

BLOCK 9

Secretase Inhibitors as Therapeutics for Alzheimer's Disease

The Amyloid Hypothesis

Histologische Befunde für Alzheimer: Plaques & Tangles

- Extracelluläre Niederschläge (senile plaques): bestehen aus einem 40-42 AA peptid – β -Amyloid (**A β**)
- Intracelluläre „Tangles“:
Hyperphosphorylated form of the microtubule associated tau protein

A β könnte Ursache von AD sein

- **A β ist neurotoxisch in vivo und in vitro**
- **Versuch der Hemmung der proteolytischen Enzyme welche A β produzieren**
- **Konzentration von A β korreliert mit Schwere von AD**

APP: β -Amyloid precursor protein

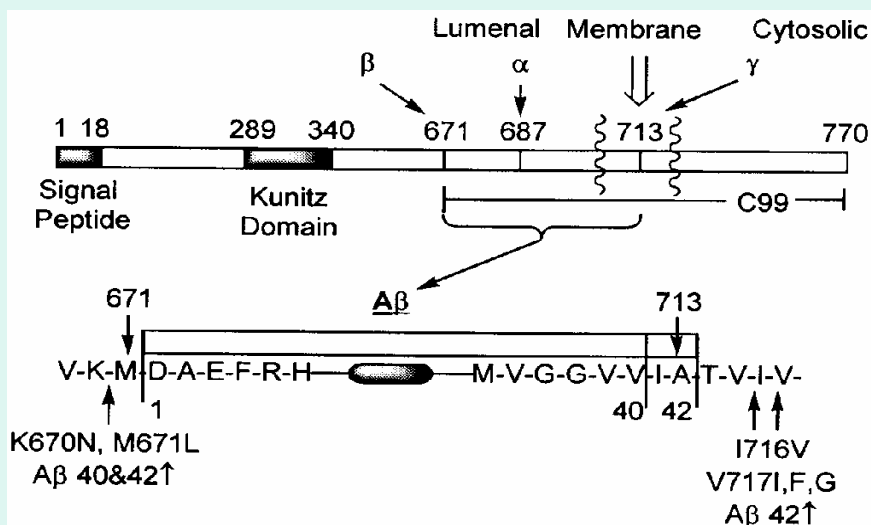
- **APP noch nicht voll verstanden: memory and cell adhesion?**

Proteolytische Kaskade

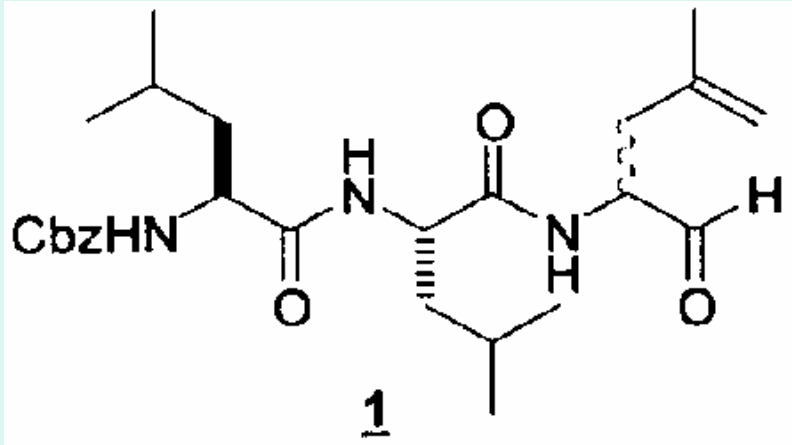
- APP wird durch Secretasen in A β gespalten

