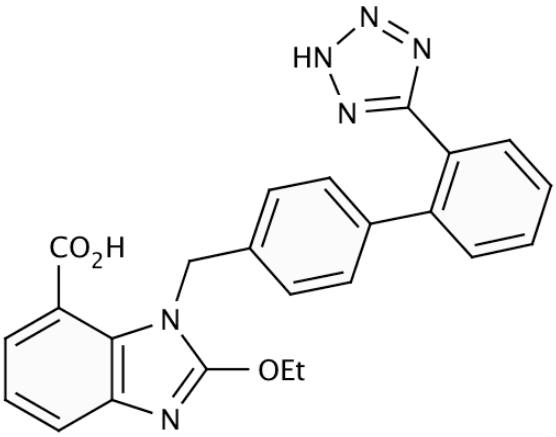
CINAPS Compound Dossier

Candesartan



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National Institute of Neurological Disorders and Stroke

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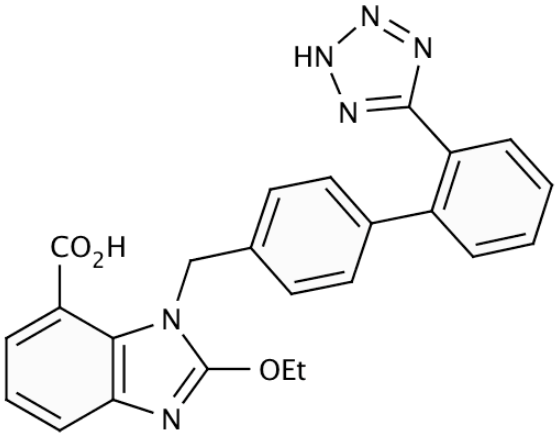
I. Compound Information

Common name: Candesartan

Structure:



PubChem ID: 2541	**Mol. Formula:** $C_{24}H_{20}N_6O_3$	**FW:** 440.45
CASRN: 139481-59-7	**Polar surface area:** 118.81	**logP:** 5.05

IUPAC name: 2-Ethoxy-3-[[4-[2-(2H-tetrazol-5-yl)phenyl]phenyl]methyl]benzimidazole-4-carboxylic acid

Other names: –

Drug class: Angiotensin II receptor antagonist

Medicinal chemistry development potential: High

II. Rationale

IIa. Scientific Rationale / Mechanism

Angiotensin Receptor Blockers (ARBs)

Candesartan is a selective antagonist of the angiotensin II (Ang II) type 1 (AT1) receptor. The pro-drug (candesartan cilexetil) is marketed for treatment of hypertension, chronic heart failure and left ventricular systolic dysfunction (**Astra Zeneca, 2009**). Several other selective and high-affinity AT1 receptor antagonists are currently available, including eprosartan, irbesartan, losartan, telmisartan and valsartan.

In vitro binding studies show that these compounds differ in their affinity for the AT1 receptor and in the duration of receptor blockade. In general, inhibition of AT1 receptors is competitive and reversible, as is the case for losartan. On the other hand, some AT1 receptor antagonists, including candesartan, have a higher affinity for the AT1 receptor and dissociate extremely slowly, thereby producing insurmountable inhibition of relatively long duration (**Culman, 2002**). EXP3174 (the active metabolite of losartan), valsartan, and irbesartan exhibit differing degrees of insurmountable inhibition.

The mechanism of action for AT1 antagonists has been demonstrated predominantly for other molecules in this class, particularly losartan, with relatively little mechanistic data for candesartan per se.

AT Receptors and the Renin-Angiotensin System (RAS)

The RAS is best known for its role in regulating blood pressure, activation of sympathetic pathways, stimulation of vasopressin release, regulating drinking behavior and cerebral blood flow (**Grammatopoulos, 2007a**). Ang II, a biologically active form of angiotensin, is generated by angiotensin converting enzyme (ACE). All the required components of the RAS, such as renin, angiotensinogen, ACE, Ang II and AT receptors, are present in the mammalian central nervous system, as well as in peripheral tissues.

