

Molecular Conceptor

Molecular Conceptor - Table of Contents

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Structure Based Drug Design

Molecular Conceptor

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(Neuro)-Transmitter

Transmitter	Agonisten	Antagonisten
Acetylcholin	Para-symphathomimetika	Cholinrezeptor Blocker
Noradrenalin / Adrenalin	Sympatomimetika	Neuroleptika
Histamin		H1-Antagonisten H2-Antagonisten
Serotonin		5HT3-Antagonisten 5HT2-Antagonisten 5HT1-Antagonisten
GABA	Benzodiazepine	Benzodiazepin-Antagonisten

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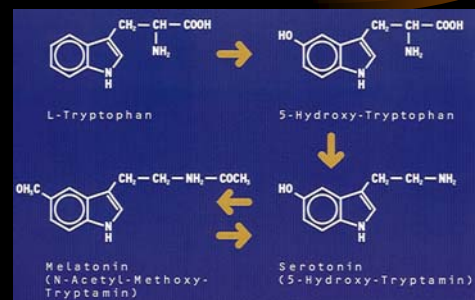
Neuroleptika

- 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
Triflupromazin (Psyquil®)	mittel	mittel
Fluspirilen (Imap®)	stark	gering
Haloperidol (Haldol®)	stark	mittel
Pimozid (Orap®)	stark	gering
Sulpirid (Dogmatil®)	stark	gering

Neurotransmitter Serotonin



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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

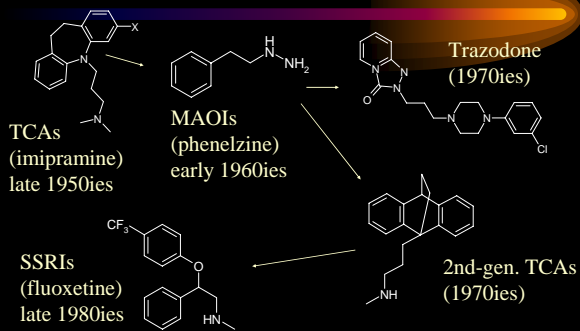
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The Vicious Cycle Of Depression



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Pharmacotherapy Of Depression: „40 Years In Conceptual Wilderness“



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Serotonin Receptor Responses

5-HT1 (A-F)	5-HT2 (A-C)	5-HT3
Cardiovascular	Vasoconstriction	Cardiovascular
Hyperphagia	Sexual effects	Nausea, emesis
Antidepressant	Muscle contraction	Anxiolytic
Sleep / sedation	Hallucinogenic	Pain
Migraine	Antipsychotic	Antipsychotic
Neuroprotection	Behavior	Migraine

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Antidepressant Receptor Interaction Profiles

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

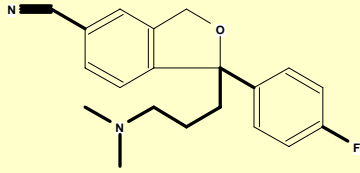
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Acrobat-Dokument

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SSRI Celexa



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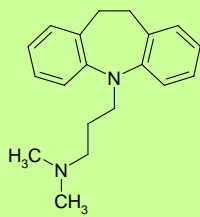
Case Studies 1

Die Identifikation von selektiven 5-HT_{2c} Rezeptor Antagonisten:

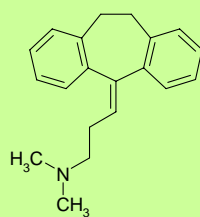
Ein neuer Ansatz zur Behandlung von Depression und Angstzuständen

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Erste Generation: Tricyclische Antidepressiva



Imipramine

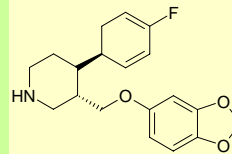


Amitryptilin (Triptisol)

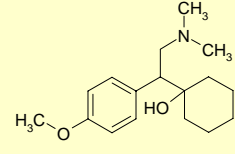
Nebenwirkungen, Suicid durch Überdosen

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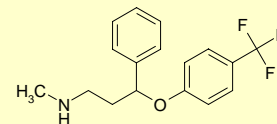
Zweite Generation Antidepressiva Selective Serotonin Reuptake Inhibitors (SSRIs)



Paroxetine, Paxil



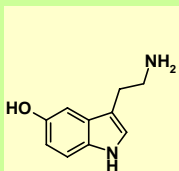
Venlafexine



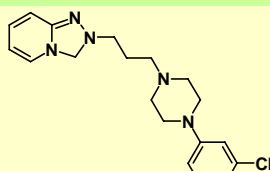
Floxetine Fluval

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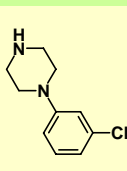
5-HT_{2c} Antagonisten