Somit könnten β -Sekretasehemmer als Anti-AD Medikamente eingesetzt werden

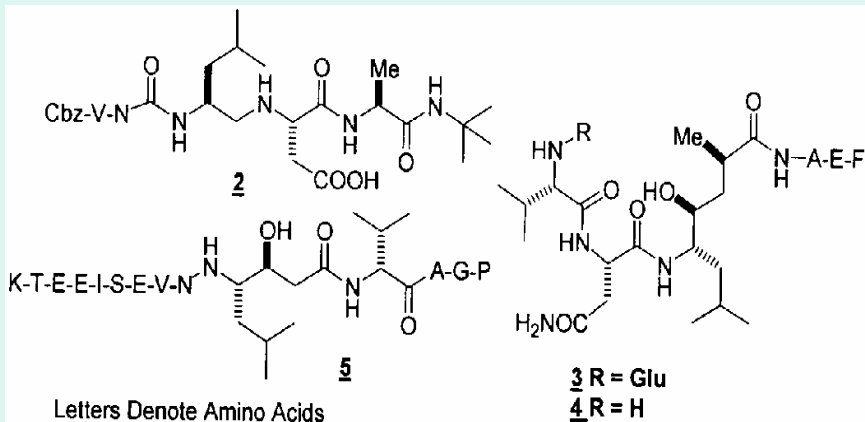
APP Processing and FAD Mutations



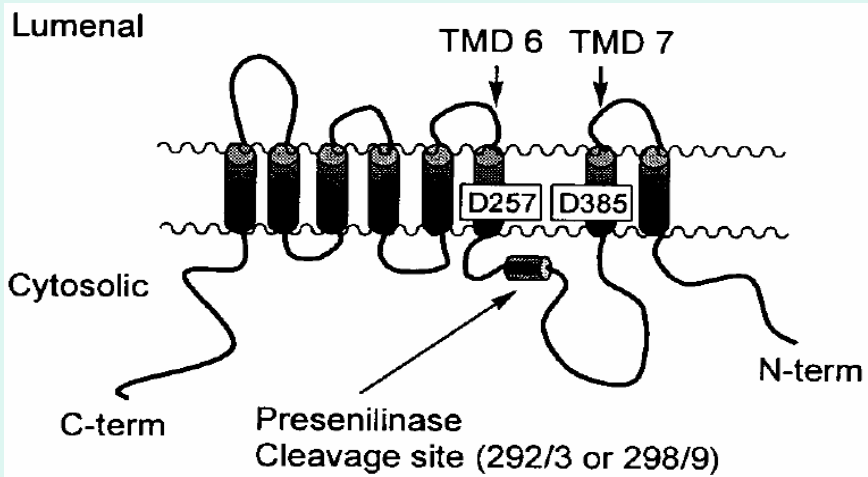
β -Secretase Inhibitors



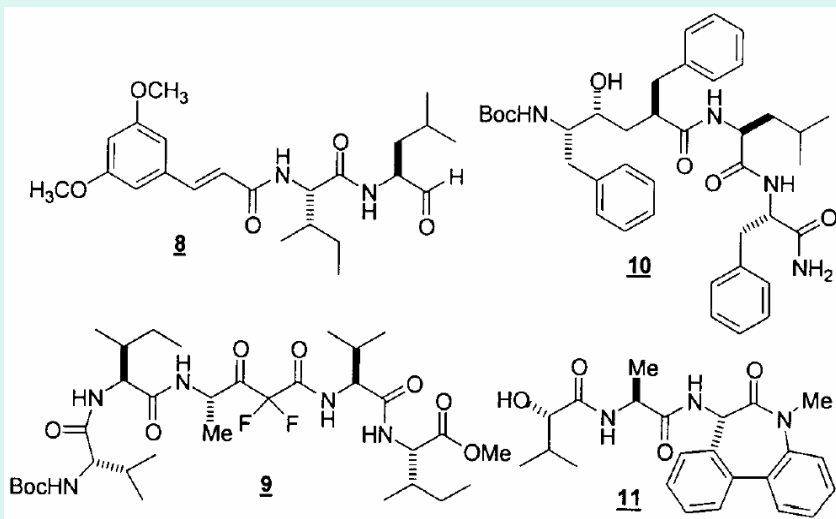
β -Secretase Inhibitors



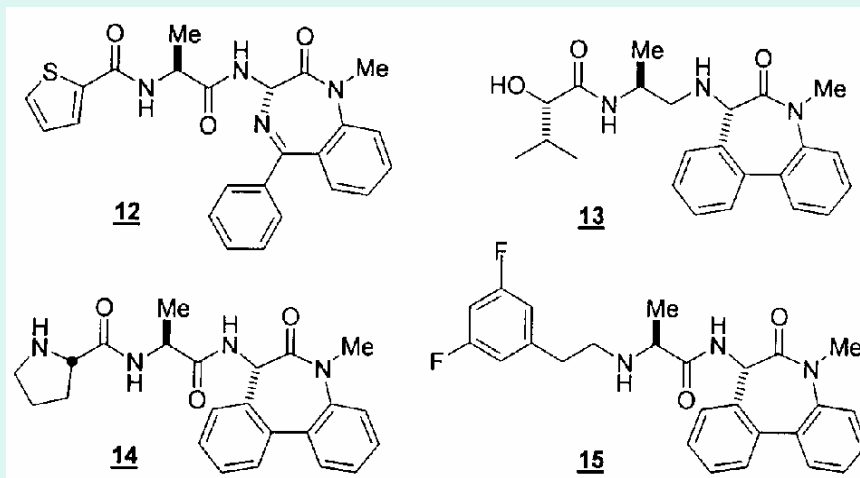
Role of Presenilins



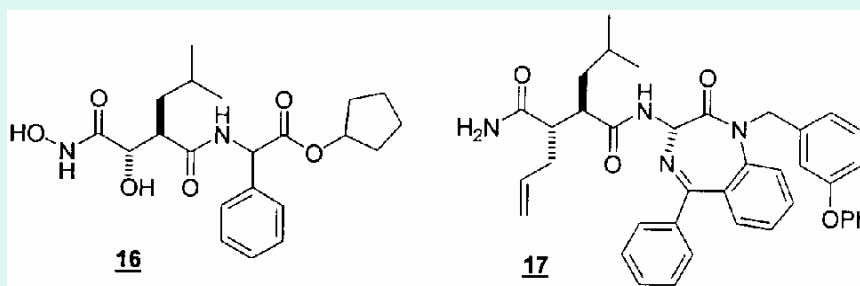
?-Secretase Inhibitors



Inhibitors of A β Production with Unreported Mechanisms



Inhibitors of A β Production with Unreported Mechanisms



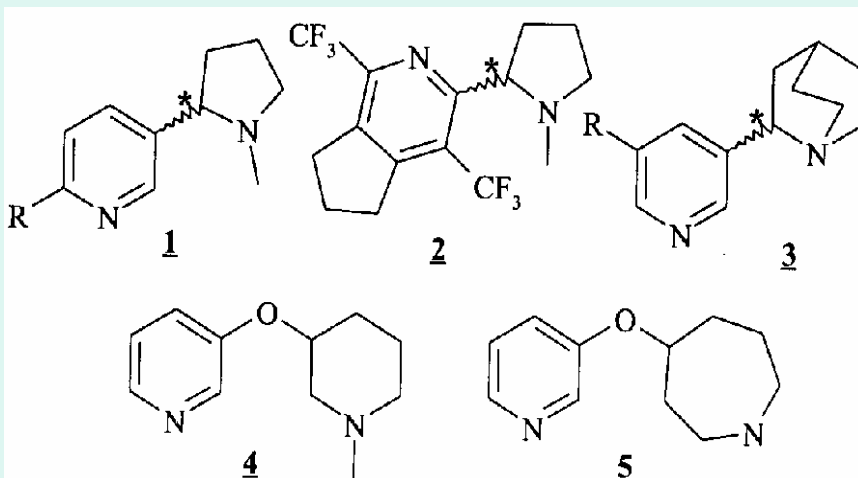
Targeting Nicotinic Acetylcholine Receptors (nAChR): Advances in Molecular Design and Therapies

- nicotinic receptors (nicotine is an agonist)
