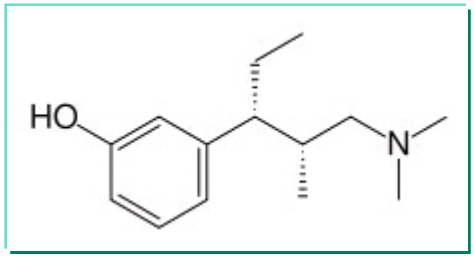
The 34th National Medicinal Chemistry Symposium

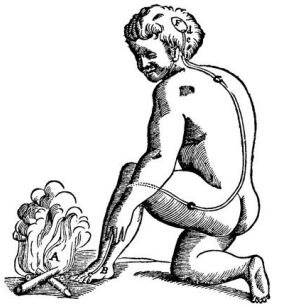
May 18-21, 2014

Charleston, South Carolina

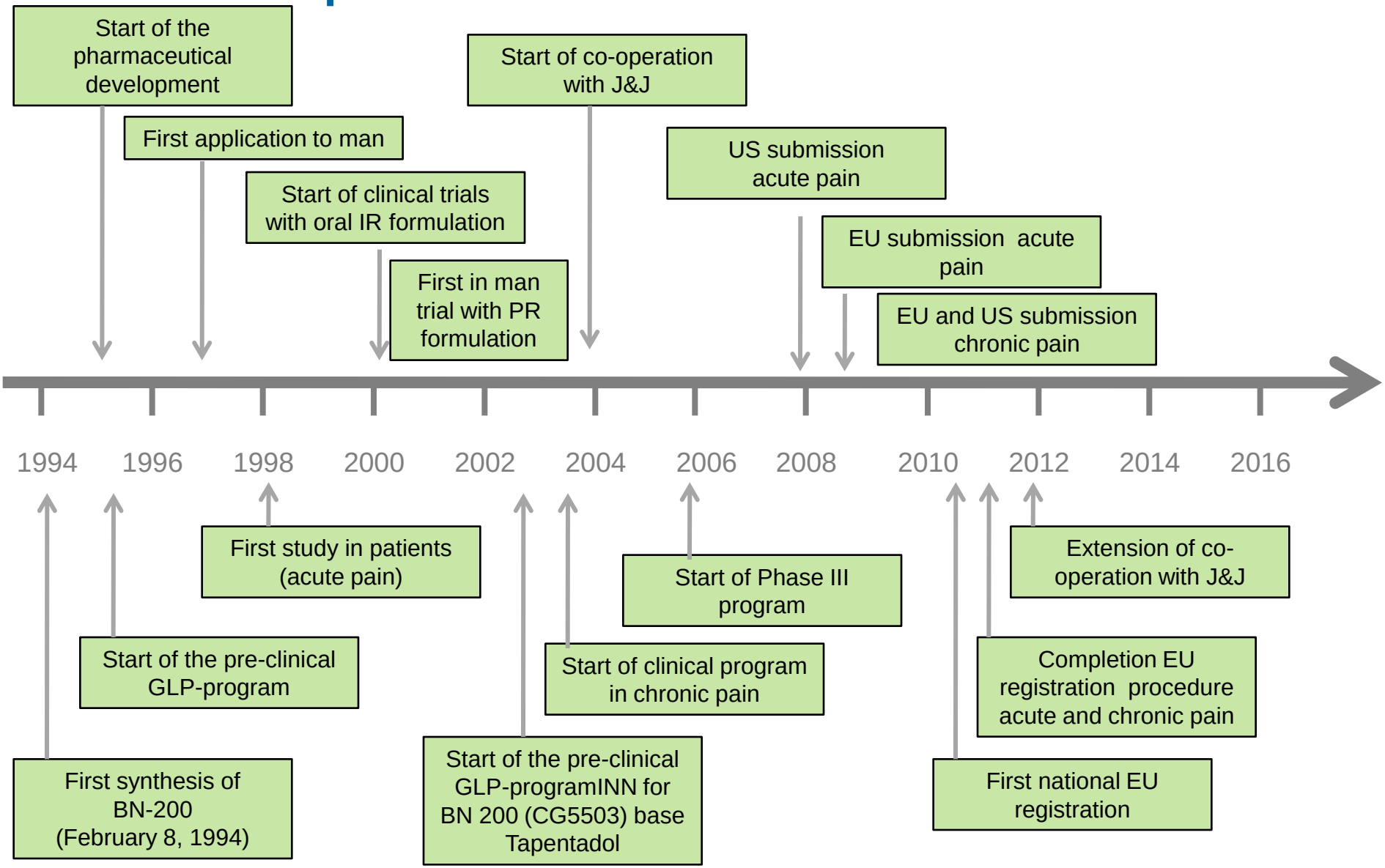
Tapentadol - From Morphine and Tramadol to the Discovery Tapentadol



Helmut Buschmann
Pharma Consulting Aachen
www.pharma-consulting-ac.de



Tapentadol – The Path To The Market



Tapentadol

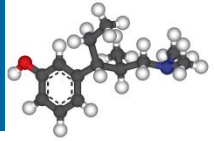
Wie es begann

How it all started

Mitte der 90er Jahre war es Aufgabe der Grünenthal Forscher in Aachen, neue zentralwirksame Schmerzmoleküle zu entwickeln.
Am 8. Februar 1994 gelang es den Kollegen um Chemiker Helmut Buschmann erstmals, einige Gramm einer neuen Substanz zu synthetisieren. Dies war die Geburtsstunde von PALEXIA®. PALEXIA® war damals noch Substanzkandidat, benannt nach seinem Erfinder „BN 200".

In the mid-1990s, Grünenthal scientists in Aachen were asked to develop novel centrally acting analgesics.
February 8th 1994 was the birthday of PALEXIA®: for the first time, chemist Helmut Buschmann and his coworkers succeeded in synthesizing a few gram of a new active substance. At that time PALEXIA® was a drug candidate named by his inventor "BN200".

Tapentadol



(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 0 693 475 B1**

(12) **EUROPÄISCHE PATENTSCHRIFT**

(45) Veröffentlichungstag und Bekanntmachung des Hinweises auf die Patenterteilung:
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(54) **1-Phenyl-3-dimethylamino-propanverbindungen mit pharmakologischer Wirkung**

1-Phenyl-3-dimethylamino-propane derivatives having pharmacological activity

Dérivés propane 1-phényl-3-diméthylamino à activité pharmocologique

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24.01.1996 Patentblatt 1996/04

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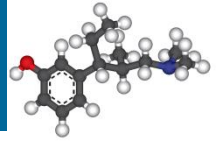
(56) Entgegenhaltungen:
EP-A- 0 176 049 **DD-A- 124 521**

- **CHEMICAL ABSTRACTS, vol. 54, no. 20, 25.Oktober 1960 Columbus, Ohio, US; abstract no. 20963c, I.N. NAZAROV ET AL. 'Synthetic analgesic substances.' Seite 20963; Spalte 1;**
- **JOURNAL OF PHARMACEUTICAL SCIENCES, Bd. 57, Nr. 9, September 1968 Seiten 1487-1493, N.D. POTTI ET AL. 'Use of 3-Azabicyclo(3.2.1)octane in the Mannich Reaction'**
- **JOURNAL OF PHAMACEUTICAL SCIENCES, Bd. 59, Nr. 7, Juli 1970 Seiten 1038-1041, PYARE PARIMOO ET AL. 'New Compounds: Some potential chemotherapeutic agents derived from aralkyl ketones'**

Bemerkungen:

Die Akte enthält technische Angaben, die nach dem Eingang der Anmeldung eingereicht wurden und die nicht in dieser Patentschrift enthalten sind.



Tapentadol - From Morphine and Tramadol to the Discovery Tapentadol

- **Pain Transduction**
- **The Analgesic Market**
- **Current Analgesic Treatment Options**
- **Pain Research Today - The Unmet Needs**
- **Tramadol – History and Pharmacology**
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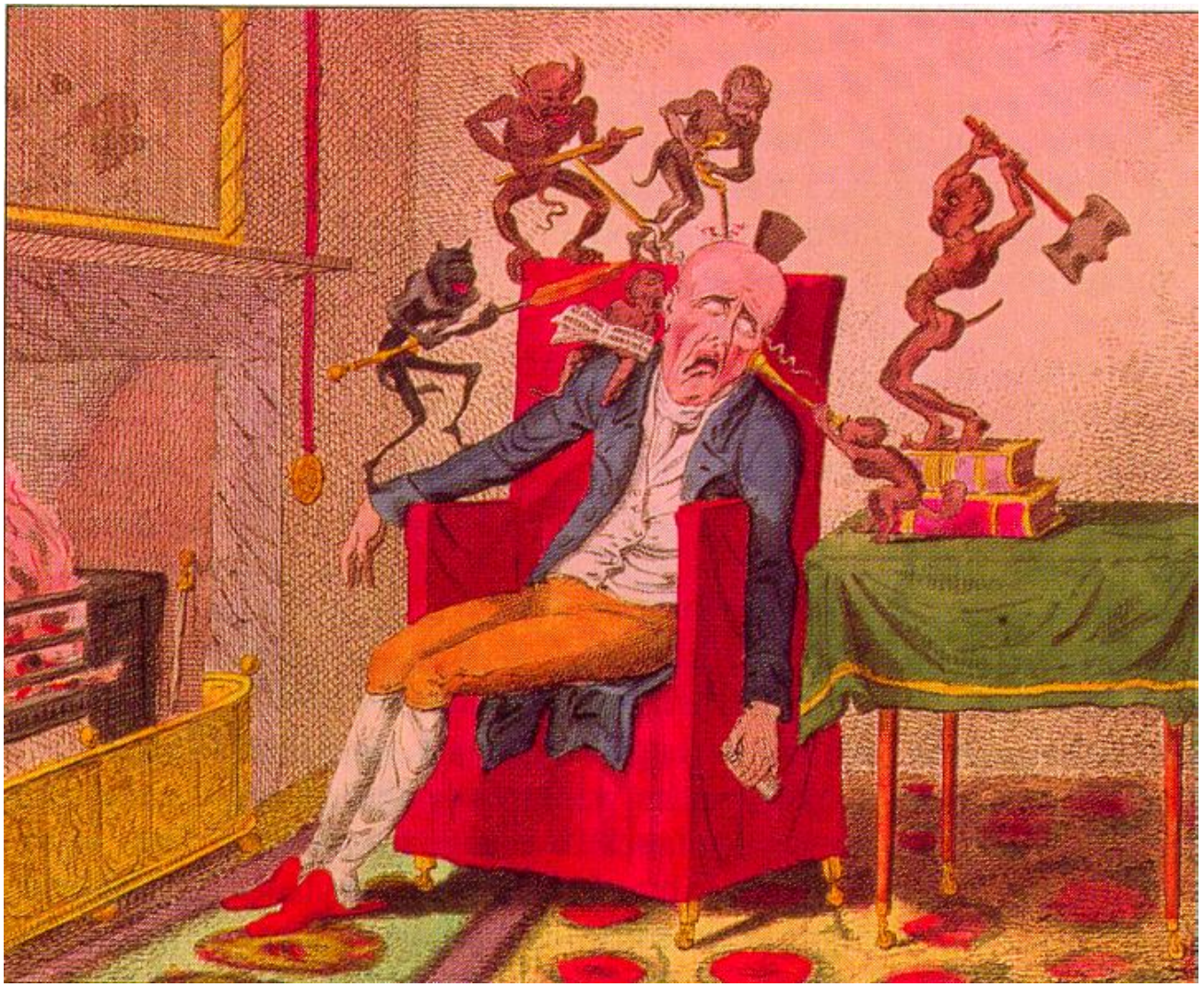
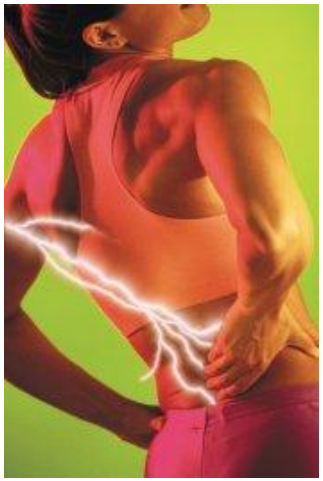
  - ***In vivo* Pharmacology**
  - **Metabolism**
  - **Synthesis**
  - **Clinical Development**

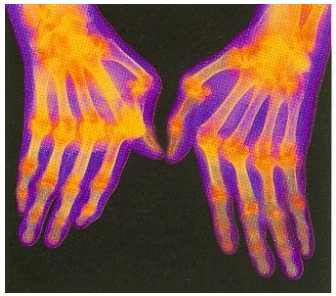
Pain



Le Mal de Tete

Facts About Pain and Pain Treatment



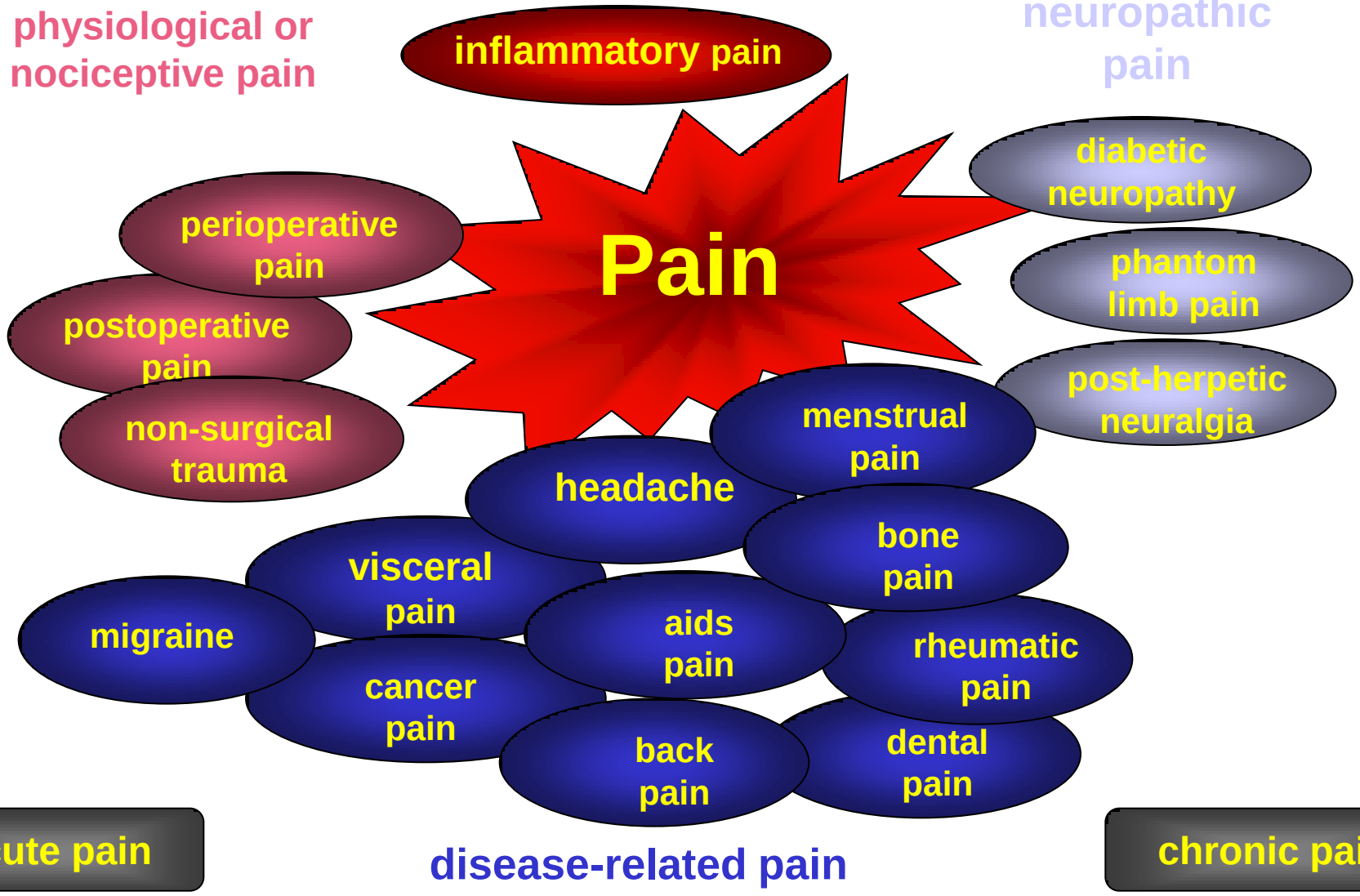


Facts about Pain

- Pain is a highly complex, heterogeneous and dynamic process that involves multiple interrelated neurotransmitter and neuromodulator systems in the spinal cord, ascending and descending spinal pathways and supraspinal sites
- **It is experienced as an unpleasant sensory and emotional experience associated with potential or real tissue damage.**
- It constitutes the body's mechanism of self-preservation; it serves as a warning to indicate harm or impending danger to body tissues and the need to avoid injury and/or take care of oneself.
- Pain has both sensory and emotional aspects, and emerges when there is a discrepancy between what an individual expects of himself and what he really is or does
- According to the International Association for the Study of Pain's Taxonomy Task Force, pain is a subjective experience that is learned by the individual through experiences relating to injuries in early life

Pain Transduction

Overview of the Different Types of Pain



Pain Transduction

Focus on Neuropathic Pain

Neuropathic pain encompasses a wide range of pain syndromes

NEUROPATHIC PAIN
Initiated or caused by a lesion or dysfunction in the nervous system (PNS or CNS)

MIXED PAIN
Pain with neuropathic and nociceptive components

NOCICEPTIVE PAIN
Pain caused by injury to body tissues

- Diabetic neuropathy
- Chemotherapy-induced neuropathic pain
- Posttraumatic neuropathy
- Trigeminal neuralgia
- Postherpetic neuralgia
- Low back pain (radiculopathy)
- CRPS
- Cancer neuropathy
- Cervical radiculopathy
- Postsurgical neuropathy
- Phantom limb pain
- Carpal tunnel syndrome
- Central post-stroke pain
- HIV neuropathy
- MS pain
- …

UNMET NEED FOR TREATMENT

Signs and symptoms:

➢Allodynia

Pain from an innocuous stimulus* that normally does not evoke pain

➢Hyperalgesia

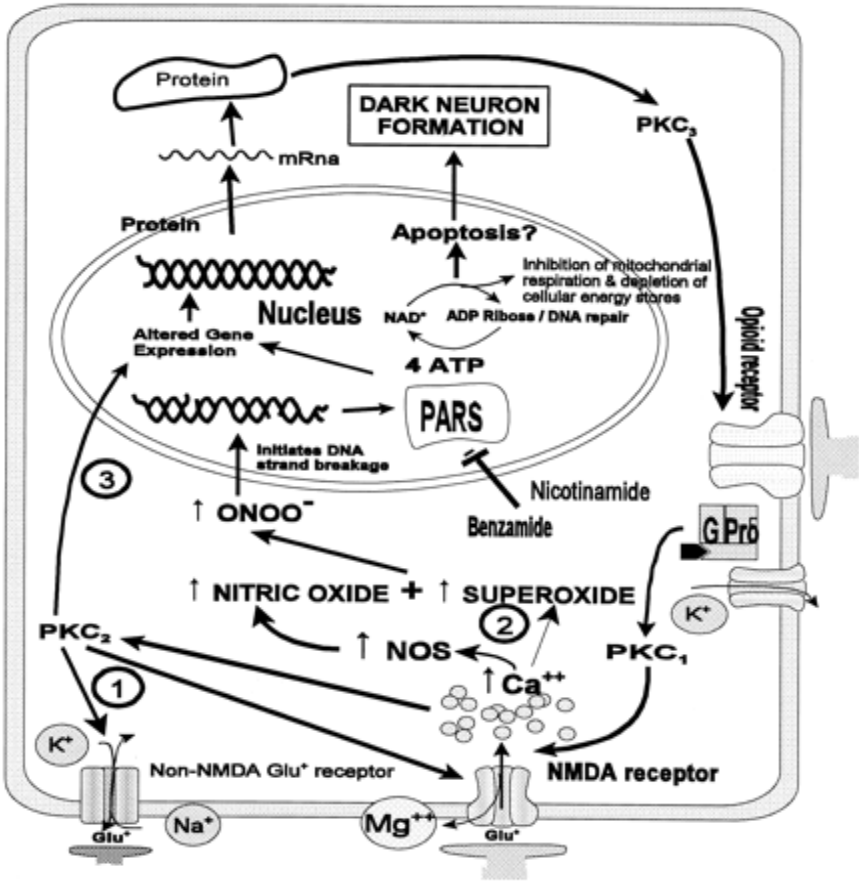
Exaggerated response to a normally painful stimulus*

* The stimulus may be mechanical or thermal

Pain Transduction

The Evolution in Pain Research

Descartes (1644)



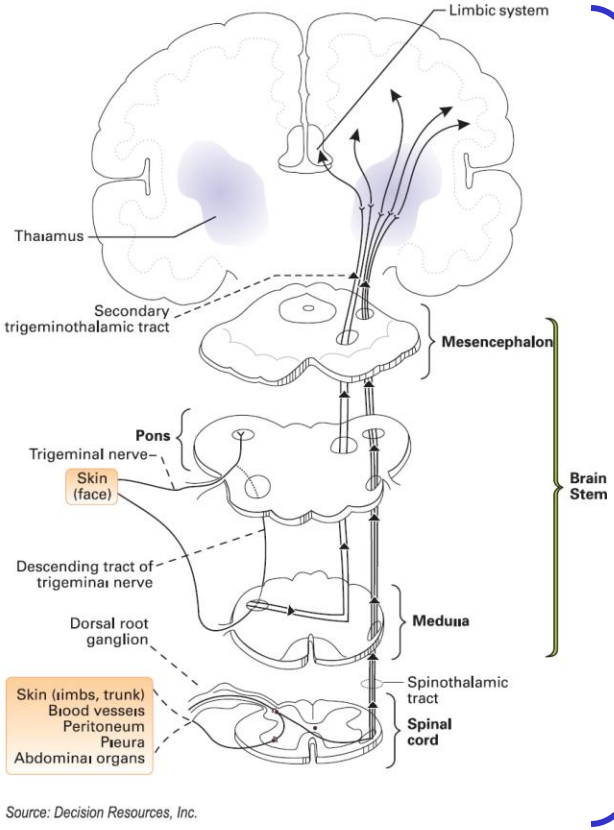
Mayer et al. (1999)

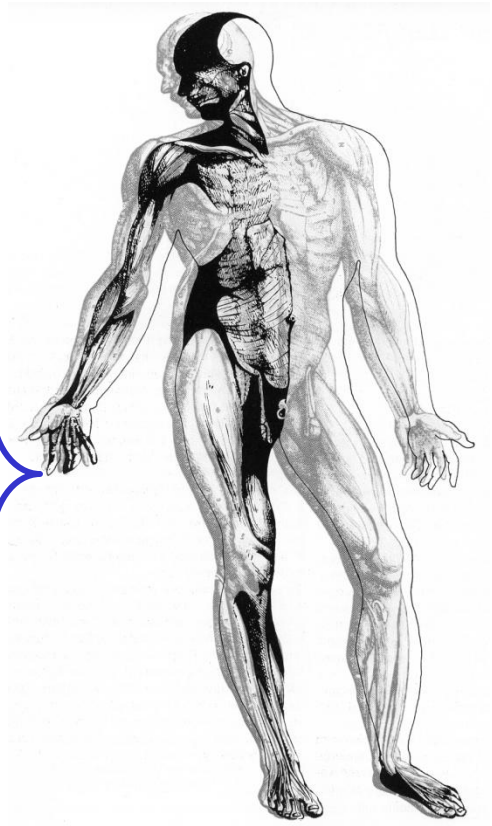
Pain Transduction

Many Targets for one Disease

Multiple Mode of Actions for Analgesics

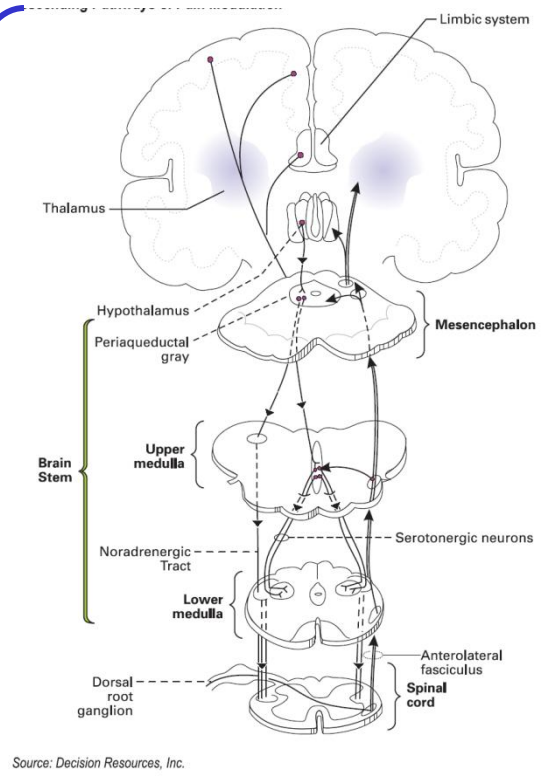
Ascending Pathways of Pain Perception





One Disease

Descending Pathways of Pain Modulation

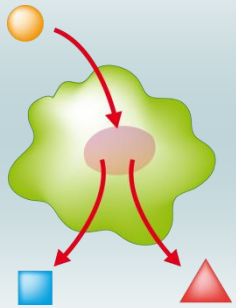


Source: Decision Resources, Neuropathic Pain Report, 2004.

Pain Transduction

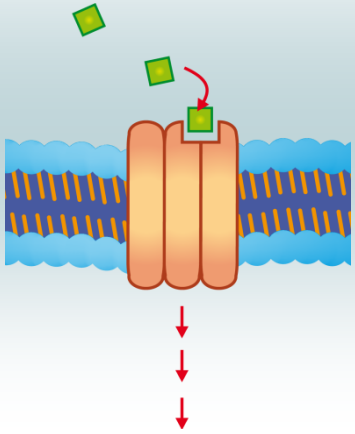
Function of the Target Location

Enzymes



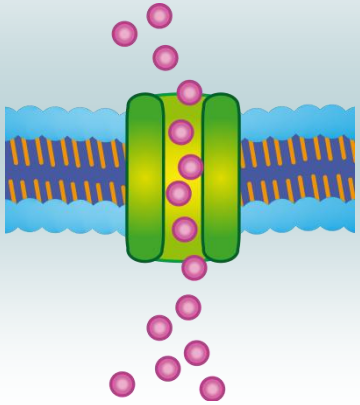
Inhibition of Formation of Pain Mediators

Receptors



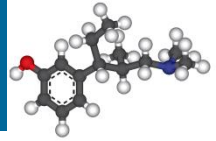
Activation of the endogene Pain Inhibition

Ion Channels / Transporters



- Change of Action Potential
- Blockade of Reuptake of Neurotransmitters

Pain Transduction



Physiology and Pathophysiology of Pain

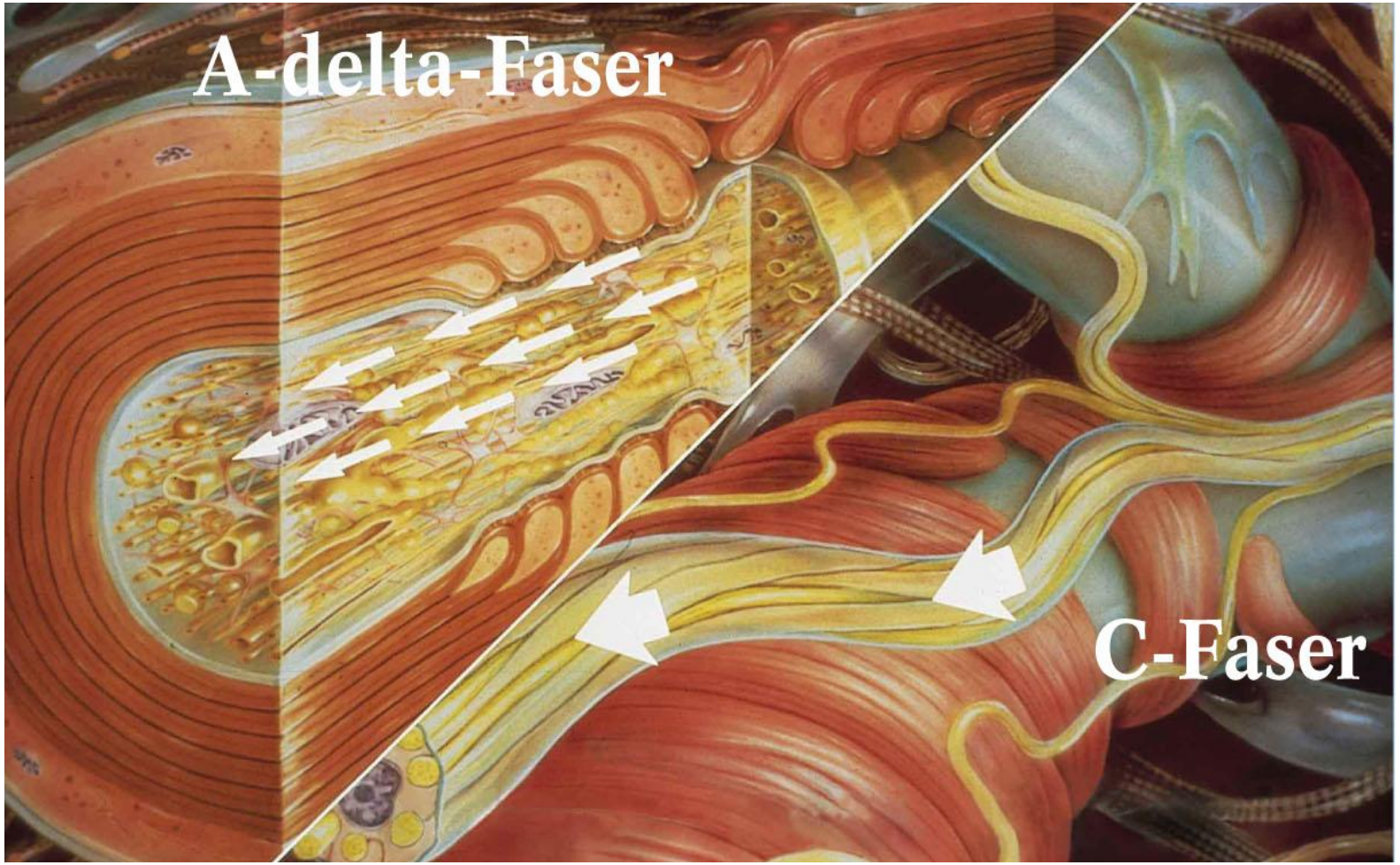
- **C-Fibre Activation**
  - The physiological aspects of lasting pain can be described as when a ***mechanical, thermal, chemical or electrical stimulus*** strong enough to damage tissue or affect cellular metabolism, stimulates the nociceptive free nerve endings of the **C-fibres**, which are found all over the surface of the body and its organs.

- **Aδ-Fibre Activation**
  - Several subtypes of **A-fibres** also carry afferent nociceptive impulses. The damaged tissue sends out nerve impulses through nerve tracts in the spinal cord to the brain (cerebral cortex) where the stimulus becomes a conscious feeling of pain.

- **Endogenous Pain Mediators**
  - In addition to nervous pain impulses, injured tissues produce inflammatory pain-producing substances, including **bradykinin** and other kinins, **serotonin**, **histamine**, **acetylcholine**, excesses of **potassium ions**, proteolytic enzymes and **prostaglandins**, which can act in synergy to increase pain levels.

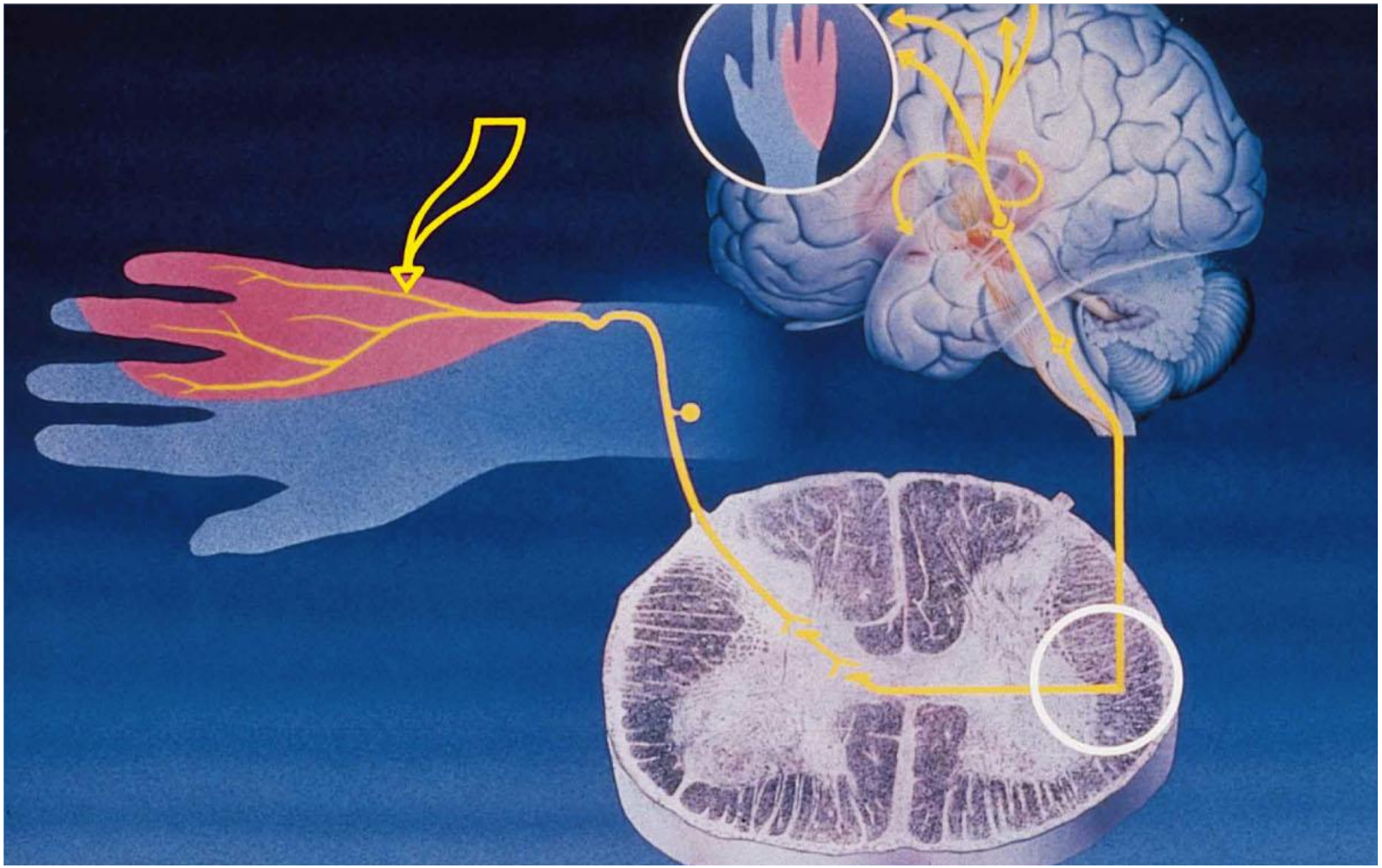
Pain Fibres

Aδ and C-Fibres



Pain Transduction

Pain Signal Transduction



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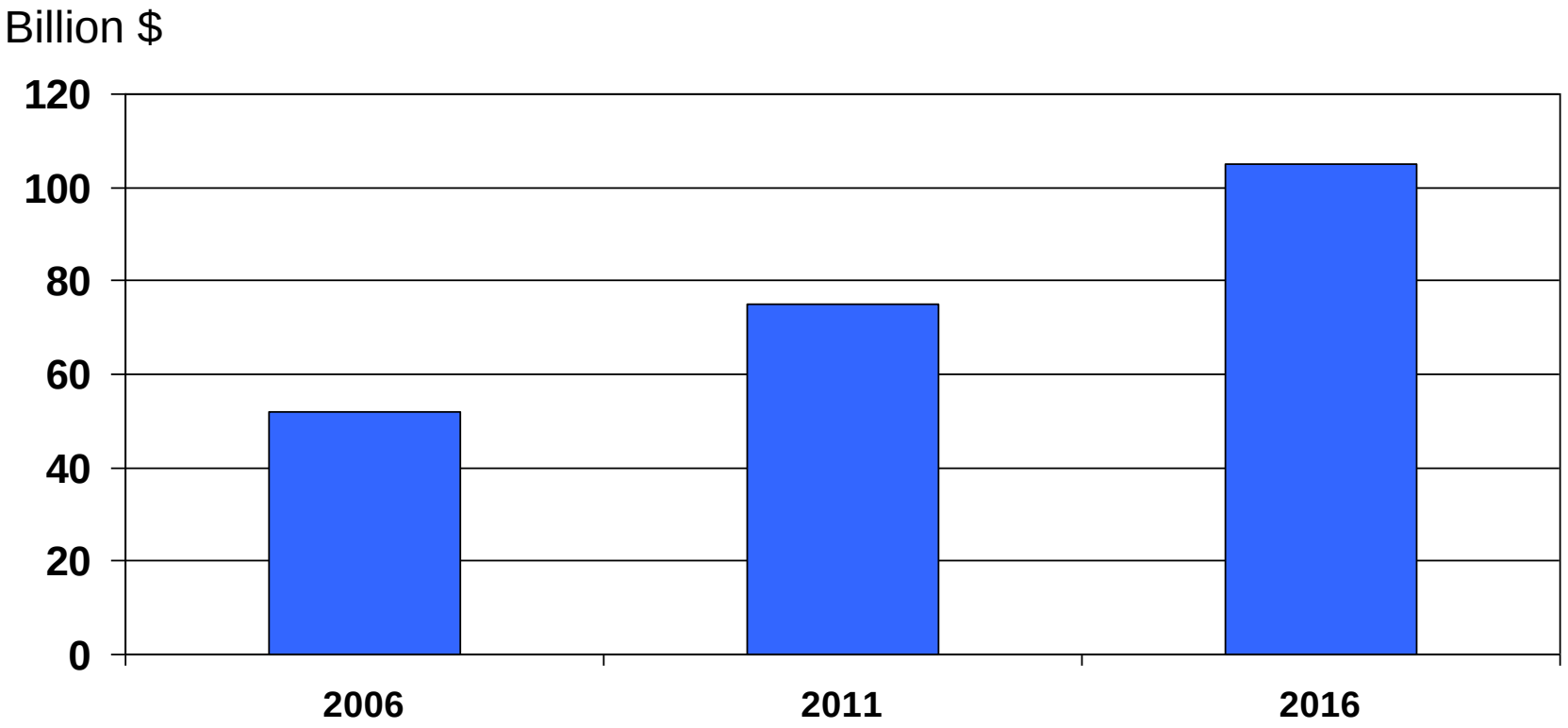
Analgesic Market

The Total Pain Market

2006-2015

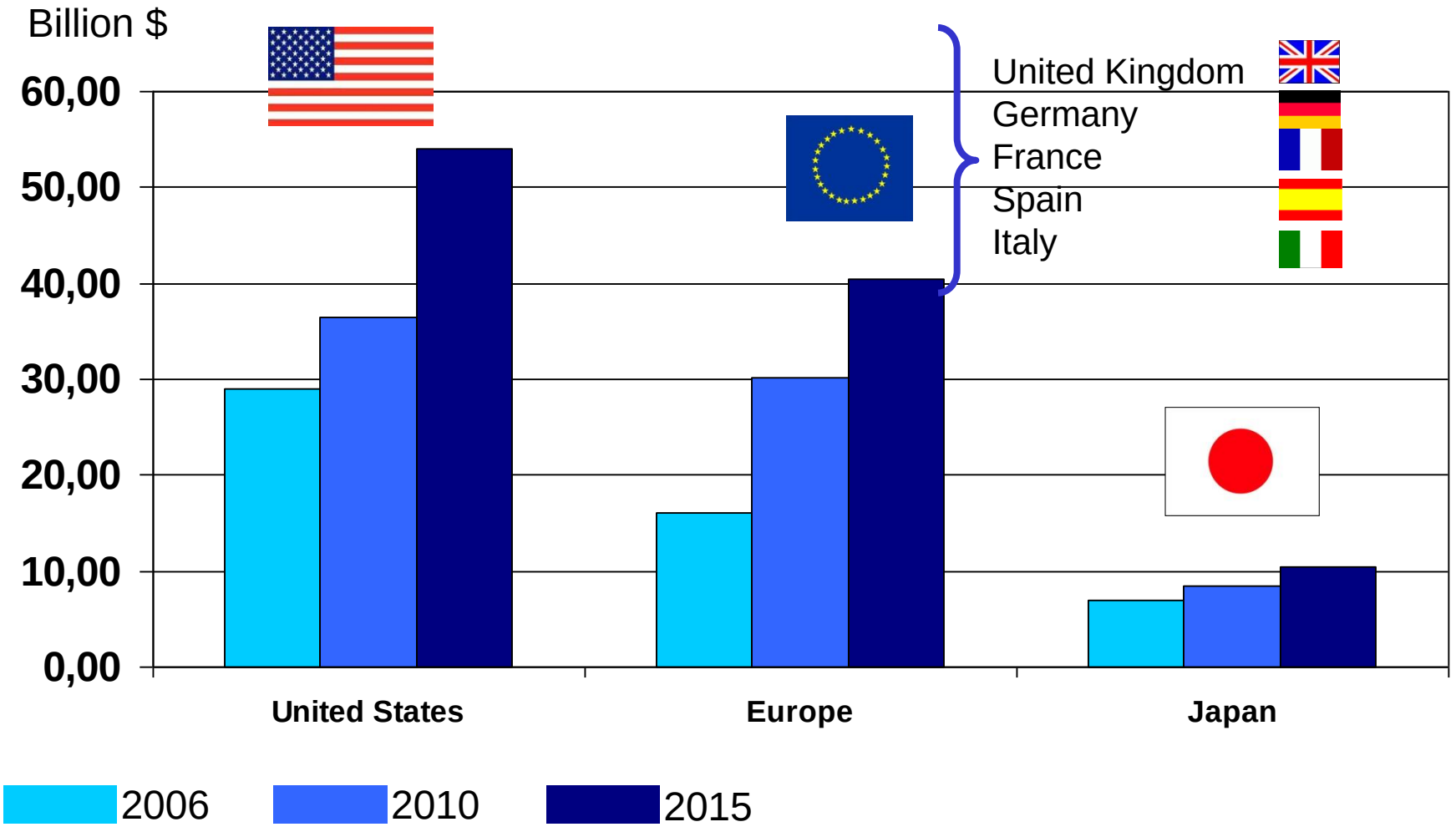


Jain PharmaBiotech Report, Pain Therapeutics – Drugs, Markets & Companies, K.K. Jain, October 2007

