

## STEREOCHEMISTRY CONSIDERATIONS

Most natural organic products, the essential products of life, are asymmetric ... This established perhaps the only well marked line of demarcation that can at present be drawn between the chemistry of dead matter and the chemistry of living matter.

*Louis Pasteur, circa. 1848*

1

---

---

---

---

---

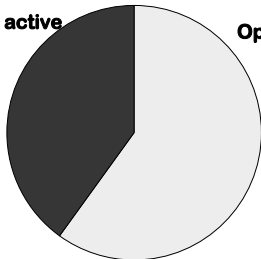
---

---

---

### Therapeutic Armamentarium

Non-optimally active  
Drugs (40%)



Optimally active  
drugs (60%)

2

---

---

---

---

---

---

---

---

## I. NOMENCLATURE

**CHIRAL CARBON:** A carbon atom which has 4 *different* ligands attached and is thereby *asymmetric*.

Result is:

nonsuperimposable mirror images  
rotate polarized light

3

---

---

---

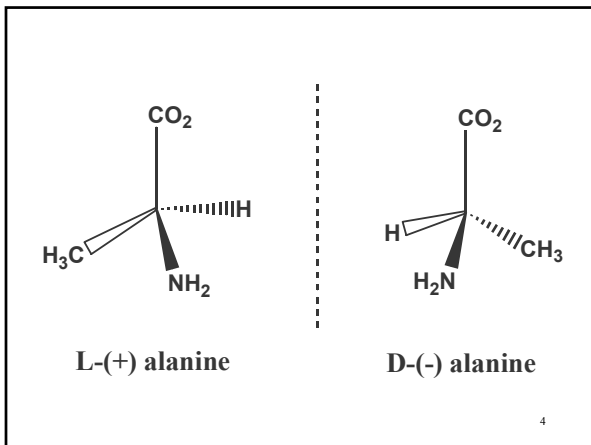
---

---

---

---

---




---

---

---

---

---

---

---

---

***Dextrarotatory – d or (+)***

***Levorotatory- l (-)***

**Terms for non-superimposable images:**  
***Optical isomers***  
***Optical antipodes***  
***Enantiomers***

**identical physical/chemical properties**

5

---

---

---

---

---

---

---

---

**rotation  $\neq$  configuration**

***R – rectus or D***  
***S – sinister or L***

**Thermodynamic equilibrium – 50:50 mixture**

***Racemic mixture: d, l or +, -***

**Ex: *d, l*-propranolol**

6

---

---

---

---

---

---

---

---

## Epimerization – formation of diastereomers

- possess > 1 chiral center
- Inversion of 1 chiral center produces a compound that is not a mirror image
- May have different chemical and physical properties

7

---

---

---

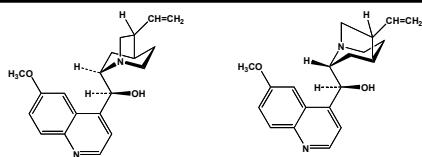
---

---

---

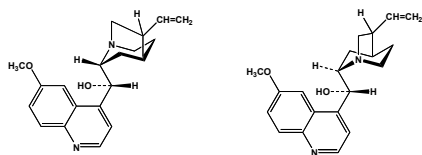
---

---



Quinidine [8R, 9S]

Epiquinidine [8R, 9R]



Quinine [8S, 9R]

Epiquinine [8S, 9S]

8

---

---

---

---

---

---

---

---

## PREFIXES USED TO DENOTE CHIRAL PROPERTIES

<u>PREFIX</u>	<u>PROPERTY</u>
<i>d-l-</i>	Rightward ( <i>dextro</i> ), clockwise/Leftward ( <i>levulo</i> ), counterclockwise, optical rotation. Used interchangeably with (+)/(-)
D-/L-	Rightward/leftward arrangement of substituents about chiral center (archaic, used for amino acids & carbohydrates)
R-/S-	Rightward ( <i>rectus</i> )/leftward ( <i>sinister</i> ) arrangement of substituents about chiral center (modern, used for drugs)