 - receptors at neuromuscular junction
 - also found in brain
 - ionotropic
 - fast, excitatory transmission
 - *blocked by curare*
- muscarinic receptors (muscarine is an agonist)
 - receptors that mediate action of parasympathetic branch of the autonomic nervous system in target tissues (e.g., heart, iris of the eye, etc.)
 - many subtypes (at least five)
 - slow response times
 - *blocked by atropine*

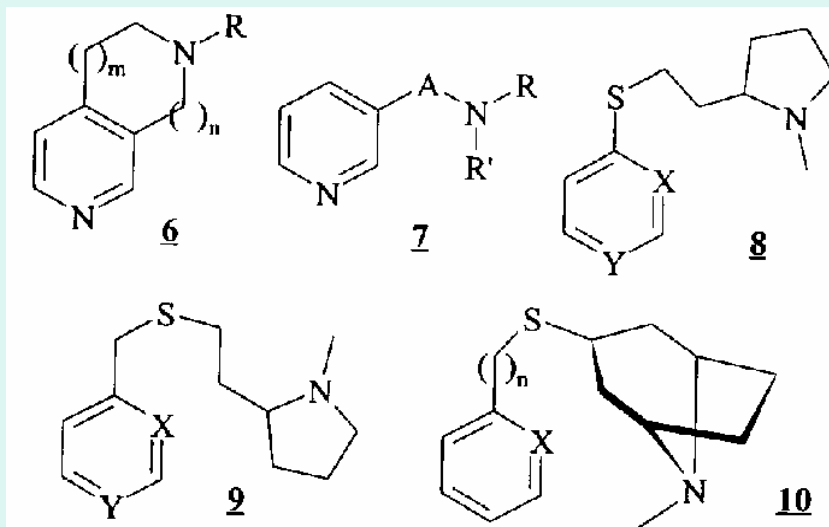
WebLinks

- <http://artsandscience.concordia.ca/psychology/psyc358/Lectures/transmit2.htm>
- <http://www.zoology.ubc.ca/~auld/bio455/lectures/nerves.html>

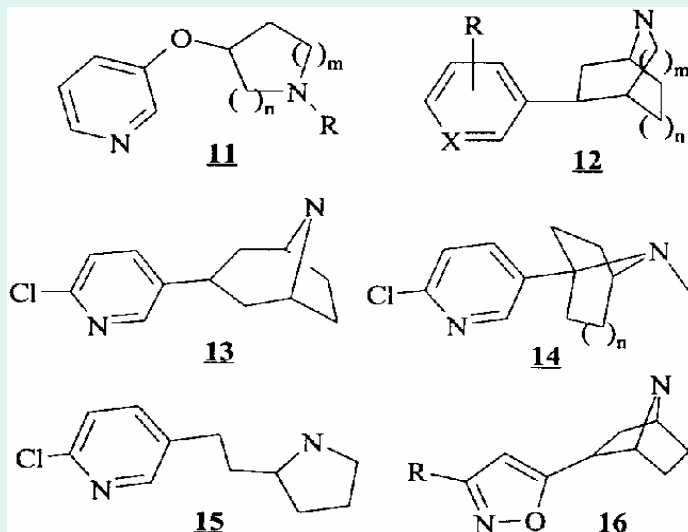
Structure-Activity Relationship of Novel nAChR Ligands