Analgesic Market

Pain markets according to geographical areas

Distribution of values of pain therapeutics in major markets 2006-2015

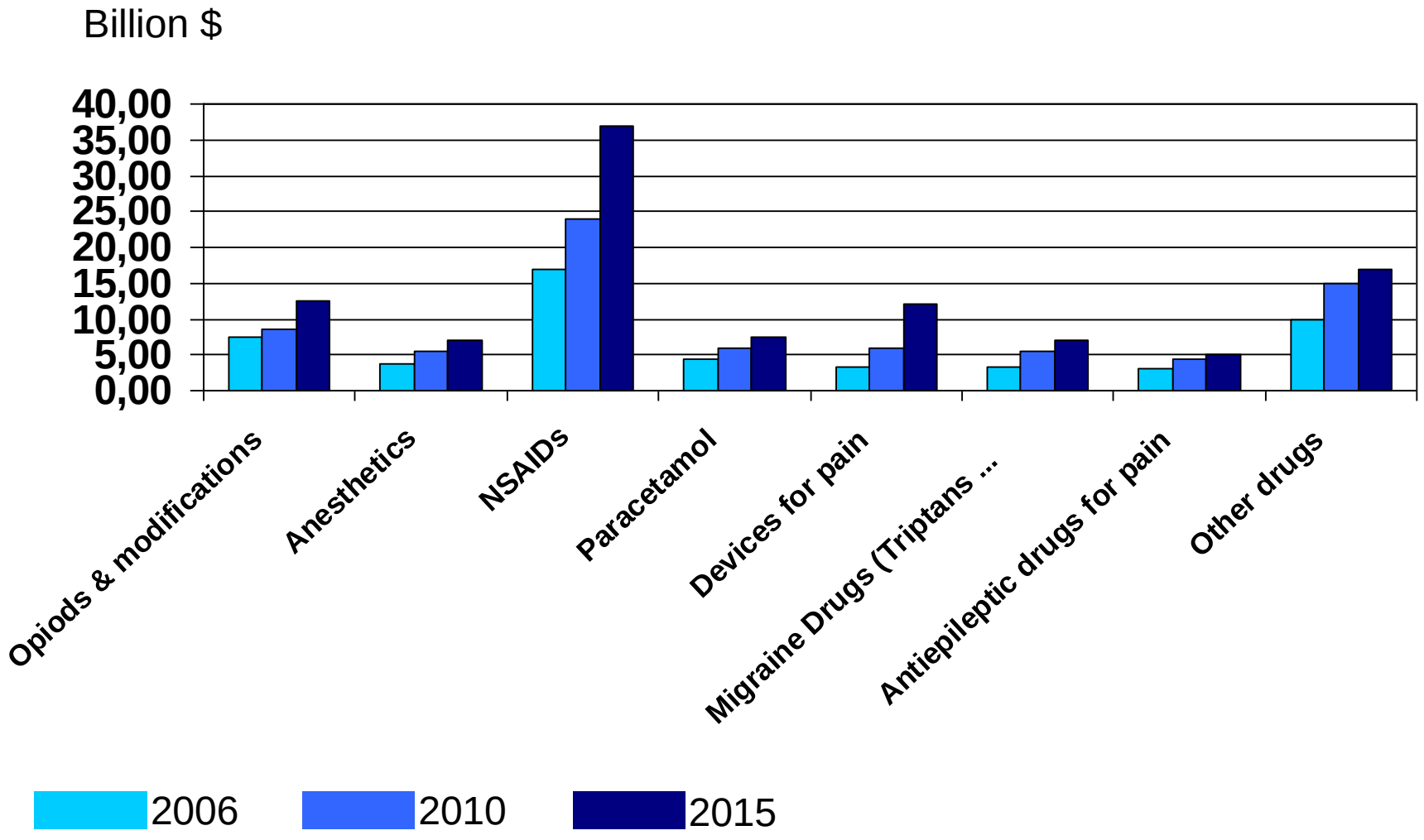


Jain PharmaBiotech Report, Pain Therapeutics – Drugs, Markets & Companies, K.K. Jain, October 2007

Analgesic Market

Pain markets based on drugs

Markets for pain according to therapies 2006-2015



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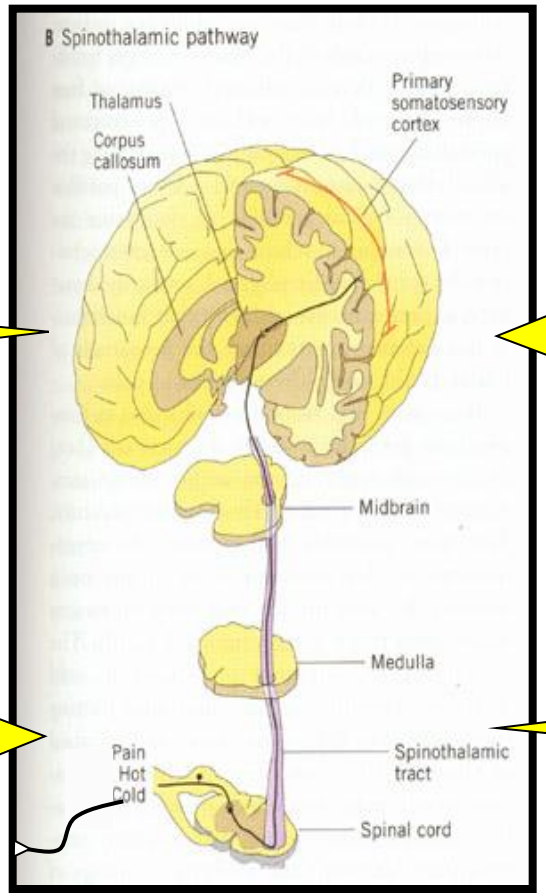
Current Analgesic Treatment Options

Most analgesics are based on two principles

Salicylates

inhibit prostaglandin synthesis



Opioids

Activate inhibitory systems

COX2- inhibitors (*Celebrex* or *Vioxx*)

Selective ligands Delivery techniques

Current Analgesic Therapy

NSAIDs

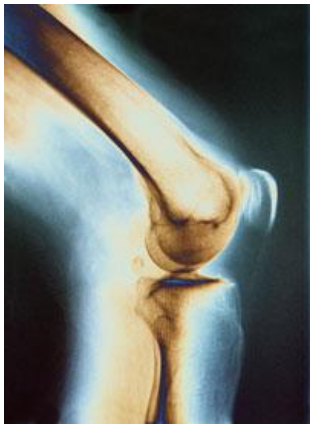
- Unselective COX inhibitors
- Selective COX-2 inhibitors
- Acetaminophen

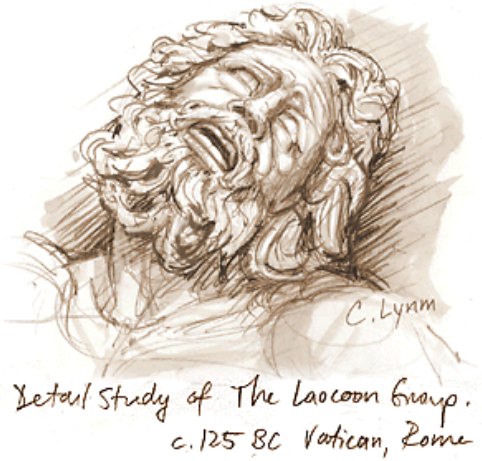
Opioids

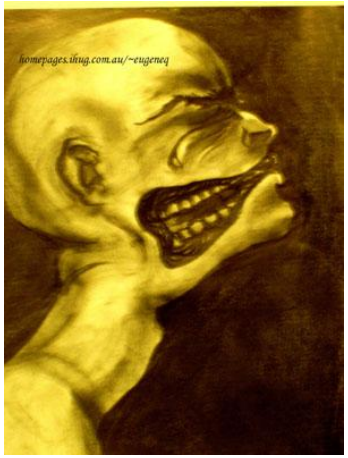
- Opiates
  - morphin, codein
- Opioids
  - N-methyl piperidines
  - 4-amido piperidines
  - 3,3-Bisarylprpylamines
  - cyclohexyl amimes

Adjuvants

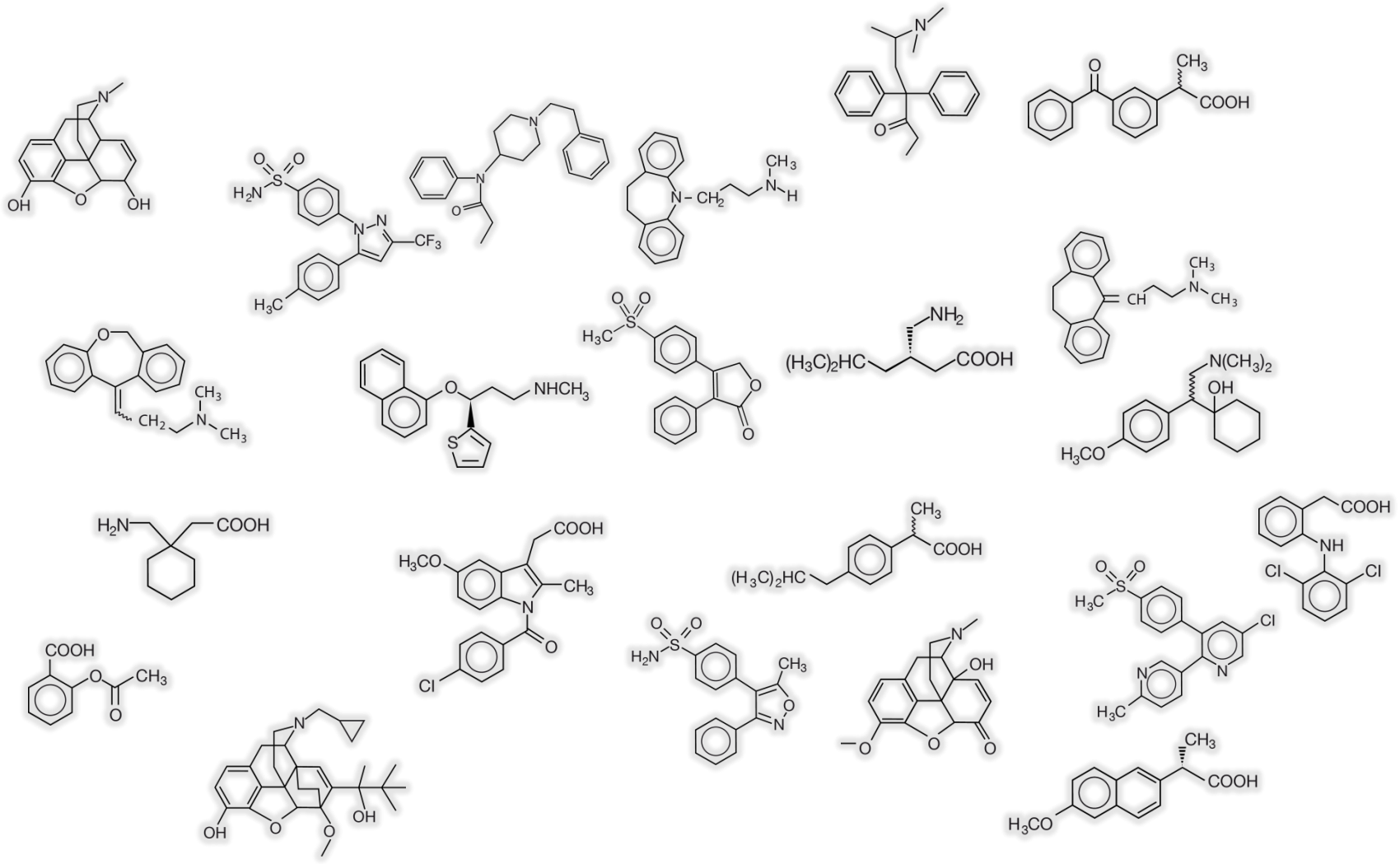
- Antidepressants
- Anticonvulsants
- Local anesthetics





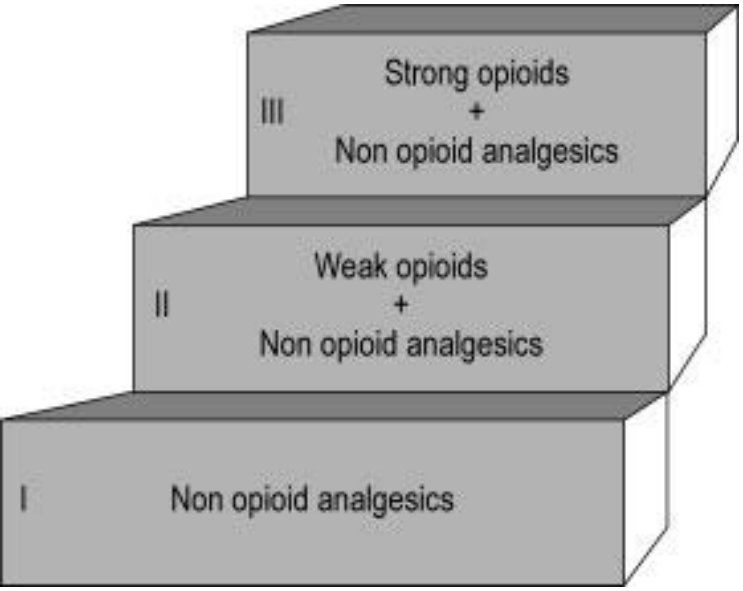


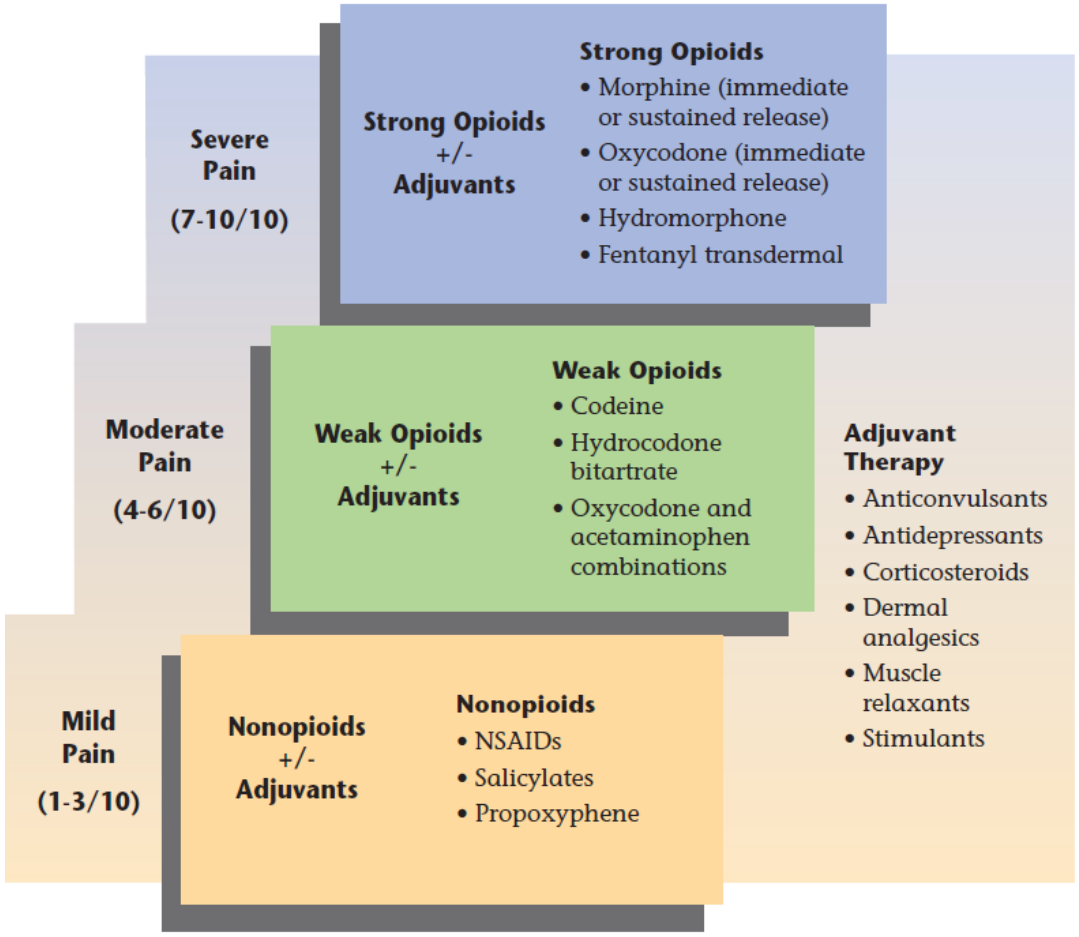
Different Structures of Current Analgesic Drugs



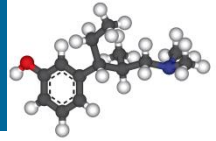
Current Analgesic Treatment Options

WHO Analgesic Ladder



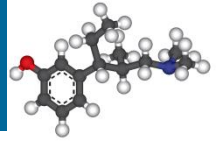


Combination of drugs are used to enhance the analgesic efficacy of opioids, treat concurrent symptoms that exacerbate pain, and provide independent analgesia for specific types of pain. **They may be used in all stages of the pain magnagement**



NSAIDs
Nonsteroidal Antiinflammatory Drugs

- NSAIDs are used in the treatment of mild to moderate pain
  - with ***analgesic, antiinflammatory, and antipyretic*** activity
  - NSAIDs are used to relieve the pain associated with headache, tooth extraction, musculoskeletal trauma, especially arthritis,
- NSAIDs are also used as adjuvants to opioids in the management of moderate to severe pain
- NSAIDs act by inhibiting the prostaglandin biosynthetic enzyme cyclooxygenase (also known as **COX** or **PGHS**, prostaglandin H_2 synhase)
  - The liberation of these arachidonic acid pathway products following local tissue injury contributes to peripheral sensitization and hyperalgesia
  - NSAIDs block prostaglandin production and thus attenuate the peripheral sensitization process
- NSAIDs have a ceiling effect in terms of their analgesic efficacy such that complete pain relief cannot be achieved even with dose escalation



NSAIDs
Nonsteroidal Antiinflammatory Drugs

NSAID side effects

- Therapeutic effects and side effects of NSAIDs are closely related to thei biochemical mechanism of action
- The side effects associated with the clasical NSAIDs include
  - *gastrointestinal bleeding*
  - *ulceration*, *lesions*, and *perforation*
  - *inhibition of platelet aggregation*
  - *Nephrotoxicity*
  - a severe side effect of NSAIDs is *bronchoconstriction* with resultant *asthmatic events*
- and in 10 % of those experiencing such side effects, death
  - **every year it is estimated that 16.000 NSAID-related deaths occur in the US alone, with 75.000 patients hospitalised**
  - because of this problems, a major target of drug research is the development of NSAIDs with anti-inflammatory and analgesic activity but without side-effects

Opioid market definition today

The opioids are divided into short- and long-acting opioids according to these molecular classes:

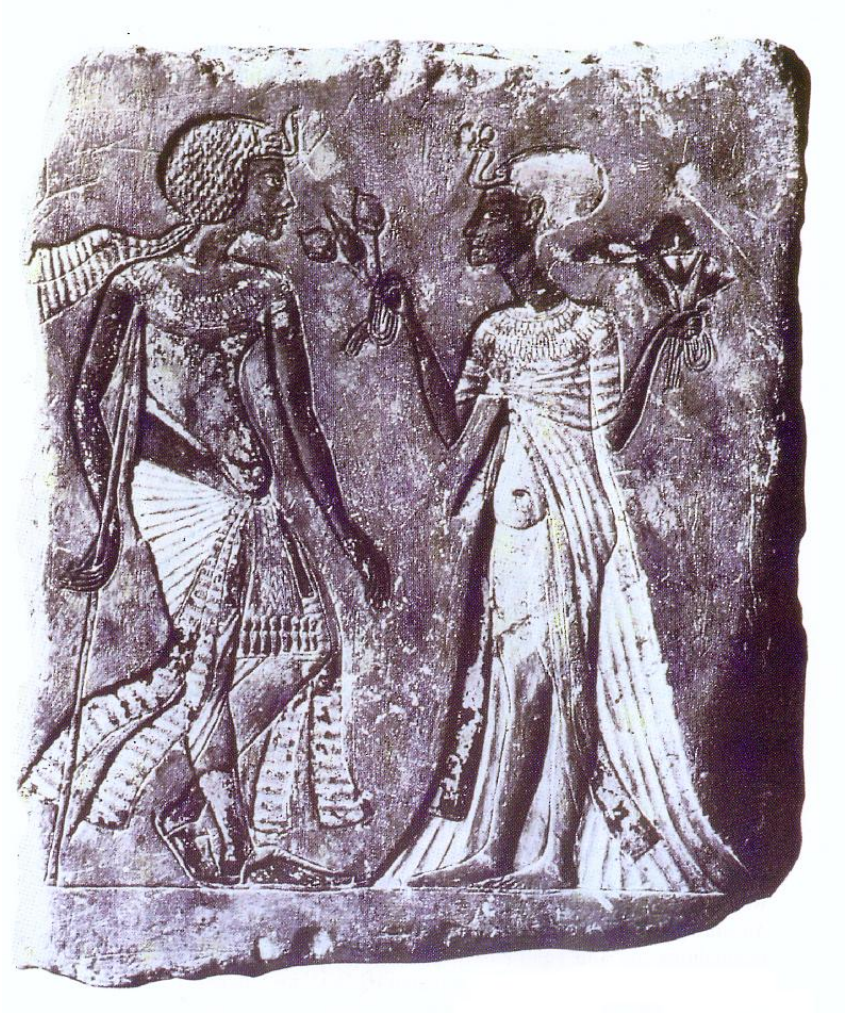
- fentanyl;
- morphine;
- oxycodone;
- others.

Short-acting opioids:
Opioids with a rapid onset of action to treat short episodes of pain (e.g. oral fentanyl).

Long-acting opioids:
Opioids with a sustained release to treat chronic pain (e.g. oxycodone controlled release).

Datamonitor Report: Commercial and Pipeline Insights: Opioids, Puplication Date 03/2008, Reference Code: DMHC2377

Opioids in History



Notretete

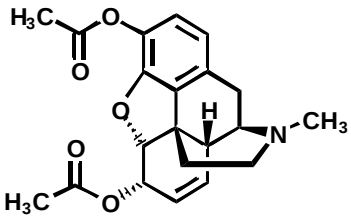
Babylonian God

Opioid Receptors

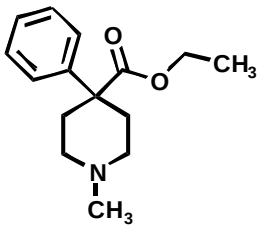
Historical Overview

Opium is the Greek term for the juice of the poppy plant

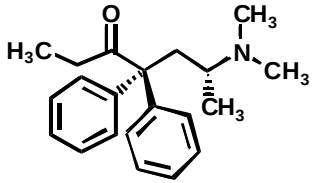
- since 3000 BC — use of the *pain relieving* and *euphoric effect* of opium in Egpt, India, and China;
- 3000 BC — cultivation of *Papaver somniferum* by the Sumerians in the area between *Euphrates* and *Tigris*
- 1st century AD — mention of opium by the greek doctor *Pendanicus Dioscorides* (De Materia Medica)
- 1806 — isolation of Morphine by *Adam Sertürner*
- 1874 — synthesis of Heroin (Diacetylmorphine)
- 1939 — synthesis of Pethidine (Meperidine)
- 1946 — synthesis of Methadone



Heroin



Pethidin

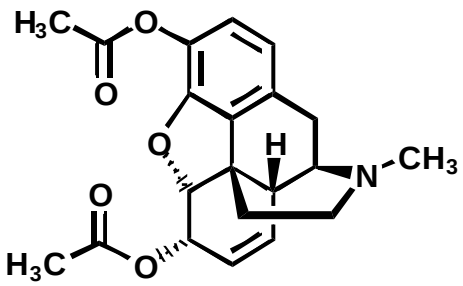


(*Levo*-)Methadon

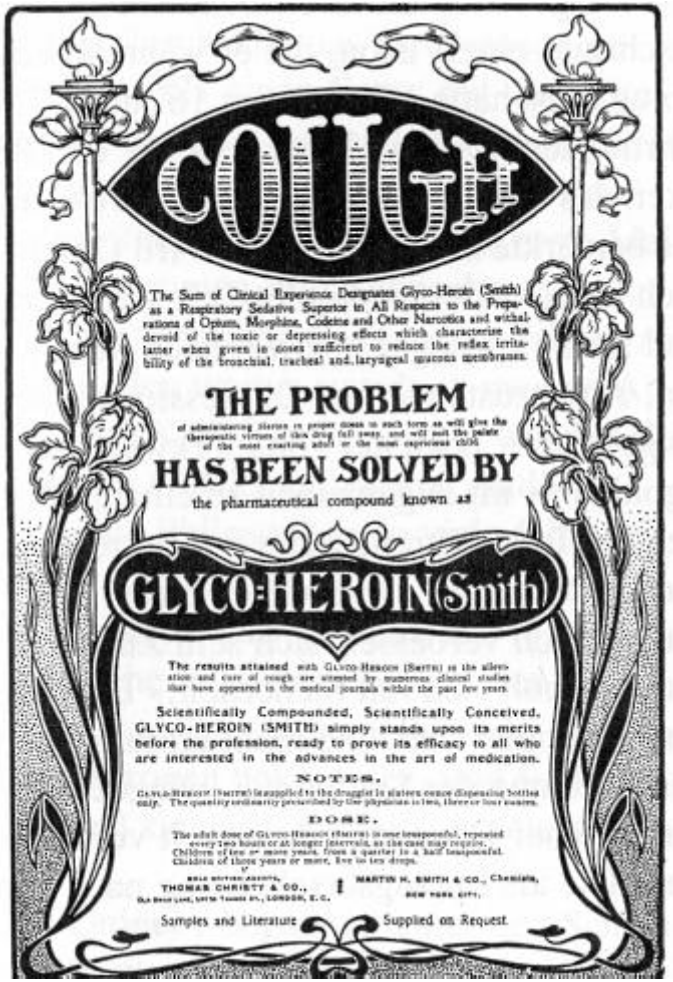
Adam Sertürner

Opioids

Historical Overview



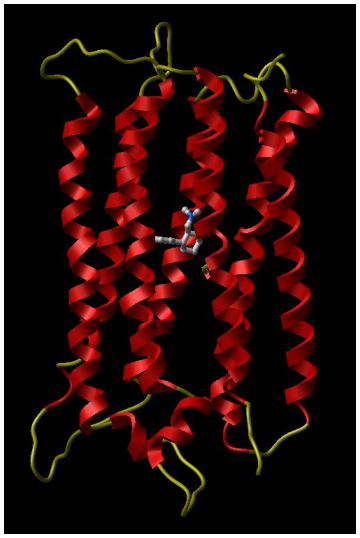
- 1874 discovery of heroin
- 1898 introducing of heroin as a sure and non addicting antitussivum



Mrs. Winslows Soothing Syrup

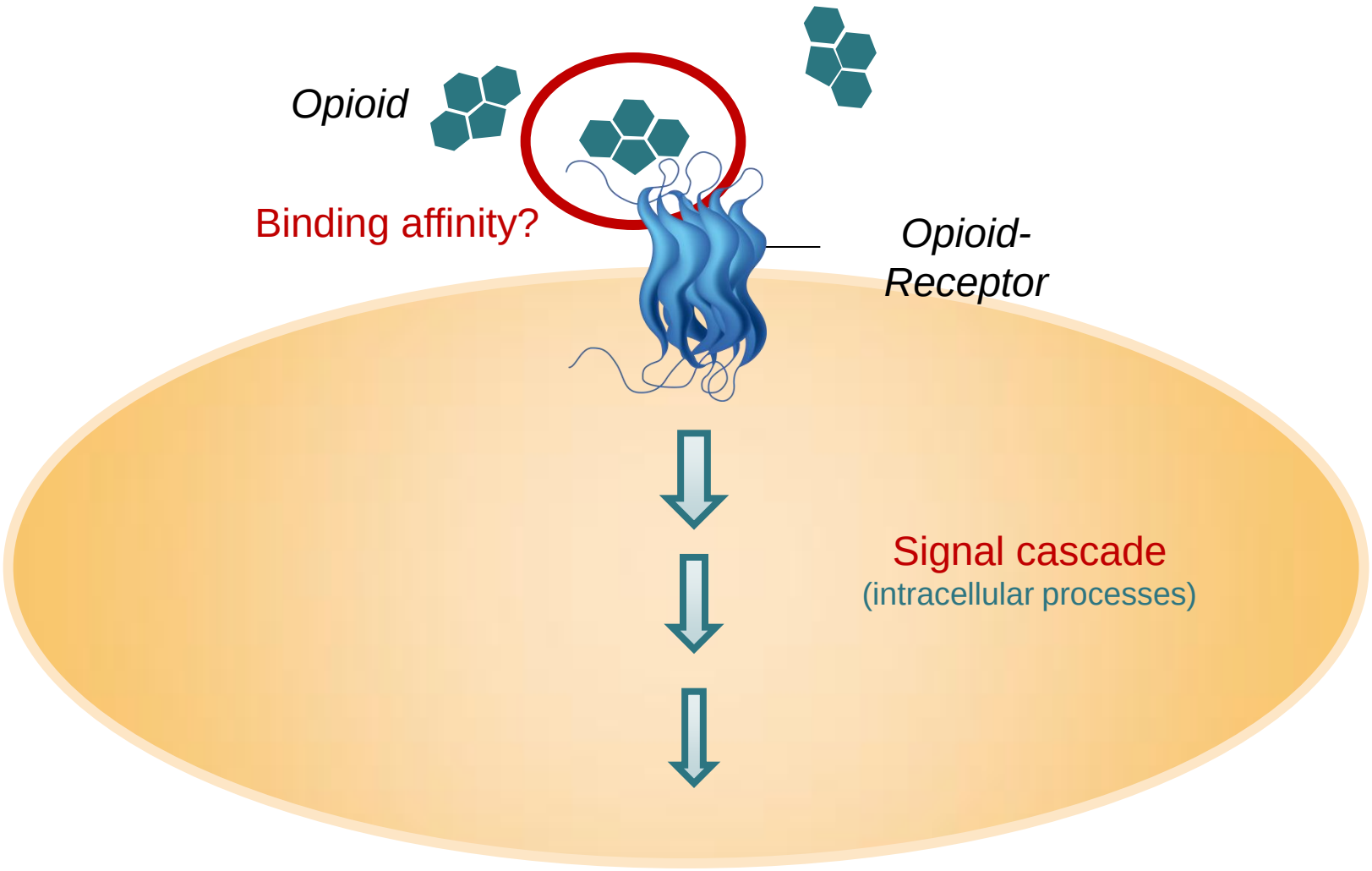
"For children teething. Greatly facilitates the process of Teething, by softening the gums, reducing all inflammation; will allay ALL PAIN and spasmodic action, and is SURE TO REGULATE THE BOWELS. Depend on it, Mothers, it will give rest to yourselves and RELIEF AND HEALTH TO YOUR INFANTS. Sold by all chemists, at 1s 1/2d per bottle."

Opioid Receptors
Subtypes

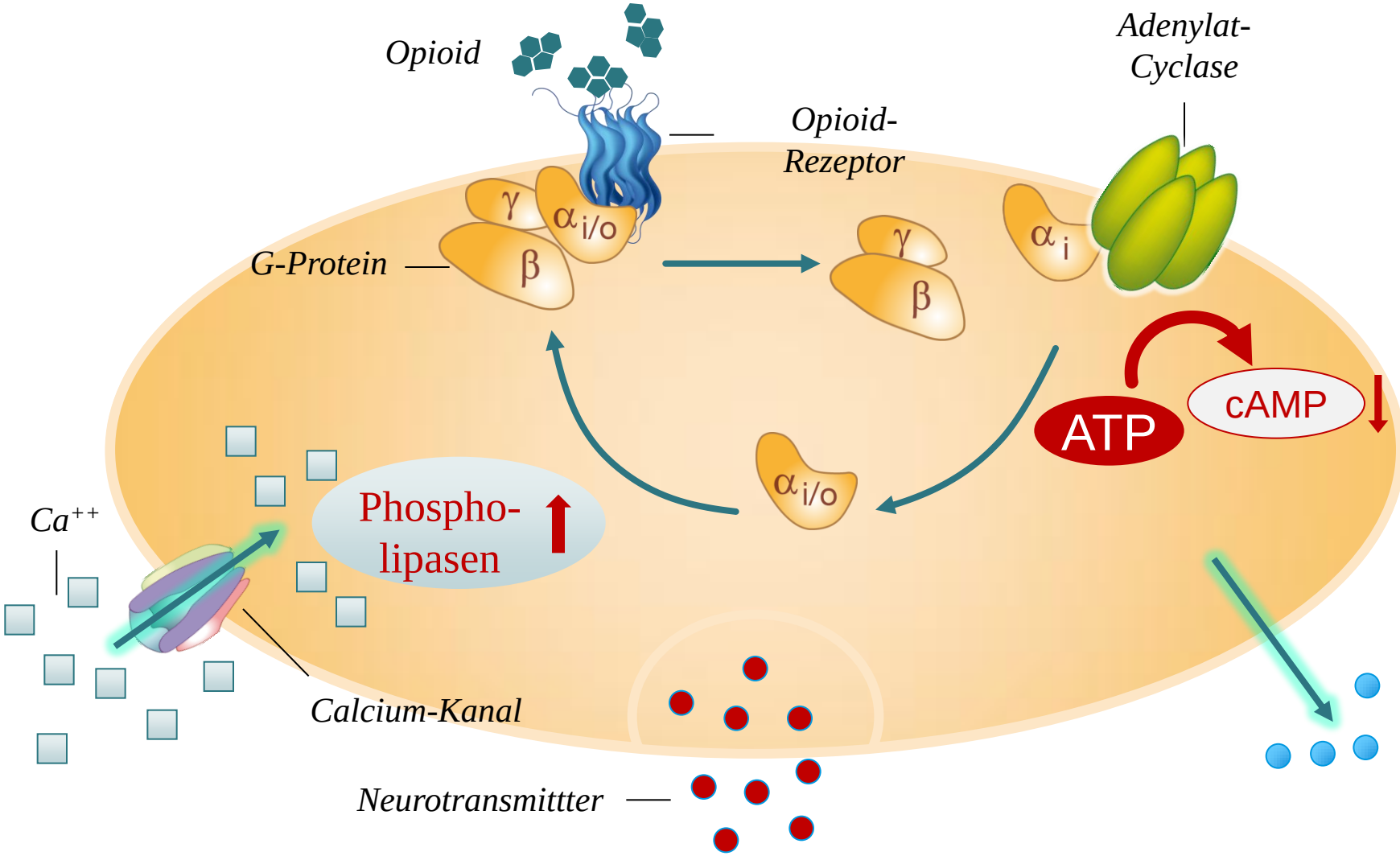


- opioids produce their effects by activating receptors in the brain and spinal cord
- the opiod receptor family is a G-protein-coupled receptor (GPCR) superfamily, characterized by a heptahelical structural motif
- opioid receptors were designated as μ, κ, and δ subtypes based on the synthetic ligands originally used to classify them
- an orphan member of the opioid receptor family, ORL-1, has also been identified
- opioid-receptor subtypes
  - ***mü-receptor:*** ***μ1, μ2***
  - ***delta receptor:*** ***δ1, δ2***
  - ***kappa receptor:*** ***κ1, κ2, κ3***
  - ***orphan receptor:*** ***ORL-1***
- morphine is the **gold standard opioid** and it is the analgesic of choice for terminal pain
  - pharmacologically, morphine is a complete agonist at the μ-receptor
  - it is the standard against which all other analgesics are compared

Wirkung der Opioide auf intrazelluläre Prozesse

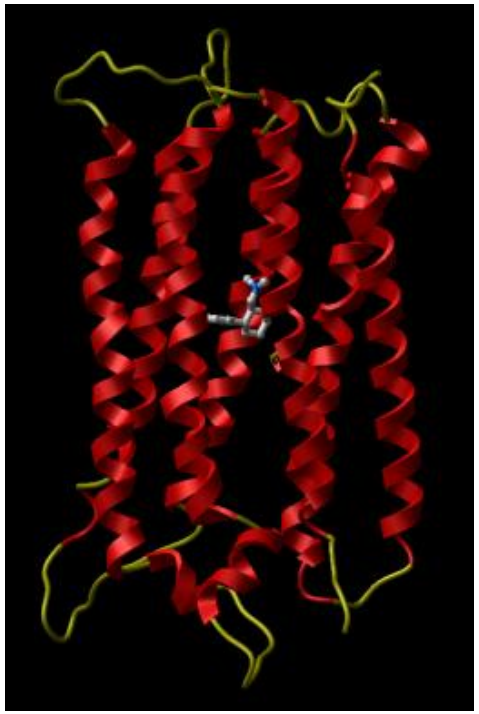


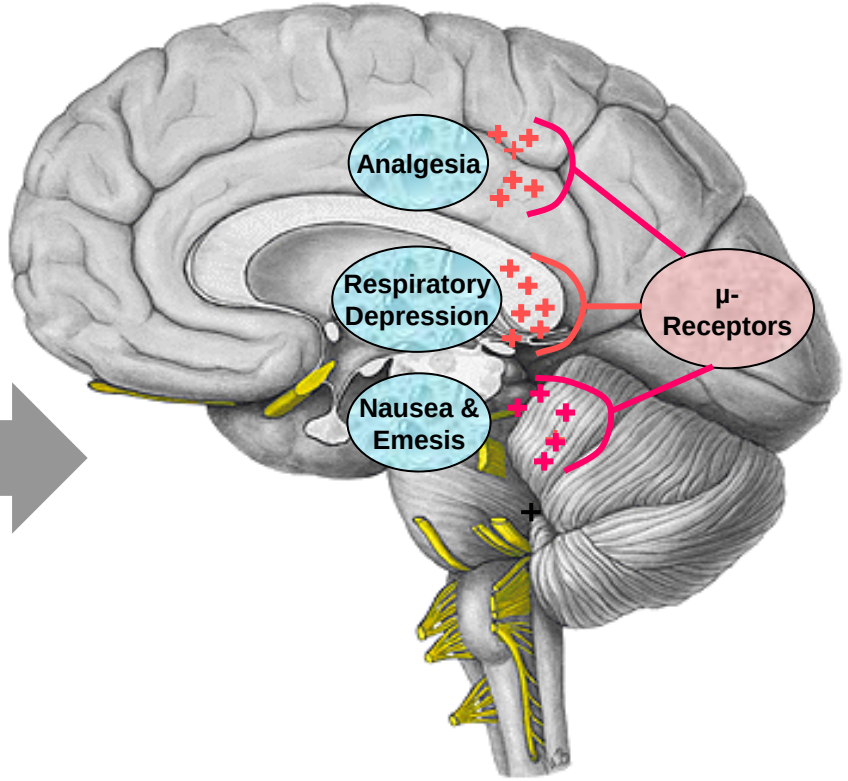
Action of Opioids on Intracellular Processes



Current Analgesic Treatment Options: Opioids

Side effects associated with clinical use of opioids

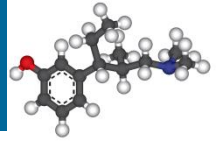




Analgesic Profile

Side Effect Profile

Current Analgesic Treatment Options: Opioids



Side effects associated with clinical use of opioids

Constipation

- due to inhibition of gut motility
- constipation is a significant side effect that is often underestimated
- and in many instances, leads the patient to choose pain over the GI side effects of opioids

Respiratory depression

- due to activation of opioid receptors in the respiratory centers of the brain stem

Cardiovascular effects

- bradycardial effects are induced by nearly all opioids

Emesis

- nausea and vomiting are often observed by opioid application, but due to the tolerance these effects normally increase

Addiction

- The social and legal issues related to use, and regulatory constraints contribute to an underutilization of opioids, particularly for the management of chronic nonmalignant pain
- In 25.000 cancer patients taking narcotics, only 7 became addicted

Tolerance

- associated with drug dependence, this phenomenon may occur with chronic administration of a drug.
- it is characterised by the necessity to progressively increase the dose of the drug to produce its original effect. Tolerance is mainly caused by neuroadaptive changes in the brain

The Discovery of Tapentadol – A New Option for Pain Treatment

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- **Pain Research Today - The Unmet Needs**
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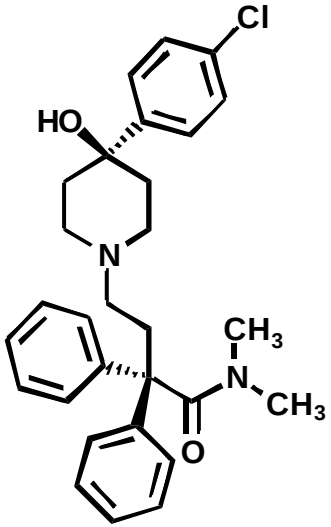
  - Synthesis

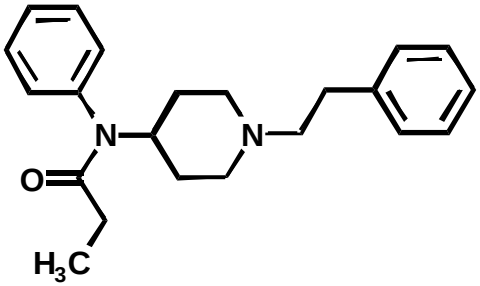
Pain Research in 1999

"Despite an intensive research effort over the past two decades involving many innovative approaches in the global academic community and by the pharmaceutical industry, the latter representing an aggregate investment in excess of $ 2.5 billion, the only new opioid-based pain medications either in clinical development or on the market are alternative dosage forms of the classical opioids, *morphine*, *loperamide*, and *fentanyl*, or compounds such as *tramadol*."

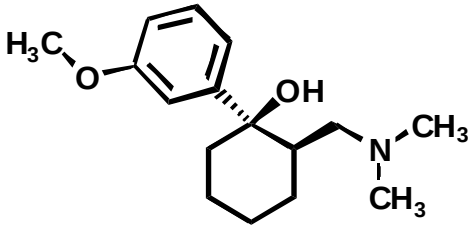
M. Williams et al., *J. Med. Chem.* **1999**, *42*, 1481-1500.



