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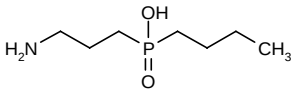
SGS-742

Treatmentof Alzheimer's Dementia
Treatment of Attention Deficit Hyperactivity Disorder
$GABA_B$ Receptor Antagonist

CGP-36742
DVD-742

(3-Aminopropyl)(butyl)phosphinic acid



$C_7H_{18}NO_2P$

Mol wt: 179.1982

CAS: 123690-78-8

EN: 153616

Abstract

Recent evidence points to a role for $GABA_B$ receptors in cognitive dysfunction. SGS-742 (formerly CGP-36742) is an orally active $GABA_B$ receptor antagonist with potential in the treatment of cognition disorders. Selective antagonism of the $GABA_B$ receptor has been demonstrated *in vitro* and it exhibited cognition-enhancing effects *in vivo*, with significant improvement in memory and learning in studies in mice, rats and rhesus monkeys. Furthermore, phase II evaluation in patients with mild cognitive impairment revealed that SGS-742 evokes a reduction in memory and attention deficits. SGS-742 has an excellent tolerability and safety profile and is rapidly absorbed, with age- and gender-independent pharmacokinetics. It is therefore a promising therapy for the treatment of Alzheimer's-related dementia and is currently in phase II development in these patients.

Synthesis

SGS-742 can be prepared by different ways:

1) Reaction of 3-aminopropylphosphinic acid (I) with benzyloxycarbonyl chloride (II) by means of NaOH in water gives the *N*-protected compound (III), which is condensed with butyl bromide (IV) by means of triethylamine and TMS-Cl in refluxing THF to yield 3-(benzyloxycarbonyl)propyl(butyl)phosphinic acid (V). Finally, this compound is deprotected by means of refluxing aqueous hydrochoric acid (1). Scheme 1.

The starting compound 3-aminopropylphosphinic acid (I) is obtained as follows:

a) Conjugate additon of (diethoxymethyl)phosphinic acid ethyl ester (VI) to acrylonitrile (VII) by means of NaH in EtOH gives (2-cyanoethyl)(diethoxymethyl)phosphinic acid ethyl ester (VIII), which is hydrogenated with H_2 over Ra-Ni in NH_3/EtOH to provide (3-aminopropyl)(diethoxymethyl)phosphinic acid ethyl ester (IX). Finally, this compound is treated first with concentrated HCl and then with propylene oxide in EtOH (2). Scheme 2.

b) Alternatively, compound (VIII) can also be obtained by reaction of (diethoxymethyl)phosphinic acid ethyl ester (VI) with HMDS at reflux followed by condensation with 3-chloropropionitrile (X) (3). Scheme 2.

c) Reaction of (diethoxymethyl)phosphinic acid ethyl ester (VI) with HMDS at reflux followed by condensation with 2-propenal (XI) in H_2O yields (diethoxymethyl)(2-formylethyl)phosphinic acid ethyl ester (XII), which by reductive amination with $NaCNBH_3$ and NH_4OAc in MeOH gives the already described (3-aminopropyl)(diethoxymethyl)phosphinic acid ethyl ester (IX) (2). Scheme 2.

2) Condensation of (diethoxymethyl)phosphinic acid ethyl ester (VI) with butyl bromide (XIII) by means of NaH in THF gives butyl(diethoxymethyl)phosphinic acid ethyl ester (XIV), which is treated with refluxing aqueous HCl and then with $ClCO_2Et$ and triethylamine in dichloromethane to yield butylphosphinic acid ethyl ester (XV). Condensation of compound (XV) with acrylonitrile (VII) by means of Na in refluxing ethanol affords butyl(2-cyanoethyl)phosphinic acid ethyl ester (XVI), which is hydrogenated with H_2 over Ra-Ni in hot ethanol containing NH_3 to provide 3-aminopropyl(butyl)phosphinic acid ethyl