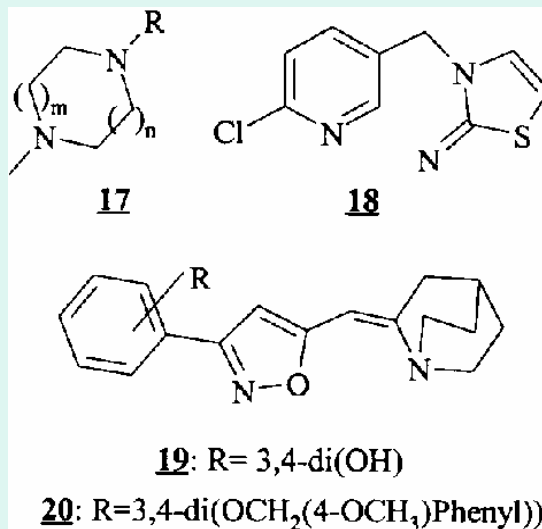
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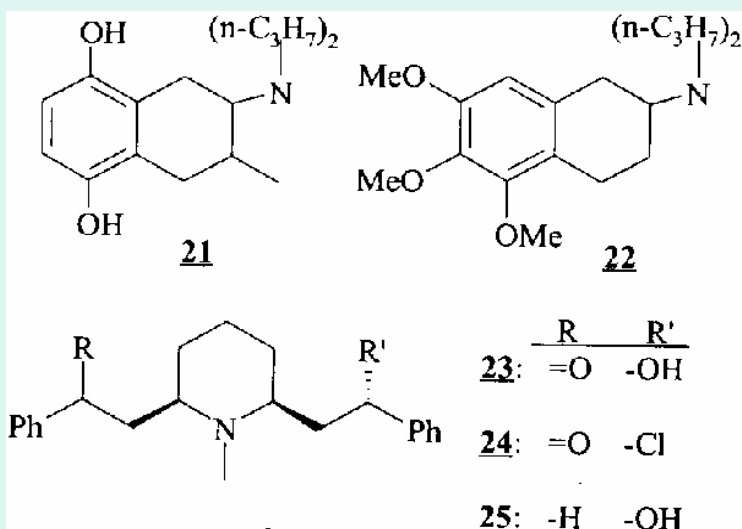
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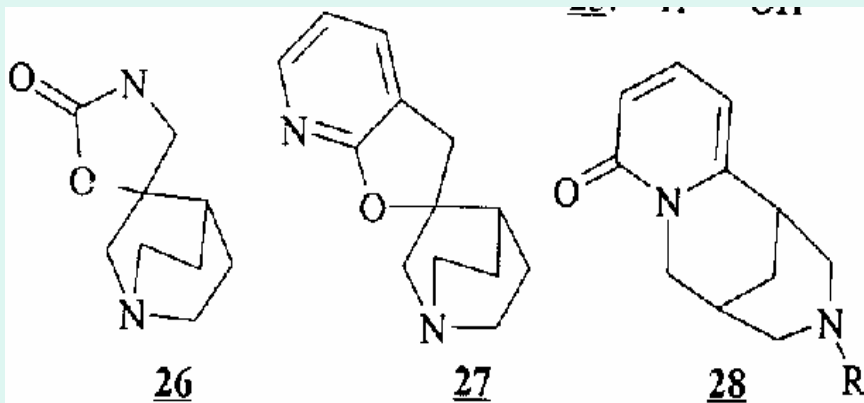
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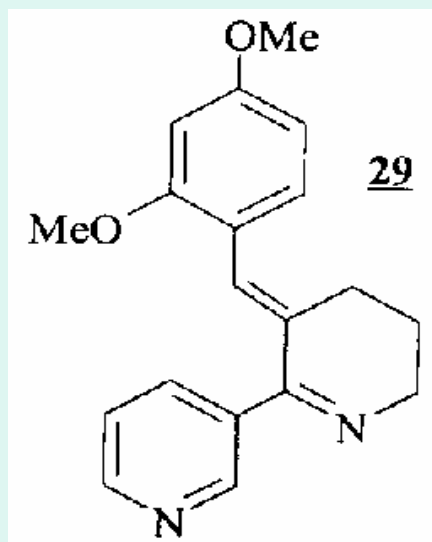
Structure-Activity Relationship of Novel nAChR Ligands



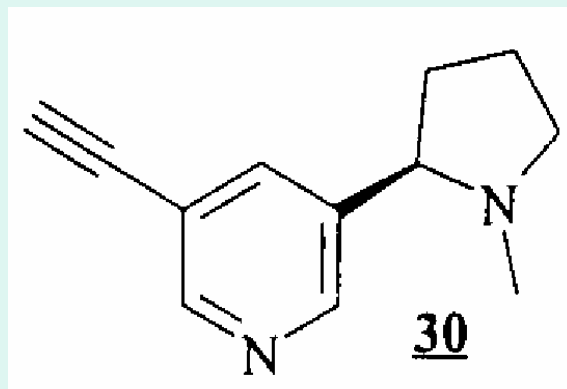
Structure-Activity Relationship of Novel nAChR Ligands



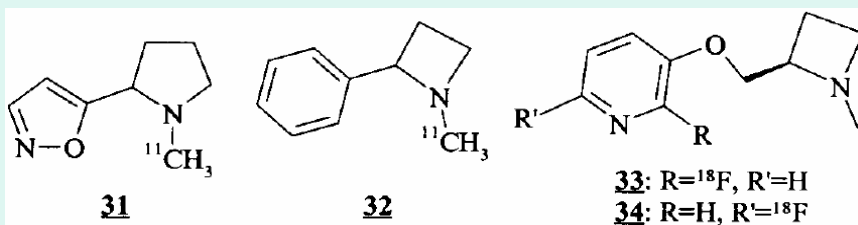
Clinical Application of nAChR Ligands – Alzheimer's Disease



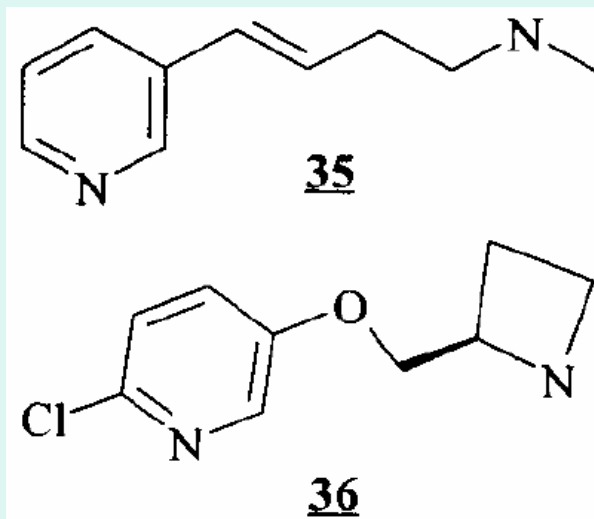
Clinical Application of nAChR Ligands – Parkinson's Disease



