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(54) Title: ALPHA-7 NICOTINIC RECEPTOR AGONISTS AND STATINS IN COMBINATION

(57) Abstract: Combinations of  $\alpha 7$ -nAChR agonists and statins, pharmaceutical compositions containing the same and methods of using the same useful for treatment or prophylaxis of neurological degenerative diseases.

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## Alpha-7 Nicotinic Receptor Agonists and Statins In Combination

### Field of Invention:

This invention is concerned with the treatment of neurological degenerative diseases  
5 and particularly with the treatment of Alzheimer's disease.

### Background

The etiology of Alzheimer's disease is complex and not entirely understood. Current  
hypotheses point to the overproduction of the amyloid peptide A $\beta$  as a causative factor in the  
cognitive deficits and neurodegeneration associated with Alzheimer's disease (Selkoe, 2001;  
10 Walsh *et. al.*, 2002). In addition, epidemiological studies have shown that  
hypercholesterolemia is a risk factor for Alzheimer's disease (Jarvik *et. al.*, 1995; Notkola *et.*  
*al.*, 1998). Further, it has recently been shown that the administration of statins is associated  
with a decreased risk of Alzheimer's disease (Jick *et. al.*, 2000; Wolozin *et. al.*, 2000). Still  
further, another recent study has shown that the statin lovastatin reduced A $\beta$  plasma levels in  
15 human subjects that had elevated plasma levels of low-density lipoprotein cholesterol  
(Buxbaum *et. al.*, 2002).

Alpha-7 nicotinic receptors ( $\alpha$ 7-nAChR) are ligand-gated ion channels that allow for  
the entry into cells of calcium and other monovalent cations (Dani, 2001).  $\alpha$ 7-nAChR have  
been shown to play an important role in regulating neurotransmitter release, hippocampal  
20 synaptic function, neuroprotection against a variety of insults, and cognition (Dani, 2001;  
Dahas-Bailador *et. al.*, 2000; Rezvani and Levin, 2001).

Recent studies imply an interaction between A $\beta$  and  $\alpha$ 7-nAChR that may contribute to  
the pathophysiology of Alzheimer's disease. A $\beta$  has been shown to potently inhibit  $\alpha$ 7-  
nAChR (Liu *et. al.*, 2001). It has been proposed that this inhibitory effect of A $\beta$  on  $\alpha$ 7-  
25 nAChR function may contribute to cognitive deficits in Alzheimer's disease.  
Neurodegeneration induced by the activation of NMDA glutamatergic receptors is also  
enhanced in the presence of A $\beta$  (Kihara *et. al.*, 2001). This A $\beta$  induced neurodegeneration is  
inhibited by activation of  $\alpha$ 7-nAChR.

### Background References:

30 Buxbaum JD, Cullen EI and Friedhoff LT: Pharmacological concentrations of the  
HMG-CoA reductase inhibitor lovastatin decrease the formation of the Alzheimer beta-  
amyloid peptide in vitro and in patients. *Frontiers in Bioscience* 7:a50-a59, 2002.

Dajas-Bailador FA, Lima PA and Wonnacott S: The  $\alpha 7$  nicotinic receptor subtype mediates nicotine protection against NMDA excitotoxicity in primary hippocampal cultures through a  $\text{Ca}^{2+}$  dependent mechanism. *Neuropharmacology* 39:2799-2807, 2000.

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Kihara T, Shimohama S, Sawada H, Honda K, Nakamizo T, Shibasaki H, Toshiaki K, and Akaike A:  $\alpha 7$  Nicotinic receptor transduces signals to phosphatidylinositol 3-kinase to block A $\beta$ -amyloid-induced neurotoxicity. *J Biol Chem* 276:13541-13546, 1998.

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Jarvik GP, Wijsman EM, Kukull WA, Schellenberg GD, Yu C and Larson EB: Interactions of apolipoprotein E genotype, total cholesterol, age, and sex in prediction of Alzheimer's disease. *Neurology* 45:1092-1096, 1995.

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Notkola IL, Sulkava R, Pekkanen J, Erkinjuntti T, Ehnholm C, Kivinen P, Tuomilehto J and Nissinen A: Serum total cholesterol, apolipoprotein E epsilon 4 allele, and Alzheimer's disease. *Neuroepidemiology* 17:14-20, 1998.

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Wolozin B, Kellman W, Ruosseau P, Celesia GG, and Siegel G: Decreased prevalence of Alzheimer's disease associated with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. *Arch Neurol* 57:1439-1443, 2000.

