3. Block

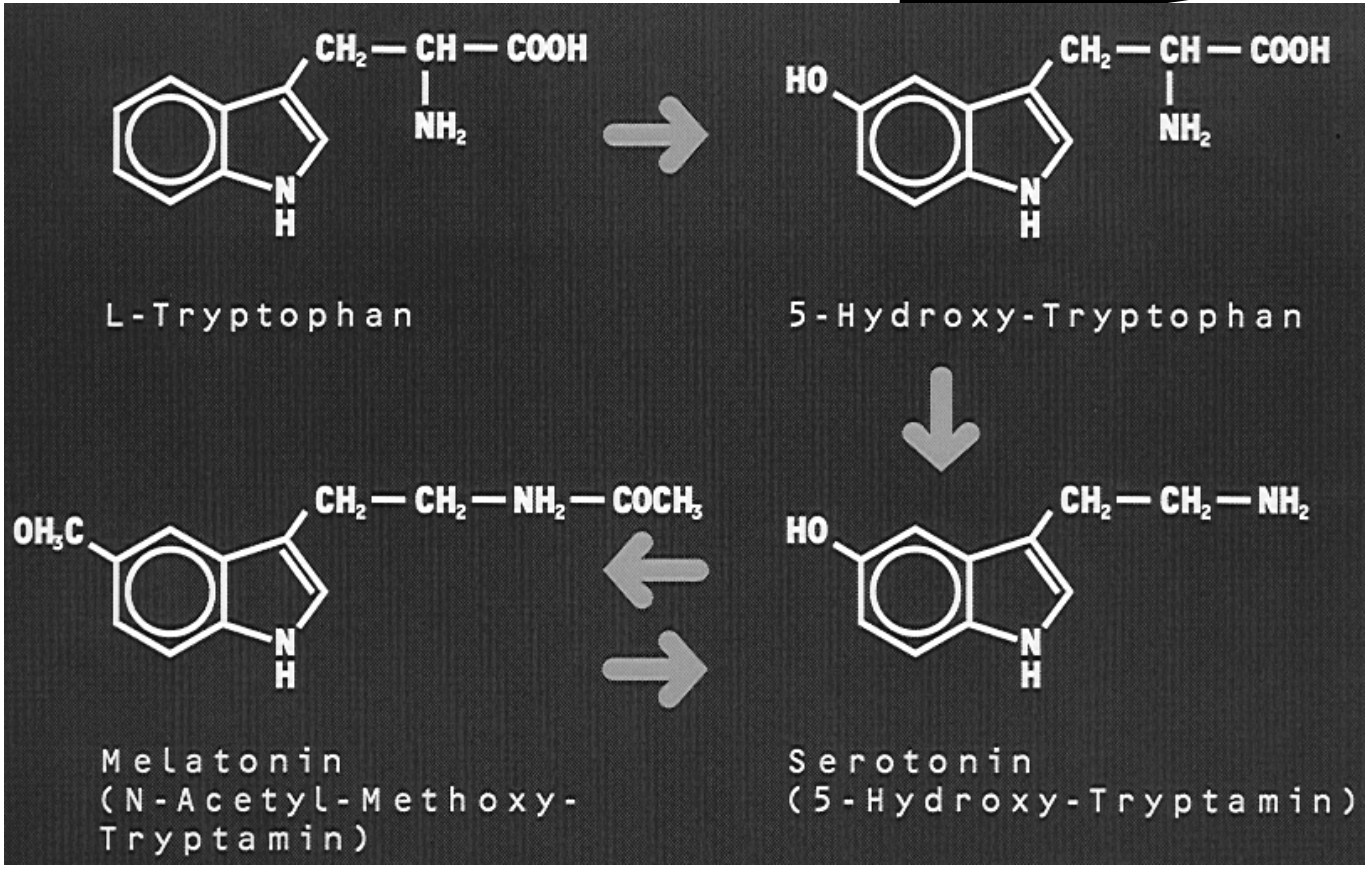
Neuroleptika

- *Mittel, die eine psychische Anspannung herabsetzen*
- *Wenn chronische Schmerzzustände mit ausgeprägten Störungen der Emotionalität (= Gefühlsbewegung) und des leiblichen Wohlbefindens einhergehen, können auch neuroleptisch wirksame Psychopharmaka (Neuroleptika) indiziert (= angezeigt) sein. Durch ihren modulierenden Einfluß auf das affektiv-motivationale (= die Gesamtheit der seelisch-dynamischen Faktoren, die das augenblickliche Verhalten bestimmen) Schmerzerleben wie auch auf die kognitive (= das Erkennen, Wahrnehmen und Denken betreffende) Schmerzverarbeitung bildet die zusätzliche Therapie mit Neuroleptika eine wertvolle Alternative zu den traditionellen Strategien der Schmerzbehandlung.*
  Ob dabei Neuroleptika selbst analgetisch (= schmerzlindernd) wirken, konnte bislang nicht eindeutig bestätigt werden.
  Die Kombination eines Neuroleptikum `s mit einem Antidepressivum erweist sich als vorteilhaft, im allgemeinen genügen dann niedrigere Dosen als bei einer Monotherapie.

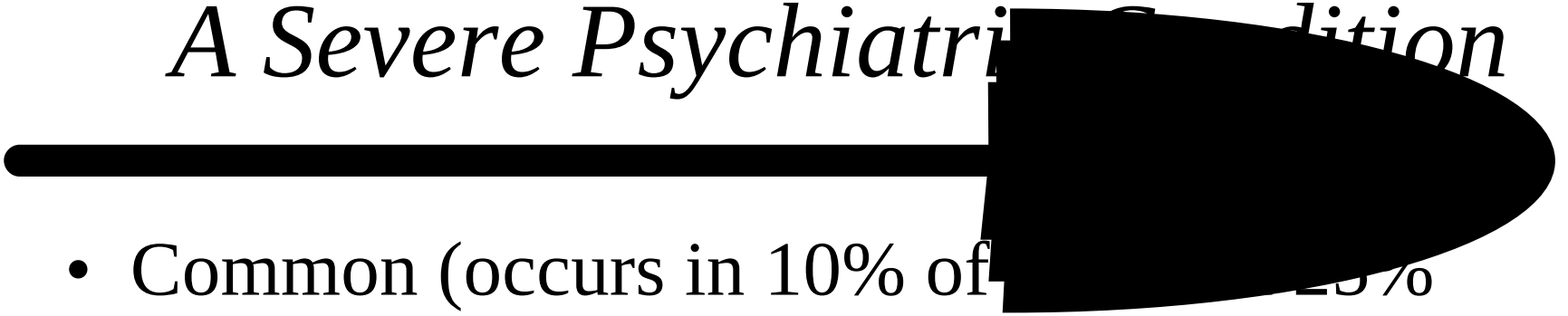
Wirkungsspektren der gebräuchlichsten Neuroleptika

Neuroleptikum	***APP***	***PMD***
Promethacin (Atosil®)	*keine*	*stark*
Chlorpromazin (Megaphen®)	*niedrig*	*stark*
Chlorprothixen (Truxal®)	*niedrig*	*stark*
Levomepromazin (Neurocil®)	*niedrig*	*stark*
Prothipendyl (Dominal®)	*niedrig*	*mittel*
Thioridazin (Melleril®)	*niedrig*	*stark*
Fluphenazin (Dapotum®)	*mittel*	*mittel*
Perazin (Taxilan®)	*mittel*	*mittel*
Trifluprom azin (Psyquil®)	*mittel*	*mittel*
Fluspirilen (Imap®)	*stark*	*gering*
Haloperidol (Haldol®)	*stark*	*mittel*
Pimozid (Orap®)	*stark*	*gering*
Sulpirid (Dogmatil®)	*stark*	*gering*

Neurotransmi[redacted]tonin

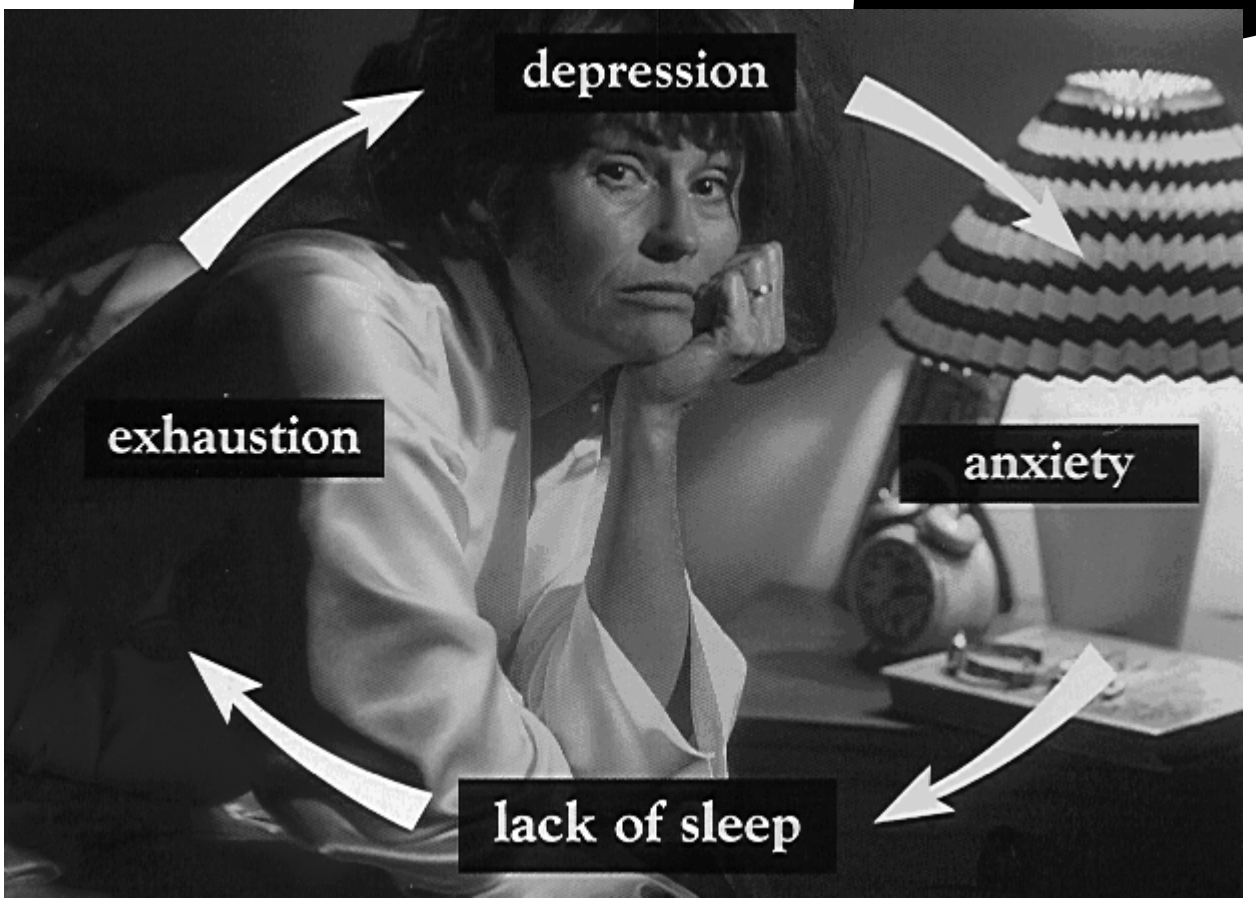


Depressive Illness: A Severe Psychiatric Condition



- Common (occurs in 10% of men and 25% of women over lifetime)
- Disabling
- Life-threatening (10% commit suicide)
- Relapse-prone
- Changes brain biochemistry
- Responds to serotonergic drugs

The Vicious Cycle Of [redacted]ssion



Pharmacotherapy Of Depression: „40 Years In Conceptual Wilderness“

(1970ies)

TCAs
(imipramine)
late 1950ies

MAOIs
(phenelzine)
early 1960ies

SSRIs
(fluoxetine)
late 1980ies

2nd-gen. TCAs
(1970ies)

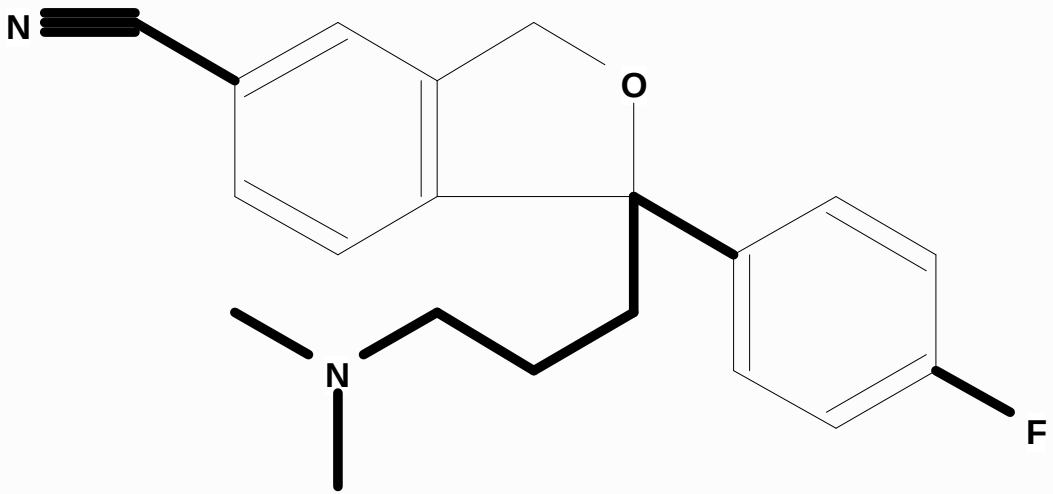
Serotonin Receptor Responses

Antidepressant Receptor Interaction Profiles

	NA	5-HT1	5-HT2	5-HT3
TCAs				
Mianserin				
SSRIs				
NaSSAs				

Acrobat-Dokument

SSRI Celexa



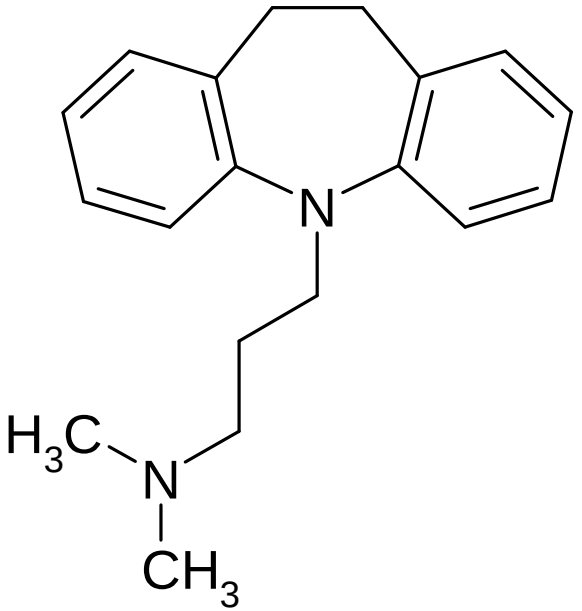
Case Studies 1

Die Identifikation von selektiven

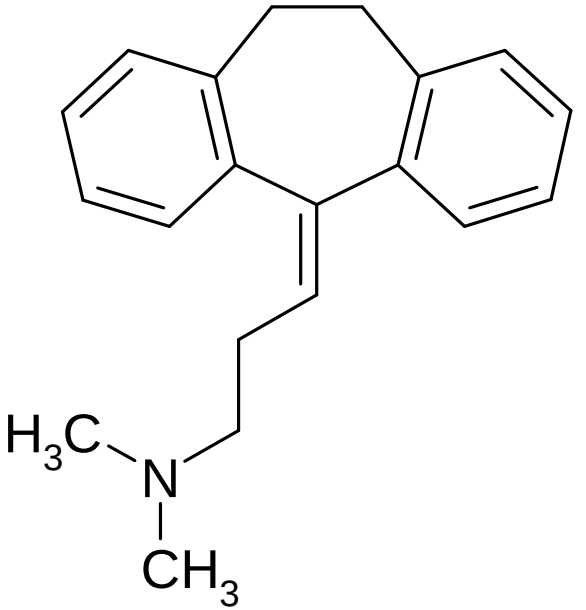
5-HT_{2c} Rezeptor Antagonisten:

Ein neuer Ansatz zur Behandlung von Depression und Angstzuständen

Erste Generation: Tricyclische Antidepressiva



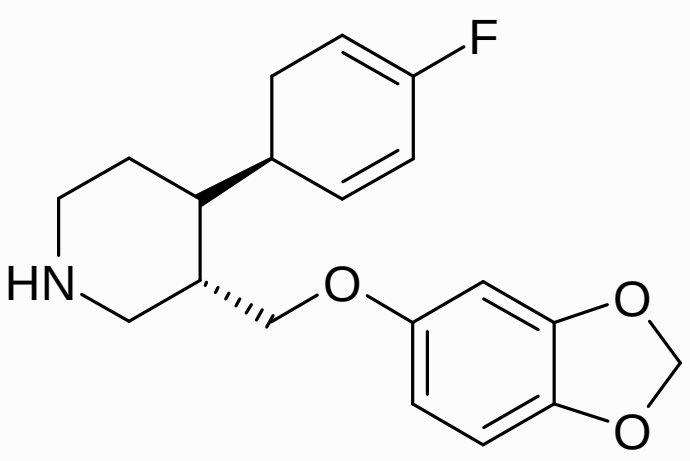
Imipramine



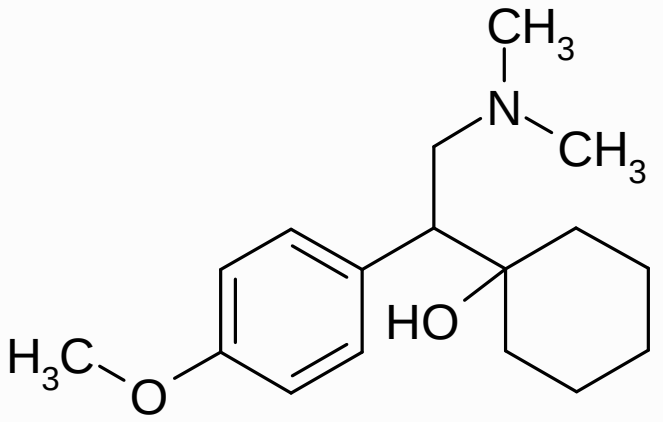
Amitryptilin (Triptisol)

Nebenwirkungen, Suicid durch Überdosen

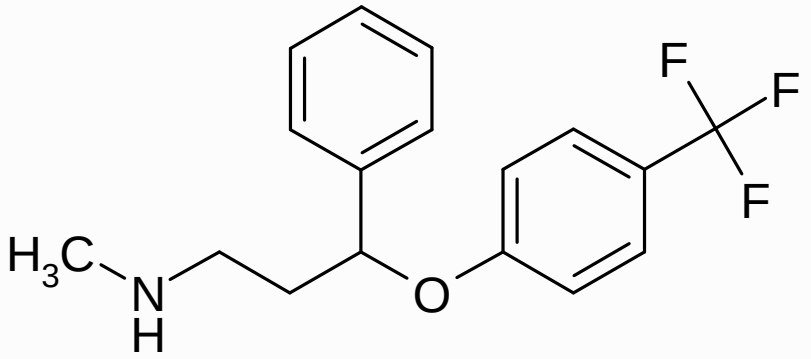
Zweite Generation Antidepressiva
Selective Serotonin Reuptake Inhibitors (SSRIs)



Paroxetine, Paxil

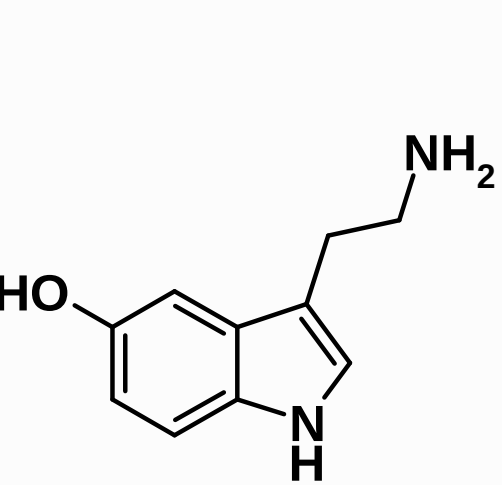


Venlafexine



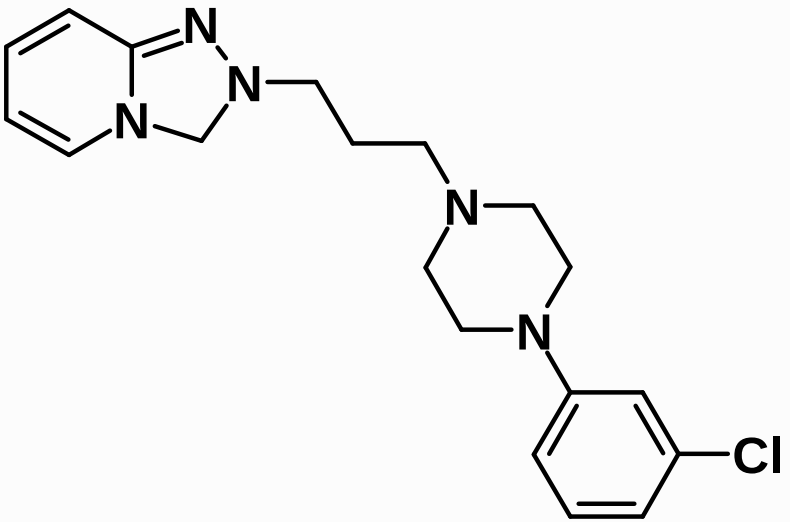
Floxetine
Fluval

5-HT_{2c} Antagonisten

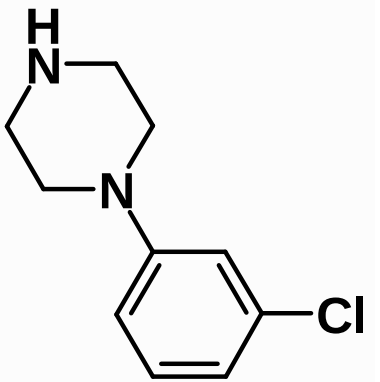


5-HT
5-Hydroxytryptamin

Serotonin



Trazodone



mCPP

Lead: SB-200646

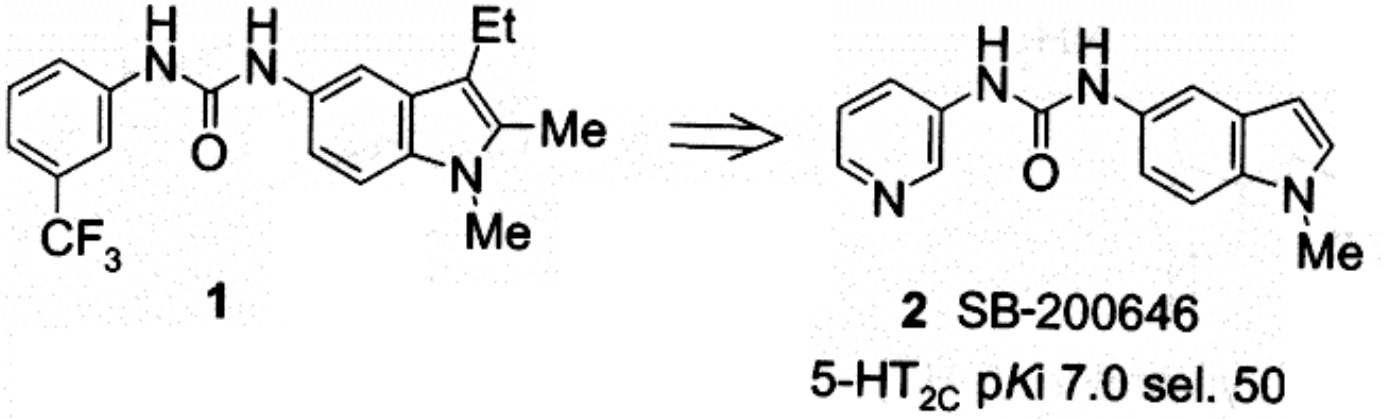


Figure 2 *Discovery of 2*

Weiterentwicklung

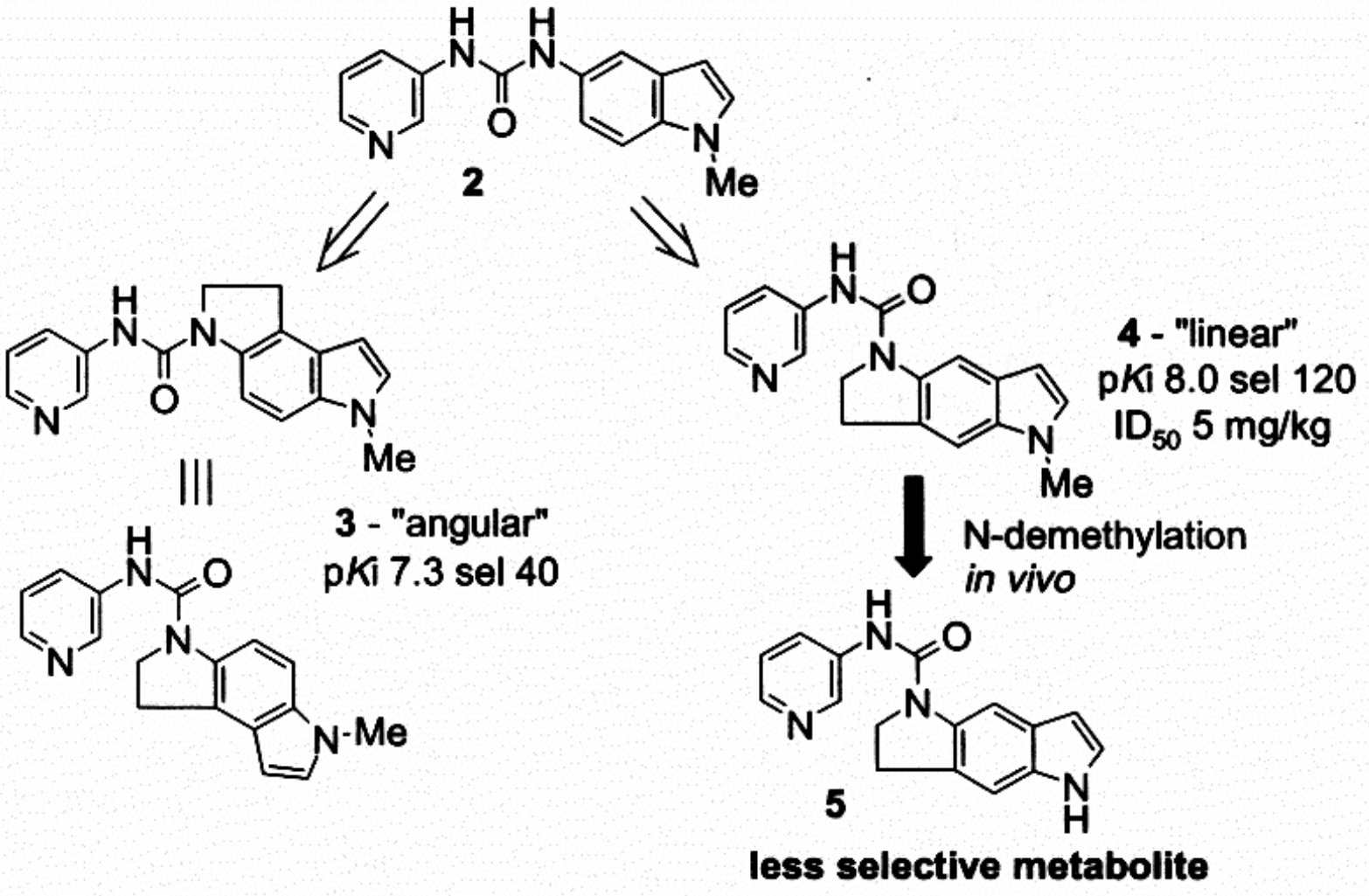


Figure 3 *Conformational restriction to give 4*

„Andock“ - Möglichkeiten

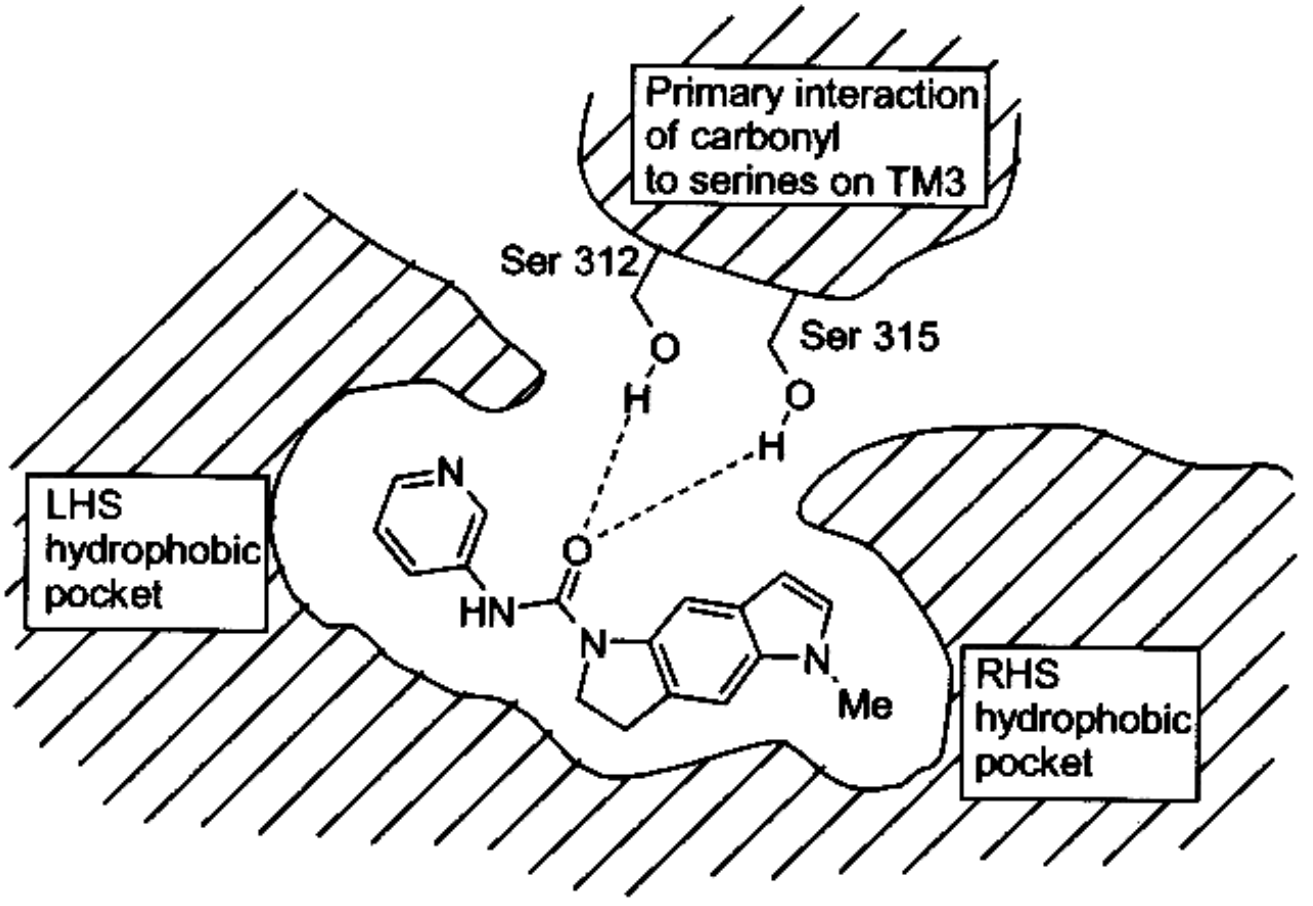


Figure 4 *Schematic representation of 4 docked into a model of the 5-HT_{2C} receptor*