Ang II is the primary agonist of the RAS and has similar affinities for the two primary AT receptors, AT1 and AT2. The AT1 receptor appears to mediate classic angiotensin functions such as the control of fluid homeostasis, blood pressure, cyclicity of reproductive hormones and sexual behavior. The AT2 has been suggested to be involved in brain development, apoptosis, vascular growth, blood flow control and NMDA receptor modulation (**Savaskan, 2005**). Recent articles point to Ang II as a stress hormone acting through the AT1 receptor to induce inflammation and oxidative stress, and also as an endogenous modulator of dopamine release (**Joglar, 2009**).

AT Receptors and Parkinson's Disease (PD)

Radio-labeled AT I receptors were decreased by approximately 70%, 70% and 90% in the caudate nucleus, putamen and substantia nigra, respectively, for patients with PD relative to matched controls. Radio-labeled AT2 receptor levels were decreased by 60% in the caudate nucleus for patients with PD relative to controls (**Ge, 1996**).

Models of Parkinson's-like cell death

Two key concepts are important in understanding the potential utility of candesartan (and other ARBs) for treatment of PD. First, Ang II-induced activation of AT2 receptors is associated with neuroprotective effects under some experimental conditions or conversely with enhancement of chemically-induced neurotoxicity. Second, blockade of AT1 receptors in the presence of Ang II is associated with enhanced neuroprotective activity, as demonstrated in models of neuronal loss (*in vitro* and *in vivo*) relevant to PD. Thus, application of a competitive, long-lasting, AT1 receptor antagonist would be expected to enhance the neuroprotective effect of Ang II not only by increasing the amount of Ang II available for binding to AT2 receptors but also by allowing Ang II to selectively activate the AT2 receptors.

In vivo models of oxidative stress-induced cell death [e.g., 6-OHDA lesioned rats (**Rey, 2007**)] and *in vitro* models of rotenone-induced neurotoxicity (**Grammatopoulos, 2005**) demonstrated that Ang II increased the toxic effects of 6-OHDA *in vivo* yet protected cultured neurons against rotenone. However, in both cases, antagonism of the AT1 receptor produced a significant level of neuroprotection. C57BL/6 mice dosed daily with losartan, s.c., for 16 days prior, during and after MPTP (4 doses at 2-hr intervals on day 3 and 1 dose 6 days later) showed significant protection of the substantia nigra pars compacta, resulting in decreased dopaminergic cell loss compared to vehicle controls (**Grammatopoulos, 2007a**).

An *in vitro* model of alpha-synuclein toxicity was used to demonstrate that Ang II protection of cultured human neuroglioma H4 cells was most effectively enhanced by coadminstration of both an AT1 and an AT2 antagonist (**Grammatopoulos, 2007b**).

General Neuroprotection

In addition to neuronal toxicity specifically related to PD, more generalized models of cellular toxicity have been examined, particularly those involving NMDA-induced excitotoxic damage and chemically-induced hypoxic insults. In both these settings, Ang II produced a partial cellular protection that was enhanced by the inclusion of an AT1 receptor antagonist (**Grammatopoulos, 2002; Jing, 2004**). These studies suggest that the neuroprotective effects are elicited by Ang II acting at the AT2 receptor and that this activity can be enhanced by compounds that compete with Ang II for binding at the AT1 receptor.

Another interesting finding, was the demonstration by Simonnet and Giorguieff-Chesselet (**Simonnet, 1979**) that Ang II stimulated dopamine release from striatal tissue slices and that this release can be blocked by losartan (**Dwoskin, 1992**). Similar results have been reported following i.c.v. Ang II (**Dwoskin, 1992**) and are supported by similar changes in dopamine metabolites (**Mendelsohn, 1993**).

The rationale for the use of an AT1 receptor antagonist for the treatment of PD is based on endogenous Ang II in Parkinson's patients being rendered more potent at protecting the dopaminergic pathways, probably through enhanced activity at the AT2 receptor. On the other hand, Ang II-induced dopamine release (which is mediated via AT1 receptors) would also be inhibited by such an antagonist and this could potentially

result in enhanced Parkinson-like symptoms as reported in the single case study with losartan (**Sarma, 2008**).