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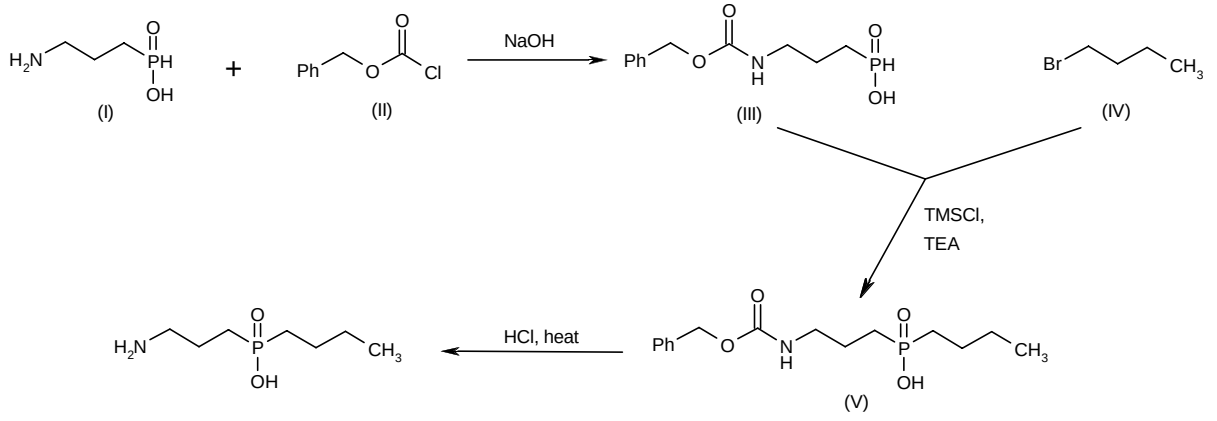
