

INSTRUCTIONAL DESIGN AND ASSESSMENT

Instructional Model to Teach Clinically Relevant Medicinal Chemistry

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Submitted October 14, 2005; accepted January 3, 2006; published August 15, 2006.

The relevance of medicinal chemistry to pharmacy practice has been questioned by many pharmacy educators as more emphasis has been placed on linking clinical knowledge and practice to pharmacy student educational outcomes. Faculty teaching in medicinal chemistry and other biomedical and pharmaceutical science courses have embraced this challenge. Various teaching methods and approaches within medicinal chemistry that emphasize application of this knowledge have been sought to improve the usefulness of this scientific discipline to the future careers of students. The newly revised ACPE guidelines and standards have reemphasized the role of the sciences in the curriculum. With this mandate, it is essential that all science faculty members adjust the way they teach to meet the new desired outcomes for pharmacy graduates. This manuscript describes an instructional model for teaching medicinal chemistry explicitly designed to meet these outcomes. A process of collaboration between experienced pharmacy faculty scholars was used to derive this approach. Pedagogy for cognitive and affective learning was incorporated. A case study using a representative drug class is presented to illustrate this model.

Keywords: medicinal chemistry, clinical relevance, ACPE guidelines, ACPE standards, therapeutic decision-making, clinical reasoning

INTRODUCTION

In the past few years, administrators, pharmacy organizations, clinical faculty members, students, and other stakeholders have questioned the relevance of medicinal chemistry to the contemporary practice of pharmacy. Faculty members teaching medicinal chemistry have sometimes struggled to explicitly demonstrate the importance of the discipline to students who will practice pharmacy. This challenge continues, as some students struggle to find the relevance, while having their own negative beliefs toward the study of chemistry. Table 1 displays a history of the literature that describes the major efforts by medicinal chemistry faculty members to introduce clinical relevance through varying content and instructional methods in course delivery.¹⁻¹⁷ Significant strides have been made by medicinal chemistry professors toward the endpoint of bringing clinical relevance to the study of medicinal chemistry.

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The newly revised Accreditation Council on Pharmacy Education (ACPE) guidelines and standards¹⁸ have clearly emphasized the role of the biomedical and pharmaceutical sciences in the pharmacy curriculum. The underlying message is that foundational knowledge in the sciences is important for students to be competent practitioners, and the curriculum should ensure the application and reinforcement of curricular content including the sciences. All pharmaceutical science faculty members now must adjust the way they teach to meet the new goals and outcomes of pharmacy graduates.

This manuscript describes an instructional model to teach medicinal chemistry that retains the foundation knowledge while integrating clinical relevance. Many aspects of this model including the structurally based therapeutic evaluation (SBTE) concept have been utilized, described, published, and tested over the years.^{5,9,13} However, in this manuscript, 4 experienced medicinal chemistry faculty scholars and a clinical faculty member with experience in teaching methodology and philosophy, collaborated and compared their reflective teaching practices to synthesize this instructional model as a template to be applied across the pharmacologic drug classes

Table 1. Historical Literature Describing Integration of Clinical Relevance into Medicinal Chemistry Courses

| Timetable | Contribution |
|----------------------|--|
| 1985 | Article by Roche utilizing chemical knowledge in rational therapeutic decision making. ¹ |
| 1990s to present day | Several articles published highlighting different strategies to introduce clinical relevance in the teaching of medicinal chemistry. ¹⁻¹⁷ Several presentations and abstracts were presented at the American Associations of Colleges of Pharmacy Annual Meeting. |
| 1994 through 1998 | Patient related case studies in medicinal chemistry ^{2,6,7} and Case Study Textbook in Medicinal Chemistry published ³ |
| 1997 through 2001 | Structurally Based Therapeutic Evaluation concept was introduced as a way to bring relevance, practical applications, interdisciplinary teaching and meeting specific ability based outcomes for pharmacy students in medicinal chemistry ^{5,9,13} |
| 1994 to present day | Computerized tutorials in medicinal chemistry. ^{4,8,10,12} |
| 2003 | Foye textbook introduces case studies at the end of each chapter. ¹⁷ |

common to medicinal chemistry courses. A case study using a representative drug class, the *beta* adrenergic antagonists, is presented to illustrate the application of this instructional model template and to provide other faculty members in medicinal chemistry and pharmaceutical and clinical sciences with a step-by-step approach to how this instructional model can be incorporated to introduce clinical relevance for their students.

DESIGN

The model was constructed using a 6-section template. These sections are:

1. Introduction
2. Pharmacophore
3. Structure activity relationships (SARs)
4. Applying SAR
5. Summary of the most common clinical decisions
6. Prediction of clinical activity

This template moves the students' thinking through a constructive process that lays a medicinal chemistry foundation of both generalized and specialized content knowledge. As students move through the content presentation to the increasingly specialized knowledge, they are presented with content that is selected based upon its connection to clinical relevance. Once the logical connection is presented between the science and the clinical relevance, the content progresses to a patient-centered context and applies this science knowledge to the prediction of clinical activity and clinical outcomes expected in the patient who is exposed to the medicinal compounds. The design of the content presentation is mapped against Bloom's taxonomy of cognitive learning (Table 2) and Krathwohl's taxonomy of affective learning (Table 3) as described below.

Students are explicitly presented with a review of Bloom's taxonomy and are challenged to think critically and perform at a higher level. Content knowledge is then presented, explanations provided to enhance student understanding, and application of the content knowledge to

patient-centered decision making described using prediction of clinical activity in the clinical reasoning process.