In primary mesencephalic cultures containing about 40% neurons, 43% astrocytes, and 12% microglial cells, 4 day application of 0.25 uM or 0.5 uM MPP^+ significantly reduced TH positive neurons (25% and 55% reduction, respectively) as measured by immunocytochemistry. By comparison, 0.1 uM MPP^+ had no significant effect. The 25% reduction in TH+ neurons caused by 0.25 uM MPP^+ was increased to 60% by co-application of 100 nM angiotensin II. The effect of MPP^+ alone or of MPP+ plus angiotensin II was blocked by addition of the AT1 receptor antagonist ZD 7155 but not by the AT2 receptor antagonist PD 123319. ZD 7155 did not significantly block the TH+ neuron loss seen upon application of 0.5 uM MPP^+ (**Joglar, 2009**).

IIb. Consistency

The literature provides appreciable evidence for the neuroprotective activity of Ang II and for enhancement of this effect by AT1 receptor antagonists in preclinical models. When extrapolating to potential therapeutic applications, an inherent assumption is that PD patients have sufficient endogenous Ang II in the brain such that neuroprotective activity can be enhanced by AT1 receptor antagonism. Significant information was not found in the published literature to support or refute such an assumption. A potential flaw in this theoretical framework is that Ang II-induced mid-brain dopamine release is mediated via AT1 receptors and thus AT1 selective blockade might result in exacerbation of Parkinson's symptoms in spite of a neuroprotective effect.

III. Efficacy (Animal Models of Parkinson's Disease)

IIIa. Animal Models: Rodent

Injection (i.p.) of 30 mg/kg MPTP every other day for 9 days (5 total injections) into male C57BL-6 mice (7 weeks old) resulted in 60% loss of TH^+ neurons in the SNc. Subcutaneous injection of 0.25 mg/kg candesartan twice daily from 2 weeks before MPTP treatment until sacrifice significantly reduced TH^+ neuron loss to 20%. TH staining was estimated as optical density in the striatum. MPTP resulted in a 70% loss of TH staining indicating significant loss of TH+ nerve terminals. This loss was reduced to 40% by candesartan treatment. Candesartan's effects were not mediated by altering the DA uptake system nor did candesartan affect striatal levels of MPP^+ (**Joglar, 2009**).

No other studies were found in which candesartan was evaluated in animal models of PD, but key studies are noted below for a related AT1 antagonist (losartan).

Eight-week-old male C57BL/6 mice (n = 4–5 per group) received subcutaneous (200 µl) injections of losartan (90 mg/kg) daily for 16 days, beginning two days prior to the first MPTP injection. Control animals received saline injections. On day 3 mice received four intraperitoneal injections of MPTP-hydrochloride (20 mg/kg of free base) in saline at 2-hour intervals followed by a single intraperitoneal injection of MPTP-hydrochloride (20 mg/kg) on day 9, and were sacrificed 7 days after the last MPTP injection. A severe loss (61.8 ± 10%) of DA neurons was observed in the SNpc of MPTP-treated mice compared to control mice treated with saline. By contrast, the number of DA neurons lost in MPTP-treated mice receiving losartan was only 25.0 ± 16%, when compared to saline-treated mice. These results show that pretreatment and daily dosing with losartan can reduce MPTP-induced DA neuronal loss in the SNpc by 60% ($p<0.05$) (**Grammatopoulos, 2007a**).

In 6-OHDA lesioned rats, unilateral application of Ang II in the non-lesioned (left) striatum caused all animals to rotate in tight head to tail turns in an ipsilateral direction to the lesion ($p<0.01$). Concomitant infusion with losartan abolished Ang II-induced turning ($p<0.05$) so that it was not significantly different from that with vehicle ($p>0.1$). Neither saline nor losartan alone had a significant effect on the animal's behaviour ($p>0.1$). Haloperidol injected one hour before the intrastriatal injection completely abolished Ang II-induced turning at 0.3, 1.0 and 3.0 nmol Ang II ($p>0.1$, $p<0.05$, $p<0.05$ respectively). In normal, unlesioned, animals intrastriatal Ang II (2 nmol) administration had no effect on behaviour. The blockade of Ang II-induced rotation by losartan is in full agreement with the ability of this antagonist to suppress Ang II induced DA release measured by microdialysis (**Mendelsohn, 1993**), and from *in vitro* slice preparations (**Simonnet, 1979**). These findings suggest the Ang II induced DA release is mediated by AT 1 receptors, in keeping with the subtype analysis from receptor mapping (**Jenkins, 1995**).