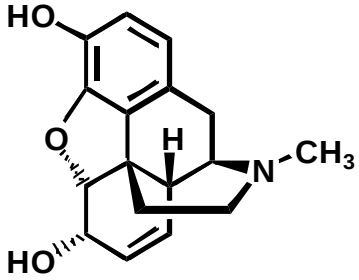
Loperamide



Fentanyl



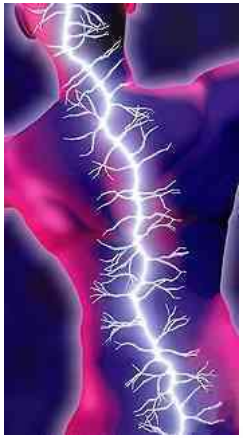
Tramadol



Morphine

Pain Tratment Today…

J.A. Butera, *Current and Emerging Targets To Treat Neuropathic Pain*, J. Med. Chem. **2007**. *50*, Miniperspectives-2543-2596

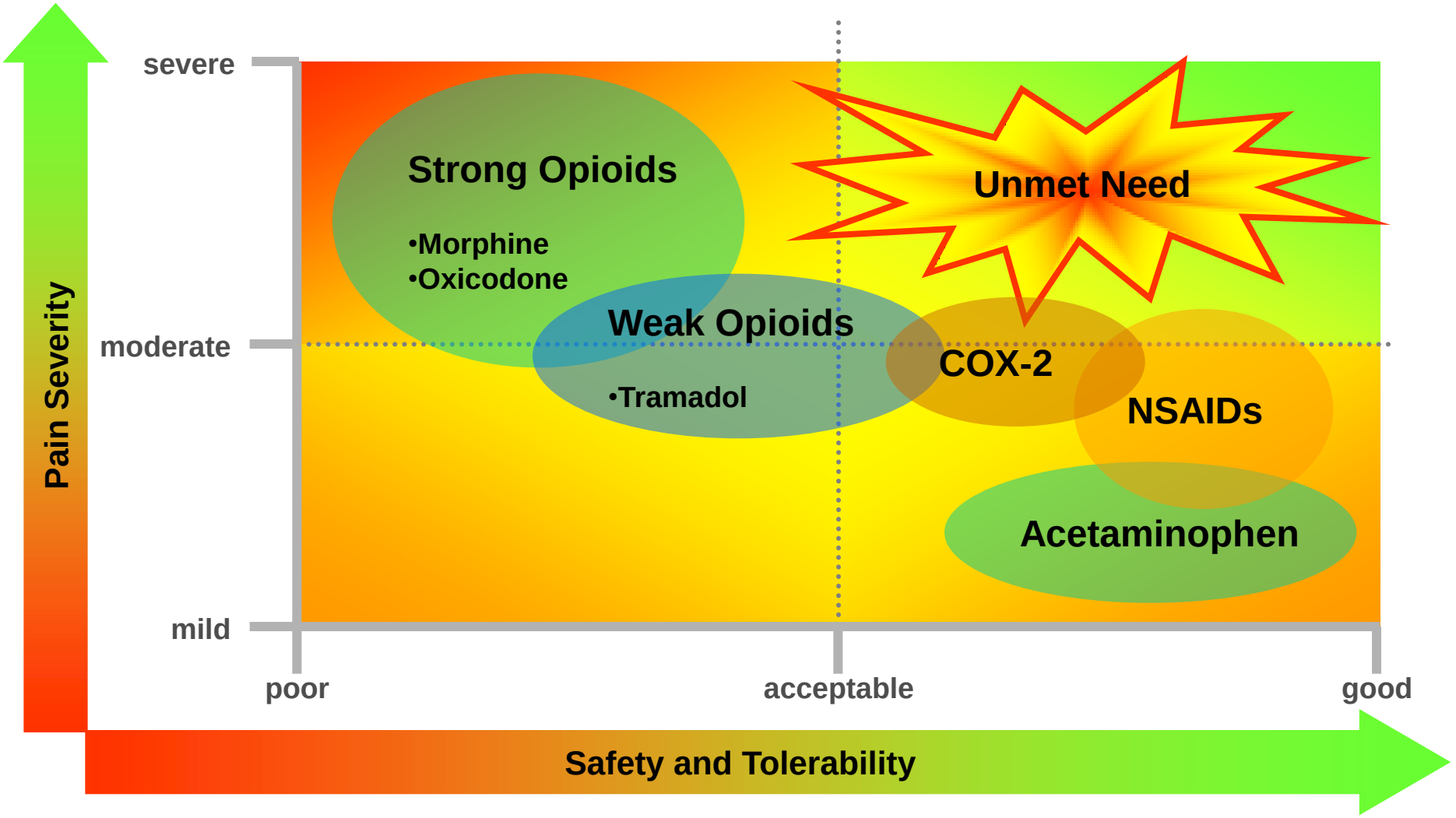


- It is estimated that neuropathic pain affects over **6 million patients in the U.S. and Europe and over 26 million patients worldwide**,
- resulting in a worldwide healthcare cost of over $3 billion per year, with a significant portion of this money paid for drug therapies that were originally developed for other medical conditions
- As physicians are faced with an **increasing number of patients** with numerous neuropathic pain symptoms most likely stemming from multiple etiologies, they are forced to resort to the **polypharmacia approach** as the mainstay therapy.
- Current pharmacological treatment for neuropathic pain will typically include some combination of agents from several of the following drug classes: *opioids, tricyclic antidepressants, anticonvulsant agents, or nonsteroidal anti-inflammatory drugs (NSAIDs)/analgesics.*
- Ironically, even with such an impressive arsenal of powerful drugs, these approaches only provide an approximate **30-50% reduction in pain in about 50% of patients**.
- Coupled with this limited efficacy, there are **low levels of compliance** due to intolerable side effect profiles associated with some of these drugs.
- These results profoundly illustrate **that treatment of neuropathic pain is a hugely unmet medical need**, and they underscore the importance of considering, validating, and pursuing alternative targets to treat refractory neuropathic pain.

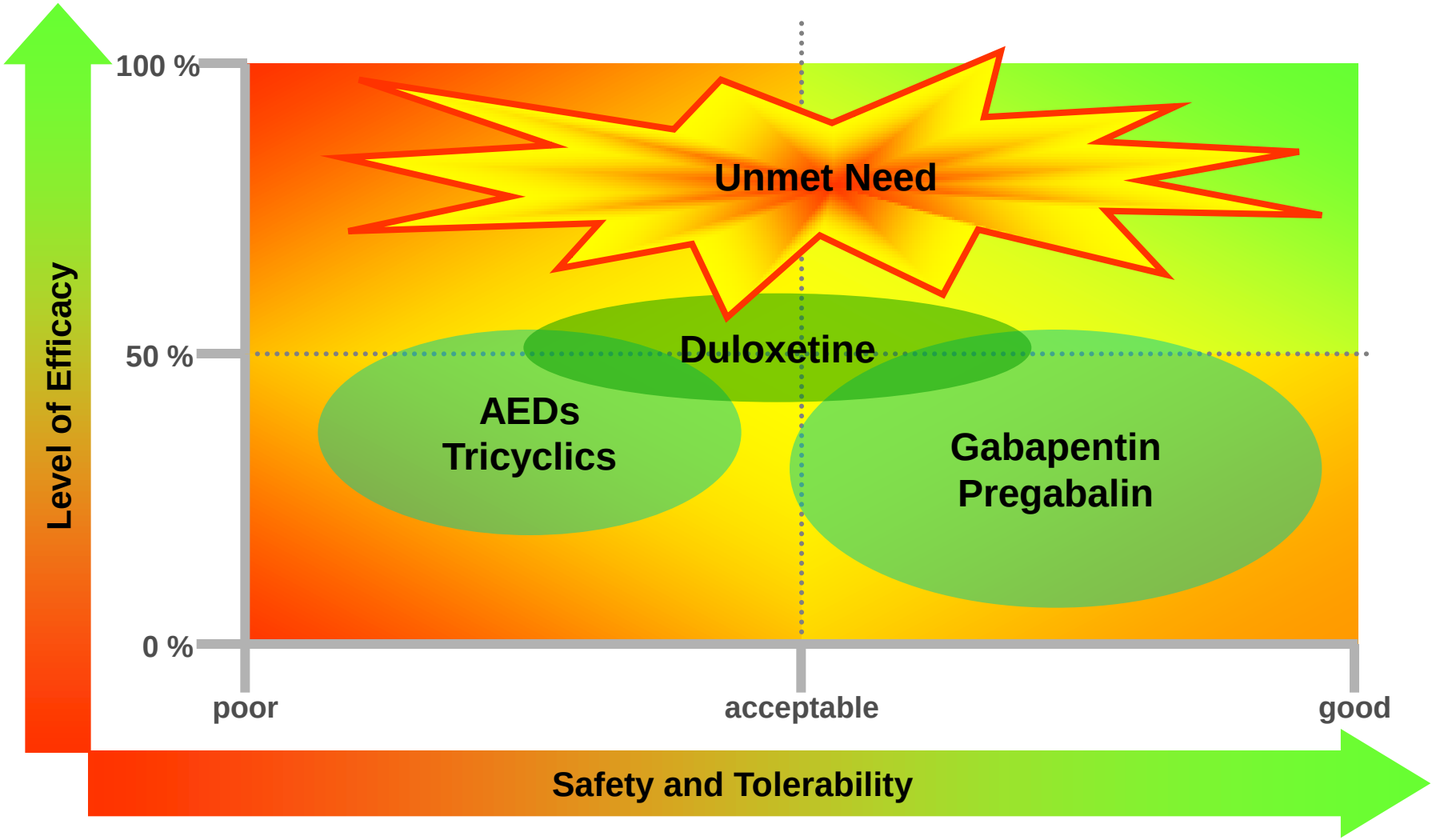
Datamonitor: Pipeline Insight: Neuropathic Pain (Publication Date: 09/2007)

Pain Research Today - The Unmet Needs

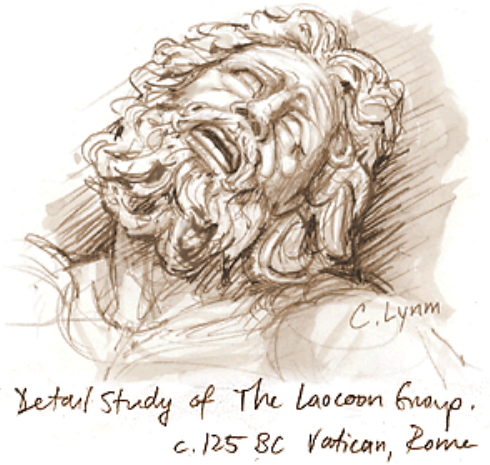
Significant Unmet Needs in Inflammatory/Nociceptive Pain Treatments

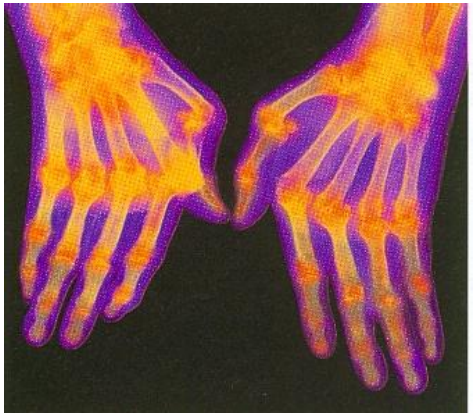


Significant Unmet Needs in Neuropathic Pain Treatments



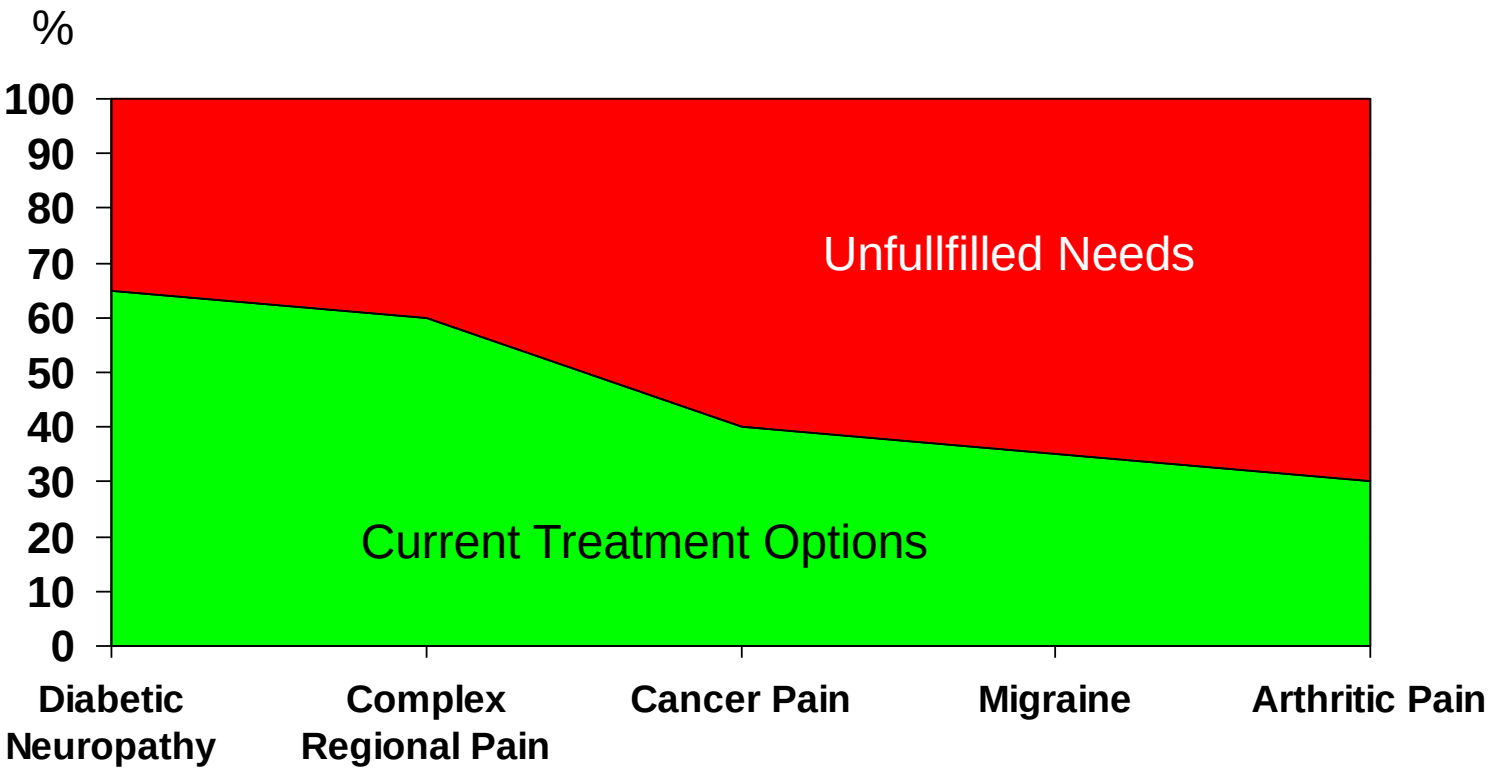
Key Needs in Pain Treatments



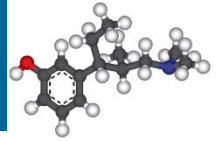


Neuropathic Pain	Inflammatory & Nociceptive Pain
▪ Greater Efficacy ▪ Faster Onset of Action	▪ New Drugs with Efficacy of Opioids but Greater Tolerability/Safety

Unfullfilled Needs In The Treatment For Chronic Pain



Jain PharmaBiotech Report, Pain Therapeutics – Drugs, Markets & Companies, K.K. Jain, October 2007



Efficacy and Tolerability of Pain Management

Efficacy

Low Dosage

High Dosage

Insufficient Efficacy

Sufficient Efficacy

+

+

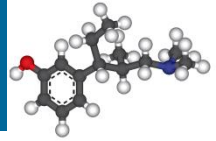
Acceptable Tolerability

Non Acceptable Tolerability

Low Dosage

High Dosage

Tolerability



Tapentadol - From Morphine and Tramadol to the Discovery Tapentadol

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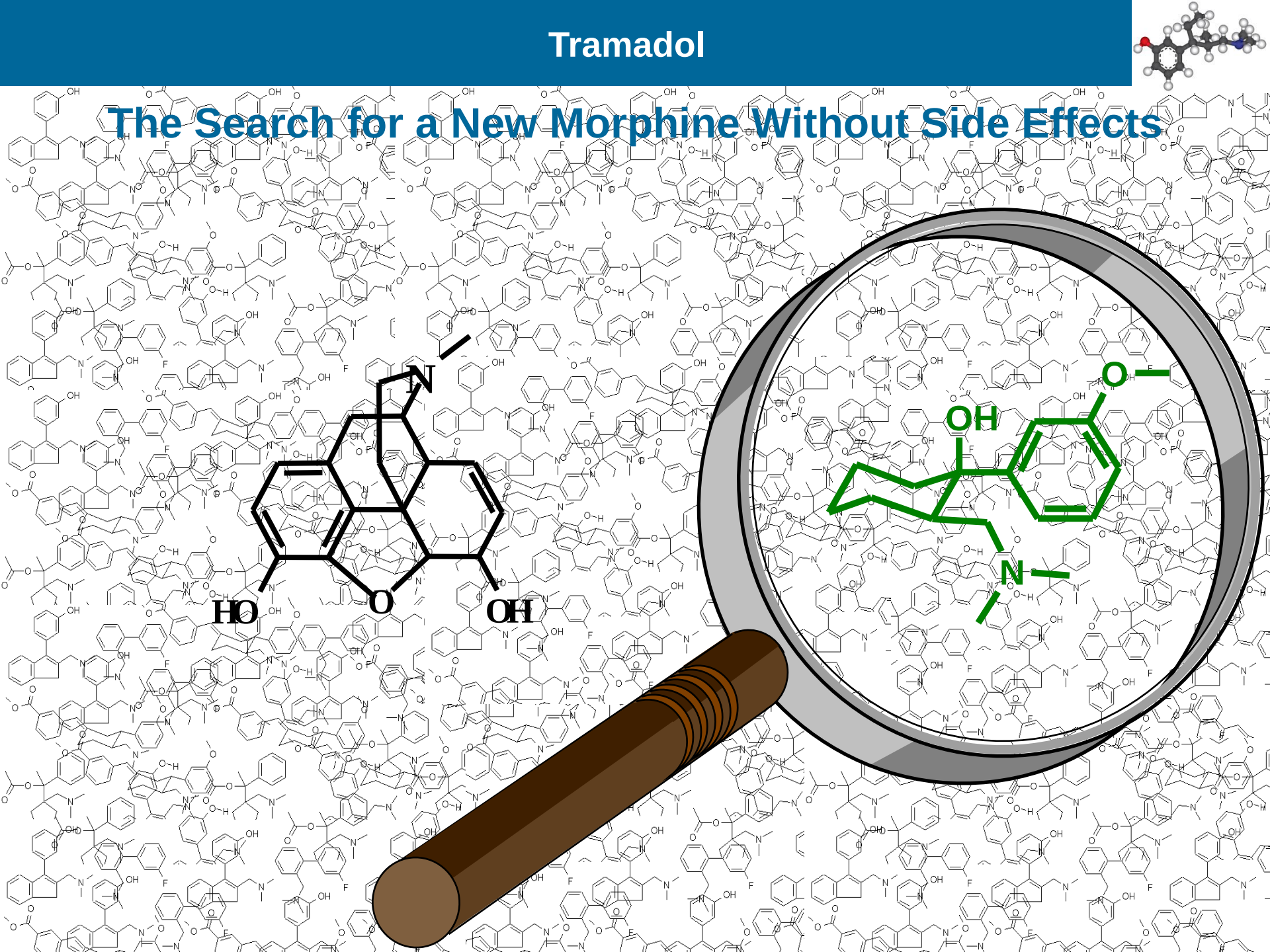
  - Synthesis

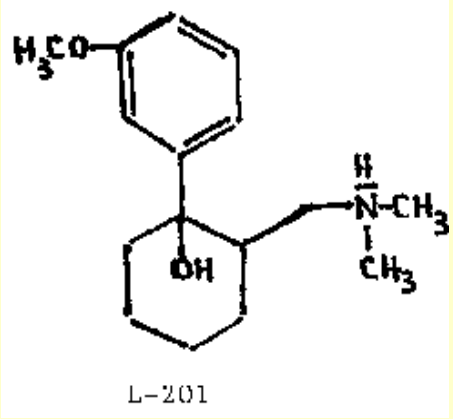
Tramadol

The Search for a New Morphine Without Side Effects



Tramadol – The History

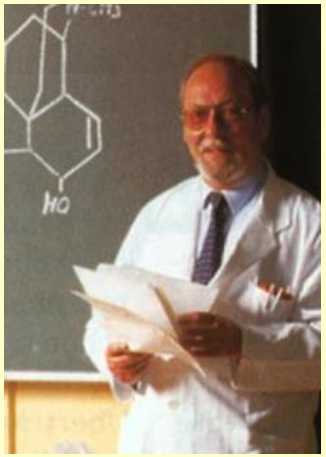
Synthesis of L 201

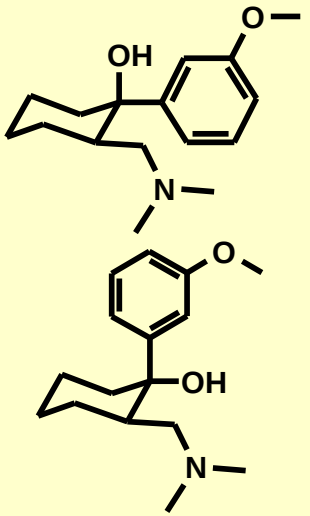


L-201

K. Flick (1962)

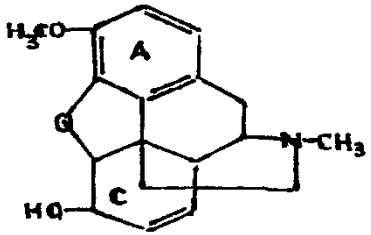
Characterization of Tramadol



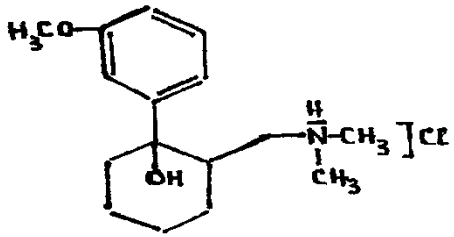


E. Frankus(1963)

mir im Frühjahr 1962 die Idee kam, die Codein-Struktur als Modell für ein neues Hustenmittel anzusehen und die komplizierte Struktur durch Abwandlung zu vereinfachen. Meine Überlegungen ließen sich verwirklichen und so entstand schließlich die chemische Verbindung: 1-(m-Methoxyphenyl)-2-dimethylaminomethyl-cyclohexan-1-ol-hydrochlorid, die unter der Bezeichnung L-201 zur pharmakologischen Testung mit dem Hinweis "Verbindung mit vermutlich antitussiven bzw. analgetischen Eigenschaften" weitergeleitet wurde.