Krathwohl's¹⁹ Taxonomy of learning within the affective domain identifies 5 critical steps to meet educational objectives as described in Table 3. A summary of how our model helps students meet the 5 critical steps is included. When students first present in medicinal chemistry class, it is common for them not to demonstrate an appreciation for the importance or usefulness of medicinal chemistry. So, it appears that influencing the valuing stage of Krathwohl's taxonomy is critical to help students meet the educational objectives. To influence this, medicinal chemistry professors spend substantial effort to create the contextual knowledge and appreciation of the discipline when students begin their studies of this component of the pharmacy curriculum. Students are usually introduced to the meaning of medicinal chemistry, and how knowing the chemical properties of a drug can help understand its kinetics, mechanism of action, place in therapeutic decision making, and potential adverse effects on the biological system. Throughout the course, the instructors expend extensive effort to prove to the students that knowledge of medicinal chemistry contributes to distinguishing the expertise of the pharmacist professional from other health care providers such as physicians and nurses. Different instructional approaches are used throughout the course that are intended to assist the student in attaining the higher levels of affective reasoning related to the use of this expert knowledge. In addition to emphasizing the valuing stage, the lesson content, organization, instructional approach, and teaching style also target other aspects of the affective taxonomy including receiving, responding, organization, and characterization as described in Table 3. A more detailed description of each step in our instructional model, including strategies to meet Bloom's and Krathwohl's taxonomy of learning, is provided below.

Table 2. Bloom's Taxonomy of Learning¹⁹ Within the Cognitive Domain As Mapped Against the Instructional Model Design

| Cognitive Taxonomy | Content Knowledge Within Instructional Template |
|---|---|
| Knowledge (Recalls learned material) | Recall of essential knowledge in chemistry, organic chemistry, anatomy, physiology and biochemistry. Review of medicinal chemistry and pharmacology essential knowledge. Introduced to pharmacophore. Introduced to major structure activity relationships (SAR). Introduced to major therapeutic decisions that can be explained by the SAR of the drug class. |
| Comprehension (Understands meaning) | Science courses, pharmacology, therapeutics and medicinal chemistry integration exercise. Rules on use of pharmacophore nomenclature for drug class identification Presentation on what is a structurally based therapeutic evaluation (SBTE)? Rules on use of SAR in SBTE scenarios. |
| Application (Uses rules, methods, concepts, principles, laws or theories in new situations) | Students use pharmacophore rules to identify drug classes when provided chemical structures. Apply the SAR to predict the activity of some of the marketed products. Apply the SAR to other marketed products and predict activity of new drugs. Conduct an SBTE analysis of a patient case: students apply seven therapeutic criteria to structural knowledge. Attempt questions from previous examinations. |
| Analysis (Breaks down a larger situation into it's components to understand it's structure) | Conduct an SBTE analysis of a patient case: students identify the pharmacophore, basic SAR and physicochemical properties of drug molecules that impact clinical decisions based on several clinical scenarios for a patient with a disease state and other co-morbidities. |
| Synthesis (Create something new) | Conduct an SBTE analysis of a patient case: students use the component forms of knowledge required to perform an SBTE to predict pharmacological action. |
| Evaluation (Judge the value based upon known criteria) | Conduct an SBTE analysis of a patient case: students solve real-life therapeutic problems to simulate application in practice post-graduation? |

Introduction. The first section is a general introduction of the drug class with emphasis on the importance of integrating information from previous course work, such as general and organic chemistry, anatomy, physiology, pathology, and pharmaceuticals. Students are challenged to engage in discussion in class with specific questions that would require them to integrate previously acquired and concurrent knowledge. These questions can be included in each lesson handout. Some faculty members have also created an integration exercise which incorporates knowledge from previous courses to challenge the students to always think about the big picture.¹³ These exercises are built to emphasize both cognitive and affective reasoning.

A review of key concepts in pharmacology is also included in the introduction. The integration of medicinal

chemistry and pharmacology is helpful for the students. Whether the 2 courses are integrated or taught separately, students in the 4 institutions where the authors of this manuscript teach do voice their satisfaction when the lessons in pharmacology and medicinal chemistry coincide and do indicate that the 2 disciplines complement each other.

Pharmacophore. In this section the students should be introduced to the pharmacophore and challenged to identify it, based on basic nomenclature. Hints based on the nomenclature to identify the key components of the pharmacophore should be provided. The goal here should be to challenge the students to identify drug classes based on the pharmacophore of each drug class (ie, similar to memorizing the name of a drug in pharmacology, students

Table 3. Krathwohl's Taxonomy of Learning¹⁹ Within the Affective Domain Targeted Within the Instructional Model Design

| Affective Taxonomy | Content Within Instructional Template |
|---|---|
| Receiving (Pays attention to input) | Emphasize the course designed around use of relevant chemistry to future career responsibilities of a pharmacist. Stress the continuum between medicinal chemistry-pharmacology and therapeutics. Introduce patient scenarios to demonstrate value of content early in course. Structured lesson plan to focus student on priorities for learning. Easy to follow and concise notes. Pre-assessment quizzes. Emphasize how this prepares the student for use of the knowledge in patient care clerkships. Encourage assertiveness of student engagement and discussion in class. |
| Responding (Willingly participates) | Emphasize student responsibility for learning. Provide exercises in the student handout and in in-class interactive sessions. Create a 'safer' classroom for inquiry by emphasizing the low risk of participation and potential harm if student is wrong in the controlled classroom environment of the course. |
| Valuing (Attaches worth to input and participation) | Introduce and emphasize oath of the pharmacist, honor code, professional responsibility. Illustrate how use of this material is essential to the student as a professional. |
| Organization (Adopts value internally) | Predictive clinical decision making is used to build internal valuing of use of this knowledge to improving patient health or reducing harm. |
| Characterization (Incorporates into daily ways) | Expectations that this approach be applied in the study and application of therapeutics in the curriculum presented to students at end of course. |

will be expected to know how to classify the structure based on the nomenclature of the pharmacophore for each drug class).