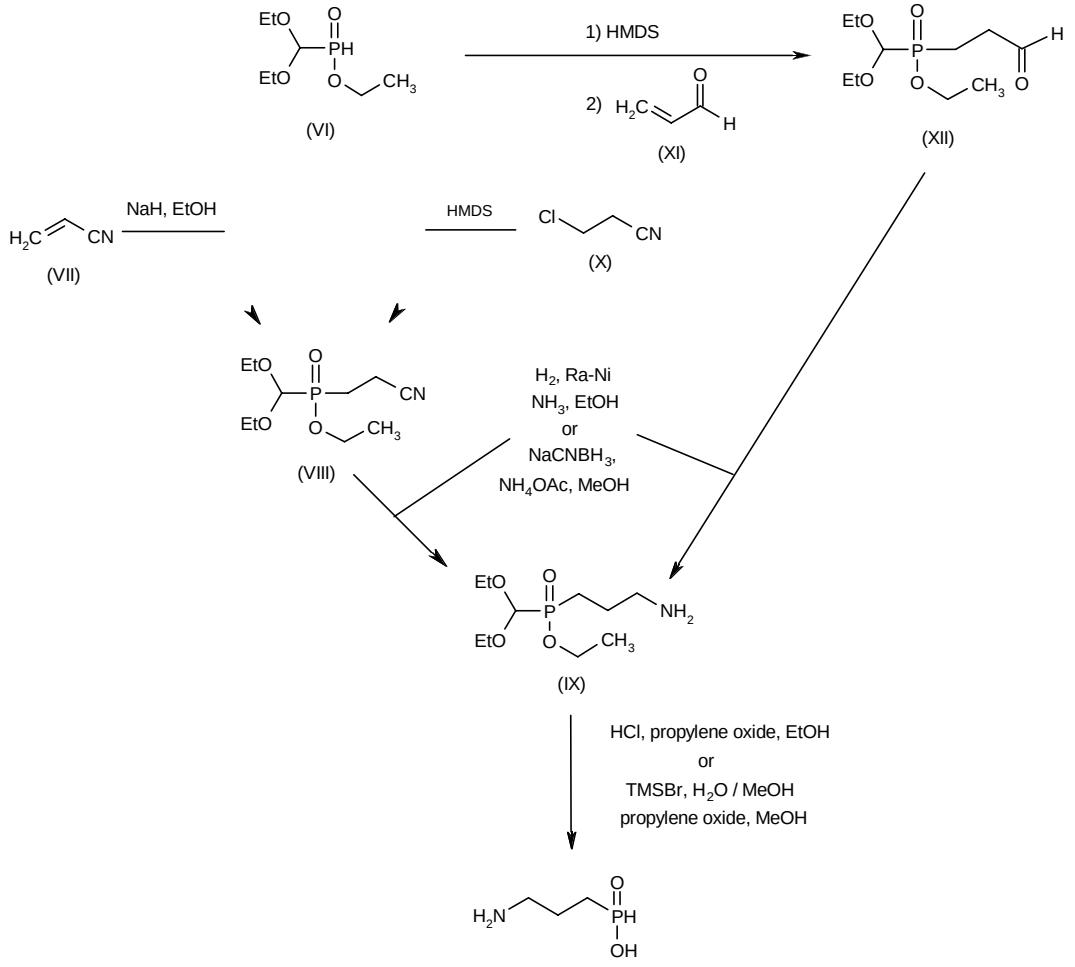
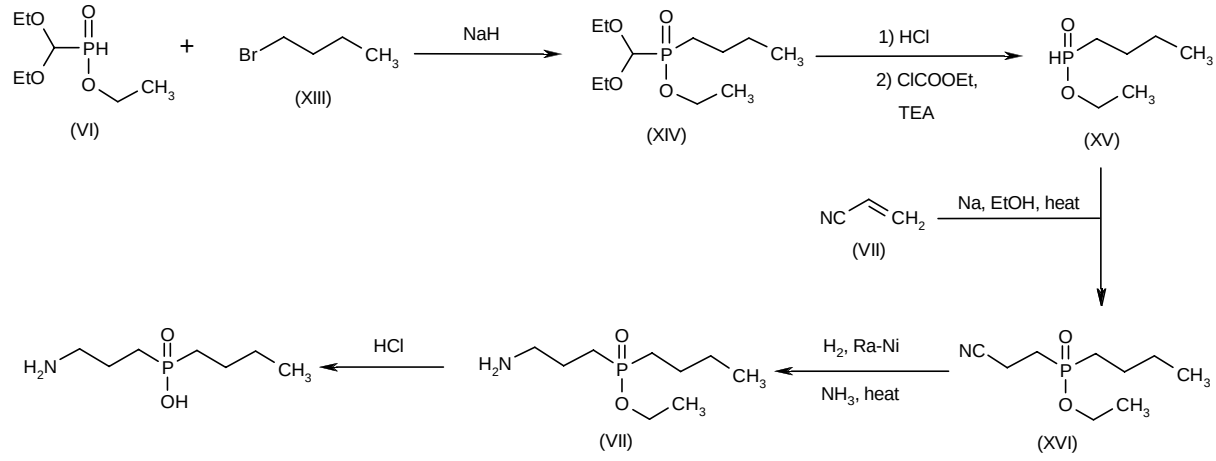
Scheme 1: Synthesis of SGS-742