30 **Description of the Invention:**

We have discovered that statins and  $\alpha 7$ -nAChR agonists in combination have the potential to alter the pathophysiology of Alzheimer's disease and symptoms. The different mechanisms by which statins and  $\alpha 7$ -nAChR agonists operate — statins by reducing the

formation of the neurotoxic substance A $\beta$  and  $\alpha$ 7-nAChR agonists by blocking the cognitive impairing and neurotoxic effects of A $\beta$  — imply that a statin and an  $\alpha$ 7-nAChR in combination will synergistically benefit patients suffering with neurological degenerative diseases and particularly patients suffering with Alzheimer's disease.

5 In one aspect the invention is a method for treating neurological degenerative diseases and particularly Alzheimer's disease comprising treatment with a combination comprising an  $\alpha$ 7-nAChR agonist and a statin.

A combination suitable for practicing the invention comprises a statin selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin sodium, simvastatin or  
 10 rosuvastatin, or a pharmaceutically-acceptable salt thereof and an  $\alpha$ 7-nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,  
 (+)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,  
 (-)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,  
 spiro[1-azabicyclo[2.2.1]heptan-3,5'-oxazolidin-2'-one],  
 15 3'-methyl spiro-[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one],  
 spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
 5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
 5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
 5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
 20 1'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline],  
 5'-(phenylcarboxamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
 b]pyridine],  
 5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
 b]pyridine],  
 25 5'-(phenylsulfonylamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
 b]pyridine],  
 5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
 5'-N-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
 5'-N,N-dimethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
 30 b]pyridine],  
 5'-N,N-diethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
 5'-N-ethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
 5'-N-benzylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

- 5'-N-formamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-N-acetamidospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline],  
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]quinoline],  
5'-ethenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(E)-(phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
b]pyridine],  
5'-(4-morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(1-azetidyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
10 5'-(E)-(2-(4-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
b]pyridine],  
5'-(E)-(2-(2-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
b]pyridine],  
5'-(2-trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
15 b]pyridine],  
5'-ethynylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(2-furyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(3-pyridyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-methylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
20 spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5' carbonitrile],  
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5' carboxamide],  
5'-N'-(3-chlorophenyl)aminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-  
(3'H)-furo[2,3-b]pyridine],  
5'-N'-(2-nitrophenyl)aminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-  
25 (3'H)-furo[2,3-b]pyridine],  
4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-methoxyspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-phenylthiospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-(N-2-aminoethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
30 b]pyridine],  
4'-phenylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-(4-N-methylpiperazin-1-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],

4'-chloro-spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine],  
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine],

5 spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide],  
spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-6'-carbonitrile],

6'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine],

6'-fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine],

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide),

10 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),

15 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide),

20 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide),

25 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide),

30 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide),

- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide),  
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*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),  
5 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide),  
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10 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-  
15 carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide),  
20 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-  
carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide),  
25 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-  
carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide),  
30 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide),

5 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide),

*N*-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide),

10 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide); *N*-

15 (1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide),

20 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);

25 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide),

30 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide),

- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide),  
5 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide),  
10 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide),  
15 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-  
carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide),  
20 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-  
carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-  
carboxamide),  
25 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-  
carboxamide),  
30 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-  
carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)[5-(4-chlorophenyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-

5 carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinoliny)thiophene-2-carboxamide),  
(*S*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);  
(*S*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),  
(*S*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),

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(*S*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-

15 carboxamide),

(*R*)-*N*-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-

20 carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-  
carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide),

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(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-  
carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide), or

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-  
carboxamide), or a pharmaceutically-acceptable salt thereof.

30

In general, it is contemplated that any statin when used in combination with any  
alpha-7-nAChR agonist will be useful in practicing the present invention.

Alpha-7-nAChR agonists contemplated to be useful in the present invention are  
described in international publications WO9606098, WO9730998, WO 9903859,

WO9956745, WO0042044, WO0129034, WO0160821, WO0132622, WO0136417, WO0132619, WO0132620, WO0136417, WO0244176, WO0220521, WO0216358, WO0216357, WO0216356, WO0216355, WO0215662 and WO0217358 and in publications EP1219622, EP1184383, EP1184384, EP1184385, JP200203084. Statins contemplated to be  
5 useful in the present inventions are atorvastatin calcium (Lipitor), cerivastatin sodium (Baycol), fluvastatin sodium (Lescol), lovastatin (Mevacor), pravastatin sodium (Pravachol), simvastatin (Zocor) and rosuvastatin (Crestor).