IIIb. Animal Models: Non-human primates

n/a

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical Studies

No clinical studies were found in which candesartan was evaluated in PD patients. One case report was found in which a related AT1 antagonist (losartan) was administered to a 65-year-old man with hypertension and PD that started at 60 years of age. The patient had been stable on L-dopa/carbidopa (100/25 mg) twice a day for PD and ramipril 5 mg/day for hypertension. Three months prior to admission, his family physician changed ramipril to losartan 25 mg/day and later increased it to 50 mg/day for better control of hypertension. The patient's PD symptoms gradually worsened with several falls, freezing episodes, and severe bradykinesia requiring constant support for activities of daily living. His UPDRS (Unified Parkinson's Disease Rating Scale) motor score was 50 at the time of admission. Losartan was stopped and L-dopa continued in the same doses. After 48 hours, the patient made remarkable improvement in bradykinesia, rigidity, and tremors. He was walking independently and had only occasional brief freezing episodes. His UPDRS motor score improved to 39. To establish the causal relationship of losartan to the parkinsonism symptoms, the patient was re-challenged with losartan 25 mg/day. After 48 hours, the patient deteriorated again with severe bradykinesia and frequent freezing episodes. His UPDRS motor score worsened to 50 again. Losartan was discontinued again. Twenty four hours later, the patient was ambulating independently, with mild bradykinesia and occasional brief freezing. His UPDRS motor score improved to 41. Patient's blood pressure was later controlled with ramipril 10 mg/day. The half-life of losartan is very short, about 2 hours. This may explain the rapid improvement that was seen in this patient after discontinuation of losartan. There is experimental evidence to suggest that angiotensin facilitates nigrostriatal dopaminergic release by acting on AT 1 receptors. Losartan blocks these receptors and inhibits dopaminergic release. Angiotensin converting enzyme inhibitors like ramipril, on the contrary, may facilitate dopaminergic release (**Sarma, 2008**).

IVb. Epidemiological Evidence

n/a

V. Relevance to Other Neurodegenerative Diseases

n/a

VI. Pharmacokinetics

VIa. General ADME

Candesartan cilexetil is currently marketed for the treatment of hypertension, chronic heart failure and left systolic dysfunction (**Astra Zeneca, 2009**). Thus, the pharmacokinetics of candesartan in humans is well understood. Information noted on the product label for Atacand® follows:

General - Candesartan is mainly excreted unchanged in urine and feces (via bile). It undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite. The elimination half-life of candesartan is approximately 9 hours. After single and repeated administration, the pharmacokinetics of candesartan are linear for oral doses up to 32 mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing. Following administration of candesartan cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (Cmax) is reached after 3 to 4 hours.

Metabolism and Excretion - Total plasma clearance of candesartan is 0.37 mL/min/kg, with a renal clearance of 0.19 mL/min/kg. When candesartan is administered orally, about 26% of the dose is excreted unchanged in urine. Following an oral dose of C-labeled candesartan cilexetil, approximately 33% of radioactivity is recovered in urine and approximately 67% in feces. Following an intravenous dose of C-labeled candesartan, approximately 59% of radioactivity is recovered in urine and approximately 36% in feces. Biliary excretion contributes to the elimination of candesartan.

Distribution - The volume of distribution of candesartan is 0.13 L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses. In rats, it has been demonstrated that candesartan crosses the blood-brain barrier poorly, relative to other compounds in this class. It has also been demonstrated in rats that candesartan passes across the placental barrier and is distributed in the fetus.

Information is available in geriatric populations indicating that candesartan is safe to be used in aging populations, including those with renal insufficiency (**FDA, 2005**).

VIb. CNS Penetration

No formal publication of CNS penetration data with candesartan were found, but circumstantial CNS activity reported in PD preclinical models has been (see studies of losartan and candesartan in PD preclinical models cited elsewhere in this dossier). The regulatory filings for Atacand® may contain further information but they were not available for review.

A recent review focused on the anti-stress and anti-anxiety properties of AT1 antagonists (**Pavel, 2008**) indicates that candesartan or losartan inhibit AT1 receptors in brain as well as in peripheral tissues following subcutaneous administration in rodents.