Neuroimaging



Current Approaches for systemic analgesics



Trends in Drug Treatment

CNS Agents

Trends in Psychiatric Drug Treatment

Disease State	Current Approaches	Experimental Approaches
Schizophrenia	DA receptor blockers – haloperidol, clozapine, chlorpromazine, risperidone, olanzepine	DA: Clozapine-like agents, partial agonists, D4 receptor antagonists. NMDA receptor/glycine modulators - D-serine, serine racemase α -7 nicotinic receptor agonists 5HT _{2A} inverse agonists – AC 90179 Neurokinin-3 and cholecystokinin ₁ antagonists
Depression	TCA's - imipramine, amitriptyline: Monoamine oxidase inhibitors (MAOIs) - tranylcypromine SSRIs- citalopram, fluoxetine SNRIs (5HT/ NE reuptake inhibitors) - venlafaxine	Improved monoamine uptake inhibitors 5HT _{1A} receptor ligands NK-1 receptor antagonists Corticotropin releasing factor (CRF) receptor antagonists
Bipolar Affective Disorder	Lithium, valproic acid, carbamazepine	Antiepileptics: pregabalin, topiramate etc. Valproate analogs - TV-1901 etc.
Anxiety: panic disorder, OCD (obsessive-compulsive disorder) GAD (generalized anxiety disorder), PTSD (posttraumatic stress disorder), acute stress disorder	Benzodiazepines (BZs)- diazepam, clonazepam 5HT _{1A} partial agonists- buspirone SSRIs	Newer BZs: pagacalone, deramciclane 5HT _{1A} agonists: lesopitron, S-15535 Orphanin FQ receptor agonists – Ro 64-6198 CRF receptor antagonists

Trends in Psychiatric Drug Treatment

Attention deficit hyperactivity disorder (ADHD)	Psychostimulants – methylphenidate d-amphetamine	α 4 β 2- nicotinic receptor agonists – ABT-089 Histamine H ₃ antagonists - GT 2331 Monoamine uptake blockers - atomoxetine
Compulsive/addictive disorders : cocaine, amphetamine, heroin, alcohol, nicotine (smoking) addiction Recreational drug use Cannabinoid, PCP Compulsive disorders: Gambling, sexual behavior, eating (obesity, anorexia, bulimia)	Methadone, LAAM Naloxone Disulfiram Acamprosate Nicotine patches Bupropion Phenylpropanolamine Sibutramine Orlistat PPAR γ antagonists - troglitazone	DA transport blockers - RTI -113 D1 receptor ligands - DAS-431, CEE 03-310 Cocaine vaccine (TA-CD) and catalytic antibodies - mAb 15A10 Obesity: Leptin modulators, CART, GLP1, amylin, galanin, neuropeptide Y, α - MSH, famoxin, fatty acid synthase (FAS) inhibitors, orexin, melanocortin - 4 (MC-4)/SLC-1 and SOCS3 antagonists
Sleep disorders: sleep pattern disruption (jet lag) Insomnia, narcolepsy	Hypnotics- Secobarbital, triazolam, estazolam Modafinil, Melatonin	Agomelatine, Adenosine agonists H ₃ agonists – SCH 50971 Orexin agonists, NBI 34060
Sexual disorders Erectile dysfunction/ Female sexual dysfunction	Sildenafil Apomorphine	IC-531, BAY 38-9456 DA agonists

Trends in Neurological Drug Treatment

Disease State	Current Approaches	Experimental Approaches
Dementias AD: early onset familial AD (EOFAD), vascular dementia, dementia with Lewy bodies (DLB), dementia associated with Parkinson's disease, AIDS and age-related dementia. Picks' dementia, frontotemporal, substance-induced and alcohol dementia	Cholinergic replacement: Donepezil, rivastigmine Galanthamine etc. Nootropics: piracetam, aniracetam idebenone	Inhibitors of oxidative stress: MAO-B inhibitors - rasagiline; free radical scavengers: ARL-16556 Nicotinic and DA D1/D5 agonists. COX-2 inhibitors – rofecoxib HMG CoA reductase inhibitors – simvastatin Trophic factor replacement /neural growth stimulators – BDNF, AIT-082, kinase signaling pathways Amyloid vaccine - AN 1792/Betabloc BACE1 inhibitors - L-685,458 Caspase inhibitors – IDN-6556
Parkinson's disease (PD)	DA replacement: L-dopa, pramipexole cabergoline, piribedil, pergolide, ropinerole	Neuroimmunophilins, GPI-1337 Adenosine A _{2A} agonists - KW 6002, SCH 58261 Inhibitors of oxidative stress: Rasagiline - Caspase inhibitors
Epilepsy	Phenytoin, carbamazepine, valproate, ethosuximide, Phenobarbital Felbamate, lamotrigine, gabapentin, tiagabine, Vigabatrin	Leviracetam . Valproate analogs: TV-1901, NPS 1776, ABS-103, DP-VPA etc. Sodium channel modulators: GW 273293, Co 102862 Calcium antagonists: zonisamide, retigabine, PNU 156654E GABA modulators: losigamone, pregabalin, Co 15279, rufinamide. Glutamate receptor antagonists: Talampanel , TV 141, PNU 191779E

