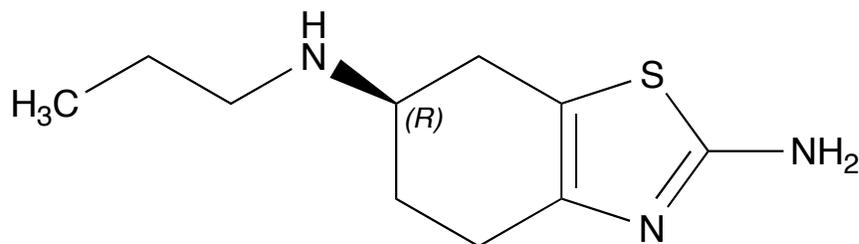


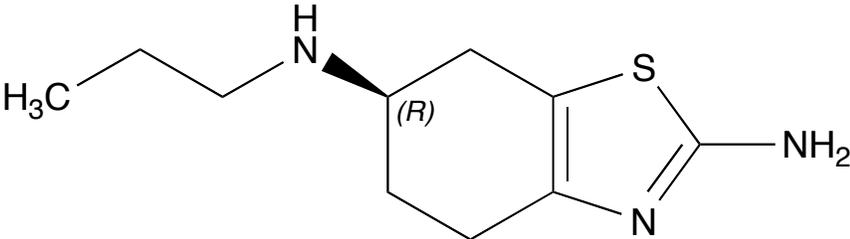
CINAPS Compound Dossier

(R)-(+)-Pramipexole



2/5/2007

I. Compound Information

Common name	(R)-(+)-Pramipexole				
Structure					
PubChem ID	119570	MF	C10 H17 N3 S	MW	211.33
CASRN	104632-28-2	Polar surface area	50.41	logP	1.168
IUPAC name	(6R)-N'-Propyl-4,5,6,7-tetrahydrobenzothiazole-2,6-diamine				
Other names	SND919CL2X				
Drug class	Antioxidant; free-radical scavenger				
Notes	Nondopaminergic enantiomer of pramipexole.				
Development status	Patent: Bennett, James P., <i>Neuronal, muscular, and/or retinal tissue function restoration with R(+)-pramipexole or other tetrahydrobenzathiazole</i> , US Patent 2006281797 (2006) Phase IIa (unpublished)				

II. Rationale

IIa. Scientific Rationale / Mechanism

Both pramipexole enantiomers possess equipotent efficacy toward reducing the generation of reactive oxygen species such as hydrogen peroxide and nitric oxide generated in vitro and inhibit cell death in glutathione-depleted neuroblastoma cells. Both enantiomers are able to confer in vivo neuroprotective effects by their ability to accumulate in brain, cells, and mitochondria. The (R)-(+)-isomer (SND919CL2x) may represent the prototype of a mitochondria-targeted neuroprotectant because it has the same antioxidative properties as the (S)-(-)-isomer without causing adverse dopaminergic effects. (Danzeisen, 2006) Both pramipexole enantiomers inhibited caspase activation and restored the loss of calcein accumulation (markers for the “mitochondrial” apoptosis pathway) induced by MPP+ in human neuroblastoma cells. (Abramova, 2002) (S)-(-)-Pramipexole protects dopaminergic cells against dopamine, 6-hydroxydopamine, and hydrogen peroxide-induced cytotoxicity. This neuroprotective effect could not be blocked by selective D2 or D3 antagonists which implies that the beneficial effect would be shared by the (R)-(+)-enantiomer. (Le, 2000) Both pramipexole enantiomers decreased cell death in response to MPP+ and rotenone in dopaminergic neuroblastoma cells. The protective effect was not inhibited by dopamine receptor antagonists. Protection occurred at concentrations at which pramipexole did not demonstrate antioxidant activity. However, pramipexole reduced caspase-3 activation, decreased the release of cytochrome c and prevented the fall in the mitochondrial membrane potential induced by MPP+ and rotenone. This suggests that pramipexole (and its enantiomer) produce direct neuroprotective, anti-apoptotic effects not dependent on dopamine receptor affinity or antioxidant activity. (Gu, 2004)

Pramipexole blocked dopaminergic neuronal death induced by glutamate. Pramipexole reduced dopamine content but did not change the levels of total or phosphorylated tyrosine hydroxylase, a rate-limiting enzyme in dopamine synthesis. The neuroprotective effect of pramipexole was not blocked by a dopamine D2 receptor antagonist. Both the dopaminergic (S)-(-)- and non-dopaminergic (R)-(+)-enantiomers of pramipexole equally suppressed dopaminergic neuronal death. These results suggest that pramipexole protects dopaminergic neurons from glutamate neurotoxicity by the reduction of intracellular dopamine content, independent of dopamine receptor activation. (Izumi, 2007)

