6. Block

Case Studies 3

Die Entdeckung von Vioxx (Rofecoxib)

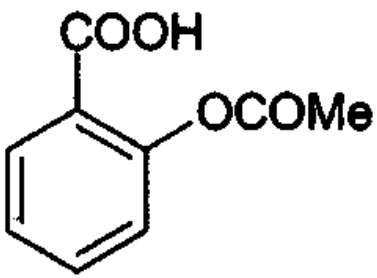
Web Link

http://www.uic.edu/labs/mesecar/Lecture1-2001.pdf

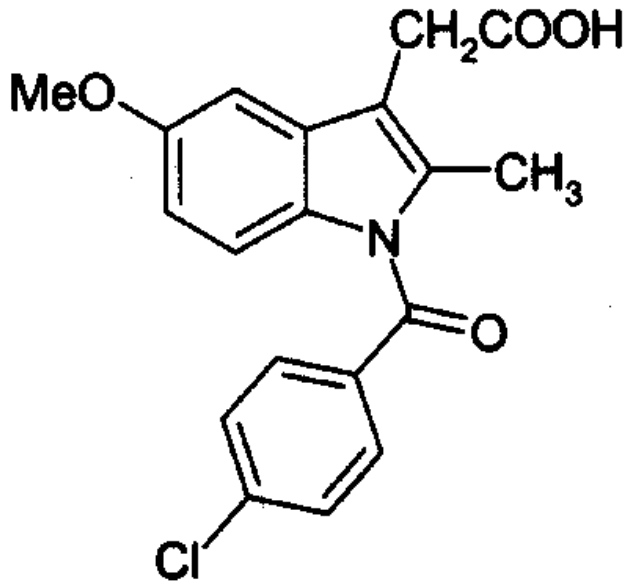
http://www.bentham.org/cmc-sample/ryn/ryn.htm