Scheme 2: Synthesis of Intermediate I



Scheme 3: Synthesis of SGS-742



ester (XVII). Finally, this ester is hydrolyzed by treatment first with refluxing aqueous HCl and then propylene oxide in MeOH or alternatively, with thimethylsilyl bromide in CH_2Cl_2, H_2O/MeOH and propylene oxide in MeOH (4, 5). Scheme 3.

Introduction

Alzheimer's disease is the most common cause of dementia in the elderly. This brain disorder is a slow disease that progresses as nerve cell damage, neuritic plaques and neurofibrillary tangles (6) extend to different parts of the brain that control thought, memory and language. Early symptoms include mild cognitive impairment with a decline in the ability to perform simple everyday tasks. Over time, patients can no longer think clearly or make judgements, language skills are diminished, and mood and personality changes may occur. Eventually, with severe brain atrophy, they become completely unresponsive and require total care (7). It is a major health problem worldwide, occurring in between 15 and 18 million individuals, which is expected to increase to 45 million people by 2050 (8).

Cholinesterase inhibitors are currently used in the treatment of Alzheimer's disease but are associated with serious side effects and unsatisfactory results (9). Compounds that treat the cognitive symptoms of Alzheimer's disease are therefore of great therapeutic value. The widespread inhibitory neurotransmitter γ-aminobutyric acid (GABA) acts at either ionotropic ($GABA_A$ or $GABA_C$) or metabotropic ($GABA_B$) receptors. $GABA_B$ receptors are present throughout the mammalian brain, spinal cord and limbic system, and recent studies have shown that two $GABA_B$ subunits exist: $GABA_{B_1}$ (which consists of two isoforms: $GABA_{B_{1a}}$ and $GABA_{B_{1b}}$) and $GABA_{B_2}$. Together they form heterodimers that exhibit functional activity. $GABA_B$ receptors are coupled to G-proteins, and activation of these receptors increases potassium and decreases calcium ion conductance, and inhibits the release of various neurotransmitters and neuropeptides (10-14). Recent evidence suggests a role for the $GABA_B$ receptor in cognitive processes and that $GABA_B$ antagonists may be useful for improving learning and memory, for example in Alzheimer's disease (4, 15-18).

SGS-742 (formerly CGP-36742) is a novel and selective, orally active $GABA_B$ receptor antagonist that has demonstrated favorable cognition-enhancing effects.

Pharmacological Actions

An *in vitro* study was performed to determine if SGS-742 antagonizes the action of the $GABA_B$ receptor agonist baclofen in preparations of rat and human cortical synaptosomes. As measured by radioimmunoassay, SGS-742 concentration-dependently antagonized the baclofen-induced inhibition of depolarization-evoked release of somatostatin, a neuropeptide which is thought to play a role in cognition, in both rat (IC_{50} = 0.14 μM) and human samples, although reduced potency was seen in the human preparations. In contrast, SGS-742 had no effect on baclofen-induced inhibition of GABA, glutamate or cholecystokinin relese at up to 100 μM (19).

In vivo studies in mice examined the effects of SGS-742 on memory retention in learning trials. Oral administration of doses between 1 and 100 mg/kg given 60 min pretrial, and doses of 0.3, 3.0 and 30 mg/kg p.o. given 5 h pretrial, significantly improved memory facilitation

Table I: Pharmacokinetic profile of SGS-742 after oral administration in humans. Influence of age and gender and effects of food (from Prous Science Integrity®).

Dose (mg)	AUC (μmol*h/l)	C_{max} (μmol/l)	t_{max} (h)	$t_{1/2}$ (h)
600 mg				
Young males (s.d.)	198	27	3.0	3.6
Young males (t.i.d. x 6 d)		48	3.0	3.9
Elderly males (s.d.)	235	29	4.0	4.4
Elderly males (t.i.d. x 6 d)		54	4.0	4.5
Young males, fasted (s.d.)	208[1]	28	4.5	2.9
Young males, fed (s.d.)	136[1]	16	4.0	2.9
900 mg				
Elderly males (s.d.)	337	41	4.5	4.1
Elderly females (s.d.)	483	64	4.0	3.7
1200 mg				
Elderly males (s.d.)	384	48	4.0	4.0
Elderly females (s.d.)	544	77	3.5	3.8

AUC, area under the concentration-time curve from 0 to 36 h; [1] AUC from 0 to infinity; C_{max}, peak plasma concentration; t_{max}, time to reach peak plasma concentration; $t_{1/2}$, elimination half-life; s.d., single dose.