Structure activity relationships. This section provides a concise, easy to follow and extensive summary of the major SAR. Unique SAR pertaining to specific drugs in this drug class should also be provided. Depending on the class, there may be a number of functional groups that are essential for or affect activity. Therefore, the use of a different color for each functional group in this section may help the students to keep track of the impact of the various groups on the SAR. A summary of the SAR can also be provided before the end of the section. Finally, students should also be shown how to apply the knowledge to 1 or 2 products on the market.

Applying SAR. This section provides the students with clear examples of how to apply the SAR to predict the activity of some of the marketed products. It also helps

the students to ultimately apply the SAR to other marketed products and predict the activity of new drugs.

Summary of clinical decisions. In this section, students are provided with a clear list of the major therapeutic decisions that can be explained by the SAR of the drug class. In addition, students are provided with SBTE scenarios to apply the knowledge. Examples of how this knowledge meets outcome objectives and ability-based outcomes for graduates are also presented. Review of major therapeutic texts such as DiPiro's *Pharmacotherapy*²⁰ or Koda Kimble's *Applied Therapeutics*,²¹ other texts and primary clinical literature are helpful to identify common therapeutic decisions that can be explained by the structure. This will also serve to provide relevant case studies to apply the SAR. For example, DiPiro provides an algorithm with a step-wise approach of how different drug classes treat a specific disease state. The students may not be required to memorize the algorithm.

However, introducing the algorithm provides the students, for example, with the step-wise approach to treating hypertension²² and when the *beta* antagonists, diuretics, angiotensin-converting enzyme inhibitors, and other antihypertensive agents may enter into the clinical reasoning process. Therefore, SBTE relevant cases can be constructed based on the SAR of the above-identified antihypertensive agents, on different patient scenarios and on some of the most common therapeutic decisions for the specific drug class. Common therapeutic decisions pertaining to the *beta* adrenergic antagonists are shown in Table 4.

Following the summary table of the most common therapeutic decisions, students are introduced to SBTE^{5,9,13} case studies and are challenged to apply their knowledge. The students are reminded that a SBTE is composed of 2 components, the first and most important is the SB (structurally based) and second component, which is the application part TE (therapeutic evaluation). When conducting an exhaustive SBTE analysis, students identify the pharmacophore, basic SAR, and physicochemical properties of drug molecules and apply 7 therapeutic criteria to translate structural knowledge into predicted pharmacological action to solve real-life therapeutic problems. These are the same criteria used to evaluate drug therapy decisions in clinical case studies, and include: (1) drug history/drug response, (2) patient compliance, (3) current medical history, (4) past medical history, (5) side effects, (6) biopharmaceutics, and (7) pharmacodynamics.⁵ The criteria are meant to simplify therapeutic decisions by identifying all aspects that affect

the therapeutic decision-making process. Students are not required to memorize the list. However, putting the SBTE to use will become helpful when relating to the “minimal” therapeutics discussed in medicinal chemistry and preparing for therapeutics in the curriculum. The assistance of clinical faculty members may be sought in constructing the case studies in addition to reviewing therapeutics texts and clinical literature. The case studies also serve to integrate information from other courses in the curriculum such as anatomy, physiology, biochemistry, clinical chemistry, and patient assessments. While for the most part, medicinal chemistry is not integrated with therapeutics, students do rise to the challenge of incorporating SAR into therapeutic decision making. However, the faculty member should be explicitly clear and concise in identifying the common therapeutic decisions that can be explained by the SAR. The summary table of common clinical decisions (Table 4) should be helpful in this regard. Also, the constructed SBTE scenarios should be at a level consistent with the student level of therapeutic knowledge and comfort as gauged by the faculty member.

Prediction of clinical activities. The final section is meant to challenge students to apply and find more therapeutic decisions that can be explained by the structure/SAR. It is also meant to emphasize the importance of the practical applications of the knowledge gained by applying it to specific SBTE scenarios. General questions would help the students to recall and apply the SAR and integrate information. Students can then be asked

Table 4. *Beta* Adrenergic Antagonists Common Therapeutic Decisions

Common Therapeutic Decisions

- *beta*₁-selective compounds are safer to use for treatment of hypertension in patients with a history of bronchitis, chronic obstructive pulmonary disease, or asthma.
 - Non-selective *beta*-antagonists ↑ triglycerides and decrease high density lipoprotein (HDL). Therefore, they are contraindicated in patients with a history of hyperlipidemia.
 - *Beta*₁-selective compounds have less effect on lipid levels compared to nonselective compounds. This is also true for *beta* antagonists with intrinsic sympathomimetic activity and *β* antagonists with *α*-blocking activity.
 - *Beta*-antagonists with ISA are a good choice to treat hypertension in a patient with a history of bradycardia.
 - Lipophilic *beta*-antagonists penetrate the blood brain barrier and this can contribute to increased central nervous system (CNS) side effects including nightmares, insomnia, psychosis and depression. Therefore, lipophilic compounds should be avoided in patients with a history of depression, sleeping disorders and psychosis. Side effects may also be detrimental to compliance.
 - A high lipophilic nature may also contribute to decrease duration of action due to extensive first pass effect which may affect patient compliance if the drug is given more often. In addition, dosage adjustment in a patient with liver disease may be warranted.
 - A high polar nature for the *beta* antagonist will decrease CNS penetration and the potential for CNS side effects, and it will contribute to enhanced excretion and a decrease in duration of action. In addition, dosage adjustment in a patient with impaired renal clearance may be warranted.
 - An intermediate lipophilic nature for a *beta*-antagonist will decrease CNS penetration but some CNS side effects may be observed. This will also prevent extensive metabolism or excretion which will enhance duration of action and compliance.
 - For topical ophthalmic application, high lipophilic nature will contribute to decrease distribution and the potential for side effects. A balanced lipophilic-polar nature will increase distribution and potential for side effects and contraindication in certain disease states.
-

more practical applications and finally students can be challenged to synthesize their own questions and case studies.