e.g., R-(-)- levorotatory, but with absolute configuration R

9

---

---

---

---

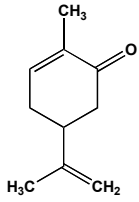
---

---

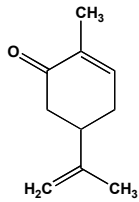
---

---

## II. PHARMACODYNAMIC SIGNIFICANCE OF STEREOISOMERS



**d-carvone  
(CARAWAY)**



**l-carvone  
(SPEARMINT)**

10

---

---

---

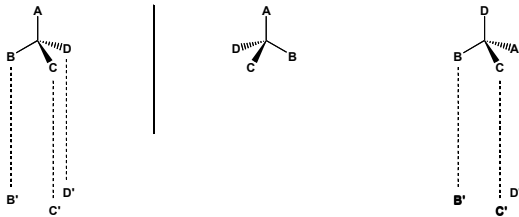
---

---

---

---

---



Enantiomeric interactions with a chiral biological macromolecule (Easson-Stedman model). The enantiomer on the left is involved with 3 simultaneous bonding interactions with complementary functionalities on the receptor, whereas that on the right interacts at 2 sites only. Alternative receptor orientations of the enantiomer on the right are possible, but only 2 complementary interactions may take place at any time. From Hutt AJ, Tan SC (1996) *Drugs* 52:S1-S12.

11

---

---

---

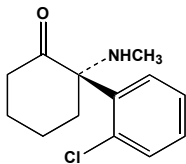
---

---

---

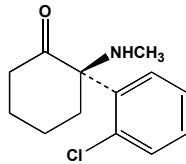
---

---



**S-(+)-Ketamine**

**2-4 times more potent than  
R-(-)-ketamine in  
anaesthesia**



**R-(-)-Ketamine**

**Causes spontaneous motor  
activity and post-emergent  
distress**

12

---

---

---

---

---

---

---

---

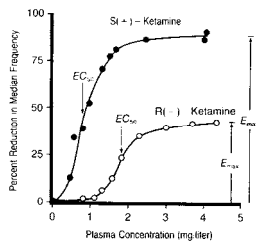


Fig. 20-1. Changes in the electroencephalographic median frequency were followed to quantify the anesthetic effect of R(-)-ketamine and S(+)-ketamine in a subject who received an infusion of these two optical isomers on separate occasions. Shown is the percent reduction in the median frequencies versus plasma concentration. Although characteristic S-shaped, or sigmoidal, curves are seen with both compounds, they differ in both the maximum effect achieved,  $E_{max}$ , and the concentration needed to produce 50 percent of  $E_{max}$ , the  $EC_{50}$ . These relationships may be considered direct ones as no significant time delay was found between response and concentration. (One mg/liter = 4.2 micromolar) (Redrawn from Schuttler, J., Stoessel, H., Schweilden, H., and Lavan, P.M.: Hypnotic drugs. In Quantitation, modeling and control in anesthesia. Edited by H. Stoessel. George Thieme Verlag, Stuttgart, 1985, pp. 196-210.)

Reproduced from: Rowland M, Tozer TN. *Clinical Pharmacokinetics – Concepts and Applications*, 3<sup>rd</sup> edition, 1995, p. 341.

13

### Relative Pharmacodynamic Potency of Selected Enantiomers

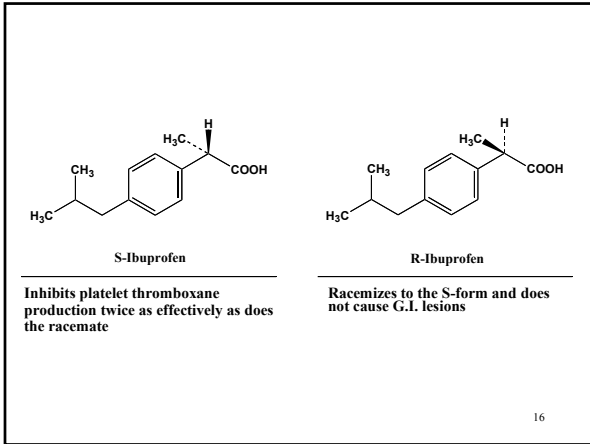
<u>Compound</u>	<u>Relative Activity</u>	<u>Biological Response</u>
terbutaline	-> + (3000:1)	trachea relaxation
propranolol	S > R (100:1)	block tachycardia
pindolol	-> + (200:1)	inhibit tachycardia
methadone	-> + (3:1)	respiratory depression
ketamine	S > R (4:1)	anesthesia
tocainide	R > S (3:1)	antiarrhythmic
flecainide	+ = -	antiarrhythmic
propafenone	+ = -	antiarrhythmic
disopyramide	S > R	antiarrhythmic
disopyramide	S > R	anticholinergic
warfarin	S > R (8:1)	anticoagulant
verapamil	-> + (5-18:1)	block AV conduction

Data from: Jamali F, et al. *J Pharm Sci* 78:695, 1989.