In another aspect the invention is a pharmaceutical composition comprising a combination of an  $\alpha 7$ -nAChR agonist and a statin as described herein together with a  
10 pharmaceutically-acceptable diluent or excipient.

In another aspect the present invention comprises providing neuroprotection or analgesia in a method of treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and  
15 Parkinson's disease which method comprises administering a therapeutically effective amount of a combination as defined in Claim 1 to a patient.

In a particular aspect the method of the invention is a method for the treatment or prophylaxis of Alzheimer's disease.

A further aspect of the invention is the use of a combination of an  $\alpha 7$ -nAChR agonist and a statin as described herein in the preparation of a medicament for providing  
20 neuroprotection or analgesia in the treatment of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease.

In a particular aspect the use of a combination of an  $\alpha 7$ -nAChR agonist and a statin as described herein is in the preparation of a medicament for the treatment or prophylaxis of Alzheimer's disease.

A particular combination for use in the present invention comprises rosuvastatin or a pharmaceutically-acceptable salt thereof and an  $\alpha 7$ -nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof.  
30

A particular pharmaceutical composition for use in the present invention comprises rosuvastatin or a pharmaceutically-acceptable salt thereof and an  $\alpha 7$ -nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier.

A particular method of the present invention is the provision of neuroprotection or analgesia for the treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease which method comprises administering a therapeutically effective amount of a combination of rosuvastatin or a pharmaceutically-acceptable salt thereof and an  $\alpha 7$ -nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof to a patient. In particular the method is useful for the treatment or prophylaxis Alzheimer's disease.

A particular embodiment of the invention is the use of a combination rosuvastatin or a pharmaceutically-acceptable salt thereof and an  $\alpha 7$ -nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one, *N*-(1-azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamide], or (2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof in the preparation of a medicament providing neuroprotection or analgesia for the treatment of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease. In particular the invention comprises the use of such a combination in the preparation of a medicament for the treatment of Alzheimer's disease.

Statins are compounds that inhibit HMG-CoA reductase, a rate-limiting enzyme in the biosynthetic pathway to cholesterol. Statins are conventionally used to reduce plasma levels of cholesterol in patients with cardiovascular disease but can also reduce A $\beta$  serum levels in patients. Alpha-7-nAChR agonists beneficially activate  $\alpha 7$ -nACh receptors and are useful for treating cognitive deficits and in the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's disease, cognitive or attention disorders, anxiety,

depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease. Accordingly, the hypothetical basis of the present invention lies in the realization that statins, by reducing the formation of A $\beta$ , may be particularly effective in combination with  $\alpha$ 7-nAChR agonists, which ameliorate cognitive deficits and inhibit neurodegeneration induced by A $\beta$ , in the treatment of Alzheimer's disease. Therefore, the treatment of Alzheimer's disease with a combination of a statin and an  $\alpha$ 7-nAChR agonist will result in enhanced efficacy over either type of agent if administered alone.

**Experimental:**

10           Assessment of the efficacy of a statin and an  $\alpha$ 7-nAChR agonist in combination in animal models is not straightforward. Existing experimental models of Alzheimer's disease include transgenic mice, which over express A $\beta$ , and animals with surgically generated fimbria-fornix lesions. These models and the uses to which they may be put are known, understood and appreciated by those of skill in the relevant art. Transgenic mice which over  
15           express A $\beta$  exhibit some of the clinical manifestations of Alzheimer's disease, *e.g.*, plaque deposition and, in some cases, cognitive deficits, but neurodegeneration is not observed. Animals with fimbria-fornix lesions have cognitive and learning deficits and have been used to assess potential approaches to treat neurodegeneration. No single experimental model exhibits the entire pathophysiological complex of Alzheimer's disease. However, to the  
20           extent that these models do mimic the pathophysiology of Alzheimer's disease they may be used to assess the effect of a statin and an  $\alpha$ 7-nAChR agonist in combination.