Therefore, the above instructional model template provides a standardized, concise, and easy to follow discussion of the SAR with several examples of the use of SAR knowledge to contemporary therapeutic decision-making. Self-assessment questions to help the students integrate information and achieve a higher level of critical thinking are incorporated. Structurally based therapeutic evaluation^{5,9,13} scenarios are provided that highlight application of biomedical and pharmaceutical sciences knowledge to meet the outcome objectives and ability-based outcomes for pharmacy graduates based on pharmaceutical care functions, professional practice skills, and ACPE standards. A case study describing the application of this template is provided.

CASE STUDY: *BETA* ADRENERGIC ANTAGONISTS

Introduction

Beta-adrenergic antagonists inhibit the action of both endogenous and exogenous sympathomimetics on adrenergic receptors. These adrenergic blocking agents (also known as sympatholytics or adrenolytics) are, with few exceptions, competitive antagonists. Many *beta*-adrenergic antagonists have non-selective action at *beta*₁ and *beta*₂, while others have selective blocking activities at *beta*₁ in low doses. Labetolol is also non-selective but it also has *alpha*₁ blocking action. There are even a few agents (pindolol and acebutolol for example) with intrinsic sympathomimetic activity at the *beta* receptor. Therefore, this class is divided into 4 distinct subclasses. In most instances, the structure will enable us to classify the compounds into the 4 subclasses.

- (1) Non-selective *beta*-adrenergic antagonists;
- (2) Selective *beta*₁ at low doses;
- (3) *Beta* antagonists with *alpha*₁ receptor blocking activity – labetalol and carvedilol; and
- (4) Non-selective antagonists with intrinsic sympathomimetic activity (ISA) – pindolol (carteolol and acebutolol to a much lesser degree).

Beta-antagonists are used primarily to treat stable (exercise-induced) angina, unstable angina, hypertension, and coronary heart disease but they are also used to treat myocardial infarction, cardiac arrhythmias, glaucoma, tremors, and migraine headaches. The *beta*-blocking agents exhibit a high degree of stereoselectivity in the production of their *beta*-blocking effects, ie, their interactions with adrenergic receptors are significantly influenced by their stereochemistry. For example, for the aryloxypropanolamines, the S form is approximately 100 times more

potent than the R form. The interaction of *beta*-adrenergic antagonists with adrenergic receptors is analogous to that of adrenergic agonists. However, their interaction occurs in a manner that inhibits activation of the receptors.

Question: Identify organic chemistry, biochemistry, anatomy, and pathophysiology concepts that are important for the SAR-based drug decision process for the *beta* antagonists.

Review of Pharmacology

Students are asked to recall from the adrenergic agonists lesson that there are 2 main types of adrenergic receptors (*alpha* and *beta*) and 2 subtypes of *alpha* (1 and 2) and 3 subtypes of *beta* (1, 2 and 3). With few exceptions (*alpha*₂ receptors on venous blood vessels being one of them), type 1 receptors (both *alpha* and *beta*) have excitatory/stimulatory actions, while type 2 receptors have inhibitory/relaxant actions. In pharmacology, students will have more extensive discussions of the type of receptors, the signal transduction pathways, distribution and the pharmacological effect(s) associated with the different types of receptors. Therefore, they are reminded that this is a good point to review these concepts. In addition, since the major therapeutic uses of this class involve the heart and the eye, it will also be helpful for students to review the anatomy and physiology of the heart and eye. Further, bronchopulmonary pharmacology, anatomy, and physiology will be important to understand the potential for bronchoconstriction with this class of drugs especially the non-selective agents.

Question: Define an agonist, partial agonist, antagonist, competitive antagonism, selectivity, affinity, intrinsic sympathomimetic activity, signal transduction pathways.

In general, the pharmacological effects seen with *beta*-adrenergic antagonists are the opposite of the effects produced by the action of adrenergic agonists on *beta*-adrenoceptors. Adrenergic antagonists produce effects that are either an attenuation of or are opposites of these effects. For example, *beta*-antagonists block the action of agonists on *beta*-receptors so the overall effect produced by the antagonists is a reduction in the intensity of the agonistic effects.

Pharmacophore

Figure 1 shows the basic pharmacophore for *beta*-adrenergic antagonists. Therefore, for any structure to be identified as a *beta*-antagonist, this basic pharmacophore has to be part of the structure. There are 2 basic

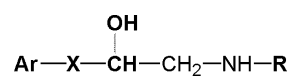


Figure 1. *Beta*-adrenergic antagonists general pharmacophore.

pharmacophores for the *beta*-adrenergic **antagonists—arylethanolamine** and **aryloxypropanolamine**. It is easy to relate to the name by “dissecting” it into its components, for example, Arylethanolamine (Figure 2): Aryl (aromatic), X = nothing, ethanol = an ethyl with an alcohol functional group, amine = NH₂. For the aryloxypropanolamine (Figure 3): the X= methylen-oxy, therefore, there is an **oxy** for the ether type oxygen on the side chain, an extra carbon on the side chain which makes it propyl and with the hydroxyl group and the terminal amine, it is propanolamine. In general, the aryloxypropanolamines are more potent than the corresponding arylethanolamines and make up a majority of the *beta*-antagonists that are presently used clinically. As antagonists, these structures have the basic characteristics of an agonist that allows/permits binding to the *beta*-receptors but they lack the essential SAR required for receptor activation.