IIb. Consistency

III. Efficacy (animal models of Parkinson's disease)

IIIa. Animal Models: Rodent

Indirect evidence: (R)-(+)-Pramipexole (100 mg/kg) prolonged the survival time and preserved motor function in superoxide dismutase 1-G93A mice, a model of familial amyotrophic lateral sclerosis. (**Danzeisen, 2006**) Treatment of rats for 4 days with (S)-(-)-pramipexole, markedly increased Bcl-2 immunoreactivity in neuronal dendritic processes in both cerebral cortex and hippocampus. (**Takata, 2000**)

IIIb. Animal Models: Non-human primates

n/a

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical studies

Clinical studies were initiated July 2004 by UVA researchers. (unpublished results)

Phase I, two-part dose escalation and maintenance from 1.5 -30 mg/d on 15 ALS subjects and 3 healthy controls. The compound was said to be well tolerated with anecdotal improvement.

Phase I 30mg/d safety study on 11 surviving ALS subjects and 40 new ALS subjects. The study is ongoing, but the compound is said to be well tolerated.

Phase II 30mg/d futility study is ongoing at 3 sites on 40 ALS subjects. The study had a 3 month off-drug lead-in and then 6 month at 30mg/d. It is set as a futility based study dependent on absence of change in rate of ALSFRS_r decline.

Phase IIa, dose escalation from 30-300 mg/d on 10 ALS patients with particular care for examination for cardiovascular safety. The study is ongoing and the drug is said to be well tolerated with no drug-related adverse events.

Results of the early study are given as: treatment with 30 mg/day of (R)-(+)-pramipexole decreases slope of decline in ALSFRS_r. (**Grate, 2006**)

A UVA study is listed on the ClinicalTrials.gov website under ID: NCT00140218. (**Bennett, 2005**)

IVb. Epidemiological evidence

n/a

V. Relevance to other neurodegenerative diseases

(R)-(+)-Pramipexole (100 mg/kg) prolonged the survival time and preserved motor function in superoxide dismutase 1-G93A mice, a model of familial amyotrophic lateral sclerosis. (**Danzeisen, 2006**) Both pramipexole enantiomers inhibited caspase activation by neurotoxic beta amyloid peptides (a marker for the “mitochondrial” apoptosis pathway associated with Alzheimer's disease). (**Abramova, 2002**)

(R)-(+)-Pramipexole is under development as a therapy for ALS by Knopp Neurosciences, Inc.

VI. Pharmacokinetics

Via. General ADME

By analogy to (S)-(-)-pramipexole, it was demonstrated that both pramipexole isomers enter and accumulate in cerebellar granule cells, astroglial cells, and isolated mitochondria. (**Danzeisen, 2006**)

By analogy to (S)-(-)-pramipexole: bioavailability >90%; T_{max} = 1 - 3 hrs.; Protein binding ≤ 20%; V_d = 400 L; Clearance = 500 mL/min; Elimination half-life = 8 - 12 hrs.; Hepatic elimination: minimal; Fraction excreted unchanged in kidneys ~ 0.9. (**Lam, 2000**)

Vib. CNS Penetration

Both (S)-(-)-PPX and (R)-(+)-PPX show a 6:1 brain-to-plasma ratio after 4 days of 200 mg/kg/day dosing in mice. (**Danzeisen, 2006**)

Vic. Calculated logBB -0.43

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

(S)-(-)-Pramipexole was well tolerated and accepted by the majority of physicians and patients in a study involving 657 PD patients. (**Reichmann, 2003**)

Unpublished data from Knopp Neurosciences, Inc. indicates that (R)-(+)-pramipexole is well tolerated with potential hemodynamic dose limitation. Initial animal data (UVA) signals no clear dose limitations and (R)-(+)-pramipexole is well tolerated in over 80 ALS patients for up to 6-18 months (30 mg – 300 mg/d). This exposure is 5 - 70-fold the (S)-(-)-isomer dosing required for a PD neuroprotective effect. The one effect noted was a mild, asymptomatic, orthostatic hypotension (~20mm Hg) noted at 300mg/d. (Grate, 2006)

VIIb. Drug Interaction Potential

The low achievable plasma concentration compared with the relatively high K_i towards CYP isoenzymes combined with the linear pharmacokinetic profile suggests that the potential for interactions with CYP-metabolized drugs is extremely low. Pramipexole apparently undergoes active tubular secretion via the organic cation transport system. Therefore, there is the potential for interaction between pramipexole and other agents transported by the same system such as procainamide, trimethoprim, and cimetidine. (**Lam, 2000**)

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