http://www.els.net/els/public/search/search_public.asp

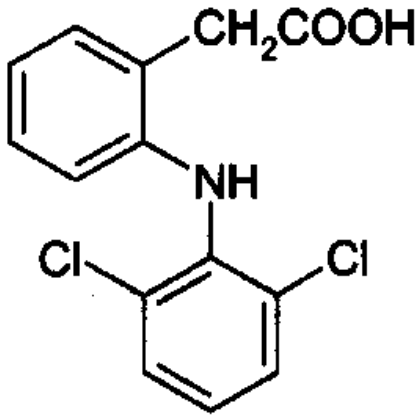
Die Vorgänger



1 Aspirin



2 indomethicin



3 diclofenac

Die beteiligten Enzyme

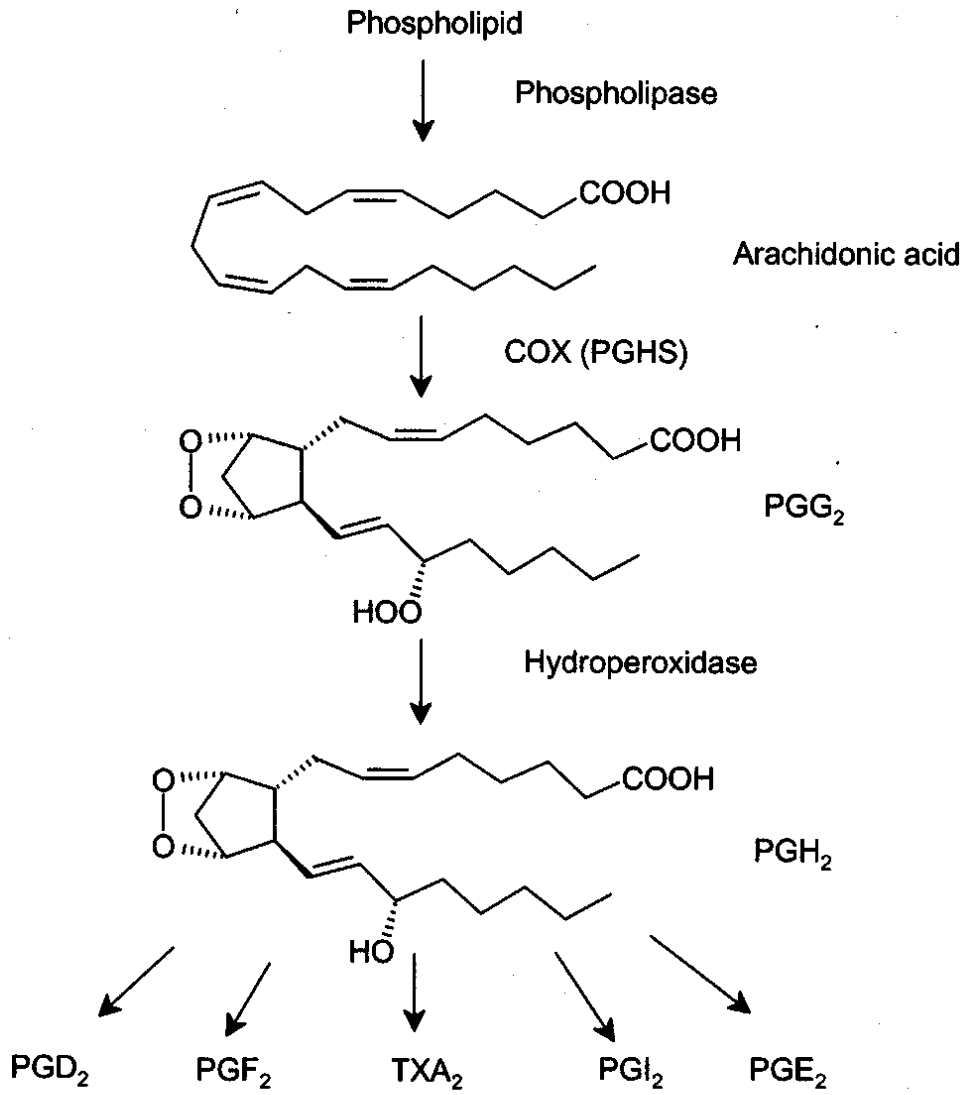
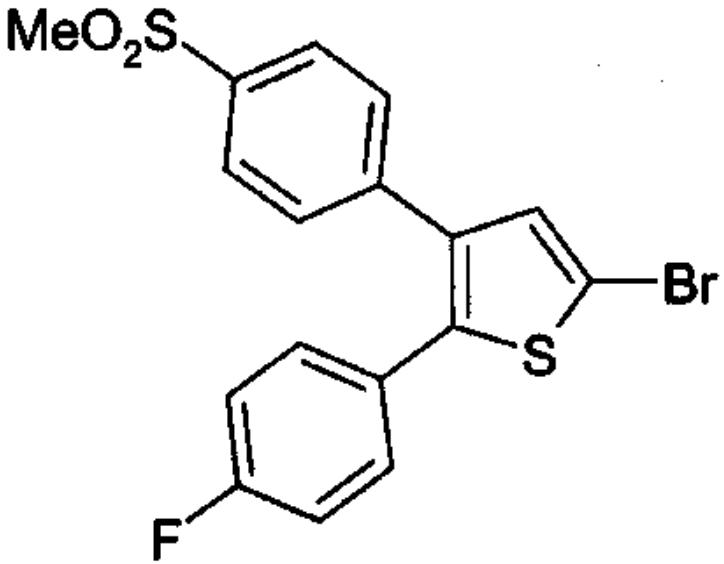
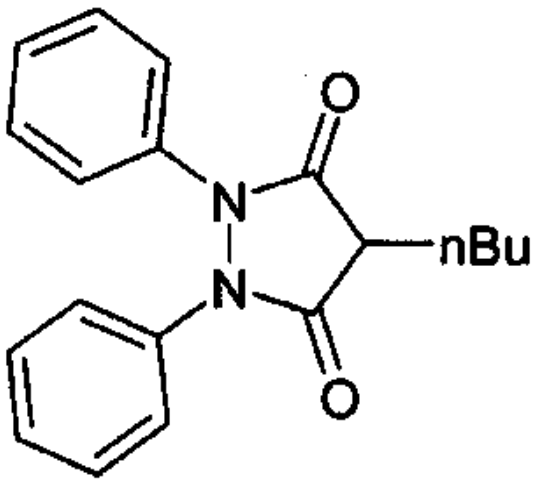


