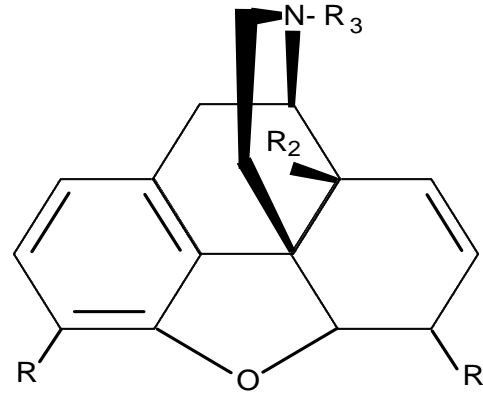






Structure-activity relationships of opioids

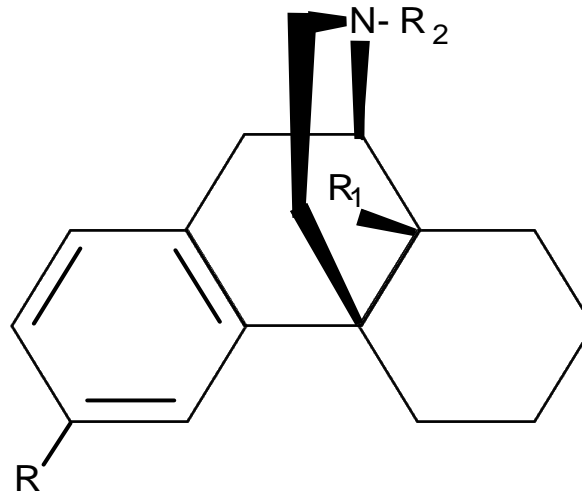
Louis S. Harris, Ph.D.
Harvey Hagg Professor

Morphines



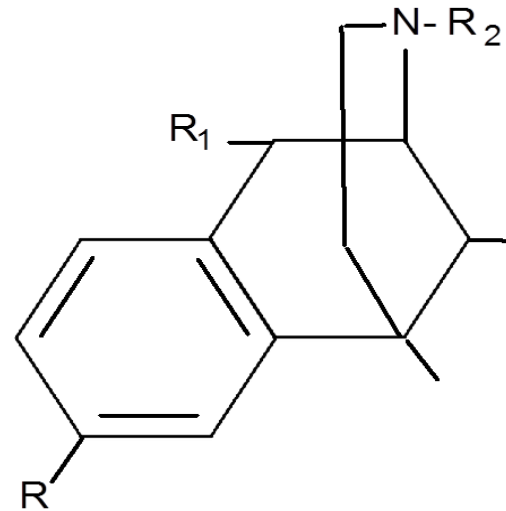
Compound	R	R ₁	R ₂	R ₃	X
Morphine	-OH	-OH	-H	-CH ₃	
Codeine	-OCH ₃	-OH	-H	-CH ₃	
Thebaine	-OCH ₃	-OCH ₃	-H	-CH ₃	Second =
Heroin	-OCOCH ₃	-OCOCH ₃	-H	-CH ₃	
Oxymorphone	-OH	=O	-OH	-CH ₃	Reduced =
Oxycodone	-OCH ₃	=O	-OH	-CH ₃	Reduced =
Nalmefene	-OH	=CH ₃	-OH	-CH ₂ 	Reduced =
Nalorphine	-OH	-OH	-H	-CH ₂ CH ₂ =CH ₂	
Naloxone	-OH	=O	-OH	-CH ₂ CH=CH ₂	Reduced =
Naltrexone	-OH	=O	-OH	-CH ₂ 	Reduced =



Morphinans



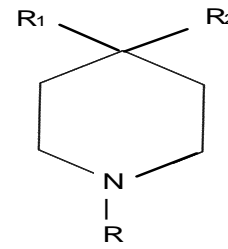
Compound	R	R ₁	R ₂	Isomer
Levorphanol	-OH	-H	-CH ₃	(-)
Dextromethorphan	-OCH ₃	-H	-CH ₃	(+)
Levallorphan	-OH	-H	-CH ₂ CH=CH ₂	(-)
Butorphanol	-OH	-OH	-CH ₂ --◇	(-)
Cyclorphan	-OH	-H	-CH ₂ ◁	(-)

