Chair: Tracy Christofero | **GC#6: Course Addition**

Request for Graduate Course Addition

1. Prepare one paper copy with all signatures and supporting material and forward to the Graduate Council Chair.
2. E-mail one identical PDF copy to the Graduate Council Chair. If attachments included, please merge into a single file.
3. ***The Graduate Council cannot process this application until it has received both the PDF copy and the signed hard copy.***

College: Pharmacy | Dept/Division: DPSR | Alpha Designator/Number: MSPS 531 | (●) Graded ( ) CR/NC

Contact Person: Blair Journigan/ H. Glenn Anderson | Phone: 6-5003

NEW COURSE DATA:

New Course Title: Medicinal Chemistry and Drug Discovery Principles

Alpha Designator/Number: MSPS 531

Title Abbreviation: Med Chem & Drug Disc

(Limit of 25 characters and spaces)

Course Catalog Description: (Limit of 30 words)
This course gives an overview of drug discovery principles for the practicing medicinal chemist, along with introductory lectures in medicinal chemistry.

Co-requisite(s):

First Term to be Offered: Fall 2017

Prerequisite(s): Admission to MSPS program

Credit Hours: 3

Course(s) being deleted in place of this addition (*must submit course deletion form*):

Signatures: if disapproved at any level, do not sign. Return to previous signer with recommendation attached.

Dept. Chair/Division Head Faruk Khan Digitally signed by Faruk Khan DN: cn=Faruk Khan, o=MUSOP, ou=DPSR, email=khanmo@marshall.edu, c=US Date: 2017.02.15 18:04:31 -05'00'	Date
Registrar	Date
College Curriculum Chair	Date 2-15-2017
Graduate Council Chair	Date

Request for Graduate Course Addition - Page 2

College: Pharmacy | Department/Division: DPSR | Alpha Designator/Number: MSPS 531

Provide complete information regarding the new course addition for each topic listed below. Before routing this form, a complete syllabus also must be attached addressing the items listed on the first page of this form.

1. FACULTY: Identify by name the faculty in your department/division who may teach this course.

Blair Journigan, Ph.D.

2. DUPLICATION: If a question of possible duplication occurs, attach a copy of the correspondence sent to the appropriate department(s) describing the proposal. Enter "***Not Applicable***" if not applicable.

Not Applicable

3. REQUIRED COURSE: If this course will be required by another deparment(s), identify it/them by name. Enter "***Not Applicable***" if not applicable.

Not Applicable

4. AGREEMENTS: If there are any agreements required to provide clinical experiences, attach the details and the signed agreement. Enter "***Not Applicable***" if not applicable.

Not Applicable

5. ADDITIONAL RESOURCE REQUIREMENTS: If your department requires additional faculty, equipment, or specialized materials to teach this course, attach an estimate of the time and money required to secure these items. (Note: Approval of this form does not imply approval for additional resources.) Enter "***Not Applicable***" if not applicable.

Not Applicable

6. COURSE OBJECTIVES: (May be submitted as a separate document)

See attached syllabus

7. COURSE OUTLINE (May be submitted as a separate document)

See attached syllabus

8. SAMPLE TEXT(S) WITH AUTHOR(S) AND PUBLICATION DATES (May be submitted as a separate document)

See attached Sample Lecture

9. EXAMPLE OF INSTRUCTIONAL METHODS (Lecture, lab, internship)

Lecture, Computational Chemistry Laboratory

10. EXAMPLE EVALUATION METHODS (CHAPTER, MIDTERM, FINAL, PROJECTS, ETC.)

Midterm and Final Exams

11. ADDITIONAL GRADUATE REQUIREMENTS IF LISTED AS AN UNDERGRADUATE/GRADUATE COURSE

N/A

12. PROVIDE COMPLETE BIBLIOGRAPHY (May be submitted as a separate document)

Handouts, Primary Literature

Burger's Medicinal Chemistry and Drug Discovery, 9th Edition. Author: Donald J. Abraham, Ph.D.; Publisher: John Wiley and Sons, Inc, 1999-2014. Online ISBN: 9780471266945. Note: Link to all volumes provided on Blackboard (register for access online).

Organic Chemistry, 7th Edition. Author: John E. McMurry; Publisher: Cengage Learning. ISBN 9780495112587/0495112585. Note: Book PDF provided on blackboard.

Request for Graduate Course Addition - Page 5

Please insert in the text box below your course summary information for the Graduate Council agenda. Please enter the information exactly in this way (including headings):

Department:
Course Number and Title:
Catalog Description:
Prerequisites:
First Term Offered:
Credit Hours:

Department: Pharmaceutical Sciences/School of Pharmacy
Course Number and Title: MSPS 531 Medicinal Chemistry and Drug Discovery Principles
Catalog Description: This course gives an overview of drug discovery principles for the practicing medicinal chemist, along with introductory lectures in medicinal chemistry.
Prerequisites: Admission to MSPS Program
First Term Offered: Fall 2017
Credit Hours: 3

MARSHALL UNIVERSITY
www.marshall.edu

School of Pharmacy

SYLLABUS
Medicinal Chemistry and Drug Discovery Principles
MSPS 531 (Fall 2017)

This syllabus is not to be construed as a contract with the student and is subject to change.

The School of Pharmacy reserves the right to change the course syllabus. *The School should notify the students through the course notification system or by an email preferably through the Blackboard system.*

Course meeting days and time	
Location	L04 and L05-08
Team Leader / Instructor	Blair Journigan, Ph.D.
Office	Coon Education Building 232
Phone	(304) 696-5003
Email	journigan@marshall.edu
Office hours/Appointments accepted	Open door or by appointment

Student: If the instructor accepts appointments, then please email the instructor for availability. The student can expect the instructor to respond to e-mails and phone messages within 72 hours.

Course Description: This course gives an overview of drug discovery principles for the practicing medicinal chemist, along with introductory lectures in medicinal chemistry. Introductory topics include the functional groups found in drug structures and their acidic or basic properties, drug solubility and absorption, concepts surrounding drug recognition, as well as drug structure considerations such as isosterism and stereochemistry. Such topics will be exemplified with the Top 200 drugs, where appropriate. Further introductory topics include the detailed metabolic pathways of drug molecules, as well as pharmacogenomics. Advanced concepts focusing on practical drug discovery principles and techniques include an overview of therapeutic structures pursued in the field, and drug discovery strategies for hit identification, hit to lead generation and preclinical lead optimization. Synthetic approaches and commonly used organic methodologies will be covered, along with structural characterization techniques. Further topics include hands on learning exercises in computational drug discovery and pharmacology. Topics for this portion of the course will be illuminated with Top 200 Drugs or small molecule preclinical and clinical candidates well represented in the scientific and patent literature.

Prerequisites: Admission to MSPS program

Required Text Books:

Organic Chemistry, 7th Edition. Author: John E. McMurry; Publisher: Cengage Learning. ISBN 9780495112587/0495112585. *Note: Book PDF provided on blackboard.*

Burger's Medicinal Chemistry and Drug Discovery, 9th Edition. Author: Donald J. Abraham, Ph.D.; Publisher: John Wiley and Sons, Inc, 1999-2014. Online ISBN: 9780471266945. *Note: Link to all volumes provided on Blackboard (register for access online).*

Software Required:
Scifinder Scholar: http://libguides.marshall.edu/c.php?g=343334&p=2312555
AutoDock 4 and AutoDock Vina: http://autodock.scripps.edu/
PyMOL: https://www.pymol.org/
Graphpad Prism:
*All software is free to academics and educational-based activities

Course Objectives:

Apply concepts surrounding the chemical and physical properties of biologically active small molecules, which are responsible for their therapeutic effects.

Apply medicinal chemistry strategies used in various stages of the early drug discovery process, including hit identification techniques, hit to lead generation, and preclinical lead optimization.

Apply synthetic medicinal chemistry/organic chemistry approaches to the accession and characterization of biologically active small molecules.

Tentative Schedule of Activities*:

Date	#	Meeting Topic	Learning Outcomes
Week 1	1	Functional groups and Acid-Base Properties of Drug Molecules (Phar 522)	•Identify functional groups in drug molecules •Apply the Lewis and Brønsted-Lowry definitions of acids and bases •Apply the concept of conjugates in acid-base chemistry •Apply how acid and base strength is expressed (pK_a) •Identify common acidic, basic and neutral functional groups commonly found in drug molecules and write out the conjugate form •Apply factors controlling control acid and base strength
Week 2	2	Acid-Base Properties of Drug Molecules (Phar 522)	•Predict the degree of ionization of a drug molecule using knowledge of trends derived from the Henderson-Hasselbalch equation •Review Lecture 1 slides: Common acid organic functional groups found in drug molecules and their ionized (conjugate base) form, Common basic organic functional groups found in drug molecules and their ionized (conjugate acid) forms •Predict the formation of salts of acidic and basic drugs •Define the pH partition theory and the significance to drug pharmacokinetics
Week 3	3	Water solubility and Drug Absorption (Phar 522)	•Apply knowledge of factors contributing to water solubility: intermolecular interactions •Predict lipophilicity or permeability using quantitative descriptors: partition and distribution coefficients (log P and log D) •Define mechanisms of drug absorption: passive diffusion and active transport •Identify common strategies used to enhance drug absorption (prodrugs) or delivery (nanomedicines and antibody-drug conjugates)
			•Define various types of targets leading to signal transduction, including post-binding intracellular events (ion channels, G-protein coupled receptors, nuclear receptors, enzymes)

