



**Trip Report for**  
**ACS Short Course “Essentials of Medicinal Chemistry and Pharmacology”**  
**Houston, TX**  
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**Abstract:** *Dr. J. Phillip Bowen, Professor of Chemistry and Biochemistry and Director of the Center for Drug Design at the University of North Carolina at Greensboro taught the ACS short Course “Essentials of Medicinal Chemistry and Pharmacology”. The course focused on the fundamentals and key concepts of medicinal chemistry and pharmacology.*

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## **Introduction**

Each participant was provided with a set of notes/slides covered during the series of lectures which were presented. Included within the notes are useful references for further reading into the key principles of medicinal chemistry and pharmacology. Listed below are the lecture topics covered along with a brief description of the content of the lecture.

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### **“Fundamental Concepts”**

This lecture was a very generalized introduction to medicinal chemistry, providing definitions for various terms in medicinal chemistry and pointing out the distinction between the two major components of medicinal chemistry, pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drug). Also described were the concepts of drug action, overview of the cell, prodrugs, drug binding interaction, drug safety (therapeutic index) and the drug approval process.

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### **“Introduction to Drug Action: Pharmacodynamics”**

This section focused on receptor theory with a detailed discussion of drug-response curves, defining full agonists, partial agonists, inverse agonists, competitive antagonists and noncompetitive antagonists.

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### **“Drug Design Concepts: Pharmacophore Development”**

A pharmacophore is defined as the three-dimensional arrangement of essential functional groups which are necessary to induce biological activity. The lecture described pharmacophore determination and development of the a pharmacophore. With an identified pharmacophore, drug development strategies include variation of substituents, extension of the structure, side chain modification, ring expansion/contraction, ring variation, isosteres, simplification of structure and rigidification of the structure.

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### **“Introduction to ADMET – Concepts and Applications”**

For successful drug design, one must consider the implications of ADMET (drug absorption, distribution, metabolism, elimination and toxicity) at an early stage. The numerous routes for drug administration were discussed; pointing out that oral administration is the preferred route with best patient compliance. When considering drug design; potency, solubility and permeability are the three key physical variables which must be addressed to enhance the activity of orally available compounds. Predictive methods were discussed, including Lipinski’s rules. Phase I and phase II metabolism was discussed and numerous examples of phase I metabolism of common functionalities were described. As part of a drug design strategy, the modifications of functional groups can be conducted to avoid metabolism and toxicity issues. The primary route of elimination of drugs from the body occur by an initial phase I metabolism to introduce polar groups into the molecule. These polar groups then undergo conjugation (glucuronide,

glutathione, and sulfate) to form very water soluble molecules which are readily excreted from the body. The concepts of apparent volume of distribution, half life, clearance and absolute bioavailability were discussed.

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### **“Overview of QSAR Methods”**

QSAR is a quantitative method for relating biological activity to structural features in a mathematical relationship. Fundamental assumptions for development of a QSAR model are that all analogs in a series react with the same receptor in an identical way and that biological activity is a direct consequence of the molecular structure of a compound. The major focus of this lecture was on the traditional Hansch 2D-QSAR approach in which biological activity can be related as a function of physicochemical properties such as sterics, electrostatics and lipophilicity. Also CoMFA methodology (comparative molecular field analysis) was briefly discussed. Validation of a QSAR analysis is necessary to avoid of potential pitfalls of chance correlations and unrecognized correlations.

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### **“Peripheral Nervous System”**

This lecture provided an overview of the nervous system, neurons and neurotransmitters. Included were the following topics: Parasympathetic nervous system, acetyl choline neurotransmitter release, biosynthesis of acetyl choline, action potential, acetyl choline metabolism and regulation, drugs affecting the parasympathetic nervous system, sympathetic nervous system, norepinephrine neurotransmitter release, biosynthesis of norepinephrine, norepinephrine metabolism and regulation and drugs affecting the sympathetic nervous system.

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### **“Enzyme Inhibitors and More”**

Examples of enzyme inhibitors and how they function were discussed with a focus on structure based design.

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### **“Computational Chemistry and Computer Assisted Drug Design”**

CADD is utilized for both lead compound identification and lead compound optimization. Lead optimization entails both an increase in desirable properties such as binding affinity and selectivity with a concomitant decrease in undesirable properties such as toxicity. The basis for rational drug design is to gain an understanding at the molecular level of the relationships between the disease causing target and potential ligands and to then utilize this information to make predictions for ligand affinity and ADMET properties. The goal of CADD is to predict the likelihood of success prior to the initiation of work.