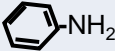
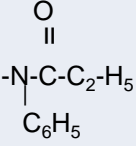

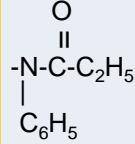

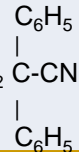
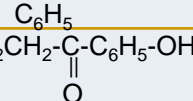
Benzomorphans



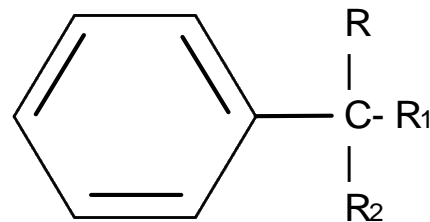
Compound	R	R ₁	R ₂	Isomer
Metazocine	-OH	-H	-CH ₃	(±)
Phenazocine	-OH	-H	-CH ₂ CH ₂ -C ₆ H ₅	(±)
N-Allyl-nor-metazocine (SKF 10047)	-OH	-H	-CH ₂ CH=CH ₂	(±)
Pentazocine	-OH	-H	-CH ₂ CH=C(CH ₃) ₂	(±)
Cyclazocine	-OH	-H	-CH ₂ - 	(±)
Ketocyclazocine	-OH	=O	-CH ₂ - 	(±)

Piperidines



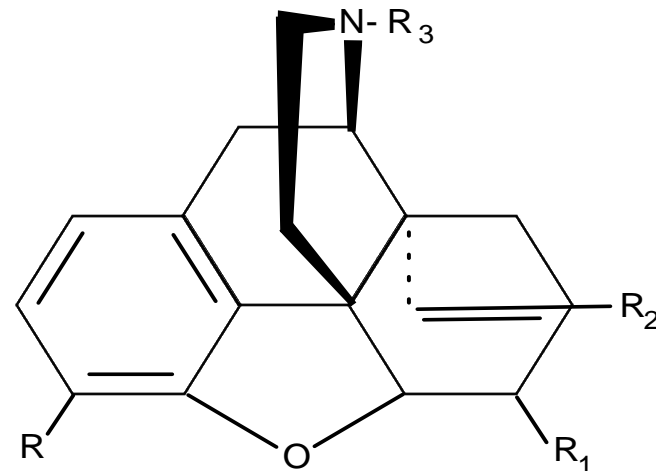
Compound	R	R ₁	R ₂
Meperidine	-CH ₃	-C ₆ H ₅	-C(=O)-OC ₂ H ₅
Ketobemidone	-CH ₃	m-OH C ₆ H ₅	-C(=O)-C ₂ H ₅
Anileridine	-CH ₂ CH ₂ -  -NH ₂	-C ₆ H ₅	-C(=O)-OC ₂ H ₅
Fentanyl	-CH ₂ CH ₂ C ₆ H ₅	-H	
Sufentanil	-CH ₂ CH ₂ - 		-CH ₂ OCH ₃
Carfentanil	-CH ₂ CH ₂ C ₆ H ₅		-N-C ₆ H ₅ C=O CH ₂ CH ₃
Diphenoxylate	-CH ₂ CH ₂ - 	-C ₆ H ₅	-C(=O)-OC ₂ H ₅
Haloperidol	-CH ₂ CH ₂ CH ₂ - 		-C ₆ H ₅ - p-Cl