Bioisosterer Ersatz

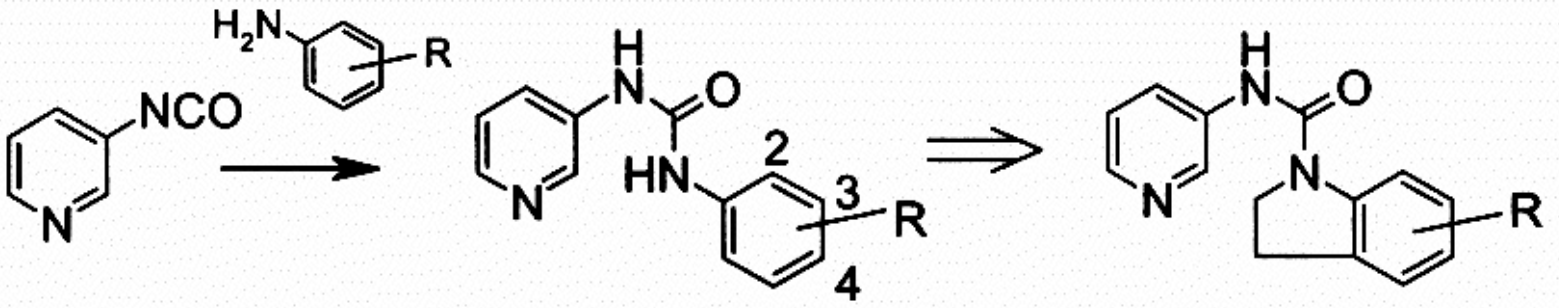
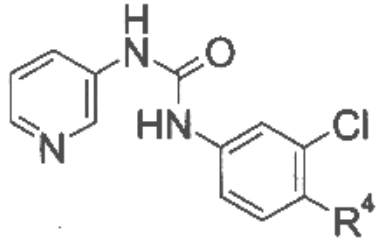


Figure 6 *Identification of metabolically stable isosteres of 4*

Affinität und Selektivität

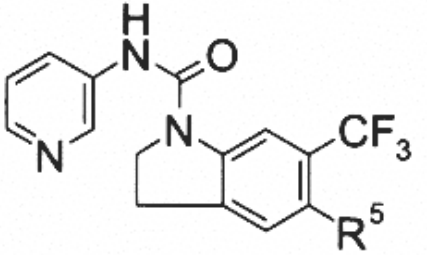
Table 1 *The 5-HT_{2C} affinities and selectivities of biaryl ureas*



R^4	π *of* R^4	5-HT_{2C} (pK_i)	*Selectivity* 5-$HT_{2C/2A}$
SO_2Me	−1.63	5.0	–
$CONH_2$	−1.49	5.1	–
CH_2OH	−1.03	5.5	–
CN	−0.57	5.9	–
COMe	−0.55	6.6	25
COOH	−0.32	7.1	80
OMe	−0.02	6.7	30
Me	0.56	7.8	40
SMe	0.61	7.5	120
Cl	0.71	7.5	50

Besonders vielversprechend

Table 2 *Activity of 5-thioalkyl-6-CF_3 indolines*



R^5	5-HT_{2C} pK_i	Selectivity 5-$HT_{2C/2A}$	ID_{50} vs *mCPP* (mg kg^{-1} p.o.)
OMe	8.0	120	0.8
SMe[a]	8.6	160	1.5
SEt	8.5	1000	4.4
S^{n}Pr	8.2	>1000	<5

[a] **6** (SB-221284).

Neue „Andock“-Möglichkeit

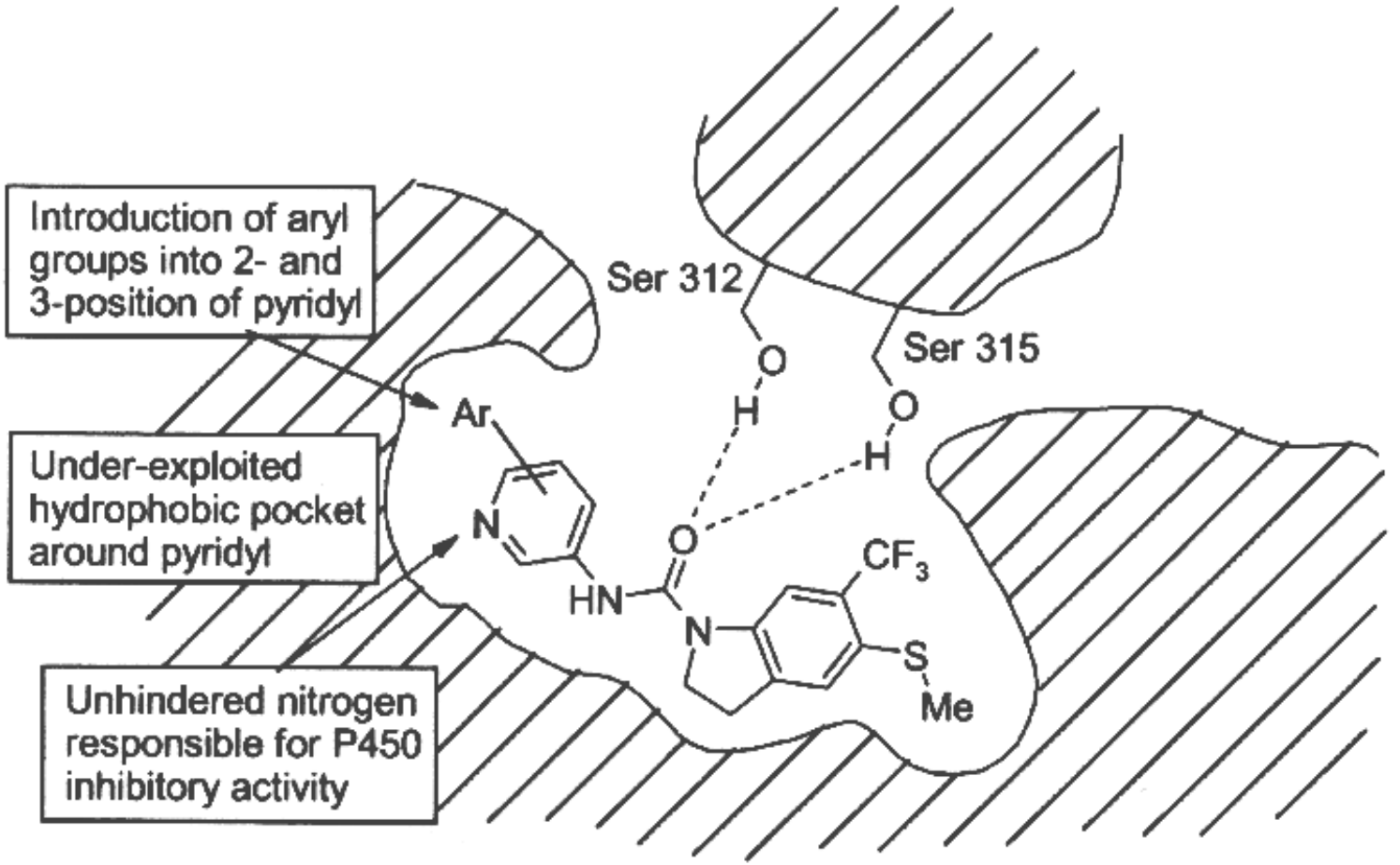
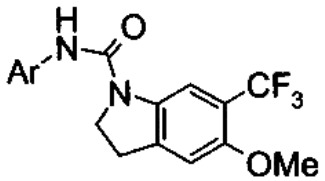
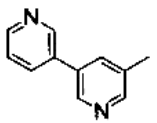
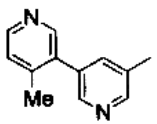
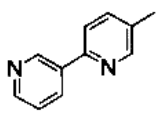
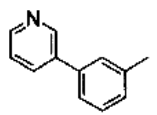
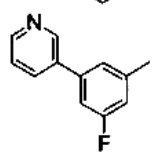


Figure 9 *Evolution of (aryl-pyridylcarbamoyl) indolines from* ***6*** *SB-221284*

Einfluß aromat. Substituenten

Table 3 *Activity of bisarylcarbamoylindolines*

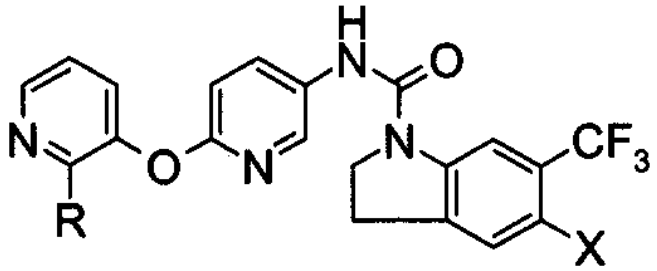


Cmpd.	*Ar*	*p*K$_i$ *5-HT$_{2C}$*	*5-HT selectivity* *2C/2A*	*2C/2B*	*ID$_{50}$ (po)* vs *mCPP*	*ID$_{50}$* vs *CYP1A2* (μM)
7		9.1	80	12	–	~5
8		9.4	250	15	5 mg kg^{-1}	0.2
9		8.3	>2000	2	Inactive	>100
10		9.0	200	8	0.6 mg kg^{-1}	4
11[a]		9.0	130	10	0.7 mg kg^{-1}	28

[a] SB-228357.

Problemlösungsansätze

Table 5 *Activity of bispyridyl ether-carbamoylindolines*



Cmpd.	*R*	*X*	pK_i *5-HT$_{2C}$*	*5-HT selectivity* *2C/2A*	*5-HT selectivity* *2C/2B*	*ID$_{50}$ (po)* vs. *mCPP* (mg kg^{-1})	*CYP1A2* (μM)
12	H	OMe	8.9	80	16	0.7	>100
13	Me	OMe	9.2	1300	80	2.8	>100
14[a]	Me	Me	9.0	160	100	0.7	>100

[a] SB-243213.

SB-243213 - Synthese

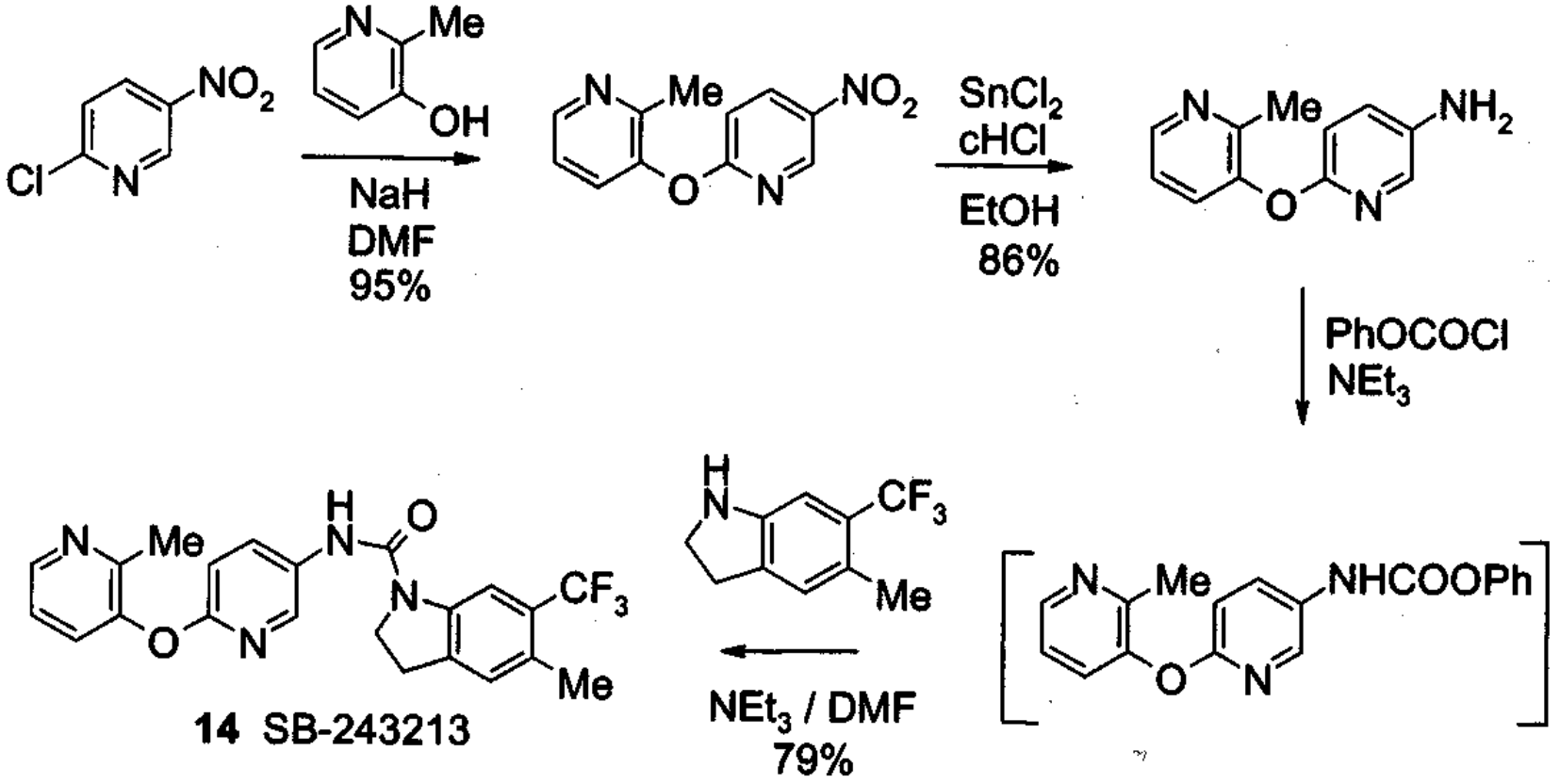


Figure 10 *Synthesis of 14, SB-243213*

SB-243213

- **Effect of acute and chronic administration of the selective 5-HT2C receptor antagonist SB-243213 on midbrain dopamine neurons in the rat: an in vivo extracellular single-cell study.** Blackburn, Thomas P.; Minabe, Yoshio; Middlemiss, Derek N.; Shirayama, Yukihiko; Hashimoto, Kenji; Ashby, Charles R., Jr. GlaxoSmithKline, Harlow, Essex, UK. Synapse (New York, NY, United States) (2002), 46(3), 129-139. CODEN: SYNAET ISSN: 0887-4476.
- http://www.gsk.com/financial/reports/ar/report/descrip_of_bus/research_dev/res_dev.html

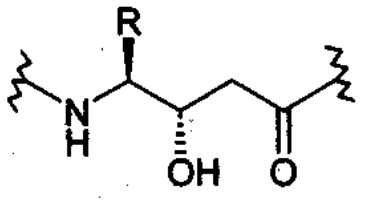
Case Studies 2

Die Identifizierung des HIV- Proteasehemmers Saquinavir

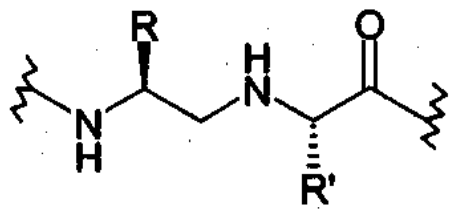
Enzyme Transition State Stabilization

- http://tutor.lscf.ucsb.edu/instdev/sears/biochemistry/tw-enz/enzyme-transition-flash.htm

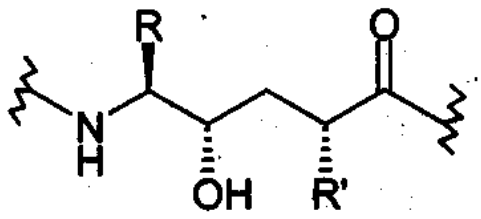
HIV – Protease-Hemmer



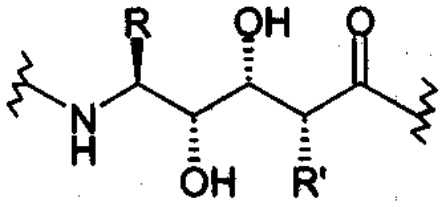
statin



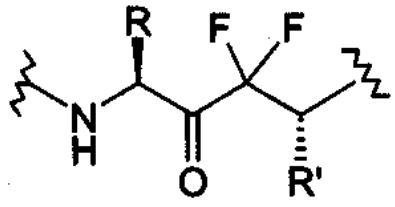
reduced amide



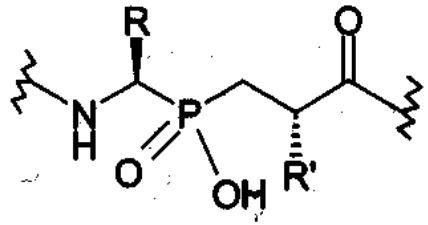
hydroxyethylene



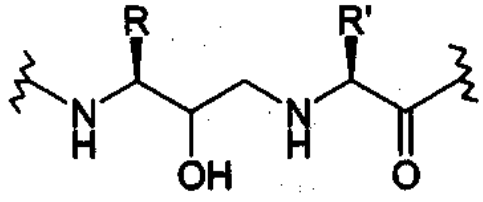
dihydroxyethylene



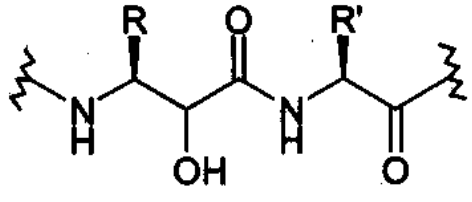
difluoroketone



phosphinic acid



hydroxyethylamine



hydroxymethylcarbonyl

Figure 1 *Transition state mimetics for aspartyl proteases*

HIV – Protease-Hemmer

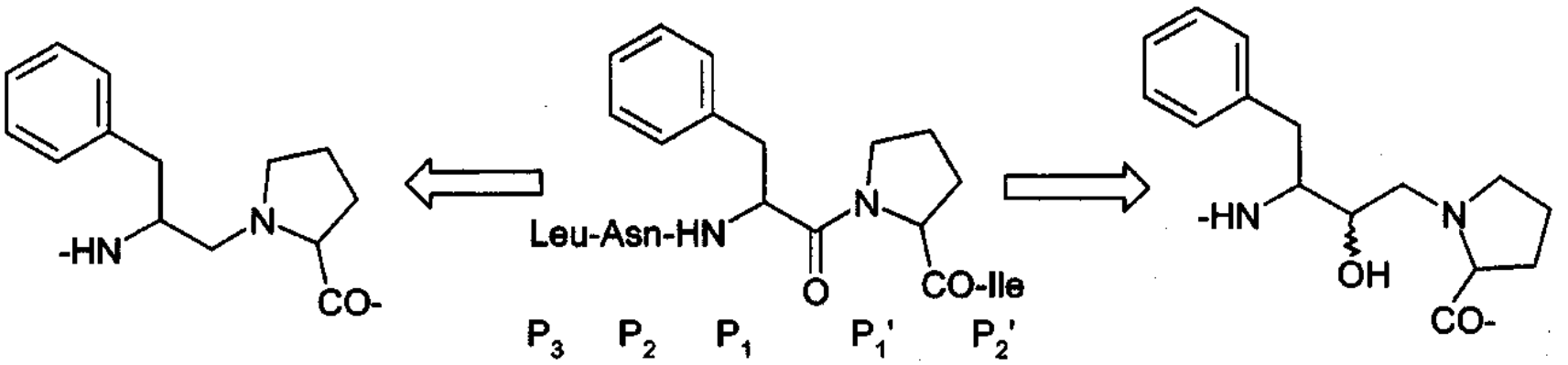
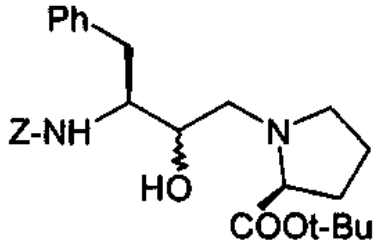
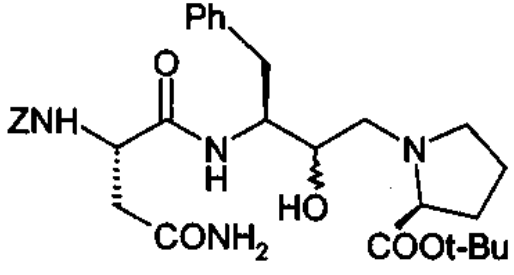
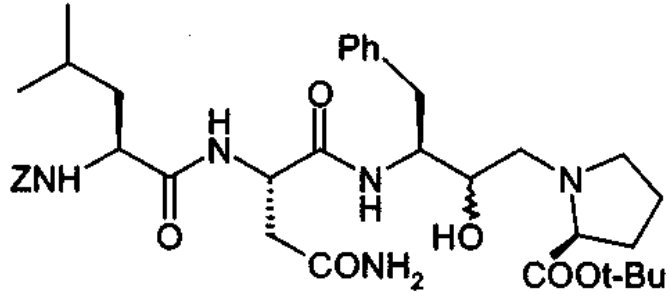


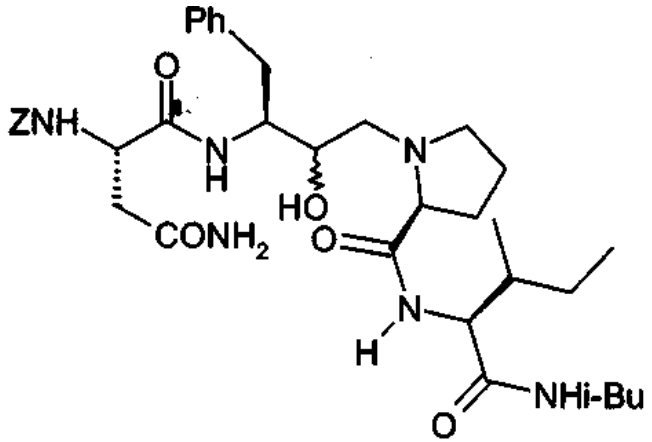
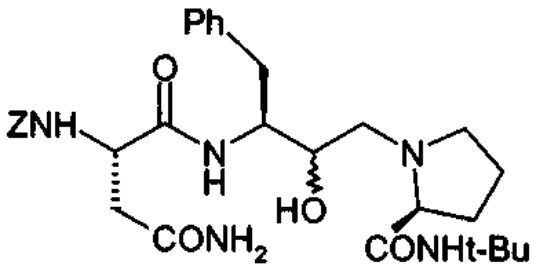
Figure 2 *Structures of HIV substrate and potential inhibitors*

HIV – Hemmstoff-Design

Table 1 *The identification of minimum inhibitor sequence*

Compound no	*Stereochemistry at -CHOH-*	*Structure*	*IC_{50} (nM) HIV-1*
1	*R*[a]		6500
2	*R*		140
3	*S*		300
4	*R*[a]		600

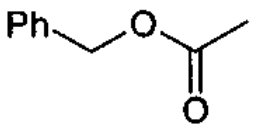
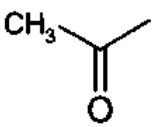
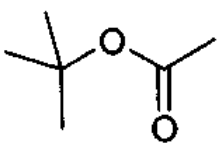
HIV – Hemmstoff-Design

5	R^a		130
6	R		210

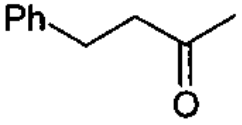
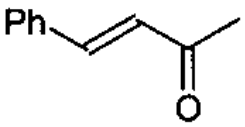
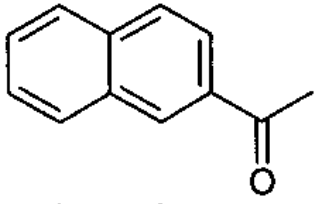
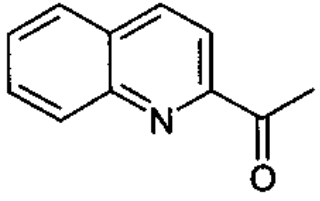
[a] More active diastereomer, probably *R*.