Week 4	4	Drug Targets and Pharmacodynamics (Phar 522)	•Define relationships between drug concentration and response, and drug potency and efficacy •Identify various types of pharmacological profiles by which drugs exert biological effects (agonist, antagonist, allosteric modulators) •Define various theories of drug action (occupancy, rate, induced-fit, macromolecular perturbation, and activation-aggregation theories)
Week 5	5	Classical/Non-Classical Isosteres and Stereochemistry (Phar 522)	•Identify classical and non-classical isosteres for various functional groups and their use in drug discovery •Apply principles of stereochemistry to bioactive molecules, including target recognition
Week 5	6	Therapeutic molecules (MSPS 531)	•Overview of various therapeutic molecules pursued as drug structures and their origins: small molecules, natural products, oligomers, peptidomimetics, biologics •Interpreting biological activity: *In vitro* binding and functional assays: target engagement and selectivity, *In vivo* assays
Week 6	7	Drug-receptor interactions (Phar 522)	•Analyze the various types of drug-receptor interactions and their relative contributions to binding affinity, including recognition of amino acid residues within the active site •Analyze drug-receptor complexes in 3D
Week 6	8	Early drug discovery strategies for hit identification (MSPS 531)	•Structure-based drug design: x-ray crystal structures and homology models, mutagenesis studies, docking, virtual screening, and computational chemistry principles and theories
Week 7	9	Introduction to Drug metabolism, pharmacogenomics, Phase I Drug metabolism (Phar 522)	○ Introduce the fundamental concepts of drug metabolism. ○ Describe the significance of drug metabolism. ○ Memorize the enzymes involved and the sites of drug metabolism. ○ Apply the concepts of drug interactions and pharmacogenomics through enzyme inducers, inhibitors, and genetic modifications of metabolic enzyme activity ○ Apply the concepts of phase I and phase II metabolic pathways
Midterm (Lectures 1-9)			
Week 7	10	Early drug discovery strategies for hit identification (MSPS 531)	•Ligand- and fragment- based drug design, the concept of privileged structures •Screening approaches: High throughput screening, combinatorial library design, NMR-based screening
Week 8	11	Phase I Drug metabolism (Phar 522)	○ Define all the pathways involved in Phase I (Functionalization) metabolism, especially the following oxidative pathways: ▪ Oxidation of: Aromatic moieties, Olefins, Benzylic & allylic C atoms and α-C of C=O and C=N, aliphatic and alicyclic C, C-Heteroatom system, C-N (N-dealkylation, N-oxide formation, N-hydroxylation), C-O (O-dealkylation), C-S (S-dealkylation, S-oxidation, desulfuration), Oxidation of alcohols and aldehydes, and miscellaneous oxidative reactions
Week 8	12	Synthetic approaches and reactions: organic chemistry	•Approaches for synthesis of various chemotypes: retrosynthesis, total synthesis, analog synthesis from common synthons

		(MSPS 531)	•Reactions most utilized in medicinal chemistry, including mechanisms: reductions, oxidations, protections/deprotections, functional group interconversion, functional group addition
Week 9	13	Phase I Drug metabolism (Phar 522)	○ Describe all the reductive and hydrolytic pathways involved in Phase I (Functionalization) metabolism, especially the following: ▪ Reduction of: Aldehydes and ketones, Nitro and azo compounds, and miscellaneous reductive metabolisms ▪ Hydrolytic Reactions of: Esters and amides, Epoxides and arene oxides by epoxide hydrolase Prodrug, soft drug and antedrugs
Week 9	14	Synthetic reactions and database searching: organic chemistry (MSPS 531)	•Reactions most utilized in medicinal chemistry, including mechanisms (cont): heteroatom alkylation and arylation, acylation and related processes, C-C bond formation, heterocycle formation •Introduction to Scifinder Scholar: Structure and reaction searching in publications and patents, text-based searches
Week 10	15	Phase I Drug metabolism (Phar 522)	○ Describe all the reductive and hydrolytic pathways involved in Phase I (Functionalization) metabolism, especially the following: ▪ Reduction of: Aldehydes and ketones, Nitro and azo compounds, and miscellaneous reductive metabolisms ▪ Hydrolytic Reactions of: Esters and amides, Epoxides and arene oxides by epoxide hydrolase Prodrug, soft drug and antedrugs
Week 10	16	Structural characterization: organic chemistry (MSPS 531)	•Structural characterization methods: Principles of Chromatography, Mass Spectrometry, and Nuclear Magnetic Resonance Spectroscopy and data interpretation
Week 11	17	Phase II Drug metabolism (Phar 522)	○ Define the fundamental concepts in Phase II (Conjugation) drug metabolism. The enzymes and coenzymes involved in glucuronic acid conjugation, sulfate conjugation, glycine and other AA conjugation
Week 11	18	Hit to lead generation: understanding the early drug discovery process (MSPS 531)	•Structure-activity relationship (SAR) studies •Mining the SAR results: 2D and 3D pharmacophores, docked and crystallized structures within the active site, the concept of ligand efficiency
Week 12	19	Phase II Drug metabolism (Phar 522)	○ Apply the fundamental concepts in following specific types of Phase II (Conjugation) drug metabolism. ▪ The enzymes and coenzymes involved in glutathione or mercapturic acid conjugation, acetylation, methylation and cholesterol conjugation ○ ALE on metabolic route of some individual drugs
		ADMET Profiling and Lead Optimization (MSPS 531)	•ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) in vitro profiling: microsomal stability, plasma protein binding, hERG liabilities, P-gp efflux •Physicochemical properties for oral bioavailability: molecular weight, pK_a, log D, Hydrogen bond acceptors/donors, Modifications to Lipinski's Rule of 5

Week 12	20		•Additional physicochemical considerations for CNS penetration: topological polar surface area (TPSA) •Lead optimization strategies: Bioisosteric replacement, chiral centers, designing out P-gp and hERG liabilities
Week 13	21	Computational drug design laboratory (MSPS 531)	Docking small molecules into the active site of a receptor with AutoDock 4 and AutoDock Vina, Visualization with PyMOL
Week 13	22	Drug discovery laboratory (MSPS 531) Guest Lecturer: Dr. Jinsong Hao	•Calculation of K_i and EC_{50} with Graphpad Prism
Final Exam (Comprehensive)			

Course Evaluation (grading):

Mid-term exam (paper-based): 50%
Final Exam (paper-based): 50%
Total: 100%

Letter grades distribution:

A = 89.50 to 100%
B = 79.50 to less than 89.50%
C = 69.50 to less than 79.50%
F = Less than 69.50%

Course Evaluation (grading): Grading for this course consists of both the mid-term and final exam, each worth 50%. Conceptual understanding of the material will be assessed at a higher level than that assessed at the Pharm D. level, in line with the expectations of the Master's program and Marshall University Graduate College.

Course Evaluation (assessment): At or near the end of the course, students are expected to complete an evaluation of the course content, learning approaches, student assessment and instructors according to School of Pharmacy procedures.

Assignment and examination grades will be posted in Blackboard within 7 business days unless otherwise stated.

Attendance policy: Each student is expected to attend class. Attendance at graded events is mandatory. Only excused absences accepted – see university and school policies. The instructor must be contacted prior to the exam, unless circumstances are prohibitory. Please note – the student is solely responsible for any materials missed.

UNIVERSITY POLICIES

University policies regarding **Grades, Probation and Dismissal, Responsible Conduct of Research and other topics can be found at http://www.marshall.edu/graduate/graduate-student-handbook/**

University policies regarding **Academic Dishonesty, Students with Disabilities, University Computing Services' Acceptable Use**, **Affirmative Action, and Sexual Harassment can be found at http://www.marshall.edu/wpmu/academic-affairs/policies/.**

School of Pharmacy Policies

SOCIAL JUSTICE POLICY STATEMENT

Marshall University is committed to bringing about mutual understanding and respect among all individuals and groups at the University. As part of Marshall University, School of Pharmacy has made a commitment to social justice. Therefore, no one will be discriminated against on the basis of race, gender, ethnicity, age, sexual orientation, religion, social class, or differing viewpoints. Each student will be viewed as a valuable member of this class and as the faculty for the course, I will strive to facilitate an atmosphere/learning environment where mutual understanding and respect are actualized.

ACADEMIC, ETHICAL, AND PROFESSIONAL CONDUCT

Student expectorations for academic, ethical, and professional conduct are defined within the school's Ethical and Professional Conduct Policy and the university's Academic Dishonesty Policy.

Test Security Policy

Refer to the following link for MUSOP's secure testing policies.

http://www.marshall.edu/pharmacy/faculty_staff/faculty-and-staff-policies/400-003-secure-testing-environment-standards/

MARSHALL

SCHOOL OF PHARMACY

Classical/Non-Classical Isosteres and Stereochemistry

MSPS 531 Medicinal Chemistry and Drug Discovery Principles

Blair Journigan, Ph.D.

Learning Objectives

- Identify classical and non-classical isosteres for various functional groups and their use in early drug discovery

- Apply principles of stereochemistry to bioactive molecules, including target recognition

  - Further reading on stereochemistry:
    "Stereochemistry", Chapter 19. Organic Chemistry, 7th Edition. Author: John E. McMurry.
    PDF is on blackboard.

  - Stereochemistry will set us up nicely for Lecture 5: Drug-receptor interactions

The concept of chirality as shown by the mirror image of a left hand.

Classical bioisosteres

TABLE 2.9 Classical Isosteres

1. Univalent atoms and groups

a.	CH_3	NH_2	OH	F	Cl
b.	Cl	PH_2	SH		
c.	Br	*i*-Pr			
d.	I	*t*-Bu			

2. Bivalent atoms and groups

a.	$-CH_2-$	$-NH-$	$-O-$	$-S-$	$-Se-$
b.	$-COCH_2R$	$-CONHR$	$-CO_2R$	$-COSR$	

3. Trivalent atoms and groups

a.	$-CH\equiv$	$-N=$			
b.	$-P\equiv$	$-As\equiv$			

4. Tetravalent atoms

a.	$-\overset{\vert}{\underset{\vert}{C}}-$	$-\overset{\vert}{\underset{\vert}{Si}}-$			
b.	$=C=$	$=\overset{+}{N}=$	$=\overset{+}{P}=$		

5. Ring equivalents

a.	$-CH=CH-$	$-S-$	(e.g., benzene, thiophene)		
b.	$-CH\equiv$	$-N=$	(e.g., benzene, pyridine)		
c.	$-O-$	$-S-$	$-CH_2-$	$-NH-$	(e.g., tetrahydrofuran, tetrahydrothiophene, cyclopentane, pyrrolidine)

Classical bioisostere: atoms, ions, or molecules in which the peripheral layers of electrons can be considered to be identical

**Example: F to CH_3 exchange, slide 4 (Celecoxib)

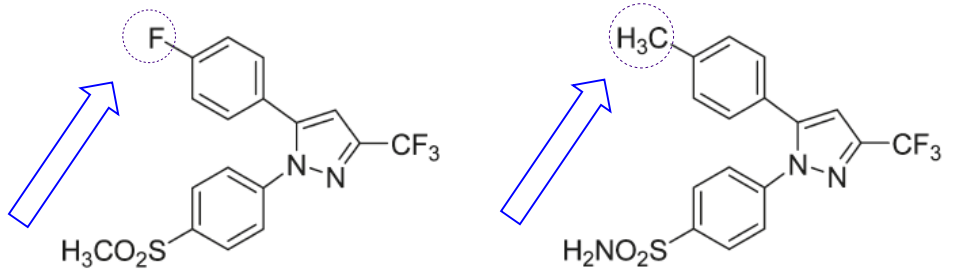
Why are they identical? Fluorine = 7 valence electrons, CH_3 = 7 total valence electrons