Figure 1 *Role of COX (PGHS) in the arachidonic acid pathway*

Problem Halbwertszeit

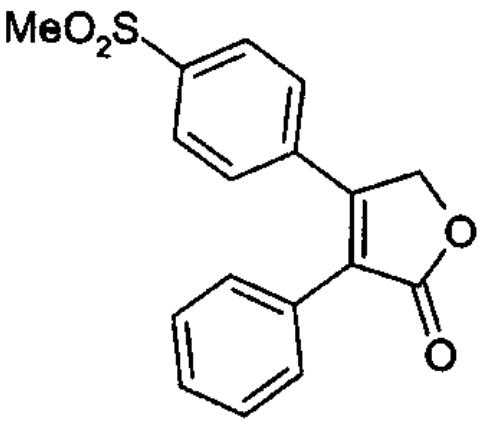


4 DuP 697

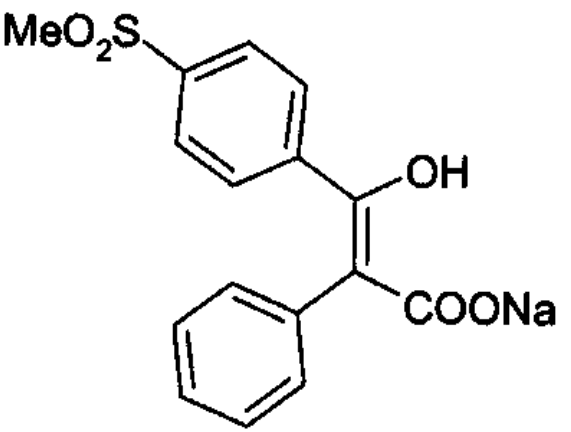


5 phenylbutazone

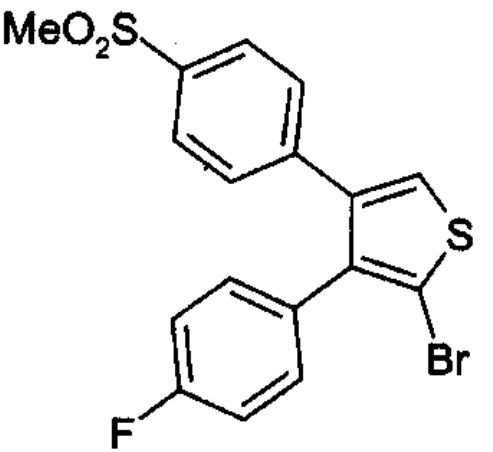
Problem Löslichkeit



6 MK-966



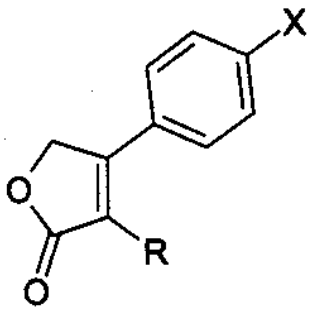
7

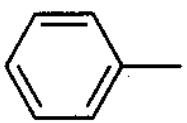
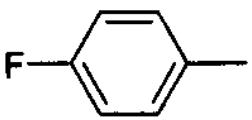