Question: What are the essential SARs for an agonist? What does the antagonist lack that prevents the intrinsic activity at the receptor?

Beta Adrenergic Antagonists SAR

R group. Since this class is acting to antagonize the effects at the *beta* receptors, the marketed products should have β directing groups. These are the same bulky groups that were identified for the agonists and include: *i*-propyl, *t*-butyl or aromatic alkyl/aralkyl.

N atom. It serves the same purpose as the nitrogen atom in the agonists. It is essential for anchoring to the receptor, as a cation.

Side chain. The side chain has a **carbinol carbon** (R₂CH-OH) which provides for an asymmetric center. The optimal stereochemistry (ie, orientation of the functional groups in space) depends on X. If you recall, the optimal stereochemistry for the agonists is the R isomer, which is more active. Therefore, for the arylethanolamine pharmacophore, the optimal isomer is the R while for the aryloxypropanolamine it is the S isomer. For the latter compounds, the addition of the methoxy group as the spacer makes the structure longer, but the spatial orientation of the structure maintains optimal binding to block the receptor. This may also play a role in selectivity since all the arylethanolamine compounds are non-selective for *beta*₁ or *beta*₂ while the aryloxypropanolamine compounds can be made selective for *beta*₁ based on the addition of specific functional features as discussed below.

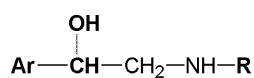


Figure 2. Arylethanolamine pharmacophore.

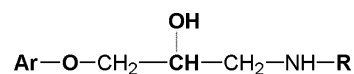
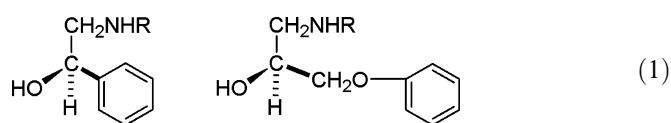


Figure 3. Aryloxypropanolamine pharmacophore.

Stereochemistry exercise: From your organic chemistry knowledge, confirm the stereochemistry of the arylethanolamine and the aryloxypropanolamine pharmacophores below by assigning group priorities. Recalling the biosynthesis of the endogenous neurotransmitter, briefly explain the respective stereochemistry of the 2 pharmacophores.



Ar (Aromatic ring). The nature of the aromatic ring and its substituents is the primary determinant of *beta*-antagonistic activity as discussed below. The structural features of the aromatic portion of the antagonists appear to interact with the receptor in a manner that prevents activation of the receptor. The aromatic group may also affect the absorption, distribution, metabolism and excretion of the *beta*-antagonists.

Ar = Phenyl. The nature of the aromatic ring also determines selectivity at *beta*-receptors. As previously discussed, the stereochemistry of the 2 pharmacophores is important for selectivity whereas only the aryloxypropanolamine compounds can be made cardio selective for the *beta*₁-receptors. Since the action of these compounds on the heart is sought after, antagonist activity on the lungs could be detrimental due to the potential to block the *beta*₂-receptors. Students should also be reminded that selectivity is relative and that at higher doses even selective *beta*₁-antagonists can have activity at *beta*₂ receptors causing bronchoconstriction. Therefore, caution is always warranted with these compounds when treating hypertension in a patient with a history of lung disease. So for the aryloxypropanolamine compounds:

- Non-substituted phenyl: promotes a non-selective β -antagonism
- *Para*-substituent on phenyl ring on an aryloxypropanolamine: provides for β ₁ selectivity. Therefore, the specific SAR requirement for β ₁-selectivity is an aryloxypropanolamine with a *para*-substituent on a phenyl ring and a *beta*-directing group on the anchoring amino nitrogen.
- Chemical nature of the aromatic *para*-substituent does not influence selectivity but affects potency, ie, the compound is still *beta*₁-selective since

many groups have been tried and all have maintained selectivity.

- Small ortho substituents along with *para*-substituents on phenyl ring maintain β_1 -selectivity.

Ar = Other than phenyl rings. All marketed products with an aromatic ring other than a phenyl are non-selective *beta*-antagonists. Examples of such rings include a naphthyl or heteroaromatic rings Figure 4.

- The naphthyl ring is highly lipophilic. It contributes to increased distribution into the CNS due to enhance penetration of the blood brain barrier resulting in increased CNS side effects. It also contributes to an extensive first pass effect and decreased duration of action. Both can be detrimental to patient compliance.
- Nadolol (Structure 1) is a marketed product with a naphthyl ring that contains 1 saturated ring and 2 hydroxyl groups. The hydroxyl groups increase the polarity, decrease penetration into the CNS and as a result, the compound has decreased side effects. As a polar compound, it is not extensively metabolized by the liver and is mainly excreted by the kidney. Therefore, it has a long duration of action and is dosed once a day. The decrease in side effects and once daily dosing increases patient compliance.
- Lipophilicity is also important when considering topical ophthalmic application for treatment of glaucoma. High lipophilic character based on the presence of lipophilic functional features will result in the drug not having systemic distribution due to the drug becoming embedded in the lipophilic membrane and concentrating at the site of action in the eye. Therefore, lower concentrations are used and the drug will not be contraindicated if the patient has a history of bronchitis or other lung disease because of minimal distribution to the lungs. Less lipophilic compounds based on the presence of polar groups will have more systemic distribution due to their ability to exit membranes. Therefore, these structures, especially if they are non-selective, and even when given topically, will have potential adverse effects on the lungs if patients have a history of lung disease.