Silverman, R. Chapter 2: Lead Discovery and Lead Modification. The Organic Chemistry of Drug Design and Drug Action. http://dx.doi.org/10.1016/B978-0-12-382030-3.00002-7

Classical bioisosteres: fluorine to methyl exchange to modulate metabolism

Classical Bioisosteres: F to CH_3 exchange (Cmpd 15 to Celecoxib)

- Introduce metabolic 'soft spot' or metabolically labile center, with atoms of same # valence electrons
  - Why do this? : Cmpd 15 has undesirably long ½ life ($T_{1/2}$ = 221 hr), F to CH_3 exchange decreases $T_{1/2}$ to 3.5 hr (Celecoxib)



15 celecoxib: $T_{1/2}$ (rat) = 3.5 h

Carbon is substituted with fluorine, metabolically stable

Carbon is substituted with methyl group, introduces metabolic soft spot or metabolically labile center

Many pharmaceuticals contain fluorine (~20%):

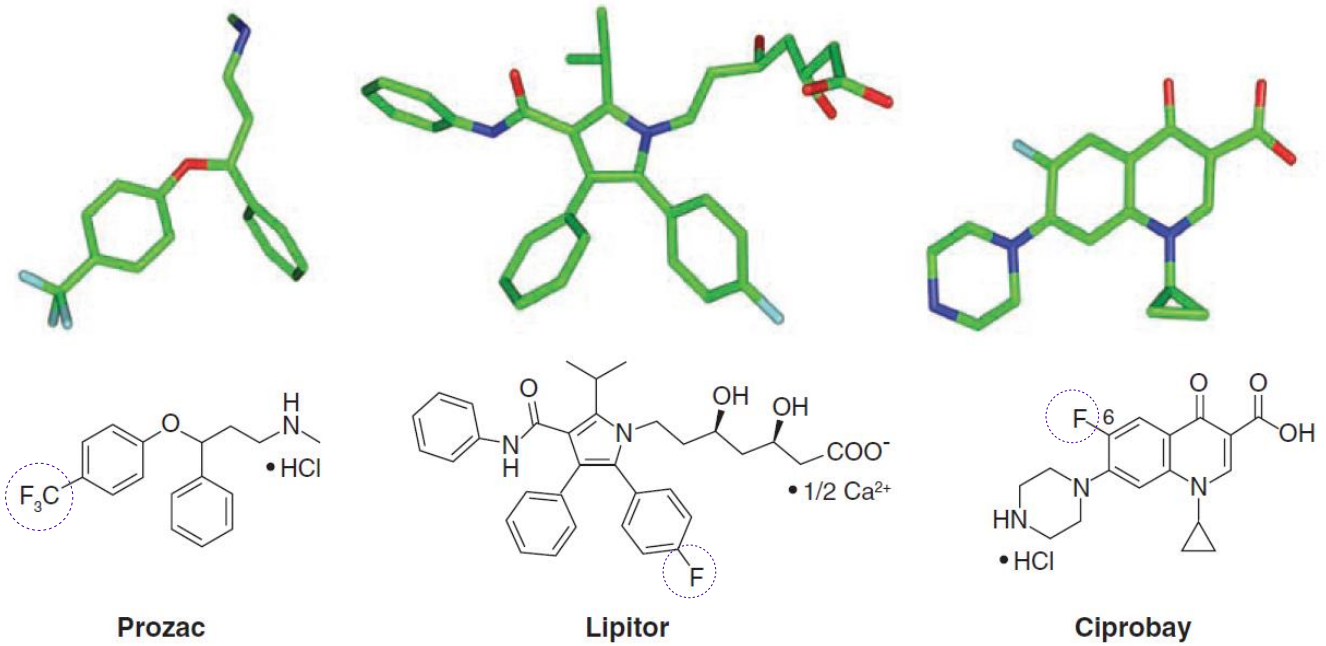
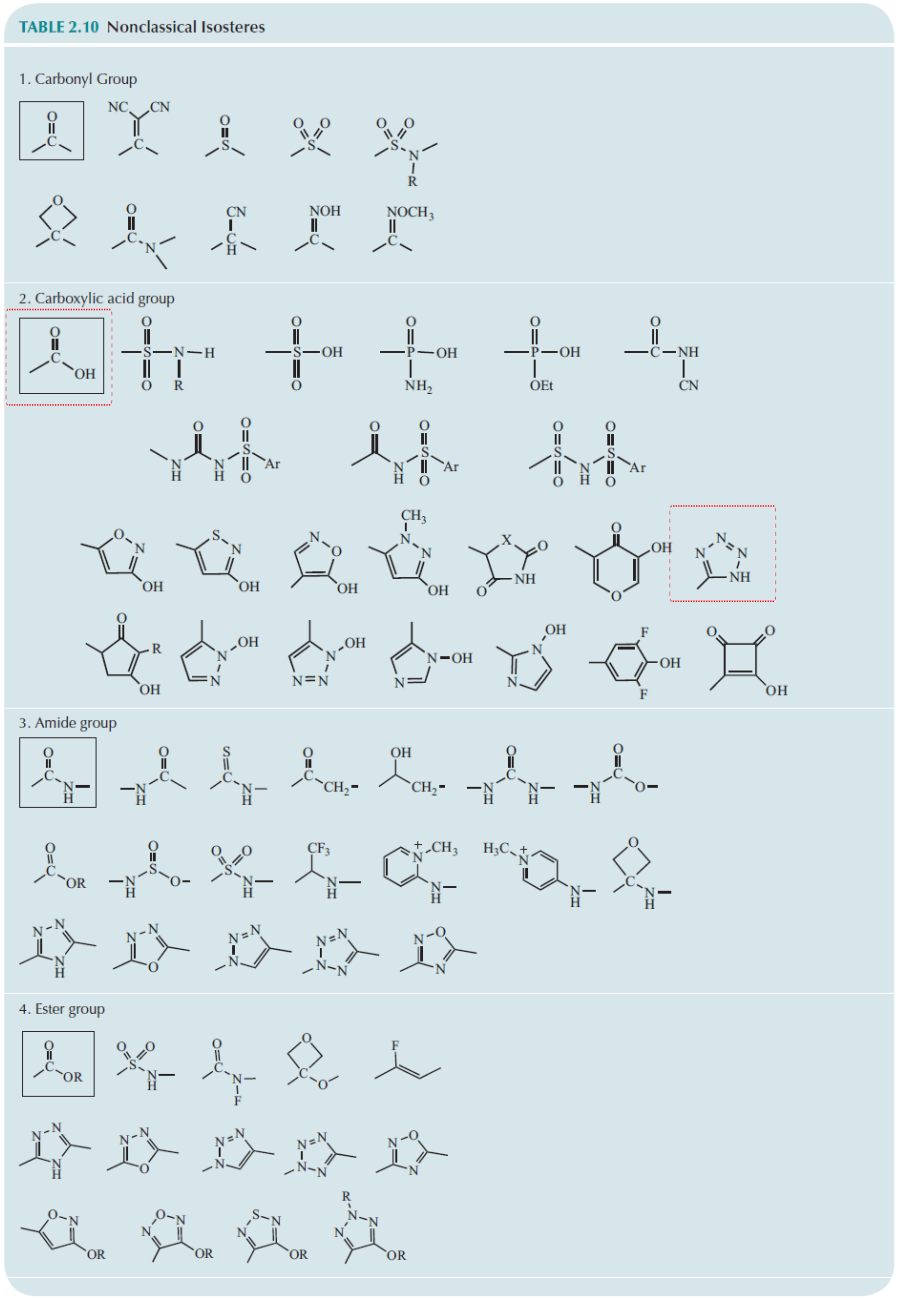


Fig. 1. Major fluorinated drugs: the antidepressant Prozac (table S1, entry 1), cholesterol-lowering drug Lipitor (table S1, entry 2), and quinolone antibiotic Ciprobay (table S1, entry 3). The molecular-model conformations are from crystal structures. Ligand Cs, green; O atoms, red; N atoms, dark blue; and F atoms, light blue. Unless otherwise stated, this color code also applies to the images in Figs. 3 and 5 and the supporting online material (SOM). Images generated with MacPyMol (*68*).

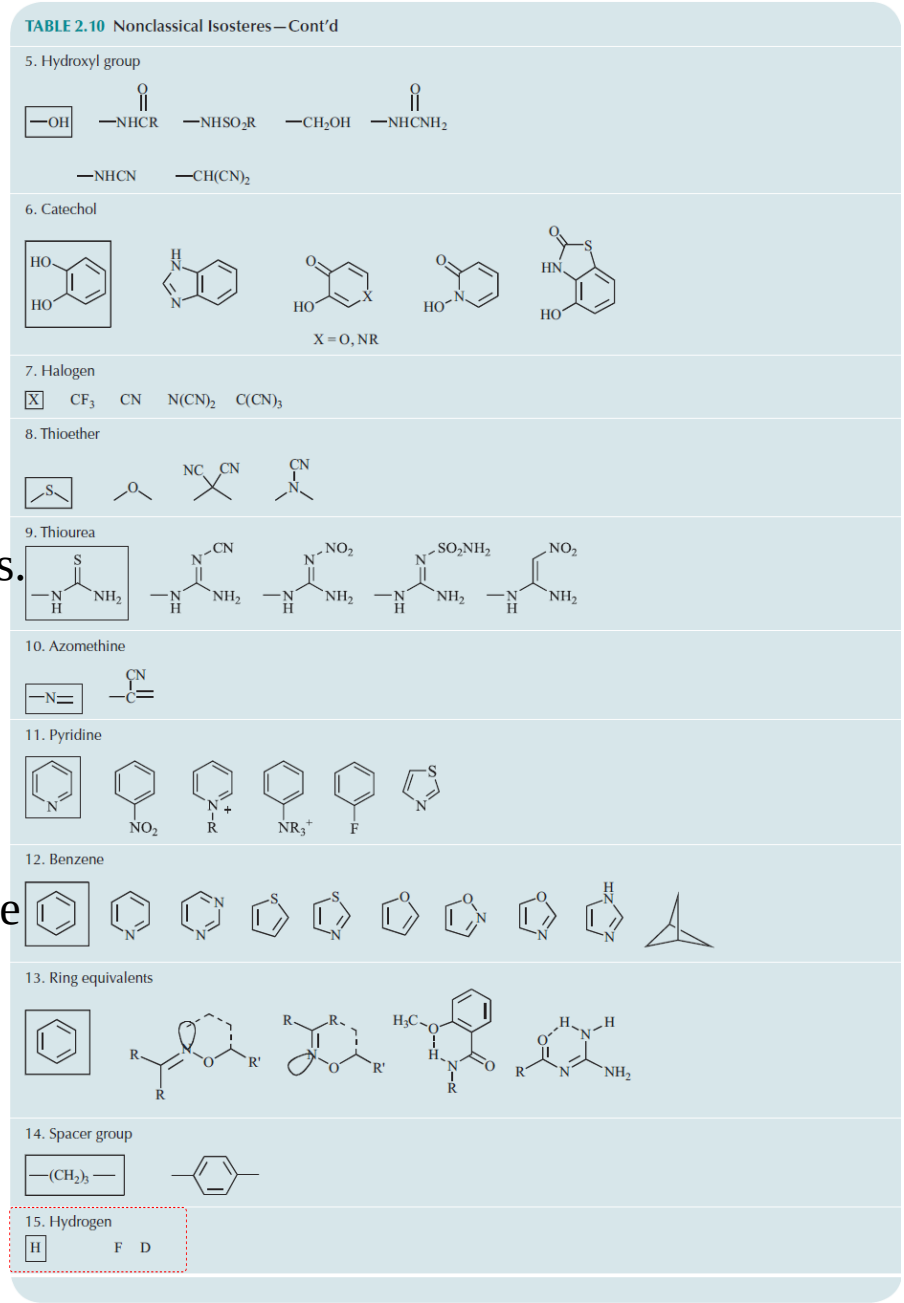
Meanwell JMC 2011, Muller et al, Science 2007

Nonclassical bioisosteres



Nonclassical bioisostere: replacements that do not have the same number of atoms and do not fit the steric and electronic rules of the classical isosteres, but do often produce similar biological activities.