5-HT
5-Hydroxytryptamin
Serotonin



Trazodone



mCPP

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Lead: SB-200646

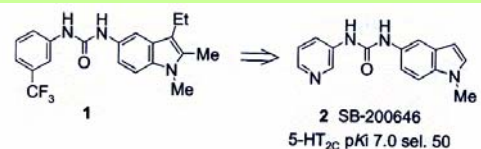


Figure 2 Discovery of 2

2 SB-200646
5-HT_{2c} pKi 7.0 sel. 50

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Weiterentwicklung

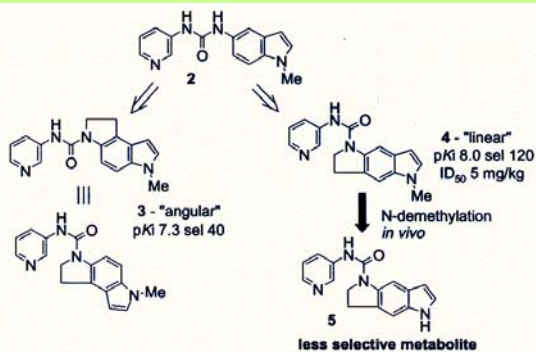


Figure 3 Conformational restriction to give 4

„Andock“- Möglichkeiten

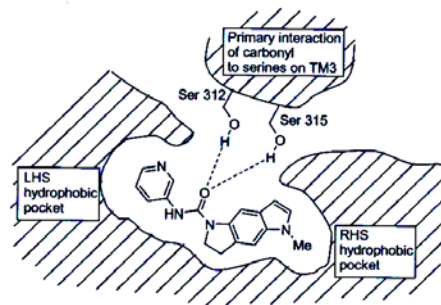


Figure 4 Schematic representation of 4 docked into a model of the 5-HT_{2C} receptor

Bioisosterer Ersatz

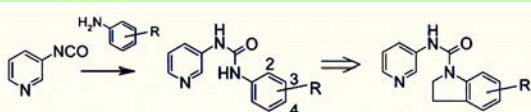


Figure 6 Identification of metabolically stable isosteres of 4

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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 ₂ Me	-1.63	5.0	—
CONH ₂	-1.49	5.1	—
CH ₂ OH	-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

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Besonders vielversprechend

Table 2 Activity of 5-thioalkyl-6-CF₃ 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 ^t Pr	8.2	>1000	<5

^a 6 (SB-221284).

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Neue „Andock“-Möglichkeit

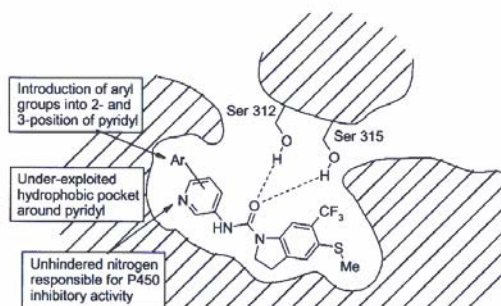
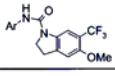


Figure 9 Evolution of (aryl-pyridylcarbamoyl) indolines from 6 SB-221284

Einfluß aromat. Substituenten

Table 3 Activity of bisarylcabamoylindolines



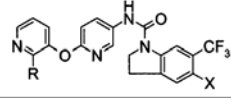
Cmpd.	Ar	pK_i 5-HT _{2C}	5-HT selectivity		ID_{50} (po) vs mCPP	ID_{50} vs CYP1A2 (μ M)
			2C/2A	2C/2B		
7		9.1	80	12	—	~5
8		9.4	250	15	5 mg kg ⁻¹	0.2
9		8.3	>2000	2	Inactive	>100
10		9.0	200	8	0.6 mg kg ⁻¹	4
11*		9.0	130	10	0.7 mg kg ⁻¹	28

* SB-228357.

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Problemlösungsansätze

Table 5 Activity of bispyridyl ether-carbamoylindolines



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

* SB-243213.

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SB-243213 - Synthese

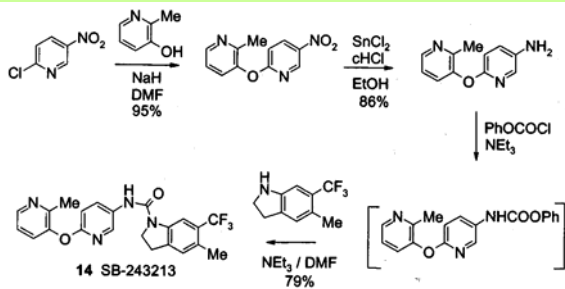


Figure 10 Synthesis of 14, SB-243213

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