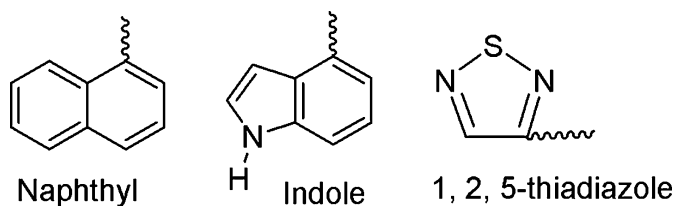


Figure 4. Aromatic ring substituents.

- The indole ring (Figure 4) in a *beta*-adrenergic antagonist may be responsible for its intrinsic sympathomimetic activity (ISA). Although the mechanism is not fully established, the authors hypothesize that it is, possibly through a hydrogen bonding interaction between the m-N-H (N_1 nitrogen atom) and SER_{204} of β receptors similar to the binding of the *beta*-adrenergic agonist with the *meta*-hydroxyl group of the catechol to the same amino acid residue on the receptor.

Unique SAR:

- Labetalol (structure 2, Figure 5) is an excellent therapeutic agent that is commonly used to treat severe hypertension both orally and by the intravenous route. The chemistry of the structure clearly explains its potent action:
- It is an aryloethanolamine with an aralkyl *beta*-directing group similar to the group present in the peripheral *beta*₂-agonists. Therefore, this does contribute to some *beta*₂-agonist activity in the periphery resulting in vasodilation and decrease in blood pressure. As an aryloethanolamine, it is a non-selective *beta*-antagonist which results in decreased blood pressure due to blocking of the *beta*₁-receptors in the heart. The structure has 2 asymmetric carbons providing 4 isomers (SS, SR, RS and RR). It is marketed as the racemic mixture. The RR isomer is responsible for non-selective *beta*-antagonism and the SR isomer has *alpha*₁-antagonism. The *alpha*₁-antagonism contributes to decreased blood pressure by preventing vasoconstriction in the periphery. Therefore, the combined effects of the above 3 structural features result in a potent decrease in blood pressure.
- The *alpha*₁-antagonistic activity is also thought to contribute to favorable effects on the lipid profile with no decrease in high density lipoprotein (HDL) or an increase in triglycerides as compared to the non-selective *beta*-antagonists. Therefore, structure 2 is a better therapeutic choice to treat a patient with hypertension and a history of hyperlipidemia.
- The carboxamide function on the aromatic ring is responsible for some *beta*₂-agonism because it is reminiscent of the salicyl group discussed under the *beta*₂-adrenergic agonists which provides for *beta*₂-agonistic activity. Therefore, it provides some safety margin in patients with a history of asthma, bronchitis, or chronic obstructive pulmonary disease. However, labetalol is still non-selective and only a selective *beta*₁-antagonist should be