Examples (slide 6): H to F exchange (Ezetimibe), CO_2H to tetrazole exchange (Losartan)



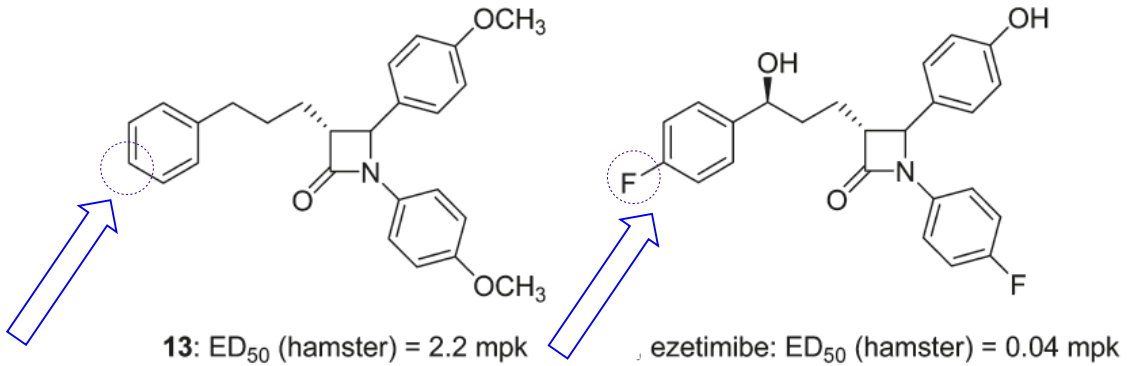
Silverman, R. Chapter 2: Lead Discovery and Lead Modification. The Organic Chemistry of Drug Design and Drug Action. http://dx.doi.org/10.1016/B978-0-12-382030-3.00002-7

Non-classical bioisosteres: Ezetimibe and Losartan

Hydrogen to fluorine exchange to modulate metabolism:

Cmpd 13 to Ezetimibe:

- Blocks metabolic 'soft spot', with atom of similar size
  - Why: C-F bond is strongest bond known between C and any other atom, and therefore chemically inert (no longer a metabolic center)



13: ED_{50} (hamster) = 2.2 mpk

ezetimibe: ED_{50} (hamster) = 0.04 mpk

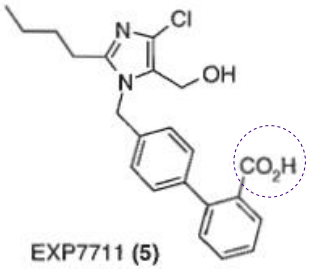
Carbon is substituted with hydrogen, metabolic soft spot

Carbon is substituted with fluorine, blocks metabolic soft spot or metabolically labile center

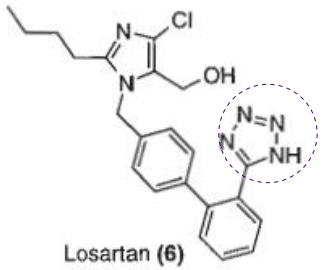
Carboxylic acid (CO_2H) to tetrazole exchange:

Cmpd 5 to Losartan:

- Increases oral bioavailability and binding affinity, with functional group of similar physiochemical properties
  - Why: tetrazole increases oral bioavailability due to increased lipophilicity (aromatic ring)
  - Why: tetrazole increases binding affinity due to better distribution of negative charge



EXP7711 **(5)**



Losartan **(6)**

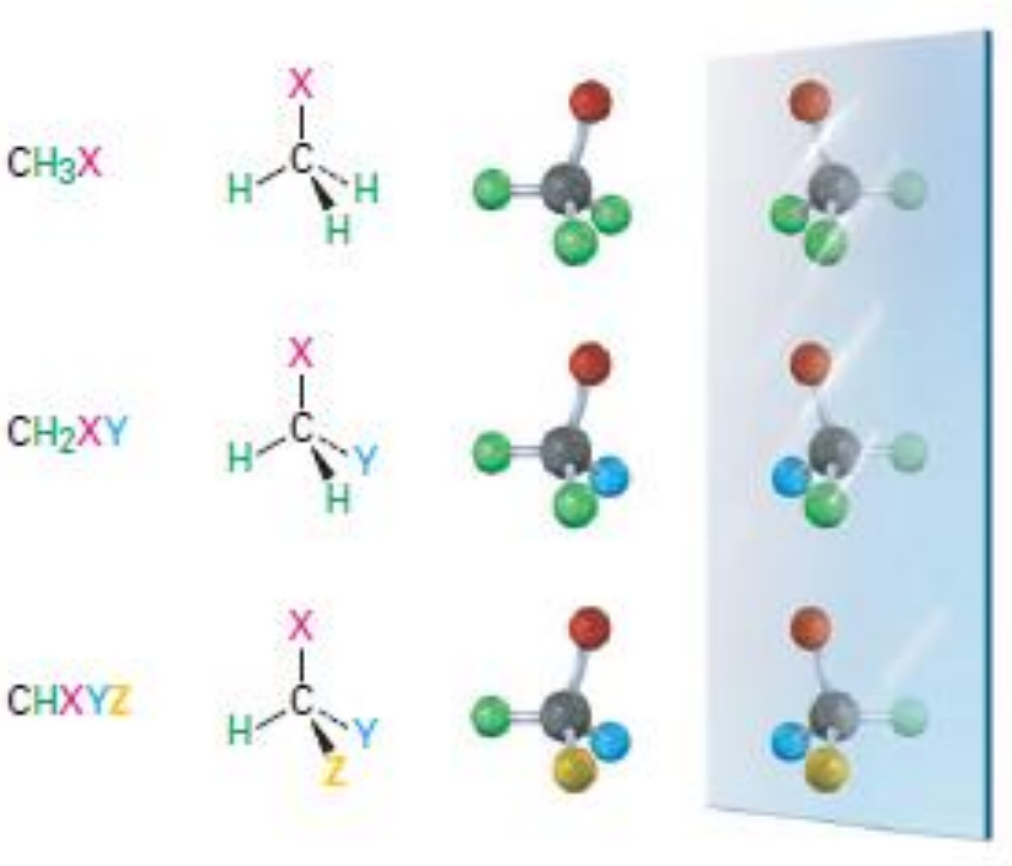
Increased binding affinity

IC_{50}	0.23 µM	0.02 µM
ED_{30} iv	3 mg/kg	0.6 mg/kg
ED_{30} po	11 mg/kg	0.8 mg/kg
pKa	4.5	5.0
logP	1.2	4.5

Increased oral bioavailability

Meanwell JMC 2011; http://www.maybridge.com/Images/pdfs/medchem_vol1.pdf

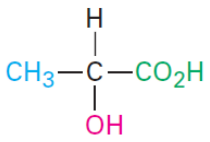
Stereochemistry: Tetrahedral carbon atoms and their mirror images

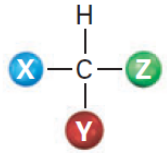


- Molecules of the type CH_3X and CH_2XY are identical to their mirror images, because they can be superimposed.

- Molecule of the type CHXYZ is <u>not identical</u> to its mirror image, because they cannot be superimposed, in the same way that a right hand cannot be superimposed upon a left hand. <u>In this case, the central carbon is chiral.</u>

Example of a chiral carbon: (+)-Lactic acid and (–)-Lactic Acid

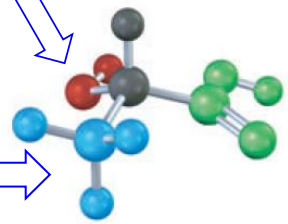


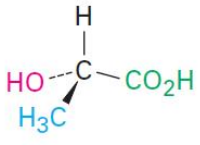


Lactic acid: a molecule of general formula CHXYZ

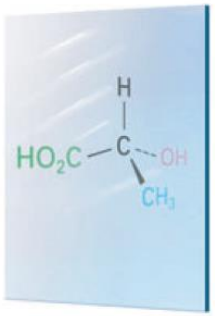
Dashed line (⋯⋯) C-OH bond means the hydroxyl is receding back behind the plane of the slide, pointing away from you

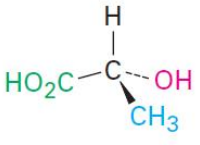
Heavy wedged(▬) C-CH_3 bond means the methyl is coming out of the plane of the slide, towards you



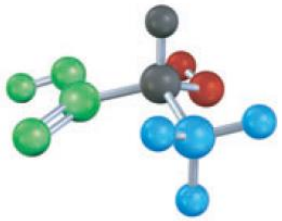


(+)-Lactic acid

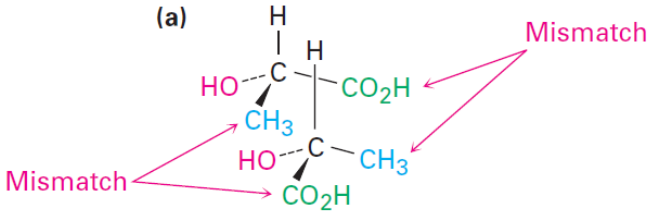


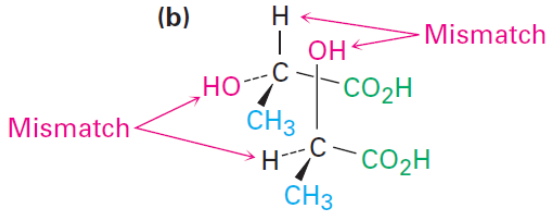


(–)-Lactic acid



(+)-Lactic acid is not identical to or superimposable upon its mirror image, (–)-Lactic acid. Therefore, the central carbon is chiral, and the molecules are enantiomers.