VIc. Calculated log([brain]/[blood]) (Clark Model)

-0.85 (candesartan)

-0.74 (candesartan cilexetil)

-0.72 (valsartan)

-0.46 (losartan)

The Clark Blood Brain Barrier (BBB) Model predicts that candesartan would not have good CNS penetration. By comparison, Atacand® (i.e., candasartan cilexetil) and valsartan would have similar (and somewhat better than candesartan) penetration. Losartan is predicted to have the best CNS penetration of the four. Thus, the pharmacokinetics of individual compounds in this class would be expected to differ with regard to distribution into the CNS.

VII. Safety, Tolerability, and Drug Interaction Potential

VIIa. Safety and Tolerability

Candesartan cilexetil (Atacand®) is currently marketed for the treatment of hypertension, chronic heart failure and left systolic dysfunction (**Astra Zeneca, 2009**). Thus, significant clinical experience and understanding of the safety and tolerability of this compound is available. The product label for Atacand® includes the following safety concerns:

Atacand® has been evaluated for safety in more than 3600 patients/subjects, including more than 3200 patients treated for hypertension. About 600 of these patients were studied for at least 6 months and about 200 for at least 1 year. In general, treatment with Atacand® was well tolerated. The overall incidence of adverse events reported with Atacand® was similar to placebo. The rate of withdrawals due to adverse events in all trials in patients was 3.3% (ie, 108 of 3260) of patients treated with candesartan cilexetil as monotherapy and 3.5% (ie, 39 of 1106) of patients treated with placebo. In placebo-controlled trials, discontinuation of therapy due to clinical adverse events occurred in 2.4% (i.e., 57 of 2350) of patients treated with Atacand® and 3.4% (ie, 35 of 1027) of patients treated with placebo. The most common reasons for discontinuation of therapy with Atacand® were headache (0.6%) and dizziness (0.3%). The adverse events that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Atacand® and at a higher incidence in candesartan cilexetil (n = 2350) than placebo (n = 1027) patients included back pain (3% vs. 2%), dizziness (4% vs. 3%), upper respiratory tract infection (6% vs. 4%), pharyngitis (2% vs. 1%), and rhinitis (2% vs. 1%). The following adverse events occurred in placebo-controlled clinical trials at a more than 1% rate but at about the same or greater incidence in patients receiving placebo compared to candesartan cilexetil: fatigue, peripheral edema, chest pain, headache, bronchitis, coughing, sinusitis, nausea, abdominal pain, diarrhea, vomiting, arthralgia, albuminuria. Other potentially important adverse events that have been reported, whether or not attributed to treatment, with an incidence of 0.5% or greater from the 3260 patients worldwide treated in clinical trials with Atacand® are listed below. It cannot be determined whether these events were causally related to Atacand®. Body as a Whole: asthenia, fever; Central and Peripheral Nervous System: paresthesia, vertigo; Gastrointestinal System Disorder: dyspepsia, gastroenteritis; Heart Rate and Rhythm Disorders: tachycardia, palpitation; Metabolic and Nutritional Disorders: creatine phosphokinase increased, hyperglycemia, hypertriglyceridemia, hyperuricemia; Musculoskeletal System Disorders: myalgia; Platelet/Bleeding-Clotting Disorders: epistaxis; Psychiatric Disorders: anxiety, depression, somnolence; Respiratory System Disorders: dyspnea; Skin and Appendages Disorders: rash, sweating increased; Urinary System Disorders: hematuria. Other reported events seen less frequently included angina pectoris, myocardial infarction, and angioedema (**FDA, 2005**). Atacand is contraindicated in pregnancy (**Astra Zeneca, 2009**).

VIIb. Drug Interaction Potential

The product label for Atacand® describes the following drug interaction potential:

No significant drug interactions have been reported in studies of candesartan cilexetil given with other drugs such as glyburide, nifedipine, digoxin, warfarin, hydrochlorothiazide, and oral contraceptives in healthy volunteers, or given with enalapril to patients with heart failure (NYHA class II and III). Because candesartan is not significantly metabolized by the cytochrome P450 system and at therapeutic concentrations has no effects on P450 enzymes, interactions with drugs that inhibit or are metabolized by those enzymes would not be expected.

Lithium - Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with ACE inhibitors, and with some Ang II receptor antagonists. An increase in serum lithium concentration has been reported during concomitant administration of lithium with Atacand®, so careful monitoring of serum lithium levels is recommended during concomitant use (**FDA, 2005**).

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