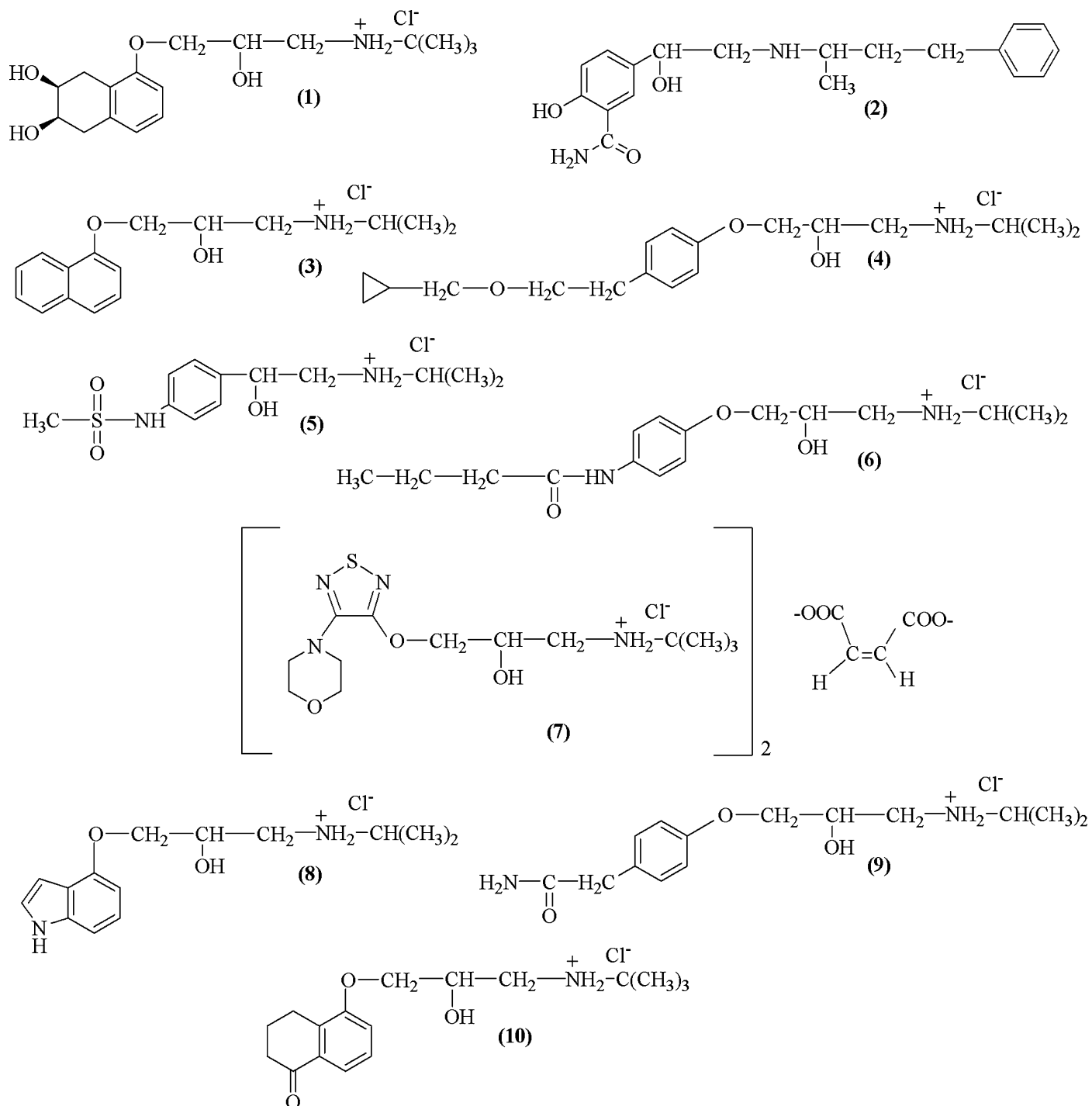


Figure 5. Structures of *beta*-adrenergic antagonists.

utilized if a *beta*-antagonist is indicated in such a patient.

Summary of Case Study Points

- There are 2 basic pharmacophores for *beta*-antagonists: aryloxypropanolamine and aryloxypropanolamine.

- Both have *beta*-directing groups.
- Both lack essential structural features for agonistic activity.
- All aryloxypropanolamine compounds are nonselective.
- For *beta*₁-selectivity: An aryloxypropanolamine with a *beta*-directing group on nitrogen is needed in combination with a *para*-substituent or a *para*-substituent with a small *ortho*-substituent.

- A polar or lipophilic *para*-substituent influences the potential for the lack or presence of CNS side effects.
- Indole for the aromatic ring may be responsible for ISA.
- Stereochemistry in labetalol provides for α_1 -blocking activity.

Applying SAR

Now that the students have the foundation knowledge in medicinal chemistry and have exercised recall of critical knowledge needed from other science disciplines such as organic chemistry, anatomy, physiology and other introductory courses, it is important that they are shown how to apply this knowledge. Therefore, a few examples are presented to help them in this process.

Example: Given the structures in Figure 5, predict the activity of each structure based on its SAR. Please follow the 2 examples discussed below.

Structure 3 (propranolol, Figure 5) is an aryloxypropanolamine. It has the appropriate distance between the aromatic naphthalene ring and the anchoring nitrogen atom. It also has the *beta*-directing isopropyl group. The naphthyl group makes it non-selective. The S isomer is the active form of the drug.

Structure 4 (betaxolol, Figure 5) is an aryloxypropanolamine. It has the appropriate distance between the aromatic phenyl ring and the anchoring nitrogen atom. It also has the *beta*-directing isopropyl group. The phenyl group has a *para*-substituent which makes it selective for blocking β_1 -receptors.

Common Clinical Decisions

A major objective in this instructional model is to clearly identify the continuum of medicinal chemistry-pharmacology and therapeutics. The introduction of the patient is challenging to the students at this level, however, it is critical to meeting outcome objectives for students and to help in the valuing step of affective learning. Therefore, the summary of some of the most common clinical decisions that can be explained by the SAR is an essential component of this instructional model (Table 4). In addition, the example case study that follows provides the students with further opportunities to apply the information at a higher level which would require more extensive analysis.

Beta Adrenergic Antagonists SBTE Case Study

A 55-year-old white male is referred to the family practice clinic with complaints of nightmares, fatigue, and insomnia. He has smoked cigarettes since he was a teenager, and he has a 4-year history of hypertension

that has been poorly controlled with structure 3. Physical and laboratory assessment reveals a well-developed, overweight individual with the following clinical data: blood pressure 160/100 mm Hg (110/85), potassium 3.2 mEq/L (3.5-5.3), uric acid 6 mg/dl (3.5-7), Creatinine clearance (Clcr) = 102 ml/min (90-120), total cholesterol 280 mg/dl (<200 mg/dl). The patient has a history of noncompliance. For all structures, refer to figure 5.

Structure 3 may have contributed to the CNS side effects that the patient is experiencing. Give a structurally based therapeutic evaluation (SBTE) to explain these adverse drug reactions.

Students understand the anatomical structure and important physiological function of the blood brain barrier (BBB) having learned in previous coursework of the network of tightly connected endothelial cells and their exclusionary impact on all hydrophilic molecules.²³ Structure 3, propranolol, is a *beta*-antagonist. The lipophilicity contributions of the different functional groups and the impact of overall lipophilic/hydrophilic character on membrane penetration and partition (log P) are 2 important organic chemistry concepts that students should apply in order to provide the SBTE. Structure 3 has the aryloxypropanolamine pharmacophore with the highly lipophilic naphthyl group. Although the relationship between the extent of CNS side effects and log P of *beta*-antagonists has never been clearly substantiated, it is well accepted that the higher incidence of CNS side effects exhibited by structure 3 (propranolol) is due to its high lipophilicity which allows better penetration through the BBB.²⁴⁻²⁶

Would switching from structure 3 to structure 1 be an appropriate therapeutic decision? Provide a SBTE for your answer.