Optimierung des N-Terminus

Table 2 *The optimisation of N-terminus*

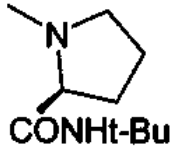
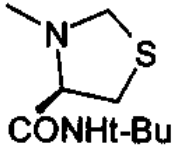
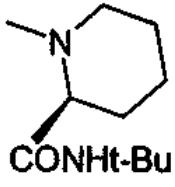
Compound no	*Structure R =*	*IC*$_{50}$ (nM *HIV-1*
2	 (Z)	140
7		8600
8	 (BOC)	8000

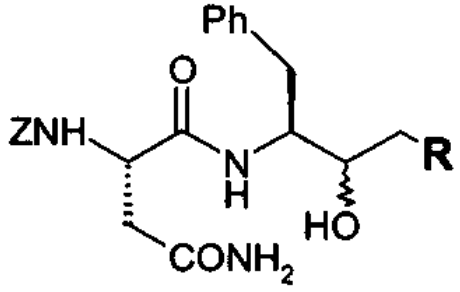
Optimierung des N-Terminus

9		240
10		240
11		46
12		23

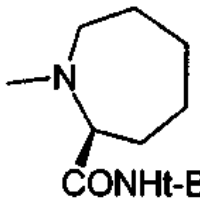
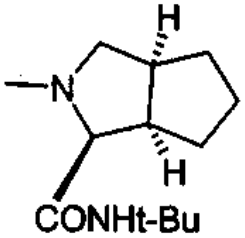
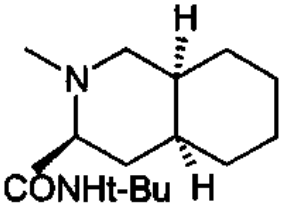
Prolin - Optimierung

Table 3 *Proline optimisation*

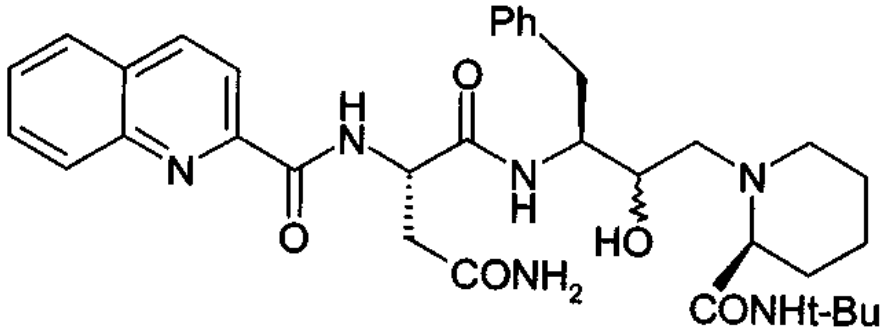
Compound no	*Stereo-chemistry at -CHOH-*	*Structure R =*	*IC_{50} (nM) HIV-1*
6	*R*		210
13	*R*		8.4
14	*R*		18



Prolin - Optimierung

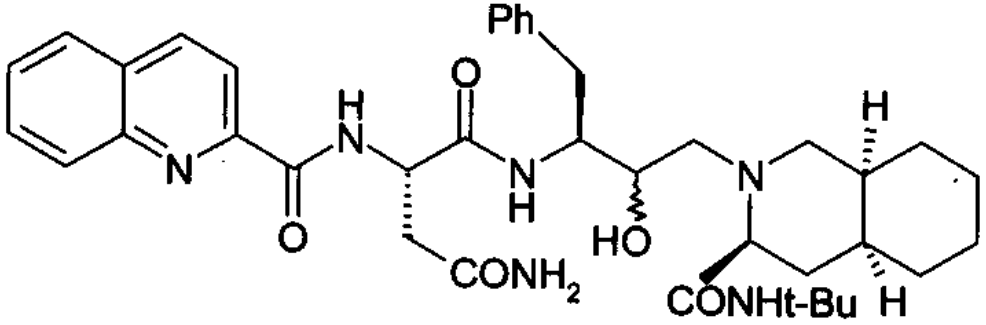
15	*R*		92
16	*R*		5.6
17	*R*		2.7
18	*S*		≫100

Resultat der Optimierung



19 R-isomer HIV-1 IC_{50} 2 nM

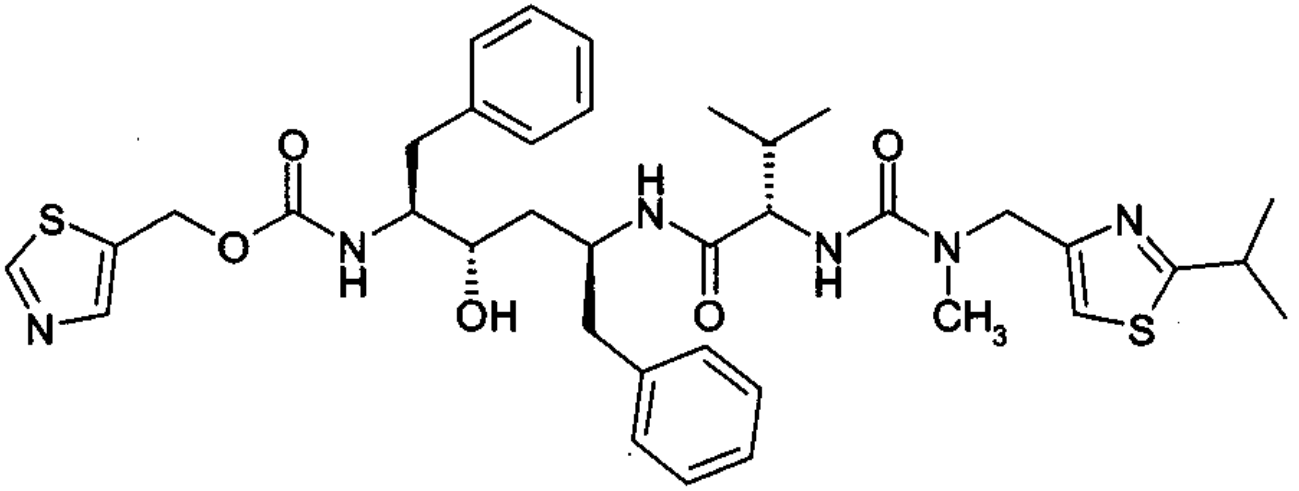
20 S-isomer HIV-1 IC_{50} 470 nM



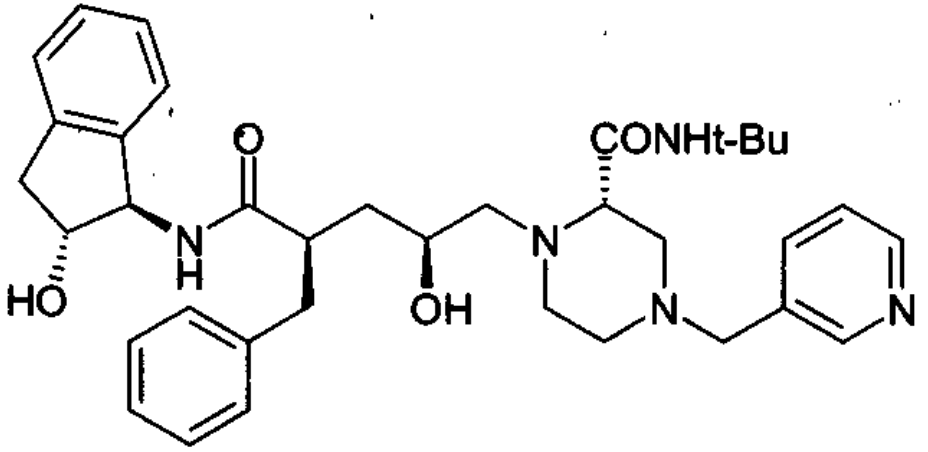
21 Ro 31-8959 (saquinavir) R-isomer HIV-1 IC_{50} <0.4 nM (Ki 0.12 nM)

22 S-isomer HIV-1 IC_{50} 620 nM

Weitere Präparate am Markt

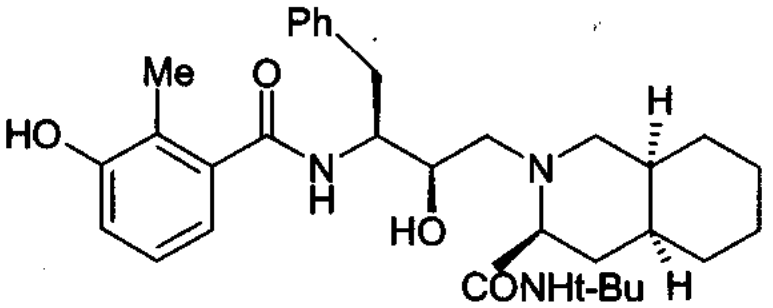


23 ritonavir

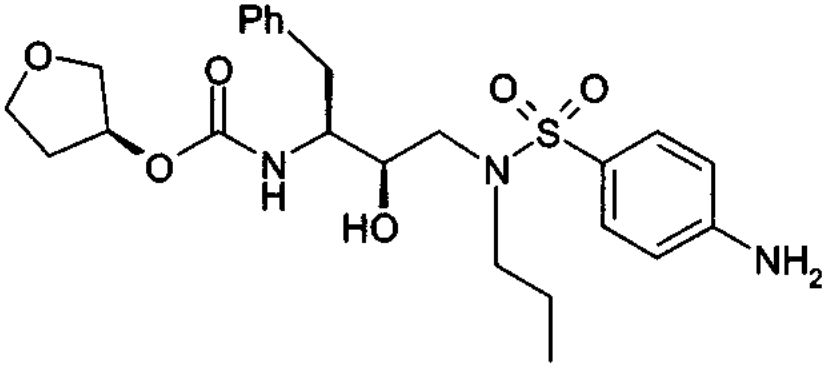


24 indinavir

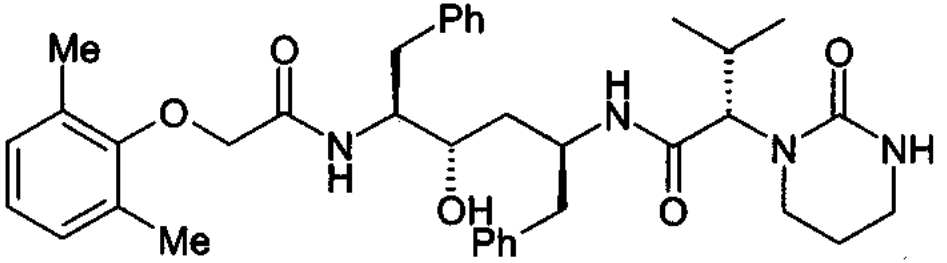
Weitere Präparate am Markt



25 nelfinavir



26 amprenavir



27 lopinavir

Röntgen - Struktur

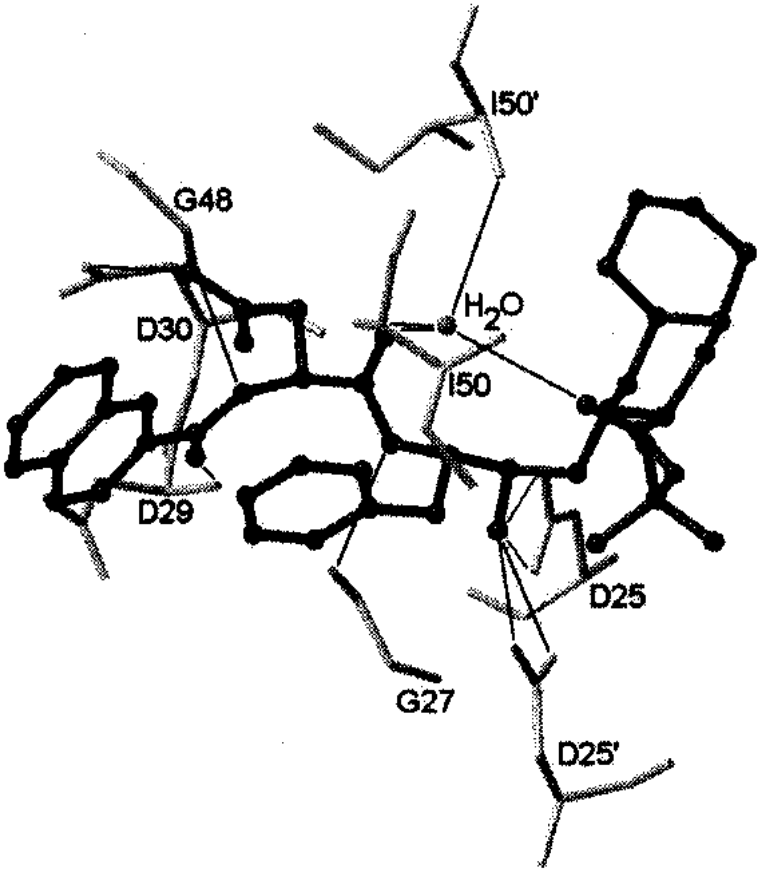


Figure 3 *X-ray structure of saquinavir* ***21*** *bound into the active site of HIV protease*

Röntgen - Struktur

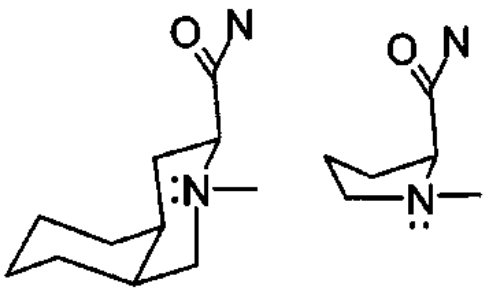
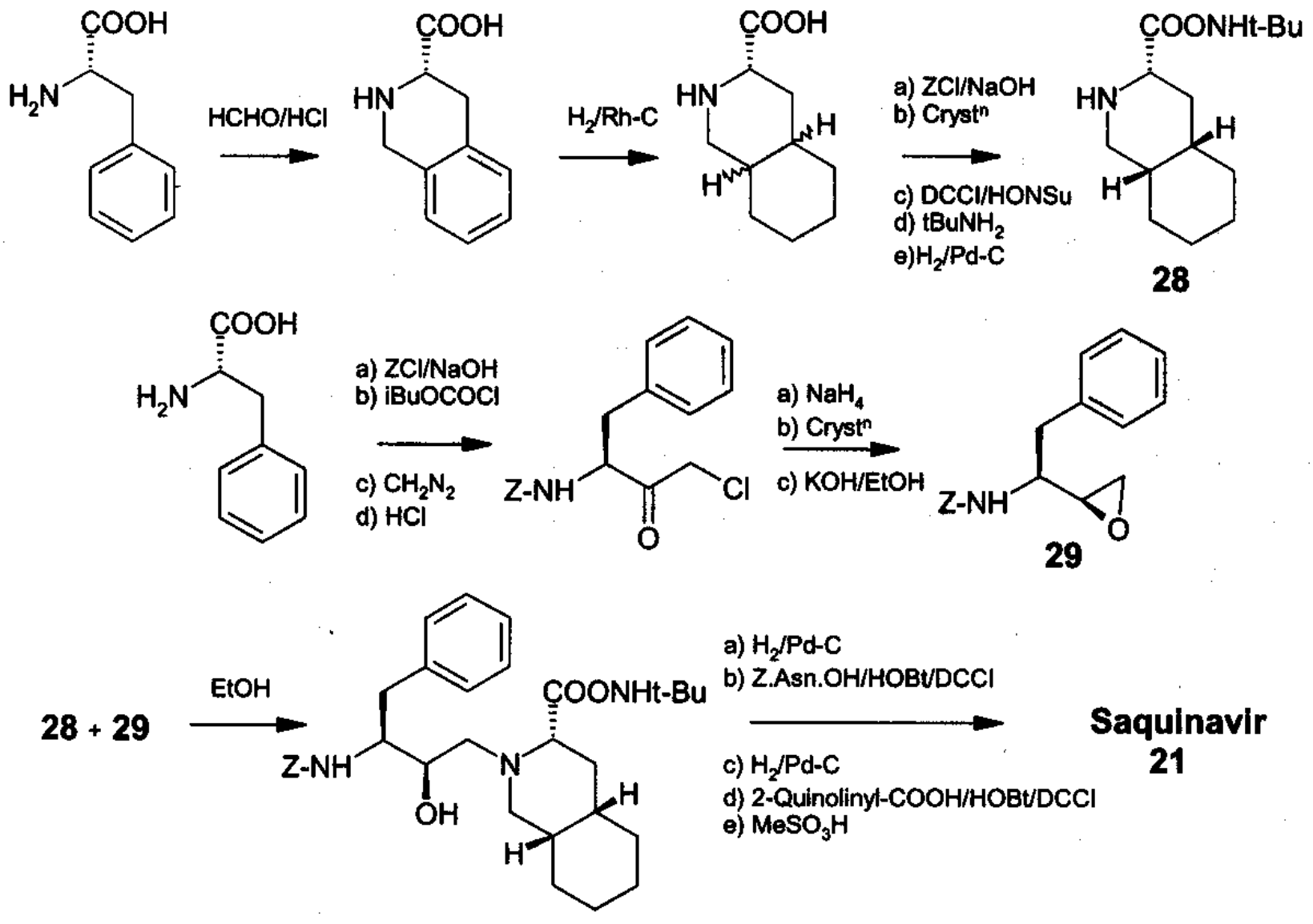


Figure 4 *Differing bound conformations of the proline and decahydroisoquinoline*

Saquinavir - Synthese



Saquinavir - Synthese

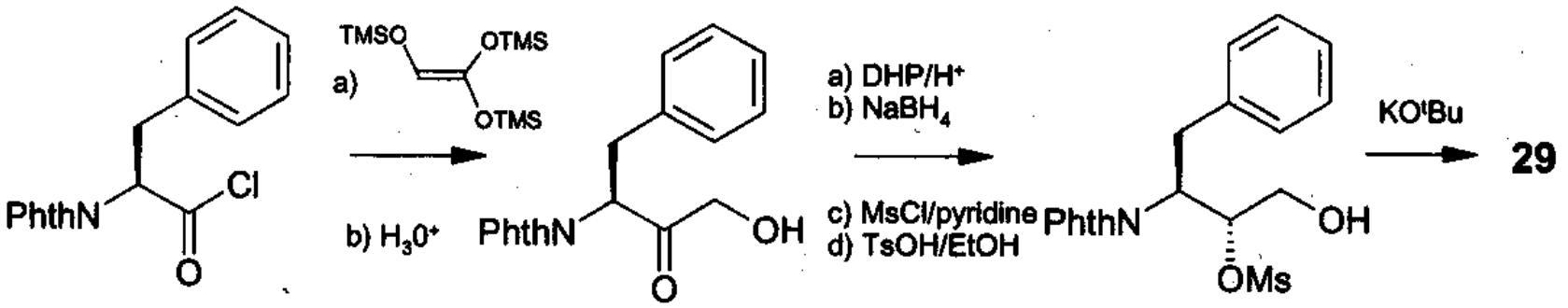
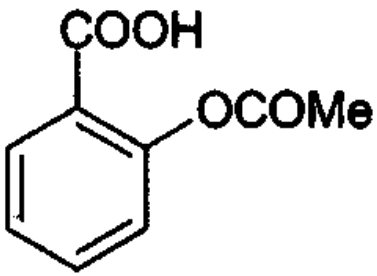


Figure 5 *Synthesis of saquinavir 21*

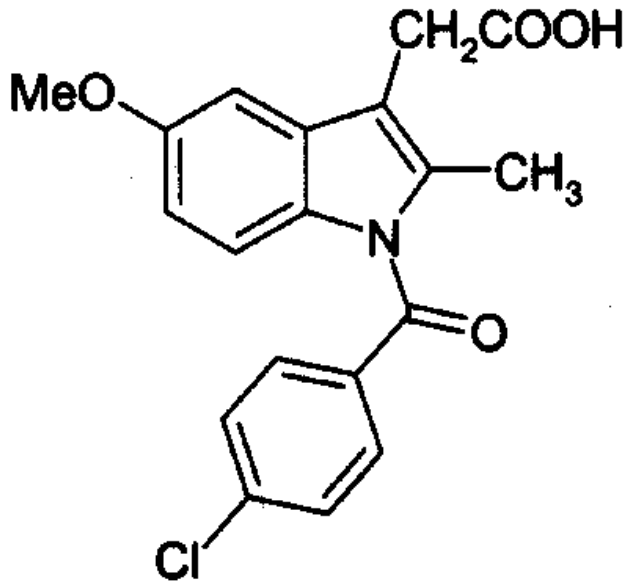
Case Studies 3

Die Entdeckung von Vioxx (Rofecoxib)

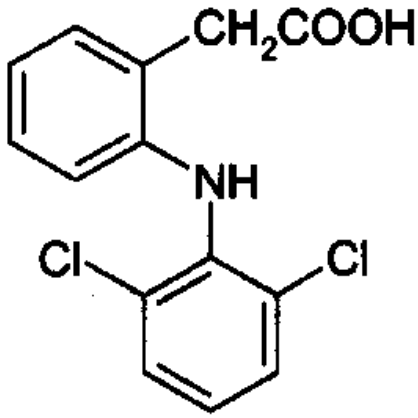
Die Vorgänger



1 Aspirin



2 indomethicin



3 diclofenac

Die beteiligten Enzyme

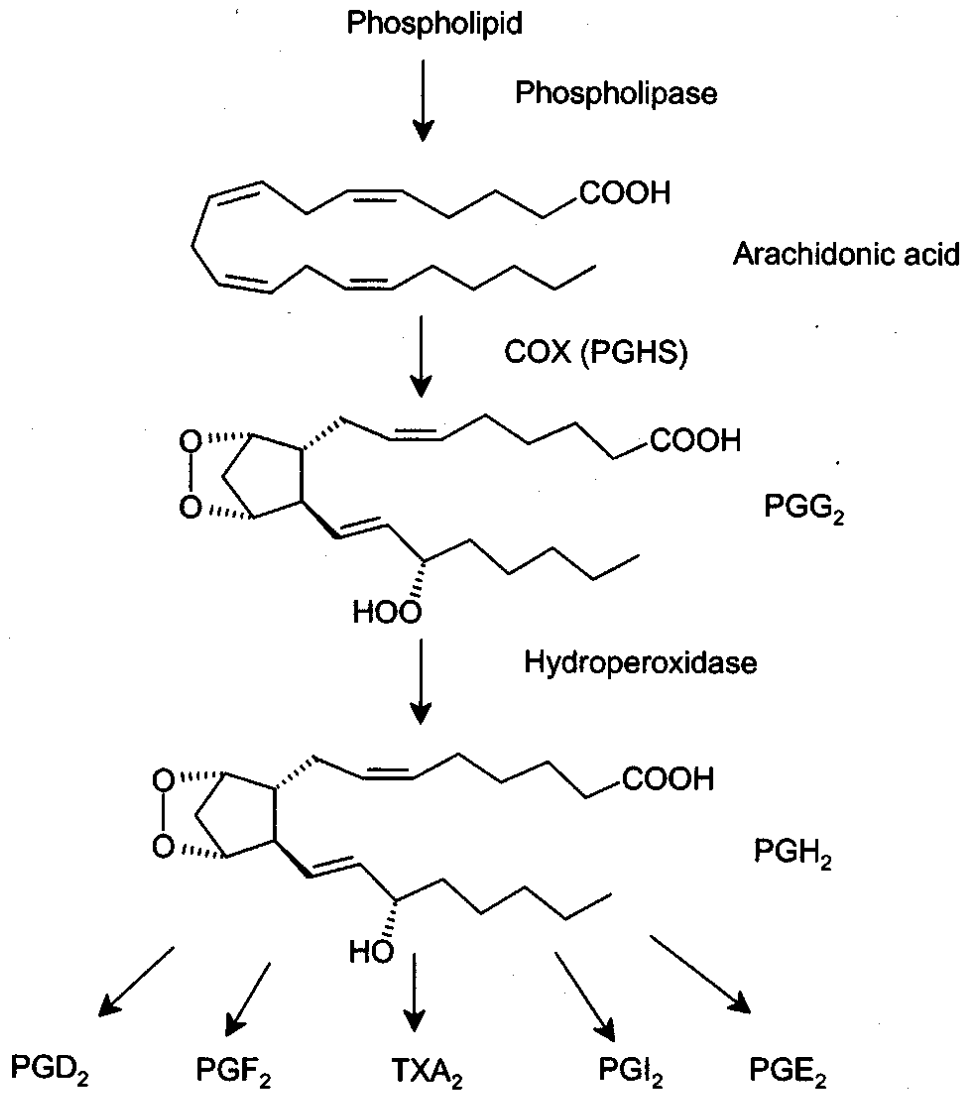
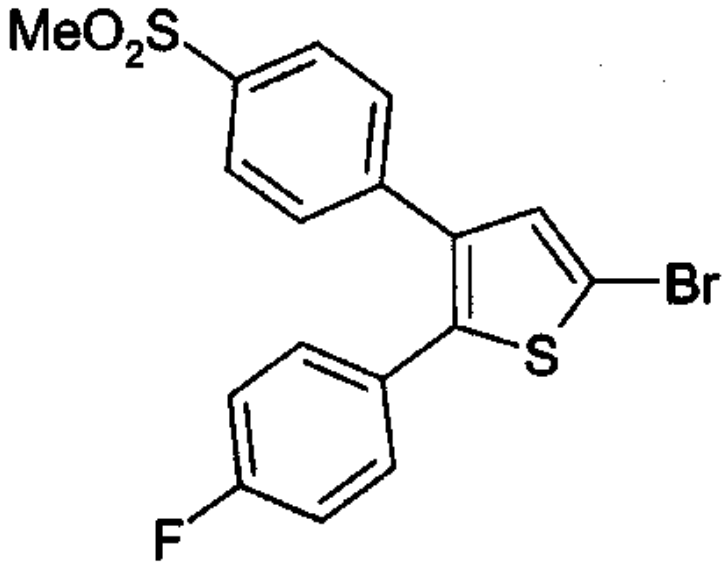
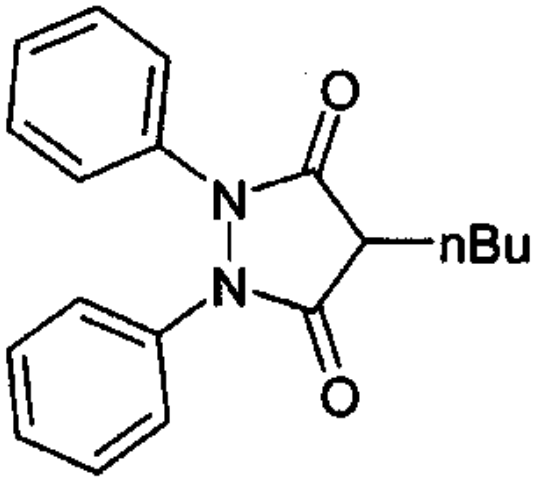