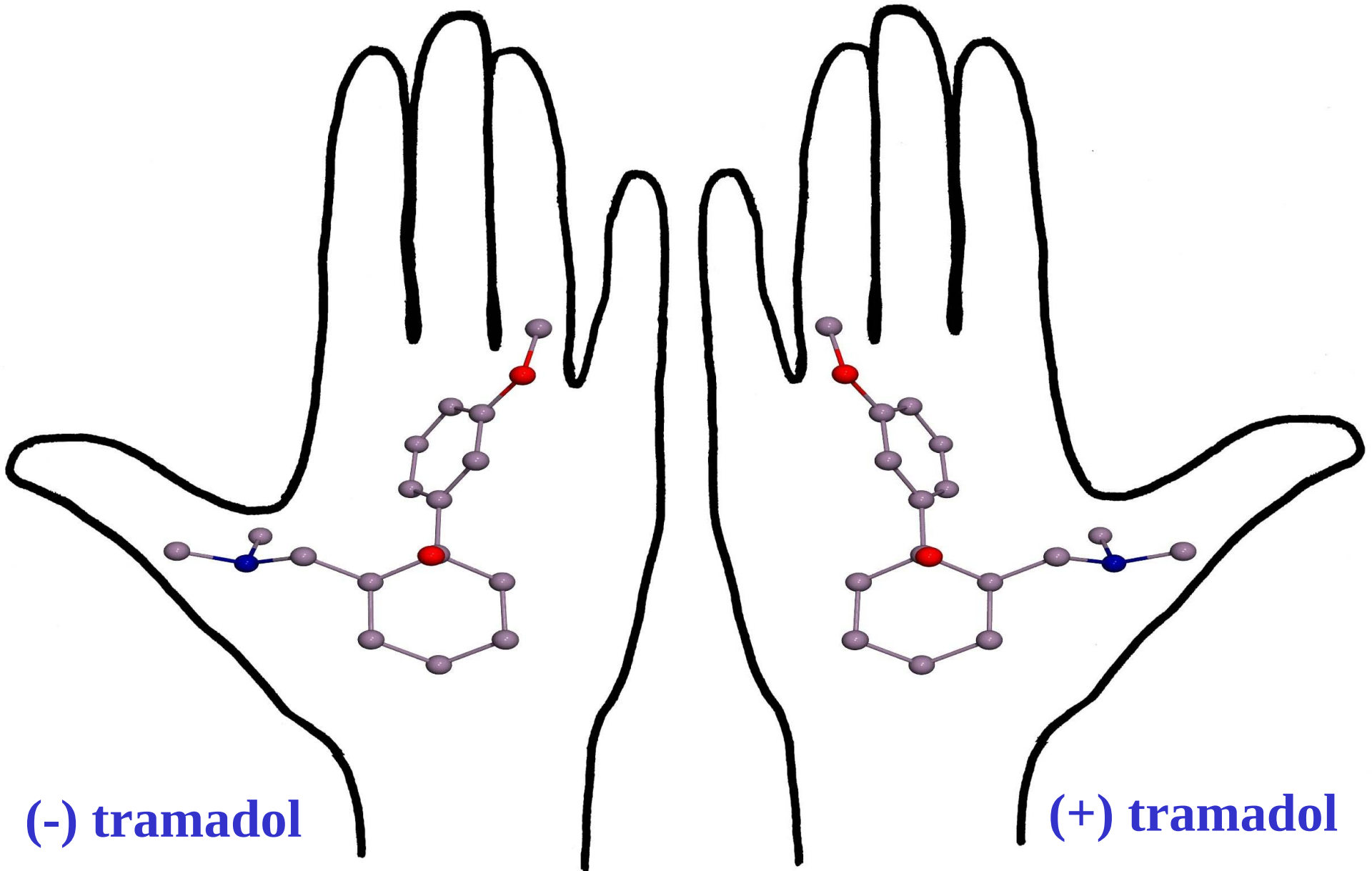
Codein



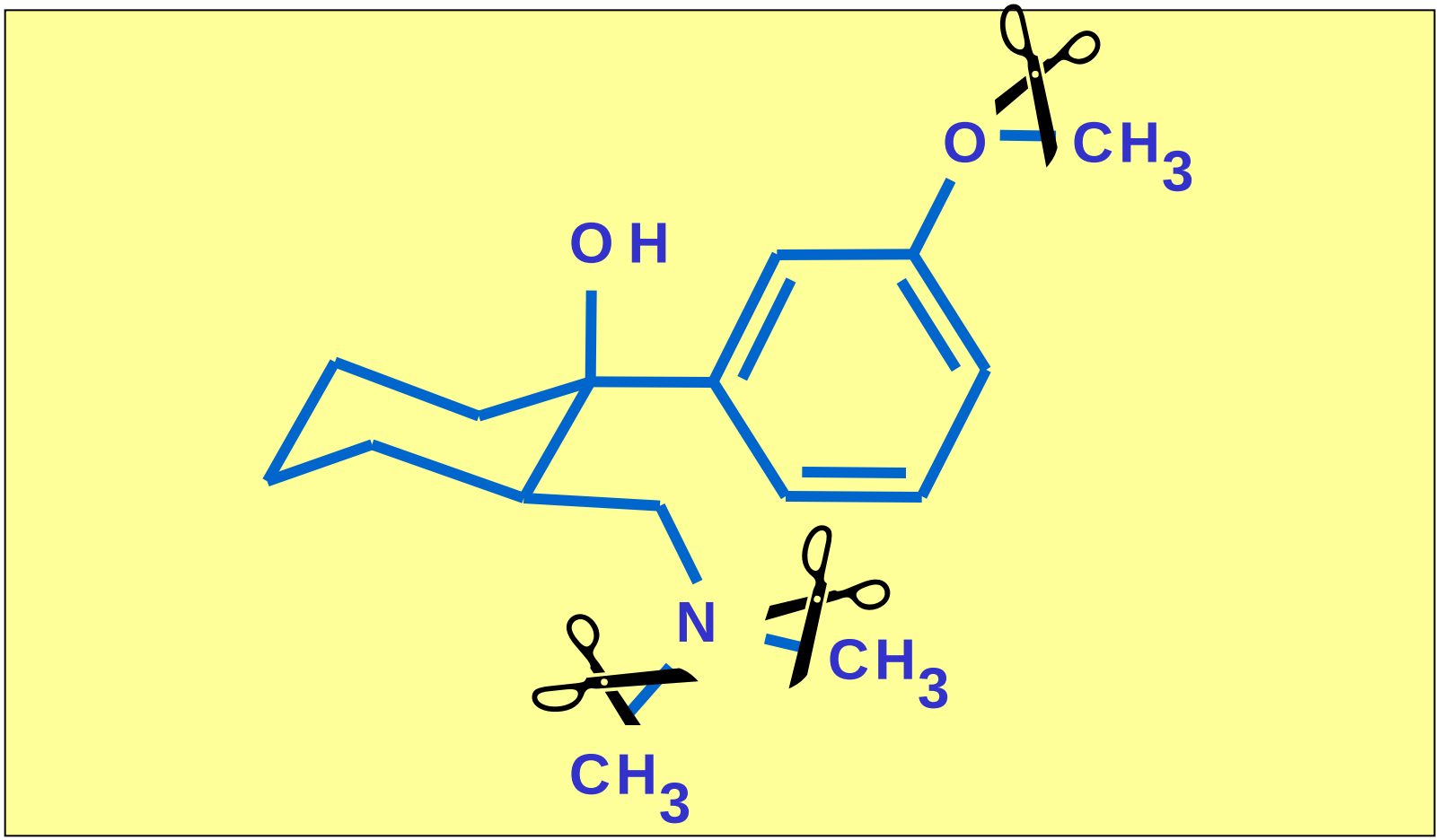
L-201

Tramadol – Pharmacological Profile

Tramadol is a racemate



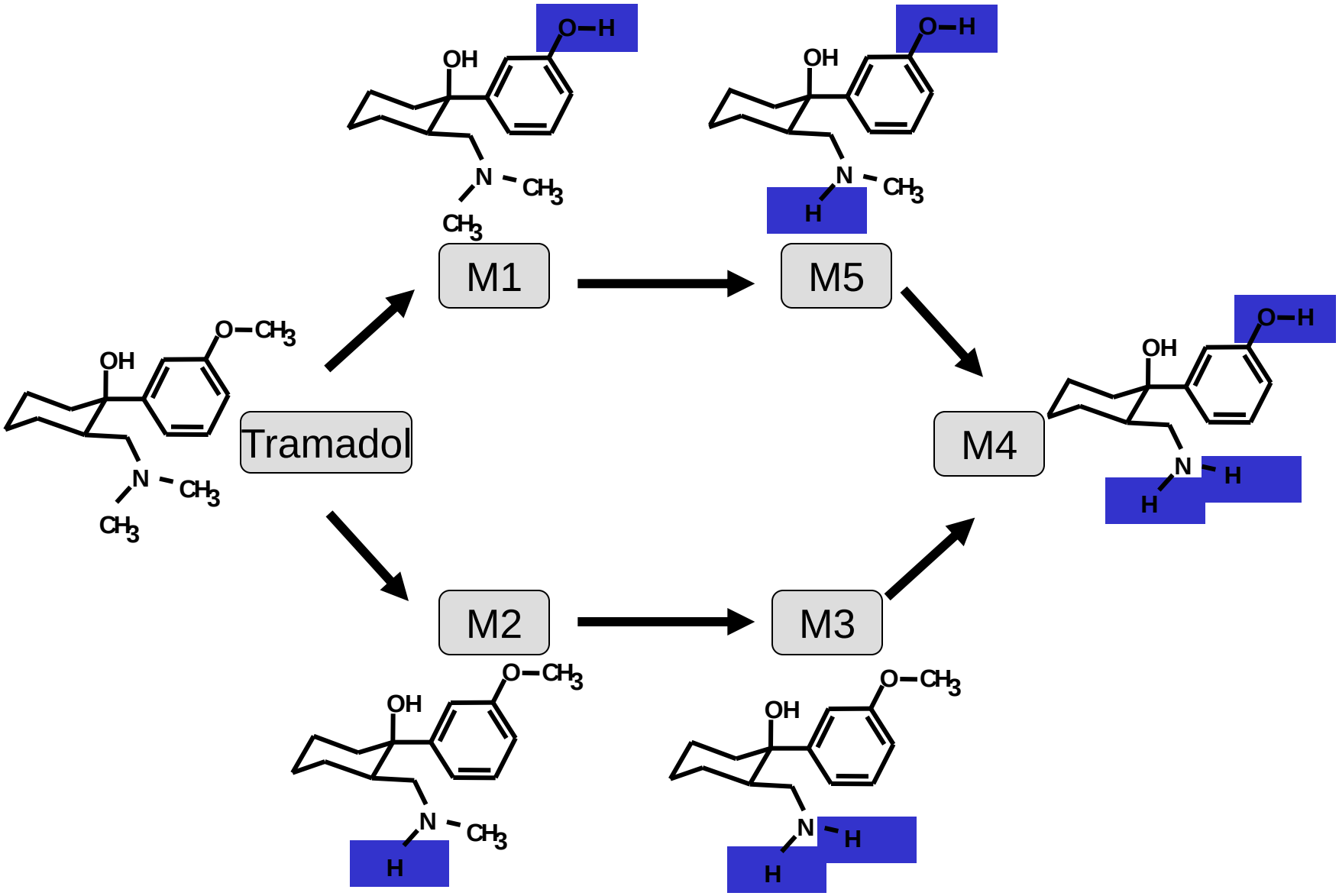
Metabolites of Tramadol



Metabolites are generated by O- or N-demethylation

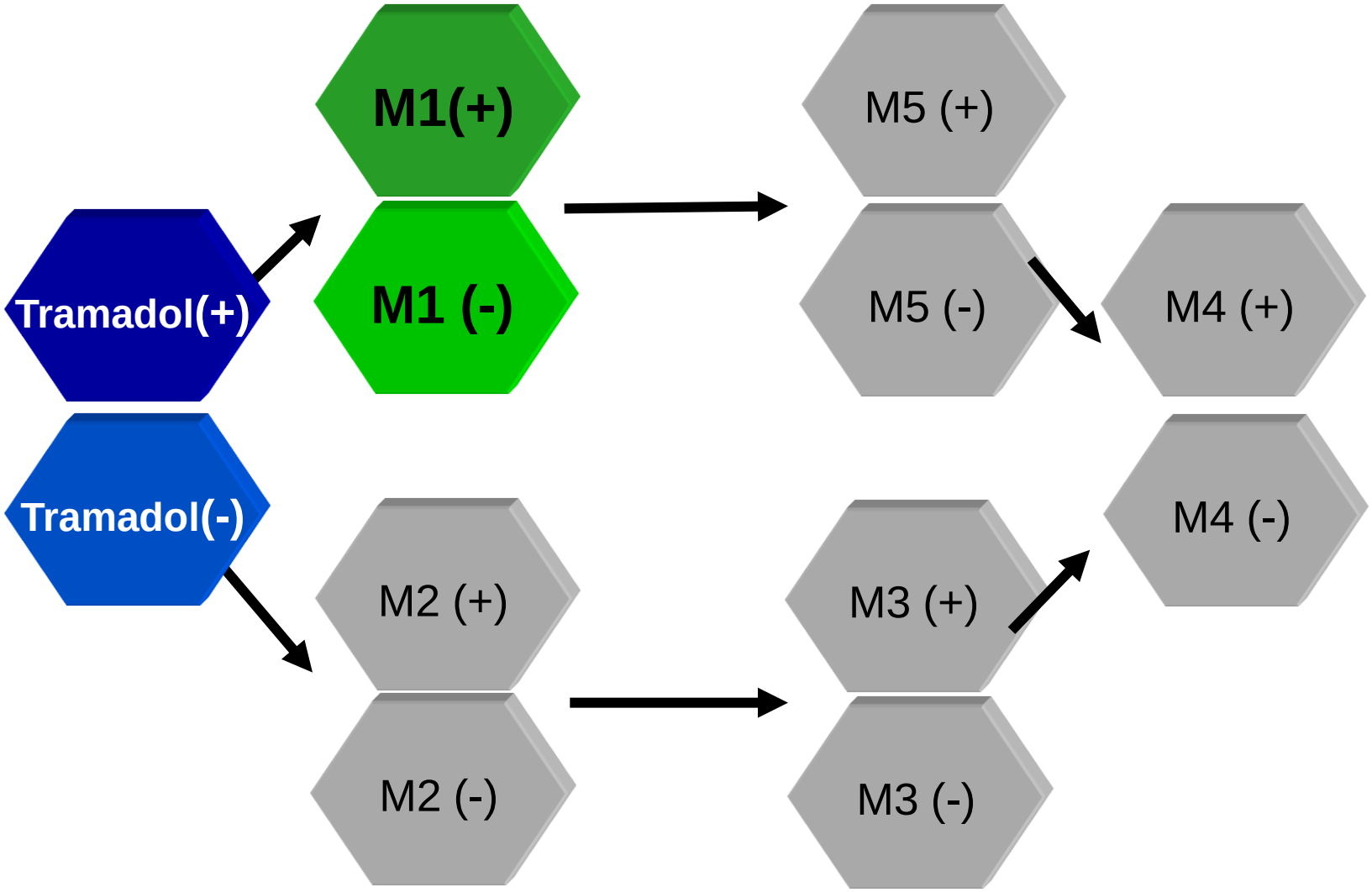
Tramadol – Pharmacological Profile

Metabolites of Tramadol

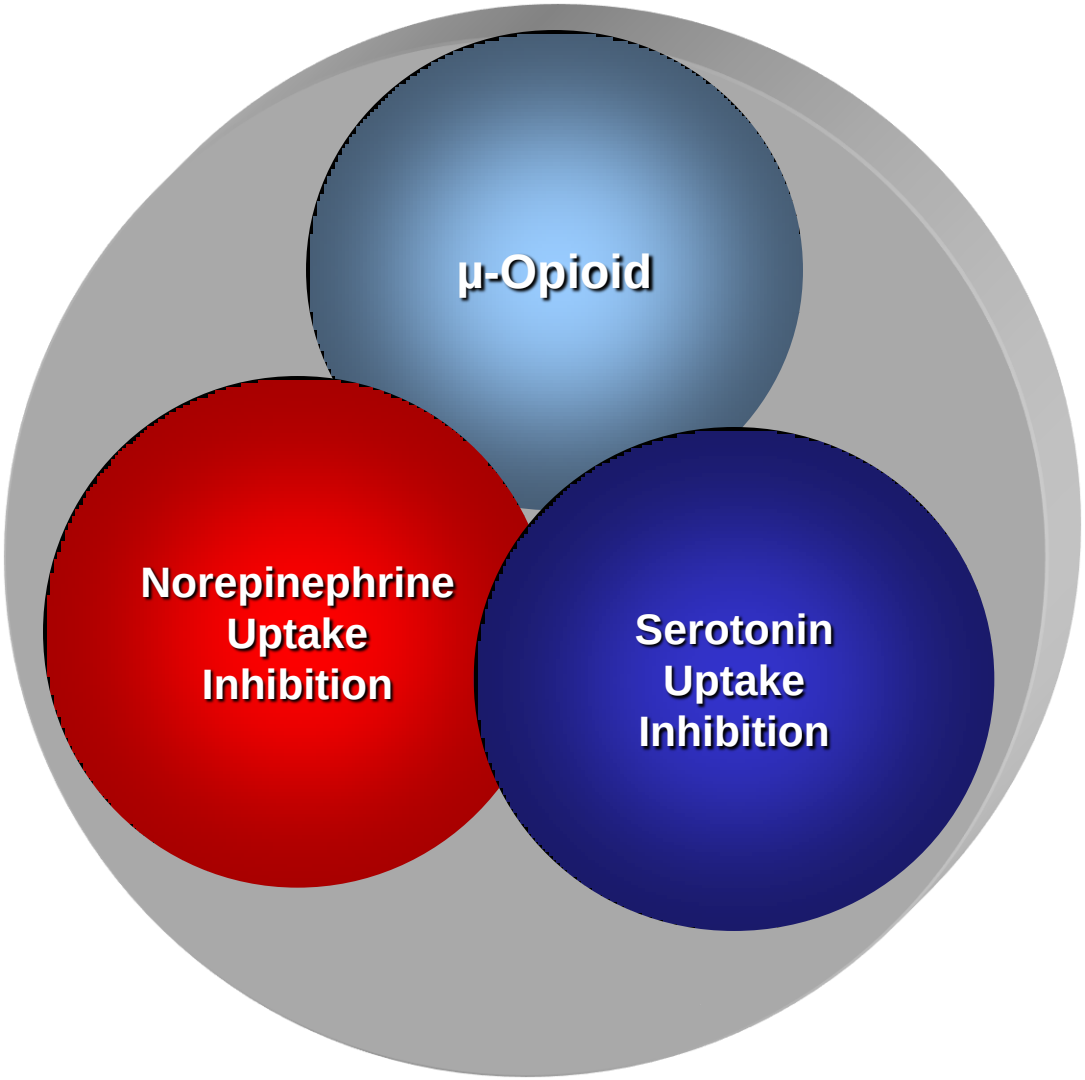


Tramadol – Pharmacological Profile

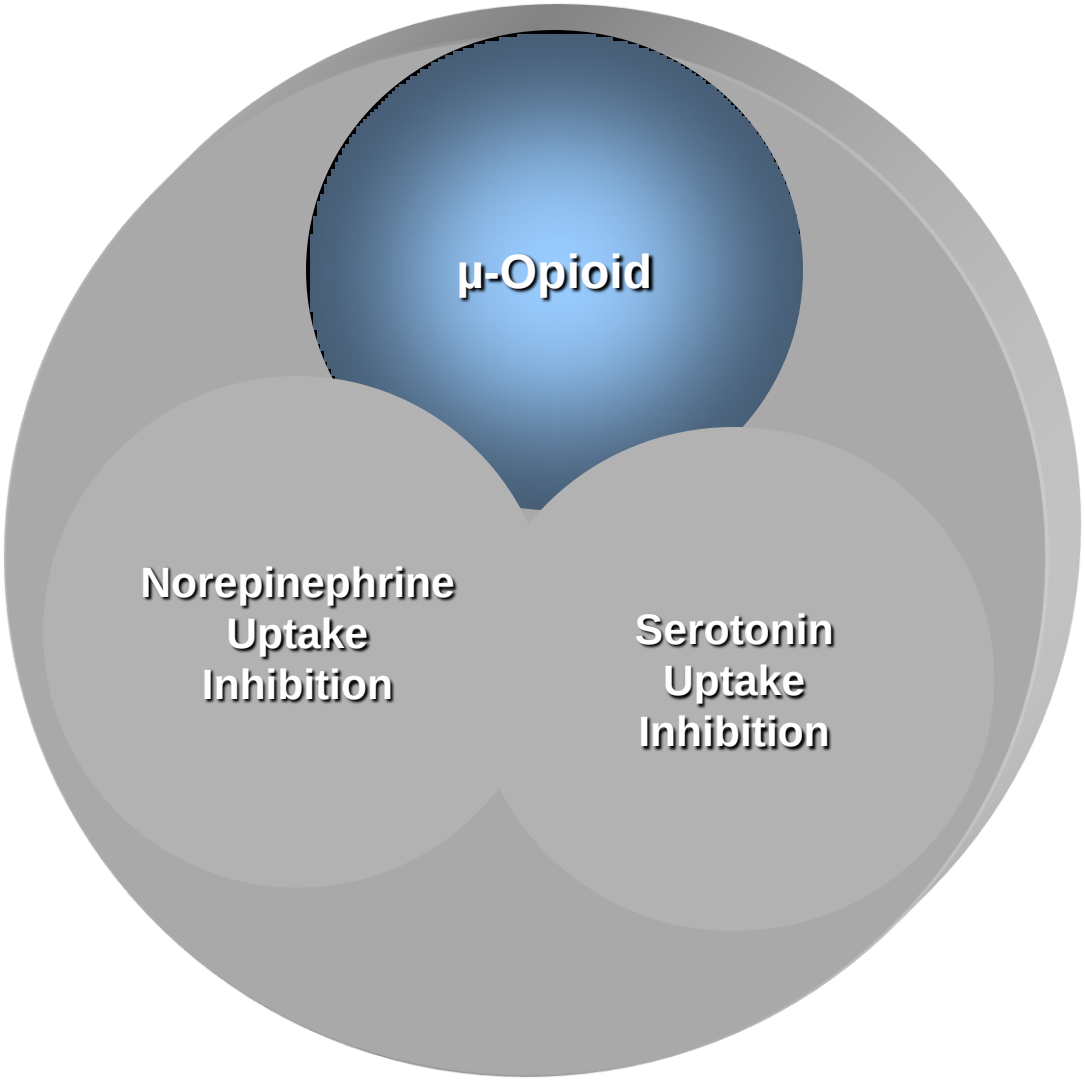
Metabolites of Tramadol



Tramadol‘s mode of action - biochemical profile

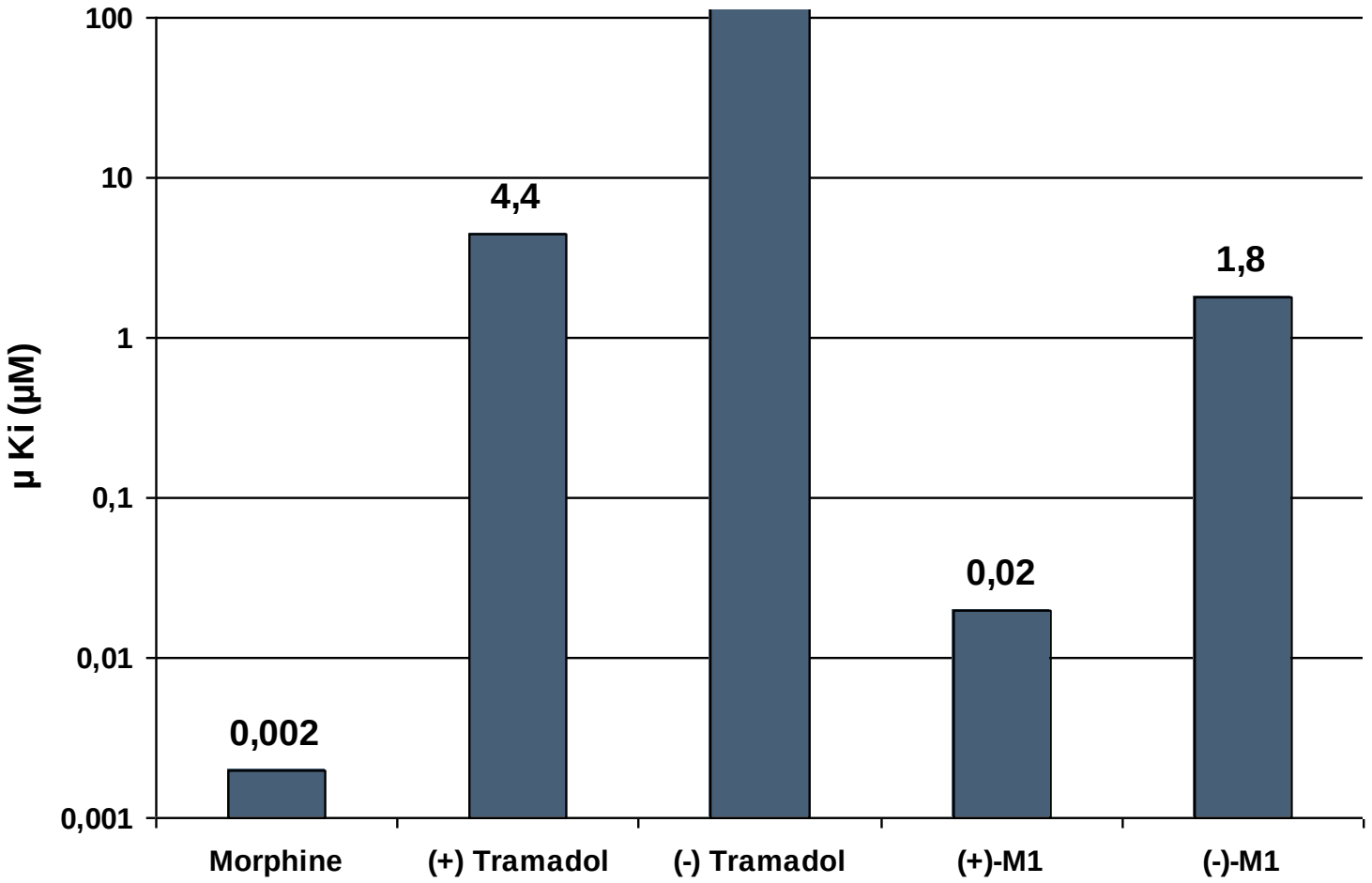


Tramadol‘s mode of action - biochemical profile



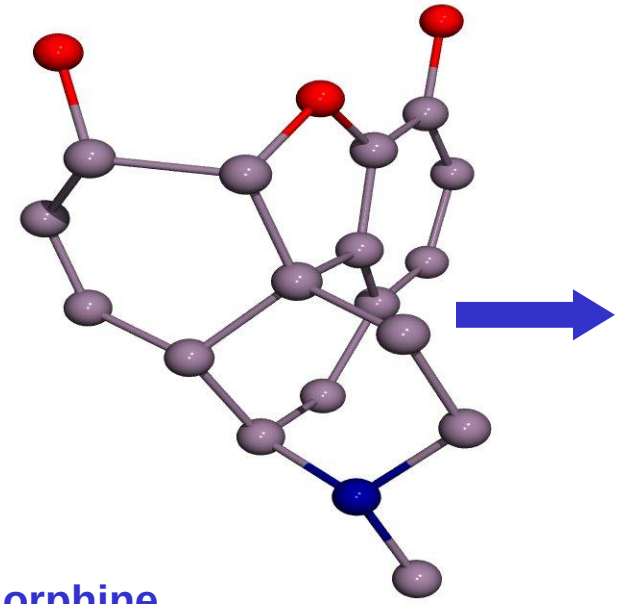
Tramadol – Pharmacological Profile

μ-Opioidbinding of tramadol and tramadol-M1

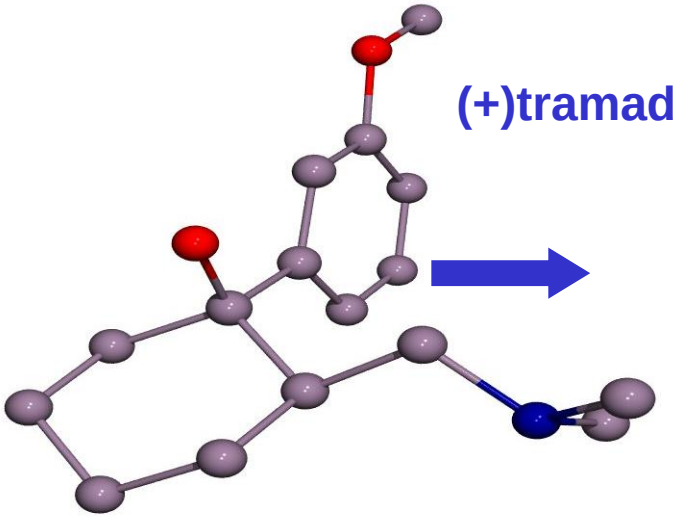


Comparison of molecular structures

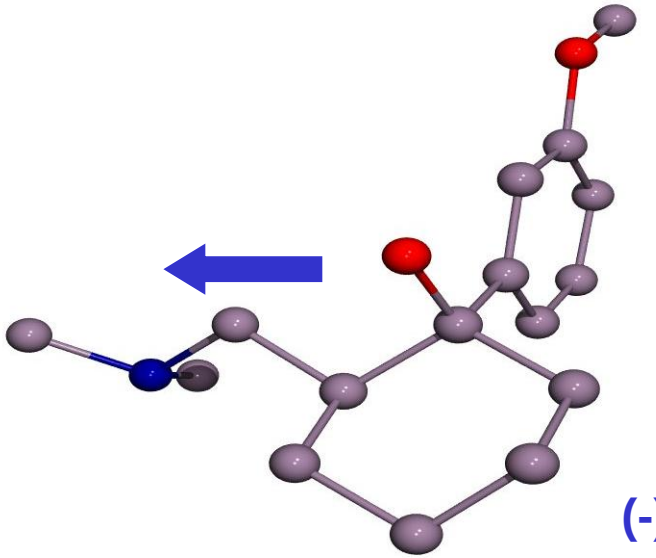
(+) Tramadol and Morphine



morphine

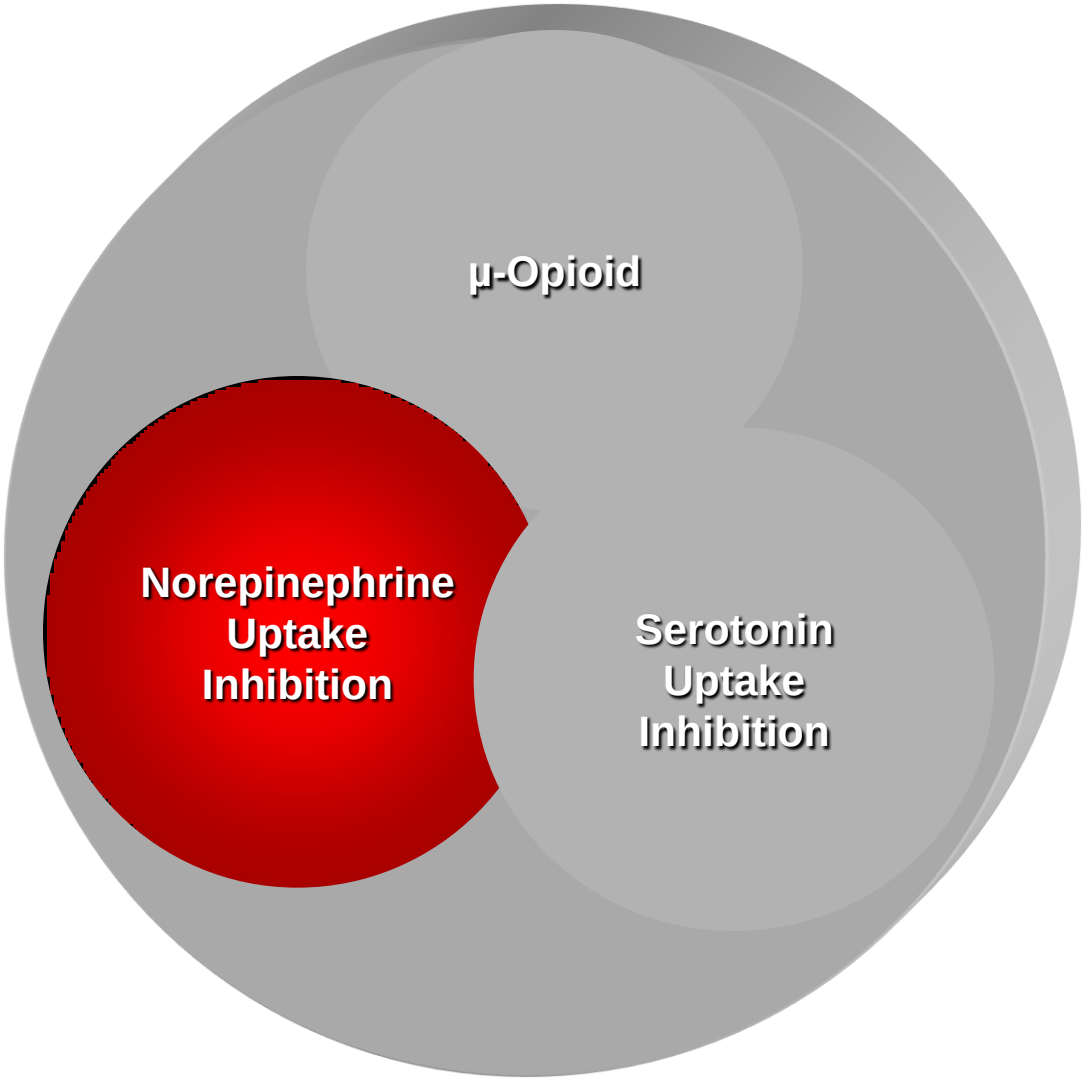


(+)tramadol



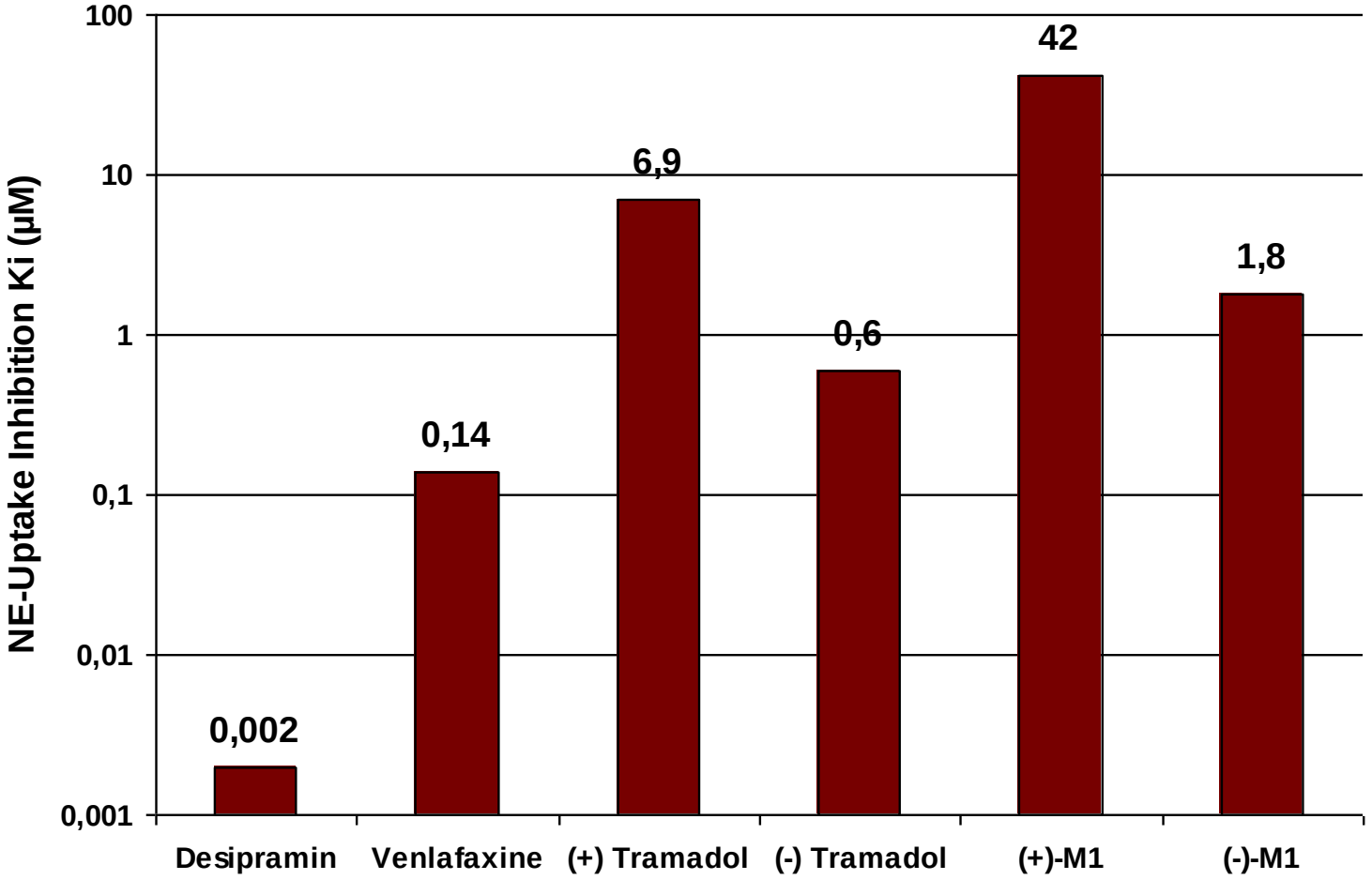
(-)tramadol

Tramadol‘s mode of action - biochemical profile

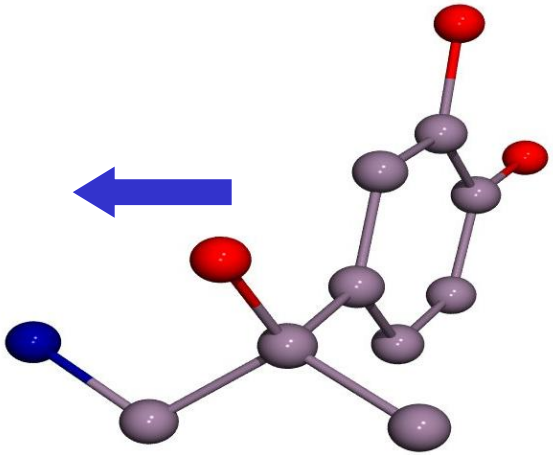


Tramadol – Pharmacological Profile

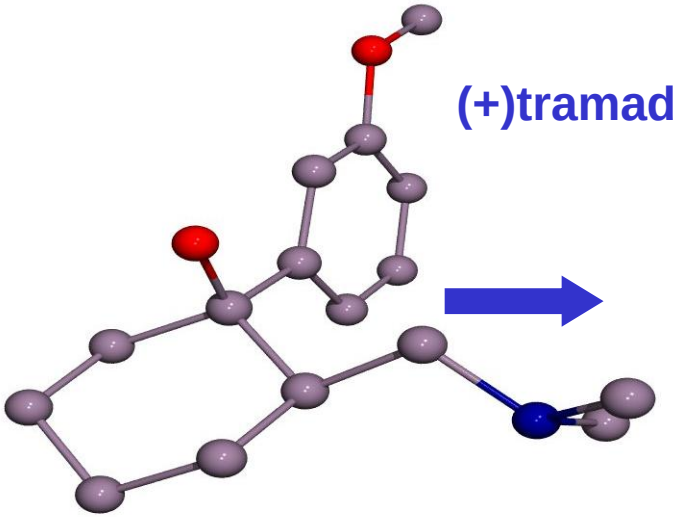
Norepinephrine-Uptake inhibition of tramadol and tramadol-M1



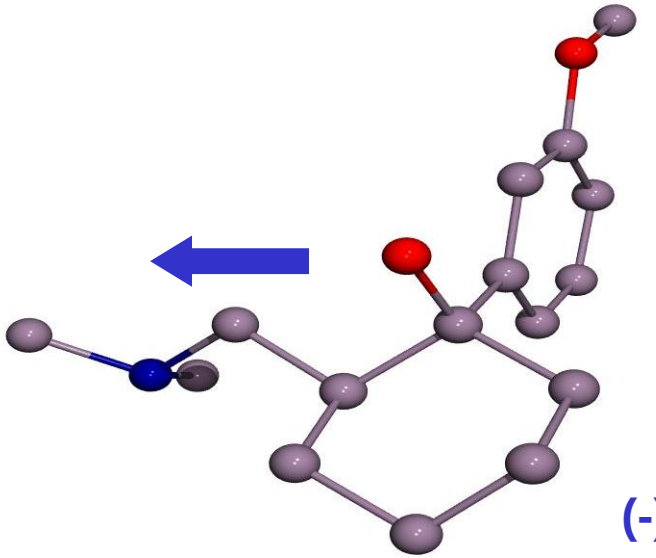
Comparison of molecular structures



norepinephrine

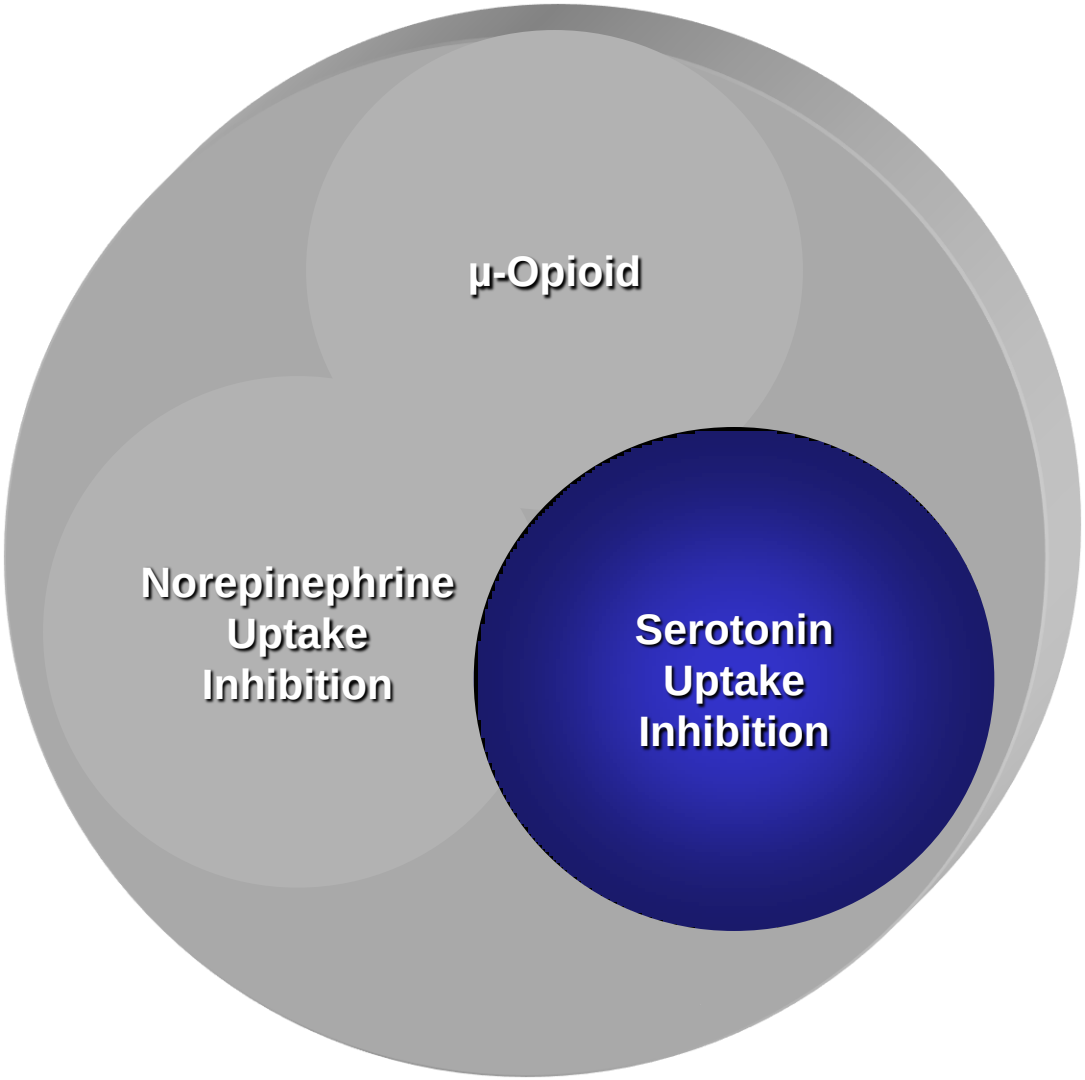


(+)tramadol



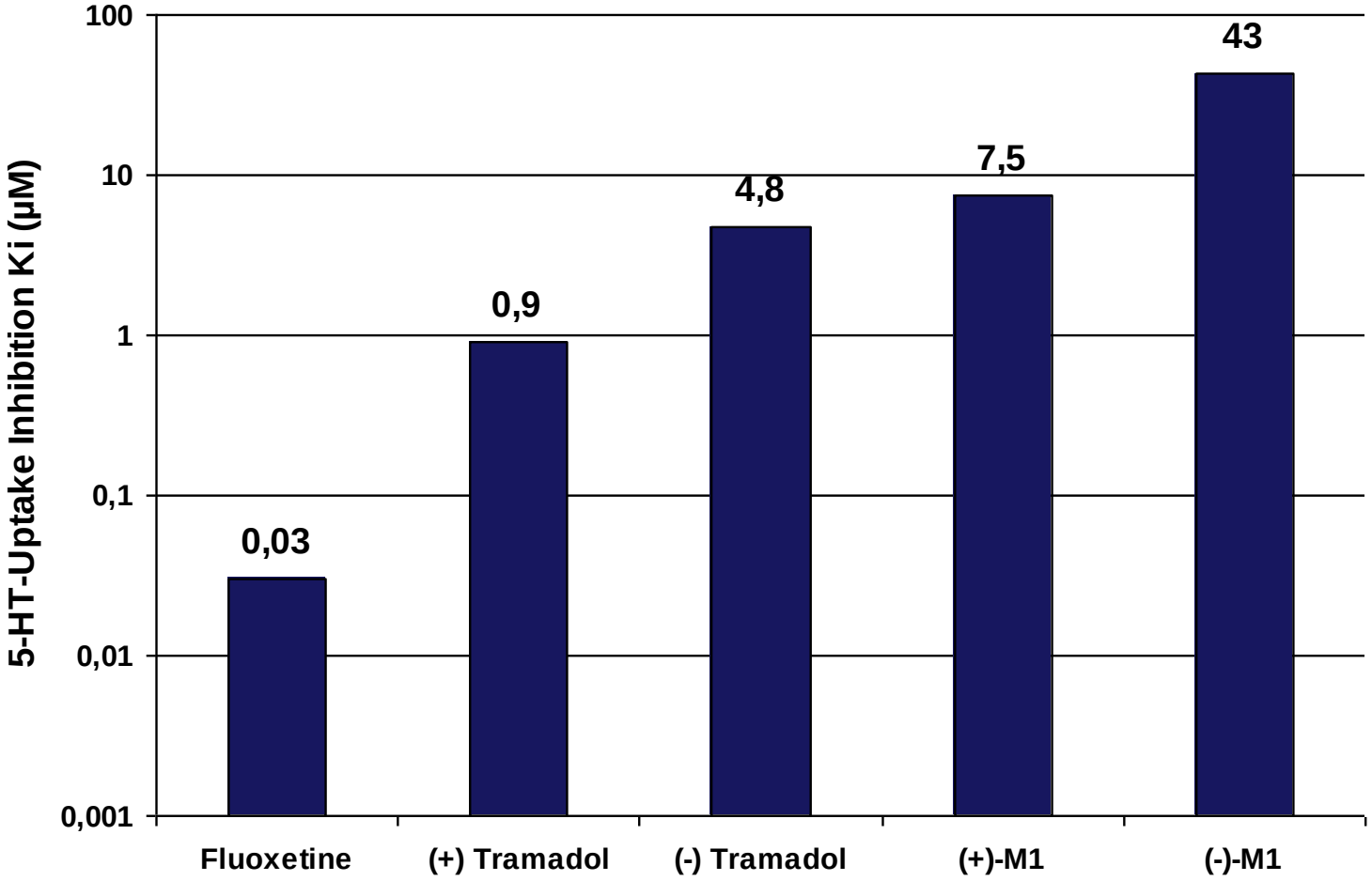
(-)tramadol

Tramadol‘s mode of action - biochemical profile

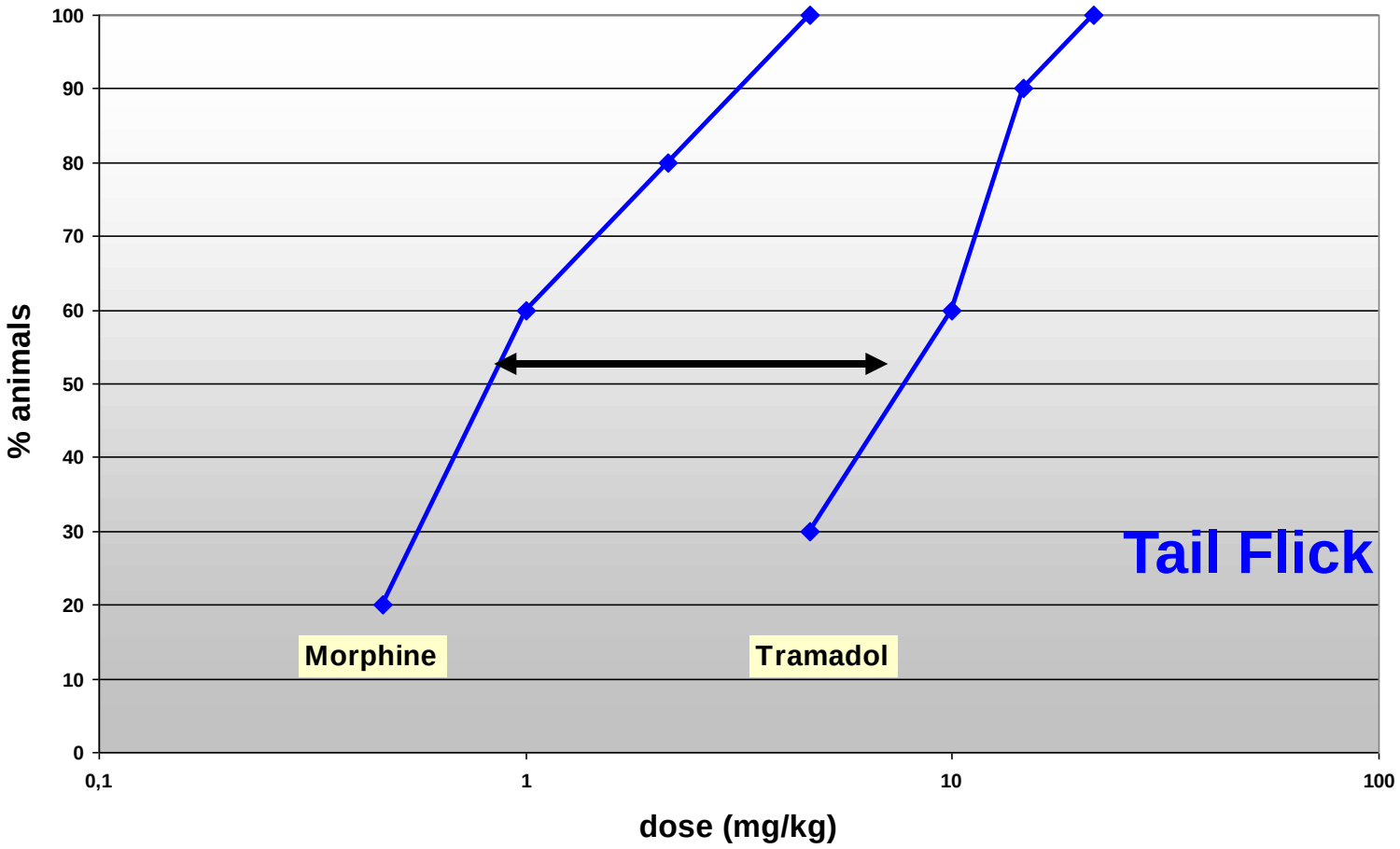


Tramadol – Pharmacological Profile

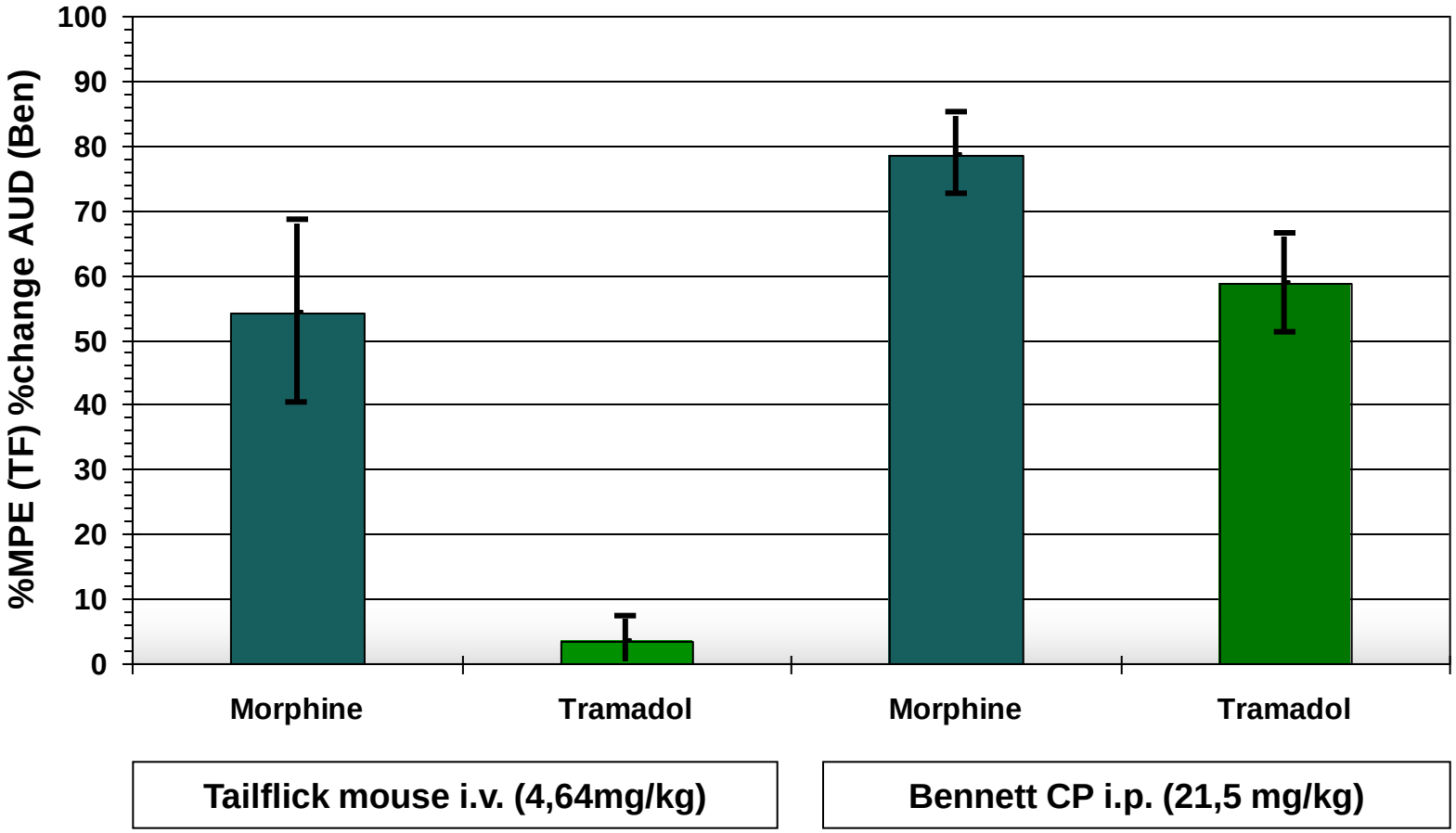
5HT-Uptake inhibition of tramadol and tramadol-M1



Comparison of acute pain (Tail Flick) and chronic inflammatory pain (Randall Selitto)

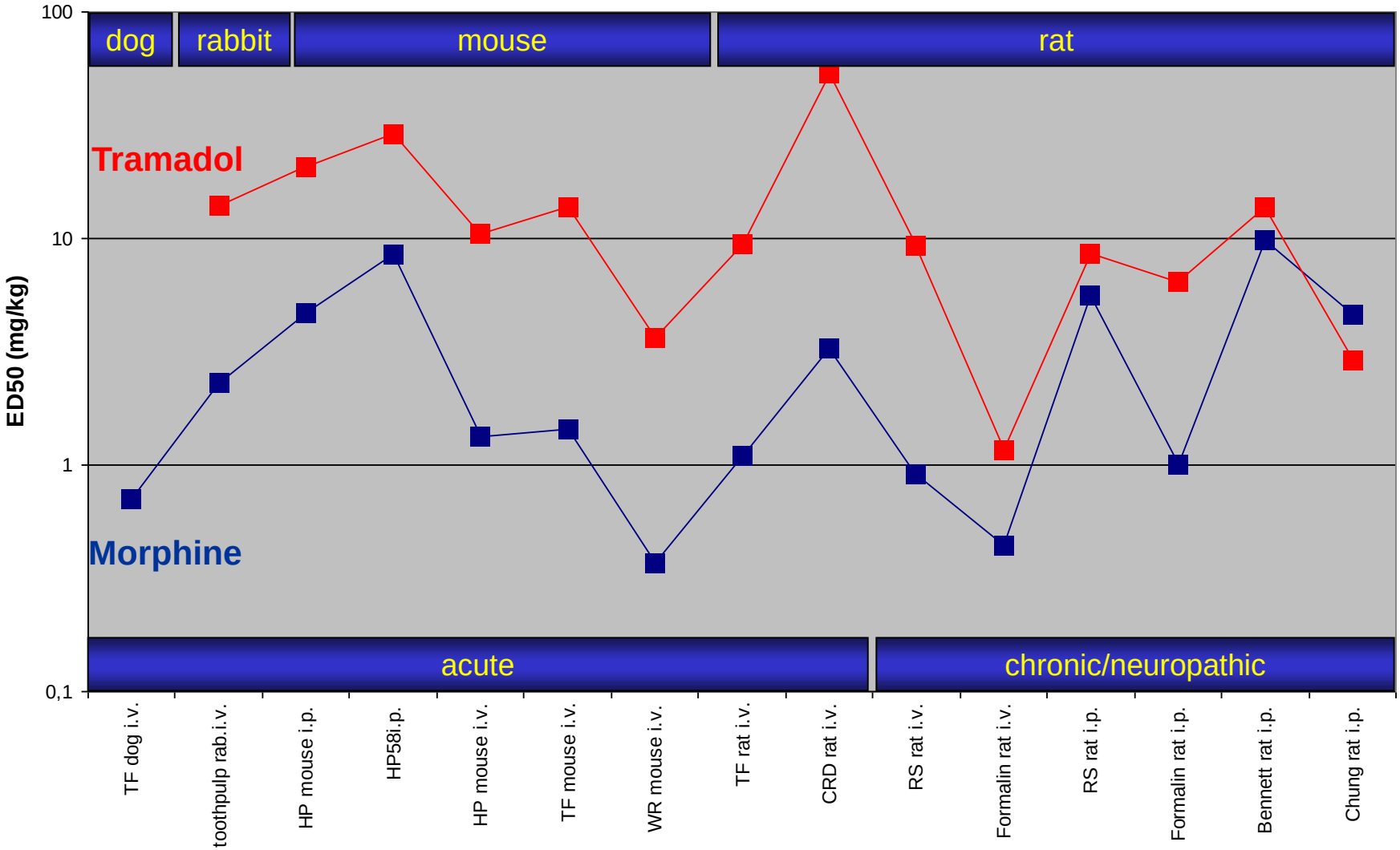


Comparison of acute pain (Tail Flick) and neuropathic pain (Bennett)

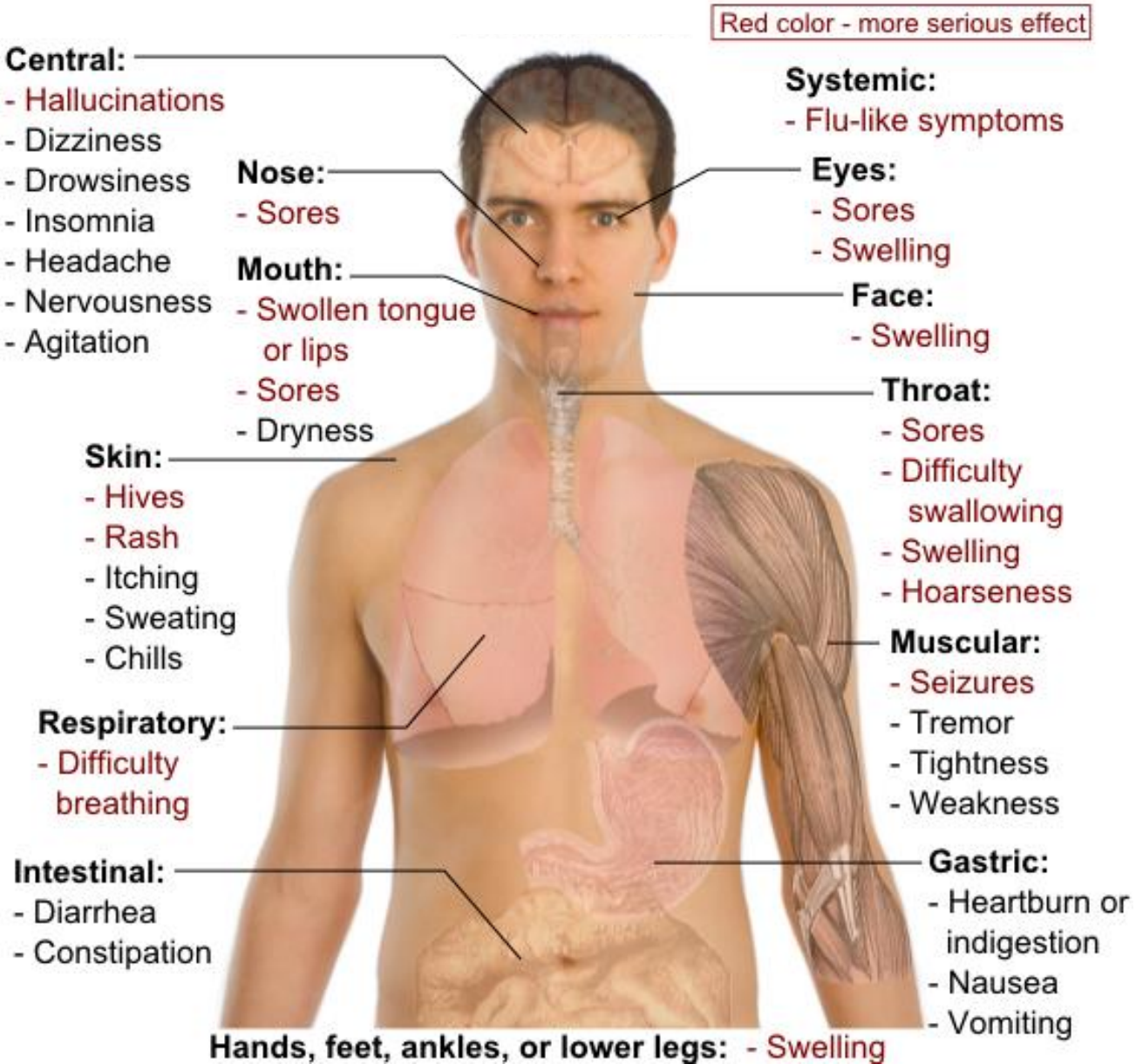


Tramadol – Pharmacological Profile

Antinociceptive Potency Profile
Comparison Morphin - Tramadol



Side Effects of Tramadol



Occurrence of the Synthetic Analgesic Tramadol in an African Medicinal Plant

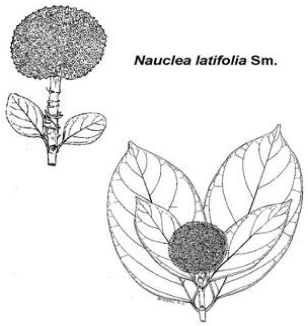
Angewandte Chemie

Natural Products

DOI: 10.1002/ange.201305697

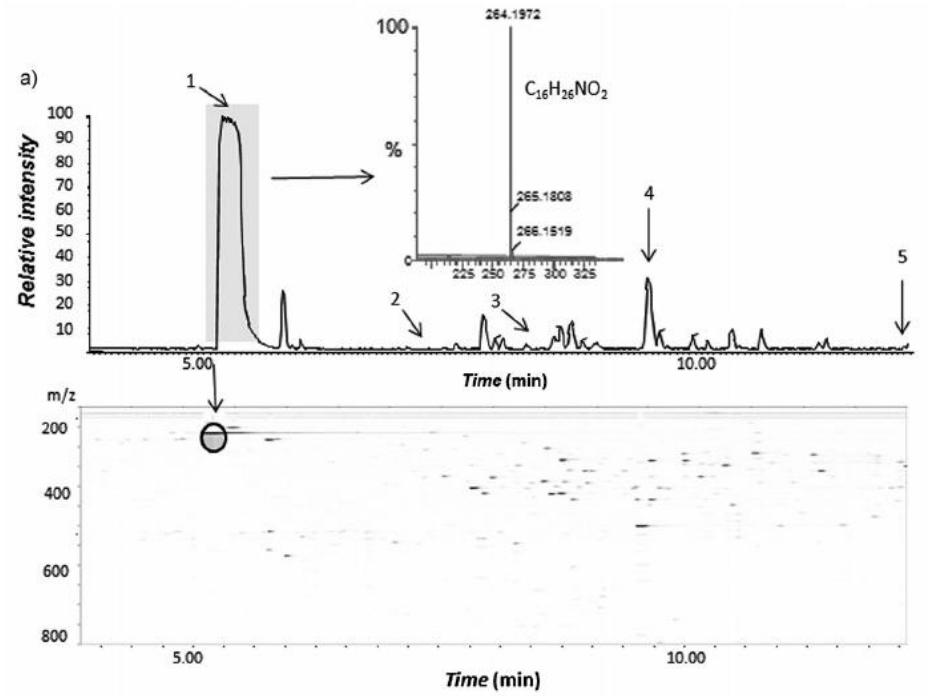
Occurrence of the Synthetic Analgesic Tramadol in an African Medicinal Plant**

Ahcène Boumendjel, Germain Sotoing Taïwe, Elisabeth Ngo Bum, Tanguy Chabrol, Chantal Beney, Valérie Sinniger, Romain Haudecoeur, Laurence Marcourt, Soura Challal, Emerson Ferreira Queiroz, Florence Souard, Marc Le Borgne, Thierry Lomberget, Antoine Depaulis, Catherine Lavaud, Richard Robins, Jean-Luc Wolfender, Bruno Bonaz, and Michel De Waard**

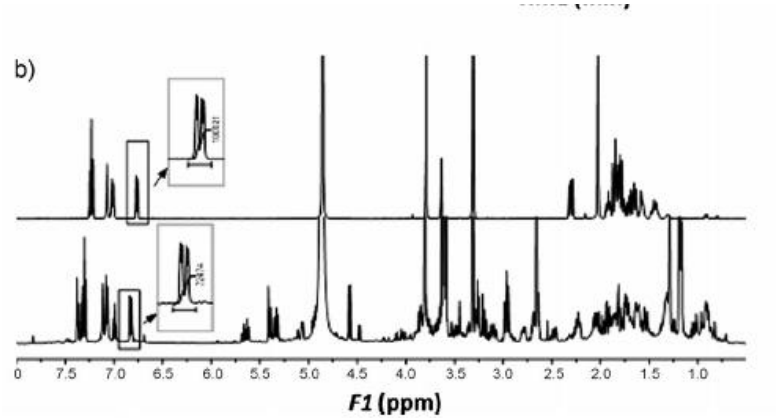


Tramadol – A Natural Product?