In general, drugs must exhibit a balance between hydrophilicity and lipophilicity to be able to effectively traverse the biological barriers separating the sites of drug administration, action, metabolism, and excretion. This is taken into account when chemical modification of a given agent to improve the therapeutic efficacy is considered. Students can readily see that structure 1, nadolol is a tetrahydronaphthalene analog of propranolol. While the reduction of an aromatic ring is a lipophilic structural change, the addition of the 2 polar hydroxyl groups significantly decreases nadolol's overall lipophilic nature and, therefore, its ability to penetrate into the CNS.²⁷ Also, the decreased lipophilicity minimizes first pass metabolism and, as a result, the duration of action is increased. Consequently, nadolol is dosed once a day. On the other hand, lipophilic propranolol undergoes extensive first pass metabolism to an active 4-OH metabolite and inactive N-dealkylated metabolites. This results in

a decrease in the duration of action, and b.i.d or t.i.d dosing is common. The once a day dosing combined with a decreased potential for CNS side effects makes nadolol a better therapeutic choice considering the patient's history of non-compliance and the CNS effects he is experiencing.

The above SBTE case with the 2 scenarios illustrates also how students can integrate previous knowledge, meet specific general ability based outcomes such as patient assessment, drug therapy evaluation, and therapeutic decision making. Other cases based on the marketed products, SAR and common therapeutic decisions can be constructed to address the pharmacophores for this drug class, SAR and other specific therapeutic decisions and ability based outcomes for the students that can be explained by the structure. For example, the case includes values for blood pressure 160/100 mm Hg which students should recognize from the patient assessment course as high. The low potassium 3.2 mEq/L (3.5-5.3) allows for including thiazide diuretic therapy as part of the original patient medication history and for the students to recognize the need for pteridine analogs or an aldosterone antagonist type structure, both potassium sparing diuretics that are used in combination with thiazides to counter the hypokalemic effect. The normal creatinine clearance (Clcr) = 102 ml/min (90-120) indicates that thiazide therapy, if needed, can be effective. The high cholesterol 280 mg/dl (<200 mg/dl) allows including a scenario where the student has to identify a β -antagonist structure that does not decrease HDL which would be contraindicated in our patient with a history of hyperlipidemia. Other clinical information can be included to address other pertinent therapeutic decisions that can be deduced from the structure. For example, if the patient is a male and a potassium sparing diuretic is warranted, then the aldosterone antagonist would not be a good choice because of its steroid-like structure and the potential to produce gynecomastia and antiandrogenic effects. If the patient is Caucasian or African-American, a structure with the pharmacophore of an angiotensin converting enzyme inhibitor or a thiazide diuretic should be chosen to treat hypertension, respectively because of the high rennin level in Caucasians and the effectiveness of thiazides in African-Americans. The overall goal here is to introduce as much clinical relevance to the information provided to the students that can be clearly explained by the SAR.

Prediction of Clinical Activities

The ultimate goal of the instructional model is for the students to be able to apply the knowledge on the examination but also to internalize the concepts behind the knowledge gained so that they can utilize it when they

are practitioners. Certainly this is not an easy task. Students are challenged to synthesize specific questions and SBTE case scenarios that show an in depth knowledge of the content and are rewarded by using some of their individual questions on the examinations. The following are examples of some of the questions that the students are challenged with.

- (1) Consider structures 4 (betaxolol), 5 (sotalol), and 6 (acebutolol) in Figure 5:
 - a. Why is a β_1 -selective antagonist useful clinically? Would a β_2 -selective antagonist have useful clinical applications?
 - b. Which structure(s) is/are β_1 -selective? Explain why or why not?
 - c. Which structure would be a good choice for a patient with hypertension and a history of bronchitis?
- (2) Given structures 4 (betaxolol) and 7 (timolol), which would be a better choice topically to treat glaucoma in a patient with a history of asthma? Provide a SBTE for your answer.
- (3) Which of the 2 structures, 5 (Sotalol) or 7 (timolol), would be more contraindicated to treat a patient with hypertension and a history of depression, sleep disorders or psychosis?
- (4) Construct a case study and 2 scenarios based on structures 8 (pindolol), 9 (atenolol), or 10 (levobunolol).

SUMMARY

Pharmacy graduates in the 21st Century have to become well-rounded pharmacy practitioners who have a solid understanding of the biomedical and pharmaceutical sciences principles that underpin the practical clinical applications of the knowledge they have learned. In order to deliver the best care, the sciences provide the in-depth knowledge needed to achieve this. The challenge for science faculty members is not how many hours they spend teaching the principles but how they teach them. The revised ACPE guidelines and standards have provided science faculty members with both an assurance and a challenge. The guidelines and standards clearly emphasize the important role that the biomedical and pharmaceutical sciences play in the preparation of future pharmacy graduates and do articulate how the curriculum should and must incorporate that knowledge. Again, the challenge is for faculty members to show how that knowledge can be packaged in a manner that maintains the essence of what the discipline is intended to impart and contribute to the future career of the graduate. In this manuscript, we attempted to provide an instructional

model that would clearly address the teaching of medicinal chemistry to meet the challenge based on the new ACPE guidelines and standards. We believe that this standardized model has a broad-based application to other science courses. The explicit integration of the cognitive and affective learning component into teaching science is a valuable tool and does provide the theory and philosophical validation for what can and should be done in the classroom. Future research on the effectiveness of the model on student performance is planned.

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