(a) When the H and OH substituents match up, the CO_2H and CH_3 substituents don't; **(b)** when CO_2H and CH_3 match up, H and OH don't. Regardless of how the molecules are oriented, they aren't identical.

Assigning *R* and *S* configurations to (–) and (+)-Lactic acid enantiomers

Figure 1:

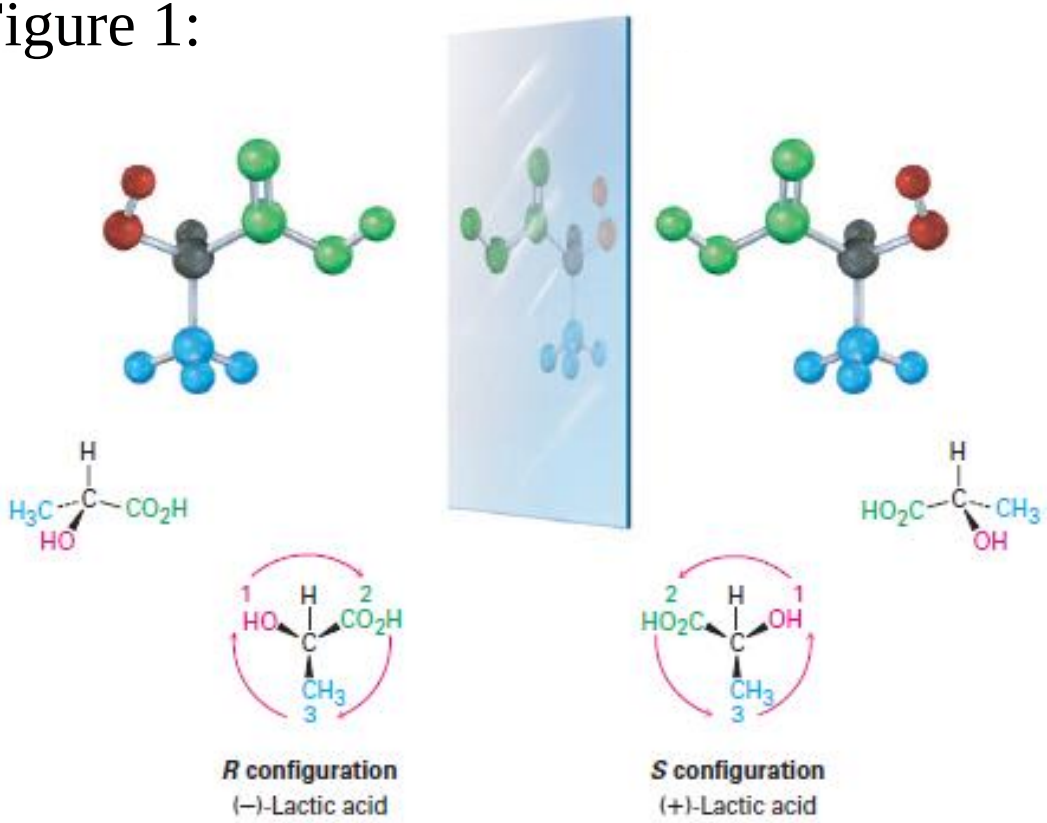
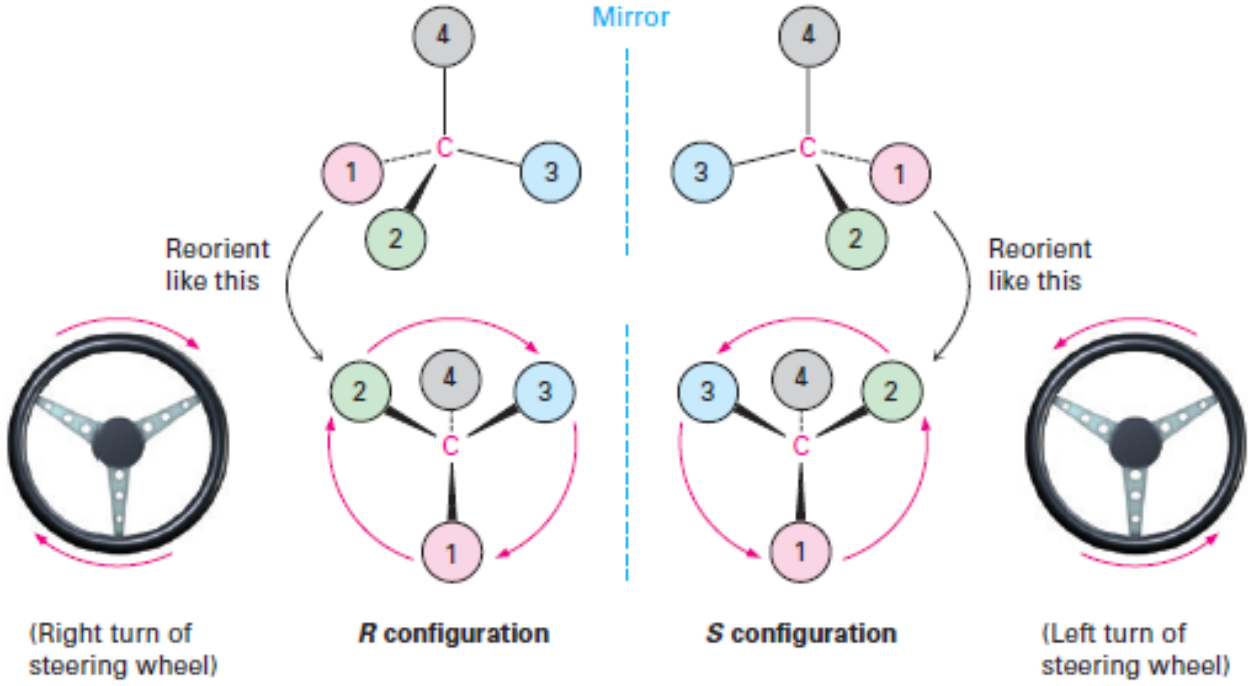


Figure 2:



- **Step 1**: Number the groups or substituents coming off of the carbon atom by priority (see Sequence Rules for specifying configuration in notes below).
- **Step 2**: Orient each molecule so that the group of lowest priority (4) is toward the rear, and the remaining three groups radiate towards the viewer like spokes of a steering wheel (see Figure 2). If the direction of travel 1→2→3 is clockwise (right turn), the center has the *R* configuration. If the direction of travel 1→2→3 is counterclockwise (left turn), the center is S.

Assigning *R* and *S* configurations to (–) and (+)-Lactic acid enantiomers

Build the two molecules of (–) and (+)-Lactic acid and prove the *R* and *S* assignments, using the Molymod molecular model kits. Then we will continue with the lecture (stereochemistry of drugs, and effects on activity).

Figure 1:

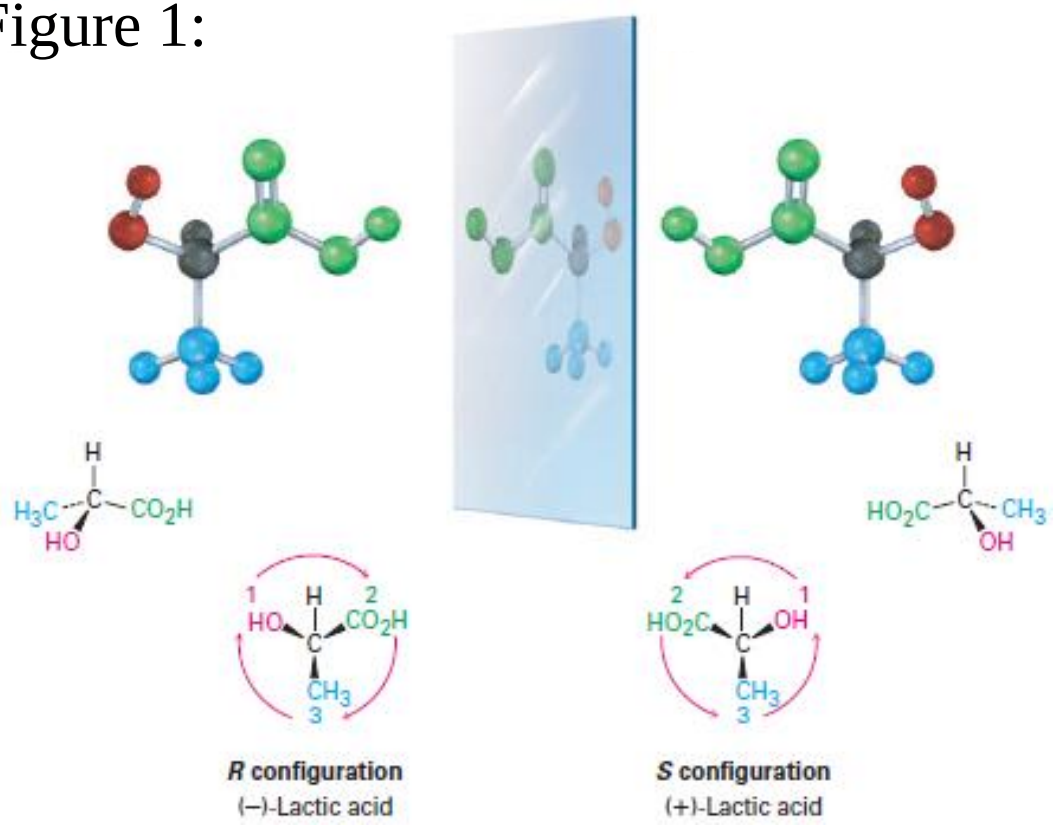
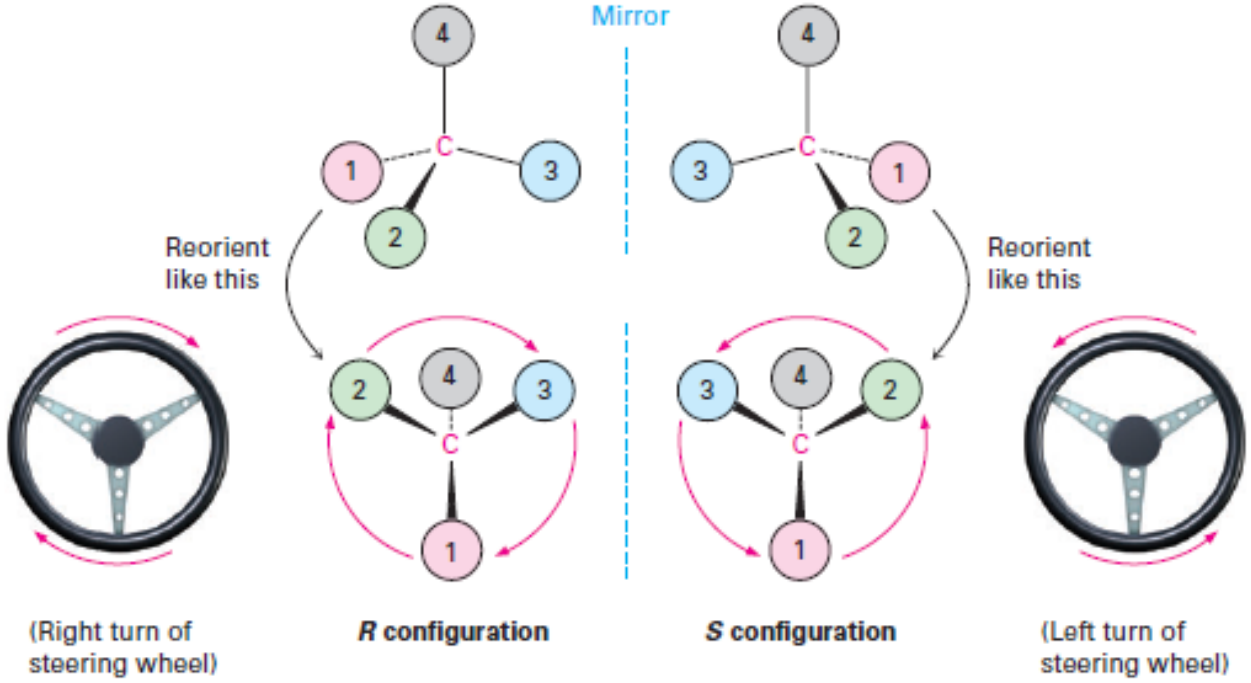
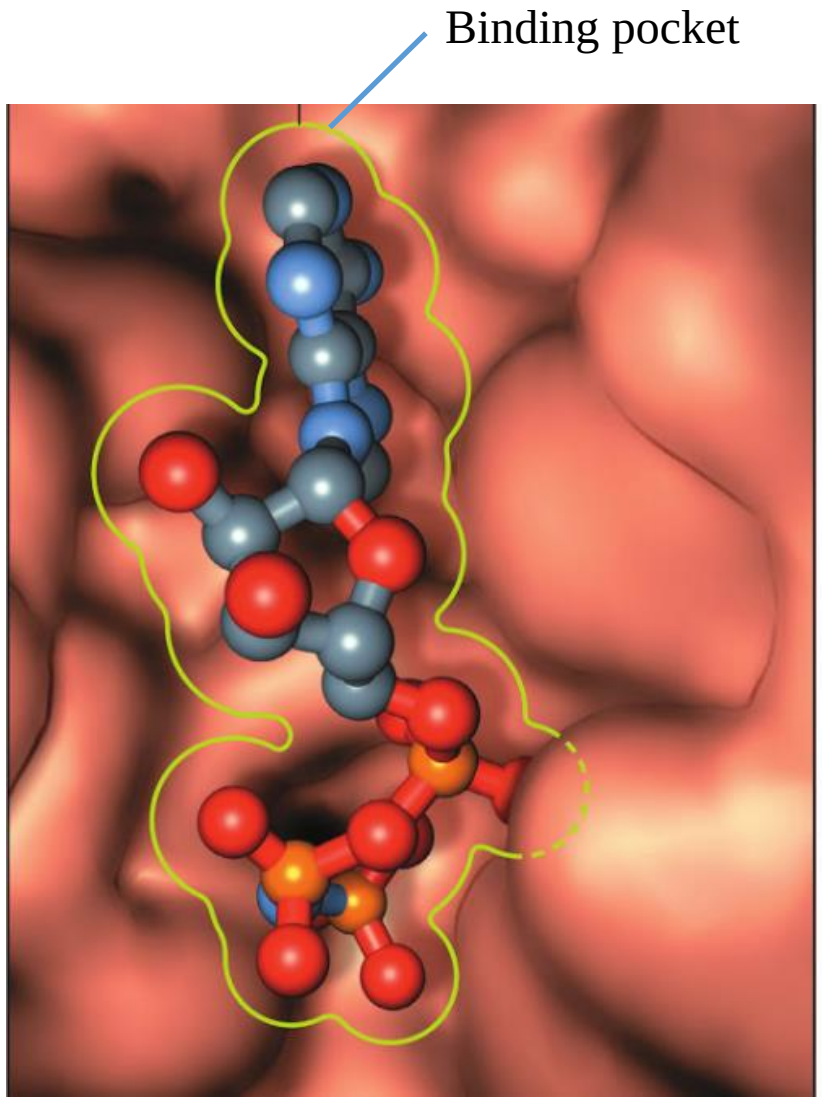


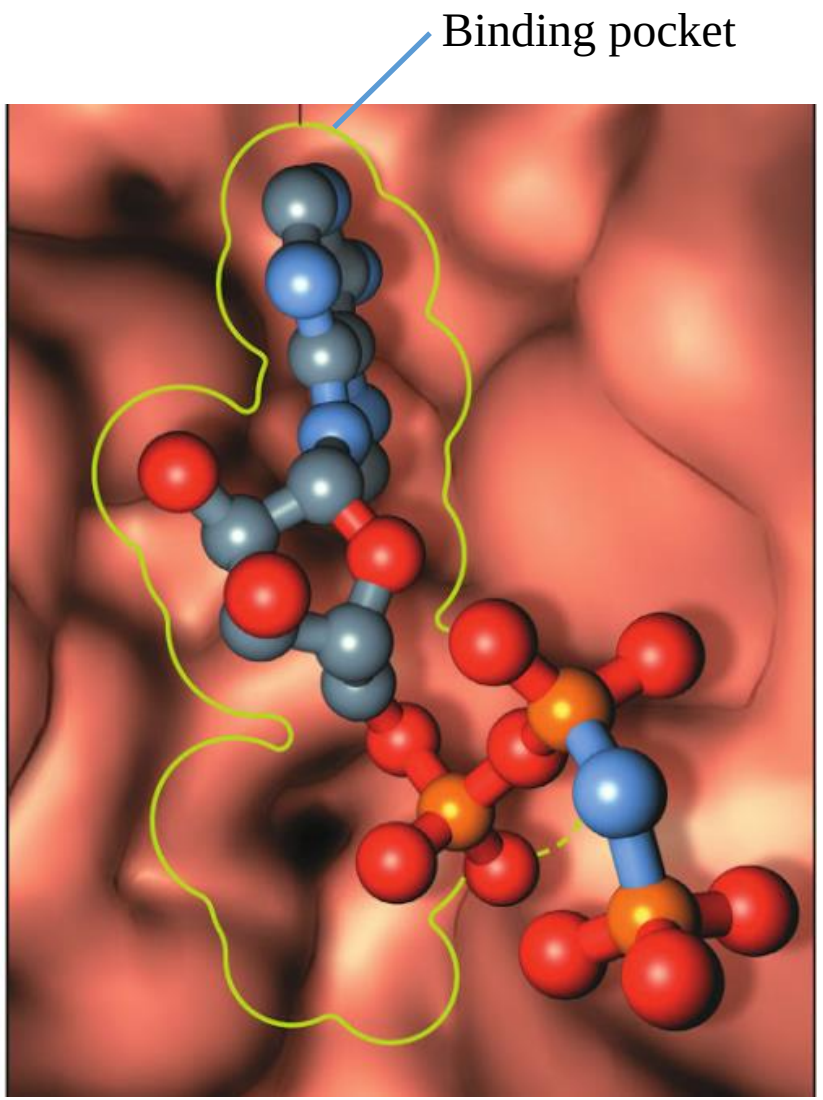
Figure 2:



Stereochemistry in action: Drug recognition by the target's active site (binding pocket)



One enantiomer fully occupies the receptor binding pocket…

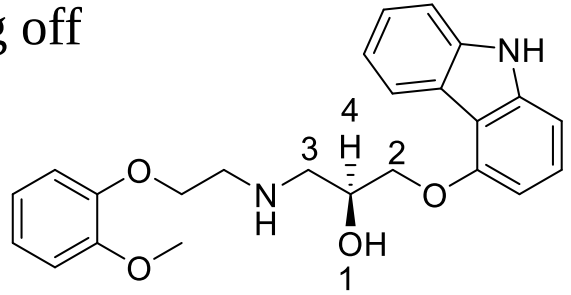


while the other enantiomer is only a partial match for the binding pocket.

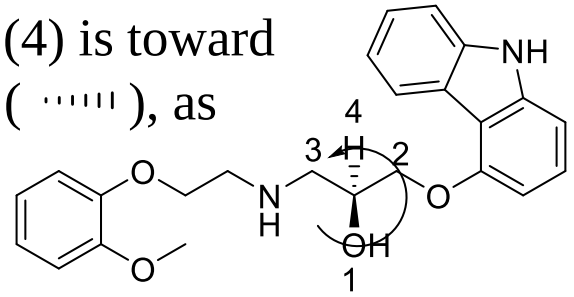
Netter's Illustrated Pharmacology

Determining S and R configuration assignments of Carvedilol (Coreg)

Step 1: Number the groups or substituents coming off of the carbon atom by priority (see Sequence rules for specifying configuration).

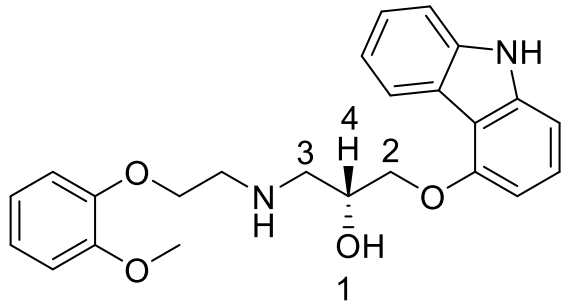


Step 2: Direction of travel 1→2→3 is <u>counterclockwise (left turn), the center is S.</u> This is true because the group of lowest priority (4) is toward the rear, as a hashed line (⋯⋯), as stated in slide 8.