Figure 1 *Role of COX (PGHS) in the arachidonic acid pathway*

Problem Halbwertszeit

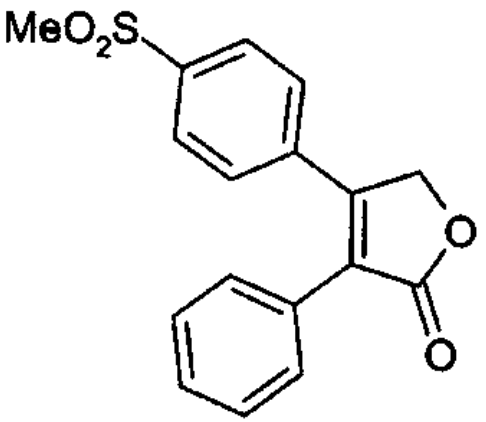


4 DuP 697

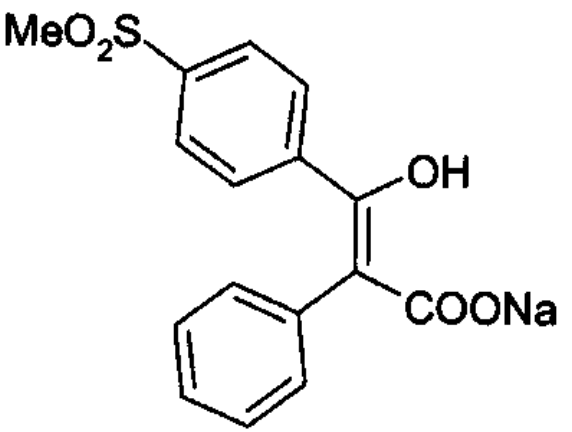


5 phenylbutazone

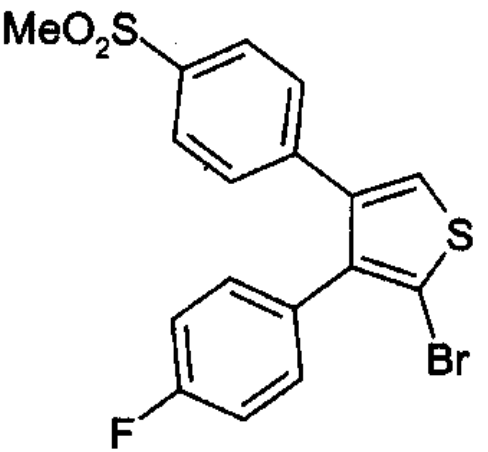
Problem Löslichkeit



6 MK-966



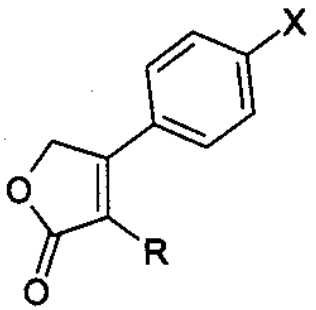
7

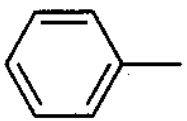
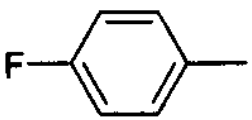


8

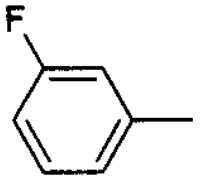
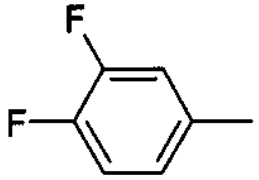
Versuchsreihe im Vergleich

Table 1 *SAR of the 3,4-diarylfuranones*



R	X	Whole cells IC_{50} µM		Human whole blood IC_{50} µM	
		COX-2	*Selectivity*	*COX-2*	*Selectivity*
	$-SO_2Me$	0.02	>750	0.5	38
	$-SO_2Me$	0.01	470	0.6	17

Versuchsreihe im Vergleich

	$-SO_2Me$	0.02	>2500	1.8	47
	$-SO_2Me$	0.03	>1600	0.9	14
	$-SO_2NH_2$	nd	nd	0.8	7
Indomethacin		0.03	0.7	0.4	0.5

NK1-Rezeptor-Gegenspieler

Veteilung im Gehirn

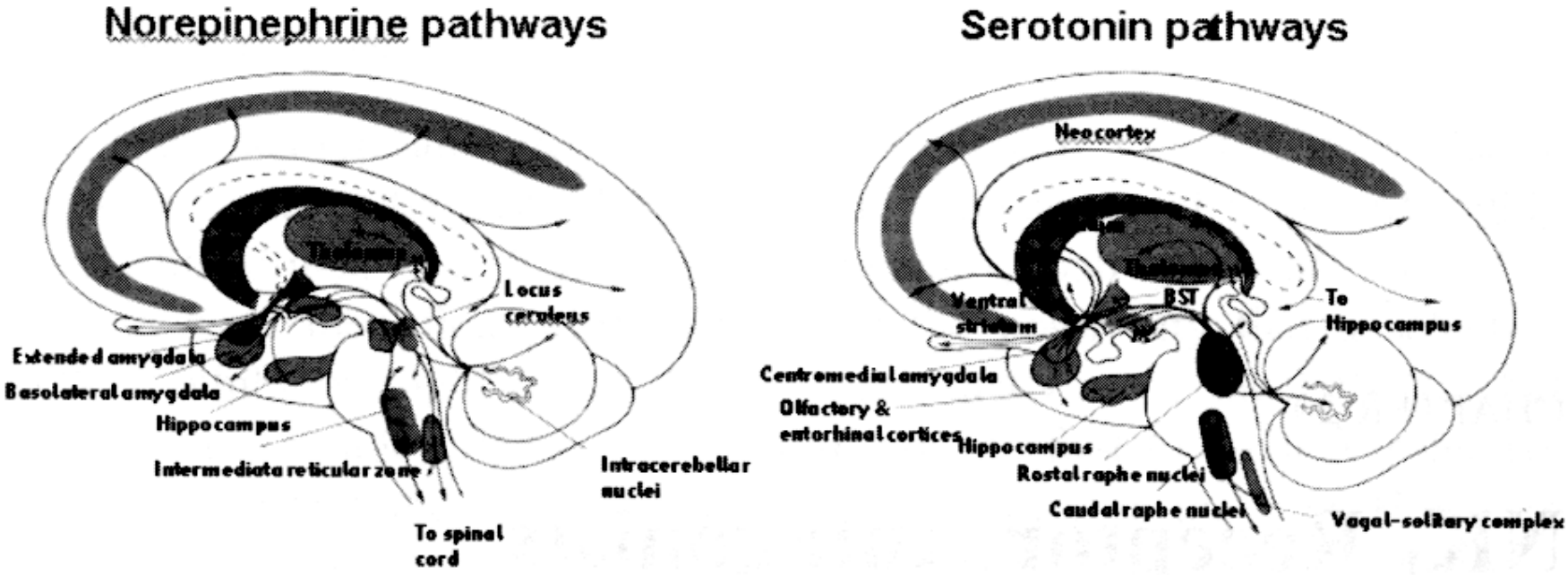
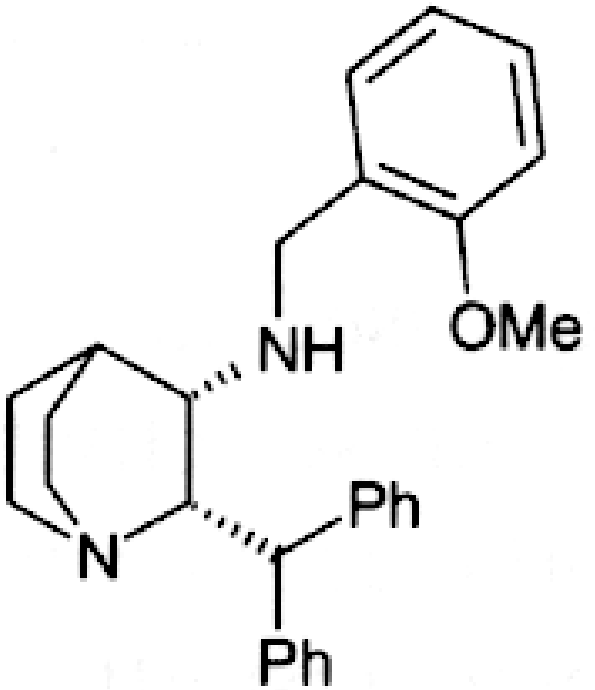


Figure 1 *Brain distribution of the NK_1 receptor*

CP-96345

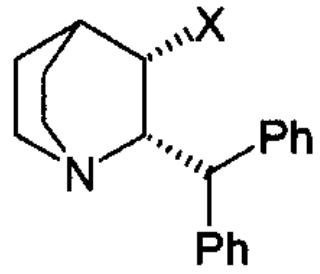
- Schlechte orale Verabreichbarkeit
- Kardiovaskuläre Nebenwirkungen

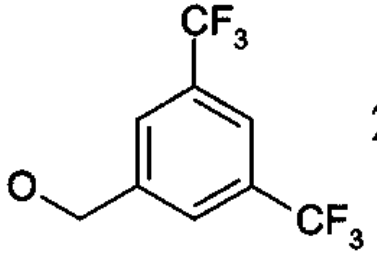


1

Vergleichende Studie

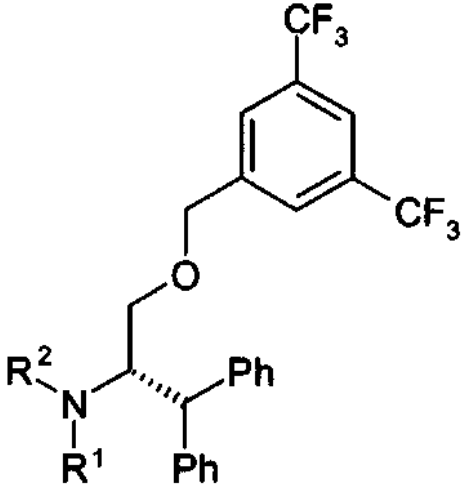
Table 1 *Structure and activities of quinuclidines*



X	IC_{50} (μM)	*X*	IC_{50} (μM)
$-NHCH_2$-Ph	0.15	–OCO-Ph	>1
$-NHCH_2CH_2$-Ph	0.70	–OCONH-Ph	>1
–NHCO-Ph	>1	$-OCH_2$-Ph	0.11
–NHCOO-Ph	>1	 **2**	0.002
–NHCONH-Ph	>1		
–NHCSNH-Ph	>1		

pK_a-Effekte in der azykl. Serie

Table 2 *Structure and activities of substituted ethanolamines as basic pharmacophore*



	R^1	R^2	hNK_1 (nM)	Ca^{2+} (nM)
1	CP-96345		0.6	240
3	H	H	10	190
	Me	Me	2.5	980
	H	CH_2cPr	100	357
4	H	CH_2CONH_2	0.8	1700

Molekül - Design

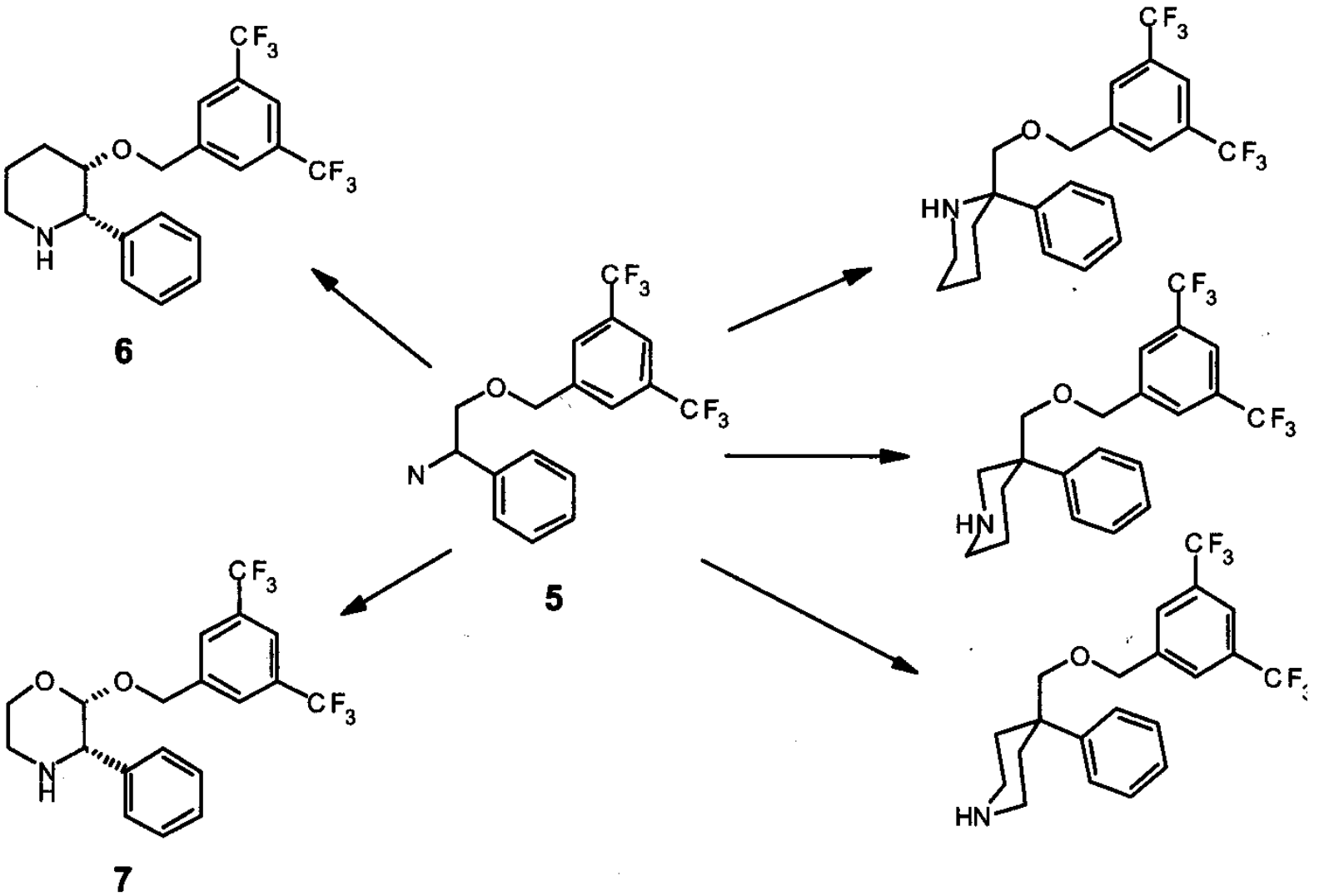
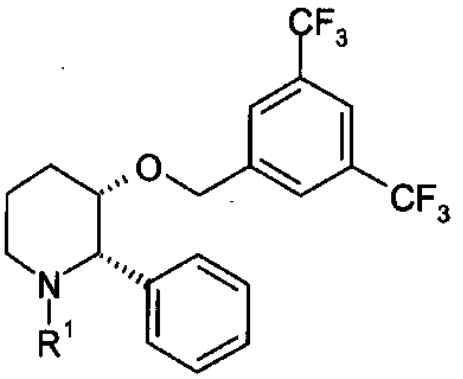
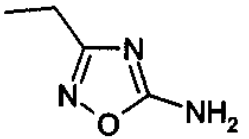
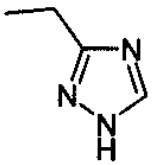
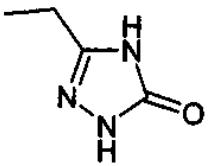
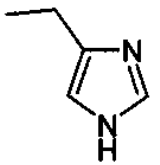


Figure 3 *Alternative conformational restraints derived from the basic pharmacophore* ***5***

Bioisosterer Amid-Ersatz

Table 3 *Structure and activities of morpholines*



No.	R^1	hNK_1 (nM)	Ca^{2+} (μM)
		0.45	>30
8		0.19	>100
9		0.1	>10
10		0.7	2.3

Verbesserte *in vivo* Aktivität

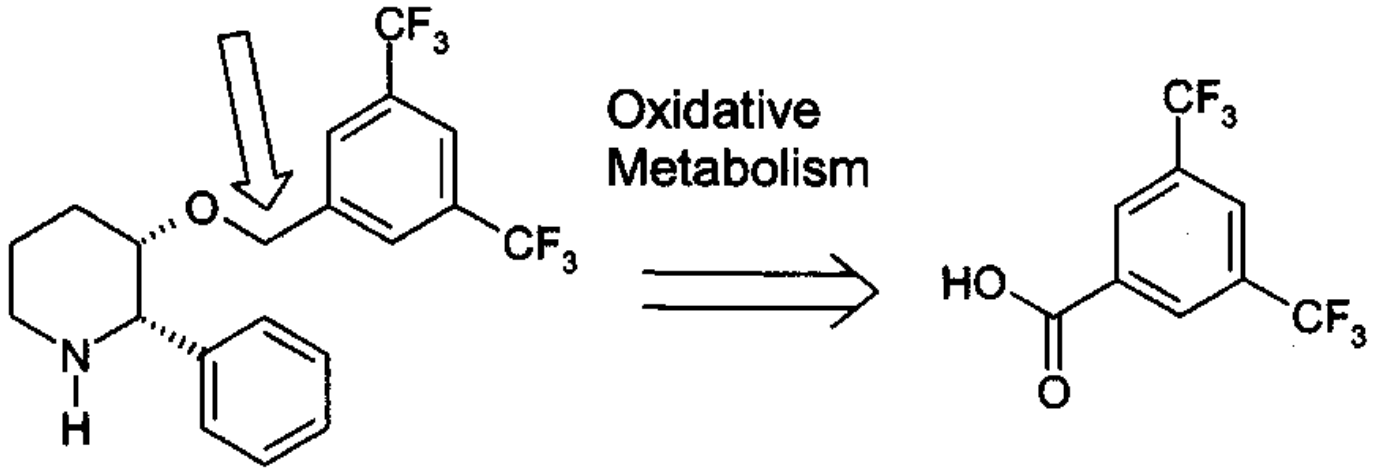
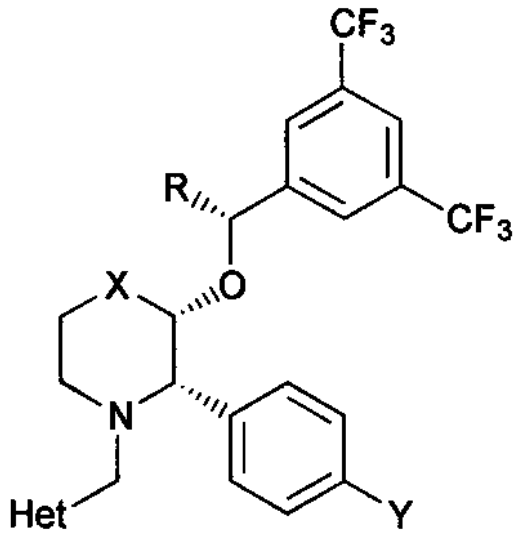


Figure 4 *Site of metabolism of the 3,5-bis(trifluoromethyl)benzyl ether 7*

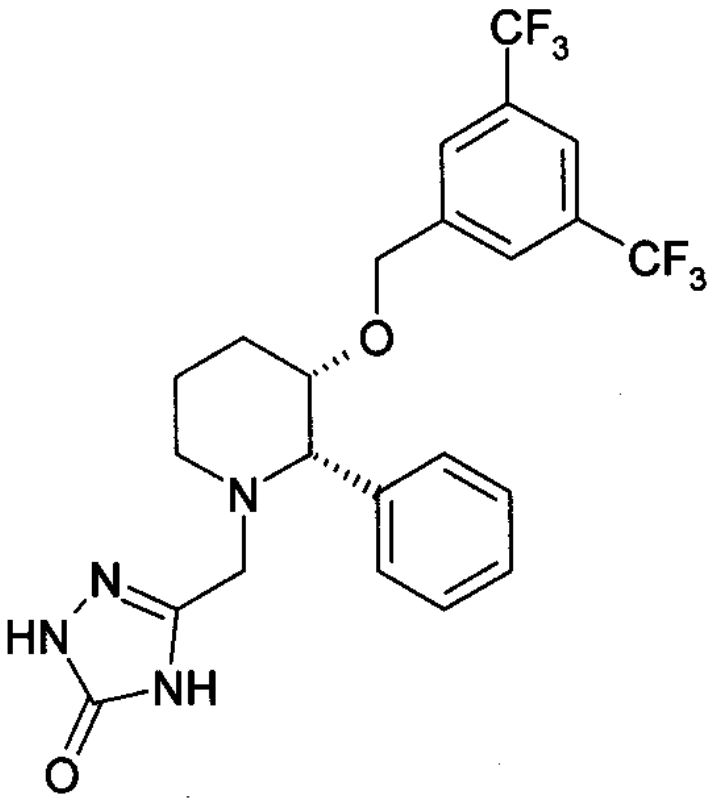
Wirkungsdauer

Table 4 *Summary of* in vitro *and* in vivo *studies (ID_{50} or % inhib. @ mg kg^{-1} p.o.)*

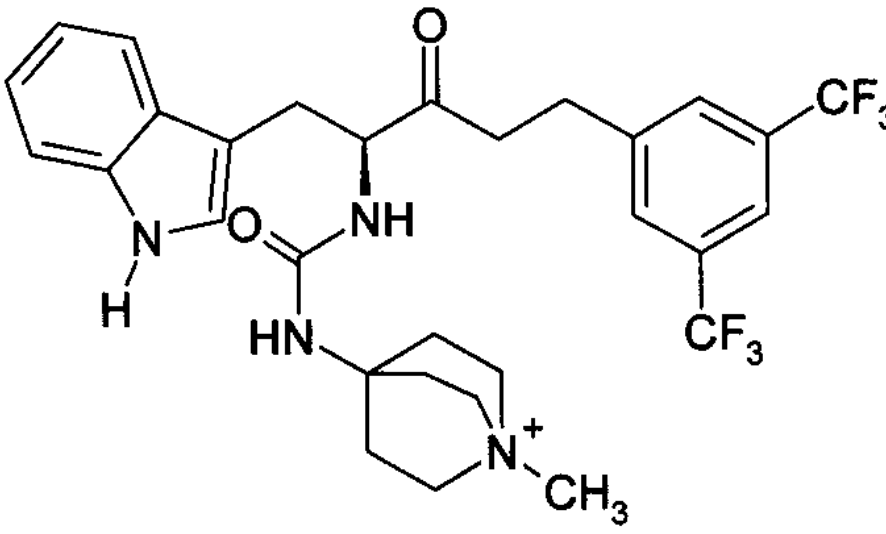


No.	*X*	*Y*	*R*	*Heterocycle*	IC_{50} (nM)	ID_{50} at 1 h (nM)	*Inhibition at 8 h*	*Inhibition at 24 h*
8	CH_2	H	H	Triazole	0.18	0.034	55% @ 1	0% @ 1
11	CH_2	H	Me	Triazole	0.16	0.06	78% @ 1	12% @ 1
12	CH_2	H	Me	Triazolinone	0.16	0.026	97% @ 1	66% @ 1
13	O	F	Me	Triazolinone	0.09	0.008	100% @ 1	0.55

Gleiche Wirkung



10 L-741671

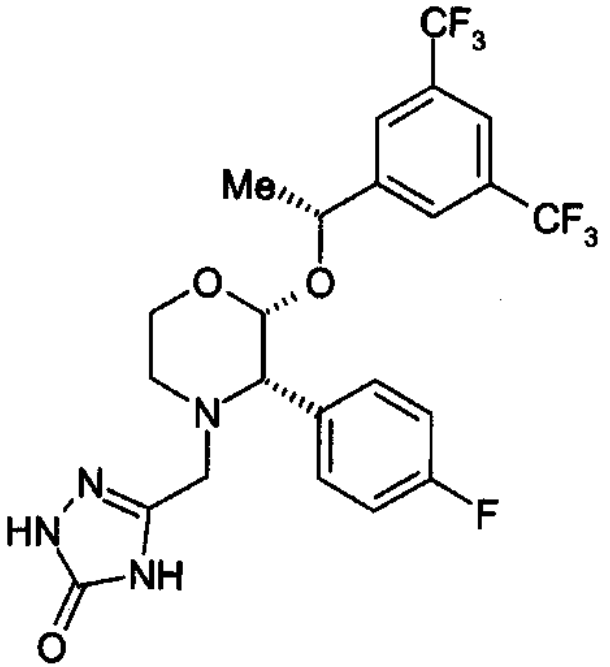


12

Figure 6 *Structures of the brain penetrant and non-penetrant NK_1 antagonists*

MK-869 Profil

Table 5 *Structure and activities of MK-869 (13)*



hNK1 IC_{50}	0.09nM
SYVAL ID_{50} (po 1 h)	0.008 mg kg^{-1}
SYVAL ID_{90} (po 24 h)	1.8 mg kg^{-1}
foot-tapping ID_{50} (iv 1 h)	0.33 mg kg^{-1}
foot-tapping ID_{50} (iv 24 h)	0.36 mg kg^{-1}

HIV und AIDS

Funktionen der HIV-Genteile

Table 1. HIV-gene functions

Genes	Functions
Structural	
gag	matrix, virion maturation and stability, capsid, virus particle maturation and release
pol	protease, reverse transcriptase, integrase
env	external envelope, receptor binding, virion infectivity
Regulatory	
tat	transcription transactivator of gene expression
rev	regulator of protein expression
tev/tnv	undefined
nef	negative factor, virus propagation
vpr	early regulatory protein
Accessory	
vif	cell-free virus transmission, *env* processing
vpu	virus maturation/release

Virus - Lebenszyklus

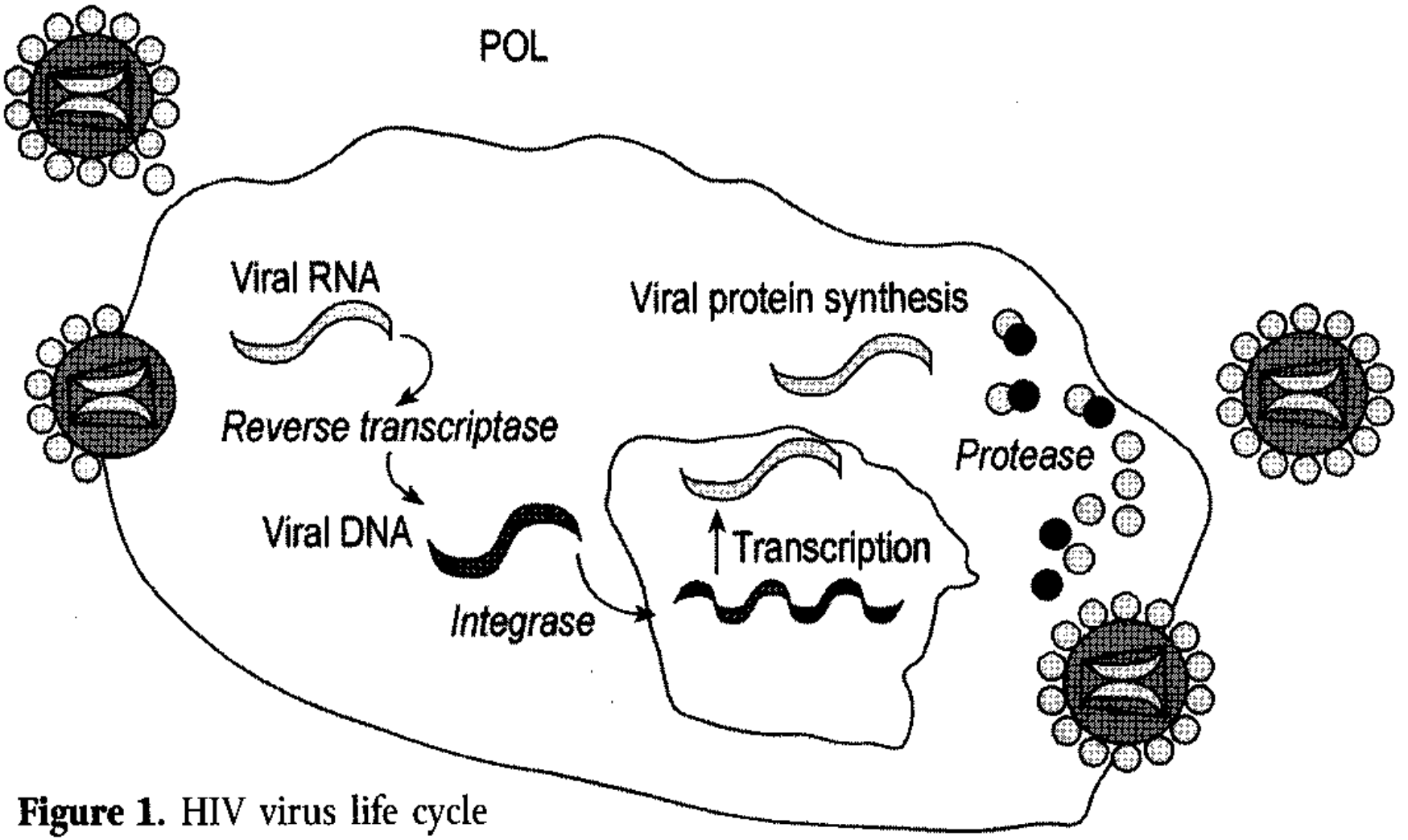
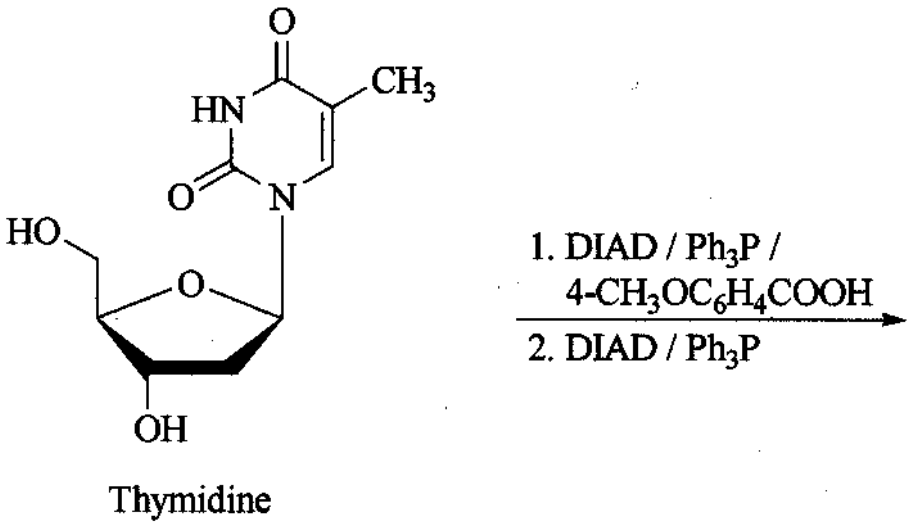