over 24 h in a passive avoidance test. Furthermore, immediate post-trial drug administration (0.3, 3.0 and 30 mg/kg i.p.) was also shown to have positive effects on memory retention. Studies in rhesus monkeys also demonstrated that, during a series of complexity tasks, pretreatment with SGS-742 (0.5 mg/kg 1 h before cognitive assessment) was associated with positive effects on cognitive function when compared to placebo (20). Maintenance of the memory-enhancing effects was assessed in a passive avoidance trial in mice administered SGS-742 at a dose of 10 mg/kg i.p. Drug-associated performance retention was sustained over a period of 4 months (21).

The efficacy of SGS-742 was also assessed in the pentylenetetrazol (PTZ)-induced kindling model in mice, which is associated with specific memory and learning deficits. SGS-742 (10 mg/kg i.p) was given pre-PTZ treatment and learning trials to an aversive stimulus were performed 7 days after kindling. Mice treated with SGS-742 displayed significantly improved learning and memory retention when retested 7 days following initial learning sessions (22, 23).

Learning and memory impairment can also be induced in mice by infusion of colchicine to the hippocampus. SGS-742 (50 mg/kg i.p.) was administered for 14 days after colchicine or saline infusion and behavioral assessments revealed significant learning and memory improvement in both colchicine- and saline- treated animals. It was suggested that these effects might be mediated via the modification or normalization of glutamate/GABA ratios and $GABA_B$ receptor levels (24).

A study in rats assessed the effect of SGS-742 on social recognition behavior. SGS-742 (0.003, 0.03, 0.3, 3.0, 30 and 300 mg/kg p.o.) or placebo was given before initial animal introduction and the effects were analyzed upon reintroduction 24 h later. All doses of SGS-742 used in this study effected a notable improvement in social recognition (20, 25).

In other behavioral studies, active avoidance was monitored over a 5-day period in a test using negative reinforcement. The number of escapes was significantly reduced in Wistar rats and genetic absence epilepsy rats of Strasbourg (GAERS) treated with 100 mg/kg i.p. SGS-742 on days 3-5 and days 2-5, respectively (26).

Experiments using the Morris water maze task in rats revealed that oral administration of SGS-742 (10, 30 and 100 mg/kg) dose-dependently improved both scopolamine- and baclofen-induced deficits in place learning, suggesting the involvement of cholinergic systems in addition to GABA receptor systems in the positive effect of the drug on learning and memory (17).

Recent work has indicated a role for $GABA_B$ receptors in anxiety and depression. The antidepressant action of SGS-742 was therefore assessed in a paradigm of learned helplessness. SGS-742 was administered to rats over a range of doses (0.03-100 mg/kg i.p.) for 14 days. Post-treatment behavioral escape responses to an aversive learned stimulus were assessed. SGS-742 improved escape deficits at doses of 30 and 100 mg/kg and its effects were comparable to those seen for the tricyclic antidepressant imipramine (3 and 10 mg/kg) (27).

Pharmacokinetics

The pharmacokinetics, tolerability and safety of SGS-742 were investigated in healthy young and elderly volunteers (Table I). A trial in 12 healthy young male volunteers showed that a single oral dose (600 mg) resulted in a C_{max} of 27 μmol/l and a median t_{max} of 3 h. A $t_{1/2}$ of 3.6 h was obtained, with a renal clearance of 125 ml/min. Absolute bioavailability was 44%. Bioavailability and C_{max} did not increase above doses of 800 mg. A further within-subject comparative crossover trial revealed that administration with food decreased the oral systemic

availability by 30% but did not influence the t_{max} or $t_{1/2}$. A multiple-dose study in healthy young and elderly male volunteers demonstrated that pharmacokinetic parameters did not differ significantly between the age groups. Similarly, a pharmacokinetic comparison between elderly males and females indicated no gender-related differences. SGS-742 was well tolerated, with no clinically relevant changes in cardiovascular variables, body temperature or blood chemistry. All reported adverse events were mild to moderate and no drug-associated adverse effects were seen (28).