8

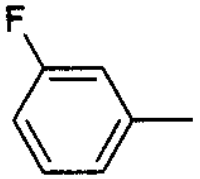
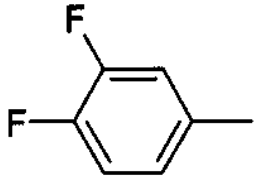
Versuchsreihe im Vergleich

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-Antagonosten

Verteilung im Gehirn

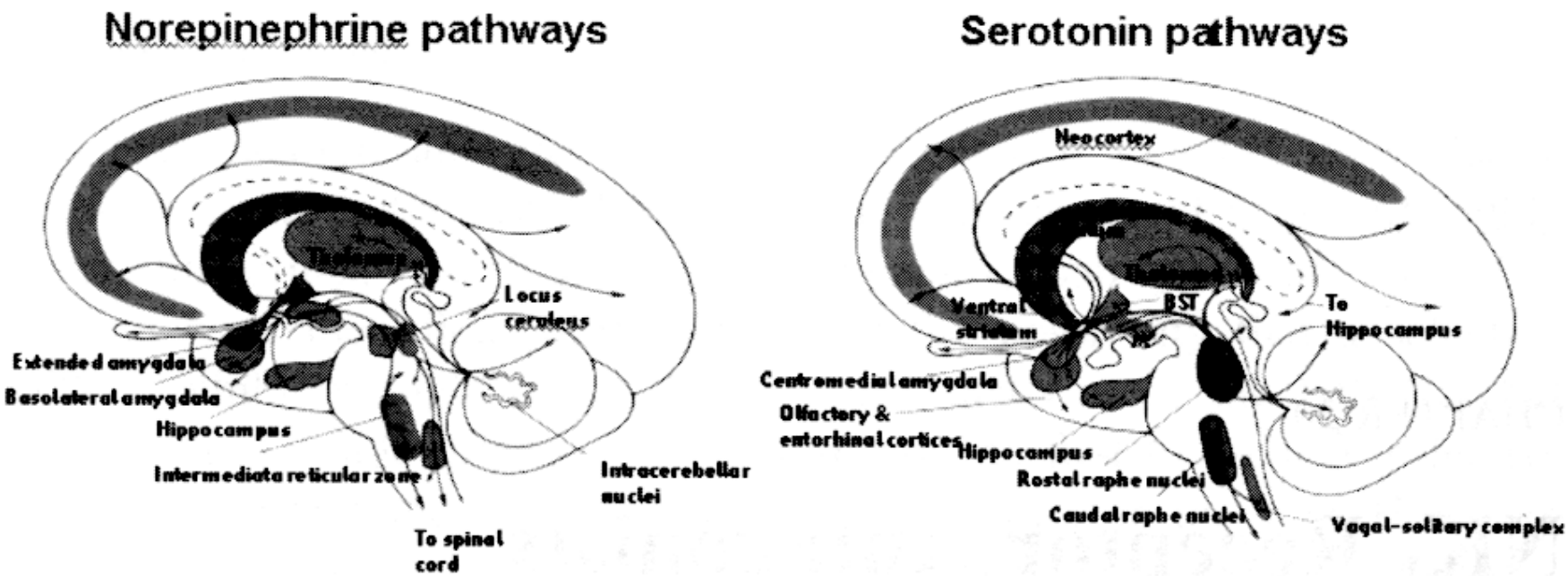
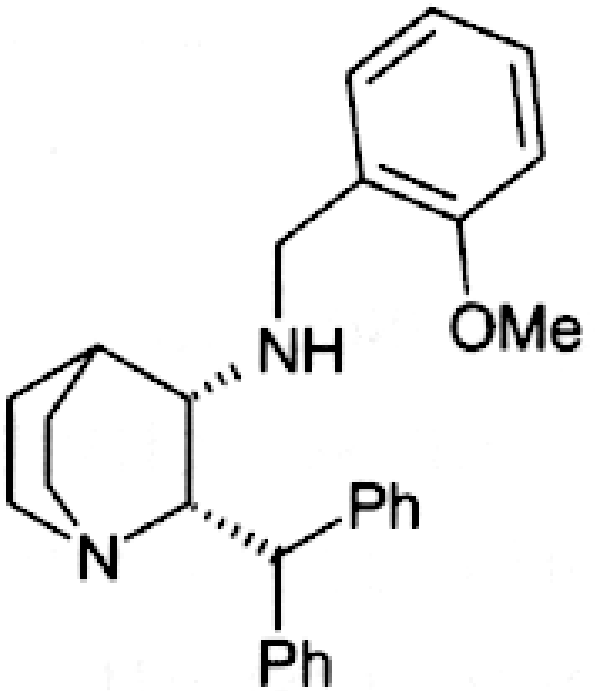