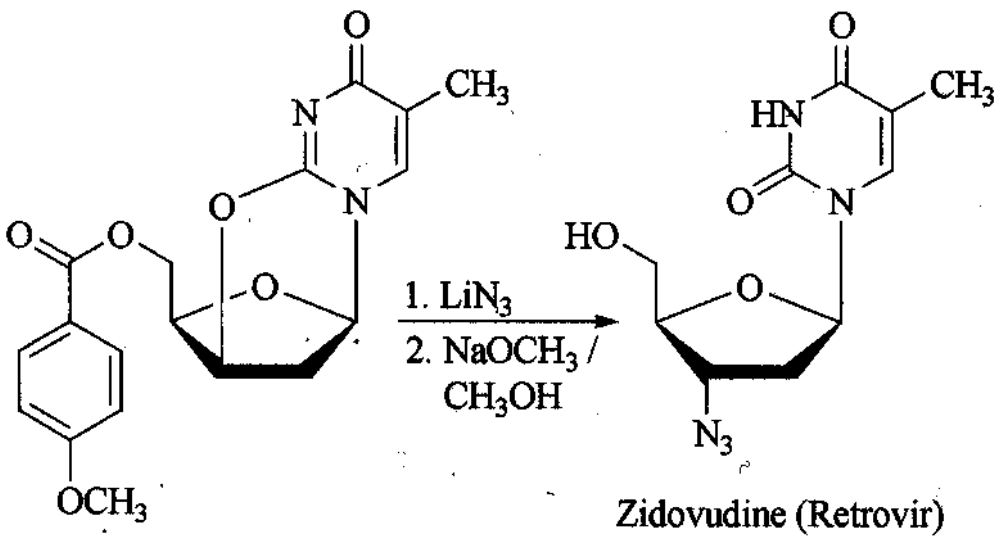
Figure 1. HIV virus life cycle

Nukleoside Analoge

Zidovudine–erster Hemmstoff

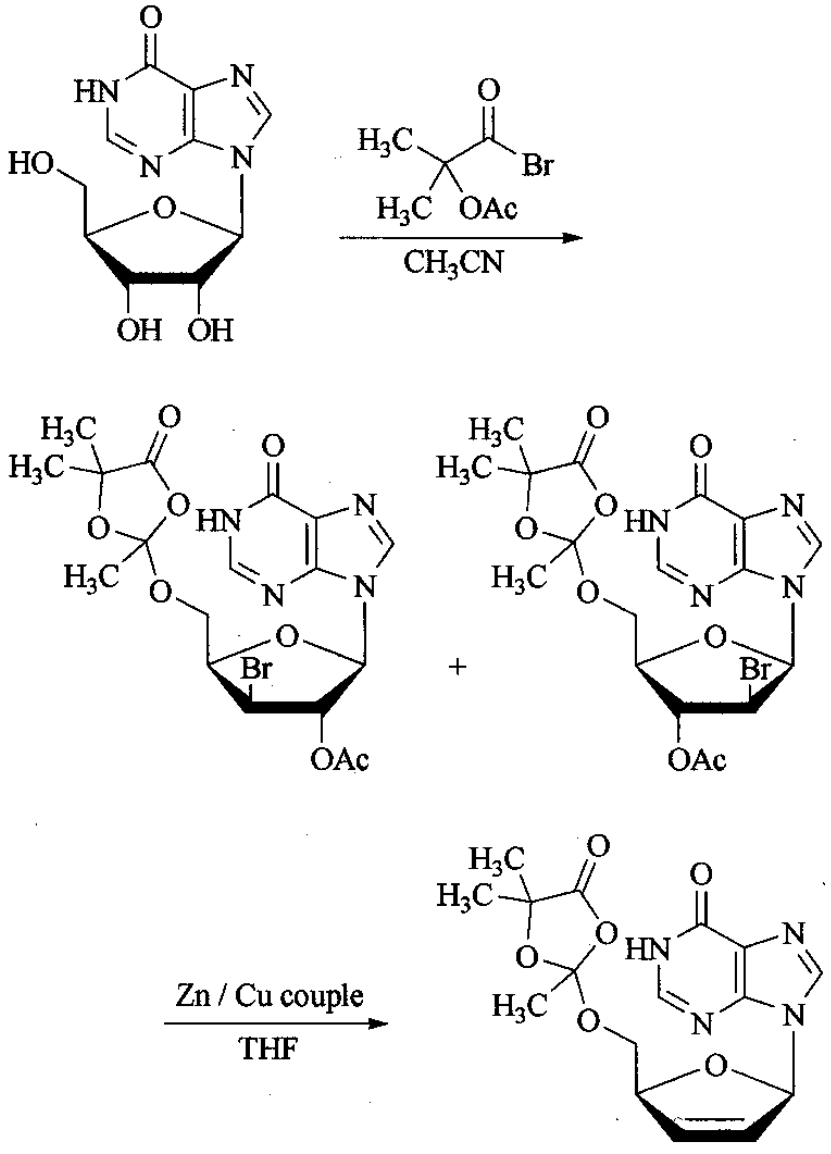


Thymidine

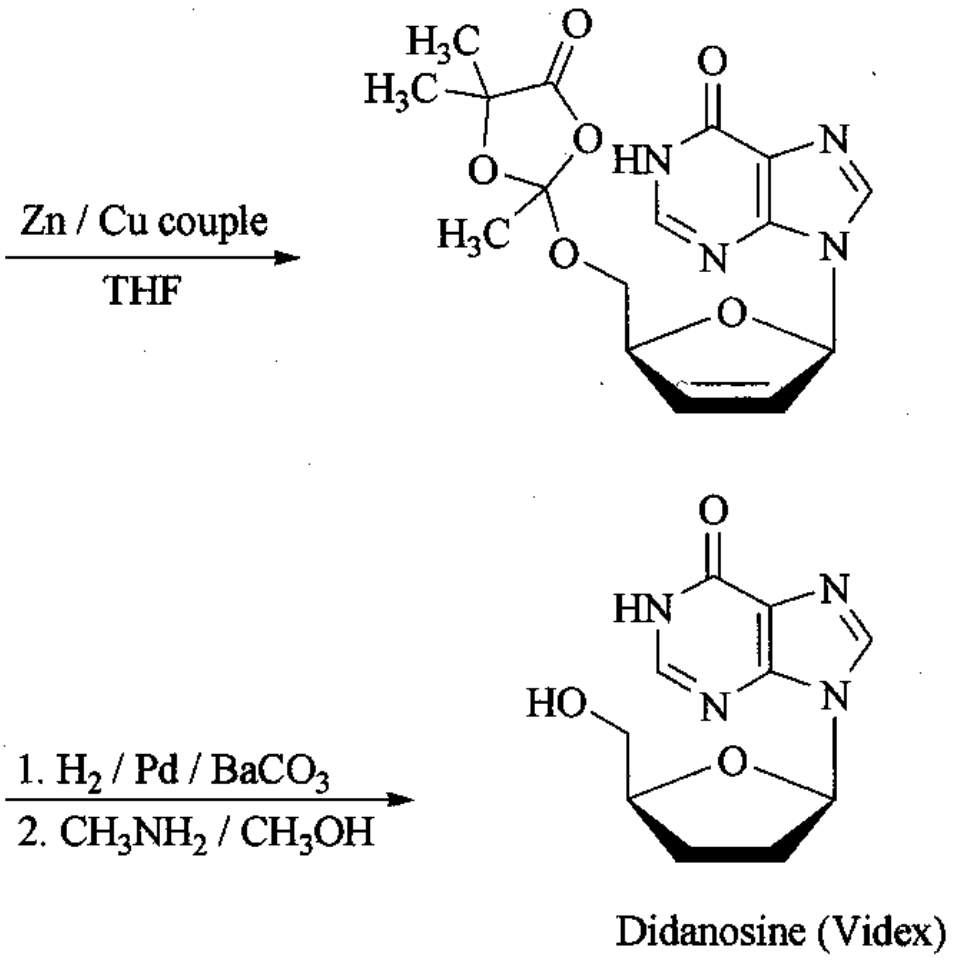


Zidovudine (Retrovir)

Didanosine



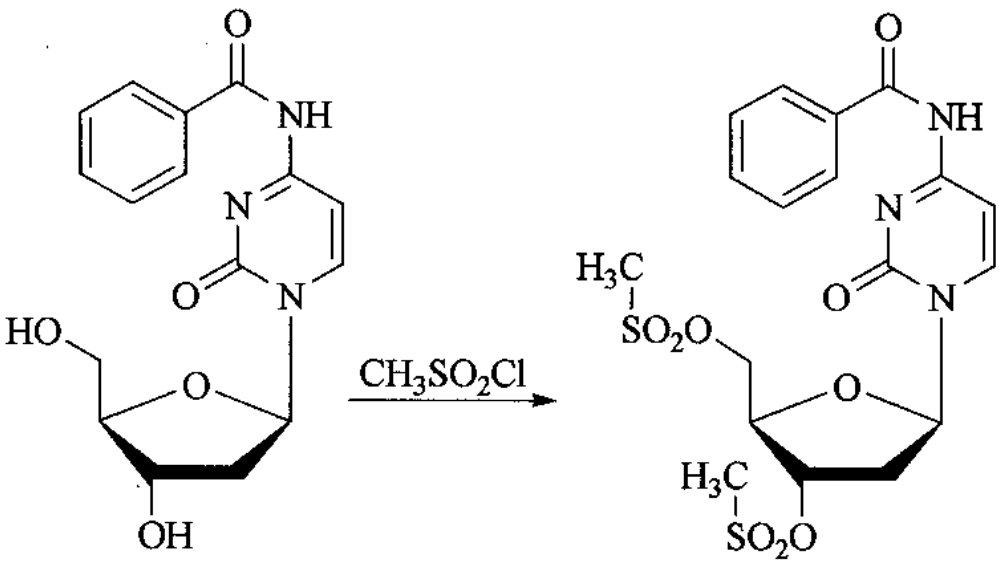
Didanosine

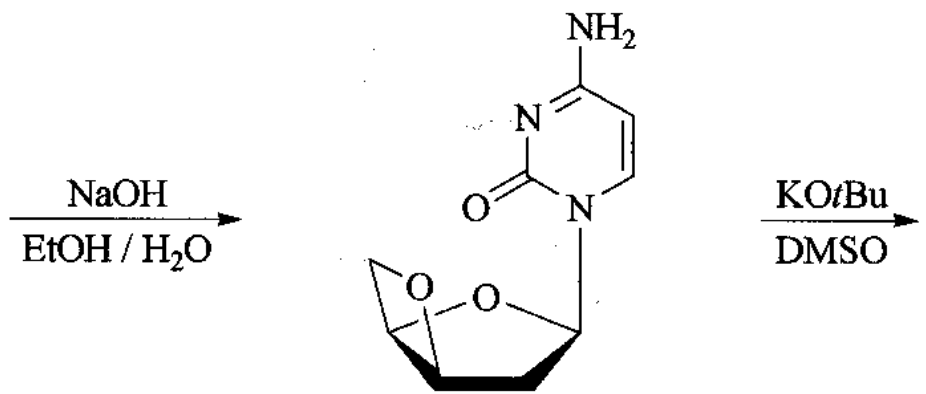


Didanosine (Videx)

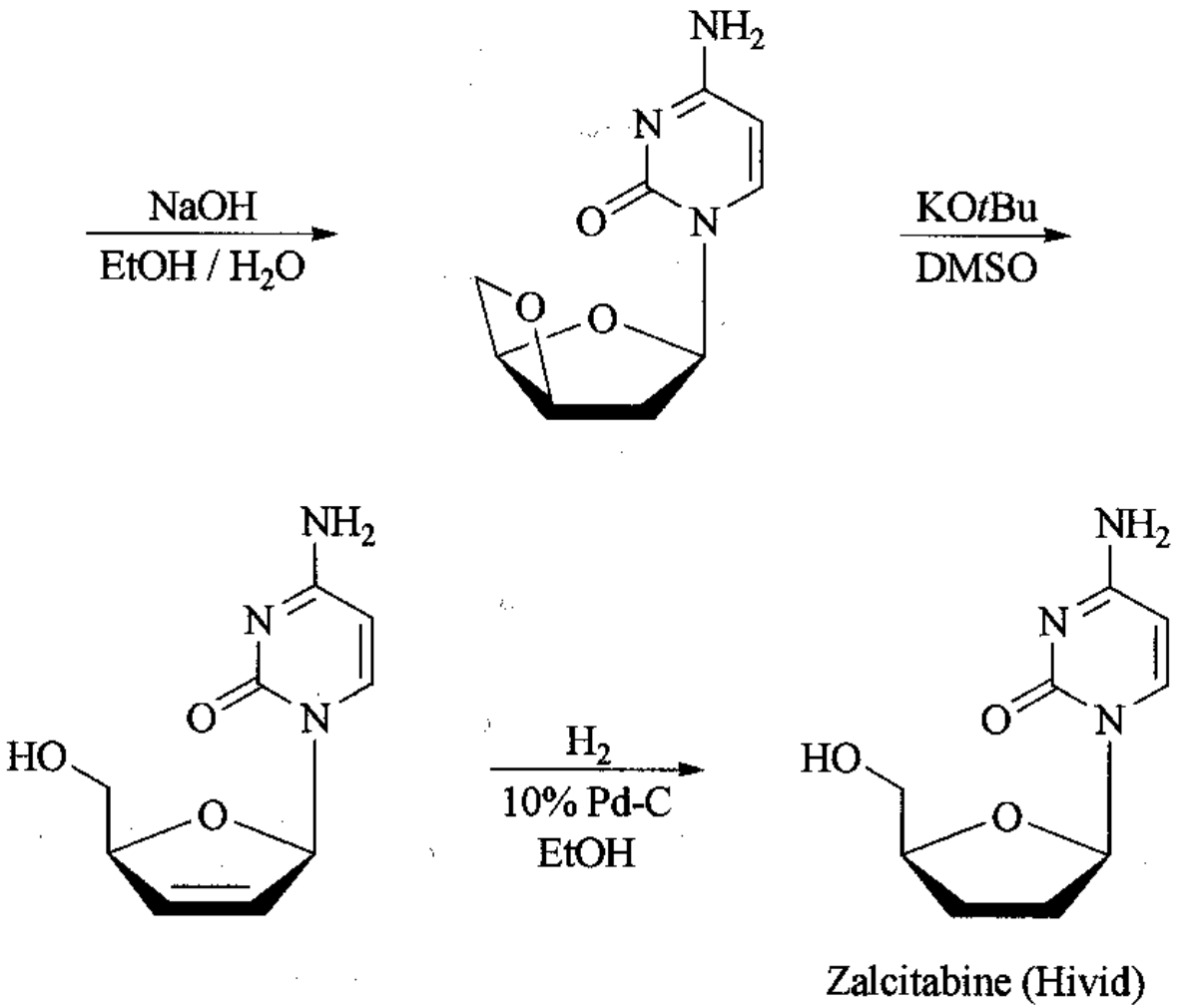
Trade name: Videx (Bristol-Myers Squibb).

Zalcitabine



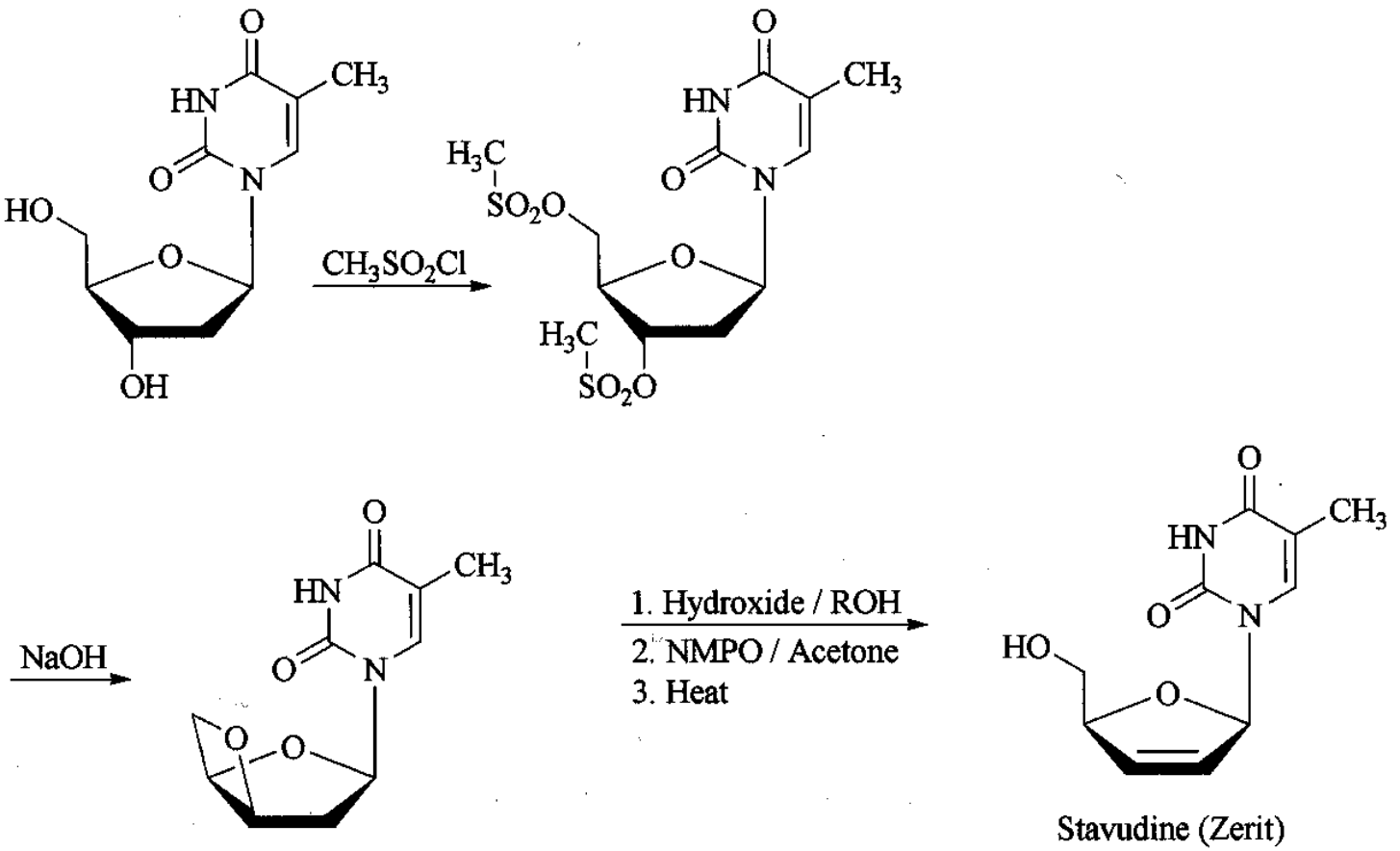


Zalcitabine



Trade name: Hivid (Hoffmann-LaRoche).

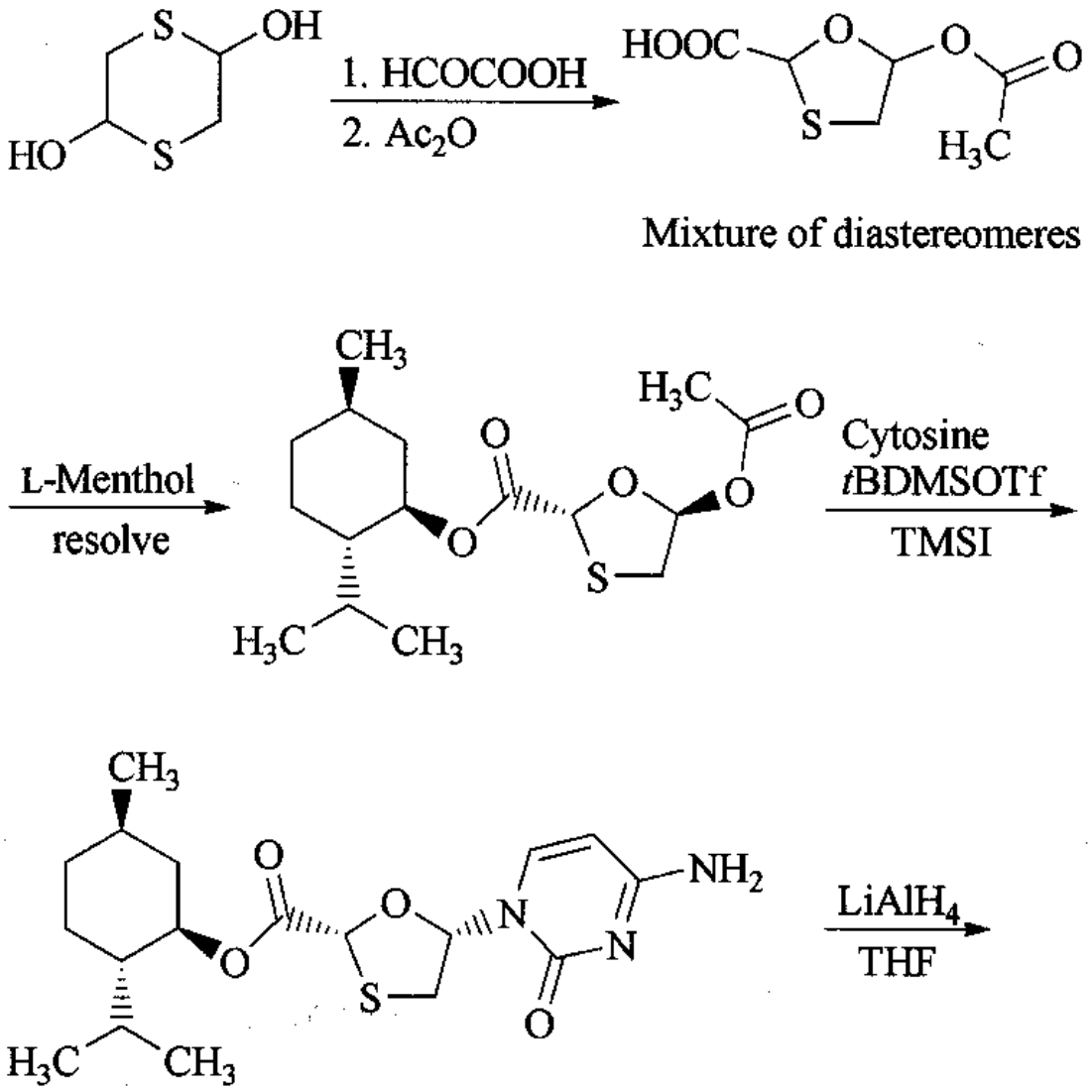
Stavudine



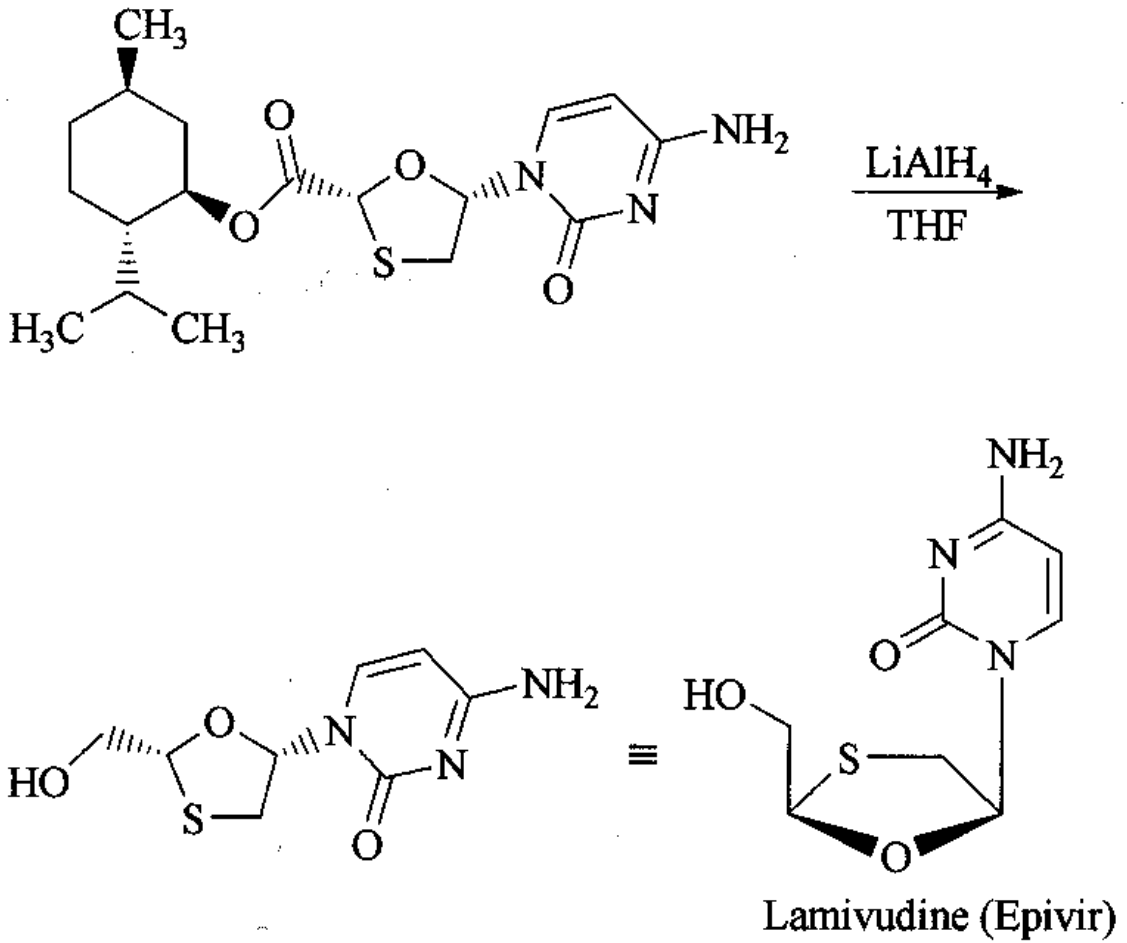
Stavudine (Zerit)

Trade name: Zerit (Bristol-Myers Squibb).