Clinical Studies

A multicenter, double-blind, placebo-controlled phase II study was conducted in 110 patients with mild cognitive impairment. Oral SGS-742 (600 mg t.i.d. for 8 weeks) significantly improved working memory, psychomotor speed and attention and was well tolerated (29).

SGS-742 is currently undergoing phase II development as a treatment for mild to moderate Alzheimer's disease (30). In addition, a new phase II trial is evaluating the compound in adult patients with attention deficit hyperactivity disorder (31).

Source

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References

1. Baylis, E.K., Bittiger, H., Fröstl, W., Hall, R.G., Maier, L., Mickel, S.J., Olpe, H.-R. (Novartis AG). *Substd. propane-phosphinic acid cpds.* AU 8826544, EP 0319479, EP 0319482, US 5051524, US 5064819, US 5190933.

2. Froestl, W., Mickel, S.J., Hall, R.G. et al. *Phosphinic acid analogues of GABA. 1. New potent and selective $GABA_B$ agonists.* J Med Chem 1995, 38: 3297-312.

3. Dingwall, J.G., Ehrenfreund, J., Hall, R.G., Jack, J. (Novartis AG). *Substd. propane-phosphonous acid cpds.* AU 8548579, EP 0181833, ES 8800250, JP 1986093189, US 4656298, US 4772738.

4. Froestl, W., Mickel, S.J., von Sprecher, G. et al. *Phosphinic acid analogues of GABA. 2. Selective, orally active $GABA_B$ antagonists.* J Med Chem 1995, 38: 3313-31.

5. Marescaux, C., Bernasconi, R., Schmutz, M., Fröstl, W., Mickel, S.J. (Novartis AG). *New antiepileptic agents.* EP 0463560, JP 1992243829, US 5229379, US 5407922.

6. Albensi B.C. *Biological mechanisms, cerebrovascular alterations and pharmacological targets in the pathology of dementia.* Drug News Perspect 2002, 15: 333-337.

7. Prous Science Drug R&D Backgrounders: *Alzheimer's disease (online publication).* Updated March 21, 2005.

8. Albert, M.S., Drachman, D.A. *Alzheimer's disease: What is it, how many people have it, and why do we need to know?* Neurology 2000, 55: 166-8.

9. Cummings, J.L., Frank, J.C., Cherry, D., Kohatsu, N.D., Kemp, B., Hewett, L., Mittman, B. *Guidelines for managing Alzheimer's disease: Part II. Treatment.* Am Fam Physician 2002, 65: 2525-3.

10. Bowery, N.G., Enna, S.J. *γ-Aminobutyric acid B receptors: First of the functional metabotropic heterodimers.* J Pharmacol Exp Ther 2000, 292: 2-7.

11. Bowery, N.G. *$GABA_B$ receptor pharmacology.* Annu Rev Pharmacol Toxicol 1993, 33: 109-47.

12. Gerber, U., Gahwiler, B.H. *$GABA_B$ and adenosine receptors mediate enhancement of the K^+ current, IAHP, by reducing adenylyl cyclase activity in rat CA3 hippocampal neurons.* J Neurophysiol 1994, 72: 2360-7.

13. Bowery, N.G., Pratt, G.D. *$GABA_B$ receptors as targets for drug action.* Arzneim-Forsch Drug Res 1992, 42: 215-23.

14. Bittiger, H., Froestl, W., Mickel, S., Olpe, H.R. *$GABA_B$ receptor antagonists: From synthesis to therapeutic applications.* Trends Pharmacol Sci 1993, 14: 391-4.

15. Bianchi, M., Panerai, A.E. *Reversal of scopolamine-induced amnesia by the $GABA_B$ receptor antagonist CGP 35348 in the mouse.* Brain Res Cogn Brain Res 1993, 1: 135-6.