NMR analysis and UHPLC-TOF-MS profiling of the crude extract from *N. latifolia* for identification and quantification of tramadol.



UHPLC-TOF-MS profiling of the crude ethanolic extract of N. latifolia with a label for compounds dereplicated (zoomed into the 0–12 min retention domain). Top panel: TOF-MS spectra of tramadol in the crude extract. Bottom panel: 2D ion map of the crude extract of N. latifolia displaying all recorded ions.

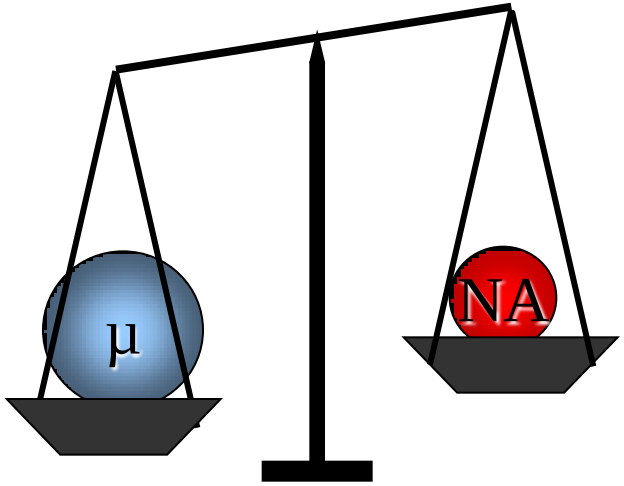


The absolute integration of the 1H NMR signal at dH=6.77 (ddd, 8.0, 2.6, 0.9 Hz, H-4') of commercial tramadol in a CD3OD solution at 263.4 mm was used as an external reference (top panel) to quantify the amount of natural tramadol in an ethanolic extract of N. latifolia (bottom panel) using the PULCON method.

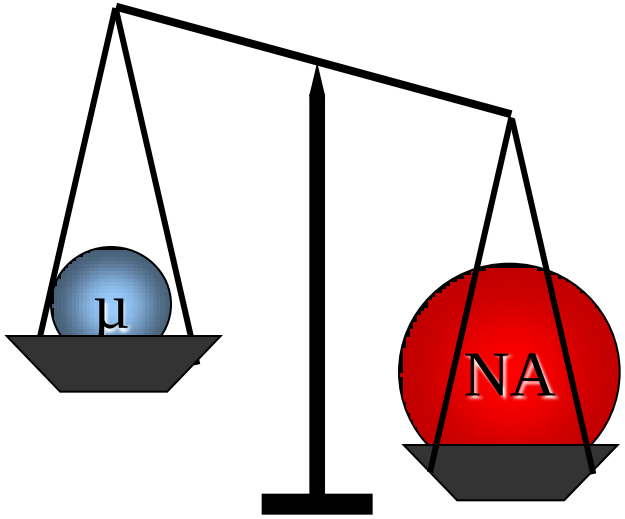
Tapentadol - From Morphine and Tramadol to the Discovery Tapentadol

- Pain Transduction
- The Analgesic Market
- Current Analgesic Treatment Options
- Pain Research Today - The Unmet Needs
- Tramadol – History and Pharmacology
- **Tapentadol – A New Analgesic With a Dual Mode of Action**
  - **Structure-Activity-Relatioship**
  - ***In vitro* Profile**
  - ***In vivo* Pharmacology**
  - **Metabolism**
  - **Synthesis**

What have we learned from the Tramadol story?



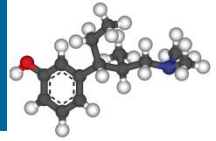
(+)-Tramadol



(-)-Tramadol

Can both principles be combined in one molecule
(one enantiomer) ?

Tramadol – The Research Strategy



Gold -standard for the relief of moderate to severe pain

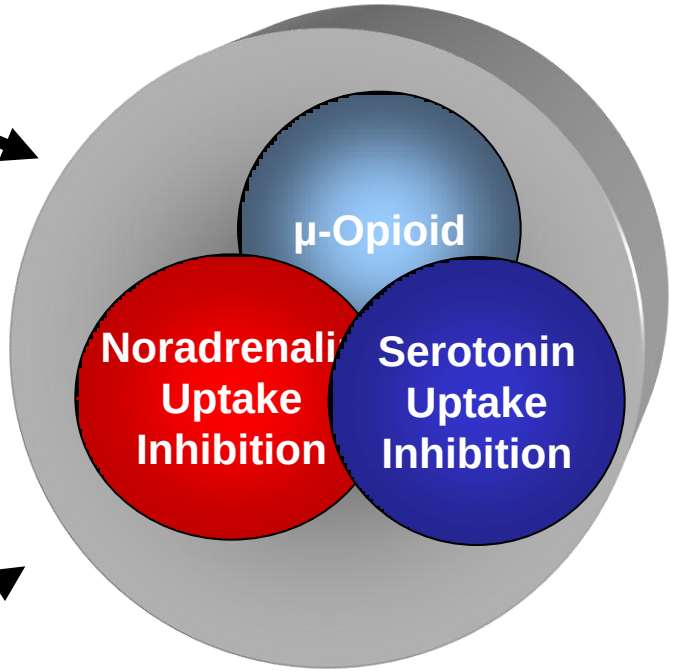
But: side effects

μ-Opioid

Noradrenalin Uptake Inhibition

Antidepressants and co-medication for chronic pain

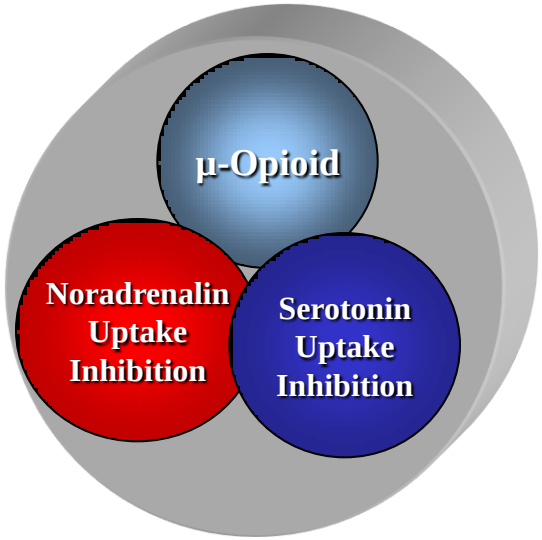
Serotonin Uptake Inhibition

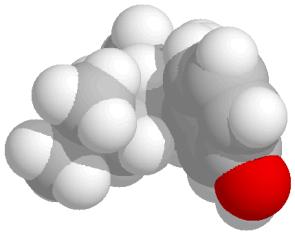


Synergistic pain relief and less opioid side effects

Tramadol – The Research Strategy

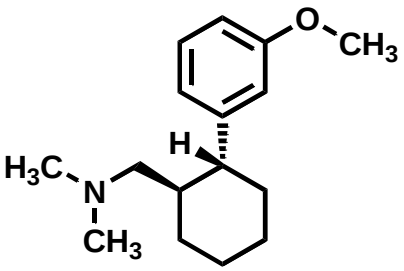
Several compounds with different biological profiles have been characterized

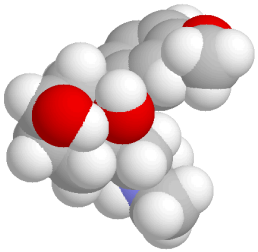




Faxeladol

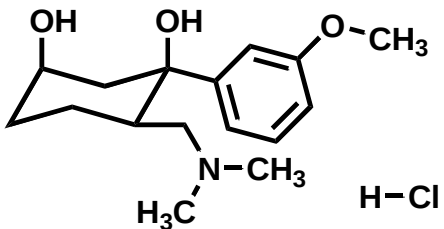
***03.12.1991**

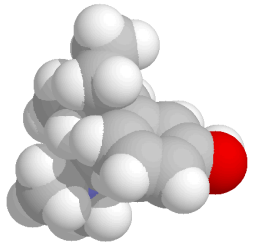




Axomadol

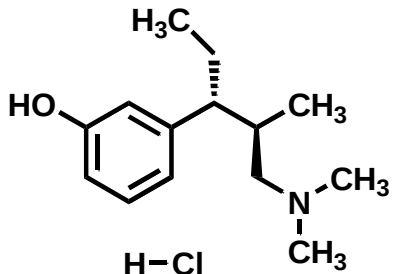
***16.07.1993**





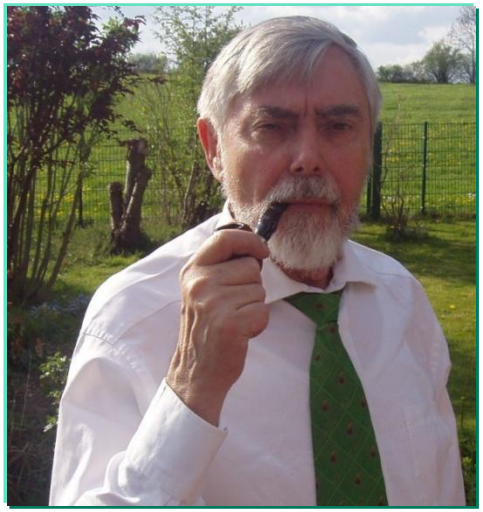
Tapentadol

***08.02.1994**

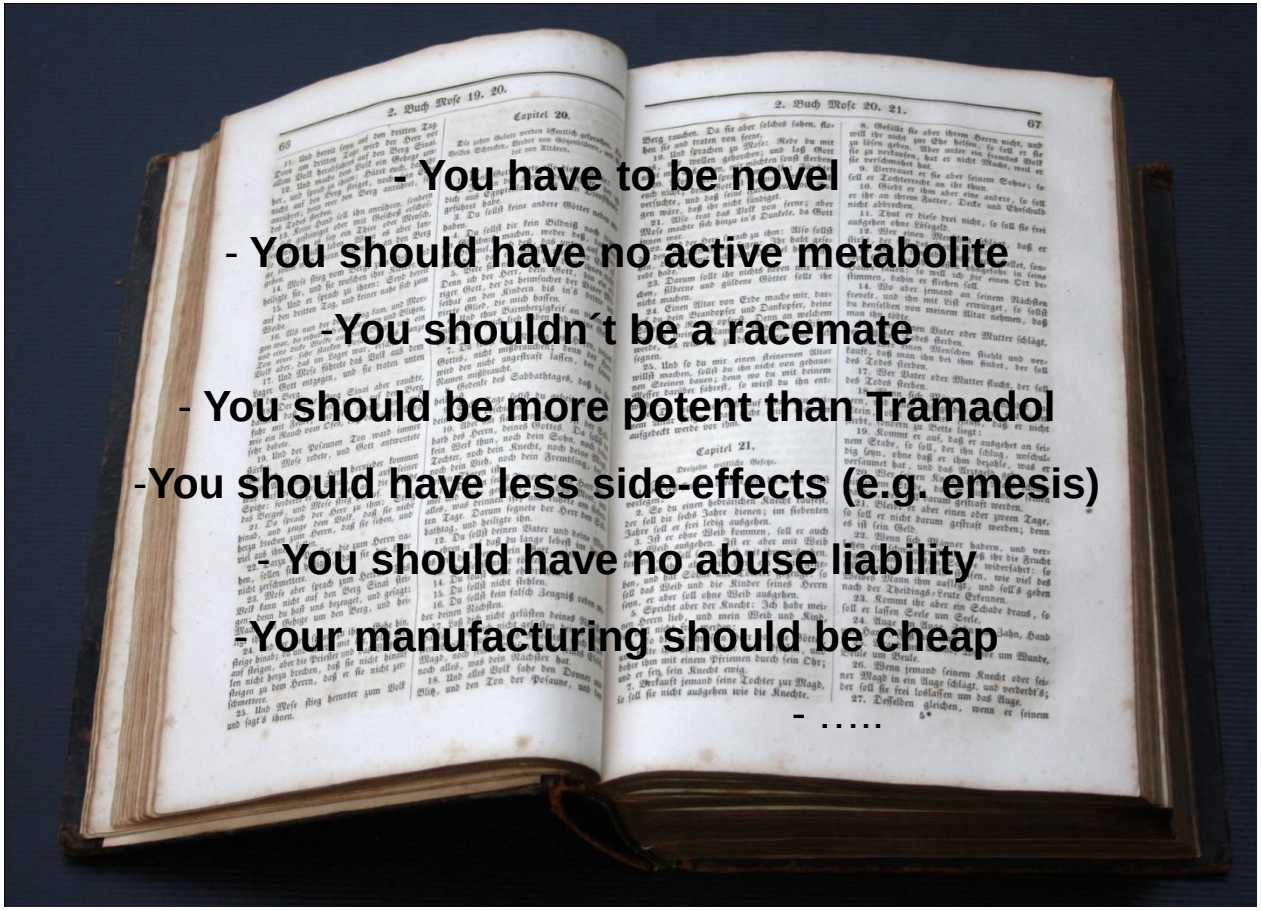


The Ten Commandments

The Golden Era of Research

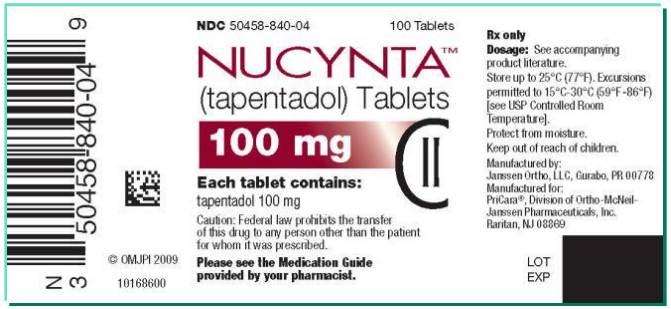


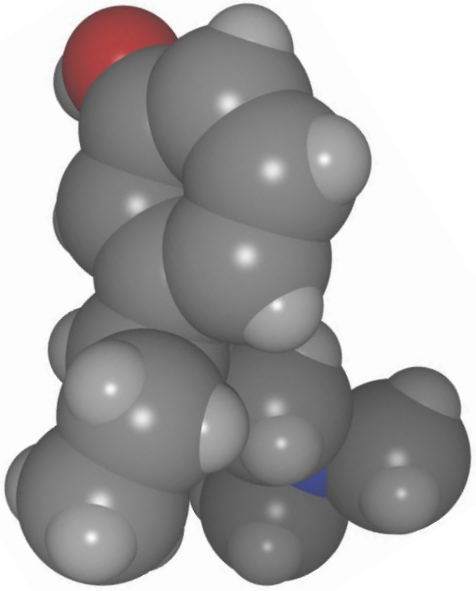
Prof. Werner Winter
(1980s – 1990s)

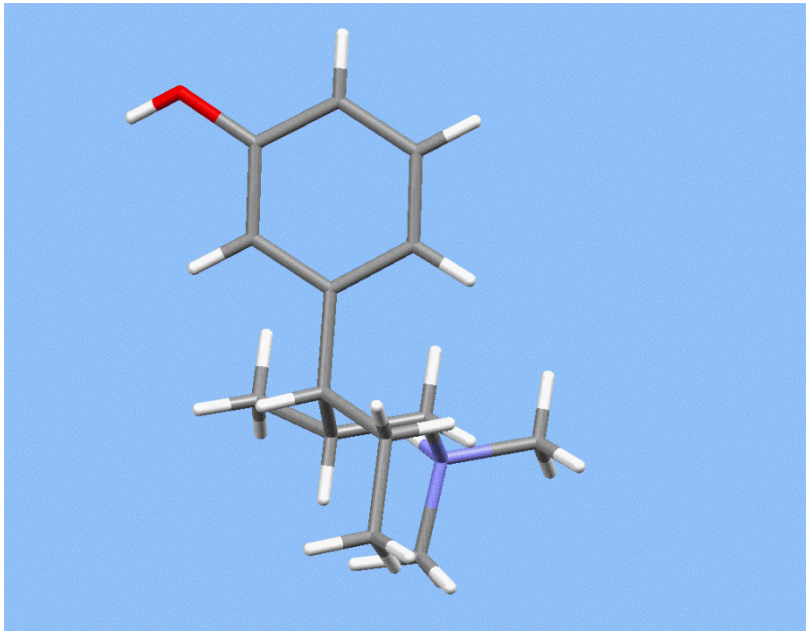


Tapentadol – A New Analgesic with a Dual Mode of Action

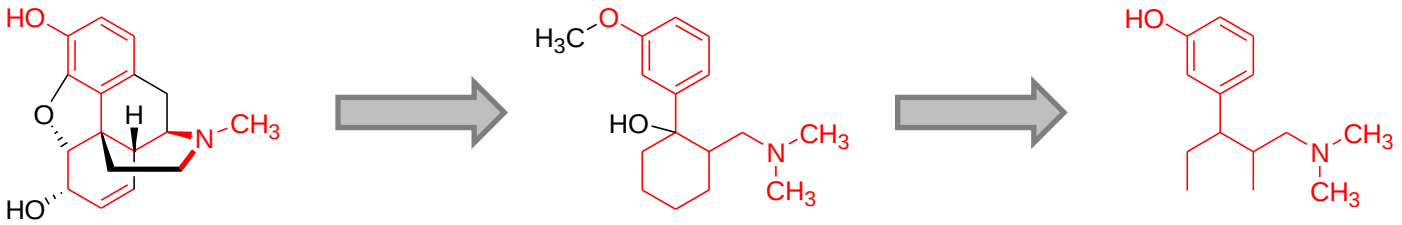
PALEXIA®
TAPENTADOL



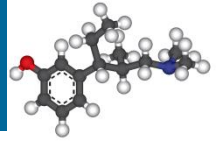




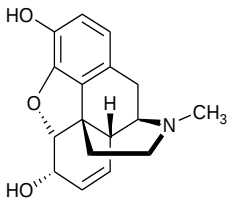
Tapentadol – A New Analgesic with a Dual Mode of Action

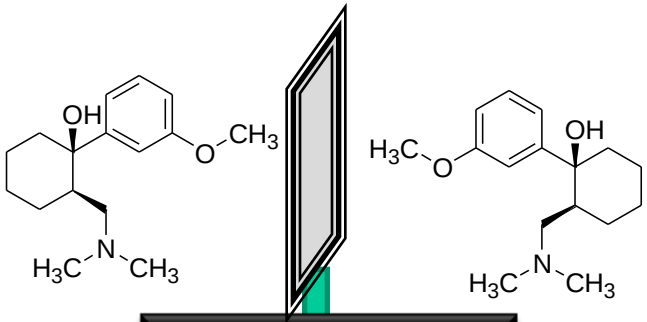


Tapentadol – A New Analgesic with a Dual Mode of Action

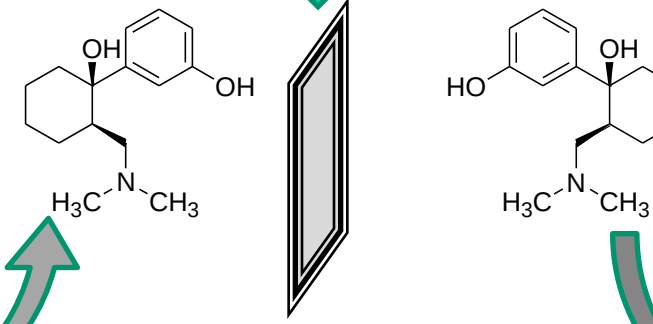


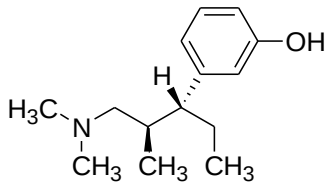
Morphine | **Tramadol** | **Tapentadol**

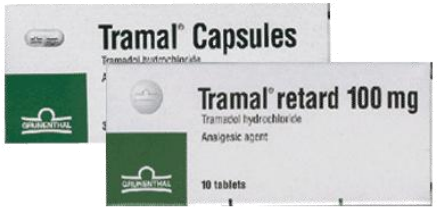




Metabolic Activation



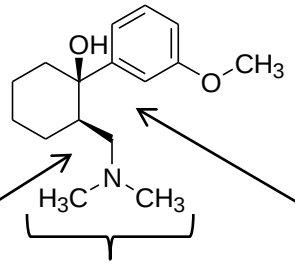




Tapentadol – A New Analgesic with a Dual Mode of Action

- Derivatisation of hydroxyl group: ester, ether, …
- Replacement of hydroxylgroup by N, H, halogen
- Elimination resulting in olefins

- Substitution of cyclohexane ring
- Size of ring system
- Introduction of hetero atoms (e. g. O, N, S)
- Aromatic rings

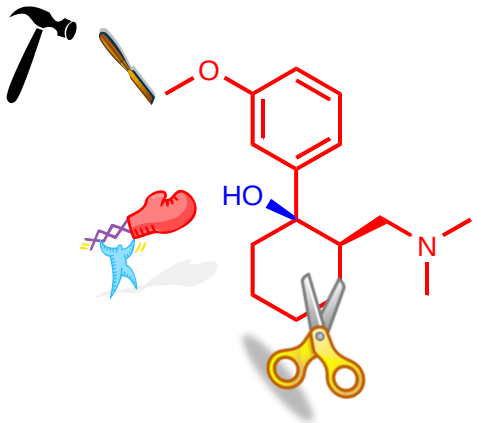


- Phenyl ring substitution
- Replacement by heterocyclic aryl rings
- Replacement by acyclic ring systems

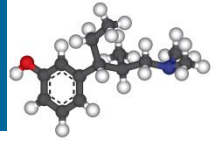
- Methylen group substitution

- N- Substitution
- N-containing ring systems

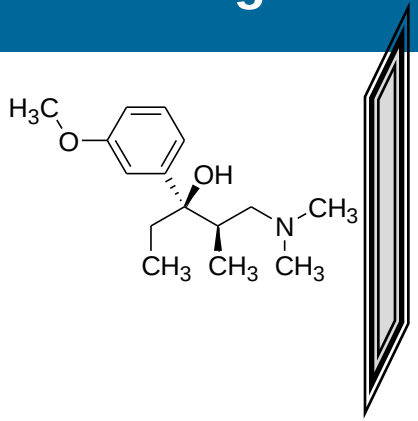
- Introduction of spacer groups between ring systems

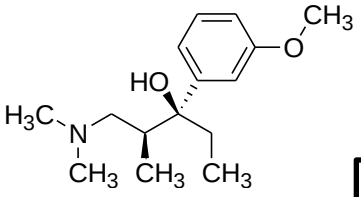


Tapentadol – A New Analgesic with a Dual Mode of Action

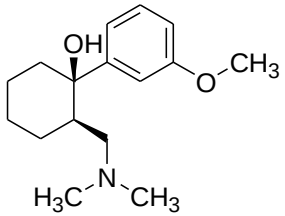


Opening of the cyclohexane ring

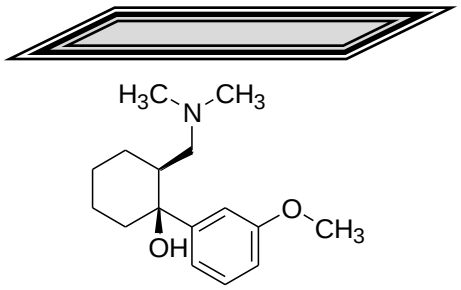




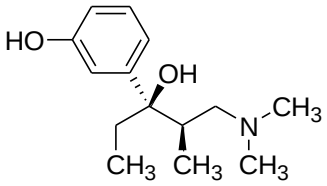
From Prodrug to direct acting drug

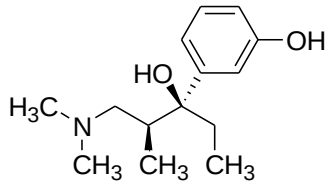


Tramadol

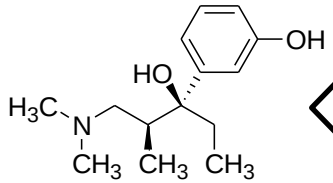


Racemate with relative stereochemistry cis

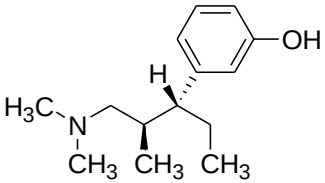




Selecting of one enantiomer

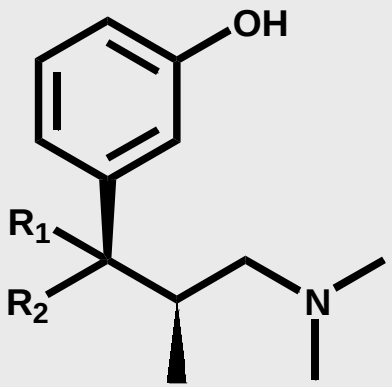


Replacement of *tert.* OH group



Tapentadol

CH_3 as replacement for C_2H_5

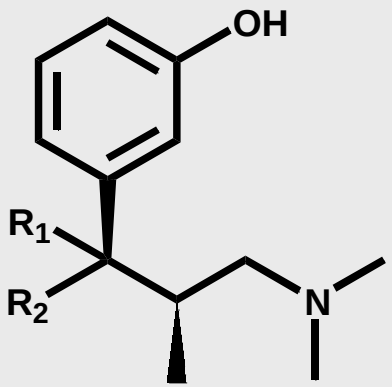


Code	R_1	R_2	μ Ki	5-HT Ki	NA Ki	TF mouse ED50
GRT6 (+)	OH	C2H5	0,009	75	4,4	0,32
GRT5 (-)	OH	C2H5	1,4	84	0,7	56,1
GRT8 (+)	OH	CH3	0,06	8,6	20	2,1
GRT7 (-)	OH	CH3	0,7	81	1	32,4

μ-binding:	(+) Enantiomer	↓
	(-) Enantiomer	-
5HT:	(+) Enantiomer	↑
	(-) Enantiomer	-
NA:	(+) Enantiomer	-
	(-) Enantiomer	-

For the (+)-enantiomer μ-binding decreased,
5-HT-binding increased

H, F as replacement for OH

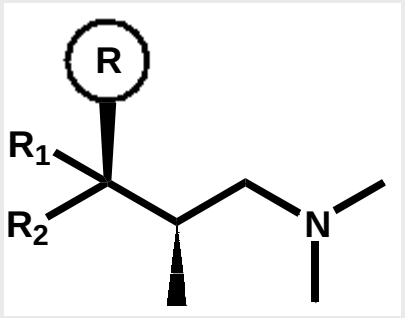


Code	R_1	R_2	μ Ki	5-HT Ki	NA Ki	TF mouse ED50
GRT6 (+)	OH	C2H5	0,009	75	4,4	0,32
GRT5 (-)	OH	C2H5	1,4	84	0,7	56,1
GRT2 (+)	H	C2H5	0,007	7,3	1,9	0,85
GRT1 (-)	H	C2H5	0,1	2,3	0,6	3
GRT4 (+)	F	C2H5	0,007	27,8	1,7	0,32
GRT3 (-)	F	C2H5	0,04	4,1	0,3	1,44

μ-binding:	(+) Enantiomer	-
	(-) Enantiomer	↑
5HT:	(+) Enantiomer	↑
	(-) Enantiomer	↑
NA:	(+) Enantiomer	-
	(-) Enantiomer	-

The (-)-enantiomers have μ-binding and NA-reuptake inhibition in a similar range

Phenol as replacement for naphtol



Code	R	R_1	R_2	μ Ki	5-HT Ki	NA Ki	TF mouse ED50
GRT10 (+)	Naphtol	OH	C_2H_5	0,02	17,4	0,2	0,6
GRT9 (-)	Naphtol	OH	C_2H_5	15%(1)	6,8	0,05	2an.(10)
GRT6 (+)	Phenol	OH	C_2H_5	0,009	75	4,4	0,32
GRT5 (-)	Phenol	OH	C_2H_5	1,4	84	0,7	56,1

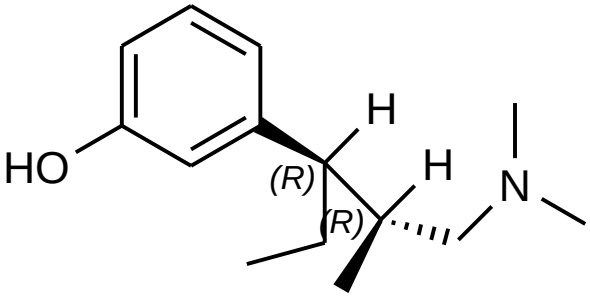
μ-binding:	(+)	Enantiomer	↑
	(-)	Enantiomer	↑
5HT:	(+)	Enantiomer	↓
	(-)	Enantiomer	↓
NA:	(+)	Enantiomer	↓
	(-)	Enantiomer	↓

μ-binding for both enantiomers increased,
5-HT and NA decreased

The „Birth Certificate“ of Tapentadol

…Is it boy or is it a girl?

Peter Jansen



STOLBERG IM RHEINLAND

Zentral-Analytik	Prüfsubstanz	Datum: 8.2.1994

Code-Nr.	Hersteller	Herst.-Datum	Charge	Vorh. Menge
BN-200	Labor Dr. Buschmann	01/94	0 Bu 322-1-1-I	1.0 g

Angenommene Struktur: (−)-(5,5) — Bezugssubstanz/Literaturangabe: BN-91

Summenformel: $C_{14}H_{24}ClNO$ (257.80) | Fp: 123.1° (Zersetzung) | Kp: /

Chemische Bezeichnung: (−)-(1S,2S)-3-(3-Dimethylamino-1-ethyl-2-methyl-propyl)-phenol-Hydrochlorid

letzter Syntheseschritt: Darstellung des Hydrochlorids
Lösungsmittel: Ether

Dünnschichtchromatographie durchgeführt: ja ☒ nein ☐
Bedingungen:
Trennschicht: DC-TLC mit Kieselgel 60 F254
Fließmittel: Cyclohexan : Methanol = 1:1
Detektion: 1. Kammer: UV

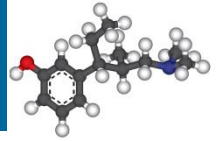
*) ^{1}H-NMR: 42852
^{13}C-NMR: 42883

**) ee > 99 %
Bu 68 #1 als Reagenz
chiral HPLC, Herr Uebel

$[\alpha]_D^{RT}$ = −27.5° (c=0.52, MeOH)

VORSICHT

Bemerkungen:
lichtempfindlich: ja ☐ nein ☐ hygroskopisch: ja ☐ nein ☐
feuchtigkeitsempfindlich: ja ☐ nein ☐ hautreizend: ja ☐ nein ☐
Sonstiges:



Morphin und Tapentadol

Vergleich der Affinität von Tapentadol und Morphin zu unterschiedlichen Opioidrezeptor-Subtypen, untersucht in Bindungsstudien an Rattenhirnmembranen (MOR, KOR,DOR) oder humanen rekombinanten Rezeptoren (NOP) (Tzschentke et al. 2006)

Substanz	K_i Wert (µM)			
	MOR	KOR	DOR	NOP
Tapentadol	0,1	0,9	1,0	>100
Morphin	0,002	0,17	0,002	>100

MOR: µ-Opioidrezeptor, KOR: κ-Opioidrezeptor, DOR: δ-Opioidrezeptor, NOP: ORL1- oder Nozizeptin-Rezeptor

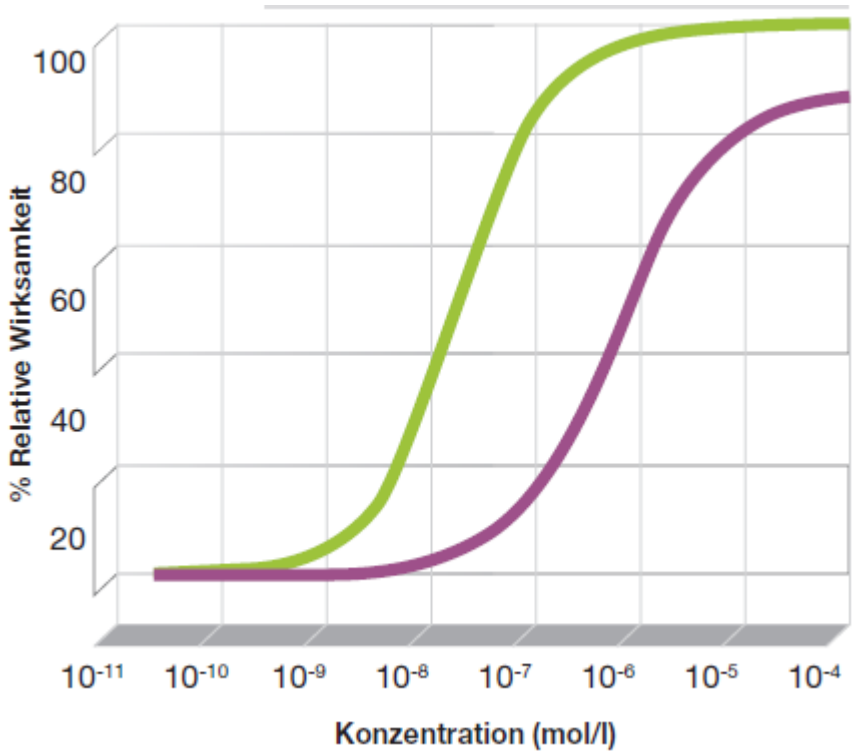
Vergleich von Tapentadol und Desipramin im Hinblick auf die Neurotransmitter-Wiederaufnahme-Hemmung, untersucht an Rattenhirn-Synaptosomen

Transmitter	K_i Wert (µM)	
	Tapentadol	Desipramin
Noradrenalin	0,5	0,001
5-HT	2,4	1,4
Dopamin	KE	KA
Cholin	39	KA

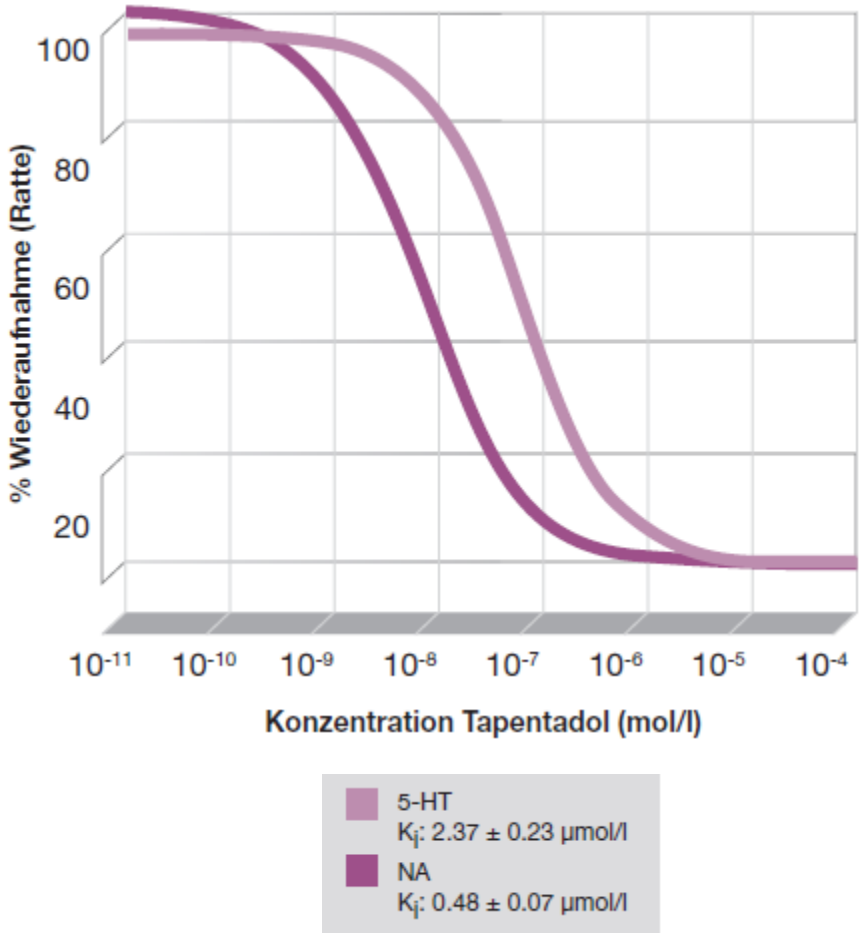
KE: kein Effekt (5 % Hemmung bei 1 µM), KA: keine Angabe.