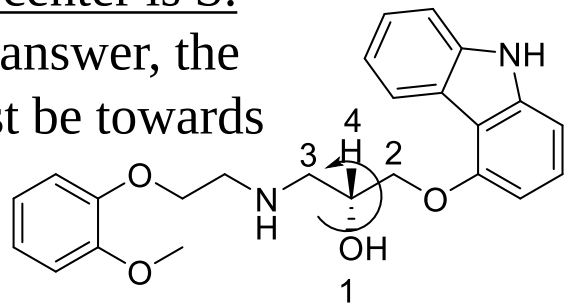


Assignment: (S)-carvedilol

Step 1: Number the groups or substituents coming off of the carbon atom by priority (see Sequence rules for specifying configuration).



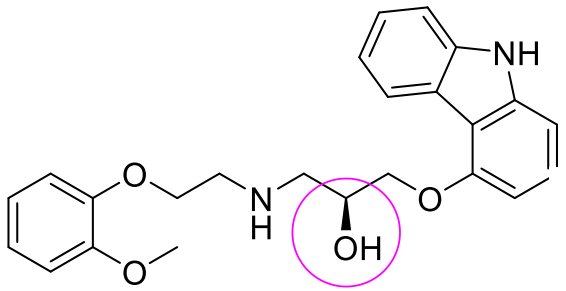
Step 2: Direction of travel 1→2→3 is <u>counterclockwise (left turn), the center is S.</u> However, for this to be the final answer, the group of lowest priority (4) must be towards the rear, as a hashed line (⋯⋯), as stated in slide 8.



For this molecule, the group of lowest priority is present as a heavy wedged bond (▬). In this case, reverse your answer to be clockwise (right turn), or R.

Assignment: (R)-carvedilol

Stereochemistry in action: Drug recognition by the target's active site (binding pocket)



(S)-carvedilol

(*S*) configuration: heavy wedged (▬) C-OH bond means the hydroxyl is coming out of the plane of the slide, towards you

OH is out of plane

OH is behind plane

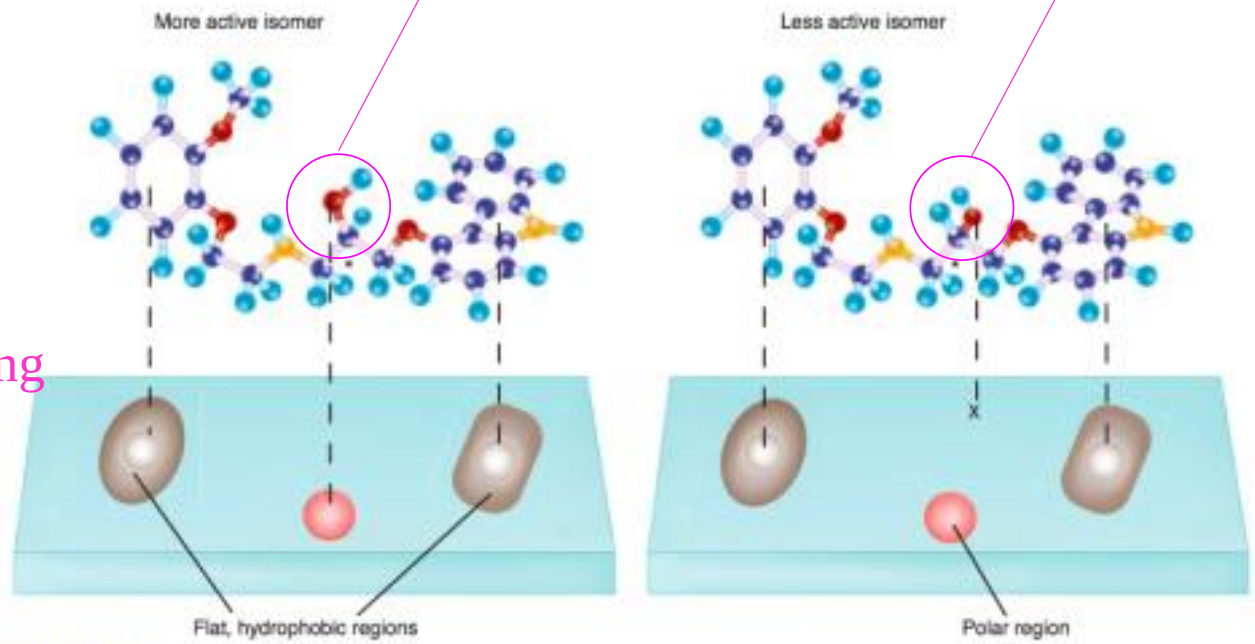
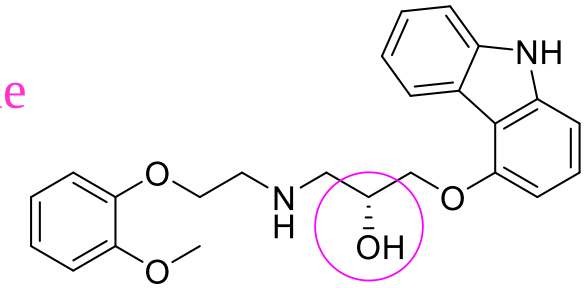


FIGURE 1–2 Cartoon illustrating the nonsuperimposibility of the two stereoisomers of carvedilol on the β receptor. The "receptor surface" has been grossly oversimplified. The chiral center carbon is denoted with an asterisk. One of the two isomers fits the three-dimensional configuration of binding site of the β-adrenoceptor molecule very well (*left*) and three areas, including an important polar moiety (an hydroxyl group), bind to key areas of the surface. The less active isomer cannot orient all three binding areas to the receptor surface (*right*). (Molecule generated by means of Jmol, an open-source Java viewer for chemical structures in 3D [http://www.jmol.org/] with data from DrugBank [http://www.drugbank.ca].)



(R)-carvedilol

(*R*)-configuration: dashed line (⋯⋯) C-OH bond means the hydroxyl is receding back behind the plane of the slide, pointing away from you

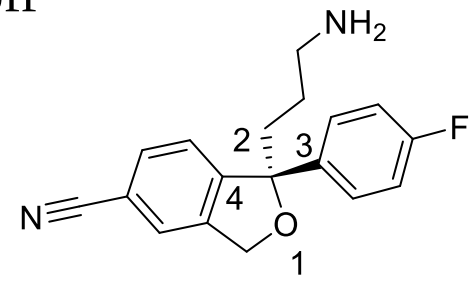
(*S*)-carvedilol: active at β adrenergic receptor due to optimal fit in active site of receptor (dictated by *S* stereochemistry)

Carvedilol is dispensed as a mixture of *S* and *R* enantiomers. Only the *S* enantiomer is responsible for β adrenergic activity

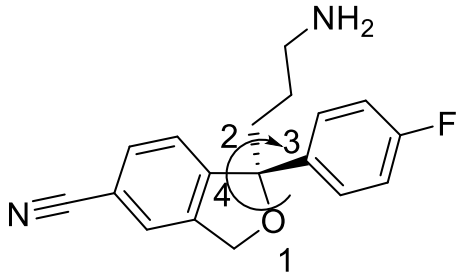
(*R*)-carvedilol: less active at β adrenergic receptor due to non-optimal fit in active site of receptor (dictated by *R* stereochemistry)

Determining S and R configuration assignment of citalopram

Step 1: Number the groups or substituents coming off of the carbon atom by priority (see Sequence rules for specifying configuration).

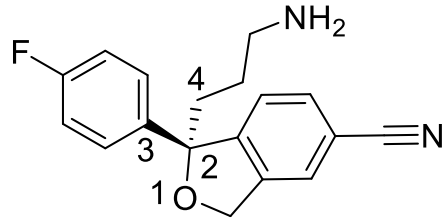


Step 2: Direction of travel 1→2→3 is <u>clockwise (right turn), the center is R.</u>

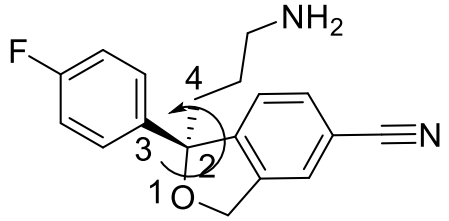


Assignment: (R)-citalopram

Step 1: Number the groups or substituents coming off of the carbon atom by priority (see Sequence rules for specifying configuration).



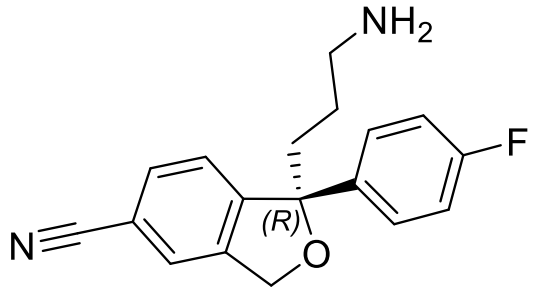
Step 2: Direction of travel 1→2→3 is <u>counterclockwise (left turn), the center is S.</u>



Assignment: (S)-citalopram

Stereochemistry in action: Drug recognition by the target's active site (binding pocket)