**Claims:**

1. A combination comprising:  
a statin selected from atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin  
5 sodium, simvastatin or rosuvastatin, or a pharmaceutically-acceptable salt thereof and  
an  $\alpha$ 7-nAChR agonist selected from spiro[1-azabicyclo[2.2.2]octane-3,5'-  
oxazolidine]-2'-one,  
(+)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,  
(-)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one,  
10 spiro[1-azabicyclo[2.2.1]heptan-3,5'-oxazolidin-2'-one],  
3'-methyl spiro-[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one],  
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-bromospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
15 5'-nitrospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
1'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline],  
5'-(phenylcarboxamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
b]pyridine],  
5'-(phenylaminocarbonylamino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
20 b]pyridine],  
5'-(phenylsulfonylamido)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
b]pyridine],  
5'-aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-N-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
25 5'-N,N-dimethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-  
b]pyridine],  
5'-N,N-diethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-N-ethylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-N-benzylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
30 5'-N-formamidospino[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-N-acetamidospino[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]isoquinoline],  
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]quinoline],

- 5'-ethenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(E)-(phenylethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(4-morpholino)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(1-azetidiny)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(E)-(2-(4-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(E)-(2-(2-pyridyl)ethenyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(2-trimethylsilylethynyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-ethynylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(2-furyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-(3-pyridyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-methylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5' carbonitrile],  
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine-5' carboxamide],  
5'-N'-(3-chlorophenyl)aminocarbonylminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
5'-N'-(2-nitrophenyl)aminocarbonylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-methoxyspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-phenylthiospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-(N-2-aminoethyl)aminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-phenylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-methylaminospiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-(4-N-methyl)piperazin-1-yl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine],  
4'-chloro-spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine],  
spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[3,2-c]pyridine],  
spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-7'-oxide],

- spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine-6'-carbonitrile],  
6'-chlorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine],  
6'-fluorospiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine],  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide),  
5 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),  
10 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide),  
15 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide),  
20 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide),  
25 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide),  
30 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide),

- N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide),  
5 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-  
10 carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-carboxamide),  
15 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-  
carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-chlorophenyl)furan-2-carboxamide),  
20 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-  
carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide),  
25 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-  
carboxamide),  
30 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide),  
*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide),

*N*-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-carboxamide),

5 *N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-carboxamide),

*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide); *N*-

10 (1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylfuran-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)furan-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-thienyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-phenylbenzamide),

15 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-pyridyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methoxyphenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-methoxyphenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-(*N*-acetylamino)phenyl)benzamide);

20 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-fluorophenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3-methylphenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-thienyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(3,5-dichlorophenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(2-naphthyl)benzamide),

25 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(3-(4-fluorophenyl)benzamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)furan-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-thienyl)furan-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-benzo[b]furanyl)furan-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)furan-2-carboxamide),

30 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-thienyl)furan-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)furan-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-methoxyphenyl)furan-2-carboxamide),

(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-fluorophenyl)furan-2-carboxamide),

- (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-naphthyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methylphenyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-furyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-furyl)furan-2-carboxamide),  
5 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(2-pyridyl)thiophene-2-carboxamide),  
10 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(4-pyridyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-(3-pyridyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)furan-2-  
carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-nitrophenyl)furan-2-carboxamide),  
15 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-trifluoromethylphenyl)furan-2-  
carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)furan-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-acetylamino)phenyl)thiophene-2-  
carboxamide),  
20 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-fluorophenyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-methoxyphenyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-ethoxyphenyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)furan-2-  
carboxamide),  
25 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3,5-dimethylisoxazol-4-yl)thiophene-2-  
carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)thiophene-2-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-3-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)[5-(4-chlorophenyl)furan-2-carboxamide),  
30 (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiazole-3-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiazole-3-carboxamide),  
(*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)thiophene-2-  
carboxamide).

5 *(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(8-quinolinyl)thiophene-2-carboxamide),  
*(S)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridyl)thiophene-2-carboxamide);  
*(S)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(4-pyridyl)thiophene-2-carboxamide),  
*(S)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide),  
*(S)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-2-carboxamide),  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenylthiophene-3-carboxamide),  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(4-phenylthiophene-2-carboxamide),  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-cyanophenyl)thiophene-2-carboxamide),  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N*-methylamino)phenyl)thiophene-2-  
 10 carboxamide),  
*(R)*-*N*-(1-aza-bicyclo[2.2.2]oct-3-yl)(5-(3-hydroxyphenyl)thiophene-2-carboxamide),  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-pyridylamino)thiophene-2-carboxamide),  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-chlorophenyl)thiophene-2-carboxamide),  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(4-morpholinyl)phenyl)thiophene-2-  
 15 carboxamide),  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(aminomethyl)phenyl)thiophene-2-  
 carboxamide),  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-phenoxythiophene-2-carboxamide),  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-aminophenyl)furan-2-carboxamide) ,  
 20 *(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(*N,N*-dimethylamino)phenyl)furan-2-  
 carboxamide),  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-formylphenyl)thiophene-2-carboxamide), or  
*(R)*-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(3-(hydroxymethyl)phenyl)thiophene-2-  
 carboxamide), or a pharmaceutically-acceptable salt thereof.