Trends in Neurological Drug Treatment

Stroke	tissue plasminogen activator, tPA	NMDA/ glycine site modulators: D-serine, licostinel, MDL 105518, GV 224029 NR1 vaccine (AAVNMDAR1) NAALADase inhibitors: 2-PMPA Caspase-3 inhibitors P2X ₇ receptor antagonists P2Y ₁₂ antagonists: AR-C 69931MX
Spinal cord injury	Steroids	NR2B NMDA antagonist - CP-101,606
Multiple sclerosis	Interferon Immunosuppressants methylprednisolone prednisone methotrexate azathioprine	Clabridine, mitoxantrone, paclitaxel, sulfasalazine, lenercept (sTNFR-IgG p55) ISIS 107248 - antisense Cannabinoid receptor agonists: R (+)-WIN 55,212, methanadamide
Pain	Opioids NSAIDs COX-2 inhibitors	α4β2 nicotinic agonists – ABT-594 NMDA receptor antagonists Neurokinin-1 antagonists Vanilloid receptor modulators P2X ₃ receptor antagonists GABA _B activated Kirs – gabapentin Voltage-gated Na ⁺ channels Growth factors – NGF

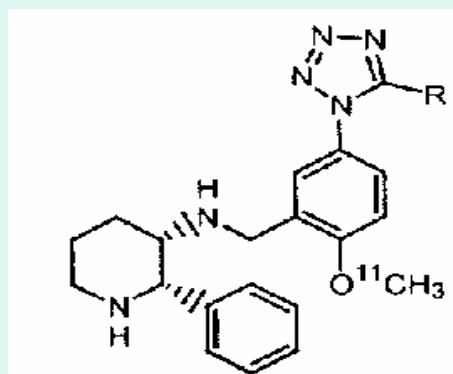
Positron Emission Tomography (PET)

Positron Emitting Radionuclides

Radionuclide	Half-Life Minutes	Photons (keV)	Nuclear Reactions
Oxygen-15	2.01	511	$^{14}\text{N}(\text{d},\text{n})^{15}\text{O}$ $^{14}\text{N}(\text{p},\text{n})^{15}\text{O}$
Nitrogen-13	9.98	511	$^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ $^{13}\text{C}(\text{p},\text{n})^{13}\text{N}$
Carbon-11	20.4	511	$^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ $^{11}\text{B}(\text{p},\text{n})^{11}\text{C}$ $^{10}\text{B}(\text{d},\text{n})^{11}\text{C}$
Fluorine-18	109.8	511	$^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ $^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$
*Bromine-76	16.3 hours	511	$^{76}\text{Se}(\text{p},\text{n})^{76}\text{Br}$
*Iodine-124	4.2 days	511	$^{124}\text{Te}(\text{p},\text{n})^{124}\text{I}$