Diphenylmethanes



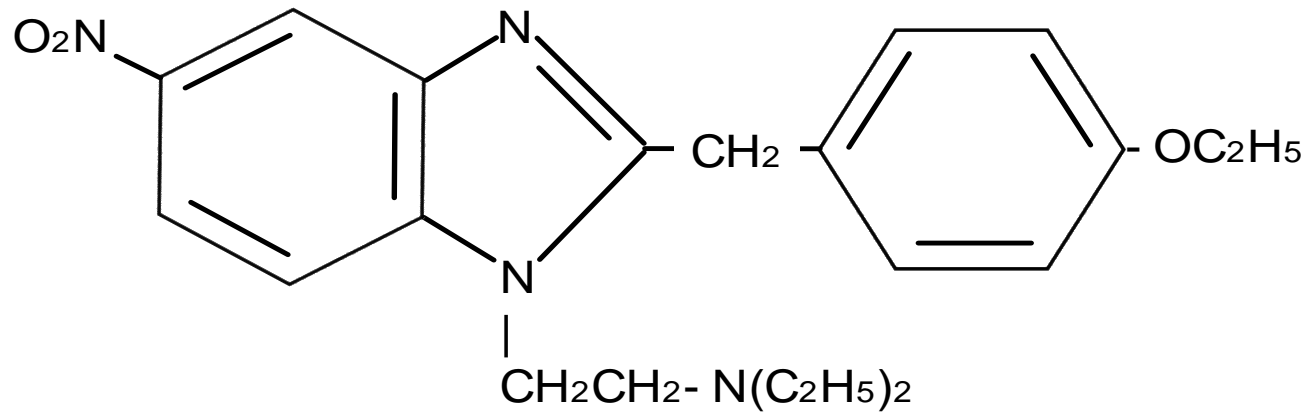
Compound	R	R ₁	R ₂
Methadone	-C ₆ H ₅	$\begin{array}{l} \text{C} \\ \parallel \\ \text{O} \\ \diagdown \\ \text{C}_2\text{H}_5 \end{array}$	$\begin{array}{l} \text{CH}_3 \\ \diagup \\ \text{CH}_2\text{CH} \text{N} \\ \quad \diagdown \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$
Levomethadyl Acetate (LAAM)	-C ₆ H ₅	$\begin{array}{l} \text{OCOCH}_3 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{C}_2\text{H}_5 \end{array}$	$\begin{array}{l} \text{CH}_3 \\ \diagup \\ \text{CH}_2\text{CH} \text{N} \\ \quad \diagdown \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$
Propoxyphene	CH ₂ C ₆ H ₅	$\begin{array}{l} \text{O} \\ \parallel \\ \text{O} \text{CC}_2\text{H}_5 \end{array}$	$\begin{array}{l} \text{CH}_3 \\ \diagup \\ \text{CH}_2\text{CH} \text{N} \\ \quad \diagdown \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$

4,5-Epoxymorphinans (Oripavines)

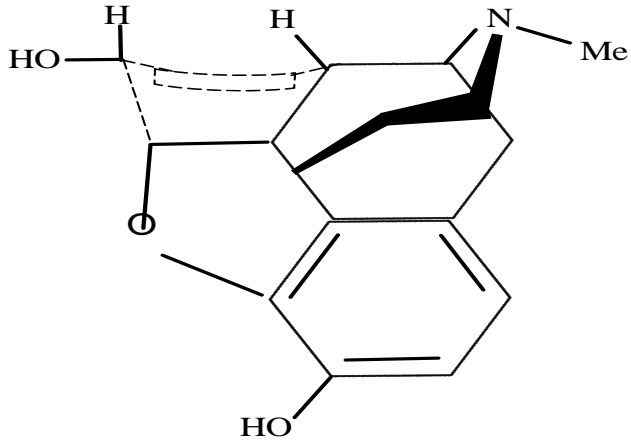


Compound	R	R ₁	R ₂	R ₃	X
Etorphine (M-99)	-OH	-OCH ₃	$\begin{array}{c} \text{OH} \\ \\ -\text{C}-\text{C}_3\text{H}_7 \\ \\ \text{CH}_3 \end{array}$	-CH ₃	
Dihydroetorphine					Reduced =
Buprenorphine	-OH	-OCH ₃	$\begin{array}{c} \text{OH} \\ \\ -\text{C}-\text{C}_4\text{H}_9 \\ \\ \text{CH}_3 \end{array}$	-CH ₂ 	