Morhin und Tapentadol

Vergleich zwischenTapentadol und Morphin-Bindung anden humanen μ-Opioidrezeptor (Tzschentke et al. 2007)

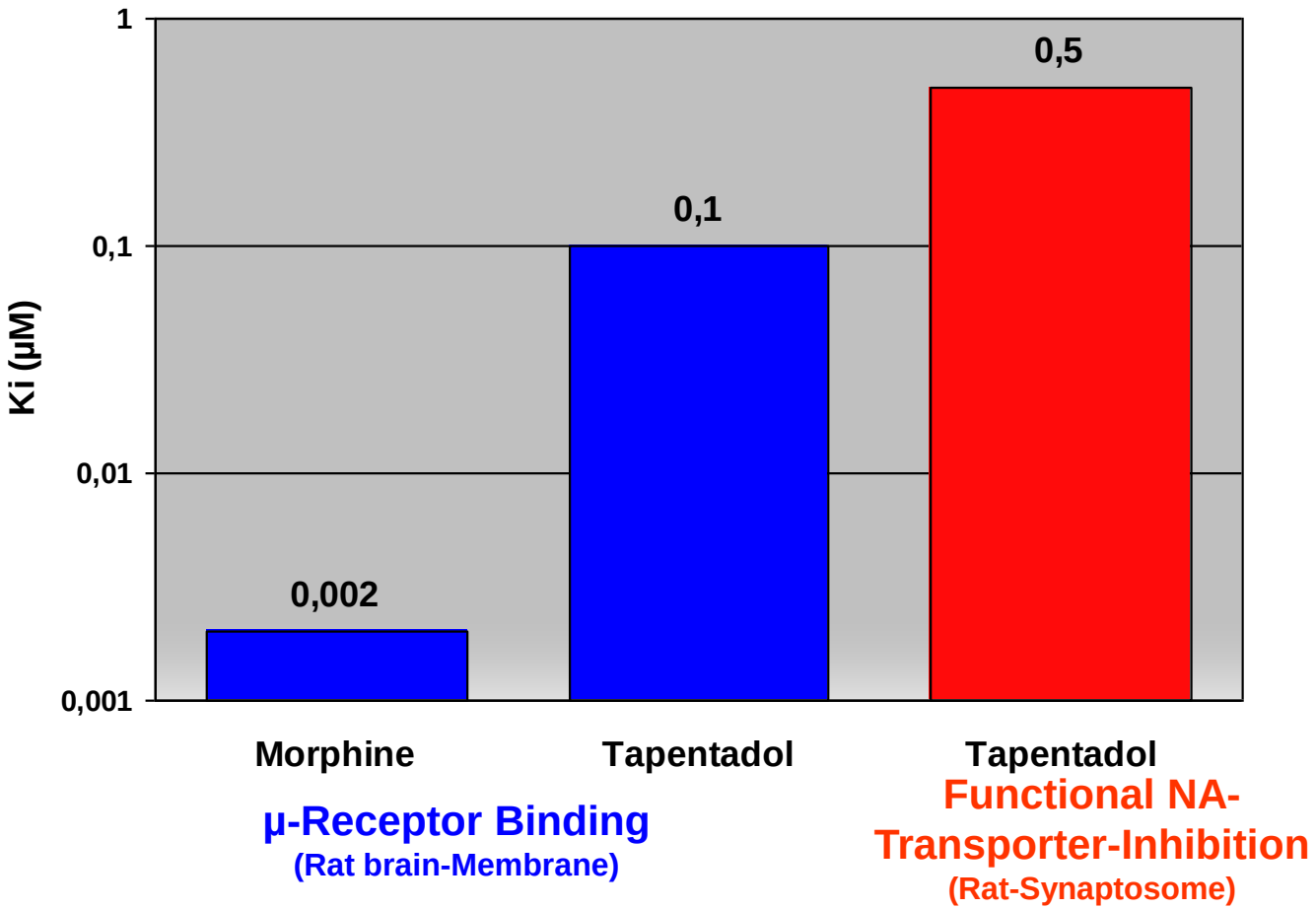


Vergleich der Hemmungdurch Tapentadol-synaptosomaleNA- und 5-HT-Wiederaufnahme (Tzschentke et al. 2007



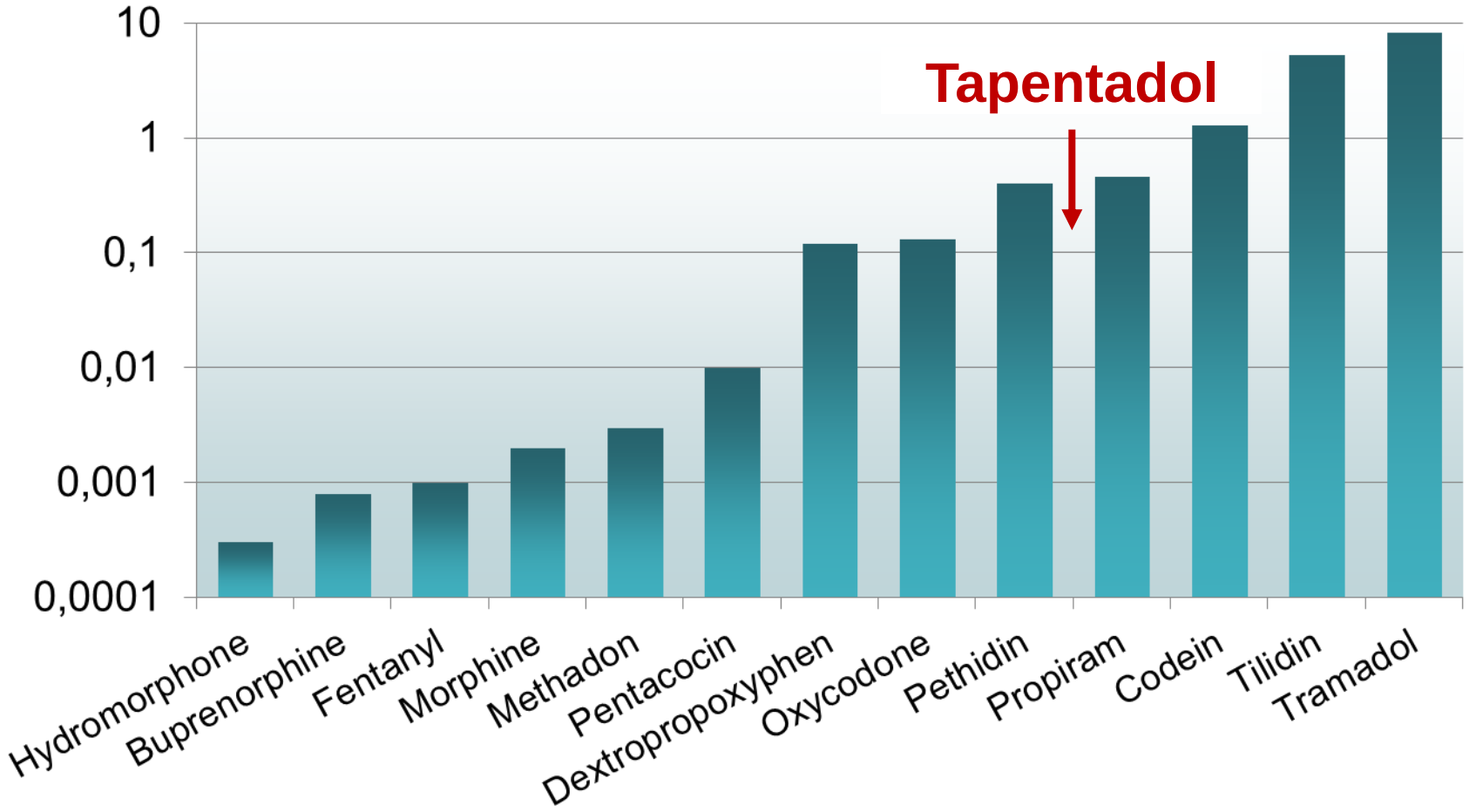
Tapentadol – A New Analgesic with a Dual Mode of Action

μ-Rezeptor-Agonism (MOR) and Noradrenalin Reuptake Inhibition (NRI)

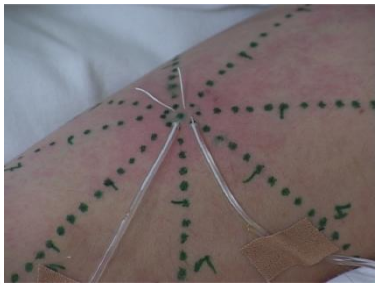


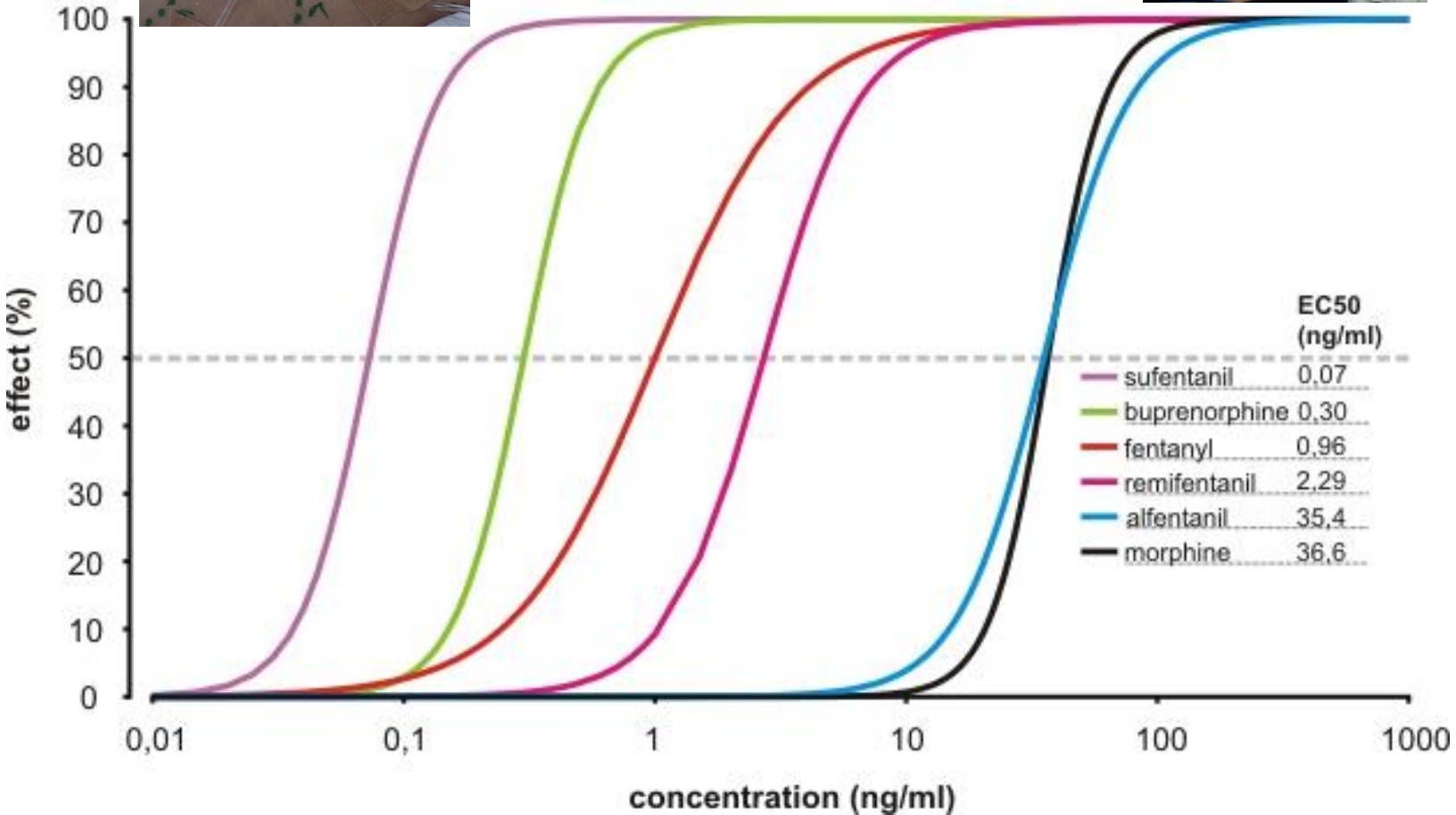
50-fold weaker μ-receptor binding in comparison to Morphine

Binding Affinity of μ-Opioids



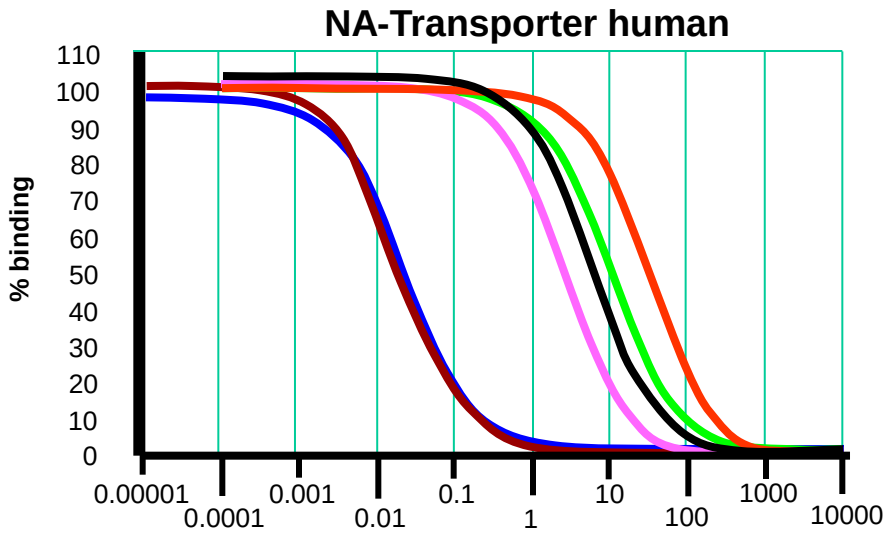
Analgetische Effekte von Opioiden

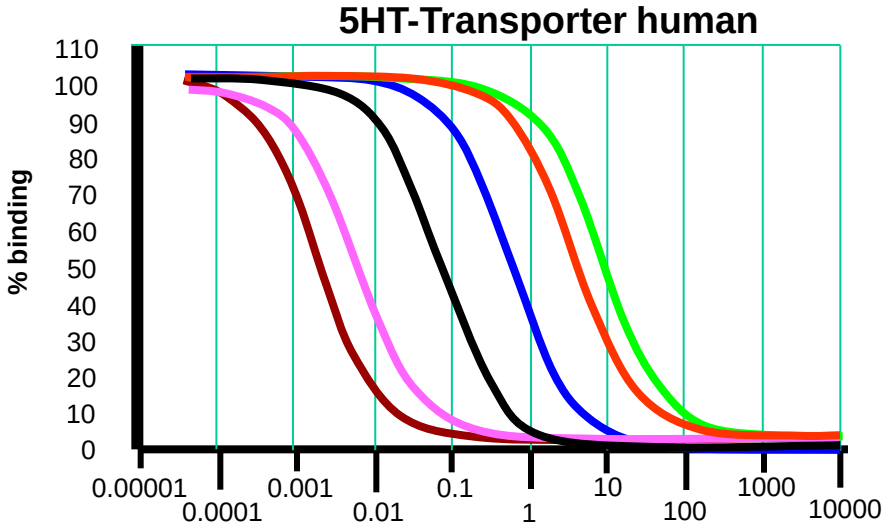


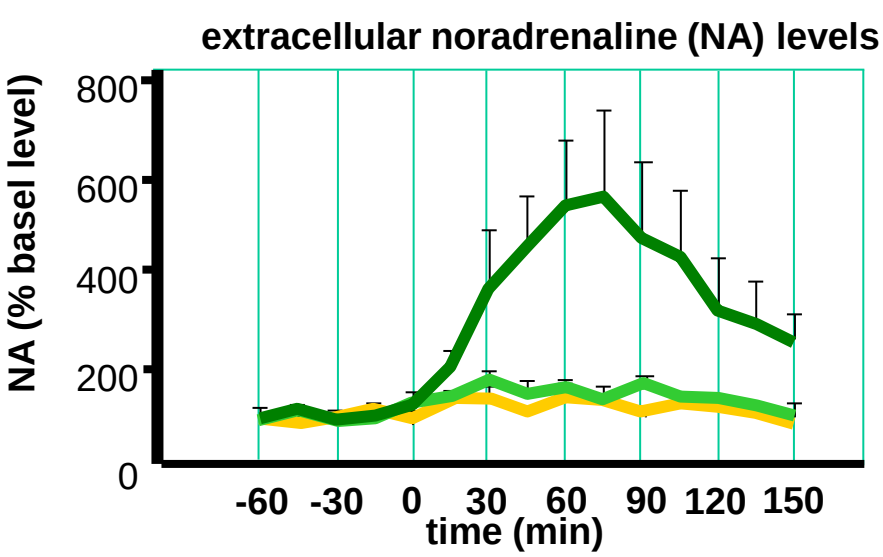


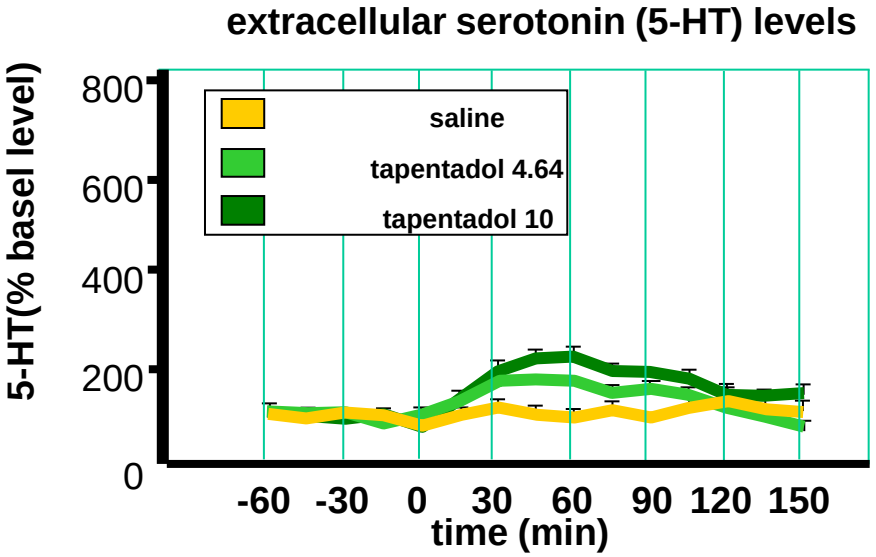
Tapentadol – A New Analgesic with a Dual Mode of Action

Effect on Noradrenalin- und Serotonin



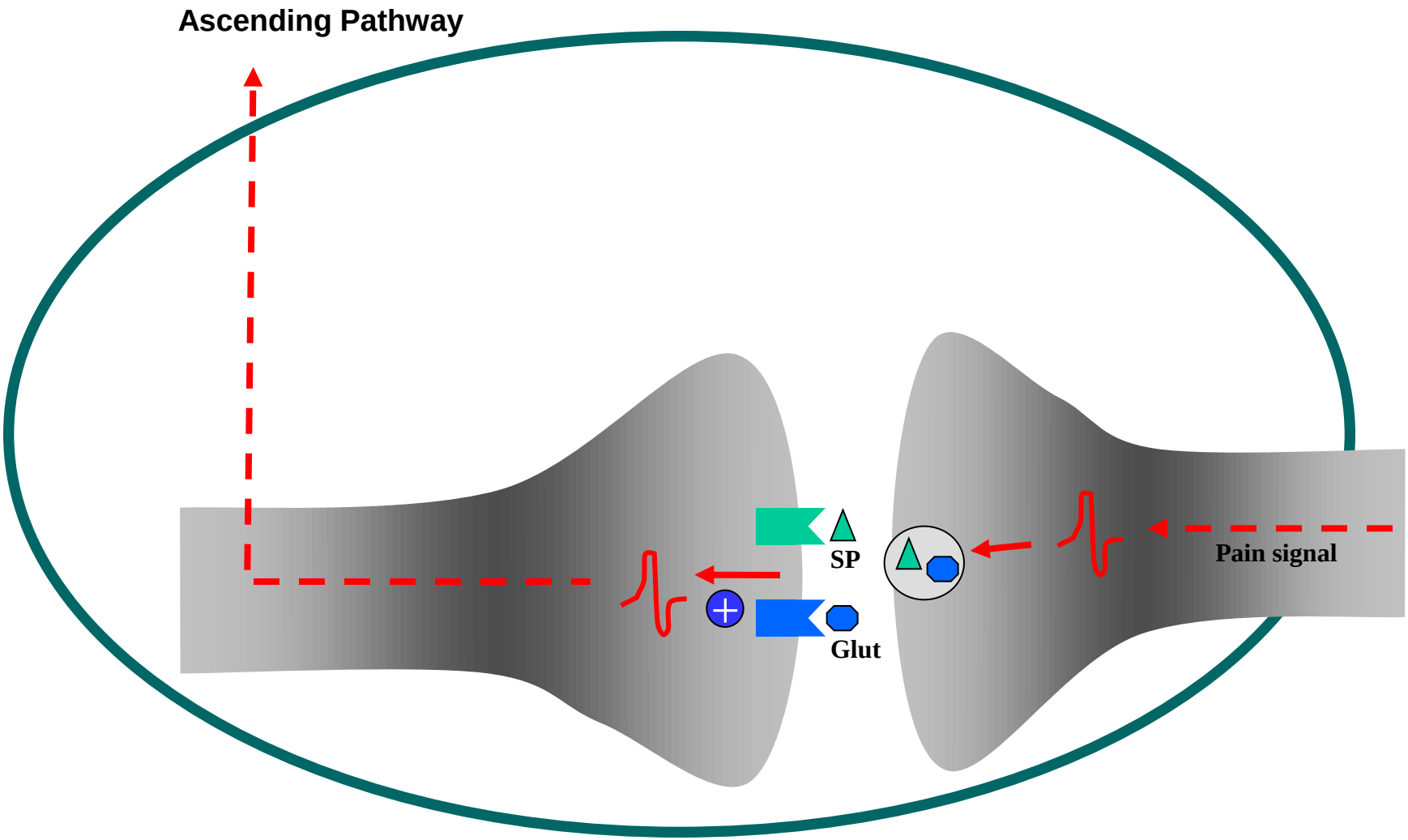




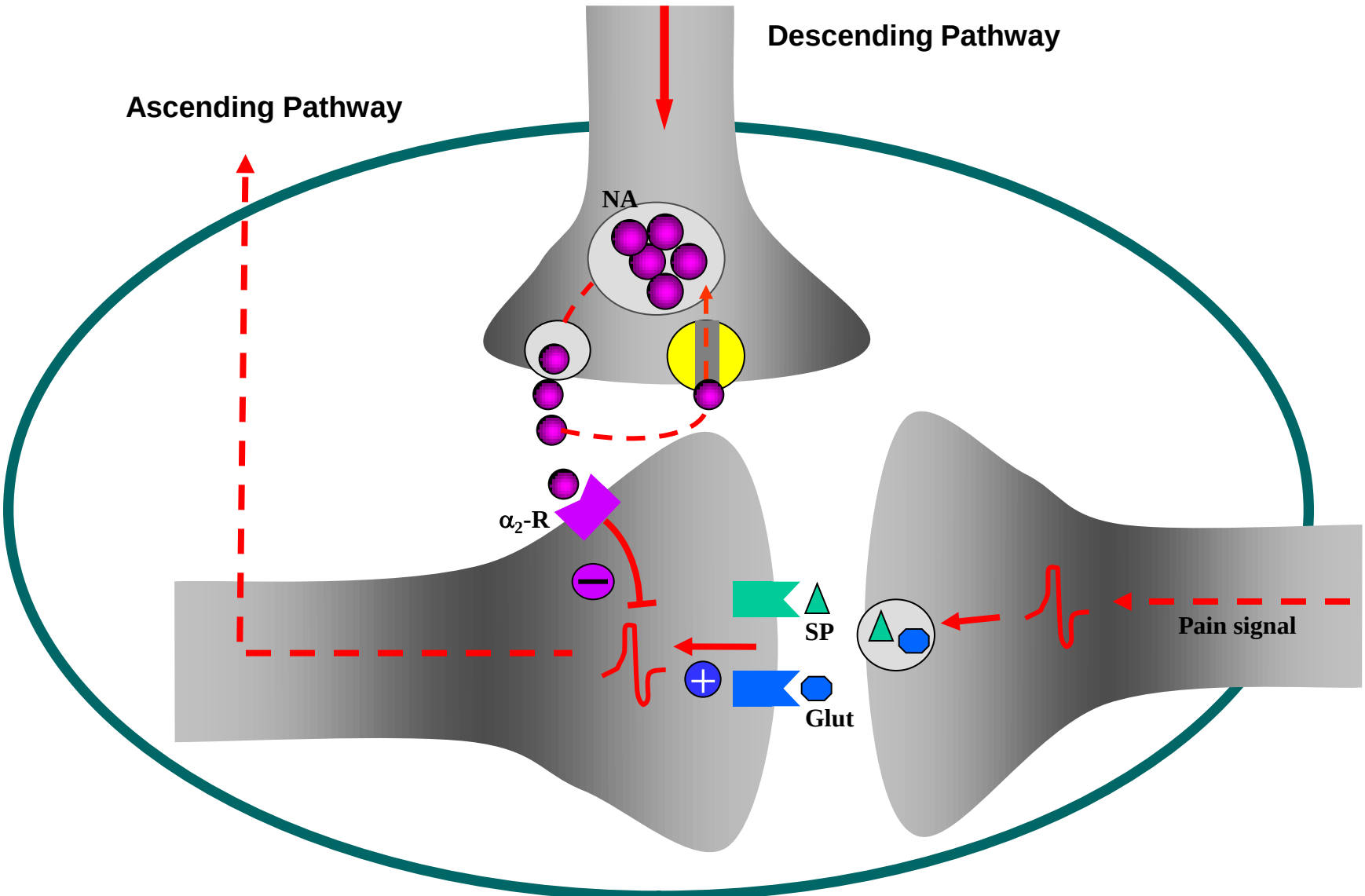


Tzschentke, JPET 2007

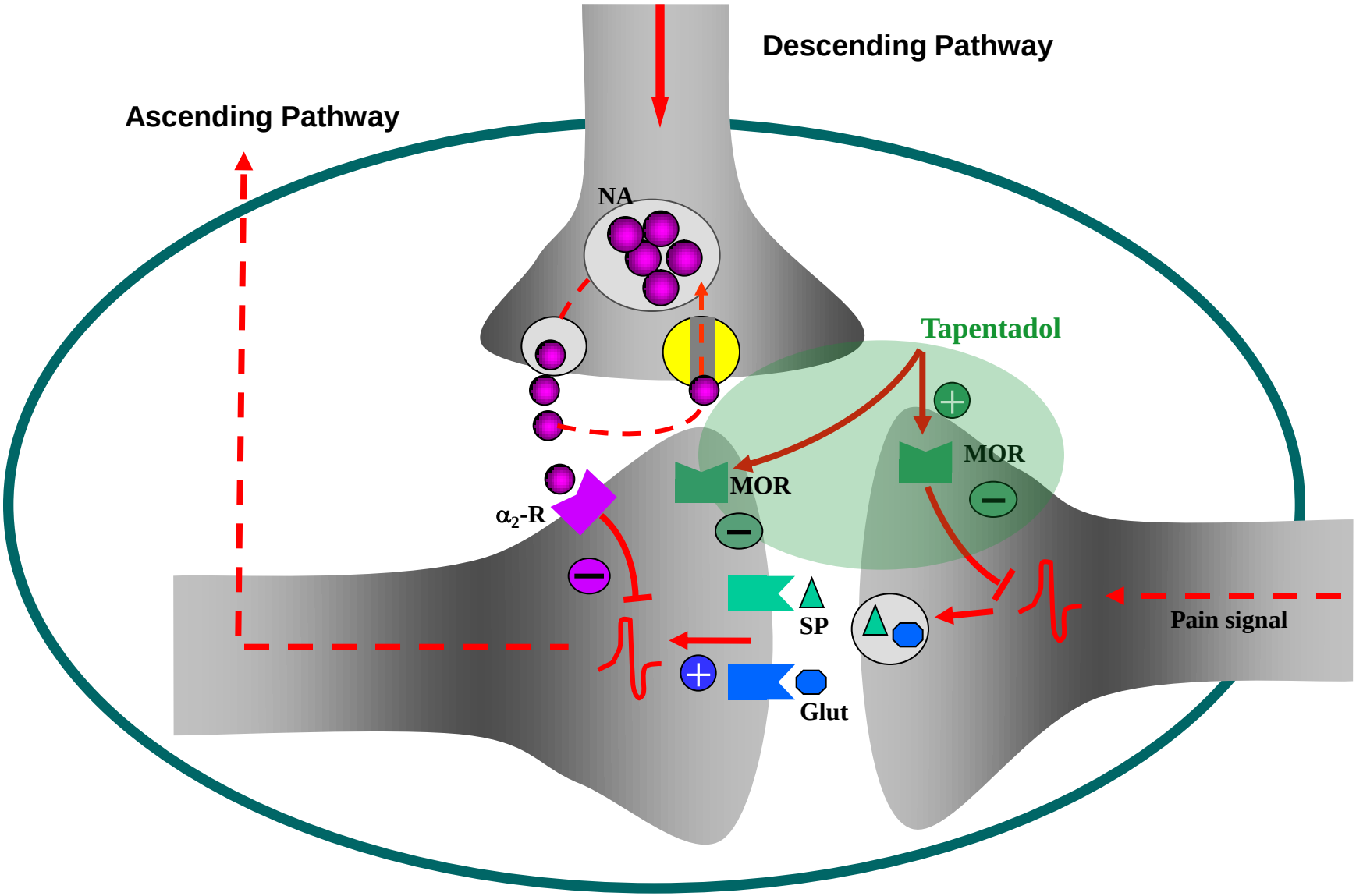
Spinal Mechanism of Action: MOR-NRI



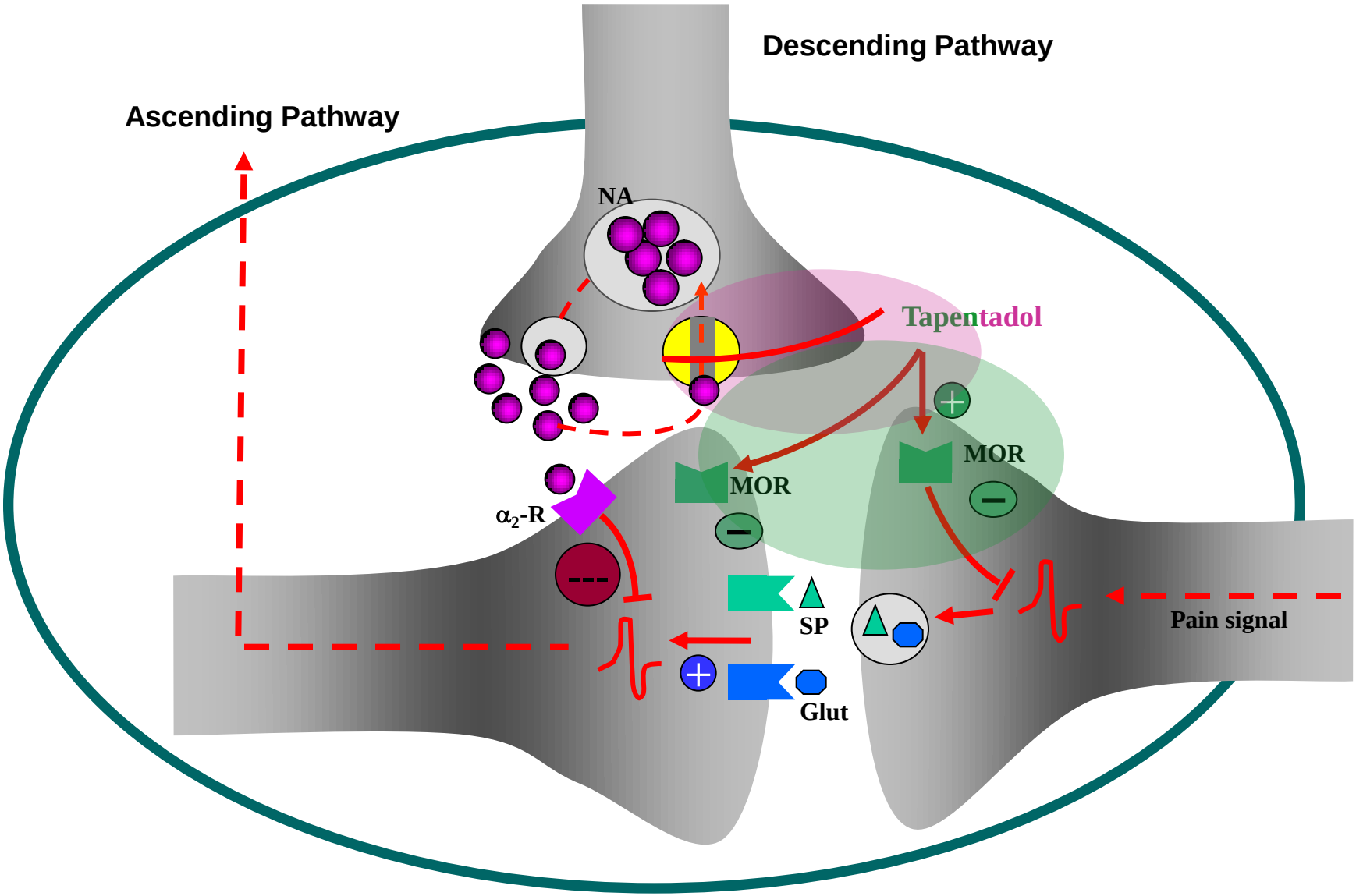
Spinal Mechanism of Action: MOR-NRI



Spinal Mechanism of Action: MOR-NRI

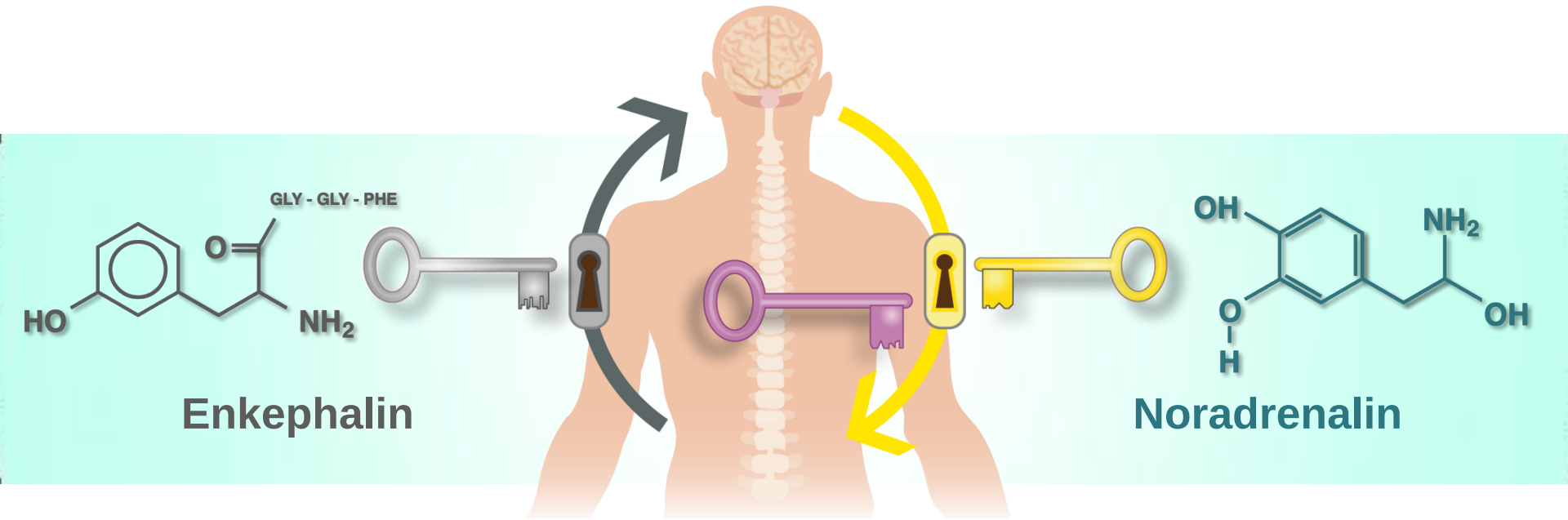


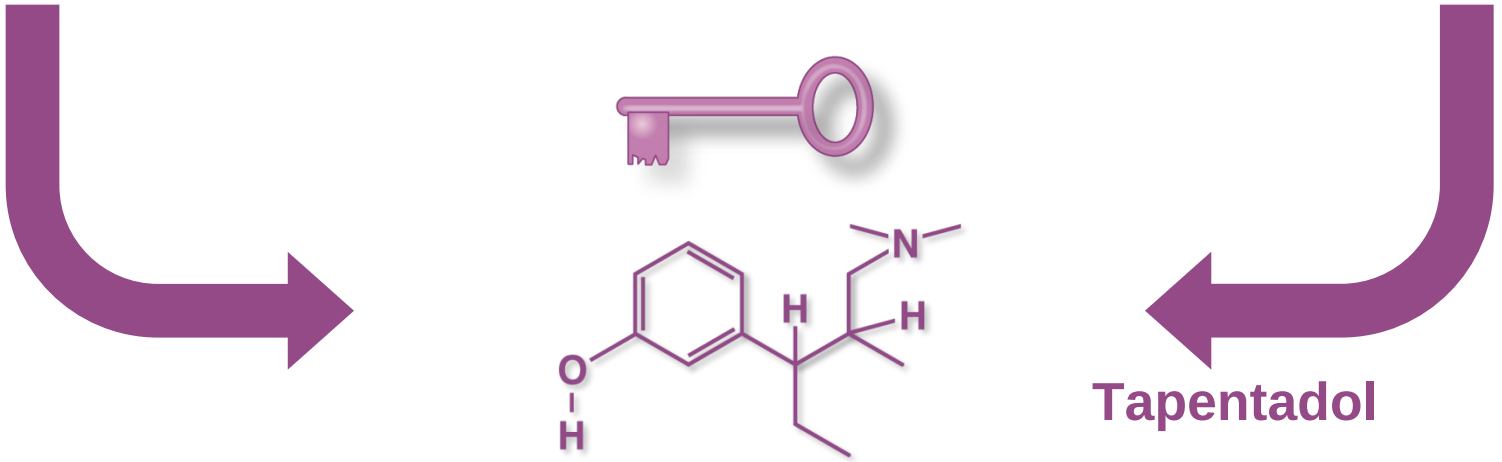
Spinal Mechanism of Action: MOR-NRI



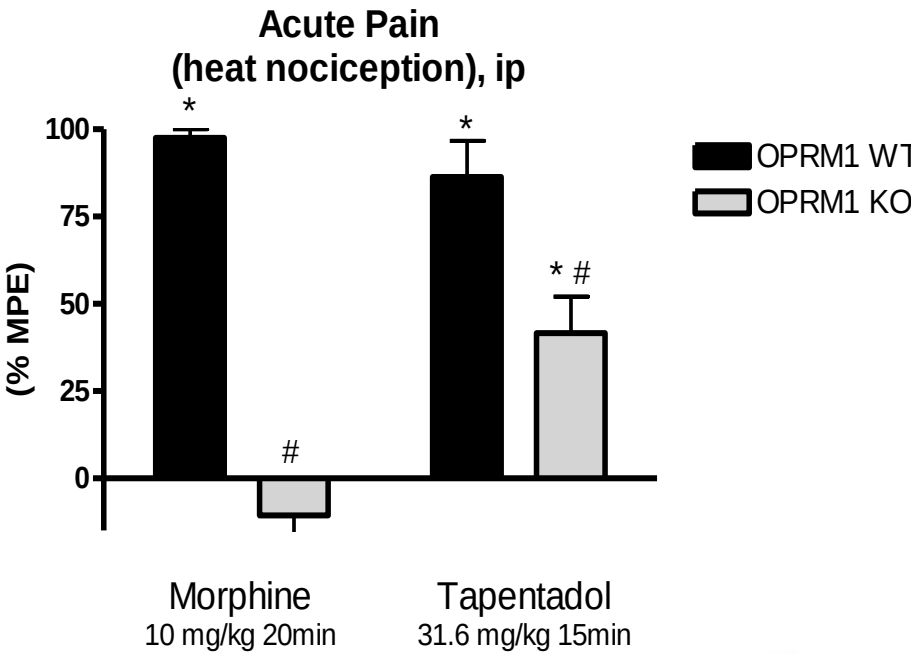
Tapentadol – A New Analgesic with a Dual Mode of Action

Neue Substanzklasse MOR-NRI

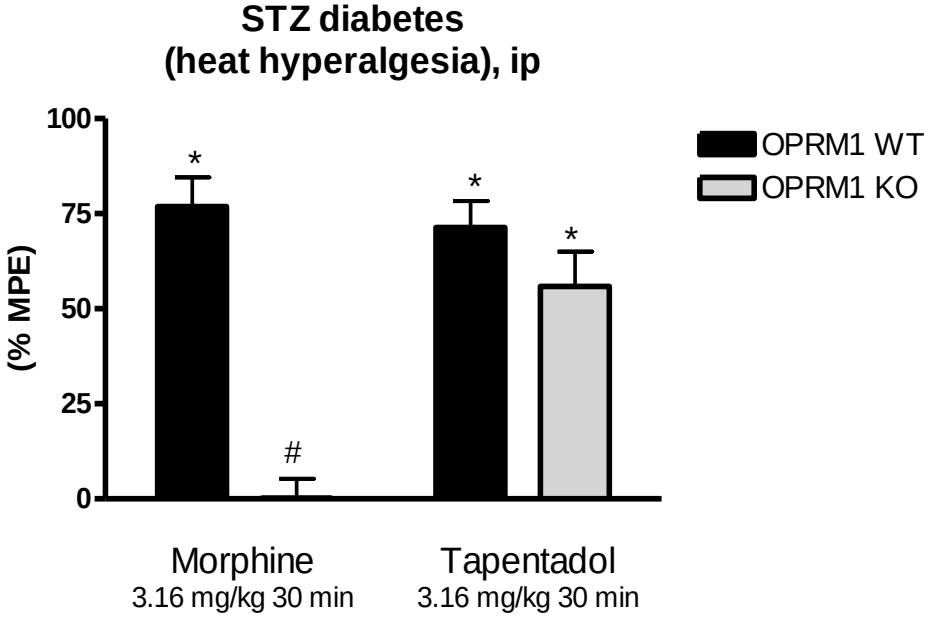




Tapentadol: Activityt in MOR knock-out- und Wildtype-Mice



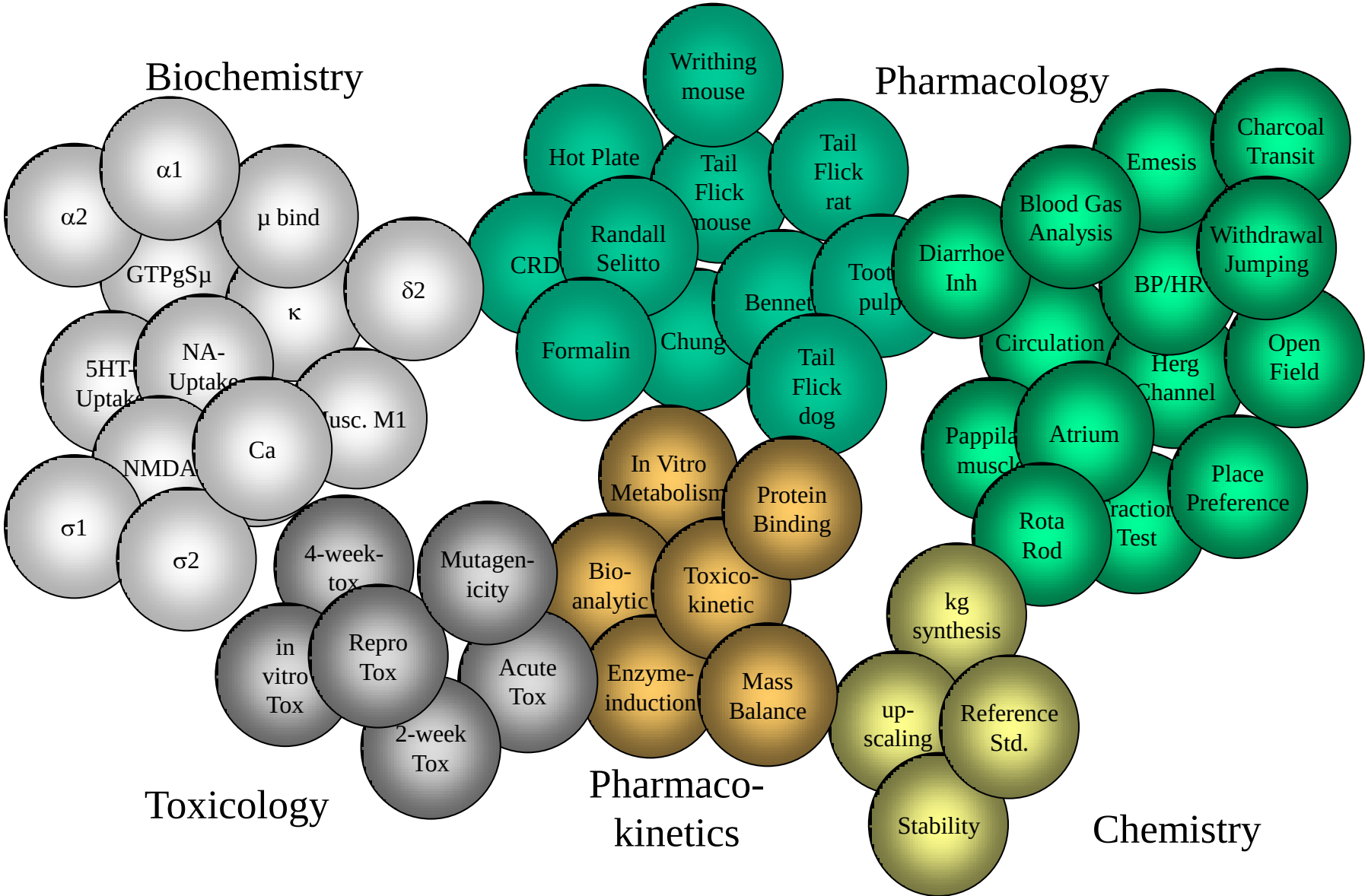
* p<0.05 treatment vs vehicle
# p<0.05 KO vs WT



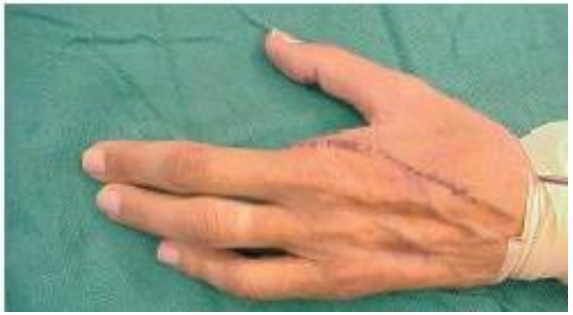
* p<0.05 treatment vs vehicle
# p<0.05 KO vs WT

