$

$$\boxed{t_{1/2} = \frac{0.693}{k_{el}}}$$

### Apparent Volume of Distribution:

$$\boxed{V_d = \frac{D}{c}}, \text{ where } D = \text{Dose}, c = \text{concentration}$$

Plasma volume = 3L, Extracellular volume = 14L, Total body volume = 45L

### Drug Clearance (CL):

$D$  = dose in mg/min,  $CL$  is the ratio of rate of drug removal (mg/min) to the concentration of the drug (mg/mL) so the units are mL/min.

$$CL = \frac{\left(-\frac{dD}{dt}\right)}{c(t)}$$

This can be figured out for each of the organs, and the assumption is made that the various  $CL$  rates can be summed to get the total  $CL$  rate.

$$CL_{total} = \sum_{organs} CL, \text{ so } -\frac{dD(t)}{dt} = kc(t), \text{ so } k=CL_t$$

$$-\frac{dD(t)}{dt} = CL_T c(t), \text{ so } CL_T = -\frac{1}{c(t)} \left[ \frac{dD(t)}{dt} \right], \text{ so } CL_T c(t) = -\frac{dD(t)}{dt}$$

We know that  $V_d c(t) = D(t)$ , and therefore  $V_d dc(t) = dD(t)$

Substituting in gives us:

$$CL_T c(t) = -V_d \frac{dc(t)}{dt}, \text{ so } CL_T c(t) = V_d \left( -\frac{dc(t)}{dt} \right)$$

And we know that  $-\frac{dc(t)}{dt} = k_{el} c(t)$ , so  $CL_T c(t) = V_d (k_{el} c(t))$ , so  $CL_T = V_d k_{el}$

$$\text{And } k_{el} = \frac{0.693}{t_{1/2}}, \text{ so } \boxed{CL_T = \frac{0.693}{t_{1/2}} V_d}$$

**Dose and Clearance Relationship: Area Under the Curve (AUC):**

$$-\frac{dD(t)}{dt} = CL_T c(t), \text{ so } -dD(t) = CL_T c(t) dt, \text{ so } -\int_{D_0}^0 dD(t) = CL_T \int_0^{\infty} c(t) dt, \text{ so}$$

$$\int_0^{D_0} dD(t) = CL_T \int_0^{\infty} c(t) dt, D_0 = \text{dose}, \text{ so } \int_0^{\infty} c(t) dt = \text{AUC}, \text{ so } \boxed{\text{Dose} = CL_T \cdot \text{AUC}}$$

$$\text{And since } CL_T = \frac{0.693}{t_{1/2}} V_d, \boxed{AUC = c_0 \frac{e^{-k_{el} t}}{-k_{el}}}$$

**Absolute bioavailability:**

$$F = \frac{D_o(oral)}{D_o(iv)}, \text{ so } F = \frac{CL_T(oral) \int_0^{\infty} c(t) dt(oral)}{CL_T(iv) \int_0^{\infty} c(t) dt(iv)}, \text{ so } \boxed{F = \frac{AUC(oral)}{AUC(iv)}}$$

## QSAR

QSAR or Quantitative Structure Activity Relationships was the next lecture. This very briefly and quickly went over the concept of relating observed biological response to

variations in structures. This in general is something that can be done to refine a pharmacophore and to help with searching databases to find other compounds that are similar that may be of a completely new structure and may be biologically active.

### **Peripheral Nervous System**

This lecture was an overview of how known drugs that effect the peripheral nervous system work. This included discussion on the structure of the nervous system, and how the various neurotransmitters are produced, transmitted, absorbed/degraded, and the sites they act on. The discussion also went over what the activation of the various receptors gave as a biological response.

We then looked at specific drugs, and used the knowledge of what receptors they were specific for, and if they were agonists or antagonists, what the expected result would be. With the limited knowledge we had about the receptors and their response, we were able to accurately predict what the biological effect the drug would have.

### **Enzyme Inhibitors and More**

In this lecture, we briefly went over the importance of knowing what the binding site of an enzyme is, and how we can use that to our advantage in designing drugs. The idea of an enzyme pocket being both acidic and basic was also discussed in detail, and helped to explain why enzymes can do reactions quickly that we would not be able to do in the lab. All of this was leading up to the concept of structure based design where knowing what the binding site crystal structure is, you can then design a drug to specifically fit into that site. Also, if one knows what the enzyme does, it may be possible to design a drug that will fit, but will not let the enzyme work, the idea of an intelligently designed antagonist. Many examples of both approaches were covered.

### **Computational Chemistry and Computer-Assisted Drug Design**

This was the last lecture of the course, and we had run out of time to cover this in great detail. The general objective of the lecture though was to stress that we should be using CADD to look at our molecules. With the help of 3-D modeling, you can easily visualize the various features of your compounds, and make finding the actual pharmacophore easier to do. CADD can help because it can go through and give you the lowest energy conformer of the molecule. The handouts that were given cover in greater detail the math that is used by many CADD programs, and gives real-world examples of where CADD has helped with design.

### **Summary**

Overall, this course was an excellent course for anyone that is working in the Med-Chem department. While it is not a comprehensive course, it does give a great overview of what all goes into medicinal chemistry. The best part of the course from my perspective was the derivation of the various PK terms. The example he went through during class

that came from the text of *The Organic Chemistry of Drug Design and Drug Action*, 2<sup>nd</sup> ed. by R.B. Silverman using actual data to determine all the terms really made it possible for me to understand what it all means.

After working on a project where all the biological data was shared with us, and we were asked to give input as to what to do next, I now understand to a greater degree what was happening. This class would have been invaluable to take prior to that project, but now that I have taken it, I think I am more prepared for the next one that comes along that is like that.