Ligands for Assessing Receptor Occupancy in Vivo

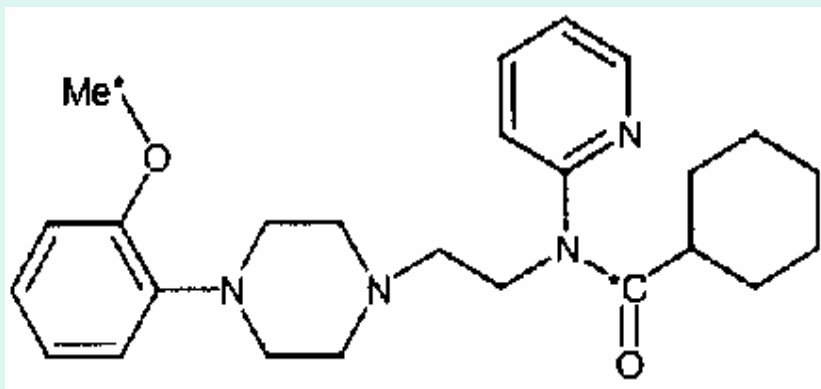
NK1 Selective Radiotracers



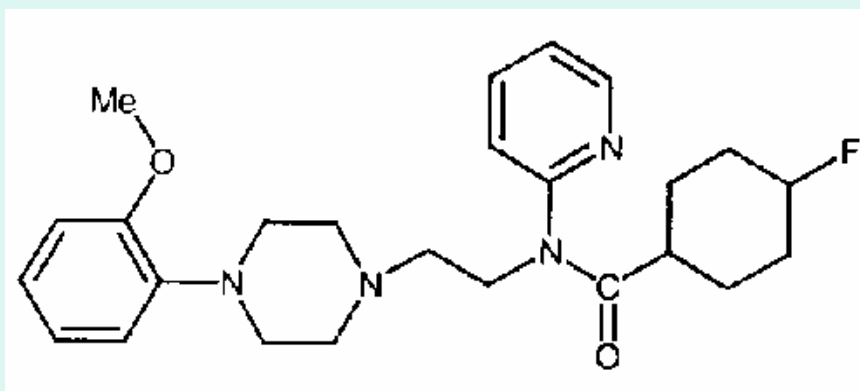
1 R=H, [^{11}C]GR203040

2 R=CF₃, [^{11}C]GR205171

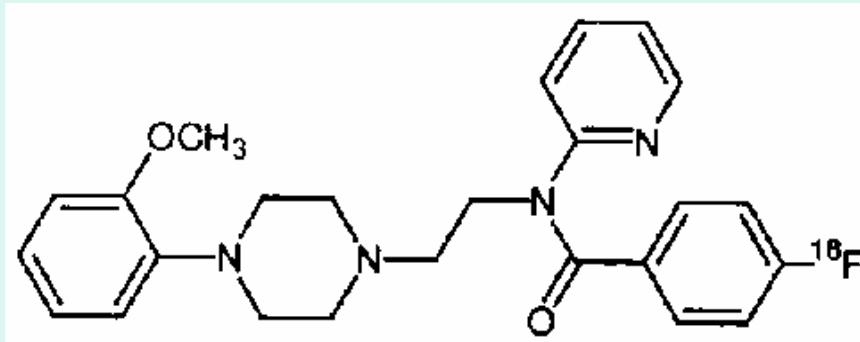
Serotonin 5-HT_{1A} Receptor



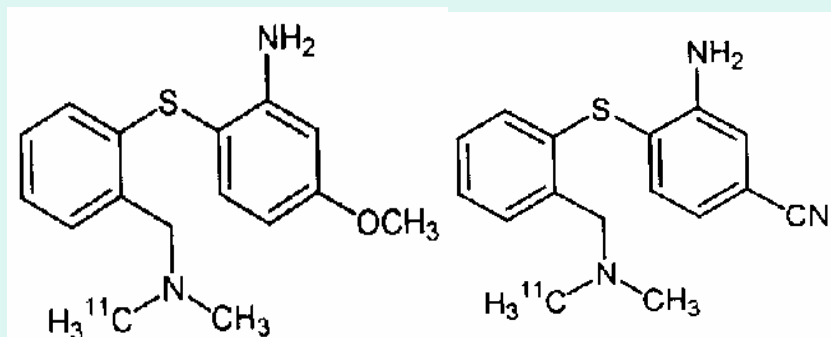
F-18 Labeled 5-HT_{1A} Tracers



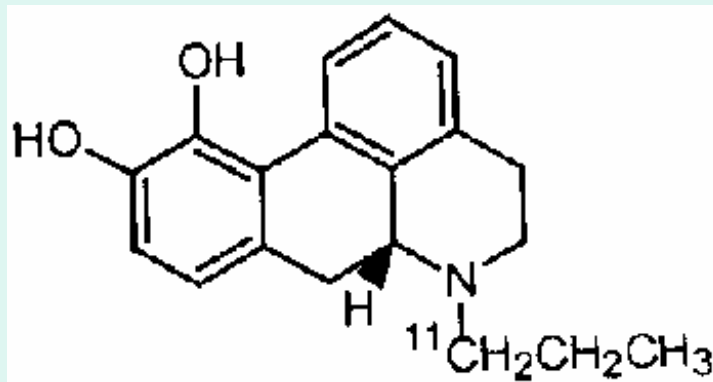
F-18 Labeled 5-HT1A Tracers



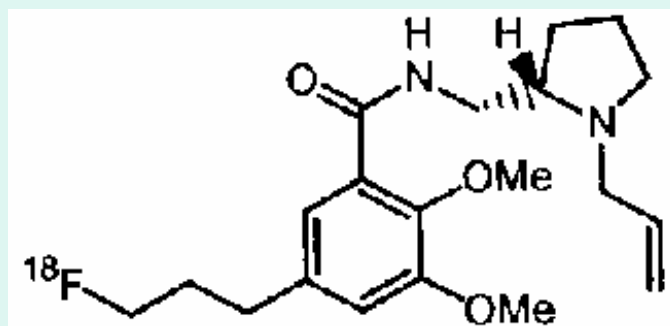
Serotonin Transporters



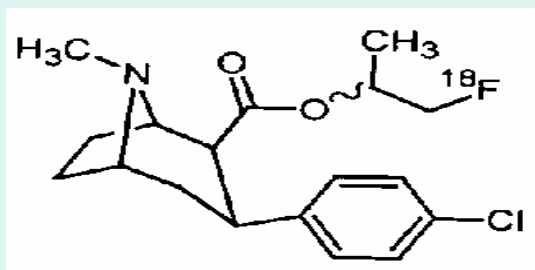
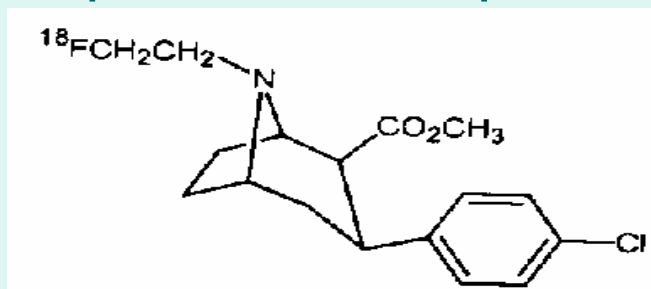
Dopamine D2 Receptors