Tapentadol remains partially active in MOR-Knock-out Mice

Characterization of Compounds

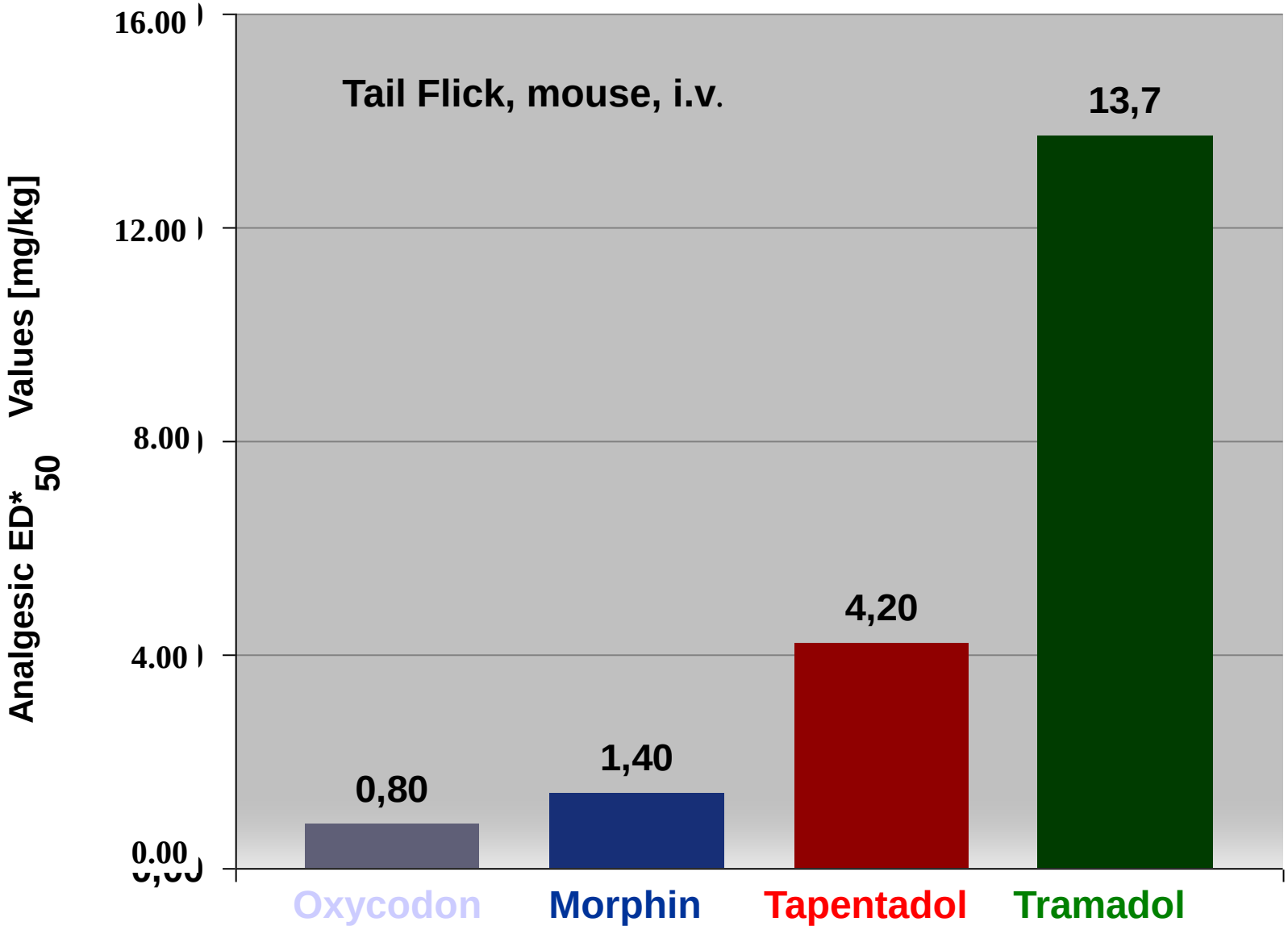


Pharmacology: Pain Models

Acute	Chronic inflammatory	Chronic neuropathic
		
		

Tapentadol – *in vivo* Pharmacology

Analgesic Potency in Acute Pain

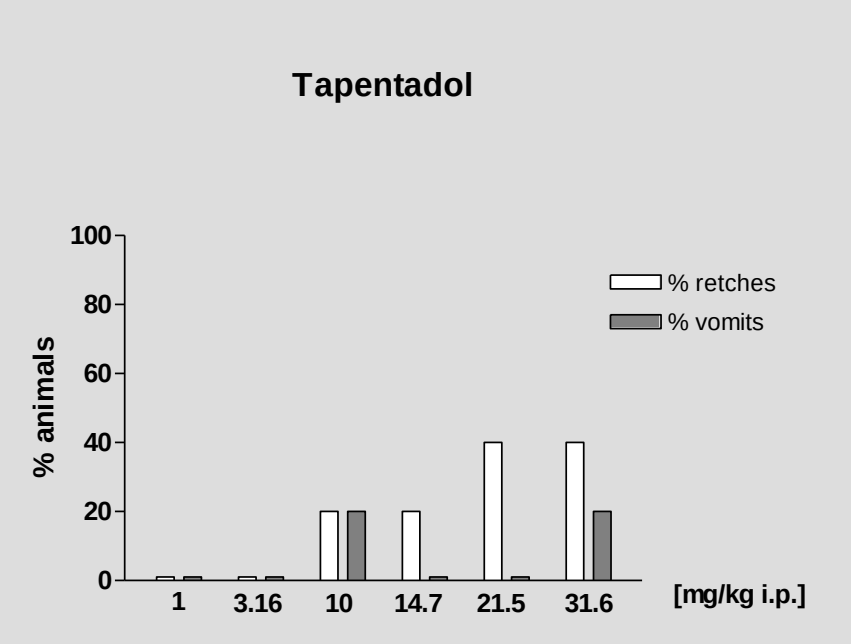


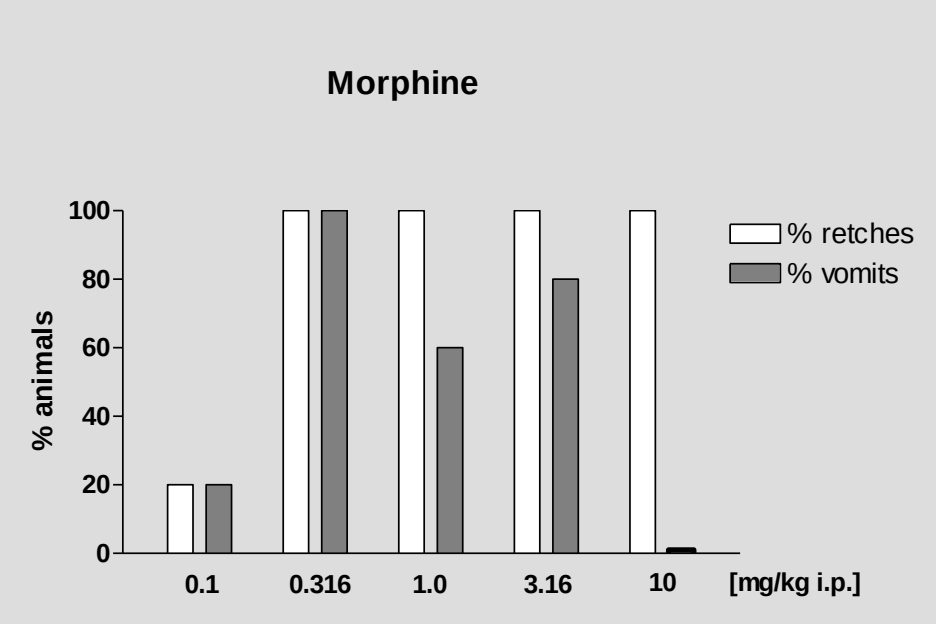
Tapentadol – *in vivo* Pharmacology – Side Effects

Tapentadol

Morphin

Opioid Induced Side Effects: Emesis





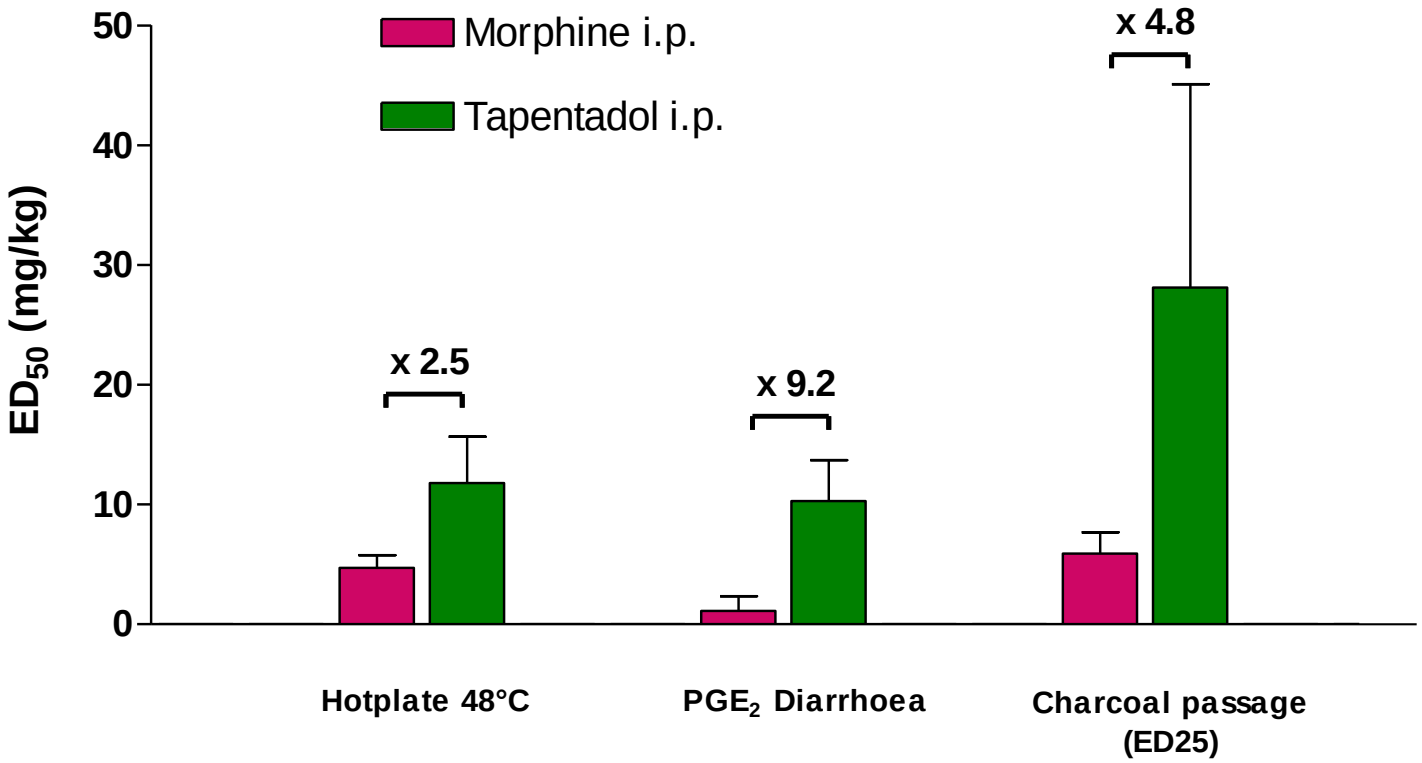
Tzschentke et al (2006) Drugs Fut 31:1053ff

Tapentadol shows a reduced emetic potential in comparison to Morphine

Opioid Induced Side Effects: Obstipation

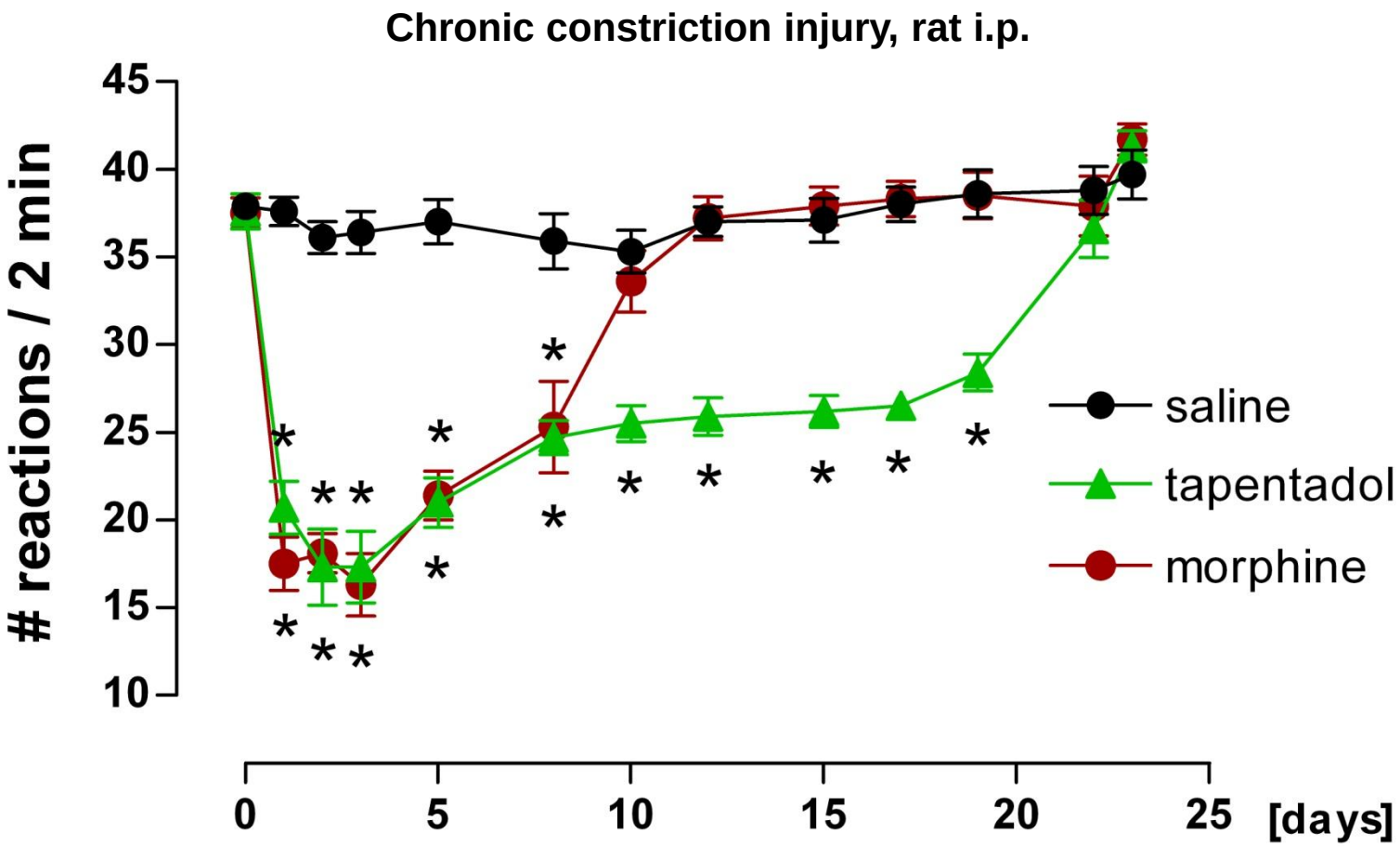
- **Increase of the intestinal charcoal passage**
- **Reduction of the PGE2 induced diarrhoe**

Opioid Induced Side Effects: Obstipation



Tapentadol shows a reduced gastrointestinal inhibitory potential in comparison to Morphine

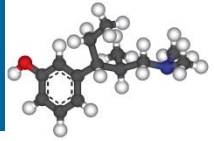
Opioid Induced Side Effects: Tolerance Development



Tzschentke et al (2007) JPET 323:265ff

Significant reduced tolerance development

Tapentadol – *in vivo* Pharmacology – Side Effects



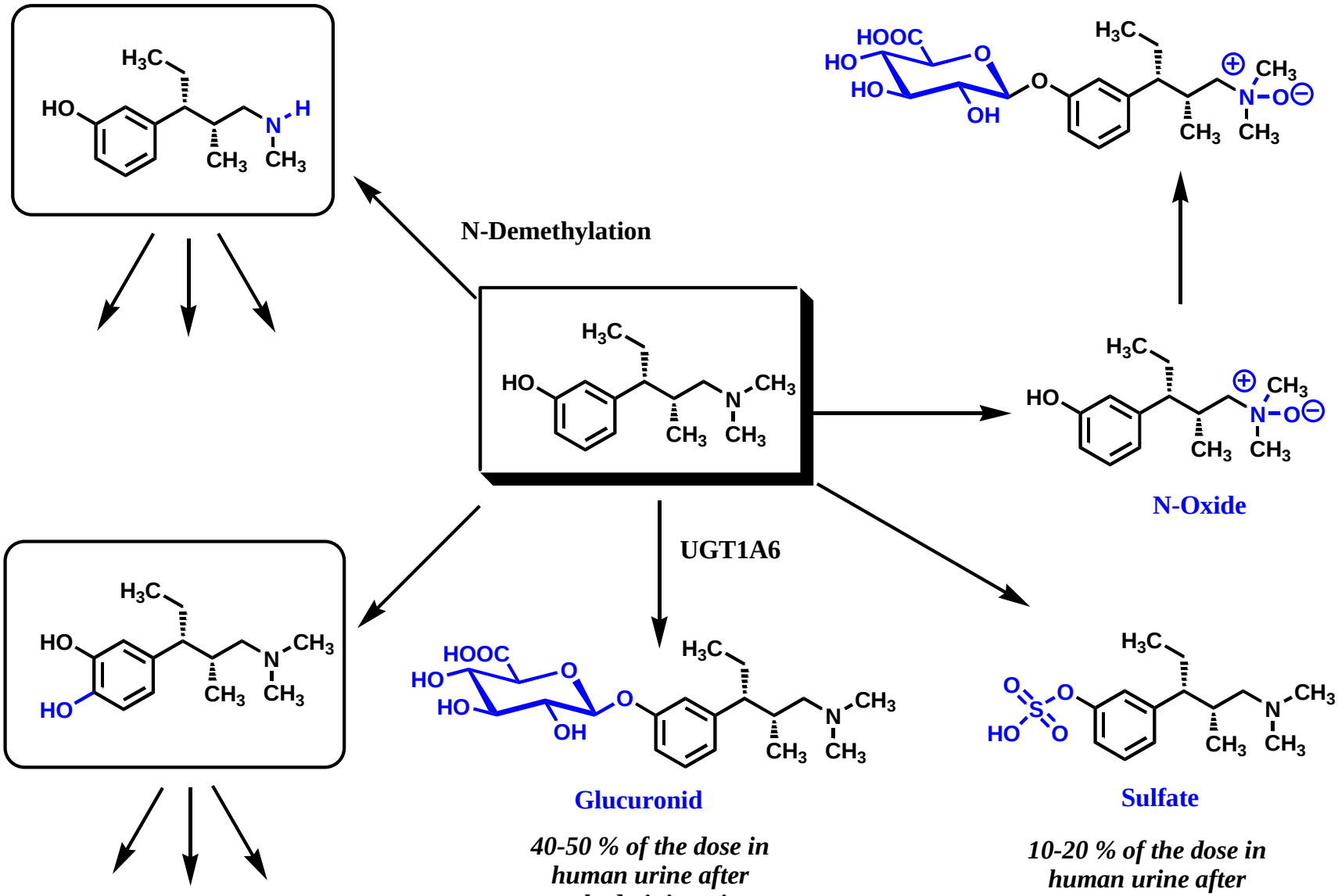
Overview of the analgesic activity of tapentadol and morphine in various animal models of acute and chronic pain

Pain model	Route of application	ED_{50} value (mg/kg)	
		Tapentadol	Morphine
Tail-flick (mouse)	i.v.	4.2	1.4
	p.o.	53.4	18.9
	i.c.v.*	65.0	0.4
Tail-flick (rat)	i.v.	2.2	1.1
	i.p.	10.0	5.8
	p.o.	121	55.7
Tail-flick (dog)	i.v.	4.3	0.7
Hot-plate 48° C (mouse)	i.v.	3.3	1.3
Hot-plate 58° C (mouse)	i.p.	27.7	8.5
Phenylquinone-induced writhing (mouse)	i.v.	0.7	0.4
	p.o.	31.3	4.7
	i.c.v.*	18.4	0.08
Tooth pulp stimulation (rabbit)	i.v.	3.1	2.3
Formalin (phase II) (rat)	i.p.	3.8	0.8
Yeast model (rat)	i.v.	2.0	0.9
	i.p.	10.1	5.6
	i.t.*	56.8	1.9
Colorectal distension-induced visceral pain (rat)	i.v.	5.5	3.5
Mustard oil-induced visceral pain (rat)	i.v.	1.5	1.0
Spinal nerve injury neuropathy (rat)	i.p.	8.3	2.9
Chronic constriction injury neuropathy (rat)	i.p.	13.0	13.8
Vincristine polyneuropathy (rat)	i.p.	5.1	3.4
Diabetic polyneuropathy (rat)	i.p.	8.9	3.0

*Dose in µg/animal. [1]All drug doses for preclinical and clinical testing are for the hydrochloride salt.

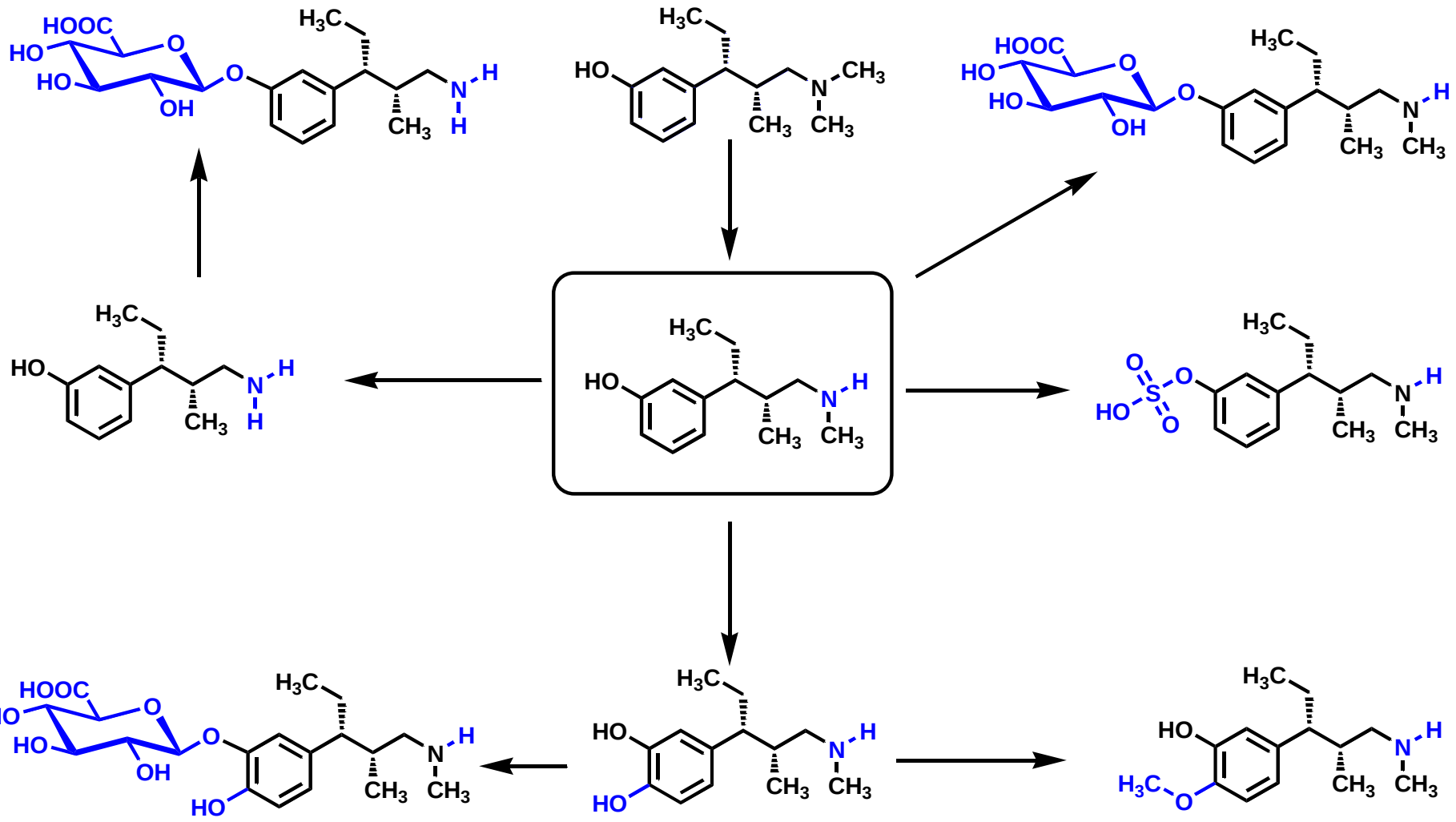
Tapentadol – *in vivo* Pharmacology – Metabolism

Metabolic Pathway



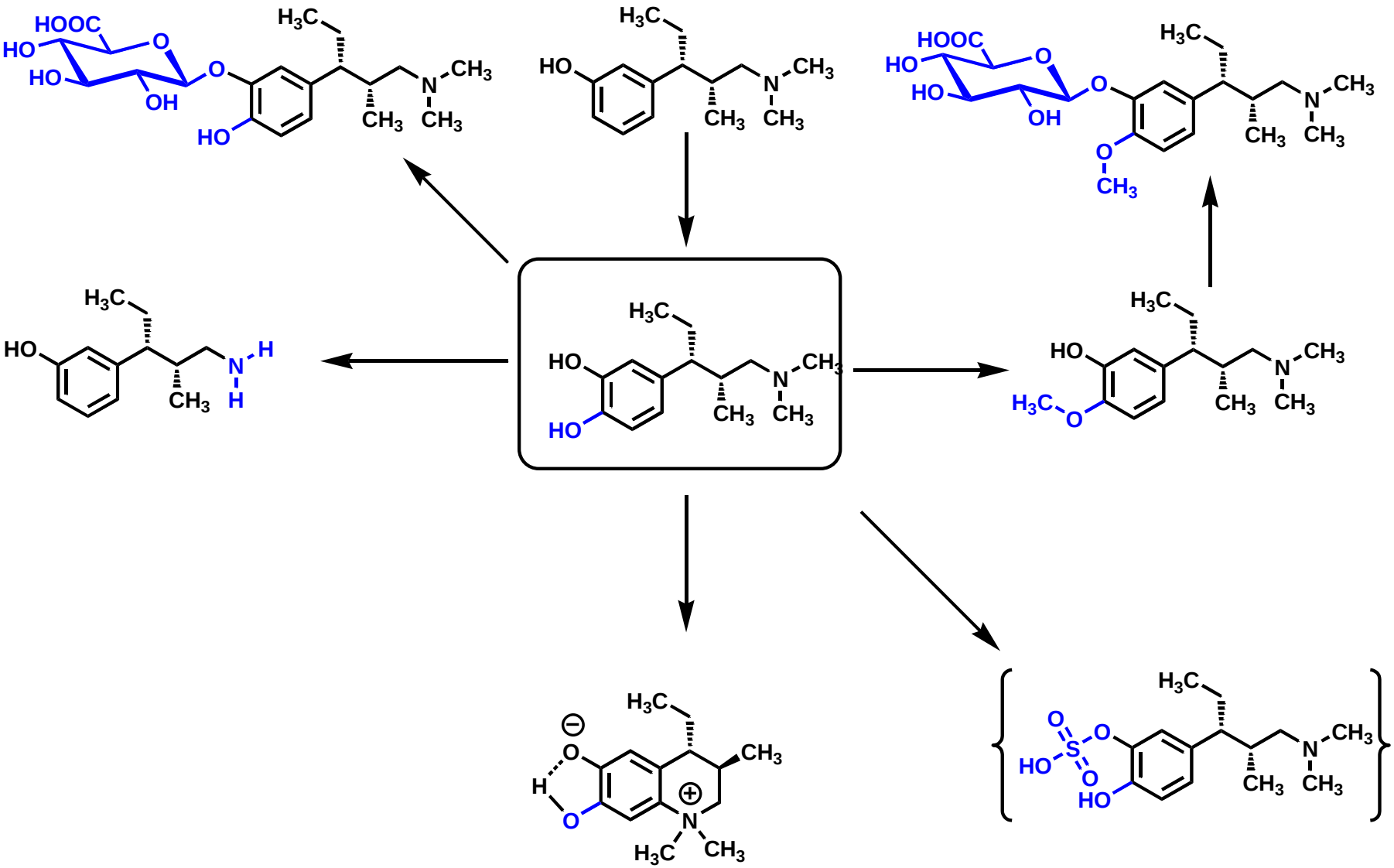
Tapentadol – *in vivo* Pharmacology – Metabolism

Metabolic Pathway

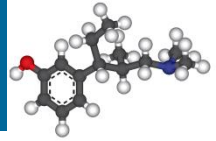


Tapentadol – *in vivo* Pharmacology – Metabolism

Metabolic Pathway



Phenolate Betaine



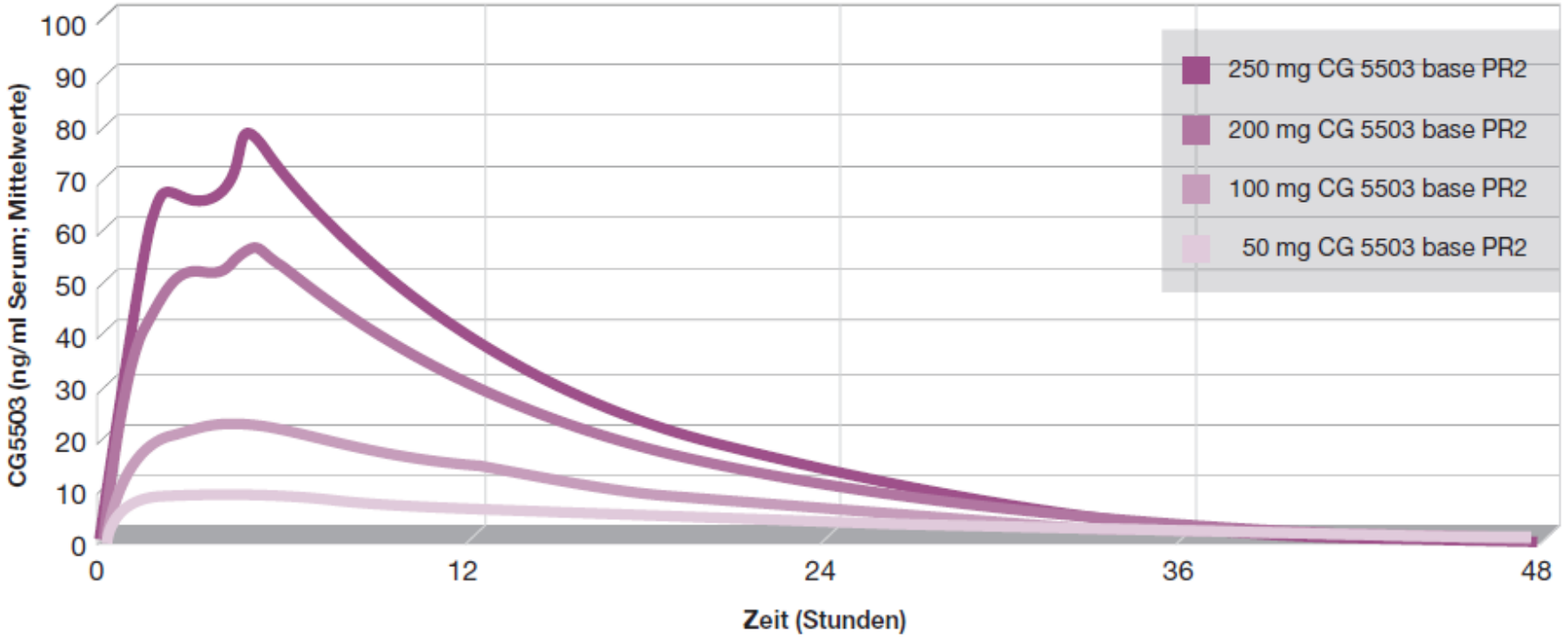
Tapentadol – Pharmakokinetik

Mittlere pharmakokinetische Parameter nach einer Einzeldosis PALEXIA® retard, Dosis normiert auf 200 mg Tapentadol

Parameter	N	Mittelwert +/- SA
AUC_{last} ng.h/ml	294	789 +/- 219
AUC_{inf}, ng.h/ml	292	805 +/- 220
$t_{1/2}$, h	292	5,9 +/- 2,0
CL_F, ml/min	292	4449 +/- 1199

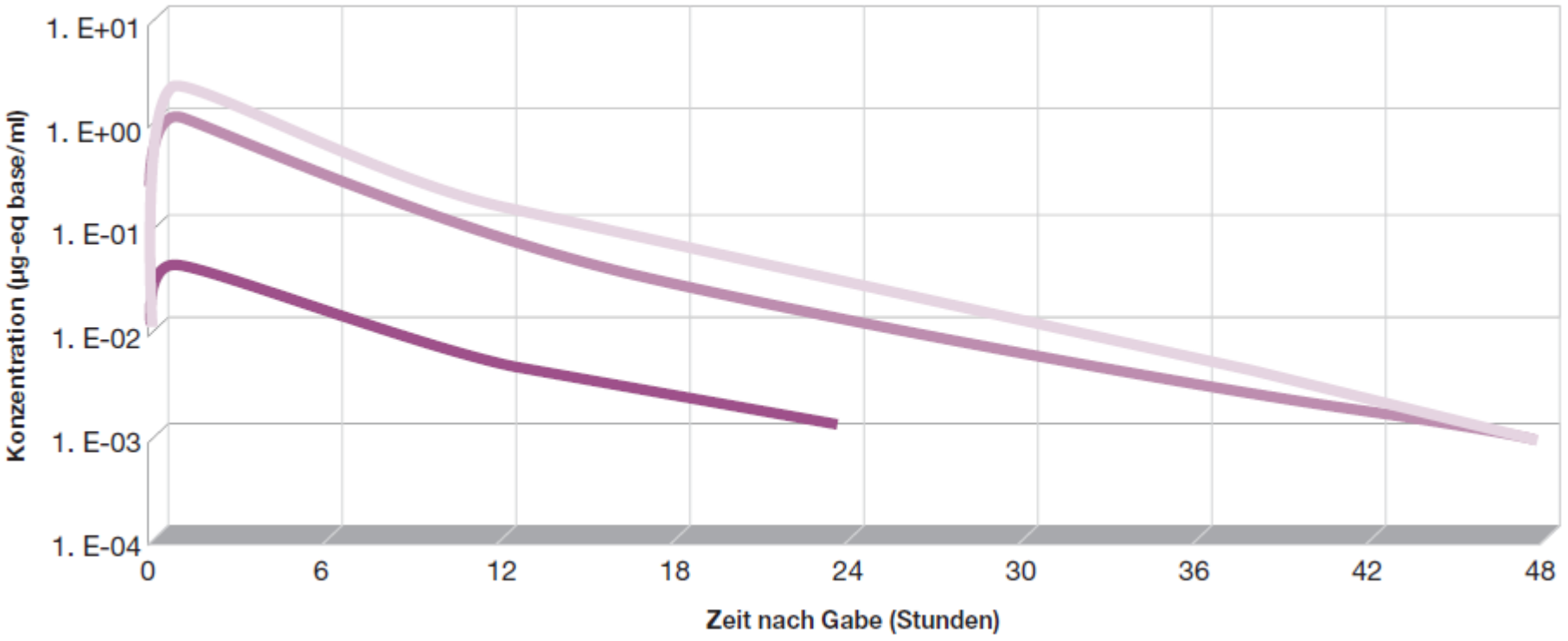
Tapentadol – Pharmakokinetik

Mittlere Serumkonzentration – Zeitprofile für CG5503-Base nach Einzeldosisgabe von CG5503-Base PR2 50, 100, 200 und 250 mg

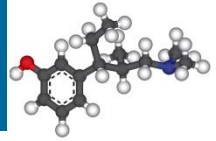


Tapentadol – Pharmakokinetik

Durchschnittliche Konzentrations- versus Zeitprofile von Tapentadol-Konjugaten, Tapentadol und Radiokohlenstoff nach oraler Verabreichung von 100 mg 14C-markiertem Tapenta dol-HCl (1,867 MBq Radiokohlenstoff) an 4 gesunden männlichen Probanden (Terlinden et al. 2006)



Werte entsprechen arithmetischen Mittelwerten, aufgeführt als semilogarithmische Koordinaten.



Tapentadol – Pharmakokinetik

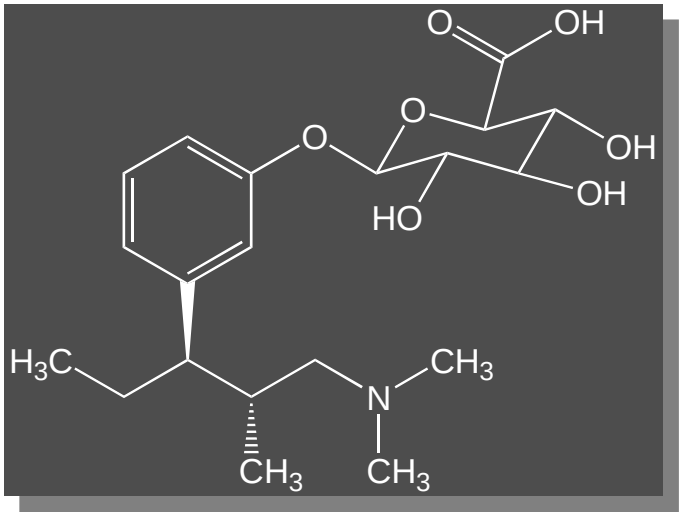
**Ausscheidung von Tapentadol-HCl bei gesunden Probanden:
Ausscheidungsbilanz für Radiokohlenstoff (% der Dosis) (Terlinden et al. 2006)**

Ausscheidungsweg	Subjekt 1	Subjekt 2	Subjekt 3	Subjekt 4	Mittelwert	SA
Urin	98,7	98,5	99,0	98,3	98,6	0,3
Stuhl (Fäzes)	1,59	0,664	0,870	1,84	1,24	0,57
Ausgeatmetes CO_2	0,039	0,048	< LLOQ	0,020	0,035	0,015
Gesamt	100	99,1	99,8	100	99,9	0,52

SA: Standardabweichung, LLOQ: Untere Quantifizierungsgrenze.

Metabolic Pathway

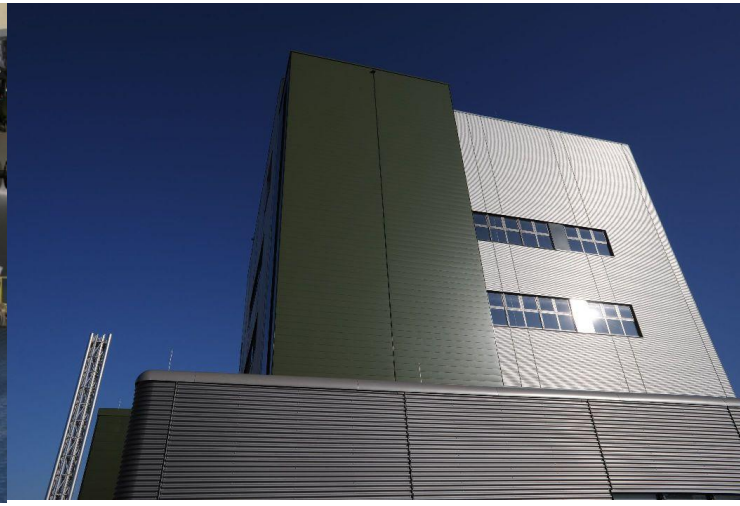
- Major Hepatic metabolism
- Phase 2 Metabolism:
- *O*-Glucuronidierung via UGTs
- 1A6, 1A9, 2B7, no CYP450
- No P-gp Substrate
- No Prodrug
- No analgesic active metabolites
- Low drug-drug interaction potential



Terlinden et al (2007) Eur J Metab Pharmacokinet 32:163ff
Kneip et al (2008) Drug Metab Letters 2:67ff

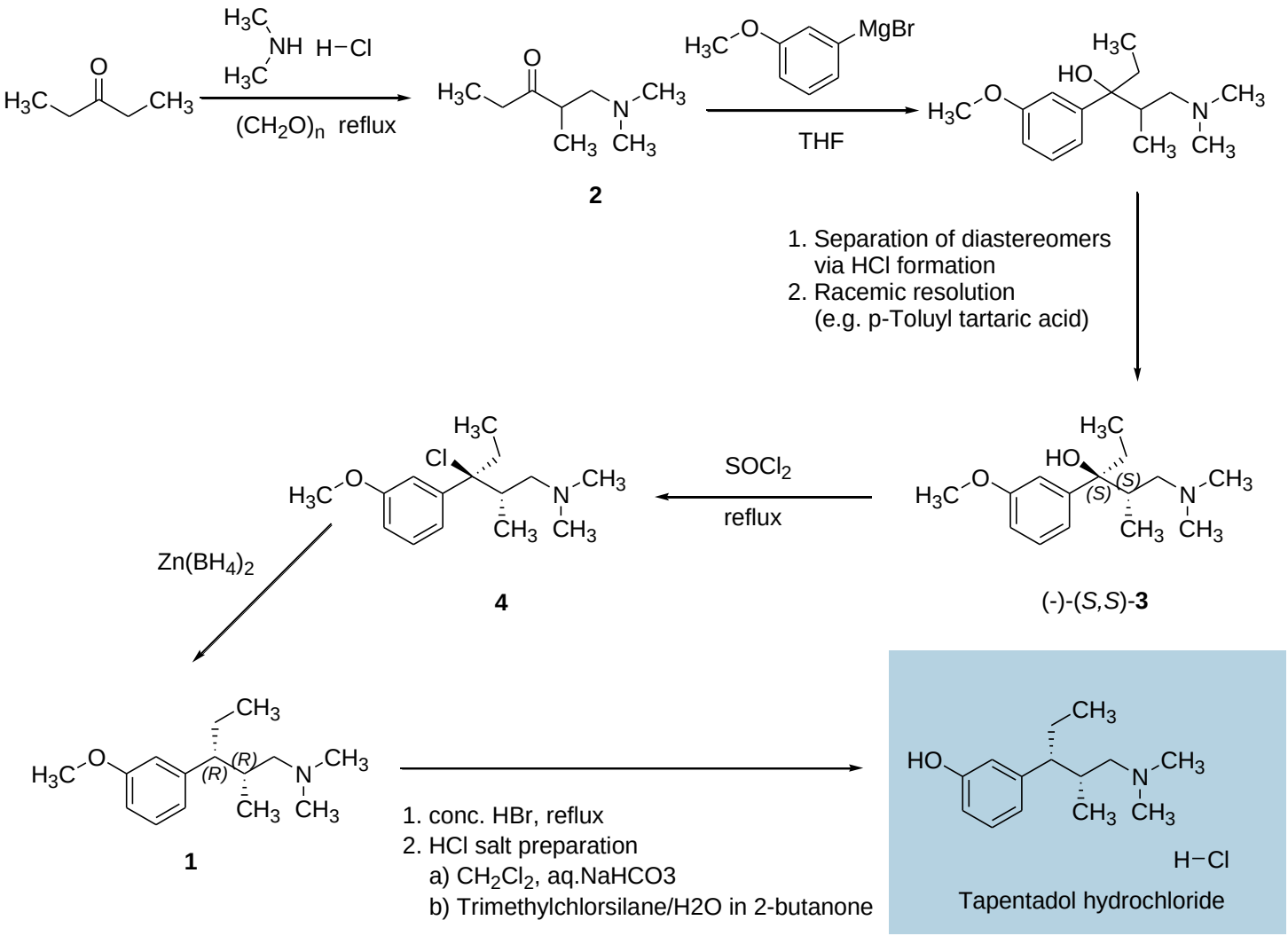
Tapentadol - Synthesis and Manufacture

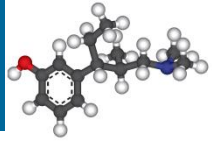


Lab Scale	Kilo-Lab	Pilot Plant	Production
0,1 – 100 g	0,5 – 5 kg	10 – 100 kg	> 50 kg