Figure 1 *Brain distribution of the NK_1 receptor*

CP-96345

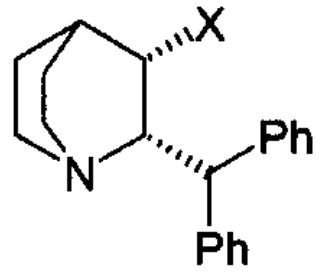
- Schlechte orale Verabreichbarkeit
- Kardiovaskuläre Nebenwirkungen

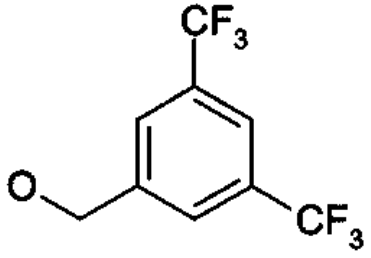


1

Vergleichende Studie

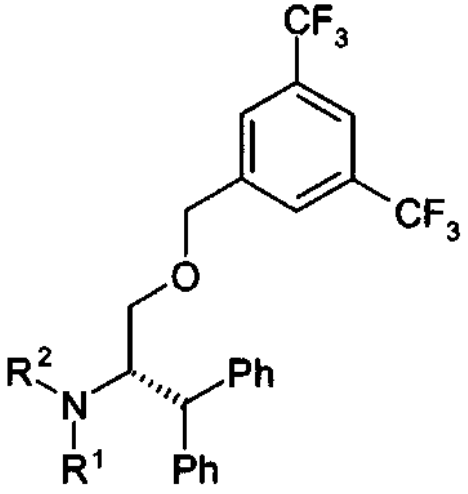
Table 1 *Structure and activities of quinuclidines*