Lamivudine


1. HCOCOOH
2. Ac2O
Mixture of diastereomeres
L-Menthol
resolve
Cytosine
tBDMSOTf
TMSI
LiAlH4
THF

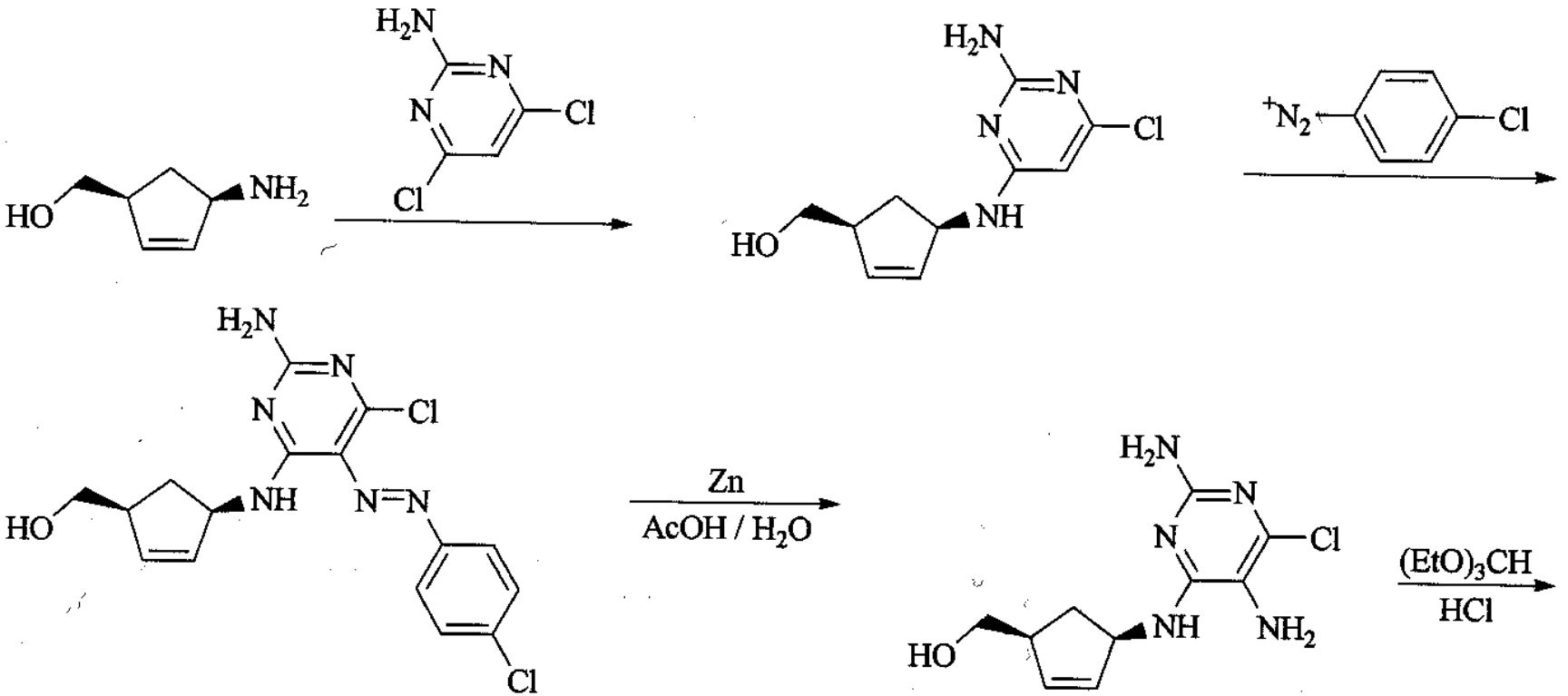
Lamivudine



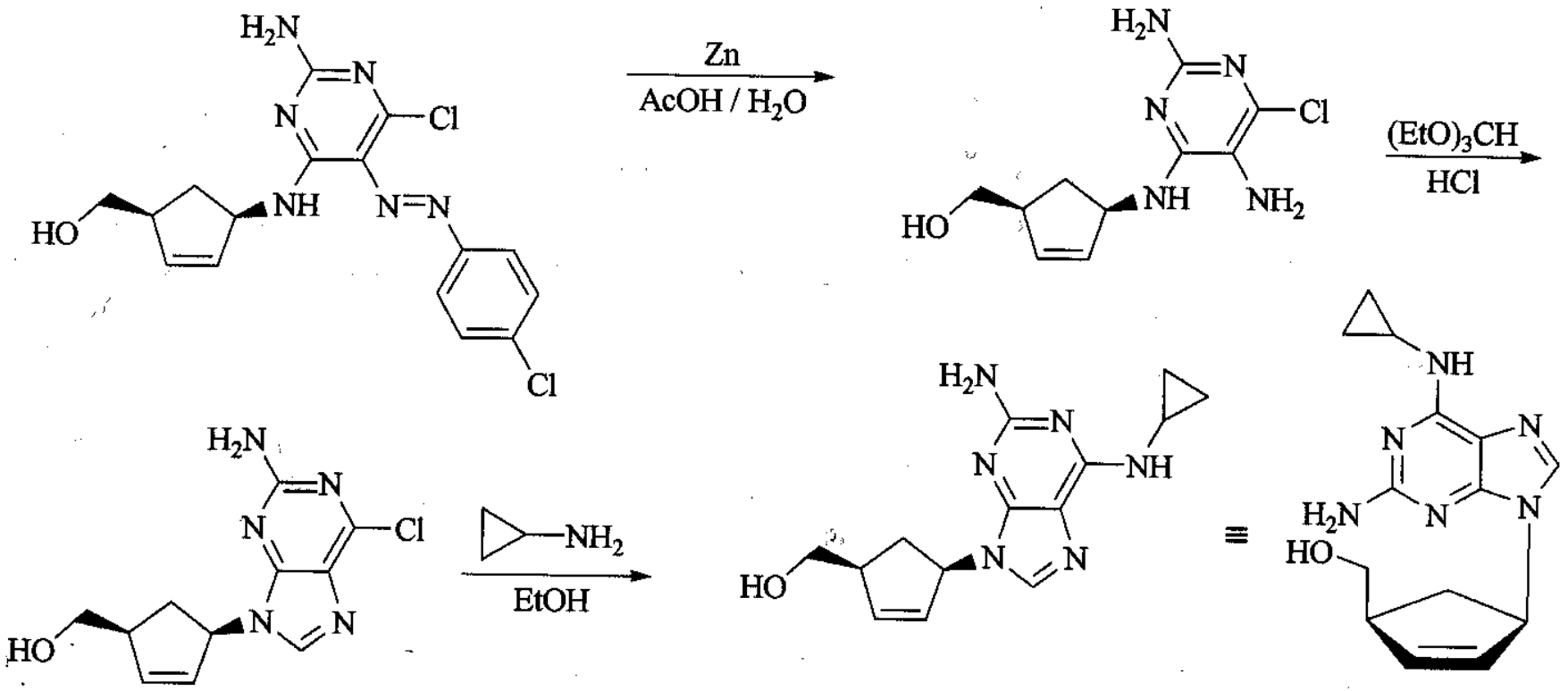
Lamivudine (Epivir)

Trade names: Epivir (BioChem Pharma, Glaxo Wellcome), Combivir (lamivudine and zidovudine combination tablets, Glaxo Wellcome).

Abacavir



Abacavir

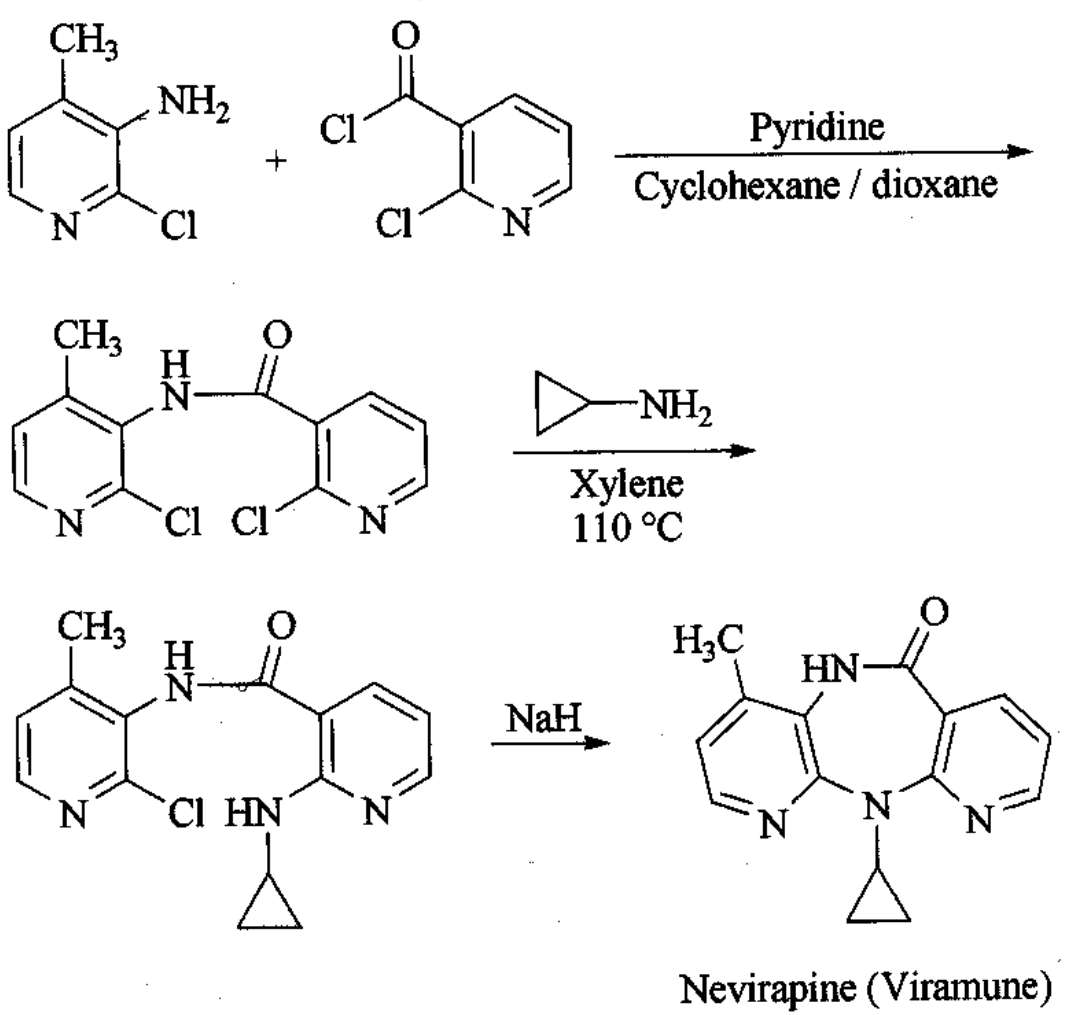


Trade name (abacavir sulfate): Ziagen, Glaxo Wellcome.

Abacavir (Ziagen)

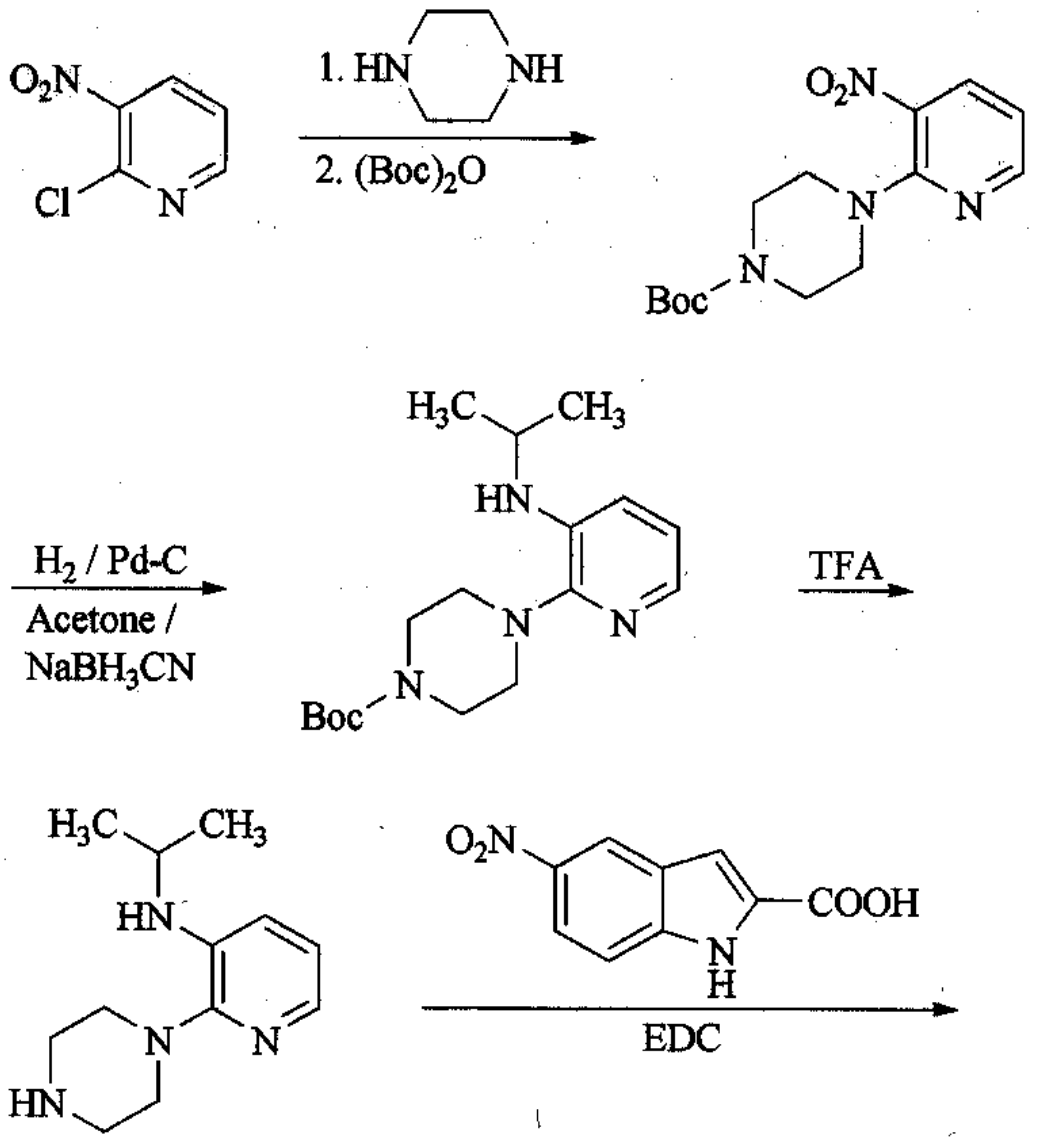
Nonnukleoside Analoge

Nevirapine

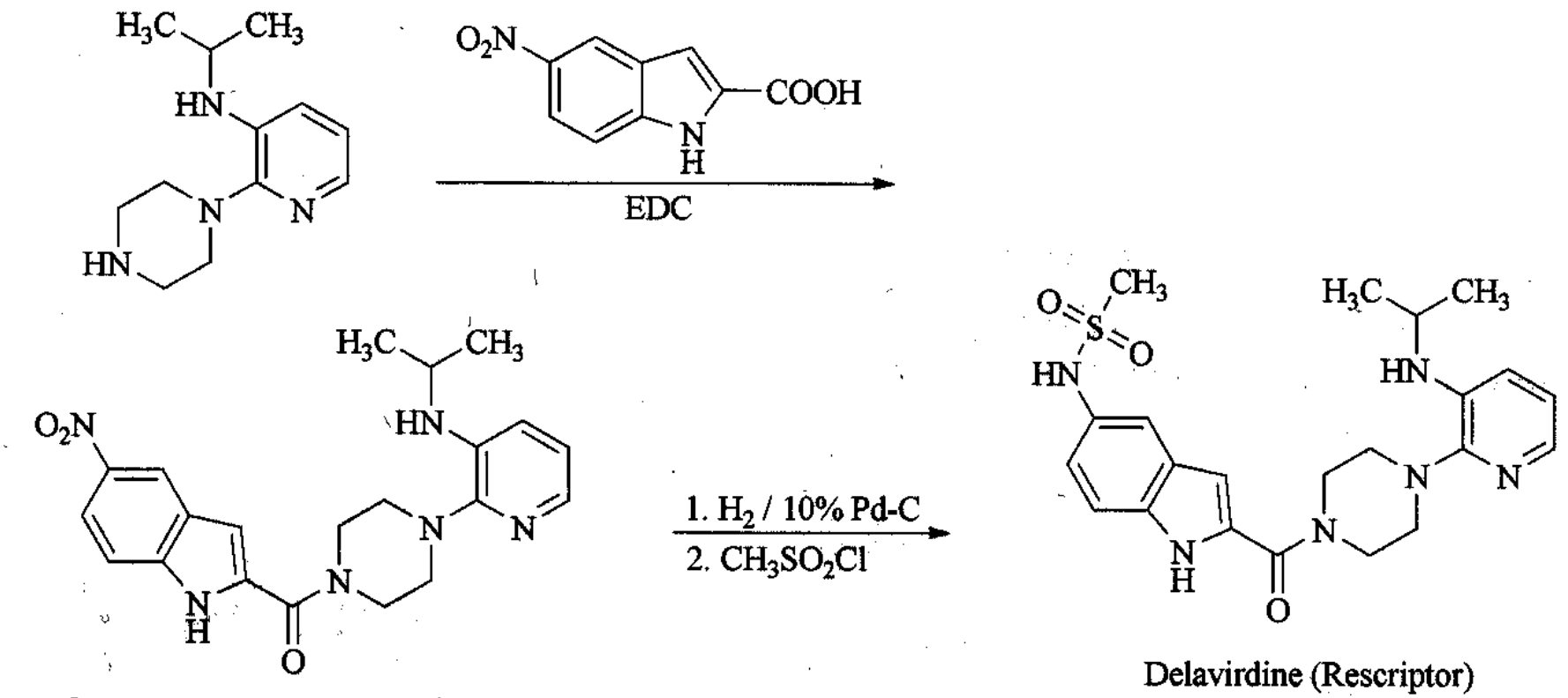


Trade name: Viramune (Boehringer Ingelheim).

Delavirdine



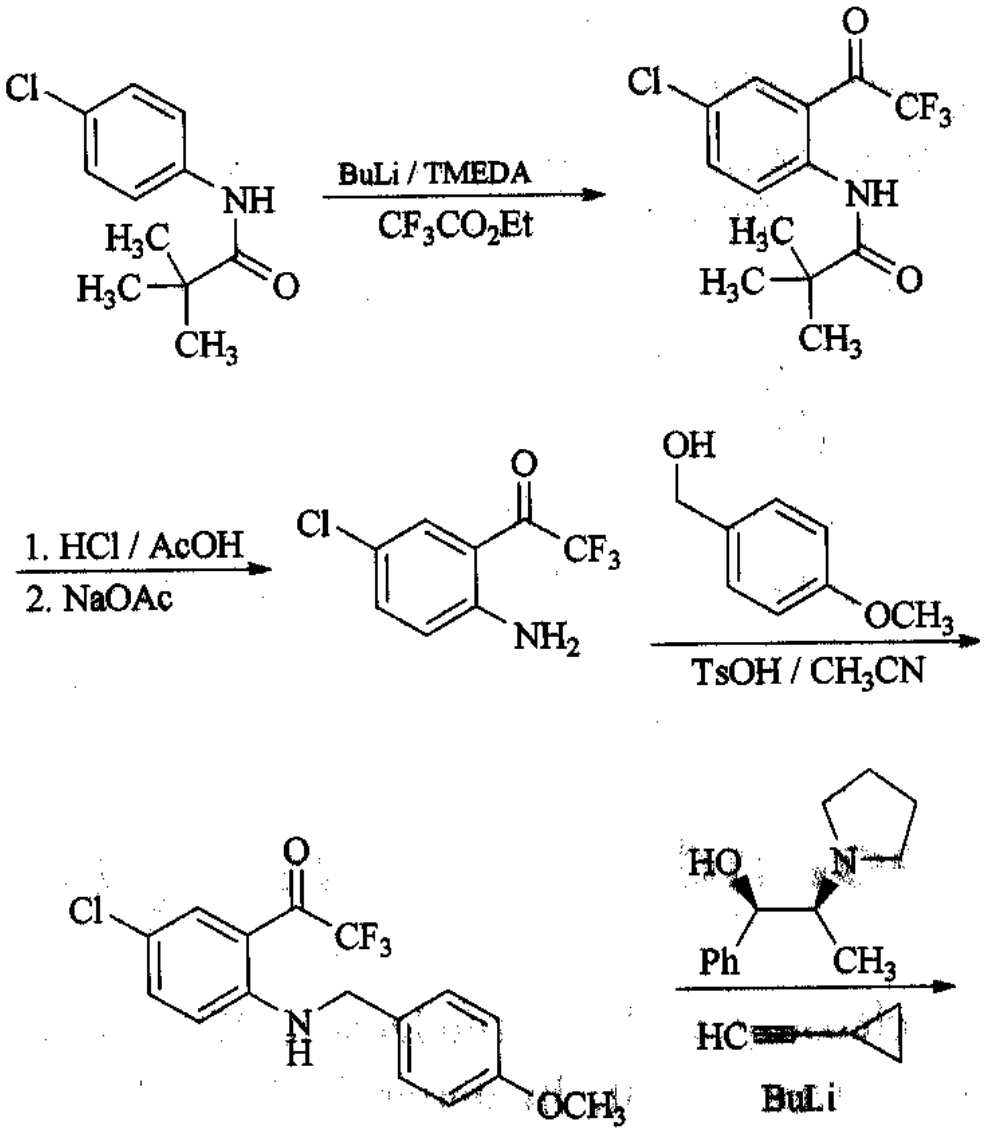
Delavirdine



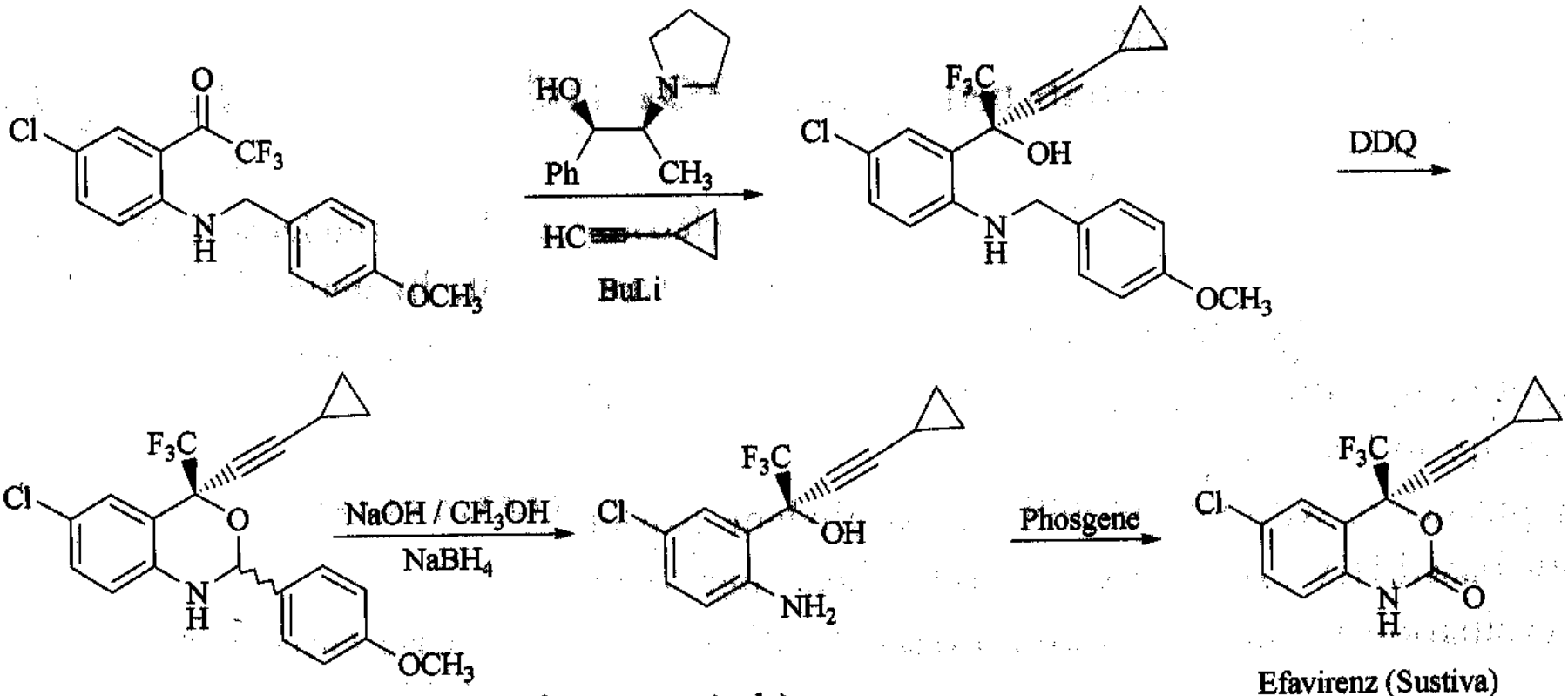
Delavirdine (Rescriptor)

Trade name: Rescriptor (Pharmacia & Upjohn).

Efavirenz

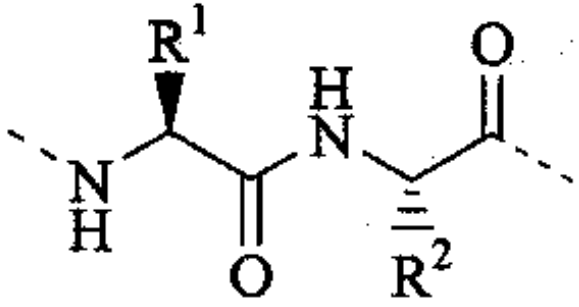

Cl
NH
H3C
H3C
CH3
O
BuLi / TMEDA
CF3CO2Et
Cl
O
CF3
NH
H3C
H3C
CH3
O
1. HCl / AcOH
2. NaOAc
Cl
O
CF3
NH2
OH
OCH3
TsOH / CH3CN
Cl
O
CF3
N
H
OCH3
HO
N
Ph
CH3
HC
BuLi

Efavirenz

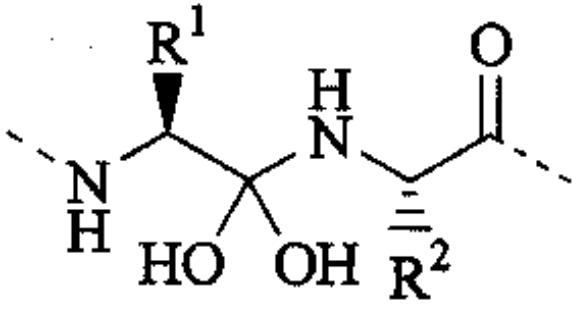


Efavirenz (Sustiva)

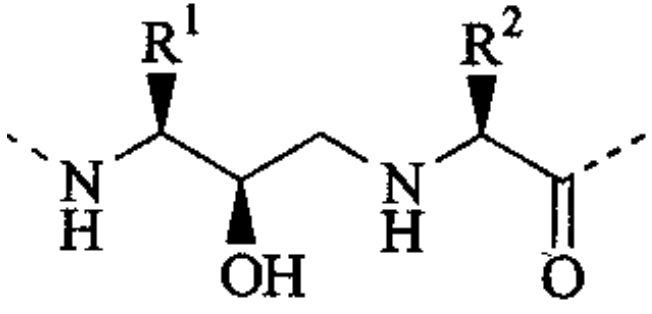
Trade name: Sustiva (DuPont Pharmaceuticals).