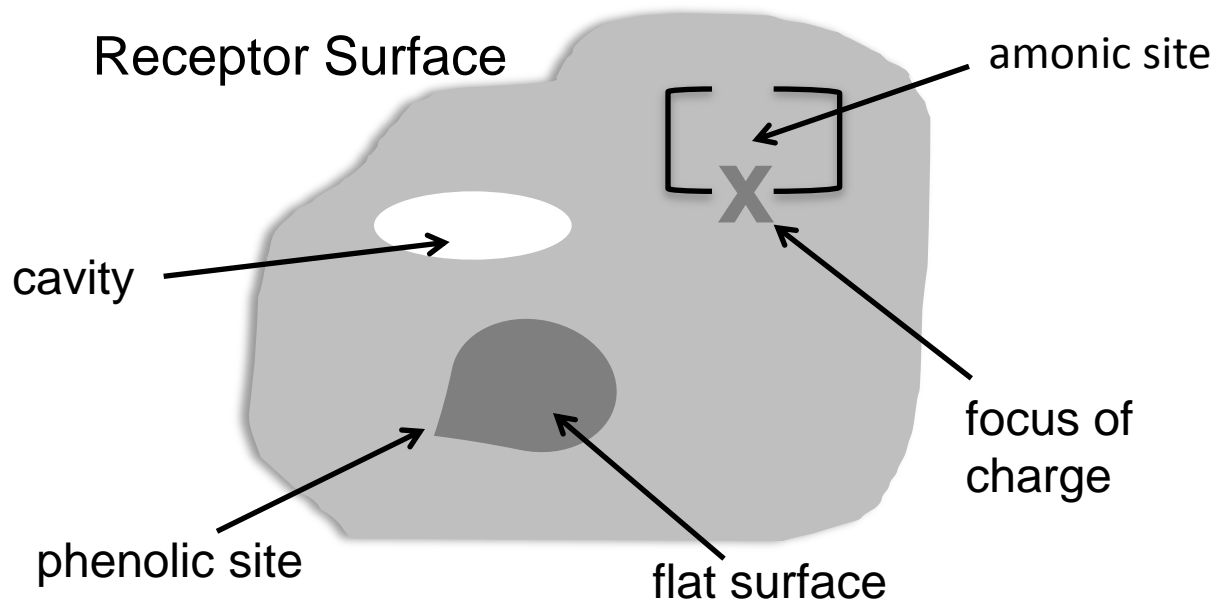
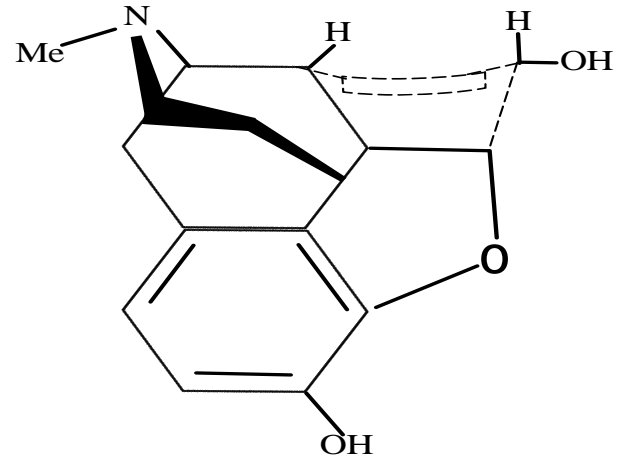
Etonitazine



(+)-Morphine



(-)-Morphine



Rank Order Correlation

	Mouse	Rat	Man	ADD
Methadone	1	2	2	1
Isomethadone	4	3	4	4
Meperidine	5	5	5	5
Ketobemidone	2	1	1	2
Codeine	7	7	6	6
Morphine	3	4	3	3
D-Propoxyphene	6	6	7	7
Mouse vs Rat	0.93	Rat vs Man		0.93
Mouse vs Man	0.93	Rat vs ADD		0.89
Mouse vs ADD	0.93			

Chemists

Archer
Bentley
Coop
Eisleb
Gates
Gordon
Jacobson
Janssen
Lewis
May
Mosettig
Portoghese
Rice
Schauman
Small
Zimmerman

Pharmacologists

Aceto
Balster
Beardsley
Deneu
Eddy
Dewey
Fantegrossi
France
Holtzman
Kosterlitz
Johanson
Mello
Mendelson
Negus
Schuster
Seevers
Swain
Takemori
Traynor
Way
Woolverton
Woods
Yanagita

Clinicians

Beecher
Fraser
Gorodetsky
Griffiths
Himmelsbach
Hollister
Houde
Isbel
Jasinski
Keats
Lasagna
Martin
Wikler