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

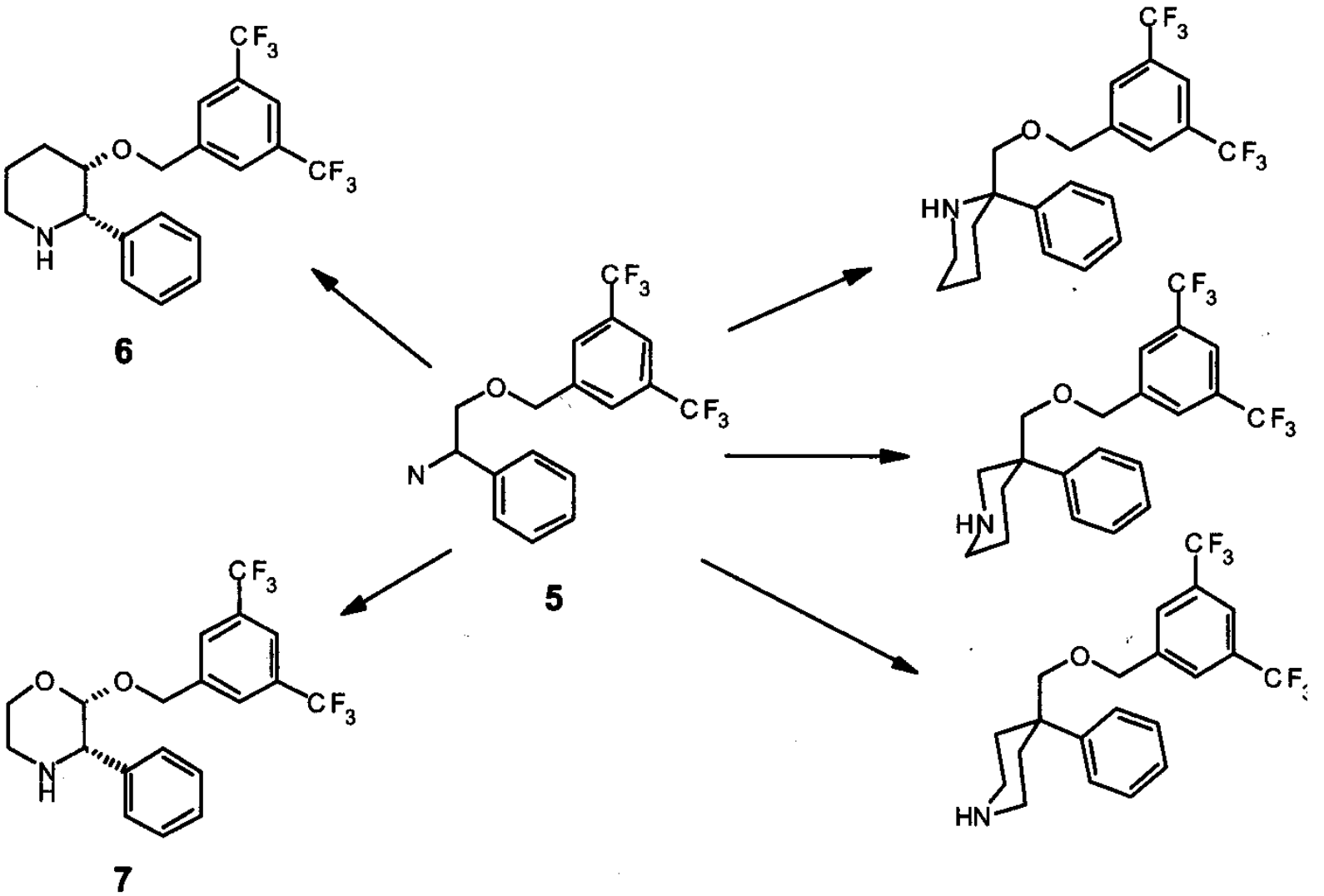
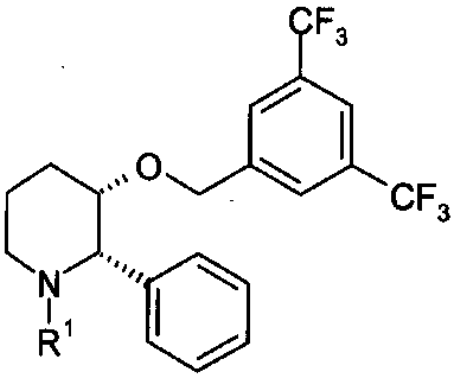
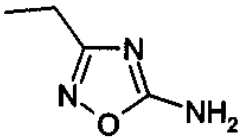
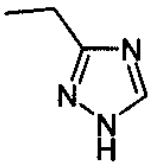
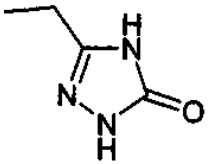
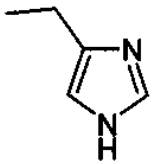


Figure 3 *Alternative conformational restraints derived from the basic pharmacophore* ***5***