14

- Enantiomers have identical efficacy and toxicity
- Enantiomers may have the same therapeutic and toxic effects, but differ in magnitude
- One enantiomer may possess virtually all the pharmacological activity while the other is essentially biologically inactive
- Both enantiomers may be pharmacologically active but have qualitatively different therapeutic and toxic effects

15




---

---

---

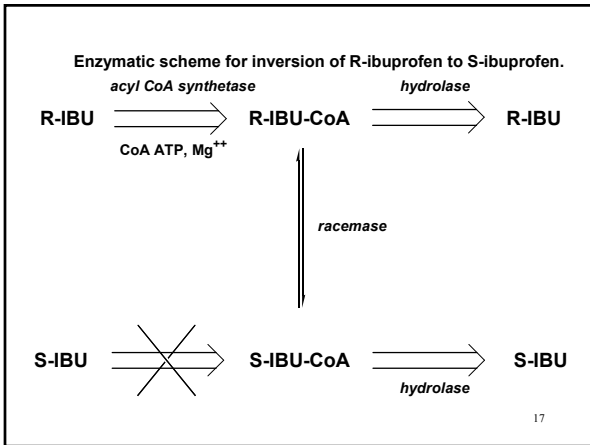
---

---

---

---

---




---

---

---

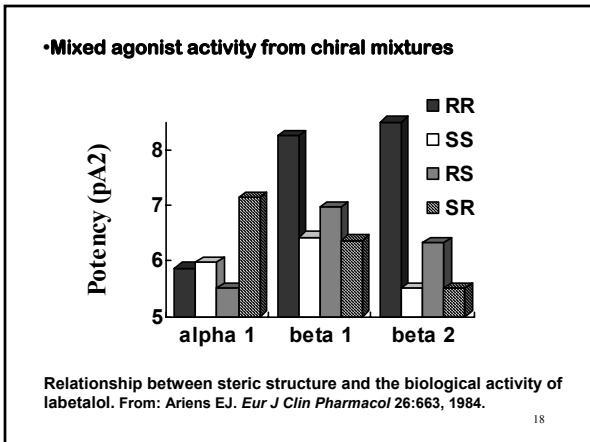
---

---

---

---

---




---

---

---

---

---

---

---

---

### III. STEREOSELECTIVITY OF PHARMACOKINETIC PROCESSES

#### A. ABSORPTION

$F_{rel}$  D-methotrexate/L-methotrexate = 0.025

19

---

---

---

---

---

---

---

---

### III. STEREOSELECTIVITY OF PHARMACOKINETIC PROCESSES

#### A. ABSORPTION

#### B. DISTRIBUTION

<u>Drug</u>	<u>Free Fraction</u>		<u>Ratio (+/-)</u>
	+	-	
disopyramide	0.27	0.39	0.7
ibuprofen	0.006	0.0039	1.5
mexilitine	0.283	0.198	1.4
methadone	0.092	0.124	0.7
propoxyphene	0.018	0.018	1.0
propranolol	0.203	0.176	1.2
tocainide	0.17	0.14	1.2
verapamil	0.064	0.11	0.6
warfarin	0.012	0.009	1.3 <sub>0</sub>

---

---

---

---

---

---

---

---

#### C. METABOLISM

<u>Drug</u>	<u>Clearance</u>	<u>Form</u>	<u>(+)</u>	<u>(-)</u>	<u>Ratio</u>
disopyramide	$Cl_{u,pr,iv}$	isomer	0.23	0.18	1.28
propranolol	$CL_{iv}$	racemate	1.21	1.03	1.17
	$CL_{u,iv}$	racemate	~6.0	~5.9	1.02
	$CL_o$	racemate	2.78	1.96	1.42
	$CL_{u,o}$	racemate	13.7	11.1	1.23
verapamil	$CL_{iv}$	isomer	0.80	1.40	1.75
	$CL_{u,iv}$	isomer	5.96	5.85	1.02
	$CL_o$	racemate	1.72	7.46	4.33
warfarin	$CL_o$	racemate	0.234	0.333	1.42
	$CL_{u,o}$	racemate	~21.9	~37.0	1.69

Data from: Tucker GT, Lennard MS. *Pharmacol Ther* 45:309-329, 1990.