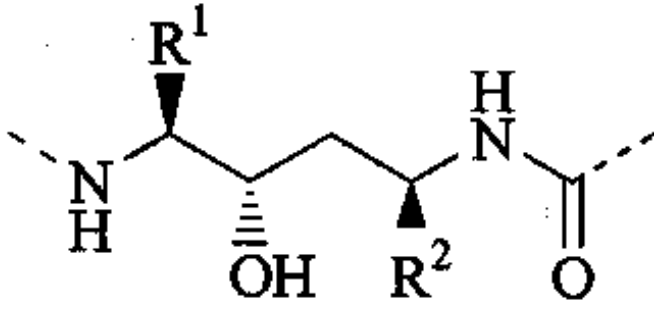
Cleavable dipeptide substrate



Amide cleavage transition state



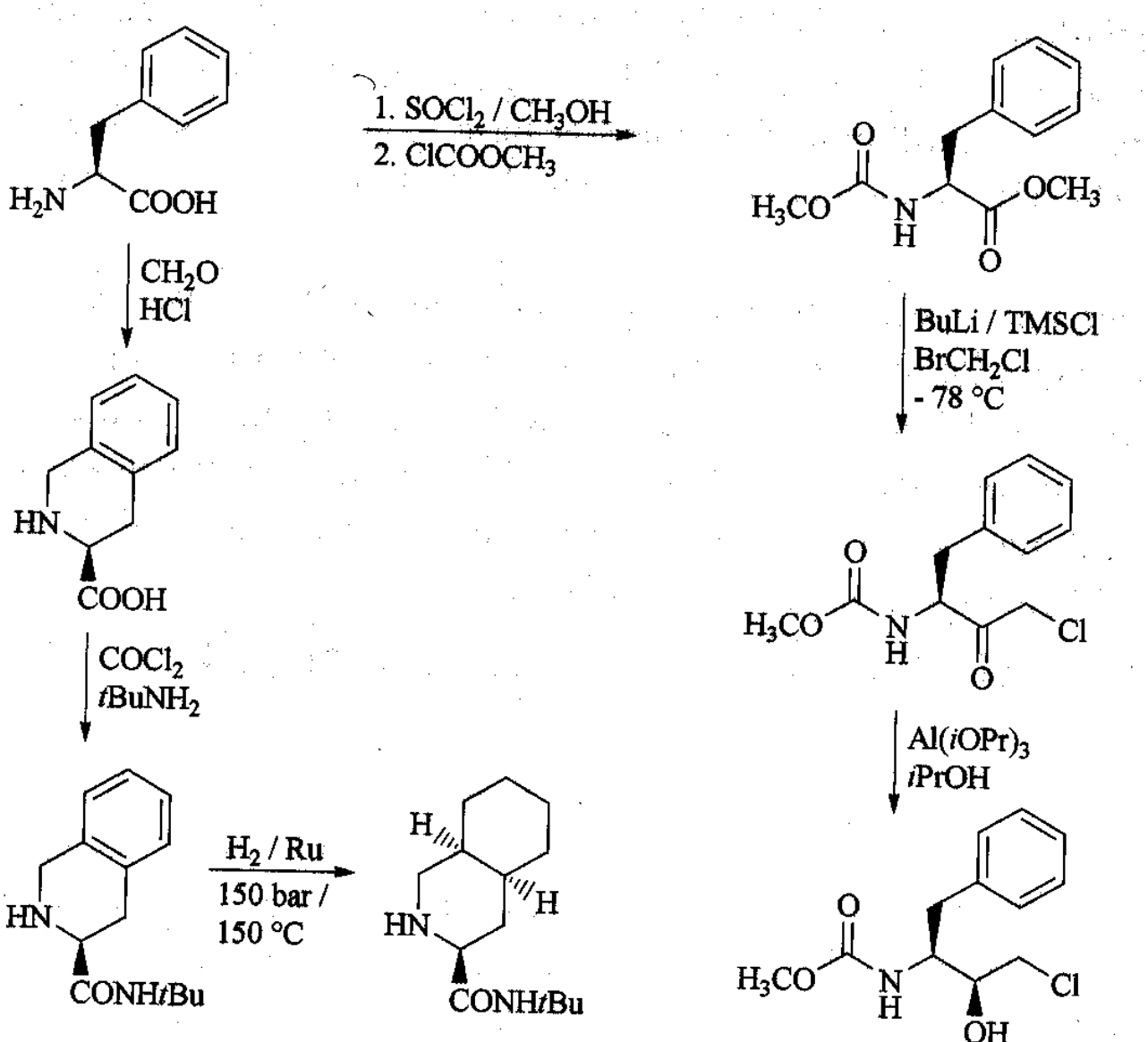
Hydroxyethylamine dipeptide isostere



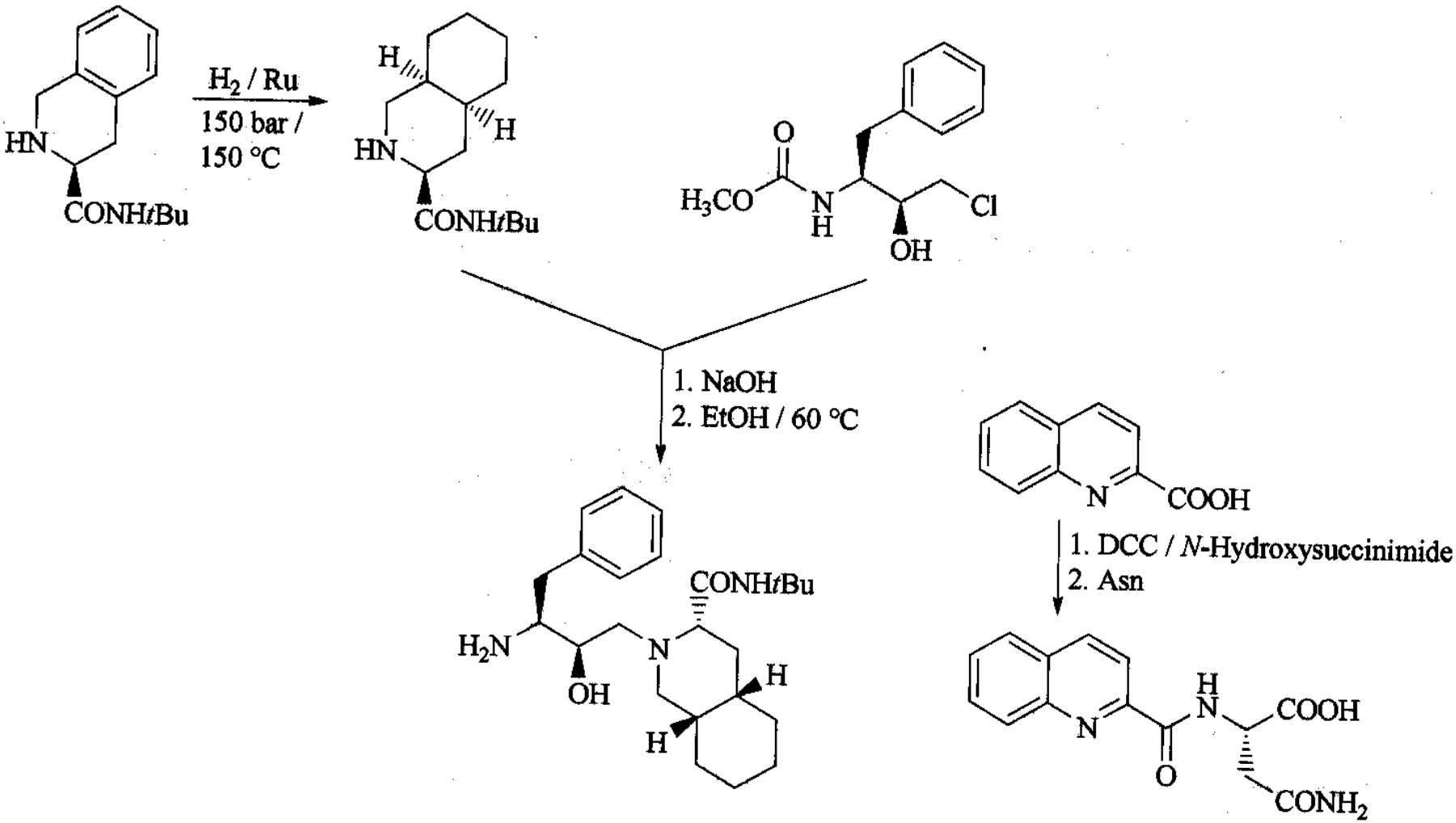
Hydroxyethylene dipeptide isostere

Protease-Hemmer

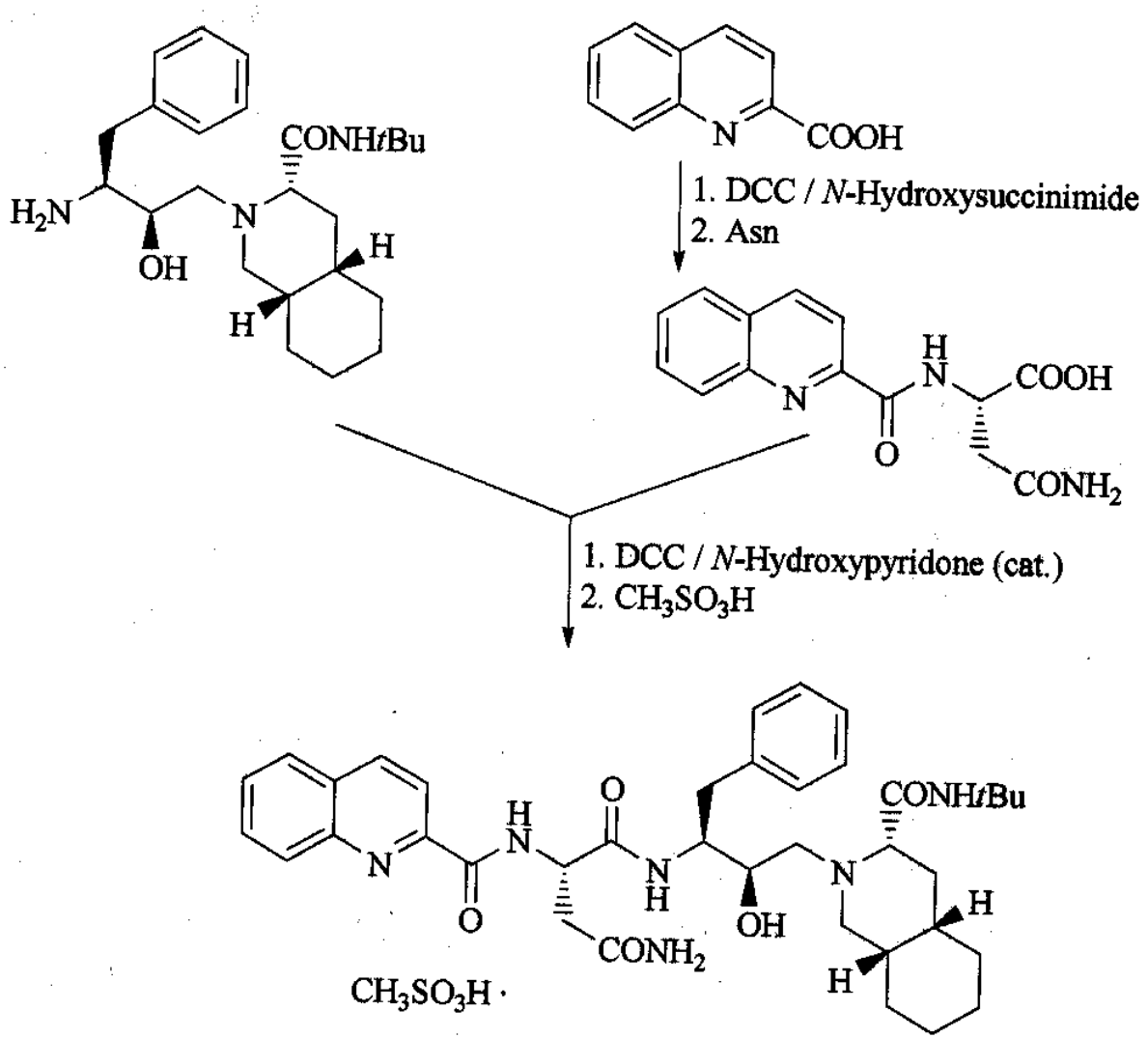
Saquinqvir


1. $SOCl_2$ / CH_3OH
2. $ClCOOCH_3$
CH_2O
HCl
BuLi / TMSCl
$BrCH_2Cl$
- 78 °C
$COCl_2$
$tBuNH_2$
H_2 / Ru
150 bar /
150 °C
Al(iOPr)$_3$
iPrOH
H_2N
COOH
H_3CO
OCH_3
HN
CONHtBu
Cl
OH

Saquinqvir

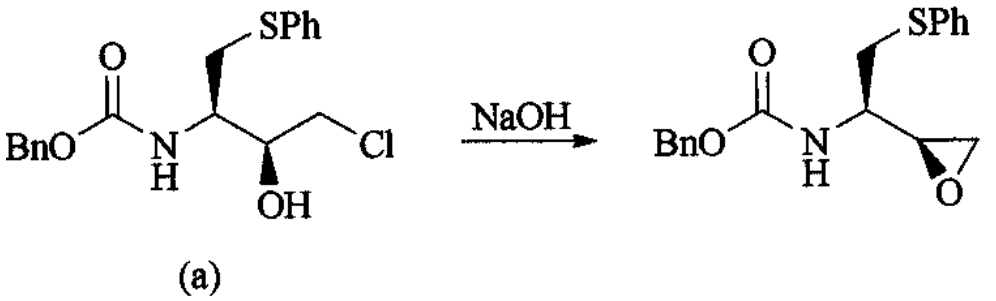

HN
CONHtBu
H2 / Ru
150 bar /
150 °C
H
H
HN
CONHtBu
O
H3CO
N
H
Cl
OH
1. NaOH
2. EtOH / 60 °C
CONHtBu
H2N
OH
N
H
H
N
COOH
1. DCC / N-Hydroxysuccinimide
2. Asn
N
H
N
COOH
O
CONH2

Saquinqvir

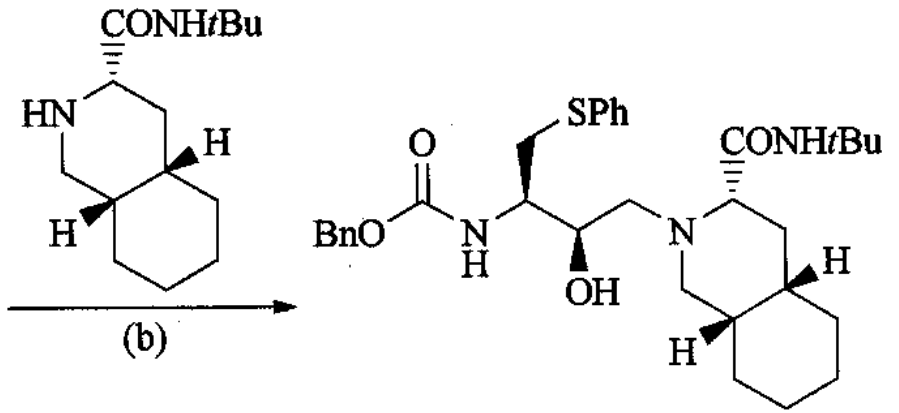


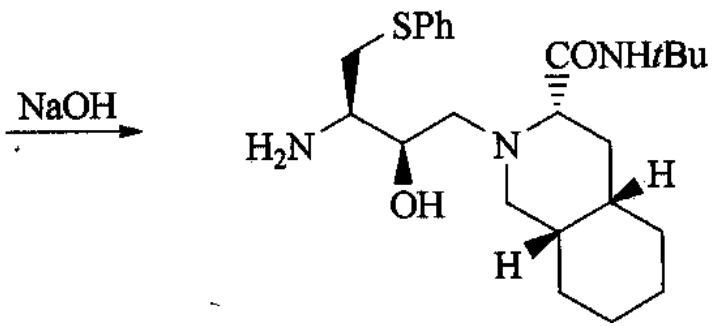
Saquinavir mesylate (Invirase)

Nelfinavir

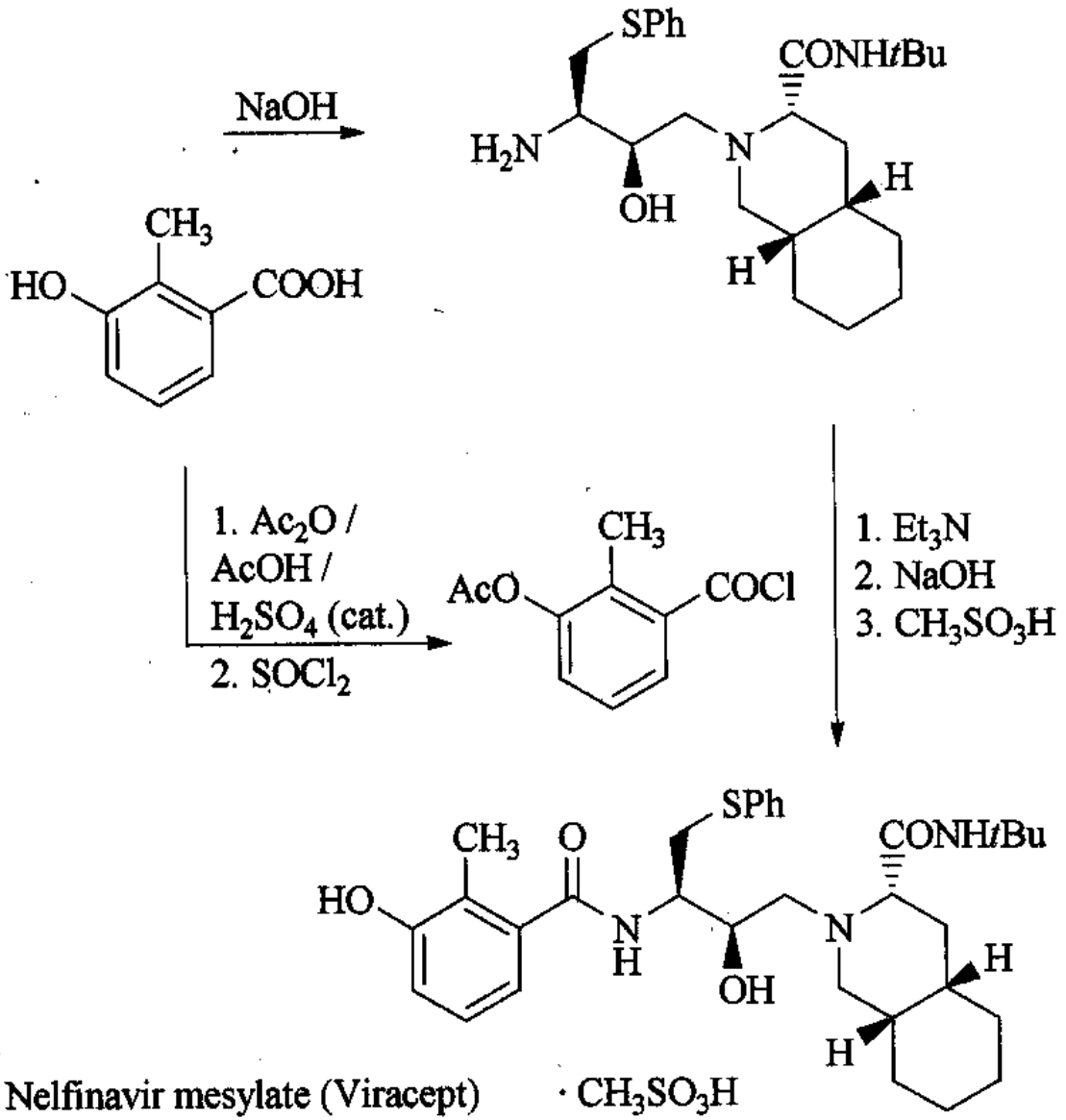


(a)



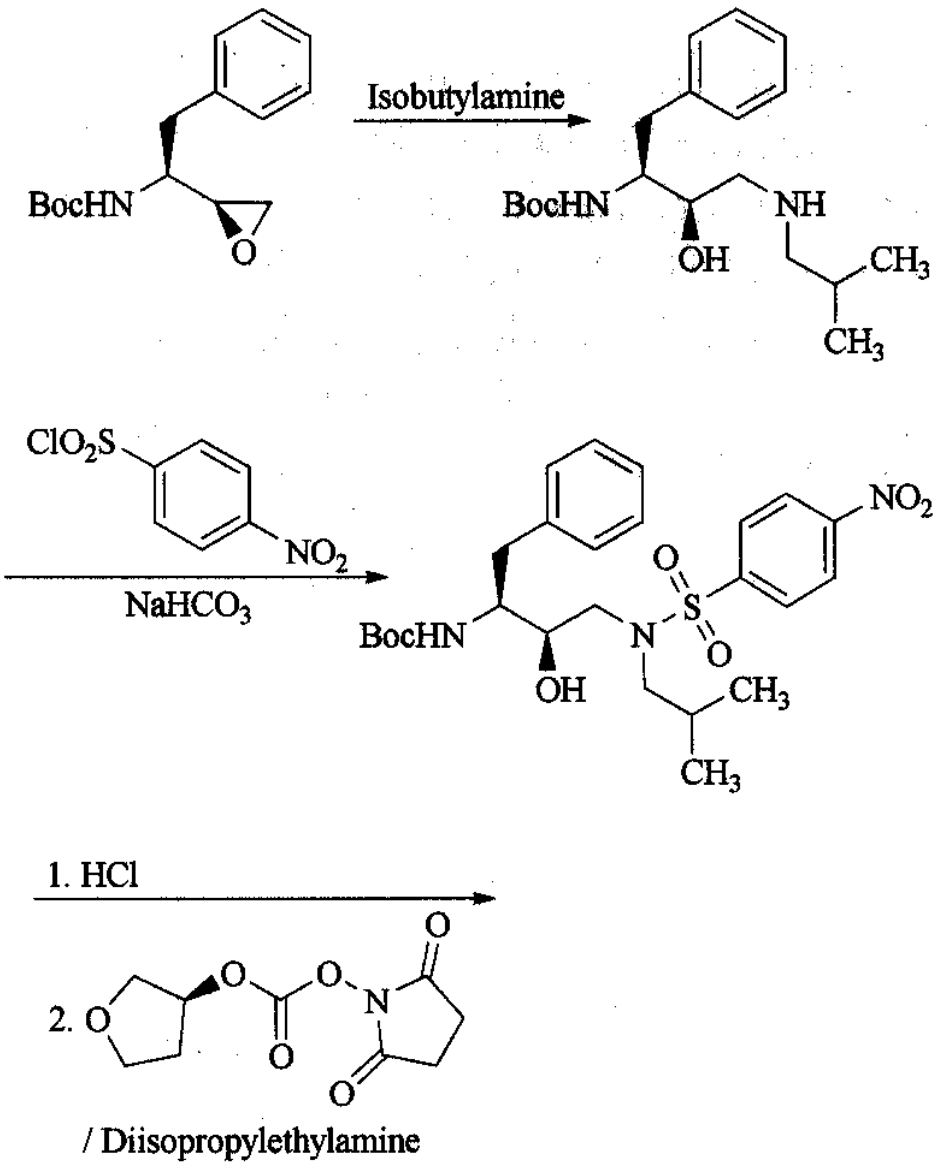


Nelfinavir

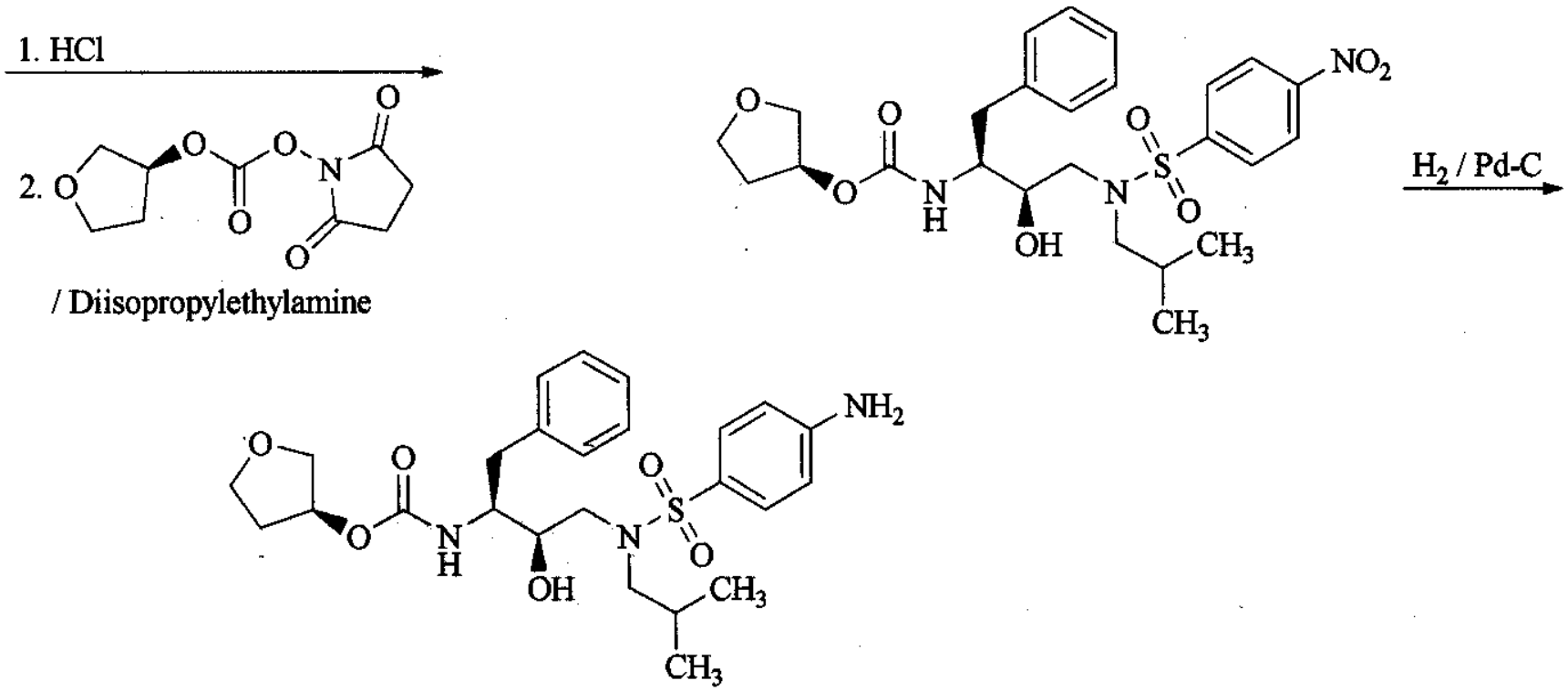


Nelfinavir mesylate (Viracept) · CH_3SO_3H

Amprenavir

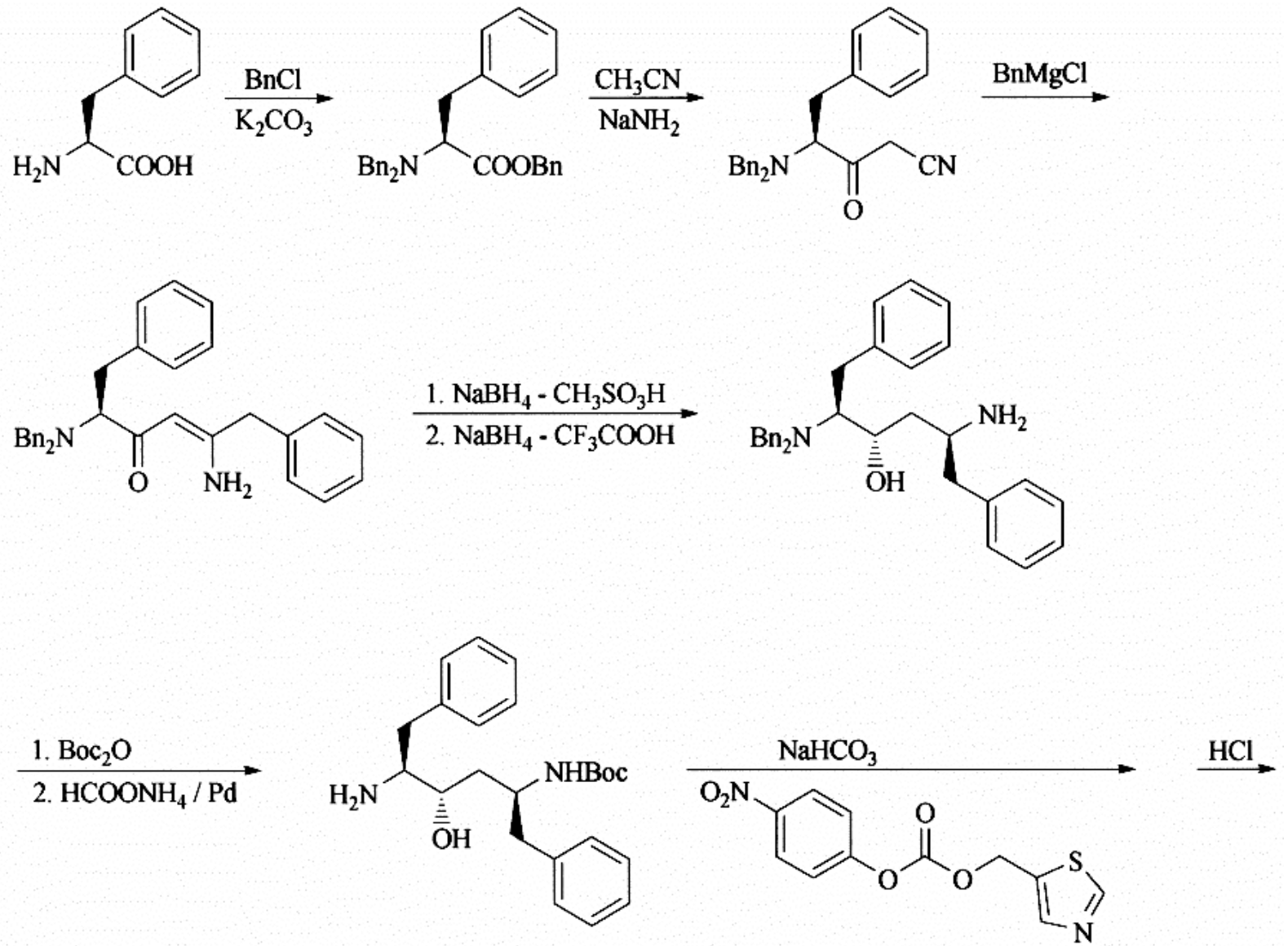

Isobutylamine
BocHN
BocHN
NH
OH
CH3
CH3
ClO2S
NO2
NaHCO3
NO2
BocHN
OH
N
S
CH3
CH3
1. HCl
2. O
/ Diisopropylethylamine