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

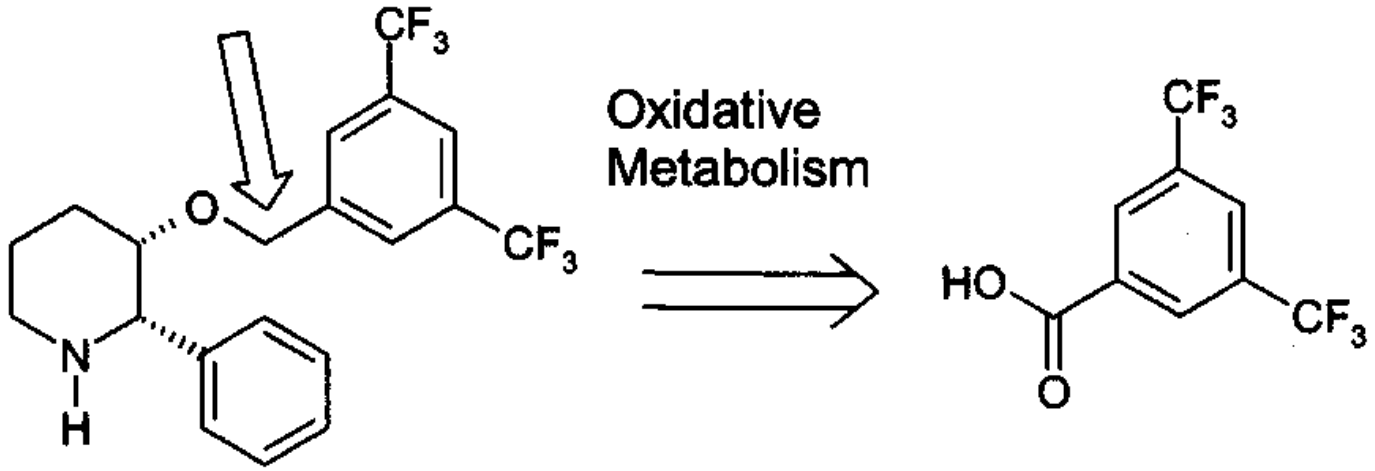
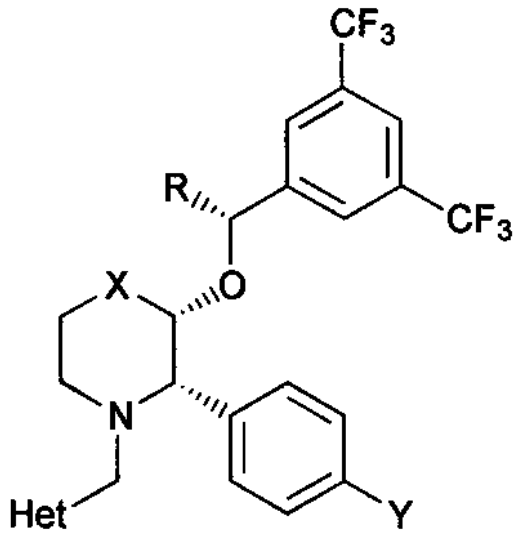