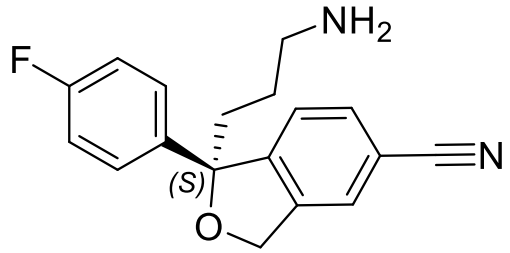
Mirror



(*R*)-citalopram

not marketed

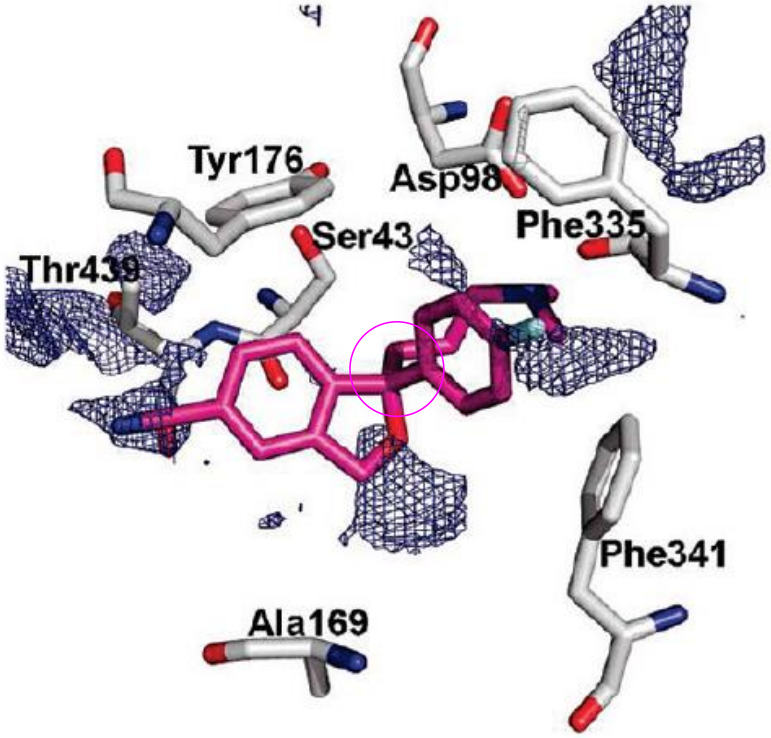
K_i SERT : 370 nM



(*S*)-citalopram

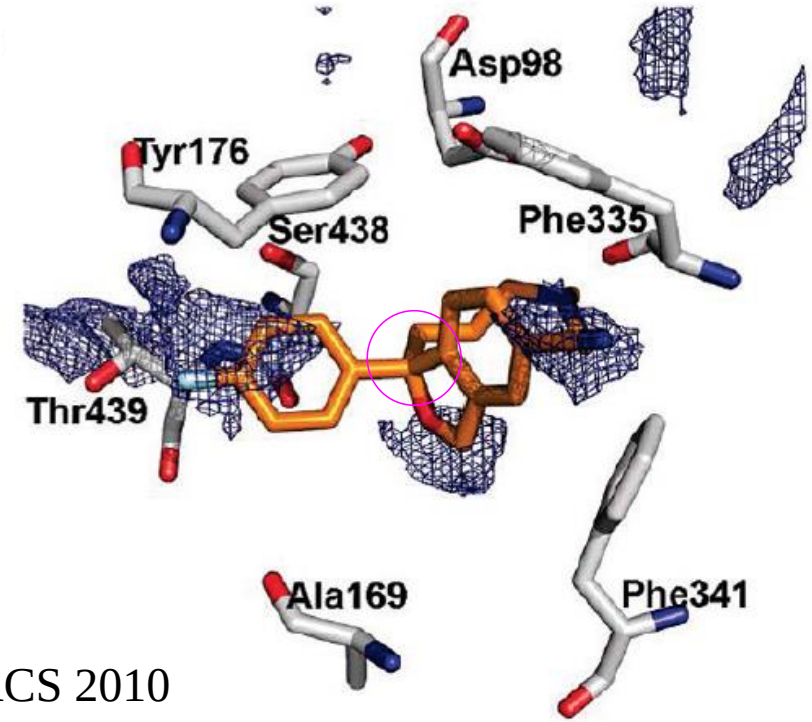
Escitalopram (Lexapro)

K_i SERT : 9.2 nM



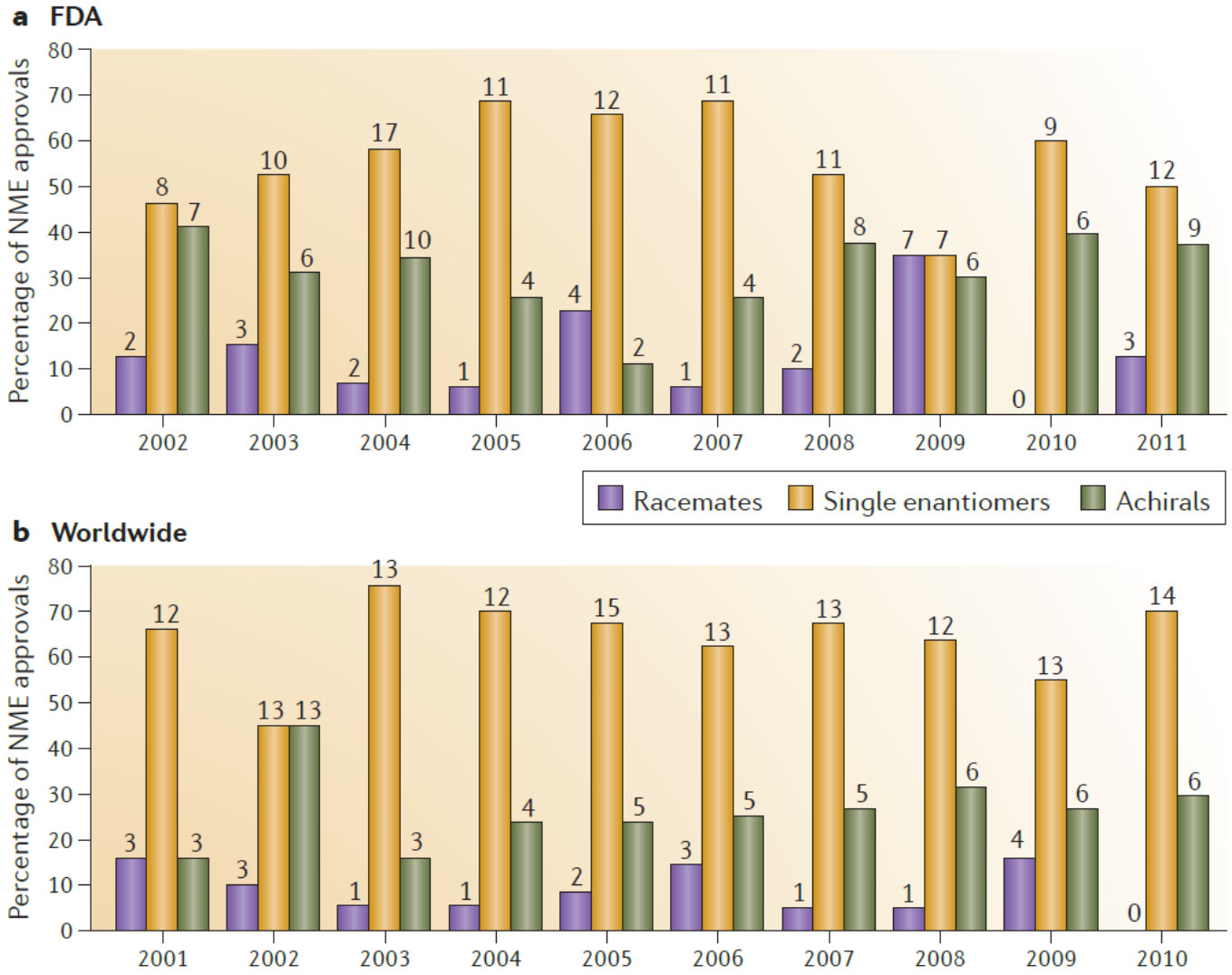
Differences in stereochemistry dictate how each isomer binds to the active site, and thus its binding affinity at the serotonin transporter, SERT

- *R*-enantiomer: binds in non-optimal fashion
- *S*-enantiomer: binds in opposite orientation, in optimal fashion ('reversed binding mode')



Koldso JACS 2010

Single enantiomers dominate FDA and worldwide approvals vs. Racemates

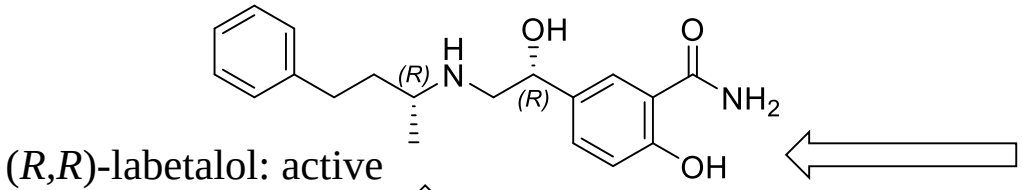


The chirality of NMEs. a | The percentage (shown on the *y*-axis) and number (shown above the bars) of US Food and Drug Administration (FDA)-approved new molecular entities (NMEs) according to the chirality of the NME are shown for the years 2002 to 2011. **b** | The percentage (shown on the *y*-axis) and number (shown above the bars) of worldwide-approved NMEs according to the chirality of the NME are shown for the 2001–2010 period. Achiral = nonchiral

Agranat Nat Rev Drug Disc 2012

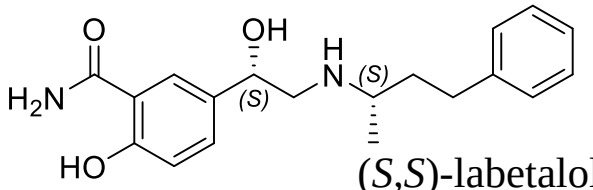
Diastereomers: Molecules with more than 1 chiral center

The molecules we have considered thus far are relatively simple because each has only one chirality center and only two stereoisomers. The situation becomes more complex, however, with molecules that have more than one chirality center. As a general rule, a molecule with *n* chirality centers can have up to 2^n stereoisomers. Molecules with more than one chiral center are called diastereomers, which are stereoisomers that are not mirror images. Note that enantiomers have opposite configurations at *all* chirality centers, whereas diastereomers have opposite configurations at *some* (one or more) chirality centers but the same configuration at others.



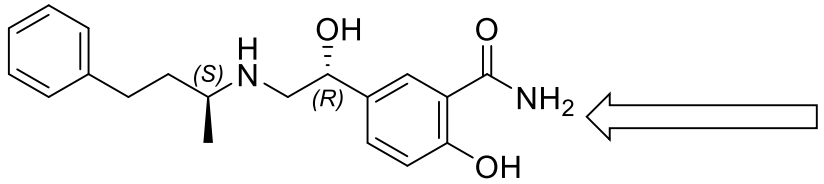
(*R*,*R*)-labetalol: active β-blocker, minimal α_1-adrenergic activity

Enantiomers, differ at all chiral centers



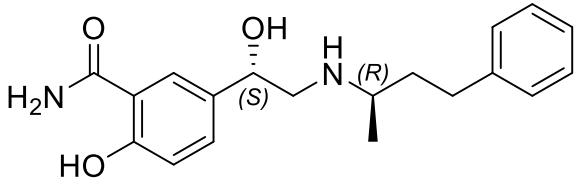
(*S*,*S*)-labetalol: inactive

Diastereomers, differ at some (in this case, one) chiral center



(*S*,*R*)-labetalol: $\alpha_1$blocker

Enantiomers, differ at all chiral centers



(*R*,*S*)-labetalol: inactive

Diastereomers, differ at some (in this case, one) chiral center

*Labetalol is dispensed as a mixture of four diastereomers. The *R*,*R* and *S*,*S* are enantiomers; as well as the *S*,*R* and *R*,*S* are enantiomers. Only the *R*,*R* diastereomer is responsible for β adrenergic activity (25%)*

Assigning priority numbering for stereochemistry: IUPAC Rules