21

---

---

---

---

---

---

---

---



## D. EXCRETION

Drug	Clearance	Form	(+)	(-)	Ratio
chloroquine	$CL_{R,u}$	racemate	824	519	1.6
Disopyramide	$CL_{R,u}$	isomer	338	182	1.8
mexilitine	$CL_R$	racemate	0.5	0.5	1.0
pindolol	$CL_{R,u}$	racemate	453	534	1.2
terbutaline	$CL_R$	isomer	2.7	1.5	1.8
tocainide	$CL_R$	isomer	55	55	1.0

25

---

---

---

---

---

---

---

---

---

---

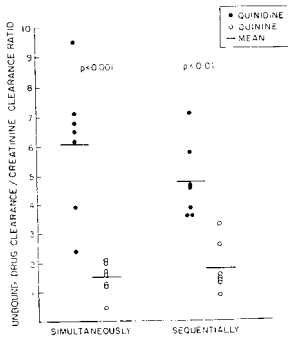


Fig. 2. Ratio of unbound drug clearance  $CL_u$  for quinidine and quinine in healthy adult subjects receiving these drugs simultaneously and sequentially on different days.

26

---

---

---

---

---

---

---

---

---

---

## IV. IMPACT OF STEREOSELECTIVITY ON PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETER ESTIMATES WHEN USING NON-SPECIFIC ANALYTICAL METHODS

27

---

---

---

---

---

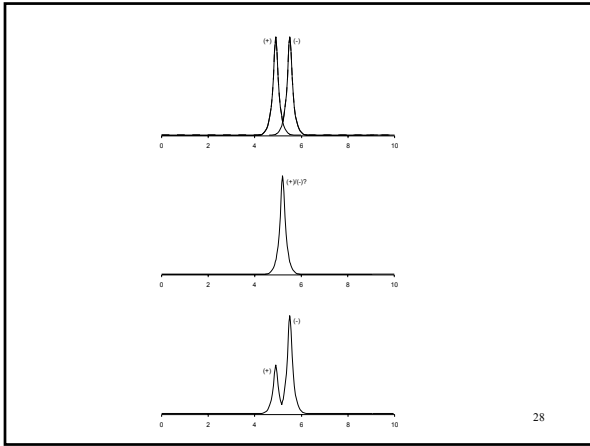
---

---

---

---

---




---

---

---

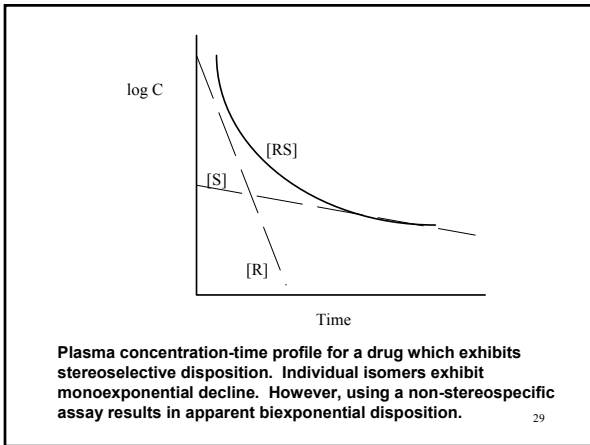
---

---

---

---

---




---

---

---

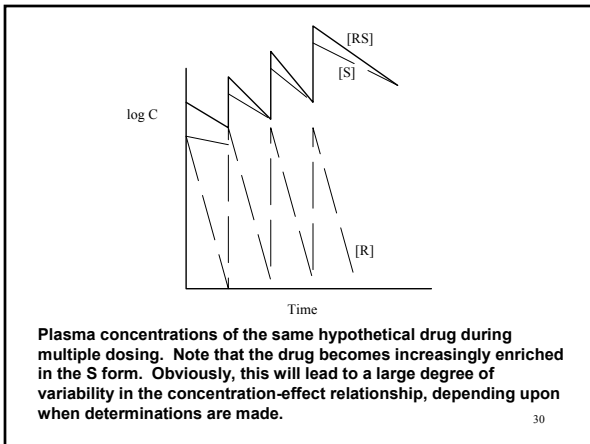
---

---

---

---

---




---

---

---

---

---

---

---

---