25

2. A pharmaceutical composition comprising a combination according to Claim 1 together with a pharmaceutically acceptable diluent or carrier.

30

3. A method providing neuroprotection or analgesia for the treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease which method comprises

administering a therapeutically effective amount of a combination as defined in Claim 1 to a patient.

4. The method according to Claim 3, for treatment or prophylaxis of Alzheimer's  
5 disease.

5. The use of a combination according to Claim 1 in the preparation of a medicament providing neuroprotection or analgesia for the treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive  
10 or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease.

6. The use of a combination according to Claim 5, in the preparation of a medicament for the treatment or prophylaxis of Alzheimer's disease.

15

7. A combination according to Claim 1, wherein said statin is rosuvastatin or a pharmaceutically-acceptable salt thereof and

said  $\alpha 7$ -nAChR agonist is selected from:

spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidine]-2'-one;

20 *N*-(1-Azabicyclo[2.2.2]oct-3-yl)[*E*-3-(2-thienyl)propenamido], or

(2'R)-5'-(3-furanyl)spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridine] or a pharmaceutically-acceptable salt thereof.

8. A pharmaceutical composition comprising a combination according to Claim 7  
25 together with a pharmaceutically acceptable diluent or carrier.

9. A method providing neuroprotection or analgesia for treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation,  
30 schizophrenia, Tourette's syndrome, and Parkinson's disease which method comprises administering a therapeutically effective amount of a combination as defined in Claim 7 to a patient.

10. The method according to Claim 9, for treatment or prophylaxis of Alzheimer's disease.
11. The use of a combination according to Claim 7, in the preparation of a medicament  
5 providing neuroprotection or analgesia for the treatment or prophylaxis of a condition or disorder involving reduced cholinergic function selected from Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, schizophrenia, Tourette's syndrome, and Parkinson's disease.
- 10 12. The use of a combination according to Claim 11, in the preparation of a medicament for the treatment or prophylaxis of Alzheimer's disease.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01352

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC7: A61K 31/505, A61K 31/439, A61K 31/40, A61K 31/351, A61K 31/22, A61K 31/404, A61K 31/4418, A61K 31/366, A61P 25/28 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC7: A61K, A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
WPI DATA, EPO-INTERNAL, CHEM. ABS DATA		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Lancet, Volume 356, 11 November 2000, H Jick et al: "Statins and the risk of dementia", page 1627 - page 1631 --	1-12
Y	Frontiers in Bioscience, Volume 7, 1 April 2002, Joseph D. Buxbaum et al: "Pharmacological concentrations of the HMG-COA reductase inhibitor lovastatin decrease the formation of the alzheimer Beta-amyloid peptide in vitro and in patients", page 50 - page 59 --	1-12
Y	WO 0132620 A1 (ASTRAZENECA AB), 10 May 2001 (10.05.01) --	1-12
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
3 December 2003		04-12-2003
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer Annå Sjölund/EÖ Telephone No. +46 8 782 25 00

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01352

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6110914 A (EIFION PHILLIPS ET AL), 29 August 2000 (29.08.00) --	1-12
Y	WO 0042044 A1 (ASTRAZENECA AB), 20 July 2000 (20.07.00) --	1-12
Y	WO 9606098 A1 (ASTRA AKTIEBOLAG), 29 February 1996 (29.02.96) --	1-12
Y	US 2002042429 A (JASON K. MYERS ET AL), 11 April 2002 (11.04.02) -- -----	1-12

# INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/SE03/01352**

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: **3-4, 9-10**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet**
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE03/01352

Claims 3-4, 9-10 relates to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practised on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds or compositions.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

06/09/03

International application No.

PCT/SE 03/01352

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0132620 A1	10/05/01	AU 1745501 A	14/05/01
		EP 1230217 A	14/08/02
		JP 2003513072 T	08/04/03
		SE 9903996 D	00/00/00
US 6110914 A	29/08/00	AT 225792 T	15/10/02
		AU 739022 B	04/10/01
		AU 8367998 A	10/02/99
		BR 9810924 A	15/08/00
		CN 1117755 B	13/08/03
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