16. DeSousa, N.J., Beninger, R.J., Jhamandas, K., Boegman, R.J. *Stimulation of $GABA_B$ receptors in the basal forebrain selectively impairs working memory of rats in the double Y-maze.* Brain Res 1994, 641: 29-38.

17. Nakagawa, Y., Takashima, T. *The $GABA_B$ receptor antagonist CGP36742 attenuates the baclofen- and scopolamine-induced deficit in Morris water maze task in rats.* Brain Res 1997, 766: 101-6.

18. Mondadori, C., Jaekel, J., Preiswerk, G. *Treatment with $GABA_B$ receptor blockade improves the cognitive performance of mice, rats, and rhesus monkeys.* Pharmacol Commun 1992, 2: 93-7.

19. Bonanno, G., Carità, F., Cavazzani, P., Munari, C., Raiteri, M. *Selective block of rat and human neocortex $GABA_B$ receptors regulating somatostatin release by a $GABA_B$ antagonist endowed with cognition enhancing activity.* Neuropharmacology 1999, 38: 1789-95.

20. Mondadori, C., Jaekel, J., Preiswerk, G. *CGP 36742: The first orally active $GABA_B$ blocker improves the cognitive performance of mice, rats, and rhesus monkeys.* Behav Neural Biol 1993, 60: 62-8.

21. Mondadori, C., Möbius, H.-J., Borkowski, J. *The $GABA_B$ receptor antagonist CGP 36,742 and the nootropic oxiracetam facilitate the formation of long-term memory*. Behav Brain Res 1996, 77: 223-5.

22. Getova, D., Froestl, W., Bowery, N.G. *Effects of $GABA_B$ receptor antagonism on the development of pentylenetetrazol-induced kindling in mice.* Brain Res 1998, 809: 182-8.

23. Genkova-Papazova, M.G., Petkova, B., Shishkova, N., Lazarova-Bakarova, M. *The $GABA_B$ antagonist CGP 36742 prevents PTZ-kindling-provoked amnesia in rats.* Eur Neuropsychopharmacol 2000, 10: 273-8.

24. Yu, Z., Cheng, G., Hu, B. *Mechanism of colchicine impairment on learning and memory, and protective effect of CGP36742 in mice.* Brain Res 1997, 750: 53-8.

25. Mondadori, C., Moebius, H.-J., Zingg, M. *CGP 36,742, an orally active $GABA_B$ receptor antagonist, facilitates memory in a social recognition test in rats.* Behav Brain Res 1996, 77: 227-9.

26. Getova, D., Bowery, N.G., Spassov, V. *Effects of $GABA_B$ receptor antagonists on learning and memory retention in a rat model of absence epilepsy*. Eur J Pharmacol 1997, 320: 9-13.

27. Nakagawa, Y., Sasaki, A., Takashima, T. *The $GABA_B$ receptor antagonist CGP36742 improves learned helplessness in rats.* Eur J Pharmacol 1999, 381: 1-7.

28. Gleiter, C.H., Farger, G., Möbius, H.-J. *Pharmacokinetics of CGP 36 742, an orally active $GABA_B$ antagonist, in humans.* J Clin Pharmacol 1996, 36:428-38.

29. Froestl, W., Gallagher, M., Jenkins, H., Madrid, A., Melcher, T., Teichman, S., Mondadori, C.G., Pearlman, R. *SGS742: The first $GABA_B$ receptor antagonist in clinical trials*. Biochem Pharmacol 2004, 68: 1479-87.

30. *Saegis Pharmaceuticals begins phase II clinical trial of SGS742 for Alzheimer's disease.* Saegis Pharmaceuticals Press Release May 3, 2004.

31. *SGS-742 evaluated in new phase II study for adult ADHD.* DailyDrugNews.com (Daily Essentials) March 29, 2005.