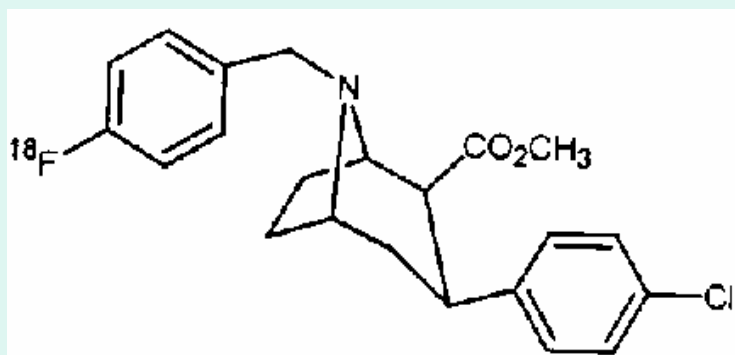
Dopamine D2 Receptors



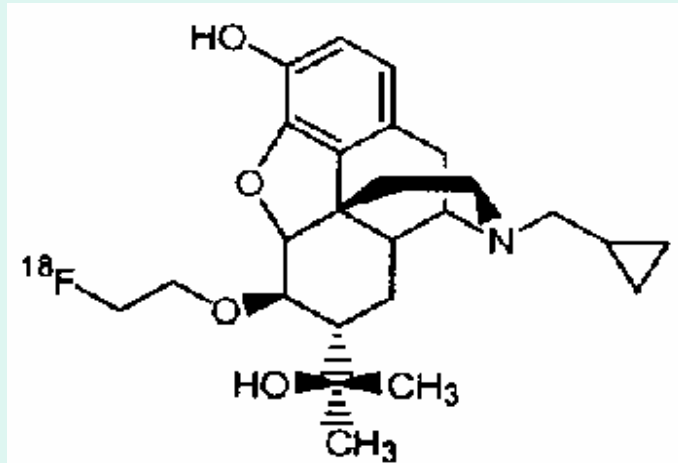
Dopamine Transporters



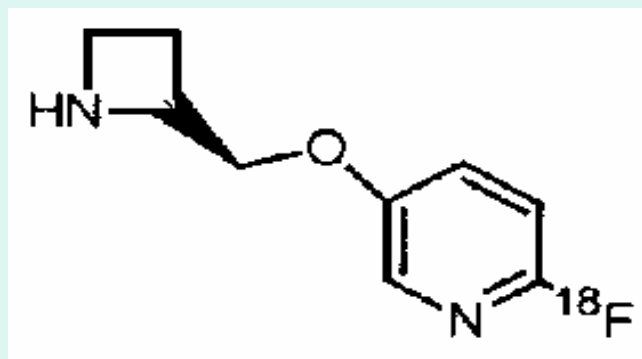
Dopamine Transporters



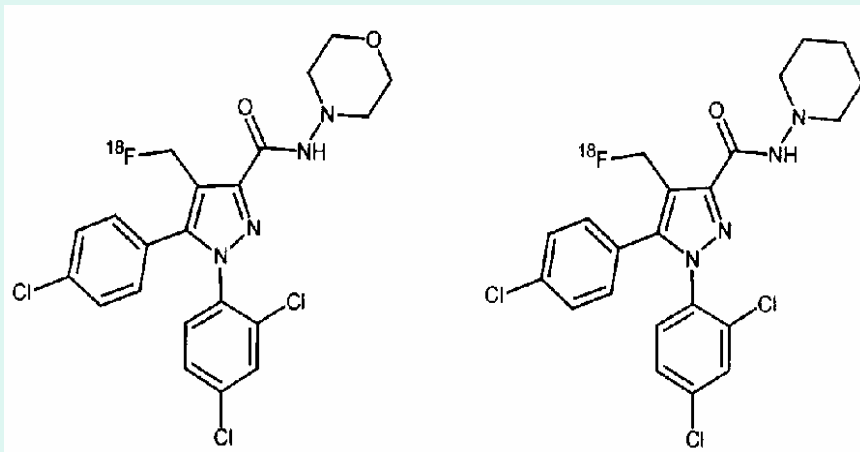
Opiate Receptors



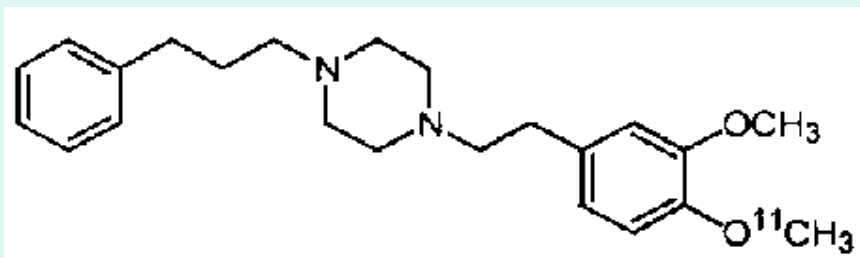
Nicotinic Receptor



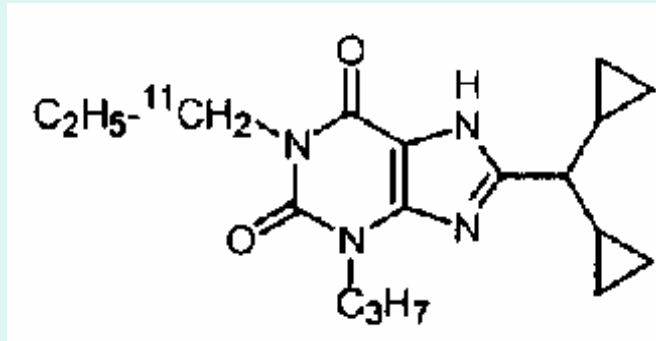
Cannabinoid Receptors



Sigma-1 Receptors



Adenosine Receptors



Adenosine Receptors