Figure 4 *Site of metabolism of the 3,5-bis(trifluoromethyl)benzyl ether 7*

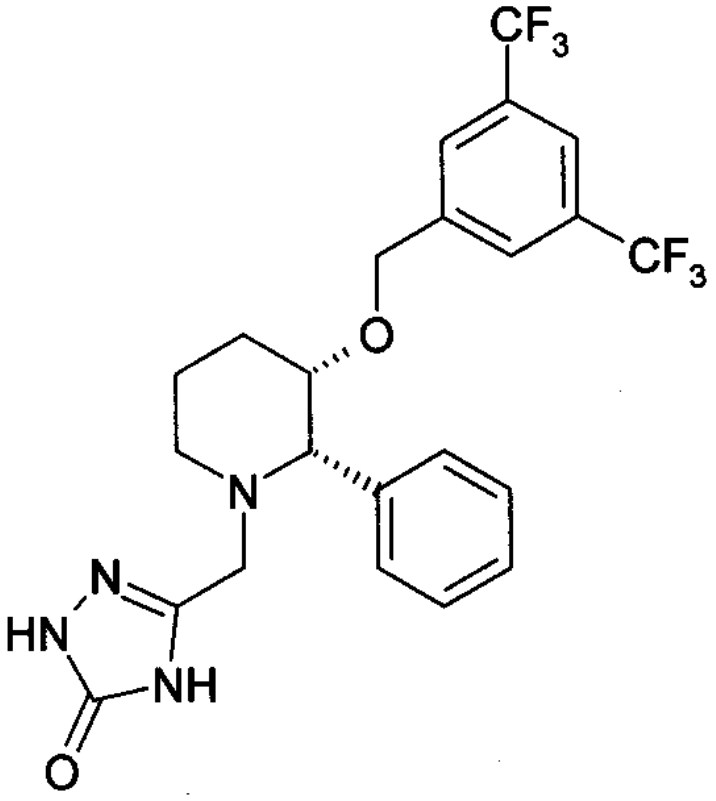
Wirkungsdauer

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

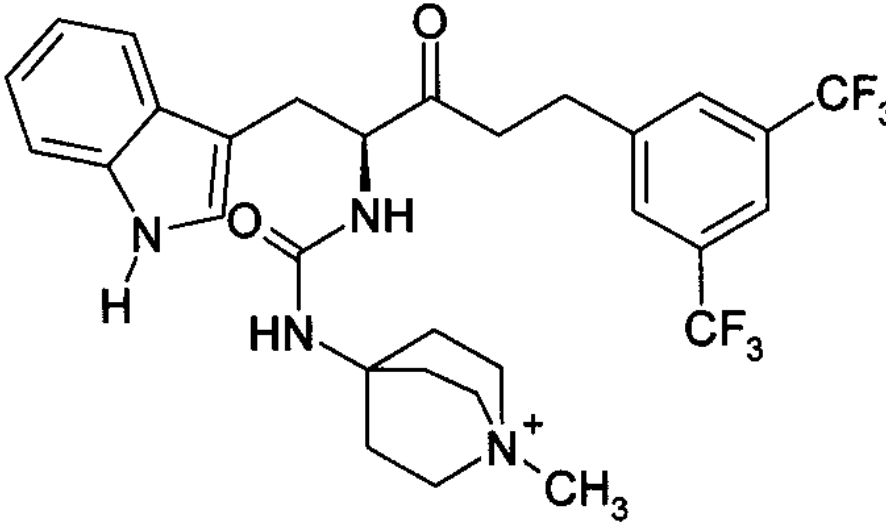


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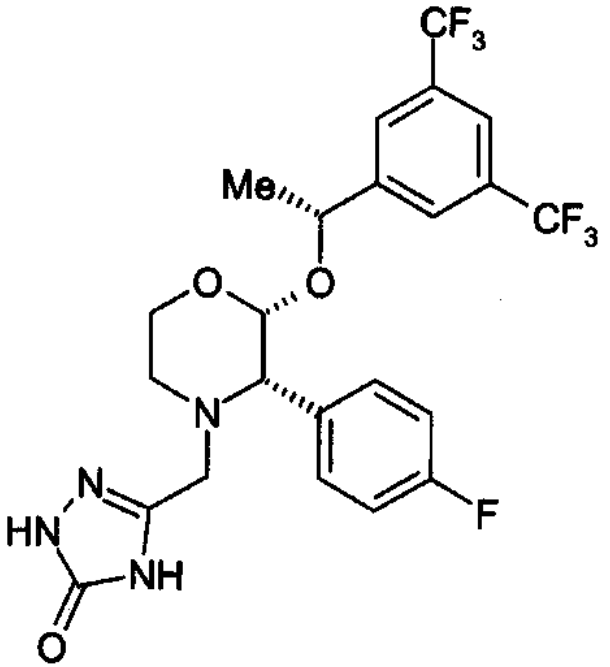
Figure 6 *Structures of the brain penetrant and non-penetrant NK_1 antagonists*

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}

Ende