Amprenavir

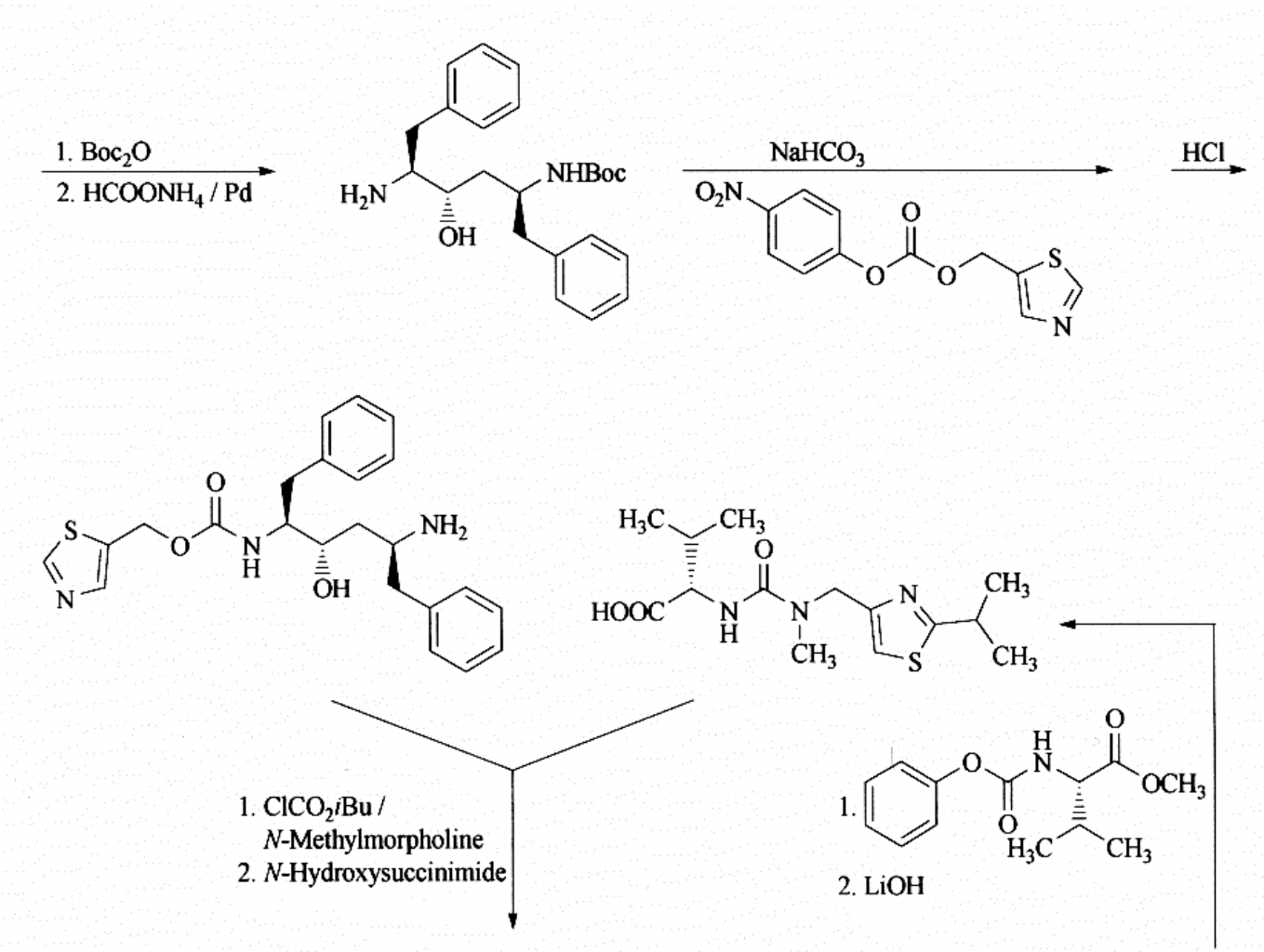


Trade name: Agenerase (Vertex Pharmaceuticals, USA; Glaxo Wellcome, UK; Kissei, Japan).

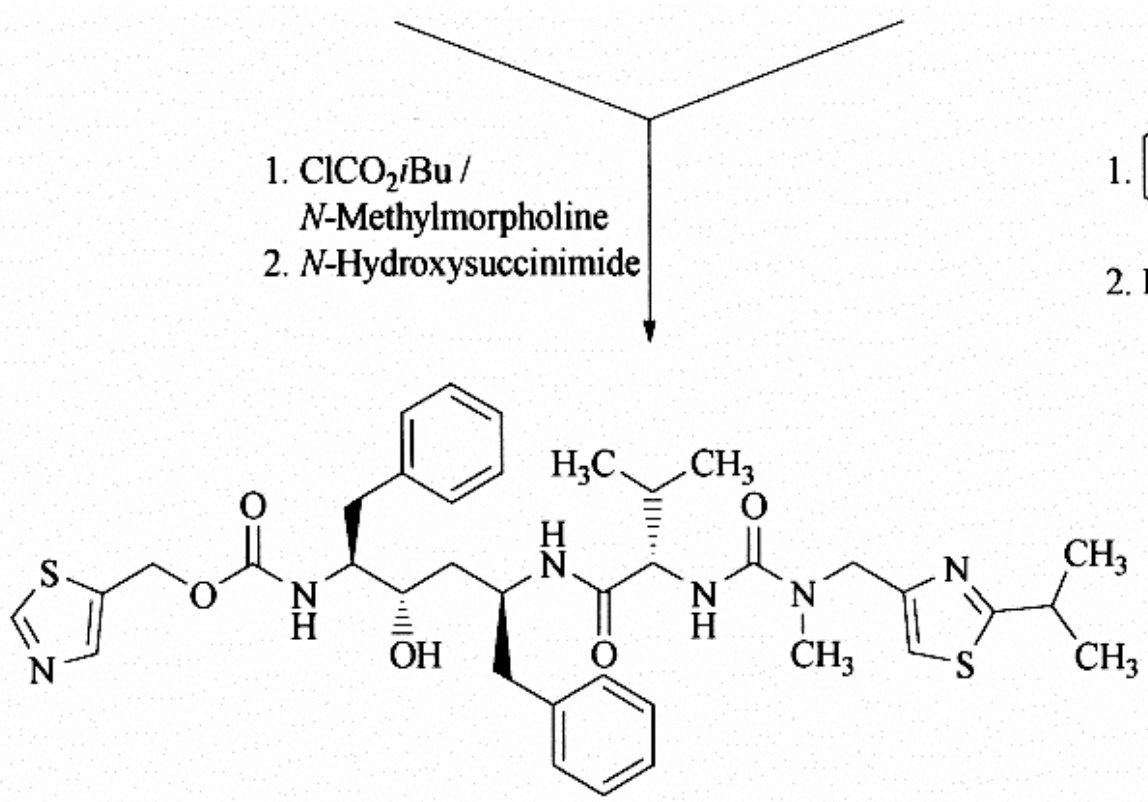
Ritonavir

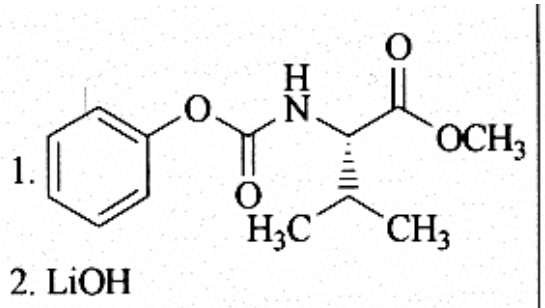

BnCl
K2CO3
CH3CN
NaNH2
BnMgCl
1. NaBH4 - CH3SO3H
2. NaBH4 - CF3COOH
1. Boc2O
2. HCOONH4 / Pd
NaHCO3
HCl

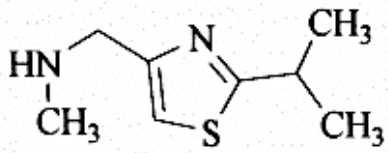
Ritonavir

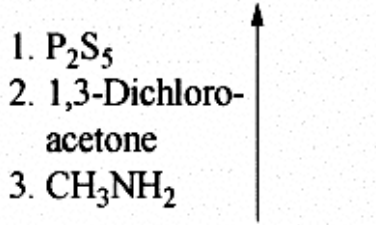

1. Boc2O
2. HCOONH4 / Pd
H2N
NHBoc
OH
NaHCO3
O2N
HCl
S
N
O
NH2
HOOC
H3C
CH3
1. ClCO2iBu /
N-Methylmorpholine
2. N-Hydroxysuccinimide
1.
OCH3
2. LiOH

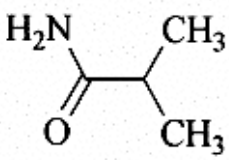
Ritonavir







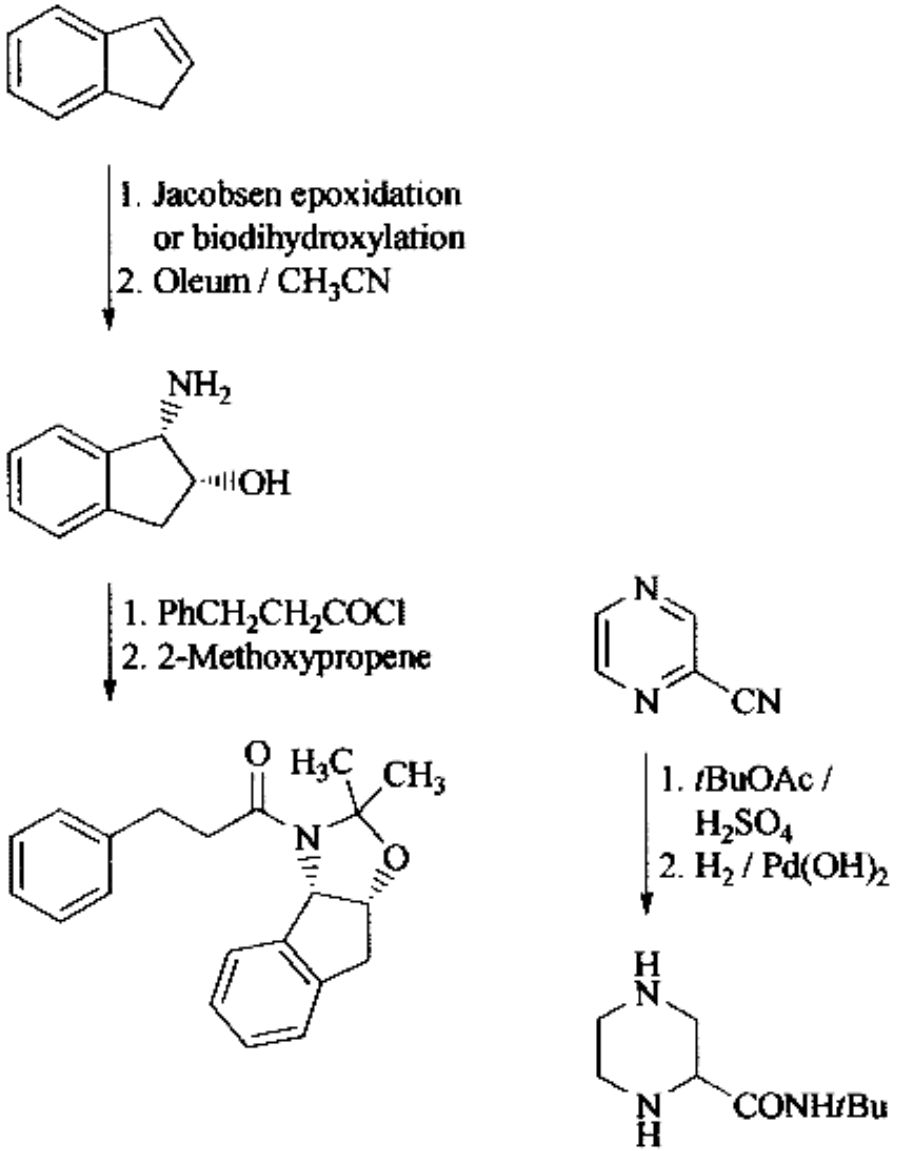




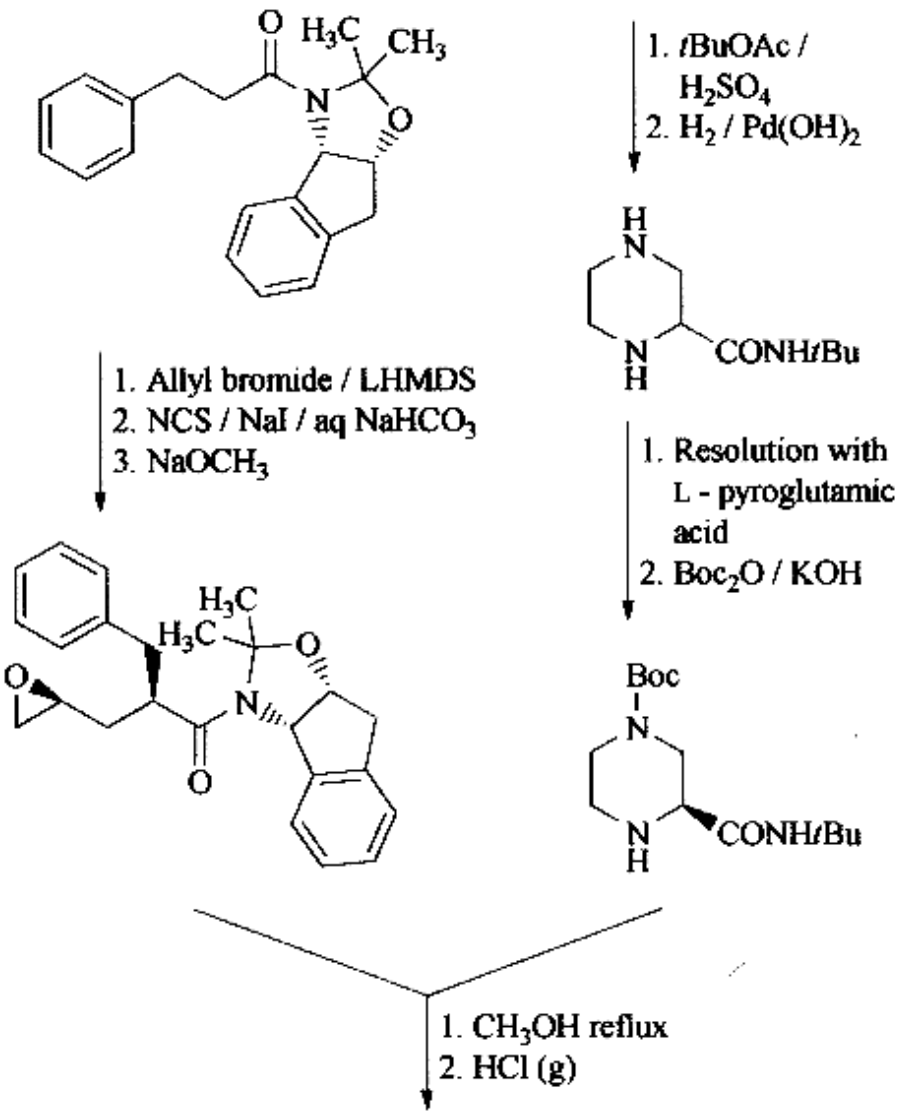
Ritonavir (Norvir)

Trade name: Norvir (Abbott, USA).

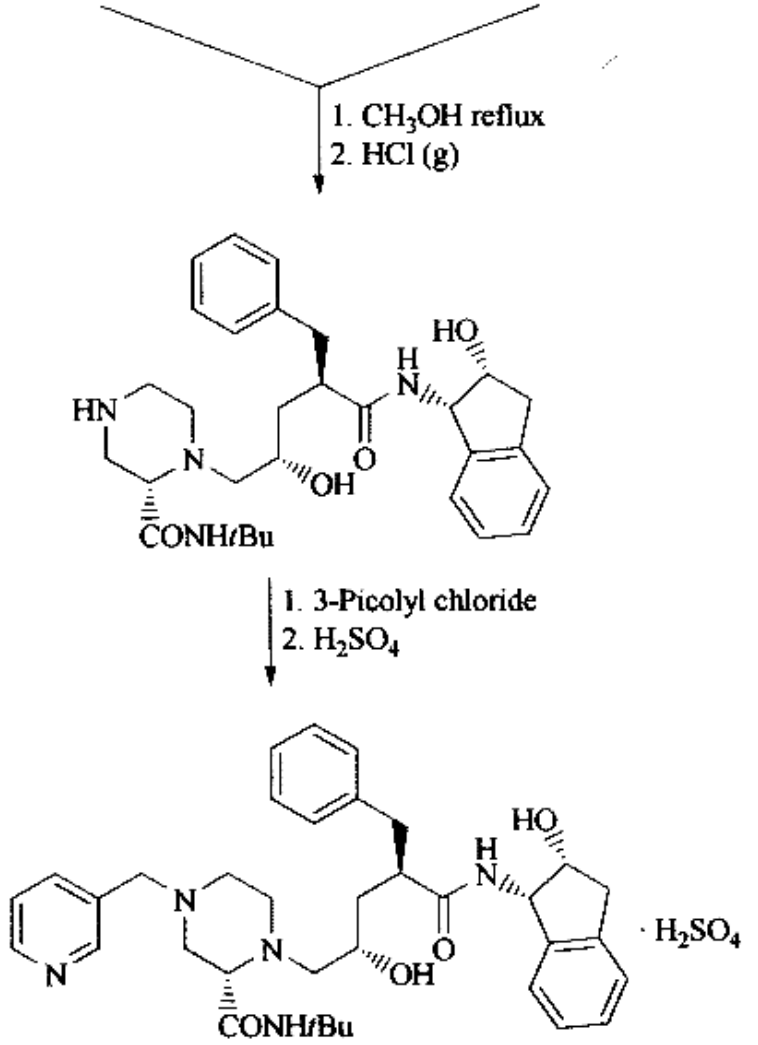
Crixivan


1. Jacobsen epoxidation
or biodihydroxylation
2. Oleum / CH_3CN
NH_2
OH
1. $PhCH_2CH_2COCl$
2. 2-Methoxypropene
O
H_3C
CH_3
N
O
N
N
CN
1. tBuOAc /
H_2SO_4
2. H_2 / $Pd(OH)_2$
H
N
N
H
CONHtBu

Crixivan


1. Allyl bromide / LHMDS
2. NCS / NaI / aq $NaHCO_3$
3. $NaOCH_3$
1. *t*BuOAc / H_2SO_4
2. H_2 / $Pd(OH)_2$
CONH*t*Bu
1. Resolution with L - pyroglutamic acid
2. Boc_2O / KOH
Boc
CONH*t*Bu
1. CH_3OH reflux
2. HCl (g)

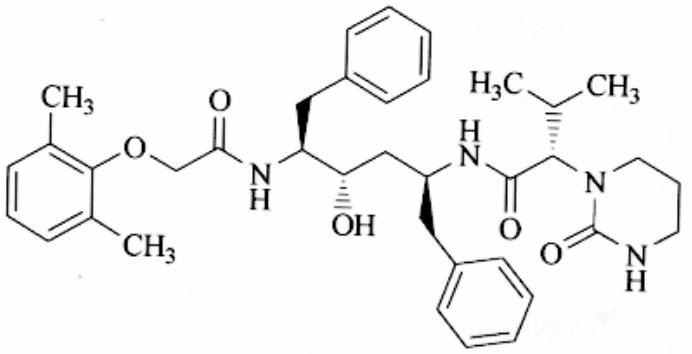
Crixivan



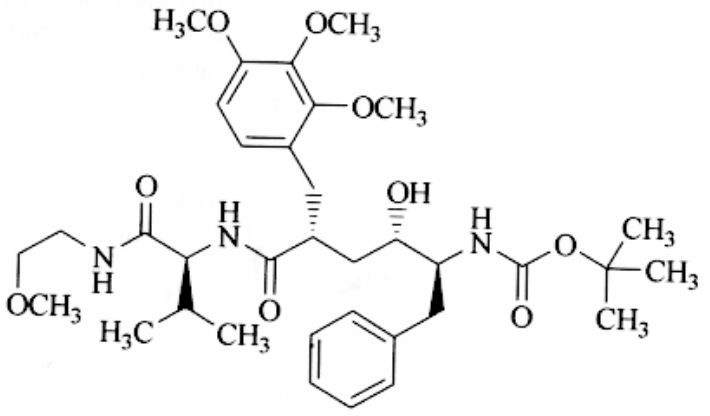
Indinavir sulfate (Crixivan)

Trade name (indinavir sulfate): Crixivan (Merck & Co. USA).

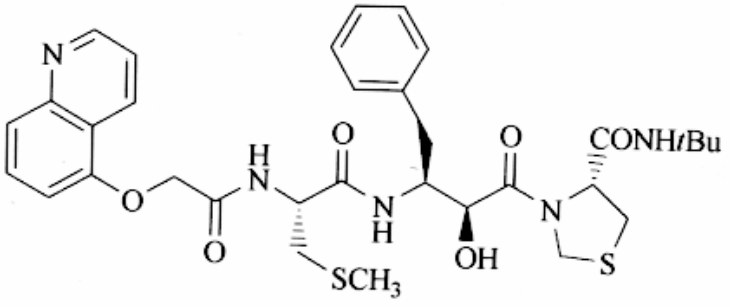
In klinischer Entwicklung



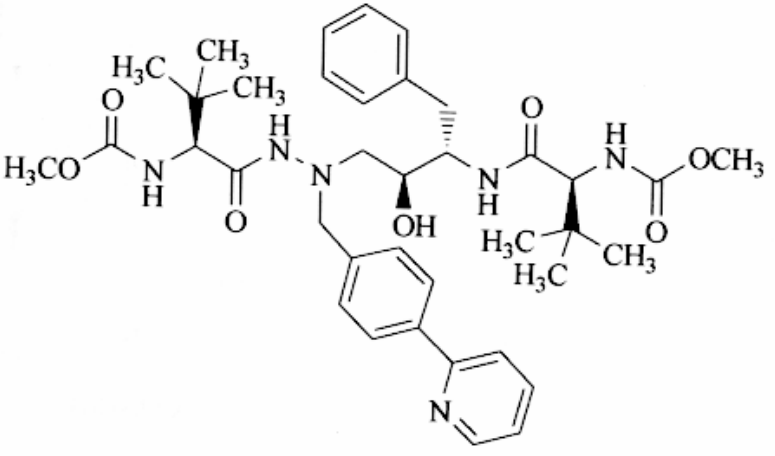
Lopinavir (ABT-378, Abbott, phase III)



Lasinavir (CGP-61755, BMS, phase I / II)

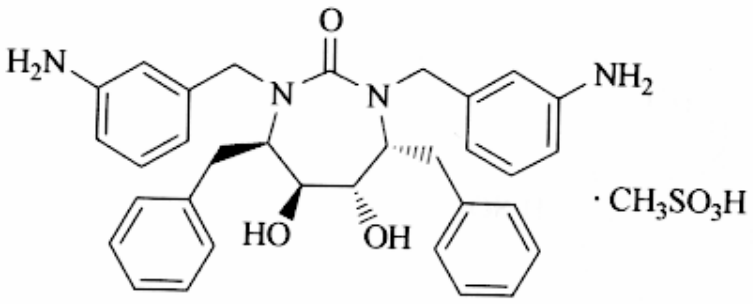


KNI-272 (Japan Energy Corporation, phase II)

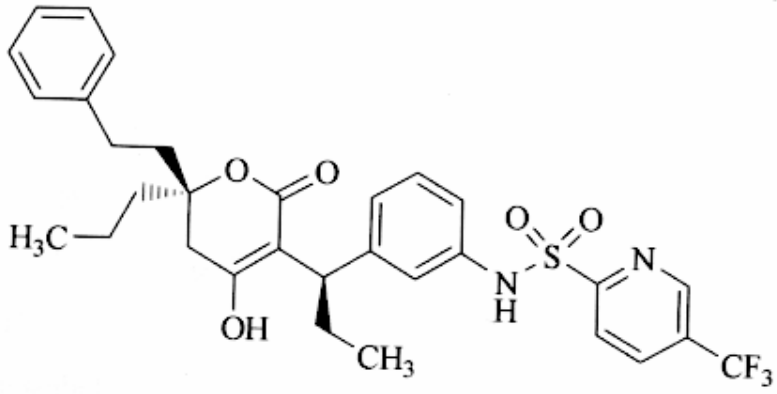


CGP-73547 (BMS, phase I)

In klinischer Entwicklung



DMP-450 (Triangle Pharmaceuticals, phase II)



Tipranavir (PNU 140690, Pharmacia & Upjohn, phase II)

Figure 3. HIV therapeutics in clinical development

Ende