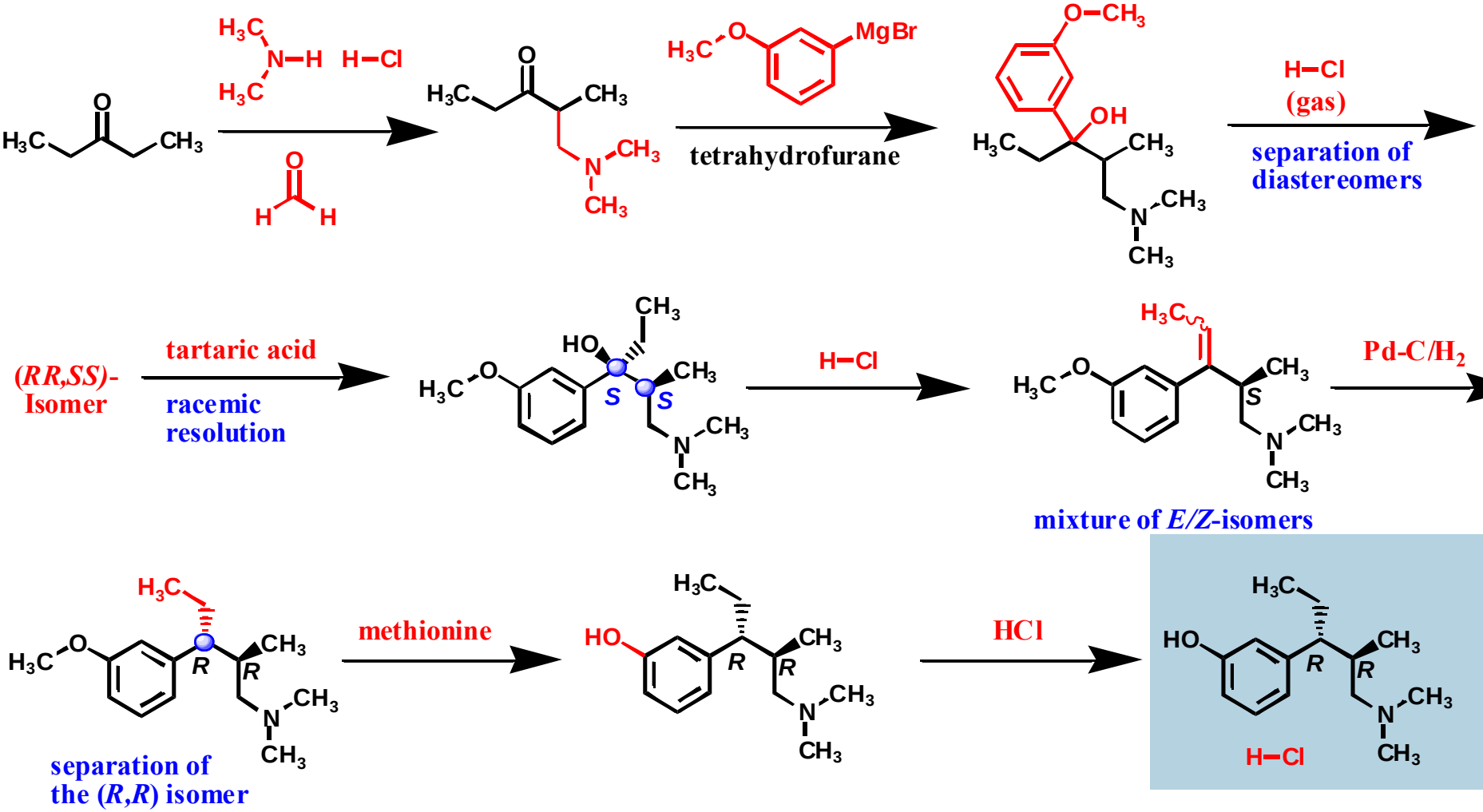
The synthesis of tapentadol hydrochloride as described in the first patent

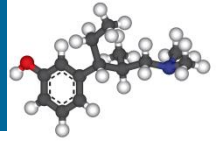




Synthesis of Tapentadol

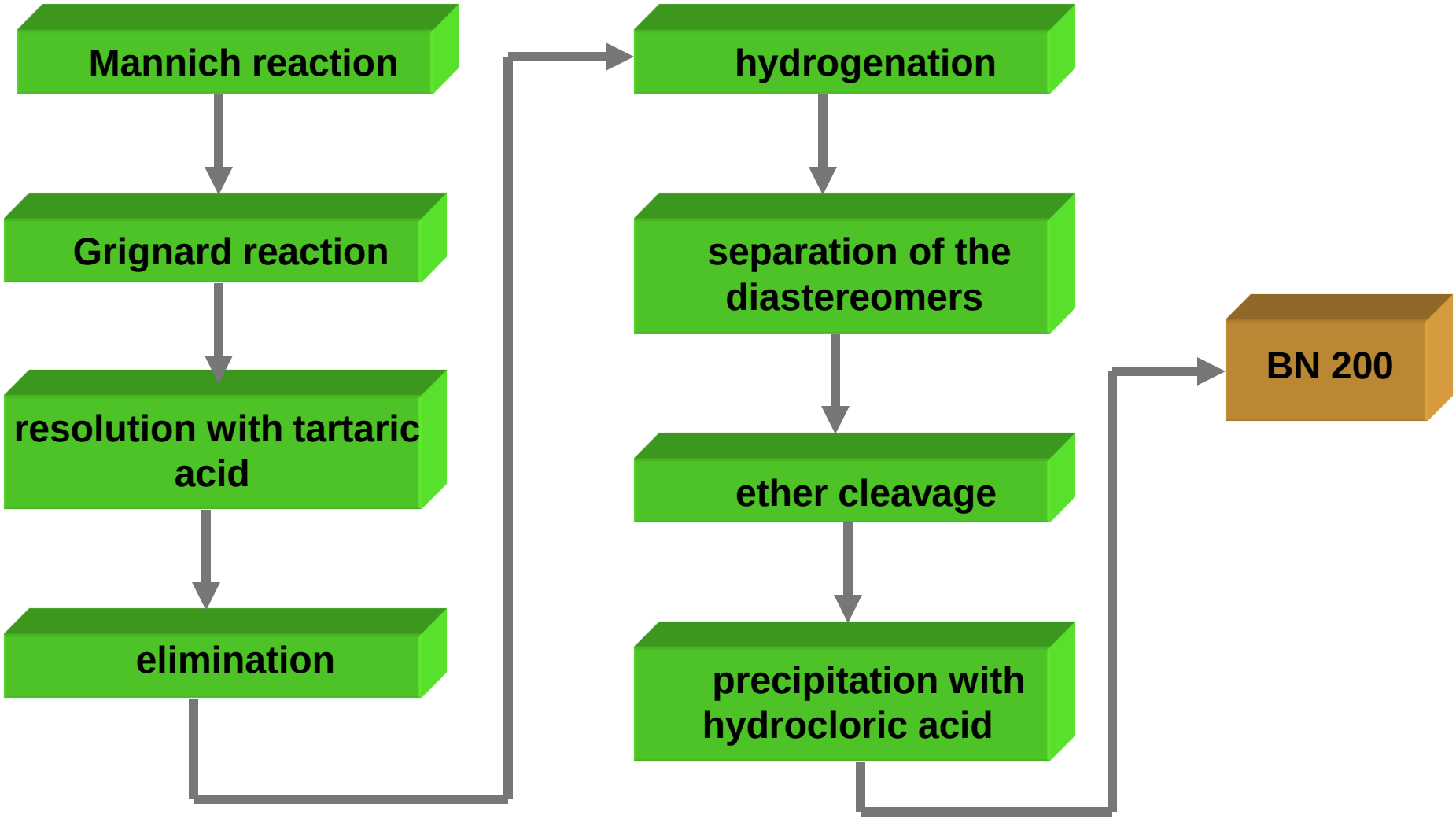
"Historical Route"

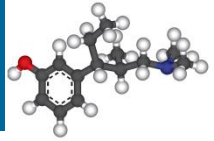




Synthesis of Tapentadol

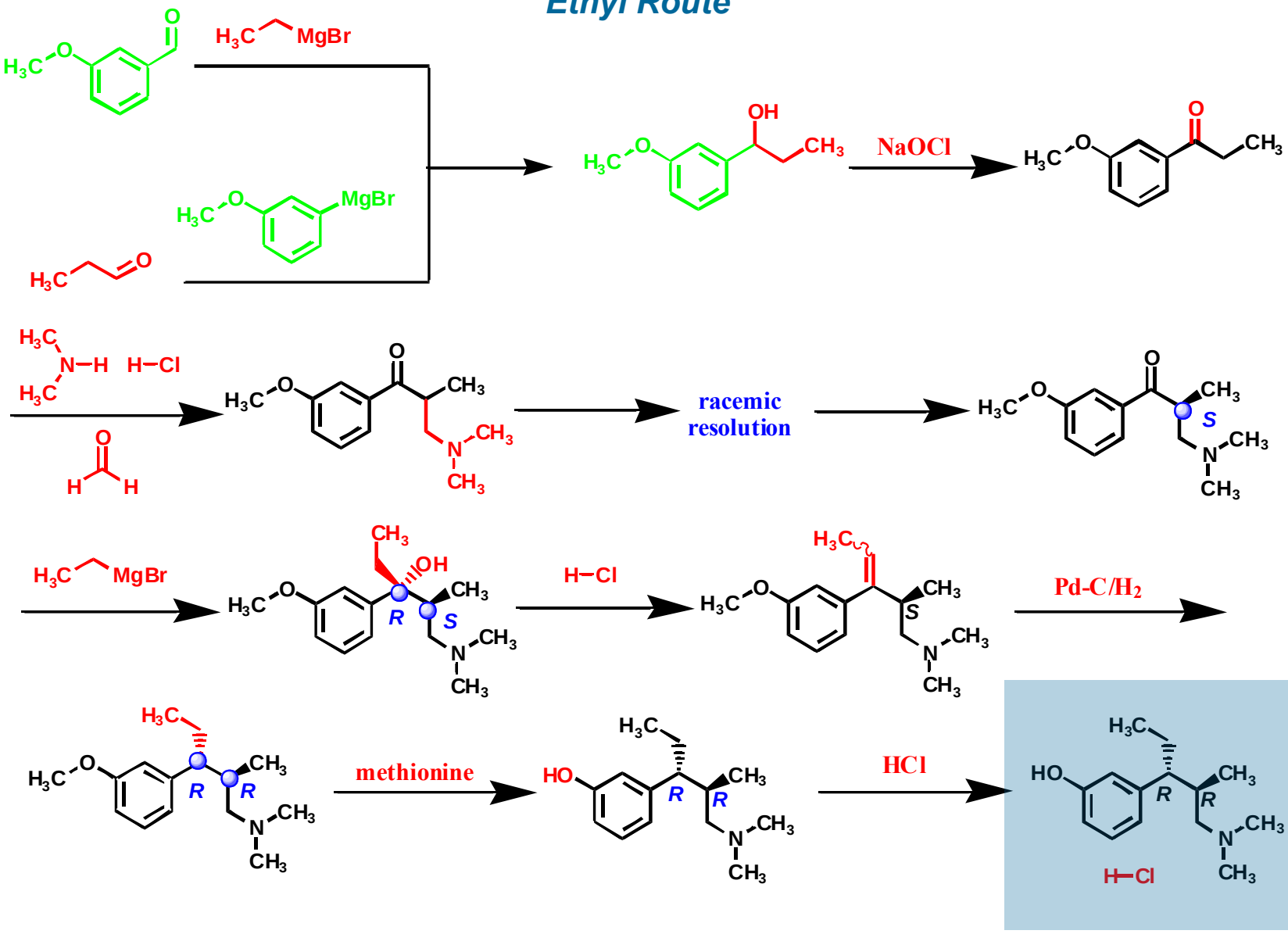
"Historical Route"



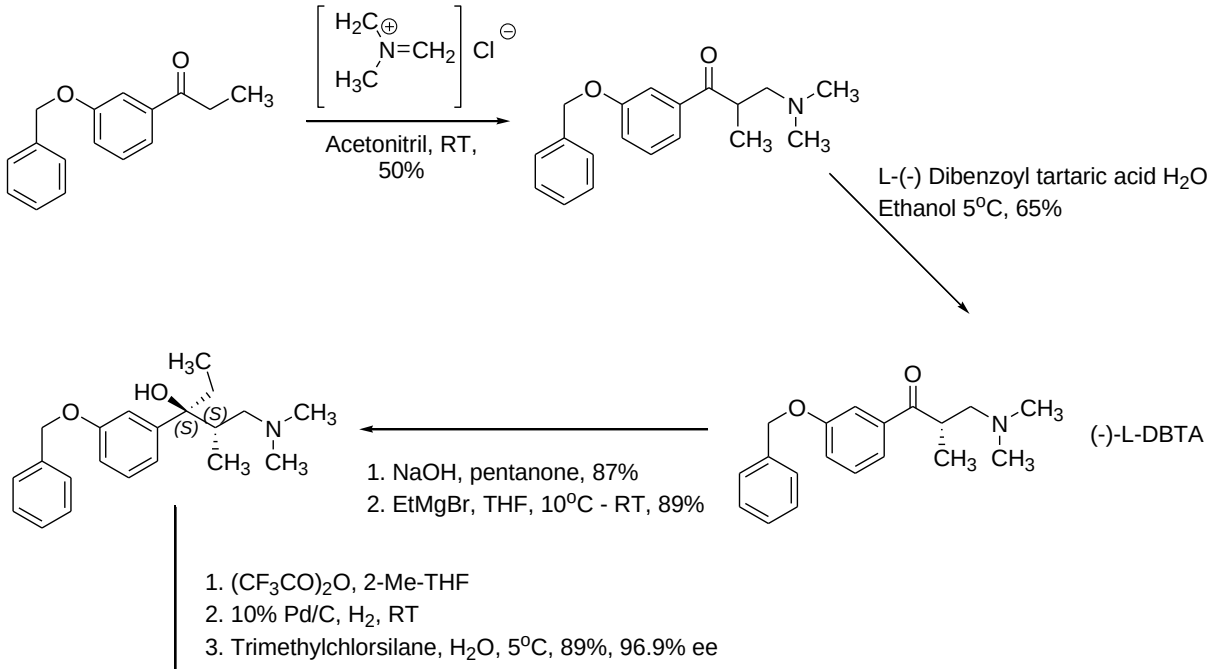


Synthesis of Tapentadol

"Ethyl Route"

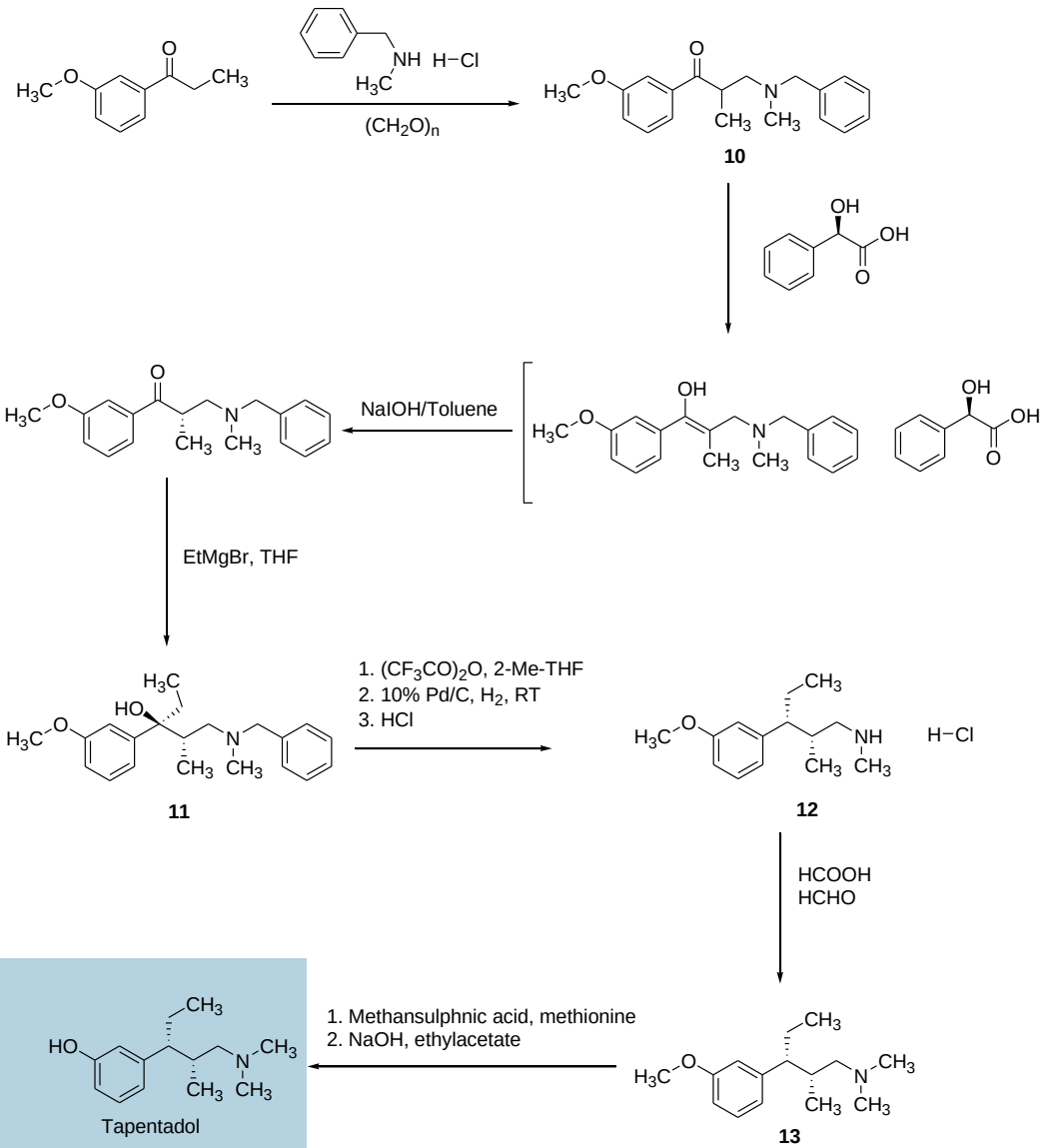


The synthesis of tapentadol hydrochloride according to WO 2008012047A1



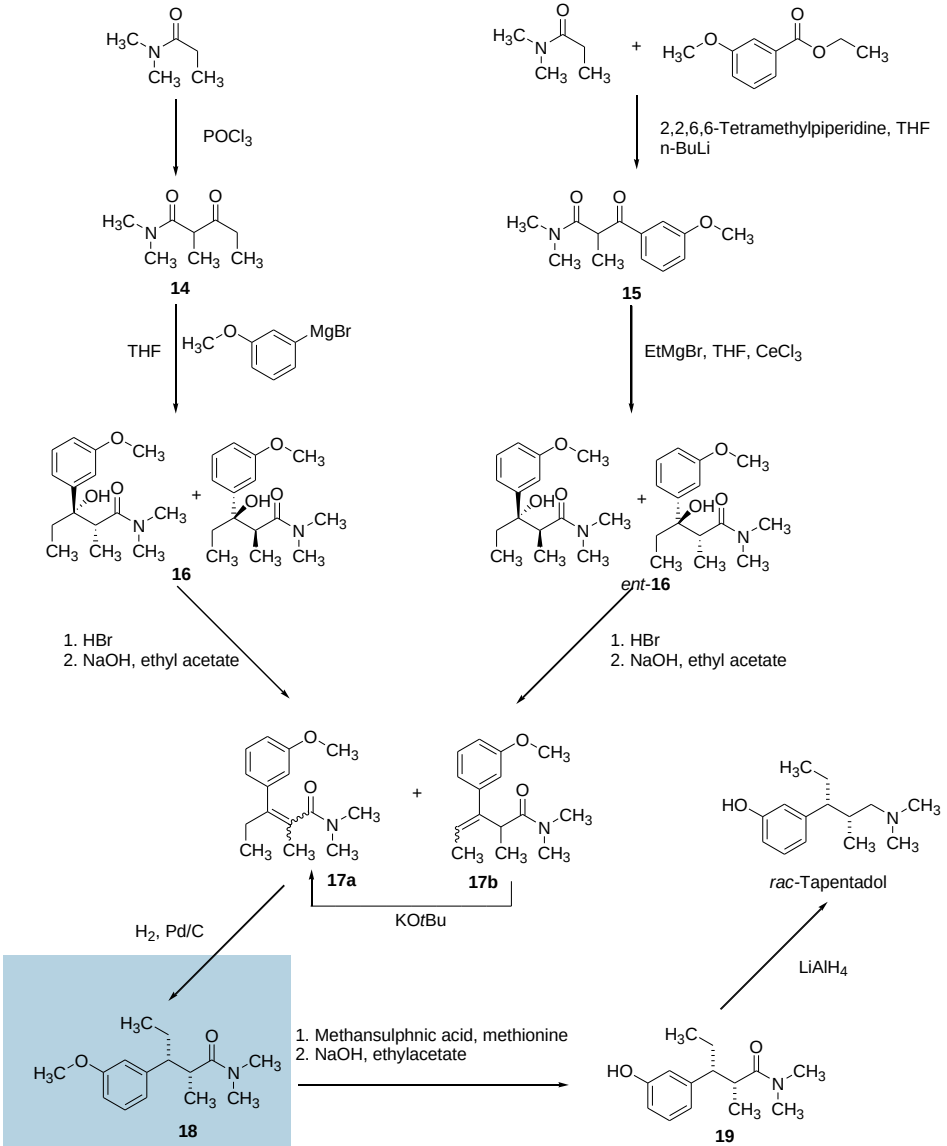
- Hell W, WO 2008012046 A1, 2008.
- Hell W; Zimmer O; Buschmann, HH; Holenz J; Gladow S, WO 2008012047A1, 2008.
- Liu KKC; Subas Sakya M; O'Donnell CJ; Flick AC; Li J, Synthetic approaches to the 2009 new drugs Bioorg. Med. Chem. 2011, 19, 1136–1154.

The synthesis of tapentadol hydrochloride according to WO 2012/001571 A1



Tapentadol - Synthesis and Manufacture

The synthesis of tapentadol hydrochloride according to WO2011/157390 A2



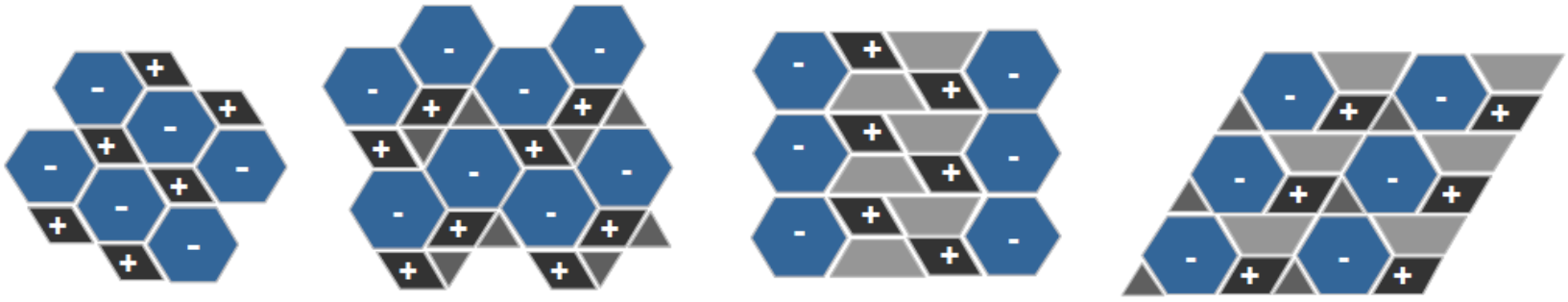
Solid Forms in Pharmaceutical Industry

Classes of Multicomponent Molecular Crystals

Neutral

1. Homomeric
2. Hydrate/solvate
3. Cocrystal
4. Cocrystal hydrate

Charged



5. Salt
6. Salt hydrate/solvate
7. Salt cocrystal
8. Salt hydrate cocrystal

Solid Forms in Pharmaceutical Industry

Relationship between the Structure and Properties of Pharmaceutical Crystals

Packing Properties

- Molar volume and density
- Refractive index
- Conductivity, electrical and thermal
- Hygroscopicity

Thermodynamic Properties

- Melting and sublimation temperatures
- Internal energy (i.e. structural energy)
- Enthalpy (i.e. heat content)
- Heat capacity
- Entropy
- Free energy and chemical potential
- Thermodynamic activity
- Vapor pressure
- Solubility

Kinetic Properties

- Dissolution rate
- Rates of solid state reactions
- Stability

A.R. Sheth, D.J.W. Grant, Relationship between the Structure and Properties of Pharmaceutical Crystals, KONA 2005, *23*, 36-47.

Relationship between the Structure and Properties of Pharmaceutical Crystals

Spectroscopic Properties

- Electronic transitions (i.e. ultraviolet-visible absorption spectra)
- Vibrational transitions (i.e. infrared absorption spectra and Raman spectra)
- Rotational transitions (i.e. far infrared or microwave absorption spectra)
- Nuclear spin transitions (i.e. nuclear magnetic resonance spectra)

Surface Properties

- Surface free energy
- Interfacial tensions
- Habit (i.e. shape)

Mechanical Properties

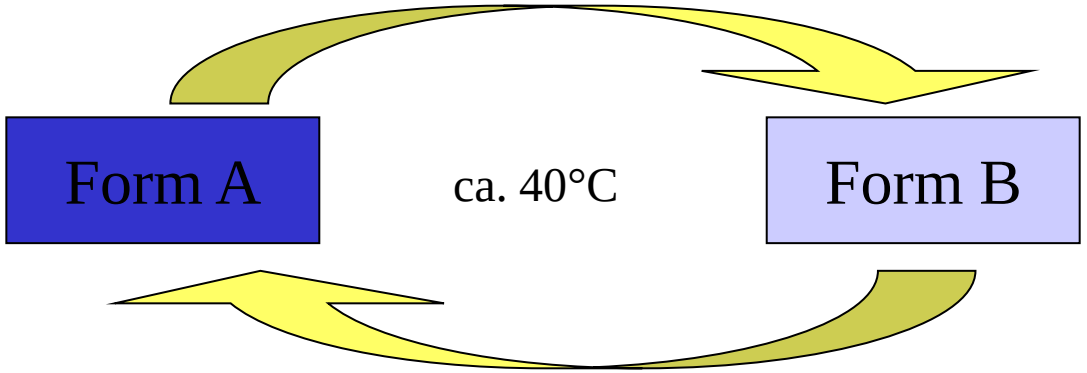
- Hardness
- Tensile strength
- Compactibility, tableting
- Handling, flow, and blending

A.R. Sheth, D.J.W. Grant, Relationship between the Structure and Properties of Pharmaceutical Crystals, KONA 2005, *23*, 36-47.

Tapentadol Hydrochloride – Polymorphic Forms

Solid Phase Characteristics

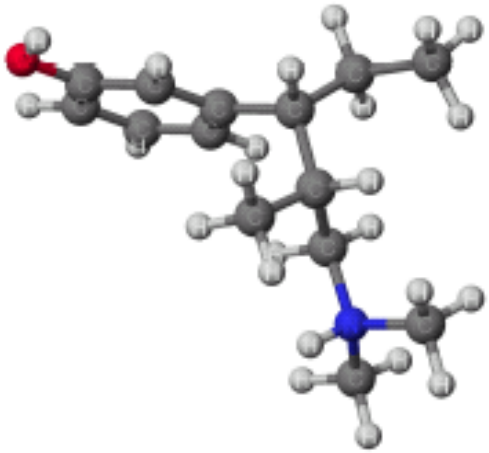
Hydrochloride Salt

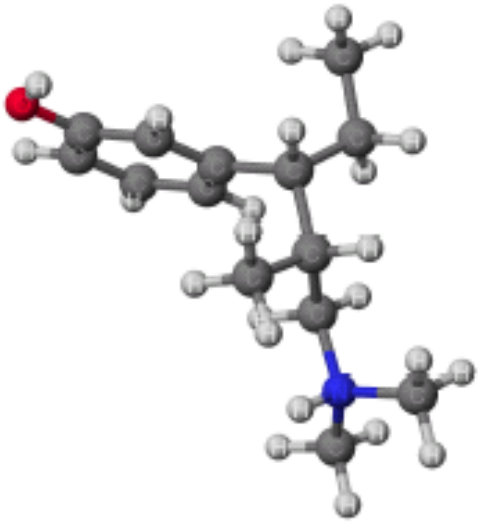


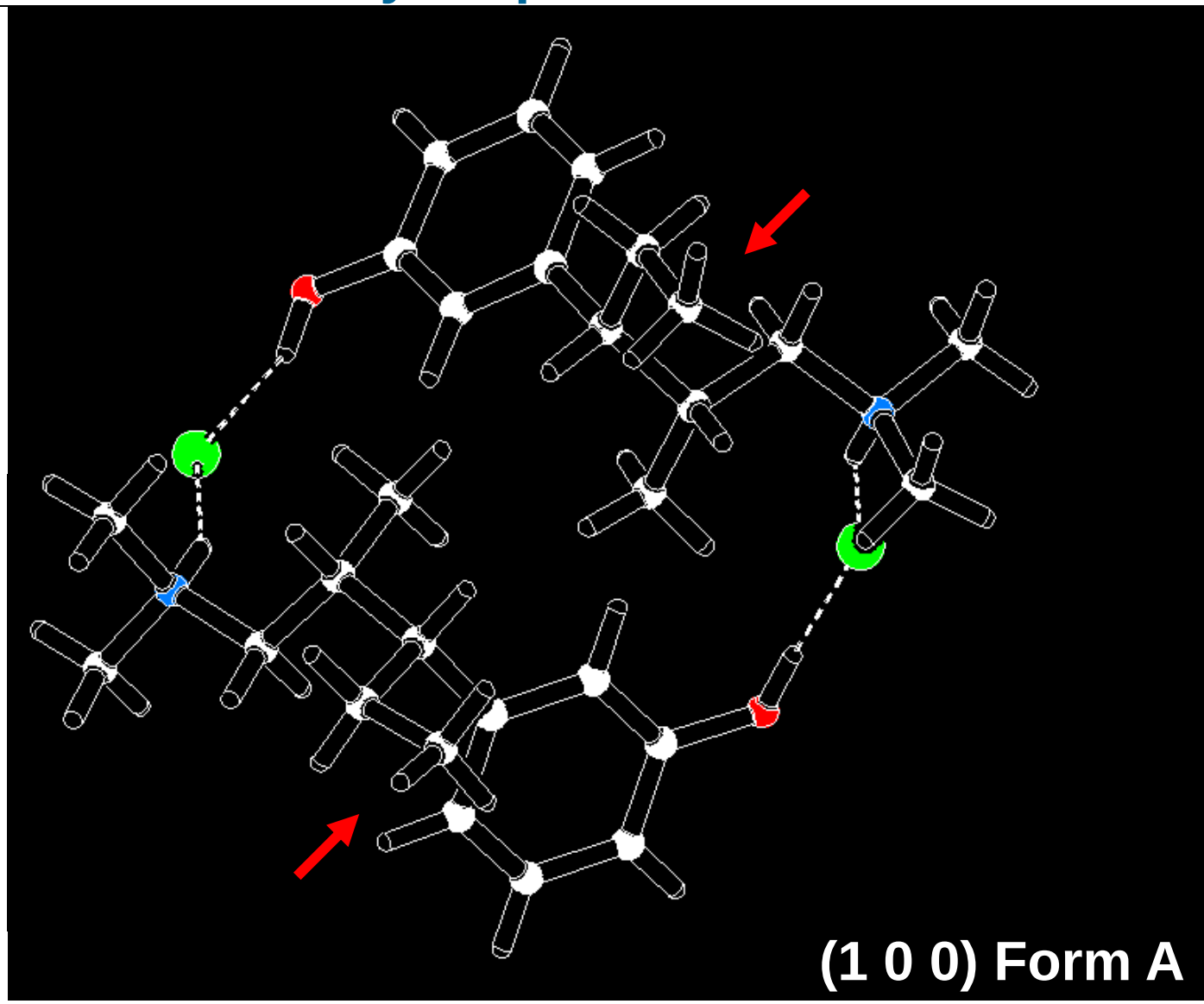
	Form A (monoklin)	Form B (orthorhombic)
Formula	C14 H24 Cl N O	C14 H24 Cl N O
M.W. / g/mol	257,79	257,79
Space group	No. 4, $P2_1$	No. 19, $P2_12_12_1$
Z (No. of Units)	4	4
a/Å	7,110(3)	7,0882(3)
b/Å	11,615(4)	11,8444(6)
c/Å	17,425(6)	17,6708(11)
α/°	90	90
β/°	95,00(3)	90
γ/°	90	90
Volume of elementary cel/Å^3	1434	1484
Density (calc.) / g/cm	1.20	1.15

Tapentadol Hydrochloride – Polymorphic Forms

GRT1: Polymorph A

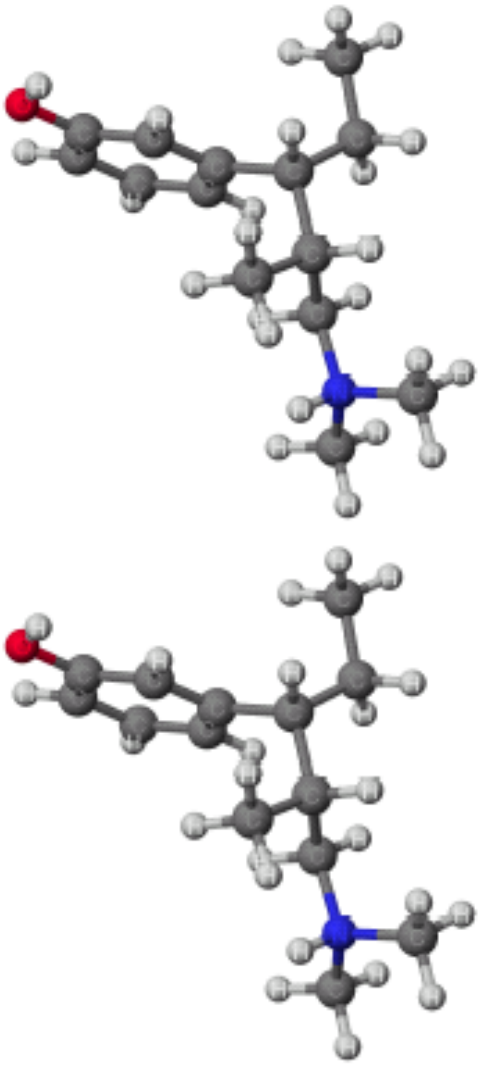


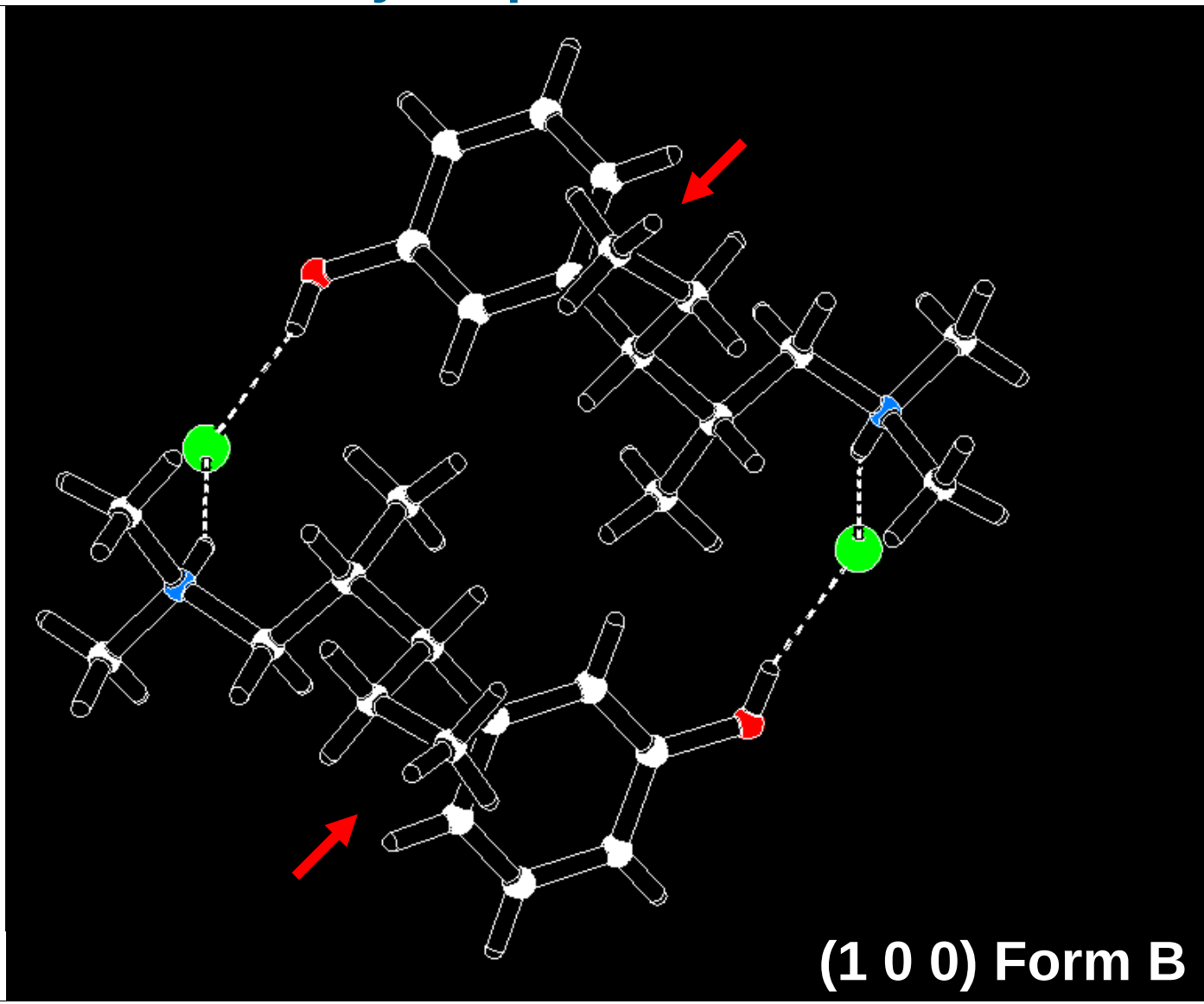




Tapentadol Hydrochloride – Polymorphic Forms

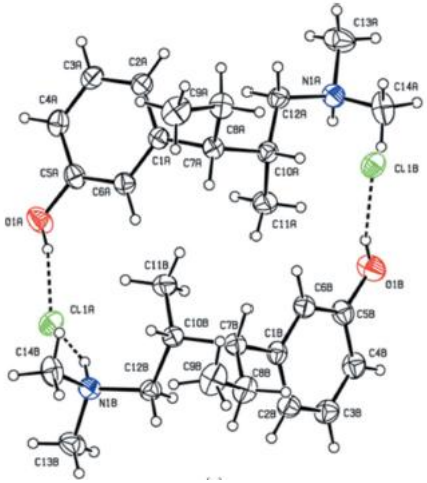
GRT1: Polymorph B



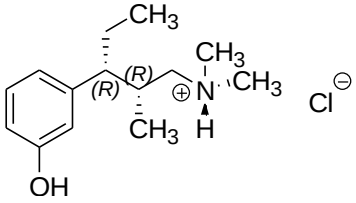


(1 0 0) Form B

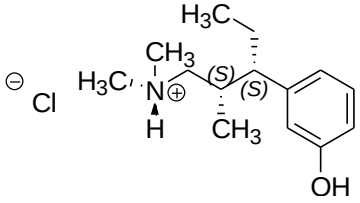
Four stereoisomers of the novel μ-opioid receptor agonist tapentadol hydrochloride

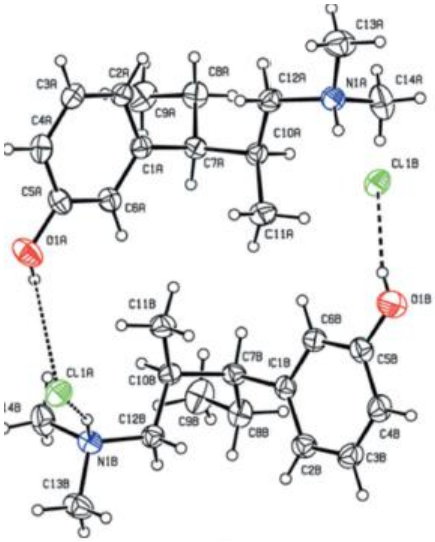


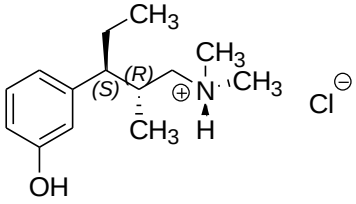
Monoclinic, $P2_1$
a = 7.1600 (15) Å
b = 11.688 (3) Å
c = 17.514 (4) Å
β = 94.535 (3)°

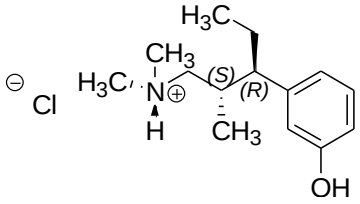


Monoclinic, $P2_1$
a = 7.160 (3) Å
b = 11.688 (5) Å
c = 17.526 (8) Å
β = 94.570 (7)°



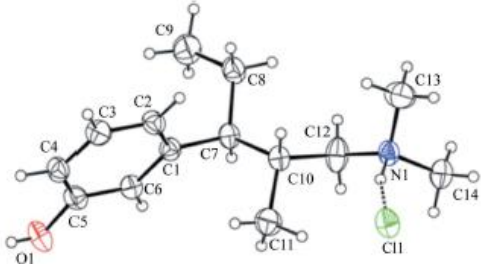


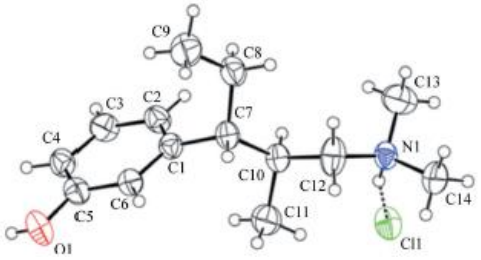




Orthorhombic, $P2_12_12_1$
a = 8.8218 (6) Å
b = 12.1304 (8) Å
c = 14.0031 (9) Å

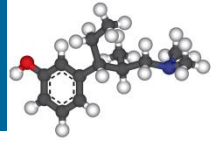
Orthorhombic, $P2_12_12_1$
a = 8.8101 (6) Å
b = 12.1094 (8) Å
c = 13.9784 (9) Å





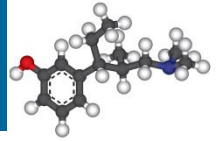
Krishnan Ravikumar, Balasubramanian Sridhar, Nitin, Pradhan and Mayur Khunt, Four stereoisomers of the novel μ-opioid receptor agonist tapentadol hydrochloride, Acta Cryst. (2011). C67, o71–o76

Tapentadol - Tramadol



- Tapentadol is a single molecule (pure enantiomer); tramadol is a racemate.
- Tapentadol has no active metabolites that contribute to its analgesic effects; tramadol has a major active metabolite.
- Tapentadol acts at MOR and NET with minimal activity at SERT; tramadol acts at MOR, NET, and SERT in a time- and patient-variable manner. Thus tapentadol has less potential to produce serotonin-related adverse effects or serotonin syndrome than does tramadol.
- The mechanisms of action of tapentadol reside in a single molecule, thus the relative ratio of mechanisms does not change over time which provides constant analgesic synergism; the mechanisms of action of tramadol reside in different molecules (enantiomers of the parent and a metabolite), thus the relative ratio of mechanisms changes as tramadol is metabolized.

Tapentadol - Tramadol



- Tapentadol is 2 to 5 times more potent than tramadol across a range of animal pain models. Likewise, clinically, tramadol is effective for treating moderate to moderately-severe pain (WHO step 2); tapentadol is effective in treating moderate to severe pain (WHO step 3).

- Tapentadol is a schedule II drug in the US and scheduling is anticipated for all countries where it is marketed; tramadol is not scheduled in most countries.

- In clinical trials, tapentadol has been shown to be equiefficacious to oxycodone with fewer gastrointestinal adverse effects

- The main pathway of tapentadol metabolism is glucuronidation; tramadol is metabolized mainly via the CYP450 enzyme complex. Therefore, there is greater chance for phenotype variability in response to tramadol.

- Fewer drugs are metabolized via UGT than CYP enzymes, so there is less chance of drug-drug interactions with tapentadol than with tramadol.

Synthetische Chemie

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Hees, Frau S.
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Janocha, Frau E.
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Krüger, T.
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Wetzels, Frau I.